



## A Comprehensive Knowledge on Review of Indole Derivatives

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**Abstract:** The aim of the present review is to review synthesis and biological significance of indole derivatives. Most of the indole derivatives has varied pharmacological activities. Indole is an aromatic heterocyclic ring, which is commonly synthesized from Fischer-Indole synthesis from phenyl hydrazine and pyruvic acid. Indole undergoes electrophilic substitution reaction at position-3. It was synthesized from Batcho synthesis, Fukuyama- indole synthesis and Gassmann indole synthesis. Indole is a versatile and privileged heterocyclic ring with wide range of pharmacological activities. A plenty of research work was undertaken to synthesis and various therapeutic prospective of this moiety. The various activities of indole derivatives are Anticancer, anticonvulsant, antimicrobial, antimalarial, antiviral and some miscellaneous uses in the last few years. The present review is useful and provide knowledge regarding synthetic process and pharmacological features that helps future medicinal chemists for new drug discovery. The present review summarises the structure property that inspire new and even more creative approaches. The indole structure was exposed to the future perspective. It helps to develop novel indole derivatives with the knowledge of our review.

**Keywords:** Indole, Synthesis, History, Indole derivatives, Indomethacin,

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## 1. INTRODUCTION

Indole was isolated in the year of 1866, has the molecular formula  $C_8H_7N$  and it is commonly synthesized from phenyl hydrazine and pyruvic acid, although several other procedures have been discovered<sup>1</sup>. In addition to tryptophan, indigo, indole acetic acid and numerous other compounds obtained from plant or animal sources contain the indole molecular structure<sup>2</sup>. The best-known group of compounds is the indole alkaloidal members of which have been isolated from plants representing more than 30 families<sup>2</sup>. Psilocin, Psilocybin, Reserpine and Strychnine belong to these groups. Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a "six-membered benzene ring" fused to a five-membered nitrogen-containing pyrrole ring. The participation of the nitrogen lone electron pair in the aromatic ring indicates indole is not a base, and it does not behave like a simple amine<sup>3</sup>. The indole structure can be found in many organic compounds like amino acid tryptophan, tryptophan-containing protein, alkaloids, and pigments. Indomethacin, is a non-steroidal anti-inflammatory drug (NSAID) with steroidal anti-inflammatory, analgesic, and antipyretic properties. NSAID's consists of agents that are structurally unrelated; the NSAID chemical classification of Indomethacin is an indole-acetic acid derivatives with the chemical name 1-(p-chlorobenzoyl)-5-methoxy-2-methyl indole-3-acetic acid<sup>3</sup>. It was first discovered in 1963 and it was first approved for use in the U.S.A the food and drug administration in 1965, along with other acetic acid derivatives such as Diclofenac and Sulindac that were also developed during the 1960s<sup>7</sup>. Since then, Indomethacin has been extensively studied in clinical trials as one of the most potent NSAID's in blocking prostaglandin synthesis and was among the first NSAID's to be used in the symptomatic treatment of migraine and for headaches that eventually became known as "Indomethacin-responsive" headache disorders. The pharmacological effect of Indomethacin is not fully understood, however, it is thought to be mediated through the potent and cyclooxygenase (COX) inhibitor which is the main enzyme responsible for catalyzes the rate-limiting step in prostaglandin and thromboxane biosynthesis via arachidonic acid pathway<sup>4</sup>. Indole undergoes electrophilic substitution mainly at 3-position. Indole is also called benzopyrrole, a heterocyclic organic compound found in some flower oils, such as jasmine, organic blossom in coal tar, and in faecal matter. It is used in perfumery industry and in making tryptophan, an essential amino acid and indole acetic acid hormone that promotes the development of root in plant cuttings<sup>4</sup>. Indole chemistry began to develop with the study of the indigo dye. Indigo can be converted to isatin and then to oxindole. In 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust. In 1869, he proposed a formula for indole nucleus. The name indole is derived from the words indigo and oleum, since indole was first isolated by treatment of the indigo dye with oleum<sup>5</sup>. Interest in indole intensified when it became known that the indole nucleus is present in many important alkaloids, tryptophan and auxins, and it remains an active area of research today<sup>5</sup>.

