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PYRAZINE AND ITS DERIVATIVES- SYNTHESIS AND ACTIVITY-A REVIEW

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ABSTRACT

Pyrazine derivatives are well-known and an important two-nitrogen-containing six-membered ring aromatic heterocyclic compounds. The substituents can be attached to one or more of the carbon atoms present in the ring. Pyrazines are a class of compounds that occur in nature. Pyrazine is a kind of natural product which can be found in plants, animals, insects, marine organisms and microorganisms. The main function of pyrazine in living organisms is used as flavor of the raw foods. Pyrazine and its derivatives were also produced in industries mainly for fragrance, flavor and pharmaceutical applications. A few methods of synthesis of pyrazines are shown in this review. The pyrazines derivatives have numerous prominent pharmacological effects, such as antibacterial, antifungal, antimycobacterial, anti-inflammatory, analgesic, anticancer for different types, antidiabetic, treatment for arteriosclerosis, antiviral.

Keywords: Pyrazine, anticancer, antitubercular agents, antibacterial and antifungal

INTRODUCTION

Diazine **[1]** is described as a compound with a monocyclic aromatic ring that contains two nitrogen atoms with a molecular formula of $C_4H_4N_2$. The three isomers of diazine are pyridazine, pyrimidine, and pyrazine **(Figure 1)**. Pyrazine, or more commonly known as

1,4- diazine, refers to the 6 membered heterocyclic compounds with two nitrogen atoms in the *para* position. Pyrazine exhibits inductive resonance properties **(Figure 2)** and demonstrates the weakest basicity among diazine compounds, even weaker than pyridine. This is due to the electron-withdrawing effect of nitrogen atoms that are positioned at the *para* position.

Figure 1. Isomers of diazine.

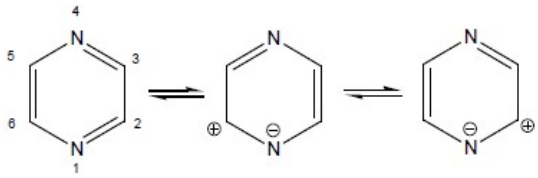


Figure 2. Inductive effects of pyrazine.

Pyrazine derivatives are well-known and important two-nitrogen-containing six-membered ring aromatic heterocyclic compounds and can carry substituents at one or more of the four-ring carbon atoms. Pyrazines are a class of compounds that occur in nature and various methods have been worked out for their synthesis. A large number of pyrazine derivatives have been found to possess diverse pharmacological properties, which has caused an increasing interest by researchers in this core.

PROPERTIES OF PYRAZINE

Various derivatives of pyrazine were produced and it was in until 1882, Wleügel was the first to propose that pyrazine composed of six-membered ring analogous to pyridine. In 1887, Mason and Wolff separately suggested that the word "pyrazine" can be utilized for the compound mentioned **[2]**. The author clarified that a six-membered ring compound, which is made up of four carbon and two nitrogen atoms, was classified as diazine. The diazines are further categorized into *o*-diazine, *m*-diazine as well as *p*-diazine respectively.

Meanwhile, the chemistry community denoted a possible bond structure of pyrazine, either it was Kekulé type or Dewar type arrangement. Kekulé type refers to the

conjugated double bond within the pyrazine molecule while Dewar type refers to the long para bond that bound the two nitrogen atoms.

SYNTHESIS

Synthetic pyrazine derivatives are actively utilized not only in the fragrance and flavor industry but also in the pharmaceutical industry **[3]**.

Formation of pyrazine through condensation

In the year 1949, Jones discovered the pyrazine derivatives synthesis pathway that involved condensation of α-amino acid amides and 1,2- dicarbonyl compounds. Jones concluded that the reaction pathway was more direct, convenient and higher yield can be easily isolated. The author performed the reaction in methanol in the presence of sodium hydroxide. Generally, the condensation of unsymmetrical dicarbonyl and α-amino acid amides are expected to give at least two isomers. The author successfully isolated single compound from the reaction of α-amino acid with methylglyoxal or phenylglyoxal to give pyrazine in the following **Scheme 1** below **[4]**.

