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Piperidine Unveiled: A Comprehensive Exploration of Structure, Applications, and Pharmacological Significance

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Abstract:

This review explores piperidine, an organic compound known for its molecular formula [CH2]5NH and unique six-membered ring structure. Piperidine is widely used in pharmaceuticals and alkaloids such as solenopsins. It is a colorless liquid with an amine odor and its name comes from the Latin word "piper," meaning pepper. The document covers its chemical properties, manufacturing processes, and applications in pharmaceuticals, rubber synthesis, corrosion inhibition, and catalysis.

Piperidine and its derivatives have significant roles in insect repellents, hair loss prevention, antipsychotic medications, and opioids. It occurs naturally in black pepper and various plants. Derivatives like N-formyl piperidine are used as solvents and bases in various chemical processes. The review highlights the complex structures of piperidine and focuses on the mechanisms of action, particularly the anti-inflammatory and anti-tumor properties of the bioactive alkaloid evodiamine.

The pharmacological spectrum of piperidine derivatives includes anti-diabetic, anti-cancer, anti-microbial, anti-inflammatory, anti-Alzheimer, anti-viral, anti-fungal, anti-hypertension, anti-malarial, and analgesic effects. Specific applications include voglibose for anti-diabetic properties and donepezil for Alzheimer's therapy. Insights extend to applications in anti-cancer chemotherapy, analgesics, anti-influenza agents, anti-tuberculosis medications, and anticoagulants. The review emphasizes the multifaceted role of piperidine and its derivatives, highlighting their ongoing significance in research and development.

Keywords:

Piperidine, chemical properties, piperidine derivatives, MOAs, and pharmacological actions.

1. INTRODUCTION:

An organic substance having the molecular formula [CH2]5NH is piperidine. This heterocyclic amine is made up of a six-membered rind with one amine bridge [-NH-] and five methylene bridges [-CH2]. It's a clear, colorless liquid with an amine-like, unpleasant smell. [1] The genus name Piper, which is the Latin word for pepper, is where the name originates. [2] Despite being a common organic compound, piperidine is most known for being a representative structural element found in many pharmaceuticals and alkaloids, including solenopsins found in nature. [3]

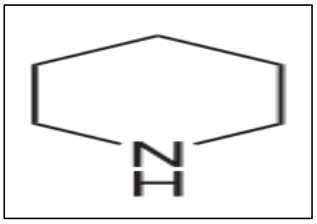

Figure 1: Chemical structure

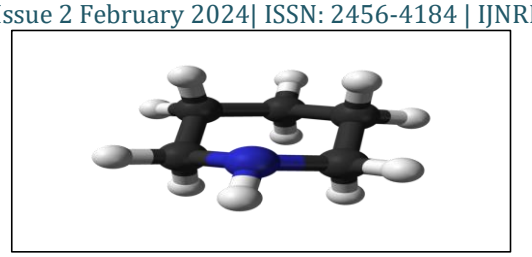

Figure 2:3D structure of piperidine

Names:

IUPAC Name: Piperidine

Preferred Name: Piperidine [4]

Other names:

- Hexahydropyridine
- Azacyclohexane
- Pentamethyleneamine
- Azinane

1.1 Properties:

Table 1: Physical properties of piperidine

Chemical formula	$C_5H_{11}N$
Molar mass	85.150 $g.mol^{-1}$
Appearance	colorless liquid
Odor	Semen-like, fishy-ammoniacal, pungent
Density	0.862 g/ml
Melting point	-7^0C [19 ^oF;266K]
Boiling point	106^0C [223^0F;379K]
Solubility of water	Miscible
Acidity[pK_a]	11.22[5,6]
Viscosity	1.573 cP at 25^0C

1.2 Production:

The French chemist Auguste Cahours named piperidine after reading about it for the first time in 1852. The Scottish chemist Thomas Anderson first reported on piperidine in 1850. [7, 8, 9]They both used nitric acid and piperine to react to produce piperidine. In the industrial setting, pyridine is hydrogenated, typically with the aid of a molybdenum disulfide catalyst, to produce piperidine. [10]

