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REVIEW ARTICLE

RECENT DEVELOPMENTS IN SYNTHETIC METHODS AND PHARMACOLOGICAL ACTIVITIES OF QUINAZOLINONE DERIVATIVES: A REVIEW

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Abstract

This review article offers A brief overview of the most current advancements in synthesis methods and with regard to the pharmacological effects of quinazolinone derivatives. A heterocyclic hybrid quinazolinone having the chemical formula $C_8H_6N_2O$. It is composed of rings that have been fused together i.e benzene and pyrimidine. The production of quinazolinone derivatives can be accomplished using a variety of methods, such as the Aza-diels-alder reaction, Aza-witting reaction, reaction aided by microwaves, metal-mediated synthesis, palladium-catalyzed reaction, copper-catalyzed reaction, ultrasound-promoted reaction, oxidative cyclization, reagent refluxing, one-pot synthesis, and aqueous media. This review paper included a wide spectrum of pharmacological activities, including a wide range of antibacterial, anti-inflammatory, and analgesic properties of quinazolinone derivatives as well as anti-cancer and anti-oxidant properties were covered in this study.

Keywords: Anti-cancer, anti-inflammatory, anti-oxidant, anti-microbial, pharmacological activity, quinazolinone, synthetic methods.

INTRODUCTION

Quinazolinone is a heterocyclic hybrid with the chemical formula $C_8H_6N_2O$. It is made up of benzene and pyrimidine rings that have been fused together. Due to their easy accessibility, varied chemical reactivity and wide variety of biological processes, including anti-fungal, anti-tumor, anti-hypertensive, anti-cancer, anti-HIV, anti-inflammatory [1-3], anti-bacterial[4], and anti-folate[5], quinazolin-4(3H)-one are of incredible interest. This wide range of pharmacological activities has been made even easier by the quinazolinones' synthetic techniques which include the Aza-diels-alder reaction, Aza-witting reaction, reaction aided by microwaves, metal-mediated synthesis, palladium-catalysed reaction, copper-catalysed reaction, ultrasound-promoted reaction, reagent refluxing, one-pot-synthesis, oxidative cyclization and aqueous media This extensive study outlines the chemistry, biological assessment, and significant effects of the several substituted quinazolinone derivatives. This overall study provides a foundation for future research on modifications to the quinazolinone structure and its application in drug research and discovery by providing an overview of the different substituted quinazolinone derivatives, their chemistry, biological assessment, and key medicinal uses.

Synthetic method of quinazolinone

Aza-diels-alder reaction

This study describes for the first time the use of 2H-indazole as a diene partner in an aza hetero-Diels-Alder reaction that produces highly substituted 4-aminoquinolines via an H-H approach. Additionally, a tandem one-pot technique has been established, beginning with 2-azidobenzaldehyde by the synthesis of 2C[6].

Aza-wittig reaction

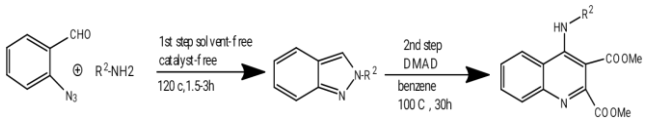
In this study, Theaza-Wittig catalytic reaction using the catalytic cycle of phosphine and phosphine oxide was explored. The aza-Wittig reaction can be carried out with just a catalytic amount of triphenylphosphine and the tetramethyl disiloxane/titanium tetraisopropoxide reductant system with good yields because the by-product triphenylphosphine oxide was reduced *in-situ*

to triphenylphosphine (Ph3P) with good chem selectivity[7].

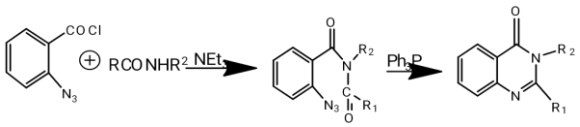
Microwave-assisted synthesis

In this study, 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine was synthesized via copper-catalyzed cascade couplings in water heated by microwaves[8].

