Review Article

Hydrazones as Promising Lead with Diversity in Bioactivity-therapeutic Potential in Present Scenario

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ABSTRACT

Hydrazones is an important class of compounds for the development of novel drug moieties. Hydrazones consists of an azomethine -NHN=CH- proton which is responsible for the development of new drugs. Hydrazides and hydrazones leads to development of many bioactive heterocyclic compounds that are of wide interest. Therefore, many researchers synthesized various hydrazone compounds as important target structures and evaluated their biological activities. viz. antimicrobial, analgesic, anti-inflammatory, antioxidant, antiproliferative, antitubercular, antimalarial, anti-HIV, antiplatelet, anticonvulsant and anti-leishmanial activities. Hydrazones can be a potential lead for future developments to get safer and effective compounds. References of the most relevant literature published by various research scientists around the world are provided.

Keywords: Hydrazones, biological activity, iproniazide, isocarboxazide, isoniazid.

INTRODUCTION

The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important research areas of today. Hydrazone is a versatile moiety that exhibits a wide variety of biological activities. Hydrazones is a class of organic compounds having the basic structure $R_1R_2C=NNH_2$. They are related to aldehydes and ketones, by the replacement of the oxygen with the $-NNH_2$ group. They are formed by the action of hydrazine on ketones or aldehydes. Hydrazones are reactants in hydrazone iodination, the Shapiro reaction and the Bamford-Stevens reaction to vinyl compounds. A hydrazone formation is an intermediate step in the Wolff–Kishner reduction. Another method to formation a hydrazone is the Japp–Klingemann reaction (from β-keto-acids or β-keto-esters and diazonium salts). N,N'-dialkylhydrazones the C=N bond can be oxidized, hydrolysed, and reduced, the N-N bond can be reduced to the free amine. The carbon atom of the C=N can react with organometallic nucleophiles. The α-hydrogen atom is more acidic by 10 orders of magnitude compared to the ketones and therefore more nucleophilic. Deprotonation with LDA (Lithium Diisopropylamide) gives an azaenolate which can be alkylated by alkyl halides, a reaction pioneered by E.J. Corey. In asymmetric synthesis SAMP (S-1-Amino-2-methoxymethylpyrrolidine) and RAMP (R-1-Amino-2-methoxymethylpyrrolidine) are two chiral hydrazines that act as chiral auxiliary with a chiral hydrazone intermediate[1,2].

Hydrazones can be synthesized in laboratory by heating the appropriate substituted hydrazines or hydrazides with aldehydes and ketones in various organic solvents like ethanol, methanol, tetrahydrofuran, butanol and sometimes with glacial acetic acid or ethanol-glacial acetic acid. Also hydrazones can be synthesized by the coupling of aryldiazonium salts with compounds containing active hydrogen.[3]

Hydrazones act as very important intermediates in the synthesis of various heterocyclic compounds but in addition to this property they are also very effective organic compounds with important biological activities. When hydrazones are used as intermediates various coupling products can be synthesized by using the active hydrogen component of azomethine group (–CONHN=CH). Large number of biologically active compounds can be synthesized by researchers, for example: iproniazide and isocarboxazide are synthesized by hydrazones reduction. Iproniazide have structure similar to isoniazid that's why used in the treatment of tuberculosis. In some patients it also shows an antidepressant and mood changing effect. Another example of clinically effective hydrazones is nifuroxazide used as an intestinal antiseptic[4].

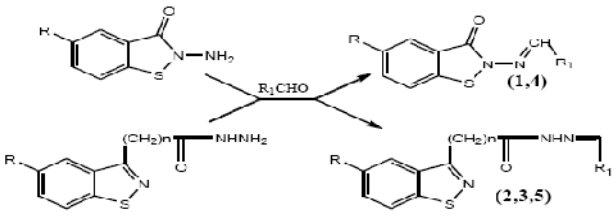
Hydrazones in which two carbon functionality as CO_2R, CN are extremely important compounds in dye industry. Nitrogen lone pair resonance renders hydrazone carbon atom electron rich and nucleophilicity of this carbon atom although have been noted in old literature has now been recognized and utilized extensively in synthesis. The most significant reactivity of the hydrazones is because of nucleophilicity of hydrazone carbon atom. Therefore various reactions like coupling reaction, Mannich reaction, and halogenations readily took place at such carbon. Recently one addition type of reactions was also described named as Michael type addition reaction. Nitrogen atom present in hydrazone however is the main site for reaction with alkylating and acylating agents. Further various investigations showed that hard nucleophiles mainly attack nitrogen atom and soft nucleophiles mainly attack at carbon atom. Various

functional substituents retain their previous reactivity pattern along with the fact that they generally become more electrophilic. Also large number of multidentate reagents in several cases leads to formation of rings involving hydrazone moiety. Further intramolecular cyclizations lead to formation of cinnolines. This literature review showed SAR and diverse biological activities of hydrazones that includes antimicrobial, anti-inflammatory, antiproliferative, anticonvulsant, antidepressant, antioxidant, radio protective and anti-leishmanial activities[5].

BIOLOGICAL ACTIVITY

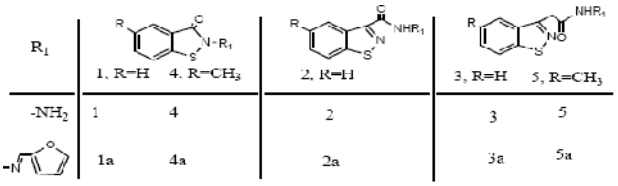
1. Anti-microbial activity

The tremendous increase in development of multi-drug resistant microbial infections in the past few years has become a serious health hazard. This leads to search for new antimicrobial agents with improved biological activity.



Scheme 1. Synthetic pathway of compounds (1,2,3,4 and 5).

A few hydrazones of 1,2-benzisothiazole hydrazides (Scheme **1**) were synthesized and evaluated for antimicrobial activity against Gram positive bacteria *Bacillus subtilis, Staphylococcus aureus*. Compounds **1** and **4** proved to be the most effective against *B. subtilis*; these compounds in combination with **2** were the only ones also active against Gram negative bacteria (*Escherichia coli*). In all cases the assayed substances showed an activity level against bacteria lower than that of ampicillin, the reference drug. Many of the tested benzisothiazolones showed antifungal properties against *Saccharomyces cerevisiae* and *Candida tropicalis*. Compounds **1**, **2** and **4** were also active against *Aspergillus niger*.

