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Comprehensive Investigation of the Potential of Hydrazine and its Derivatives for the Synthesis of Various Molecules with Biological Activity

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Abstract

This review paper provides a comprehensive and in-depth analysis of the versatile utility of hydrazine as a precursor for the synthesis of several significant hydrazides and related heterocyclic compounds as beneficial molecules for biological activities. This study investigates the intrinsic features and synthetic processes underlying these molecules, with a special emphasis on their applications in microbiology, pain treatment, antioxidant therapy, and antimalarial tactics. This review, based on a large body of research, elucidates the sophisticated synthetic processes used for the synthesis of hydrazides and their heterocyclic derivatives *via* moiety transformation. It provides a critical appraisal of today's cutting-edge synthesis techniques, emphasizing their relevance and efficiency in the context of modern scientific research. Furthermore, this review serves as an invaluable resource for scholars, researchers, and professionals seeking to navigate the complex landscape of hydrazides and its derivatives. It provides a comprehensive overview of the chemical diversity of these compounds and their potential to promote innovation and boost research efforts across a wide range of scientific areas by bridging the gap between fundamental chemistry and practical applications.

Keywords: Hydrazine, Hydrazide, Biological activity, Pyrano [2,3-c] pyrazole

Full-length article **Corresponding Author*, e-mail: mrmoham2@ncsu.edu

1. Introduction

Hydrazine, a colorless and extremely reactive chemical compound with the formula N_2H_4, is a versatile and essential substance in chemistry. It is frequently used as a reducing agent, a propellant in rocket propulsion systems, and a precursor for a variety of chemical reactions. Its ability to donate hydrogen atoms and function as a potent reducing agent in chemical processes makes hydrazine valuable in industries ranging from agriculture to pharmaceuticals. They are reported to possess diverse pharmacological activities such as antiviral, antioxidant, antimicrobial, antimalarial, anti-inflammatory, analgesic activity, anticancer, antifungal, and antibacterial [1-3]. Hydrazides are one of the most significant hydrazine derivatives. One or both of the hydrogen atoms in the hydrazine molecule are replaced with an acyl group (R-CO-) to form these compounds. The resultant molecules, known as hydrazides, possess a vast array of chemical properties and applications. Hydrazides are also used as intermediates in the synthesis of numerous organic compounds, making them an important class of hydrazine derivatives with a wide range of applications in chemistry and industry [4-6].

The purpose of this in-depth study is to explore the complex domain of hydrazide derivatives and their significant biological functions. Our study will specifically examine a comprehensive investigation of the varied pharmacological characteristics of the subject, including its antiviral, antioxidant, antibacterial, antimalarial, analgesic, anti-inflammatory, and anticancer capabilities. Furthermore, a comprehensive analysis will be conducted on the diverse synthetic techniques utilized in the manufacturing of hydrazine derivatives. This review aims to offer a thorough and insightful examination of the various aspects of hydrazide derivatives, explaining their

significant contribution to current medicinal and chemical investigations [7].

2. Biological Activities of Hydrazide Derivatives

The versatile hydrazine compound's derivatives, called hydrazides, have a variety of biological effects. This section introduces the several uses of hydrazide derivatives in medical chemistry and pharmacology, including its potential to treat neurological [8], cancerous, and microbial diseases [9]. It provides a peek at chemicals' revolutionary potential in the life sciences.

2.1. Hydrazide as antiviral

Shiryaev *et. al.* [10], synthesized a new series of hydrazide derivative 1 which showed good activities against *Herpes simplex* type-1 (HSV-1) [11]. A series of hydrazides 2 and 3 were synthesized and showed a good activity as antiviral. Also, the hydrazide 4 was prepared for testing their anti-viral showed more active having percentage inhibition of 57.5 and 60.3 at a concentration of 10 µg/ml and 20 µg/ml, respectively than the reference drug, amantadine [12]. Additionally, a set of hydrazide derivatives 5 has been produced and subsequently assessed for their antibacterial efficacy against two pathogenic Gram-negative bacteria in an in *vitro* setting (Escherichia coli and Pseudomonas aeruginosa) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and fungal strain *Candida albicans* and *Aspergillus Niger*. All newly synthesized compounds exhibited promising activity [13-15]. The chemical structures of compounds 1-5 are illustrated in Figure 1.

2.2. Hydrazides as antioxidant

Since they possess the ability to neutralize dangerous free radicals and lessen oxidative stress in the body, hydrazides have been investigated for their antioxidant qualities. The carbohydrazides of quinoline 6 were prepared and showed promising in *vitro* antioxidant activity. As well as Al-Mamery *et. al.* [8, 16], reported the hydrazide derivatives 7 and 8 as potent antioxidant activity [17]. Also, the hydrazide of benzosuberone 9 synthesized and tested as antioxidant showed strong antioxidant activity [18]. The chemical structures of compounds 6-9 are illustrated in Figure 2.

2.3. Hydrazides as antimicrobial

By rupturing bacterial cell walls and obstructing crucial metabolic processes, hydrazide chemicals, such as isoniazid, have shown antibacterial effects. Although isoniazid is used to treat tuberculosis, antimicrobial drugs are less frequently employed than antibiotics. Future synthesis of more efficient hydrazide derivatives might come from current research. A series of hydrazide derivatives 10 and 11 showed moderate antimicrobial activity against some bacteria and fungi [19]. The hydrazide 12 was prepared for testing their antimicrobial, they showed most activity against Staphyloccocus pneumoniae [20]. Furthermore, Mohamed *et al.* accomplished a synthesis of a hydrazide derivative 13, which exhibited the most potent activity against Mycobacterium TB H37Rv. M. tuberculosis [21]. A series of hydrazide derivatives 14 and 15 showed similar antimicrobial activity to that of ampicillin against *S.* aureus and *E.* coli [22]. The chemical structures of compounds 10-15 are illustrated in Figure 3.

2.4. Hydrazides as antimalarial

Ryckebusch *et al.*, synthesized a series of hydrazide derivatives 16 which showed excellent antimalarial activity against a chloroquine-resistant strain *Plasmodium falciparum* provided the best result of the synthesized hydrazone derivatives [23, 24]. The 4-flourobenzohydrazide 17 showed good antimalarial activity [25]. The 7-chloroqinoline hydrazide 18 showed high activity against a series of *plasmodium falciparum strains* [26]. The chemical structures of compounds 16-18 are illustrated in Figure 4.

2.5. Hydrazides as analgesic

In general, hydrazides are not frequently employed as analgesics. Although hydrazides may have a variety of biological actions, they are not a common family of chemicals for pain treatment. Analgesics are drugs that are primarily used to relieve pain. Analgesics, conversely, usually refer to drugs like NSAIDs (nonsteroidal anti-inflammatory drugs), opioids, and other specialized treatments made to target and treat pain. Hydrazide derivatives 19 were prepared and tested as analgesic agents which showed good activity [27]. Belowar synthesized the hydrazide derivatives 20 and 21 which showed good analgesic activities [28]. The chemical structures of compounds 19-21 are illustrated in Figure 5.

2.6. Hydrazides as anti-inflammatory

Hydrazides have been investigated for their potential as anti-inflammatory treatments, but their use and study in this area are less widespread than that of well-known anti-inflammatory medications like NSAIDs or corticosteroids. The 4-chloro-benzohydrazide derivatives 22 were prepared and showed good anti-inflammatory activity [29]. Also, the indole- based hydrazide derivative 23 exhibited good anti-inflammatory which is comparable with standard drug diclofenac sodium [30]. Moreover, the hydrazide derivatives 24 and 25 showed high activity as anti-inflammatory agent [31]. However, Tributino *et. al* [32]., stated that the hydrazide 26 showed good anti-inflammatory activity [33]. The chemical structures of compounds 22-26 are illustrated in Figure 6.

2.7. Hydrazide as anticancer

As hydrazides may have anti-cancer capabilities, other well-known medicines are more frequently used to treat cancer. Further study is required to determine their therapeutic utility in the treatment of cancer because their effectiveness varies, with laboratory studies serving as the main source of evidence. It is reported that the simple hydrazide 27 based on indole compound showed good anticancer activity against all the tested cancer cell lines, except DU-145 and MDA-MB-231 cells [34, 35]. Also, the hydrazide 28 was prepared for testing their anticancer showed most active with their IC_{50} values of 5.7 and 2.4 µM and MCF-7 against SH- SY5Y and Kelly neuroblastoma cells and breast adenocarcinoma cell lines. Also, compound 29 showed high active with their IC_{50} values of 2.9 and 1.3 µM against the SH-SY5Y and Kelly

cells, and values of 14.1 and 18.8 μM for MCF-7 and MDA-MB-231 breast cancer cells [36, 37]. Bis[thio-hydrazide amide] compounds 30 showed good anticancer activity with IC_{50} values 0.005, 0.05 and 0.01 μM against the multi-drug resistant cell lines MES-SA/DX5, HL-60/TX1000 and Bowes/OV2, respectively [38, 39]. Also, the IC_{50} for bis[thio-hydrazide amide] compounds 31 showed significant anticancer activity ranged from 0.05 to 0.005 μM against MES- SA/DX5 tumors in nude mice [40]. However, Chen *et al.*, produced a series of hydrazide derivatives 32 which superior anti-proliferative activity against MES-SA/Dx5 cancer cell line (IC_{50} = 50 nM) and moderate *in vitro* activities in inducing Hsp70 (EC_{50} = 0.75 μM) [41]. The chemical structures of compounds 27-32 are illustrated in Figure 7.

