INTRODUCTION

Intensive research on indoles, the compounds present in living cells of plants and animals, have been lasting for over 10 years. Because of their properties these compounds were applied in medicine and agriculture. Complexing reactions of indoles with biometals resulted in a creation of a number of compounds, which are now used to treat such diseases as depression, rheumatism, migraine, some types of cancer and even AIDS (1-5).

Many compounds which contain the indole skeleton play a very important role in medicine. These compounds are essential for the proper functioning of the entire brain and nervous system, therefore they play an important role in the synthesis of new pharmaceutical products. Many painkillers contain this moiety. Number of evidences prove the influence of indoles derivatives, on both animal and vegetable organisms. These compounds strongly affect mammals immune and nervous systems. It was found that in the future indole compounds, derivatives and complexes can be used as drugs that assist a treatment of a human immune and neurological disorders (1,2).

Analogs of indole may have a great importance for agriculture, because they speed up growth of plants and improve their immunity diseases. Antibacterial action of these compounds against the plant harmful bacteria, has also been demonstrated. Many fertilizers and soil conditioners for plants contain an indole moiety (6-9).

INDOLE ANALOGS USED IN MEDICINE

Indoles, are heteroaromatic organic compounds, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Other aromatic or heteroaromatic rings may also be attached to a double bond of the heterocycle (10).

Indole (2,3-benzopyrrole) ring system (Figure 1) often occurs in natural compounds. It is formed in the tryptophan biosynthesis and it is one of products of protein decomposition. Indole is a solid. It has an odor of manure, but when highly diluted, it smells like jasmine. Although indole is present in jasmine and orange flowers, its derivatives can also be found in cells of many plants and animals. Indole and its derivative – scatol (3-methylindol) – are very valued perfume components. Both indole and scatol are components of white flowers, such as jasmine, narcissus, tuberose and lily (10,11).

One of the major derivatives of indoles is indole-3-acetic acid. This is a plant hormone that occurs in tissues of different maize varieties. It produces strong hallucinations (12,13).

Many indole-3-acetic acid derivatives are used in pharmacy and medicine, for example indomethacin, (2-[1-(4-chlorobenzoyl)-5-methoxy-
2-methylindol-3-yl]-acetic acid) (Figure 2), which is a non-steroidal, anti-inflammatory drug. It also has an analgesic and antipyretic activity. It is used in rheumatoid diseases, joint and tendon inflammations. It improves movement activity. However, after prolonged usage it is harmful to the upper gastrointestinal system of patients (14,15).

A similar effect is induced by acemetacin – 2-[(1-(4-chlorobenzoyl)]-5-methoxy-2-methyl-indol-3-yl]-acetyl]-acetic acid (Figure 5) – is an analgesic, antiphlogistic and antipyretic drug. It is mainly used in pain and inflammatory states of movement organs – injuries, rheumatism, arthritis (17).

Figure 3 – Acemetacin

Figure 2 – Indomethacin

Figure 4 – Sulindac

Figure 5 – Etodolac

Figure 6 – Strychnine

5-methoxy-2-methyl-indol-3-yl]-acetyl]-oxoacetic acid (Figure 3) – but its activity is stronger. It is mainly recommended for rheumatic origin, tendon and muscle inflammations (16).

Sulindac – (1Z)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)benzylidene]-1H-indene-3-yl]-acetic acid (Figure 4) – is also an analgesic, antiphlogistic, antipyretic and antirheumatic drug. It is used in pain and inflammatory states of movement organs – injuries, rheumatism, arthritis (17).

Etodolac – 2-(1,8-diethyl-4,9-dihydro-3H-pyranoyl)indol-1-yl]-acetic acid (Figure 5) – is another drug, which has an analgesic, antiphlogistic and antipyretic properties. The drug metabolism occurs in the liver and kidneys. It works slowly, passes from the blood into joints, tendons and bones for a long time. It is suitable for long-term treatment of rheumatoid arthritis, chronic inflammatory conditions of soft tissue (vessels, tendons), inflammation states of nerves and osteoporosis (18).

Indole-3-methanol (1H-indol-3-yl-methanol) is a well known drug which belongs to indoles class. Many plants contain indole-3-methanol. It can be found in all types of Brassica from Cruciferae family vegetables, for example in tissues of such vegetables as brussels sprouts, cauliflower, cabbage, lettuce, kale, broccoli and others. Extract from Brassica vegetables occurs in a drug which in the pharmaceutical industry is called indole-3-carbinol (19-21).

Indole-3-methanol is used in breast cancer treatment. It can be applied at each stage of the disease, because it inhibits the development of cancer cells. Those properties are related to its influence on the level of estrogen. It was found that breast cancer cells grow in the presence of estrogen and the only way to stop that process is to inhibit the production of estrogen. Indole-3-methanol inhibits the secretion of estrogen in the glands even to 70%, as a result, the growth of cancer cells is stopped (19-23).

Rising interest in indole derivatives can be explained by the variety of their biological activity. Indole-2-carboxylic acid and its derivatives have antimicrobial and antifungal properties. They affect the nervous system. They can be used in pharmacology as antidepressants. They also improve memory and work of brain and remove convulsions (4). There is evidence that the 5-metoxyindole-2-carboxylic acid may become a drug in the early stage of cancer (5).

