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PIPERAZINE: A PROMISING SCAFFOLD WITH ANTIMICROBIAL ACTIVITY

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ABSTRACT

Piperazine's all-encompassing and intoxicating function has been recorded as one of the biologically essential platforms. Piperazine was discovered to have the greatest effectiveness against bacterial infections. This review focuses on the most up-to-date information on the most effective active piperazine analogues which have been discovered to have significant biological effects, such as antibacterial and antifungal capabilities etc. As a result of these findings, statistics for future molecular changes most important to molecules with superior positive pharmacological characteristics may be derived. This review demonstrates recent trends in piperazine and demonstrates their biological activities.

Keywords-: Piperazine, Antimicrobial, Biological activity, Heterocycles, phytochemical, GABA

INTRODUCTION

Heterocyclic chemistry is the field of chemistry that deals only with the synthesis, characteristics, and applications of heterocyclic molecules, which are particularly important in medication design. When oxygen, nitrogen, sulfur, or an atom

of a related element is substituted for a carbon atom in an organic structure, a heterocyclic compound is formed. Heterocyclic compounds can be natural or manufactured, and because of their unique biological features, they are frequently used as important components in biological functions. Quinine, emetine, papaverine, procaine, codeine, and morphine are just a few of the nitrogen-containing heterocycles that have left an indelible mark as phytochemical remedies. Diazepam, isoniazid, chlorpromazine, barbituric acid, captopril, chloroquine, and antipyrine are all synthetic drugs that contain nitrogen heterocycles as a key structural unit.

Heterocyclic compounds are of very much interested in our daily life. Heterocyclic chemistry receives a significant amount of chemical research in this area.

1.1 Piperazine

Piperazine was used to treat gout at the beginning of the century in the early 1900s. Its first efficacy in the treatment of helminthiasis led to widespread usage as an anthelmintic in humans and animals, and for more than 50 years, the drug has been used to treat Ascaris lumbricoides and Enterobius vermicularis infections, and several of its ingredients used for the treating cancer and angina pectoris.

Piperazine is a six-membered organic saturated cyclic amine with two opposing nitrogen atoms. Piperazine was first employed as a uric acid solvent, and its function as an anthelmintic agent was discovered in 1953. Its compounds have antihistaminic, anticancer, anticonvulsant, antiepileptic, and antibacterial properties. Piperazine has an amazing ability to liquefy uric acid and produce soluble urates outside the body, but it has not been as effective in clinical trials. Piperazine is found in the form of tiny basic deliquescent crystals having a saline taste. Piperazine's IUPAC name is 1, 4-diaza cyclohexane. Piperazine refers to a category of chemical compounds that include an essential piperazine functional group and have key pharmacological properties. A piperazine moiety is commonly utilized in pharmaceutical and pesticide chemistry. Piperazine has the ability to effectively alter the physicochemical properties of pharmaceuticals while also increasing their pharmacokinetic qualities and biological activity. Piperazine byproducts function as histamine and serotonin receptor antagonists in the inflammatory regulation.

1.2 Chemistry of piperazine-: The piperazine moiety has two nitrogen atoms, with each nitrogen atom attaching two

carbon atoms and one hydrogen atom. This moiety's nitrogen atom has one lone pair/non-bonding pair/unshared pair of electrons. Piperazine is chemically related to piperidine, a piperazine ingredient found in the black piper plant family piperaceae. Piperazine is also known as 1, 4-hexahydropyrazine by the IUPAC. Cyclizines and ethylenediamine are piperazine's synonyms. Piperazine heterocyclic molecule has four carbons and two nitrogens in the 1 and 4 positions of the ring structure.

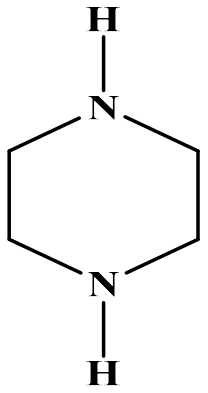

Figure 1

1.3 Description

Piperazine acts as a gamma-aminobutyric acid (GABA) receptor agonist in parasites, potentially with antihelminthic action.

