Investigation on the role of Piperazine, a six membered heterocycle at the centre of many unique classes of drugs

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Abstract:

Piperazine core has the unique structural feature which is widely exploited in medicinal chemistry. Substitution on piperazine provides a way to build library of compound which are bioactive. Bioactivity of piperazine core has been utilised in manufacturing of many classes of drugs which are commercially available. Structures of these drugs contain piperazine unit with either one side substitution or both, thus this small unit provide a unique way to build a huge library of compounds. Therapeutic action of these drugs provides significant breakthrough in providing the mechanism for prevention of fatal diseases. Here we present a few classes of drugs containing piperazine moiety and discussed their therapeutic action in the living system.

Introduction:

Heterocycles compounds having nitrogen atoms in the ring have drawn considerable interest of the scientists from the last few decades, considering to their excellent therapeutic properties (1,2). These heterocyclic compounds whether naturally occurring or synthesized ones, due to their interesting biological activities are found to be involved as structural key components and play an important role in the biological processes (3). Nitrogen heterocycles have shown remarkable importance in phytochemical drugs such as ellipticine, quinine, emetine, theophylline, procaine, papaverine, morphine and codeine (4) Piperazine is a six-membered heterocyclic compound and consists of two nitrogen atoms at opposite side of the ring. Piperazine is considered as the structural component during screening of drugs and have been designated for many successful applications in biochemistry and medicinal field (5). The piperazine scaffold is regarded as the active core and is frequently observed in naturally occurring bioactive compounds across a variety of naturally occurring medicines (6). A large number of potent commercially available drugs like fluphenazine, flunarizine, lomerizine, cinnarizine, HIV protease, crixivan, ciprofloxacin, etc. contain a piperazine core are good examples of bioactive piperazine derived compounds (1). Owing the presence of polar nitrogen atom in the piperazine ring it confers bioactivity to its derivatives by increasing the favourable interactions with bio molecules (7) and play major role in the biochemical processes in living cells. Moreover, many of the enzymes have heterocycles as coenzymes for their active functioning (8). These nitrogen sites are responsible in water solubility of the organic molecules and thereby playing an active role in the bioavailability. Also, piperazine
derived compounds are extensively used in drug discovery because they permit synthetic medicinal chemist to design such molecules in which basicity is retained.

Piperazine ring with its versatile binding properties acts as a part of the molecular backbone of the ligand. It acts as a potent and selective ligand for a range of different biological targets in medicinal chemistry and accordingly it is considered as a privileged structure (14). The major role of this privileged structure, in medicinal chemistry, is to provide a way to build a library of compounds based on one piperazine structural motif and screen it against an assortment of different receptors (15) for different therapeutic areas (6) such as antibacterial (16–19), antifungal (20–21), anticancer (22–24), antihistaminic (25), antipsycholytic (26-27). Among a wide verities of currently available drugs, few examples that contain piperazine unit are shown in the table 1 (2,9–13).

### Table 1: Drugs with piperazine moiety

<table>
<thead>
<tr>
<th>Area of therapeutic</th>
<th>Drug’s Name</th>
<th>Substitution on piperazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Amoxapine,</td>
<td>Monosubstituted</td>
</tr>
<tr>
<td></td>
<td>Buspirone,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Befuraline</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td>Anticancer</td>
<td>Imatinib</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td>Antianginal</td>
<td>Ronolazine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Trimetazidine</td>
<td>Monosubstituted</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Cetrizine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Cyclizine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Meclizine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Cinnarizine</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>Perphinazine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Fluphenazine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Trifluparazine,</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine</td>
<td>Unsymmetrically disubstituted</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Ciprofloxacin</td>
<td>Monosubstituted</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Itraconazole</td>
<td>Unsymmetrically disubstituted</td>
</tr>
</tbody>
</table>
Antidepressant drugs containing piperazine moiety:

Antidepressant drugs are the medicine used to treat depression. There are many potent drugs available commercially which are used nowadays. Some example of drugs containing piperazine core are amoxapine (28), buspirone (29,30), befuraline (31). Amoxapine is a tricyclic antidepressant drug derived from the dibenzoxazepine group (32) and have similar activity to reference antidepressant drugs in acute toxicity, undesirable effects, and efficacy.

Anticancer drugs containing piperazine moiety:

Cancer is the most dangerous and most challenging disease in the current time. Ability of piperazine nitrogen and other heteroatom to bind with DNA have provoked remarkable interest in this moiety. The drugs that
possess anticancer activity is imatinib with a piperazine moiety. Imatinib (33) effectiveness has been proved in treatment of Chronic Myeloid Leukaemia (CML) and it also act as synthetic tyrosine kinase inhibitor.

**Figure 4. Structure of Imatinib**

**Antianginal drugs containing piperazine moiety:**

Ranolazine (34,35) and trimetazidine (36) are class of antianginal drugs used to treat angina, a symptom for heart attack and give immediate relief from angina attack. Ranolazine is a novel antianginal agent capable of producing anti-ischemic effects without reducing heart rate or blood pressure. Trimetazidine also act as novel antianginal by limiting intracellular acidosis and sodium and calcium accumulation.

**Figure 5. Structure of Ronolazine**

**Figure 6. Structure of Trimetazidine**
Antihistamine drugs containing piperazine moiety:

Cetrizine (37), cyclizine (38) and meclizine are class of antihistamine drugs which are used to treat allergy symptoms like sneezing, watery eyes, hives, and a runny nose by blocking effect of histamines. All the three drugs have structural similarity and possess piperazine nucleus as backbone unit.

Figure 7. Structure of Cetrizine

Figure 8. Structure of Cyclizine

Figure 9. Structure of Meclizine
Antipsychotic drugs containing piperazine moiety:

Perphenazine (39), fluphenazine, trifluperazine, prochloroparazine are antipsychotic class of drugs that are used to treat symptoms of psychosis like delusions, confused thoughts, paranoia or hallucinations. They are used in the treatment of anxiety, schizophrenia, and depression. All the drugs have structural similarity and contain piperazine unit and differ only with small substitution of Cl or CF₃ groups.

Figure 10. Structure of Perphenazine

Figure 11. Structure of Fluphenazine

Figure 12. Structure of Trifluoperazine
Antibiotic drugs containing piperazine moiety:
Antibiotics are the drugs which are used to prevent microbial infections. Ciprofloxin (40) is a fluoroquinolone derived compound containing piperazine moiety and have broad spectrum activity in therapeutics because several pathogens which are resistance to other drugs, are susceptible to ciprofloxin. Also due to high efficacy of this drug, it has been used to treat various other infections in urinary and respiratory track, skin infections and disease that are sexually transmitted.

Antifungal drugs containing piperazine moiety:
Itraconazole (41) is an antifungal drug containing triazole moiety with built in piperazine unit possess broad spectrum activity against several systemic fungal pathogens. Its hydroxyl derivative also possesses remarkable antifungal activity with high efficacy and considerable tolerability. Two new variables of itraconazole with cyclodextrin have been reported which have increased water solubility of this drug and enhanced bioavailability with affecting tolerability profile and are better than original itraconazole capsules.
Conclusion:
This mini review reveals the immense importance of piperazine as core structural unit in many of commercially available drugs. Piperazine derived molecules exhibit bioactivity and performs large varieties of therapeutic action and is effective against wide range of infectious diseases. For a synthetic chemist piperazine act as building block to construct a variety of functionalised molecule analogue to the desired pharmacophoric fragment. Ability of piperazine and its derivative with suitable donor atoms to bind with metals further have explosive growth of this medicinal field as biochemical processes in living organisms involves metals complexes.

References:


