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"Project report on Indole - Its synthesis and Pharmacological Applications"

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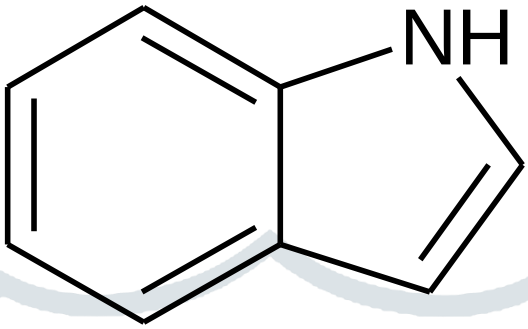
Abstract:
Various bioactive aromatic compounds containing the indole nucleus showedclinical and biological applications. Indole scaffold has been found in many of the important synthetic drug molecules which gave a valuable idea for treatment and binds with high affinity to the multiple receptors helpful in developing new useful derivatives. Indole derivatives possess various biologicalactivities, i.e., antiviral, anti-inflammatory, anticancer, anti-HIV, antioxidant, antimicrobial, antitubercular, antidiabetic, antimalarial, anticholinesterase activities, etc. The indole nucleus is an important heterocyclic compound containing nitrogen, and it has been a source of vital therapeutic agents. This review highlighted recent achievements of indole lead molecules in biological, chemical, and pharmacological activity having diverse perspectives on the various biological activities of indole. The presence of carboxamide moiety in indole derivatives causes hydrogen bonds with a variety of enzymes and proteins, which in many cases, inhibits their activity. In this review, synthetic strategies of indole 2 and 3-carboxamide derivatives, the type, and mode of interaction of these derivatives against HLGP, HIV-1, renin enzyme, and structure activity studies of these compounds were investigated. It is hoped that indole scafolds will be tested in the future for maximum activity in pharmacological compounds.

Keywords:
Indole, antiviral, anti-inflammatory, anticancer, anti-HIV, antioxidant, antimicrobial, antitubercular, antidiabetic, antimalarial, anticonvulsant.

Introduction:
Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. The name indole is 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 Indole is a notable privileged lead scaffold that arises inseveral natural products such as alkaloids, peptides, and various synthetic compounds. Indole and its derivatives have been employed as an exclusive platform in heterocyclic chemistry containing a nitrogen atom. it is an aromatic heterocyclic organic compound having a formula of C8H7N in which a bicyclic structure

comprised of a benzene skeleton is merged with pyrole moiety with derivatives possess various biological applications in medicinal chemistry 1, 2. Indole is a hetero-atomic planar lead molecule. The name indole is 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. Indole is a benzopyrrole in which the benzene and pyrrole rings are fused through the 2- and 3-positions of the pyrrole nucleus. The indole ring is also found in many natural products such as the indole alkaloids, fungal metabolites and marine natural products.



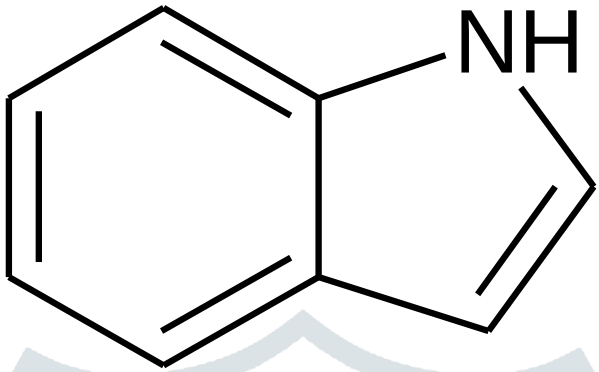
INDOLE

IUPAC name	Indole
Other names	2,3-Benzopyrrole, ketole,1-benzazole
Molecular formula	C_8H_7N
Molar mass	117.15 g/mol
Appearance	White solid
Density	1.22 g/cm^3, solid
Melting point	52 - 54°C (326 K)
Boiling point	253 - 254°C (526 K)
Solubility in water	0.19 g/100 ml (20 °C) Soluble in hot water
Acidity (p*K*a)	16.2 (21.0 in DMSO)
Basicity (p*K*b)	17.6
Molecular shape	Planar
Dipole moment	2.11 D in benzene

Chemical Synthesis of the Indole Ring:

Conventional synthesis of the indole nucleus by various methods have beenreported in the literature. It involves a number of starting materials and different strategies as: Mori indole synthesis, Buchwald indole synthesis, Sundberg indole synthesis, Hemetsberger indole synthesis, Kanematsu indole synthesis, Van Leusen indole synthesis, Nenitzescu indole synthesis, Modeling indole synthesis, and Fischser indole synthesis. Pharmacological Evaluation of Indole Compounds: Due to the universal nature of indole

derivatives, it has gained vast recognition among the organic and medicinal chemists. Many leaddrug molecules containing indole moiety are found to be under investigation and research to control various disease conditions such as bacterial, malaria, fungal, viral, tubercular, and HIV infections. [1-9]



Synthesis of Indole:

1. Fischer Indole Synthesis:

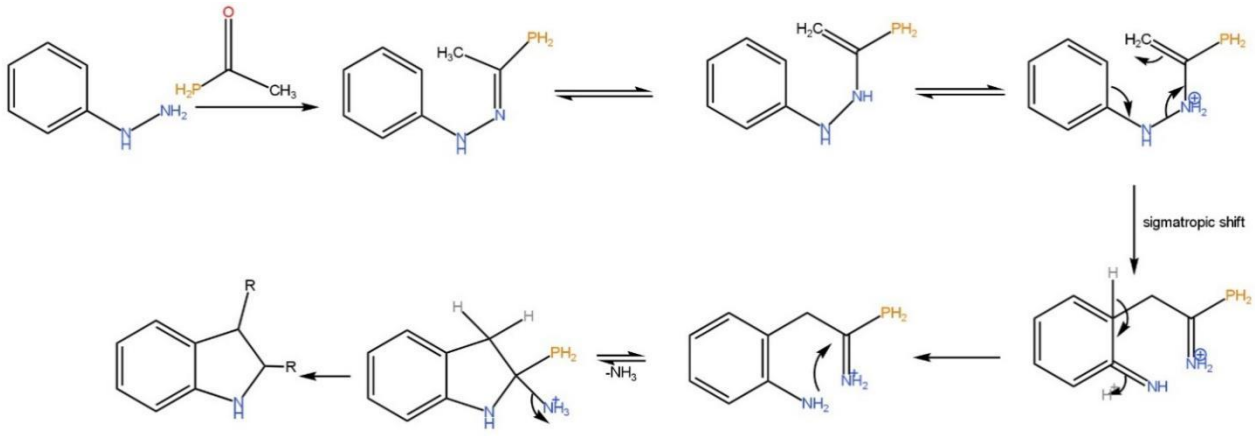
➢ This reaction was discovered in 1983 by Emil Fischer and so far remained the most extensivelyused method of preparation of indoles.

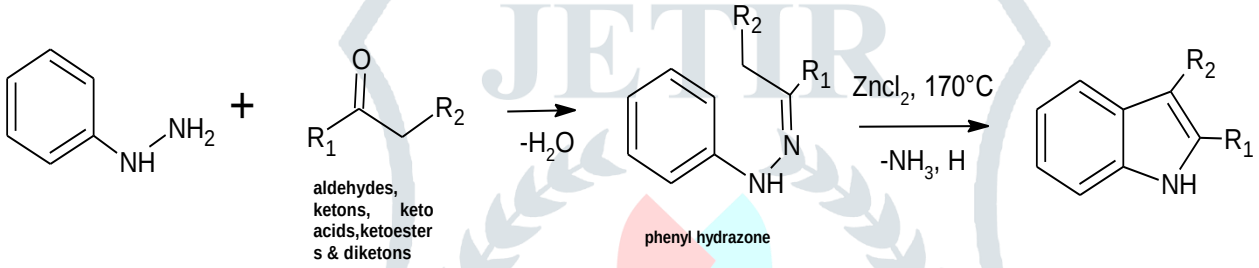
➢ The synthesis involves cyclization of arylhydrazones under heating conditions in presence ofprotic acid or lewis acids such as ZnCl2, PCl3, FeCl3, TsOH, HCl, H2SO4, PPA etc.

