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The versatile biological and chemical reactivity of quinoline derivatives, a source of innovation for the chemist

La versátil reactividad química y biológica de los derivados de quinolina, fuentes de innovación para el químico

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Abstract

Innovation is a particularly important word for the chemical industry as it is daily exercised when looking for drugs with improved biological effect and reduced side effects. It is also fundamental in the development of new materials, supplements, colorants among other chemically important products. The quinoline moiety is a versatile system used for several purposes as it has been stated in specialized literature. Chemically speaking quinoline, 1-aza-naphthalene or benzo[b]pyridine is a well-known heterocyclic compound present in several organisms with various potential applications in the pharmaceutical, chemical and material science areas. Maybe one of its most remarkable application of such a type of compounds is the used of related quinoline compounds in the treatment of malaria. This work is minted to summarizing the general synthetical procedures as well as the innovative applications of quinoline related systems with final thoughts about the potential uses in the chemical industry in general and interest in the pharmaceutical industry.

Quinoline, Malaria, Innovation

Resumen

Innovación es un término muy importante para la industria química al ser un ejercicio diario en la búsqueda de nuevos fármacos con actividad biológica mejorada y efectos secundaros mínimos, así como en el desarrollo de nuevos materiales, suplementos, colorantes entre otros productos químicamente importantes. La quinolina es un sistema orgánico muy versátil empleado con diferentes propósitos como queda de manifiesto en la revisión de la literatura especializada. La quinolina, 1-aza-naftaleno o benzo[b]piridina, es un compuesto heterocíclico bien conocido, presente en diversos organismos y con aplicaciones en las áreas farmacéuticas, química y en el desarrollo de materiales. Tal vez una de las aplicaciones más reconocidas de este tipo de compuestos es su uso en el tratamiento de la malaria. El objetivo de este trabajo consiste en resumir procedimientos de síntesis más reconocidos, así como las aplicaciones innovadoras de sistemas derivados de quinolina en diferentes áreas, con ideas finales sobre los potenciales usos de tales derivados en la industria química en general, pero con principal interés en la industria farmacéutica.

Quinolina, Malaria, Innovación

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1. Introduction

Chemistry is considered in general terms as the central science. Thanks to the development of chemical concepts, society has benefited from the creation of textiles, plastic materials, drugs for the treatment of common and emerging diseases, specialized foods, dyes, flavorings, among others.

Heterocyclic chemistry as a branch of chemistry is an area of intense development and application. Of the commercially successful drugs internationally an important percentage contains heterocyclic functions. Heterocyclic chemistry is the science that is responsible for the study of the physicochemical properties and reactivity of heterocyclic compounds, which are described in general terms as cyclic organic compounds with at least one of the components of the cycle being a different carbon element. The non-carbon atoms present in the cycle are termed heteroatoms, nitrogen, oxygen and sulfur heteroatoms being more common. Of the most recognized and studied heterocycles, six-membered heterocycles with aromatic nitrogen, sulfur and oxygen occupy an important place.

Quinoline is a heterocyclic system resulting from the fusion of a benzene ring and a pyridine ring, both aromatic and six-member cycles (Figure 1). The quinoline molecule contains a C9H7N molecular formula and a molar mass of 129.15 g / mol. It was isolated for the first time in 1834 by Runge from coal tar and in 1842 it was obtained from the alkaline pyrolysis of cinchonina, an alkaloid derived from the cinchona tree. It has a partition coefficient of 2.04 a pKb = 4.85 and a pKa = 9.5. It is considered a weak base that can form salts with acids and shows a reactivity similar to that of pyridine and benzene. It presents electrophilic substitution reactions, attributable to its aromatic nature, as well as nucleophilic substitution reactions, mainly driven by nitrogen with its free electron pair. It is a molecule frequently present in pharmaceutical compounds and associated with several pharmacological effects[1,2].

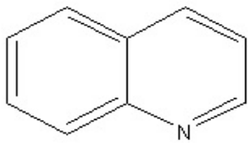

Figure 1 Structural formula of quinoline

Quinoline derivatives have been described in the specialized literature and available in the clinic as antibacterials [3,1], antifungal [4,5,6,7], anti-inflammatory [8,9,10], antimalarials [11,2], antileishmania [12,13], anticancer [14,15,16,17], antiviral [18,19,20], among others.

