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Review

Biological Activities of Hydrazone Derivatives

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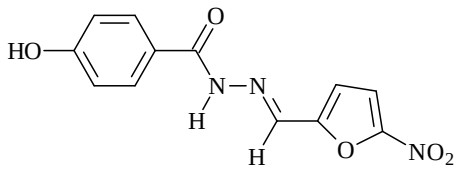
Abstract: There has been considerable interest in the development of novel compounds with anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, vasodilator, antiviral and antischistosomiasis activities. Hydrazones possessing an azometine -NHN=CH- proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.

Keywords: Hydrazones, hydrazide-hydrazones, biological activity, isoniazid.

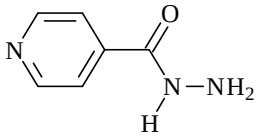
Contents:

Introduction

Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities. For example, isonicotinoyl hydrazones are antitubercular; 4-hydroxybenzoic acid[(5-nitro-2-furyl)methylene]-hydrazide (nifuroxazide) is an intestinal antiseptic; 4-fluorobenzoic acid[(5-nitro-2-furyl)methylene]-hydrazide [1] and 2,3,4-pentanetrione-3-[4-[[(5-nitro-2-furyl)methylene]hydrazino]carbonyl]phenyl]-hydrazone [2], which were synthesized in our Department, have antibacterial activity against both *Staphylococcus aureus* ATCC 29213 and *Mycobacterium tuberculosis* H37Rv at a concentration of 3.13 µg/mL. N^1-(4-Methoxybenzamido)benzoyl]-N^2-[(5-nitro-2-furyl)methylene]hydrazine, which was also synthesized in our Department [3], demonstrated antibacterial activity. In addition, some of the new hydrazide-hydrazones that we have recently synthesized were active against the same strain of *M. tuberculosis* H37Rv between the concentrations of 0.78-6.25 µg/mL [4].

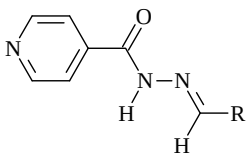


Nifuroxazide



Isoniazid

Isonicotinic acid hydrazide (isoniazid, INH) has very high *in vivo* inhibitory activity towards *M. tuberculosis* H37Rv. Sah and Peoples synthesized INH hydrazide-hydrazones **1** by reacting INH with various aldehydes and ketones. These compounds were reported to have inhibitory activity in mice infected with various strains of *M. tuberculosis* [5]. They also showed less toxicity in these mice than INH [5, 6] Buu-Hoi *et al*. synthesized some hydrazide-hydrazones that were reported to have lower toxicity than hydrazides because of the blockage of $-NH_2$ group. These findings further support the growing importance of the synthesis of hydrazide-hydrazones compound [7].



1

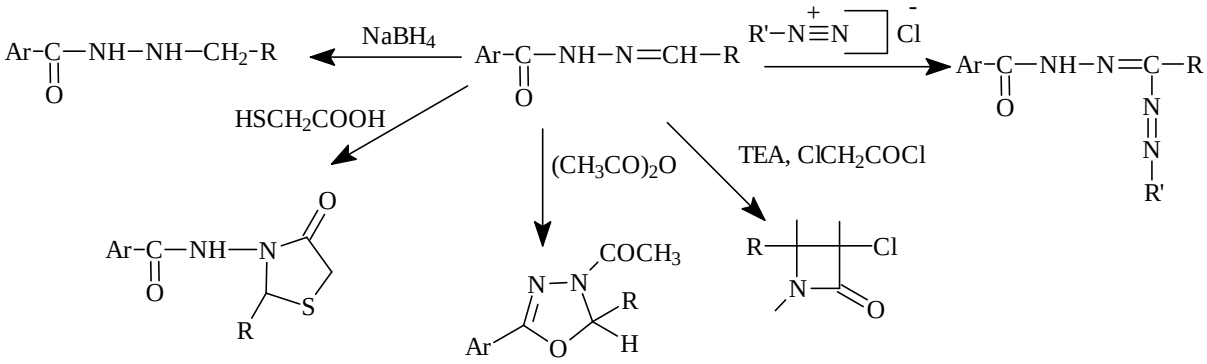
Iron is necessary for the biochemical reactions of living organisms. Desferrioxamine is an agent which is used for the treatment of a complication called “Iron Overload Disease”. Researchers have synthesized hydrazones of INH by using various aldehydes and their iron complexes and evaluated

these complexes for their antitumoral activity. The mechanism of antitumoral activity of iron complexes is the inhibition of ribonucleotide reductase, which is an important enzyme for conversion of ribonucleotides to deoxyribonucleotides. Copper complexes of INH that facilitate the intercellular transport of INH were synthesized and evaluated for their antitubercular activity.

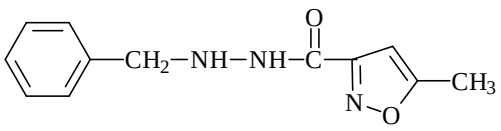
Hydrazones containing an azometine -NHN=CH- proton are synthesized by heating the appropriate substituted hydrazines/hydrazides with aldehydes and ketones in solvents like ethanol, methanol, tetrahydrofuran, butanol, glacial acetic acid, ethanol-glacial acetic acid. Another synthetic route for the synthesis of hydrazones is the coupling of aryldiazonium salts with active hydrogen compounds. In addition, 4-acetylphenazone isonicotinoylhydrazones was prepared by Amal and Ergenç [8] by exposing an alcohol solution of 4-acetylphenazone and INH to sunlight or by mixing them with a mortar in the absence of the solvent.

Hydrazide-hydrazones compounds are not only intermediates but they are also very effective organic compounds in their own right. When they are used as intermediates, coupling products can be synthesized by using the active hydrogen component of –CONHN=CH- azometine group [9]. *N*-Alkyl hydrazides can be synthesized by reduction of hydrazones with $NaBH_4$ [10], substituted 1,3,4-oxadiazolines can be synthesized when hydrazones are heated in the presence of acetic anhydride [1,11,12]. 2-Azetidinones can be synthesized when hydrazones react with trietylamine chloro acetylchloride[13]. 4-Thiazolidinones are synthesized when hydrazones react with thioglycolic acid/ thiolactic acid [3,14] (Scheme 1).

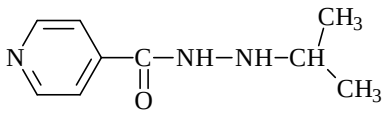
Scheme 1



Many effective compounds, such as iproniazide and isocarboxazide, are synthesized by reduction of hydrazide-hydrazones. Iproniazide, like INH, is used in the treatment of tuberculosis. It has also displays an antidepressant effect and patients appear to have a better mood during the treatment. Another clinically effective hydrazide-hydrazones is nifuroxazide, which is used as an intestinal antiseptic.



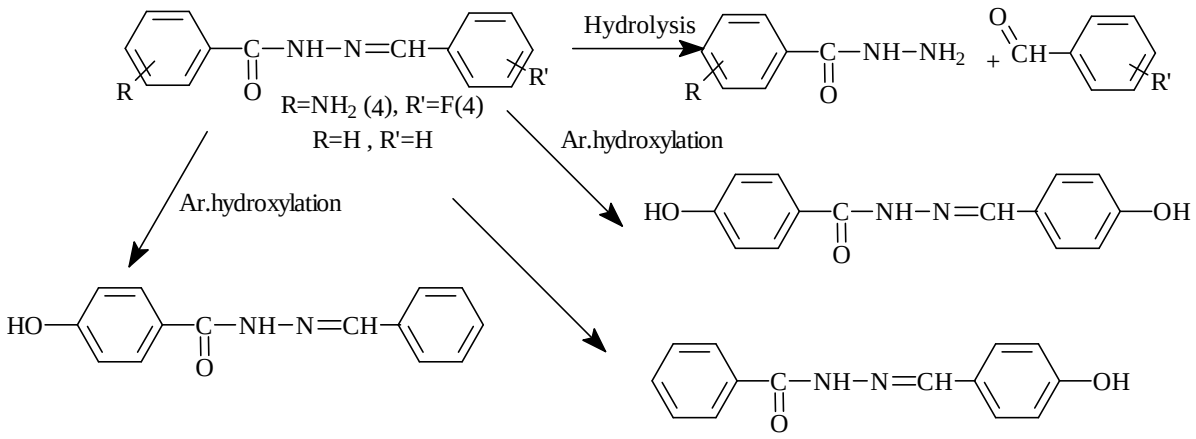
Isocarboxazide



Iproniazide

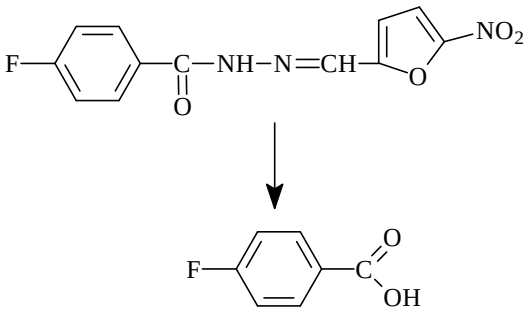
A number of studies have investigated the *in-vitro* and *in-vivo* metabolism of hydrazide-hydrazones. In *in-vitro* metabolism studies, it has been found that hydrazide-hydrazones undergo hydrolytic reactions and aromatic rings undergo aromatic hydroxylation reactions [15,16] (Scheme 2).

