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REVIEW ARTICLE

# Review on recent development of quinoline for anticancer activities

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**KEYWORDS**

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Synthesis;
Anticancer activity;
Antiproliferative activity

**Abstract** Quinoline is an efficient scaffold for anticancer drug development as its derivatives have shown potent results through several mechanisms like growth regulators through "apoptosis, disruption of cell migration, inhibition of angiogenesis, modulation of nuclear receptor responsiveness and cell cycle arrest, etc.," The potential of quinoline derivatives has been proved in several cancer cell lines like breast cancer, colon cancer, lung cancer, colorectal cancer, renal cancer, etc. This review article aims to provide information about the synthesis, potential of the anticancer property, cytotoxicity, and level of clinical treatments, which could lay out the research to develop more effective quinoline-derived anticancer drugs.


## 1. Introduction

Cancer is a primary cause of death and a significant hindrance to extending life span across the world. In 2020, 19.3 million cancer cases were recorded, and around 10 million victims have died primarily due to cancer (Sung et al., 2021). It is the most dangerous disease characterized by the uncontrolled growth of cells spreading throughout the body. To date, various cancer causes have been proposed, including genetic factors (Giri et al., 2018) and environmental elements (Rudolph, Chang-Claude and Schmidt, 2016). It also occurs due to the habits of human beings like smoking tobacco (Didkowska et al., 2016), consuming alcohol (Choi, Myung and Lee, 2018), and eating red meat (Zhao et al., 2020), etc., A few kinds of cancer are also caused by *Helicobacter pylori* (Wroblewski, Peek and Wilson, 2010), HPV (Chan et al., 2019), and HBV infections (Mani and Andrisani, 2018). Anticancer drugs are used to prevent cancer cells from developing and multiplying; if this happens, the tumour cells usually die. for this reason a series of research have been employed to develop a more efficient anti-cancerous drug. Yet it is a continuous process for profound progress in developing a drug without any side effects (Tabassum, Ashfaq and Oku, 2020). Regardless, antitumor drugs like daunorubicin, trastuzumab (Vu and Claret, 2012), sunitinib (Motzer et al., 2017), etc have been authorized by the FDA. But those drugs contain some serious side effects like stasis of the lower bowel, mouth sores, diarrhea, full hair loss, neuropathy, bone marrow suppression, and life-threatening problems, that are difficult to identify. In

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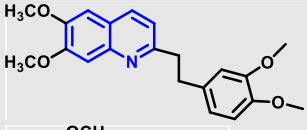
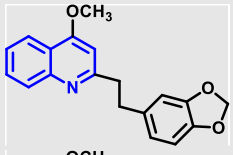
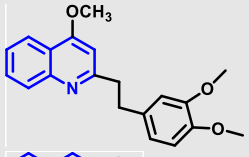
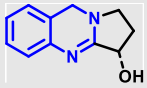
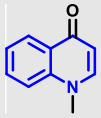
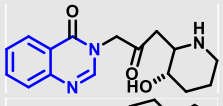
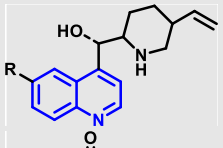
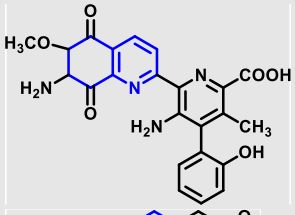
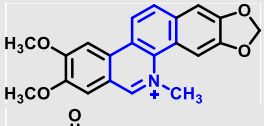
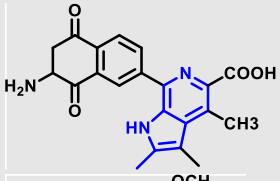
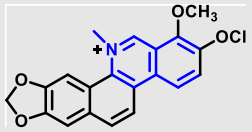
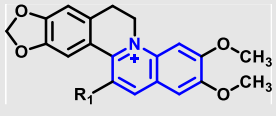
the recent past, heterocyclic compounds have served as an effective pharmacophore in the treatment of a variety of illnesses (Afzal et al., 2015). Among the heterocyclic compounds, quinoline is an efficient scaffold for the development of drugs.

Quinoline is an aromatic heterocyclic organic compound with the chemical formula $C_9H_7N$; whose structure is formed by a fusion of benzene ring with pyridine at two neighboring carbon atoms, giving a double-ring structure (Moor et al., 2021). Benzopyridine, benzo[*b*]pyridine, 1-benzazine, and benzazine are other name of quinoline. It's a hygroscopic, yellowish oily liquid that's soluble in alcohol, ether, and a variety of other solvents. (Jain et al., 2019) Quinoline plays a crucial role in medicinal chemistry due to the presence of nitrogen atom, which pulls electrons by resonance. This bicyclic aromatic compound is an electron-deficient system with weak tertiary base properties. It demonstrates both electrophilic and nucleophilic substitutions, and pyridine exhibits similar substitutions. The clinical observation proves that even when a human inhales a 0.001 ppm level of quinoline for 8 h was perfectly nontoxic and this case is quite opposite to benzene; even a smaller concentration of benzene leads to various biological disorders like cancer.

Quinoline can be derived from different natural sources. Naturally existing quinoline alkaloids like Cuspareine, Cusparine, Galipine (Angosturaalkaloide, 1911), Vasicine, Echinopsine, Fabrifugine (Mathada, 2022), Cinchona, Streptonigrin (Rao, Biemann and Woodward, 1963), Nitidine (Douglas and Hughes, 1991), Lavendamycin (Balitz et al., 1982), Chelerythrine, Berberine derivative (Guamán Ortiz et al., 2014), Dictamnine (Mariano et al., 2002), Camptothecin (Mao et al., 2020), and Chelidonine (Santos and Adkilen, 1932). These alkaloids have potent anticancer activity. Table 1 represents the various naturally existing significant quinoline compounds.

Table 2 represents the marketed anticancer compounds for various cancer. Quinoline is an essential system of several drugs used in therapeutic settings to treat a variety of disorders. Here we addressed the anticancer drug that is found in commercialized and clinical treatments. (Dittrich et al., 2003) (Singh et al., 2015) (Somagond et al., 2018) (Wang et al., 2016).

**Table 1** Structural representation of quinoline-based natural alkaloids.

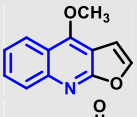
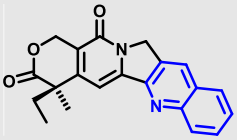
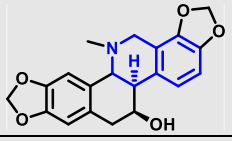
| S.No | Chemical Structures | Alkaloids/ Natural sources |
|---|---|---|
| 1 |  | Cuspareine |
| 2 |  | Cusparine |
| 3 |  | Galipine |
| 4 |  | Vasicine |
| 5 |  | Echinopsine |
| 6 |  | Fabrifugine |
| 7 |  | Cinchona |
| 8 |  | Streptonigrin |
| 9 |  | Nitidine |
| 10 |  | Lavendamycin |
| 11 |  | Chelerythrine |
| 12 |  | Berberine derivative |

## 2. Traditional methods of making quinoline compounds

There are various traditional methods for quinoline synthesis. The majority of the naming reactions are usually used to develop quinolines from simple anilines. Aryl amine is used as one of the precursors in the following naming reactions.

(a) *Riehm synthesis:* When aniline reacts with acetone in the presence of aluminium chloride to form quinoline compound
(b) *Gould-Jacobs reaction:* When aniline reacts with ethyl ethoxy methylene malonate in the presence of Con. $H_2SO_4$ to form quinoline compound.
(c) *Doebner reaction:* When aniline reacts with aldehyde and pyruvic acid to form quinoline compound.
(d) *Doebner-Miller reaction:* When aniline reacts with $\alpha, \beta$-unsaturated carbonyl compound in the presence of p-toluenesulfonic acid to form quinoline compound.

**Table 1** (*continued*)

| S.No | Chemical Structures | Alkaloids/ Natural sources |
|---|---|---|
| 13 |  | Dictamnine |
| 14 |  | Camptothecin |
| 15 |  | Chelidonine |

(e) *Conrad-Limpach synthesis:* When aniline reacts with β-ketoester in the presence of sulfuric acid to form a quinoline compound.
(f) *Combes quinoline synthesis:* When aniline reacts with β-diketones in the presence of sulfuric acid to form a quinoline compound.
(g) *Skraup reaction:* When aniline reacts with glycerol and nitrobenzene in the presence of sulfuric acid to form a quinoline compound.
(h) *Povarov reaction:* When aniline reacts with benzaldehyde in the presence of activated alkene to form a quinoline compound. The synthetic approaches of these traditional methods are recapped in the Fig. 1

The remaining naming reactions are commonly used to develop quinoline compounds from substituted anilines or similar precursors in the following reactions.

(i) *Friedlander synthesis:* When 2-amino benzaldehyde reacts with carbonyl compounds in the presence of trifluoroacetic acid to form a quinoline compound.
(j) *Knorr quinoline synthesis:* When β-ketoanilide reacts with sulfuric acid to form a quinoline compound
(k) *Niementowski quinoline synthesis:* When anthranilic acid reacts with carbonyl compound to form quinoline compound.
(l) *Pfitzinger reaction:* When isatin reacts with carbonyl compound in the presence of potassium hydroxide as a base to form quinoline compound.
(m) *Camps quinoline synthesis:* When o-acylaminoacetophenone reacts with the hydroxide to form a quinoline compound.
(n) *Meth-Cohn synthesis:* When acylanilides react with dimethyl formamide in the presence of phosphorous oxychloride to form a quinoline compound. Fig. 2 presents an overview of the synthetic schemes of quinoline compounds.

The ability of a quinoline molecule to preferentially target cancer-specific signals or enzymatic routes will be essential for the development of efficient and safe anticancer treatments (Zhou et al., 2021). The wide application of biochemical and biological properties has been further aided by quinoline synthetic diversity permits the creation of various types of structurally diverse derivatives. Quinoline compounds have wide range of biological activities like anti-bacterial (Ranjbar-Karimi and Poorfreidoni, 2018), anti-fungal (Hamama et al., 2018), antimalarial (Kalaria, Karad and Raval, 2018), anti-leishmanial (Upadhyay et al., 2019), anti-cancer (Jain et al., 2019), etc.

Quinoline and its derivatives were demonstrated to inhibit tyrosine kinases (Karnik, Sarkate, Tiwari, Azad, Burra, et al., 2021), topoisomerase (Elbadawi et al., 2021), tubulin polymerization (Khelifi et al., 2017), and DHODH kinase (Parikh, Ghate and Vyas, 2015) in the latest research. Fig. 3 shows a schematic representation of different types of inhibitors for anticancer activity of quinoline compounds and Table 3 represents the overall outline of quinoline derivatives against various cancers. In this review article, we gathered the antitumor potential of quinoline-based compounds on a goal approach, which will aid biomedical scientists to progress in advanced antitumor medicine.

### *2.1. Inhibitors for anticancer activity*

#### *2.1.1. Topoisomerase I and II inhibitor*

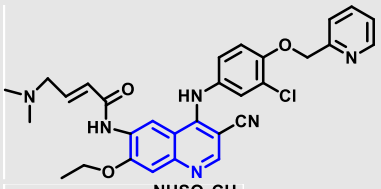
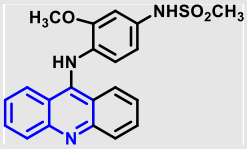
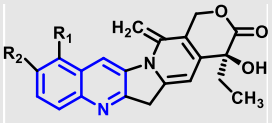
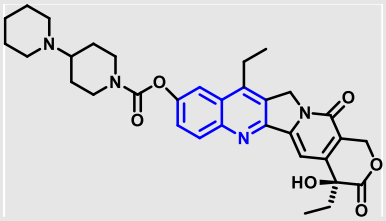
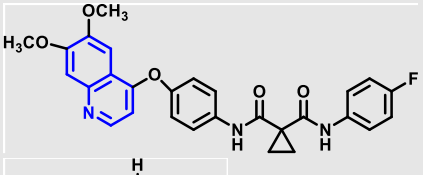
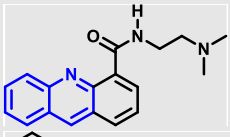
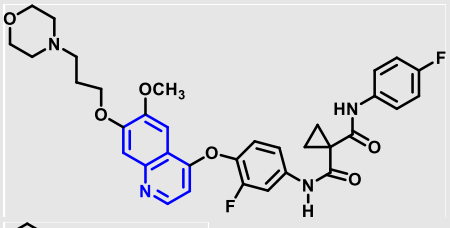
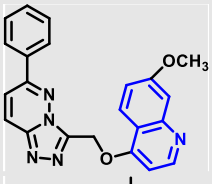
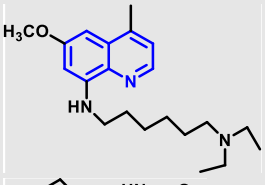
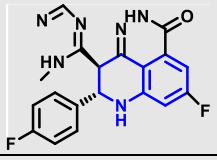
DNA topoisomerase is classified into two kinds like topoisomerase-I (topos-I) and topoisomerase-II (topos-II). (Capranico, Marinello and Chillemi, 2017) A comparison of topoisomerase-I and topoisomerase-II is shown in Table 4.

The majority of these drugs target topoisomerase (types II) enzymes, which are currently used to treat human cancers. Topoisomerase inhibitors are known as "poisons" because they generate cleavable complexes with DNA, resulting from lasting DNA impairment that sets off a sequence of biological processes that progressively lead to programmed cell death or cell death in different ways. (Schmidt, Osheroff and Berger, 2012) They can relax positive or negatively supercoiled deoxyribonucleic acid, topos are common nuclear enzymes that regulate the topological form of DNA and perform a variety of other tasks such as replication and transcription (Wang, 2002) TopII enzymes are the target of most presently used antitumor medications in the therapy of cancer and many new medication sequences are now being developed for the treatment of human cancers, target topos enzymes.

A series of new methoxy-based quinoline compounds were found to have anti-cancer properties *in vitro* by Elbadawi and co-workers. (Elbadawi et al., 2021) taking 2-aminoacetophenone and benzoyl chloride as starting substrate in the presence of triethyl amine at 0 $^{0}$C in overnight; further reacts with dioxane under nitrogen atmosphere to form a cyclized compound; it reacts with an alkyl halide from chloro substituted compound and then finally product reacts with the amine to form **Q1-3** compounds **(**Scheme 1**).**

Two novel sequences of quinoline derivatives were designed and synthesized to develop prospective antitumor drugs targeting Topoisomerase I (TOP1), depending on SAR of previously reported Topoisomerase I inhibitors and structural characteristics required for Topoisomerase I - deoxyribonucleic acid cleavage complex stabilization. The

**Table 2** Comprehensive list of anticancer drugs with their structure.

| S.No | Drug Names | Chemical Structures | Types of cancers |
|---|---|---|---|
| 1 | Neratinib |  | Breast cancer |
| 2 | Amsacrine |  | Acute leukemia |
| 3 | Quinoline analog |  $R_1$= H, $CH_2N(CH_3)_2$<br>$R_2$ = H,OH | Blood Cancer |
| 4 | Irinotecan |  | Colorectal cancer |
| 5 | Cabozantinib |  | Thyroid cancer |
| 6 | Acridine carboxamide |  | Lunger cancer and brain and central nervous system tumors |
| 7 | Foretinib |  | Breast cancer |
| 8 | AMG-208 |  | Prostate cancer |
| 9 | Sitamaquine |  | Prostate cancer |
| 10 | Talazoparib |  | Breast cancer |

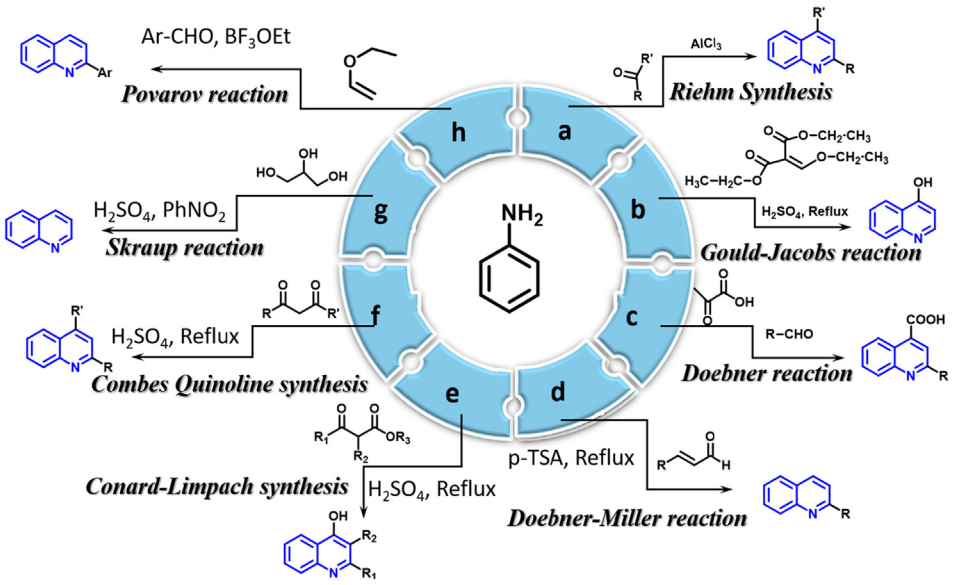



**Fig. 1** Traditional methods for synthesis of quinoline compounds.

National Cancer Institute (NCI-60) tumor cell lines panel was used to investigate the antitumor properties of these two sequences of drugs *in vitro* at a single treatment stage. Most active compounds had a *para*-substituted phenyl at Carbon-2 and a propyl group link at Carbon-4 and were chosen for assay at five dose levels, where they showed potent anticancer activity at sub-micromolar levels vs various tumor cell lines. The NCI procedure was used to evaluate all substances for their anticancer potential. **Q1** compound was found to be the most effective in causing rectal cancer, melanoma, and leukemia at submicromolar levels. As a result, **Q2** and **Q3** substances were discovered to be promising lead compounds for the creation of more active anticancer medicines with TOP1 inhibitory action, both substances have promising pharmacokinetics and drug-likeness properties.

Naphthyridine-based quinoline compounds **(**Scheme 2**)** were designed and developed by Ramakant. **Q4** and **Q5** compounds had high potent antiproliferative agents towards the epithelial carcinoma and breast cancer cells. (Kardile et al., 2021) Both the compound have a substantial binding site of the DNA topoisomerase I protein was confirmed by molecular docking. Assessing the Top-I inhibitory efficacy of **Q4** **(72.4 %)** and **Q5** **(60.6 %)** compounds vs camptothecin **(61.4 %)**. From this result, both compounds have notable cytotoxicity by using MTT assay and inhibit the proliferation of cancer cells.

Amelia Galdino Ribeiro et al., (Ribeiro et al., 2019) reported a novel 4-quinoline-thiosemicarbazone **(Q6)** variant from hydrazine and substituted isothiocyanate at 25 $^{0}$C; further condensation reaction between 4-quinolinal **(**Scheme 3**).** The thiosemicarbazone derivatives showed DNA and BSA binding ability. The N-(4-ethylphenyl)-2-(quinoline-4-ylmethy lene) hydrazine carbothioamide molecule was emphasized because it had a higher Kb and Ksv value for DNA and BSA binding, indicating a possible method of DNA intercalation, which was confirmed by absorption methods, CD, and molecular docking. **Q6** derivative also had a lower $IC_{50}$ value for MCF7 lines (0.82 $\mu m$) and inhibited topos-II partially, making it an interfacial antitumoral inhibitor. The antitumor effect was not disrupted by the reduction of the acridine ring to a quinoline ring, demonstrating that substitution patterns are critical for biomolecule contact affinity.

