Derivatives Of Indole

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ABSTRACT-

The heterocyclic section serves as a perfect framework on which pharmacophores can be effectively attached to evolve novel drugs. Among different heterocyclic compounds, nitrogen-based heterocycles have been investigated as they constitute the main structure of numerous biologically relevant molecules. Due to the versatility of indole, it has been a highly "privileged motif" for the target-based design and development of various types of drugs. Indole is used in making various types of drugs such as anticancer agents (For example- 5,6,7- tribromoisatin), anti-diabetic agents (For example- a,N,N,N-timethyl tryptophan betain), anti-malarial agents(TCMDC-134281), anti- tubercular agents(indole-3-thiosemicarbazone), anti-HIV agents(Umifenovir analogs), anti-fungal agents(Ketoconazole) etc. And many more applications of indole are there. Indole can be derived chemically (by BARTOLI INDOLE SYNTHESIS, BISCHLER INDOLE SYNTHESIS, FISCHER INDOLE SYNTHESIS) and naturally (from Apocynaceae, Rubiaceae, Nyssaceae, and Loganiaceae plants).

Indole is a privileged heterocyclic nucleus set up in diverse natural products, endogenous molecules, and medical agents. Even though it has diversified actions as an anti-inflammatory agent (Indomethacin, tenidap). Indole is used as a synthon for the preparation of a large number of bioactive heterocycles and paved the way to develop effective targets.

In this, we will discuss indole derivatives used in the treatment of cancer, diabetes, HIV (Human Immunodeficiency Virus), malaria, and tuberculosis (TB).

1. INTRODUCTION –

Indole is a benzo (Pyrrole formed by the alliance of benzene ring).It is the first segregated by the pyrolysis of oxindole (C8H7NO) with Zinc dust. Oxindole was initially acquired by the reduction of Isatin, which in turn was acquired by the oxidation of indigo. Indigo is a blue dye manufactured in India, which is why it is named indole commercially it is materialized from coal tar. Indole is the most universally scattered heterocycliccompound.

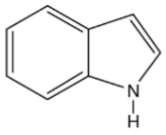


Figure 1- Indole

Indole is a basic part of thousands of naturally raised alkaloid drugs and other compounds.

For example –

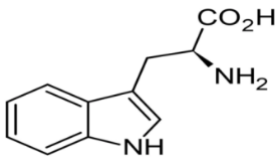
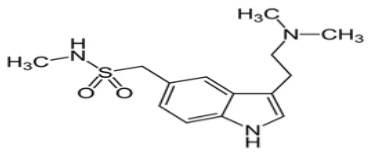


Figure 2- Tryptophan

The body utilizes tryptophan to aid in producing melatonin and scrotin. melatonin helps balance the sleep-wake cycle and serotonin is thought to help regulate appetite, sleep, mood, and pain. liver also usestryptophan[1].



Sumatriptan

1. It is medicine for migraines.

2. It is used to cure minor migraines in adults.

2. PROPERTIES OF INDOLE

A. ANTI – CANCER PROPERTIES –

The derivative of indole shows anti-cancer activities.The tested derivatives of 3-indolylmethylene-2-indolinone derivatives show anti-tumor activities.

There are two types of indole derivatives present here -

1. Pyridine derivatives

2. Piperazine derivatives

The pyridine derivatives were far more active than piperazine. the bis indole derivatives are potent against human cancer cell lines, such as cancer of the breast, ovary, lungs, and colon[6].

Among the synthesis series of 2,4-disubstituted furo [3,2-b] indole derivatives the (5-(12-(hydroxymethyl)-4H-furo [3,2-b] indole-4yl)methyl) furan-2-yl)-methanol (figure 3).

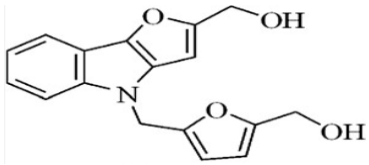


Figure 3- (5-(12-(hydroxymethyl)-4H-furo [3,2-b] indole-4-yl) methyl) furan-2-yl)-methanol

It was found to show highly selective anti-cancer activity against human tumor(NCI-60) cell lines and significant inhibitory activity against A498 renal cancer cells.

The pyrido [3,4-b] indoles show cell growth inhibiting tendency against human cancer lines comprising colon,breast, lungs, and prostate cancer cell lines[6].

A series of indole hybridized diazenyl derivatives synthesized by the condensation of diazotized p-aminoacetophenone with indole or nitro indole succeeded by the reaction with different aromatic heteroatomic amines and assessed for cytotoxicity against human lung cancer cell lines and normal cell lines.

1H – INDOLE – 2,3 – DIONE Derivatives -

These derivatives got appreciable recognition because of their potent biological activities such as antioxidant, anti-inflammatory, anti-cancer, anti-HIV, and anti-viral. it is obtained by the oxidation of indigo dye by HNO3 and chromic acid. it is also found in the plants of the genus Isatis,calanthe.

It goes through several types of reactions due to the existence of different reaction centers. compounds of the 1H – INDOLE – 2,3 – DIONE series are efficient in entering into N-alkylation and N-acylation and the mannish and micheal reactions through the -NH group. their Schiff bases and mannich bases are known to have a wide range of pharmacological properties including anti-bacterial, anti-convulsant, anti-HIV, anti-cancer, and anti-viral[4].

Anti-cancer activity of 1H – INDOLE – 2,3 – DIONE derivatives -

The range of replaced 1H – INDOLE – 2,3 – DIONE (isatin) shows cytotoxicity against human monocyte–like histiocytic lymphoma (U937) cell lines.

These compounds exhibit high selectivity towards blood cancer (leukemia) and lymphoma cells over breast, prostate, and colorectal carcinoma cell lines. the most active compound is 5,6,7-tribromoisatin (figure 4)[13].

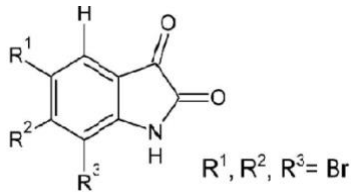


Figure 4- 5,6,7-tribromoisatin

A series of di or tri-substitutedisatin-descendantswere derived and assessed for anti-cancer activities against human T-lymphocyte cells. SAR (structure-activity relationship) study put forward that the alliance of 1-benzyl and 5-[trans-2-(methoxycarbonyl)ethen-1-yl] replacement greatly enhanced their cytotoxic activities.

A series of 5 or 7 substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl) phenylimino}-indolin-2-one derivatives (figure 5) shows anti-cancer activity against HeLa (derived from thefirst two letters of HENRIETTA LACKS first and last name) cancer cell lines[4].

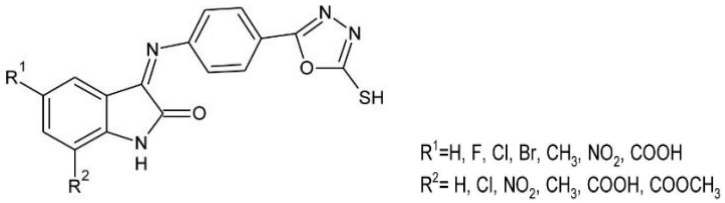


Figure 5- A series of 5 or 7 substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl) phenylimino}-indolin-2-one derivatives.

The 3,3-diindolyl oxindole derivatives (figure 6) oppose a panel offive human cancer lines and most of them displayed potent cytotoxicity.

