

## INDOLE - AN INTERESTING SCAFFOLD IN DRUG DISCOVERY

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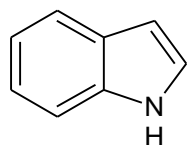
### ABSTRACT

Indole represents one of the most important heterocyclic ring which provides privileged scaffolds in drug discovery. Indole derivatives and its pharmacological significance provides tremendous opportunities to discover novel drugs with different modes of action. Several natural alkaloids having indole as their basic ring are found to be therapeutically active agents. A lots of synthetic drugs have been synthesized & found to be promising antimicrobial, anticonvulsants, anticancer & antidiabetic agents. In the present review the several newer activities have been concluded as Liver x receptor (Ixr) agonist, Tyrosine kinase inhibitor, Hepatoprotective, Antiviral, Melanotoninanalogus etc.

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

### INTRODUCTION

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.<sup>1</sup>

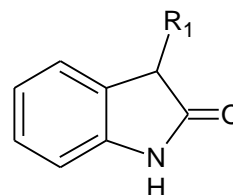


Indole

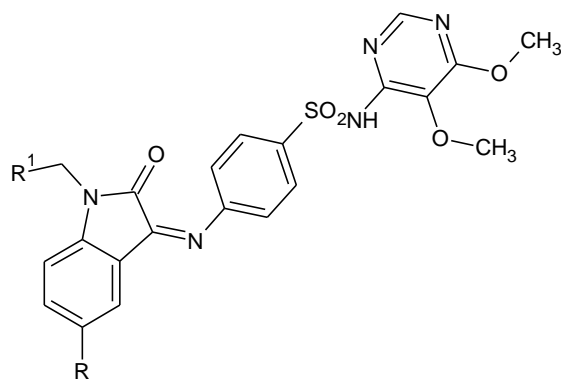
Indole derivatives are found to contain several biological activities those including antimicrobial, antibiotic, anti-inflammatory, analgesic, anticonvulsant, antimalarial, anticancer, antiulcer, & antileishmanial, contraceptive, antioxidant etc. The derivatives are also found to have agonistic effects on several receptors such as Liver x receptor, 5-HT<sub>1D</sub> receptor etc.

### 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*.<sup>2</sup>

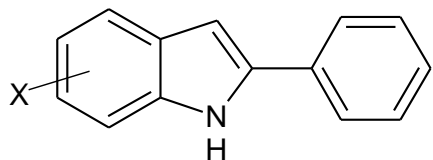


Pandeya *et al* synthesized Schiff bases of isatin and 5-methyl isatin with sulphadoxine. The piperidino methyl compounds (2) were found to be the most active ones among all compound prepared. Compounds were active against *Candida albicans*, *Candida neoformis*, *Histoplasma capsulatum*, *Microsporium audouinii* and *Trichophyton mentagrophytes*.<sup>3</sup>



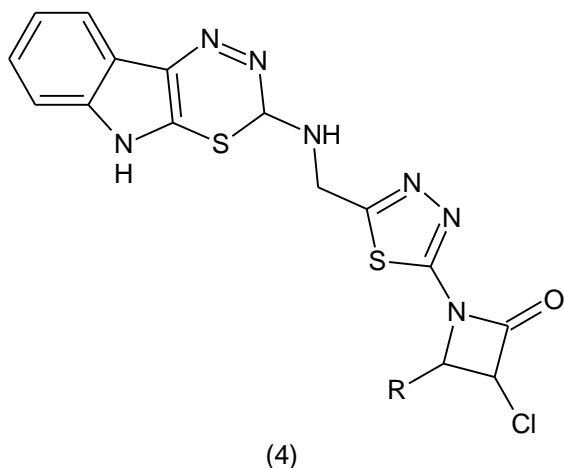
R=H, CH<sub>3</sub>, R=N(CH<sub>3</sub>)<sub>2</sub>, N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, 1-pyrrolidinyl, 4-morpholinyl

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<sup>4</sup>.



