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Indole Derivatives acting on Central Nervous System – Review

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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. There are also amazing numbers of indole containing drugs in the market as well as compounds in clinical evaluation. This review serves as a comprehensive overview of currently published indole containing central nervous system acting agents with the main objectives in comprehensive listings of indole containing central nervous system drugs on market or compounds in clinical evaluation and to focus on recent developments of indole derivatives which are currently evaluated in experimental studies and their central nervous system activities.

KEYWORDS: Indole, anticonvulsant, antidepressant, antianxiety, sedative, hypnotic

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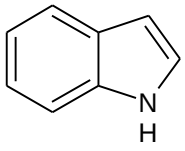
1. INTRODUCTION

The name *indole* is portmanteau of the words *indigo* and *oleum.* Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a benzene ring and a pyrrole nucleus are fused in 2, 3 positions of the pyrrole ring. Indole is non-basic nitrogenous compound.[1-3] Indole chemistry began to develop with the study of the dye indigo. The word Indole is coined from the word India, a blue dye imported from India known as Indigo. Indigo can be converted to isatin and then to oxindole.[4-5] In 1866, Adolf von Baeyer reduced oxindole to indole **(1)** by using zinc dust. In 1869; he proposed a formula for indole



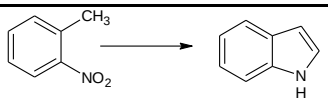
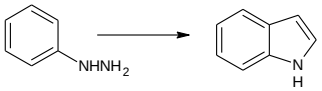
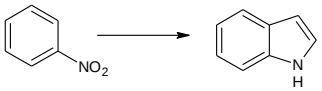
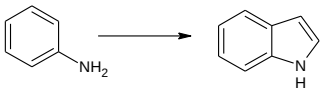
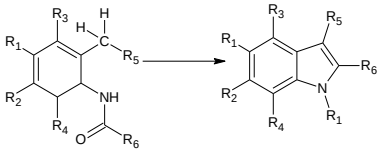
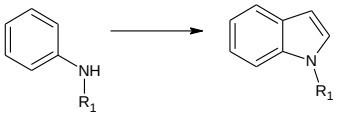
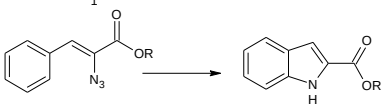
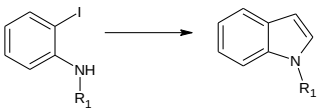
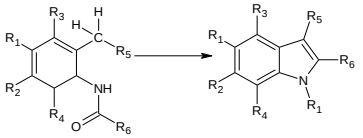
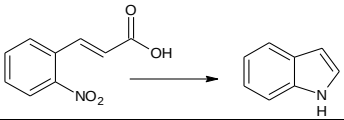
(1) Baeyers structure for indole, 1869

As indole ring plays very important role in drug discovery process so interest is developed in finding new methods for synthesis of indole derivatives. Indole and its derivatives are synthesized via variety of methods listed in **Table 1.**

Indole derivatives occure widely in natural products, plants, animals and marine organisms.[16] Many natural products contains indole nucleus like heteroauxin **(2)**, tryptophan **(3)**, hypaphorine **(4)**, bufotenin **(5)** and gramine

(6) (Fig. 1). Various plants contains indole as a core component like Robinia pseudacacia, Jasmine, citrus fruits and orange blossoms.17 Serotonin (7) contains indole nucleus and biochemically derived from tryptophan, is a neurotransmitter and is found in all bilateral animals. Melatonin (8), is a hormone found in animals, plants, and microbes and meant for the control of diurnal rhythm of physiological fuctions.18, 19 An indole alkaloid like Ajmaline (9), Reserpine (10) is used to treat high blood pressure and severe agitation in patients with mental disorders. Vinblastine is anticancer agent being recognized tubulin polymerization inhibitor and used in the treatment of acute lymphoblastic leukemia and against both Hodgkins and non-Hodgkin's lymphoma.[20-22] Sumatriptan **(11)** and ondansetron **(12)** are highly selective medicines for the treatment of migraine and suppression of nausea, vomiting caused by cancer chemotherapy respectively.[23,24] Indomethacin **(13)** is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness and swelling by inhibiting production of prostaglandin.[25]

Table 1: Methods for indole synthesis

Sr. No.	Method	Reaction	References
1.	Leimgruber-Batcho indole synthesis		Batcho A. D. *et al.* [6]
2.	Fischer indole synthesis		Bratulescu G. *et al.* [7]
3.	Bartoli indole synthesis		Bartoli G. *et al.* [8]
4.	Bischler-Mohlau indole synthesis		Pchalek K. *et al.* [9]
5.	Fukuyama indole synthesis		Fukuyama T. *et al.* [10]
6.	Gassman indole synthesis		Gassman P. G. *et al.* [11]
7.	Hemetsberger indole synthesis		Gribble G. W. *et al.* [12]
8.	Larock indole synthesis		Larock R. C. *et al.* [13]
9.	Madelung indole synthesis		Houlihan W. J. *et al.* [14]
10.	Baeyer-Emmerling indole synthesis		Lockyer *et al.* [15]

