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Review Article

REVIEW ON INDOLE DERIVATIVES USED AS ANTIULCER AGENTS

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ABSTRACT

Ulcer is a common gastrointestinal disorder, which is widely occurring among the human beings. Ulceration generates when there is impairment of the normal equilibrium caused by either enhanced aggression or reduced mucosal resistance. Peptic ulcer is a broad term that imparts ulcer of digestive tract in the stomach or duodenum. Varieties of natural and synthetic drugs are available for the management and treatment of ulcer. At present scenario, Indole is found most multifaceted heterocyclic ring having as it has numerous therapeutic and medicinal properties. Indole and its several derivatives possess significant antiulcer activity, antimicrobial activity, antiviral activity, anticancer activity, analgesic activity. In this review article there have been emphasized on the treatment of ulcer with the help of indole and its various derivatives. Here we review the literature of indole and its derivatives, which contain fruitful and significant antiulcer activity.

Keywords: Indole, Antiulcer, *Helicobacter pylori* and Therapeutic activity.

1. INTRODUCTION

1.1 Ulcer

An ulcer is a discontinuity or break in a body membrane that impedes the organ of which that membrane is a part from continuing its normal functions. In pathology, ulcer is the breach of the continuity of skin, epithelium or mucous membrane caused by sloughing out of inflamed necrotic tissue.[1]

A lesion that is eroding away the skin or mucous membrane. Ulcer can have various causes, depending on their location. Ulcer developed on the skin are usually due to irritation, as in the case of bedsores, and may become inflamed or infected as they grow. Ulcers in the gastrointestinal tract were once attributed to stress, but most are now believed to be due to infection with the bacterium *Helicobacter pylori*. Gastrointestinal ulcers, however, are often made worse by stress, smoking, and other noninfectious factors[2].

1.2 Causes of ulcer

Main cause of an ulcer is due to infection generated with the bacterium *Helicobacter pylori*.

Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen etc.

Excess acid (hyperacidity) in the stomach, which may be related to genetics, lifestyle (stress, smoking), and certain foods.

Zollinger-Ellison syndrome, a rare disease that makes the body produce excess stomach acid.

Certain factors and behaviors can put us at higher risk for developing stomach ulcers:

Smoking.

Frequent use of steroids (such as those for treating asthma).

Hypercalcemia (overproduction of calcium).

Family history of stomach ulcers.

Being over 50 years old, diminishing the routine function of stomach.

Excessive consumption of alcohol is also a major cause of ulcer[3].

1.3 Symptoms

An ulcer may or may not have symptoms. When symptoms occur, they may include

- A gnawing or burning pain in the middle or upper stomach between meals or at night.
- Bloating.
- Heartburn.
- Nausea or vomiting.

In severe cases, symptoms can include dark or black stool (due to bleeding)[4].

1.4 Pathophysiology

The gastroduodenal mucosal lining and defense mechanisms that normally limit the injury. Aggressive factors include gastric juice (including hydrochloric acid, pepsin and bile salts refluxed from the duodenum), *Helicobacter pylori*, and NSAIDs. Mucosal Peptic ulcers result from an imbalance between factors that can damage defenses comprise a mucus bicarbonate layer secreted by surface mucus cells forming a viscous gel over the gastric mucosa; the integrity of tight junctions between adjacent epithelial cells and the process of restitution, whereby any break in the epithelial lining is rapidly filled by adjacent epithelial and mucosal stromal cells migrating and flattening to fill the gap. Mucosal defenses depend on an adequate blood supply and on formation within the gastric mucosa.[5]

In duodenal ulcers, chronic *Helicobacter pylori* infection confined mainly to the gastric antrum leads to impaired secretion of somatostatin and consequently increased gastrin release, resulting in gastric acid hypersecretion. In Zollinger-Ellison syndrome, a gastrin-secreting neuro-endocrine tumor is stimulus for high rates of gastric acid secretion.

In gastric ulcers, longstanding *Helicobacter pylori* infection throughout the stomach accompanied by severe inflammation results in gastric mucin degradation, disruption of tight junctions between gastric epithelial cells[6].

