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RESEARCH ARTICLE

CARBAZOLE: IT'S BIOLOGICAL ACTIVITY

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ABSTRACT

Carbazole alkaloids constitute an important class of naturally occurring heterocycles, isolated from the Rutaceae-family. First Carbazole alkaloids were isolated as natural products from *Murraya koenigii* that exhibited strong antimicrobial activity[4]. The stem bark of *Murraya koenigii* contains dimeric carbazole alkaloids along with six carbazole alkaloids[3]. Traditionally, this plant is used as stimulant, stomachic, febrifuge, analgesic and for the treatment of diarrhoea, dysentry and insect bites. Along with these activities it also shows antimicrobial property.

Key words: *Murraya koenigii,* Carbazole alkaloids

INTRODUCTION:

Carbazole and its derivatives are an important type of nitrogen containing heterocyclic compounds that are widespread in nature[1]. The chemistry and biology of carbazole have attracted an increasing interest over the last 50 years because it possess a desirable electronic and charge transport properties, as well as large π-conjugated system so various functional groups are easily introduced into structurally rigid carbazolyl ring. These characteristics result in the extensive potential application of carbazole in the field of chemistry (photoelectrical material, dyes, supramolecular recognition) and medicinal chemistry (antitumor, anti-inflammatory, antimicrobial, psychotropic, anti-oxidative) [1,2].

Carbazole alkaloids constitute an important class of naturally occurring heterocycles, isolated from the Rutaceae-family. First Carbazole alkaloids were isolated as natural products from *Murraya koenigii* that exhibited strong antimicrobial activity[4]. The stem bark of *Murraya koenigii* contains dimeric carbazole alkaloids along with six carbazole alkaloids[3]. Traditionally, this plant is used as stimulant, stomachic, febrifuge, analgesic and for the treatment of diarrhoea, dysentry and insect bites. Along with these activities it also shows antimicrobial property[2, 3].

Many derivatives of the naturally occurring alkaloids elipticine and 9-methoxyelipticine which contain carbazole ring in their structure have been developed and tested for their anticancer activity.

Carbazole ring are also present in a variety of naturally occurring medicinally active substances. For example, the carbazomycins are an unprecedented class of antibiotics with a carbazole framework. Carbazomycins A and B inhibit the growth of phytopathogenic fungi and have antibacterial and anti-yeast activities[1]. Heptaphylline and 7-methoxyheptaphylline are strong cytotoxic carbazole alkaloids that obtain from roots of *Clausena* hamandian[3].

Numerous researches have focused on the various biological activities of natural occuring carbazole alkaloids as well as total synthetic analogues. Therefore, we embarked on an investigation of the possible usage of carbazole derivatives. This report presents the potent biological activity of carbazole derivatives, particularly against clinical antibiotic resistant bacteria[17], human leukaemia cells[7, 15], diabetes[13], hypertension, antiinflammation[14], psychotropic and HIV[16, 10].

Chemistry of carbazole:

Carbazole is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of two six-membered benzene ring fused on either side of a five-membered nitrogen-containing ring. The structure of compound is based on the indole structure in which a second benzene ring is fused onto the five-membered ring at the 2–3 position of indole (equivalent to the 4a–9a double bond in carbazole)[5].

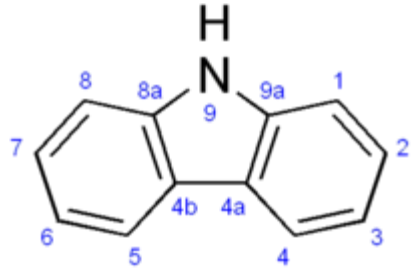

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Figure 1: Carbazole (9*H*-carbazole)

Table 1: General properties[5]

IUPAC name	9*H*-carbazole
Molecular formula	$C_{12}H_9N$
Molar mass	167.206 g/mole
Density	1.301g/cm^3
Melting point	246.3°C
Boiling point	354.69°C
Appearance	Off-white crystalline powder