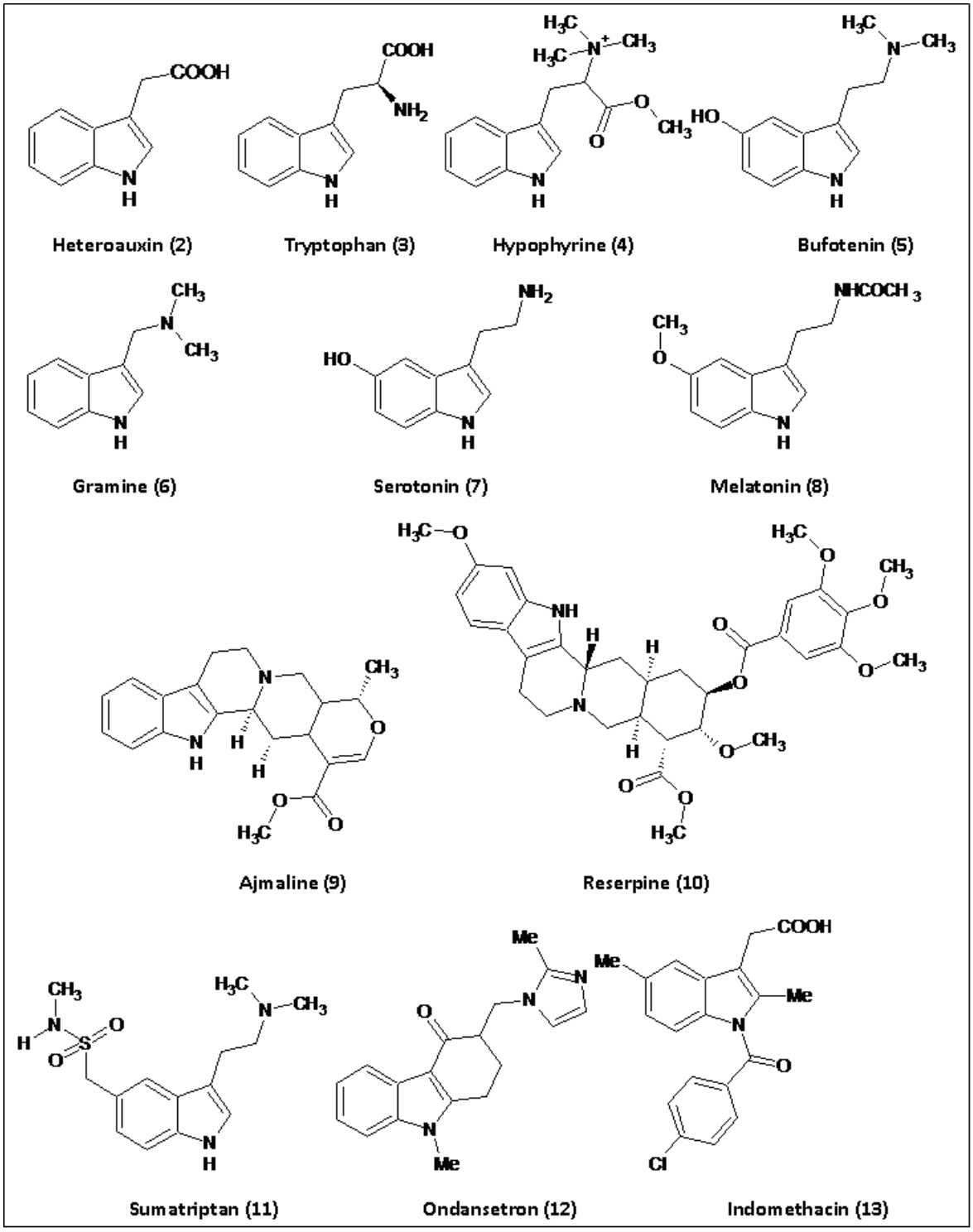


Fig 1. Structures of indole containing natural products and drugs

Indole represents one of the most important structural motifs in drug discovery, and it is described as one of the "privileged scaffolds".[26] Indole derivatives and its pharmacological significance provides tremendous opportunities to discover novel drugs with different modes of action. There are also an amazing number of indole containing drugs in the market as well as compounds in clinical evaluation shown in **(Fig. 2**).

A central nervous system disease can affect either the spinal cord (myelopathy) or brain (encephalopathy), both of which are part of the central nervous system. Some familiar central nervous system diseases include bipolar disorder, catalepsy, epilepsy/seizures, meningitis,

migraine, alzheimer's, parkinsons, depression, anxiety. Central nervous system diseases can lead to serious and potentially life-threatening complications. It is estimated that central nervous system disease are responsible for about 1% of deaths and account for almost 11% of disease burden all over the world. Altogether central nervous system disorders now affect 300 million persons. The proportionate share of the total global burden of disease due to neurologic disorders is projected to rise to 14.7% by 2020 which highlights an urgent need for more drugs to treat CNS disorders. [27-30]

Drugs acting on central nervous system disease plays very important role in balancing socioeconomic burden but still there is need for newer drugs to improve upon the current therapy as well as target specificity. Owing to the vast number of indole-containing molecules in the literature, this review focused primarily on central nervous system acting agents. This review serves as a comprehensive overview of currently published indole containing central nervous system acting agents with the main objectives in comprehensive listings of indole containing central nervous system drugs on market or compounds in clinical evaluation and to focus on recent developments of indole derivatives which are currently evaluated in experimental studies and their central nervous system activities.

