"Indole" A Versatile Nucleus In Pharmaceutical Field.

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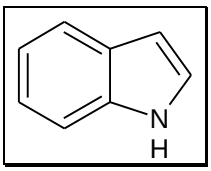
Abstract:

The present review article is related to the method of preparation, importance,, and medicinal application of Indole. The studies of heterocycles are an evergreen field in the branch of organic chemistry and always attract the attention of chemists working not only in the area of natural products but also in synthetic chemistry. Moreover, many useful drugs have emerged from the successful investigation carried out in this branch. The derivatives of indoles exhibit antibacterial, anticancer, antioxidants, anti-inflammatory, antidiabetic, antiviral, antiproliferative, antituberculosis, antispermetogenic activity, antipsychotic drugs etc.

Keywords:- Indole, Isatin, Anticancer, Antiviral, Anticonvulsant.

INTRODUCTION:

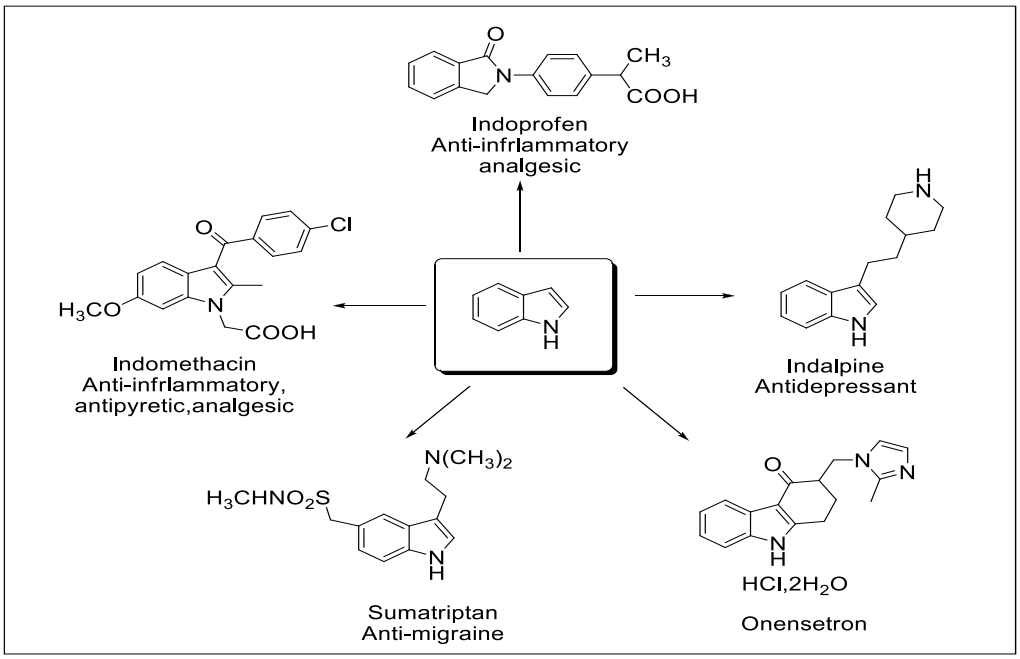


INDOL

In 1866 Bayer[1]and Knop in the course of study the structure of indigo and isatin .The work was continued by Bayer and Emerling[2] who proposed the structure of Indole . Indole are a pervasive class of compounds found in abundance in biologically active compounds such as pharmaceuticals, agro- chemicals and Alkaloids. Therefore indole derivatives have captured the attention of organic synthetic chemists. Medicines and Biochemistry are also interested in many aspects of indole chemistry. Indole derivatives occur widespread in many natural products. Various plants also have yielded Indole, among such as pseudacacia[3], Jasmines[4-6], Citrus plants[7] and orange blossoms. It is found in animal body wherever pus formation occures[8] and in the liver, pancreas[9] brain[10], and in bile[11].

