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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 quinazolinodione 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(3H)-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(3H)-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 SO₃H-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(3H) 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(3H) 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 quinazolin-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(3*H*)-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)-5*H*-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 1*H*-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 mifellastrum* 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 IC₅₀ than the most frequently prescribed anticancer drug 5-fluorouracil

Figure 7.
 Chemical structure of anticancer compounds.

against human leukemia K562 (IC₅₀ 21 μ M) and colon cancer SW1116 (IC₅₀ 28 μ M) cell lines with IC₅₀ 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 hexacyclic 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 auranomides B and C (30, 31) isolated from *Penicillium aurantiogriseum* fungus derived from sponge and showed moderate activities (IC₅₀ values of 52–54 μ g/mL against HL-60 and P-388 for auranomide B and IC₅₀ values of 48–62 μ g/mL against P-388 and BEL-7402 for auranomide C) [53].

Mahdavi et al. [54] developed a new N-substituted 2-arylquinazolinones bearing transstilbene moiety 32 showed good profile (IC₅₀ < 5 μ M) 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(3H)-one (33, R = Acetyl, Propionyl) showed potent anti-cancer activity [55]. While, 3-(2-chloro benzylidinediamine)-2-(furan-2-yl)quinazoline-4(3H)-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 assay showed IC₅₀ value of 2.51 μ M, whereas, the reference drug (methotrexate) exhibited an IC₅₀ value of 2.4 μ M, 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 μ M) and HCT116 (IC₅₀ = 46.00 μ M) cells lines [59].

Ahmed and Belal reported 2-furylquinazolinone derivatives including compound **38** that explored IC₅₀ value equal to 7 μ M/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 prostanooids [62]. **Figure 8** shows the chemical structure of the anti-inflammatory quinazolinone compounds. *Spiro* [(2*H*,3*H*) quinazoline-2,10-cyclohexan]-4(1*H*)-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 μ mol/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(1*H*)-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, OCH₃) 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 $\pm$ 1.16, 45 $\pm$ 0.82, 46 $\pm$ 1.36 and 54 $\pm$ 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; $n = 2,3$, $R = \text{Cl}, \text{NO}_2$).

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; $R_1 = \text{CH}_3$, $R_2 = \text{o-tolyl}$, $R_3 = \text{H}$), etaqualone (49; $R_1 = \text{CH}_3$, $R_2 = 2\text{-ethylphenyl}$, $R_3 = \text{H}$), mecloqualone (49; $R_1 = \text{CH}_3$, $R_2 = \text{o-chlorophenyl}$, $R_3 = \text{H}$), methylmethaqualone (49; $R_1 = \text{CH}_3$, $R_2 = 2,4\text{-dimethylphenyl}$, $R_3 = \text{H}$), piriqualone (49; $R_1 = \text{CH}_3$, $R_2 = (\text{E})\text{-2-pyridin-2-ylethenyl}$, $R_3 = \text{H}$) and afloqualone (49; $R_1 = \text{fluoromethyl}$, $R_2 = \text{o-tolyl}$, $R_3 = \text{NH}_2$) [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 phenylacetyl 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 series 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-styrylquinazolin-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 quinazolinones

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, CH₃, C₂H₅) 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, CH₃, C₂H₅) 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(3*H*)-quinazolinones as anti-influenza A virus agents. Of these derivatives, compounds (84–87) revealed potent activity ($IC_{50} = 51.6\text{--}93.0\ \mu\text{M}$) 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- κ B pathway, although it was not as effective as ribavirin (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(1*H*)-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(1*H*)-one (**88**; R = F) and 2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (**88**; R = Cl) substituted compounds showed maximum inhibition on cathepsin B. Whereas for cathepsin H, 2,3-dihydro-2-(4-methylphenyl)quinazolin-4(1*H*)-one (**88**; R = Me) and 2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-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, NO₂, CH₃O, (CH₃)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, NO₂, CH₃O, (CH₃)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 (IC_{50} 181.0–474.5 μ M) than reference drug acarbose (IC_{50} = 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 (IC_{50} = 12.70 ± 1.87 , 28.54 ± 1.22 , 45.65 ± 4.28 , 72.28 ± 4.67 and 83.87 ± 5.12 μ M, respectively) compared with the reference standard acarbose (IC_{50} = 143.54 ± 2.08 μ M) [94].

Javaid et al. [95] reported a quinazolinone derivative (**111**; **Figure 15**) with IC_{50} value of 0.3 ± 0.01 μ M 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-(1H)-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(3*H*)-ones. Of these compounds, compound (119; **Figure 16**) is the most potent inhibitor of bovine liver DHFR (with IC_{50} = of 0.02 μ M). It was reported that 2-mercaptoquinazolin-4(3*H*)-one derivative is a potent bovine liver DHFR inhibitor (120; **Figure 16**) (IC_{50} = 0.01 μ M) [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 (IC_{50} = 42.9 ± 1.0 and 59.5 ± 1.9 μ M, 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(3*H*)-quinazolinones [105].