➢ The starting material arylhydrazoles can be obtained from aldehydes, ketones, keto acids,keto esters and diketones etc.

➢ Reaction produces 2,3-disubtituted products. Unsymmetrical ketones can give a mixture ofindoles.[19]

Mechanism :





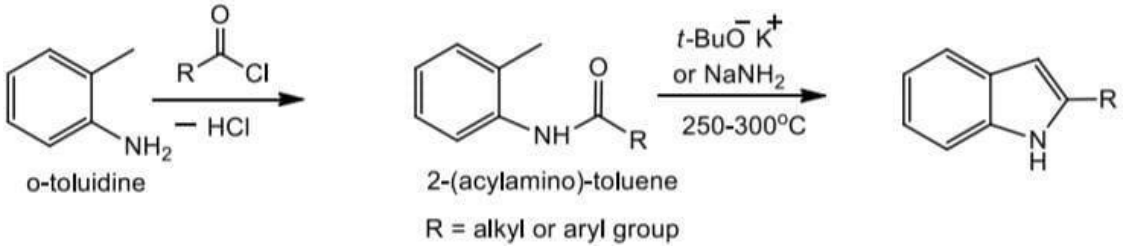
2. **Madelung Synthesis**:

➢ Base catalyzed cyclization of 2-(acylamino)-toluenes under very harsh conditions (typically sodium amide or potassium t-butoxide at 250-300oC

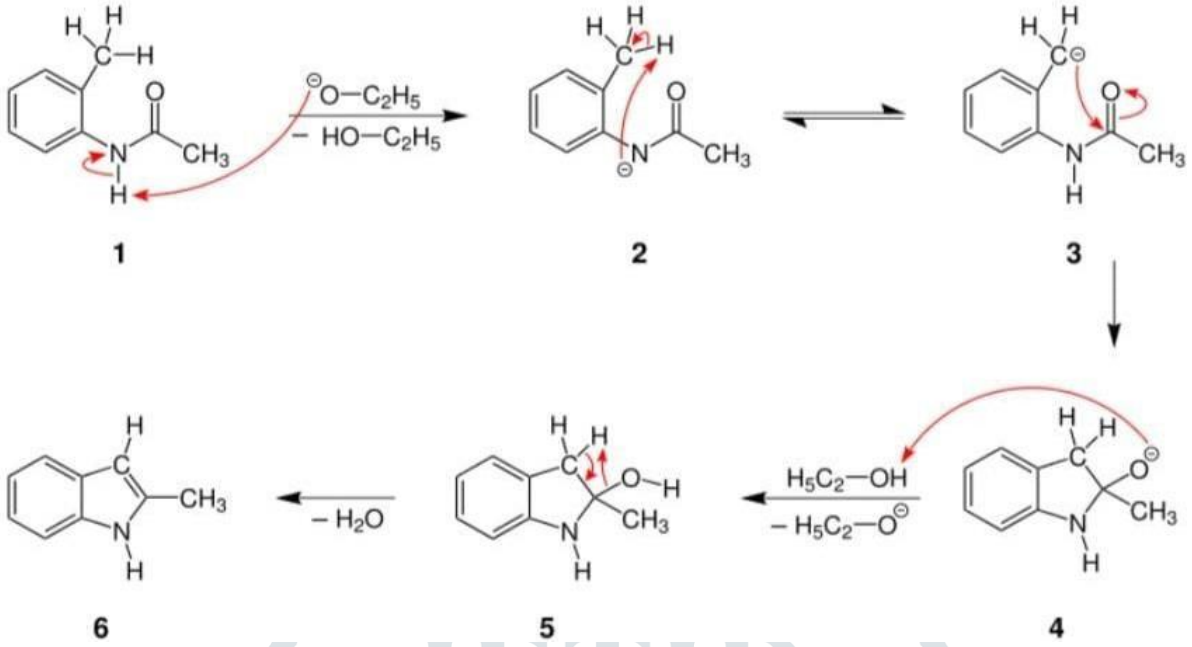
➢ Limited to the synthesis of simple indoles such as 2-methyl indoles without having any sensitive groups.

➢ A modern variant of madelung reaction is performed under milder conditions by the use of alkyllithiums as bases.

➢ 2-Substituted indoles bearing sensitive groups can be synthesized using this method[19]



Mechanism:



3. Reissert indole synthesis

Reissert indole synthesis is a multistep reaction:

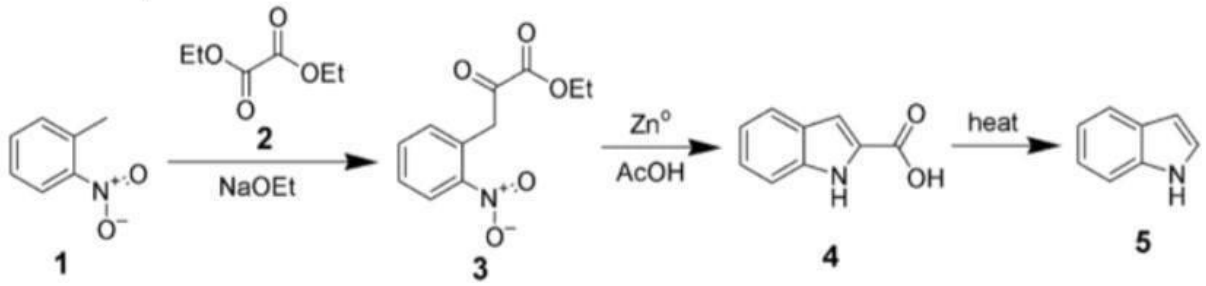
Step1: Base catalysed condensation of o-nitrotoluene with oxalic ester(methyl oxalate) to give o-nitro-phynyl-pyruvic ester

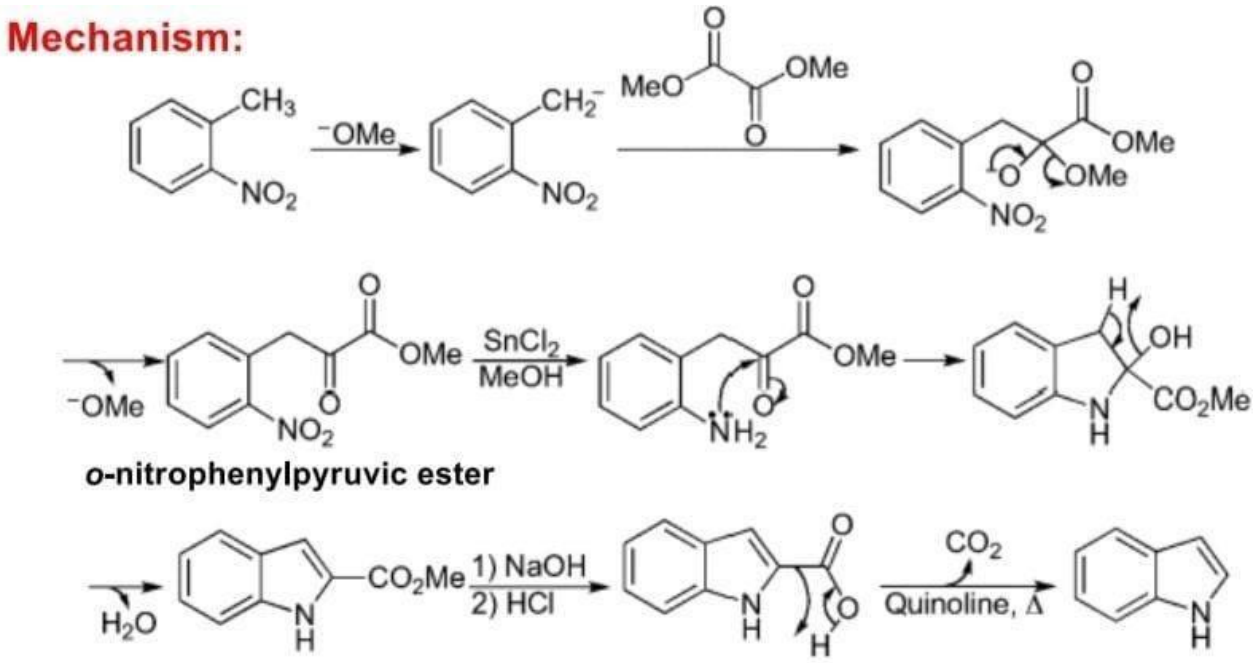
Step2: Reduction of the nitro group to an amino group