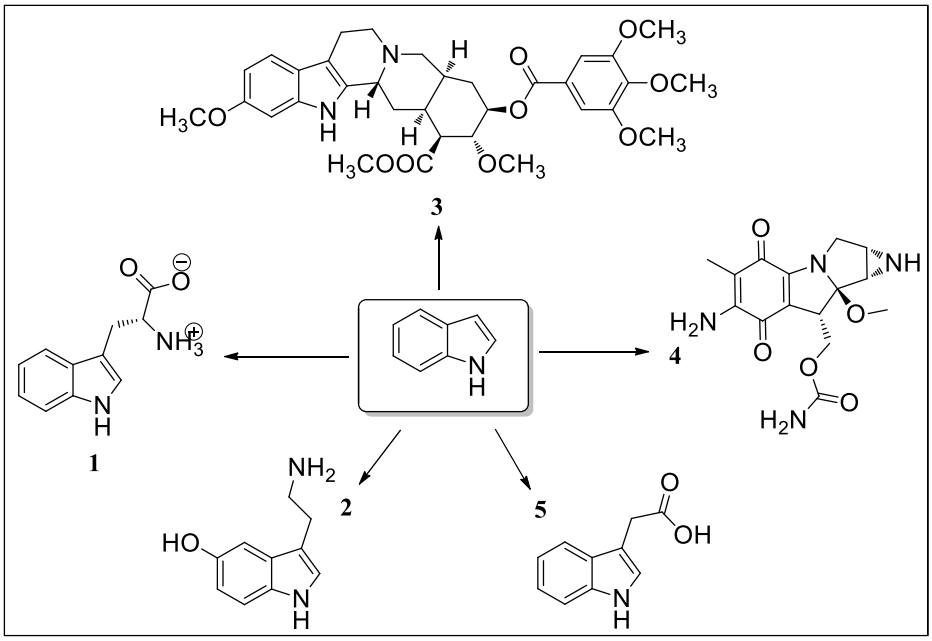
Indole has been also found in coal tar[12] in the fraction of boiling between 240-260^0 C from which it may be isolated as its sodium and potassium derivative, after treatment with sodium amide. Sodium or Potassium hydroxide, Molasses tar has also yielded some of its bases.[13] The discovery of indomethacin[14] as a successful agent for clinical treatment of anti-inflammatory disorder has lead to the exploration of Indole moiety to obtain better anti-inflammatory agents.

Indole and its analogs constitute the active class of compounds possessing wide spectrum of Biological activities, such as anti-inflammatory [15-25]. Antimicrobial[26-28], Antibacterial[29-30], Anticonvulsant[29-30] and Anticardiovascular[35]. Another aspect of Indole occupies a distinct place in drug discovery research. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Some of the important drugs molecules containing indole moiety, which are used as a pharmaceutical agent are shown below (Fig. 1.2). Furthermore, fluoro substituted indole derivatives have received wide attention from either synthetic or pharmaceutical view for long time due to their wide potential bioactivities [37-40].



❖ Some of the important drugs molecules containing indole moiety, which are used as a pharmaceutical agent.

The Indole is a crucial heterocyclic skeleton often associated of a number of natural occurring alkaloids. Today there have been many more Indoles added to the list of naturally occurring alkaloids and many of these have important pharmacological activities. Some natural product based bioactive indoles are discussed here. Indole alkaloids include such pharmacologically and structurally diverse compounds as tryptophan **1** (essential amino acid), the recognition of the importance of tryptophan in animal and human nutrition and the discovery of the plant harmones served to bring about a renaissance in indole chemistry and therefore, indole derivatives have been synthesized and isolated from nature in abundance. Serotonin **2** is one of the key neurotransmitters in animals (anticholinesterase-monoamine oxidase inhibitor), Reserpine **3** is used to lower blood pressure and reduce the heart rate and used as a tranquilizer and sedative. Other some examples of bioactive indole alkaloids Mytamycin **4** and its analogues are gaining much important because of their extensive use in cancer chemotherapy and strong antibacterial activities. Indole-3-acetic acid **5** a naturally plant growth hormone, indole acetic acid known as hetroauxin is another important derivatrive of Indole.

