Review Article

A Review on Biological Importance of Hydrazones

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ABSTRACT

Hydrazone derivatives of carbonyl compounds considered to be biologically important class of compounds. Hydrazone nucleus is found in natural and synthetic products of biological interest. Literature studies revealed that hydrazones and various substituted hydrazones are associated with a broad spectrum of biological activities such as antioxidant, antibacterial, antiviral, analgesic, antiplatelet, antimicrobial, and anticancer activities etc. The present review focuses on the different biological activities possessed by hydrazones. Hopefully, this will allow the development of innovative new strategies for the development of novel compounds.

Keywords: Activities, biological importance, broad spectrum, hydrazones.

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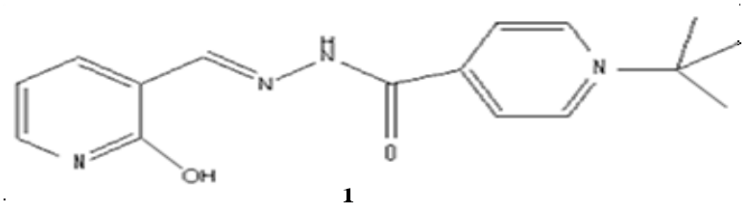
INTRODUCTION

Hydrazone and acylhydrazone derivatives have been considerable interest in the development of novel compounds with anticonvulsant, antiinflammatory, antidepressant, analgesic, antiplatelet, antimalarial, antimicrobial, antimycobacterial, anticancer activities. Hydrazones containing an azomethine –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. Hydrazide-hydrazones compounds are not only intermediates but 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- azomethine group.

Hydrazones and acylhydrazones possessing an azomethine –NHN=CH- and O=C-NH-N=CH proton constitute an important class of compounds for new drug development.

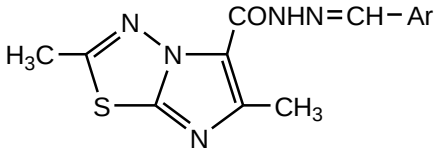
Hydrazone derivatives with anticancer activity

D. R. Richardson synthesized cytotoxic analogs of the iron(iii) chelator pyridoxal isonicotinoyl hydrazone **(1)** : effects of complexation with copper(ii), gallium(iii), and iron(iii) on their antiproliferative activities.



1

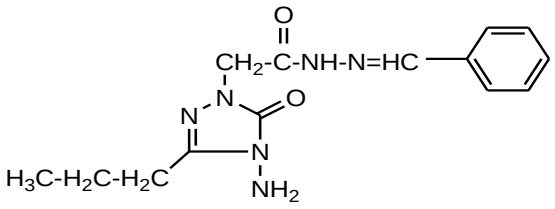
Novel 2, 6- dimethyl- N′- substituted phenyl methylene - imidazo [2, 1-b]-[1, 3, 4] thiadiazole-5-carbohydrazides were synthesized. 2, 6-dimethyl-N′-(2-hydroxy-phenylmethylidene) imidazo [2, 1-b] [1, 3, 4] thiadiazole -5 carbohydrazide **(2)** showed the most favourable cytotoxicity.



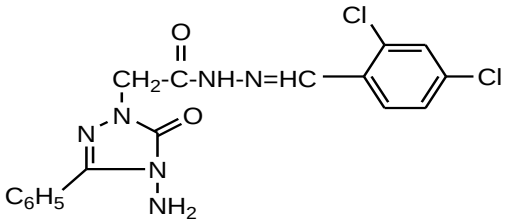
Ar = 2-HOC_6H_4

2

Demirbas *et al.,* synthesized the new hydrazide-hydrazones containing 5-oxo-[1, 2, 4] triazole ring **(3)**. Some of these compounds had inhibiting effect on mycelial growth where as compounds **3a & 3b** were found to possess antitumor activity in breast cancer [1].

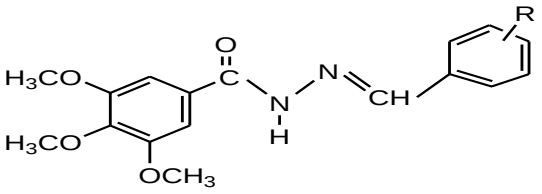


3a



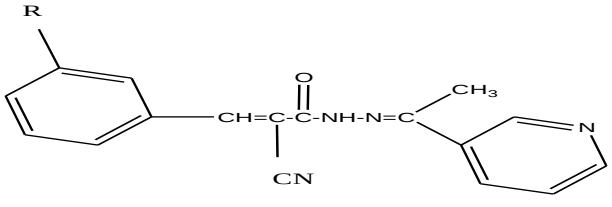
3b

N′-substituted-benzylidene-3, 4, 5-trimethoxy benzohydrazide **(4)** 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. R=2-F, 3-F, 4-F, 4-CF3 were highly effective against PC3 cells and R=2-F, 4-F, 4- CF_3 showed moderate activities against B cap 37 [2].



4

Novel Hydrazide-Hydrazone derivatives **(5a-5c)** were synthesized and their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor activity [3].

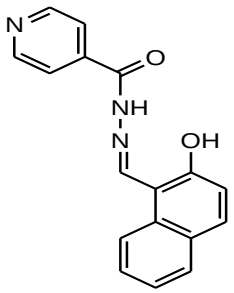


a) R=H
b) R=Cl
c) R=OCH_3

5

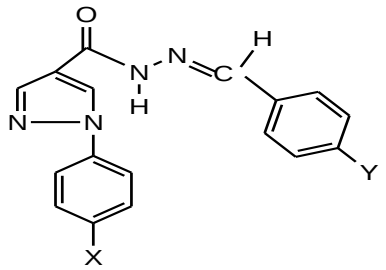
Hydrazone derivatives with Antimalarial activity

The aroyl hydrazone chelator 2-hydroxy-1-naphthyladehyde isonicotinoyl hydrazone **(6)** showed greater antimalarial activity than desferrioxamine against chloroquine - resistant and –sensitive parasites [4].



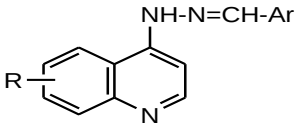
6

1-substituted phenyl-N′-[(substituted phenyl) methylene]-1H-pyrazole-4-carbohydrazides **(7)** were synthesized and their leishmanicidal and cytotoxic effects were compared to the prototype drugs (Ketoconazole, benzmidazole, allopurinol and pentamidine) in vitro. The 1H-pyrazole-4-carbohydrazide derivatives with X=Br, Y=NO2 and X=NO2, Y=Cl demonstrated the highest activity [5].



