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Recent Advances on Quinazoline

Edited by Ali Gamal Al-Kaf

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Contributors
Ali Gamal Al-Kaf, Atta ul Haq, Ayesha Rafiq, Huseyin Istanbullu, Magdi E.A. Zaki, Matloob Ahmad, Muhammad Jawwad Saif, Rana Abdullah Al-Robaidi, Sami A. Al-Hussain, Sana Aslam, Tooba Jabeen, Wafa Mohamed Al Madhagi

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Meet the editor

Prof. Dr. Ali Gamal Al-Kaf obtained a Ph.D. in Pharmaceutical Sciences in 2006. He is the previous Chief Council for Accreditation and Quality Assurance and former dean of the Faculty of Pharmacy, Sana'a University, Yemen. He is currently the dean of the Faculty of Medical Sciences and a professor in the Medicinal Chemistry Department at the National University. He is a member of the Yemeni Higher Medical Council and many other associations and international groups. He is also chairman of the *Universal Journal of Pharmaceutical Research*. Dr. Al-Kaf is an editor and associate editor of several international journals. His research interests include the synthesis and biological activity of 4-oxopyrimidine and quinazolinone -4 derivatives, structural biology and bioinformatics in drug design, Yemeni medicinal plants, development and validation of spectrophotometric and high-performance liquid chromatography (HPLC) methods for different drugs, and antibiotic and antimicrobial resistance in Yemen. He is the author of more than ninety articles and fifteen books. He also has four patents to his credit.

Contents

Preface

The biological activities of quinazoline have attracted the interest of medicinal chemists. *Recent Advances on Quinazoline* presents the newest research in quinazoline, focusing on its biological activities and modern methods of its synthesis.

The book presents information on this organic compound in a condensed and cohesive form, ca-tering to the needs of readers in medicine and pharmacy. It includes six chapters that cover re-cent advances in the field, the synthesis of imidazoquinoline and benzimidazoquinazoline, the use of computational studies in discovering new active quinazoline derivatives, the medicinal im-portance of triazoloquinazoline, quinazoline and its derivatives, and the biological activities of quinazoline.

I would like to thank the authors for their excellent contributions. I am also grateful to IntechOpen, especially Publishing Process Manager Mr. Tonci Lucic.

We welcome any suggestions, comments, and criticism on the subject matter of the book. We hope that this work will prove beneficial for students, teachers, and scientists.

Dr. Ali Gamal Al-Kaf
Professor,
Medicinal Chemistry Department,
Faculty of Pharmacy,
Previous Dean of Faculty of Pharmacy,
Sana'a University,
Yemen

Dean of Faculty of Medical Sciences,
Department of Pharmacy,
National University,
Yemen

Section 1

Overview on Quinazoline and Its Pharmacological Activities

Chapter 1

Introductory Chapter: Recent Advances on Quinazoline

Ali Gamal Al-Kaf

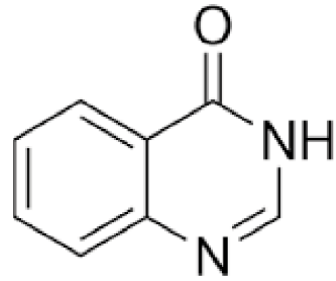
1. Introduction

Quinazolines are heterocyclic systems with numerous reactive centers, which make them interesting research topics. The quinazoline molecule (1,3-diazanaphthalene) is composed of two pyrimidine and benzene rings, which are fused six-membered simple aromatic rings. Another name for it is benzopyrimidine. Along with quinoxaline, phthalazine, and cinnoline, it is isomeric. Among the heterocycles, quinazolines are widely recognized for their extensive pharmacological activity and their utility as synthetic intermediates. Many pharmacological activities, including analgesic and anti-inflammatory, antimicrobial, anti-tubercular, antihistaminic, antitussive, bronchodilator, antidiabetic, antidiuretic, antihypertensive, sedative-hypnotic activity, antidepressant, antiparkinsonian, antibacterial, anticancer, analgesic, antiallergic, anticonvulsant, antimalarial, and other effects, have been reported to be present in them [1–6].

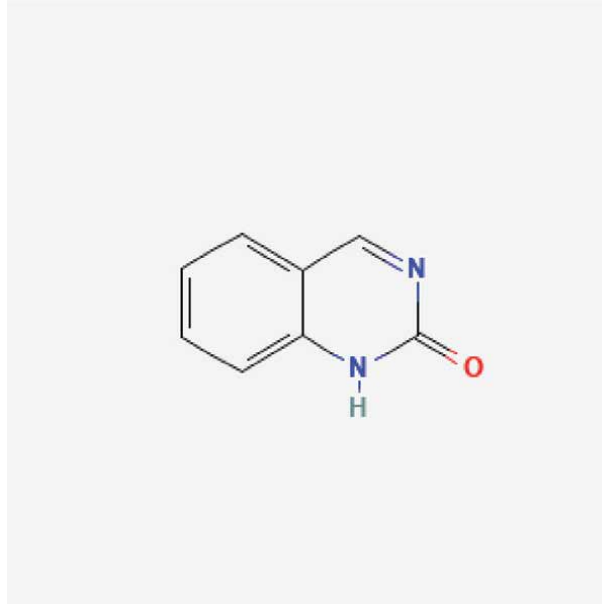
The purpose of heterocyclic rings with nitrogen and sulfur is significant since they are more active both pharmacologically and therapeutically. These substances serve as the foundation for numerous pharmacological products. Due to its numerous pharmacological properties and low number of side effects, quinazoline is one of the heterocyclic moieties selected for this investigation [7]. The chemical formula for quinazoline, a well-known heterocyclic molecule, is C8H6N2. Quinazoline, sometimes called 1,3-diazanaphthalene, is a light yellow crystalline substance made up of one pyrimidine and one benzene ring. In 1895, August Bischler and Lang reported on the synthesis of quinazoline by decarboxylating a 2-carboxy derivative [8]. By using Niementowski synthesis, anthranilic acid treated with amide produced 4-oxo-3,4-dihydroquinazolies [9]. Quinazoline also has other isomers, such as quinoxaline. Quinazoline also has other isomers, such as quinoxaline, cinnoline, and phthalazine [10]. Quinazolines further. the components of over 200 naturally occurring alkaloids that have been separated from microbes and plants and animals [11, 12]. In 1888, Adhatoda vasica yielded the first known quinazoline alkaloid, known as vasicine (±) or peganine. It works quite well against bronchodilators' engagement [13].

One quinazoline derivative that is just as active as quinazoline is quinazolinone [14]. As seen in **Figure 1** [15], Quinazolinones are further divided into smaller groups, such as 4-quinazolinone (a) and 2-quinazolinone (b) based on the substitution pattern.

Because quinazoline is a structure that is present in many medications, clinical candidates, and bioactive compounds, it is therefore of tremendous importance in the field of pharmaceutical chemistry. This introductory chapter centers on the possible



4-quinazolinone (a).



2-quinazolinone (b)

Figure 1.
(a) 4-quinazolinone. (b) 2-quinazolinone.

biological activity of derivatives of quinazoline. The information in this chapter about the most recent advancements on quinazoline analogs with distinctly different pharmacological activity, such as anticancer, antibacterial, antimalarial, antiviral, and antidiabetic properties, will be helpful. Moreover, this chapter will be encouraging for scientists to develop, synthesize, and improve the potential of essential medication containing quinazoline moieties for the future treatment of various illnesses.

In our research project, several chapters have been included, such as Recent Approaches for the Synthesis of Imidazoquinazolines and Benzimidazoquinazolines, Triazoloquinazoline: Synthetic Strategies and Medicinal Importance, computational studies for the quinazoline derivatives, Synthesis and Antiviral activities of some Triazolo Quinazolines Derivatives, Synthetic and Kinetic study of analogues natural occurring chalcones and Flavanone and Quinazoline and its Derivatives: Privileged

Heterocyclic Scaffolds in Antileishmanial Drug Discovery. These chapters included in this book concentrate on the recent advances in methods for medicinal synthesis with more important, valuable, and interested pharmacological activities such as anticancer, antibacterial, antimalarial, antiviral, antidiabetic, and antileishmanial properties to enable medicinal chemists and scientists to design novel drugs with distinctly different pharmacological activity.

In medicinal chemistry, quinazoline and quinazolinone structures are frequently encountered. Quinazolines and quinazolinones exhibit noteworthy properties, including antidepressant, antineoplastic, and antipsychotic properties, while certain quinazoline and quinazolinone compounds are shown to be useful medications with sedative, hypnotics, antimicrobial, anti-inflammatory, antifungal, antimalarial, anticonvulsant, anticoccidial, antiparkinsonian, anticancer, analgesic, and antipsychotic properties [16–18].

I am grateful to all of the authors who contributed to this book for their insightful, worthwhile, and significant discussions on Recent Advances on Quinazoline.

The book, which covers all newer medications in brief, will be very beneficial to readers. The primary goal in developing this book was to meet readers who are employed in the medical and pharmaceutical fields in particular by presenting the material in an understandable, concise, and unified manner. Additionally, I would like to express my gratitude to everyone who helped to complete the book. We greatly thank the publishers and Intech for Science, Technology, and Medicine's collaboration in making this book possible. It would be impossible to overlook the assistance that I obtained from Mr. Tonci Lucic, the Publishing Process Manager.

Author details

Ali Gamal Al-Kaf[1,2]

1 Faculty of Pharmacy, Medicinal Chemistry Department, Sana'a University, Yemen

2 Faculty of Medical Sciences, Department of Pharmacy, National University, Yemen

*Address all correspondence to: alialkaf21@gmail.com; lialkaf@national-univ.net

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Section 2

Recent Medicinal Chemistry Methods for Synthesis of New Compounds

Chapter 2

Recent Approaches for the Synthesis of Imidazoquinazolines and Benzimidazoquinazolines

Ayesha Rafiq, Sana Aslam, Matloob Ahmad, Muhammad Jawwad Saif, Sami A. Al-Hussain and Magdi E.A. Zaki

Abstract

Heterocyclic ring systems are gaining attention due to their pivotal role in drug design and medicinal chemistry. Quinazolines are nitrogen-containing heterocyclic pharmacophoric units found in abundance in natural and pharmaceutical products. Imidazoquinazolines and benzimidazoquinazolines are fused tricyclic and tetracyclic heterocyclic moieties, respectively. Different isomeric forms of imidazoquinazolines and benzimidazoquinazolines exhibited a plethora of biological applications such as antitumor, antimicrobial, antioxidant, anti-inflammatory, antitubercular, anticancer, antihypertensive, anticonvulsant, antiviral, antimalarial, antiapoptotic, anti-proliferative activities, etc. This chapter addressed the recent synthetic strategies for medicinally privileged scaffolds; imidazoquinazolines and benzimidazoquinazolines. The synthetic routes of various isomeric forms of above-mentioned heterocycles have also been discussed.

Keywords: Quinazoline, Imidazoquinazoline, Benzimidazoquinazoline, synthetic methodologies, medicinal importance

1. Introduction

Heterocycles gain much attention because of their vast applications in biology [1–3] and material sciences [4, 5]. Heterocycles possessed a lot of medicinal benefits [6–9] and played an important role in drug design and development. Among the heterocycles, quinazoline is a bicyclic *N*-containing heterocycle that possesses a broad range of pharmaceutical applications, such as anti-inflammatory [10], antimicrobial [11], anticonvulsant [12], antimalarial [13], antitubercular [14], antioxidant [15], antihypertensive [16], antiviral [17] activities, etc.

Imidazole and benzimidazole are heterocyclic moieties and important pharmacophores in medicinal chemistry. Imidazole is a five-membered aromatic heterocycle that exhibits a number of biological applications, such as antibacterial [18], anticancer [19], antiepileptic [20], antitubercular [21] activities, etc. Benzimidazoles are privileged structures related to their roles in medicinal chemistry, e.g., they play their role in antibacterial [22], antidiabetic [23], antiviral [24], antiulcer [25] activities, etc. Drugs containing quinazoline, imidazole, and benzimidazole are given in **Figure 1**.

Imidazoquinazoline and benzimidazoquinazoline moieties play significant roles as active biological agents. Imidazoquinazoline I is a PI3K inhibitor [26], imidazoquinazoline II is antiapoptotic [27] and benzimidazoquinazoline III is antitumor [28] in its action (**Figure 2**).

2. Imidazoquinazoline

Imidazoquinazoline is a fused tricyclic structure containing imidazole and quinazoline and has three nitrogen atoms in its molecular architecture. It is an

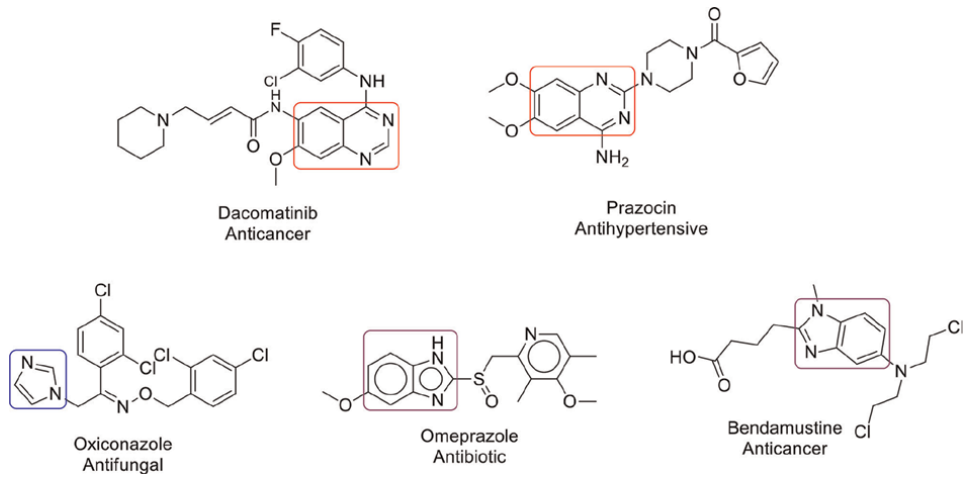


Figure 1.
Quinazoline, imidazole, and benzimidazole-based drugs.

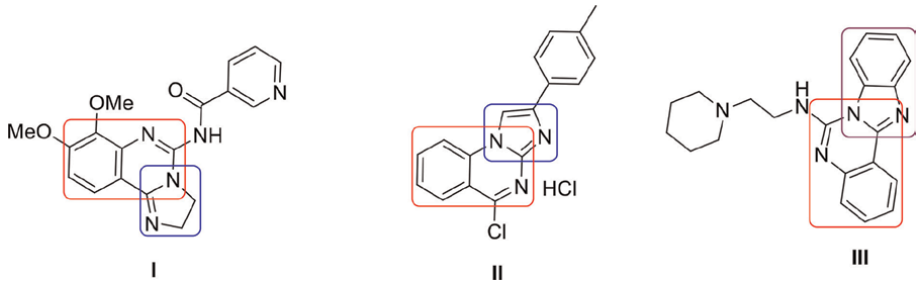


Figure 2.
Biologically active analogues.

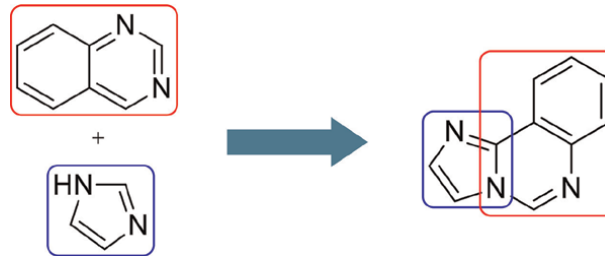


Figure 3.
Structure of Imidazoquinazoline.

Figure 4.
Different isomeric forms of Imidazoquinazoline.

important scaffold in drug molecules such as antithrombotic and anticardiotonic agents [29]. Certain derivatives of imidazoquinazolines show a plethora of biological applications, i.e., antitumor [30], anticonvulsant [31], antihypertensive [32], etc.

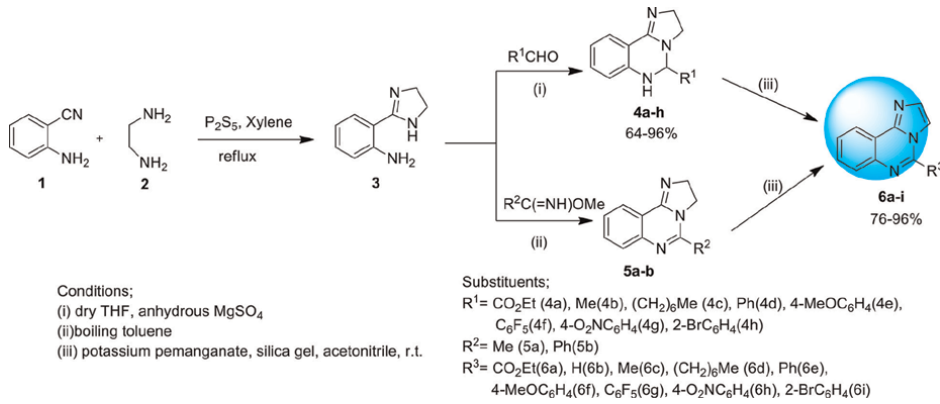
Structures of imidazoquinazoline and their different isomeric forms are given in **Figures 3** and **4**.

2.1 Imidazo[1,2-*c*]quinazoline

Imidazo[1,2-*c*]quinazoline gains much attention for its synthesis because of its large-scale applications in pharmaceuticals as well as in material sciences. Imidazo [1,2-*c*] quinazolines play pivotal roles as anti-inflammatory [33], antimicrobial [34], antiapoptotic [35], anticancer agents [36], and as efficient dopants in OLEDs [37]. Following are the different synthetic strategies of imidazo [1,2-*c*]quinazoline.

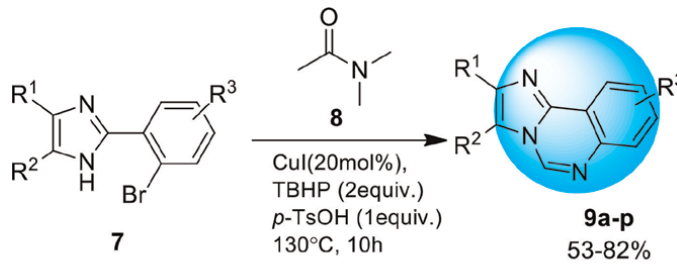
2.1.1 One-pot exhaustive dehydrogenation

An expedient way to synthesize imidazo [1,2-*c*]quinazoline is the reaction of *o*-cyanoaniline (1) with phenylenediammine (2) in xylene under reflux to get an intermediate (3). The aminophenyl imidazole (3), when reacted with various aldehydes, resulted in the formation of 2,3,5,6-tetrahydroimidazoquinazoline (4a-h) in good yields. The aminophenyl imidazole (3) treated with imidates in boiling toluene afforded dihydroimidazoquinazolines (5a-b). The imidazo [1,2-*c*] quinazolines (4a-h) and (5a-b), when underwent the oxidative dehydrogenation conditions, i.e., potassium permanganate and silica gel, using acetonitrile at room temperature separately, afforded the respective targeted products (6a-i) in high yields [38]. A similar study was carried out by Claudi et al. following exhaustive dehydrogenation [39].



2.1.2 Ullmann coupling reaction

Imidazo[1,2-*c*]quinazolines (9a-p) were synthesized in moderate yields through a tandem reductive amination reaction. The reaction of 2-(2-bromophenyl)-4,5-disubstituted-1*H*-imidazole (7) with dimethyl acetamide (8) in the presence of CuI, *tert*-butylhydroperoxide, and *p*-toluenesulphonic acid at 130°C for 10 h afforded a series of desired products [40]. The Ullmann-type C–N coupling reactions in a tandem fashion were also observed by Nandwana et al. [41, 42].



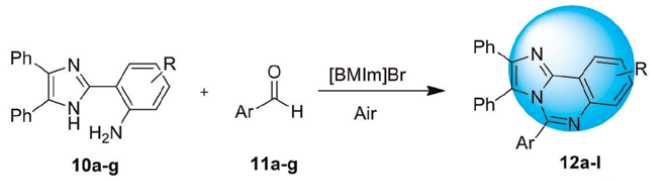
Substituents;

R^1 & R^2=Ph; 9a,9f-g,9k,
R^1 & R^2=Me-Ph; 9b, 9h, 9l
R^1 & R^2= OMe-Ph; 9c,9d,9i,
R^1 & R^2= F-Ph; 9e,9j,9m,
R^1 & R^2=Me; 9o-p,

R^3=H; 9a-e,9n,9o
R^3=F; 9g-j,9p
R^3=8,9-OMe_2; 9k-m
R^3=Me; 9f

2.1.3 Conventional or oxidative coupling

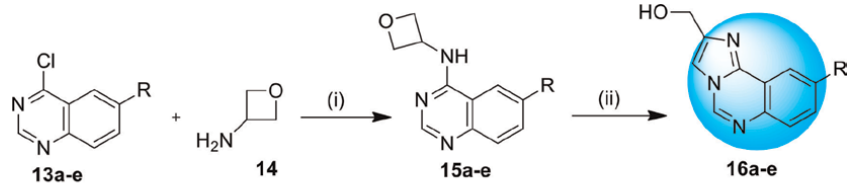
Imidazo[1,2-*c*] quinazolines (12a-l) can be prepared *via* one-pot, catalyst-free, and environment-friendly synthesis using ionic liquids as a solvent in excellent yields by the reaction of imidazolyl anilines (10a-g) with various aromatic aldehydes (11a-g) [43]. The formation of imidazo [1,2-*c*]quinazoline through oxidative coupling catalyzed by AgOTf was studied by Wu et al. [44].



Substituents;
R= 9-Br(10a, 12a), H(10b, 12b), 8-Br(10c,12c), 8-Cl(10d, 12d), 8,9-$(MeO)_2$ (10e, 12e)
9-MeO(10f, 12f), 9-OH (10g, 12g-l)
Ar= 4-BrC_6H_4 (11a,12a,12j), 3,5-$(OCH_3)_2C_6H_3$ (11b,12b), 2-$OCH_3C_6H_4$(11c,12c-d, 12g),
4-ClC_6H_4(11d,12e,12k), 3-BrC_6H_4(11e,12f,12i), 3,4-$Cl_2C_6H_3$(11f, 12h), 4-FC_6H_4(11g,12l)

2.1.4 Intramolecular C-N coupling

Imidazo[1,2-*c*] quinazolines were synthesized by Bagal, S. K. et al. The S_NAr reaction was shown between chloroquinazolines (13a-e) and aminooxetane (14), using K_2CO_3 in acetonitrile to afford (15a-e). Intramolecular cyclization reactions were observed in (15a-e) during reflux in methanol, and finally, imidazo [1,2-*c*] quinazolines (16a-e) were achieved in 15–57% yields [45]. Imidazo [1,2-*c*]quinazoline synthesis through intramolecular C-N coupling was also practiced by Khoza et al. [46].



Conditions;
(i) K_2CO_3, MeCN, 50-90°C
(ii) MeOH, 70-100°C

Substituents;
a; CO_2Et,57% b; NO_2, 54% c;OMe,31%
d;I, 32%, e;Me, 15%

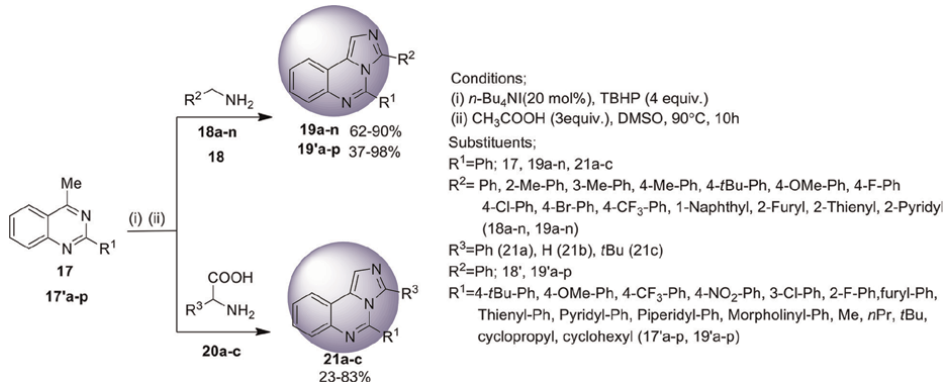
2.2 Imidazo[1,5-*c*]quinazline

Imidazo[1,5-*c*]quinazoline possesses a novel imidazo-*N*-heterocyclic skeleton. The following is the metal-free tandem approach to synthesizing it:

2.2.1 Oxidative domino sp^3 C–H amination

An oxidative domino synthesis pathway for the formation of imidazo [1,5-*c*] quinazolines is the *n*-Bu_4NI catalyzed reaction of 4-methyl-2-phenyl-quinazoline (17) with various benzylamines (18a-n) using *tert*-butylhydroperoxide, acetic acid, and DMSO yielded imidazo [1,5-*c*] quinazolines (19a-n) in high yields. Similarly, by following the same reaction conditions, various 4-methyl-2-substituted quinazolines (17'a-p) were reacted with benzylamine (18′) to give (19'a-n) in poor to high yields. Imidazo[1,5-*c*]quinazoline can also be prepared from amino acids. 4-methyl-2-phenyl-quinazoline (17) got reacted with various amino acids (20-c) under the same

conditions and yielded various imidazo [1,5-*c*] quinazolines (21a-c) in poor to good yields (23–83%) [47].



2.3 Imidazo[2,1-*b*]quinazoline

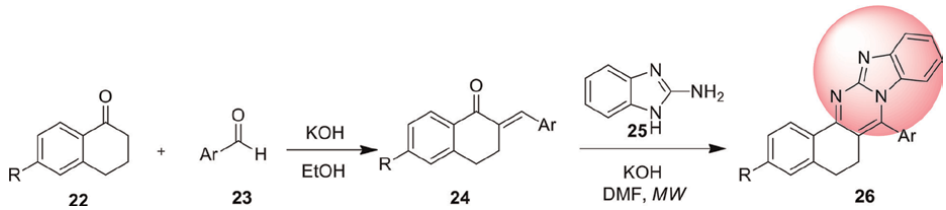
Imidazo[2,1-*b*]quinazoline is an imidazole-blend quinazoline molecule. These types of heterocycles have applications in luminophores, optical lasers, and optoelectronics [48, 49]. Following is the synthetic approach to afford imidazo[2,1-*b*] quinazoline.

2.3.1 Cascade reaction

A cascade microwave-promoted reaction involving Claisen-Schmidt, aza-Michael, and cyclization reactions in the formation of imidazo[2,1-*b*]quinazoline was reported. Claisen–Schmidt reaction was observed between various active methylene ketones **(22)** and numerous aromatic aldehydes **(23)** using KOH and ethanol, resulting in the formation of a series of chalcones **(24)**. These chalcones **(24)** underwent aza-Michael and cyclization reactions with benzimidazole **(25),** using KOH as a base and microwave irradiation as a catalytic tool in DMF to afford the targeted product **(26)** [50]. Imidazo[2,1-*b*]quinazoline was synthesized by Devipriya & her coworkers under UV-light in a cascade fashion [51].

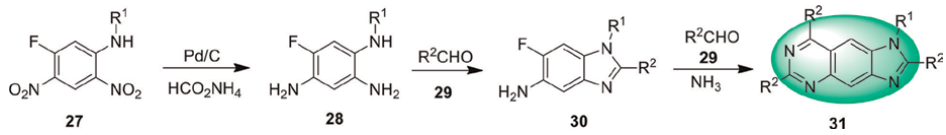
2.4 Imidazo[4,5-*g*]quinazoline

Imidazo[4,5-*g*]quinazoline was discovered as traces in the long-term storage of 5-aminobenzimidazole. Following is the reported multicomponent reaction involved in the synthesis of imidazo[4,5-*g*]quinazoline.



2.4.1 Reductive coupling

Imidazo[4,5-*g*]quinazoline was synthesized by a novel multicomponent reaction that involved a series of reactions, i.e., Schiff base formation, Diels-Alder reaction, deflourination, and dehydrogenation. The substituted dinitrobenzenes (27) were dehydrogenated using Pd/C as a dehydrogenating agent in THF, ethanol, and ammonium formate to afford (28). The intramolecular hetero-Diels-Alder reaction was observed, followed by Schiff base formation in compounds (28) with various aldehydes (29), resulting in the formation of (30). These substituted-benzimidazoles (30) underwent deflourination and dehydrogenation reactions followed by Schiff base formation with a variety of aldehydes (29) to afford targeted products (31) in poor to moderate yields [52]. Reductive amination to prepare imidazo[4,5-*g*]quinazoline as ATP site inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor was practiced by Rewcastle et al. [53].



3. Benzimidazoquinazoline

Benzimidazoquinazoline is a fused tetracyclic structure containing benzimidazole and quinazoline, having three nitrogen atoms in its molecular architecture. Benzimidazoquinazoline derivatives act as potent immunosuppressors [54] and possess promising antitumor activity [55] as well.

Structures of benzimidazoquinazoline and their different isomeric forms are given in **Figures 5** and **6**.

3.1 Benz[4,5]imidazo[1,2-*c*]quinazoline

Benzo[4,5]imidazo[1,2-*c*]quinazoline is a planar heteroacene that possesses both benzimidazole and quinazoline structures fused together *via* a shared bond. Benz[4,5]imidazo[1,2-*c*]quinazoline derivatives showed a wide range of biological applications, i.e., antimicrobial [56], antiviral [57], anticancer [58], anticonvulsant [59], and

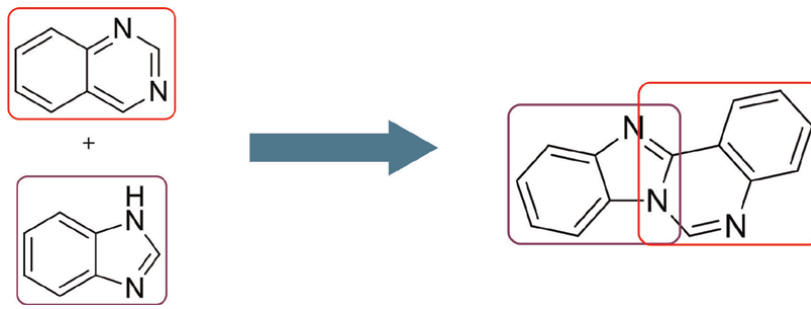


Figure 5.
Structure of benzimidazoquinazoline.

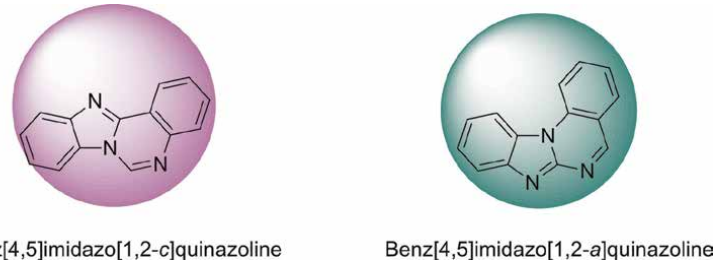
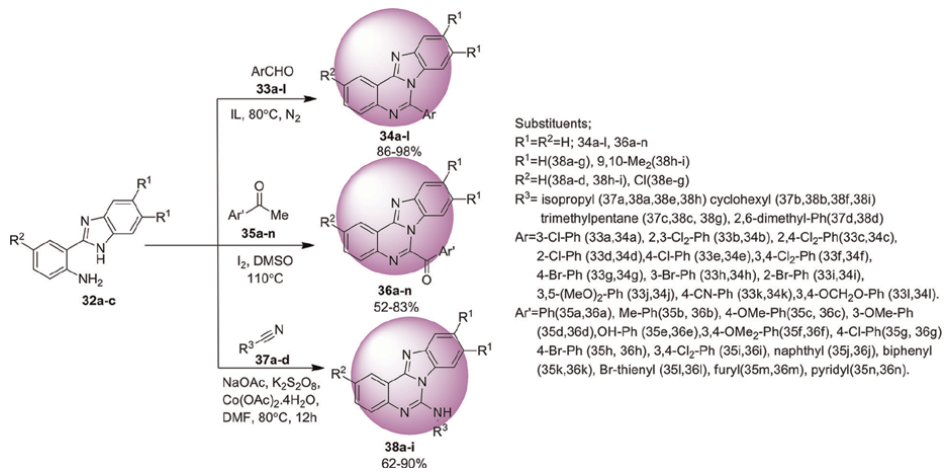


Figure 6.
Different isomeric forms of benzimidazoquinazoline.

anti-inflammatory [60]. Following are the different synthetic methods reported in the literature to afford benz [4,5]imidazo[1,2-*c*]quinazoline.

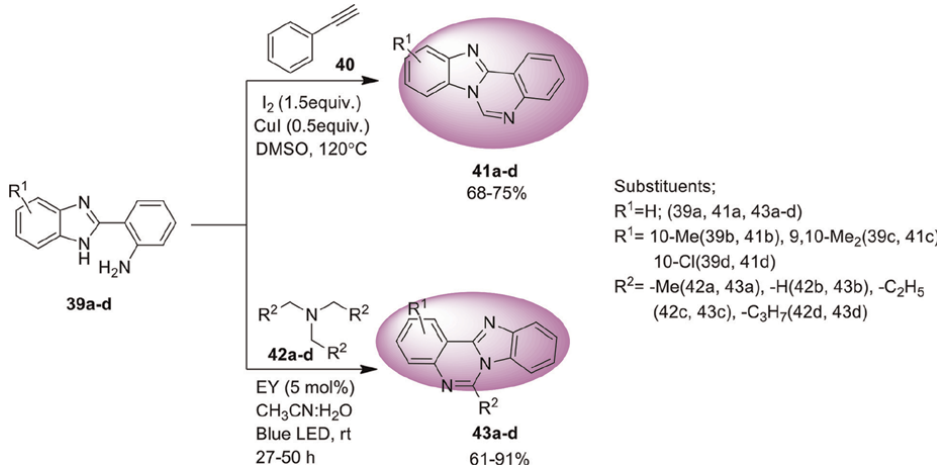
3.1.1 Conventional or oxidative coupling

Benz[4,5]imidazo[1,2-*c*]quinazolines **(34a-I)** can be prepared by green synthesis using ionic liquids by reacting benzimidazolyl anilines **(32a-c)** with various aldehydes **(33a-l)** in a catalyst-free environment in good to excellent yields [61]. Another facile access to afford [4,5]imidazo[1,2-*c*]quinazolines **(36a-n)** is the I_2-catalyzed oxidative cross-coupling reaction between anilines **(32a-c)** and various aromatic methyl ketones **(35a-n)** in moderate to good yields [62]. An efficient protocol was reported to synthesize benz[4,5]imidazo[1,2-*c*]quinazolines **(38a-i)** in moderate to good yields by cobalt-catalyzed isocyanide insertion reactions by reacting anilines **(32a-c)** with various isocyanides **(37a-d)** using sodium acetate, $K_2S_2O_8$, and $Cu(OAc)_2.4H_2O$ under reflux [63].



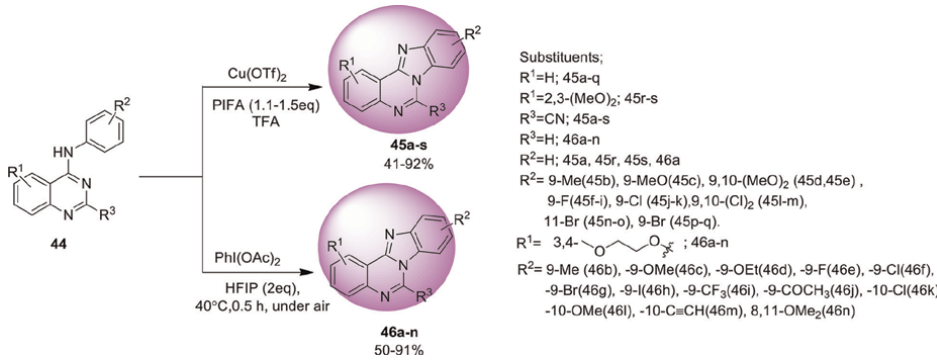
A domino synthetic approach for benz[4,5]imidazo[1,2-*c*]quinazoline formation was the reaction of benzimidazolyl anilines (39a-d) with ethynyl benzene (40) using I_2 and CuI as catalysts in DMSO at 120°C to afford the desired products (41a-d) in moderate to good yields [64]. Highly functionalized benz[4,5]imidazo[1,2-*c*] quinazolines (43a-d) were synthesized under metal-free, photocatalytic conditions by reacting benzimidazolyl (39a-d) with trialky amine (42a-d) using eosin Y (EY) as a

catalyst in aqueous acetonitrile in the presence of blue LED at room temperature for 27–50 h to obtain the desired products [65].