Concepcion Alonso et al., (Alonso et al., 2018) have reported the synthesis of new hydroquinoline and quinoline having phosphorous linkers including phosphine oxide, phosphine, and phosphine sulphide. The "Povarov reaction" is used for synthesis **(**Scheme 4**).** A multicomponent reaction is used in the synthesis, which allows for the chosen creation of two stereocentres in a quick, effective and repeatable manner. Q-7–9 compounds were tested against kidney, lungs, and ovarian cancer cell lines for cytotoxicity; **Q7** exhibited potent activity against the lung cancer cell line (0.25 ± 0.03 $\mu m$); **Q8** and **Q9** both compounds showed a better activity agains the lung cancer cell line 0.08 ± 0.01 $\mu m$ and 0.03 ± 0.04 $\mu m$. Additionally, selectivity towards cancer cells like A549 rather than noncancerous cells like MRC5 has been reported by the Alonso group. These compounds are showing notable cytotoxicity and inhibit the growth of tumor cells; may be excellent antiproliferative candidates due to their structural system.

The preparation of sequences of "2-amino, 5-amino, and 2,5-diamino substituted benzimidazo[1,2-*a*]quinolines" using microwave-assisted amination without catalysis was described by Natasa Perin et al., (Perin et al., 2016) **(**Scheme 5**)** 4-fluorobenzaldehyde reacts with benzimidazole derivative in the presetonce of piperidine and ethanol as a solvent to form intermediate; cyclized and then reacts with the amine to form product **Q10** and **Q11,** similarly 4-fluoro benzoyl chloride taking as a substrate to form **Q12** product. These compounds were tested against the colon, breast and lung cancer cell lines for anticancer properties due to the presence of 4-methyl and 3,5-dimethyl-1-piperazinyl groups. The compounds were designed and evaluated for 3D-QSAR (Quantitative struc-

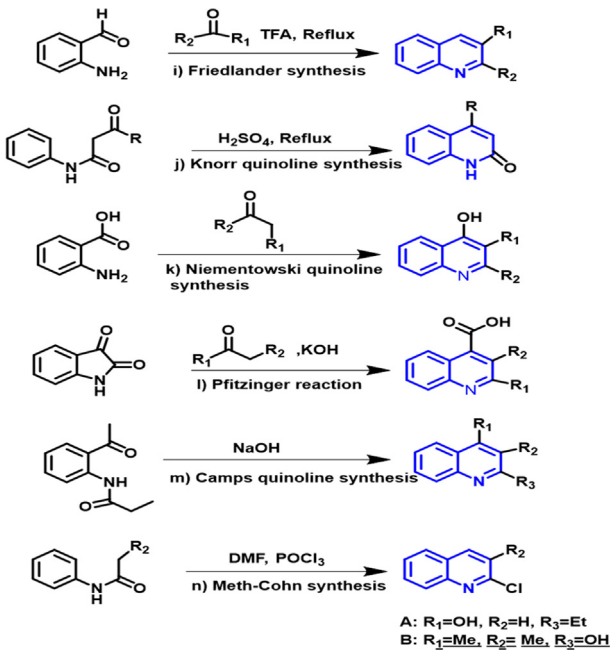



**Fig. 2** Synthetic schemes of quinoline compounds.

ture–activity relationship) analysis, DNA binding abilities, and antiproliferative properties. 2-amino-substituted analogs had the highest antiproliferative activity while 5- amino and 2,5 diamino substituted compounds were significantly decreased.

Vladimir V et al., (Kouznetsov et al., 2017) reported the synthesis of "4-methyl-2-(2-, 3- and 4-pyridinyl) quinolones" heterocycles from p-substituted anilines and pyridine carboxaldehyde in the presence of sodium sulfate under dichloromethane solvent. Scheme 6 **Q13-14** compounds were synthesized using altered Kametani reaction and evaluated for biological activities *in vitro*. These compounds have significant anticancer activities, but they also had a small safe margin, as seen with doxorubicin. Human tumor cell lines like SKBR3, MCF7, PC3, and HeLa were evaluated *in vitro* for cytotoxicity, with human skin fibroblasts serving as non-cancer cells. As a promising method for anticancer medicines against prostate carcinoma, "4-methyl-2-(3-pyridinyl)quino line (PQ)" is unique out for its low non-specific cytotoxicity and highly outstanding selectivity for PC3 cells ($IC_{50}$ = 4.40-$\mu$m). **Q-13** compound revealed greater efficiency ($IC_{50}$ = 0.016-$\mu$ m) and exceptional selectivity (SI = 4168.1). **Q-14** compound showed a great efficiency activity ($IC_{50}$ = 0.38$\mu$ m) towards breast malignancy.

Dina I.A. Othman et al., (Othman et al., 2019) described the synthesis of thiophene-1-benzopyridine compounds with isooxazole,trizole, and phenyl molecules linked by the OH functional group using click chemistry methods (Scheme 7**).** In vitro testing of the produced molecules towards 4 human tumor cell lines such as HepG2, HeLa, HCT-116, and MCF7 was performed using the MTT assay. **Q-15** and **Q-16** compounds had very effective antitumor properties toward breast cancer ($IC_{50}$ = 38.14 $\mu m$ and 28.36 $\mu m$). According to SAR analysis, the significant cytotoxic effect was strengthened by replacing the 1,2-oxazole and 1,2,4-triazole groups with

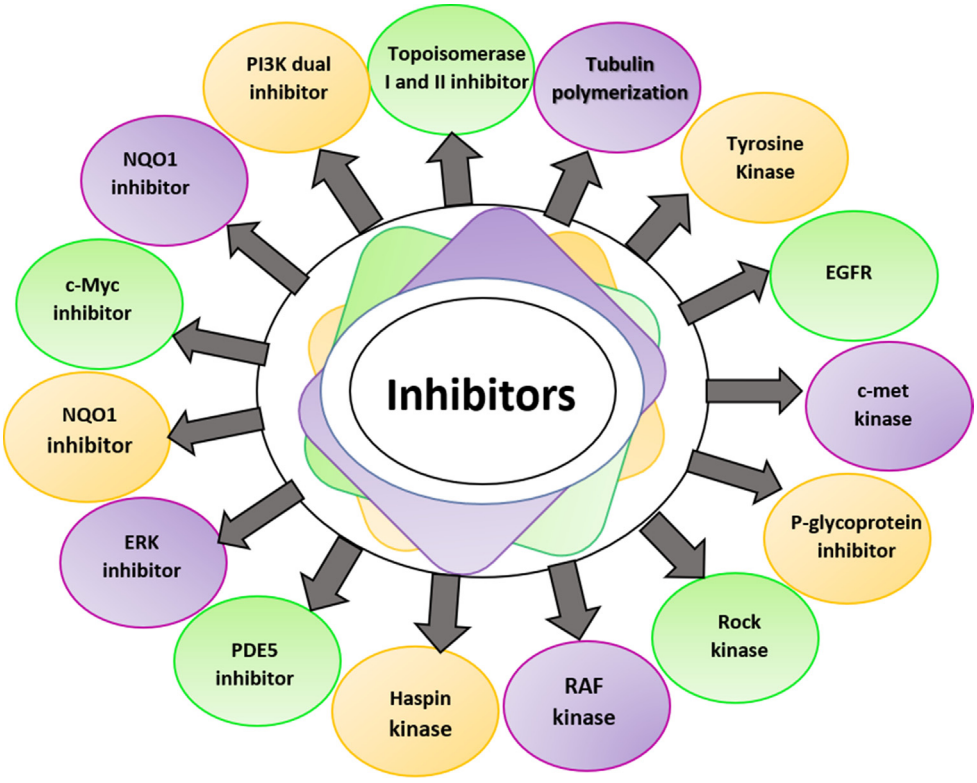



**Fig. 3** Various types of inhibitors for anticancer activity.

**Table 3** An overall outline of quinoline compounds and their activity in cancer.

| Type of Inhibitors/ Combinations | Quinolines | Type of cancers | $IC_{50}$ values | Ref. |
|---|---|---|---|---|
| Topoisomerase-I [(2-(2-amino-4,5-dimethoxyphenyl)-2-oxoethan-1-ylium and halo substituted benzoyl chloride] | Q1 | Colon cancer, leukemic, and melanoma | 0.875, 0.904 and 0.926 $\mu m$ | (Elbadawi et al., 2021) |
| Topoisomerase-I [(2-(2-amino-4,5-dimethoxyphenyl)-2-oxoethan-1-ylium and halo substituted benzoyl chloride] | Q2 | Melanoma and renal caner | 1.40 and 1.66 $\mu m$ | (Elbadawi et al., 2021) |
| Topoisomerase-I [(2-(2-amino-4,5-dimethoxyphenyl)-2-oxoethan-1-ylium and halo substituted benzoyl chloride] | Q3 | Breast and melanoma | 1.13 and 1.19 $\mu m$ | (Elbadawi et al., 2021) |
| Topoisomerase-I [Bromoaniline and malonic acid] | Q4 | Epithelial carcinoma and breast cancer | 0.44 and 0.62 $\mu m$ | (Kardile et al., 2021) |
| Topoisomerase-I [Bromoaniline and malonic acid] | Q5 | Epithelial carcinoma and breast cancer | 0.69 and 0.54 $\mu m$ | (Kardile et al., 2021) |
| Topoisomerase-I [Diazene and thiocyanate] | Q6 | Breast cancer | 0.82 $\mu m$ | (Ribeiro et al., 2019) |
| Topoisomerase-I [Aromatic aldehyde and (2-aminophenyl) diphenylphosphine oxide ] | Q7 | Lung cancer | 0.25 $\pm$ 0.03 $\mu m$ | (Alonso et al., 2018) |
| Topoisomerase-I [Aromatic aldehyde and alkenyl substituted benzene] | Q8 | Lung cancer | 0.08 $\pm$ 0.01 $\mu m$ | (Alonso et al., 2018) |
| Topoisomerase-I [Aromatic aldehyde and (2-aminophenyl) diphenylphosphine sulfide] | Q9 | Lung cancer | 0.03 $\pm$ 0.04 $\mu m$ | (Alonso et al., 2018) |
| Topoisomerase-I [Aniline and benzaldehyde] | Q13 | Prostate cancer | 4.40 $\mu m$ | (Kouznetsov et al., 2017) |
| Topoisomerase-I [Aniline and benzaldehyde] | Q14 | Cervical cancer | 0.016 $\mu m$ | (Kouznetsov et al., 2017) |
| Topoisomerase-II [Phenyl acetamide and 2-bromothiophene] | Q15 | Breast cancer | 38.41 $\mu m$ | (Othman et al., 2019) |
| Topoisomerase-II [Phenyl acetamide and 2-bromothiophene] | Q16 | Breast cancer | 28.36 $\mu m$ | (Othman et al., 2019) |
| Tubulin polymerization [2-chloro-5-methoxyquinoline and m-nitroaniline] | Q17 | Colon cancer | 0.888 $\mu m$ | (El-Damasy et al., 2020) |
| Tubulin polymerization [2-chloro-5-methoxyquinoline and m-nitroaniline] | Q18 | Colon cancer | 0.229 $\mu m$ | (El-Damasy et al., 2020) |
| Tubulin polymerization [4-chloro-2-methylquinoline and *N*-tosylhydrazone | Q19 | Malignant gliomas, chronic myeloid leukemia, bone marrow, lung cancer, and colon caner | $< 10nm$ | (Khelifi et al., 2017) |
| Tubulin polymerization [4-chloro-2-methylquinoline and 4-methoxy-3-nitroaniline] | Q20 | Colon cancer | $1.5 - 3.9nm$ | (Zhou et al., 2017) |
| Tubulin polymerization [3,4,5-trimethoxybenzaldehyde, 2-oxopropanoic acid, and 3,4,5-trimethoxyaniline] | Q21 | Breast cancer, ovarian metastatic cancer | 16.28 and 11.44 $\mu m$ | (Shobeiri et al., 2016) |
| Tubulin polymerization [Halo substituted quinoline and alkyl substituted aniline] | Q25 | Human ovarian carcinoma, cisplatin-resistant human ovarian carcinoma, breast cancer, mitoxantrone-resistant human breast cancer, and normal Huvec cancer | 0.50 $\pm$ 0.07, 1.21 $\pm$ 0.22, 1.11 $\pm$ 0.26, 1.66 $\pm$ 0.27 and 9.94 $\pm$ 2.68 $\mu m$ | (Jafari et al., 2019) |
| Tubulin polymerization [Halo substituted quinoline and alkyl substituted aniline] | Q26 | Human ovarian carcinoma, cisplatin-resistant human ovarian carcinoma, breast cancer, mitoxantrone-resistant human breast cancer, and normal Huvec cancer | 1.44 $\pm$ 0.16, 1.13 $\pm$ 0.22, 1.79 $\pm$ 0.26, 1.67 $\pm$ 0.17 and 7.82 $\pm$ 2.44 $\mu m$ | (Jafari et al., 2019) |
| Tubulin polymerization [phenyl acetamide and 1-argiothiourea] | Q27 | Cervical cancer, lung, urinary bladder, and ovarian adenocarcinoma cancers | 4.4 to 8.7 $\mu m$ | (Fang et al., 2021) |
| Tubulin polymerization [Indole and methyl iodide] | Q28 | Hepatocellular carcinoma of the mouse | 0.008 $\pm 0.001 \mu m$ | (Li et al., 2019) |
| Tubulin polymerization [Indole and formaldehyde] | Q29 | Hepatocellular carcinoma of the mouse | 0.006 $\pm 0.001 \mu m$ | (Li et al., 2019) |

(*continued on next page*)

**Table 3** (*continued*)

| Type of Inhibitors/ Combinations | Quinolines | Type of cancers | $IC_{50}$ values | Ref. |
|---|---|---|---|---|
| Tyrosine kinase [mercaptoacetic acid and substituted quinoline derivative | Q30 | Colorectal cancer | 0.19 $\mu m$ | (Zhou et al., 2021) |
| Tyrosine kinase [2-chloro-5-methoxyquinoline and nitroamine] | Q31 | Human foreskin fibroblasts | 1.62 $\mu m$ | (El-Damasy et al., 2016) |
| EGFR-TK [4-substituted benzaldehyde and benzamide derivative] | Q32 | Breast cancer | 3.46 $\mu m$ | (Ibrahim et al., 2015) |
| EGFR-TK [ 2,2-dimethyl-1,3-dioxane-4,6-dione and trimethyl orthoformate] | Q33 | Lung and breast cancer | 1.03 ± 0.37 and 1.45 ± 0.19 $\mu m$ | (Li et al., 2022) |
| EGFR-TK [Aniline derivative and isoindoline] | Q34 | Lung cancer | 0.91 $\mu m$ | (Karnik, Sarkate, Tiwari, Azad and Wakte, 2021) |
| EGFR-TK [3-amino-2-bromobenzoic acid and diethyl 2-(ethoxymethylene)malonate] | Q35 | Breast and non-small lung cancer | 3.42 and 5.97 $\mu m$ | (Abdellatif et al., 2017) |
| EGFR-TK [4-(6,7-dichlorobenzo[*d*] thiazol-2-yl)aniline and 3-(2-bromoacetyl)-4-hydroxy-1-methylquinolin-2(1H)-one] | Q36 | Breast cancer and hepatic cancer | 0.398 and 02.25 $\mu m$ | (Bolakatti et al., 2021) |
| EGFR-TK [4-(6,7-dichlorobenzo[*d*] thiazol-2-yl)aniline and 3-(2-bromoacetyl)-4-hydroxy-1-phenylnaphthalen-2(1H)-one] | Q37 | Breast cancer and hepatic cancer | 2.97 and 2.48 $\mu m$ | (Bolakatti et al., 2021) |
| EGFR-TK [Indoline-2,3-dione and acetophenone] | Q38 | Lung, breast, and colon cancer | 6.1 ± 0.8, 7.5 ± 1.2 and 7.8 ± 1.4 $\mu m$ | (Mohassab et al., 2021) |
| EGFR-TK [Indoline-2,3-dione and acetophenone] | Q39 | Lung, breast, and colon cancer | 3.6 ± 0.05, 3.3 ± 0.08 and 3.5 ± 0.02 $\mu m$ | (Mohassab et al., 2021) |
| EGFR-TK [Indoline-2,3-dione and acetophenone] | Q40 | Lung, breast, and colon cancer | 6.9 ± 0.3, 6.8 ± 1.6 and 6.9 ± 1.1 $\mu m$ | (Mohassab et al., 2021) |
| EGFR-TK [Indoline-2,3-dione and acetophenone] | Q41 | Lung, breast, and colon cancer | 3.9 ± 0.6, 3.2 ± 0.08 and 3.8 ± 0.2 $\mu m$ | (Mohassab et al., 2021) |
| EGFR-TK [Indoline-2,3-dione and acetophenone] | Q42 | Lung, breast, and colon cancer | 4.7 ± 0.4, 4.9 ± 0.6 and 4.9 ± 0.2 $\mu m$ | (Mohassab et al., 2021) |
| EGFR-TK [8-nitro-2,3-dihydroquinolin-4(1H)-one, benzaldehyde and pyrrolidine] | Q43 | Breast and lung cancer | 14.26 and 15.41 $\mu m$ | (Arasakumar et al., 2017) |
| EGFR-TK [Amine substituted quinoline and Furaldehyde derivative] | Q44 | Breast cancer | 3.355 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [Amine substituted quinoline and Furaldehyde derivative] | Q45 | Breast cancer | 3.647 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [Amine substituted quinoline and morpholine] | Q46 | Breast cancer | 5.069 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [Amine substituted quinoline and allylisothiocyanate] | Q47 | Breast cancer | 3.617 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [Amine substituted quinoline and allylisothiocyanate] | Q48 | Breast cancer | 0.839 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [Amine substituted quinoline and benzyl chloride] | Q49 | Breast cancer | 10.85 $\mu m$ | (Aly et al., 2017) |
| EGFR-TK [6-methoxy-3,4-dihydronaphthalen-1(2H)-one and benzaldehyde] | Q50 | Breast cancer | 7.70 ± 0.39 $\mu m$ | (Abdelsalam et al., 2019) |
| EGFR-TK [(E)-2-(argiomethylene)-6-methoxy-3,4-dihydronaphthalen-1 (2H)-one and ethyl 2-cyanoacetate] | Q51 | Breast cancer | 7.21 ± 0.43 $\mu m$ | (Abdelsalam et al., 2019) |
| EGFR-TK [6-bromo-8-iodo-4-oxo-1,4-dihydroquinoline-3-carbaldehyde and aromatic acetylene derivative] | Q53 | Breast cancer | 14.48 ± 0.48 $\mu m$ | (Mphahlele et al., 2020) |
| EGFR-TK [6-bromo-8-iodo-4-oxo- | Q54 | Breast cancer | 11.33 ± 0.53 $\mu m$ | (Mphahlele |