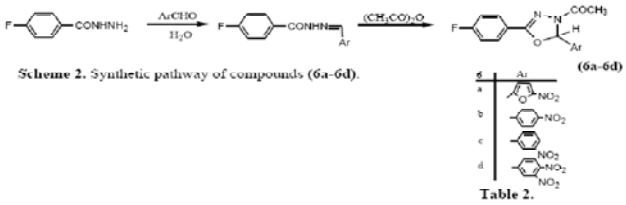


R_1	1, R=H 4, R=CH_3	2, R=H	3, R=H 5, R=CH_3
$-NH_2$	1 4	2	3 5
-N	1a 4a	2a	3a 5a

Table 1.

Some substances displayed a growth inhibition against yeasts higher or comparable to that of miconazole, the reference drug. The hydrazones **1a, 2a, 3a, 4a** and **5a** (Table **1**) were synthesized from cyclic (**1** and **4**) or acyclic (**2**, **3** and **5**) 1,2-benzisothiazole hydrazides[6].

Some new hydrazones of 4-fluorobenzoic acid hydrazide (Scheme **2**) were synthesized and evaluated for antimicrobial activity against *S. aureus*, *E. coli*, *P. aeruginosa* and *C. albicans*. Out of different compounds **6a-6d** given in Table **2** remarkable activity was found in compound **6d** carrying 2,4-dinitrophenyl moiety. Compound **6c** having m-nitrophenyl was more active than the corresponding p-nitrophenyl derivative. The most active compound was **6a** having 5-nitro-2-furanyl moiety[7].



Scheme 2. Synthetic pathway of compounds (6a-6d).

(6a-6d)

Table 2.

Hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazides (Scheme **3**) were synthesized and evaluated for antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Most active hydrazones **(7a-7e)** were given in Table **3**[8].

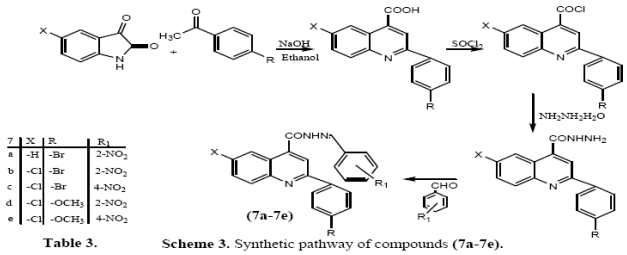
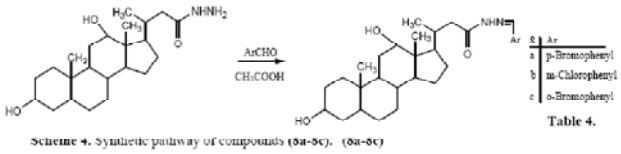


Table 3.

Scheme 3. Synthetic pathway of compounds (7a-7e).

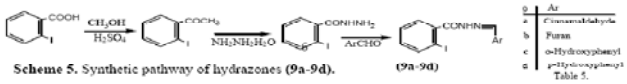
Cholic acid (Scheme **4**) hydrazone analogues were synthesized and evaluated for antimicrobial activity against *Staphylococcus aureus, E. faecalis*, *Bacillus megaterium, E. coli, Pseudomonas aeruginosa* and *Enterobacter aerogens*. Most compounds showed stronger antimicrobial activity than cefaclor and cefixime. Compounds **8a-8c** (Table **4**) indicated 15-fold stronger antimicrobial activities against *Enterobacter faecalis*[9].



Scheme 4. Synthetic pathway of compounds (8a-8c). (8a-8c)

Table 4.

Some 2-iodo-*N*'-[(1*E*)-substituted phenylmethylidene] benzohydrazide analogues (Scheme **5**) were synthesized and evaluated their antibacterial activity against different strains of bacteria such as *Bacillus subtilis*, *Staphylococcus aureus*, *Kleibsella pneumoniae* and *Pseudomonas aeruginosa* using by norfloxacin as reference drug. The antifungal activity was evaluated against *Aspergillus niger* and *Candida albicans* by using griseofulvin as reference drug. Compounds **9a-9d** (Table **5**) was highly significant against tested pathogenic micro-organism[10].



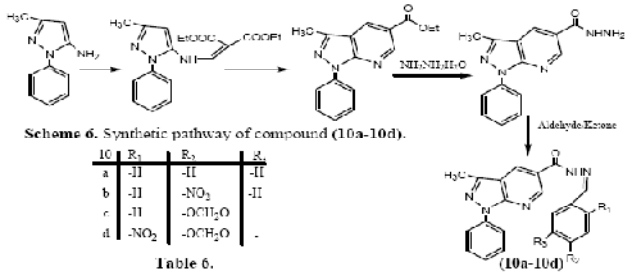
Scheme 5. Synthetic pathway of hydrazones (9a-9d).

(9a-9d)

2. Analgesic activity

A series of 5-acyl-arylhydrazone 1H-pyrazolo [3,4-b]pyridine derivatives (Scheme **6**) were synthesized and evaluated for analgesic activity. The compounds **(10a-10d)** synthesized were given in Table **6**.

The compounds of this series presents a powerful analgesic activity in the test of abdominal contortions induced by acetic acid, indicating the participation of the acyl-arylhydrazone moiety as well as the relevance of the substituent of aryl ring in the activity[11].



Scheme 6. Synthetic pathway of compound (10a-10d).

10	R_1	R_2	R_3
a	-H	-H	-H
b	-H	$-NO_2$	-H
c	-H	$-OCH_2O$	
d	$-NO_2$	$-OCH_2O$	

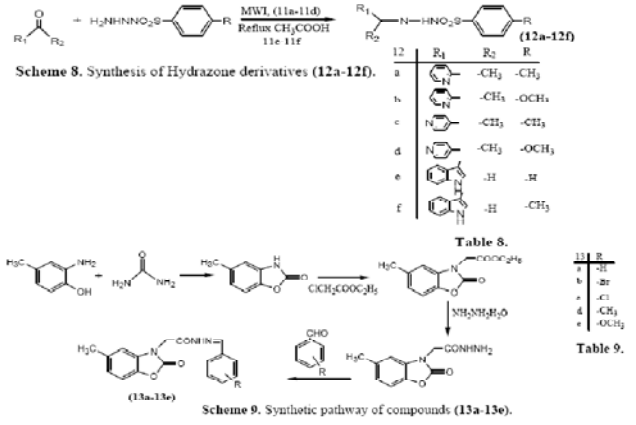
Table 6.

