

Natural and Synthesized Indole Derivatives and their Biological Activities

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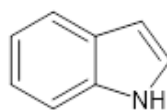
ABSTRACT

Indole compounds are found widely in nature, particularly in plants, bacteria, fungi, and animals, and many of them have significant pharmacological or physiological effects. These indole compounds also have been synthesized by the various methods and reported as a most bioactivities compounds. This manuscript provides a comprehensive overview of the natural sources, synthesis way, biological activities, and therapeutic potential of bioactive indoles, with a focus on their relevance in drug discovery and human health. In this paper, we have reviewed biological activities indole compounds with two categories bases on bioactivities of natural and synthesized indole derivatives.

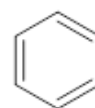
I. INTRODUCTION

The name indole is a portmanteau of the words indigo and oleum, since indole was first isolated by treatment of the indigo dye with oleum. Indole chemistry began to develop with the study of the dye indigo. Indigo can be converted to isatin and then to oxindole. Then, in 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust [1]. In 1869, he proposed a formula for indole [2].

Indole (1) is a bicyclic aromatic heterocyclic compound which is benzene (2) fused through 2 and 3 position of Pyrrole ring (3).



Indole
(1)



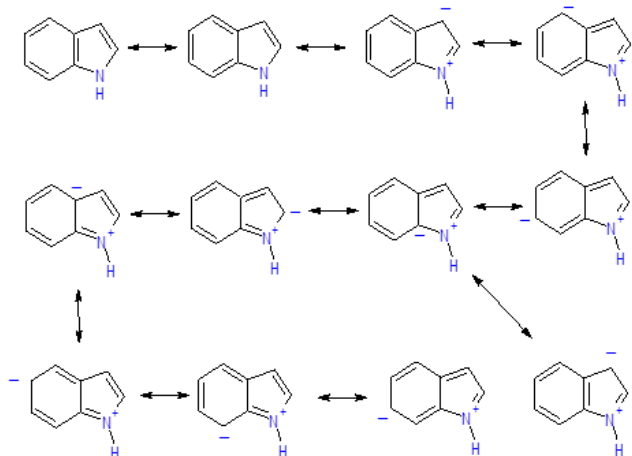
Benzene
(2)



Pyrrole
(3)

Indole has 10 π electrons arising from double bonds and lone pair on nitrogen which are delocalized around the indole ring. In all resonance structures (Scheme 1), some negativity and increased electron density on carbon atoms lead to their description as π -excessive [3]. Because of the delocalization of 10 electrons on 9 atoms (eight carbons and one nitrogen), indole is called as a π -excessive heterocycle. Because of the π -excessive property, indole shows enhanced

reactivity in electrophilic aromatic substitution, compared to benzene [4] {Scheme I}.



Scheme I: Resonance structures of Indole

As lone pair of nitrogen is involved in aromatic ring current, indole behaves as a weak base, like Pyrrole. So, indole and its derivatives are quite reactive towards strong acids. As a result of various molecular orbital calculations, the C-3 site of indole has the highest electron density and it is the most reactive position towards electrophilic substitution reactions. The C-2 position is the second most reactive site of indole toward electrophiles. The N-H bond in the indole skeleton is weakly acidic. Strong bases can be used to deprotonate the N-H proton. So, under basic conditions, N-substitution reactions, such as alkylation's, acylation's and transition metal catalysed arylation take place [5].