Qhobosheane et al. reported seven quinazolinone compounds ($IC_{50} < 1$ μ M) ascertained as potent and specific MAO-B inhibitors, among them the most potent inhibitor, 2-[(3-iodobenzyl)thio]quinazolin-4(3*H*)-one (128; **Figure 17**), with IC_{50} value of 0.142 μ M. Although these derivatives have been proved as reversible and competitive MAO-B inhibitor (K_i = 0.068 μ M), 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 ($IC_{50} = 2.9 \times 10^{-9}$ 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 anti-hypertensive drug by Lederle pharmaceutical company and was recently withdrawn from the market.

Fenquizonone'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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References

- [1] Polshettiwar V, Varma RS. Greener and sustainable approaches to the synthesis of pharmaceutically active heterocycles. *Current Opinion in Drug Discovery & Development*. 2007;**10**:723-737. PMID: 17987524
- [2] Jiang S, Zeng Q, Gettayacamin M, Tungtaeng A, Wannaying S, Lim A, et al. Antimalarial activities and therapeutic properties of febrifugine analogs. *Antimicrobial Agents and Chemotherapy*. 2005;**49**(3):1169-1176. DOI: 10.1128/AAC.49.3.1169-1176.2005
- [3] Ghorab MM, Ismail ZH, Abdalla M, Radwan AA. Synthesis, antimicrobial evaluation and molecular modelling of novel sulfonamides carrying a biologically active quinazoline nucleus. *Archives of Pharmacal Research*. 2013;**36**(6):660-670. DOI: 10.1007/s12272-013-0094-6
- [4] Ghoraba MM, Ismail ZH, Radwan AA, Abdalla M. Synthesis and pharmacophore modeling of novel quinazolines bearing a biologically active sulfonamide moiety. *Acta Pharmaceutica*. 2013;**63**:1-18. DOI: 10.2478/acph-2013-0006
- [5] Devi K, Kachroo M. Synthesis and antitubercular activity of some new 2, 3-disubstituted quinazolinones. *Der Pharma Chemica*. 2014;**6**:353-359. Available from: <http://derpharmachemica.com/archive.html>
- [6] El-Azab AS, El-Tahir KE. Design and synthesis of novel 7-aminoquinazoline derivatives: Antitumor and anticonvulsant activities. *Bioorganic & Medicinal Chemistry Letters*. 2012;**22**:1879-1885. PMID: 22326394
- [7] Radwan AA, Alanazi FK, Al-Dhfyhan A. Synthesis, and docking studies of some fusedquinazolines and quinazolines carrying biological active isatin moiety as cell cycle inhibitors of breast cancer cell lines. *Drug Research (Arzneimittelforschung)*. 2013;**63**:129-136. DOI: 10.1055/s-0032-1333306
- [8] Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Saeed A. Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification. *Bioorganic & Medicinal Chemistry*. 2016;**24**:2361-2381. DOI: 10.1016/j.bmc.2016.03.031. Epub 2016 March 18
- [9] Malamas MS, Millen J. Quinazolineacetic acids and related analogs as aldose reductase inhibitors. *Journal of Medicinal Chemistry*. 1991;**34**:1492-1502. DOI: 10.1021/jm00108a038
- [10] Priya MGR, Girija K, Ravichandran N. Invitro study of anti-inflammatory and antioxidant activity of 4-(3h)-quinazolinone derivatives. *Rasayan Journal of Chemistry*. 2011;**4**:418-424. Available from: rasayanjournal.co.in/vol-4/issue-2/28.pdf
- [11] Yousefi B, Azimi A, Majidinia M, Shafiei-Irannejad V, Badalzadeh R, Baradaran B, et al. Balaglitazone reverses P-glycoproteinmediated multidrug resistance via upregulation of PTEN in a PPAR γ dependent manner in leukemia cells. *Tumor Biology*. 2017;**39**:1-11. DOI: 10.1177/1010428317716501
- [12] Traxler P, Green J, Mett H, Séquin U, Furet P. Use of a pharmacophore model for the design of EGFR tyrosine kinase inhibitors: Isoflavones and 3-phenyl-4(1H)-quinolones. *Journal of Medicinal Chemistry*. 1999;**42**:1018-1026. DOI: 10.1021/jm980551o
- [13] Sahu M, Nerkar AG. In silico screening, synthesis and *in vitro* evaluation of some quinazolinone

derivatives as dihydrofolate reductase inhibitors for anticancer activity. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;**6**:193-199. Available from: <https://pdfs.semanticscholar.org/39de/8f154b7087ca23349b80a8aed6804c988e6a.pdf>

[14] Örfi L, Kökösi J, György S, Kövesdi I, Mak M, Teplan I, et al. Heterocondensed quinazolinones: Synthesis and protein-tyrosine kinase inhibitory activity of 3,4-dihydro-1H,6H-[1,4]oxazino[3,4-b]quinazolin-6-one derivatives. Bioorganic & Medicinal Chemistry. 1996;**4**:547-551. DOI: 10.1016/0968-0896(96)00040-5

[15] Hour MJ, Huang LJ, Kuo SC, Xia Y, Bastow K, Nakanishi Y, et al. 6-Alkylamino- and 2,3-dihydro-3'-methoxy-2-phenyl-4-quinazolinones and related compounds: Their synthesis, cytotoxicity, and inhibition of tubulin polymerization. Journal of Medicinal Chemistry. 2000;**43**:4479-4487. DOI: 10.1021/jm000151c

