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Quinazolines and Quinazolinones as Pharmacophores: Synthetic Approaches and Biomedical Applications of Quinazolines and Their Analogies

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Abstract

Quinazoline and their based scaffolds can be defined as nitrogenious heterocyclic motifs with distinguished biomedical and chemical applications. Quinazoline and their derivatives comprise a family of more than 200 naturally occurred alkaloids. Recently, novel quinazolinone based molecules have been investigated, applied in designing numerous efficient protocols to produce more biomedical and pharmaceutical active scaffolds. This review evaluated the recent advanced protocols investigated for designing and synthesis quinazolines and their based scaffolds. Additionally, estimated the biomedical and therapeutical activities of these molecules. The information included in this review would assist the chemical and biomedical researches in designing novel quinazoline analogues can be considered as drug like candidates in different pharmaceutical approaches.

Keywords: Quinazolines; quinazolinones, biomedical applications.

Introduction

Quinazolines are 1,3-diazanaphthalenes named also benzo[a]pyrimidines, phenmiazine or 5,6-benzopyrimidines; their oxo-analogies were known as quinazolinone. Quinazolinones are made by fusion of benzene ring with 4-pyrimidinone, 2-pyrimidinone, or a 2,4-pyrimidinion ring (figure **1**). They are a major class of N-fused heterocyclic compounds with a wide range of biological functions. Quinazoline and quinazolinone based molecules have gained a significant interest in organic and medicinal chemistry owing to their high natural abundance and unique vital range of pharmaceutical and biological applications including antimicrobial, anti-HIV, anticancer, anti-inflammatory, antifungal, anticoccidial, anticonvulsant, antimutagenic, antioxidant, antidiabetic and antihypertensive activities[1–9]. They revealed a variety of biomedical functions as Ligands to GABAA Receptor subtype in the central nervous system [10–12], as EGFR kinase inhibitors [13]. Also, some of them can act as multi-kinase inhibitor for the treatment of AML and solid tumors [14]. Quinazolines have potent adrenergic blocking activities.

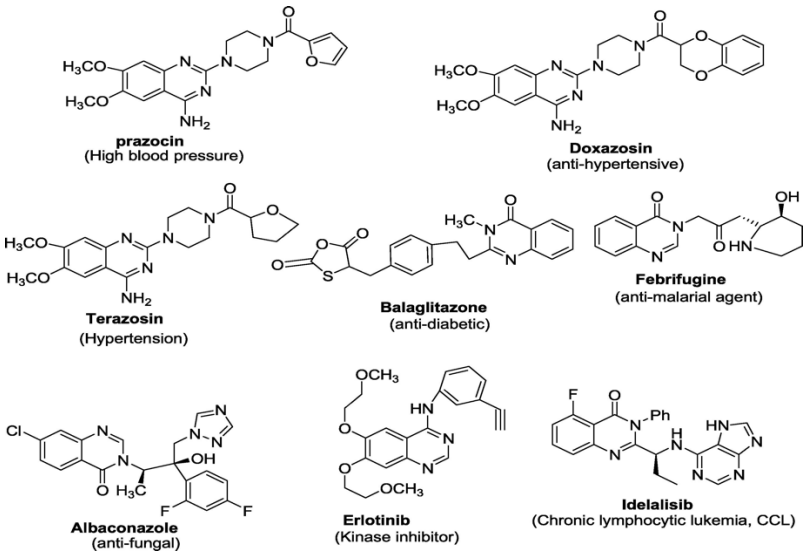

Figure 1. Chemical composition of some Quinazolines, quinazolinone and quinazolinedione based scaffolds, [21]**, This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).**

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Meanwhile, Quinazolin-2,4(1*H*,3*H*)-diones are a type of pharmacophore scaffolds [3,8,15,16] that widely spread in nature in different biologically active natural products; they are the core structure of more than 200 natural alkaloids extracted from different maicroorganisms and plants families including, *Peganum nigellastrum, Bouchardatia neurococca, Bacillus cereus and Dichroa febrifuga*.[17,18]. Some quinazoline derivatives [19,20] with distinguished biomedical and biological activities were illustrated in **figure1**.