Step3: cyclization to indole-2carboxylic acid

Step4: Decarboxylation[20]

Synthesis:



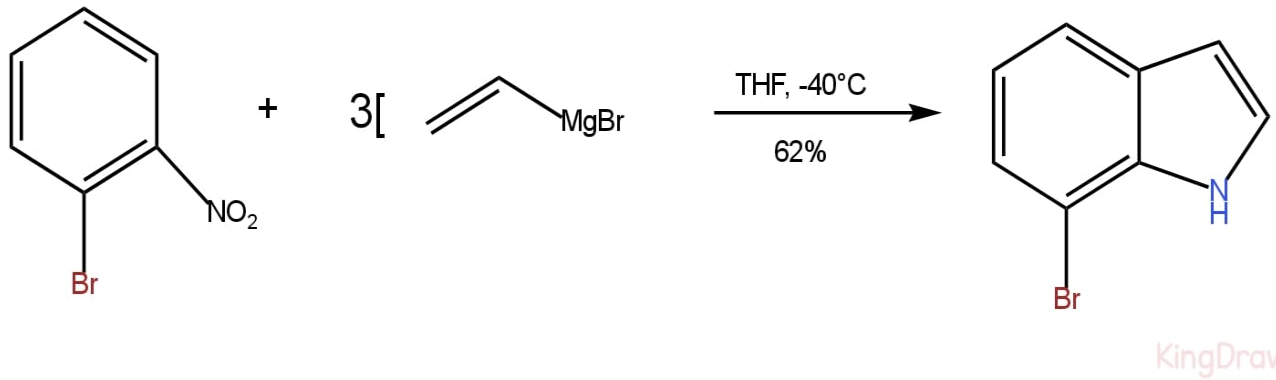


Reissert Indole Synthesis

4. Bartoli Indole Synthesis:

➢ Efficient and extremely practical approach for indole synthesis

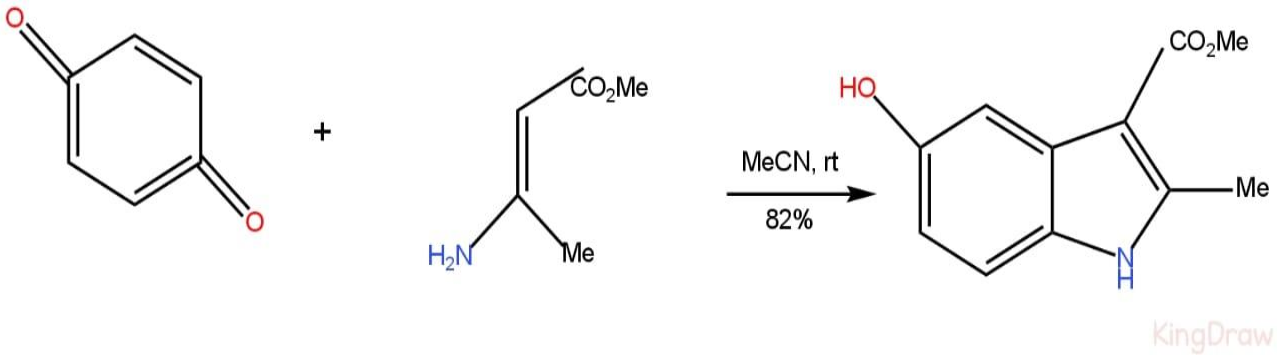
➢ Ortho-substituted nitro-benzenes react with three mole equivalents of vinyl magnesiumbromide (Grignard reagent) to give 7-substituted indoles.[18]



5. Nenitzescu Synthesis:

➢ Reaction provides direct route for the synthesis of 5 hydroxy-indoles.

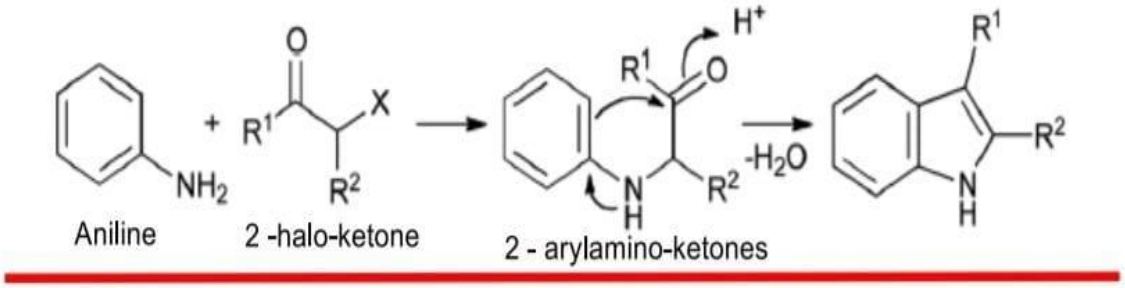
➢ Condensation of substituted 1,4-benzoquinone with a β- amino-substituted -α, βunsaturatedcarbonyl compounds with ring closure to a 5-hydroxyindole[18]

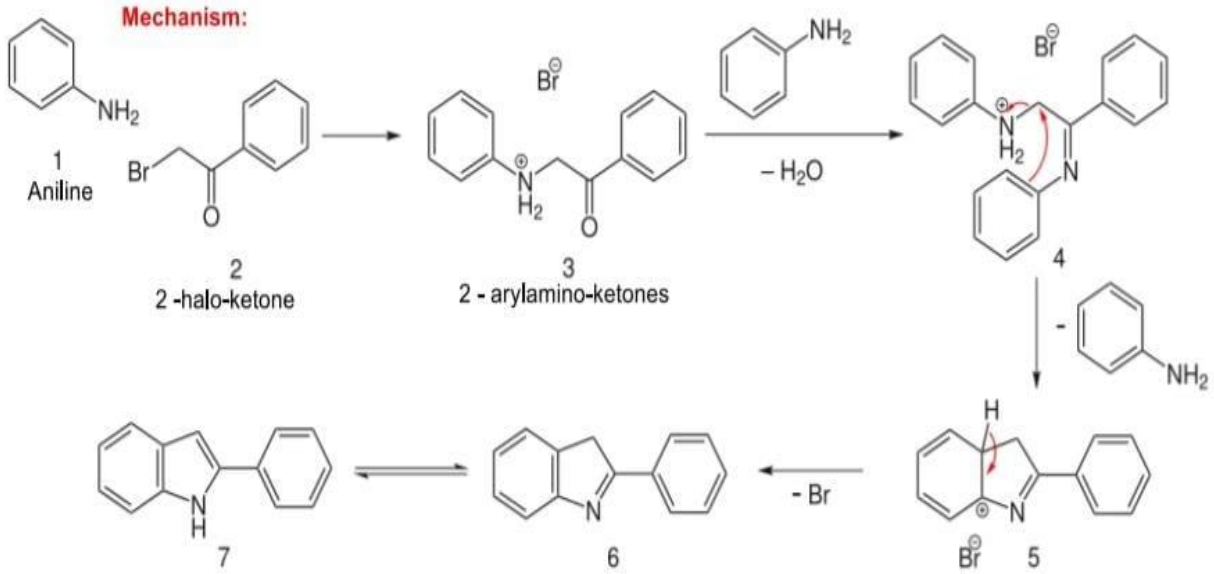


6. Bischler Indole Synthesis:

➢ Reaction involves acidic treatment of 2-arylamino-ketones (produced from a 2–halo-ketone and an arylamine) to bring about electrophilic cyclisation onto the aromatic ring

