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Review on Synthesis of Isoniazid Based Hybrid Derivatives

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Abstract

Isoniazid is a first-line therapy for tuberculosis infection. Clinically, it has a track record as the most successful and extensively studied anti-tubercular drug in literature. It is an aromatic molecule having one nitrogen atom in a six-membered ring connected to an acid hydrazide moiety via a ketonic functional group. The presence of highly reactive sites in the molecule is largely responsible for its therapeutic action. The attractive molecular design of Isoniazid permits the preparation of numerous derivatives incorporating suitable moieties in drug design directed towards the development of more potent molecules for treating infectious diseases. We summarized the strategies for such synthesis of Isoniazid derivatives described in the literature over the last three years in this review.

Keywords

Synthesis of Isoniazid, Mycobacterium tuberculosis, Anti-cancer; Anti-microbial, Anti-malarial, Anti-tuberculosis, Isoniazid hybrid derivatives

Introduction

One of the most fundamental and promising creative approaches for the design of new lead structures and the identification of novel and strong medications in the field of medicinal chemistry is the hybridization of bioactive natural and synthetic molecules [1]. A synthetic substance with two or more fragments obtained from natural products connected by at least one carbon-carbon bond is called a natural product hybrid (also known as a conjugate or chimaera). This concept was inspired by nature as many of the recognized natural products are composed of fragments like this that come from various biosynthetic pathways [2]. The idea of combining bioactive molecule fragments appears to offer benefits since, in light of recent developments in molecular biology and concurrent synthetic organic chemistry, an almost infinite diversity of such hybrid structures can be produced and may be available [3]. Tuberculosis (TB) is considered as a global pandemic [4]. This infectious disease mainly affects the lungs and transmitted by sneezing, coughing, direct contact with patients and breathing in a bacteria-polluted environment [5]. If untreated, the disease also affects different parts of the body such as bones, liver, heart, brain and kidney. TB is an infectious disease of concern because its symptoms appear after many weeks or months, or in some cases after years of the infection. During this period, transmission to another person can occur [6]. The tuberculosis-causing organisms are part of the Mycobacterium tuberculosis complex (TB). This micro-organism is mostly a pulmonary pathogen (causing pulmonary TB), but it can also spread disease to any other portion of the body, which is known as extrapulmonary TB. Latent TB infection (LTBI), which affects a portion of the population, is asymptomatic, not contagious, and often treatable [7,8].

Drugs Containing Isoniazid Moiety:

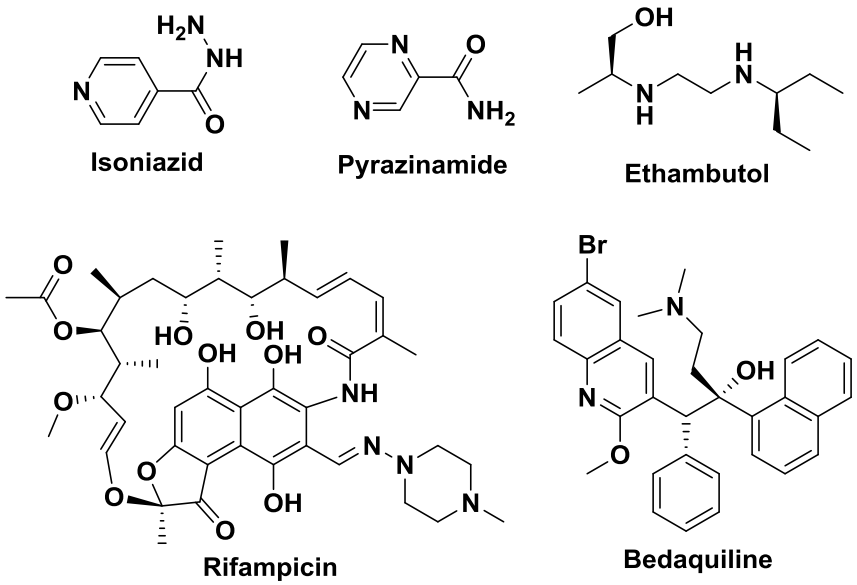


Figure 1. Structures of Different Antitubercular Drugs.

Due to its wide range of biological effects, including its analgesic, anti-convulsant, anti-viral, anti-fungal, anti-tumor, and anti-mycobacterial qualities, nitrogen-containing heterocycles have gotten a lot of attention in medicinal chemistry [9-16]. Pyridine ring as a heterocyclic moiety has been found to have several activities present in drugs, flavorings, dyes, plants, food, adhesives, vitamins, rubber products, insecticides, and herbicides [17]. One such pyridine containing compound is Isoniazid, known commonly by its chemical names isonicotinic acid hydrazide or isonicotinyl hydrazine – often abbreviated as INH. Meller and Malley in 1912 first reported Isoniazid [18], and in 1951 its anti-TB property was disclosed. Isoniazid has the molecular weight of 137.14, the chemical formula $C_6H_7N_3O$, and a melting point between 171°C and 173°C. The structure of Isoniazid is provided in Figure 1. Isoniazid not only has anti-tubercular activity [19-21], but it also has several other properties which have not yet found significant attention such as anti-mycobacterial [22], anti-bacterial [23-24], anti-viral [25], anti-microbial [26], anti-malarial [27], anti-fungal [28-31], anti-cancer [32-34], analgesic [35], anti-convulsant [36-38], anti-corrosive and anti-inflammatory activities [39-41]. The primary need for the development of more potent Isoniazid derivatives is because the bacterium *Mycobacterium tuberculosis* (Mtb) is now known to be resistant towards Isoniazid and Pyrazinamide (PZA), Ethambutol (EMB), Rifampicin (RIF), and Bedaquinine are among more first-line medicines. (Figure 1) [42, 43].

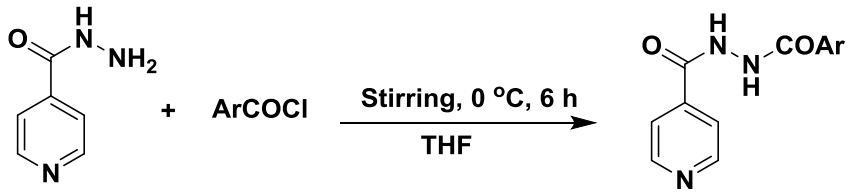
Nearly 5000 people die from tuberculosis every day, which affects one-fourth of the world's population [44]. Multidrug-resistant tuberculosis (MDR-TB) is still a serious public health issue and a security risk, nevertheless. Globally, 206,030 patients with rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB) were found and informed in 2019, an increase of 10% from 186,883 in 2018 [45]. All around the world, there are cases of tuberculosis (TB). In 2019, according to WHO the South-East Asian region of saw the largest percentage of new TB cases (44%) followed by the African region (25%) and the Western Pacific region (18%). 87 percent of new TB cases in 2019 were concentrated in 30 countries

with high TB burdens. Two-thirds of newly discovered TB cases were found in India, Indonesia, China, Pakistan, Nigeria, the Philippines, Bangladesh, and South Africa. The WHO estimates that the TB epidemic will be eradicated by 2030 if the United Nations Sustainable Development Goals (SDGs) are met.

Keeping in view the worldwide spread of the disease; its potential effect on public health; the evolving resistance to drugs including Isoniazid; the potential for development of various derivatives of INH with better properties and improved anti-tubercular activity, it is important to explore methods of synthesis of new Isoniazid derivative compounds. Isoniazid and its derivatives have been the subject of several reviews outlining their synthetic and biological potential [46-50]. These reviews provide important insights into the synthetic routes adopted so far. A careful study of such previously published articles will help other scientists to understand the rationale behind the change in properties of referenced compounds in this review articles and will also help them in designing novel compounds in the future.

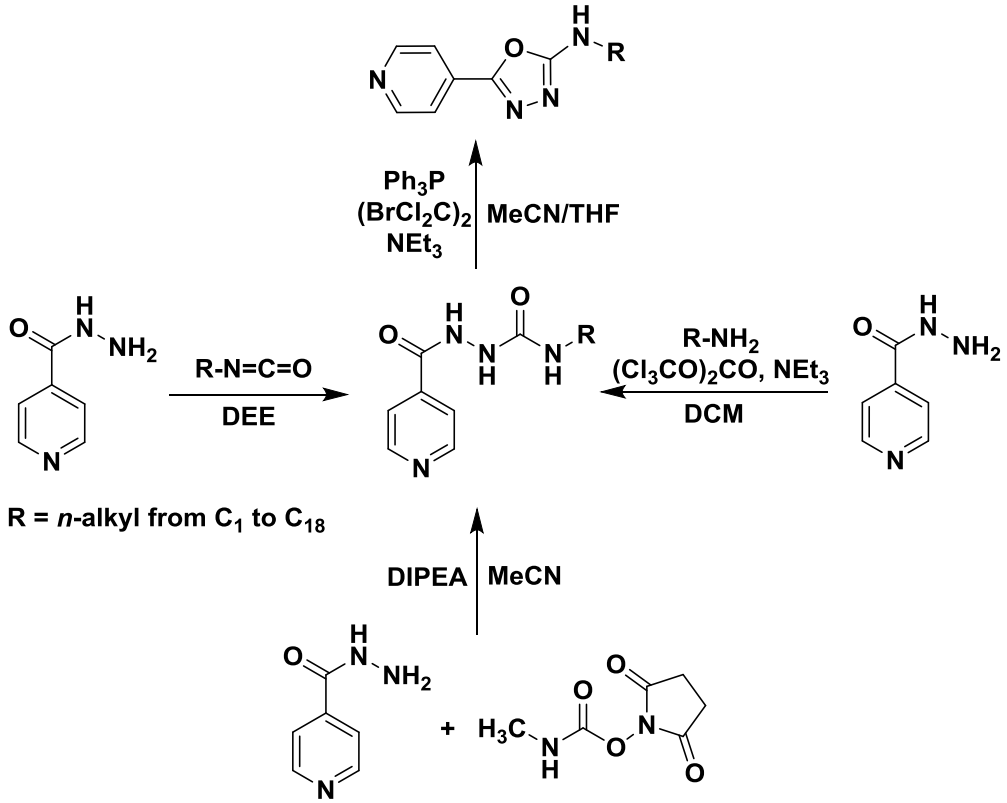
Synthetic Strategies

As depicted in Scheme 1, Dhaneshwar et al produced amide prodrugs of isoniazid and phenolic acids using the Schotten Baumann reaction (gallic acid, syringic acid, and vanillic acid) [51].



Scheme 1. Synthesis of Prodrug of Isoniazid

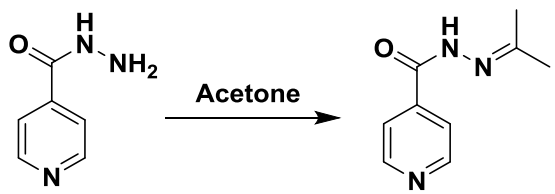
The majority of N-alkyl-2-isonicotinoylhydrazine-1-carboxamides were produced by Vinová et al. (Scheme 2) utilising isoniazid and easily accessible isocyanate (Method A; yields 72-92%) [52]. Using N-succinimidyl N-methylcarbamate as a methyl isocyanate substitution and isoniazid in the presence of N,N-diisopropylethylamine (DIPEA; Method B with 87% yield), 2-isonicotinoyl-N-methyl hydrazine-1-carboxamide was produced. With yields of 65-76%, three carboxamides were made using the appropriate amines, triphosgene (bis(trichloro methyl)carbonate), and isoniazid. (Process C).



Scheme 2. Synthesis of *N*-alkyl-2-isonicotinoylhydrazine-1-carboxamides and their derivatives

N-substituted 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-amines were created by cyclizing the 2-isonicotinoyl-hydrazine-1-carboxamides with triphenylphosphine in anhydrous solvent with 1,2-dibromo-1,1,2,2-tetra chloroethane. They had yields ranging from 52 to 68 percent [53].