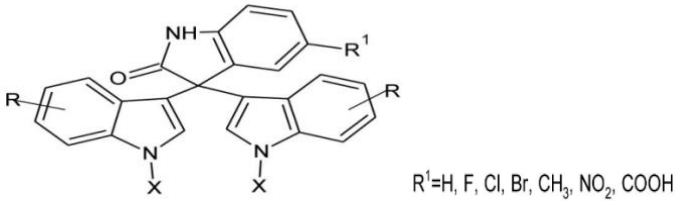


Figure 6- 3,3-diindolyl oxindole derivatives.

A series of 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene) thiazolidine-2-ethylidene)amino) benzene sulfonamide (figure 7) show their inhibitory activity against breast cancer MCF-7 and colorectal cancer caco-2 cell lines[16].

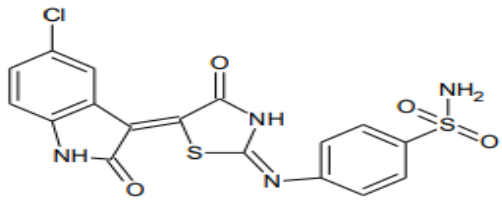


Figure 7- 4/3-(4-oxo-5-(2-oxoindolin-3-ylidene) thiazolidine-2-ylidene)amino) benzene sulfonamides derivative.

A series of triazole-linked 3-benzylidene Isatin hybrids are evaluated against DU145, PC-3 (prostate cancer cells),MDA-MB-231, BT549 (breast cancer cell), A549 (lung),HeLa (cervical) cancer cell lines.

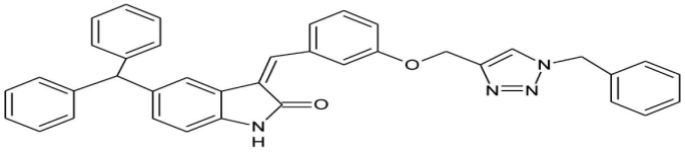


Figure 8- 3-benzylidene Isatin hybrid.

A sequence of Isatindescendants of Podophyllotoxin shows cytotoxic activity against human blood cancer K562 cells[13].

The sixteen synthesized coumarins bearing hydride-hydrazone section show anti-cancer activities against pancreatic carcinoma cells. Bromo coumarins were found to be the most active anti-tumor agent against drug–resistant pancreatic carcinoma cells.

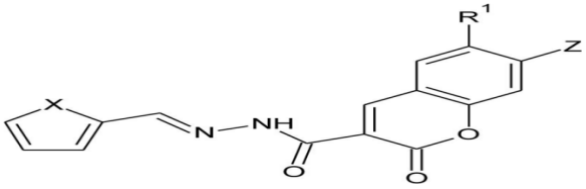


Figure 9

Spiro-indole derivatives (indole substituted with heterocyclic rings at the 3- position) –

It was obtained that different alkaloids and compounds we get from marinesmollusksand shellfish are heterocyclic cyclic compounds having a spiro system at the 3rd position of the 2 indolinone skeleton.

With C3 as spiro, Spiro-indole has gained appreciable recognition as all sorts of rings beginning from a ring system to a three-ring system. Moreover, Spiro oxindole derivatives cover a special place in organic and medicinal chemistry[4].

Example-

Figure 10 and 11

Anti-cancer activity of spiro indole derivatives –

Among the tryout compounds(5'Z)-5'-(benzylidene) -3'- (4-chlorophenyl) spiro[3H-indole -3,2'- thiazolidine] -2,4'(1H)-dione (figure 12a) and (5'Z)-3'-(4-chlorophenyl)-5'-[4- (1-methyl ethyl) -benzylidene]spiro[3H-indole3,2'-thiazolidine]-2,4'(1H)-dione (figure 12b) were boss to other related compounds and may be considered due to the presence of 4-thiazolidinone group.

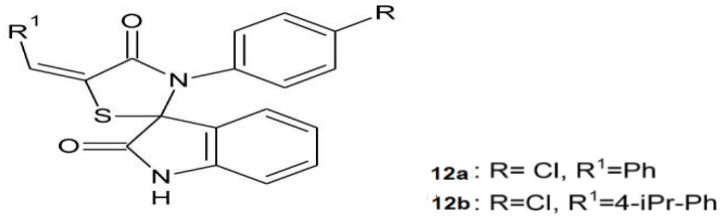


Figure 12a- (5'Z)-5'-(benzylidene) -3'- (4-chlorophenyl) spiro [3H-indole -3,2'- thiazolidine] -2,4'(1H)-dione

12b - (5'Z)-3'-(4-chlorophenyl)-5'- [4- (1-methylethyl) - benzylidene] spiro[3H-indole3,2'-thiazolidine]-2,4'(1H)- dione.

The anti-cancer activity of Spiro[pyrrolidine-3,3'-oxindole] descendants (figure 13) was tried out on Huh7, MV, HCT116, and MCF7 cancer cell lines.

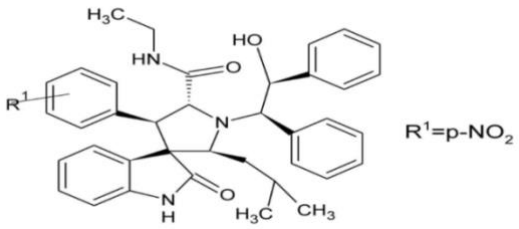


Figure 13- Spiro[pyrrolidine-3,3'-oxindole] descendant.

It was found that the above-exhibitedcompound showsthe most potent inhibitory activity.

The 3'-spirocyclic-oxindole compounds based on Spiro[indole-3,5′-isoxazolidin]-2(1H)-one(figure 14), the 2′H-spiro [indole-3,6′- [1,3]oxazinane] -2,2′(1H)-dione(figure 15) and the 2′H-spiro[indoline-3,3′-pyrrolo[1,2- c][1,3′]oxazine]-1′,2(1H)-dione(figure16) heterocyclic compounds . two of these exhibit notable cytostatic activity on cancer lines.

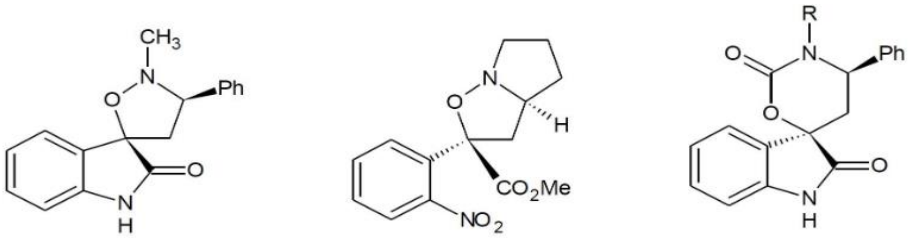


Figure 14,15 and 16

The Spiro oxindole hybrids have been evaluated in vitro for their suppressing effect against colon cancer HCT116,hepatocellular carcinoma (HepG2), and prostate cancer (PC3).

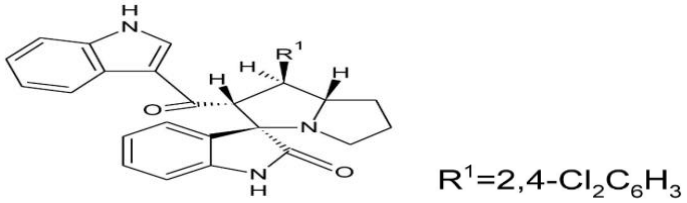


Figure 17- Spiro oxindole hybrid.