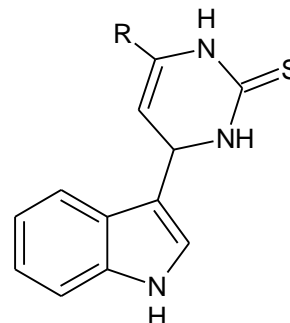
#### ANTI-INFLAMMATORY ACTIVITY

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 activity against carrageenan induced rat's paw oedema<sup>5</sup>.



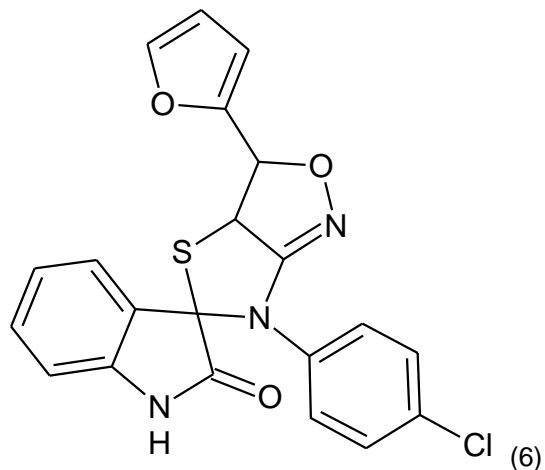
R=C<sub>6</sub>H<sub>5</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>

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<sup>6</sup>.

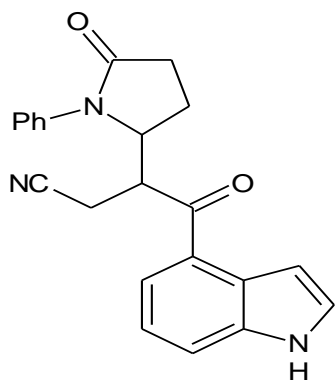


R= phenyl, 4-chlorophenyl, 2, 4-dichlorophenyl, 4-methylphenyl, 3,4-dimethylphenyl

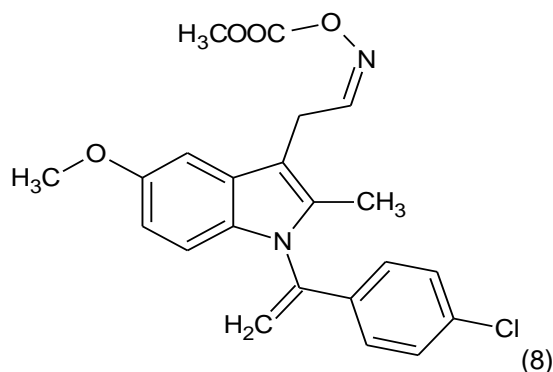
Maneet *al* synthesized a series of novel derivative of indole, containing the thiazole and isoxazole moieties, (6) by isatin and evaluated for anti-inflammatory activities. Anti-inflammatory activity was performed by carrageenan induced oedema method. The compound showed significant anti-inflammatory activity<sup>7</sup>.



Radwanet *al* synthesized and evaluated the analgesic activity of 3-substituted indole derivatives. The Tholidine-4-one derivative (7) was found to exhibit analgesic activity<sup>8</sup>.

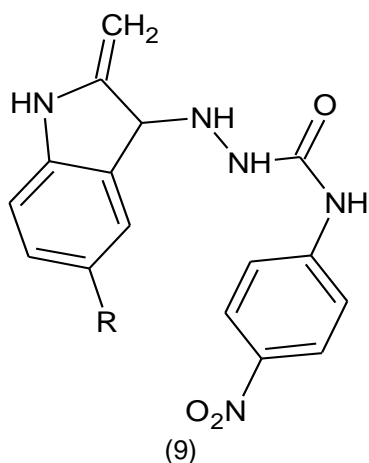


Abele *et al* synthesized isatin and indoleoximes and the compound (8) was found to be the most active analgesic<sup>9</sup>.



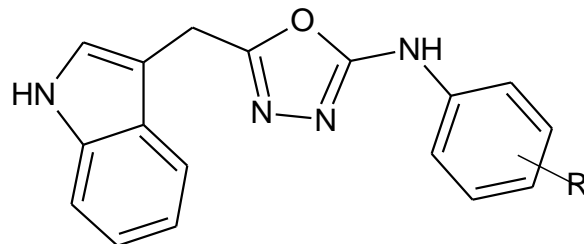
### ANTICONVULSANT ACTIVITY

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<sup>10</sup>.