Scheme 2



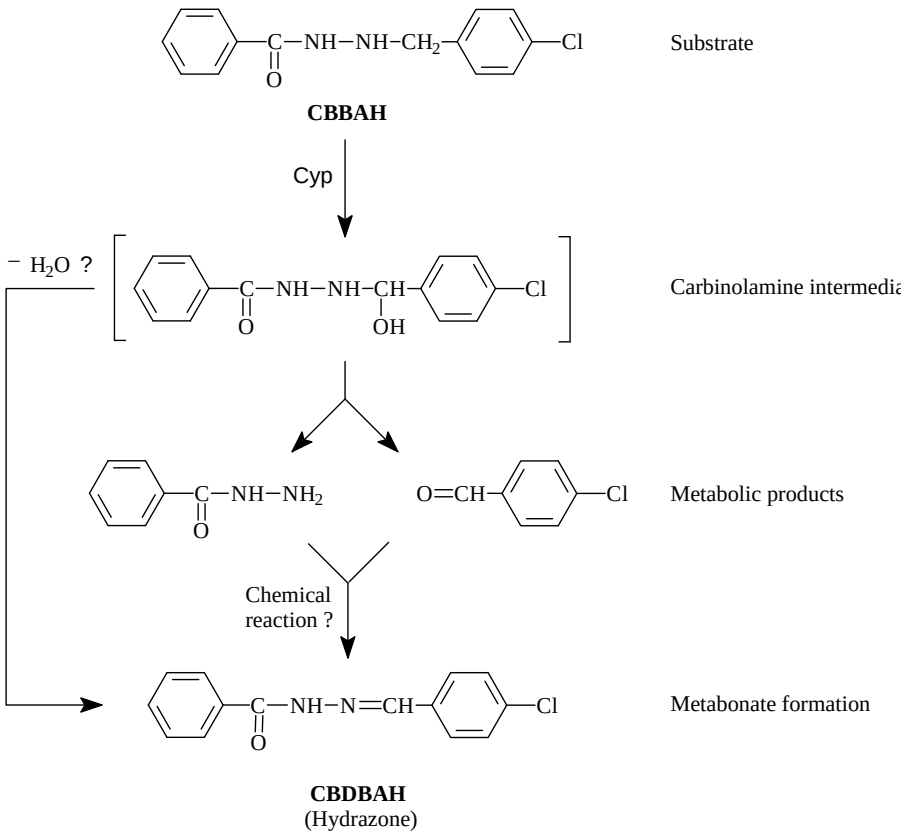
Gülerman *et al*. investigated the *in vivo* metabolism of 4-fluorobenzoic acid ((5-nitro-2-furyl)-methylene-hydrazide, a hydrazide derivative that is effective against *S. aureus* ATCC 29213. They confirmed the presence of the substrate and 4-fluorobenzoic acid metabolite in blood and blood cells [17] (Scheme 3).

Scheme 3



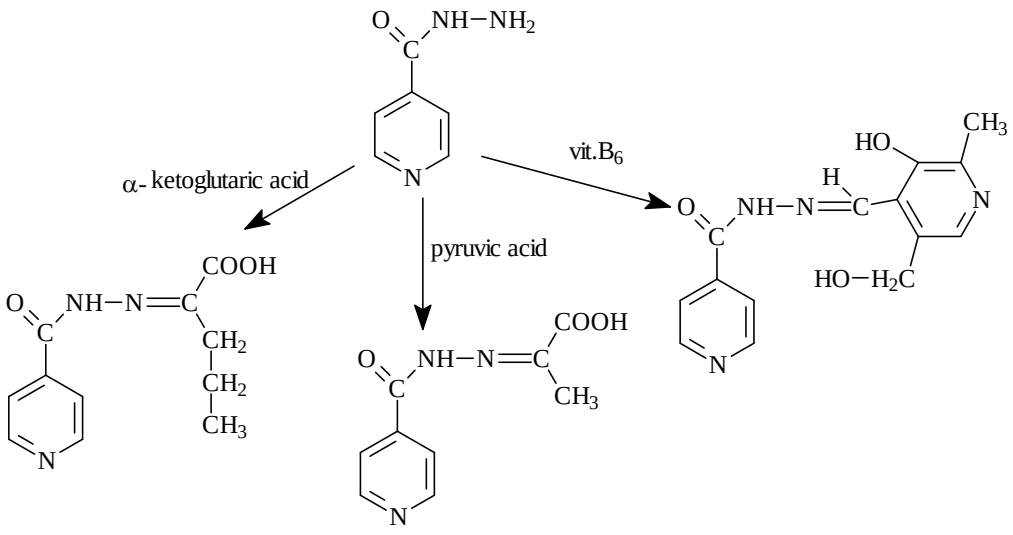
Küçükgüzel *et al*. studied the *in vitro* hepatic microsomal metabolism of *N*-(4-chlorobenzyl)-*N*′-benzoylhydrazine (CBBAH). The corresponding hydrazone, namely benzoic acid (4-chlorophenyl)-methylenehydrazide was detected as the major *in vitro* metabolic product [18] (Scheme 4).

Scheme 4



It has been known that the hydrazides (like INH) form α-ketoglutaric acid and form hydrazones with vitamin B6 and pyruvic acid. It is clinically important that when tuberculosis patients are treated with INH, reaction of INH with vitamin B6 leads to formation of a hydrazone and development of vitamin B6 deficiency, therefore, patients who are treated with INH should be administered vitamin B6 (Scheme 5).

Scheme 5



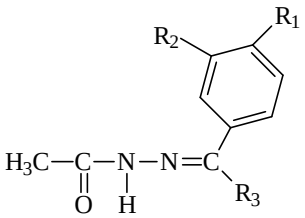
This review critically evaluates the pharmacological activity of the hydrazones that were reported in the past ten years.

2. Biological activity

2.1. Anticonvulsant Activity

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archieved during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity.

The biological results revealed that in general, the acetylhydrazones **2** provided good protection against convulsions while the oxamoylhydrazones **3** were significantly less active. [19].



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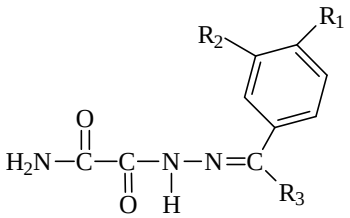
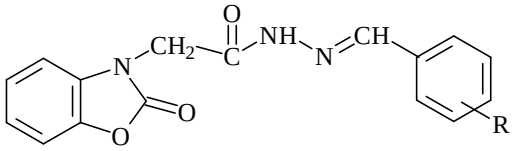


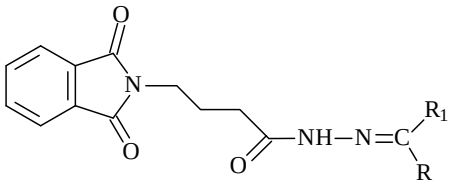
3

Fifteen new hydrazones of (2-oxobenzoxazoline-3-yl)acetohydrazide **4** were synthesised and their antiepileptic activity was tested in scPTZ test. The 4-fluoro derivative was found to be more active than the others [20].



4

4-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain. GABA hydrazones **5** were designed and synthesized and evaluated for their anticonvulsant properties in different animal models of epilepsy such as MES, scPTZ, subcutaneous strychine (scSTY) and intraperitonal picrotoxin (ipPIC) induced seizure tests. Some of the compounds were effective in these models [21].