Piperazine binds to GABA inhibitor receptors in sensitive worms, activating chloride channels and causing hyperpolarization.

This paralyses the worm's musculature, allowing regular peristalsis to remove the worm from the intestinal lumen, causing the worm to be evacuated from the body.

2. Synthetic approaches of piperazine containing derivative

Because of the biological importance of piperazine derivatives, broad approaches for the synthesis of the piperazine nucleus have been studied extensively, with increasing promise for utilization in biological systems. The manufacture of the compound and its analogues by numerous methods, the bulk of which rely on cyclization activities, is one example of substituted piperazine synthesis. For example, piperazine rings have been produced by heating N1-(2-aminoethyl) ethane-1,2-diamine with Raney nickel at an intense heat of roughly 150°C, with ammonia liberation **[1]**.

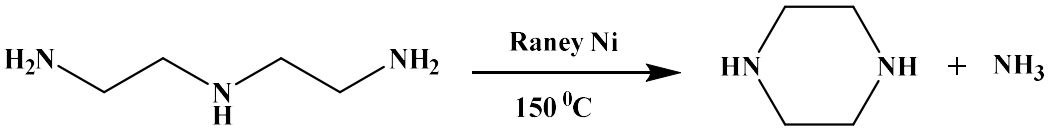

Figure 1

2.2 From diethanolamine

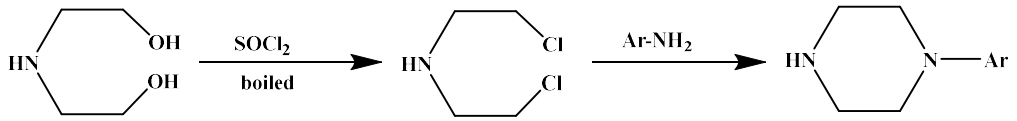

Figure 2

2.3 From ethylenediamine

The reaction of 2-phenyl-oxirane with ethylenediamine in the presence of methanol under reflux yielded 2-(2-aminoethylamino)-1-phenyl-ethanol, which was then reduced with Raney nickel **[2]**.

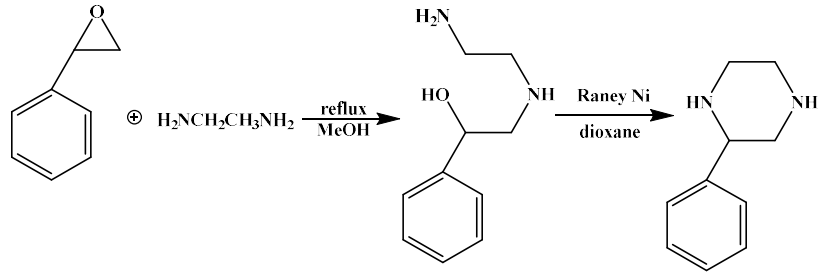

Figure 3

A substituted piperazine derivative easily synthesised, as indicated in **Figure 4**. In base media, the N, N-dibenzylethylendiamine was doubly alkylated with 3, 4-dibromobutyronitrile to yield (1, 4-dibenzyl-piperazin-2yl)-acetonitrile **[3]**.

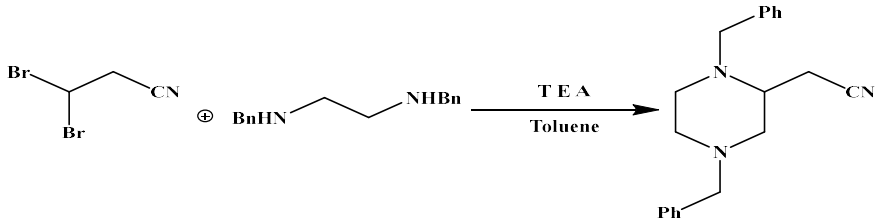

Figure 4

A piperazine derivative synthesize which is sustainable and cost-effective method for synthesizing piperazine in aqueous environments by cyclo condensation of 1-phenyl-ethane-1, 2-diol and ethylenediamine in the presence of [CpIrCl2]$_2$ **[4]**.