### 1.1 STRUCTURE

Indole is widely distributed in the natural environment and can be produced by a variety of bacteria. As an intercellular signal molecule, indole regulates various aspects of bacterial physiology including spore formation, plasmid stability, resistance to drugs, biofilm formation and virulence. The

amino acid tryptophan is an indole derivative and the precursor of the neurotransmitter serotonin<sup>6</sup>.

### 1.2 PROPERTIES

It is solid at room temperature. It naturally occurs in faeces and has an intense faecal odour at very low concentration however, it has a flowery smell. It is a constituent of many perfumes. It also occurs in coal tar<sup>7</sup>. Mass: 117.151 gm mol<sup>-1</sup> Density: 1.1747 gm/cm<sup>3</sup> Melting point: 52-54°C; Boiling point: 253-254°C Solubility in water: 0.19 gm/100ml (20°C) Soluble in hot water. Acidity: 16.2 Basicity: 17.8

### 1.3 SYNTHESIS

Indole and its derivatives can be synthesized by various methods. The industrial method of preparation of indole is vapour phase reaction with ethylene glycol in the presence of catalyst. The reaction is carried out at a temperature of 200°C - 300°C. The percentage yield is 60%, and the obtained product is formyl touridines, 2-ethyl aniline and 2-(2-nitrophenyl). They undergo recrystallization in ethanol<sup>8</sup>.

### 1.4 FISCHER INDOLE SYNTHESIS

One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer Indole synthesis, developed in 1833 by Emil Fischer. Although the synthesis of Indole itself is problematic using the Fischer-Indole synthesis as it is often used to generate indole substituted in the 2 (or) 3-positions. Indole can still be synthesized however using the Fischer Indole synthesis by reacting phenyl hydrazine with pyruvic acid followed by decarboxylation of the formed indole 2-carboxylic acid. This has also been accomplished in a one pot synthesis using microwave irradiation<sup>9</sup>. By this method we can synthesize the indole derivatives which are substituted at 2 and 3-position.

### 1.5 LEIMGRUBER-BATCHO INDOLE SYNTHESIS

The Leimgruber Batcho indole synthesis is an efficient method of synthesizing indole and substituted indoles. This method provides high yield and can generate substituted indoles. This method is especially popular in the pharmaceutical industry where many pharmaceutical drugs are made up of specifically substituted indole<sup>10</sup>. It is a series of organic reactions that produces indoles from o-nitrotoluenes. The 1<sup>st</sup> step is the formation of an enamine using N,N-dimethylformamide dimethyl acetal and pyrrolidine. The desired indole is then formed in a 2<sup>nd</sup> step by reductive cyclisation<sup>11</sup>. In the above scheme the reductive cyclization is affected by Raney nickel and hydrazine. Palladium-on-carbon and hydrogen, stannous chloride, sodium hydrosulphite/or iron in acetic acid are effective reducing agents. This reaction is especially designed to carry out in presence of catalysts such as Raney nickel.

### 1.6 BARTOLI INDOLE SYNTHESIS

Bartoli Indole synthesis also called as Bartoli reaction, is the chemical reaction of ortho substituted nitroarenes and nitrosoarenes with vinyl Grignard reagents to form substituted indoles<sup>12</sup>. The reaction is often unsuccessful without the substitution ortho group assist in the [3,3]-sigma tropic rearrangement required for product formation. Three equivalents of the vinyl Grignard reagent are necessary for

the reaction to achieve full conversion when performed on nitroarenes and only two equivalents performed on nitrosoarenes. The method has become one of the short and most flexible routes to 7-substituted indoles. The Leimgruber Batcho Indole synthesis gives similar flexibility region specificity to indole derivatives. One advantage of BARTOIL indole substitution is on both the carboxylic ring and the pyrrole ring which is difficult to do with the Leimgruber Batcho Indole synthesis<sup>13</sup>. This method is highly sensitive and uses Grignard reagent.

