



From Classical to Contemporary: A Review on the Synthesis and Biological Activities of Quinoline and Its Derivatives

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Abstract

Quinoline-derived analogues have considerable significant attention due to their wide range of pharmacological activities and promising therapeutic applications. The recent advancements in the synthesis of quinoline-based hybrid, bioconjugates, highlighting their role in enhancing pharmacological properties and targeting specific biological pathways is very important to study due to its vast activity potential. The present topic is based on various synthetic strategies employed to develop hybrid structures, including the incorporation of quinoline moieties into diverse pharmacophores through innovative coupling and conjugation methods. The study of hybrids with improved efficacy in antimalarial, anticancer and antibacterial activities and emphasising their structure-activity relationships (SARs) and molecular mechanisms of action is also existing in this present topic. The integration of these moieties with other bioactive fragments is shown to offer synergistic effects, leading to compounds with potent and selective biological profiles. Looking ahead, several future directions are identified to further advance the field, including the exploration of new synthetic methodologies to streamline the production of quinoline hybrids and the use of computational techniques for more precise design and optimisations. Collaborative efforts in structural biology and pharmacokinetics are also crucial for the advancement of these compounds. Overall, continued innovation and interdisciplinary research will be essential for realising the full potential of quinoline based hybrids in therapeutic applications.

Key words: Quinolines; Quinoline-hybrid; Quinoline-bioconjugates; Structure-activity relationship; Pharmacological activity; Chemistry techniques, synthetic.

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Introduction

Quinoline is a widely utilised heterocyclic aromatic compound consisting dicyclic ring that has achieved the prominent position in the medicinal chemistry due to their remarkable pharmacological and biological properties.¹ The impure form of quinoline was first obtained from coal tar and can also obtain as degradation product

from quinine and cinchonine.² The pure form of quinoline is in colourless oily hydroscopic liquid form with 4.85 pKa value in the water at 20 °C with molecular formula of C₉H₇N and molecular weight of 126.16. It is used as a high-boiling solvent and weakly tertiary base.³ It executes both types of electrophilic and nucleophilic substitu-

tion reaction.⁴ Moreover, it can react with acids to form salt molecules and carry out the reaction similar to pyridine and benzene. Quinoline is derived from naphthalene ring by replacing the one of α -CH units by nitrogen atom and also named as benzo pyridine, 1- benzazine and 1- azonaphthalene.⁵ The success of quinoline in numerous biological activities has solidified its position as common approach in drug discovery.⁶

Quinolines exhibit significant biological activities consequent nitrogen atom in the nucleus, such as antimalarial,⁷ antimicrobial,⁸ antimycobacterial,⁹ antidepressant,¹⁰ anti-inflammatory,¹¹ anti-convulsant,¹² antiviral,¹³ anticancer,¹⁴ antihypertensive¹⁵ and also being used broadly in urinary tract infection,¹⁶ respiratory infection,¹⁷ sexually transmitted diseases,¹⁸ pneumonia,¹⁹ prostatitis,²⁰ bone joint infection²¹ and acute bronchitis.²² Quinoline derivatives are most commonly used as antimicrobial that works by two mechanisms either they restrained DNA synthesis by target-

ing cleavage of bacterial DNA gyrase or inhibits type IV topoisomerase, which lead instant death of bacteria.²³ In addition, several drugs contain quinoline moiety in their core structure such as chloroquine, saquinavir, bedaquiline, clioquinol, hydroxychloroquine, camptothecin, dibucaine, norfloxacin (Figure 1).

The synthesis of the quinoline heterocyclic ring is a fundamental pursuit in organic chemistry, evidenced by the extensive research on reaction methodologies.²⁴ Quinolines boast a versatile core structure accessible through numerous methods, including the reliable Skraup synthesis, introduced in 1880, later in 1882 more versatile quinoline synthesis reactions were introduced named Friedlander synthesis and Doebner-von Miller reaction.²⁵ Over time, researchers have developed a diverse arsenal of reaction to synthesise quinolines such as Conrad-Limpach reaction, Combes quinoline synthesis, Povarov reaction²⁶ (Figure 2).

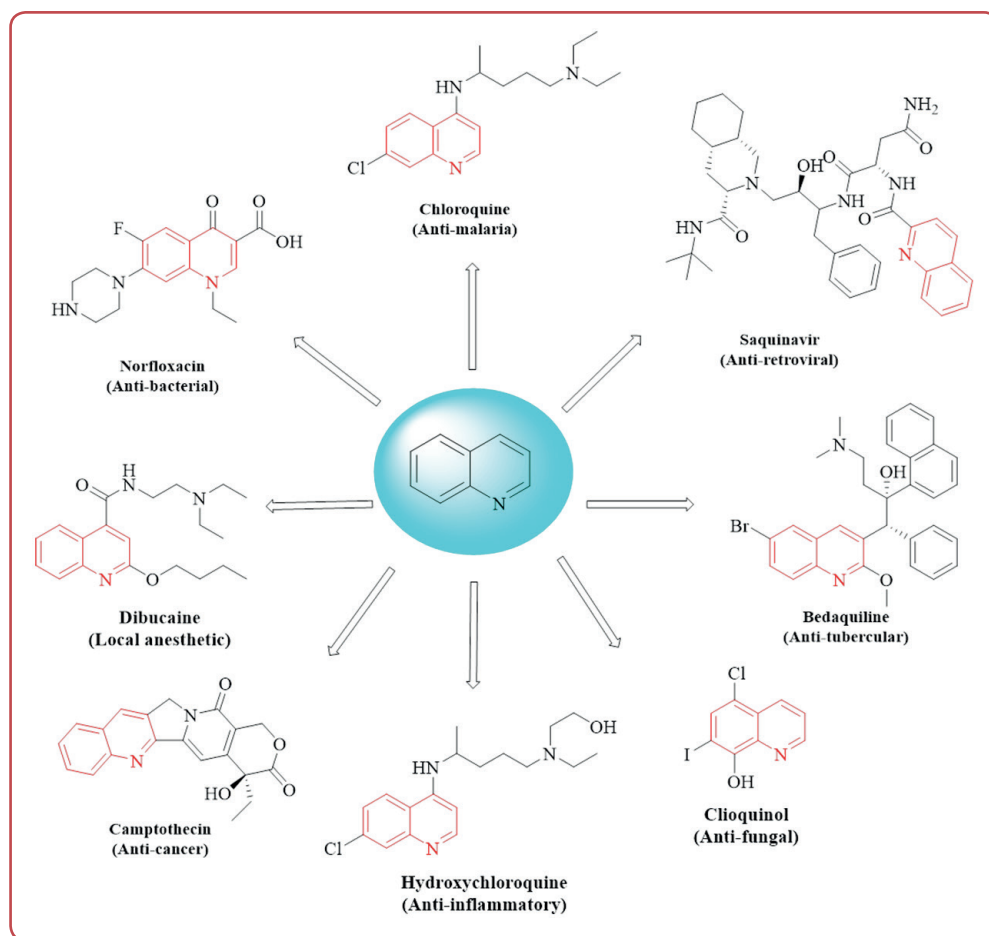


Figure 1: Structures of quinoline pharmacophore, quinoline-containing drugs with their pharmacological action

