Synthetic approaches and potential bioactivity of different functionalized quinazoline and quinazolinone scaffolds

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Drug discovery and optimization constitutes one of the most important targets in medicinal chemistry. Because of their wide bioactivity spectra, nitrogen-containing heterocycles have received significant attention in many bio(organic) studies. The current review is a simple summary of different environmentally benign synthetic procedures that afford a variety of quinazoline and quinazolinone scaffolds with promising biological potential. The molecular modeling of various classes has also been discussed to elucidate the molecular reasons that led to the observed inhibition profile of different protein kinases, including which amino acids in their active sites would be involved in the anticipated bonding interactions. Furthermore, this article aims to investigate which classes deserve further development to get more specific and more potent quinazoline and quinazolinone candidates in various biological targets.

Keywords:
biological activities, molecular docking, protein kinase inhibitors, quinazoline, quinazolinone, synthesis

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Introduction

Quinazoline **1** is 1,3-diazanaphthalene. This nucleus is also called 5,6-benzopyrimidine or benzo[*a*] pyrimidine or phenmiazine [1]. Its 4-oxo derivative is named 4(3*H*)-quinazolinone **2** (Fig. 1) [2]. Depending on the wide spectra of their different pharmacological activities, both nuclei have attracted considerable attention from many scientists and chemists worldwide. They exhibit antimalarial [3], antimicrobial [4], anti-inflammatory [5], anticonvulsant [6], antihypertensive [7], antidiabetic [8], and antitumor activities [9–11]. At the same time, various quinazoline derivatives are considered, such as inhibitors of various forms of cellular phosphorylation [12], in addition to their essential activities in the central nervous system (CNS), such as ligands for benzodiazepine and γ-aminobutyric acid receptors [13]. Also, many quinazoline derivatives act as DNA-binding agents or as effective adrenergic blockers [14].

Many quinazolinone derivatives also constitute the building blocks for about 150 natural alkaloids isolated from various classes of the plant kingdom, from microorganisms, and from animals (Fig. 2). Earlier studies conducted in the 1950s and 1960s led to the discovery of febrifugine, a quinazolinone alkaloid, which possesses antimalarial potential, from the Chinese plant aseru (*Dichroa febrifuga* Lour) [15].

Chemistry of quinazolines

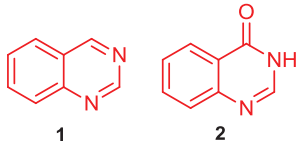
Gabriel [16] was the first scientist to prepare quinazoline nucleus in the laboratory in 1903. Widdege [17] was the first scientist to propose the name quinazoline (German: chinazolin) for this nucleus on the basis of its appearance as an isomer with the quinoxaline ring [18].

The synthesis of various compounds containing quinazoline as the main nucleus is largely based on the substitution patterns on the 1,3-diazine moiety of the system.

4(3*H*)-Quinazolinones

The facile preparation of quinazolin-4(3*H*)-one (**4**), which involves heating the logical starting material

Figure 1



1 2

Chemical structures of quinazoline **1** and 4(3*H*)-quinazolinone **2**.

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anthranilic acid (**3**) with excess formamide in an open container at 120°C, was known as Niementowski reaction (Fig. 3) [19]. In addition, Ahmed *et al.* [20] used formyl anthranilamide (**5**) for the preparation of **4** by means of intramolecular condensation reaction (Fig. 3).

The 7-chloro-substituted derivative (**7**) [21] has been prepared through condensation of 4-chloroanthranilic acid amide (**6**) with triethyl orthoformate (Fig. 4).

2-Substituted-4(3*H*)-quinazolinones and quinazolines

The general method for producing the cinnamamide derivative **10** involves the treatment of 2-aminobenzonitrile (**8**) with 3-phenyl cinnamoyl chloride (**9**). Under alkaline conditions, intramolecular cyclization was carried out to afford 2-styryl-4(3*H*)-quinazolinone (**11**) [22] (Fig. 5). This procedure was tolerated to a wide range of different substituted benzene rings, and in most cases the intermediate *N*-(2-cyanophenyl)cinnamamide (**10**) could be isolated.

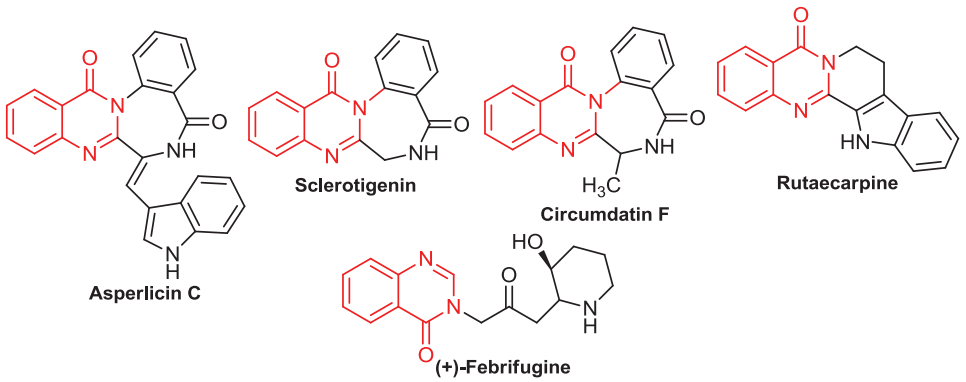
Refluxing of anthranilamide (**12**) with aryl, alkyl, or heteroaryl aldehydes or ketones (**13**) in 2,2,2-trifluoroethanol in the absence of catalysts led to the formation of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones (**14**) in excellent yields. The characteristic physiochemical properties of fluorous solvents, such as low nucleophilicity, high polarity, and high ability of hydrogen bond donation, has led to their utilization in organic reactions (Fig. 6) [22].

Microwave (MW) conditions were used by Rad-Moghadam and Mohseni [23] to synthesize 2-substituted-4(3*H*)-quinazolinones (**16**). This strategy involved the reaction of anthranilic acid (**3**), ammonium acetate, and orthoesters (**15**) to yield the desired products (Fig. 7).

Complete conversion of anthranilic acid (**3**) to 2-substituted-4(3*H*)-quinazolinones was gained in efficient yields (75–84%) under MW conditions over 10 min at a temperature of 200°C at 200 W. Heating anthranilic acid (**3**), acetic anhydride, and formamide in a sealed tube at 200°C (200 W) for 10 min leads to rapid decomposition of formamide during the interaction of anthranilic acid and anhydride. The formed ammonia (*in situ*) reacts with the benzoxazine derivative (**17**). An efficient yield of 3-methylquinazolin-4-one (**18**) was achieved after purification (Fig. 8) [24].

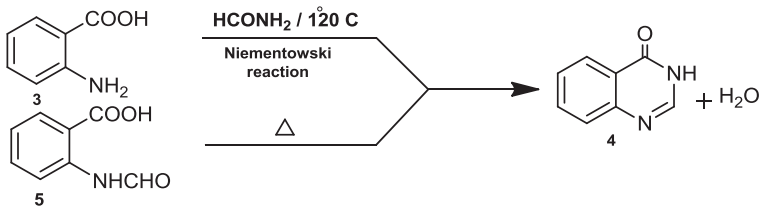
Abdel-Jalil *et al.* [25] revealed that the intermediate Schiff's bases (**19**) were synthesized in good yields within 3 h at 70 °C through treatment of anthranilamide (**12**) with suitable aldehydes in ethyl

Figure 2



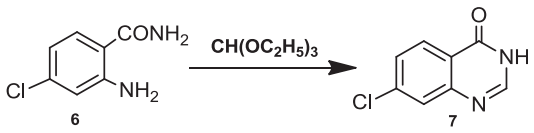
Structures of alkaloids incorporating quinazolinone frameworks.

Figure 3



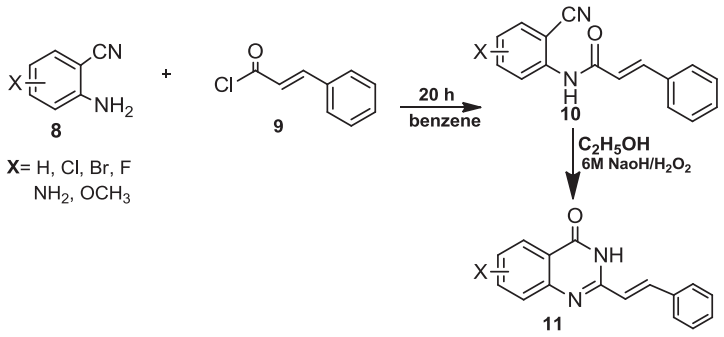
Preparation of 4(3*H*)-quinazolinone using anthranilic acid or formyl anthranilamide.

Figure 4



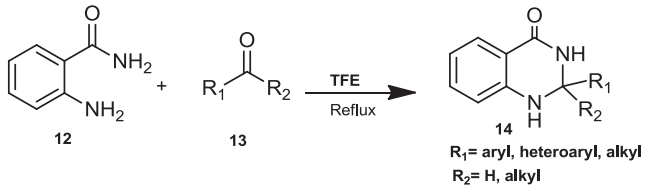
Preparation of 7-chloroquinazolin-4(3*H*)-one.

Figure 5



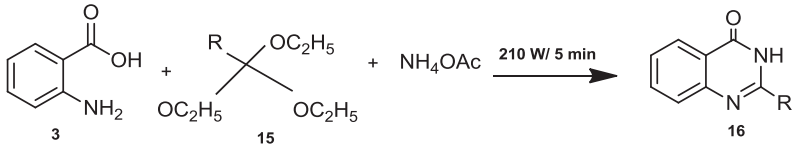
Preparation of 2-styryl-4(3*H*)-quinazolinone derivatives.

Figure 6



Preparation of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones. TFE, 2,2,2-trifluoroethanol.

Figure 7



Preparation of 2-substituted-4(3*H*)-quinazolinone derivatives.

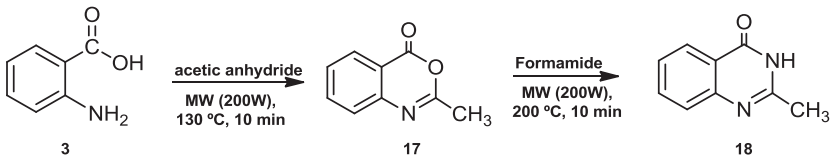
alcohol. The conversion of Schiff's bases to the corresponding 2-substituted quinazolinones (**16**) was carried out within 2 h in refluxing ethanol containing three equivalents of copper chloride. However, these quinazolinones (**16**) could be also obtained in 88% yield through a one-step reaction procedure by refluxing ethanolic solution of anthranilamide (**12**), the appropriate aldehyde, and copper chloride for 2–3 h (Fig. 9).

Erba *et al*. [26] introduced a three-component reaction to obtain 2-alkylquinazolines (**22**). First, a suitable aldehyde was allowed to react with morpholine to form the intermediate (**20**). In the second step, compound **20** was treated with an aryl azide to obtain the 1,2,3-triazoline derivatives (**21**) in good yields. Further, the triazolines (**21**) were exposed to an ethanolic solution saturated with ammonia in a sealed vessel at 150°C to afford the desired quinazoline products (**22**). Alternatively, the same compounds (**22**) could be obtained when the triazolines (**21**) were treated with ammonium acetate in boiling toluene within half an hour. The intramolecular cyclization of the triazolines afforded the 2-alkylquinazoline derivatives (**22**) in 92–95% yields (Fig. 10).

Kotsuki *et al.* [27] developed condensation of cyano-activated and nitro-activated *o*-fluoro-benzaldehydes (**23**) with amidine (**24**) to afford different substituted quinazoline derivatives (**25**) in promising yields. Cyclization of the imine with the aldehydic functional group occurred. Nucleophilic substitution of the fluorine atom was carried out leading to intramolecular cyclization to afford the quinazoline derivatives (**25**). The reaction was performed under reflux in acetonitrile containing potassium carbonate in the presence of powdered molecular sieves. Chromatographic purification was carried out for the crude products (Fig. 11).

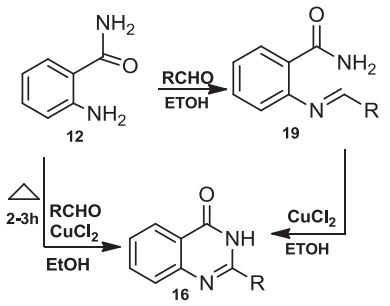
The amino-quinazolin-4(3*H*)-one (**28**) was derived by Hess *et al.* [28]. It was synthesized by means of the reaction of the corresponding methyl anthranilate (**26**) with an excess amount of guanidine (**27**) in ethyl alcohol containing sodium ethoxide. The yield of this reaction was moderate (Fig. 12).

Figure 8



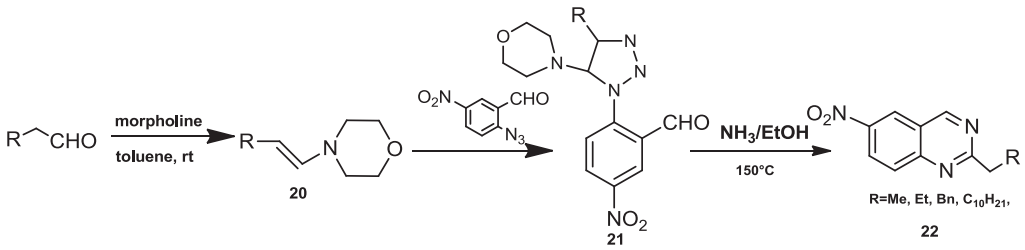
Preparation of 3-methylquinazolin-4-one under microwave (MW) conditions.

Figure 9



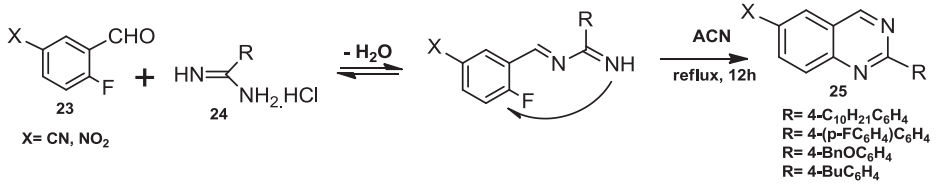
Preparation of 2-substituted quinazolinones.

Figure 10



Preparation of 2-alkylquinazoline derivatives.

Figure 11



Preparation of different substituted quinazoline derivatives.

3-Substituted-4-quinazolinones

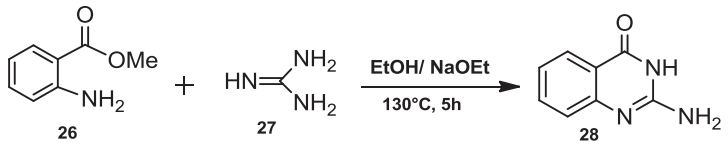
Clark and Wagner [29] have reported the use of isatoic acid anhydride (**29**) for the preparation of 3-substituted-4(3*H*)-quinazolinone derivatives (**30**) by heating with primary amines and triethyl orthoformate (Fig. 13).

Majo and Perumal [30] developed the 3-substituted-4(3*H*)quinazolinones (**34** and **35**) in which the Vilsmeier reagent (chloromethyleneiminium salt) (**32**) reacted with 5-substituted-2-amino benzoic acid derivatives (**31**) to give the corresponding acid chlorides (**33**), which reacted through two possible routes: A and B (Fig. 14).

4-Substituted-quinazolines

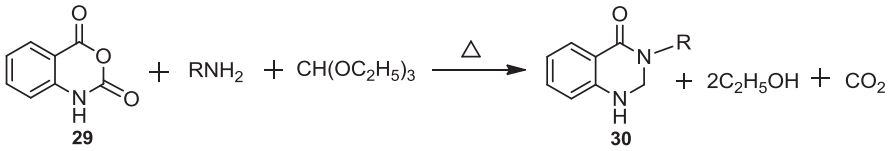
Because of the reported high biological potential of 4-arylaminoquinazolines as anticancer agents, there has

Figure 12



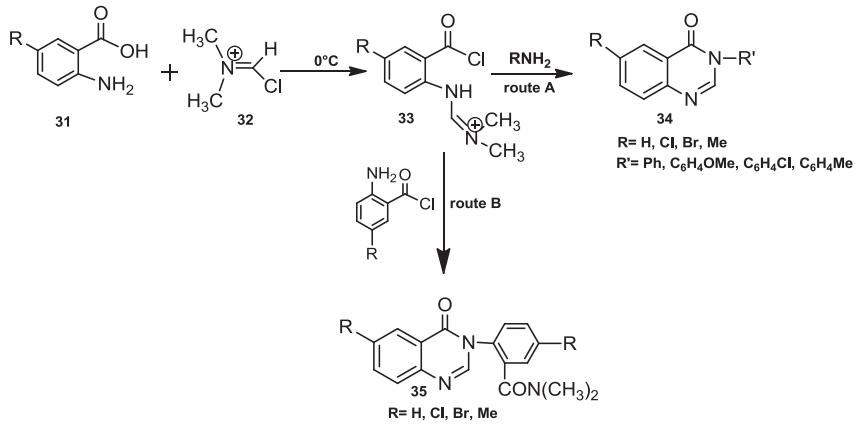
Preparation of 2-amino-quinazolin-4(3*H*)-one.

