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A Review of Biological potential of *Pyrazinamide* derivatives

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Abstract

Plan: *A review on the importance of pyrazinamide derivatives for the treatment of tuberculosis*
Prologue: *Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. Pyrazinamide (PZA) is an important front-line drug for the treatment of tuberculosis (TB). Pyrazinamide, along with isoniazid and rifampicin, forms the cornerstone of modern TB therapy. Drug resistance in M. tuberculosis is attributed primarily to the accumulation of mutations in the drug target genes; these mutations lead either to an altered target or to a change in titration of the drug. The problem of resistance demand to search and synthesize new classes of compounds effective against pathogenic microorganisms that have developed resistance to the drugs used in the current regimen.*
Outcome: *In the present study, we have made an attempt to compile the reports on biological potential of pyrazinamide and its derivatives. The pyrazinamide derivatives possess unexplored potential that can be utilized for the development of new chemical entities (NCEs) to treat the mycobacterial infections.*
Keywords: *Pyrazinamide (PZA), Antimycobacterial, Antimicrobial, Antibacterial, Antifungal*

1. Introduction

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. Despite the availability of effective chemotherapies, Tuberculosis, among those infectious diseases caused by a single etiology, is still a leading cause of death[1]. The HIV virus pandemic, which contributes substantially to the morbidity and mortality from tuberculosis[2,3] and the emergence of multidrug resistant strains of *Mycobacterium tuberculosis* have compounded the problem[4,5]. At present only a few alternative chemotherapeutic regimens are available, resulting in poor therapeutic outcomes and high mortality rate among multidrug resistant tuberculosis patients[6].

Multidrug-resistant strains of *Mycobacterium tuberculosis* seriously threaten tuberculosis (TB) control and prevention efforts. Molecular studies of the mechanism of action of antitubercular drugs have elucidated the genetic basis of drug resistance in *M. tuberculosis.*

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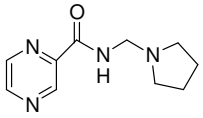
Drug resistance in *M. tuberculosis* is attributed primarily to the accumulation of mutations in the drug target genes; these mutations lead either to an altered target (e.g., RNA polymerase and catalase-peroxidase in rifampicin and isoniazid resistance, respectively) or to a change in titration of the drug (e.g., InhA in isoniazid resistance).Development of specific mechanism–based inhibitors and techniques to rapidly detect multidrug resistance will require further studies addressing the drug and drug-target interaction. The above facts created an urgent need to develop new effective anti tuberculosis drugs with bactericidal mechanisms different from those of the presently available agents.

At present a number frontline drugs are available for the treatment of tuberculosis but most of them exhibit a variety of side effects. Further, the low efficacy of the majority of ordinary antimycobacterial drugs in treating tuberculosis disease is principally due to their low susceptibility to *M. tuberculosis*. Pyrazinamide (PZA) is an important front-line drug for the treatment of tuberculosis (TB). Pyrazinamide, along with isoniazid and rifampicin, forms the cornerstone of modern TB therapy. Pyrazinamide plays a unique role in shortening the therapy from previously 9–12 months to 6 months, because it kills a population of semi-dormant tubercle bacilli in acidic pH environments that are not killed by other TB drugs[7]. Experimental evidences suggest that PZA diffuse into *Mycobacterium tuberculosis* through passive conduction and after that it is converted in pyrazinoic acid (POA) by pyramidase, which promotes an accumulation of this metabolite in the mycobacterial cytoplasm. This accumulation is possible because *M. tuberculosis* has an inefficient efflux system thereby occurs a decrease of the intracellular pH. The inhibition of the growth of bacteria is caused due to the deactivation of fatty acid synthetase enzyme. In view of all these facts we have planned to collect and compile the biological potential of pyrazinamide and its derivatives.

Biological potential of pyrazinamide derivatives

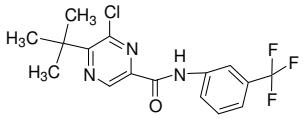
Chung *et al.* reported the inhibition of *M. tuberculosis*, *in vitro*, in monocytes and in mice by aminomethylene pyrazinamide analogs. They found that the synthesized aminomethylene amide derivatives have higher activity at acidic pH conditions where pyrazinamide is inactive against pyrazinamide resistant *M. tuberculosis*. These new compounds have shown an improved antituberculous activity in infected human macrophages relative to pyrazinamide. *N*-(Pyrrolidin-1-ylmethyl) pyrazine-2-carboxamide (**1**) in combination with rifamycin was especially effective in both infected human macrophages and in a murine model of infection[8].



