Exploring Pharmacological Significance and Reaction Dynamics of PiperazineMoiety.

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Abstract:

Piperazines and their analogs are amongst the most important backbones in today's drug discovery industries. The purpose of this paper is to provide an overview of the pharmacological properties of piperazines and Reaction dynamics. The synthesis of of 4-(4-methyl piperazine-l-yl) benzaldehyde a variety of Nitrogen containing aldehyde is described with proper choice of base, solvent and temperature conditions. This work is underway to ameliorate difficulties which remain, especially in finding suitable reaction dynamics that efficiently increases the yield. . The synthesized compounds were characterized by IR, [1]HNMR and MS Spectroscopy.

Keywords: Piperazines Nitrogen-containing-aldehyde, Reaction dynamics, N-arylation .

Introduction:

Synthetic chemistry provides corpucopia of heterocyclic systems. 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 [1].

An important aspect of medicinal chemistry is to establish as relationship between chemical structure and pharmacological activity. Piperazine is a sex membered ring structure containing twoopposing nitrogen atoms. Nitrogen containing compounds is used as structural components of pharmaceuticals and agrochemicals due to their high biological activities. 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 [2].

Owing to the high number of positive hits encountered in biological screens with this heterocycle and its congeners, the piperazine template certainly deserves the title of "privileged scaffold" in medicinal chemistry. (Privileged scaffolds are molecular backbones with versatile binding properties representing a frequently-occurring binding motif, and providing potent and selective ligands for a range of different biological targets). Moreover, the piperazine scaffold occurs regularly in complex natural products. Thus, it is no wonder that there is a plethora of different synthetic methods that allow for the fast and efficient assembly of these heterocyclic.

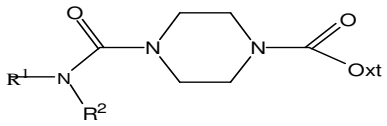
Pharmacological significance of piperazines.

Piperazine nucleus is one of the most important heterocycles, exhibiting remarkable pharmacological activities anthelminitis[4], anti- HIV agent, antanginals[5], urological[6]and anticonvulsant compounds[7].

. The piperazine nucleus is used in various compounds as anthelminitis, perfumes and starting materials in pharmaceutical and agrochemical industries.

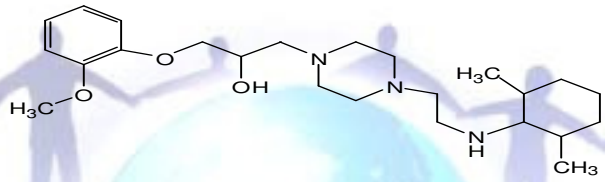
Piperazine has significant pharmaceutical propertiesPiperazine was first introduced as anthelminitic in 1953. A large number of piperazine compounds have anthelminitic action [8].

Many currently notable drugs contain piperazine ring as a part of their molecular structure [9]. N-methyl piperazine is used for the preparation of Anti HIV agents [10].



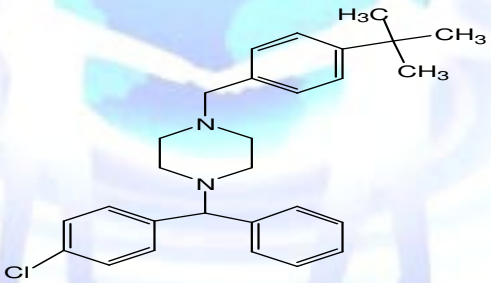
Piperazine containing active carbamates.

Antanginals a like Ranolazineand Trimetazidine have piperazine moiety[11].



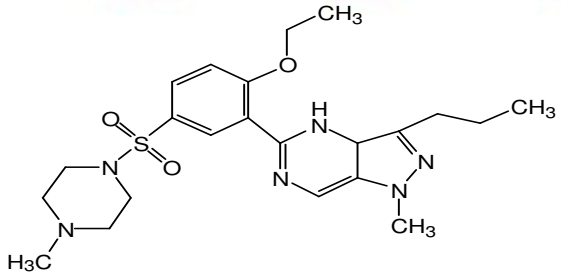
Ranolazine

Antihistamines as like Buclizine and Cetrizine have piperazine moiety.