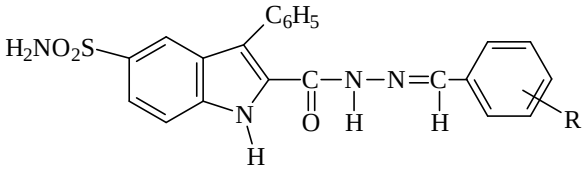


5

2.2. Antidepressant Activity

Iproniazide, isocarboxazide and nialamide, which are hydrazide derivatives, exert their action by inhibiting the enzyme monoamine oxidase (MAO). Inhibition results in increased levels of norepinephrine, dopamine, tyramine and serotonin in brain neurons and in various other tissues. There have been many reports on the antidepresant / MAO-inhibiting the activity of hydrazones derived from substituted hydrazides and reduction products.

Ten new arylidenehydrazides **6** which were synthesized by reacting 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes, evaluated for their antidepresant activity. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid 3,4-methylenedioxy / 4-methyl / 4-nitrobenzylidene-hydrazide showed antidepresant activity at 100 mg/kg [10].

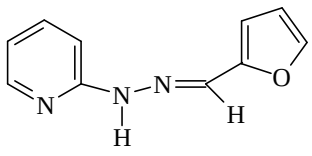


6

2.3. Analgesic, Antiinflammatory and Antiplatelet Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the hydrazone moiety present in some compounds possess a pharmacophoric character for the inhibition of COX.

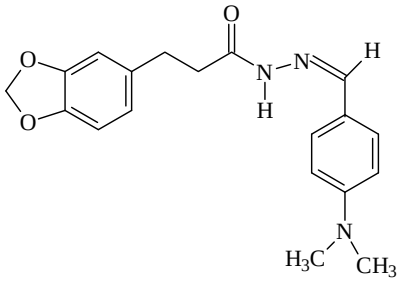
The most important antiinflammatory derivative 2-(2-formylfuryl)pyridylhydrazone **7** presented a 79 % inhibition of pleurisy at a dose of 80.1 μmol/kg. The authors also described the results concerning the mechanism of the action of these series of *N*-heterocyclic derivatives in platelet aggregation that suggests a Ca^{2+} scavenger mechanism. Compound **7** was able to complex Ca^{2+} in in-vitro experiments at 100 μM concentration, indicating that these series of compounds can act as Ca^{2+} scavenger depending on the nature of the aryl moiety present at the imine subunit [22].



7

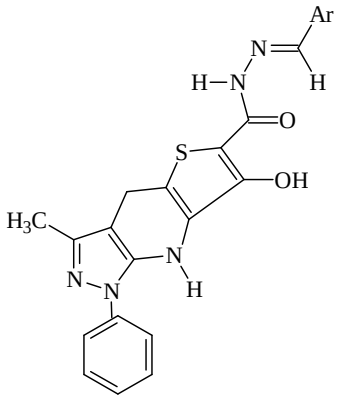
A new series of antinociceptive compounds that belong to the N-acylarylhydrazone class were synthesized from natural safrole.[(4′-N,N-Dimethylaminobenzylidene-3-(3′,4′-methylenedioxyphenyl)

propionylhydrazine] **8** was more potent than dipyrone and indomethacine, are used as standard antiinflammatory/antinociceptive drugs [23].



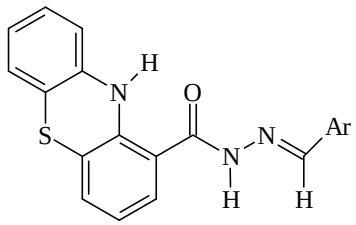
8

The antiplatelet activity of novel tricyclic acylhydrazone derivatives **9** was evaluated by their ability to inhibit platelet aggregation of rabbit platelet-rich plasma induced by platelet-activating factor (PAF) at 50 nM. Benzylidene- / 4′-bromobenzylidene 3-hydroxy-8-methyl-6-phenylpyrazolo[3,4-b]thieno-[2,3-d]pyridine-2-carbohydrazide were evaluated at 10 μM, presenting, respectively, 10.4 and 13.6% of inhibition of the PAF-induced platelet aggregation [24].



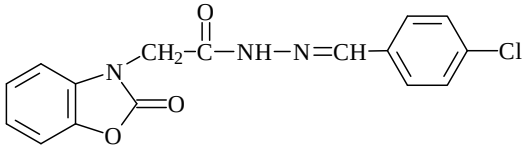
9

The evaluation of platelet antiaggregating profile let to identification of a new potent prototype of antiplatelet derivative, that is benzylidene 10H-phenothiazine-1-carbohydrazide (IC_{50}=2.3 μM) **10**, which acts in the arachidonic acid pathway probably by inhibition of platelet COX-1 enzyme. Additionally, the change in *para*-substituent group of acylhydrazone framework permitted to identify a hydrophilic carboxylate derivative and a hydrophobic bromo derivative as two new analgesics that are more potent than dipyrone, which is the standard, possessing selective peripheral or central mechanism of action [25].

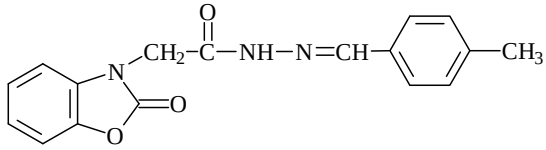


10

Gökhan-Kelekçi *et al*. synthesized hydrazones containing 5-methyl-2-benzoxazoline. The analgesic effects of 2-[2-(5-methyl-2-benzoxazoline-3-yl)acetyl]-4-chloro- / 4-methyl benzylidene hydrazine **11c** and **11d** were found to be higher than those of morphine and aspirin. In addition, 2-[2-(5-methyl-2-benzoxazoline-3-yl)acetyl]-4- methoxybenzylidene hydrazine **11e** at 200 mg/kg dose possessed the most antiinflammatory activity [26].

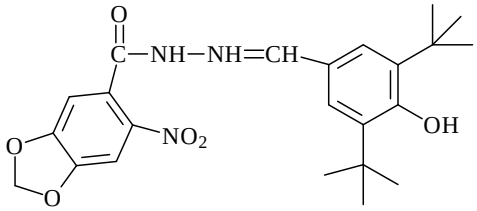


11c



11d

Duarte *et al*. have described *N*′-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1,3-benzodioxole-5-carbohydrazine **12c** as a novel antiinflammatory compound [27].

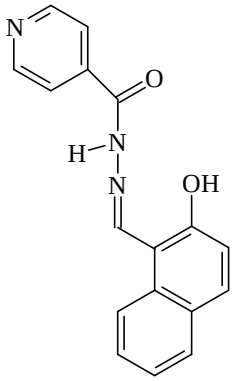


12c

2.4. Antimalarial Activity

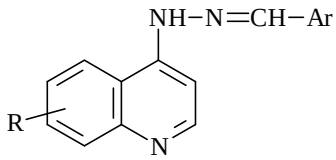
Malaria is a disease caused by parasitic protozoa of the genus *Plasmodium* which afflicts more than 500 million people worldwide and causes approximately 2 million deaths each year. The spread of multidrug-resistant *Plasmodium falciparum* has highlighted the urgent need to discover new antimalarial drugs.

The aroylhydrazone chelator 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone **13** showed greater antimalarial agent activity than desferrioxamine against chloroquine-resistant and -sensitive parasites [28].

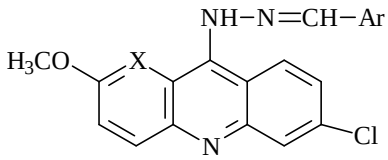


13

A series of N^1-arylidene-N^2-quinolyl- **14** and N^2-acrydinylhydrazones- **15** were synthesized and tested for their antimalarial properties. The new synthesized compounds, including **14d-g** and **15a-c** showed an antiplasmodial activity against the chloroquine-sensitive D10 strain in the same range of chloroquine (CQ). Similarly, **14f** and **14g** displayed the same activity as CQ against chloroquine-sensitive 3D-7 strain, while compound **15b** was 10 times more potent than CQ. Two analogues **15b** and **15c,** were more active against W2 CQ-resistant than D10 CQ-sensitive strains [29].

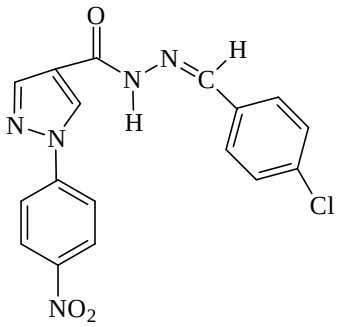


14d-g



15a-c

1-Substituted phenyl-*N*′-[(substitutedphenyl)methylene]-1*H*-pyrazole-4-carbohydrazides **16** were synthesized and their leishmanicidal and cytotoxic effects were compared to the prototype drugs (ketoconazole, benznidazole, allopurinol and pentamidine) *in vitro*. The 1*H*-pyrazole-4-carbohydrazide derivatives with X = Br, Y = NO_2 and X = NO_2, Y = Cl demonstrated the highest activity and they were more effective on promastigotes forms of *L. amazonensis* than on *L. chagasi* and *L. braziliensis* species [30].