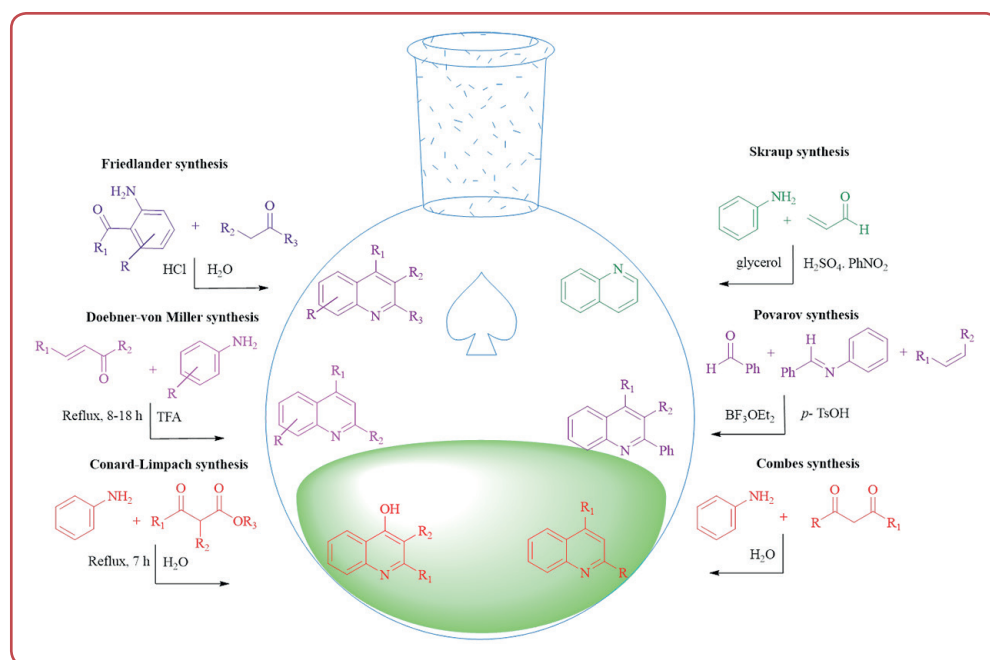


Figure 2: Traditionally naming reaction for quinoline synthesis

In general, existing methods offer versatile routes to a wide array of quinolines synthesis, from simple to complex structure, however, they often suffer from limitations such as low efficiency, harsh conditions and restricted functional group tolerance.²⁷ Consequently, researchers have continuously sought to refine these approaches to overcome these challenges.²⁸

Recent trends in quinoline synthesis

Skraup reaction involves refluxing of aniline and glycerol for an extended period of time with an antioxidant along with sulfuric acid. However, due to harsh synthesis conditions, low yield and temperature control, do not recommend this process for practical use. Over the last decade, the microwave energy is being in used than traditional heat sources, this reduces the reaction time and increases the yield.²⁹ Amarsekara and Hasan enforced the microwave energy to the Skraup reaction, substituted aniline **1** and glycerol **2** in 1:3 ratio and replacing the concentrated sulfuric acid with imidazolium cation-based sulfonic acid ion liquid that will improve the reaction outcome, as a result of these modification quinoline **3** will obtain with good yield.³⁰

Doebner reaction is other method to produce

quinoline from aniline, pyruvic acid and benzaldehyde to form quinoline analogues with carboxylic acid, usually involves long reaction time and low yield.³¹ In advance approach quinoline synthesis is taken by condensation of aniline **1** with aldehyde **4** and replacing the pyruvic acid with aldehyde, thus acquiring 2,3- substituted quinoline **5**.³² Additionally, H_2O_2 act as environment-friendly oxidant alternative and catalytic amount of AlCl_3 to increase the yield of quinoline product.³³

The Doebner-Von Miller (DVM) reaction is used to produce 2-substituted quinolines by consuming α , β -unsaturated carbonyl compound and substituted aniline components.³⁴ However, low yield is the main problem in this process, thereby the use of two-phasic reaction medium to isolate the carbonyl compound in an organic phase, proved to be a breakthrough, as it effectively prevented polymerisation and led to a substantial increase in product yield.³⁵ The advance synthesis scheme follows the use of acrolein **6** in a biphasic reaction medium and undertaking the reaction in dilute HCl, result as production of diverse variety of quinoline derivatives with great yields. The mechanism followed as aniline **1** reacts through conjugate addition with intermediates formed from acid-catalysed hydrolysis of acrolein diethyl acetal: protonated acrolein or an oxocarbenium ion. The resulting product undergoes dehydrative ring closure followed by oxidation to afford the quinoline products **7**.³⁶

Conrad-Limpach reaction is the universal method to form quinoline-4-ols under heat conditions by using aryl amines and β -ketoesters. Although, several challenges such as original solvent-free method had limitations and use of expensive, inefficient solvents such as Dowtherm A, mineral oil, diphenyl ether and are not worth using.³⁷ Conard-Limpach-like multicomponent reaction (MCR) is new approach to synthesis of 4-acetylquinolines **10** MCRs are powerful tool to construct the complex structure: quinolines are formed via naphthylamine **8** by this process, under aldehyde **4** and β -ketoester **9** reacting in camphorsulfonic acid (CSA) catalysis.³⁸ This reaction likely proceeds via a Michael-type and activated -CSA β -ketoester added to a pre-synthesised imine. The resulting reaction intermediate undergoes cyclisation and aromatisation to produce quinolines with high yield.³⁹ MCR strategy bypass a high-energy intermediate typically seen in such reactions, enabling the use of low-boiling acetonitrile as a solvent.⁴⁰

Povarov reaction is well suited example to synthesise the aza-heterocyclic compounds via MCR. Typically, Povarov reaction combines aryl amines, aldehydes and activated alkenes to create tetrahydroquinolines through an inverse electron-demand Diels-Alder process.⁴¹ Hu et al introduced a streamlined method to synthesise quinolines using iodine as a catalyst. This process directly covert aniline **1** and aldehyde **4** and an alkyl **11** into quinoline derivatives. Initially, aniline and aldehyde form a Schiff base, which then interacts with iodine to create a complex, further, undergoes a Diels-Alder reaction proceeds with formation of dihydro intermediate by alkyne, which is subsequently oxidised by atmospheric oxygen to yield 2- and 4- substituted quinolines **12** in moderate to high amounts⁴² (Figure 3).

Friedlander reaction is classic and simple method for quinoline synthesis, among many well-established quinoline synthesis procedures.⁴³ It is known for its versatility but faces challenges in

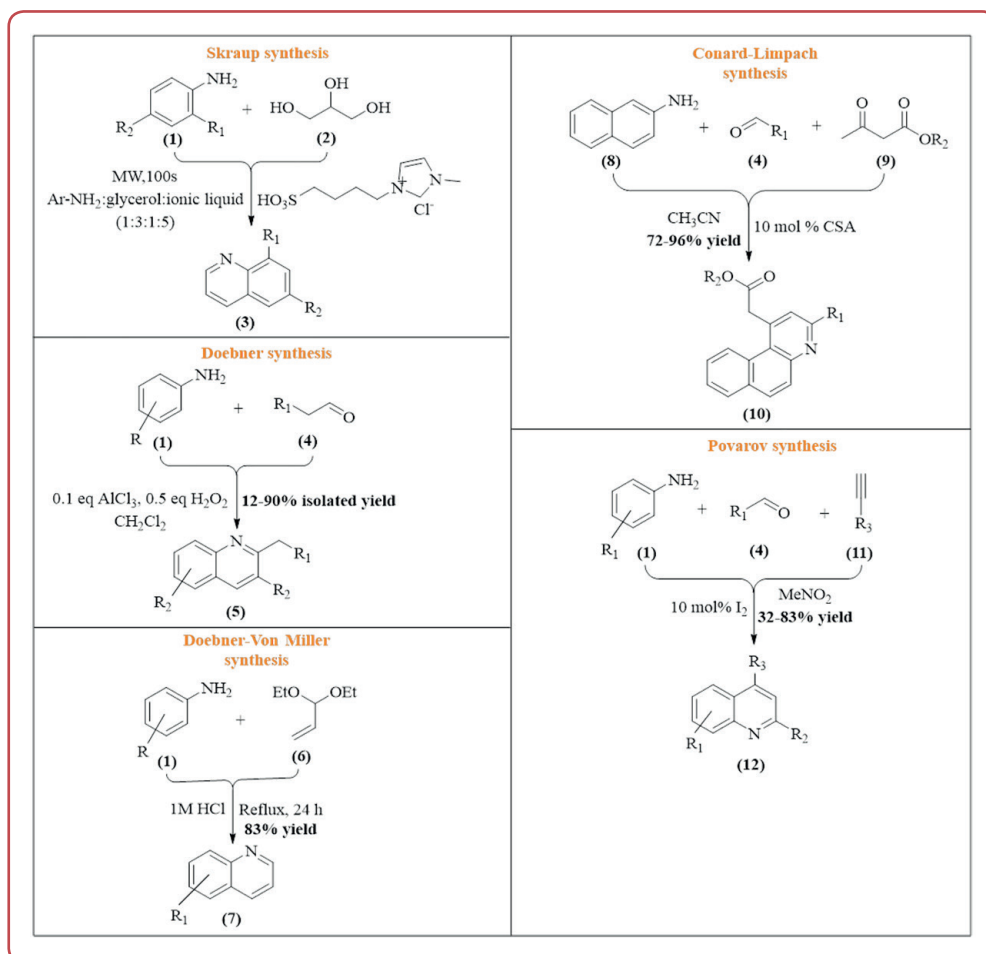


Figure 3: Recent trends in quinoline synthesis

regioselectivity when using unsymmetrical ketones.⁴⁴ To overcome this limitation, researchers have been exploring modified approaches to enhance the reaction's efficiency and control.