3. Preparation of Hydrazide Derivatives

The simplest and more facile way to prepare the hydrazides is the using hydrazine hydrate or phenyl hydrazine to replace of -$NHNH_2$ or =N-NH_2 moieties with a leaving group such as –OR group of esters, or condensation with a carbonyl one, as shown in the following examples.

3.1. Synthesis of cyanoacetic acid hydrazide

The most known laboratory method to prepare cyanoacetic acid hydrazide 35 is the careful addition of hydrazine hydrate 33 to ethanolic solution of ethyl cyanoacetate 34 with stirring at 0°C [42] as illustrated in Scheme 1.

3.2. Synthesis of acyl hydrazides from aldehydes

Acyl hydrazides 38a-e have been synthesized by the reaction of an aromatic aldehyde 36 with a dialkyl azodicarboxylate 37 through a C–H activation process [43] as illustrated in Scheme 2.

3.3. Synthesis of benzoic acid hydrazide

Benzoic acid hydrazide derivatives 40a-k have been synthesized by refluxing a mixture of methyl benzoate 39a-k with hydrazine hydrate 33 in ethanol for 4 h [45, 46] as illustrated in Scheme 3.

3.4. Synthesis of 2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide derivatives

The hydrazide 42 was obtained by hydrazinolysis of (7-hydroxy-2-oxo- 2*H*- chromen-4-yl)-acetic acid ethyl ester 41 with hydrazine hydrate in methanol at room temperature [47]. Also, the hydrazides 44a-l were prepared from the condensation of different aromatic aldehydes 43a-l and carbohydrazide 42 in presence of ethanol and acetic acid (24:1) [14], as illustrated in Scheme 4.

3.5. Synthesis of the hydrazide-hydrazones

Hydrazide-hydrazone 46 derivatives were synthesized through the reaction of cyanoacetyl-hydrazine 35 and 3-acetylpyridine 45 [48]. Also, the reaction of 46 and benzaldehyde derivatives 36a-c gave the corresponding benzal derivatives 47 [49], as illustrated in Scheme 5.

3.6. Synthesis of 4-methoxy-ω-bromoaceto-phenone-cyanoacetyl-hydrazone

Hydrazide hydrazone derivative 48 has been produced by the reaction of cyanoacetyl-hydrazine 34 with ω-bromo-(4-methoxyacetophenone) 47 in presence of 1,4-dioxan by stirred at room temperature for 1 hr. in ice/water mixture [50]. Moreover, 4-Methoxy-ω-cyanoaceto-phenonecyanoacetylhydrazone 50 has been prepared from hydrazide hydrazone derivative 49 and KCN on water bath for 30 min at 60 °C [51]. Additionally, compound 51 was obtained by the reaction of 4-methoxy ω-bromoaceto-phenone-cyanoacetylhydrazone 50 with phenylhydrazine under reflux for 3 h [52], as illustrated in Scheme 6.

3.7. Synthesis of pyrazine-2-carboxylic acid hydrazide

The pyrazine-2-carboxylic acid hydrazide 52 was prepared as shown below by hydrazinolysis of pyrazine-2-carboxylic acid 51 with hydrazine hydrate in dry ethyl chloroformate and triethylamine as catalyst [53, 54], as illustrated in Scheme 7.

3.8. Preparation of biphenyl-4-carboxylic acid hydrazide

Biphenyl-4-carboxylic acid hydrazide 55 has been synthesized by refluxing a mixture of biphenyl-4-carboxylic acid methyl ester 54 with hydrazine hydrate in ethanol for 3hr. [55], as illustrated in Scheme 8.

3.9. Synthesis of indole-2- carboxylic acid hydrazide

The indole-2-carboxylic acid hydrazide 57 was obtained by the reaction of 2-indole-2-carboxylic acid ethyl ester 56 and hydrazine hydrate in ethanol for 4hr. [56], as illustrated in Scheme 9.

3.10. Synthesis of hydrazinyl hydrazide

The ethyl 2-(1, 2, 3, 6-tetrahydro-6-oxo-2-thiopyrimidin-4-yl)acetate **58** were obtained by reaction of diethyl 3-oxopenteanedioate **57** with thiourea in presence of potassium hydroxide and ethanol . The latter compound **58** was subjected to methylation by treating it with methyl iodide in alcoholic sodium acetate solution yielding ethyl 2- (1, 6-dihydro-2-(methylthio)-6-oxopyrimidin-4-yl) acetate **59,** then reacted with hydrazine hydrate in ethanol to give 2-(2- hydrazinyl-1,6-dihydro-6-oxopyrimidin-4-yl) acetohydrazide **60** (Zeytün *et al.*, 2021), as illustrated in **Scheme 10**.

3.11. Synthesis of malonyl dihydrazide derivatives

However, the reaction of diethyl malonate **6 2** with hydrazine hydrate gave the corresponding malonyl dihydrazide **63** [57]. Also, the fusion of phenyl hydrazine and diethyl malonate in an oil bath at 120° afforded the malonyl-bisphenylhydrazide **64** [58], as illustrated in **Scheme 11**. Recently, many of acylhydrazide Schiff base derivatives were prepared by acetic acid-catalyzed condensation of acylhyrazide with different aromatic aldehydes and acetophenones in ethanol under reflux conditions.