### 1.7 BISCHLER-MOHLAU INDOLE SYNTHESIS

It is also often referred to as Dischler Indole synthesis and is a chemical reaction that a 2-aryl indole forms  $\alpha$ -bromo acetophenone and excess aniline. This process is named after August Bischler and Richard Mohlau. In spite of long history, this classical reaction has received relatively little attention in comparison with other methods for indole synthesis, owing to the unpredictable regioselectivity. Recently milder methods have been developed including the use of lithium bromide as a catalyst and an improved procedure involving the use of microwave irradiation<sup>14</sup>.

### 1.8 FUKUYAMA INDOLE SYNTHESIS

Fukuyama indole synthesis is a versatile fine mediated chemical reaction that results in the formulation of 2,3-di substituted indoles, a particle one pot reaction that can be useful for the creation of di substituted indoles<sup>5</sup>. Most commonly tributyrin hydride is utilized as the reducing agent, with azo bis isobutyro nitrile nitride as a radical indicator. The reaction can begin with either an ortho-isocyano styrene or a 2-allylthioanilidine derivatives both forming the indole through radical cyclization via a  $\alpha$ -stanolimidoyl radical. The R group can be a range of both basic and acidic sensitive functional groups such as ester, THP ether, and  $\beta$ -lactams' in addition the reaction is not stereo specific, and can be used to obtain the desired product.<sup>7</sup>

### 1.9 GASSMAN INDOLE SYNTHESIS

It is a series of chemical reactions used to synthesize substituted indole by addition of aniline and a ketene bearing a thioether substituent. This is a one-pot chemical reaction, and none of the intermediates are isolated. R<sub>1</sub> can be hydrogen or alkyl, while R<sub>2</sub> works best with aryl but can also be alkyl. Electron rich anilines, such as 4-methoxy aniline, tend to trail in this reaction. The 3-position thioethyl group is often removed using Raney nickel to give the 3-H indole.<sup>3</sup>

### 1.10 HEMETS BERGER INDOLE SYNTHESIS

It is also called the Helmets Berger-knittel synthesis and is a chemical reaction that thermally decomposes a 3-aryl-2-azido-propenoic ester into an indole 2-carboxylic ester. Yield is typically above 70%, however this is not a popular reaction due to the lack of stability and difficulty in synthesizing the starting material<sup>15</sup>. This method is used to synthesis indole 2-carboxylic ester.

### 1.11 LAROCK INDOLE SYNTHESIS

It is a hetero annulation reaction that uses palladium as a catalyst to synthesize indoles from an ortho nitroaniline and adistribute alkynes. It is also known as LA Rock photo

annulation. The reaction is extremely versatile and can be used to produce varying types of indoles. LaRock indoles synthesis was 1<sup>st</sup> proposed by Richard LaRock is 1991 at Iowa state university. The reaction usually occurs with o-indo aniline or its derivatives, 2-5 equivalents of an alkyne's palladium, an excess of sodium or potassium carbonate base, PPH<sub>3</sub> and 1 equivalent of LiCl or n-Bu<sub>4</sub>NCl, N-methyl, N-acetyl and N-tosyl derivatives of ortho-nitroanilines have been shown to be the most successful anilines that can be used to produce good to excellent yield. This method is useful for the preparation of various derivatives of indoles.<sup>5</sup>

### 1.12 MANDELUNG SYNTHESIS

The Mandelbug synthesis is a chemical reaction that produces indoles by the intramolecular cyclization of n-phenyl amides using a strong base at high temperature. The Madelung synthesis was reported in 1912 by Walter Madelung. He observed that 2-phenylindole was synthesized using n-benzoyl o-toluidine and two equivalents of sodium ethoxide in a heated, airless, common reaction condition. The inclusion of sodium or potassium alkoxide as base in hexane or tetra hydrofuran solvents was at temperatures ranging between 200-400°C. A hydrolysis step is one of the few known reactions that produce indoles and form a base catalysed thermal cyclization of n-acyl-o-toluidine. The overall reaction for the Madelung synthesis then follows. The methods are essentially continued to the preparation of 2-alkylindoles (not easily accessible through electrophilic aromatic substitution) because of the vigorous reaction condition.<sup>9</sup> This method is helpful for the preparation of 2-alkyl indoles.