2. Synthesis of quinazoline scaffold analogues

2.1. Metal-catalysed synthesis of quinazolines

2.1.1. Quinazolines production *via C–H* activation and *C–N* coupling reactions

Otherwise, transition metal-catalyzed *C-H* functionalization and activation approaches are considered of the most promising and simple routes for synthesis of quinazoline analogies comparing to the covenantal methods with no need for pre-functionalizing the starting materials. Paul and co-workers [22] have developed novel quinazoline derivatives in a good yield via the atom-efficient reaction of 2-aminobenzyl alcohol with the appropriate nitriles through the biomimetic dehydrogenative condensation/coupling pathway (**Figure 2**). Singlet biradical Ni(II) with two anti-ferromagnetically connected singlet biradical diamine was utilized as catalyst in this reaction.

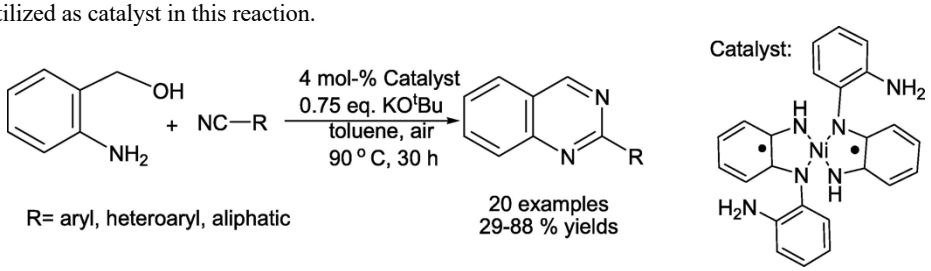


Figure 2. Singlet diradical diamine Ni(II) catalyzed synthesis of aryl quinazolines. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

2.1.2. Quinazolines synthesis utilizing ferrous chloride as catalyst

Chen et al., [23] (**Figure 3**)has developed a new group of quinazolines through the reaction of 2-alkylamino benzonitriles with selected organometallic reagents affording a series of 2-alkylamino N–H ketimine species followed by $FeCl_2$-catalysed C(sp^3)-H oxidation of the alkyl group employing tert-BuOOH, intramolecular formation of C-N bond, then aromatization giving a broad range of 2,4-disubstituted quinazoline analogs in good to excellent (43–86 %).

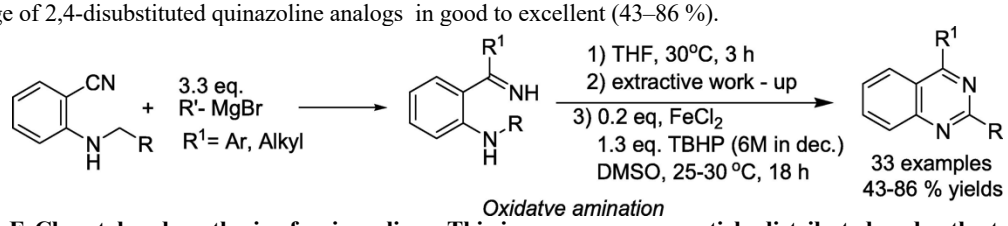
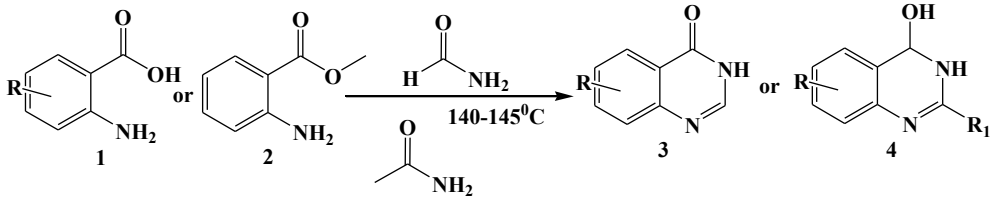


Figure 3. $FeCl_2$-catalysed synthesis of quinazolines. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY)

