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QUINAZOLINE A SCAFFOLD WITH ANTIMICROBIAL AND ANTICONVULSANT ACTIVITY: OVERVIEW

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ABSTRACT

Pharmacologicaly active benzofused moieties mostly possess heterocyclic ring structures and presence of heteroatoms or groupings evinces privileged specificities in their pharmacological targets. Among the heterocyclic compounds, quinazolines has emerged as cardinal construction motif, which plays pivotal role in drug development. Quinazoline scaffold is known to possess some prime pharmacological activities like anti-mycobacterial, anti-microbial, anti-viral, anti-oxidant, anti-inflammatory, anti-hypertensive, anti-convulsant etc. This broad spectrum of biological and biochemical activities has been further assisted by the synthetic flexibility of quinazoline, which permits development of large number of structurally diverse derivatives. Therefore, it is necessary to compile the latest information along with earlier information to understand present status of quinazoline nucleus in drug discovery. In the present review, various derivatives of quinazoline possessing antimicrobial, anti-convulsant potential are brought into limelight and their activity has been elucidated in accordance with structure activity relationship studies.

KEYWORDS: Heterocycles, Quinazoline, Antimicrobial, anti-colvulsant.

INTRODUCTION

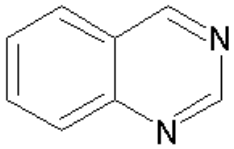
Medicinal organic chemistry has emerged research field with increasing importance as heterocycle-based chemical entities and most prevalently benzofused five/six membered nitrogen containing heterocyclic systems provide framework for development of drug molecules with diverse biological activities. Among the benzofused five/six membered nitrogen containing heterocycles, quinazoline has emerged as important heterocyclic system due to its presence in wide range of biological/pharmacological activity like antimicrobial,

anticonvulsant, antitumor, antihypertensive, antidiabetic, anti-inflammatory, anti-HIV, antioxidant, analgesic, etc. Optimisation of different functional groups around quinazoline scaffold has resulted in drugs with diversified therapeutic potential like Prazosine as antihypertensive; Gefitinib as EGFR inhibitor; Alfuzosin as α_1 receptor antagonist in treatment of benign prostatic hyperplasia(BPH); Bunazosin in treatment of glaucoma; Vandetanib as anticancer agent in treatment of thyroid cancer; Proquazone as non-steroidal anti-infalmmatory drug; Albaconazole as antibacterial agent and many other lead molecules in variety of other therapeutic areas.[1]

Owing to the diverse pharmacological activities possessed by this scaffold, active research has been sparked across the globe in order to design and develop quinazoline based drug molecules. In the present review, we have attempted to explore the insights of applications of quinazoline nucleus in different therapeutic fields.

Chemistry

Quinazoline is a class of heterocyclic aromatic organic compound which share a fundamental structural features of six membered benzene fused to pyrimidine ring system. Quinazoline was first prepared in laboratory by Gabriel in 1903.[2] The name quinazoline was first proposed by Weddige as it is isomeric with compounds cinnoline and quinoxaline. Numbering of quinazoline ring(Fig1) was suggested by Paal and Bush.[2] The presence of fused benzene ring alters the properties of pyrimidine ring considerably.



Quinazoline offer prodigious therapeutic potential and synthetic flexibility, thus efforts have been made from time to time to generate libraries of these compounds. In past decade, efforts have been made by many researchers for development of efficient and environment friendly synthetic routes for synthesis of quinazoline and its analogues.

Biological Activitites

Quinazoline moiety came into picturesque with the discovery of febrifungine, a quinazolinone alkaloid, potential anti-malarial agent obtained from Chinese plant aseru and this sparked the initiation of active research on quinazolines. Earlier research revealed that

quinazolines possess anti-malarial as well as antimicrobial potential. Quinazolines were brought into limelight with the discovery of soporific and sedative action of 2-methyl-3-aryl-4-quinazolinone derivatives.

