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Review Article

"INDOLE" A VERSATILE NUCLEUS IN PHARMACEUTICAL FIELD

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Abstract : (The indole nucleus is found to be very active nucleus in pharmacy field as several natural alkaloids having indole as their basic ring are found to be therapeutically active agents. In the recent years a lots of synthetic drugs have been synthesized & found to be promissing anticancer, antimicrobial, anticonvulsants, & antidiabetic agents. In the present review the several newer activities have been concluded as Liver x receptor (lxr) agonist, Tyrosin kinase inhibitor, Hepatoprotective, Antiviral, Melanotonin analogus etc.)

Keywords :- (Indole, Isatin, Anticancer, Antiviral, Anticonvulsant)

INTRODUCTION

The name *indole* is portmanteau of the words ***ind****igo* and ***ole****um*, 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. [1]

Indole derivatives are found to contain several biological activities those including antimicrobial, antibiotic, anti-inflammatory, analgesic, anticonvulsant, antimalarial,

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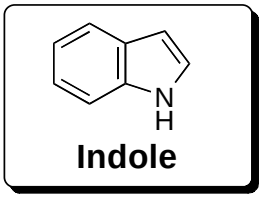
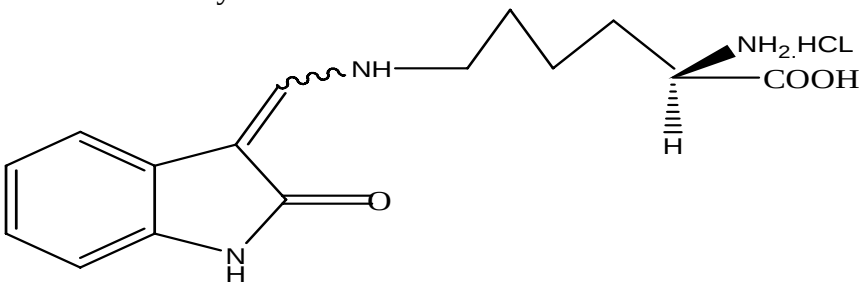
anticancer, antiulcer, & Antileishmanial , contraceptive, antioxidant etc. The derivatives are also found to have agonistic effects on several receptors such as Liver x receptor, 5-HT_{1D} receptor etc.



BIOLOGICAL ACTIVITIES

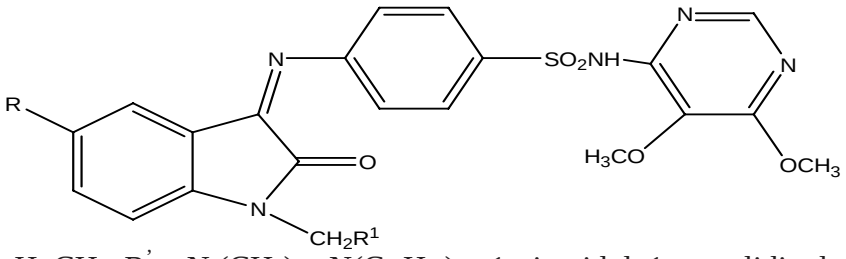
ANTIMICROBIAL ACTIVITY

- Moreau *et al* synthesized a series of indolin-2-one derivatives substituted in the 3-position by an aminomethylene group bearing either an ornithine or a lysine residue . (1) The antibacterial activities were tested against two Gram-positive bacteria Bacillus cereus and Streptomyces chartreusis, a Gram-negative bacterium Escherichia coli and a yeast Candida albicans.[2]



(1)

- Pandeya *et al* synthesized Schiff bases of isatin and 5-methyl isatin with sulphadoxine. The piperidino methyl compounds (2) were found to be the most active ones among all compound prepered. Compounds were active against *Candida albicans, Candida neoformis, Histoplasma capsulatum, Microsporum audounii* and *Trichophyton mentagrophytes.*[3]

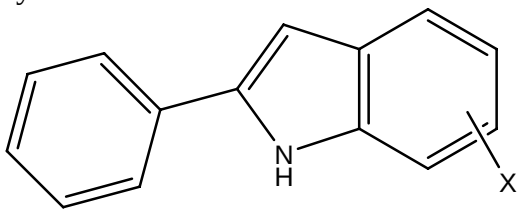


R = H, CH_3, R' = N $(CH_3)_2$, N(C_2 H_5 $)_2$, 1-piperidyl, 1-pyrrolidinyl, 4-morpholinyl,

(2)

- Kumar *et al* synthesized a series of 2-phenyl sulpha/substituted indoles (3) by the interaction of sulpha/substituted anilines and phenacyl halide. The newly

synthesized compounds were tested for antibacterial and anti-inflammatory activity.[4]

