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Structures with Indole Rings Present in Natural Products

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ABSTRACT: This article presents the general notions, chemical structures, physico-chemical properties, biomedical applications and the various natural sources of indole compounds that researchers in the field have used to extract these compounds. The sources of indolic compounds are varied, they are present in different forms, and their role in the discovery of new drugs remains an important topic of research until now.

KEYWORDS: indolic structures, natural products, gels.

I. INTRODUCTION

Indole chemistry is a fascinating and complex field. The foul-smelling indole molecule is the building block for various natural and chemical products. Moreover, some indole derivatives are vital pharmaceutical products or essential intermediates [1].

Indole ring compounds are part of the class of aromatic heterocyclic compounds with one heteroatom, and the indole ring is the most widespread heterocycle [2].

Indole (benzopyrrole) - the representative of the class, is found in coal tars, namely in the fraction with m.p. 220°C- 26°C (3-5%) from where it is isolated industrially in the form of potassium salt [3].

It occurs freely in small amounts in some flower essences (orange blossoms) but also naturally in human feces and has an intense odor. At very low concentrations, however, it has a floral odor and is a constituent of some floral odors (such as orange blossom) and perfumes.

The name indole is formed from the words ind (indigo) and ole (oleum) because indole was first isolated in the reaction of indigo dye with oleum (sulfuric acid). Indole chemistry began to develop with the study of the dye indigo.

Indigo can be transformed into isatin and then into oxindole.

In 1866, Adolf von Bayer reduced oxindole to indole using zinc dust, and three years later, in 1869, he proposed the indole formula (Fig. 1.) [4].

II. INDOLE STRUCTURES

Certain indole derivatives were known as essential dyes until the end of the 19th century [5]. In the 1930s, interest in indole intensified when it became known that the indole nucleus is present in many essential alkaloids, as well as in tryptophan and auxins, and it remains an active area of research to this day.

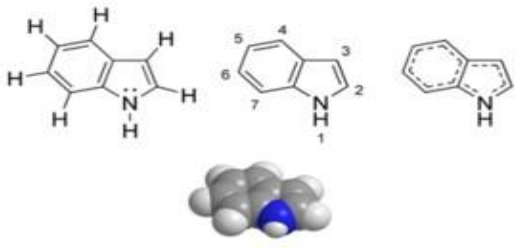

Fig. 1.Chemical indole strucures [6]

Tryptophan is the most widespread and vital derivative of indole, an essential amino acid in most proteins. Following biochemical changes, all natural indolic compounds originate from tryptophan [7].

Alkaloids are natural compounds with an indole ring that have been isolated from plants. Indole alkaloids contain an indole ring and can be found in fungi, such as ergine and psilocybin, the neurotransmitter serotonin, and LSD. These alkaloids can interfere with or compete with the action of serotonin in the brain [8].

Auxins are endogenous substances called growth regulators or plant hormones. These substances' names come from the Greek language, auxin, a term that defines their role in cell elongation. Auxins contain the indole ring with the formula $C_{10}H_9O_2N$ and are compounds derived from 3-indolacetic acid (AIA) or β-indolyl acetic acid [9].

III. INDOLIC NATURAL COMPOUNDS

The indole ring is also well known as one of the most essential scaffolds for drug discovery and has been a research focus for generations [10].

In the specialized literature, there are numerous biological studies of the compounds indole-3carbinol (I3C) and 3,30-diindolylmethane (DIM), which are present at relatively high levels in cruciferous vegetables such as broccoli and cabbage. These compounds have been the subject of ongoing research due to their interesting anticarcinogenic, antioxidant, and antiatherogenic effects [11].

Ajmalicin 7 (d-yohimbine or raubazine), an indole alkaloid found naturally in various plants, is a drug used to treat hypertension [12].

It acts as an α1-adrenergic receptor antagonist, preferentially affecting α2-adrenergic receptors, which underlie hypotensive rather than hypertensive effects [13].

Reserpine 8 is an indole alkaloid used to treat high blood pressure and agitation in patients with psychiatric disorders [14].