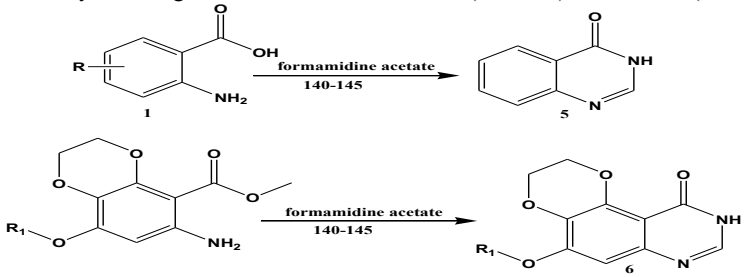
2.2. Non-metal catalyzed quinazolines derivatives synthesis

Cyclization reaction of the anthranilic acid (**1**) or ester anthranilate (**2**) with acetamide or formamide in acidic medium yielded the quinazolines (**3**, **4**)[24–26] either as intermediates or main products in a good yield. (**Scheme 1**).



Scheme 1: Synthesis of quinazolines 3 and 4

Another study discussed the synthesis of quinazolineone analogues (**5**, **6**) and other fused analogues from formamidine acetate and anthranilic acid (**1**) in the presence of catalyst. All the reactions are performed under reflux giving the desired quinazolineones in short time in yields ranged from medium to excellent (84-95 %) as shown in (**Scheme 2**).



Scheme 2. Synthesis of quinazolines/quinazolineones from substituted anilines, pyrazole amine, and different amidines[27–30]

2.3. Green and sustainable approaches in synthesis of quinazoline and quinazolinone derivatives

Numerous research papers are designed to describe the different traditional methods for the synthesis of quinazolines and their derivatives using various reaction conditions such as multistep reactions, expensive catalysts, high temperature, toxic organic solvents, etc. But moving toward the safest ecofriendly approaches, utilizing of nanocatalysts have been emerged recently as powerful conditions owing to their distinguished characters, high surface area which increase the active sites exposed to the reactants which reduce the quality of the catalyst requirements and increase the selectivity. In addition, alternative sources of energy were utilized in the quinazolinone derivatives eco-friendly synthesis to enhance the recyclability and efficiency. Different green approaches are established and reported for efficient synthesis of quinazoline and quinazolinone derivatives (**Figure 4**).[31–34]

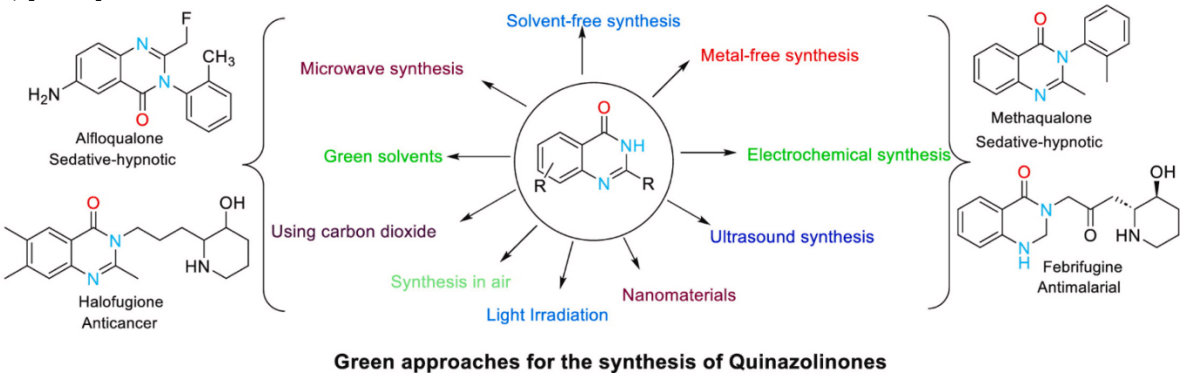


Figure 4: Eco-friendly methods for synthesis of quinazoline derivatives. Copyright 2025. Reproduced with permission from Elsevier[31]**,** *https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=d12c53d8-3f0e-4869-a68c-716ebf78f4f*