Where, R=H, Cl, NO<sub>2</sub>

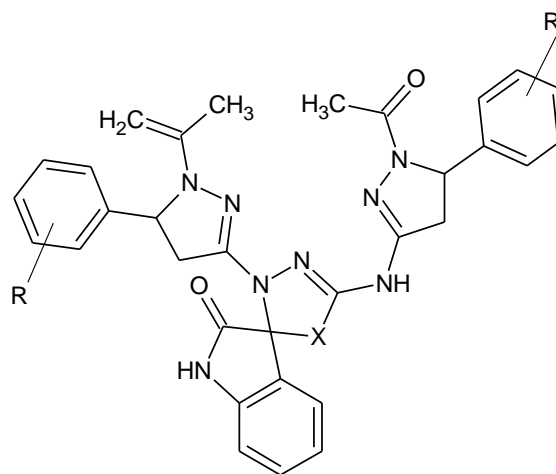
Siddiquet *al* synthesized & evaluated the anticonvulsant activities of 2-(1*H*-indol-3-yl)acetyl-*N*-(substituted phenyl)hydrazine carbothioamides (10) and their related heterocyclic derivatives<sup>11</sup>.



(10)

R =H, 2-Cl, 2-OCH<sub>3</sub>, 4-OCH<sub>3</sub>, 2-CH<sub>3</sub>, 3-CH<sub>3</sub>, 4-CH<sub>3</sub>

Kumar *et al* synthesized some new pyrazolonyl/isoxazolonylindol-2-ones (11). These compounds were screened for their anticonvulsant activity against maximum electroshock induced seizures<sup>12</sup>.

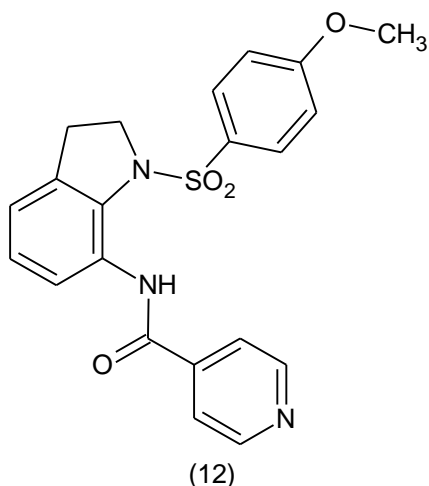


(11)

R = 2-OH, 4-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 4-OH, 4-N(CH<sub>3</sub>)<sub>2</sub>,  
2-OH, 4-OCH<sub>3</sub>, 3-OCH<sub>3</sub>, 4-OH, N(CH<sub>3</sub>)<sub>2</sub>  
X = O, S

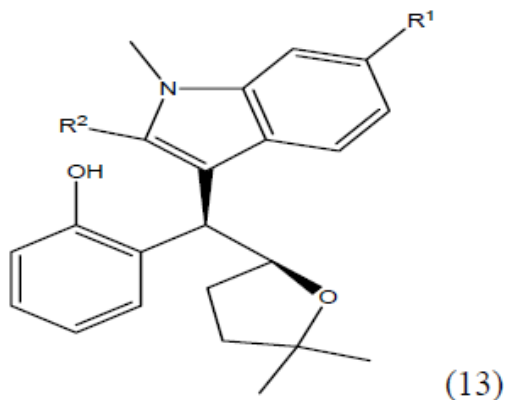
### ANTICANCER ACTIVITY

Liouet *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<sup>13</sup>.



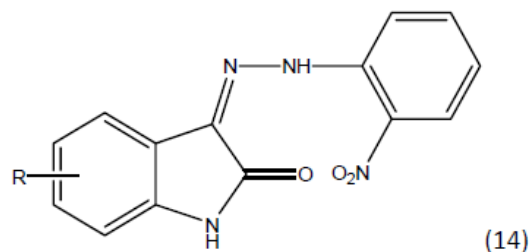
Derivative	R <sup>1</sup>	R <sup>2</sup>
15	Br	H
16	Cl	H
17	F	H

Sigmanet *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<sup>14</sup>.