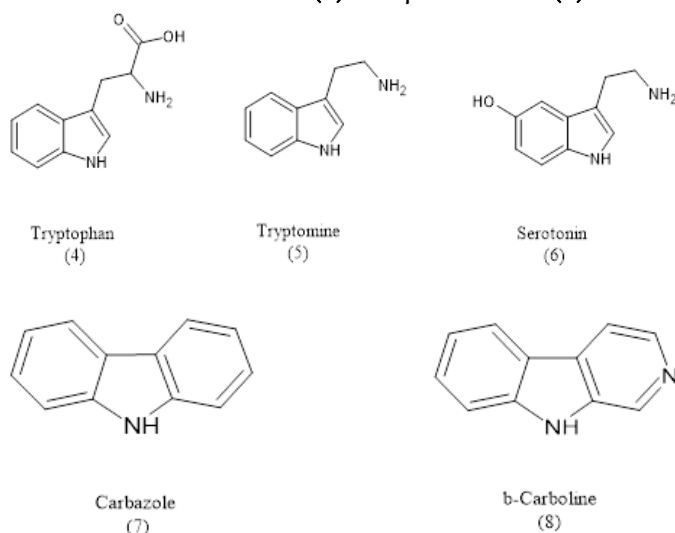
II. NATURAL BIOACTIVE INDOLE COMPOUNDS

Indole derivatives have been a topic of substantial research interest and continue to be one of the most active areas of heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities [6]. A large numbers of indole derivatives are at the fore as pharmacologically active lead compounds for drug development. Indole derivatives also occur widely in many natural products such as those from plants [7], fungi [8], and marine organisms

[9]. Indole is also found in human faces and has an intense faecal odour. At a very low concentration it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes [10].

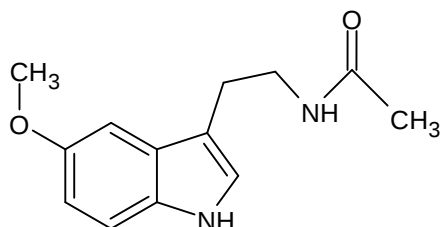
The isolation, biological evaluation and chemical properties of natural products have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacists. Chemical and biological researches have also presented a great challenge to synthesis and optimize highly efficient and economical synthetic routes to novel biological active substances.

There are several thousand indole alkaloids known [11], which include simple and more complexly functionalized indole derivatives. In the simple indole derivatives, pyrrole ring fused with benzene ring such tryptophan (4), tryptamine (5) and serotonin (6) and in complex indole derivative generally one additional ring most cases a six membered ring is fused with indole such as carbazole (7) and β -carboline (8).



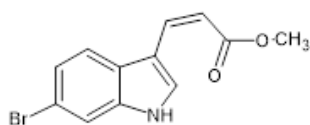
Tryptophan is a one of the most important indole derivative in the 22 naturally occurring amino acids. This amino acid can't be synthesized by the organisms but must be in their daily diet. In protein biosynthesis tryptophan plays an important role as a building block. Proteins which have tryptophan ring reducing effect on depression and insomnia related with hormonal fluctuations.

Serotonin (5-hydroxytryptamine) (6) is a key neuron-transmitter in the central nervous system, and melatonin (9) hormone is regulates function of smooth muscle in the cardiovascular and gastrointestinal systems [12]. Serotonin is structurally closely related to psychedelic substances like psilocybin and bufotenin [13-15].

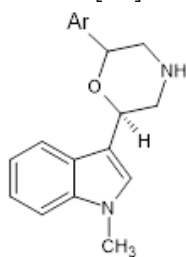


Melatonin
(9)

Methyl-(E)-(6-bromo-3-indolyl)-3-propenoate (10) has been isolated from a number of sponges [16-18] and known as sponge metabolite. Alkaloid (±)-chelonin-A (11) is also isolated from a marine sponge of the *Chenolaplysilla* sp. and showed potent antimicrobial and anti-inflammatory activities [19].

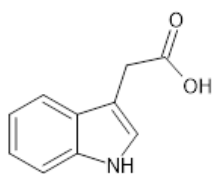


Methyl-(E)-(6-bromo-3-indolyl)-3-propenoate
(10)

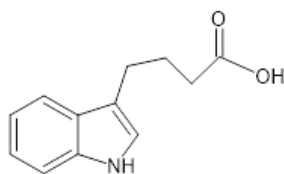


(±)-chelonin A
(11)

The plant growth hormone Auxin is found in nature as indole-3-acetic acid (12) and also synthesized as indole-3-butyric acid (13) form [20].

