Synthesis and Characterization of Chemotherapeutic Agent Quinolinolinol Series

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Abstract- Cancer, which remains an ever-increasing threat to the people’s health worldwide, has become the second most common cause of death nowadays Considerable efforts have been made by a growing number of researchers to design new therapeutic anticancer agents. A new series of N-substituted azetidinones (9a–h) synthesized by condensation of 4-aryliden hydrazine 1-isobutyl-1H-imidazo [4, 5-c] quinolines (8a–h) with chloroacetyl chloride afforded 4-arylazetidin-2-ones (9a–h). The synthesized compounds were characterized by 1H NMR, 13C NMR, mass spectral and elemental analyses. All synthesized compounds were screened for their anticancer activities. Compounds 9a and 9b exhibited good anticancer activity. In a molecular docking study compounds 9a and 9b showed minimum binding energy and good affinity towards the active pocket. Thus, are believed to be good inhibitors of β-tubulin.

Although there are several existing methods available, there are no routes that synthesize 4-quinolones in flow. Additionally, most syntheses focus on the carboxylated quinolone, where as the route described in this thesis leads to 3- unsubstituted quinolines. The result is a product that has increased diversity toward the accessibility of target structures, making the chemistry even more valuable.

Keywords: Anticancer activity, hydroxyl quinoline, carboxylated quinolone.

1. Introduction:
The World Health Organization (WHO) reported that an estimated 10 million cases of cancer occurred worldwide in 1998. Furthermore WHO predicted that the situation would get worse with numbers rising to 14.7 million over the next 20 years.

Cancer has afflicted our ancestors throughout the history of mankind, but it has become a major cause of mortality only in the last century. Although cancer can occur at all ages, it becomes more prevalent as people grow older. Epidemiological analysis shows dramatic increases in cancer incidence with age, which accounts for the prevalence of cancer in our time. The average life expectancy has increased substantially as a result of the elimination of infectious diseases this century. This has resulted in a larger fraction of older individuals in our population and consequently an increased incidence of cancer.

“The disease that causes cells to uncontrolled growth, resulting in tumor and abridged function in the immune system is referred to as cancer. All cancer diseases are finally lethal if participants do not take the proper medication.”

1.2 Types of cancer

The precise types of cancers originate in a piece common categories are as follows: –
Carcinoma: Carcinoma is the most wide spread variety of cancer. That instigates in the epithelial tissue (skin) or tissues that line interior vital body organs, such as kidney or liver. It may reach other body parts, or be confined to the primary location.
1. Sarcoma: It instigates in the bones or tissues (soft) of the body (cartilage, muscle, fat, blood vessels, fibrous tissue, or other supportive tissue).
2. Leukemia: The leukemia is a cancer of the blood cells. It starts in blood generation tissues
Including bone marrow and lymphatic system. Leukemia is mainly of four types: (a) Acute myeloid Leukemia (AML), (b) Chronic Myeloid Leukemia, (c) Acute Lymphocytic Leukemia, and (d) Chronic Lymphocytic Leukemia.
3. Lymphoma and myeloma: This type of cancer initiates in infection-fighting cells of the Immune system, called lymphocytes. These cells are in the lymph glands, spleen, thymus, Bone marrow and different parts of the body. There are two main types:
   (1) Non-Hodgkin lymphoma and
   (2) Hodgkin lymphoma.

Myeloma is also a type of blood cancer, which develops from cells in the bone marrow (Spongy tissue found inside the central cavity of many large bones of the body), called plasma cells.
4. **Central nervous system (CNS) cancer**: CNS cancer that starts in the normal cells/brain tissues and spinal cord called ‘neurons’ and ‘glia’. The meningioma, primitive Neuroectodermal tumors, gliomas, pituitary tumors, pineal tumors, etc. are the primary tumors of the brain.

5. **Mixed Types**: The kind machinery may be within one group or from different groups. A few Examples are adenosquamous carcinoma, carcinosarcoma, and teratocarcinoma.