Several modified forms of Friedlander quinoline synthesis have been reported by many researchers (Figure 4). Dughera and colleagues previously used *o*-benzene disulphonamide as catalyst in several synthesis due to its corrosive-resistant, low volatility and reusable properties. Using this catalyst, a solvent-free Friedlander reaction proceeds by reacting 2-aminoaryl carbonyl compound **13** with numerous carbonyl-containing compounds **14**. This reaction produced variety of 2,3-bis-substituted quinolines **15**, including structures with fused five-membered rings, in moderate to high yields.⁴⁵ Reddy et al also explored a catalyst, Bronsted acid for Friedlander reactions. They investigated that solid Chitosan- SO₃H acid, is an extremely productive activator for the annulation of 2-aminoaryl carbonyl compound **13** with diverse carbonyl compounds **14**, even with cyclised and sterically restricted moieties. This reaction produced wide range of 2,3,4- tri-substituted quinolines derivatives **16** in excellent yield with brief reflux period.⁴⁶ The acid catalyst was readily retrieved and reactivated from homogeneous mixture and utilised again with good success.⁴⁷

Gu and coworkers reported an unexpected reaction that produced benzazepine-fused quinolines. They used Lewis's acid catalysts, 2-aminobenzaldehydes **17**, 2- methyl indole **18** and acetophenone **19** as starting materials. This mechanism commences with a Lewis acid-facilitated union of 2-aminobenzaldehyde and 2-methylindole. Subsequent to this, the intermediate undergoes a nucleophilic cyclisation event, culminating in the scission of the C-N bond. The liberated aryl-amine subsequently engages in a nucleophilic assault upon acetophenone, leading in the production of an intermediate. This intermediate then go through an Mannich-type enamine-activated cyclisation, affording benzazepine- fused quinolines **20** in respectable to exceptional yields.⁴⁸⁻⁵⁰

Kwon et al described a reliable phosphine-catalysed coupling of *N*-tosylated 2- amino aryl carbonyl compounds **21** with alkynes **22**, yielding hydrogenated quinoline derivatives **23**. These intermediates were readily transformed into quinolines through a mild quench using dilute HCl. Three potential mechanistic pathways proposed by Kwon and endeavoured to discern the right sequence by primarily intermediates via NMR spectroscopy. Although this eventually proved unsuccessful and concluded with that the reaction proceeds by a mechanism involving base

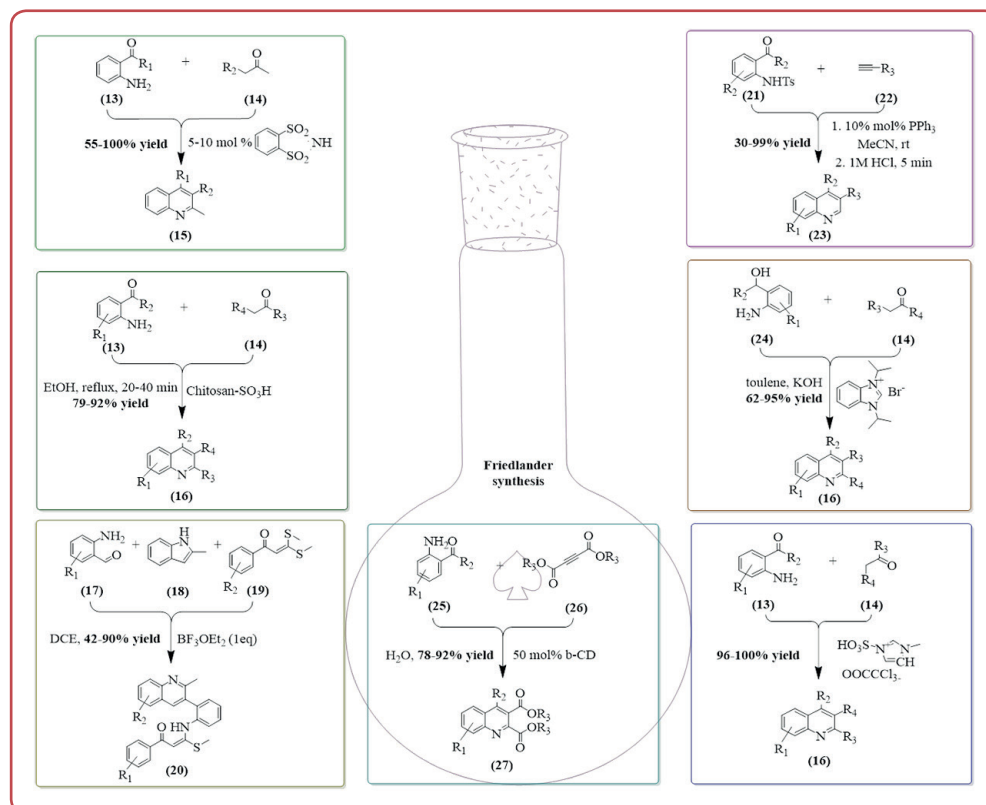


Figure 4: Recent trends in Friedlander synthesis

catalysis. The phosphine activated by alkyne initially and afterwards abstracts a proton due to the presence of tosyl group, amine become highly acidic. The resulting amine act as nucleophile and attacked a second alkyne molecule, resulting in cyclisation.⁵¹

Cai and Zhu employed N- containing heterocyclic carbenes, a distinct Lewis base, to synthesise diverse quinolines derivatives from Ketones **14** and 2-aminobenzyl alcohols **24**. They postulated that the N-heterocyclic carbenes, formed in situ through the deprotonation of precursor by hydroxide, likely facilitate the sequential hydride and proton transferred from benzyl alcohol to ketone. This process generates reactive intermediates that subsequently experience cyclisation and crossed aldol addition with the concomitant H₂O loss, ultimately affording the end quinoline prod-

ucts **16** with high to excellent yields.⁵² Sarma et al explored the utilisation of liquid ionic Bronsted-acidic as catalysts in a traditional Friedlander reaction. Their findings indicated that the newly developed liquid ionic catalyst [Msim] [OCCCCl] exhibited comparable efficiency to other established acid catalysts and ionic liquids, resulting in the production of quinolines **16** with yields of up to 100 % from 2-aminoarylketones **13** and carbonyl group **14**. Notably, the catalyst's capacity for recycling and reusability presented an attractive attribute.⁵³

Madhav et al utilised heating of supramolecular catalyst β -CD in aqueous medium and further, reacted with 2-aminobenzophenone **25** and dialkyl acetylene dicarboxylate **26** which yields substituted quinoline **27**.⁵⁴

Natural sources of quinolines

The antimalarial and antiarrhythmic property found in *Cinchona* bark, a cinchona alkaloid plays a vital role in medical history.⁵⁵ In 2018, Murauer and Ganzera utilised supercritical fluid chromatography (SFC) for separation of 6 derivatives of quinoline, which are quinine **28a**, cinchonidine **28b**, dihydroquinine **28c**, quinidine **28d**, cinchonine **28e** and dihydroquinidine **28f**. They could be separable in less than 7 min and three of them were quantified directly in the crude plant extract⁵⁶ (Figure 5).