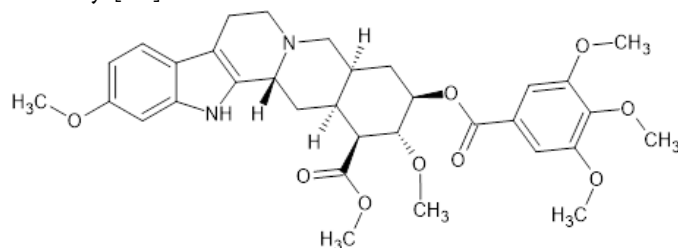


Indole-3-acetic acid
(12)

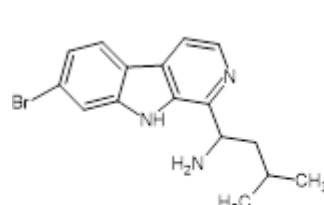


Indole-3-butyric acid
(13)

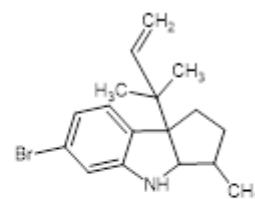
The fused indole derivatives are also showing most bioactivities. The indole derivatives reserpine (14) is isolated from the dried root of *rauwolfia serpentina* (Indian snakeroot) and used as antipsychotic and antihypertensive drug for treatment of various side effects [21]. Cytotoxic eudistalbin (15) and dihydroflustramine (16) are isolated from marine organisms and has anti-microbial and anti-parasitic activities [22]. Ellipticine (17) is show an anti-tumor activity [23].



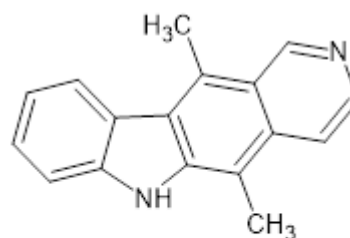
Reserpine
(14)



Eudistalbin
(15)



Dihydroflustramine
(16)



Ellipticine
(17)

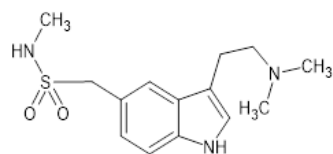
Consequence the nature is the big source of the bioactive indole derivatives.

III.THERAPEUTIC IMPORTANCE OF INDOLE DERIVATIVES

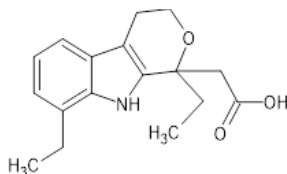
The indole ring system represents a privileged structure in drug discovery. Bioactivities of Indole ring containing compounds can be scarcely classified in to different categories [24-26] such as.

Antimicrobial [19]
 Anti-parasitic [22]
 Analgesic [27]
 Anti-allergic [28]
 Antibacterial [29]
 Anticonvulsant [30]
 Antifungal [31]
 Antihistaminic [32]
 Anti-inflammatory [33]
 Antitumor [34]
 Antiviral [35]
 β -adrenergic/ Beta receptor [36]
 Diuretic [37]
 Insecticidal [38]
 Anticancer [39]
 Anti HIV [40]
 Anti-hypertensive [41]
 Cardiovascular [42]
 Antioxidant [43]

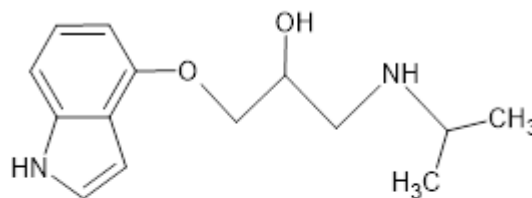
Indole ring containing drugs such as Sumatriptan (**18**) is used in treatment of migraine headaches, Ethodolac (**19**), are used as non-steroidal anti-inflammatory drug, and Pindolol (**20**) is used as a beta-blocker [44, 45].