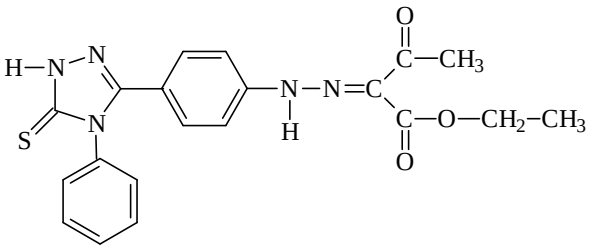


16

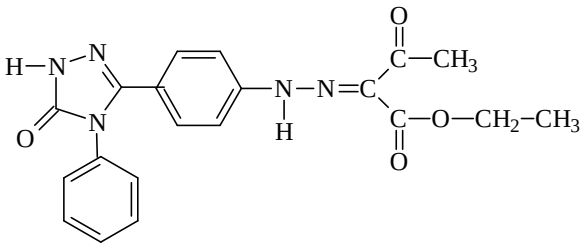
2.5. Antimicrobial Activity

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists.

Ethyl 2-arylhydrazono-3-oxobutyrates **17** were synthesized in order to determine their antimicrobial properties. Compound **17d** showed significant activity against *S. aureus* whereas the others had no remarkable activity on this strain. Compound **17e** was found to be more active than the others against *Mycobacterium fortuitum* at a MIC value of 32 μg/ml [31].

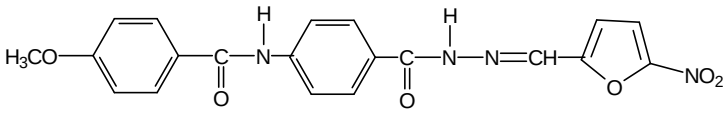


17d



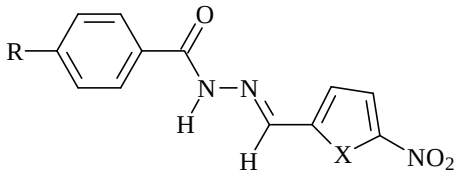
17e

N^1-(4-methoxybenzamido)benzoyl]-N^2-[(5-nitro-2-furyl)methylene]hydrazine **18** inhibited the growth of several bacteria and fungi [3].



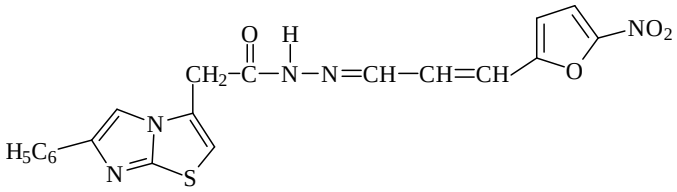
18

Nifuroxazide and six analogs **19** were synthesized by varying the substituent at the *p*-position of the benzene ring and the heteroatom of the heterocyclic ring. These compounds were evaluated for their antimicrobial activity against *S. aureus* ATCC 25923 and found to be active at concentration 0.16-63.00 μg/mL [32].



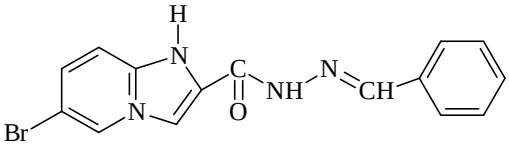
19

N^2-Substituted alkylidene/arylidene-6-phenylimidazo[2,1-b]thiazole-3-acetic acid hydrazides **20** were synthesized and evaluated for their *in vitro* antimicrobial activity. Some compounds showed antimicrobial activity against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *T .mentagrophytes var.Erinacei* NCPF-375, *T. rubrum* and *M. audounii* (MIC 25-0.24 μg/mL) [33].

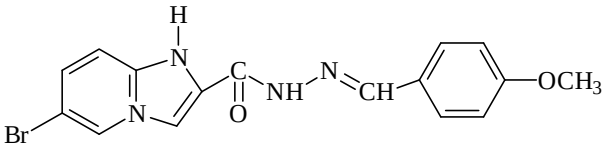


20j

Turan-Zitouni *et al*. found 5-bromoimidazo[1,2-a]pyridine-2-carboxylic acid benzylidene-hydrazide **21** and 5-bromoimidazo[1,2-a]pyridine-2-carboxylic acid 4-methoxybenzylidenehydrazide **22** to possess antimicrobial activity at 3.9 μg/mL against *E. fecalis* and *S. epidermis* [34].

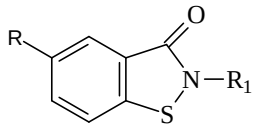


21

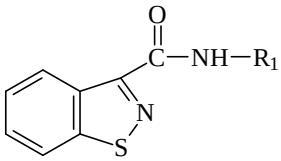


22

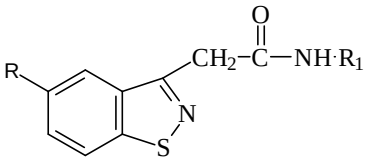
A series of hydrazones derived from 1,2-benzisothiazole hydrazides (R_1=H**) 23-27** as well as the parent cyclic (**23** and **26**) and acyclic (**24**, **25** and **27**) 1,2-benzisothiazole hydrazides, were synthesized and evaluated as antibacterial and antifungal agents. All of the 2-amino-1,2-benzisothiazole-3(2H)-one derivatives, belonging to series **23** and **26** showed good antibacterial activity against Gram positive bacteria. Most of them were also active against yeasts, too [35].



23 (R=H), 26 (R=CH_3)

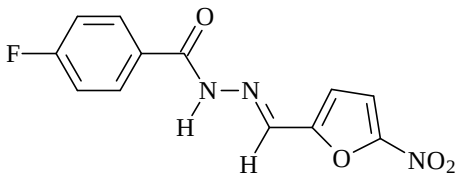


24



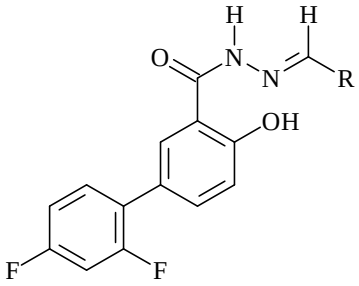
25(R=H), 27 (R=CH_3)

Rollas *et al*. synthesized a series of hydrazide hydrazones **28** and 1,3,4-oxadiazolines of 4-fluoro-benzoic acid hydrazide as potential antimicrobial agents and tested these compounds for their antibacterial and antifungal activities against *S. aureus, E. coli*, *P. aeruginosa* and *C. albicans.* From these compounds, 4-fluorobenzoic acid[(5-nitro-2-furyl)methylene] hydrazide (**28a**) showed equal activity as ceftriaxone against *S. aureus*. In addition, the MIC values of compounds **28c** and **28d** for the same strain were in the range of those reported for ceftriaxone according to NCCLS 1997 [1].



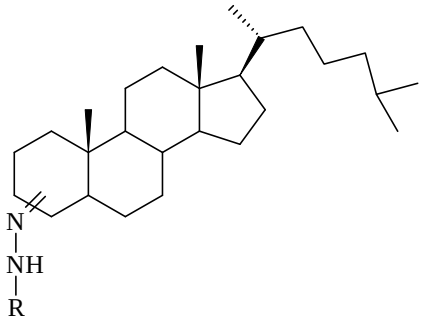
28a

Küçükgüzel *et al*. synthesized diflunisal hydrazide-hydrazone derivatives. 2′,4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(5-nitro-2-furyl)methylene] hydrazide (**29a**) has shown activity against *S. epidermis* HE-5 and *S. aureus* HE-9 at 18.75 μg/mL and 37.5 μg/mL, respectively. 2′,4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(2,4,6-trimethylphenyl)methylene] hydrazide (**29e**) has exhibited activity against *Acinetobacter calcoaceticus* IO-16 at a concentration of 37.5 μg/mL, whereas Cefepime, the drug used as standard, has been found to be less active against the same microorganisms [36].