C5H5N + 3 H2 →C5H10NH

1.3 Natural occurrence of piperidine derivatives:

It has been reported that Petrosimonia monandra, Psilocaulon absimile (Aizoaceae), and black pepper all contain piperidine [11, 12]. The piperidine structural motif is present in many alkaloids found in nature. Piperine, found in black pepper, is responsible for its spicy flavor. Other examples of alkaloids with the piperidine structure include lobeline from Indian tobacco, anabasine (a nicotine analog) from tree tobacco (Nicotiana glauca), solenopsins (the fire ant toxin) [15], and coniine from poison hemlock, which was used to kill Socrates. [16] Figure: Piperidine alkaloids (black pepper, Psilocaulon ab simile)

1.4. Uses:

Piperidine is a highly versatile compound that serves as both a solvent and a base. Its derivatives, such as N-formylpiperidine, act as polar aprotic solvents, while others like 2, 2, 6, and 6-tetramethylpiperidine act as sterically hindered bases. Piperidine finds its applications in a wide range of industries including pharmaceuticals, rubber, corrosion inhibition, catalysis, organic synthesis, dye and pigment production, and plastics.

1.5. LIST OF PIPERIDINE MEDICATIONS:

Piperidine and its derivatives are ubiquitous building blocks in pharmaceuticals and fine chemicals. The piperidine structure is found in, for example:

- Lcaridin -Insect repellent
- Minoxidil –prevent hair loss
- Paroxetine -selective serotonin reuptake inhibitors
- Stimulants and nootropics-methylphenidate, Ethylphenidate
- Vasodilators - minoxidil
- Antipsychotic medications - Droperidol, Haloperidol, Melperone, Mesoridazine, Risperidone, Thioridazine
- Opioids: Dipipanone, Fentanyl and analogs Loperamide, Pethidine(meperidine), Prodine
- Arylcyclohexylamines -PCP and analogs
- anticholinergic chemical weapons- Ditran

1.6. Applications:

Piperidine derivatives, which are organic compounds containing the piperidine ring structure, have a variety of uses in different fields. Here are some common applications:

A) Pharmaceuticals:

Antihistamines: Some piperidine derivatives, such as fexofenadine and loratadine, are used as antihistamines to treat allergies.

Antipsychotics: Piperidine derivatives like pimozide and pipotiazine are used as antipsychotic medications.

Analgesics: Some piperidine derivatives, including meperidine, are used as analgesics (painkillers).

Antivirals: Certain piperidine derivatives exhibit antiviral properties and are being researched for potential use in antiviral medications.

B) Agrochemicals:

Piperidine derivatives have biological activity against pests and can be utilized in the creation of various pesticides and insecticides.

C) Chemical Intermediates:

Piperidine derivatives serve as important intermediates in the synthesis of other organic compounds, including pharmaceuticals, agrochemicals, and specialty chemicals.

D) Rubber Accelerators:

Piperidine derivatives are used in the production of rubber accelerators, which are substances that speed up the vulcanization of rubber. A significant industrial application of piperidine is for the production of "Di-

piperidinyl dithiocarbamate tetrasulfide." which is used as an accelerator of the sulfur vulcanization of rubber. [17]

E) Corrosion Inhibitors:

Some piperidine derivatives have been studied for their ability to inhibit corrosion in metal surfaces and are used in corrosion protection formulations.

F) Solvents:

Piperidine itself, as well as some of its derivatives, can be used as solvents in various chemical processes.

G) Research Chemicals:

Piperidine derivatives are used in chemical research for the synthesis of novel compounds and the study of their properties.

