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Mini-review

Quinazoline pharmacophore in
therapeutic medicine

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Abstract

This present study comprehensively expatiates the functionalized utilization of quinazoline scaffolds in drug development and furnishes latest updates in pharmacological appositeness of its derivatives in order to reveal novel pathways for therapeutic targets. It traverses numerous biological potentials of quinazoline in the contemporary time to allow researchers' unhindered access to the beneficial role of quinazoline in fighting infectious diseases for future drug discovery. This work provides broad overview of medicinal survey of quinazoline chemistry valuable in the discovery of more efficient clinical trials and to summarize the most promising molecular targets for drug design.

Introduction

Over the years, heterocyclic chemistry has gained tremendous attention because of its unavoidable pharmacological diversity in medicinal chemistry research. There has been considerable attention on the preparation of useful heterocyclic compounds in organic synthesis (Ajani and Nwinyi, 2009). These structures can either be aromatic or non-aromatic rings (Joule and Mills, 2000). Pyrimidine falls under the common azines 6-membered aromatic nitrogen heterocycles (Eicher and Hauptmann, 2003), while quinazoline falls under the category of benzo-fused azines because it resulted from the fusion of a benzene ring and a pyrimidine atom (Asif, 2014). Heterocyclic frameworks constitute most of the active ingredients and building blocks of many pharmaceuticals, agrochemicals and veterinary products (Ouahrouch et al., 2014; Murgan et al., 2003).

In comparison with our earlier review, quinazoline is an heterocycle which belongs to benzodiazine family with its heteroatomic nitrogen located at 1- and 3-positions (Ajani, 2014). Evolution of quinazolines began only with discovery of febrifugine, a 'quinazolinone alkaloid', which was isolated from the Chinese plant

Aseru (*Dichroa febrifuga* Lour) and was reported to possessing antimalarial potential. It was first synthesized by Gabriel in the year 1903 and was first isolated from the Chinese plant aseru (Selvam and Kumar, 2011).

Quinazoline is the most commonly experienced heterocyclic core in medicinal research, owing to its wide spectrum of pharmacological potential (Luo et al., 2014; Selvam et al., 2008) and a huge amount of its derivatives are referred to be salient structural synthons of numerous physiological relevance and pharmaceutical applications (Luo et al., 2014). These include usage in drug design and medicinal researches because they have been reported to display anti-tobacco mosaic virus (anti-TMV), anti-HIV, anti-cancer, antimicrobial, antifungal (Patel and Patel, 2011), anti-inflammatory (Kumar et al., 2010), anti-hypertensive, antimalarial (Werbel and Degnan, 1987) and anti-convulsant (Aly et al., 2010) activities among others.

Furthermore, quinazoline and quinazolinone compounds are also used in the preparation of various functional materials for synthetic chemistry and also present in various drugs molecule (Rajput and Mishra,



2012). Novel quinazoline-urea analogues were recently reported as modulators for A β -induced mitochondrial dysfunction making them valuable template in the treatment of various neurodegenerative disorders (Elkamhawy et al., 2014). Sulfonamides containing quinazoline core structure was reported to be suitable toolbox for better comprehension of the usefulness of bacterial carbonic anhydrases in pathogenesis (Alafeefy et al., 2014). Quinazolinyloxybiaryl urea was identified as a new class of inhibitor against SUMO activating enzyme 1 which is an excellent oncology target (Kumar et al., 2013). Quinazoline core was not left out in the new advancement in phenocustering of diverse model systems as an option for the recognition of targeted site in drug development (Williams and Hong, 2013). Linear and angular 4',5'-dimethylfuroquinazolines proved to intercalate within the DNA double helix, however they could not photo-bind DNA bases in the presence of ultraviolet radiation (Miolo et al., 2014). Fluorescence relays increased sequential identification of Cu²⁺ and CN⁻ through effect of novel quinazoline scaffold (Liu et al., 2013; Tang et al., 2013) and their role as turn on fluorescence for cysteine and chemodosimeter for NO has also been reported (Anand et al., 2014). Some quinazoline motifs were shown to display bronchodilatory effect at low micromolar concentrations on isolated rat trachea, and low toxicity both on Balb/c 3T3 mouse fibroblast cells and in mice (Špulák et al., 2014). Some valuable quinazoline-based compounds include antitumor erlotinib **1**, anti-cancer iressa **2** and kinase inhibitor lapatinib **3** (Sharma et al., 2013a; Garofalo et al., 2011) as presented in Figure 1.

Physical properties

Quinazoline is a nitrogen-based heterocyclic entity which contains a fusion of benzene structure on a pyrimidine heterocycle. Hence, it qualifies to be called

benzopyrimidine. It is a yellow colored solid compound having the chemical formula C₈H₆N₂ and a molecular mass of 130.1 g/mol. It is usually found in crystalline state and it is isomeric with other naphthyridines including quinoxaline, phthalazine and cinnoline (Selvam et al., 2008).

Natural occurrence

Quinazoline occurs mostly as alkaloid in root and leaves of some medicinal plants such as *Dichroa febrifuga* (also called Chinese quinine) which belongs to the Saxifragaceae family (McLaughlin et al., 2014). They are present there as isomeric alkaloids (+)-febrifugine **4a** and (+)-isofebrifugine **4b**. The recent review summarized historical isolation information and the chemistry studies which culminated in the correct structural elucidation of this naturally occurring quinazoline-based alkaloid called febrifugine and its isomer, isofebrifugine (McLaughlin et al., 2014). Hydrachine A **5**, a natural quinazoline-core, was isolated from the roots of *Hydrangea chinensis* (Chang et al., 2003). The structures of these naturally occurring quinazoline motifs are as shown in Figure 2.

Structure of quinazoline/quinazolinone

In quinazoline structure, the reactivity behaviour of heteroatomic six-membered ring is significantly affected by the incorporated benzene nucleus. The two N-heteroatoms are slightly different in their reaction, and the existed polarization of the π bond at 3,4-position is unveiled in the marked reactions of quinazoline. The substituted quinazolines nature is mainly determined by position of substituents attachment, i.e. if they are either attached to the heteroatomic ring portion or benzene nucleus. Another factor has to do with whether there is complete conjugation in the pyrimidine ring or not (Vijayakumar et al., 2013).

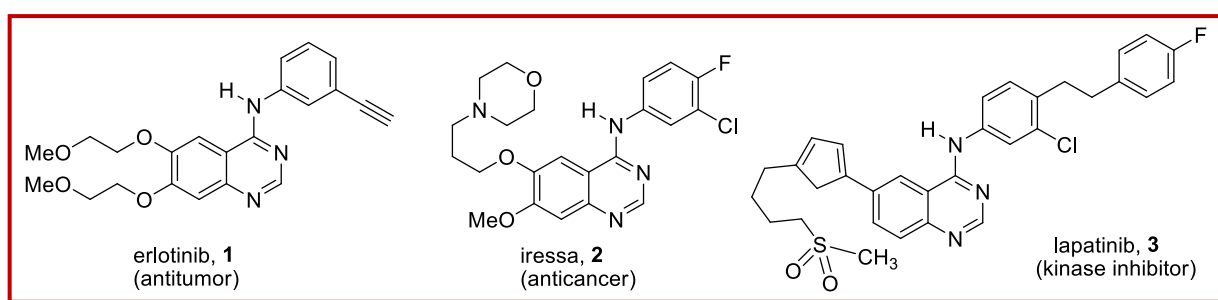


Figure 1: Selected commercially available drug bearing quinazoline core

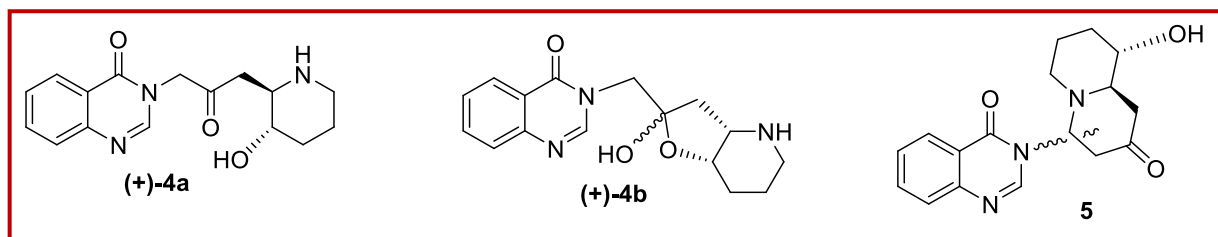


Figure 2: Structural identity of some naturally occurring quinazoline motifs

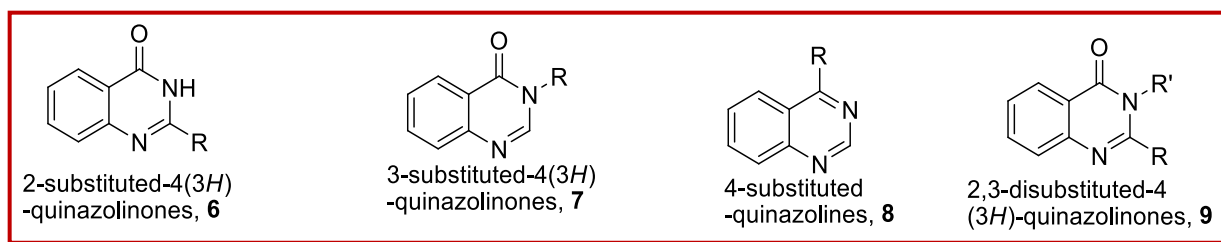
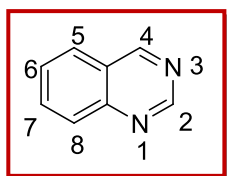