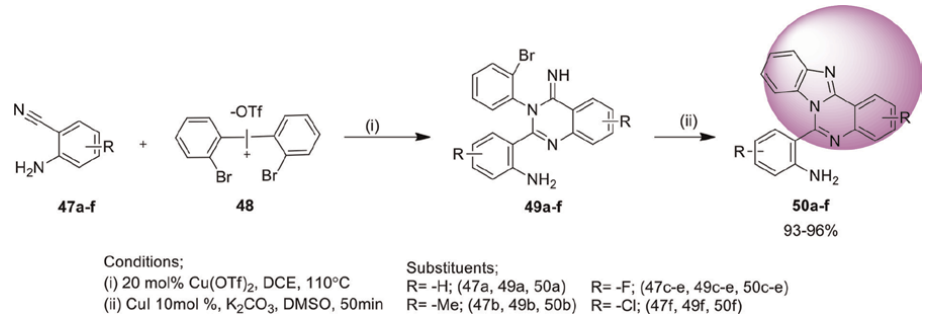
3.1.2 Intramolecular C-N coupling via C-X activation

Another approach to synthesize benz[4,5]imidazo[1,2-*c*]]quinazolines (45a-s) was the cycloamination reaction between substituted anilinoquinazolines (44) and phenyliodine *bis*(triflouroacetate) (PIFA) using $Cu(OTf)_2$ in TFA in poor to good yields [66]. Bioactive Erlotinib analogues containing the benz[4,5]imidazo[1,2-*c*] quinazoline (46a-n) moiety were synthesized by the metal-free intramolecular amination reaction of anilinoquinazolines (44) with hexafluoroisopropyl alcohol (HFIP), using phenyliodide diacetate as a catalyst at 40°C for half an hour to afford the targeted product [67].



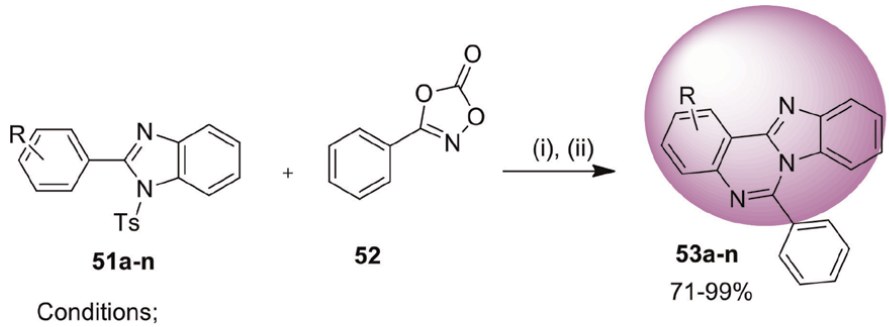
3.1.3 Ullmann N*-arylation reaction*

An easy way found to synthesize benz[4,5]imidazo[1,2-*c*]quinazolines (50a-f) was the Ullmann *N*-arylation reaction. The tandem reaction between *o*-cyanoanilines (47a-f) and diaryl iodonium salt (48) using $Cu(OTf)_2$ as a catalyst in DCE at 110°C afforded intermediates (49a-f). The further treatment of quinazolin-4(3*H*)-imines (49a-f) with CuI resulted in the formation of desired products [68].



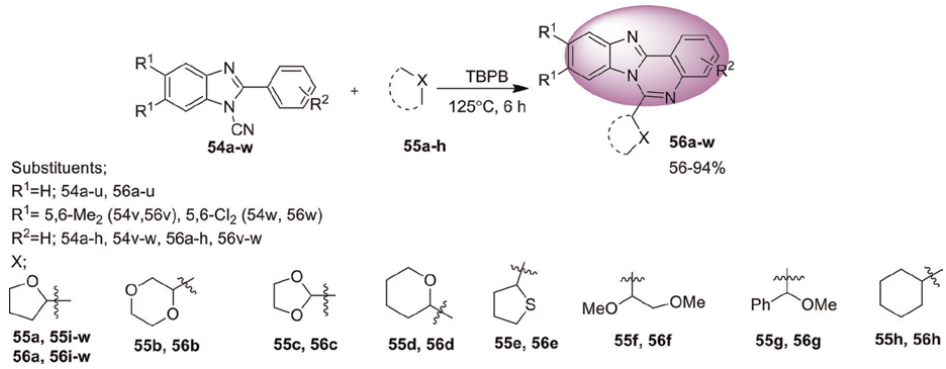
3.1.4 Directed arylic C-H amidation

Another efficient protocol reported to synthesize benz[4,5]imidazo[1,2-*c*] quinazolines (53a-n) was the reaction between *N*-tosyl-2-phenyl benzimidazoles (51a-n) and phenyl dioxolone (52) using Rh(III) catalyst in the presence of silver *bis*(triflimide) in DCE to afford the targeted product in 71–99% yields [69]. Directed arylic C-H amidation approach aided by Rh(III) catalyst was adopted by Xu and his colleagues to synthesize benz[4,5]imidazo[1,2-*c*] quinazolines [70].



3.1.5 Double C-H functionalization

A metal-free pathway for the synthesis of benz[4,5]imidazo[1,2-*c*]quinazoline was reported by Xiaojing, T. et al. Accordingly, the desired products (56a-w) can be obtained in 56–94% yields by reacting *N*-cyanobenzimidazoles (54a-w) with (55a-h) under oxidative conditions in the presence of *tert*-butyl peroxybenzoate [71]. Double C-H functionalization approach assisted by visible-light photoredox catalysis was executed by Xu et al. [72].

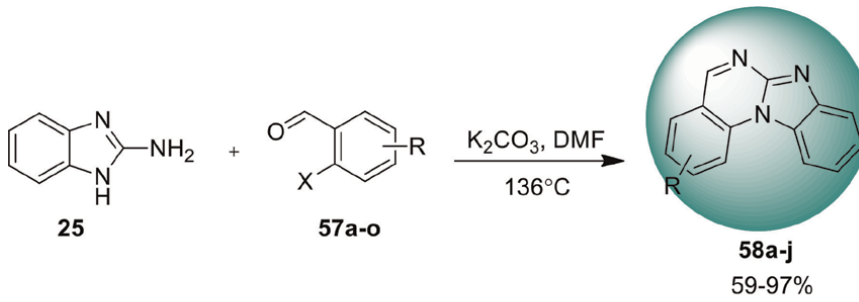


3.2 Benz[4,5]imidazo[1,2-*a*]quinazoline

Here are the methods for the synthesis of another isomer, benz[4,5]imidazo[1,2-*a*] quinazoline, reported in the established literature;

3.2.1 Transition metal-free tandem process

One-pot regioselective synthesis of benz[4,5]imidazo[1,2-*a*]quinazoline was reported by Fang, S. et al. Anilinobenzimidazole (25) showed a reaction with various aromatic aldehydes bearing halogen groups and a nitro group (57a-o) in DMF to afford the targeted products (58a-j) in 59–97% yields [73]. Transition metal-free coupling reaction to form benzimidazoquinazoline was carried out by Kim et al. under recyclable magnetic MOF-199 catalysis [74].

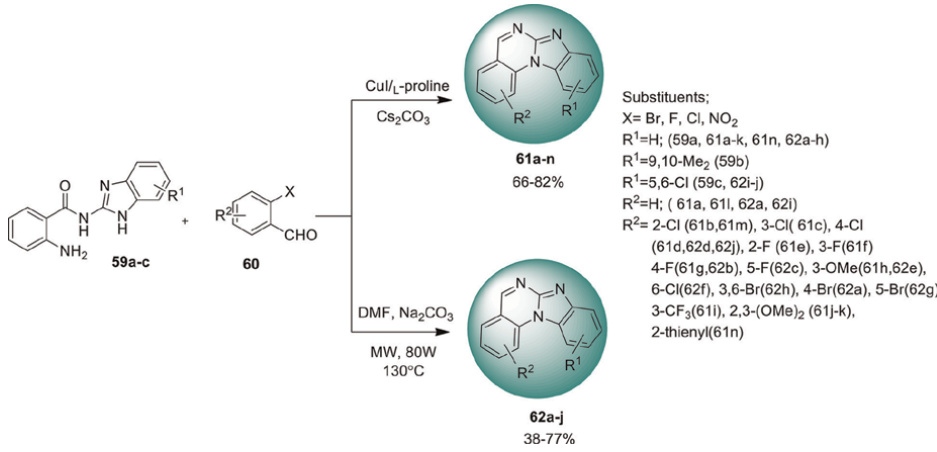


Substituents;
X= F,Cl, Br, NO_2,
R=H; 57a-d, 58a
R= 5-CF_3 (57e), 5-Br(57f, 57n), 4-Br(57g), 4-OMe(57h),
6-F(57i, 57l), 5-Cl(57j, 57k), 5-NO_2 (57m), 5-OMe (57o)
R= -3-CF_3 (58b), -3-Br(58c), 2-Br(58d), 2-OMe(58e), 4-F(58f)
3-Cl(58g), 3-F(58h), 3-NO_2(58i), 3-OMe(58j).

3.2.2 Intramolecular C: N bond formation

Benz[4,5]imidazo[1,2-*a*]quinazolines can be prepared from *N*-(2-benzimidazolyl)-2-aminobenzamides (59a-c) and *o*-halogenated aromatic aldehydes

(60). When both moieties showed a reaction using $CuI/_L$-proline in the presence of base Cs_2CO_3, the desired products (61a-n) can be achieved in good yields [75]. Another synthetic approach was the metal-free microwave-assisted reaction, which was designed by using the same reactants in DMF at 130°C to get the benz[4,5] imidazo[1,2-*a*]quinazoline (62a-j) in 38–77% yields [76].



4. Conclusion

The fused heterocyclic moieties tend to achieve the top of the list position in drug design because of their wide range of pharmacological applications. In this context, this chapter is focused on the different synthetic approaches of imidazoquinazolines and benzimidazolquinazolines. These biological scaffolds were prepared by a large number of synthetic routes that are summarized in this chapter. These routes include Ullmann cross-coupling reaction, Claisen–Schmidt reaction, Aza–Michael reaction, cyclization reaction, $Cu(OTf)_2$ catalyzed reaction, Iodine-mediated oxidative annulation reaction, oxidative and nonoxidative C-N coupling reaction, photoredox catalyzed synthesis, metal-free synthesis, green synthesis, microwave mediated synthesis, oxidative domino synthesis, transition metal-free and transition metal-catalyzed tandem processes. These synthetic strategies will be helpful in bringing novelty to the synthesis of bioactive compounds and in exploring a new area of medicinal research.

Author details

Ayesha Rafiq[1], Sana Aslam[2], Matloob Ahmad[1*], Muhammad Jawwad Saif[3], Sami A. Al-Hussain[4] and Magdi E.A. Zaki[4*]

1 Department of Chemistry, Government College University, Faisalabad, Pakistan

2 Department of Chemistry, Government College Women University, Faisalabad, Pakistan

3 Department of Applied Chemistry, Government College University, Faisalabad, Pakistan

4 Faculty of Science, Department of Chemistry, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Saudi Arabia

*Address all correspondence to: matloob.ahmad@gcuf.edu.pk and mezaki@imamu.edu.sa

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Chapter 3

Triazoloquinazoline: Synthetic Strategies and Medicinal Importance

Tooba Jabeen, Sana Aslam, Matloob Ahmad, Atta ul Haq, Sami A. Al-Hussain and Magdi E.A. Zaki

Abstract

Triazoloquinazoline is a fused heterocyclic nucleus, formed by the fusion of two fundamental heterocyclic moieties; triazole and quinazoline. This class of compound is known for its potential as a therapeutic agent and is endowed with several pharmacological applications. Triazoloquinazoline and its derivatives have shown a variety of biological applications such as anticancer, anti-inflammatory, antimicrobial, antiviral, antihypertensive, anticonvulsant, antidiabetic, antioxidant, adenosine receptor antagonist, and significant cytotoxic activities. Hence, this privileged scaffold could act as an important candidate in the field of drug development. Many synthetic protocols have been developed to efficiently synthesize this fused heterocycle and its derivatives. Triazole and quinazoline rings fused at different positions which occurs in various isomeric forms such as, 1,2,4-triazolo[1,5-*c*]quinazoline, 1,2,4-triazolo[1,5-*a*] quinazoline, 1,2,4-triazolo[4,3-*c*]quinazoline, 1,2,4-triazolo[4,3-*a*]quinazoline, etc. This book chapter covers the synthesis of various isomeric forms of triazoloquinazoline as well as their biological activities.

Keywords: Triazoloquinazoline, synthesis, 1,2,4-triazolo[4,3-*c*]quinazoline, 1,2,4-triazolo[1,5-*c*]quinazoline, triazoloquinazoline derivatives, medicinal importance

1. Introduction

Heterocyclic compounds have gained a significant reputation in pharmaceutical chemistry and drug development [1–4]. Among them, five or six-membered heterocycles containing sulfur and nitrogen atoms have a broad range of biological applications [5–7]. Triazoloquinazoline is a fundamental fused heterocyclic compound that contains pharmacologically active triazole and quinazoline moieties and possesses a broad bioactivity spectrum. Both heterocyclic moieties have shown considerable interest in the field of medicine and drug development. Quinazoline derivatives have been found to play a substantial role in the development of multitarget agents [8] with a wide range of biological activities such as anticancer [9], anti-inflammatory [10], antimicrobial [11], antihyperlipidemic [12], antihypertensive [13], anticonvulsant [14], antidiabetic [15], cellular phosphorylation inhibition [16], and dihydrofolate

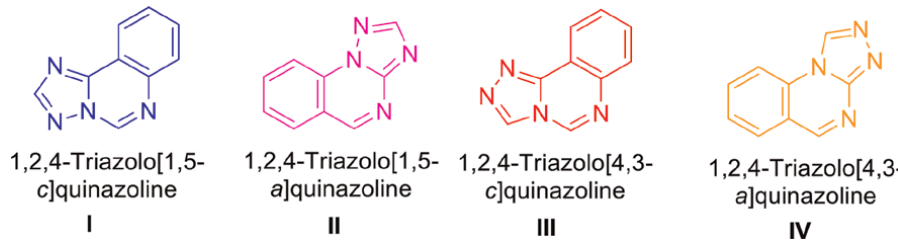


Figure 1.
Various isomeric forms of triazoloquinazoline.

reductase inhibition [17]. 1,2,4-Triazole-containing compounds have been reported for pharmacological properties like anticonvulsants, muscle relaxants [18], and anti-histaminic activities [19]. Therefore, the combination of these two active components produce medicinally important scaffold, triazoloquinazoline, which occurs in various isomeric forms such as, 1,2,4-triazolo[1,5-*c*]quinazoline **I**, 1,2,4-triazolo[1,5-*a*]quinazoline **II**, 1,2,4-triazolo[4,3-*c*]quinazoline **III**, 1,2,4-triazolo [4,3-*a*]quinazoline **IV,** etc (**Figure 1**). Many synthetic strategies have been proposed for the facile synthesis of 1,2,4-triazoloquinazoline from 4-hydrazinoquinazoline [20]. 1,2,4-Triazolo[1,5-*c*]quinazolines have been synthesized by the treatment of 4-hydrazinoquinazolines with aliphatic carboxylic acids [21]. Various substituted 1,2,4-triazoloquinozolines were obtained from hydrazide intermediates [22] and from corresponding thiosemicarbazide derivatives [23, 24]. *N*-Cyanoimidocarbonates and substituted hydrazinobenzoic acids also act as precursors for the formation of this compound [25, 26]. Various facile synthetic routes such as multicomponent reactions and microwave-assisted synthesis have also been developed (**Figure 1**) [27–30].

Triazoloquinazoline constitutes a pharmacologically interesting class of compounds showing a diverse range of biological profiles. This class of compounds and their derivatives have shown prominent biological activities such as anti-hypertonic activity [31], antirheumatic and antianaphylactic activity [21], anti-hypertensive [32], neuro-stimulating activity [21], anti-inflammatory [33], antiviral [34], anti-fungal [35], anti-microbial [35], anti-bacterial [36], anti-oxidant [37], anti-convulsant [38], adenosine receptor antagonists [39], and significant cytotoxic activities [40, 41]. In summary, triazoloquinazoline is an important class of organic compounds that has drawn attention to its potential as a pharmacologically active agent. A number of publications have been made on different synthetic routes as well as medicinal importance of this fused heterocycle.

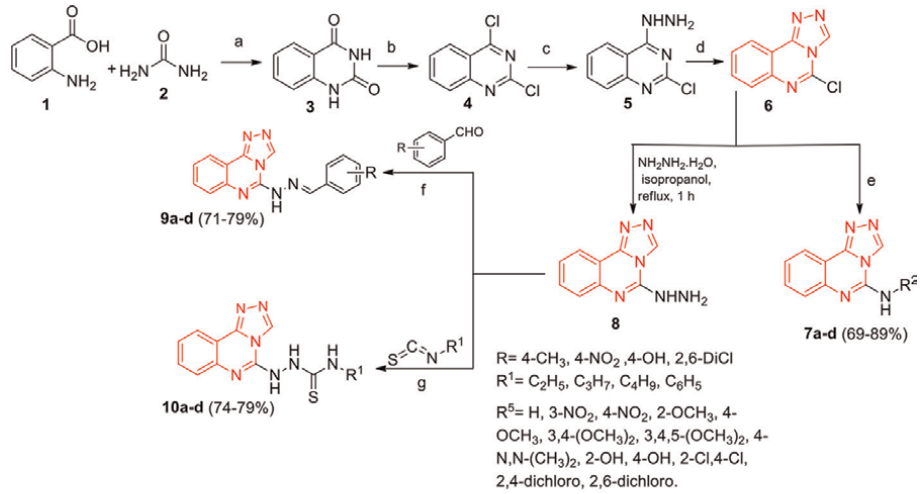
2. Synthetic pathways of triazoloquinazolines and derivatives

2.1 Synthesis of [1,2,4]-triazolo[4,3-*c*]quinazoline

2.1.1 Synthesis from 2-aminobenzoic acid

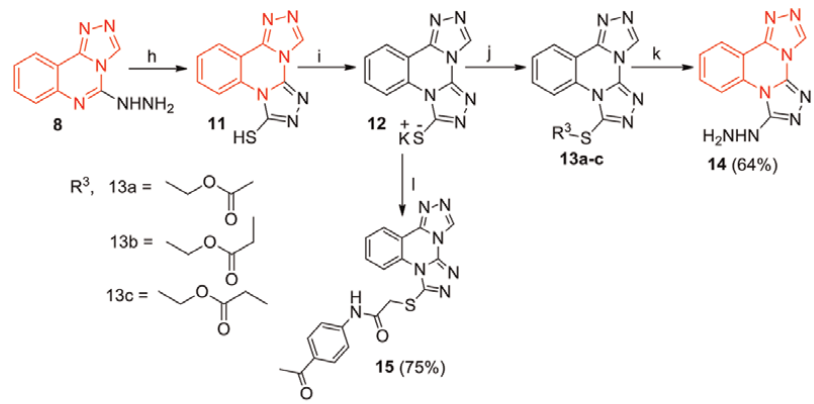
Many synthetic routes have been developed to efficiently synthesize [1,2,4]-triazolo[4,3-*c*]quinazolines starting from the commercially available 2-aminobenzoic acid **1**. In this regard, Alesawy *et al*. synthesized derivatives **7a-d**, **9a-d**, and **10a-d**. The compound **1** was reacted with urea **2** at 200°C for 6 h to afford the intermediate **3** which was further treated with phosphorus oxychloride to get

2,4-dichloroquinazoline **4**. Then, the dropwise addition of hydrazine hydrate followed by cyclization using triethyl orthoformate yielded compound **6**. Compound **6** was further refluxed with various substituted amines to afford **7a-d**. The derivatives **9a-d** were obtained by reacting compound **8** with aromatic aldehydes using the catalytic amount of glacial acetic acid in ethanol. Finally, the treatment of compound **8** with isothiocyanates in ethanol afforded the derivatives **10a-d** [40, 42].

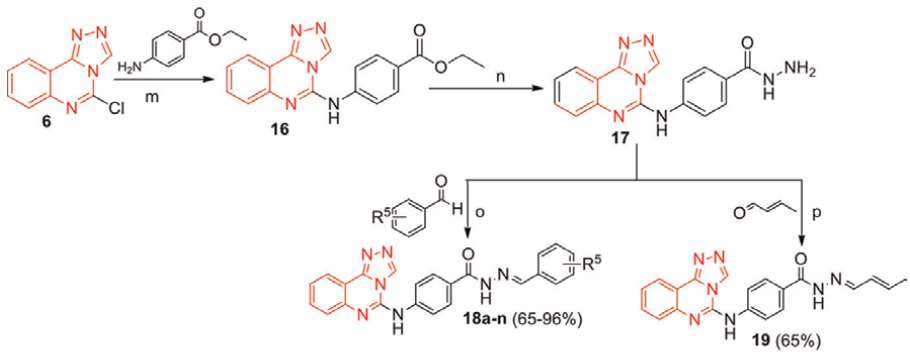


Reagents and conditions: (a) Fusion , 200 °C, /6 h (b) $POCl_3$/ TEA, reflux, 7 h (c) $NH_2NH_2.H_2O$, 0-5 °C, 2h,C_2H_5OH (d) triethylorthoformate, reflux, 1 h (e) isopropanol, reflux, 1-7 h, amine/ substituted amines (f) C_2H_5OH, heating, acetic acid, reflux,6 h (g) C_2H_5OH, reflux, 3 h

Similarly, Azab *et al*. in 2022 afforded the derivatives **18a-n** and **19**. The intermediate **6** was obtained through a similar reaction pathway and further, it was reacted with methyl 4-aminobenzoate under reflux in acetonitrile to afford compound **16**. The targeted compounds were obtained by the treatment of **16** with hydrazine hydrate followed by a reaction with appropriate aldehydes in ethanol [43]. El-Adl *et al*. reacted intermediate **8** with carbon disulfide in KOH using ethanol to afford derivative **11**. The derivatives **13a-c** were obtained by treating **12** with various substituted chloroacetates in DMF. Furthermore, the final compound **14** was afforded through a reaction with hydrazine hydrate in ethanol. The acetamide derivative **15** was also obtained via treatment with the corresponding reagent [44].



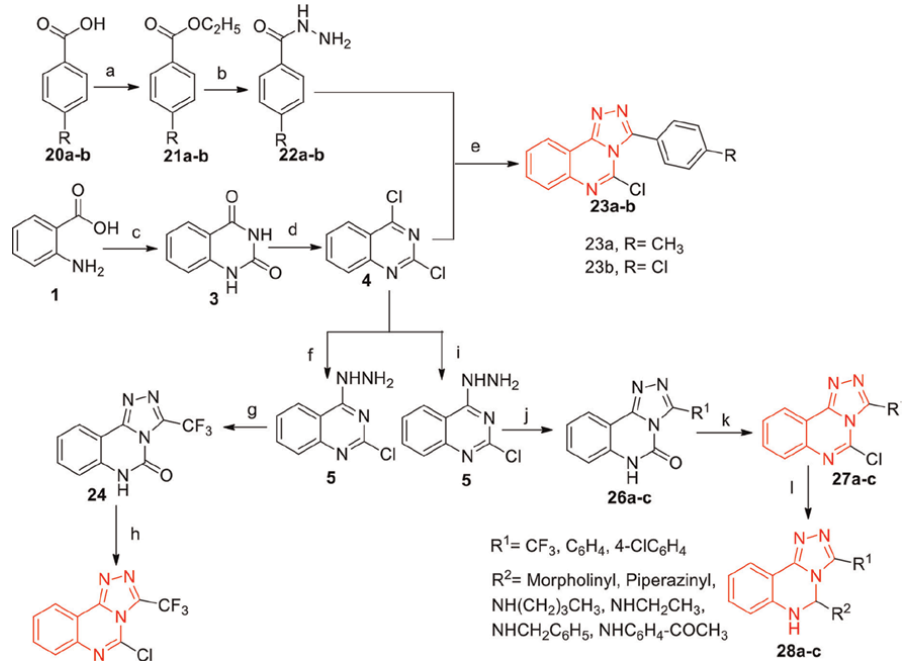
Reaction conditions: (h) i- CS_2/KOH, C_2H_5OH, reflux, 5 h, ii-HCl (i) KOH, C_2H_5OH, heating,0.5 h (j) DMF, KI,reflux, 3 h,ethyl 2,2-dichloroacetate,ethyl 2-chloroacetate,ethyl 3-chloropropanoate (k) $NH_2NH_2.H_2O$, C_2H_5OH, reflux, 2 h (l) DMF, KI, Reflux, 5 h,*N*-(4-acetylphenyl)-2-chloroacetamide



Reagents and conditions: (m) acetonitrile, reflux, 1 h (n) NH_2NH_2,H_2O, EtOH, reflux, 6 h (o) AcOH,EtOH, reflux, 4 h.

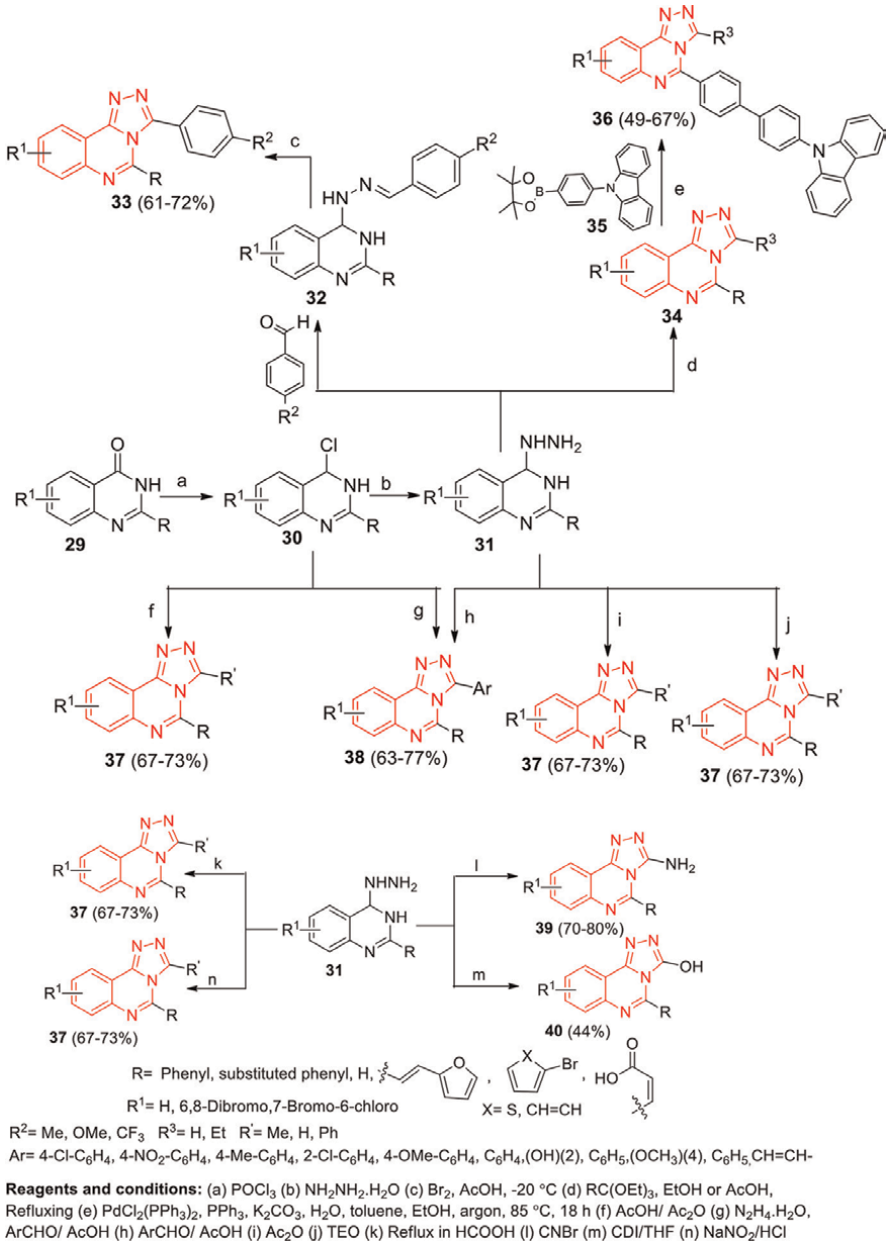
2.1.2 Synthesis from 2,4-dichloroquinazoline

The intermediate 2,4-dichloroquinazoline **4** was used to obtained various [1,2,4]-triazolo[4,3-*c*]quinazoline derivatives **23(a, b)**, **25**, and **28a-c**. The ester derivatives **21a, b** were afforded through Fischer Esterification reaction between corresponding benzoic acid using conc. sulfuric acid as a catalyst in the presence of ethanol. These intermediates **21a, b** further reacted with hydrazine hydrate to afford compounds **22a, b** followed by cyclocondensation with compound **4** in dioxane to obtain derivatives **23a, b**. The reaction of compound **4** with hydrazine hydrate afforded compound **5** which was further reacted under different reaction conditions to get derivatives **24**, **26a-c**. The targeted compound **25** was obtained from the treatment of **24** with $POCl_3$ at 110°C. On the other hand, the derivatives **28a-c** were obtained by treating **26a-c** with trifluoroacetic acid followed by the reaction with appropriate amines in isopropanol [45, 46].



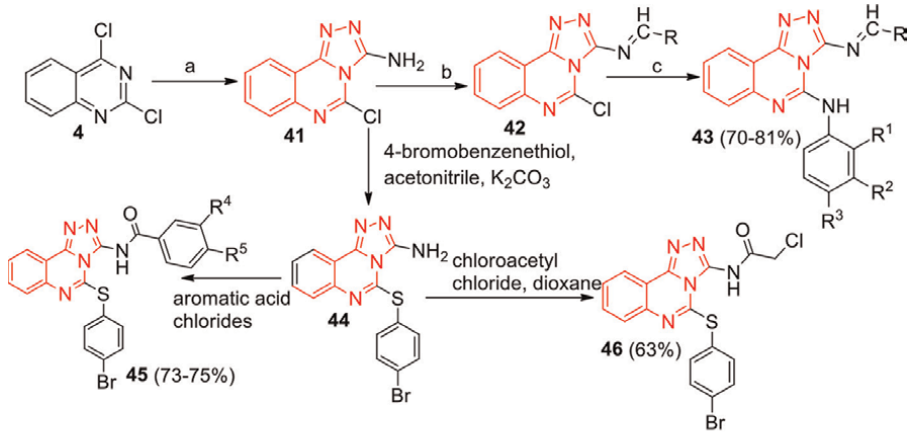
2.1.3 Synthesis from 4-hydrazinoquinazolines

Many biologically active [1,2,4]-triazolo[4,3-*c*]quinazoline derivatives have been prepared by the treatment of intermediate **31** with various reagents. The reaction of 4-hydrazinoquinazolines **31** with different substituted aldehydes afforded aryl hydrazones **32** which were further cyclized to form tricyclic compounds **33** in the presence of Br_2/AcOH [47]. The condensation of hydrazine derivative **30** with orthoesters produced compound **34** which was modified using a pinacol ester derivative **35** to afford the product **36** [48]. Different researchers employed the intermediate **31** to get various substituted triazoloquinazoline derivatives (**37**, **38**, **39**, **40**) under different reaction conditions [12, 38, 49–51].

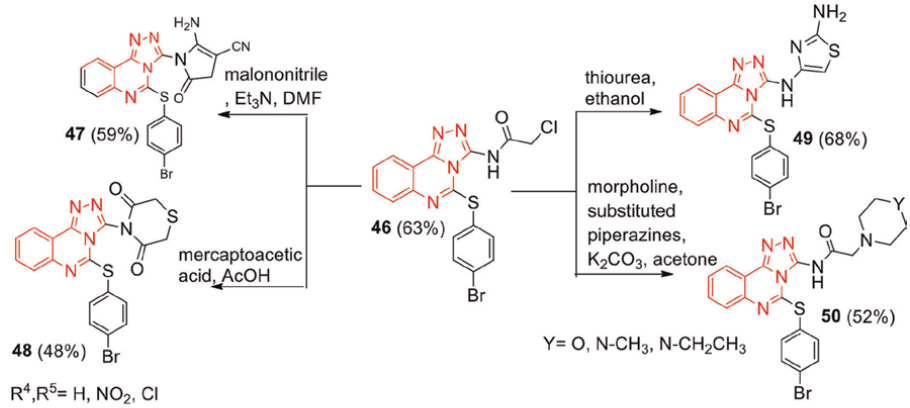


2.1.4 Synthesis of various substituted triazoloquinazoline derivatives

Ewes *et al*. synthesized various triazoloquinazoline derivatives from the treatment of dichloroquinazoline **4** with thiosemicarbazide in the presence of *n*-butanol. The derivative **43** was obtained through the reaction of Schiff bases **42** with aromatic amines in xylene or ethanol. Moreover, the reaction of intermediate **41** with 4-bromobenzenethiol in basic media using acetonitrile afforded amine derivative **44** which was further treated with aromatic acid chlorides to get compound **45**. The derivatives **47**, **48**, **49**, and **50** were obtained through the treatment of compound **46** with corresponding reagents [52].



Reaction conditions: (a) Thiosemicarbazide, *n*-butanol (b) aromatic aldehyde, benzene (c) aromatic amines, xylene or ethanol



R^4,R^5= H, NO_2, Cl

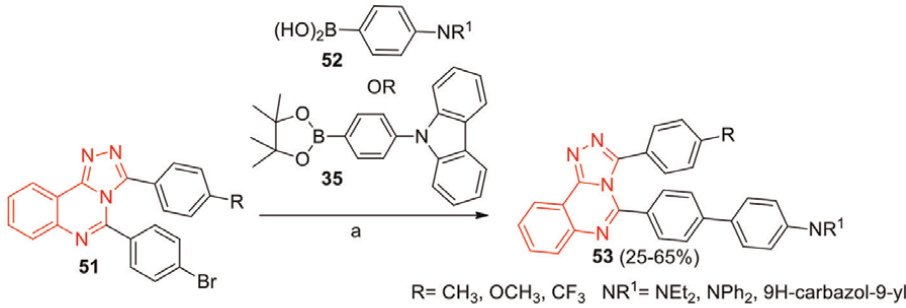
R= C_6H_5 , 3-NO_2-C_6H_4 , 4-FC_6H_4 , 3-OH,4-$OCH_3C_6H_3$, CH=CH-C_6H_5 , C_4H_3O

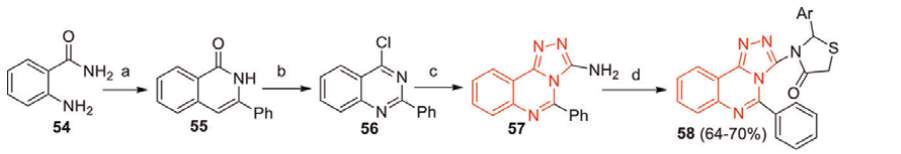
R^1= H, NH_2, R^2= H, CH_3, R^3= H, CH_3, NO_2

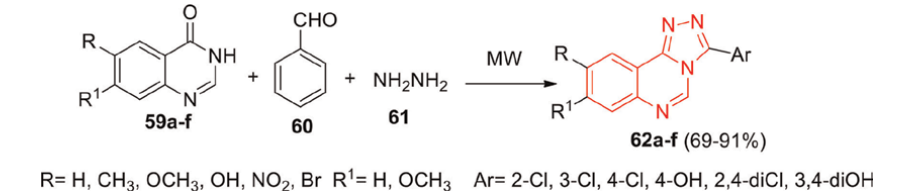
2.1.5 Suzuki-Miyaura coupling and one-pot multicomponent approach

Kopotilova *et al*. prepared the fluorophores **53** through Suzuki-Miyaura coupling reaction between bromophenyl derivatives **51** and boronic acid or pinacol ester derivative [53]. Reddy *et al*. employed one-pot reaction between compound **57**, substituted aldehydes, and thioglycolic acid in the presence of $ZnCl_2$ using toluene to get thiazolidinone derivatives **58**. The intermediate **57** was obtained through the reaction of compound **56**

with thiosemicarbazide using ethanol. The starting compound was anthranilamide which undergoes oxidative cyclocondensation with benzaldehyde to afford **55** which was further refluxed with $SOCl_2$ in the presence of DMF to give intermediate **56** [54]. In 2016, Dhongade-Desai *et al*. described a multicomponent reaction between substituted quinazolinone **59a-f**, hydrazine hydrate, and aromatic aldehydes under catalyst-free and microwave irradiation conditions to get derivatives **62a-f** [27].



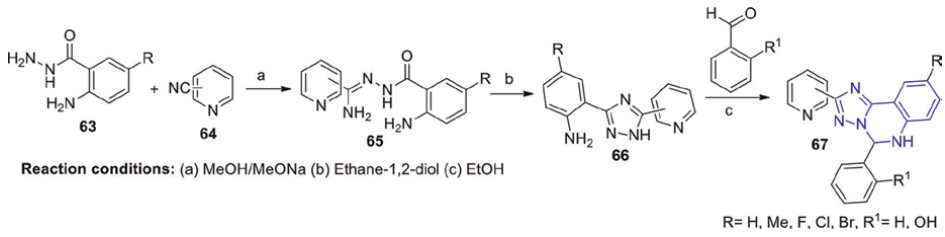




2.2 Synthesis of [1,2,4]-triazolo[1,5-*c*]quinazoline

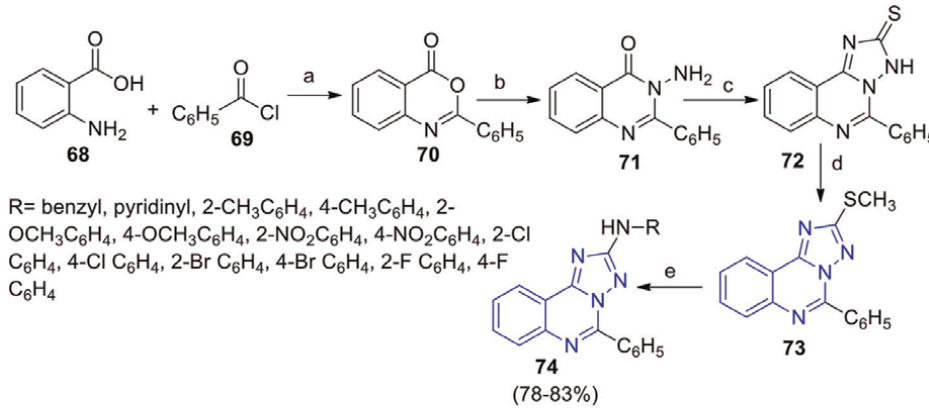
2.2.1 Synthesis from aromatic aldehydes

Gusev *et al*. synthesized [1,2,4]-triazolo[1,5-*c*]quinazoline derivatives **67** through the reaction between various aromatic aldehydes and intermediate **66** in the presence of ethanol. Intermediate **66** was obtained by the reaction of nitrile **64** with hydrazide **63** using MeOH/MeONa followed by a reaction with ethane-1,2-diol [55].