It's important to note that the specific uses of piperidine derivatives can vary based on their chemical structure and properties. Additionally, ongoing research may uncover new applications for these compounds in various industries

2. PIPERIDINE DERIVATIVES:

- The term "piperidine derivatives" describes a group of organic substances with a piperidine ring structure. The heterocyclic amine piperidine is made up of one nitrogen atom and five carbon atoms in its six-membered ring.
- Different functional groups are added to the piperidine ring to create derivatives with different chemical structures and characteristics.
- Furthermore, because of the versatile reactivity of the piperidine ring, piperidine derivatives can also be used as building blocks in the synthesis of different organic compounds. Because of the ongoing exploration and development of new derivatives for various applications, piperidine is a useful scaffold in organic chemistry.
- Changes or substitutions made to this piperidine ring give rise to a variety of chemical entities with different characteristics and purposes, which is the general structure of piperidine derivatives.

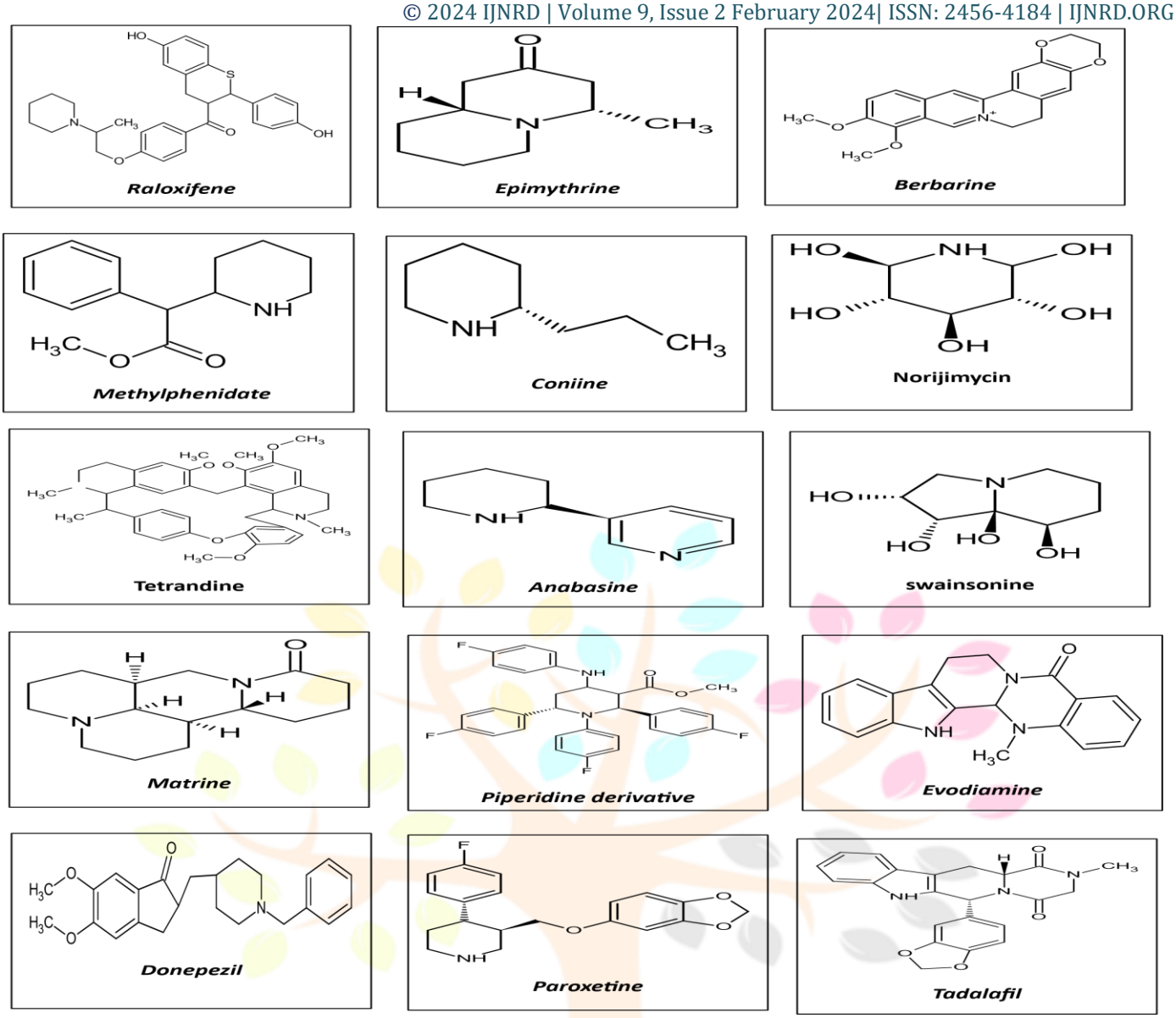

Figure 4: Structures of piperidine derivatives

2. MECHANISM OF ACTION OF PIPERIDINE DERIVATIVES:

The mechanism of action (MOA) of piperidine derivatives can vary significantly depending on the specific component and its intended application. The heterocyclic amine piperidine ring consists of six members, each containing one nitrogen atom. Derivatives of piperidine are used in various fields, including medical chemistry. Evodiamine, a bioactive alkaloid found in the fruit of Evodia rutaecarpa, is used in traditional Chinese medicine. Although ongoing research is being conducted on evodiamine, its exact mechanism of action (MOA) remains unclear. Inappropriate, excessive production of NO is largely responsible for the pathogenesis of various inflammatory diseases. [18]

Evodiamine is a compound derived from piperidine, which is used to inhibit the production of nitric oxide (NO) by interfering with IFN-γ-initiated signaling events that activate inflammatory cells. In addition to this, evodiamine has been found to inhibit the action of nuclear factor kappa-B (NF-κB), and the transcription of COX-2 and hypoxia-inducible factor 1α (HIF-1α), by dephosphorylating the serine protein kinase B (PKB/Akt) and 70 kDa ribosomal S6 kinase. These findings suggest that evodiamine possesses a novel mechanism for its anti-inflammatory activity. [19]