In 1966, Wall et al discovered camptothecin **29**, a quinoline alkaloid derivative as anticancer drug

and isolated from bark and stem of *Camptotheca aucminata*, a traditional Chinese therapy for cancer.⁵⁷ Govindachari et al and Pendrak et al identified mappicine ketone **30**, an analogue of mappicine **31** which is isolated from *Mapia foetida* as antiviral and anticancer therapies respectively.⁵⁸ Further, antituberculosis activity have been shown by 4-methoxy-2-phenylquinoline **32**, grave-olinine **33** and kokusagine **34**, these are quinoline alkaloids derived from *lunasiaamara*.⁵⁹ The antimicrobial property of berberine **35**, isolated from stem of *berberis aristate* as methanolic extract.⁶⁰ Sylwia et al, reported excellent antifungal activity against *C albicans* by chelerythrine **36**

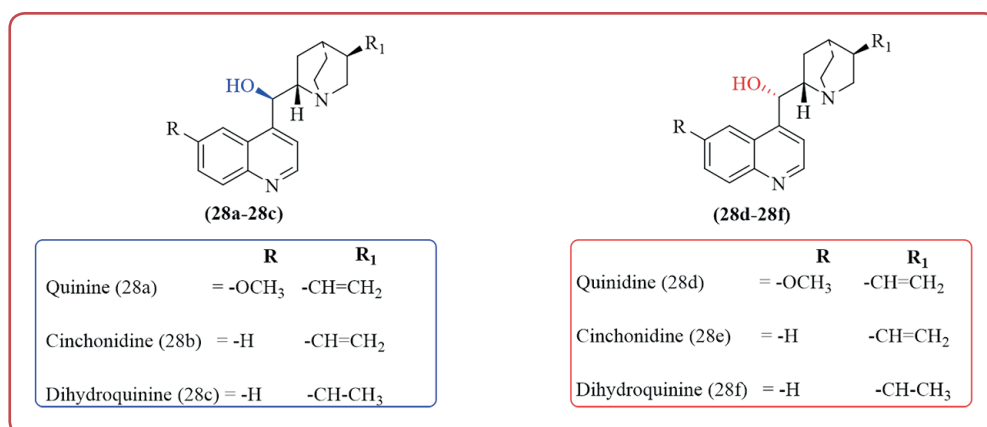


Figure 5: Quinoline natural derivatives

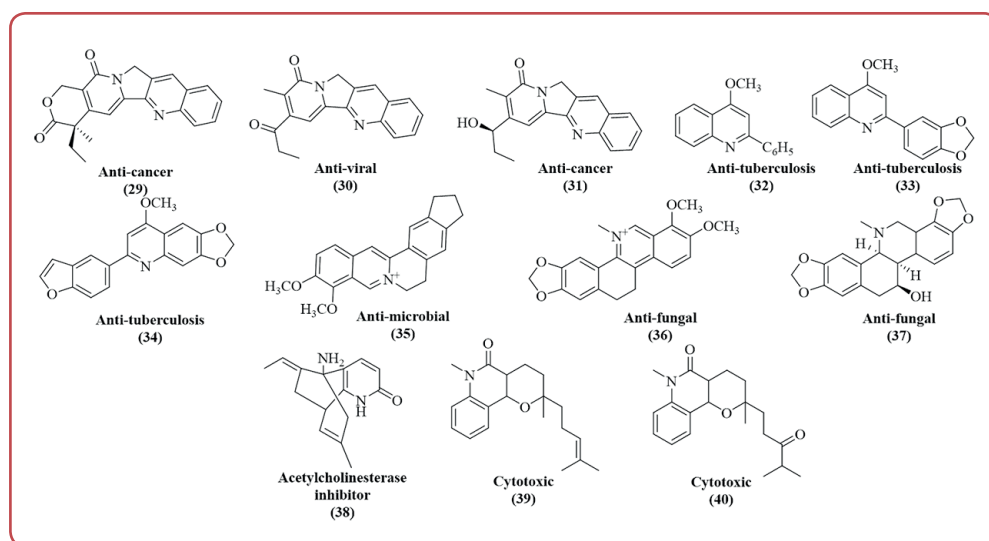


Figure 6: Derivatives of quinoline with their therapeutic activity

and chelidonine **37**.⁶¹ The activity against acetylcholinesterase which is primarily compound to cause Alzheimer disease was derived from huperzine **38 A**, a lycopodium alkaloid derived from *Huperzia serrata*.⁶² In 1994, quinoline alkaloids zanthosimuline **39** and huajiapsimuline **40** were evaluated for cytotoxic property by Chen and co-workers, these compounds were isolated from bark of *Zanthoxylum simulans*⁶³ (Figure 6).

Quinoline- bioconjugation derivatives

Quinoline glycoconjugation

Dominska et al designed a series of novel compound targeting GLUT transporters for anti-cancer treatment which capitalising on the increased demand for glucose targeting GLUT transporters. Among all the series, the findings suggest that the most potent compounds are the glycoconjugate D- glucose analogues, whereby the quinoline consisting triazole is directly linked to the D-glucose unit by the triazole nitrogen atom at the C-6 position.⁶⁴ Firstly, the primary group at C-6 position **41** of D-glucose, underwent selective protection by the introduction of a sterically large trityl (triphenylmethyl) group employing trityl chloride under small amount of 4-dimethylaminopyridine (DMAP). The reaction was conducted in pyridine until the entirely conversion into the final product, as determine by TLC (thin-layer chromatography). Then acetyl chloride was

poured into reaction and further, 33 % HBr added in acetic acid and trityl protection group was removed from C-6. Subsequently, the introduction of a readily removable p-toluene sulfonyl group (tosyl, Ts) at the 6-OH position was carried out using p-toluene sulfonyl chloride, then azide moiety by the reaction of sodium azide group in DMF (dimethylformide) yielding 1,2,3,4-tetra-O-acetyl-6-azido-6-deoxy-D-glucopyranose **42**.⁶⁵ It is noteworthy that the incorporation of azide group necessitated heat up the reaction mixture at 80 °C for a duration of 2 h.⁶⁶ In the next step, acetyl protecting groups was removed from product **42** and by using solution of methanol containing sodium methoxide to give desired product 6-azidp-6-deoxy-D-glucopyranose **43** with 83 % yield. The glycoconjugate with potentially anti-cancer activity was synthesised by reacting the **42** and 8-(2-propyn-1-yloxy) quinoline **44** under reacting influence of CuSO_4 , $5\text{H}_2\text{O}$, NaAsc, i-PrOH/THF/H₂O for 24 hours and product **45** was obtained with yield of 98 %. Similarly, compound **43** reacts with **44** under same reaction conditions to give product **46** with 69 % yield. Further, the reactant **47** was reacting with **44** under similar conditions of reaction mention above to give product **48** with yield 76 % and De-O-acetylation of compound **47** gave component **49** which further reacted in same manner to give product **50** with yield 62 % (Figure 7).⁶⁵

Cytotoxic activity: The cytotoxic activity of quinoline conjugates was determined by MTT test by IC_{50} [μM] activity as given in Table 1.



