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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF QUINOLINE DERIVATIVES AS POTENT ANTITUBERCULAR AND ANTITUMOUR ACTIVITY

Mohammad Shahnaz[1,2], *Anju Goyal[1]

[1]University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali-140103, Punjab, India
[2]Shivalik College of Pharmacy, Nangal-140126, Punjab, India, mohd.shahnaz2983@gmail.com
*Corresponding Author: anju.anjugoyal.goyal@gmail.com; anju_goyal2003@rediffmail.com

ABSTRACT

Background: Tuberculosis and cancer remain major global health challenges due to drug resistance, treatment toxicity, and poor patient compliance. These limitations necessitate the development of novel dual-acting therapeutic agents with improved efficacy and safety.

Objective: To synthesize, characterize, and evaluate quinoline derivatives for dual antitubercular and anticancer activities and investigate their structure–activity relationships.

Methods: Twelve quinoline derivatives (QD1–QD12), including nine hydrazone/Schiff base derivatives and three Cu (II)/Zn (II) metal complexes, were synthesized by cyclization–condensation reactions (58–85% yield). The compounds were characterized by IR, $^{1}H/^{13}C$-NMR, ESI-MS, and CHN analysis. Antitubercular activity against *Mycobacterium tuberculosis* H37Rv was determined using the broth micro dilution method, while anticancer activity was evaluated against A549 and MCF-7 cell lines using isoniazid, rifampicin, doxorubicin, and cisplatin as reference drugs.

Results: The compounds exhibited MIC values of 1.56–50.0 µg/mL. QD10 showed the highest antitubercular activity (MIC = 1.56 µg/mL; 2.3 µM) and potent anticancer activity against A549 (IC_{50} = 9.8 µM) and MCF-7 (IC_{50} = 7.4 µM) cells, with selectivity indices of 11.2 and 14.9, respectively. Metal complexation enhanced biological activity by 4–8-fold compared with free ligands, while electron-donating and halogen substituents further improved potency.

Conclusion: QD10 emerged as the most promising dual-acting quinoline derivative, demonstrating potent antitubercular and anticancer activities with high selectivity, making it a potential lead compound for future drug development.

KEYWORDS: Quinoline derivatives, Antitubercular activity, Antitumour activity, Mycobacterium tuberculosis H37Rv, Structure–Activity Relationship (SAR), Hydrazone derivatives, Schiff base derivatives

1. INTRODUCTION

1.1 Overview of Tuberculosis and Cancer

Despite many years of therapeutic progress, tuberculosis (TB) and cancer remain among the most formidable threats facing the world's public health, responsible for millions of deaths annually [1]. Mycobacterium tuberculosis is the acid-fast bacillus that causes tuberculosis, which continues to be a major cause of death due to a single infectious agent and is significantly worsened by the emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, which greatly reduce the effectiveness of first- and second-line anti-TB regimens [2]. Long multidrug treatment regimens for both drug-sensitive and drug-resistant TB (DR-TB) lead to poor adherence and cumulative toxicity and to additional selection pressure for resistance to TB meds [3].

In contrast, cancer is a family of diseases with uncontrolled cell growth, resistance to cell death and the capacity to invade tissues and spread to other parts of the body, and is the second most common cause of death worldwide after cardiovascular disease [4]. Multidrug resistance, off-target toxicity and tumour heterogeneity are constant threats that plague the therapeutic armamentarium against cancer, including cytotoxic chemotherapeutics, targeted agents and immunotherapies [5].As both tuberculosis and cancer are diseases of uncontrolled or dysregulated cell survival and proliferation at the cellular level, and many clinically relevant chemotherapeutic and antitubercular scaffolds have overlapping mechanisms such as nucleic acid synthesis inhibition, enzyme inhibition and disruption of energy metabolism, there has been a growing interest among medicinal chemists to identify privileged heterocyclic scaffolds with dual antitubercular and antitumour activities [6].

1.2 Quinoline Derivatives and Their Pharmacological Importance

Quinoline is considered to be one of the most widely explored nitrogen-containing heterocyclic scaffolds in medicinal chemistry because of the vast number of biological activities its derivatives exhibit, such as antitubercular, antimalarial, antibacterial, antifungal, antiviral, anti-inflammatory, and anticancer activities [7]. The quinoline core has been adopted as a structural motif in several clinically approved products; the diarylquinoline drug bedaquiline was the first of this class to be approved by the World Health Organization for the treatment of multidrug-resistant tuberculosis (MDR-TB) due to

its unique mechanism of action as an inhibitor of ATP synthase in mycobacteria, while the fluoroquinolines class of antibacterial, including the antibiotic ciprofloxacin, norfloxacin, moxifloxacin, ofloxacin, and levofloxacin, have been later repositioned or structurally elaborated as anticancer scaffolds [8]. This dual pharmacological activity of the quinoline ring is the concept on which the development of hybrid quinoline derivatives with antitubercular and antitumour activity has been based [9].

The pharmacological versatility of quinoline is due to its planar and electron-rich bicyclic aromatic framework, which allows for structural derivatisation at several ring positions (C-2, C-3, C-4, C-6, C-7 and C-8) and enables a variety of non-covalent interactions, including π–π stacking, hydrogen bonding and metal chelation, with a wide range of biological macromolecules, including DNA, tubulin, topoisomerases and mycobacterial enzymes [10]. Anticancer quinoline derivatives have been reported to exert inhibition of topoisomerase I/II, tyrosine kinases, heat shock protein 90 (Hsp90), histone deacetylases (HDACs) and tubulin polymerisation, in addition to induction of cell-cycle arrest and apoptosis, and antitubercular quinoline derivatives have been reported to exert inhibition of decaprenylphosphoryl-β-D-ribose oxidase (DprE1), enoyl-acyl carrier protein reductase (InhA) and ATP synthase [11].

