JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Quinoline Based 2-Azetidinones, 4-Thiazolidinones and Their Potential Pharmacological Activities

Govindarao Kamala*[1], Sri Laya A[2], Sri Nandini G[2], Shirin D[2], Anjaleena D[2], Sudha Rani S[2], Anusree P[2]

[1] *Professor, Department of Pharmaceutical Chemistry, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India*
[2] *UG Scholar, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India*

Publication history: Received on 16th June; Revised on 24th June; Accepted on 2nd July 2024

Article DOI: 10.69613/r73gtb07

Abstract: Globally, many diseases with unmet therapeutic needs persist, including cancer, tuberculosis, and various infectious diseases. The rapid development of new drugs is crucial to counteract these health challenges. Medicinal chemists, in collaboration with other scientists, continuously strive to design and develop novel lead molecules with potential therapeutic applications. Molecular hybridization is a common approach in this field, often resulting in the synthesis of new compounds with synergistic or novel activities. Quinoline-based hybrid molecules, particularly those incorporating 2-azetidinone and 4-thiazolidinone moieties, have shown promise in addressing multiple disease targets. These hybrid derivatives have demonstrated potential efficacy against infectious diseases, cancer, and tuberculosis. The combination of quinoline, a privileged scaffold in medicinal chemistry, with 2-azetidinones and 4-thiazolidinones, known for their diverse therapeutic properties, offers a promising avenue for drug discovery. Ongoing research in this area aims to uncover new lead molecules that could significantly impact the treatment of diseases with current therapeutic limitations.

Keywords: Quinoline; 2-Azetidinone; 4-Thiazolidinone; Anticancer; Antioxidant; Antimalarial; Anti-tubercular activity.

1. Introduction

Quinoline and 2-azetidinones are two significant single-nitrogen heterocyclic molecules. Compounds containing these scaffolds have been linked to a wide range of biological functions. They are a key structural component of a wide range of medicinal compounds used to treat everything from malaria to advanced malignancies [1].

Quinoline and 2-azetidinone (β-lactam) are single nitrogen compounds that comprise bicyclic aromatic and monocyclic nonaromatic rings. The effectiveness of these two scaffolds in the design and identification of new anticancer drugs has been carefully examined [2]. Both of these scaffolds are crucial components of commercially available medicines with different therapeutic applications (Figure 1).

Quinoline nucleus is an appealing scaffold for medicinal chemists since it is simple to produce and has favorable "drug-like" qualities. Some of the therapeutically useful agents containing quinoline ring have Anticancer-Irinotecan, Topotecan, Belotecan (topoisomerase inhibitors), Foretinib, Cabozantinib, Lenvatinib, Bosutinib, Neratinib (tyrosine kinase inhibitors); Antimalarial-Chloroquine, Primaquine; Antiviral-Saquinavir; Antitubercular-Bedaquiline activities [3]. Quinoline derivatives have been shown to have anticancer [4] antiproliferative [5], antimalarial [6], antitubercular [7], and antibacterial [8] effects, among others. Many antimicrobial medications, such as penicillins, cephalosporins, nocardicins, and β-lactamase inhibitors, use 2-azetidinone as the core ring for their action [9].

Thiazolidinone is a five-membered nonaromatic heterocyclic ring containing nitrogen and sulfur heteroatoms. Molecules containing the thiazolidinone scaffold comprise a wide variety of pharmacological and biological applications. Thiazolidinone is found as a core element for the activity of drugs used in the treatment of different disorders making it an attractive and privileged motif for medicinal chemists for designing and developing new class of drugs [10]. The general structures of thiazolidine and its oxidized forms viz thiazolidin-2-one and thiazolidin-4-one are represented in Figure 2

* Corresponding author: Govindarao Kamala

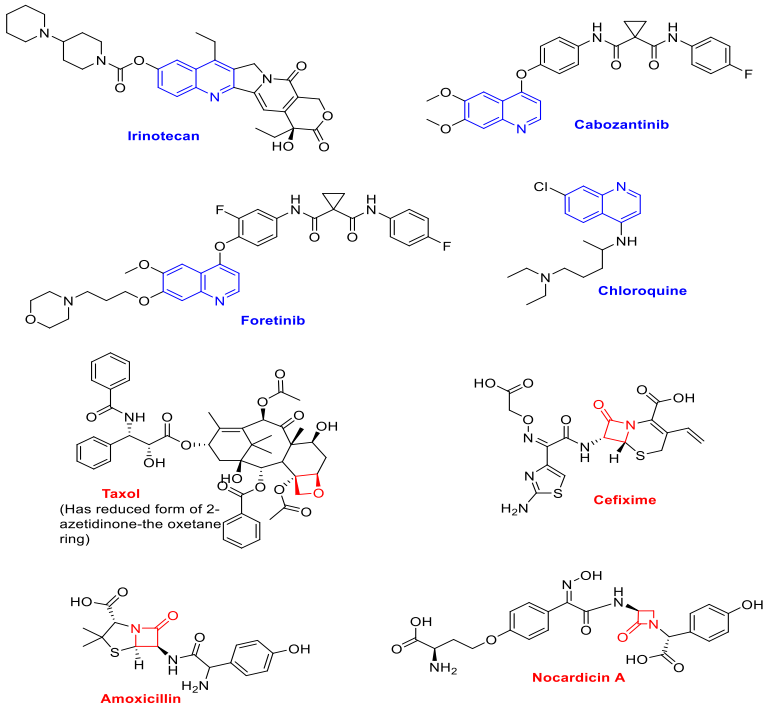


Figure 1. Structures of drug molecules bearing quinoline and 2-azetidinone moieties highlighted in blue and red respectively.

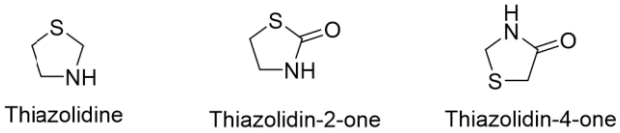


Figure 2. Chemical structures the privileged heterocycles-Thiazolidine, Thiazolidin-2-one and Thiazolidin-4-one.

Thiazolidine ring is a popular scaffold among medicinal chemists since it is easy to make and has "drug-like" properties. Some therapeutically effective compounds with thiazolidine ring have been discovered to have use as antibacterial agents for the treatment of infectious diseases like penicillins which comprise the large share in the market. Additionally, the thiazolidine derivatives are also seen in antidiabetic thiazolidinones/glitazones (Rosiglitazone, Troglitazone, Pioglitazone etc), anticonvulsants (Ralitoline), loop diuretic (Etozoline) and anti-inflammatory drug-Darbufelone [11]. The structures of the drugs that are thiazolidine derivatives are summarized in Figure 3

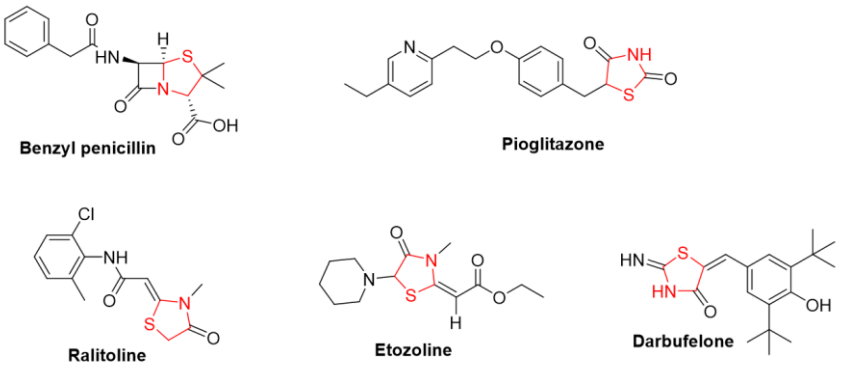


Figure 3. Drug molecules containing thiazolidine as a core element.