Compound	HCT-116	MCF-7	NHDF-Neo
45	83.51 ± 1.91	52.84 ± 0.75	129.73 ± 1.49
46	191.15 ± 2.46	54.92 ± 8.71	317.22 ± 9.46
48	46.26 ± 3.12	30.71 ± 0.99	34.48 ± 0.39
50	53.44 ± 5.14	34.04 ± 0.95	70.66 ± 0.75

Chalcone serves as a natural product compound, demonstrating diverse pharmacological activities, particularly anticancer properties. Owing to its simple chemistry and facile synthesis, numerous chalcone derivatives have been synthesised, exhibiting a range of several biological activities.⁶⁹ Gaun et al synthesised a chain of novel quino-line-chalcone bioconjugation as anticancer agents. The synthesis proceeds by reacting 4-aminoacetophenone **54** and aromatic aldehydes **55a-55j**, achieved substituted components **56a-56j** under EtOH and sodium at 25 °C. Further, reaction between **56a-56j** and 4-chloro-2-methylquinoline **57** gave target substituted molecules **58a-58j** in presence of HCl in EtOH at 80 °C (Figure 9).⁷⁰

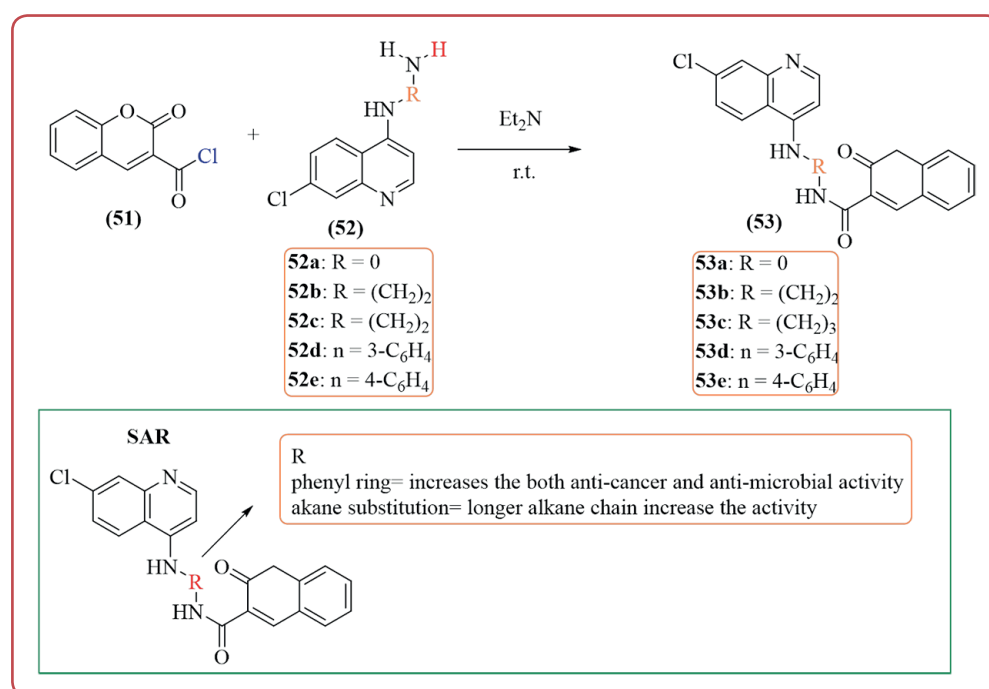


Figure 8: Synthesis and with structure-activity relationship (SAR) of quinoline-coumarin conjugates

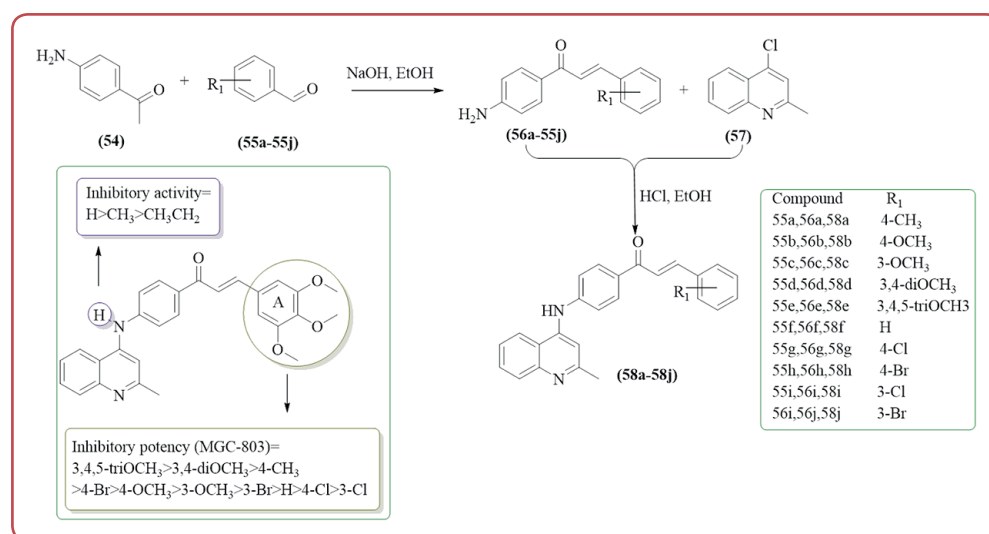


Figure 9: Synthesis and structure-activity relationship (SAR) of quinoline-chalcone derivatives

Antiproliferative activity and SAR

The novel target compounds **58a-58j** were evaluated and among all compound **58e** demonstrated an excellent inhibitory activity against MGC-803 (human gastric cancer cell line), HCT-116 human colon cancer cell line (HCT-116) and MCF-7 (human breast cancer cell line) with IC₅₀ values of 1.38, 5.34 and 5.21 μM.⁷⁰

Indolo-[2,3-*b*]-quinoline

Hydroxycinnamic acids (HCA) have been become the intensive research topic to investigate the novel hybrid compounds as a potent anticancer

molecules.⁷¹ The analogue of natural alkaloid neocryptopine, 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (DiMIQ), has been demonstrated the high potency against human mouth epidermal carcinoma (KB cells) as cytotoxic activity at similar doses of doxorubicin.⁷² 73. Cybulski et al synthesised fused conjugates of 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline, with preferred ROS-modulating HCA. The designed conjugates synthesised by protected HCAs **59a-59c** as coupling with 9-amino- DiMIQ **60** and compound **61a-61c** formed which further reacted with Et₃SiH, Pd(PPh₃)₄, in DMF, desired compounds **62a**, **62b** was synthesised (Figure 10).⁷³

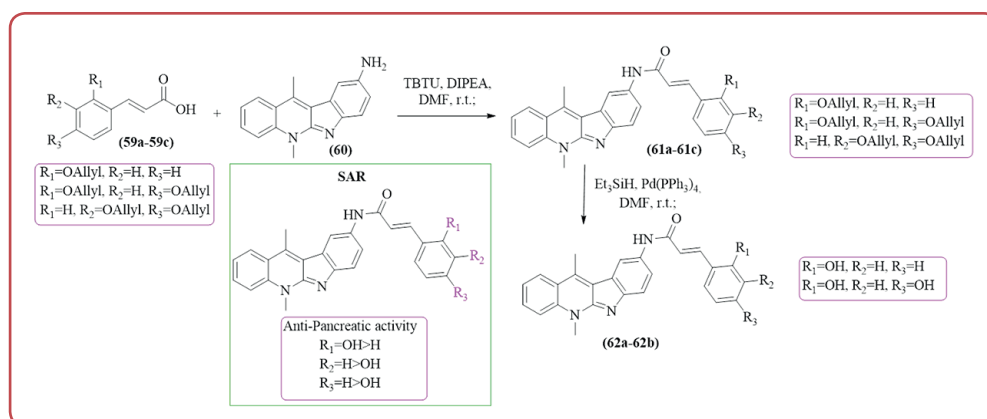


Figure 10: Synthesis and structure-activity relationship (SAR) of quinoline-indole conjugates

Anticancer activity: The fused compounds **62a** and **62b** demonstrated significant dose-dependent cytotoxic activity against pancreatic cancer (AsPC-1 and BxPC-3). Compound **62a** showed potent against both pancreatic cancer cells with IC_{50} 400 μ M.⁷³

idoethyl-benzene **64** by reacting 2-bromoethyl-benzene **63** with NaN_3 , DMF at 80 °C for 30 minutes and further **64** reacting with DCM: H_2O in 1:1 ratio, $CuSO_4 \cdot 5H_2O$, sodium ascorbate for 2 h at room temperature and resultant compound 8-((1-phenethyl-1*H*-1,2,3-triazol-4-yl) methoxy) quinoline **65** obtained. The compound **65** subsequently react with 2-azido-*O*-ethyl tosylate **66** in the presence of same substrates and final product of 2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl 4-methylbenzenesulfonate **67** obtained with yield of 90 % (Figure 11).

