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EXPLORING PHARMACOLOGICAL SIGNIFICANCE OF PIPERAZINE SCAFFOLD

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ABSTRACT

Piperazines and their heterocyclic analogues possess a number of interesting biological properties. Clinical trials have shown that these compounds reached reasonable plasma concentration and are well-tolerated. For this reason they are an object of continuously growing interest amongst the scientists. The purpose of this review is to provide an overview of the pharmacological properties as well as therapeutic applications of piperazine depending upon the pattern of substitution on the piperazine ring and their presence in many widely used drugs. This article highlights an interrelationship of yield and other reaction dynamics for piperazine moity.

KEYWORDS: Heterocycles, Piperazines, drugs containing piperazine ring.

INTRODUCTION

Heterocycles are inextricably woven into life processes. Synthetic chemistry provides corpucopia of heterocyclic systems Heterocyclic chemistry is one of the most valuable sources of novel compounds with diverse biological activity. To medicinal chemists, the true utility of heterocyclic structures is the ability to synthesize one library based on one core scaffold and to screen-it against a variety of different receptors, yielding several active compounds.[1-3] Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclics frameworks with the most diverse physical, chemical and biological properties.[4] More than 90% of new drugs contain heterocycles and the interface between chemistry and biology. The modern day medicinal chemistry is based on heterocyclic molecules and we owe to them, due to their close association with numerous

biological as well as pharmacological activities. Nitrogen containing heterocycles is subunit found in numerous natural products and in many biologically active pharmaceuticals.[5-6]

There are many nitrogen containing chemicals, ranging from simple structural compounds as pyridine to complicated compounds as pharmaceuticals ingredients and their number is growing rapidly year by year.[7]

Piperazine derivatives is amongst the most privileged structural motifs in the field of nitrogen heterocyclic chemistry. They occur in several natural and synthetic bioactive compounds. Rather they are widely used in medicine. Tens of thousands of compounds of this series have been synthesized and studied by now; more than 300 of them are used in medical practice as drugs.[8]

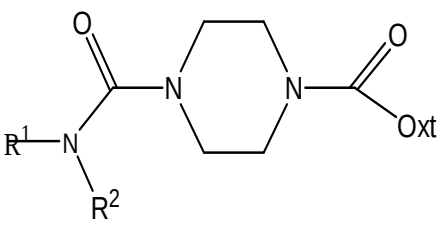
Pharmacological significance of piperazines

They include drugs with central and peripheral neurotropic effects (local anesthetics, M-cholinoblockers, agonists and antagonists of other pharmacological receptors, analgesics etc.,) agents that act on the cardiovascular system (coronary dilative, anti-arrhythmic,anti-hypertensive), spasmolytics, diuretics, broncholytics, antiemetics, antinuclear drugs and many others.[9-11]

Piperazine nucleus is one of the most important heterocycles, exhibiting remarkable pharmacological activities. The piperazine nucleus is used in various compounds as anthelminitis, perfumes and starting materials in pharmaceutical and agrochemical industries.[12-13]

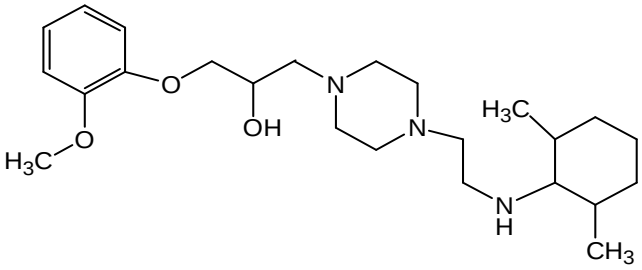
Piperazine has significant pharmaceutical properties Piperazine was first introduced as anthelminitic in 1953. A large number of piperazine compounds have anthelminitic action.[14]

Many currently notable drugs contain piperazine ring as a part of their molecular structure . N-methyl piperazine is used for the preparation of Anti HIV agents.[15]



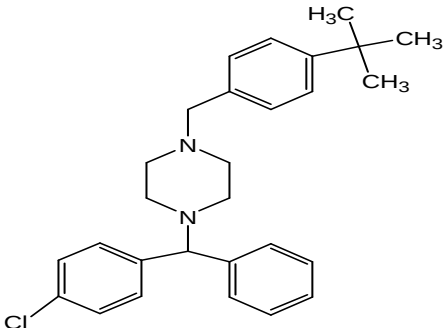
Piperazine containing active carbamates.