Quinazoline and its analogues possess diversified therapeutic potential and these analogues mediate their actions through variety of possible mechanisms. Some principle biological activities shown by quinazolines are depicted in (Fig 2).

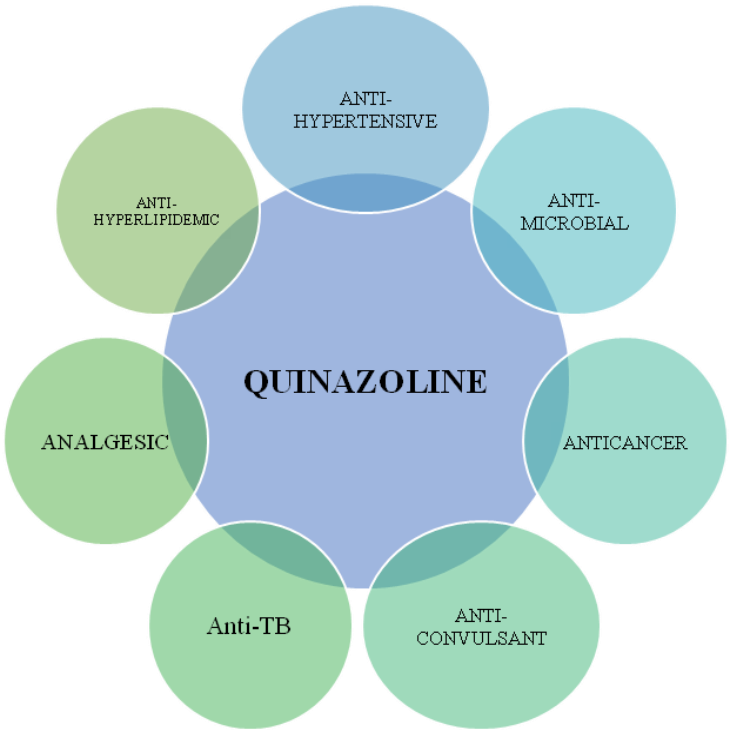


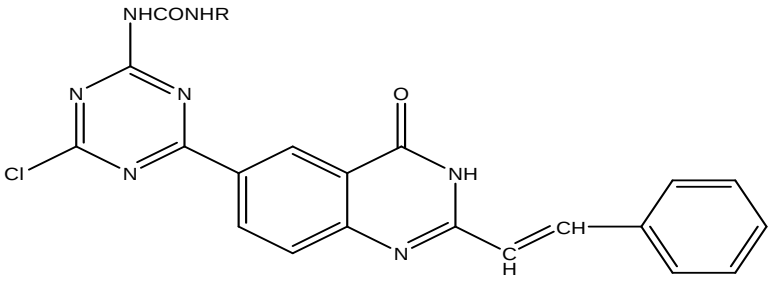
Fig. 2: Activity spectrum of quinazoline and its analogues.

Antimicrobial Activity

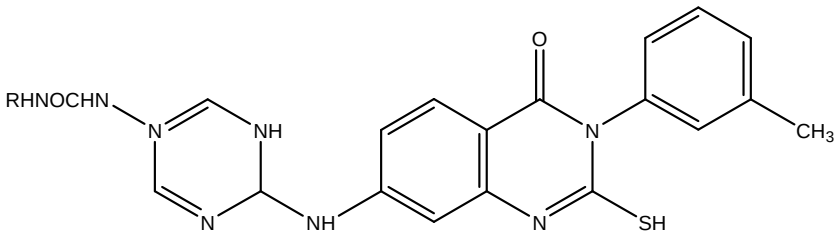
Anti-microbial drugs are the greatest contribution of the 20th century to therapeutics. Their Advent changed the outlook of the physician about the power drugs can have on diseases. Extensive research is being carried out for development new and effective anti-microbial agents, since microbial drug resistance is one of the serious issues with some microbial strains being resistant to all available commercial anti-microbial agents. Efforts are being made in the field of drug development to overcome this issue using heterocycle-based moieties, especially quinazoline and its substituted analogues, as they offer priotising results. The structure activity relationship studies of quinazolinone derivatives in various literatures have revealed that substitution at positions 2 and 3, existence of halogen atom at 6 and 8 positions and substitution at 4th (mainly amine or substituted amine) can improve their

antimicrobial activities. Presence of substituted aromatic ring at 3 and methyl, amine and thiol groups at position 2 are essential for antimicrobial activities.