Vinblastine 9 is used to treat several types of cancer, including Hodgkin's disease, Kaposi's sarcoma, non-Hodgkin's lymphoma, and breast or testicular cancer [15].

Gramine is an indole alkylamine alkaloid that has been identified in several plant species, including sprouted barley and other grasses. It is a white, crystalline, toxic powder with a melting point of 133°C.

Gramine has a reactive -N(CH3)2 group, which is why it is used in the synthesis of many indolic compounds and also of many medicines. It is synthesized in plants from a shikimic acid precursor [16].

Indolylacetic acid is formed in nature from tryptophan. It stimulates plant growth (branches, roots) and functions as a plant hormone (auxin).

Indigo has been known since ancient times in Egypt and India and was described by Pliny.

Plants from the Indigofera genus (Isatis tinctoria, Isatis anil, Indigofera tinctoria) that grow in India were used to obtain indigo.

In Europe, starting in the 18th century, an indigo-producing plant, Drobusorul or Cardama (Isatis tinctoria), was cultivated [17].

Carbazole or dibenzo pyrrole is found in large quantities in coal tars in the anthracene or phenanthrene oil fraction. It is separated by dissolving it in potassium hydroxide. Carbazole, like indole, is weakly acidic, forming a potassium salt even with hydroxide.

By heating carbazole to 150°C in the presence of acetylene and basic catalysts (KOH), vinyl carbazole is obtained (Fig. 2.).

Polycyclic alkaloids with an indolic ring are nitrogenous compounds of vegetable origin with a heterocyclic structure and physiological action. Indole alkaloids are a class of alkaloids that contain an indole structural moiety; some also contain isoprene groups.

The amino acid tryptophan is the biochemical precursor of indole alkaloids. More than 4100 different compounds constitute one of the largest classes of alkaloids.

Many alkaloids with an indole ring are of particular physiological importance. They are used as medicines, the most notable being those from Ergot (a parasitic disease of the rye horn) and Rauwolfia.

It can be polymerized to obtain a transparent mass used as an electrical insulator.

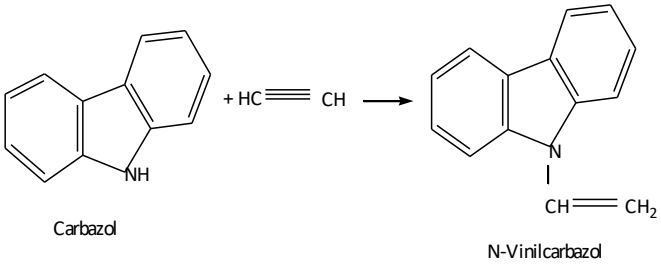

Fig. 2. The reaction to obtain vinylcarbazole

IV. EXAMPLES OF POLYCYCLIC ALKALOIDS

Natural lysergic acid and lysergic acid diethylamide (LSD), which is synthetically obtained from it, have the most potent hallucinogenic action known. The latter was discovered in 1938 and is made from lysergic acid.

Lysergic acid amide (LSA), a precursor of lysergic acid diethylamide (LSD), is found in the seeds of the Hawaiian baby woodrose plant (Argyreia nervosa) and the seeds of morning glory (Batatas violacea), both belonging to the Convolvulaceae family.

Strychnine and brucine are strong toxicants. R. Robinson (1946) established the structure of strychnine chemically and by X-ray crystallographic analysis by Bijvoet and Robertson (1950) [18].

Reserpine. Rauwolfia serpentina is a perennial shrub that grows in moist deciduous and even bamboo forests in some areas of India, Pakistan, Sri Lanka, Burma, and Thailand.

The Hindus discovered it, and different parts of it (the root, the stem, and the leaf) were used for their febrifuge effect as an antidote for venomous reptiles in the treatment of dysentery and other intestinal ailments. In the last 50 years, the extracted alkaloids are also used in allopathic medicine as drugs for blood pressure control and sedatives.