A series of new 4-arylhydrazone 1H- pyrazolo [3,4-b]pyridine derivatives (Scheme **7**) were synthesized and evaluated for analgesic activity. Analgesic activity was tested for abdominal contortions induced by acetic acid. The compound **11a-11d** (Table **7**) were strongly active showing a good analgesic activity[12].

11	Ar
a	p-methoxyphenyl
b	p-fluorophenyl
c	O_2N
d	2-furyl

Table 7.

Some amidine and hydrazone derivatives were synthesized and evaluated for analgesic activity. 2-Acetylpyridine and 4-acetylpyridine were condensed with sulfonylhydrazides by microwave irradiation in solid phase to give corresponding hydrazones **(12a–12d)** and Indole-3-carboxaldehyde was condensed with sulfonylhydrazides by refluxing in acetic acid (Scheme **8**) to give corresponding condensation product **(12e, 12f)**. All compounds synthesized were given in Table **8**. Analgesic activity evaluation was carried out using acetic acid induced writhing assay and compound **12f** showed good analgesic activity[13].



Scheme 8. Synthesis of Hydrazone derivatives (12a-12f).

12	R_1	R_2	R
a		$-CH_3$	$-CH_3$
b		$-CH_3$	$-OCH_3$
c		$-CH_3$	$-CH_3$
d		$-CH_3$	$-OCH_3$
e		-H	-H
f		-H	$-CH_3$

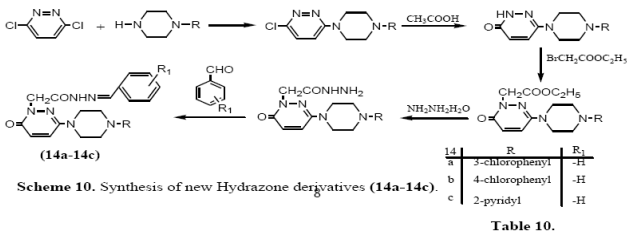
Table 8.

Scheme 9. Synthetic pathway of compounds (13a-13e).

11	R
a	-H
b	-Br
c	-Cl
d	$-CH_3$
e	$-OCH_3$

Table 9.

A series of hydrazones containing 5-methyl-2-benzoxazolinones were synthesized and evaluated for analgesic and anti-inflammatory. The treatment of 5-methyl-2-benzoxazolinone with aromatic aldehydes (Scheme **9**) resulted in the formation of arylidene hydrazides as cis–trans conformers **(13a–13e)** given in Table **9**. The analgesic activity of the compounds was studied by using both the acetic acid-induced writhing test and hot plate test in mice. The analgesic effects of **13c** and **13d** were higher than those of both morphine and aspirin[14].



Scheme 10. Synthesis of new Hydrazone derivatives (14a-14c).

14	R	R_1
a	3-chlorophenyl	-H
b	4-chlorophenyl	-H
c	2-pyridyl	-H

Table 10.

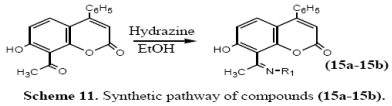
A series of 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted/nonsubstitutedbenzal) hydrazone derivatives (Scheme **10**) were synthesized and evaluated for analgesic activity. Out of various synthesized compounds three compounds **14a-14c** (Table **10**) was more potent than aspirin. Side effects of the compounds were examined on gastric mucosa[15].

3. Anti-inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a very important clinical use in the treatment of inflammation and various painful conditions such as rheumatoid arthritis, soft tissue, oral cavity lesions, respiratory tract infections and fever. In contrast to opioid analgesics NSAIDs relieves pain without interacting with opioid receptors, reduces elevated body temperature (antipyretic effect), possess anti-inflammatory property and antiplatelet activity. NSAIDs acts by inhibiting COX-1 (cyclooxygenase-1), whereas inhibition of COX-2 leads to gastrointestinal injury, suppression of TXA_2 formation and platelet aggregation. The combination of such type of interactions is the reason for gastrointestinal bleeding as the most serious adverse effect of these drugs. Some studies suggest that the presence of hydrazone moiety in some compounds have such a pharmacophoric effect which leads to inhibition of COX.

Some amidine and hydrazone derivatives were synthesized and evaluated their anti-inflammatory and analgesic activity. 2-Acetylpyridine and 4-acetylpyridine were condensed with sulfonylhydrazides by microwave irradiation in solid phase to give corresponding hydrazones **(12a–12d)**. Indole-3-carboxaldehyde was condensed with sulfonylhydrazides by refluxing in acetic acid (Scheme **8**) to give corresponding condensation product **(12e, 12f)**. All the six compounds synthesized were given in Table **8**. Anti-inflammatory activity evaluation was carried out using carrageenan induced paw oedema assay and compound **12e** exhibited good anti-inflammatory activity[13].

A series of novel benzopyranone congeners were synthesized for their expected activity as anti-inflammatory.



Scheme 11. Synthetic pathway of compounds (15a-15b).

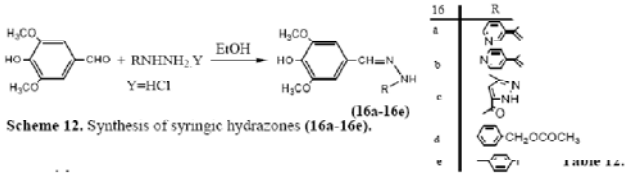
15	R_1
a	
b	

Table 11.

8-Acetyl-7-hydroxy-4-phenyl-2H-benzopyran-2-one used as starting material (Scheme **11**) for synthesis of a number 8-substituted derivatives i.e. hydrazones **15a-15b** (Table **11**). Hydrazone **15a** showed only slight anti-inflammatory activity while **15b** has antipyretic activity[16].

