Chapter

Biological Activity of Quinazolinones

Awwad A. Radwan and Fars K. Alanazi

Abstract

The chemical structure of quinazolinones includes benzene ring fused with 2-pyrimidinone (1), 4-pyrimidinone (2) or 2,4-pyrimidinedione (3) ring, and are named as quinazolin-2(1H)-one, quinazolin-4(3H)-one or quinazolin-2,4(1H, 3H)-one, respectively. The chemical structure of quinazolinones constitutes a crucial scaffold of natural and synthetic compounds with various therapeutic and biological activities. Quinazolinones are first synthesized by Stefan Niementowski (1866–1925) and named after Niementowski quinazolinone synthesis. Quinazolinones have strongly attracted the interest of medicinal chemist as they constitute a large class of compounds that exhibited broad spectrum of biological activities including antimicrobial, antimalarial, anticonvulsant, anticancer, anti-leishmanial, anti-inflammatory, etc. This chapter provides a brief overview on the recent advances on chemical and pharmacological aspects of quinazolinone derivatives published in the last decade.

Keywords: quinazolinones, antimicrobial, antimalarial, anticancer

1. Introduction

Heterocyclic compounds are organic cyclic compounds having at least one atom other than carbon in their ring structures. Quinazolinones are formed by fusion of benzene ring with 2-pyrimidinone (1), 4-pyrimidinone (2) or 2,4-pyrimidinedione (3) ring, and are named as quinazolin-2(*1H*)-one, quinazolin-4(*3H*)-one or quinazolin-2,4(*1H, 3H*)-one, respectively (**Figure 1**).

Quinazolinones are pharmacophoric scaffold ubiquitous in various biologically active natural products, synthetic compounds, pharmaceutical drugs, agrochemicals and veterinary products [1]. The chemical structure of quinazolinones constitute a crucial scaffold of compounds with various therapeutic and biological activities such as antimalarial [2], antimicrobial [3, 4], antitubercular [5], anticonvulsant [6], anticancer [7], antihypertensive [8], anti-diabetic [9], anti-inflammatory [10], anti-cholinesterase [11], cellular phosphorylation inhibition [12], dihydrofolate reductase inhibition [13], kinase inhibitory activities [14], inhibitors of tubuline polymerization [15], diuretic [16], antipsychotic [17], dopamine agonists [18] and anti-HIV [19]. Quinazolinones (**Figure 1**) is a core scaffold for the structure of more than 200 naturally occurring alkaloids isolated from different plant families and from various microorganisms such as *Bacillus cereus, Peganum nigellastrum, Dichroa febrifuga and Bouchardatia neurococca* [20]. Depending on the position of the keto group, they can be classified into three types. Among the 2(1H)-quinazolinones (**1**), 4(3H)-quinazolinones

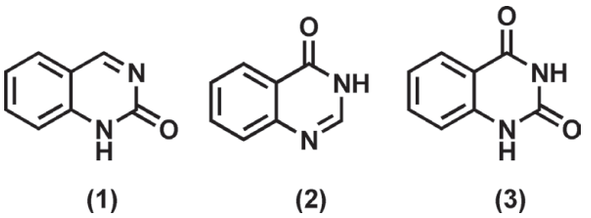

Figure 1.
Quinazolinone and quinazolinedione structures.

and 2,4(1H,3H)-quinazolinediones (**2**), 4(3H)-quinazolinones (**3**) are most prevalent and significant in medicinal chemistry possessing a multitude of pharmacological actions [21]. Quinazolinones are generally classified into four classes, 2-substituted quinazolinones, 3-substituted quinazolinones, 2,3-disubstituted quinazolinones and quinazolinone derivatives including fused quinazolinones [22].

2. Synthetic methods of quinazolinones

The number of synthetic methods of quinazolinone cores has intensely increased from year to year. These advancements in methods of synthesis lead to the access to new and effective quinazolinone compounds with augmented structural diversity starting from affordable and easily accessible substrates. In this chapter, we depict different methods of synthesis of quinazolinone derivatives from cheap and readily available starting precursors.

2.1 Synthesis of quinazolinone compounds from 2-aminobenzoic acid

Quinazolin-4(3*H*)-one (4) was synthesized by the reaction of formamide with 2-aminobenzoic acid at 125–130°C and cyclization of 2-aminobenzoic acid takes place as described in **Figure 2** [23]. Synthetic works started from esterification of 2-aminobenzoic acid and subsequently followed by reaction with isocyanates afforded 1,3-disubstituted quinazol-2,4(*1H, 3H*)-diones (5) [24] (**Figure 2**). 2-mercapto-3-substituted quinazolin-4(3*H*)-one derivatives (6) (**Figure 2**) have been synthesized through the interaction between 2-aminobenzoic acid and corresponding isothiocyanate reagent.

In 1960, Ried et al. reported [25–27] the reaction of imidates and 2-aminobenzoic acid in methanol at 80°C to afford the desired quinazolinones (7) in good yields (**Figure 2**).

A recently reported route, to the synthesis of 2-substituted quinazolin-4(3H)-ones (7) under microwave conditions was reported by Rad-Moghadam and Mohseni [28]. This approach involves the condensation of 2-aminobenzoic acid, orthoesters and ammonium acetate which afford the 2-substituted-4(3H)-quinazolinone (7) **Figure 2**.

A solvent-free approach was reported by Li et al. [29] for the synthesis of 2,3-disubstituted-4(*3H*)-quinazolinones (8). The approach involves the interaction between 2-aminobenzoic acid, acyl chlorides and aromatic/aliphatic amines in the presence of SO_3H-functionalized Brønsted acid ionic liquids as a catalyst under microwave irradiation (**Figure 2**). Langer and Döring [30] reported the reaction of 2-aminobenzoic acids with oxalic acid bis(imidoyl) chlorides to prepare quinazolinones (9) **Figure 2**.

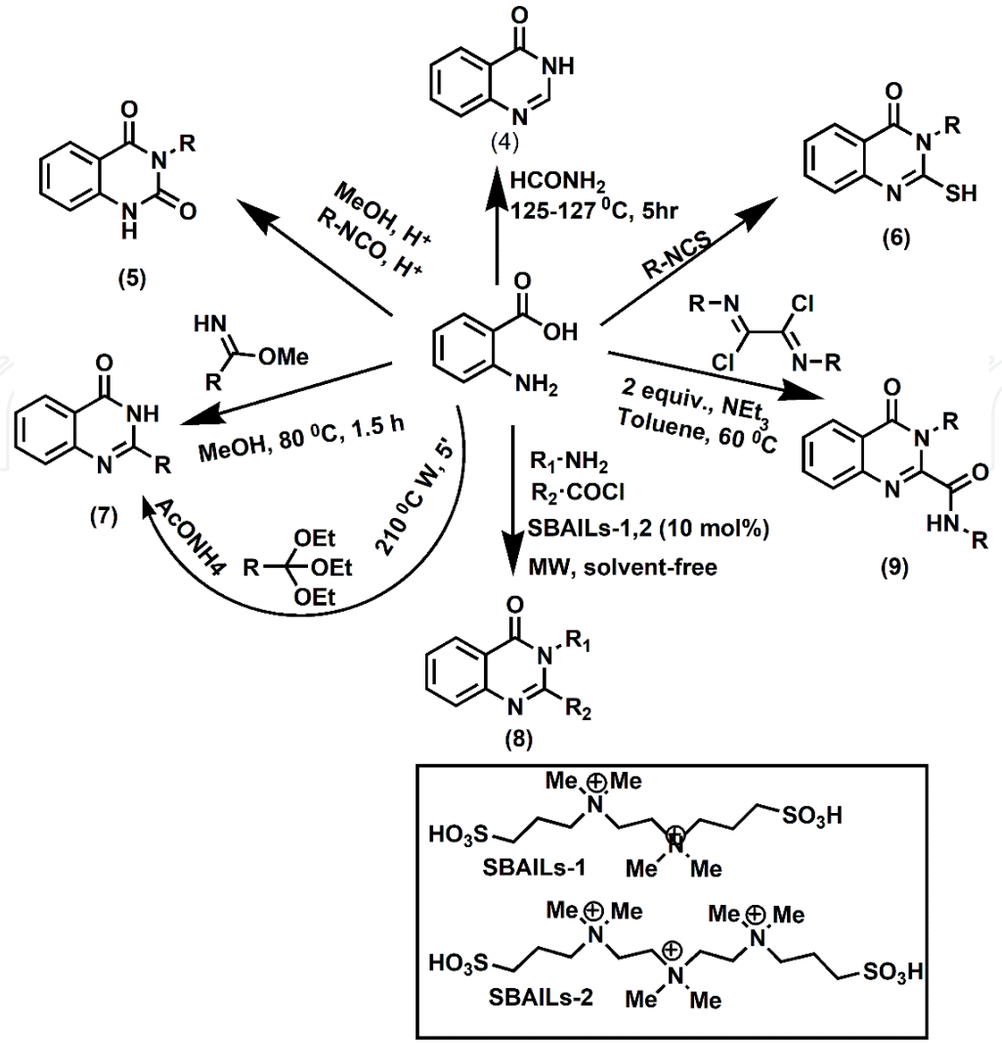

Figure 2.
Synthesis of quinazolin-4(3H) one from 2-aminobenzoic acid.

2.2 Synthesis of quinazolinone compounds from 2-aminobenzamide

In 1962, Bake and Almaula [31] have reported the synthesis of 2-carboethoxy-quinazoline-4(3H)-one **10** through the reaction of anthranilamide and diethyl oxalate (**Figure 3**). Shaterian and Rigi [32] reported a starch sulfate-catalyzed method for synthesis of 2-substituted-1,2,3,4-tetrahydro-4-quinazolinones **11** (**Figure 3**). Zhang and co-workers [33] reported a MnO_2-catalyzed method for the synthesis of 2-substituted quinazolinones **12**. Anthranilamides undergo a-MnO_2-catalyzed oxidative cyclization with alcohols using TBHP as an oxidant (**Figure 3**). Compound **12** could be obtained through the condensation of anthranilamide with an aldehyde in refluxing ethanol in the presence of $CuCl_2$ [34]. Schiff base intermediate was first obtained and, in turn, is transformed into the 2-substituted quinazolinones **12** (**Figure 3**).

In 1887, when Körner reported that the acylation of anthranilamide results in diamide intermediate which upon treatment with sodium carbonate or sodium hydroxide yielded 2-phenylquinazolin-4(3H)-one **12** (**Figure 3**) [35].

Quinazolin-4(3*H*) one compound **12** have been developed by Yang et al. via selective cleavage of the triple bond of ketoalkynes. A reasonable mechanism was suggested for this reaction (**Figure 3**). Michael addition of the amino group of the anthranilamide to the triple bond of the ketoalkyne generated the enaminone

intermediate which upon acid catalyzed intramolecular cyclization with subsequent C-C bond cleavage afforded final product **12**.

2.3 Synthesis of quinazolinone compounds from o-substituted aniline

Yan et al. [36] reported a C(sp3)-H oxidative amination, tandem condensation oxidation, catalyzed by iodine method to access quinazolinone compound **13** (**Figure 4**).

Natte and co-workers [37] reported the reaction of 2-iodoanilines, amines and trimethyl orthoformate catalyzed by Pd/C afforded quinazolin-4(3*H*) one compounds **13** (**Figure 4**).

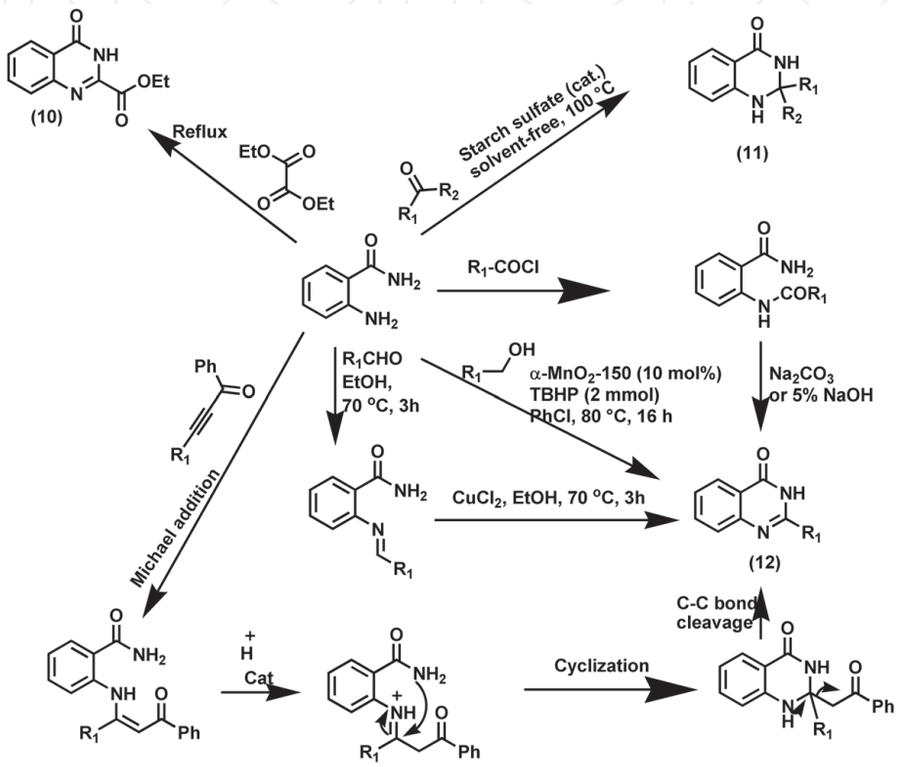

Figure 3.
Synthesis of quinazolin-4(3H) one from 2-aminobenzamide.

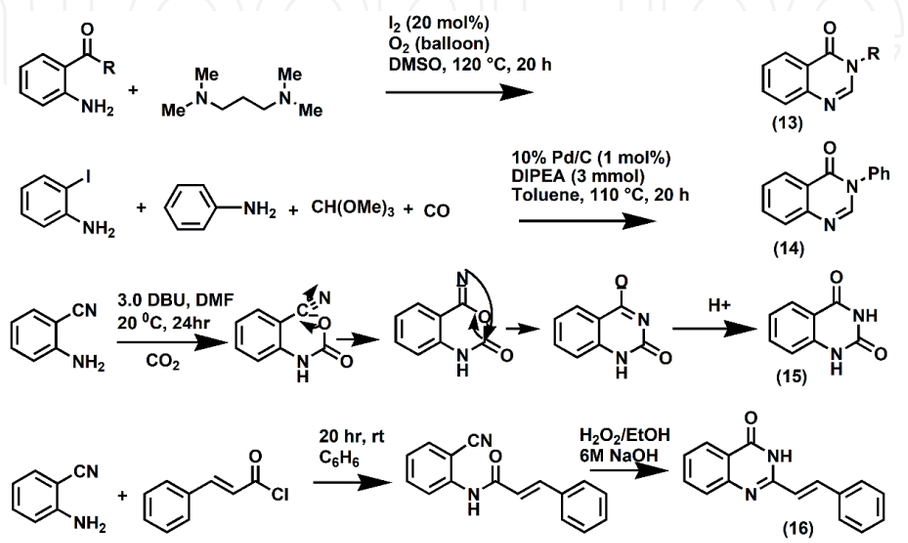

Figure 4.
Synthesis of quinazolinone compounds from o-substituted aniline.

Mizuno et al. [38] synthesis of qiunazolin-2,4-(1*H*,3*H*) ones (2,4-dihydroxyquinazolines) **15** using 2-aminobenzonitriles starting materials in the presence of carbon dioxide and suitable base. The reaction first generates the carbamate salts followed by nucleophilic cyclisation via attack of the carbamate oxygen onto the cyano group with subsequent rearrangement into an intermediate that is protonated yielding the desired 2,4-dihydroxyquinazoline **15** (**Figure 4**). Also, amidation of anthranilamide with 3-phenylacryloyl chloride with subsequent oxidative ring closure using base catalyst revealed 2-styryl-4(3*H*) quinazolinone **16** (**Figure 4**) [39].

2.4 Synthesis of spiroquinazolinones

Revathy and Lalitha [39] reported a method of *p*-Toluene sulfonic acid-catalyzed synthesis of spiroquinazolinones **17** using anthranilamide and with ketones as starting materials (**Figure 5**). Tajbakhsh et al. [40] reported a H_3PO_3-catalyzed method for synthesis of spiro2,3-dihydroquinazolin-4(1*H*)-ones **18** using isatoic anhydride, hydrazides and cyclic ketones, in the presence of H_3PO_3 catalyst (20 mol %, in ethanol) (**Figure 5**).

2.5 Synthesis of heterocycle-fused quinazolinones

Yang et al. [41] reported the synthesis of tricyclic quinazolinones **19** using formic acid-catalyzed intramolecular cyclization of 3-(2-aminoalkyl)-2-(phenylamino) quinazolin-4(3H)-ones (**Figure 6**).

Reddy et al. [42] reported a CuI/DMSO-catalyzed domino oxidative method for the synthesis of tryptanthrin compound **20** through the interaction of 2-aminoacetophenone and isatoic anhydrides (**Figure 6**).

Foldesi et al. [43] reported the synthesis of the tetracyclic pyrrolotriazepinoquinazolinone derivative **21** the interaction between 1-aryl-4-(methylsulfanyl)-5H-pyrrolo[2,1-d] [1, 2, 5] triazepines and anthranilic acid under reflux in acetic acid (**Figure 6**).

Yuan et al. [44] developed a process to prepare 1H-pyrimido[2,1-b]quinazoline-2,6-dione derivatives **22.** The product was accessed through a tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction of (E)-methyl 2-((2-azidobenzamido)methyl)-3-phenylacrylate with triphenylphosphine and isocyanates (**Figure 6**).

Wang and Ganesan [45] reported the synthesis of luotonin A, **23** through the reaction of anthranilic acid with 1*H*-pyrrolo[2,3-b]quinolin-2(3*H*)-one (**Figure 6**).

