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INDOLE DERIVATIVES AND THEIR BIOLOGICAL APPLICATIONS- A REVIEW

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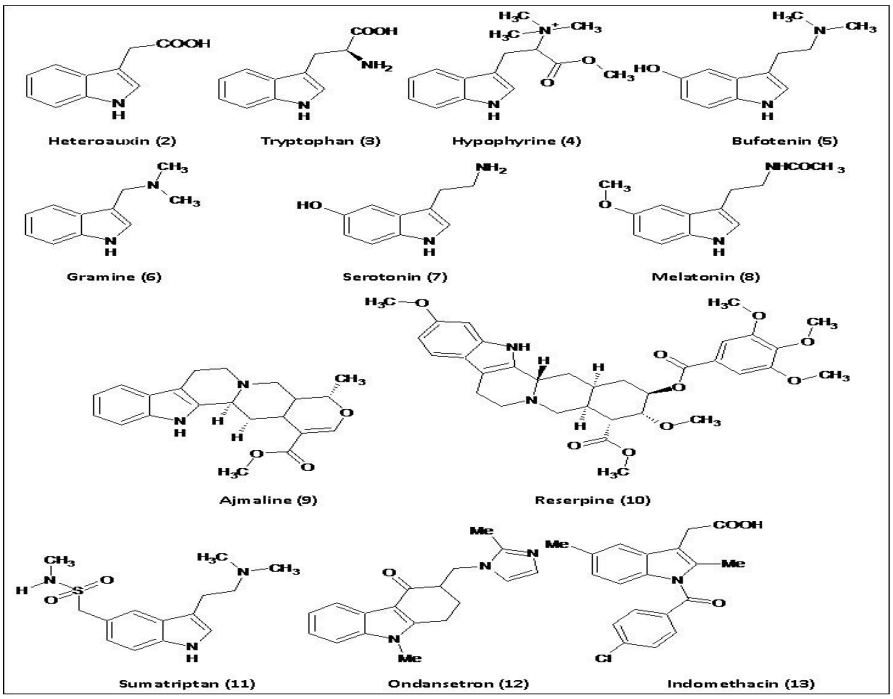
ABSTRACT

Indole represents one of the most important heterocyclic rings which provide privileged scaffolds in drug discovery. Indole derivatives and its pharmacological significance provide tremendous opportunities to discover novel drugs with different modes of action. There are also amazing numbers of indole containing drugs in the market as well as compounds in clinical evaluation. The indole nucleus is an important element of many natural and synthetic molecules with significant biological activity. This review serves as a comprehensive overview of currently published indole containing central nervous system acting agents with the main objectives in comprehensive listings of indole containing central nervous system drugs on market or compounds in clinical evaluation and to focus on recent developments of indole derivatives which are currently evaluated in experimental studies and their central nervous system activities.

KEYWORDS: Indole, pharmacological, scaffolds, biological activity.

INTRODUCTION

The name indole is portmanteau of the words indigo and oleum. Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a benzene ring and a pyrrole nucleus are fused in 2, 3 positions of the pyrrole ring. Indole is non-basic nitrogenous compound. 1-3 Indole chemistry began to develop with the study of the dye indigo. The word Indole is coined from the word India, a blue dye imported from India known as Indigo. Indigo can be converted to isatin and then to oxindole.4-5 In 1866, Adolf von Baeyer reduced oxindole to indole by using zinc dust.



