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A Comprehensive Study on Synthesis of Heterocyclic Compound by Using Cyanoacetohydrazide Of Pyrazole

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Abstract: *Use of cyanoacetohydrazides as precursors in reactions leading to construction of heterocycles is reviewed. In addition to some common heterocyclic compounds, synthesis of other uncommon heterocycles such as thiadiazole, oxadiazole, fused heterocycles, and some seven- and eight-membered heterocycles such as benzodiazepine, oxazepine, and benzoxocine starting with cyanoacetohydrazides and their derivatives is also reported. The main aim of this review is to show the application of cyanoacetohydrazides in heterocyclic synthesis via different types of reaction, including cyclocondensation and cyclization. The results are arranged in terms of the type of heterocycle formed, from five-, six-, seven-, to eight-membered and fused rings. This review aims to cover literature up to 2018, showing the distribution of publications involving use of cyanoacetohydrazides for preparation of heterocycles. This study reviewed the use of cyanoacetohydrazide as versatile precursor for synthesis of some heterocyclic compounds, as it contains five different functional groups (cyano group, No. 1, active methylene group, No. 2, carbonyl group, No. 3, amido group, No. 4 and hydrazine group, No.5) The reviewed reactions were classified according to the active centers of cyanoacetohydrazide involved. Accordingly, they are divided into 12 classes in which heterocycles was obtained via the utility of the following functional groups: a - groups No. 1, 2, b - groups No. 1,5, c - groups No. 2, 3 , d - groups No. 2,4 , e - groups No. 2,5 , f- groups No. 3,5 , g- groups No. 4,5 , h- groups No. 1,2,5, i- groups No. 1,4,5, j- groups No. 2,4,5, k- groups No. 1,2,4,5, l-groups No. 2,3,4,5 .This review covers literature up to 2021. This research project investigates the synthesis of heterocyclic compounds using cyanoacetohydrazides in one-pot reactions. Heterocyclic compounds are an essential class of compounds in medicinal chemistry, as they exhibit a wide range of biological activities. The use of cyanoacetohydrazides in a one-pot synthetic approach offers a versatile and efficient route to the construction of various heterocyclic systems. The project aims to explore different reaction conditions, mechanisms, and the potential of these reactions for creating new bioactive heterocycles.*

Keywords: Cyanoacetohydrazides, Cyanoacetic acid hydrazide, Heterocycles, Cyclization.

I. INTRODUCTION

Cyanoacetohydrazide is a versatile reagent as it contains five different functional groups (cyano, active methylene, carbonyl, amido and hydrazino groups). Some of them could act as a nucleophile or as an electrophile. Also they could act in pairs as a bidentate reagent affording several probabilities. the predominance of which depends on the reaction conditions and the other reactants. Among several commercially available substituted hydrazides, cyanoacetic acid hydrazide has received the most attention recently, representing a versatile and convenient intermediate for synthesis of a wide variety of heterocyclic compounds. This substrate can act as an ambident nucleophile, that is, as both an N- and C-nucleophile. Upon treatment of cyanoacetic acid hydrazide with various reactants, attack can take place at five possible sites; nucleophiles can attack the carbon atom of the carbonyl group (position 3) and the carbon atom of the nitrile function (position 5).

In addition, the carbon atom of the active methylene group (position 4) and the nitro- gen atoms of the hydrazine portion (position 1 and position 2) are liable to attack by electrophiles. Reactions of cyanoacetic acid hydrazide with

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numerous reactants (nucleophiles and electrophiles) are used in synthesis of a variety of polyfunctional heterocyclic compounds of biological interest (Fig. 1) [1].