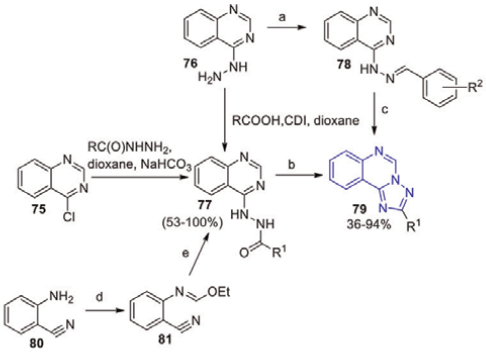
2.2.2 Synthesis from anthranilic acid

A series of [1,2,4]-triazolo[1,5-*c*]quinazoline derivatives **74** were prepared by Alagarsamy *et al*. through the reaction of compound **73** with different aryl amines. Anthranilic acid was used as a starting material and a further simple synthetic pathway leads to the formation of intermediate **73** [56].



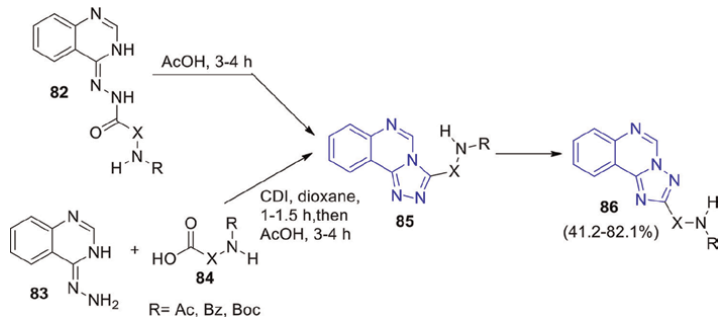
Reaction conditions: (a) pyridine, r.t, stirr, 1h (b) hydrazine hydrate, alcohol reflux, 3 h (c) thiourea, 220 °C, 15 min (d) Alcoholic NaOH, DMS, ice-cold conditions, 3 h (e) R-NH_2, Na_2CO_3, DMF, reflux

Kovalenko *et al*. synthesized a library of novel anti-cancer agents **77**,**79** in 53–100% yields following two reaction methodologies. Firstly, the reaction of 4-chloroquinozoline **75** with acid hydrazide afforded the targeted products in reasonable yields. Secondly, the acylation of **76** through the treatment with carboxylic acids using *N*, *N*-carbonyldiimidazole in the presence of dioxane. The hydrazone derivatives **78** were obtained through the reaction of compound **76** with aromatic aldehyde in the presence of 2-propanol or dioxane [57].



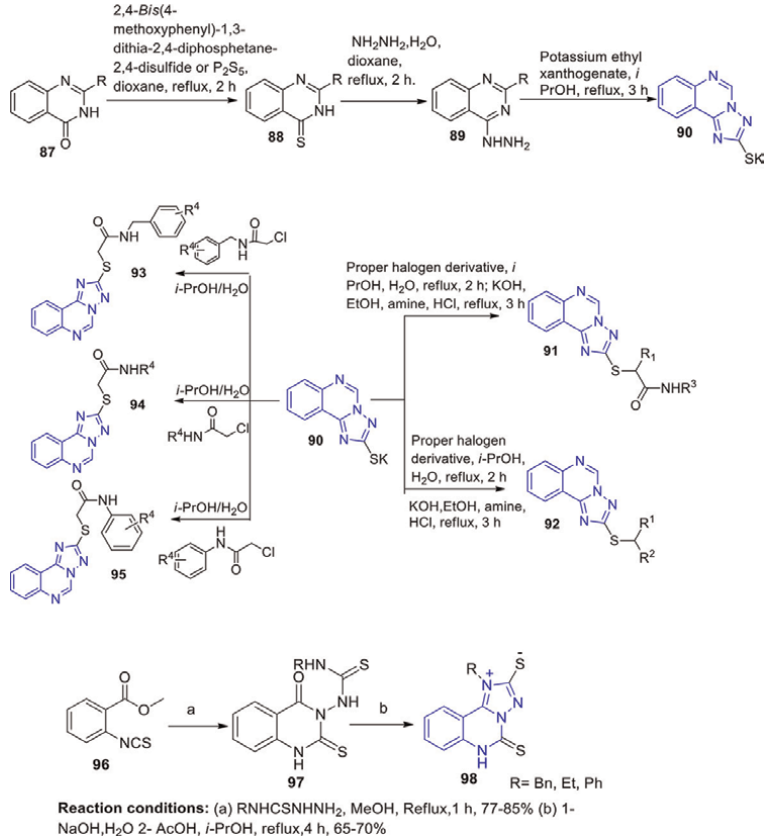
Reaction conditions: (a) 2-propanol or dioxane (b) CH_3COOH, heat (c) Br_2/ CH_3COOH (d) $HC(OEt)_3$ (e) CH_3COOH, R-C_4H_6-$CONHNH_2$

Martynenko *et al*. employed the heterocyclization of (3*H*-Quinazoline-4-ylidene) hydrazides of *N*-protected amino acids through refluxing in the presence of acetic acid for 3 h. The targeted compounds were obtained by using 4-hydrazinoquinazoline **83** as a starting material. The products were obtained in moderate to high yields (41.2–82.1%) [22].



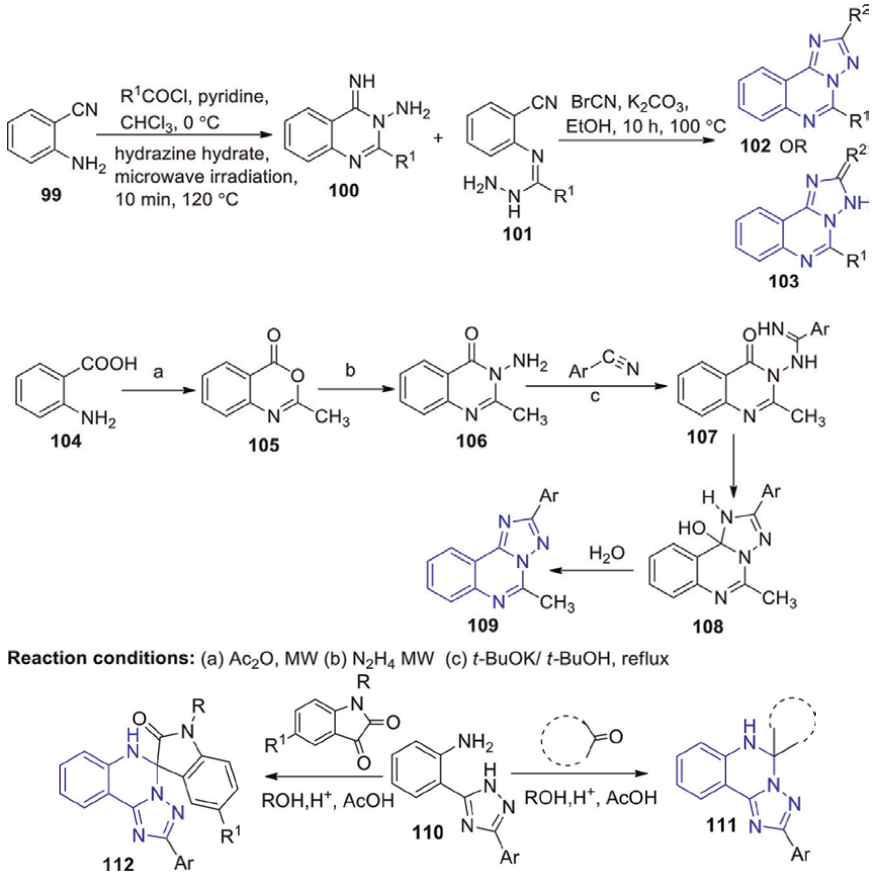
2.2.3 Synthesis of thio derivatives of [1,2,4]-triazolo[1,5-c]quinazoline

Thio derivatives of [1,2,4]-triazolo[1,5-*c*]quinazoline **91–95** were synthesized in moderate to high yields through the reaction of intermediate **90** with various reagents. The intermediate **90** was obtained by the treatment of quinazoline-4(3*H*)-one **87** with Lawesson's reagent in the presence of dioxane followed by refluxing with hydrazine to afford compound **89**. The next step was the cyclization of **89** with potassium ethyl xanthogenate in *i*-PrOH to form targeted intermediate **90** [58, 59]. Kovalenko *et al*. elaborated the one-pot synthetic protocol for the synthesis of novel 1-substituted-5-thioxo-5,6-dihydro-[1,2,4]triazolo[1,5-*c*]quinazolin-1-ium-2-thiolates **98** by the reaction of compound **96** with thiosemicardazide followed by a base-catalyzed reaction of intermediate **97** in the presence of *i*-PrOH [60].



2.2.4 Synthesis of [1,2,4]triazolo[1,5-c]quinazolines based heterocyclic compounds

[1,2,4]Triazolo[1,5-*c*] quinazoline-based heterocyclic compounds **102**, **103** were prepared by Burbiel *et al*. The first step involves the reaction of 2-aminobenzonitrile **99** with acyl halides in the presence of chloroform using pyridine as a base followed by the reaction with hydrazine hydrate under microwave irradiations. The resulting compound **100** was treated with nitrile derivative **101** to afford the final compounds [39]. Zeydi *et al*. refluxed compound **106** with aromatic nitriles using potassium tert-butoxide to get compound **109** [61]. Synthesis of spirocompounds with [1,2,4]triazolo [1,5-*c*]quinazoline moieties was elaborated by Kholodnyak *et al*. in 2016 by treating the intermediate **110** with cycloalkanones and diones to afford final products **111** and **112**, respectively [62].

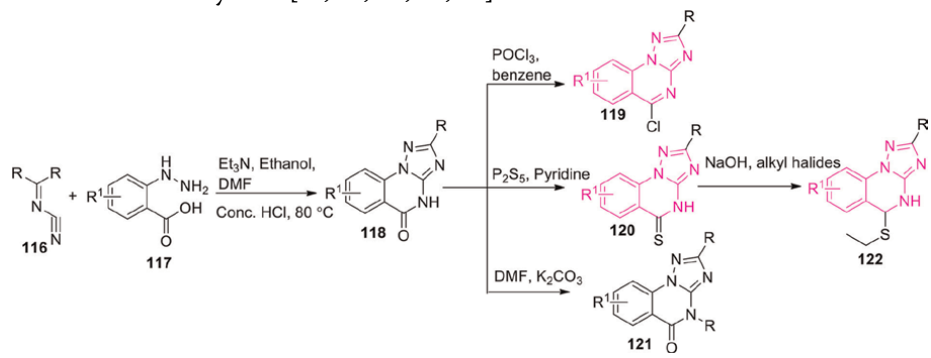


2.3 Synthesis of [1,2,4]-triazolo[1,5-*a*]quinazoline

2.3.1 Synthesis from dialkyl/phenyl N-cyanoimidocarbonates

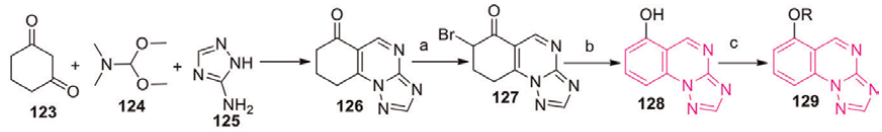
Different researchers reported the formation of [1,2,4]-triazolo[1,5-*a*]quinazoline **118** through the coupling of dialkyl/phenyl *N*-cyanoimidocarbonates or dialkyl/phenyl *N*-cyanoimidodithiocarbonate **116** with the substituted 2-hydrazinobenzoic acids **117** using triethylamine as a base in the presence of ethanol. The compound **118** was

further reacted with several reagents to get derivatives **119**, **120**, **121**, and **122** in moderate to excellent yields [11, 25, 26, 32, 35].



2.3.2 Reaction between cyclohexane-1,3-dione, (DMF-DMA) and aminotriazole

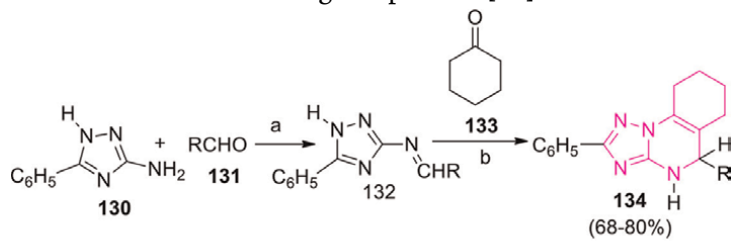
Reaction of cyclohexane-1,3-dione **123** with dimethoxy-*N*, *N*-dimethylmethanemine (DMF–DMA), and aminotriazole **125** afforded triazoloquinazoline **126** in high yields. The compound **127** was obtained by the reaction of **126** with NBS and further reaction of compound **127** using potassium carbonate in ethanol produced the dehydrohalogenated product **128**. The final derivative **129** was resulted from the treatment of compound **128** with various alkyl halides in DMF using K_2CO_3 as a base [63].



Reaction conditions: (a) NBS, CCl_4 (b) i- C_2H_5OH/ K_2CO_3 ii- HCl (c) RX/ DMF, K_2CO_3

2.3.3 Schiff base as an intermediate

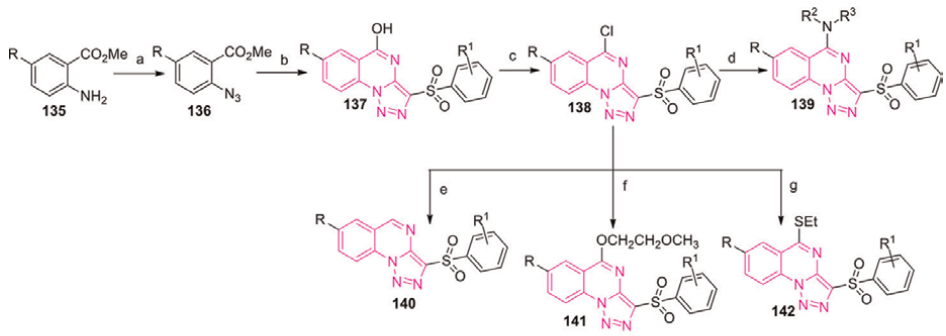
Schiff base **132** was used as an intermediate for the facile and efficient synthesis of compound **134**. The prepared Schiff base was coupled with cyclohexanone in $ZnCl_2$ using glacial acetic acid to afford the targeted product [64].



Reaction conditions: (a) $AlCl_3$, EtOH (b) Glacial acetic acid, anhydrous $ZnCl_2$

2.3.4 Synthetic route through diazotization reaction

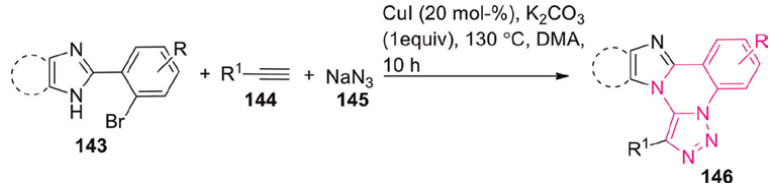
Diazotization of compound **135** afforded azide **137** which was reacted with arylsulfonylacetonitriles in ethanol to get intermediate **138**. The derivatives **139**, **140**, **141**, and **142** were obtained by the treatment of **138** with various reagents [65].



Reaction conditions: (a) sodium azide, (b) arylsulfonylacetonitrile, ethanol, sodium ethoxide (c) $POCl_3$, Et_3N (d) $R^2R^3NH_2$, DMF, Et_3N, 100-120 °C, 1 h (e) H_2. Pd/ C, MeOH/ PhH,r.t, 12 h (f) $MeOCH_2CH_2OH$, Et_3N, 110 °C, 12 h (g) EtSK, DMSO, r.t.

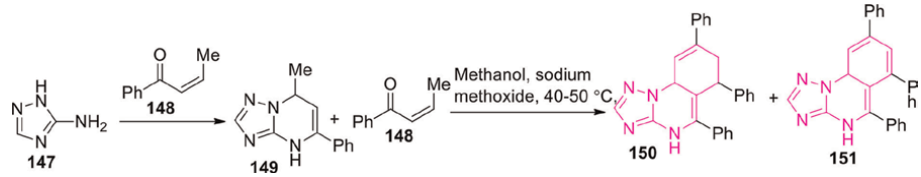
2.3.5 Copper-catalyzed synthesis

Nandwana *et al*. developed one-pot copper-catalyzed synthetic protocol for the formation of [1,2,4]-triazolo[1,5-*a*]quinazoline in excellent yield. The reactants for this synthesis were 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles **143**, alkynes **144**, and sodium azide **145** which reacted in the presence of copper catalyst using K_2CO_3 at 130°C [66].



2.3.6 Reaction between pyrimidine derivative and chalcone

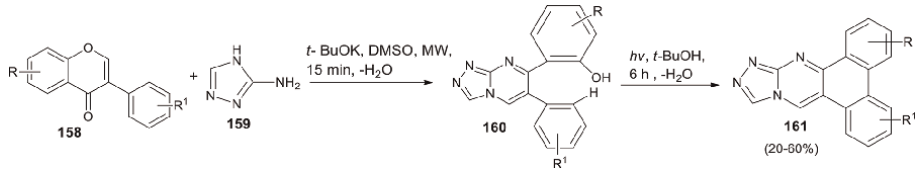
The reaction of pyrimidine derivative **149** with chalcone **148** in the presence of methanol using sodium methoxide at 40–50°C afforded a mixture of products **150** and **151** which were separated by crystallization using propan-2-ol. The starting material **149** was obtained from the reaction between 3-aminotriazole **147** and 1-phenylbut-2-en-1-one **148** [67].



2.4 Synthesis of [1,2,4]-triazolo[3,4-*b*]quinazoline

2.4.1 Synthesis through two-step reaction

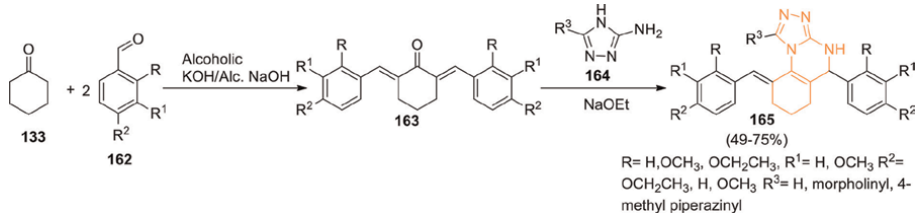
[1,2,4]-Triazolo[3,4-b]quinazoline derivative **161** was synthesized by Xue *et al*. through a two-step reaction. The first step involves the reaction between isoflavone **158** and 3-amino-1,2,4-triazole **159** in the presence of *t*-BuOK under microwave irradiations to get intermediate **160**. In the second step, this intermediate was undergone photocyclization to afford final derivative **161** in moderate yields [30].



2.5 Synthesis of [1,2,4]-triazolo[3,4-*a*]quinazoline

2.5.1 Synthesis of diarylidene derivative

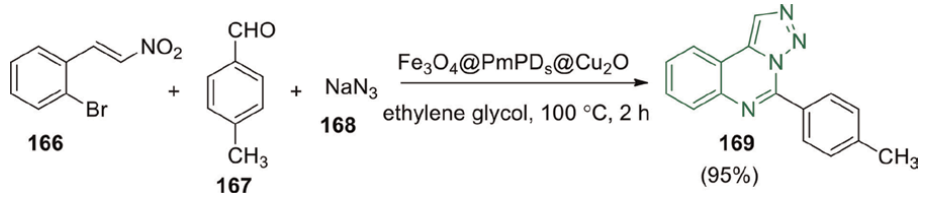
Almutaleb *et al*. reported the synthesis of derivatives **165** by the coupling of aromatic aldehydes **162** with active methylene **133** in the presence of alcoholic KOH to afford intermediate **163** which was further interacted with compound **164** under basic conditions to afford diarylidene derivatives **165** [68].



2.6 Synthesis of [1,2,3]-triazolo[1,5-*c*]quinazoline

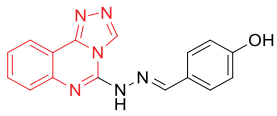
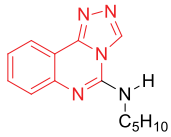
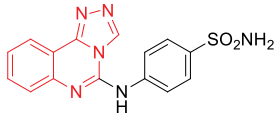
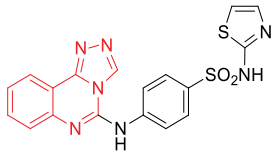
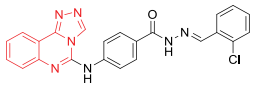
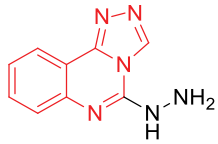
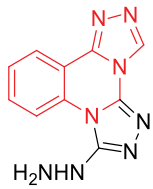
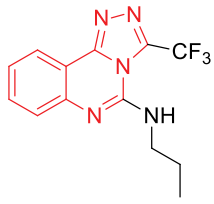
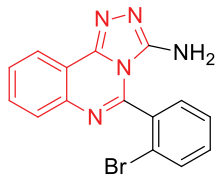
2.6.1 The use of a nanocatalyst for facile synthesis

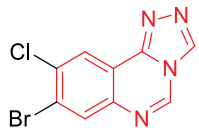
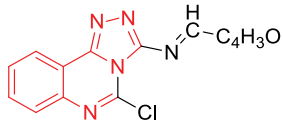
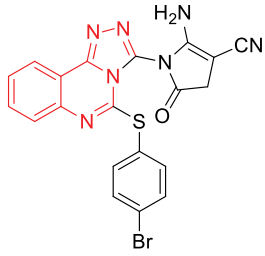
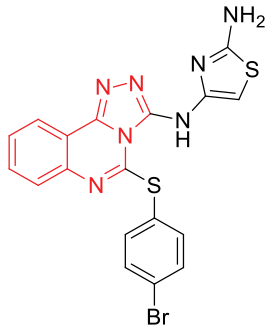
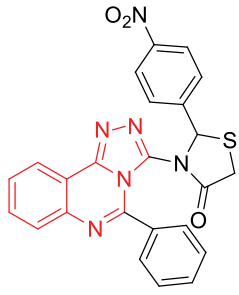
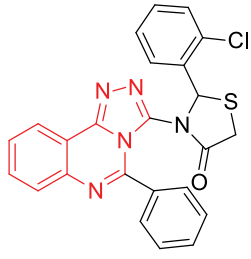
A Nanocatalyst named Fe_3O_4@poly(*m*-phenylenediamine)-@Cu_2O was employed by Rawat *et al*. for the efficient synthesis of [1,2,3]-triazolo[1,5-*c*]quinazoline derivative **169** from (*E*)-1-bromo2-(2-nitrovinyl)benzenes **166**, aldehydes **167**, and sodium azide **168** under mild reaction conditions. The optimized reaction conditions were the use of ethylene glycol as solvent at 100°C for 2 hours [69].

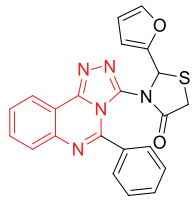
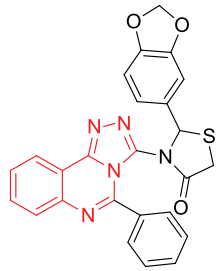
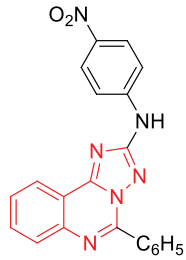
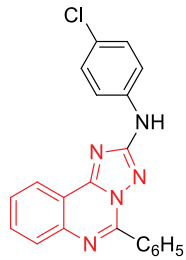
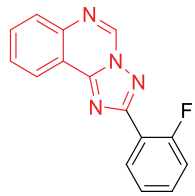
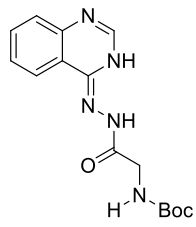


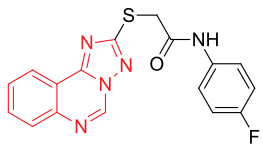
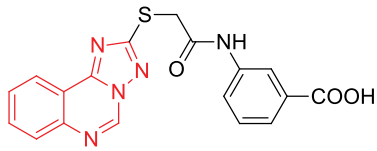
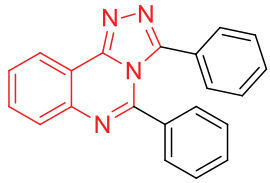
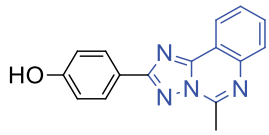
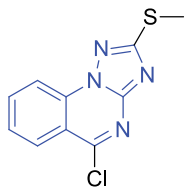
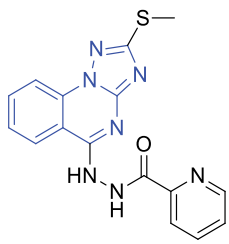
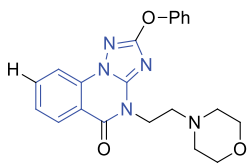
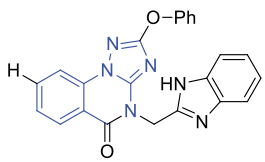
3. Medicinally important triazoloquinazoline derivatives

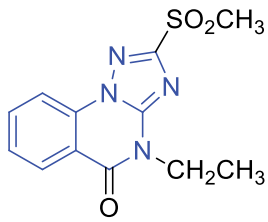
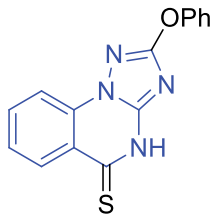
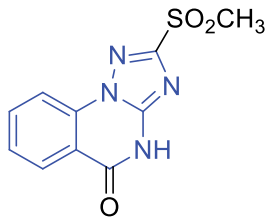
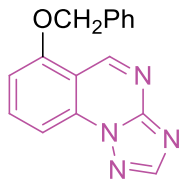
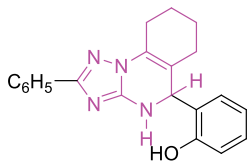
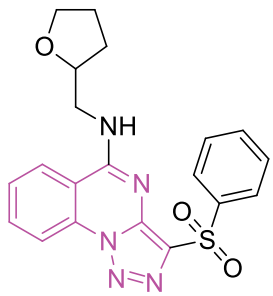
Triazoloquinazoline and its derivatives have been reported for various biological applications. Structures of some potent derivatives and their biological activities are described in **Table 1**.

Entry	Compound	Biological activity	IC_{50} value	Reference
1		Topo II inhibitors and DNA intercalators	5.22 ± 0.3 (μM)	[40]
2		Topo II inhibitors and DNA intercalators	9.39 ± 0.4 (μM)	[40]
3		Anti-proliferative activity and DNA intercalators	25.80 ± 2.1 (μM) against HepG2 14.32 ± 1.5 (μM) against HCT116	[42]
4		Anti- proliferative activity and DNA intercalators	23.44 ± 2.9 (μM) against HepG2 12.63 ± 1.2 (μM) against HCT116	[42]
5		Anti-proliferative Activity	4.88 (μM) against HepG2 5.21 (μM) against HCT116	[43]
6		Anti-proliferative activity and DNA intercalators	5.18 ± 0.3 (μM) against HepG2 6.40 ± 0.4 (μM) against HCT116	[44]
7		Anti-proliferative activity and DNA intercalators	7.16 ± 0.6 (μM) against HepG2 4.97 ± 0.2 (μM) against HCT116	[44]
8		Topo II inhibitors and DNA intercalators	6.29 ± 0.3 (μM) against HepG2 2.44 ± 0.1 (μM) against HCT116	[45]
9		Anti-Convulsant activity	ED_{50} value of 27.4 mg/kg	[38]

Entry	Compound	Biological activity	IC_{50} value	Reference
10		Cytotoxic activity	3.39 μg/ml	[12]
11		EGFR-TK Inhibitors	15.02 ± 1.4 μM against HePG2	[52]
12		EGFR-TK Inhibitors	15.30 ± 1.4 μM against HePG2	[52]
13		EGFR-TK Inhibitors	10.30 ± 1.7 μM against HePG2	[52]
14		Antimicrobial and Nematicidal activity	1.56 lg/mL 190 (LD_{50})	[54]
15		Antimicrobial and Nematicidal activity	1.56 lg/mL 200 (LD_{50})	[54]

Entry	Compound	Biological activity	IC_{50} value	Reference
16		Antimicrobial and Nematicidal activity	1.56 lg/mL 170 (LD_{50})	[54]
17		Antimicrobial and Nematicidal activity	1.56 lg/mL 160 (LD_{50})	[54]
18		Anti-HIV and Antibacterial Activities	3 µg/mL 6.25 µg/mL (anti-tubercular activity) 7.15 µg/mL (anti-HIV)	[56]
19		Anti-HIV and Antibacterial Activities	3 µg/mL	[56]
20		Anti-cancer activity	GI_{50} = 2.29	[57]
21		Anti-inflammatory activity	91.92% (zone of inhibition)	[22]

Entry	Compound	Biological activity	IC_{50} value	Reference
22		Anti-microbial activity	15 mm (inhibitory zone)	[58]
23		Anti-microbial activity	15 mm (inhibitory zone)	[58]
24		Adenosine Receptor Antagonists	1.16 nM	[39]
25		Anti-bacterial activity	17–27% (zone of inhibition)	[61]
26		Anti-microbial activity	6.25 mg/mL	[70]
27		Anti-microbial activity	6.25 mg/mL	[70]
28		Anti-Microbial activity	MIC = 0.12–7.81 (μg/mL)	[35]
29		Anti-microbial activity	MIC = 0.06–7.81 (μg/mL)	[35]

Entry	Compound	Biological activity	IC_{50} value	Reference
30		Anti-hypertensive activity	—	[32]
31		Anti-hypertensive activity	—	[32]
32		Anti-hypertensive activity	—	[32]
33		Anti-convulsant activity	ED_{50} value of 78.9 mg/kg	[63]
34		Anti-bacterial activity	12 mm- 25 mm (Zone of inhibition)	[64]
35		5-HT6R antagonist	75.4 nM	[65]

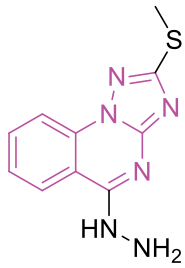
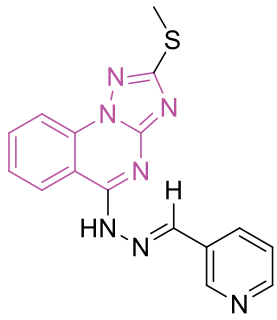
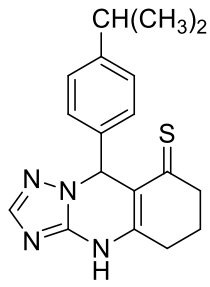
Entry	Compound	Biological activity	IC_{50} value	Reference
36		Anti-oxidant activity	—	[71]
37		Anti-oxidant activity	—	[71]
38		Anti-oxidant activity	—	[28]

Table 1.
Structures and biological activities of triazoloquinazoline derivatives.

4. Conclusion

Since triazoloquinazoline and its derivatives are known for several pharmacological applications, a number of synthetic methodologies have been established for the synthesis of this compound. Some of the most commonly used approaches include; conventional condensation reaction between quinazoline and azide or nitrile, synthesis from chloroquinazoline, copper-catalyzed alkyn-azide cycloaddition reaction, microwave-assisted synthesis, and multicomponent reactions. Moreover, various other simple and efficient synthetic routes have also been reported from time to time. This book chapter compiles the synthetic strategies as well as biological applications of different triazoloquinazoline derivatives published in the past years (2006–2023). This chapter will be very helpful for the researchers working in the field of medicinal chemistry and it would help them to synthesis new triazoloquinazoline derivatives with excellent biological profile.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Tooba Jabeen[1], Sana Aslam[2*], Matloob Ahmad[1], Atta ul Haq[1], Sami A. Al-Hussain[3] and Magdi E.A. Zaki[3*]

1 Department of Chemistry, Government College University, Faisalabad, Pakistan

2 Department of Chemistry, Government College Women University, Faisalabad, Pakistan

3 Faculty of Science, Department of Chemistry, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh, Saudi Arabia

*Address all correspondence to: dr.sana@gcwuf.edu.pk and mezaki@imamu.edu.sa

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Chapter 4

Quinazoline and Its Derivatives: Privileged Heterocyclic Scaffolds in Antileishmanial Drug Discovery

Huseyin Istanbullu

Abstract

Leishmaniasis is a parasitic disease caused by protozoa belonging to the genus Leishmania. Over one billion people are living in areas endemic to leishmaniasis and are at risk of infection. Each year, more than one million new cases are reported. Although few drugs are available for the treatment of leishmaniasis, none of them are ideal due to their high resistance and toxicity risk. Many compounds with quinazoline scaffold were synthesized and reported to have promising antiparasitic and antileishmanial activities. This review aims to evaluate the reported antileishmanial activities of quinazoline and its derivatives with a special focus on their structure-activity relationships.

Keywords: quinazoline, privileged scaffold, antileishmanial, heterocyclic compounds, medicinal chemistry

1. Introduction

Quinazolines are aza-derivative of quinolone and represent a large group of heterocyclic compounds that are composed of a fused benzene ring and a pyrimidine ring, also known as 1,3-diazanaphthalene. Quinazolinones and quinazolinediones are quinazolines in which one and two carbonyl groups, respectively, are present on the pyrimidine ring and are the most commonly encountered quinazoline derivatives. Quinazolinone has two isomers: quinazolin-2-one and quinazolin-4-one (**Figure 1**).

2. Antileishmanial quinazoline derivatives

One of the first publications on the therapeutic potential of quinazolines was the development of *folic acid* analogs in which the pteridine ring was replaced by quinazoline for acute leukemia treatment and immunosuppression (**Figure 2**) [1]. The research group synthesized 2,4,6-trisubstituted compounds that were prepared as analogs of the folic acid/pteridine ring [2]. These compounds were reported as folate antagonists against parasitic diseases such as Chagas disease and malaria. **PAM 1392** was also tested against *Trypanosoma cruzi* (**Figure 2**) [3]. 2,4,6-triaminoquinazoline

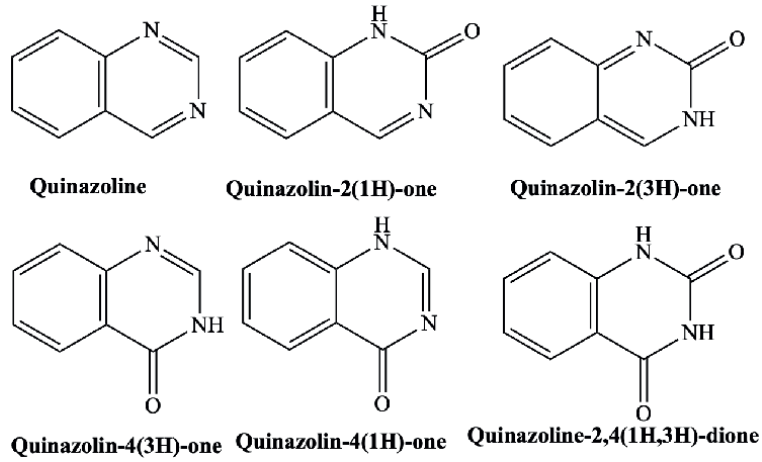

Figure 1.
Quinazoline, quinazolinones, and quinazolinedione structures.