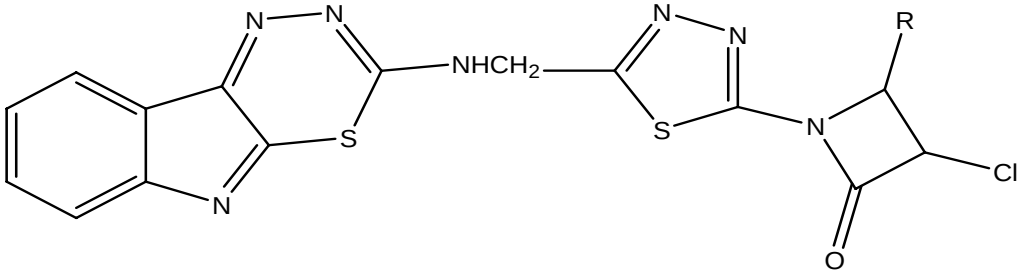


X = Cl, F, NO_2, $C_6H_5SO_2NH_2$

(3)

ANTI-INFLAMMATORY ACTIVITY

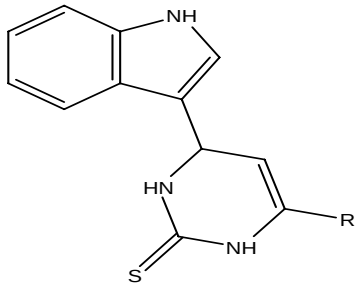
- Kumar *et al* synthesized a series of new substituted azetidinoyl and thiazolidinoyl-1,3, 4-thiadiazino (6,5-b) indoles (4) and tested for anti inflammatory activities Anti-inflammatory against carrageenan induced rat's paw oedema.[5]



R = C_6H_5, 4-ClC_6H_4, $OCH_3C_6H_4$,4-OHC_6H_4

(4)

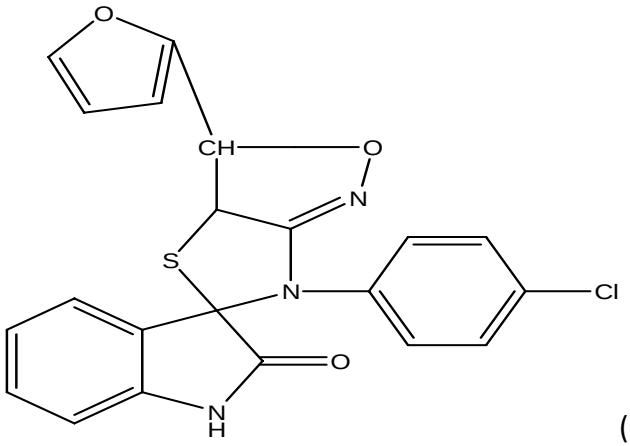
- Amir *et al* prepared and screened for the biological activities of some 4-(1*H*-indol-3-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidin-2-ones/thiones (5) as potent anti-inflammatory agents.[6]



(5)

R= phenyl, 4-chlorophenyl,2,4-dichlorophenyl,4-methylphenyl,3,4-dimethylphenyl

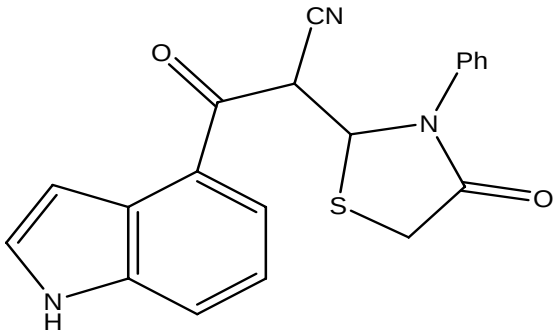
- Mana *et al* synthesized a series of novel derivative of indole, containing the thiazole and isoxazole moieties, (6) by isatin and evaluated for anti-inflammatory activitiey. Anti-inflammatory activitiy was performed by carrageenan induced oedema method. The compound showed significant anti-inflammatory activity.[7]



(6)

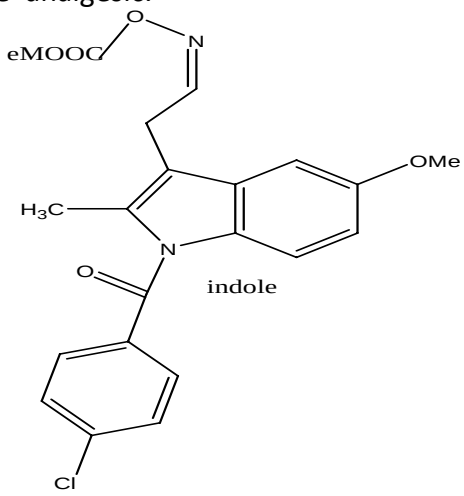
ANALGESIC ACTIVITY

- Radwan *et al* synthesized and evaluated the analgesic activity of 3-substituted indole derivatives . The Tholidine-4-one derivative (7) was found to exhibit analgesic activity.[8]