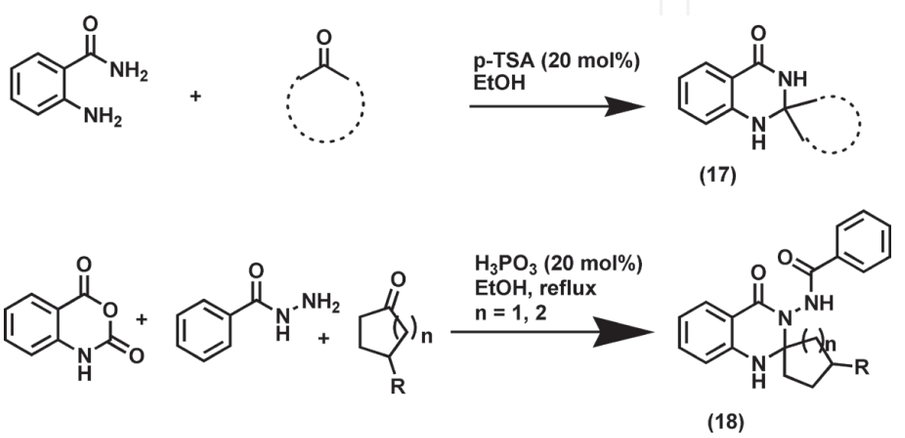

Figure 5.
Synthesis of spiroquinazolinones.

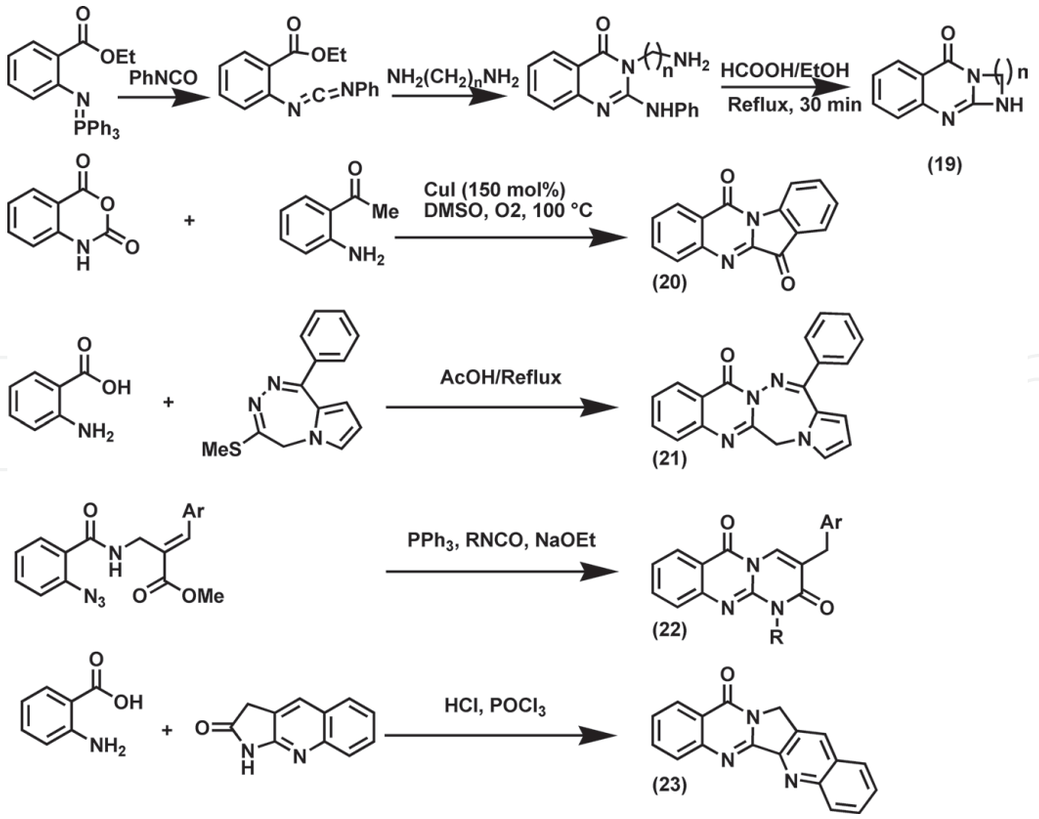

Figure 6.
Synthetic methods of heterocycle-fused quinazolinones.

3. Biological applications of quinazolinones

Natural quinazolinones that widely used in traditional folk medicines are isolated from the plants and microorganisms while the major quinazolinone derivatives are accessed through synthetic process by some chemical reactions. Quinazolinone compounds constitute most privileged class of biologically active heterocyclic compounds. Because of their wide spectrum of biological activities, quinazolinones either from natural source or from synthetic origin, have prompted the medicinal chemist for structural design of these active compounds to develop high selective and potent pharmacological activities.

3.1 Anticancer activity

The natural cytotoxic quinazolinones are depicted in **Figure 7**. The Chinese herbal medicinal plant, Luotonin A **23**, **Figure 7** is a cytotoxic natural alkaloid possessing pentacyclic fused-quinazolinone moiety. It was first isolated from *Peganum migellastrum* in 1997 and it is in clinical use as anticancer agent and showed low human human topoisomerase-I inhibitor activity [46].

Topoisomerases being major targets for anticancer drug design, the luotonin A was used as a lead compound for development of analogs with increased potency [47]. In comparison with the luotonin A, the majority derivatized analogs explored higher activity for topoisomerase I inhibition and better *in vitro* cytotoxicity than lutonin A [47]. In view of these results, luotonin A is considered as a pharmacophoric core for the design of new topoisomerase I inhibitors [48].

In 2006, (−)-chaetominine **24**, a tetracyclic tripeptide alkaloid (**Figure 7**) was isolated from an endophytic fungus, Chaetomium sp. IFB-E015, and showed smaller IC_{50} than the most frequently prescribed anticancer drug 5-fluorouracil

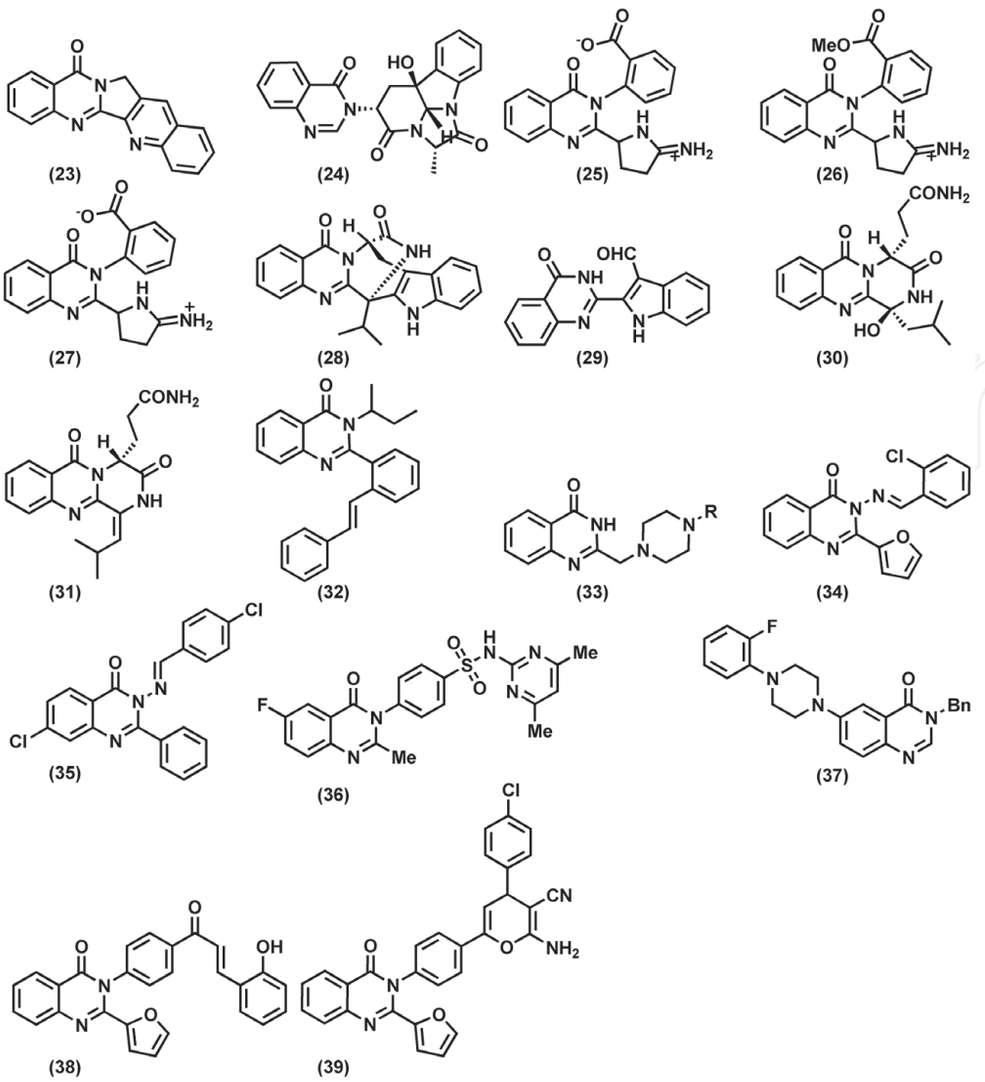

Figure 7.
Chemical structure of anticancer compounds.

against human leukemia K562 (IC50 21 μM) and colon cancer SW1116 (IC50 28 μM) cell lines with IC_{50} values [49].