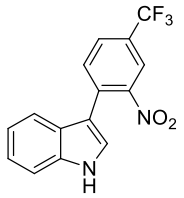


❖ Natural products containing Indole moiety which are used as Active natural molecules which are a pharmaceutical substances.

INDOLE LITERATURE REVIEW

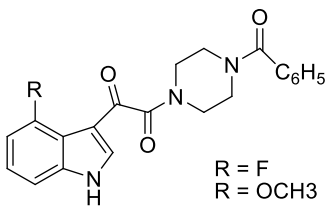
Literature survey reveals that there are various molecules containing indole moiety synthesized and evaluated for their biological activities.

Hiari *et al* [41] reported the synthesis and antibacterial activity of some substituted 3-(aryl) and 3-(heteroaryl) indoles. The most active compound was reported to be 3-(4-trifiuoromethyl 2- nitrophedyl). Indole **1** exhibiting MIC = 7 µg/cm^{3}against *Escherichia soli* and *Staphylococcus aureus*.



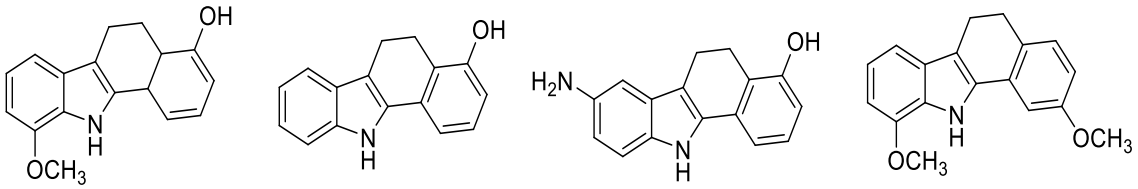
1

Tao Wanga *et al* .[42] have synthesized, 4-fluoro- and 4-methoxy-1-(4-ben zoyl piperazin-1-yl)-2-(1*H*-indol-3-yl) ethane-1, 2-dione **2** and **3**, respectively have been characterized as potent inhibitors of HIV-1.



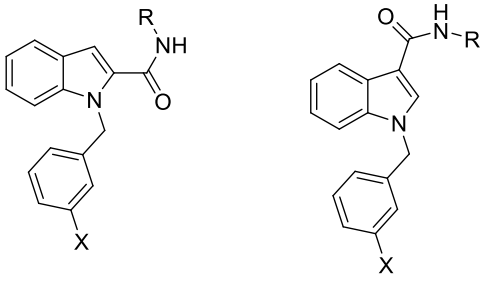
2, 3

Hong *et al.*[43] have synthesized of series of various tricyclic and tetracyclic Indoles and were evaluated for their anticancer activity where the compounds **4**, **5**, **6** and **7** were found to exhibit highest *in vitro* activity against human nasopharyngeal carcinoma (HONE-I) and gastric adenocarcinoma (NUGC-3) cell lines.



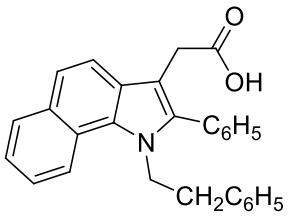
4 **5** **6** **7**

Enien *et al* [44] synthesized and biologically evaluated a series of indole derivatives and found that Indole-2 and 3, carboxamides were having antioxidant properties. (**8a** and **8b)**



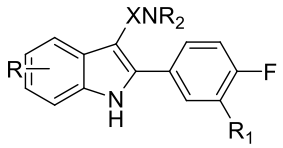
8a **8b**

Kalaskar *et al* [45] have synthesized indole-3-acetic acids **09** and evaluated them for their in vivo anti-inflammatory activity.



09

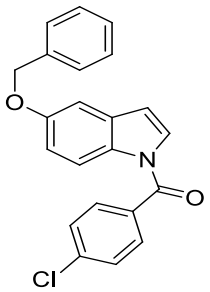
Joshi and co-workers[46] reported the synthesis and CNS activity of some fluorine containing 3- indolyl tryptamines **10**.