Antanginals a like Ranolazine and Trimetazidine have piperazine moiety.[16]



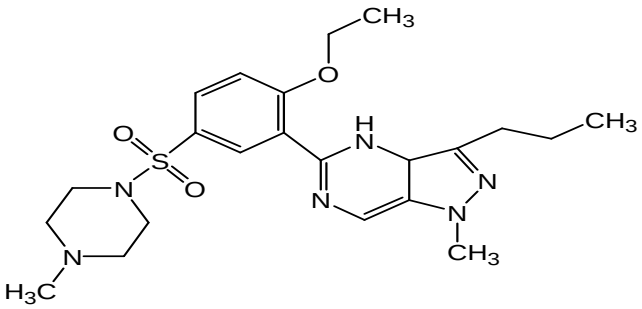
Ranolazine

Antihistamines as like Buclizine and Cetrizine have piperazine moiety.



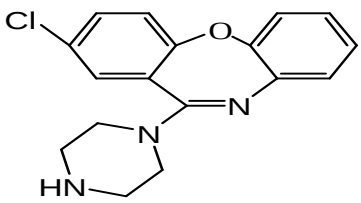
Buclizine [CAS-129-74-8]

Urological as like Sidlenafil Citrate, Levofloxacin, Olanzapine, Quatiapine are compounds containing piperazine as core moiety.



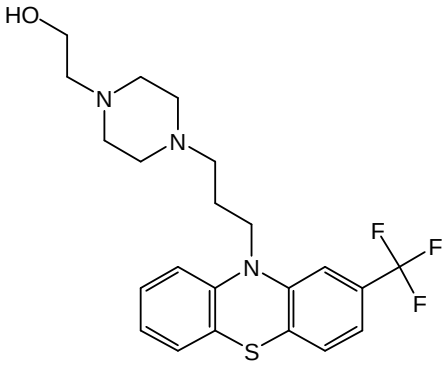
Sidlenafil Citrate [CAS-171599-83-0]

Amoxapines and Befuraline are some piperazine representing commonly used anti depressants[17-18]



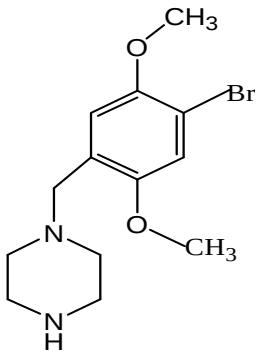
Amoxapine [CAS-14028-44-5]

Antipsychotics like Fluphenazine and Perphenazine have piperazine as core nucleus.



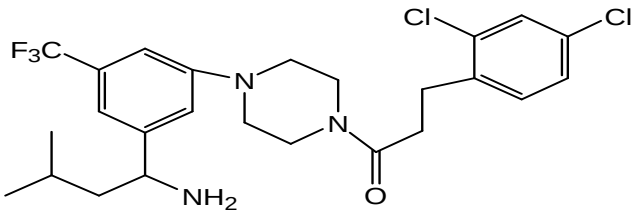
Fluphenazine [CAS-33098-48-5]

The recreational drugs like (2C-B-BZP), MDBZP and TFMPP do contain piperazine moiety.[19-20]

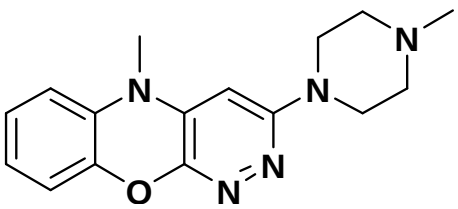


(2C-B-BZP) [CAS-1094424-37-9]

Phenyl piperazines and pyridinyl piperazines were synthesized and characterized as potent and selective antagonist of the Melanocortin-4-receptor (MCAR).These compounds were also profiled in rodent for their pharmaco-kinetic properties.[21-22]



