Chapter

Quinazolinone and Quinazoline Derivatives: Synthesis and Biological Application

Satyendra Mishra

Abstract

Drug discovery and optimization comprise one of the most significant targets in medicinal chemistry. Quinazoline and quinazolinone derivatives and nitrogen-containing heterocycles have received significant attention due to their widely and distinct biopharmaceutical activities. Quinazolines and quinazolinones are considered as noteworthy chemical for the synthesis of diverse physiological significance and pharmacological utilized molecules. Quinazolines are building blocks for about 150 naturally occurring alkaloids with a broad range of biological activity. The various substituted quinazolines and quinazolinones displayed important, for example, sedative hypnotics, antibacterial, anti-inflammatory, analgesic, antipsychotic, antifungal, antimalarial, anticonvulsant, anti-Parkinsonism, cancer, and other activities. This chapter aims to highlight the latest evidence of quinazolinone and quinazoline derivatives as a privileged scaffold in medicinal chemistry.

Keywords: quinazoline, quinazolinones, antioxidant and anticancer, antibacterial, structure-activity relationship

1. Introduction

Emergence of drug resistance has created a critical and unmet medical requirement for the innovation and development of novel classes of antibacterial agents [1–4]. Due to the appearance of drug resistance bacterial strains, there is an escalating need for the development of novel antibiotics to treat the resistant bacteria stain. Diverse set of biological activities of quinazolinones (fused heterocyclic system) such as anti-inflammatory, anticonvulsant, anticancer, antibacterial, antifungal, anti-HIV and anti-analgesic [5–16], have encouraged to abundant of medicinal chemists to investigate this fused heterocycles as a novel drug molecules. Several research groups have successfully investigated and reported the promising antimicrobial properties and structure-activity relationships (SAR) of various quinazolinone derivatives.

Quinazolines and quinazolinones emerged as a privileged class of nitrogen containing heterocyclic scaffolds; exhibits a broad spectrum of pharmacological activities, viz. anti-inflammatory, antitubercular, and antiviral activities [17]. Number of quinazoline derived compound have been approved as a drug; for example prazosin and doxazosine are used to treat benign prostatic hyperplasia and post-traumatic stress disorder [18], and erlotinib and gefitinib both are used for the curing of lung and pancreatic cancers (**Figure 1**) [19].