The alkaloids with an indolic ring in this plant are serpentine, sarpagina, reserpine, ajmalicine, etc., but the most important is reserpine.

Physostigmine. The fruit of the African vine Physostigma venenosum, called Calabar seed, contains several alkaloids, of which physostigmine (eserine) $C_{15}H_{21}O_2N_3$ is the most important.

This is a potent poison, and the Calabar seed was used by the populations of West Africa for the administration of "divine justice," i.e., saving the accused from a deadly intoxication through the emetic effect of a substance contained in the shell of this seed.

The combination includes a hydrogenated and methylated indole nucleus, condensed with a pyrrolidine ring, also methylated.

By treating with alkaline bases, physostigmine hydrolyzes, forming methylamine, CO_2, and eseroline $C_{13}H_{18}ON_2$, in which the OH group has replaced the CH_3NHCOO group.

Eserolin is an anticholinesterase opioid drug that causes neuronal cell death through a cell ATP loss mechanism.

Thus, the formation of eseroline can amplify the toxic effect of physostigmine [19].

Ibogaine is a slightly psychoactive indole alkaloid, isolated from the bark of the root of the plant called Tabernanthe iboga from central Africa, a plant that indigenous tribes have used since ancient times in social and religious rituals.

It is currently considered to be the most effective treatment for drug addiction (cocaine, heroin, methadone), alcohol, and tobacco addiction.

In the West, ibogaine is usually administered as ibogaine hydrochloride, a fine, white powder obtained either by chemical laboratory synthesis or extracted from the bark of Tabernanthe Iboga root. A single dose of ibogaine can eliminate the effects of drug consumption and also reduce drug cravings for a certain period after administration.

Psilocin and psilocybin. Some mushrooms contain a psychoactive alkaloid called psilocin (4-hydroxy-N, N-dimethyltryptamine), a tryptamine derivative that is the active form of psilocybin (O-phosphoryl-4-hydroxy-N, N-dimethyltryptamine).

Psilocybin has been isolated from the mushrooms Psilocybe mexicana and Stropharia and can cause a euphoria in which the individual remembers things long forgotten.

It has a structure similar to serotonin and acts as a partial agonist of serotonin receptors in the brain, mimicking the effects of serotonin.

Vinca Alkaloids: Vincristine, Vinblastine, Vinrolebin, Vincamine

The Vinca alkaloids are other alkaloids with an indole ring of particular importance in medicine.

Vinca alkaloids inhibit cell division by blocking mitosis, inhibiting purine and RNA synthesis, and ultimately causing the death of rapidly dividing cells. Vincristine (Fig. 3.) and Vinblastine (Fig. 4.), two essential indole alkaloids, were isolated from the Vinca Rosea L. plant, and their extracts have antitumor activity. Vinorelbine (Fig. 5.) is an indole alkaloid derived semisynthetically from plant extracts of the plant Vinca minor L.

Vincristine was approved for use in cancer chemotherapy in 1963, Vinblastine in 1965 and Vinorelbine in 1994.

They have become the major components of many combination anticancer regimens, mainly used in treating acute leukemia, Hodgkin's disease and other lymphomas, various sarcomas, Wilms' tumors, neuroblastoma, and breast and lung cancers.

Vinca alkaloids are given intravenously, usually at one- or two-week cycles with other agents. Vinca alkaloids are available in generic forms and under the trade names Oncovin (vincristine), Velban (vinblastine), Navelbine (vinorelbine), and Oxybral (vincamine).