Thiazolidine analogues were reported with bioactivities like antibacterial and antifungal anticancer, antioxidant, antimalarial, antitubercular activities [12]. Recent studies have highlighted the potential of thiazolidinone derivatives as promising antiviral agents, particularly against influenza and coronaviruses [13].

The heterocyclic ring derivatives such as quinoline conjugated 2-azetidinone, and 4-thiazolidinone have outstanding biological characteristics, and these moieties are present in a variety of drug candidates and drug molecules used for different diseases (Figure 1.4). Due to their broad spectrum of activities (Figure 4), these rings are considered as the privileged structures for medicinal chemists for their drug discovery research. The actions of these ring derivatives have been documented to include antibacterial and antifungal [14], anticancer [15], antioxidant [16], antimalarial [17], antitubercular [18] activities etc. The combination of these pharmacophores through molecular hybridization has emerged as a promising strategy to develop novel therapeutic agents with enhanced efficacy and reduced side effects [19].

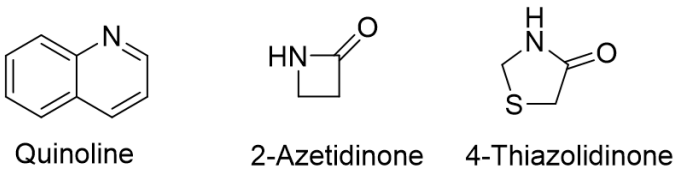


Figure 4. Nitrogen and sulfur containing heterocyclic scaffolds-Quinoline, 2-Azetidinone and 4-Thiazolidinone

2. Quinoline

Because of its medical implications, researchers have been studying heterocyclic rings with nitrogen for a long time. Quinoline (also known as azanaphthalene, Figure 5) derivatives were one of the numerous miniature heterocyclic rings used in medicinal chemistry to find and produce pharmacologically useful compounds. Quinoline-based bioactive molecules have improved pharmacodynamic and pharmacokinetic properties. Quinoline had become a well-known scaffold for the development of novel pharmaceutical compounds due to its unique characteristics [20].

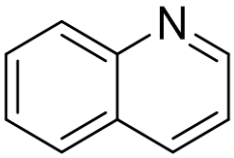


Figure 5. Structure of quinoline

A large number of drugs comprise quinoline ring as a major scaffold responsible for their therapeutic activity. For instance, quinoline moiety is found in anticancer drugs that target the topoisomerase enzyme (Irinotecan, Topotecan, Belotecan) as well as in the drugs that are tyrosine kinase inhibitors (TKIs) like Foretinib, Cabozantinib, Lenvatinib, Bosutinib, Neratinib. The ring is also present in drugs having antimalarial (Chloroquine, Primaquine), antitubercular (Bedaquiline, Ciprofloxacin) and antiviral (Saquinavir) properties [21] (Figure 6). Furthermore, quinoline derivatives have shown potential as anti-inflammatory [22], anticonvulsant [23], and antidiabetic agents [24].

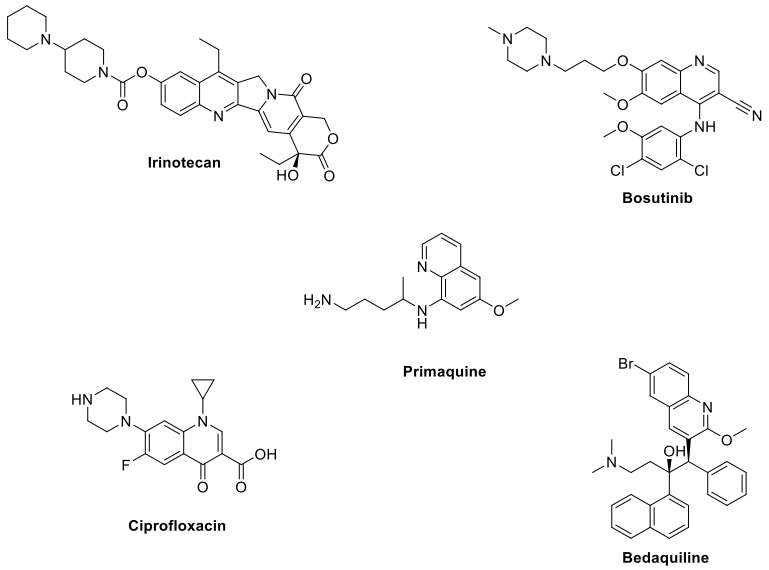
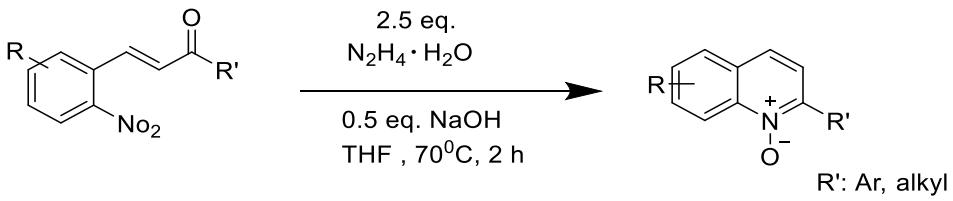


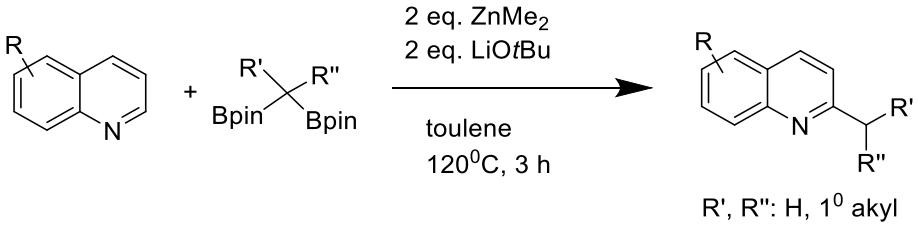
Figure 6. Selected drugs bearing quinoline ring

2.1. Methods of synthesis of quinoline derivatives

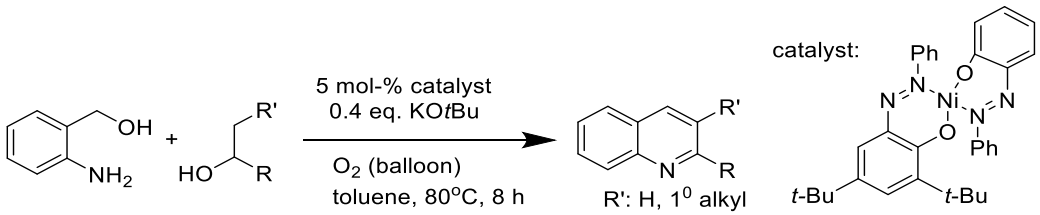
1. Visible light-mediated metallaphotoredox catalysis enables a highly chemo selective deoxygenation of N-heterocyclic N-oxides using Hantzsch esters as the stoichiometric reductants and only a tiny amount of the catalyst within a few minutes at room temperature. The reaction tolerates a wide range of functional groups, such as carbamates, esters, ketones, nitrile groups, nitro groups, and halogens [25].



