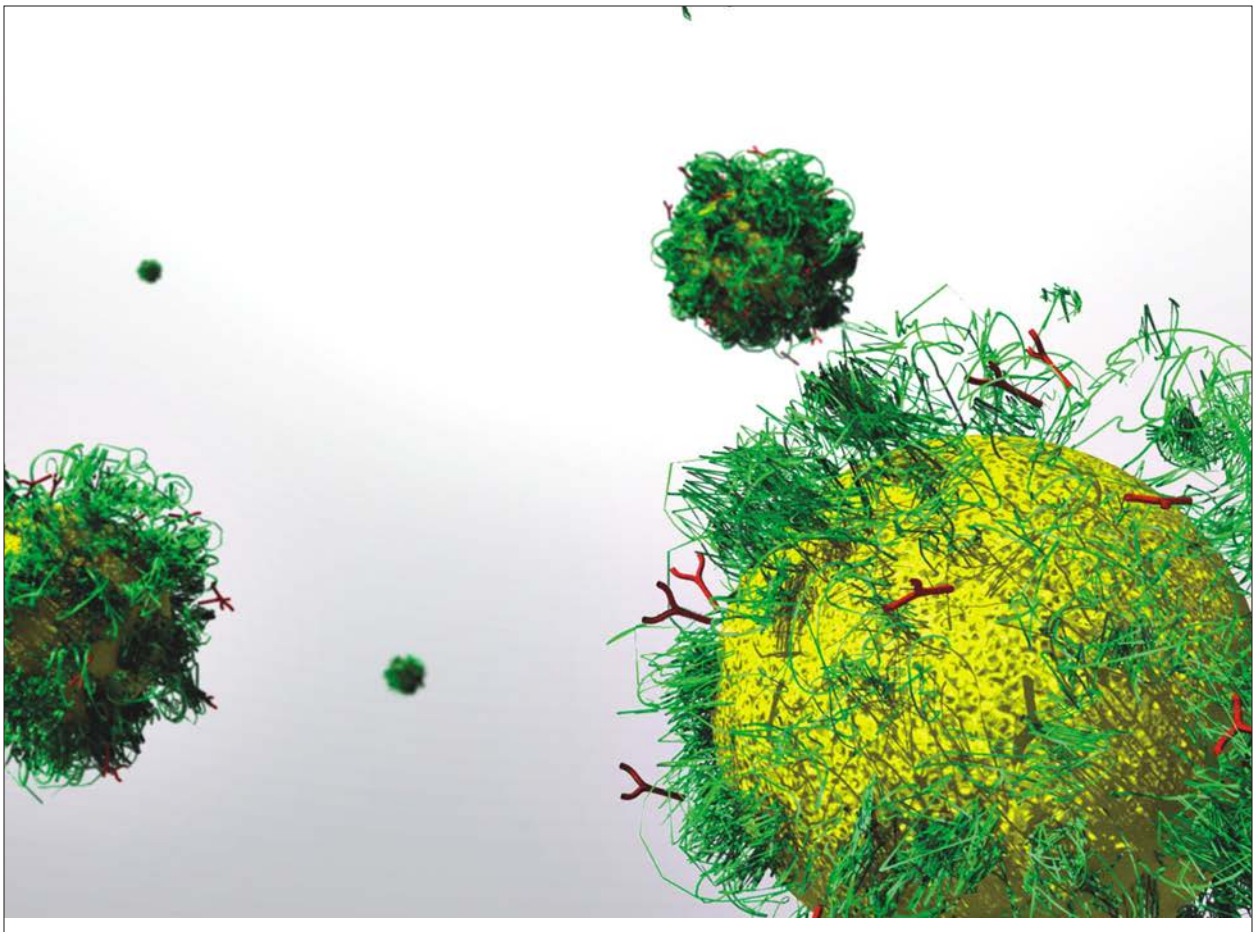

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Review Article
Undeniable Pharmacological Potentials of Quinazoline Motifs in Therapeutic Medicine

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Abstract

Despite the advances in technology and understanding of biological systems, drug discovery is still a lengthy, expensive, difficult and inefficient process owing to low rate of new therapeutic discovery. Among the numerous N-heterocyclic scaffolds, quinazoline core structural frameworks have received considerable attention because they form a privileged class of pharmacophores with diverse spectrum of therapeutic potential. Various conventional synthetic approaches methodologies for quinazoline synthesis by various synthetic chemists were explored in this review wherein their bases for structural validation were expatiated using analytical data and spectroscopic means such as FT-IR, UV-Visible, ^{1}H- and ^{13}C-NMR as well as mass spectra. Quinazoline derivatives are among the most useful heterocyclic compounds from both synthetic and medicinal chemistry aspects. They are considered as important precursors for the synthesis of various physiologically significant and pharmacologically utilized molecules. This present study unveils quinazoline core as a multifunctional nucleus which serves as a resourceful toolbox of information for synthetic modifications of old existing candidates in order to tackle drug resistance bottlenecks in therapeutic medicine. Based on diverse bioactivities and pharmacological potentials were explored, quinozaline motifs were concluded to be arsenals of warfare against infectious diseases in therapeutics. Hence, quinazolines might pave way to new drug discovery for fighting infectious diseases and increase researchers' choice of quinazoline as excellent candidates for future drug design.

Key words: Quinazoline, cytotoxic study, structure activity relationship, HIV-1, antitumor activity

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Heterocyclic compounds form the basis for pharmaceutical industrial operations, especially, in the synthesis of drugs. Also, most marketed drugs constitute of common structural units of heterocyclic compounds which could also be useful in the synthesis of biologically active agrochemicals[1]. Nitrogen-containing heterocyclic compounds are very crucial in drug design. In the recent years, there has been considerable attention on the preparation of useful N-heterocyclic compounds in organic synthesis[2,3]. Thus, the motivation for this present study was the known widespread application of benzo-fused N-heterocycles. For instance, in the pharmaceutical industry, among the top two hundred branded drugs, we have more than 75% of them which have heterocyclic fragments in their structures[4]. Quinazoline is a fused bicyclic heterocyclic framework which was formerly known as benzo-1,3-diazine or 1,3-diazanaphthalene[5]. Natural occurrence of quinazoline core has shown it to be isolated from the Chinese plant aseru[6]. Quinazolines are classes of fused heterocycles that are of significant interest because of the varied range of their biological properties[7,8]. They have also drawn a huge attention owing to their expanded applications in the field of pharmaceutical chemistry[9].

Furthermore, quinazolines are considered an attractive target for medicinal chemists, because they are the scaffold of several potent antitumor drugs. Leading examples are the well-known erlotinib (trade name tarceva) and gefitinib (trade name iressa)[10-12]. Among the heterocyclic compounds, quinazoline is of great importance due to its important biological actions as well as synthetic applications in medicinal chemistry. Numerous compounds containing quinazoline moieties have been reported to exhibit diverse biological and pharmacological properties which include antimicrobial[7], antitumor[9], antimitotic[10], anticancer[11] and kinase inhibitory[12] activities among others. The specific objectives are to: Highlight major synthetic pathways of valuable quinazoline derivatives, explore recent advances in pharmacological diversity of quinazoline for effective drug design and draw attention of researchers into the beneficial role of quinazoline in fighting diseases.

Classification of quinazolinones: Quinazoline can have different types of substituents attached to it, forming different derivatives of the parent quinazoline. Substituted quinazolines have properties which largely depend on: The nature of the substituent, position of substituent and type of conjugation in pyrimidine ring[7]. Quinazolines have many derivatives such as ketoquinazolines with a ketone substituent attached to it; it can otherwise be referred to as quinazolinones. Quinazolinones which are based on the substitution patterns of the ring system can be classified into the following five categories: 2-substituted-4(3H)-quinazolinones, 3-substituted-4(3H)-quinazolinones, 4-substituted-quinazolin ones, 2,3-disubstituted-4(3H)-quinazolinones and 2,4-disubstituted-4(3H)-quinazolinones[7,13].

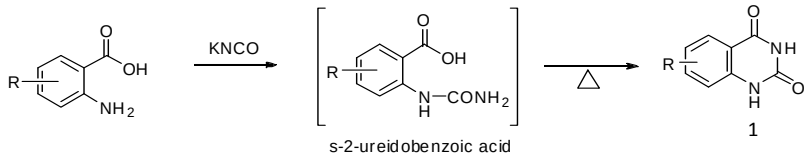
CHEMISTRY

Synthetic methods: In the past decade, a variety of synthetic methods have been employed for the preparation of functionalized quinazoline and quinazolinone motifs derivatives have been synthesized with the aim of obtaining more biologically active materials. Due to high diversity and level of interest in the current domain, many synthetic approaches have been utilized in preparing quinazoline and their polycyclic derivatives which have resulted in high output in highly relevant publication databases. 4-(Furan-2-yl)-4,4a,5,6,7,8-hexahydroquinazolin-2(3H)-one containing completely saturated pyrimidine ring system was synthesized by the reaction of α, β-unsaturated carbonyl otherwise known as chalcone with urea in the presence of silica sulfuric acid as the reusable heterogeneous catalyst[14]. Some specific synthesis of some selected quinazoline derivatives were as given below:

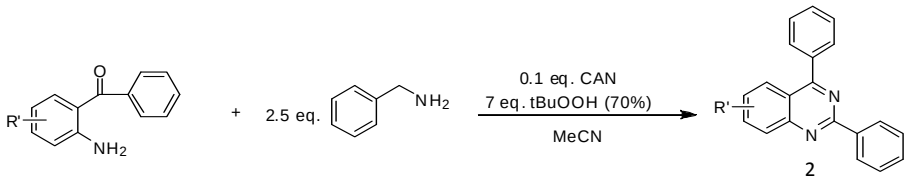
Synthesis via thermal cyclization of o-ureidobenzoic acid: Reaction of substituted anthranilic acid with potassium cyanate was reported to give o-ureidobenzoic acid which was subsequently treated with acid or alkali under high thermal condition for easy cyclization in order to produce substituted-1,2,3,4-tetrahydro-2,4-dioxoquinazolines, 1 as shown in the Scheme 1 below[15].