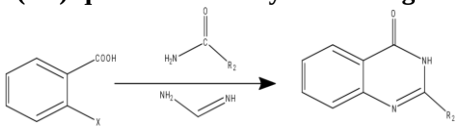
The interaction of 6-Iodo-2-undecylquinazolin-4(3H)-one (2) with various alkyl halides is discussed in this study. When a molecule was hydrazinolyzed, it produced acetohydrazide, which, when combined with various carbon electrophiles, produced 2- undecyl-4(3H)-quinazolinone derivatives whether used conventionally or with microwave assistance[9].



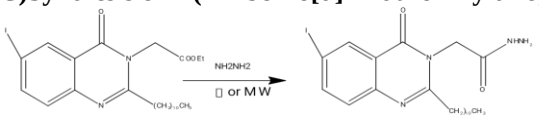
Scheme1: Creating highly substituted 4-aminoquinoline-like compounds by the aza hetero-Diels-Alder reaction.



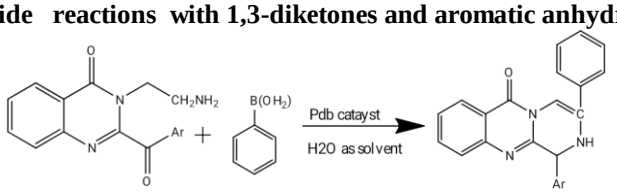
Scheme2: Synthesis of 4(3H)-quinazolinones by Aza-Wittig reaction within molecules.



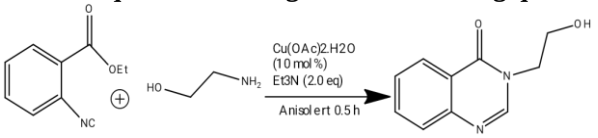
Scheme 3: (MW, DMSO, HOAC)Synthesis of 4-(1H-benzo[d]imidazol-2-ylthio)-6-methoxypteridine in water.



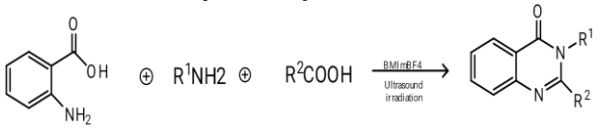
Scheme 4: hydrazide reactions with 1,3-diketones and aromatic anhydrides under M.W.



Scheme 5: Techniques for creating and transforming quinazolinones.



Scheme 6: Synthesis of natural compounds by Cu catalysed isocyanide insertion.



Scheme 7: A carboxylic acid, an anthranilic acid, and a primary aromatic amine were condensed with an ionic liquid (BMImBF4) while being exposed to ultrasound.

Metal-mediated reaction

Palladium-catalyzed reaction

In order to create 1,3-diaryl-6H pyrazino[2,1-b]quinazolin-6-one in water, a unique cyclization, aromatization, and cascade C-C coupling of 2-(4 oxoquinazolin-3(4H)-yl) acetonitrile derivatives with arylboronic acids have been carried out in a single pot using palladiumexplored[10].

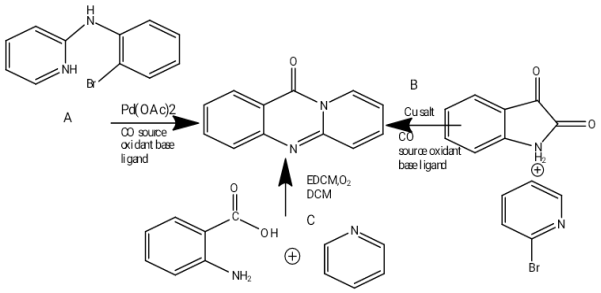
Copper-catalyzed reaction

In order to make quinazolin-4-ones, this publication described a unique, Imidoylative cross-coupling/ cyclocondensation process involving amines and 2-isocyanobenzoates catalyzed by copper. Anisole is a suggested sustainable solvent for the reaction, which uses Cu (II) acetate as a catalyst and works well in combination with a moderate base. The reaction does not require microwave heating, dry environments or inert atmosphere for best results.[11].

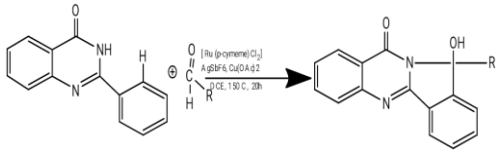
Ultrasound-promoted synthesis

In this study, A carboxylic acid, an anthranilic acid, and a primary aromatic amine were condensed with an ionic liquid (BMImBF4) while being exposed to ultrasound to create 4(3H)-quinazolinones. The benefits of this approach include a straightforward catalyst system, improved yields, a lack of organic solvent, and a straightforward synthesis process[12].