The above-depicted compound regains high cytotoxic activity and is judicious against colon cancer HCT116.

A series of spiro oxindole-O-naphthoquinone-tetrazolo[1,5-a]pyrimidine hybrids were synthesized and evaluated as the most potential anti-tumor agent. These hybrids show comparatively high cytotoxic activity against cancer cell lines HepG2.

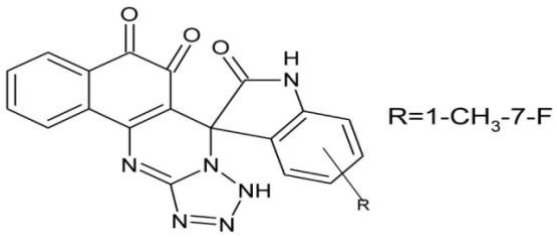


Figure 18- Spiro oxindole-O-naphthoquinone-tetrazolo[1,5-a]pyrimidine hybrid.

This is the most active Anti-cancer agent.

A new series of heterocycles having spiro oxindole and pyrrolidine rings were evaluated against breast cancer cell lines (MCF7) and leukemia (K562)[16,13].

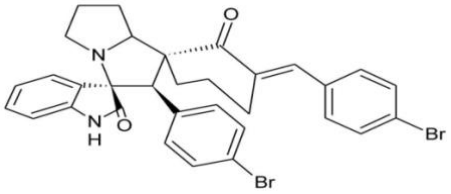


Figure 19

This compound proved to be the most potential anti-cancer agent against breast cancer cells.

B. ANTI-DIABETIC PROPERTIES-

Diabetes mellitus (DM) is a kind of incurable or chronic disease identified by high blood glucose and dyslipidemia.

There are two types of diabetes, 1-primary DM and 2-secondary DM. The former DM consists of two types first non-insulin dependent diabetes mellitus (NIDDM) and second insulin dependent diabetes mellitus (IIDM). More than 90% of diabetic patients suffer from non-insulin-dependent diabetes mellitus. the efficacies of all the oral antidiabetic agentsnaturally decrease with long-term application in the patients. there is a continuous need to come up with new antidiabetic drugs. Especially in the fact that diabetes is becoming a widespread disease in the world[5].

Indole compounds –

Simple indole compounds –
Carboline compounds –
Semi-terpenoid indole compounds –
Mono-terpenoid indole compounds –
Bis-indole compounds –

Carbazole compounds –

Simple indole compounds– they contain only one indole ring. Some of them are derived from natural sources, mainly from plants. In comparison, most of the others are chemically synthesized.

An a-N, N, N-Trimethyl tryptophan betaine(figure 20) named hypophora isolated from erythrina hypophora seeds. This also serves as a sleep-promoting agent.

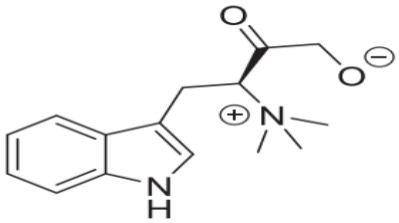


Figure 20- a-N, N, N-Trimethyl tryptophan betaine.

13 components are derived from Chinese black ant out of which 4-((1H-indole-3yl)methyl) nicotinamide(figure 21).it is believed that this compound has the potential to treat diabetes nephropathy (DN) in the upcoming time.

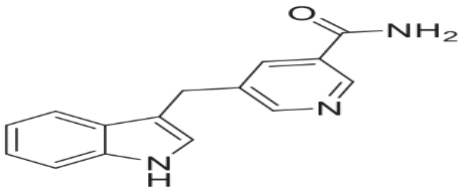


Figure 21- 4-(1H-indole-3yl)methyl) picolinamide.

Some of the indole alkaloids are derived from sweet potato leaves and are believed to possess α-glucosidase inhibitory activity.

The freshly derived indole descendant, 1-(4-chlorobenzene)-5-hydroxy-2-methyl-3-indoleacetic acid(figure 22) was certified to have the potential against diabetes.

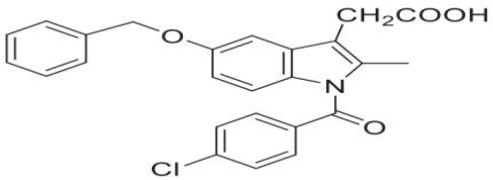


Figure 22- 1-(4-chlorobenzene)-5-hydroxy-2-methyl-3-indoleacetic acid.

According to SAR study,it has been found that the indole compound 9-(5-bromo-1H-indol-3-yl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one(figure 23) was the most potent inhibitor of alpha-glucosidase.

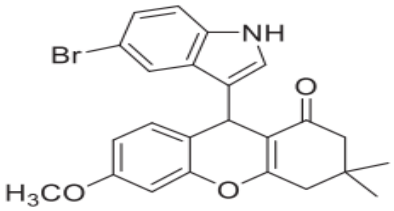


Figure 23- 9-(5-bromo-1H-indol-3-yl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one.

GRP119 is a member of the G protein-coupled receptor and has become an attractive drug target these years in drug discovery.

In recent times, β-methyltryptophan has drawn more and more attention in medical chemistry as a potential diabetic agent.

Various activities of benzoxazineglyconeswerenoted using some molecular techniques. Among all the derived benzoxazine only six of them show the most potent activity against diabetes.

An N-β-D-xylosylindole descendant 4-chloro-3-(4-cyclopropylbenzyl)-1-(β-D-xylo pyranosyl)-1H-indole(figure 24) was derived and noted for its antidiabetic activity.

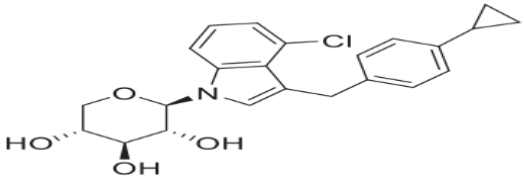


Figure 24- descendant 4-chloro-3-(4-cyclopropylbenzyl)-1-(β-D-xylo pyranosyl)-1H-indole.

Thiazole derivatives have gained appreciable attention for their antidiabetic activity in recent times. The successfully synthesized substituted pyrazoles derivatives covering indole and thiazole heterocycles 2-(5-(1H-indol-3-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-bromo phenyl)thiazole(figure 25) showed inhibitory activity on α-glucoside.

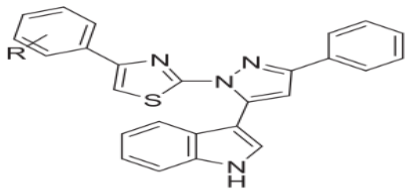


Figure25- 2-(5-(1H-indol-3-yl)-3-phenyl-1H-pyrazol-1-yl)-4-(4-bromo phenyl) thiazole.