Solid phase synthetic approach: Solid phase synthetic reaction of aminobenzophenone with benzylamine was successfully achieved using Ceryl Ammonium Nitrate (CAN) in acetonitrile to afford substituted-2,4-diphenylquinazoline, 2 in good yield[16]. It is worthy to note that 2.5 equivalent of benzylamine precursor and 0.1 equivalent of CAN-TBHP catalyst were used for efficient production of quinazoline derivative, 2 as show in Scheme 2.

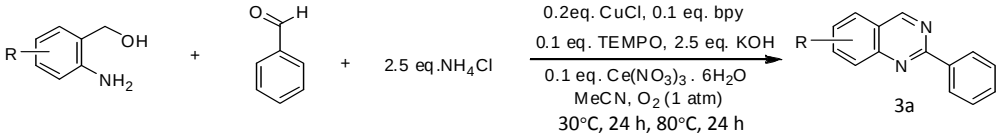
Cascade reaction of (2-aminophenyl) methanols with aldehydes: According to a report, an efficient cascade reaction of (2-aminophenyl)methanols with aldehydes using the combination of cerium nitrate hexahydrate and ammonium chloride under the influence of catalytic amount of copper chloride (0.2 eq.) led to the formation of a wide



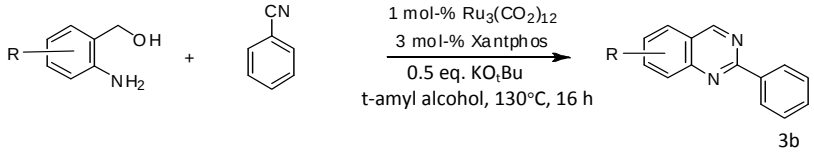
Scheme 1: Route for the synthesis of substituted-1,2,3,4-tetrahydro-2,4-dioxoquinazolines, 1



Scheme 2: Route for the synthesis of substituted-2,4-diphenylquinazoline, 2



Scheme 3: Route for the synthesis of substituted-2-phenylquinazolines, 3a



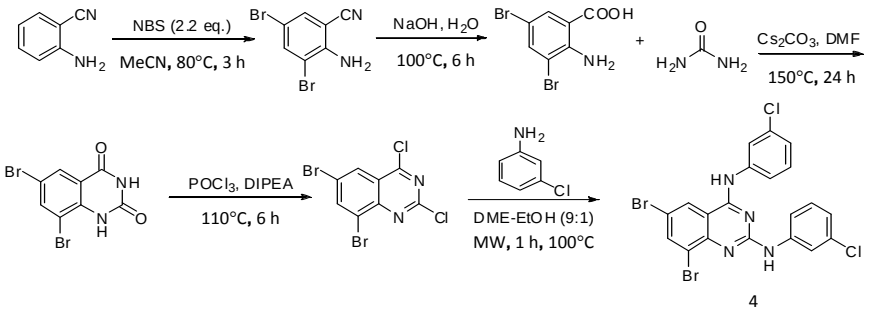
Scheme 4: Route for the ruthenium-catalyzed synthesis of substituted-2-phenylquinazolines, 3b

range of substituted-2-phenylquinazolines, 3a in good yields[17] as shown in Scheme 3. The method was a convenient and practical strategy for synthesis of 2-substituted quinazoline derivatives that have only one phenyl substituent on heterocyclic ring of pyrimidine[17].

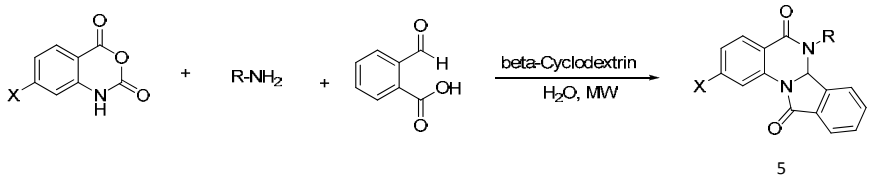
Ruthenium-catalyzed dehydrogenative synthetic approach: A commercially available $Ru_3(CO_2)_{12}$/Xantphos/t-BuOK catalyst system enables a straight forward ruthenium-catalyzed dehydrogenative synthesis of 2-arylquinazolines, 3b. It was recently adopted for the preparation of 2-arylquinazolines, 3b with substitution on its benzene ring by heating the reacting mixture under reflux for 16 h at 130°C as shown in Scheme 4. It was reported that this synthetic method offered operational simplicity, high atom efficiency and broad substrate scope[18].

Microwave-assisted synthetic approach: A tandem experimental and efficient synthesis of 2,4-disubstituted-6,8-dibromoquinazolines, 4 through chemoselective sequential bis-S_NAr/bis-Suzuki-Miyaura reactions under microwave irradiation technique has been recently reported[19]. This study was reported to allow rapid and efficient access to desired products in high yields when the procedure started with the bromination of 2-aminobenzonitrile as shown in Scheme 5.

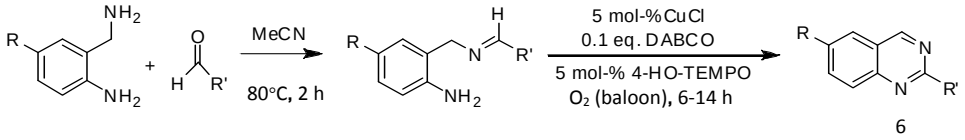
β-Cyclodextrin-mediated MCR approach: β-cyclodextrin (β-CD) mediated multi-component reaction under microwave irradiation has been considered as green processes which have remarkable advantages over the reactions performed under conventional heating[20]. They have successfully used



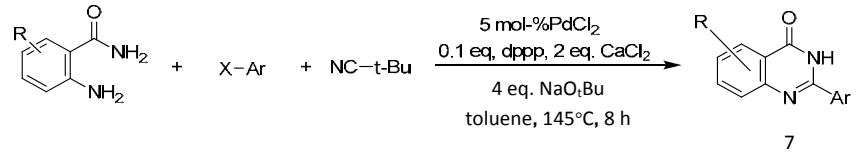
Scheme 5: Microwave-assisted synthesis of 2,4-disubstituted-6,8-dibromoquinazolines, 4



Scheme 6: β-Cyclodextrin-mediated synthesis of dihydroisoindolo[2,1-a]quinazoline-5,11-dione, 5



Scheme 7: Route for the aerobic synthesis of 2,6-disubstituted quinazoline, 6

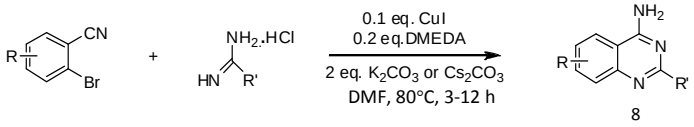


Scheme 8: Route for the synthesis of substituted 2-arylquinazolin-4(3H)-ones, 7

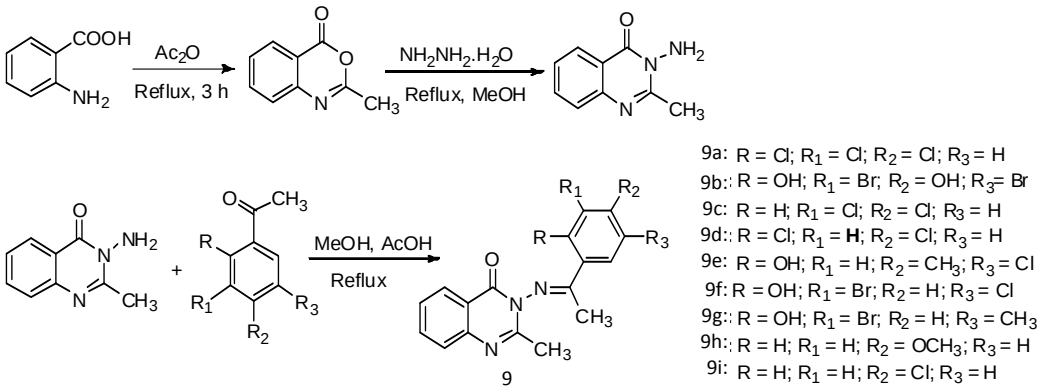
this approach in the synthesis of dihydroisoindolo[2,1-a]quinazoline-5,11-dione derivatives, 5 by reaction of isatoic anhydride, amine and 2-formylbenzoic acid as MCR using β-cyclodextrin as shown in Scheme 6.

Aerobic cyclizative synthetic approach: Thermal cyclization reaction of aldehydes with 2-aminobenzylamines after refluxing for 2 h in the presence of acetonitrile was reported to give an imine intermediate which subsequent underwent efficient aerobic oxidative cyclization in the presence of CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant to afford 2,6-disubstituted quinazoline 6 as shown in Scheme 7[21].

Three-component one-pot synthetic approach: An operational simple palladium-catalyzed three-component reaction of readily available 2-aminobenzamides, aryl halides and tert-butyl isocyanide was efficiently constructed under one-pot to afford substituted 2-arylquinazolin-4(3H)-ones, 7 in good yields[22] as shown in Scheme 8. This synthetic study was reported to proceed via a palladium-catalyzed isocyanide insertion/cyclization sequence at an elevated temperature of 145°C in toluene solvent[22]. Similar reaction condition was used to synthesized quinazolin-4(3H)-one derivative by isonitrile insertion in 1.5 molar equivalent of cesium carbonate (Cs_2CO_3) in up to 10 h reflux in toluene solvent[23].