1

The antimycobacterial, antifungal, photosynthesis inhibiting and antialgal activity of 20 newly synthesized unsubstituted, halogenated and/or alkylated pyrazine-2-carboxylic acid amides connected via –CONH- bridge with substituted anilines was reported by Dolezal *et al*[9].

5-tert-Butyl-6-chloro-*N*-(3-trifluoromethylphenyl)pyrazine-2-carboxamide (**2**) has shown the highest activity against *Mycobacterium tuberculosis* H37Rv (MIC = 3.13 µg/mL). The highest antifungal effect against *Trichophyton mentagrophytes*, the most susceptible fungal strain tested, was found for *N*-(3-trifluoromethylphenyl)pyrazine-2-carboxamide (**3**, MIC = 62.5 µM/ml).



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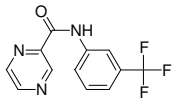

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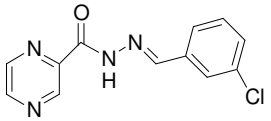
Vergara *et al.* reported the antimycobacterial activity of a series of *N*'-[(*E*)-(mono substituted benzylidene)]-2-pyrazinecarbohydrazide derivatives. They found that *N*'-[(*E*)-(3-chlorophenyl) methylidene]-2-pyrazinecarbohydrazide (**4**), *N*'-[(*E*)-(3-cyanophenyl) methylidene]-2-pyrazinecarbohydrazide (**5**) and *N*'-[(*E*)-(2-nitrophenyl) methylidene] -2-pyrazinecarbohydrazide (**6**) were the most active antimycobacterial agents against *Mycobacterium tuberculosis* H37Rv[10].



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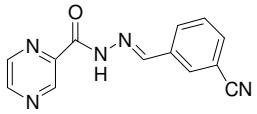

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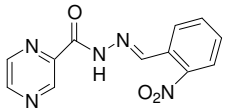
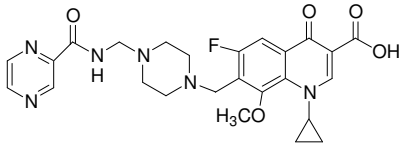


6

A series of pyrazinamide Mannich bases was synthesized by reacting PZA, formaldehyde, and various substituted piperazines using microwave irradiation by *Sriram.D et al.* The synthesized compounds were evaluated for antimycobacterial activity *in vitro* and *in vivo* against *Mycobacterium tuberculosis* H37Rv (MTB). 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-4-((pyrazine-2-carbox-amido)methyl)piperazin-1-yl)-4-oxoquinoline-3-carboxylic acid (**7**) was found to be the most active compound *in vitro* with MIC of 0.39 and 0.2 µg/ml against MTB and multidrug-resistant MTB, respectively[11].



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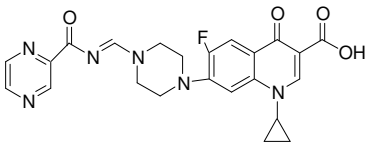
Imramovsky *et al.* reported a new modification of antitubercular active molecules and synthesized compounds **8** and **9** having pyrazine-2-carboxylic acid nucleus and found both these compound were highly active antimycobacterial agents with MIC values 0.78 µg/ml and 0.10 µg/ml against *M. tuberculosis* H37Rv[12].



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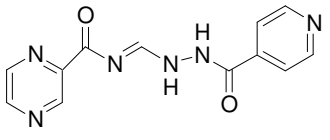
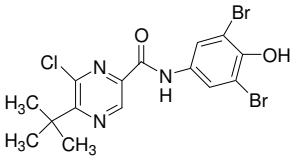


9

Dolezal *et al.*[13] synthesized a series of substituted pyrazine carboxamides and evaluated their antimycobacterial, antifungal and photosynthesis-inhibiting activity. 3,5-Bromo-4-hydroxyphenyl derivatives of substituted pyrazinecarboxylic acid, **10-12**, showed the highest activity against *Mycobacterium tuberculosis* H37Rv (54-72% inhibition). The highest antifungal effect against *Trichophyton mentagrophytes*, was found for 5-*tert*-butyl-6-chloro-*N*-(4-methyl-1,3-thiazol-2-yl)pyrazine-2-carboxamide (**13**, MIC = 31.25 µmol/ml).