R<sup>2</sup> = Ph, R<sup>1</sup> = H (G1 phase arrest), R<sup>2</sup> = H, R<sup>1</sup> = COOCH<sub>3</sub> (G2 phase arrest)

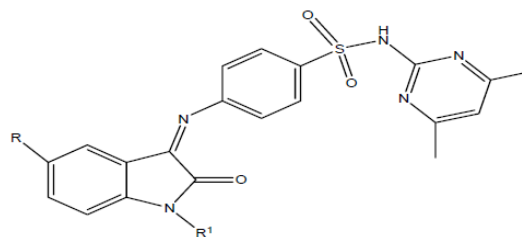
Popp and Pajouheshet *al* synthesized 3-o-nitrophenyl hydrazones of isatin (14) by condensation of isatin with o-nitrophenyl hydrazine. These compounds were found to be active intramuscularly against Walker carcinoma-256 and inactive against L-1210 lymphoid leukaemia<sup>15</sup>.



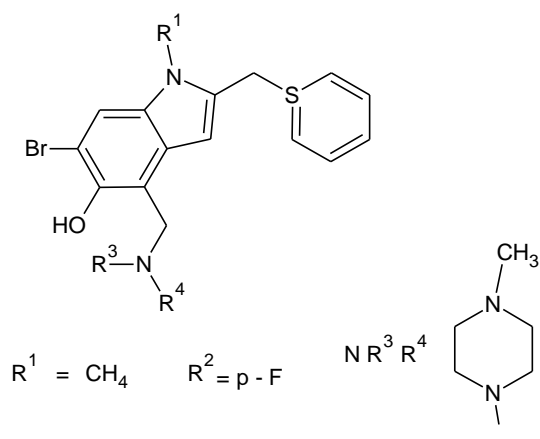
R = H, 1-CH<sub>3</sub>, 1-COCH<sub>3</sub>, 4-CF<sub>3</sub>, 5-Br, 5-Cl, 5-SO<sub>3</sub>H etc.

### ANTIVIRAL ACTIVITY

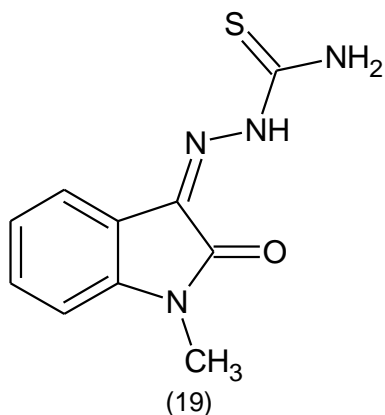
Selvamet *al* prepared 4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-N-(4,6-dimethyl-2-pyrimidin-2-yl)benzenesulphonamide and its derivatives (15,16,17). The related compounds were tested for antiviral activity against influenza A (H1N1, H3N2, and H5N1) and B viruses in Madin Darby canine kidney (MDCK)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



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<sup>17</sup>.



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

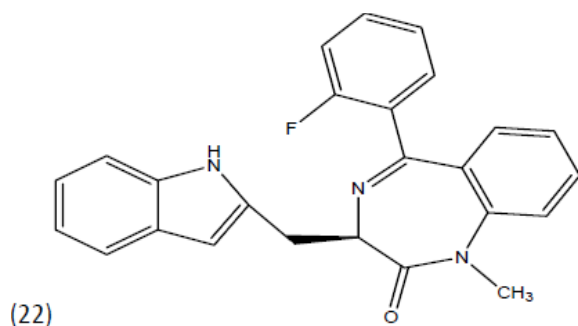


#### ANTIMALARIAL ACTIVITY

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

#### ANTIARRHYTHMIC ACTIVITY

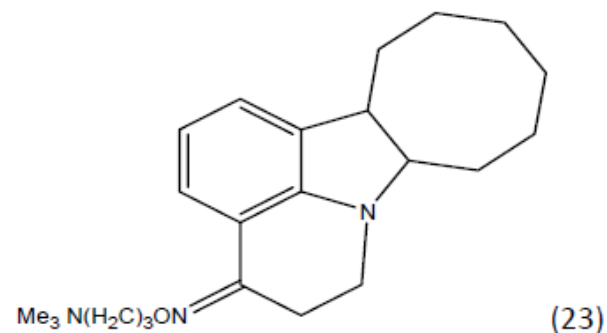
Compound R-L3 or L-364 373 [(3-*R*)-1, 3-dihydro-5-(2-fluorophenyl)-3-(1*H*-indol-3-ylmethyl)-1-methyl-2*H*-1, 4-benzodiazepin-2-one] (22) is an activator of Kv7.1 channel and thus leads to hyperpolarizing effect<sup>20</sup>.