[16] Bouley R, Ding D, Peng Z, Bastian M, Lastochkin E, Song W, et al. Structure-activity relationship for the 4(3H)-quinazolinone antibacterials. Journal of Medicinal Chemistry. 2016;**59**(10):5011-5021. DOI: 10.1021/acs.jmedchem.6b00372

[17] Bojarski AJ, Kowalski P, Kowalska T, Duszynska B, Charakchieva-Minol S, Tatarczynska E, et al. Synthesis and pharmacological evaluation of new Arylpiperazines. 3-{4-[4-(3-chlorophenyl)-1-piperazinyl] butyl}-quinazolidin-4-one—A dual serotonin 5-HT_{1A}/5-HT_{2A} receptor ligand with an anxiolytic-like activity. Bioorganic & Medicinal Chemistry. 2002;**10**:3817-3827. DOI: 10.1016/S0968-0896(02)00349-8

[18] Grosso JA, Nichols DE, Kohli JD, Glock D. Synthesis of 2-(alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines and evaluation

as potential dopamine agonists. Journal of Medicinal Chemistry. 1982;**25**:703-708. DOI: 10.1021/jm00348a018

[19] Mohamed YA, El-galil A, Amrb C, Mohamed SF, Abdalla MM, Al-omar M, et al. Cytotoxicity and anti-HIV evaluations of some new synthesized quinazoline and thioxopyrimidine derivatives using 4-(thiophen-2-yl)3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thione as synthon. Journal of Chemical Sciences. 2012;**124**:693-702. DOI: 10.1007/s12039-012-0242-4

[20] Wattanapiromsakul C, Forster PI, Waterman PG. Alkaloids and limonoids from *Bouchardatia neurococca*: Systematic significance. Phytochemistry. 2003;**64**:609-615. DOI: 10.1016/S0031-9422(03)00205-X

[21] Asif M. Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. International Journal of Medicinal Chemistry. 2014;**2014**:1-27. DOI: 10.1155/2014/39563

[22] Kshirsagar UA. Recent developments in the chemistry of quinazolinone alkaloids. Organic & Biomolecular Chemistry. 2015;**13**(36):9336-9352. DOI: 10.1039/C5OB01379H

[23] Tee OS, Patil GV. Mechanism of bromination of 4(3H)-quinazolinone, its 3-methyl and its 1, 3-dimethyl derivatives in aqueous acidic solutions. The Journal of Organic Chemistry. 1976;**41**:838-845. DOI: 10.1021/jo00867a020

[24] Lowe JA, Archer RL, Chapin DS, Cheng B, Helweg D, Johnson JL, et al. Structure-activity relationship of quinazolinone inhibitors of calcium-independent phosphodiesterase. Medicinal Chemistry. 1991;**34**:624-628. DOI: 10.1021/jm00106a024

- [25] Ried W, Stephan W. Über eine neue synthese von substituierten 4-hydroxy-6,7-benzo-chinazolinen. *Chemische Berichte*. 1963;**96**:1218-1220. DOI: 10.1002/cber.19630960507
- [26] Ried W, Stephan W. Über die Reaktion von freier Anthranilsäure mit freien Imidsäureestern. *Chemische Berichte*. 1962;**95**:3042-3047. DOI: 10.1002/cber.19620951230
- [27] Ried W, Sinharay A. Über Nitroacetimidsäure-ester. *Chemische Berichte*. 1963;**96**:3306-3311. DOI: 10.1002/cber.19630961230
- [28] Rad-Moghadam K, Mohseni M. An expeditious and solvent-free route to the synthesis of 2-substituted quinazolin-4(3H)-ones under microwave conditions. *Journal of Chemical Research*. 2003;**2003**:487-488. DOI: 10.3184/030823403103174632
- [29] Li X, Lin Q, Wang L. One-pot solvent-free synthesis of 2,3-disubstituted 4(3H)-quinazolinones catalyzed by long-chain double SO₃H-functionalized Brønsted acidic ionic liquids under microwave irradiation. *Journal of the Iranian Chemical Society*. 2015;**12**:897-901. DOI: 10.1007/s13738-014-0553-0
- [30] Wuckelt J, Döring M, Beckert R, Langer P. Efficient synthesis of quinazolin-4-ones and axially chiral 2,2'-bisquinazolin-4-ones by reaction of anthranilic acid derived nucleophiles with oxalic acid-bis(imidoyl)chlorides. *Synlett*. 1999;**7**:1100-1102. DOI: 10.1055/s-1999-2760
- [31] Baker BR, Almaula PI. Nonclassical antimetabolites. X.1,2 a facile synthesis of 4-quinazolinone-2-carboxylic acid and the structure of Bogert's ammonium salt. *The Journal of Organic Chemistry*. 1962;**27**:4672-4674. DOI: 10.1021/jo01059a524
- [32] Shaterian HR, Rigi F. An efficient synthesis of quinazoline and xanthene derivatives using starch sulfate as a biodegradable solid acid catalysts. *Research on Chemical Intermediates*. 2015;**41**:721-738. DOI: 10.1007/s11164-013-1223-z
- [33] Zhang Z, Wang M, Zhang C, Zhang Z, Lua J, Wang F. The cascade synthesis of quinazolinones and quinazolines using an α -MnO₂ catalyst and tert-butyl hydroperoxide (TBHP) as an oxidant. *Chemical Communications*. 2015;**51**:9205-9207. DOI: 10.1039/C5CC02785C
- [34] Guo S, Li Y, Li T, Zhang W, Fan X. ChemInform abstract: Rapid assembly of quinazolinone scaffold via copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia: Application to the synthesis of the alkaloid tryptanthrin. *RSC Advances*. 2014;**4**:59289-59296. DOI: 10.1039/C4RA10799C
- [35] Connolly DJ, Cusack D, OSullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. *Tetrahedron* 2005;**61**:10153-10202. DOI: 10.1016/j.tet.2005.07.010
- [36] Yan Y, Xu Y, Niu B, Xie H, Liu Y. I₂-catalyzed aerobic oxidative C(sp³)-H amination/C-N cleavage of tertiary amine: Synthesis of quinazolines and quinazolinones. *The Journal of Organic Chemistry*. 2015;**80**:5581-5587. DOI: 10.1021/acs.joc.5b00474
- [37] Natte K, Neumann H, Wu X-F. Pd/C as an efficient heterogeneous catalyst for carbonylative four-component synthesis of 4(3H)-quinazolinones. *Catalysis Science & Technology*. 2015;**5**:4474-4480. DOI: 10.1039/C5CY00907C
- [38] Mizuno T, Okamoto N, Ito T, Miyata T. Synthesis of 2,4-dihydroxyquinazolines using carbon dioxide in the presence of DBU under mild conditions. *Tetrahedron Letters*. 2000;**41**:1051-1053. DOI: 10.1016/S0040-4039(99)02231-5