- Carbazole is an extremely weak base.
- It dissolves in quinolone, acetic acid, petroleum ether, benzene, absolute alcohol and concentrated sulphuric acid.
- With potassium hydroxide (KOH), carbazole yields *N*-potassium salt.
- It is an important dye intermediate used in making of photographic plate.
- Due to extended *pi*-electron bond, carbazole is used in luminescence chemistry as a photosensitising and additional charge transport material.
- Poly (9-vinylcarbazole) is an organic semiconductor.
- 4, 4'-Bis (carbazol-9-yl) biphenyl is used as an OLED hole transport material.
- It exhibits strong fluorescence and long phosphorescence on exposure to ultra violet light.
- Carbazole is used as a reagent in analysis of carbohydrates, lignin and formaldehydes.

Various biological activities of carbazole derivatives:

1) Anticancer activity:

Cancer is a class of disease characterized by uncontrolled division of cells[6]. Carbazole and their derivatives is potent antineoplastic agent exhibiting the multimodal mechanism of action. These derivatives act by intercalation into DNA and inhibit DNA topoisomerase II activity[6]. They also form covalent DNA adducts that mediated by its oxidation with cytochromes P450 (CYP) and peroxidases[7]. A number of natural and synthetic carbazole derivatives reported as antineoplastic agent such as Elipticine[7], Elliptinium acetate[7], Olivacine[15, 21], mahanimbine[8, 19], Rebaccamycin , Mukonine and Koenoline[20].

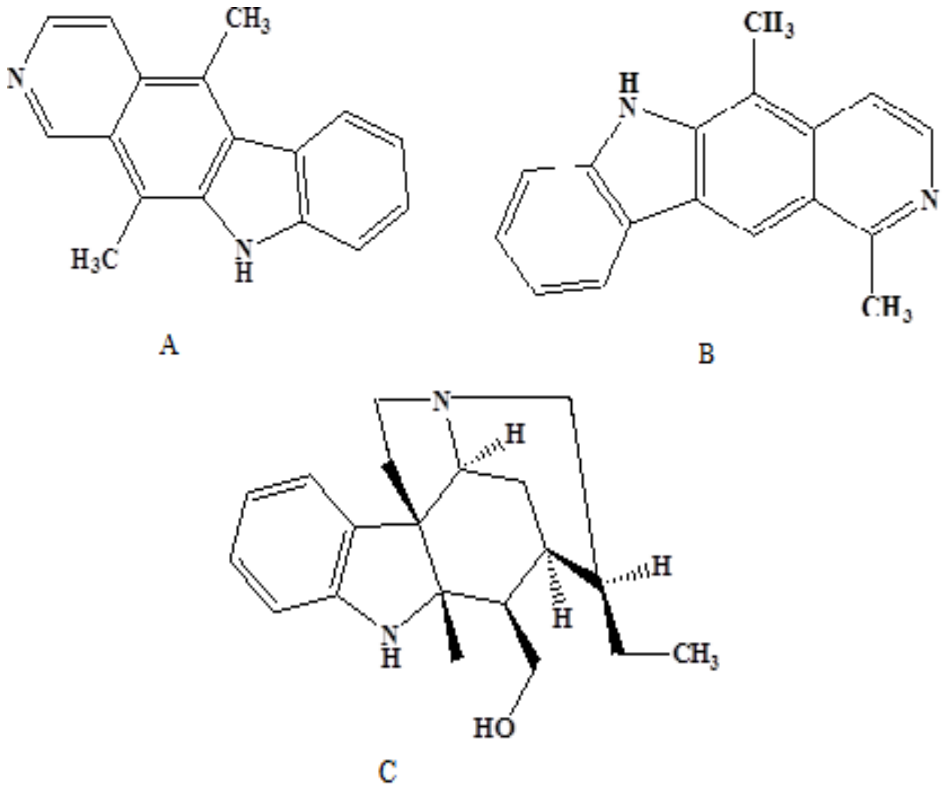

Figure 2: (A) Elipticine, (B) Olivacine (C) Geissoschizoline

2) Antimicrobial:

A number of natural and synthetic carbazole derivatives were reported as potent antimicrobial agent. They are active against bacteria, fungi and other microbes. Among them most of carbazole alkaloids obtain from rutaceae family. Methanolic extract from murraya koenigii show good antimicrobial activity[17, 18].