(7)

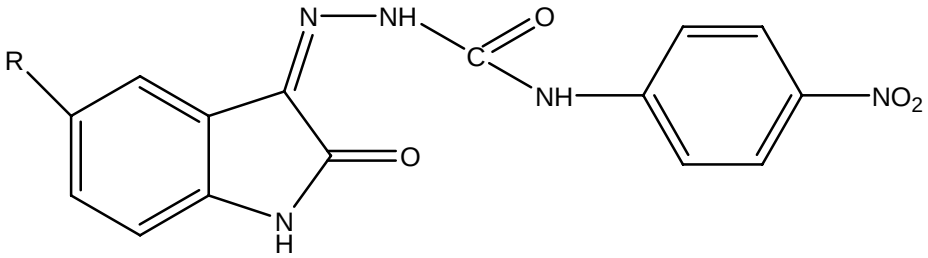
- Abele *et al* synthesized isatin and indole oximes and the compound (8) was found to be the most active analgesic.[9]



(8)

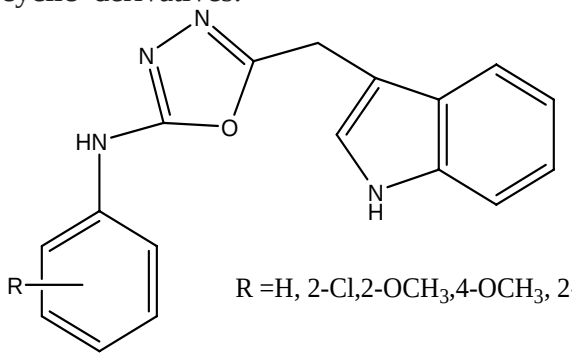
ANTICONVULSANT ACTIVITY

- Pandeya *et al* synthesized a series of *p*-nitrophenyl substituted semicarbazones (9) and their anticonvulsant activities were screened against maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (scSTY) tests.[10]



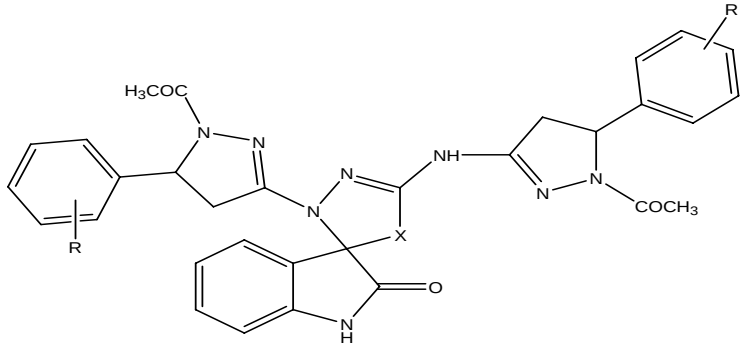
R == H, Cl, NO_2 (9)

- Siddiqu *et al* synthesized & evaluated the anticonvulsant activities of 2-(1*H*-indol-3-yl)acetyl-*N*-(substituted phenyl)hydrazine carbothioamides.(10) and their related heterocyclic derivatives.[11]



R =H, 2-Cl,2-OCH_3,4-OCH_3, 2-CH_3, 3-CH_3, 4-CH_3 (10)

- Kumar *et al* synthesized some new pyrazolinyl /isoxazolinylindol-2-ones (11). These compounds were screened for their anticonvulsant activity against maximum electroshock induced seizures.[12]

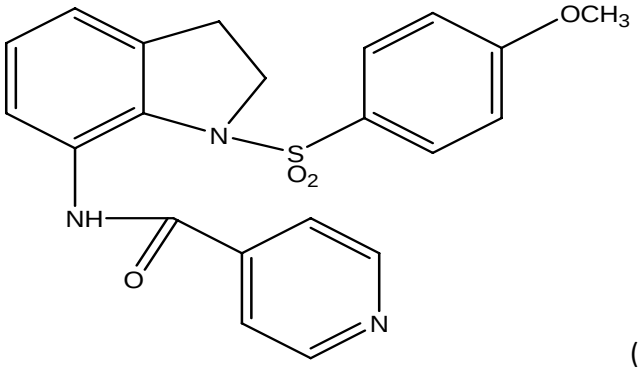


(11)

R = 2-OH, 4-OCH_3, 3-OCH_3, 4-OH, 4-$N(CH3)_2$, 2-OH,4-OCH_3,3-OCH_3,4-OH,$N(CH3)_2$ X= O,S

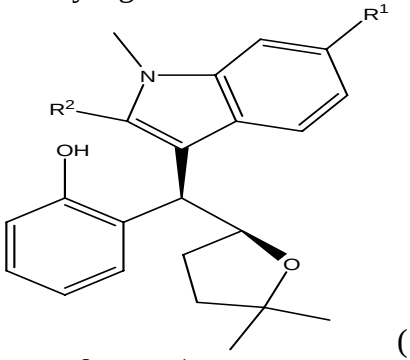
ANTICANCER ACTIVITY

- Liou *et al* synthesized a novel oral indoline-sulfonamide agent, j30 (12) exhibiting potent activity against human cancer cells *in vitro* and *in vivo* through the disruption of microtubule.[13]