2.3.1. Synthesis of quinaqzolines *via* Niementowski reaction or by Besson's microwave conditions

4 (3*H*)-quinazolinone was synthesized for the first time in 1869 via the reaction of anthranilic acid with cyanogenes by Griess[35] after that the field attracted various chemical researchers to establish more and more conventional protocols for synthesizing novel quinazoline analogues[36–39]. Most of these approaches applied the Niementowski reaction, the fusion of anthranilic acid analogues with amides at temperature ranged from 130 to 150 °C. the reaction was passed through the formation of an *o*-amidobenzamide intermediate [40] (**Figure 5**). However, the products obtained from this reaction is impure and the contamination is very difficult to be removed neither via recrystallization nor by the column chromatography. In addition the yield of this reaction is very low[40]. To improve the yield and speed up the reaction time, Besson *et al.* used the microwave irradiation in the synthesis of the 4(3*H*)- quinazolinones through Niementowski reaction[41][42][43][44] (**Figure 5**).

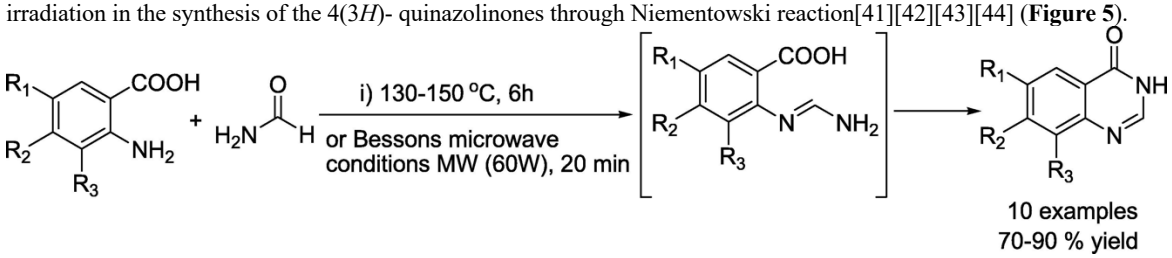


Figure 5. Synthesis of quinazoline by Niementowski reaction or by Besson's microwave conditions. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

3. Biological Importance of Quinazolines & quinazolinones

3.1. Quinazolines as Inhibitors to Epidermal growth factor receptor EGFR and Vascular Endothelial Growth Factor Receptor (VEGFR-2)

The metastasis and the tumor growth are closely associated with the angiogenesis and the tumor cell differentiation and maturation which controlled by a number of kinases proteins such as Raf, Ras and VEGER. Angiogenesis is a vital process in which a new blood vessels were formed from the originally pre-existing ones to support the tumor cells with both ntrients and oxygen to survive and maturation[45–47]. The EGFR which is known as the epidermal growth factor receptors are transmembrane glycoproteins, Epidermal growth factor receptors (EGFR) and Vascular Endothelial Growth Factor Receptors (VEGFR2) are potentially emerged as promising attractive targets for cancer treatment. They have a fundamental role in the tumor development, angiogenesis and also metastasis. EGFR was first discovered in 1968 [48] is the first member of the ErbB proteins family that is a family of four tyrosine kinases named ErbB-1(or HER1/EGFR), ErbB-2(or HER2), ErbB-3(or HER3) and ErbB-4(or HER4) [49]. Their crystallographic data revealed structural similarity between the four proteins which make the designing of drug specific for each protein is a challenge. EGFR is a protein with an extracellular binding site, a transmembrane region that is helical and an intracellular tyrosine kinase domain (**figure 6**).

