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Review Paper

Pharmacologically potentials of hydrazonone containing compounds: a promising scaffold

Mohammad Asif

Department of Pharmacy, GRD (PG) IMT, Dehradun, (Uttarakhand), 248009, India
E-mail: aasif321@gmail.com

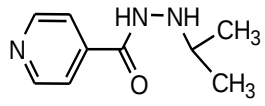
Abstract

Hydrazones considered as an important class of compounds for new drug development. Hydrazones are present in many of the bioactive compounds having wide interest because of their diverse biochemical applications. This created interest in researchers to developed variety of hydrazone compounds with effective biological activities. Therefore many compounds have been developed as target structures for their biological activities. This review is focus on the diverse biological activities of hydrazones.

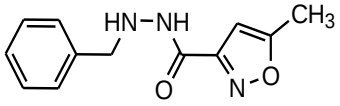
Keywords: *Hydrazones, Biological Activities, Azomethine, Pharmacological Potential.*

1. Introduction

Hydrazones have wide interest because of their diverse biological applications. Hydrazones possess various biological activities like anticonvulsant, antidepressant, analgesic, anti-inflammatory, antiplatelet, antimalarial, antimicrobial, antitubercular, anticancer, vasodialator, antiviral, antischistosomiasis, anti-HIV, anthelmintic, antidiabetic, and trypanocidal activities (Ali et al., 2012; Kumar et al., 2010). Hydrazide-hydrazones are not only intermsediates but they are also effective organic compounds. Some effective compounds like iproniazide and isocarboxazide. Iproniazid, like isoniazid is used in the treatment of tuberculosis (TB) and also showed antidepressant effect. Another effective hydrazidehydrazones is nifuroxazide, which is used as an intestinal antiseptic (Negi et al., 2012; Rollas and Kucukguzel. 2007). The 2-Chloroquinolinyl hydrazone derivative are anticonvulsants and ribavirin hydrazone derivatives are anticancer (Liu et al., 2009), hydrazones of indane-1, 3-dione are anticoagulant and antimicrobial activity (Jubie et al., 2010), 4-arylhydrazono-2-pyrazoline-5-one derivatives are anti-TB activity (Guniz et al., 2007). Some hydrazide hydrazones were active against Mtb H37Rv between the concs of 0.78-6.25µg/ml (Kaymakçıoglu, et al., 2006). A series of hydrazide-hydrzones reported antidepressant, sedative and analgesic activities (Mohareb et al., 2010).



Iproniazide



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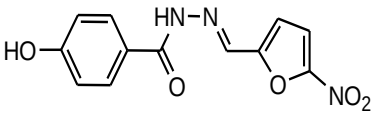
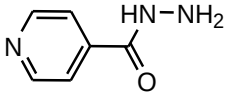


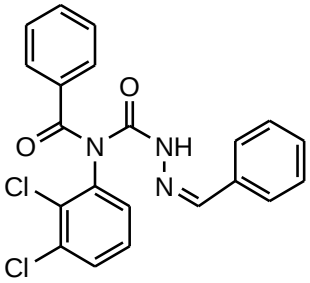
Nifuroxazide



Isoniazid

2. Antimicrobial activity

The antibacterial activity of hydrazine derivatives [1] against various pathogenic bacterial strains (Sharma et al., 2011) and other hydrazine derivatives [2], [3] are also showed antibacterial activity (Jubie et al., 2010). Benzimidazole derivatives with hydrazone moiety [4] (Ozkay et al., 2010), chloropyrrole derivatives of aroylhydrazone [5] (Rane and Telvekar. 2010) and some hydrazonoyl substituted pyrimidinones [6], [7] showed antibacterial activity (Edrees et al., 2010). Vanillin based hydrazines [8], [9] showed antibacterial activity against S. aureus and P. aeruginosa (Govindasami et al. 2011). 2-quinoxalinone-3-hydazine derivative [10] exhibited antibacterial activities against different bacterial strains (Ajani et al., 2010). Various hydrazones [11], [12] were act as selective inhibitors of S. aureus β-ketoacyl carrier proteinsynthase-3 (Lee et al., 2012). Aryloxyacetic acid hydrazide [13] having promising antibacterial activity against some bacterial strains (Abdel-Wahab et al., 2012). Cholic acid based hydrazones [14] showed antibacterial activity against Escherichia faecalis and E. coli (Rasras et al., 2010). Anthraquinone based hydrazones [15] showed promising bacteriostatic activity against P. auriginosa (Gouda et al., 2010). Various benzyledine-hydrazides [16] showed bactericidal activity against S. aureus (Kumar et al., 2010). Some hydrazone with imidazoles [17] were exhibited antibacterial activity against various bacteria (Abdel-Wahab et al., 2011). The 2, 4-disubstituted thiazoles [18] have antibacterial activity against different strains (Vijesh et al., 2010). The 4-fluorobenzoic acid (5-nitro-2-furyl)-methylene-hydrazide, is effective against S. aureus (Gülerman et al., 2000).



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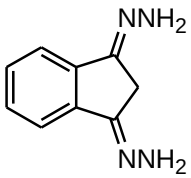

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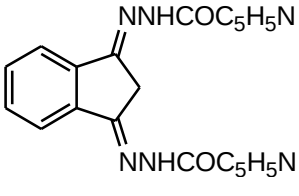

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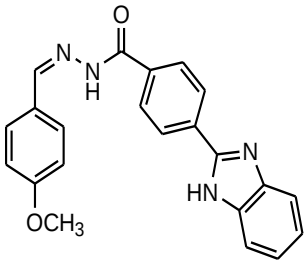

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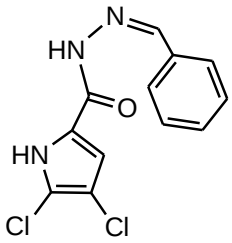

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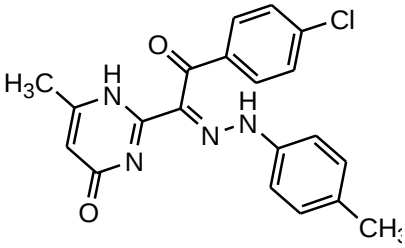

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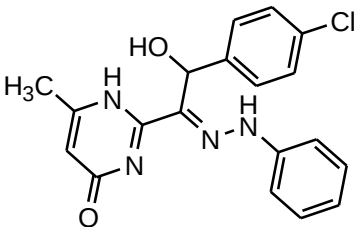

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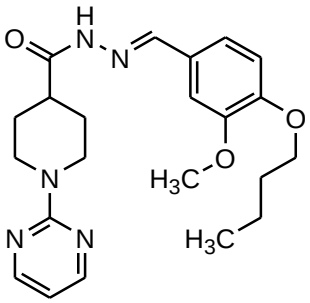

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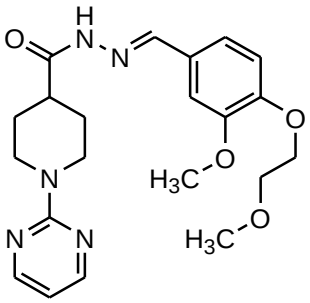

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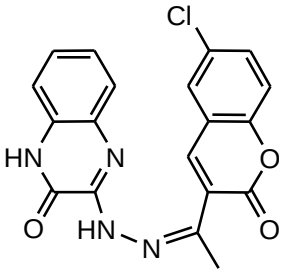

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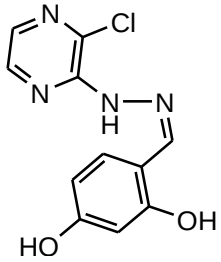

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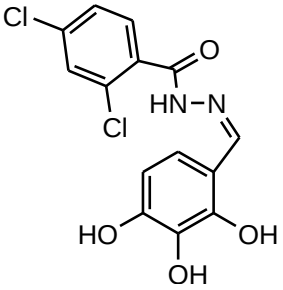

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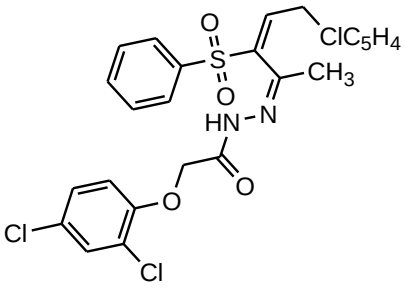

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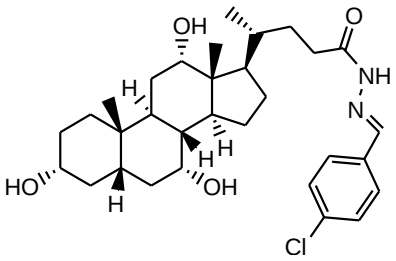

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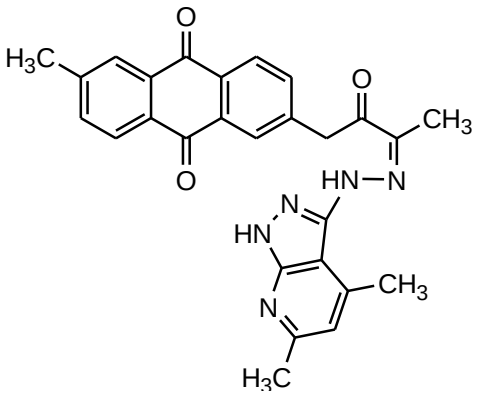

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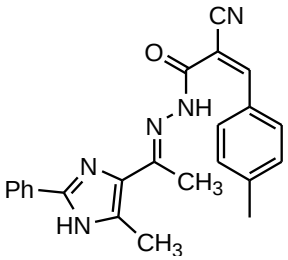

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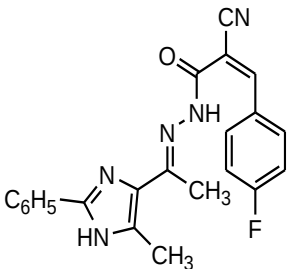

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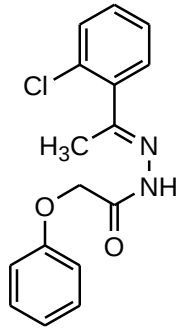

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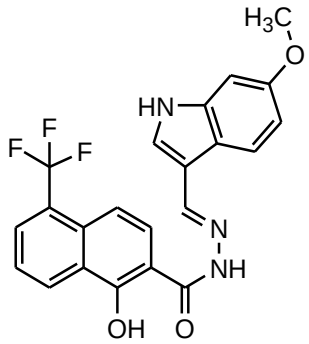

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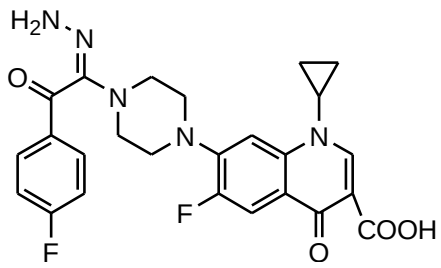

