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A Comprehensive Review on Chemistry, SAR and Pharmacology of 4-amino-2-chloro-6, 7-dimethoxyquinazoline Derivatives.

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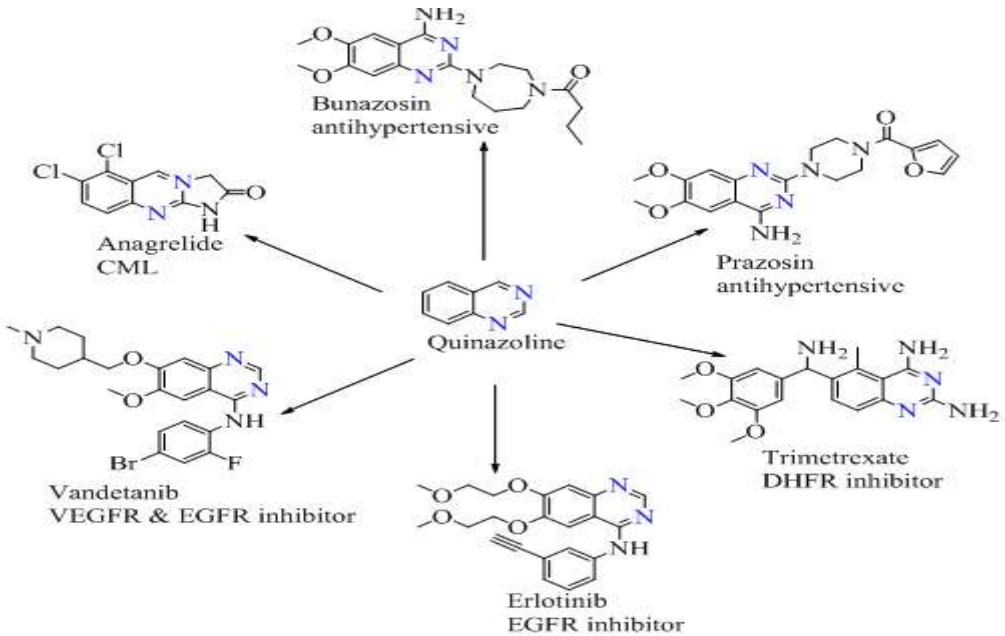
ABSTRACT
Quinazoline and its derivatives are employed in drug discovery in the field of pharmaceutical medicinal chemistry. The unique structural features of quinazoline and a wide range of biological activities of its derivatives made it privileged structure in drug discovery. Recently, quinazoline scaffold has emerged as a pharmacophore of choice to design active agents in multiple clinically approved targets to pave the way for future research, there is a need to collect the latest information in this promising area. In the present review, we have collated published reports on this versatile core to provide an insight so that its full therapeutic potential is coupled with the proven information to understand the current status of quinazoline moiety in medicinal chemistry research and therefore, we correlated the structure activity relationship with the pharmacology of the moiety.

Keywords: Quinazoline, Biological activity, Drug discovery, Pharmacophore

I. INTRODUCTION

Over the years of active research, quinazoline has evolved as an important heterocyclic moiety due to its presence in a wide range of bioactive compounds like antiparasitics, anticonvulsants, analgesics, antihypertensive, antidiabetic, antituberclosis, antiviral, anticancer, antifungal and anti-inflammatory agents . Optimization of substituent around the quinazoline nucleus has resulted in many drugs like balaglitazone as antidiabetic, Gefitinib as anticancer, albaconazole as antifungal and prazosin as antihypertensive and many lead compounds in a wide range of other therapeutic areas[1]. The research and development of bioactive molecules from quinazoline still is ongoing.