Figure 13



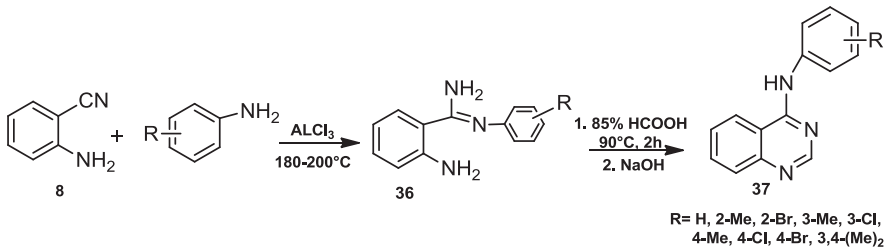
Preparation of 3-substituted-4(3*H*)quinazolinone derivatives.

Figure 14



Preparation of 3-substituted-4(3*H*)quinazolinone derivatives.

Figure 15



Preparation of 4-arylaminoquinazoline derivatives.

been renewed interest in their syntheses [31]. Amidines (**36**) were readily formed by the interaction of 2-aminobenzonitrile (**8**) with different substituted anilines and anhydrous aluminum chloride. It was observed that the highest yield of the amidine intermediates **36** was achieved by the use of excess amounts of suitable aniline and aluminum chloride. Limited production of the intermediates (**36**) was obtained from the pattern of aromatic substitution on the aniline ring. 2-Aminobenzonitrile (**8**) did not react with 3,4-dichloroaniline or nitroanilines possibly because the nucleophilicity of the amino functionality is minimized in each case. Good yields (70–92%) of the 4-arylaminoquinazoline derivatives (**37**) were achieved when the 2-amino-*N*-arylbenzamides (**36**) were heated with 85% formic acid (Fig. 15) [32].

An efficacious method for the preparation of 4-anilinoquinazolines (**40**) was reported by Tsou *et al.* [33]. Condensation of 5-nitroanthranilonitrile (**38**) with dimethylformamide-dimethyl acetal yielded compound **39**. When compound **39** was heated with 3-bromoaniline in acetic acid it afforded the target quinazoline derivative (**40**) in an outstanding yield. This method is beneficial as the synthesis of the quinazoline ring system and its conjugation with the 4-anilino moiety take place in the same step (Fig. 16).

The treatment of (*E*)-*N*′-(2-cyano-3-fluorophenyl)-N,N-dimethylformimidamide (**41**) with 2-chlorobenzylamine (**42**) to obtain the quinazoline compound **43** using MW irradiation was reported by Yoon *et al.* [34] (Fig. 17).

2,3-Disubstituted-4(3*H*)-quinazolines

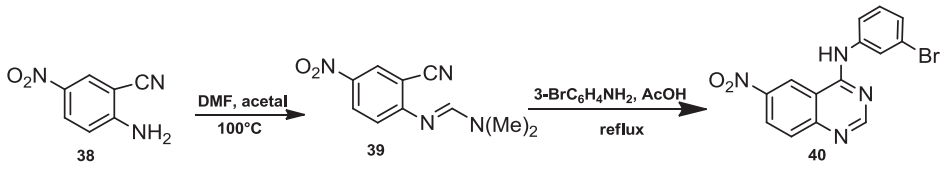
Ager *et al.* [35] obtained 2,3-disubstituted-4(3*H*)-quinazolinone derivatives (**45**) through the treatment of *N*-acylanthranilic acid (**44**) with the appropriate aryl amines in the presence of phosphorous oxychloride (Fig. 18).

Furthermore, a group of researchers [36] reported that the 3-substituted-2-metyl quinazolinones (**47**) were prepared by the reaction of methyl-2-acetamido benzoate (**46**) with the desired amine in the presence of trimethyl aluminum in 1,2-dichloroethane (Fig. 19).

Benzoxazinone derivatives are the most common intermediates in the formation of 2,3-disubstituted quinazolinone derivatives. Welch *et al.* [37] stated that refluxing of anthranilic acid (**3**) with acetic anhydride in acetic acid yielded 2-methyl-4*H*-benzo[d][1,3]oxazin-4-one (**17**), which was heated with amines in acetic acid or ethanol to yield the corresponding quinazolinones (**48**) (Fig. 20).

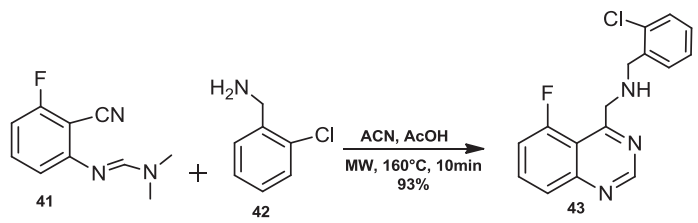
Dandia *et al.*[38] disclosed that the 4-benzoxazinone derivative (**50**) was synthesized *in situ* by the cyclodehydration of 2-phenylacetylamino benzoic acid (**49**) with acetic anhydride using inorganic solid supports. Also, the condensation of the 4-benzoxazinone derivative (**50**) with various para/meta/ortho-substituted anilines has been studied to obtain the desired derivatives (**51** and **52**) (Fig. 21).

Figure 16



Preparation of 4-anilinoquinazoline derivatives.

Figure 17

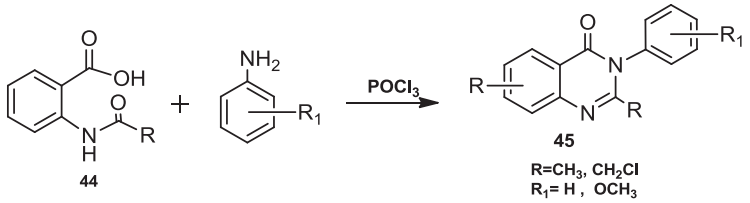


Preparation of *N*-(2-chlorobenzyl)-1-(5-fluoroquinazolin-4-yl)methanamine derivatives. MW, microwave.

Moreover, a rapid one-step MW reaction by cyclocondensation of anthranilic acid (**3**), phenyl acetyl chloride (**53**), and different substituted aniline derivatives for the synthesis of quinazoline derivatives **54** was documented by Dandia *et al.*[38]. The reaction yield was 87–92% (Fig. 22) [38].

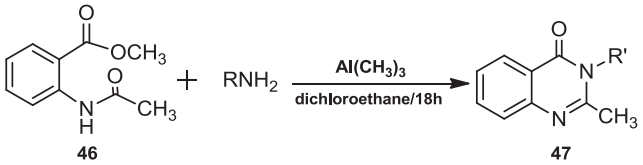
Lee *et al.* [39] developed a facile method for the formation of 3-substituted-2-cyano-4(3*H*)-quinazolinone compounds (**57**) in moderate to good yields by the treatment of primary alkylamines with the intermediate derivative (**56**). The latter compound was synthesized by the treatment of methyl anthranilate (**26**) with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) (**55**) in pyridine. Its yield was 50%. The cyano group of quinazolinone products (**57**) could be replaced by different nucleophiles to furnish the corresponding 2-substituted quinazolinone derivatives in high yields. This leads to the synthesis

Figure 18



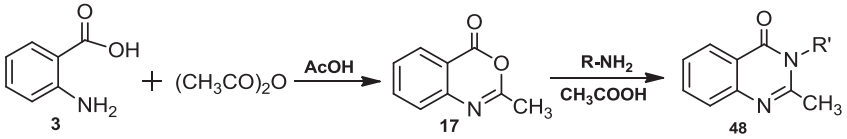
Preparation of 2,3-disubstituted-4(3*H*)-quinazolinone derivatives.

Figure 19



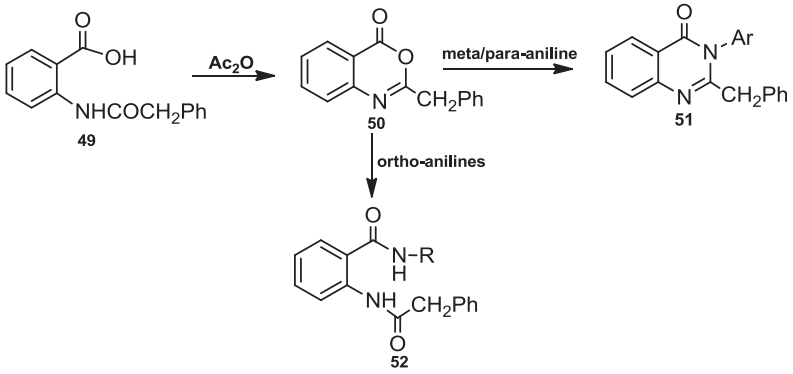
Preparation of 3-substituted-2-metyl quinazolinones.

Figure 20



Preparation of 2,3-disubstituted quinazolinone derivatives.

Figure 21



Preparation of 3-substituted-2-benzylquinazolin-4(3*H*)-one derivatives.

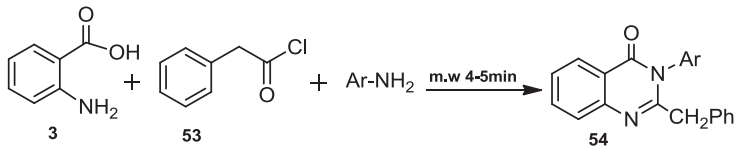
of new quinazoline systems rapidly and efficiently (Fig. 23).

2,4-Disubstituted-4(3*H*)-quinazolinones and quinazoline

The synthesis of 4-aminoquinazolines (**58**) using MW irradiation was documented by Seijas *et al.* [40]. This reaction was performed by the treatment of the cyanoaromatic derivatives with anthranilonitrile (**8**) in a MW oven. 2-(Thiophen-2-yl)quinazolin-4-amine was gained at a high yield by heating anthranilonitrile, 2-thienylnitrile, and potassium tert-butoxide in a test tube for 60 s. A remarkable decrease in reaction time, the absence of solvents, and the use of a base in a catalytic amount are attractive features of this method (Fig. 24).

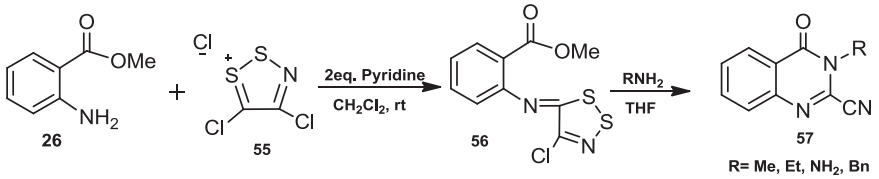
Mizuno *et al.* [41] reported the preparation of 2,4-dihydroxyquinazoline derivatives using various 2-aminobenzonitrile compounds **8** and carbon dioxide containing 1,8-diazabicyclo[5,4,0]undec-7-ene under

Figure 22



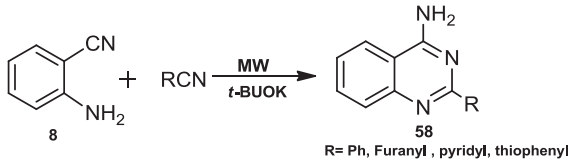
Preparation of 3-substituted-2-benzylquinazolin-4(3*H*)-one derivatives.

Figure 23



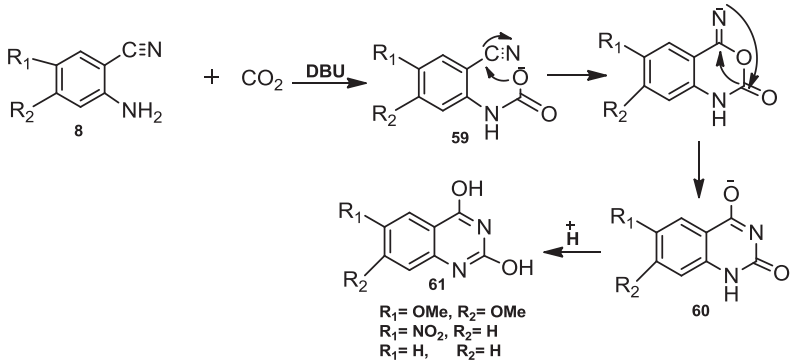
Preparation of 3-substituted-2-cyano-4(3*H*)-quinazolinone derivatives. THF, tetrahydrofuran.

Figure 24



Preparation of 4-aminoquinazoline derivatives. MW, microwave; t-BUOK, potassium tert-butoxide.

Figure 25



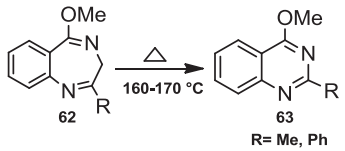
Preparation of 2,4-dihydroxyquinazoline derivatives. DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene.

mild conditions. The reaction was carried out using a suitable base to synthesize the carbamate salt (**59**). In the subsequent step the oxygen of carbamate moiety attacked the nitrile group, leading to nucleophilic cyclization. Then, rearrangement took place to produce the intermediate (**60**), which was protonated to give the target 2,4-dihydroxyquinazolines (**61**) (Fig. 25).

The thermolysis of 5-methoxy-(3*H*)-1,4-benzodiazepines to furnish 4-methoxyquinazoline derivatives was studied by Kaname *et al.* [42]. Ring contraction was the proposed mechanism. The 4-methoxyquinazoline derivatives (**63**) were the only obtained products in moderate yields (41–46%) upon heating the 5-methoxy-(3*H*)-1,4-benzodiazepines (**62**) in refluxing diphenyl ether at 160–170°C for 6 h (Fig. 26).

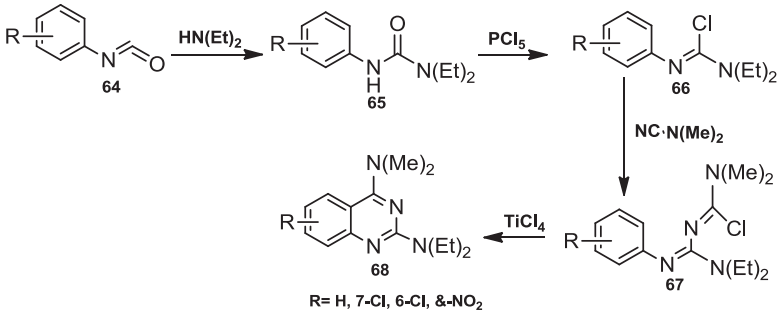
Zielinski *et al.* [43] developed a procedure to synthesize dimethylquinazoline-2,4-diamine derivatives by treating chloroamidines with dialkylcyanamides. Reaction of various phenyl isocyanate derivatives (**64**) with *N*,*N*-diethylamine led to the formation of the substituted urea derivatives (**65**), which were subsequently chlorinated with phosphorus pentachloride to produce the corresponding compounds (**66**). As an example, 2-(*N*,*N*-diethylamino)-4-(*N*,*N*-dimethylamino)quinazoline (**68**) was synthesized in 79% yield by cyclization of compound **67**, which was obtained by the treatment of

Figure 26



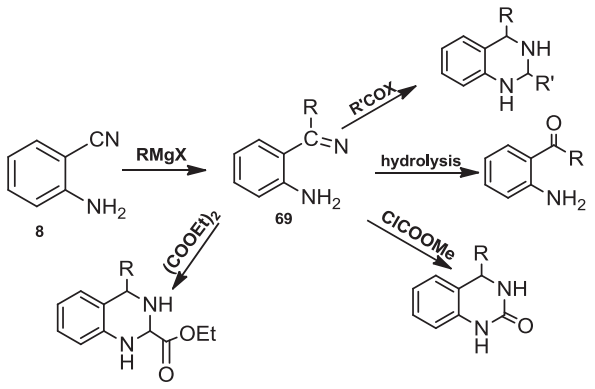
Preparation of 4-methoxyquinazoline derivatives.

Figure 27



Preparation of dimethylquinazoline-2,4-diamine derivatives.

Figure 28



Preparation of various 2,4-disubstituted quinazoline derivatives.

chloroamidine (**66**) with *N*,*N*-dimethylcyanamide (Fig. 27).