X= CH2CH2 R= 5-F OR 6-F
R1= H,F R2= CH3,C2H5

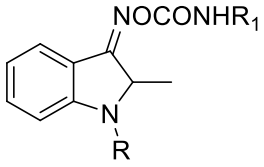
10

Li *et al* [47] describes that some of the indole derivatives are insulin sensitizing and glucose lowering effects. The Indole derivative **11** showed increase in activity of PPARr agents, which shows decreased serum glucose and contributing to antidiabetic activity.



11

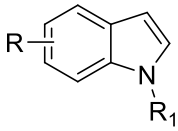
Abele *et al*[48] describes the synthesis of indole oxime, carbamoyl derivative of indole-3-oxime **12**, exhibited the most potent antiviral activity among the isatin and indole oximes.



R = H,methyl,ethyl
R1= methyl,phenyl

12

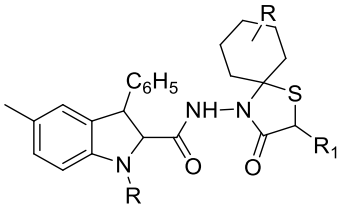
Jing-Ping Liou *et al*[49] describes synthesis of a novel series of 4- and 5-aroylindole derivatives **13** and evaluated them for antitumor activity. Several compounds of this series showed excellent antiproliferative activity as inhibitors of tubulin polymerization.



R = 4-(3,'4',5' trimethoxybenzoyl
5-(3,'4',5' trimethoxybenzoyl
R1= H,CH_3,C_2H_5,CH_2OHI

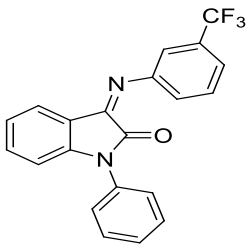
13

Ozlen Guzel, *et al* [50] synthesized a series of new 5-methyl-N-(3-oxo-1-thia-4-azaspiro[4.5]sdec-4-yl)-3-phenyl-1*H*-indole-2-carboxamide derivatives. **14, 15** compounds were evaluated for *in vitro* antituberculosis activity against *M.tuberculosis* H37Rv. Some of compounds were found to provide the highest (90%) inhibition of mycobacterial growth in the primary screen conducted at 6.25 µg/ml.



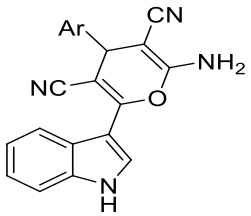
14, 15

Konkel *et al* [51] synthesized a series of 3arylimino- 2-indolones and the compounds were reported to be as Galanine GAL_3 receptor antagonists. The compound **16** was found to be most potent antagonist with Kb = 29Nm



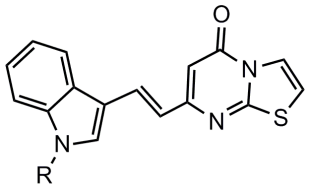
16

Neelakandan Vidhya Lakshmi *et al* [52] newly synthesized 3-pyranyl indoles **17** were evaluated for anti-microbial, antioxidant, and anticancer activities. Some of the compounds are showed good anticancer activity against MCF-7 breast cancer cell lines on comparison with of standards drugs.



17

Babasaheb zine *et al* [53] newly synthesized N- substituted indolyl thiazolo pyrimidinones **18,** all the synthesized compounds displayed almost comparable antifungal and antibacterial properties in different cultures on comparison with of standards drugs.



18

CONCLUSION

The literature survey indicates that, Indole have pivotal role in the medicinal chemistry, as most of the essential drugs are having these heterocycles in their compositions. It has been also observed that the clinically used some of the heterocycles are accompanying with severe side effects and the synthetic paths employed for them are tedious, non-economic and less ecofriendly. It is also revealed that still there is ample scope in the process development of existing heterocyclic drugs and towards the synthesis of new heterocycles.