In addition to the obvious applications in therapeutics, systems derived from quinolines have been used in the preparation of nanomaterials and mesostructures with notable electronic and photonic applications [21,22,23,24]. The potential of the quinolines derivatives is very promising in areas such as the synthesis of agrochemicals and pesticides, preparation of dyes for tissues and foods, chemical sensors, among many more [25,26].

This work is intended to describe the most important synthesis procedures and in general the reactivity and biological application of quinoline and quinoline derivatives, which in recent times are subject to study due to the wide variety of biological and synthetic applications. According to our knowledge, there is no work that summarizes these relevant aspects of the chemical and biological reactivity of quinoline and its derivatives. Due to the wide application, that this family of compounds can have in chemical and pharmacological processes, this material is fundamental for the processes of innovation in the subject, of the following years. Section 2 will review the main processes of synthesis of quinoline and quinoline derivatives, with special interest in those processes friendly to the environment.

Section 3 of this work will address some of the properties and reactivity characteristics of this family of heterocyclic compounds. Section 4 will describe the main biological applications of quinoline-derived compounds and the most recognized biological activity structure relationships. Section 5 summarizes the latest trends in patents generated for compounds with quinolinic structure and their potential applications.

Finally, the most important research areas on the biological properties of quinoline and its derivatives will be discussed with the intention of presenting those that imply clear sources of innovation (Section 6).

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2. Synthesis of quinolines and quinolinic derivatives

The synthesis of new molecules is an activity without limits, which probably scientists, we will not finish exploring. In the past, the synthesis of new molecules was basically due to the study of the reactivity of these, that is, new molecules were synthesized in order to study the reactivity and to test the theories and hypothesis that, on chemical knowledge, that were being formulated in the way. For example, the development of many aromatic compounds was the result of the verification of the aromaticity theory. In the past synthesis was very dependent on the intuition of the chemist, since there were no concrete rules, known and studied.

Currently the synthesis of new molecules obeys a more rational design. There are very specific objectives and characteristics of the biological or chemical reactivity that a new molecule must have and that makes the synthetic steps to be analyzed very carefully. The synthesis of a molecule, which commonly refers to a family of molecules, will have specific reactive, spatial, connective, and biological characteristics. A combination of factors that make the task of synthesis quite complicated, but that facilitate the possibility of adapting the molecule or family of molecules to useful functions for humanity, such as the development of new drugs, more powerful and with fewer side effects.

Fortunately, in this work of designing new molecules, the chemist is no longer alone, he has at hand the development of computer systems and statistical packages that analyze experimental and theoretical databases to establish, for example, qualitative biological activity structure relationships and quantitative, and that investigate in detail the structural needs and physicochemical properties of the new molecules that will be used for the treatment of some disease. The same reasoning can be established for the development of catalysts, materials, paints and coatings, etc. In addition, the development of innumerable techniques and experimental procedures for the characterization of proteins, active sites, catalytic sites, to name a few, generates knowledge about the functional and structural characteristics of proteins and any chemical compound with which the new molecule can interact efficiently.

The theoretical calculation methodologies that are based on molecular mechanics, quantum mechanics and semi-empirical, allow calculations to be made for the estimation of the optimal geometry and the energy contents of new molecules and bonding sites, which also contribute to facilitate the design needs rational of new molecules. Finally it is important to mention that the better knowledge of the molecular bases of the pharmacological action, of the catalytic processes, among others, have made possible a more delicate analysis of the design of new molecules.

Although there is a vast number of synthetic strategies for obtaining quinolines [27] and its derivatives, the search for new synthesis processes continues to represent an attractive area of research. The first successful methods of quinolin synthesis comprise reactions of heterocyclic ring closure from ortho-substituted anilines and aniline derivatives without ortho-substitution. Skraup, Austrian chemist, in 1881 obtained quinoline from anilines and glycerin in a medium of sulfuric acid or phosphoric acid and an oxidizing agent (nitrobenzene, arsenic acid, lead dioxide or ferric salts and the quinoline is believed to be formed via the formation of acrolein (Figure 2) The main limitation of this synthesis is that quinlines substituted in the pyridine ring can not be obtained by this method.