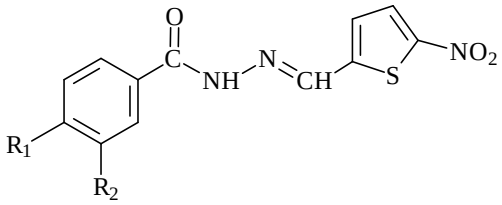
29

A series of hydrazones synthesized from various cholesterol derivatives **30** were evaluated for their *in vitro* antimicrobial properties against human pathogens. The activity was highly dependent on the structure of the different compounds involved. The best results have been obtained with tosylhydrazone cholesterol derivatives exhibiting activities against *C. albicans* (CIP 1663-80) at a concentration of 1.5 μg/mL [37].



30

4-Substituted benzoic acid [(5-nitro-thiophene-2-yl)methylene]hydrazides **31** were synthesized as potential bacteriostatic activity and some of them indeed showed bactericidal activity [38].



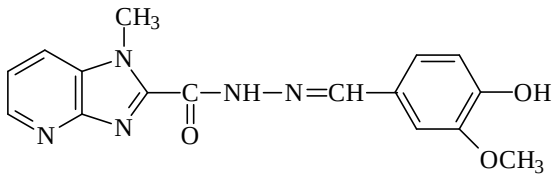
31

2.6. Antimycobacterial Activity

Tuberculosis is a serious health problem that causes the death of some three million people every year worldwide [39]. In addition to this, the increase in *M. tuberculosis* strains resistant to front-line antimycobacterial drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis. Meyer and Mally prepared new hydrazones by reacting isoniazid (INH) with benzaldehyde, o-chlorobenzaldehyde and vanilin [5]. Shchukina *et al*. prepared INH hydrazide-hydrazones **1** by reacting INH with various

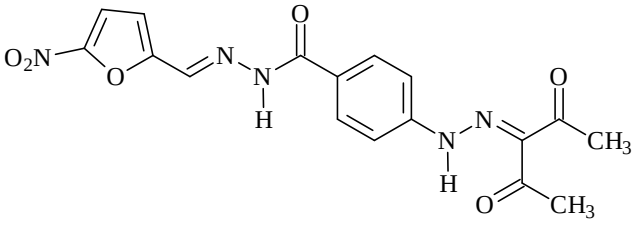
aldehydes and ketones; the compounds were reported to have activity in mice which had been infected with various strains of *M. tuberculosis*, and also indicated lower toxicity than INH [5,6].

The reaction of 1-methyl-1H-2-imidazo[4,5-b]pyridinecarboxylic acid hydrazide with substituted aldehydes yielded the corresponding hydrazide-hydrazones. Compound **32** exhibited antimycobacterial activity against *M.tuberculosis H37 Rv, M. tuberculosis 192, M. tuberculosis 210*, isolated from patients and resistant against INH, ethambutol, rifampicine at 31.2 μg/mL[40].



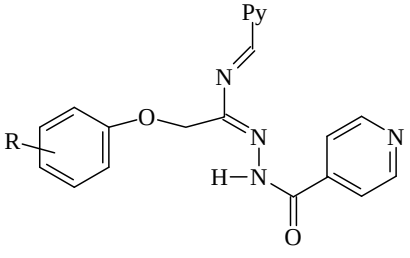
32

Various different 2,3,4-pentanetrione-3-[4-[[(5-nitro-2-furyl/pyridyl/substituted-phenyl)-methylene]hydrazino]carbonyl]phenyl]hydrazones **33** were synthesized. All the synthesized compounds were evaluated for their antimycobacterial activity against *M. fortuitum* ATCC 6841 and *M. tuberculosis* H37Rv. Of the compounds screened, **33e** and **33g** were found to be active against *M. fortuitum* at an MIC value of 32 μg/mL. Compound **33a**, which exhibited > 90% inhibition in the primary screen at 12.5 μg/mL against *M. tuberculosis* H37Rv, was the most promising derivative for antituberculosis activity. Results obtained from the level II screening showed that the actual MIC and IC_{50} values of **32a** were 3.13 and 0.32 μg/mL, respectively. The same compound was also tested against *Mycobacterium avium*, which was observed not to be susceptible to **33a** [2].



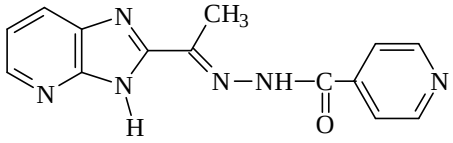
33a

Isonicotinoylhydrazones have been further reacted with pyridinecarboxaldehydes to give the corresponding pyridylmethyleneamino derivatives **34**. The new synthesized hydrazones and their pyridylmethyleneamino derivatives were tested for their activity against mycobacteria, Gram-positive and Gram-negative bacteria. The cytotoxicity was also tested. Several compounds showed a good activity against *M. tuberculosis* H37Rv and some isonicotinoylhydrazones showed a moderate activity against a clinically isolated *M. tuberculosis* (6.25-50 μg/mL) which was INH resistant [41].



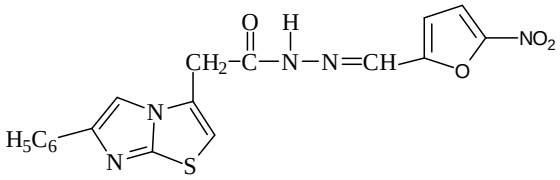
34

The reaction of 2-acetylimidazo[4,5-b]pyridine with INH yielded the corresponding hydrazide-hydrazones **35**. This compound exhibited activity against *M. tuberculosis H37 Rv* , *M. tuberculosis 192*, *M. tuberculosis 210*, isolated from patients and resistant against INH, ethambutol, rifampicine at 3.13 μg/mL [42].



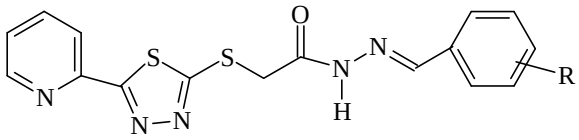
35

N^2-Substitutedalkylidene/arylidene-6-phenylimidazo[2,1-b]thiazole-3-acetic acid hydrazides **20** were synthesized and evaluated for *in vitro* antimycobacterial activity. The compounds exhibited different degrees of inhibition (17-98 %) against *M. tuberculosis H37 Rv* [33].



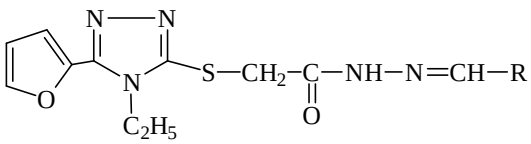
20i

[5-(Pyridine-2-yl)-1,3,4-thiadiazole-2-yl]thio]acetic acid arylidene-hydrazide derivatives **36** were synthesized and tested for their in vitro antimycobacterial activity. Some compounds showed activity at 20 μg/mL against *M. tuberculosis* and at 40 μg/mL against *M. avium* [43].



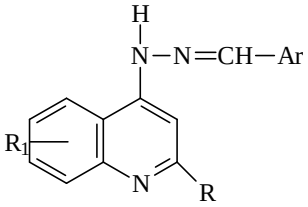
36

N-Alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides **37** were synthesized and evaluated for in vitro antimycobacterial activity. The compounds exhibited different degrees of inhibition (3-61%) against *M. tuberculosis H37 Rv* at 6.25 μg/mL [44].



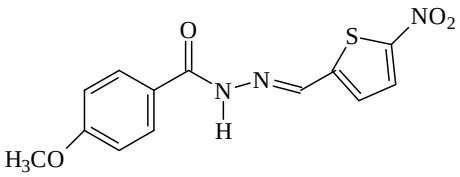
37

A series of 4-quinolylhydrazones **38** were synthesized and tested against *M. tuberculosis* H37Rv. Preparation of the title compounds was achieved by reaction of 4-quinolylhydrazine and aryl- or heteroarylcarboxaldehydes. Most of the derivates had antitubercular properties; two compounds were identified with the highest activity and they were tested also against *M. avium* [45].



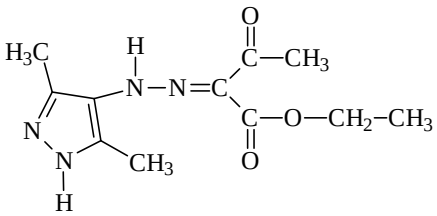
38

Benzoic acid [(5-nitro-thiophene-2-yl)methylene] hydrazide series **39** were synthesized and tested against *M. tuberculosis* H37Rv. Rando and co-workwers have applied *Topliss* methodolgy to a set of nitrogen analogues. 4-Methoxybenzoic acid[(5-nitrothiophene-2-yl)methylene] hydrazide (**39a**) was demonstrated as being the most active, with a MIC value of 2.0 μg/mL [46].

