Advances in Bioresearch
Adv. Biores., Vol 10 (4) July 2019: 01-09

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.10.4.19

Advances in Bioresearch

REVIEW ARTICLE

Hydrazones: origin, reactivity and biological activity

Kamel Mokhnache, Khither Hanane, EL-Khamsa Soltani, Soraya Madoui, Ahlem Karbab, Noureddine charef, Lekhmici Arrar
Laboratory of Applied Biochemistry, University Ferhat Abbas Setif 1,19000, Algeria
Corresponding author Email: kamelmokhnache@yahoo.com

ABSTRACT
This review aims at highlighting the origin, reactivity and diverse biological activities of hydrazones.
Keywords: *Hydrazone, Synthesis, Origin, Reactivity, Bioactivity*

Received 04.04.2019 Revised 18.04.2019 Accepted 06.06.2019

How to cite this article:
K Mokhnache, K Hanane, EL-Khamsa Soltani, S Madoui, A Karbab, N Charef, L Arrar. Hydrazones: origin, reactivity and biological activity. Adv. Biores., Vol 10 [4] July 2019.01-09.

INTRODUCTION

Hydrazones are a special class of organic compounds in the Schiff base family [1]. They have a general formula of (R_1R_2-C=N-NH) [2]. Duo to the ease of preparation, increased hydrolytic stability and tendency toward crystallinity, hydrazones have been under study for a long time in organic chemistry [3].

Synthetic pathways

Hydrazones can be prepared by three synthetic pathways: (**a**) condensation between hydrazines and ketones or aldehydes, (**b**) Japp–Klingemann reaction; coupling between aryl diazonium salts and beta-keto esters or acids, and (**c**) coupling reaction between aryl halides and non-substituted hydrazones. These methods lead to the formation of hydrazones with crystalline forms, which facilitate their purification (**Figure1**) [4].

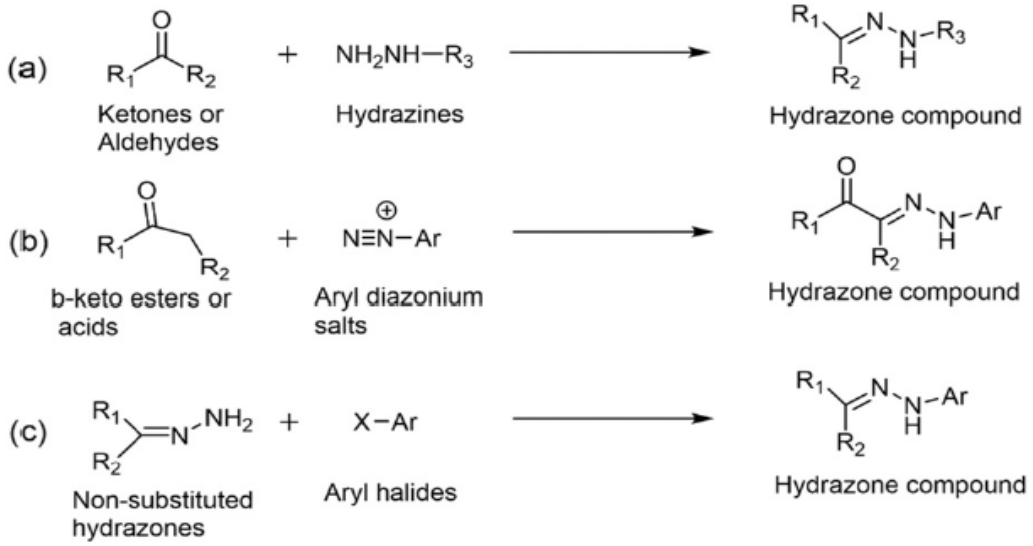


Figure 1. The synthesis methodologies for hydrazone linkages (a) condensation between hydrazine and ketone/aldehyde (b) the Japp-Klingemann reaction and (c) substitution of aryl halide with non-substituted hydrazones [4].

Mechanism of formation

Hydrazones are formed from the condensation of hydrazine (**A**) and a carbonyl compound (aldehyde or ketone) (**B**) with water being the sole byproduct. The reaction starts by a proton-catalyzed attack of the nucleophile on the carbonyl carbon atom of electrophile. Upon proton transfer, tetrahedral intermediate (**C**) was formed. This intermediate can undergo dehydration *via* protonation of the hydroxyl function and subsequent elimination of water. The resulting protonated intermediate is represented by two resonance forms (**D/E**). The final deprotonation yields hydrazone [1] (**Figure 2**).