- [39] Revathy K, Lalitha A. p-TSA-catalyzed synthesis of spiroquinazolinones. *Journal of the Iranian Chemical Society*. 2015;**12**:2045-2049. DOI: 10.1007/s13738-015-0680-2
- [40] Tajbakhsh M, Ramezanpour S, Balalaie S, Bijanzadeh HR. Novel one-pot three-component reaction for the synthesis of functionalized spiroquinazolinones. *Journal of Heterocyclic Chemistry*. 2015;**52**:1559-1564. DOI: 10.1002/jhet.2138
- [41] Yang X, Wu M, Sun S, Huang C, Guo H, Wang J, et al. Synthesis of tricyclic quinazolinones via intramolecular cyclization of 3-(2-aminoalkyl)-2-(phenylamino)quinazolin-4(3H)-ones. *Molecular Diversity*. 2016;**20**:551-556. DOI: 10.1007/s11030-015-9636-9
- [42] Reddy BVS, Reddy DM, Reddy GN, Reddy MR, Reddy VK. Domino oxidative cyclization of 2-aminoacetophenones for the one-pot synthesis of tryptanthrin derivatives. *European Journal of Organic Chemistry*. 2015;**2015**:8018-8022. DOI: 10.1002/ejoc.201501079
- [43] Foldesi T, Dancsó A, Simig G, Volk B, Milen M. Synthesis of a new tetracyclic ring system: Pyrrolotriazepinoquinazolinone derivatives. *Tetrahedron*. 2015;**71**:6759-6763. DOI: 10.1016/j.tet.2015.07.033
- [44] Yuan D, Kong H-H, Ding M-W. New efficient synthesis of 1H-pyrimido[2,1-b]quinazoline-2,6-diones via a tandem aza-Wittig/nucleophilic addition/intramolecular cyclization/isomerization reaction starting from the Baylis-Hillman adducts. *Tetrahedron*. 2015;**71**:419-423. DOI: 10.1016/j.tet.2014.12.006
- [45] Wang H, Ganesan A. Total synthesis of the cytotoxic alkaloid luotonin a. *Tetrahedron Letters*. 1998;**39**:9097-9098. DOI: 10.1016/S0040-4039(98)02004-8
- [46] Venkatesh R, Ramaiah MJ, Gaikwad HK, Janardhan S, Bantu R, Nagarapu L, et al. Luotonin-a based quinazolinones cause apoptosis and senescence via HDAC inhibition and activation of tumor suppressor proteins in HeLa cells. *European Journal of Medicinal Chemistry*. 2015;**94**:87-101. DOI: 10.1016/j.ejmech.2015.02.057
- [47] González-Ruiz V, Pascua I, Fernández-Marcelo T, Ribelles P, Bianchini G, Sridharan V, et al. B-ring-aryl substituted luotonin a analogues with a new binding mode to the topoisomerase 1-DNA complex show enhanced cytotoxic activity. *PLoS One*. 2014;**9**:e95998. DOI: 10.1371/journal.pone.0095998
- [48] Cagir A, Jones SH, Eisenhauer BM, Gao R, Hecht SM. Synthesis and biochemical properties of E-ring modified luotonin A derivatives. *Bioorganic & Medicinal Chemistry Letters*. 2004;**2004**(14):2051-2054. DOI: 10.1016/j.bmcl.2004.02.069
- [49] Jiao RH, Xu S, Liu JY, Ge HM, Ding H, Xu C, et al. Chaetominine, a cytotoxic alkaloid produced by endophytic chaetomium sp. IFB-E015. *Organic Letters*. 2006;**8**:5709-5712. DOI: 10.1021/ol062257t
- [50] Song F, Ren B, Yu K, Chen C, Guo H, Yang N, et al. Quinazolin-4-one coupled with pyrrolidin-2-iminium alkaloids from marine-derived fungus *penicillium aurantiogriseum*. *Marine Drugs*. 2012;**10**:1297-1306. DOI: 10.3390/md10061297
- [51] Buttachon S, Chandrapatya A, Manoch L, Silva A, Gales L, Bruyère C, et al. Sartorymensin, a new indole alkaloid, and new analogues of tryptoquivaline and fiscalins produced by *Neosartorya siamensis* (KUFC 6349). *Tetrahedron*. 2012;**68**:3253-3262. DOI: 10.1016/j.tet.2012.02.024
- [52] Rao Y, Liu H, Gao L, Yu H, Tan JH, Ou TM, et al. Discovery of natural