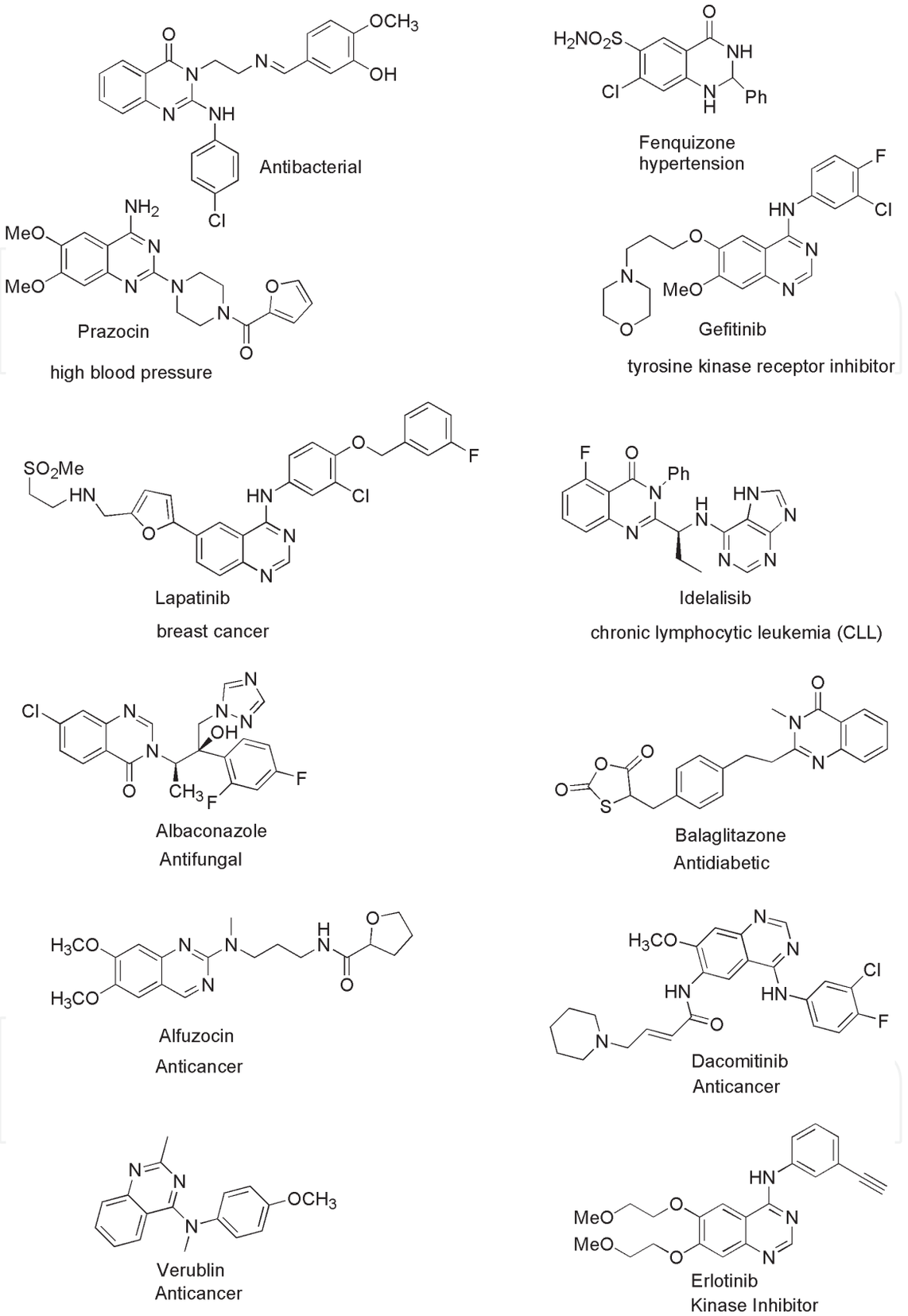


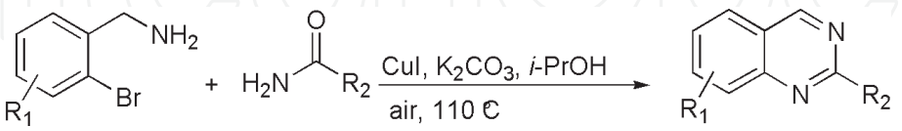
Figure 1.
Quinazoline and quinazolinone-based drugs.

Several quinazolinone-based drugs including idelalisib and fenquizone have been shown to exhibit a broad spectrum of antimicrobial, antitumor, antifungal, and cytotoxic activities [20]. Lapatinib has been displayed to be effective in combination therapy for breast cancer [21]. In the recent years, various synthetic strategies for the synthesis of quinazolines and quinazolinones derivatives have

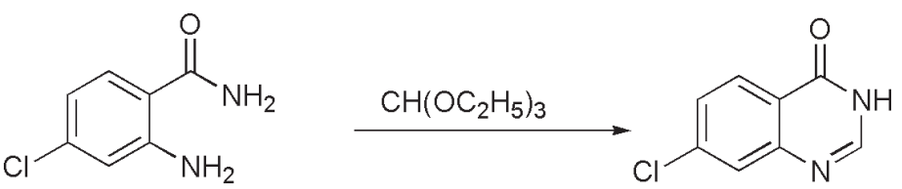
been developed to accomplish the budding requirements of medicinal chemist [22]. Many research groups have successfully utilized copper catalyzed Ullmann-type coupling procedures of aryl bromides and benzamidines for the synthesis of quinazoline derivatives [23].

2. Synthesis of quinazoline and quinazolinone derivatives

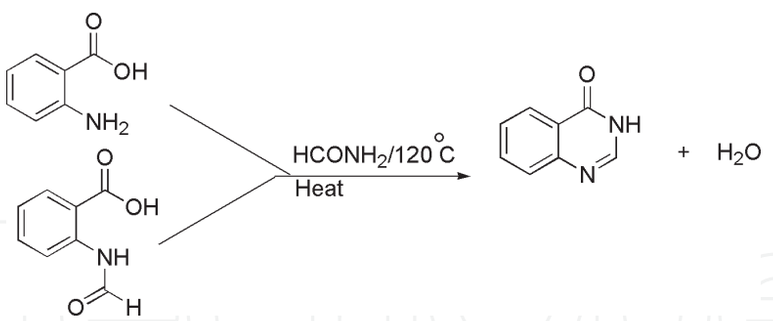
1. Synthesis of 4(3H)-quinazolinone using anthranilic acid or formyl anthranilamide [24].



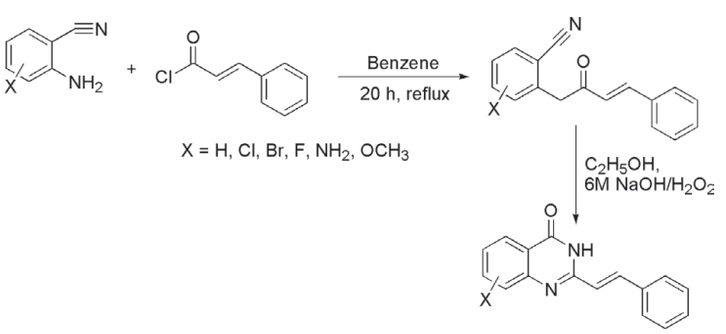
2. Via condensation reaction of 4-chloroanthranilic acid amide with triethyl orthoformate, the 7-chloro-substituted derivative has been prepared [25].