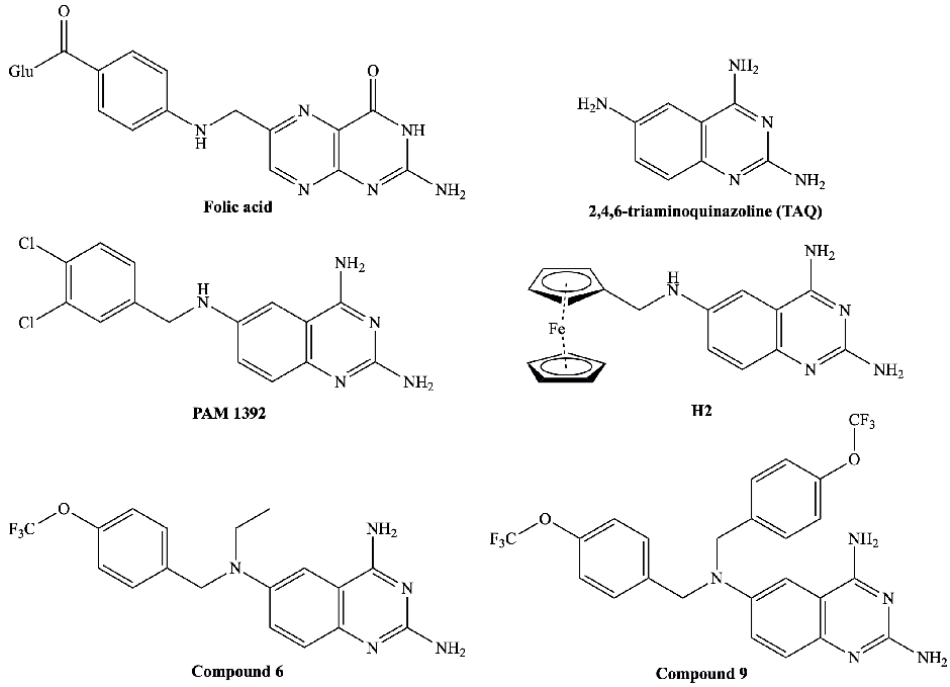

Figure 2.
Folic acid and reported quinazoline derivatives with antitrypanosomal and antileishmanial activity [1–7].

(**TAQ**), first identified by Davoll as an antiparasitic agent, functions as a folic acid analog (**Figure 2**) [4]. The antileishmanial potential of **TAQ** as a *Leishmania major* pteridine reductase inhibitor was reported by McLuskey et al. [5].

Mendoza-Martínez et al. reported a series of **TAQ** derivatives with *in vitro* antileishmanial activity against *Leishmania mexicana*. Their first article reported N^6-monosubstituted compounds. Among them, N^6-(ferrocenmethyl)

quinazolin-2,4,6-triamine (**H2**) showed activity against promastigotes and intracellular amastigotes and low cytotoxicity in mammalian cells (**Figure 2**) [6]. Their second article reported N^6-mono- and disubstituted TAQ derivative compounds. The compounds were designed based on docking studies on the *Leishmania* dihydrofolate reductase and pteridine reductase enzymes. Among them, **Compound 6** and **Compound 9** had the lowest LC_{50} against *L. mexicana* promastigotes (**Figure 2**) [7].

Berman et al. synthesized 2,4-diaminoquinazoline derivatives and evaluated their antileishmanial activity against *L. major* amastigotes in human monocyte-derived macrophages. **Compounds 1** and **2** showed IC_{50} values of 12 and 91 pg./mL, respectively (**Figure 3**) [8]. This group also measured the inhibitory activities of the compounds of the *Leishmania* DHFR enzyme; however, the results were not well correlated with antileishmanial activity. One of the positive controls used in the study, the quinazoline derivative trimetrexate (**TMQ**), which is a dihydrofolate reductase inhibitor used against pneumocystis pneumonia, was inactive against amastigotes in this model (**Figure 3**).

Khabnadideh et al. investigated the inhibitory effects of a series of 2,4-diaminoquinazolines against the *L. major* dihydrofolate reductase and evaluated their antileishmanial activity against axenic *L. donovani* amastigotes. An alkene derivative, **compound 12,** was the most potent against *L. donovani* with high selectivity compared to mammalian L6-cells. The authors reported little correlation between enzyme inhibition and parasite growth (**Figure 3**) [9].

Since several studies have identified trypanothione and the trypanothione system and its role in the oxidative stress defense mechanisms of the Kinetoplastida *Leishmania* and *Trypanosoma*, it has been a target in antileishmanial and antitrypanosomal drug discovery [10].

A series of 2-piperazin-1-yl-quinazolin-4-ylamine derivatives were reported and tested as antitrypanosomal and antileishmanial lead drug candidates against trypanothione reductase (TR) by Cavalli et al. (**Compound 14**, **Figure 4**) [11]. Docking of the quinazoline core showed interactions with the TR active site. However, there was a poor correlation between enzyme inhibition and trypanocidal activity.

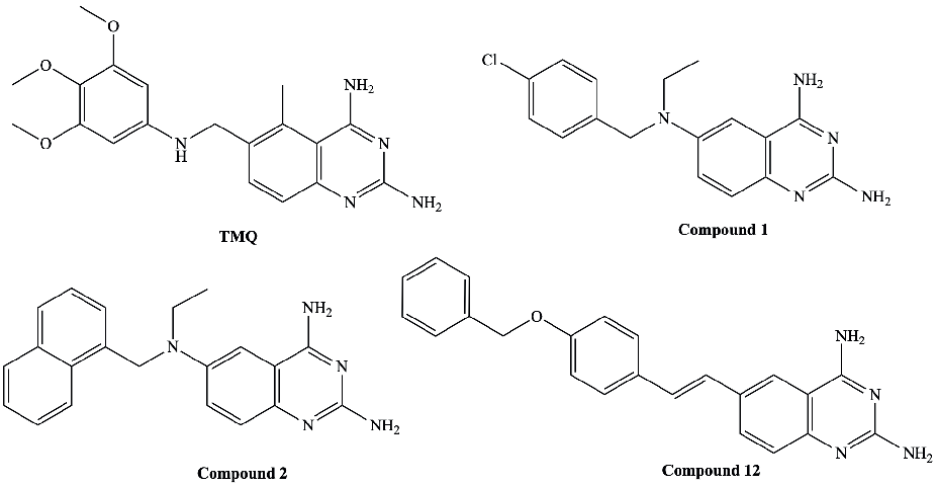

Figure 3.
TMQ and reported quinazoline derivatives with antileishmanial activity [8, 9].

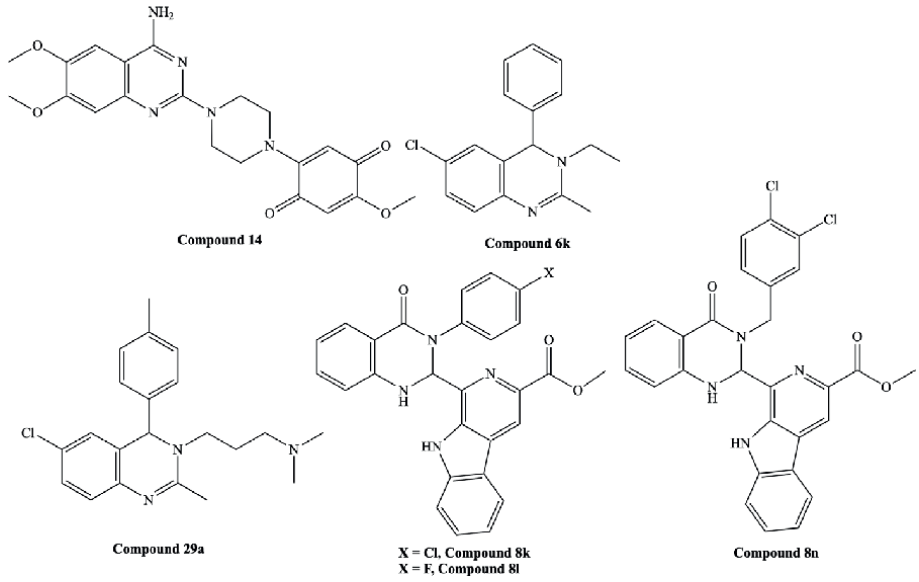

Figure 4.
Reported quinazoline derivatives with antitrypanosomal and antileishmanial activity [11–13].

Patterson et al. reported 3,4-dihydroquinazoline analogs as TR inhibitors as new antitrypanosomal agents. The compounds were tested against the bloodstream form of *T. brucei* and MRC-5 cells for toxicity in mammals. **Compounds 6 k** and **29a** were reported as good starting points for further structure-based drug design studies (**Figure 4**) [12].

Chauhan et al. reported new *β*-carboline–quinazolinone hybrid as inhibitors of *L. donovani* TR and antileishmanial activities against extracellular promastigotes and intracellular amastigotes of *L. donovani* [13]. **Compounds 8 k**, **8 l,** and **8n** were the most active with high selectivity compared to mammalian cells and were also potent TR inhibitors, showing good activity against intracellular amastigotes (**Figure 4**).

Kumar et al. reported a series of a new class of 4-(hetero)aryl-2-piperazino quinazolines and assessed their *in vitro* activity against extracellular promastigotes and intracellular amastigotes of *L. donovani* [14]. **Compound 4ab,** which is hardly selective in antileishmanial assays, showed low IC_{50} values in antiproliferative assays (**Figure 5**). However, the replacement of indole moiety with an aryl ring in the form of 2,3-dimethoxybenzene (**compound 4cb**) and 2,3,5 trimethoxybenzene (**compound 4bb**) together with an N-methyl group remarkably enhanced the antileishmanial activity (**Figure 5**).

Kabri et al. reported quinazoline derivatives with antiplasmodial, antitoxoplasmic, and antileishmanial activity. **Compound 19** showed moderate antileishmanial activity against *L. donovani* promastigotes (**Figure 5**) [15].

Arfan et al. reported the antileishmanial activity of 2,3-disubstituted-3H-quinazolin-4-one derivatives [16]. The compound 3-benzyl-2-phenylquinazolin-4(3H)-one (**compound 11**) was found to be more potent against *L. major* promastigotes than the positive control and is therefore expected to be a more effective leishmanicidal candidate (**Figure 5**).

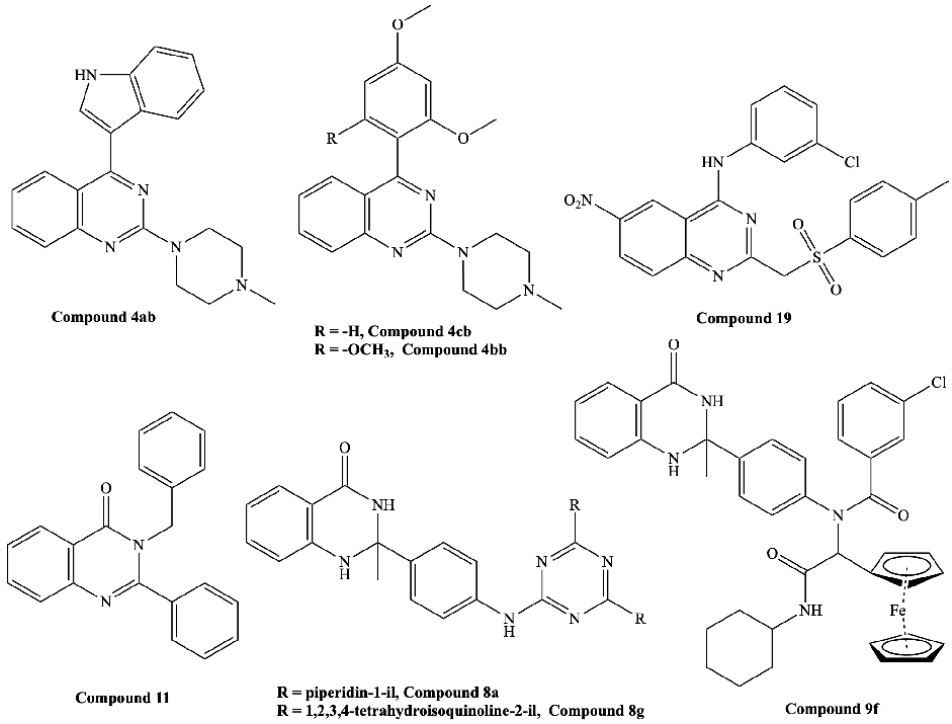

Figure 5.
Reported quinazoline derivatives with antileishmanial activity [14–17].

Sharma et al. carried out studies on 2,3-dihydroquinazoline, tetrahydroquinazoline, and their ferrocene derivatives [17]. **Compounds 8a**, **8 g,** and **9f** showed very consistent and promising leishmanicidal activity against intracellular amastigotes as well as *in vivo* efficacy in the golden hamster model and did not show any toxicity to macrophages and Vero cells (**Figure 5**).

Birhan et al. synthesized compounds that showed significant antileishmanial activities compared to standard drugs [18]. (*E*)-2-(4-Chlorostyryl)-3-*p*-tolyl-4(*3H*)-quinazolinone (**compound 7**) was the compound with the most promising antileishmanial activity (**Figure 6**). It is approximately 4 and 250 times more active than the standard drugs amphotericin B and miltefosine, respectively.

Van Horn et al. reported the antileishmanial activity of a series of N^2,N^4-disubstituted quinazoline-2,4-diamines [19]. The compounds were tested for *in vitro* antileishmanial potency against intracellular *L. donovani* and *L. amazonensis* parasites. The potency of **compounds 15**, **16**, and **23** against intracellular antimony-resistant clinical isolate *L. donovani* and antimony-sensitive isolate *L. donovani* was also evaluated (**Figure 6**). These results led to the testing of **compounds 15**, **16**, and **23** in an *in vivo* murine visceral leishmaniasis model. While **compounds 15** and **16** had no activity *in vivo*, **compound 23** reduced parasitemia by 37% when administered intraperitoneally at 15 mg/kg/day for 5 consecutive days.

Zhu et al. investigated N^2,N^4-disubstituted quinazoline-2,4-diamines as novel antileishmanial agents [20]. Based on their *in vitro* antileishmanial potency, N^4-benzyl-N^2-(4-chlorobenzyl)quinazoline-2,4-diamine (**15a**) and

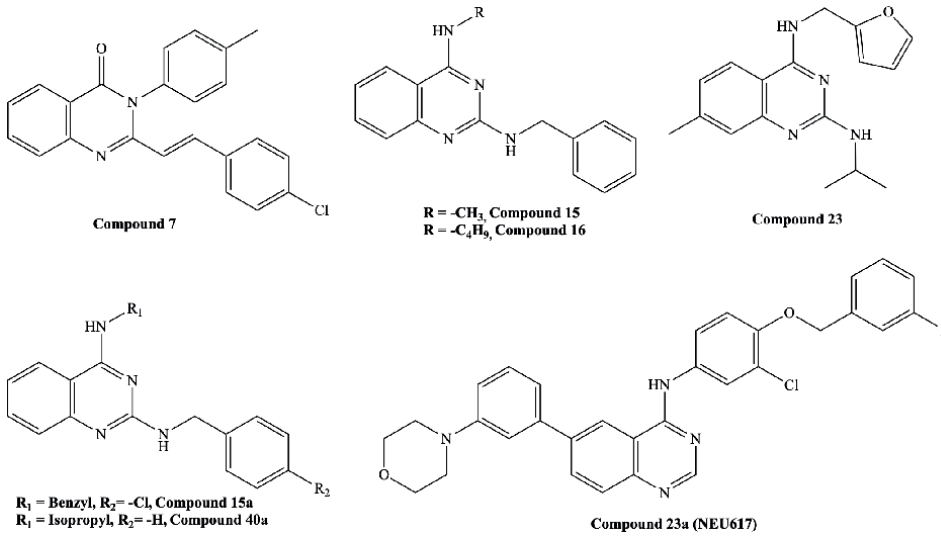

Figure 6.
Reported quinazoline derivatives with antitrypanosomal and antileishmanial activity [18–22].

N^2-benzyl-N^4-isopropylquinazoline-2,4-diamine (**40a**) were selected for *in vivo* pharmacokinetic and antileishmanial evaluation (**Figure 6**).

Katiyar et al. reported that the 4-anilinoquinazolines canertinib and lapatinib, which are kinase inhibitors, killed bloodstream *T. brucei in vitro* with a low micromolar range [21]. Patel et al. studied lapatinib analogs, which provided an excellent starting point for optimizing the new antiparasitic chemotype [22]. One of these compounds, **compound 23a** (**NEU617**), was reported to be a potent inhibitor of *T. brucei* growth (**Figure 6**).

Woodring et al. also investigated lapatinib analogs [23]. They replaced the quinazoline scaffold with [3,2-d] and [2,3-d] thienopyrimidine. They found that the compounds were active against *T. cruzi, L. major* amastigotes, and *P. falciparum*. The most potent analog of all scaffolds against *L. major* amastigotes was **compound 4e**. Only the thieno[3,2-d]pyrimidine derivatives showed a sub-micromolar activity against *L. major* promastigotes (**Figure 7**).

Saad et al. reported 4-arylamino-6-nitroquinazoline derivatives with antileishmanial activities [24]. Among all the derivatives, **compounds 21** and **8** showed excellent antileishmanial activities; they were more active than the tested standard (**Figure 7**).

Enciso et al. have studied quinazolin-2,4-diones as new antileishmanial agents [25]. **Compound 6e** displayed an attractive profile, including antileishmanial activity against *L. Mexicana*, which was superior to the positive standard, with high selectivity over a macrophage cell line (**Figure 7**).

Macedo et al. reported that when Glucantime® was incubated with the quinazoline derivative **QNZ** (a TNF-α blocking agent and NF-κB inhibitor), a higher activity was observed against the growth of amastigotes (**Figure 7**) [26].

Agarwal et al. reported fused quinazoline derivatives and tested them against *L. donovani* promastigotes [27]. Among the compounds tested, **compound 6 l** was reported to be the most active compound (**Figure 7**).

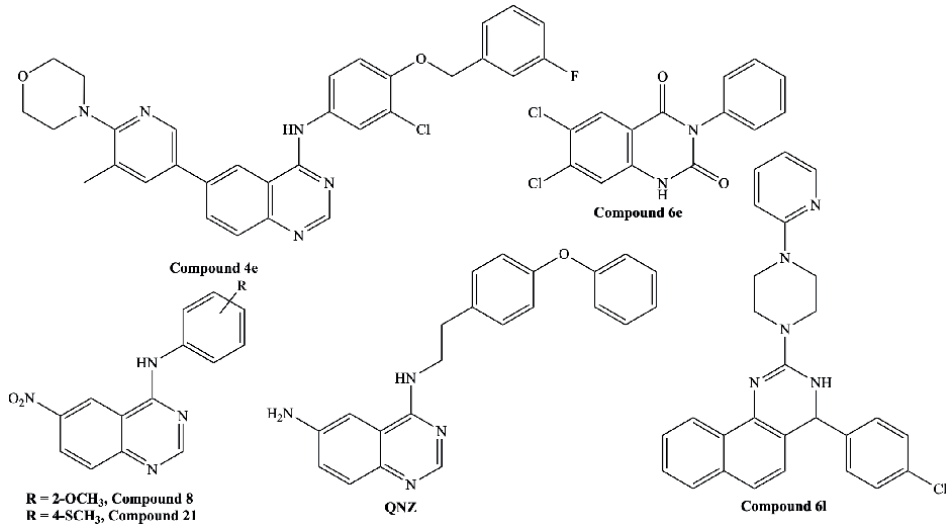

Figure 7.
Reported quinazoline derivatives with antitrypanosomal and antileishmanial activity [23–27].

3. Conclusions

Quinazoline and quinazolinone scaffolds are one of the privileged scaffolds of medicinal chemistry. Among the various activity reports, we tried to summarize the reports that showed antiparasitic activity, especially antileishmanial activity. According to these reports, compounds containing quinazoline-quinazolinone have promising antileishmanial activity. Compounds with this scaffold are an important starting point in the search for antileishmanial drug candidates.

Conflict of interest

The author declares no conflict of interest.

Author details

Huseyin Istanbullu
Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Izmir Katip Celebi University, Cigli, Izmir, Turkey

*Address all correspondence to: huseyin.istanbullu@ikc.edu.tr

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Section 3

Computational Studies of the Quinazoline Derivatives

Chapter 5

Importance and Application of Computational Studies in Finding New Active Quinazoline Derivatives

Wafa Mohamed Al Madhagi

Abstract

Quinazoline derivatives have shown promising pharmacological activities against various diseases, including cancer, inflammation, and cardiovascular disorders. Computational studies have become an important tool in the discovery and optimization of new quinazoline derivatives. In this chapter, the importance and application of computational studies in finding new active quinazoline derivatives were discussed. The various computational techniques, such as molecular docking, molecular dynamics simulations, quantum mechanics calculations, and machine learning algorithms, which have been used to predict the biological activities and optimize the structures of quinazoline derivatives, were described. Examples of successful applications of computational studies in the discovery of new quinazoline derivatives with improved pharmacological activities were added. Overall, computational studies have proven to be valuable in the development of new quinazoline derivatives and have the potential to accelerate the drug discovery process.

Keywords: quinazoline derivatives, computational studies, drug discovery, molecular docking, pharmacological activities

1. Introduction

Computer-aided drug design (CADD) is a computational method used in drug discovery. Nowadays, the discovery of new and novel therapeutic compounds for the treatment of different diseases needs to pass through the clinical trials. The examples of clinical trials used for this method are:

i. inhibitor of carbonic anhydrase dorzolamide, accepted in 1995 [1].

ii. the inhibitor of angiotensin-converting enzyme (ACE) captopril, accepted in 1981 as an antihypertensive drug [2]

iii. three therapeutics for the treatment of human immunodeficiency virus [3]: saquinavir, accepted in 1995.

iv. ritonavir and indinavir, both approved in 1996 [4].

Two main categories of computer-aided drug design have been classified as structure-based and ligand-based. Structure-based CADD depends on the understanding of the target protein structure to calculate the binding energies for all tested compounds, whereas ligand-based CADD relies on the data of chemical similarity finding or building of predictive, quantitative structure-activity relation (QSAR) models for known active and inactive compounds [5]. The place of CADD in drug discovery is summarized in **Figure 1**, where the target site for a drug to be designed and developed is determined therapeutically, accounting on the knowledge availability of structure information, a structure-based approach, or a ligand-based approach. The data obtained from successful CADD will permit the identification of multiple lead compounds that is often followed by numerous cycles of lead optimization and successive lead identification [6].

Structure-based CADD is mostly favored compared to other methods because of the high-resolution structural data of the target protein that can be obtained, that is, soluble proteins that can readily be crystallized. On other hand, ligand-based CADD is more commonly preferred when there is either no or slight structural information in existence, regularly if the process involves membrane protein targets. The fundamental aim of structure-based CADD is to design compounds that bind firmly to the target with lower binding energy, enhancing drug metabolism and pharmacokinetics/

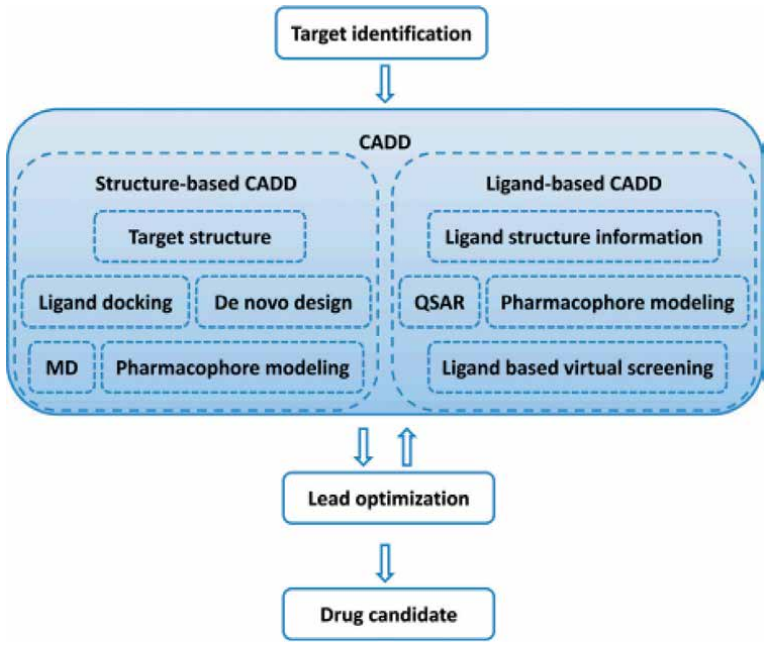


Figure 1.
Computer-aided drug design in drug design and discovery [6].

absorption, distribution, metabolism, elimination, and toxicity (DMPK/ADME/T), that is, would show less off-target properties [7].

2. Structure-based drug design

Structure-based drug design (SBDD) depends on study 3D structures of biological molecules with the aid of a computer. The main concept of this approach accounts on the ability of the compound to bind to the binding site to utilize the desired biological activity. Hence, the molecules that share similar favorable binding will give similar biological activities, as showed in **Figure 2**.

The new and novel compounds can be further explained through the careful study of a protein's binding site. SBDD analysis needs structural information for target protein because the SBDD will assist in discovering a large number of compound drug targets [9]. Large 3D database of human and pathogenic proteins structure depending on the biophysical results of X-ray crystallography and NMR spectroscopy are also accessible in the database. The case of example that relates to this is the record of over 81,000 protein structures that could be found in RCSB Protein Data Bank, with 5671 PDBbind database and 129 co-crystal of ligand-protein [10]. Therefore, it is safe to conclude that computational approaches in drug discovery permit rapid screening of a large compound library and allow for the evaluation of binder potential during modeling/simulation and visualization methods [11].

Molecular docking is a computational technique that explores the probable binding pose of protein for a given ligand and calculates the binding affinity. Thus, research of a computational tool to find out new objectives is required. The adverse outcome can be eliminated or reduced if the unfavorable and unexpected binding of drugs or lead molecules to the targets happen. In addition, the drug's indication can also be increased through reposition of drugs. As a result, reverse docking approaches have many more potential for further exploration and are currently receiving an increase in interest from researchers [12].

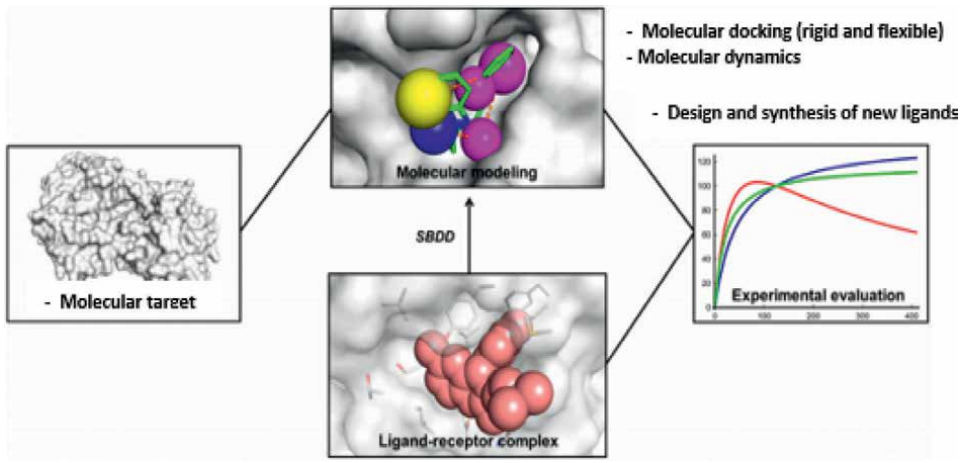


Figure 2.
Structure-based drug design outlines [8].

3. Molecular docking

Molecular docking is a computational technique that gives prediction of a macromolecule (receptor) binding efficiency to a small molecule (ligand). In addition, it gives illumination to the fundamental biochemical practices [13]. Docking can be obtained through two correlated ways; the first being ligand conformation in the protein active sites, followed by a ranking of these conformations by scoring function [14]. The mechanism of ligand-receptor binding is formerly elucidated according to a lock-and-key theory proposed by Fischer [15] where the ligand fits into the receptor according to lock-and-key approach as illustrated in **Figure 3** in which the ligand and receptor are rigid.

Then, Koshland improves the lock-and-key theory into "induced-fit theory," by arguing that the protein active site is reshaped by binding to a ligand; thus, the ligand and receptor should be flexible during docking (**Figure 4**) [16]. This theory covers more accurate binding events in comparison to the rigid run. Nowadays, the most popular method is to perform docking with flexible ligand and a rigid receptor [17, 18].

In addition, there is a theory that has been recently discovered that focuses on how the conformation ensemble model describes the proteins as preexisting ensemble of conformational states and that the protein's flexibility permits large changes in conformation (**Figure 5**).

The three different models, the lock-and-key, induced-fit, and the conformation ensemble model all focus on the process of recognition. To be simply put, the lock-and-key module presents the 3D complementarity concepts, the induced-fit model clarifies how complementarity is done, and the ensemble model explains the proteins conformational complexity (**Figure 6**).

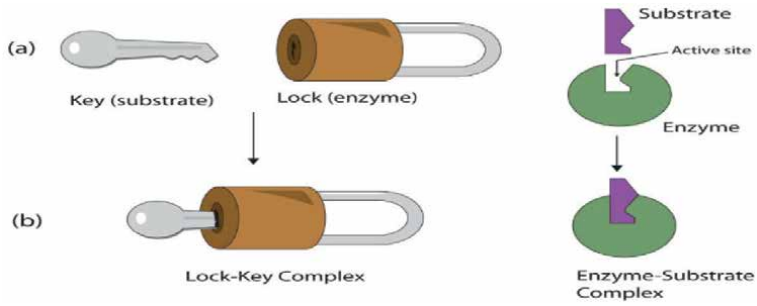


Figure 3.
Lock-and-key theory such as enzyme mechanism of action [15].

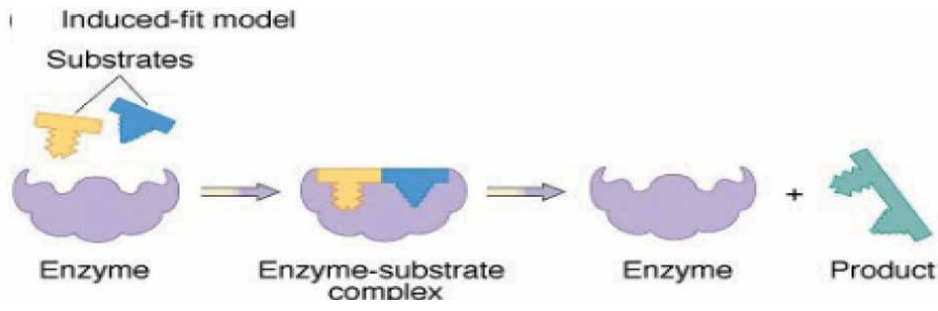


Figure 4.
Induced fit model [16].

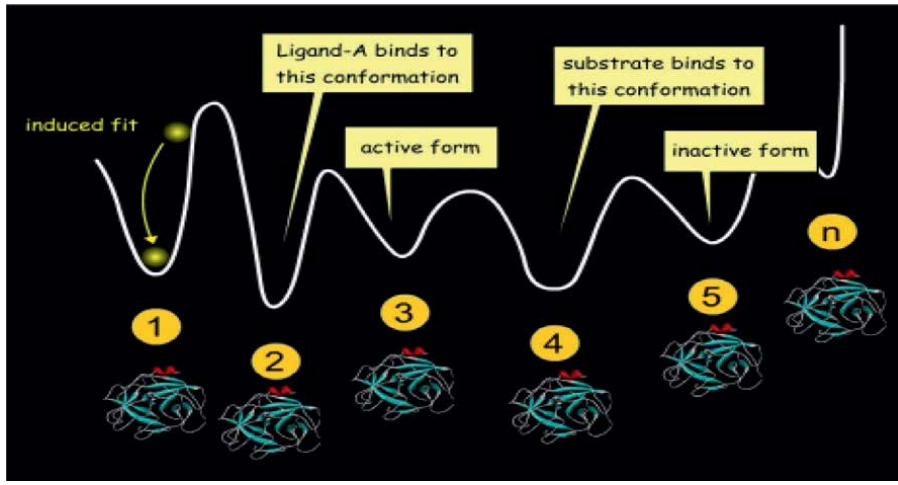


Figure 5.
Conformation ensemble model.

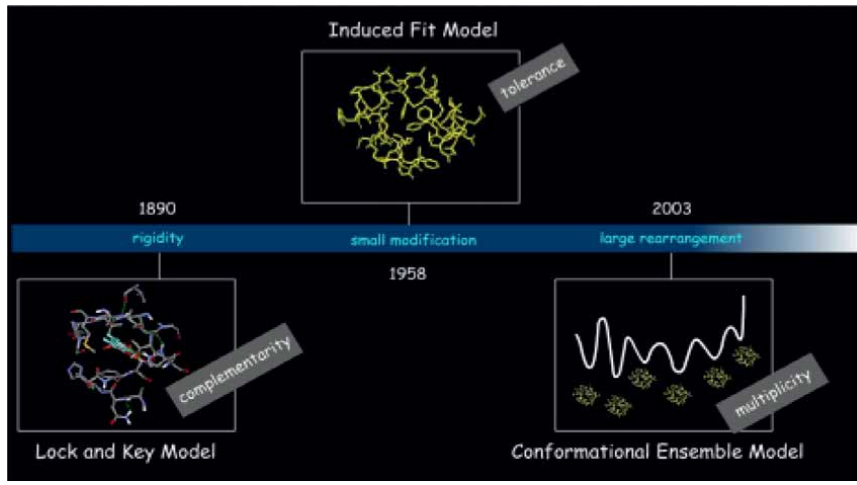


Figure 6.
Different ligand-receptor binding models.

3.1 Docking approach

There are two docking approaches that are well recognized in the molecular docking community. The first approach employs the technique of matching, which defines the protein and the ligand as complementary planes [19–21]. The second approach simulates the actual docking practice in which the interactions of ligand-protein energies are calculated [22].

3.2 Binding sites

Binding sites are known sites of protein where ligands/compounds are bound actively. The different site of binding is commonly labeled as binding modes. They

also predict the binding strength, the complex energy, the types of the signal produced, and the binding affinity's calculation between two molecules by using scoring functions. The most awaited situation is the protein–ligand interaction type, which has prominent functions in medicine.

3.3 Types of interactions

The interactions between particles are classified into four groups:

- Electrostatic forces: Forces of electrostatic origin due to the charges residing in the matter. The most common interactions are charge-charge, charge-dipole, and dipole-dipole.

- Electrodynamics forces: The most common force is the Van der Waals interaction, which is intermolecular forces between macromolecules and ligand such as charge-charge, charge-dipole, and dipole-dipole.

- Steric forces: Steric forces produced by entropy. Such as, in cases where entropy is limited, there may be forces to minimize the free energy of the system, which are due to entropy.

- Solvent-related forces: Solvent-related forces are formed because of the solvent structural changes. These structural changes are produced when ions, colloids, proteins, and so forth are added to the solvent structure like hydrogen bond and hydrophobic interactions.

- Other physical factors: The conformational changes in the protein and the ligand are often required for a successful docking process.

3.4 Reverse docking

Reverse docking is a computational study and is commonly used to identify receptors and explore new targets for ligand used (drugs or natural compounds) over a large number of receptors. In addition, it gives the necessary explanation for polypharmacology, molecular mechanism, alternative usage through the repositioning of drugs, and adverse effect and toxicity determination [12]. The reverse docking is classified as structure-based approach that uses 2D fingerprint-based reverse virtual screening, 3D similarity search, and pharmacophore (reverse pharmacophore mapping) [23, 24]. Reverse pharmacophore mapping, for example, pharmacophore model of proteins in the list of targets, is the starting point for the comparison of the pharmacophore models with the studied ligand [23]. A freely accessible web server known as PharmMapper is considered as a valuable resource of pharmacophore-based reverse screening [25]. It attempts to find the potential target applicants for small-molecule drugs, natural compounds, or novel compounds whose targets are still unidentified [26, 27]. As of now, PharmMapper produces the "best mapping poses of the query" against all pharmacophore models in the core database.

Generally, the ligand-based methods may offer extra benefits, some of which are the immediate computations and ability to support a large variety of data. Direct or indirect use of target structural information is compulsory, depending if one is concerned in exploring potential targets for a set of ligands. Comparable to traditional

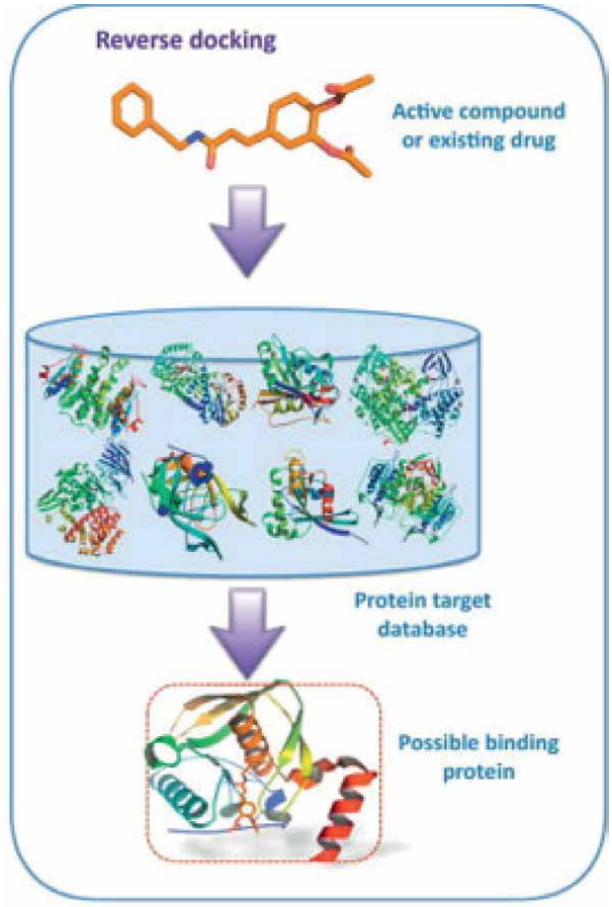


Figure 7.
Overview of reverse docking [28].

virtual screening, the collective use of structure and ligand-based tools in reversed virtual screening can give rise to higher enhancement of the hits [26]; the overview of reverse docking was summarized in **Figure 7** [12].