Desai et *al.* explored the synthetic strategies and anti-microbial potential of some quinazolines and mercaptoquinazolines. Among the study compounds, 2'-methylphenylureido, 3'-nitrophenylureido and 4'-methylureido derivatives showed the maximum potency against S. *aureus*, E.*coli* and K. *pneumoniae* respectively(1, 2,).[3]

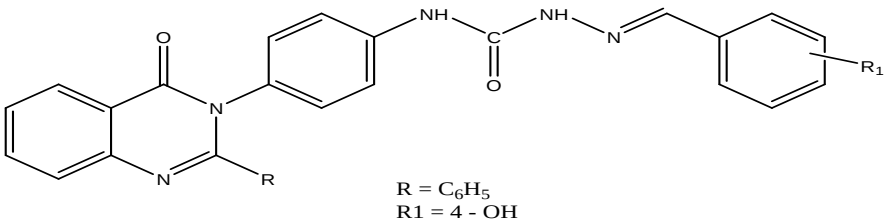


(1)



(2)

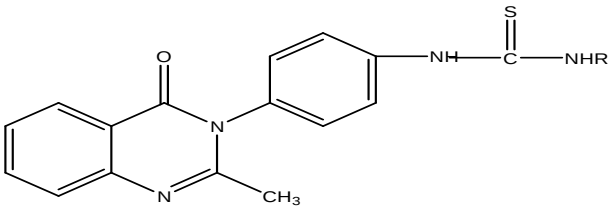
Saravanan et al. Reported the synthesis of some entities bearing quinazolinone scaffold and evaluated these compounds for their anti-microbial activity. Their studies suggest compound 3 shows better activity of all synthesised molecules. SAR studies reveal that, analogs substituted with electron donating groups showed promising results. 2-phenyl quinazolinones were found to be more active than 2-methyl quinazolinones (3).[4]



R = C_6H_5
R1 = 4 - OH

(3)

Hasan *et al.* studied some quinazolinones substituted with thiazolines and thiazolidinones for their anti-microbial potential. Thiazolines proved to be more active against selective microbial strains as compared to the thiazolidinones substituted quinazolinones (4, 5, 6).[5]



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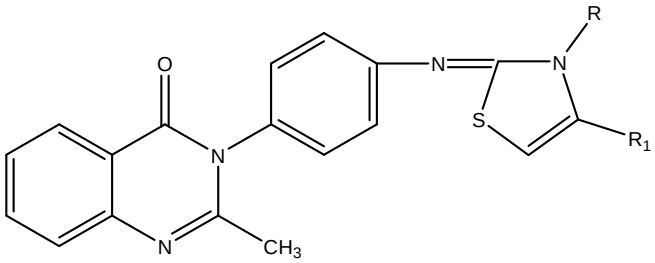

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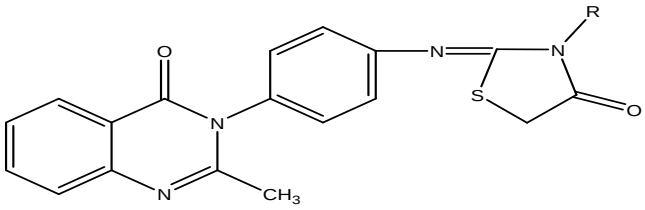
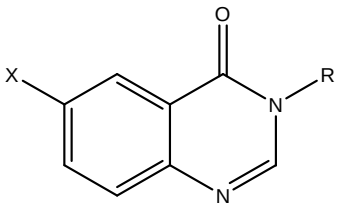