The reaction of various Grignard reagents with 2-aminobenzonitrile (**8**) resulting in the formation of intermediates (**69**) was demonstrated by Bergman *et al.*[44]. The formed derivatives (**69**) were very important for obtaining many types of quinazoline derivatives. Upon their cyclization with acid chlorides, anhydrides, and formates they formed the corresponding quinazoline derivatives in moderate to good yields. This general method for the preparation of various 2,4-disubstituted quinazoline derivatives is highly flexible and useful (Fig. 28).

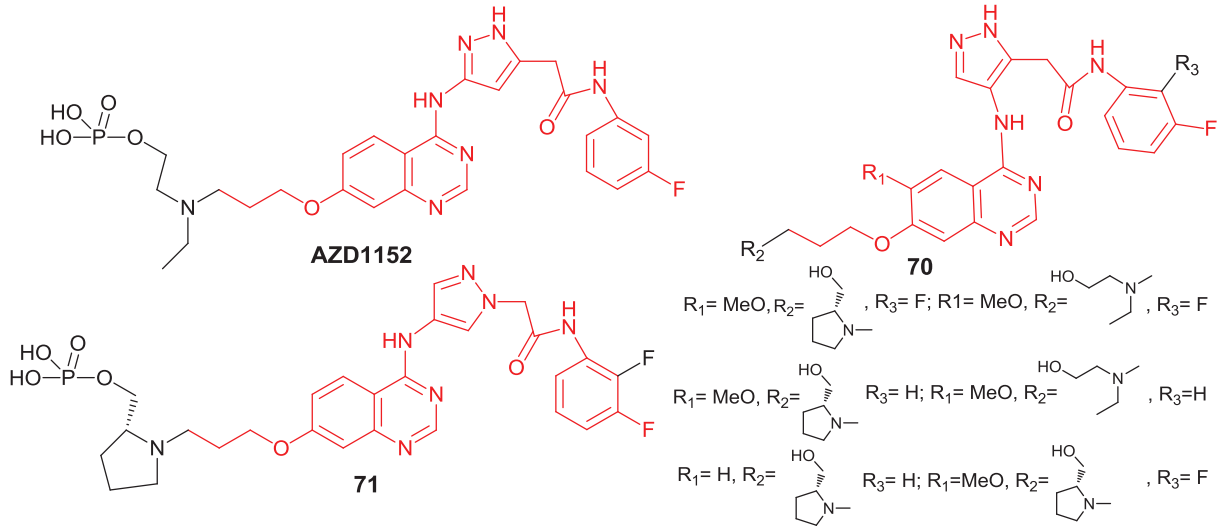
Pharmacological applications

Anticancer activity

Aurora proteins inhibitors

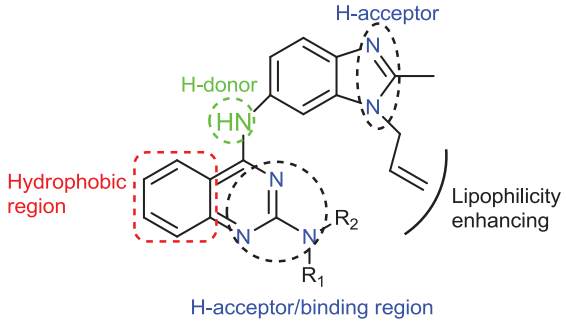
Aurora proteins constitute a small class of serine/threonine kinases that are generated during the period of mitosis. They play important functions in chromosomal segregation and cytokinesis. There are three types of aurora kinases formed in human beings: aurora A, B, and C. These protein kinases have been recently considered attractive drug targets because of their importance in mitosis and their irregular overexpression in cancer cells [45]. Inhibition of both aurora A and aurora B causes the formation of different cellular phenotypes. Synthesis of a set of 5-acetanilide-3-aminopyrazole(3-pyrazole)-substituted quinazoline derivatives that showed high selectivity for aurora B over aurora A resulted in the synthesis of AZD1152 (Fig. 29). AZD1152 has exhibited significant anticancer activity in different preclinical models and was recently used in phase I clinical experiments [46]. Taking into consideration the structural characteristics of AZD1152, a novel class of 1-acetanilide-4-aminopyrazole-substituted quinazoline compounds (compounds **70**) was formed by Foote *et al.* [46].

Figure 29



Structures of quinazoline derivatives as aurora protein inhibitors.

Figure 30



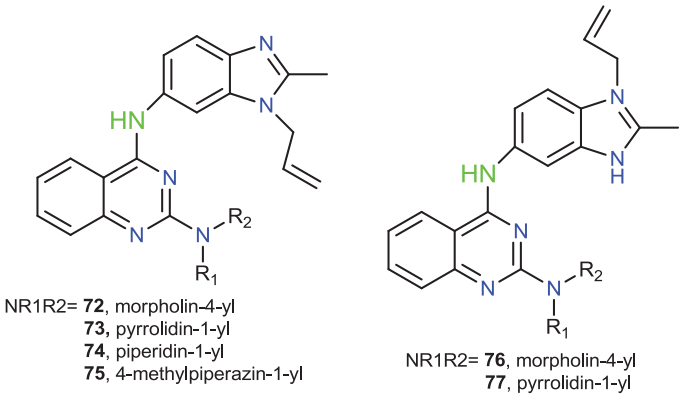
Proposed hypothetic model for hybrid compounds.

In summary, it has been observed that the 4-pyrazole derivatives exhibited significant inhibition against aurora B kinase, whereas less activity was observed against aurora A. Potent cellular activities were achieved by the presence of fluoro groups favorably at C_2 and C_3 of the phenyl ring. The conjugation of different basic side chains with the quinazoline ring system at C_7 also delivered high activity. The displacement of the methoxy group with a proton at quinazoline-C_6 enhanced the selectivity for aurora B over aurora A. The cellular potency for the 4-pyrazole derivatives is significant and even higher than that of the corresponding 3-pyrazole analogs. Many 4-pyrazole derivatives exhibited cellular EC_{50} less than 10 nmol/l and some, such as compounds **70**, showed cellular EC_{50} less than 1 nmol/l (Fig. 29). The optimized compound **71** exhibited potency at doses less than that in other reported series in preclinical in-vivo models (Fig. 29).

Topoisomerase (I and II) inhibitors

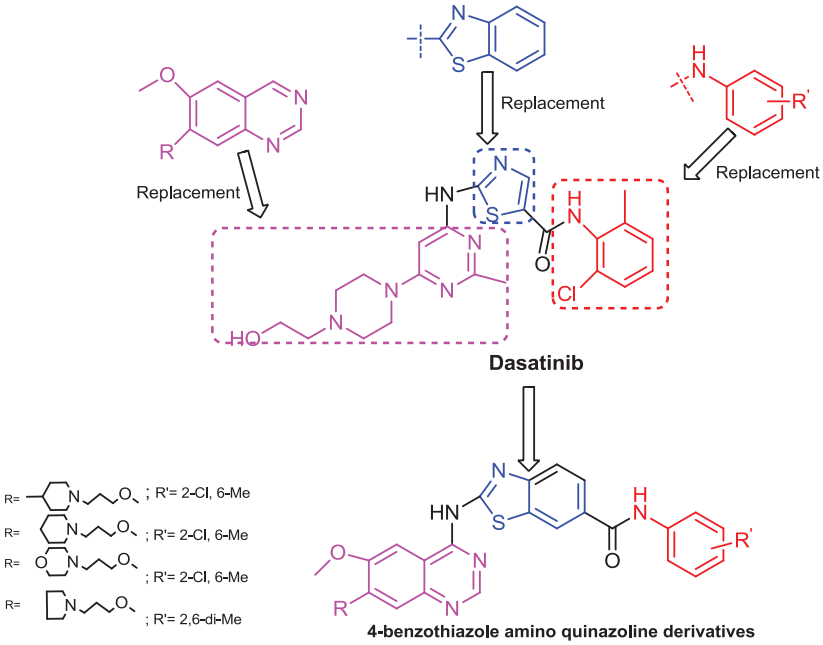
Benzimidazole–quinazoline hybrids, substituted with various secondary amines, demonstrate the effects of electron-donating and electron-accepting nitrogen groups within the groups [47,48]. Lipophilicity of polar compounds, an important property for the activity of different drugs, increases because of the attachment of alkyl or allyl functionalities to the benzimidazole ring and aryl moieties to the quinazoline ring (Fig. 30).

Figure 31



Structures of hybrids of benzimidazole and quinazoline analogs.

Figure 32



Novel 4-benzothiazole amino quinazoline derivatives.

Novel regioisomeric hybrids (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)–(2-substituted-quinazolin-4-yl)-amine derivatives (**72–75**) and (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)–(2-substituted-quinazolin-4-yl)-amine derivatives (**76–77**) were derived by Sharma *et al.*[47] and evaluated as novel compounds for their anticancer activity. Preliminary in-vitro antitumor screening proved that the derivatives **72** and **73** had potent inhibitory effect (>60%) for the growth of most of the tested tumor cell lines, whereas all the compounds exhibited selective activity toward the renal cancer cell line A498. Also, the anticancer evaluation confirmed that (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)–(2-amino-quinazolin-4-yl)-amine derivatives (**72**, **73**, and **75**) are more effective anticancer compounds than their regioisomeric analogs (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)–(2-aminoquinazolin-4-yl)-amine derivatives **76** and **77** (Fig. 31). Molecular docking studies of compound **73** indicated that the formation of hydrogen bonds with the active sites of ribonucleotide reductase, topoisomerase I, and topoisomerase II also enhanced its potency. These benzimidazole and quinazoline hybrids could be further used as anticancer compounds of significant potency. Further derivatization and optimization studies of the anticancer profiles of these compounds are currently ongoing.

Dual Src/Abelson murine leukemia viral oncogene homolog 1 (Abl) kinase inhibitors

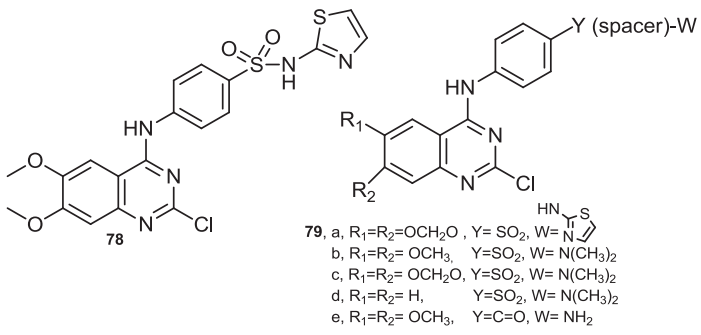
The design and preparation of various new 4-benzothiazole amino quinazoline analogs were carried out by Cai *et al.* [49] (Fig. 32). The synthesis of these novel hybrids depends on the structure–activity relationship (SAR) analysis of dasatinib, which was used as the leading compound, and also on the basic drug design principles of ring addition and combination.

In-vitro cytotoxic activity evaluation by MTT-based assay was carried out for all target compounds. The activity was investigated against six human cancer cell lines (HCT-116, DLD1, K562, U937, A549, and NCI-H661). The obtained data showed that most of the tested derivatives exhibited a remarkable growth inhibition against the six cell lines compared with the parental dasatinib. In addition, the target compounds were tested as Src and Abl kinase inhibitors. The enzyme inhibitory assay showed that the derivatives bearing 2-methyl piperidine moiety attached to the quinazoline ring are the most potential dual Src/Abl kinase inhibitors. Thus they are potential lead ligands to be prepared and optimized as alternatives for the current dasatinib therapy or for patients who show imatinib resistance, potentially by simultaneously blocking multiple receptor tyrosine kinase (RTK) signaling pathways (Fig. 32).

Epidermal growth factor receptor and vascular endothelial growth factor receptor 2 inhibitors

Novel 2-chloro-4-anilino-quinazolines were designed and examined as inhibiting agents for both epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 2 (VEGFR-2) protein kinases [50]. It has been documented that EGFR and VEGFR-2 are validated targets in cancer therapy, and combined inhibition might be synergistic for both antitumor activity and resistance prevention. The results of the enzyme inhibitory test proved that 2-chloro-4-anilino-quinazoline derivatives produced potential activity against both EGFR and VEGFR-2. Compound **79e** was nearly seven times more active against VEGFR-2 and nearly 11 times more active against EGFR in comparison with the prototype **78** that was previously synthesized by Abouzid and Shouman [51]. SAR and molecular docking studies investigated the pharmacophoric moieties for both EGFR and VEGFR-2 protein

Figure 33



Structures of novel 2-chloro-4-anilino-quinazolines.

kinases and investigated the worth of the presence of a hydrogen bond donor at the aniline-C_4 for binding with the conserved glutamate and aspartate amino acids in the binding sites of both EGFR and VEGFR-2, which promotes a significant increase in potency (Fig. 33).

Also, new 6,7-disubstituted-4-(arylamino)quinazoline derivatives were synthesized by Zhang *et al*. [52]. These compounds were developed to function as irreversible inhibiting agents for the EGFR protein kinase. Fortunately, they revealed significant activity. Compared with afatinib, some of them revealed significant enhanced potency against H1975 cells (EGFR-T790M). Moreover, the optimized compounds **80** and **81** also showed acceptable pharmacokinetic properties and oral bioavailability. Depending on the developed safety and activity against EGFR-T790M resistance, the derivatives **80** and **81** could be used for further development and optimization in future research (Fig. 34).

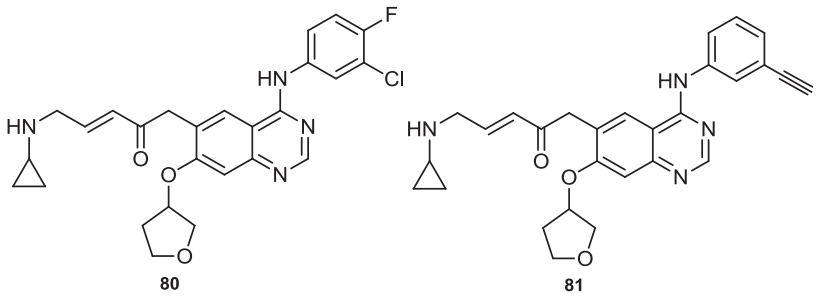
Erythropoietin-producing hepatocellular receptor tyrosine kinase A inhibitors

The erythropoietin-producing hepatocellular (Eph) RTKs play very important roles in various physiological and pathological conditions, including embryogenesis, patterning, neuronal targeting, vascular development, and cancer progression. There is overexpression of Eph RTKs and their cell-presented ligands, ephrins, in a large number of cancer types such as breast, lung, gastrointestinal cancers, and neuroblastomas. At present, there are two main classes of Eph RTKs: EphA (EphA1–10) and EphB (EphB1–6) [53]. EphA2 has particularly been correlated to breast, prostate, lung, ovarian, and cervical cancer as well as to malignant melanoma. Further, the degree of malignancy and poor prognosis depend on the level of EphA2 expression in the tumor cells. Novel 4-substituted quinazoline derivatives bearing the 7-(morpholin-2-ylmethoxy) group (compounds **82**) were designed and prepared by Lim *et al*. [53]. The new derivatives showed significant inhibition toward EphA2. The most potent compound was **82e** (Fig. 35).

Poly(ADP-ribose)polymerase-1 enzyme inhibitors

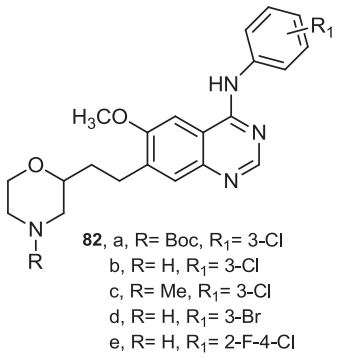
It was demonstrated that poly(ADP-ribose) polymerase-1 (PARP-1) plays a pivotal role in the repair of single-strand breaks of DNA through the base excision repair pathway. Therefore, the inhibition of PARP-1 enzyme can synergize the cytotoxic effects

Figure 34



Structures of 6,7-disubstituted-4-(arylamino) quinazoline derivatives.

Figure 35



82, a, R= Boc, R_1= 3-Cl
b, R= H, R_1= 3-Cl
c, R= Me, R_1= 3-Cl
d, R= H, R_1= 3-Br
e, R= H, R_1= 2-F-4-Cl

Structures of 4-substituted quinazoline derivatives bearing 7-(morpholin-2-ylmethoxy) group.

of the DNA-damaging agents [e.g. temozolomide (TMZ), cyclophosphamide, and camptothecin], which cause lesions normally repaired by the base excision repair pathway [54]. Novel 1-benzyl-quinazoline-2,4(1*H*,3*H*)-dione derivatives were designed and prepared as human PARP-1-inhibiting agents. Depending on the SAR studies, it was found that the quinazoline-2,4(1*H*,3*H*)-diones (**83**) produce potent inhibitory activity against the PARP-1 enzyme of IC_{50} values at nanomolar levels. Compound **83c** produced a potent dual-inhibition effect against PARP-1 and PARP-2 and it could selectively damage the breast cancer cells MX-1 and MDA-MB-468 with mutated BRCA1/2 and PTEN, respectively, compared with homologous recombination proficient cell types such as the breast cancer cell line MDA-MB. Moreover, compound **83c** exhibited the strongest potentiation effect of potentiation factor (PF_{50}) on TMZ in MX-1 cells ($PF_{50}=3.77$) (Fig. 36).