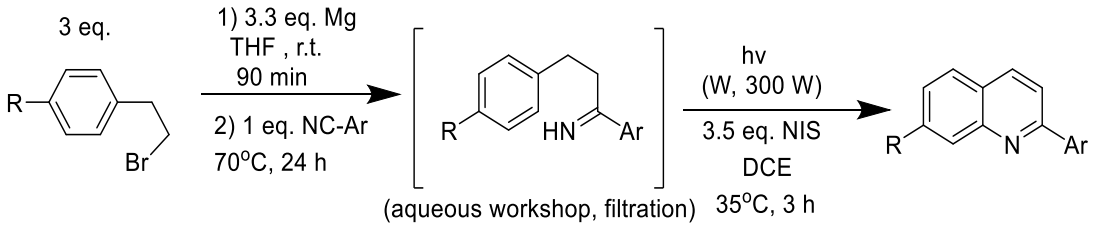
2. $ZnMe_2$ promotes a direct C2- or C4-selective primary and secondary alkylation of a broad range of pyridines and quinolines using 1,1-diborylalkanes as alkylation sources. While substituted pyridines and quinolines exclusively afford C2-alkylated products in good yields, simple pyridine delivers C4-alkylated pyridine with excellent region selectivity [26].



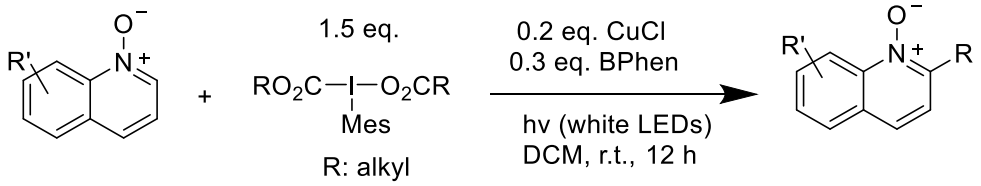
3. A convenient and eco-friendly nickel-catalyzed synthesis of quinoline and quinoxaline via double dehydrogenative coupling starting from 2-aminobenzyl alcohol/1-phenylethanol and diamine/diol, respectively, operates at mild reaction temperatures. The inexpensive molecularly defined catalyst can easily be regenerated under aerobic/O_2 oxidation [27].



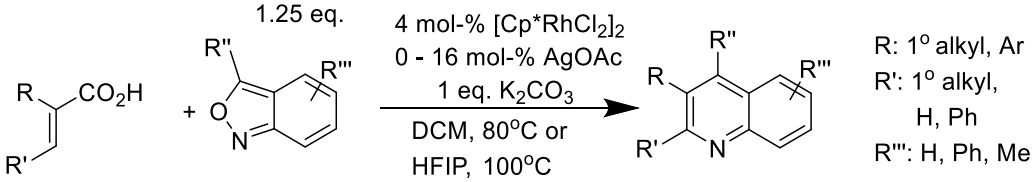
4. Treatment of 2-arylethylmagnesium bromides, prepared from 2-arylethyl bromides and magnesium, with aromatic nitriles, followed by reaction with water and then with N-iodosuccinimide under irradiation with a tungsten lamp, provides 2-arylquinolines in good yields under transition-metal-free conditions. 2-Alkylquinolines could be also obtained in moderate yields [28].



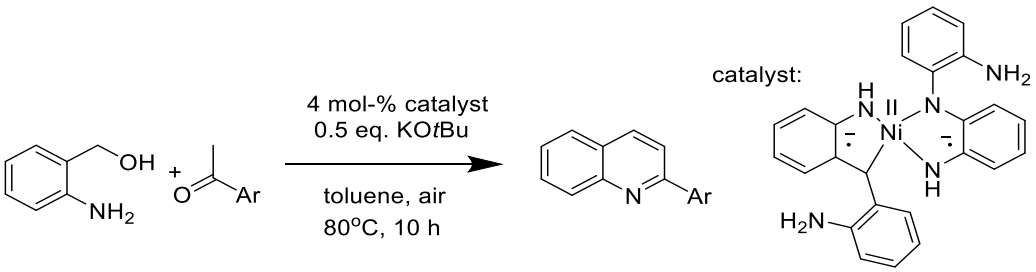
5. The use of hypervalent iodine (III) carboxylates as alkylating agents enables a highly site-selective alkylation of heteroarene N-oxides the presence of a cheap copper catalyst under visible light conditions. This mild method proceeds at room temperature in an air atmosphere [29].



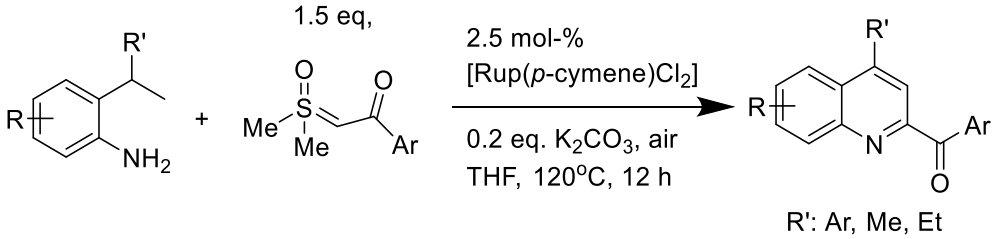
6. COOH as a weakly coordinating and traceless directing group is essential for a synthesis of diverse polysubstituted quinolines from readily available acrylic acids and anthranils. Diverse polysubstituted quinolines were obtained under mild reaction conditions with simple H_2O and CO_2 as by-products [30].



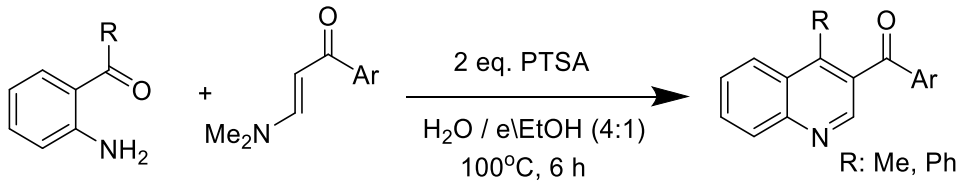
7. Singlet diradical Ni(II) featuring two antiferromagnetically coupled singlet diradical diamine type ligands catalyze simple, straightforward, and atom economic syntheses of quinolines, 2-aminoquinolines, and quinazolines in good yields via biomimetic dehydrogenative condensation/ coupling reactions [31].