Quinazolinone alkaloids, auranomides A–C (**25–27**) were isolated from *Penicillium aurantiogriseum* and showed moderate cytotoxicity against human tumor cells [50]. Sartorymensin (**28**), a hexcyclic indoloazepine-fused quinazolinone derivative was isolated from *Neosartorya siamensis* fungus (KUFC 6349) showed a moderate *in vitro* growth inhibitory activity of several cancer cell lines [51]. The 2-substituted quinazolinone alkaloid, bouchardatine (**29**), isolated from *Bouchardatia neurococca* (*Rutaceae*), showed anti-cancer effects [52]. The aurantiomides B and C (**30**, **31**) isolated from *Penicillium aurantiogriseum* fungus derived from sponge and showed moderate activities (IC50 values of 52–54 μg/mL against HL-60 and P-388 for aurantiomide B and IC50 values of 48–62 μg/mL against P-388 and BEL-7402 for aurantiomide C) [53].

Mahdavi et al. [54] developed a new N-substituted 2-arylquinazolinones bearing transstilbene moiety **32** showed good profile (IC50 < 5 μM) against human ductal breast epithelial tumor (T-47D) and human breast adenocarcinoma (MCF-7 and MDA-MB-231) showing two-fold potency more than etoposide standard drug. 2-(piperazin-1-*yl*-methyl)quinazolin-4(3*H*)-one (**33**, R = Acetyl, Propionyl) showed potent anti-cancer activity [55]. While, 3-(2-chloro benzylidinamine)-2-(furan-2-yl)quinazoline-4(3*H*)-one (**34**) showed high activity against ovarian

and non-small cell lung cancer [56]. 7-chloro-3-{[(4-chlorophenyl)methylidene] amino}-2-phenylquinazolin-4(3H)-one (**35**), explored significant activity against CNS Cancer cell line [57].

Zayed et al. [58] developed a quinazolinone-bearing sulphonamide moiety compound **36** which upon MTT ass showed IC50 value of 2.51 μM, whereas, the reference drug (methotrexate) exhibited an IC50 value of 2.4 μM, against Michigan Cancer Foundation-7 (MCF-7) breast cancer cells, National Cancer Institute (NCI) lung cancer cells and Human Embryonic Kidney-293 (HEK-293) normal kidney cell. 6-Substituted quinazolinone compound **37** was reported by Malinowski et al., revealed significant activity toward both HT29 (IC50 = 50.90 μM) and HCT116 (IC50 = 46.00 μM) cells lines [59].

Ahmed and Belal reported 2-furylquinazolinone derivatives including compound **38** that explored IC50 value equal to 7 μM/mL on MCF7 cells, and promising inhibitory activity against EGFR-TK [60], and compound **39** depicted a 24-fold higher potency than doxorubicin on HCT116 cancer cells, with IC50 values of 0.2 nmol/mL. Also, compound **39** showed a similar potency to the doxorubicin on MCF7 cell lines and remarkable EGFR inhibitor activity compared with erlotinib standard drug [61].

3.2 Anti-inflammatory activity

The inflammation is a biochemical reactions response that protects the body from infection and injury. It reflects the response of the organism to various stimuli and is related to many disorders such as arthritis, asthma and psoriasis which require prolonged or repeated treatment. The major cause of inflammation the release of chemicals from tissues such as the prostaglandins, histamine, leukotrienes, bradykinin, platelet-activating factor and interleukin-1. Corticosteroids inhibit the synthesis of both PGs and LTs through the release of lipocortin, which inhibits phospholipase A2 and subsequently reduces arachidonic acid release alleviating the inflammation of either rheumatoid arthritis or asthma. While nonsteroidal anti-inflammatory drugs NIASID relieve the inflammation through the inhibition of the cyclooxygenase enzyme and reducing the synthesis of prostanoids [62]. **Figure 8** shows the chemical structure of the anti-inflammatory quinazolinone compounds. *Spiro* [(*2H,3H*) quinazoline-2,10-cyclohexan]-4(*1H*)-one compounds **40** and **41** were reported as potent anti-inflammatory and analgesic activity of superior GIT safety margin in rats model compared with indomethacin (10 mg/kg) and tramadol (20 mg/kg) as reference standards [63].

Abbas SE et al. [64] reported a new quinazolinone-pyrimidine hybrid compound (**42**) which showed more activity and less ulcerogenicity than diclofenac (IC50 = 116.73 μmol/kg; ulcer index = 11.38). The compound explored two-fold more selective inhibition of COX-2 than COX-1.

Hemalath K et al. [65] reported a novel quinazolinone derivative (**43**) that explored 36.3 inhibition of oedema in animal model and showed anti-inflammatory activity as same as phenyl butazone reference drug at a p.o. dose of 25, 50, and 100 mg/kg. Hemalath K et al. [65] also developed a 2,3-dihydroquinazolin-4(1H)-one (**44**) succeeded to produce higher protection against bovine serum albumin (BSA) denaturation that displayed higher protection than diclofenac sodium reference drug. Manivannan et al. [66] designed new quinazolinone derivatives (**45**; R1 = H, Br, R2 = H, Cl; R3 = H, OCH_3) and assayed the derivatives for cyclooxygenase inhibitions by ovine COX and carrageenan-induced rat paw oedema methods. Four compounds showed potent anti-inflammatory activity with oedema inhibition percentage of 49 ± 1.16, 45 ± 0.82, 46 ± 1.36 and 54 ± 1.83 using indomethacin drug as reference.

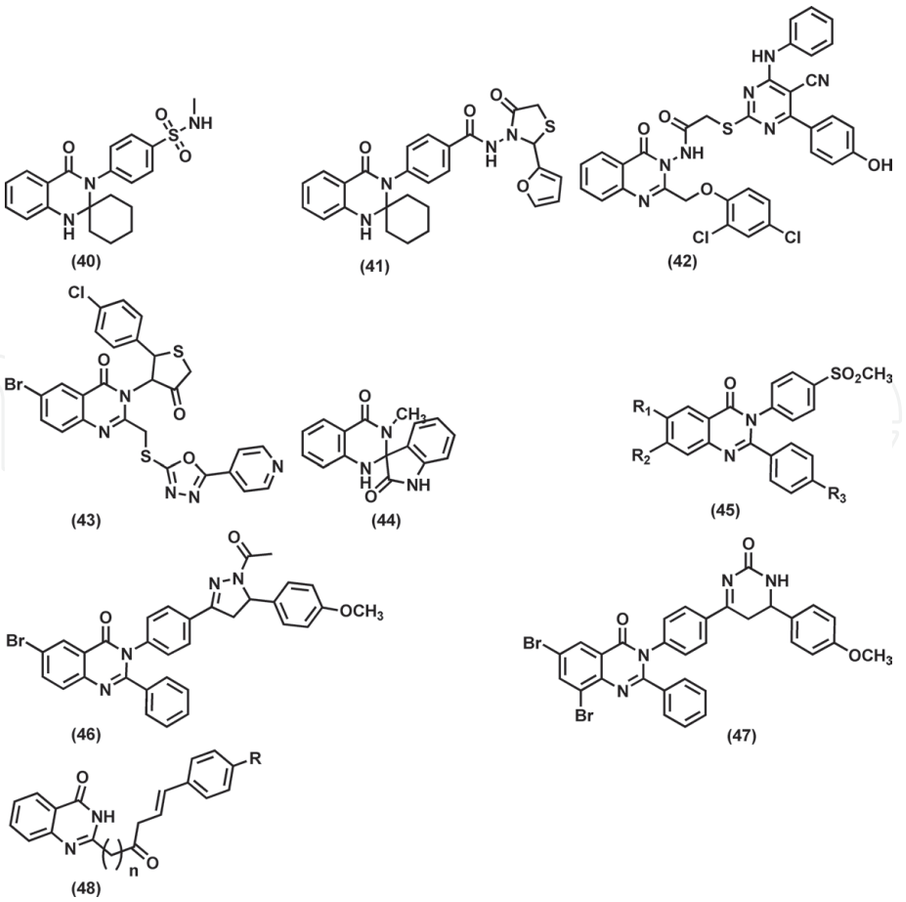

Figure 8.
Chemical structure of anti-inflammatory quinazolinone derivatives.

Mohamed MS et al. [67] have synthesized a series of 2-phenyl-4(3H) quinazolinone derivatives of which to compounds (**46**, **47**) showed considerable potent anti-inflammatory activity in rats model with oedema inhibition percentage of 46 ± 1.26, 43 ± 1.82 using indomethacin standard drug in 3 hrs.

Rakesh et al. [68] have synthesized a series of Schiff base derivatives of quinazolinone and got excellent anti-inflammatory activity for synthesized compounds (48; n = 2,3, R = Cl, NO_2).

3.3 Anticonvulsant activity

Epilepsy is defined a chronic neurological syndromes and marked by neuronal firing and neuronal hyperexcitability. Although, the available antiepileptic therapeutics explore satisfactory seizure control in about 70% of epileptic patients, it has become very urgent to search for new antiepileptic compounds with fewer side-effects and less toxicity.