#### ANTIHYPERTENSIVE ACTIVITY

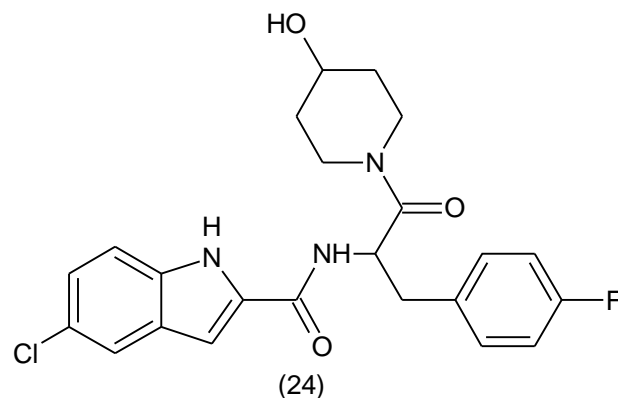
Among the various isatin and indoleoximes reported by the Abele *et al* compound (23) was

found to contain hypotensive activity lowering the blood pressure in rats by 28 %<sup>21</sup>

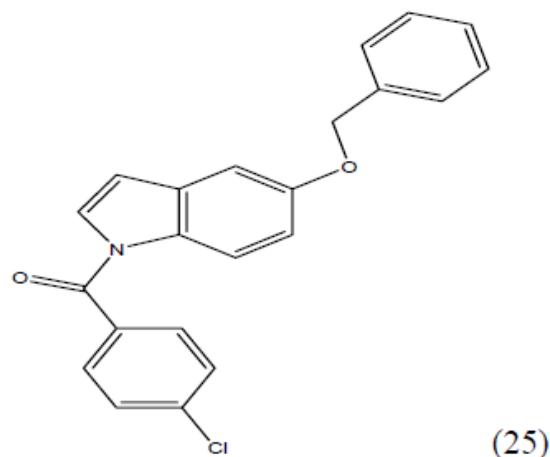


#### ANTIDIABETIC ACTIVITY

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)<sup>22</sup>.

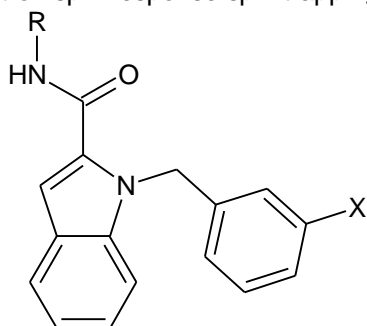


Li *et al* synthesized the indole derivatives (25) which were evaluated for their insulin sensitizing and glucose lowering effects<sup>23</sup>.



**ANTIOXIDENT ACTIVITY**

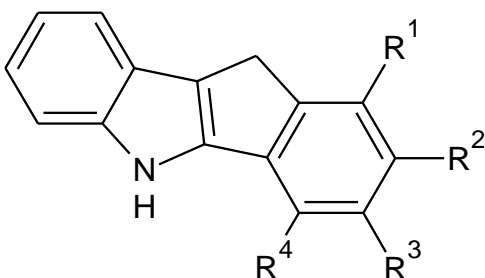
Enienet *et al* synthesized indole-2 and 3-carboxamides (26) and evaluated their biological activities as antioxidant by chemoluminescence and electron spin response spin trapping<sup>24</sup>.



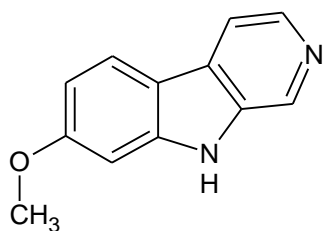
(26)

X=H, R=Thiazoylindole 2-carboxamide

Talazet *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<sup>25</sup>.