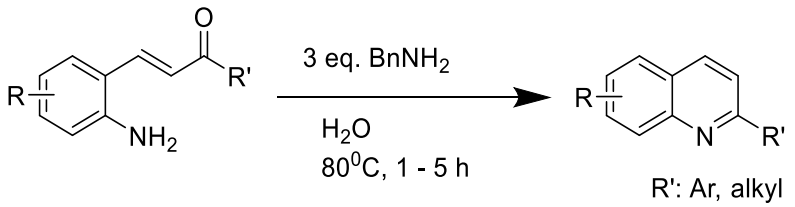
8. A ruthenium-catalyzed [5+1] annulation of 2-alkenylanilines with sulfoxonium ylides provides highly functionalized quinolines with good yields and excellent functional group tolerance [32].



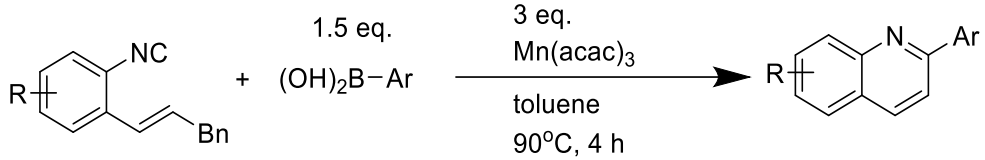
9. Synergistic control of the temperature and amount of catalyst enables a divergent synthesis of N-arylenaminones and 3-aroylquinolines from 2-aminoaryl ketones and N, N-dimethylenaminones in the presence of 4-toluenesulfonic acid. The protocols offer mild conditions, good functional-group tolerance, operational simplicity, and excellent yields [33].



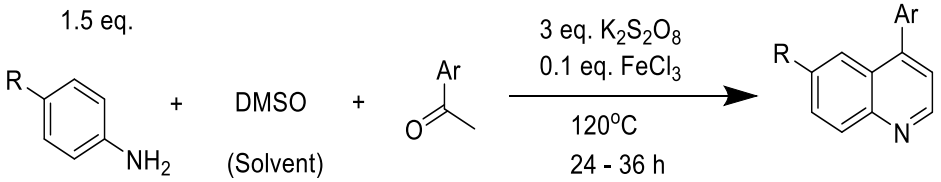
10. Benzylamine as the nucleophilic catalyst enables an on-water synthesis of 2-substituted quinolines in excellent yields from 2-aminochalcone derivatives. This protocol offers simple operation, broad substrate scope, good functional group tolerance, easy product isolation by simple filtration, recycling of the catalyst, and gram-scale synthesis [34].



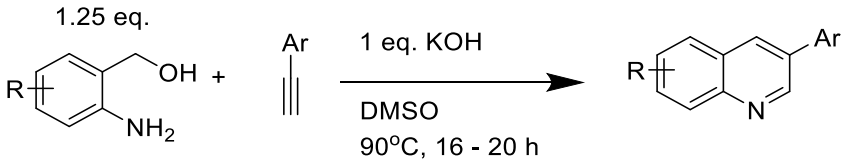
11. Selective addition of radicals to isonitriles enables a general route for the preparation of N-heteroaromatics. This method utilizes alkenes as synthetic equivalents of alkynes by coupling homoallylic ring expansion to yield the formal 6-endo products with aromatization via stereoelectronically assisted C-C bond scission [35].



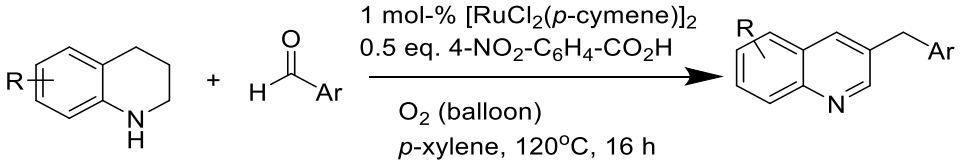
12. An oxidative annulation involving anilines, aryl ketones, and DMSO as a methine (=CH−) equivalent promoted by K2S2O8 provides 4-arylquinolines, whereas activation of acetophenone-formamide conjugates enables the synthesis of 4-arylpyrimidines [36].



13. Cycloaddition of azadienes (in situ generated from 2-aminobenzyl alcohol) and terminal alkynes enables a highly efficient metal and protection-free approach for the regioselective synthesis of C-3-functionalized quinolines, which are difficult to access [37].



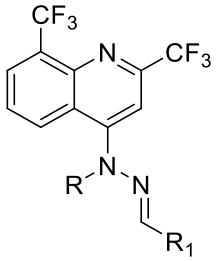
In a new benzylation protocol, various 1,2,3,4-tetrahydroquinolines were efficiently converted in combination with aryl aldehydes into β-benzylated quinolines by employing readily available [RuCl2(p-cymene)]2 as a catalyst and O2 as a sole green oxidant. This step- and atom-economic reaction offers excellent functional group tolerance and chemo-selectivity [38].



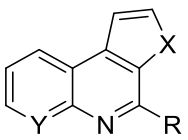
2.2. Pharmacological roles of quinoline derivatives

Quinoline is one of several heterocyclic rings researched by chemists due to its potential uses in a variety of sectors. Through constructive and critical reviews, several authors have emphasized the synthetic and biological relevance of this ring in chemical and medicinal chemistry [39]. The bioactivities of a variety of quinoline analogues are discussed here.

Eswaran et al. had produced several new antitubercular and antibacterial quinolines (1) utilizing mefloquine as the lead, with active pharmacophores such as hydrazones, ureas, thioureas, and pyrazoles coupled at the 4th position that had useful activity against tuberculosis bacteria [40].



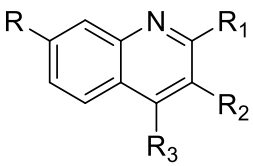
R=R1=Alkyl, Allyl, Heteroaryl

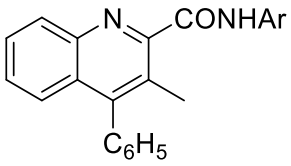


R=Aromatic, X=O,S, Y=N, CH

(1) (2)

Anupam et al. reported a new synthetic approach for the synthesis of fused thieno/furoquinoline (2) compounds, as well as anti-tubercular activity screening of the molecules, with compounds carrying a fused furo[2, 3-c][1, 8] naphthyridine skeleton showing the most activity. 4-(4-methoxyphenyl)furo[2, 3-c] [1, 8] naphthyridine had the best MIC value of 5.6 µmol, which was determined to be superior to the present first-line anti-tubercular medication ethambutol that had an MIC 7.6 µmol [41] .