2. Classification of antiulcer drugs

2.1 Reduction of gastric acid secretion

2.11 H_2 antihistaminic

Cimetidine, Ranitidine, Famotidine, Roxatidine, Loratidine etc.

2.12 Proton Pump Inhibitors

Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole etc.

2.13 Anti-cholinergic

Pirenzepine, Propantheline, Oxyphenonium etc.

Prostaglandin analogues

Misoprostol, Enprostil, Rioprostil etc.

2.2 Neutralization of gastric acid

Antacids are used for neutralizing the gastric acid in the stomach. These drugs are known as antacids.

2.21 Systemic antacids

Sodium bicarbonate ($NaHCO_3$), sodium citrate etc.

2.22 Non-systemic antacids

Magnesium hydroxide ($Mg(OH)_2$), Magnesium trisilicate, Aulminium hydroxide gel, Calcium carbonate ($CaCO_3$) etc.

2.3 Ulcer protective

Ulcer protectives protect the ulcers by covering them and they consist of mainly polymers i.e. Sucralfate, Colloidal Bismuth subcitrate (CBS) etc.

2.4 Ulcer Healing Drugs

Carbenoxolone sodium.

2.5 Anti H-pylori drugs

Ulcer is also caused due to the action of the bacterium *Helicobacter pylori*, so for treating the ulcers caused by the bacterium, antibiotics are given[7].

Amoxicillin, clarithromycin, tetracycline are given in adjuvant therapy with antiamoebics drugs like metronidazole, tinidazole for eradication of *Helicobacter pylori* and ulcer.

Antiulcer agents and medications for acid peptic disease are commonly used drugs that rarely cause liver injury. Most agents act by inhibition of gastric acid production, neutralization of acid or protection of the gastrointestinal mucosa from acid injury. These agents are used for both prevention and therapy of duodenal and gastric ulcer disease as well as to alleviate acid reflux, esophagitis and minor upper intestinal discomforts[8].

The most commonly used antiulcer agents are antacids such as aluminium or magnesium hydroxide and calcium carbonate. Antacids are minimally absorbed and have no known adverse effects on the liver. Antacid use may cause a minor rise in urinary pH and rarely the calcium salts cause hypercalcemia.

Other antiulcer drugs include mucosal protective agents such as sucralfate and prostaglandin analogues (misoprostol). Sucralfate (Carafate and others) is a sulfated

polysaccharide that becomes a viscous polymer adhering to ulcers in mucosal surfaces and aiding in healing. Carafate is not absorbed and has not been linked to liver injury. Misoprostol is a synthetic prostaglandin E-1 analogue that inhibits acid secretion and aids in ulcer healing. Misoprostol is absorbed systemically, but has not been linked to liver injury, probably because its other side effects and need for four times daily dosing limit the duration and degree of exposure[9].

The major, most potent and effective antiulcer medications are the selective histamine type-2 receptor blockers (H_2-blockers) and the proton pump inhibitors (PPIs). Both classes of antiulcer medications block the pathways of acid production or secretion, decreasing gastric acidity, improving symptoms and aiding in healing of acid-peptic diseases.[10]

3. Indole and its derived analogues

Indole and its several derived drugs are available which show fruitful and significant antiulcer activity.

3.1 Indole or Benzpyrrole

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. Indole is a popular component of fragrances and the precursor to many pharmaceuticals.[11]

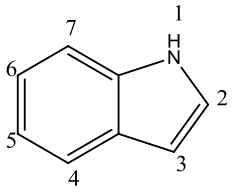

Fig. 1: Indole

Name: Indole (2,3-benzopyrrole), ketole, 1-benzazole
Chemical Formula: C_8H_7N
Molar Mass: 117.14788g
State of Matter: White solid
Mass Percent: C 82.020 %; H 6.0227 %; N 11.956 %.
Isomers: p-tolunitrile

3.2 History of Indole

Indole chemistry began to develop with the study of the dye indigo. Indigo can be converted to isatin and then to oxindole. Then in 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust. In 1869, he proposed a formula for indole.