Three series of staurosporine descendants[figure 26(a-b)-28(a-b)] were derived and these compounds were recorded for their activities of PKC beta-selective inhibitors in which the JTT010(figure 29) series was noted to have the most potent inhibitory actions. Due to the good curative effects, it is expected to be used in diabetic neuropathy and nephropathy

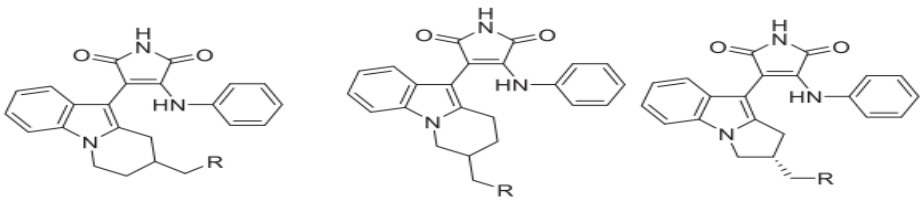


Figure 26a-28a –R=N(CH_3)$_2$

Figure 26b-28b –R=OH

Figure 26-28- staurosporine descendants.

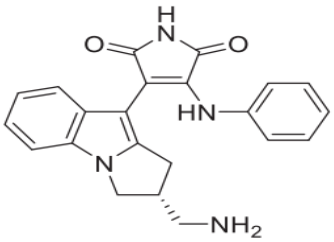


Figure 29- JTT010.

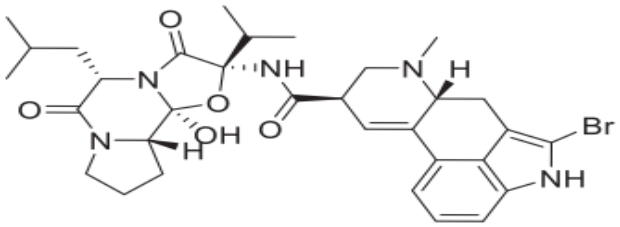
Carboline compounds-These are types of compounds identified by the presence of pyrido indoles in the structure. The carboline compounds are divided into four categories and $beta-carboline$ compounds covermost ofthe carboline compounds portion. They are mainly derived from marine organisms and plants.

e.g.-

Indoloquinoline compounds were derived from cryptolepissanguinolent.

Semiterpenoid indole compounds- They are mainly derived naturally, and few were synthesized chemically. They are also known as ergot alkaloids because of their distribution in Calviceps purpurea.

Bromocriptine(figure 30) is a dopamine D2 receptor agonist that has been developed into an antidiabetic agent widely used in clinical practice.



[6]

Figure 30- Bromocriptine.

Cabergoline(figure 31) is also a dopamine agonist and has been proven to be helpful in glycemic control.

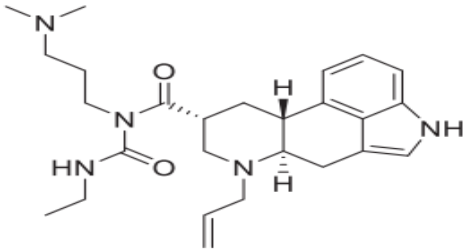


Figure 31- Cabergoline.

Monoterpenoid compounds - like semiterpenoid compounds they are also obtained naturally.

For eg–

DHIM (16,17-dihydro-17b-hydroxy isomitraphylline) (figure 32)was derived from the leaves of Mitragyanaparvifolia.

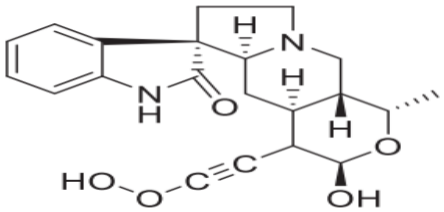


Figure 32- DHIM.

Strictosamide (figure 33) was derived from Uncariarhynchophlly. Later it was discovered in Sarcocephaluspobeguinii.

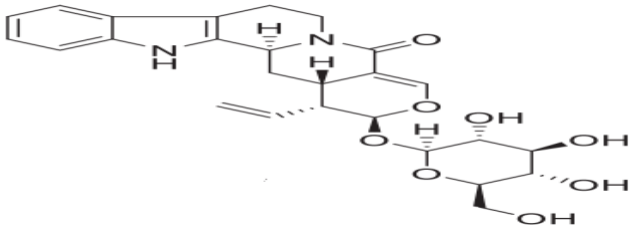


Figure 33- Strictosamide.

Vincamine (figure 34) is derived from Madagascar periwinkle.

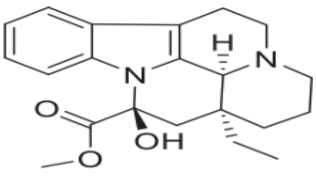


Figure 34- Vincamine.

The above-listed examples are used in the treatment of diabetes.

Bisindole compounds-

Bisindole compounds are synthesized by the condensation of two molecular monoterpenoid indole compounds, making the molecular structure more complicated. They are also isolated from plants.

For eg-3,3’-diindolylmethane (figure 35) was derived from cruciferous plants and then derived from indole-3-carbinol

The study shows that the above-exampled bisindole compound could ameliorate the symptoms of T1D as well as diabetic nephropathy.

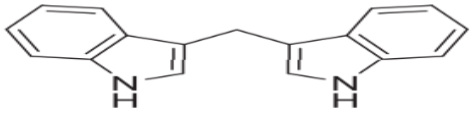


Figure 35- 3,3’-diindolylmethane.

Conophylline (figure 36) displayed good effects on some metabolic disorders, such as diabetes, steatohepatitis, obesity, and neurodegenerative disease. It is derived from the leaves of Ervatamia micophylla.

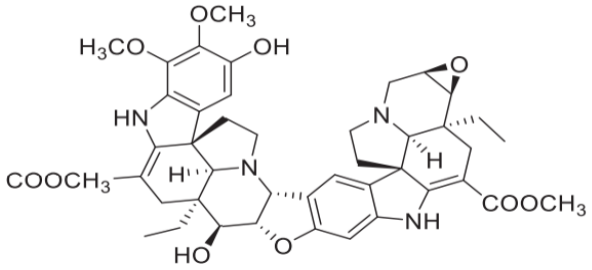


Figure 36- Conophylline.

A kind of 3,3-bisindole derivative (figure 37) exhibited inhibitory activity on α-glucosidase with 2-flurobenzyl group in structure, which was the most potent one in this group.

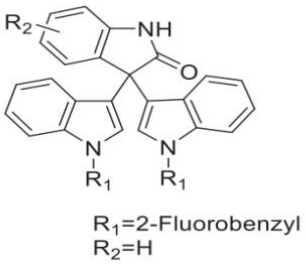


Figure 37- 3,3-bisindole derivative.

Demethylasterriquinone B1 (DAQ B1) (figure 38), we got this from Aspergillus terreusand pseudomassaria fungi exhibited antidiabetic effects in clinical trials.

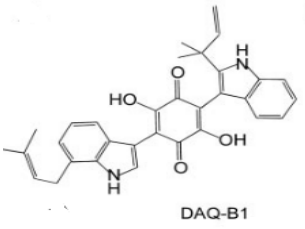


Figure 38

Carbazole compounds-

These compounds are not found easily in nature. These compounds are very rare in nature, so they are derived by various methods. In the carbazole compounds class, they exhibit potent hypoglycemic activity along with insulin weakening or softening effects.It also reduces total cholesterol and serum triglyceridelevels[5].