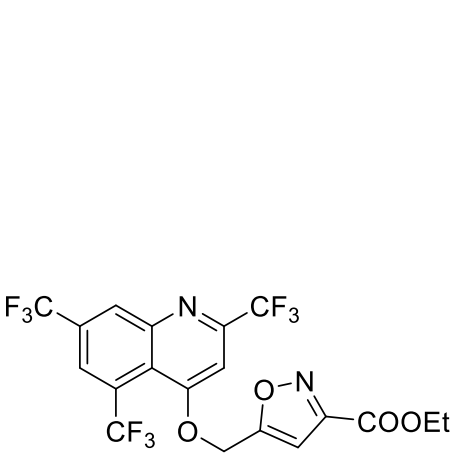




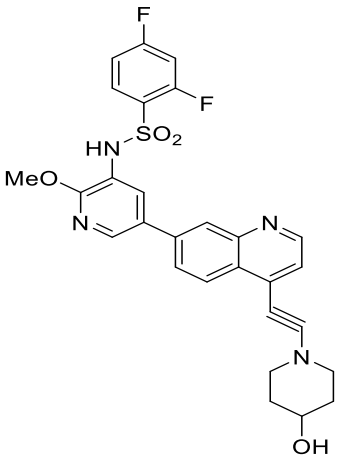
(3) (4)

Asit et al. designed, prepared, and tested two series of quinoline (3 and 4) based compounds that possess excellent anti-tubercular activity against M. tuberculosis H37Rv [42]. The compounds showed promising results, with some derivatives exhibiting MIC values comparable to or better than standard antitubercular drugs.

A quinoline ring-based isoxazole derivative with a side chain (5) was synthesized by Lilienkampf et al. that had significant antituberculosis activity [43]. The compound demonstrated potent inhibition of mycobacterial growth, making it a potential candidate for further development as an antitubercular agent.

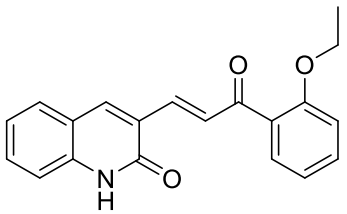


(5)

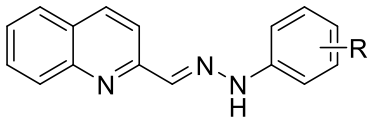


(6)

Hu et al. developed, synthesized, and physiologically assessed a new series of 4-alkynyl-quinoline derivatives (6) for their PI3K inhibitory activities and anti-proliferative effects against two cancer cell lines PC-3 and HCT-116 [44]. The study identified several compounds with potent anticancer activity, highlighting the potential of quinoline derivatives as PI3K inhibitors. In a series of quinoline-conjugated chalcone hybrids, compound 7 had exhibited excellent anticancer activity with an IC50 = 1.05 µM against the tested cancer cell lines [45]. The hybrid molecule demonstrated superior cytotoxicity compared to the individual pharmacophores, showcasing the synergistic effect of combining quinoline and chalcone moieties.



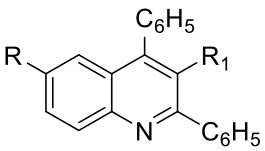
(7)



R=Different electron releasing/withdrawing groups

(8)

Suzen et al. synthesized, characterized, and studied in vitro antioxidant activity of quinoline-2-carbaldehyde hydrazone (8) analogues as bioisosteric mimics of Melatonin [46]. The compounds exhibited promising antioxidant properties, indicating their potential as melatonin analogues with enhanced bioactivity.



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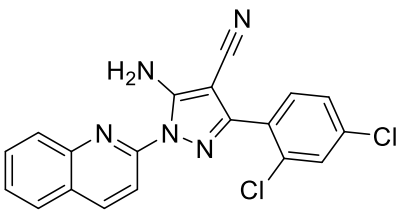
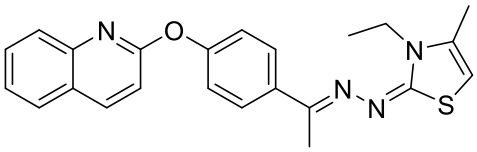


(10)

In vitro tests were used by Luchese et al. to evaluate the antioxidant impact of a novel family of quinoline compounds (9). The antioxidant activity of substances was assessed using lipid peroxidation, thiol peroxidase-like, and free radical scavenging activities [47]. The results demonstrated the potential of these quinoline derivatives as effective antioxidant agents. 5-amino-3-(2,4-dichlorophenyl)-1-(quinolin-2-yl)-1H-pyrazole-4-carbonitrile (10) had shown excellent antibacterial activity (MIC values (0.12–0.98 µg/mL) in the study conducted Mohamed et al [48]. The compound emerged as a promising antibacterial agent with potent activity against a range of bacterial strains.

Sally and colleagues had clubbed quinoline via a phenyloxy group to thiazoline carbohydrazide (11) that resulted in the development of new compounds with potent antibacterial and antifungal activities [49]. The hybrid molecules demonstrated enhanced bioactivity compared to their individual components, highlighting the potential of molecular hybridization in drug discovery.



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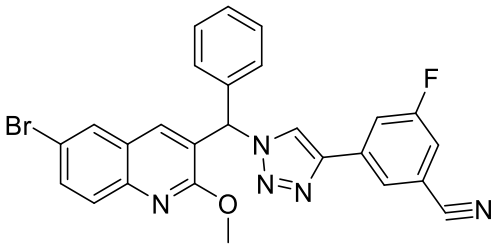


(12)

Desai et al. synthesized a series of 2-{4-[2-(7-substituted-quinolin-4-yloxy)ethyl]phenyl}-5-(4-nitrophenyl)-1,3,4-oxadiazoles (12) and evaluated their antibacterial and antifungal activities [50]. Several compounds exhibited potent antimicrobial activity, with some derivatives showing superior efficacy compared to standard drugs like ciprofloxacin and fluconazole.

Antimalarial activity of 4-aminoquinoline-clubbed 1,3,5-triazine derivatives was reported by Kumar et al [51]. The study identified several compounds with potent antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum, indicating their potential as novel antimalarial agents. Bhagat et al. designed and synthesized a series of novel 4-aminoquinoline-1,3,5-triazine conjugates and evaluated their antimalarial activity against Plasmodium falciparum [52]. The compounds demonstrated promising antimalarial activity, with some derivatives exhibiting IC50 values in the nanomolar range.

3. 2-Azetidinone (B-Lactam)

2-Azetidinone, commonly known as β-lactam, is a four-membered cyclic amide. It is a crucial structural component of several antibiotic families, including penicillins, cephalosporins, carbapenems, and monobactams [53]. The β-lactam ring is responsible for the antibacterial properties of these drugs, as it inhibits the synthesis of the bacterial cell wall.