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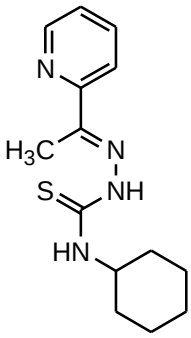

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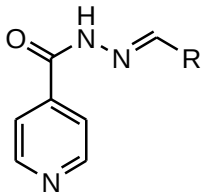
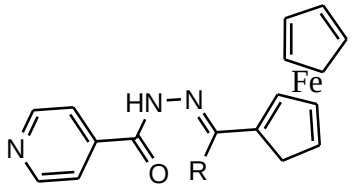


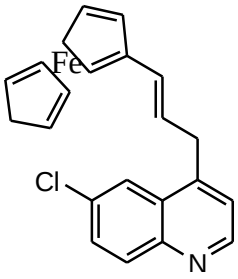
[R=2-($OCH_2C_6H_5$)C_6H_4];
[R=t-CH-CH_2-$OCH_3C_6H_4$]

22 and 23



R= H and CH_3

24 and 25



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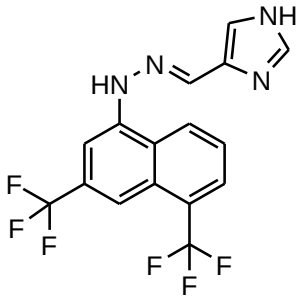

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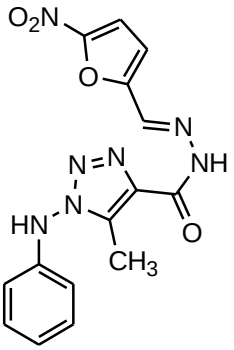

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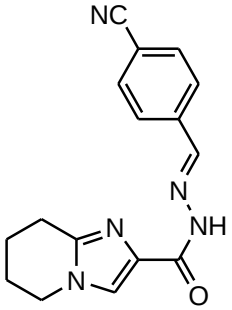

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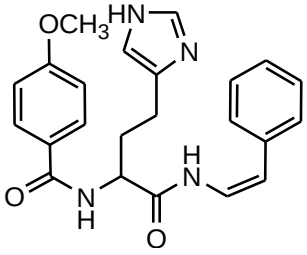

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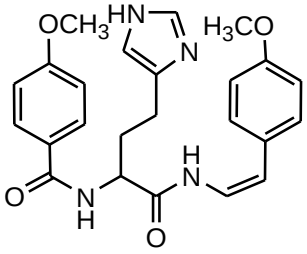

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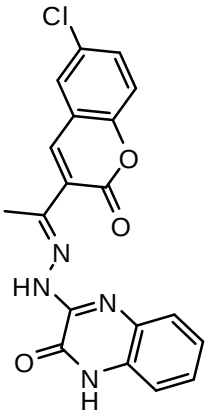
Few hydrazone derivatives (Raja et al., 2010), 4-OH-8-trifluro methylquinoline derivatives [19] (Thomas et al., 2011), fluorine-containing hydrazones [20] (Vavrikova et al., 2011) and some hydrazines [21], [22] and [23] showed promising antibacterial activity (Pavan et al., 2010). Ferrocenyl hydrazones [24], [25] (Maguene et al., 2011) and ferrocene-based hydrazone derivatives [26] showed significant antibacterial potential (Mahajan et al., 2011). Hydrazones [27] (Eswaran et al., 2010) and hydrazone derivatives [28] showed anti-TB activity (Jordao et al., 2011). Hydrazone derivatives [29] against different Candida spp, have promising antifungal potential (Ozdemir et al., 2010). Hydrazone derivatives [30], [31] have antiviral activity against viral HIV1-CA (Jin et al., 2010).

Various 2-quinoxalinone-3-hydrazone derivatives showed antimicrobial activities against the various pathogenic microbes, compounds 3-{2-(1-(6-chloro-2-oxo-2H-chromen-3-yl) ethylidene) hydrazinyl}quinoxalin-2(1H)-one [32], 3-(2-(propan-2-ylidene) hydrazinyl) quinoxalin-2[1H]-one [33] showed antibacterial and antifungal activity (Olayinka et al., 2010). A aroyl-hydrazone, N(2-pyridinecarbaldehyde(-N-(4-(4-chlorophenylsulfonyl) benzoyl) hydrazone and its Cu(II), Co(II) and Ni(II) complexes showed antibacterial activity against Gram positive bacteria: S. aureus, B. subtilis and Gram-negative bacteria: P. aeruginosa, E. coli. The activity of N-(2-pyridinecarbaldehyde)-N-(4-(4-chloro-phenyl sulfonyl) benzoyl)-hydrazone becomes more pronounced when coordinated to the metal ions (Angelusiua et al., 2010). Sulfonyl hydrazone derivatives and their nickel complexes were exhibited antibacterial activity against gram-positive bacteria (S. aureus, B. subtilis, B. magaterium) and gram-negative bacteria (Salmonella enteritidis, E. coli) and possess broad spectrum of activity at MIC values between 145 and 683μg/ml and presence of electron rich atoms (O, S, N, etc.) in ligands increase the antimicrobial activity

(Ozdemir and Gulcin. 2008). Biphenyl-4-carboxylic acid hydrazide hydrazone exhibited in-vitro antimicrobial activity against two gram negative strain E. coli, P. aeruginosa and two Gram positive strain, B. subtilis, S. aureus and fungal strain, C. albicans, A. niger and presence of electron withdrawing groups on aromatic ring improved the antimicrobial activity (Deep et al., 2010).



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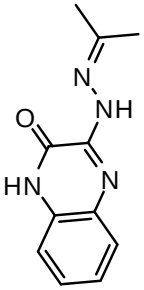

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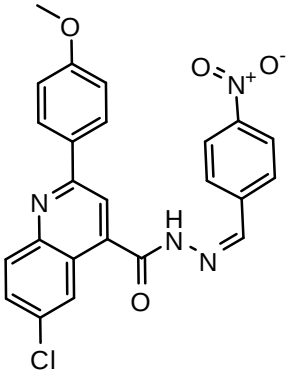

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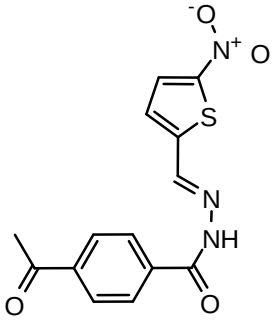

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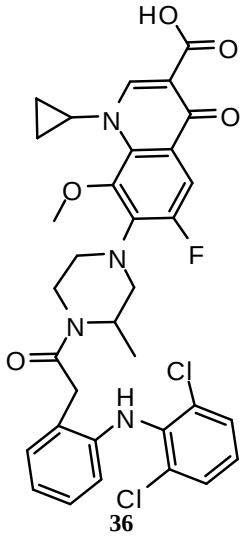
A series of 2-arylquinoline-4-carboxalic acid hydrazidhydrazones were exhibited in vitro antimicrobial activity against S. aureus, E. coli and C. albicans. Out of these compounds 6-chloro-2-(4-methoxyphenyl) quinoline-4-carboxylic acid (4-nitrobenzylidene)-hydrazide [34] was found to be most potent (Metwally et al., 2006). Some p-substituted benzoic acid ((5-nitro-thiophen-2-yl)-methylene)-hydrazides were showed antimicrobial activity against standard and MDR strains of S. aureus. The 4-Acetyl-benzoic acid ((5-nitro-thiophen-2-yl)-methylene)-hydrazide [35] was the most active compound (Masunari, and Tavares. 2007). Derivatives of acylhydrazine such as substituted-2-mercapto-1, 3, 4-oxadiazoles, their corresponding ester, amide and benzene diasulfonamides were showed antimicrobial activity, the acyl hydrazine benzene diasulfonamide derivative was having antimicrobial activity (Zareef et al., 2008).

Anti-TB Activity: Various diclofenac acid hydrazones and amides were exhibited anti-TB activities against Mtb. The 1-cyclopropyl-6-fluoro-8-methoxy-7-((N4-(2-(2-(2,6-dichloro phenyl amino)phenyl)acetyl)-3-methyl)-N1-piperazinyl)-4-oxo-1,4-dihydro-3-quinoline carboxylic acid [37] was found to be the most active compound in-vitro than anti-TB drug Isoniazid (INH). In the in vivo model, these compounds decreased the bacterial load in lung and spleen tissues (Sriram et al., 2006). Two series of 2-substituted quinolines 4-(adamantan-1-yl) group were exhibited in-vitro anti-TB activities against drug-sensitive Mtb H37Rv strain. Compound 4-adamantan-1-yl-quinoline-2-carboxylic acid (2-chlorobenzylidene) hydrazide [37] inhibited drug sensitive Mtb H37Rv and equipotent to INH (Nayyar et al., 2007). During the coumarin-4-acetic acid benzylidene hydrazides as anti-TB agents against Mtb H37Rv strain, (7-Hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid (3-nitro-benzylidene) hydrazide [38] was found to be most potent (Manvar et al., 2008). Some 5, 6, 7, 8-tetrahydronaphthalen acetic acid benzylidene hydrazide derivatives showed anti-TB activity and compounds having –OH and –NO_2 in ortho and Meta position of aromatic ring having high anti-TB activity (Ozemir et al., 2010). Aryl acetic acid hydrazones showed moderate activity against Mtb H37 RV strain (Srivastava et al., 2010).



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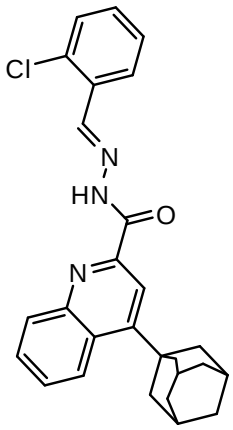

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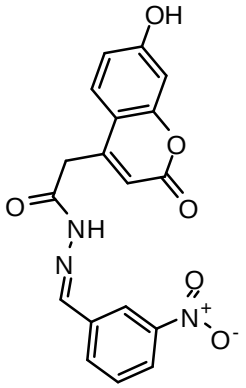
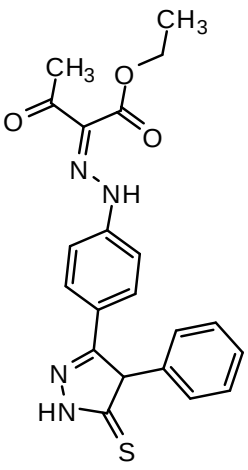


38

Some hydrazone compounds [39], [40] and N1-(4-methoxy benzamido) benzoyl)-N2-((5-nitro-2-furyl) methylene) hydrazine 41 inhibited the growth of several bacteria and fungi (Kuçukguzel et al., 2002). N2-Substituted alkylidene/arylidene-6-phenylimidazo [2], [1-b] thiazole-3-acetic acid hydrazides 42 were evaluated for their in vitro antimicrobial activity (Ulusoy et al., 2000). The 5-bromoimidazo [1], [2-a] pyridine-2-carboxylic acid benzylidene hydrazide 43 and 5-bromoimidazo [1], [2-a] pyridine-2-carboxylic acid 4-methoxy benzylidene hydrazide 44 to possess antimicrobial activity against E. fecalis and S. epidermis (Turan-Zitouni et al., 2001).