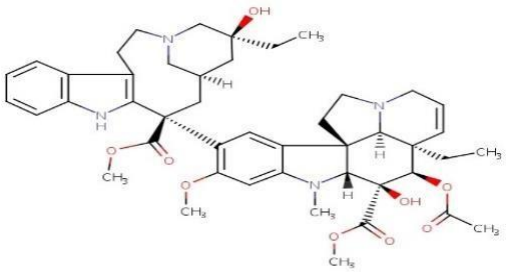

Fig. 3. Vincristine chemical structures

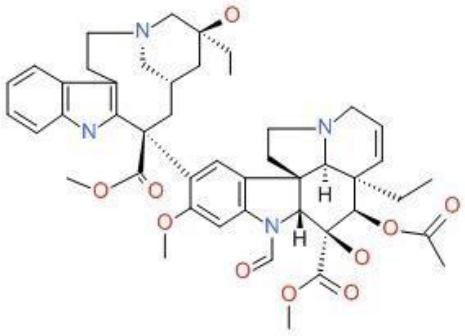

Fig. 4. Vinblastine chemical structures

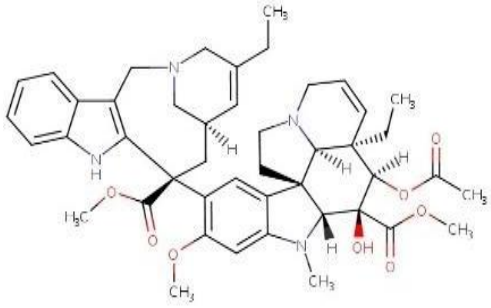

Fig. 1.5. Vinorelbine chemical structures

Vincamine (Fig. 6.), another extremely important indolic alkaloid in medicine, was isolated from the plant Vinca minor L., found under the popular name of Saschiu.

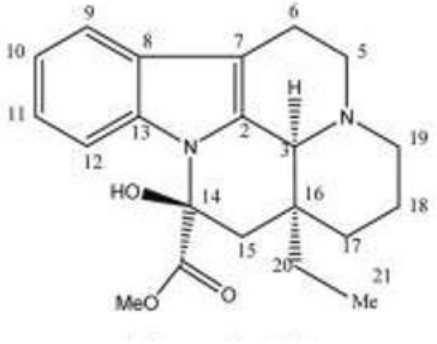

Fig. 6. Vincamine chemical structures

Vinca minor L. is a perennial, indigenous plant that grows spontaneously in our country in the alpine and subalpine areas. To date, more than 50 indole-type alkaloids have been isolated from the aerial parts of this plant, some of which have quaternary structures, such as 4-methylraucubainium chloride, 4-methylstrictamine chloride, and 4-methylacamicinium chloride.

This perennial plant contains indole alkaloids of the monomeric eburnamine type, including vincamine, which modulates brain circulation.

In folk medicine, vincamine is used internally to treat circulatory disorders and cerebral circulatory deficiencies and support brain metabolism.

A large body of clinical evidence indicates a favorable effect of vincamine in several conditions in elderly patients, such as memory impairment, vertigo, transient ischemic attacks, and headaches.

Vincamine increases cerebral blood flow, oxygen consumption, and glucose utilization. At the skin level, vincamine contributes to the healing of bleeding ulcers, open wounds, ecchymoses, and contusions by speeding up the healing process.

Auxins (plant hormones) have a structure very close to that of the amino acid tryptophan. The natural auxin compound found in various plant tissues was named heteroauxin and chemically identified with beta-indoleacetic acid or indole-3-acetic acid (AIA), with the crude formula $C_{10}H_9O_2N$.

This compound was taken as a model for elucidating the biogenesis of endogenous auxin substances.

Tryptophan, an amino acid existing in living protoplasm, is transformed by chemical oxidation at a certain level of fertilization and, regardless of the light regime, produces auxins (it is their precursor).

Indole derivatives are widely found in natural products in various plants, animals, and marine organisms.

The indole ring is an almost ubiquitous component of biologically active natural products. For example, indole-3-acetic acid represents one of the most common natural phenomena, a plant hormone from the auxin class.

Auxin causes the growth and multiplication of plant cells. It contributes to introducing H+ into the cell walls, and the higher pH activates enzymes to break the bonds in the wall and allow new cells to form through division. In this way, it contributes to the growth and development of the plant. Auxin is involved in the absorption of vital minerals and the coloring of leaves in autumn.

When a leaf reaches maximum growth, its auxin production decreases.

In deciduous plants, this triggers a series of metabolic actions that lead to the reabsorption of valuable materials (such as chlorophyll) and their transport into the branch or stem for storage during the winter months.