(12)

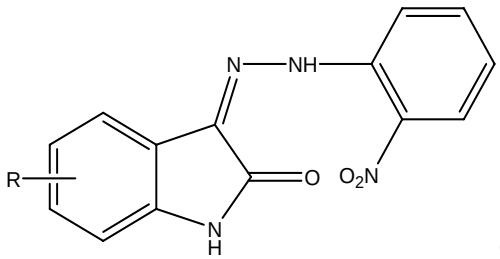
- Sigman *et al* synthesized and carried out the preliminary biological studies of 3-substituted Indoles (13) accessed by a palladium-catalyzed enantioselective alkene difunctionalization reaction. Evaluation of several of the compounds revealed promising anticancer activity against MCF-7 cells.[14]



(13)

R^2= Ph, R^1= H (G1 phase arrest), R^2= H, R^1= $COOCH_3$ (G2 phase arrest)

- Popp and Pajouhesh *et al* synthesized 3-*o*-nitrophenyl hydrazones of isatin (14) by condensation of isatin with *o*-nitrophenyl hydrazine. These compounds were found to be active intramuscularly against Walker carcinoma-256 and inactive against L-1210 lymphoid leukaemia.[15]

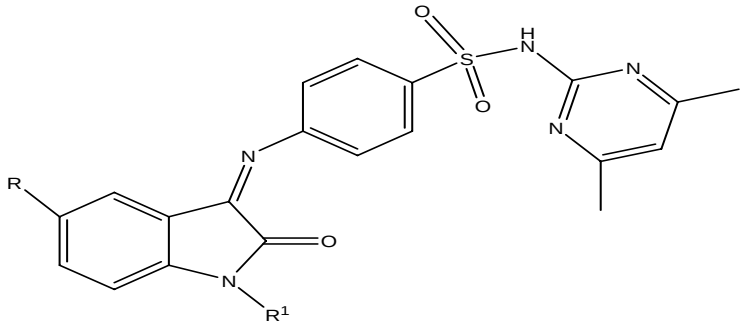


(14)

R= H, 1-CH_3, 1-$COCH_3$, 4-CF_3, 5-Br, 5-Cl, 5-SO_3H etc.

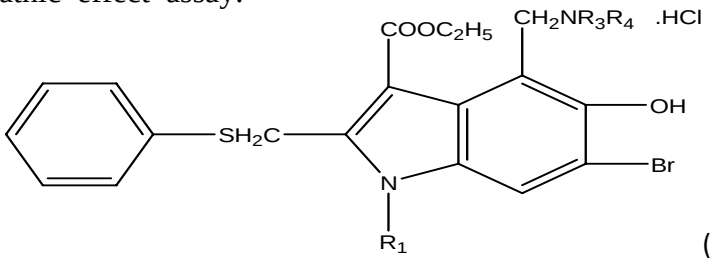
ANTIVIRAL ACTIVITY

- Selvam *et al* prepared 4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-*N*-(4,6-dimethyl-2-pyrimidin-2-yl)benzenesulphonamide and its derivatives (15,16,17). The related compounds were tested for antiviral activity against influenza A (H1N1, H3N2, and H5N1) and B viruses in Madin Darby canine kidney (MDCK) cell culture. [16]

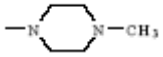


Compounds	R	R_1
15	Br	H
16	Cl	H
17	F	H

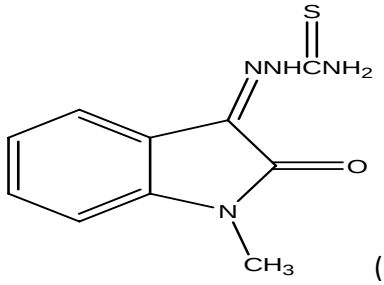
- Dun Wang *et al* synthesized some new derivatives of 3-ethoxycarbonyl-6-bromo-5-hydroxyindoles (18) and their antiviral activity were determined in cell culture with virus cytopathic effect assay.[17]



(18)

R_1	R_2	NR_3R_4
$-CH_3$	*p*-F	

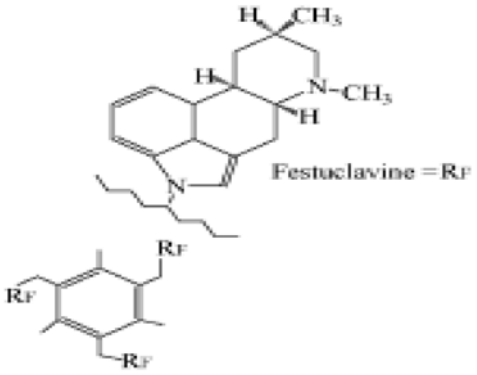
- Methisazone (*N*-methyl isatin-3-thiosemicarbazone) (19) was found to be an effective compound against *variola* and *vaccinia* viruses[18].