The computational docking of a specific small molecule to receptor structure library is firstly explained by Chen and Zhi [29] using the term "inverse docking technique". This technique is beneficial for the identification of the new potential biological targets for known compounds [30–32], as it specifies compounds targets over a family of related receptors [33]. The approach gives rise to the achievement in identifying the receptors homology models [33]. The approach may also be useful for generating a predicted pharmacological profile for compound [34] or to create a virtual selectivity profile that illustrates the promiscuity of the inhibitors [35]. In addition, inverse docking is also able to give multifaceted nature to pharmacologically active compound and can produce new hypotheses for the mechanism of action [28].

Thus, it has been proven that reverse docking is a vital tool in the computational study, particularly in identifying novel macromolecular targets for a drug or ligand related to its mechanism of action and/or the side effects [28, 36]. Moreover, it is the tool that involves docking of small molecules or drugs in potential binding sites of clinically relevant macromolecular targets [26].

4. Target structure databases

Target structure collection with details of potential binding sites is important for computational efficiency, applicability, and accuracy of docking results. Receptor binding sites or binding pockets are the precise areas of the receptors where ligands bind to form interactions. Known binding pockets are supportive for reverse docking because the time needed to examine proper docking site between ligands and receptors [12] would be decreased. Mostly, there are two ways that are used to get the binding site; one is formed by protein data bank (PDB) complex structures, and the other meaning is to use pocket-searching programs such as SiteMap or F pocket. An automatic procedure to define binding sites is more desirable and favorable because a large number of targets should be examined in reverse docking process [12].

There are different databases used for a target structure, as summarized in **Table 1**, for example, sc-PDB, a library for 3D ligand binding site that has entries for protein-ligand complex structures in PDB [37]. The sc-PDB keeps three databases for structure information: (i) the target protein coordinate data, (ii) the ligand coordinate data, and (iii) the active site coordinate data. ScPDB's database explains the active sites of the reference proteins using information in PDB, UniProt [38], and the information are presented on the web (http://bioinfo-pharma.u-strasbg.fr/scPDB/). Currently, it has 9283 entries of binding site from 3678 proteins and 5608 ligands. In addition to that, potential drug target database (PDTD) is an alternative web with accessible target database for small molecules target identification [39].

Information type	Database name	Content	Coverage
Protein	PDB	Structural of proteins	107,667 proteins structures
	UniProt	Cross references of proteins	550,552 proteins for Swiss-Prot60, 971,489 proteins for TrEMBL
Target protein	TTD	Disease, pathway, drug-related to therapeutic targets	2025 targets, 17,816 drugs
	sc-PDB	Coordinate data of proteins, ligands, and active sites	9283 binding sites 3678 proteins, 5608 ligands
	PDTD	Binding structures, related diseases, biological function, associated pathways	1207 binding structures 841 target proteins
	Target DB	Integrated databases of TTD, PDTD, Drug Bank, and PDB	6920 protein entries
	DART	Target associated with drug adverse reaction	618 proteins, 529 ligands
	DITOP	Targets associated with drug-induced toxicity	236 proteins, 1327 ligands
	CSD	Cambridge structural database	>800,000 protein entries

Information type	Database name	Content	Coverage
Drug	Drug Bank	Drugs and drug targets	7677 drugs
	PubChem	Structures and activities of chemicals	52 million chemicals
	ChEMBL	Information on drug-like bioactive compounds	2.4 million bioassays
	ZINC	Chemical compounds	>35 million compounds
Protein-ligand complex	Astex diverse set	Apo and holo form of protein complexes with drug-like ligand	85 protein-ligand complexes

Table 1.
Different docking-based target identification databases.

The target proteins of PDTD are collected from both scientific studies and other databases containing therapeutic target database (TTD), Drug Bank, and Thomson Pharma. However, it is important to note that only protein ligand of complex structures are collected. PDTD covered relevant information about related illnesses, biological purpose, and associated signaling pathways. In addition to determination of the target protein and active sites. One of the benefits of PDTD is that users can alter the target list as they wish. The PDTD's active site definition seems to match with sc-PDB. Note that PDTD also allows redundant records, so the proteins flexibility could be evaluated even with rigid receptor docking. PDTD is available for use on the web server (http://www.dddc.ac.cn/pdtd/), and at the moment, it contains 1207 entries covering 841 target proteins.

4.1 Drug-like properties (Lipinski's "rule of five")

For oral delivery and according to the world drug index (WDI), [40] Lipinski "rule of five'' are required to be considered. These properties are:

- Molecular mass < 500 daltons (Da),
- Calculated octanol/water partition coefficient (CLOGP) <5,
- Number of hydrogen-bond donors <5,
- Number of hydrogen-bond acceptors <10.

This rule of five needs to be visible as a qualitative absorption/permeability predictor [41], in preference to a quantitative predictor [42]. The assets distribution in drug-related chemical databases has been studied as any other method to apprehend "drug-likeness" [43, 44]. These aforementioned analyses all point to a crucial aggregate of physicochemical and structural properties [45], which to a massive extent may be manipulated by the medicinal chemist (**Figure 8**) [46]. Physicochemical properties as well as pharmacokinetic and toxic properties had been ignored for a long time by most medicinal chemists, who in lots of cases best had the quest for most powerful receptor binding as the ultimate goal.

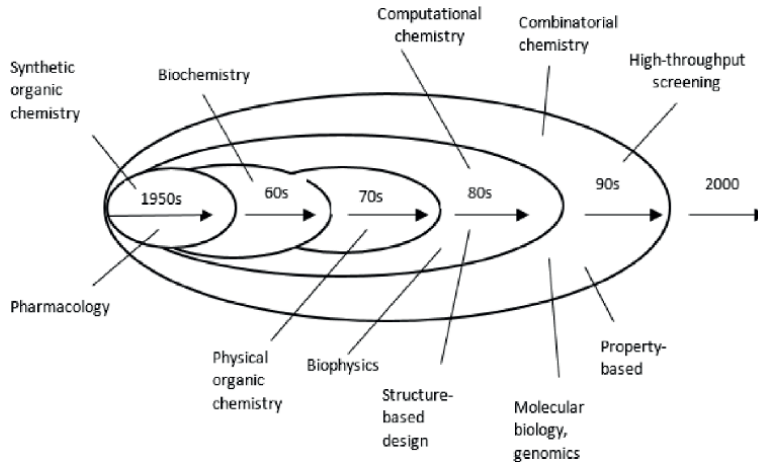


Figure 8.
Property-based design [46].

Based on the Lipinski's rule of five, if two parameters of the compound were out of the range, a poor absorption or permeability may be arisen. Unless, few oral active drugs were found out to follow the Lipinski rule of 5 such as antibiotics, antifungals, vitamins, and cardiac glycosides. The main reason for activity of such therapeutics groups was structural features that lead compounds to act as a substrate for naturally occurring transporters [40].

4.2 ADME/T studies

Because the capability for organic screening and chemical synthesis has dramatically expanded, the needs for large portions of early records on absorption, distribution, metabolism, excretion (ADME), and toxicity data (collectively called ADME/T information) have been increased. In addition, the study of pharmacokinetics was very critical in drug development as the failure of drug development could be recognized because of poor pharmacokinetics (39%) and animal toxicity (11%) as summarized in **Figure 9**.

Those early predictions of ADME/T residences help researchers to pick out the excellent applicants for drug development, in addition to rejecting those with a low chance of success. The evaluation of ADME/T can be in one of three approaches; first, selection of different *in vitro* assays that further automated through the use of robotics and miniaturization. Second, *in silico* models have been used to help in the selection of both appropriate analyses as well as in the selection of compounds to go through these screens. Third, predictive approaches have been established that might ultimately emerge as sophisticated enough to replace *in vitro* assays and/or *in vivo* assays [47]. The combination data obtained from ADME/T properties prediction and computational (*in silico*) had been significantly satisfying [48, 49]. Hou et al. [50] have achieved broad study on *in silico* modeling of various ADME/T-related properties, among them are the blood-brain barrier, human intestinal absorption (HIA), Caco-2 permeability, oral absorption, oral bioavailability, and P-glycoprotein inhibition [50]. Combined information based PKKB [Pharmaco Kinetics Knowledge Base] [51], collecting structures, pharmacological data, significant experimental or predicted physiochemical properties and experimental ADME/T data for 1685 drugs.

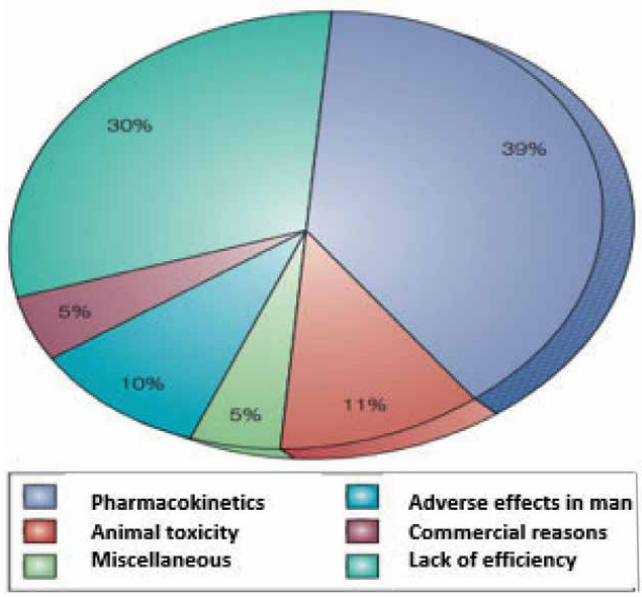


Figure 9.
The main reasons for attrition in drug development [47].

This information plays an important role as valuable resources for pharmacokinetic studies and for endorsing the accuracy of current ADME/T predicative models reliable.

4.3 Computational studies for the quinazoline derivatives

Molecular properties refer to the physical and chemical characteristics of a molecule that determine its behavior and interactions with other molecules. These properties are important in understanding the biological activity and pharmacological effects of a compound [52]. Some of the key molecular properties that are often studied in computational chemistry include:

1. Molecular weight: the molecular weight of a compound is the sum of the atomic weights of all the atoms in the molecule. Molecular weight can influence the pharmacokinetic properties of a compound, such as its absorption, distribution, metabolism, and excretion.

2. Lipophilicity: lipophilicity refers to the ability of a molecule to dissolve in lipids or nonpolar solvents. Lipophilic compounds tend to have better membrane permeability and can more easily cross cell membranes to reach their targets.

3. Polarizability: polarizability is a measure of the ability of a molecule to be distorted by an electric field. Polarizable molecules tend to have more interactions with other molecules, such as protein-ligand interactions.

4. Hydrogen bonding: hydrogen bonding is a type of intermolecular interaction in which a hydrogen atom is shared between two electronegative atoms such as

oxygen or nitrogen. Hydrogen bonding can affect the solubility, stability, and activity of a compound.

5. Electrostatic potential: electrostatic potential is a measure of the electrostatic forces between the charged particles in a molecule. It can provide insight into the interactions between a molecule and its target protein.

6. Computational methods such as molecular modeling, molecular dynamics simulations, and quantum mechanics calculations can be used to predict and analyze these molecular properties, which can help in the design and optimization of new drug candidates

7. Surface area: the surface area of a molecule is an important factor in determining its solubility, as well as its interactions with other molecules and surfaces.

8. Charge distribution: the distribution of charges within a molecule can affect its interactions with other charged species, including proteins and other biomolecules.

9. Dipole moment: the dipole moment of a molecule is a measure of its polarity and can influence its interactions with other polar molecules and surfaces.

10. Molecular shape: the shape of a molecule is important in determining its interactions with other molecules, particularly in the case of protein-ligand interactions where the shape of the ligand must complement the shape of the protein binding site.

11. Conformational flexibility: the ability of a molecule to adopt different conformations can affect its interactions with other molecules, as well as its pharmacological properties.

Computational methods can be used to predict and analyze these molecular properties, which can provide insight into the potential biological activity and pharmacological effects of a compound. By understanding these properties, researchers can design and optimize new drug candidates with improved efficacy and safety profiles.

Quinazoline derivatives have been the subject of numerous computational studies due to their diverse biological activities, including anticancer, antitumor, antiviral, and anti-inflammatory properties. Computational studies have been used to predict the molecular properties of these compounds, investigate their biological activities, and design new derivatives with improved activity [53].

One common approach in computational studies of quinazoline derivatives is molecular docking, which involves the prediction of the binding affinity of a ligand to a target protein. This technique has been used to investigate the binding of quinazoline derivatives to various protein targets, including tyrosine kinases and tubulin. In addition to molecular docking, other computational techniques such as molecular dynamics simulations, quantum mechanics are used.

Quinazoline derivatives have been found to exhibit a wide range of biological activities, making them potentially useful in the development of therapeutic agents for various diseases. Some of the most commonly studied biological activities of quinazoline derivatives include:

1. Anticancer and antitumor activity: quinazoline derivatives have been shown to exhibit potent anticancer and antitumor activity by inhibiting various signaling pathways involved in cancer cell growth and proliferation. For example, some quinazoline derivatives have been found to inhibit the activity of tyrosine kinases such as EGFR (epidermal growth factor receptor) and HER2 (human epidermal growth factor receptor 2), which are commonly overexpressed in cancer cells [54], and there are numerous quinazoline scaffold-based compounds present in the market such as erlotinib, gefitinib (structures 1 and 2), and structures 3–6, with high cytotoxic activity toward different cancerous cell lines (**Figure 10**) [55]

2. Antiviral activity: quinazoline derivatives have also been found to exhibit antiviral activity against various viruses, including HIV, herpes simplex virus (HSV), and hepatitis C virus (HCV). Some of these compounds act by inhibiting the viral enzymes responsible for viral replication, while others inhibit viral entry into host cells.

3. Anti-inflammatory activity: quinazoline derivatives have been shown to exhibit anti-inflammatory activity by inhibiting the activity of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the production of inflammatory mediators such as prostaglandins and leukotrienes.

4. Antioxidant activity: some quinazoline derivatives have been found to exhibit antioxidant activity by scavenging free radicals and preventing oxidative damage to cells and tissues.

Here are a few examples of computational studies on quinazoline derivatives:

- "Design, synthesis, and biological evaluation of novel quinoline derivatives as small molecule mutant EGFR inhibitors targeting resistance in NSCLC: In vitro

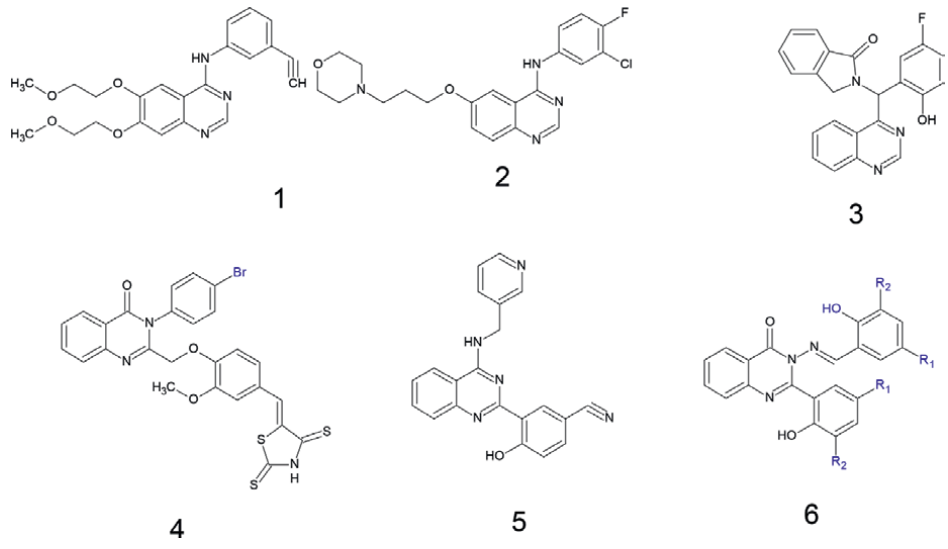


Figure 10.
Examples of anticancer agents with quinazoline scaffold.

screening and ADME predictions'' by [56]. This study used computational methods such as molecular docking and molecular dynamics simulations to design and evaluate novel quinazoline derivatives as inhibitors of the EGFR kinase [54].

- "Molecular docking, molecular dynamics simulation and QM/MM calculations study of quinazoline derivatives as tubulin inhibitors" by Mir et al. [57]. This study used a combination of computational methods to investigate the binding of quinazoline derivatives to tubulin, a protein involved in cell division. The study also included quantum mechanics/molecular mechanics (QM/MM) calculations to investigate the reaction mechanism of these compounds [57].

- "3D-QSAR and molecular docking studies on a series of 2-phenylquinazoline-4(3H)-ones as antitumor agents" by Liu et al. [27]. This study used 3D-QSAR modeling and molecular docking to investigate the structure-activity relationships of a series of quinazoline derivatives with antitumor activity [58].

- "Computational investigation of quinazoline derivatives as potential inhibitors of hepatitis C virus NS5B polymerase" by Nain et al. [59]. This study used molecular docking and molecular dynamics simulations to investigate the binding of quinazoline derivatives to the NS5B polymerase of the hepatitis C virus, with the aim of identifying potential inhibitors of viral replication [59].

Some additional examples of computational studies that have been used to investigate quinazoline derivatives:

1. Structure-based drug design: structure-based drug design involves using the three-dimensional structure of a target protein to design small molecules that bind to it with high affinity and specificity. This approach has been used to design quinazoline derivatives that target specific tyrosine kinases involved in cancer cell growth and proliferation.

2. Pharmacophore modeling: pharmacophore modeling is a computational method used to identify the essential structural and chemical features of a ligand that are required for binding to a protein target. This approach has been used to identify the pharmacophoric features of quinazoline derivatives that are responsible for their binding to specific protein targets.

3. ADMET prediction: ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction is a computational method used to predict the pharmacokinetic and toxicological properties of compounds. This approach has been used to predict the ADMET properties of quinazoline derivatives and identify potential drug candidates with improved pharmacokinetic profiles and reduced toxicity.

4. Molecular modeling of drug resistance: molecular modeling techniques have been used to investigate the mechanisms of drug resistance in cancer cells, particularly in the case of tyrosine kinase inhibitors. These studies have provided insights into the structural changes that occur in target proteins that lead to drug resistance and have helped in the design of new quinazoline derivatives that overcome drug resistance.

5. Structure-activity relationship (SAR) studies: SAR studies involve investigating the relationship between the chemical structure of a compound and its biological activity. SAR studies have been used extensively to optimize the biological activity of quinazoline derivatives, particularly in the case of anticancer activity.

Overall, computational studies have been instrumental in the discovery and optimization of quinazoline derivatives with diverse biological activities and have provided valuable insights into the molecular mechanisms of action and structure-activity relationships of these compounds. Here are some ways in which computational studies can help in the design of quinazoline derivatives:

- Identification of pharmacophoric features: computational methods such as pharmacophore modeling and molecular docking can help identify the essential structural and chemical features of quinazoline derivatives that are required for binding to specific protein targets. This information can be used to design new derivatives with improved binding affinity and selectivity; **Figure 11** shows an example of pharmacophoric features to on a set of 133 compounds of quinazoline derivatives to identify the pharmacophoric feature [60].

- Optimization of molecular properties: computational methods such as molecular dynamics simulations and ADMET prediction can be used to optimize the molecular properties of quinazoline derivatives, such as their solubility, stability, and pharmacokinetic properties. This can help improve the efficacy and safety profiles of these compounds.

- Exploration of chemical space: computational methods such as virtual screening and machine learning can be used to explore large chemical space and identify potential drug candidates with desired biological activities. This can help speedup the drug discovery process and reduce the cost of drug development.

- Prediction of drug resistance: computational methods can be used to predict the potential for drug resistance in cancer cells, particularly in the case of tyrosine

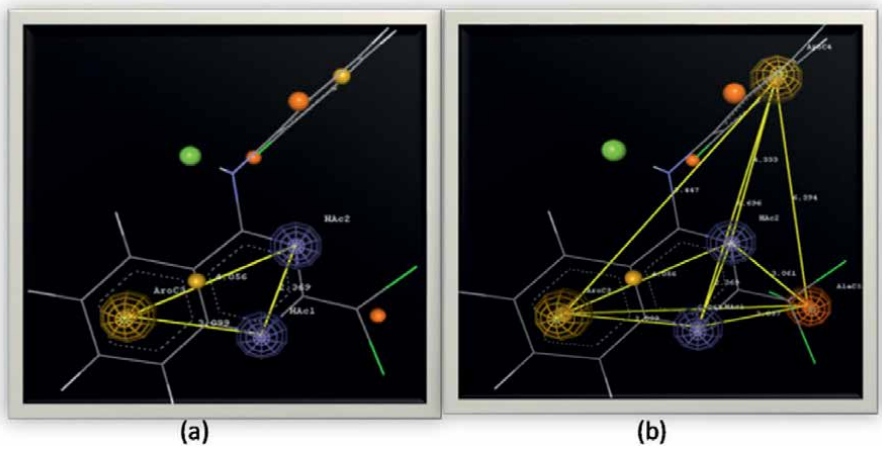


Figure 11.
Pharmacophoric features (a) three point biophore, and (b) five point biophore [60].

kinase inhibitors. This information can be used to design new quinazoline derivatives that overcome drug resistance.

- Structural optimization: computational methods such as structure-based drug design and SAR studies can be used to optimize the chemical structure of quinazoline derivatives for specific biological activities. This can help improve the potency and selectivity of these compounds.

Overall, computational studies provide a powerful tool for the design and optimization of quinazoline derivatives with diverse biological activities. By combining computational approaches with experimental methods, researchers can accelerate the drug discovery process and develop more effective and safer drugs for the treatment of various diseases. Here is an example of a quinazoline derivative that was optimized using computational methods:

Erlotinib (trade name Tarceva) is a quinazoline derivative that acts as an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, which is overexpressed in many types of cancer. Erlotinib was designed using a combination of computational and experimental methods. Computational studies were used to optimize the chemical structure of erlotinib for binding to the EGFR kinase domain. Molecular docking studies were used to predict the binding mode and affinity of erlotinib to the EGFR kinase (**Figure 12**), and molecular dynamics simulations were used to investigate the stability and flexibility of the erlotinib-EGFR complex [61]. Based on the results of these computational studies, a series of erlotinib analogs were synthesized and tested for their ability to inhibit EGFR kinase activity. The most promising analogs were then subjected to further optimization using a combination of computational and experimental methods. This approach led to the development of erlotinib, which was approved by the FDA in 2004 for the treatment of non-small cell lung cancer and later for pancreatic cancer. Erlotinib has since been used in the treatment of various types of cancer and has been shown to provide significant clinical benefits in some patients.

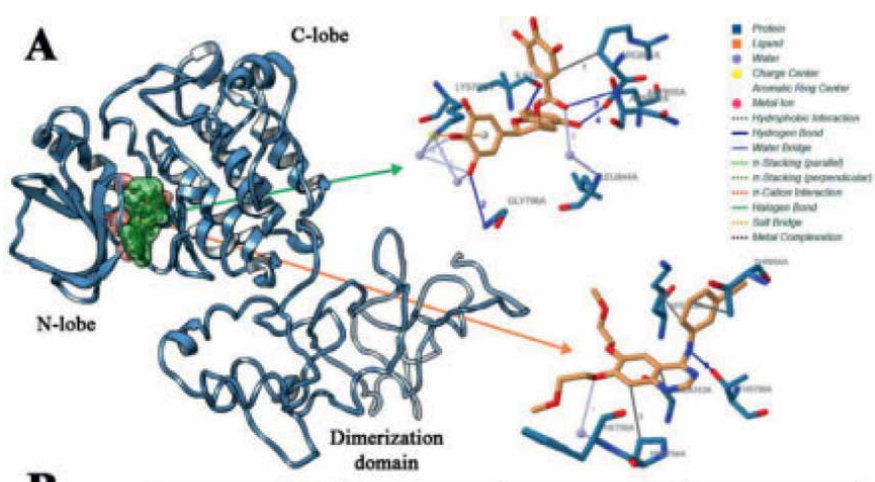
Overall, the successful development of erlotinib highlights the importance of using computational methods in the design and optimization of quinazoline derivatives for the treatment of cancer.

Quinazoline derivatives have been studied extensively for their potential as anticancer agents and have been investigated for the treatment of various types of cancer [62]. Here are some examples:

- Non-small cell lung cancer (NSCLC): quinazoline derivatives such as erlotinib and gefitinib have been approved for the treatment of NSCLC, which is the most common type of lung cancer [63].

- Colorectal cancer: quinazoline derivatives such as lapatinib and afatinib have been investigated for the treatment of colorectal cancer, which is the third most common cancer worldwide [62].

- Breast cancer: quinazoline derivatives such as lapatinib and afatinib have also been investigated for the treatment of breast cancer, particularly in the case of HER2-positive breast cancer [62].



B

Residues	Erlotinib			EGCG		
	Apolar interactions	Hbond interactions	Water bridges	Apolar interactions	Hbond interactions	Water bridges
Ser 724					x	
Gly 725	x		x			
Val 730	x	x		x		
Ala 747	x	x			x	
Lys 749	x	x		x		
Gln 788					x	
Met 790					x	
Cys 794					x	
Arg 838					x	
Leu 841	x			x		
Asp 852		x				

Figure 12.
Binding mode of erlotinib and EGCG in association with wild-type EGFR domain (A), and interactions list of erlotinib and EGCG with wild-type EGFR (B). The 3D binding mode of erlotinib (orange) and EGCG (green) has been reported [61].

- Head and neck cancer: quinazoline derivatives such as gefitinib and erlotinib have been investigated for the treatment of head and neck cancer, which is the sixth most common cancer worldwide.

- Glioblastoma: quinazoline derivatives such as lapatinib and erlotinib have been investigated for the treatment of glioblastoma, which is a highly aggressive form of brain cancer.

- Prostate cancer: quinazoline derivatives such as zalutumumab and lapatinib have been investigated for the treatment of prostate cancer, which is the second most common cancer in men worldwide.

Overall, quinazoline derivatives have shown promise as anticancer agents in the treatment of various types of cancer. The development of new quinazoline derivatives with improved potency, selectivity, and pharmacokinetic properties is an active area of research in medicinal chemistry.

4.4 Other types of biological quinazoline derivatives

Quinazoline derivatives have been investigated for the treatment of various diseases beyond cancer. Here are some examples:

- Neurological disorders: quinazoline derivatives have been investigated for the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, and epilepsy. For example, quinazoline derivatives such as donepezil and tacrine have been used as acetylcholinesterase inhibitors for the treatment of Alzheimer's disease [64].
- Inflammation: quinazoline derivatives have been investigated for their anti-inflammatory activity. For example, quinazoline derivatives such as quinazoline-4-carboxylic acid and its derivatives have shown anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines [65].
- Cardiovascular diseases: quinazoline derivatives have been investigated for the treatment of cardiovascular diseases such as hypertension and heart failure. For example, quinazoline derivatives such as prazosin and terazosin have been used as alpha-1 adrenergic receptor antagonists for the treatment of hypertension [66].
- Diabetes: quinazoline derivatives have been investigated for the treatment of diabetes. For example, quinazoline derivatives such as imatinib have been shown to improve insulin sensitivity and glucose metabolism in animal models of diabetes.
- Immune system: quinazoline derivatives have been investigated for their immunomodulatory activity and potential applications in the treatment of autoimmune diseases and cancer immunotherapy. For example, quinazoline derivatives such as imatinib have been shown to have immunomodulatory activity by inhibiting the c-kit receptor, which is expressed on mast cells and plays a role in the immune response.
- Infectious diseases: quinazoline derivatives have been investigated for their activity against infectious diseases such as malaria, tuberculosis, and viral infections. For example, quinazoline derivatives such as mefloquine and hydroxyquinoline have been used as antimalarial agents, and quinazoline derivatives have shown activity against viruses such as HIV and hepatitis C.
- Metabolic disorders: quinazoline derivatives have been investigated for the treatment of metabolic disorders such as diabetes and obesity. For example, quinazoline derivatives such as imatinib have been shown to improve insulin sensitivity and glucose metabolism in animal models of diabetes.

Overall, quinazoline derivatives have a wide range of biological activities and potential therapeutic applications beyond cancer. Ongoing research in this area is focused on developing new quinazoline derivatives with improved potency and selectivity for the treatment of various diseases.

4.5 Determination of the selectivity of quinazoline derivatives for specific targets

Researchers determine the selectivity of quinazoline derivatives for specific targets using a variety of experimental and computational methods. Here are some examples [67]:

- Biochemical assays: biochemical assays are commonly used to measure the inhibitory activity of quinazoline derivatives against specific targets, such as tyrosine kinases. These assays can provide information on the potency and selectivity of quinazoline derivatives for specific targets.

- Cell-based assays: cell-based assays are used to measure the activity of quinazoline derivatives in living cells and can provide information on the selectivity of these compounds in a more physiological context. For example, cell-based assays can be used to measure the activity of quinazoline derivatives against cancer cells that overexpress specific tyrosine kinases.

- Proteomics: proteomics is a large-scale analysis of proteins and can be used to identify the targets of quinazoline derivatives in a complex biological system. For example, mass spectrometry-based proteomics can be used to identify the proteins that are bound by quinazoline derivatives in cancer cells.

- Computational modeling: computational methods such as molecular docking and molecular dynamics simulations can be used to predict the binding affinity and selectivity of quinazoline derivatives for specific targets. These methods can provide valuable information on the structural and energetic factors that contribute to the binding of quinazoline derivatives to specific targets.

- Kinome profiling: kinome profiling is a high-throughput method used to measure the activity of quinazoline derivatives against a panel of kinases. Kinome profiling can provide information on the selectivity of quinazoline derivatives against a large number of kinases and can help identify them.

There are several examples of quinazoline derivatives that have been found to be selective for specific targets. Here are some examples:

- Lapatinib: lapatinib is a dual tyrosine kinase inhibitor that selectively targets both the epidermal growth factor receptor (EGFR) and HER2, which are overexpressed in many types of cancer. Lapatinib has been approved for the treatment of HER2-positive breast cancer.

- Vandetanib: vandetanib is a tyrosine kinase inhibitor that selectively targets the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and RET kinase, which are involved in the development and progression of various types of cancer. Vandetanib has been investigated for the treatment of thyroid cancer and non-small cell lung cancer.

- Gefitinib: gefitinib is a tyrosine kinase inhibitor that selectively targets the EGFR kinase, which is overexpressed in many types of cancer. Gefitinib has been approved for the treatment of non-small cell lung cancer.

- Afatinib: afatinib is a tyrosine kinase inhibitor that selectively targets the EGFR and HER2 kinases, which are overexpressed in many types of cancer. Afatinib has been approved for the treatment of non-small cell lung cancer and HER2-positive breast cancer.

- BIBW2992: BIBW2992 is a dual tyrosine kinase inhibitor that selectively targets the EGFR and HER2 kinases. BIBW2992 has been investigated for the treatment of non-small cell lung cancer and HER2-positive breast cancer.

Overall, the development of quinazoline derivatives with increased selectivity for specific targets has been a major focus of research in medicinal chemistry. By developing selective quinazoline derivatives, researchers can minimize the potential for off-target effects and improve the efficacy and safety of these compounds as potential drugs for the treatment of various diseases, including cancer.

5. Challenges of synthesis of new quinazoline derivatives

Developing new quinazoline derivatives as potential drugs can be challenging due to several factors. Here are some of the challenges:

- Selectivity: quinazoline derivatives are known to inhibit multiple tyrosine kinases, which can lead to off-target effects and toxicity. Developing derivatives with increased selectivity for specific targets can be challenging.

- Resistance: cancer cells can develop resistance to tyrosine kinase inhibitors, including quinazoline derivatives, by acquiring mutations in the target kinase or activating alternative signaling pathways. Developing derivatives that are effective against resistant cancer cells can be challenging.

- Pharmacokinetics: quinazoline derivatives can have poor pharmacokinetic properties, such as low solubility, poor bioavailability, and rapid metabolism. Developing derivatives with improved pharmacokinetic properties can be challenging.

- Toxicity: quinazoline derivatives can cause various adverse effects, including skin rash, diarrhea, and liver toxicity. Developing derivatives with reduced toxicity can be challenging.

- Intellectual property: quinazoline derivatives are a well-established class of compounds, and developing new derivatives that are sufficiently different from existing compounds to be patentable can be challenging.

Overall, developing new quinazoline derivatives as potential drugs requires a multidisciplinary approach that includes medicinal chemistry, pharmacology, and computational modeling. Overcoming these challenges is essential for developing new and effective quinazoline derivatives as potential drugs for the treatment of various diseases, including cancer.

Author details

Wafa Mohamed Al Madhagi[1,2]

1 Department of Medicinal Chemistry, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen

2 Department of Pharmacy, Faculty of Medical Sciences, Al-Nasser University, Sana'a, Yemen

*Address all correspondence to: wafalmadhaji2020@gmail.com

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Section 4

Biological Activity of Quinazoline

Chapter 6

Biological Activities of Recent Advances in Quinazoline

Ali Gamal Al-Kaf and Rana Abdullah Al-Robaidi

Abstract

Quinazolines are important stable heterocyclic compounds of great biological activates. Naturally, they are found in many plants that are the source of these quinazolines in addition they are synthesized chemically. Recently quinazolines represent a nucleus of the vast majority of novel compounds that have promising biological activity. They show different activities by acting on different body targets such activities are anticancer, antihypertensive, antimicrobial, antifungal, antibacterial, analgesic, anti-inflammatory, antituberculosis, and antimalarial activity. This chapter highlights the recent advance in the biological activates of quinazolines and quinazolines derivatives on different biological targets.

Keywords: quinazolines, biological activities, quinazolines derivatives, novel compounds, hybrid compounds

1. Introduction

Heterocyclic compounds represent the biggest group in the field of medicinal chemistry for the treatment of diseases and infections; among this group, is quinazoline moiety. Quinazoline is a heterocyclic system having two aromatic six-membered rings. One of them contains two nitrogen atoms named as pyrimidine ring and this ring is fused to the second aromatic benzene ring. Therefore, quinazoline is a phenyl pyrimidine compound. Quinazolines have a wide range of pharmacological activities. They are used as anticancer, antiviral, antibacterial, antitubercular, analgesic, antihypertensive, anti-inflammatory, antidiabetic, sedative-hypnotic, antihistaminic, anticonvulsant, and many other uses [1]. Scientists have been interested in quinazoline alkaloids since 1888, when (+)-peganine, a natural representative of the class, was discovered (vasicine). The vasicine biosynthetic pathway: The amide synthesis that follows the anthranilate nitrogen's neucleophilic attack on the pyrrolinium cation easily explains the structure of the peganine skeleton. Surprisingly, Justicia adhatoda does not use this pathway; instead, there is a much less predictable sequence involving aspartic acid and acetylanthranilic acid [2]. Due to their extensive spectrum of antibacterial, antifungal, anti-inflammatory, antimalarial, anti-HIV, antiviral, and antituberculosis characteristics, along with their capacity to inhibit thymidylate synthase, poly-(ADP-ribose) polymerase (PARP), and tyrosine kinase, quinazolinones and quinazolines hold significance in the field of medicinal chemistry.

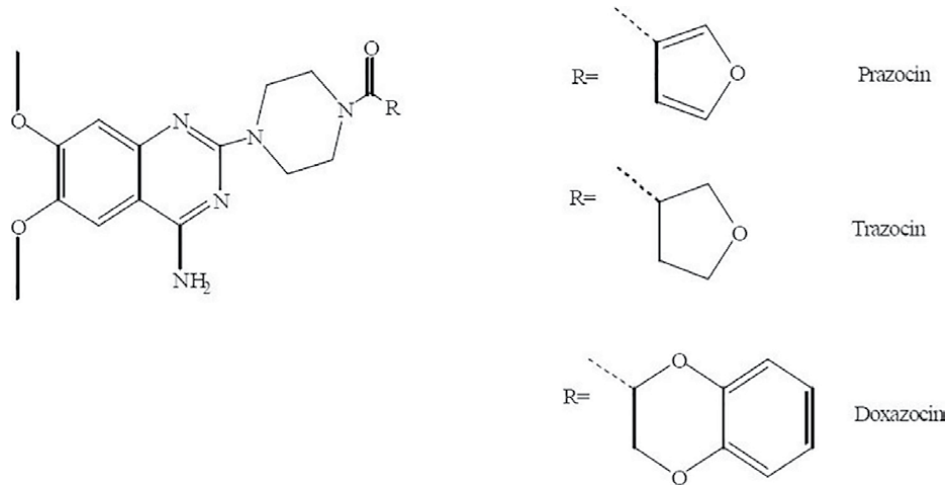


Figure 1.
Quinazoline-containing approved and marketed medications.

Several licensed medications with quinazoline structure are available on the market, including doxazosine mesylate, terazosine hydrochloride, and prazosin hydrochloride (**Figure 1**) [3].

2. Therapeutic potential of quinazoline and quinazolinone compounds

One of the most beneficial heterocyclic substances originating from the perspectives of synthetic and therapeutic chemical analysis are quinazolines and quinazolinones. Because of its wide range of biological efficacy, varied chemical reactivity, and easily accessible nature, the scaffolds' structural design has attracted a lot of attention. Despite a substantial corpus of literature containing many instances of these themes demonstrating possible biological processes, we have concentrated here on the latest changes in these compounds' activity profiles [4].