STRUCTURAL ACTIVITY RELATIONSHIP

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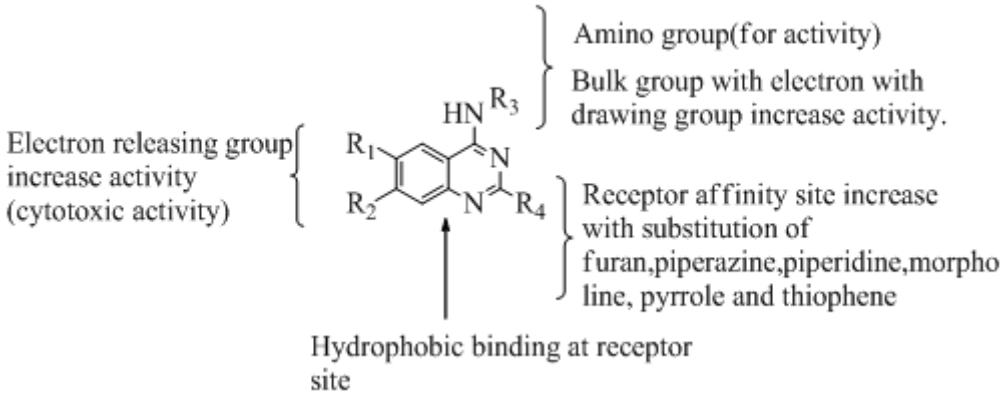
The activity of quinazoline scaffold based drugs is directly proportional to their structural conformation.

Structural Model of 2-chloro-4-amino (6, 7-dimethoxy) quinazoline

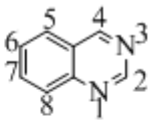


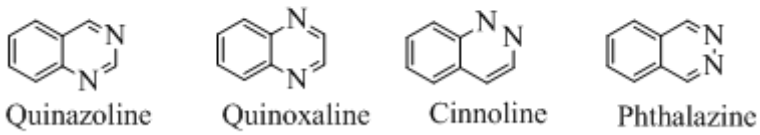
The amino group increase hydrophility and bioavailability, proven as more the 50% of anticancer agents approved by USFDA posses the group.

They normally attached frequently use antitumor moieties at C-2 (R_4) position such as mopholine, piperazine, and piperidine to elevate the activity of quinazoline, quinazoline moiety is important as its biological and pharmacological activity depends on its structure, Present of halogen, N, O, and S exhibit biological action.

Chemistry

1, 3-diazanaphthalene is a scaffold made up of two condensed six-membered aromatic rings, a pyrimidine ring and a benzene ring. Quinazoline is double nitrogen containing fused heterocyclic molecule exhibiting 4 isomeric forms (diazanaphthalene) i.e., benzopyrimidine, benzopyrazine, benzopyridazine and benzo-orthodiazine differing by nitrogens locus, only quinazoline and quinazolinone (carbonyl group on quinazoline ring) are medicinally potent isomers[2].





1. Anticancer agents:

These are medications used in pharmacotherapy of cancer (uncontrolled proliferation: carcinoma, sarcoma, leukemia, myeloma, lymphoma), example Chlorambucil acting by activation of apoptosis or forming covalent bond with nucleophiles. The main causes of cancer is the loss of balance between cell proliferation and cell death when cells skip death due to absence of apoptotic signals, uncontrolled cell proliferation occurs leading to cancer. The apoptotic signals are generated through two major pathways i.e. intrinsic and extrinsic pathways. **Tomeh et al (2019)**

Poudapally et al have synthesized novel quinazoline sulfonamide as anticancer agent. Different aryl, heteroaryl, alkyl aryl and cyclopropylsulfonamide. N-(2-chloro-6,7-dimethoxyquinazolin-4-yl)thiophene-2-sulfonamide evaluated for anticancer activity against DU145, THP1, U937 and Colo205 showing IC_{50} values of 16.45µg/ml, 11.21µg/ml,

