REVIEW ON PIPERIDINE AND PYRAZINE CONTAINING MOLECULES HAVING DIFFERENT PHARMACOLOGICAL ACTIVITIES

Submitted in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

By

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CERTIFICATE

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This is to certify that the project entitled**, "Piperidine and Pyrazine containing molecules having different pharmocological activities"** is a bonafide work of **1. SHAIKH SABRINA MAQSOOD AALAM (17PH52) 2. SHAIKH SAJIDA IRSHAD (17PH54) 3. SHAIKH YAHYA AFTAB (17PH56) 4. SAYYED ZUBER JAVED (15PH39)** submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutical chemistry.

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ABSTRACT

Efforts were made to synthesize different heterocyclic compounds and their derivatives and were found to posses promising pharmacological compounds. Although piperidine and pyrazine moiety is six membered heterocyclic compounds but is fascinated by scientists because of the diverse biological activities by not only piperidine and pyrazine but its various substituted derivatives as well and having diverse pharmacological activities such antitumor, anticonvulsant, antidepressant, analgesic, antimicrobial, antitubercular and anti diabetic, antihistamine, anti-inflammatory and other activities. Some compounds also use as flavoring agent in foods. This review is focused on the piperidine and pyrazine derivatives due to its wider applications. They may replace many existing heterocyclic based pharmaceutical compounds. Many drug that containing piperidine and pyrazine moiety while several compounds are in clinical trials.

Keywords: piperidine, pyrazine

Approval for Bachelor of Pharmacy

This project entitled, **"Piperidine and Pyrazine containing molecules having different pharmocological activities"** by 1.Shaikh Sabrina Maqsood Aalam (17PH52) 2. Shaikh Sajida Irshad (17PH54) 3. Shaikh Yahya Aftab (17PH56) 4. Sayyed Zuber Javed (15PH39) is approved for the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry.

Examiners

1.....

2.....

Supervisors

1.....

2.....

Declaration

I declare that this written submission represents my ideas in my own words and where others ideas or words have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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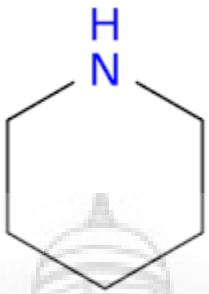
INTRODUCTION

Piperidine:



Piperidine is an organic compound with the molecular formula (CH2)5NH. This heterocyclic amine consists of a six-membered ring containing five methylene bridges (–CH2–) and one amine bridge (–NH–). It is a colorless liquid with an odor described as objectionable, and typical of amines. The name comes from the genus name Piper, which is the Latin word for pepper. Although piperidine is a common organic compound, it is best known as a representative structure element within many pharmaceuticals and alkaloids, such as natural-occurring solenopsins.

Piperidine itself has been obtained from black pepper, from *Psilocaulon absimile* (Aizoaceae), and in *Petrosimonia monandra*. The piperidine structural motif is present in numerous natural alkaloids. These include piperine, which gives black pepper its spicy taste. This gave the compound its name. Other examples are the fire ant toxin solenopsin,the nicotine analog anabasine of tree tobacco (*Nicotiana glauca*), lobeline of Indian tobacco, and the toxic alkaloid coniine from poison hemlock, which was used to put Socrates to death[1]

Other names:

Hexahydropyridine

Azacyclohexane

Pentamethyleneamine

Azinane

Chemical formula: C5H11N

Molar mass: 85.150 g·mol−1

Appearance: Colorless liquid

Odor: Semen-like,[3] fishy-ammoniacal, pungent

Density: 0.862 g/mL

Melting point: −7 °C (19 °F; 266 K)

Boiling point: 106 °C (223 °F; 379 K)

Solubility in water: Miscible

Acidity (pKa): 11.22

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:

- Icaridin (Insect repellent)
- SSRIs (selective serotonin reuptake inhibitors)
- stimulants and nootropics:
    1. Methylphenidate
    2. Ethylphenidate
    3. Pipradrol
    4. Desoxypipradrol
- SERM (selective estrogen receptor modulators)

  Raloxifene
- Vasodilators

  Minoxidil
- Antipsychotic medications:
    1. Droperidol
    2. Haloperidol
    3. Melperone
    4. Mesoridazine
    5. Risperidone
    6. Thioridazine
- Opioids:
    1. Dipipanone
    2. Fentanyl and analogs
    3. Loperamide
    4. Pethidine (meperidine)
    5. Prodine
- Arylcyclohexylamines:

  PCP and analogs

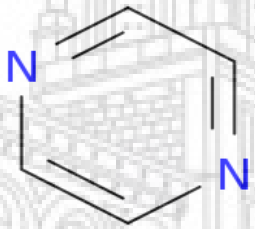
Anticholinergic

- chemical weapons

Ditran

N-Methyl-3-piperidyl benzilate

Pyrazine:



Pyrazine is a heterocyclic aromatic organic compound with the chemical formula C4H4N2. It is a symmetrical molecule with point group D2h. Pyrazine and a variety of alkylpyrazines are flavor and aroma compounds found in baked and roasted goods. Tetramethylpyrazine (also known as ligustrazine) is reported to scavenge superoxide anion and decrease nitric oxide production in human polymorphonuclear leukocytes.[2]

Chemical formula: C4H4N2

Molar mass: 80.09 g/mol

Appearance: White crystals

Density: 1.031 g/cm3

Melting point: 52 °C (126 °F; 325 K)

Boiling point: 115 °C (239 °F; 388 K)

Solubility in water: Soluble

Acidity (pKa): 0.37[1] (protonated pyrazine)

DRUG	DRUG DESCRIPTION
Bortezomib	A proteasome inhibitor used to treat multiple myeloma in patients who have not been successfully treated with at least two previous therapies.
Pyrazinamide	An antituberculosis agent used as a component of tuberculosis (TB) treatment.
Eszopiclone	A sedative-hypnotic used in the treatment of insomnia, improving both the latency phase and the maintenance phase of sleep.
Amiloride	A pyrizine compound used to treat hypertension and congestive heart failure

LITERATURE REVIEW

1. Mohammed asif et.al1. reported pyrazine moieties have shown a wide spectrum of biological activities. The various substituted pyrazine derivatives having significant antianginal, antidepressant, antpsychotic, antidiabetic, antihistamines, hypolipidemic in year 2015

2. Pallavi Goel et.al. Eur J reported Piperidine is an important pharmacophore, a privileged scaffold and an excellent heterocyclic system in the field of drug discovery which provides numerous opportunities in studying/exploring this moiety as an anticancer agent by acting on various receptors of utmost importance in 2018.

3. Manjusha R K et.al4. Reported Piperidine is a saturated heterocyclic ring, considered as a privileged scaffold in view of its role in wide range of biological activities. Piperidine is good candidate molecule for obtaining potent antioxidant agents. The planar nature of this heterocyclic nucleus allows the introduction of substituent groups at different positions on the ring in year 2018.

4. Bibek Pati et.al. Reported Piperidine heterocycle have gained a considerable attention in the field of drug discovery. The wide range of its therapeutic application paved the way to the researchers to insert the nucleus every now and then in diversified pharmacophore, so as to generate novel therapeutic profile in year 2012.

5. Pankaj B Miniyar et.al. Mini Rev reported Pyrazine is one of the important class of heterocyclic compounds that can be obtained naturally or

synthesized chemically. Pyrazine ring has got importance in exhibiting various biological activities in association with other scaffolds like pyrrole, pyrazole, imidazole, triazole, tetrazole, thiophene, oxazole, pyridine, piperidine and piperazine. Presence of pyrazine ring as a basic scaffold in various clinically used drugs exhibits its importance in drug design in year 2013.

6. Martin Dolezal et.al. Reported Various pyrazine derivatives have been synthesized and successfully evaluated as agents with diverse pharmacological effects.

7. Sabrina Batista Ferreria et.al2. Reported Pyrazines are a class of compounds that occur in nature and various methods have been worked out for their synthesis. A large number of pyrazine derivatives have been found to possess diverse pharmacological properties, which has caused an increasing interest by researchers in this core in year 2012.

DISCUSSION

PIPERIDINE:

Piperidine scaffold has found beneficial roles in numerous pharmaceutical drugs that are currently available in the market (Perumal et al., 2014, Das and Brahmachari, 2013, Sumati Anthal et al., 2013). Piperidine derivatives can be isolated from plant materials and synthesized using one or more of the many chemical reactions that have been established for the synthesis of piperidine derivatives (Anthal et al., 2013). The synthesis of piperidines and their derivatives have attracted the attention of organic and medicinal chemists, as these are commonly used in numerous natural products, pharmaceuticals and agrochemicals (Pizzuti et al., 2008). Alogliptin (1), ritalin (2), and risperidone (3) are pharmaceutically available drugs containing the piperidine nucleus that are utilized for the treatment of diabetes, improved concentration in children, and reduce schizophrenia. The drug CP-690550 (4) also known as Janus kinase 3 (JAK3), inhibits autoimmune diseases and used in transplant patients.[4]