Cyanoacetohydrazide has a hydrazine component. Hydrazines and their derivatives constitute an important class of compounds that has found wide utility in organic synthesis. The chemistry of the carbon–nitrogen double bond of hydrazone is becoming the backbone of condensation reactions in benzo-fused N-heterocycles, which also constitute an important class of compounds for new drug development. It has been claimed that a number of hydrazide hydrazone derivatives possess interesting bioactivity, as explained in Sect. 6 [2]. Reaction of cyanoacetohydrazide with various reactants results in unique properties, many of which are still unknown. To ethyl cyanoacetate 2 in ethanol, hydrazine hydrate 3 is added dropwise at molar ratio of 1:1 with stirring at 0 °C to give the corresponding hydrazide 1. White product is obtained by recrystallization from ethanol (Scheme 1) [3]. In 1999, Galal et al. developed a one-step synthesis of N-sulfonylated pyrazoles via intramolecular cyclization of cyanoaceto-N-arylsulfonylhydrazides. It has been found that cyanoacetohydrazide 1 reacts with arylsulfonyl chloride 4 in ethanol to afford the corresponding cyanoaceto-N-arylsulfonylhydrazides 5. The structures of 5 were established and confirmed on the basis of their elemental analysis and spectral data. On refluxing in ethanol, compounds 5 undergo intramolecular cyclization to give the 5-amino-1-arylsulfonyl-4-pyrazolin-3-ones 7 as major products or the tautomeric5-amino-1-arylsulfonyl-3-hydroxypyrazole structures 8 as minor products (Scheme 2) [4]. In 2008, Marcos and coworkers described a reaction between cyanoacetohydrazide 1 and 1,3- dicarbonyl compounds or α,β-unsaturated systems 9 (such as [aryl]alkylidenemalononitrile, cyanobutanoates) in water.

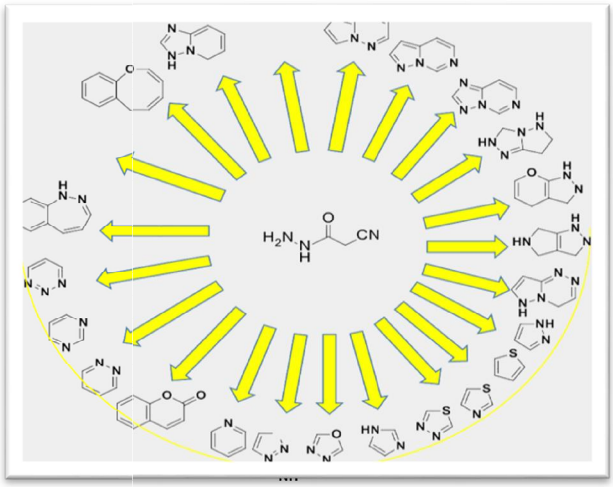

Fig 1: Summary of various heterocyclic compounds synthesized using cyanoacetohydrazide

In 1998, Erian et al. reported a synthesis of 1,3,4-thiadiazole derivatives. They found that treatment of cyanoacetohydrazide 1 with benzoyl isothiocyanate 74 in acetone as solvent afforded exclusively the corresponding 1,3,4-thiadiazole derivative 78. It is believed that 1 reacts initially with benzoyl isothiocyanate 74 to yield the thiosemicarbazide derivative 75, which then cyclizes under the reaction conditions to yield the thiadiazole 76. The latter then condenses with ketone 77 to yield 78. Isolation of 75, 76 was reported earlier from their laboratories. This synthetic methodology could be generalized using a variety of ketones in dioxane as inert solvent. Thus, compounds 78 were obtained in a one-pot reaction on treatment of a boiling mixture of 1 and 74 with acetophenone, benzoylacetonitrile, and phenacyl thiocyanate (Scheme 18) [16]. In 2006, Shams and coworkers studied the treatment of cyanoacetic hydrazide 1 with benzoyl isothiocyanate 74, which led to hydrazinecarbonothioylbenzamide 79. Reaction of 79 with α-haloketones (XCH2C(O)R; X = Cl, R = OEt; X = Cl, R = CH3; X = Br, R = Ph) afforded the respective imidazolethione derivatives 81a–c (Scheme 19) [17]. In 2002, Allam and Nawwar synthesized cyanomethyloxadiazole spiroindoline 84. They found that the condensation product of cyanoacetohydrazide with isatin 82 could be cyclized in acidic medium via its C=N group and its enolic OH to give the oxadiazolo-2-spiroindoline structure 84 (Scheme 20)