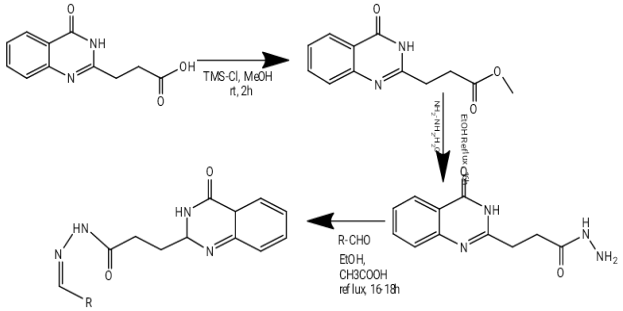
Scheme 8: Yb(OTf)3 promoted synthesis of 4(3H)-quinazolines by microwave (MW) irradiation or ultrasonication (US).



Scheme 9: Methods for synthesis of pyridoquinazolinones.



Scheme 10: Quinazolinones and activated aldehydes by oxidant methods.



Scheme 11: R= Different substituted, synthesis of the quinazolinone–schiff's compounds using reagent base.

In this study, 4(3H) quinazoline derivatives were made from 2 aminobenzonitrile and acyl chlorides in solvent-free condition and with the aid of microwave or ultrasonic radiation and $Yb(OTf)_3$ (10 mol%). This research demonstrated a Niementowski-like reaction induced by ultrasound[13].

Oxidative cyclization

In this study, oxidative conditions were used for the first time to synthesize fused quinazolinones from N-pyridylindoles, and a combination of K2S2O8 and DIB [(diacetoxy)iodo]benzenegenerated moderate to high yields of 11H-pyrido[2,1-b]quinazolin-11-one derivatives. An in-situ generated 2-hydroxy-1-(pyridin-2-yl) indolin-3-one is believed to be the primary chemical step. It experienced a C-C bond cleavage to yield an electrophilic C-3 site in N-pyridyl indole. It then undergoes cyclization as a result of pyridyl nitrogen's nucleophilic assault. This metal-free reaction has a wide substrate range, is easily operationalized, and takes little time to complete[14].

In this study, 2-aryl quinazolinones and activated aldehydes underwent a C-H hyroxyalkylation reaction with ruthenium (II) catalysis in a redox-neutral environment. This procedure permits the C-H addition and subsequent intramolecular cyclization to form biologically active tetracyclic isoindoloquinazolinones in the presence of $Cu(OAc)_2$, an external oxidant[15].

Reagent refluxing

This study produced many amino acids that were coupled to quinazolinone-Schiff bases and then used reagent refluxing to describe them analytically and spectroscopically[16].

One-pot synthesis

In this paper Using $[Cp^*IrCl_2]_2$ (Cp*pentamethyl cyclopentadienyl) as a catalyst in a one-pot oxidative cyclization process with o-aminobenzamides to produce quinazolinones under hydrogen transfer conditions[17].

In aqueous media

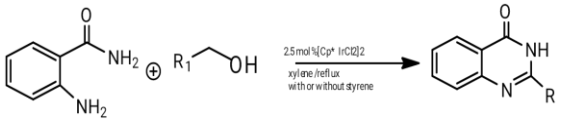
More SV *et al*., uses water at room temperature, ceric (IV) substituted o-phenylenediamines, aryl/heteroaryl 1,2-diketones, alkyl/aryl 1,2-diketones, and ammonium nitrate (CAN) as a catalystand aryl/heteroaryl 1,2-diketones to produce quinoxaline derivatives.

Numerous organic oxidative reactionsuse the one-electron oxidant CAN. This approach is cost-effective, efficient, and high-yielding.