Figure 3: Classification of quinazoline and quinazolinone derivatives



Classification of quinazolinones

Based on substitution pattern of its ring system, quinazolinones can be classified into the following categories: 2-substituted-4(3H)-quinazolinones **6**, 3-substituted one **7**, 4-substituted one **8** and 2,3-disubstituted type **9** (Mhaske and Argade, 2006) as shown in Figure 3. Based on the location of oxo group, quinazoline could be further categorized into three other classes which include: Quinazolin-2(1H)-ones, quinazolin-4(3H)-ones and quinazoline-2,4(1H,3H)-dione (Mahato et al., 2011). It is worthy to note that, of all the templates, quinazolin-4(3H)-ones are the commonest privileged in terms of naturally occurring molecular features or intermediates in numerous reported construction route in biosynthesis (Mahato et al., 2011).

Justification for expository study on quinazoline derivatives

The recent development in the medicinal importance of quinazoline derivatives has necessitated strong international effort for the development of new and better synthetic strategies for their preparations. The relinquishable attribute of its characteristic offers an effective justification for the discovery of these techniques (Portela-Cubillo et al., 2009). Synthetic chemists are continuously engaging the preparation of quinazoline and its derivatives by simple and effective methods because of its diverse biological applications such as anti-cancer, antiviral and antitubercular agents. The quinazoline unit is represented in a number of useful natural product scaffolds with laudable activities against numerous pharmacological disorders. On this note, quinazoline moieties are one of the strongest ever reported inhibitors cellular phosphorylation and tyrosine kinase. These heterocycles have functioned as common ligands in deoxyribonucleic acid, which link to adenosine receptors, as well as being efficacious as tough antibacterial agents (Portela-Cubillo et al., 2009).

No wonder their frameworks serve as the foundation in the application that have to do with lots of pharmaceutical, agrochemical, and veterinary products (Portela-Cubillo et al., 2009). The increasing significance of quinazolines around therapeutic research has been noticed based on the reported highly voluminous selling of the quinazoline-based drugs called erlotinib **1**, which serves a well-recognized curing agent for various kinds of tumours (Fung and Grandis, 2010; Portela-Cubillo et al., 2009) and prazosin, which serves as a blocking agent for R-adrenergic blocker. In the same vein, iressa **2**, which serves as an inhibitor of EGFR, has been certified by the United State Food and Drug Administration for the treatment of lung cancer (Portela-Cubillo et al., 2009). Prozosin, which is another r-adrenergic blocker, is a popular drug bearing the quinazoline unit. Quinazolin-4(3H)-one bearing a benzyl functionality at 2-position has been reported to have selective inhibitory efficiency on human leucocyte elastase as well as on serine protease while 1,3-dimethyl-1 H-quinazoline-2,4-dione did not only act against inflammation but also showed strong and encouraging analgesic as well as anticonvulsant potentials (Connolly et al., 2005; Maskey et al., 2004). 4(3H)-Quinazoline derivatives possess a broad spectrum of biological activities and have been identified as antidiabetic and CNS depressants (Ding et al., 2004). Due to the existence of microorganisms' resistance phenomenon to drugs currently available in the market and consistent increase in the outbreak of new diseases, it is highly imperative and necessary to continuously design and prepare novel heterocyclic scaffolds which display improved druggability relevance for medicinal research (Ajani, 2014). Therefore, the main goal of this review herein is to harness the valuable updated information in the medicinal applications and pharmacological expertise of quinazoline motifs so as to unfold novel routes toward active targets in drug development.

Synthetic methods

Quinazoline is relatively easy to prepare and many derivatives have been synthesized in order to obtain biologically active motifs. Medicinal chemistry researchers have designed series of quinazoline templates having diverse bioactivities by incorporating and attaching several active functionalities to the quinazoline core with the aid of improved synthetic

methodologies (Wang and Gao, 2013). In an earlier review, the representative synthetic methods for quinazoline moieties, either traditional or novel were summarized, and they were classified into five main categories which include: Aza-reaction, microwave-assisted reaction, metal-catalyzed reaction, ultrasound-promoted reaction and phase-transfer catalysis (Wang and Gao, 2013). First quinazoline compound, 2-cyano-3,4-dihydro-4-oxoquinazoline (Maheswari et al., 2010), was prepared in 1869 through the reaction of cyanogens with anthranilic acid and later documented by Armarego in 1967.

Biological importance of quinazoline

Quinazoline and its quinazolinone skeletons are recurrently encountered heterocyclic compounds in therapeutic medicine's literature with wide range of utilization including antidiabetic, antileishmanial, antihypertensive, CNS depressant, anticonvulsant, antitubercular, anti-HIV, antibacterial, anti-cancer activities among others.

Anti-cancer activity

Cancer has continued to be topic of great attention in all regions of the world due to its global health challenge issue to be a leading health problem in developed as well as developing countries. It has been consistently associated with high mortality rate due to various worldwide factors (Antonello et al., 2006). Cancer is an abnormal cell growth which is identify through a shift in the controlled mechanisms which guides cell proliferation and differentiation (Al-Omary et al., 2012). Quinazoline bearing sulfonamide functionalities were recently recognized as categories of cancer chemotherapeutics which exhibited noticeable therapeutic potentials on solid tumours (Mohamed et al., 2015). 4-Anilinoquinazoline bearing sulfonamide at 6-position was reported to inhibit the breast cancer cell line growth at as low as $IC_{50} = 5.5 \mu M$ based on the result of investigation of the screening carried out by Yassen et al. (2014) whereas when the sulfonamide was on para position of the aniline ring there was a reduction in anti-cancer activity to $IC_{50} = 77.9 \mu M$ (Ghorab et al., 2016). Quinazolinone-based redox modulators, 6-((3-acetylphenyl)amino)quinazolinone-5,8-dione, was discovered as therapy for pancreatic cancer since the oxidative stress enhanced through it, catalyzed activation of stress kinases (p38/JNK) thereby leading to cancer cell death (Pathania et al., 2014).

EGFR inhibitory activity

Comprehensive clinical studies showed that inhibiting EGFR family receptor TKs represent a major advance in the treatment of solid tumor. Gefitinib and erlotinib are quinazoline-based compounds which happened to be earlier reported salient EGFR inhibitor authorized for the curing of diseases related to NSCLC (Wang et al.,

2016). Their mechanism of action was through competitive binding to adenosine triphosphate (ATP)-binding pocket of the intracellular EGFR TK site according to docking study report; hence, effectively block the aberrant EGFR down-stream signaling required during tumor survival as well as its proliferation (Wang et al., 2016; Hynes and Lane, 2005). Owing to this ability, structural modifications of earlier discovered gefitinib and erlotinib have been achieved to produce more effective EGFR inhibitors. For instance, EGFR was reported clinically authenticated during rational drug design as targeted entity for cancer chemotherapy. In addition, various small molecular inhibitors have been designed and made available to members of public (Zhang et al., 2013a) as quinazoline-based reversible inhibitor, e.g. icotinib (Tan et al., 2012) and irreversible inhibitors namely; afatinib (Minkovsky and Berezov, 2008), canertinib and newly reported afatinib derivative (Zhang et al., 2013a). According to results of the molecular docking study showed in Figure 4, the comparison between the binding modes of the 6,7-dimethoxy-derivative of quinazoline (LASSBio-1814; $IC_{50} = 2.4 \mu M$ for EGFRwt and $1.02 \mu M$ for VEGFR-2) and the 6,7-methylenedioxy-derivative of quinazoline (LASSBio-1815; $IC_{50} = 34.6 \mu M$ for EGFRwt and $26.9 \mu M$ 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 (Barbosa et al., 2014).