**Table 3** (*continued*)

| Type of Inhibitors/ Combinations | Quinolines | Type of cancers | $IC_{50}$ values | Ref. |
|---|---|---|---|---|
| 1,4-dihydroquinoline-3-carbaldehyde and aromatic acetylene derivative] | | | | et al., 2020) |
| EGFR-TK [Aniline and 2-chloronicotinic acid] | Q55 | Lung, hepatocellular carcinoma, and breast caner | 0.23, 0.42 and 0.21 $\mu m$ | (Zhou et al., 2020) |
| c-met kinase [mercaptoacetic acid and substituted quinoline derivative | Q56 | Colorectal cancer | 0.31 $\mu m$ | (Tang et al., 2018) |
| c-met kinase [2-chlorobenzoic acid and aniline] | Q57 | Lung cancer | 1.25 $nM$ | (Tang et al., 2016) |
| Rapidly accelerated fibrosarcoma kinase [2-amino-4,5-dimethoxybenzaldehyde and 1-(4-nitrophenoxy)propan-2-one] | Q60 | Leukemia, colon, melanoma, ovarian, renal, prostate, and breast cancer | 0.98, 1.16, 1.31, 1.09, 1.46, 1.08, 1.01, and 0.93 $\mu m$ | (El-Gamal et al., 2017) |
| Rapidly accelerated fibrosarcoma kinase [Bromo aniline and methyl vinyl ketone] | Q61 | Various types of breast caner | 0.80, 0.67,1.30, 5.0 and 1.30 $nM$ | (El-Gamal et al., 2017) |
| PI3K [1H-indazol-6-amine and benzaldehye] | Q62 | Colon cancer | 14 $nM$ | (He et al., 2021) |
| PDE5 [4-chloro-2-methylquinoline and (4-fluorophenyl)methanamine] | Q64 | Lung cancer | 0.96 $\mu m$ | (Ibrahim et al., 2020) |
| PDK1 [6-chloro-4-hydroxyquinolin-2(1H)-one and 2,3-dichloronaphthalene-1,4-dione] | Q65 | Melanoma caner | 3.7 $\mu m$ | (Vennila et al., 2018) |
| ERK [6-chloro-4-hydroxyquinolin-2(1H)-one and 7-hydroxy-5-phenylphenanthridine-6,9(5H,10*H*)-dione] | Q66 | Melanoma caner | 0.13 $\mu m$ | (Aly et al., 2019) |
| ERK [naphthalene-1,2-dione and 2,2-dimethyl-1,3-dioxane-4,6-dione] | Q67 | Breast cancer | 3.06 ± 0.38 $\mu m$ | (Aly et al., 2019) |
| NQOL [6,7-dihydroquinoline-5,8-dione and aniline] | Q68 | Cervical cancer | 0.44 ± 0.08 $\mu m$ | (Wu et al., 2020) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q73 | Breast and Malignant melanoma | 4.14 ± 1.72, 24.03 ± 0.02 $\mu m$ | (Petrović et al., 2020) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q74 | Breast and Malignant melanoma | 1.77 ± 0.57, 8.96 ± 0.05 $\mu m$ | (Petrović et al., 2020) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q75 | Breast and Malignant melanoma | 3.47 ± 0.91, 10.75 ± 0.07 $\mu m$ | (Petrović et al., 2020) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q76 | Breast and Malignant melanoma | 2.52 ± 0.72, 13.79 ± 0.05 $\mu m$ | (Petrović et al., 2020) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q77 | Colon and breast cancer | 1.56 $\mu m$ | (Vyas et al., 2019) |
| DHODH kinase [Aniline, 2-oxopropanoic acid, and benzaldehyde] | Q78 | Colon and breast cancer | 1.22 $\mu m$ | (Vyas et al., 2019) |
| C-myc [Quinolin-4-ol and benzocaine] | Q79 | Liver cancer | 12.6 ± 0.1 $\mu m$ | (Zhao et al., 2013) |
| C-myc [Quinolin-4-ol and benzocaine] | Q80 | Liver cancer | 27.3 ± 1.7 $\mu m$ | (Zhao et al., 2013) |

phenyl moiety. In addition, anticancer activity was improved by compounds bearing a halogen group at the 4-position on the phenyl ring. A cell growth study and a cell death test were also performed. Breast cancer cells in the second growth phase before mitosis have been demonstrated to be inhibited by these compounds. Furthermore, these perspective compounds were found to have a potent inhibitory effect against the topos-II and epidermal growth factor receptor tyrosine kinase enzymes.

### *2.1.2. Tubulin polymerization*

Microtubules are essential for all eukaryotic organisms. This structure is made up of α and β tubulin heterodimers organized in the form of a slender filamentous tube and tightly arranged both spatially and temporally. Cell cycle arrest in the G2-M phase and the development of aberrant mitotic spindles can both occur from microtubule disruption. This characteristic makes microtubules an appealing target for the development

**Table 4** Comparision between topoisomerase-I and topoisomerase-II.

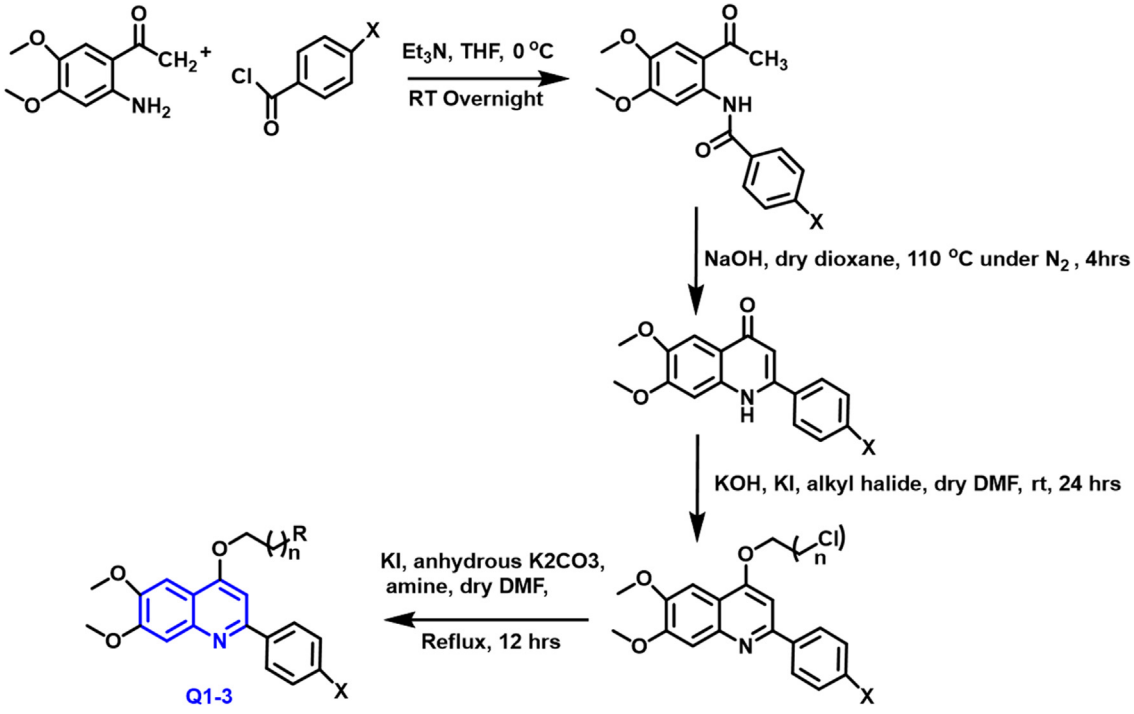
| | Topoisomerase-I | Topoisomerase-II |
|---|---|---|
| Definition | Type-I topoisomerase is an enzyme that causes single-strand breaks and relegation to vary the degree of DNA supercoiling. | Type-II topoisomerase is an enzyme that causes double-strand breaks and relegation to vary the degree of DNA supercoiling |
| Structure | Monomer | Heterodimer |
| DNA breaking | It performs single-strand breaks | It performs double-strand breaks |
| ATP hydrolysis | Its actions aren't dependent on hydrolysis | Its actions are dependent on hydrolysis |
| Found | It found in eukaryotic | It found in both eukaryotic and prokaryotic |
| Modify the linking number of circular deoxyribonucleic acid | It modifies the linking number of circular deoxyribonucleic acid by a unit of 1. | It modifies the linking number of circular deoxyribonucleic acid by units of + or − 2. |
| Potent anticancer compounds | Irinotecan drug used to cure colorectal cancer | Amacrine drug used to cure cute leukemia cancer |

of anticancer drugs because it is crucial for mitosis and cell division.(Field, Kanakkanthara and Miller, 2015).

Ashraf K. El-Damasy and coworkers (El-Damasy et al., 2020) have designed and synthesized a unique sequence of *n*-phenylquinolin-2-amine-based acrylamide from 2-chloro-5-methoxy quinoline and meta or para nito aniline taking as starting material at 160 $^{0}$C in two hours reaction (Scheme 8). These compounds were tested against various cancer such as colon, renal and ovarian. **Q17** and **Q18** compounds have a potent anticancer activity due to the presence of piperazine substituted phenyl ring; moreover, this compound is more active than imatinib drugs. At the National Cancer Institute, a set of potential compounds was tested for anticancer efficacy against a board of sixty tumor cell lines at a dose of 10 $\mu m$. The amide binding to the met-position of the *n*-phenylquinolin-2-amine framework is effective for anti-cancer properties, according to the SAR report. **Q-17** and **Q-18** compounds had very effective antitumor properties toward colon cancer ($IC_{50}$ = 0.888 $\mu m$ and 0.229 $\mu m$). Both the compounds were found to cause morphological alteration, cell death, and cell division cycle arrest in colon cancer cells in an *in vitro* mechanistic analysis. Furthermore, benzamide-based compounds like paclitaxel changed the microtubule polymerization sequence**.** This compound showed inhibitory activity against proto-oncogene B-Raf 600E and C-Rapidly accelerated fibrosarcoma kinases.

Ilhem Khelifi et al., (Khelifi et al., 2017) developed a method for the synthesis of Isocombreat quinoline derivative through the reaction of 4-chloroquinaldine and *N*-tosylhydrazones in the presence of palladium catalyst under a sealed tube reaction (Scheme 9)**. Q-19** compound binds to the colchicine binding site of tubulin by docking experiments. It showed significant cytotoxicity toward cancer cell lines like malignant gliomas, chronic myeloid leukemia, bone marrow, lung, and colon at 10 nM. This compound shows anticancer activity due to the presence of hydroxy and methoxy phenyl ring system.

Yuanyuan Zhou et al., (Zhou et al., 2017) developed a series of 4-anilinoquinoline compounds as potent anti-cancer



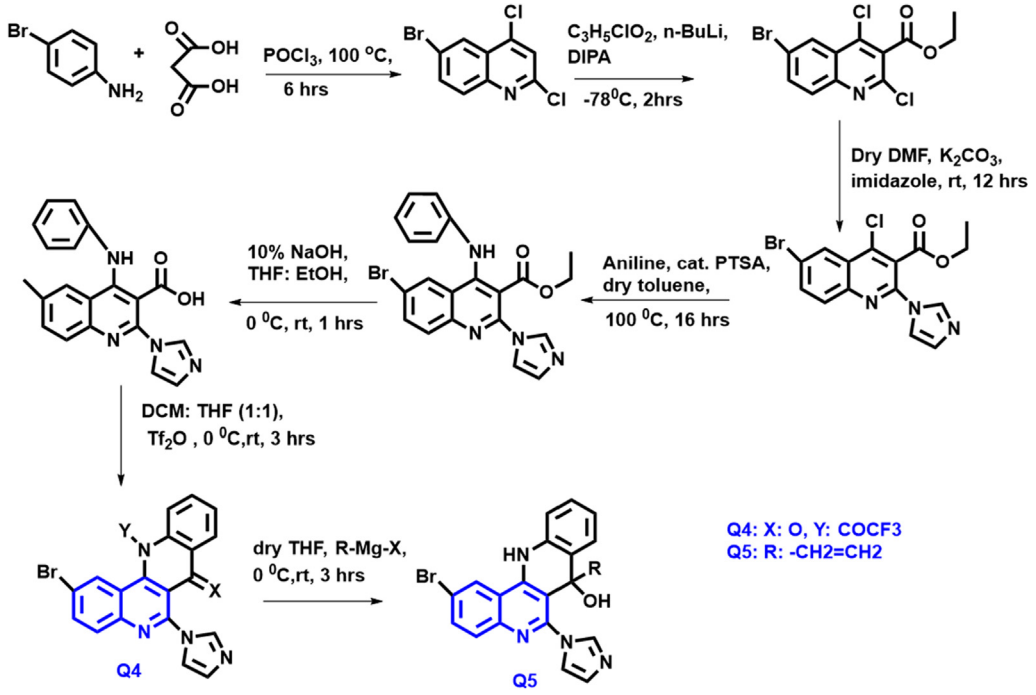

**Scheme 1** Synthesis of 4-alkoxy-2-arylquinoline compounds.

properties (Scheme 10). **Q-20** molecule had the high effective cytotoxic activity towards all tumor cell lines studied, with an $IC_{50}$ = 1.5–3.9 nM, and in MDR (Multiple Drug Resistant ) tumor cells, demonstrated encouraging efficacy. This compound also demonstrated powerful anticancer activity without substantial weight loss in body weight by using *in vivo* effectiveness testing of the heterograft model. All the studies represented that the compound shows a potent anticancer treatment; especially for colon cancer.

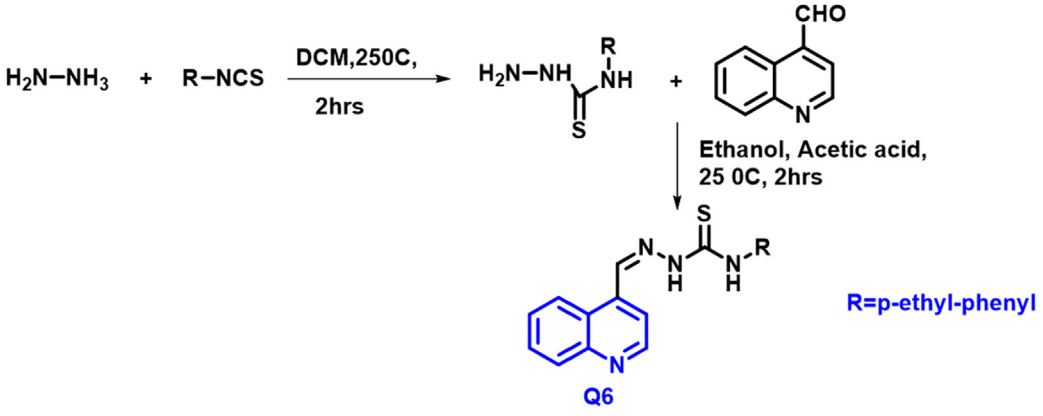
Nikta Shobeiri, and coworkers (Shobeiri et al., 2016) have reported that methoxylated flavones were utilized as lead compounds in the methods and synthesis of a new sequence of 2-aryl-trimethoxyquinoline analogs as tubulin inhibitors (Scheme 11). Their cytotoxic activity has been tested on 4 human beings tumor cell lines breast, resistant breast, ovarian, and human ovarian carcinoma cells. **Q21** compound has a potent anticancer activity toward breast and ovarian cancer ($IC_{50}$ = 16.28 and 11.44 $\mu m$). They have high cytotoxicity effect due to presence of methoxy group; and it had equal cytotoxic potency against either of the original and receptive cell lines.

It was discovered to be a highly active tubulin-inhibitor, causing cell growth arrest in the second growth phase process and apoptosis. Interaction between the **Q-21** and colchicine-binding site of tubulin was studied by molecular docking.

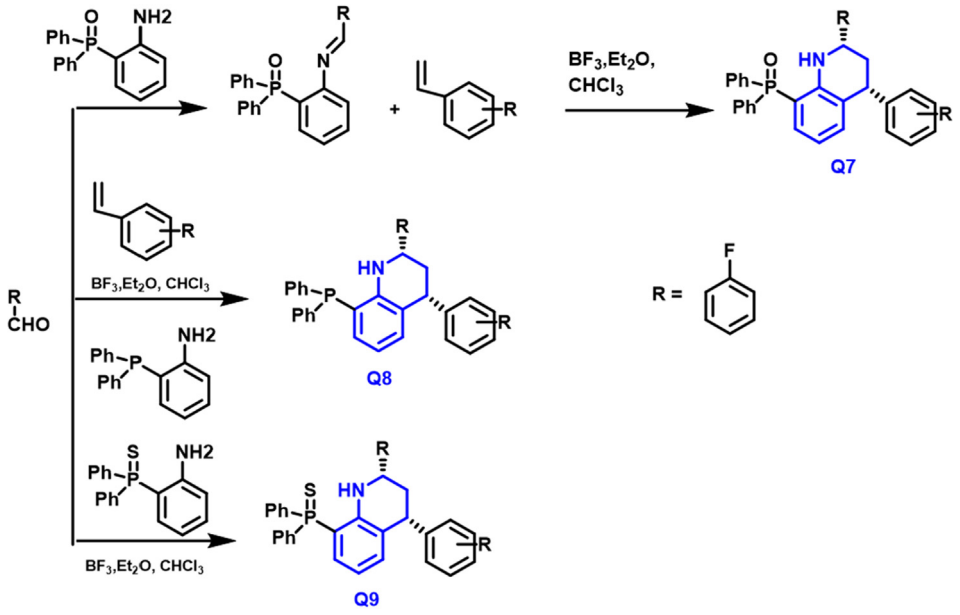
Florian Schmitt et al., (Schmitt, Schobert and Biersack, 2019) developed a series of pyrano-based quinoline compounds from 8-hydroxyquinoline and aryl aldehyde in the presence of piperidine and ethanol as a solvent under reflux conditions for 30 min reaction (Scheme 12). m-nitro and m-halophenyl-based compounds were tested against the six human tumor cells for anticancer activity. The compounds were extremely active, having an $IC_{50}$ in the nanomolar range. The **Q-22** to **Q-24** compounds showed promise in inhibiting tumor cell development while not



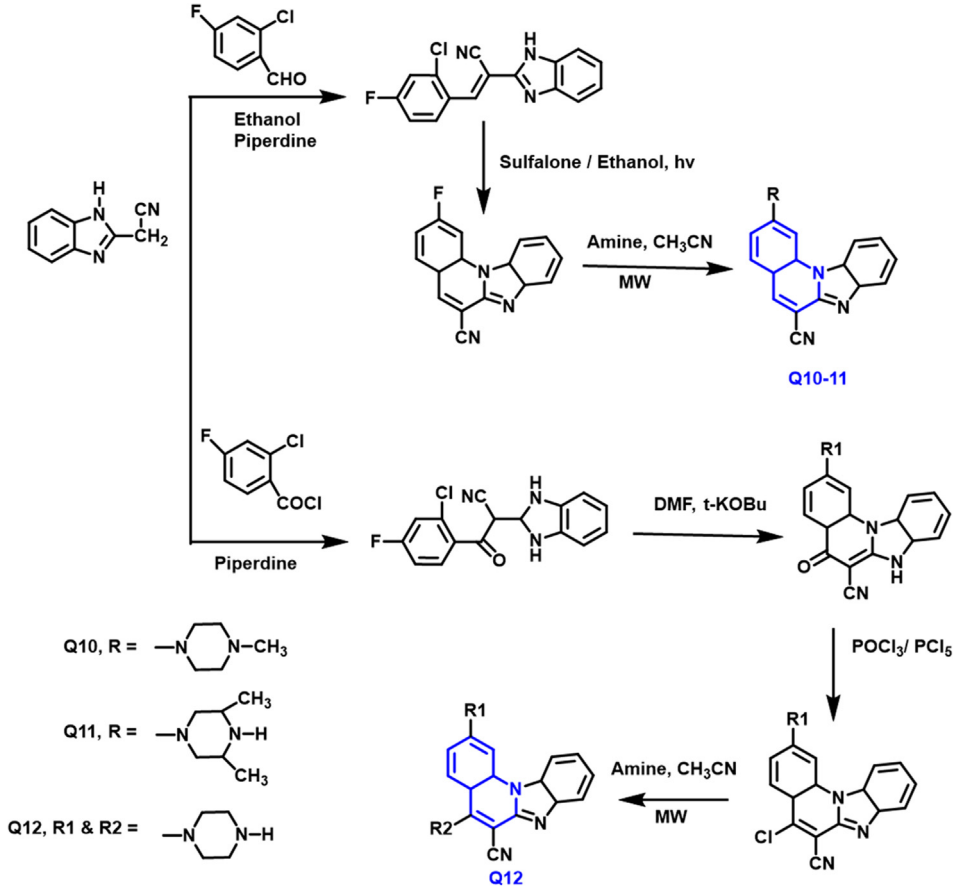

**Scheme 2** Synthetic route of the quinoline derivatives.




**Scheme 3** Synthesis of the quinoline derivatives based on thiosemicarbazones.



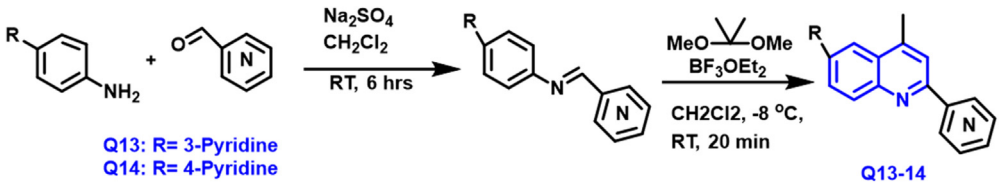

**Scheme 4** Synthetic pathway of quinoline derivatives based on phosophorus.



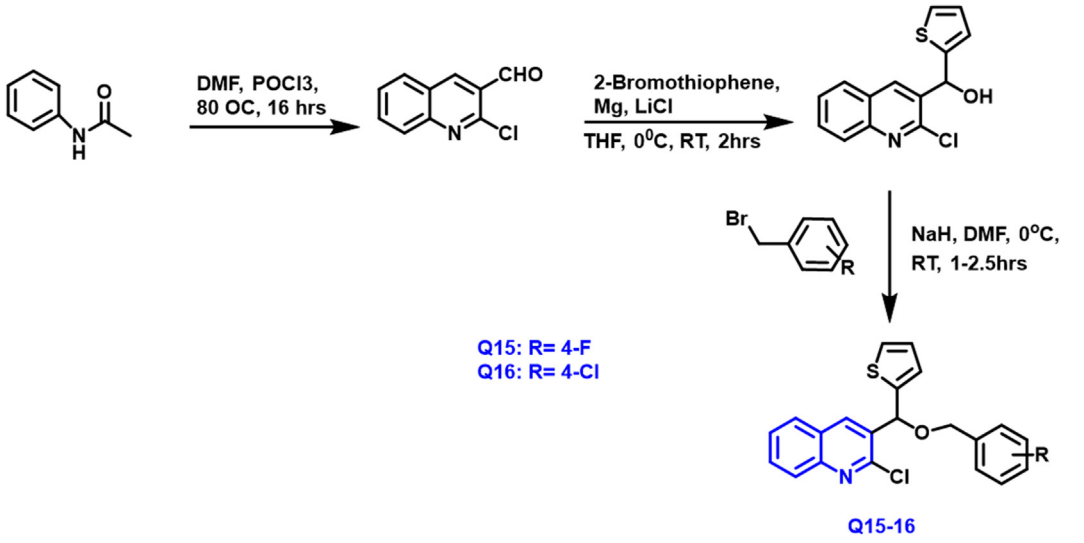

**Scheme 5** Synthesis of 2-amino and 2,5 diamino substituted quinoline derivatives.

affecting non-malignant fibroblasts. These compounds have a vascular-disrupting property that was confirmed *in ovo* studies, and also boosts the reactive oxygen species (ROS) in tumor cells.

