

## Piperazine and Pyrazine containing molecules and their diverse pharmacological activities

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### Abstract

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

**Keywords:** Heterocyclic, antitumor, antidepressant, antipsychotic, anticonvulsant, antimicrobial, anti-tubercular and anti-diabetic, biological activities

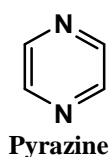
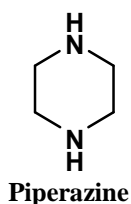
### 1. Introduction

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceedingly complex and involves talents of people from variety of disciplines. An important aspect of medicinal chemistry has been to establish a relationship between chemical and biological activity. Although many natural products are used in pharmaceuticals in their original chemical structures, successful efforts have been made to improve their pharmaceuticals and therapeutics property by structural modification. Another approach to improve therapeutic property is to identify that portion of a natural molecule responsible for biological activity and to synthesize new molecules, which are based on it. For more than a century heterocyclic compounds rank against the most important organic compounds. They participate in important biochemical processes, and are the constituents of main substances in live cells. It has been established that half of the therapeutic agents consist of heterocyclic compound. The heterocyclic

ring comprises the core of the active moiety or pharmacophore. An especially big attention is given to nitrogen containing heterocyclic compounds, as they possess a broad spectrum of biological activities, and are used in various fields of pharmacy [1-4].

Medicinal chemistry is the important sector of pharmaceutical science concerned with determining the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity. Pharmaceutical chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have six membered two nitrogen containing heterocyclic ring in their structures, two such important compound are piperazine and pyrazine. Structural frameworks have been described as privileged structures and in particular, Nitrogen

containing polycyclic structures has been reported to be connected with a wide range of biological activities. In the field of six membered heterocyclic structures piperazine and pyrazine nucleus shows various properties. Piperazine and pyrazine show numerous physiological effect such as- antituberculosis, anthelmentics, antianginals, anti-cancer, analgesic, antidepressant, antipsychotic, antidiabetic, antihistamines, hypolipidemic and flavouring agent and these drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents [5].



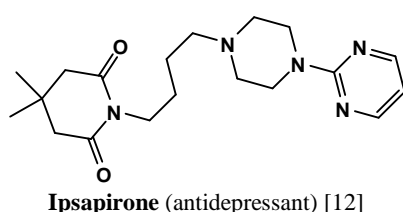
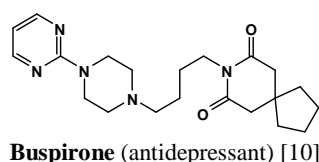
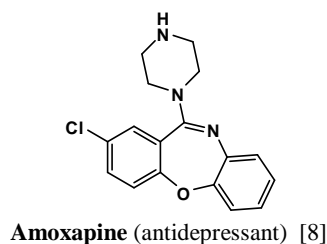
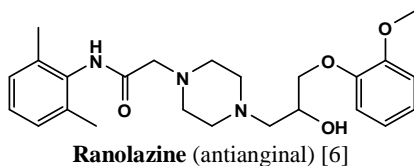
## 2. Pharmacological activities of piperazine and pyrazine derivatives

Piperazine is a symmetrical organic compound that consists of a six-membered ring containing two nitrogen atoms at opposite positions

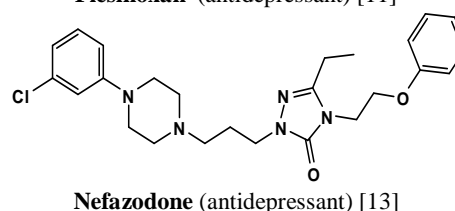
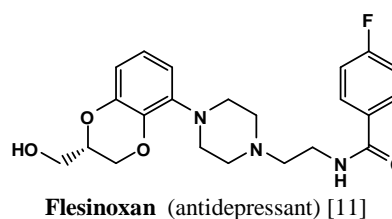
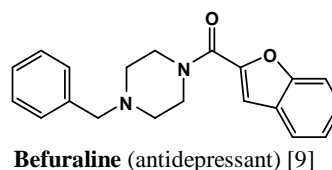
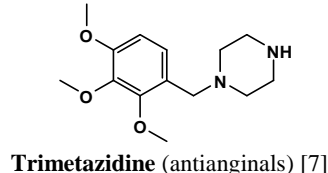
in the ring with the chemical formula  $C_4H_{10}N_2$ . Piperazine exists as small alkaline deliquescent crystals with a saline taste. The piperazines are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine functional group. Given below is a brief account of various alterations conducted on piperazine ring containing few important marketed drug and their associated biological activities. 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 antitumor, antibiotic 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 [5].