(PIPERIDINE ANALOGS) -

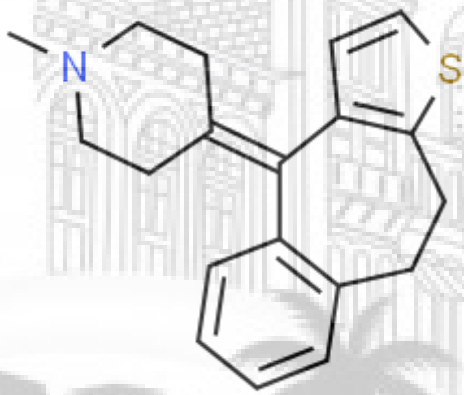
PIPERIDINE NUCLEUS CONTAINING DRUGS:

Piperidine analogs are mainly MPPP, MPTP, OPPPP (1-(3-Oxo-3-phenylpropyl)-4-phenyl-4-piperidinol propionate) and PEPAP (1-Phenethyl-4-phenyl-4-piperidol acetate (ester). They have both euphoriant and analgesic properties. They may cause, for example, convulsions and respiratory depression. MPPP is a powerful analgesic but it has never been used in clinical medicine. MPTP has been

identified as the causative agent of the frozen addicts syndrome. The number of potential drugs in this class has not been estimated.

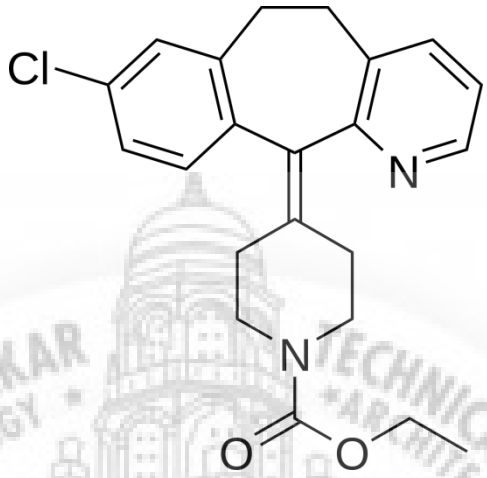
ANTI-HISTAMINE:

Pizotifen



Pizotifen has been shown to have efficacy for the prophylaxis of vascular headaches (classic migraine, common migraine, and cluster headache). It is a derivative of benzocycloheptathiophene and is structurally related to the tricyclic antidepressants and cyproheptadine.[5]

Loratadine

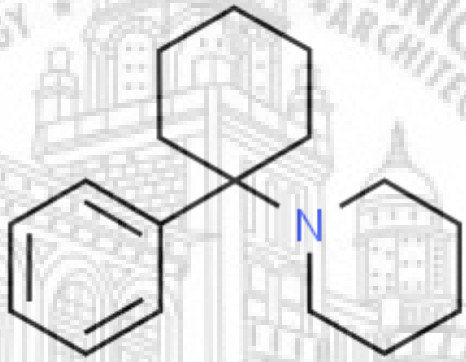


Loratadine is a piperidine, tricyclic, selective, long-acting H_1 antihistamine with minimal sedative and anticholinergic effects. Its major metabolite, descarboethoxy-loratadine (desloratadine), also is a biologically active antihistamine. After oral administration, maximum plasma levels of loratadine are reached within 0.7 to 1.3 hours (2.5 hours for desloratadine), with a mean elimination half-life of 8 to 11 hours (17 hours for desloratadine). Renal and hepatic impairment, as well as advanced age, appear to have no major influence on the drug's pharmacokinetics. However, a lower dose of loratadine is officially recommended for patients with chronic renal or hepatic disease. After a single 10 mg dose, loratadine suppresses the whealing effect of intradermal histamine for up to 12 hours. This suppression may last considerably longer after a higher dosage. Repeated loratadine doses does not appear to induce tolerance (tachyphylaxis). Although loratadine can alter myocardial potassium channels, there is no clinical evidence that it causes cardiac dysrhythmias. Coadministration of drugs that interfere with CYP3A4 (e.g., macrolide antibiotics and azole

antifungal agents such as ketoconazole and itraconazole) does not adversely affect the metabolism or safety profile of loratadine.[6]

RECREATIONAL DRUG:

PHENCYLIDINE

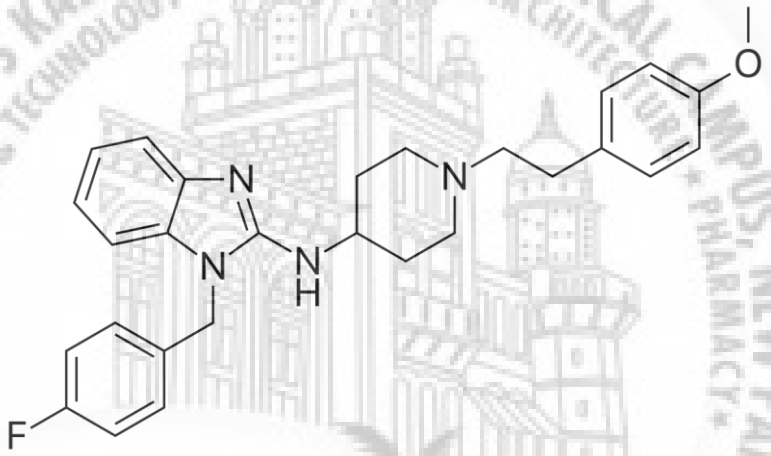


Phencyclidine piperidine (PCP, *Angel dust*) is taken orally or smoked in combination with marijuana, tobacco and *oregano*. Severe intoxication may be associated with anticholinergic side effects, and severe respiratory depression, cardiovascular and CNS effects requiring treatment. Phencyclidine is rapidly absorbed in the small intestine following oral ingestion. It crosses the placenta and can accumulate in fetal tissue. Animal experiments have shown degeneration of fetal cortical neurons (review in Schardein 2000). Microcephaly, facial asymmetry and a complex intra- and extra-cranial birth defect syndrome have been described in single case reports of human maternal phencyclidine abuse during pregnancy. Intrauterine growth restriction and disordered postnatal neurological adjustment have also been observed in addition to typical opiate withdrawal

symptoms. A follow-up study of 57 phencyclidine exposed children showed that 65% experienced neonatal narcotic withdrawal syndrome. At 1 year of age there was no difference in a behavioral assessment compared to a control group (Wachsman 1989).[7]

NON-SEDATIVE :

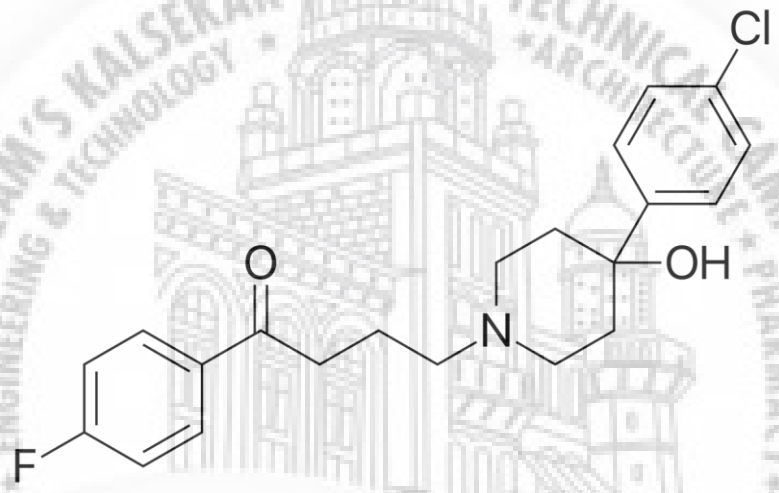
ASTEMIZOLE



A derivative of piperidine, astemizole is a long-acting, non-sedative histamine H_1-receptor antagonist used for the symptomatic relief of allergic conditions including seasonal allergic rhinitis Simola et al (1996) and the skin disorder chronic idiopathic urticaria Breneman et al (1995). It has also been shown to be of benefit in allergic asthma Cistero et al (1992). Administered orally, astemizole has no anticholinergic (antimuscarinic) side effects. However, its manufacture was discontinued in 1999 due to an increased risk of developing cardiac dysrhythmias Barbey et al (1999) and has now been withdrawn from clinical use in most countries.[8]

ANTI-PSYCHOTIC AGENTS:

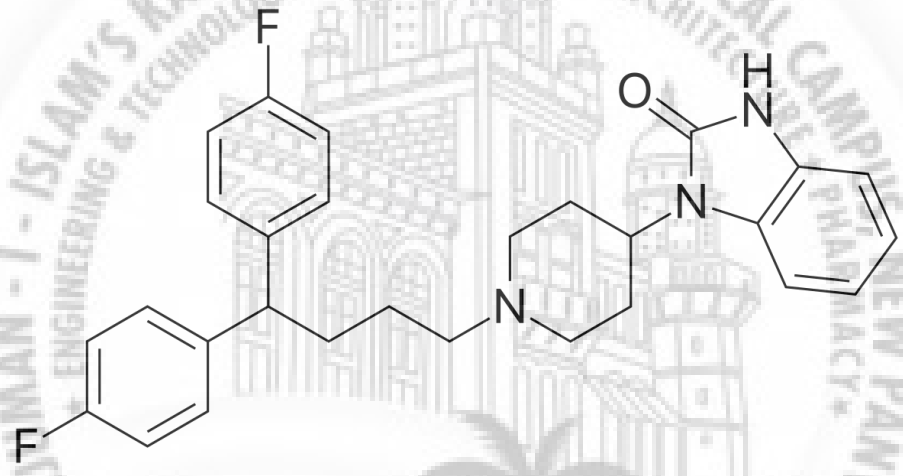
The aliphatic and piperidine phenothiazines (e.g., chlorpromazine, thioridazine, and mesoridazine) have direct negative inotropic and quinidine-like (type IA) antiarrhythmic effects on cardiac myocytes.



HALOPERIDOL

These agents block voltage-gated fast sodium channels; blockade is enhanced at less negative membrane potentials and faster heart rates. Thus, conduction disturbances will be augmented for drugs that also produce tachycardia (e.g., those with anticholinergic properties) or tissue acidemia (e.g., as a result of drug-associated seizure or shock). In addition, certain antipsychotic agents antagonize delayed-rectifier, voltage-gated potassium channels (encoded by the HERG gene)

responsible for membrane repolarization during phase 3 of the action potential.Potassium channel antagonism is concentration, voltage, and reverse frequency dependent; block is augmented at higher drug tissue concentrations, less negative membrane potentials, and slower heart rates.Potassium channel blockade may induce early after depolarization and triggered ventricular activity (e.g., torsades de pointes [TdP]). Some neuroleptics, (e.g., haloperidol, mesoridazine, pimozide, and thioridazine) are also calcium channel antagonists.

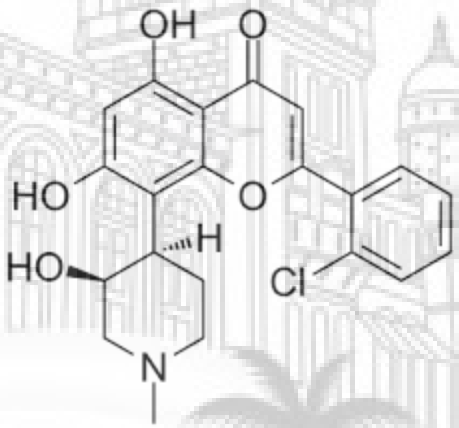


PIMOZIDE

The cardiac channel effects of antipsychotics produce a depressed rate of phase 0 depolarization, decreased amplitude and duration of phase 2, and prolongation of phase 3. In addition, early after-depolarizations that result from the blockade of the rectifying potassium channels can trigger ventricular arrhythmias (e.g., TdP).[9]

ALKALOIDS:

The piperidine chromone alkaloid rohitukine from *Dysoxylum acutangulum* Miq. was cytotoxic against human promyelocytic leukemia (HL-60) (CS 1.71) and human colorectal carcinoma (HCT-116) cells, with IC_{50} values equal to 7.5 μM and 8.8 μM, respectively.Rohitukine from *Dysoxylum binectariferum* (Roxb.) Hook. f. ex Bedd. (Meliaceae Juss.) was converted into a chlorophenyl derivative named flavopiridol (CS 1.72), a compound that attracted a tremendous amount of interest because of its ability to inhibit the enzymatic activity of cyclin-dependent kinases (CDK) which control cell-cycle progression.