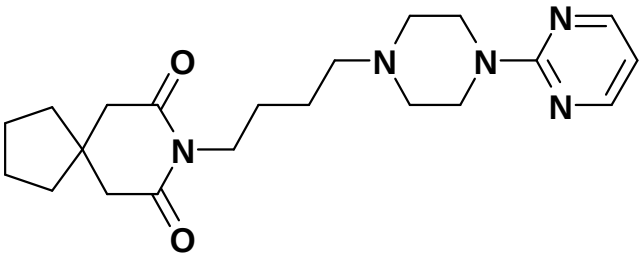
Phenyl Piperazines [CAS-4004-95-9]



Pipofezine

(5-methyl-3-4-methylPiperazine-1-yl) pyridazino [3, 4-b][1,4] benzoxazine)

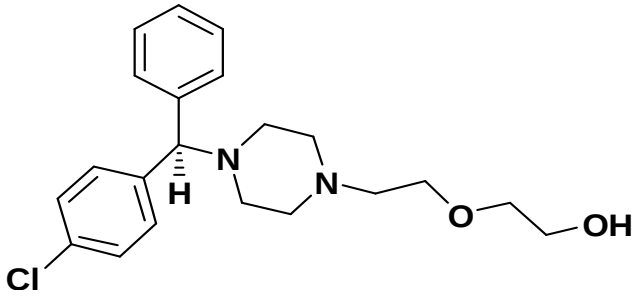
Pipofezine (Azafen or Azaphen) is atricyclic antidepressant (TCA) approved in Russia for treatment of depression. It was introduced in the late 1960s and is still used today.[23-25]



Buspirone

(8-[4-(4-pyrimidin-2-yl Piperazine-1-yl)butyl]-8-azaspiro [4.5] decane-7,9- dione)

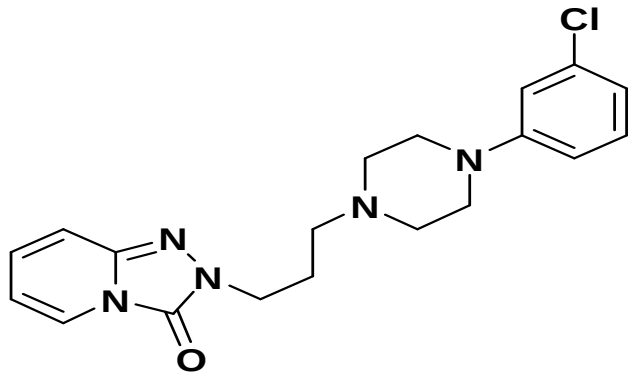
Busiprone containing piperazine moiety is used as Anxiolytics(A drug used to relieve Anxiety).[26]



Hydroxyzine

(8-[4-(4-pyrimidin-2-yl Piperazine-1-yl)butyl]-8-azaspiro [4.5] decane-7,9- dione)

Hydrooxyzine is commonly used as Anxiolytics,Antihistamines and Antiallergics.[27-28]