alkaloid bouchardatine as a novel inhibitor of adipogenesis/lipogenesis in 3T3-L1 adipocytes. *Bioorganic & Medicinal Chemistry*. 2015;**23**:4719-4727. DOI: 10.1016/j.bmc.2015.05.057

[53] Xin ZH, Fang Y, Du L, Zhu T, Duan L, Chen J, et al. Aurantiomides A-C, quinazoline alkaloids from the sponge-derived fungus *Penicillium aurantiogriseum* SP0-19. *Journal of Natural Products*. 2007;**70**:853-855. DOI: 10.1021/np060516h

[54] Mahdavi M, Pedrood K, Safavi M, Saeedi M, Pordeli M, Ardestani SK, et al. Synthesis and anticancer activity of N-substituted 2-arylquinazolinones bearing trans-stilbene scaffold. *European Journal of Medicinal Chemistry*. 2015;**95**:492-499. DOI: 10.1016/j.ejmech.2015.03.057

[55] Murahari MS, Prakash RSJ, Kar SS, Kumar TG, Raj VP, Raju DS. Synthesis, characterization and in vitro anti-cancer activity of quinazolinone derivatives. *Journal of Pharmacy Research*. 2012;**5**:2743-2746. Available from: jpr.solutions.info/newfiles/journal-file-56b9f4b60d7c57.58954497.pdf

[56] Noolvi MN, Patel HM, Bhardwaj V, Chauhan A. Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: Search for anticancer agent. *European Journal of Medicinal Chemistry*. 2011;**46**:2327-2346. Available from: <http://dx.doi.org/10.1016/j.ejmech.2011.03.015>. PMID: 21458891

[57] Noolvi MN, Patel HM. Synthesis, method optimization, anticancer activity of 2, 3, 7-trisubstituted quinazoline derivatives and targeting EGFR-tyrosine kinase by rational approach: 1st cancer update. *Arabian Journal of Chemistry*. 2013;**6**:35-48. DOI: 10.1016/j.arabjc.2010.12.031

[58] Zayed MF, Ahmed HEA, Ihmaid S, Omar A-SM, Abdelrahim AS. Synthesis

and screening of some new fluorinated quinazolinone-Sulphonamide hybrids as anticancer agents. *Journal of Taibah University Medical Sciences*. 2015;**10**:333-339. DOI: 10.1016/j.jtumed.2015.02.007

[59] Malinowski Z, Fornal E, Nowak M, Kontek R, Gajek G, Borek B. Synthesis and biological evaluation of some amino- and sulfanyl-3H-quinazolin-4-one derivatives as potential anticancer agents. *Monatshefte fuer Chemie*. 2015;**146**:1723-1731. DOI: 10.1007/s007

[60] Ahmed MF, Belal A. Design, synthesis, and molecular docking studies of 2-(furan-2-yl)-quinazolin-4-one derivatives as potential antiproliferative agents. *Archiv der Pharmazie-Chemistry in Life Sciences*. 2015;**348**:487-497. DOI: 10.1002/ardp.201400468

[61] Ahmed MF, Belal A. Synthesis, characterization, and biological evaluation of new quinazolin-4-one derivatives hybridized with pyridine or pyran moiety. *Research on Chemical Intermediates*. 2016;**42**:659-671. DOI: 10.1007/s11164-015-2048-8

[62] Vane J, Botting R. Inflammation and the mechanism of action of anti-inflammatory drugs. *The FASEB Journal*. 1987;**1**(2):89-96. PMID: 3111928

[63] Amin KM, Kamel MM, Anwar MM, Khedr M, Syamb YM. Synthesis, biological evaluation and molecular docking of novel series of spiro [(2H,3H) quinazoline-2,10-cyclohexan]-4(1H)-one derivatives as anti-inflammatory and analgesic agents. *European Journal of Medicinal Chemistry*. 2010;**45**:2117-2131. Available from: <http://dx.doi.org/10.1016/j.ejmech.2009.12.078>. PMID: 20137837

[64] Abbas SE, Awadallah FM, Ibrahim NA, Said EG, Kamel GM. New quinazolinonepyrimidine hybrids: Synthesis, anti-inflammatory, and