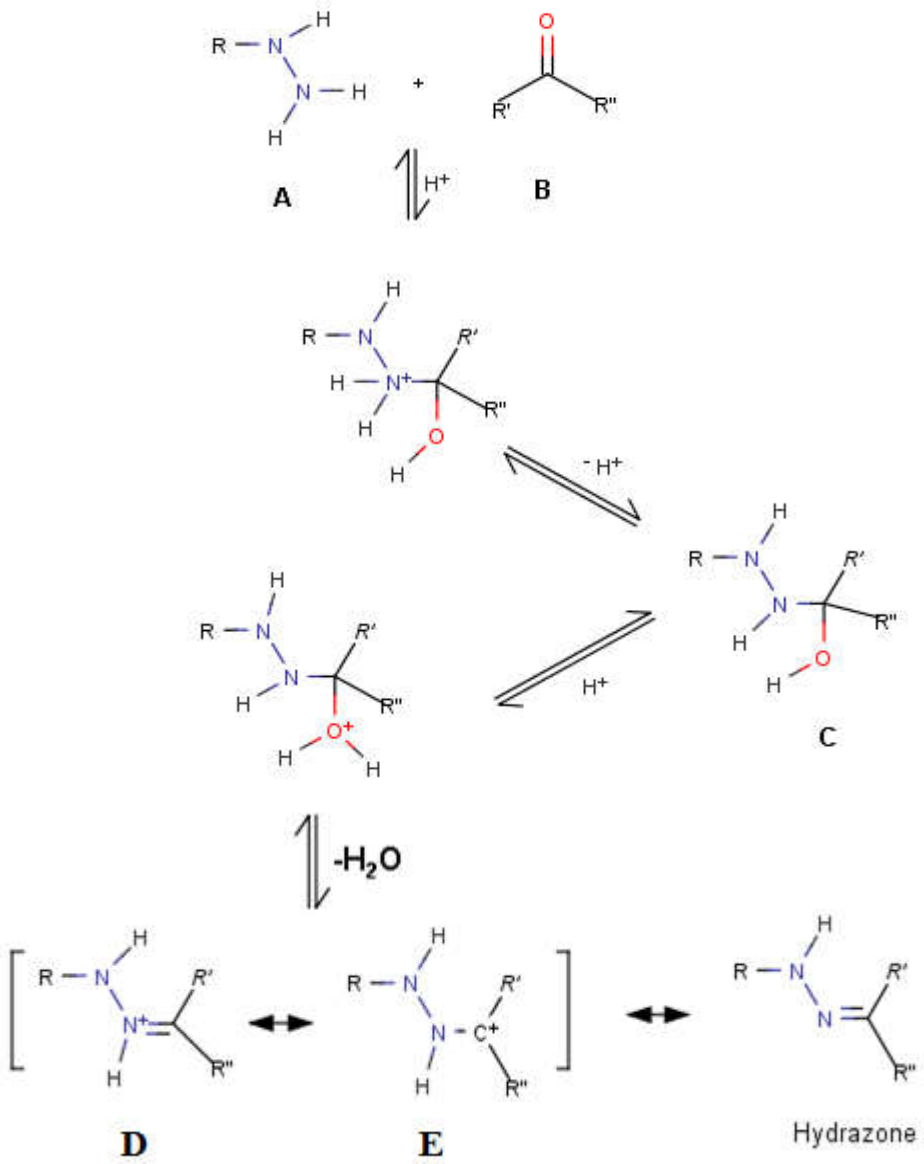
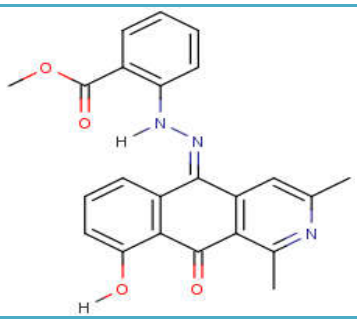
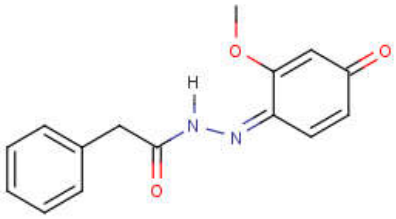
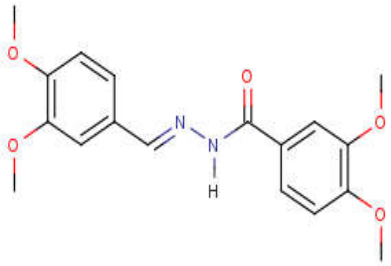
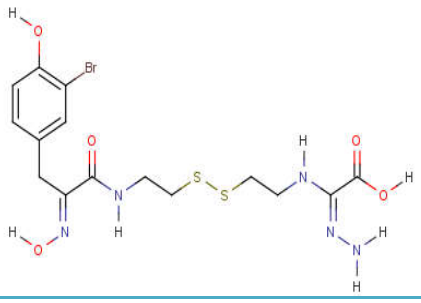


Figure 2. Standard Mechanism of hydrazones formation [1]

Biosynthetic hydrazones

Hydrazones are widely present in nature [5], which could be biosynthesized by bacteria, fungi, plants, and marine organisms, and can be isolated by different ways such as solvent extraction and fermentation. **Table1** summarizes various natural hydrazones and their sources.