Certain indole derivatives were important dyestuffs until the end of the 19th century. In the 1930s, interest in indole intensified when it became known that the indole substituent is present in many important alkaloids (e.g., tryptophan and auxins), and it remains an active area of research today.[12]

4. Physical properties of Indole

Table 1: The above table reveals the physical properties of Indole

Chemical formula	C_8H_7N
Molar mass	117.15 g/mol
Appearance	White solid
Odor	Feces or jasmine like
Density	1.1747 g/cm^3, solid
Melting point	52 to 54 °C (126 to 129 °F; 325 to 327 K)
Boiling point	253 to 254 °C (487 to 489 °F; 526 to 527 K)
Solubility in water	0.19 g/100 ml(20 °C) Soluble in hot water
Acidity (pK_a)	16.2 (21.0 in DMSO)
Basicity (pK_b)	17.6
Magnetic susceptibility (χ)	$-85.0 \cdot 10^{-6}$ cm^3/mol
Structure	
Crystal structure	$Pna2_1$
Molecular shape	Planar
Dipole moment	2.11 D in benzene

Compounds that contain an indole ring are called indole derivatives. In last few years, it was reported that indole, its bioisosters and derivatives had antimicrobial activity against gram-negative, gram-positive bacteria and the yeast *Candida albicans* and antimicrobial activity especially against *Enterobacter*, *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus* epidermidis.[13-14]

Fischer Indole Synthesis

This is the common and widely prescribed synthesis for indole. **Fig. 2: (Fischer indole synthesis, it is often used to generate indoles substituted in the 2- and 3-positions)**

5. BIOLOGICAL ACTIVITIES OF INDOLE AND ITS DERIVATIVES

This large group of alkaloids has been the source of many of the most potent hallucinogenic drugs and other pharmaceutical drugs. This group of alkaloids contain many poisons including strychnine.

As a rule Indole Alkaloids act on the nervous system, ranging from a strong sedative and tranquilizing effect to total paralysis. In many indole alkaloids, the paralysis can be long lasting and is extreme enough to cause death. A very small variation in dosage of indole alkaloids has a very high probability of causing instant death. Many fatalities have been linked to accidental ingestion of herbs containing indole alkaloids and in most cases, the amount of herb ingested was very small[15-16].

The therapeutic and biological activities of the indole or benzo-pyrrole involves are as follows consecutively: anticancer activity, antihypertensive activity, antidepressant activity, anti-psychotic activity, anti-inflammatory activity, antiemetic activity, analgesic activity, anti-asthmatic activity, antiviral activity, antiarrhythmic activity and beta-blocker activity.

Indole acts as agonist for the cannabinoid receptor. Indole acts as Non-Nucleoside reverse transcriptase inhibitor. Indole acts as opioid agonist[17-20].

6. ANTIULCER ACTIVITY OF INDOLE DERIVATIVES

An important class of alkaloid is the indole constituted by melatonin, cantinone, hirsuteine, reserpine, lysergic acid (LSD), yohimbine and nigakinone. Melatonin has been found in algae and humans. Pineal gland and gastrointestinal cells secrete this human hormone. The gastrointestinal hormones (or gut hormones) constitute a group of hormones secreted by enteroendocrine cells in the stomach, pancreas, and small intestine that control various functions of the digestive organs. Moreover, it has antiulcer activity because showed to protect the gastric mucosa from the damage caused by ischemia-reperfusion and absolute ethanol through of the attenuation of the gastric blood flow failed and scavenging of free radicals. Reserpine was isolated of *Rauvolfia serpentina* (Apocynaceae) and did not show antiulcer effect in the dose of 25 mg/kg when the gastric ulcers were induced by stress in mice while yohimbine, obtained of *Pausinystalia yohimbe* (Rubiaceae), was active in the reduction of gastrointestinal ulceration. Other alkaloids such as hirsutine, hirsuteine, and rhynchophylline isolated from the domestic plant *Uncaria rhynchophylla* Miq. showed mild central depressive, anti-spasmodic and hypotensive effects in mice or rats. These substances also were effective in the dose of 60 mg/kg against gastric lesions, while isorhynchophylline didn´t have a preventive effect on the development of gastric erosions in mice. Nigakinone and methylnigakinone are also indole alkaloids and they can be found in *Picrasma quassioides*, *P.allantoides* or *Ailanthus* altissima.[21-22] Lewis and Hanson, 1991 ascertained that the exploitation of the old herbal books led to the discovery of the first modern anti-ulcer drug-carbenoxolone.[23] **(Fig. 3: Chemical Structure of Carbenoxolone i.e. antiulcer drug).**