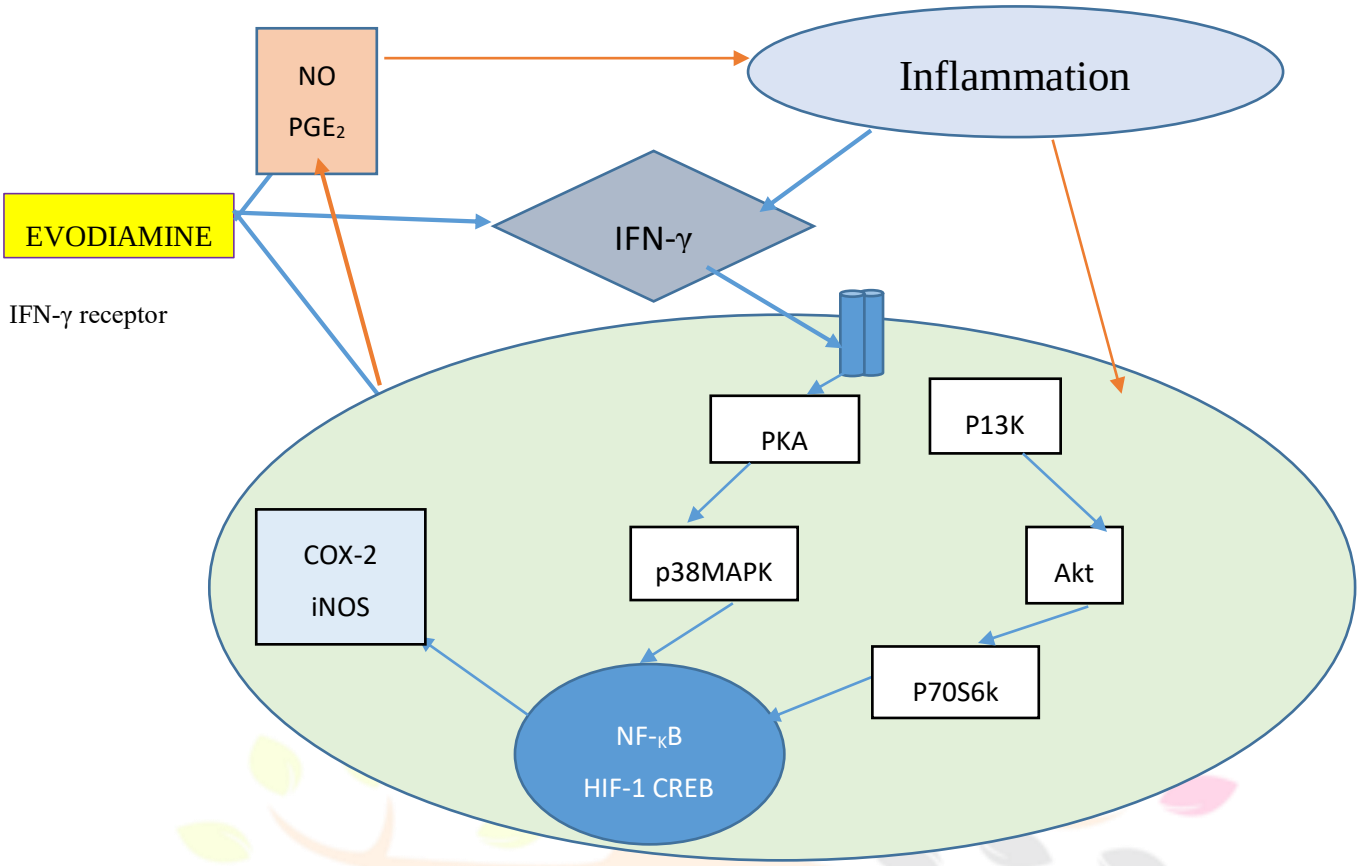

Figure 5: Indicates the inhibitory effects of evodiamine on inflammation, shown by T-lines.

Evodiamine is a type of piperidine derivative that has been found to have anti-tumor properties. It works by inhibiting the proliferation of various cancer cell lines. Evodiamine has been observed to arrest cell cycle progression (G2/M phase) by activating Cdc2/cyclin B. Additionally, it has been found to exhibit apoptotic activity by modulating NF-κB activation, and this inhibition is regulated by gene products of Cyclin D1, X chromosome-linked IAP, and Bcl-Xi. The P13K/Akt and extracellular signal-regulated kinases (ERKs) signaling pathways also play essential roles in response to tumor cells induced by evodiamine. Furthermore, evodiamine acts as a dual inhibitor of Topoisomerases 1 and 2, which shows its potential anti-tumor properties and possible underlying mechanisms. [20, 21, 22, 23]