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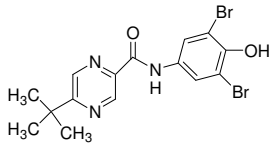

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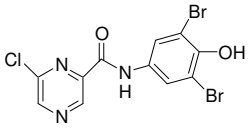

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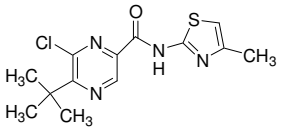
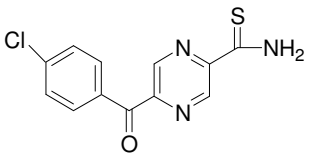


13

A series of 5-aroylpyrazine-2-carboxylic acid derivatives was synthesized by homolytic aroylation of pyrazine nucleus with various substituted aromatic carbaldehydes and evaluated for their antimycobacterial and antifungal potential. 5-(4-chlorobenzoyl)-pyrazine-2-carbothioamide (**14**) showed promising activity (90% inhibition) against *Mycobacterium tuberculosis*. The highest antifungal effect (MIC < 1.95 µmol/mL) against *Trichophyton mentagrophytes*, was found for 5-benzoylpyrazine-2-carbothioamide (**15**). Thioamides exhibited higher *in vitro* antimicrobial activity than the corresponding amides[14].



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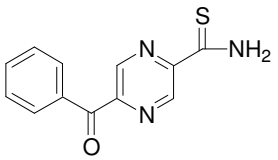
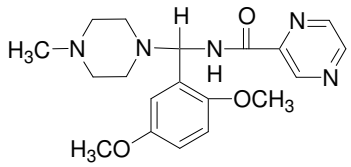


15

Chaluvaraju and Ishwar[15] synthesized a series of pyrazinamide Mannich bases by the reaction of aromatic aldehydes with pyrazinamide and secondary amines. The synthesized derivatives were assayed for their *in vitro* antimicrobial activity against *E. coli, B. subtilis, S. aureus, A. niger* and *C. albicans.* Pyrazine-2-carboxylic acid [(2,5-dimethoxy-phenyl)-(4-methyl-piperazin-1-yl)-methyl]-amide (**16**) was found to be the most active antimicrobial agent amongst the synthesized derivatives.



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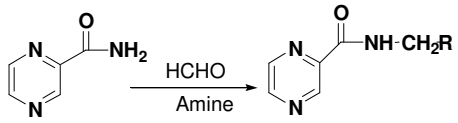
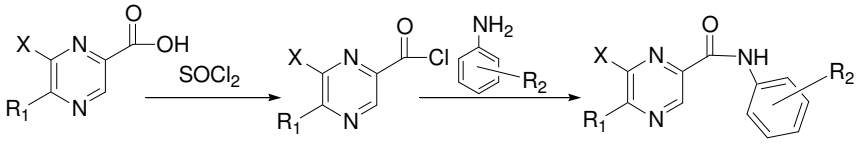
2. *Strategies employed for the synthesis of pyrazinamide derivatives*

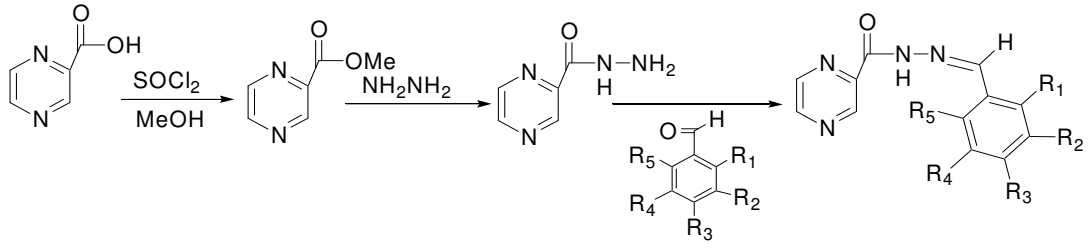
1. *Synthesis of Mannich bases of pyrazinamide*[8,11]



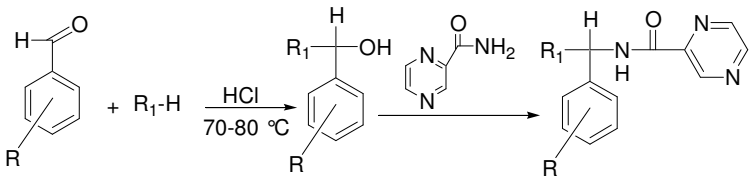
2. *Synthesis of substituted pyrazine-2-carboxamides*[9]



3. *Synthesis of N'-[(E)-(mono substituted benzylidene)]-2-pyrazine- carbohydrazide derivatives*[10]



4. Synthetic Protocol of Amino benzylated Mannich Bases[15]



3. Conclusion

Pyrazinamide and its derivatives were reported to have antimycobacterial and antimicrobial activities. Further, it has been found that pyrazinamide derivatives can be synthesized in a number of ways. Summarizing, the pyrazinamide derivatives possess the unexplored potential that can be utilized for the development of new chemical entities (NCEs) to treat the mycobacterial infections.

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