DNA-damaging activity

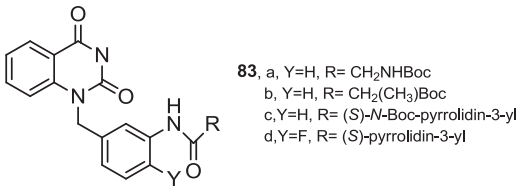
Nitrogen mustards are the earliest bifunctional alkylating agents. They interrupt DNA biosynthesis, leading to DNA disruption and damage. The biggest disadvantage of these drugs is their high genotoxicity, which produces many side effects on the patients [55]. Many nitrogen mustards have been synthesized in clinical applications. Chlorambucil, melphalan, and cyclophosphamide are the most important drugs belonging to this class. Hoping to obtain novel potential antiproliferative derivatives, a new class of quinazoline-nitrogen mustards (compounds **84**, **85**, and **86**) were designed and synthesized by Li *et al.* [55]. In this work, a nitrogen mustard group was directly introduced to the quinazoline ring depending on its efficiency as an ideal carrier for nitrogen mustards.

Most of the new quinazoline-nitrogen mustard derivatives revealed selective cytotoxicity toward specific types of cancer cells, and the conjugation of the quinazoline ring generally reduced the virulent side effects of the nitrogen mustard. Various studies have demonstrated that compound **85b** shows cell cycle delay and arrests the cell cycle progression predominantly at the S and G2/M boundary, and produces cell apoptosis, while its host toxicity is small. Thus, this work revealed some methods for synthesis and optimization of new quinazoline-nitrogen mustards of high tumor affinity taking quinazoline ring as a nitrogen mustard transporter (Fig. 37).

Antimitotics and tubulin polymerization inhibiting activity

A novel class of pyrrolo[3,4-*b*]quinazolines has been successfully prepared by fusion of the pyrimidine ring with the isoindole moiety (Fig. 38) [56]. Some of the new compounds have shown interesting cytotoxicity in many tumor cell lines and were active even in a multidrug-resistant cell line. The most cytotoxic derivatives, **87a–d** and **88e**, induced cell death mainly by apoptosis, as demonstrated by the onset of the apoptotic peak in cell cycle analysis and by the classical annexin-V/PI test. Moreover, the involvement of mitochondria and, in a later stage, of lysosomes was

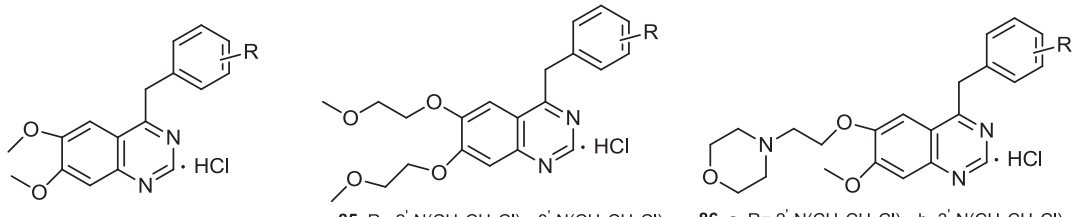
Figure 36



83, a, Y=H, R= CH_2NHBoc
b, Y=H, R= $CH_2(CH_3)Boc$
c,Y=H, R= (*S*)-*N*-Boc-pyrrolidin-3-yl
d,Y=F, R= (*S*)-pyrrolidin-3-yl

Structures of 1-benzyl-quinazoline-2,4(1*H*,3*H*)-dione derivatives.

Figure 37



84, R= 2'-N($CH_2CH_2Cl)_2$, 3'-N($CH_2CH_2Cl)_2$, 4'-N($CH_2CH_2Cl)_2$

85, R= 2'-N($CH_2CH_2Cl)_2$, 3'-N($CH_2CH_2Cl)_2$, 4'-N($CH_2CH_2Cl)_2$

86, a, R= 2'-N($CH_2CH_2Cl)_2$, b, 3'-N($CH_2CH_2Cl)_2$, c, 4'-N($CH_2CH_2Cl)_2$

Structures of quinazoline-nitrogen mustard derivatives.

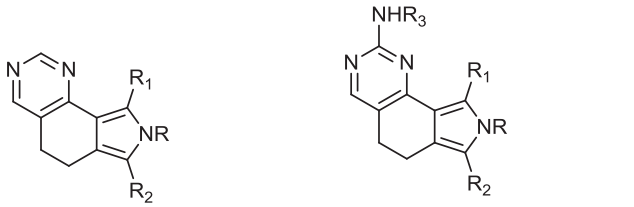
demonstrated. It was observed that most cytotoxic quinazoline derivatives act as antimitotics and inhibit tubulin polymerization *in vitro*. These derivatives also presented some antiangiogenic effects that could be useful for disrupting the tumor vascular network, thus inducing extensive cell death at its core.

A new set of 6-chloro-2-*p*-tolylquinazolinone compounds (**89** and **90**) and 9-chloro-5-*p*-tolyltetrazolo[1,5-*c*] quinazoline (**91**) was prepared in order to examine them as in-vitro anticancer agents (Fig. 39) [57]. The tested candidates were examined against 60 cancer cell lines at 10 μmol/l concentration. The obtained data showed that compounds **89** and **90** had significant wide-spectrum antitumor potency. The derivative **91** selectively inhibited the growth of non-small-cell lung cancer using 5-fluorouracil as a reference drug. Also, it was demonstrated that compound **90** had ~1.5 fold more potency (mean GI_{50} = 15.8 μmol/l) in comparison with 5-fluorouracil (mean GI_{50} = 22.6 μmol/l).

Mitochondrial translocator protein inhibiting activity

Glioblastoma multiforme (GBM) is the most common and malignant primary human brain tumor with very poor prognosis. Patients diagnosed with GBM usually undergo surgical intervention by Food and Drug Administration for the treatment of late-stage metastatic medullary thyroid cancer, as well as resection, radiation, and chemotherapy using the DNA alkylating agent TMZ, but the mean life expectancy is less than 14 resistance induction because of the activation of DNA repair proteins rendering the drug ineffective [58]. Recent reports indicated that the mitochondrial translocator protein is selectively

Figure 38

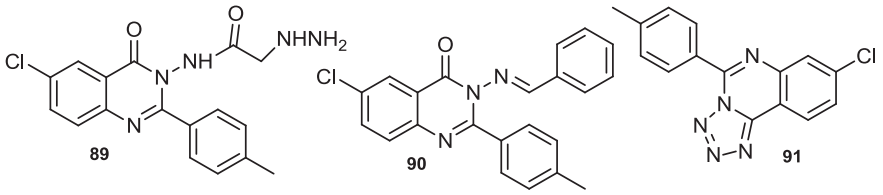


87, a, R= Bn*p*OMe, R_1=R_2= H
b, R= Bn*p*OMe, R_1=Me, R_2=CO_2Et
c, R= Bn*p*Me, R_1=H, R_2=Ph
d, R= Bn*p*OMe, R_1=h, R_2=Ph

88, a, R= Bn*p*Me, R_1=R_2= R_3= H
b, R= Me, R_1= R_2= H, R_3= Ph
c, R= Bn*p*Me, R_1= H, R_2= R_3= Ph
d, R= Bn*p*OMe, R_1= H, R_2=R_3= Ph
e, R= R_1= Me, R_2= CO_2Et, R_3= Ph

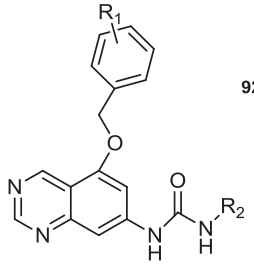
Structures of pyrrolo[3,4-*h*]quinazoline derivatives.

Figure 39



Structures of 6-chloro-2-*p*-tolylquinazolinone (**89**, **90**) and 9-chloro-5-*p*-tolyltetrazolo[1,5-*c*]quinazoline (**91**) derivatives.

Figure 40



92, a, R_1= 3-F, R_2= 1-naphthyl
b, R_1= 3-F, R_2= 3,4-dichlorophenyl
c, R_1= 2-F, R_2= 2-F-phenyl
d, R_1= 3-Cl, R_2= 3-Cl-phenyl
e, R_1= 3-Cl, R_2= 1-naphthyl
f, R_1= 2-Cl, R_2= 3-F-phenyl
g, R_1= 2-Cl, R_2= 3-Cl-phenyl
h, R_1= 2-Cl, R_2= 3,4-dichlorophenyl

Structures of quinazoline-urea derivatives.

overexpressed in the brains of GBM patients. In this regard, compounds inducing the mitochondrial permeability transition pore (mPTP) opening through translocator protein targeting were suggested as chemotherapeutic agents for glioma and glioblastoma cells. Elkamhawy *et al.* [58] reported on novel quinazoline-urea compounds (Fig. 40). In this study, the mPTP opening was aimed to be inhibited. Most of the bulky derivatives of R_2 of the urea side chain exhibited an opposite effect on the mitochondrial membrane potential, which could be a promising approach for GBM therapy. The eight compounds **92** showed excellent selectivity indices for GBM cells compared with a normal astrocyte cell line. Compound **92e** manifested potent tumoricidal effects on TMZ-resistant GBM cells even at submicromolar concentrations accompanied by a safe toxicity profile. Taken as a whole, this report presents compound **92e** as a potent, selective, and safe GBM cytotoxic agent, giving new promise for action against TMZ-resistant GBM.

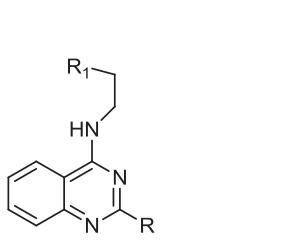
Transcription factor protein complex (nuclear factor κB) inhibiting activity

Nuclear factor κB (NF-κB) is a transcription factor protein complex. It is present in almost all animal cell types and plays a pivotal role in some tumors and inflammatory responses. It increases the rate of proliferation and inhibits apoptosis, in addition to creating more blood flow to ensure the survival of cancer. Thus, blocking the NF-κB pathway is one of the most important approaches in the cancer therapeutic field. A new class of quinazoline scaffold pharmacophores (**93** and **94**) of expected high binding affinity with the p50 subunit of NF-κB was designed and synthesized (Fig. 41) [59]. Biological studies showed that the compounds carrying phenyl substituents at the quinazoline-C_2 position appeared to be potent inhibitors of NF-κB function. These candidates also reduced the proliferation rate of many cancer cell lines. The compound **93c** exhibited a mean GI_{50} of 2.88 μmol/l against the NCI-60 cell lines and produced a remarkable apoptosis in the EKVX cell line at a dose of 1 μmol/l.

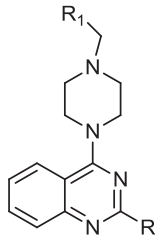
Inducing apoptosis activity

Novel compounds of *m*-(4-morpholinoquinazolin-2-yl) benzamides were designed, prepared, and characterized by Wang *et al.* [60] (Fig. 42). The new derivatives were examined as anticancer agents against two types of human cancer cells (HCT-116 and MCF-7). Most of the candidates exhibited potent antiproliferative activity,

Figure 41



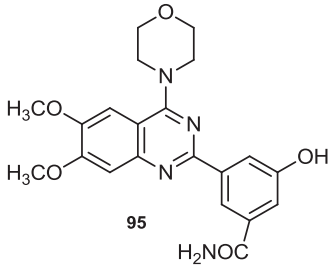
93, a, R= Ph, R_1= 3,4-(methylenedioxy)phenyl
b, R= H, R_1= 3,4-(methylenedioxy)phenyl
c, R= Ph, R_1= 3-indolyl
d, R= H, R_1= 3-indolyl



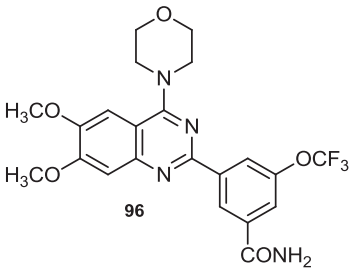
94, a, R= Ph, R_1= 4-OH-Ph
b, R= H, R_1= 4-OH-Ph
c, R= Ph, R_1= 2-OH-5-Br-Ph
d, R= H, R_1= 2-OH-5-Br-Ph

Structures of 2-sustituted quinazoline derivatives.

Figure 42



95



96

Structures of *m*-(4-morpholinoquinazolin-2-yl)benzamide derivatives.

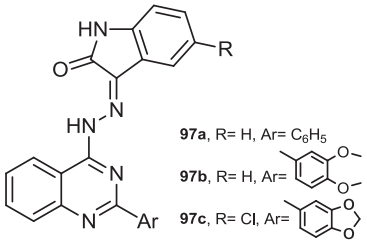
especially compound **96**, which represented a significant in-vitro potency in the Hoechst staining assay. Furthermore, the cell cycle and apoptosis assay showed that the analog **96** might arrest HCT-116 cells in G2/M and G0/G1 phase and lead to apoptosis. Also, compounds **95** and **96** exhibited selective inhibition of the PI3Kα enzyme, as revealed by the enzyme assay results. Also, western bolt assay proved that analog **96** could block the PI3K/Akt/mTOR pathway. These results directly revealed *m*-(4-morpholinoquinazolin-2-yl)benzamide derivatives as new antitumor candidates. The SAR of the title compounds reveals that the benzamide moiety is important for the maintenance of the antiproliferative activity of the title compounds. In addition, a trifluoromethoxy moiety at *m*-position of the amide group and methoxy at six and seven positions of the quinazoline ring are also favorable substituents.

Molecular hybridization led to the design and synthesis of new isatin–quinazoline hybrids (Fig. 43) [61]. The new hybrids were examined as in-vitro anticancer agents against the liver HepG2, breast MCF-7, and colon HT-29 cancer cell lines. Significant selective inhibition was gained against the HepG2 cancer cell line. The derivatives **97a**, **97b**, and **97c** produced the strongest activity (IC_{50} = 1.0–2.4 μmol/l). Further, they led to apoptosis in HepG2 cells, as seen by increased proapoptotic protein Bax expression and decreased expression of the antiapoptotic protein Bcl-2, as well as enhanced caspase-3 levels.

Marketed anticancer drugs carrying quinazoline core

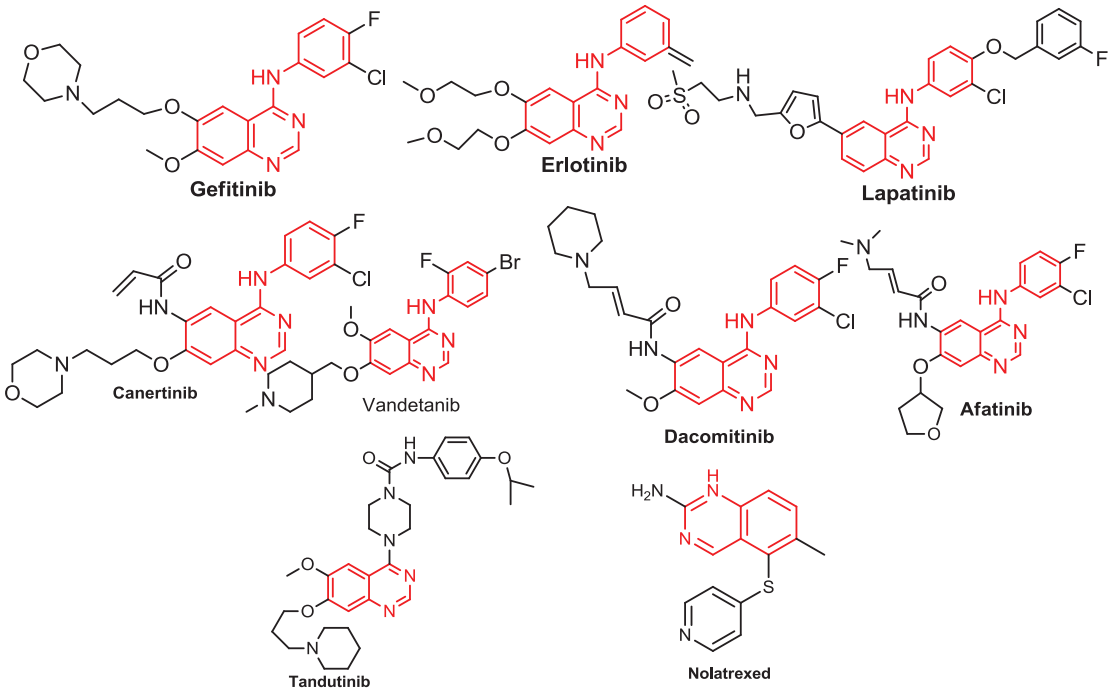
The drugs gefitinib (Iressa), erlotinib (Tarceva), and lapatinib (Tykerb) (Fig. 44), which selectively inhibit the EGFR protein kinase, were approved by the Food and Drug Administration in 2003, 2004, and 2007,

Figure 43



Structures of isatin–quinazoline hybrid derivatives.