- ulcerogenicity studies. *European Journal of Medicinal Chemistry*. 2012;**53**:141-149. DOI: 10.1016/j.ejmech.2012.03.050
- [65] Hemalath K, Madhumith G, Vasavi CS, Munusami PJ. 2, 3-Dihydroquinazolin-4 (1H)-ones: Visible light mediated synthesis, solvatochromism and biological activity. *Journal of Photochemistry and Photobiology B: Biology* 2015;**143**:139-147. DOI: 10.1016/j.jphotobiol.2014.12.028
- [66] Manivannan E, Chaturvedi SC. Analogue-based design, synthesis and molecular docking analysis of 2,3-diaryl quinazolinones as non-ulcerogenic anti-inflammatory agents. *Bioorganic & Medicinal Chemistry*. 2011;**19**:4520-4528. DOI: 10.1016/j.bmc.2011.06.019
- [67] Mohamed MS, Kamel MM, Kassem EMM, Abotaleb N, Nofal SM, AhmedMF. Novel 3-(p-Substitutedphenyl)-6-bromo-4 (3H)-quinazolinone derivatives of promising anti-inflammatory and analgesic properties. *Acta Poloniae Pharmaceutica*. 2009;**66**(5):487-500. PMID: 19894645
- [68] Rakesh KP, Ramesh S, Kumar HMM, Chandan S, Gowda DC. Quinazolinones linked amino acids derivatives as a new class of promising antimicrobial, antioxidant and anti-inflammatory agents. *European Journal of Chemistry*. 2015;**6**:254-260. DOI: 10.5155/eurjchem.6.3.254-260.1233
- [69] El-Azab AS, Eltahir KE. Synthesis and anticonvulsant evaluation of some new 2,3,8-trisubstituted-4(3H)-quinazoline derivatives. *Bioorganic & Medicinal Chemistry Letters*. 2011;**22**:327-333. DOI: 10.1016/j.bmcl.2011.11.007
- [70] Al-Salem HS, Hegazy GH, El-Taher KF, El-Messery SM, Al-Obaid AM, El-Subbagh HI. Synthesis, anticonvulsant activity and molecular modeling study of some new hydrazinecarbothioamide, benzenesulfonohydrazide, and phenacylaceto hydrazide analogues of 4(3H)-quinazolinone. *Bioorganic & Medicinal Chemistry Letters*. 2015;**25**:1490-1499. DOI: 10.1016/j.bmcl.2015.02.025
- [71] Popova E, Kostov M, Kупenova P. Effects of dopamine D1 receptor blockade on the ERG b- and d-waves during blockade of ionotropic GABA receptors. *Eye and Vision* (London). 2016;**3**:32. DOI: 10.1186/s40662-016-0064-4
- [72] Abuelizz HA, Dib RE, Marzouk M, Anouar EH, A Maklad Y, N Attia H, Al-Salahi R. Molecular Docking and Anticonvulsant Activity of Newly Synthesized Quinazoline Derivatives. *Molecules*. 2017;**22**:1094. DOI: 10.3390/molecules22071094
- [73] Jatav V, Mishra P, Kashaw S, Stables JP. CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. *European Journal of Medicinal Chemistry*. 2008;**43**:1945-1954. DOI: 10.1016/j.ejmech.2007.12.003
- [74] Patel NB, Patel JC. Synthesis and antimicrobial activity of Schiff bases and 2-zetidinones derived from quinazolin-4(3H)-one. *Arabian Journal of Chemistry*. 2011;**4**:403-411
- [75] Jantová S, Stankovsky S, Spirkova S. *In vitro* antibacterial activity of ten series of substituted quinazolines. *Biologia Bratislava*. 2004;**59**:741-752
- [76] Vani KV, Ramesh G, Rao CV. Synthesis of new triazole and oxadiazole derivatives of quinazolin-4(3H)-one and their antimicrobial activity. *Journal of Heterocyclic Chemistry*. 2016;**53**:719-726. DOI: 10.1002/jhet.2353
- [77] Kohli D, Hashim SR, Vishal S, Sharma M, Singh AK. Synthesis and