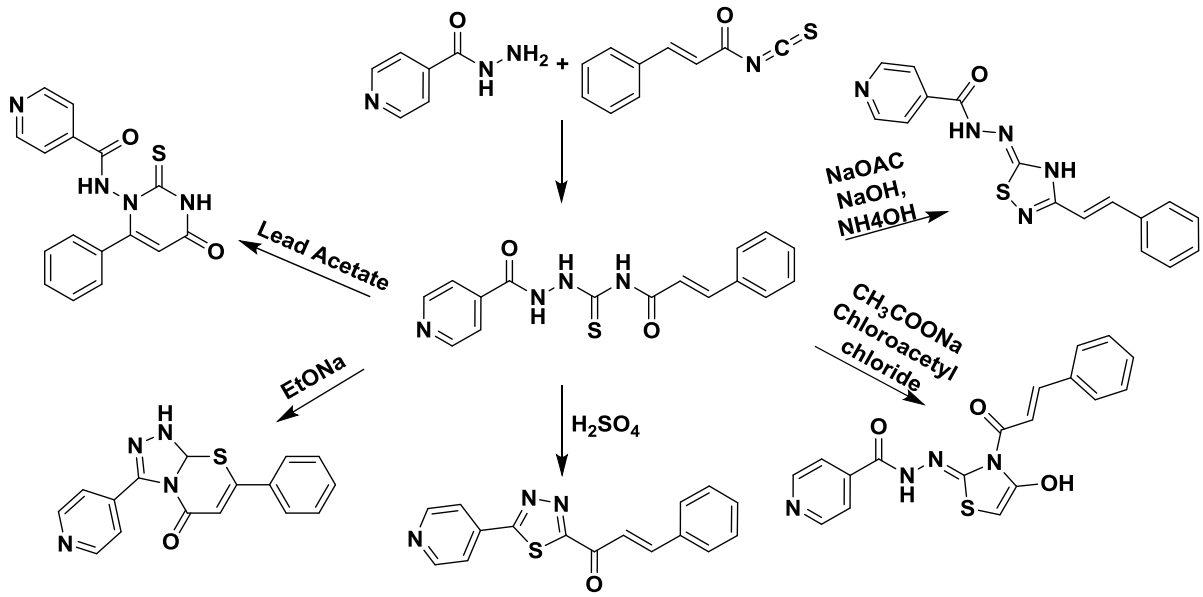
Su et al in Scheme 3 illustrates the chemical process used to create N-(propan-2-ylidene)-isonicotinohydrazide. Isoniazid was dissolved in acetone and placed into the jacket crystallizer. In this instance, acetone is used as both the reactant and the solvent. The reaction temperature was set at 318 K. Following complete dissolution of salicylamide, the temperature of the jacket crystallizer was decreased to 5 ^{o}C at a rate of 20 C/h. During cooling, power ultrasound was introduced at a programmed sonication intensity and duration. The crystals were then filtered using filter paper, and the resulting wet cake was dried in a 50° Celsius oven [54].



Scheme 3. Reaction scheme for the synthesis of *N*-(propan-2-ylidene)-isonicotinohydrazide

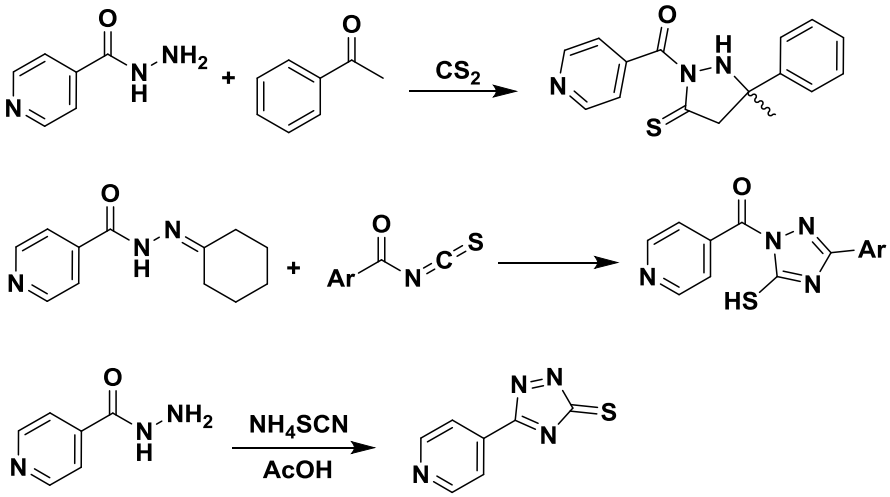
In accordance with Scheme 4, Farhan et al. showed that N-(2-isonicotinoylhydrazine-carbonothioyl) cinnamamide was produced by the Michael addition reaction between isoniazid and cinnamoyl isothiocyanate, hydrogen transfer, and 1,3-H shift [55]. Triazolothiazine was obtained by heating thiosemicarbazide with sodium ethoxide, followed

by thiazine cyclization, cyclocondensation, and dehydration. The acylation of cinnamoyl thiosemicarbazide with chloroacetyl chloride while sodium acetate was present yielded the thiazole derivative. The reaction can begin with the formation of the anion of the more acidic NH, followed by chloroacetylation and enolization to create the final product, as shown in Scheme 4 [56].



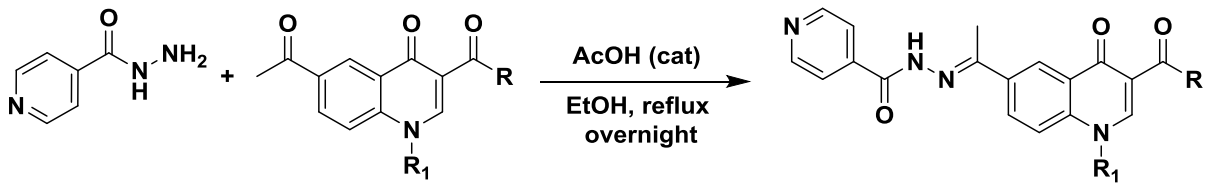
Scheme 4. Synthesis of *N*'-(2-isonicotinoylhydrazine-1-carbonothioyl)cinnamamide and their derivatives

By cyclizing the Schiff base, the compound was treated with carbon disulfide and KOH to produce thiadiazolothione. Triazolothione was created in one step by adding hydrazide to ammonium thiocyanate by thiosemicarbazide N-cyclization and oxidation. Arylisothiocyanates (Ar = Ph, PhCH=CH) and hydrazone were combined to create triazolothione. According to Scheme 5 [56], the production of thiosemicarbazone, followed by cyclodehydration and enamine hydrolysis, may occur before the reaction [57,58].



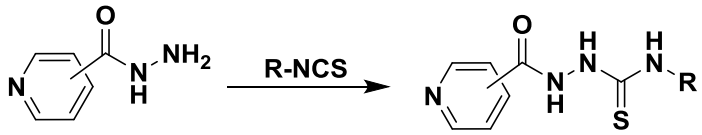
Scheme 5. Synthesis of 1,3,4-thiadiazole and 1,3,4-triazole

Khanye et al. synthesized quinoline isoniazide hybrids in ethanol and catalytic amount of acetic acid under overnight reflux. (Scheme 6) [59].



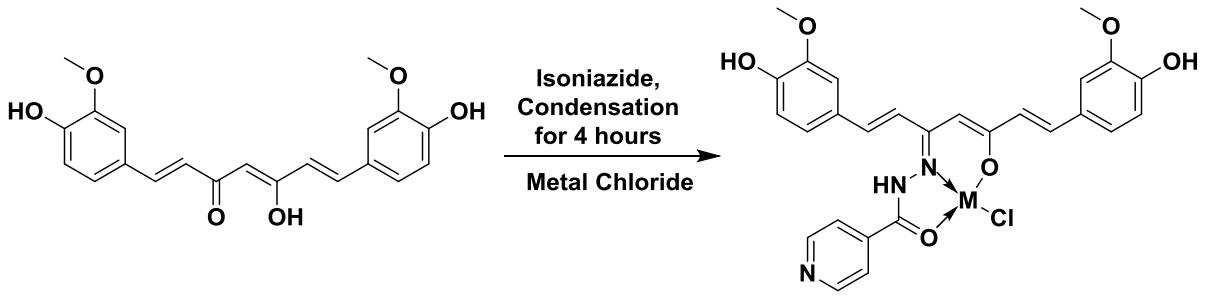
Scheme 6. Synthesis of Quinolone-isoniazid hybrids

Pitucha et al synthesized isoniazide analogues containing thiosemicarbazide system with potential antitubercular activity (Scheme 7) [60, 61].



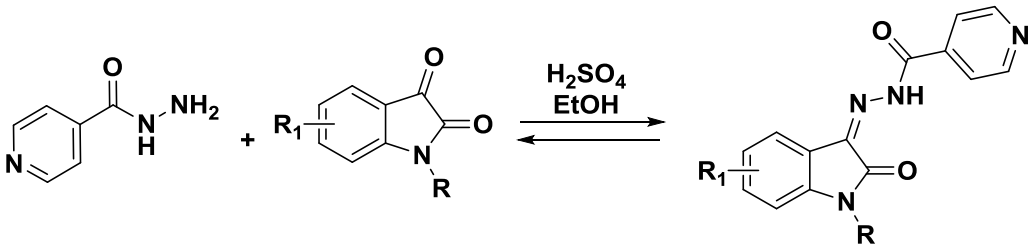
Scheme 7. Synthesis of Thiosemicarbazide Derivatives

Raman et al. investigated Isoniazide-hydrazone metal complexes and studied their electrolytic character. The metal chloride employed (Cu(II), Ni(II), Co(II), and Zn(II) in a ratio of 1:1. The geometry and composition of metal complexes are predicted using a variety of spectroscopic and analytical techniques. The non-electrolytic character of metal complexes is revealed through conductive measurements. Schemes 8 [62] shows the schematic techniques for the production of ligand and metal complexes.



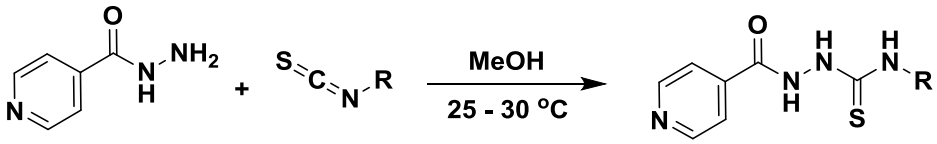
Scheme 8. Synthesis of Isoniazide hydrazone metal complexes.

Fahmi et al. investigated how substituents and the heterocyclic moieties affected the antitubercular activity of isoniazide-hydrazone hybrids against Mycobacterium TB H37Rv [63,64]. Hydrazone derivatives were obtained by condensing hydrazine and carbonyl compounds in acidic conditions [65]. In acidic conditions, the condensation reaction between hydrazine and carbonyl compound can be carried out (Scheme 9) [66].



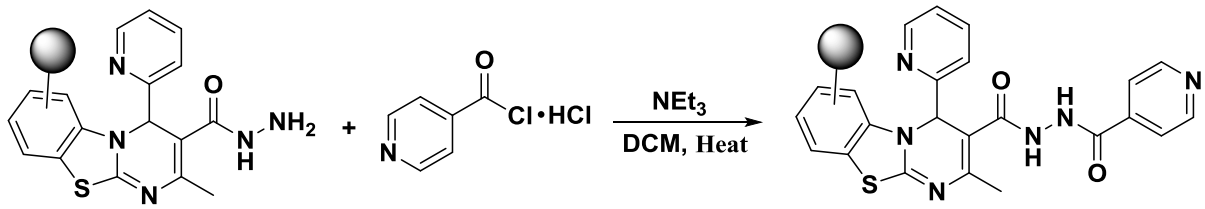
Scheme 9. Condensation reaction between hydrazine and carbonyl compounds to form hydrazone derivatives

Siddiqui et al. have created thiosemicarbazide derivatives of isoniazid by interacting with various isothiocyanates at the terminal NH_2 (Scheme 10) [67, 68].