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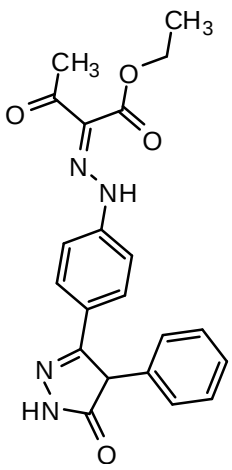

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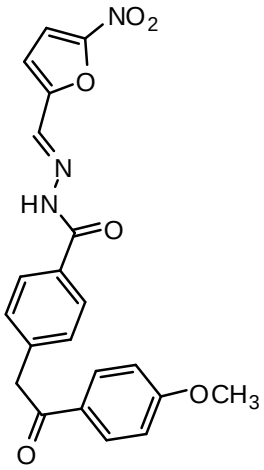

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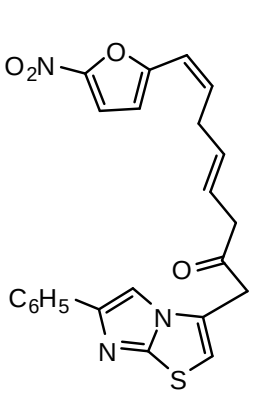

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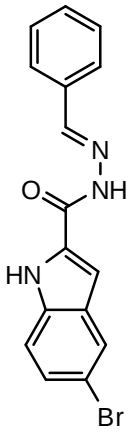

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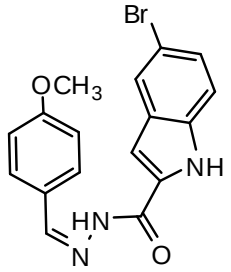

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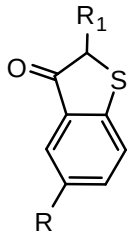
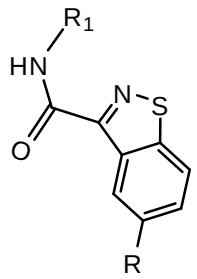


45[R=H], 46[R=CH$_3$]



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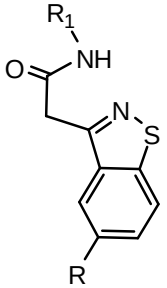
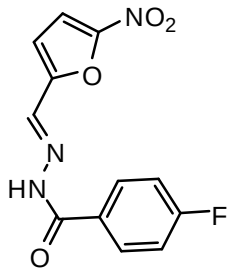


48[R=H], 49[R=CH$_3$]

A series of hydrazones derived from 1, 2-benzisothiazole hydrazides (R_1=H) 23-27 as well as the parent cyclic [45] and [46] and acyclic [47], [48] and [49] 1, 2-benzisothiazole hydrazides, were showed antibacterial and antifungal activity. The 2-amino-1,2-benzisothiazole-3(2H)-one derivatives, compound 45 and 46 showed antibacterial activity against Gram positive bacteria and most of them were also active against yeasts (Vicini et al., 2002). A series of hydrazide hydrazones and 1, 3, 4-oxadiazolines of 4-fluorobenzoic acid hydrazide as antibacterial and antifungal activities against S. aureus, E. coli, P. aeruginosa and C. albicans. The compound 4-fluorobenzoic acid ((5-nitro-2-furyl) methylene) hydrazide [50] showed equal activity as ceftriaxone against S. aureus (Rollas et al., 2002). The 2′, 4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid ((5-nitro-2-furyl) methylene) hydrazide has shown activity against S. epidermis HE-5 and S. aureus HE-9, respectively. 2′, 4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid ((2, 4, 6-trimethyl phenyl) methylene) hydrazide [51] has exhibited activity against Acinetobacter calcoaceticus (Kucukguzel, et al., 2003). A series of hydrazones from cholesterol derivatives 52 were exhibited antimicrobial properties against pathogens. The tosylhydrazone cholesterol derivative exhibited activity against C. albicans (Loncle et al., 2004). 4-Substituted benzoic acid ((5-nitro-thiophene-2-yl) methylene) hydrazides 53 were exhibited bacteriostatic and some compounds showed bactericidal activity (Masunari, and Tavares. 2007).



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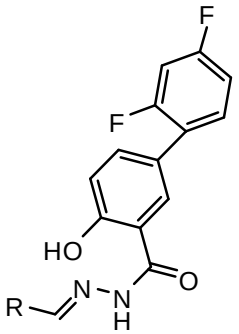

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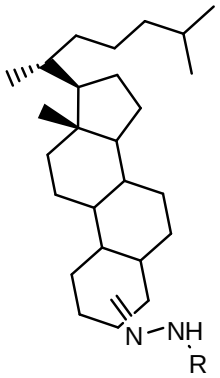

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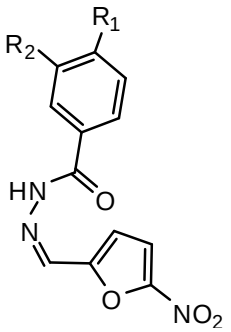
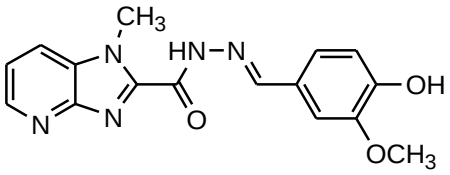


53

Isoniazid (INH) hydrazide-hydrazones 1, the compounds have activity against various strains of Mtb, with lower toxicity than INH. The 1-methyl-1H-2-imidazo[4], [5-b]pyridinecarboxylic acid hydrazides, compound 54 showed anti-TB activity against Mtb H37 Rv, Mtb 192, Mtb 210, isolated from patients and resistant against INH, ethambutol, RIF at 31.2 µg/mL (Bukowski and Janowiec. 1996). The 2-acetylimidazo[4], [5-b] pyridine with INH, this hydrazide hydrazones 55, exhibited anti-TB activity against Mtb H37 Rv, Mtb 192, Mtb 210, isolated from patients and resistant against INH, ethambutol, RIF (Bukowski et al., 1999). Various 2, 3, 4-pentanetrione-3-(4-(((5-nitro-2-furyl/pyridyl/substituted-phenyl)-methylene) hydrazine) carbonyl) phenyl) hydrazones were exhibited anti-TB activity against M. fortuitum ATCC 6841 and Mtb H37Rv. Some compounds were active against M. fortuitum. Compound, which exhibited >90% inhibition at 12.5µg/mL against Mtb H37Rv, was the most promising compound for anti-TB activity. The actual MIC and IC_{50} values of were 3.13 and 0.32 µg/mL. The compound 55 was also tested against M. avium (Kuçukguzel et al., 2000). The pyridylmethyleneamino derivative, compound 56 was showed activity against Gram negative, Gram positive Mtb H37Rv starins and some isonicotinoylhydrazones also showed a moderate activity against clinically isolated Mtb (6.25-50 µg/mL) which was INH resistant (Cocco et al., 2005). The N2-Substituted

alkylidene/arylidene-6-phenylimidazo [2], [1-b] thiazole-3-acetic acid hydrazides 57 were showed in vitro anti-TB activity against Mtb H37Rv (Ulusoy et al., 2000). (5-(Pyridine-2-yl)-1, 3, 4-thiadiazole-2-yl) thio) acetic acid arylidene-hydrazide derivatives 58 were exhibited in-vitro anti-TB activity, some compounds showed activity at 20µg/mL against Mtb and at 40µg/mL against M. avium (Mamolo et al., 2001). N-Alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides 59 were showed in-vitro anti-TB activity against Mtb H37 Rv at 6.25µg/mL (Ulusoy et al., 2001). The 4-quinolylhydrazones, compound 38 was active against Mtb H37Rv. The 4-quinolylhydrazine and aryl- or heteroaryl carboxaldehydes, most of the derivates had anti-TB properties (Savini et al., 2002). Benzoic acid ((5-nitrothiophene-2-yl) methylene) hydrazide series 60 were tested against Mtb H37Rv. 4-Methoxybenzoic acid ((5-nitrothiophene-2-yl) methylene) hydrazide [61] was the most active, with a MIC value of 2.0 µg/mL (Rando et al., 2002). Ethyl 2-((3, 5-dimethylpyrazole-4-yl) hydrazono)-3-oxobutyrate 62 and methyl 2-((3, 5-dimethylpyrazole-4-yl) hydrazono)-4-methoxy-3-oxobutyrate 63 showed 29 and 28% inhibition against Mtb H37Rv (Kaymakçıoglu and Rollas. 2002). Compound 64 was exhibited anti-TB activity against Mtb H37Rv and M. avium. Compound 64 was found potent with the MIC value of 6.25µg/mL against Mtb H37Rv (Kuçukguzel and Rollas. 2002).