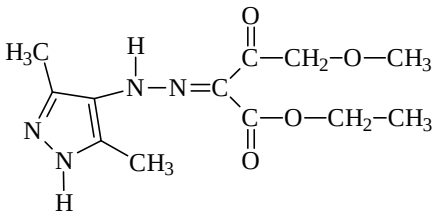


39a

Both hydrazone products, ethyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-3-oxobutyrate **40d** and methyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-4-methoxy-3-oxobutyrate **40e** showed 29 and 28% inhibition against *M. tuberculosis* H37Rv, respectively [47].

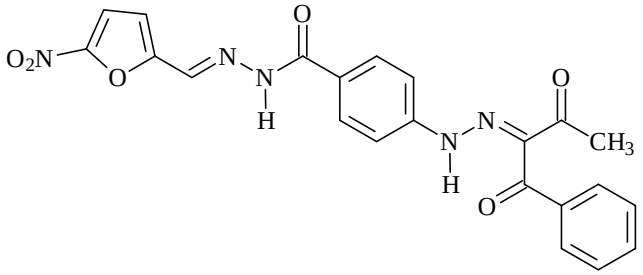


40d



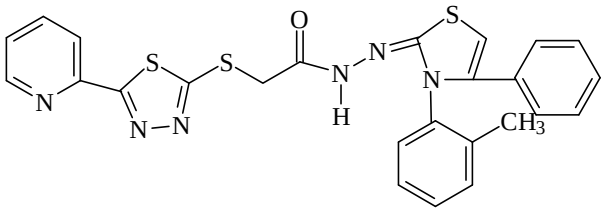
40e

Novel coupling products **41** were synthesized and evaluated for their antimycobacterial activity against *M. tuberculosis* H37Rv and *M. avium*. Compound **41b** was found to be the most potent derivatives of these series with the MIC value of 6.25 μg/mL against *M. tuberculosis* H37Rv [48].



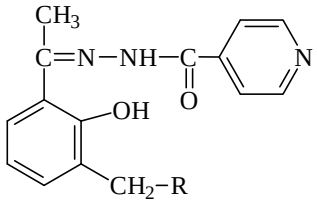
41b

[5-(Pyridine-2-yl)-1,3,4-thidiazole-2-yl]acetic acid (3,4-diaryl-3H-thiazole-2-ylidene)hydrazide derivatives **42** were synthesized and tested for their *in vitro* antimycobacterial activity towards three strains. Compound **42s** was exhibited at 20 μg/mL against *M.tuberculosis* 190, isolated from bronchial aspirates [49].



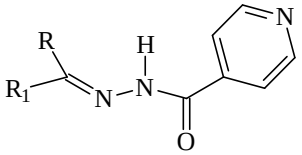
42s

N'-{1-[2-hydroxy-3-(piperazine-1-yl-methyl)phenyl]ethylidene}isonicotinohydrazide **43** was found to be the most active compound with the MIC of 0.56 μM, and it was more potent than INH (MIC of 2.04 μM). After 10 days of treatment, same compound decreased the bacterial load in murine lung tissue by 3.7-log10 as compared to controls, which was equipotent to INH [50].



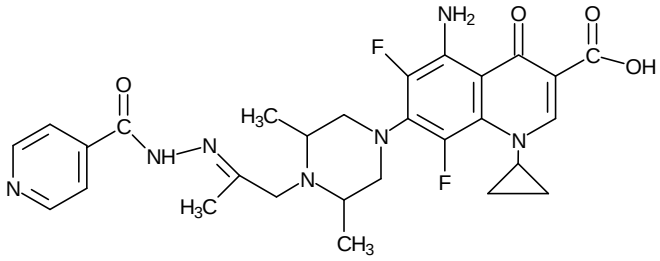
43

As a part of an ongoing search for the new isoniazid-related isonicotinoylhydrazones (ISNEs), 2'-monosubstituted isonicotinohydrazides and cyanoboranes **44-48** were studied and evaluated *in vitro* advanced antimycobacterial screening. Some of tested compounds displayed excellent (MICs ranging from 0.025 to 0.2 μg/mL) to moderate (6.25 to 12.5 μg/mL) MICs against ethambutol- and rifampin-resistant strains [51].



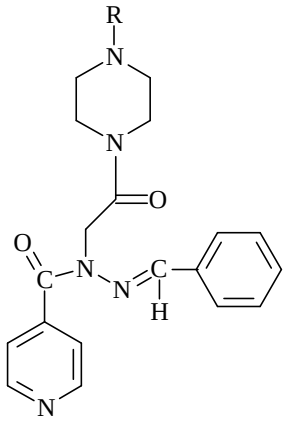
44-48

Novel fluoroquinolones **49** containing a hydrazone structure were synthesized and evaluated *in vivo* against *M. tuberculosis* H37Rv in Swiss albino mice by Shindikar *et al*. Results of the study indicate the potent antitubercular activity of the test compouds [52].



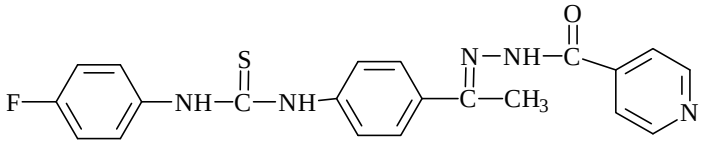
49

N′-Arylidene-*N*-[2-oxo-2-(4-aryl-piperazin-1-yl)ethyl]hydrazide derivatives **50** containing INH hydrazide-hydrazones were synthesized and evaluated antimycobacterial activity against *M. tuberculosis* H37Rv ATCC 27294 and *M. tuberculosis* clinical isolates. Compound **50h** showed *in vitro* activity against *M. tuberculosis* H37Rv ATCC 27294 (at 1 μg/mL) and clinical isolates (sensitive and resistant at 0.25-0.5, 2-4 μg/mL, respectively) [53].



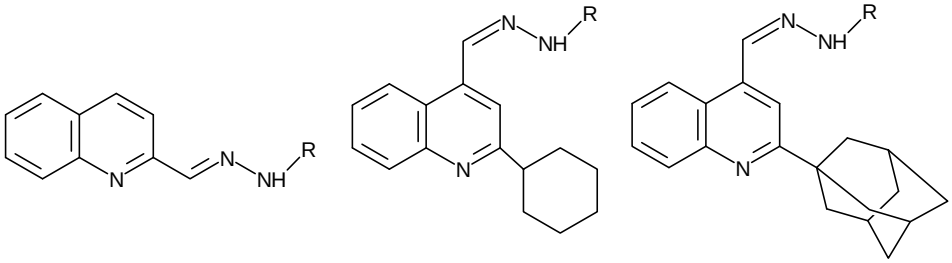
50

Sriram *et al*. synthesized a new series of antimycobacterial agents **51** containing INH hydrazide-hydrazones. 1-(4-Fluorophenyl)-3-(4-{1-[pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea **51d** was found to be most potent compound, with MIC of 0.49 μM against *M. tuberculosis* H37Rv and INH-resistant *M. tuberculosis* [54].



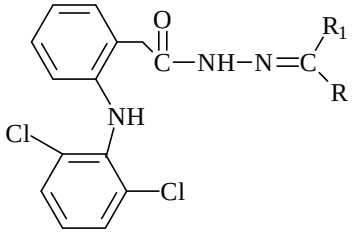
51d

In 2006 Nayyar *et al*. found that the most active compounds of type **52**, *N*-(2-fluorophenyl)-*N*′-quinoline-2-yl-methylenehydrazine, *N*-(2-adamantan-1-yl)-*N*′-quinoline-4-yl-methylene)-N′-4-fluorophenyl)hydrazine and *N*-(2-cyclohexyl)-*N*′-quinoline-4-yl-methylene)-(2-fluorophenyl)hydrazine exhibited 99% inhibition at the lowest tested concentration of 3.125 μg/mL against drug-sensitive *M. tuberculosis* H37 strain [55].



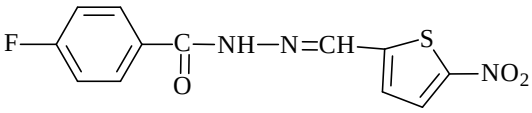
52

Various diclofenac acid hydrazones **53** were synthesized and evaluated for their antimycobacterial activities against *M. tuberculosis in vitro* and *in vivo*. Preliminary results indicated that most of the compounds demonstrated better *in vitro* antimycobacterial activity at concentrations ranging from 0.0383 to 7.53 μM [56].