Figure 9 shows chemical structures of anticonvulsant agents. The structure-activity relationship of the anticonvulsant activity of 4(3H)-quinazolinones nucleus revealed the crucial role of a methyl group at position 2 and a substituted aromatic ring at position 3 for the anticonvulsant activity of compounds such as methaqualone (**49**; R1 = CH3, R2 = o-tolyl, R3 = H), etaqualone (49; R1 = CH3, R2 = 2-ethylphenyl, R3 = H), mecloqualone (**49**; R1 = CH3, R2 = o-chlorophenyl, R3 = H), methyl-methaqualone (**49**; R1 = CH3, R2 = 2,4 = dimethylphenyl, R3 = H), piriqualone (49; R1 = CH3, R2 = ((E)-2-pyridin-2-ylethenyl), R3 = H) and afloqualone (**49**; R1 = fluoromethyl, R2 = o-tolyl, R3 = NH2) [69]. Against electroshock induced convulsions methaqualone is 1.5 times more potent anticonvulsant than phenytoin sodium and

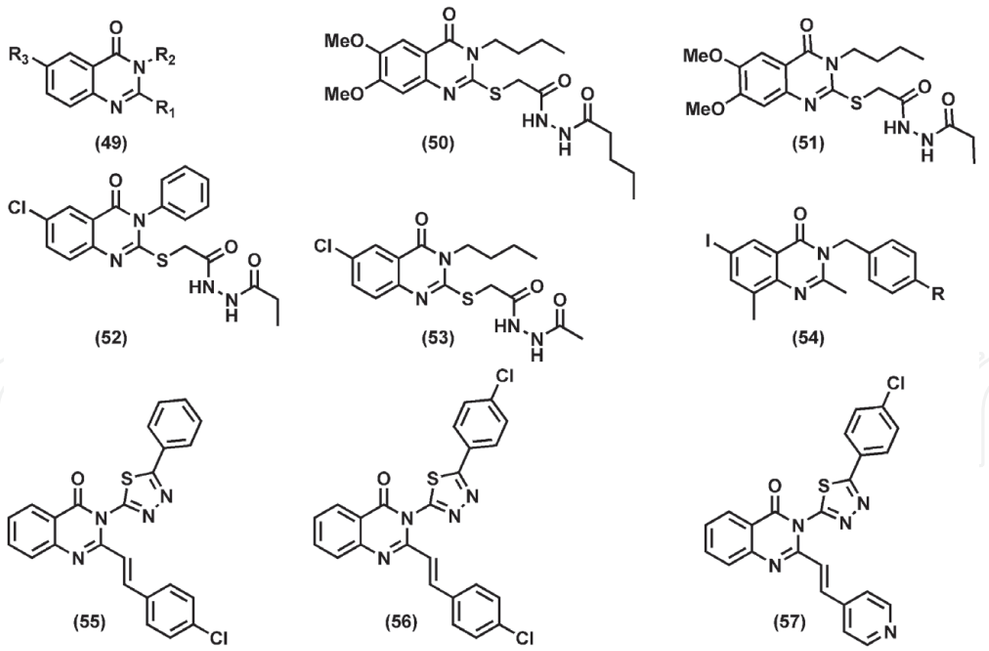

Figure 9.
Chemical structure of anticonvulsant agents.

against pentylenetetrazol-induced seizures it is 10 times more potent than troxidone [70]. Methaqualone produces anticonvulsant effects, through the GABA type A receptors, at low doses while at higher doses, it produces muscle-relaxant and sedative effects [71].

Al-Salem et al. [70] reported 4(3H)-quinazolinone bearing hydrazinecarbothioamide, benzenesulfonohydrazide or phenylacyl acetohydrazide moiety. Compounds **50–53** were most potent with 100% protection against PTZ-induced convulsions compared with the reference drug sodium valproate. Abuelizz HA et al. [72] synthesized a of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3H)-ones analogues (**54**; R = Cl, Br, F) that revealed good anticonvulsant activity as evaluated by the maximal electroshock-induced seizure and subcutaneous pentylenetetrazole tests.

A series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-one derivatives has been synthesized by Jatav et al. [73]. Of this series, compounds **55** and **56** revealed anticonvulsant activity results at 0.5 and 4 h in both MES and scPTZ test models, whereas compound **57** explored anticonvulsant activity results at 4 h in MES model and at 0.5 and 4 h in scPTZ model.

3.4 Antimicrobial activity of quniazolinones

2-oxo-azetidinyl-quinazolin-4(3H)-ones (**58**) possess antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli* and *C. albicans* [74]. 2-Mercapto-3-(4-chlorophenyl)-6-iodo-3H-quinazolin-4-one derivatives (**59–62**) were reported to show a significant antimicrobial activity and could be useful as lead compounds for further design and discovery of more potent antimicrobials [75].

Vani et al. [76] synthesized a series of quinazolin-4(3H)-one-triazole hybrids (**63–65**) quinazolin-4(3H)-one and oxadiazole hybrids (**66–68**). Compounds **64–67** showed significant antibacterial activity against all the bacterial strains, Gram-positive bacteria *(Staphylococcus aureus, Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), while compounds (**63**, **67**, **68**) showed highest activity against fungal species, *Candida albicans* and *Aspergillus niger* compared with ciprofloxacin and fluconazole as reference drugs, respectively.

Kohli et al. reported the antimicrobial activity of the derivatives of 4-Oxo-2-phenylquinazolin-3(4H)-yl-amine (**69**; R = H, CH_3, C_2H_5) against bacterial strains *Staphylococcus aureus* and *Escherichia coli* using ampicillin drug reference at a concentration 100 μg/ml [77].

Sowjanya et al. [78] reported the synthesis of 2-(Substituted styryl)-quinazoline-4(*3H*)-ones (**70**; R = H, CH_3, C_2H_5) as antibacterial agents against bacterial strains *Bacillus subtilis*, *Staphylococcus aureus* (Gram-positive), *Escherichia coli* and *Proteus vulgaris* (Gram-negative) using 100 μg/ml of streptomycin and penicillin as standard drugs.

El-Hashash et al. [79] reported the synthesis of quinazolinones bearing sulfonamide moiety (**71–73**) as antimicrobial against *Gram*-positive bacteria *S. aureus* and *B. cereus* and *Gram*-negative bacteria *S. marcescens* and *P. mirabilis* and as antifungal agents against *A. ochraceus Wilhelm* and *P. chrysogenum* using ampicillin and mycostatin as standards, respectively. **Figure 10** shows the chemical structure of antimicrobial compounds (**58–73**).

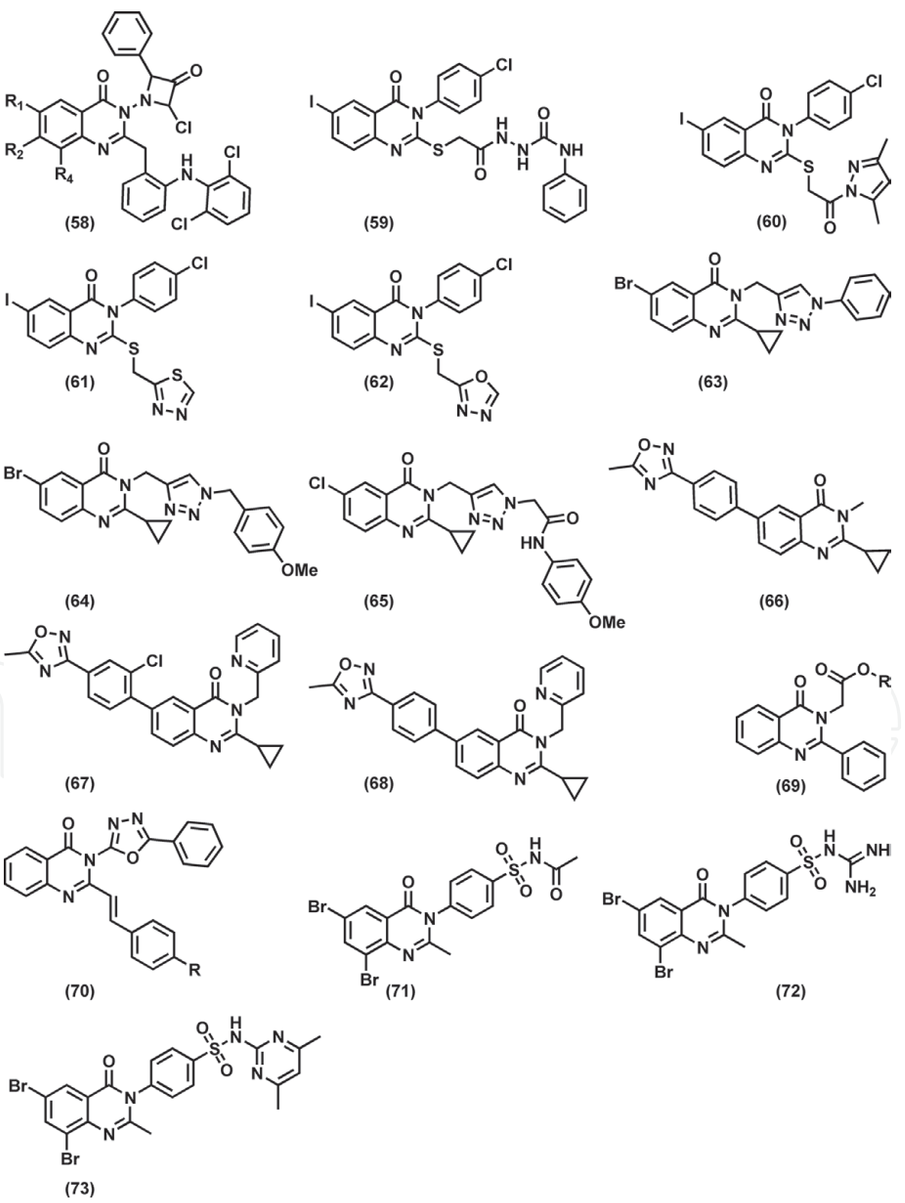

Figure 10.
Chemical structure of antimicrobial compounds.