Figure 44



Chemical structures of different anticancer drugs carrying quinazoline pharmacophores.

respectively. They are active in locally advanced or metastatic cancer chemotherapy [49,62–64]. Vandetanib, targeting EGFR and VEGFR-2, was approved in April 2011.

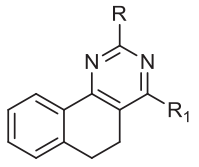
Anti-inflammatory activity

New basic 5,6-dihydrobenzo[*h*]quinazoline derivatives **98a–h** carrying various amino groups at positions 2 and 4 were designed and synthesized in order to obtain novel antiplatelet/analgesic and anti-inflammatory agents with a safe gastrointestinal profile (Fig. 45) [65].

The new derivatives (**98a–h**) exhibited variable antiplatelet activity on the in-vitro platelet aggregation test. The derivatives **98a** and **98e** emerged as having the strongest activity by inhibition of all the aggregating stimuli. The in-vivo examination found that the conjugation of different amino groups at position 4 was important for producing the analgesic potency of compounds **98a–h** – in particular, compound **98h**. This derivative exhibited 51% pain inhibition at a dose that did not lead to any sedation as the treated mice exhibited the same degree of locomotor activity as those treated with the vehicle only, in the same experiment. Data showed that **98a** and **98h** inhibited both cyclooxygenase (COX) 1 (maximal inhibition = 50.5 and 28.7%, respectively) and COX2 (maximal inhibition = 38.6 and 50.7%, respectively) at a dose of 1 mmol/l. These data confirm the hypothesis that both **98a** and **98h** have promising antiplatelet activity with no relation to COX inhibition, acting through other modes of action. Computational study on compounds **98a** and **98h** was also performed. Docking simulation studies of both compounds showed that compound **98a** directed the dihydrobenzo[*h*]quinazoline portion toward Tyr355, Leu523, and Leu531 and can form one H-bond with the key residue Tyr385 through the aniline moiety nitrogen atom, whereas the anilino group of compound **98h** is directed toward Leu523, Leu531, and Tyr355 without forming any H-bonds with the Ser530 or Tyr385 key residues.

Tumor necrosis factor (TNF)-α is one of the most common inflammatory mediators in different inflammatory diseases, such as rheumatic arthritis. The compound 2-chloro-*N*-(4-(2-morpholinoethoxy)phenyl)quinazolin-4-amine (**99**) was discovered by Pu *et al.* [66]. It inhibits TNF-α production (IC_{50} = 8.86 μmol/l in RAW264.7 cells), leading to promising inflammatory activity. In-vivo study revealed that compound **99** was a potent antiarthritic candidate as it enhanced the arthritic score, decreased the infiltration of inflammatory cells, and protected the joints from destruction (Fig. 46).

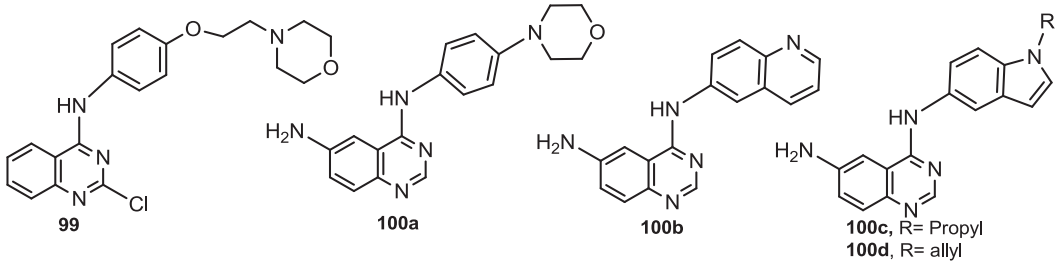
Figure 45



98, a, R= NH_2, R_1= NHC_6H_5; b, R= NH_2, R_1= $NHCH_2C_6H_5$
c, R= NH_2, R_1= $NHCH_2CH_2C_6H_5$; d, R= NH_2, R_1= 1-pyrrolidino
e, R= NH_2, R_1=1-piperidino; f, R= NH_2, R_1= 4morpholino
g, R= $NHCH_3$, R_1= NHC_6H_5; h, R= $N(CH_3)_2$, R_1= NHC_6H_5

Structures of 5,6-dihydrobenzo[*h*]quinazolines.

Figure 46



99 **100a** **100b** **100c,** R= Propyl **100d**, R= allyl

Structures of novel 4-amino quinazoline derivatives.

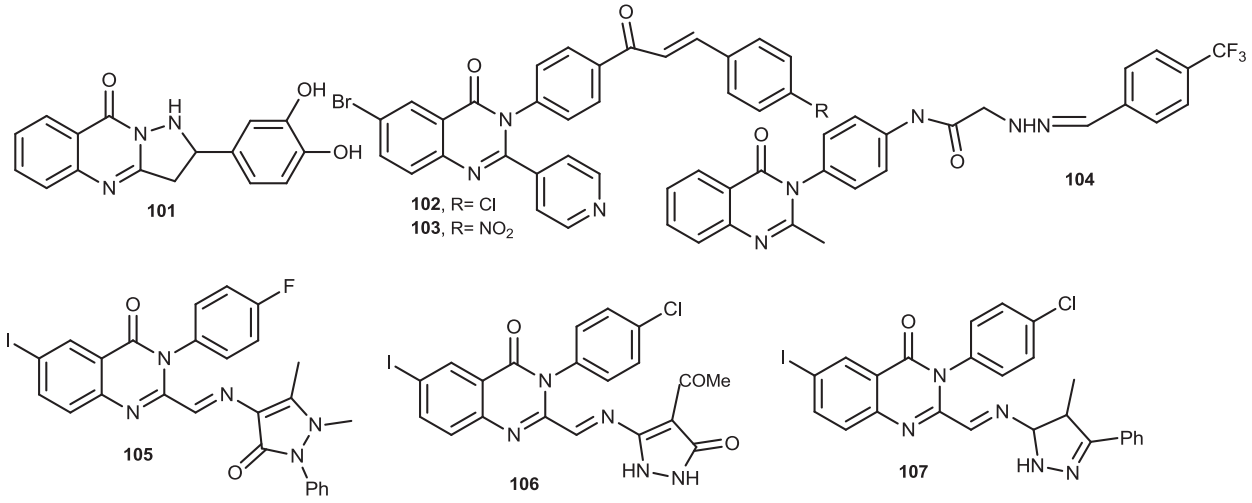
Furthermore, novel 4-amino quinazoline derivatives were synthesized. They were tested as anti-inflammatory agents in lipopolysaccharide (LPS)-induced macrophages [67] (Fig. 46). The four most active derivatives **100a**, **100b**, **100c**, and **100d** showed inhibition of TNF-α and interleukin-6 release depending upon the used concentration. The results revealed that derivatives **100b** and **100d**, especially **100d**, alleviated lung histopathological changes, inflammatory cell infiltration, and cytokine mRNA expression initiated by LPSs. In view of these results, this study proved that **100b** and **100d** could alleviate acute lung injury by in-vivo and in-vitro inhibition of the inflammatory response. Thus, it was indicated that various quinazolines could act as potential relieving agents in acute lung injury and serve as basic scaffolds in drug development and research.

A novel class of 2,3-dihydro-2-(substituted-phenyl) pyrazolo[5,1-b]quinazolin-9(1*H*)-ones was reported by Hussein *et al*. [68]. The new derivatives were examined for their anti-inflammatory activity using diclofenac sodium as a reference standard. The tested compound **101** showed remarkable potency when compared with the reference drug (Fig. 47).

At the same time, Eweas *et al*. [69] designed and prepared new 2-pyridyl(3*H*)-quinazolin-4-one derivatives for anti-inflammatory evaluation. The whole evaluated compounds showed promising activity comparable to that of the standard drug indomethacin. Among them, compounds **102** and **103** revealed the most potent anti-inflammatory activity.

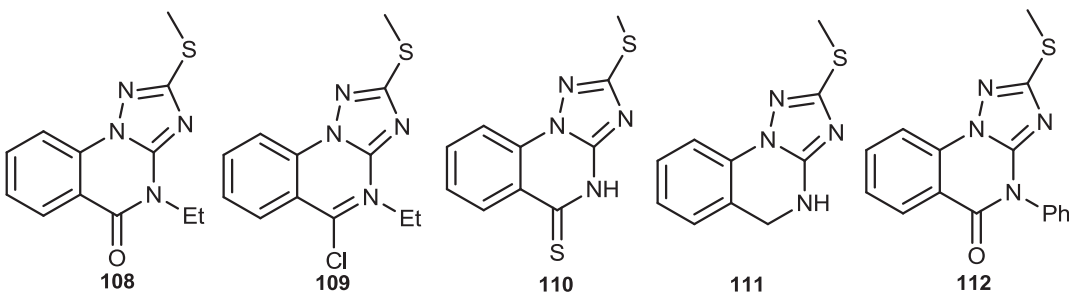
New quinazolin-4(3*H*)-one derivatives were prepared by Saravanan *et al*. [70] for anti-inflammatory evaluation. The derivatives that were substituted with halogen atoms, particularly those carrying trifluoromethyl groups, revealed potent anti-inflammatory activity. Among all tested compounds, trifluoromethyl analog **104** exhibited more potent activity compared with diclofenac (Fig. 47).

Figure 47



Structures of different quinazolone derivatives with anti-inflammatory activity.

Figure 48



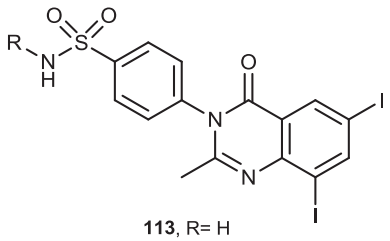
Structures of 2-methylsulfanyl-[1,2,4]triazolo[1,5-*a*]quinazoline derivatives.

Farag *et al.* [71] reported the synthesis of novel 3-(4-chlorophenyl or 4-fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazoline derivatives carrying Schiff bases and various heterocyclic motifs such as oxazolone, imidazolidine, pyrazolidine, pyridine, and pyrimidine (Fig. 47). The anti-inflammatory evaluation in chronic models showed that 3-(4-fluorophenyl)-2-[(1, 5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1 *H*-pyrazol-4-ylimino)-methyl]-6-iodo-3 *H*-quinazolin-4-one (**105**), which has –N=CH–pyrazoline moiety at C_2 position and fluorophenyl at C_3 position, produced the strongest anti-inflammatory activity. Other derivatives such as **106** and **107** incorporating –N=CH-substituted pyrazoline moieties at C_2 positions also showed potent anti-inflammatory activity but slightly less than that of compound **105**.

Al-Salahi *et al.* [72] prepared a novel set of 2-methylsulfanyl- [1, 2, 4] triazolo [1, 5-*a*] quinazoline derivatives (Fig. 48). The new analogs were tested as anti-inflammatory agents. The tested samples showed varying degrees of anti-inflammatory activity. Some compounds showed potential potent anti-inflammatory activity with respect to that of dexamethasone and the control, which varied from 75 to 86% inhibition, comparable to that of LPS-induced cells. Some others possessed moderate activity, with inhibition ranging from 50 to 70%. Overall, these results indicated that compounds **108–112** are promising multipotent anti-inflammatory agents.

Zayed and Hassan [73] prepared novel analogs of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3*H*)-ones carrying sulfonamide moieties (Fig. 49). The newly

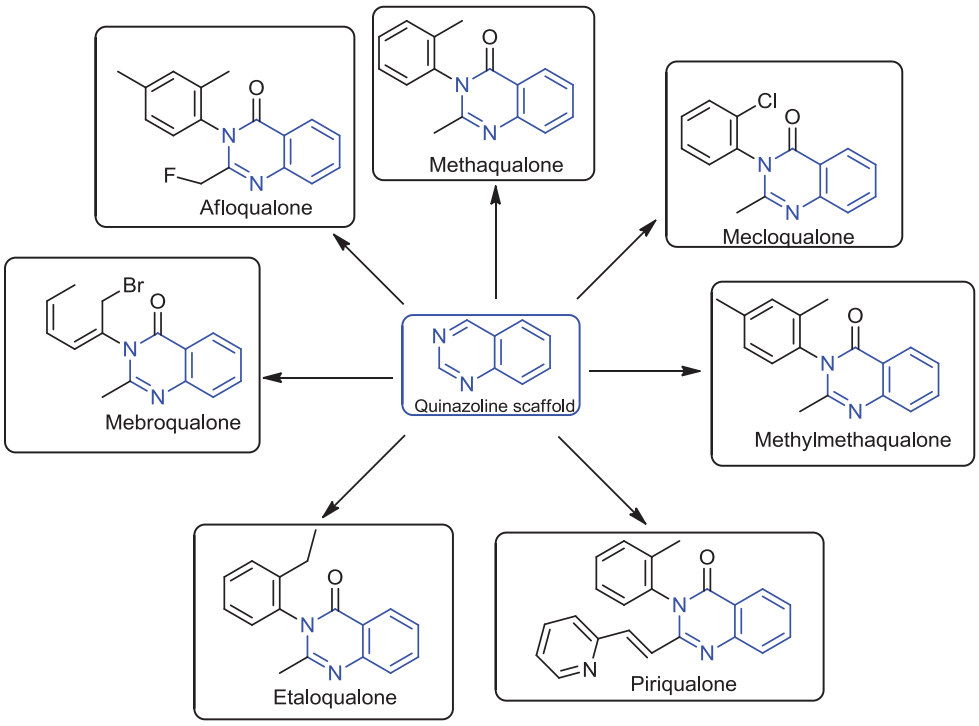
Figure 49



113, R= H
114, R= COMe

Structures of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3*H*)-ones.

Figure 50



Some of the potent anticonvulsant drugs bearing the 4(3*H*)-quinazolinone ring.

synthesized derivatives were examined as anti-inflammatory candidates using the carrageenan-induced hind-paw edema test. Ibuprofen was used as a reference standard. Among the screened compounds, **113** and **114** with aliphatic side chains showed higher activity than those bearing aromatic moieties. Compound **114** was found to be the most active one with a relative potency of 74% of the ibuprofen potency.

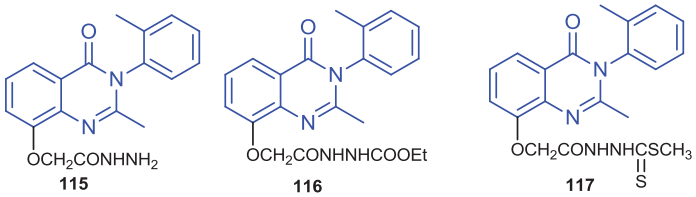
Anticonvulsant activity

The quinazoline ring system is considered the 'master key' in anticonvulsant therapy. It constitutes the basic scaffold of many common anticonvulsant drugs [74,75]. Examples of the potent anticonvulsant drugs containing quinazoline core are mentioned in Fig. 50.

In medicinal chemistry, the 4(3*H*)-quinazolinone scaffold is considered one of the most important heterocycles for synthesis of various anticonvulsant agents. Many studies have reported that the attachment of a methyl group at position 2 and a substituted aromatic ring at position 3 of the 4(3*H*)-quinazolinone ring is essential for CNS depression and anticonvulsant activities. Novel 2,3,8-trisubstituted-4(3*H*)-quinazoline derivatives were prepared and assessed as antiepileptic agents, being compared with the reference drugs methaqualone and sodium valproate [76]. Compounds 2-[3,4-dihydro-2-methyl-3-(2-methylphenyl)-4-oxoquinazolin-8-yloxy] acetic acid hydrazide (**115**), ethyl-2-[2-(2-methyl)-3-(2-methylphenyl)-4(3*H*)-quinazolin-8-yloxy) acetyl]hydrazincarboxylate (**116**), and methyl-2-[2-(2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolin-8-yloxy) acetyl] hydrazinecarbodithioate (**117**) (Fig. 51) produced the strongest activity in this class with relatively low neurotoxicity. The resultant data showed that the most potent analogs could serve as basic templates for further optimization and development to obtain more potent anticonvulsant candidates.