7

A series of N^1-arylidene-N^2-quinolyl **(8)** and N^2-acrydinyl hydrazones **(9)** were synthesized and tested for their antimalarial properties. The newly synthesized compounds showed antiplasmodial activity [6].



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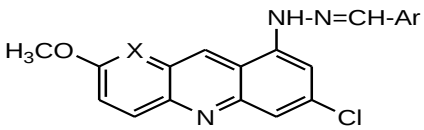
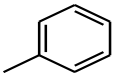
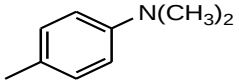
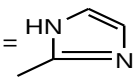


9

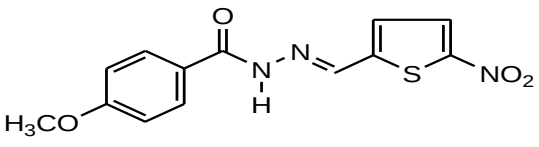
R	Ar
8-OCH_3	
6-OCH_3	

X = CH or N

Ar = 

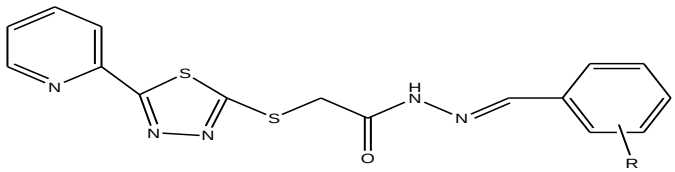
Hydrazone derivatives with Antitubercular activity

Benzoic acid [(5-nitro-thiphene-2-yl) methylene] hydrazide series **(10)** were synthesized and tested against *M.tuberculosis* H37 RV. Rando and co-workers have applied Topliss methodology to a set of nitrogen analogues. 4-methoxybenzoic acid [(5-nitrothiphene-2yl) methylene] hydrazide **(10)** was demonstrated as being the most active compound.



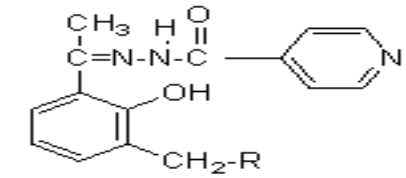
10

Mamolo M.G. Falagiani, V.; Zampieri *et al* synthesized [5-(Pyridine-2-yl)-1,3,4-thiadiazole-2-yl]thio]acetic acid arylidene-hydrazide derivatives **(11)** and tested for their in vitro antimycobacterial activity.

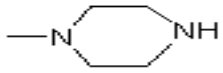


11

Some recently synthesized compounds **(12&12a)** were found to possess Antitubercular activity. N′-{1-[2-hydroxy-3-(piperazine-1-yl-methyl) phenyl] ethylidene} isonicotinohydrazide **(24)** was found to be the most active compound [7].



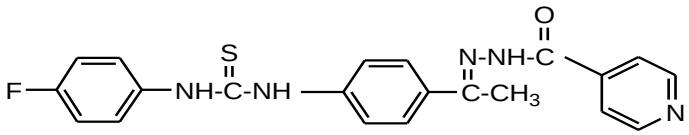
12



12a

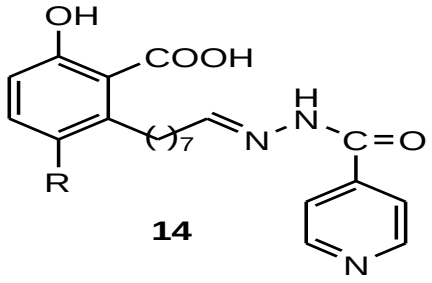
Sriram *et al.,* synthesized a new series of antimycobacterial agents **(13)** containing INH hydrazide-hydrazone.

1-(4-Fluorophenyl)-3-(4-{1-[pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea **(13)** was found to be most potent compound [8].



13

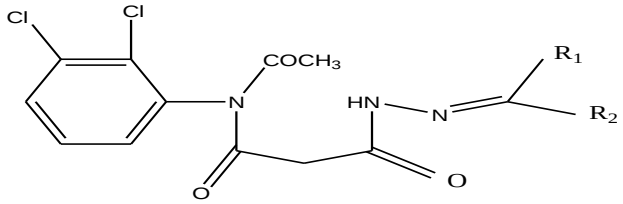
Isonicotinoyl hydrazones were synthesized from a natural product anacardic acid, a major constituent of cashew nut shell. The unsaturated side chain in anacardic acid and its 5-nitro derivative were converted into C_8-aldehydes by oxidative cleavage. C_8-aldehydes are then coupled with isoniazid to obtain N-isonicotinoyl-N′-8-[(2′-carbohydroxy-3′-hydroxy) phenyl] octanal hydrazone **(14).** These isonicotinoyl hydrazones of anacardic aldehydes showed potent antimycobacterial activity against *mycobacterium smegmatis mc²155*. The synergistic studies of **14a** and **14b** with isoniazid showed more inhibitory activities than isoniazid alone. These compounds also showed activity against *mycobacterium tuberculosis H_{37} RV* [9].



14

a R = H
b R = NO_2

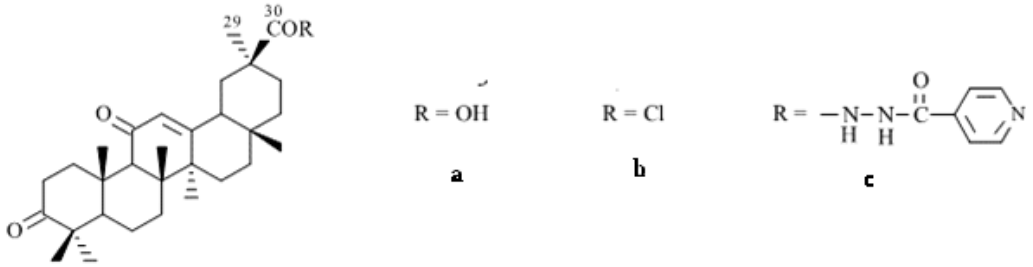
New acid hydrazones derived from Ethyl-2-[(N-Acetyl) 2, 3- dichloroanilido] acetohydrazide **(15)** and screened for anti tubercular activities.