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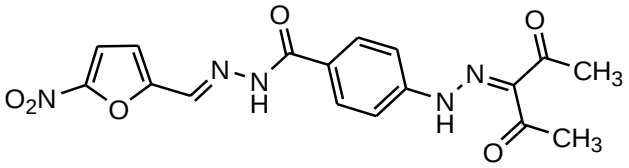

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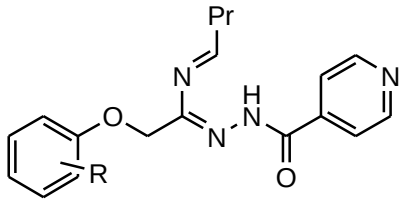

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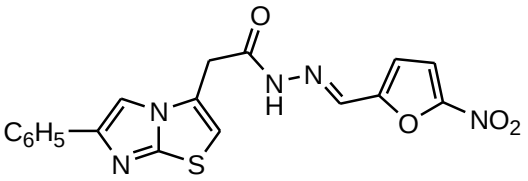

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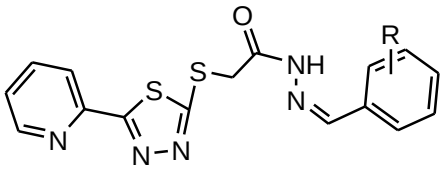

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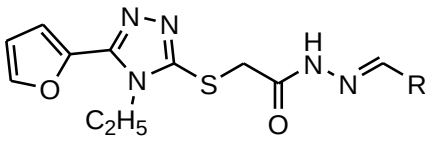

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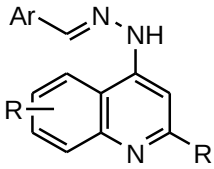

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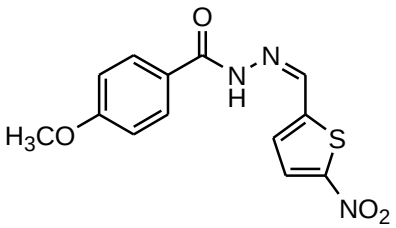

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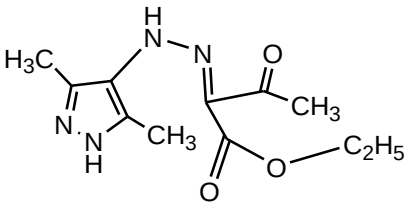

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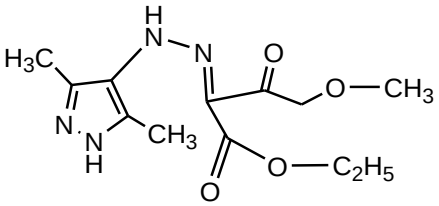

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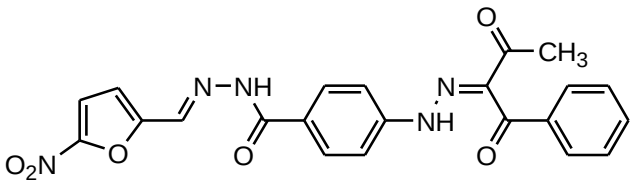

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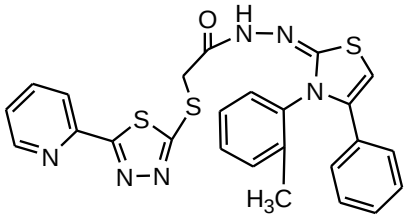

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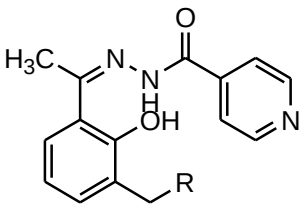

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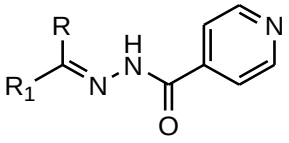

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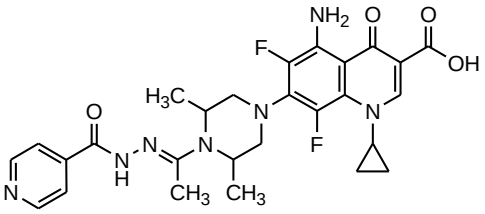
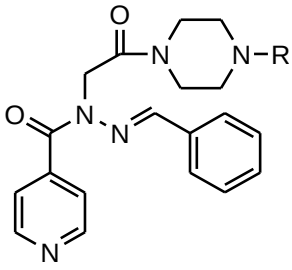


68

The (5-(Pyridine-2-yl)-1, 3, 4-thidiazole-2-yl) acetic acid (3, 4-diaryl-3H-thiazole-2-ylidene) hydrazide derivatives 65 were exhibited in vitro anti-TB activity. Compound 65 was exhibited at 20μg/mL against Mtb 190 (Mamolo et al., 2003). N'-{1-(2-hydroxy-3-(piperazine-1-yl-methyl) phenyl) ethylidene} isonicotinohydrazide 66 was found to be the most active compound with the MIC of 0.56 μM, and more potent than INH (Sriram et al., 2005). The INH-related isonicotinoyl hydrazones (ISNEs), 2'-monosubstituted isonicotino hydrazides and cyanoboranes 67 were exhibited in vitro anti-TB activity. Some compounds showed excellent (MICs 0.025 to 0.2 μg/mL) to moderate (6.25 to 12.5 μg/mL) MICs value against EMB and RIF resistant strains (Maccari et al., 2005). Fluoroquinolones 68 containing a hydrazones were exhibited in vivo against Mtb H37Rv (Shindikar and Viswanathan. 2005). N′-Arylidene-N-(2-oxo-2-(4-aryl-piperazin-1-yl)ethyl) hydrazide derivatives 69 containing INH hydrazide-hydrazones were showed anti-TB activity against Mtb H37Rv ATCC 27294 and Mtb clinical isolates (Sinha et al., 2005). Compound 70 containing INH hydrazidehydrazones, 1-(4-Fluorophenyl)-3-(4-{1-(pyridine-4-carbonyl) hydrazono) ethyl} phenyl) thiourea was found potent compound, with MIC of 0.49 μM against Mtb H37Rv and INH-resistant Mtb (Sriram et al., 2006). The compounds 71,72,73, N-(2-fluorophenyl)-N′-quinoline-2-yl-methylene hydrazine, N-(2-adamantan-1-yl)-N′-quinoline-4-ylmethylene)-N′-4-fluorophenyl) hydrazine and N-(2-cyclohexyl)-N′-quinoline-4-yl-methylene)-(2-fluorophenyl) hydrazine exhibited 99% inhibition at the lowest tested conc. of 3.125 μg/mL against drug-sensitive Mtb H37 strain (Nayyar et al., 2006). Various diclofenac acid hydrazones 74 were exhibited anti-TB activities against Mtb in vitro at dose ranging from 0.0383 to 7.53 μM (Sriram et al., 2006). Hydrazide-hydrazones with 4-substituted benzoic acid 75 were showed anti-TB activity. 4-Fluorobenzoic ((5-nitrothiophene-2-yl) methylene) hydrazide 75 showed the inhibition (99%) at conc. (6.25 μg/mL) (Bijev. 2006). New hydrazones, compound 76, 77 containing a pyrrole ring was showed potential TB statics and some compouds showed 92-100% inhibition of Mtb H37Rv at 6.25μg/mL (Kucukguzel et al., 2006). The N-(3-({2-((2E)-2-Benzylidenehydrazino)-2-oxoethyl}sulfanyl)-5-(-({2((acetyl)amino)-1,3 thiazol -4-yl}methyl)-4H-1,2,4-triazol-4-yl)-3-nitrobenzamide 78 and N-(3-({2-((2E)-2-benzylidene hydrazine)-2-oxoethyl}sulfanyl)-5-(-({2((benzoyl) amino)-1,3-thiazol-4-yl}methyl)-4H-1,2,4-triazol-4-yl))-3-nitrobenzamide 79 have most active, with MIC values ranging from 0.39 to 0.78μM (Shiradkar et al., 2007). A series of hydrazones, compound 80 was synthesized from INH, PZA, p-aminosalicylic acid (PAS), EMB and ciprofloxacin. 2-Hydroxy-4 {((isonicotinoyl hydrazono) methyl) amino} benzoic acid 57d showed the highest inhibition (96%) of Mtb H37Rv at 0.39 μg/mL (Imramovsky et al., 2007).



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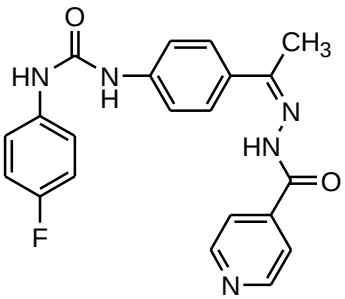

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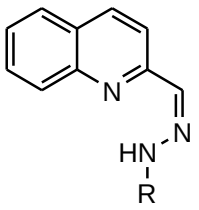

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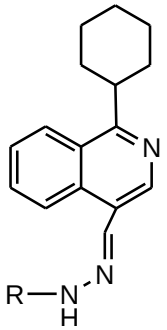

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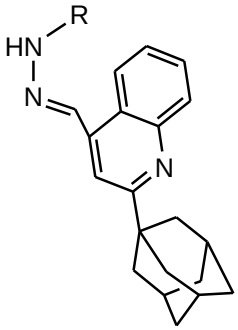

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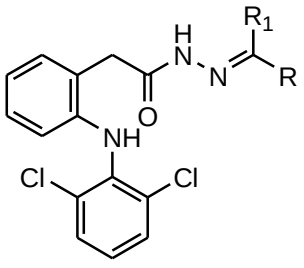

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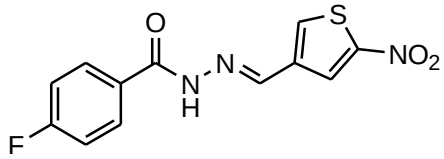

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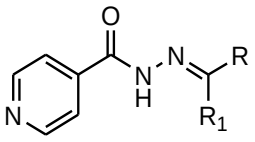

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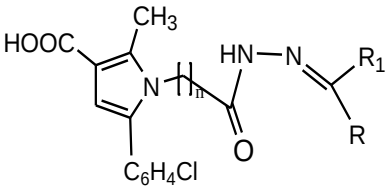

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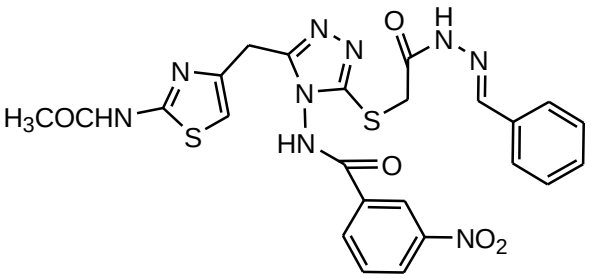

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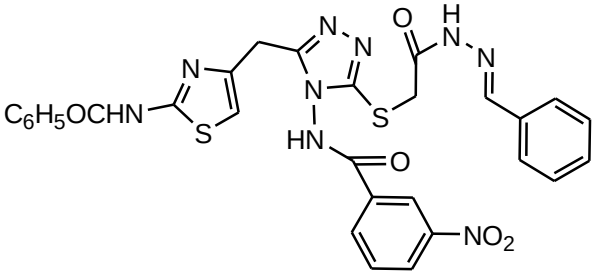

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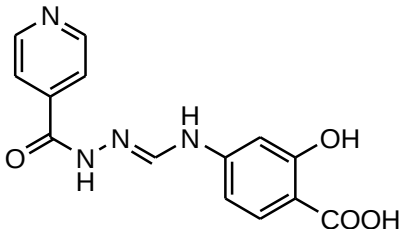

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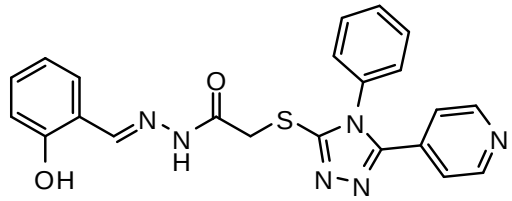
The 2, 3, 4-pentanetrione-3-(4-(((5-nitro-2-furyl) methylene) hydrazino) carbonyl) phenyl)-hydrazone, have antibacterial activity against both S. aureus and Mtb H37Rv at a conc. of 3.13 µg/mL. N1-(4-Methoxy benzamido) benzoyl)-N2-((5-nitro-2-furyl) methylene) hydrazine showed antibacterial activity. Some of the hydrazide-hydrazones were active against the same strain of Mtb H37Rv between the conc.s of 0.78-6.25µg/mL (Kaymakçıoglu, et al., 2006).