2. INDOLE 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 Lurasidone **(14)**, Vilazadone **(15)**. Meanwhile, a number of indole derivatives are actively undergoing different phases of clinical evaluation, such as indalpine **(16)**, siramesin **(17)**, oxypertine **(18)**, roxindole **(19)**. **(Fig. 2)**

Lurasidone (Latuda)

Lurasidone represents one of the most highly functionalized indole-containing drugs. It is an atypical antipsychotic developed by Dainippon Sumitomo Pharma and marketed by Sunovion in the USA. [31] It has received regulatory approval in the UK in September 2014. The 5 short-term and 3 long-term studies suggests that lurasidone is effective at treating psychotic symptoms, and at preventing relapse in adults with schizophrenia. Lurasidone has completed phase III clinical trial for extended use study in India. Lurasidone acts as an antagonist of α1 & α2 adrenergic receptors, D1 & D2 receptors and 5HT receptors.[32]

Vilazadone (Viibryd)

Vilazodone is a serotonergic antidepressant developed by Clinical Data for the treatment of major depressive disorder. It was developed by Merck (Germany) and majorly use in the United States to treat major depressive disorder in 2011.[33] Vilazadone acts as a serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist.[34]

Indalpine (LM-5008)

Indalpine is an selective serotonin reuptake inhibitor (SSRI) class drug that was discovered in 1977 by the pharmacologists Le Fur and Uzan at Pharmuka, a small French pharmaceutical firm in New York. Indalpine was firstly reach to the market by Pharmuka.

Dr. Shopsin a consultant at Pharmuka, performed a thorough indalpine research and resulted in the marketing in France and then worldwide, in 1982. It was found that it causes an adverse effect neutropenia so swiftly withdrawn from the market.[35]

Siramesine (Lu 28-179)

Siramesine is a sigma receptor agonist, selective for the σ2 subtype. It was developed by the pharmaceutical company H Lundbeck for the treatment of anxiety, although development was discontinued after clinical trials showed a lack of efficacy in humans. It produces enhanced effects when administered with NMDA antagonist. [36, 37]

Oxypertine (Opertil)

Oxypertine is an antipsychotic drug used in the treatment of schizophrenia. Like reserpine and tetrabenazine, oxypertine depletes catecholamines and produce neuroleptic effect. Oxypertine, was evaluated in a group of 30 patients having severe anxiety condition. The results shows that administration of oxypertine 20 mg daily provides anxiolytic effect. [38, 39]

Roxindole (EMD-49,980)

Roxindole (EMD-49,980) is a dopaminergic and serotonergic drug. Roxindole is a dopamine autoreceptor agonist and used in the treatment of major depression. In