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[18].In 2014, Thorat reported synthesis of 2- substituted-5-(2′-thiophene)-1,3,4- Oxadiazole 87 using microwave irradiation. Firstly, cyanoacetic acid hydrazide 1 was obtained by careful addition of hydrazine hydrate to ethyl cyanoacetate 85 in ethanol with stirring at 0 °C. On condensation with 2-thiophenecarbaldehyde, the hydrazide yielded the corresponding hydrazone 86, which on oxidative cyclization with chloramine-T under microwave irradiation yielded the corresponding 2,5- disubstituted-1,3,4-oxadiazole 87. To the mixture of hydrazone 86 and chloramine-T in molar ratio of 1:1, two drops of dimethylsulfoxide (DMSO) were added, and the clear liquid obtained was heated under microwave irradiation for 12 s, followed by addition of alcohol to give solid product (Scheme 21) [19]. In 2002, Demirbas et al. explored the treatment of compound 1 with tertbutox- ycarbonylhydrazone esters 88 in an oil bath at 115 °C, leading to 1,2,4-triazole derivatives 92. Nucleophilic addition of NH2 group on carbon of hydra- zone 88 leads to intermediate 89, which tautomerizes to 90. Intramolecular cyclization of 90 affords product 91. Formation of 3-alkyl-4-amino-5-cyanome- thyl-4H-1,2,4-triazoles 92 was achieved when compounds 91 were refluxed in water (Scheme 22) [20].

II. LITERATURE REVIEW

The Importance of Cyanoacetohydrazide Products in Medicine:-

Pyridine Derivatives:-Pyridine derivatives are currently an important group of organic compounds that are used as bactericides [61], fungicides [62], and anticancer agents [63–66]. Furthermore, 2-pyridones represent a unique class of pharmacophores, found in various therapeutic agents [67]. Pyridine and its substructures are widely scattered and dominantly found in natural products, pharmaceuticals, vitamins, and other functional as well as essential materials. In fact, the pyridine ring system forms the integral backbone of more than 7000 drugs which are already in existence. In recent years, 2-pyridones have garnered much importance, as they exhibit several biological activities such as antitumoral [68], antimalarial [69], analgesic [70], and anti- human immunodeficiency virus (HIV) [71] properties. Moreover, 2-pyridones are a class of recently discovered potent antibacterial agents that are of particular interest due to their in vitro and in vivo antibacterial potencies against bacterial type II DNA topoisomerases, which include two highly homologous enzymes: DNA gyrase and topoisomerase IV [72]. The 2- oxo-3-cyanopyridine nucleus is analogous to the alkaloid ricinine, the first known alkaloid containing a cyano- group. The importance of 2-oxo-3-cyanopyri- dine as a pharmacologically as well as physiologically active potential molecule is highlighted by the synthesis and study of the nonglycosidic cardiotonic agent milrinone, an inhibitor of dipyridine phosphodiesterase (Fig. 3) [73]. In 2011, Al-Said and coworkers studied the anticancer activity of sulfonamide- containing compounds, where the nitrogen of –SO2NH– group is either free or substituted. Compounds 316f and 316b showed significant cytotoxic activity, even higher than that of the reference drug doxorubicin, while compound 316e was nearly as active as doxorubicin. Doxorubicin HCl, one of the most effective anticancer agents, was used as reference drug in this study [12]

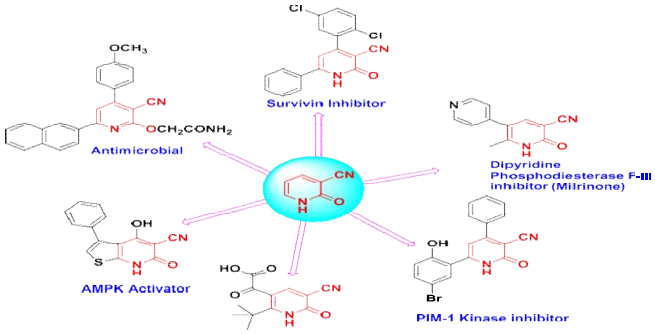

Fig. 2:- Biodynamic activities of different derivatives of 2-oxo-3-cyanopyridine

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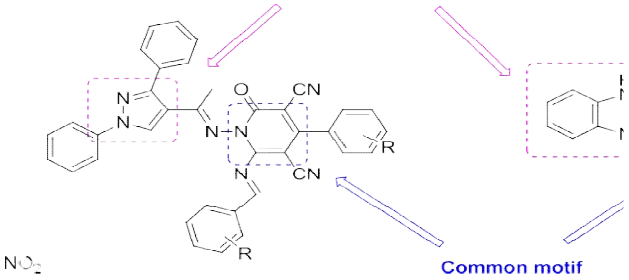