3. Antiviral activity

Some hydrazones have potent inhibitors of ribonucleotide reductase activity. N-Arylaminoacetylhydrazones and O-acetylated derivatives of sugar Narylamino acetylhydrazones were showed antiviral activity against Herpes simplex virus-1(HSV-1) and hepatitis-A virus (HAV). Some compounds showed promosing antiviral activity against HAV-27 and HSV-1 (enzyme for viral replication) (Zhang et al., 2004). The salicylhydrazide compounds for potent HIV-1 integrase inhibitory activity, (4-Phenyl-5-pyridin-4-yl-4H-[1], [2], [4] triazol-3-ylsulfanyl)-acetic acid (2-hydroxy-benzylidene)-hydrazide [81], displayed weak HIV-1 integrase inhibitory activity (Al-Macrosaur et al., 2007; Abdel-Aal et al., 2006).



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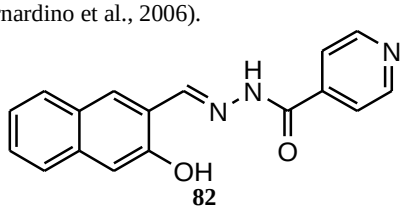
4. Antimalarial activity

The N1-arylidene-N2- quinolyl- and N2-acrydinylhydrazones were showed in-vitro antimalarial activity against P. falciparum strains, namely chloroquine-sensitive D10 and 3D7, and the CQ resistant W2 and K1. The N-(7-Chloro-quinolin-4-yl)-N'-(4-pyrrolidin-1-ylmethyl-benzylidene)-hydrazine was most active compound (Gemma, et al., 2006). The aroylhydrazone chelator 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone 82 showed good antimalarial agent activity than desferrioxamine against chloroquine-resistant and sensitive parasites (Walcourt et al., 2004). A series of N1-arylidene-N2-quinolyl- 83 and N2-acrydinylhydrazones- 15 were exhibited antimalarial properties. The compounds 14d-g and 15a-c showed an antiplasmodial activity against the chloroquine-sensitive D10 strain in the same range of chloroquine (CQ). Similarly, some compounds showed the same activity as CQ against chloroquinesensitive 3D-7 strain, while compound 84 was 10 times more potent than CQ. Two analogues were more active against W2 CQ-resistant than D10 CQ-sensitive strains (Gemma, et al., 2006). 1-Substituted phenyl-N′-((substituted phenyl) methylene)-1H-pyrazole-4-carbohydrazides 85 were leishmanicidal and cytotoxic effects were compared to the prototype drugs (ketoconazole, benznidazole, allopurinol and pentamidine) in vitro. The 1H-pyrazole-4- carbohydrazide derivatives with X = Br, Y = NO_2 and X = NO_2, Y = Cl showed the highest activity and they were more effective on promastigotes forms of L. amazonensis than on L. chagasi and L. braziliensis species (Bernardino et al., 2006).



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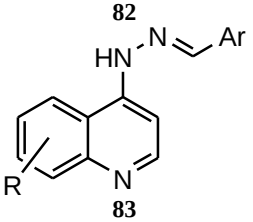

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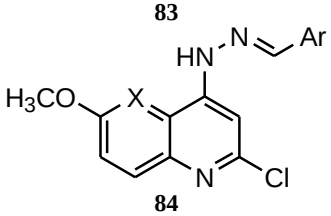

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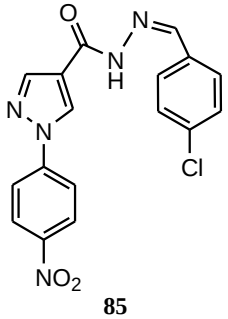

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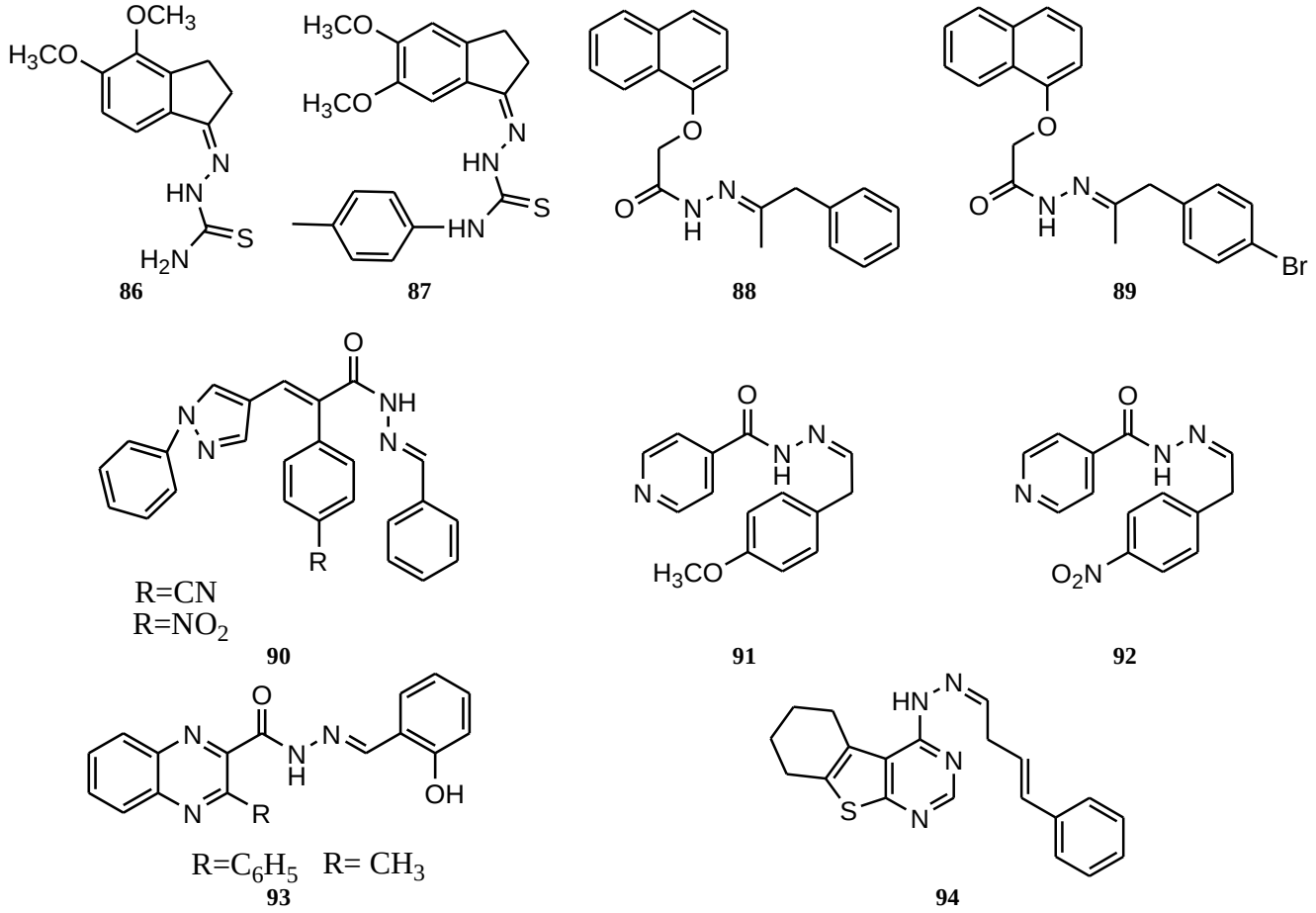
5. Antiprotozoal activity

The inhibitory activity of hydrazones [86], [87] showed against cruzipena major cysteine protease of T.cruzi (Caputto et al., 2011). The in-vitro antiamoebic activity of hydrazones [88], [89] against the HM1: IMSS strain of Entamoeba histolytica. The compounds are reported to have IC50 value of 0.03 and 0.04μM respectively (Hayat et al., 2010). Hydrazone derivatives [90], [91] described to be of high utility in Chagas disease (Vaio et al., 2009). Some hydrazone derivatives [92], [93] were showed antiamoebic activity (Siddiqui et al., 2012), some hydrazone derivatives [94], [95] act as cruzin inhibitors (Romeiro et al., 2009) and some hydrazone derivatives showed antitrypanosomal activity [96] (Aponte et al., 2010).

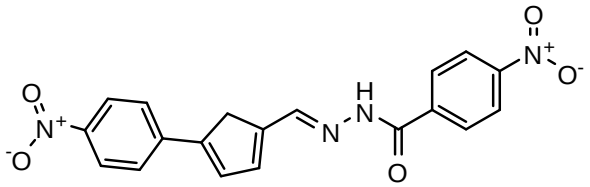


86 **87** **88** **89** **90** **91** **92** **93** **94**

Figure 2 Chemical structure of hydrazone derivatives no.44-75

6. Trypanocidal activity

A non-peptidyl acyl hydrazide acted as proteinase inhibitor for inhibition of brucipain (major cystein proteinase). The compound showed IC_{50} values <40 μM against Trypanosoma bruceiin cell culture. Some acyl hydrazides showed 50% or more inhibition of trypanosome replication at <1 μM. The trypanocidal activity of most effective compound 4-Nitro-benzoic acid (4-(4-nitrophenyl)-cyclopenta-1, 3-dienylmethylene)-hydrazide [97] was comparable to drugs sumarin and diminazineaceturate (Caffrey et al., 2002). A series of thiosemicarbazone and amino acyl thiazolidones derivatives, 2-{N'-(2-(4-Chloro-phenylsulfanyl)-ethylidene)-hydrazino}-5-methyl-thiazol-4-one [98] exhibited significant in vitro activity against epimastigot Trypanosoma cruzi (Leite et al., 2006).