Scheme 9: Route for the synthesis of substituted 2-arylquinazolin-4(3H)-ones, 8



Scheme 10: Route to substituted 2-methyl-3-((1-phenylethylidene)amino)quinazolin-4(3H)-one, 9

CuI-DMEDA mixed catalyst synthetic approach: An efficient reaction of substituted 2-bromo-benzonitriles with amidines allows an economical and practical synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives[24]. The reaction was carried out in the basified medium using CuI-DMEDA mixed catalyst reaction technique at a refluxing temperature of 80°C in DMF solvent as shown in Scheme 9.

Synthesis of Schiff base via acetic acid catalyzed approach: In quest for the quinazoline-based synthesis of some novel heterocyclic Schiff bases, a series of novel quinazolinone 9 has been designed and achieved recently[25]. This targeted compounds were prepared by condensation of 3-amino-2-methyl-3H-quinazolin-4-one with different substituted acetophenones in presence of acetic acid under classical procedure. The 3-amino-2-methyl-3H-quinazolin-4-one reactive intermediate used was earlier synthesized by the reaction of anthranilic acid with acetic anhydride under refluxing[25] for 3 h. The pathway for this is as shown in Scheme 10.

BIOLOGICAL ACTIVITIES

Biological importance of quinazoline: Quinazoline and its quinazolinone skeletons are recurrently encountered heterocyclic com pounds in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, CNS depressant, anticonvulsant, antifungal, antimalarial, anticoccidial, anticancer activities among others. The wide reported biological activities of quinazoline derivative might have emanated from the fact that its corresponding monocyclic counterpart, pyrimidines are being prebiotic in nature to living cells in biodiversity which made them to be highly privileged motifs for the development of molecules of biological and pharmaceutical interest[26].

Anticancer activity: Cancer is a disease characterized by a shift in the controlled mechanisms that govern cell proliferation and differentiation. Food and Drug Administration (FDA) has approved several quinazoline derivatives such as gefitinib, erlotinib, lapatinib and vandetanib as salient anticancer drugs. Compound 10 was found to be a particularly active growth inhibitor of the renal cancer (GI_{50} = 4.07 μM), CNS cancer (GI_{50} = 7.41 μM), ovarian cancer (GI_{50}= 7.41 μM) and non-small cell lung cancer (GI_{50} = 7.94 μM)[27]. Investigation carried out on the anti-proliferative activity of quinazoline-based compounds against breast cancer cell line, revealed that 11 inhibited the cell growth at as low as IC_{50} = 5.52 μM[28]. Quinazolinedione-based redox modulators 12 had been discovered as therapy for pancreatic cancer since the oxidative stress induced by it, promoted activation of stress kinases (p38/JNK) resulting in cancer cell death[29]. Compound 13 has broad spectrum

anti-cancer showing efficiency toward numerous cell lines that belong to different tumor subpanels (Fig. 1)[30]. In the evaluation of HepG2 xenograft model, 14 exhibited significant cancer growth inhibition with low host toxicity *in vivo*[31]. Quinazoline 15 was the most promising among the motifs screened against human[32] cancer cell line A549.

EGFR inhibitory activity: The epidermal growth factor receptor (EGFR, erbB1, Her1) is a member of the erbB receptor protein[33] which plays a critical role in many of the signal transduction pathways that regulate numerous cellular functions, such as proliferation, differentiation, migration, angiogenesis and apoptosis. The EGFR has been clinically validated as a rational target for cancer therapy and several small molecule inhibitors have been developed and released as quinazoline-based reversible inhibitor[34], e.g., icotinib 16 and irreversible inhibitors namely; afatinib 17[35], canertinib 18 and newly reported[36] afatinib derivative 19 as shown in Fig. 2.

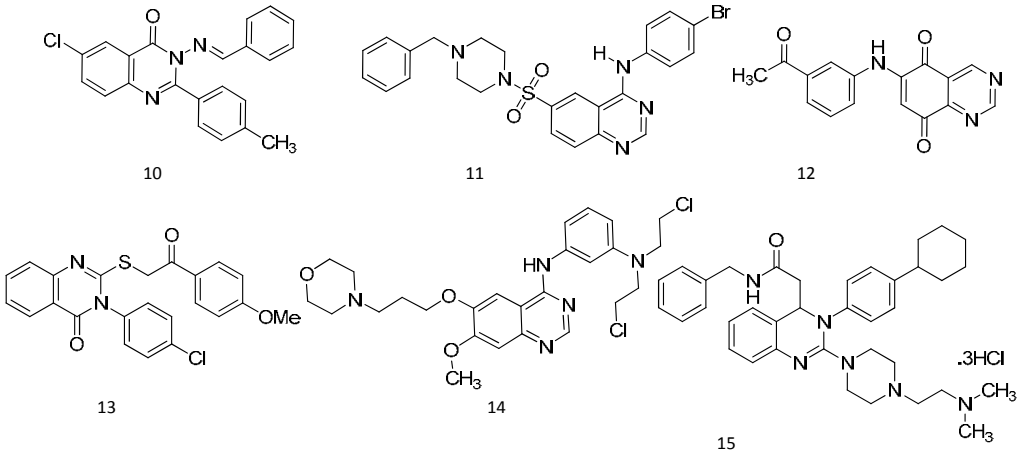


Fig. 1: Some quinazoline derivative with reported anti cancer activity

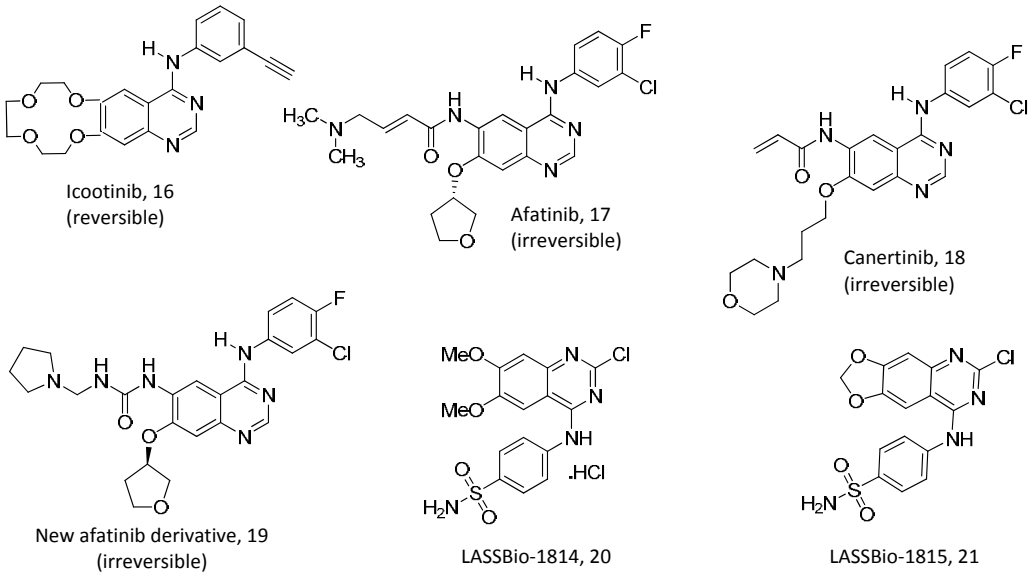


Fig. 2: Some reversible and irreversible EGFR inhibitors

According to results of the molecular docking study showed in Fig. 3, the comparison between the binding modes of the 6,7-dimethoxy-derivative 20 (LASSBio-1814; IC_{50} = 2.37 µM for EGFRwt and 1.02 µM for VEGFR-2) and the 6,7-methylenedioxy-derivative 21 (LASSBio-1815; IC_{50} = 34.6 µM for EGFRwt and 26.9 µM for VEGFR-2) demonstrated that the structural modification performed led to the loss of important hydrophobic interaction with Val726, Leu718 and Leu792 amino acid residues in EGFRwt binding site and with Val848, Leu840 and Phe918 amino acid residues in VEGFR-2 binding site[37].

Antiproliferative activity: The successful synthesis of some 13-aryl-13H-benzo[g]benzothiazolo [2,3-b]quinazoline-5,14-dione derivatives was reported and compound 22 (IC_{50} = 5.52 µM) was established as the most potent antiproliferative compound against two different human cancer cell lines[38]. Compound 23 displayed broad spectrum of antiproliferative activity on NCI 60-cell lines panel[39] with mean GI_{50} of 1.53 µM. Antiproliferative activity investigation of 4-substituted-piperazine-1-carbodithioate derivatives of 2,4-diaminoquinazoline revealed 24, 25 and 26 as the most active members with IC_{50} values in the range of 1.58-2.27, 1.84-3.27 and 1.47-4.68 µM, respectively against five cancer cell lines examined (Fig. 4)[40].