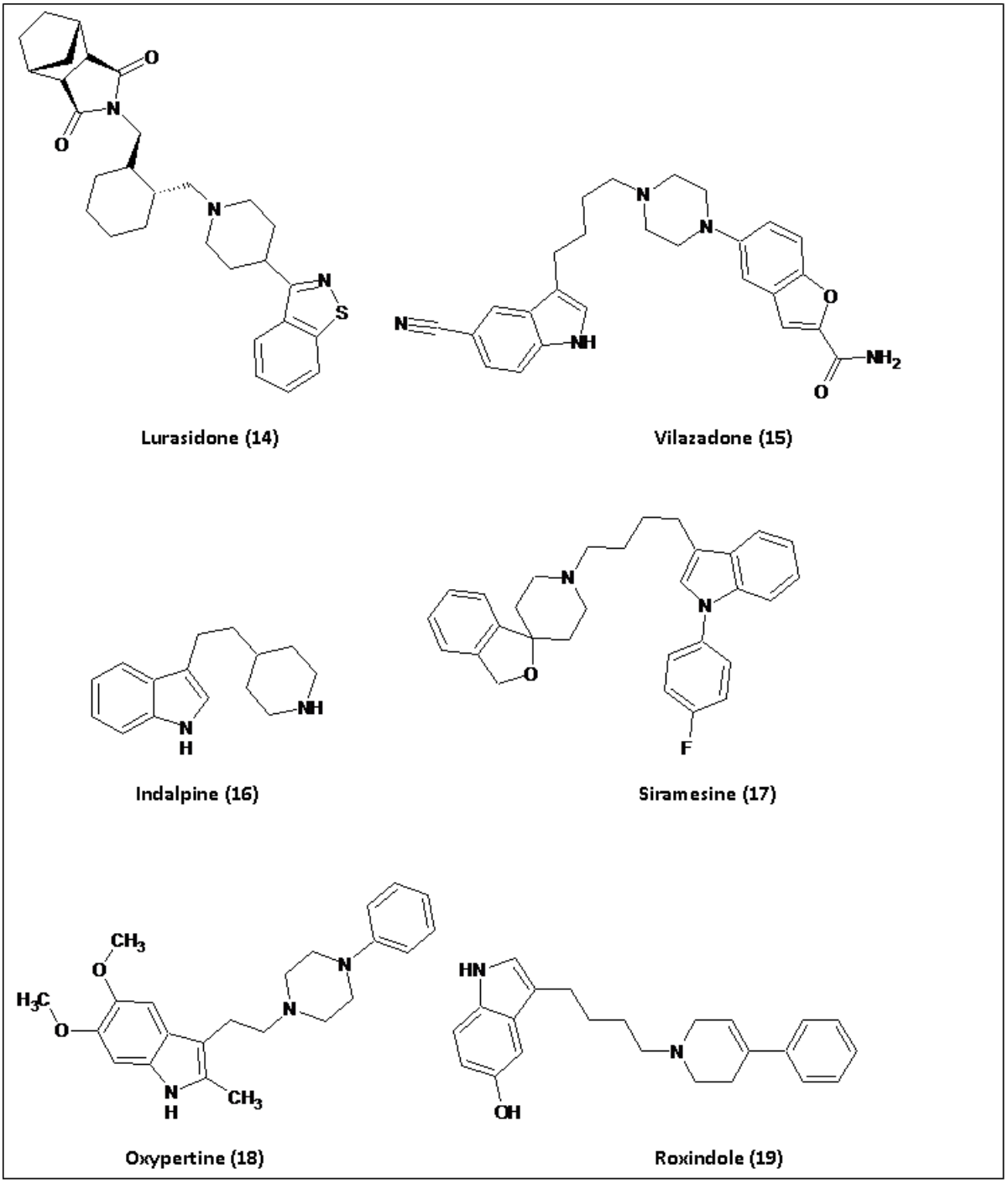


Fig 2. Structures of indole containing drugs in market and clinical evaluation

clinical trial study 12 patients suffering from a major depressive episode (DSM-III-R) were treated with roxindole for 28 days in a fixed dosage of 15 mg per day. Roxindole produced remarkably rapid onset of antidepressant action. [40, 41]

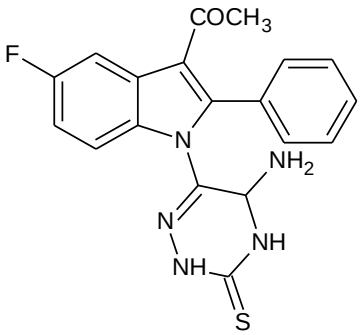
3. RECENT DEVELOPMENTS OF INDOLE DERIVATIVES IN EXPERIMENTAL STUDIES

The general idea of modern central nervous system acting agents drug design is to identify the receptors and the channels through which drugs can give pharmacological effects. Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects or by actually designing the candidate at the molecular level with a computer-aided design program. The agents acting on central nervous system includes anticonvulsants,

antianxiety, antipsychotic, antidepressant, monoamine oxidase inhibitors, sedative and hypnotics. Some important drugs along with its mechanism of action are given in **Table 2**.The recent progress in discovery and design of indole derivatives as central nervous system agents are described below.

3.1 Indole derivatives as anticonvulsant agents

Priya Ahuja *et al*., developed a novel series of thirty indole C-3 substituted 5-amino-6-(5-substituted-2-phenyl-1H-indol-1-yl)-4,5-dihydro-1,2,4-triazine-3(2H)-thione derivatives to explore prospective anticonvulsant agents. The derivative 1-(1-(5-amino-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-5-fluoro-2-phenyl-1H-indol-3-yl)ethanone **(20)** had significant activity in maximal electroshock test with minimal duration of limb extension (5.40-0.61 s) and quantitative median dose of 7 mg/kg. Insubcutaneous pentylenetetrazole screen 1-(5-amino-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-5-fluoro-2-phenyl-1H-indole-3-sulfonamide **(21)** increased the seizure latency to onset of clonus and was effective at a median dose of 35 mg/kg.[42]



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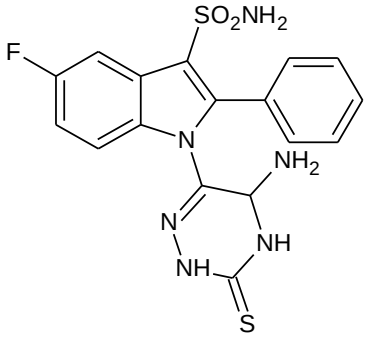
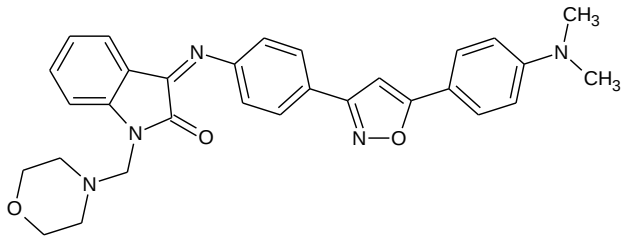