### 1.3 Causes of cancer

- Chemical or toxic compound exposures: Aromatic hydrocarbons like benzene, toluene, glass wool, some metal like nickel, chromium (VI) and cadmium, arsenic, vinyl chloride (chloroethene), benzidine (1,1-biphenyl-4,4′-diamine), nitrosamines (N-nitrosamines), tobacco (nicotine and harmine are the active ingredients), and aflatoxin (produced by fungi), etc.
- Expose to radiation: Radioactive elements like uranium and radon, ultra-violet rays, radiation from α, β, γ, and X-ray emanating sources.
- Pathogens: Epstein-Barr virus, human papilloma virus, hepatitis B and C viruses, Kaposi’s sarcoma-associated herpes virus, Merkel cell polyomavirus, Schistosoma spp., and Helicobacter pylori; other bacterial strains are being researched as probable agents.
- Genetics: Numerous definite neoplasms have been associated with human genes; these include ovarian, breast, melanoma, etc.
- Diet and exercise: Over 30–35% of cancer deaths are mainly related to unhealthy diet, physical apathy, and obesity. [3-4]

### 1.4 Cancer symptoms [8]

The six symptoms were described by the American Cancer Society for cancers that may be present as follows.

1. Changes in habits of bowel or bladder
2. Incurable throat pain
3. Bizarre blood loss or liberation
4. Thickening in the breast, testicles, or elsewhere
5. Digestive disorders
6. Irritating or dry cough.

**NORMAL CELL DEVELOPMENT**

**ABNORMAL CELL GROWTH**

**Fig. 1.4**

### 1.5 Treatment for cancer
The following general methods are used in cancer treatment [9-10]:

- **Chemotherapy** is introduced by Paul Ehrlich, aim to destroy tumor cells. This technique affects by controlling the tumor cells from dividing, growing, and multiplying.

- **Hormone therapy** involves medication that sluggish or ends the growth of cancer that utilizes hormones to produce. It is also called endocrine therapy or hormone treatment.

- **Immunotherapy** engages curative that assists the immune system battle against cancer. The immune system helps our body battle infections and other diseases. It is made up of leukocytes and tissues of the lymph organization.

- **Precision medicine** (PM), the health care providers can recommend and plan specific care for their patients. It involves using genetic testing (examining DNA, chemical database) to decide the most suitable treatments for a person's particular presentation of cancer. It’s sometimes called personalized care or medicine.

- **Radiotherapy** (RT, XRT) is a cancer treatment that uses high doses of radiation to destroy or control the malignant cells and shrink neoplasms. This therapy most often uses X-rays but protons or other types of energy also can be used.

- **Bone marrow transplant** or Stem cell can be particularly favorable for patients with blood cancers (such as myeloma, leukemia, or lymphoma). This treatment replaces the bone marrow with healthy cells (either from own body or from a donor). It entails eliminating cells, such as RBC’s or WBC’s, which chemotherapy has destroyed.

- **Surgical oncology** (SO) is habitually a branch of a curative arrangement when an individual has a tumor cell. The orthopedic doctor may stamp out the tumor and nearby tissue during an operation to reduce or avert the disease extend.

1.5 **Quinoline series**: Quinoline stands out among the most essential N-based biologically active heterocyclic compounds. The presence of nitrogen atoms significantly increases the basic character of quinoline-containing compounds. Moreover, the quinoline nitrogen may engage in hydrogen bonding with the target enzymes. Polarity is an additional significant property that can be used as a method for reducing the lipophilic character, increasing water solubility and thus oral absorption in drug design strategies. The quinoline scaffold possesses a variety of biological activities, including anti-HIV, antipsychotic, antibiotic-anti-inflammatory, PDE4B inhibitors and antihypertensive activities. Drugs containing the quinoline ring motif, such as mefloquine, chloroquine, quinine, and amodiaquine, are used as effective drugs for the treatment of malaria. Moreover, the quinoline nucleus is the milestone structural motif for some important anticancer drugs that are available on the market [10].
Quinolines are one of the most important classes of heterocyclic alkaloids, which have been widely reported to possess a broad range of pharmaceutical activities. Derivatives have also been extensively studied as potential antitumor agents. With the development of cytobiology and molecular biology, the essential principles of tumorigenesis, invasion, migration, and metastasis induced by quinoline derivatives have been further explained. Antitumor mechanisms of quinoline derivatives include alklylation DNA, inhibiting c-Met kinase, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF). Quinoline derivatives also display excellent anticancer activities via different mechanisms of action, such as the inhibition of tyrosine kinase, alklylation agents, cell cycle arrest, angiogenesis inhibition, apoptosis induction, cell migration disruption, targeting Bcl-2, and inhibition of antimitotic tubulin polymerization.\textsuperscript{[11-12]}