3.5 Antimalarial activity

Malaria is a parasitic disease caused by *Plasmodium* species parasite. It is widespread in several regions in Africa, Asia and South America. These parasites have developed a drug resistance to almost all the commercially available antimalarial drugs. The good antimalarial potency and the less side effects of quinazolinone compounds promote the researchers for the development of new antimalarial compounds [80].

In 1948, Febrifugine (**74**), a Chinese traditional herb, has been extracted from leaves of *Dichroa febrifuga* that was found in the garden plant Hydrangea. It has 50–100 times as antimalarial as quinine in *in vivo* model. Febrifugine analogues WR140085 (**75**), WR090212 (**76**), WR146115 (**77**) were reported as potent antimalarial agents. The gastrointestinal side effects of (**74**) and the macrophage cells mediated clearance of (**75–77**) requested further therapeutic development and discovery of new antimalarial drugs [2]. Birhan et al. [81] have synthesized 3-aryl-2-(substituted styryl)-4(3*H*)-quinazolinone derivatives (**78**, **79**) as potent antimalarial agents (**Figure 11**).

3.6 Antiviral activity

Wang et al. [82] reported quinazolinone derivatives (**80**, **81**) with potent antiviral activity against HIV and TMV. Gao et al. [83] have synthesized a series of 2-aryl- or 2-methyl-3-(substituted benzalamino)-4(3*H*)-quinazolinone derivatives and found that the compounds (**82**) and (**83**) exhibit good antiviral activity against TMV (**Figure 12**).

Liu et al. [84] reported a series of 2-pyridinyl-3-substituted-4(3H)-quinazolinones as anti-influenza A virus agents. Of these derivatives, compounds (**84–87**) revealed potent activity (IC50 = 51.6–93.0 μM) better than that of the clinically used drug, ribavirin. Also, it was reported that compound (**87**) could inhibit influenza A virus propagation through inhibition of cellular NF-kB pathway, although it was not as effective as ribvarin (**Figure 12**).

3.7 Cathepsin inhibitor activity

Cathepsins B and H are cysteine proteases that plays a major role in cancer progression as they degrade extracellular matrices facilitating invasion, angiogenesis and metastasis. Therefore the research community has been prompted to the discovery of potent cathepsins inhibitor hemotherapeutics [85].

Singh and Raghav [86] reported the synthesis of a series of 2,3-dihydroquinazolin-4(*1H*)-ones and evaluated it as cathepsins inhibitors, **Figure 13**. Of these

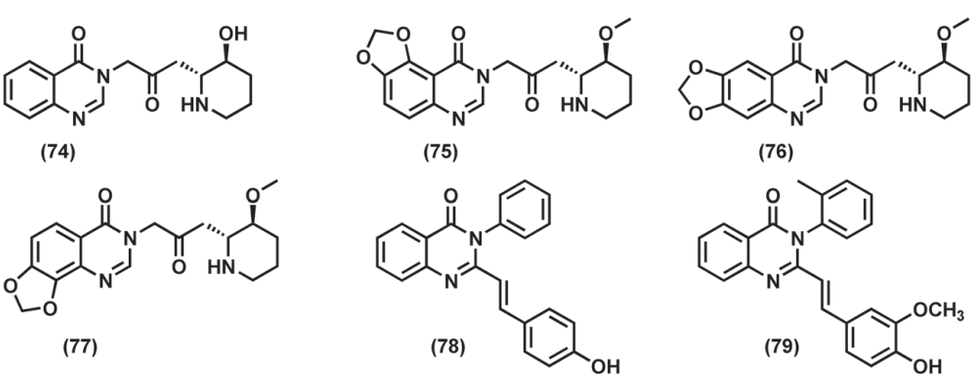

Figure 11.
Antimalarial compounds.

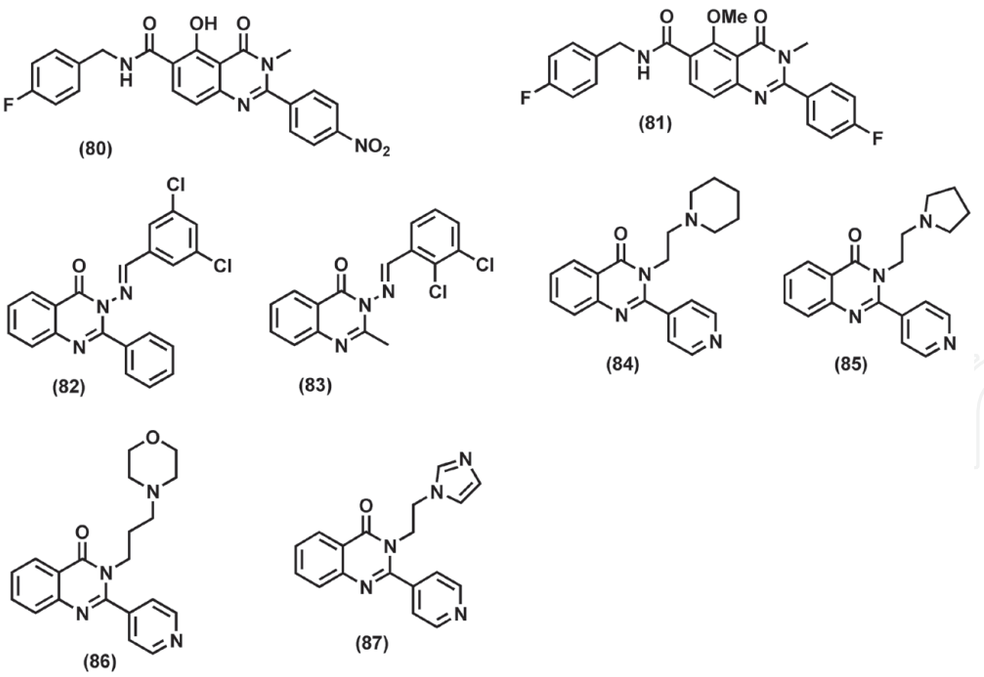

Figure 12.
Antiviral compounds.

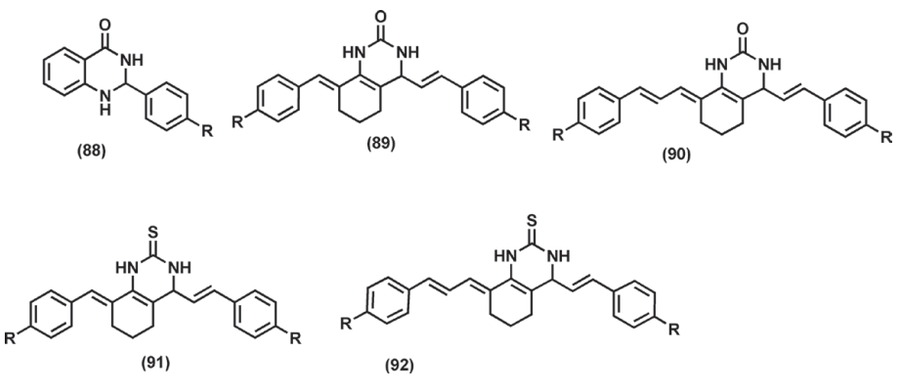

Figure 13.
Chemical structure of cathepsins inhibitors.

compounds, 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(*1H*)-one (**88**; R = F) and 2-(4-chlorophenyl)-2,3-dihydro quinazolin-4(*1H*)-one (**88**; R = Cl) substituted compounds showed maximum inhibition on cathepsin B. Whereas for cathepsin H, 2,3-dihydro-2-(4-methylphenyl)quinazolin-4(*1H*)-one (**88**; R = Me) and 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(*1H*)-one (**88**; R = F**)** have been found to be the most potent inhibitors.

Raghav and Singh [87] reported the synthesis of bischalcones and their quinazoline-2(1*H*)-one (**89**, **90**; R = H, NO_2, CH_3O, $(CH_3)_2N$) and quinazoline-2(1*H*)-thione (**91**, **92**) derivatives as cathepsin B and cathepsin H inhibitors, (**Figure 13**). Bischalcones and their quinazoline-2(1*H*)-thione derivative (**91**, **92**; R = H, NO_2, CH_3O, $(CH_3)_2N$) inhibited both cathepsins in a competitive manner whereas quinazoline-2(1*H*)-one derivative (**89**, **90**) inhibited both cathepsins in a non-competitive manner.

3.8 Topoisomerase inhibitor activity

The DNA replication process is controlled essentially by DNA topoisomerase I (Top1) through the relaxation of the nucleic acid's supercoiled structure. Basically,

DNA Top1 attracts the interests of research community as a cancer chemotherapy target [88]. Efforts to overcome side effects of these clinically used anticancer Top1 inhibitors, particularly bladder toxicity, had led to the development of luotonin A alkaloid and discovery of its Top1 inhibitory activity [89].

Ibric et al. reported the development of novel luotonin A isomeric congeners bearing an amino at positions 1, 2, 3, and 4, (**93–97**) **Figure 14** [90]. These compounds revealed significant profile of cytotoxic activity and G2/M cell cycle arrest, proposing either Top1 is not the only target, or some atypical mechanism is accountable for inhibition of Top1 enzyme.

Khadka et al. [91]. synthesized 2-arylquinazolinone derivatives (**98–100**) to investigate these compounds as effective, safe, and selective cytotoxic agents targeting topoisomerases (topos). These compounds showed superior potency as topo I-inhibitors but were inactive against topo IIa.