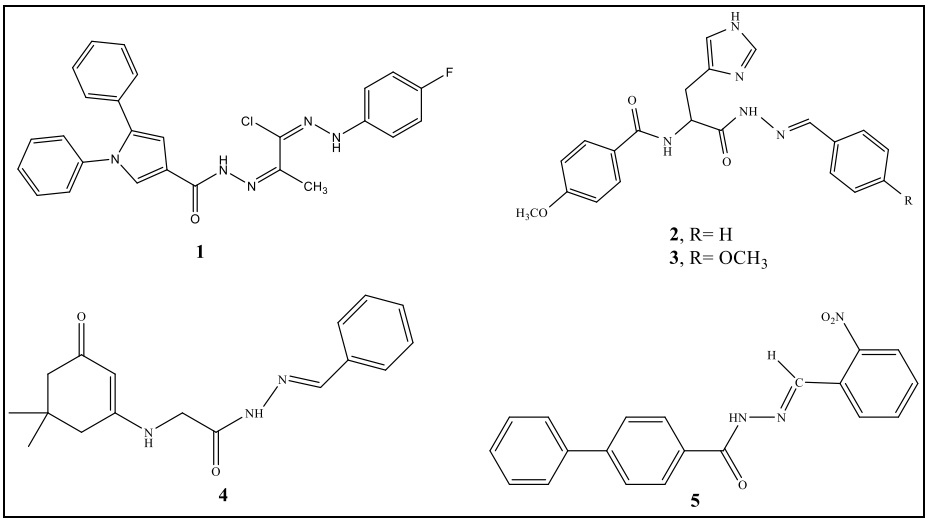


Figure 1: Some hydrazide derivatives used as antiviral

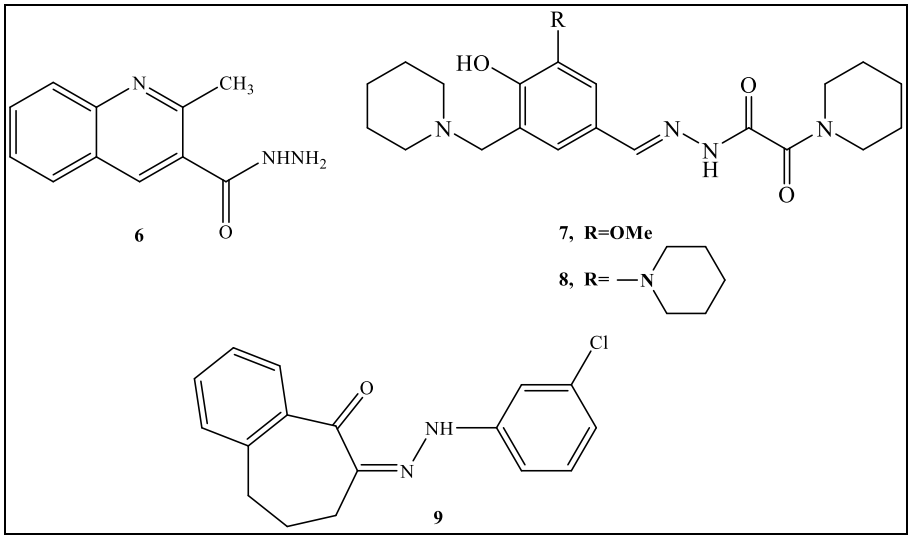


Figure 2: Hydrazide derivatives used as antioxidants

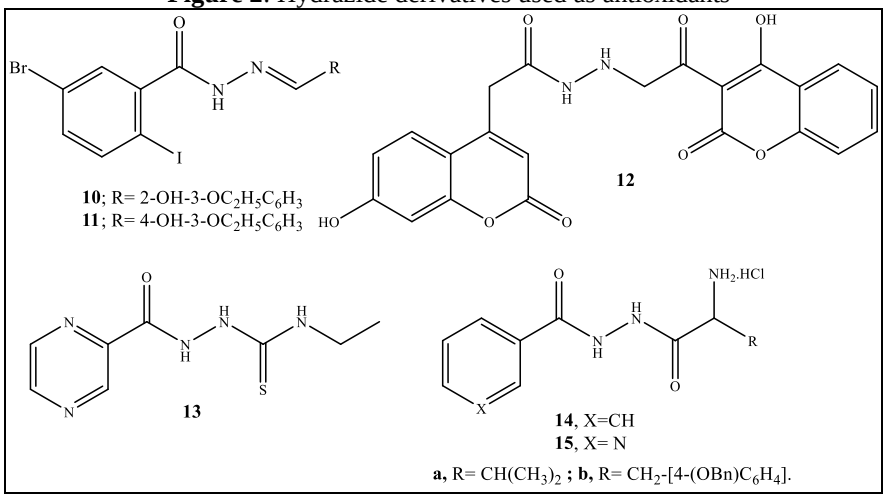


Figure 3: Hydrazide derivatives used as antimicrobial

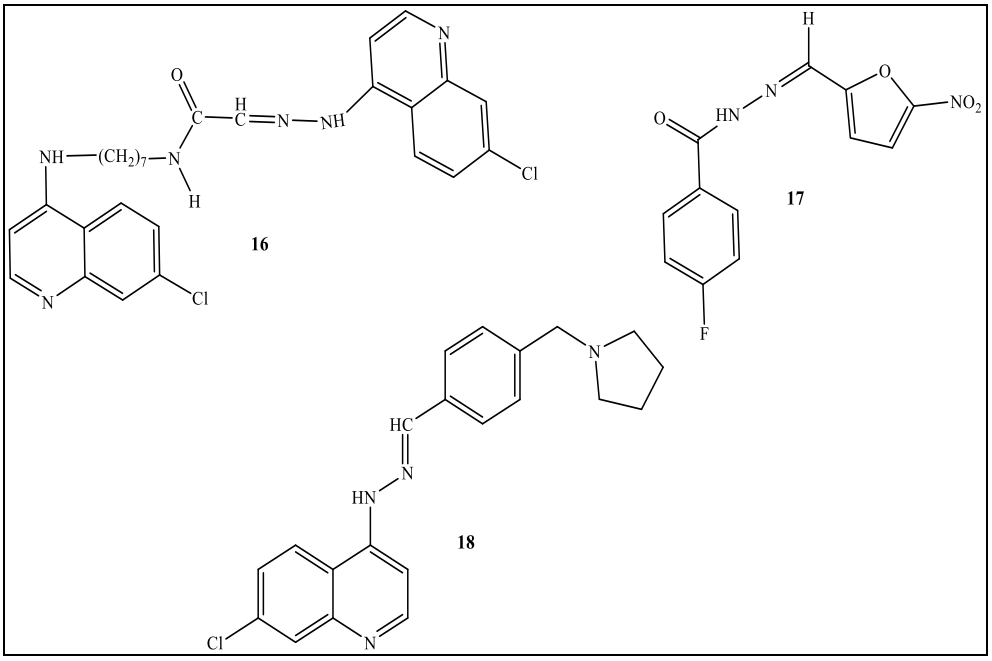


Figure 4: Hydrazide derivatives used as antimalarial

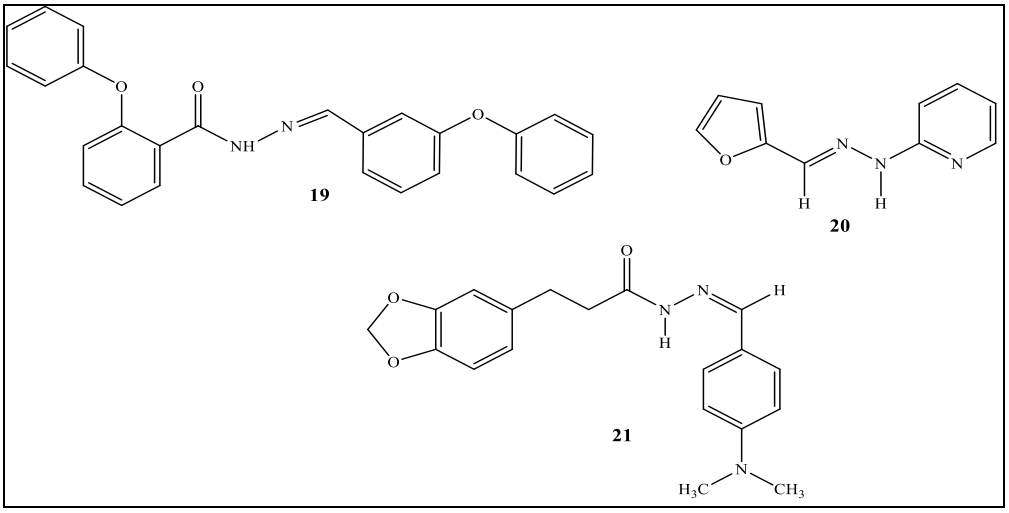