Fig. 3:- Structural relation of compounds 149a–r with previously synthesized compounds NCD1–20

The benzimidazole nucleus is the key building block for numerous compounds that play beneficial roles in the functioning of biologically important molecules [78] and are remarkably effective with respect to both their inhibitory activity and favorable selectivity ratio [79–81]. Benzimidazoles are considered a promising class of bioactive heterocyclic compounds encompassing a diverse range of biological activities such as antiulcer [82], antihelminthic [83], antihypertensive [84], anticoagulant [85], antiinflammatory [86], antimicrobial [87–89], and antiparasitic [90] effects. The azole group of heterocyclic compounds possesses a significant pharmacokinetic profile and lipophilicity that influence the ability of drug to reach the target via transmembrane diffusion, along with promising activity against resistant tuberculosis (TB) by inhibiting biosynthesis of lipids [91, 92].

The intermediates 146, 148 and target compounds 149a–r were investigated for their in vitro antibacterial activity against two Gram-positive and two Gramnegative bacteria and yeast-like pathogenic fungus Candida albicans using conventional broth dilution method. The minimum inhibitory concentration (MIC) was defined as the concentration of compound required to obtain complete inhibition of bacterial growth. MICs of the synthesized compounds were compared with ciprofloxacin and chloramphenicol, and the results are depicted in Table 3. From the bioassay, it was observed that the final analogues 149a–r with substitutions of phenyl ring were most active against all the pathogenic strains studied compared with the intermediate hydrazone 146 and 2-pyridone derivative

148. Therefore, target compounds 149a–r were found to exhibit broad-spectrum antimicrobial efficacy. This can be correlated with the structural variations and different aromatic substitutions in phenyl ring. Among all final active analogues, compound 149q (3-Br, Clog P = 3.9272) exerted highest inhibition against all the bacterial strains and showed highest effi- cacy against Staphylococcus aureus with MIC of 12.5 µg/mL when compared with standards ciprofloxacin (50 µg/mL, Clog P = −0.7252) and chloramphenicol (50 µg/ mL, Clog P = 1.293).

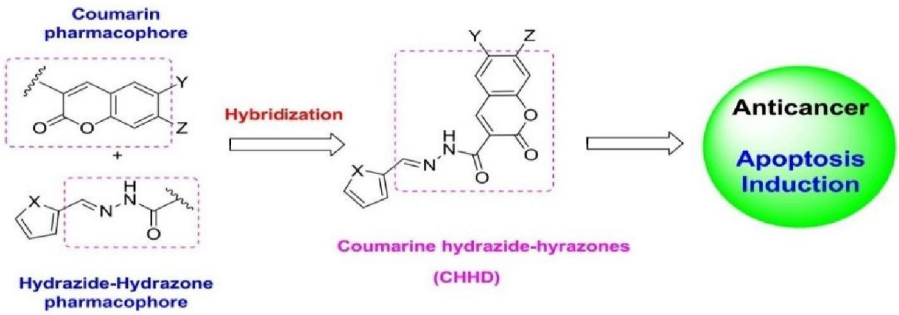

Fig.4 Design of CHHDs as anticancer agents

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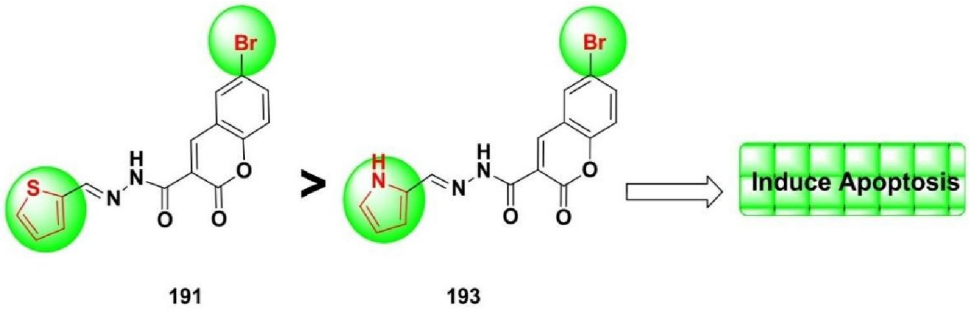