REFERENCES

1. Baeyer A., Knop C. *A. Ber., 140*, 1, **1866**.
2. Baeyer A., Emmerling *A. Ber., 2*, 679, **1869**.
3. Elze F. *Chem. Ztg., 34*, 814, **1910**.
4. Cerighelli R. *Compt. Rend.*, *179*, 1193, **1924**.
5. Hesse A., Zeitschel O. *J. Prakt. Chem.*, *66*, 481, **1924**.
6. Soden H. V. *J. Prakt. Chem., 69*, 256, **1904**.
7. Sack J. *Pharm. Weekblad, 48*, 307, **1911**.
8. Porcher C. *Compt. Rend., 147*, 214, **1908**.
9. Nencki M. *Ber., 7*, 1593, **1874**.
10. Stockly F. *J. Prakt. Chem., 24*, 17, **1881**.
11. Ernst C. *Physiol. Chem., 16*, 208, **1892**.
12. Weissberger R. *Ber., 43*, 3520, **1910**
13. Boes. *J. Pharm. Ztg., 47*, 131, **1902**.
14. Flower R. J., Moncada S., Vane J.R. Goodman and Gilman's *The Pharmacological Basis of Therapeutics, seventh ed*. *695*, **1985**.
15. Misra U., Hitkari A., Saxena A.K., Gurtu S., Shanker K., *Eur. J. Med. Chem*. *31* 629-634, **1996**.
16. Andreani A. M., Rambaldi A., Locatelli G., Pifferi, *Eur. J. Med. Chem. 29* 903-906, **1994**.
17. Ebeid M.Y., Lashine S.M., El-Ad S.M., Abou K.M.I., Zagazig, *J. Pharm. Sci. 3* , 40-48, **1994**.
18. Rani P.,Srivastava V.K., Kumar A. *Eur. J. Med. Chem. 39*, 449-452, **2004**.
19. Dubey P.K., Venkateshwar Kumar T., Raddanna P., Anil Kumar K. *Indian J. Chem. 45B*, 2128-2132, **2006**.
20. Agarwal R., Agarwal C., Singh C., Misra V.S., *J. Chem. Soc. Pak. 6*, 89, **1984**.
21. Verma M., Tripathi M., Saxena A.K., Shanker K., *Eur. J. Med. Chem. 29*, 941-946, **1994**.
22. Kumar A., Saxena A.K., Shanker K. *Pharmazie 43*, 45-46, **1998**.
23. Inion H., De Vogelaer H., Descamps M., Bauthier J., Colot M., Richard J., Charlier R. *Chem. Abstr. 88*, 601, **1978**.