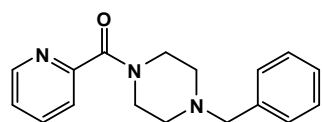
## 3. Piperazine ring containing drugs

### Drugs Use and Reference

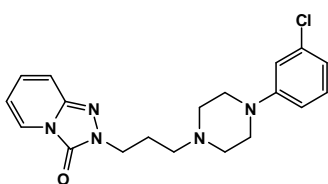


### Drugs Use and Reference

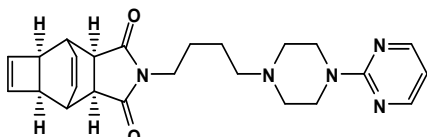




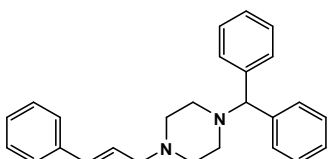
**Piberaline** (antidepressant) [14]



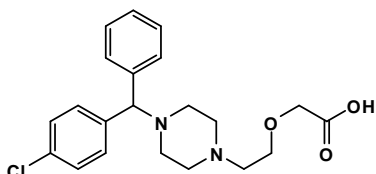
**Trazodone** (antidepressant) [16]



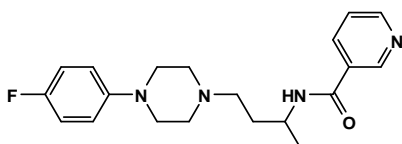
**Zalospirone** (antidepressant) [18]



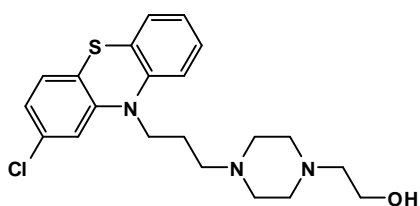
**Cinnarizine** (antihistamine) [20]



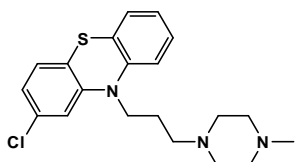
**Cetirizine** (antihistamine) [22]



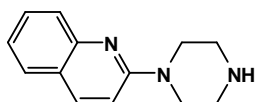
**Niaprazine** (antihistamines) [24]



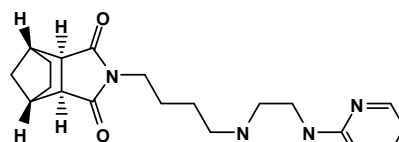
**Perphenazine** (antipsychotic) [26]



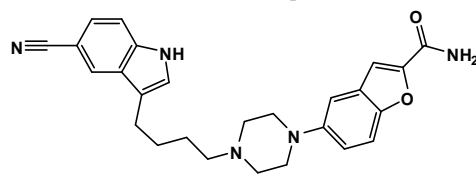
**Prochlorperazine** (antipsychotic) [28]



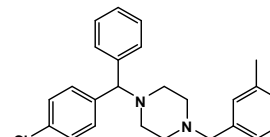
**Quipazine** (scientific research) [30]



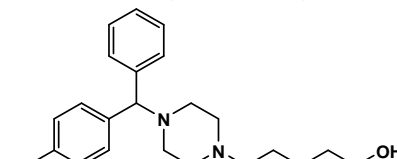
**Tandospirone** (antidepressant) [15]



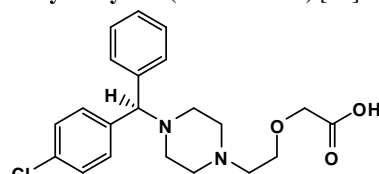
**Vilazodone** (antidepressant) [17]



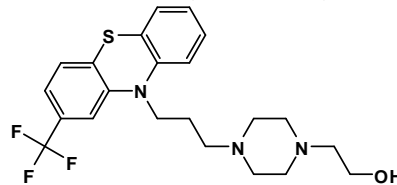
**Meclozine** (antihistamine) [19]



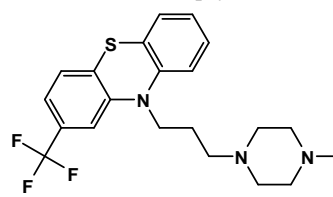
**Hydroxyzine** (antihistamine) [21]



