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# A REVIEW OF ANTI INFLAMMATORY POTENTIAL OF INDOLE AND ITS DERIVATIVES

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## ABSTRACT

Indole is a privileged heterocyclic nucleus set up in diverse natural products, endogenous molecules and medicinal agents. Even though it has diversified actions, the role of indole in anti-inflammatory therapy is of prime interest which is prominently shown in the drug molecule Indomethacin. The efficacy of the indomethacin and tenidap is primarily due to the inhibition of the cyclooxygenase (COX) enzyme activity. The adverse reactions of most of the NSAIDs (Non Steroidal Antiinflammatory Drugs) are due to the irritating moiety present in the molecule or due to the decreased production of cytoprotective prostaglandins. In this review, the various structural modifications of indole have been studied to enlist the improvement in the therapeutic profile of the nucleus. *A new series of 1,5-disubstituted indole derivatives such as 5-(acetylamino)-1-[(4-flurophenyl)carbonyl]-1H-indole-3-carboxylicacid, 1-[(4 fluorophenyl)carbonyl]-5-[(phenylcarbonyl)amino]-1H-indole-3-carboxylic acid, 1-(4-flurobenzoyl)-5-(4-ethylbenzamido-1H- indole-3-carboxylic acid, 5-(4-nitrobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid, 5-(4- bromobenzamido)-1-(4-flurobenzoyl)-1H-indole-3-carboxylic acid were synthesized. All the newly synthesized derivatives of 1,5-disubstituted indole derivatives are characterized by spectroscopically and analytically,* Indole containing isoxazole derivatives were reported by Pedada et al. as $sPLA_2$ inhibitory agents. Compound *N*-((3-(4-fluoro-3-(trifluoromethyl) phenyl) isoxazol-5-yl) methyl) (5-methyl-1*H*-indol-3-yl) methanamine hydro- chloride (28) showed significant $sPLA_2$ inhibition activity that is comparable or more to ursolic acid (positive con- trol).

**KEYWORDS**: Inflammation, Anti-inflammatory Agents, Indole derivatives, Resonance in indole molecule, indomethacin**,** Modern synthesis of indomethacin.

## INTRODUCTION

Inflammation is an essential response to tissue injuries that occur due to physical, chemical or biological insults.[1,2,3,] The classic signs of inflammation are heat, redness, swelling, pain, and loss of function. These are manifestations of the physiologic changes that occur during the inflammatory process. The three major components of this process are changes in the caliber of blood vessels and the rate of blood flow through them, Increased capillary permeability and exudation[2,3] Both acute and chronic inflammations play essential roles in the restoration of homeostasis. However, the mechanisms by which activated leukocytes combat germs and tumor cells and eliminate tissue debris in areas of inflammation lead to the production of oxidants and/or of cytotoxic cytokines.[1] Several gastrointestinal, cardiovascular, neurological and psychiatric disorders show involvement of pro-inflammatory mediators acting as culprits in the inflammatory process. Categorically inflammation process can be divided into three distinct phases, the first phase characterized by increased vascular permeability and exudation of fluids namely the acute phase followed by the second phase involving infiltration of leuckocytes and granuloma formation called as the sub-acute phase ultimately followed by the third and last phase of chronic inflammation typically characterized by regulated production of pro and anti-inflammatory mediators like the TNF-α, (IL)-1β and IL-6,chemokines, and inducible enzymes.[3] The pro- inflammatory cytokines tumor necrosis factor alpha (TNF-a) and interleukin 1-beta (IL-1b) are small molecular weight proteins secreted mainly by the immune cells. They act as important mediators involved in the pathophysiology of several chronic inflammatory diseases, including rheumatoid arthritis (RA), inflammatory bowel disease, septic shock, and osteoporosis. [4] Cyclooxygenases are the endogenous enzyme system mainly responsible for cellular prostaglandin biosynthesis and catalyze the reactions in which Arachidonic acid (AA) is converted to prostaglandin H2 (PGH2). COX exists in two isomeric forms such as COX-1and COX-2. Among the two isomeric forms, COX-2 mainly acts as target of commonly used anti- inflammatory drugs.[5] The anti-inflammatory activity of various isatin semicarbazide derivatives were evaluated by carrageenan-induced paw edema test in rats. The compound containing trifluoro methyl substituent displayed significant anti-inflammatory activity at the dose of 10 and 20 mg/kg and one- third of ulcer index compared to the reference drug diclofenac and aspirin.[6] Indole substituted in the 3rd position with various chalcones, pyrazolines and azo-compounds were evaluated for their anti-inflammatory activity. The compound showed a maximum of 47% anti-inflammatory activity among the compounds. It also exhibited less ulcerogenic liability than the standard drug.[7]