4. Antioxidant activity

A syringic hydrazones family was synthesized and evaluated for antioxidant activity. A novel series of hydrazones **(16a-16e)** given in Table **12** were derived from syringaldehyde (Scheme **12**). The carbonyl scavenger efficacy was evaluated by measuring the ability to decrease the protein carbonyl content in cells challenged with oxidized LDL[17].

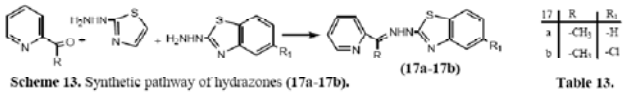


Scheme 12. Synthesis of syringic hydrazones (16a-16e).

5. Antiproliferative activity

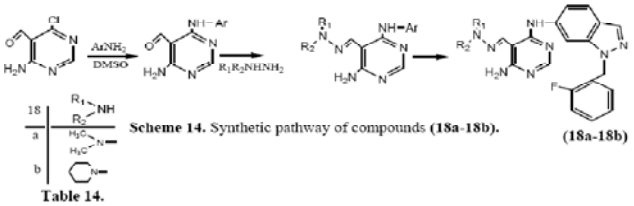
Large numbers of antiproliferative drugs are currently in clinical use. The search for more effective antiproliferative drugs led to the discovery of several hydrazones having antiproliferative activity.

Thiazolyl and benzothiazolyl hydrazones derived from α-(N)-acetylpyridines and diazines (Scheme **13**) were synthesized and evaluated for antiproliferative activity. Hydrazones compounds **17a-17b** (Table **13**) was found to be 13-900 times more potent than hydroxyurea and no cross-resistance to hydroxyurea was observed[18].



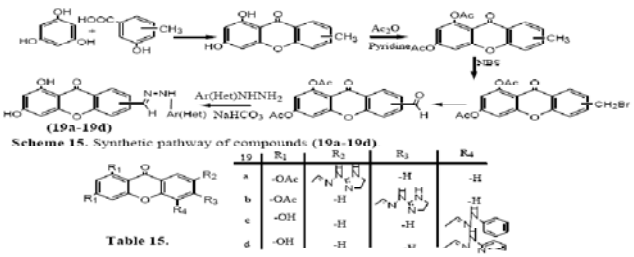
Scheme 13. Synthetic pathway of hydrazones (17a-17b).

Members of a novel class of 4-amino-6-arylamino-pyrimidine-5-carbaldehyde (Scheme **14**) hydrazones were synthesized as potent ErbB-2/EGFR dual kinase inhibitors and evaluated for antiproliferative activity. These compounds inhibited the growth of ErbB-2 over-expressing human tumor cell lines *in-vitro*. Compound **18a-18b** (Table **14**) emerged as a key lead and showed significant ability to inhibit growth factor-induced receptor phosphorylation in SK-BR-3 cells and cellular proliferation *in-vitro*[19].



Scheme 14. Synthetic pathway of compounds (18a-18b).

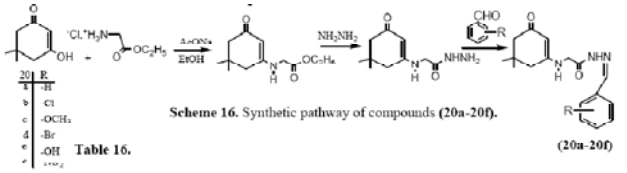
Aryl and heteroaryl hydrazones derived from xanthone carbaldehydes (Scheme **15**) were synthesized and evaluated for antiproliferative activity. Variation in the position of the aldehydic function led to three sets of compounds, bearing the hydrazonomethyl chain at positions 5, 6 or 7 on the xanthone nucleus respectively. The antiproliferative effect of the compounds was evaluated *in vitro* using the MTT colorimetric method against two human cancer cell lines breast adenocarcinoma and squamous cell oral carcinoma. Among the series, four compounds **19a-19d** (Table **15**) exhibited interesting growth inhibitory effects against both the cell lines. Xanthone derivatives showed moderate cytotoxic effects in comparision to doxorubicin[20].



Scheme 15. Synthetic pathway of compounds (19a-19d)

Table 15.

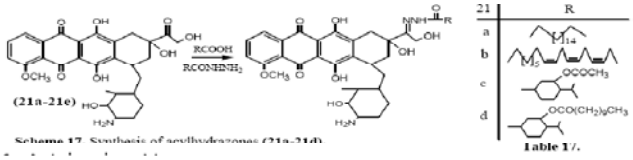
A series of new acridines and hydrazones derived from cyclic β-ketone were prepared and evaluated for cytotoxic and antiviral activity. They use dimedone to prepare different chemical entities whether such as acridines, thiadiazole and triazole or acyclic systems as hydrazide, hydrazones (Scheme **16**). The antiviral activity of the new compounds **20a-20f** (Table **16**) against *Hepatitis A Virus (HAV)* using the plague infectivity reduction assay revealed that the hydrazone **20b** was more active than the reference drug amantadine[21].



Scheme 16. Synthetic pathway of compounds (20a-20f).

Table 16.

Some fatty acyl and terpenyl hydrazones were synthesized and conjugated with doxorubicin to modulate doxorubicin activity in cancer cells. The hydrazones **21a–21d** (Table **17**) was prepared from heptadecanoic acid, oleic acid, linoleic acid or linolenic acid and doxorubicin hydrochloride (Scheme **17**). Doxorubicin N-acylhydrazones derivatives were tested for anticancer activity in cells of human leukaemia, melanoma and cervix carcinomas. The N-heptadecanoyl hydrazone was more cytotoxic than its unsaturated C_{18}-fatty acyl analogues[22].

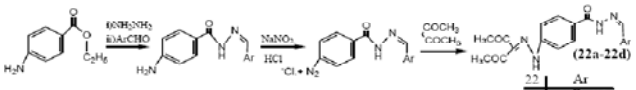


6. Antitubercular activity

Tuberculosis is an infectious disease caused by several species of *Mycobacteria.* This is a serious health problem that may leads to death of some three million people every year worldwide. Further the increase in *M. tuberculosis* strains resistant to first line antimycobacterial drugs such as rifampin and INH has further worsened the situation. This clearly indicates the

need of more effective drugs for the treatment of tuberculosis.