53

Hydrazide-hydrazones **54**, based on series of 4-substituted benzoic acid were synthesized and screened for antituberculosis activity. 4-Fluorobenzoic [(5-nitrothiophene-2-yl)methylene]hydrazide **54a** showed the highest inhibition (99%) at a constant concentration level (6.25 μg/mL) [4].

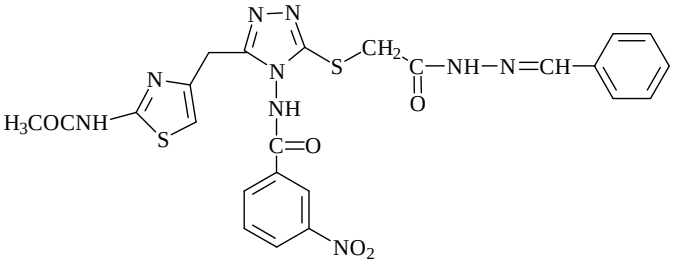


54a

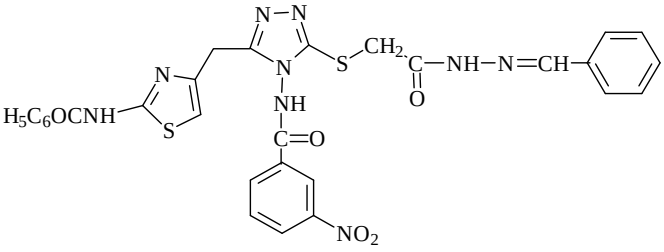
Sixteen new hydrazones **55** containing a pyrrole ring were synthesized as potential tuberculostatics and nine showed 92-100% inhibition of *M. tuberculosis* H37Rv at 6.25 μg/mL. Two leads exhibited low minimum inhibitory concentrations (MIC) and excellent selectivity indexes (SI) [57].

55

N-[3-({2-[(2*E*)-2-Benzylidenehydrazino]-2-oxoethyl**}**sulfanyl**)**-5-(-({2[(acetyl)amino]-1,3-thiazol-4-yl**}**methyl)-4H-1,2,4-triazol-4-yl]-3-nitrobenzamide **56f** and *N*-[3-({2-[(2*E*)-2-benzylidene-hydrazino]-2-oxoethyl**}**sulfanyl**)**-5-(-({2[(benzoyl)amino]-1,3-thiazol-4-yl**}**methyl)-4H-1,2,4-triazol-4-yl]-3-nitrobenzamide **56g** have been proven to be most active, with MIC values ranging from 0.39 to 0.78μM [58].

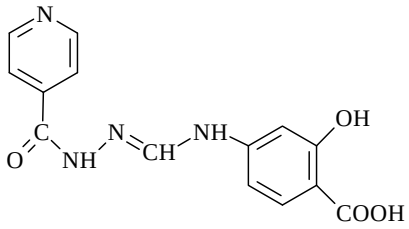


56f



56g

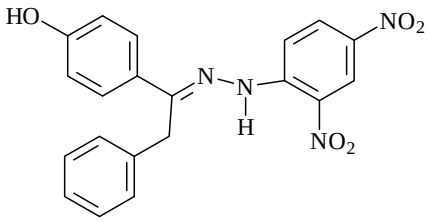
A series of hydrazones **57** were synthesized from INH, pyrazineamide, *p*-aminosalicylic acid (PAS), ethambutol and ciprofloxacin. 2-Hydroxy-4-{[(isonicotinoylhydrazono)methyl]amino**}**benzoic acid **57d** showed the highest inhibition (96%) of *M. tuberculosis* H37Rv at 0.39 μg/mL [59].



57d

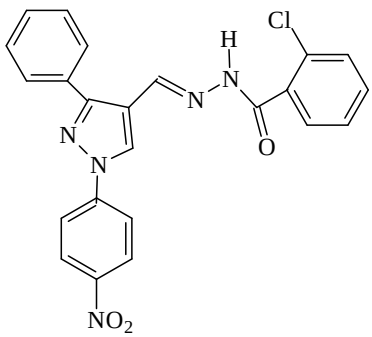
2.7. Antitumoral Activity

A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several hydrazones having antitumoral activity. Some of diphenolic hydrazones showed maximum uterotrophic inhibition of 70%, whereas compound **58** exhibited cytotoxicity in the range of 50-70% against MCF-7 and ZR-75-1 human malignant breast cell lines [60].



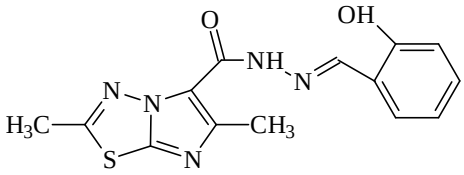
58

N′-(1-{1-[4-nitrophenyl-3-phenyl-1H-pyrazole-4-yl}methylene)-2-chlorobenzohydrazide **59** was found to be the most active, with full panel median growth inhibition, total growth concentration and median lethal concentration mean graph mid-point of 3.79, 12.5 and 51.5 μM, respectively [61].



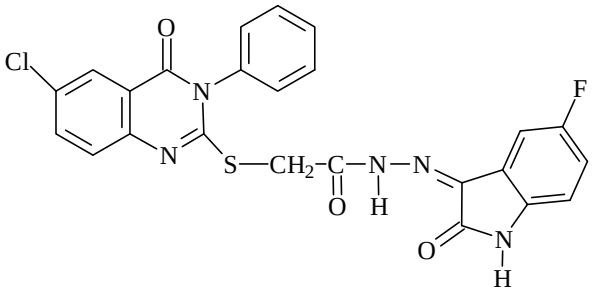
59

Some novel 2,6-dimethyl-N′-substituted-phenylmethyleneimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazides **60** were synthesized. (2,6-Dimethyl-*N*′-(2-hydroxyphenylmethylidene)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazide **60c** showed the most favorable cytotoxicity. In the *in vitro* screening of National Cancer Institute's 60 human tumor cell lines, this compound demonstrated the most marked effects on the ovarian cancer cell line (OVCAR $\log_{10}$ GI_{50} value −5.51) [62].



60c

3-[[(6-Chloro-3-phenyl-4(3*H*)-quinazolinone-2-yl)mercaptoacetyl]hydrazono]-5-fluoro-1*H*-2-indolinone **61o** showed the most favourable cytotoxicity against the renal cancer cell line UO-31 ($\log_{10}$ GI_{50} value −6.68) [63].



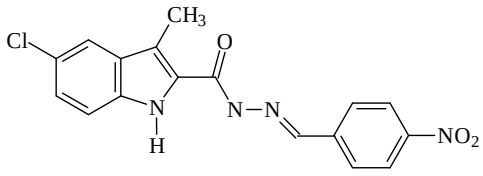
61o

Some recently synthesized compounds were found to possess antiproliferative properties. The most active compound of the series was the 3- and 5-methylthiophene-2-carboxaldehyde α-(*N*)-heterocyclichydrazones derivatives **62**, which exhibited tumor growth inhibition activity against all cell lines at GI_{50} values between 1.63 and 26.5 μM [64].

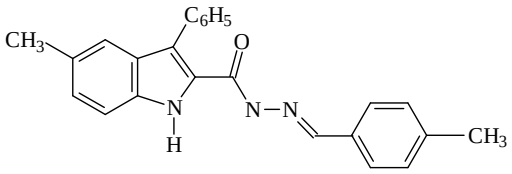
62

5-Chloro-3-methylindole-2-carboxylic acid(4-nitrobenzylidene)hydrazide **63a** was found to arrest T47D cells in G_2/Mphase of the cell cycle and to induce apoptosis as measured by the flow cytometry analysis. A 20-fold increase of apoptotic activity was achieved from the screening hit to 5-methyl-3-phenylindole-2-carboxylic acid(4-methylbenzylidene) hydrazide **64a** and 5-chloro-3-phenylindole-2-carboxylic acid(4-nitrobenzylidene)hydrazide **64b**, with EC_{50} values of 0.1 μM in the caspase activation assay in T47D breast cancer cells. Compound **64b** also was found to be highly active in a standard growth inhibition assay with a GI_{50} value of 0.9 μM in T47D cells. Compound **63a** and its

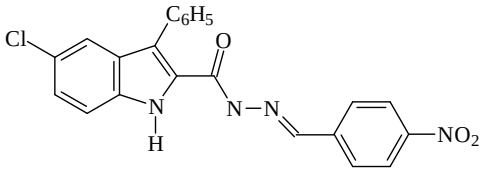
analogs were found to inhibit tubulin polymerization, which is the most probable primary mechanism of the action of these compounds [65].