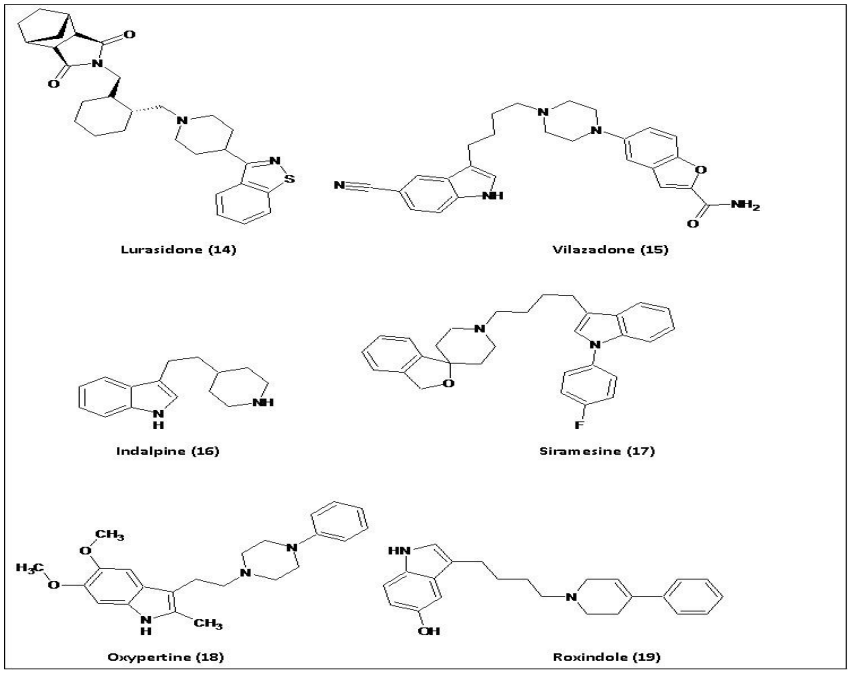
Heterocyclic chemistry is one of the most valuable sources of novel compounds with diverse biological activity, mainly because of the unique ability of the resulting compounds to mimic the structure of peptides and to bind reversibly to proteins.[1–4] To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and to screen it against a variety of different receptors, yielding several active compounds. Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical and biological properties. The fusion of several rings lead to geometrically well-defined rigid polycyclic structures and, thus, holds the promise of a high functional specialization resulting from the ability to orient substituents in three dimensional space. Therefore, efficient methodologies resulting in polycyclic structures from biologically active heterocyclic templates are always of interest to both organic and medicinal chemists.

Compounds with heterocyclic rings are inextricably woven into the most basic biochemical processes of life.[5-6] If one were to choose a step in a biochemical pathway at random there would be a very good chance that one of the reactants or products would be a heterocyclic compound. Even if this was not true, participation of heterocycles in the reaction in question would almost be certain as all biochemical transformations are catalyzed by enzymes and three of the twenty amino acids found in enzymes contain heterocyclic rings. Of these, the imidazole ring of histidine in particular would be likely to be involved; histidine is present at

the active sites of many enzymes and usually functions as a general acid-base or as a metal ion ligand. Furthermore, many enzymes function only in the presence of certain small non–amino acid molecules called coenzymes (or cofactor), which more often than not are heterocyclic compounds. But even if the enzyme in question contained none of these coenzymes or the three amino acids referred to above, an essential role would still be played by heterocycles as all enzymes are synthesized according to the code in DNA, which of course is defined by the sequence of the heterocyclic bases found in DNA.[7-9]

Chemotherapy concerns the treatment of infectious, parasitic or malignant diseases by chemical agents, usually substances that show selective toxicity towards the pathogen.[10-12] The diseases of bodily dysfunction and the agents employed are mainly compounds that affect the functioning of enzymes, the transmission of nerve impulses or the action of hormones on receptors. Heterocyclic compounds are used for all these purposes because they have a specific chemical reactivity for example epoxides, aziridines and β-lactams, because they resemble essential metabolites and can provide false synthons in biosynthetic processes, for example antimetabolites used in the treatment of cancer and virus diseases because they fit biological receptors and block their normal working, or because they provide convenient building blocks to which biologically active substituents can be attached. The introduction of heterocyclic groups into drugs may affect their physical properties, for example the dissociation constants of sulfa drugs, or modify their patterns of absorption, metabolism or toxicity.[13]

Tryptophan-derived substances in the plant kingdom include indole-3-ylacetic acid, a plant growth-regulating hormone and a huge number and structural; variety of secondary metabolites the indole alkaloids[12] (Figure 5). In the past, the potent physiological properties of many of these led to their use in medicines, but in most instances these have now be supplemented by synthetic substances, although vincristine, a “dimeric” indole alkaloid is still extremely important in the treatment of leukemia. Brassinin[14] isolated from turnips, is a “phytoalexin”-one of a group of compounds produced by plants as a defence mechanism against attack by microorganisms.