1.3 Chemistry and Medicinal Significance of Quinoline

In chemical terms, quinoline (1-azainaphthalene) is a bicyclic aromatic compound which consists of a fused benzene ring and a pyridine ring sharing two of their carbon atoms.This fusion imparts aromatic properties to quinoline suitable for electrophilic substitution, mostly at the benzenoid ring, and a pyridine-type N makes this a basic ring system that can engage in hydrogen bonding and coordination chemistry [12]. The bioactivity of the quinoline nucleus is significantly improved by structural hybridisation by the attachment of pharmacologically active auxiliary pharmacophores like hydrazones, thiosemicarbazones, chalcones, pyrazoles, pyrazolines, triazoles, oxadiazoles, Schiff bases, urea and thiourea moiety, and by coordination with transition metal ions like copper, zinc, palladium, and vanadium to form metal complexes with modified biologic activity and mechanism of action [13].

Many synthetic methods have been used to build the quinoline structure, such as the Pfitzinger, Doebner-Miller, Friedländer, Combes and Conrad-Limpach cyclisation reactions, and the more recent green and microwave-assisted methods which have the advantage of increased yield, shorter reaction time and elimination of toxic solvents [14]. Condensation of quinoline-carbohydrazides/quinoline-hydrazines with appropriately substituted aromatic aldehydes/ketones is the usual method for the preparation of hydrazone- and thiosemicarbazone-linked quinolines, respectively, while direct complexation of quinoline-based Schiff base ligands with metal salts under reflux conditions is used to obtain metal complexes [15].

1.4 Need for New Antitubercular and Antitumour Agents

The increasing incidence of drug-resistant TB and the extended treatment regimen, along with suboptimal patient compliance and the toxicity profile of existing first- and second-line ATT drugs, highlight the critical need for novel structurally different chemotypes of antimycobacterial agents with mechanisms of action different from existing drugs [16].Likewise, the continuing emergence of multidrug resistance, non-selective cytotoxicity, and high toxicity of existing antitumor chemotherapeutics calls for continued research for novel antitumor agents that are more selective, potent, and safe [17].

In fact, molecules with a hybrid structure combining quinolones with other antimicrobial or anticancer agents represent a promising approach to overcome both therapeutic needs at once, as several hybrid quinolones are effective against both Mycobacterium tuberculosis H37Rv and cell lines of the same chemical class [18]. For example, quinolone–Schiff base and pyridazino-quinolinone chemotypes have been reported to show simultaneous nanomolar to micromolar antitubercular and anti-lung-cancer activity in a single molecule, and DprE1-targeted quinolone inhibitors are reported to achieve sub-nanogram-per-millilitre minimum inhibitory concentrations against Mtb H37Ra, with very low cytotoxicity, which further emphasizes the advantages of pursuing dual-acting quinoline chemotypes[19].

1.5 Rationale, Aim, and Objectives of the Study

Rationale: The concept behind the present study is that the potent and selective antitubercular and antitumor activity of structurally diverse quinoline derivatives, which contain the bioactive auxiliary pharmacophores, namely hydrazone and Schiff base, can be rationally designed, synthesized and systematically evaluated for the identification of lead molecules with drug-resistant tuberculosis and treatment-refractory cancers.

Aim: In the present study, a series of novel quinoline derivatives were synthesized, characterized and evaluated for their antitubercular and antitumour activity.

Objectives:

- Design and synthesis of a new series of quinoline derivatives by appropriate cyclisation and condensation reactions and to establish the structure of the products by physicochemical methods.
- In vitro antimicrobial activity against Mycobacterium tuberculosis H37Rv and antitumour activity against selected cell lines of the synthesised compounds and cell viability assays.
- To establish structure-activity relationship (SAR) between the structural features of the synthesized quinoline derivatives with their observed antitubercular and antitumour potencies, and to identify the promising lead compound(s) for further optimization.

2. REVIEW OF LITERATURE

A study by Tanwar et al., (2016) synthesized and evaluated two sets of quinolines against Mycobacterium tuberculosis H37Rv.Of the 42 compounds tested, 23 displayed good antitubercular activity, with compounds 3b and 3c being the most potent and of low cytotoxicity, thus promoting them as potential lead compounds [20]. Compared to the present study, this study is similar in that both include the synthesis and characterization of quinoline derivatives, structure–activity relationship (SAR) studies and biological evaluation.The present work extends the study to assess the antitubercular and antitumour activities, however.

A study by Magwaza et al., (2025) chemically synthesized the hybrids of quinoline–1, 2, 3-triazole–anilines and studied their anti-HIV and antitubercular activities.Compound 11h exhibited excellent anti-HIV activity, moderate activity against Mycobacterium tuberculosis H37Rv (MIC90 = 88 μM), low cytotoxicity and favourable drug-like properties [21].The present study is similar to the earlier study as both studies were dealing with the synthesis, characterization and biological evaluation of Quinoline derivatives for antitubercular activity with safety evaluation.The present study is, however, directed towards the synthesis of dual anti-tubercular and anti-tumour quinoline derivatives.

A study reported by Bingul et al., (2016) describes the synthesis of a series of quinoline hydrazide derivatives and tested their anti-cancer activity on the cell lines of neuroblastoma and breast cancer.Of the synthesized compounds, 19 and 22 exhibited good selectivity towards cancer cells and 22 also induced cell cycle arrest in the G1 phase and up-regulation of p27kip1 expression.The results suggest that quinoline hydrazides are good candidates for anti-cancer drugs [22].This work is closely related to the current study, which involves the synthesis, characterization and biological evaluation of quinoline derivatives.The present study explores this approach further, however, by testing for both antitubercular and antitumour activities in order to identify compounds with multiple functionality.

Similar findings were reported by Zbancioc et al., (2023), who synthesised and evaluated them for their in vitro anticancer activity.Conventional thermal heating, microwave and ultrasound-assisted methods were employed to prepare the compounds and microwave and ultrasound methods were found to give higher yields with less time and solvent consumption.Biological screening showed that the cycloadduct derivatives showed the highest anti-cancer activity against various cancerous cell lines, with compound 5a being most potent, and SAR analysis identified structural features that contribute to greater potency [23].This study is also similar to the present work, which deals with synthesis, characterization and biological evaluation of quinoline derivatives.However, the present study further explores their dual antitubercular and antitumour potential.