R_1= H, phenyl
R_2= H, 4-hydroxy-3-methoxy phenyl

15

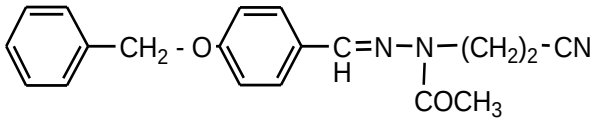
A number of betulinic acid , olealonic acid , ursolic acid derived hydrazones **(16a-16c)** were synthesized and screened for the anti tubercular activities.



16

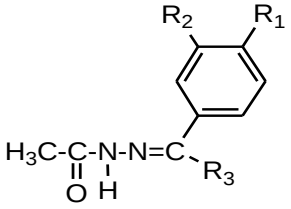
Hydrazone derivatives with Anticonvulsant activity

The synthesis and evaluation of the monoamine oxidase A and B inhibitory activities of new substituted acyl hydrazones of various aromatic aldehydes and 4-(benzyloxy)acetophenone, and four substituted semicarbazones of benzaldehyde and 4-(benzyloxy) benzaldehyde were reported. 4-(benzyloxy) phenyl group contributing to a high lipophilicity led to the most active compounds. One of these, compound **(17)** was found to act as a reversible and probably tight-binding inhibitor. The studied acyclic hydrazones and semicarbazones are structurally related to other reversible and potent inhibitors, e.g., heterocyclic compounds such as 1, 3, 4-oxadiazol-2(3H)-one derivatives in which the hydrazone group is intracyclic [10].



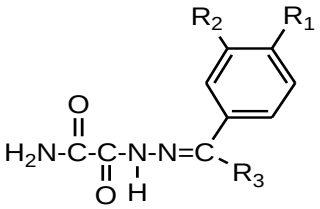
17

The biological results revealed that in general, the acetyl hydrazones **(18)** provided good protection against convulsions while the oxamoyl hydrazones **(19)** were significantly less active.



18

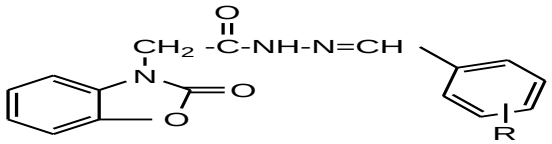
$R^1 = R^2 = R^3 = H$



19

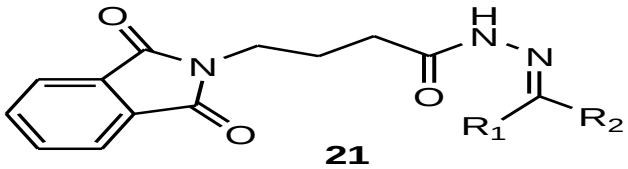
$R^1 = R^2 = R^3 = H$

New hydrazones of (2-oxobenzoxazoline-3-yl) aceto hydrazide **(20)** were synthesized and their antiepileptic activity was tested in scPTZ test. The 4-fluoro derivative **(20a)** was found to be more active than the other compounds [11].



20 R= 4-F

4-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain. GABA hydrazones **(21)** were designed and synthesized and evaluated for their anticonvulsant properties.



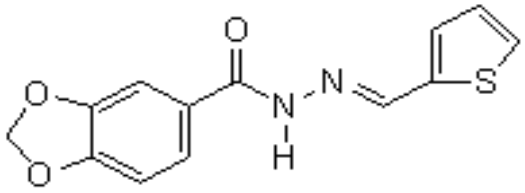
21

$R_1 = CH_3$

$R_2 = C_6H_5$ or 4-OH-C_6H_4

Hydrazone derivatives with Vasodilator Activity

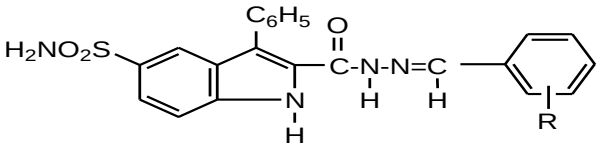
A new bioactive compound of the N-acylhydrazone class, 3,4-methylene-dioxybenzoyl-2-thienyl hydrazone **(22)** named LASSBio-294, was shown to have inotropic and vasodilatory effects. New derivatives of LASSBio-294 were designed and tested on the contractile responses of rat vascular smooth muscle in vitro [12].



22

Hydrazone derivatives with Antidepressant activity

New arylidene hydrazides **(23)** which were synthesized by reacting 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes, evaluated for their antidepressant activity. 3-phenyl-5-sulfonamidoindole-2-carboxylic acid 3,4-methylenedioxy/4-methyl/4-nitro benzylidene hydrazide **(23a, 24b, 25c)** showed most favourable activity [13].

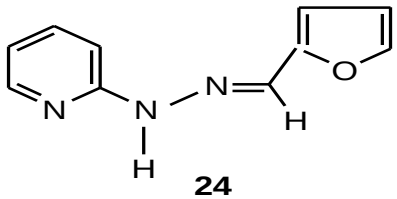


23

	R
23a	3,4-methylenedioxy
23b	4-CH_3
23c	4-NO_2

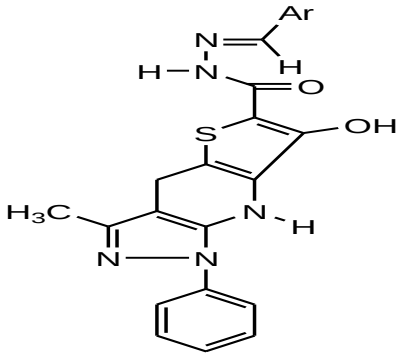
Hydrazone derivatives with Antiplatelet activity

The most important antiplatelet derivative, 2-(2-formylfuryl)pyridyl hydrazone **(24)** were synthesized and evaluated for their Antiplatelet properties [14].



24

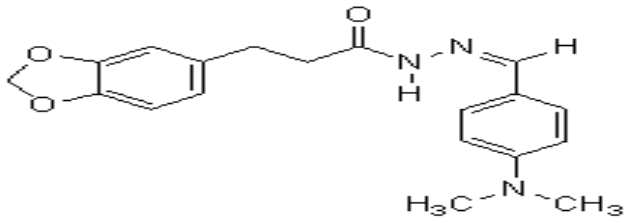
The antiplatelet activity of novel tricyclic acylhydrazone derivatives **(25)** was evaluated by their ability to inhibit platelet aggregation of rabbit platelet-rich plasma induced by platelet activating factor (PAF) at 50nM [15].