Figure 5: Hydrazide derivatives used as analgesic

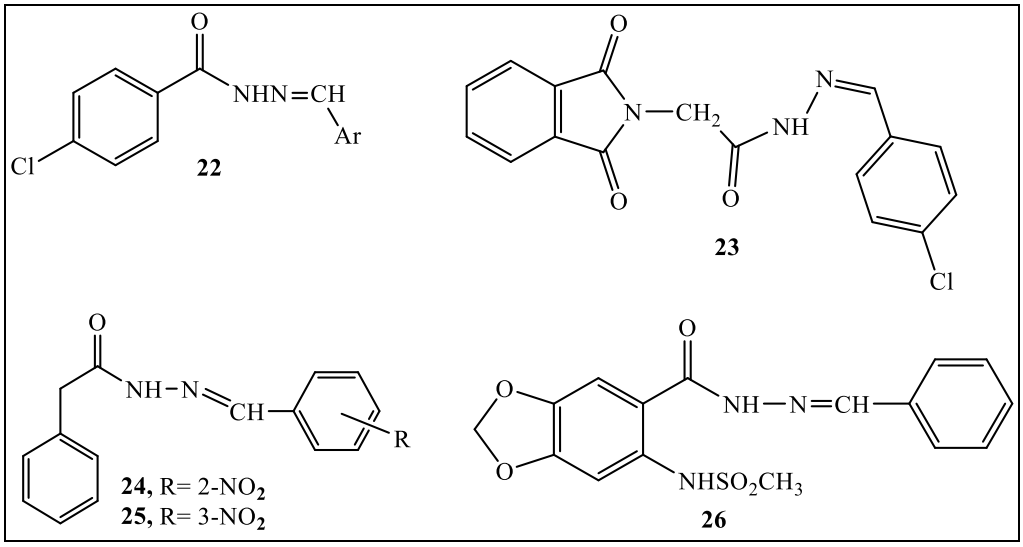


Figure 6: Hydrazide derivatives used as anti-inflammatory

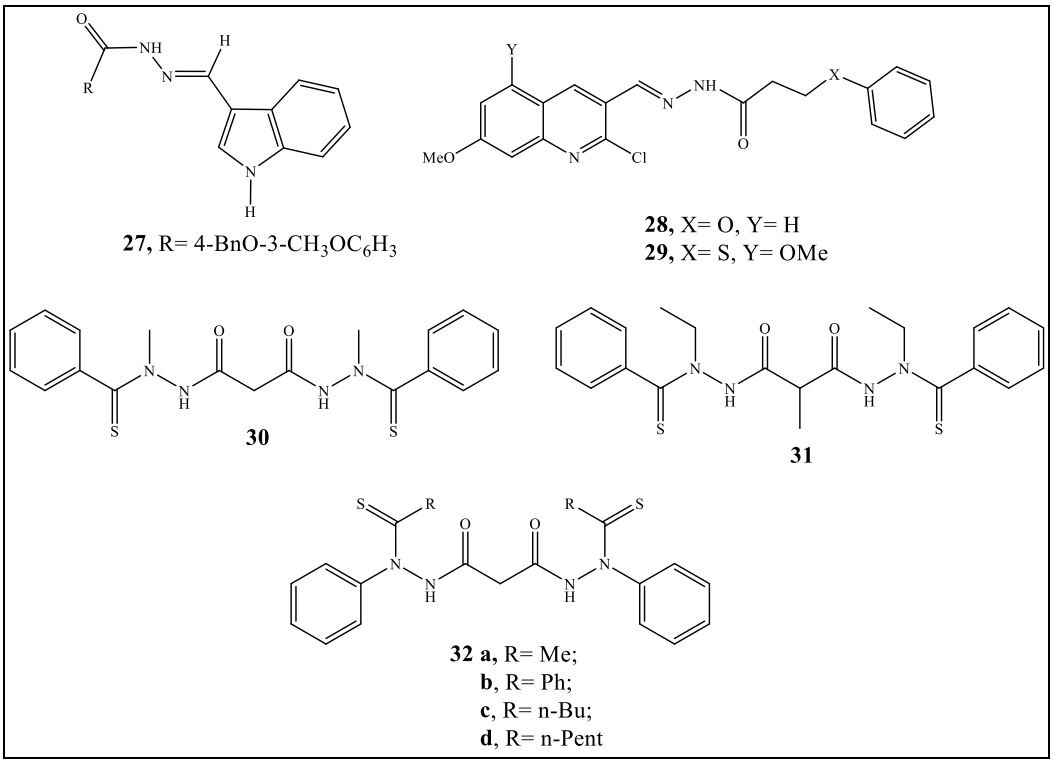
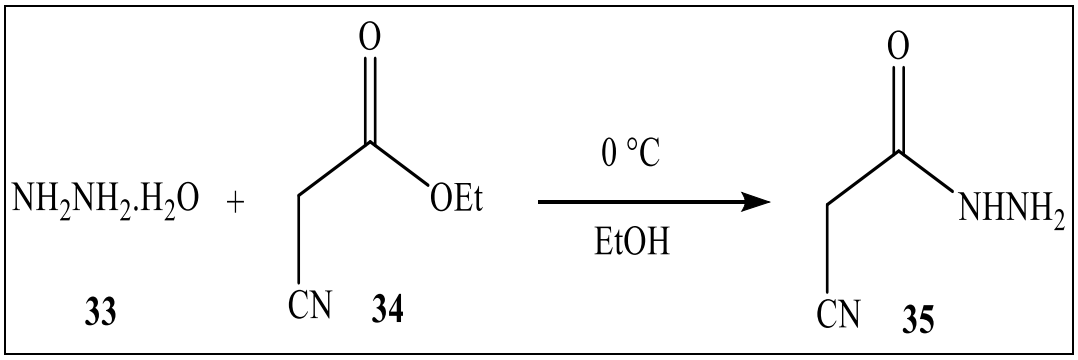
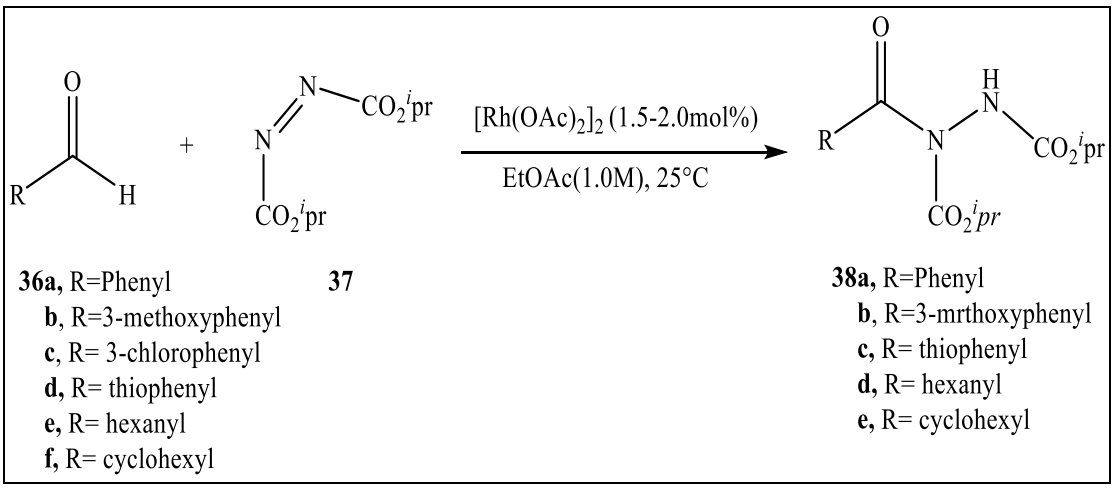


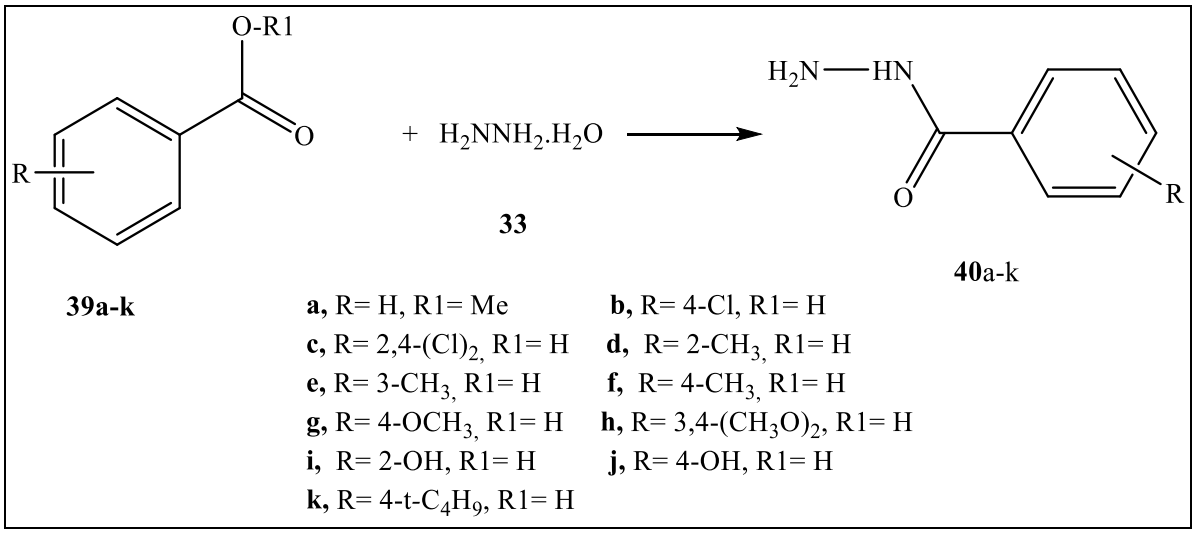
Figure 7: Hydrazide derivatives used as anti-inflammatory



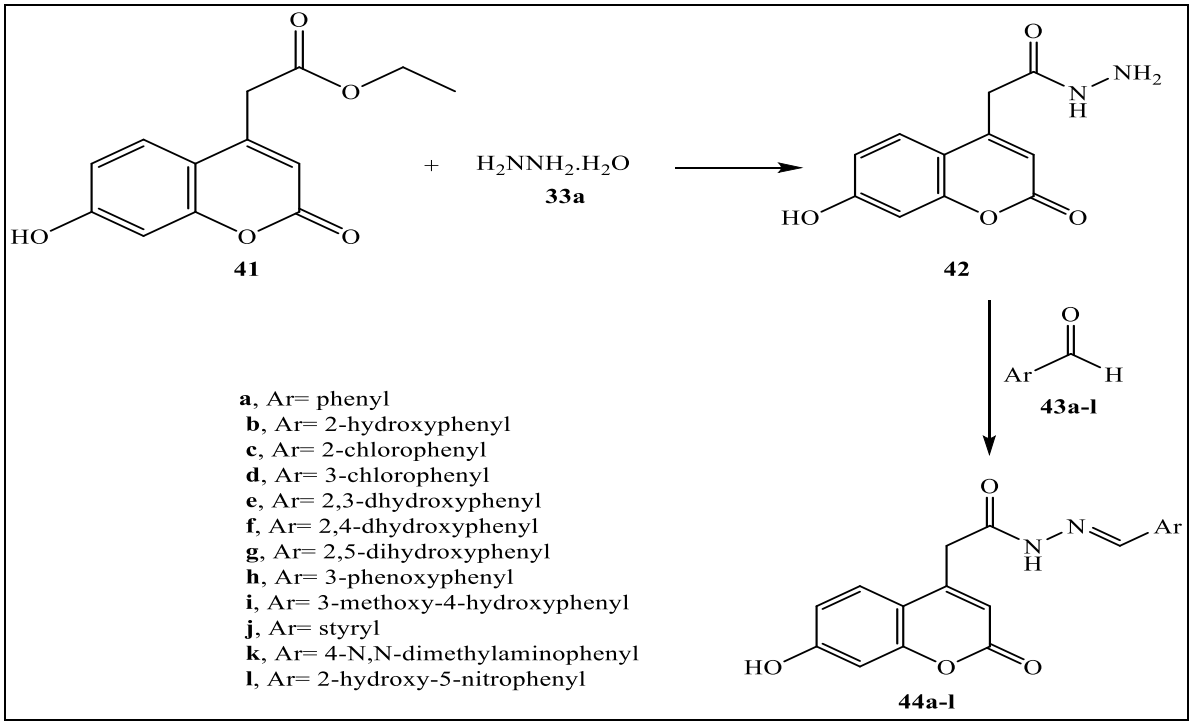
Scheme 1: Synthesis of cyanoacetic acid hydrazide **35**