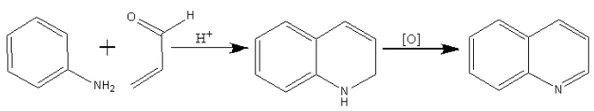

Figure 2 Chemical equation of synthesis of quinoline proposed by Skraup

In 1887 the Conrad-Limpach method was described, which is frequently used in the preparation of quinolones, precursors of several compounds of pharmaceutical importance. In this process, anilines, beta-ketoesters, which at high temperatures produce the ethanol elimination and the formation of the nitrogen heterocycle are used.

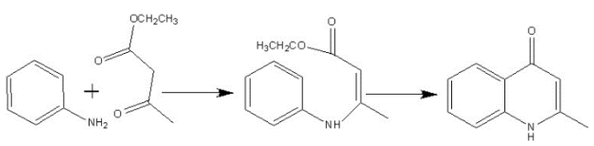

Figure 3 Chemical synthesis equation of 4-quinolone, quinoline precursor, Conrad-Limpach method

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Another synthesis process widely used in the production of quinolines is the Friedländer reaction (1883), which imparts greater versatility in the synthesis of substituted quinolines in both rings. It is a synthesis procedure still in force, although with modifications. It involves the reaction of an ortho-substituted aniline and a carbonyl compound that contains methyls or methylenes in the alpha position. A condensation of amino group and an aldol condensation are suggested for the formation of the heterocycle (Figure 4). Its main limitation lies in the ease of synthesis of precursors.

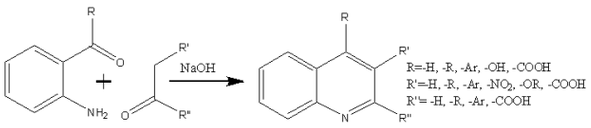

Figure 4 Chemical equation of synthesis of quinoline proposed by Friedländer

The synthesis of 4-carboxyquinoline acids of Pfitzinger is obtained from ketones and isatinic acid27,28 (obtained In situ, from isatin), or modification from enaminones29 in aqueous medium (Figure 5).

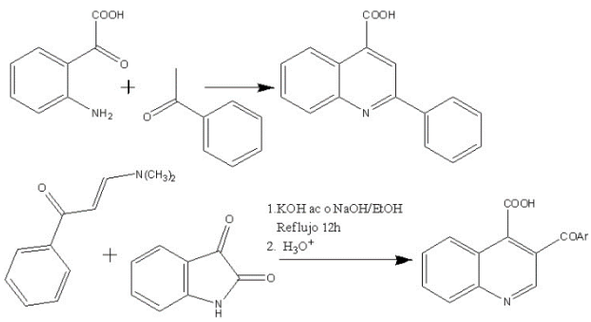

Figure 5 Pfitzinger synthetic method of quinolinic derivatives

Zhou[30] reported the synthesis of polysubstituted quinolines from 2-amino aromatic ketones and alkynes with good yields (Figure 6).

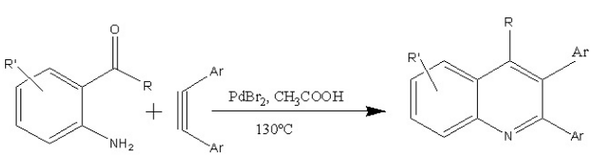

Figure 6 Synthetic method quinolinic derivatives according to Zhou

Efforts to develop cleaner methodologies resulted in synthesis protocols such as the one proposed by Zhao[30], in which quinoline derivatives are obtained in aqueous medium and facilitated by a silver catalyst, in which a high economy of atoms and few residues are observed (Figure 7).

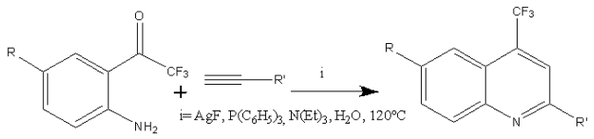

Figure 7 Synthetic method quinolinic derivatives according to Zhou

Other less popular methodologies, but yielding quinolin derivatives, aimed at obtaining compounds with pharmacological activity have been described in the literature [31].

One of the most innovative proposals in recent times, consists of the synthesis of derivatives of 1,4,6,8-tetrahydroquinolines [32,33], One of the most innovative proposals in microwave-assisted, at room temperature and above all avoiding the use of extreme reaction conditions (high temperatures, aggressive reagents) and the generation of large amounts of by-products and waste. The synthetic methodology is described in Figure 8 recent times, consists of the synthesis of derivatives of 1,4,6,8-tetrahydroquinolines.