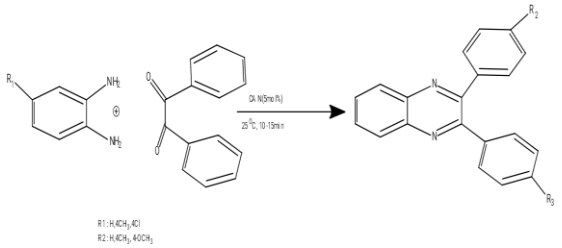
Pharmacological activities of quinazolinone

Anti-microbial activity

A highly effective and flexible synthetic method was used to create five annelated quinazoline derivatives[18,19].



Scheme 12: One- pot synthesis using [Cp*IrC12]$_2$-catalyzed Quinazolinone compound.



Scheme 13: Synthesis of Quinazoline derivatives by aqueous media.

Through the reaction of 2-(oaminophenyl) indole with a variety of arylaldehydes, indolo[1,2c]quinazoline derivatives were produced in good yields and demonstrated activity against a number of gram-positive, gram-negative, and pathogenic fungal strains, including *Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus pyogenes*. Reference substances included ampicillin and ketoconazoleThe antibacterial activity of 6-iodo-2-thienylquinazolin-4(3H)-one and its fused heterocyclic counterparts was investigated. The antibacterial activity of compounds 4, 8, 14, and 24 was remarkably broad- spectrum[20]. The antibacterial activity of 6-iodo-2-thienylquinazolin-4(3H)-one and its fused heterocyclic counterparts was investigated. The antibacterial activity of compounds 8, 14, and 24 was remarkably broad-spectrum. Utilizing the traditional microdilution method, it was discovered that synthesized derivatives have antimicrobial activities against three species of Gram-negative bacteria, including Escherichia coli, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, and three species of Gram-positive bacteria, including *S. aureus*, *B. subtilis*, and *Listeria monocot* genes[21].

Table 1: Summary of different synthetic methods of quinazolinone derivatives.

S. N.	Objective	Methods	Findings	Reference
1	An innovative method for creating highly substituted 4-amionquinoline drug-like compounds using aza hetero-Diels-Alder reaction.	Aza-Diels-Alder reaction	Scheme 1	29
2	Reversible P(III)/P(V) redox: 4(3H)-quinazolinones and the naturally occurring vasicinone are synthesized using the catalytic aza-Wittig reaction.	Aza-Wittig reaction	Scheme 2	30
3	i) Effective and selective synthesis of quinazolinone derivatives in aqueous solution using microwave assistance and copper catalysis. ii)Ecofriendly and highly efficient microwave- induced synthesis of novel quinazolinone-undecyl hybrids with *in vitro* antitumor activity	Microwave-assisted synthesis	i) Scheme 3 ii) Scheme 4	19,17
4	Cascade reactions in aqueous environments catalyzed by palladium: synthesis and photophysical characteristics of pyrazino-fused quinazolinones	Palladium-catalyzed reaction	Scheme 5	31
5	Quinazolin-4-one Synthesis by Copper-Catalyzed Isocyanide Insertion	Copper-catalyzed reaction	Scheme 6	5
6	i) Promoted by Ultrasound and Catalyzed by Ionic Liquid Cyclocondensation Reaction for 4 (3 H)-Quinazolinone Synthesis ii) Under Yb (OTf) 3 catalysis, ultrasound aided in the synthesis of four (three H) quinazolines.	Ultrasound-promoted synthesis	i) Scheme 7 ii) Scheme 8	24, 13
7	i) Oxidative cyclization of N-pyridylindoles to produce fused quinazolinones without the need for transition metals Synthesis of fused quinazolinones without transition metals through oxidative cyclization of N-pyridylindoles ii) Oxidative cyclization of 2-aryl quinazolinones with activated aldehyde and C-H addition catalyzed by Ru(ii)	Oxidative cyclization	i) Scheme 9 ii)Scheme 10	16, 8
8	Molecular docking, SAR, and synthesis of amino acid conjugated quinazolinone-Schiff's bases as possible antibacterial agents.	Reagent refluxing	Scheme 11	26
9	Quinazolinones are synthesized in a single pot using hydrogen transfers catalyzed by iridium.	One-pot synthesis	Scheme 12	32