Kamata et al. have prepared series of pyrimidoacridones (101), Pyrimidocarbazoles (**102**) and pyrimidophenoxadines (**103**) (**Figure 14**), and as topoisomerase II inhibitors [92]. Against P388 and KB cell lines, pyrimidocarbazoles and pyrimidophenoxadines were more potent than pyrimidoacridines. Pyrimidocarbazoles inhibited the *in vivo* tumor growth of mouse sarcoma M5076 with T/C values of 42% at 3.13 mg/kg/d, and increased the level of DNA-topo II cross-linking in P388 cells.

3.9 α-Glucosidase inhibitor activity

Diabetes is a reduced ability to convert glucose into energy inside the body. The role of insulin is the glucose transfer from blood into cells. A large number of antidiabetic agents with different mechanism of action are available in the market.

Saeedi M et al. [93] reported a series of quinazolinone-1,2,3-triazole hybrids 10a-p as potent α-glucosidase inhibitors for use as anti-diabetic agents that exhibited

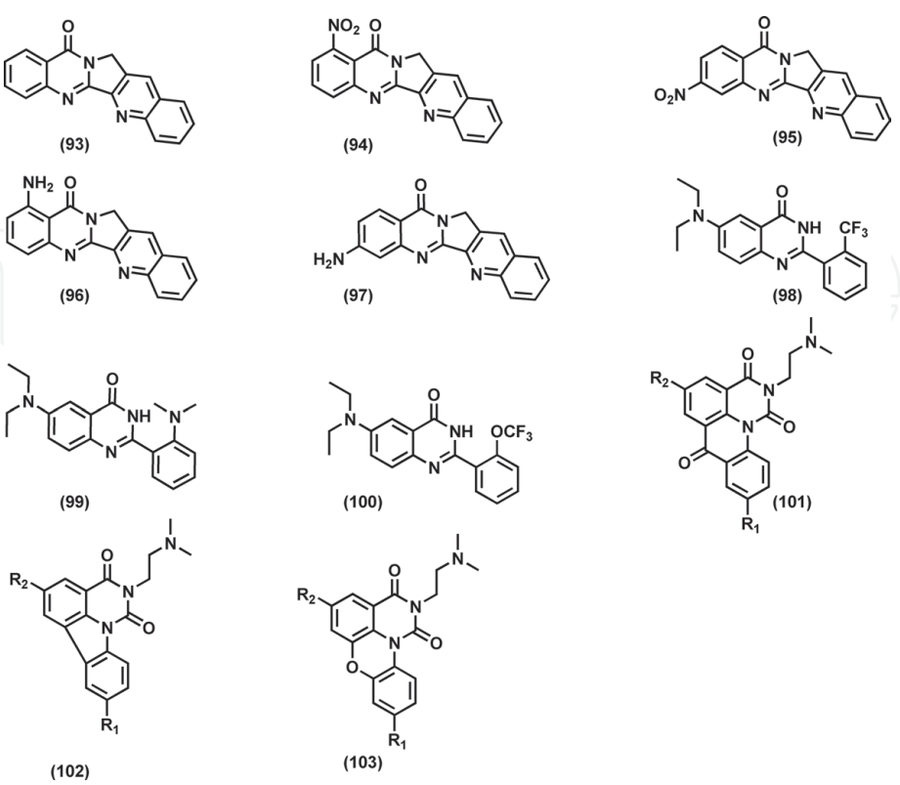

Figure 14.
Chemical structure of topoisomerase enzyme inhibitors.

more potent inhibitory activity against yeast α-glucosidase (IC50 181.0–474.5 μM) than reference drug acarbose (IC50 = 750.0). From these compounds, quinazolinone-1,2,3-triazoles possessing 4-bromobenzyl moiety connected to 1,2,3-triazole ring (**104**, **105**; **Figure 15**) demonstrated the most potent α-glucosidase inhibitor activity. Triazoloquinazoline compounds (**106–110**; **Figure 15**) were reported as highly potent inhibitor of α-glucosidase enzyme (IC50 = 12.70 ± 1.87, 28.54 ± 1.22, 45.65 ± 4.28, 72.28 ± 4.67 and 83.87 ± 5.12 μM, respectively) compared with the reference standard acarbose (IC50 = 143.54 ± 2.08 μM) [94].

Javaid et al. [95] reported a quinazolinone derivative (**111**; **Figure 15**) with IC50 value of 0.3 ± 0.01 μM which is about 2800-fold more potent than acarbose reference standard drug. Rahman et al. [96] synthesized a series of hybrid compounds consisting of N-substituted-(4-oxo-2-substituted-phenylquinazolin-3-(4H)-yl) substituted benzene sulfonamide derivatives. From this series, compounds (**112–116**; **Figure 15**) explored significant antidiabetic activity.

3.10 Thymidine synthase inhibitor activity

Thymidylate synthase enzyme (TS) plays a crucial role in the DNA biosynthesis that it catalyzes the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), one of the nucleotides that constitute the DNA. Inhibition of TS results in imbalance of deoxynucleotides that increase the level of dUMP and finally leads to DNA damage [97]. TS is considered as interesting chemotherapeutic target for treatment of pancreatic, colorectal, ovarian, breast and gastric cancers [98].

In 1998, raltitrexed (**117**) a quinazolin-4-(1*H*)-one compound that has been clinically approved by EMA for treatment of colorectal cancer. Also, pemetrexed

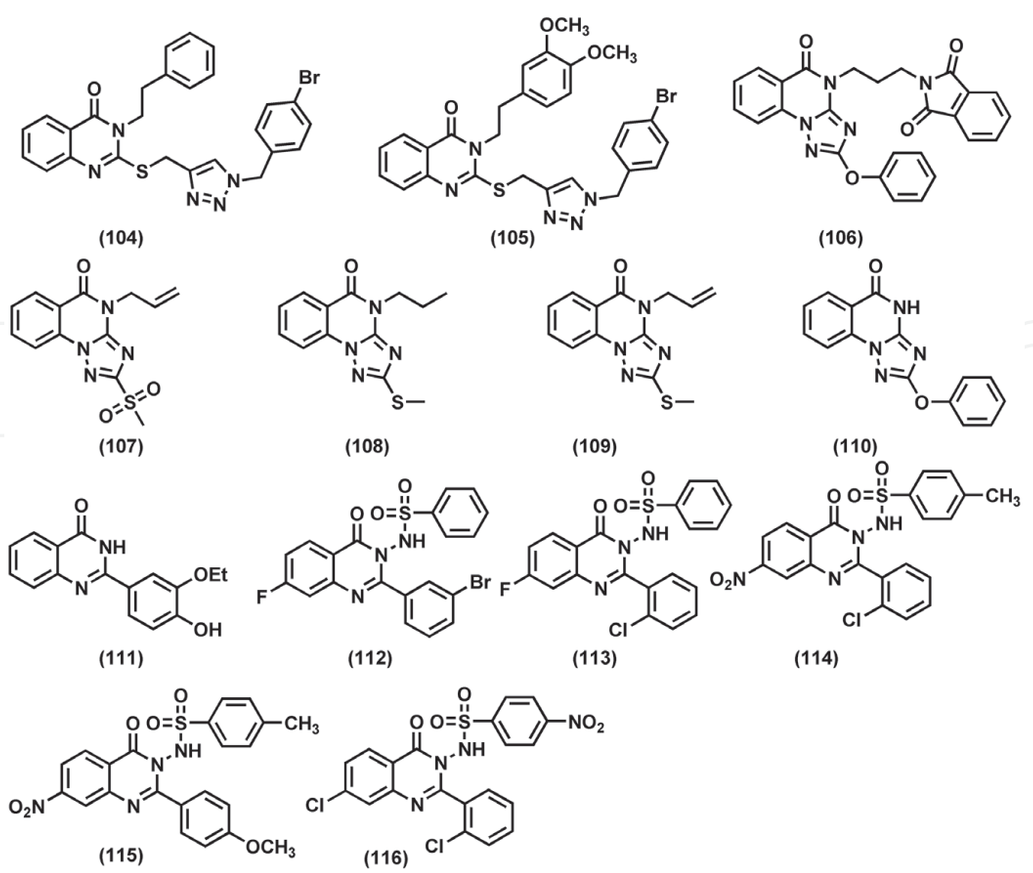

Figure 15.
Chemical structure of compounds with α-glucosidase inhibitor activity.

(**118**) is a quinazolin-4(1*H*)-one compound that is clinically approved by EMA and FDA in 2001. Both raltitrexed and pemetrexed are considered as classical antifolates as they are folate analogs containing a pterin ring and a charged glutamate tail, therefore they need active internalization into the cells through folate carrier system [99].

In recent studies, El-Messery SM et al. [100] synthesized a series of 2,3,6-substituted quinazolin-4(3H)-ones. Of these compounds, compound (**119**; **Figure 16**) is the most potent inhibitor of bovine liver DHFR (with IC50 = of 0.02 μM). It was reported that 2-mercaptoquinazolin-4(3*H*)-one derivative is a potent bovine liver DHFR inhibitor (**120**; **Figure 16**) (IC50 = 0.01 μM) [101]. Javaid and co-workers [102] reported a series of 25 2-arylquinazolin-4(3*H*)-ones as potent thymidine phosphorylase inhibitors among these derivatives compounds (**121**, **122**; **Figure 16**) were identified as the lead compounds (IC50 = 42.9 ± 1.0 and 59.5 ± 1.9 μM, respectively).