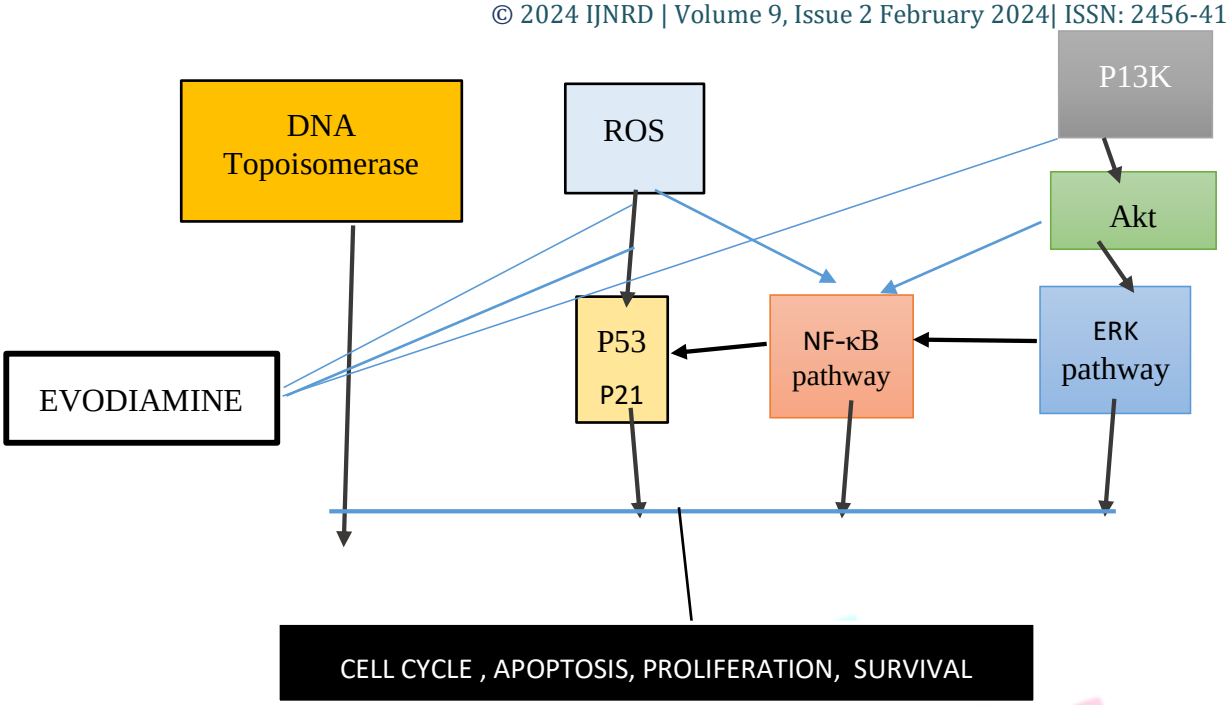

Figure 6: The potential anti-tumor properties and potential mechanisms of evodiamine

4. PHARMACOLOGICAL ACTION OF PIPERIDINE DERIVATIVES:

The piperidine derivative compounds show various pharmacological actions such as anti-diabetic, anti-cancer, anti-microbial, anti-inflammatory, anti-abelian, anti-viral anti-fungal, anti-hypertension, anti-malarial, analgesic, anti-psychotic agents, etc. then we can see some of the mechanisms of action of these piperidine compounds.

Anti-diabetic activity:

Piperidine derivatives have been investigated for various pharmacological activities, including potential anti-diabetic effects. However, it's important to note that research in this field is ongoing, and the development of effective anti-diabetic drugs involves complex processes, including preclinical and clinical studies.

One example of a piperidine derivative with anti-diabetic activity is voglibose. Voglibose is an alpha-glucosidase inhibitor, and it belongs to the class of oral anti-diabetic drugs.

Voglibose inhibits alpha-glucosidase enzymes in the intestine, which are responsible for breaking down complex carbohydrates into simpler sugars. By inhibiting these enzymes, voglibose delays the absorption of glucose, leading to reduced postprandial (post-meal) blood glucose levels. [24, 25]

Alzheimer's disease therapy:

Alzheimer's disease is the most lethal and burdensome illness of the last century. It has no particular treatment other than symptomatic treatment. The neurotransmitter acetylcholine is one of the important components of normal brain function. Deficiency of the cholinergic system has been seen in the brains of Alzheimer's patients, leading to the pathophysiology of memory impairment.[26]The main goal of modern therapy is to maintain the level of acetylcholine through the inhibition of cholinesterase acetylcholinesterase(AChE) and butyrylcholinesterase(BuChE).[27]The main drug among acetylcholinesterase inhibitors is DONEPEZIL, a piperidine derivative. The active agent is capable of inhibiting both AChE and BuChE enzymes and is a proposed indolylpiperidine analog of donepezil.[27]Thus compound was extended in AChE interaction and failed in BuChE interaction. Thus, (Liu et al.) expanded this field with 4-N-phenylamino quinoline derivative [28] via piperidine moiety introduction to a previously reported lead compound.[29] Piperidine incorporation improved the brain exposure of the resulting dual inhibitor. In addition, the compound showed antioxidant and mental chelating properties.