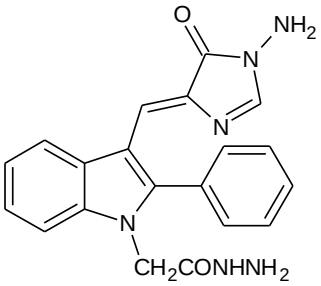
(21)

Govindaraj Saravanan *et al*., synthesized 1-(morpholinomethyl)-3-substituted isatin derivatives and investigated them for antiepileptic activity using MES and scPTZ seizures tests. Among the synthesized analogs, the most active one was **(22)** that revealed protection in MES at a dose of 30 mg/kg (i.p.) after 0.5 h and 4 h. This molecule also provided protection in the scPTZ at a dose of 100 mg/kg (0.5 h) and 300 mg/kg (4 h). [43]



(22)

MSY Khan *et al*., synthesized indole derivatives and were tested for their anticonvulsant activity in MES and scPTZ animal models. The compound **(23)** showed significant anticonvulsant activity and could be considered for further investigations. [44]

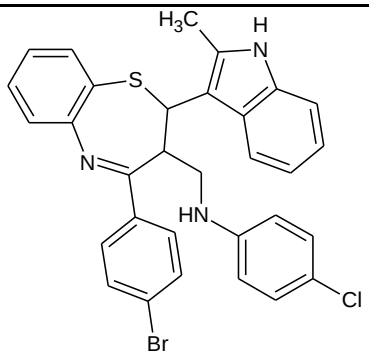


(23)

Anil Kumar *et al*., synthesized new series of 3-(4-substituted phenyl)-3-(substituted phenyl aminomethylene)-2,3-dihydrobenzoxazepin/benzothiazepin-2-yl)-2,5-disubstituted indoles and screened them for its anticonvulsant potential. Out of the compounds screened, compound **(24)** was found most potent anticonvulsant agent than standard drug phenytoin sodium at a dose of 30 mg/kg i.p. While some other compounds were found to possess activity equipotent to that of reference drug. [45]

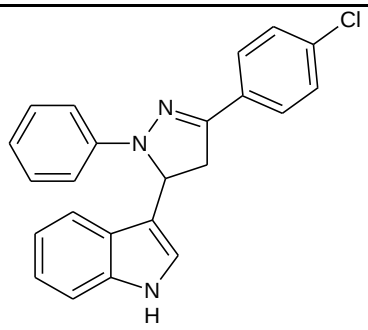
Table 2: Drugs with their Mechanism of action

Sr. No.	Category	Drugs used	Brand name	MOA (Mechanism of Action)	Use in treatment of
1.	Anticonvulsant	Carbamazepine Felbamate Gabapentin	Carbatrol Felbatol Gabarone	Inhibition of Sodium channel, calcium channel and excitatory amines, GABA agonism	Convulsion, Anxiety
2.	Antianxiety	Citalopram Fluoxetine	Celexa Prozac	Blocks the absorption of serotonin at the synapse thus making more serotonin available in the brain.	Anxiety, Depression
3.	Antipsychotic	Haloperidol	Haldol	Antagonise of dopamine receptor	Psychosis, Schizophre-nia
4.	MAO Inhibitors	Phenelzine Selegiline	Nardil Emsam	Blocks the activity of an enzyme monoamine oxidase and prevents the breakdown of serotonin, dopamine, norepinephrine, and epinephrine	Anxiety, Depression
5.	Sedative and Hypnotics	Diazepam Amobarbital	Valium Amytal	Depresses excitatory synaptic transmission	Anxiety, Psychosis and Migraine
6.	Antidepressant	Fluvoxamine	Luvox	Increase level of serotonine in the brain	Depression



(24)

Pravin O. Patil *et al*., carried out synthesis of series of 4,5-dihydropyrazole bearing indole derivatives and screened it for anticonvulsant activity against the pentylenetetrazole induced convulsions in mice. The results revealed that derivatives **(25)** and **(26)** were found to be potent anticonvulsant molecules of this series when compared with the reference drug diazepam at a dose of 100 mg/kg. It was observed that compounds **(25,26)** carrying an electron withdrawing group on the phenyl ring C3 of pyrazoline had shown profound activity in comparison to compounds having electron releasing group. [46]



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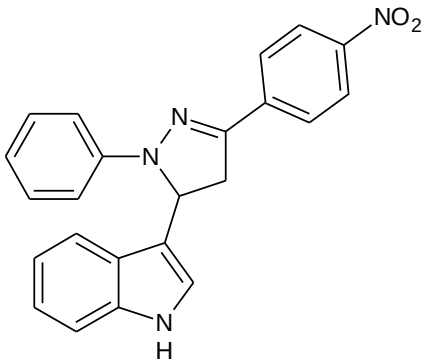
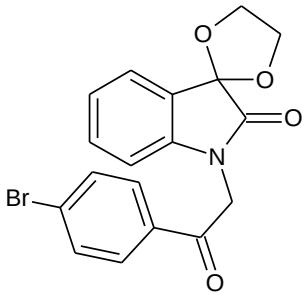


(26)