The therapeutic targeting of the inflammatory response is an important field of study.[8]
It is characterized by following characteristic. Pain, Heat, Redness, Swelling.

There are three significant elements of aggravation. To start with, aggravation is the initial phase in the mending or fix process after some physical or synthetic injury or stress. Second, inflammation prevents the spread of damaged cells to other areas of the body that could cause secondary problems and third, inflammation rids the body of damaged and dead cells. This very important task is more than just an act of housecleaning. There are two types of inflammation.

**Types of Inflammation**

A. Acute inflammation.

B. Chronic inflammation.

**A. Acute inflammation**: The intense incendiary reaction to a physical or compound pressure can last as long as three days, with the entire fix process taking as long as about a month and a half Components are vascular and cellular events. Which are mediated by chemical factors (mediators). **B. Chronic Inflammation**: Chronic inflammation is an abnormal condition that can associated with ill health and disease ceaseless irritation is a fiery reaction of delayed length - weeks, months, or even inconclusively - Whose allinclusive time course is incited by industriousness of the causative upgrade to irritation in the tissue. The incendiary procedure unavoidably causes tissue harm and is joined by synchronous endeavors at recuperating and fix. The exact nature, extent and time course of chronic inflammation is variable, and depends on a balance between the causative agent and the attempts of the body to remove it.[9]

**Anti-inflammatoryAgents**

**Non-Steroidal anti-inflammatory drugs (NSAIDs)**

NSAIDs are among the most commonly used drugs worldwide, used by more than 30 million people every day. More than 111 million prescriptions are written for NSAIDs in the USA annually, and they account for approximately 60% of the USA over-the-counter (OTC) analgesic market.[10]

**NSAIDs classification, COX selectivity and efficacy** NSAIDs can be classified on the basis of their chemical and pharmacological properties, and COX selectivity. On the basis

of theirchemical structure, they are classified as. [11]

1. **Salicylic acid derivates**: acetylsalicylic acid (aspirin), sulfosalazine
2. **Para-aminophenol derivates**: acetaminophen (paracetamol)
3. **Indole and indene acetic acids**: indomethacin, etodolac, sulindac
4. **Hetero-aryl acetic acids**: diclofenac, ketorolac, tolmetin
5. Aryl-propionic acids: ibuprofen, ketoprofen, flurbiprofen, naproxen, fenoprofen, oxaprozin aceclofenac, fenclofenac
6. **Anthranilic acids (fenamates):** mefenamic acid, meclofenanic acid
7. **Enolic acids (oxicam):** piroxicam, tenoxicam, meloxicam
8. **Alkanones:** nabumetone
9. **Pyrazolidinediones:** phenylbutazone, oxyphenylbutazone
10. **Diarylheterocycles (selective COX-2 inhibitors):** celecoxib, rofecoxib, valdecoxib, lumiracoxib, parecoxib, eterocoxib.

