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REVIEW ON ISONIAZID DERIVATIVES AS ANTI-TUBERCULOSIS AGENT

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ABSTRACT

The appearance of tuberculosis and emergence of drug resistance requires focused attention and need to approve the various derivatives of isoniazid. Isoniazid is frontline drug is used for treatment of tuberculosis and it is key drug used for chemotherapy of tuberculosis. The present article contains compilation of various derivatives of isoniazid and their biological activity like anti-mycobacterial, anti-fungal, anti-viral activities. The emphasis is given on various reported synthetic routes for isoniazid derivatives which will be a help to researchers.

KEYWORDS: Isoniazid, Antimycobacterial, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) caused by multidrug resistance strains of *Mycobacterium tuberculosis* is the most prevalent infectious diseases worldwide.[1, 2] According to world health organization (WHO) report 1.5 million people died from TB in 2018 and an estimated 10 million people fell ill with tuberculosis. WHO estimates that there were 484 000 new cases with resistance to rifampicin the most effective first-line drug, of which 78% had MDR-TB. Ending the TB epidemic by 2030 is among the health targets.[3] The effective combination of five first-line drugs namely isoniazid (INH), rifampicin, ethambutol, streptomycin and pyrazinamide are used in most parts of the world to treat TB effectively.[4] If the patient developed bacterial resistance to this first line drugs then, second, line drugs such as amino-salicyclic acid, cycloserine, kanamycin etc. are available but cannot be employed due to their high toxicity.[5] In spite of toxicity on repeated dosing, isoniazid is considered to be first line drug for TB Based upon this assumption and to get a new drug for resistance strain various researchers synthesised novel isoniazid-based derivatives.[6] In our present article we have reported

synthetic routes of different isoniazid derivatives which will be helpful for development of novel derivatives.[7]

REPORTED ISONIAZID DERIVATIVES

Reported isoniazid derivatives found in literature survey have been classified based upon scaffold are as follows.

Pyrazoline based derivatives reported in literature is given in **Figure 1.**

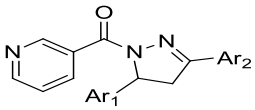
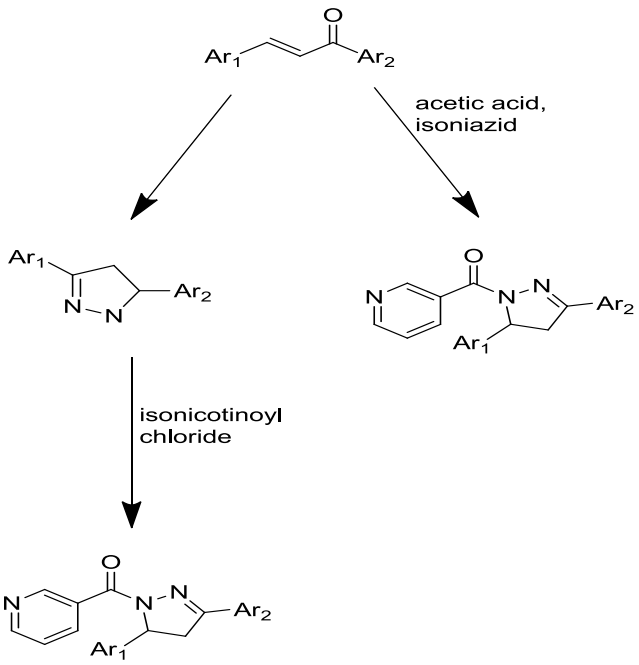


Fig. 1: Structure of pyrazoline based derivatives.

Mamolo et al., in 2001 synthesised pyrazoline substituted derivatives by cyclising chalcones with hydrazine and further reacting it with isonicotinoyl chloride.[8] Whereas Ali et al., in 2013 synthesized a series of pyrazoline derivatives by cyclising chalcones with isoniazid in presence of glacial acetic acid. Similar derivatives were prepared by alternative pathway wherein chalcone was first treated whereas hydrazine and further pyridinoyl chloride these were tested for anti-mycobacterium activity, in vitro, against *M. tuberculosis* H37Rv and INH resistant *M. tuberculosis* using BACTEC-460 by using radiometric system and agar dilution method.[7] Schematic representation is given in **Scheme 1.**



Scheme 1: Synthetic scheme for pyrazoline based derivatives.