### 1.13 NENITZESCU INDOLE SYNTHESIS

The Nenitzescu Indole synthesis is a chemical reaction that forms 5-hydroxyindole derivatives from benzoquinone and  $\beta$ -aminochromone esters. The reaction was named for its discovery Nenitzescu, who 1<sup>st</sup> reported it in 1929. It can be performed with a number of different combinations of R-groups, which include methyl, methoxy, ethyl, propyl, and H-substituents. There is also a solid-state variation in which the reaction takes place on a highly cross-linked polymer scaffold. The synthesis is particularly interesting because indoles are the foundation for a number of biochemically important molecules, including neurotransmitters and a new class of antitumor compounds. This method is useful for the preparation of hydroxyl indole derivatives.<sup>8</sup>

### 1.14 REISSERT-INDOLE SYNTHESIS

The Reissert indole synthesis is a series of chemical reaction designed to synthesize indoles or substituted indoles (4 and 5) from ortho-nitrotoluenes, diethyl oxalate and potassium ethoxide. The first step of the synthesis is the condensation of o-nitrotoluene 1 with a diethyl oxalate 2 to give 0-nitrophenyl pyruvate 3. The reductive cyclization of 3 with zinc in an acetic acid gives 2-carboxylation with heat to give indole. This method is useful for the preparation of the 2-carboxylated indole derivatives.<sup>9</sup>

### 1.15 BAYER-EMMERLING INDOLE SYNTHESIS

The Baeyer Emmerling Indole synthesis is a method for synthesizing indole from a (substituted) ortho nitro cinnamic acid and iron powered in strongly basic cinnamic acid and iron powder in a strongly basic solution. The reaction was discovered by Adolf von Baeyer and Adolph Emmerling in

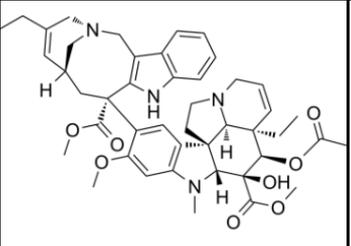
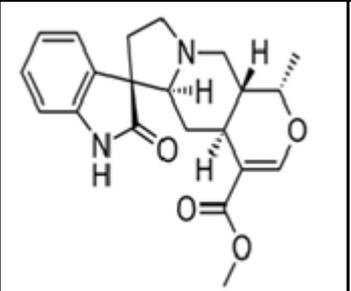
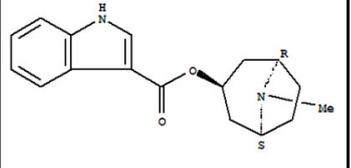
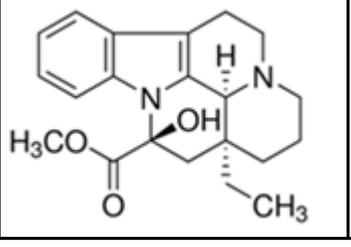
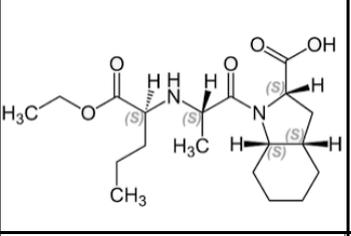
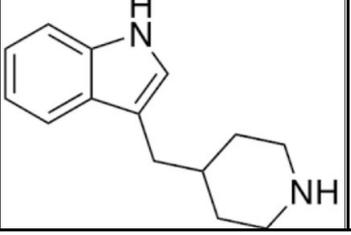
1869. This method is useful for the preparation of substituted derivatives.<sup>8</sup>