**Classification of naids on the basis of their cox inhibitionactivity.**[12]

| | | |
|---|---|---|
| Group 1 | Poorly selective NSAIDs that fullyinhibit both COX-1 and COX-2 (<5-fold COX-2 selectivity) | Ibuprofen, diclofenac,aspirin, piroxicam, Naproxen |
| Group 2 | NSAIDs capable of inhibiting bothCOX-1 and COX-2 with a preferential selectivity toward COX-2 (5 to 50 fold COX-2 selectivity) | Celecoxib, meloxicam, nimesulide, Etodolac |
| Group 3 | NSAIDs that strongly inhibit COX-2 butonly weakly inhibit COX-1 (>50-fold COX-2 selectivity) | Rofecoxib,NS-398 |
| Group 4 | NSAIDs that seem to be only weak inhibitors of both COX-1 and COX-2 | Sodium salicylate, nabumetone |

**Mechanism of action of NSAIDs**

Despite their structural diversity, all NSAIDs inhibit COX. The mechanismof action of NSAIDs was discovered by Vane, but it was only fully explained after Simmons reported the presence of COX-2.[13] PGs are the end productsof fatty acid metabolism, and are produced via the COX pathway. They have long been known to act as major physiological and pathological mediators in a number of therapeutic areas including inflammation, pain, pyrexia, cancer and neurological diseases.[14]

**Pharmacodynamics and Pharmacokinetics of NSAIDs**

The major therapeutic actions of NSAIDs are primarily enacted by their ability to block

certain PGs synthesis through the cyclooxygenase enzymes (COX-1 and COX-2) inhibition. COX-1 produces prostaglandins and thromboxane A2 which control mucosal barrier in GI-tract, renal homeostasis, platelet aggregation and other physiological functions. COX-2 produces PGs that related to inflammation, pain and fever. COX-1 is expressed in normal cells, while COX-2 is induced in inflammatory cells. [15] COX-2 inhibition most likely represents the desired effect of NSAIDs' anti-inflammatory, antipyretic and analgesic response; while COX1 inhibition plays a major role in the undesired side effects such as GI and renal toxicities. Most NSAIDs are well absorbed in the gastrointestinal tract and have high bioavailability. Some drugs such as diclofenac undergo hepatic first-pass metabolism which resulted in the reduction in bioavailability. While some drugs such as sulindac and parecoxib are pro-drugs and need hepatic metabolism to become their active metabolites (sulindac sulfide and valdecoxib, respectively). NSAIDs are highly bound to plasma proteins. NSAIDs are usually metabolized in the liver and excreted in the urine. Common NSAIDs drug have a variable half-life; they can be anywhere from 0.25-0.3 hours such as aspirin or 45-50 hours such as piroxicam.[16]

**Adverse reactions**

Peptic ulcer diseases (PUD) cause major complications, such as upper gastrointestinal bleeding (about 70% of cases).[17]

The greatest common adverse proceedings associated with oral NSAID treatment are those affecting gastrointestinal system,[19] about 30 to 50% of NSAID users suffering from ulcerations.[19]

A recent study exhibited that 86.6% were at increased gastrointestinal risk and 22.3% were considered at high risk for gastrointestinal effects.

NSAIDs postponement ulcer curative by reducing prostaglandin, which playsa critical role in mucosal maintenance and protection.[20]

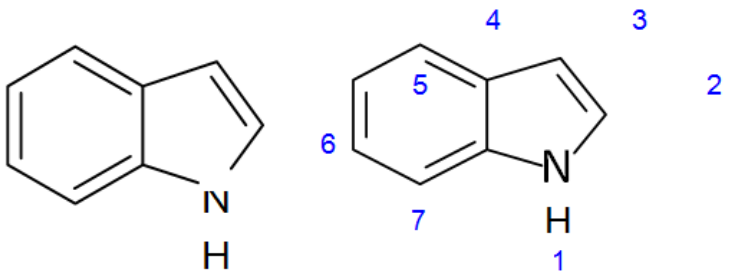
Notwithstanding their extensive use and valuable effects, NSAIDs increase the risk of gastroduodenal ulcers, the consequences of which can sometimes be life-threatening bleeding or perforation. [21]