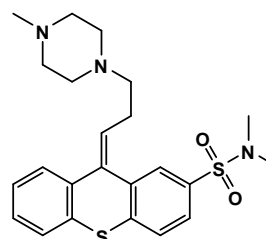
**Levocetirizine** (antihistamine) [23]



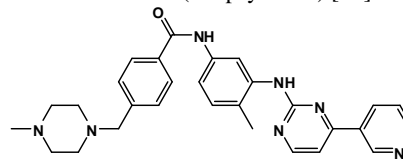
**Fluphenazine** (antipsychotic) [25]



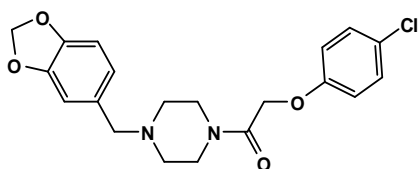
**Prochlorperazine** (antipsychotic) [27]



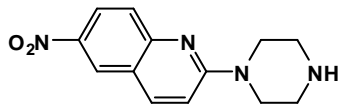
**Thiothixene** (antipsychotic) [29]



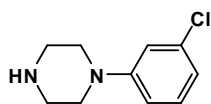
**Imatinib** (treat certain cancers) [31]



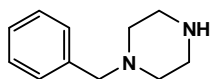
**Fipexide** (nootropic drug) [32]



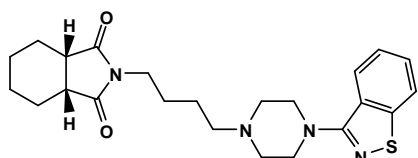
**6-Nitroquipazine** (selective serotonin reuptake inhibitor) [34]



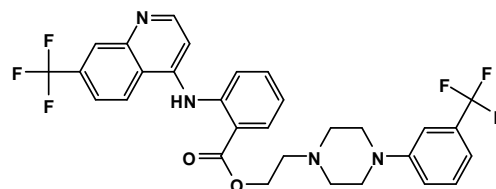
**meta-Chlorophenylpiperazine** (psychoactive) [36]



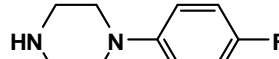
**Benzylpiperazine** (euphoric, stimulant properties) [38]



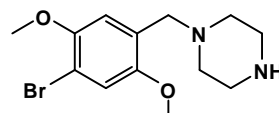
**Perospirone** (atypical antipsychotic) [40]



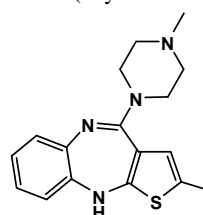
**Antrafenine** (analgesic and anti-inflammatory) [33]



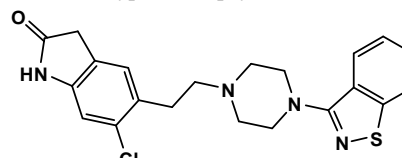
**para-Fluorophenylpiperazine** (mildly psychedelic and euphoriant effects) [35]



**2C-B-BZP** (Psychoactive) [37]



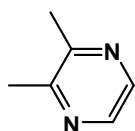
**Olanzapine** (atypical antipsychotic) [39]



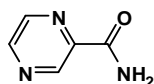
**Ziprasidone** (atypical antipsychotic) [41]

## 4. Pyrazine ring containing drugs

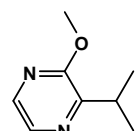
### Drugs Use and Reference



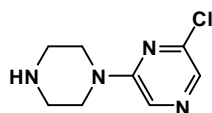
**Alkylpyrazine** (Contribute to the taste and aroma of various foods) [42]



**Pyrazinamide** (Used in treatment of T.B) [44]

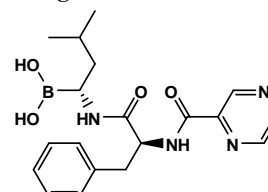


**Isopropyl methoxy pyrazine** (flavour compound in coffee) [46]

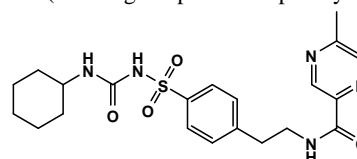


**MK-212** (Promotes the secretion of serum prolactin and cortisol in humans) [48]

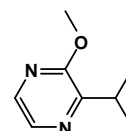
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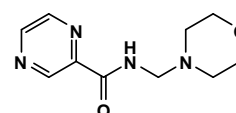
**Bortezomib** (Treating relapsed multiple myeloma) [43]