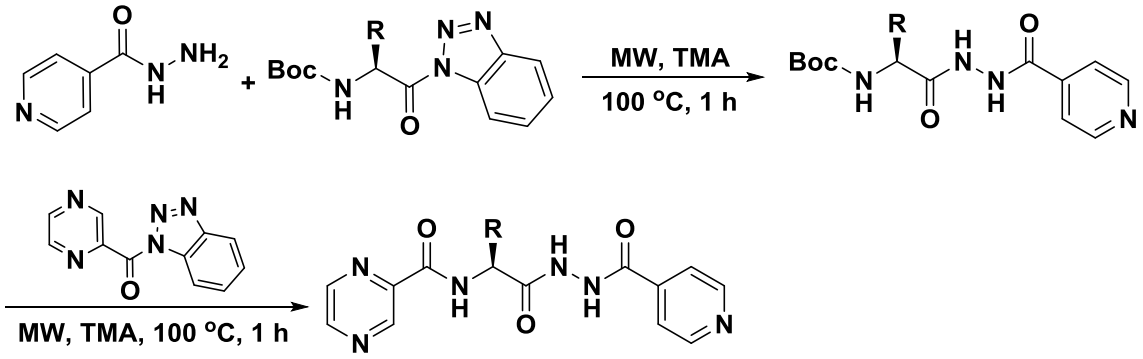
Scheme 10. Synthesis of thiosemicarbazide derivatives of isoniazid

Patel et al illustrated the titled compounds were synthesized by a sequence of reaction shown in Scheme 11. The intermediate hydrazine hydrate derivative dissolved in dichloromethane and reacted with hydrochloride salt of isonicotinoyl chloride using triethylamine as a base to yield *N*-isonicotinoyl-2-methyl-4-(pyridin-2-yl)-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carbohydrazide derivatives with good (65-80%) practical yield [69].



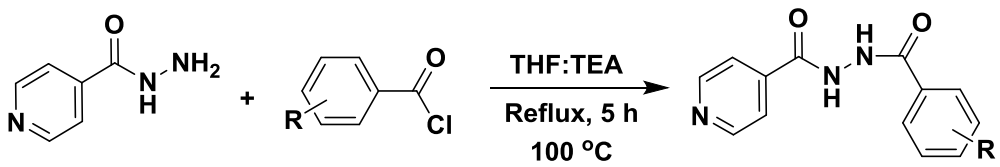
Scheme 11. Synthetic protocol for the synthesis of isoniazid-based compounds

By activating the Boc-protected amino acids with 1H-benzotriazole, Panda et al. created the pyrazinoic acid-Isoniazid hybrids that were initially examined. In accordance with the described approach [70], the pyrazinoic acid was activated as a benzotriazolyl derivative, and it was then coupled with free amino acids for two hours at 20 ^{o}C in the presence of 1.5 equivalents of trimethylamine to produce coupled compounds. To obtain our desired conjugates in good yields without compromising the chiral integrity, these compounds were microwave-irradiated with isoniazid in the presence of trimethylamine at 100 ^{o}C for 1 h [71].



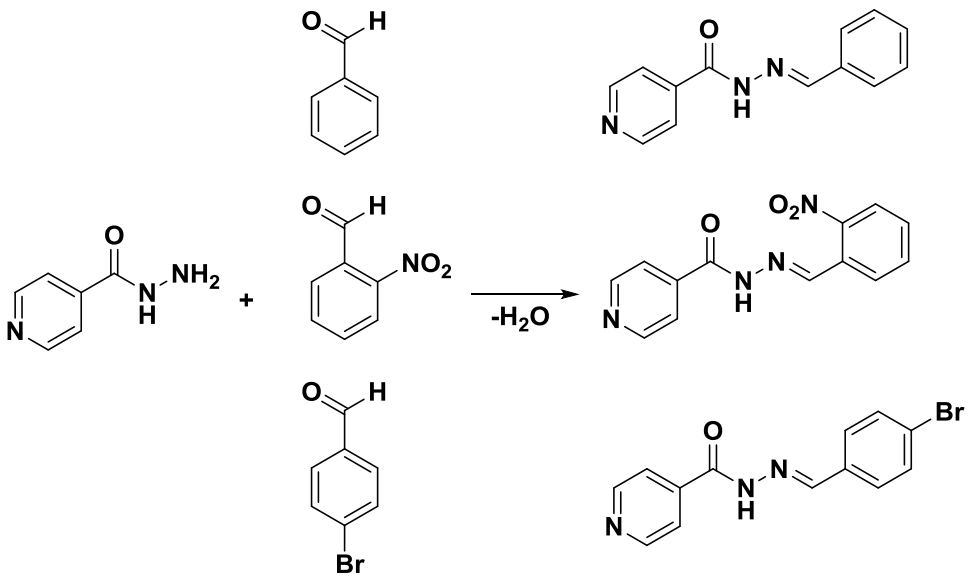
Scheme 12. Synthesis of pyrazinoic acid-Isoniazid hybrids

N'-benzoylisonicotinohydrazide derivatives, as indicated in Scheme 13, were synthesized from isonicotinohydrazide and benzoyl chloride in a single step by Ruswanto et al. Nucleophilic acylation of benzoyl chloride derivatives with isonicotinohydrazide yielded N'-benzoyl-isonicotino-hydrazide derivatives; the nucleophile was isonicotino hydrazide [72].



Scheme 13. Synthesis of the *N*'-benzoylisonicotinohydrazide derivatives.

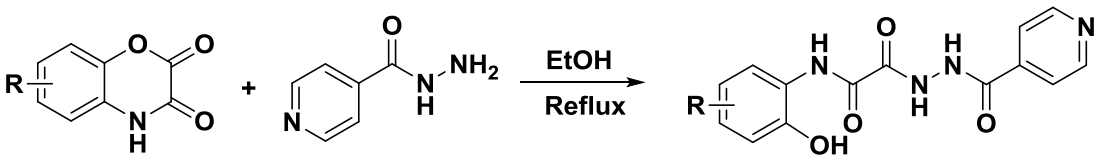
A 1:1 molar ratio condensation reaction between isoniazid and benzaldehyde, 2-Nitro-benzaldehyde, and 4-Bromo-benzaldehyde was demonstrated by Dragostin [73] and Stan [74] et al.



Scheme 14. The general scheme for obtaining the three isonicotinoylhydrazones

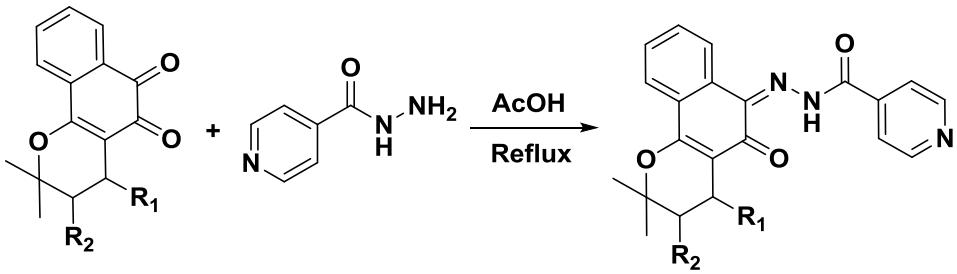
Zampieri et al. created the isoniazid-analogues by treating isoniazid with 2H benzo[β][1,4] oxazine-2,3(4H)-dione intermediates with the substituted 6-chloro and 7-chloro intermediates

with a typical Schiff reaction to yield the oxoacetamide compounds in place of the anticipated benzoxazin-3-one-isoniazid hybrids [75].



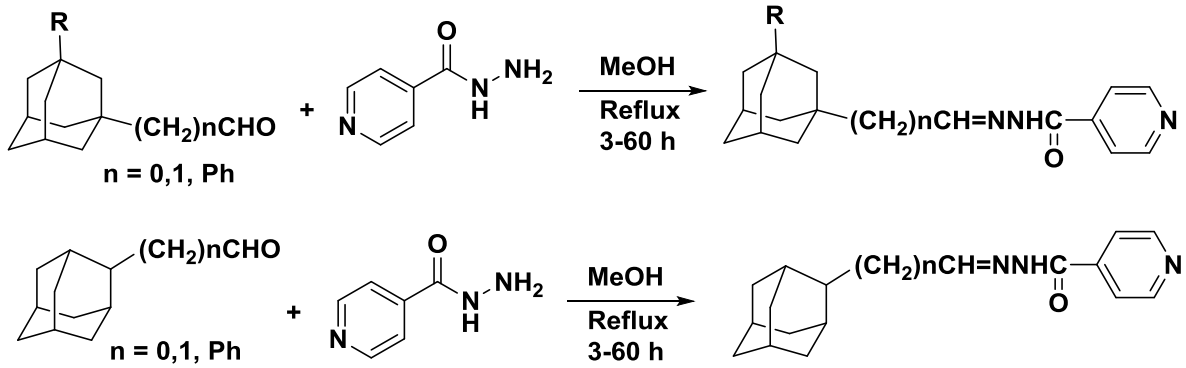
Scheme 15. Synthesis of the Benzoxazinone derivatives and open-ring analogues

Silva Junior et al. found that the isoniazid-naphthoquinone hybrid compounds could be easily made by refluxing the appropriate quinone and isoniazid in acetic acid. β-lap analogues and their hybrids were isolated as crystalline solids in modest yields (Scheme 16) [76].



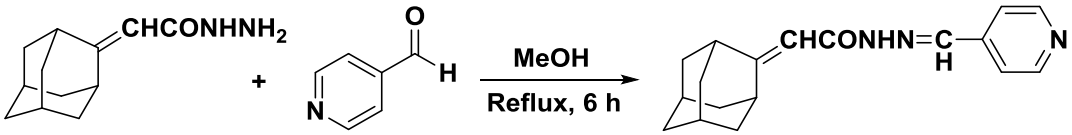
Scheme 16. Synthesis of β-lap analogs and their hybrid derivatives

The synthesis of the adamantane hydrazones developed by Papanastasiou et al. [77] is shown in Scheme 17a–17b. The equivalent carbohydrazide hydrazones were produced by refluxing the adamantane aldehydes, 1-adamantanecarboxaldehyde, 1-adamantan-eacetaldehyde, 3-phenyl-1-adamantanecarboxaldehyde, 3-cyclopentyl-1-adamantane-carboxaldehyde, and 2-adamantanecarboxaldeh Due to their higher activity, 4-(1-adamantyl) and 4-(2-adamantyl) benzaldehydes conducted the same reaction at room temperature. For 10 hours, isoniazid was refluxed with 1,3-adamantanedicarboxaldehyde to produce the bis-substituted adamantane hydrazone. The 1-adamantanecarbohydrazide and 1,3-adamantanedi-carbohydrazide, which were combined with 4-pyridinecarboxaldehyde, were used to make the isomeric carbohydrazide hydrazones.



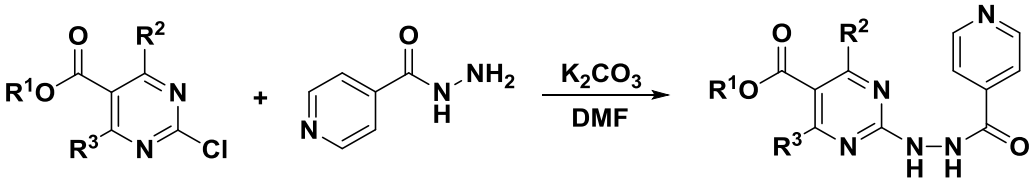
Scheme 17a. New isoniazid-based adamantane derivatives

After that, the hydrazide was transformed to unsaturated hydrazone. The traditional approach for preparing acyl hydrazides, equivalent to the acyl hydrazide, was not followed because it resulted in a pyrazolidinone by-product due to an intramolecular Michael addition [78].



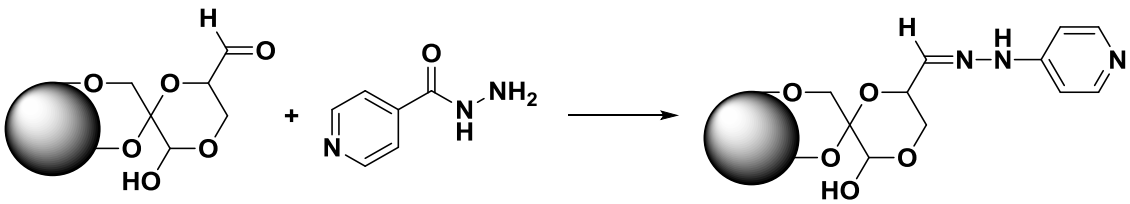
Scheme 17b. New isoniazid-based adamantane derivatives

Alkyl 4-methyl/phenyl-2-pyrimidines (2 isonicotinoyl hydrazinyl) were produced in high yields (84–96%) by Singh et al. using a nucleophilic substitution reaction between chloro-pyrimidines and isoniazid (Scheme 18) [79].