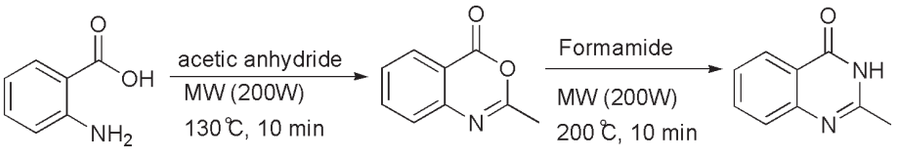
3. Quinazolin-4(3H)-one was synthesized by the reaction of anthranilic acid with excess formamide at 120°C in an open air. This is also known as Niementowski reaction [26].



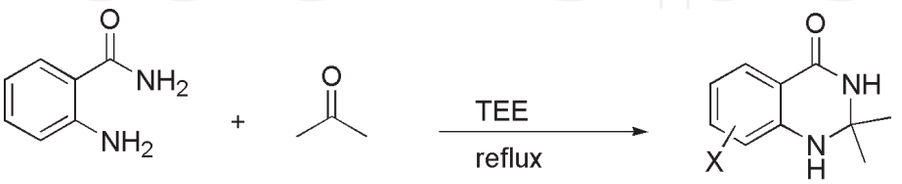
4. 2-styryl-4(3H)-quinazolinone derivatives were prepared using starting substrate 2-aminobenzonitrile with 3-phenyl cinnamoyl chloride. Under alkaline conditions, intramolecular cyclization of cinnamamide derivative was carried out to afford 2-styryl-4(3H)-quinazolinone. This procedure was tolerated to a wide range of different substituted benzene rings [27].



5. Reaction of anthranilic acid with ammonium acetate, followed by formamide under microwave at 200 W yields the desired 2-substituted-4(3H)-quinazolinones products [28].

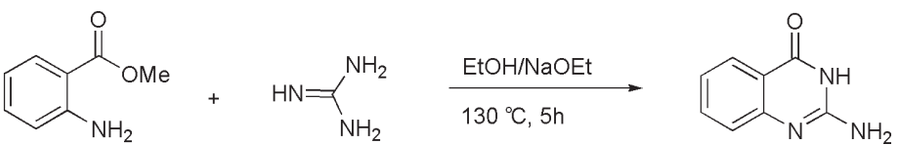


6. Reaction of anthranilamide with substituted aldehydes or ketones in 2,2,2-trifluoroethanol under reflux condition led to the formation of 2-substituted-2,3-dihydro-4(1H)-quinazolinones in excellent yields [27].

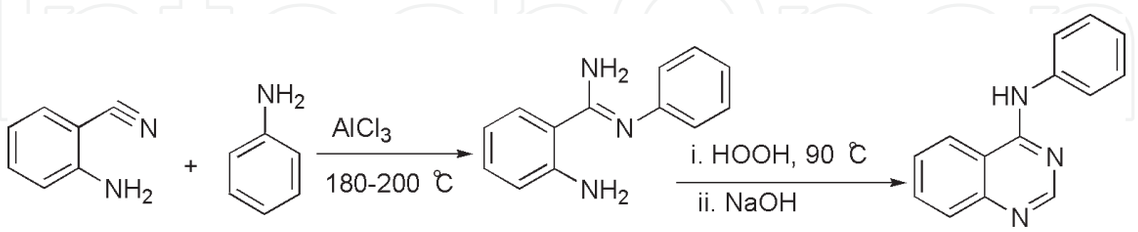


2,2,2-Trifluoroethanol = TEE

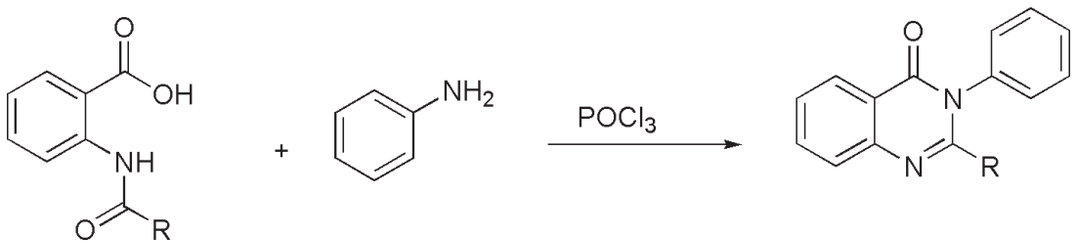
7. The amino-quinazolin-4(3H)-one was synthesized by means of the reaction of the corresponding methyl anthranilate with an excess amount of guanidine in ethyl alcohol containing sodium ethoxide in moderate yield [29].



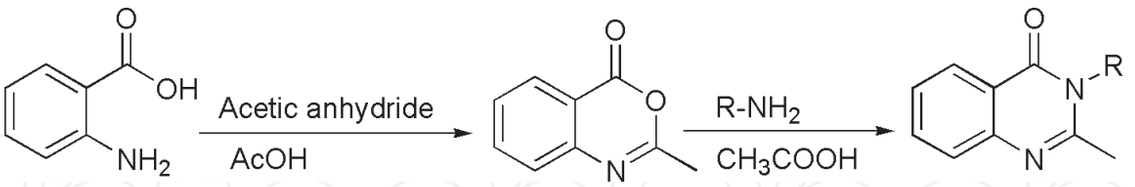
8. 4-Arylaminoquinazolines has vast biological potential as anticancer agents, thus there has been great interest in their syntheses. Through the reaction of 2-aminobenzonitrile with different substituted anilines and anhydrous aluminum chloride, amidines were readily produced. Highest yield of the amidine intermediates was obtained, when excess amounts of suitable aniline and aluminum chloride were used [30].



