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A SYSTEMATIC REVIEW ON THE SYNTHESIS OF NICOTINIC ACID HYDRAZIDE HYDRAZONES

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ABSTRACT
The hydrazide-hydrazone Schiff bases attract the attention of researchers due to their broad coverage in medicinal field and pharmaceutical applications. There has been considerable interest in the development of novel compounds of Schiff bases hydrazones. A Schiff base is considered as an aldehyde with a C=N group instead of C=O group. Hydrazones possessing an azomethine proton constitute an important class of compounds for drug development. Hydrazone derivatives are obtained by coupling hydrazide compounds with aldehydes and ketones. In this paper review is focused on the overview of the literature findings covering the research on hydrazones Synthesized from Nicotinic acid hydrazides.

Keywords: Nicotinic acid hydrazide, aldehydes, ketones, Schiff basses and hydrazones.

INTRODUCTION

Nicotinic acid hydrazide, which was first introduced in tuberculosis therapy in the 1950, is regarded as one of the most commonly used and efficient drugs in the treatment of human tuberculosis [1-2]. Also reduce the levels of both triglycerides and cholesterol in the plasma and act as anti-hyperlipoproteinemic drug [3-4]. Nicotinic hydrazide derivatives have been used for the synthesis of products with important biological properties [5-6]. Nicotinic hydrazide has been used as a corrosion inhibiting agent. [7] A wide variety of heterocyclic molecules with good medicinal properties are obtained from nicotinic acid hydrazide. They are used as anticonvulsant[8], antituberculosis[9], antimicrobial[10], and anticancer[11]. In this regards, nicotinic acid hydrazide is one of the most researched antitubercular agents as evident in several reports of a range of its analogues, with anti-tubercular potentials and a number of promising candidates. Inspired by these considerations and in continuation with our studies on hydrazone Schiff bases derived from similar acid hydrazides [12-13].

Review literature for Synthesis of hydrazones from nicotinic acid hydrazide with carbonyl compounds like aryl aldehydes and aryl ketones. The formation of Nicotonic hydrazones complexes

attracts the attention due to their structural diversity and many potential applications. It was therefore our endeavor work to review about hydrazones of nicotoinic acid hydrazides obtained from with enhanced aromatic aldehydes and ketones.

Diouf *et al*., have prepared a nicotinic acid hydrazones by the reaction of different types of aryl aldehydes and aryl ketones like O-vanillin, salicylaldehyde and 2-hydroxyacetophenone with Nicotinic acid hydrazide [Fig 1] [14].

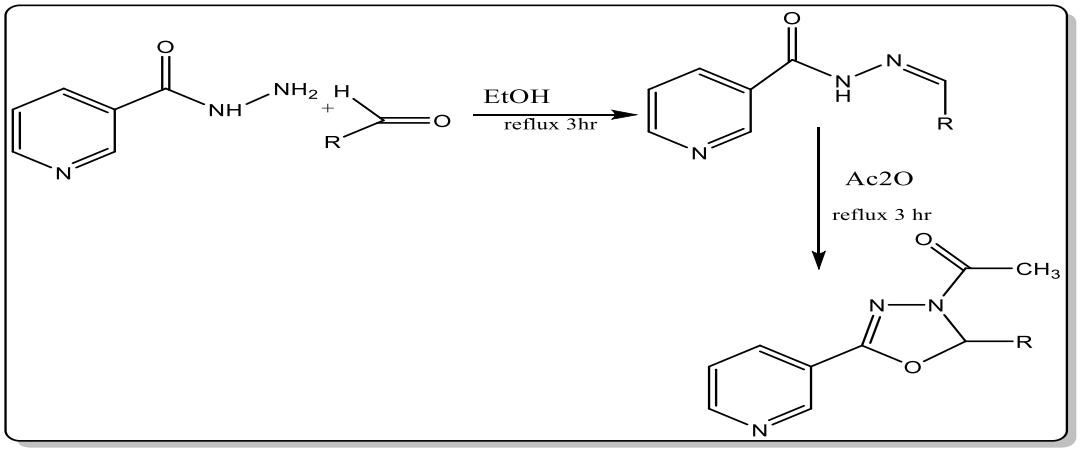

Figure 1: Scheme lead by Diouf *et al*.,

Paruch *et al*., The starting material as nicotinic acid which were combined with different aldehydes, formation of a series of twelve acylhydrazones, the compounds showed promising activity against Gram-positive bacteria (MIC = 1.95–15.62 _g/mL) [15]. **Strazic *et al*.**, Aroylhydrazones have been synthesized by mixing of nicotinic acid hydrazide with different substituted benzaldehyde or ketone. [Fig 2] [16].