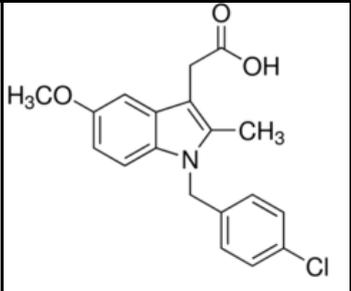
### 1.16 DIELS-REESE REACTION

It is a reaction between hydrazo benzene and dimethyl acetylene dicarboxylate (or related esters) 1<sup>st</sup> reported in 1934 by Otto Diels and Johannes Reese. Later work by others extended the reaction scope to include substituted hydrazobenzene<sup>16</sup>. The exact mechanism is not known. By changing the acidic or basic nature of the solvent the reaction gives different products with acetic acid as, the reaction gives

a diphenyl pyrazolone with xylene as solvent which is neutral in nature. The reaction gives an indole, a carbomethoxy quinolines which can be degraded to a dihydro quinoline. Dimethyl acetylene dicarboxylate reacts with 1,2-diphenylhydrazine to an adduct, which in xylene gives dimethyl indole 2,3- dicarboxylate and aniline with other solvent. Other products are formed with glacial acetic acid a pyrazoline and with pyridine - a quinoline<sup>17</sup>. This method is particularly useful for the preparation of dimethyl indole derivatives. This method is useful for the preparation of indole derivatives in the acedic and basic environment.<sup>4</sup>

Table I: structures of indole derivatives

SLNO	STRUCTURE	IUPAC NAMES	NAME	DERIVATIVES
1		Methyl(1R,9R,10S,11R,12R,19R)-11-acetyloxy-12-ethyl-4-[(12S,14R)-16-ethyl-12-methoxycarbonyl-1,10-diazabicyclo[12.3.1.03,11.04,9]octadeca-3(11),4,6,8,15-pentaen-12-yl]-10-hydroxy-5-methoxy-8-methyl-8,16-diazabicyclo[10.6.1.01,9.02,7.016,19]nonadeca-2,4,6,13-tetraene-10-carboxylate	Vinorelbine	Anticancer <sup>3-5</sup>
2		Methyl(1S,4aS,5As,6R,10Ar)-1-methyl-2'-oxospiro[1,4a,5,5a,7,8,10,10a-octahydropyrano[3,4-f]indolizine-6,3'-1H-indole]-4-carboxylate	Mitraphylline	Anticancer <sup>6-9</sup>
3		[(1R,5S)-8-azabicyclo[3.2.1]octan-3-yl]1H-indole-3-carboxylation	Tropisetron	Antiemetic <sup>6-8</sup>
4		Methyl(15S,17S,19S)-15ethyl-17hydroxy-1,11-diazapentacyclo[9.6.2.0 <sup>2,7</sup> .0 <sup>8,18</sup> .0 <sup>15,9</sup> ]nonadeca-2,4,6,8(18)-tetraene-17-carboxylate	Vincamine	Vasodilators <sup>8-9</sup>
5		(2S,3As,7As)-1-[(2S)-2-[[[(2S)-1-ethoxy-1-oxopentanal-2yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid	Perindopril	Anti-hypertensive <sup>8-10</sup>
6		3-(2-piperidin-4-ylmethyl)1H-indole	Indalpine	Antidepressant <sup>8</sup>

7		2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-yl]acetic acid	Indomethacin	Anti-inflammatory <sup>9-10</sup>
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### 1.17 Biological use

Indole has a benzene and pyrrole ring sharing one double bond. Indole is a building molecule for amino acid tryptophane. It also provides skeletal structure for biologically active compounds such as Strchnine and LSD. The indole derivatives named as Indomethacin is used as NSAID drug. The biological evaluation of 3-substituted indole was carried out by Radwin et al<sup>9</sup> and are having anti-inflammatory and analgesic activity. 3-aryl, 3-hetero aryl indole are reported for antimicrobial activity.<sup>8</sup> Indole 8-one derivatives has selective dopamine agonistic activity. 8 beta substituted hydromorphine derivatives has opiod antagonistic activity. The oxime of indole amino ketone exhibits anti-depressant, tranquillising and anticonvulsant activity.<sup>6</sup>