Oxadiazole based derivatives reported in literature is given in **Figure 2.**

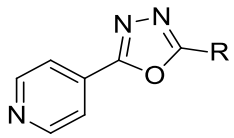
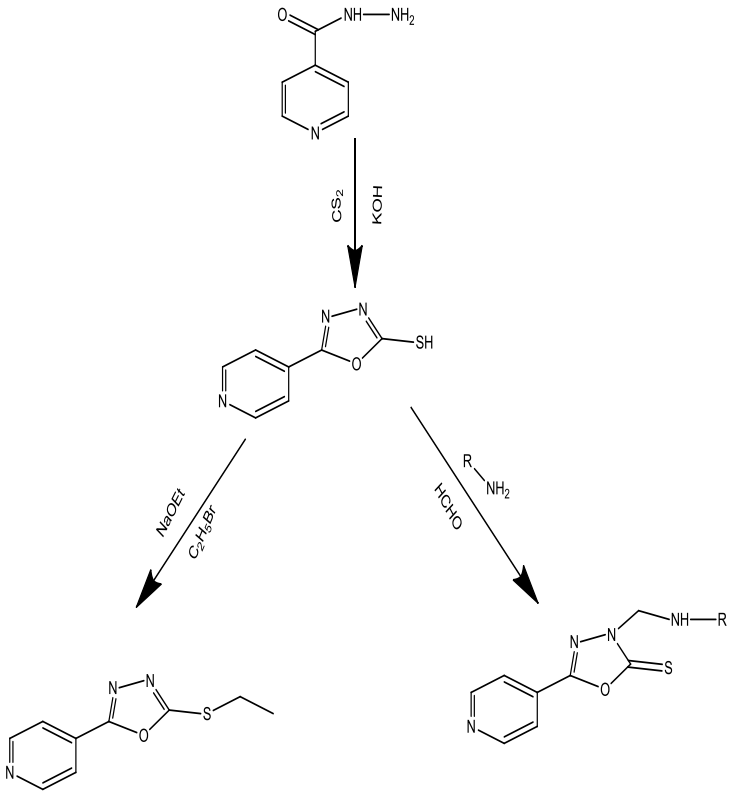


Fig. 2: Structure of oxadiazole based derivatives.

Bayrak et al., in 2009 reported synthesis of oxadiazole derivatives starting from isoniazid was reacted with chlorine in presence of potassium hydroxide giving mercapto oxadiazole derivatives. Further N-substituted oxadiazole derivatives was prepared by treatment with alkyl amine and formaldehyde[9] whereas substituted oxadiazole was prepared by treatment with alkyl bromide.[10] Schematic representation is given in **Scheme 2.**



Scheme 2: Synthetic scheme for oxadiazole based derivatives.

Triazole based derivatives reported in literature is given in **Figure 3.**

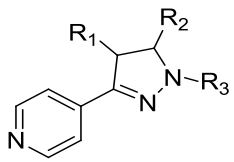
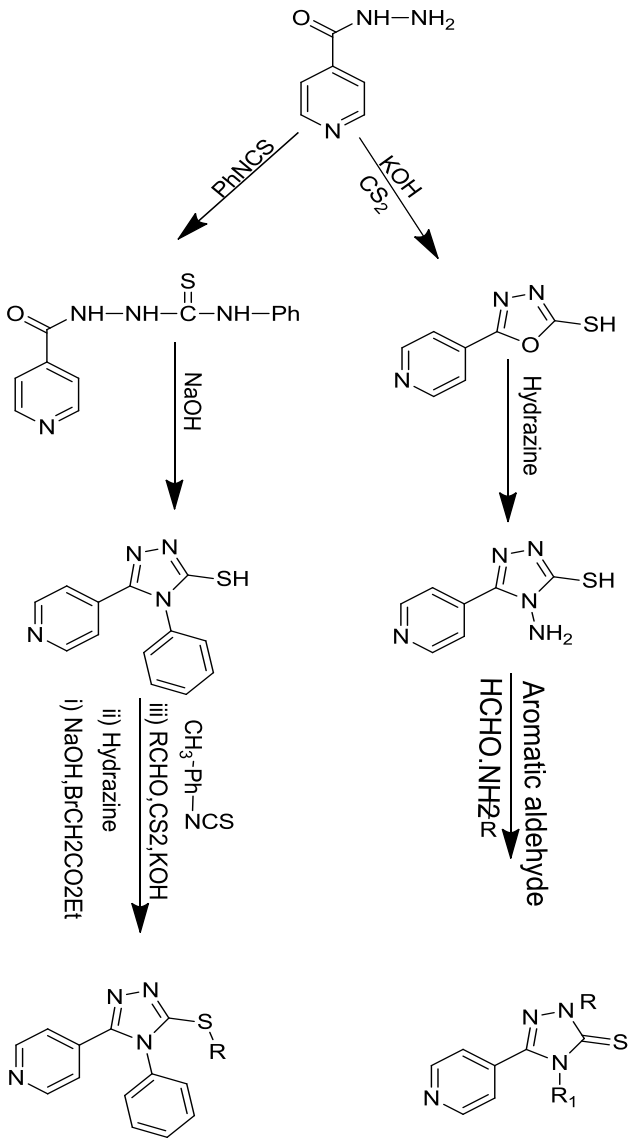


Fig. 3: Structure of pyrazoline based derivatives.