Table 1. Origin, chemical structures, and names of natural hydrazones

Origin	Chemical structure	Name/ Date of isolation
Bacteria [6] *Streptomyces sp*. IFM 11299		Katorazone (2012)
Fungi [7] *Penicillium minioluteum* F-4627		NG-061 (1999)
Plants [6] Thai plant *Wedelia biflora*		Veratrylidenehydrazide (1993)
Marine organisms Sponge [6] *Pseudoceratina purpurea*		Psammaplin G (2003)

Semi-synthetic of hydrazones

The semi-synthesis of hydrazones was demonstrated by the administration of the antitubercular drug isoniazid **(INH)** by healthy human. Analysis of urine indicates the formation of hydrazones, which resulted from **INH** conjugation with endogen substances (amino acids) or theirs metabolites such as leucine and/or isoleucine, lysine, tyrosine, tryptophan, and phenylalanine. **Figure 3,** summarizes various hydrazones(**1-10**) formed by **INH** conjugation with various metabolites; 3-(1*H*-indol-3-yl)-2-oxopropanoic acid, 2-oxo-3-phenylpropanoic acid, 3-(4-hydroxyphenyl)-2-oxopropanoic acid, 2-oxohexanedioic acid, 4-methyl-2-oxopentanoic acid, 3-methyl-2-oxopentanoic acid, α-ketoglutaric acid, glycine, and glucose and 5-hydroxy-4-(hydroxymethyl)-6-methylpyridine-3-carbaldehyde [8].

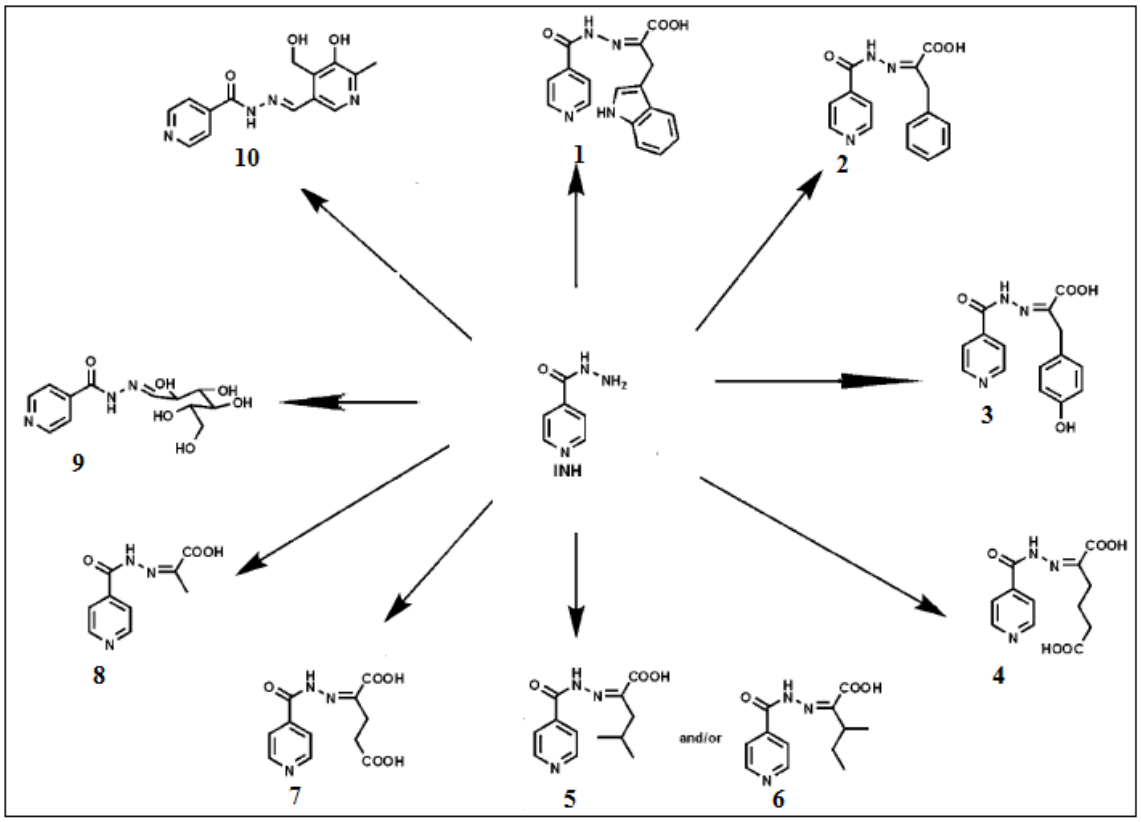


Figure 3. Semi-synthesis of hydrazones [8].

Reactivity of hydrazones

Hydrazones contain two connected nitrogen atoms of different nature and a carbon- nitrogen double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structural fragments are mainly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino- type nitrogen is more reactive. The carbon atom of hydrazone group has both electrophilic and nucleophilic characters [9]. Shown in **Figure 4** are the active centers of N-monosubstitutedhydrazones (**A**), N,N-dialkylhydrazones (**B**), and N-acyl hydrazones **(C).**