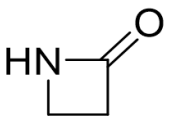
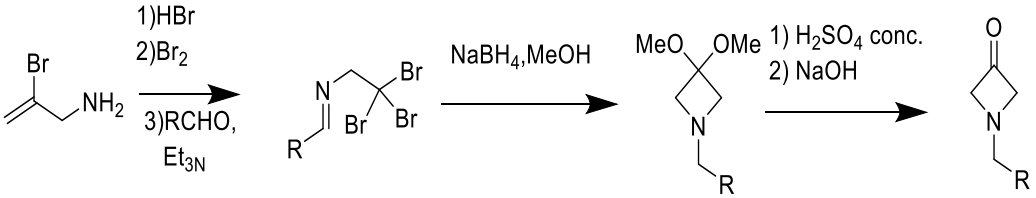


Figure 7. Structure of 2-azetidinone (β-lactam)

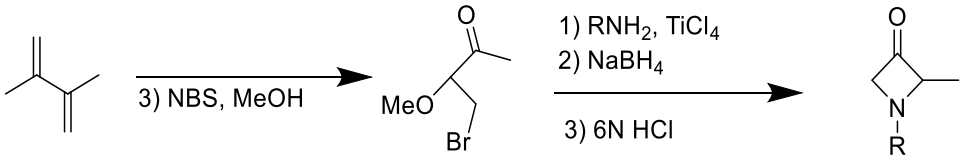
3.1. Methods of synthesis of 2-azetidinone derivatives

De Kimpe's group106 has developed new syntheses of N-substituted azetidine-3-ones. Compound are obtained in six simple steps and 30-40% overall yield from 2-bromo allylamine [54].



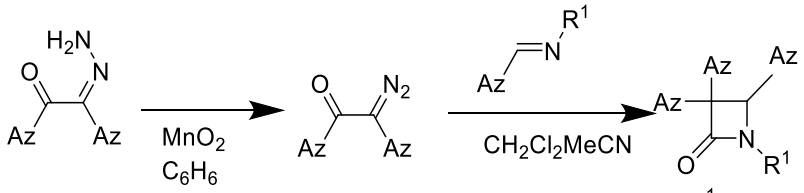
R= $CHMe_2$	29%
R= $CHEt_2$	29%
R = c-Hex	37%
R = Ph	29%
R = 4-MeC_6H_4	28%
R = 4-$MeOC_6H4$	40%

2-Methyl-N-alkyl azetidine-3-ones were synthesized from butane-2,3-dione in six simple steps and similar overall yield [55].

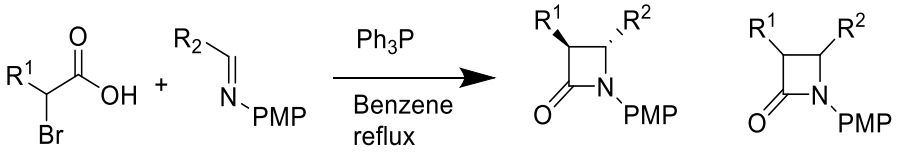


R = *i*-Pr 57%
R = *i*-Bu 63%
R = *Bu* 64%

Di(2-azulenyl) ethanedione monohydrazone was oxidized with MnO2 to the R-diazoketone that, upon heating in the presence of imines, afforded the corresponding –lactams[56].

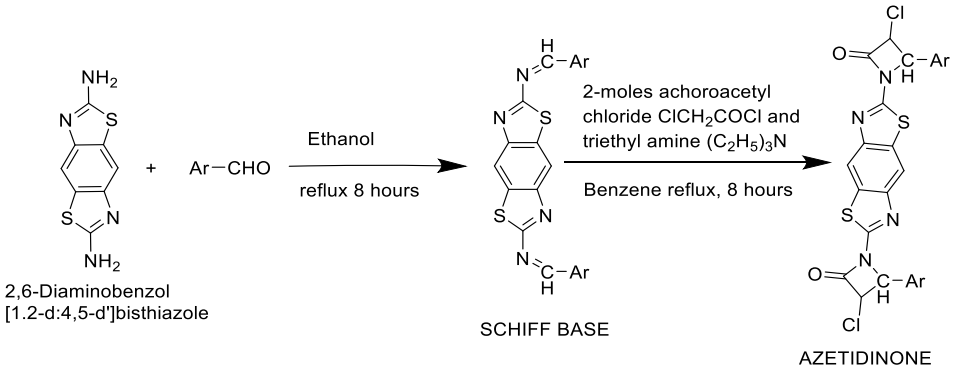


The reaction between R-bromo-carboxylic acids and imine can be mediated by triphenylphosphine. The reaction occurs in refluxing benzene with a moderate-to-quantitative yield and a remarkable selectivity toward the trans stereoisomer [57].

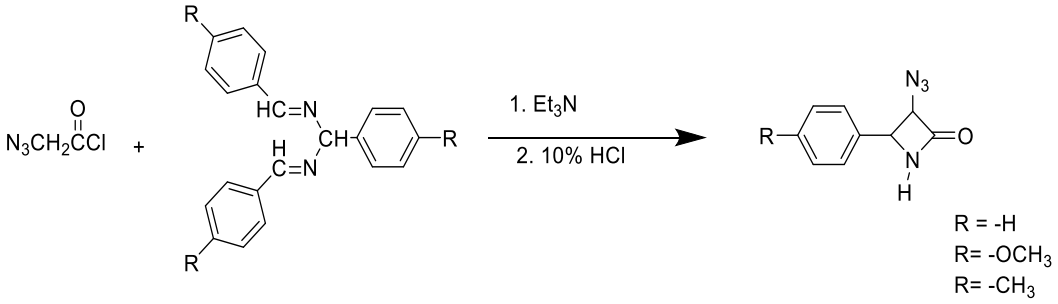


R^1 = Ph R^2 = 4 - $(MeO)C_6H_4$
R^1 = Ph R^2 = Ph
R^1 = Ph R^2 = 4- ClC_6H_4
R^1 = Ph R^2 = 4- $(NO_2)C_6H_4$

2,6-Diaminobenzo[l,2-d:4,5-d']bisthiazole was taken in alcohol. Benzaldehyde (0.05 mol, 5.3g) was added. The mixture was then refluxed with occasional stirring for 5 hours. After 5 hours the alcohol was distilled off to get the product. The schiff base was recrystallized from alcohol. Other substituted Schiff Bases were prepared in a similar manner. The above synthesized schiffs base (0.0075 mol, 30 g) in benzene was taken in a 500 ml flat bottomed flask. To it chloroacetyl chloride (0.015 mol, 1.68 g) and triethyl amine (0.015 mol,l -5 g) in benzene were added slowly. The mixture was then refluxed for 8-10 hours. The product was filtered, dried and washed with water to remove triethyl aminehydrochloride and was recrystallized from alcohol. Other substituted azetidinones were prepared in a similar manner [58].



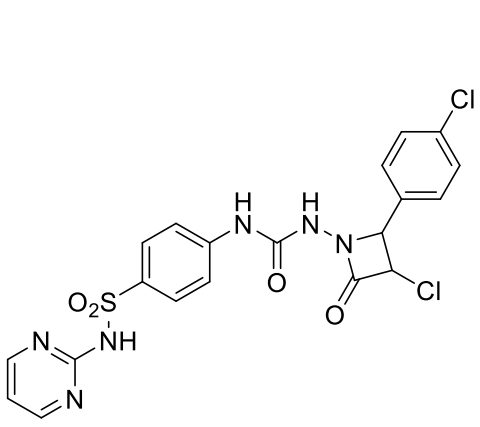
The synthesis of N-unsubstituted 2-azetidinones was achieved by the cycloaddition of acidoacetyl chloride to the corresponding α, α-dibenzylideniminotoluen-(hydrobenzamide) in the presence of triethylamine followed by hydrolysis [58].