![Fig no: 2 structure of Quinoline](image)

Generally two basic approaches are used in the synthesis of quinoline derivatives (a) biosynthetic approach (b) synthetic approach. As per biosynthetic approach, anthranilic acid has been postulated to be a key intermediate in the biosynthesis of quinolone and acridone alkaloids, which occur in abundance in plants of the family of Rutaceae. As per Synthetic approaches the synthesis of quinoline is a challenging aspect until now. Versatile methods have been developed for quinoline and its derivative production, such as, the combes quinoline synthesis which is a chemical reaction involving the condensation of unsubstituted anilines (1) with \( \beta \)-diketones (2) to form substituted quinolines (4) after an acid-catalyzed ring closure of an intermediate Schiff base (3) \textsuperscript{[7, 8]}. The Conrad-Limpach synthesis is the chemical reaction of anilines (1) with \( \beta \)-ketoesters (2) to form 4-hydroxyquinolines (4) via a Schiff base (3).

2.1.2 Classification of Quinoline\textsuperscript{[16]}

<table>
<thead>
<tr>
<th>Generation</th>
<th>Drug</th>
<th>Characteristic features</th>
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<tbody>
<tr>
<td>First</td>
<td>Naldixic acid</td>
<td>Active against some Gram negative bacteria.</td>
</tr>
<tr>
<td></td>
<td>Oxolinic acid</td>
<td>Highly protein bound drugs.</td>
</tr>
<tr>
<td></td>
<td>Pipemidic acid</td>
<td>Short half life.</td>
</tr>
<tr>
<td>Second</td>
<td>Norfloxacin</td>
<td>Protein binding (50%).</td>
</tr>
<tr>
<td></td>
<td>Enoxacin</td>
<td>Longer half life than previous agents.</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>Improved activity against Gram negative bacteria.</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lomefloxacin</td>
<td></td>
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<tr>
<td>Third</td>
<td>Temafloxacin</td>
<td>Active against Gram negative bacteria.</td>
</tr>
<tr>
<td></td>
<td>Sparafloxacin</td>
<td>Also active against Gram positive bacteria.</td>
</tr>
<tr>
<td></td>
<td>Grepafloxacin</td>
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Synthesis of quinolines by Traditional methods[17]

The anticancer activity of quinoline derivates has been widely recognized and investigated. Our group synthesized a series of quinoline derivatives and evaluated their anticancer effect. A total of 27 compounds were examined for anticancer activities against cancer cell lines of hepatocellular carcinoma (Hep3B), lung carcinoma (A549), and oesophageal squamous cell carcinoma (HKESC-1, HKESC-4, and KYSE150) [20]. Quinoline compound 83b inhibited cancer growth in oesophageal squamous cell carcinoma by down regulating COX-2 and PGE2. The cytotoxic potential of six quinoline derivatives was examined both in vitro and in vivo. 2-Formyl-8-hydroxyquinolinium chloride was prepared and its anticancer activity was evaluated both in vitro and in vivo. The relationship between structure and activity was also researched, and the presences of a bromine atom and hydroxyl group are likely the favourable structural components for molecules to exert a strong anticancer effect. The identification of the target of studied compounds is an important step in advancing the field of drug development [13-1]