3.2 Indole derivatives as antianxiety agents

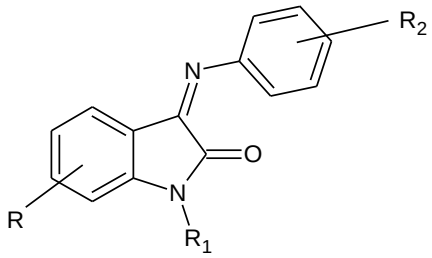
Athina Geronikaki *et al*., discovered new anxiolytics by prediction of biological activity with computer programs PASS and DEREK for a heterogeneous set of 5494 highly

chemically diverse heterocyclic compounds. They found out that indole containing derivative **(27)** shows most potent anxiolytic activity. [47]



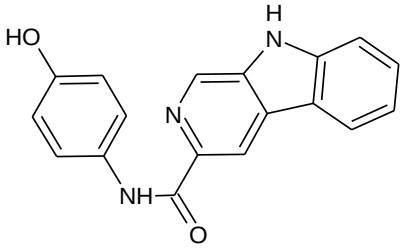
(27)

G.S. Palit *et al*., synthesized a series of schiff bases of *N*-methyl and *N*-acetyl indole-2,3-dione derivatives **(28)**. They studied the behavioural effects of indole-2,3-dione to induce anxiety in rodents. Pentylenetetrazol (PTZ) an anxiogenic agent, was used for comparison. Indole-2,3-dione (20 mg/kg, i.m.) induced behavioural responses comparable to those produced by PTZ (20 and 30 mg/kg, i.m.) which were indicative of anxiety and agitation. However, an increase in the dose (50 mg/kg, i.m.) of indole-2,3-dione resulted in reduction or loss of anxiogenic activity. Diazepam (1 mg/kg, i.v.) inhibited the behavioural effects of indole-2,3-dione (20 mg/kg, i.m.) and PTZ (20 mg/kg, i.m.), and the increase in plasma cortisol levels produced by them. The results indicate that, indole-2,3-dione induces an anxiogenic response in primates within a narrow dose range. [48]



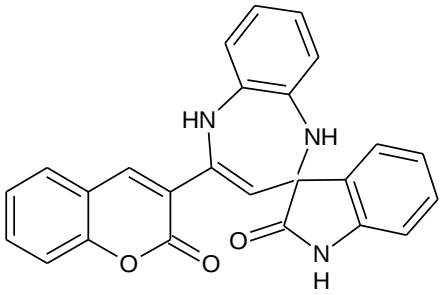
(28)

Keerti Vishwakarma *et al*., synthesized a series of β-carboline derivatives and evaluated for their anxiolytic activity. Newly synthesized compounds were tested for anxiolytic activity using elevated plus maze model. Among the synthesized compounds, N-(4-hydroxyphenyl)-9H-β-carboline-3-carboxamide **(29)** was found to be most active with the maximum no. of entries in open arm and time spent in open arm due to presence of hydroxyaniline at C-3 position of β-carboline ester. [49]



(29)

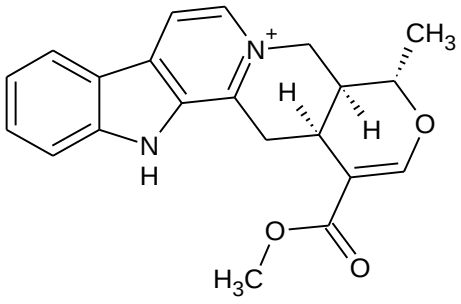
Raviraj A Kusanur *et al*., carried out synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. All the newly synthesised benzodiazepines were screened for their antianxiety activity in mice on plus maze apparatus. Compound (**30)** have shown comparable activity with the standard sodium pentabarbitone and the other compounds are moderately active. [50]



(30)

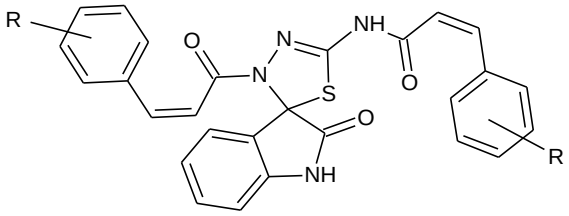
3.3 Indole derivatives as antipsychotic agents

Viviane M. Linck *et al*., represents the original mechanism of antipsychotic action by indole alkaloids Alstonine (*Picralima nitida*) **(31)**. Alstonine has an antipsychotic experimental profile comparable with that of clozapine and compatible with alleged effects in mental patients. Alstonine does not bind to D2 dopamine receptors and differentially regulates dopamine in the cortical and limbic areas. It indirectly modulates DA receptors by modulating DA uptake. This mechanism of for DA transmission modulation contributes antipsychotic action. [51]



(31)

Hemlata Kaur *et al*., synthesized some new pyrazolinyl/isoxazolinylindol-2-ones derivatives **(32, 33, 34)** and screened it for their antipsychotic activity at a dose of 30 mg/kg i.p. using chlorpromazine (4mg/kg, i.p.) as standard drug. They showed that derivatives containing thiadiazole ring showed better antipsychotic activity. [52]