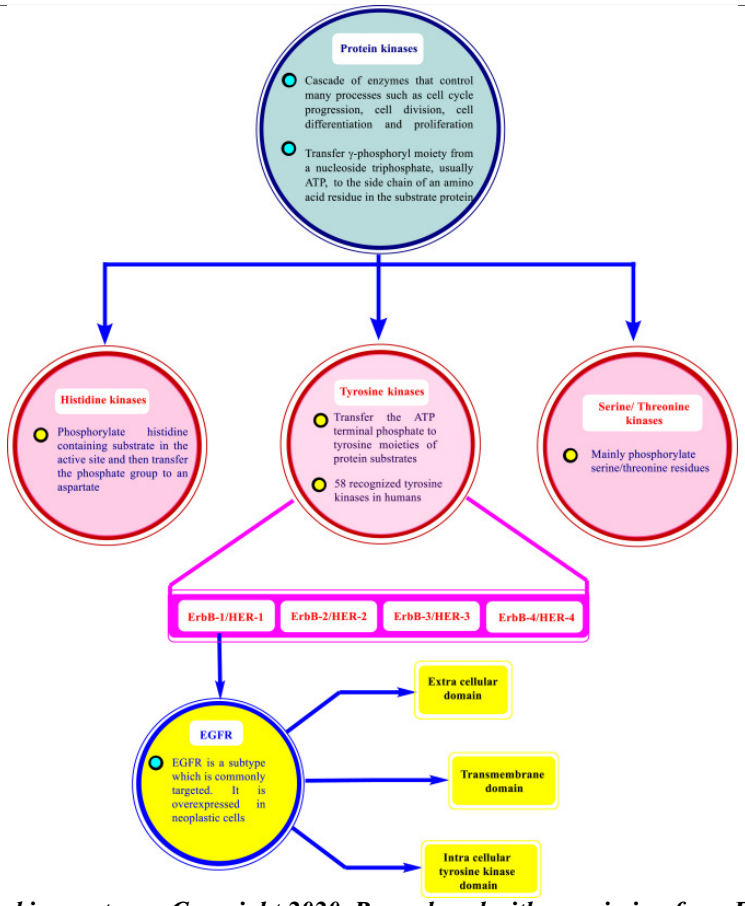


Figure 6. protein kinases types. Copyright 2020. Reproduced with permission from Elsevier, https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=77416009-f590-4ef0-bbb1-47999bf69141

It was found that the overexpression of EGFR was associated with the progression and occurrence of carcinomas as breast cancer, lung cancer and pancreatic cancer. EGFR receptors were recognized as important target in the management of solid tumors. In this regard, the inhibition of them represents a promising approach in the field of cancer treatment. Additionally, it was found that the main receptor which activated by the VEGF-A and VEGFR-2 plays a fundamental role in the tumor angiogenesis. Consequently, its inhibition considered as a potential treatment can improve the prognosis of the malignant patients. Quinazoline and their containing analogs have been reported to exhibit inhibition activity against EGFR and VEGFR-2 and hence can reveal anti-tumor potency. For instance, Wei Huang et al. and his research group has developed a new AuNPs-new sorafenib derivatives containing quinazoline moiety. **Figure 7**.

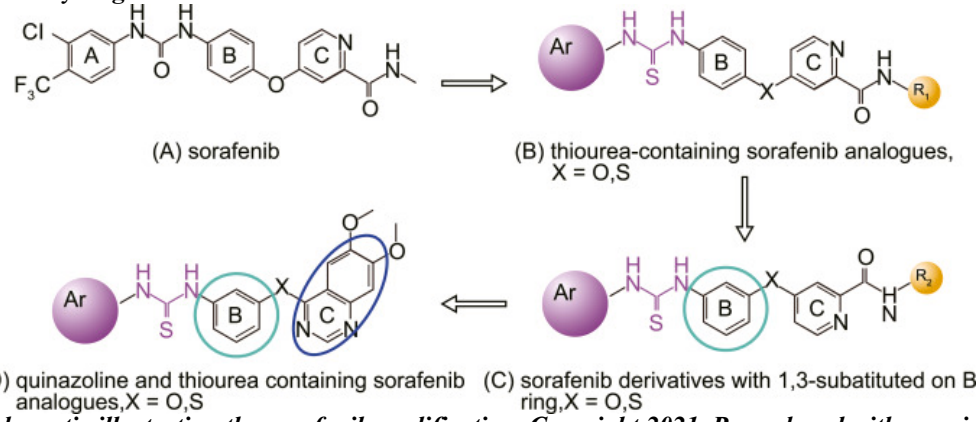


Figure 7. schematic illustration the sorafenib modification. Copyright 2021. Reproduced with permission from Elsevier, https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=5ddef0e9-62c1-4e85-9ea0-47cf54e47165

The results revealed that the newly synthesized derivatives exhibited a potential anti-proliferative and anti-angiogenic activities against the malignant cells through targeting of EGFR /VEGFR-2.