Classical preparation of pyrazine

Pyrazine can be conveniently prepared from oxidation of dihydropyrazine, which was the condensation product of 1,2-dicarbonyl with 1,2-diaminoethane in **Scheme 2**. Copper (II) oxide and manganese oxide are commonly used as oxidizing agents for dihydropyrazine. Eicher *et al*. suggested that symmetrical starting compounds gave the best results. The authors reported that the reaction of diketone and diaminomaleonitrile to give pyrazine **[5, 6]**.

Besides that, pyrazine can be produced from the self-condensation of two moles of α- aminocarbonyl to give 3,6-dihydropyrazine, followed by oxidation under mild condition.

A pyrazine and its derivatives were also produced in industries mainly for fragrance, flavor, and pharmaceutical applications In general, synthetic approaches namely condensation reaction, ring closure, metal catalysis, green reaction, the acid catalyst on their reactions **[7]**.

A series of pyrazine carboxamide derivatives was synthesized by the condensation of the pyrazine-2-carboxylic acid chloride with various substituted amino pyridines. The structures of these derivatives were elucidated based on IR, 1H-NMR, and mass spectral data. These compounds were further evaluated for their antimycobacterial activity and antifungal activity **[8]**.

Pyrazinamidrazones were obtained by direct addition of respective hydrazines to pyrazinenitriles or by the reaction of

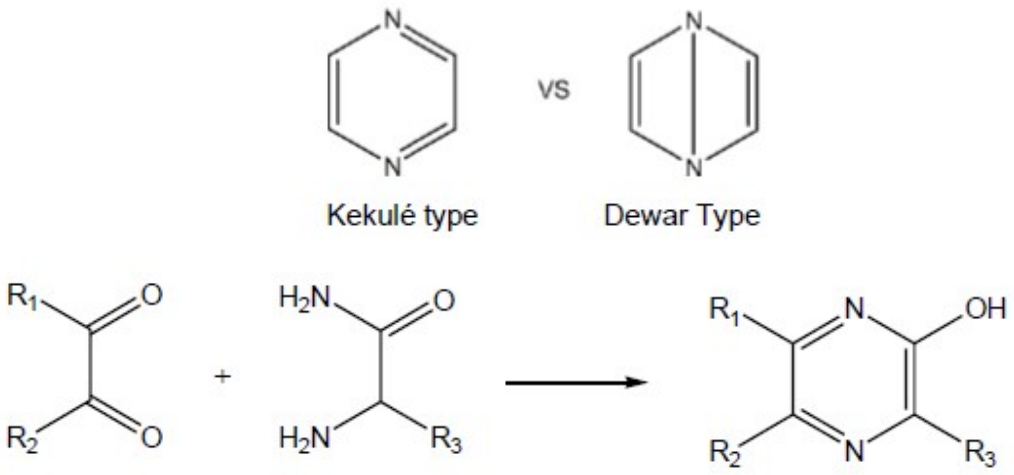
pyrazinenitriles with appropriate pyrazin-iminoesters according to the methods described previously **[9]**.

Begland *et al.* (1974) reported the condensation reaction of diiminosuccino-nitrile and diaminomaleo-nitrile in the presence of strong acid. The strong acid was used to protonate the diiminosuccinonitrile and promote elimination of ammonia. Different amounts of strong acid produced three different pyrazine products. The use of one equivalent of acid led to aminotricyano-pyrazine, while excess amount of acid gave tetracyanopyrazine. The reaction using catalytic amount of acid gave 2,3- diamino-5,6-dicyanopyrazine **[10] (Scheme 3)**.