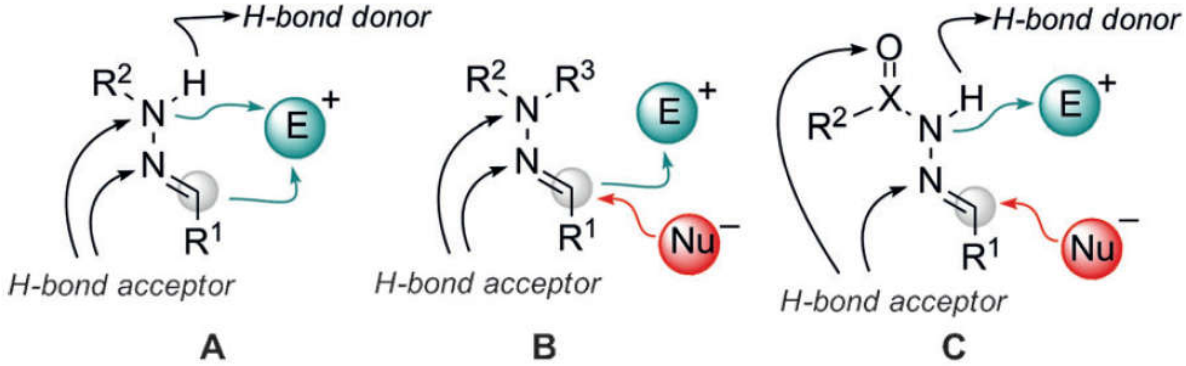


Figure 4. Active centers of hydrazones [9].

Hydrazones display diverse reactivity, taking part in reactions with nucleophiles, electrophiles, and other chemical reagents. Being a bidentate nucleophiles, hydrazones react with electrophilic reagents with participation of either nitrogen atom (compounds **1, 2**), or the carbon atom of the azomethine group (compounds **3**). Strong bases deprotonate hydrazones to form anions of types **4** and **5**, whereas nucleophiles attack the azomethine carbon atom to form products of both addition **6, 7** and substitution **8**. Furthermore, hydrazones can be reduced to amines **9** or oxidized to diazo compounds **10** [10] (**Figure 5**).

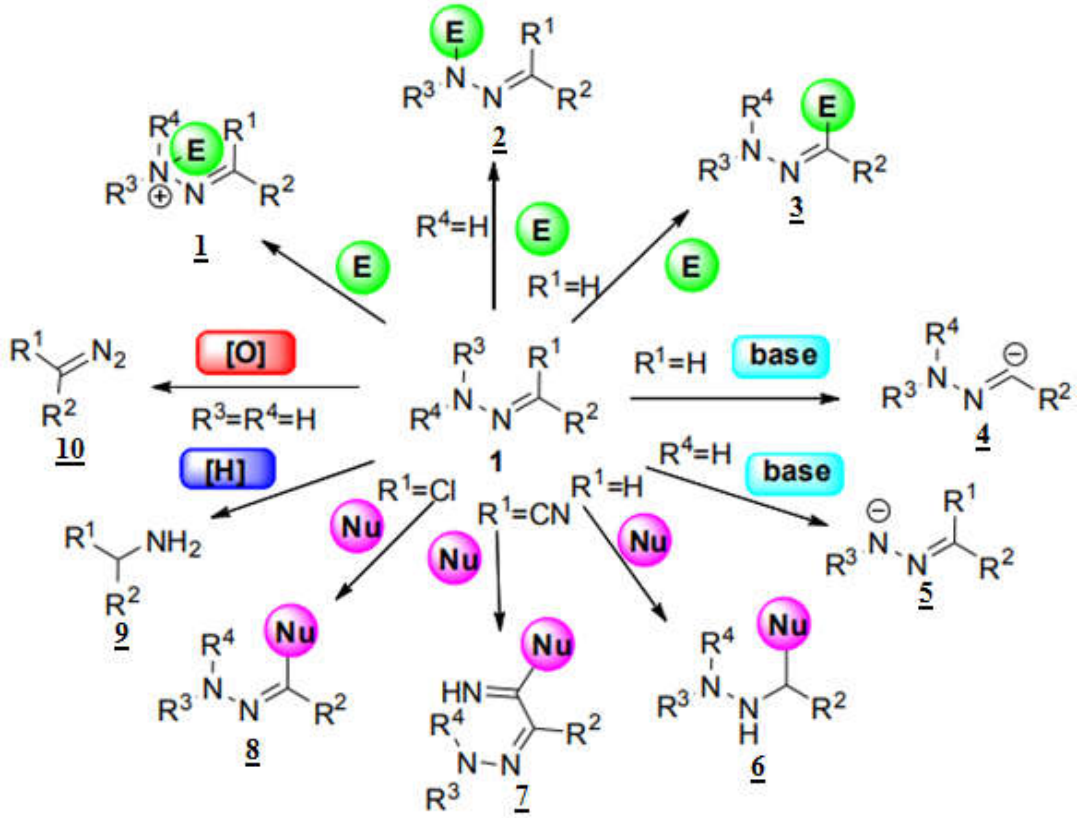


Figure 5. Reactions of hydrazones with different types of reagents [10].