Anti-proliferative activity

Over the years, it has been established that anti-proliferative and cytotoxic drug serve vital functions in oncology drug design, either being used in isolation or in conjunction with other remedial medical procedures which include surgery, radiation and pharmacotherapy (Arya et al., 2014; Jabir et al., 2012). Arya et al. (2014) reported that novel fluorinated benzothiazolo[2,3-b]quinazoline they synthesized via greener approach possessed highly promising photo-anti-proliferative activity upon human keratinocytes cell line (Arya et al., 2014) and carcinoma cell line such as HL-60 as well as LoVo cell lines (Arya et al., 2014). Novel array of isatin-based quinazolines have been reported to displayed distinctive selective growth inhibitory effect ($IC_{50} = 1.0 \pm 0.2$ to $2.4 \pm 0.4 \mu M$) by making use of molecular hybridization technique (Fares et al., 2015).

Anti-tubercular activity

Tuberculosis (TB) is noted to be one of the oldest and most-pervasive diseases in history of mankind (Ankita et al., 2014; Yves, 2007). It has been projected that close to 1000 million of world population will be newly infected, above 150 million individuals will develop

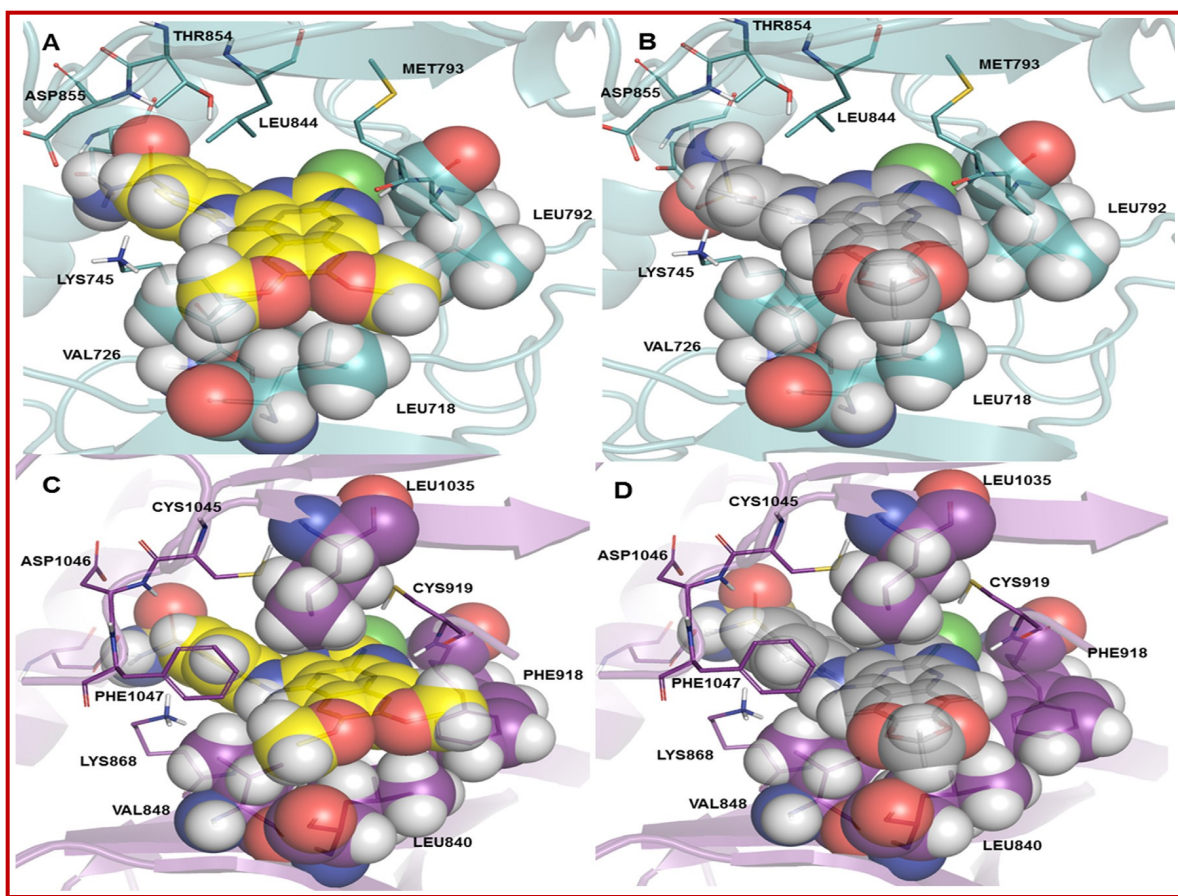


Figure 4: (A) Binding interactions of 6,7-dimethoxy-derivative of quinazoline (yellow) with EGFRwt. (B) Binding interactions of methylenedioxy-derivative of quinazoline (gray) with EGFRwt. (C) Binding interactions of 6,7-dimethoxy-derivative of quinazoline (yellow) with VEGFR-2. (D) Binding interactions of methylenedioxy-derivative of quinazoline (gray) with VEGFR-2. Docking studies were performed with the GOLD 5.1 program. Apolar hydrogen atoms were omitted to improve clarity. The images were generated with PyMol Software (Barbosa et al., 2014)

diseases and 36 million will die of TB, between 2002 and 2020, if adequate preventive and proper control measures are not in place (Ankita et al., 2014; Corbett et al., 2003). Due to the difficulty in the treatment of drug resistant forms of *Mycobacterium tuberculosis*, the development of novel antituberculosis drug entities which exhibit new mechanisms of action is urgently demanded with the aim of designing more potent combination therapy (Mathew et al., 2013). An array of new 2-trichloromethyl quinazoline moieties containing substituted secondary amine side chain at 4th position were designed and investigated via *in vitro* screening for anti-tubercular potential upon *M. tuberculosis* H37Rv ATCC (Srivastav and Shantakumar, 2013) using Alamar Blue assay. 8-Methoxy-4-[4-[2-(1-piperidyl)ethoxy]phenyl]-5,6-dihydrobenzo[h]quinazolin-2-amine exhibited significant anti-tubercular activity at MIC values 50 μ M and the *in vitro* cytotoxicity data using THP-1 cells indicated that it was safe as its MIC value was much lower than the cytotoxic value as documented by Maurya et al. (2013).

Anti-inflammatory activity

For the past few decades now, a probable conjunction between the application of non-steroidal anti-inflammatory agents (NSAIDs) and modified cases of cancer has continued to exist as special topic that needs intense evaluation and research (Chandrika et al., 2008). Using NOS-II as biomarker indicator, generally, quinazoline motifs are well-known to exhibit significant anti-inflammatory properties as inhibitors of NOS-II (Farag et al., 2013; Tinker et al., 2003), NFKB, TNF- α (Serya et al., 2015), IMPDH-II (Rajput and Mishra, 2012), MAPK, IL-6, PDE-3 and PDE-4 (Serya et al., 2015). A series of novel 8/10 trifluoromethyl-substituted-imidazo[1,2-c] quinazolines were synthesized and investigated *in vivo* (rat paw edema) for their anti-inflammatory activity and *in silico* (docking studies) to recognize the hypothetical binding motif (Rajput and Mishra, 2012; Kumar et al., 2003) with the Cyclooxygenase enzymes (COX-1 and COX-2) employing GOLD (CCDC, 4.0.1 version) software and found that compounds (Rajput and Mishra, 2012)