Yang, 2007 discovered that new inorganic-based drug delivery systems with suspended drug-release character through the hybridization of indole-3-acetic acid and zinc basic hydroxide salt with the coordinative unsaturated $Zn(OH)_3$ units were prepared.[24] Other important derivatives are also formed like 2-carboxy-1-methyl-3-indol-acetic acid which are also combined with different salts to get important drug deliver systems[24].

The other important indole derived drug oomeprazole possess gastric antisecretary and consequently anti-ulcerative activity. **(Fig. 4: Omeprazole (Proton Pump Inhibitor's showing antiulcer activity), (Fig. 5: Indole-3-carbinol (Showing antiulcer activity)) and (Fig. 6: 2-carboxy-1-methyl-3-indol-acetic acid (Showing antiulcer activity)).**

These substances had antiulcer effects associated with decreases in gastric acid/pepsin secretions and protection of the mucous membrane. Cantin-6-one and 4-methoxycantinone are alkaloids extracted from *Simaroubaceous* plants. These substances were found in *Quassia amara, Simaba multiflora, S. polyphylla, S. feruginea* and

Eurycoma longifolia, which are popularly, indicated for gastrointestinal disorders, obesity, anti-inflammatory, stimulant of the intestinal motility and central nervous system activities. These compounds were effective against gastric lesions induced by ethanol and indomethacin.[25]

The various indole-derived drugs, which were found to have actions against ulcer, are as follows

- 6-(1-(3-(2-Benzyl(ethoxycarbonyl) aminoethyl)-indole-2-yl)ethyl)-2,9-diethyl-1,2,3,4,4a,9a-hexahydro-pyrido[3,4-b]indole.
- 6-(1-(3-(2-Benzyl(benzyloxycarbonyl) aminoethyl)-indole-2-yl)ethyl)-2,9-diethyl-1,2,3,4,4a,9a-hexahydro-pyrido[3,4-b]indole.
- 6-(1-(3-(2-Ethyl(benzyloxycarbonyl) aminoethyl)-indole-2-yl)ethyl)-2,9-diethyl-1,2,3,4,4a,9a-hexahydro-pyrido[3,4-b]indole.
- 6-(1-(3-(2-Ethyl(ethoxycarbonyl) aminoethyl)-indole-2-yl)ethyl)-2,9-diethyl-1,2,3,4,4a,9a-hexahydro-pyrido[3,4-b]indole.
- 2,9-Diethyl-6-(3-(2-dibenzylaminoethyl)-1-tosyl-indole-2-yl)hydroxymethyl-1,2,3,4,4a,9a-hexahydro-pyrido[3,4-b]indole.

7. PROPERTIES OF INDOLE

7.1 Basicity

Unlike most amines, indole is not basic. The bonding situation is analogous to that in pyrrole. Strong acids such as hydrochloric acid can protonate indole. Indole is primarily protonated at the C-3, rather than N-1, owing to the enamine-like reactivity of the portion of the molecule located outside of the benzene ring. The protonated form has a pK_a of 3.6. The sensitivity of many indolic compounds (e.g. tryptamines) under acidic conditions is caused by this protonation.[26]

7.2 Electrophilic substitution

The most reactive position on indole for electrophilic aromatic substitution is C3, which is 10 times more reactive than benzene. It is alkylated by phosphorylated serine in the biosynthesis of amino acid tryptophan. Vilsmeier-Haack formylation of indole will take place at room temperature exclusively at C-3. **(Fig. 7: (The most reactive position on indole for electrophilic aromatic substitution is C3, which is 10^{13} times more reactive than benzene)).**

Since the pyrrole ring is the most reactive portion of indole, electrophilic substitution of the carbocyclic (benzene) ring generally takes place only after N-1, C-2, and C-3 are substituted. A noteworthy exception occurs when electrophilic substitution is carried out in conditions sufficiently acidic to exhaustively protonate C-3. In this case, C-5 is the most common site of electrophilic attack[27-30].