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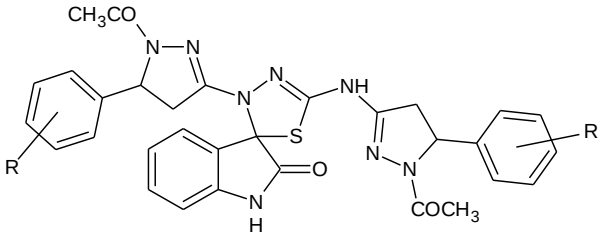
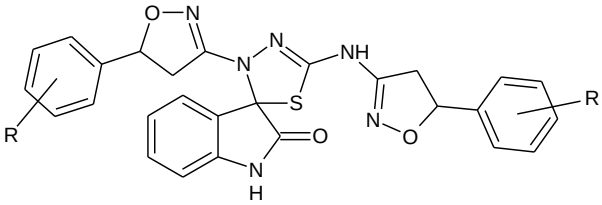


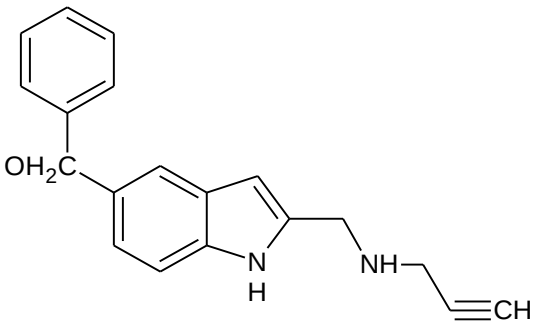
(33)



(34)

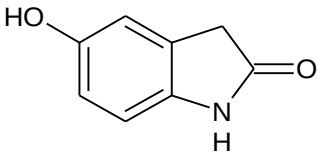
3.4 Indole derivatives as Monoamine oxidase inhibitors

Virgili Perez *et al*., showed the relevance of benzyloxy group in 2-indolyl methylamines is selective for MAO-B inhibition. Amongst all the benzyloxy-indolyl methylamines, N-(2-propynyl)-2-(5-benzyloxyindol)methylamine FA-73 **(35)** was the most potent MAO-B inhibitor. The IC_{50} values of FA-73 for dopamine uptake in striatal synaptosomal fractions and in human caudate tissue from rats were 150+8 *u*M and 0.36+0.015 *u*M respectively. Moreover, mouse brain MAO-B activity was 90% *ex vivo* inhibited by FA-73 1 h after 4 mg/kg administration whereas MAO-A activity was not affected. [53]



(35)

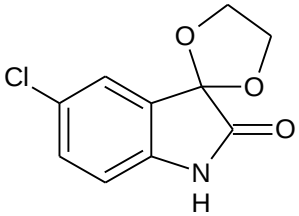
Arias *et al.,* compared the *in vitro* inhibition of MAO type A (MAO-A) and MAO type B (MAO-B) on rat brain non-synaptic mitochondria using 5-hydroxyoxindole with isatin derivatives. Among the all compounds studied, 5-Hydroxyoxindole **(36)** was found to be less potent MAO-A inhibitor (IC_{50} 56.8 µM) than isatin (31.8 µM) and 5-hydroxyisatin (6.5 µM), but it was the only highly selective MAO-A inhibitor (IC_{50} MAO-A : IC_{50} MAO-B = 0:044).[54]



(36)

3.5 Indole derivatives as sedative and hypnotic agents

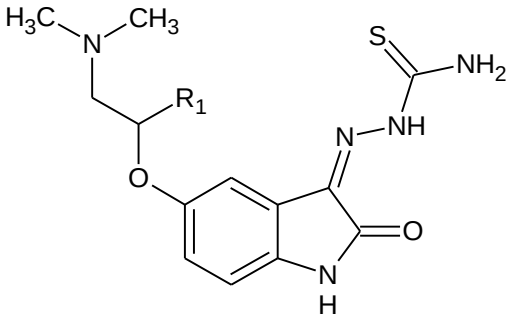
Sudo *et al.* synthesized dioxolane, dioxane ketal derivatives and evaluated their hypnotic, sedative and anesthetic potentials by locomotor activity, pentobarbital induced sleeping time evaluation and intravenous infusion respectively. The dioxolane ketal derivatives were more potent than dioxane ketals for inducing sedative–hypnotic states, causing up to a three-fold increase in pentobarbital hypnosis. Hypnosis and anesthesia were also observed during intravenous infusion of 5′-chlorospiro-[1,3-dioxolane-2,3′-indolin]-2′-one (**37**) in conscious wistar rats. [55]



(37)

K. Swathi *et al.* carried out synthesis and sedative-hypnotic activity of novel series of isatin hydrazone and

isatin thiosemicarbazone derivatives by using potentiation of pentobarbitone induced Narcosis method. Among all the newly synthesized derivatives, Compound **38, 39** and compound **40, 41** potentiated the sedative-hypnotic activity very significantly against standard drug diazepam (50mg/kg). [56]