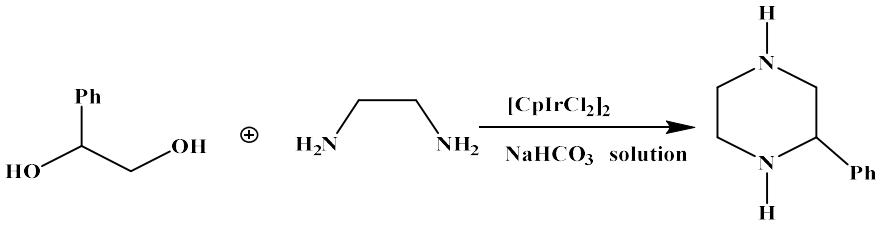

Figure 5

3. Biological activities: A chain of azole-containing piperazine analogues was synthesized and evaluated for antibacterial, antifungal activity *in vitro*. The initial findings suggested that the majority of compounds have mild to considerable antibacterial and antifungal activity *in vitro*. Compounds (6&7) shown considerable and wide-spectrum antibacterial property against all test organism, with MIC values in the range from 3.1 to 25µg/ml, and demonstrated activity almost similar to the conventional medicine's chloramphenicol and fluconazole in the clinic. Furthermore, compound (7) was found to become the most potent against the PC-3 treated cells in vitro **[5]**.

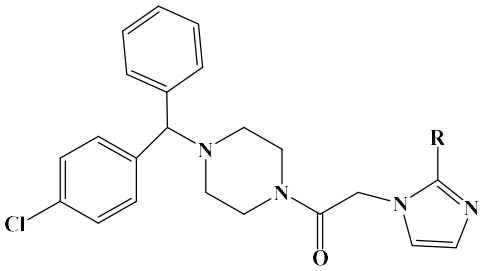

Figure 6

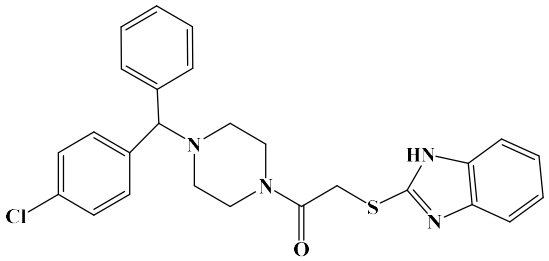

Figure 7

Yu *et al* developed 1-ethyl-6-fluoro-7-[4-(furan-2-carbonyl)-piperazin-1-yl] The antibacterial activity of norfloxacin and its derivatives against 5 plant pathogens and 3 fungi were tested in vitro. Substances exhibited superior antibacterial activity against *Xanthomonas oryzae* than norfloxacin, and many of the chemicals tested antibacterial activity versus X. oryzae than agricultural streptomycin sulphate. Erwiniaaroideae and *Xanthomonas axonopodis* among the compounds in the series, compound (8) shown best antifungal activity against *Rhizoctonia solani*, inhibiting fungal growth by 83 percent **[6]**.

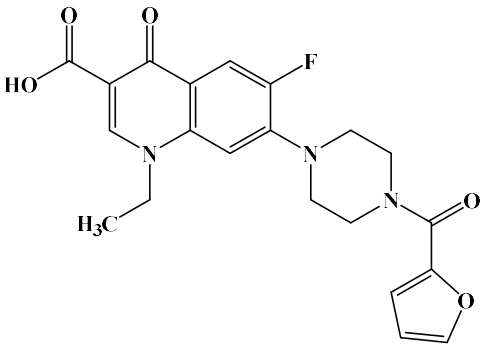

Figure 8

Group of scientists in 2007 developed 31 isomeric naphthalene sulphonyl derivatives, including 1- and 2- [4-(4-chloro phenyl) phenyl methyl-1piperazinyl] sulphonyl naphthalene's, using p-chloro benzophenone and naphthalene as the major starting reagent and a piperazine bond. The antibacterial properties of these compounds have also been investigated **[7]**.