2.1 Anti-inflammatory properties

Two sets of derivatives based on 2-phenyl-4(3H) quinazolinone demonstrated potent anti-inflammatory and analgesic effects in experimental rats, exhibiting an improved gastrointestinal safety profile in comparison to the reference drug. In experimental rats, a few chemical entities showed the strongest inflammation-inhibiting effects when compared to the reference drug indomethacin (**Figure 2**) [2].

Anti-inflammatory activity [5] of two novel quinazoline derivatives were synthesized, identified as 25 and 26 (**Figure 3**) and their anti-inflammatory properties were evaluated. Isoquino-quinazolinone 25 and quinazolino-quinazolinone 26 were substituted for these derivatives. However, in contrast to the high potency observed in the substituted 2-phenyl-quinazoline compound 24, neither of them demonstrated a comparable level of activity.

Taking regular piroxicam at 4 mg/kg, the anti-inflammatory activity of additional variations of compound 27 (**Figure 4**) was evaluated. Compound 27's derivatives without substitution, those with a 4-methyl substitution, and those with a 3-nitro

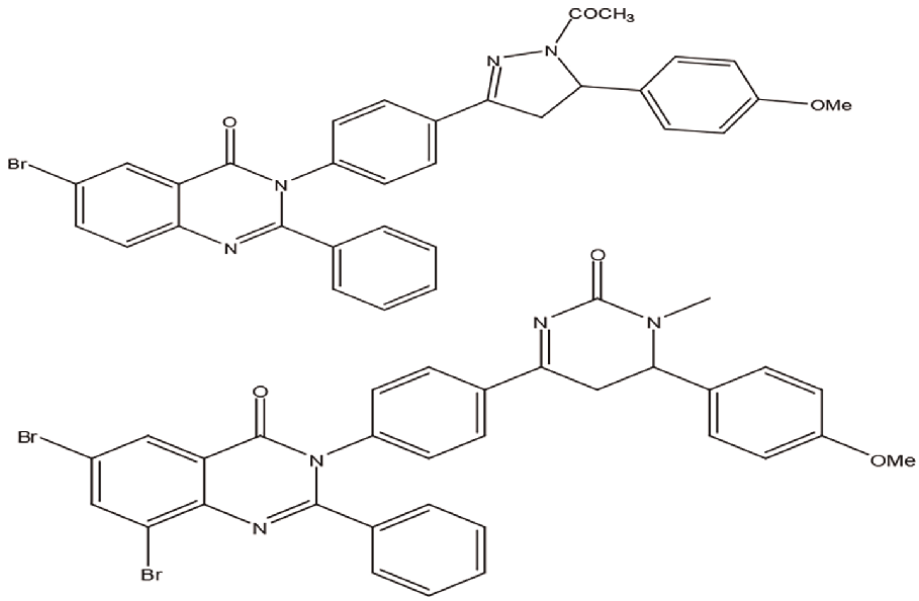


Figure 2.
Derivatives based on 2-phenyl-4(3H) quinazolinone.

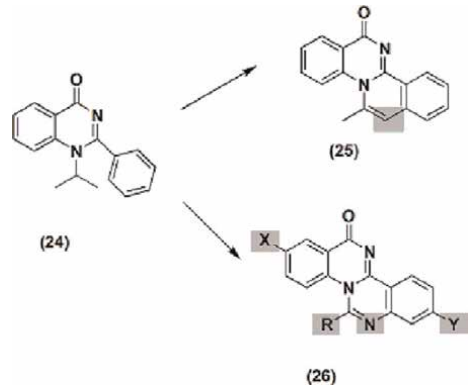


Figure 3.
The quinazolines 24, 25, and 26 have anti-inflammatory properties.

substitution produced higher activity than regular piroxicam, according to a structure-activity relationship (SAR) study. An administration of three derivatives at a dose of 4 mg/kg exhibited less activity than piroxicam diclofenac. To increase the anti-inflammatory activity, thiadiazole with a nicotinyl moiety was added to the structure at position C-3 of compound 28. The highest activity was produced by substituted 2-phenylquinazoli's nicotinyl-5-pyridyl thiadiazole, which is similar to regular ibuprofen. The activity range of substituted quinazolinedione derivatives 29 and 30 was 12.7–58.2%. 10-Iodosubstitution significantly increased the anti-inflammatory activity, according to SAR studies. Furthermore, the anti-inflammatory activity was improved by substituting 4-phenylaminomethyl and 6-methoxyphenylaminomethyl.

31-Phenyl quinazolinone derivatives were synthesized in order to assess their potential as inflammation-inhibiting drugs. Among these variations, the most potent was the compound with a two-piperidenomethyl substitution., followed by

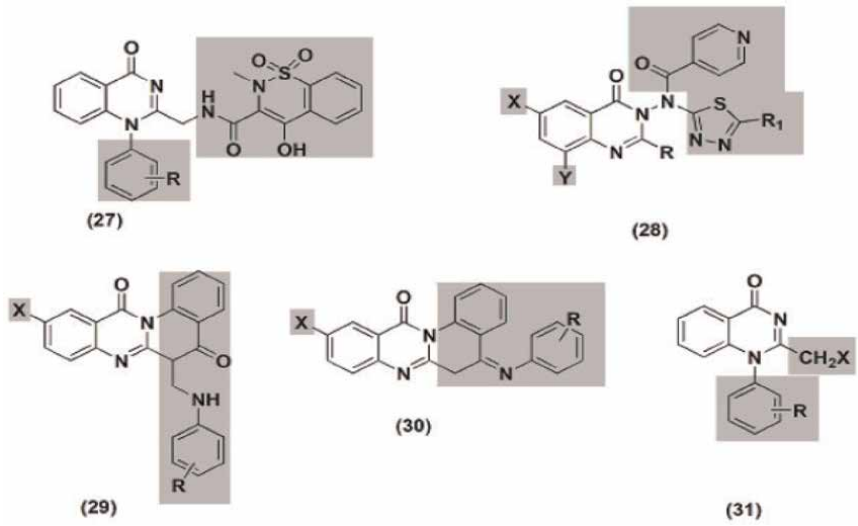


Figure 4.
The compounds 27, 28, 29, 30, and 31 exhibit anti-inflammatory characteristics.

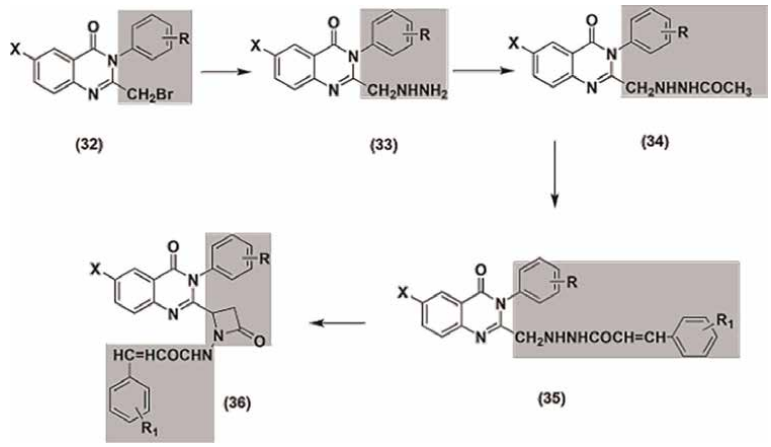


Figure 5.
The compounds 32, 33, 34, 35, and 36 are agents with anti-inflammatory properties.

two-methlyl and two-dimethylaminomethyl. The 2-chloromethyl substituents were the least active. The anti-inflammatory potential of the 2,3,6-trisubstituted quinazolinone derivatives 32–36 (depicted in **Figure 5**) was explored through development, synthesis, and evaluation as potential medications. The variable activity range for these derivatives was 10.28–53.33%. The activity of compounds containing p-dimethylaminophenyl at C-2 and o-methoxyphenyl substituents at C-3 was higher than that of standard phenylbutazone. Furthermore, the ulcerogenic potential of these derivatives was examined. When compared to regular phenylbutazone, the potent anti-inflammatory derivatives showed less ulcerogenic activity.

Assessing against indomethacin as the reference, the anti-inflammatory properties of various newly developed derivatives from benzothiazole-substituted 2-phenyl quinazolinones 37, 38 (illustrated in **Figure 6**) were investigated. Each of the derivatives

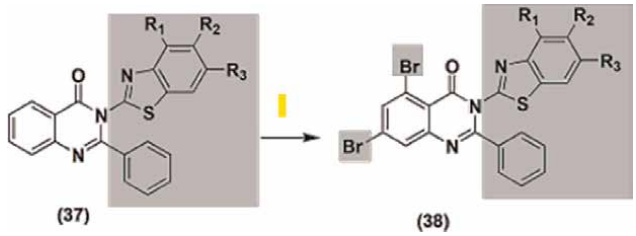


Figure 6.
Quinazolines 37 and 38 with anti-inflammatory properties.

exhibited reduced efficacy (ranging from 21.3% to 77.5% protection) compared to indomethacin, which provided 80.9% protection. The efficacy of the derivatives with bromine substitution (38) was inferior, with protection ranging from 21.3% to 27%, compared to the unsubstituted derivatives, which showed protection between 30% and 77.5%. A SAR investigation revealed that compounds featuring electron-withdrawing groups, like 4-nitro and halogen, exhibited reduced activity compared to compounds with electron-releasing groups, such as 4-alkyl and alkoxy. Moreover, when assessed for their inhibitory effects on COX-I and COX-II, these derivatives displayed limited activity against COX-I and substantial activity against COX-II. The IC50 values for COX-I ranged from 98 to 100 μM, while for COX-II, they ranged from 0.39 to 1.87 μM. In contrast, COX-I showed 0.22 μM and COX-II showed 2.64 μM with standard indomethacin. Furthermore, at an oral dose of 100 mg/kg/day, the effective derivative exhibited a favorable gastrointestinal safety profile with no ulceration, in stark contrast to the 100% ulceration observed with the equivalent dose of indomethacin.

Quinazolinone 39 new derivatives (**Figure 7**) showed comparable efficacy to ibuprofen at a dose of 200 mg/kg. Four-nitrostyryl-substituted quinazolinone and four-hydroxystyryl-substituted quinazolinone were the most active derivatives. The edema volume was reduced in an activity range of 62.2–80.7%. The anti-inflammatory properties of the quinazolinone derivatives 40, which are substituted with phenylaphtalene (**Figure 8**), were evaluated at 50 mg/kg. They produced inhibition ranging from 19.69% to 59.61% and demonstrated a favorable gastrointestinal safety profile, with ulcerogenic activity in the range of 30–70%. The most effective derivative among these was 6-bromosubstituted-quinazolinone. Standard phenylbutazone had 50% ulcerogenic activity and 38.9% anti-inflammatory activity.

Novel derivatives 41–43 were created when thiazolidindione and azetidinone were added to quinazolinone at C-3 (**Figure 9**). The anti-inflammatory properties of these

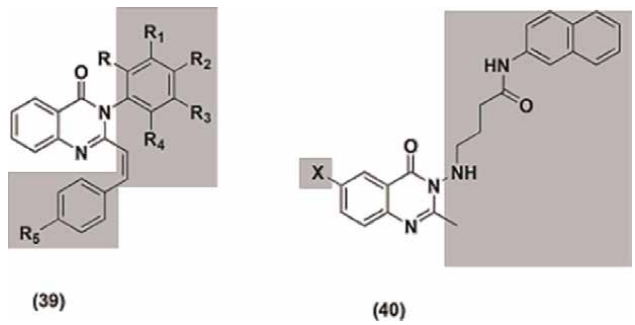


Figure 7.
The anti-inflammatory quinazolines 39 and 40.

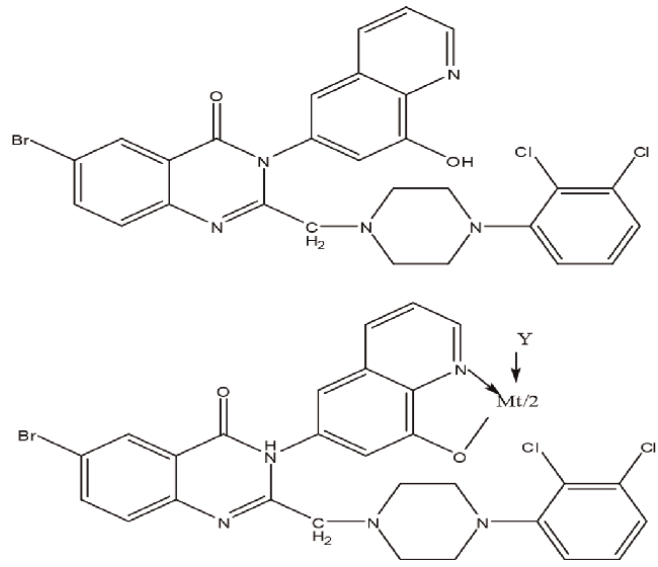


Figure 8.
Quinazoline compound with corresponding chelates shows antifungal activity.

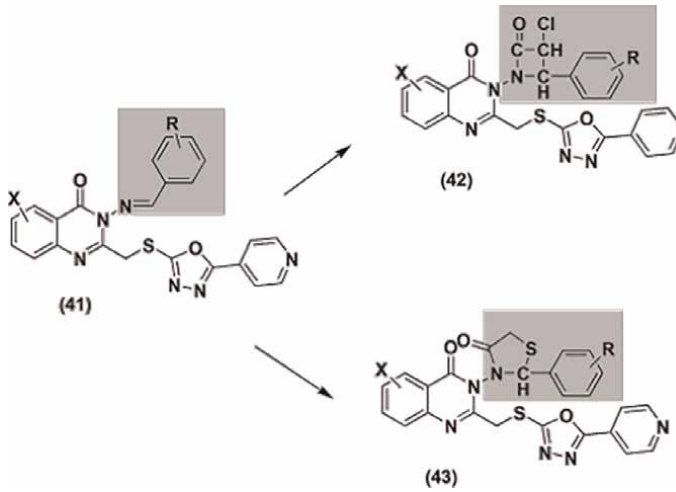


Figure 9.
Quinazolines 41, 42, and 43 with anti-inflammatory properties.

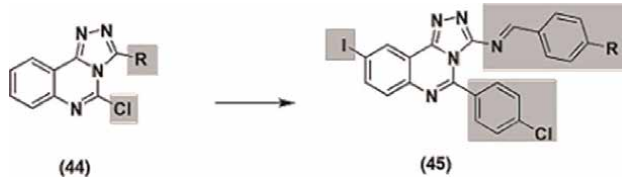


Figure 10.
Quinazolines 44 and 45 with anti-inflammatory properties.

derivatives were assessed. At a dosage of 50 mg/kg, they produced activity that was comparable to standard phenylbutazone (16.33–36.3%). Compound 41's arylidene underwent cyclization, yielding azetidinone derivative 42 and thiazolidinone derivative 43. When compared to the azetidinone derivative series, the thiazolidinone derivative series exhibited greater anti-inflammatory activity.

An examination of the anti-inflammatory properties of the triazoloquinazoline derivative with a 5-chloro-2 substitution. Compound 44 (**Figure 10**) indicated that its activity ranged from more potent to equipotent compared to the reference ketoprofen. The carrageenin-induced paw edema test was employed to formulate, synthesize, and assess the anti-inflammatory activity of an additional set of triazolo-quinazoline derivatives with substitutions, illustrated as compound 45 in **Figure 10**. The outcomes revealed activity that was similar to that of the reference indomethacin.

Inflammatory conditions such as rheumatoid arthritis, autoimmune diseases, and ulcerative colitis are addressed using alternative derivatives of piperidinyl-substituted quinazolinone. Compound 46 was assessed for its anti-inflammatory properties. (**Figure 11**). It proved to have potent anti-inflammatory qualities. Strong anti-inflammatory properties against multiple molecules involved in inflammation, including prostaglandin (PGE-2), nitric oxide (NO), and tumor necrosis factor-alpha (TNF-α), and macrophages stimulated by bacterial endotoxin lipopolysaccharide (LPS), have been reported for 5-chloro-2-methylsulfonyl-triazoloquiazoline 47 (**Figure 11**).

2.2 Antifungal activity

The antifungal efficacy of the ligand 6-bromo-2[(4-(2,3-dichlorophenyl)) piperazine-1-yl)methyl]-3-[8-hydroxyquinoline-5-yl]-3-quinazolin-4-one and its corresponding transition metal chelates (**Figure 8**).

By condensing 2-phenyl-3,1-benzoxazine-4-one with 4-substituted phenyl ureas, a collection of innovative compounds, namely 4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-substituted phenyl amides), was successfully synthesized. The synthesis

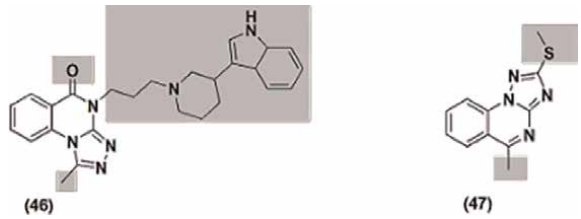


Figure 11.
Quinazolines 46 and 47 with anti-inflammatory properties.

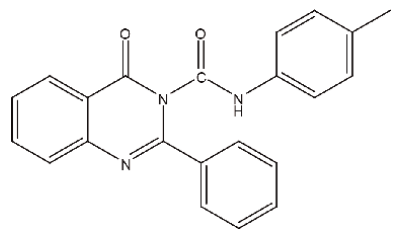
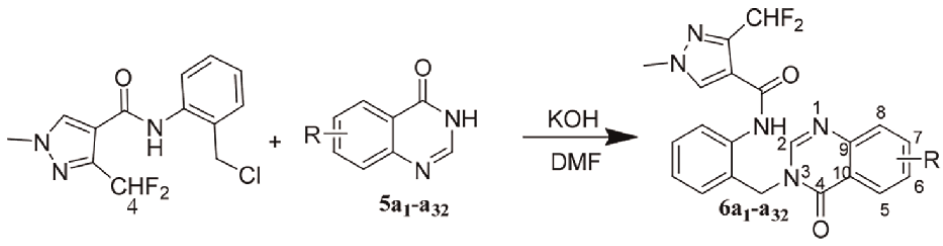


Figure 12.
4-Oxo-2-phenyl-4H-quinazoline-3-carboxylic acid.



$6a_1$:R=H	$6a_9$: R=7-F	$6a_{17}$:R=6-Cl-8-Me	$6a_{25}$:R=7-OMe
$6a_2$:R=5-Me	$6a_{10}$:R=8-F	$6a_{18}$:R=5-Br	$6a_{26}$:R=8-OMe
$6a_3$:R=6-Me	$6a_{11}$:R=6,7-diF	$6a_{19}$:R=6-Br	$6a_{27}$:R=6,7-diOMe
$6a_4$:R=7-Me	$6a_{12}$:R=5-Cl	$6a_{20}$:R=7-Br	$6a_{28}$:R=5-NO_2
$6a_5$:R=8-Me	$6a_{13}$:R=6-Cl	$6a_{21}$:R=8-Br	$6a_{29}$:R=6-NO_2
$6a_6$:R=7,8-diMe	$6a_{14}$:R=7-Cl	$6a_{22}$:R=6,8-diBr	$6a_{30}$:R=7-NO_2
$6a_7$:R=5-F	$6a_{15}$:R=8-Cl	$6a_{23}$:R=5-OMe	$6a_{31}$:R=8-NO_2
$6a_8$:R=6-F	$6a_{16}$:R=6,8-diCl	$6a_{24}$:R=6-OMe	$6a_{32}$:R=6-I

Figure 13.
Synthesis of the target compounds 6a1–a32 [5].

involved combining N-benzoyl anthranilic acid with acetic anhydride to produce 2-phenyl-3,1-benzoxazine-4-one. Subsequently, sodium cyanide was employed to condense various 4-substituted anilines, leading to the formation of 4-substituted phenyl ureas. The *in vitro* antifungal activity of all synthesized compounds against four pathogenic fungi was evaluated using the standard agar dilution method. The resulting zone of inhibition was then determined. Clotrimazole was employed as the reference standard. However, none of the compounds exhibited activity against Aspergillus fumigatus (**Figure 12**) [2].

In an effort to find a novel fungicide against *Rhizoctonia solani*, 32 new pyrazole carbamide derivatives with quinazolinone scaffold were designed and synthesized. 3-(difluoromethyl)-N-(2-((6,7-difluoro-4-oxoquinazolin-3(4H)-yl) methyl)phenyl)-1-methyl-1H-pyrazole-4-carboxamide (6a11) single-crystal X-ray diffraction verified the target compounds' structure. At 100 μg mL^{-1}, the target compounds' *in vitro* antifungal activity against *R. solani* was assessed. According to the findings of the SAR analysis, antifungal activity peaked at position 6 when the substitution activity was there. Furthermore, the antifungal activity was directly impacted by the location and quantity of chlorine atoms. Following additional *in vitro* bioassays, it was discovered that 6a16 (EC50 = 9.06 mg/L) exhibited superior antifungal activity against *R. solani* compared to fluconazole (EC50 = 12.29 mg/L), but less so than bixafen (EC50 = 0.34 mg/L). According to 7.33 (SEM), scanning-electron microscopy, N-(2-((6,8-dichloro-4-oxoquinazolin-3(4H)-yl)methyl)phenyl)-3-(difluoromethyl) additionally, -1-methyl-1H-pyrazole-4-carboxamide (6a16) had an impact on the mycelial shape. The results showed that creating antifungal candidates through molecular hybridization was a useful technique. In the meantime, compounds containing a quinazolinone fragment in pyrazolecarbamide showed possible antifungal activity against *R. solani* (**Figure 13**) [6].

2.3 Anticancer activity

A class of diseases known as cancer arises when aberrant cells proliferate uncontrollably and have the ability to infiltrate other tissues. Cancer cells have the

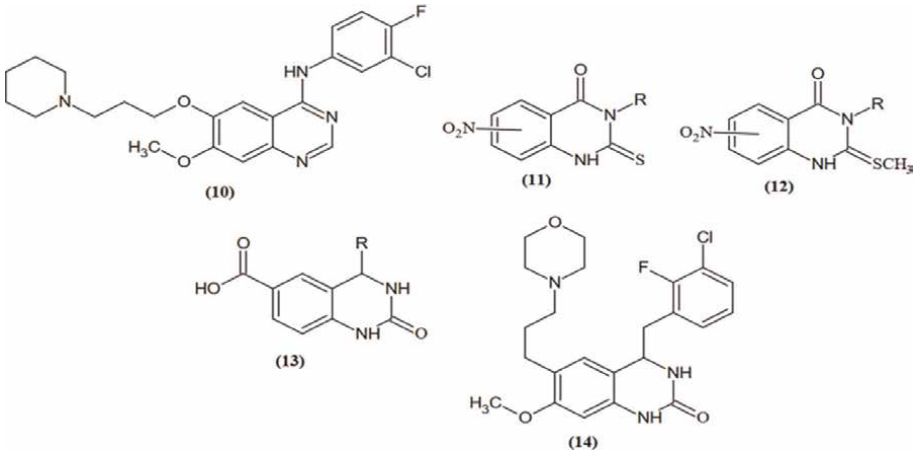


Figure 14.
Promising derivatives' anti-cancer activity [10–14].

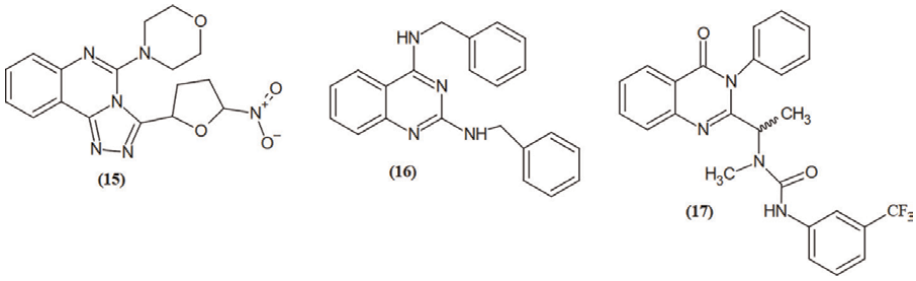


Figure 15.
Compounds [15–17].

ability to travel through the blood and lymphatic systems to other areas of the body. Many anti-cancer medications have an incomplete precise mechanism of action, and most of the time it is unknown what causes their marginal anti-tumor selectivity. Promising derivatives' anti-cancer activity [7–11] is demonstrated by the following: the percentage of control cells that survive decreases as concentrations increase, indicating the cytotoxic characteristics of the derivatives. Upon analysis, there was a discernible suppression of tumor growth (**Figure 14**).

After being tested against three human cancer cells for their antiproliferative properties, the following newly synthesized compounds [12–14] showed a notable inhibition of tumor growth. 8–10. These substances have cytotoxic properties and stop the body from spreading (**Figure 15**) [15].

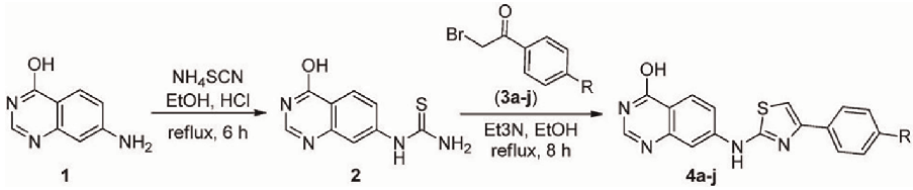


Figure 16.
The synthetic pathway for preparing the target.

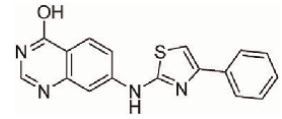
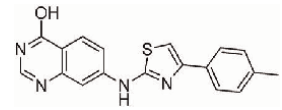
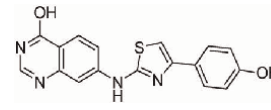
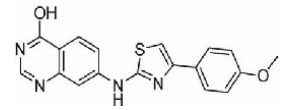
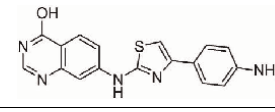
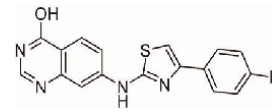
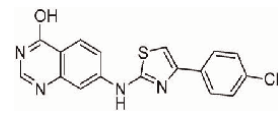
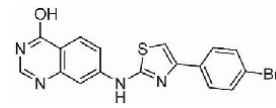
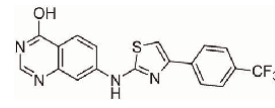
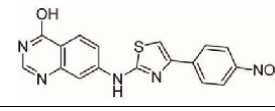
Compound	R	Final structure
4a	—H	
4b	—CH3	
4c	—OH	
4d	—OCH_3	
4e	—NH2	
4f	—F	
4 g	—Cl	
4 h	—Br	
4i	—CF3	
4j	—NO_2	

Table 1.
Structures of the derivatives 4a–j.

We conceived and synthesized innovative thiazole compounds based on quinazoline as inhibitors of EGFR-mutant kinase, aiming at treating non-small cell lung cancer (NSCLC) along with human breast (MCF-7), liver (HepG2), and lung (A549) cancer cell lines. **Figure 16** outlines the pathways for generating novel thiazole derivatives based on quinazoline, while **Table 1** presents the structures of the derivatives 4a–j (**Table 2**) [16].

Compound	IC50 (μM)			
	MCF-7	HepG2	A549	Vero
4a	6.21 ± 0.33	11.86 ± 0.71	24.73 ± 0.95	>50
4b	6.28 ± 0.58	12.59 ± 1.02	27.04 ± 1.09	>50
4c	7.43 ± 0.91	14.16 ± 0.83	31.16 ± 0.97	>50
4d	9.75 ± 1.03	17.28 ± 0.98	24.97 ± 1.14	>50
4e	8.29 ± 0.44	15.03 ± 0.81	29.61 ± 1.22	>50
4f	3.71 ± 0.47	7.92 ± 0.63	19.02 ± 0.83	>50
4 g	4.14 ± 0.69	9.36 ± 1.15	20.84 ± 1.24	>50
4 h	4.92 ± 0.31	9.85 ± 0.97	22.86 ± 1.06	>50
4i	2.86 ± 0.31	5.91 ± 0.45	14.79 ± 1.03	>50
4j	3.09 ± 0.45	6.87 ± 0.59	17.92 ± 0.95	>50
Erlotinib	3.16 ± 0.22	6.83 ± 0.51	19.42 ± 1.28	>30

Table 2.
Cytotoxicity of compounds 4a–j on cancer cell lines.

2.4 Antihypertensive activity

In an attempt to create novel pulmonary hypertension treatments with PDE5 inhibitors, twenty N2, N4-2,4-diamines of disubstituted quinazoline were recently designed based on the sildenafil-like nature of their pharmacophore. Six of them exhibited promising inhibitory effects on rat PDE5 (compounds 4, 5, 8, 9, 10, and 11). One compound (compound 8, N2-methyl-N4-[(thiophen-2-yl) methyl]quinazoline-2,4-diamine) demonstrated when testing their vasorelaxant effect on rat pulmonary arteries in comparison to aortas, they showed five times more selectivity for aortas than pulmonary arteries, highlighting its possible usefulness as a systemic vasodilator. The following were looked at in the current study: (i) *in vivo*: compound 8's acute hypotensive effect in normotensive rats, and for

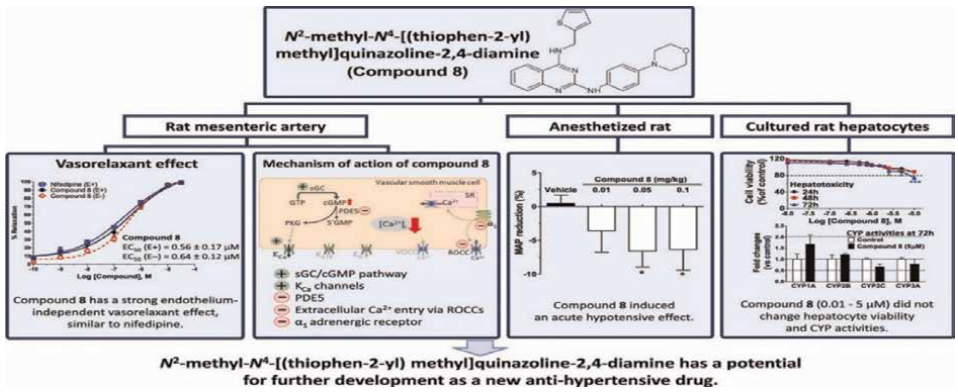


Figure 17.
A N2-methyl-N4-[quinazoline-2,4-diamine](thiophen-2-yl)methyl) was found in the current study to have a strong vasodilation impact on the resistance vasculature [https://ars.els-cdn.com/content/image/1-s2.0-S0014299923003400-ga1_lrg.jpg].

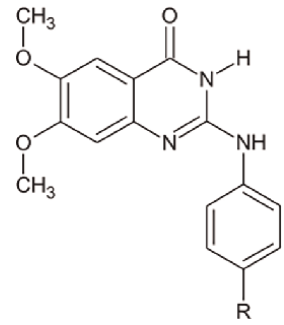


Figure 18.
2, (phenylamino)quinazoline-6,7-di methoxy-4(3H)-one.

the early evaluation of its drugability; (ii) *ex vivo*: compound 8's vasorelaxant effect and the mechanisms involved in rat isolated mesenteric artery; (iii) toxicity on isolated hepatocytes; and (iv) its effect on liver cytochrome P450 (CYP) activities. The primary objectives of this study were to determine whether compound 8 can induce vasodilation in resistance arteries within the systemic vasculature and to comprehend its underlying mechanisms. Nifedipine served as the reference comparator (refer to **Figure 17**) [17].

Vasodilation impact on the resistance vasculature, which was linked to a hypotensive effect. Its relaxing action includes KCa channel opening, α1-adrenergic receptor and transmembrane calcium influx inhibition, and sGC/cGMP Course potentiation. If compound 8 proves to be a promising new drug candidate for the management of high blood pressure, more research needs to be done [17]. The ability of the derivatives of 6,7-di methoxy-2(phenylamino) quinazolin-4(3H)-one (**Figure 18**) to inhibit alpha-1 adrenergic receptors was tested [7].

2.5 HIV-related activity

Several dihydrobenzo(h)quinazoline derivatives were synthesized starting from quinazloline derivatives and aryl methylene thiopyrimidine. Based on biological screening, many of these compounds demonstrated significant efficacy against viral infection [7]. Using an industrial-scale microwave-assisted production method, a set of hydrophilic 2,3-substituted quinazolinones, 4-oxo-2-phenylquinazoline-3(4H)-carboximidamide (Qg), and 4-oxo-2-phenylquinazoline-3(4H)-carboxamide (Qu), were produced in promising yields. These agents possess both antiviral and antibacterial properties. They were produced by reacting urea or guanidine hydrochloride with 2-benzamidobenzoyl chloride in DMF's potassium carbonate solution. Geometrical optimization and vibrational frequency analysis of the compounds were performed using DFT calculations. The DFT calculations of the free energies of solvation (ΔGsol) for Qg and Qu provide evidence in favor of their hydrophilicity. We looked into the anti-HIV-1 properties of the small-molecule quinazolinone derivatives Qu and Qg. *In vitro*, the synthons have a low cytotoxicity (EC50 = 50.53 nM for Qu and EC50 = 97.92 nM for Qg) and prevent HIV entry in receptor cells. The two benzo-fused pyrimidine derivatives, which were previously reported to exhibit antitubercular activity, are identified in the study in terms of their antiviral characteristics. Our results point to the need for additional synthetic

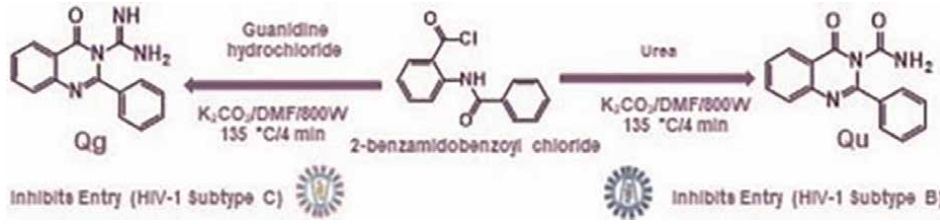


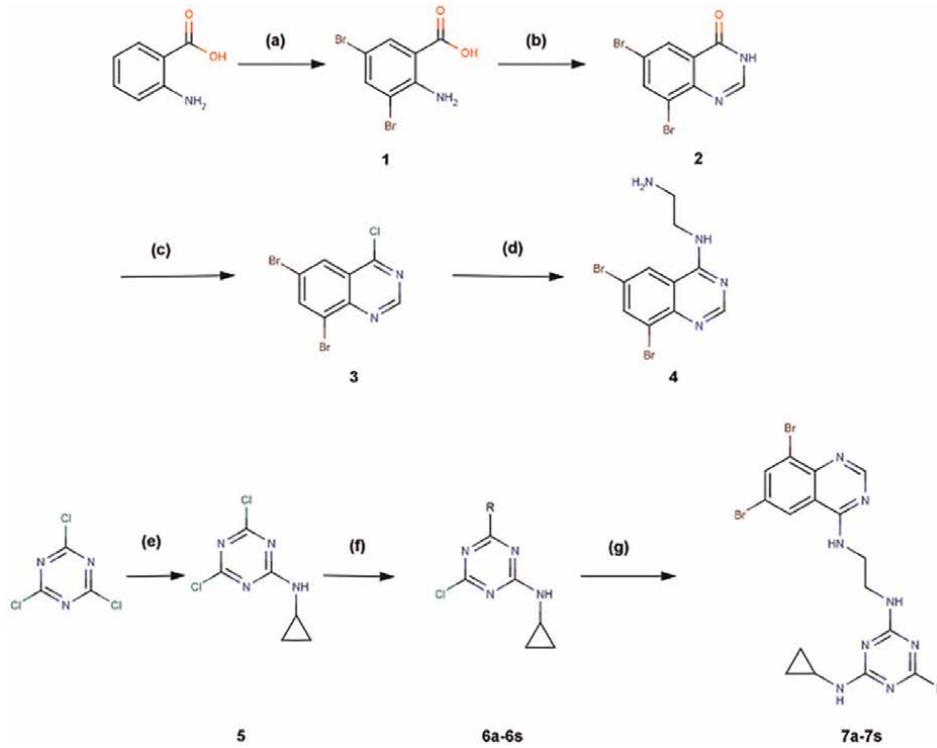
Figure 19.
Small-molecule quinazolinone derivatives Qu and Qg.

investigations into these quinazolinone scaffolds, which may result in the creation of viable substitutes for use in clinical research, pharmaceutics, and drug design (**Figure 19**) [8].

Human T-lymphocyte (MT-4) cells were used to test the novel synthetic compounds 6a–s and 7a–s for their *in vitro* anti-HIV-1 (strain IIIB) and -HIV-2 (strain ROD) activity. The inhibition of the virus-induced cytopathic effect in MT-4 cells was used to determine the inhibitory concentrations (IC50) of synthetic compounds on HIV-1 and HIV-2 replications (**Figure 20**) [9].

2.6 Antioxidant activity

Novel analogs of quinazolines, along with their combined heterocyclic counterparts, have been synthesized. It was observed that certain molecules exhibited a remarkable inhibition of aldehyde oxidase, surpassing 98% [7].