7.3 N-H acidity and organometallic indole anion complexes

The N-H center has a pK_a of 21 in dimethyl sulfoxide, so that very strong bases such as sodium hydride or *n*-butyl lithium and water-free conditions are required for complete deprotonation. The resulting organometallic derivatives can react in two ways. The more ionic salts such as

sodium or potassium compounds tend to react with electrophiles at nitrogen-1, whereas the more covalent magnesium compounds.

Indole Grignard reagents and especially zinc complexes tend to react at carbon 3 (see figure below). In analogous fashion, polar aprotic solvents such as Dimethyl Furamide tend to favor attack at the nitrogen, whereas nonpolar solvents such as toluene favor C3 attack.[31-34]

(Fig. 8: (Resonance as shown in Indole) and (Fig. 9: (The more ionic salts such as the sodium or potassium compounds tend to react with electrophiles at nitrogen-1, whereas the more covalent magnesium compounds indole Grignard reagents and especially zinc complexes tend to react at carbon-3)).

7.4 Carbon acidity and C-2 lithiation

After the N-H proton, the hydrogen at C-2 is the next most acidic proton on indole. Reaction of *N*-protected indoles with butyl lithium or lithium diisopropylamide results in lithiation exclusively at the C-2 position. This strong nucleophile can then be used as such with other electrophiles[35-38].

Bergman and Venemalm developed a technique for lithiating the 2-position of unsubstituted indole.

(**Fig. 10: (Reaction of *N*-protected indoles with butyl lithium or lithium diisopropylamide results in lithiation exclusively at the C-2 position))**

Alan Katritzky also developed a technique for lithiating the 2-position of unsubstituted indole.[39]

7.5 Oxidation of indole

Due to the electron-rich nature of indole, it is easily oxidized. Simple oxidants such as *N*-bromosuccinimide will selectively oxidize indole to oxindole.[40-43.]

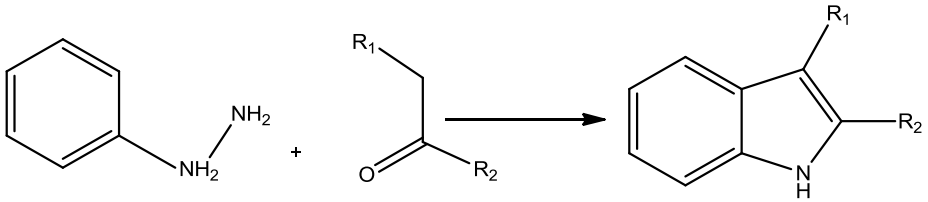

Fig. 2: (Fischer indole synthesis, it is often used to generate indoles substituted in the 2- and 3-positions)