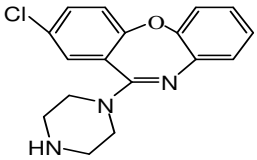
Buclizine [CAS-129-74-8]

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



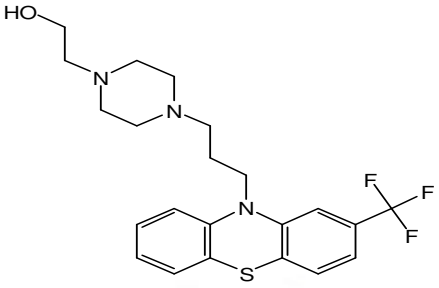
Sidlenafil Citrate [CAS-171599-83-0]

Amoxapines and Befuraline are some piperazine representing commonly used anti depressants.



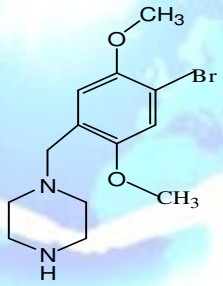
Amoxapine [CAS-14028-44-5]

Antipsychotics like Fluphenazine and Perphenazine have piperazine as core nucleus.



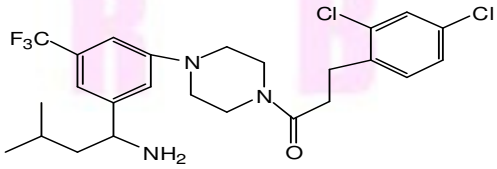
Fluphenazine [CAS-33098-48-5]

The recreational drugs like (2C-B-BZP), MDBZP and TFMPP do contain piperazine moiety [12].



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

Phenylpiperazines and pyridinylpiperazines 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 [13].



Phenyl Piperazines [CAS-4004-95-9]

Apart from these, the pharmacological activities like anticonvulsant, antiarrlythmic, antimicrobial, antioxidant, antimalarial and cytotoxic activites are reported by compounds having piperazine molecules [14].

Present Work:

As the emergence of new diseases is prevailing, there is outmost needed 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 and temperature) can be responsible.

Synthesis of 4-(4-methyl-piperazine-1-yl) benzadehyde.

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.

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

Table.1- Effect of different bases

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%

Table.2- 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

Table.3-Effect of different Temperatures

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*

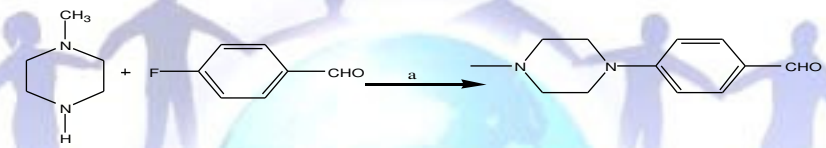
*- no of spots formed on TLC.

Material and methods:

All the melting points were carried out in open capillary tubes and are uncorrected. The Thin Layer Chromatography was performed on precoated silica plates and Iodine vapor is used for visualization.IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer. 1HNMR spectra were recorded in DMSO-d6 on a Brucker Advance II- 400 MHz Spectrometer using TMS as an internal standard. Mass spectra were recorded on VG7070H mass spectrometer.

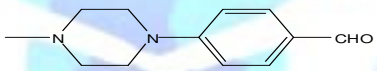
Synthesis of 4-(4-methyl piperazine-l-yl) benzaldehyde.

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 heated at 80^{0}C. with stirring. After 30 min 4-flurobenzaldehyde (0.124 gm, 0.001mol) was added and heating was continued for 6 hours. 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, 80^{0}C.

Spectral Analysis :



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

^{1}HNMR: (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 (m/z): 204

Conclusion:

Our studies showed that K2CO3 was the most effective base, while the use of other bases such as CsCO3and Na2CO3 was less successful. DMF was found to be the optimal solvent, although the use of DMSO was also effective.

In conclusion,

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