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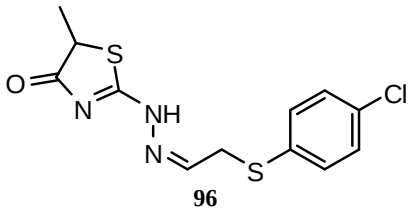

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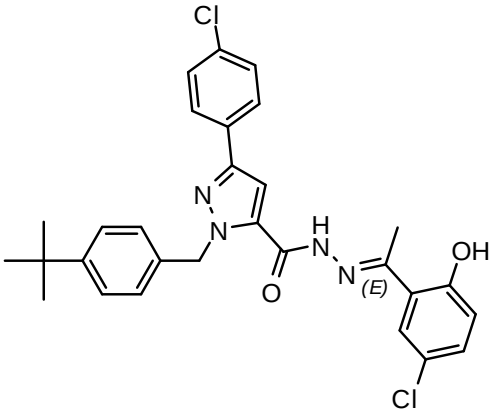
7. Leishmanicidal activity:

Two trans (Pt $(Hpy1)_2(Cl)_2$) and trans ($Pt(Hpy2)_2$ $(Cl)_2$) complexes by the reaction of K2PtCl4 with sterol hydrazone ligands 20-hydrazone-pyridin-2-yl-5a-pregnan-3b-ol (Hpy1) and 22-hydrazone-pyridin-2-yl-chol-5-ene-3b-ol (Hpy2). These compounds are specific inhibitors of sterol methyl transferase (SMT). Promastigotes of Leishmania (L) Mexicana were treated for 48 h with 10 μM of the sterol hydrazones Hpy1 or Hpy2 alone or coordinated to Pt. Hpy1 produced higher leishmanistatic activity than Hpy2 (39% growth inhibition vs. 16%), which significantly increased (71%) when the complex trans- (Pt $(Hpy1)_2(Cl)_2$) was used (Visbal et al., 2008).

8. Antitumoral activity

Substituted pyrazole-5-carbohydrazide hydrazone derivatives were showed potent apoptosis inducer in A549 lung cancer cells. The (E)-1-(4-tert-butylbenzyl)-N'-(1-(5-chloro-2-hydroxyphenyl) ethylidene)-3 (4-chlorophenyl) -1H-pyrazole-5-carbohydrazide [99] showed the highest growth inhibitory effect and induced apoptosis of A549 cells (Zheng et al., 2009). Several benzo (d) isothiazolehydrazones showed potential antiretroviral activity. Among the compounds benzo (d) isothiazole-3-carboxylic acid (4-methoxy-benzylidene) -hydrazide [100] was found to be the most potent antiproliferative compound (Vicini et al., 2006).



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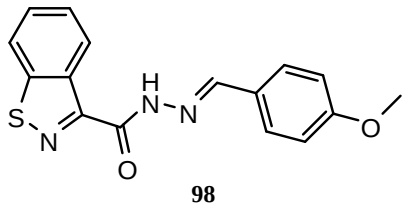

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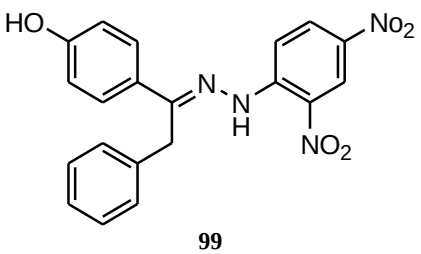
Some of diphenolic hydrazones showed uterotrophic inhibition of 70%, whereas compound 101 exhibited cytotoxicity in the range of 50-70% against MCF-7 and ZR-75-1 human malignant breast cell lines (Pandey et al., 2002). N′-(1-{1-(4-nitrophenyl-3-phenyl-1H-pyrazole-4-yl} methylene)-2-chlorobenzohydrazide 102 was found to be the most active (Abadi et al., 2003). Some 2, 6-dimethyl-N′-substituted-phenylmethyleneimidazo [2], [1-b] [1], [3], [4] thiadiazole-5-carbohydra zides, (2, 6-Dimethyl-N′-(2-hydroxy phenyl methylidene) imidazo[2], [1-b] [1], [3], [4] thiadiazole-5-carbohydrazide 103 showed the cytotoxicity. In the in vitro screening of 60 human tumors cell lines, this compound showed marked effects on the ovarian cancer cell line (Terzioğlu and Gursoy. 2003). 3-(((6-Chloro-3-phenyl-4(3H)-quinazolinone-2-yl) mercapto acetyl) hydrazono)-5-fluoro-1H-2 indolinone 104 showed the favourable cytotoxicity against the renal cancer cell line UO-31 (Gürsoy and Karali. 2003). Some active compound was the 3- and 5-methylthiophene-2-carboxaldehyde α-(N)-heterocyclichydrazones derivatives 105, which exhibited tumor growth inhibition activity against all cell lines at GI50 values between 1.63 and 26.5 μM (Savini et al., 2004).



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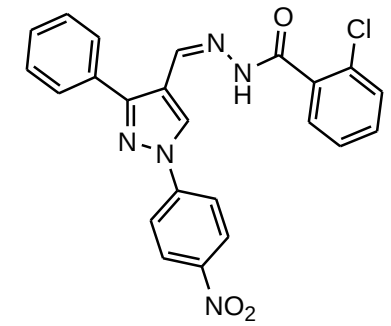

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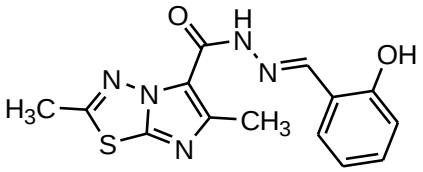

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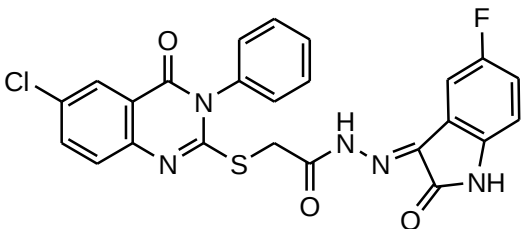

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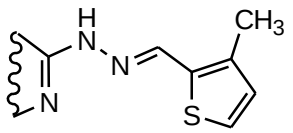

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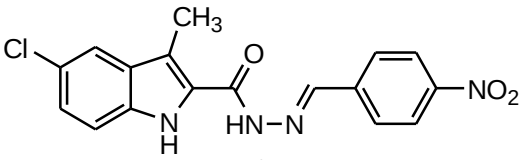

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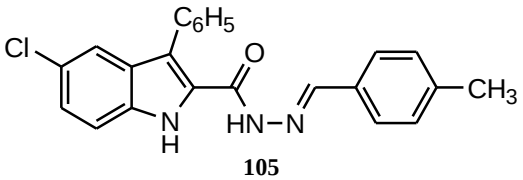

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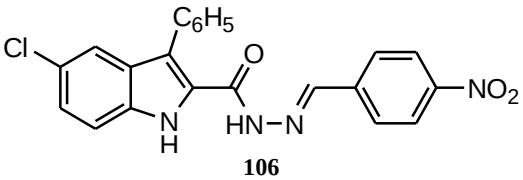

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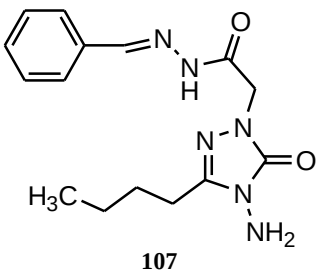

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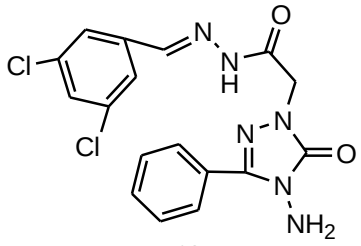

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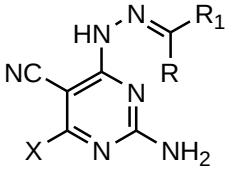

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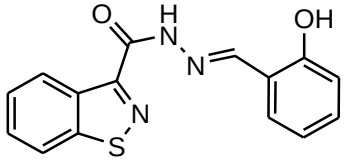

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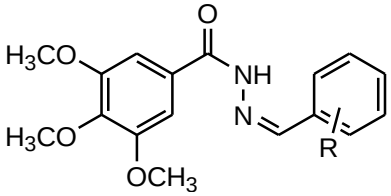

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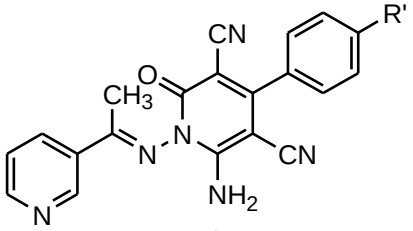

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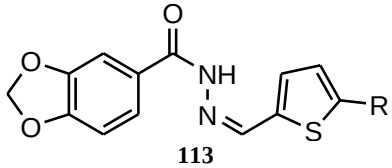

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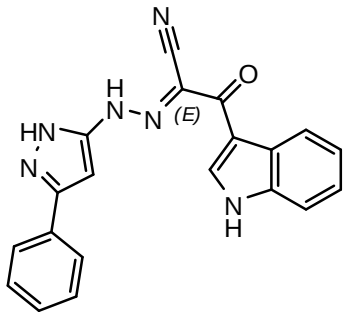
5-Chloro-3-methylindole-2-carboxylic acid (4-nitrobenzylidene) hydrazide 106 arrests T47D cells in G2/Mphase of the cell cycle and to induce apoptosis. A 20-fold increase of apoptotic activity was achieved from the 5-methyl-3-phenylindole-2-carboxylic acid (4-methylbenzylidene) hydrazide 107 and 5-chloro-3-phenylindole-2-carboxylic acid (4-nitrobenzylidene) hydrazide 108, with EC_{50} values of 0.1 μM in the caspase activation assay in T47D breast cancer cells. Compound 108 was found to be highly active in a standard growth inhibition assay with a GI50 value of 0.9 μM in T47D cells. Compound 106 and its analogs were found to inhibit tubulin polymerization (Zhang et al., 2004). Hydrazide-hydrazones containing 5-oxo-[1], [2], [4] triazole ring. Some compounds had inhibitory effect on mycelial growth whereas compounds 109 and 110 were found antitumor activity in breast cancer (Demirbas et al., 2004). Hydrazino pyrimidine derivatives 111 were showed in vitro antitumoral activity in nine different types of human cancers. Some compounds demonstrated inhibitory effects on the growth of a wide range of cancer cell lines (Cocco et al., 2005). Several benzo (d) isothiazole hydrazones have been tested for antitumoral activity. Compound 112, bearing a hydroxy group at o-position of the benzylidene moiety, was the most potent, thus acting equally potent as 6-mercaptopurine against the haematological tumors (Vicini et al., 2006). N′-Substituted-benzylidene-3, 4, 5-trimethoxy benzohydrazide 113 were showed antitumoral activity against some cancer cells. Many hydrazone compounds showed good antitumor activity against PC3 cells and showed moderate activities against Bcap37 and BGC823 cells (Jin et al., 2006). 6-Amino-4-aryl-2-oxo-1-(1-pyrid-3-yl- or 4-yl-ethylidene-amino)-1, 2-dihydropyridine-3, 5-dicarbo-nitrile series 114 exhibited a high percentage of tumor growth inhibition all cancer cell lines (Gürsoy and Güzeldemirci-Ulusoy. 2007). N′-(3, 5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1, 3-benzo dioxole-5-carbohydrazine as a novel anti-proliferative compound. They observed that was able to inhibit T-cell proliferation (66 % at 10μM) (Duarte et al., 2007). A series of arylidenehydrazides were evaluated against the full panel of 60 human tumour cell lines. Compound 115 demonstrated the most effect on prostate cancer cell line (El-Hawash et al., 2006).