Maria Letícia et al., and coworkers have been designed and developed a series of novel 2-chloro-4-anilino-quinazolines and evaluated their dual inhibitory effects toward EGFR and VEGFR-2. The Structure–activity relationship (SAR) for the EGFR and VEGFR-2 inhibition and the *in silico* studies lead to the identification of the pharmacophoric function groups for both kinases. The results demonstrated also the essential role of the H-Bond donor group at the para position of the aniline moiety for the inhibition potency.

In a previous study, Abouzid and Shouman has demonstrated the preparation of a novel class containing a series of 2-chloro-4-anilino-quinazoline derivatives which are designed and studied by virtual screening to be EGFR inhibitors. The results revealed that compound **7** (**figure 8**) showed promising anti-proliferative efficacy on the MCF-7 human breast cancer cell lines overexpressing EGFR (IC50 = 0.13nM). but they did not report any data about its EGFR inhibition potency. Maria Letícia et al., and coworkers evaluated the EGFR inhibition efficacy of compound **7** and the results revealed that it exhibited only weak inhibition activity for EGFR

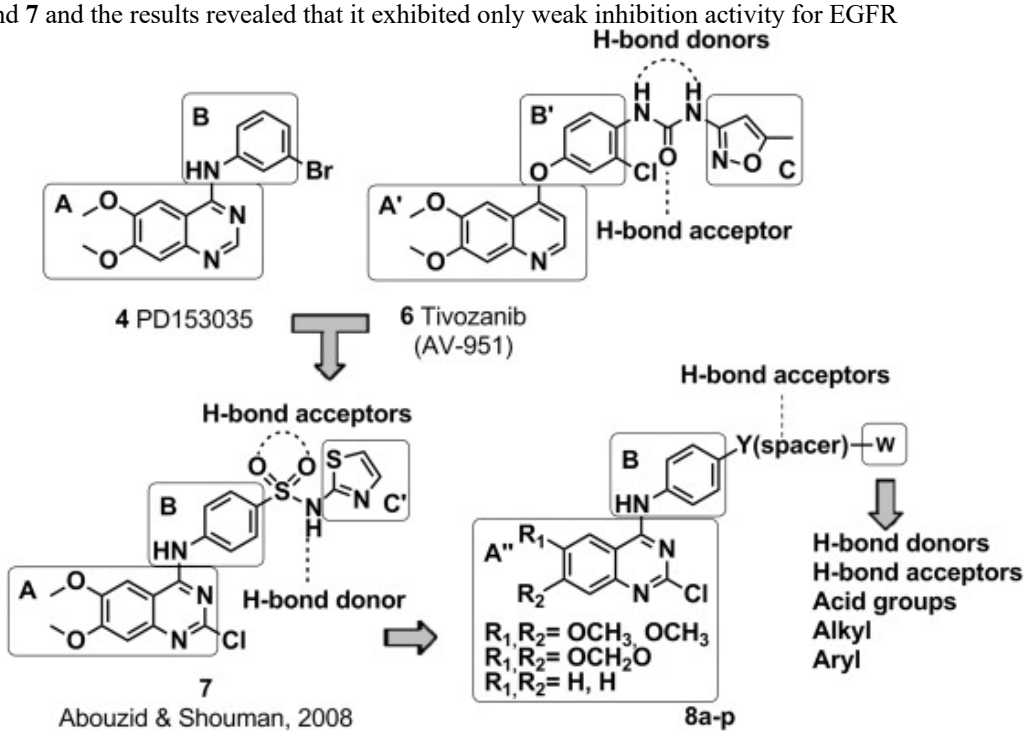


Figure 8. Synthetic procedures and chemical structure of new series of 2-chloro-4-anilino-quinazoline derivatives. Copyright 2014. Reproduced with permission from Elsevier.
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3.2. Quinazolines as Poly (ADP-ribose) polymerase-1 (PARP-1) enzyme inhibitors