25

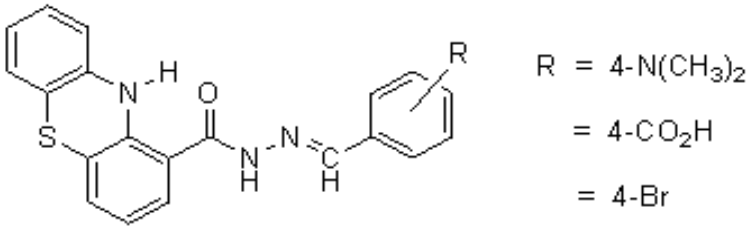
Hydrazone derivatives with Analgesic activity

A new series of antinociceptive compounds that belong to the N-acylarylhydrazone class were synthesized from natural safrole. [(4′-N,N-Dimethyl aminobenzylidene-3-(3′, 4′-methylene dioxy phenyl) propionyl hydrazine] **(26)** was more potent than dipyrone and indomethacine, which are used as standards analgesic drugs [16].



26

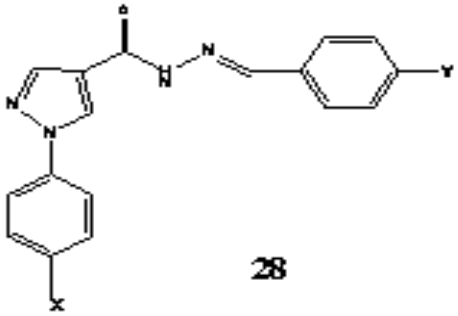
The analgesic and anti-inflammatory activities of the 10H-phenothiazine-1-acyl-hydrazone derivatives (**27**) were evaluated using the carrageenan-induced rat paw edema test and the classical acetic acid induced mice abdominal constriction test, p.o. with indomethacin and dipyrone as standards. Compounds presenting 4-dimethylamino and 4-carboxy groups were able to inhibit significantly the formation of edema (20.5% and 51.2% respectively). In spite of poor anti-inflammatory profile of most of the 10H-phenothiazine-1-acylhydrazone derivatives and acylhydrazide intermediates, all of them inhibited significantly the constrictions induced by acetic acid in a range from 23% to 70%. Additionally the change of para-substituent group of acylhydrazone frame work resulted in identifying hydrophilic carboxylate derivative and hydrophobic bromo derivative as two new leads of analgesics more active than dipyrone used as standard and with selective peripheral or central mechanism of action [17].



27

Hydrazone derivatives with Leshmanicidal activity

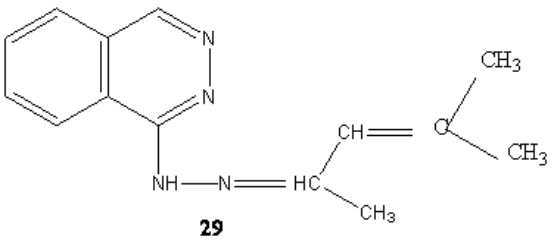
1- Substitutedphenyl -*N*′-[(substitutedphenyl) methylene]-1*H* pyrazole-4-carbohydrazides **(28)** were synthesized and their leishmanicidal and cytotoxic effects were compared to the prototype drugs (ketoconazole, benznidazole, allopurinol and pentamidine) *in vitro*. The 1*H*-pyrazole-4-carbohydrazide derivatives with X = Br, Y = NO2 and X = NO2, Y = Cl demonstrated the highestactivity and they were more effective on promastigotes forms of *L. amazonensis* than on *L. chagasi* and *L. braziliensis* species.



28

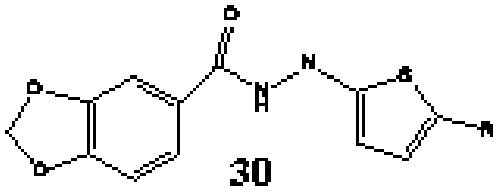
Hydrazone derivatives with Antihypertensive activity

M. Minami *et.al.,* elucidated the effects of a new vasodilating antihypertensive drug, Budralazine (Mesityl oxide -1- phthalazinyl hydrazone) **(29)** on drinking behavior of water and humoral factors including plasma nor ephinephrine, angiotensin II, arginine vasopressin (AVP), serotonin (5-HT) concentrations, urinary aldosterone and catecholamine excretion rates in rats.



29

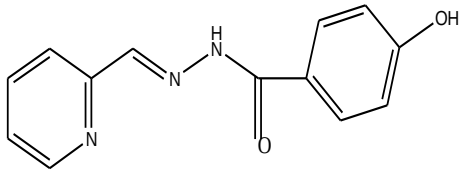
Silva A.G, Zapata-Suto *et al* introduced a new bioactive compound of the *N*-acylhydrazone class, 3,4-methylene dioxybenzoyl -2 -thienyl hydrazone **(30)** shown the vasodilatory activities.



30

Hydrazone derivatives with activity against Toxoplasma gondii

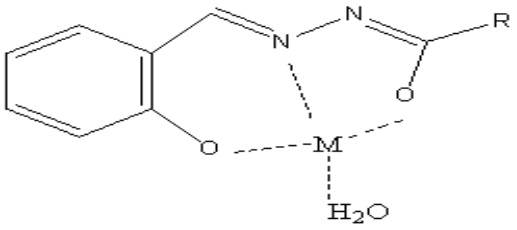
Ck Lim *et al*., synthesized new hydrazone molecule and that compound **(31)** showed protection against hydrogen peroxide mediated cytotoxicity in Freidreich's ataxia fibroblasts using novel iron chelators of the 2-pyridyl carboxaldehyde isonicotinoyl hydrazone class [18].



31

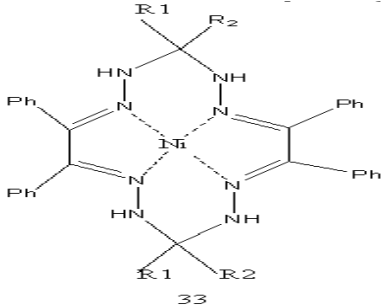
Hydrazones act as a Ligand for Metal Complexes

RK. Lonibala *et al* synthesized protonation constant of salicylidine(N-benzoyl)glycylhydrazone complexes **(32)** and its coordination behavior towards some bi valent metal ions [19].