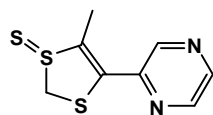
**Glipizide** (anti-diabetic drug) [45]



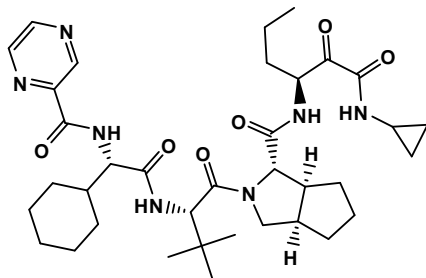
**Methoxypyrazines** (produce odors) [47]



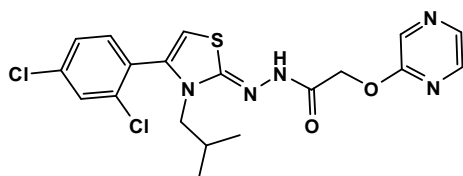
**Morinamide** (Used in the treatment of tuberculosis) [49]



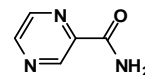
**Oltipraz** (used in tumor prevention) [50]



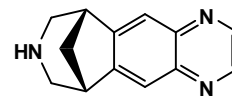
**Telaprevir** (Used for treatment of hepatitis C) [52]



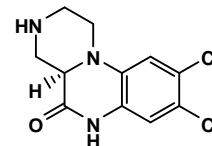
**WAY-208,466** (antidepressant and anxiolytic) [55]



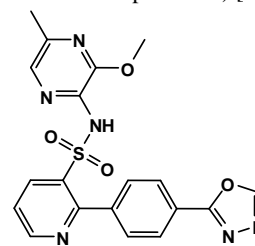
**Pyrazinamide** (Used to treat tuberculosis) [51]



**Varenicline** (Used to treat smoking addiction) [53]



**WAY-161503** (Linked to pulmonary hypertension and cardiac valve problems) [54]



**Zibotentan** An anti-cancer candidate [56]

## 5. Discussion

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceedingly complex and involves talents of people from variety of disciplines. An important aspect of medicinal chemistry has been to establish a relationship between chemical and biological activity. It has been established that half of the therapeutic agents consist of heterocyclic compound. The heterocyclic ring comprises the core of the active moiety or pharmacophore. An especially big attention is given to nitrogen containing heterocyclic compounds, as they possess a broad spectrum of biological activities, and are used in various fields of pharmacy. It is well known that a number of heterocyclic compounds containing nitrogen exhibited a wide variety of biological activities. Compounds carrying the piperazine and pyrazine ring have reported to demonstrate a wide range of pharmacological activities which include antimicrobial, antifungal, antitubercular, antihistamines, antitumor, antidiabetic, analgesic, antiinflammatory, antiallergic, anticonvulsant and other biological activities. Low choice of preparations, toxicities, and limited spectrum of action as well as risk of resistant strains prove the need of new effective medicines for systemic infectious and other diseases. Therefore, it is necessary to seek for new and less toxic compounds. Moreover, the emergence of resistance to currently

available antimicrobials is of great concern and has led to susceptibility testing of new antimicrobial agents. To investigate the activity profiles of piperazine and pyrazine derivatives bearing different substituent position have been prepared for the useful diverse pharmacological activities [1-5].

## 6. Conclusion

The pyperazine and pyrazine moieties have shown a wide spectrum of biological activities. The various substituted pyperazine and pyrazine derivatives having significant antianginal, antidepressant, antpsychotic, antidiabetic, antihistamines, hypolipidemic, activities and some compounds are also used as flavouring agent. Some of the important marketed pyperazine and pyrazine nucleus containing drugs are having different types of pharmacological activities. The pyperazine and pyrazine based pharmaceuticals will be produced on a large scale by modern drug discovery companies by different research development processes and will become available commercially for therapeutic uses. In future therapeutic pyperazine and pyrazine drugs will play a vital role in the treatment of different diseases. The biological profiles of this new generation of pyperazine and pyrazine represent much progress with regard to the older compounds. The pyperazine and pyrazine nucleus based pharmaceuticals are rapidly becoming very important class of therapeutic agents and are likely to replace

many existing organic based pharmaceuticals in the very near future.

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