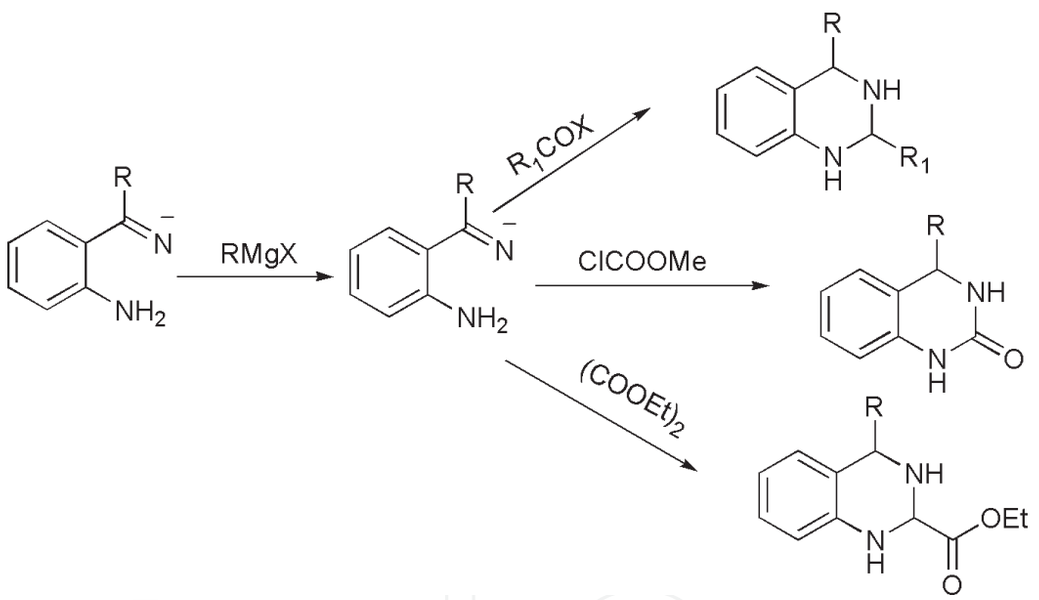
9. 2,3-disubstituted-4(3H)-quinazolinone derivatives were prepared through the treatment of N-acylanthranilic acid with the appropriate aryl amines in the presence of phosphorous oxychloride [31].



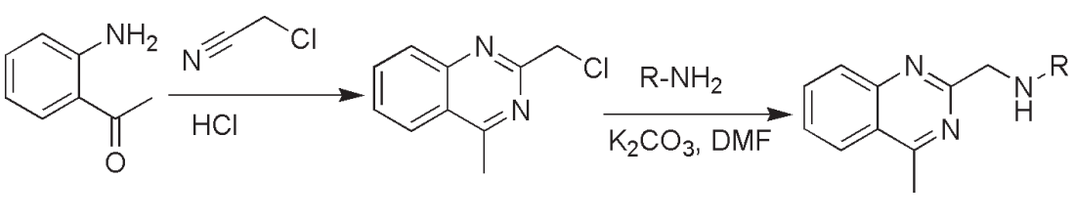
10. Benzoxazinone derivatives are the most widespread intermediates in the formation of 2,3-disubstituted quinazolinone derivatives. 2-methyl-4H-benzo[d][1,3]oxazin-4-one was prepared by refluxing mixture of anthranilic acid with acetic anhydride in acetic acid [32].



11. The reaction of 2-aminobenzonitrile with Grignard reagents yields the intermediates. The produced intermediate derivatives were very significant for getting many types of quinazoline derivatives. Upon their cyclization with acid chlorides, anhydrides, and formates, they formed the corresponding quinazoline derivatives in moderate to good yields. This general method for the preparation of various 2,4-disubstituted quinazoline derivatives is highly flexible and useful [33].



12. As shown in the scheme 2-chloromethyl-4-methyl-quinazoline derivatives were synthesized by the reaction 1-(2-amino-phenyl)-ethanone with HCl gas in anhydrous condition in presence of chloro acetonitrile to get 2-chloromethyl-4-methyl-quinazoline. Subsequently treatment of 2-chloromethyl-4-methyl-quinazoline with different amine derivative in presence of base furnished 2-chloromethyl-4-methyl-quinazoline derivatives [34].



3. Biological activities of quinazolinone and quinazoline derivatives

Subsequently the innovation of quinazoline ring numeral of structural modifications have been made in order to raise the biological activities such as antitubercular,

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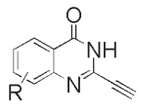
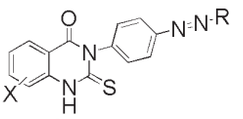
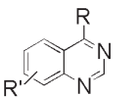
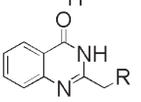
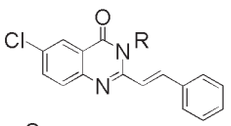
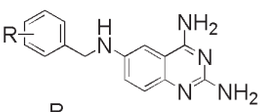
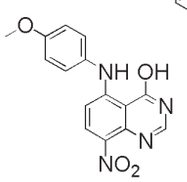
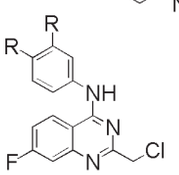
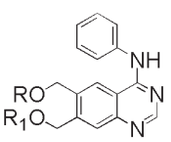
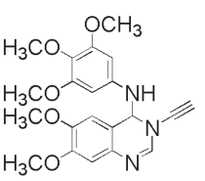
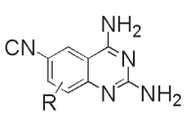
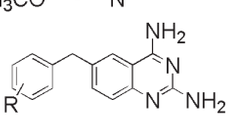
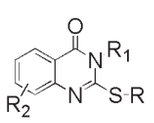
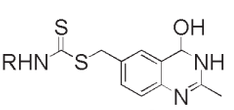
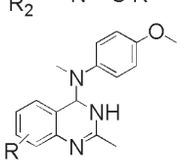
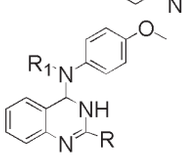
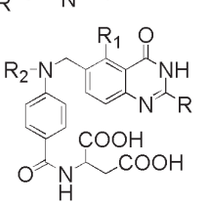
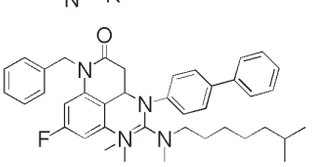
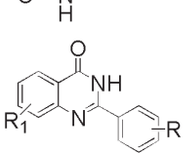
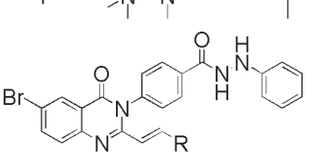
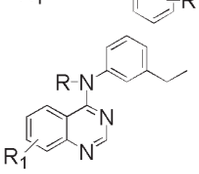
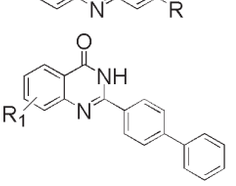
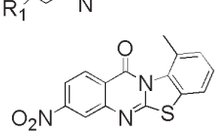
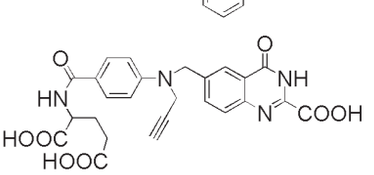
	[35]		[47]
	[36]		[48]
	37]		[49]
	[38]		[50]
	[39]		[51]
	40]		[52]
	[41]		[53]
	[42]		[54]
	[43]		[55]
	[44]		[56]
	[45]		[57]
	[46]		[58]

Figure 2.
Anticancer activities of quinazolinone and quinazoline derivatives.

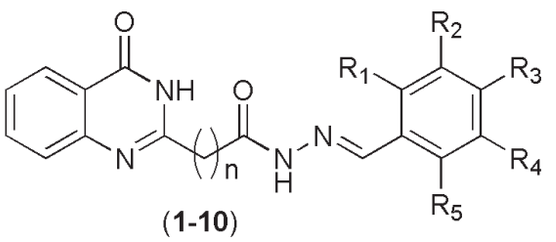
antihistaminic, analgesic, anticonvulsant, antibacterial, antifungal, and anti-inflammatory activity which attracted the interest of medicinal chemists.

Cancerous augmentation is the main reasons of global human mortality. Numerous antineoplastic drugs are in the market and the majority of the compounds are under

clinical trials. Studies make known that these antineoplastic drugs have exhibited the diverse kinds of side effects, as a result researchers around the world are engaged in the designing of more proficient and novel antineoplastic drugs. Recently, quinazoline and its derivatives have been considered as a novel class of neoplastic chemotherapeutic agents to facilitate activity against diverse tumors. Quinazoline is one of the most attractive novel bioactive compounds between all the heterocyclic compounds.

Quinazolinone derivatives, the privileged structures in the field of medicinal chemistry not only act as good anticancer agents but also act as good DNA intercalates [1, 2]. A systematic report is depicted herein for quinazoline ring. A number of quinazolinone and quinazoline derivatives (compounds **1**–**24**) have been reported for their various anticancer activities (**Figure 2**) [35–56].

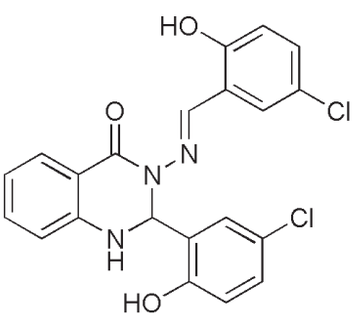
A series of quinazolinone derived Schiff base derivatives were synthesized and evaluated for their in vitro H+/K+-ATPase inhibition. Many quinazolinone derived Schiff base exhibited outstanding potency, compared to the reference drug omeprazole. Especially, hydroxy and methoxy derivatives were the most potent compounds, contributing positively to gastric H+/K+-ATPase inhibition. Preliminary structure-activity relationship revealed that the compounds **25**–**30** with electron donating moiety (OH, OCH_3) were found to be excellent activity and compounds **31**–**34** with electron withdrawing moiety (Cl and NO_2) were found to be least antiulcer agents [57].



(**1-10**)

n = 2	n= 3	R_1	R_2	R_3	R_4	R_5
25	26	H	H	OH	H	H
27	28	H	H	OCH3	H	H
29	30	H	OCH3	OH	H	H
31	32	H	H	Cl	H	H
33	34	H	H	NO2	H	H

Quinazolinone derived Schiff base derivatives were also used as novel antioxidants and anti-inflammatory agents. The in vitro antioxidant activities of these compounds were evaluated and compared with commercial antioxidants viz. ascorbic acid (AA), gallic acid (GA), butylated hydroxytoluene (BHT), (DPPH) assay, etc. Data illustrates that quinazolinone derived Schiff base with electron donating moiety (OH, OCH_3) were found to be excellent antioxidants and compounds with electron withdrawing moiety (Cl, NO_2) were found to be excellent anti-inflammatory agents [58].



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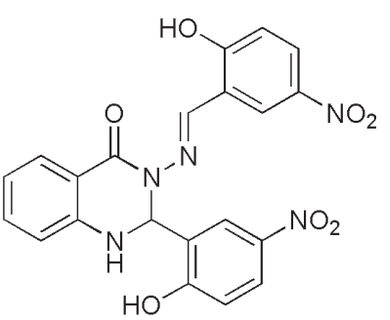

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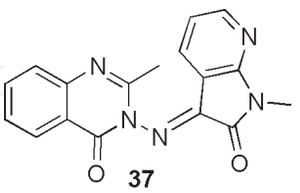
Plausible pathways induced by inhibitors were assessed by evaluating the cytotoxic effect of inhibitors such as 3-(5-chloro-2-hydroxybenzylideneamino)-2-(5-chloro-2-hydroxyphenyl)-2,3-dihydroquinazolin-41(H)-one (**35**) and 3-(5-nitro-2-hydroxybenzylideneamino)-2-(5-nitro-2-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**36**) on MCF-7, MDA-MB-231, MCF-10A and WRL-68 cells. MTT assay results of both the compounds showed significant inhibition of MCF-7 cell viability [59].



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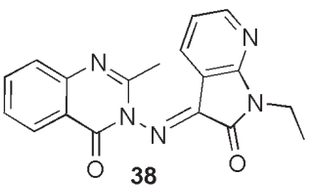

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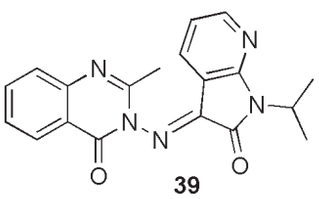

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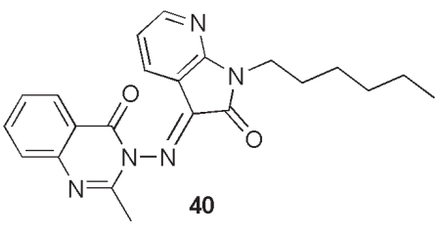
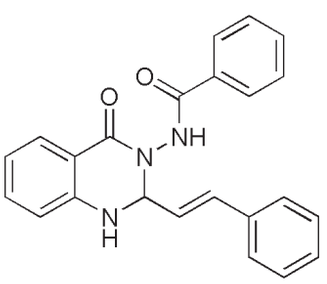


40

Azaisatins derivative containing 4(3H) quinazolinones has been designed and synthesized and were screened for their potential antimicrobial activities, which exhibited some authentic results towards testing organism *in vitro* and *in vivo* studies. Azaisatins derivatives with $-C_6H_{13}$ (**40**) display good antimicrobial activity compare to other synthesized Azaisatins [60].



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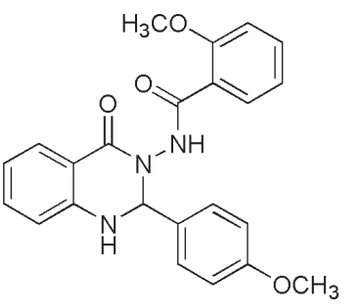

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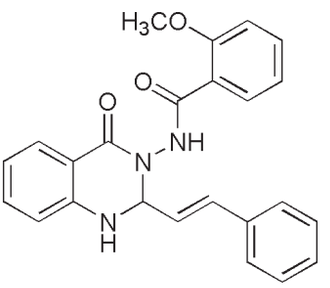
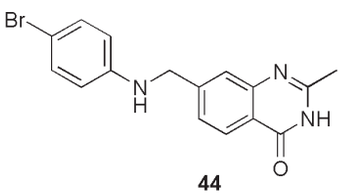


43

Quinazolinone derivatives containing 3-acrylamino motifs were screened for antifungal activities against four phytopathogenic fungi by minimum inhibitory concentration (MIC) method. Compounds **41**–**43**, exhibited broad antifungal activities and substituent's play important role in activities [61].