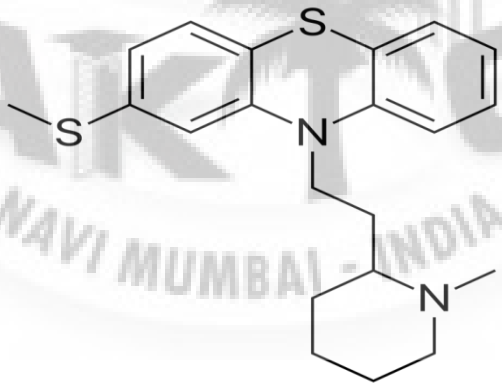


Flavopiridol induced apoptosis in human chronic lymphocytic leukemia (WSU-CLL) and human chronic B-cell leukemia (I83CLL) cells by downregulation of the anti-apoptotic protein Bcl-2 at a concentration of 400 nmol/L.Other investigations showed that 0.1 μmol/L of flavopiridol induced dramatic reductions in the levels of the anti-apoptotic myeloid leukemia cell differentiation protein (Mcl-1) and X-linked inhibitor of apoptosis protein (XIAP) in B-CLL cells. In fact the main mode of action of flavopiridol is the inactivation of the positive transcription elongation factor b (PTEF-b) CDK9/cyclin T complex. In normal conditions, this complex phosphorylates the C-terminal repeat domain

(CTD) of RNA polymerase, which undertakes the transcription of various anti-apoptotic proteins such as phosphatidylinositol 3-kinase (PI3K) and survivin. In brief, flavopiridol suppresses gene transcription by interfering with CDK9/cyclin T function and consequently induces apoptosis with precipitated loss of mitochondrial membrane potential followed by caspase 3 activation and cleavage of PARP (Poly [ADP-ribose] polymerase).Other observations on the apoptotic mechanism of flavopiridol include, notably, the disruption of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, by inhibiting the IκB kinase, and the accumulation of pro-apoptotic protein (p53) in the wild-type p53 cancer cells.[10]

Retinal toxicity of systemic and topical medications:

Thioridazine



Thioridazine is a piperidine antipsychotic drug that was previously widely used in the treatment of schizophrenia and psychosis. Due to concerns

about cardiotoxicity and retinopathy at high doses, this drug is now prescribed less than previously and is mostly used for refractory cases.

Blurred vision, dyschromatopsia (reddish or brownish discoloration of vision), and nyctalopia characterize acute toxicity with thioridazine.In the earliest stages the retinal appearance may be normal or display only mild granular pigment stippling . An intermediate stage is characterized by circumscribed nummular areas of RPE loss from the posterior pole to the midperiphery. In late stages of thioridazine toxicity, widespread areas of depigmentation alternating with hyperpigmented plaques, vascular attenuation, and optic atrophy are seen.

Retinal toxicity from thioridazine is dependent more on the total daily dose than on the cumulative amount of drug received. With higher daily doses, toxicity can occur rapidly, even within the first 2 weeks of therapy.Toxicity is rare at dosages less than 800 mg/day. Nonetheless, a few cases have been reported with lower doses given over several years. As a result, any patient taking thioridazine, regardless of the daily dose, should be monitored for the development of visual symptoms or retinal changes.[11]

Alkaloid

Pharmacological Activity

Lobeline

Structural similarity to nicotine

Exerts nicotine-like effects on choline receptors in autonomous ganglia, neuromuscular junctions, aorcid and carotid bodies; no activity on CNS cholinoceptors.

Increase of pulmonary and systemic blood pressure

In veterinary medicine:

For respiratory tract examination at a dose of 0.1 mg/kg bw (i.v.) and 0.2 mg/kg bw (i.m. or s.c.)

Rapid (3–12 min) increase of respiratory frequency, and tidal volume for a few minutes,

Therapeutic doses in human medicine: 0.06 mg/kg (i.v.), or 0.1 mg/kg bw (s.c.); single oral dose: 2 mg/person (ca. 0.3 mg/kg bw)

As smoking deterrent: daily oral dose of 6 mg (3×2 mg), ca. 0.1 mg/kg bw.

Piperine

Antidiarrheal, antipyretic, analgesic, insecticidal, antitumor, anti-inflammatory, and antidepressant properties. cytotoxic against cancer cell lines increased catecholamine secretion metabolized by cytochrome P450, it increases the concentration of several medicines (rifampin, propranolol, phenytoin, theophylline)

Nicotine

Liquid alkaloid, a CNS poison

Spasmolytic in digestive system, increases the secretion of HCl and saliva
Hypertensive due to contraction of peripheral vessels
In controlled amounts used in smoking cessation

PYRAZINE:

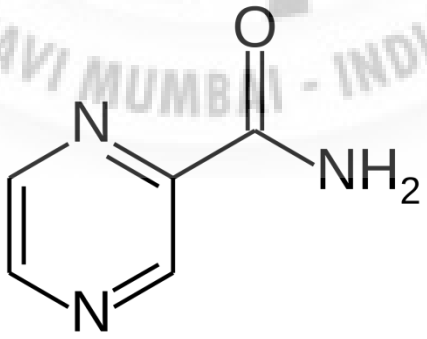
Pyrazine is a heterocyclic symmetrical aromatic organic compound with the chemical formula $C_4H_4N_2$. Pyrazine derivatives such as phenazine are well known for their anti-tumor, anti-biotic and diuretic activities. Pyrazine is less basic in nature than pyridine, pyridazine and pyrimidine. Tetramethylpyrazine (also known as ligustrazine) is reported to scavenge superoxide anion and decrease nitric oxide production in human polymorphonuclear leukocytes, and is a component of some herbs in traditional Chinese medicine. Some of the pyrazine derivatives contain various pharmacological effects.