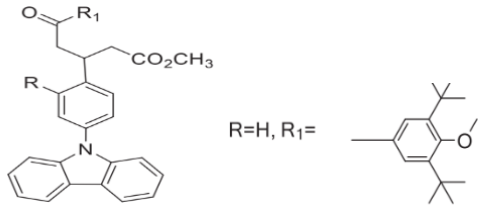


Figure 39

C. ANTI-INFLAMMATORY PROPERTIES –

NSAIDs (Non-Steroidal Anti-inflammatory Drugs) are the most often directed drugs for the therapy or treatment of pain and inflammation. It is a multiplex process involving various endogenous substances.NSAIDs include various categorizations of functional groups and the Indomethacin cyclooxygenase enzyme has to be perturbed with paramount care[6].

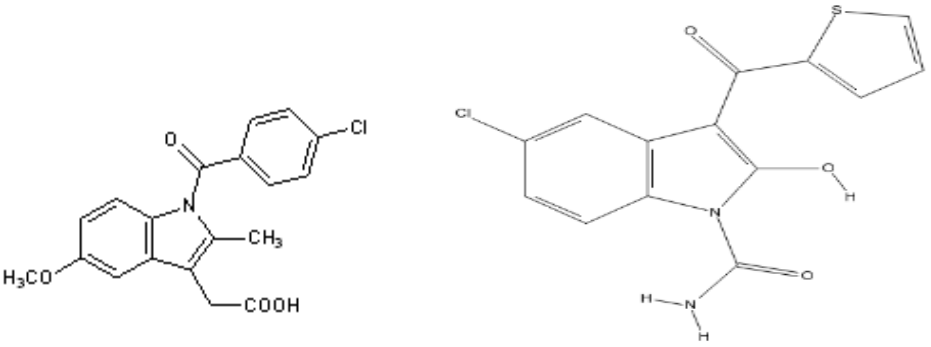


Figure 40- Indomethacin and Tenidap

Indole and its Anti-inflammatory activities of indole -

The selectivity of the cyclooxygenase enzyme was evaluated by changing the substituents at the N-1 and C-3 positions of the indole ring. The outcomes showed that all the compounds exhibited more potent against COX-2 enzyme than COX-1 enzyme. The compound 1-benzoyl-3-[(4-trifluoromethylphenylimino)methyl] indole (figure 41) shows significant COX-2 inhibition[1].

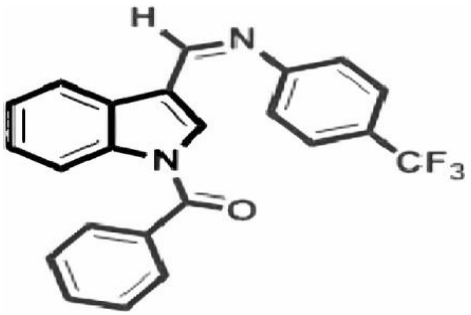


Figure 41- 1-benzoyl-3-[(4-trifluoromethylphenylimino)methyl] indole.

The compound having trifluoro methyl substituent exhibits significant anti-inflammatory activity.

Indole was substituted in the 3rd position with different chalcones, pyrazolines, and azo compounds were noted for their anti-inflammatory activity. The compound exhibits a maximum of 47% anti-inflammatory activity among compounds extracted in the different three stages. The relative venture can be described in such a way that pyrazolines are more active than chalcones and azo-compounds (Pyrazolines>Azo-compounds>Chalcones)[1].

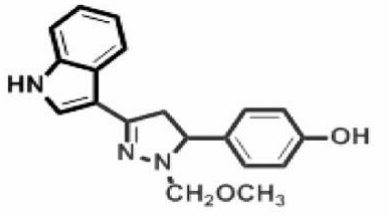


Figure 42

A chain of novel 1,3,4-oxadiazole and 1,2,4-triazole sections substituted in the indole ring at the C-3 position was noted for anti-inflammatory activity. Even though all the compounds showed astonishing activity, the compound (figure 43) was superior to the other compounds.

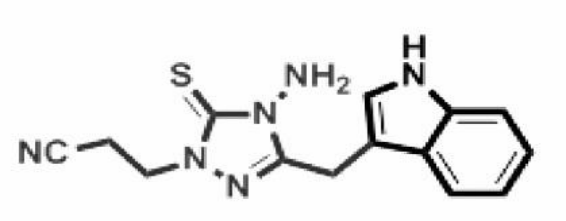


Figure 43

The after-effects of varying 4-octyl remainder and bioisosteric replacement of carboxylic acid in 1-[3-(4-octyl phenoxy)-2 oxopropyl] indole-5-carboxylic acid (figure 44) a double inhibitor of cPLA2α (cytosolic phospholipase A2α) and FAAH (fatty acid amide hydrolase) was studied and as a result most of the compound is active against both enzymes and it was resulted that an anti-inflammatory agent can be produced by dual inhibition of enzyme rather selective inhibition[1].

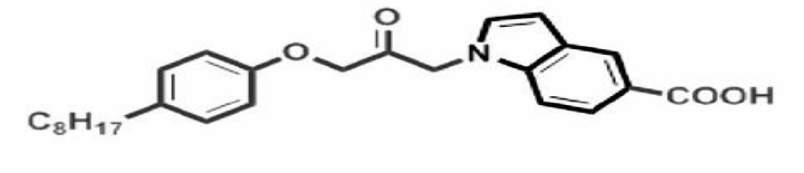


Figure 44- 1-[3-(4-octylphenoxy)-2 oxopropyl] indole-5-carboxylic acid.

[2-{(4-substituted-pyridin-2-yl] carbonyl} -(6 or 5-substituted)-1H-indole-3-yl] acetic acid cognate (figure 45) was derived. All the compounds exhibited towards COX-2 than the COX-1 enzyme. The compounds showed potent activity for the COX-2 enzyme[1].

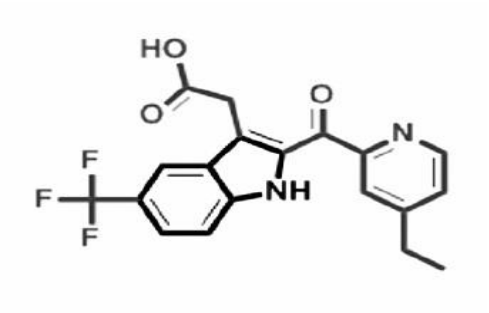


Figure 45- [2-{[(4-substituted-pyridin-2-yl] carbonyl} -(6 or 5-substituted)-1H-indole-3-yl] acetic acid cognate.

The gastro toxicity applied by the direct contact of the acidic drug such as indomethacin was corrected by the ester prodrug formation. The prodrug compound (figure 46) noted a low ulcer index and displayed comparable anti-inflammatory activity with that of the standard drug indomethacin[1].

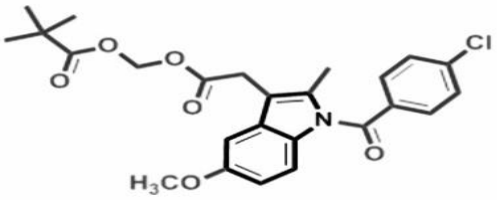


Figure 46

Pyrano(2,3-c) pyrazole nucleus replaced at the 3rd position of the indole section (figure 47) were reported with appreciable anti-inflammatory activity and the existence of halogen atom affected the venture than the other compound[20].