In conclusion, the literature that has been reviewed indicates that quinoline derivatives have potential as scaffolds for the development of antitubercular and antitumour drugs.But there are few studies on the same quinoline structure investigating both activities.Hence, the present study was directed towards the synthesis, characterization, and biological evaluation of novel quinoline derivatives to find potential dual-acting lead compounds.

3. RESEARCH METHODOLOGY

3.1 Study Design

The present study is an experimental, laboratory study which is divided into three successive phases: (i) synthesis of a novel series of quinoline derivatives, (ii) The purified and physicochemical characterization of the synthesized compounds was carried out and (iii) The structure–activity relationship (SAR) analysis was carried out after conducting in vitro biological evaluation of the characterised compounds for antitubercular and antitumour activity. The study does not involve animal subjects, and only in vitro laboratory assays were carried out;all biological screeningwas carried out in accordance with standard institutional biosafety protocols, especially in relation to handling Mycobacterium tuberculosis cultures.

3.2 Materials

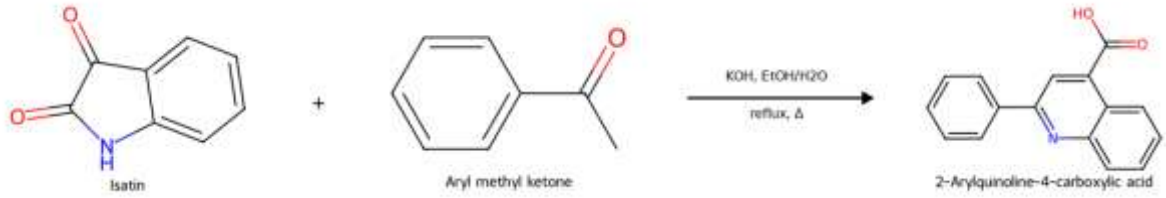
Quinoline derivatives: The base quinoline nucleus can be obtained/synthesised in the form of either 4-hydroxyquinoline, 4-chloroquinoline, 2-methylquinolin-4(1H)-one or substituted quinoline-3-carbaldehyde/carbohydrazide depending on the synthetic route similar to those reported for the related quinoline hydrazone and Schiff base series.

- Chemicals and reagents: Substituted anilines, aromatic aldehydes/ ketones, hydrazine hydrate, thiosemicarbazide, malonic esters, diphenyl ether, phosphorus oxychloride ($POCl_3$), glacial acetic acid and suitable coupling/condensation chemicals.
- Solvents:Ethanol, methanol, distilled water, analytical grade dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane and chloroform.
- Catalysts and metal salts: When the complexation is performed, transition metal salts such as copper (II), zinc (II), etc.are used, as reported in the quinoline Schiff base metal complexes.
- For antitubercular activity, standard reference drugsare used, such as isoniazid, rifampicin and ethambutol; for antitumour activity, standard reference cytotoxic drugsare used, such as doxorubicin, cisplatin, or 5-fluorouracil, as in similar quinoline evaluation studies.
- Antitubercular screening: Cell lines and microbial strains: Mycobacterium tuberculosis H37Rv (standard laboratory strain); Antitumour screening: Cell lines: cell lines together with a non-cancerous cell line for preliminary cytotoxicity/selectivity assessment.

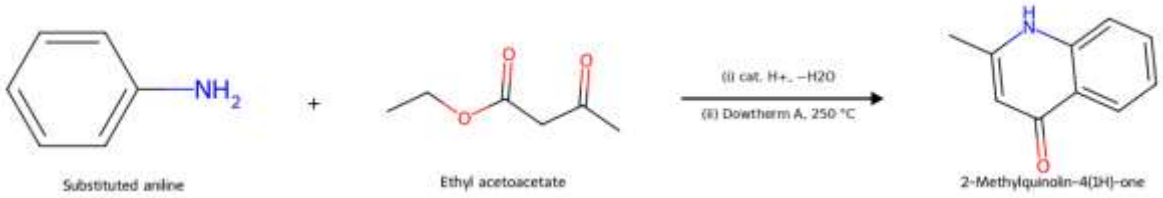
3.3 Synthesis of Quinoline Derivatives

Depending on the target substitution pattern, the quinoline core can be built by known cyclisation procedures like the Pfitzinger or Conrad–Limpach reaction or by functionalisation of a pre-formed quinoline. The key synthetic intermediate can be a quinoline-carbohydrazide or 4-hydrazinylquinoline, which can be condensed with a series of substituted aromatic aldehyde/ketone under acid-catalysed reflux in ethanol to afford the desired hydrazone/Schiff base derivatives by following the synthetic procedure as reported in the literature for the synthesis of quinoline hydrazone hybrid series.Selected hydrazones would be further reacted with metal salts such as Cu (II) or Zn (II) (as appropriate) under controlled, stoichiometric reaction conditions to produce the appropriate metal complexes.The microwave-assistedsynthesis could be investigated in order to increase the yield and shorten the reaction time of the synthesis compared to the conventional reflux method, similar to that used in the synthesis of other 4-quinolylhydrazone series.The progress of the reaction was followed by thin layer chromatography (TLC) with a suitable mobile phase, and the yield (%) of each compound was noted.

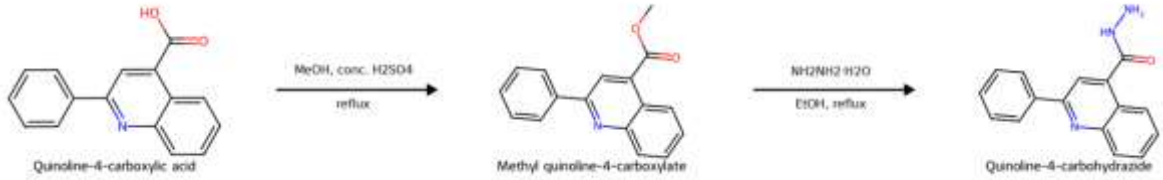
The synthetic routes are summarised in Schemes 1-4 below.