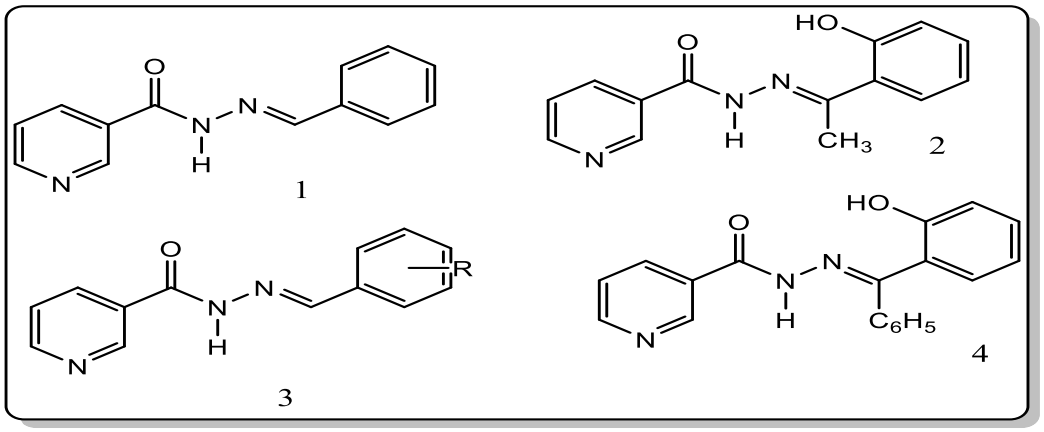

Figure 2: **Scheme lead by strazic et al.**

Moradi *et al.*, reported the synthesis of various substituted arylidene -2- phenoxynicotinic acid hydrazide by the condensation reaction of different substituted aromatic aldehydes or acetophenones with nicotinic acid hydrazide in absolute ethanol. These hydrazones compounds showed good result in analgesic and anti-inflammatory activities [Fig 3] [17].

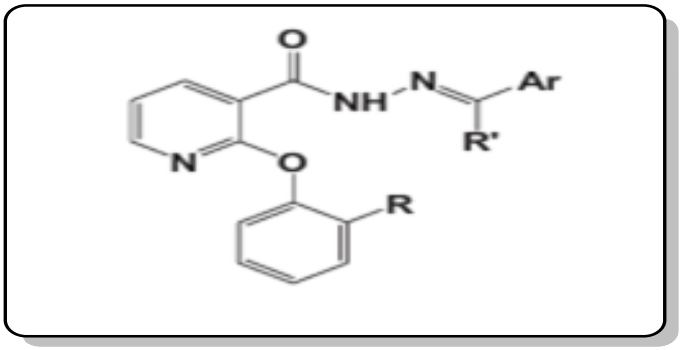

Figure 3: Scheme lead by Moradi *et al.*,

Vijayan., have been worked on synthesis of N and S heterocycles of 2- thiophenecarboxaldehyde nicotinic hydrazones and 2-thiophenecarboxaldehyde benzhydrazone in methanol by the presence of glacial acetic acid by refluxing. The reaction mixture was cooling and the obtained products are colorless solids [Fig 4] [18].

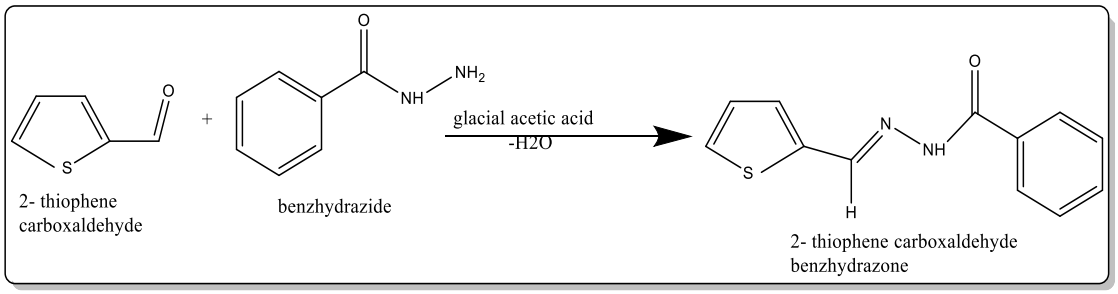

Figure 4: Scheme lead by Vijayan

Eldehna *et al*., synthesis a series of three different compounds, 6-aryl-2-methylnicotinohydrazides, N′-arylidene-6-(4- bromophenyl)-2-methylnicotino hydrazides and N′-(un/substituted 2-oxoindolin-3-ylidene)-6-(4-fluorophenyl)-2-methylnicotinohydrazides. The results showed that isatin hydrazides are remarkably more active than the parent hydrazide [Fig 5] [19].