Some derivatives act as PI3K p110α inhibitors. P13K are signaling proteins in different cell types responsible for phosphorylation of lipids in cell membranes (Kendall et al., 2012). Various bis (indolyl) based hydrazones active against multiple cancer cell lines (Kumar et al., 2012). Hydrazone derivative was showed potent activity against HL-60 leukaemia and 518A2 melanoma (Effenberger et al., 2010). Acylhydrazones have potent activity against the human promyelocytic leukemic cells (Hl-60) [Cui et al., 2010). Copper based hydrazone derivatives are act against integrin β4 in H322 lung carcinoma cell lines (Fan et al., 2010). Palladium based hydrazones have active against human head and neck squamous carcinoma cell lines SQ20B and SCC-25 (Abu-Surrah et al., 2010). Various hydrazones derivatives, 2-phenylindole based hydrazone exhibited against breast carcinoma cell lines and reported to have an IC50 of 1.60nM (El-Nakkady et al., 2012; Al-Said et al., 2011; Hassan et al., 2011).

9. Analgesic, anti-inflammatory and antiplatelet activity

A series of NArylhydrazone derivatives mefenamic acid were showed analgesic and anti-inflmmatory activity. The pyridine rings at the aryl moiety of the arylhydrazones have good analgesic activity in comparision to mefenamic acid. Compounds possessing the 4-tolyl or 4-flurophenyl moiety are more active than 4-bromophenyl and 4-N, N-dimethylaminophenyl. The anti-inflammatory some potent compounds showed that replacement of carboxylic acid group of mefenamic acid with N-arylhydrazone moiety cannot produce any advantage in the anti-inflammatory property (Ali et al., 2005). Analgesic activity of some (4Z)-3-methyl-1-((2-oxo-2Hchromene-4-yl) carbonyl)-1H-pyrazole-4, 5-dione 4-((4-substitutedphenyl) hydrazine) some of them showed significant analgesic activity. The presence of 4-chloro, 4-bromo, 3, 4-dichloro, 3, 4-dibromo and 4-methyl group in the aromatic ring of 4-position of the pyrazole-hydrazono nucleus gave rise to an increased analgesic activities (Sivakumar et al., 2010). Hydrazone derivatives of quinoxalinone were evaluated for anti-inflammatory activity which showed that compounds having methoxy group at the para position showed comparatively good percentage of inhibition of edema (Khan et al., 2009). The 3-(1H-Indol-3-yl)-3-oxo-2-((5-phenyl-2H-pyrazol-3-yl)-hydrazono)-propionitrile [116] was found to possess appreciable analgesic and anti-inflammatory activity (Radhwan et al., 2007). The antiplatelet activity of tricyclic acylhydrazone derivatives was showed ability to inhibit platelet aggregation. Benzylidene-/4′-bromobenzylidene 3-OH-8-CH_3-6- phenylpyrazolo [3], [4-b] thieno-[2], [3-d] pyridine-2-carbohydrazide were exhibited inhibition of the PAF-induced platelet aggregation (Todeschini et al., 1998). The benzylidene 10H-phenothiazine-1-carbohydrazides were acts in the AA pathway probably by inhibition of platelet COX-1 enzyme (Fraga et al., 2000).



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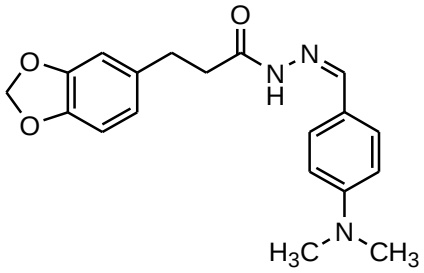

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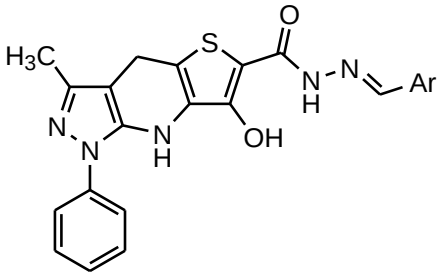

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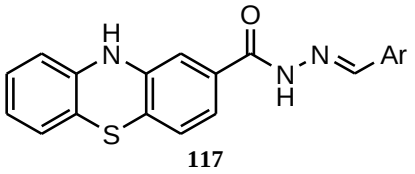

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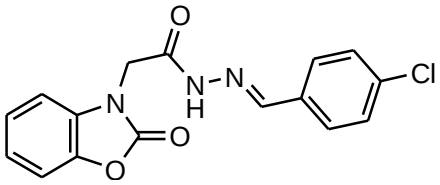

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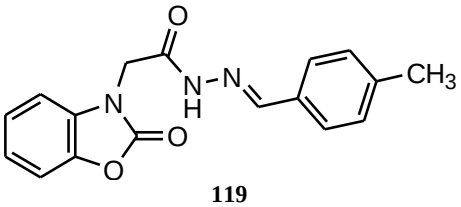

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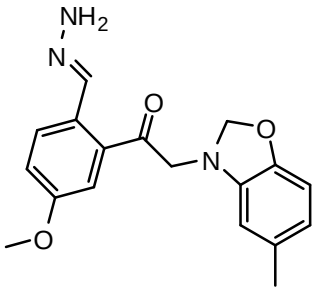

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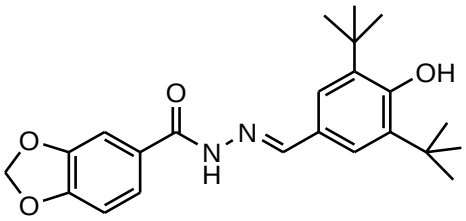

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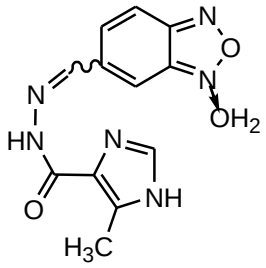

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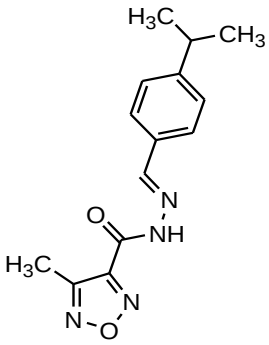
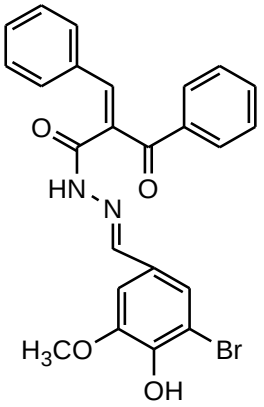


123

N-acylarylhydrazone class, ((4′-N, N-Dimethylaminobenzylidene-3-(3′, 4′methylene dioxy phenyl) propionylhydrazine) 117 was more potent than dipyrone and indomethacine (Lima et al., 2000). The tricyclic acylhydrazone derivatives 118 were showed antiplatelet activity. Benzylidene-/4′-bromobenzylidene 3-hydroxy-8-methyl-6-phenyl pyrazolo [3], [4-b] thieno-[2], [3-d] pyridine-2-carbohydrazide were evaluated as PAF-induced platelet aggregation inhibitor (Fraga et al., 2000). The benzylidene 10H-phenothiazine-1-carbohydrazide (IC_{50}=2.3μM) 119, inhibit COX-1 enzyme. The change in para-substituent group of acylhydrazone permitted to identify a hydrophilic carboxylate derivative and a hydrophobic bromo derivative as analgesic that are more potent than dipyrone, possessing selective peripheral or central mechanism of action (Silva et al., 2004). 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 120 and 121 were found to be higher than those of morphine and aspirin. In addition, 2-(2-(5-methyl-2-benzoxazoline-3-yl) acetyl)-4- methoxy benzylidene hydrazine 122 at 200 mg/kg dose possessed the most antiinflammatory activity (Salgın-Gokşen et al., 2007). N′-(3, 5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1, 3-benzodi oxole-5-carbohydrazine 123 as an antiinflammatory compound (Duarte et al., 2007). Compound furoxanyl-N-acylhydrazones [124], [125] were showed Analgesic and anti-inflammatory activity (Hernandez et al., 2012). The anti-inflammatory activity exhibited by some aryl hydrazones [126] (Rajitha et al. 2011). Various hydrazone derivatives [127] have promising in-vivo anti-inflammatory activity (Moldovan et al., 2011). Hydrazone derivatives [128], [129] with selective COX-2 inhibition with ED_{50} value of 0.2 mmol/Kg (El-Sayed et al., 2011). Benzo-thiophene derivatives [130] have inhibition of 50.2% inflammation (Isloor et al., 2010).



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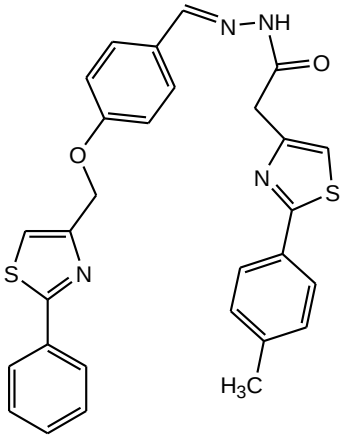

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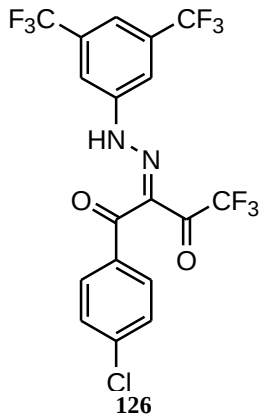

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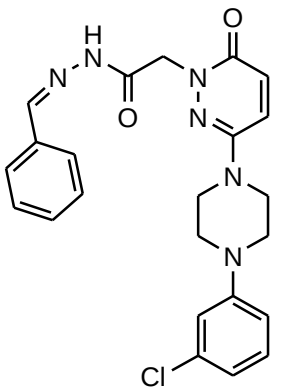

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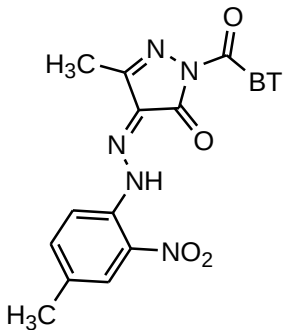
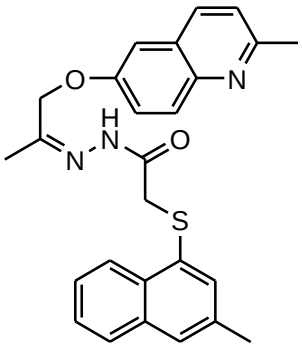


128

10. Central nervous system

Hydrazones [131] have inhibited PDE10A-a phosphodiesterase responsible for neurological and psychological disorder such as Parkinson's, Schizophrenia and Huntington's disease (Gage et al., 2011). The anticonvulsant potential of some hydrazone derivatives [91], [92] having long duration of action and a rapid onset of action (Kaushik et al., 2010). Antidepressant activity of hydrazones [93] has been reported (de Oliveira et al., 2011). The in-vitro β-amyloid aggregation inhibitory activity showed by hydrazone derivatives [96] with an IC_{50} of 23μM (Catto et al., 2010).