Fig.5 The most potent CHHDs against Hep-G2 cancer cell line

Coumarin Derivatives:-

Natural and synthetic coumarins have attracted great attention due to their wide range of biological properties, including anticancer [94], anti-HIV [95], antiinflammatory [96], and antibacterial [97] activities. Furthermore, their cancer chemo- preventive properties have been recently emphasized [94, 98]. The apoptosis and differentiation-induced activities of coumarins extend to several different cell line models in vitro, and they appear to be the most promising in terms of cancer treatment [99]. Coumarins can exert their anticancer activity by different mechanisms, by either inhibiting the telomerase enzyme [100], inhibiting protein kinase activity and downregulating oncogene expression [101], or inducing caspase-9-mediated apoptosis. Furthermore, it is well known that the hydrazone group plays an important role in the antimicrobial activity. Indeed, a number of hydrazide–hydrazones are claimed to exhibit inter- esting antibacterial–antifungal [104–107], anticonvulsant [107], anti-inflammatory [108], antimalarial [109], and antituberculosis activities [110] (Figs. 5, 6, 7).

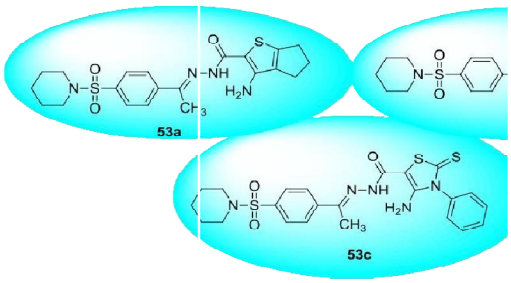

Fig.6 Novel sulfonamides with thiophene and thiazole moieties as anti-breast cancer compounds

Pyrazolopyridine Derivatives

In 2013, Kabirifard et al. studied the synthesis of pyrazolo[3,4-b]pyridine-4-carboxylate 285 by condensation of the cyanoacetic acid hydrazide 1 with ethyl benzoylpyruvate 284 in glacial acetic acid at 70–80 °C. Presumably, the reaction mechanism includes formation of ethyl 2-benzoylmethylene-3-cyano-4-oxo- 4-hydrazinobutanoate 286 from cyanoacetohydrazide 1 and ethyl benzoylpyruvate 284, which then undergoes intramolecular ring closure by attack of NH2 group on nitrile group to give intermediate 287.

Pyrrolopyridazine Derivatives

In 2007, Abdelrazek and coworkers developed the synthesis of pyrrolo[1,2-b]pyridazine 292. Firstly, compound 289 was allowed to react with N-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature to afford the brominated derivative 290. Compound 290 reacts with cyanoacetohydrazide through the terminal hydrazine moiety with elimination of HBr to afford the nonisolable acyclic inter- mediate 291, which undergoes two cyclizations via addition of NH to CN group in position 1, and of the active methylene to the other CN group in the assumed formed pyrrole to afford the pyrrolo[1,2-b]pyridazine derivative 292 [55].