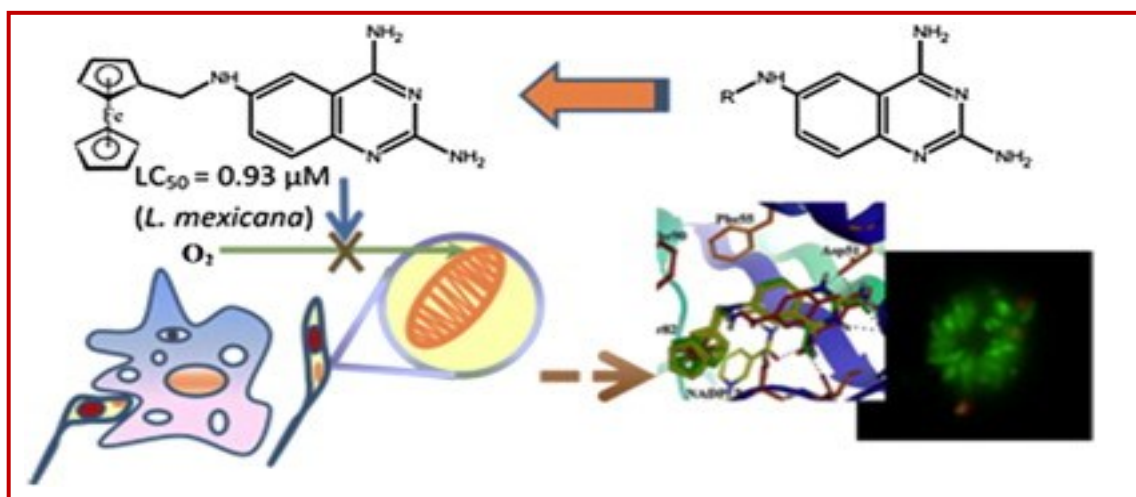


Figure 5: Molecular docking study *N*⁶-(ferrocenmethyl)quinazolin-2,4,6-triamine as anti-leishmanial agent

showed good anti-inflammatory activity against standard, indomethacin. Quinazoline derivatives are also found to show bronco-dilatory properties (Jindal et al., 2002). Using tumor necrosis factor- α (TNF- α) as the biomedical pathway, ethyl 4-(2-carbamoyl anilino)quinazoline-2-carboxylate was discovered to be a promising anti-inflammatory quinazoline derivative with 68% average inhibition on PDE4B enzyme at concentration of 10 μ M (Serya et al., 2015).

Antileishmanial activity

Leishmaniasis, otherwise known as African trypanosomiasis or Chagas disease are vector-borne infectious diseases whose causative agent are parasites of the kinetoplastida order (WHO, 2016; Mendoza-Martínez et al., 2015). It is quite alarming to note that approximately 1.5 million of new cases of cutaneous leishmaniasis emerge every year while there is an outbreak of about 500 000 of new cases of visceral diseases in similar vein. Statistics have shown that cutaneous leishmaniasis is endemic over 70 countries of the World today (Tiumana et al., 2011). Comprehensive review of anti-leishmanial drugs discovered for the last decade projected quinazoline as highly promising in this regard (Sangshetti et al., 2015). A series of quina-zoline-2,4,6-triamine were synthesized and evaluated *in vitro* against *Leishmania mexicana*. Among them, *N*⁶-(ferrocenmethyl)quinazolin-2,4,6-triamine showed activity on promastigotes and intracellular amastigotes as well as low cytotoxicity in mammalian cells (Mendoza-Martínez et al., 2015) as shown in Figure 5. In the recent review by Sangshetti et al. (2015) about anti-leishmanial drug discovery, quinazoline core was not left out.

Antitumor activity

Literature survey revealed that 4-anilinoquinazoline and quinazolinone derivatives are important scaffold

used in drug design of effective antitumor agents (Hassan et al., 2015). Structure-activity relationship studies have revealed the significant role of 4-anilino substituent in the antitumor diversity of quinazoline motifs. From the screening of a series of structurally related 4-anilinoquinazoline with *N*-adamantyl formamide in 4-position **10a-f**; specifically, compound **10d** ($R_1 = H$; $R_2 = Cl$; $R_3 = 4$ -morpholinyl-(CH_2)₃; $R_4 = CH_3$), with an IC_{50} value of 2.06 μ M against A431 cells with the wild-type EGFR and of 0.009 μ M against the gefitinib-sensitive cells (Mendoza-Martínez et al., 2015) (Figure 6). It displayed efficacy that was about 5-fold active than the lead compound to inhibit the growth of the cells harboring the EGFR (T790M) mutant (Yu et al., 2016; Mendoza-Martínez et al., 2015). The synthesis, structural elucidation as well as *in vitro* antitumor properties of ruthenium(ii) polypyridyl complexes of 4-anilinoquinazolines was recently reported (Du et al., 2016). The reported complexes exhibited substantial enhancement in antitumor activity compared to their precursor ruthenium polypyridyl moieties. They also displayed a dual-targeting manner that can both bind to the DNA minor groove and inhibit EGFR (Du et al., 2016). Caspase-3 activity and cell cycle regulation studies revealed that 4-anilinoquinazoline **11** exerted antitumor properties with IC_{50} of 3.4 μ M (Palop et al., 2013). Compared with the parental dasatinib, most of the new compounds synthesized by Cai et al. (2013), especially 2,4,6-trimethylaniline **12**, demonstrated significant antitumor activities against six cell lines (Figure 7).

Kinase inhibitory activity

A series of benzimidazole-based quinazoline derivatives were reported to serve as active inhibitor of Aurora according to the investigation carried out through structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR)

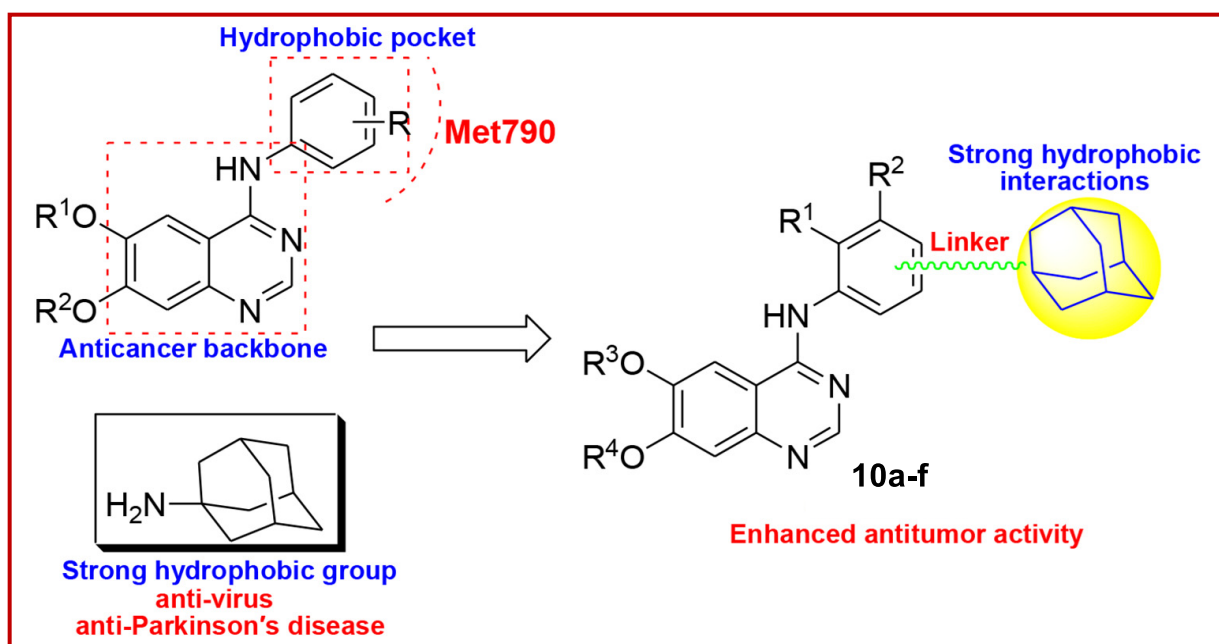


Figure 6: SAR study showing the significant role of 4-anilinoquinazoline as antitumor

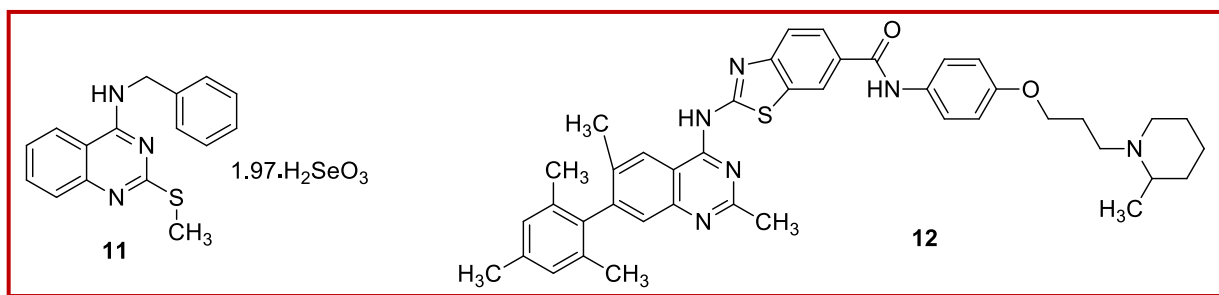


Figure 7: Some quinazoline motifs with antitumor activity

studies (Sharma et al., 2016). Their noticed activity depended on the nature of various substitution patterns of the amine which was present in C2 position of this heterocycles (Sharma et al., 2016). They were established to exhibit improved efficacy as Aurora kinase inhibitors, with IC_{50} values between 0.035 and 0.532 μ M (Sharma et al., 2016). The erythropoietin-releasing hepatocellular (Eph) receptor tyrosine kinases was documented to be of great significance in many physiological and pathological actions (Lim et al., 2014). Compound **13** provided a potent starting point (IC_{50} = 12 nM) for inhibition of Mps1 kinase with submicromolar cellular toxicity, reduced MW and TPSA, while **14** provided a further boost in biochemical potency with IC_{50} = 2 nM (Bursavich et al., 2013). Thus, the comparative study of the two structurally related quinazoline revealed that presence of methylsulfonamide along the axis of 2-substituent is crucial for enhanced kinase inhibitory activity (Figure 8).