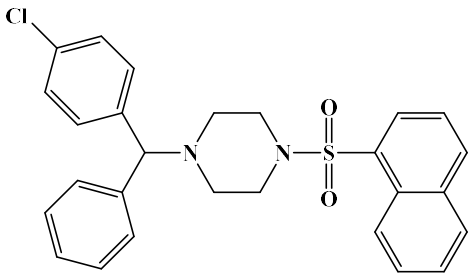

Figure 9

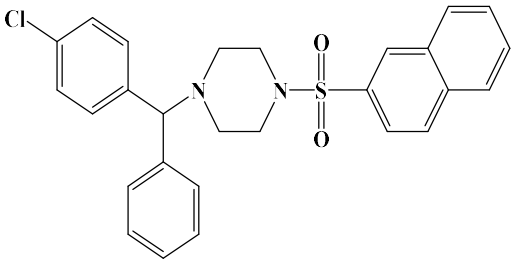

Figure 10

A piperazine derivative has been synthesized (11) as potent anti-hookworm medication **[8]**. *N*-(2- substituted ethyl)-*N*'-aryl piperazine

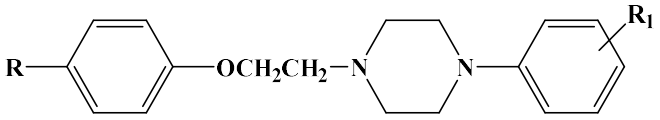

Figure 11

A compound developed with piperazine nucleus that is 1-(4-methoxycinnamoyl)-4[5-(4-chloro/bromo) phenyl-4-oxo-2oxazine-2-yl] -piperazine demonstrated significant antiplasmodium berghei and antimalarial activity **[9]**.

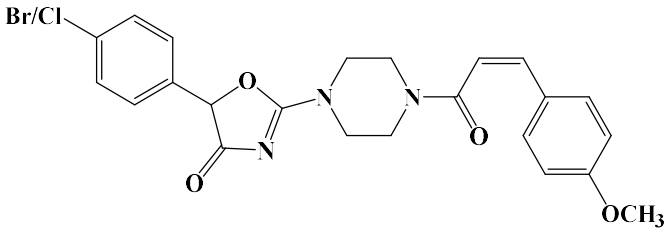

Figure 12

S. Paris *et al* synthesized and verified pyrrole [3, 2, 1-I, j] quinoline as a suitable asthma treatment **[10]**.

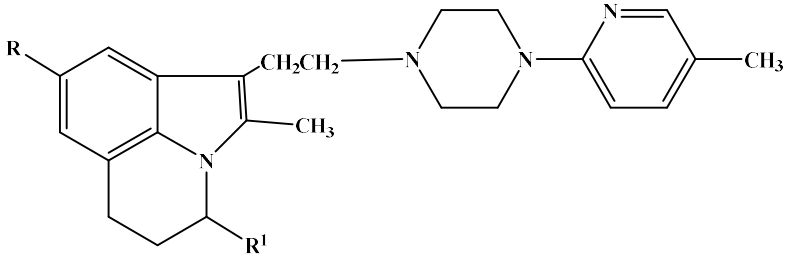

Figure 13

G.Hanauer *et al* have been synthesized [(piperazine) alkylthio] pyridine suggested for control of *helicobacter pylori* bacterial infection **[11]**.

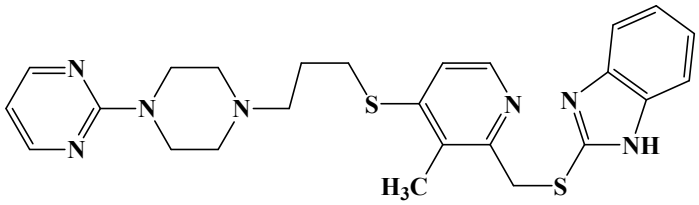

Figure 14

Derivative of piperazine has been synthesized moderate to considerable activity from dimeric compounds of dithioacetals with piperazine. When compared to gram positive bacteria, these compounds demonstrated significantly higher efficacy against gram negative **[12]**.