Quinoline-conjugates

Quinoline-1*H*-1,2,3-triazole hybrid

Today, the world faces a significant problem with drug-resistant pathogens that pose a risk to human existence. Research into antimicrobial drugs has made progress, but harmful microbes are adapting, making infections that were once treatable now harder to control. This increases the risk of drug-resistance infections affecting the success of treatment.⁷⁴ Awolade et al synthesised the quinoline- 1*H*-1,2,3-triazole hybrids with improved biological profile using molecular hybridisation (MH) approach. The synthesis began with the preparation of 2-azidoethyl-benzene **64** by reacting 2-bromoethyl-benzene **63** with NaN_3 , DMF at 80 °C for 30 minutes and further **64** reacting with DCM: H_2O in 1:1 ratio, $CuSO_4 \cdot 5H_2O$, sodium ascorbate for 2 h at room temperature and resultant compound 8-((1-phenethyl-1*H*-1,2,3-triazol-4-yl) methoxy) quinoline **65** obtained. The compound **65** subsequently react with 2-azido-*O*-ethyl tosylate **66** in the presence of same substrates and final product of 2-(4-((quinolin-8-yloxy)methyl)-1*H*-1,2,3-triazol-1-yl)ethyl 4-methylbenzenesulfonate **67** obtained with yield of 90 % (Figure 11).

Antimicrobial studies

The compound **67** is the strong inhibitor with 64.8 % of inhibition power for *P aeruginosa* at 75.39 μ M. Despite being less potent vancomycin and colistin, its structure presents a favourable foundation for the development of antibacterial agents (broad-spectrum) with enhanced potency. Furthermore, compound **67** demonstrated an MIC_{80} value of 2.36 μ M against *C neoformans*, indicating an 11-fold increase in potency compared to fluconazole. This heightened anticryptococcal activity is potentially attributed to the inclined

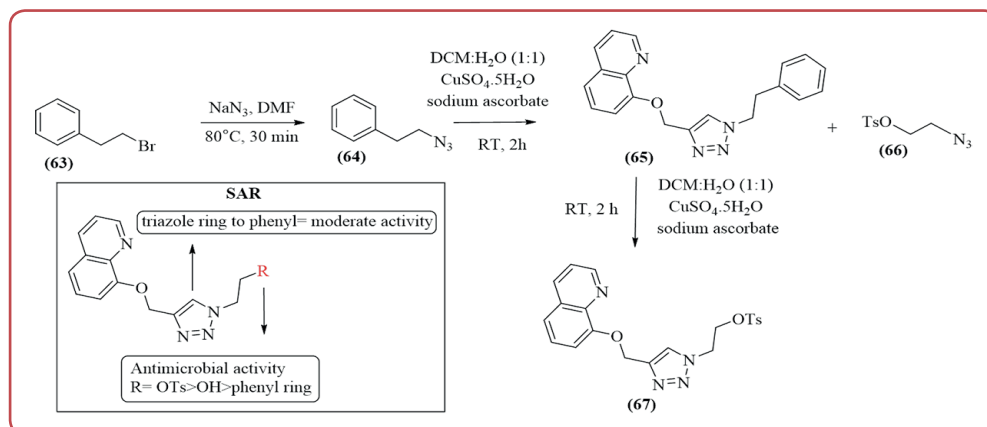


Figure 11: Synthesis and structure-activity relationship (SAR) of quinoline-triazole derivatives

lipophilicity of compound, which facilitates effective inhibition of fungal growth through enhanced cellular membrane penetration.⁷⁴

Quinoline-1,3,4-oxadiazole hybrid

Quinoline serve as inhibitors of the essential enzyme topoisomerase II and topoisomerase IV, they have fundamental role in bacterial DNA replication, transcription and recombination within cell. Targeting these enzymes is a critical aspect in the quest for novel antibacterial drugs, as it serves to impede bacterial multiplication.⁷⁵ Recent studies have found that specific quinoline derivatives demonstrated better antibacterial activity than standard drugs.⁷⁶ On the other hands 1,3,4-oxadiazole heterocycles are good bio isosteres of ester and amides, which contribute in several biological activities such as antiviral, antimicrobials and antimalarials.⁷⁷⁻⁷⁹ Hofny et al synthesised the target compound **69** was with aniline **1** reacting with benzaldehyde **68** to yield 2-phenyl-quinoline-4-carboxylic acid **69** under pyruvic acid in EtOH and then reacted with hydrazide hydrate and yielded 2-phenyl-quinoline-4-carboxylic acid hydrazide **70** further compound **71** was cyclised with KOH in EtOH and CS₂ to afford 5-(2-phenyl-quinolin-4-yl)-1,3,4-oxadiazole-2-thione **72**. The reaction was proceeded by compound **71** refluxed with 4-(2-chloroethyl) morpholine hydrochloride or (2-chloroethyl) dimethylamine in sodium acetate/EtOH to yield components **72a** and **72b** respectively. Upon stirring compound **72** with unsubstituted phenacyl bromide, aryl chlo-

ride and alkyl iodide in presence of DMF/K₂CO₃, compound **72c-72j** were obtained in favourable yields (Figure 12).⁸⁰

DNA gyrase and topoisomerase IV inhibitor

A variety of compounds designed and synthesised, then activity against DNA gyrase evaluated with a focus on identifying the most potent compounds for the further assessment against topoisomerase IV. The evaluation focused on DNA gyrase and among all the compounds **72c**, **72e** and **72f**, demonstrated IC₅₀ values of 34 nM, 26 nM and 32 nM respectively, against topoisomerase IV. Each of these compounds contains an (un)substituted phenacyl group, a 1,3,4-oxadiazole-5-thiol moiety and a phenyl containing quinoline core. Notably. Compound **72e** exhibited an IC₅₀ value of 26 nM against *Escherichia coli* gyrase and 0.24 µM against *Staphylococcus aureus* gyrase. Furthermore, it displayed efficacy against *E coli* topoisomerase IV, with an IC₅₀ of 0.47 µM and against *S aureus* topoisomerase IV, with an IC₅₀ of 0.92 µM. Compound **72f** demonstrated the second highest efficiency among the evaluated compounds, exhibiting equilibrium activity against all 4 tested enzymes. It possessed an IC₅₀ value of 1.1 µM against *S aureus* topoisomerase IV, in contrast to novobiocin, which has an IC₅₀ of 27 µM. Consequently, both compounds **72e** and **72f** presented themselves as promising dual-target inhibitors that merit further optimisation.⁸⁰

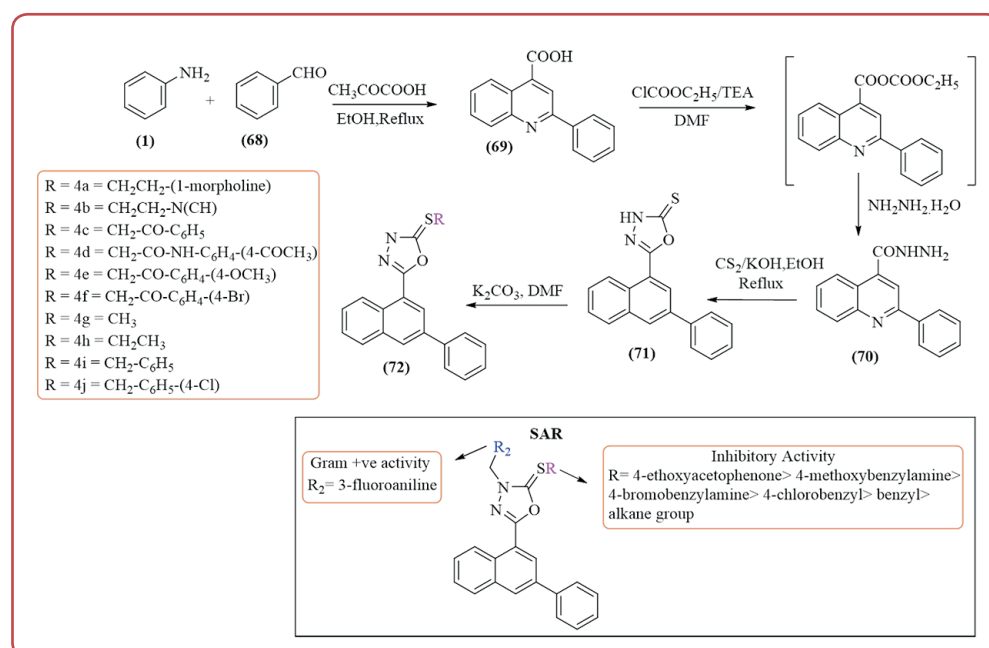


Figure 12: Synthesis and structure-activity relationship (SAR) of quinoline-oxadiazole hybrid