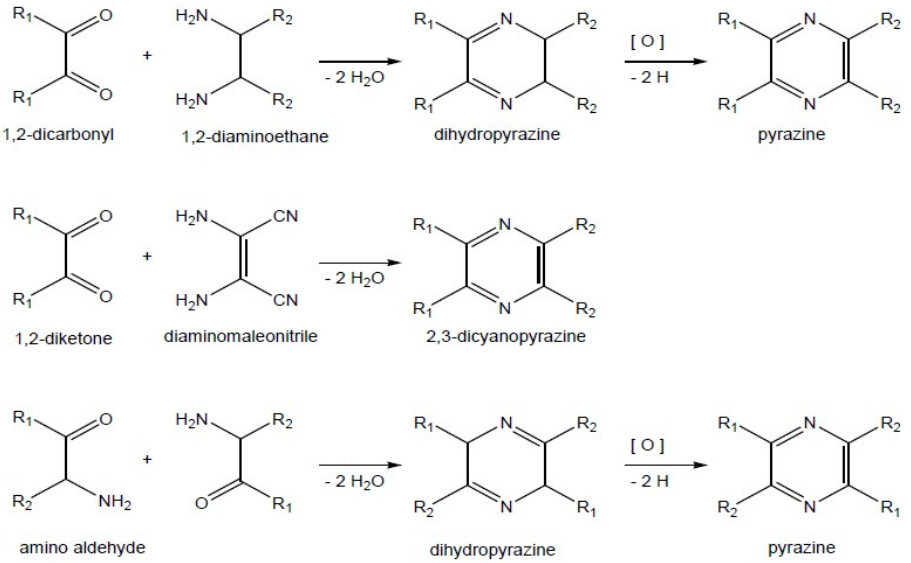
Keir *et al* (1971) reported the condensation of 1,2 dicarbonyl with ethyl-2-amidino-2-amino acetate dihydrochloride to yield pyrazine **[11] (Scheme 4)**.

SYNTHESIS RELATED TO THE PYRAZINE SCHIFF BASE DERIVATIVES (Scheme 5)

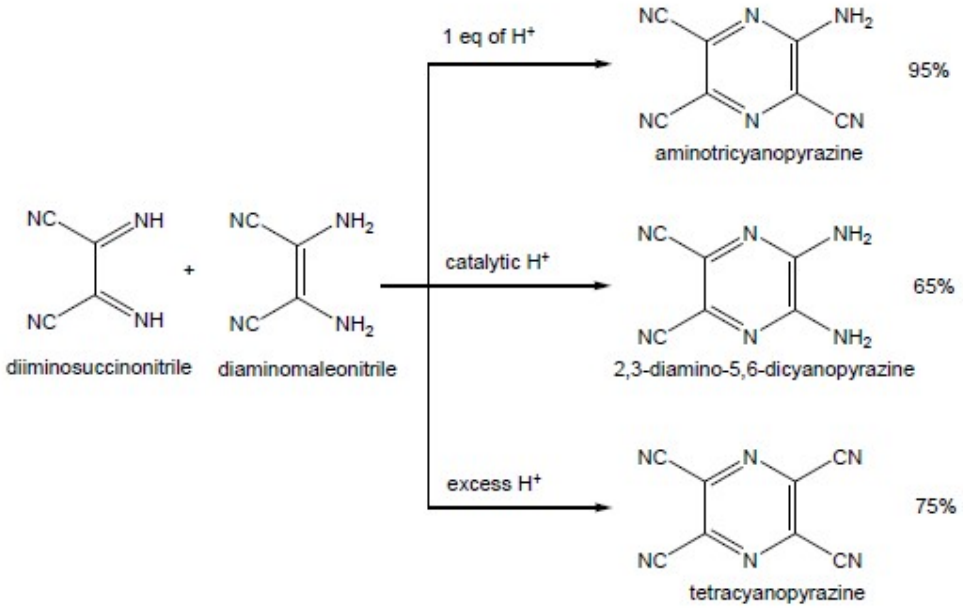
The ligand was prepared by refluxing an equimolar mixture of furan-2-carbaldehyde with pyrazine-2-carboxamide in methanol in presence of a few drops of acetic acid for about 3 hours. The solid that separated was filtered, washed with water and recrystallized from methanol **[12]**.