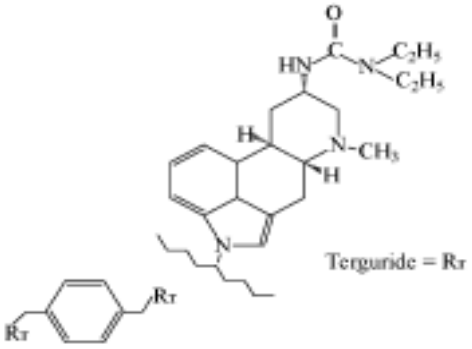
(19)

ANTIMALARIAL ACTIVITY

- The only indole semi-synthetic antiplasmodial compounds known are derivatives of ergolines, which are either natural compounds isolated from *Claviceps purpurea* (festuclavine.) or semi-syntheticcompounds used in clinical routine (terguride.). There are two derivatives of interest: a dimeric derivative of terguride (20) and a trimeric derivative of festuclavine (21).[19]



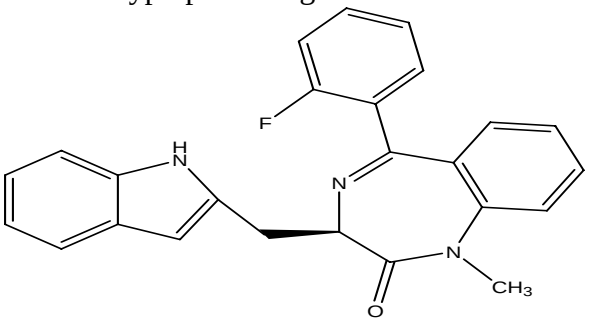
Trimeric derivative (21)



Dimeric derivative (20)

ANTIARRYTHMIC ACTIVITY

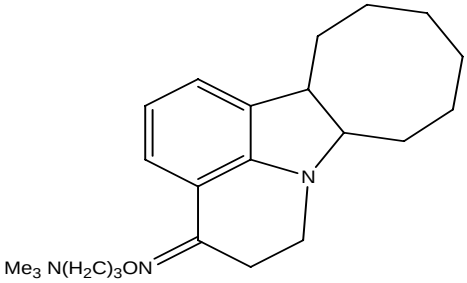
- Compound R-L3 or L-364 373 [(3-R)-1, 3-dihydro-5- (2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-methyl-2H-1, 4-benzodiazepin-2-one)] (22) is an activator of Kv7.1 channel and thus leads to hyperpolarizing effect.[20]



(22)

ANTIHYPERTENSIVE ACTIVITIY

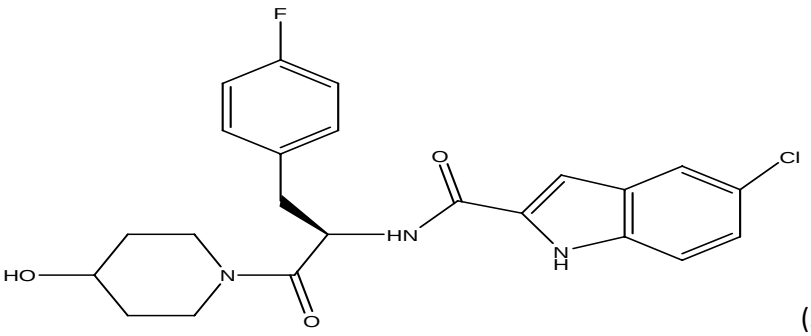
- Among the various isatin and indole oximes reported by the Abele *et al* compound (23) was found to contain hypotensive activity lowering the blood pressure in rats by 28 %.[21]



(23)

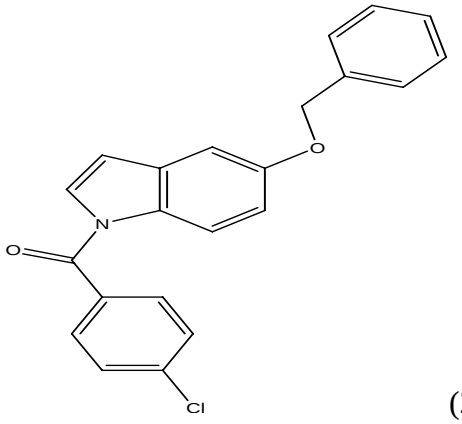
ANTIDIABETIC ACTIVITY

- A distinct site at the monomer interface known as the indole inhibitor site. Compound (24) inhibited liver and muscle GP in the nM range in enzyme kinetics and was active in forskolin-induced, cell-based glycogenolysis in the mM range (1.9 mM).[22]