Piperidine alcohol and ketone alkaloids:

There is a type of alcohol called piperidine alcohol, which is also known as 2-(1-hydroxyalkyl) piperidine conhydrine. However, not much is known about the pharmacological uses of piperidine alcohols and ketones. Piperidine ketone analogs, such as pelleterines, have been studied and found to be effective as anthelmintic agents. N-methyl pelleterine works within the gastrointestinal tract to eliminate tapeworms and is also used for treating muscle cramps and convulsions. [30]

Anti-Cancer activity:

Doxorubicin is a chemotherapy medication that is frequently used in cancer treatment. It possesses a piperidine ring that is accountable for its anti-cancer effects. The drug functions by attaching to DNA and obstructing RNA and DNA synthesis. This causes oxidative damage inside cells, ultimately inducing programmed cell death and contributing to its cytotoxic effects. [31]

Analgesic activity:

It has been observed that a compound with a methyl function at the para position exhibits analgesic activity. The efficacy of the methyl function as an analgesic compound is increased by the presence of the methyl group. However, when the methyl group is replaced by a nitrogen atom in the piperidine, the phenacyl function decreases and the analgesic activity reduces. This information has been reported in [32]

Anti-influenza activity:

Piperidine compounds that contain the pharmacophore group of rimantadine and a six-membered carbon skeleton near the adamantane moiety, such as piperidine derivative 4-azatetracyclo tetradecane, have been found to have increased anti-influenza A virus activity and excellent selectivity. This is because the rigid carbon in the piperidine fits better than a free-rotating group into a lipophilic pocket in the M2 receptor.

It's worth noting that piperidine compounds are inactive against the influenza B virus. Additionally, piperidine was tested for its trypanocidal activity, but it was found to have no activity against Trypanosoma brucei. [33]

Anti-tuberculosis activity:

Piperine, which is similar to piperidine, is used to inhibit Rv1258c, a gene of mycobacterium tuberculosis. When combined with rifampicin, a trans-trans isomer of 1-piperoyl-piperidine, it reduces the mutation prevention concentration (MPC) and minimum inhibitory concentration (MIC) of rifampicin for M. tuberculosis H37Rv. Time-kill studies have shown that piperine enhances the bactericidal effect of rifampicin and also extends its post-antibiotic effect. When rifampicin is present, the M. tuberculosis rifampicin-resistant mutant shows a 3.6-fold overexpression of the Rv1258c gene. To understand the binding of piperine to the active site, the silicon modeling technique was used to analyze the 3D structure of the Rv1258c protein. [34]

Anti-coagulant activity:

Compounds containing 4-(piperidine-1-yl)-pyridine derivatives have shown strong factor IIa inhibition and exhibited good anticoagulant effects. [35]Piperidine diamine derivatives have displayed a great inhibitory effect on factor Xa and have been found to have anticoagulant activity. [36] Carbamoyl pyridine and carbamoyl piperidine derivatives have been synthesized, and they have shown a platelet aggregation inhibition effect. Among these derivatives, carbamoyl piperidine derivatives are more potent as anti-platelet aggregation agents. [37]

5 . CONCLUSION:

Piperidine is a versatile compound with numerous applications. Its natural occurrence and structural importance in alkaloids, as well as its use in pharmaceuticals and industrial settings, highlight its versatility. The compound has a wide range of pharmacological properties, including anti-diabetic and anti-cancer effects, which demonstrate its broad therapeutic potential. Examples like evodiamine and donepezil emphasize its

impact on anti-inflammatory and Alzheimer's therapies. Piperidine's ability to combat influenza, tuberculosis, and coagulation disorders adds to its significance. Overall, piperidine is a valuable and multifaceted component that contributes significantly to scientific and industrial advancements in both natural and synthetic domains.

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