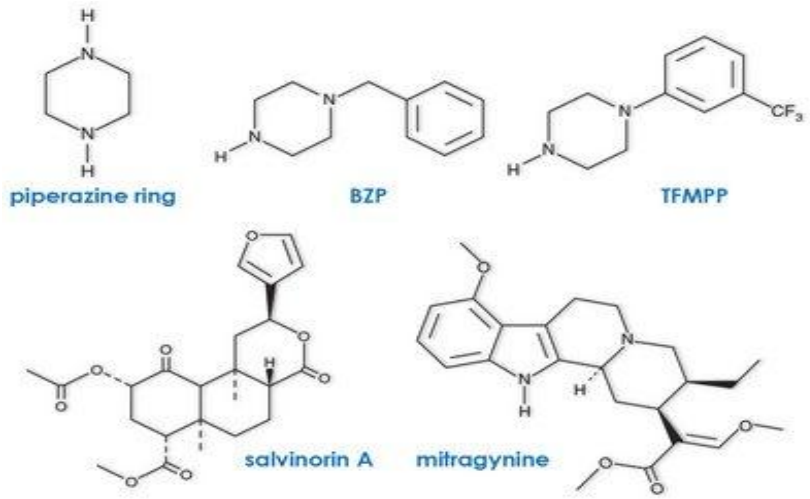


Trazodone HCl

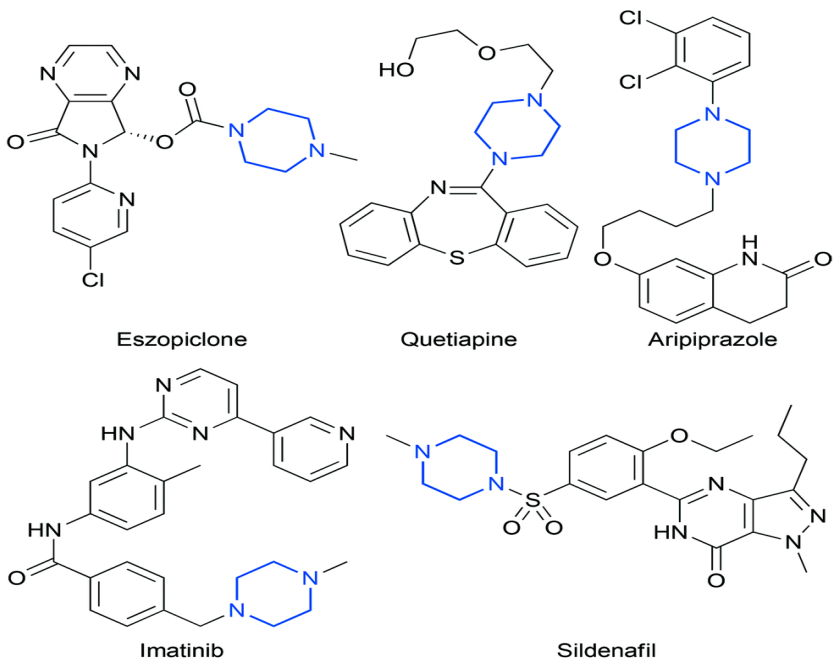
2-(3-[4-(3-chlorophenyl)Piperazine-1-yl]propyl)-[1, 2, 4] triazolo [4, 3-*a*] pyridin-3(2*H*)-one

Trazodone HCl is also as piperazine moiety containing drug used as Anxiolytics as well as Anti deepressents.[29]

Many Medicinal Chemists have showed significant results of use of Piperazine moiety for treatment of psychological and neurological disorders.[30]



Apart from these, the pharmacological activities like anticonvulsant, antiarrlythmic, antimicrobial, antioxidant, antimalarial and cytotoxic activites are reported by compounds having piperazine molecules.[31] The potential of these compounds to penetrate into the blood brain barrier was computed through an online software program and the values obtained for the compounds suggested good brain permeation.[32-33]



Here, only a few of the many examples have been mentioned in which the piperazine core has been used as a scaffold to generate biologically active molecules. Thus, it appears that the piperazine core acts as a privileged structural element for the construction of bioactive molecules

MATERIALS AND METHODS

The literature survey revealed that the remarkable array of piperazines as biochemical and pharmacological actions, suggest that certain members of this group of compounds may significantly affect the function of various mammalian cellular systems. The piperazines are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity.

Hence there is a outmost need to investigate and design new compounds of biological interest. As per the review about the recent trends in the chemistry of piperazine derivatives, their demand in pharmaceuticals is increasing and much still lies scope for the exploration of pharamaco-kinetics of these compounds.

All these facts were driving force to study the synthesis of the 4(-4methyl piperazine-l-yl) benzaldehyde.

The present work is concerned solely with the chemistry i.e. the yield of the above mentioned products, for which the dynamics of the environment (solvent base temperature and reaction conditions) can be responsible.

EXPERIMENTAL

Study of Reaction dynamics

Piperazine moiety is of considerable current interest because of their potentially beneficial pharmacological properties. Owing to their importance, it was planned to conduct a thorough study of the following parameters on the yield of 4-(4-Methyl-piperazine-l-yl) benzaldehyde.

a) Effect of different bases

The Piperazine benzaldehyde was subjected to different bases. The analysis is reported as follows.