32

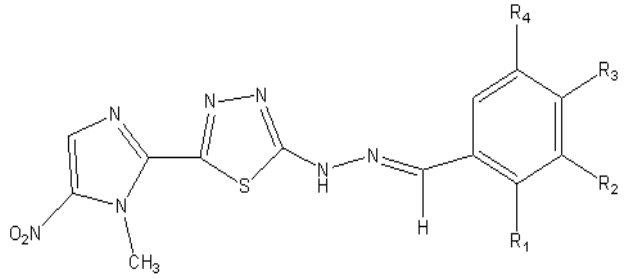
John Maria Xavier and his co workers synthesized hydrazone based 14-membered octa aza macrocyclic Ni (II) complexes **(33)** [20].



33

Hydrazone derivatives with Antitrypanocidal activity

1,3,4-thiadiazole 2-aryl hydrazone derivatives **(34)** are screened for antitrypanocidal activity. The most active hydrazone compounds of this new series were 3-nitrophenyl and 5-nitrovanillyl named Brazilian N derivatives.

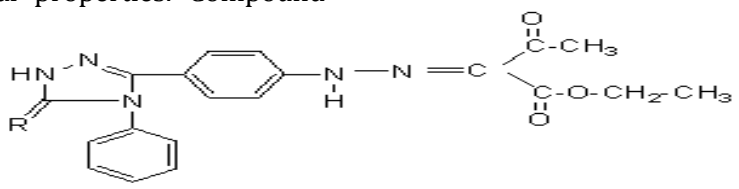


34

R_1	R_2	R_3	R_4
H	OH	OH	H
H	NO_2	OH	OCH_3

Hydrazone derivatives with Antimicrobial activity

Ethyl 2-arylhydrazono-3-oxobutyrates **(35)** were synthesized in order to determine their antimicrobial properties. Compound **35a** showed significant activity against *S.aureus*. Compound **35b** was found to be more active than the others against *mycobacterium fortuitum* [21].

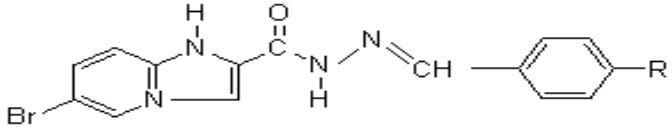


35

35a R=S

35b R=O

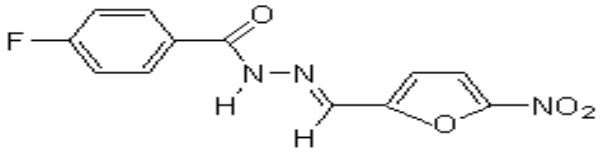
Turan-Zitouni *et al.,* found 5-bromoimidazo[1,2-a]pyridine-2-carboxylic acid benzylidene hydrazide **(36a)** and 5-bromoimidazo[1,2-a]pyridine-2-carboxylic acid 4-methoxy benzylidene hydrazide **(36b)** to possess antimicrobial activity at 3.9µg/mL aginst *E.fecalis* and *S. epidermis* [22].



36a R = H

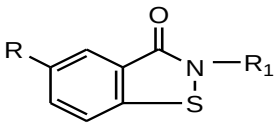
36b R = OCH_3

Rollas *et al.,* synthesized a series of hydrazide hydrazones **(37)** 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 **(37a)** showed highest activity.



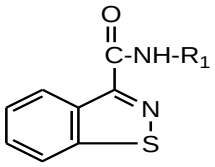
37a

A series of hydrazones derived from 1,2-benzisothiazole hydrazides (R_1=H) **(38-40)** as well as the parent cyclic **(38a&38b)** and acyclic **(39,40a&40b)** 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 **38a & 38b** showed good antibacterial activity against gram positive bacteria.

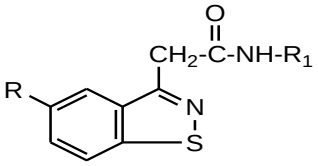


38a R=H

38b R=CH_3



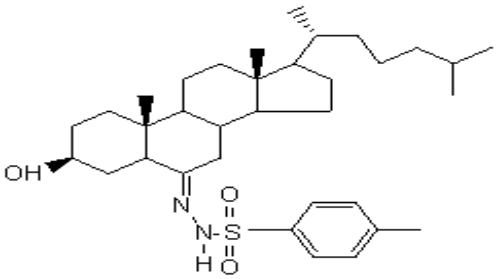
39



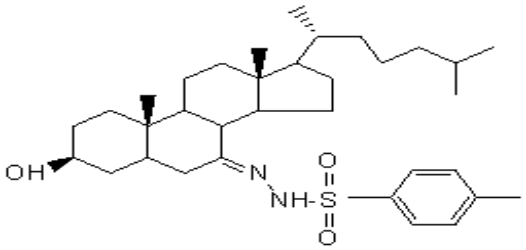
40a R=H

40b R=CH_3

A series of hydrazones synthesized from various cholesterol derivatives 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 **(41a)** and **(41b)** exhibiting activities against *C. albicans* [23].

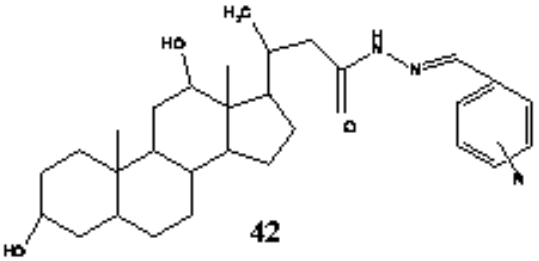


41a



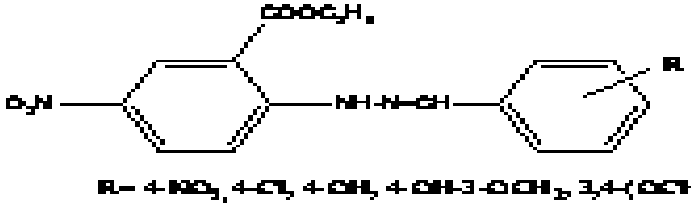
41b

Goldie Uppal *et al*.,2011 found Therapeutic Review Exploring Antimicrobial Potential of Hydrazones as Promising Lead **(42).**



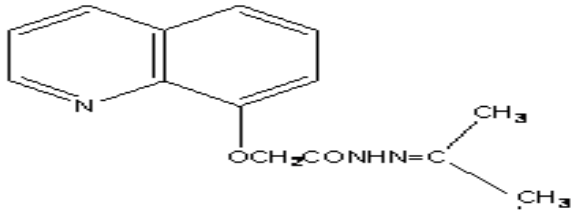
42

Adithya Adhikariet *et al*., synthesized 1-(substituted benzylidine)-2-(2-carbethoxy-4-nitrophenyl) hydrazines **(43)** and screened for *antioxidant, antibacterial and antifungal activity* [24].