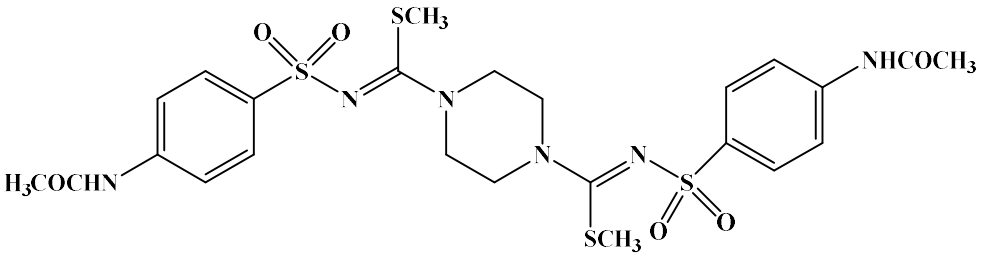

Figure 15

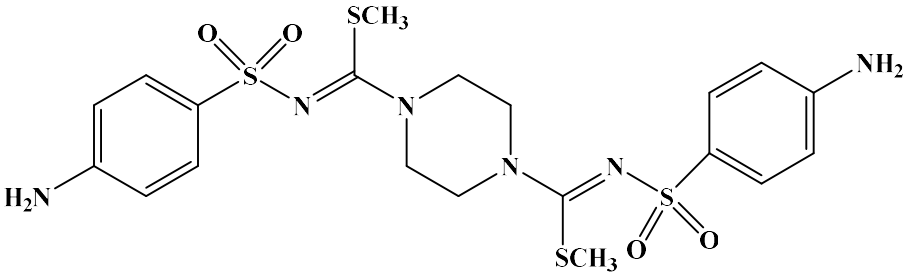

Figure 16

S. J. Brickner *et al* synthesized a potent synthetic oxazolidione. This is now under clinical trials for gram-positive bacterial infections induced by staphylococci, and enterococci strains. *In vitro*, these chemicals have significant anti-mycobacterium tuberculosis action **[13]**.

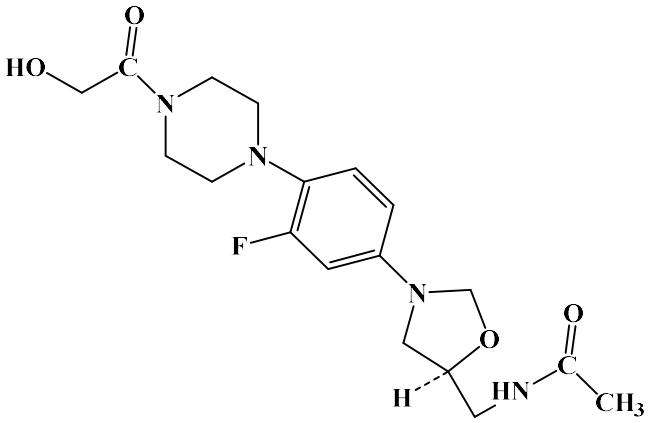

Figure 17

Substituted piperazinyl-phenyl-oxazolidione derivatives used as antimicrobial agent against *S. aureus* **[14]**.

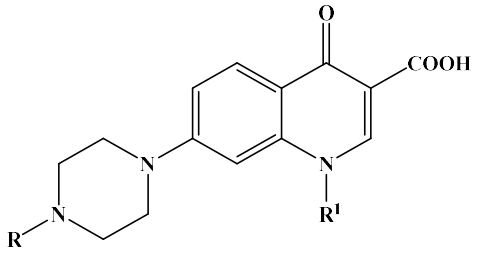

Figure 18

G. L. Talessara *et al* have been synthesized N^1-(2- substituted-4-nitrophenyl)-piperazines which shows antifungal agent property **[15, 16]**.