**Indole derivatives**

**Introduction**

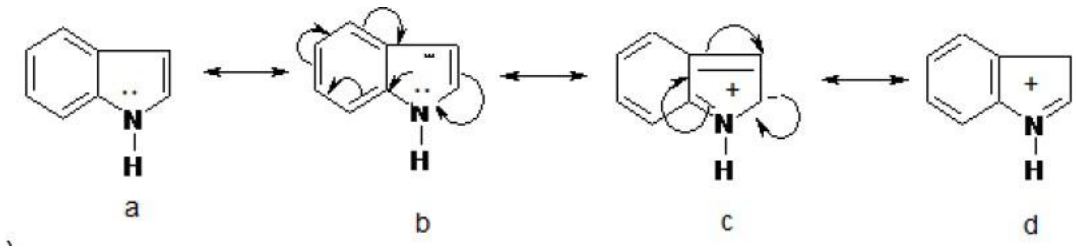
**1.1 Indole and its Derivatives**: - The word Indole is instituted from the word India, a blue color imported from India known as Indigo. Indigo can be changed over to isatin and afterward to oxindole At that point in 1866, Adolf von Baeyer decreased oxindole to indole utilizing zinc dust. In 1869, he proposed a formula for indole

Indole is non-basic nitrogenous compound in which a benzene ring and a pyrrole nucleus are fused in 2, 3 positions of the pyrrole ring. It is aromatic heterocyclic organic compound. It has a bicyclic structure. Indole is colorless crystalline solid and melts at 52'C, soluble in alcohol, benzene and ether. It may be recrystallized from water.




Indole is a trivial name of benzopyrrole in which 2 and 3 carbon atoms of the nitrogen ring are members of a benzenoid nucleus. Indole is a planar molecule with 10 electrons. It's resonance energy is 47-49 K cal/mole. It is a very weak base with pKa value 3.63. The electrophilic attack results at third positionsince Presence of high electron thickness at third position. It has been like wise upheld by the estimation of electron thickness and by sub-atomic orbital strategy.

**Resonance in indole molecule**

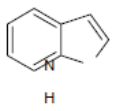



It undergoes all types of reactions for example: Protonation, nitration, sulfonation, acylation, halogenations, and formation of various metal complexes etc. it gives electrophilic as well as

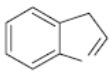
nucleophilic reactions. Indoles are probably the most widely distributed heterocyclic compound in nature. Tryptophan and essential amino acid assuchis constituent of most proteins.

Indole is a basic functional unit in plants as well as animals. It can be produced by bacteria as a degradation product of the amino acid tryptophan. It is found in jasmine and in certain citrus plant. Indole is a well known part of aromas and the antecedent to numerous pharmaceuticals At low fixations, in any case, it has a fancy smell, and is a constituent of many bloom fragrances, (for example, orange blooms) and perfumes. Indole and homologous of indole have been found in coal tar and in molasses tar. It is also found in liver, pancreas, brain and bile. Indole accompanied by its β-methyl homologue, skatole, is found in the feces of human, animal and in the content of intestine. Exacerbates that contain an indole ring are called indoles.

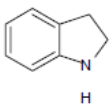
As isomer of indole in which the nitrogen atom takes part in the double bond is termed 3-pseudoindole or indolenin (1.2) and 2, 3 saturated compounds are known as indoline (1.3). There are some other oxygenated derivatives of indole are: oxindole (1.4), indoxyl (1.5), dioxindole (1.6) and indole2, 3-dione or isatin (1.7).