### 1.18 Recent development of indole containing antiviral drugs

The indole containing antiviral drugs include Arbidol and delaviridine. A number of indole derivatives actively undergoes different phases of clinical evaluation such as Ateviridine, golotimode. Panibinostat represents one of the highly functionalized indole containing drugs which are used for the prevention of influenza and SARS.<sup>9</sup> Delaviridine which is a first generation non-nucleoside reverse transcriptase inhibitor is used for the treatment of AIDS. Ateviridine has anti-HIV activity and inhibits HIV-1 replication. Enfuvirtide the peptide anti-HIV drug FDA approved drug of non nucleoside reverse transcriptase inhibitor targeting gp4/N-terminal heptad was approved by US FDA. Rilpivirine is a FDA approved drug of NNRTS Inhibitor.<sup>11</sup>

## 2. Discussion

Indole has the molecular formula  $C_8H_7N$  and it is commonly synthesized from phenylhydrazine and pyruvic acid, although several other procedures have been discovered. It was also synthesized from Fischer- indole synthesis, in which phenyl hydrazine hydrochloride, cyclohexanone were used and it is a base catalyzed reaction.<sup>9</sup> It was also prepared from other reactions such as Leimgruber indole synthesis, Gassmann indole synthesis, Batcho synthesis, Fukuyama indole synthesis, Larockindole synthesis. Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a "six-membered benzene ring" fused to a five membered nitrogen containing pyrrole ring. The participation of the nitrogen lone electron pair in the aromatic ring means that indole is not a base and it does not behave like a simple amine.<sup>11</sup> The indole structure can be found in many organic compounds like the amino acid tryptophan, Tryptophan containing protein, alkaloids, and pigments.<sup>9</sup> Indole is an aromatic heterocyclic organic compound. Indomethacin

(NSAID) displays a linear pharmacokinetics profile where the plasma concentration and area under the curve are dose-proportional, whereas half-life ( $t_{1/2}$ ), plasma and renal clearance are dose-dependent.<sup>8</sup> Indomethacin is readily and rapidly absorbed from the gastrointestinal tract.<sup>5</sup> The bioavailability is virtually 100% following oral administration and about 90% of the dose is absorbed within 4 hours. The bioavailability is virtually 100% following oral administration and about 80-90% following rectal administration.<sup>8</sup> There are various derivatives of indole are Vincristine (Anticancer), Vinblastine (Anticancer), Vincamine (Vasodilator) and some more derivatives which are having anticancer (Vinca alkaloids), vasodilator (Vincamine), antihypertensive (Perindopril) activities.<sup>7</sup> Some of the indole derivatives shows antiemetic (Tripisetron), vasodilators, antileukemic, antihypertensive (Perindoprine), antidepressant, anti-HIV (Delaviridine) activity.<sup>8</sup> Indomethacin which is a COX-2 inhibitor and it is administered as oral and i.v. It binds to the plasma proteins.<sup>7</sup> It is metabolized by the liver involving glucuronidation, O-demethylation, N-deacetylation. It is excreted through urine. The study of IR, NMR, MASS are used to know the characteristic structure of indole derivatives.<sup>4</sup>

## 3. CONCLUSION

A number of drugs were designed to treat various infections and disorders that are having indole structure. Those drugs have commercially available in the market and are approved by FDA. There are various indole derivatives obtained from natural and synthetic origin are under clinical trials. Researchers are working on indole containing drugs targeting different diseases by removing the side effects and improving biological activity. In this maximum information is provided regarding synthetic origin and pharmacological activity. This information is useful for upcoming scientist to develop novel indole derivatives.

## 4. AUTHOR CONTRIBUTION STATEMENT

All the authors equally contributed to the work.

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## 6. CONFLICT OF INTEREST

Conflict of interest declared none.

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