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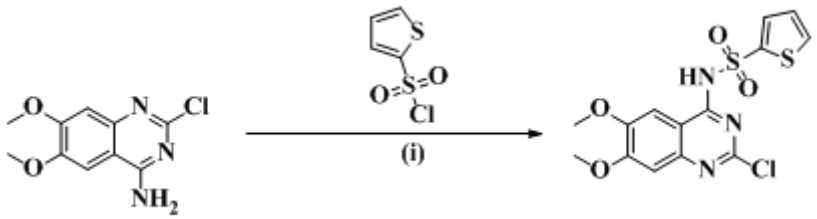
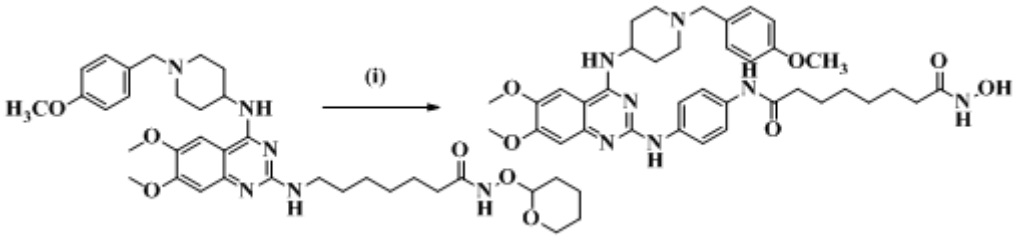
10.06µg/ml, and 27.51µg/ml respectively better than standard compound etoposide[3].



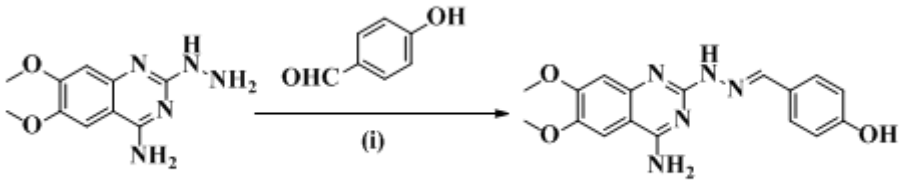
Reagents and conditions; (i) NaH, DMF: THF (1:2), 0^{o}C, 5h, rt, 4h

Uttara et al discovered potent histone deacetylase (HDAc) 3/6 selective dual inhibitor, N1-(4-((6,7-dimethoxy-4-((1-(4-methoxybenzyl)piperidin-4-yl)amino)quinazolin-2-yl)amino)phenyl)-N8-hydroxyoctanediamide exhibited IC_{50} value of 2.6nM (HDAc6) and 34 nM (HDAc3)[4].



Reagents and conditions: (i) THF/dioxane, TFA, overnight.

Gulhan et al outline antimalaria and cytotoxic evaluation using invitro micro dilution and cell culture techniques of new quinazoline derivatives. (E)-4-((2-(4-amino-6,7-dimethoxyquinazolin-2-yl)hydrazono)methyl)phenol showed MIC value of 0.2mg/ml against candida albican ATCC90028[5].



Reagents and conditions: (i) GAA, 12h reflux.

Aaron et al have designed and synthesized of small molecules agonist of EphA2 receptor. 1-(4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl)-2-(4-(benzyloxy)phenyl)ethanone showed better activity of IC_{50} value of 4.28 nM than standard compound Doxazosin with IC_{50} value of 0.74nM[6].

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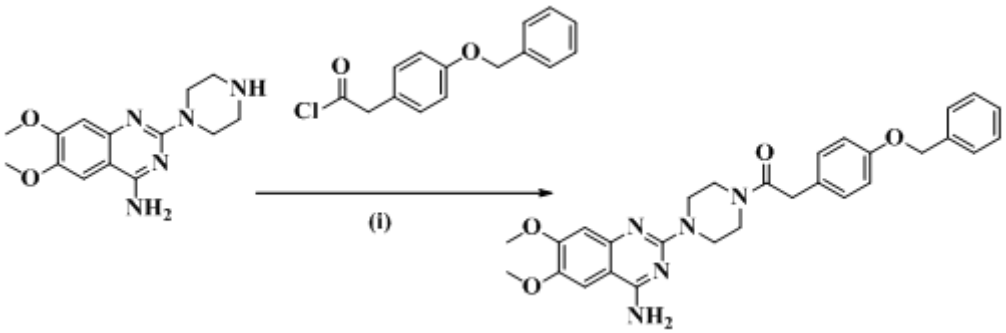
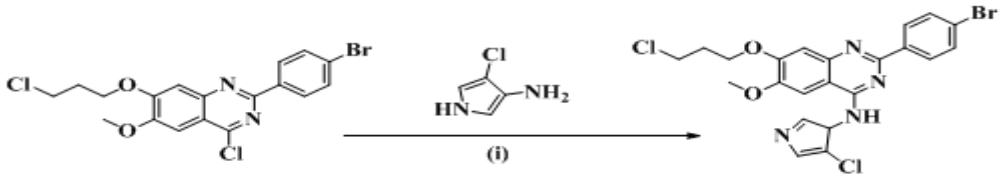