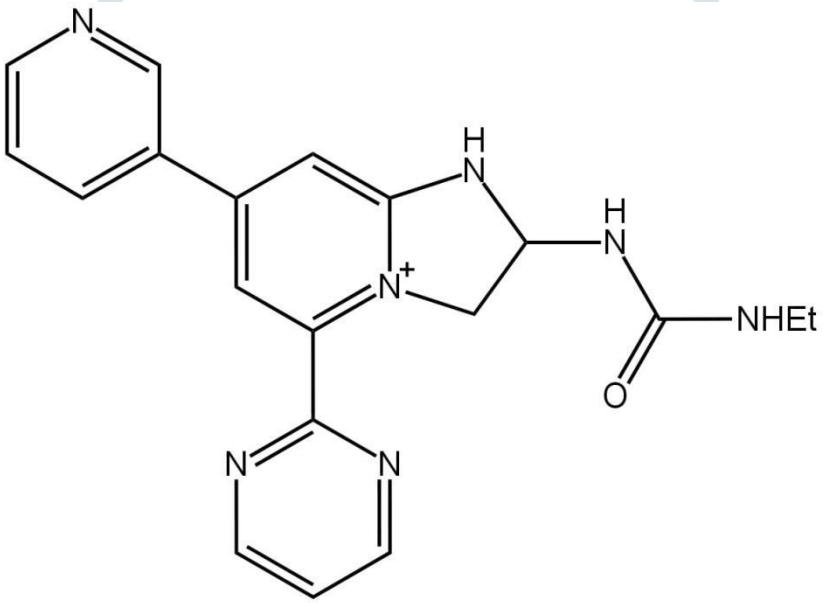
➢ Often result in mixtures of products via rearrangements. By Dr. Divya Kushwaha 3. Reactions of Indole.[21]



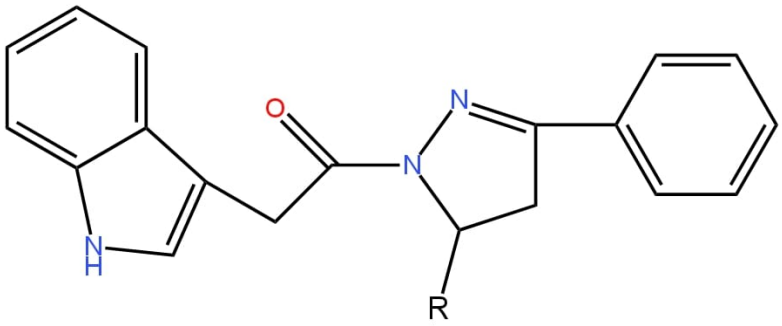


Biological Activities of Indole:

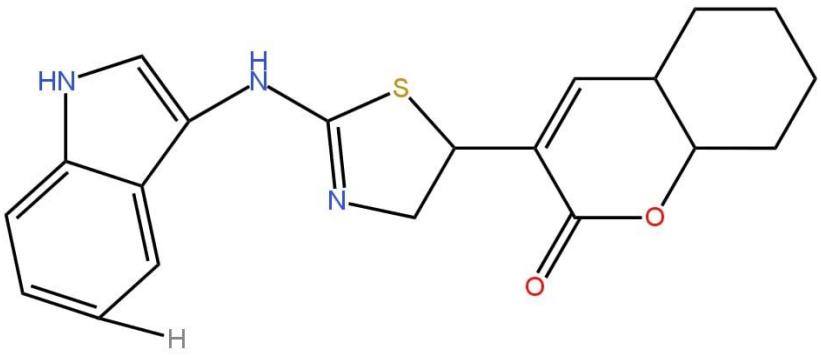
- **Antimicrobial Activity**:
  - In general, antibacterial action of clinically approved drugs and newly reportedmoiety are based on bactericidal or bacteriostatic mode of action. Antibiotic acts either acting directly on bacterial cell wall or enzyme based hacked systems. Bacterial cell wall is composed of complex polysaccharides which is targeted by antibiotics and caused cell wall degradation or fragmentation and thereby causing cytoplasmic content to be oozed or released. This may be a potential mechanism of bacteria death. Another aspect is enzyme mediated ornuclear mechanism. There are several enzymes responsible for a cell physiological normal process. However, bacterial cells are differentiated from mammalian cells in several terms which seek an attention for the drug discovery scientist. This was a basis new drug development such as rifampicin which primarily acts on bacterial mRNA dependent DNA polymerase.[10]



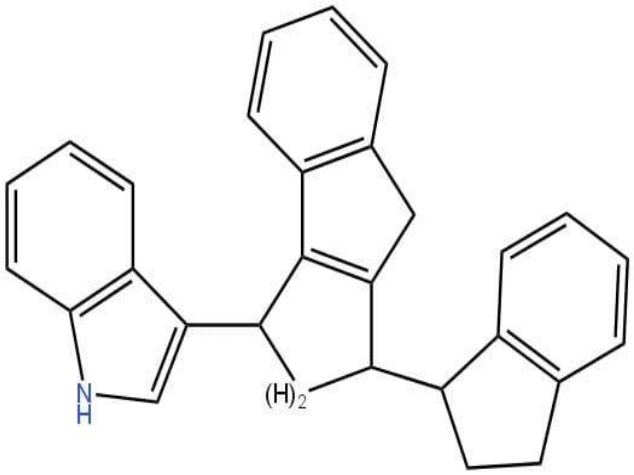
- (zone of inhibition < 0.5 cm) showed good activity against Gram-positive bacteria and compound (zone of inhibition < 0.1 cm), has good activity against fungal strain Macrophominaphaseolina and Sclerotiumrolfsii. A new class of imidazole-based indole moities were prepared and evaluated against bacterial strains S. aureus, S. pyogenes, Shigella flexneri, Proteus mirabilis, Vibrio cholera and on fungalstrains such as Candida albicans, C. glubrate, and C. crusei[24]



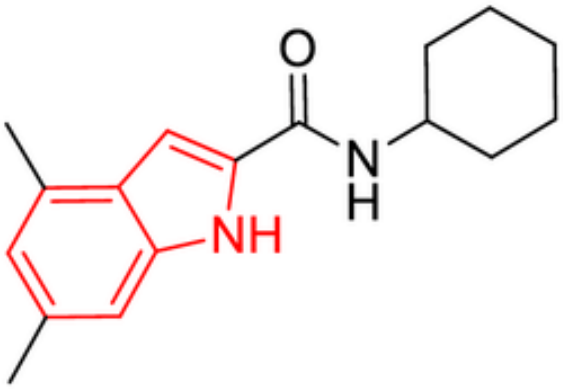
- Gali et al., 2015 investigated the synthesis of thiazolylcoumarins substituted indole derivatives and further evaluated against B. subtilis and E. coli. SAR highlighted that the occurrence of unsubstituted thiazolyl coumarins was favorable for the evaluation. Compound (11) (zone inhibition < 18 mm) was initiate highly potent as compared to reference drug streptomycin (zone of inhibition < 30 mm)[23]