(6)

Ouyang et *al.* Carried synthesis of some 3-alkylquinazolin-4-one derivatives and screened them for anti-fungal potential. From all synthesised derivatives, compound 7 showed comparable activity to that of the standard drug used i.e., Hymexazol.[6]



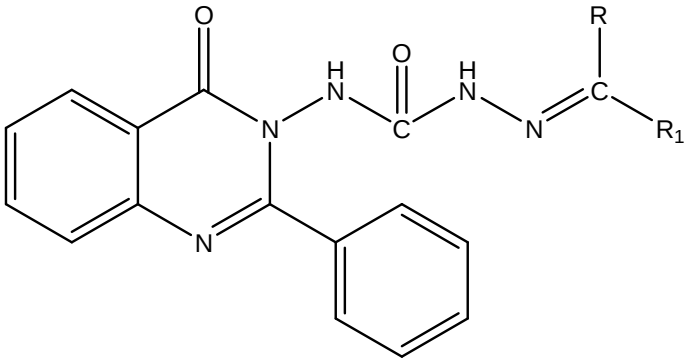
(7)

Anticonvulsant Activity

Epilepsy is a chronic disorder of the brain that effects people of all age groups. Approximately 50 million people worldwide have epilepsy, making it one of the most

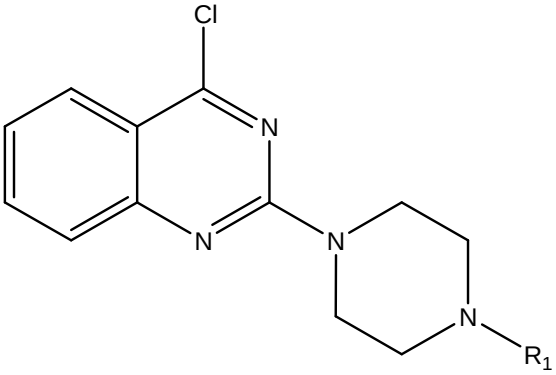
common neurological diseases globally. Nearly 80% of the people with epilepsy live in low and middle income countries. People with epilepsy respond to treatment approximately 70% of the time.[7] In recent years, the chemistry of quinazoline and its derivatives has received considerable attention owing to their synthetic and effective biological importance. The anti-convulsant activity of quinazoline derivatives was attributed to its ability to bind the non-competitive acid (AMPA) receptors.[8]

Ilangoan *et al,* reported the synthesis of novel quinazoline derivatives and evaluated them for anticonvulsant activity. Substitution at N3 position lead to increase in biological efficieny. Among the sysnthesised compounds, compound 8,9,10 were proved to be useful in treating general tonic-clonic and complex partial seizures.[8]



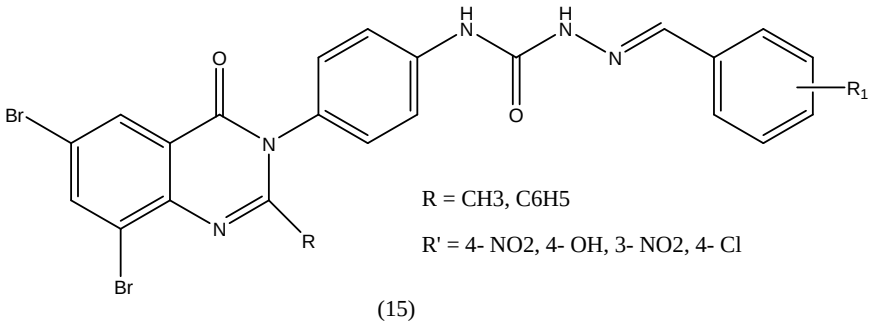
	R	R1
(8)	H	- C_6H_5
(9)	H	- 4 NO_2Ph
(10)	H	- 4 MeOPh