(24)

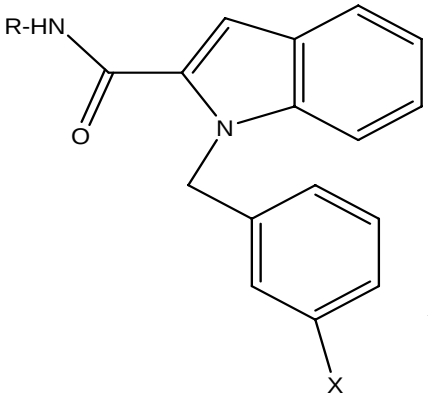
- Li *et al* senthesized the indole derivatives (25) which were evaluated for their insulin sensitizing and glucose lowering effects.[23]



(25)

ANTIOXIDENT ACTIVITY

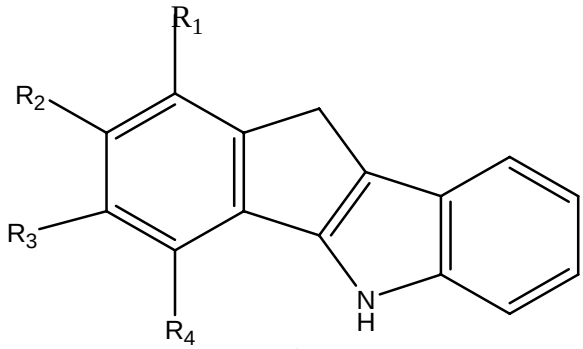
- Enien *et al* synthesized indole-2 and 3- carboxamides (26) and evaluated their biological activities as antioxidant by chemoluminesence and electron spin response spin trapping.[24]



X=H, R= Thiazoyl indole 2-corbexamide

(26)

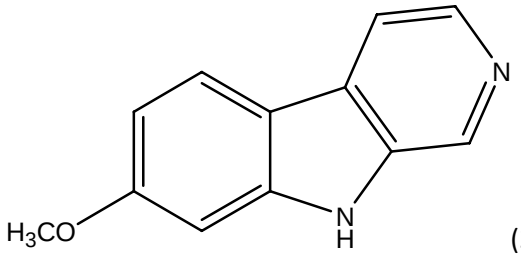
- Talaz *et al* described the synthesis of 5,10- dihydroindolo[1,2-b]indoles (27) containing substituents such as methoxy, hydroxyl, and halogens on indeno part and their antioxidant activities were assayed by various in vitro assays.[25]



R_1= 0Me, R_2=H, R_3=H, R_4= OMe (27)

ANTILEISHMANIAL ACTIVITY

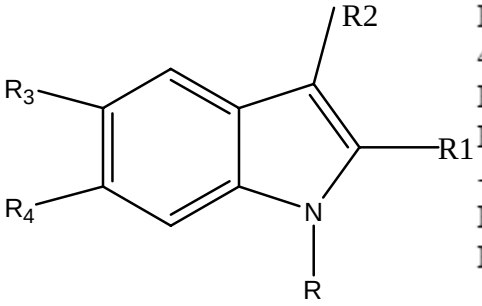
- Mishra *et al* presented a review on natural products as antileishmanial and showed the Harmaline (28) is an indole alkaloid and a potent leishmanisidal agent.[26]



(28)

ANTIFERTILITY ACTIVITY

- Chaudhary *et al* showed that various indole derivatives (29) act as effective antifertility agents.[27]

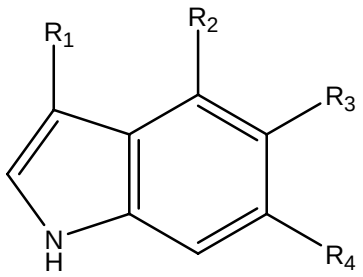


R=H, COCH, COPh, 4-COC_6H_4Cl
4-COC_6H_4OH, 4-$CH_2CH_2N(C_2H_5)_2$
R_1=H, Ph, 4-FC_6H_4, Me
R_2=H, CH_2COOH,-$CH_2CH_2NH_2$,
-$CH_2CH_2NHCOMe$, $CH_2(NHAc)COOH$
R_3=H, MeO, F
R_4=H, Cl, F

(29)