Some coupling products from 4-aminobenzoic acid hydrazones were synthesized and tested for antimicrobial activity against *Mycobacterium fortuitum* and *Mycobacterium tuberculosis.* Various hydrazones **22a–22d** (Table **18**) were synthesized by the reactions of acetylacetone with the diazonium salts of 4-aminobenzoic acid hydrazides at 0–5 °C (Scheme **18**). Compounds **22b** and **22c** were more active against *Mycobacterium fortuitum* and compound **22a** against *Mycobacterium tuberculosis*[23].



Scheme 18 Synthetic pathway of compounds (22a-22d).

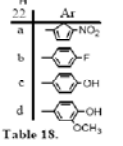
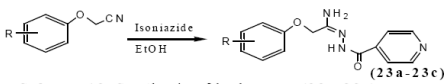


Table 18.

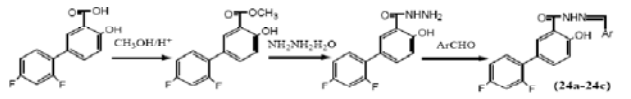
A series of isonicotinoylhydrazones were prepared by addition of some aryloxyacetonitriles with isonicotinoylhydrazine in basic medium (Scheme **19**). The new synthesized hydrazones derivatives were evaluated for their activity against *Mycobacterium tuberculosis*. Several compounds **23a-23c** (Table **19**) showed a good activity against *Mycobacterium tuberculosis*[24].



Scheme 19. Synthesis of hydrazone (23a-23c).

Table 19.

A series of diflunisal hydrazide-hydrazones (Scheme **20**) were synthesized and evaluated for antimycobacterial activity against *Mycobacterium tuberculosis*. Out of synthesized compounds **24a-24c** (Table **20**) showed activity against *Staphylococcus epidermis* and *Staphylococcus aureus*. Compound **24c** have exhibited activity against *Acinetobacter calcoaceticus* using cefepime as reference drug. The synthesized compounds were found to provide 12-34% inhibition of mycobacterial growth of *M. tuberculosis*[25].



Scheme 20. Synthetic pathway of compounds (24a-24c).

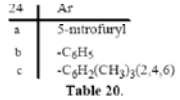
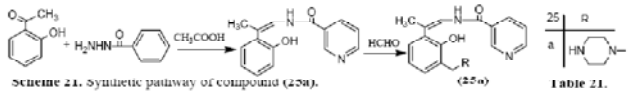


Table 20.

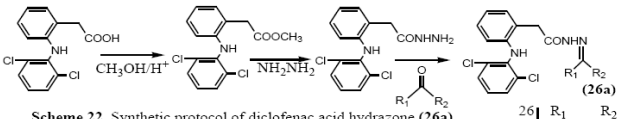
Isonicotinoyl hydrazones were synthesized (Scheme **21**) and evaluated for *in-vitro* and *in-vivo* antimycobacterial activity against *Mycobacterium tuberculosis* strain. All the compounds synthesized are screened against *Mycobacterium tuberculosis*. Compound **25a** (Table **21**) was equipotent to isoniazid[26].



Scheme 21. Synthetic pathway of compound (25a).

Table 21.

A series of diclofenac acid hydrazones (Scheme **22**) were synthesized and amides and evaluated for *in-vitro* and *in-vivo* antimycobacterial activities against *Mycobacterium tuberculosis.* The most active was compound **26a** given in Table **22**. Most of the compounds demonstrated better *in vitro* antimycobacterial activity against diclofenac and ciprofloxacin[27].



Scheme 22. Synthetic protocol of diclofenac acid hydrazone (26a).

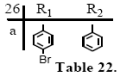
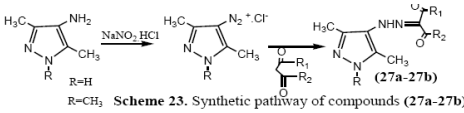


Table 22.

Some hydrazones were synthesized and evaluated for antitubercular activity against *Mycobacterium tuberculosis*. Several new hydrazone derivatives were prepared by the reaction of some active hydrogen compounds with the diazonium salts of 4-amino-3,5-di-1,3,5trimethylpyrazoles at 0–5°C (Scheme **23**). Hydrazones **27a** and **27b** (Table **23**) showed 29% and 28% inhibition against *M. tuberculosis*[28].



R=H R=CH3 Scheme 23. Synthetic pathway of compounds (27a-27b).

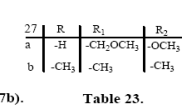
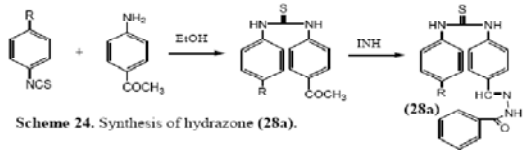


Table 23.

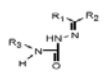
Various isonicotinyl hydrazones were prepared by reacting isonicotinyl hydrazide with 1-(4-acetylphenyl)-3-[(4-sub) phenyl]thiourea (Scheme **24**) and evaluated for *in-vitro* antimycobacterial activity against *Mycobacterium tuberculosis* and INH-resistant *M. tuberculosis*. Among synthesized compounds **28a** (Table **24**) was found to be the most potent against *M. tuberculosis* and INH-resistant *M. tuberculosis*[29].



Scheme 24. Synthesis of hydrazone (28a).

Table 24.

A candidate drug was identified for the development of anti-tuberculosis therapy from previously synthesized compounds based on the thiosemicarbazones, semicarbazones, dithiocarbazates and hydrazide/ hydrazones compounds against *Mycobacterium tuberculosis*. General structure of hydrazide/hydrazones is given in Scheme **25**. The best compounds hydrazide/hydrazones are found to be **29a-29c** (Table **25**). The results are comparable to or better than those of "first line" or "second line" drugs commonly used to treat TB[30].



Scheme 25. General structure of Hydrazones (29a-29c).

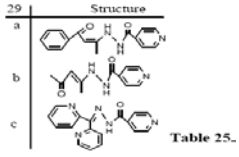
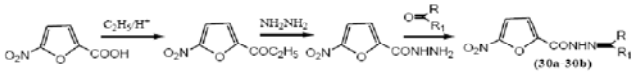


Table 25.