Anticonvulsant activity

Epilepsy is in fact several disorderly phenomena which

is identified through neuronal hyperexcitability as well as neuronal firing. Statistics have shown it to be a terrible menace affecting one percentage of global population (King et al., 2011; Chen et al., 2007). The anticonvulsants used to treat this condition are known as antiepileptic drugs and are among the most widely used drugs for the treatment of central nervous system disorders. New fluorinated quinazolinone motifs have been reported as promising anticonvulsant in this regard (Zayed, 2014). The outcome of MES and PTZ screening carried out on *N*-(substituted)-1-methyl-2,4-dioxo-1,2-dihydroquinazoline-3(4*H*)-carboxamides unveiled them to possess improved and better anticonvulsant activity when compared with clinical standard drugs which are valproate and methaqualone (Deepakumari et al., 2016). Methaqualone **15** as a quinazoline analog is an important landmark in the field of synthetic anticonvulsants (Kashaw et al., 2009). The modification of **15** was carried out by El-Azab et al. (2013) to obtain quinazolinone scaffold **16** which proved to be 2-fold more active than anticonvulsant drug sodium valproate. According to the findings of El-Azab and El-

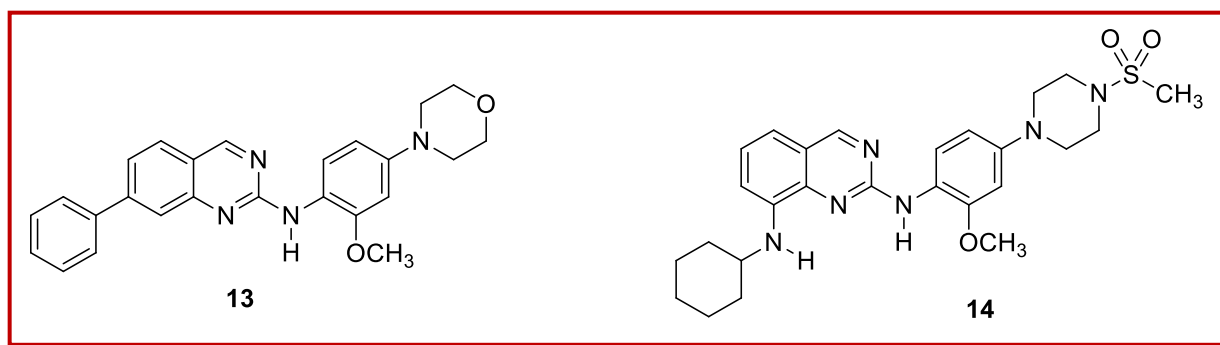


Figure 8: Some quinazoline motifs with kinase inhibitory activity

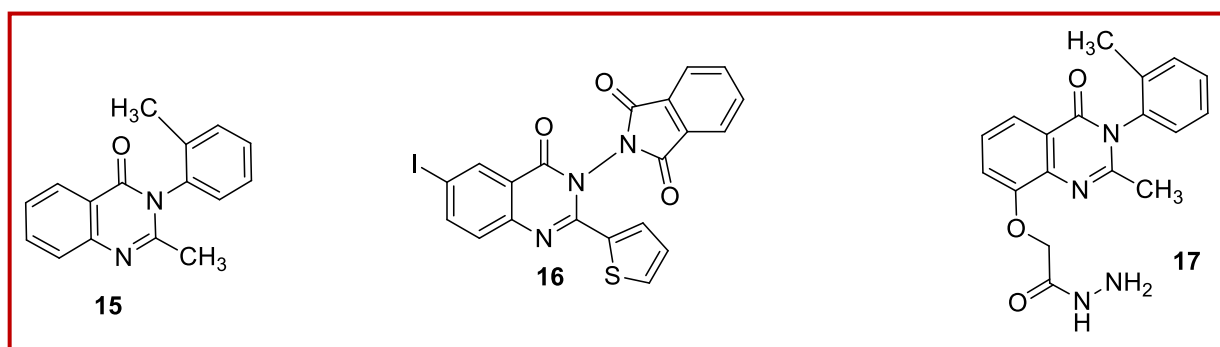


Figure 9: Some quinazoline motifs with anticonvulsant activity

Tahir, (2012), 8-substituted-4(3*H*)-quinazolinone **17** demonstrated a better anticonvulsant activity and lower toxicity than the reference drugs (Figure 9).

Antimalarial activity

Malaria is a well-known parasitic disease in tropical regions of the World affecting billions of global population today (Birhan et al., 2015; Franklin et al., 2011). Taking drug resistant challenge into consideration, an impressive and violent universal attempt is continuously engaged for efficient development new antiplasmodial drugs for treatment of this well-known illness (Birhan et al., 2015; Olliaro and Wells, 2009). Although, the volume of cases and mortality rate linked with his illness are reducing according to recent update, yet it is the deadliest disease known globally (Birhan et al., 2015). The *in vivo* antimalarial activities of the series of quinazolines evaluated with the aid of 4 days suppressive standard experiment against mice infected with *Plasmodium berghei* ANKA which were chloroquine-sensitive isolates revealed that 3-aryl-2-(substitutedstyryl)-4(3*H*)-quinazolinones possessed improved and enhanced antimalarial properties activities having mean suppression of 67.6% (Birhan et al., 2015). The mean parasitemia level in mice treated with this compound (17.7 ± 0.4) was noticed to have been 4 times lesser than that of negative control (65.2 ± 0.7) (Birhan et al., 2015). This shoed that the targeted compounds have significantly decreased

parasite load (Birhan et al., 2015). Previous studies showed that the presence of amino substituents on positions 2 and 4, enhanced the antimalarial potential of 6-substituted quinazoline (Rojas-Aguirre et al., 2012; Jäntschi and Bolboacă, 2006). Hence, this led to the strong effect of quinazoline derivative **18** as an antimalarial motif on human erythrocytes and on cell membrane molecular model (Rojas-Aguirre et al., 2012). Likewise, antimalarial activity of quinazoline **19** was reported to be by topological and geometrical nature and was strongly dependent on partial changes as predicted by MDF SAR methodology (Jäntschi and Bolboacă, 2006). Nonetheless, for the pyrrolo[3,2-*f*]quinazoline **20**, acetamido moieties on positions 2 and 4 was an essential pharmacophoric framework for magical anti-plasmodial potential work in another study (Guan et al., 2005; Figure 10).