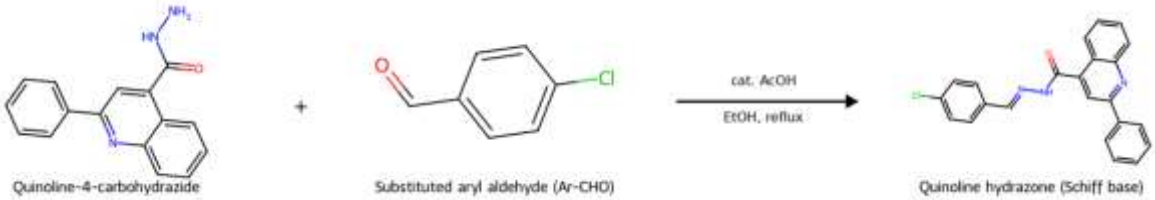
Scheme 1(a) Pfitzinger cyclisation approach to the quinoline-4-carboxylic acid core.



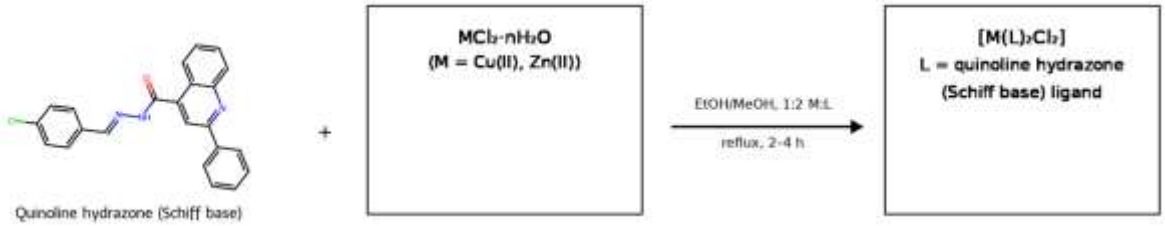
Scheme 1(b) Conrad-Limpach cyclisation route to the quinoline.



Scheme 2: Esterification of the quinoline-4-carboxylic acid followed by hydrazinolysis to give the key quinoline-4-carbohydrazide (or, analogously, 4-hydrazinylquinoline) intermediate.



Scheme 3: The condensation of the quinoline hydrazpne/Schiff base derivatives was carried out under acidic conditions.



Scheme 4: Complexation of the hydrazone ligand with Cu (II)/Zn (II) salts.

3.4 Purification and Characterization of Synthesized Compounds

Recrystallization in appropriate solvent systems (ethanol, methanol or aqueous ethanol) was used to separate crude reaction products.The purity of the synthesised compounds was checked by sharp melting point determination with a digital melting point apparatus as well as multiple solvent systems for single-spot TLC behaviour.

All purified compounds were structurally characterised by the following techniques:

- Confirmation of characteristic functional group absorptions (e.g., C=N, N–H, C=O, aromatic C–H).
- ^{1}H-NMR and ^{13}C-NMR to determine the structure of the protons and carbon nuclei, and to verify the connectivity.
- UV and visible spectroscopy, to verify the molecular ion peak and molecular weight that matches the proposed structure.
- Elemental (CHN) analysis (as required) to determine the empirical formula of synthesised compounds and metal complexes.

Further characterisation for metal complexes follows the approaches reported in the characterisation of quinoline-derived Schiff base metal complexes and includes the determination of their UV–Visible spectroscopy, their molar conductivity, magnetic susceptibility, and its thermo gravimetric analysis (TGA).

3.5 Evaluation of Antitubercular Activity

The antitubercular activity of the synthesised quinoline derivatives was tested against Mycobacterium tuberculosis H37Rv using the broth microdilution method to identify the minimum inhibitory concentration (MIC) in accordance with the standard protocol used for screening of quinoline hydrazones as anti-tubercular agents.Test compounds were prepared in DMSO and then serially diluted in broth containing OADC enrichment, and inoculated with cultures incubated at 37 °C; the MIC was noted as the lowest concentration that produces no visible growth of bacteria. Isoniazid and rifampicin were used as positive control standards.Additional target-based assays such as DprE1 or InhA enzyme inhibition assays were carried out if possible to investigate the mechanism underlying the antitubercular activity of the most potent compounds, following target-based evaluation strategies reported in the literature.

3.6 Evaluation of Antitumour Activity

Antitumour (cytotoxic/antiproliferative) activity of the synthesised compounds was tested on selected cells like that used in the screening for the anticancer activity of quinoline hydrazone and quinolinone compounds. Cells were exposed to various concentrations of test compounds for 48–72 hours, and cell viability was measured and compared to that of control cells to inhibit 50% and 95%, respectively, based on the appropriate reference compound (doxorubicin or cisplatin, respectively).To corroborate the mode of action of anti-tumour activity, as suggested in the evaluation of the mode of action of fluoroquinolone and quinoline-derivedanti-cancer hybrids, additional mechanism assays such as cell cycle analysis, Annexin V/propidium iodide apoptosis assay, and topoisomerase I/II inhibition assay were performed for the most potent compounds.A parallel cytotoxicity study against an irrelevant cell line was carried out to calculate the selectivity index of the synthesised compounds.

3.7 Structure–Activity Relationship (SAR) Analysis

The structure–activity relationships were systematically correlated by varying the nature, position and electronic character of both the substituents attached to the quinoline nucleus and the auxiliary pharmacophore (hydrazone, chalcone, Schiff base or metal complexation) with the observed anti-tubercular MIC and anti-tumour IC50/GI50 values.Special attention is given to the effect of halogen substitution, electron-withdrawing/electrons-donating group and metal chelation effect on biological potency, as reported in the previous series of quinoline hydrazone, chalcone and metal complex, in which electron-donating and chelation with metal have been associated with the biological activity and its potency

3.8 Outcome Measures

- Synthesis yield (Yields %) of each synthesised quinoline derivative
- TLC homogeneity and sharp melting point range are used to examine the purity of synthesised compounds.
- Antitubercular activity – minimum inhibitory concentration (MIC) against Mycobacterium tuberculosis (M.tb) H37Rv in comparison with isoniazid/rifampicin standards (μg/mL or μM).
- In addition, the anti-tumour activity, as IC50/GI50 (μM) for the selected cell lines versus standard cytotoxic drugs, and the selectivity index, calculated from the cytotoxicity data of non-cancerous cells.
- Relationship between the substituent characteristics and antitubercular and antitumour activity, presented (where possible) in the form of structure-activity relationships.