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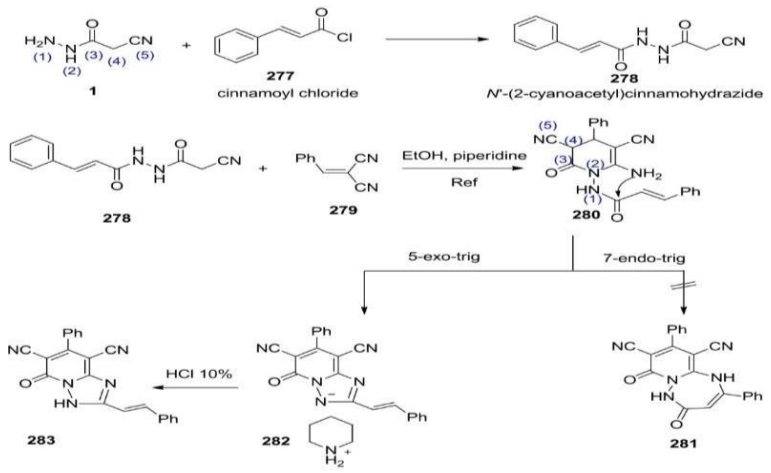
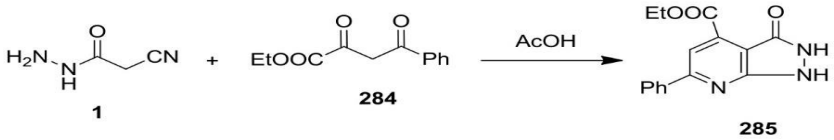
Pyrazolopyrimidine Derivatives

In 2004, Napoles et al. reported the synthesis of pyrazolo[1,5-a]pyrimidines 294 from cyanoacetohydrazide 1 and push–pull systems. Starting from cyanoacetohydrazide 1 and cinnamonitrile derivatives 293 in DMF, the target compounds could be obtained in just one step, but with low yield due to formation of several byproducts. It was considered that the presence of appropriate reactive center in the ketene-S,S-acetals and 1,3-dithiethanes used as push–pull systems enables the necessary intramolecular cyclizations after the initial nucleophilic attack of the cyanoacetohydrazide [56].



Scheme :- Synthesis of triazolopyridine 283



Scheme :- Synthesis of pyrazolo[3,4-b]pyridine-4-carboxylate 285

Cyanoacetohydrazide as a Versatile Compound (Precursor):-

Cyanoacetohydrazide is a versatile compound extensively utilized in the synthesis of various heterocyclic structures due to its rich functional group composition, including cyano, active methylene, carbonyl, amido, and hydrazino groups. These functional groups enable cyanoacetohydrazide to participate in diverse chemical reactions, leading to the formation of numerous heterocyclic compounds.

A comprehensive review by Hosseini and Bayat (2018) delves into the applications of cyanoacetohydrazides in heterocyclic synthesis. The authors discuss the formation of both common and uncommon heterocycles, such as thiadiazoles, oxadiazoles, fused heterocycles, and larger ring systems like benzodiazepines and oxazepines. The review categorizes the synthesized heterocycles based on ring size, ranging from five- to eight-membered and fused rings, and emphasizes the role of reactions like cyclocondensation and cyclization in these syntheses.

III. METHODOLOGY

The methodology for using cyanoacetohydrazide in the synthesis of heterocyclic compounds involves a series of well-established organic reactions. These methodologies exploit the functional groups present in cyanoacetohydrazide, such as the cyano group (-CN), carbonyl group (C=O), and hydrazide (-NH-NH2), to form various heterocyclic frameworks. Below is an overview of the general approaches used:

Cyclization Reactions

Condensation with Carbonyl Compounds:

Cyanoacetohydrazide reacts with aldehydes or ketones to form hydrazones, which can undergo cyclization to produce heterocyclic rings such as pyrazoles, pyridazines, and others.

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Example: Reaction with aromatic aldehydes to yield substituted pyrazoles. Reaction with Dicarbonyl Compounds:
In the presence of diketones or ketoesters, cyclization leads to the formation of pyrazolines, pyrazolidines, or fused ring systems.
Example: Reaction with 1,3-diketones to form pyrazolines.
Cyclocondensation with Bifunctional Compounds
Cyanoacetohydrazide reacts with bifunctional compounds like isothiocyanates, urea, or thiourea to form heterocycles such as thiadiazoles, oxadiazoles, and triazoles.
Example: Reaction with isothiocyanates produces thiadiazoles.
Michael Addition
The active methylene group in cyanoacetohydrazide participates in Michael addition with α,β-unsaturated carbonyl compounds or nitriles. Subsequent cyclization yields pyrimidines, pyridazines, or other heterocyclic systems.
Multicomponent Reactions (MCRs)
Cyanoacetohydrazide is used in multicomponent reactions involving aldehydes, amines, and other nucleophiles to construct complex heterocyclic frameworks in a one-pot process.
Example: Biginellitype reactions to form dihydropyrimidinones

Reaction with Sulfur or Selenium Donors
Cyanoacetohydrazide reacts with sulfur or selenium sources to yield heterocycles like thiadiazoles, selenadiazoles, or related fused systems.
Formation of Fused Heterocycles
By reacting with compounds containing multiple reactive centers (e.g., phthalic anhydride or maleic anhydride), cyanoacetohydrazide can form polycyclic fused heterocycles such as benzodiazepines or oxazepines.