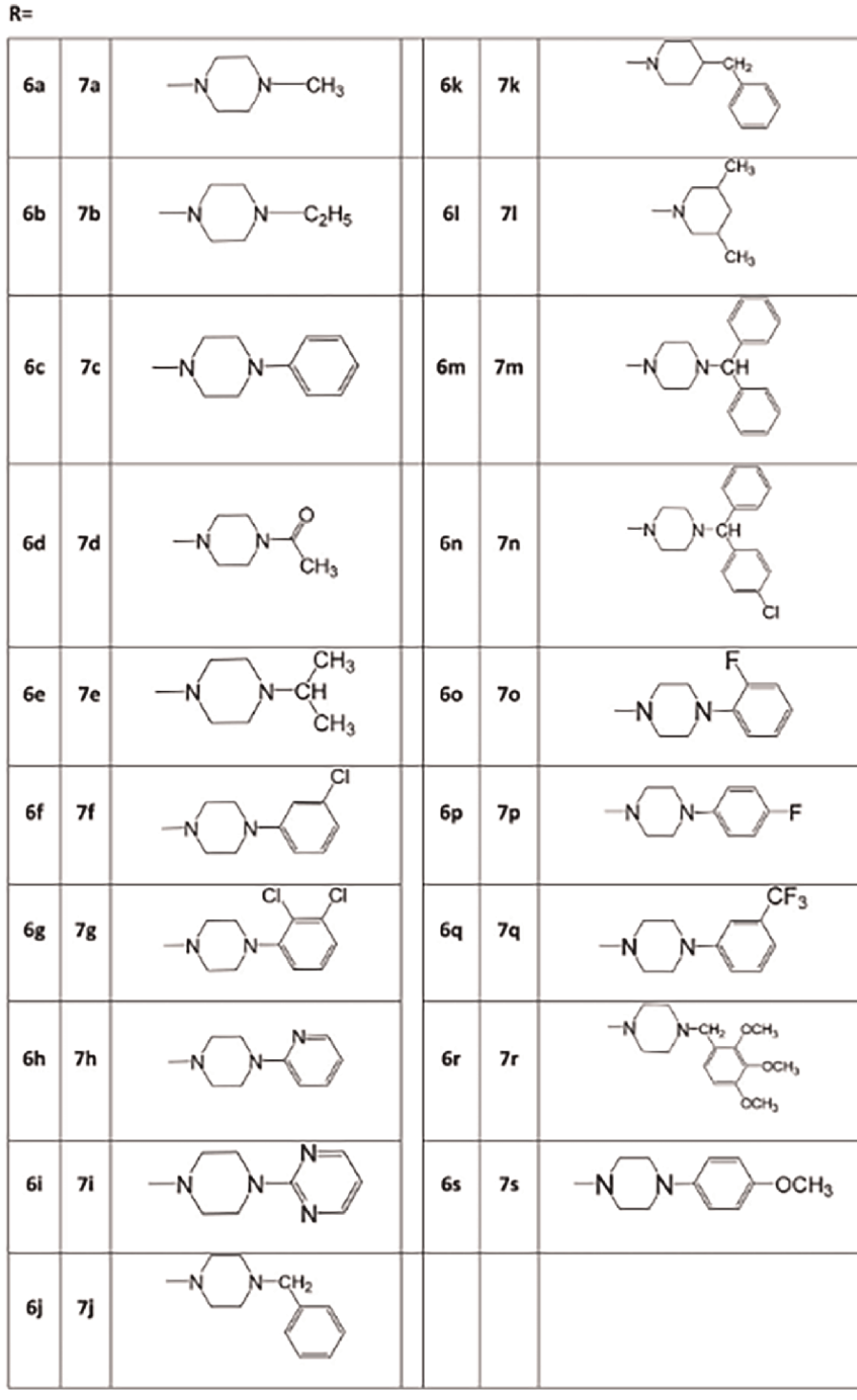


Figure 20.
Overview of the synthetic strategy for the synthesis of N2-cyclopropyl-N4-(2-(6,8-dibromoquinazolin-4-ylamino) ethyl)-6-R-1,3,5-triazine-2,4-diamine (7a–7s).

2.7 Antiviral activity

The investigation involved assessing the activity of a representative series of 4-amino-tetrahydroquinazoline derivatives 13 with aliphatic and aromatic substituents, as well as with an adamantyl framework (**Figure 21**), in porcine embryo kidney (PEK) cells in relation to TBEV reproduction. The antiviral activity was found to be influenced by the presence of a bulky hydrophobic adamantane fragment. Quinoxaline derivatives represent a burgeoning class of heterocyclic compounds that exhibit a broad spectrum of biological activities and find applications in various therapeutic contexts. The synthesis of various quinoxaline derivatives and the assessment of their cytotoxic and antiviral efficacy against diverse RNA and DNA viruses are currently areas of active research. Enteroviruses worldwide distribution of CV-B4 and CV-B5 infections is responsible for numerous serious illnesses. In immunocompromised children, CV-B5 is linked to encephalitis and myocarditis; in older adults, it is linked to central nervous system disease. Three compounds (compounds 14aa–ac) exhibited cytotoxicity against various cell lines (MT-4, MDBK, BHK, and Vero-76) as well as very strong and selective antiviral activity against CV-B5. Furthermore, compound 14aa blocks penetration that may be directed at the viral capsid protein VP1. Several nucleophilic reactions were used to create distinct quinoxalin-2-one derivatives. The synthesized compounds were assessed for their antiviral activity against HCV (Hepatitis C Virus), HBV (Hepatitis B Virus), and HSV-1 (Herpes Simplex Virus type 1).

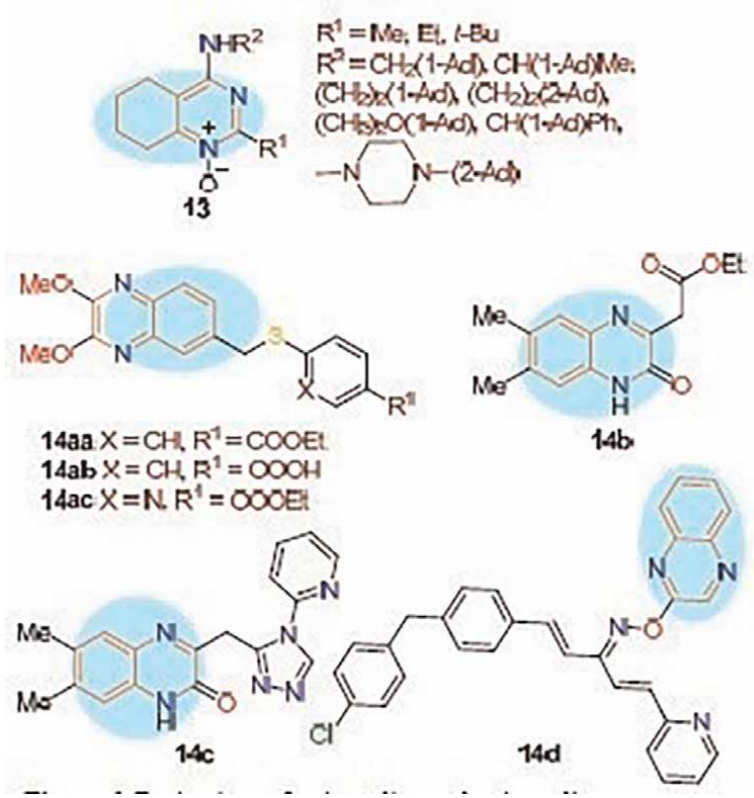


Figure 21.
Derivatives of quinazoline and quinoxaline as antiviral.

Concurrently, their safety profile and selectivity against various viral strains were studied. Consequently, two of the test compounds, namely quinoxalin-2-ones 14b and 14c, exhibited a low cytotoxicity index concerning cell viability. Moreover, they demonstrated potent activity and selectivity against HCV when compared to ganciclovir. Following synthesis, the antiviral effectiveness of a series of penta-1,4-dien-3-one oxime ethers containing a quinoxaline moiety was evaluated against TMV (Tobacco Mosaic Virus). Compound 14d demonstrated exceptional TMV-specific healing, preventive, and inactivating capabilities. In the control experiment, the commercial agent Ningnanmycin was used to assess the antiviral activity of this compound using the half-leaf method.

This review underscores the increasing interest in the development of heterocyclic compounds and their potential applications in treating viral infections. Antiviral medications with high potency and specificity are currently accessible to treat various viral types. The need for novel chemical scaffolds in targeted therapy stems from the rise in viral resistance. Numerous research teams focus on therapeutic agents that contain heterocycles, as they have the potential to be effective against various virus strains. Future studies will focus on chemically modifying specific heterocyclic moieties to improve their inhibitory efficacy, transforming them into a robust antiviral platform with direct implications for the environment and society [10].

2.8 Antimalarial activity

It was possible to create substitute quinazolinoes that structurally resemble febrifugine and ketofebrifugine (**Figure 22**). The anti-plasmodial activity of the synthesized compounds against *Plasmodium berghei* in mice was demonstrated at a dose of 5 mg/kg body weight. By comparison, these compounds have a more feasible synthetic scheme than artemisinin and chloroquin [7].

2.9 Antibacterial

The antimicrobial activity for the following Quinazoline derivatives [18–27] was carried out by different Techniques. These shows the successful anti-microbial activity against Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli. The present study of Quinazoline derivatives shows the Several successful attempts

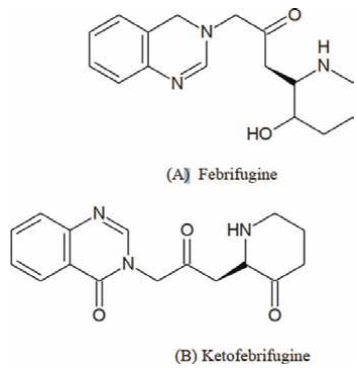


Figure 22.
Febrifugine and ketofebrifugine.

have been made and recorded in the literature demonstrating promising outcomes (**Figure 23**) [15].

For the recently synthesized compounds, the antibacterial evaluation was achieved were hybrids of quinazolin-2,4-dione with bioactive scaffolds like amide, sulfonamide, hydrazone, thiourea linkage, and/or N-heterocyclic cores like pyrrolidine-2,5-dione, pyrazole, and oxadiazole, utilizing two G +ve (Bacillus subtilis ATCC 6633 and Staphylococcus aureus NRRL B-767) and two G −ve (Escherichia coli ATCC 25955 and Pseudomonas aeruginosa ATCC 10145) bacteria. Compound 3c demonstrated a distinctive antimicrobial efficacy **Figure 24** against every tested pathogenic strain at a concentration lower than the tested standard drug, ranging from 2.5 to 10 μg mL^{-1}. The synthesized compounds displayed a range of activities against the tested pathogens.

As shown in **Figure 25**, our starting 2 was created by reacting hydrazine hydrate in absolute ethanol with the synthesized ester diethyl-2,2′-(2,4-dioxoquinazoline-1,3 (2H,4H)-diyl)-diacetate 1.

By treating 2,2′-(2,4-dioxoquinazoline-1,3(2H,4H)-diyl)di(aceto hydrazide) 2 with different aromatic aldehydes, such as benzaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, and furfural, respectively, several arylidene hydrazide derivatives (Schiff bases) 3a–e were synthesized in good to excellent yields (**Figure 26**).

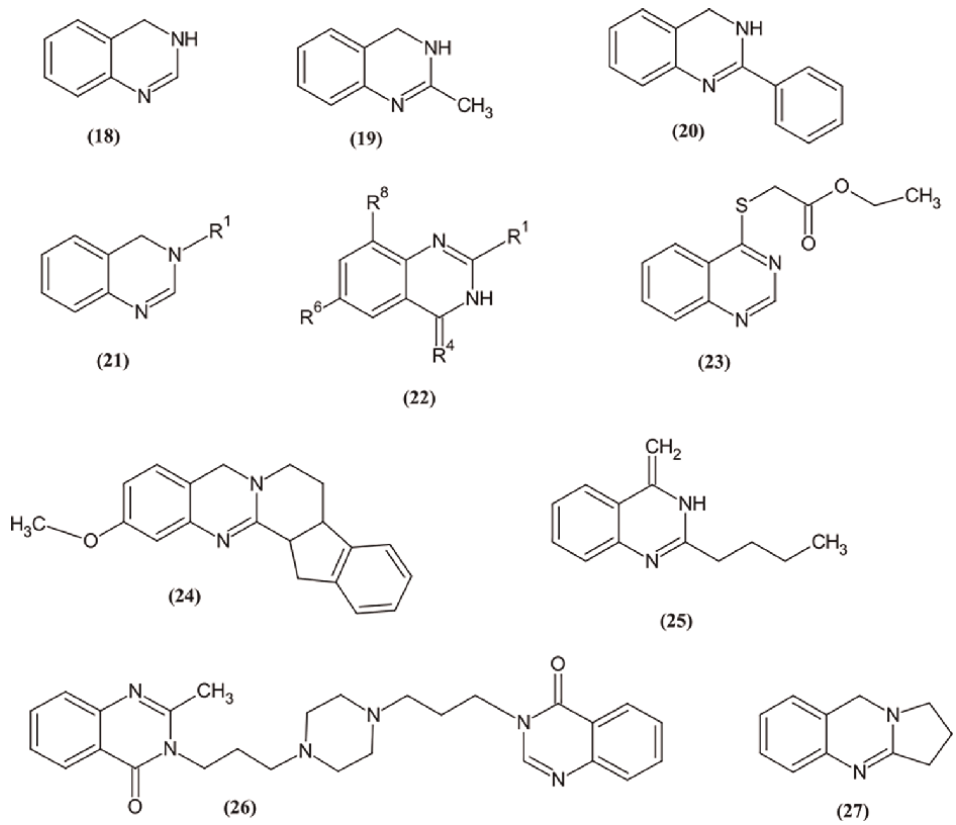


Figure 23.
Quinazoline derivatives [18–27] had their antimicrobial activity tested using various methods.

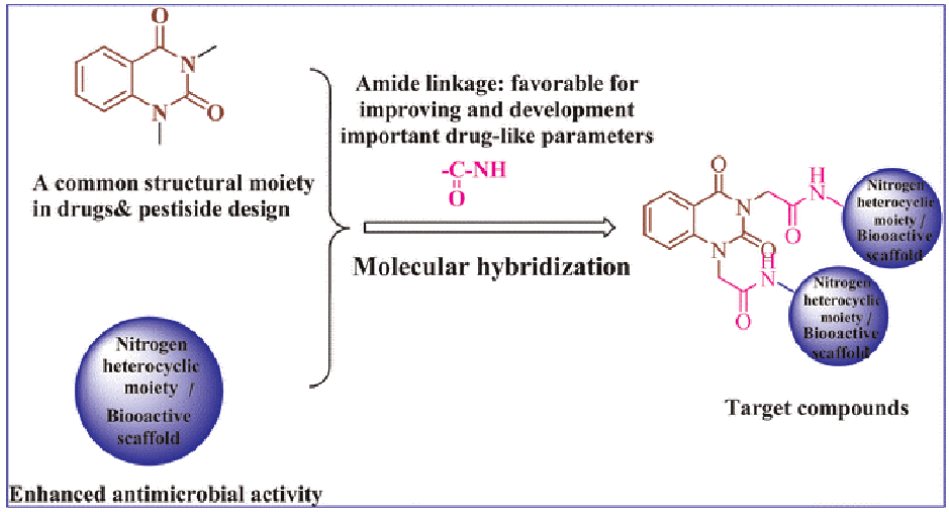


Figure 24.
Design of the target compounds

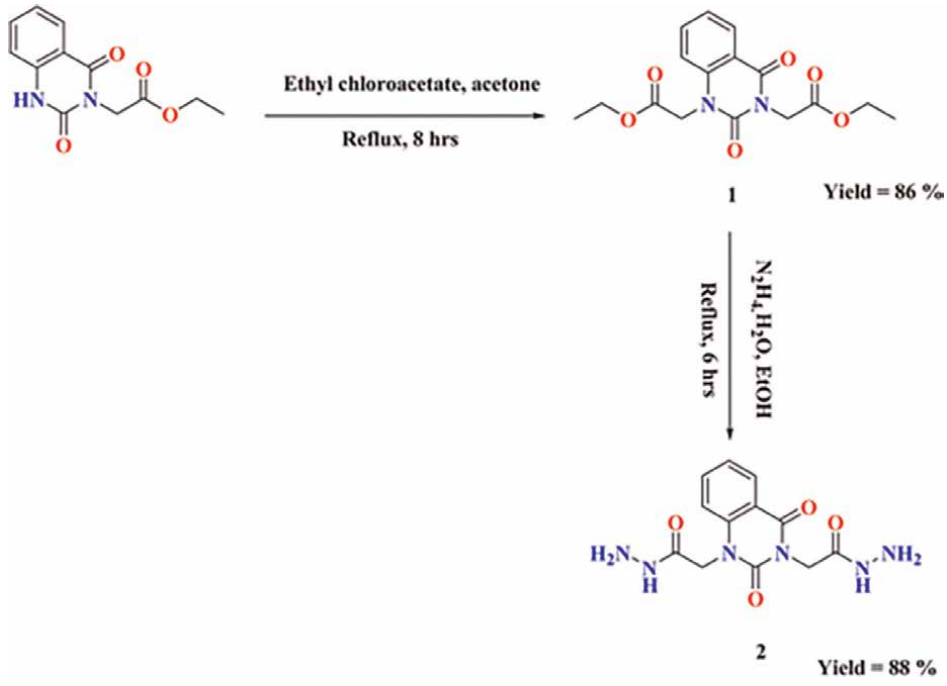


Figure 25.
Synthesis of starting material 2.

Moreover, quinazolin-2,4-dione containing pyrazole and pyrazolone moieties 7a–b were synthesized based on condensation of 2 with active methylene compounds such as acetylacetone and ethyl acetoacetate *via* Knorr pyrazole reaction, as declared in **Figure 27** [11].

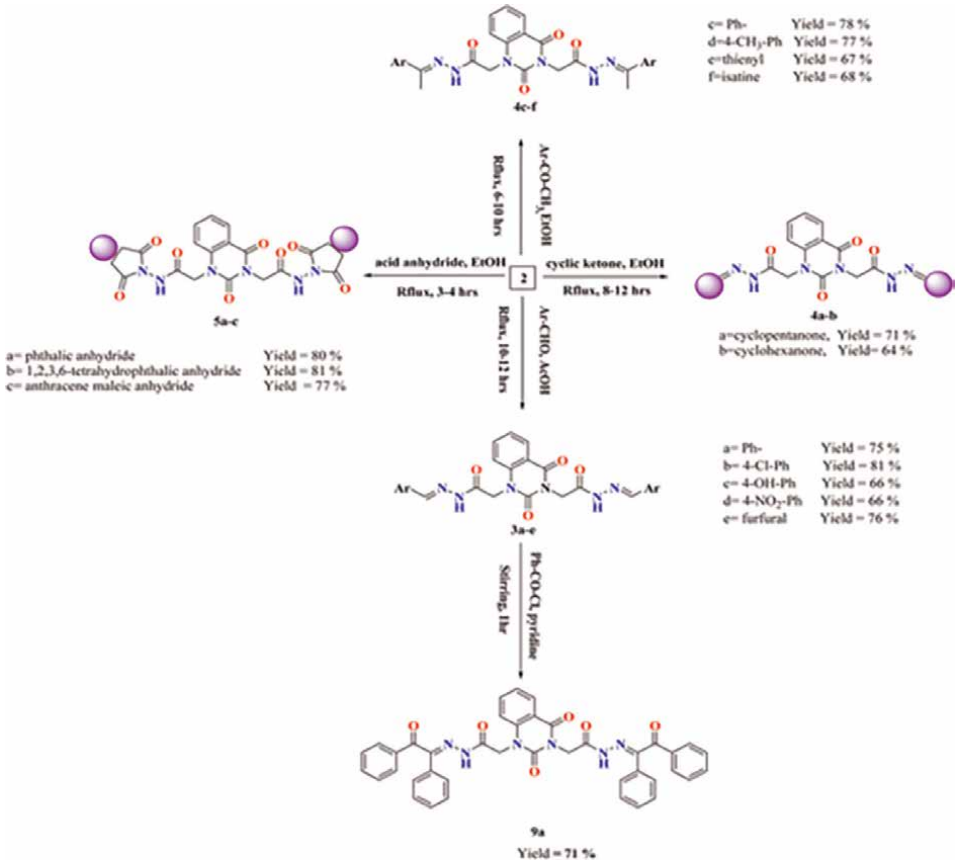


Figure 26.
Compound 3-5 and compound 9a's synthesis.

2.10 Anti-leishmanial hybrids

One of the main goals for the development of anti-leishmanial drugs is to demolish the metabolic pathways that are necessary to allow the parasite to remain within the host [12]. One of the vital enzymes in charge of the parasite's antioxidant defense is trypanothione reductase (TR). In earlier studies, a variety of anti-leishmanial agents were synthesized, demonstrating potent activity across different series, including β-carboline, dihydro-β-carboline, and quinazolinone. Taking these variables into account, Chauhan et al. [12] synthesized hybrids based on quinazolinone and β-carboline and then tested them *in vitro* for anti-leishmanial activity. After conducting *in vitro* enzyme inhibition against the LdTR enzyme, numerous compounds exhibited activity in inhibiting the enzyme. It was discovered that compounds on quinazolinone with aromatic groups were just as active as those with aliphatic substituents. Compounds 100, 101, and 102, which are aromatic groups with substituents that withdraw electrons, exhibit greater inhibition than unsubstituted phenyl or phenyl rings with substituents that donate electrons (**Figure 28**). Competitive inhibition has been demonstrated by all enzyme inhibitors. Additionally, anti-leishmanial activity was assessed, and the anti-leishmanial activity and the outcomes of the enzyme assay were correlated. Compounds 100, 101, and 102 were identified as the most potent in the series, displaying IC50

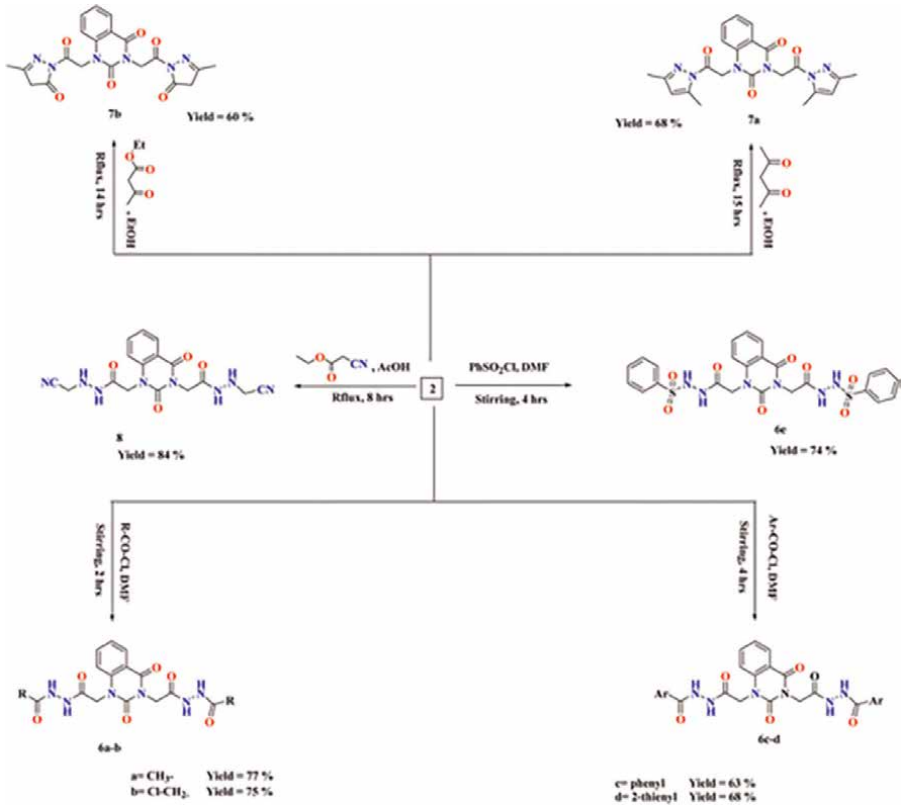


Figure 27.
Synthesis of compounds 6–8.

values of 4.4, 6.0, and 4.3 μg mL^{-1}, respectively, against intracellular amastigotes of *Leishmania donovani*. The standards employed in this analysis were miltefosine (with an IC50 of 8.1 μg mL^{-1}) and SSG (with an IC50 of 54.4 μg mL^{-1}).

Four series of quinazolinone-based hybrids were created by Sharma et al. [12] (**Figures 29** and **30**). In these series, there are members such as quinazolinone-pyrimidine hybrids (a), quinazolinone-triazine hybrids (b), quinazolinone-peptide hybrids (c), and quinazolinone-tetrazole hybrids (d). All of the compound series, with the exception of the tetrazole series, were discovered to be active following the viewing process for anti-leishmanial activity.

2.11 Hybrids that fight diabetes

An essential enzyme called α-glucosidase breaks down carbohydrates so that glucose and other monosaccharides can be absorbed [12]. By inhibiting this enzyme, the risk of postprandial hyperglycemia is lowered by lowering the postprandial blood glucose level. Prior studies have illustrated the significance of quinazolinone and triazole in inhibiting α-glucosidase. Considering these aspects, Saeedi et al. [12] created hybrids based on quinazolinone and triazole and assessed how well they inhibited α-glucosidase. Using acarbose as the reference drug (IC50 of 750 μM), it was found that all the synthesized hybrid analogs inhibited the α-glucosidase enzyme through competitive inhibition, with IC50 values falling within the range of 181–474.5 μM.

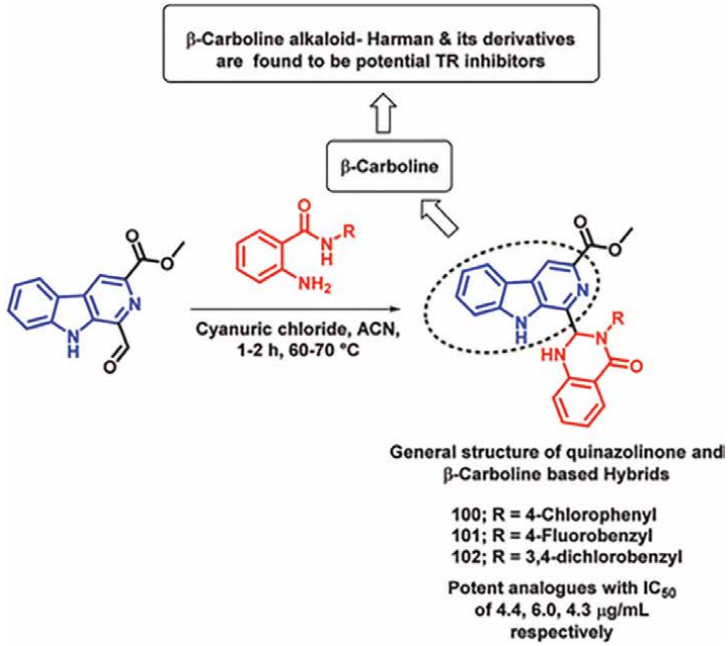


Figure 28.
Formulation for β-carboline-quinazolinone blends.

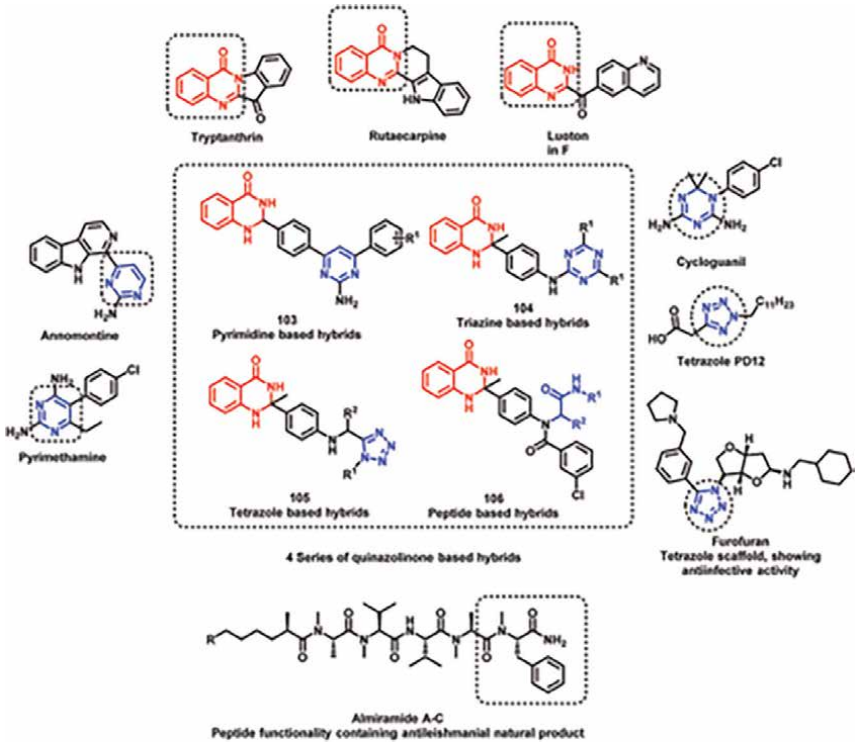


Figure 29.
Plan the design of quinazoline hybrids containing peptide, tetrazole, triazine, and pyrimidine.

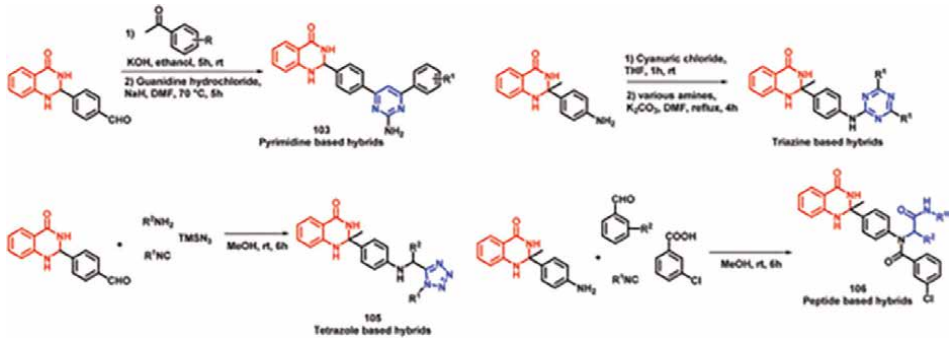


Figure 30.
Quinazoline hybrids: a synthetic scheme involving pyrimidine, triazine, tetrazole, and peptide.

Compounds 111 and 112, which exhibited the highest potency, had IC50 values of 181.0 and 192.3 μM, in that order (**Figure 31**).

Jangam et al. [12] 122 hybridized thiazolidinediones (rosiglitazone, pioglitazone, and troglitazone) with the medicinally significant quinazolinone scaffold, taking into account the significance of these compounds as PPAR-γ agonists. All of the designed compounds demonstrated good binding at the PPAR-γ receptor's active site (PDB: 4PRG) according to the docking study. When the synthesized compounds were tested on diabetic rats induced by streptozotocin, compounds 113, 114, 115, and 116 demonstrated a significant anti-diabetic potential (**Figure 32**). The compounds under investigation underwent testing for a range of biochemical parameters, including glycated hemoglobin (HbA1C), insulin, alanine transaminase (ALT), aspartate transaminase

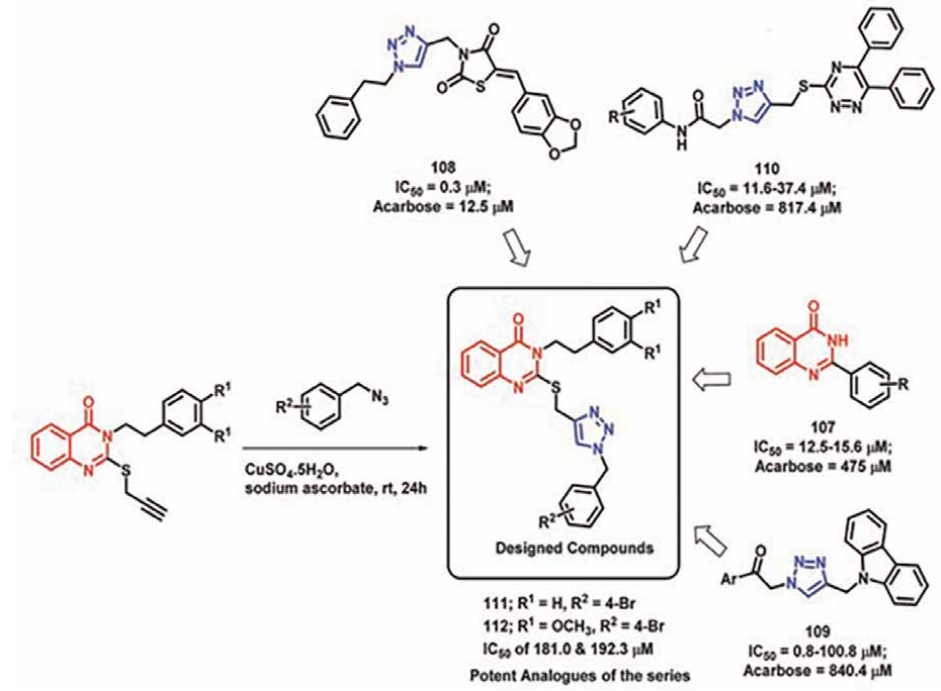


Figure 31.
Triazole-linked quinazolinone hybrids: synthesis and design strategy focused on α-glucosidase.

Figure 32.
Creation of hybrids between quinazolinone and thiazolidinone.

(AST), as well as the levels of total protein, triglycerides, cholesterol, high-density lipoprotein (LDL), and low-density lipoprotein (LDL). It was discovered that each of these parameters was significant.

2.12 Hybrid anti-convulsant

A category of disorders known as epilepsy is characterized by neuronal hyperexcitability [12], often accompanied by episodes of motor, sensory, or autonomic phenomena, with or without a loss of consciousness. Derivatives of quinazolinone, including methaqualone, afloqualone, and mecloqualone, are clinically approved medications with the potential for treating epilepsy. Because of their antagonistic action against AMPA, benzothiazole derivatives (e.g., Riluzole) are also attracting interest for their anti-convulsant properties. In order to create some hybrid analogs, Malik et al. [12] combined the AMPA antagonistic and GABA agonistic properties of benzothiazoles and quinazolinones, respectively, into a single hybrid scaffold. The following pharmacophoric characteristics were added to the molecule to increase the anti-convulsant potential of the created analogs. The distal hydrophobic domain (d), electron donor moiety (c), hydrogen bonding domain (b), and hydrophobic domain (a) are examples of these characteristics. In this manner, hybrids based on benzothiazoles and quinazolinones were created (**Figure 33**). In mice, seizure models in relation to subcutaneous pentylenetetrazole (scPTZ) and maximal electroshock (MES) were created in order to screen the synthesized hybrids for anti-convulsants.

Compound 133 exhibited greater potency compared to the positive controls, with an ED50 of 92 μmol kg^{-1} for MES (Maximal Electroshock Seizure) and >3540 μmol kg^{-1} for scPTZ (subcutaneous pentylenetetrazole), surpassing the effects of phenytoin and ethosuximide.

Anti-convulsant analogs containing quinazolinone (methaqualone, ethaqualone, and mecloqualone) suggest that quinazolinone's third aromatic ring substitution is necessary for its CNS depressant and anti-convulsant properties. To create powerful CNS-acting medications, numerous researchers have attempted to replace a number of aromatic ring substituents. Taking these facts into account, Jangam et al. [12] connected 4-oxothiazolidine at the quinazolinone backbone's third position to create hybrids based on quinazolinone (**Figure 34**). Using MES-induced mice as a screening model, many of the synthesized compounds demonstrated moderately to very effectively anticonvulsant. The SAR study demonstrated the significance of groups that withdraw electrons for anti-convulsant activity at the para, meta, and

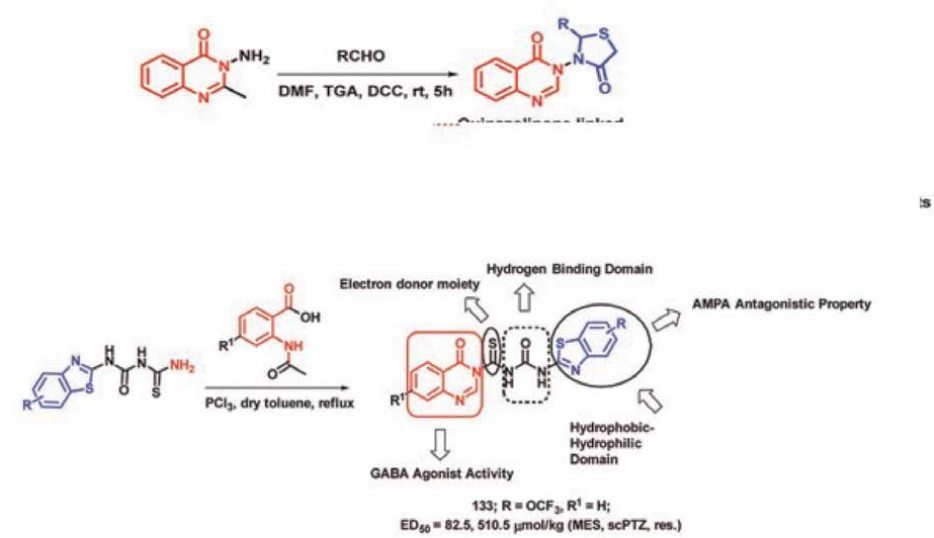


Figure 33.
Quinazolinone-benzothiazole hybrid synthetic approach highlighting the significance of structure.