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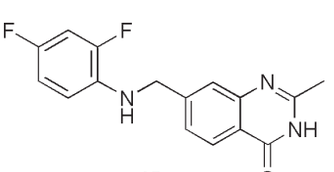

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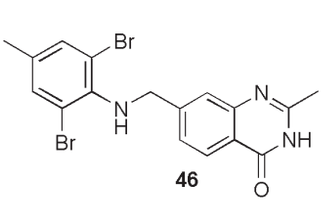

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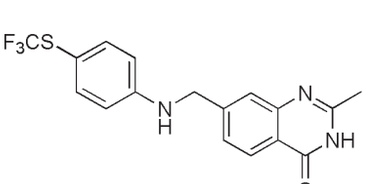

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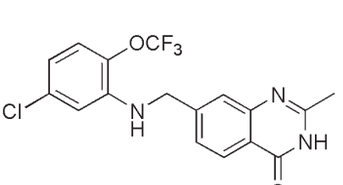

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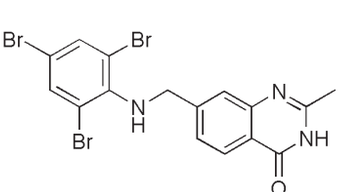
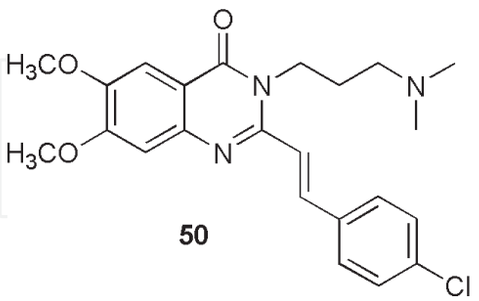


49

A series of novel quinazolinone derivatives containing an amino substituted amino moiety were reported for their cytotoxic and antibacterial activities. Among the synthesized compounds **47**–**49** showed broad-spectrum cytotoxic activities giants at least four cancer cell lines at low concentrations. Compounds **44**–**46** exhibited good to moderate antibacterial activities against gram positive and gram negative bacterial strains [62].



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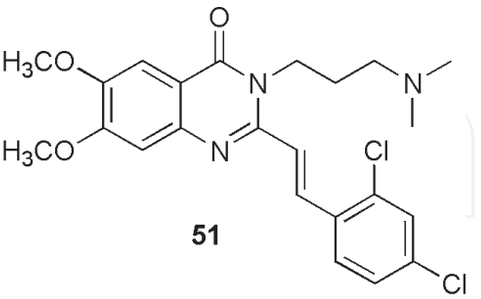
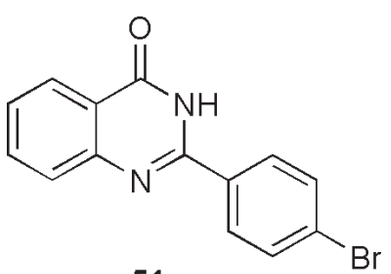


51

Quinazolinone derivatives manipulate mutant p53 proteins and their corresponding cellular response in p53 mutant cancer cells. Compounds **50** and **51** exhibited promising broad-spectrum anti-cancer effects, while **50** demonstrated selective and exclusive inhibition activity in p53 mutant cancer cell lines. Quinazolinone derivatives **50** dictate mutant p53 function for apoptotic cell death [63].



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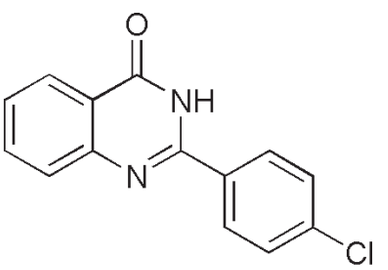
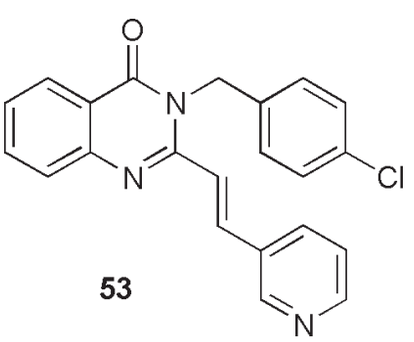


52

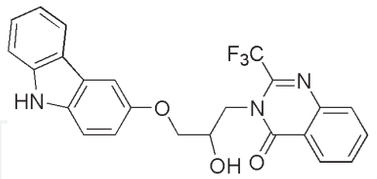
2-(4-bromophenyl)-quinazolin-4(3H)-one (**52A**) and 2-(4-chlorophenyl)-quinazolin-4(3H)-one (**52B**) exhibited α-glucosidase inhibitory activity with IC50 values of 12.5 ± 0.1 lM and 15.6 ± 0.2 lM, respectively. Spectroscopy methods were performed to analyze the inhibitory mechanisms of both compounds on α-glucosidase. The outcome of inhibitory mechanism disclosed, that the compounds, inhibited α-glucosidase in reversible and non-competitive manner. Briefly, the quinazolinone derivatives could be potentially promising candidates in the field of anti-diabetic agents development [64].