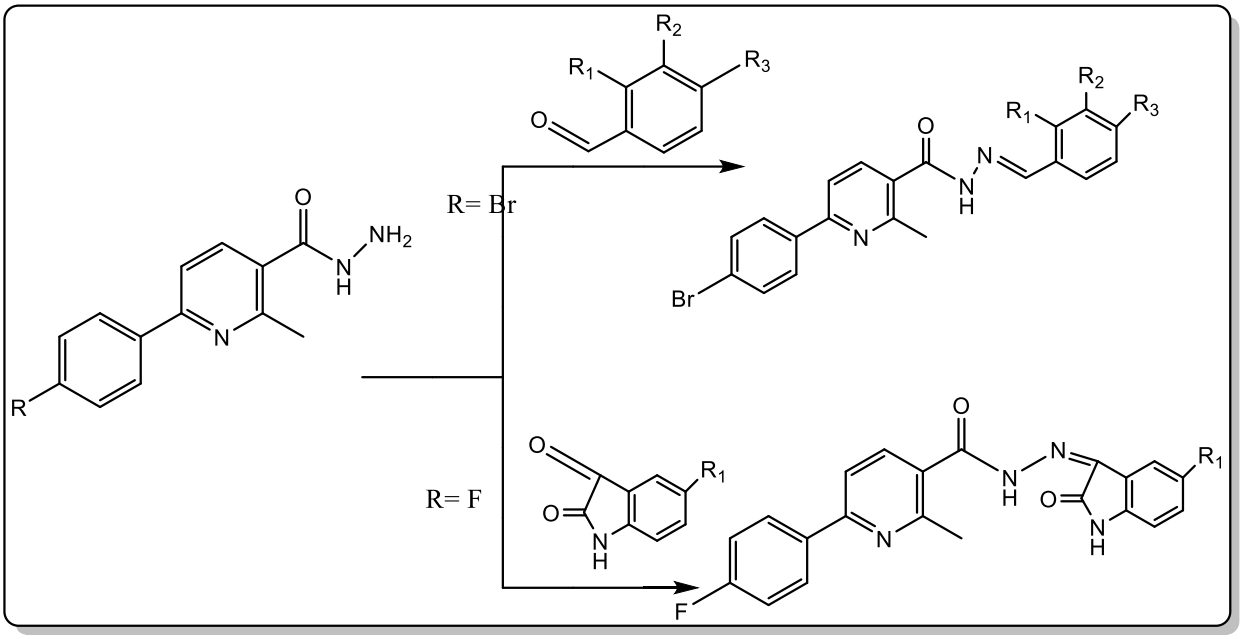

Figure 5: Scheme lead by Eldehna *et al.*,

Mikwa *et al.*, worked on metal complexes of Iron (II) and manganese (II) of N'-(1-(pyridin-2-yl) ethylidene) nicotinohydrazide (LH) have been synthesized and characterized by elemental analysis, IR, and 1H NMR spectroscopy [Fig. 6] [20].

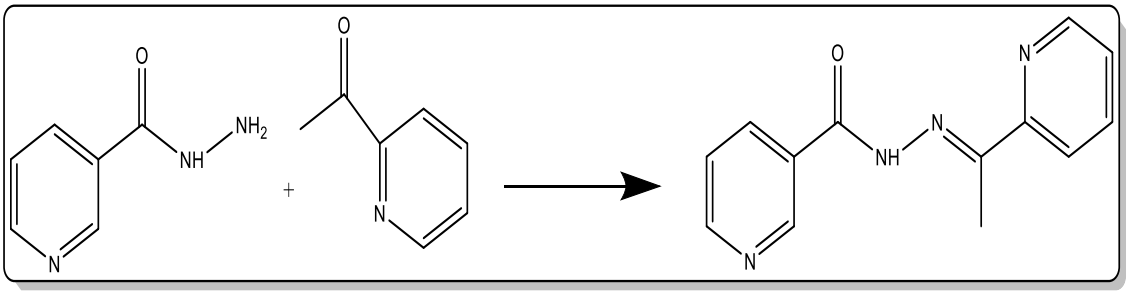

Figure 6: Scheme lead by Mikw *et al.*,

Sreeja *et al.*, have synthesized 2- hydoxyacetophenone nicotinic acid hydrazone (H_2ApNH). These hydrazone compounds were analysis by NMR, COSY homonuclear and HMQC heteronuclear techniques [Fig 7] [21].