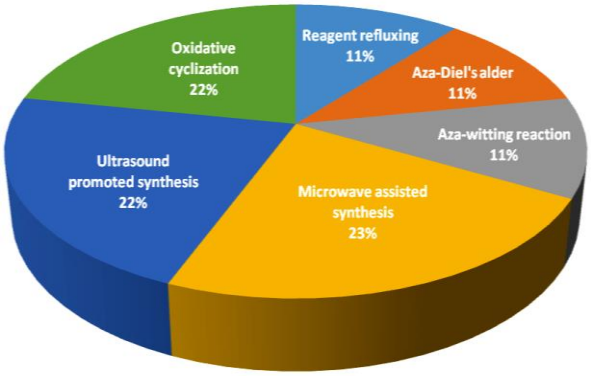


Figure 1: Ratio of synthetic methods.

It was created using pyridine, anthranilic acid, and derivatives of 4-substituted and unsubstituted benzoyl chloride. By combining 2-(4-substituted)Phenyl-3-amino Quinazoline -4-3(H)one and 2-Phenyl-3-amino Quinazoline-4-3(H)one with various substituted aromatic aldehydes in glass vials and heating them in an oil bath at 80 degrees Celsius, a set of six Schiff bases were created. Structure has been clarified using spectroscopic methods (Figure 6)[22].

Anti-inflammatory and analgesic

In this study, two A number of compounds of 2,4,6-trisubstituted quinazolines were created and assessed for their analgesic and anti-inflammatory properties. Significant action was produced by fifteen compounds. Four substances were discovered to be analgesics. A total of seven substances showed their capacity to reduce both pain and inflammation. Acute toxicity tests on the compound revealed a good safety margin (Figure 7)[23]. Molecular docking, biological assessment, and synthesis of the novel series of spiro [(2H, 3H) quinazoline -2,1'-cyclohexan]-4(1H)-one derivatives as analgesics and anti-inflammatory drugs. There are nineteen different compounds were assessed as analgesics and anti-inflammatory drugs. After experiments on animals.

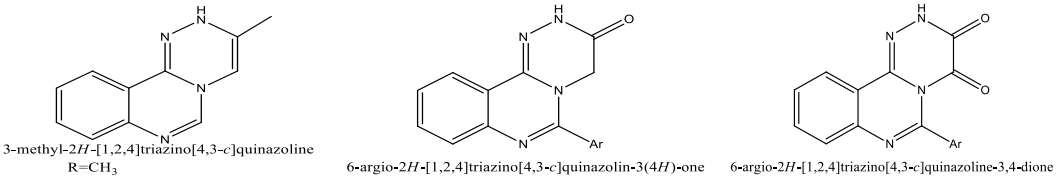


Figure 2: Heterocyclic quinazoline derivatives with antimicrobial activity.

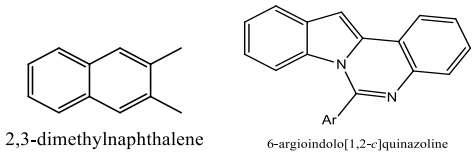


Figure 3: Quinazoline derivatives with antibacterial activity.

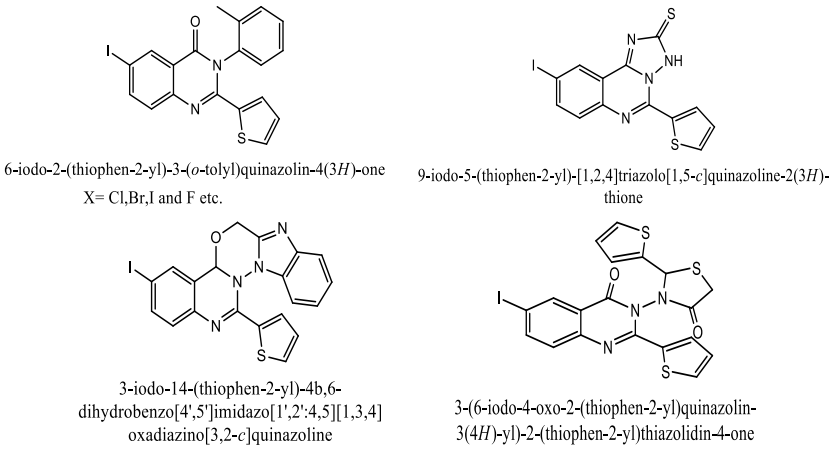


Figure 4: Heterocyclic quinazoline derivatives with antibacterial activity.