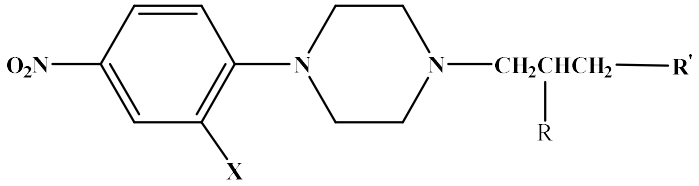

Figure 19

N-(2-chlorophenyl)-2-((6-(4-(2-hydroxyethyl) piperazin-1-yl)-2-methylpyrimidin-4-yl) amino)-4,5-dihydrothiazole-5-carboxamide has been prepared. It has a strong anticancer activity **[17]**.

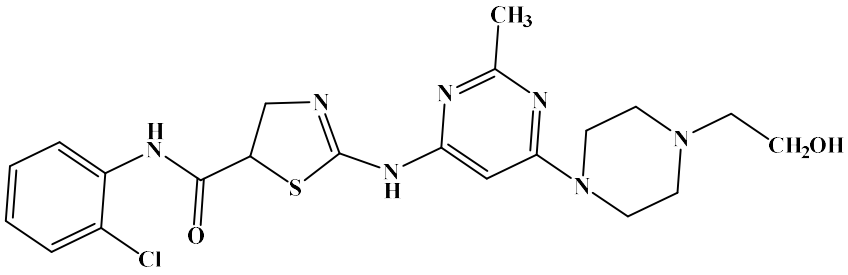

Figure 20

Antimicrobial property toward gram-negative bacteria was discovered in a set of ciprofloxacin mimics having a 3-carboxamate molecule.

To enhance the relative antimicrobial properties against some pathogens typically occurring in the hospital environment, researchers modified the piperazinyl moiety at ciprofloxacin's 7-position with an extra carbopiperazinyl group and developed different N-benzoyl and N-benzene sulfonyl substituents to the carbopiperazinyl moiety in this study **[18]**.

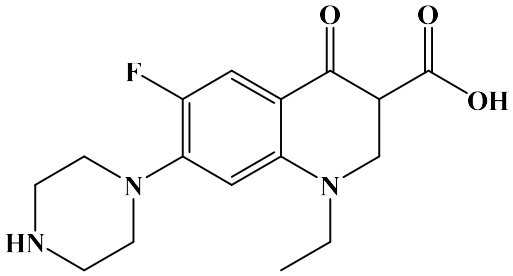

Figure 21

Kerru, N *et al*. synthesized novel chains of substituted phenyl acetamide piperazine compounds has been synthesized. All of the produced compounds were investigated for antibacterial properties against Gram-positive bacteria (*Streptococcus pyrogenes*) and Gram-negative bacteria (*Escherichia coli*). Ciprofloxacin was meant to be used as a standard medicine in the antibacterial movement. The antifungal campaign was aimed at *Candida albicans* and *Aspergillus niger*. When combined with the conventional medicine Griseofulvin, one molecule had good antifungal activity against *Aspergillus niger* **[19]**.

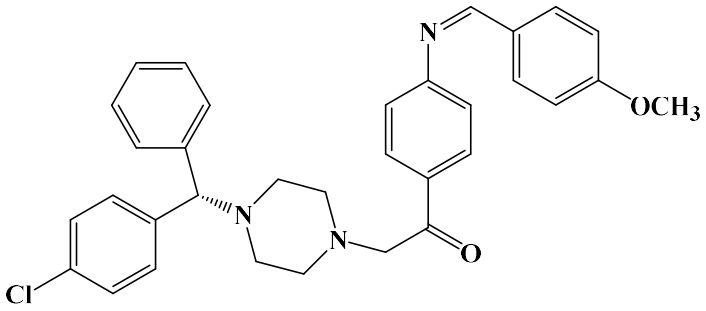

Figure 22

Chaudhary *et al* created a chain of exchanged piperazine compounds and evaluated them for antimicrobial mobility. Antibacterial activity was investigated against *Staphylococcus aureus*, and *Escherichia coli*, as well as antifungal activity against Aspergillus fumigates When compared to Gentamycin, the reference antibiotic, all produced compounds demonstrated significant action over strains of bacteria but were shown to be less effective against tested fungi **[20]**.