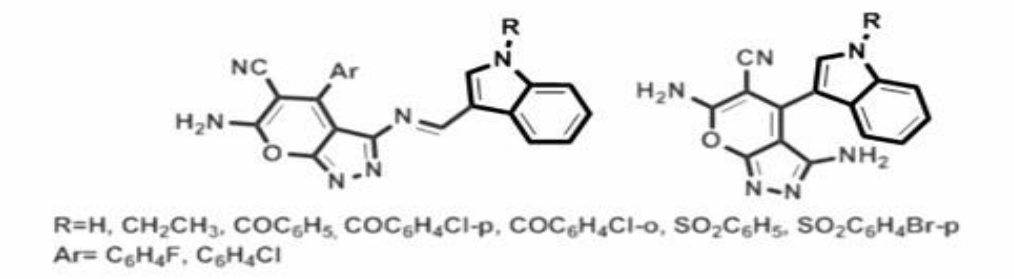


Figure 47

The effect of the nitro group over the anti-inflammatory activity was discussed and the outcome was (figure 48) comtaining6-nitro group and the chlorophenyl section show often anti-inflammatory activity[1].

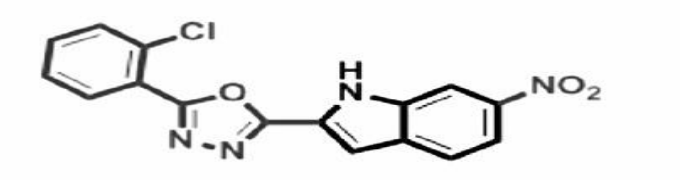


Figure 48

D. ANTI-TUBERCULAR PROPERTIES-

Tuberculosis (TB), is an infectious disease caused by the bacteria Bacillus mycobacterium tuberculosis (Mtb). In 2017, TB gained attention and the World Health Organization (WHO) announced it as a matter of high priority. Streptomycin was the first drug discovered to cure tuberculosis and the following entry of thioacetone and para-aminosalicylic acid into the market upgraded the cure rate of the disease. The evolution of resistance to streptomycin resulted in the outcome of new anti-tubercular drugs such as isoniazid (INH), pyrazinamide, cyclomerize, ethionamide, rifampicin, and ethambutol[6].

Indole-based anti-tubercular compounds -

The iso-indole-based compound 2-hydroxy-4-(4-nitro-1,3-dioxoisoondolin-2-yl) benzoic acid (IDDB40) (figure 49) shows high activity towards all strains of MTB with mycolic acid inhibition. The 2-hydroxy-4-(4-nitro-1,3-dioxoisoindolin-2-yl) benzoic acid (IDDB40) compound has been found to have isoniazid activity in an introductory study of mycolic acid inhibition and maybe thepotential anti-tuberculosis-agent [2].

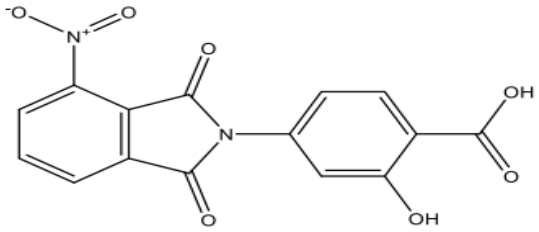


Figure 49- 2-hydroxy-4-(4-nitro-1,3-dioxoisoondolin-2-yl) benzoic acid (IDDB40).

Enoyl acyl carrier protein reductase inhibitors- The two important extension systems that lead to mycolic acid biosynthesis are fatty acid synthase type (I) and fatty acid synthase type (II). The enoyl acyl carrier protein reductase of the FAS II system indulged in the catalysis of NADH-relied on the reduction of the double bond at the second position of the enlarging fatty acid chain[2].

The Mtb ENR exhibited to be a potential target for deriving anti-TB drugs. The succinimide and indole platform containing the cognate 3-(9H-fluoren-9-yl)-1-(1H-indol-5-yl carbonyl)-2,5-pyrrolidine-dione (figure 50) potentially inhibit InhA from Mtb[2].

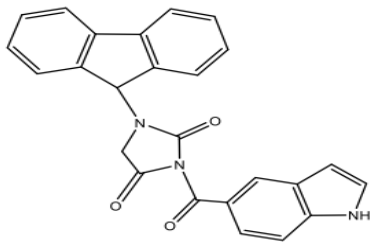


Figure 50- GEQ analog 3-(9H-fluoren-9-yl)-1-(1H-indol-5-yl carbonyl)-2,5-pyrrolidinedione.

The derived complexes of indol-3-thiosemicarbazone,5-methoxy indole-3-thiosemicarbazone (figure 51), and indole-N1-methyl-3-thiosemicarbazone with copper (I) and silver (I) have been noted for their binding affinity by docking against ENR.

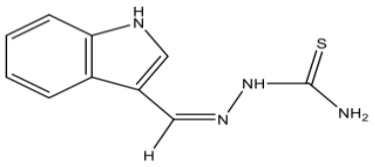


Figure 51- Indol-3-thiosemicarbazone.

The assessment of a series of indole and pyridine-based 1,3,4-oxadiazole derivatives has been executed to determine anti-TB activity against Mtb H37 and mycobacterium bovisBCG, in both active and inactive states. Some of them exhibited favorable anti-TB activity[2].

Decaprenylphosphoryl-β-D-ribose 2'-epimerase inhibitor-

The target DprE1 is an important enzyme in cell wall derivation in Mycobacterium.It also plays an important role in the derivation of arabinogalactan and lipoarabinomannam. The 1,4-azaindoles are very likely drug candidates for the handling of TB through the non-covalent inhibition of DprE1[2].

A triazole-diindolylmethane (figure 52) conjugate compound has been instituted to have considerable activity against Mtb H37Ra.

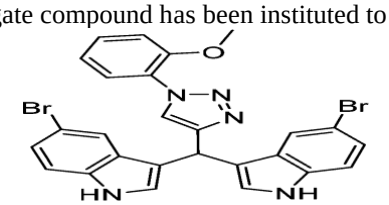


Figure 52- triazole-diindolymethane conjugate.

β – ketoacyl ACP synthase I (KasA) inhibitor-

KsaAis an important member of three β – ketoacyl synthase encrypted in the genome of *Mtb.* The JSF-3285 (figure 53) has been derivated to optimize D167. *Mtb* indole chalcones have been represented to inhibit the H37Rv strain of *Mtb* with a MIC of 210μM to exhibit favorable binding toward KsaA[2].

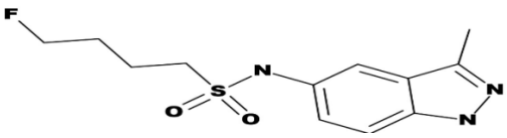


Figure 53- JSF-3285

Chorismate mutase (CM) inhibitor-

The Mtbchorismate mutase brings out the change in chorismite to prephenate. A series of isatin inhibitors have been noted to have likely CM inhibitory activity at nanomolar concentrations[2].

A novel indole carrying an o-(RSO2) C6H4 group at C-2 (figure 54) has been assessed for MtbH37Rv CM inhibitor activity.

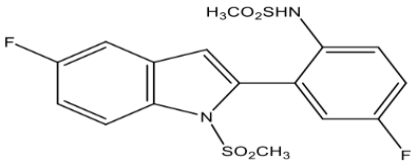


Figure 54- o-(RSO2) C6H4 group at C-2.

A promising CM inhibiting agent has been evolved by joining the structural features of indole and the quinoxaline sections in a single molecule, 2-chloro-3-(5,6-difluoro-1H-indol-3-yl) quinoxaline (figure55).