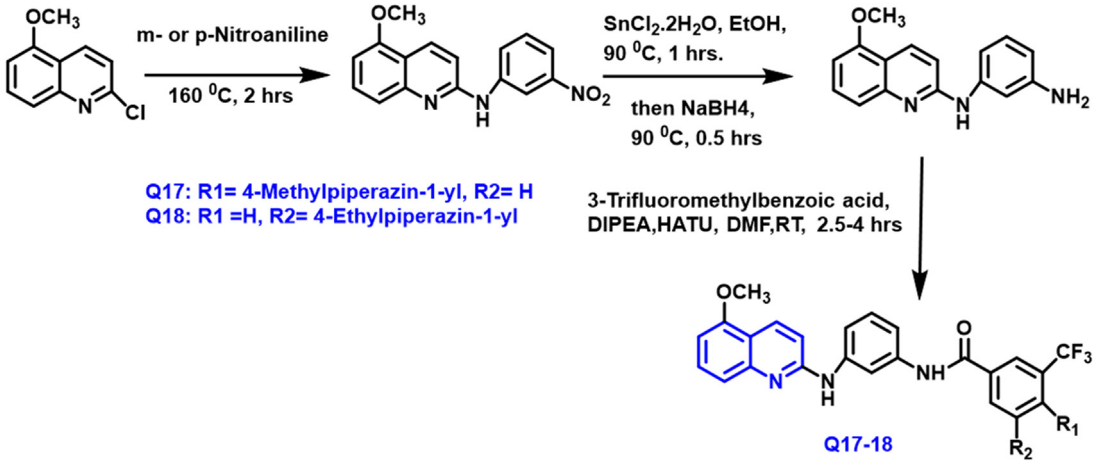
Salimeh Mirzaei et al., (Mirzaei et al., 2020) reported that anticancer drugs and tubulin polymerization inhibitors, a novel class of styrylquinolines were developed and produced (Scheme 13). 4 human tumor cells cultures were investigated



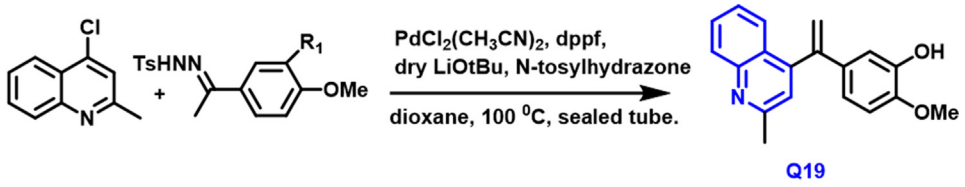

**Scheme 6** Synthesis of quinoline compound based on pyridine moiety.




**Scheme 7** Synthesis of quinoline compound based on thiophene group.

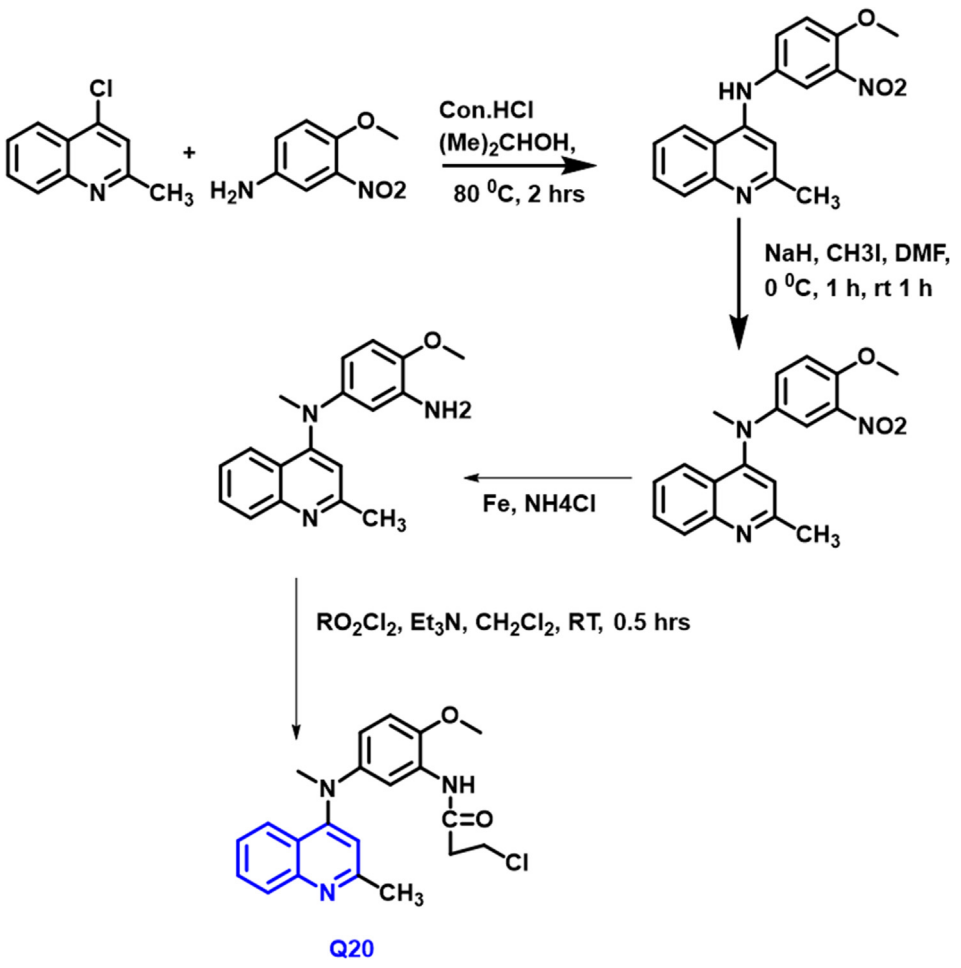



**Scheme 8** Synthesis of quinoline compound based on arylamide group.

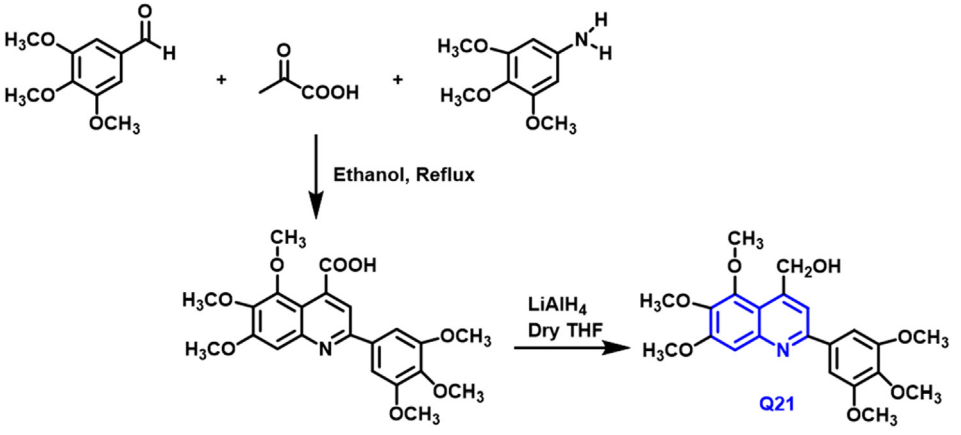



**Scheme 9** Synthesis of quinoline compound as an anticancer agent.

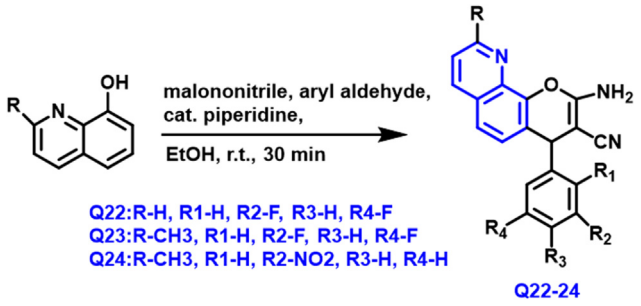
*in vitro* with the synthesized quinolines. That cell lines are ovarian carcinoma, cisplatin-resistant human ovarian carcinoma, breast, and umbilical vein endothelical cells. In general, compounds containing *N*-trimethoxy phenyl demonstrated greater cytotoxic action towards the 4 tumor cell cultures, with Half-maximal inhibitory values ranging from 0.38 to 5.01 $\mu m$ the forty-eight freshly synthesized quinolines. The cytotoxic activity of **Q-25** and Q-**26** as significantly higher than that of the other compounds and comparable to that of the reference drug like combrestatin (0.011 $\mu m$). Moreover, molecular dock-




**Scheme 10** Synthesis of quinoline compound as a novel potent tubulin depolymerization agent.




**Scheme 11** Synthesis of quinoline compound based on flavones group.




**Scheme 12** Synthesis of quinoline compound based on pyrano group.

ing investigations of two compounds into tubulin's colchicine-binding region revealed the compounds' probable interactions with tubulin.

Yilin Fang et al., (Fang et al., 2021) reported that possible anticancer drugs, and sequences of new 2-quinolone compounds including 1,3-Thiazol-2-amine were developed and produced (Scheme 14**).** Using the MTT assay, the synthesized substances were tested for *in vitro* cytotoxicity towards the cervical, hypotriploid, urinary bladder, and ovarian tumor cell cultures. In these, the **Q-27** compound displayed the most powerful effect on the tumor cell lines tested, with the half-maximal inhibitory concentration varying from 0.0044 to 0.0087 M. This compound inhibited the polymer of tubulin *in vitro*, according to the consequence of the polymer of tubulin assay. Meanwhile, molecular docking research demonstrated that the compound may bind to tubulin's colchicine site and create H-bonds with critical amino acids in the active center. This compound is a prospective candidate for developing effective microtubule inhibitors for tumor treatment.

Wenlong Li et al., (Li et al., 2019) reported that a new class of quinoline-indole compounds has been developed and produced (Scheme 15**).** **Q-28** and **Q29** compounds are the most effective for 5 tumor cell lines, with $IC_{50}$ values ranging from 2 to 11 nM. **Q-28** compound hindered the microtubule by attaching to the colcrys region. It had the strongest antitumor efficacy and anti-vascular property *in vitro*. Furthermore, those compounds dramatically reduced tumor development in liver xenograft mice design and absence of toxic effects, it indicating **Q-28 and Q29** compounds are promising anticancer medicines for cancer treatment.

### *2.1.3. Tyrosine kinase*

PTKs are tyrosine kinase proteins that play a role in cell development, differentiation, and death, as well as a variety of physiological and biochemical activities (Wang and Cole, 2014) PTK expression abnormalities, may influence 'carcinogenesis, tumor invasion and secondary tumor, tumor neovascularization, and tumor treatment resistance'. (Drake, Lee and Witte, 2014)(Knösel et al., 2014) As a result, it has emerged as a popular focus for anti-tumor medication development. (Jiao et al., 2018) Receptors and non-receptor are two types of tyrosine kinases (Gotink and Verheul, 2010).

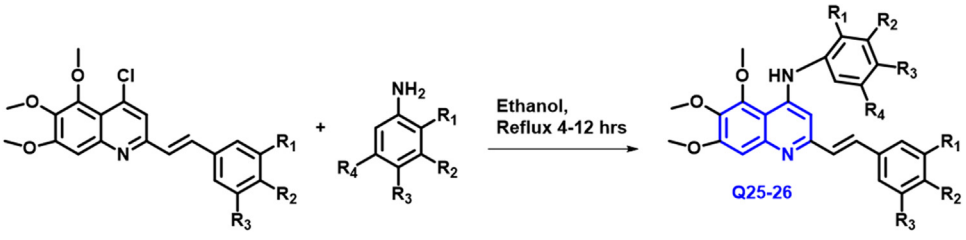
Yuting Zhou and coworkers (Zhou et al., 2021) reported the production of 1-benzopyridine derivatives based on thiazolidinone with biological activity (Scheme 16). Based on the findings of the biological assessment and docking investigation, a structure–activity connection analysis was carried out. A most effective carboxamide-based molecule has the potential to suppress the activity of recepteur d'origine natais, tyrosine-protein kinase met, and proto-oncogene tyrosine-protein kinase among other proteins. **Q30** compound demonstrated good antitumor activity on human colorectal adenocarcinoma cells. Flow cytometry results showed that the compound may cause significant cell growth arrest in the growth 2 phase stage in human colorectal adenocarcinoma cells. Furthermore, there was neither antiproliferative nor cytotoxic effect. FHC was found in human normal colorectal mucosa epithelial cells (NCM460). The compound had toxicity to normal cells of 10.0$\mu$ g/mL, indicating that it was considerably less than Regorafenib. This set of molecules may act as an effective starting point for the creation of high powerful kinase inhibitors as antitumor medicines in the future, with further structural modification to increase inhibitory action.

Ashraf Kareem El-Damasy et al (El-Damasy et al., 2016) have noted a sequence of novel '2-anilinoquinolines' with a '3-(morpholino or 4-methylpiperazin-1-yl)propoxy' group at the Carbon-5 of the 1-benzopyridine have been developed and prepared (Scheme 17).

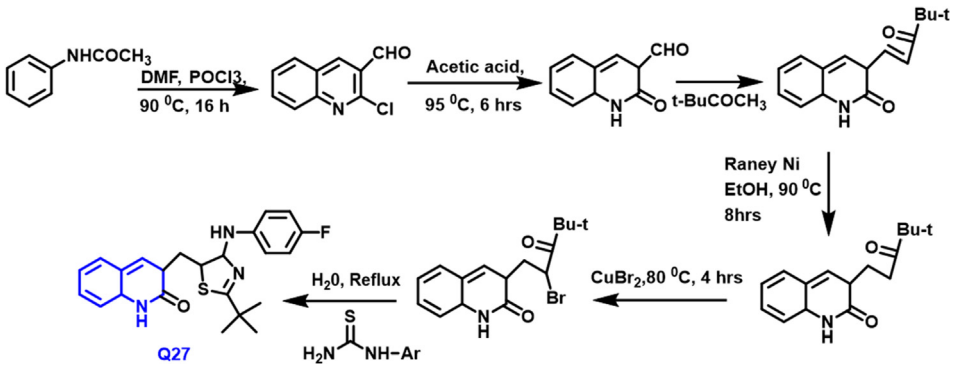
The majority of the substances examined had an antiproliferative activity that was both strong and wide in the spectrum. **Q-31** was evaluated towards a board of 47 oncogenic kinases and shown to have a specific prohibitor impact (96 percent inhibition) on TrkA kinase. Furthermore, against the HFF-1 normal cell type, the most powerful chemicals had modest cytotoxic effects. At the NCI, their antitumor effects have been assessed towards sixty tumor cell lines. These compounds have more potential than gefitinib drugs during the several tested cell lines.

### *2.1.4. Epidermal growth factor receptor tyrosine kinase (EGFRTK)*

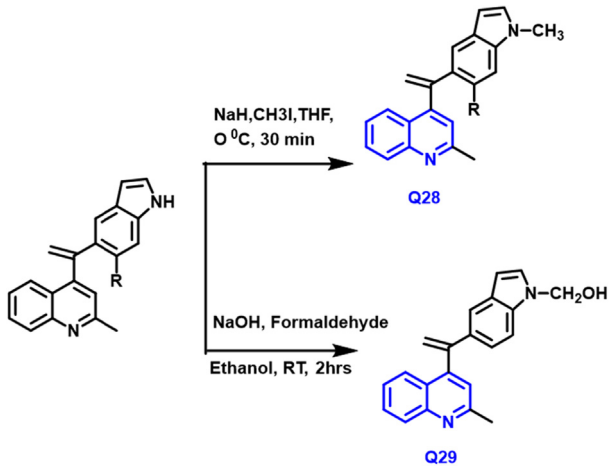
The epidermal growth factor receptor is a member of the tyrosine kinase receptor family. Cell proliferative signaling system in cancer cells representing in Fig. 4.



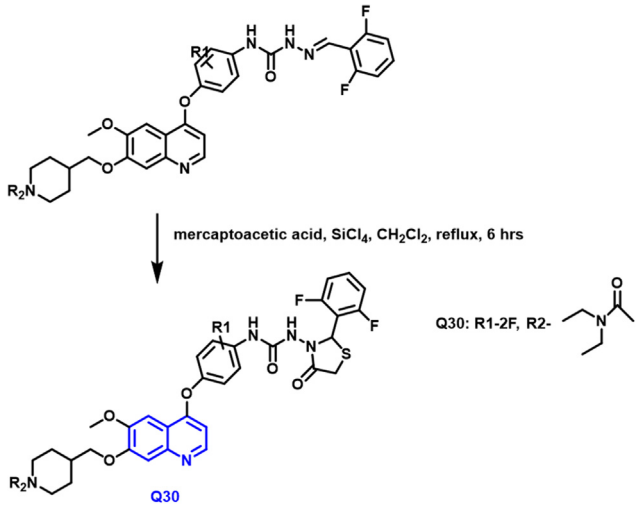

**Scheme 13** Synthetic route of strylquinoline derivatives.




**Scheme 14** Synthesis of quinoline derivative based on arylaminothiazole moiety.




**Scheme 15** Synthesis of quinoline derivative based on indole group.




**Scheme 16** Synthetic route of quinoline derivatives.

When ligands like EGF connect to the epidermal growth factor receptor (EGFR), the receptor changes shape, releasing the dimerization domain further permitting homodimerization with a second EGFR or different dimerization with another group of the EGFR family. Now EGFR has activated the results of its autophosphorylation to the key tyrosine groups. These groups trigger important downstream signaling cascades, such as the PI3K/AKT pathways. These tracks act in a coordinated manner to promote cell survival. These kinds of receptors are broadly spread in cell membranes and they often influence a variety of functions like cell growth, cell death, and cell multiplication. This protein plays a significant role in the growth and development of many different forms of solid cancers, breast, lung, colorectal, neck, and head tumors types (Guardiola et al., 2019).