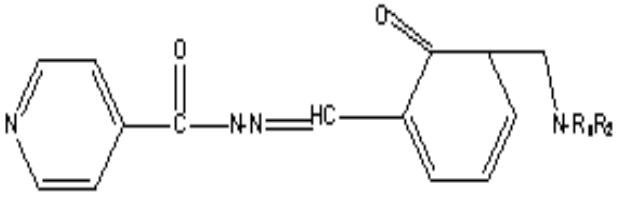
43

S. M. Bhagat et al., 2012 synthesized novel hydrazones and screened for anti bacterial, antifungal activities of some transition metal ion chelates of 2-(cinnamyl)-4-bromo-6-methyl benzothiazolyl hydrazones **(44).**



44

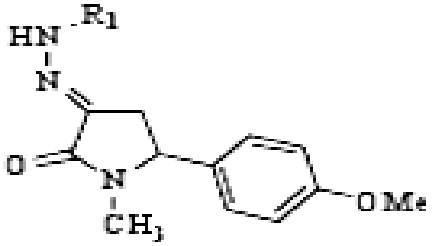
A novel series of Mannich bases containing isoniazid 2-propoxybenzylideneisonicotino-hydrazide **(45)** and screened for their potential antimicrobial activity [25].

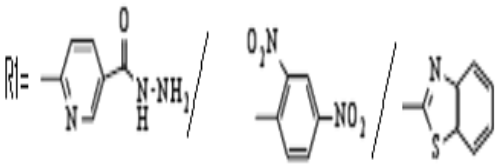


45

Hydrazone derivatives with Antioxidant activity

Mohd Fazli Mohammat *et al*, synthesized the new hydrazone moieties i.e., 2-oxo-5-aryl-3-hydrazone and 2-oxo-5-aryl-4-hydrazone pyrrolidine derivatives **(46)** by component reaction and Dieckmann cyclization resp. Successive functional group transformations which include decarboxylation and hydrazonation afforded 2-oxo-5-aryl-3-hydrazone and 2-oxo-5-aryl-4-hydrazone pyrrolidine derivatives and screened for their neurotoxic, neuroprotective function against oxidative stress [26].

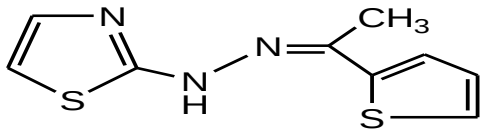




46

Hydrazone derivatives with Anti-inflammatory activity

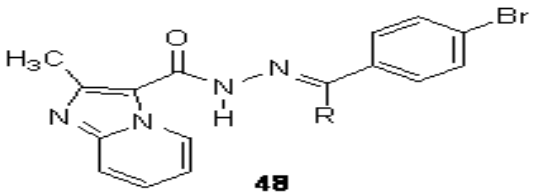
CBS-1108, 2-acetylthiophene-2-thiazolyl-hydrazone **(47)** inhibits 5-lipoxygenase activity in polymorpho-nuclear leucocytes (PMNS), 12-lipoxygenase and cyclooxygenase in platelets. Inhibition of the two pathways of arachidonic acid cascade could lead to additional beneficial antiinflammatory activity. In fact, inhibitors of both cyclooxygenase and lipooxygenase such as NGDA and CBS-1108 inhibit leucocyte migration in an animal model of acute inflammatory response [27].



47

CBS-1108

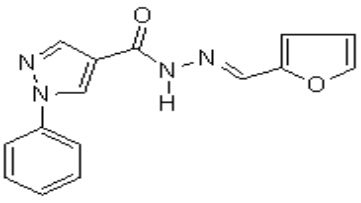
N-heterocyclic functionalized acyl aryl hydrazone compounds were synthesized and evaluated for their analgesic and anti-inflammatory activity. These compounds were structurally planned applying classical ring bioisosterism strategies on 4-acyl-(N-phenyl pyrazolyl)-aryl hydrazone. The para-substituent **(48)** at the pharmacophore acyl aryl hydrazone moiety gives good and persistent anti-inflammatory activity [28].



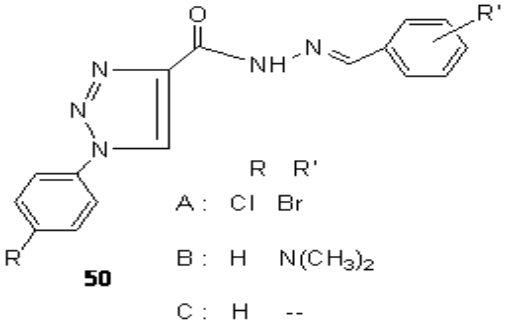
48

R = H

Classical heteroaromatic ring bioisosterism strategies were applied to the previously reported N-phenylpyrazolyl-4-acylhydrazone derivative **(49),** elected as lead compound due to its important anti-aggregating profile on arachidonic acid induced platelet aggregation (IC_{50} = 24 ± 0.5 μM), from which emerge this new series. The N-para-chlorophenyl isoster, **(50A)** was the most potent antiplatelet compound in the AA and collagen induced tests. The compound **(50A)** was much more potent (27 fold) than the N-nor-para-chlorophenyl analogue **(50B).** Compound **(83A)** was also more potent as an antiplatelet agent than the lead derivative **(49)**, representing an optimization of this initial series. Interestingly, the N-acylheteroaryl hydrazones **(50C)** presented an IC_{50} value (21 ± 2 μM) similar to compound **(49)** [29].

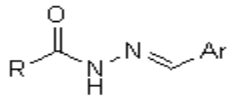


49

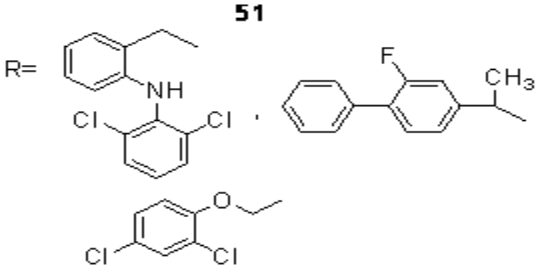


50

Various hydrazone derivatives **(51)** of diclofenac, flurbiprofen and 2, 4-dichloro phenoxy acetic acid have been synthesized and evaluated for their antiinflammatory activity. The tested compounds showed anti-inflammatory activity in the range from 64.83% to 79.48%, where as the standard drugs diclofenac, flurbiprofen and ibuprofen showed 80.76%, 95.57% inhibition respectively in carrageenan induced rat paw edema.