Sumatriptan
(18)

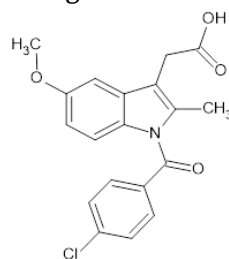


Ethodolac
(19)

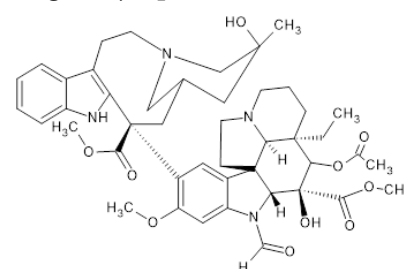


Pindolol
(20)

Indomethacin (**21**) is a non-steroidal anti-inflammatory drug inhibiting the production of prostaglandins and treatment reduce fever, pain, stiffness, and swelling [46]. Vincristine (**22**) is anti-tumour agents being recognized tubulin polymerization inhibitors and used to treatment of acute lymphoblastic leukaemia and against both Hodgkin's and non- Hodgkin lymphoma [47].

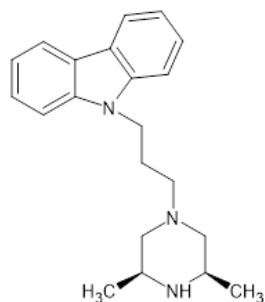
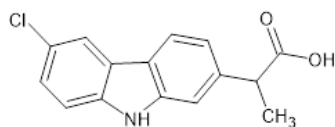
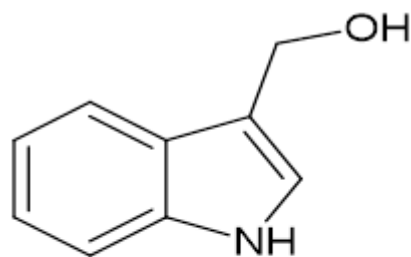


Indomethacin
(21)

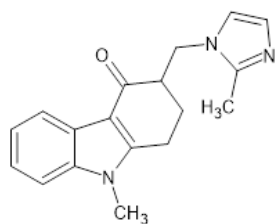
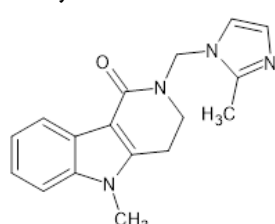


Vincristine
(22)

Carbazole is used in the production of pigment Violet-23, Rimcazole and Carprofen. Rimcazole (**23**) is act as sigma receptor [48, 49], reuptake inhibitor [50], and reduced the effect of cocaine [51]. Carprofen (**24**) is a non-steroidal anti-inflammatory drug used to treatment of various types of joint pain as well as post-operative pain [52-55].

Rimcazole
(23)Carprofen
(24)Indole-3-carbinol
(27)

Indole ring containing drug Ondansetron [56] (**25**) is used for the repression treatment of the nausea and vomiting caused due to cancer chemotherapy and radiotherapy. Other drug alosetron [57] (**26**) is used for the treatment of irritable bowel syndrome.

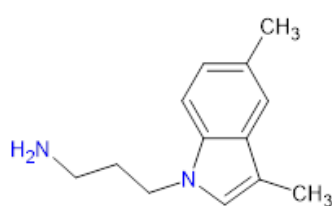
Ondansetron
(25)Alosetron
(26)

Indole ring containing indole-3-carbinol (**27**) is an important antitumor agent. Controlled researches on the indole-3-carbinol which have been conducted on using laboratory animal and cultured cells show that it prevents the binding of aflatoxin to DNA. As a result of this blocking, the carcinogenic effects of aflatoxins decrease [58-60]. A different research also indicates that indole-3-carbinol is effective in the prevention of breast cancer via eliminating the estrogen receptor sites on the membranes of breast [61]. Some studies were also carried out on indole-3-carbinol synthesis which showed that it has positive effect on the treatment of skin cancer [62].

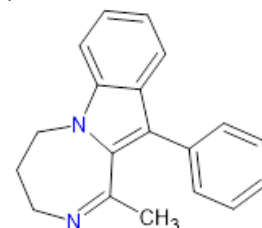
IV.SYNTHESIZED BIOACTIVE INDOLE DERIVATIVES

Indole compounds have shown many biological activities. Therefore, chemists have also show their interest toward the synthesis of indole derivatives. Indole derivatives are most widely used in the medicinal areas and show various activities against pathogens.