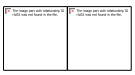


- El-Sayed, et al., 2015, bisindolyl-substituted cycloalkane-anneallated indoles as a new series of antibacterial activity. The new active derivatives (14) was containing cyclohexane indole moiety when evaluated against S. aureus and MRSA (methicillin resistance S. aureus) 72. Choppara, et al., 2015, synthesized two classes of new analogues bis (indole) and selected for their antimicrobial, antitumor activities, and the SAR. Compound (15) N (-((5-bromo-1H-indol-3-yl) methylene)-2-(1H-indol-3-yl) acetohydrazide) was establish to be active potent.[22]

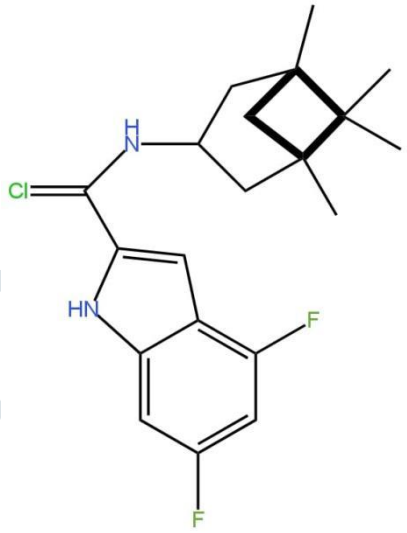


- **Anti-tubercular Activity:**
- Tuberculosis is global and deadly air borne infectious disease caused by Mycobacterium tuberculosis affecting lungs as well as other parts of the bodyeach derivative.[11]

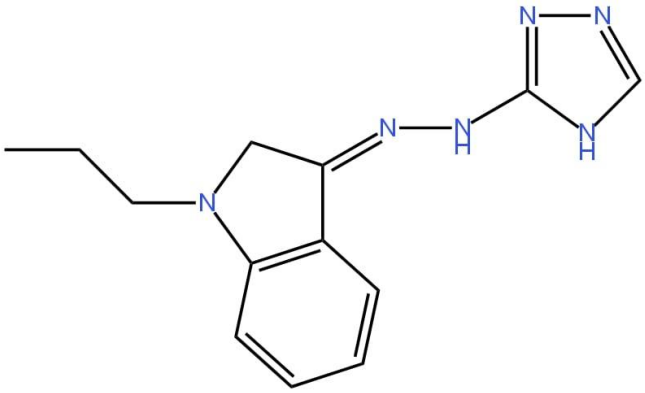




- Lipophilic compounds exhibited higher activity compared to hydrophilic derivatives. The compound was of potential activity (MIC = 0.012 μM) against multidrug-resistant and extensively drug-resistant M. tuberculosis strains. Apart from this, docking studies were also conducted, showing the maximum binding of 21 (MIC = 0.29 μM) with MmpL3 protein[25]

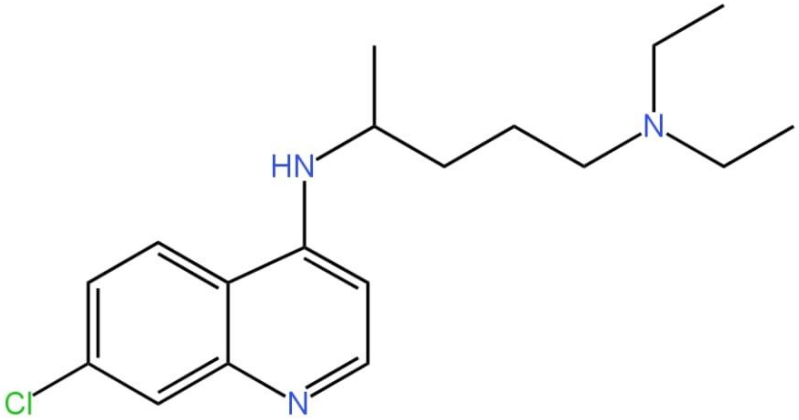


- Tehrania and colleagues synthesized and evaluated various Schiff' based based indole derivatives. All the synthesized compounds are further evaluated using a microtitre plate on the Gram-positive and Gram-negative strain. SAR studies concluded that urea-based derivatives were highly potent. Compounds (MIC = 3.91 μg/mL) exhibited maximum potency as compared with standard drug ethambutol (MIC = 0.75 μg/mL)[26]

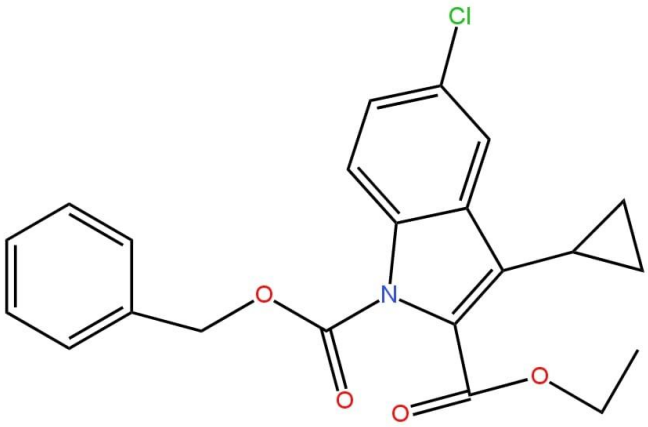


➢ Anti-malarial Activity:

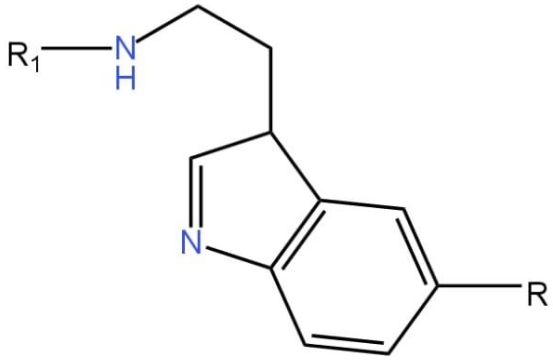
- Malaria is the most infectious ailment infected by Plasmodium parasite. They synthesized derivatives having an inhibitory effect on the cell cycle of P. falciparum. The in-vitro studies were conducted in P. falciparum culture, and a flow cytometer was used for activity calculation.[12]



➢ SAR studies explained that alkyl substitution with carboxylate at 1st and 2nd position and aryl at the 3rdposition of indole was favorable for the activity. Compounds (27) showed high potency, having MIC value not more than 0.70 µg/mL on comparing to the standard drugs quinine (MIC = 0.270 µg/mL) and chloroquine (MIC = 0.02 µg/mL).[27]

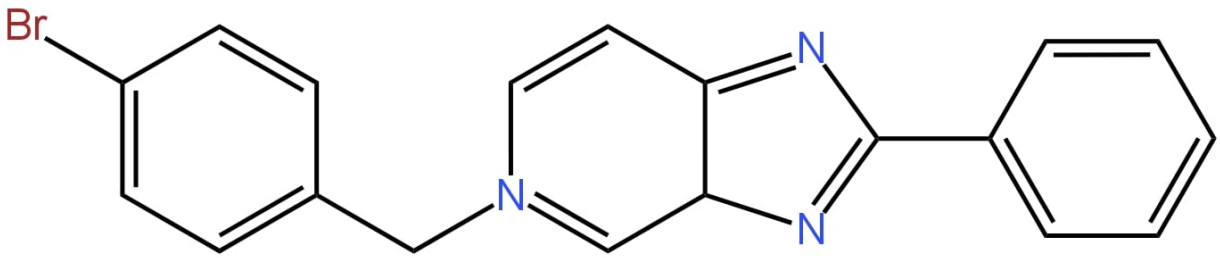


➢ The in-vitro studies were conducted in P. falciparum culture, and a flow cytometer was used for activity calculation. SAR studies explained that carbo-xamide at the C-3 position of indole was decisive for the activity. Compounds (29) (IC50 = 2.93 µM) exhibited maximum antimalarial activity. Alkyl and aryl substitution with carboxamide at the C-3 and methoxy group the C-5 gave maximum potency. Amongst the entire major heterocyclic nucleus, quinoline derivatives are the well known antimalarial agents acting through the inhibition of DNA synthesis of microorganism.[28]