24. Mohamed Radwan A. A., Ragab E. A., Sabry N. M., Shenaw Ely S. M., *Bioorg. Med. Chem.,15*, 3832-3841, **2007**.
25. Zheng M.kF., Zheng M., Deng D.Y., Oils S., Luo X., Chen K., Liu H., Jiang H. *Bioorg. Med. Chem. Lett. 17*, 2414-2420, **2007**.
26. Sharma P., Kumar A., Pandey P. *Indian J. Chem. 45B*, 2077-2082, **2006**.
27. Panwar R.S., Verma H., Srivastava V.K., Kumar A. *Ind.J. Chem*., 2099-2104, **2006**.
28. Bhusare S.R., Shinde A.B., Pawar R.P., Vibhute Y.B. *Ind. J. Pharm. Sci. 3*, 228-231, **2004**.
29. Dandia A., Sehgal V., Singh P. *Ind. J. Chem. 32 B,* 1288-1291, **1993**.
30. Holla B.S., Udupa K.V. *J. Ind. Chem. Soc. 65 (7)*, 524, **1988**.
31. Archna Rani P., Bajaj K., Chandra R., Kumar A., *Arzneim.-Forsch./Drug Res.* 301-306, **2003**.
32. Archna Rani P., Srivastava V.K, Kumar A. *Indian J. Pharm. Sci. 65 (4)* 356-362, **2003**.
33. Bajji A.C., Channabasavaraj K.P., Swamy K.M.K. *Indian Drugs 31 (6)*, 269-272, **1994**.
34. El-Gendy Adel A., Abdou Naida A., El-Taber Z.S., El-Banna Hosny A., Alexandria *J. Pharm. Sci. 7*, 99-103, **1997**.
35. Kumar A., Saxena K.K., Gurtu S., Sinha J.N., Shanker K. *Indian Drugs 24*, 1-5, **1986**.
36. Bru-Magniez N., Guenger T., Tenton J.M., (Laboratories UPSA. Fr.) U.S.U 5,480,983 (Cl. 536-27, 62; C07H19/167), 2 Jan 1996, FR Appl. 92/ 138, 8 Jan 1992; 30 pp. Cont-in- part of U.S. 5,229,505 (Eng.) *Chem. Abstr. 124* (17) **1996**.
37. Kuethe J.T., Wong A., Smitrovich C., Qu, J., Davies I.W., Hughes D.L. *J. Org. Chem.,70*, 2555-2567, **2005**.
38. Van Zandt M.C., Jones M.L.,Gunn D.E., Geraci L.S., Jones J.H., Sawicki D.R., Sredy J., Jacot J.L., Dicioccio A.T., Petrova T., Mitschler A., Podjarny A.D. *J. Med. Chem.,48*, 3141–3152, **2005**.
39. Li J.J., Gribble G.W., Baldwin J., Williams (Eds.) R.M. *Heterocyclic Chemistry, 20, 73*-181, **2000**.
40. Glennon R.A. *J. Med. Chem., 30*, 1-12, **1987**.
41. Hiari Y. M. A., Qaisi. A. M., Abadelah M. M., Voelter W., *Monatshefte. Fur Chemie, 137*, 243, **2006**.
42. Tao Wanga, John F. Kadow, Zhongxing Zhang, Zhiwei Yin, Qi Gao, Dedong Wub, Dawn DiGiugno Parker, Zheng Yang, Lisa Zadjura, Brett A. Robinson, Yi-Fei Gong, Wade S. Blair, Pei-Yong Shi, Gregory Yamanaka, Pin-Fang Lin ,Nicholas A. Meanwell *Bioorg. Med. Chem. Lett. 19*, 5140-5145, **2009.**
43. Hong B. C., Jiang Y., Chang Y., Lee S. *J Chin Chem Soc., 53*, 647, **2006.**
44. Enein H. Y. A., Kruk I., Lichszteld K., Michalska T., Kiadna A., Marczynski *S.,* Olgen *S. Luminescence, 19,* 1, **2004**.
45. Kalaskar G. P., Girisha, M., Purohit M. G., Thippeswamy B. S., Patil B. M. *Indian J. Heterocycl. Chem.,16*,325, **2007**.
46. Joshi K.C., Pathak V.N & Chand P., Agric. *Bioi.Chem 42(9),* 1723, **1978** *Chem.Abstr. 90*.22729, **1979**
47. Li Y. Y., Wu H. S., Tang L., Feng C. R., Yu H.Y., Yang, Y. *S.,* Yang B. J *Pharmacol Res, 56*,335, **2007.**
48. Abele E., Abele R., Dzenitis O., Lukevics E. *Chem. Heterocycl. Compd., 39, 3*, **2003.**
49. Jing-Ping Liou, Chang-Ying Wu, Hsing-Pang Hsieh, Chi-Yen Chang, Chi-Ming Chen, Ching-Chuan Kuo, and Jang-Yang Chang *J. Med. Chem., 50 (18)*, 4548-4552, **2007.**
50. Ozlen Guzel, Nalan Terziog Lu, Gultaze Capan, and Aydi Salman *ARKIVOC (xii)* 98-110, **2006**.
51. Konkel M. J.,Lagu B., Boteju L.W., Jimenez H., Noble S., Walker M.W., Koirnberg B. E., Gregory T., Pugsley T.A., Zoski K., Wise L.D*J. Med. Chem.,49*,3757, **2006**.
52. Neelakandan V. L., Prakasam T., Noorulla K.M. **2010**.

53. Zine B., Jadhav S., Dixit P., Farooqui M., *J. of Ultrachem.,* Vol. 13(2), 30-34, **2017.**