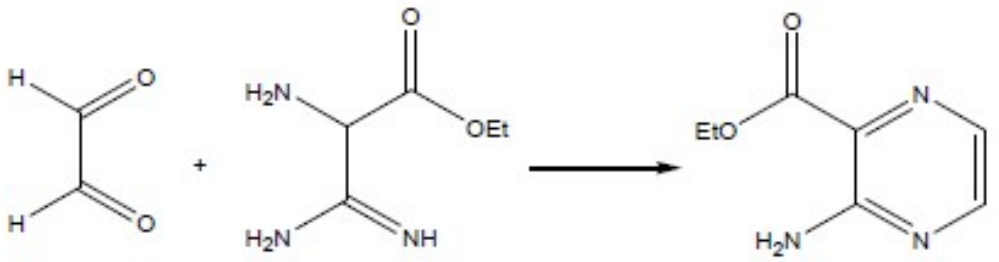
Scheme 1: Formation of pyrazine



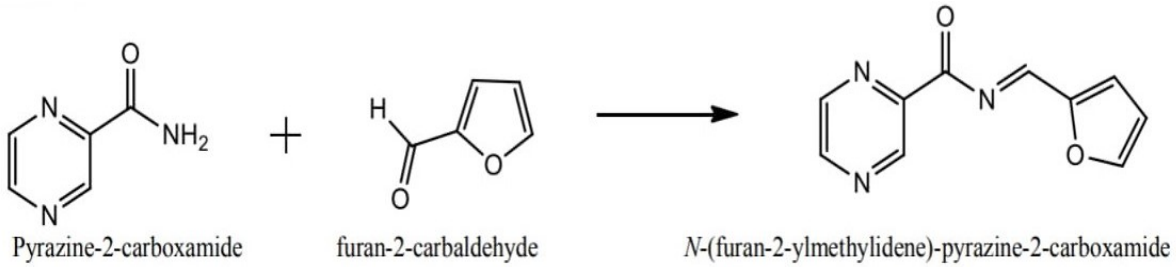
Scheme 2. Classical formation of pyrazine.



Scheme 3: Condensation reaction of diiminosuccinonitrile and diaminomaleonitrile



Scheme 4: Condensation of 1,2 dicarbonyl with ethyl-2-amidino-2-amino acetate dihydrochloride



Scheme 5: Synthesis Related To The Pyrazine Schiff Base Derivatives

ACTIVITY

The diversity of pyrazines derivatives found in organisms in nature with different applications began to arouse the interest of research in this nucleus. The pyrazines derivatives have numerous prominent pharmacological effects, such as antibacterial, antifungal, antimycobacterial, anti-inflammatory, analgesic, anticancer for different types, antidiabetic, treatment for arteriosclerosis, antiviral **[13]**.

Pyrazine nucleus has shown numerous physiological effects, such as anti-HIV, proteasome inhibitor, narcotic addiction, fungal antibiotic, pulmonary heart disease, hypnotic, and eye drops for glaucoma or ocular hypertension.

Antibacterial studies:

The Schiff base ligand $(C_2H_2NC_2HN)C(O):N=CH(C_4H_3S)$ and its metallic compounds have been evaluated for in vitro antibacterial activities. The former displayed activity towards the screened bacteriological organisms; *Staphylococcus aureus, P. aeruginosa, B. cereus* and *K. oxytoca, E. coli* and *P. mirabilis* with inhibitory zones of 9.0-18.0 mm range, which could be attributed to hydrogen bonding between the cellular constituents of the microbial cell and imine nitrogen as well as the ketonic oxygen atoms. Expectedly, the

metallic complexes of Co^{2+}, Ni^{2+} and Cu^{2+} were considerably active against the tested bacterial species with inhibitory growth zones of 17.0-28.0 mm, a consequence of chelation impact. Excitingly, Cu^{2+} complex was outstanding with higher growth inhibitory zones greater than that of uncoordinated Schiff base ligand against microorganisms **[14]**.