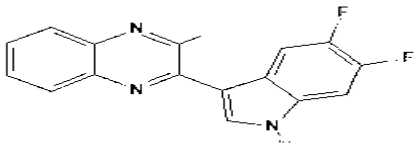


Figure 55- 2-chloro-3-(5,6-difluoro-1H-indol-3-yl) quinoxaline.

DNA gyrase inhibitor-

DNA gyrase is the only medically accepted target of fluoroquinolones, which resist replication and are used to cure multi-drug inhabitant TB.

A series of 2-(1H-indol-3-yl) ethyl thiourea (figure 56) descendants have been derived and noted for their antimicrobial activity against gram cocci, gram-negative rods, and fungi[2].

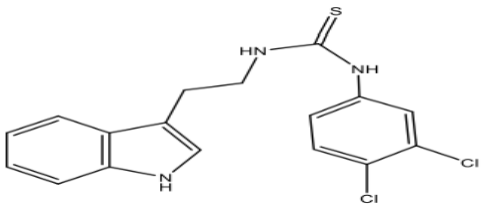


Figure 56- 2-(1H-indol-3-yl) ethyl thiourea.

Dihydrofolate reductase (DHFR) inhibitor-

DHFR is a key enzyme that participates in deriving tetrahydrofolate, which is important for bacterial liveliness.

The selective and potent inhibition of Mtb-DHFR by 4-((3-acetyl-1-benzyl-2-methyl-1H-indol-5-yl)oxy)butanoic acid (figure 57) has been represented in a structural comparison of Mtb-DHFR human DHFRs bioisoteric substitution of these compound has concluded in a new series of 1-(1-benzyl-2-methyl-5-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-1H-indol-3-yl)ethanone and ethyl 1-benzyl-2-methyl-5-((1-phenyl-1H-1,2,3-triazol-4-yl)-1H-indole-3-carboxylate derivatives, some of which have exhibited selectivity and favorable activity against Mtb-DHFR[2].

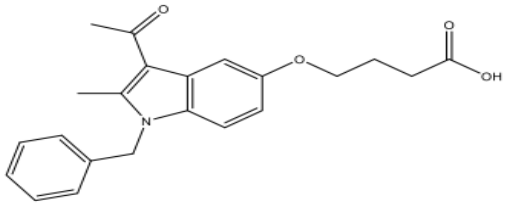


Figure 57- 4-(3-acetyl-1-benzyl-2-methyl-1H-indol-5-yl) oxy) butanoic acid.

E. ANTI-MALARIAL PROPERTIES-

Malaria is one of the deadliest diseases in the world. It took millions of lives in the past and also in the present time. In the present time, this disease is continuously affecting the lives of people. According to the reports two hundred twenty-eight million malarial cases were reported in 2018 compared to 2010, clear proof that the reduction in prevalence of malaria has stalled after several years of decline.

After so much research some anti-malarial drugs have been developed some anti-malarial drugs are currently under trial[6].

Scaffolds in currently available Anti-malarial agents-

Quinine (figure 58), from the bark of the Cinchona calisaya tree, was the first universally antimalarial drug. The contribution from quinoline anti-malarial was extended by non-natural descendants such as chloroquine which was globally used as the first-line anti-malarial agent. The clinical use of chloroquine is falling at an accelerated rate owing to a rapid surge in resistance[3].

The endoperoxide scaffold artemisinin-based combination therapies are presently the central component for the treatment of uncomplicated malaria[3].

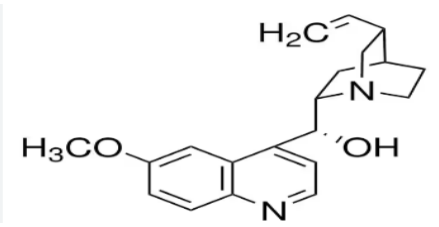


Figure 58- Quinine.

Propitious indole-anti-plasmodium agents –

Piperidine Indoles
Bisindole
Spiro indoles
Conjugated indole analogs
Indole-3-glyoxylic tyrosine derivative
Prenylated indole alkaloids

Piperidine indoles-

Screening of lately publicized Tres Cantos set (TCAMS) of gsk led to the discovery of a piperidine indole descendant TCMDC-134281 (figure 59). The modification decreased the net lipophilicity and molecular weight, thereby improving the drug-likeness[3].

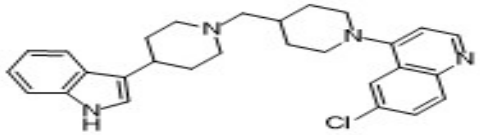


Figure 59 - TCMDC-134281.

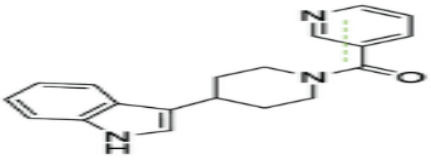


Figure 60- Improved TCMDC-134281 drug-likeness.

Bisindoles-

Different compounds carrying bisindolesections fixed or inserted somewhere in their structure have shown potent plasmodial properties. Dihydrousamabarensine (figure 61) derived from Strychnos usambarenisshowed more potent against CQ-resistant strains than CQ-sensitive strains[3].

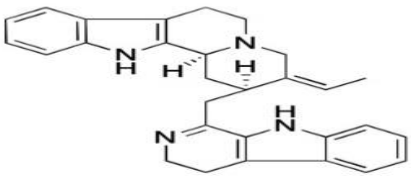


Figure 61- Dihydrousamabarensine.

Pygmies from Cameroon have a tradition of curing malaria fever with the use of S.icsja. A novel bisindole alkaloid flinderole was derived from Flindersia acuminata.

Spiroindolones-

They are also known as spiro tetrahydro-β-carbolines and are the latest class of antimalarial agents. Spiro indoles have a mode of action different from medically available antimalarial agents through inhibition of PfATP4, a plasmodium plasma membrane.

In Spiro indoles, the structural manipulations of racemic spiroazirine indole led to the derivation of NITD609 renamed as KAE609, and now rebranded as Cipragamin (figure 62)[2].

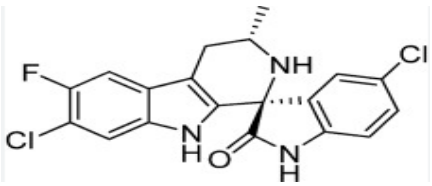


Figure 62- Cipragamin.

Conjugated indole analogue –

Isatin, 1H-indole-2,3-dione, is the most common indole descendant in natural products and pharmaceuticals. Chain of 1H-1,2,3-triazole-tied isatin-7-chloroquinoline and piperazine-tied isatin-7-chloroquinoline proceedings was noted and the length of the alkyl spacer and a replacement at C-5 position of the isatin were the reasons for Anti plasmodial activity[3].

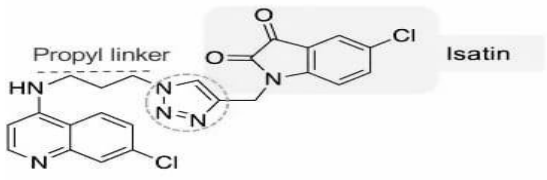


Figure 63

Most active anti-malarial derivative of this series.

Some other conjugated indole analogs –

Cryptolepine (figure 64) is an indolequinoline derived from the root of Cryptolepissanguinolent.