Heterocyclization of hydrazide-hydrazones

Hydrazide-hydrazones are very effective organic compounds. Several researchers reported on the synthesis of heterocyclic compounds from these compounds. Rollas et al. [11] prepared four substituted 1,3,4-oxadiazolines from 4-fluorobenzoic acid (substituted methylene) hydrazides and acetic anhydride. In addition, Thomas et al. [12] synthesized a series of 2-azetidinones from the reaction of N'-[(1Z)-(substituted aromatic) methylidene]pyridine-4- carbohydrazides and chloroacetylchloride, bynovel methods; microwave irradiation and stirring/sonication. Furthermore, Patel et al. [13] prepared a series of 4-thiazolidinones from the cyclocondensation of hydrazide-hydrazones with thioglycolic acid in dry 1,4-dioxane. These reactions are shown in **Figure 6**.

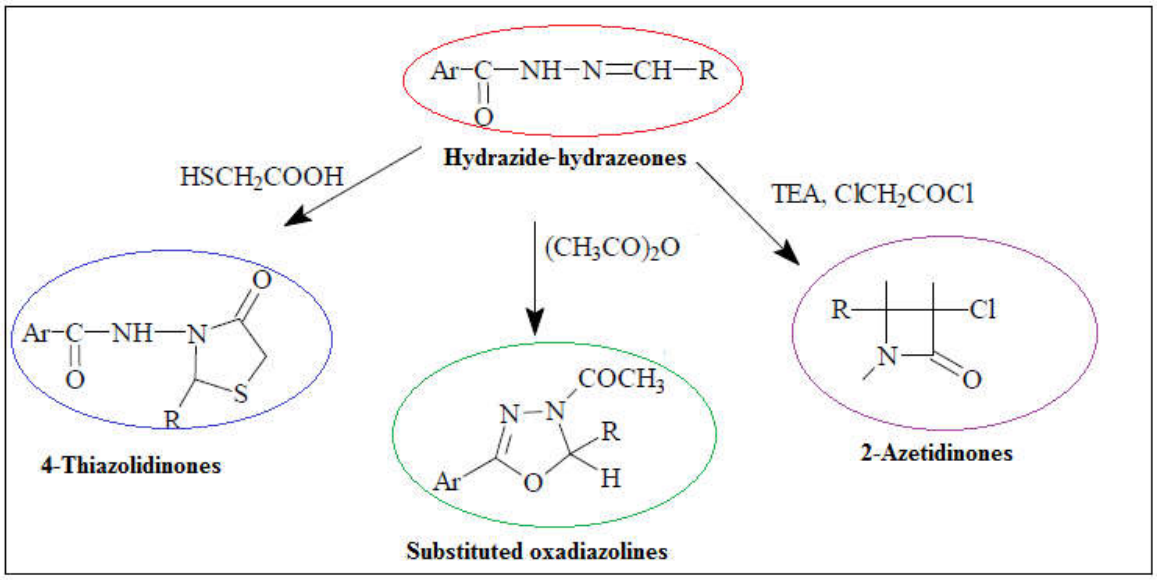


Figure 6. Heterocyclic compounds formed from hydrazide-hydrazones.

Biological activity of hydrazones

Hydrazones are a bioactive compounds with clinical and pharmacological proprieties. Nifuroxazide is an oral nitrofuran antibiotic used in anti-dehydration and colitis treatment. It neutralizes microbacterials in diarrhea, and has "a spectrum which covers most enteropathogenic microbacterials, *Shigella, Escherichia coli, Salmonella, Staphylococci, Klebsiella,* and *Yersinia* (**Figure 7**) [14].

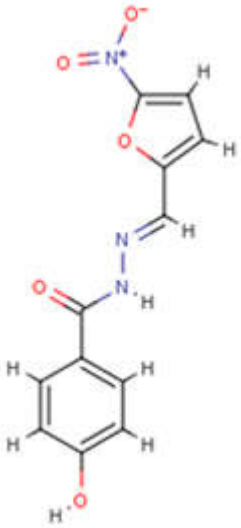
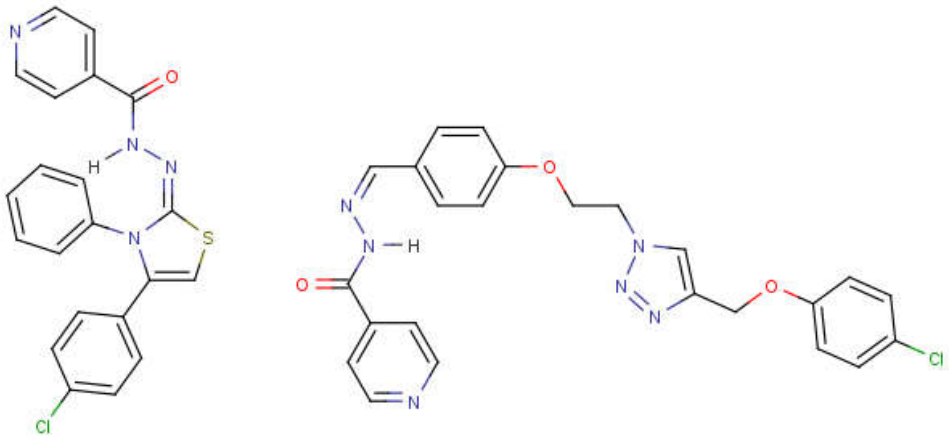


Figure 7. Structure of nifuroxazide [14].