3-(3,5-Dimethyl-1*H*-indol-1-yl)propan-1-amine (**28**) and 1-Methyl-11-phenyl-4,5-dihydro-3*H*-[1,4]diazepino[1,2-*a*]indole (**29**) have been synthesized and showed antiserotonin activity [63].

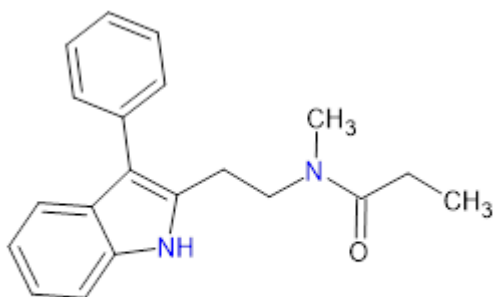


(28)

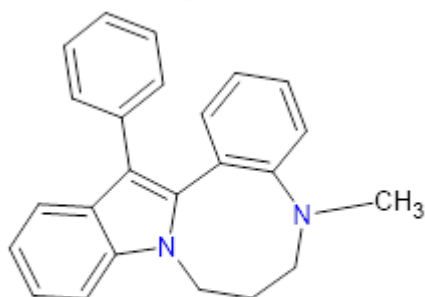


(29)

N-Methyl-N-[2-(3-phenyl-1*H*-indol-2-yl)ethyl]propanamide (**30**) and Indole-1,5-benzodiazocine (**31**) have been synthesized and reported as antidepressant agent [64] and potential activity in the central nervous system (CNS) [65] respectively.

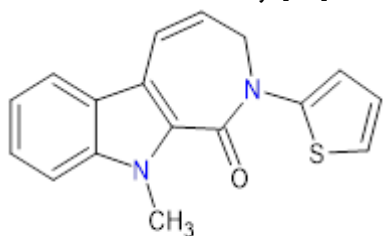


(30)

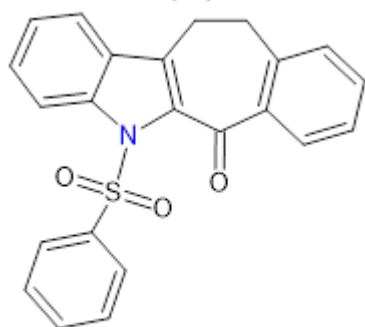


(31)

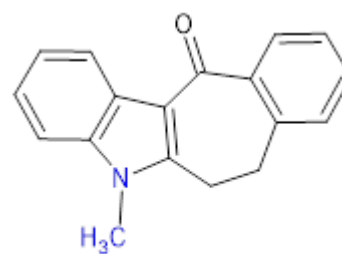
10-Methyl-2-(thiophen-2-yl)-3,10-dihydroazepino[3,4-*b*]indol-1(2*H*)-one [66] (**32**) and 5-(benzenesulfonyl)-10,11-dihydrobenzo[5,6]cyclohepta[b]indol-6(5*H*)-one (**33**) have been synthesized and exhibited antitumor activity against murine leukemia L1210 cell lines. Compound (**33**) has also shown antitumor activity against HT29 cell lines [67]. 5-Methyl-6,7-dihydrobenzo[4,5]cyclohepta[1,2-*b*]indol-12(5*H*)-one (**34**) also has been synthesized and showed potent antitumor activity [68].



(32)

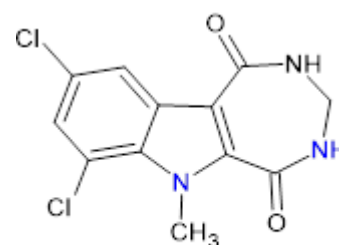


(33)



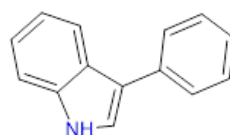
(34)

7,9-Dichloro-6-methyl-3,4-dihydro[1,3]diazepino[5,6-*b*]indole-1,5(2*H*,6*H*)-dione (**35**) has been synthesized and showed antibacterial activity against *E. coli* and *S. aureus* [69].