Antitubercular activity: There is an urgent demand for new antitubercular drugs possessing novel mechanisms of action with the goal of developing more effective combination treatments against drug resistant forms of *Mycobacterium tuberculosis*[41]. The discovery of 27 as potent apoptosis inducers with strong antitubercular activity was reported[42]. An unexpected intramolecular condensation with the formation of 3,4-dihydrobenzo[g]quinazoline heterocyclic system took place via click chemistry and the rifamycin mimetic obtained, 28 was reported to inhibit the growth of

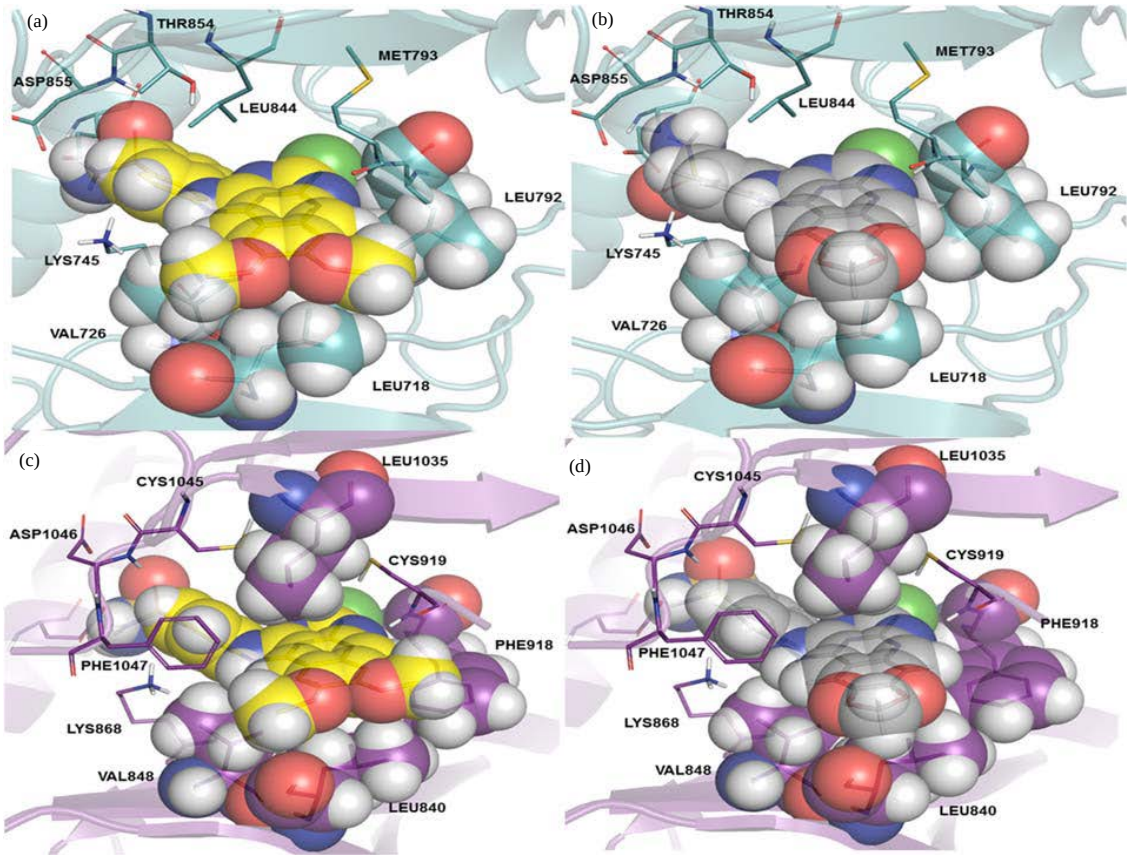


Fig. 3(a-d): (a) Binding interactions of 20 (yellow) with EGFRwt, (b) Binding interactions of 21(gray) with EGFRwt, (c) Binding interactions of 20 (yellow) with VEGFR-2 and (d) Binding interactions of 21 (gray) with VEGFR-2. Docking studies were performed with the GOLD 5.1program. Apolar hydrogen atoms were omitted to improve clarity. The images were generated with PyMol software[37]

Mycobacterium tuberculosis appreciably[43]. Compounds 29 exhibited significant anti-tubercular activity at MIC values 50 μM and the *in vitro* cytotoxicity data using THP-1 cells indicated that 29 was safe as its MIC value was much lower than the cytotoxic value as documented[44] and shown in Fig. 5.

Anti-inflammatory activity: Quinazoline exhibits containment of inflammatory disorders such as osteoarthritis[45] neurodegenerative impairments[46] and inflammatory bowel syndrome[47] and some of the anti-inflammatory drug bearing quinazolone nucleus[48] are 30 and 31. *In vivo* experiment revealed that compound 32, could attenuate LPS-induced ALI in rats, via decreasing inflammatory cytokine production[48], protein concentration in the BALF, pathological changes and macrophage infiltration. Schiff base 33 (IC_{50} = 52±0.81 μM) was reported to possess excellent anti-inflammatory due to its IC_{50} lower than that of aspirin standard drug[49] (IC_{50} = 66±1.24 μM). Compound 34 (62.08% inhibition)[50] showed in Fig. 6, competed favourably with indomethacin standard at 1.67 mL as the mean difference in paw volume after 4 h. Using Tumor Necrosis Factor-α (TNF-α) as the biomedical pathway, 35 was discovered to be a promising anti-inflammatory quinazoline derivative with 68% average inhibition on PDE4B enzyme at concentration[51] of 10 μM (Fig. 6).

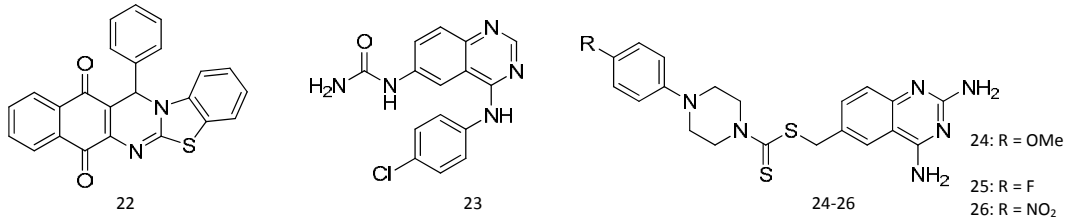


Fig. 4: Quinazolinescaffolds with antipoliferative activity against various cell lines

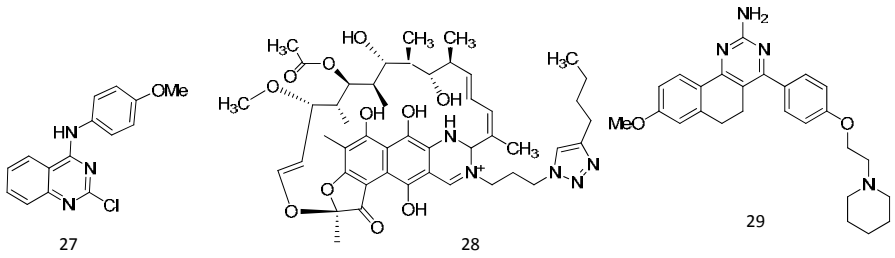


Fig. 5: Selected quinazoline with antitubercular activity

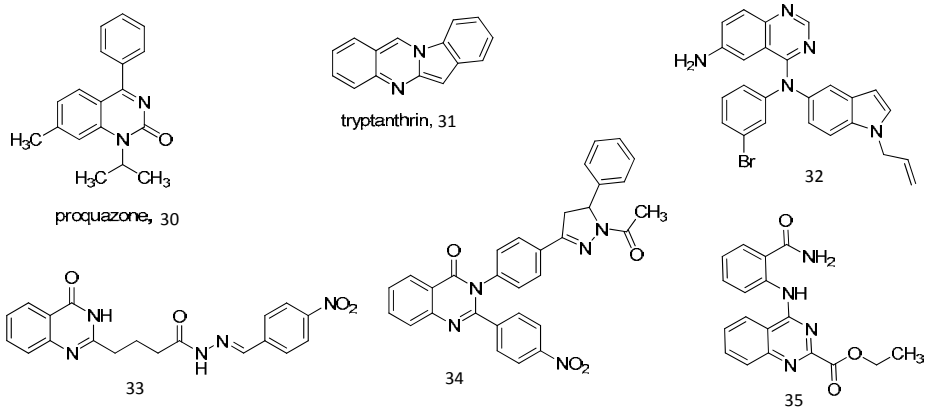


Fig. 6: Reported quinazoline motifs with anti-inflammatory activity

Antileishmanial activity: In the recent review about antileishmanial drug discovery, quinazoline core was not left out[52]. Compound 36 (IC_{50} = 3.16 μM) exhibited higher anti-amastigote activity against *L. donovani* when compared with standard drug sodium stibogluconate[53] (IC_{50} = 7.92 μM). A series of N^2,N^4-disubstituted quinazoline-2,4-diamines was synthesized and tested against *Leishmania donovani* and *L. amazonensis* intracellular amastigotes, wherein 37 emerged as the highly promising antileishmanial among the group[54]. Compounds 38 and 39 were reported to be effective against *L. donovani* at EC_{50} of 0.61±0.13 and 0.38±0.09 μM, respectively[55]. A series of quinazoline-2,4,6-triamine were synthesized and evaluated *in vitro* against *Leishmania mexicana*. Among them, 40 showed activity on promastigotes and intracellular amastigotes as well as low cytotoxicity in mammalian cells[56]. When administered *in vivo* in a hamster model, percentage inhibition of *L. donovani* parasite was found[57] to be 73.15±12.69 μM for compound 41 (Fig. 7).

Antitumor activity: Most of the antitumor agents exert their effects by inhibiting both at the protein level and/or transcription level. Antitumor efficacy of quinazoline showed them to be biomimetic to the quinoxaline motif. This might be because they both belong to benzodiazine family[58]. Compound 42 possessed remarkable broad-spectrum antitumor activity which was almost sevenfold more active than the known drug 5-fluorouracil (5-FU) with GI_{50} values of 3.16 and 22.60 μM, respectively[59]. Among the series designed in another study, compounds 43 proved to be fifteen fold more active than the known antitumor 5-FU, with MG-MID GI_{50}, TGI and LC_{50} values of 1.5, 46.8, 93.3 μM, respectively[60]. Caspase-3 activity and cell cycle regulation studies revealed that 44 exerted antitumor properties[61] with IC_{50} of 3.4 μM. Bioassay results indicated that most of the prepared compounds demonstrated good activities against various cancer cells with 6-chloro-quinazoline derivatives 45 being the most active antitumor among the series[62]. Compared with the parental dasatinib, most of the new compounds synthesized, especially 2,4,6-trimethylaniline 46, demonstrated significant antitumor activities against six cell lines[63] (Fig. 8).