Mahanimbicine, mahanimbin, mahanine, murrayanol, murrayanine, girinimbine-obtain from murraya koenigii[9].

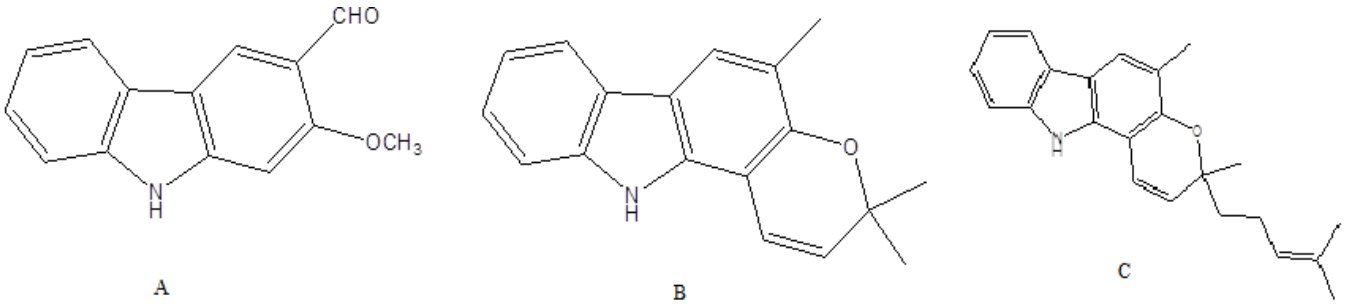

Figure 3: (A) Murrayanine (B) Girinimbine (C) Mahanimbin

3) Anti HIV:

AIDS is one of the most serious infections among all viral infection, which may cause death. Human immune deficiency virus type (HIV-1) causative agent of acquired immune deficiency syndrome (AIDS). A number of carbazole derivatives are reported as potent Anti HIV agent these derivatives are competitive inhibitors of integrase enzyme[10].

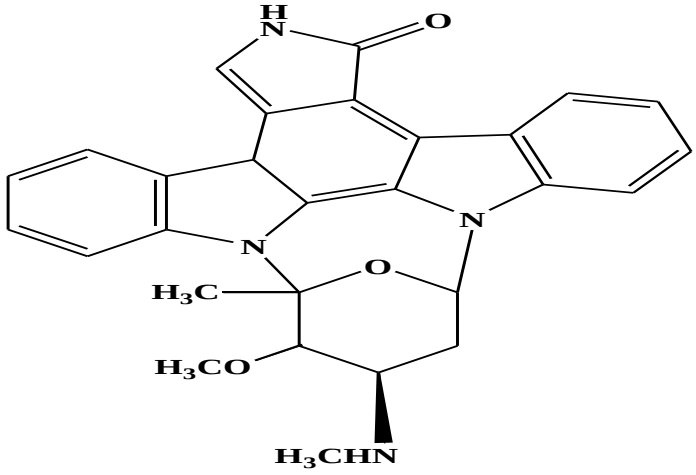

Figure 4: Staurospirone

4) Rheumatoid arthritis:

Rheumatoid arthritis is a chronic inflammation and autoimmune disease of synovial lining of joints, by release of various cytokine and mediators of inflammation[6]. Carbazole and its derivative were reported as potent anti-inflammatory agents that are Specific Serotonin ($5HT_3$) Receptor Antagonist[14].