Bayrak et al., reported synthesis of triazole derivatives by using two distinct synthetic pathways. in 2008, they reported synthesis of 1,2,4-triazole-3-thiol derivatives by using 1-isonicotinoyl-4-phenyl thiosemicarbazide. Further, triazole-3-thiol was reacted to obtained N-substituted and S-substituted derivatives.[9] Whereas, in 2009 reported synthesis of 1,2,4-triazole-3-thiol derivatives by reacting 1,3,4-oxdiazole-2-thiol as starting material. Further, 1,2,4-triazole-3-thiol derivatives where converted to corresponding Mannich bases and thione derivatives.[10] Schematic representation is given in **Scheme 3.**



Scheme 3: Synthetic scheme for triazole based derivatives.

Isonicotinoyl hydrazine-based derivatives reported in literature is given in **Figure 4.**

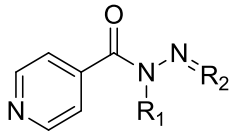
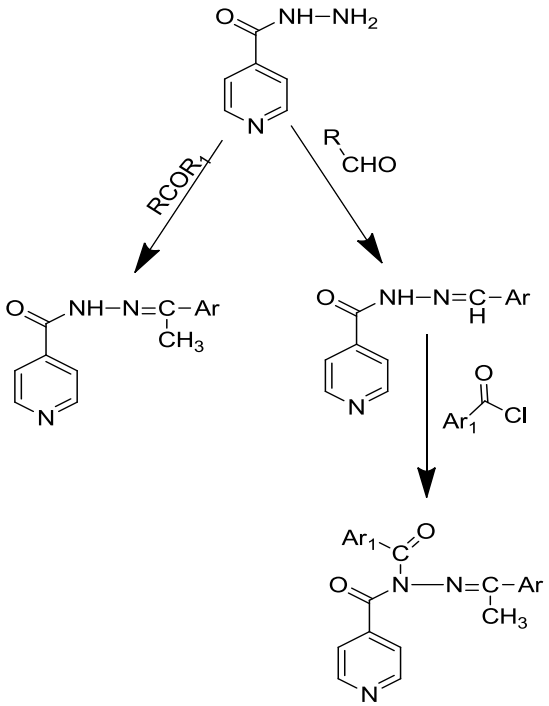


Fig. 4: Structure of isonicotinoyl hydrazine-based derivatives.

Judge et al., 2011 and Sriram et al 2005 synthesised a series of isonicotinicacid-1-(substituted phenyl)-ethylidene/cycloheptylidenehydrazide derivatives by using aldehyde and ketones.[11] The synthesise compound were screened for anti-mycobacterial activity against *M. tuberculosis* H37Rv using the Alamarblue Susceptibility test.[12,13-16] Schematic representation is given in **scheme 4.**



Scheme 4: Synthetic scheme for Isonicotinoyl hydrazine-based derivatives.

Isonicotinylhydrazino amide/carbothioamide based derivatives reported in literature is given in **Figure 5.**

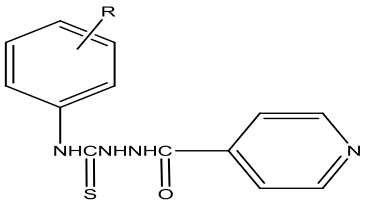
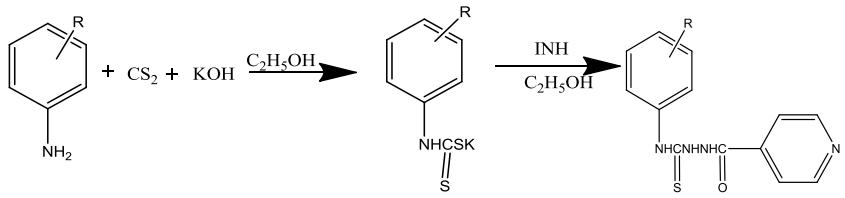


Fig. 5: Structure of isonicotinoylhydrazino amide/carbothioamide based derivatives.

Various isonicotinoylhydrazinocarbothioamides were prepared by reacting isonicotinoyl hydrazide (INH) with appropriate potassium salt of substituted phenyl thiocarbamate and were tested for their anti-mycobacterial activityin-vitro against *Mycobacterium tuberculosis* H37Rv and INH resistant using agar dilution method.[10,14-18] Schematic representation is given in **scheme 5.**



Scheme 5: Synthesis scheme for Isonicotinylhydrazino amide/carbothioamide based derivatives.