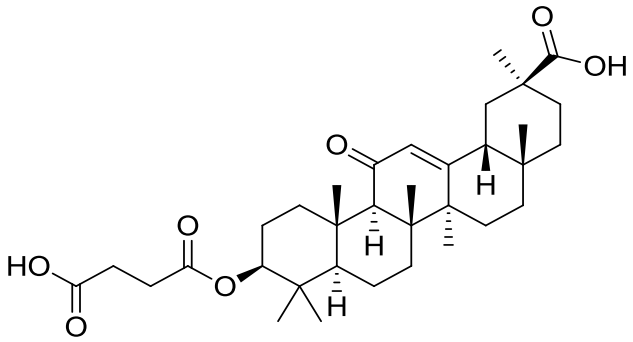

Fig. 3: Chemical Structure of Carbenoxolone i.e. antiulcer drug

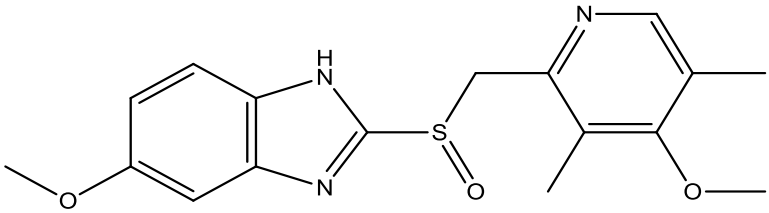

Fig. 4: **Omeprazole (Proton Pump Inhibitor's showing antiulcer activity)**

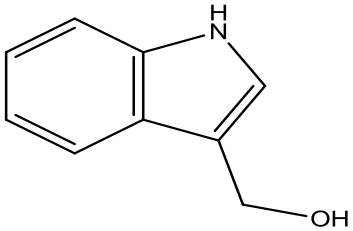

Fig. 5: Indole-3-carbinol (Showing antiulcer activity)

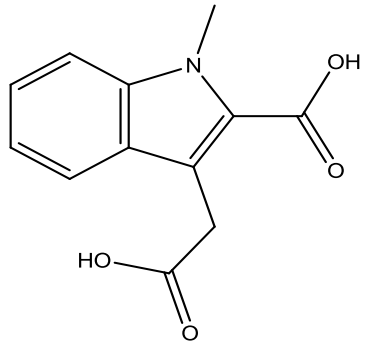

Fig. 6: 2-carboxy-1-methyl-3-indol-acetic acid (Showing antiulcer activity)

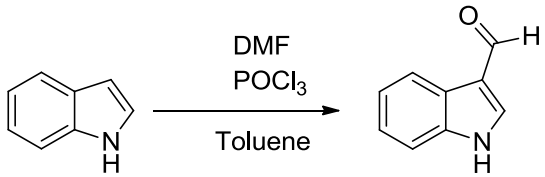

Fig. 7: (The most reactive position on indole for electrophilic aromatic substitution is C3, which is 10^{13} times more reactive than benzene)

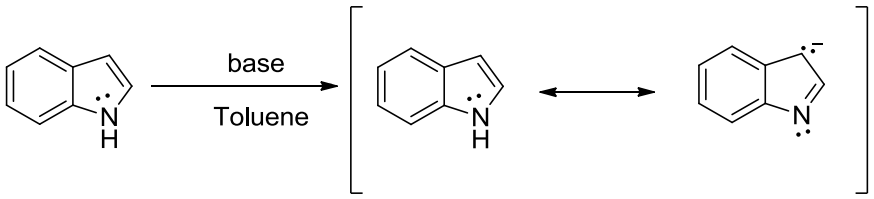

Fig. 8: (Resonance as shown in Indole)

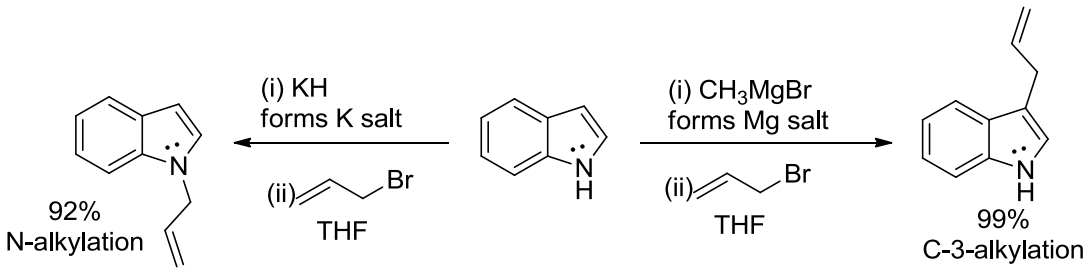

Fig. 9: (The more ionic salts such as the sodium or potassium compounds tend to react with electrophiles at nitrogen-1, whereas the more covalent magnesium compounds indole Grignard reagents and especially zinc complexes tend to react at carbon-3)