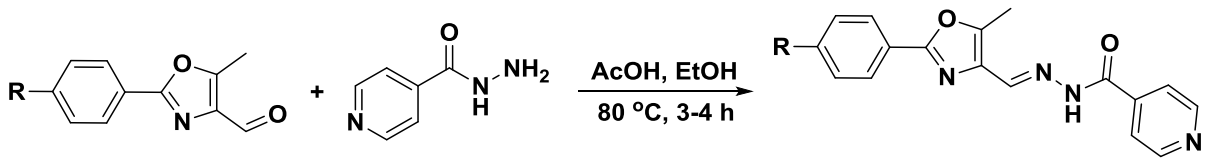
Scheme 18. Synthesis of isoniazid–pyrimidine conjugates

Periodate oxidation of polysaccharides including inulin, dextran, starch, and cellulose allows the covalent attachment of amine to generate acid-labile Schiff base bonds, according to Garg et al. Isoniazid to inulin conjugation was a two-step reaction procedure (Scheme 19). To begin, sodium periodate was used to oxidise the vicinal hydroxyl groups on inulin, leading in the creation of a highly reactive hemiacetal aldehyde derivative. The INH hydrazide group was conjugated to the oxidised inulin aldehyde group via hydrazone linkage in the second stage [80].



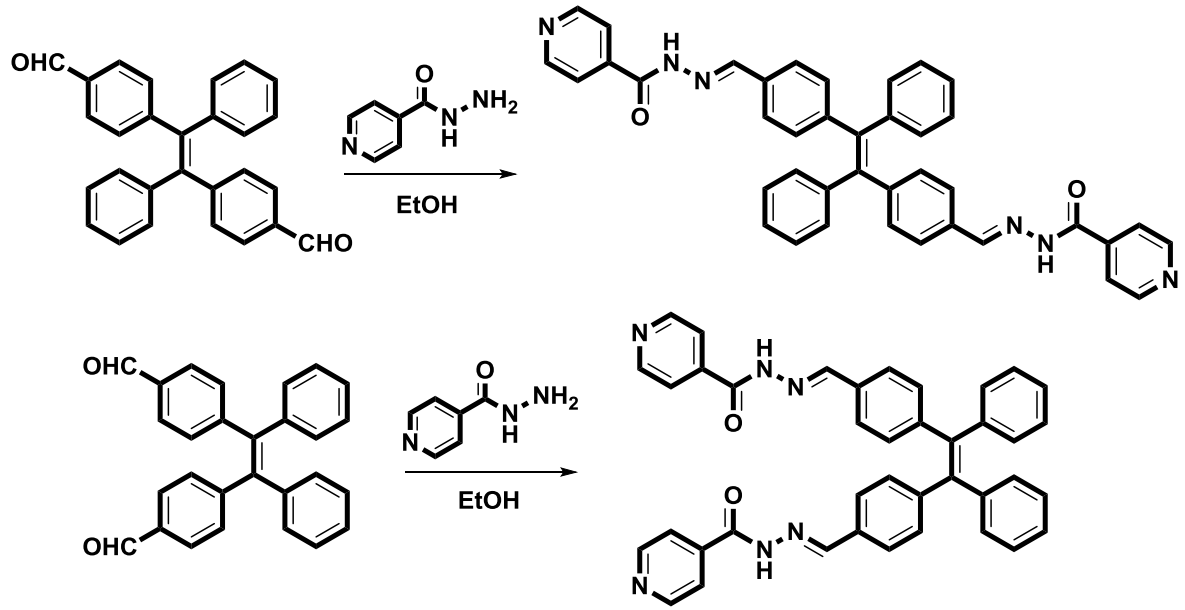
Scheme 19. Coupling of isoniazid to inulin particles

Katariya et al prepared the 2-aryl-5-methyl-1,3-oxazole-4-carbaldehydes were obtained by reacting 2-aryl-4-(chloromethyl)-5-methyl-1,3-oxazoles with bis-TBAC (Bis-Tetrabutyl ammoniumdichromate) in chloroform (Scheme 20). To further understand the interactions between powerful hybrids and the target enzyme, molecular docking studies were conducted against the InhA enzyme. As a result, these kinds of hybrids have the potential to lead to the development of novel antitubercular agents that could be used to combat and eradicate tuberculosis [81].



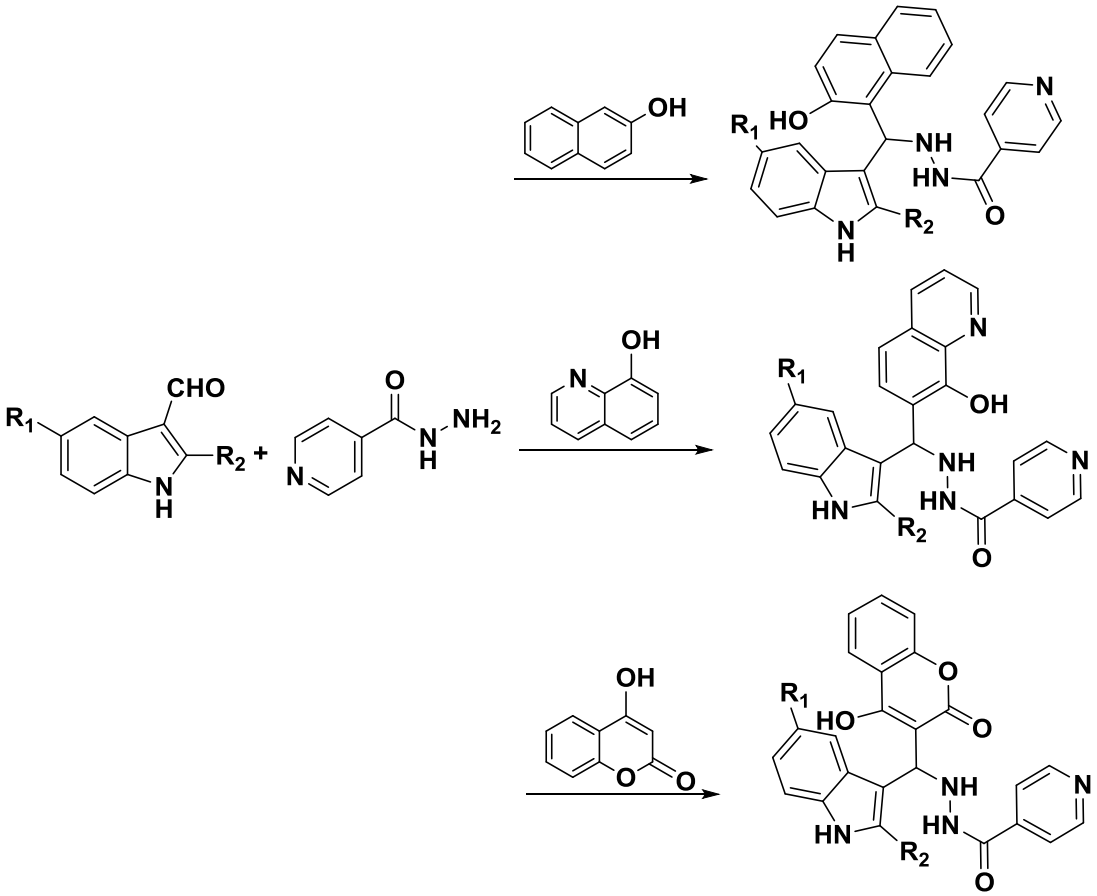
Scheme 20. Synthesis of 1,3-oxazole-isoniazid hybrids

The yellow and pink 1,2-bis-(4-methylphenyl)-1,2diphenylethene derivatives were produced by Zhang et al using a Schiff base condensation process with isoniazid in ethanol as shown in Scheme 21 [82]. When heated in methanol, the configuration of 1,2-bis-(4-methylphenyl)-1,2diphenylethene aldehyde did not change, and the spatial configuration did not change following the reaction with isoniazid.



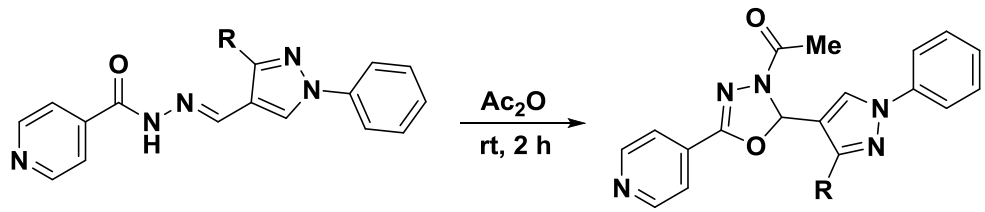
Scheme 21. Synthesis of Isoniazid based 1,2-bis-(4-methylphenyl)-1,2diphenylethene derivatives

Rathod et al. generated isoniazid derivatives with varied indole and phenol fragments by combining substituted indole-3-carbaldehydes with isoniazid and naphthalen-2-ol, quinolin-8-ol, or 4-hydroxycoumarin in a one-pot synthesis under three different reaction conditions. In order to create the matching Schiff base, which acted as an electrophile toward the phenolic molecule to produce the desired isoniazid derivatives, the main amino group of the isoniazid was nucleophilically attached to the carbonyl group of indole-3-carbaldehyde (Scheme 22) [83].



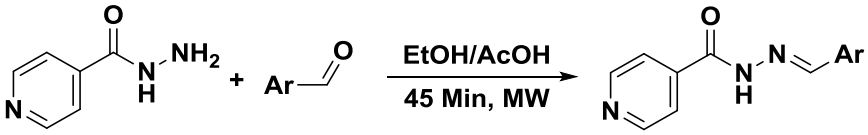
Scheme 22. Synthesis of indole and isoniazid derivatives

Chaudhary et al. developed a quick and effective ultrasound-assisted procedure for cyclizing isoniazid hydrazones into 2,5-bishetaryloxadiazolines at room temperature. Acetic anhydride supported intramolecular oxidative cyclization together with N-acylation of oxadiazoline [84].



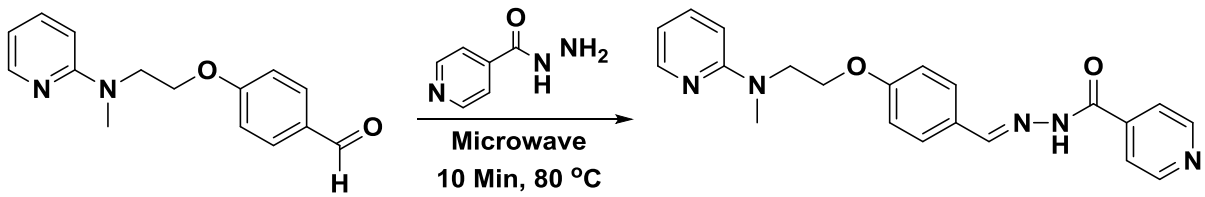
Scheme 23. Facile synthesis of isoniazid derivatives

Because the condensation methods for making acylhydrazones require heating under reflux for longer than an hour, the syntheses were done under high pressure in a microwave reactor to hasten the creation of derivatives. According to Scheme 24, isoniazid and the associated aldehydes were subjected to a 45-minute microwave-assisted reaction at 140 °C in ethanol as the solvent. Following that, acylhydrazone derivatives were generated in good to excellent yields (65–95%) [85].



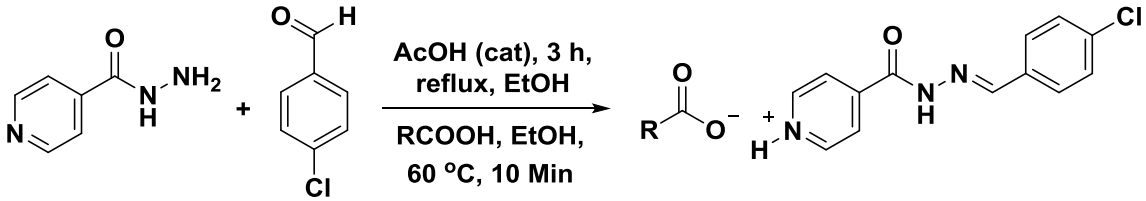
Scheme 24. Synthesis of acylhydrazone derivatives of Isoniazid

Microwave-assisted synthesis of N′-(4-(2-(methyl(pyridin-2- yl)amino)ethoxy) benzylidene) isoniazid was described by Chaouiki et al. The isoniazid (E)-N′-(4-(2-(methyl(pyridin-2-yl)amino) ethoxy) benzylidene) was synthesised, described, and investigated experimentally and theoretically as an MS corrosion inhibitor in HCl. In general, the findings of this investigation show that the inhibitory impact of INH inhibitor is particularly striking due to its functional features [86].