3.11 Monoamine oxidase inhibitor activity (MAO)

In human, monoamine oxidases (MAOs) are mitochondrial bound enzymes that are responsible for oxidative deamination metabolism of neurotransmitters such as dopamine, serotonin, norepinephrine and epinephrine. In the brain, MAO-A enzyme isoform metabolizes serotonin, therefore specific MAO-A inhibitors are used the treatment of anxiety and depression disorder [103]. On the other hand, MAO-B enzyme metabolizes dopamine in the brain thus MAO-B specific inhibitors are prescribed for the treatment of Parkinson's disease [104].

Quinazolinone moiety, one of numerous MAO inhibitor scaffolds, it has been explored as lead for the further development of potent MAO inhibitors. Compounds (**123–127**; **Figure 17**) are representative MAO-inhibitor examples of 4(3H)-quinazolinones [105].

Qhobosheane et al. reported seven quinazolinone compounds (IC50 < 1 μM) ascertained as potent and specific MAO-B inhibitors, among them the most potent inhibitor, 2-[(3-iodobenzyl)thio]quinazolin-4(3H)-one (**128**; **Figure 17**), with IC50 value of 0.142 μM. Although these derivatives have been proved as reversible and competitive MAO-B inhibitor (Ki = 0.068 μM), none of the them were MAO-A inhibitors [106].

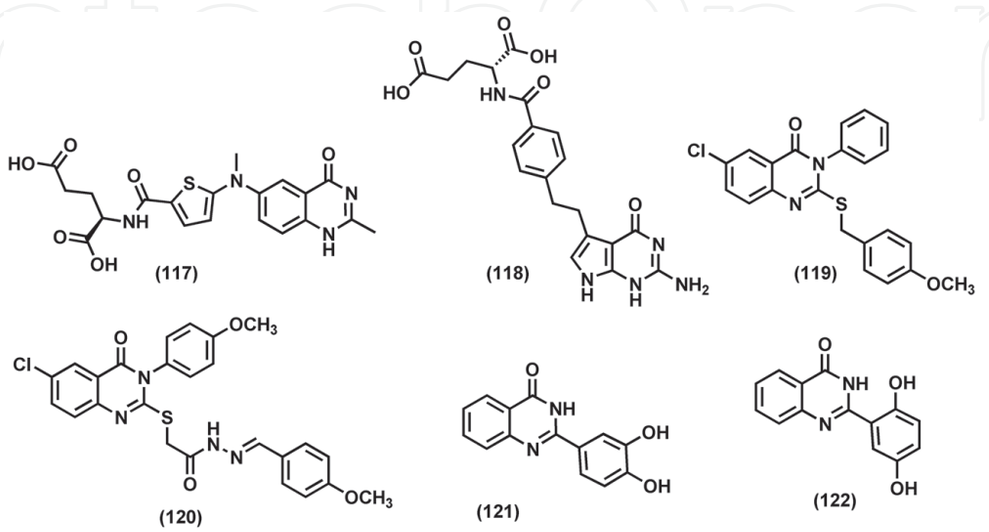

Figure 16.
Thymidine synthase and phosphorylase inhibitors.

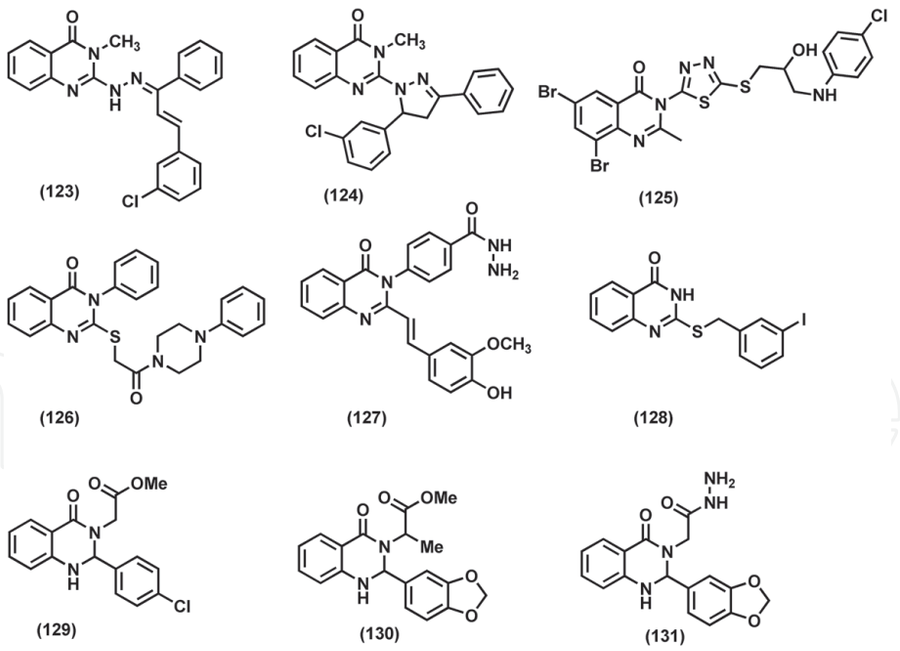

Figure 17.
Chemical structure of monoamine oxidase (MAO) inhibitors.

Khattab et al. [107] reported a series of quinazolinone bearing amino acid ester or amino acid hydrazides (**129–131**; **Figure 17**) that revealed competitive higher inhibitory activity toward MAO-A than MAO-B. The anti-MAO-A activity were comparable with that of the standard reference clorgyline (IC50 = 2.9×10^{-9} M). Compounds (**130**, **131**) were the most selective MAO-A inhibitors with selectivity index of **131** (SI = 39,524) superior to that of the reference drug clorgyline (SI = 33,793).

4. Marketed quinazolinone drugs

Proquazone is non-steroidal anti-inflammatory drug (Biarison®) (**132**; **Figure 18**) manufactured by Novartis pharmaceutical company. Also, it is used in the treatment of degenerative joint disease.

Nolatrexed [108] compound (**133**; **Figure 18**) is a thymidylate synthase inhibitor drug manufactured by Agouron pharmaceutical company under trade name Thymitaq®. In 1998, Zarix licensed Thymitaq® from Agouron. It is used in treatment of liver cancer.

Quinethazone or Hyromox® [109] (**134**; **Figure 18**) has been marketed as antihypertensive drug by Lederle pharmaceutical company and was recently withdrawn from the market.

Fenquizone's brand name is Idrolone® (**135**; **Figure 18**) [110], it is marketed by Maggioni pharmaceutical company. It is a low-ceiling diuretics used in the treatment of oedema and hypertension.

The brand name of albaconazole [111] is Albaconazole® (**136**; **Figure 18**). It was marketed by GlaxoSmithKlyne pharmaceutical company as an oral and topical antifungal agent.

Febrifugine, Dichroin B® or ChangShan® (**137**; **Figure 18**) [112] was isolated from Chinese herb Dichroa febrifuga as potent antimalarial drug and was marketed by Hawaii Pharm pharmaceutical company.

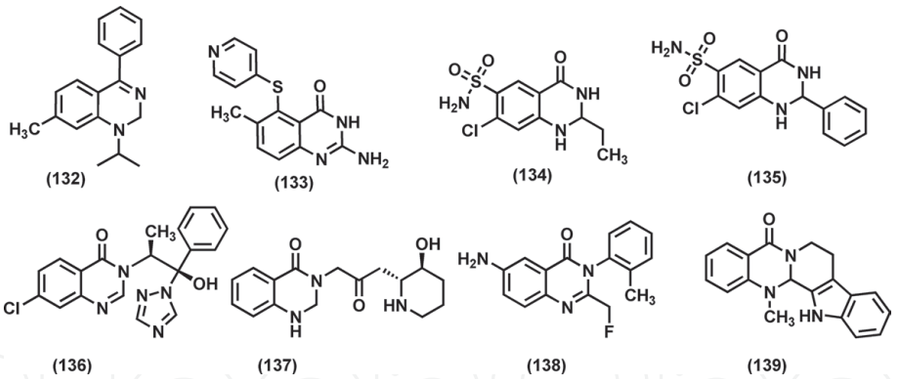

Figure 18.
Chemical structure of marketed quinazolinone drugs.

The brand name of afloqualone is Arofuto® (**138**; **Figure 18**) [113]. It is marketed by Mitsubishi Tanabe Pharma pharmaceutical company as sedative and muscle relaxant drug.

Evodiamine (**139**; **Figure 18**) [114] has been isolated from the Evodia plants and was found to reduce fat uptake in animal model. It is used for bodybuilding as over the counter supplements.

5. Conclusions

This chapter depicts different methods of synthesis of quinazolinone derivatives starting from affordable and easily accessible substrates including 2-aminobenzoic acid, 2-aminobenzamide, o-substituted aniline in addition to the synthetic methods of spiroquinazolinones and heterocycle-fused quinazolinones. Also, the chapter discusses different biological applications of both natural and synthetic quinazolinones. The last section in this chapter lists common quinazolinone drugs that have been approved in the market.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Awwad A. Radwan[1,2*] and Fars K. Alanazi[1,3]

1 Kayyali Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

2 Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Egypt

3 Department of Pharmaceutics, College of Pharmacy, King Saud University, Riydh, Saudi Arabia

*Address all correspondence to: aradwan@ksu.edu.sa; dhna_2001@hotmail.com

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