CONCLUSION

Tuberculosis (TB) one of the threatful disease catches attention of the researchers. Development of multidrug resistance drug for treatment of TB has become a challenge to the researchers. Many novel derivatives with different scaffold have been synthesized and reported but to get the derivatives with lesser cytotoxic effect to host cell is another challenge to the researchers. Considering these factors, we focused on already available drug isoniazid as it has lesser cytotoxic effect on the host cell. Isoniazid also possesses the potential as an anti-TB scaffold. In the present article we have emphasized on reported synthetic routes for synthesis of isoniazid derivatives which will be helpful for the researchers.

REFERENCES

1. Huebner, R. E.; Castro, K. G. Annu. Rev. Med., 1995; 46,47.
2. Sudre, P.; Dam, G.; Kochi, A. Bull. World Health Organ, 1992; 70: 149.
3. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
4. Mandell GL, Sande MA. Antimicrobial agents: drugs used in the chemotherapy of tuberculosis and leprosy. In: Gilman AG, Goodman LS, Rall TW, Vies AS, Taylor P, editors. The pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990; 1146e53.
5. Mandell, G. L.; Sande, M. A. In The Pharmacological Bass of Therapeutics; 8th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Vies, A. S., Taylor, P., Eds.; Pergamon: New York, 1990; 1146.

6. Blair, I. A.; Timoco, R. M.; Brodie, M. J.; Clarc, R. A.; Dollery, T.; Timbrell, J. A.; Beever, I. A. Hum. Toxicol, 1985; 4: 202.
7. Ali MA, Yar MS, Kumar M, Pandian GS (2007) Synthesis and antitubercular activity of substituted novel pyrazoline derivatives. Nat Prod Res., 21(7): 575–579.
8. Mamolo MG, Zampieri D, Falagiani V, Vio L, Banfi E (2001) Synthesis and antimycobacterial activity of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole derivatives. IL Farmaco, 56: 593–599.
9. Bayrak H, Demirbas A, Demirbas N, Karaoglu SA (2009a) Synthesis of some new 1,2,4-triazoles starting from isonicotinic acid hydrazide and evaluation of their antimicrobial activities. Eur J Med Chem., 44: 4362–4366.
10. Bayrak H, Demirbas A, Karaoglu SA, Demirbas N (2009b) Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. Eur J Med Chem., 44: 1057–1066.
11. Cocco MT, Congiu C, Onnis V, Pusceddu MC, Schivo ML, De Logu A (1999) Synthesis and antimycobacterial activity of some isonicotinoylhydrazones. Eur J Med Chem., 34: 1071–1076.
12. Judge V, Narasimhan B, Ahuja M, Sriram D, Yogeeswari P, De Clercq E, Pannecouque C, Balzarini J (2011a) Isonicotinic acid hydrazide derivatives: synthesis, antimicrobial activity and QSAR studies. Med Chem Res. doi:10.1007/s00044-011-9662-9 (in press).
13. Judge V, Narasimhan B, Ahuja M, Sriram D, Yogeeswari P, De Clercq E, Pannecouque C, Balzarini J (2011b) Synthesis, antimycobacterial, antiviral, antimicrobial activity and QSAR studies of Isonicotinic acid-1-(substituted phenyl)-ethylidene/ cycloheptylidene hydrazides. Med Chem Res. doi: 10.1007/s00044-011-9705-2 (in press).
14. Mohamad S, Ibrahim P, Sadikun A (2004) Susceptibility of Mycobacterium tuberculosis to isoniazid and its derivative, 1-isonicotinyl-2-nonanoyl hydrazine: investigation at cellular level. Tuberculosis, 84: 56–62.
15. Rando DG, Doriguetto AC, Tomich de Paula da Silva CH, Ellena J, Sato DN, Leite CQF, Varanda EA, Ferreira EI (2006) Aduplicatednitrotienyl derivative with antimycobacterial activity: synthesis, X-ray crystallography, biological and mutagenic activity tests. Eur J Med Chem., 41: 1196–1200.
16. Sriram D, Yogeeswari P, Madhu K (2005) Synthesis and in vitro and in vivo antimycobacterial activity of isonicotinoylhydrazones. Bioorg Med Chem Lett., 15: 4502–4505.

17. Sriram D, Yogeeswari P, Madhu K (2006) Synthesis and in vitro antitubercular activity of some 1-[(4-sub)phenyl]-3-(4-{1-[(pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea. Bioorg Med Chem Lett., 16: 876–878.
18. Sriram D, Yogeeswari P, Priya DY (2009) Antimycobacterial activity of novel N-(substituted)-2-isonicotinoylhydrazinocarbothioamide endowed with high activity towards isoniazid resistant tuberculosis. Biomed Pharmcother, 63: 36–39.