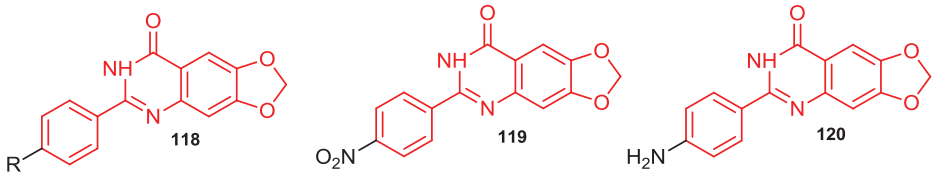
Also, a new set of 2-aryl-6,7-methylenedioxy-3*H*-quinazolin-4-ones was prepared and examined for their antiepileptic activity. They are considered to be prototypes of the 2,3-benzodiazepine core structure, thus providing a rationale for compounds **118**, **119**, and **120** to demonstrate significant anticonvulsant and neuroprotective actions (Fig. 52) [77].

Figure 51



Structures of novel 4(3*H*)-quinazolinone derivatives.

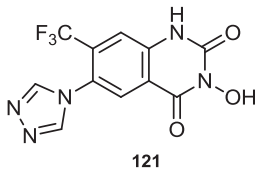
Figure 52



R= H, F, Cl, Br

Structures of novel 2-aryl-6,7-methylenedioxy-3*H*-quinazolin-4-ones.

Figure 53



Structure of the 6-(1,2,4-triazol-4-yl)-quinazoline derivative.

Also, Colotta *et al.*[78] prepared new 3-hydroxy-quinazoline-2,4-diones carrying a trifluoromethyl group at quinazoline-C_7 position and different functionalities at C_6 position. Glycine (Gly)/N-methyl-D-aspartate receptor (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and kainic acid (KA) receptor binding data showed that the 7-trifluoromethyl moiety improved the affinity and selectivity toward AMPA and KA receptors compared with the 7-chlorine atom. In the new class, 6-(1,2,4-triazol-4-yl) derivative **121** (Fig. 53) exhibited the most affinity and selectivity toward the AMPA receptor, displaying efficient anticonvulsant activity with decreasing neuronal damage [78].

According to the molecular docking results of compound 121, the quinazoline ring exhibited hydrogen bonding with iGluRs: Arg96, Thr91, and Pro89 at the AMPA receptor (Fig. 55) and with Arg131, Thr126, and Pro124 at the Gly/NMDA receptor. The NH group of the compound acts as a proton donor toward the backbone C=O of Pro89, whereas the 2-carbonyl group accepts a hydrogen bond from the backbone –NH– of Thr91 at the AMPA receptor site. Moreover, both 2-carbonyl and 3-hydroxy groups interact with the side chain of Arg96. The triazole nucleus accepts a hydrogen bond from the Thr174 side chain.

A novel class of 1,9-disubstituted-8-chloro-pyrazolo [1,5-*c*]quinazoline-2-carboxylates was prepared by Varano *et al.*[79]. The binding affinities of the new derivatives toward AMPA, Gly/NMDA, and KA receptors were tested. The obtained data revealed that the attachment of 1,2-dicarboxylic acid groups and suitable substituted benzene moieties to the basic pyrazole-quinazolinone core (compounds **122**) (Fig. 54) was essential to obtain new selective candidates of AMPA receptor antagonistic action.

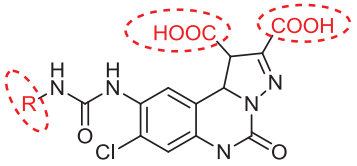
At the same time, a class of new 3-[5-substitutedphenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones (compounds **123**) (Fig. 55) was synthesized by Jatav *et al.*[80]. The anticonvulsant activity evaluation exhibited that the derivatives bearing phenyl, *p*-chlorophenyl, and *m*-chlorophenyl substituents on the thiadiazole ring had promising antiepileptic potency in the MES screen. When tested for neurotoxicity, the derivative bearing a phenyl residue on the thiadiazole moiety displayed promising potency devoid of neurotoxicity.

The antiepileptic and inhibitory activity against the monoamine oxidase enzyme of different methaqualone analogs (Fig. 56) was tested by Misra *et al.* [81]. It was observed that quinazolines possessing hydramide moiety had selective antiepileptic activity. The attachment of the 2-hydroxy-3,5-dichlorophenyl group at the Ar-moiety enhances the antiepileptic potency. At the same time, in the case of hydrazide analogs, the attachment of a chlorine atom at position 2 of the phenyl ring and a styryl residue at position 2 of the quinazolone ring also enhances the antiepileptic activity.

It has been noted that 6-chloro-3-(4-benzhydrazide)-2-(2′-chlorostyryl)-4-quinazolones (compounds **124**) produced the strongest antiepileptic potency and produced 60% protection against Pentylenetetrazole (PTZ)-induced seizures in mice.

3-Hydroxy-quinazoline-2,4-diones (compounds **125**) have been designed and synthesized by Catarzi *et al.* [82] (Fig. 57). The affinity toward the AMPA receptor was assessed by the new quinazolinone derivatives. The

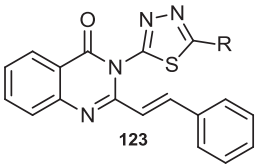
Figure 54



122, R= CH_2COOH, CH_2CH_2COOH, CH_2CH_3, C_6H_5, $CH_2C_6H_5$, 3-$COOHC_6H_5$, 4-$COOHC_6H_5$, $CH(COOH)CH_2C_6H_5$

Structures of different pyrazolo[1,5-*c*]quinazolinone derivatives.

Figure 55

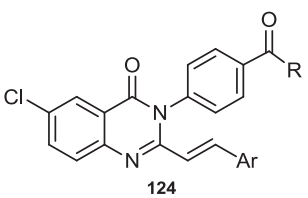


123

R= C_6H_5, *p*-ClC_6H_5, *m*-Cl-C_6H_5

Structures of 1,3,4-thiadiazole-quinazoline-4(3*H*)-one derivatives.

Figure 56



124

Ar= C_6H_5, R= $NHNHH_2$
Ar= 2-ClC_6H_4, R= $NHNHH_2$
Ar= 4-ClC_6H_4, R= $NHNHH_2$
Ar= 2-OH, 5-$Cl_2C_6H_2$, R= $NHNHH_2$
Ar= 2-OHC_6H_4, R= $NHNHH_2$
Ar= 3-$OCHC_6H_4$, R= $NHNHH_2$
Ar= 4-$N(CH_3)_2C_6H_4$, R= $NHNHH_2$
Ar= 3-$NO_2C_6H_4$, R= $NHNHH_2$
Ar= 3-OH, 5-$NO_2C_6H_3$, R= $NHNHH_2$

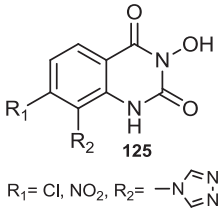
Structures of different methaqualone analogs.

data obtained showed that conjugation of a N^3-nitrogen-containing heterocycle at position 8 of the basic backbone plays a very important role in inducing potency and selectivity toward the AMPA receptor. Also, the introduction of potent electron-withdrawing groups, such as chlorine atom, trifluoromethyl, or nitro substituents at position 7 of the quinazolinone heterocycle, enhanced the activity and selectivity toward the same target [82].

The novel derivative 5-phenyl-[1,2,4]triazolo[4,3-*c*] quinazolin-3-amine (**126**) was synthesized by Zheng *et al.*[83] (Fig. 58). This derivative exhibited promising antiepileptic activity (ED_{50} = 27.4 mg/kg). Compound **126** exhibited clonic seizure inhibition by 30%, and absolute protection against the tonic seizures. It has been demonstrated that the antiepileptic potency of compound **126** was mediated by the γ-aminobutyric acid) system [83].

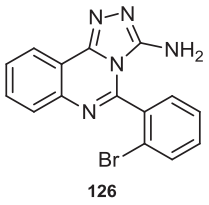
El-Azab and El-Tahir [76] have synthesized new 7-substituted-4(3*H*)-quinazolinone compounds [76]. The new derivatives were evaluated as anticancer and anticonvulsant agents. Compounds **127**, **128a,b**, and **129a,b** showed remarkable antiepileptic activity with lower neurotoxicity compared with the standard drugs methaqualone and valproate (Fig. 59). The most potent agents were selected for further examinations at various concentrations for quantification of their antiepileptic potency. The compounds exhibited ED_{50} values of 0.74, 0.31, 0.35, 0.70, and 0.40 mmol/kg, respectively. Methaqualone and valproate showed ED_{50} values of 1.40 and 1.5 mmol/kg, respectively. Interestingly, ED_{50} values of the tested agents appeared to be lower than those of the reference drugs at the same molar concentrations. The data revealed that these derivatives

Figure 57



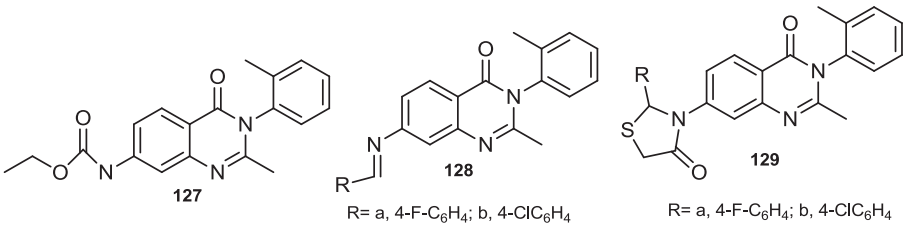
Structures of 3-hydroxy-quinazoline-2,4-dione derivatives.

Figure 58



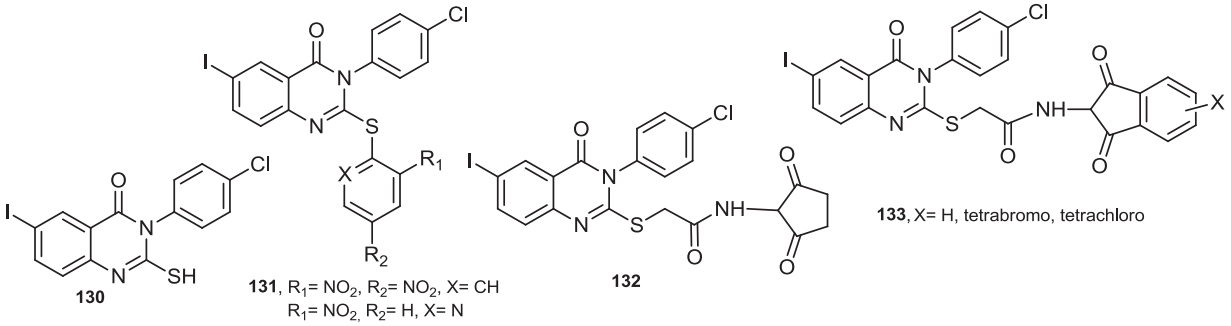
Structure of the [1,2,4]triazolo[4,3-*c*]quinazoline derivative.

Figure 59



Structures of 7-substituted-4(3*H*)-quinazolinone derivatives.

Figure 60



Structures of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodoquinazolines.

might be valuable scaffolds for further design and improvement in order to obtain more potent agents [76].

Kadi *et al.* [84] produced a new class of 2-mercapto-3-(4-chlorophenyl)-4-oxo-6-iodoquinazolines (Fig. 60). The antiepileptic potency of the new derivatives was evaluated using the PTZ seizure threshold test. Compounds 130–133 showed significant anticonvulsant activity with complete disappearance of seizures during the course of the assay. According to the obtained data, these compounds showed potent CNS depressant effects, accompanied by sedation and hypnosis [84].

New derivatives of the quinazolinedione nucleus conjugated with sulfonamide moieties were prepared by Orain *et al.* [85]. The newly synthesized compounds appeared as competitive AMPA receptor antagonists with better characteristics, particularly compound **134** (Fig. 61).

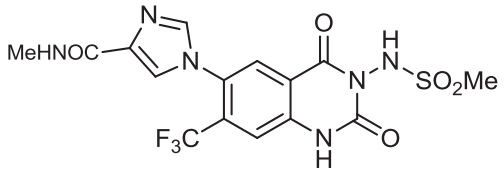
The central skeleton of **134** formed a favorable π–π stacking with Tyr450 and hydrogen bonds with the residues Pro478, Thr480, and Arg485. Additional hydrogen bonds were also formed by the derivative **134** with Thr686 and Glu402 (NH amide), which might be responsible for higher affinity [85].

Quinazoline-2,4-diones attached to sulfonamide groups have been prepared as a new set of effective competitive AMPA receptor antagonists of strong receptor affinity and significant oral in-vivo activity. Compound **135** (Fig. 62) showed nanomolar receptor affinity [86].

Koller *et al.* [86] constructed the human receptor hGluA2 and successfully cocrystallized it with the antagonist **135**. An X-ray structure investigated the binding mode of the two chemo types. Compound **135** was directed such that a favorable *p*-stacking with Tyr450 occurred and then formed the hydrogen bond. The sulfonamide nitrogen reacts with H3Np–Arg485, revealing that this nitrogen was negatively charged, which led to a strong Coulomb interaction. The ring –HN group exhibited significant hydrogen bonding interaction with the carbonyl group of Pro478. The imidazole moiety formed a hydrogen bond with the side chain hydroxyl group of Thr686, and the adjacent nitro substituent made water-mediated contact with Tyr405 and Thr707.

Patents for quinazolines as antiepileptics were recently granted at World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO), and European Patent Applications and Specifications related to quinazolines. These patents proved that quinazolines are very useful in seizure disorders. Floersheim *et al.* [87] claimed that quinazolines are effective pharmaceuticals in the treatment of epilepsy, especially in partial seizures

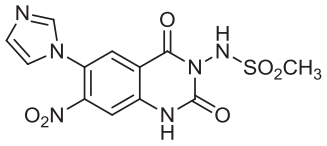
Figure 61



134

Structure of the quinazolinedione-sulfonamide derivative.

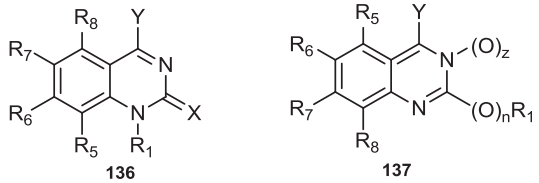
Figure 62



135

Structure of the quinazoline-2,4-dione-sulfonamide derivative.

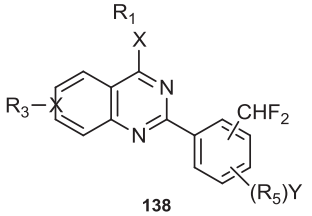
Figure 63



136 **137**

Chemical structures of different quinazoline derivatives. R_1 = alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, araalkynyl, heteroaralkyl, cyanoalkyl, azidoalkyl, alkoxyalkyl; R_5 and R_6 = hydrogen, halogen, haloalkyl, heterocyclic, heteroaryl, nitro, cyano, amino, thiol, carboxy, carbonylamido, thioalkoxy; R_6 and R_7 taken together to form a five or six membered carboxylic or heterocyclic rings; R_8 = optionally substituted lower alkyl. X = O or S; Y = aryl or heteroaryl; $n = z = 0$ or 1.

Figure 64



138

Chemical structures of quinazolines as inhibitors of ion channels. R_1 and R_2 are each independently an optionally substituted group selected from hydrogen C_{1-6} aliphatic. CY is a 5–7-membered monocyclic aryl ring or an 8–10-membered bicyclic aryl ring having 0–3 heteroatoms alkyl. R_3 comprises alkylidend side chains.

(simple, complex, and partial evolving to secondarily generalized seizures) and generalized seizures [absence (typical and atypical), myoclonic, clonic, tonic, tonic–clonic, and atonic]. Further, the compounds of the general chemical structures **136** and **137** (Fig. 63) were combined with other drugs to be more active in various conditions such as epilepsy. They could be combined with other anticonvulsants like barbiturates, benzodiazepines, carboxamides, hydantoins, succi-nimides, valproic acid, and other AMPA antagonists.

Floersheim *et al.*[87] documented that quinazolines were valuable inhibitors of voltage-gated sodium channels and calcium channels. The invention also produced suitable quinazoline pharmaceuticals to treat different neurodegenerative diseases including seizure disorders. Also, they decreased the severity of trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, neurodegenerative disorders, and pychiatric disorders such as anxiety, depression, and myotonia (Fig. 64).