51



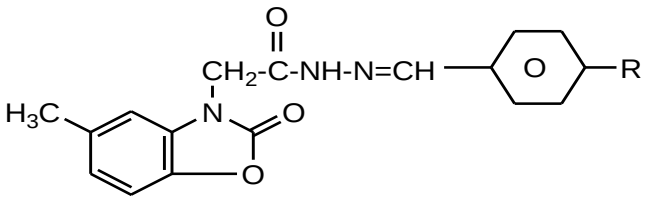
Ar

-phenyl

2-hydroxy phenyl

4-methoxy phenyl

Gokhan-kelekci *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 (**52a&52b)** were found to be higher than those of morphine and aspirin. In addition 2-[2-(5-methyl-2-benzoxazoline-3-yl) acetyl] -4methoxy benzylidene hydrazone **52c** at 200mg/kg dose possessed the most anti-inflammatory activity [30].



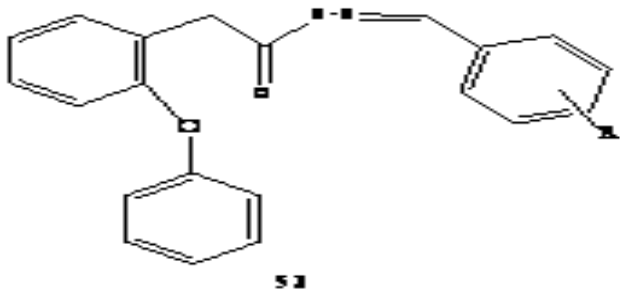
52

52a R=Cl

52b $R=CH_3$

52c $R=OCH_3$

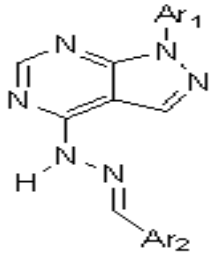
Maral Shekarchi *et al.,* 2011 synthesized N-arylidene-2-(2-phenoxyphenyl) acetohydrazides **(53)** and screened for anti inflammatory activities.



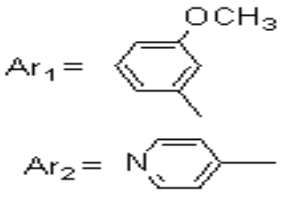
53

Hydrazone derivatives with GSK-3 inhibitors

A series of [1-aryl-1H-pyrazolo [3, 4-d] pyrimidin-4-yl] aryl hydrazones **(54)** were discovered as novel inhibitors of glycogen synthase kinase-3 (GSK-3). Based on initial modeling a detailed SAR was constructed. Modification of the interior binding aryl ring (Ar_1) determined this to be a tight binding region with little room for modification. As predicted from the model, a large variety of modifications could be incorporated into the hydrazone aryl ring. Inhibitors of GSK-3 may have utility in the treatment of Type 2 diabetes and Alzheimer's disease.



54



CONCLUSION

Hydrazones are selected as the target molecules for this review as, at present in many of the bioactive heterocyclic compounds they are of wide interest because of their diverse biological and clinical applications. This created interest in the researchers who have synthesized variety of hydrazone derivatives and screened them for their various biological activities viz. anticonvulsant, antidepressant, analgesic, anti-

inflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, anticancer, vasodialator, antiviral, antischistosomiasis, , anti-HIV, anthelmintic, , antidiabetic, and trypanocidal activities. These observations based on the present review have been guiding for the development of new hydrazones that possess varied biological activities.

REFERENCES

1. Demirbas N, Karaoglu S, Demirbas A., Sancak K.(2004) Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5- oxo-[1,2,4] triazole derivatives. Eur. J. Med. Chem. 39: 793-804.
2. Jin L, Chen J, Song B, Chen Z, Yang S Li Q, Hu D, Xu R. (2006) Synthesis, structure, and bioactivity of N′-substitutedbenzylidene-3,4,5-trimethoxy benzo hydrazide and 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Bioorg.Med. Chem. Lett. 16: 5036-5040.
3. Rafat M. Mohareb. Novel Synthesis of Hydrazide-Hydrazone Derivatives and their utilization in the Synthesis of coumarin, pyridine, thiazole and thiophene derivatives with antitumor Activity. Molecules. 2011, 16, 16-27.
4. Walcourt A, Loyevsky M, Lovejoy D.B, Gordeuk V.R, Richardson D.R.(2004) Novel aroylhydrazone and thiosemicarbazone iron chelators with anti-malarial activity against chloroquine-resistant and -sensitive parasites. Int. J. Biochem. Cell Biol. 36: 401-407.
5. Bernardino A, Gomes A., Charret K, Freitas A, Machado G. Canto-Cavalheiro M, Leon L, Amaral V. (2006) Synthesis and leishmanicidal activities of 1-(4-X-phenyl)-N′-[(4-Yphenyl) methylene]-1H-pyrazole- 4-carbohydrazides Eur. J. Med. Chem. 41: 80-87.
6. Gemma S, Kukreja G, Fattorusso C, Persico M, Romano M, Altarelli M, Savini L, Campiani G, Fattorusso E, Basilico, N. (2006) Synthesis of N1-arylidene-N2-quinolyl- and N2-acrydinylhydrazones as potent antimalarial agents active against CQ-resistant P. falciparum strains. Bioorg. Med. Chem. Lett. 16: 5384-5388.
7. Sriram D, Yogeeswari P Madhu K. (2005) Synthesis and in vitro and in vivo antimycobacterial activity of isonicotinoyl hydrazones. Bioorg. Med. Chem. Lett. 15: 4502-4505.
8. Sriram D, Yogeeswari P, Madhu K. (2006) Synthesis and in vitro Anti tubercular activity of some 1-[(4-sub)phenyl]-3-(4-{1-[(pyridine-4-carbonyl hydrazono] ethyl} phenyl)thiourea. Bioorg. Med. Chem.14: 876-878.
9. Narayana Swamy B, T. K Suma, G. Venkateswara Rao, G. Chandrasekara Reddy. (2007) Synthesis of isonicotinoyl hydrazones from anacardic acid and their in vitro activity against Mycobacterium smegmatis. Eur. J. Med. Chem. 42: 420-424.
10. Bernard S, C Paillat, T Oddos, M Seman, R Milcent. (1995) Selective and potent monoamine oxidase type B inhibitors: substituted semicarbazones and acylhydrazones of aromatic aldehydes and ketones. Eur. J. Med. Chem. 30: 471-482.
11. Çakır B, Dağ Ö, Yıldırım E, Erol K, Şahin M.F. (2001) Synthesis and anticonvulsant activity of some hydrazones of 2-[(3H)-oxobenzoxazolin- 3-yl-aceto]hydrazide. J. Fac. Pharm. Gazi. 18: 99-106.
12. Silva A.G, Zapata-Suto G, Kummerle A.E, Fraga C.A.M, Barreiro E.J, Sudo R.T. (2005) Synthesis and vasodilatory activity of new N-acylhydrazone derivatives, designed as LASSBio-294 analogues. Bioorg. Med. Chem. 13: 3431-3437.
13. Ergenç N, Günay N.S. (1998) Synthesis and antidepressant evaluation of new 3-phenyl-5-sulfonamidoindole derivatives. Eur. J. Med. Chem. 33: 143-148.
14. Adriane R. Todeschini, Ana Luisa P. da Miranda, Kelly Christine M. da Silva, Sregio C. Parrini, Eliezer J. Barreiro. (1998) Synthesis and evaluation of analgesic, anti-inflammatory and antiplatelet properties of new 2-pyridylarylhydrazone derivatives. Eur. J. Med. Chem. 33: 189-199.
15. Fraga A.G.M, Rodrigues C.R, Miranda A.L.P, Barreiro E.J, Fraga C.A.M. (2000) Synthesis and pharmacological evaluation of novel heterocyclic acylhydrazone derivatives, designed as PAF antagonists. Eur. J. Pharm. Sci. 11: 285-290.
16. Patricia C. Lima, Lidia M. Lima, Kelli Cristine M. da Silva, Paulo Henrique O. Leda, Ana Luisa P. de Miranda. Carlos A.M. Fraga, Eliezer J. Barreiro. (2000) Synthesis and analgesic activity of novel N-acylarylhydrazones and isosters, derived from natural safrole. Eur. Med. Chem. 35: 187-203.
17. Gildasio A. Silva , Luciana M. M. Costa, Fernanda C.F. Brito, Ana L.P. Miranda, Eliezer J. Barreiro and Carlos A. M. Fraga. (2004)