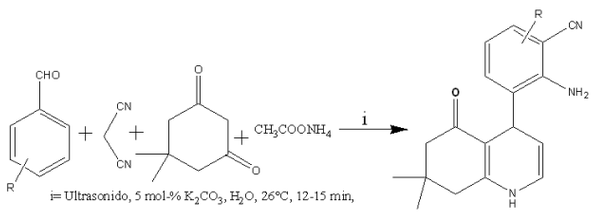

Figure 8 Synthetic method used to obtain tetrahydroquinolines using ultrasound radiation

Other quinoline derivatives with important applications are the 4-hydroxyquinoline-2-ones and the 2,4-quinolindiones, of which significant synthesis efforts have been developed and their physicochemical and biological properties described in the literature[34]. Using the Web of Science database, using the theme corresponding to the synthesis of quinolines and derivatives, there are about 3609 citations between 1980 and 2018. In 1980, 31 documents were published reporting novel synthesis processes of quinoline derivatives and 2017, said databases accounted for 244 jobs.

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This represents an increase of almost 800% and trends indicate that this trend will continue.

3. Chemical reactivity of quinoline and quinolinic derivatives

As already mentioned in the introduction, quinoline derivatives are of interest in different areas of science due to their potential applications. For example, quinoline derivatives have a wide range of pharmacological activities and among them we can mention antimicrobial, antiparasitic, antifungal, cardiovascular, antiviral, antimalarial, antidiabetic, among others. This diversity of pharmacological applications directly depends on the physicochemical properties of such heterocyclic systems.

And not only that, quinoline derivatives have been used for the fluorescent recognition of metal ions, in optical, electrochemical devices, in the preparation of pigments, nanomaterials and alloys.

Quinoline is a very stable light yellow liquid. A slightly higher density than water (1.093 g / mL, 25 ° C), a melting point of -17 to -13 ° C, a boiling point of 237 ° C and a vapor pressure of 0.07 mmHg at 20 ° C. It is very little soluble in water and very soluble in benzene, dichloromethane, to mention a few.

Quinoline is a molecule that exhibits fluorescence of the S1 state (n, π *) and phosphorescence of the T1 state (π, π *) in the vapor phase. In addition, quinoline is an organic molecule that emits a T1 (π, π *) - S0 fluorescence in vapor phase[35].

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The chemical properties of quinoline come mainly from the pyridine portion of the heterocycle. It is also undeniable that in part their reactivity is explained in terms of the aromaticity of the molecule. Quinoline is a flat molecule, with carbons in sp2, cyclic hybridization and having 10 aromatic electrons, as predicted by Huckel's formula. The nitrogen in the quinoline has a pair of electrons that does not participate in the aromaticity, for which, like pyridine, the quinoline presents basic properties, with a pKa = 4.9. From this fact, the natural tendency of the quinoline to react by attacking electrophiles with the pair of free electrons of the heteroatom, including the protons.

It also shows reactivity similar to pyridine against nucleophilic substitution reactions such as displacement, hydrogen substitution, among others. Because it is an aromatic compound, it is expected to present typical reactions of electrophilic aromatic substitution (SEAR). Unlike pyridine, where the aromatic electrophilic substitution is difficult, in quinoline and its derivatives is much easier since there are two aromatic cycles and of them the carbocycle is more reactive by not having the influence of nitrogen in the heterocycle. That is why by means of SEAR substituents are introduced in the carbocyclic aromatic ring, mainly in the C5 and C8, favored both by the electron distribution and by the stability of the intermediates formed (Figure 9).

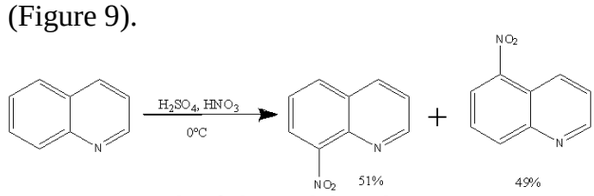

Figure 9 Example of electrophilic substitution reaction in quinoline

Unlike the SE_{ar} favored in the carbocycle, it is possible to incorporate substituents in the heterocyclic ring by addition reactions after the binding of an electrophile to the nitrogen in the C2 of the derivative (Figure 10). The most activated positions for nucleophilic attack are C2 and C4.