Antimicrobial Activity:

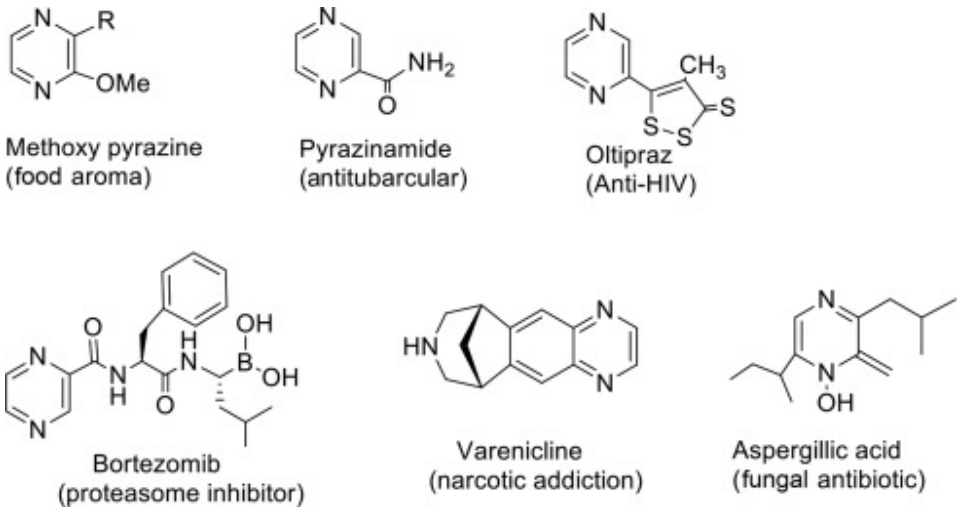
The antimicrobial activity of Schiff bas activities and its complexes has been studied against bacteria *Bacillus megaterium* (Gram +ve), and *Klebsiella pneumonia* (Gram -ve) and fungi: *Penicillium rubrum* and *Aspergillus niger* wherein the zone of inhibition measured in the mm. The results indicate that the complexes are in general more active than the free ligand. Further, Hg complex, of all the compounds, exerts highest activity on the bacteria as well as fungi studied

IMPORTANCE IN NATURAL PRODUCTS, MEDICINES, AND MATERIALS

Pyrazines are present in heat-processed food such as beef products, toasted barley, cocoa, coffee, peanuts, potato chips as well as in fresh foods like tomatoes, peas, green bell peppers, etc. Pyrazines are thought to arise by spontaneous heat-induced condensation between amino acids and sugars through Strecker's degradation.

Several natural products containing this nucleus have been isolated. For instance, clavulazine isolated from Okinawa soft coral *Clauvlaria Viridis*, botryllazine A from the red ascidian *Botryllus leachi*, and barrenazine from unidentified tunicate collected from Madagascar **[15]**.

Pyrazine nucleus is responsible for the flavor and pleasant aroma of several foodstuffs. Pyrazines have also shown interesting anti-HIV, antitubercular, and antibacterial activities. Pyrazines have also been used as pharmaceutical intermediates, for example, 2-methyl pyrazine has been used for the synthesis of the antitubercular drug pyrazinamide. Pyrazinamide, itself a pyrazine derivative, along with rifampicin and ethambutol, constitute first-line drugs for tuberculosis therapy.



Substituted pyrazines have been found as subunits of multiple synthetically constructed therapeutic agents, as well as several natural products. Pyrazine-based skeletons were incorporated into agents targeting a range of ailments. Many derivatives were synthesized and evaluated as potential cancer treatments. Compounds were found to be potent inhibitors of P38α MAP kinase, the Wnt2/β-catenin pathway in non-small-cell lung cancer cell lines, the folate cycle, Pim kinase, Aurora kinase, CHK1 and Nek2. The diaminopteridine-benzenesulfonamide was evaluated as an inhibitor of carbonic anhydrases and dihydrofolate reductase, while the phenazine was evaluated as an inhibitor of quinone reductases 1 and 2, and inducible nitric oxide synthase. Several quinoxaline *N*-oxide derivatives, including, were found to be potent anticancer agents.