Kinase inhibitory activity: The erythropoietin-producing hepatocellular (Eph) receptor tyrosine kinases have well established roles in the multitude of physiological and pathological processes. According to high throughput screening result, compound 47 displayed potent inhibitory activities[64] toward EphA2 with IC_{50} of 0.17 μM. Out of the six quinazoline analogues synthesized via Biginelli approach, 48 was the most effective inhibitor of kinase[65]; although, being the most toxic too.

Also, compound 49 carrying dioxygenated rings fused on the benzenoid portion and the biphenylamino substituent on pyrimidine portion of quinazoline, was identified as inhibitor of kinase[66] at IC_{50} of 0.08±0.01 μM. Compound 50 provided a potent starting point (IC_{50} = 12 nM) for inhibition of Mps1 kinase with submicromolar cellular toxicity, reduced MW and TPSA, while 51 provided a further boost in biochemical potency[67] with IC_{50} = 2 nM. Amino acid derived quinazoline 52 possessed sub-nanomolar inhibition of Rock and PKA, nanomolar potency in ppMLC cell based assays, low to fair cytochrome P-450 inhibition and good human microsomal stability[67] (Fig. 9).

Anticonvulsant activity: Methaqualone 53, as a quinazoline analog, is an important landmark in the field of synthetic anticonvulsants[68]. The modification of 53 was carried out to obtain quinazolinone scaffold 54 which proved to be twofold

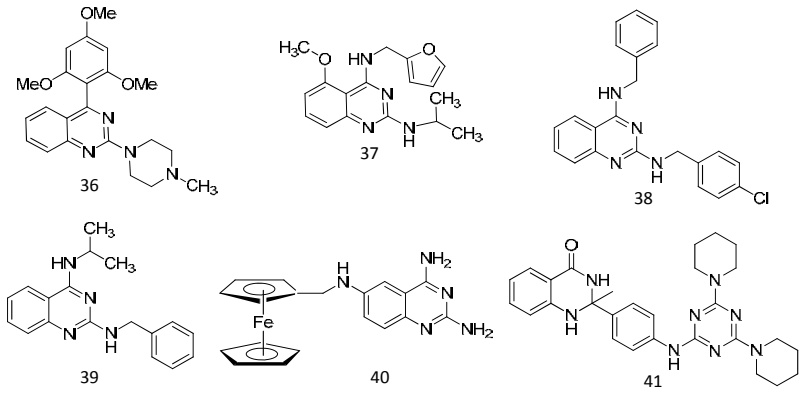


Fig. 7: Some quinazoline motifs with anti-leishmanial activity

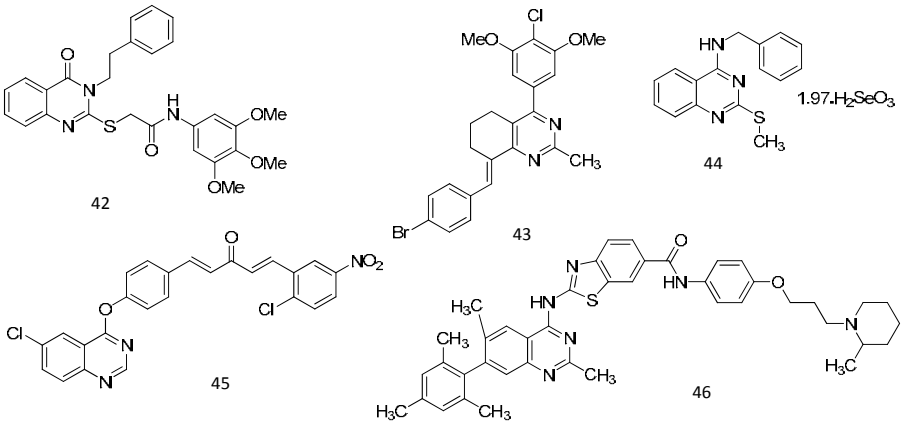


Fig. 8: Some quinazoline motifs with antitumor activity

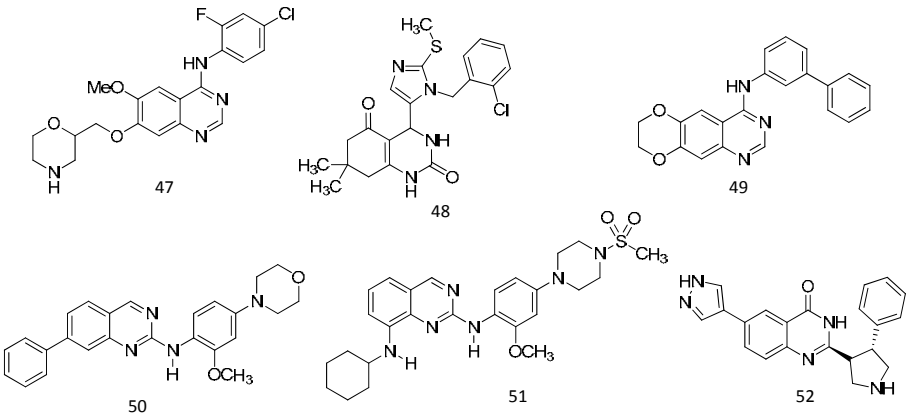


Fig. 9: Some quinazoline motifs with kinase inhibitory activity

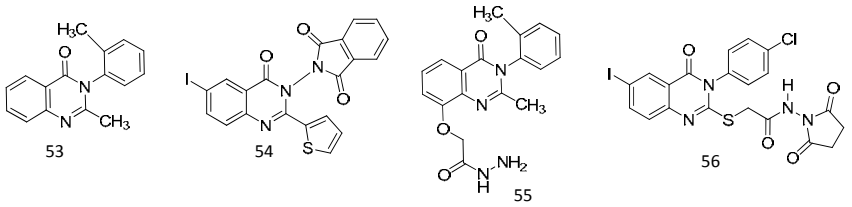


Fig. 10: Some quinazoline motifs with anticonvulsant activity

more active than anticonvulsant drug sodium valproate[69]. According to the findings of another study, 8-substituted-4(3H)-quinazolinone 55 demonstrated a better anticonvulsant activity and lower toxicity than the reference drugs[70]. Compound 56 showed a significant anticonvulsant activity at 200 mg kg^{-1} (dose level) and marked CNS depressant activities associated with sedation and hypnosis[71] (Fig. 10).

Antimalarial activity: The strong effect of quinazoline derivative 57 as an antimalarial motif on human erythrocytes and on cell membrane molecular model was reported[72], while quinazoline 58 was reported to inhibit the growth of *Plasmodium falciparum*[73] at IC_{50} of 43.4 nM. Among the series of 4(3H)-quinazolinones screened against *P. berghei*, 59 was the most active antimalarial compound[74]. Owing to the fact

that malaria has become a devastating global health issue in tropical and subtropical regions, other research efforts yielded promising antimalarial quinazoline derivatives[75-77] 60 and 62 (Fig. 11).

HDAC inhibitory activity: Histone deacetylases (HDAC) play crucial roles in numerous biological processes[78]. The encouraged activity of compound 63 against HDAC conformed to the reported information that hydroxamic acid generally showed more potent HDAC inhibitory activity than carboxylic acids[79] while quinazoline 64 with meta-substitution and unsaturation near hydroxamic showed even more potency[78] with IC_{50} of 0.16±0.02 μM. Out of 26 different structural classes that showed anti-inflammatory effects in a pre-screen in HEK293T cells, quinazoline 65 was one of the best three classes which exhibited improved *in vitro* HDAC inhibition in a commercial fluorescence assay[80] (Fig. 12).

Anti-HIV activity: Synthesis and anti-HIV1 activity of quinazoline-4(3H)-one derivatives was evaluated, where it was found that 66 exhibited wide range[81] of anti-HIV-1. Some 2,3-disubstituted quinazolin-4(3H)-ones synthesized by condensation of benzo[1,3]oxazine-4-one and primaquine were screened *in vitro* against HIV-1 in MT-4 cell and 67 was reported to exhibit 15% maximum protection against replication of HIV-1 (IIIB) in acutely infected MT-4 cells[82]. A series of dihydrobenzo[h]quinazoline derivatives were synthesized for the purpose of anti-HIV examination[83]. They reported that 68 (IC_{50} = 2.11 μM) emerged as the best anti-HIV among the series with therapeutic index of 1.89×10^5 (Fig. 13).