Anti-mycobacterial activity

Due to the increasing number of drug resistant *Mycobacterium tuberculosis* strains, there is an urgent need for new anti-tubercular drugs, capable of overcoming the resistance mechanisms. Along this line, some new 3,4-disubstituted thiazolylidene-isonicotino hydrazide derivatives were synthesized and tested *in vitro* against *Mycobacterium tuberculosis* H37Ra 7131 strains. Among the potential compounds, N'-(4-(4-chlorophenyl)-3-phenylthiazol-2(3H)-ylidene) isonicotinohydrazide (**1**), which exhibited MIC value of 1.99 µg/mL [15]. In addition, hydrazone derived from thriazol-1-yl ethoxy phenyl, compound (**2**), has a potential anti-tubercular effect with MIC values ranging from 0.09 to 0.19 µg/mL (**Figure 8**) [16].



1 **2**

Figure 8. Structures of thiazolylidene-isonicotino hydrazide derivatives [15][16].

Anticancer activity

Structure-activity relationship (SAR) study of thirty-two isoniazid derivatives, demonstrated that the presence of a hydroxyl group on the aromatic ring, especially the *ortho*-position, plays an important role in the anticancer activity against human cancer cell lines: OVCAR-8 (ovary), SF-295 (glioblastoma), HCT-116 (colon), and HL-60 (leukemia). Shown in **Figure 9** are the structures of three compounds that

exhibited good cytotoxic activity when compared to the reference drug doxorubicin; these compounds are considered new anticancer agents [17].

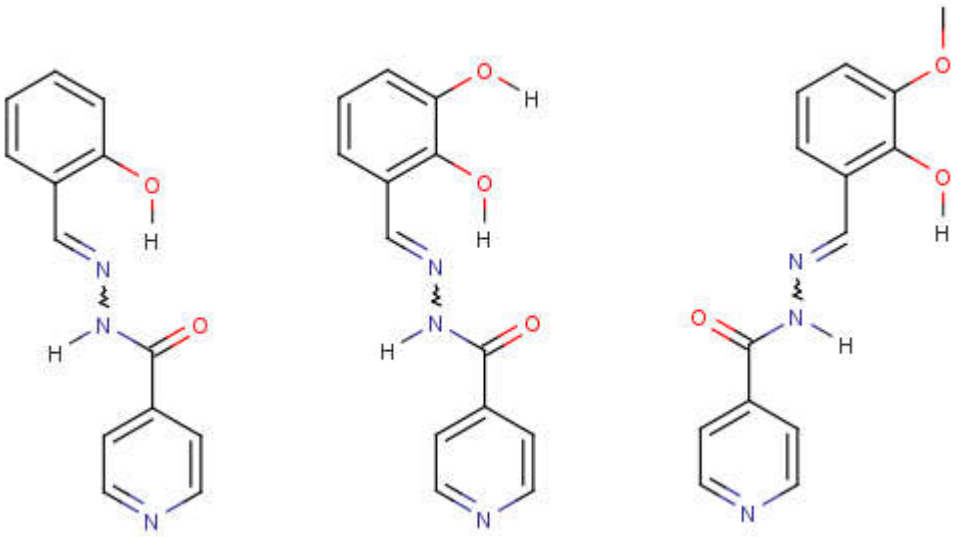


Figure 9. Structure of anticancer, monohydroxylated, dihydroxylated, and methoxylated hydrazones [17].

Leishmanicidal activity

Hydrazones and their thiosemicarbazone derivatives displayed antileishmanial effects. For this, **INH**-derivatives hydrazones (**HPAmIH** and **HPCIH**) were prepared and tested against intracellular amastigote form of *Leishmania (Viannia) braziliensis* strains and exhibited leishmanicidal effects (**Figure 10**) [18].

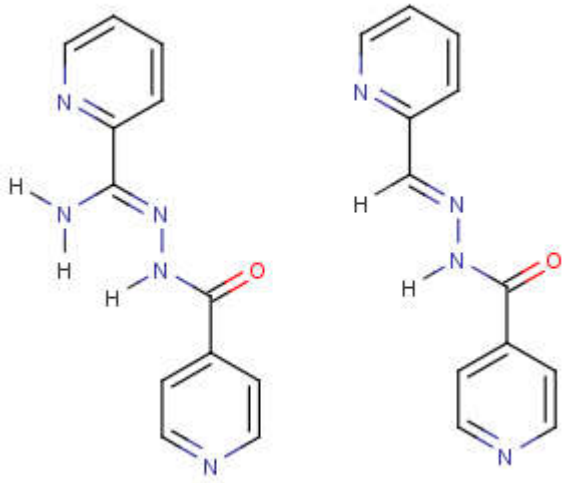


Figure 10. Structure of leishmanicidal hydrazones (**HPAmIH** and **HPCIH)** [18].