➢ Antiviral Activity:

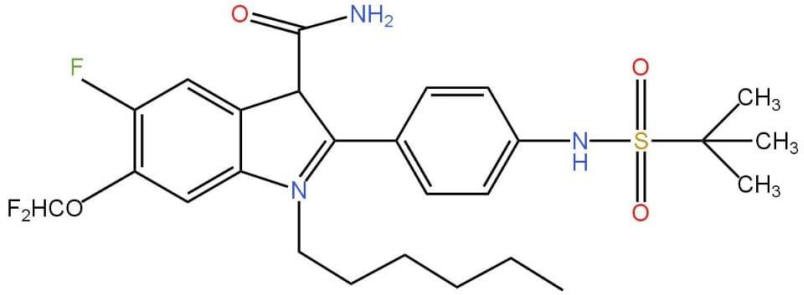
➢ A viral infection spreads by pathogenic viruses and infectious virus particles when enters inside the body. Various antiviral drugs are available in the marketagainst HIV, Herpes viruses, hepatitis B and C viruses.[13-14]



➢ Hepatitis C Virus Activity:

Various indole derivatives are used in treatment of Hepatitis C

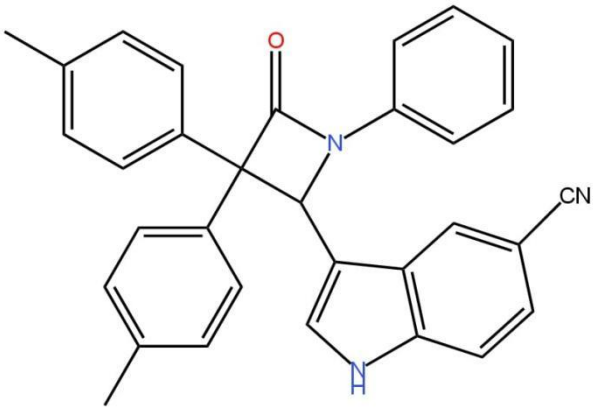
➢ Zhang et al., 2005 reported and prepared a new series of 2-(4 sulfonamidophenyl) -indole 3-carboxamides derivatives and evaluated against the HCV genotype 1b replicon. Compound (51) 6(difluoromethoxy)-2-(4-(1,1-dimethyl ethyl sulfonamido) phenyl)-5-fluoro-1-hexyl-1H-indole-3-carboxamide exhibit good potency[29]



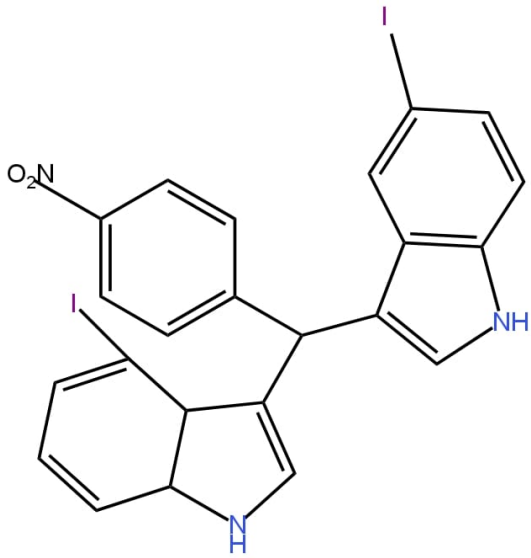
➢ Anti-leishmanial Agents:

➢ Leishmaniasis is a parasitic disease spread by female sand-fly belonging to genus Leishmania, which can appear in the visceral, cutaneous, diffuse and mucocutaneous form.[15]

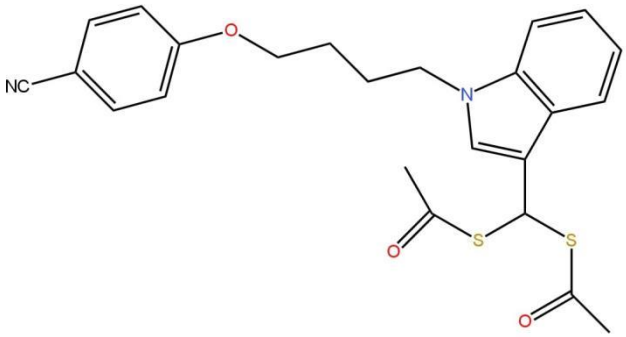
➢ SAR studies concluded that methyl substitution to the imine attached to the indole enhanced the activity. Conversion of imine intoazetidin-2-one resulted in a drastic increase in the activity. (0.56 ± 0.06 µg/mL) was found to be highly potent as compared with standard drug amphotericin B amongst them (0.56± 0.001 µg/mL)[30]



- SAR studies concluded that 4-nitroaryl substitution was favorable for the activity. (IC50 < 8.37 μM) was found to be highly potent as compared with pentamidine (IC50 <8.39 μM) and amphotericin B (IC50 < 0.17 μM) 133. Leishmania cysteine protease is essential for the growth, differentiation, and multiplication of parasite. Azetidine derivatives are one of the prominent inhibitors of this enzyme. Based on this fact, Singh et al., synthesized and evaluated azetidine-indole derivatives and screened them through an in-vitro study using Leishmania major promastigotes.[31]

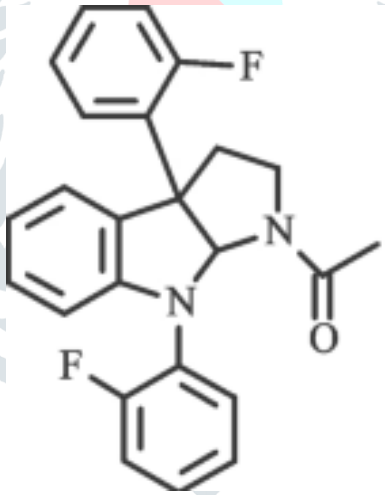


- All the new derivatives were evaluated through in-vivo study against Leishmania donovani. SAR report showed that the presence of H2S at the C-3 and p-cyanophenoxy, N-phenyl, pentyl chain at nitrogen atom and dimethyl-sulphoxide at 3rdposition of indole was most important for the activity. (% inhibition = 96-99 %) showed maximum activity 130. Felix et al., 2016, also reported the synthesis of thiophene-indole hybrids and evaluation against L. donovani. SAR study concluded the role of 5-cyano,5-methyl were found to be favorable for the activity[32]

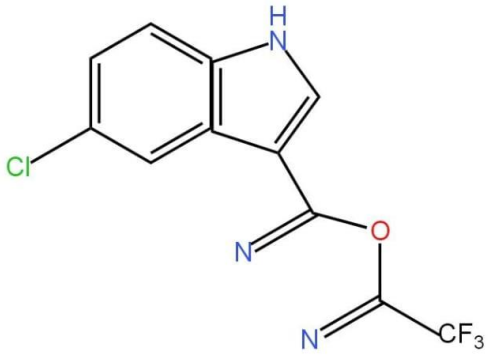


➢ Anti-fungal Activity:

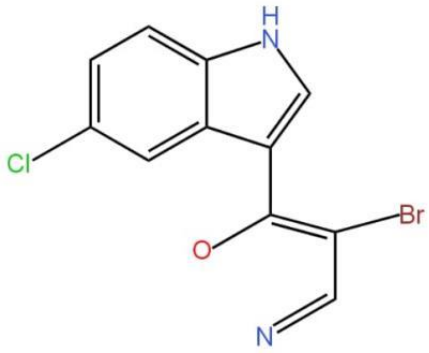
➢ The introduction of chloro and bromo substitution at the 4th position of oxazole ring increases the activity. Compounds were found to be highly potent analogues showing 81-100% control of the disease. Similarly, novel derivatives of streptochlorine were synthesized with more active heterocycles having improved antifungal activity Compounds were establishing highly potent. 1H-Indole-4, 7-diones were reported and evaluated for in-vitro antifungal activity. The analogue 1Hindole-4, 7-diones generally exhibit good antifungal activity against Candida krusei, Cryptococcus neoformans, and Aspergillus niger. The results commented that 1H-indole-4, 7-diones would be better potent antifungal activity..[16]



➢ The introduction of chloro and bromo substitution at the 4th position of oxazole ring increases the activity. It were found to be highly potent analogues showing 81-100% control of the disease, Similarly, novel derivatives of were synthesized with more active heterocycles having improved antifungal activity. All analogues were studied against Pythium dissimile, Alternariasolani, Uromycesviciae-fabae, Gibberellazeae, Alternariasolani, Phytophth-orainfestans, Zymoseptoriatritici. The compound was found to be highly potent on Alternaria solani.[33]



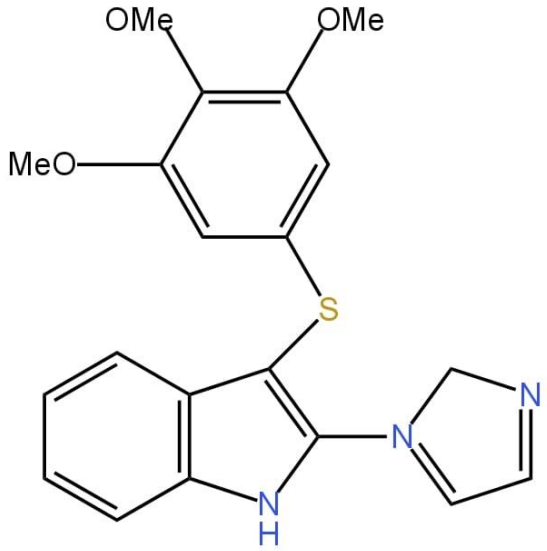
- All the newly prepared compounds were tested against Pythium dissimile, Septoriatritici and Uromyces viciaefabae and compared with pimpirine alkaloid. SAR study concluded that halogen substitution is favorable for the activity. it were found to be potent Motivated by the promising results, this study was further extended with streptochlor in an indole alkaloid obtained from marine actinomycetes. Synthesized streptochlor in analogs were evaluated against Pythium dissimile, Alternaria-solani, Uromycesviciaefabae, Gibberel-lazeae, Alternariasolani, Phyto-phthorainfestans, Zymo-septoriatritici and A. Solani



Anti-cancer activity:

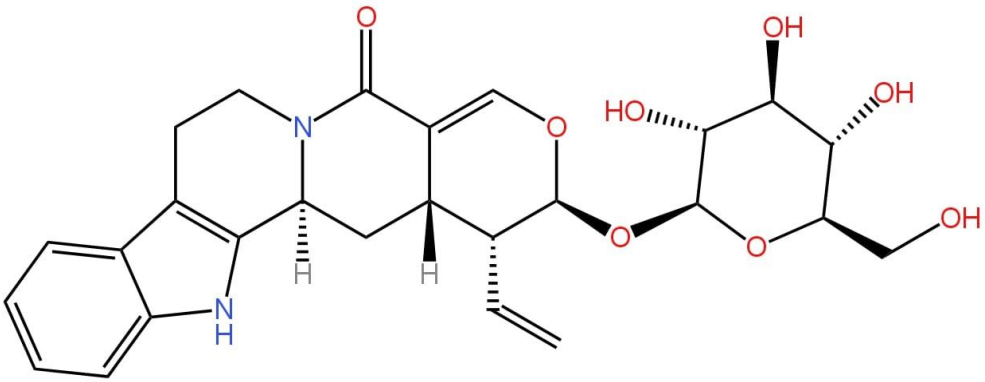
Cancer is a disease caused by the abnormal growth of cell leading to disturbance to other parts of the body, it is one of the most dangerous health problems nowadays. The number of death from AIDS, malaria and tuberculosis combined is far less than people dying due to cancer. The indole and its analogs have exhibited broad spectrum of anticancer activity. The available anticancer drugs in market have suffering from some limitations; therefore, the development of new drugs is essential for the society.

They revealed that compound 48 exhibited significant anticancer activities at various cell lines of CNS cancer, non small cell lung cancer (NSCLC), ovarian cancer, colon cancer, renal cancer (95 % inhibition of TK-10) and breast cancer.



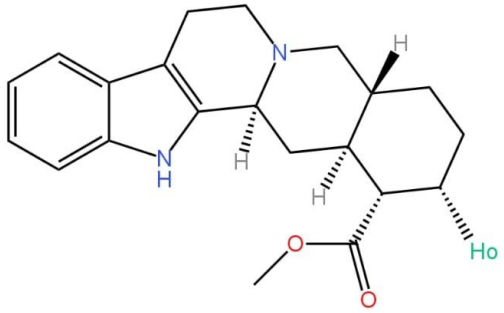
Anti-inflammatory and Analgesic activity:

Inflammation is the body's complicated response to damaging stimuli such as bacteria, damaged cells, and irritants. Tissue healing is complicated by inflammation. However, it has harmful consequences on the body when it is persistent. Anti-inflammatory drugs reduce swelling and discomfort by treating inflammation. The indole has been discovered to be a powerful cyclooxygenase inhibitor.

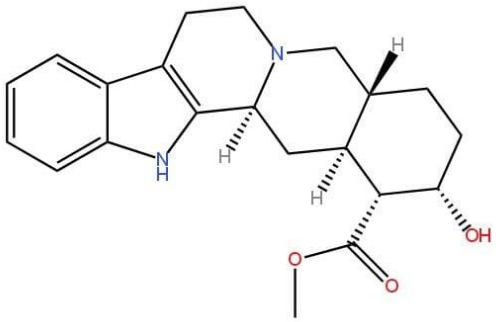


Indole Ring Containing Important Marketed Drug Molecules :-

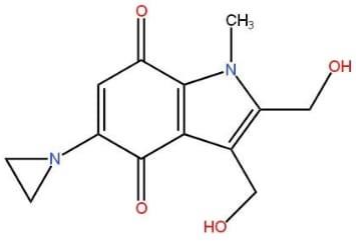
- indole ring-containing marketed drugs and their associated biological activities. Recently, the indole ring-containing compound yohimbine (17α-hydroxyyohimban-16α-carboxylic acid methyl ester, was proved by researchers for the treatment of sexual disfunction. Yohimbine was also explored as a remedy for type-2 diabetes in animal and human models, carrying polymorphisms of the α2A-adrenergic receptor gene.[34]



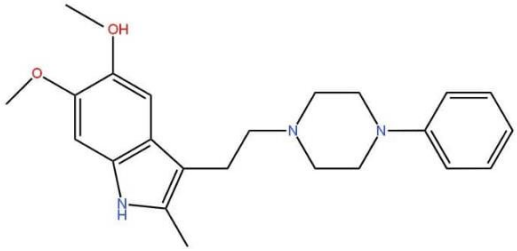
- Delavirdine an inhibitor of cytochrome P450 isozyme CYP3A4, is also a drug with an indole ring developed for the treatment of HIV type 1.The indole-based pharmaceutical constitute very important class of therapeutic molecules and are likely to replace many existing pharmaceuticals in the future. The biological profiles of this new generation of indoles represent much progress with regard to the older compounds. [34]