HDAC inhibitory activity

HDACs and histone acetyltransferases (HATs) work in contrary to altered chromatin and therefore provide a guidance for gene expression (Lin et al., 2016; Pickup et al., 2013). HDACs could forcefully suppress the transfer of genetic code through existence of chromatin condensation with regard to in response to the dismissal of acetyl functionality from histone ends (Lin et al., 2016; Bolden et al., 2006). A quinazoline-based HDAC inhibitor was reported to affect genetically expressed routes towards cholesterol biosynthesis via mevalonate within prostate cancer cells (Lin et al.,

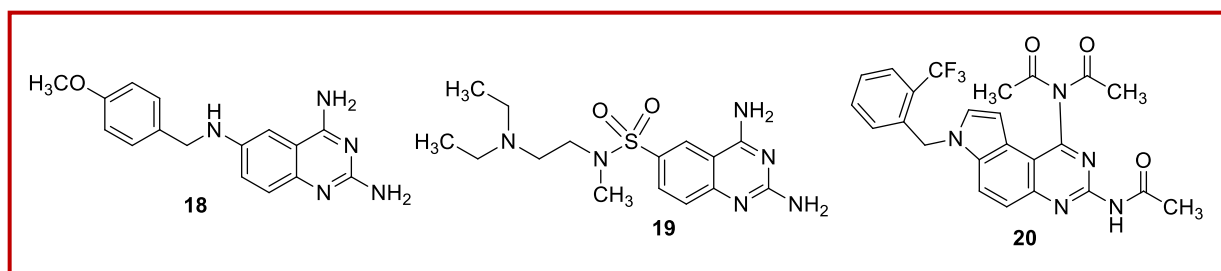


Figure 10: Some quinazoline motifs with antimalarial activity

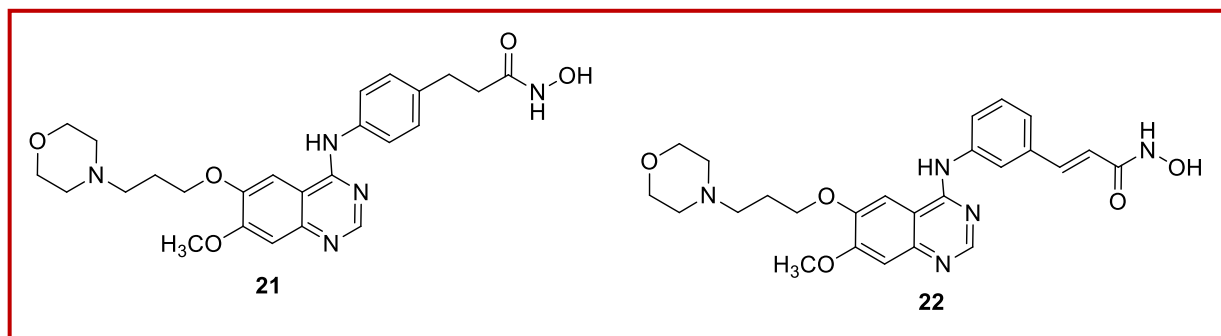


Figure 11: Some quinazoline motifs which served as HDAC inhibitors

2016). Histone deacetylases (HDAC) play crucial roles in numerous biological processes; hence, HDAC inhibitory potential of two structurally related quinazoline **21** and **22** was compared based on the effect of the substituents on the anilino-phenyl at 4-position of quinazoline. The encouraged activity of compound **21** against HDAC (Zhang et al., 2013b) concurred with established fact that hydroxamic acid commonly exhibit better efficacy as HDAC inhibitor than carboxyl-based ones (Zhang et al., 2013b; Kramer, 2009) while quinazoline **22** with meta-substitution and unsaturation near hydroxamic showed even more potency with IC_{50} of $0.2 \pm 0.02 \mu\text{M}$ (Zhang et al., 2013b) (Figure 11).

Anti-HIV activity

HIV-1 is an etiological agent of AIDS which is universal pandemic disease that has led to the death of over 34 million of the world population (Famiglini and Silvestri, 2016). In 2014 alone, AIDS was responsible for approximately 1.2 million mortality cases reported globally in 2014 (WHO, 2015). Review by Famiglini and Silvestri, (2016) exemplified many studies carried out on the evaluation of influence of chirality upon antiretroviral properties of highly rated HIV-1 NNRTI molecules, which include alkenyl substituted quinazolinone and nevirapine (Famiglini and Silvestri, 2016). The chiral segregation, enantiospecific synthesis, in addition to biological activity of the HIV-1 NNRTIs were fully expatiated (Famiglini and Silvestri, 2016). An array of new quinazoline-triazine scaffolds were prepared from the reaction of cyanuric halide and anthranilic acid via a sequential pathway (Mendoza-

Martínez et al., 2015) and confirmed to possess encouraging anti-HIV activity (Modh et al., 2014). A series of dihydrobenzo[*H*]quinazolin derivatives were synthesized by Mohamed et al. (2012) for the purpose of anti-HIV examination. They reported that 4-thiophen-2-ylquinazolin derivative ($IC_{50} = 2.1 \mu\text{M}$) emerged as the best anti-HIV among the series with therapeutic index of 1.9×10^5 . Concerning the mechanism of action as anti-HIV, these compounds were reverse transcriptase inhibitors.

Phosphodiesterase (PDE) inhibitors

PDE groups possess numerous variants which are commonly special tissue-expression traits, gene controlling, enzymatic regulation via phosphorylation and regulatory proteins, subcellular localization, as well as collaboration with association proteins (Omori and Kotera, 2007). Mono-substitution on position 6 of quinazoline core was crucial for effective inhibition wherein substituents of priority which possessed tight package and hydrophobicity are: Methoxy (**23b**, $IC_{50} = 0.23 \mu\text{M}$), methyl (**23c**, $0.10 \mu\text{M}$), chloro (**23d**, $0.019 \mu\text{M}$), thiomethyl (**23f**, $0.031 \mu\text{M}$), and cyano (**23p**, $0.090 \mu\text{M}$) functionalities (Takase et al., 1994) as shown in Figure 12. Administration of 3-substitutedquinazolin-2,4-dithione as optimized PDE7 inhibitor improved brain damage and enhanced behavioral aftermath in a permanent middle cerebral artery obstruction (pMCAO) stroke model (Redondo et al., 2012; Susín et al., 2012). Sánchez et al. (2013) reported the inhibitory potencies of quinazoline-4-thione **24** at submicromolar levels against the catalytic domain of PDE7. Small-molecule phosphodiesterase probe investigation

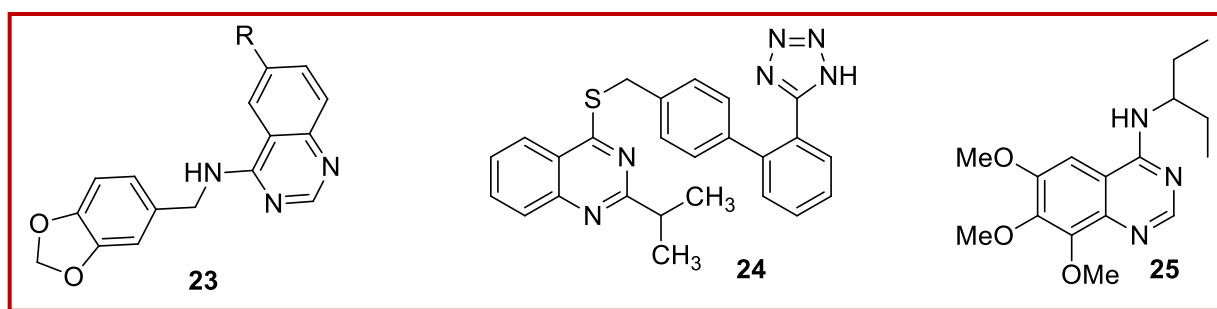


Figure 12: Selected quinazoline motifs with notable PDE inhibitory efficiency

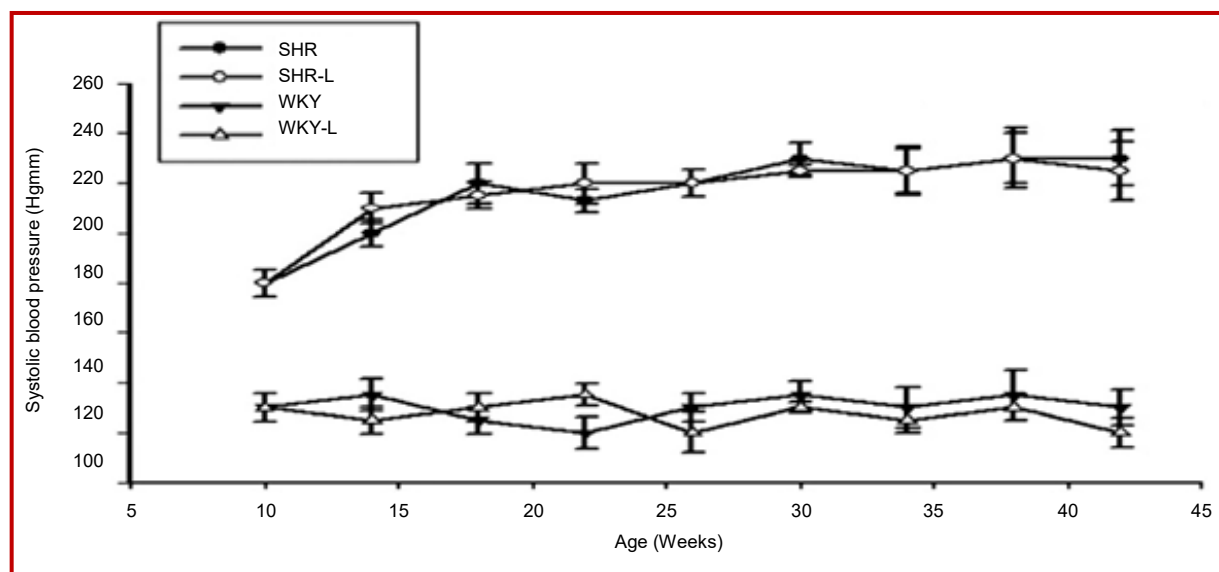


Figure 13: SBP values of normotensive (WKY-C, WKY-L) and hypertensive (SHR-C, SHR-L) rats. Values are means \pm SEM. * $p < 0.05$ (Magyar et al., 2014)

established 4-aminoquinazoline **25** as PDE1 inhibitors that readily cross the blood brain barrier (Humphrey et al., 2014).