Reagents and conditions: (i) K_2CO_3/DMF, 8h reflux

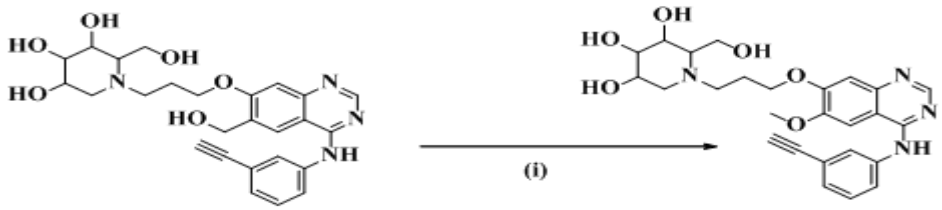
Bathula et al evaluated quinazoline-pyrrole hybrid for MCF-7 and A-549 cell lines, 2-(4-bromophenyl)-N-(4-chloro-3H-pyrrol-3-yl)-7-(3-chloropropoxy)-6-methoxyquinazolin-4-amine showed IC_{50} 0f 49.93µm, 43.99µm against A-549 and MCF-7 cell line respectively[7].



Reagents and conditions: (i) isopropanol, reflux 2h

2. **Antidiabetic Agents:** These are agents that treat diabetes mellitus by altering the glucose level in the blood in the treatment of metabolic disorder characterized by hyperglycemia, glycosuria and ketonaemia, example insulin, hypoglycemic agents. Diabetes mellitus type 2 (DMT2) is an endocrine disease of global proportions which is currently affecting 1 in 12 adults in the world, with still increasing prevalence. World Health Organization (WHO) declared this worldwide health problem, as an epidemic disease, to be the only non-infectious disease with such categorization (**Jelena et al 2017)**

Yaling et al have modified quinazoline-1-deoxynojirimycin hybrids as dual inhibitor of EGFR and α-glucosidase.
1-(3-((4-((3-ethynylphenyl)amino)-6-methoxyquinazolin-7-yl)oxy)propyl)-2-(hydroxymethyl)piperidine-3,4,5-triol exhibited IC_{50} value of 4.87nM against EGFR and 0.09nM against α–glucosidase[8].



Reagents and conditions: (i) HCl, KI, K_2CO_3, 70°c, 8h

Ali et al combined quinazoline-3, 4-(4H)-diamine linked with thiazoline moiety as novel category for DPP-4 and DPPH inhibitor. The compound showed potency with IC_{50} value of 0.76nM Compare to standard compound Linagliptin[9].