Neurodegenerative diseases have threated the human health in a wide range around the world. Most of the neurodegenerative diseases revealed unknown or unidentified signs, but the most common significant signs of the neurodegenerative disease are the behavioral symptoms and cognitive dysfunction [50,51]. Many different factors mostly affect the normal functions of the brain likewise, the oxidative stress, the neuroinflammtion, protein or a gene. Poly (ADP-ribose) polymerase was a member of the nuclear family of enzymes which exhibited an essential role in processing different cellular vital activities while PARylation i.e., the presence of the poly (ADP-ribose) chains close to the desired target molecules. Poly (ADP-ribose) polymerase- (PARP)-1 is a DNA damage actuated protein found in the nucleus of the cells mostly overexpressed as a result of DNA damage[52–54]. Its overexpression is predominantly associated with various metabolic alteration and central nervous system diseases neurodegenerative disorders likewise Amyotrophic lateral sclerosis (ALS), Stroke, Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington (HD). NAD+ depletion PARP related cell death occurred only when an extreme high oxidation treatment was used [52,55,56]. The inhibition of the PARP1/2 may promote the replication related cell death owing to the irreversible damage of the DNA. Moreover, Poly (ADP-ribose) polymerase-(PARP)-1 plays an important vital role in the pathway for DNA recovery and it function as the center for cellular stress responses. Additionally, PARP-1 induced the DNA repair through recruiting DNA repair factors likewise DNA helicases, histones, and topoisomerases which is known as homologous recombination repair pathway. The DNA damage stimulated the activation of the PARP-1 enzyme which catalyzed the interaction of the poly (ADP-ribosylation) with the post-translational modification of the proteins involved in various physiological vital processes likewise preservation of genomic stability, the gene expression and the cell death [57]. Generally, all the previous studies revealed that the targeting of the PARP-1 and the inhibition of it is a promising approach for

minimizing the harmful effects of the central nervous system neurodegenerative diseases. Meanwhile, *Poly*(ADP-ribose) polymerase-1 (PARP-1) has been considered recently in the last few years as a promising anticancer drug target owing to its essential role in the DNA repair process. Haiping et al.,[58] and his coworkers have developed a new 1-benzyl-quinazoline-2,4(1H,3H)-dione series (**Figure 9**) and their efficacy as human PARP-1 inhibitors has been studied and reported. The SAR was conducted and revealed a number of effective potent PARP-1 inhibitors with IC50 values of single or double digit nanomolar level. The study showed that compound 7j exhibited the most potent PARP-1 and PARP-2 inhibition activity and it can be used selectively as anti-breast cancer (MX-1 and MDA-MB-468) with mutated BRCA1/2 and PTEN, respectively, comparing with the homologous recombination proficient cell types likewise the breast cancer cells named MDA-MB-231. Additionally, the study demonstrated that compound 7j exhibited the strongest efficacy on the temozolomide in MX-1 cells (PF50 = 3.77) in the newly synthesized series of the PARP-1 inhibitors [1,58,59].

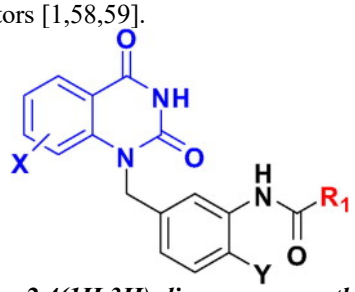

Figure 9. A new series of quinazoline-2,4(1H,3H)-diones were synthesized and evaluated as inhibitors of* poly*(ADP-ribose) polymerase-1 (PARP-1). X, Y = H or F; R1 = a range of amino acid fragments; IC50: 9.51–5290 nM.

4. Conclusion and future prospect

Investigation and development of potent eco-friendly methods for synthesis and production of novel nitrogenious heterocyclic compounds with expected biomedical and pharmaceutical importance has attracted a green interest recently. The current review illustrated an up-to-date overview of the most recent advanced strategies established for the production of quinazoline and quinazolinone compounds. The review also discussed the future chemical transformations for production of biologically active novel molecules. Additionally, from notable advantages of investigation of novel quinazoline analogies their distinguished pharmaceutical and biomedical applications. They revealed great biological applications as monoamine oxidase inhibitors, anticancer, antimicrobial anti-inflammatory, anti-oomycete agents, antihyperlipidemic along with many other biological activities. Generally, different synthetic methods either thermal or ecofriendly methods for production of more and more biologically active quinazolinone-based heterocycles will be useful for further investigation and development of drug like candidates for medicinal chemistry research.

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