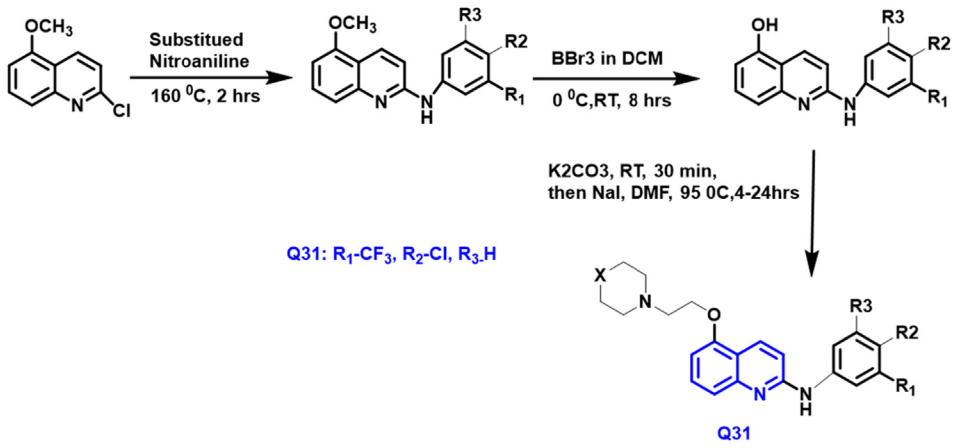
Diaa A. Ibrahim and colleagues (Ibrahim et al., 2015) have developed a new class of 4-anilinoquinoline-3-carboxamide derivatives from 6-acetyl quinoline-3-carboxamide reacts with 4-substituted benzaldehyde in the presence of sodium hydroxide under reflux condition at 90 $^0$C. (Scheme 18). All the derivatives were tested against breast cancer but only the **Q32** compound showed substantial activity toward breast cancer. The early results showed that carboxamide-based compound showed a powerful inhibitory effect in cancer development and highly powerful property on the EGFR-TK enzyme having sixty-seven percent growth inhibition comparison with ATP, which might be a promising antitumor drug.

The methoxy-based quinoline compound was the layout and developed by Xin-yang Li (Scheme 19). **Q33** compound had potent antiproliferative activity toward lung and breast cancer. This drug can reduce breast tumor growth and angiogenesis by acting as a dual target inhibitor of EGFR and HER-2. (Li et al., 2022).

Karnik and coworkers designed and developed the quinoline-derived compounds from acetoacetanilide and polyphosphoric acid (Karnik, Sarkate, Tiwari, Azad and Wakte, 2021). (6-chloro-2-(isoindolin-2-yl)-4-methylquinoline) the compound had potent inhibitory activity towards the mutant EGFR kinase ($IC_{50}$ = 0.91$\mu$ M).

Karnikand coworkers have developed a good antiproliferative activity towards lung cancer (Scheme 20) (Karnik, Sarkate, Tiwari, Azad and Wakte, 2021) When acetoacetanilide reacts with poly phosphoric acid to form hydroxy substituted quinoline compound; it was chlorinated using phosphorus oxychloride to form chloro substituted quinoline compound; it was further reacted with isoindoline in the presence of cuI to form quinoline derivative **(Q34)** as a potent anticancer property against lung cancer.

The Gould–Jacobs reaction was used to make a novel class of '4-(4-substituted-anilino)quinoline' derivatives from amine




**Scheme 17** Synthetic pathway of quinoline derivatives.

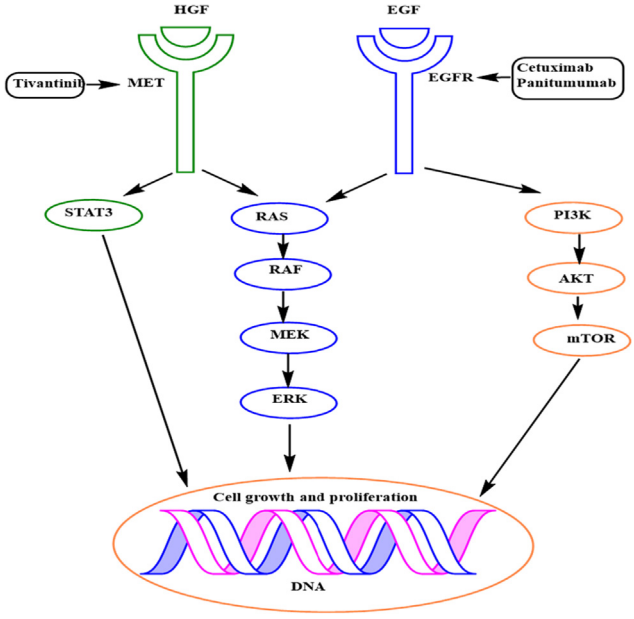


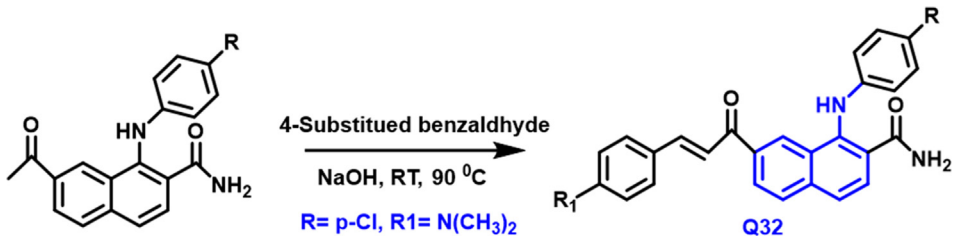

**Fig. 4** Targeted EGFR mechanism against cancer.

derivatives has been developed by Khaled R and collaborators (Scheme 21) (Abdellatif et al., 2017) The cytotoxic activity of all produced compounds was tested towards breast and lung cancer. The chemicals examined exhibited a wide variety of activity for MCF7 and A549. The **Q-35** compound ($IC_{50}$ = 3.42 and 5.97 $\mu m$) was shown to be highly potent towards both breast and lung tumor cell lines. Furthermore, molecular docking investigations were undertaken, with the results correlating with the *in vitro* cytotoxic data.

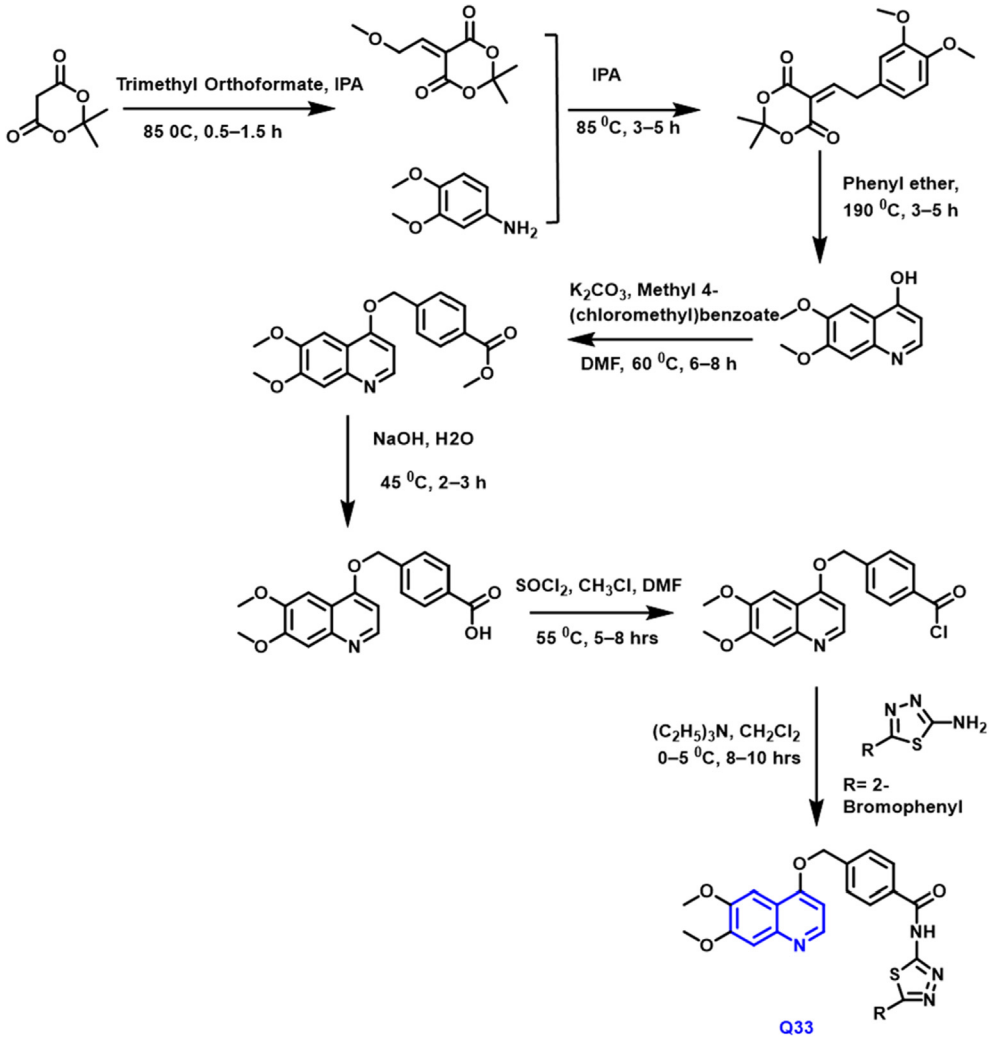
Girish Bolakatti and coworkers (Bolakatti et al., 2021) have developed a unique sequence of the quinoline-based compound (Scheme 22). All the derivatives were tested against the MCF7 and WRL-68 tumor cells for cytotoxicity studies; from these results, **Q37** had a more potent antitumor action than other derivatives and the **Q36** compound had a significant binding nature. Docking experiments were performed to better understand the binding mechanism of the title molecules at the target enzyme's active center. The new quinolone-based hybrid is a potential outcome that might be used to build potential anticancer/antimicrobial medicines.

Aliaa et al.(Mohassab et al., 2021) had reported the synthesis of triazole-based quinoline derivatives from the istain and acetophenone taking as a starting material under reflux conditions (Scheme 23). The synthesized compounds have an average to better anticancer property on various cell lines. **Q38-Q42** compounds exhibit a potent anticancer property towards lung, breast, and colon cancer. These compounds had a significant site center of EGFR and BRAF kinase was confirmed by docking studies; **Q38, Q41,** and **Q42** compounds have a significant binding site; this pattern is similar to erlotinib drug.

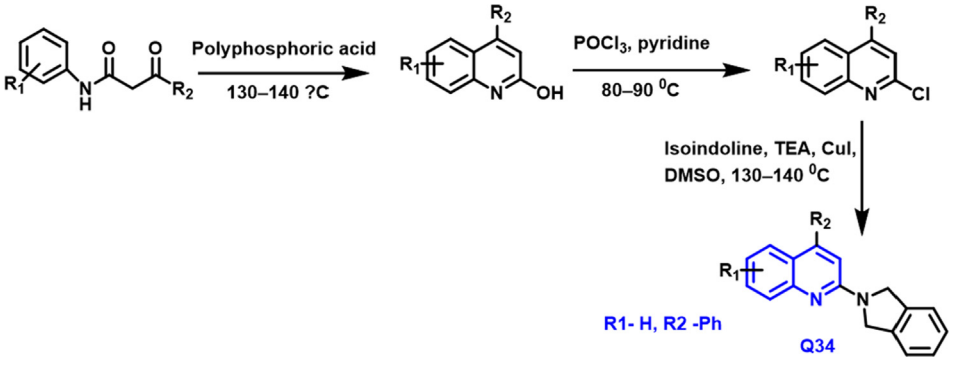
A novel family of 'pyrazolo[4,3-c] and pyrano[3,2-c] quinoline' derivatives have been produced by Thangaraj Arasakumar and coworkers.(Arasakumar et al., 2017) Microwave conditions were used to develop and synthesize derivatives in medium to outstanding yields (Scheme 24). A




**Scheme 18** Synthesis of quinoline derivatives as a anticancer agent.




**Scheme 19** Synthetic route of quinoline compound.




**Scheme 20** Synthetic pathway of quinoline compound as anticancer agent.

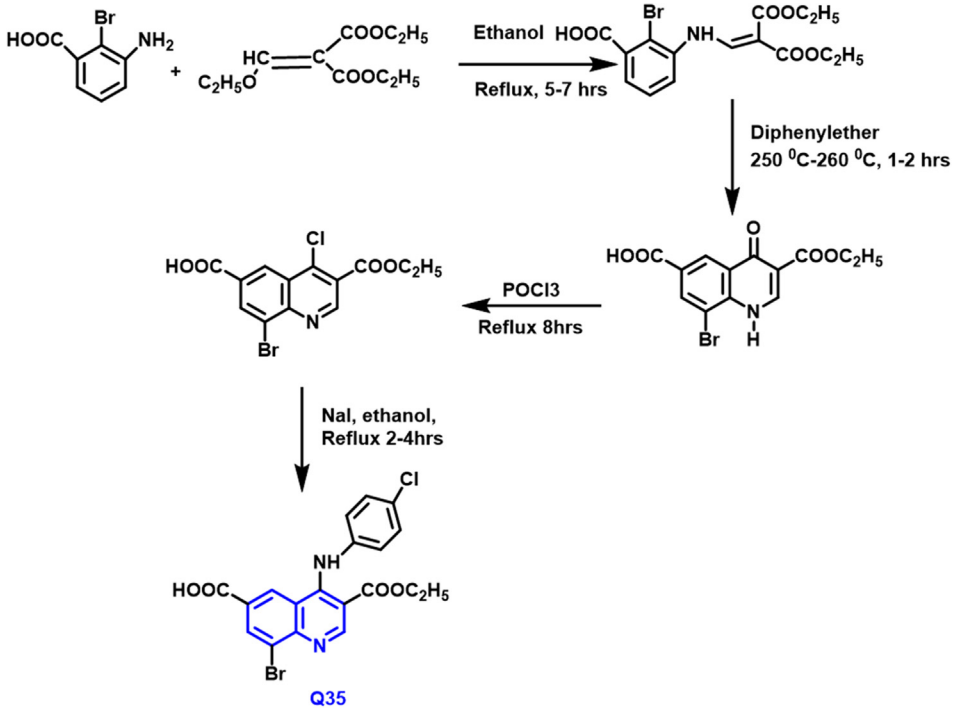
multicomponent one-pot process has been devised to increase the production of pyrano quinoline derivatives. **Q43** compound was tested for cytotoxicity toward breast and lung tumor cell lines. Against these cell growth lines, the preponderance of the drugs had moderate to strong cytotoxic activity. In this experiment, the pyrano[3,2-c] quinoline derivative compound was shown to be very active and also caused apoptosis, which resulted in cell death. The molecular interactions of the EGFR inhibitor were determined using molecular docking experiments.

Rasha M. Aly et al (Aly et al., 2017) designed a 3,4,6-trisubstituted quinoline compound from 4-(N, *N*-dimethylamino)benzaldehyde with 5-(3- or 4-substituted phenyl) furan-2-carbaldehydes, malononitrile and benzyl chloride

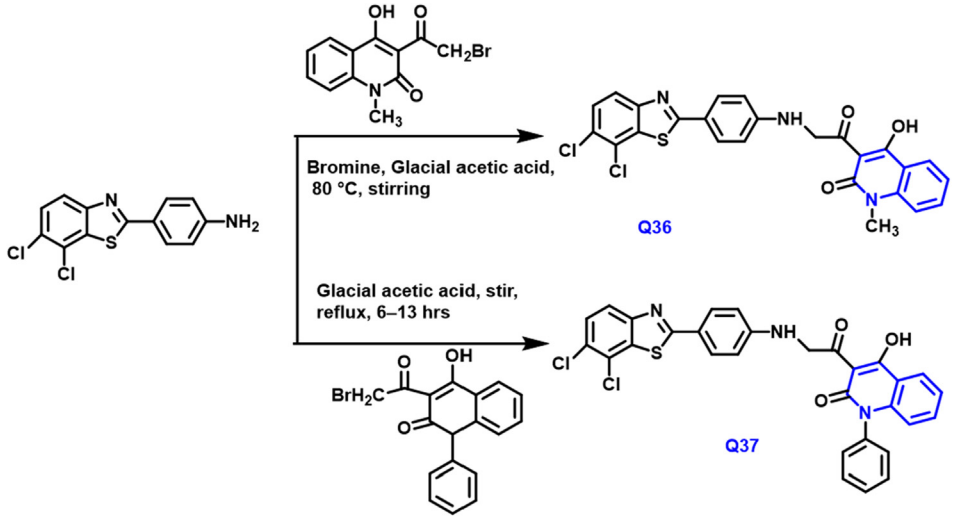
under reflux and stirring condition. Scheme 25 **Q-44–49** have a good yield and showed a potent anticancer agent for breast cancer. Especially, Q-44 has a furan derivative showing $IC_{50}$ 2.61 $\mu m$, Q-46 have a thiophene derivative showing $IC_{50}$ 0.49 $\mu m$ and Q-49 have a benzyloxy derivative showing $IC_{50}$ 1.73 $\mu m$ in EGFR. Its exihibted as consequential cytotoxicity towards breast cancer due to the presence of quinoline-3-carboxamides.

The preparation of benzo-based isoindazole, 1-benzopyridine, and 1,3-diazanapthalene derivatives (Scheme 26) has been described by Esraa A et al., (Abdelsalam et al., 2019) The antitumor properties of all the produced derivatives were tested towards tumor cell-growth lines like breast, HepG2, HCT116, and Caco-2. **Q50** and **Q51** compounds had potent antiproliferative properties against breast cancer ($IC_{50}$ = 7.70 ± 0.39 and7.21 ± 0.43 $\mu m$). The docking investigated the binding mechanism and potential connection between both the produced chemicals and the EGFR kinase domain's ATP binding site.

Kshipra S and colleagues (Karnik, Sarkate, Tiwari, Azad, Burra, et al., 2021) have reported the synthesis of new substituted quinoline compounds from substituted chloride compounds that react with phenyl benzoate derivate in the presence of sodium methoxide and acetonitrile as a solvent




**Scheme 21** Synthetic route of quinoline compound.




**Scheme 22** Synthesis of quinoline compound based on benzo[*d*]thiazoyl group.

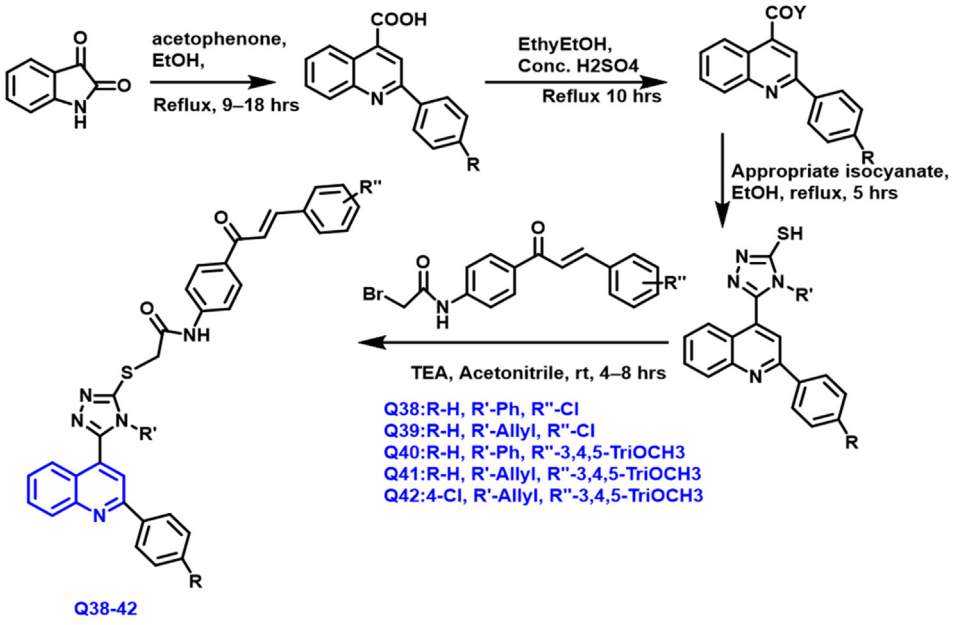
under room temperature (Scheme 27); this reaction is Suzuki coupling reaction for C—C bond formation. **Q52** compound had a significant antiproliferative property; and also acts as inhibitory property against the EGFR kinases.