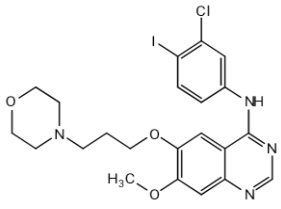
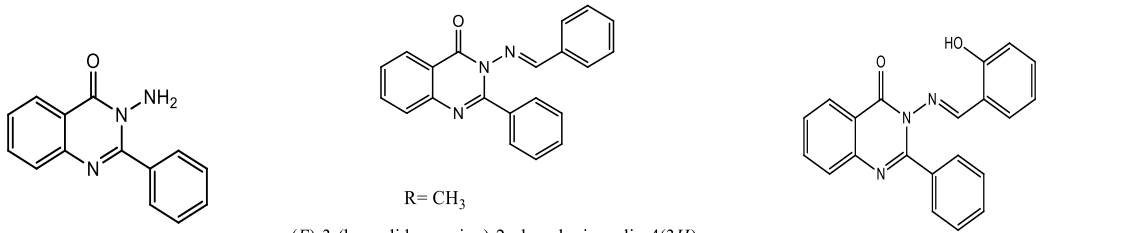


Figure 5: Heterocyclic quinazoline derivatives with antimicrobial activity.



3-amino-2-phenylquinazolin-4(3*H*)-one (*E*)-3-(benzylideneamino)-2-phenylquinazolin-4(3*H*)-one (*E*)-3-((2-hydroxybenzylidene)amino)-2-phenylquinazolin-4(3*H*)-one

Figure 6: Structure has been clarified using spectroscopic methods.

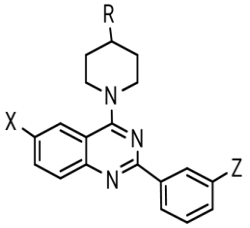


Figure 7: Quinazoline analogues with anti-inflammatory and analgesic activity.

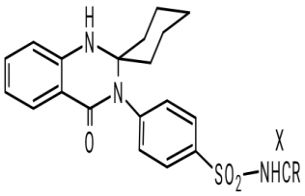


Figure 8: Quinazoline analogues with analgesic activity.

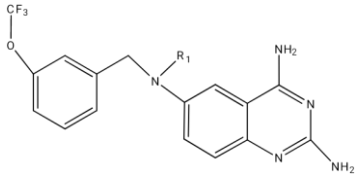


Figure 9: Quinazoline analogues with ant-trypanosomatid and anti-plasmodial agents.

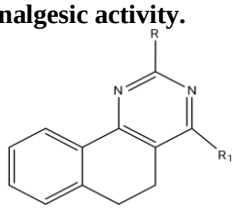


Figure 10: Quinazoline analogues with antiplatelet/antiphlogistic properties.

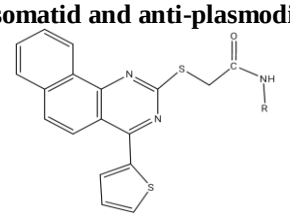


Figure 11: Quinazoline analogues with anticancer activity.

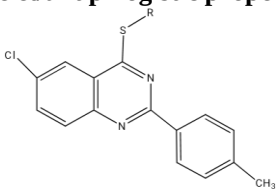


Figure 12: Quinazoline analogues with anticancer property.

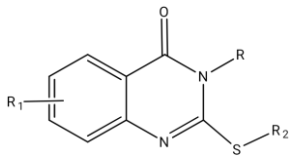


Figure 13: Quinazoline analogues with anticancer effects.

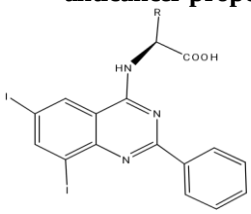


Figure 14: Quinazoline analogues with cytotoxic agents on a lymphoma cell line *in vitro*.