Quinoline-piperazine hybrid

Gnanavelu et al synthesised series of novel quinoline-piperazine hybrids, conjugated with sulphonamide and benzamide groups, were synthesised by modifying the main core quinolone structure while preserving the 3rd position. These compounds were tested against antibiotic-resistant (AMR) and multidrug-resistant tuberculosis (MDR-TB) strains.⁸¹ The active pharmacophores, piperazine-coupled sulphonamide and amide ring incorporate methoxy and fluoro- groups at 6th position which have been strategically incorporated at the 2nd position of the quinoline moiety. It is anticipated that this modification will enhance biological activity.⁸² The synthesis proceeds by *p*-substituted aniline **73a-73b**, conversion to 3-(4-fluoro-phenylamino)-but-2-enoic acid ester **74a-74b** by adding catalytic amount of *p*-toluene sulfonic acid (*p*-TsOH) in toluene and heating the **73a-73b** with ethyl acetoacetate at 110 °C for duration of 8 h, resulting in a favourable yield. Following this, the compound **74a-74b** underwent cyclisation using polyphosphoric acid along with a catalytic quantity of POCl₃, pursuant to a previously established protocol, leading

to the synthesis of 4-hydroxyquinoline derivative **75a-75b** at 75 °C. Afterwards, compounds **75a-75b** were reacted with dimethyl sulphate in toluene at reflux to yield 2-methylquinolines substituted derivatives **76a-76b**. These compounds were brominated with *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) in acetonitrile, achieving an improved yield of about 20 %. Intermediate **77a-77b** were interact with *N*-Boc piperazine under DMF with K₂CO₃ at 60 °C to produce Boc-protected compound **78a-78b**. The Boc group was then cleaved with trifluoroacetic acid (TFA) in DCM at 0 °C, resulting in 6-substituted-4-methoxy-2-[(piperazin-1-yl)] quinoline **79a-79b** as TFA salt. Additionally, compounds **79a-79b** yield quinoline-piperazine hybrids of sulphonamide **80a-80i** then amides **81a-81f** by undergoing reaction with sulfonyl chlorides under presence of Hunig's base (Figure 13).⁸¹

Antibacterial and antituberculosis profile

The novel synthesised compounds, researchers tested them against several bacteria, containing gram-negative and gram-positive strains. Antimicrobial susceptibility (AST) was done by

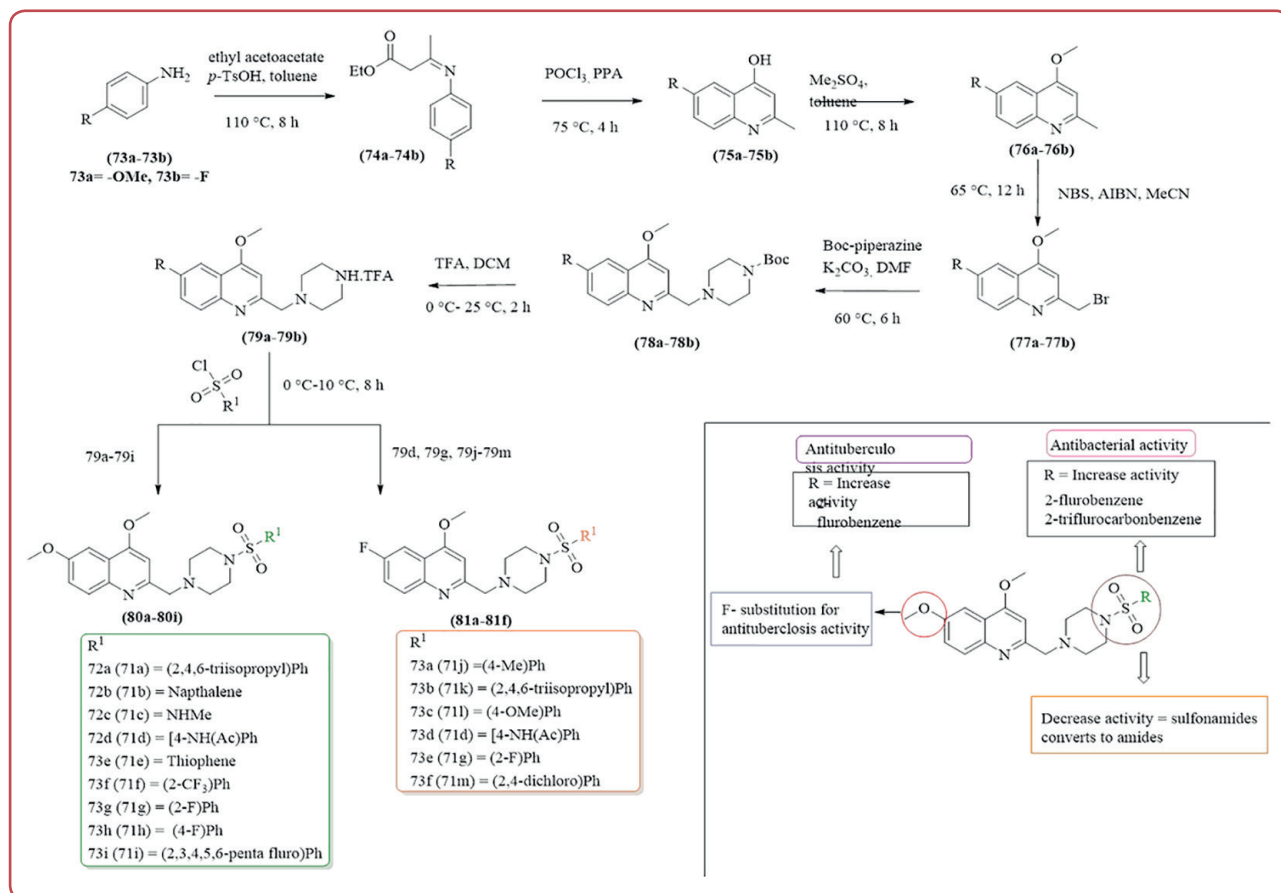


Figure 13: Synthesis and structure-activity relationship (SAR) of quinoline-piperazine hybrid

evaluating the MIC of synthesised antimicrobial agents. The 4,6-dimethoxy quinoline piperazine-coupled sulphonamide, substituted 2nd position with fluorine on benzene ring **80g** reported as excellent activity against *M aureus* and *M catarrhalis* with observed MIC $0.03 \mu\text{g mL}^{-1}$ and $0.06 \mu\text{g mL}^{-1}$ respectively and also emerged as potent inhibitor against *M tuberculosis* and multi-drug resistant MDR-TB with lowest MIC values of $0.06 \mu\text{g mL}^{-1}$ and $0.5 \mu\text{g mL}^{-1}$ respectively. Similarly, 2nd position on benzene substituted with difluorocarbene **81f** reported good activity against *M catarrhalis* with MIC $1 \mu\text{g mL}^{-1}$. Likewise, **81a**, **81d**, **81e** showed average bacterial inhibition activity. However, compound **81e** reported as effective against three strains, *M smegmatis*; $1 \mu\text{g mL}^{-1}$, *M tuberculosis* $4 \mu\text{g mL}^{-1}$ and MDR-TB $11 \mu\text{g mL}^{-1}$.⁸²

Quinoline-thiazole hybrids

Thiazole moieties are essential in medicinal chemistry due to their wide therapeutic effects as antibacterial, antifungal, anti-cancer, anti-inflammatory, anti-HIV properties. Moreover, thiazole derivatives are significant antimicrobial agents and serve as key scaffolds for penicillin derivatives.⁸²⁻⁸⁶ Eissa et al synthesised novel series of quinolines substituted at 2nd position, consisting nucleus of thiazole distinct by hydrophobic linker as antimicrobial agents. The reactivity of carbonyl compound (aldehyde) **4** and acetophenone **82** towards thiosemicarbazides has been evaluated. Thiosemicarbazones **83a-83c** were obtained when **4** underwent condensation with thiosemicarbazides by refluxed with ethanol. In contrast, **82** was condensed with the thiosemicarbazides refluxed with acetic acid, yielding thiosemicarbazones **83d-83f**. A series of thiazolidines **84a-84f** was obtained when **83a-83f** reacted with chloroacetone fused with sodium acetate (Figure 14).⁸⁷