**ANTILEISHMANIAL ACTIVITY**

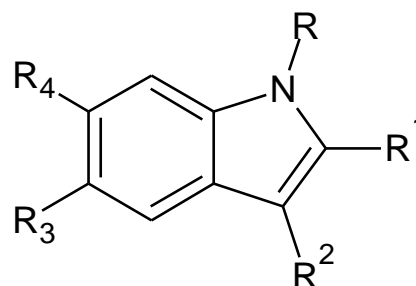
Mishra *et al* presented a review on natural products as antileishmanial and showed the HarmalineM



(28)

**ANTIFERTILITY ACTIVITY**

Chaudhary *et al* showed that various indole derivatives (29) act as effective antifertility agents<sup>27</sup>.



(29)

R=H, -COCH<sub>3</sub>, -COPh, 4-COC<sub>6</sub>H<sub>4</sub>Cl, 4-COC<sub>6</sub>H<sub>4</sub>OH, 4-CH<sub>2</sub>CH<sub>2</sub>N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>

R<sub>1</sub>=H, Ph, 4-FC<sub>6</sub>H<sub>4</sub>, -Me

R<sub>2</sub>=H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>NHCOMe, CH<sub>2</sub>(NHAc)COOH

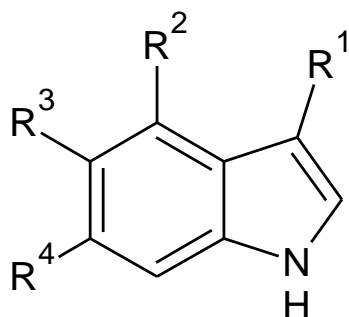
Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
(30)Bufotenine	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	OH	H
(31)Psilocin	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	OH	H	H
(32) 6-Hydroxy-diethyltryptamine	(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	H	OH
(33)Dimethyltryptamine	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	H	H

R<sub>3</sub>=H, MeO, F

R<sub>4</sub>=H, Cl, F

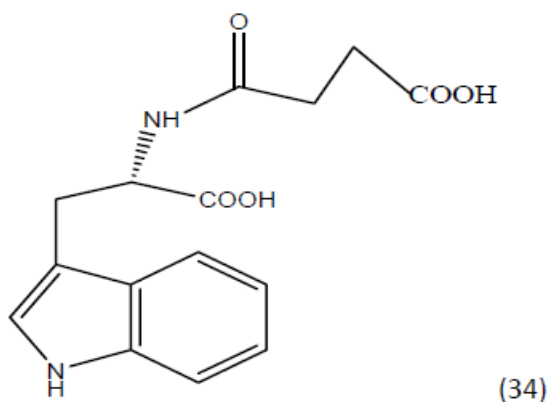
**HALLUCINOGENIC ACTIVITY**

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<sup>28</sup>.



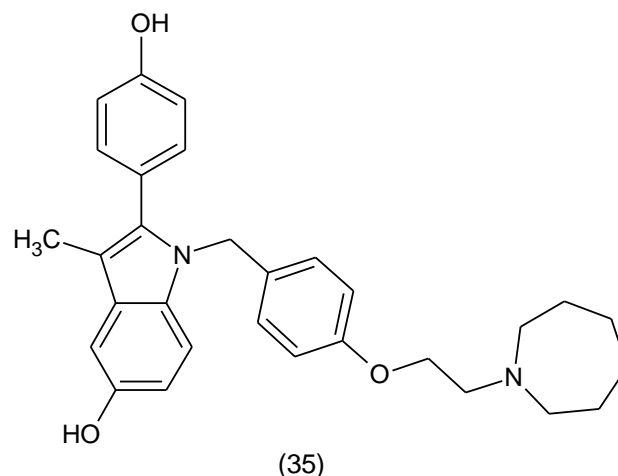
### IMMUNOMODULATORY ACTIVITY

Oglufanide (34), at one time called thymogen, is a dipeptide isolated from calf thymus. The immunomodulatory 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<sup>29</sup>.