Carprofen is a non-steroidal anti-inflammatory drug (NSAID) that is used by veterinarians as a supportive treatment for the relief of arthritic symptoms in geriatric dogs[24].

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity[24].

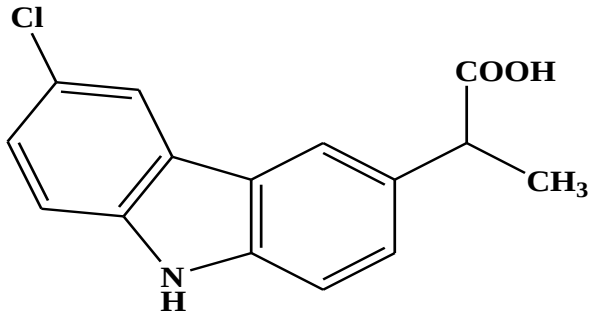

Figure 5: Carprofen

5) Antihypertensive:

Hypertension is high blood pressure that leads a higher risk for heart disease. Mainly occur due to

(i) Inability of kidney to excrete sodium salt

(ii) An overactive renin-angiotension system as well as sympathetic nervous system[6].

A number of carbazole derivatives were reported as potent antihypertensive drug. These drugs lower the high blood pressure by act on renin-angiotension system.

Carvedilol is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF). It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors[23].

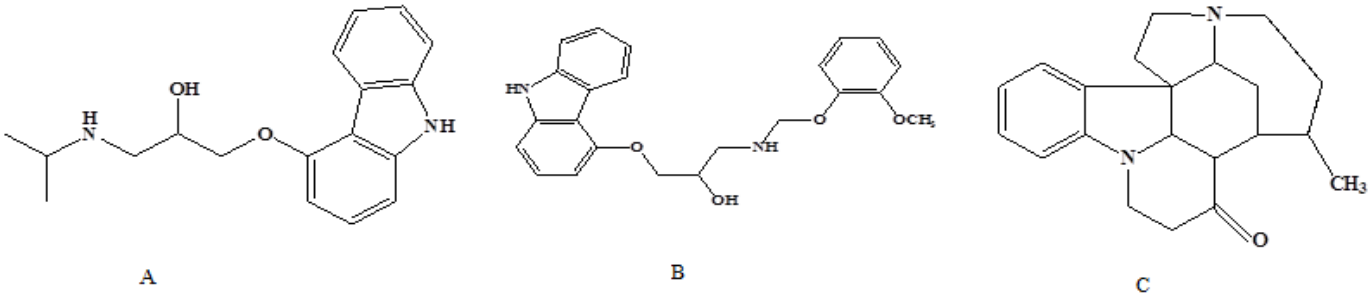

Figure 6: (A) Carbazolol (B) Carvedilol (C) Strychnine

6) Antiparkinsonian activity:

Parkinsonian is a movement disorder marketed by tremors, rigidity, slow movements and posture intability is caused by degeneration of nerve cells in the substatia nigra and the locus ceruleus where is dopamine is produced and stored[6].

Rimcazole is one of the carbazole containing drug that show potent antiparkinsonian activity. It is antagonist of sigma receptor[11].

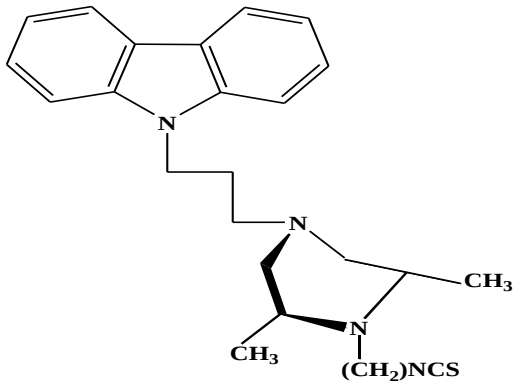

Figure 7: Rimcazole

7) Antipsychotic activity:

It is mental illness characterized by radical change in personality, impaired functioning and a distorted or non-existent sense of objective reality. There is excess of dopamine in the limbic system[6].