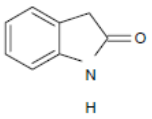

Indole (1.1)



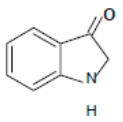
indolenin (1.2)



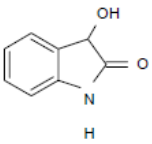

Indoline (1.3)



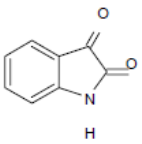

Oxindole (1.4)




Indoxyl (1.5)



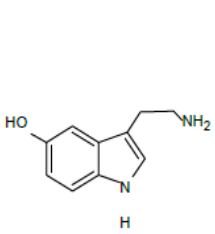

Dioxindole (1.6)



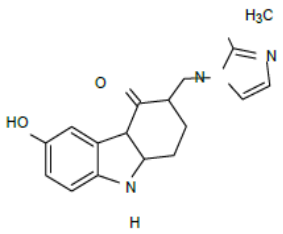

2,3-dione Indole (1.7)

Indole derivatives derived from animals are serotonins (5-HT) and melatonin. Some widely used derivatives are ondansetron for the suppression of nausea and alosteron for treatment of

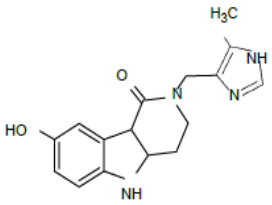
irritable bowel syndrome.




Serotonin (1.8)



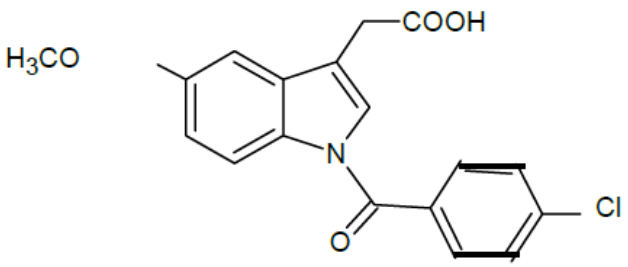

Ondensterone (1.9)




Alosetron (1.10)

From plant, tryptophan derived substances are also useful. Vincristine, an indole alkaloid is still extremely important in treatment of cancer. Brassinin, isolated from turnips is a phytoalexin. It prevents plants from microbial attack.

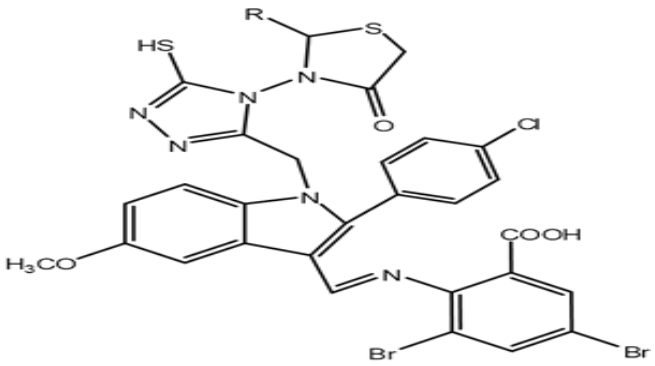
Indole moiety shows various biological activities like antimicrobial, CNS depressant, anti-HIV, anti- inflammatory, analgesic and many other activities e.g. indomethacin (1.11) is useful in treatment of rheumatoid arthritis, explains why indole and its derivatives are still a very interesting molecule since its synthesis in 1866[22-24].




Indomethacin (1.11)

**A Pharmacological Activities of Indole Derivatives Anti-Inflammatory Activity**

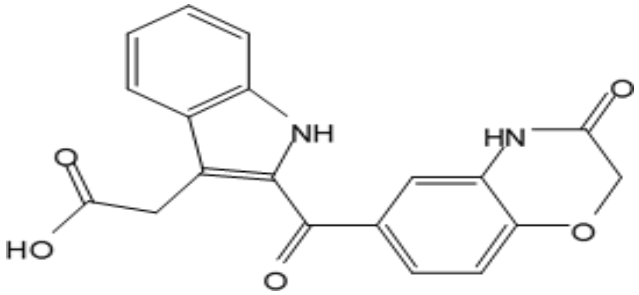
Ashok Kumar et, al[25] synthesized a series of novel substituted indole derivatives and were evaluated for their in vitro anti-inflammatory activity. It was found that the compound 2-(p-chlorophenyl)-1-[4-(2-(p-chorophenyl)-4- oxo-thiazolidin-3-yl]-5-mercapto[1,2,4,]-trizole-3-yl methyl]-3[4,6-dibromo- 2-carboxyphenyliminomethyl]-5-methoxyindole had shown prominent anti- inflammatory activity at the three graded dose of 25, 50 and 100mg/kg p.o.