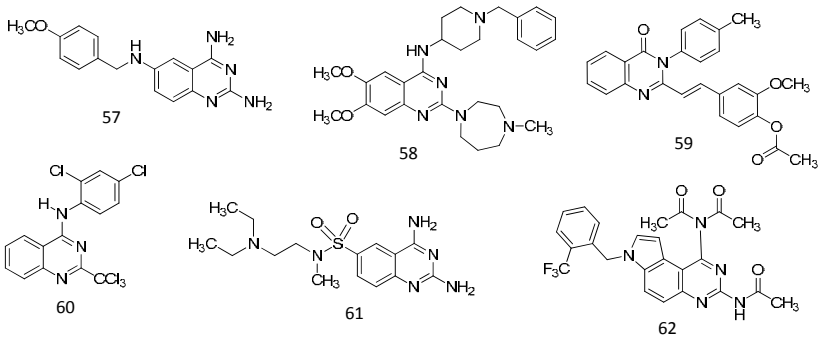


Fig. 11: Some quinazoline motifs with antimalarial activity

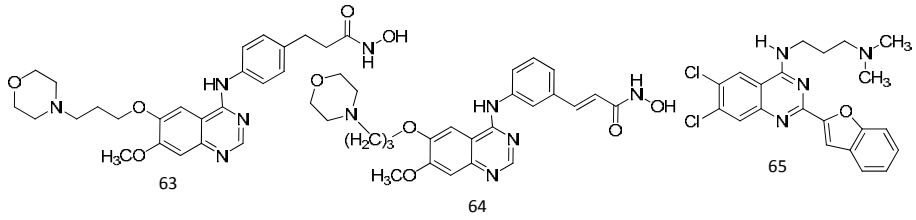


Fig. 12: Some quinazoline motifs which served as HDAC inhibitors

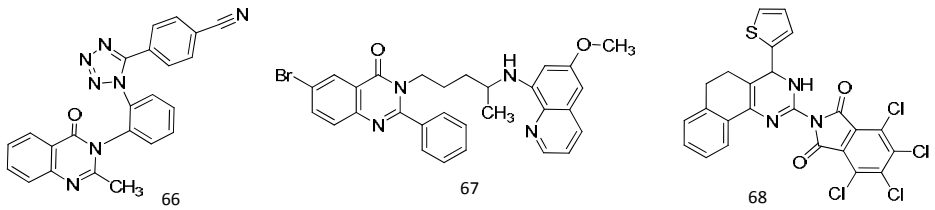


Fig. 13: Some quinazoline motifs with anti-HIV activity

Concerning the mechanism of action as anti-HIV, these compounds were reverse transcriptase inhibitors.

Phosphodiesterase (PDE) inhibitors: The PDE families contain many splice variants that are mostly unique in tissue-expression patterns, gene regulation, enzymatic regulation by phosphorylation and regulatory proteins, subcellular localization and interaction with association proteins[84]. The inhibitory potencies of quinazoline-4-thione 69 at submicromolar levels against the catalytic domain of PDE7 was reported[85]. Small-molecule phosphodiesterase probe investigated later, established 4-aminoquinazoline 70 and the 4-indanylquinazoline 71 as PDE1 inhibitors that readily cross the blood brain barrier[86]. Administration of 72 as optimized PDE7 inhibitor ameliorated brain damage and improved behavioral outcome in a permanent middle cerebral artery occlusion (pMCAO) stroke model[87] (Fig. 14).

Antihypertensive activity: All members of the series of quinazoline synthesized were examine *in vivo* and showed moderate to good antihypertensive activity in albino rat[88]. Out of these templates that operated through α_1-adrenergic blocking mechanism, 73 emerged as the most potent. In another study, 74 was reported to exhibit antihypertensive activity greater than the reference drug prazocine[89]. Quinazoline motif 75 was shown to have considerable impact on the heart rate and blood pressure based on it substitution pattern[90] (Fig. 15). Inhibition of PARP by L-2286 influenced beneficially, the signaling pathways in hypertension induced cardiac remodeling[91]. The effect of L-2286 on Systolic Blood Pressure (SBP) was investigated in a study, where it was discovered that during the 32-week treatment period, systolic blood pressure of hypertensive (SHR-C, SHR-L) rats was significantly higher than that of normotensive (WKY) rats (at the age of 10 weeks SHR[92]: 180±5.6 mmHg, WKY: 130±5.4 mmHg, at the age of 42 weeks SHR-C: 230±6.3, SHR-L: 225±2.4 mmHg, WKY-C: 130±5.4, WKY-L: 135±5.5 mmHg, $p < 0.05$; SHR-C vs. WKY-C, SHR-C vs. WKY-L $p<0.05$; SHR-L vs. WKY-C, SHR-L vs. WKY-L $p<0.05$). Treatment with L-2286 did not alter systolic blood pressure of SHR animals during the 32-week treatment period (Fig. 16).

Melanin-concentrating hormone receptor 1 antagonists: Melanin-concentrating hormone receptor 1 (MCHR1) antagonising quinazoline derivatives are proved to possess remarkable and distinct anti-obesity activity[93]. Pharmacokinetic profile showed that oral administration of 30 mg kg^{-1} b.i.d. of 4-morpholinyl quinazoline 76 led to 12% weight reduction within fourteen days in DIOC57BL/6 J. mice. The 4-amino-2-cyclohexylamino quinazoline 77[94] and 4-dimethylamino quinazoline 78 were reported to exhibit highly promising anti-obesity for suitable weight loss programme due to their good affinity for human MCHR1 (Fig. 17). Non-peptidic nature of these orally active melanin-concentrating hormone receptor 1 antagonists, play a key role in anxiolytic- and antidepressant-like profile[95] of ATC0065 and ATC0175.

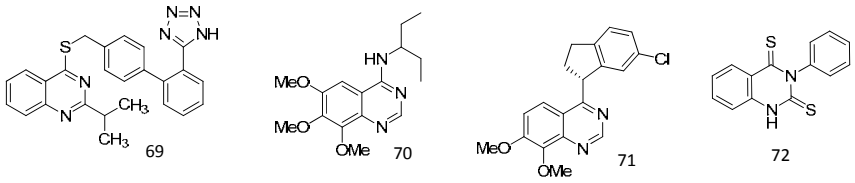


Fig. 14: Selected quinazoline motifs with notable PDE inhibitory efficiency

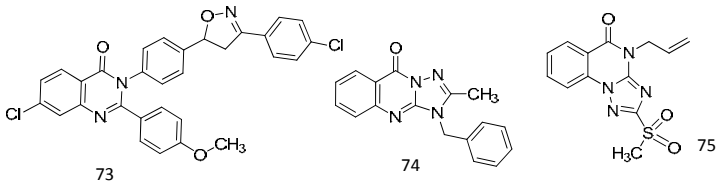


Fig. 15: Some quinazoline motifs with antihypertensive activity

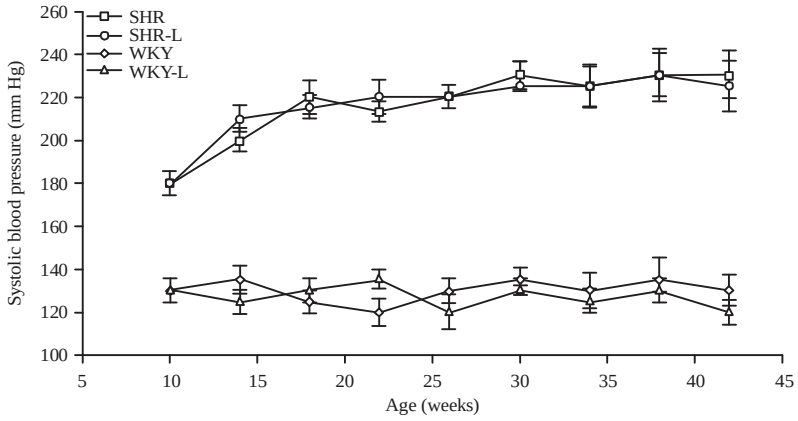


Fig. 16: SBP values of normotensive (WKY-C, WKY-L) and hypertensive (SHR-C, SHR-L) rats. Values are means ± SEM. *p < 0.05 (WKY groups vs. SHR groups)[92]

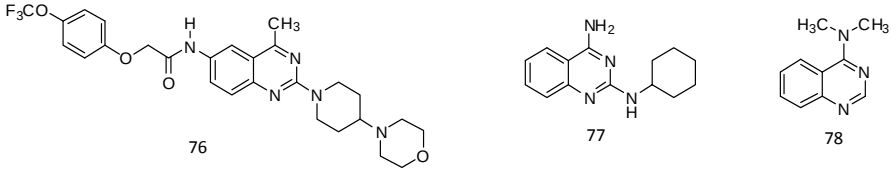


Fig. 17: Selected quinazoline motifs as MCHR1 antagonists

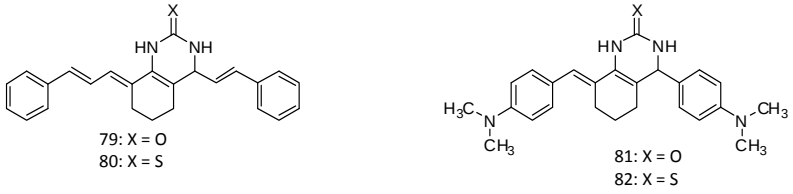


Fig. 18: Selected bischalcones with cathepsin inhibitory activity

Cathepsin inhibitory activity: Bischalcones containing quinazoline-2(1H)-ones and quinazoline-2(1H)-thiones analogs were synthesized and screened for their inhibitory potential against cathepsin B and cathepsin H[96]. It was found that 79 showed maximum inhibition at 0.1 nM while the thione analog 80 showed maximum inhibition at 0.05 nM which was two-fold more active[76] than 79. Among quinazoline derivatives, 2,6-bis(4′-(dimethylamino)benzylidene)cyclohexanone 81 was found to exhibit 100% inhibition at 0.1 nM which was four times more active than the thione counterpart 82 with maximum inhibition of 0.025 nM (Fig. 18).

Antibacterial activity: The antibacterial properties of several quinazolines was evaluated against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* and 83 was reported to be the most potent among the quinazoline series screened[97]. Quinazoline metabolite, lapatin B 84 showed moderate inhibitory activity against aqua-pathogenic bacteria *Vibrio harveyi*[98]. The efficacy of 85 against biofilm formation in *S. aureus* represents a promising additional mode of action[99]. The primary *in vitro* bioassay at 100 mg mL^{-1} against tobacco and tomato bacterial wilt revealed 86 and 87 as strong antibacterial agents using turbidimeter test[100]. Also, ligand 88 was reported to exhibit large zones of inhibition against bacterial strains metal while its metal complex 89 competed favourable with gentamicin standard antibiotic (MIC = 10 μg mL^{-1}) against *E. coli* growth inhibition[101] (Fig. 19).