HALLUCINOGENIC ACTIVITY

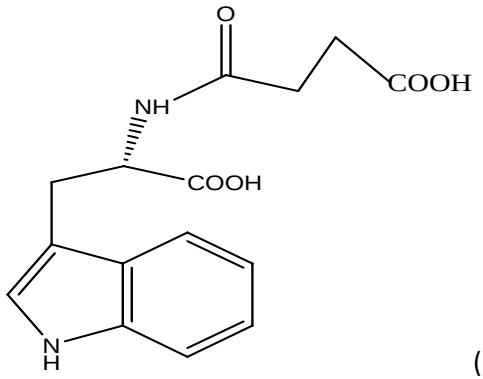
- Indole is the base for a diverse group of hallucinogenic agents that may be subdivided into simple indole, harmine and polycyclic derivatives. Many of the 3-substituted derivatives show potent hallucinogenic activities.[28]



Compounds	R1	R2	R3	R4
(30)Bufotenine	$(CH_2)_2N(CH_3)_2$	H	OH	H
(31) Psilocin	$(CH_2)_2N(CH_3)_2$	OH	H	H
(32) 6-Hydroxy-diethyltryptamine	$(CH_2)_2N(C_2H_5)_2$	H	H	OH
(33)Dimethyltryptamine	$(CH_2)_2N(CH_3)_2$	H	H	H

IMMUNOMODULATRY ACTIVITY

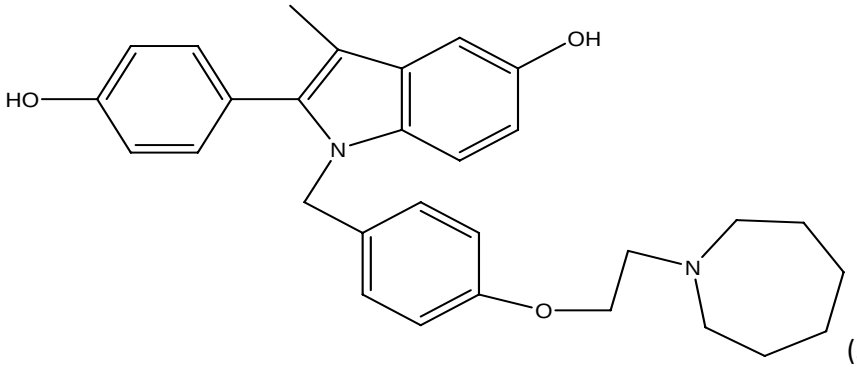
- Oglufanide (34), at one time called thymogen, is a dipeptide isolated from calf thymus. The imunnomodulatory properties of both the natural product and the subsequent synthetic version s have been extensively studied as agents that enhances immune function. The compound currently is undergoing clinical trials in patients infected with the hepatitis C virus.[29]



(34)

ESTROGEN ANTAGONISTIC ACTIVITY

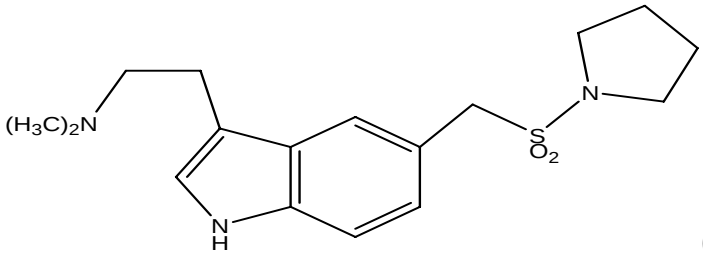
- An indole provides the nucleus for the estrogen antagonist bazedoxifene (35); not only the ring system, but also the connectivity of the benzene ring that carries the basic ether differs from earlier compounds.[29]



(35)

5-HT$_3$ ANTAGONIST

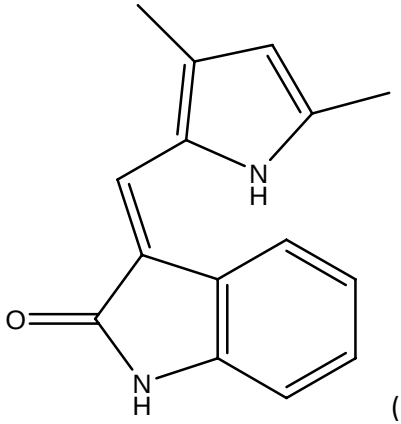
- Almotriptan is a indole derivative (36) and is a 5-HT$_3$ antagonist.[29]



(36)

TYROSINE KINASE INHIBITOR

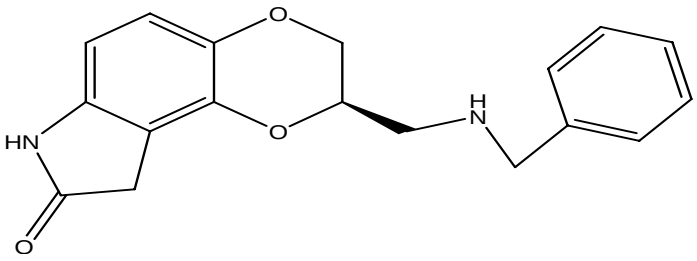
- Semaxanib (37) is a tyrosine kinase inhibitor & has shown promising early activity against solid tumors; this compound inhibits neoangiogenisis and also shows antimetastatic activity.[29]