Some 5-nitro-2-furoic acid hydrazones (Scheme **26**) were synthesized and evaluated for *in-vitro* activities against *Mycobacterium tuberculosis* and isocitrate lyase (ICL)

enzyme inhibition studies. Among various compounds two compounds were most active **30a** and **30b** given in Table **26**, out of which 5-nitro-N-[(5-nitro-2-furyl)methylidene]-2-furohydrazide **(30b)** was found to be the most active compound *in-vitro*[31].



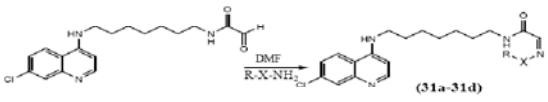
Scheme 26. Synthesis of hydrazone (30a-30b).

30	R	R_1
a	F_3C	-H
b	O_2N	-H

Table 26.

7. Antimalarial activity

Malaria is a disease caused by parasitic protozoa of the genus *Plasmodium* and is characterized by fever with rigor, anemia and splenomegaly. The disease is a major global public health problem. The development of multidrug-resistant *Plasmodium falciparum* has highlighted the necessary need to discover new antimalarial drugs.



Scheme 27. Synthesis of Hydrazones (31a-31d).

31	X	R
a	O	4-nitrobenzyl
b	NH	2,4-dinitrophenyl
c	NH	2,6-dichloro-4-(trifluoromethyl)phenyl
d	NH	7-methoxy-1,2,4-benzotriazin-3-yl

Table 27.

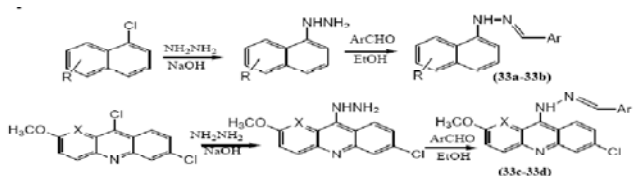
Glyoxylylhydrazone (Scheme **27**) were synthesized and evaluated for antimalarial activity against chloroquine resistant strain of *Plasmodium falciparum*. Out of various synthesized compounds, four compounds **31a-31d** (Table **27**) were most active[32].

Some acylhydrazones were synthesized and evaluated for antimalarial activity. A library of acylhydrazone iron chelators was synthesized (Scheme **28**) and tested for its ability to inhibit the growth of a chloroquine resistant strain of *Plasmodium falciparum*. Some of these new compounds **32a-32c** (Table **28**) are significantly more active than desferrioxamine[33].

Scheme 28. Synthesis of Hydrazone Derivatives (32a-32c).

32	R	R_1
a	5-Me	4-chlorophenyl
b	5-t-But	4-methoxyphenyl
c	5-Br	4-t-butylphenyl

Table 28.



Scheme 29. Synthetic pathway of compounds (33a-33d).

33	R	Ar	X
a	6-OCH_3		
b	7-Cl		
c			CH
d			N

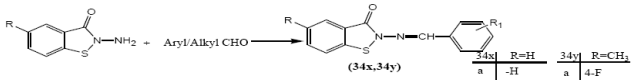
Anti-HIV activity

A novel series of N1-arylidene-N2-quinolyl and N2-acrydinylhydrazones (Scheme **29**) were synthesized as potent antimalarial agents active against CQ-resistant *P. falciparum* strains. A new series of novel and highly active antimalarial agent **33a-33d** (Table **29**) were synthesized. These compounds showed remarkable antimalarial activity especially against CQ-resistant *P. falciparum* strains and they represent promising lead structures for the development of new antimalarial drugs[34].

8. Anti-HIV activity

HIV infection and AIDS is the first diseases for which the discovery of drugs was performed entirely on the basis of rational drug design approaches. Current treatment regimens are termed as highly active antiretroviral therapy. Some hydrazones are found to be the potent inhibitors of ribonucleotide reductase.

A series of benzo[d]isothiazole hydrazones were synthesized and evaluated for anti-HIV activity. All the benzo[d]isothiazole hydrazones were obtained through condensation of the amino intermediates, namely the cyclic or acyclic hydrazides (Scheme **30**). Compounds **34x(a)** and **34x(c)** showed good activity against HIV-1 wild type, while compounds **34x(a), 34x(b), 34x(d), 34x(e), 34x(f), 34y(a), 34y(b), 34y(c) and 34y(d)** (Table **30**) showed good activity against the EFVR (efavirenz-resistance) mutant[35].

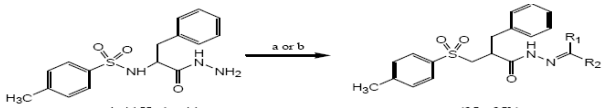


Scheme 30. Synthesis of Benzo[d]isothiazolehydrazones (34x,34y).

34x	R=H	34y	R=CH_3
a	-H	a	4-F
b	3-F	b	4-Cl
c	4-F	c	3-NO_2
d	4-Cl	d	3-OH
e	3-NO_2		
f	4-OH		

Table 30.

Some novel acylhydrazone derivatives (Scheme **31**) were synthesized and evaluated for antiviral activity targeting HIV-1 capsid protein. The synthesized compounds were tested for their antiviral activities and cytotoxicities using CEM cells (lymphoid suspension cells). Some derivatives assayed for their ability to inhibit HIV-1 CA assembly *in-vitro*. Among them compounds **35a** and **35b** (Table **31**) display the most promising potency[36].



Acid Hydrazide (35a-35b)

Scheme 31. **35a** - R_1COR_2, anhy. CH_3OH, Rf. !-2hr.
35b - R_1COR_2, anhy. CH_3OH, Glacial Acetic Acid, Rf. 3-8hrs

35	R_1	R_2
a	-H	3-CH_3OH, 4-OH Ph
b	-H	

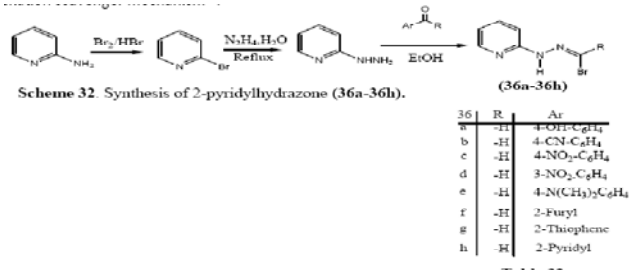
Table 31.