Carbazole derivatives are serotonin reuptake inhibitor/dopamine D_2 partial agonists to show antipsychotic activity[12].

Ciclindole is potent carbazole containing drug use in the treatment of schizophrenia

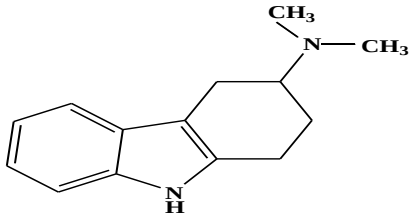

Figure 8: Ciclindole

8) Anti-diabetic activity:

Diabetes usually refers to diabetes mellitus mainly caused by kidney and pituitary gland damage. It is mainly two types.

(i) Type I[st] : insulin depended (β cells of islets of langerhans)

(ii) Type II[nd] : insulin independed (defective secretion of insulin)[6]

Mahanimbine is a carbazole alkaloid and present in leaves, stem bark and root of *Murraya koenigii*[9]. That could be used as anti-diabetic agent in the management of diabetes associated with abnormalities of lipid profiles[13].

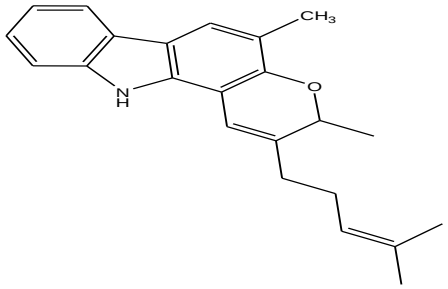

Figure 9: Mahanimbine

A novel carboline guanidine derivative tiruchenduramine has beenIsolated from the Indian ascidian *Synoicum macroglossum* that shows mild to moderate hypoglycaemic activity by inhibiting the alpha glucosidase.

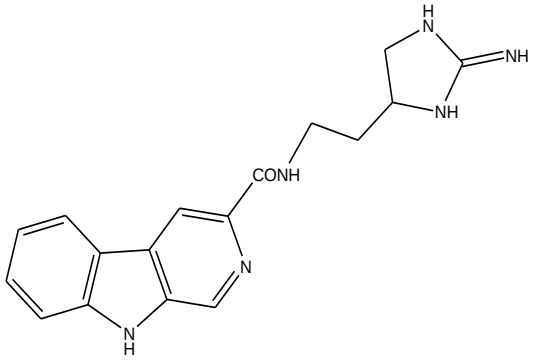

Figure 10: Tiruchenduramine

9) Anti-emetic:

Vomiting occurs due to stimulation of the emetic centre situated in the medulla oblongata. Antiemetic's are the drugs used to prevent or suppress the vomiting[25].

Ondansetron is a carbazole derivative that is competitive serotonin type 3 receptor antagonists and effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs[26].

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT_3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT_3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone[26].

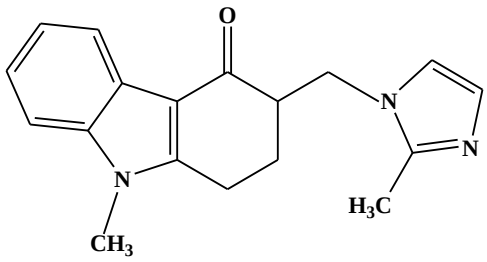

Figure 11: Ondansetron

CONCLUSION:

We have concluded that carbazole is very important heterocyclic compound due to diversity in its biological application. A number of natural or synthetic derivatives have been reported, that is potent drug and use in various treatment like in cancer, diabetes, hypertension, psychosis. Natural derivatives are carbazole alkaloids that mainly found in *Rutaceae* family. Most of these carbazole alkaloids are potent antimicrobial agent and show good activity against bacteria, fungi, virus and other microbes.

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