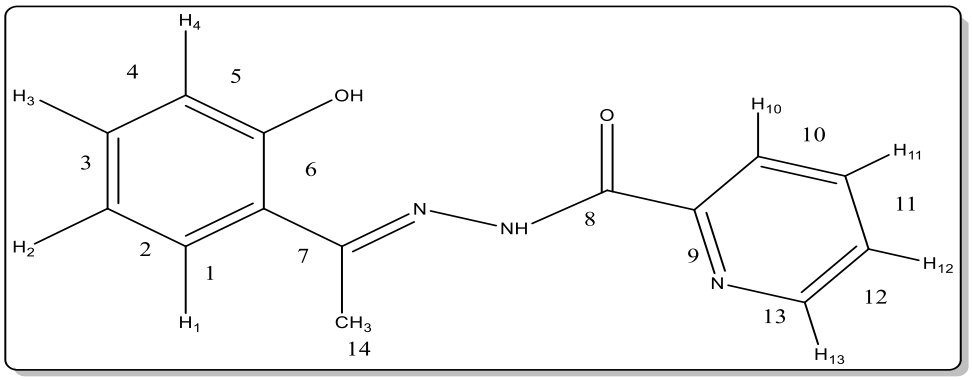

Figure 7: Scheme lead by Sreeja *et al.*,

R. Narang et al., prepared series of Naphthalen-1-yloxy-acetic acid hydrazides derivatives. The compounds having 3,4,5-trimethoxy benzaldehyde and m-nitro acetophenone substituents shows active biological screening against tested strains[22]. **Benkovic *et al.*,** The various compounds of N′-(2,3-dihydroxyphenylmethylidene)-3 pyridine carbohydrazide, N′-(2,5-dihydroxyphenylmethylidene)-3-pyridine carbohydrazide, N′-(3-chloro-2-hydroxy-phenylmethylidene)-3-pyridinecarbo-hydrazide, and N′-(2-hydroxy-4-methoxyphenyl-methylidene)-3-pyridine-carbo-hydrazide have been synthesized [Fig 8] [23].

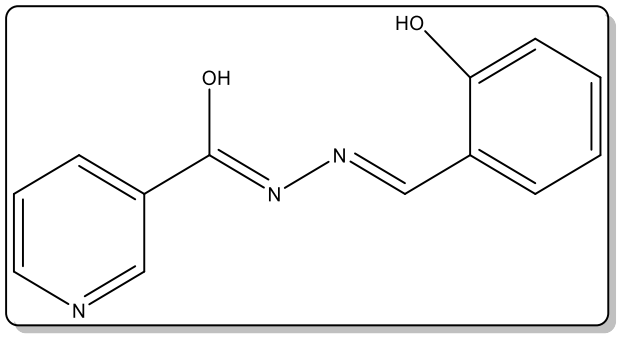

Figure 8: Scheme lead by R. Narang et al.,

Galic *et al.*, Synthesized and characterized of aroylhydrazones derived from salicylaldehyde, O- vanillin with nicotinic acid hydrazide. The molecular and crystal structure of N$^{/}$ -salicylidene-3-pyridinecarbohydrazide has been determined by X-ray diffraction [Fig 9] [24].

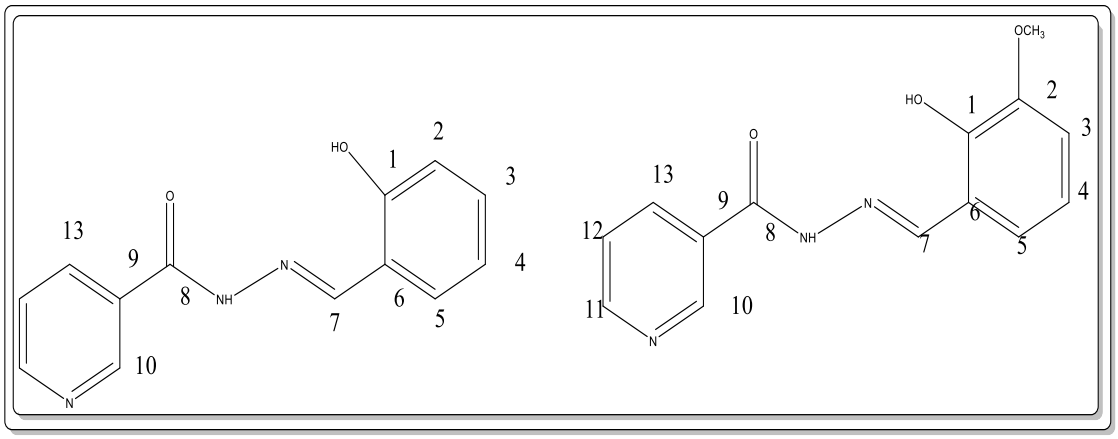

Figure 9: Scheme lead by Galic *et al.*,

Basaran *et al.*, have synthesized of some novel hydrazones compounds which are very significant for ongoing cancer treatment. The synthesized compounds were characterized by various spectra techniques like (1H NMR, 13C NMR and FT-IR) [Fig 10] [25].