R= chlorobenzylideneamino

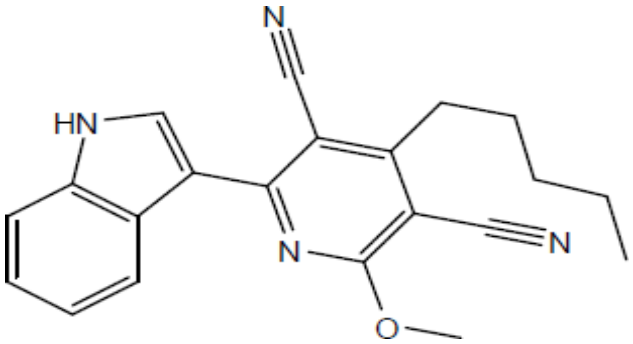
**2-(4-Chlorophenyl)-1-{4'-(4-chlorobenzylidine) amino-5'-(2- aminothiazol-4-ylthio)-[1',2',4']-triazol-3'-yl-methyl-3-(4",6"-dibromo- 2"-carboxyphenyliminomethyl }-5-methoxy-indole.**

Dubey et, al[26] synthesized a series of novel [2-(3-oxo-3,4-dihydro-2H- benzo[1,4]oxazin-6 carbonyl)-1H-indol-3yl]aceticacid derivatives and evaluated for their anti-inflammatory activity. It was found that the compounds had shown prominent COX-2 inhibitor properties.




**[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-carbonyl)-1H- indol-3yl]acetic acid**

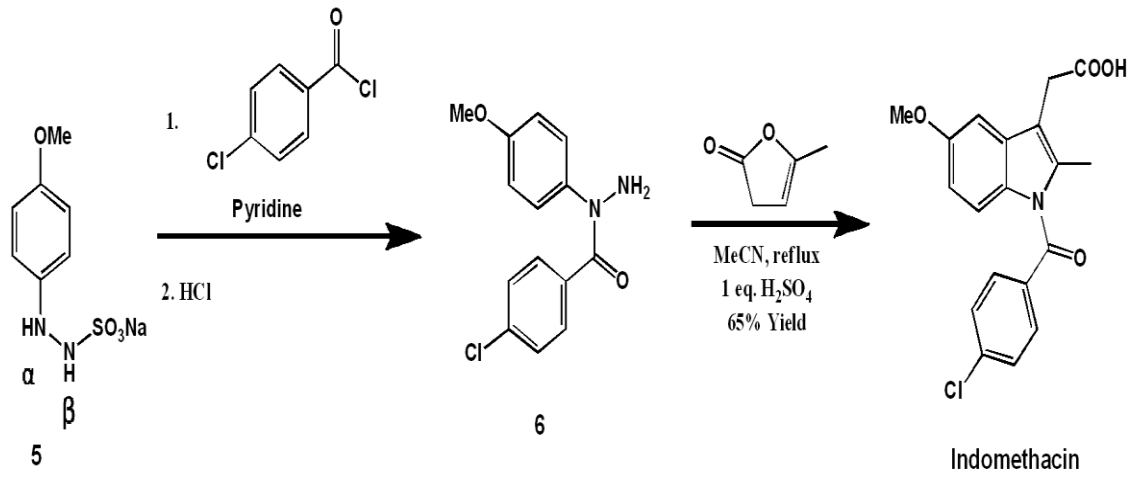
Thirumurugan prakasam et, al.[27] synthesized a various 2-(1H-indol-3-yl)-6- methoxy-4-pentylpyridine-3,5-dicarbonitrile derivatives and was screened for their anti-inflammatory activity. Most of the compounds had shown potent anti-inflammatory activity.