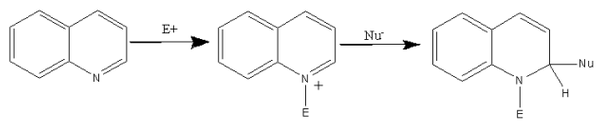

Figure 10 Quinoline reactivity and justification of addition reactions on pyridinic ring

The behavior of the quinoline against the reduction (hydrogenation) depends on the nature of the reducing agent. In the presence of molecular hydrogen and a nickel or platinum catalyst, the pyridine heterocycle is first hydrogenated, forming tetrahydroquinolines. A prolonged hydrogenation results in the hydrogenation of the carbocycle as well[27]. The reduction is more selective in the presence of lithium aluminum hydride. In the same way in the case of oxidation, this depends on the oxidizing agents. It is important to mention that, since the oxidation depends on the availability of electrons, due to the deficient character of pi electrons of the pyridine ring in the quinoline, the carbocyclic ring will be the main oxidation site.

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In the presence of potassium permanganate the breakdown of the benzene ring is generated with the formation of carboxylated derivatives of pyridine[27] (Figure 11).

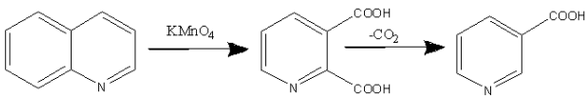

Figure 11 Chemical equation of quinoline oxidation

In addition to the heterocyclic reactivity characteristic of quinoline, it is a very good binder that can react with transition metals, lanthanides and actinides to form coordination compounds[36,37,38,39,40,41].

In the case of metals, when you have coordination compounds, it has been discovered that many times the biological effect of the binder (the organic portion) is increased by the presence of the metal[42,43,44] and in that sense it is that compounds of coordination with different metals have been prepared, among which ruthenium, gold, cobalt, nickel, zinc, copper and some metals of the family of the lanthanides and actinides described in the specialized literature stand out.

4. Biological applications of quinolines and quinolinic derivatives

The quinolinic derivatives were administered for the treatment of diseases certainly since ancient times, even before the identification of said compounds. The use of remedies obtained from leaves, fruits, barks, herbs, flowers, animals and insects, have been described in ancient documents of Indian, Egyptian and Chinese culture, to name a few. Perhaps one of the naturally occurring compounds that has received the most attention is quinine. Quinine is an alkaloid, organic nitrogenous compound that is synthesized by plants, considered a secondary metabolite, whose presence is not essential for survival of the plant, but have defined functions for the protection of the same against insects and other pests that often threaten the proliferation and permanence of it. The cinchona tree, containing high concentrations of quinine in its bark, and infusions of the bark were associated with the improvement of symptoms of bacterial infections, but especially in the treatment of malaria.

It was during the Second World War that an epidemic of malaria was unleashed and, consequently, the demand for medicine stimulated several research projects aimed at the synthesis in the laboratory of the active principles extracted from plants. From these efforts arose chloroquine and various substances chemically related to it. The treatment of malaria with chloroquine continues being one of the most used alternatives in our times (Figure 12).

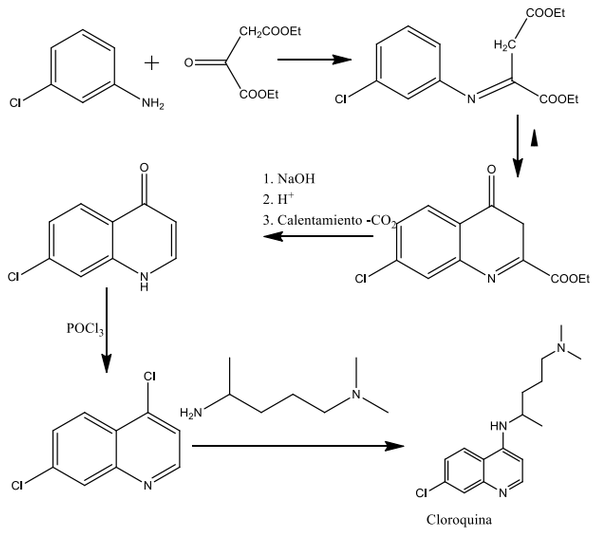

Figure 12 Synthetic route for obtaining chloroquine

Although one of the first applications of quinoline-derived compounds was as antiparasitic, for the specific treatment of malaria, quinoline derivatives have proven to be extremely versatile with respect to their application in the field of pharmacology. Important antibacterial agents are known[3,1], antifungal [4,5,6,7], anti-inflammatory [8,9,10], antimalarials [11,2], antileishmania [12,13], anticancer [14,15,16,17], antiviral [18,19,20], among others (Figure 13).