Antibacterial activity

Malhotra et al. [19] prepared a series of hydrazones by condensation of 2-ethoxybenzaldehyde with isoniazid. Aminomethylation of these hydrazones with formaldehyde and substituted secondary amines formed the new hydrazones, which were tested for their antimicrobial activity. Results revealed that the compounds **3**, **4**, and **5** showed excellent effects against bacterial strains, such as *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Escherichia coli* (**Figure 11**).

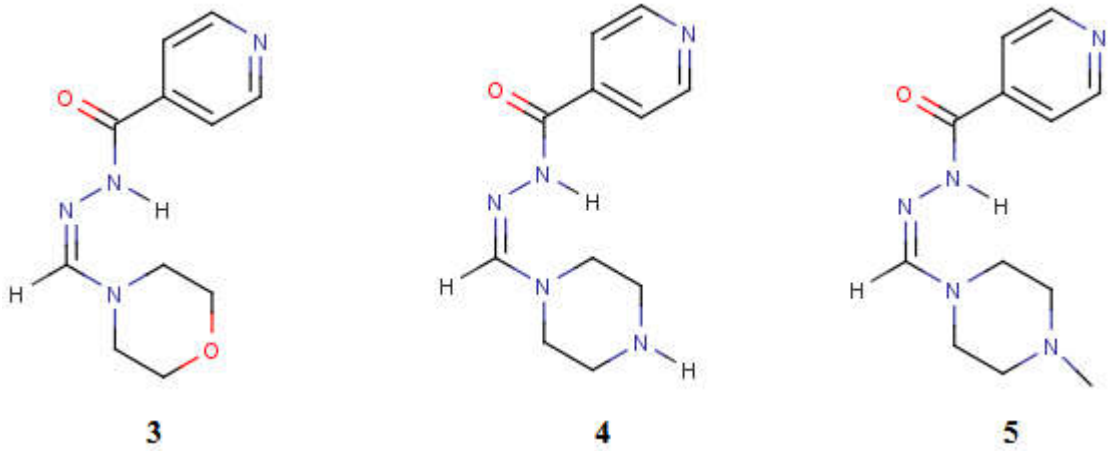


Figure 11. Structure of antibacterial hydrazones **3**, **4**, and **5** [19].

Antifungal activity

Cordeiro et al. [19] synthesized a series of hydrazones derived from **INH** and evaluated their antifungal activity against *Coccidioides posadasii*. Three compounds of the series, N'-[(E)-1-(4-methoxyphenyl)ethylidene]pyridine-4-carbohydrazide (**A**), N'-[(E)-1-(4-methylphenyl) ethylidene] pyridine-4-carbohydrazide (**B**), and N'-[(E)-1-(phenyl)ethylidene]pyridine-4-carbohydrazide (**C**) exhibited significant antifungal activity (**Figure 12**).

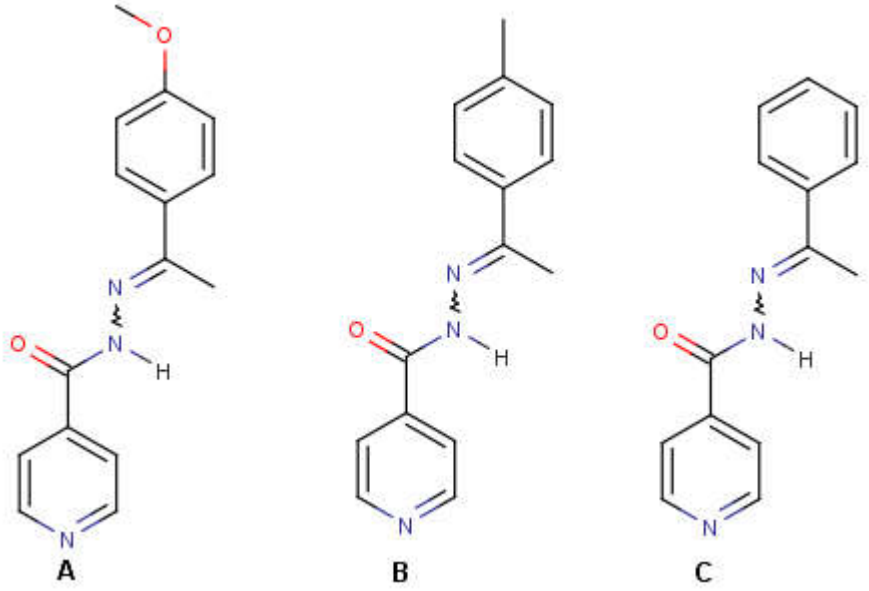


Figure 12. Structure of antifungal hydrazones (**A**, **B**, and **C**) [19].