- antibacterial activity of quinazolinones derivatives. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2009;**1**:163-169. Available from: <https://innovareacademics.in/journal/ijpps/Vol%201%20Issue%201/130.pdf> [Accessed: 09 November 2019]
- [78] Sowjanya C, Bharathi VR, Devi GK, Rajitha G. Synthesis and evaluation of some novel 3-[5-phenyl-1,3,4-oxadiazole-2-yl]-2-(substituted styryl)-quinazoline-4(3H)-ones for antibacterial activity. *Journal of Chemical and Pharmaceutical Research*. 2011;**3**:212-216. Available form: www.jocpr.com [Accessed: 09 September 2019]
- [79] El-Hashash MA, Guirgui DB, El-Badry YA. Synthesis and evaluation of new 2, 3- and 2, 4-disubstituted quinazoline derivatives as potential antibacterial and antifungal agents. *Der Pharma Chemica*. 2011;**3**:147-159. Available from: <http://derpharmachemica.com/archive.html> [Accessed: 09 September 2019]
- [80] Zhu S, Wang J, Chandrashekar G, Smith E, Liu X, Zhang Y. Synthesis and evaluation of 4-quinazolinone compounds as potential antimalarial agents. *European Journal of Medicinal Chemistry*. 2010;**45**:3864-3869. DOI: 10.1016/j.ejmech.2010.05.040
- [81] Birhan YS, Bekhit AA, Hymete A. In vivo antimalarial evaluation of some 2,3-disubstituted-4(3H)-quinazolinone derivatives. *BMC Research Notes*. 2015;**8**:589. DOI: 10.1186/s13104-015-1578-x
- [82] Wang Z, Wang M, Yao X, Li Y, Tan J, Wang L, et al. Design, synthesis and antiviral activity of novel quinazolinones. *European Journal of Medicinal Chemistry*. 2012;**53**:275-282. DOI: 10.1016/j.ejmech.2012.04.010
- [83] Gao X, Cai X, Yan K, Song B, Gao L, Chen Z. Synthesis and antiviral bioactivities of 2-aryl- or 2-methyl-3-(substituted-benzalamino)-4(3H)-quinazolinone derivatives. *Molecules*. 2007;**12**:2621-2642. DOI: 10.3390/12122621
- [84] Liu S, Wang W, Jiang L, Wan S, Zhang L, Yu R, et al. 2-Pyridinyl-4(3H)-quinazolinone: A scaffold for anti-influenza a virus compounds. *Chemical Biology & Drug Design*. 2015;**86**:1221-1225. DOI: 10.1111/cbdd.12589
- [85] Carlos L-O, Lynn M. Emerging roles of proteases in tumour suppression. *Nature Reviews. Cancer*. 2007;**7**:800-808. DOI: 10.1038/nrc2228
- [86] Singh M, Raghav N. 2,3-Dihydroquinazolin-4(1H)-one derivatives as potential non-peptidyl inhibitors of cathepsins B and H. *Bioorganic Chemistry*. 2015;**59**:12-22. DOI: 10.1016/j.bioorg.2015.01.005
- [87] Raghav N, Singh M. Design, synthesis and docking studies of bischalcones based quinazoline-2(1H)-ones and quinazoline-2(1H)-thiones derivatives as novel inhibitors of cathepsin B and cathepsin H. *European Journal of Pharmaceutical Sciences*. 2014;**54**:28-39. DOI: 10.1016/j.ejps.2013.12.018
- [88] Pommier Y. DNA topoisomerase I inhibitors: Chemistry, biology, and interfacial inhibition. *Chemical Reviews*. 2009;**109**:2894-2902. DOI: 10.1021/cr900097c
- [89] Liang JL, Cha HC, Jahng Y. Recent advances in the studies on luotonins. *Molecules*. 2011;**16**:4861-4883. DOI: 10.3390/molecules16064861
- [90] Ibric A, Eckerstorfer S, Eder M, Louko I, Tunjic L, Heffeter P, et al. Position-selective synthesis and biological evaluation of four isomeric A-ring amino derivatives of the alkaloid luotonin A. *Molecules*. 2019;**24**:716. DOI: 10.3390/molecules24040716

- [91] Khadka DB, Tran GH, Shin S, Nguyen HTM, Cao HT, Zhao C, et al. Substituted 2-arylquinazolinones: Design, synthesis, and evaluation of cytotoxicity and inhibition of topoisomerases. *European Journal of Medicinal Chemistry*. 2015;**103**:69-79. DOI: 10.1016/j.ejmech.2015.08.040
- [92] Kamata JJ, Okada T, Kotake YKN, Uenaka T, Yamaguchi A, Tsukahara K, et al. Synthesis and evaluation of novel pyrimidoacridone, -phenoxazine, and -carbazole as topoisomerase II inhibitors. *Chemical & Pharmaceutical Bulletin (Tokyo)*. 2004;**52**:1071-1081. DOI: 10.1248/cpb.52.1071
- [93] Saeedi M, Mohammadi-Khanaposhtani M, Pourrabia P, Razzaghi N, Ghadimi R, Imanparast S, et al. Design and synthesis of novel quinazolinone-1,2,3-triazole hybrids as new anti-diabetic agents: *In vitro* α -glucosidase inhibition, kinetic, and docking study. *Bioorganic Chemistry*. 2019;**83**:161-169. DOI: 10.1016/j.bioorg.2018.10.023
- [94] Abuelizz HA, Anouar E, Ahmad R, Azman NIIN, Marzouk M, Al-Salah R. Triazoloquinazolines as a new class of potent α -glucosidase inhibitors: in vitro evaluation and docking study. *PLoS One*. 2019;**14**(8):e0220379. DOI: 10.1371/journal.pone.0220379
- [95] Javaid K, Saad SM, Rasheed S, Moin ST, Syed N, Fatima I, et al. 2-Arylquinazolin-4(3H)-ones: A new class of α -glucosidase inhibitors. *Bioorganic & Medicinal Chemistry*. 2015;**23**:7417-7421. DOI: 10.1016/j.bmc.2015.10.038
- [96] Rahman MU, Rathore A, Siddiqui AA, Parveen G, Yar MS. Synthesis and characterization of quinazolinoderivatives: Search for hybrid molecule as diuretic and antihypertensive agents. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2014;**29**:733-743. DOI: 10.3109/14756366.2013.845820
- [97] Stroud RM, Santi DV, Hardy LW, Montfort WR, Jones MO, Finer-Moore JS. Atomic structure of thymidylate synthase: Target for rational drug design. *Science*. 1987;**235**:448-455. DOI: 10.1126/science.3099389
- [98] Peters GJ, Backus HH, Freemantle S, van Triest B, Codacci-Pisanelli G, van der Wilt CL, et al. Induction of thymidylate synthase as a 5-fluorouracil resistance mechanism. *Biochimica et Biophysica Acta*. 2002;**1587**(2-3):194-205. DOI: 10.1016/S0925-4439(02)00082-0
- [99] Wang M, Yang J, Yuan M, Xue L, Li H, Tian C, et al. Synthesis and antiproliferative activity of a series of novel 6-substituted pyrido[3,2-d]pyrimidines as potential nonclassical lipophilic antifolates targeting dihydrofolate reductase. *European Journal of Medicinal Chemistry*. 2017;**128**:88-97. DOI: 10.1016/j.ejmech.2017.01.033
- [100] El-Messery SM, Hassan GS, Nagi MN, Habib ESE, Al-Rashood ST, El-Subbagh HI. Synthesis, biological evaluation and molecular modeling study of some new methoxylated 2-benzylthio-quinazoline-4(3H)-ones as nonclassical antifolates. *Bioorganic & Medicinal Chemistry Letters*. 2016;**26**:4815-4823. DOI: 10.1016/j.bmcl.2016.08.022
- [101] El-Gazzar YI, Georgey HH, El-Messery SM, Ewida HA, Hassan GS, Raafat MM, et al. Synthesis, biological evaluation and molecular modeling study of new (1,2,4-triazole or 1,3,4-thiadiazole)-methylthio-derivatives of quinazolin-4(3H)-one as DHFR inhibitors. *Bioorganic Chemistry*. 2017;**72**:282-292. DOI: 10.1016/j.bioorg.2017.04.019