One of the areas of health where innovation is being given an important boost with respect to quinolinic compounds is in the treatment of tuberculosis. Tuberculosis is a lung infection caused by the bacterium Mycobacterium tuberculosis. TB is considered one of the most dangerous, contagious and fatal infections and represents a public health problem. Given the new threats that this disease brings, the development of new drugs is imperative, and quinoline offers an important alternative. It is believed that some quinoline-derived compounds are polar enough to traverse cell membranes and efficiently intro- duce into the bacterium.

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Once inside the bacteria, it is believed that quinoline derivatives bind to DNA gyrases and thereby inhibit their proliferation by altering their DNA production[38,45].

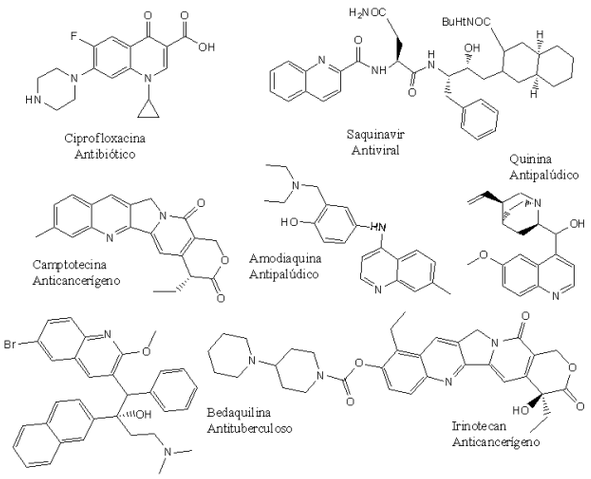

Figure 13 Compounds derived from quinoline with pharmaceutical application

5. Patents related to the synthesis of quinolinic derivatives

Starting from the wide variety of applications that the quinoline-derived compounds have, it is not surprising that there are 57727 patents available in the patent office of the United States of America, which comprise quinoline-derived compounds. There are patents related to the construction of optical and electronic devices, various organometallic and coordination compounds with outstanding optical properties, patents for molecules to be used in the treatment of conditions such as hepatitis C, prodrugs for the treatment of autoimmune diseases, antidiabetic compounds, antimalarials, potentials treatments in erectile dysfunction, anticancer, dyes, resins, adhesives.

In the same database in 2017, 19 patents were given related to the invention of products with quinoline derivatives present. In 2016, 26 patents were found, while in 2015, 35 patents.
In the particular case of patents of quinoline-derived compounds with anticancer properties, different targets of anticancer action are mentioned. Patents of quinoline derivatives have been described as inhibitors of c-Met kinase, which participates in processes of wound recovery and embryonic development, whose hyperactivity causes cancer[46].

There are also patents of anticancer compounds derived from quinolines with PI3K / AKT / mTOR inhibitory capacity, a fundamental protein for the regulation mechanisms of different cellular functions and which is very active in cancerigenic processes. Other patented quinoline derivatives are considered inhibitors of EGFR / VEGFR receptors, surface receptors to which growth factors (proteins and steroid hormones) bind, thus allowing the transmission of signals between cells. These communication mechanisms are fundamental for the development of certain types of cancer.

6. Concluding Observations

Quinoline and its derivatives are very important for their pharmacological and industrial applications, and they are also a fundamental part of many living systems. This importance is evident in the increasing number of investigations into the physicochemical and reactive properties of quinoline derivatives, with the aim of innovating with pharmaceutical products, optical devices, electronics, nanomaterials, among others.

The information contained in this document shows conclusively that quinolinic compounds continue to represent an important synthetic challenge, especially due to the wide variety of applications that this type of structure can have in different areas of science. It also demonstrates the growing interest of the industry in these systems, as the data of the number of patents indicates. In such a way that we anticipate an important development of the knowledge in synthesis and applications of these compounds, with special interest in the development of relations structure activity, that facilitate the development of better materials in the different fields of application, from finer adjustments of structures, for a biological effect or particular physicochemical property and for the benefit of humanity.

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