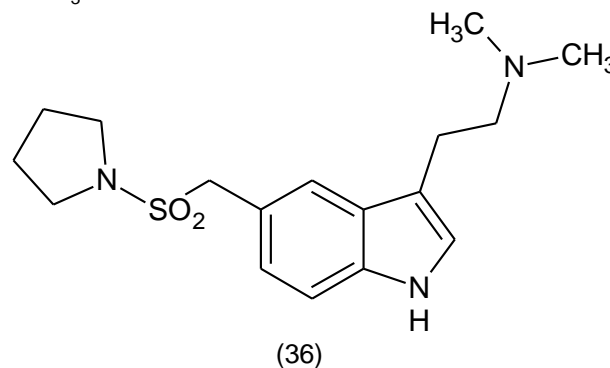
### ESTROGEN ANTAGONISTIC ACTIVITY

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<sup>29</sup>.



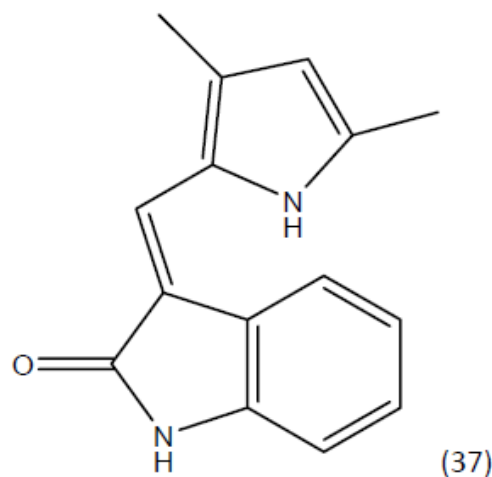
### 5-HT<sub>3</sub> ANTAGONIST

Almotriptan is an indole derivative (36) and is a 5-HT<sub>3</sub> antagonist<sup>29</sup>.



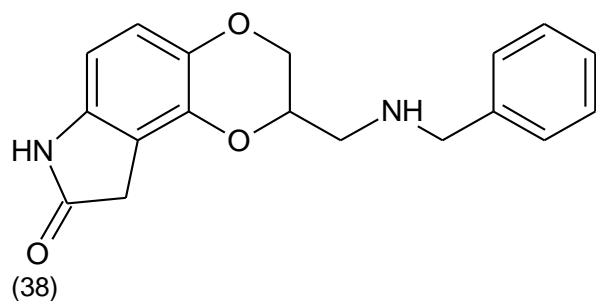
### TYROSINE KINASE INHIBITOR

Semaxanib (37) is a tyrosine kinase inhibitor & has shown promising early activity against solid tumors; this compound inhibits neoangiogenesis and also shows antimetastatic activity<sup>29</sup>.

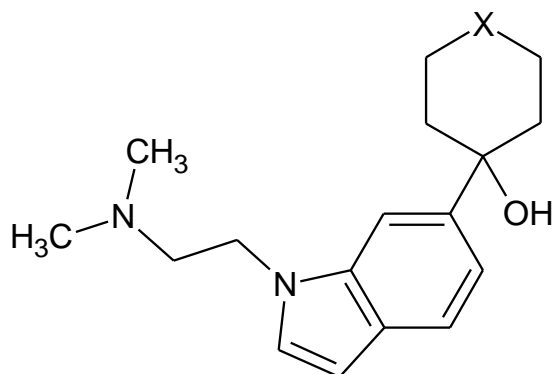


**ANTIPARKINSON ACTIVITY**

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 indoloneaplindore (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"<sup>29</sup>

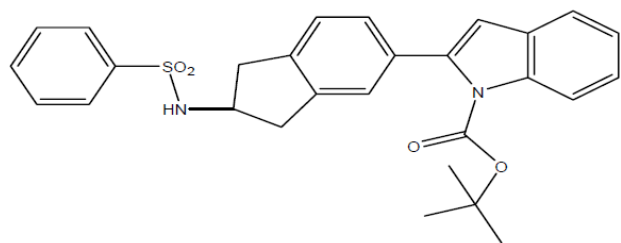
**5-HT<sub>1D</sub> AGONISTIC ACTIVITY**

Isaac *et al* synthesized a novel series of highly potent human 5-HT<sub>1D</sub> agonists (39), dimethyl-[2-[6-substituted-indol-1-yl]-ethyl]-amine<sup>30</sup>.