There are six derivatives shows good pharmacological activities with gastrointestinal, and eleven compound found as anti-inflammatory agents and active against COX-2 (Figure 8)[24]. To design, synthesis and biological evaluation of quinazoline derivatives as ant-trypanosomatid and anti-plasmodial agents. Biological evaluation of quinazoline-2,4,6-triamine derivatives as Agents that were anti-plasmodial, anti-leishmanial, and trypanocidal were discovered. Leishmania Mexicana promatigotes and bloodstream trypomastigotes of *T. cruzi* (NINOA and INC-5 strains) were evaluated for *in vitro* by all substances. (MHOM/BZ/61/M379 strain). There are 5, 6, 8, and 9 were found most active biological activity (Figure 9)[25]. To evaluate the 2,4-diamino substituted 5,6-dihydrobenzo [h] Quinazoline's antiplatelet/antiphlogistic properties. In this study, the chemical 5a-5h was shown to have analgesic and anti-inflammatory effects on rat paw oedema (Figure 10)[26].

Quinazoline as anti-cancer

Using the synthon 4-(thiophen-2-yl)-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thione, certain newly Quinazoline and thioxopyrimidine derivatives that were produced were assessedfor cytotoxicity and anti-HIV activity. The most potent cytotoxic activity was demonstrated by few compounds against cell lines of melanoma (G361 and SK-MEL-28), leukemia (HL60, U937, and K562), neuroblasts (GOTO and NB-1), and normal cell carcinoma (W138). (Figure 11)[27]. This study created, synthesized 27, and physiologically assessed new quinazoline derivatives with an IC50 range of 3.35 to5.59 mg/ml as possible anticancer drugs.

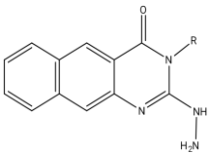


Figure 15: Quinazoline analogues with antioxidant activity.

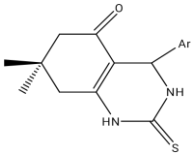


Figure 16: Quinazoline analogues with antioxidant activity using DPPH.

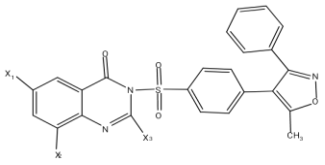


Figure 17: Quinazoline derivatives with anti-bacterial activity.

Table 2: Summary of different pharmacological activity of quinazolinone.

S. N.	Objective	Pharmacological activity	Findings	Reference
1	i) Creation of new quinazoline derivatives for use as antibiotics ii) Investigation of newly synthesized 6-substituted indolo[1,2-c]quinazolines for antimicrobial properties A few novel substituted iodoquinazoline compounds are synthesized, and their antibacterial properties are screened. iv) Synthesis, docking investigations, and antibacterial assessment of several new quinazolinone Schiff base derivatives v) Novel quinazoline compounds synthesized in a single pot and their antibacterial properties	Anti-microbial activity	i) I(a),I(b),I(c) ii) II(a),II(b) iii) III(a),III(b),III(c),III(d) iv) IV v) V(a),V(b),V(c),V(d)	i) 4 ii)27 iii) 3 iv) 23 v) 15
2	i) Synthesis, assessment of several new quinazoline derivatives as analgesics and anti-inflammatory ii) Biological assessment and molecular docking of new series as remedies for pain and inflammation. Design, synthesis, and biological assessment of quinazoline derivatives as antiplasmodial and antitrypanosomatid drugs (iii). iv) Evaluation of antiplatelet and antiphlogistic actions.	Anti-inflammatory and Analgesic	i) VI ii) VII iii) VIII iv) IX	i)3 ii) 4 iii) 14 iv) 7
3.	i)A few newly synthesized quinazoline and thioxopyrimidine derivatives were evaluated for cytotoxicity and anti-HIV properties. ii) Design, synthesis, and biological assessment of new quinazoline derivatives as possible anticancer agents: molecular docking analysis iii) 33 iv) Design, Synthesis, and Biological Assessment Research of New Quinazoline Derivatives as Cytotoxic Substances.	Anti-cancer	i) X ii) XI iii) XII iv) XIII	i)21 ii) 11 iii) 20
4	Pharmacological Reports.	Anti-oxidant	XIV	20
5	Investigation of several new quinazolinones' antibacterial and anti-inflammatory properties	Anti- bacterial	XV	22

