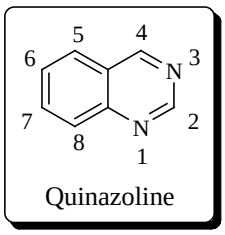
Section II

Chapter 3: Research Envisaged

3. Research Envisaged

The review of literature reveals that enormous studies on the quinazolinone scaffold for different types of medicinal activities have been done. However, exploration of the quinazolinone moiety still continues as it is a promising heterocycle for further research. We developed interest in the quinazoline scaffold because of its reported potential to show favourable CNS activity.



Quinazoline

Quinazolinones have been reported for their CNS effects including analgesic, anti-Parkinsonian, CNS depressant, CNS stimulant, tranquilizing, antidepressant, and anticonvulsant effects. These compounds also act as psychotropic, hypnotic, cardiotonic, and antihistamine agents and possess cardiovascular (antihypertensive, antiarrythmic, vasodilatory, and lipid-lowering effects) and anti-inflammatory activities (inhibition of cyclooxygenase activity and leukocyte function). Many reports suggest more active compounds can be obtained by substitution of the quinazolinone ring at the position 2 and 3. Some of the better acting quinazolinones are depicted in Fig. 3.1

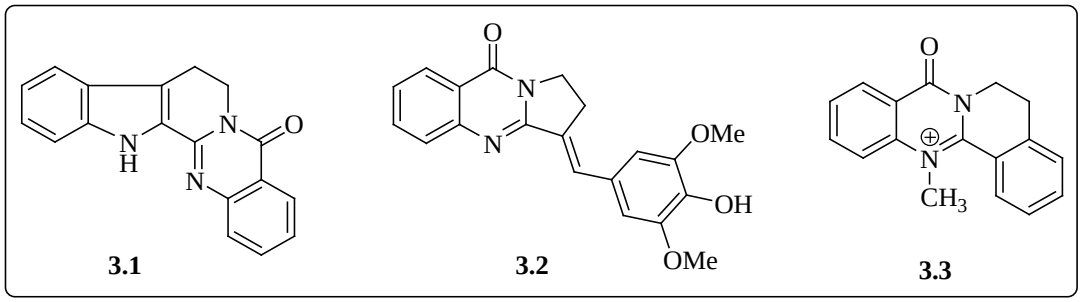


Fig. 3.1: 2,3-Substituted Quinazolinones as CNS acting agents

The above compounds show good anticholinesterase activity, useful for the treatment of AD. The acridine derivative tacrine (I) was one of the earliest ChEI developed to treat AD. Some natural compounds obtained from plant and animal sources have been studied for AD, among which oroidin (II) from *Agelas oroides* (Turkish marine sponge) showed a moderate level of AChE inhibition and possessed cyclic guanidine in the structure. Keeping in mind the above facts, the structure of tacrine (tricyclic ring

system) and the presence of guanidine base in cyclic ring system in oroidin (II), it was planned to synthesize a quinazolinone ring system of type III and to evaluate the resulting derivatives for cholinesterase inhibition activity (Fig 3.2).

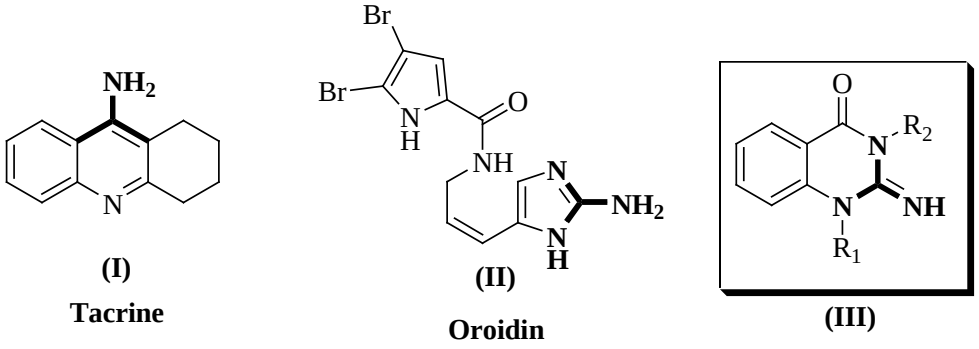


Fig. 3.2: Compounds with good anticholinesterase activity

There are only five drugs approved for the treatment of Alzheimer's disease and all of these have shown side effects like seizures, hepatic discomfort, cardiac failures etc., hence, there is a great need for discovery of newer agents for the management of the disease. It has been observed that butyrylcholine esterase activity increases in the brain during the latter phase in Alzheimer's patients. Therefore, there is a need of newer agents having activity against AChE (to treat the early stage of AD) as well as BuChE (to treat late stageof AD). Further, at molecular level, there are two active sites in AChE, peripheral anionic site (PAS) and catalytic anionic site (CAS), and both the sites are 14Å far away from each other. Hence, it was planned to synthesize compounds that would bind to both the sites for good anti-Alzheimer activity.

3.1 Objectives

- The primary aim of the study was to search for easier and faster synthetic approaches to produce multiple compounds for the development of new and more promising CNS active quinazolinones.

- To synthesize a novel series of compounds with a cyclic guanidine motiff incorporated into 4-quinazolinone as benzoannelated heterocycles on the basis of fundamental principles of synthetic chemistry using isatoic anhydride as one of the starting materials and different halides, amines, cynogen bromide etc. Also, to develop and optimize scheme under different reaction conditions for obtaining the best practical yield.

- To prepare quinazolinone scaffold with different substituents at various positions to obtain potent AChE and BuChE inhibitors.

- Further, to evaluate the synthesized compounds for their anti-Alzheimer's potential.

The development of new and different quinazolinone derivatives as AChEIs and BuChEIs for Alzheimer's disease is a very important objective and much of the research efforts are directed toward the design of new anti-AD agents. Hence, our aim was to develop newer cholinesterase inhibitors with selectivity for AChE and BuChE both.