A number of tubulin polymerization inhibitors characterized by the presence of an indole nucleus have been obtained from natural sources or have been prepared by semi-synthesis. Vincristine and vinblastine are among the earliest anti-tumor agents being recognized since 1,965 as tubulin polymerization inhibitors. These drugs remain of clinical interest. Vincristine[15] is anti-tumor agents being recognized tubulin polymerization inhibitors and used in combination in the treatment of acute lymphoblastic leukemia and against both Hodgkin's and non- Hodgkin lymphoma. Vinblastine is mainly used in the clinical treatment of advanced Hodgkin's disease against germ cell cancer of the testes.[17] Many efforts have been taken aiming at the identification of novel, more active and less cytotoxic semi-synthetic Vinca alkaloids. Among the large number of derivatives synthesized by academic or industrial groups, two semi-synthetic derivatives, vindesine and vinorelbine have been employed in anti-cancer therapy.[16] The indole nucleus is the core structure of a great number of tubulin polymerization inhibitors. The indolyl-3-glyoxamide D-24851[18-20] and the 2-aroylindoles D-64131[21-23] and D-68144[24-25] were discovered by Baxter Oncology. Compounds are highly active against various tumors, including those resistant to paclitaxel.[26] Several 2-phenylindoles were designed by von Angerer as simple analogues of 12-formyl-5,6-dihydroindolo[2,1-a]isoquinoline. Among them, indole 2-phenylindole completely blocked microtubule assembly at a concentration of 40 µM.[27] On the basis of the structure of the natural product combretastatin A-4 (CSA4), some 2,3-diarylindoles, known as heterocombretastatins , were prepared by Medarde[22] Flynn et al. reported the tubulin

polymerization inhibitory activity of 2,3-diarylindoles and 2-aryl-3-arylcarbonylindoles.

Important marketed drugs derived from indole

Table 1 lists important indole ring-containing marketed drugs and their associated biological activities. Recently, the indole ring-containing compound yohimbine was proved by researchers for the treatment of sexual dysfunction.[28] Yohimbine was also explored as a remedy for type-2 diabetes in animal and human models, carrying polymorphisms of the α2A-adrenergic receptor gene. Delavirdine, an inhibitor of cytochrome P450 isozyme CYP3A4, is also a drug with an indole ring developed for the treatment of HIV type 1.[29-31] The indole-based pharmaceutical constitute very important class of therapeutic molecules and are likely to replace many existing pharmaceuticals in the future. The biological profiles of this new generation of indoles represent much progress with regard to the older compounds. Apaziquone is an indolequinone that is a prodrug and a chemical analog of the older mitomycin C. In a hypoxic environment, such as those on the inner surface of the urinary bladder, apaziquone is converted to active metabolites by intracellular reductases. The active metabolites alkylate DNA and lead to apoptotic cell death. This activity is preferentially expressed in neoplastic cells.[32]

Table 1

Drug	***Application***	***Drug***	***Application***	***Drug***	***Application***
Vincristine	Anticancer	Vincamine	Vasodilator	Roxindole	Schizophrenia
Vinblastine	Anticancer	Reserpine	Antihypertensive	Delavirdine	Anti-HIV
Vinorelbine	Anticancer	Peridopril	Antihypertensive	Atevirdine	Anti-HIV
Vindesine	Anticancer	Pindolol	Antihypertensive	Arbidol	Antiviral
Mitraphylline	Anticancer	Binedaline	Antidepressant	Zafirlukast	Anti-Asthmatic
Cediranib	Anticancer	Amedalin	Antidepressant	Bucindolol	β-Blockers
Panobinostat	Anti-leukamic	Oxypertine	Antipsychotic	Pericine	Opioid agonist
Apaziquone	Anticancer	Siramesine	Antidepressant	Mitragynine	Opioid agonist
Tropisetron	Antiemetic	Indalpine	Antidepressant	Pravadoline	Analgesic
Doleasetron	Antiemetic	Yohimbine	Sexual Disorder	Bufotenidine	Toxin
Oglufanide	Immunomodulatory	Indomethacin	Anti-inflammatory	Proamanullin	Toxin

CONCLUSION

As heterocyclic rings are abundantly present in nature, indole is commonly found in biologically active natural products and pharmaceuticals. Due to that there has been increased interest in the use of indole derivatives against many diseases. Indole derivatives are very important heterocyclic compounds in the drug-discovery studies. They represent a very important class of molecules that play a major role in cell biology and are potential naturally

occurring products. There has been an increasing interest in the use of indole derivatives as bioactive molecules against microbes, cancer cells, and various kinds of disorder in the human body. This paper reviews the current status and the recent studies of biologically important indole derivatives. The review is meant to present a general overview of the various research activities in this expanding field.

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