Once the chlorophyll disappears, other typical color pigments become visible in autumn.

Auxins are not synthesized everywhere, but every plant cell retains the potential ability to do so, and auxin synthesis will only be activated under certain conditions. In agriculture, synthetic auxins are used as growth and development stimulants.

Indole glucosinolates come from the hydrolysis of glucobrassicin, a compound found in cruciferous vegetables. After ingestion in the gastric acid environment, indole molecules combine and form condensation products that are the most biologically active.

Researchers became interested in their preventive potential in certain types of cancer when it was found that rations rich in cruciferous vegetables were associated with a decrease in the incidence of cancer.

Indole-3-carbinol (I3C) is a compound from the category of indole-3-glucosinolates that was identified relatively recently (as such and in the form of hydroxy- and methoxy-derivatives) in several cruciferous vegetables from the Brassicaceae family. They are found in suitable concentrations in broccoli, cabbage, cauliflower, Brussels sprouts, Chinese cabbage (bok choi), and turnips. Indole-3-carbinol is not seen as such in these vegetables; it is synthesized from indole-3-glucosinolate or glucobrassicin (GBS) through the catalytic hydrolysis of the enzyme myrosinase, which is physically separated in the intact cells of the plant and activated only after maceration vegetables.

When the plants are chopped or prepared for consumption, myrosinase converts glucobrassicin to indole. When myrosinase is inactivated by boiling, glucosinolate hydrolysis is reduced, mainly due to intestinal bacteria.

These compounds are of particular interest for research due to their anticarcinogenic potential. I3C shows antioxidant and antiarterogenic effects and shows apoptotic activity on some cancer cells from some forms of cancer (breast, endometrial, prostate, etc.).

V. THE ROLE OF INDOLIC COMPOUNDS IN DRUG DISCOVERY

Indole represents one of the most important structural motifs in drug discovery and is described as one of the "privileged schemes," a term initially introduced to define schemes that can serve as ligands for a diverse range of receptors.

Indole derivatives have the unique property of mimicking the structure of peptides and reversibly binding to enzymes, which provides enormous opportunities to discover new drugs with different modes of action.

Seven commercial drugs contain indole compounds among the top 200 best-selling drugs at US retailers in 2012.

This is highlighted by Cialis, a drug approved for the treatment of male erectile dysfunction (ED), signs and symptoms of benign prostatic hyperplasia (BPH).

There are also a staggering number of approved drugs on the market that contain indole compounds and are currently going through various clinical phases or registration status.

Modern medicines benefit from immunological research to gather significant information about the functioning of the immune system. A key area of research is related to the immunosuppressive environment of tumor cells.

Mushrooms have been used for their nutritional and medicinal properties for centuries.

They have been a significant therapeutic raw material in folk medicine; for example, Ganoderma lucidum (Lingzhi or Reishi mushroom) has been considered a panacea in traditional Chinese medicine.

Modern research confirms the therapeutic effect of the traditionally used species.

The specialized literature describes the indole compounds extracted from mushrooms as substances with antioxidant and anti-inflammatory properties.

It is known that edible mushroom species are a good source of carbohydrates, mainly chitin, which has a dietary role.

They represent a valuable source of proteins containing essential amino acids and, therefore, can be considered an alternative to animal products.

In addition, mushrooms are low in calories due to their low-fat content but are rich in polyunsaturated fatty acids (PUFA) that are beneficial to health.

Mushrooms contain secondary metabolites that show a series of beneficial properties, such as antioxidant, antibacterial, antiviral, anticancer, and anti-inflammatory properties, and they can also improve the functioning of the cardiovascular system.

That is why these mushrooms' indolic compounds potently affect the immune and nervous systems. Indole derivatives found in mushrooms include those with hallucinogenic effects such as psilocybin, but also those with non-hallucinogenic effects, L-tryptophan, 5-hydroxy-L-tryptophan, tryptamine or serotonin.