9. Antiplatelet activity

Some new 2-pyridylarylhydrazone derivatives **36a-36h** (Table **32**) were synthesized (Scheme **32**) and evaluated for antiplatelet activity. Compound **36f** shows good antiplatelet activity by complexation scavenger mechanism[37].

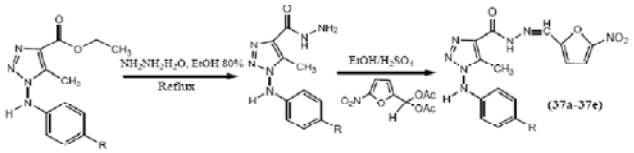
Some novel N-substituted-phenylamino-5-methyl-1H-1,2,3-triazole-4-carbohydrazides were synthesized and

evaluated for antiplatelet activity. These compounds were synthesized (Scheme **33**), characterized and screened for their *in-vitro* antiplatelet profile against human platelet aggregation using arachidonic acid and adrenaline as agonists. Among these the compounds **37a-37e** (Table **33**) were the most promising molecules with significant antiplatelet activity[38].



Scheme 32. Synthesis of 2-pyridylhydrazone (36a-36h).

36	R	Ar
a	-H	4-OH-C_6H_4
b	-H	4-CN-C_6H_4
c	-H	4-NO_2-C_6H_4
d	-H	3-NO_2-C_6H_4
e	-H	4-$N(CH_3)_2C_6H_4$
f	-H	2-Furyl
g	-H	2-Thiophene
h	-H	2-Pyridyl



Scheme 33. Synthesis of Acylhydrazones (37a-37e).

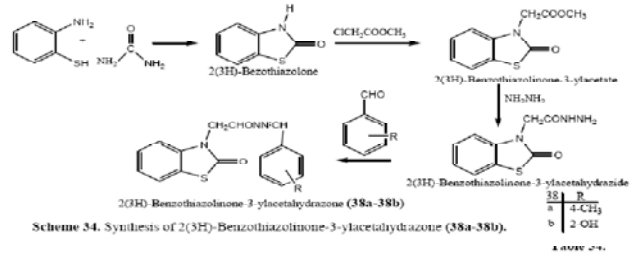
37	R	Ar
a	-H	Phenyl
b	-H	Pyrid-4-yl
c	-H	5-Bromo-thein-2-yl
d	-H	Fur-2-yl
e	-Cl	Fur-2-yl

Table 33.

10. Anticonvulsant activity

Drugs used in the treatment of epilepsy can be divided into two categories: drugs which used to abolish seizures called as anticonvulsants and drugs which are used prophylactically to prevent seizures.

Some(2:4-substituted)benzaldehyde(2-oxobenzothiazolin-3-yl)acetohydrazones were synthesized (Scheme **34**) and evaluated for anticonvulsant activity. Their anticonvulsant activity was tested by a pentylenetetrazole induced seizure test. Compounds **38a** and **38b** (Table **34**) were found to be the most promising among the others[39].

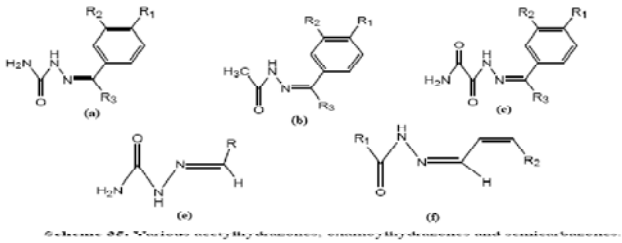


Scheme 34. Synthesis of 2(3H)-Benzothiazolinone-3-ylacetalhydrazone (38a-38b).

38	R
a	4-CH_3
b	2 OH

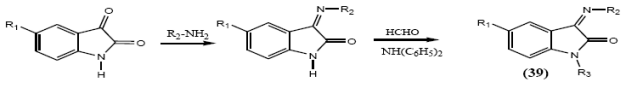
Various acetylhydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds were synthesized and evaluated for anticonvulsant activity.

Various acetylhydrazones, oxamoylhydrazones and semicarbazones were prepared (Scheme **35**) as candidate anticonvulsants with a view to examine the viability of a putative binding site hypothesis.



The biological results obtained revealed that in general the acetylhydrazones and semicarbazones exhibited good protection against convulsions while the oxamoylhydrazones were significantly less active[40].

Hydrazones of isatin derivatives (Scheme **36**) were synthesized and evaluated for anticonvulsant properties. Anticonvulsant activity of hydrazones of isatin was evaluated by maximal electroshock method (MES) and metrazol-induced convulsions (MET). Large number of compounds is synthesized, out of which most active hydrazone **39a** was given in table **36**. All the compounds exhibited lesser neurotoxicity compared to phenytoin. All the active compounds showed greater protection than sodium valproate[41].



Scheme 36. Synthesis of N-Mannich Bases (39)

39	R_1	R_2	R_3
a	$-CH_3$	4-CH_3-phenyl	-H

Table 36.

A series of 4-(2-(2,6-dimethylphenylamino)-2-oxoethylamino)-N-(substituted)butanamides were synthesized and evaluated for anticonvulsant activity. The synthesis of pharmacophoric hybrids of ameltolide-GABA-amides was presented as in Scheme **37**. The title compounds **40a-40e** (Table **37**) showed promising activity in scPIC screen indicating the involvement of GABA-mediation[42].

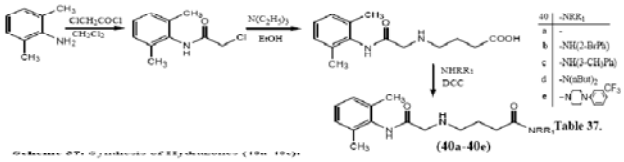
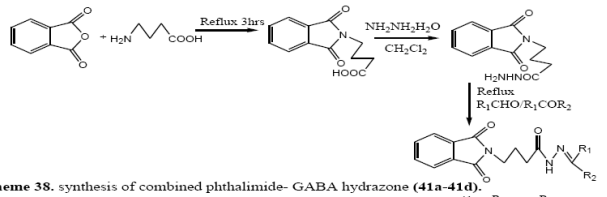


Table 37.