The novel sequence of pyrrolo- based quinoline compounds was described by Malose J. et al., (Mphahlele et al., 2020) (Scheme 28). Their structure was studied using IR, nuclear magnetic resonance (proton and carbon), and MS. In the solid-state, XRD single crystal was employed to identify their framework. The samples were screened *in vitro* for cytotoxicity toward breast cancer cell lines and human embryonic kidneys. These chemicals can cause cell death in the breast cell line, according to a preliminary apoptotic experiment utilizing a DNA laddering assay. **Q-53** and **Q-54** compounds had a significant inhibitory action on the VEGFR-2 and cyclooxygenase-2. The inhibitory nature of COX-2 controls the growth of breast cancer cells in both animals and human beings.

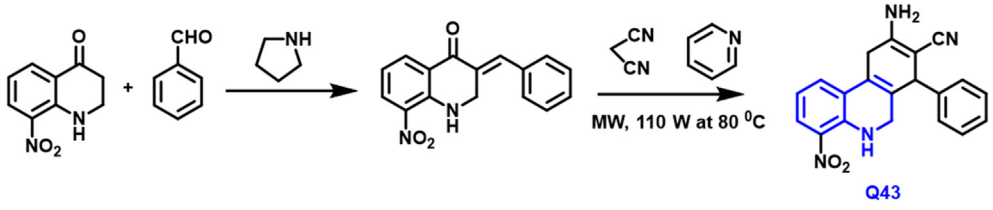
### *2.1.5. c-met kinase*

The HGFR or (c-Met) was identified in the 1980 s. The tyrosine-protein kinase met belongs to the receptor tyrosine kinases.(Qi et al., 2013)(Liu et al., 2012) In the extracellular domain, the hepatocyte growth factor or c-MET kinase routes activate numerous complicated signaling pathways that play a crucial role.(Clavijo-Cornejo et al., 2013) This kind of kinase is used to detect liver, breast, pancreatic, ovarian, gastric, and prostate cancers; the c-Met signal provides for the growth, and cell division from its starting site and colonization. An appealing target for cancer treatment is c-Met. (Papa et al., 2017).

Yuting Zhou and colleagues (Zhou et al., 2020) discovered and produced a new family of quinoline analogs containing thiazolidinones was developed and their biological activities were assessed (Scheme 29). Supported by the findings of the biological assessment and docking investigation; a structure–activity relationship analysis was conducted. The powerful **Q-55** molecule has been found as a multikinase inhibitor. The compound showed good antitumor, cyto-toxicity, and induction of HT-29 cell apoptosis. Furthermore, the **Q-55** compound caused a minor cell cycle arrest in HT29 cells during the G2/M stage. As per the results of cancer progression and cell growth studies, other factors that promote cell death could be candidates for the molecule. Compound cell selectivity revealed that it was inactive against NCM356 cells at doses as low as 10.0$\mu$ g/mL. The findings of cell selectivity showed that the compound had considerably lower toxicity to normal



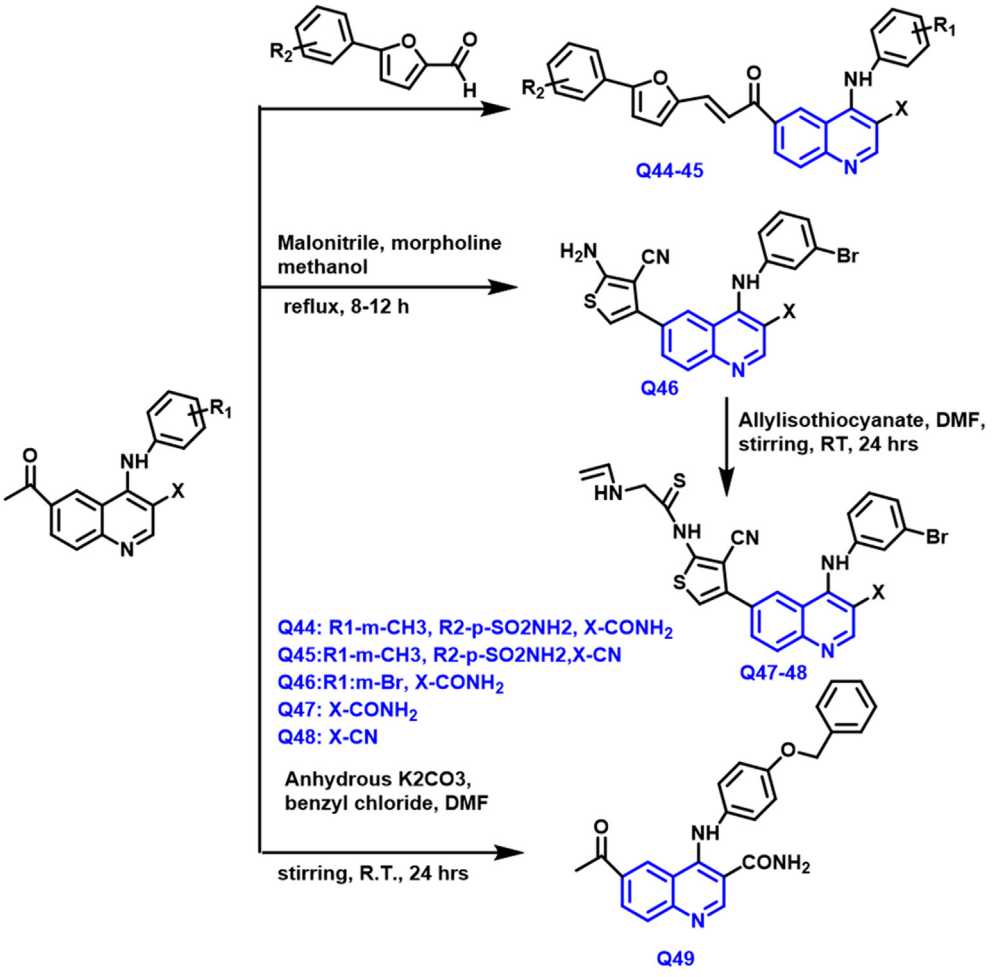

**Scheme 23** Synthesis of quinoline compound based on 1,2,4-triazole group.



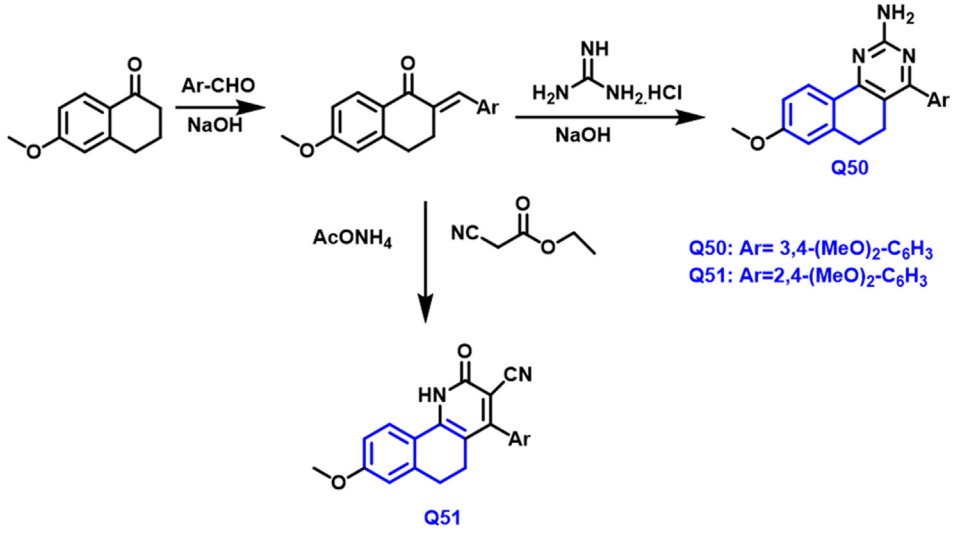

**Scheme 24** Synthetic pathway of quinoline compound.

cells than Regorafenib. The findings encourage future structural modifications to the compound to increase its inhibitory action, resulting in more powerful kinase inhibitors as anticancer medicines.

The biological activities of a series of '6,7-disubstituted-4-phenoxyquinoline' compounds were developed, produced, and assessed by Qidong Tang et al., (Tang et al., 2018) (Scheme 30) Antitumor efficacy was evaluated in tumor cell-



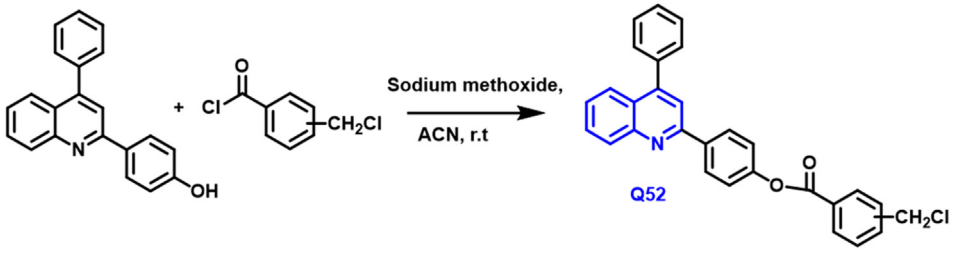

**Scheme 25** Synthetic pathway of quinoline compound as an anticancer agent.



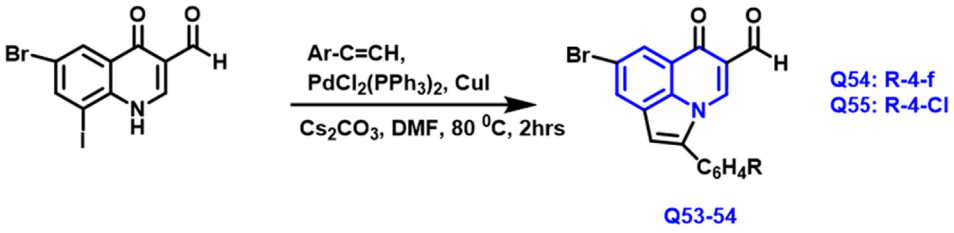

**Scheme 26** Synthesis of novel quinoline compounds based on quinazoline and indazole groups.

line like breast, lung, and liver. Quinoline-based derivatives were tested for c-Met kinase activity. A very effective molecule **Q-56** ($IC_{50}$ c-Met 14.36$\mu$ m) showed outstanding action towards 3-tumor cell lines. This compound was further tested for its ability to inhibit several kinases. Mono-EWG (Electron withdrawing groups) at the 4-position of moiety C was found to be a crucial element in enhancing anticancer efficacy in structure–activity relationship studies.

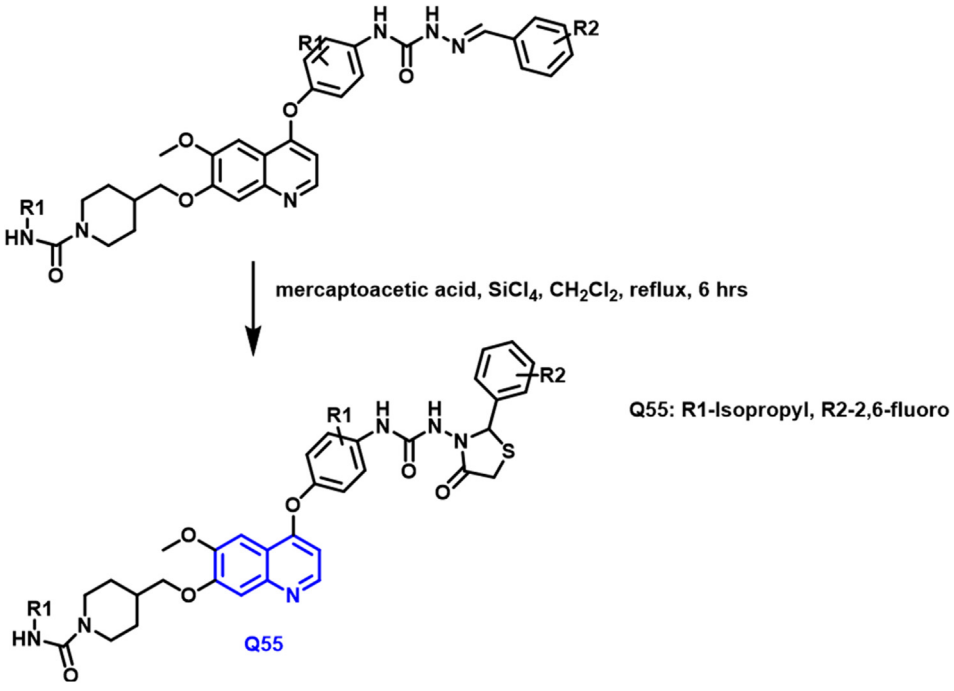
Palak Parikh et al., (Parikh, Ghate and Vyas, 2015) reported that Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA), a varied collection of seventy-four c-MET kinase inhibitors made up of phenoxy-based quinoline derivatives were employed (3D QSAR). These protein kinases are a well-known candidate for the treatment of cancer therapy. The activity of the compound is determined by the presence of H-bonding and hydrophobic groups; CoMSIA analysis gives this kind of information and on another side, CoMFA analysis provides information about the steric and electrostatic nature of the group. The CoMSIA design appeared to have a stronger performance than the CoMFA design.




**Scheme 27** Synthetic pathway of novel quinoline compound.




**Scheme 28** Synthesis of novel quinoline compounds based on pyrrole moiety.




**Scheme 29** Synthesis of quinoline derivative based on thiazolidinone group.

The discovery of a sequence of '6,7-disubstituted-4-phenox yquinoline' derivatives with antitumor properties towards 5 tumor cell lines such as H460, HT-29, MKN-45, A549, and U87MG was reported by Qidong Tang and collaborators (Tang et al., 2016) (Scheme 31). **Q57** phenoxy-based quinoline derivative demonstrated more antitumor properties against lung tumors due to the presence of amine and EWG at the 4-site of the phenyl ring was confirmed by the SAR study. **Q57** was 6.1, 2.4, and 2.1 times more active than foretinib in its ability to kill lung, colon, and malignant cell lines, respectively.

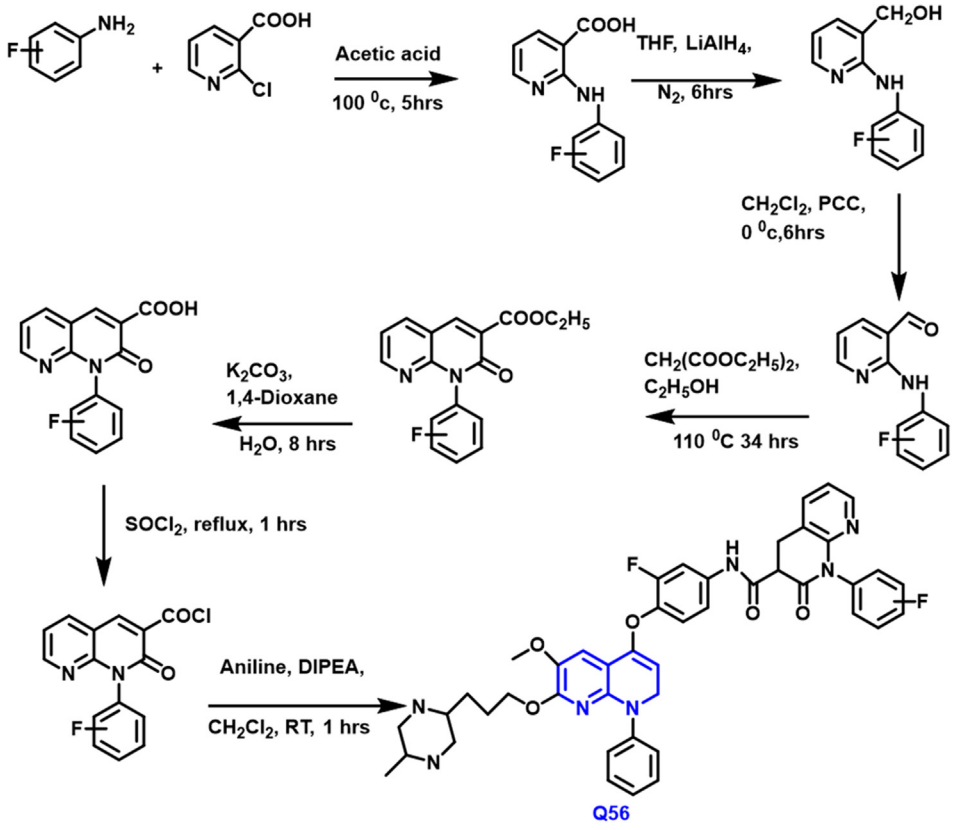
Alanazi and colleagues (Alanazi et al., 2021) designed and prepared a novel sequence of bis([1,2,4]triazolo)[4,3-a:3′,4′-c] quinoxaline derivatives as a good anticancer agent for the human hepatoma and breast cancer cells. 4-methoxy benzene substituted quinoxaline compound have a more potent antiproliferative activity than other derivatives; $IC_{50}$ is 3.2 *μm* in inhibitory activity and they have similar binding pattern like sorafenib was confirmed by in silico studies.

Baohui Qi and coworkers (Qi et al., 2018) reported the biological activities of twenty-nine new molecules containing 'N1 -(2-aryl-1, 3-thiazolidin-4-one)–N3 -aryl ureas' were developed, produced, and assessed (Scheme 32). This set of chemicals SAR and binding processes were investigated simultaneously. **Q-58** compound was discovered to be highly effective against a variety of TKIs. IncuCyte live-cell imaging showed this compound antiproliferative and cytotoxic activity *in vitro* against the A549 cancer cell line.

### *2.1.6. P-glycoprotein inhibitors*

Permeability glycoprotein is abbreviated as P-gp or Pgp. It is a 1280 protein encoded by the MDR1 gene. It's one of the ABC transporter families with the most research done on it. Pgp is play an important role in the body and distribution of xenobiotics and toxic compounds. It prevents the drug from absorbed, retained and permeabilized from the cells. Overexpression of P-gp, a critical protein controlling MDR in many types of tumor cells. As a result, decreasing P-gp activity and lowering anti-cancer medication efflux have become key strategies for reversing MDR. (Endicott and Ling, 1989) (Binkhathlan and Lavasanifar, 2013)(Nobili et al., 2012).

Mutta Kairuki et al., (Kairuki et al., 2019) developed and synthesized two sequences of isoquinoline component Pgp inhibitors based on tetrahydro and triazole (Scheme 33). MDR is a term that refers to a cancer cell's cross-resistance to one drug, as well as other medicines with distinct mechanisms and structures. It is one of the most significant challenges in clinical chemotherapy. P-glycoprotein (P-gp) overexpression has been investigated extensively as a cause of MDR. As a result, blocking P-gp has emerged as a key approach for reversing MDR. **Q-59** compound showed impressive MDR reversal activity, and a preliminary mecha-




**Scheme 30** Synthesis of novel quinoline compound.

nistic investigation was conducted. All of the findings suggested that the compound might be a viable P-gp-mediated MDR reversal option.