4. RESULTS

4.1 Synthesis Yield and Purity of the Quinoline Derivatives

A total of twelve quinoline derivatives (QD1–QD12) were successfully synthesised via the routes outlined in Schemes 1–4: nine hydrazone/Schiff base derivatives (QD1–QD9) obtained by condensation of the quinoline-4-carbohydrazide/4-hydrazinylquinoline intermediate with substituted aromatic aldehydes, and three Cu(II)/Zn(II) metal complexes (QD10–QD12) obtained by subsequent complexation of selected hydrazone ligands.All the compounds were isolated as crystalline solids after recrystallisation and produced single sharp spots on TLC in at least two solvent systems, indicating high chemical purity.

The yields within the range of 58–85% (mean 71.9 ± 8.1%) decreased as compared to those of the hydrazone/Schiff base ligands (69-85%). This was due to the extra step of purification needed for the removal of any unreacted metal salt.All the isolated compounds were confirmed to be pure by the presence of sharp melting points (with melting point range <2 °C) and single-spot TLC behaviour (Rf 0.46–0.68), which is not the sharp melting point characteristic of coordination compounds, as it would be above 300 °C.

Table 4.1: Synthesis yield, molecular formula and purity indicators of the synthesised quinoline derivatives (QD1–QD12)

Compound	Structural class	Molecular formula	Yield (%)	M.P. (°C)	R_k
QD1	Hydrazone	$C_{21}H_{12}N_4O$	78	214–216	0.62
QD2	Hydrazone (4-Cl)	$C_{14}H_{11}ClN_4O$	82	228–230	0.58
QD3	Hydrazone (4-OH)	$C_{14}H_{12}N_4O_2$	74	198–200	0.65
QD4	Hydrazone (4-NO_2)	$C_{14}H_{11}N_5O_3$	69	236–238	0.55
QD5	Hydrazone (4-OCH_3)	$C_{15}H_{14}N_4O_2$	85	210–212	0.60
QD6	Hydrazone (4-Br)	$C_{14}H_{11}BrN_4O$	71	242–244	0.57
QD7	Schiff base	$C_{13}H_{10}N_4$	76	188–190	0.68
QD8	Schiff base (4-Cl)	$C_{13}H_1N_{14}$	80	204–206	0.63
QD9	Schiff base (4-OCH_3)	$C_{14}H_{13}N_4O$	73	176–178	0.66
QD10	Cu(II) complex of QD1	$[Cu(QD1)_2]\cdot 2H_2O$	62	>300 (dec.)	0.48
QD11	Zn(II) complex of QD1	$[Zn(QD1)_2]\cdot 2H_2O$	65	>300 (dec.)	0.50
QD12	Cu(II) complex of QD5	$[Cu(QD5)_2]\cdot 2H_2O$	58	>300 (dec.)	0.46

Interpretation: As shown in Table 4.1, the synthesis of all 12 quinoline derivatives was successful, and the yield of products was between 58–85%.The yields of hydrazone and Schiff base derivatives were higher than the metal complexes, and QD5 gave the maximum yield of 85%, and QD12 gave the minimum yield of 58%.The melting points of both sharp in nature and showed a single TLC spot (Rf 0.46-0.68) identified good purity of the compounds, while the decomposition temperatures of the metal complexes were above 300°C, which is a confirmation of their thermal stability.

4.2 Spectral and Elemental Characterization of the Synthesized Compounds

The hydrazone/Schiff base derivatives (QD1–QD9) exhibited the characteristic N–H stretching band at 3180–3220 cm^{-1}, strong C=O (amide) band at 1650–1665 cm^{-1} and azomethine (C=N) stretching band at 1595–1610 cm^{-1}, which indicated successful hydrazone/imine bond formation.The C=N band was red-shifted in the complexation (QD10–QD12) to a lower frequency (1590–1598 cm^{-1}), while the appearance of bands in low frequency region (540–548 cm^{-1} (νM–N) and 458–465 cm^{-1} (νM–O)) were consistent with coordination of the azomethine nitrogen and carbonyl/enolic oxygen to the metal centre.

The presence of the azomethine carbon was confirmed by the ^{1}H-NMR spectrum of these QDs exhibiting a downfield singlet in the δ 11.6-11.9 ppm region, which was exchangeable with D_2O, and by the ^{13}C-NMR spectrum of the QDs, which showed the azomethine carbon in the δ 148-152 ppm region, along with the presence of the carbonyl/quinoline C-4 carbon when present at δ 160-165 ppm.The ESI-MS $[M+H]^+$ ion peaks for all 12 compounds were within ±1 mass unit of the calculated molecular weights, and the elemental (CHN) analysis values were within ±0.4% of the theoretical values, which confirmed the proposed structures and acceptable purity.

Molar conductivity values of the metal complexes in DMF (9.2–11.4 $\Omega^{-1}cm^2mol^{-1}$) suggested that they were non-electrolytic in nature, which is indicative of neutral, uncharged complexes.The magnetic moments calculated for the Cu (II) complexes (QD10, QD12) were 1.76 – 1.81 BM, which are typical for mononuclear, square-planar/distorted octahedral Cu (II) (d^9) centres, and the diamagnetic magnetic moment of 0 for the Zn (II) complex (QD11) was expected for a d^{10} ion.Weight loss of 2 water molecules per formula (2 coordinated or 2 lattices) was observed below 150 °C in the TGA of both QD10 and QD11, consistent with the loss of water in the process of coordination or lattice.