(PYRAZINE ANALOGS) -

PYRAZINE NUCLEUS CONTAINING DRUGS:

ANTI-MYCOBACTERIAL:

Pyrazinamide:



Pyrazinamide is the pyrazine analogue of nicotinamide.

It is converted to pyrazinoic acid by bacterial pyrazinamidase. Pyrazinoic acid inhibits mycolic acid synthesis, and it disrupts cell wall function. It had widespread use in the 1960s but proved to be hepatotoxic in the doses used and was relegated to secondary status after the development of isoniazid and rifampin. More recently, pyrazinamide in reduced dosage has reemerged as the third most important anti-tuberculosis agent. Resistance to the drug in *M. tuberculosis* infection is associated with the loss of pyrazinamidase activity.

Pyrazinamide is well absorbed after oral administration and is distributed throughout the body. It is metabolized primarily in the liver and excreted largely in the urine.

Pyrazinamide is administered with other anti-tuberculosis drugs to decrease the duration of therapy required to effect a cure of uncomplicated tuberculosis. **Hepatotoxicity** is the most common adverse effect, but this has been less evident with the lower dosages currently used. Other toxic effects associated with current regimens are relatively benign or infrequent. Gastrointestinal disturbances, arthralgias, fever, and rash have been noted. Pyrazinamide may cause hyperuricemia, and the drug represents a risk in patients with gout.[12]

Aldosterone Antagonists, Amiloride, and Triamterene.

Amiloride

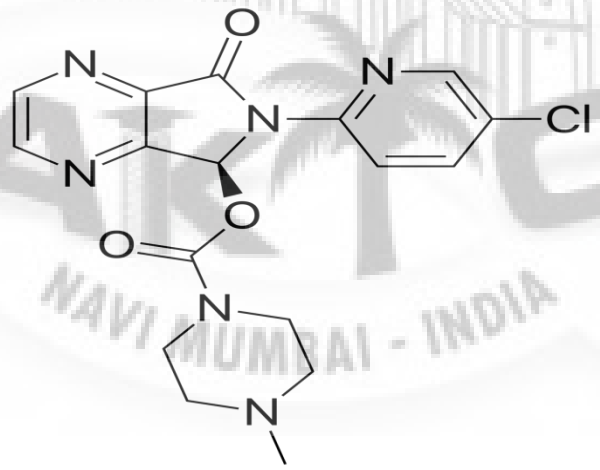
Amiloride hydrochloride, a pyrazine-carbonyl-guanidine, is chemically unrelated to other known diuretics. By binding to sodium channels in the distal convoluted tubule and collecting ducts, amiloride inhibits sodium reabsorption, producing a mild natriuresis and diuresis. Sodium channel blockade also leads to a decrease in the net negative potential of the tubular lumen, reducing the secretion of potassium and hydrogen ions into the urine. Compared with thiazides and loop diuretics, amiloride is therefore potassium sparing and may be used to offset potential kaliuresis in patients taking these more potent potassium-wasting diuretics. Improved adherence to therapy may be achieved through fixed-dose combination preparations, which incorporate thiazide diuretics, as treatment for conditions leading to edema and for ascites and hypertension. Amiloride is absorbed readily from the gastrointestinal tract and is excreted predominantly unchanged by the kidneys. It does not undergo any hepatic metabolism. Recommended dose ranges from 2.5 to 5.0 mg daily. Monitoring of serum electrolyte values and careful assessment for additional factors that could potentiate hyperkalemia are important.[13]

Cerebrocardiac Vascular Agent

A series of novel acylpiperazinyl ligustrazine derivative was reported by Cheng et al. These compounds were evaluated for their protective effect on vascular endothelial cells (ECV-304) and antiplatelet aggregation activity. Among the series, compound (78) containing salicyloyl group was found to be most active with EC50 6.13 !M. Compound was found to be the most active antiplatelet aggregation agent Chen et al. have reported a series of compound based on ligustrazinyloxy-cinnamic acid core. Among the reported series, compound (80-82) found to be the most potent anti-platelet aggregation agent with IC50 0.157, 0.161 and 0.054 nM respectively.