**2-(1H-indol-3-yl)-6-methoxy-4-pentylpyridine-3,5-dicarbonitrile**

**Modern synthesis of indomethacin**

Indomethacin (sometimes also called indometacin) is a widely used nonsteroidal anti-inflammatory drug (NSAID). Like other members of this family, it works by inhibiting the cyclooxygenase enzymes (COX-1 and 2), thereby decreasing prostaglandin levels. This is medically useful for decreasing inflammation, fever, and pain. I begin with a retrosynthetic analysis and illustrate a "traditional" synthesis of this compound. Next, I present a more efficient, modern synthesis developed by scientists at Merck.the importance of this compound as a pharmaceutical has motivated attempts to reduce the number of steps and improve the overall yield of the synthesis. The result of Merk scientists' efforts are summarized below, in an elegant two-step synthesis.[28]

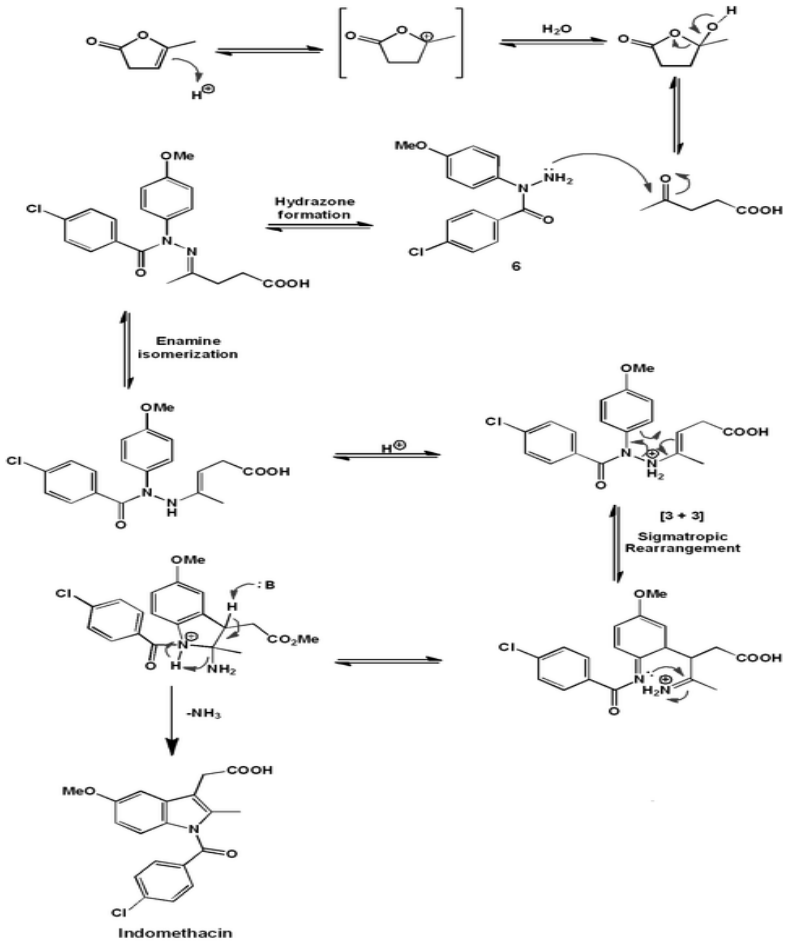



Here the chlorobenzamide group is coupled onto the molecule before the indole-forming step, eliminating the need for carboxylate protection. The synthesis starts with, a β-sulfonate modified aryl hydrazine. Acylation of aryl hydrazines normally occurs preferentially at the β-nitrogen. In contrast, The sulfonate group of is electron-withdrawing, reducing the nucleophilicity of the β-nitrogen and favoring acylation at the α-position [2]. The α-acyl-