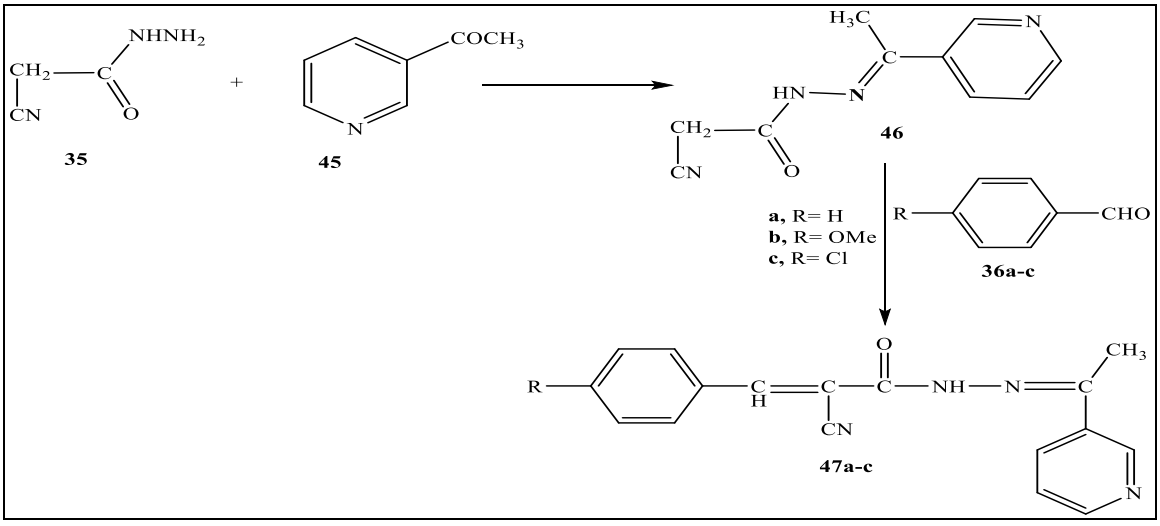
Scheme 2: Synthesis of acyl hydrazides **38a-e**.



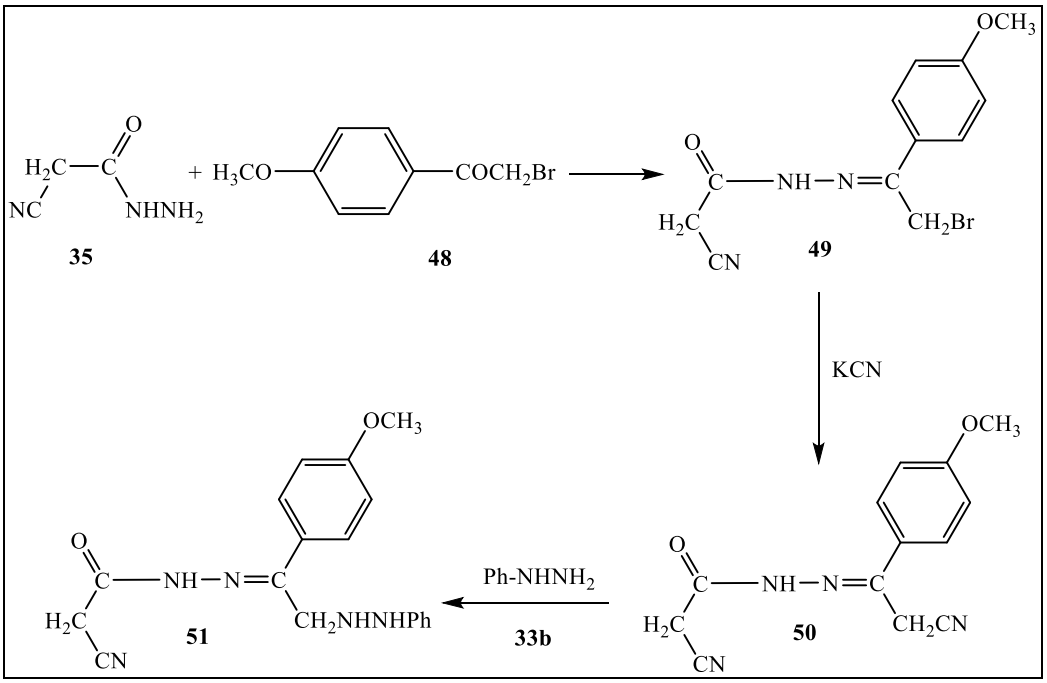
Scheme 3: Synthesis of Benzoic acid hydrazide derivatives **40a-k**



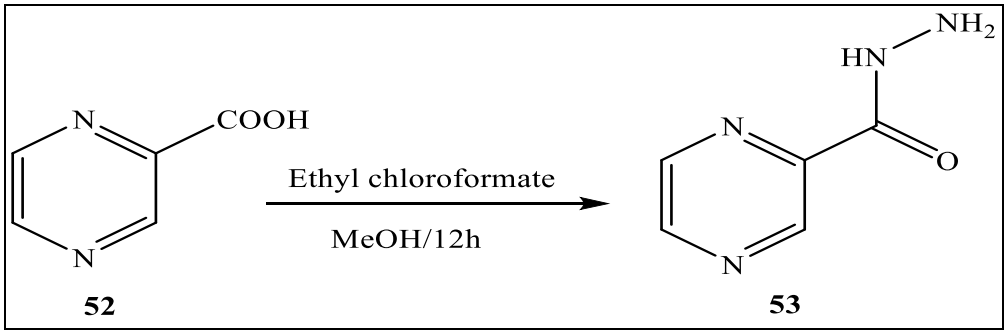
Scheme 4: Synthesis of 2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide derivatives **44a-l**



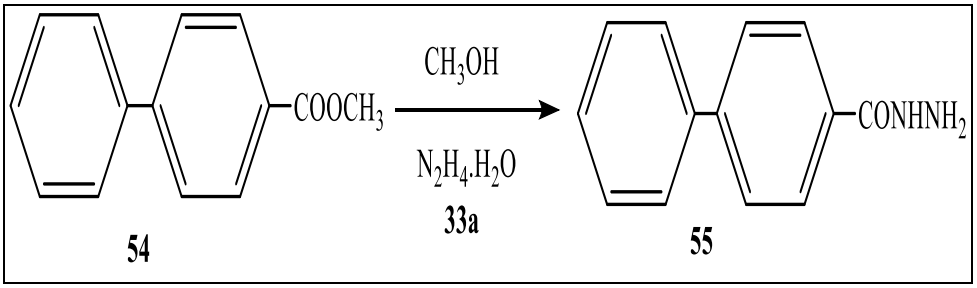
Scheme 5: Synthesis of hydrazide-hydrazones **46** and the corresponding benzal derivatives **47**



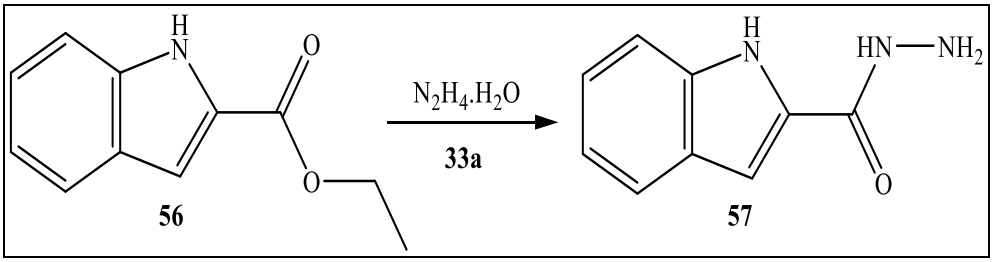
Scheme 6: Synthesis of Cyanoacetyl-hydrazone derivatives **49-51**



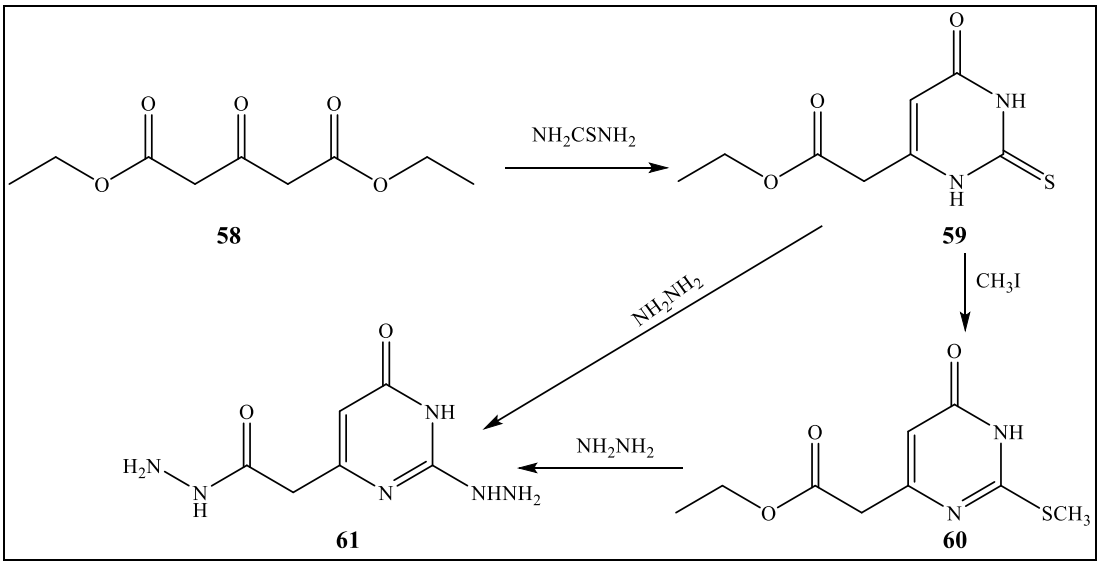
Scheme 7: Synthesis of pyrazine-2-carboxylic acid hydrazide **53**