Antifungal activity: The activity of compound 90 was 8-fold stronger than that of fluconazole on *Candida albican*[102]. From the result of sensitivity testing, 91 inhibited the candida growth with zone of inhibition[103], Z.O.I. being 14 mm. In

another study, a series of benzo[h]thiazolo[2,3-b] quinazolinone was designed and successfully evaluated for their antifungal activity[104]. It was noticed that 92 was the most active compound of the series with Z.O.I. of 18 mm on *C. albican*, *A. niger* and *A. parasiticus*. According to SAR analysis of some tetrazolo[1,5-c]quinazoline-5-thione derivatives against *Candida albicans*, 93 emerged as the most potent at concentration[105] of 100 μg (Fig. 20).

Antiviral activity: Systematic evaluation of a series of thioquinazoline against Tobacco Mosaic Virus (TMV) led to the discovery of 94 which possessed appreciable protective activities against TMV *in vivo*, with 50% effective concentration (EC_{50}) values of 138.1 μg mL^{-1} which was superior to that of Ribavirin (436.0 μg mL^{-1}) standard[106]. The result of screening showed 95 to be the most potent against TMV at concentration 500 μg mL^{-1} with the curing and protection rates of 55.55 and 52.33%, respectively[107], while the curative effect[108] of 96 was 52%. High indicator of the antiviral activity of 97 against influenza type A H3N2 was due to insertion of carcass amine[109]. A series of quinazoline prepared via Schiff bases formation were screened against herpes simplex virus-1 (KOS), virus-2 (G), vaccinia virus, vescular stomatitis virus, reovirus-1 wherein 98 emerged as the most promising antiviral motif against the entire tested virus[110] while compound 99 was reported to possessed antiviral activity due to induction of up-regulation[111] of PR-1a and PR-5 (Fig. 21).

Antioxidant activity: Radical scavenging activities screening showed 100 to exhibit 19.2% DPPH inhibition which is about 50% of that of standard butylated hydrotoluene BHT[112], while 101 was twice more active than the same standard[113] at 25 g mL^{-1}. Using reducing power assay[114,115], 102 and 103 competed favourable with standard antioxidant. Other quinazoline scaffolds with highly promising antioxidant potentials[116-118] are 104, 105 and 106 as shown in Fig. 22.

Antidiabetic activity: GPR119 agonist has emerged as a promising target for the treatment of type 2 diabetes. The analogues bearing azabicyclic amine substituents 107 exhibited better EC_{50} values than that of OEA though they appeared to be partial agonists[119]. Quinazolinone 108 was tested using sublethal dose level (10 mg kg^{-1} b.wt. day^{-1} for 3 weeks) and was found to have potent anti-hyperglycemic and antidiabetic properties[120]. The one-pot synthesis of a series of quinazolin-4-one in the presence of $[BMIM^+][BF_4^-]$ as

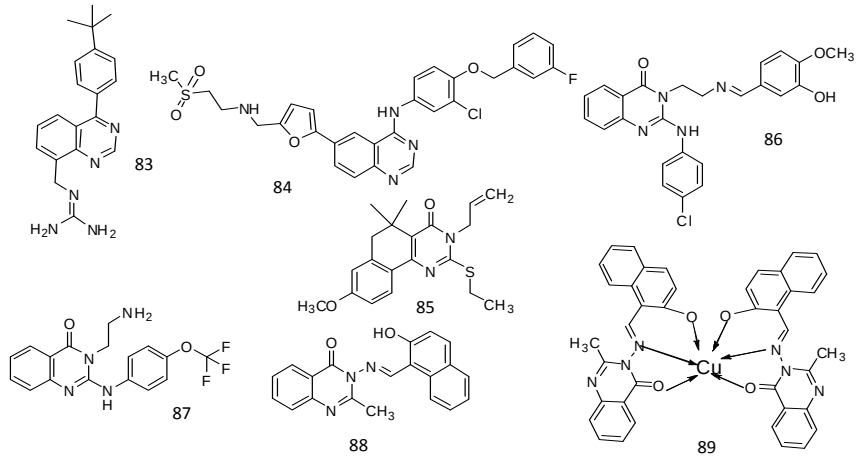


Fig. 19: Selected quinazoline motifs with antibacterial activity

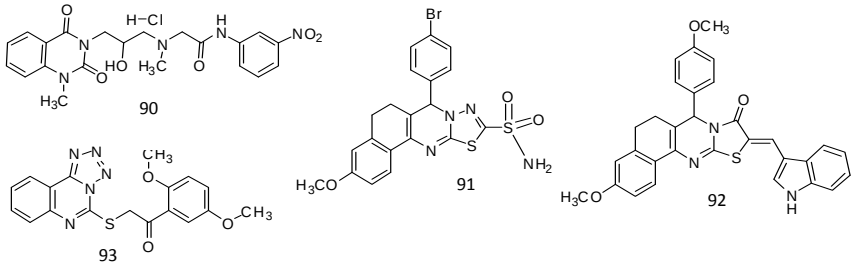


Fig. 20: Selected quinazoline motifs with antifungal activity

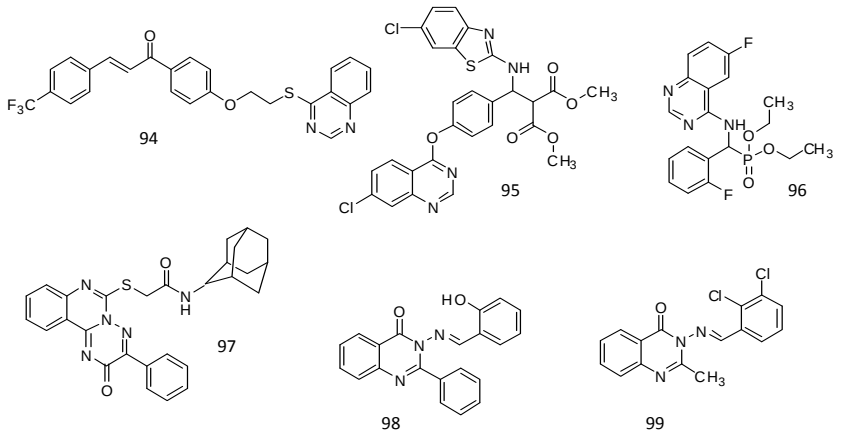


Fig. 21: Selected quinazoline motifs with antiviral activity

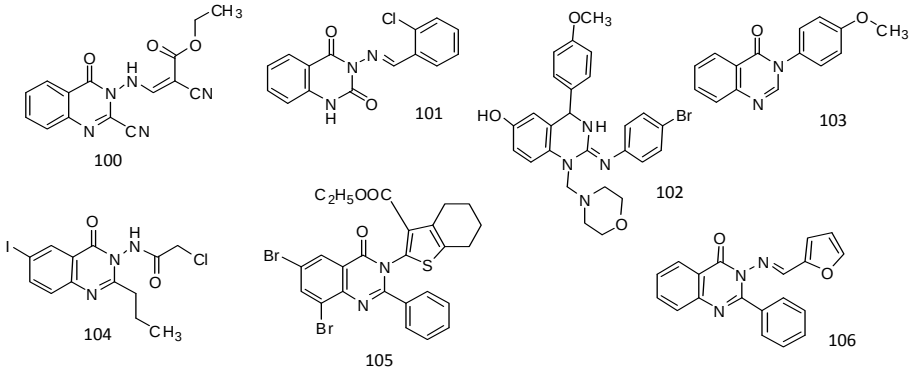


Fig. 22: Selected quinazoline motifs with antioxidant activity

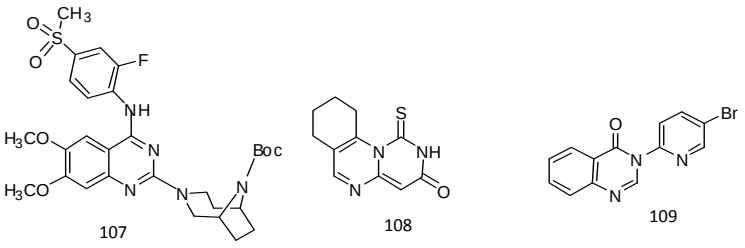


Fig. 23: Selected quinazoline motifs with antidiabetic activity

green and reusable catalyst was reported and the attempted investigation of antidiabetic activity showed 109 to be the most active in this series[121] (Fig. 23).

Heat shock protein (Hsp90) inhibitor: Heat shock protein (Hsp90) is a molecular chaperone that plays a role in the conformational stability, maturation and function of several proteins[122]. The FAXS NMR titration measurement of 110 was performed and it was considered as a suitable Hsp90 inhibitor based on its binding activity constant, K_i of 32.2 μM which corresponded to a ligand efficiency[123] of 0.37. Quinazoline derivatives 111 was a promising lead with a 30,000 fold gain in activity, relative[124] to 110. Other prominent Hsp90 inhibitors are 112, 113 and 114 (Fig. 24). The structural explanation of the binding study of the structurally related compounds 113 and 114 in the active site[124] of Hsp90 is as shown in Fig. 25.