### 2.1.7. RAF kinase

Rapidly Accelerated Fibrosarcoma is known as RAF; it plays an important role in the development of organism, control of the cell cycle, the multiplication and differentiation of cells, lifespan of cell and mortality of cells as well as many other cellular and physiologicl processes.

Mohammed I. El-Gamal et al., (El-Gamal et al., 2017) have noted that a new family of diarylurea derivatives with quinoline nuclei has been developed, synthesized, and biological screening (Scheme 34).

The National Cancer Institute chose nine target compounds for antiproliferative *in vitro* testing towards a board of fifty-eight tumor cell-lines from nine various tumors. The most promising counterparts were **Q-60** and **Q-61**. Two substances were shown to have high efficacy and board anticancer action towards the various tumor examined.

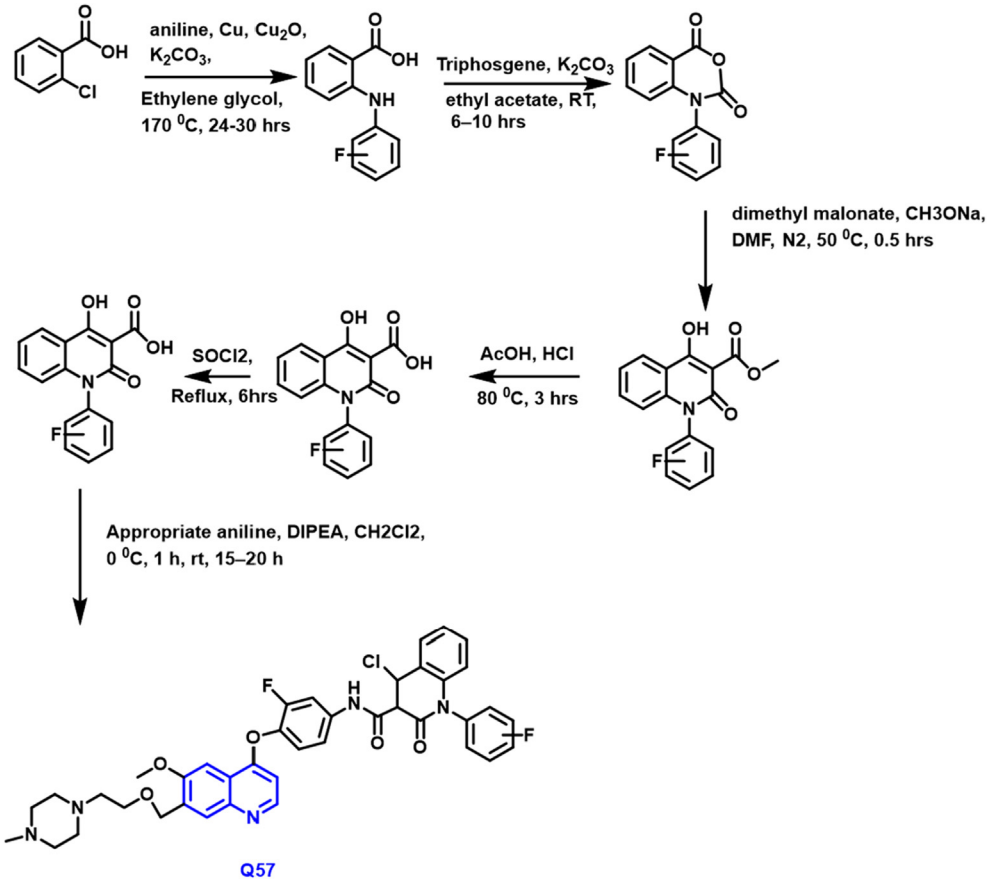
### 2.1.8. PI3K/mTOR dual inhibitor

Ruoyu He et al., (He et al., 2021) reported that the amido-based 1-benzopyridine compounds were designed and synthesized as potent anticancer agents (Scheme 35).

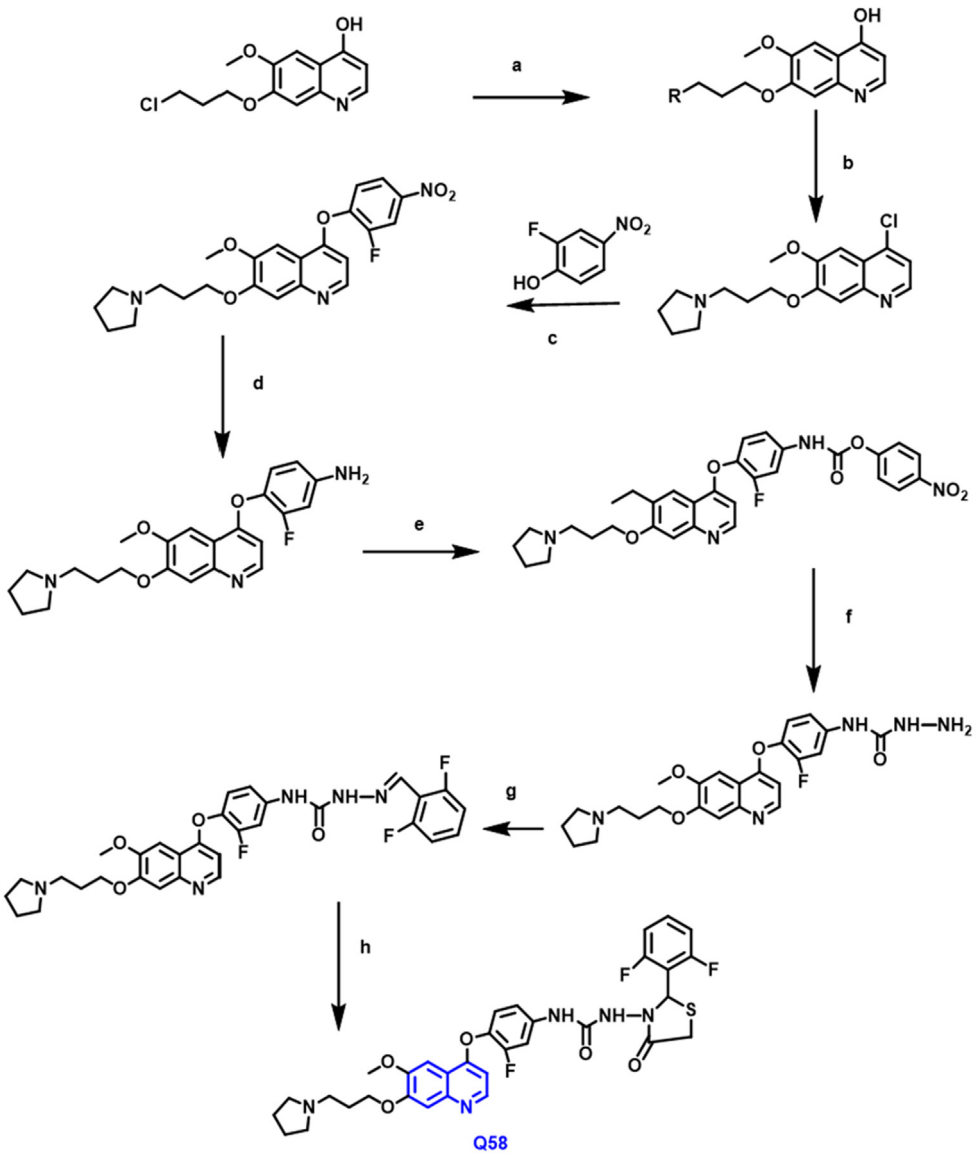
**Q62** compound showed potent anti-proliferative property due to the presence of 4-acrylamido functional group; it create some steric hindrance to the molecules. As a consequence, the **Q-62** compound demonstrated substantial anti-proliferative and enzymatic activity, as well as inhibiting PI3K/mTOR signaling in a Western Blot experiment *in vitro* at nanomole concentrations. *In vivo*, the compound was shown to have substantially better oral exposure than its beta-position unsubstituted analog. In an Uppsala 87 malignant glioma GBM xenograft design *in vivo,* this compound showed substantial therapeutic effectiveness.

### 2.1.9. Haspin kinase inhibitors

The serine/threonine kinase Haspin (haploid germ cell-specific protein kinase) is associated with histone phosphorylation, notably at Thr3 (H3T3) throughout mitosis (Dai et al., 2005) Haspin is expressed in a variety of cell types, and its activation (or) overexpression causes H3T3 phosphorylation.(Rossetto, Avvakumov and Côté, 2012) Depletion of has pin by RNA interference led to reduced H3T3 phosphorylation, resulting in chromosomal misalignment at metaphase, as reported by Dai et al. As a result, haspin is considered to have a function in chromosomal segregation and tumor development. Because haspin has a bright future as an anticancer target, there are only a few inhibitors known. (Dai et al., 2005).




**Scheme 31** Synthesis of novel quinoline compound as an anticancer agent.




(a) 1-bromo-3-chloropropane, $K_2CO_3$, DMF, rt; (b) R3, $CH_3CN$, reflux; (c)4-fluoronitrobenzene, $Cs_2CO_3$, $CH_3CN$, reflux; (d) ) Fe, conc. HCl, 95% EtOH-$H_2O$, reflux; (e) 4-nitrophenyl carbonochloridate, $CH_2Cl_2$, pyridine, rt ; (f) $NH_2NH_2\$H_2O$, xylene, 70 °C; (g) 2, 6-difluorobenzaldehyde, i-PrOH, HOAc, reflux; (h) $SiCl_4$, mercaptoacetic acid, 50 °C

**Scheme 32** Synthesis of novel quinoline compound as an anticancer agent.

The inhibitors of haspin kinase property can stop cancer cells from multiplying were reported by Clement Opoku-Temeng and coworkers (Opoku-Temeng et al., 2018). One pot synthesis of Doebner or Povarov reaction; Scheme 36 the synthesized compounds were tested against the HCT116 and HeLa and A375 cell lines. **Q63** derivatives had a potent anticancer activity.

### *2.1.10. PDE5 inhibitor*

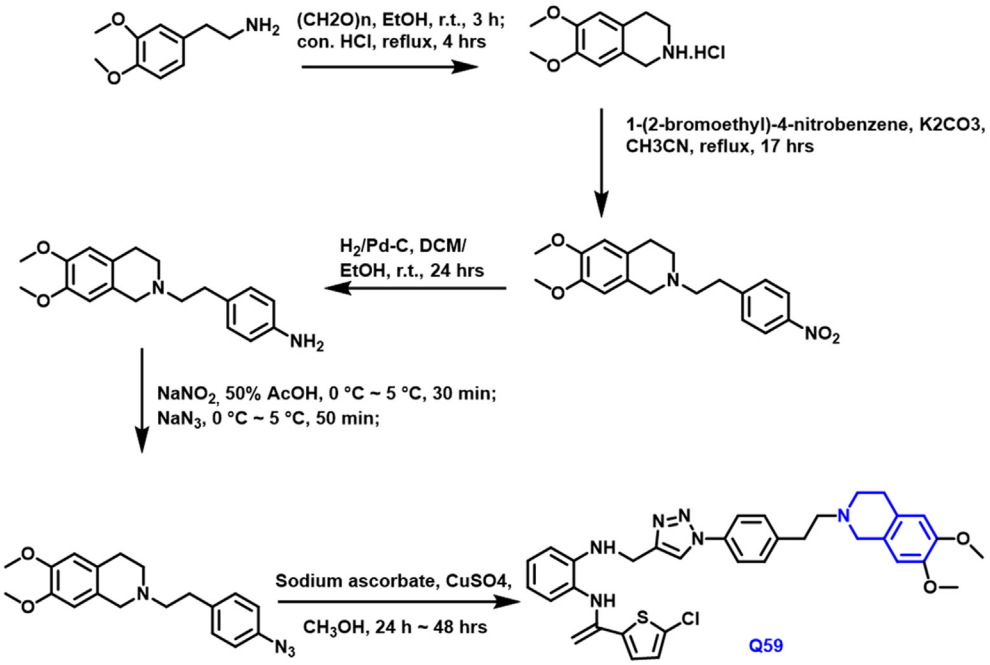
Phosphodiesterase type 5 (PDE5) inhibition appears to be a viable strategy for restoring normal intracellular cyclic guanosine monophosphate (cGMP) signaling. As a result, several downstream compounds are activated, which limit cancer cell proliferation, motility, and invasion. PDE5 is linked to the aetiology and treatment of a wide range of cancers, according to several studies. (Barone et al., 2017) Because of its overexpression in several forms of human carcinomas; Phosphodiesterase type 5 provides a unique and effective approach for inducing cell death and inhibiting cancer cell proliferation.

The synthesis of 18 new innovative pyrazole-based 1-benzopyridine molecules Scheme 37 was reported by Tarek S. Ibrahim and colleagues. (Ibrahim et al., 2020) NCI characterizes them and tests them for cytotoxic properties towards sixty tumor cell lines. The majority of them exhibited effective

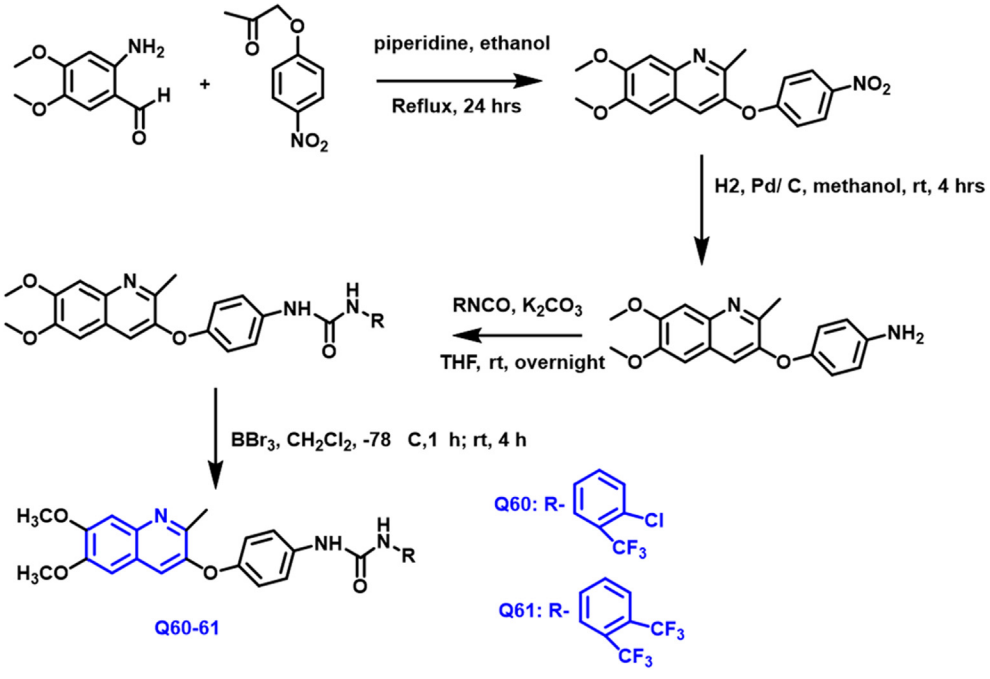
PDE5 inhibition, especially the **Q-64** compound, which was strengthened by a molecular docking analysis, making it a viable option for ED therapy. This compound shows strong PDE5 inhibition as a possible explanation for its robust anticancer activity. Generally, the anticancer and PDE5 inhibitory actions of new hybrids are strongly linked. Furthermore, Vivo and clinical studies on the compound are needed. This might pave the way for a deeper knowledge of these chemical substances and the development of new cancer treatments.

*2.1.11. Pdk1:*

Protein kinases provide a wealth of targets for the creation of chemical assay and therapies, as their abnormal regulations of protein phosphorylation contribute to the growth of a variety of malignancies. As a result, various 3-Phosphoinositide-dependent kinase 1 inhibition methods and pharmacological attempts are published regularly in the hopes of developing a highly effective therapeutic medication. Tamgüney et al., (Tamgüney et al., 2008) found that inhibiting PDK1 has no



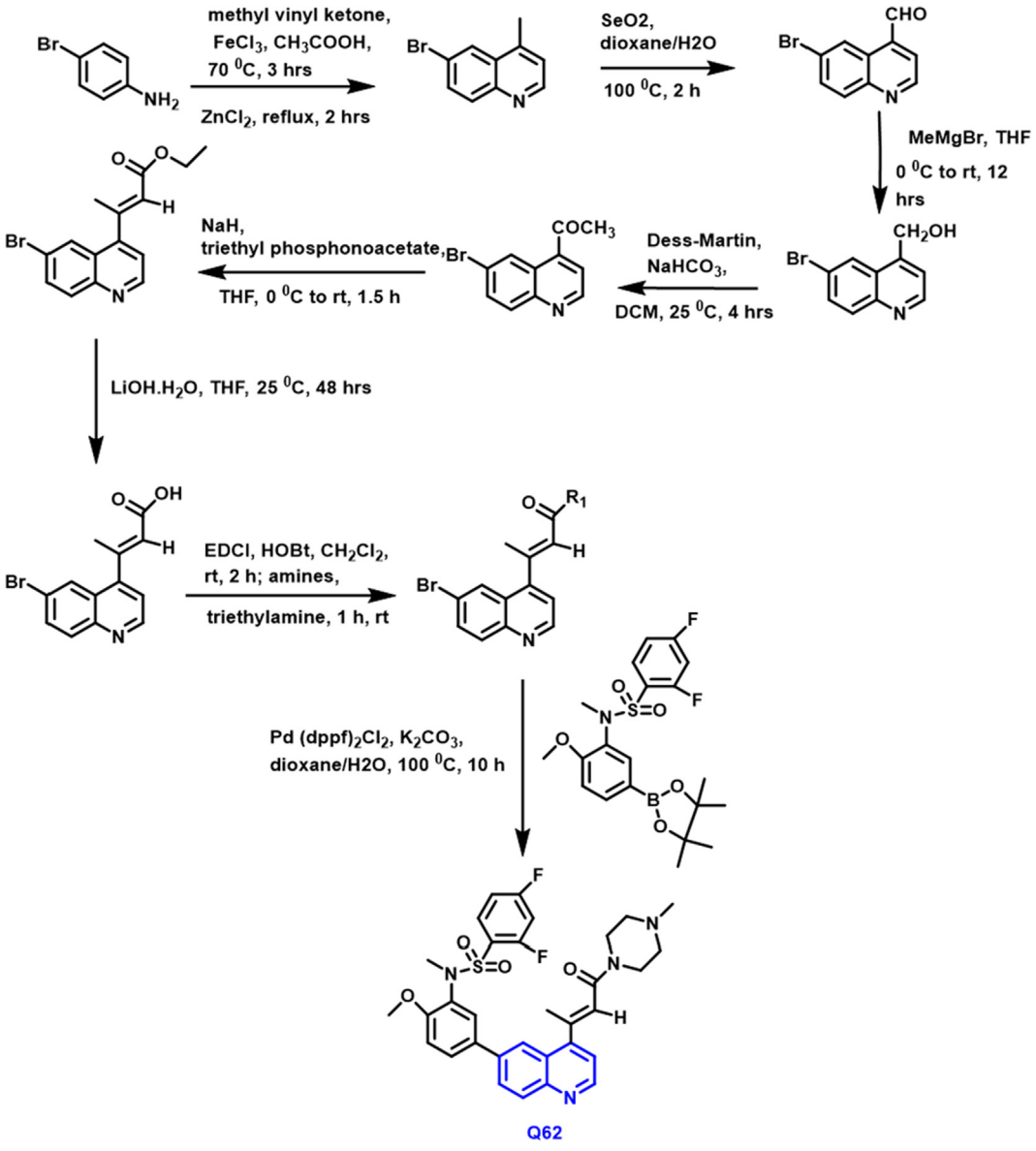

**Scheme 33** Synthetic pathway of novel quinoline compound as an anticancer agent.



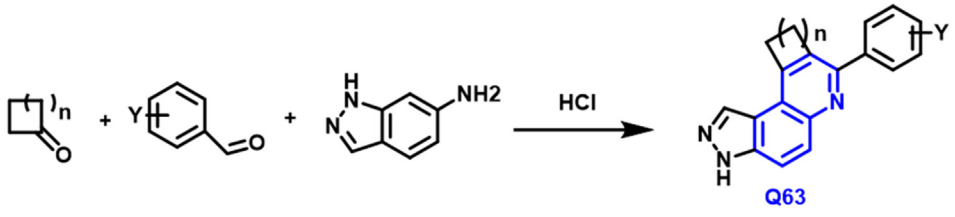

**Scheme 34** Synthetic pathway of novel quinoline compound as an antiproliferative agent.

effect on cell proliferation in standard culture conditions while sensitizing cells to apoptotic triggers. Targeting PDK1 alone or in conjunction with conventional chemotherapeutics has also been considered a possible cancer therapy.