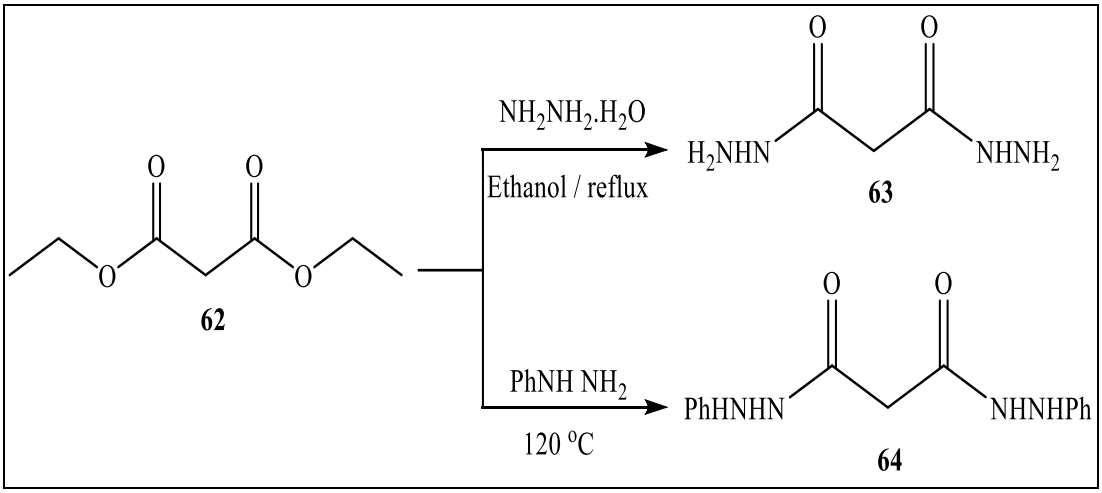
Scheme 8: Synthesis of biphenyl-4-carboxylic acid hydrazide **55**



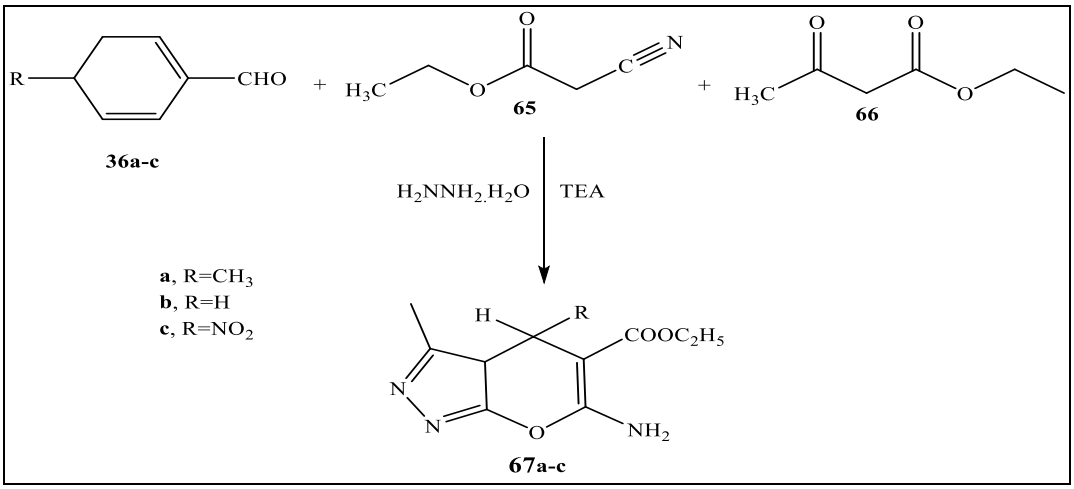
Scheme 9: Synthesis of indole-2- carboxylic acid hydrazide hydrazide **57**



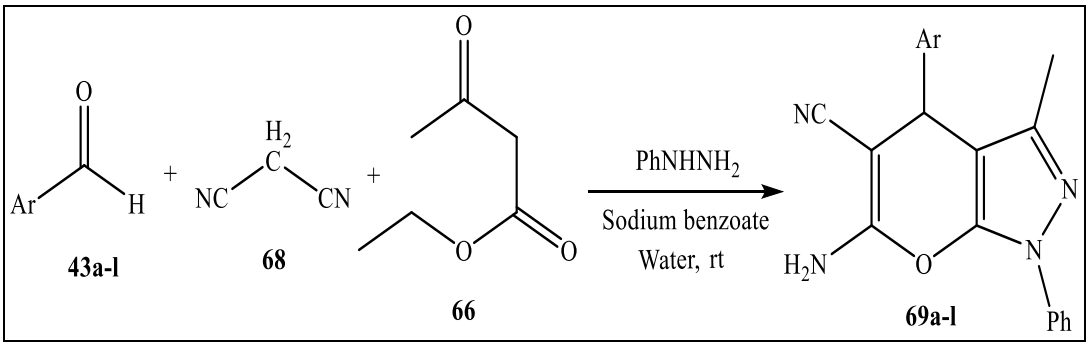
Scheme 10: Synthesis of hydrazinyl hydrazide **61**



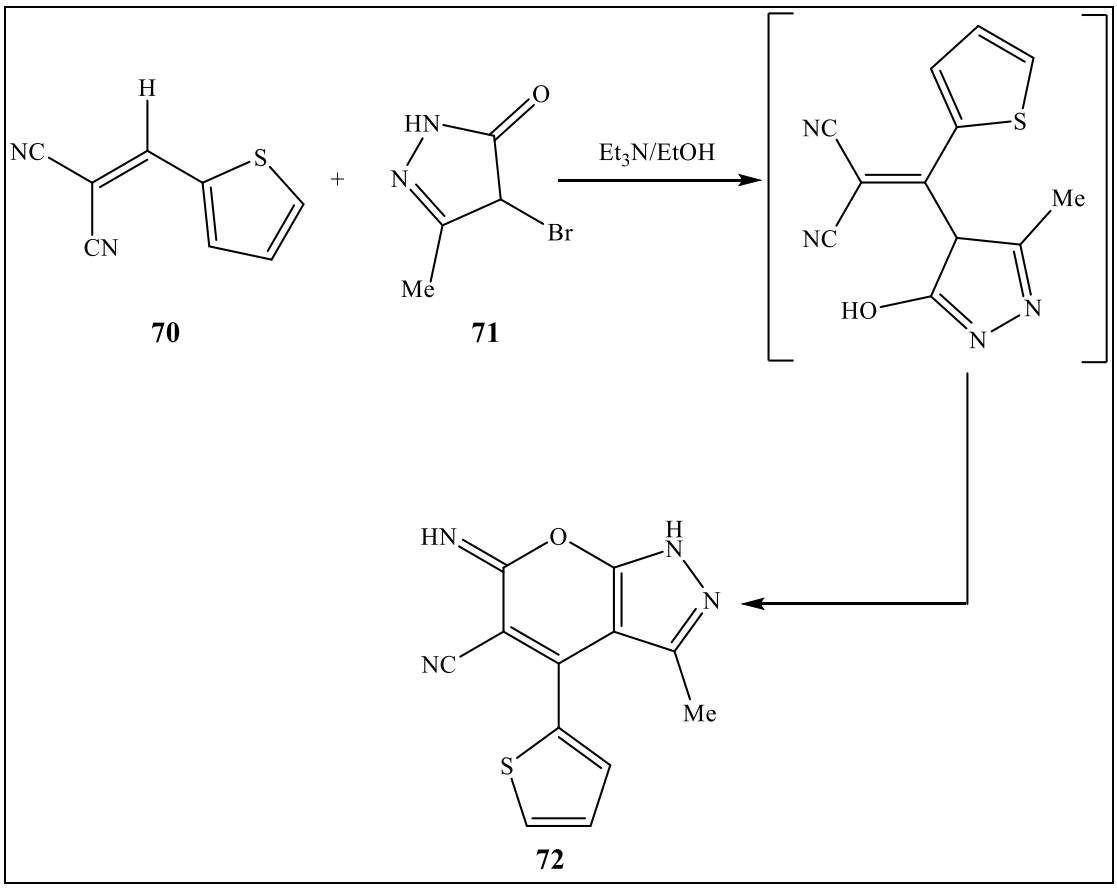
Scheme 11: Synthesis of malonyl dihydrazide derivatives **63** and **64**