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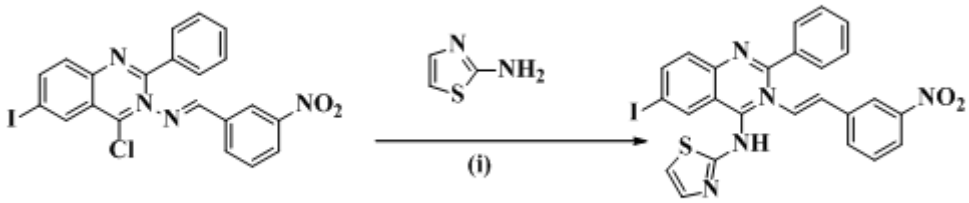
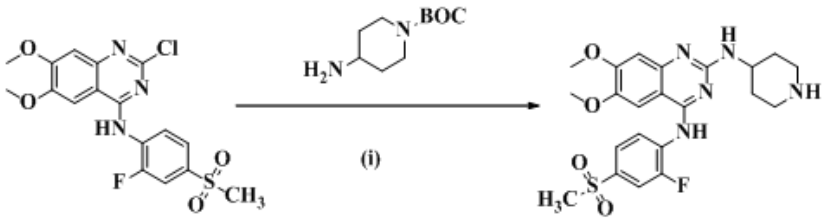


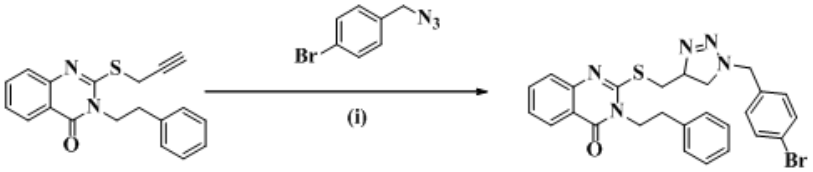
Reagents and conditions: (i) phenol, reflux, 4h

Pham et al modified existing new 2, 4-disubstituted quinazoline analogues as pancreas cells agonist. N4-(2-fluoro-4-(methylsulfonyl) phenyl)-6,7-dimethoxy-N2-(piperidin-4-yl)quinazoline-2,4-diamine showed EC_{50} value of 1.0μm[10].



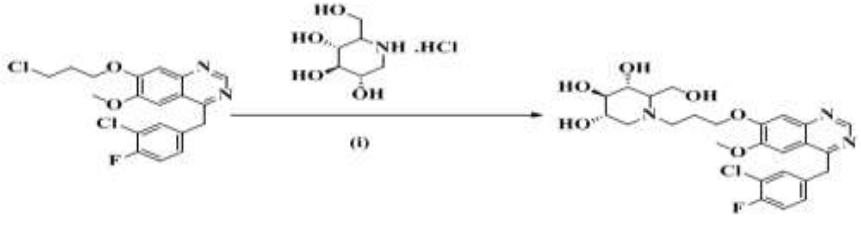
Reagents and conditions: (i) Hunig's base, n-BuOH, reflux, 1 day.

Saeedi et al designed and synthesized new quinazolinone-1, 2, 3-triazole hybrids as antidiabetic agent. α-glucosidase inhibition, and docking study of 2-(((1-(4-bromobenzyl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one produces IC_{50} of 181.0 μm against α-glucosidase[11].



Reagents and conditions; (i) $CuSO_4.5H_2O$/24h, sodium ascorbate

Zhang et al designed quinazoline with antidiabetic, 1-DNJ with α-glucosidase targeting both EGFR and α-glucosidase. (3R,4R,5S)-1-(3-((4-(3-chloro-4-fluorobenzyl)-6-methoxyquinazolin-7-yl)oxy)propyl)-2-(hydroxymethyl)piperidine-3,4,5-triol showed IC_{50} value of 0.39m, 1.79nM against α-glucosidase and EGFR respectively[12].



Reagents and conditions; (i) KI, K_2CO_3, DMF, 75^OC, 8h

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II. CONCLUSION:

It is worth-while to mention that quinazoline have enormous potentials to show wide range of pharmacological activities including antioxidant, anti-inflammation, antimicrobial, antituberculosis, antibacterial, antidiabetic, antiparasitic, anticancer and cognitive properties. Furthermore, despite improvements in understanding the pathophysiological mechanisms of diseases state, the discovery of ultimate magic drug is still a dream. This reports explained the use of quinazoline derivatives in approved drugs therapeutics. The present review provides drug designers with worthy information on quinazoline scaffold.

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