Many pyrazine derivatives were synthesized and evaluated for antimicrobial or antiviral activity. The pyrido[1,2,3-*de*]quinoxaline-6-carboxamide was evaluated for the ability to inhibit human cytomegalovirus polymerase . Quinoxaline 1,4-di-*N*-oxide derivatives were synthesized and evaluated for antitubercular activity . The phenazine-1-carboxylic acid derivative showed potent antifungal activity against rice sheath blight. A pyrazine derivative was evaluated as a HCV NS5B polymerase inhibitor.

Pyrazines and quinoxaline derivatives were also reported to be useful in a host of other miscellaneous applications. The dithieno [3,2-*f*:2′,3′-*h*]quinoxaline was used as a donor moiety in a copolymerization for potential development as photovoltaic cells. The power conversion efficiencies and photoresponses of small bandgap polymers were reported, and a quinoxaline derivative

was evaluated as a fluorescent anion sensor. Several pyrazine-based derivatives were used as dyes or fluorescent probes. The indolo [2,3-*b*]quinoxaline dye was synthesized and investigated by optical, electrochemical, theoretical, and thermal studies.

Substituted pyrazines have been found as subunits of multiple synthetically constructed therapeutic agents, as well as several natural products. In 2009, the reported biological activity in which these pyrazine-based scaffolds possessed spanned the gamut. Specifically, compounds were furnished as inhibitors of type II FMS and EphB4 tyrosine receptor kinases, as well as human aldose reductase , and agonists were evaluated for the 5-HT_3 receptor . Also, pyrazine motifs have been reported as antitubercular agents, as antagonists of gonadotropin-releasing hormone (GnRH) receptor, and as antimicrobial compounds. A study was disclosed to better understand the mechanism, and time frame, in which tetramethylpyrazine treats neural ischemia/reperfusion injury in rats, while another investigation was conducted on benzenesulfonamide to evaluate its ability to affect leishmanicidal activity **[16]**.

Pyrazinamide, as one of the three main classes of tuberculosis drugs, was again the subject of intense study. Pyrazinamide-loaded liposomes were prepared as an alternative drug-delivery system. Aspirin, ibuprofen, and diarylquinolone were found to enhance the effectiveness of pyrazinamide in treating tuberculosis in mice. Pyrazinoic acid and n-propyl pyrazinoic ester were found to have antimycobacterial properties. HPLC methods were developed for the simultaneous chromatography of pyrazinamide and other tuberculosis drugs. Comparisons of bile and blood in rats indicated that excretion of pyrazinoic acid (a pyrazinamide metabolite) may be inhibited by silibinin **[17]**.

Pyrazine derivatives possess a wide range of biological activities. They are found in a variety of naturally occurring compounds such as aspergillic acid, hydroxyaspergillic acid, and other antibiotics of similar structure, which possess antibacterial activities. Emimycin (3-hydroxypyrazine N-oxide) has also antibacterial properties. Synthetic pyrazine derivatives exhibit a wide variety of pharmacological properties, including hypoglycemic and diuretic action. Sulfonamides with pyrazine moiety are known to have high antibacterial activity. Pyrazinamide and its morpholino– methylene derivative act as tuberculostatic agents. Nicotinic and isonicotinic amidrazones are also reported in the literature as antibacterial

agents. They also act as a diuretic, antimycotic, and circulatory system agents. The therapeutic potential activity of amidrazone derivatives with pyrazine moiety can be developed as potential antibacterial drugs **[18]**.

SUMMARY AND CONCLUSION

The above review article shows that pyrazines are present both natural and can be synthesized too. The pyrazine derivatives show diversified pharmacological activities such as antibacterial, antifungal, anti-mycobacterial, anti-inflammatory, analgesic, anticancer for different types, antidiabetic, treatment for arteriosclerosis, antiviral.

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