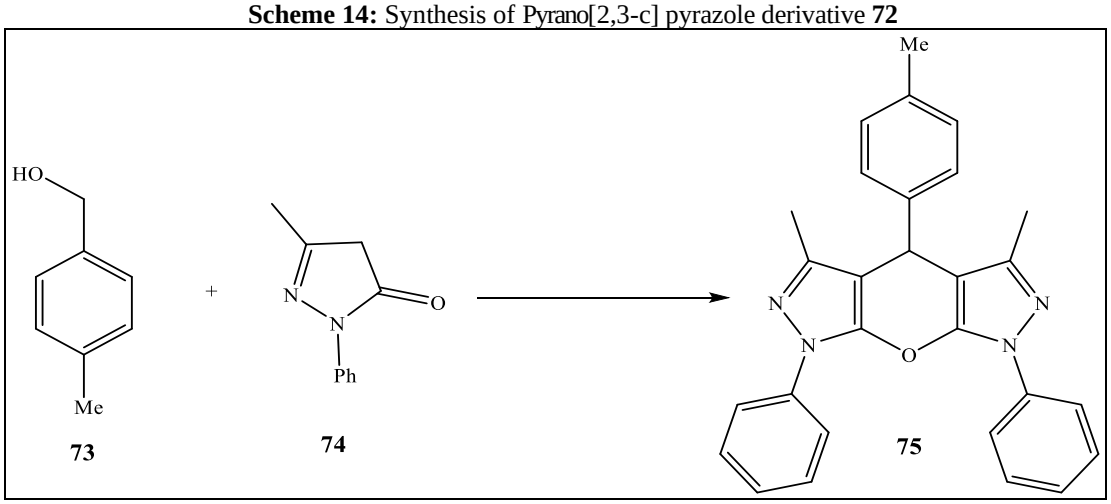
Scheme 12: Synthesis of Pyrano[2,3-c] pyrazole **67**



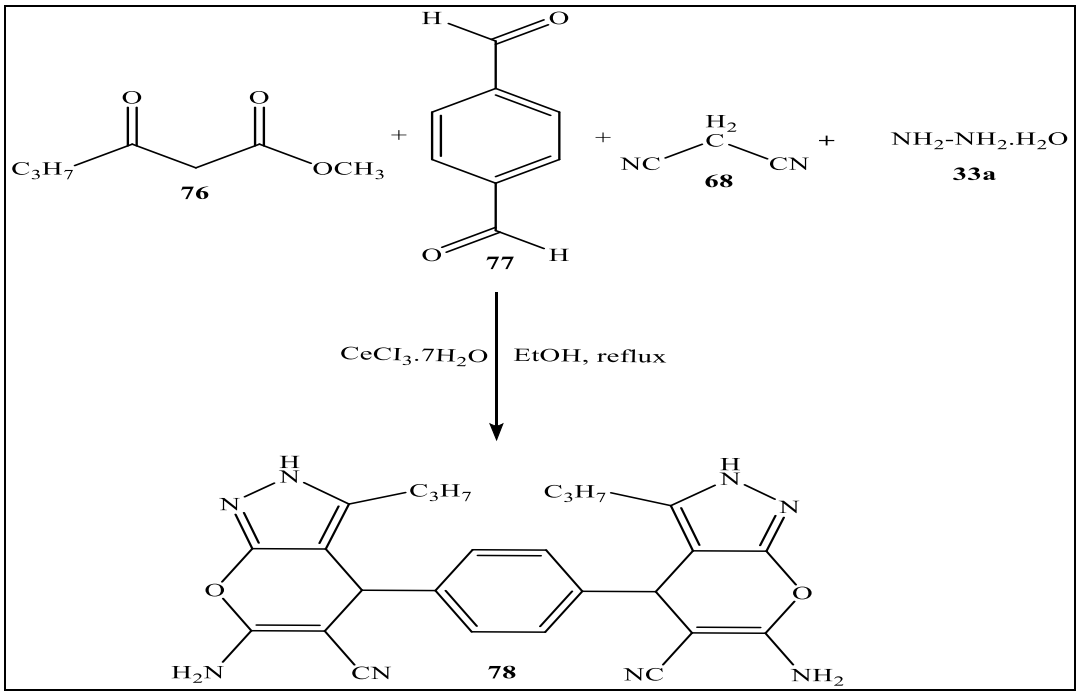
Scheme 13: Synthesis of Pyrano[2,3-c] pyrazole derivatives **69a-l**



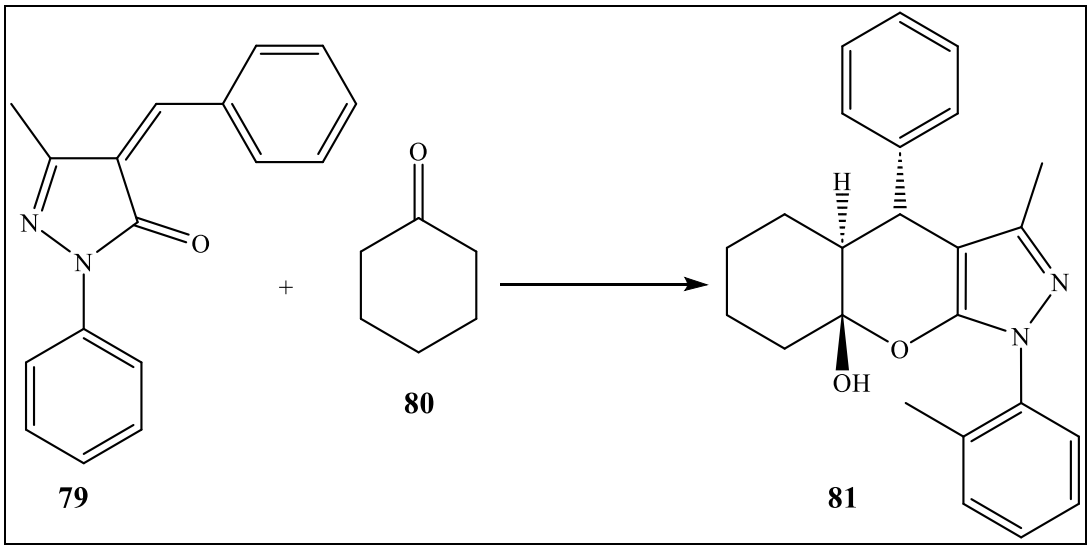
Scheme 14: Synthesis of Pyrano[2,3-c] pyrazole derivative **72**



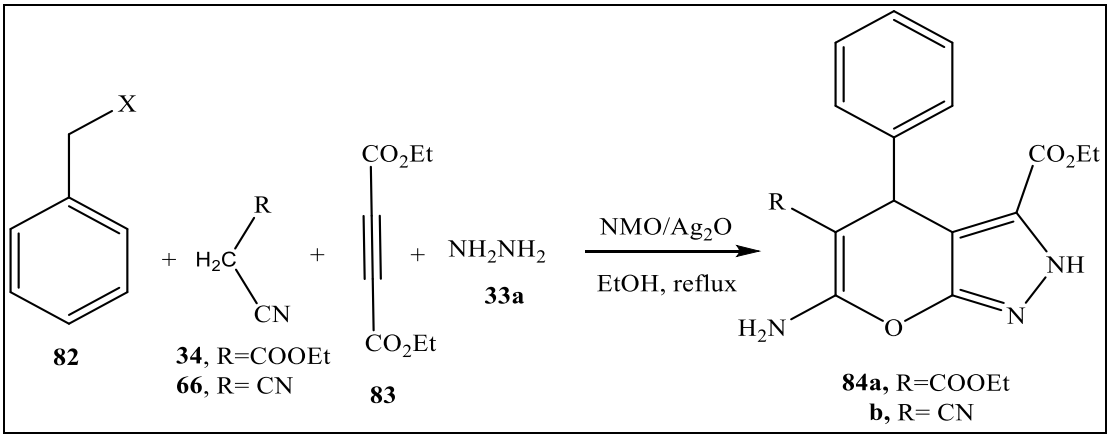
Scheme 15: Synthesis of pyrano dipyrazole-2-one derivative **75**