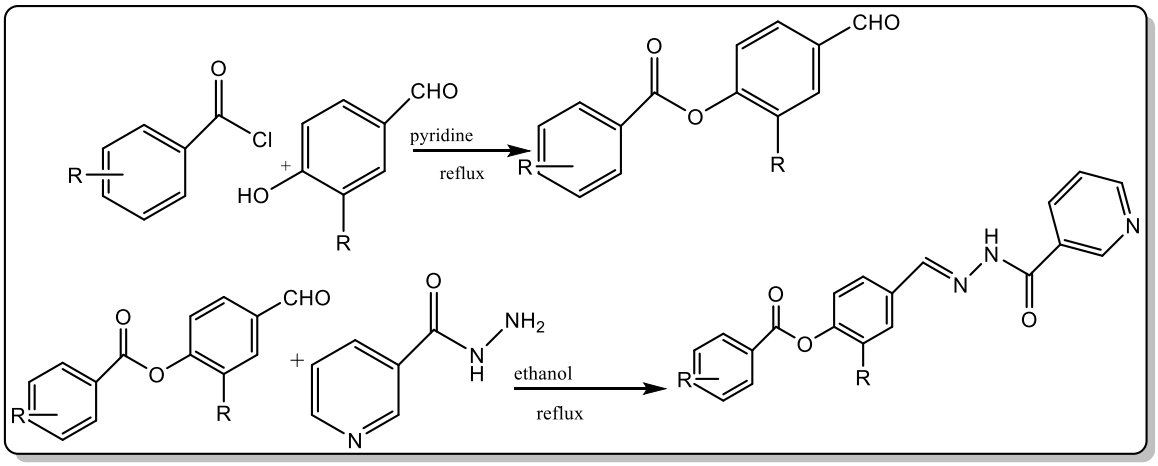

Figure 10: Scheme lead by Basaran *et al.*,

Aboelez *et al.*, N acyl hydrazones have prepared from condensation of nicotinic acid hydrazide with the corresponding benzaldehydes. The concentration of high cholesterol diet fed rat model in hypolipidemic. The formation of hydrazones showed that decrease in level of total cholesterol and triglycerides in hyperlipidemic rats [Fig 11] [26].

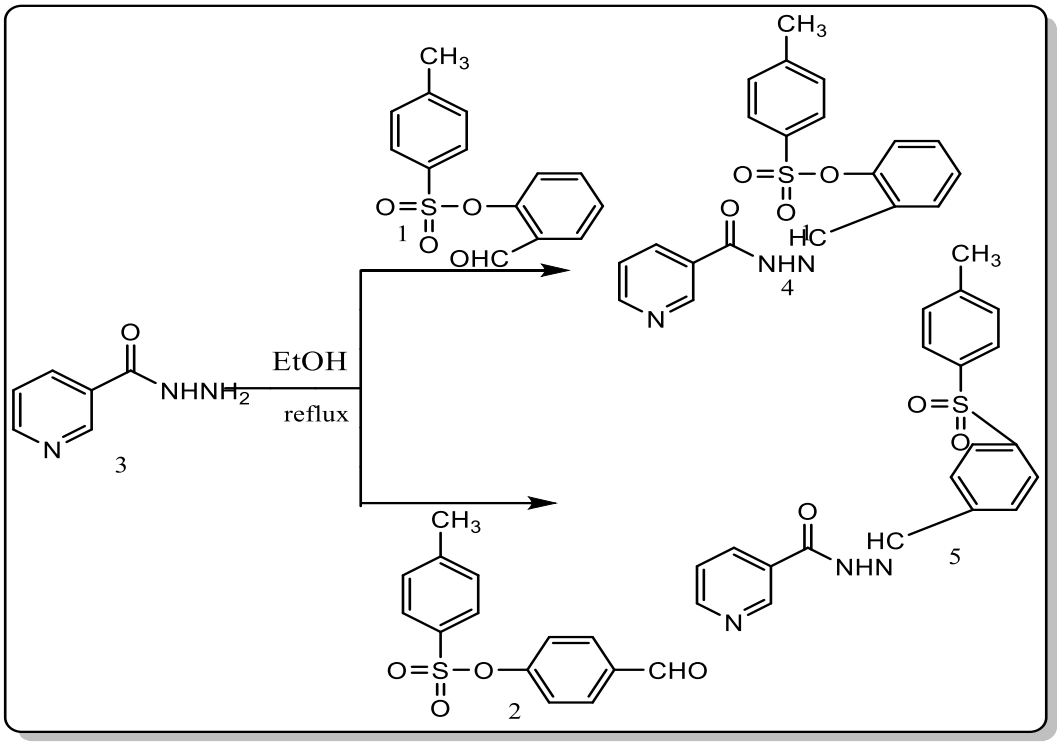

Figure 11: Scheme lead by Aboelez *et al.*,

A. Muhammad *et al.,* described the synthesis of hydrazones from the reaction of nicotinic acid hydrazide with derivatives of benzaldehydes in ethanolic solution. The solubility of the compounds presents in DMSO and methanol. These compounds showed *in vitro* antibacterial and antifungal properties[27]. **Biliz *et al.,*** A series of N-acyl hydrazones prepared from methyl *δ*-Oxo pentanoate with different substituted groups were synthesized as anticancer agents. These newly hydrazones showed the most potent anticancer activities against MCF-7 and PC-3 cells, respectively[28]. **Paruch *et al.*,** have used nicotinic acid as initial compound for undergoing series of condensation reaction with appropriate aldehydes. The result of these reaction for the formation of 12 acylhydrazones [Fig 12] [29].