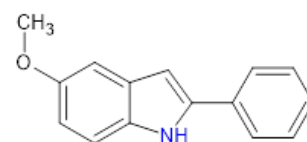


(35)

3-Phenyl-1*H*-indole (**36**) and 5-methoxy-2-phenyl-1*H*-indole (**37**) have been prepared and displayed potent antimicrobial activity against the *Bacillus cereus* [60].

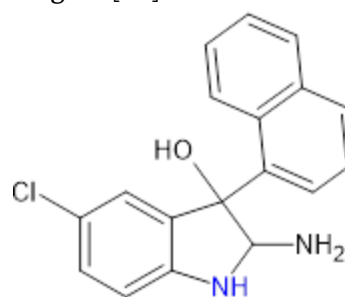


(36)



(37)

2-Amino-5-chloro-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-indol-3-ol (**38**) has been synthesized and reported as antimalarial agent [61].



(38)

5-Fluoro-*N*²-(cyclohexylidene)-3-phenyl-1*H*-indole-2-carbohydrazide (**39**) and 5-fluoro-*N*-(3-oxo-1-thia-4-azaspiro [4.5]dec-4-yl)-3-phenyl-1*H*-indole-2-carboxamide (**40**) derivatives have been synthesized

and assessed anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv [62].

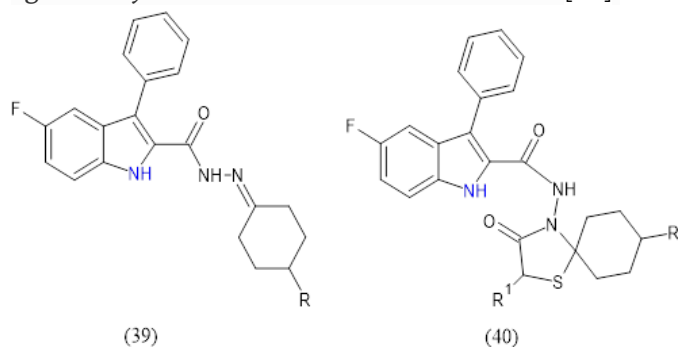


Table-1 Indole Ring Containing Important Marketed Drug Molecules [62]

S. No.	Used in Treatment	Drugs
1	Anticancer	Apaziquone, Cediranib, Mitraphylline, Vinblastine, Vincristine, Vindesine, Vinorelbine, indole-3-carbinol
2	Antiemetic	Tropisetron, Doleasetron
3	Antihypertensive	Peridopril, Pindolol, Reserpine, Amedalin, Binedaline, Indalpine, Siramesine
4	Anti-leukemic	Panobinostat
5	Antipsychotic	Oxypertine
6	Anti-inflammatory	Indomethacin, Ethodolac, Carprofen
7	Anti-Asthmatic	Zafirlukast
8	Antiviral	Arbidol
9	Anti-HIV	Atevirdine, Delavirdine
10	Analgesic	Pravadoline
1	β -Blockers	Bucindolol, Pinodol
2	Immunomodulatory	Oglufanide
3	Opioid agonist	Mitragynine, Pericine
4	Sexual Disorder	Yohimbine
5	Schizophrenia	Roxindole
6	Vasodilator	Vincamine
7	Toxin	Bufotenidine, Proamanullin
8	Sigma receptor	Rimcazole

V. CONCLUSION

Thus, natural and synthesized indole compounds show significant bioactivities and play the most important role in human being life. Specifically, the 3-substituted indole alkaloids with additional imidazole ring and indole alkaloid with additional substituted imidazole ring show most biological activities and their applications are very advantageous in different fields of science. Consequently, this review highlights the bioactivities of natural and synthesized indole compounds and their therapeutic importance with a focus on their relevance in drug discovery and human health

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