The substantial inhibitory activity of two compounds in comparison to other of the same series was further substantiated by molecular docking studies. These studies also contribute to a more detailed understanding of the numerous interactions between the ligands and the enzymes' active areas, which in turn aids in the development of new, powerful inhibitors[28]. The cytotoxic activity of the suggested quinazoline derivatives was evaluated using three cell lines: the human cervix cell line (HELA), human liver cell line (HEPG2), and human breast cell line (MCF-7). With an IC50 range of 3.35 to 6.81 mg/ml, all investigated compounds demonstrated strong and specific action against breast cancer (MCF-7) cells (Figure 12) [28]. In this study, 26 synthetic compounds were tested for their efficacy against the HeLa and MDA-MB231 cancer cell lines. Three of these compounds were shown to have the strongest anticancer effects and to likely act through the EGFR-TK pathway quinazoline derivatives (Figure 13)[29].

This study designed, synthesized a total of eight compounds, and assessed the biological effects of three novel quinazoline derivatives as cytotoxic agents on a lymphoma cell line *in vitro* (Figure 14)[30].

Quinazoline as anti-oxidant

Based on three antioxidant experiments, benzoquinazolines showed antioxidant activity. The impacts of Methoxy (a group that donates electrons), hydrazine (which supplies hydrogen atoms), and phenyl (an electron-rich moiety) can be credited for the compounds 3, 9, and 15 having the highest FRAP, DPPH radical scavenging activity, and lowering power capabilities, in that order. Future studies to develop novel, more potent antioxidants chemicals will take into account the findings of the molecular docking and SAR investigations (Figure 15)[31]. Twenty-seven new

quinazolinones derivatives were synthesized, and three of them (compounds 1, 2, and 3) had EC50 values of 0.220, 0.275, and 0.380 mg, respectively, when tested for high antioxidant activity using DPPH. Four of these substances demonstrated outstanding antiproliferative properties (Figure 16).

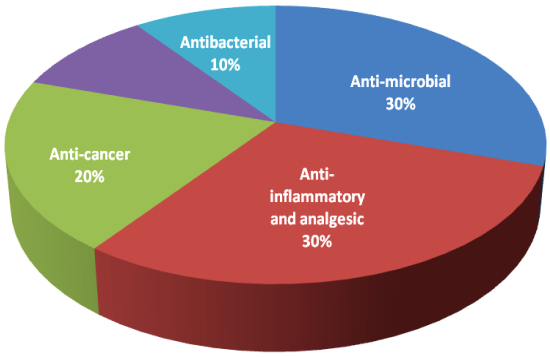


Figure 18. Ratio of pharmacological activities of quinazolinone.

Quinazolinone as anti-bacterial

The investigated substances in this study were also examined for their ability to inhibit the growth of *S. aureus* and *E. coli* strains at 200 g/ml and 1 mg/ml, respectively. At higher tested concentrations, the tested compounds outperformed standard lincomycin in terms of activity against *S. aureus*. None of the compounds are as effective against *E. coli* as ceftazidime in its conventional form (Figure 17)[32].

CONCLUSIONS

It's crucial to remember that the combination of N-heterocyclic quinazolinone and its derivatives requires more rigid and complex structures. Fundamental techniques for the production of chemicals that are heterocyclic include the Aza-synthetic method, refluxing, and oxidative cyclization, which are still widely used for the synthesis of quinazolinone derivatives. This review article, however, summarized a number of novel synthetic techniques, such as the Aza-diels-alder reaction, Aza-witting reaction, metal-mediated reaction, and microwave-assisted reaction, palladium-catalyzed reaction, copper-catalyzed reaction, ultrasound-promoted reaction, One-pot synthesis, reagent refluxing, and oxidative cyclization, and aqueous media, and these techniques would improve the synthetic research on quinazolinone. Pharmacological activities like those that are anti-bacterial, anti-inflammatory, analgesic, anti-cancer and anti-oxidant were also summarized in this review article. It can be inferred from the research progress above that in the future, drug design will focus on increasing activity by incorporating various active groups and novel techniques.

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AUTHOR'S CONTRIBUTIONS

Meftah ON: Research topic idea, manuscript writing , literature review and final manuscript checking. **Ali A:** critical evaluation. **Alkaf A:** Manuscript checking. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

CONFLICT OF INTEREST

None to declare.

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