63a

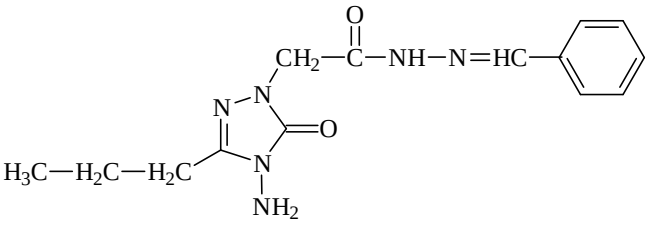


64a

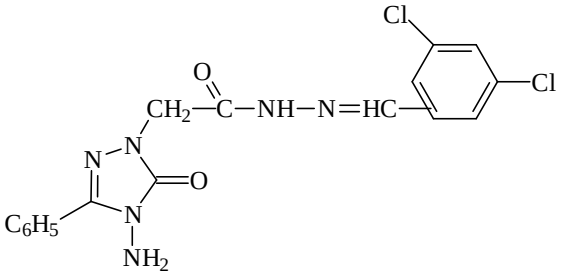


64b

Demirbaş et al. synthesized the new hydrazide-hydrazones containing **65** 5-oxo-[1,2,4]triazole ring**.** Some of these compounds had inhibitory effect on mycelial growth whereas Compounds **65c** and **65f** were found to possess antitumor activity in breast cancer. [66].

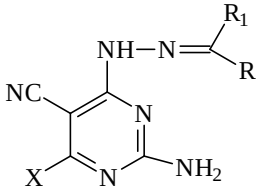


65c



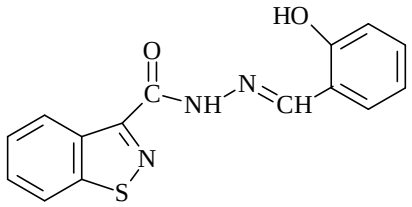
65f

Hydrazinopyrimidine derivatives **66** were evaluated for their *in vitro* antitumoral activity in nine different types of human cancers. Some of the newly prepared compounds demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M to 10^{-7} M concentrations [67].



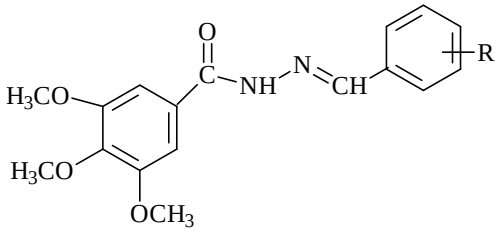
66

Several benzo[*d*]isothiazole hydrazones have been tested for antitumoral activity. Compound **67h**, bearing a hydroxy group at *o*-position of the benzylidene moiety, was the most potent, with the IC50 against the various cell lines ranging between 0.5 and 8.0 μM, thus acting equally potent as 6-mercaptopurine against the haematological tumors [68].



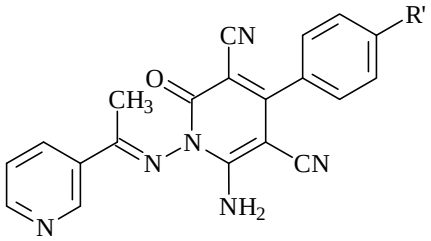
67h

N′-Substituted-benzylidene-3,4,5-trimethoxybenzohydrazide **68** were synthesized and evaluated for their antitumoral activity against some cancer cells. Many hydrazone compounds containing the active moiety (-CONH-N=CH-) showed good antitumor activity. Compounds **68a**-**c** and **68f** were highly effective against PC3 cells and **68a**, **68c** and **68f** showed moderate activities against Bcap37 and BGC823 cells [69].



68

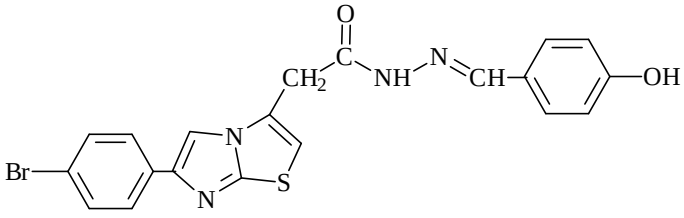
6-Amino-4-aryl-2-oxo-1-(1-pyrid-3-yl- or 4-yl-ethylidene-amino)-1,2-dihydropyridine-3,5-dicarbo-nitrile series **69** exhibited a high percentage of tumor growth inhibition at concentrations of 10^{-5} to 10^{-7} M in all cancer cell lines [70].



69

Duarte *et al*. described *N*′-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1,3-benzodioxole-5-carbohydrazine **12c** as a novel antiproliferative compound. They observed that **12c** was able to inhibit T-cell proliferation (66 % at 10μM) [27].

A series of arylidenehydrazides **70** were synthesized and evaluated in the National Cancer Institue's against the full panel of 60 human tumour cell lines. Compound **70c** demonstrated the most effect on prostate cancer cell line [71].

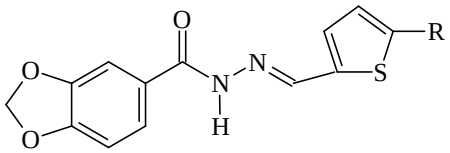


70c

2.8. Vasodilator Activity

Conventional therapy to treat hypertension often involves arterial vasodilation. It is important to find new vasodilators with a potential for clinical use.

A new bioactive compound of the *N*-acylhydrazone class, 3,4-methylenedioxybenzoyl-2-thienyl hydrazone **71**, named LASSBio-294, was shown to have inotropic and vasodilatory effects. New derivatives of LASSBio-294 were designed and tested on the contractile responses of rat vascular smooth muscle *in vitro*. Phenylephrine-induced contractions of aorta was inhibited by the derivatives *N*-methyl-2-thienylidene-3,4-methylenedioxy-benzoyl hydrazine, named LASSBio-785 and *N*-allyl-2-thienylidene-3,4-methylenedioxy-benzoyl hydrazine, named LASSBio-788. The concentrations necessary to cause 50% reduction in maximum contractions (IC50) were 10.2 +/- 0.5 and 67.9 +/- 6.5 μM. Vasodilation induced by both derivatives is likely to be mediated by a direct effect on smooth muscle because it was not dependent on the integrity of vascular endothelium. LASSBio-785 was seven times more potent than the reference compound LASSBio-294 (IC50 = 74 μM) in producing an endothelium-independent vasodilator effect [72].



71

2.9. Antiviral Activity

HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART). Some thiourea compounds were reported to be non-nucleoside inhibitors (NNIs) of the reverse transcriptase (RT) enzyme of the human immunodeficiency virus (HIV). Such hydrazones have been reported to be the potent inhibitors of ribonucleotide reductase activity.

N-Arylaminoacetylhydrazones and *O*-acetylated derivatives of sugar *N*-arylaminoacetyl hydrazones were synthesized and evaluated for their antiviral activity against *Herpes simplex* virus-1 (HSV-1) and hepatitis-A virus (HAV). Some compounds revealed the highest antiviral activity against HAV-27 and HSV-1 [73].

3.0. Schistosomiasis

Schistosomiasis or bilharzia is a parasitic disease caused by several species of flatform. Currently, schistosomiasis affects roughly 200 million people in tropical countries, and in certain African communities the process of overcoming schistosomiasis is an important rite of passage. Schistosomiasis causes debilitating nutritional, hematologic and cognitive deficits, with substantial morbidity and mortality in populations. There are five species of flatworms that cause schistosomiasis. *Schistosoma mansoni*, *S. intercalatum*, *S. haematobium*, *S. japonicum* and *S. mekongi*. *Schistosoma mansoni* and *S. intercalatum*, *S. japonicum* and *S. mekongi* cause intestinal and Asian intestinal

schistosomiasis, respectively. *S. haematobium* resides in the venous plexus, which causes urinary schistosomiasis [74].

9-Acridanone hydrazones have been developed by Hoffmann-La Roche (Basel-Switzerland). One of these compounds (RO 15-5458/000) was administered at two dose levels 25 mg and 15 mg/kg body-weight to *S. mansoni* infected vervet-monkeys [75]. In addition, same compounds were found to be effective against *S. mansoni* in mice, killing almost all the skin schistosomules, when administered at the dose of 100mg/kg. In experiments carried out with Cebus monkeys, the compound RO 15-5458 / 000 was shown to be fully effective at 25 mg/kg [76].

3. Review articles related with hydrazones

There critical reviews have been published recently, and they may give an outlook on the latest research developments on antimycobacterial substances [77-79].

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Sample Availability: Samples are available from the authors.

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