(37)

ANTIPARKINSON ACTIVITY

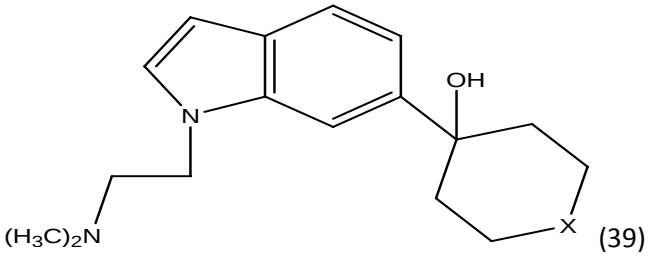
- Parkinson's disease is conversely traceable to a deficiency of dopamine. Most treatments for that disease involve administration of compounds that make up for that deficiency. The indolone aplindore (38), acts as a partial agonists at the subclass of dopamine receptors associated with Parkinson's. The drug is currently in the clinic for that indication. The compound also interestingly shows some promise for treating "restless leg syndrome"[29]



(38)

5-HT$_{1D}$ AGONISTIC ACTIVITY

- Isaac *et al* synthesized a novel series of highly potent human 5-HT1D agonists (39), dimethyl-{2-[6-substituted-indol-1-yl]-ethyl}-amine.[30]

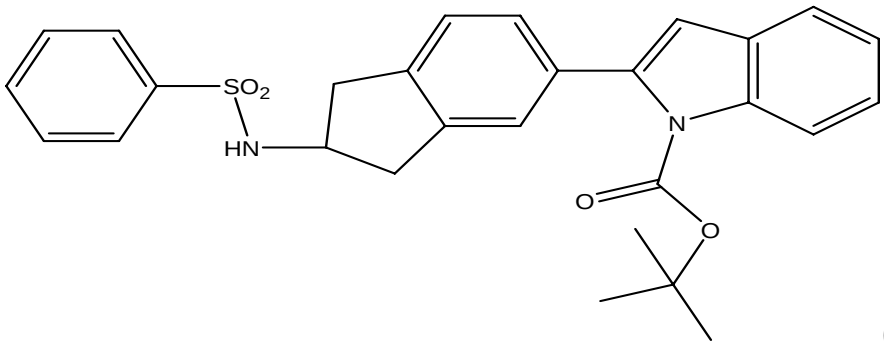


(39)

LIVER X RECEPTOR (LXR) AGONISTIC ACTIVITY

- A structurally novel liver X receptor (LXR) agonist **(**40**)** was identified from internal compound collection utilizing the combination of structure-based virtual

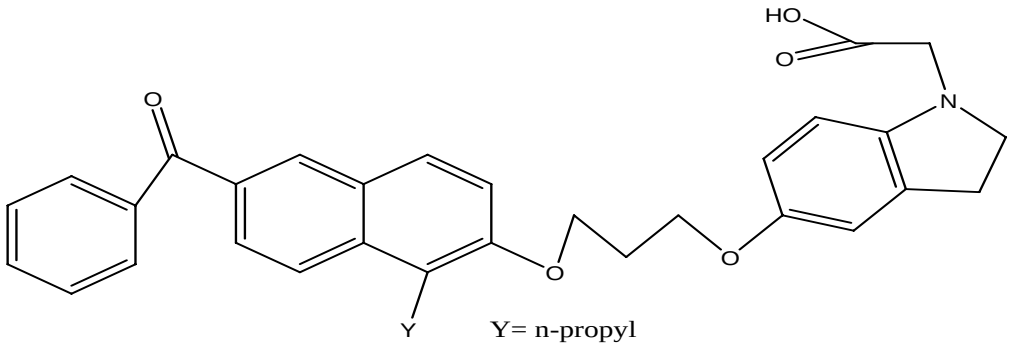
screening and high-throughput gene profiling. Compound increased ABCA1 gene expression by eightfold and SREBP1c by threefold in differentiated THP-1 macrophage cell lines. Confirmation of its agonistic activity against LXR was obtained since the co-factor recruitment and reporter transactivation assays.[31]



(40)

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTIC ACTIVITY

- Mahindroo *et al* synthesized and evaluated a series of indole based PPAR agonists. The compound (41) was found to be the most potent PPAR agonist with IC50 = 0.050 µM.[32]



(41)

CONCLUSION

As the therapeutic value of indole derivatives are shown above, the indole is found to be a very versatile nucleus in the pharmaceutical field. The derivatives are very much used as anticancer, antimicrobial, antiviral, anti-inflammatory agents etc. In addition to synthetic derivatives, several natural products having indole moieties are very important, such as those including indole alkaloids which are used as antimalarial, anticancer, hallucinogenic etc.

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