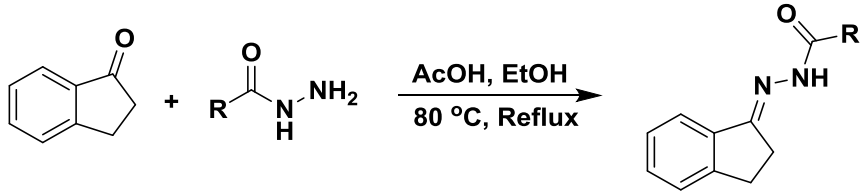
Scheme 25. Synthesis of *N*′-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy) benzylidene) isonicotinohydrazide

Ramya Rajan et al. showed that reacting isoniazid with p-chlorobenzaldehyde at reflux produced the needed starting material, which was then complexed with the appropriate carboxylic acids to produce multiple isoniazid-hydrazone complexes. Scheme 26 depicted the synthesis method for isoniazid-hydrazone complexes [87].



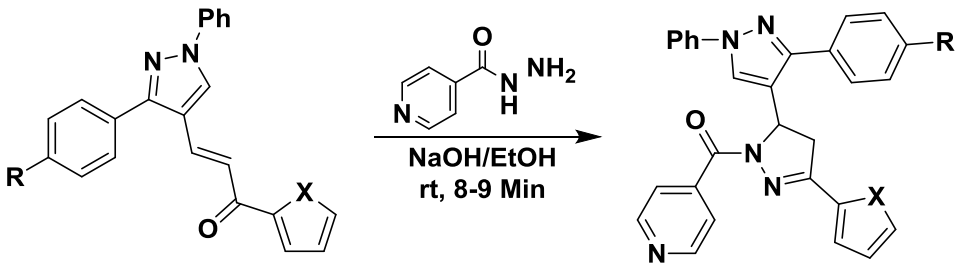
Scheme 26. Synthetic route for isoniazid-hydrazone complexes

Ali et al. created a 1-indanyl isoniazid Schiff base by using traditional methods to functionalize isoniazid at N-2. By combining isoniazid with 1-indanone, a ketone, in ethanol at 800 oC and utilising glacial acetic acid as a catalyst, the equivalent Schiff base was created. Similar hydrazides were treated with 1-indanone at the same temperature, with the same solvent, and with the same catalyst to create other hydrazide Schiff base derivatives. [88].



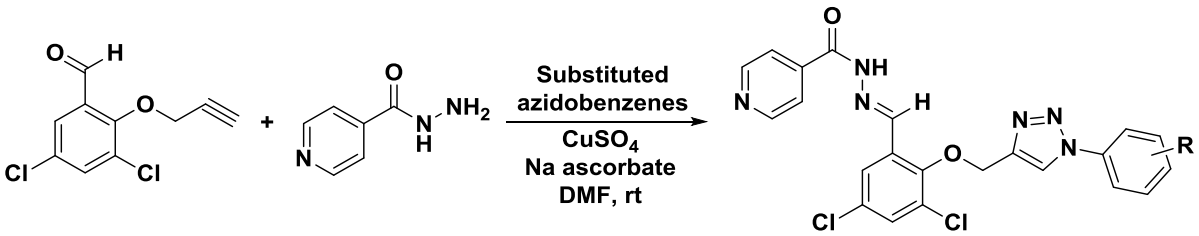
Scheme 27. Synthesis of novel 1-indanyl isoniazid and hydrazide derivatives

The crucial intermediates, chalcones, were synthesised in high to outstanding yields by base-catalyzed Claisen–Schmidt condensation of aldehydes with 2-acetylthiophene and 2-acetylfuran in aqueous ethanol at room temperature in the presence of NaOH (5 mol%). Cyclization of these chalcones with isoniazid in ethanol at room temperature using NaOH as a catalyst yielded Isoniazid-Hydrazide moieties (Scheme 28) [89].



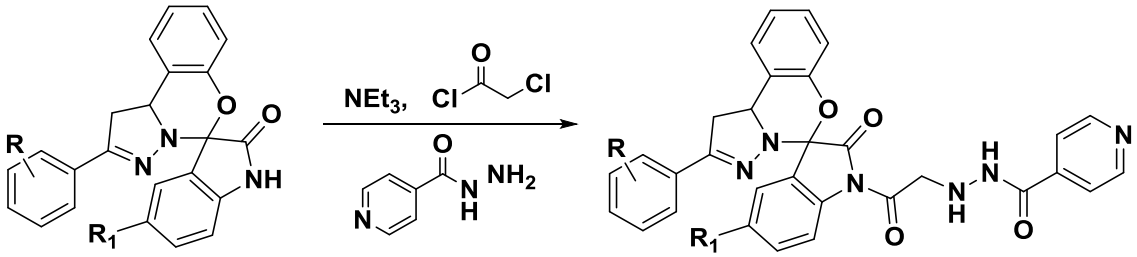
Scheme 28. Synthesis of Isoniazid-Hydrazide Moieties

The isoniazid-1,2,3-triazole derivatives were synthesised by Haval et al using the chemical sequence outlined in Scheme 29. The condensation of 3,5-dichloro-2-(prop-2-yn-1-yloxy)benzaldehyde and isonicotinohydrazide was performed in diisopropylethylammonium acetate (DIPEAc) to furnish the (E)-N'-(3,5-dichloro-2-(prop-2-yn-1-yloxy)benzylidene) isonicotinohydrazide. Cycloaddition Click reaction of (E)-N'-(3,5-dichloro-2-(prop-2-yn-1-yloxy)benzylidene) isonicotinohydrazide and various substituted azidobenzenes by using $CuSO_4.5H_2O$ and sodium ascorbate was performed to obtain the corresponding (E)-N'-(3,5-dichloro-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzylidene)isonicotinohydrazide derivatives in 80-90% yields [90].



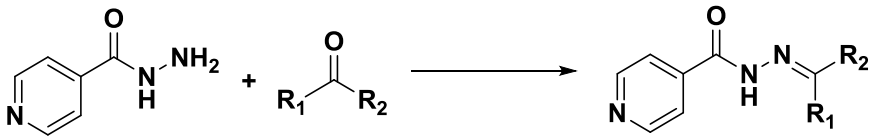
Scheme 29. Synthesis of isoniazid-1,2,3-triazole derivatives

The intriguing spirooxindole derivatives were created by Patel et al. They reacted with chloroacetyl chloride in the presence of triethylamine at 0 °C, and then with isoniazid to produce N'-(2-oxo-2-(2-oxo-2-phenyl-1,10b-dihydrospiro [benzo[□] Pyrazole (1.5-c) [1,3]oxazine-5,3-indolin] hydrazide of 1-yl) ethyl)isonicotine with a good practical yield of 60–80% [91].



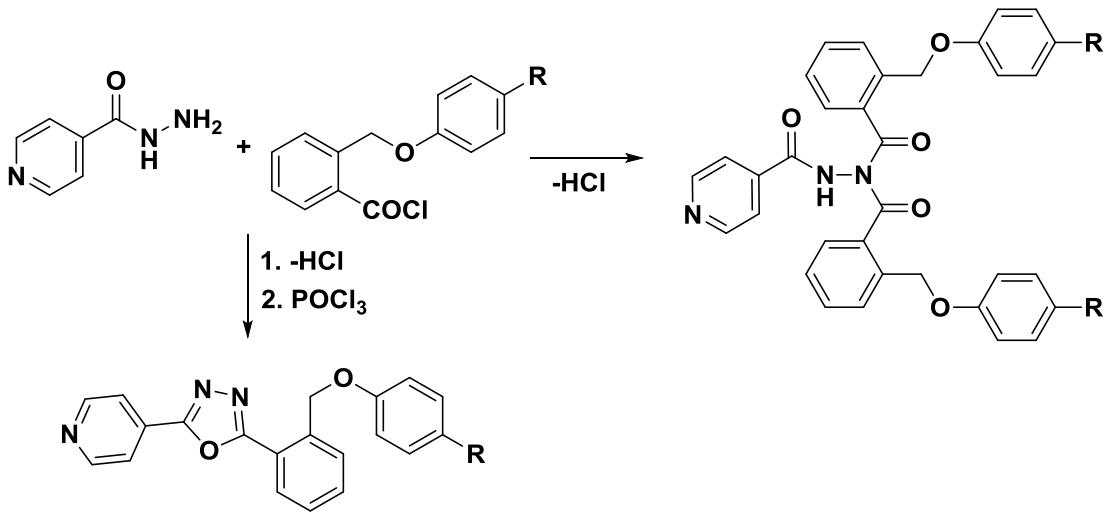
Scheme 30. Synthetic pathway for the synthesis of isoniazid-spirooxindole derivatives

Volynets et al innovated the isonicotinic acid hydrazide treated with corresponding aldehyde, acetophenone or pyruvic acid ethyl ester in water-ethanol (1:1) solution was reflux for 20–60 min to give resulted compounds. The obtained compounds did not require further purification and recrystallization. (Scheme 31) [92].



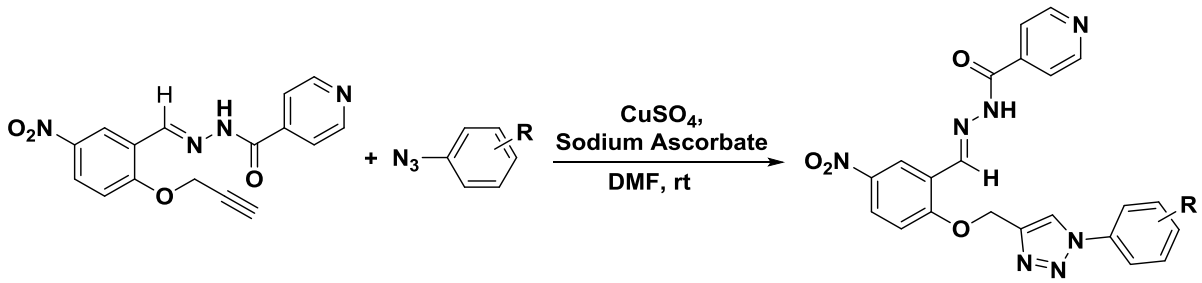
Scheme 31. Synthesis of isonicotinic acid hydrazide derivatives

Radulescu et al reacted crude acid chloride with isoniazid dissolved in dichloromethane to get the required derivatives (Scheme 32). In the case of 2-(4-methyl/methoxy/ethyl-phenoxymethyl)-benzoic acid derivatives, two new compounds were found in each reaction. Freshly made N,N'-diacylhydrazines were diluted in toluene before being subjected to phosphoryl chloride treatment. After being refluxed for six hours, the reaction mixture was stirred at room temperature for an entire night. Using ethanol, the reaction products 1,3,4-oxadiazoles were recrystallized [93].



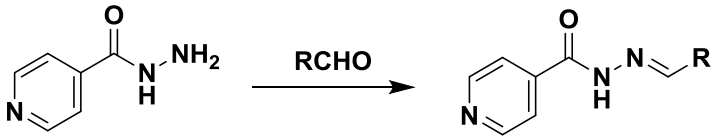
Scheme 32. Synthesis of novel Acyl Hydrazides and 1,3,4-Oxadiazole Derivatives

In order to create the corresponding triazole compounds in good yields, Haval et al. synthesised the click reaction of alkyne and substituted azidobenzenes in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate, as indicated in Scheme 33 [94].