Treatment of Alzheimer's disease

The overproduction of β-amyloid (Aβ) peptide and its extracellular deposition is the most important factor associated with the etiology of Alzheimer's disease [88]. Elkamhawy *et al.* [88] had synthesized a novel class of quinazoline-urea derivatives. Their blocking potency against Aβ peptide was assessed. Seven compounds, **139a–g** (Fig. 65), displayed higher potency compared with the standard cyclosporin A. MTT assay showed that the new candidates had excellent cellular viability. The quinazoline-urea compound **139 g**, as the most active agent, produced activity that was two-fold higher than that of cyclosporin A, thus giving new direction for the design and synthesis of novel Aβ peptide blockers.

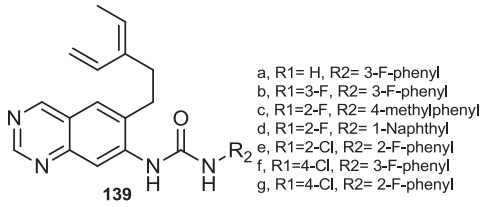
Xanthine oxidase inhibitory activity

Xanthine oxidase (XO) is a well-characterized druggable target in the treatment of diseases due to increased uric acid levels, such as hyperuricemia and gout, because of its significant role in catalytic oxidative hydroxylation of hypoxanthine and xanthine to produce uric acid. Further, XO is also associated with various diseases such as inflammation, metabolic disorders, cellular aging, reperfusion damage, atherosclerosis, hypertension, and carcinogenesis as it generates superoxide anions, H_2O_2, and highly reactive species (reactive oxygen species) during the catalytic process [89]. Therefore, the selective inhibition of XO leads to therapeutical relief from gout, cancer, inflammation, and oxidative damage [89]. Kumar *et al.* [89] designed and synthesized pyrazolo[1,5-*c*]quinazoline derivatives (compounds **140a–e**) (Fig. 66) to be tested as in-vitro XO inhibitors. The compounds **140d**, **140e**, and **140c** significantly inhibited XO. The most potent XO inhibitor and free radical scavenger was compound **140d**, when compared with allopurinol. The molecular docking of **140d** into the XO active site highlighted its mode of binding and important interactions such as hydrogen bonding and π–π stacking with amino acid residues like Ser876, Thr1010, Phen914, Phe1009, and Phe649.

Immunotherapeutic activity

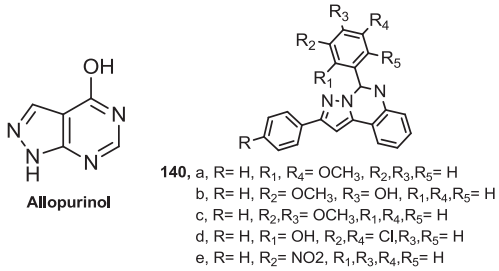
Toll-like receptors (TLRs) are critical components of the innate immune system that regulate immune recognition in part through NF-κB activation. A human cell-based high-throughput screen exhibited substituted 4-aminoquinazolines to be small-molecular-weight activators of NF-κB. Synthetic modifications of the

Figure 65



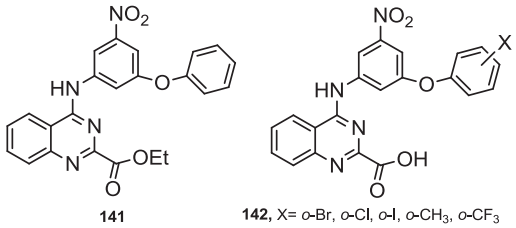
Structures of novel quinazoline-urea derivatives.

Figure 66



Structures of novel pyrazolo[1,5-*c*]quinazoline derivatives.

Figure 67



Structures of novel substituted 4-aminoquinazoline derivatives.

quinazoline scaffold at the two and four positions led to the formation of the hit compound **141**, which activated the interferon signaling pathway resulting in type I interferon production [90]. The attachment of different moieties such as bromine, chlorine, and methyl at the orthoposition of the phenyl ring enhanced the immunological potency (Fig. 67). Computational studies showed that the 4-aminoquinazoline compounds **142** bound primarily to human MD-2 in the TLR4/MD-2 complex. These molecules, which preferentially stimulate the human immune cells, may be valuable adjuvants or immunotherapeutic agents [90].

Clinical transplantation is a routine procedure, and its success is based on the matching of the major histocompatibility complex, on immune suppressive drugs, and on technical skills. Most transplants need immunosuppressants, which might be toxic, leading to cancer and infection. Induction of specific tolerance, which would inhibit the response to the graft without compromising host defense, is now characterized as the 'holy grail' of immunology. Sagiv-Barfi *et al.* [11] synthesized a new class of quinazoline derivatives that were examined as inhibitors of T-cell proliferation. *N*-*p*-tolyl-2-(3,4,5-trimethoxyphenyl)quinazolin-4-amine (**143**) (Fig. 68) appeared to be the most potent analog inhibiting the growth of T cells with IC_{50} in the submicromolar range.

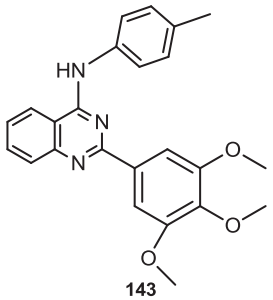
5-Hydroxy tryptamine$_{2A}$ receptor antagonistic activity

The 5-hydroxy tryptamine (5-HT)$_{2A}$ receptor is a G-protein-coupled receptor that generally mediates excitatory neurotransmission. One of the most fundamental biological functions of the 5-HT_{2A} receptor is the regulation of dopamine release in three dopaminergic pathways. 5-HT_{2A} is involved in a wide array of etiological processes including schizophrenia, depression, anxiety, migraine, hallucinations, insomnia, and addiction [91]. Nevertheless, 5-HT_{2A} antagonists have joined with D_2 dopamine antagonists as the most frequently used atypical antipsychotic agents. A new class of compounds carrying the quinazoline nucleus was prepared and assessed as new effective 5-HT_{2A} receptor ligands [91]. Compound **144a** (Fig. 69) was particularly attractive as 5-HT_{2A} and was discovered by pharmacophore-based virtual screening against the 5-HT_{2A} receptor, followed by biological assays. Compound **144e** is composed of a quinazoline core, an arm (piperazinyl-ethanol) and a tail (dimethoxy-aniline). Molecular modeling studies used this structural model to design and form a novel set of *N*-(substituted phenyl)-2-(piperazin-1-yl)quinazolin-4-amine derivatives (compound **144b–e**). Compound **144e** showed relatively high binding affinity to the 5-HT_{2A} receptor (K_i = 14.04 nmol/l), as well as antagonist activity (IC_{50} = 1.66 μmol/l). This is the first time that quinazoline analogs have been discovered to be highly effective and selective ligands for the 5-HT_{2A} receptor [91]. Investigations of more potent and selective quinazoline derivatives are required for their practical and therapeutic applications in the future.

Antidepressant activity

New 4-(substituted-phenyl)tetrazolo[1,5-*a*]quinazolin-5(4*H*)-ones (Fig. 70) were designed and prepared to be tested as antidepressant agents [92]. The biological assays revealed that derivatives **145a**, **145b**, and **145c** at a dose of 50 mg/kg significantly decreased the immobility time of

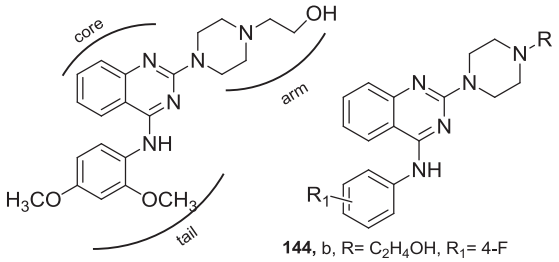
Figure 68



143

N-*p*-tolyl-2-(3,4,5-trimethoxyphenyl)quinazolin-4-amine.

Figure 69

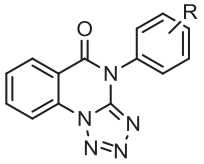


144e

144, b, R= C_2H_4OH, R_1= 4-F
c, R= C_2H_4OH, R_1= 4-Cl
d, R= C_2H_4OH, R_1= 4-Br
e, R= H, R_1= 4-Cl

Structures of piperazine–quinazolines.

Figure 70



145a, R= *o*-F
145b, R= *m*-CH_3
145c, R= *p*-CH_3

Structures of tetrazolo[1,5-*a*]quinazolin-5(4*H*)-one derivatives.

mice in the forced swimming test. The most potent derivative was 4-(*p*-tolyl)tetrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**145c**), which reduced the immobility time by 82.69% at 50 mg/kg. This result was approximately equivalent to the antidepressant effect of fluoxetine. The underlying mechanisms of these compounds might be due to the regulation of the brain monoamine neurotransmitter homeostasis, based on the detected increased levels of noradrenaline and 5-HT and the reduced content of monoamine oxidase enzyme in mouse brain tissues.

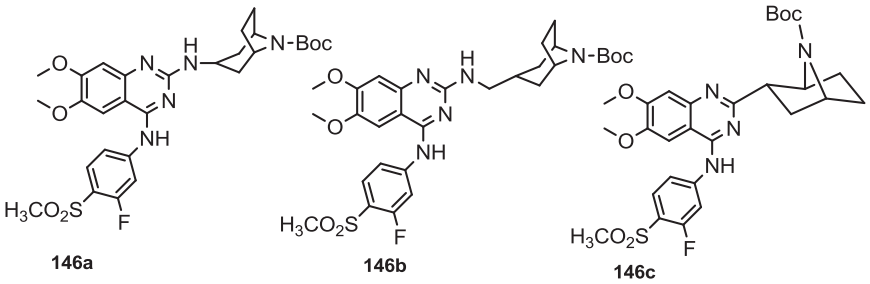
Antidiabetes mellitus type 2

GPR119 is a G-protein-coupled receptor predominantly expressed in pancreatic β cells and intestinal enteroendocrine cells. GPR119 agonists enhance insulin secretion *in vitro* and reduce the elevated blood glucose level *in vivo*. In addition, they enhance the secretion of incretin (GLP-1 and GIP). Accordingly, GPR119 agonists were recently considered as important targets for the treatment of type 2 diabetes and obesity by controlling glucose homeostasis [93]. New derivatives of 2,4-disubstituted quinazolines incorporated with heterocyclic alcohols and azabicyclic amine groups (Fig. 71) have been synthesized and tested as GPR119 agonists. It has been shown that the derivatives carrying (2-fluoro-4-methylsulfonyl) phenylamino and azabicyclic amine groups with N-Boc (**146a–c**) have promising EC_{50} values. The obtained results suggested that the steric bulkiness of the attached groups enhanced the bioactivity, while the configuration (endo vs. exo) did not produce a remarkable effect. Better bioactivity was obtained by the electronic effects of the conjugated groups at position 2 of the benzene ring as well as the N-Boc group of azabicyclic amines. Further SAR studies to obtain more effective GPR119 agonists carrying different heterocyclic scaffolds are under progress [93].

Antiobesity activity

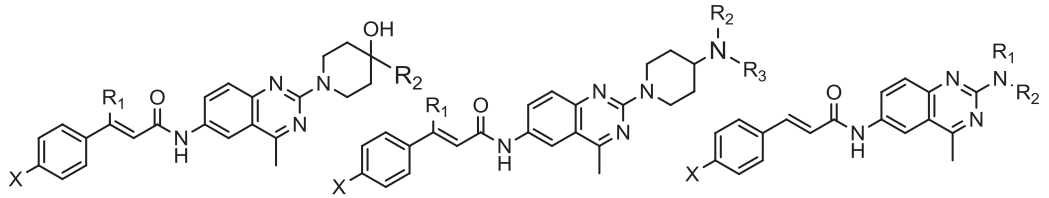
Melanin-concentrating hormone is a 19-amino-acid cyclic neuropeptide expressed predominantly in the lateral hypothalamus and zona incerta. The pivotal roles of melanin-concentrating hormone and the melanin-concentrating hormone receptor 1 (MCHR1) in the body weight and feeding regulation ensure the hypothesis that MCHR1 antagonists constitute new targets for the treatment of obesity [94]. The quinazoline compounds **147**, **148**, and **149** (Fig. 72) were characterized as potent MCHR1 antagonists. It has been found that the efficacy of compound **147a** could be obtained with a safe cardiovascular profile.

Figure 71



Structures of novel 2,4-disubstituted quinazoline derivatives.

Figure 72



147, R_1=H, R_2= Pr, X= Cl
R_1=H, R_2= CH_2Ac, X= Cl

148, R_1=H, R_2,R_3= -$(CH_2)_2O(CH_2)_2$-,, X= Cl
R_1=H, R_2,R_3= -$(CH_2)_2O(CH_2)_2$-, X= OCF_3
R_1=H, R_2,R_3= -$COCH_2O(CH_2)_2$-, X= OCF_3
R_1=H, R_2,R_3= -$CO(CH_2)_4$-, X= OCF_3
R_1=H, R_2,R_3= -$CO(CH_2)_3$-, X= OCF_3

149, R_1=H, R_2= -$(CH_2)_3NHCOPr$-, X= OCF_3
R_1=H, R_2= -$(CH_2)_2NHCOPr$-, X= OCF_3

Structures of novel 7-substituted-quinazoline derivatives.

Bronchodilatory activity

A series of quinazoline-heterocyclic derivatives were prepared analogs to vasicinone (vasicine and vasicinone are major quinazoline alkaloids isolated from *Justicia adhatoda* L. and are known to have a moderate bronchodilatory effect), in which the vasicinone C-ring was replaced with the alkyl chain terminated by tertiary amine [95]. The new derivatives (**150**) (Fig. 73) displayed bronchodilatory effect at low micromolar concentrations (ED_{50} = 0.178–1.90 mmol/l, ED_{50} of theophylline 2.090 mmol/l, ED_{50} of vasicinone 2.864 mmol/l) on isolated rat trachea, and low toxicity both on Balb/c3T3 mouse fibroblast cells and in mice.

Antimicrobial activity

A new series of 6,7-bis(arylthio)-quinazoline-5,8-dione and furo[2,3-*f*]quinazolin-5-ol derivatives were prepared and evaluated as in-vitro antifungal agents against *Candida* spp., *Aspergillus* spp., and *Cryptococcus neoformans*. Among them, 2-amino-4-arylthio-5-hydroxyfuro[2,3-*f*]quinazoline derivatives (**151a,b**) (Fig. 74) exhibited complete growth inhibition of the tested *Candida* spp. and *Aspergillus* spp. at an minimum inhibitory concentration (MIC) level of 12.5 μg/ml. The obtained data suggested that furo[2,3-*f*] quinazolines could be promising antifungal agents [96].

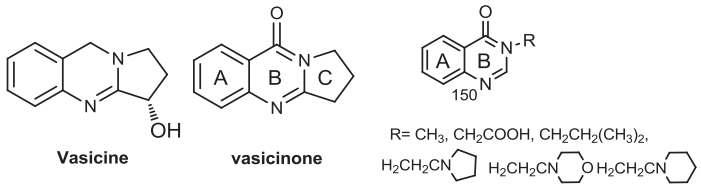
Maurya *et al*. [97] have synthesized various substituted 5,6-dihydro-8 methoxybenzo[*h*]quinazolin-2-amine derivatives in good yields, following an efficient method. Compounds **152a**, **152b**, and **152c** (Fig. 75) exhibited significant antitubercular activity at MIC values of 50, 100, and 50 μmol/l, respectively, in an in-vitro assay against the *Mycobacterium tuberculosis* H37Rv strain.

The 2-mercaptoquinazoline compound (**153**) exhibits antifungal activity through the physiological pathway and through cytotoxicity (Fig. 76). It is hypothesized that it first attacks the cell wall and destroys the fungal cell, exerting its fungicidal effect through cytotoxicity. Second, it directly prevents energy metabolism, protein biosynthesis, and enzyme activity and indirectly prevents the building of the cell architecture through the physiological pathway [98].

A new set of 1-methyl-3-substituted quinazoline-2,4-dione derivatives were designed and prepared (Fig. 77) [99]. They were evaluated as chitin synthase inhibiting agents and as antifungal agents. Results showed that compounds **154a–d** had a strong inhibitory effect against chitin synthase. Compound **154b** showed the highest activity of IC_{50} = 0.08 mmol/l, whereas polyoxin B as a standard drug exhibited IC_{50} of 0.18 μmol/l.

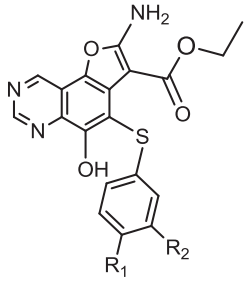
Plasmodium, the parasite that infects humans with malaria, multiplies in the liver and is then released into circulating erythrocytes. Therefore, the

Figure 73



Structures of quinazoline-heterocyclic derivatives analogous to vasicinone alkaloids.