ANTI CONVULSANT:

Eszopiclone



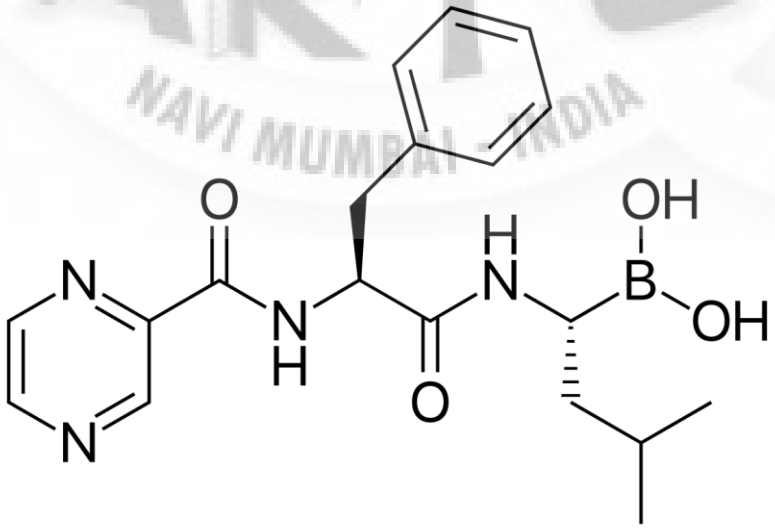
Eszopiclone rapidly induces sleep and decreases sleep latency. It also aids in the maintenance of sleep, preventing frequent awakenings This drug has shown

anticonvulsant and muscle relaxant properties in animals but is used in humans for its sedating effects.

Eszopiclone is a central nervous system depressant with various effects. These include changes in alertness and motor coordination and the risk of next morning impairment, increasing with the amount of eszopiclone administered. Exercise caution and advise against driving a motor vehicle or activities that require full mental alertness the next morning.Complex sleep behaviors may result from eszopiclone use. Eszopiclone should be discontinued in these cases. Avoid the use of alcohol and other CNS depressants when eszopiclone is administered. Advise patients to skip the eszopiclone dose if alcohol has been consumed before bed or during the evening. Use the smallest dose of eszopiclone as possible, especially in elderly patients, who may experience exaggerated drug effects. Though the potential for dependence and abuse with eszopiclone is lower than for other hypnotic drugs, this drug has been abused and is known to cause dependence. [14]

PROTEOSOME INHIBITOR:

BORTEZOMIB



Bortezomib works to target the ubiquitin-proteasome pathway, an essential molecular pathway that regulates intracellular concentrations of proteins and promotes protein degradation.[1] The ubiquitin-proteasome pathway is often dysregulated in pathological conditions, leading to aberrant pathway signalling and the formation of malignant cells. In one study, patient-derived chronic lymphocytic leukemia (CLL) cells contained 3-fold higher levels of chymotrypsin-like proteasome activity than normal lymphocytes. By reversibly inhibiting proteasome, bortezomib prevents proteasome-mediated proteolysis. Bortezomib exerts a cytotoxic effect on various cancer cell types *in vitro* and delays tumour growth *in vivo* in nonclinical tumour models.Bortezomib inhibits the proteasome activity in a dose-dependent manner. In one pharmacodynamic study, more than 75% of proteasome inhibition was observed in whole blood samples within one hour after dosing of bortezomib. Voorhees PM, Dees EC, O'Neil B, Orlowski RZ: The proteasome as a target for cancer therapy.

CONCLUSION

Heterocyclic play an important role in biochemical processes. Heterocyclic compounds have upheld the interest of researchers through decades because of their biological activities and unique structures that led to several applications in diverse areas of agrochemical research, pharmaceutical and material sciences. Piperidine and Pyrazine are the most important and well known heterocyclic compounds which are common and integral feature of a variety of natural products and medicinal mediator.

Pyrazine and piperidine nucleus are present as a core structural component in various drugs, and become the main cause of interest for pharmacists due the vast and significance range of promising biological activities since last few decades. Thus the pyrazine and piperidine nucleus could be considered as the magic potion for the management of various diseases.

The present review is an attempt to appraise the different biological activities reported for pyrazine and piperidine heterocyclic in the existing literature with research findings on these nuclei.

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