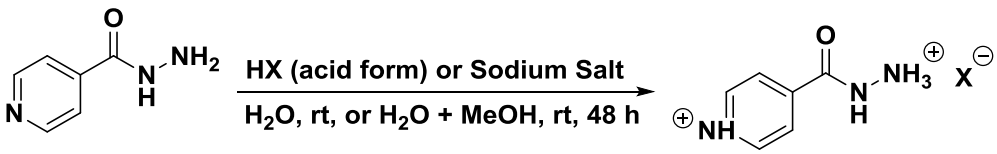
Scheme 33. Synthesis of isoniazid embedded triazole derivatives

To produce a satisfactory yield of the matched hydrazones, Guru et al employed substituted aromatic/heteroaromatic aldehydes (Scheme 34) [95].



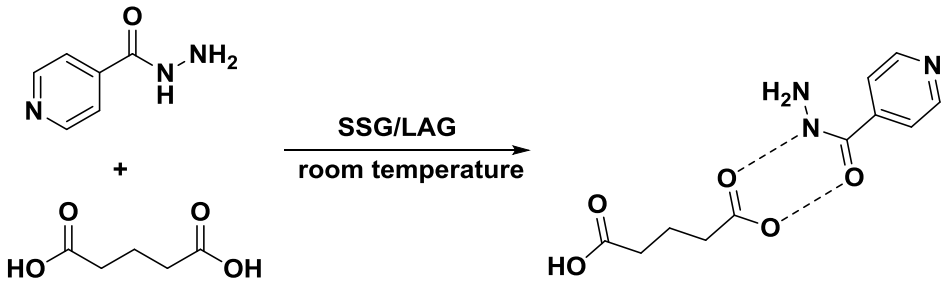
Scheme 34. Synthesis of Isoniazid Hydrazones

Branco et al. synthesized organic salts with isoniazid as a cation by protonation with acids or by metathesis reaction. Direct protonation by proper acid addition or anion-exchange processes under optimum conditions were used in two alternative synthesis techniques. The direct protonation strategy does not require any extra purification procedures, but the anion-exchange approach requires the inorganic salt to be eliminated by precipitation using a suitable organic solvent (Scheme 35) [96].



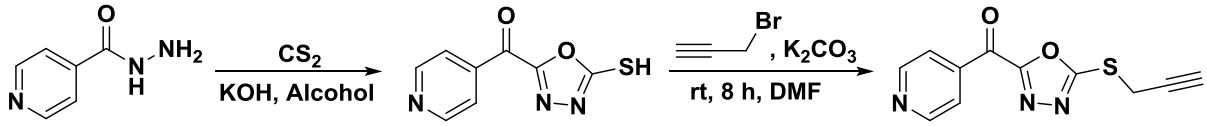
Scheme 35. Isoniazid as a cation in organic salts: production techniques

Samsodien et al. created both 2:1 co-crystals utilising solid-state grinding and solvent-assisted grinding techniques. Initially, the screening for the co-crystal was done using solid-state grinding, which involves milling mixes of isoniazid:glutaric acid in different molar ratios (1:1; 2:1; 1:2) using a mortar and pestle. The milling method was used to replicate both co crystals (Scheme 36) [97].



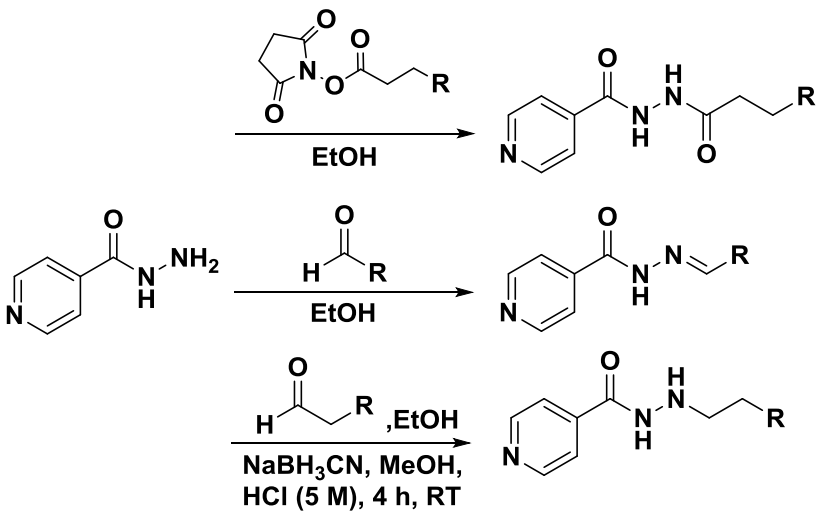
Scheme 36. Proposed molecular mechanistic for the formation of co-crystals of isoniazid with glutaric acid.

The reaction of the hydrazide moiety with CS_2 in the presence of KOH, discovered by Jwaid et al, is the most prevalent reaction to create 1,3,4-oxadiazole derivatives (Scheme 37). In a solution of basic alcohol, an acyl hydrazide interacts with carbon disulfide, followed by acidification of the combination. As indicated in Scheme 38, the mechanism involves replacing hydrogen from the thiol group with K+ from the base (K_2CO_3), followed by nucleophilic substitution. The kind of solvent has a significant impact on this reaction [98].



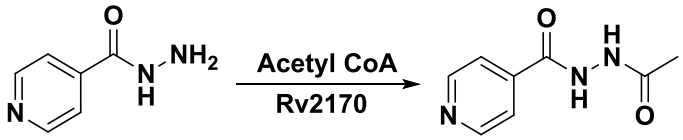
Scheme 37. Synthesis of Isonicotinoyl Hydrazide containing 1,3,4-Oxadiazole moiety

Treatment of isoniazid with the suitable N-succinimidyl active esters containing ortho-/meta-/para-carborane clusters for three to four days at room temperature in 100% EtOH resulted in the condensation products hydrazide with no complications, according to Olejniczak et al [99]. Depending on the type of carborane cluster, the yield of products ranged from 56 to 72 percent. The corresponding isonicotinoyl hydrazones were isolated as a crystalline solid (Scheme 38) [100] after reductive amination of isoniazid with an appropriate aldehyde-bearing ortho-/meta-/para-carborane group [96] in absolute EtOH or anhydrous ethyl acetate at 35–40 ^oC or at rt.



Scheme 38. Synthesis of Isoniazid-carborane hybrids

Kumar et al proposed the isoniazid acetylation reaction catalysed by Rv2170 is shown in Scheme 39. However, how acetylisoniazid gets converted into INA and AH is not clear from our study. Taken together, the results suggest that Rv2170-mediated acetylation of INH is a novel strategy adopted by at least some of the INH resistant MTB strains [101].



Scheme 39. Schematic representation of acetylation of isoniazid by Rv2170

Conclusion

The scientific community has faced significant obstacles in dealing with Mycobacterium Tuberculosis. Many synthetic and biological solutions have been used to solve these difficulties. The development of newer isoniazid hybrids/derivatives is one of the most explored tactics among them. The numerous ways of manufacturing Isoniazide derivatives from various commercially available and synthetic starting materials are summarised in this review article. INH can be made more potent by making structural changes or substituting at different positions. It is anticipated that in the coming years, drug regulatory agencies throughout the world will authorise safer and more effective medications that will permit the development of isoniazid hybrids/derivatives for the treatment of tuberculosis. This is critical since millions of people are still infected with tuberculosis. It does, however, become a need for future study in this field.

References

[1] For excellent reviews on natural product hybrids, see: (a) Tietze, L. F., Bell, H. P., & Chandrasekhar, S. (2003). Natural product hybrids as new leads for drug discovery. *Angewandte Chemie International Edition*, *42*(34), 3996-4028 (b) Mehta, G., & Singh, V. (2002). Hybrid systems through natural product leads: An approach towards new molecular entities. *Chemical Society Reviews*, *31*(6), 324-334 (c) Meunier, B. (2008). Hybrid molecules with a dual mode of action: dream or reality?. *Accounts of chemical research*, *41*(1), 69-77.

[2] (a) Mann, J. *Secondary Metabolism,* Second Edition, Clarendon Press, Oxford, 1987. (b) McMurray, J.; Begley, T. *The Organic Chemistry of Biologycal Pathways*, Roberts & Company Publishers 2005.

[3] Burke, M. D., & Schreiber, S. L. (2004). A planning strategy for diversity- oriented synthesis. *Angewandte chemie international edition*, *43*(1), 46-58.

[4] Miotto, P., Zhang, Y., Cirillo, D. M., & Yam, W. C. (2018). Drug resistance mechanisms and drug susceptibility testing for tuberculosis. *Respirology*, *23*(12), 1098-1113.

[5] Cox, V., Cox, H., Pai, M., Stillo, J., Citro, B., & Brigden, G. (2019). Health care gaps in the global burden of drug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *23*(2), 125-135.

[6] Vasava, M. S., Nair, S. G., Rathwa, S. K. Patel, D. B. & Patel, H. D. (2018). Development of new drugregimens against multidrug-resistant tuberculosis. *Indian Journal of Tuberculosis*, *66*(1), 12-19.

[7] Pai M, BehrMA, Dowdy D, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2:16076.

[8] Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. Nat Rev Drug Discov. 2013;12(5):388–404.

[9] Martins F., Santos S., Ventura C., Elvas-Leitao R., Santos L., Vitorino S., Reis M., Miranda V., Correia H.F., Aires-de-Sousa J., Kovalishyn V., Latino D.A.R.S., Ramos J.,

Viveiros M., Design, Synthesis and Biological Evaluation of Novel Isoniazid Derivatives with Potent Antitubercular Activity, Eur. J. Med. Chem. 81: 119-138 (2014).

[10] Xia L., Xia Y.F., Huang L.R., Xiao X., Lou H.Y., Liu T.J., Pan W.D., Luo H., Benzaldehyde Schiff Bases Regulation to the Metabolism, Hemolysis, and Virulence Genes Expression in Vitro and Their Structure–Microbicidal Activity Relationship, Eur. J. Med. Chem. 97: 83-93 (2015).

[11] Judge V., Narasimhan B., Ahuja M., Sriram D., Yogeeswari P., De Clercq E., Pannecouque C., Balzarini J., Synthesis, Antimycobacterial, Antiviral, Antimicrobial Activity and QSAR Studies of N2-acyl isonicotinic Acid Hydrazide Derivatives, Med. Chem. 9: 53-76 (2013).

[12] Malhotra M., Sharma S., Deep A., Synthesis, Characterization and Antimicrobial Evaluation of Novel Derivatives of Isoniazid, Med. Chem. Res., 21: 1237-1244 (2012).

[13] Dandawate P., Khan E., Padhye S., Gaba H., Sinha S., Deshpande J., Swamy K.V., Khetmalas M., Ahmad A., Sarkar F.H., Synthesis, Characterization, Molecular Docking and Cytotoxic Activity of Novel Plumbagin Hydrazones Against Breast Cancer Cells, Bioorg. Med. Chem. Lett. 22: 3104-3108 (2012).

[14] Wei M.X., Feng L., Li X.Q., Zhou X.Z., Shao Z.H., Synthesis of New Chiral 2,5-Disubstituted 1,3,4-Thiadiazoles Possessing □-Butenolide Moiety and Preliminary Evaluation of in Vitro Anticancer Activity, Eur. J. Med. Chem. 44: 3340-3344 (2009).

[15] Nigade G., Chavan P., Deodhar M., Synthesis and Analgesic Activity of New Pyridine-Based Heterocyclic Derivatives, Med. Chem. Res. 21: 27-37 (2012).

[16] Malhotra M., Monga V., Sharma S., Jain J., Samad A., Stables J., Deep A., Synthesis, Characterization and Pharmacological Evaluation of (E)-N′-(Substituted-Benzylidene)Isonicotinohydrazide Derivatives as Potent Anticonvulsant Agents, Med. Chem. Res. 21: 2145-2152 (2012).

[17] Hearn MJ,Cynamon MH, Chen MF, et al. Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid**,**European Journal of Medicinal Chemistry, 2009;44(10): 4169-78.

[18] Unissa AN,Subbian S,Hanna LE,Selvakumar N,Overview on mechanisms of isoniazid action and resistance in Mycobacterium tuberculosis, Infection, Genetics and Evolution, 2016;45: 474-492.

[19] Kaymakçıoğlu BK,Rollas S,Synthesis, characterization and evaluation of antituberculosis activity of some hydrazones, Il Farmaco, 2002; 57: 595-599.