Catalysis and Reaction Conditions
Catalysts such as Lewis acids (e.g., $ZnCl_2$, $AlCl_3$), bases (e.g., piperidine, triethylamine), or green catalysts (ionic liquids, metal-organic frameworks) are employed to enhance reaction efficiency.
Solvent systems include ethanol, methanol, or water, with some reactions performed under solvent-free conditions for greener synthesis.
Functional Group Modifications
The functional groups in cyanoacetohydrazide can be selectively modified before or after heterocyclic ring formation to introduce additional substituents, increasing molecular diversity.
Representative Reactions:
Formation of Pyrazoles:
Cyanoacetohydrazide + Aldehyde + Acid catalyst → Substituted pyrazoles.
Synthesis of Thiadiazoles:
Cyanoacetohydrazide + Isothiocyanate → Thiadiazoles (under basic or neutral conditions).
Construction of Fused Systems:
Cyanoacetohydrazide + Phthalic anhydride → Benzodiazepines (under thermal or catalyzed conditions).
These methodologies demonstrate the versatility of cyanoacetohydrazide in constructing a wide range of heterocyclic compounds with diverse applications in pharmaceuticals, materials science, and agrochemicals.
Methods of Experimental Work on Cyanoacetohydrazide in the Synthesis of Heterocyclic Compounds of Synthesis of Pyrazoles:-
SYNTHESIS OF PYRAZOLES:

IV. MATERIALS

Cyanoacetohydrazide
Aromatic aldehyde (e.g., benzaldehyde) Glacial acetic acid (as a catalyst) Ethanol (solvent)

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PROCEDURE:
Mix cyanoacetohydrazide (1 mmol) and aromatic aldehyde (1 mmol) in ethanol (10 mL).
Add a few drops of glacial acetic acid as a catalyst
Stir the reaction mixture at room temperature for 2-4 hours.
Monitor the reaction using thin-layer chromatography (TLC).
After completion, filter the precipitate and wash it with cold ethanol.
Recrystallize the product from ethanol to obtain pure pyrazole derivatives.

CHARACTERIZATION
Melting point determination.
Spectroscopic analysis (IR, NMR, and Mass spectroscopy) to confirm the structure. General Notes for Experimental Work:-
Safety Precautions: Handle reagents like isothiocyanates and strong acids with care in a well-ventilated fume hood.
Purity Check: Perform TLC during the reaction and melting point analysis to ensure product purity.
Yield Optimization: Vary the reaction temperature, solvent, and catalyst to maximize yield.
These experiments demonstrate cyanoacetohydrazide's versatility in producing various heterocyclic compounds with straightforward methods. Each reaction can be optimized to improve yield and purity.

IV. FUTURE SCOPE

The versatility and reactivity of cyanoacetohydrazide make it a valuable starting material for heterocyclic synthesis. Its potential can be further explored in various fields, as highlighted below: The versatility and reactivity of cyanoacetohydrazide make it a valuable starting material for heterocyclic synthesis. Its potential can be further explored in various fields, as highlighted below:

Development of New Heterocyclic Frameworks:- Design of Novel Scaffolds: Cyanoacetohydrazide can be used to synthesize previously unexplored heterocyclic frameworks with enhanced bioactivities. Multifunctional Heterocycles: The incorporation of additional functional groups into heterocycles can lead to compounds with tailored properties, suitable for pharmaceuticals and materials science.