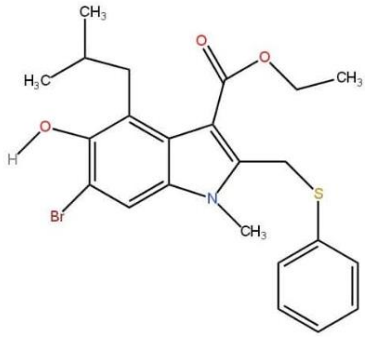
- Apaziquone is an indolequinone that is a prodrug and a chemical analog of the older mitomycin C. In a hypoxic environment, such as those on the inner surface of the Molecules urinary bladder, apaziquone is converted to active metabolites by intracellular reductases. The active metabolites alkylate DNA and lead to apoptotic cell death. This activity is preferentially expressed in neoplastic cell. [34]



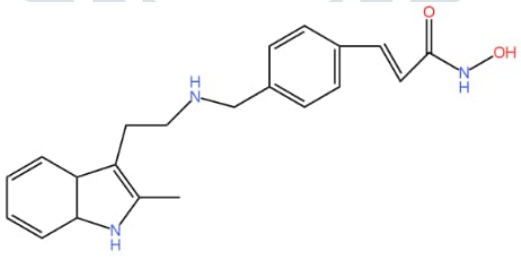
- Oxypertine is an antipsychotic and antidepressant used in the treatment of schizophrenia. Chemically, it is an indole derivative similarly to molindone and a member of the phenylpiperazine class. [34]



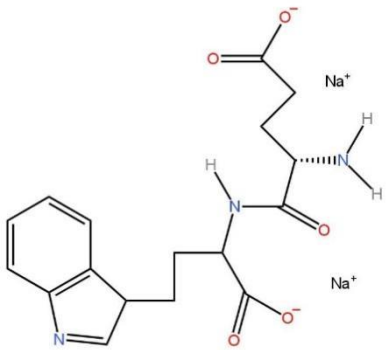
- Arbidol is an antiviral treatment for influenza infection used in Russia and China. The drug is manufactured by Pharmstandard and since 2005 it has been the number one best-selling over-the-counter drug in Russia. Chemically, arbidol features an indole core, functionalized at all positions but one with different substituents. The drug inhibits viral entry into target cells, and also stimulates the immune response. [34]

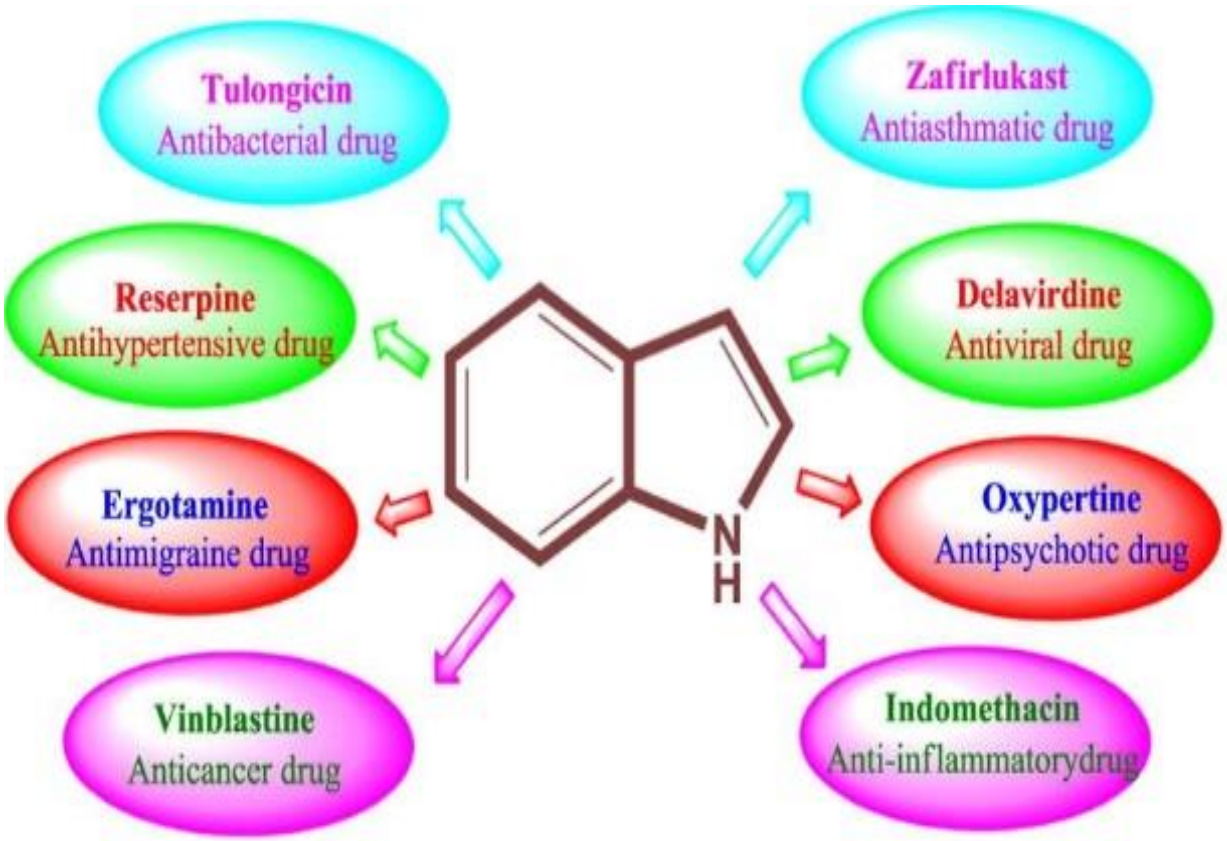


- Panobinostat is also a drug developed by Novartis for the treatment of various cancers. Panobinostat was tested against Hodgkin's Lymphoma, cutaneous T cell lymphoma and other types of malignant disease in Phase III clinical trials, against myelodysplastic syndromes, breast cancer and prostate cancer in Phase II trials, and against chronic myelomonocytic leukemia in a Phase I trial. [34]



- Oglufanide , at one time called thymogen, is a dipeptide isolated from calf thymus. The immunomodulatory properties of both the natural product oglufanide and the subsequent synthetic versions of oglufanide have been extensively studied as an agent that enhances the immune function. The compound is currently undergoing clinical trials in patients infected with the hepatitis C virus. [34]





Medicinal chemistry of indole derivatives :-

Indole containing drugs under advanced stage of devolpment; the clinical trials is to effectively prevent, diagnose and treat disease. A large pool of data is available of the FDA approved and under clinical trial indole containing drugs. Along with indole, various other isoforms of indole i.e oxindole and indoline, due to similar mechanism of action, have distinct biological significance in the variety of diseases condition. They are ,therefore, also among the potential drug candidates which are under clinical trial. Maximum drugs have successfully.

Pharmacological profile of indole derivatives:-

Due to the versatile nature of indole, it had gained huge popularity among the organic

Conclusion:

Indole moiety is present in many compounds possessing various biomedical applications. Various synthetic drug molecules contain an indole nucleus as a part of their pharmacophore structure and it helps in affixing drugs to the residues of the binding site of desired targets. Derivatives holding indole core exhibit different biological activities namely antidiabetic, anticancer, anti-microbial, anti-HIV, antiviral, anti-inflammatory, antioxidant, anticholinesterase, antitubercular, and anti-malarial activities, etc. Due to these activities, indole has attracted the attention of researchers in the discovery of novel chemical entities

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