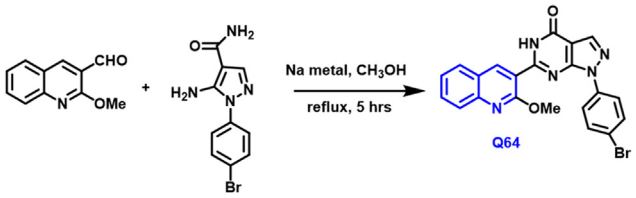
K.N. Vennilaa et al., (Vennila et al., 2018) have reported the conventional grid of amino-based 1-benzopyridine is decided to carry out and 8 derivatives are produced Scheme 38. The necessary H- bonding contacts with amino-acid sequences in the orthosteric region of PDK1 are formed as a result of the lock-key docking of the amino-based quinoline framework (PDK1). The binding mechanism of four crystal structures with PDK1′s adenosine triphosphate (ATP) site has been investigated. **Q65** compound had potent anticancer properties against lung cancer ($IC_{50}$ value of 0.96$\mu$ M) which is lower



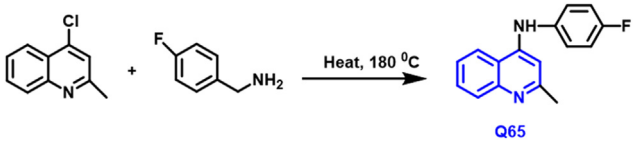

**Scheme 35** Synthetic route of novel quinoline compound as an anticancer agents.



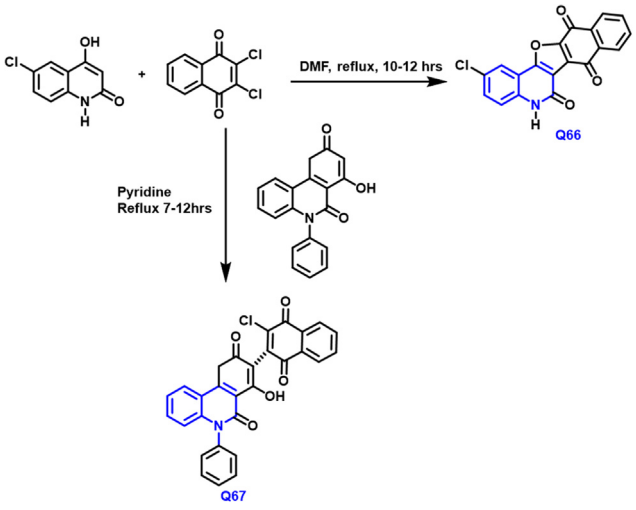

**Scheme 36** Synthetic pathway of novel quinoline compound as an anticancer agents.



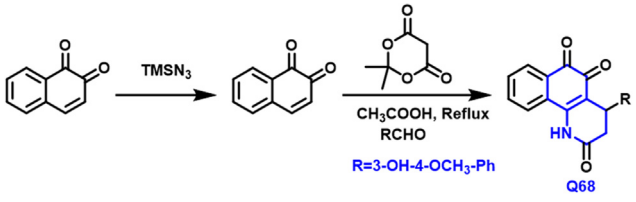

**Scheme 37** Synthesis of novel quinoline compounds based on pyrazole moiety.




**Scheme 38** Synthesis of novel 4-Substituted quinoline compound as an anticancer agent.




**Scheme 39** Synthesis of novel substituted quinoline compound as an anticancer agent.




**Scheme 40** Synthesis of novel quinoline compounds based on trione moitety.

than Alimta chemo drug, a commercial lung tumor medication.

### *2.1.12. ERK inhibitors*

The Renin-angiotensin system (RAS) / Rapidly Accelerated Fibrosarcoma (RAF) / mitogen-activated protein kinase kinase (MEK) / extracellular signal-regulated kinases (ERK) pathway has a high frequency of anomalous activation in human malignancies, making it a possible therapeutic target. (Blake et al., 2016)(Sullivan et al., 2018) ERK is a signaling nodes that connects two downstream kinases ERK1 and ERK2. (Morris et al., 2013) Various ERK inhibitors have been developed and have shown to be effective in the face of resistance. (Maik-Rachline and Seger, 2016).

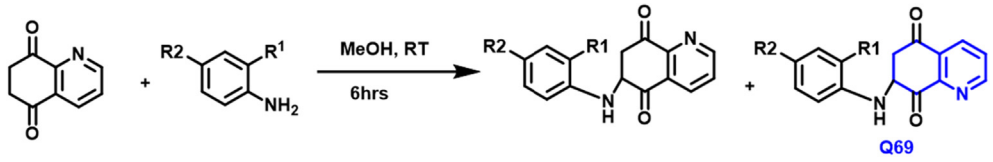
The development and production of a new series of pyrano, trione, and tetraone-based 1-benzopyridine as possible Extracellular Signal-Regulated Kinase stimulators was disclosed by Ashraf A. Aly (Aly et al., 2019) **(**Scheme 39**).** The six novel prohibitions were evaluated *in vitro* towards the NCI-60 panel of tumor cell lines for their antitumor potential**. Q-66** and **Q-67** compounds were shown to be highly effective in the majority of human tumor cell lines examined. Furthermore, with $IC_{50}$s of 3.7 and 0.13$\mu$ M, both compounds reduced the growth of BRAF mutant A375 melanoma cells. They also prevented anchorage-dependent colony development. Lastly, a molecular docking analysis demonstrated that compounds can interact with ERK2′s ATP catalytic binding site.

### *2.1.13. NQO1 inhibitor*

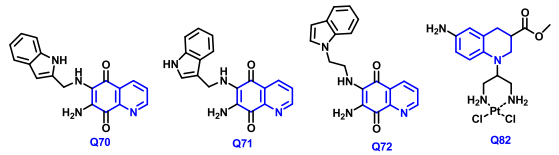
NQO1 is a NAD(P)H quinone oxidoreductase-1 or DTD, and is one of the flavoproteins found in eukaryotic cells. The de electro reduction reaction, it contributes to the metabolism of different quinones as well as the biological activation of quinone medicines**.** (Danson et al., 2004).

Li-Qiang Wu et al., (Wu et al., 2020) have reported the NQO1-directed anticancer drugs, a new sequence of the quinoline-based compound was developed, prepared, and physiologically assessed (Scheme 40). **Q-68** compound was shown to be excellent NQO1 substrates, with higher metabolic rates as compared to beta–lapachone. Furthermore, breast, liver, and lung tumor cells were all potently suppressed by compounds. The quinoline-based compound reduced tumor development in a HepG2 xenograft rat model at a dosage of 20 mg/kg without altering the animal weights. As a result, this compound might be a promising lead or medication candidate for further research.

Yong Ling et al., (Ling et al., 2018) have reported the new amino-based quinoline compounds from Quinoline-5,8-dione with amine or anilines in the presence of methanol under reflux conditions with a reaction time of 6 hrs **(**Scheme 41**). Q-69** compound had a strong anticancer agent for cervical cancer; also exhibited potent cytotoxicity due to the presence of an amino group at 6 and 7 positions of quinoline compound.




**Scheme 41** Synthesis of novel substituted quinoline compound as an antiproliterative agent.

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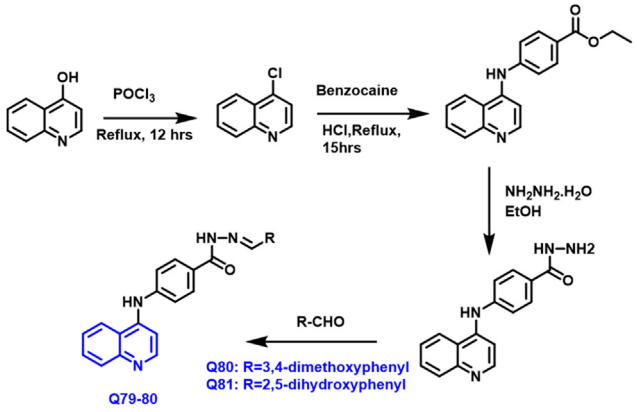
Maryam Gholampour et al., (Gholampour et al., 2021) have reported the synthesis of diaminoquinoline-5,8–dione derivatives using a molecular method based on silico design. Molecular docking was first utilized to investigate critical amino acid sequences and binding energies at the enzyme's active center. Depending on the outcomes, **Q-70** to **Q-72** molecules were chosen for a hundred molecular dynamics simulations because they have a high enzyme binding affinity and are oriented against the active center of this inhibitor. It has shown to be a viable treatment in antitumor drug development.

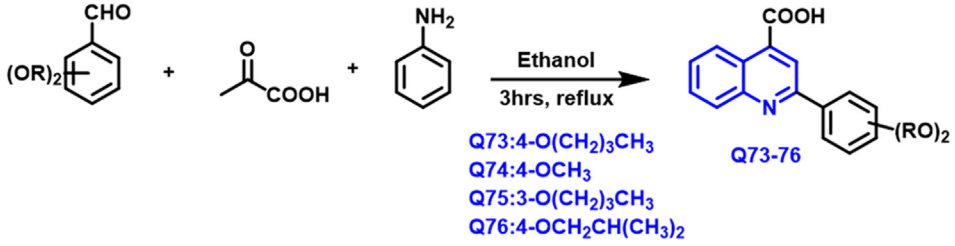
### *2.1.14. Dihydroorotate dehydrogenase inhibitor*

Human dihydroorotate dehydrogenase (hDHODH) is a suitable target for chemotherapeutic medicines since it is one of the most significant enzymes in cancer cell growth**.** (Madak et al., 2019) Milena M. Petrovi et al., (Petrović et al., 2020) has reported sequences of new carboxylic acid-based quinoline compound were prepared by using the Doebner reaction (Scheme 42). **Q-73** and **Q-76** compounds were shown to be effective hDHODH inhibitors whereas other few compounds had strong cytotoxic activity and high selectivity towards breast and melanoma cells. Molecular docking was used to show the pharmacology of the molecule at the molecular level, revealing the structural distinctions that separate highly active hDHODH inhibitors from moderate and lesser potent prohibit.

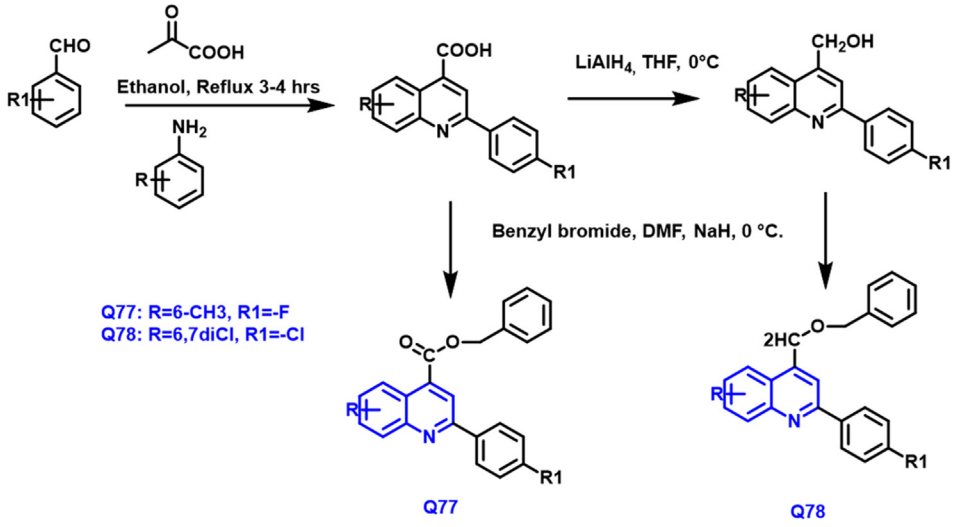
Vivek K et al., (Vyas et al., 2019) designed novel quinoline derivatives from benzaldehyde and substituted aniline in the presence of pyruvic acid and ethanol under reflux conditions to form 2-(4-substituted phenyl)-6,7-substituted-quinoline-4-Carboxylic acid by Doebner reaction. It further reacts with benzyl bromide in the presence of sodium hydride and dimethyl formamide as a solvent from the **Q77** compound as




**Scheme 44** **Synthesis of** N'-substituted methylene-4- **(quinoline-4-amino) benzoylhydrazides as an anticancer agent.**




**Scheme 42** Synthesis of novel quinoline-4-carboxylic acid derivates as an anticancer agents.




**Scheme 43** Synthetic pathway of novel quinoline compound as an antiproliferative agent.

a potent anticancer agent. The carboxylic derivative is reduced by lithium aluminum hydride to form alcoholic derivatives; it further reacts with benzyl bromide in the presence of sodium hydride and dimethyl formamide as a solvent to form **Q78** compound as a potent anticancer agent (Scheme 43). Q77 and Q78 have an $IC_{50}$ value of 1.56 μM and 1.22 μM towards hDHODH. Both the compounds have a notable antitumor agent against colon and breast cancer; non-toxicity in nature and potent hDHODH inhibitors.

### *2.1.15. c-Myc inhibitor*

The most prevalent kind of liver cancer, as well as the most frequent primary malignant tumor of the liver, is hepatocellular carcinoma. Hepatocellular carcinoma's morbidity and mortality have continued to rise in recent years, necessitating immediate action. As a result, it is critical to accelerating the development of hepatocellular cancer target medicines. C-Myc is a transcription factor that affects cell proliferation, cell growth promoter, development, cell death, and cell migration. c-Myc abnormal regulation is a frequent finding in several cancers (Dang, Le and Gao, 2009)(Eilers and Eisenman, 2008).

RNAi-mediated downregulation of c-Myc in HepG2 cells could be dramatically reduced HepG2 cell motility, invasion, and proliferation. As a result, c-Myc is being considered a possible therapeutic target for hepatocellular cancer. (Zhao et al., 2013) Baicun Lia and coworkers (Li et al., 2020) have reported that anticancer drugs were created by synthesizing novel N′-substituted methylene-4-(quinoline-4- amino) benzoylhydrazide derivatives (Scheme 44). **Q79** and **Q80** had strong antiproliferative activity toward lung cancer ($IC_{50}$ = 12.6 ± 0 .1 and 27.3 ± 1.7 *μm*) and also contain lower cytotoxic activity in normal cells.

### *2.1.16. Metal ion chelator:*

Yuxia Zhang and associates (Zhang et al., 2021) have reported the **Q-81** compound from substituted quinoline reacts with (4-(bromomethyl) phenyl)boronic acid in the presence of potassium carbonate and acetone as a solvent under reflux conditions. Scheme 45 Q-81 has a strong inhibitor than 8-hydroxyquinoline was confirmed by *in vivo* studies; it inhibits the growth of pancreas tumors. Q-85 has a potent anticancer agent due to the presence of nitric oxide and 8-hydroxyquinoline conjugates. The cytotoxicity, metal-binding capacity, and (NO)-releasing effectiveness of these conjugates were all tested. **Q-81** is a prodrug, that was shown to effectively limit the growth of several tumor cells. Several transition metal ions like copper, iron, and zinc metals are chelated by the 8-hydroxyquinoline molecule. **Q-81** had potent cytotoxicity toward pancreatic cancer and was confirmed by MIT assays.

### *2.1.17. Cis-platin-based quinoline derivatives*

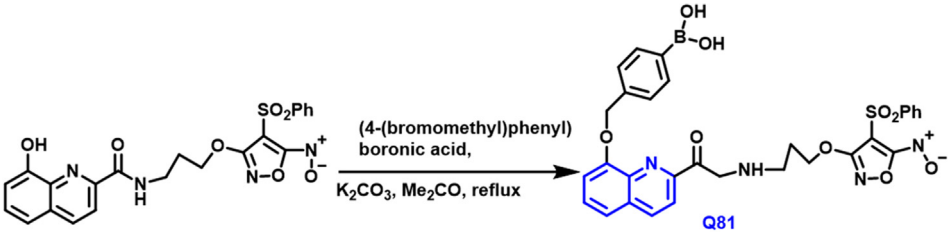
Cisplatin is still one of the most effective anticancer medicines on the market, and it is included in the World health organization of needed drugs. It's used to treat malignancies of the testicles, bladder, ovary, cervix, head, neck, and esophagus. (Johnstone, Suntharalingam and Lippard, 2016) The capacity to construct deoxyribonucleic acid interconnection through nitrogen-7 purine bases and guanine bases is core to its antitumor property. However, the shortage of specificity among both tumor and non-cancer cells frequently causes side effects such as myelosuppression, immunosuppression, nephron-toxicity, hearing loss, and so on**.** (Jamieson and Lippard, 1999) (Florea and Büsselberg, 2011) (Yao et al., 2007).

Sateeshkumar Kumbhakonam et al., (Kumbhakonam et al., 2020) have reported that a novel cisplatin-based quinoline derivative (**Q82**) was produced. When compared to mouse fibroblast NIH3T3 cells, they showed greater selectivity for cancer cells (A549), with cytotoxicity at the same level as cisplatin. ROS levels varied depending on the structure, and they may potentially kill cells, as indicated by the concentration of cells in the sub-G1 phase.

K. Pluta et al., (Pluta et al., 2016) reported a unique preparation of thiazine-based quinoline derivatives. Certain molecules like the reference drug cisplatin showed antitumor efficacy in breast tumor cell lines. The anticancer activity of the quinobenzothiazine system is dependent on the nature of the substituents, as well as the position and kind of fusion.

## *2.2. Conclusion*

This review, is a comprehensive overview of the quinoline-derived compounds, and their activity toward various cancer has been discussed in detail, in a nutshell, the synthesis involved in each compound is demonstrated. Plenty of quinoline-bearing compounds were developed and screened for anticancer activity. Currently, Bosutinib, Camptothecin, Lenvatinib, Cabozantinib, Topotecan, Irinotecan, and some other quinoline derivatives are being used as potential drugs for various cancer treatments. Though these drugs have greater potential for cancerous treatment, some of the newly reported quinoline-derived compounds show still higher anticancerous activity. Among these compounds, the Q4 compound shows greater potential and low cytotoxicity level for cancer therapy and there is a great possibility for this compound to be a successful clinical trial. In addition to these, most of the quinoline-based compounds are in laboratory trial and we hope these compounds will move on to clinical trial after required investigation. Despite several quinoline-derived compounds having potent progress reached, some of the




**Scheme 45** Synthesis of novel quinohne compounds based on 8-hydroxy moiety.

quinoline derivatives mentioned in this review certain obstacles to overcome to be a better anticancer drug. The major challenge among many is drug resistance, low efficiency, and damage to normal cells. From our point of view, the researchers have to address these obstacles to make quinoline compounds commerically viable. As a result, we anticipate that the current study will be beneficial to medicinal chemists and the drug discovery community; since it will aid in the synthesis of novel anticancer drugs that are targeted at various human cancers.

## CRediT authorship contribution statement

**Mohan Ilakiyalakshmi:** Writing – review & editing. **Ayyakannu Arumugam Napoleon:** Supervision, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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