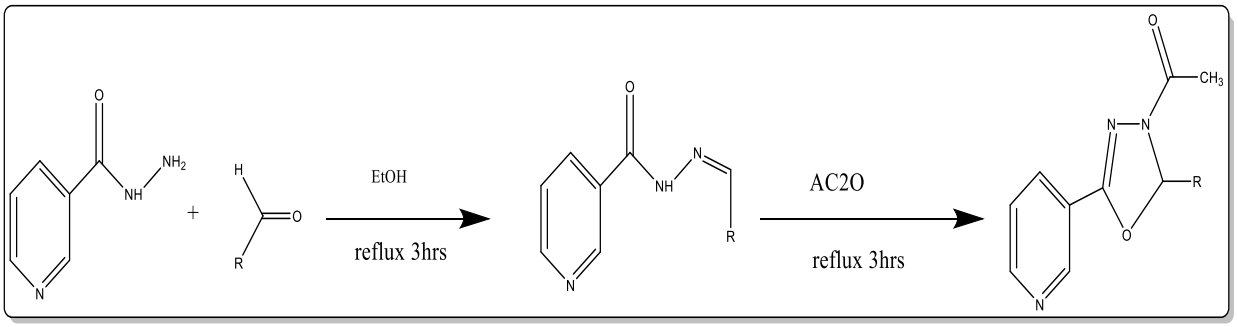

Figure 12: Scheme lead by Paruch *et al.,*

Pisk *et al.,* A series of reaction have been applied for the synthesis of hydrazones, quinazolines and hydrazones Schiff bases obtained by combining of 2,3- or 2,4-dihydroxybenzaldehyde with four hydrazides that is nicotinic, isonicotinic and 2- or 4-aminobenzoic acid hydrazide [Fig 13] [30].

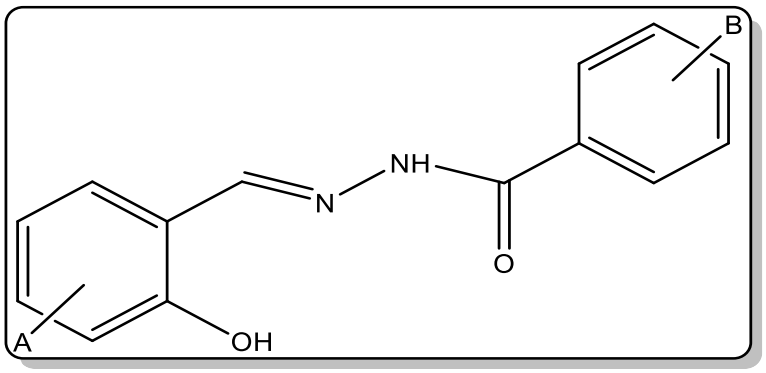

Figure 13: Scheme lead by Pisk *et al.,*

Dege *et al.,* In his research article the synthesized compounds have been reported by theoretical as well as experimental methods. The nicotinic acid [1-(2,3-dihydroxyphenyl) methylidene] hydrazide) molecule[31]. **Judge *et al.,*** have synthesized a series of isonicotonic acid hydrazide derivatives [32]. **Morjan *et al.,*** have worked on synthesis of novel N-acylhydrazones which were formed from condensation reaction of nicotinic acid hydrazide with corresponding aldehydes and ketones [33]. **Sidhaye *et al.,*** have prepared nicotinic acid hydrazide from phosphorous pentachloride and anhydrous carbon tetrachloride followed by reaction with hydrazine hydrate. The compound on further reaction with acetyl acetone, ethyl acetoacetate, ethylcyanoacetate and different substituted aromatic acids yielded the corresponding (3,5-dimethyl-1H-pyrazol-1-yl) (pyridine-3-yl) methanone 3, 3-methyl-1-nicotinoyl-1H-pyrazol-5(4H)-one 4, 3-amino-1-nicotinoyl-1H-pyrazol-5(4H)-one [34]. **Narang *et al.,*** The derivatives of nicotinic acid benzylidene hydrazide (1–18) were synthesized and tested in vitro for biological evaluations. The presence of electron-withdrawing halogen groups at para position of the phenyl ring showed increase in their biological activity [Fig 14] [35].