Pharmaceutical Applications:- Drug Discovery: Cyanoacetohydrazide-derived heterocycles (e.g., pyrazoles, pyrimidines) can be further explored as potential drugs for treating various diseases, including cancer, inflammation, and microbial infections.Structure-Activity Relationship (SAR) Studies: New derivatives can be synthesized to study their pharmacological profiles and improve potency, selectivity, and bioavailability.Hybrid Molecules: Combining cyanoacetohydrazide-based heterocycles with other bioactive moieties could lead to hybrid molecules with enhanced therapeutic properties.

Green and Sustainable Chemistry:- Eco-Friendly Synthesis: Future studies can focus on developing greener reaction conditions, such as solvent-free reactions, microwave-assisted synthesis, and the use of renewable catalysts. Biocatalysis: Employing enzymes to catalyze reactions involving cyanoacetohydrazide could lead to sustainable and selective synthesis of heterocycles. Atom Economy: Optimization of multicomponent reactions (MCRs) to minimize waste and maximize yield will align with sustainable practices.

Nanotechnology and Material Science:- Functionalized Materials: Cyanoacetohydrazide-based heterocycles can be explored for applications in material science, such as semiconductors, organic light-emitting diodes (OLEDs), and liquid crystals. Coordination Chemistry: These compounds can act as ligands in coordination complexes for developing metal-organic frameworks (MOFs) and catalytically active materials.

Agricultural and Industrial Applications:- Agrochemicals: Cyanoacetohydrazide derivatives can be studied for their potential as pesticides, herbicides, or growth regulators in agriculture. Industrial Catalysts: The development of heterocyclic derivatives for catalytic applications in chemical industries is another avenue to explore.

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6. Theoretical and Computational Chemistry:- Mechanistic Studies: Advanced computational techniques, such as density functional theory (DFT), can be employed to understand reaction mechanisms involving cyanoacetohydrazide. Prediction of Novel Structures: Computational tools can predict new heterocyclic structures and their properties, guiding experimental efforts. QSAR Models: Quantitative structure-activity relationship studies can help identify the most promising derivatives for specific applications.
7. Biomedical Imaging and Diagnostics:- Fluorescent Probes: Cyanoacetohydrazide based heterocycles with unique photophysical properties can be developed as fluorescent probes or imaging agents. Biosensors: Derivatives with selective binding properties can be explored for biosensing applications, such as detecting biological analytes or environmental pollutants.
8. Exploration of Unconventional Reactions:- Photochemical and Electrochemical Reactions: Investigating cyanoacetohydrazide in photo- or electrochemical reactions could lead to the discovery of new synthetic pathways. Radical Chemistry: Radical-based transformations can be studied to access unique heterocyclic systems. By leveraging advances in synthetic methods, computational tools, and interdisciplinary approaches, cyanoacetohydrazide's potential in heterocyclic synthesis can be significantly expanded, contributing to innovations across pharmaceuticals, materials science, and sustainable chemistry.

V. ACKNOWLEDGEMENT

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VI. CONCLUSION

The constantly increasing number of papers describing synthesis of heterocyclic compounds based on cyanoacetohydrazide and cyanoacetohydrazide derivatives indicates their growing importance as building blocks with high synthetic potential. The aim of this review is to demonstrate the widespread applications of cyanoacetohydrazides in organic synthesis and the outlook for potential future developments. Due to their chemical reactivity and versatility, cyanoacetohydrazide derivatives constitute valuable synthetic units giving rise to a number of useful classes of organic compounds. Despite the extensive research conducted so far, the future holds numerous opportunities for expanding its applications. Advances in green chemistry, computational tools, and innovative synthetic strategies can further optimize its use, making it an essential tool in modern heterocyclic chemistry. Cyanoacetohydrazide is a highly versatile and valuable building block in the synthesis of heterocyclic compounds due to its multifunctional nature and reactivity. Its functional groups, including the cyano, hydrazide, and active methylene units, enable it to participate in a wide range of chemical reactions such as cyclization, cyclocondensation, and multicomponent reactions. These properties have been extensively utilized to construct various heterocyclic frameworks, including pyrazoles, pyrimidines, thiadiazoles, triazoles, and fused ring systems. In conclusion, cyanoacetohydrazide remains a cornerstone in heterocyclic synthesis, with significant potential for further exploration and innovation across scientific and industrial domains.
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