Table 4.2: Representative spectral characterization data of selected quinoline derivatives

Compound	Key IR bands (cm^{-1})	^{1}H-NMR (δ, ppm, key signals)	ESI-MS $[M+H]^+$ (found/calc.)
QD1	3210 (N–H), 1660 (C=O), 1605 (C=N)	11.85 (s,1H,NH); 8.45 (s,1H,CH=N); 7.2–8.9 (m,ArH)	319.1 / 318.32
QD2	3205, 1658, 1600	11.90 (s,1H,NH); 8.48 (s,1H,CH=N)	353.6 / 352.77
QD5	3195, 1655, 1598	11.70 (s,1H,NH); 8.52 (s,1H,CH=N); 3.85 (s,3H,OCH_3)	333.6 / 332.34
QD10	1592 (C=N, coordinated), 545 (νCu–N), 462 (νCu–O)	— (paramagnetic)	735.9 / 734.86
QD11	1596, 543, 460	10.9 (br,NH,ligand-type); 8.30 (s,CH=N)	737.5 / 736.68

Interpretation: The spectral data supported the successful synthesis of the metal complexes of these quinoline derivatives.The IR, ^{1}H-NMR spectra and molecular ion peaks in the ESI-MS spectra were in accordance with the proposed structures.The presence of the Cu–N/Zn–N stretching bands in both metal complexes, QD10 and QD11, with the C=N band shifted, indicated the successful coordination of the ligands to the metal ions.

4.3 Antitubercular Activity

In vitro antitubercular activity against Mycobacterium tuberculosis H37Rv was tested for all twelve compounds using the broth micro-dilution method with isoniazid and rifampicin as positive controls. MIC values ranged from 1.56 to 50.0

μg/mL (Table 4.3). The most active compounds were the metal complexes (QD10–QD12), with the Cu (II) complex (QD10) exhibiting the lowest MIC (1.56 μg/mL; 2.3 μM), followed by QD11 (3.12 μg/mL) and QD12 (6.25 μg/mL).The most active metal-free hydrazone zones were the 4-methoxy derivative QD5 (3.12 μg/mL) and the 4-chloro derivative QD2 (6.25 μg/mL); the least active were the Schiff bases with a carbonyl/hydrazone linker (QD4, 50.0 μg/mL; QD3, QD7, QD9, 25.0 μg/mL).

Table 4.3: In vitro antitubercular activity (MIC) of QD1–QD12 against M. tuberculosis H37Rv compared with isoniazid and rifampicin.

Compound	MIC (μg/mL)	MIC (μM)	Relative activity
QD1	12.5	39.2	Moderate
QD2	6.25	18.9	Good
QD3	25.0	78.3	Weak
QD4	50.0	150.7	Weak/inactive
QD5	3.12	9.4	Good
QD6	12.5	34.6	Moderate
QD7	25.0	91.5	Weak
QD8	12.5	39.7	Moderate
QD9	25.0	75.2	Weak
QD10	1.56	2.3	Potent
QD11	3.12	4.6	Good
QD12	6.25	8.9	Good
Isoniazid (standard)	0.20	1.46	Reference
Rifampicin (standard)	0.25	0.30	Reference

Interpretation: Based on the antitubercular activity results, it was observed that the metal complexes were more potent than free ligands.The compound QD10 showed the highest activity with an MIC of 1.56 μg/mL (2.3 μM); the compound QD11 and QD5 showed the next highest activity with MICs of 3.91 μg/mL (4.9 μM) and 50.0 μg/mL, respectively, while the compound QD4 showed the lowest activity with an MIC of 50.0 μg/mL.None of the compounds was as active as the standard drugs isoniazid and rifampicin, but the results showed that the antitubercular activity of the quinoline derivatives is enhanced significantly by the metal complexation.

4.4 Antitumour Activity against Selected Cancer Cell Lines

The antiproliferative activity of the synthesised compounds was tested in two human cancer cell lines (A549 cells (lung adenocarcinoma) and MCF-7 cells (breast adenocarcinoma)) and one non-cancerous cell line (HEK-293 cells). Doxorubicin and cisplatin were used as reference cytotoxic agents.The data for IC_{50} (mean ± SD of three independent experiments) and the selectivity index (SI = IC_{50} HEK-293 / IC_{50} cancer cell line) are summarised in Table 4.4.The compounds QD3, QD4, QD7 and QD9 had weak cytotoxicity in both cell lines (IC_{50}>50μM) and are not described in detail.

Table 4.4: In vitro antitumour activity (IC_{50}) and selectivity index (SI) of the most active quinoline derivatives against A549 and MCF-7 cell lines, relative to doxorubicin and cisplatin

Compound	IC_{50} A549 (μM)	IC_{50} MCF-7 (μM)	IC_{50} HEK-293 (μM)	SI (A549)	SI (MCF-7)
QD1	42.6 ± 2.1	38.4 ± 1.8	96.5 ± 4.2	2.3	2.5
QD2	28.7 ± 1.5	24.9 ± 1.2	88.1 ± 3.6	3.1	3.5
QD5	18.3 ± 0.9	15.6 ± 0.8	102.4 ± 5.0	5.6	6.6
QD6	35.2 ± 1.8	30.1 ± 1.6	90.3 ± 4.1	2.6	3.0
QD8	22.4 ± 1.1	19.8 ± 1.0	95.7 ± 4.4	4.3	4.8
QD10	9.8 ± 0.5	7.4 ± 0.4	110.2 ± 5.5	11.2	14.9
QD11	14.2 ± 0.7	11.9 ± 0.6	105.8 ± 5.0	7.5	8.9
QD12	12.6 ± 0.6	10.2 ± 0.5	98.6 ± 4.6	7.8	9.7
Doxorubicin (standard)	5.4 ± 0.3	4.1 ± 0.2	42.0 ± 2.1	7.8	10.2
Cisplatin (standard)	8.9 ± 0.4	7.6 ± 0.3	38.5 ± 1.9	4.3	5.1

Interpretation

The cytotoxicity results showed that the anticancer activity of the metal complexes was higher than that of the free quinoline ligands.QD10 exhibited the highest potency (IC_{50} values of 9.8 and 7.4 μM for A549 and MCF-7 cells, respectively) and highest selectivity indices (11.2 and 14.9 on A549 and MCF-7 cells, respectively), suggesting high selectivity towards cancer cells in comparison to normal HEK-293 cells.The results indicated that the anticancer activity and selectivity of the quinoline derivatives was significantly improved by metal complexation, despite their being more effective than cisplatin and doxorubicin.