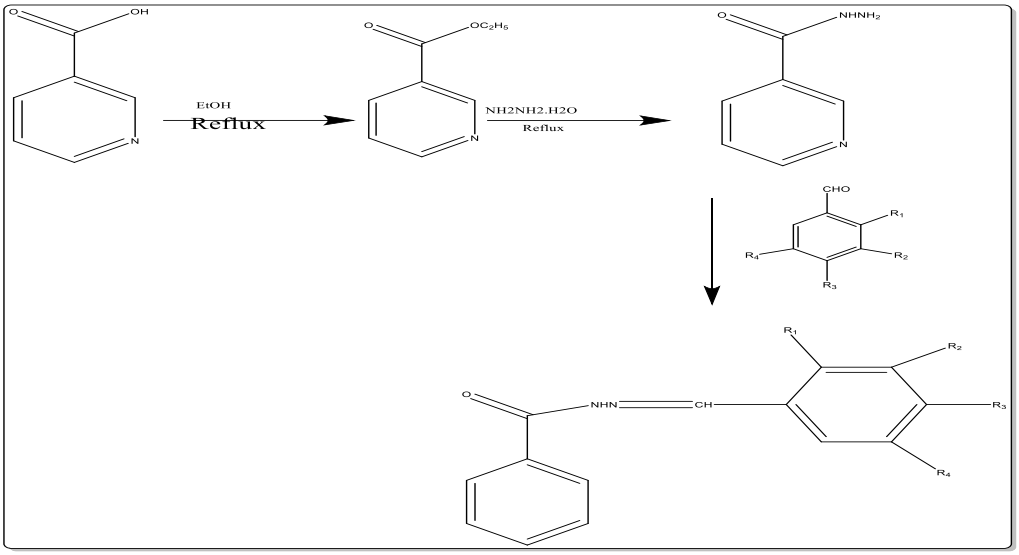

Figure 14: Scheme lead by Narang *et al.*,

Navidpour *et al.*, synthesised a new compound of 2-(3-chloroanilino) nicotinic acid hydrazides. The compounds were evaluated by showing anti-inflammatory and analgesic activities[36]. **Abdel *et al.*,** have worked on of 6-aryl-2-methylnicotonic acid hydrazides and their synthesis of hydrazones. The chemical structure of hydrazones were confirmed by X-ray single crystal diffraction [37]. **Ahmad Muhammad *et al.*,** have prepared numbered of compounds like N'-(2-pyridinylmethylene) nicotinohydrazide A, N'-(4 pyridiny-methylene) nicotine-hydrazide B, N'-(2- ethoxybenzylidene) nicotinohydrazide C, N'-(4-ethoxybenzyldene) nicotinohydrazide D and N'-(2-hydroxyl- 5-methoxybenzylidene) nicotinohydrazide E were prepared by conventional method of refluxing the ethanolic solution of nictonic acid hydrazide and ethanolic solutions of 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2- ethoxybenzaldehyde, 4-ethoxybenzaldehyde and 2-hydroxy-5-methoxybenzaldehyde with molar ratio of 1:1 M [Fig 15] [38].

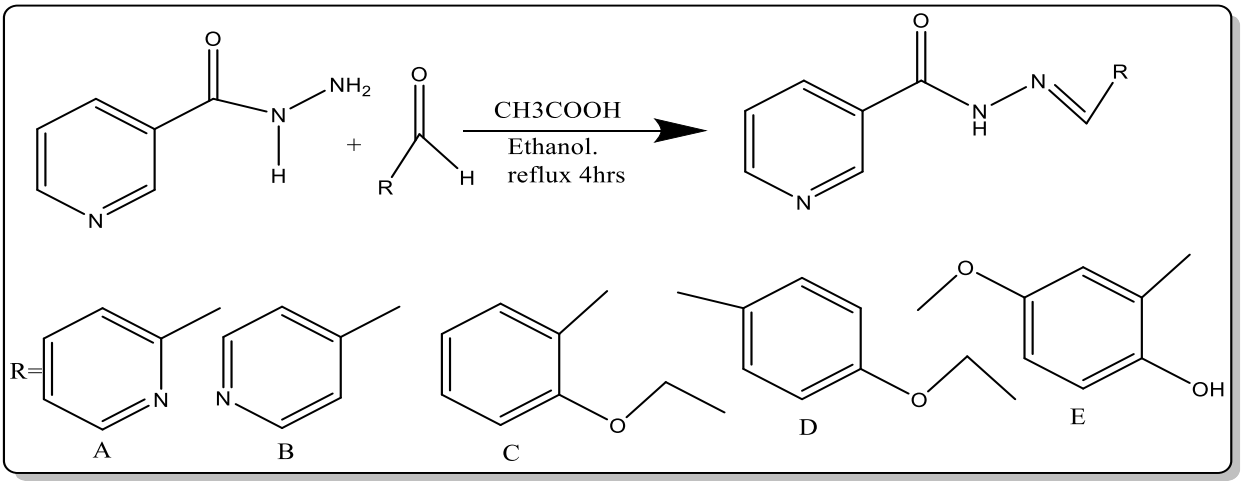

Figure 15: Scheme lead by Ahmad Muhammad *et al.*,

Krishna Mehta *et al.,* synthesized a series of substituted 2- pyrazolines derivatives by refluxing of different substituted chalcones and nicotinic acid hydrazide. The synthesized compounds were confirmed by special techniques like elemental analysis and spectra analysis [Fig 16] [39].