Indole-3-carboxylic acid is another indole derivative. There are numerous studies on the reactivity and the general influence of the acid on the human body. This acid has a strong impact on human both nervous and immune systems (24-29).

Indole-3-carboxylic acid is a natural compound. The first proof of its existence in nature have been revealed by the research carried out on seaweeds, algae (1). This acid has become an interesting compound for pharmacology. A series of tests have been undertaken to prove that the acid in combination with other organic or inorganic origin compounds, as well as the acid derivatives, such as esters, aldehydes, alcohols, or amides, can be used as drugs in diseases of the human nervous system (30,31). The use of indole-3-carboxylic acid in the treatment of schizophrenia is still under investigation (1,2,19,28,32,33).

Indole-3-carboxylic acid derivatives have been found in the frog adrenal glands. The studies have shown that the gland could be a good model for tracking the indole-3-carboxylic acid action mechanism (34).

Small quantities of indole-3-carboxylic acid have been found in a Chinese plant, kalanchoe pinnata (Phyllanthus). These herbs are used in natural medicine as a treatment to strengthen the resistance of the organism, after long-term antibiotic cures. They also improve the work of the liver (35).

Indole-3-propionic acid is a compound similar to indole-3-carboxylic acid. This acid has been detected the first time in asparagus female plant (Asparagus officinalis). It was found that indole-3-propionic acid might act as growth hormone of that plant (13). Indole-3-propionic acid can be used to manufacture a drug improving the work of the human brain and memory (36). There are many evidences of the presence of indole-3-carboxylic acid, indole-3-acetic acid and indole-3-propionic acid in the nature. They can be found in cells of both plants and animals (19,28,32,33,37).

Many of indole derivatives are alkaloids (plant compounds), with a strong basic properties. This group includes such alkaloids as gramine, derivatives of a lysergic acid, (it occurs in ergot), reserpine, (effective high blood pressure drug, used as a sedative to assist the treatment of schizophrenia; it occurs in the roots of the genus Rauwolfia plants), yohimbine, (a tranquilizer used in the treatment of mental disorders), strychnine (Figure 6), brucine and others (38).

Most alkaloids, for example a lysergic acid diethylamide (LSD) which is a derivative of the lysergic acid, have hallucinogenic properties. Moreover, the lysergic acid diethylamide is a strongly hallucinogenic substance that causes drug addiction (38).

Complexes of Indoles With Biometals

It has been proven that the complexes
of indoles with biometals have a similar action as indoles without metals. Moreover they don’t cause any side-effects on patients taking long-term medications. Additionally biometals have a positive influence on the human body. Synthesis of indole complexes has provided many long-term use drugs, which are not harmful to the patient (15).

An indomethacin copper (II) complex is an example of a drug, which has indole system. A need for a strong but harmless drug to the human gastrointestinal system, has led to the synthesis of this compound. Crystals of this compound contain two copper (II) ions, combined with carboxylic groups of indomethacin as connecting elements. It has been proven that the complexes of copper have a greater effect against inflammation than free indoles. Additionally, these compounds are analogical (15).

Complexes of indomethacin with zinc ions have similar properties. Derivatives of indomethacin with zinc ions have been used in veterinary pharmacology for a long time, providing evidence that they are harmless to organisms of mammals (39).

Complexes of etodolac with copper (II) ions enhance the anti-inflammatory and anti-rheumatic effects, without damaging the mucosal lining of the stomach and duodenum. Complex of sulindac with copper (II) behaves in a similar manner. This medicine has also anti-inflammatory properties and can be used in the long-term cure (40).

Taking into account the very favorable pharmacological properties of the indomethacin with copper (II) and zinc ions complexes, the investigation of the other indole complexes has been undertaken. Complexes of indole-3-carboxylic acid with copper (II) and zinc ions and indole-3-propionic acid with zinc ions have been synthesised. The precise crystalline structures of these complexes have been defined by spectroscopic methods (FT-IR and FT-Raman). Investigation of their properties are still in progress. However, it is supposed that they will have an application in pharmacology (29,36,41).

An interesting noteworthy compound which has been described in 1995 is indole-3-acetic acid with palladium (II) ions complex. Although palladium itself hasn’t got biological significance, its combination with the ligand (indole-3-acetic acid) resulted in a compound that can be used as an analgesic (12).

CONCLUSIONS

Studies on indole derivatives and their complexes with biometals are very important because of their broad application in medicine. Indoles have analgesic, antipyretic and anti-inflammatory properties. They are essential to maintain healthy functioning brain, nervous and immune systems. They are often used in the synthesis of new pharmaceuticals. Currently available drugs on the pharmaceutical market, containing the skeleton of indoles, eg indomethacin, acemetacin, sulindac, etodolac, indole-5-carbolin, are becoming popular and are frequently recommended by doctors and pharmacists. The number of these drugs is constantly growing up all over the world. It has been found that complexes of indoles with biometals are better assimilated by the patient body than the indoles themselves. These pharmaceuticals can be used long-term without damaging the organism.

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