Antibacterial and antifungal activity

The newly compounds were synthesised to evaluate against gram-negative and gram-positive pathogens. The findings indicated that quinoline analogues containing thiazole moiety significantly **84e**, exhibited the excellent antimicrobial activity, encompassing both activity against gram-negative and gram-positive bacteria as well as anti-fungal activity. This derivative possesses an ethylidene hydrazone-2,3-dihydrothiazole pharmacophore in addition to an EDG.⁸⁷

Quinoline-imidazole derivatives

α -Glucosidase is a hydrolase enzyme produces the monosaccharides primarily glucose which enters the bloodstream, leading in postprandial hyperglycaemia, causing diabetes.⁸⁸ Thus, α -glucosidase inhibition may lead to reduction in digestion of carbohydrates, detention in glucose uptake and therefore, declined in blood sugar levels.⁸⁹ Noori et al synthesised quinoline-benzo[d]imidazole derivatives to inhibit the α -glucosidase enzyme to lower the levels of blood sugar. The synthesis proceeded by taking the *N*-phenylacetamide **85** and reflux it with phosphoryl chloride in DMF for 15 h to achieve 2-chloroquinoline-3-carbaldehyde **86**. Further, compound **86** stirred at room temperature for 2h with sodium sulphide dissolved in DMF to obtained 3-formyl-2-mercaptoquinoline **87**. Again, compound **87** reacted with *O*-phenylenediamines **88** under sodium metabisulfite in DMF for 2 h at 150°C to obtain final product **91**. By performing reaction of chloroacetylchloride **90** with aniline derivatives **89a-89r** in DMF, compounds **92a-92f**. Further, the compounds **93a-93r** obtained by reacting **91** and **92a-92f** in acetone in presence of K_2CO_3 (Figure 15).⁹⁰

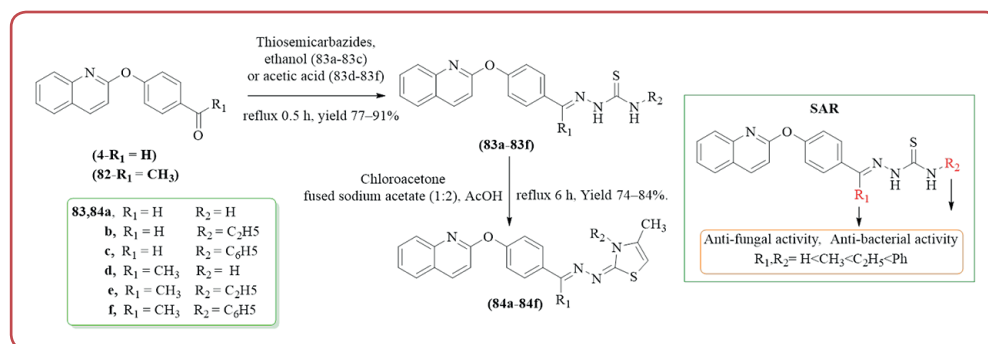


Figure 14: Synthesis and structure-activity relationship (SAR) of quinoline-thiazole hybrid

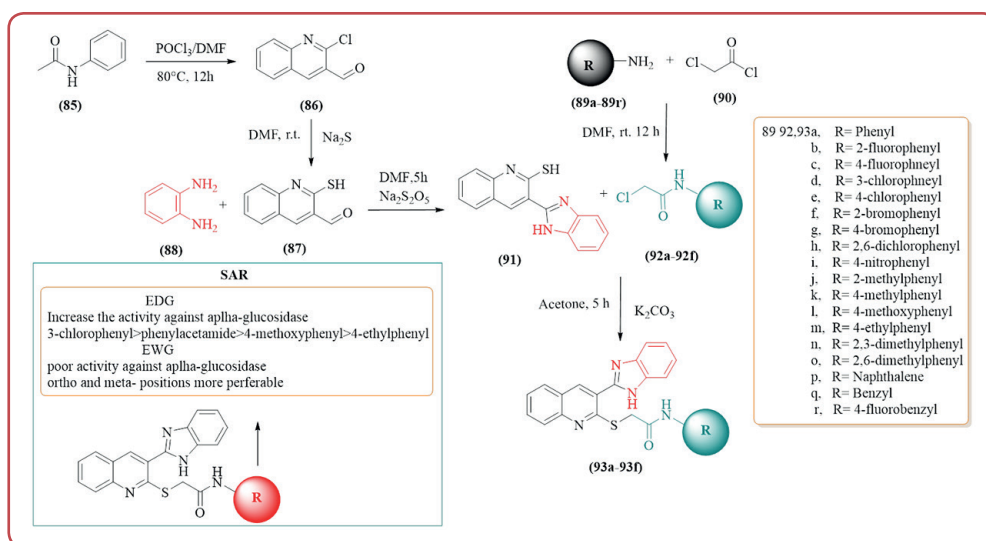


Figure 15: Synthesis and structure-activity relationship (SAR) of quinoline-imidazole hybrid

α -Glucosidase inhibitory activity: The compound **93d** was most potent among all, bearing IC_{50} value of $3.2 \pm 0.3 \mu M$ with 3-chlorophenyl introduced at R-position. Compounds **93l** and **93m** bearing IC_{50} values of $5.7 \pm 0.3 \mu M$ and $55.6 \pm 0.2 \mu M$ respectively. Compound **93a** exhibited the activity against α -glucosidase with IC_{50} value of $30.2 \pm 0.4 \mu M$.⁹⁰

Future prospectives: Quinoline-derivatives in the next generation of medicinal science

The gifted nature of quinoline moiety with proven biological activities, pries quinoline-conjugations as advance candidates for future therapeutic innovations. Several key areas assure further investigation and utilisation of quinoline moiety beyond current applications. As mentioned, the several quinoline- hybrids bearing different pharmacological properties with sustainable synthesis procedures. These hybrids showing potential anti-bacterial, anti-microbial, anti-viral, anti-tuberculosis, anti-cancer, anti-fungal and activity against cytotoxicity and DNA gyrase that open the doors for future researchers. Quinoline scaffold numerous considerable bioactivities as:

Neurodegenerative disorders: Future of quinoline prioritise elucidating the mechanism to combat neuronal damage and oxidative stress, significantly for Alzheimer's and Parkinson's disease.

Anti-microbial resistance: Quinoline-conjugations bearing activity against multi-drug-resistant fungi and bacteria, offer a promising avenue against drug-resistant tuberculosis and broad-spectrum antifungal drugs.

Cancer therapies: The exploration of quinoline-containing compounds as anticancer yielding excellent results, can be used in combinational therapies or targeting specific molecular target.

Advancements in synthesis: The synthesis of quinoline analogues is sustainable, ecofriendly and cost-effective.

The future of quinoline-hybrids in medicinal chemistry is excellent, by innovative approaches, scientists can explore the full therapeutic potential of quinoline and contribute to design of next-generation therapies for a wide range of diseases.

Conclusion

This review has mentioned the remarkable journey of quinoline, from initial discovery and classical synthesis procedures to the contemporary methodology with wide application in new researches. The nature of quinoline moiety, its structural versatility and pharmacological activities, making it leading cornerstone of medicinal chemistry. The recent trends in quinoline synthesis and transition from tradition-

al to modern procedures were explored. This advancement has expanded the advance techniques for the synthesis of new quinoline-conjugations. The research of quinoline-bioconjugates with wide pharmacological activities such as antifungal activities, antimicrobial, anti-viral, antibacterial, antituberculosis, anti-cancer, neuroprotective agents and inhibition of topoisomerase, DNA gyrase and cytotoxicity. The future of quinoline lies in the research of refine synthesis strategies, exploration of novel disease targets and the development of multi-drug target therapies.

Ethics

This study was a secondary analysis based on currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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