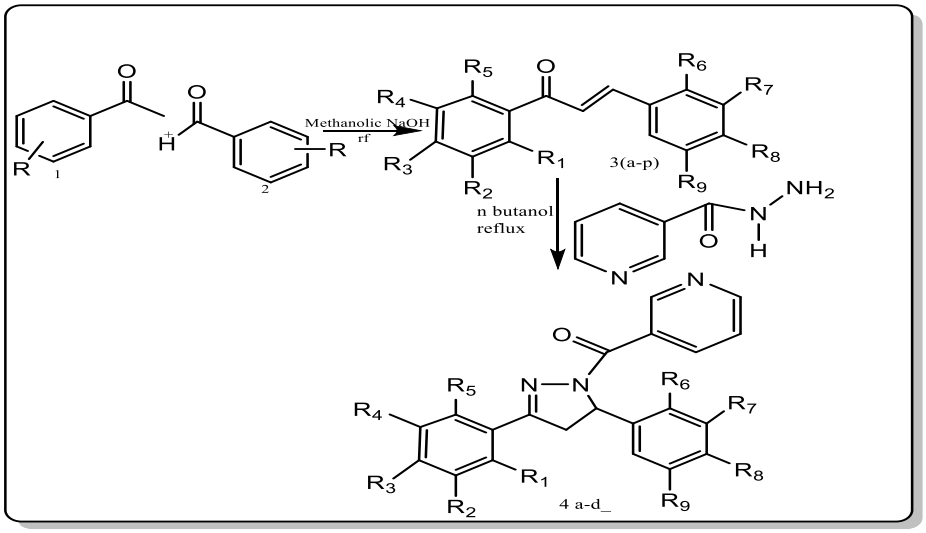

Figure 16: Scheme lead by Krishna Mehta *et al.,*

Jana Pisk *et al.,* have worked for the synthesis of various hydrazones formation (1a–4a and 1b–4b), quinazolines (3C: MeOH and 3d: MeOH) and Schiff bases hydrazones (4c-4d) gained by mixing of suitable aldehydes like (2,3- or 2,4-dihydroxybenzaldehyde) with four hydrazides as nicotinic acid hydrazide, isonicotonic and 2 or 4 amino benzoic acid hydrazides [Fig.16] [40].

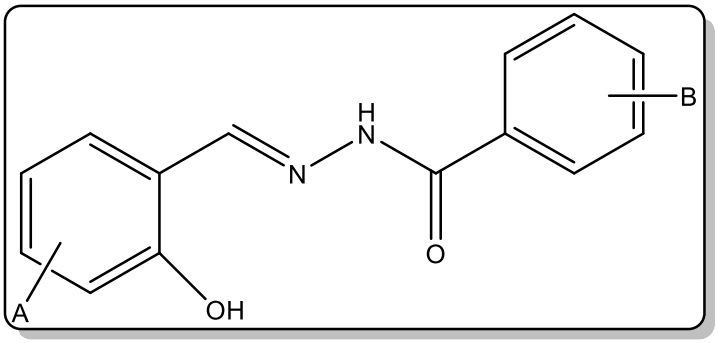

Figure 17: Scheme lead by Jana Pisk *et al.,*

N Khalifa *et al*, synthesized a hydrazones compounds obtained from 2 hydroxy acetophenone treated with nicotinic acid hydrazide and with fluoride anion. On addition of fluoride, a change in color were observed. A chemo sensing behavior of hydrazones were detected by changing in electronic environment around the N-H and O-H bonding sites receptors [Fig.18] [41]

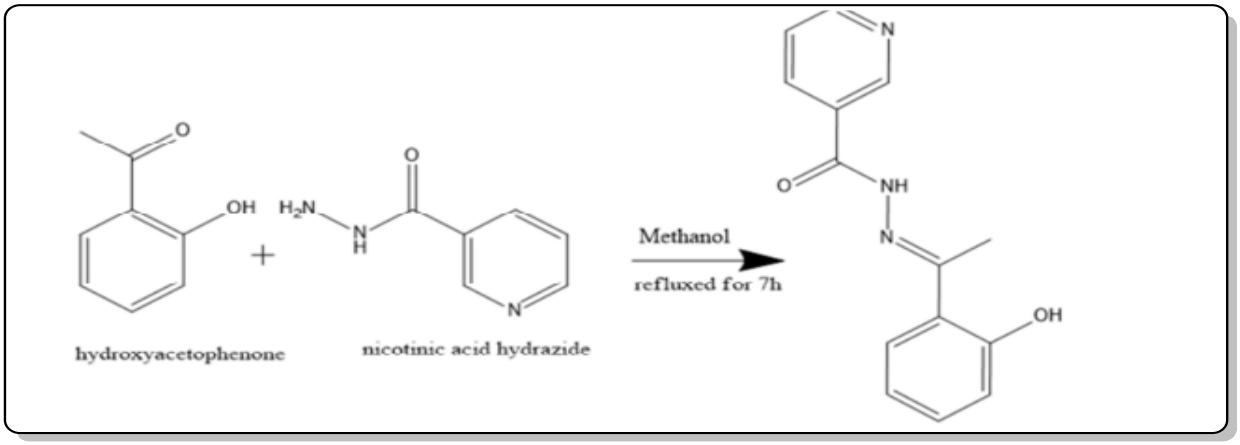

Figure 18: Scheme lead by N Khalifa *et al*,

CONCLUSION

Synthesis of hydrazones of nicotinic acid hydrazides with dicarbonyl compounds like aryl aldehydes or aryl ketones. The literature review reveals that different nicotinic acid hydrazide derivatives posses a potential biological activity and clinical applications like antidepressant, anticonvulsant, analgesic, anti-inflammatory, analgesic, antimicrobial and anticancer. The hydrazones of nicotinic acid hydrazide mostly used for tuberculosis and also act as an antibiotic role for inhibiting the growth of bacteria. The reported work shows the systematic synthesis and biological activity of nicotinic acid hydrazones.

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