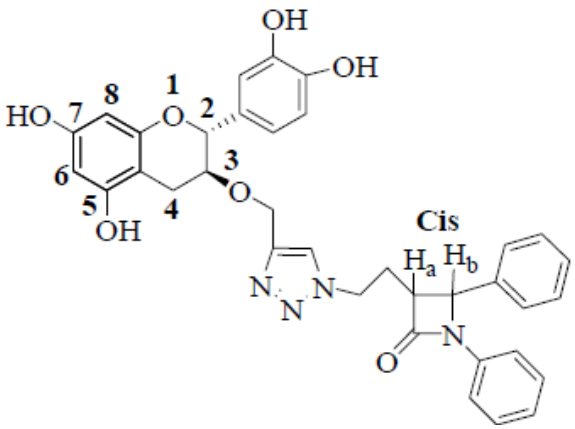
3.2. Pharmacological roles of 2-azetidinone derivatives

2-Azetidinones, or β-lactams, are well-known for their antibacterial properties and are the core structure of several antibiotic families, such as penicillins, cephalosporins, carbapenems, and monobactams [59]. However, recent studies have revealed that 2-azetidinone derivatives possess a wide range of pharmacological activities beyond their antibacterial effects.

Because of the widespread interest in azetidinones, much research on their synthesis and the assessment of their biological activity has been conducted. Medicinal chemists have analysed the structural properties of azetidinones that are responsible for their various actions, and this has been highlighted in a number of reviews [45]. Some of the azetidinones derivatives with useful bioactivities has synthesized and tested a new series of 2-azetidinones as potential antioxidant leads and shown that compound 4-(3-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl) ureido)-N-(pyrimidin-2-yl)benzenesulfonamide (**1**) had significant antioxidant activity that is more than the standard ascorbic acid in the DPPH assay [60].



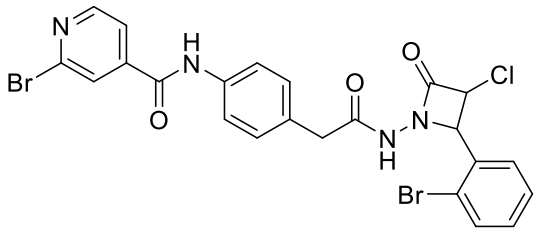
(1)



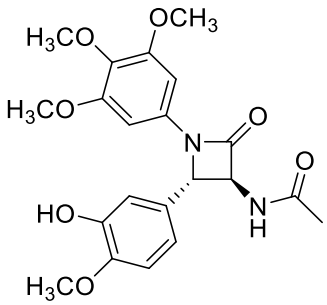
(2)

Catechins were connected to the 2-azetidinone scaffold via a triazole linker (2) and these class of compounds had elicited excellent antibacterial activity against the bacterium Escherichia coli in a study [61].

Rakesh et al had investigated the antitubercular activity of Bromo-pyridyl conjugated 3-chloro 2-azetidinones and found that compound 3 had elicited excellent activity with and MIC of 25.0 μg/mL [62].



(3)



(4)

Farida and colleagues had evaluated the anticancer activity of amino-2-azetidinone derivatives against colorectal cancer cell lines. The compound 4 had shown the highest potency among the other derivatives [63-65].

4. 4-Thiazolidinone

4-Thiazolidinones are five-membered heterocyclic compounds containing sulfur and nitrogen atoms (Figure 2.4). They are known for their diverse pharmacological activities, including antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and antidiabetic properties [66]. The 4-thiazolidinone scaffold is considered a privileged structure in medicinal chemistry due to its ability to interact with multiple biological targets.

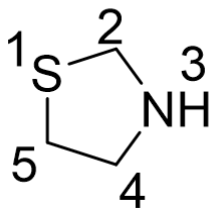
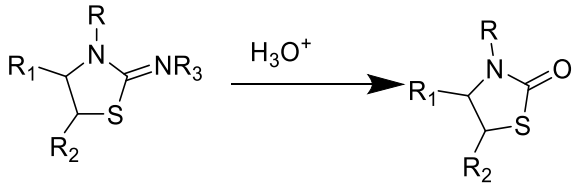


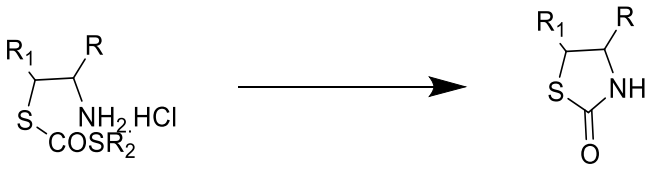
Figure 8. Structure of 4-thiazolidinone

4.1. Methods of synthesis of 4-thiazolidinone derivatives

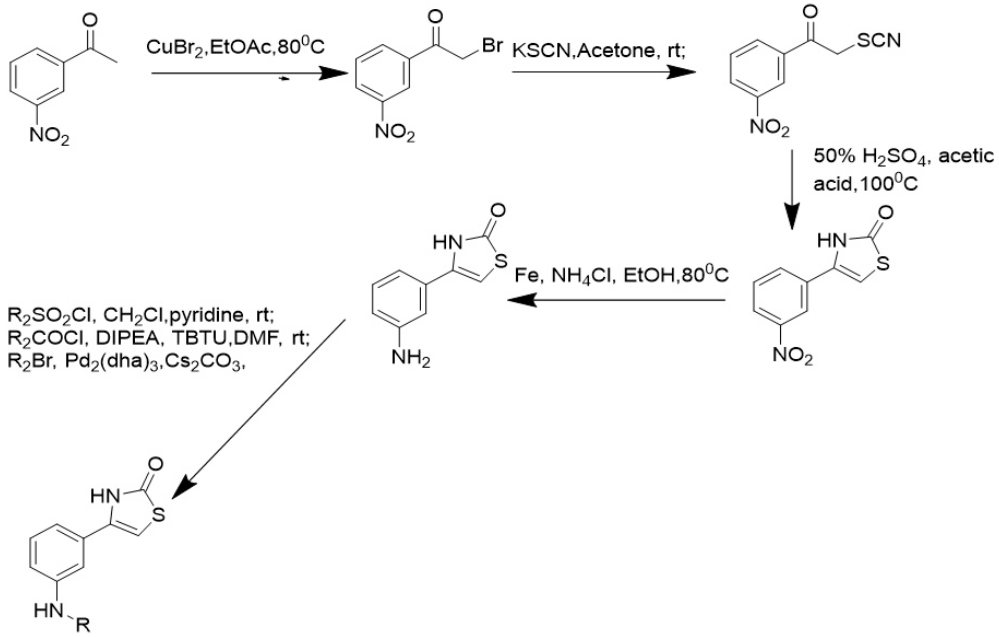
The most common method for the synthesis of 4-thiazolidinones involves the condensation of primary amines with thiocarbonyl compounds, such as carbon disulfide, thiourea, or dithiocarbamates, followed by cyclization with α-halocarboxylic acids or their derivatives [67]. Acid hydrolysis of 2-iminothiazolidines yields good yields of the corresponding 2-thiazolidinones [68].