A combined phthalimide-GABA-anilide and hydrazone pharmacophore were synthesized and evaluated for anticonvulsant activity. The synthetic protocols employed for the preparation of hydrazones **41a-41d** (Table **38**) are presented in Scheme **38**. Initial anticonvulsant activity was determined using intraperitoneal picrotoxin (ipPIC)-induced seizure, subcutaneous strychnine (scSTY), subcutaneous pentylenetetrazole (scPTZ) and intraperitoneal maximal electroshock-induced seizure (MES) threshold tests. Most of the compounds were found to be effective in the scSTY and ipPIC models and very few compounds showed protection in the scPTZ model[43].

A series of 3,4-dialkyloxy thiophene bishydrazones synthesized and evaluated for anticonvulsant activity.

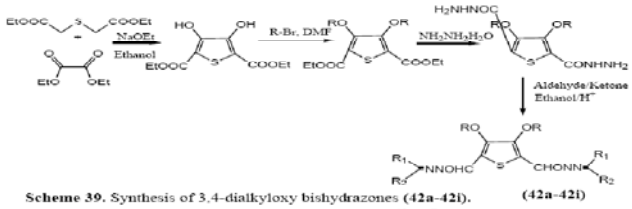
Various new bishydrazones were synthesized starting from ethyl thiodiglycolate through multi-step reactions (Scheme **39**). The anticonvulsant activity of the title compound was established after intraperitoneal administration in three seizure models, which include maximal electroshock (MES), subcutaneous pentylenetetrazole (scPTZ) and 6 Hz screens and their neurotoxicity was also evaluated. Out of various bishydrazones **42a-42i** (Table **39**) **42a** was most active compound with no neurotoxicity[44].



Scheme 38. synthesis of combined phthalimide- GABA hydrazone **(41a-41d).**

41	R_1	R_2
a	$-CH_3$	$-C_6H_5$
b	$-CH_3$	$4\text{-}NO_2\text{-}C_6H_4$
c	$-CH_3$	$2\text{-}OH\text{-}C_6H_4$
d	$-CH_3$	$4\text{-}OH\text{-}C_6H_4$

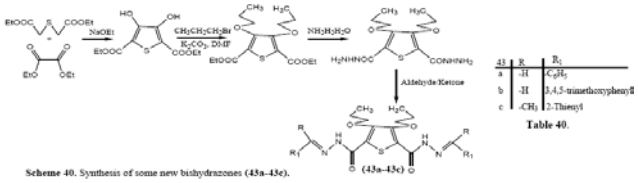
Table 38.



Scheme 39. Synthesis of 3,4-dialkyloxy bishydrazones **(42a–42i).** **(42a–42i)**

42	R_1	R_2
a	2-isatinyl	3-isatinyl
b	-H	4-OH,3-OCH3phenyl
c	-H	N-ethyl-3-carbazolyl
d	-H	Phenyl
e	-H	4-NO2phenyl
f	-H	3,4,5-trimethoxyphenyl
g	-H	2-Fluorenyl
h	-H	N-dodec-yl-3-carbazolyl
i	-H	2-Thienyl

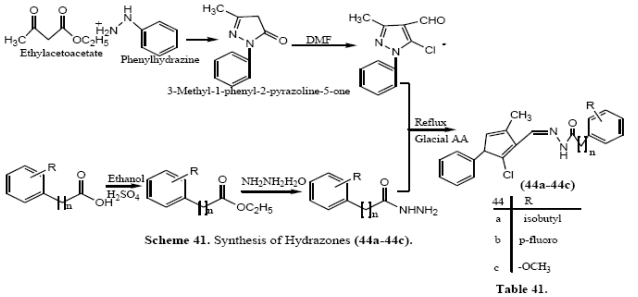
Some new bishydrazones derived from 3,4-dipropyloxythiophene (Scheme **40)** were synthesized and evaluated their anticonvulsant activity. Also they were screened for neurotoxicity. From the results of antiepileptic activity, it can be concluded that three compounds **43a-43c** displayed good activity with less neurotoxicity given in Table **40**[45].



Scheme 40. Synthesis of some new bishydrazones **(43a–43c).**

41	R	R_1
a	-H	$-C_6H_5$
b	-H	3,4,5-trimethoxyphenyl
c	$-CH_3$	2-Thienyl

Table 40.



Scheme 41. Synthesis of Hydrazones **(44a-44c).**

44	R
a	isobutyl
b	p-fluoro
c	$-OCH_3$

Table 41.

A series of hydrazones of N'-[(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene] 2/4-substituted hydrazides (Scheme **41**) were synthesized and evaluated their anticonvulsant activity. Among the compounds tested **44a-44c** (Table **41**) showed maximum activity[46].

11. Anti-Leishmanial activity

Platinum–sterol hydrazone complexes were synthesized and determined their biological activity against *Leishmania mexicana.* Leishmaniasis is a parasitic zoonosis caused by protozoans of the genus *Leishmania* transmitted by insects known as *Phlebotomines*, which are found in wild or urban environments. The disease occurs in tropical and sub-tropical areas, mainly in Asia, Europe, Africa and the Americas. At present, there is no effective treatment for this disease. In the search for new rational chemotherapeutic alternatives, two novel trans $[Pt(Hpy1)_2(Cl)_2]$ and trans $[Pt(Hpy2)_2(Cl)_2]$ complexes were synthesized by the reaction of K_2 $PtCl_4$ 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)** (Scheme **42**). These organic compounds are specific inhibitors of sterol methyl transferase (SMT)[47].

CONCLUSION

According to these preliminary studies, it appears that the introduction of a heteroaryl and heteroacylhydrazone moiety on the basic ring nucleus is potentially of interest to obtain various biologically active compounds. All these findings support the need for further investigations to clarify the features underlying the various biological activities of these new hydrazone derivatives. This review thus gives an overview of therapeutic and diverse biological properties of hydrazones. Therefore, these observations have been guiding for the development of hydrazones, which can be a lead nucleus for future developments to get safer and effective compounds. Thus this paper proves to be significant for further research work on the bioactive hydrazone derivatives.

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