Quinoline derivatives are fast spreading from anticancer drugs to almost every branch of medicinal chemistry. Quinoline derivatives represent a large number of antiproliferative agents exhibiting cytotoxicity through DNA intercalation, causing interference in the replication process (Ryckebusch et al., 2008). Actinomycin D, doxorubicin, mitoxantrone and streptonigrin are quinoline analogues possessing antibacterial or anticancer activity through DNA intercalation. Most of these drugs are currently used in the treatment of human malignancies target topoisomerase (types II) enzymes. Topoisomerase inhibitors designated as “poisons” interact with DNA to form cleavable complexes, causing permanent DNA damage that triggers a series of cellular events finally inducing apoptosis or other types of cell death. Topoisomerases are nuclear enzymes that regulate topological and conformational changes in DNA, critical to cellular processes such as replication, transcription, chromosome segregation and mitosis. There are two classes of DNA topoisomerase: (i) type I enzyme breaks one DNA strand for the passage of a second strand, and (ii) type II enzyme breaks both strands of one DNA duplex for the passage of a second DNA double strand. DNA topoisomerases (types II) are the primary target for a number of quinoline derivatives, including doxorubicin and mitoxantrone etc. Most of the anticancer drugs currently used in the treatment of human malignancies, as well as several new series of drugs under development, are targeted at topoisomerase II enzymes. Most of the quinoline based anticancer drugs currently used in the treatment of human malignancies, as well as several new series of drugs under development, are targeted at topoisomerase enzymes.
Among the many possible strategies for improving the therapeutic effectiveness of anticancer drugs, one of the most important is the synthesis of new derivatives with modified structure. In the search for new derivatives with advantageous biological properties many structural modifications have already been attempted. Such modifications appear to be a promising way for improvement of biological properties in comparison with those of the parent anticancer compounds, because such modifications exhibited lower toxicity and were found to be highly cytotoxic to several neoplastic cell lines with multidrug resistance.

**Application of Quinoline:**
1: Antimicrobial activity of some azoles containing quinoline
2: Antimalarial activity
3: As a chemotherapeutics agents.
4: Antituberculosis activity
5: Anticonvulsant Activity of 1- (2- (8- (benzyloxy) quinolin-2-yl)-1-butryl)cyclopropyl)-3-Substituted.
6: Immunosuppressant activity.

**Synthesis of compounds**
Synthesis of (quinoline -4-yl methylene) - 4- (trifluromethyl) benzenamine (Compound C1) About 40 ml dry ethanol were taken in a 100ml RB flask , to that 0.5 g of quinoline-4-carboxaldehyde were added, and stirred till dissolved. To the resulting solution, 1 to 2 ml of the glacial acetic acid, was added and stirred for half an hour .To the above reaction mixture 4-trifluro methyl aniline were added(1.3eq) followed by 2 hrs magnetic stirring and 4 hrs reflux on the water bath. The color was changed from colorless to brown color. The completion of the reaction was determined by TLC. The reaction mixture was kept overnight. There was a formation of the brown precipitated on addition of the crushed ice. The product was filtered and dried and purification was done by column chromatography with different proportion of the hexane and ethyl acetate.

**Characterization of Quinoline:**
1: Quinoline is mainly used as the building block to other special chemicals. Its principle use is a precursor for 8-hydroxy quinoline which is versatile chelating agent and precursor to pesticide.
2: If its aged sample is exposed to light, it turns became yellow and later brown.
3: Generally two basic approaches are used in the synthesis of quinoline derivatives (a) Biosynthetic approach (b) Synthetic approach. As per biosynthetic approach, anthranic acid has been postulated to be a key intermediate in the biosynthesis of quinolone and acridone alkaloids.
4: Quinoline derivatives are fast spreading from anticancer drugs to almost every branch of medicinal chemistry.
5: Thia diazole ring also give rise to compounds with varied bioactivities, such as anticancer, anticonvulsant, antimicrobial, antitubercular and antiviral properties.

**Conclusion:**
In the present review, we have summarized our knowledge on quinoline derivatives with respect to their anticancer activities, mechanisms of action, structure-activity relationship (SAR), and selective and specific activity against various cancer drug targets. In particular, we focus our review on synthesis of quinoline derivatives by using various traditional methods in changes the concentration of chemical constituents. Heterocyclic compounds such as quinoline derivatives, since the quinoline newline derivatives are well known as antimicrobial agents. In this work we have chosen quinoline as a newline main skeleton and various heterocyclic compounds such as thia diazole, pyrazole, triazole, n win methiazole and carbohydrazides are substituted to enhance the antimicrobial activity. All the newline synthesized compounds were confirmed by IR, NMR, LCMS and screened for their newline antimicrobial activity.

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