- [102] Javaid S, Saad SM, Perveen S, Khan KM, Choudhary MI. 2-Arylquinazolin-4(3H)-ones: A novel class of thymidine phosphorylase inhibitors. *Bioorganic Chemistry*. 2015;**63**:142-151. DOI: 10.1016/j.bioorg.2015.10.006
- [103] Lum CT, Stahl SM. Opportunities for reversible inhibitors of monoamine oxidase-A (RIMAs) in the treatment of depression. *CNS Spectrums*. 2012;**17**(3):107-120. DOI: 10.1017/s1092852912000594
- [104] Fernandez HH, Chen JJ. Monoamine oxidase-B inhibition in the treatment of Parkinson's disease. *Pharmacotherapy*. 2007;**27**(12 Pt 2):174S-185S. DOI: 10.1592/phco.27.12part2.174S
- [105] Mostert S, Petzer A, Petzer JP. Indanones as high-potency reversible inhibitors of monoamine oxidase. *ChemMedChem*. 2015;**10**(5):862-873. DOI: 10.1002/cmdc.201500059
- [106] Qhobosheane MA, Petzer A, Petzer JP, Legoabe LJ. Synthesis and evaluation of 2-substituted 4(3H)-quinazolinone thioether derivatives as monoamine oxidase inhibitors. *Bioorganic & Medicinal Chemistry*. 2018;**26**:5531-5537. DOI: 10.1016/j.bmc.2018.09.032
- [107] Khattab SN, Haiba NS, Asal AM, Bekhit AA, Amer A, Abdel-Rahman HM, et al. Synthesis and evaluation of quinazoline amino acid derivatives as mono amine oxidase (MAO) inhibitors. *Bioorganic & Medicinal Chemistry*. 2015;**23**:3574-3585. DOI: 10.1016/j.bmc.2015.04.021
- [108] Hughes AN, Rafi I, Griffin MJ. Phase I studies with the nonclassical antifolate nolatrexed dihydrochloride (AG337, THYMITAQ) administered orally for 5 days. *Clinical Cancer Research*. 1999;**5**(1):111-118. PMID: 9918208
- [109] Cohen E, Klarberg B, Vaughan JR. Quinazolinone sulfonamides. A new class of diuretic agents. *Journal of the American Chemical Society*. 1960;**82**:2731-2735. DOI: 10.1021/ja01496a020
- [110] Maggi GC, Donati C, Gueli AD. Single dose pharmacokinetics of fenquizone in healthy volunteers. *Arzneimittel-Forschung*. 1985;**35**:994-998. PMID: 4026929
- [111] Guedes PM, Urbina JA, de Lana M, Afonso LC, Veloso VM, Tafuri WL, et al. Activity of the new triazole derivative albaconazole against *Trypanosoma* (Schizotrypanum) *cruzi* in dog hosts. *Antimicrobial Agents and Chemotherapy*. 2004;**48**(11):4286-4292. DOI: 10.1128/AAC.48.11.4286-4292.2004
- [112] McLaughlin NP, Evans P. Dihydroxylation of vinyl sulfones: Stereoselective synthesis of (+)- and (-)-febrifugine and halofuginone. *The Journal of Organic Chemistry*. 2010;**75**(2):518-521. DOI: 10.1021/jo902396m
- [113] Ochiai T, Ishida R. Pharmacological studies on 6-amino-2-fluoromethyl-3-(O-tolyl)-4(3H)-quinazolinone (afloqualone), a new centrally acting muscle relaxant. (II) Effects on the spinal reflex potential and the rigidity. *Japanese Journal of Pharmacology*. 1982;**32**(3):427-438. DOI: 10.1254/jjp.32.427
- [114] Kobayashi Y. Capsaicin-like anti-obese activities of evodiamine from fruits of *Evodia rutaecarpa*, a vanilloid receptor agonist. *Planta Medica*. 2001;**67**(7):628-633. DOI: 10.1055/s-2001-17353