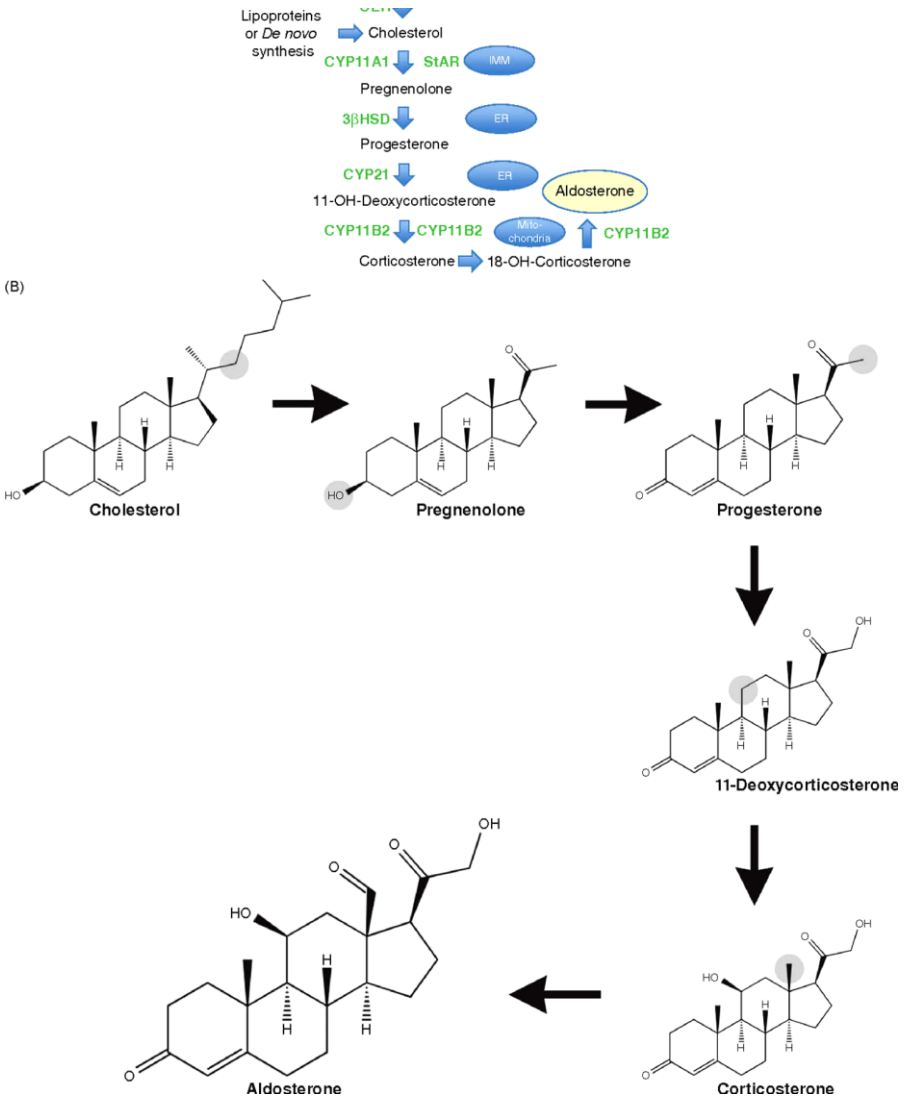
arylhydrazine can therefore be prepared from by pyridine-catalyzed acylation with 4-chlorobenzoic acid chloride. This process is mechanistically equivalent to the pyridine-catalyzed acylation of the previous synthesis. Afterward, the sulfonate is readily hydrolyzed by treatment with dilute acid.

The indole ring is formed by treatment of with α-Angelica lactone under acidic conditions. This dihydropyran functions as a ketone equivalent in the Fischer indole synthesis, as shown mechanistically below. Efficiently, under the conditions developed, the hydrazine formation and the [3 + 3]-sigmatropic rearrangement occur simultaneously under one reaction condition.

**Synthesis of indomethacin**




**Aldosterone synthesis:-** Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex through four enzymes, cholesterol desmolase (CYP11A1), 21-hydroxylase (CYP21A2), aldosterone synthase (CYP11B2) and 3β-hydroxysteroid dehydrogenase (3β-HSD).[29]

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