[20] Patole, J.; Sandbhor, U.; Padhye, S.; Deobagkar, D.N.; Anson, C.E.; Powell, A.Structural chemistry and In vitro antitubercular activity of acetylpyridine benzoyl hydrazone and its copper complex against Mycobacterium smegmatis, Bioorganic & Medicinal Chemistry Letters, 2003; 13(1): 51-55.

[21] Maccari R,Ottanà R,Vigorita MG, In vitro advanced antimycobacterial screening of isoniazid-related hydrazones, hydrazides and cyanoboranes: part 14, Bioorganic & Medicinal Chemistry Letters, 2005;*15:* 2509-2513.

[22] Martins F, Santos S, Ventura C et al. Design, synthesis and biological evaluation of novel isoniazid derivatives with potent antitubercular activity, European Journal of Medicinal Chemistry, 2014; 81,119-138.

[23] Xia L, Xia YF, Huang LR,Benzaldehyde Schiff bases regulation to the metabolism, hemolysis, and virulence genes expression in vitro and their structure–microbicidal activity relationship, European Journal of Medicinal Chemistry,2015;*97*: 83-93.
[24] Judge V,Narasimhan B, Ahuja M,Synthesis, antimycobacterial, antiviral, antimicrobial activity and QSAR studies of N(2)-acyl isonicotinic acid hydrazide derivatives.Medicinal Chemistry,2013; 9(1): 53-76.
[25] Rollas S, Gulerman, N, Erdeniz H,Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5- disubstituted-1,3,4-oxadiazolines, Il Farmaco. 2002;57: 171–174.
[26] Melnyk P, Leroux V, Sergheraert C, Grellier P, Design, synthesis and in vitro antimalarial activity of an acylhydrazone library, Bioorganic & Medicinal Chemistry Letters, 2006; 16: 31-35.
[27] Malhotra M, Sharma S, Deep A,Synthesis, characterization and antimicrobial evaluation of novel derivatives of isoniazid, Medicinal Chemistry Research,2012; 21: 1237-1244.
[28] Loncle C, Brunel JM, Vidal N, Dherbomez M, Letourneux Y,Synthesis and antifungal activity of cholesterol-hydrazone derivatives, European Journal of Medicinal Chemistry, 2004; 39(12): 1067-1071.
[29] Papakonstantinou-Garoufalias S,Pouli N, Marakos P, Chytyroglou-Ladas A,Synthesis antimicrobial and antifungal activity of some new 3 substituted derivatives of 4-(2,4-dichlorophenyl)-5-adamantyl-1H-1,2,4-triazole, Il Farmaco. 2002; 57: 973–977.
[30] Vicini P, Zani F, Cozzini P, Doytchinova I, Hydrazones of 1,2-benzisothiazole hydrazides: synthesis, antimicrobial activity and QSAR investigations, European Journal of Medicinal Chemistry, 2002; 37: 553–564.
[31] Dandawate P, Khan E, Padhye S, Synthesis, characterization, molecular docking and cytotoxic activity of novel plumbaginhydrazones against breast cancer cells,Bioorganic & Medicinal Chemistry Letters, 2012; 22:3104-3108.
[32] Wei MX, Feng L, Li XQ, Zhou XZ, Shao ZH, Synthesis of new chiral 2,5-disubstituted 1,3,4-thiadiazoles possessing gamma-butenolide moiety and preliminary evaluation of in vitro anticancer activity, European Journal of Medicinal Chemistry,2009; 44: 3340-3344.
[33] Agarwal S, Gupta M, Choudhury B, Solvent free biocatalytic synthesis of isoniazid from isonicotinamide using whole cell of Bacillus smithii strain IITR6b2,Journal of Molecular Catalysis B: Enzymatic,2013; 97: 67-73.
[34] Lienhardt C, Raviglione M, Spigelman M, et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future, Journal of Infectious Diseases, 2012; 205:S241-249.
[35] Nigade G, Chavan P, Deodhar M,Synthesis and analgesic activity of new pyridine-based heterocyclic derivatives, Medicinal Chemistry Research, 2012; 21: 27-37.
[36] Malhotra M, Monga V, Sharma S, et al. Synthesis, characterization and pharmacological evaluation of (E)-N0 -(substitutedbenzylidene) isonicotinohydrazide derivatives as potent anticonvulsant agents, Medicinal Chemistry Research,2012; 21: 2145-2152.
[37] Sridhar S.K, Pandeya SN, Stables JP, Atmakuru R, Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives, European Journal of Pharmaceutical Sciences, 2002; 16: 129-132.

[38] Küçükgüzel SG, Mazi A, Sahin F,Öztürk S, Stables JP,Synthesis and biological activities of diflunisal hydrazide-hydrazones, European Journal of Medicinal Chemistry, 2003; 38: 1005-1013.
[39] Kajal A, Bala S, Sharma N, Kamboj S, Saini V, Therapeutic potential of hydrazones as anti-inflammatory agents, International Journal of Medicinal Chemistry, 2014.
[40] Narasimhan B, Kumar P, Sharma D,Biological activities of hydrazide derivatives in the new millenniumActa. Pharmaceutica. Sciencia. 2010; 52: 169-180.
[41] Quraishi MA,Sardar R, Jamal D,Corrosion inhibition of mild steel in hydrochloric acid by some aromatic hydrazides, Materials Chemistry and Physics. 2001; 71: 309-313.
[42] Lougheed KEA, Taylor DL, Osborne SA, Bryans JS, Buxton RS,New anti-tuberculosis agents amongst known drugs, Tuberculosis. 2009; 89: 364-370.
[43] Du TLC, Pillay V, Danckwerts MP,Tuberculosis chemotherapy: current drug delivery approaches,Respiratory Research. 2006; 7: 118.
[44] World Health Organization, Global Tuberculosis Report 2014, http://apps.who.int/medicinedocs/en/d/Js21634en/
[45] Ali, M. H., Alrasheedy, A. A., Kibuule, D., Godman, B., Hassali, M. A., & Ali, H. M. H. (2019). Assessment of multidrug-resistant tuberculosis (MDR-TB) treatment outcomes in Sudan; findings and implications. Expert review of anti-infective therapy, 17(11), 927-937.
[46] Ali, M. H., Alrasheedy, A. A., Hassali, M. A., Kibuule, D., & Godman, B. (2019). Predictors of multidrug-resistant tuberculosis (MDR-TB) in Sudan. Antibiotics, 8(3), 90.
[47] Ayushi Tripathi, Nadaf Y. F., Dinesh Bilehal, Swarnagowri Nayak,Santosh L Gaonkar A Review On Synthesis Of Isoniazid Derivatives And Their Biological Properties International Journal Of Pharmaceutical Research |January- March 2019 | Vol 11 | Issue 1 21-36
[48] Piyush Kumar, Pinki Rawat And Pooja Singh Medicinal Chemistry And Development of Antitubercular Drugs IJPSR, 2013; Vol. 4(6): 2080-2093.
[49] Aparna Bahuguna, Diwan S. Rawat An overview of new antitubercular drugs, drug candidates, and their targets Med Res Rev. 2019;1-30.
[50] Mohd. Imran, Abdulhakim Bawadekji, Mouhanad Al Ali Recent Isoniazid Derivatives as Anti-Tubercular Agents: Review Article Journal of the North for Basic and Applied Sciences (JNBAS), (2019/1441 H), Vol. (4), Issue (2), 139-158
[51] N. V. Bhilare & S. S. Dhaneshwar & K. R. Mahadik Phenolic acid tethered isoniazid for abrogation of drug-induced hepatotoxicity: design, synthesis, kinetics and pharmacological evaluation *Drug Delivery and Translational Research* 2018; 8; 770–779
[52] Z. Rychtarčíková, M. Krátký, M. Gazvoda, M. Komlóová, S. Polanc, M. Kočevar, J. Stolaříková, J. Vinšová, *N*-Substituted 2-Isonicotinoylhydrazinecarboxamides – New Anti-mycobacterial Active Molecules, *Molecules* (2014) 19, 3851-3868.
[53] Vosátka, R.; Krátký, M.; Švarcová, M.; Janoušek, J.; Stolaříková, J.; Madacki, J.; Huszar, S.; Mikušová, K.; Kordulakova, J.; Trejtnar, F., New lipophilic isoniazid derivatives and their 1, 3, 4-oxadiazole analogues: synthesis, antimycobacterial activity and investigation of their mechanism of action. *European journal of medicinal chemistry* **2018**, 151, 824-835.
[54] Yang Z-Y, Yen S-K, Hu W-S, Huang Y-Z, Yang T-M, Su C-S. Sonocrystallization—Case Studies of Salicylamide Particle Size Reduction and Isoniazid Derivative Synthesis and Crystallization. *Crystals*. 2018; 8(6):249.

[55] Assy, M., Some reaction with ethyl 2-aryl-4-mercapto-6-methylpyrimidine-5 carboxylates. *Sulfur Lett*, **11**, 75-82 (1990).

[56] Mona E. Farhan and Mohammed G. Assy Heterocyclization of Isoniazid: Synthesis and Antimicrobial Activity of Some New Pyrimidine, 1, 3-Thiazole, 1, 2, 4-Thiadiazole, and 1, 2, 4 Triazole Derivatives Derived from Isoniazid Egypt. J. Chem. Vol. 62, No. 2 pp. 171 - 180 (2019)

[57] Villani Jr, F.J., Ethoxycarbonyl Isothiocyanate. Encyclopedia of Reagents for Organic Synthesis, (2001).

[58] Stork, G., Brizzolara, A., Landesman, H., Szmuszkovicz, J., and Terrell, R.. The enamine alkylation and acylation of carbonyl compounds. Journal of the American Chemical Society, 85(2), 207-222 (1963).

[59] R. M. Beteck, R. Seldon, A. Jordaan, D. Warner, H. C. Hoppe, D. Laming, L. J. Legoabe and S. Khanye, Quinolone-isoniazid hybrids: Synthesis and preliminary in vitro cytotoxicity and anti-tuberculosis evaluation *Med. Chem. Commun.*, **2019**, DOI: 10.1039/C8MD00480C

[60] Rane, R.A.; Naphade, S.S.; Bangalore, P.K.; Palkar, M.B.; Shaikh, M.S.; Karpoormath, R. Synthesis of novel 4-nitropyrrole-based semicarbazide and thiosemicarbazide hybrids with antimicrobial and anti-tubercular activity. Bioorg. Med. Chem. Lett. **2014**, 24, 3079–3083.

[61] Pitucha M, Karczmarzyk Z, Swatko-Ossor M, Wysocki W, Wos M, Chudzik K, Ginalska G, Fruzinski A. Synthesis, In Vitro Screening and Docking Studies of New Thiosemicarbazide Derivatives as Antitubercular Agents. *Molecules*. 2019; 24(2):251.

[62] Porkodi Jeyaraman, Arunadevi Alagarraj & Raman Natarajan (2019): *In silico* and *in vitro studies* of transition metal complexes derived from curcumin–isoniazid Schiff base, Journal of Biomolecular Structure and Dynamics

[63] Xin S, Aprahamian I. Hydrazone-based switches, metallo-assemblies and sensors. Chem Soc Rev. 2014; 43: 1963-81.

[64] Fahmi MRG, Khumaidah L, Ilmiah TK, et al. 2-Thiophenecarboxylic acid hydrazide derivatives: synthesis and anti-tuberculosis studies. IOP Conf. Series: Mater Sci Eng. 2018; 349: 012039.

[65] Belskaya NP, Dehean W, Bakulev VA, Synthesis and properties of hydrazones bearing amide, thioamise, and amidine functions. Arkivoc. 2010;1:275-32.

[66] Fahmi MRG, Kurniawan YS. Heterocyclic hydrazone derivatives as potential antitubercular agent against Mycobacterium tuberculosis. J Exp Clin Microbiol 2019;2(2):16-21.

[67] Yahyazadeh, A. & Ghasemi, Z. Synthesis of unsymmetrical thiourea derivatives. *Eur. Chem. Bull.* **2**, 573–575 (2013).

[68] Rizvi, F., Khan, M., Jabeen, A. *et al.* Studies on Isoniazid Derivatives through a Medicinal Chemistry Approach for the Identification of New Inhibitors of Urease and Inflammatory Markers. *Sci Rep* **9,** 6738 (2019).