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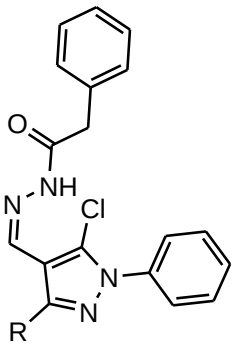
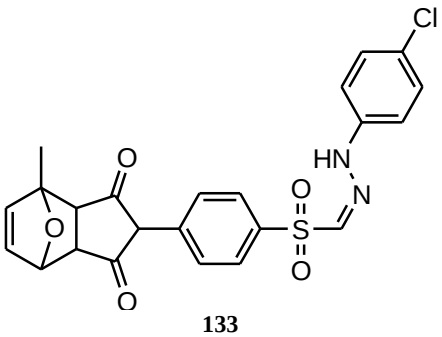


R=Isobutyl & R= H

130-132



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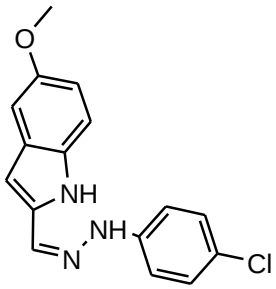
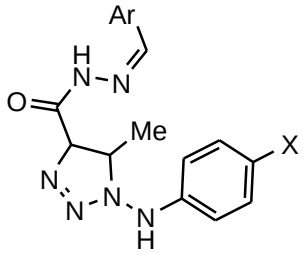


134

Antiplatelet activity: Antiplatelets prevent the formation of thrombus. Hydrazone derivatives [136], [137], and [138] exhibited in-vitro antiplatelet activity (Jordao et al., 2011).

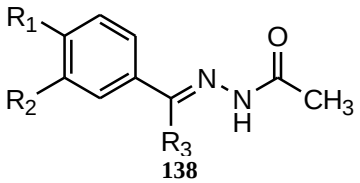


Ar=Ph, X=H
Ar=Pyrid-4-yl, X=H
Ar= 2-nitrofuryl, X=4-Cl

135 – 136 - 137

11. Anticonvulsant Activity

The acetylhydrazones 139 provided good protection against convulsions while the oxamoylhydrazones 140 were significantly less active (Dimmock et al., 2000). Some hydrazones of (2-oxobenzoxazoline-3-yl) acetohydrazide 141 were testeted for their antiepileptic activity against scPTZ test. The 4-fluoro derivative was found to be more active than the other compounds (Çakır et al., 2001). The GABA hydrazones 142 were showed anticonvulsant properties (Ragavendran et al., 2007). The 2-Chloroquinolinyl Hydrazone [143] derivatives have anticonvulsant activity (Kumar et al., 2010).



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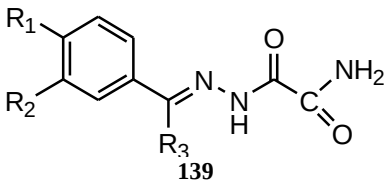

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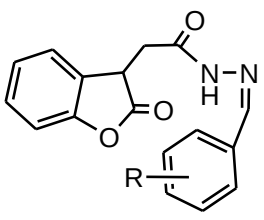

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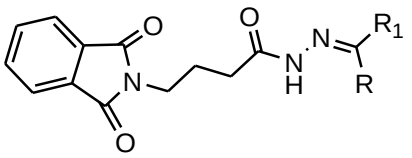

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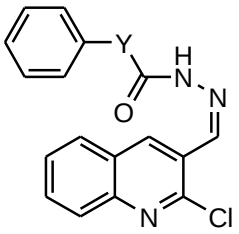
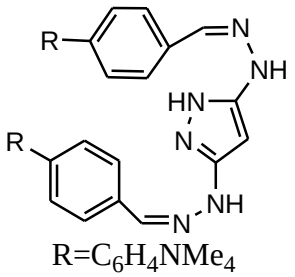


141

The N'-((5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene) 2/4-substituted hydrazides showed anticonvulsant activity, aryl derivative exhibited activity against MES and scPTZ models. When the para to the aryl ring was substituted with electron withdrawing group the compounds were found to be more potent and active in both models as compared to electron donating group. The 3, 4-di (substituted) oxy-N2, N5-bis (substituted) thiophene-2, 5-dicarbohydrazide exhibited anticonvulsant activity against MES, and scPTZ induced seizure (Darpan et al., 2010). Some hydrazide-hydrazone derivatives showed antidepressant activity (Mohareb et al., 2010). A series of 2-(1H-indol-3-yl) acetyl-N-(substituted phenyl) hydrazine carbothioamides and their related heterocyclic derivatives exhibited anticonvulsant activity against MES method. The hydrazone-indole based heterocyclic derivatives were found to have encouraging anticonvulsant activity (Siddiqui et al., 2012). Anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore, all of the compounds were ineffective in the MES test. Most of the compounds were found to be effective in the scSTY and ipPIC models and very few compounds showed protection in the sc PTZ model. The pharmacophoric combinations of phthalimide-GABA-anilide/hydrazones are as anticonvulsants. The phthalimide GABA-anilides were found to be more effective than the corresponding phthalimide-GABA-hydrazone derivatives (Darpan et al., 2010; Ragavendran et al., 2007).

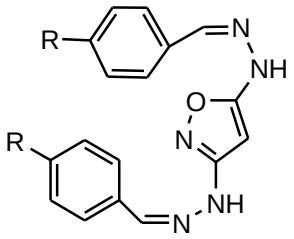
12. Antioxidant activity

Hydrazone derivatives [144], [145] were exhibited free radical scavenging activity (Musad et al., 2011). Imidazoline based hydrazones [146], [147] reported as promising antioxidant activity (Abdel-Wahab et al., 2011).



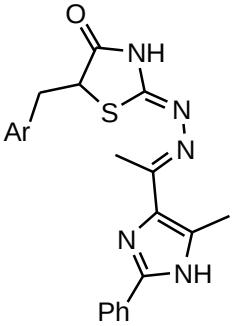
$R=C_6H_4NMe_4$

142



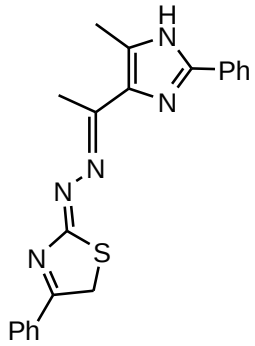
R=C_6H_4OH

143



Ar=2-thiaenyl

144

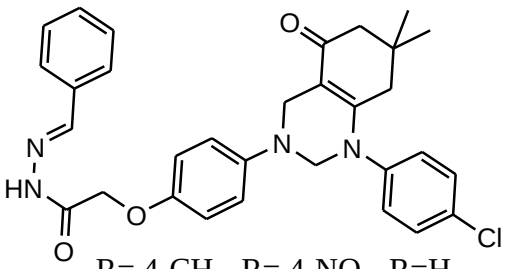


Ar=2-thiaenyl

145

13. Vasodilator activity

The octahydroquinazolinehydrazones [148], [149], and [150] were exhibited potential hypotensive agents (El-Sabbagh et al., 2010). A compound of the N-acylhydrazone, 3, 4-methylene dioxybenzoyl-2-thienyl hydrazone, (LASSBio-294), showed inotropic and vasodilatory effects. Derivatives of LASSBio-294 were exhibited contractile responses of rat vascular smooth muscle. Phenylephrine-induced contractions of aorta was inhibited by the derivatives N-methyl-2-thienylidene-3, 4-methylenedioxy-benzoyl hydrazine (LASSBio-785) and N-allyl-2-thienylidene-3, 4-methylenedioxy-benzoyl hydrazine (LASSBio-788). LASSBio-785 was seven times more potent than the LASSBio-294 in endothelium-independent vasodilator effect (Silva et al., 2005).

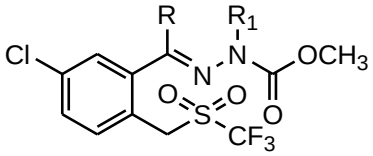


R= 4-CH_3, R= 4-NO_2, R=H

146 – 147 – 148

14. Antiparasitic activity

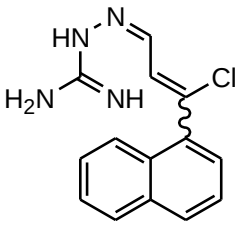
The anti-parasitic activity of hydrazone derivatives [151], [152] showed against Ctenocephalides felis and Rhipicephalus sanguineusas (Ali et al., 2010). Hydrazone derivatives [153], [154] as a urease inhibitors, urease catalyzes the hydrolysis of urea to ammonia and carbamate and it is beneficial for the pathogenesis of urolithiasis, pyelonephrities, ammonia and hepatic encephalopathy, hepatic coma and urinary catheter encrustation (Aslam et al., 2011).



R=CH_3, R_1=C_2H_5

R=C_2H_5, R_1=C_2H_5

149 - 150



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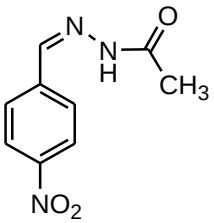

152

15. Antidiabetic activity

Pyrimidylhydrazonesas inhibitors of glycogen synthase kinase-3 (GSK-3) with the most active compound exhibited antidiabetic activity (Smalley et al., 2006).

16. Discussion

Hydrazones constitutes an important class of compounds for various biological activities. These observations promot us for the development of new hydrazones that possess varied biological activities and has been considerable interest in the development of novel compounds with diverse biological activities (Govindasami et al., 2011; Rajitha et al., 2011; Uppal et al., 2011; Belskaya et al., 2010; Scior and Garcés-Eisele. 2006; Nayyar and Jain. 2005). Vast works have been done on hydrazones across the world for the development of better biological molecules as well as with low toxicity profiles. Different hydrazones have been developed and found to be active pharmcologically.

17. Conclusion

The use of hydrazones as lead for development of newer agents and hydrazone moiety possesses an array of activity.) With proper synthesis of potential compounds can be designed for different biological activity.

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