Antihypertensive activity

Hypertension is well-known to be major community health challenge among both middle-aged and older population (Deadwania, 2011). The administration of L-2286 in hypertensive animals has been hypothesized to decrease oxidative stress, modulate signaling pathways (PI-3K-Akt, MAP kinases) and attenuate NF- κ B activation, thereby reduces the hypertension-induced adverse vascular changes (Magyar et al., 2014). It is well established that PARP inhibitors can prevent oxidative stress induced tissue damage; they can favorably modulate PI-3-kinase/Akt-1 and MAP kinase pathways, and inhibit NF- κ B activation (Radnai et al., 2012). Although, PARP inhibition did not have any anti-hypertensive effect, it enforces salient safeguarding upon process of change of hypertensive heart disorder to heart failure in SHRs (Magyar et al., 2014; Bartha et al., 2009). A series of novel substituted quinazolin-4(3H)-one derivatives, with acute $LD_{50} > 1000$ mg/kg, showed enhanced bioactivity than standard drug prazosin,

which plays unique role as anti-hypertensive agent through α_1 blocking procedure (Pathak et al., 2014). The effect of L-2286 on systolic blood pressure (SBP) was investigated by Magyar et al. (2014). It was discovered that within 32 week of experimental duration, SBP of hypertensive (SHR-C, SHR-L) rats was remarkably greater as compared with normotensive (WKY) rats (Magyar et al., 2014) and the detail of the finding is shown in Figure 13. Administering L-2286 was noticed to contribute no significant change to SBP of SHR rats during the 32 week treatment period (Magyar et al., 2014).

Melanin-concentrating hormone receptor 1 antagonists

Obesity is a chronic universal epidemic disease (Pokin et al., 2012) which affects a large number of people globally. Over the past 30 years in United States; 60% of adults are currently either obese or overweight (Hurt et al., 2010). Based on recent National Health and Nutrition Examination Survey, it was established that great than one-third of the adults (36%) population in US are obese due to body mass index (BMI) above 30 kg/m^2 (Högberg et al., 2012). Melanin-concentrating hormone (MCH) is a crucial mediator of energy

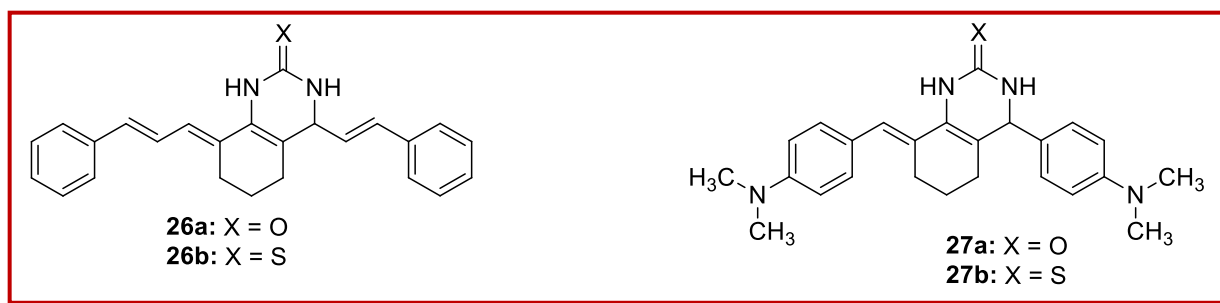


Figure 14: Selected bischalcones with cathepsin inhibitory activity

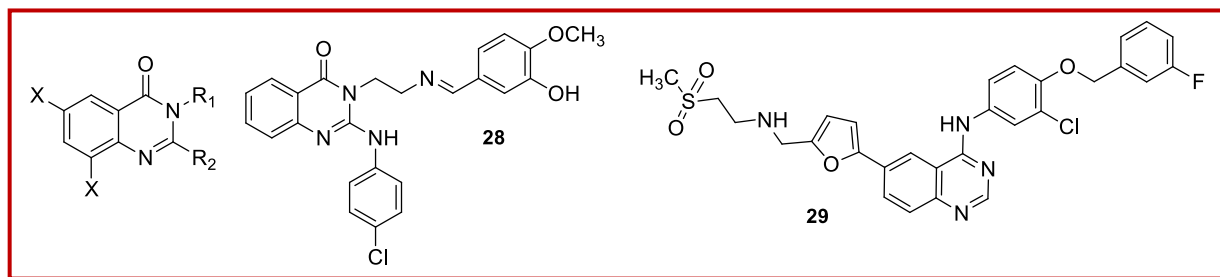


Figure 15: Selected quinazolinone motifs with antibacterial activity

homeostasis (Jeon and Cheon, 2009) which stimulates ingested food in mice upon intra cerebro-ventricular (icv) injection. Hence, Melanin-concentrating hormone receptor 1 (MCHR1) antagonist was reported to be a viable option for the treatment of obesity (Högberg et al., 2012). Melanin-concentrating hormone receptor 1 (MCHR1) antagonising quinazolinone derivatives were authenticated to exhibit remarkable and significant anti-obesity properties (Sasmal et al., 2012). Pharmacokinetic profile showed that oral administration of 30 mg/kg b.i.d. of 4-morpholinyl quinazolinone led to 12% weight reduction within fourteen days in DIOC57BL/6 J mice. 4-Amino-2-cyclohexyl aminoquinazolinone and 4-dimethylaminoquinazolinone were reported to exhibit highly promising anti-obesity for suitable weight loss programme due to their good affinity for human MCHR1 (Kanuma et al., 2005).

Cathepsin inhibitory activity

Bischalcones containing 2(1H)-quinazolinones and 2(1H)-quinazolinethiones analogs were designed and evaluated for inhibitory potential (Khan et al., 2015) against cathepsin B and cathepsin H (Raghav and Singh, 2014). It was found that **26a** (X = O) showed maximum inhibition at 0.1 nM while the thione analog **26b** (X = S) showed maximum inhibition at 0.05 nM which was 2-fold more active than **79** (Raghav and Singh, 2014). Among quinazolinone derivatives, 2,6-bis(4'-(dimethylamino)benzylidene)cyclohexanone **27a** (X = O) was found to exhibit 100% inhibition at 0.1 nM which was four times more active than the thione counterpart **27b** (X = s) with maximum inhibition of 0.025 nM (Figure 14).

Antibacterial activity

Bacterial resistance to existing drugs is a growing

problem in the world. Considerable researches have been performed on the synthesis of new quinazolinone derivatives with potent antibacterial activity against the Gram +ve bacteria via the way they interact within the cell wall and DNA cores (Mohamed et al., 2013). From valuable information gathered by a previous review, 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 (mainly amine or substituted amine) at 4th position of the quinazolinone ring can improve their antimicrobial activities (Jafari et al., 2016). For instance, the primary *in vitro* bioassay at 100 mg/mL against tobacco and tomato bacterial wilt revealed 2,3-disubstituted quinazolin-4-one **28** (Wang et al., 2014) as strong antibacterial agents using turbidimeter test (Wang et al., 2013) According to the findings of Liu et al. (2014), 4,6-disubstituted quinazolinone metabolite, lapatin B **29** showed moderate inhibitory activity against aqua-pathogenic bacteria *Vibrio harveyi* (Figure 15).