[69] Bhoi, M.N., Borad, M.A., Jethava, D.J., Acharya, P.T., Pithawala, E. A., Patel, C.N., Patel, H.D., 2019. Synthesis, biological evaluation and computational study of novel isoniazid containing 4H-Pyrimido [2,1-b] benzothiazoles derivatives. Eur. J. Med. Chem. 177, 12–31.

[70] S. S. Panda, A. M. Asiri, M. Elagawany, D. D. Buchanan, B. Torkian, K. Bathala, S. J. Thomas, J. E. Capito, M. N. Arshad and A. N. Al-Romaizan, Efficient synthesis of pyrazinoic acid hybrid conjugates, SynOpen, 2017, 1, 50–58.

[71] Panda, S.S.; Girgis, A.S.; Mishra, B.B.; Elagawany, M.; Devarapalli, V.; Littlefield, W.F.; Samir, A.; Fayad, W.; Fawzy, N.G.; Srour, A.M.; et al. Synthesis, Computational Studies, Antimycobacterial and Antibacterial Properties of Pyrazinoic Acid-Isoniazid Hybrid Conjugates. RSC Advances **2019**, 9, 20450–20462.

[72] Ruswanto, Richa Mardianingrum, Tresna Lestari, Tita Nofianti, Nur Rahayuningsih Synthesis and molecular docking of isonicotinohydrazide derivatives as anti-tuberculosis candidates *Malaysian Journal of Fundamental and Applied Sciences* Vol. 15, No. 3 (2019) 367-371.

[73] I. Dragostin, O.M. Dragostin, S. Keshari, S. Dash, R. Tatia, M. Dragan, C.M. Ghiciuc, D. Diculencu, E. Lupu, C.L. Zam, New isoniazid derivatives with improved pharmaco-toxicological profile: obtaining, characterization and biological evaluation, *Eur. J. Pharm. Sci.* 137 (2019) 104974.

[74] Oana-Maria Dragostin, Ionuț Dragostin, Alexandra-Simona Zamfir, Luminița Confederat, Cătălina Daniela Stan, Maria Drăgan, Cristina Tuchiluș, Carmen Lăcrămioara Zamfir New Isoniazid Derivatives For Antimicrobial Spectrum Extension And Hepatotoxicity Reduction Of Parent Compound: In Vitro And In Vivo Assays Farmacia, 2020, Vol. 68, 3

[75] Daniele Zampieria, Maria Grazia Mamoloa, Julia Filingeria, Sara Fortunaa, Alessandro De Logub, Adriana Sannac, Davide ZanondDesign, synthesis and antimycobacterial activity of benzoxazinone derivatives and open-ring analogues: Preliminary data and computational analysis Bioorganic & Medicinal Chemistry Letters 29 (2019) 2468–2474.

[76] Wallace J. Reisa, Icaro A.O. Bozzia, Matheus F. Ribeiroa, Priscila C.B. Halickib, Lais A. Ferreirab, Pedro E. Almeida da Silvab, Daniela F. Ramosb, Carlos A. de Simonec, Eufranio N. da Silva Juniora, Design of hybrid molecules as antimycobacterial compounds: Synthesis of isoniazid-naphthoquinone derivatives and their activity against susceptible and resistant strains of Mycobacterium tuberculosis Bioorganic & Medicinal Chemistry 27 (2019) 4143–4150.

[77] Andria Papageorgiou, Angeliki-Sofia Foscolos, Ioannis P Papanastasiou, Marilena Vlachou, Angeliki Siamidi, Anthony Vocat, Stewart T Cole, Tahsin F Kellici, Thomas Mavromoustakos & Andrew Tsotinis Synthesis, biology, computational studies and in vitro controlled release of new isoniazid-based adamantane derivatives Future Medicinal Chemistry vol. 11, No. 21

[78] Kaur, H., Singh, L., Chibale, K. *et al.* Structure elaboration of isoniazid: synthesis, in silico molecular docking and antimycobacterial activity of isoniazid–pyrimidine conjugates. *Mol Divers* 24, 949–955 (2020).

[79] Franklin Afinjuomo , Thomas G. Barclay, Ankit Parikh, Rosa Chung, Yunmei Song, Gayathri Nagalingam, Jamie Triccas, Lixin Wang, Liang Liu, John D. Hayball, Nikolai Petrovsky and Sanjay Garg, Synthesis and Characterization of pH-Sensitive Inulin Conjugate of Isoniazid for Monocyte-Targeted Delivery Pharmaceutics 2019, 11, 555.

[80] Shailesh R. Shah, Kanubhai D. Katariya 1,3-Oxazole-isoniazid hybrids: Synthesis, antitubercular activity, and their docking studies J Heterocyclic Chem. 2020;1–10.

[81] Zhixiang Lu, Shuhan Lu, Yi Cheng, Yu Qin, Shaoxiong Yang, Xiaolan Liu, Wenwen Fan, Liyan Zheng, Hongbin Zhang Synthesis of isoniazid-substituted tetraphenylethylene stereoisomers with dramatic differences on aggregate morphologies, optical and mechanocharomic properties Journal of Photochemistry & Photobiology A: Chemistry 392 (2020) 112357.

[82] A. S. Rathoda,*, P. V. Reddyb, and J. S. Biradara Microwave-Assisted Synthesis of Some Indole and Isoniazid Derivatives as Antitubercular Agents and Molecular Docking Study Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 4, pp. 662–670

[83] Faryal Chaudhry, Munawar Ali Munawar, Misbahul Ain Khan Facile synthesis of isoniazid derivatives-1-[2-(3-aryl(hetaryl)-1-phenyl-1H-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3 (2H)-yl]ethanones Chemistry of Heterocyclic Compounds 2020, 56(5), 615–618

[84] Daniela Correa Santos, Ruan Roberto Henriques, Marcos Antonio de Abreu Lopes Junior, Andre Borges Fariasa, Thayssa Lisboa do Couto Nogueiraa, Joao Victor Fernandes Quimasa, Nelilma Correia Romeiro, Leandro Louback da Silva, Andrea Luzia Ferreira de Souza, Acylhydrazones as isoniazid derivatives with multi-target profiles for the treatment of Alzheimer's disease: Radical scavenging, myeloperoxidase/ acetylcholinesterase inhibition and biometal chelation Bioorganic & Medicinal Chemistry 28 (2020) 115470

[85] Chaouiki, A., Lgaz, H., Salghi, R., Chafiq, M., Gaonkar, S. L., Bhat, K. S., Oudda, H., Ali, I. H., & Chung, I. M. (2020). Inhibitory effect of a new isoniazid derivative as an effective inhibitor for mild steel corrosion in 1.0 M HCl: combined experimental and computational study. *Research on Chemical Intermediates*.

[86] M.P. Ramya Rajan, Ramaswamy Rathikha, Rajendran Nithyabalaji, Rajendran Sribalan Synthesis, characterization, in silico studies and in vitro biological evaluation of isoniazid-hydrazone complexes Journal of Molecular Structure 1216 (2020) 128297

[87] Nazim, Urooj; Ali, Syed Imran; Ishrat, Ghazala; Hassan, Amir; Ahmed, Mansoor; Ali, Mohsin; Ali, Zaheer; Noori, Muahammad Yahya Synthesis, characterization and SEM studies of novel 1-indanyl isoniazid and hydrazide Schiff base derivatives as new anti-tubercular agents Pak. J. Pharm. Sci., Vol.33, No.3, May 2020, pp.1095-1103

[88] M. Zalaa, J. J. Vora, and H. B. Patel Synthesis, Characterization, and Comparative Study of Some Heterocyclic Compounds Containing Isoniazid and Nicotinic Acid Hydrazide Moieties Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 10, pp. 1795–1800

[89] Badar, A. D., Sulakhe, S. M., Muluk, M. B., Rehman, N. N. M. A., Dixit, P. P., Choudhari, P. B., … Haval, K. P. (2020). Synthesis of isoniazid-1,2,3-triazole conjugates: Antitubercular, antimicrobial evaluation and molecular docking study. Journal of Heterocyclic Chemistry Volume 57, Issue10 October 2020 Pages 3544-3557

[90] Mayuri A. Borad, Divya J. Jethava, Manoj N. Bhoi, Chirag N. Patel, Himanshu A. Pandya, Hitesh D. Patel Novel isoniazid-spirooxindole derivatives: design, synthesis, biological evaluation, in silico ADMET prediction and computational studies Journal of Molecular Structure 1222 (2020) 128881

[91] Galyna P Volynets, Michail A Tukalo, Volodymyr G Bdzhola, Nataliia M Derkach, Mykola I Gumeniuk, Sergiy S Tarnavskiy & Sergiy M Yarmoluk Novel isoniazid derivative as promising antituberculosis agent Future Microbiology Vol. 15, No. 10

[92] Zarafu I, Matei L, Bleotu C, Ionita P, Tatibouët A, Păun A, Nicolau I, Hanganu A, Limban C, Nuta DC, Nemeş RM, Diaconu CC, Radulescu C. Synthesis, Characterization,

and Biologic Activity of New Acyl Hydrazides and 1,3,4-Oxadiazole Derivatives. *Molecules*. 2020; 25(14):3308

[93] Pravin S. Patila, Sanghratna L. Kasarea, Nitin B. Havala, Vijay M. Khedkarb, Prashant P. Dixitc, Estharla Madhu Rekhad, Dharmarajan Sriramd, Kishan P. Haval Novel isoniazid embedded triazole derivatives: Synthesis, antitubercular and antimicrobial activity evaluation Bioorganic & Medicinal Chemistry Letters 30 (2020) 127434

[94] S. L. Gaonkar, S. S. Hakkimane, B. R. Bharath, V. P. Shenoy, U. N. Vignesh And B. R. Guru, Stable Isoniazid Derivatives: In Silico Studies, Synthesis And Biological Assessment Against Mycobacterium Tuberculosis In Liquid Culture Rasayan J. Chem., 13(3), 1853-1870 (2020)

[95] Filipa Santos, Luís C. Branco and Ana Rita C. Duarte Organic Salts Based on Isoniazid Drug: Synthesis, Bioavailability and Cytotoxicity Studies Pharmaceutics 2020, 12, 952

[96] Ngilirabanga JB, Aucamp M, Pires Rosa P and Samsodien H (2020) Mechanochemical Synthesis and Physicochemical Characterization of Isoniazid and Pyrazinamide Co-crystals With Glutaric Acid. Front. Chem. 8:595908

[97] Mazen Mohammed Jwaid, Karima Fadhil Ali, Mayada Hadi Abd-alwahab Synthesis, Antibacterial study and ADME Evaluation of Novel Isonicotinoyl Hydrazide Derivative Containing 1,3,4-Oxadiazole Moiety Al Mustansiriyah Journal of Pharmaceutical Sciences, 2020, Vol. 20, No.4

[98] Ró˙ zycka, D.; Le´snikowski, Z.J.; Olejniczak, A.B. Synthesis of boron cluster analogs of penicillin and their antibacterial activity. J. Organomet. Chem. 2019, 881, 19–24.

[99] Marshall, J.; Hooton, J.; Han, Y.; Creamer, A.; Ashraf, R.S.; Porte, Y.; Anthopoulos, T.D.; Stavrinou, P.N.; Mclachlan, M.A.; Bronstein, H.; et al. Polythiophenes with vinylene linked ortho, meta, and para-carborane sidechains. Polym. Chem. 2014, 5, 6190–6199.

[100] Różycka D, Korycka-Machała M, Żaczek A, Dziadek J, Gurda D, Orlicka-Płocka M, Wyszko E, Biniek-Antosiak K, Rypniewski W, Olejniczak AB. Novel Isoniazid-Carborane Hybrids Active In Vitro against *Mycobacterium tuberculosis Pharmaceuticals* 2020; 13(12):465

[101] K. B. Arun, Aravind Madhavan, Billu Abraham, M. Balaji, K. C. Sivakumar, P. Nisha, R. Ajay Kumar Acetylation of isoniazid - a novel mechanism of isoniazid resistance in Mycobacterium tuberculosis Antimicrobial agents and chemotherapy, 2020, 1-26.