Sr.No.	Name of Base Used	% Yield obtained
1)	K_2CO_3	92%
2)	$CsCO_3$	88%

3)	Na_2CO_3	87%
4)	$KHCO_3$	85%
5)	$NaHCO_3$	80%

b) Effect of different solvents

Sr.No.	Name of Solvent Used	% Yield obtained
1)	DMF	95%
2)	DMSO	90%
3)	Toulene	70%
4)	Xylene	75%
5)	Methanol	No reaction
6)	Acetone	No reaction

c) Effect of different Temperature

Sr.No.	Different Temperature Range	% Yield obtained
1)	80-90^{0}C	86%
2)	110-120^{0}C	60%
3)	150-160^{0}C	Decomposed*

*- no of spots formed on TLC.

d) Effect of different Reaction Conditions

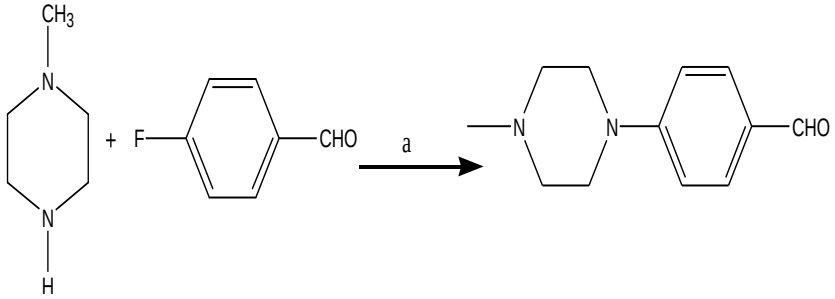
Sr.No.	Different Reaction Conditions	% Yield obtained
1)	Conventional Heating	85%
2)	Microwave	92%
3)	Ultra Sonic bath	89%

RESULTS AND DISCUSSION

Considering the results of all the above experiments, it is evident that the 4-(4-methyl piperazine-1-yl) benzaldehyde was obtained in maximum yield by the use of K_2CO_3 base, DMF solvent and by Microwave irradiation.

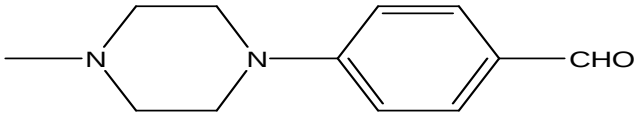
Synthesis of 4-(4-methyl piperazine-l-yl) benzaldehyde

In 4.0 ml of DMF, 1-methyl piperazine (0.1 gm. 0.001mol) was dissolved. To this solution K_2CO_3 (0.20gm, 0.00015 mol) was added and kept in microwave for 1-3 mins at 30 seconds interval. with stirring. after 3 min 4-flurobenzaldehyde (0.124 gm, 0.001mol) was added and kept in microwave for 2-5 mins at 30 seconds interval. On completion of reaction, the reaction mixture was cooled and added drop wise to ice-water. The separated product was filtered and dried. The product obtained was pure and used further without any purification.(M.P. 60-62^{0}C)



Reagents (a)- K_2CO_3, DMF, MW.

Spectral Analysis



IR

IR spectra was recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

(cm^{-1}): 1686 (C=O); 1561 (C=C).

^{1}HNMR

^{1}HNMR spectra was recorded in DMSO-d6 on a Brucker Advance II- 400 MHz Spectrometer using TMS as an internal standard.

(DMSO) ∂ppm

2.0 (s,3H,CH_3); 2.3 (t,4h,CH_2); 3.3 (t,4H CH_2); 7.2 (dd, 2H, aromatic) 8.1 (dd, 2H, aromatic); 9.9 (s, 1H, CHO)

Mass

Mass spectra was recorded on VG7070H mass spectrometer.

Mass (m/z): 204

CONCLUSION

Based on the literature it may be concluded that Piprazine containing drugs are important and it throws attention to set the Reaction dynamics to carry out the work for developing its various analogous used in Neurological & Psychological disorders which can ultimately beneficial for humans beings.

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