Mukherjee *et al*, performed the synthesis and evaluation of anticonvulsant activity of substituted quinazolines. Compounds 11,12,13,14 were proved to be effective in the management of pentylene tetrazole induced threshold seizures.[9]



	R1
(11)	Cl
(12)	Ph
(13)	EtOH
(14)	-CH_2-O-C_2H_5OH

Govindaraj Saravanan *et al.* designed, synthesised and screened novel quinazolinone derivatives for antiepileptic activity using MES and PTZ model. Schiff bases of quinazolinone were synthesized by reacting substituted quinazoline hydrazides with appropriate aldehyde in ethanol and glacial acetic acid. Compound 15.[10]

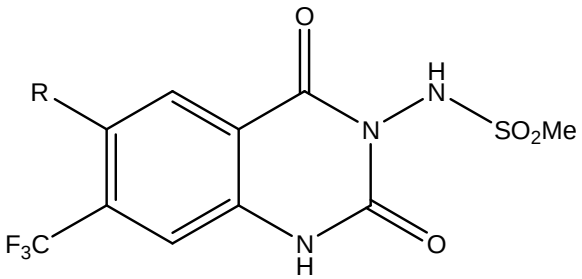


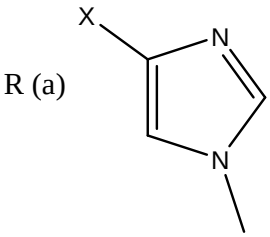
R = CH3, C6H5

R' = 4- NO2, 4- OH, 3- NO2, 4- Cl

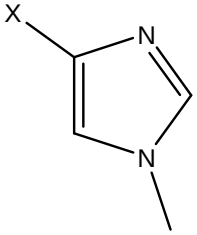
(15)

David Orain et al. synthesized new set of quinazolinedione sulfonamide derivatives as competitive AMPA receptor antagonist with improved properties. Various key intermediate were substituted with varieties of substituents. All compounds were tested in a binding assay for the orthosteric ligand binding site of AMPA receptor using rat brain homogenates and the radioligand [^{3}H]-CNQX (16 a, 16 b).[11]





R (a) X = CONHMe

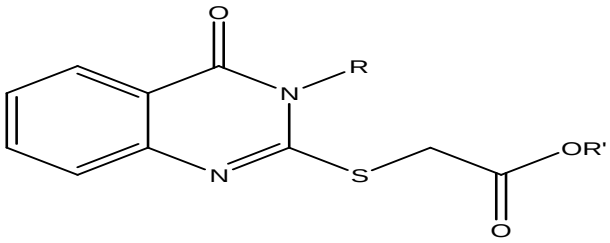


R (b) X = $CONHMe_2$

(16 a, b)

Abdel Ghany El-Helby et al, synthesized a novel series of 3 substituted-3H-quinazoline- 4-one derivatives. Compounds showed highest anticonvulsant activity at low doses where as at higher doses, they showed a stimulant effect on CNS that potentiated effect of convulsive

agent PTZ. Substitution at N3 position of 3H quinazoline-4-one nucleus by CH_3 and C_6H_5 showed increase in anticonvulsant effect Compound 17.[12]



R = CH_3, C_2H_5, C_6H_5

R' = C_6H_5, $C_{10}H_9$, $C_6H_4CH_3$

(17)

CONCLUSION

Numerous studies in the field of pharmaceutical medicinal chemistry has revealed that quinazoline derivatives can act on variety of targets and are capable of fostering therapeutic effects. This fact had drawn the attention of many researchers and thus quinazoline derivatives are being intensively investigated for their potential therapeutic properties. Quinazoline has emerged as promising bioactive heterocyclic compound that will best exemplary results in the nearest scientific future. The present review is expected to be helpful to researchers and academicians while exploring therapeutic potential of quinazoline and its derivatives.

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