Figure 74



151, a, R_1= CH_3, R_2= H
b, R_1= F, R_2= F

Structures of 5-hydroxyfuro[2,3-*f*]quinazoline derivatives.

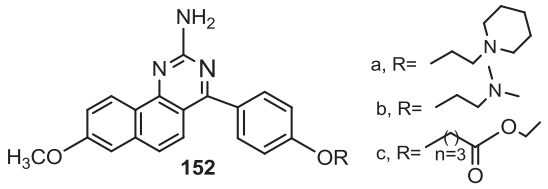
erythrocyte cell membrane has an essential role in the potency of different antimalarial drugs or in inducing resistance against them. The antiplasmodial activity of N^6-(4-methoxybenzyl) quinazoline-2,4,6-triamine (**155**) is produced in human erythrocytes and on their cell membranes [100] (Fig. 78).

Antiviral activity

Chen *et al.* [101] identified several indole-based quinazoline derivatives with antihepatitis activity (Fig. 79). SAR studies of the indole substituents optimized the potency and protein kinase (PK) properties. Optimization of C_4, C_5, and C_6 substituents led to the formation of 4,5-furanylindole as the best core for antihepatitis activity. The C_2 carboxylic acids exhibited better PK properties than the corresponding acylsulfonamides. Accordingly, the derivative (**156**) was considered as a promising lead with high activity. Leivers *et al.* [102] discovered small-molecule type III phosphatidylinositol 4-kinase α (PI4KIIIα) inhibitors as antihepatitis C virus (anti-HCV) agents. They have also described the methods for their preparation and SARs associated with their biological inhibition of PI4KIIIa and HCV replication. The biological data revealed that the pyridine-based quinazolinone derivative (**157**) has high selectivity for PI4KIIIa and potently inhibits HCV replication *in vitro*.

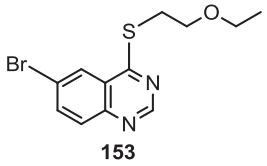
A new set of (1*E*,4*E*)-1-aryl-5-[2-(quinazolin-4-yloxy) phenyl]-1,4-pentadien-3-one derivatives has been prepared by Luo *et al.* [103]. The derivatives were tested as antiviral agents. Antiviral bioassays proved that most of the compounds exhibited promising in-vivo antiviral bioactivity against the tobacco mosaic virus and the cucumber mosaic virus at 500 mg/ml. Also, it has been revealed that the compounds (**158a–c**) (Fig. 80) could possess appreciable protective bioactivities on tobacco mosaic virus *ex vivo* by ~50% (EC_{50}) at 257.7, 320.7, and 243.3 mg/ml.

Figure 75



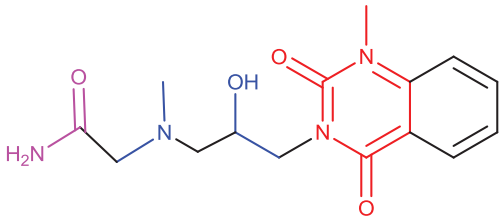
Structures of 5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine derivatives.

Figure 76



Structure of the 2-mercaptoquinazoline derivative.

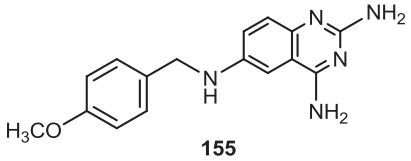
Figure 77



154, a, R_1= H, R_2= $CH_2C_6H_5$,b, R_1= H, R_2= 4-$CH_3C_6H_4$
c, R_1= H, R_2= 4-Cl-C_6H_4, d, R_1= H, R_2= 4-CF_3-C_6H_4

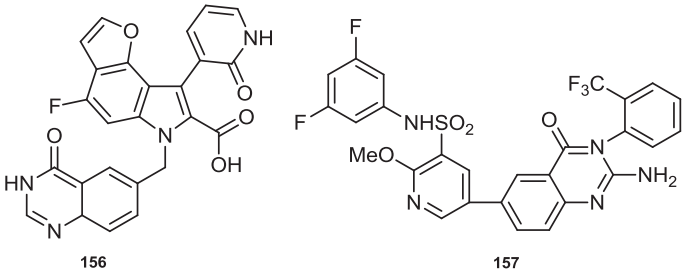
Structures of 1-methyl-3-substituted quinazoline-2,4-dione derivatives.

Figure 78



Structure of quinazoline-2,4,6-triamine derivative.

Figure 79



Structures of indole/pyrido-based quinazoline derivatives.

Antitrypanosomatid and antiplasmodial activity

A novel set of 2,4,6-triaminequinazoline derivatives has been designed and synthesized as potential trypanocidal, leishmanicidal, and antiplasmodial agents [104]. The new derivatives were rationalized using docking studies of the dihydrofolate reductase (from *Trypanosoma cruzi*, *Leishmania major*, and *Plasmodium vivax*) and pteridine reductase (from *T. cruzi* and *L. major*) architectures. All of the newly synthesized analogs were examined *in vitro* against both bloodstream trypomastigotes of *T. cruzi* (NINOA and INC-5 strains) and promastigotes of *Leishmania mexicana* (MHOM/BZ/61/M379 strain) and also for cytotoxicity using the Vero cell line. The derivatives (**159b–d**) (Fig. 81) were the most active agents against *T. cruzi*, exhibiting better activity compared with standard drugs nifurtimox and benznidazole. Also, the analogs (**159b–e**) exhibited the strongest potency against *L. mexicana*, compared with glucantime (the reference drug). In the cytotoxicity assay, protozoa were more susceptible than Vero cells. *In vivo*, the *Plasmodium berghei* assay (ANKA strain) showed that the analogs (**159a–e**) had more potency than chloroquine and pyrimethamine (reference drugs) upon oral administration. The antiprotozoal potency of these compounds represents an important point in therapeutical chemistry in the treatment of Chagas' disease, leishmaniosis, and malaria.

Antileishmanial activity

The derivative N^6-(ferrocenmethyl)quinazolin-2,4,6-triamine (**160**) is one of a set of quinazoline-2,4,6-triamines (Fig. 82) that were prepared and assessed *in vitro* against *L. mexicana*[104]. It displayed potency on promastigotes and intracellular amastigotes stages of the parasite besides its drawbacks in human tissues. Interestingly, antiparasitic effect is mainly related to the presence of the ferrocene group. This moiety affords important characteristics to the molecule, primarily as a result of the readily oxidized iron atom. According to various studies, the ferrocene group can exert its effect through redox reactions by means of its ability to exert reactive oxygen species, principally the hydroxyl radicals. Additionally, the quinazoline-2,4-diamine scaffold is required for further biological activity.

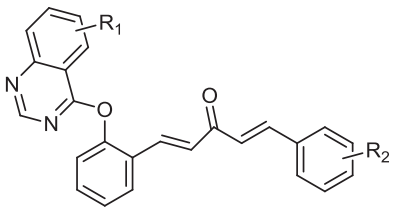
Various quinazoline derivatives of miscellaneous activities

Amin *et al.* [105] synthesized a new class of spiro[(2*H*,3*H*)quinazoline-2,1′-cyclohexan]-4(1*H*)-one analogs as PARP-1 inhibitors. Twenty-one derivatives that exhibited the best fit to the target enzyme according to the docking study were selected to assess their in-vitro cytotoxic potency. It has been found that most of the synthesized quinazoline derivatives exhibited effective antiproliferative activity against breast carcinoma cell lines and showed effective inhibitory effect on the target PARP-1 enzyme (compounds **161–167**) (Fig. 83).

Also, a series of spiroquinazoline-2,1′-cyclohexan-4(1*H*)-one derivatives conjugated to various aromatic and/or heterocyclic ring systems such as benzenesulfonamide, pyrazoline, oxazoline, pyrimidin-2-thione, 2-oxo(imino) pyridine, imidazoline, and thiazolidinone have been designed and synthesized as anti-inflammatory and analgesic agents [106]. It has been found that the tested derivatives exhibited dual pharmacological activities with superior gastrointestinal safety profile compared with the reference drug indomethacin (Fig. 84).

Recently, a new set of hybrids bearing *N*-phenylquinazolin-4-amine and hydroxamic acid moieties (compounds **172**) were synthesized and identified as dual VEGFR-2/HDAC (histone deacetylase-like protein) inhibitors with IC_{50} ranging in the nanomolar levels [107] (Fig. 85).

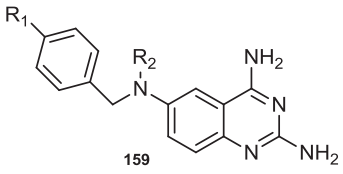
Figure 80



158, a, R_1= H, R_2= 4-F
b, R_1= 6-Me, R_2= 4-NO_2
c, R_1= 6-Me, R_2= 4-F

Structures of (quinazolin-4-yloxy)phenyl-1,4-pentadien-3-one derivatives.

Figure 81

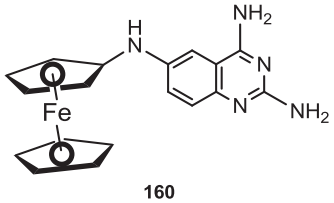


159

a, R_1= OCH_3, R_2= H
b, R_1= OCF_3, R_2= H
c, R_1= OCF_3, R_2= CH_2CH_3
d, R_1= OCH_3, R_2= 4-F-COC_6H_4
e, R_1= OCF_3, R_2= 4-F-COC_6H_4

Structures of 2,4,6-triaminoquinazoline derivatives.

Figure 82



160

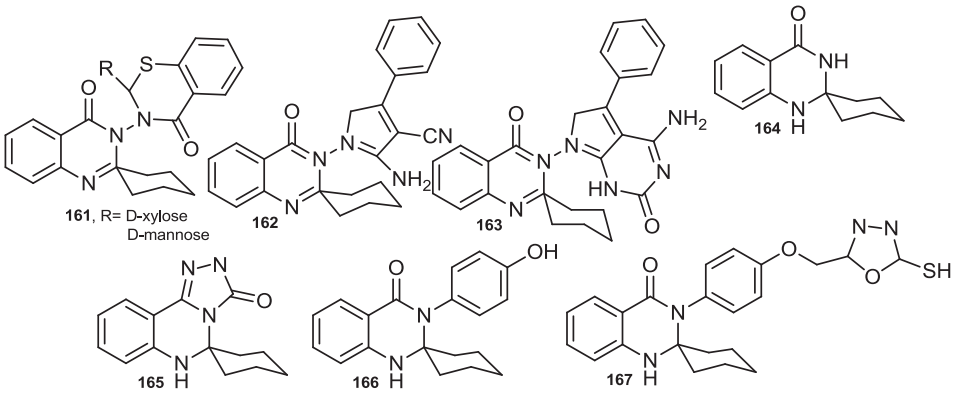
Structures of quinazoline-2,4,6-triamine derivative.

A novel class of 7- or 8-substituted 4-morpholine-quinazoline compounds was designed and prepared. The inhibitory effects of the new derivatives against the PI3Kα enzyme and seven tumor cell lines, PC-3, DU145, MCF-7, BT474, SK-BR-3, U937, and A431, were examined *in vitro*. The derivative **173** exhibited high PI3Kα inhibition potency ($IC_{50}=4.2$ nmol/l) and promising cancer activity. Also **173** displayed a remarkable inhibitory action against the PI3K/Akt/mTOR pathway as a potent PI3K inhibitor and anticancer agent [108,109] (Fig. 86).

Conclusion and perspectives

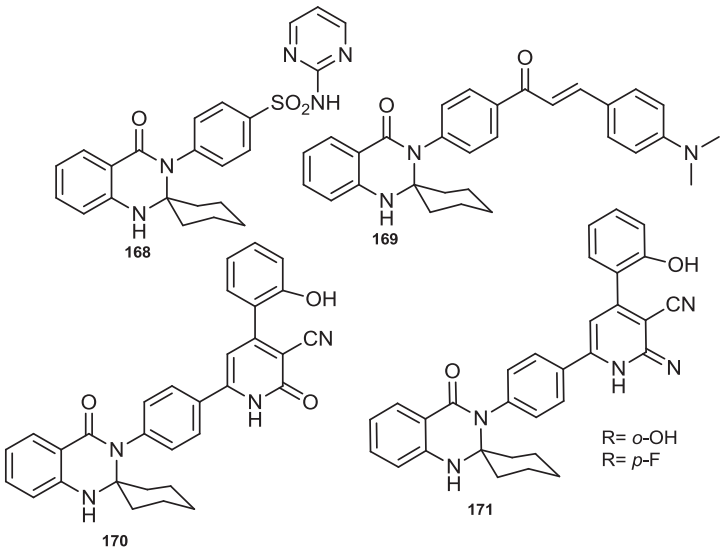
Drug discovery and improvement of existing drugs has a pivotal role in the progress of therapeutic chemistry. Significant attention is being diverted to the development of the molecular architecture of heterocyclic compounds in (bio)organic chemistry. In this review, we have introduced a wide range of novel, effective, mild, and simple routes of synthesis to gain various substituted quinazoline and quinazolinone derivatives through readily available and cheap starting materials. Several strategies including metal-catalyzed reactions, MW irradiation, and conventional heating methods have been successfully employed to achieve these diversely decorated skeletons, which are of significant importance in pharmaceutical and agrochemical industries. This review also discusses numerous biological targets with significant bioactivities. Several quinazoline-based and quinazolinone-based drugs have already made their way to clinics and are being successfully used against various disorders. The SAR showed that obtaining the required biological potency for the synthesized compounds depends on the selection of a

Figure 83



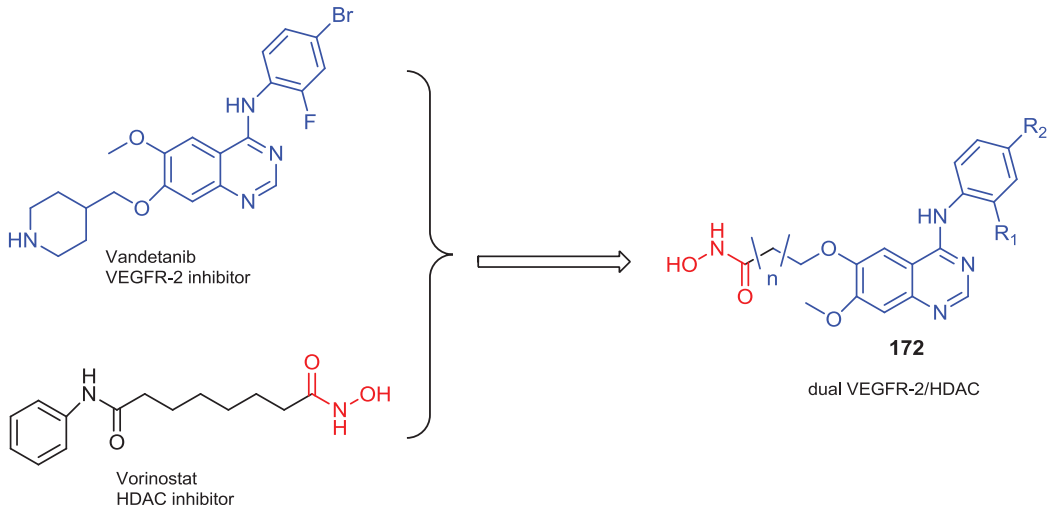
Structures of spiro[(2*H*,3*H*)quinazoline-2,1′-cyclohexan]-4(1*H*)-one derivatives.

Figure 84



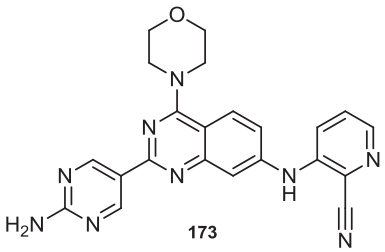
Structures of novel derivatives of spiroquinazoline-2,1′-cyclohexan-4(1*H*)-one derivatives.

Figure 85



Structures of novel *N*-phenylquinazolin-4-amin-hydroxamic acid hybrids. HDAC, histone deacetylase; VEGFR-2, vascular endothelial growth factor receptor 2.

Figure 86



7-Substituted-4-morpholine-quinazoline derivatives.

suitable substitution pattern, including electron-donating and electron-withdrawing, as well as some heterocyclic moieties, on the basic backbone. Furthermore, because of the simplicity of synthetic methods enabling the construction of core scaffolds of many marketed drugs, we hope to see further research in the design of novel functionalized quinazoline and quinazolinone derivatives, with exploitation of their biological activities in diverse ways. Chemical and biological studies should be continued on these scaffolds with the aim to obtain novel drugs with various biological activities of high selectivity and potency and devoid of the side effects of the parent drugs.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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