Cantharellus cibarius mushrooms have a high level of serotonin-17.6mg/100g, as well as lower amounts of melatonin, L-tryptophan, 5-hydroxy-L-tryptophan, 5-methyltrichophane, indole and indole-3acetonitrile.

Research has shown that the content of indole compounds in in vitro cultures (mycelium) can be considerably higher than that of fruit organisms.In humans, L-tryptophan can be converted into other indole derivatives with high biological activity, for example, serotonin, melatonin, and niacin (vitamin B3). Melatonin protects cells against pathogens.

Melatonin can regulate cytokine production by preventing the nuclear translocation of NF-κB.

It was also found that melatonin has a favorable effect on the evolution of neurodegenerative diseases associated with inflammation, such as dementia, Alzheimer's disease, Parkinson's, or multiple sclerosis.

In vitro studies have shown that indole derivatives, melatonin, acetylserotonin, or 6methyloxytryptamine, have properties to reduce lipid peroxidation.

Serotonin (5-hydroxytryptamine) is a neurotransmitter synthesized in the central nervous system and in mast cells, blood platelets, and intestinal enterochromat cells.

The opinion that the emotional state influences the functioning of the immune system can be explained by the effect of serotonin.

Mainly associated with its role in treating depression, serotonin also regulates the activation and migration of immune system cells through receptors and protein serotonylation.

Serotonin influences the activity of monocytes, prevents their apoptosis, and regulates the production of cytokines and chemokines.

The indole scaffold is also widely used in antiviral research. Examples of marketed antiviral drugs containing indole compounds include Arbidol and Delavirdin. Meanwhile, several indole derivatives are actively being investigated in various phases of clinical evaluation, such as Atevirdine, GSK2248761 (IDX-12899),

Golotimod, Panobinostat (LBH589) and Enfuvirtide.

Arbidol 10 (Umifenovir) represents one of the drugs that contain the most indole functions.

Arbidol is a Russian-developed broad-spectrum antiviral widely used in Russia and China since the 1990s.

It is used for the treatment and prophylactic prevention of influenza viruses A and B, respiratory syncytial virus, and SARS.

Arbidol has immunomodulatory and anti-influenza effects, especially against influenza groups A, B, and SARS.

It prevents virus contact and entry into cells by inhibiting the fusion of viral lipid membranes with cell membranes.

Arbidol 10 has interferon-inducing action, stimulates humoral and cell-mediated immunity, helps the phagocytic action of macrophages, increases the body's ability to fight infections, reduces the frequency of complications associated with viral infections, and diminishes the effects of chronic bacterial diseases.

In addition, Arbidol 10 also exhibited in vitro and in vivo activities against a group of human respiratory viruses, including influenza A virus (FLU-A, A / PR / 8 / 34H1N1),

respiratory syncytial virus (RSV), human rhinovirus (HRV), adenovirus type 7 (AdV-7) and HCV. For the past fifty years, natural products have served as a significant source of drugs; approximately fifty percent of today's commercial drugs are derived from natural products.

In the meantime, research efforts have been made regarding natural products containing indolic compounds to discover new natural antiviral products with a new mode of action. Sattazolin is an indole acyline natural product reported to exhibit potent antiviral activity against herpes simplex virus type 1 (HSV1) and type 2 (HSV2) (Hsieh P.W., 2004).

Minghua Chen et al. reported the isolation of seventeen new indole alkaloids and fourteen known analogs from an aqueous root extract of Isatis indigotica, and the compound Arvelexin showed antiviral activity against influenza A virus. The literature highlights that indole derivatives can exhibit favorable medicinal properties, including good solubility, increased lipophilicity, improved membrane penetration, improved metabolic stability and good oral bioavailability with pharmacokinetic properties and desired pharmacodynamics.

CONCLUSIONS

In concludes structures with indole rings present in natural products, includes a first direction of research that had as its objective the study of indole compounds in order to highlight their physico-chemical properties and the different natural sources of indole compounds, which researchers in the field -used to extract these alkaloids, as well as their importance in drug discovery.

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