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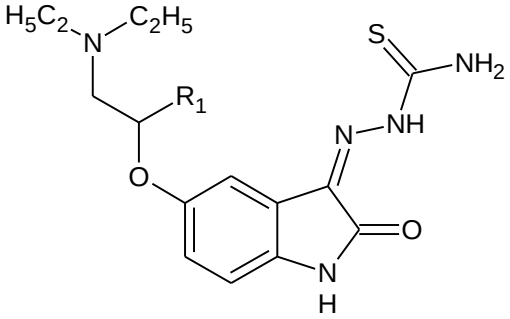

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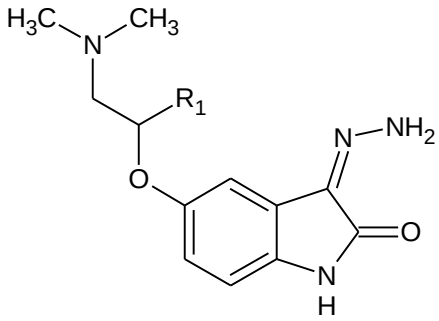

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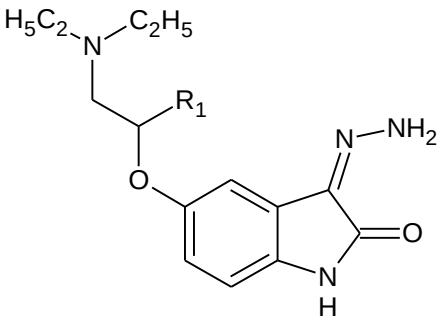
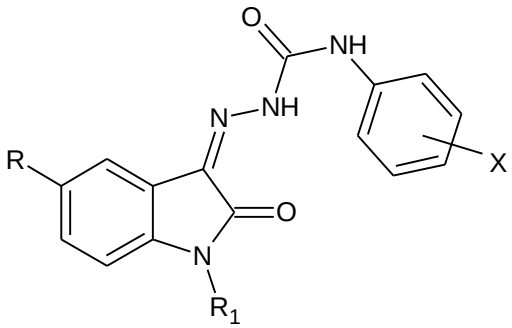


(41)

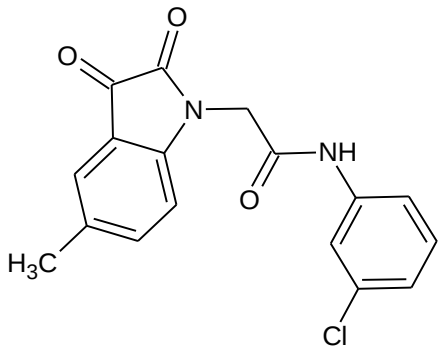
Sivakumar Smitha *et al*., synthesize a series of N-methyl/acetyl isatin-3-semicarbazones and screened it for anticonvulsant and sedative-hypnotic activities. Nearly all the compounds **(42)** are found to potentiate the narcosis and found to have significant sedative-hypnotic activity. [57]



(42)

3.6 Indole derivatives as antidepressant agents

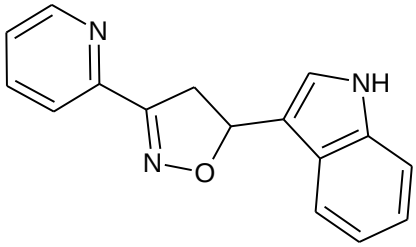
Xinghua Zhen *et al*., performed synthesis of new series of 2-(5-methyl-2,3-dioxoindolin-1-yl)acetamide derivatives and evaluated for their anticonvulsant activity in a pentylenetetrazole (PTZ)-evoked convulsion model and antidepressant activity in the forced swimming test (FST) model. Among all the newly synthesized derivatives, Compound **43** was found to have the most potent antidepressant activity and significantly reduced the duration of immobility time at 100mg/kg dose level when compared to the vehicle control, which is similar to the reference drug fluoxetine. [58]



(43)

Pravin Patil *et al*., performed Synthesis of Some New 5-(1***H***-Indol-3-yl)-3-(substituted aryl)-4,5-dihydroisoxazoline Derivatives and evaluated for antidepressant activity by using forced swim test in mice and their locomotor activity was assessed using actophotometry. Compounds **44** and **45** were found to

be potent molecules of this series, when compared with the reference drugs imipramine and fluoxetine.[59]



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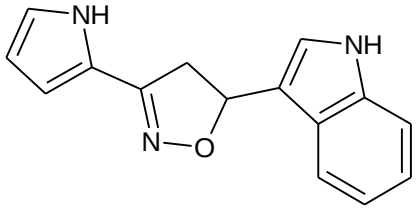

(45)

4. CONCLUSION

As heterocyclic rings are abundantly present in nature, indole is commonly found in biologically active natural products and pharmaceuticals. Due to that there has been increased interest in the use of indole derivatives against many diseases. This review serves a comprehensive overview on indole containing central nervous system acting agents in the market, clinical evaluation and currently evaluated in experimental studies. Information provided in this review article may be useful for molecular modifications as better central nervous system acting agents. Further we can conclude that many other derivatives of indole can be synthesized which will be expected to show potent pharmacological activities in future.

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