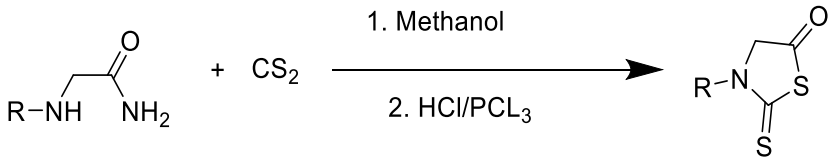
Thiazolidinones were synthesized using the starting material 2-aminoethyl benzyl dithiocarbamate hydrochloride [69].



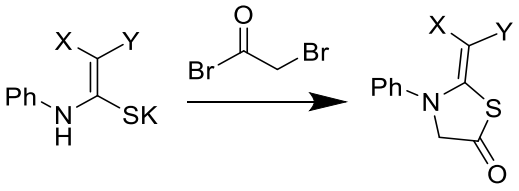
A group of researchers created C-3 substituted 2-thiazolidinones in order to investigate the biological relevance of the understudied 2-thiazolidinone moiety. They developed these scaffolds utilizing a fragment-based drug design technique and synthesized them in many phases [70].



The reaction of N-methylglycine amide with carbon disulfide in the presence of methanol to create N-methyl-N-(carbamoylmethyl) ammonium N-methyl-N-(carbamoylmethyl) dithiocarbamate yielded 2-thio-3-methyl-5-thiazolidinone derivatives. To make the final product, the dithiocarbamate was acidified with strong HCl or PCl_3 [71].



The thiazolidin-5-ones are produced via KBr and HBr elimination of non-ionizable chemicals with bromo acetyl bromide [72].



2. A one-pot, three-component reaction of primary amines, aldehydes, and mercaptoacetic acid or thioglycolic acid in the presence of a suitable catalyst, such as ZnCl2 or p-toluenesulfonic acid, provides an efficient and eco-friendly approach for the synthesis of 4-thiazolidinones [68]. This protocol offers mild reaction conditions, good yields, and a broad substrate scope.

3. A microwave-assisted synthesis of 4-thiazolidinones via the condensation of Schiff bases with thioglycolic acid or mercaptoacetic acid has been developed [69]. This method significantly reduces reaction times and improves yields compared to conventional heating methods.

4. An asymmetric synthesis of 4-thiazolidinones using chiral auxiliaries, such as Evans oxazolidinones or chiral amines, has been reported [70]. This approach enables the preparation of optically active 4-thiazolidinone derivatives with high enantioselectivity.

5. A biocatalytic approach for the synthesis of 4-thiazolidinones using lipases or esterases has been developed [71]. This method involves the kinetic resolution of racemic 4-thiazolidinone derivatives, followed by further functionalization. The biocatalytic approach offers high enantioselectivity and mild reaction conditions.

4.2. Pharmacological roles of 4-thiazolidinone derivatives

4-Thiazolidinones are known for their wide range of pharmacological activities, including antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and antidiabetic properties. The following sections discuss some of the recent advances in the pharmacological applications of 4-thiazolidinone derivatives.

4.2.1. Antibacterial and antifungal activities of 4-thiazolidinone derivatives

Desai et al. synthesized a series of 4-thiazolidinone derivatives and evaluated their antibacterial and antifungal activities [73]. Several compounds exhibited potent antimicrobial activity against a wide range of bacterial and fungal strains, with some derivatives showing superior efficacy compared to standard drugs like ciprofloxacin and fluconazole.

A novel series of 4-thiazolidinone-benzimidazole hybrids were designed, synthesized, and evaluated for their antibacterial and antifungal activities by Patel et al [74]. The compounds demonstrated promising antimicrobial activity, with some derivatives showing potent inhibition of both Gram-positive and Gram-negative bacteria, as well as various fungal strains.

4.2.2. Anticancer activity of 4-thiazolidinone derivatives

Havrylyuk et al. reported the synthesis and anticancer activity of a series of 4-thiazolidinone derivatives bearing a pyrazoline moiety [75]. The compounds were evaluated for their cytotoxicity against various cancer cell lines, and several derivatives exhibited potent anticancer activity, with IC50 values in the micromolar range.

A novel series of 4-thiazolidinone-quinoline conjugates were designed, synthesized, and evaluated for their anticancer activity by Malki et al [76]. The compounds demonstrated promising cytotoxicity against several cancer cell lines, with some derivatives showing superior efficacy compared to standard anticancer drugs like doxorubicin.

4.2.3. Antidiabetic activity of 4-thiazolidinone derivatives

Patil et al. synthesized a series of 4-thiazolidinone derivatives and evaluated their antidiabetic activity in streptozotocin-induced diabetic rats [77]. Several compounds exhibited potent glucose-lowering effects and improved lipid profiles, with some derivatives showing superior efficacy compared to standard antidiabetic drugs like rosiglitazone.

A novel series of 4-thiazolidinone-pyrazole hybrids were designed, synthesized, and evaluated for their antidiabetic activity by Chauhan et al [78]. The compounds demonstrated promising glucose-lowering effects in both in vitro and in vivo models, with some derivatives showing superior efficacy and reduced side effects compared to standard antidiabetic drugs.

4.2.4. Anti-inflammatory activity of 4-thiazolidinone derivatives

Ottanà et al. reported the synthesis and anti-inflammatory activity of a series of 4-thiazolidinone derivatives [79]. The compounds were evaluated for their ability to inhibit cyclooxygenase (COX) enzymes and reduce carrageenan-induced paw edema in rats. Several derivatives exhibited potent anti-inflammatory activity, with some compounds showing superior selectivity for COX-2 over COX-1.

A novel series of 4-thiazolidinone-indole hybrids were designed, synthesized, and evaluated for their anti-inflammatory activity by Rajput et al [80]. The compounds demonstrated promising anti-inflammatory activity in both in vitro and in vivo models, with some derivatives showing superior efficacy and reduced side effects compared to standard anti-inflammatory drugs like indomethacin.

5. Conclusion

In conclusion, quinoline, 2-azetidinone, and 4-thiazolidinone derivatives have emerged as promising scaffolds for the development of novel therapeutic agents with diverse pharmacological activities. The structural modifications and molecular hybridization of these privileged heterocycles have led to the discovery of numerous bioactive compounds with potent anticancer, antibacterial, antifungal, antimalarial, antioxidant, anti-inflammatory, and antidiabetic properties. The recent advances in synthetic methodologies, such as multicomponent reactions, microwave-assisted synthesis, asymmetric synthesis, and biocatalytic approaches, have greatly facilitated the efficient and eco-friendly preparation of these heterocyclic compounds. Moreover, the structure-activity relationship (SAR) studies and molecular docking simulations have provided valuable insights into the binding interactions and mechanisms of action of these bioactive compounds, guiding the rational design of more potent and selective derivatives. Despite the significant progress made in the development of quinoline, 2-azetidinone, and 4-thiazolidinone derivatives as therapeutic agents, there is still a need for further optimization and preclinical studies to address issues related to solubility, bioavailability, and toxicity. Additionally, the identification of novel molecular targets and the exploration of new pharmacological applications for these heterocyclic scaffolds remain active areas of research

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