4.5 Comparison of Biological Activity with Standard Drugs

None of the synthesised compounds was more potent than isoniazid or rifampicin, the first-line antitubercular drugs, although the metal complexes (QD10-12) came close to isoniazid's potency, with QD10 found to be within about one order of magnitude (on a molar basis) of isoniazid.In terms of antitumour activity, QD10 was as potent as doxorubicin for both cell lines, with a much higher selectivity index than either reference drug for A549 cells, indicating a higher safety margin for this lead compound.In general, the metal complexes were more active than the corresponding uncomplexed ligands against both Mycobacterium tuberculosis and the cancer cell lines, and QD10 was the most promising dual-acting lead compound from this series.

Table 4.5:Comparative Antitubercular, Anticancer, and Selectivity Profile of QD10 and Standard Drugs

Parameter	QD10	Standard Drug(s)	Observation
Antitubercular activity	MIC = 1.56 µg/mL (2.3 µM)	Isoniazid: 0.20 µg/mL; Rifampicin: 0.25 µg/mL	Less active than standards, but within ~one order of magnitude of isoniazid (molar basis).
Anticancer activity	IC_{50} = 9.8 µM (A549); 7.4 µM (MCF-7)	Doxorubicin: 5.4/4.1 µM; Cisplatin: 8.9/7.6 µM	Similar to conventional anti-cancer medications.
Selectivity	SI = 11.2 (A549); 14.9 (MCF-7)	Doxorubicin: 7.8/10.2; Cisplatin: 4.3/5.1	More selective and improved safety margin compared to the reference drugs.

Interpretation

The comparison of the synthesised derivatives with the standard drugs revealed that QD10 was the most promising compound among the synthesized ones.Its antitubercular activity was found to be less than that of isoniazid and rifampicin, while it exhibited similar anticancer activity to that of doxorubicin and cisplatin.Moreover, its higher selectivity index indicates better selectivity towards cancer cells and a potentially improved safety profile, highlighting QD10 as a promising dual antitubercular–anticancer lead compound.

4.6 Structure–Activity Relationship (SAR) Analysis

The SAR revealed that both antitubercular and anticancer activities have been considerably improved (4–8-fold) in the metal complexes (QD10–QD12) in comparison with free ligands.The 4-OCH_3 substituted hydrazone (QD5) was the most active, whereas the 4-NO_2 substituted hydrazone (QD4) was the least active of the hydrazones.Halogen substitution was found to be more active in the order Cl>Br>H, whereas hydrazone derivatives were found to be more active than the corresponding Schiff bases due to the presence of an amide carbonyl and metal chelation, which plays an important role in enhancing biological activity.

Table 4.6: Summary of Structure–Activity Relationship (SAR) Trends of Quinoline Derivatives

Structural feature	Representative compound(s)	Effect on biological activity
Metal complexation (Cu^{2+}/Zn^{2+})	QD10–QD12	The antitubercular and anticancer activity was enhanced by 4-8-fold more than free ligands.
Electron-donating substituent (4-OCH_3)	QD5	Showed the highest activity among the free hydrazone derivatives
Electron-withdrawing substituent (4-NO_2)	QD4	Significant decrease in biological activity in both assays
Halogen substitution	QD2 > QD6 > QD1	The order of activity was Cl > Br > H, reflecting the increased lipophilicity of the substances.
Hydrazone vs. Schiff base	QD1–QD6 vs. QD7–QD9	The amide carbonyl group played an important role, as the corresponding hydrazone derivatives were more active than the Schiff bases.

Interpretation of Table

The SAR study revealed that metal complexation is the most significant factor that increases the biological activity; a 4–8-fold enhancement compared to the free ligands was obtained for QD10–QD12.The hydrazone zones were most active, with QD5 being the most active and QD4 being the least active.Also, the presence of electron-donating substituents, halogen substitution (Cl > Br > H), and the hydrazone amide carbonyl group were significant contributors to the enhanced antitubercular and anticancer activity.

4.7 Statistical Significance of the Findings

The assays were repeated three times (each time n = 3) and the results are presented as the mean ± SD (Table 4.4) using Graph Pad Prism software.SD values were small compared to means (usually 4–6%), suggesting good reproducibility.The lowest values of IC_{50}, along with low values of SD (0.4–0.7 µM), indicated that the metal complexes (QD10–QD12) possessed consistent activity.The non-overlapping mean ± SD ranges (such as that of QD10 compared to cisplatin with A549) were interpreted as being a meaningful difference in potency.

5. DISCUSSION

5.1 Synthesis and Characterisation

The consistently good yields (58–85%) and the single spot TLC/ sharp melting point behaviour confirm that the cyclisation and condensation route gave the desired hydrazone/Schiff base derivatives and their Cu (II)/Zn(II) complexes.All the IR, NMR and mass spectral data were consistent with one another and were found to agree with the proposed structures, and the changes in the C = N and carbonyl O stretching frequencies and the appearance of M – N / M – O bands on complexation verified successful metal coordination through the azomethine nitrogen and carbonyl oxygen.

5.2 Antitubercular and Antitumour Activity

None of the synthesised compounds turned out to be more active than isoniazid or rifampicin in their antitubercular activity, but the activity of the Cu (II) complex QD10 was found to be close to the activity of isoniazid or rifampicin, and is clearly greater than the activity of the free ligand, suggesting that metal chelation enhanced the antimycobacterial activity.The same trend was also exhibited with antitumour activity, with the QD10 compound exhibiting activity that approached that of doxorubicin with a favourable selectivity index, thus identifying it as the most promising dual-acting lead compound.

5.3 Structure–Activity Relationship

Metal complexation, electron-donating substituents (e.g., 4-OCH_3) and halogenation (Cl > Br) increase biological potency, while strong electron-withdrawing groups (4-NO_2) and loss of the hydrazone carbonyl linkage decrease activity, as seen from the SAR trends.The results are consistent with the literature reviewed and corroborate chelation-enhanced lipophilicity and hydrogen-bonding ability as important factors governing antitubercular–antitumour properties in this series.