**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

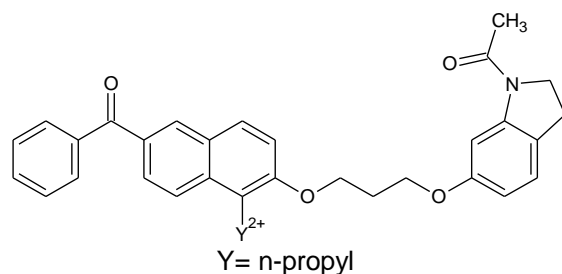
since the co-factor recruitment and reporter transactivation assays<sup>31</sup>.



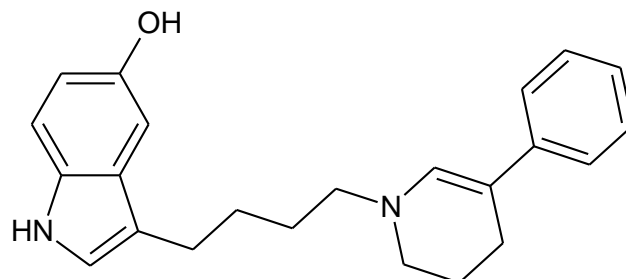
(40)

**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 IC<sub>50</sub> = 0.050 μM<sup>32</sup>.

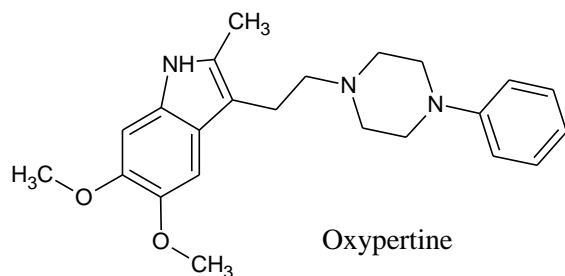
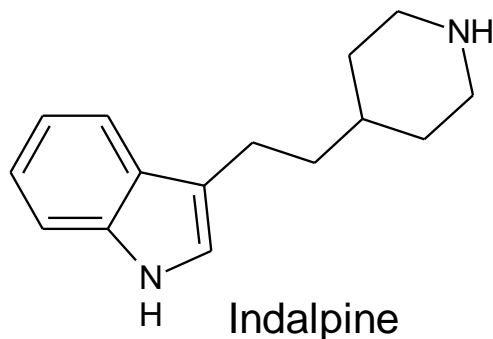
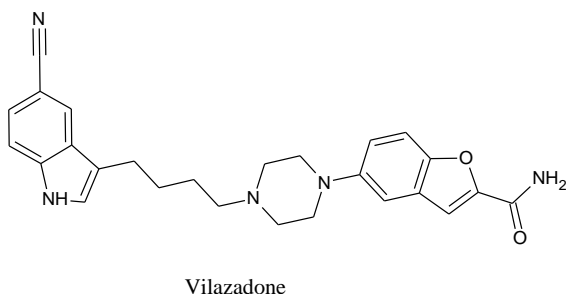
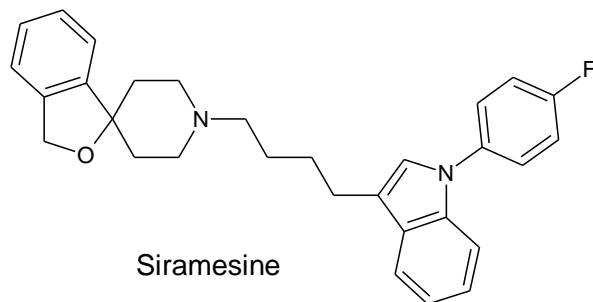
**CENTRAL NERVOUS SYSTEM ACTING DRUGS ON MARKET OR COMPOUNDS IN CLINICAL EVALUATION**

Indole scaffold is widely used in central nervous system disease research. Examples of marketed indole containing central nervous system acting drugs includes Vilazodone. Meanwhile, a number of indole derivatives are actively undergoing different phases of clinical evaluation, such as indalpine, siramesin, oxypertine, roxindole.<sup>33-39</sup>



Roxindole





## 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. A number of indole derivatives are actively undergoing different phases of clinical evaluation for Central Nervous activity.

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