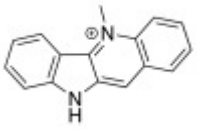


Figure 64

Ellipticine (figure 65) was derived from the bark of the Amazonian tree Aspidosperma vargasii.

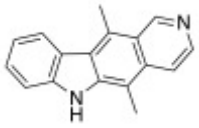


Figure 65

Trytanthrin (figure 66) is derived from different plant sources

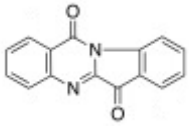


Figure 66

Indole-3-glyoxylic Tyrosine derivative-

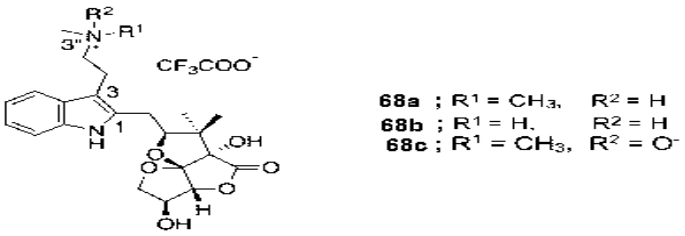
They show the anti-plasmodium properties against the 3D7 strain of malaria.

Figure 67a and 67b

Compound (b) (figure 67b) exhibits potential Anti plasmodium activity against 3D7 strain[3].

Prenylated indole Alkaloids-

They are derived from the plants of the genus Flindersia,F. acuminate,and F.amboinensis. They are the source of antimalarial alkaloids of the indole and quinoline types. Pimentelamine exhibits a new class of indole alkaloids derived from F.pimentelianawith a biosynthetic root or origin through cyclization of 2-prenyl-N, N-dimethyltryptamine with semi-dehydroascorbic acid radical[3].



F. ANTI-HIV PROPERTIES-

On the grounds of drug design of antiviral agents, heterocyclic molecules such as benzimidazole, oxadiazole, and thiazoles have been used to build well-organized drug molecules.

Indoles shape a group of alluring pharmacological agents because of which researchers are working to upgrade the antiviral activities of indole derivatives[6].

Indole as HIV resistor-

HIV attacks the immune system of an individual and permits life-hazarding opportunistic infection to bloom. The therapy of HIV/AIDS normally involves multiple antiretroviral drugs. Despite antiretroviral therapy, the consequences and rapid emergence of drug inhibitors are the limitations that have hampered the continuous development of new anti-HIV compounds[30].

The Umifenovir correlatives (figure 690 have been noted to have a broad-spectrum antiviral activity. However, cyclopropyl correlatives have represented higher anti-HIV activity but are inferior to rac-MC-1501(used as a reference compound)[11]

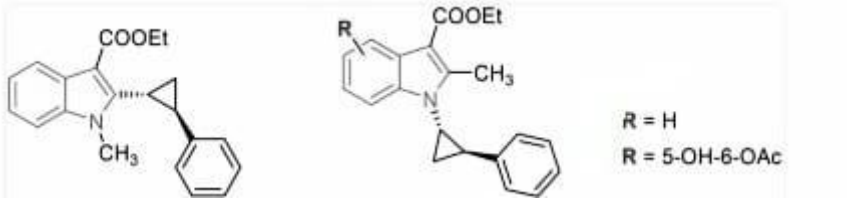


Figure 69- Umifenovir analogs

Halogenated carbazole scaffolds consisting of dimethyl phenyl rings are produced to inspect anti-HIV activity towards NL4.3X4 and Bal R5 variants. Weak anti-HIV activity properties have been exhibited by 2,5-dimethyl carbazole analogs connected with 7-choro groups, while 8-chloro carbazole without –NO2/NH2 group showed average resistance activity and stronger Bal R5 resistance potency[30].

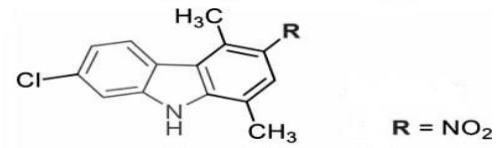


Figure 70

This compound with R=NO2 exhibits great potency against HIV as compared to all of its derivatives.

By experimenting with a wide range of structural variants into compounds a chain of indole–based HIV-1 attachment resistors are produced out of which some show great resistance against HIV, and some are less potent. Some selected compounds have been tested for their ability to resist HIV. Most of the compounds exhibited poor activity. Whereas 5,6-dihydroxyindole carboxamide (figure 71) descendants have exerted stronger HIV inhibition potency[30].

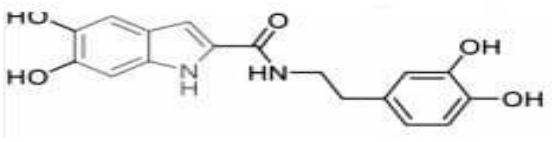


Figure 71- 5,6-dihydroxyindole carboxamide.

Considering electron acceptor groups such as halogen (X) only 4-bromoaniline (figure 72) correlatives represent HIV-1-inhibitor activity[30].

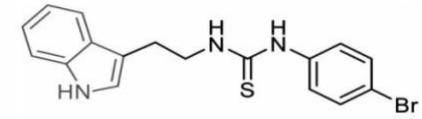


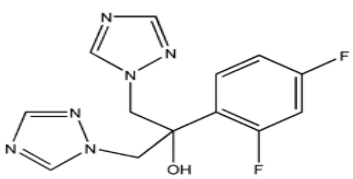
Figure 72- 4-bromoaniline.

G. ANTI-MICROBIAL PROPERTIES-

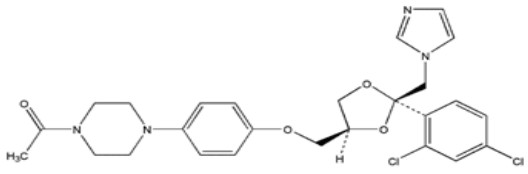
Antimicrobial hostility is often used as a definition for drug inhibition, which happens when microorganisms such as **bacteria, viruses, fungi, and parasites** withstand a drug that was intentionally to cure the infection[23].

The methicillin-resistant Staphylococcus aureus(MRSA) led to the foundation of some serious infections such as pneumonia, endocarditis, and skin and soft tissue infections with in-depth or intensive care units. The indole descendants have favorable antimicrobial activity against MRSA. The main grantor is NorA efflux. NorA efflux is capable of exporting a variety of structurally unrelated drugs such as Fluoroquinolones, Ethidium bromide, Cetrimide, Benzalkonium Chloride, Tetraphenylphosphonium Bromide and Acriflavine[24].

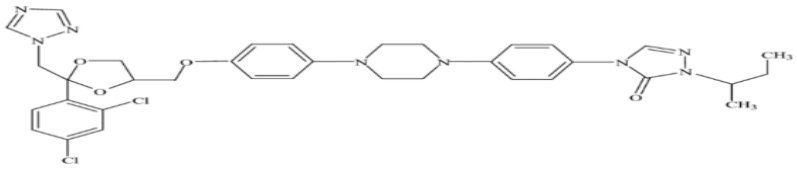
Azole has compounds such as Fluconazole, ketoconazole, and itraconazole (figure 73) the universally used antifungal agents. However, Fluconazole is ineffective against Candida Krusei.



Fluronazole



Ketoconazole



Itraconazole

Figure 73

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