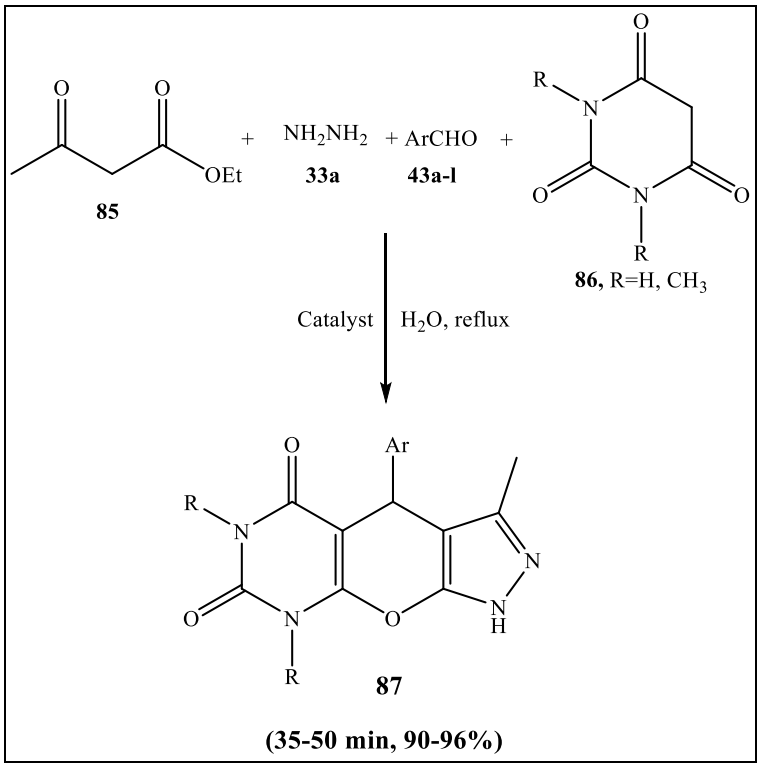
Scheme 16: Synthesis of bispyranopyrazole **78**



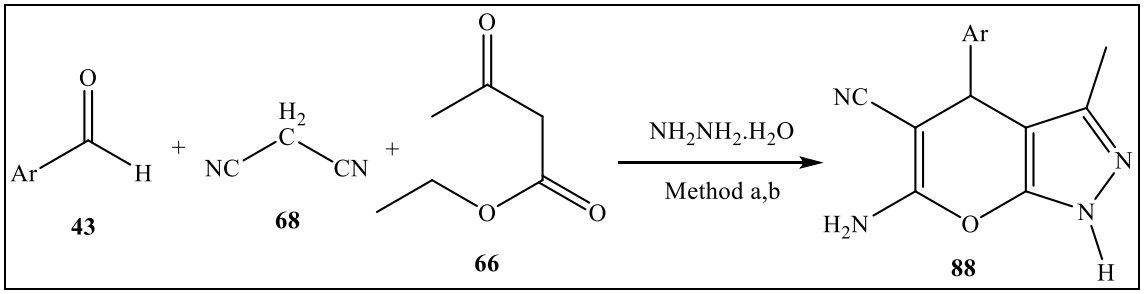
Scheme 17: Synthesis of tetrahydropyrano[2,3-c] pyrazoles **81**



Scheme 18: Synthesis of tetrahydropyrano[2,3-c]pyrazoles **84a,b**



Scheme 19: Synthesis of Methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates **87**



Scheme 20: Synthesis of Fused pyranopyrazoles **88.** Where method (a): Glycine/ H_2O, rt & method (b): Ethanol/80ºC/ (ß -CD)

3.12. Hydrazides for the synthesis of pyrano[2,3-c] pyrazole

Actually, our aim in this review was to prepare some new pyrano[2,3-c]- pyrazole derivatives using very simple strategy based on reaction of malonyl bis-phenylhydrazide **64** and the laboratory available arylidene malononitrile derivative, but unfortunately, we did not obtain the taget pyranopyrazole [59]. So, we herein present some examples for the preparation of those compounds related to our plane. Pyranopyrazols are an essential class of compounds that contains pharmaceuticals and exhibit a wide variety of biological activities such as anticancer, anti-bacterial and anti-inflammatory activities [60, 61].

Kumarswamyreddy and Kesavan suceeded to prepare pyrano[2,3-c]pyrazoles derivatives **67a-c** by multi component reaction of hydrazine hydrate, ethyl acetoacetate, aromatic aldehyde **36a-c**, and ethyl cyanoacetate **65** in presence of triethylamine at room temperature with stirring for 20–30 min [62], as illustrated in **Scheme 12**. On the other hand, the pyrano[2,3-c] pyrazoles **69a-l** have been synthesized from the condensation of aromatic aldehydes **43a-l**, malononitrile and phenyl hydrazine with ethyl acetoacetate. This reaction was carried out under aqueous conditions in the presence of sodium benzoate, as shown in **Scheme 13**. Moreover, the reaction of arylidene thinonitrile **70** with 4-bromo-3-methylpyrazol-5- one **71** in ethanol and catalytic amount of triethylamine produce pyrano-[2,3-c] pyrazole derivative **72**, as shown in **Scheme 14**.

3.13. Synthesis of pyrano dipyrazole-2-one derivatives

The pyrano dipyrazole-2-one derivative **75** has been prepared from various benzyl alcohols **73** with substituted pyrazol-5(4*H*)-ones **74** in metal/catalyst in the presence of hydrogen peroxide in water medium [63], as shown in **Scheme 15**. Additionally, bispyranopyrazole **78** was obtained by reaction of terethalaldehyde **77** with β-keto esters **76**, hydrazine monohydrate, and malononitrile in presence 10 mol% $CeCl_3 \cdot 7H_2O$ [64], as illustrated in **Scheme 16**.

Tetrahydropyrano[2,3-c]pyrazoles **81** have been prepared by the reaction of substituted pyrazolone **79** and cyclohexanone **80** in presence hydroquinine derived amine (20 mol%) and 2-fluorobenzoic acid (20 mol%) as catalyst [65], as illustrated in **Scheme 17**.

3.14. Synthesis of methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano- [2,3-c] pyrazole -3 -carboxylates

Reaction of benzyl halide with malanonitrile **34** and/or ethyl cyanoacetate **66**, diethyl acetylenedicarboxylate **83**, and hydrazine hydrate **33a** was reported to obtained pyrano[2,3-c]pyrazoles **84a,b** with 84-92% yield [66], as illustrated in **Scheme 18.** Moreover, methyl 6-amino-5-cyano-4-aryl-2,4-dihydropyrano[2,3-c]pyrazole-3- carboxylates **87** have been prepared by reaction of barbituric acid **86**, ethyl acetoacetate **85**, hydrazine hydrate and aromatic aldehydes **43a-l** [67], as illustrated in **Scheme 19**.

3.15. Synthesis of pyranopyrazoles in the presence of glycine

Fused pyranopyrazoles **88** were obtained in 85-95% yield *via* the reaction of ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes and malononitrile in aqueous medium at 25°C [68]. In addition, a multi-component reaction gave pyrano[2,3-c]pyrazole derivatives **88** with 83-92% yield by the reaction of aromatic aldehydes, hydrazine hydrate, malononitrile and β-ketoester in H_2O-EtOH (9:1) at 80 °C in presence supramolecular β -cyclodextrin (β -CD) as catalyst [69] as illustrated in **Scheme 20**.

4. Conclusions

In this extensive review, we have thoroughly explored the synthesis of hydrazides and their derivatives using hydrazine as a common precursor. Our investigation has primarily centered around the potential applications of these compounds in microbiology, pain treatment, antioxidants, and antimalarials. Through a comprehensive examination of their biological activities, we have unveiled the diverse roles that hydrazide derivatives play in addressing challenges across these sectors. These derivatives exhibit considerable promise, particularly as potent antiviral agents capable of inhibiting viral replication, disrupting viral entry mechanisms, and influencing host immune responses. These findings present exciting possibilities for the development of novel antiviral therapies, especially in the face of emerging viral threats and drug-resistant strains. Moreover, hydrazides have showcased notable antimicrobial properties, demonstrating efficacy against a spectrum of microbial pathogens. Their varied mechanisms of action position them as valuable candidates for the creation of new antimicrobial agents. Additionally, our review has underscored their potential in combatting malaria, offering optimism for improved antimalarial treatment and prevention strategies. Furthermore, hydrazide derivatives show promise as analgesic and anti-inflammatory agents, potentially contributing to pain management and alleviating inflammatory disorders. While ongoing research delves into their potential as anticancer agents, initial findings suggest cytotoxic effects on cancer cells, paving the way for further exploration. Concurrently, our review has delved into the preparation of hydrazide derivatives, providing a comprehensive overview of various synthetic pathways. From the synthesis of simple compounds like cyanoacetic acid hydrazide to the creation of complex derivatives such as pyranopyrazoles, our compilation serves as a valuable resource for chemists and researchers involved in the design and synthesis of hydrazide compounds for diverse application.

5. Future prospects and challenges

As we look to the future, the prospects for hydrazide derivatives are promising, with the potential to address critical issues in microbiology, pain management, malaria control, and beyond. However, several challenges must be addressed, including the need for further preclinical and clinical studies to validate the efficacy and safety of these compounds [70-74]. Additionally, the scalability and cost-effectiveness of their synthesis processes require optimization. With ongoing research and collaborative efforts, we anticipate that hydrazide derivatives will continue to evolve as essential components in the development of innovative solutions for pressing global challenges, ultimately benefiting society, and improving healthcare and wellbeing [75-78].

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