REFERENCES

1. A. Kajal, S. Bala, N. Sharma, S. Kamboj, V. Saini, (2014).Therapeutic Potential of Hydrazones as Anti-Inflammatory Agents,*International journal of medicinal chemistry*. 2014 1–11.
2. A. Kivrak, C. Yilmaz, M. Konus, H. Koca, S. Aydemĭr, J. A. Oagaz, (2018). Synthesis and biological properties of novel 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene) hydrazine analogues, *Turkish journal of chemistry*. 42 306–316.
3. H.G. Bonacorso, G.R. Paim, L.M.F. Porte, E.P. Pittaluga, M. A.P. Martins, N. Zanatta. (2012). 6-Hydrazinonicotinic acid hydrazide: a useful precursor for chemo- and regioselective synthesis of new heteroaryl-linked pyridinohydrazones. *Arkivoc.* viii 214–225
4. X. Su, I. Aprahamian, (2014). Hydrazone-based switches, metallo-assemblies and sensors, *Chemical Society Reviews*. 43 1963–1981.
5. J. Patocka1, R. Pita, K. Kuca, (2012).Gyromitrin, mushroom toxin of gyromitraspp, *Military Medical Science Letters*. 81 61–67.

6. M. S. Abdelfattah, K. Toume , M. A. Arai , H. Masu , M. Ishibashi, (2012) Katorazone, a new yellow pigment with a 2-azaquinone-phenylhydrazone structure produced by *Streptomyces sp*. IFM 11299, *Tetrahedron Letters* **.**53 3346–3348.
7. G. Le Goff, J. Ouazzani, (2014) Natural hydrazine-containing compounds: biosynthesis, isolation, biological activities and synthesis, *Bioorganic & medicinal chemistry***.** 22 6529–6544.
8. F. Li, Y. Miao, L. Zhang, S. A. Neuenswander, J. T. Douglas, X. MA, (2011) Metabolomic Analysis Reveals Novel Isoniazid Metabolites and Hydrazones in Human Urine, *Drug Metabolism and Pharmacokinetics*. 26 569–576.
9. R. Brehme, D. Enders, R. Fernandez, J. M. Lassaletta, (2007) Aldehyde N,N-Dialkylhydrazones as Neutral Acyl Anion Equivalents: Umpolung of the Imine Reactivity, *European Journal of Organic Chemistry*. 34 5629–5660.
10. N.P. Belskaya, W. Dehaen, V.A. Bakulev, (2010) Synthesis and properties of hydrazones bearing amide, thioamide and amidine functions, *Arkivoc* 275–332.
11. S. Rollas, N. Gülerman, H. Erdeniz, (2002) Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4oxadiazolines, *Farmaco Edizione Scientifica*. 57 171–174.
12. A.B. Thomas, R. K. Nanda, L.P. Kothapalli, S.C. Hamane. (2016) Synthesis and biological evaluation of Schiff's bases and 2-azetidinones of isonocotinylhydrazone as potential antidepressant and nootropic agents, *Arabian Journal of Chemistry***.** 9 79–90.
13. N.B. Patel, F.M. Shaikh, (2010) Synthesis of New Pyridine Based 4-Thiazolidinones Incorporated Benzothiazoles and Evaluation of Their Antimicrobial Activity, *Journal of Sciences, Islamic Republic of Iran.* 21 121–129.
14. N. Singh, R.Ranjana, M.Kumari, B.kumar, (2016) A Review on Biological Activities of Hydrazone Derivatives, *International Journal of Pharmaceutical* and *Clinical Research*. 8 162–166.
15. M.A. Elhakeem, A.T. Taher, S.M. Abuel-Maaty, (2015) Synthesis and anti-mycobacterial evaluation of some new isonicotinylhydrazide analogues, *Bulletin of Faculty of Pharmacy*, Cairo University. 53 45–52.
16. N. Nayak, J. Ramprasad, U. Dalimba. (2015) New INH–pyrazole analogs: Design, synthesis and evaluation of antitubercular and antibacterial activity, *Bioorganic* & *Medicinal Chemistry Letters***.** 25 5540–5545.
17. F.A.R. Rodrigues, A.C.A. Oliveira, B. C. Cavalcanti, C. Pessoa, A.C. Pinheiro, M, V. N. de Souza. (2014) Biological Evaluation of Isoniazid Derivatives as an Anticancer Class, *Scientia Pharmaceutica*. 82 21–28.
18. R.S. Amim, G.S.S. Firmino, A.C.P.D. Rego, A.L. Nery, S.A.G. Da-Silva, M.V.N. de Souza, C. Pessoa, J.A.L.C. Resende, J.D. Figueroa-Villarf, J.A. Lessa. (2016) .Cytotoxicity and Leishmanicidal Activity of Isoniazid-Derived Hydrazones and 2-Pyrazineformamide Thiosemicarbazones. *Journal of the Brazilian Chemical Society*. 27 769-777.
19. M. Malhotra, S. Sharma, A. Deep, (2012) Synthesis, characterization and antimicrobial evaluation of novel derivatives of isoniazid, *Medicinal Chemistry Research*. 21 1237–1244.
20. R.A. Cordeiro, C.V.S. Melo, F.J.F. Marques, R. Serpa, A.J.J. Evangelista, E.P. Caetano, J. Mafezoli, M.C.F. Oliveira, M.R. Silva, T.J.P.G. Bandeira, J.L.B. Moreira , R.S.N. Brilhante, M.F.G. Rocha, J.J.C. Sidrim. (2016) Synthesis and in vitro antifungal activity of isoniazid-derived hydrazones against *Coccidioides posadasii*, *Microbial Pathogenesis*. 98 1–5.