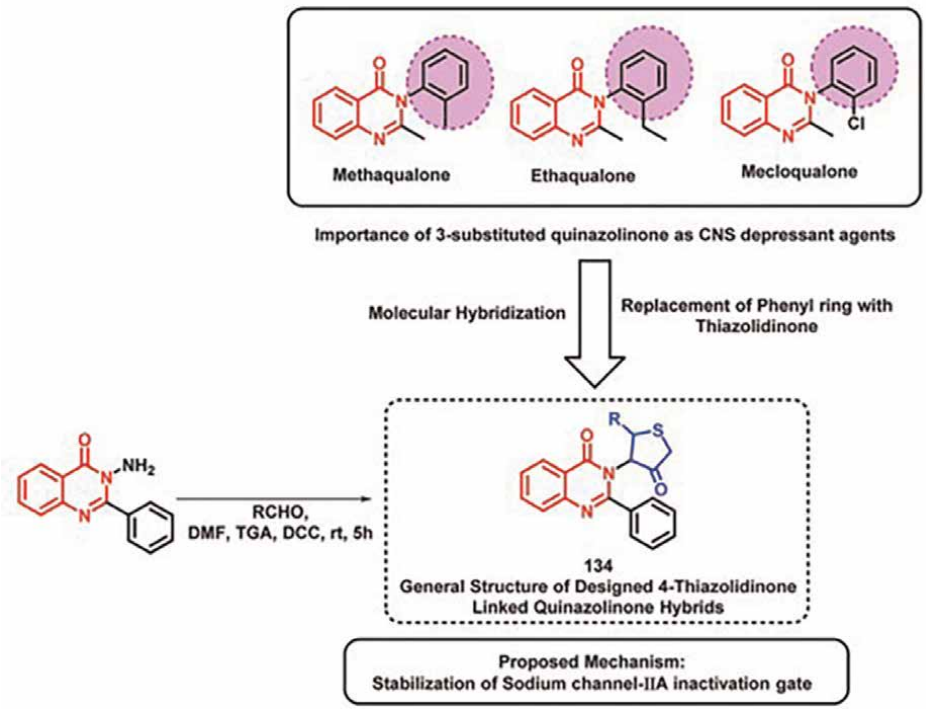


Figure 34.
The synthesis and design methodology for quinazolinone and 4-oxothiazolidine hybrids.

ortho positions of the phenyl ring attached at the second place of thiazolidine. The sodium channel IIA inactivation gate's active site was docked with these designed analogs (PDB ID: 1BYY), and their binding energy ranged from −5.15 to −6.13 kcal mol^{-1}, indicating appropriate binding at the active site of the receptor.

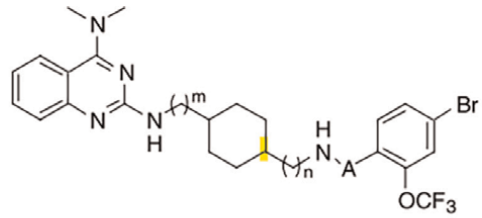
2.13 Melanin-concentrating hormone receptor 1 antagonists

It has been demonstrated that quinazoline derivatives that bind to MCHR1 have unique anti-obesity properties. Sasmal et al. explored the potential anti-obesity properties of quinazoline derivatives, identifying them as antagonists for the melanin-concentrating hormone receptor 1 (MCHR1) [13]. By switching out the substituent groups, a number of compounds were produced, such as 4-morpholinyl-quinazoline, 4-hydroxypiperidine-quinazoline, 4-propyl-quinazolinone, 4-pyrrolidin-quinazolinone, and so forth. First, these compounds' solubility and metabolic stability in blood were investigated. Subsequently, these derivatives were evaluated for their potential in preventing obesity. A prototype molecule, 4-Morpholinyl-quinazoline (**Figure 35**), was selected due to its favorable oral pharmacokinetic (PK) profile for further investigation of its effects in diet-induced obese (DIO) C57BL/6 J mice. And after receiving that compound orally for 14 days (30 mg/kg, b.i.d.), the tested mice clearly lost 12% of their body weight. According to the findings, 4-morpholinyl-quinazoline, a representative compound, had a pronounced anti-obesity effect. However, it was also noted that additional stability enhancement of the compound in plasma concerning the oxymethylene linker was required [14, 18, 19].

In addition, a variety of other quinazoline derivatives, such as 4-amino-2-cyclohexyl aminoquinazoline and 4-dimethylamino quinazoline, exhibit strong inhibitory activity for MCHR1. ATC0065 (N2-[cis-4-({2-[4-bromo-2 (trifluoromethoxy) phenyl]ethyl}amino)cyclohexyl]- N4,N4-dimethylquinazoline-2,4-diamine dihydrochloride) and ATC0175 (N-(cis-4-{[4-(dimethylamino)quinazolin-2-yl] amino}cyclohexyl)-3,4-difluoro-benzamide hydrochloride) are two of these compounds that function as MCHR1 antagonists. We now present profiles of ATC0065 and ATC0175 *in vitro* and *in vivo* in a range of rodent tests indicative of anxiolytic and antidepressant action (**Figure 36**) [19].

2.14 Platelet-derived growth factor receptor phosphorylation inhibitors

Numerous proliferative illnesses, including liver cirrhosis, pulmonary fibrosis, cancer, glomerulonephritis, glomerulosclerosis, atherosclerosis, and restenosis following PTCA, are brought on by the aberrant platelet-derived growth factor receptor (PDGFR)-induced cell proliferation. One possible treatment option for these proliferative diseases is to use PDGFR phosphorylation inhibitors [20].



Compound	Conformation	*m*	*n*	A	MCH-R1 IC_{50}[a] (nM)
AR129330	*trans*	1	1	SO_2	160
1a	*cis*	0	1	CH_2	4.9
2a	*cis*	0	0	CH_2	35

Figure 35.
A prototype molecule, 4-morpholinyl-quinazoline.

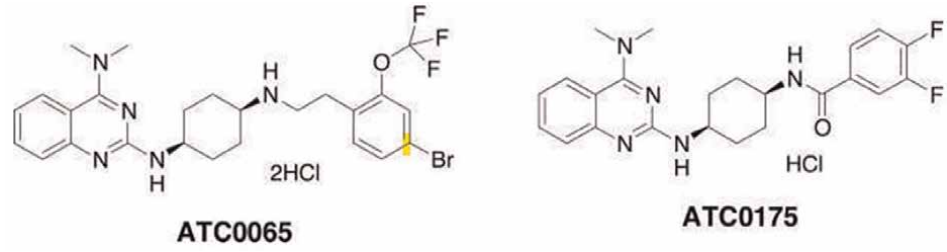


Figure 36.
As 4-amino-2-cyclohexyl aminoquinazoline and 4-dimethylamino quinazoline, exhibit strong inhibitory activity for MCHR1.

Matsuno et al. screened PDGFR phosphorylation inhibitors and discovered a number of compounds with a 4-piperazinyl substituted quinazoline core [20]. In the analysis of SAR, KN1022 was selected as the prototype inhibitor. The 4-nitrobenzene urea moiety was scrutinized, revealing that compounds with substitutions at position 4 of the benzene ring exhibited optimal performance. However, compounds with more than two substituents on the benzene ring showed diminished activity. In their study, various derivatives of KN1022 (77) with promising activity were synthesized, including 4-(4-methylphenoxy)phenyl, 4-tert-butylphenyl, and 4-phenoxyphenyl. These three compounds were orally administered to Sprague-Dawley rats at a dose of 30 mg/kg, twice daily, for *in vivo* assessments. Next, it was shown that 4-isopropoxyphenyl (80), 4-chlorophenyl (78), and 4-bromophenyl (**Figure 37**) (79) comparable had clear inhibitory action against the development of neointima in the carotid artery of the balloon catheter de-endothelialized vessel in the rats [21].

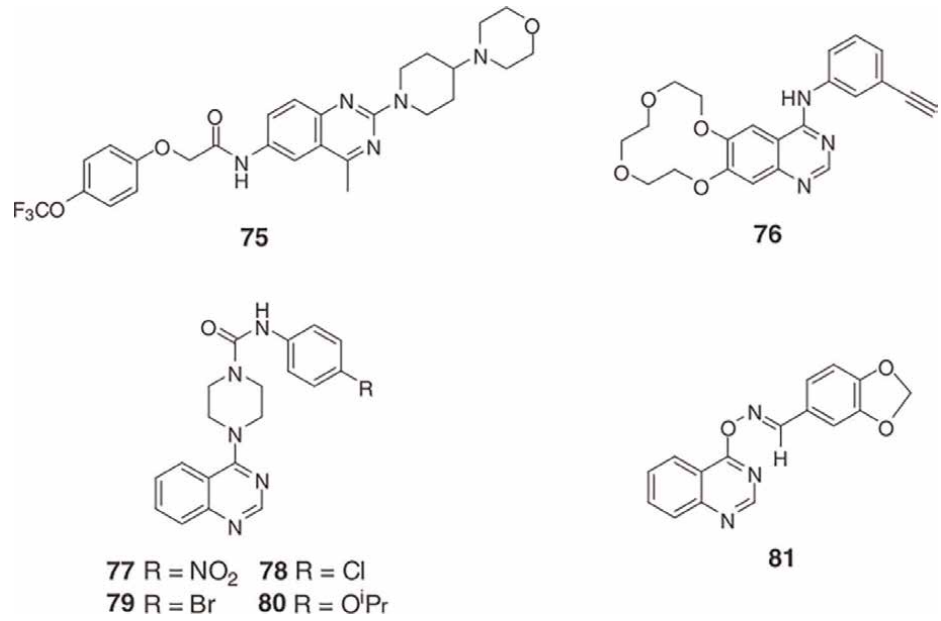


Figure 37.
Typical 4-substituted quinazoline structures with bioactivity.

2.15 Germicide

In an effort to find new acaricides, Li et al. [12] combined and assessed a number of 4-quinazoline oxime ether compounds biologically [24]. The compounds found in this study were shown to suppress the phytovirus TMV to varying degrees. Of these compounds, compound 81 (**Figure 37**) exhibited strong activity both *in vivo* and *in vitro* against TMV, with 65% and 61% of the total, correspondingly. Additionally, following virus vaccination, compound 81 demonstrated positive inhibitory activities against PVX, PVY, and CMV, according to bioassays [21].

2.16 Anti-TB activity

In the quest for new anti-TB drugs, quinazoline has already been used to create a large number of unique compounds, some of which have shown encouraging anti-TB activity. This review offers a comprehensive overview of recent progress in the development of quinazoline-based medications for the treatment of tuberculosis (TB) 4-Alkylthioquinazoline derivatives and their synthesis. Shashikant et al. [22] synthesized a series of N3[4-(4-chlorophenyl thiazole2-yl)-2-aminomethyl] quinazoline-4(3H)-one analogs in 2006, and different spectroscopic analyses, including FT-IR and 1H NMR spectra, confirmed the structure of the novel compounds. The *in vitro* anti-TB activity of the compounds was assessed on Lowenstein-Jensen egg medium (LJ Medium) using the H37RV strain. All of the synthesized compounds showed moderate to excellent anti-TB activity, with MIC ranges of 100–10 μM.

Among the compounds, 3f, 3 h, and 3j exhibited the most significant anti-TB activity at a concentration of 10 μg mL^{-1}. Compounds 3c, 3d, and 3 g demonstrated moderate activity, whereas compounds 3a, 3b, and 3e did not exhibit noticeable activity. Compound 3i, on the other hand, showed no antitubercular activity at 100 μg mL^{-1}. The potent anti-TB activity of 3f, 3 h, and 3j was attributed to the combination of quinazolinone with isoniazid, pyrazinamide, and para-aminosalicylic acid, respectively (**Figure 38**) [23].

2.17 Allosteric modulators of glutamate receptors

Lindsley and colleagues introduced a new class of substituted pyrazolo[1,5-a] quinazolin-5(4H)-ones, acting as negative allosteric modulators of metabotropic glutamate receptors 2 and 3 (mGlu2 and mGlu3, respectively). The SAR profile of these substances was relatively steep, with slight framework alterations resulting in notable efficacy losses. Introducing a 3-sulfonylphenyl or 3-pyridyl group at R2 resulted in inhibitors with low-micromolar to high nanomolar IC50 values for both mGlu2 and mGlu3, as long as R1 remained a phenyl ring and R3 remained a methyl group. Installing a phenyl or 4-methoxyphenyl at this location, on the other hand, produced compounds that had very little effect. Significantly reduced activity at both receptors was also the outcome of truncating a methyl group in this position. A number of substances were discovered to be strong inhibitors overall, such as quinazolin-5(4H)-one, 4-methyl-2-phenyl-8-(pyrimidin-5-yl)pyrazolo[1,5-a],which was found to have excellent selectivity against the other mGluRs and to have potent *in vitro* activity as dual mGlu2 /mGlu3 NAMs (**Figure 39**) [24].

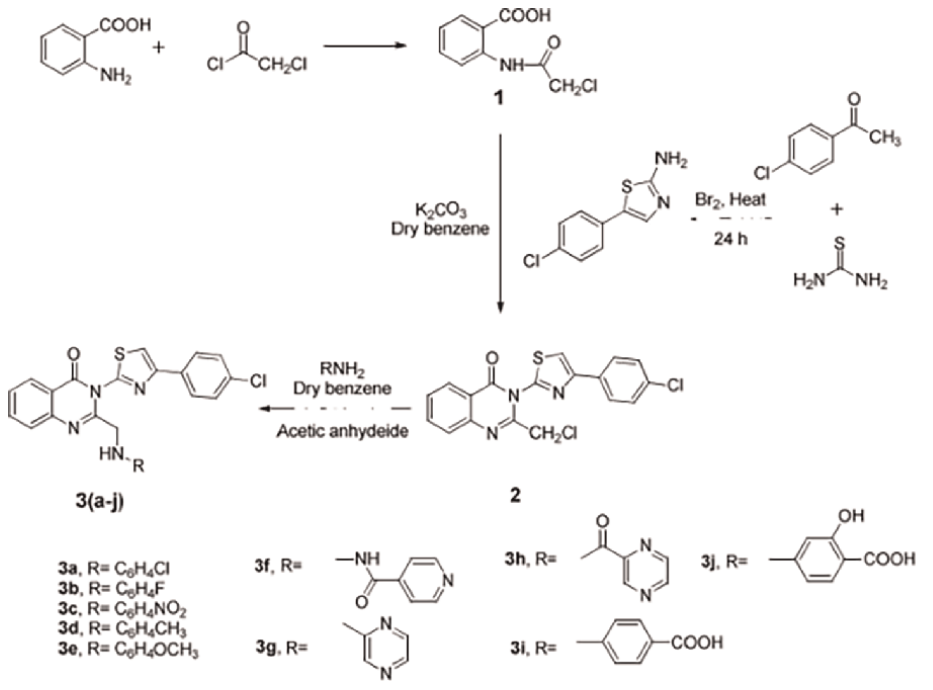


Figure 38.
AntiTB.

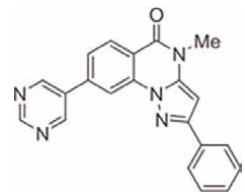


Figure 39.
Quinazolin-5(4H)-one, 4-methyl-2-phenyl-8-(pyrimidin-5-yl)pyrazolo[1,5-a].

2.18 Cathepsin inhibitors

New analogs based on quinazoline-2(1H)-ones and quinazoline-2(1H)-thiones, bischalcones, were conceptualized and synthesized by Raghav and Singh. The compounds that were produced were evaluated for their potential as novel inhibitors of cathepsin B and H. 3-Hexahydro-3phenylallylidene)-4-styrylquinazoline-2(1H)-one 283 the compound was found to exhibit the highest level of inhibition among the others, exhibiting 100% inhibition at 1.0104 M concentration and 50% inhibition at ~0.1104 M concentration. The assessment of cathepsin B activity was also conducted with regard to substituted benzylidene-3,4,5,6,7,8-hexahydro-quinazoline-2(1H) thione derivatives. That 3,4,5,6,7,8hexahydro-3-phenylallylidene)-4-styrylquinazoline-2(1H)-one 284 had the greatest inhibitory effect, showing 100% inhibition at 0.50104 M concentration and half maximum inhibition at approximately 0.01104 M concentration. Similar to this, benzylidene-3,4,5,6,7,8-hexahydro-quinazoline2(1H)-one and its derivatives at various concentrations were synthesized and used to

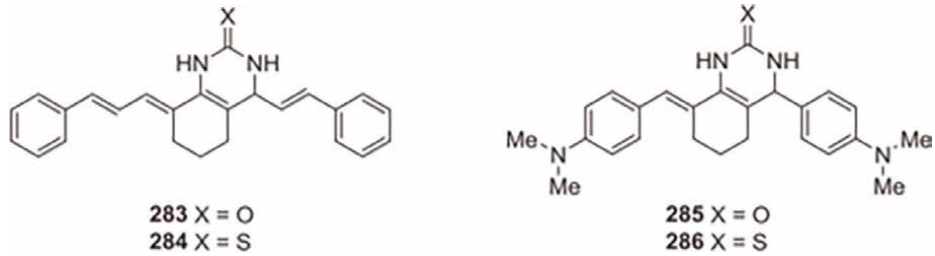


Figure 40.
New analogs based on quinazoline-2(1H)-ones and quinazoline-2(1H)-thiones, bischalcones.

calculate the activities of cathepsin H. Within quinazoline derivatives, 2,6-bis(4′ (dimethyl amino) benzylidene) cyclohexanone 285 exhibited the most potent inhibition, reaching half-maximum inhibition at approximately 0.15×10^{-4} M concentration and achieving 100% inhibition at $1.0 \times 10^{-}4$ M concentration. Benzylidene-3,4,5,6,7,8hexahydro-quinazoline-2(1H)-one derivatives were also found to exhibit 100% maximum inhibition of 2,6-bis(4′(dimethyl amino) benzylidene) cyclo hexanone 286 at ∼0.25104 M concentration (**Figure 40**) [25].

2.19 Phosphodiesterase inhibitors

A novel class of quinazoline PDE1 inhibitors that are selective and penetrate the central nervous system was revealed by Humphrey et al. [26] based on the two file screen hits' SAR development. After structurally refining the lead compounds using a combination of conventional and parallel organic synthesis, molecular modeling and X-ray crystallography, the resultant compounds were identified as PF-04471141) for aminoquinazoline 287 and PF-04822163) for indanylquinazoline 288. These compounds are among the best-defined and most potent PDE1 inhibitors discovered to date. In rodents, studies on pharmacokinetics show that all compounds reach systemic concentrations higher than their IC50 figures. Therefore, compounds 288 and 287 present a great deal of promise as chemical probes for additional research into the biological processes of the central nervous system that are affected by PDE1 function, as well as for evaluating the pan-PDE1 inhibition's potential as a therapeutic in order to address neuropsychiatric disorders. Abdel-Aziz and associates [27] created and produced a novel series of hybrids between the Schiff base and quinazolin-4(3H)-one. The *in vitro* activity of the synthesized compounds in inhibiting phosphodiesterase 4 (PDE4) was evaluated, with Rolipram employed as a positive reference for PDE4 inhibition. When compared to rolipram, a few of them displayed good-to-moderate activity. Compound 289, with an IC50 of 1.60 mM, was the most potent in this series of PDE4 inhibition. The outcome of the activity showed that the inhibitory activity requires the Schiff base part's hydroxyl-substituted phenyl to exist. The base of the Schiff 290 demonstrated a modest degree of inhibition with a 29.3 mM IC50. Trihydroxyphenyl Schiff base 289, however, demonstrated in this series' maximum PDE4B inhibitory activity. The Schiff bases with methoxyphenyl groups were the least active in this series, highlighting the importance of the free OH groups on the aryl ring of the Schiff base. Furthermore, the inhibitory action of the compounds that were created was not enhanced by the 5-methyl substitution. The compounds displaying PDE4 inhibition were subsequently evaluated for their antiproliferative potential against various human tumor cell lines. Compound 290 was found to have noteworthy

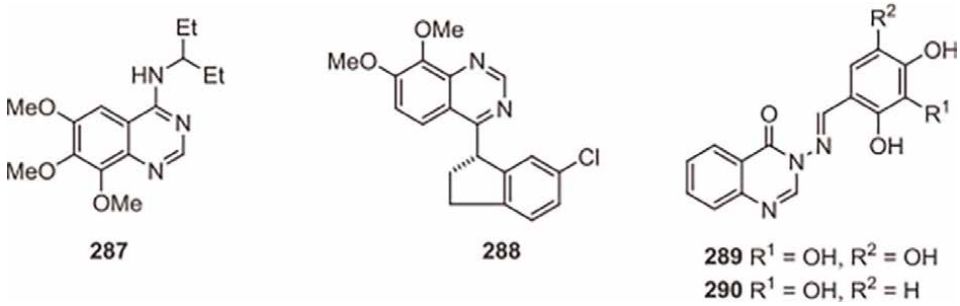


Figure 41.
A novel class of quinazoline PDE1.

antiproliferative activity in breast, lung, and colon tumor cells, with IC50 values of 140, 79, and 320 nM, respectively. Additionally, compound 289 was docked in the PDE4B active site to determine a potential binding mode, which offers information for future improvements to this unique scaffold that inhibits PDE4 (**Figure 41**).

2.20 Antihistamine agents

Alagarsamy and colleagues [28] created and combined a number of unique four (3H)-quinazolinone compounds by reacting 2-(3-(4chlorophenyl)-2-(2-(4-substituted)-2oxoethylthio)acetyl chloride of 4-oxo-3,4-dihydroquinazolin-2-ylthio) with different amines. For assessing the *in vivo* H1-antihistaminic activity on conscious guinea pigs at a dose level of 10 mg/kg, chlorpheniramine maleate served as the reference standard. It was discovered that every tested compound had strong antihistaminic properties. Every test substance in the series demonstrated substantial defense in the 65–771% range, according to percentage protection data. According to biological research, the biological activity of substituents placed over the quinazoline ring's third position varies. Significant activity was demonstrated by the existence of the group of piperazinyl (292, Log P¼ 3.43). Potency is retained as soon as the heteroatom piperazinyl's nitrogen is substituted with an oxygen compound (Log P¼ 3.27, morpholinyl substitution, 293), and after piperazinyl's nitrogen is eliminated (pyrrolidinyl substitution, 294, Log P¼ 3.99). Activity decreased when ethyl and diethyl substituents were added. The most effective of the series was, compound 3-(4-chlorophenyl) in general-2-(2-(1-methylpiperazin)292.) quinazolin-4(3H)-one-2-oxoethylthio. It is evident from **Figure 42** that lipophilicity (Log P) is a significant factor in their antihistaminic action.

2.21 Cholinesterase inhibitors

Utilizing 1-H-benzo-6-(benzyloxy)[d] [1, 3], a simple 6-substituted quinazolinone synthesis was developed. Oxazine-2,4-dione was the initial substance by Decker and associates [29]. The ability of each target compound to inhibit butyryl and acetylcholinesterase was examined. Compared to AChE, tacrine exhibited a potency of 3 times lower (IC50 ¼ 71.5 nM) for the enzyme in humans, while AChE showed an IC50 of 24.1 nM. The inhibitors of piperidinyl 311–316 exhibited inhibitory activities against the AChE derived from electric eels that were 7e 39 times higher. Additionally, docking studies were performed to look into a potential binding mode for AChE (**Figure 43**).

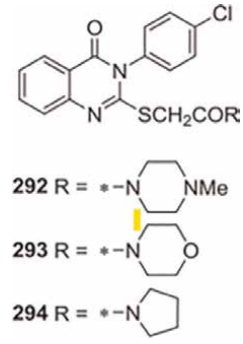


Figure 42.
Unique Four(3H)-quinazolinone with antihistamine activity.

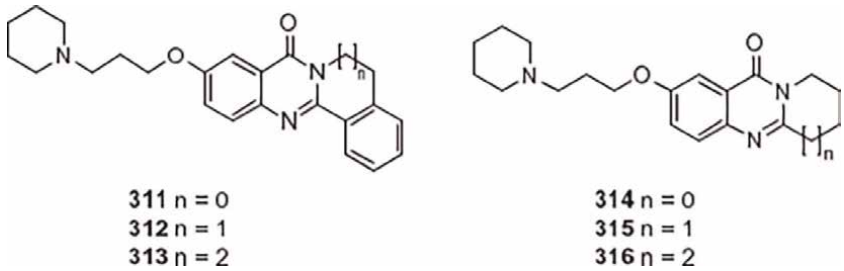


Figure 43.
Cholinesterase inhibitors.

2.22 Inhibitors of chitin synthase

Ji et al. [30] created, produced, and described a number of unique derivatives of quinazoline-2,4-dione that are 1-methyl-3-substituted. One-step ELISA analysis of chitin generated from UDP utilized wheat germ agglutinin (WGA) labeled with horseradish peroxidase (HRP) as the probe. -Glc-NAc was used to measure the prepared compounds' inhibitory activity against CHS. The assay's positive control in this case was polyoxin B. Each compound's half-inhibition concentration (IC50) was found. Out of all the substances that were assessed, a few analogs showed strong inhibitory effects in comparison to polyoxin B, and their IC50 values were lower against CHS, which was 0.18 millimoles. Compound 322 is the most potent inhibitor among these, with an IC50 value of 0.08 mmol/L. 323–325's inhibitory actions were similar to those of polyoxin B. Other substances exhibited modest to negligible inhibition. Using aryl R2 as a substituent in these active compounds resulted in greater inhibitory activities against CHS compared to using alkyl R2. To increase inhibitory activities in aryl R2, a substituent that donates electrons on the aromatic ring is preferable over an electron-withdrawing substituent (**Figure 44**).

2.23 Anti-asthmatic properties

Using a murine model of asthma, Rayees et al. synthesized several derivatives of azepino [2,1-b] quinazoline [31] and assessed their ability to prevent asthma. In animals with asthma, the compounds 345–349 significantly reduced the secretion of Th2 cytokines and eosinophilia. However, in the case of the animals treated with 349,

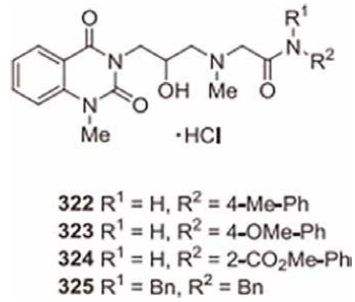


Figure 44.
Chitin synthase inhibitors.

the decline was quite noteworthy. Compound 349 was the subject of molecular modeling studies involving the transcription factors GATA3 and STAT6, which are primarily responsible for Th2 cell differentiation. Additionally, after oral and intravenous administrations, the pharmacokinetics of 349 were studied in mice (**Figure 45**).

2.24 Bronchodilator activity

Taking vasicinone and theophylline as prescribed, many quinazoline and quinazolinone derivatives were reported by Špulak et al., who also tested them for their ability to act as *in vitro* bronchodilators on isolated rat trachea [32]. Remarkably, nearly every derivative had a greater biological impact than theophylline. Compared to their alkoxy and alkylamino analogs, the 4alkylsulfanyl derivatives were more potent and showed the most noticeable effect. With an ED50 in the micromolar range, among the synthesized derivatives, compound 244, which contains the 1-piperidylpropyl fragment, exhibited the highest level of activity. When considered collectively, these results make the compounds intriguing targets for additional methodical research and development (**Figure 46**).

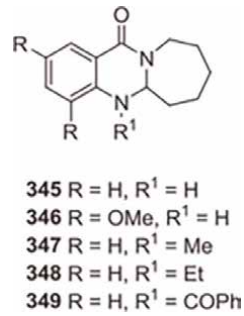


Figure 45.
Anti-asthmatic activity.

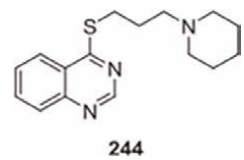


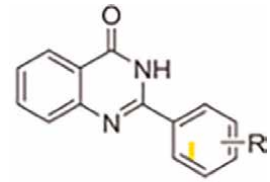
Figure 46.
Bronchodilator activity.

2.25 Glucuronidase inhibitors

Using $CuCl_2.2H_2O$ as a catalyst, Khan and colleagues created a fresh run of analogs of 2-arylquinazolin-4(3H)-one derived from anthranilamide and various benzaldehydes. The b-glucuronidase inhibitory potential of the synthesized 2-arylquinazolin-4 (3H)-ones were assessed utilizing 1,4-lactone of D-saccharic acid (IC50 ¼ 45.75 ± 2.16 mM). Considering the activity results that were obtained, the link between structure and activity for these compounds was looked into, suggesting that the phenyl ring substitutions, located at C-2 of the quinazolin4(3H)-one skeleton, are the primary source of the compounds in this class's ability to inhibit b-glucuronidase [33] Compound 257 (IC50 ¼ 0.6 ± 0.45 mM) demonstrated the highest b-glucuronidase inhibition among all the structures evaluated; 76 times higher than the standard D-saccharic acid 1,4-lactone. It was shown that the two methoxy groups at positions C-30 and C-40 were in the best configuration to interact with the enzyme. The activity was reduced to nearly half when a hydrogen atom was substituted for one methoxy group at C-30, compound 258 (IC50 ¼ 1.1 ± 0.05 mM) as an example. The level of activity dropped five times when the hydroxyl group at C-30 was replaced with a methoxy group, compound 259 (IC50 ¼ 2.8 ± 0.05 mM) as an example. Compound 261 exhibited 65-fold greater potent activity than the reference (IC50 ¼ 0.7 ± 0.01 mM). Substituting hydroxyl groups for both methoxy groups in compound 257 caused the activity to decrease by two times; exchanging ethoxy groups for hydroxyl groups reduced the activity by a factor of 14. In total, an IC50 trend of inhibition for the enzyme within the range of 0.6–198.2 mM was noted and contrasted with the reference (**Figure 47**).

2.26 Kinase inhibitors

Additives 271 and 272, which have an alternative oxazole scaffold showed stronger inhibitory effects on EGFR at the 7-positions (IC50D 1.21 and 0.95 mmol/L) in comparison to compounds 273 and 274, which only include amino or nitro groups where they are found. Hou et al. created and produced a novel category of quinazoline compounds, through the fusion of oxazole and quinazoline fundamental structures into a single heteroaromatic unit. The EGFR inhibitory potency and anti-proliferative properties of the synthesized structures were examined [34]. Their actions followed the same trends and had a positive correlation with antiproliferative actions. In order to find new EGFR inhibitors, it is feasible and required to continue investigating the bioactivity and alteration of quinazoline analogs substituted through an oxazole



257 R = 3,4-diOMe
258 R = 4-OMe
259 R = 3-OH-4-OMe
260 R = 3,4-diOH
261 R = 2-OEt

Figure 47.
Glucuronidase inhibitors.

scaffold, even though the outcomes did not possess a structure reminiscent of the positive control Erlotinib (EGFR IC50 ¼ 0.03 mmol/L). A new class of quinazolines (2-chloro-4-anilino) was designed and synthesized by de Castro Barbosa and colleagues [35] as dual inhibitors of EGFR and VEGFR-2, and their inhibitory effects were assessed. The acquired biological data indicated that derivatives of 2-chloro-4-anilino-quinazoline have the potential to act as dual inhibitors of VEGFR-2 and EGFR. The IC50 values for the derivatives featuring a hydrogen bond donor at the para position of the aniline moiety were lower. Compound 275 was identified as the most active, with an IC50 of 0.90 mM for EGFR and 1.17 mM for VEGFR-2. Compared to the prototype 276, this compound was about 7 times more potent on VEGFR-2 and about 11 times more powerful on EGFR. Pharmacophoric groups for both kinases were identified through SAR and docking studies, revealing the critical importance of a hydrogen bond donor for interaction with conserved Glu and Asp amino acids in EGFR and VEGFR-2 binding sites, particularly at the para position of the aniline moiety. A new series of unique 4-anilinoquinazoline derivatives was designed and synthesized by Waiker and colleagues [36] who then assessed them as possible inhibitors of protein kinases linked to Alzheimer's disease. Five distinct kinases were tested for potential inhibitory effects of the 6,7-dimethoxy-N-phenylquinazolin-4amines produced artificially: CK1d/ε (casein kinase 1), GSK-3a/b (Glycogen Synthase Kinase 3a/b), DYRK1A (dual-specificity, tyrosine phosphorylation regulated kinase), CDK5/p25 (CDK5/p25), and CLK1 (cdc2-like kinase 1). At the highest concentration tested (10 mM), none of the synthesized anilino quinazolines showed inhibitory activity against CDK5/p25, DYRK1A, or CK1d/ε, based on the results of kinase inhibitory assays. Given that four compounds (277–280) exhibited inhibitory activity on CLK1, it appeared that the 4anilinoquinazolines were the most effective against the enzyme. At concentrations below 10 mM, two of the ten anilinoquinazolines that were produced—279 and 280—exhibited notable strength of the inhibitor against CLK1. Remarkably, compound 279, which features a 3,4-

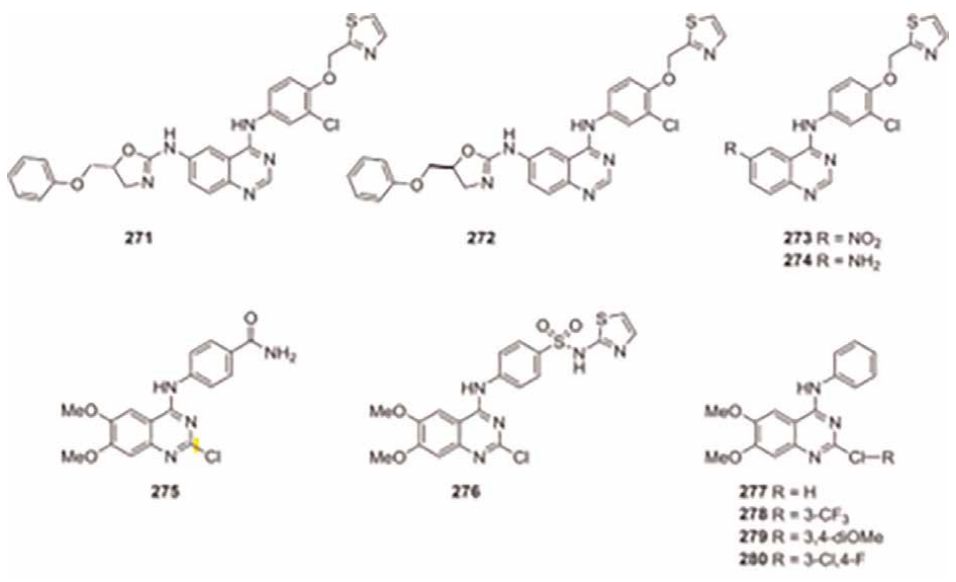


Figure 48.
Kinase inhibitors.

dimethoxy substitution on the aryl ring of the aniline moiety, inhibits the enzymes CLK1 (IC50 = 1.5 mM) and GSK-3a/b (IC50 = 3 mM) at concentrations less than 5 mM. Interestingly, compound 280 exhibited no inhibition on GSK-3a/b and a 5-fold reduction in inhibition on CLK1 (IC50 = 7.6 mM) due to the presence of 3-fluoro and 4-chloro substitution in the aryl ring. Docking studies were conducted to elucidate how the compounds bind to the active sites of GSK-3β and CLK1. According to the study's findings, compound 279 might be a useful model for the creation of dual inhibitors of the GSK-3a/b and CLK1 enzymes that could be used as a treatment for Alzheimer's disease (**Figure 48**).

3. Conclusion

In conclusion, the quinazolines are heterocyclic stable nucleus that is susceptible to different chemical reactions to give biologically active compounds which treat a different life-threatening diseases such as cancer, bacterial, fungal, viral, infections, hypertension, and other pandemic disease such as malaria. In addition, these compounds represent a goal for hybridization approach for drug design as they are biologically active pharmacophores. They give a variety of hydride compounds with other bioactive nuclei that could be heterocyclic, alicyclic, benzylic, and allylic potentiate its activity and altered pharmacokinetics and pharmacodynamics of the combined drugs and increase the biological targets react with, results in a variety of chemical bioactive compounds for different diseases such as antidiabetic, anticholinesrase, dihydrofolate reductase inhibition, and cellular phosphorylation inhibition.

Author details

Ali Gamal Al-Kaf[1,2*] and Rana Abdullah Al-Robaidi[1]

1 Faculty of Pharmacy, Medicinal Chemistry Department, Sana'a University, Yemen

2 Faculty of Medical Sciences, Department of Pharmacy, National University, Yemen

*Address all correspondence to: alialkaf21@gmail.com; alialkaf@national-univ.net

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Edited by Ali Gamal Al-Kaf

This book investigates and identifies novel therapeutic compounds for the treatment of a range of illnesses. Heterocyclic compounds are a significant class of substances with biological activity. Among them, quinazoline has attracted a lot of interest because of its important biological properties. Numerous compounds with quinazoline moiety have been shown to exhibit a wide range of therapeutic properties, including antioxidant, antifungal, antiviral, antidiabetic, anticancer, anti-inflammatory, and antibacterial activities. This book presents a comprehensive overview of quinazoline and its derivatives. The chapters address recent advances in the synthesis of several different heterocyclic compounds, the use of computational studies for finding new active quinazoline derivatives, the biological activities of quinazoline, and much more.

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