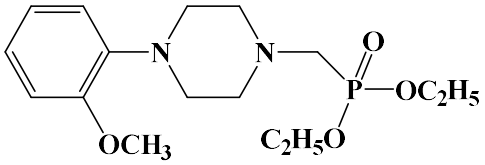

Figure 23

Using Ciprofloxacin and Griseofulvin as reference medicines, some piperazine derivative created an innovative chain of [1,3,5] triazinyl piperazine analogues and calculated their in-vitro antibacterial effect against Gram-positive (B. subtilis), Gram-negative (*P. aeruginosa*), and two fungal species (*C. albicans* and *A. niger*). The majority of the synthesised compounds shown potential antibacterial activity **[21]**.

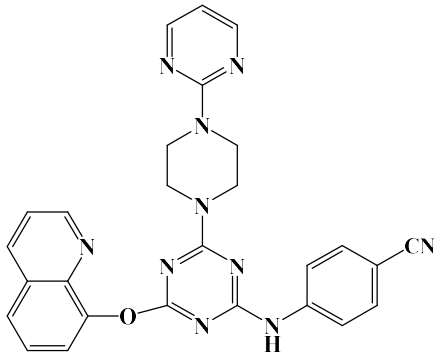

Figure 24

Forge *et al* used a quick colorimetric *in-vitro* assay to screen a tiny library of different chains of 1, 4-diarylpiperazines and correspondents against a laboratory Mycobacterium tuberculosis strain. The most confident chemicals were designed to treat a multi-drug resistant clinical isolate. The amides were examined for their capacity to eliminate cytoplasmic Mycobacterium tuberculosis in mice macrophages after the standard medication isoniazid had been exhausted. Finally, a relationship was discovered between the compounds' structural alterations and their anti-mycobacterial efficacy **[22]**.

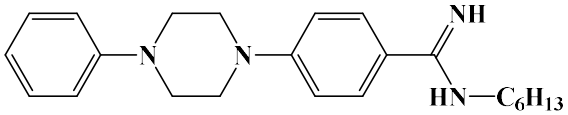

Figure 25

The Staudinger reaction was used to synthesize a number of new iminophosphorane analogues of piperazine with high yields (70-80 percent). IR, ^{1}H, ^{13}C,

^{31}P-NMR, mass spectrum investigations, and fundamental examinations were used to validate the molecular structures of the produced compounds. Using Streptomycin as a reference medication, all of the noble compounds demonstrated promising antimicrobial activity **[23]**.

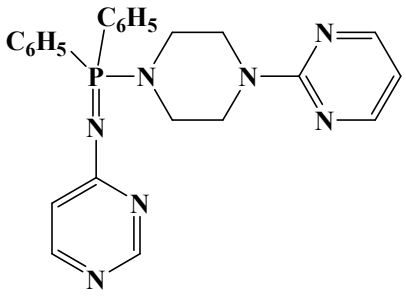

Figure 26

Some 4-substituted-1-(4-substituted phenyl)-piperazine byproducts were synthesized. The antibacterial motion of the produced complexes was investigated using Ampicillin as a reference medication against 4 strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *E. coli*. When compared to a typical medication, one molecule demonstrated exceptional antibacterial activity **[24]**.

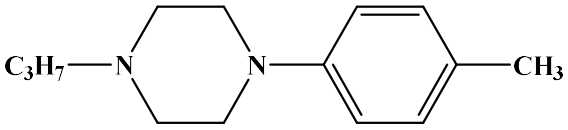

Figure 27

CONCLUSION

Piperazine is a promising scaffold with antimicrobial activity. Piperazine is the basic moiety of various drugs having various actions. It is also show best action against the diseases caused by the microbes and here in this review extract the derivatives of piperazine from various sources (research and review articles) which work as antimicrobial agent. Aim of the article is to summarize the numerous types of antimicrobial piperazine derivatives and some other biological activities.

Acknowledgment

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