New class of potent antinociceptive and antiplatelet 10H-phenothiazine-1-acylhydrazone derivatives. Bioorg. & Med. Chem. 12: 3149-3158.
18. Lima P.C, Lima L.M, Silva K.C, Leda P.H, Miranda A.L.P, Fraga C.A.M, Barreiro E.J. (2000) Synthesis and analgesic activity of novel N-acyl hydrazones and isosters, derived from natural safrole. Eur. J. Med. Chem. 35: 187-203.
19. R.K. Lonibala.; T.R.Rao. Protonation constant of salicylidine (N- benzoyl) glycyl hydrazone and its coordination behavior towards some bivalent metal ions. Journal of chemical society. 2006, vol 118, no 4, 327-334.
20. John Maria et al., synthesized 14 - membered octaaza macrocyclic Ni (II) complexes. Journal of chemical and pharmaceutical research. 2012, 4(2), 986-990.
21. Küçükgüzel Ş.G, Rollas S, Erdeniz H, Kiraz M. (1999) Synthesis, Characterization and Antimicrobial Evaluation of Ethyl 2-Arylhydrazono- 3-oxobutyrates, Eur. J. Med. Chem. 34: 153-160.
22. Turan-Zitouni G, Blache Y, Güven K. (2001) Synthesis and antimicrobial activity of some imidazo-[1,2-a]pyridine-2-carboxylic acid arylidene hydrazide derivatives. Boll. Chim. Farm. 140: 397-400.
23. Loncle C, Brunel J, Vidal N, Dherbomez M, Letourneux Y. (2004) Synthesis and antifungal activity of cholesterol-hydrazone derivatives. Eur. J. Med. Chem. 39: 1067-1071.
24. Adithya Adhikaria.; Balakrishna Kallurayaa.; K. V. Sujitha.; Gouthamchandrab and Riaz Mahmood.; Synthesis and pharmacological studies of some 1 (substituted benzylidine)-2-(2-carbethoxy-4-nitrophenyl) hydrazines, Scholars Research Library Der Pharmacia Letter. 2011, 3(1): 214-220.
25. Manav Malhotra.; Manu Arora.; Abdul Samad.; Kapendra Sahu.; Priyanka Phogat and Aakashdeep. Synthesis and evaluation of some novel of 2-propoxybenzylideneisonicotinohydrazide for their potential antimicrobial activity. J. Serb. Chem. Soc.2012, 77 (5) 589–597.
26. Mohd.A and Kumar.S (2005) Synthesis of some hydrazone derivatives and their Antinflammatory Activity. Indian Drugs. 42(2): 73-77.
27. Chantal Bertez, Martine Miquel, Claude Coquelet, Daniel Sincholle and Claude Bonne. (1984) Dual inhibitors of Cyclooxygenase and lipoxygenase by 2-Acetylthiophene 2-thiazolylhydrazone (CBS-1108) effect on leukocyte migration in vivo. Biochem. Pharmaco. 33: 1757-1762.
28. Izabella G. Ribeiro, Kelly Christine M. Da Silva, Sergio C. Parrini, Ana Luisa P. de Miranda, Carlos A. M. Fraga, Eliezer J. Barreori. (1998) Synthesis and Antinociceptive properties of new structurally planned imidazo[1,2-a]pyridine 3-acylarylhydrazone derivatives. Eur. J. Med. Chem. 33: 225-235.
29. Anna, C., Cunha Juliana, M., Figueiredo, Jorge, LM., Tributino, Ana, L.P., Miranda, Helena C. Castro, Russolina B. Zingali, Carlos A.M. Fraga, Maria Cecilia, B.V., d souza, Vitor, F., Ferreira, Eliezer, J., Barreiro. (2003) Antiplatelet Properties of Novel N-substituted – Phenyl – 1, 2, 3 triazole – 4-acylhydrazone Derivatives. Bio. Org. Med. Chem. 11 : 2051-2059.
30. Salgın-Gökşen U, Gökhan-Kelekçi N, Göktaş Ö, Köysal Y, Kılıç E, Işık Ş, Aktay G, Özalp M. (2007) 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones: Synthesis, analgesic-anti-inflammatory and antimicrobial activities. Bioorg. Med. Chem. 15: 5738-5751.