Antimimotic activity: A new series of pyrrolo[3,4-h]quinazolines was conveniently prepared with a broad substitution pattern. Most of these compounds showed antimitotic activity and a reduction of tubulin polymerization in a concentration-dependent manner. Compound 115 was active[10] at 10 μM whereas, another study investigation led to the discovery of 5,8-disubstituted quinazolines 116 which

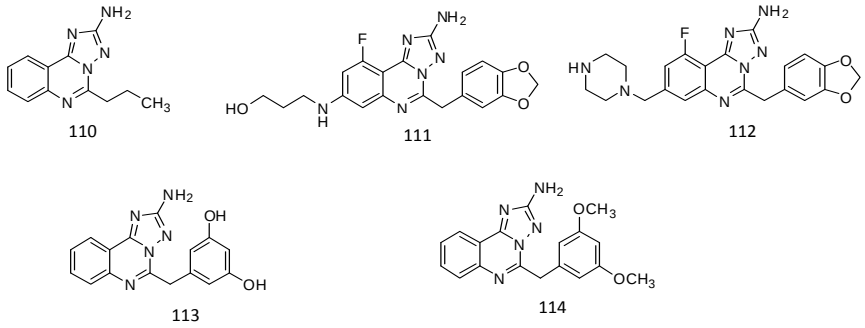


Fig. 24: Selected quinazoline motifs which serve as Hsp90 inhibitors

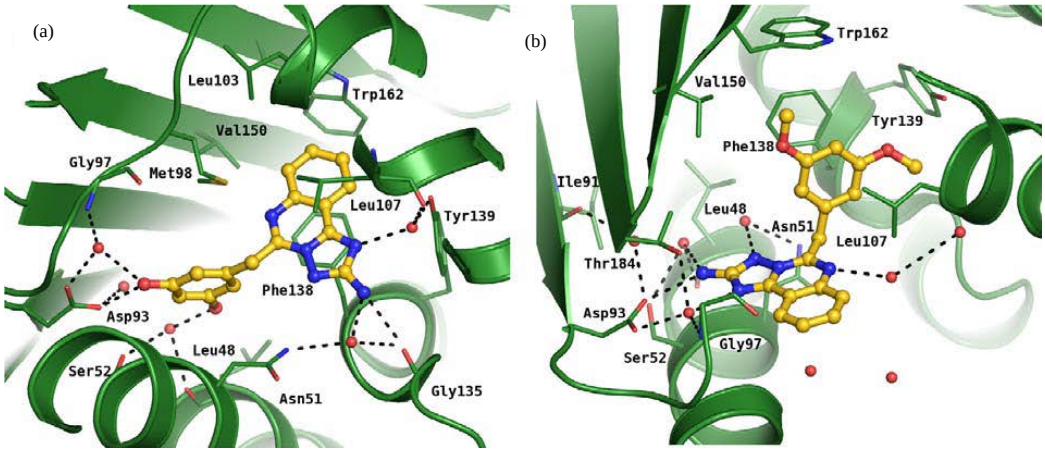


Fig. 25(a-b): (a) View of compound 113 bound in the active site of Hsp90. Compound 113 (yellow carbons atoms) and key residues of the active site (green carbon atoms) are shown as sticks, ordered water molecules are shown as red spheres and hydrogen bonds as black dashed lines and (b) View of compound 114 bound in the active site of Hsp90 114 (yellow carbons atoms) and key residues of the active site (green carbon atoms) are shown as sticks, ordered water molecules are shown as red spheres and hydrogen bonds as black dashed lines [124]

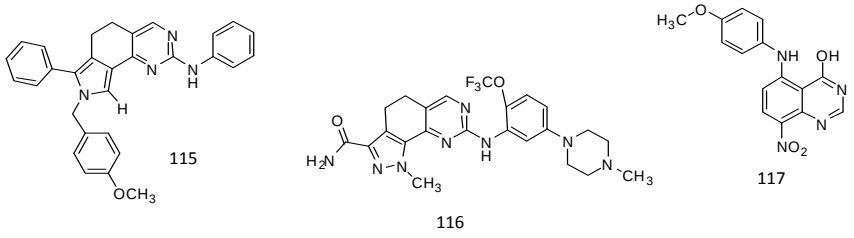


Fig. 26: Selected quinazoline motifs with antimimotic activity

blocked mitosis and induced apoptosis of tumor cells by inhibiting microtubule polymerization[125]. Compound 117 was identified as potent and selective PLK1 inhibitor which was in turn reported as valuable antimitotic agent[126] (Fig. 26). This is owing to PLK1 being a key component of the cell cycle control machinery with important roles in the mitotic entry, centrosome duplication, bipolar mitotic spindle formation, transition from metaphase to anaphase, cytokinesis and maintenance of genomic stability[127].

Anticoccidial activity: Synthetic modification of the ring of febrifugine resulted in quinazoline 118 with noticeable anticoccidial activity against *Eimeria tenella* in the chicken at a dose[128] of 9 mg kg^{-1}. In another study, a series of 4-(2-methoxyphenyl)-2-oxobutylquinazoline derivatives were synthesized via facile synthetic approach and 119 emerged as the motif with highest anticoccidial activity among this series[129] as shown in Fig. 27. Thus, 119 may serve as an open door of opportunity in future

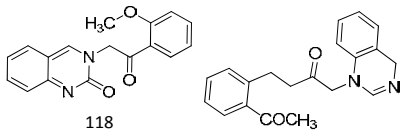


Fig. 27: Selected quinazoline motifs with anticoccidial activity

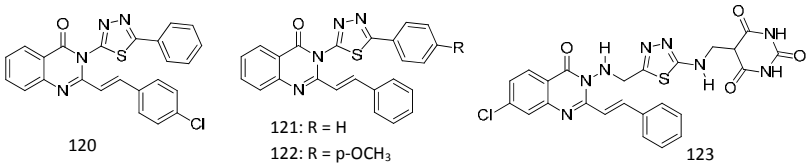


Fig. 28: Selected quinazoline motifs with antidepressant activity

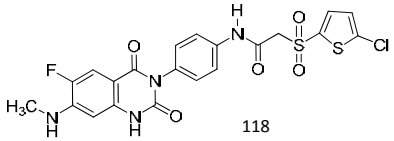


Fig. 29: Elinogrel as selected quinazoline-based antithrombotic marketed drug

veterinary drug design due to its reported strong anticoccidial properties in the preliminary screening.

Antidepressant activity: According to the finding of a study on a series of quinazoline motif, 120 showed high antidepressant properties similar to that of the standard drug and without any neurotoxicity[130]. From the result of the antidepressant drug screening via forced swim pool method, quinazoline without any substituent on the phenyl ring 121, emerged as the most active while the counterpart with p-methoxy 122 was projected as a promising antidepressant agent for future drug development[131]. Also compound 123 was unveiled as a candidate for further study due to its improved CNS antidepressant nature[132] (Fig. 28).

Antithrombosis activity: Activated factor X (FXa) is an important player in the coagulation cascade responsible for thrombin generation, which is activated during atrial fibrillation. Activated factor X FXa and tachyarrhythmia act synergistically to increase expression of protease-activated receptors and inflammatory mediators[133]. Some quinazoline derivative exerted inhibition of inflammation via this route. Elinogrel 118, the structure shown in Fig. 29 is a marketed available antithrombosis drug containing quinazolinone moiety[134].

Structure Activity Relationship (SAR) study: Structure Activity Relationship (SAR) of the reported compounds revealed that the choice of a suitable substitution pattern including electron-donating, electron-withdrawing groups as well as some heterocyclic moieties, on the basic skeleton plays a key role in regulating the biological potential of the synthesized compounds. From the painstaking examination of the SAR, it was collectively noted that the positions 2, 4 and 6 are major points of biological relevance for improved activities for possible drug design[135]. Hence, 2-, 4- and 6-positions substituted quinazoline analogs remain majority among the products of this family of heterocycle and various 2,4, 6-trisubstituted quinazoline derivatives have been evaluated for bioactivity[136]. In addition, the substitution on the pyrimidine ring shows more of an anti-malarial activity variation of a quinazoline derivative[137]. Triazolo-fused quinazoline 119 with morpholinyl in 2-position and chloro on 6-position was the most potent antimicrobial scaffold among the series synthesized in a recent research endeavor[138]. Presence of electron donating diamine at 4-position increased the anti-inflammatory efficacy[80] of 120. Introduction of polar group such as hydroxamate on the 4-position of the quinazoline core was reported to likely provide a potent HDACi/HER2i hybrid as seen in 121 which was the most potent HDAC inhibitor among the quinazolines designed and synthesized in a recent study[78]. The isopropyl group on 2-position of 69 was reported to enhance its PDE-7 inhibitory potential being the most active in the series screened recently[85]. Some structural representations of quinazoline templates for SAR study are as shown in Fig. 30.

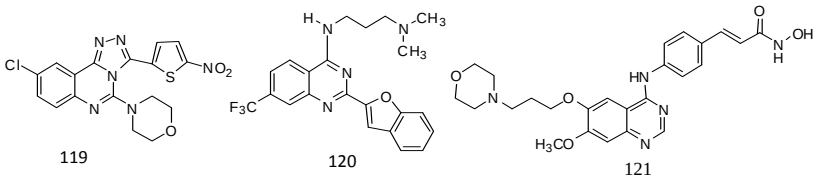


Fig. 30: Representative quinazoline motifs for SAR study

CONCLUSION

In conclusion, it is reported that in recent times lots of pathogens and causative agent of diseases have grown resistant abilities to the old existing and commercially available drugs, which have made the cure of these diseases harder and almost impossible. This present article provides the researchers with a pool of diagnostic information in quinazoline templates and thorough understanding of their structure activity relationship study in order to help mankind against the adverse effect of drug-resistance pathogens and newly occuring infectious diseases. This further helps in designing large number of quinazoline and quinazolinone compounds with a strong impact in curing many fatal disorders and infectious diseases. Quinazoline derivatives are thereby presented as resourceful tools in the designing of expeditious pharmacophores which may serve as great opening to new drug discovery and development in the therapeutic medicine.

SIGNIFICANT STATEMENT

- Recent advances on quinazoline motifs were reviewed herein
- Relevant binding and SAR studies were expatiated for information on druggability
- Their diverse bioactivities and pharmacological potentials were explored
- They were unveiled as arsenals of warfare against infectious diseases in therapeutics
- Quinazoline cores are undeniable toolbox in public health and human total wellbeing

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