Antifungal activity

Three-component design of quinazolinone scaffolds bearing 3-acrylamino side chain was evaluated with the aid of catalytic amount of CeO₂ nanoparticles followed by *in vitro* screening of the targeted quinazolinone for antifungal potential upon selected phytopathogenic fungi (Zhang et al., 2016). The importance of amide was verified and docking study revealed the potential antifungal mechanism of action of the quinazolinone was via chitinase inhibition (Zhang et al., 2016). Among quinazolinone examined upon *Candida*, *Aspergillus* species and *Cryptococcus neoformans*, most of 5-hydroxy-furo[2,3-f]quinazolines showed good antifungal activity by complete inhibition of the growth of *Candida*

and *Aspergillus* species when examined at the MIC value 12.5 µg/mL (Ryu et al., 2012). In another study, a series of benzo[*h*]thiazolo[2,3-*b*]quinazolinone designed and successfully evaluated for their antifungal activity (Gali et al., 2014) while SAR analysis of some tetrazolo[1,5-*c*]quinazoline-5-thione derivatives for their inhibitory activity against *Candida albicans*, show them to be very potent at concentration of 100 µg (Antypenko et al., 2013).

Antiviral activity

Viral diseases threaten latest therapeutic breakthrough because of high mutation rates found among viruses, which empower them to escape immune systems and develop resistance to old existing commercially available drugs (Al-Salahi et al., 2016; Jaime et al., 2013). Benzoquinazoline compounds have been reported to exhibit an interesting antiviral activity which was why evaluation of recently prepared 2-thioxo-based benzo[*g*]quinazolin-4(3*H*)-ones was reported against herpes simplex and coxsackie virus (Al-Salahi et al., 2016). Systematic evaluation of a series of thioquinazoline against Tobacco Mosaic Virus (TMV) led to the discovery of quinazolin-4-yl based prop-2-en-1-one that exhibited encouraging protection properties (EC₅₀ = 138.1 µg/mL) upon TMV *in vivo*, which was over three times more active than Ribavirin (EC₅₀ = 436.0 µg/mL) standard (Wan et al., 2015). A series of quinazoline prepared via Schiff bases formation were screened against herpes simplex virus-1 (KOS), virus-2 (G) and vaccinia virus (Ali et al., 2007), wherein (E)-3-((2-hydroxybenzylidene) amino)-2-phenyl quinazolin-4(3*H*)-one emerged as the most promising antiviral motif against the entire tested virus (Kumar et al., 2010). It has also been reported that high indicator of the antiviral activity of *N*-methyl-2-((2-oxo-3-phenyl-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-6-yl)thio)acetamide (Kolavenko et al., 2013) bearing-adamantane against influenza type A H3N2 was due to insertion of carcass amine.

Anti-oxidant activity

Reactive oxygen species (ROS) which include ¹O₂, O₂⁻ and OH free radicals and hydrogen H₂O₂ were commonly produced as side products from either biochemical interaction or through exogenous factors (Sergey et al., 2010). ROS play a vital role as far as aging and pathogenetic traits of age responsive diseases are concerned (Vagdevi et al., 2012; Manasa et al., 2011). An array of quinazoline-2,4-dione Schiff bases were reported to possess over 50% inhibitory efficiency upon DPPH (IC₅₀ = 25-50 µg/mL) and most of the compounds showed a dose dependent behavior in FRAP assay (Vagdevi et al., 2012). 2-Methyl-3-(pyrrolidin-2-ylidene amino)quinazolin-4(3*H*)-one was reported to be much higher in activity compared with ascorbic acid standard (Al-Azawi, 2016). It also served as a powerful and highly resourceful scavenger against DPPH and

Nitric oxide (Al-Azawi, 2016).

Antidiabetic activity

Due to widespread nature of diabetes mellitus globally, a great deal of effort in applied research is on-going for the discovery of new heterocyclic molecules as anti-diabetic agents with a well detailed information on its mode of action (Islam and Loot, 2009; Cheng, 2005). Sublethal dosage testing for 1-thioxo-1,2,7,8,9,10-hexahydro-3*H*-pyrimido[1,6-*a*]quinazolin-3-one showed that it has remarkable potential in (n-STZ) diabetic male as antihyperglycemic agent (Ahmed et al., 2012). The (n-STZ) diabetic male model used in the study acquired biological and pathological diagnostic sign related to the type 2 diabetes in mankind (Islam and Loot, 2009). The one-pot synthesis of a series of quinazolin-4-one in the presence of [BMIM⁺][BF₄⁻] as green and reusable catalyst was reported and the attempted investigation of antidiabetic activity showed 3-(5-bromopyridin-2-yl)quinazolin-4(3*H*)-one to be the most active in this series (Dongamanti et al., 2012).

Antithrombosis activity

Activated factor X (FXa) is a formidable player in thrombin generation through coagulation cascade responsibility during the process of atrial fibrillation (Bukowska et al., 2013). Activated factor X FXa and tachyarrhythmia act synergistically to increase expression of protease-activated receptors and inflammatory mediators (Bukowska et al., 2013). Some quinazoline derivative exerted inhibition of inflammation via this route. Elinogrel **30**, the structure shown in Figure 16 is a marketed available antithrombosis drug containing quinazolinone moiety (Nayyar and Arpanarana, 2011).

Structure-activity relationship study (SAR)

The SAR study carried out on the selected molecules showed that electron-withdrawing and electron-donating could inform a synthetic chemist about the choice of a suitable substitution pattern. Some heterocyclic moieties attachments are the basic templates responsible for the regulation of biological activity of targeted quinazoline derivative synthesized. 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 (Wang and Gao, 2013). Various 2,4,6-trisubstituted positions of quinazoline derivatives have been evaluated as essential pharmacophoric placement for the enhancement of bioactivity (Chandrika et al., 2009). In addition, the substitution on the pyrimidine ring shows more of an antimalarial activity variation of a quinazoline derivative (Khan et al., 2014). Triazolo-fused quinazoline **31** with morpholinyl in 2-position and chloro on 6-position was the most potent antimicrobial scaffold among the series synthesized by Jantova et al, (2005). Presence of electron donating

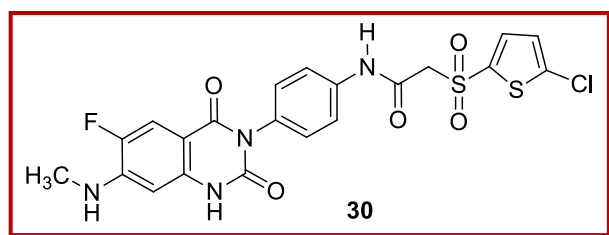


Figure 16: Elinogrel as selected quinazoline-based antithrombotic marketed drug

diamine at 4-position increased the anti-inflammatory efficacy of **32** (Lin et al., 2010). Polar functionality like hydroxamate when inserted at position-4 of quinazoline templates, core was reported to probably provide a very active HDACi/HER2i hybrid as seen in **33** which was the most potent HDAC inhibitor among the quinazolines designed and synthesized by Zhang et al. (2013b). Some structural representations of quinazoline templates for SAR study are as shown in Figure 17.

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. Quinazoline derivatives are considered as important precursors for the synthesis of various physiologically significant and pharmacologically utilized molecules. 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 occurring 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 therefore projected as valuable tools for the development of novel pharmacological entities treatment of diverse infectious diseases and disorder in the therapeutic medicine.

Conflict of Interest

Authors hereby declare that there are no conflict of interest as regard to this work.

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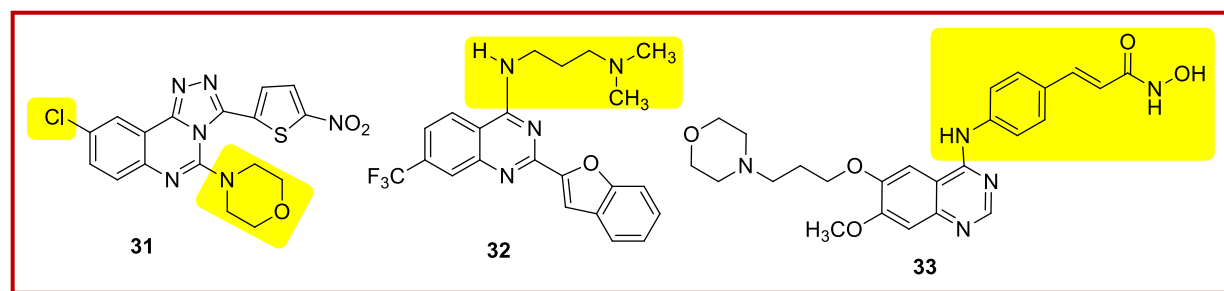


Figure 17: Representative quinazoline motifs for SAR study

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