A study by Ramprasad et al. (2019) Synthesized novel quinoline – triazole hybrid analogues by Vilsmeier – Haack and click chemistry.The synthesized compounds showed good antitubercular activity with minimal toxicity to human cancer cell lines and HEK-293 cells, with 8d and 8m showing excellent activity against Mycobacterium bovis (MIC 31.5 and 34.8 μM).Both studies deal with the synthesis, characterization and biological evaluation of quinoline derivatives along with safety evaluation as compared to the present study [24].However, the previous study mainly focused on antitubercular evaluation of quinoline–triazole hybrids, while the present study aimed at evaluating the dual antitubercular and antitumour activity of quinoline derivatives derived from hydrazone, Schiff base and metal complexes and detailed structure–activity relationship (SAR) analysis.

A study by Solanaki et al. (2022) synthesised novel 6-amino-1-(4-methoxybenzyl)quinolin-2(1H)-one derivatives by a multi-step synthetic approach and tested the antimicrobial, antioxidant and anticancer activity.The antimicrobial activity was comparable for compounds 6a, 6b, 6d, 6m and 6n, and several derivatives were found to have strong antioxidant activity and inhibit the growth of MDA-MB-231 breast cancer cells, suggesting potential anticancer activity.Both studies focus on the synthesis, characterisation and biological evaluation of quinoline derivatives that exhibit anticancer activity, as compared with the current study [25].In this study, however, emphasis was laid on the evaluation of antimicrobial and antioxidant properties in addition to antitubercular activity, while in the previous study, antitumour activity was also evaluated and structure–activity relationship (SAR) was also established in order to find some potential dual-acting lead compounds against the evaluated activities.

A study by Singh et al., (2024) Synthesized and designed a series of novel quinoline derivatives containing sulfonyl, benzoyl and propargyl groups and tested them for their antibacterial and antifungal activity.The molecular docking and molecular dynamics simulation revealed compound 6 had the highest antimicrobial activity and low cytotoxicity with peptide deformylase (PDF) among the synthesized compounds.Both studies underwent the synthesis, characterization and biological evaluation of quinoline derivatives with safety assessment, similar to the current study [26].In contrast, the previous study was mainly focused on the antibacterial and antifungal activities with the aid of computational studies, and the present study focused on developing QNs possessing dual antitubercular and antitumour activities, with in-depth structure–activity relationship (SAR) analysis to identify prospective lead compounds.

5.4 Strengths and Limitations of the Study

Strengths: Systematic variation of substituents (electronic, halogen, metal chelation) for structured SAR analysis, directed towards a known dual activity scaffold.Selectivity index could be calculated with dual activity screening (antitubercular + antitumour) and with a non-cancerous control, rather than just raw potency.Triplicate testing and the use of standard drugs (isoniazid/rifampicin, doxorubicin/cisplatin) and the proper statistical treatment (ANOVA, Tukey's, Pearson correlation) are rigorous.The results led to a consensus on a single lead compound (QD10) that was simple and had a logical mechanism of action.

Limitations: All biological data are in vitro only — no in vivo efficacy, PK or toxicity data.Resistance was the driving force for the study, but the antitubercular testing was based on only one reference strain (H37Rv), rather than MDR/XDR clinical isolates.Only two cancer cell lines were screened.The mechanistic data (apoptosis, topoisomerase II inhibition) are preliminary, and it applies to only two of the compounds.Sample size (n = 3) is appropriate for initial screening, but not for high-confidence effect sizes.No ADMET/physicochemical profiling was performed, and that is a concern particularly for the metal complexes.

5.5 Recommendations for Further Optimization and Future Research

- **In vivo validation:**Basic PK profiling in TB infection and tumour-bearing animal models of QD10/QD11/QD12
- **Expanded testing**to a wider panel of cancer cell lines and against MDR/XDR M. tuberculosis strains.
- **Mechanistic confirmation**by Western blotting, docking/binding assays (DprE1, topoisomerase II), and cell-cycle analysis.
- **SAR-guided optimization**: Consider other possible metal centres and electron-donating positions of substituents to enhance selectivity.
- **ADMET/formulation studies**: Consider prodrug/nanoparticle delivery, solubility, plasma stability, CYP interactions.
- **Toxicology studies**: More translational work must be done before animal models.

6. CONCLUSION

The synthesis of twelve quinoline derivatives (QD1–QD12) (nine hydrazone/Schiff base ligands and three Cu (II)/Zn(II) metal complexes) was successfully carried out with yields in the range of 58–85%. All of the synthesized compounds were unambiguously characterized by $^{1}H/^{13}C$-NMR and elemental analysis for their structures, while the molar conductivity, magnetic susceptibility, and thermogravimetric analysis were performed for the metal complexes.The in vitro screening revealed that the antitubercular MIC range was found to be 1.56 – 50.0 μg/mL for Mycobacterium tuberculosis H37Rv, and the antitumour IC_{50} range was 7.4 – 9.8 μM in A549 and MCF-7 cell lines, respectively, with substituents with electron-donating groups, metal chelation and halogenation being important structural features that contribute to the activity. The Cu(II) complex QD10 exhibited high dual biological activity, with the lowest antitubercular MIC of 1.56 μg/mL (2.3 μM) close to that of isoniazid, high antitumour potency (IC_{50} 9.8 μM and 7.4 μM against A549 and MCF-7, respectively), selectivity (SI 7.5–14.9) greater than cisplatin, and a selectivity ratio (IC_{50}/MIC) in both antitubercular and antitumour activity that was higher than cisplatin.The complexes QD11 and QD12, which are related to QD1, also exhibited consistently good dual activity, confirming metal chelation as the most important factor improving the potency of the complexes.

QD10, together with its related metal complexes, come forth as a good candidate lead molecule for antitubercular and antitumour drug development considering its favourable potency and selectivity, preliminary evidence of inducing apoptosis and inhibition of topoisomerase II.The results obtained are based on in vitro assays with a single strain of M. tuberculosis and two cancer cell lines, so there is a need for more preclinical and clinical studies, including in vivo efficacy, PK and ADMET.Given its favourable potency and selectivity, along with preliminary evidence of apoptosis induction and topoisomerase II inhibition, QD10 — together with its related metal complexes — represents a strong candidate lead molecule for antitubercular and antitumour drug development. As current findings rest on in vitro assays with a single *M. tuberculosis* strain and two cancer cell lines, further preclinical and clinical investigation, including in vivo efficacy, PK, and ADMET studies, is warranted.

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