53

RAD51 is an essential component of the homologous recombination DNA repair pathway and is over expressed in drug-resistant cancers, including aggressive triple negative breast cancer (TNBC). Structure activity relationships study of

quinazolinone derivatives showed that inhibitor (**53**) as a novel RAD51 inhibitor exhibited up to 15-fold enhanced inhibition of cell growth. Furthermore, inhibitors 17 notably hamper TNBC cell sensitivity to DNA damage. This would be potentially targeted therapy for cancer treatment [65].



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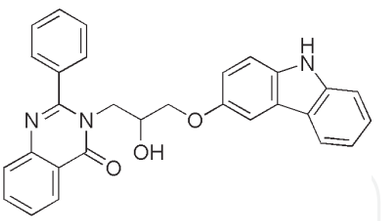

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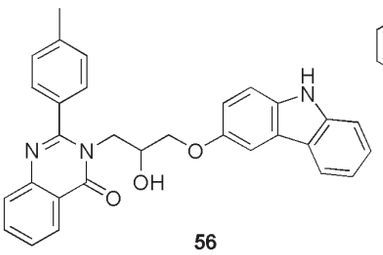
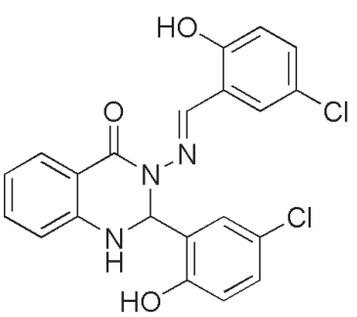


56

A series of novel carbazolyloxy phenylquinazoline derivatives have been developed as angiotensin converting enzyme (ACE) inhibitors. Amongst them compounds (**54–56**) showed maximum inhibitory potency in enzyme based assays. The most potent (**54–56**) compounds have common active site with the Lisinopril binding site [66].



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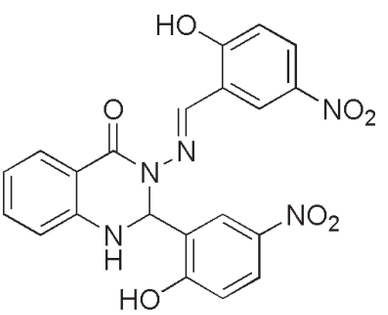
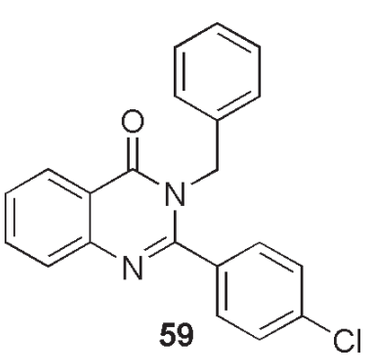


58

Compounds, 3-(5-chloro-2-hydroxybenzylideneamino)-2-(5-chloro-2-hydroxyphenyl)-2,3-dihydroquinazolin-41(H)-one (**57**) and 3-(5-nitro-2 -hydroxybenzylideneamino)-2-(5-nitro-2-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**58**) were screened for their cytotoxic effect on MCF-7, MDA-MB-231, MCF-10A and WRL-68 cells. The mechanism involved in apoptosis, induced by compound **57** and **58** was also evaluated. Additionally, caspase-8 illustrates significant potency, followed by inhibition of NF-κB activation in **57**- and **58**-treated MCF-7 cells. The results indicated that A and B could induce apoptosis via a mechanism that involves either extrinsic or intrinsic pathways [59].



59

Substituted quinazolinones derivatives were tested for their antimicrobial activity against Gram-negative bacteria and Gram-positive bacteria. Among the prepared products, 3-benzyl-2-(4-chlorophenyl) quinazolin-4(3H)-one (**3a**) was found to exhibits the most potent *in vitro* anti-microbial activity against *Staphylococcus aureus*.

4. Conclusions

Over the past few decades, more effort has been established into searching of better drugs with minimal side effects. Herein number versatile synthetic procedures are discussed for the synthesis of quinazolinone and quinazoline derivatives. In general, quinazolinone and quinazoline derivatives are known to possess wide range of activities. A specific activity depends on the substituent present at an appropriate position of quinazoline. The study of natural and synthetic quinazolinone and quinazoline derivatives identified as potentially promising candidates for developing as novel therapeutic agents. There is possibility for further development as new research into study of medicinal chemistry related field.

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Conflict of interest

The author declares no conflict of interest.

Author details

Satyendra Mishra
Department of Physical Sciences, Institute of Advanced Research, Gandhinagar, Gujarat, India

*Address all correspondence to: satyendramishra1@gmail.com

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