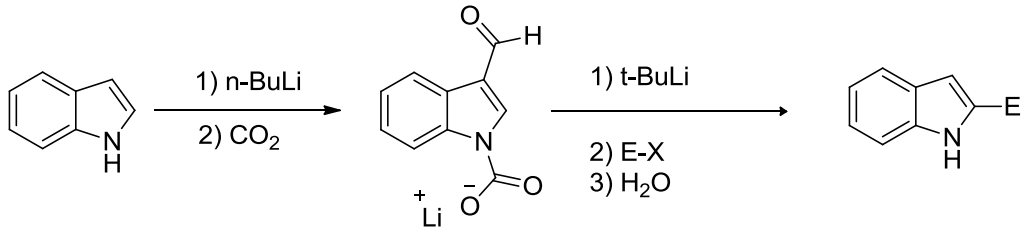

Fig. 10: (Reaction of *N*-protected indoles with butyl lithium or lithium diisopropylamide results in lithiation exclusively at the C-2 position)

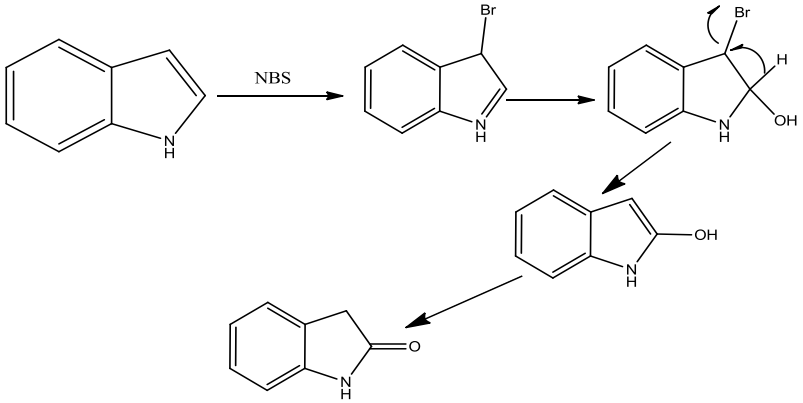

Fig. 11: Oxidants such as *N*-bromosuccinimide will selectively oxidize indole to oxindole

8. RESULTS AND DISCUSSION

The indole derivative drugs were found to be showing significant and good ulcerogenic activity. The therapeutic window, therapeutic index as well as safety parameters were also found to be good as per review of literature study data. All the above derivatives of indole have been found to possess moderate to potent antiulcer activity as it cleared from the available literature studies data.

9. CONCLUSION

As ulcer is a very painful and widely occurring disease now a day in human beings, several drugs have been found and available in the clinic since the discovery of ulcer. Now better drugs with less toxic effects are available for the diagnosis, prophylaxis as well as treatment of it.

Ulcers has various causes, so to prevent its occurrence or treat it, various alternatives of antiulcer drugs are also needed. One of the important category of antiulcer drugs is indole derivatives.

Indole derivative drugs were found to show significant and potent antiulcer activity.

It was also discovered that chances of ulcer were greatly minimized due to administration of these drugs.

It can be safely concluded that Indole derivative drugs are a very beneficial category of drugs in case of different types of ulcers.

In addition, indole drugs show a plethora of actions like antihypertensive, antianxiety, neuroleptic etc.

Both the forms of ulcer have been cured from indole-derived drugs as it is evidenced from review of the literature collection.

Still the research has been proceeding on several indole derivatives. The SAR study parameters have also kept in consideration for better ulcerogenic activity.

10. FUTURE ASPECTS

A great deal of work is being done in the discovery of antiulcer drugs belonging to the category of indole. Every year new analogues of indole are being discovered showing more improved and safer antiulcer activity.

The SARs and QSARs of indole drugs are being developed which are further helping in improvement of their antiulcer action.

In addition, the R & D department is much involved in identification of more such action in indole compounds with the sole purpose of a better treatment and improved quality of these drugs.

It is also possible that in coming years new

technologies in drug delivery, novel drug delivery for instance, will also be incorporated into designing of indole drugs for ulcer treatment, which will make it a lot easier for the indole drugs to show their actions on particular targets.

Finally, it can be concluded that the future of indole compounds in ulcer therapy is very vast and promising.

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