Thesis

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ABSTRACT

Benzodiazepine derivatives are a well-established class of heterocyclic compounds that have gained considerable importance due to their wide-ranging biological properties and applications in medicinal, pharmaceutical science. Initially, their synthesis has depended on conventional methods over the years, which frequently use hazardous chemicals, produce toxic waste, and require a significant amount of energy and time. Increasing significant risks to the environment and human health along with questions about their long-term sustainability and economic viability. Currently, the world of researchers steadily moving towards more sustainable and environmentally friendly methods of chemical synthesis in response to these difficulties. By utilizing safer reagents, non-toxic reusable catalysts, energy-efficient techniques and most important evolution of green chemistry, has created exciting opportunities for the environmentally friendly synthesis of benzodiazepine-based compounds. These advance techniques include biocatalysis, solvent-free conditions, photocatalysis, nano catalysis, ultrasound-assisted synthesis, microwave-assisted reactions, and even reactions that don't require a catalyst at all. Consequently, producing higher yields, better selectivity, and quicker reaction times in addition to minimizing environmental harm. With a focus on advancements in sustainable solvents, energy-saving technologies and catalytic systems, this thesis examines current trends in the environmentally friendly synthesis of benzodiazepines derivatives. It also talks about how these developments help to achieve larger sustainability goals and reduce the environmental load of the chemical industry without sacrificing scalability or efficiency. Even though great progress has already been made but continuous efforts are still going on to create more advancement and resolve the underlying issues like exorbitant prices, restricted scalability, and the requirement for standardized processes that still exist. However, it is anticipated that continued study and development in this area will improve these techniques even more, opening the door to a more ethical and sustainable future for chemical manufacturing.

TABLE OF CONTENTS

TITLE	PAGE NO.
Acknowledgment	ii
Declaration	iii
Certificate	iv
Abstract	v
Contents	vi
List of Tables	viii
List of Figures	ix

CHAPTER 1

INTRODUCTION..... 1

1.1. Background of benzodiazepine derivatives and its applications

1.1.1. Historical background of Benzodiazepine

1.1.2. Natural occurrence of Benzodiazepine

1.1.3. Physical properties of Benzodiazepine

1.1.4. Chemical structure of Benzodiazepine and its applications

1.2. Importance of sustainable chemistry in synthesis

1.2.1. Environmental and Economic Benefits

1.2.2. Catalytic Innovations

1.2.3. Synthetic Efficiency

1.2.4. Pharmaceutical applications

1.3 Brief comparison of traditional and green synthesis methods

CHAPTER 2

LITERATURE REVIEW..... 7

2.1 Overview of traditional synthesis methods

2.2 Green Synthesis Approaches

2.3 Deep Eutectic Solvent (DES)

2.4 Research gap

2.5 Objectives of the Study

CHAPTER 3

EXPERIMENTAL WORK:

Green Synthesis of Benzodiazepines Derivatives Using DES……20

3.1 Materials and methods

3.2 Preparation of DES

3.2.1 Synthesis of Choline Chloride- Urea DES

3.2.2 Synthesis of Chloline chloride- glycerol DES

3.2.3 Synthesis of Guanidinium Chloride-Urea DES

3.3 Optimization of DES

3.4 Characterization

CHAPTER 4

RESULTS & DISCUSSION..... 27

4.1 Choline Chloride- Urea DES

4.2 Choline chloride- glycerol DES

4.3 Guanidinium Chloride-Urea DES

CHAPTER 5

FUTURE PROSPECTS, CONCLUSION & SOCIAL IMPACT 30

REFERENCES..... 33

LIST OF TABLES

Table 1: Comparative Overview of Traditional vs. Green Synthesis Methods for Quinoline Derivatives
Table 1:

LIST OF FIGURES

FIGURE 1: Different sources of Quinoline

FIGURE 2: Pharmacologically Active Quinoline Derivatives: Structural Overview

FIGURE 3: Key Domains Highlighting the Importance of Sustainable Chemistry in the Synthesis of Quinoline Derivatives.

FIGURE 4: Traditional quinoline methods with respective key reactants

FIGURE 5: Green synthesis approaches for quinoline derivatives

FIGURE 6: Properties, principles, and applications of deep eutectic solvents (DES)

FIGURE 7: Classification of DESs and its Applications

FIGURE 8: Structures of the HBAs and HBDs used for deep eutectic solvent formation

FIGURE 9: Tartaric acid–imidazole DES prepared via heating and mixing

FIGURE 10: Maltose-urea DES preparation via heating and mixing

FIGURE 11: N-Hydroxysuccinimide-Citric acid DES prepared via heating and mixing

FIGURE 12: N-Hydroxysuccinimide-imidazole acid DES prepared via heating and mixing

FIGURE 13: Preparation of DES

CHAPTER 1
INTRODUCTION

1.1 Background of benzodiazepine derivatives and their applications

1.1.1 Historical background of Benzodiazepines

The discovery of benzodiazepines is credited to Leo Sternbach at Hoffmann–La Roche. In 1955, while working on heterocyclic compounds, Sternbach synthesized chlordiazepoxide, the first benzodiazepine derivative, was one of the first therapeutic applications of benzodiazepines derivatives. Pharmacological screening of chlordiazepoxide revealed that it possessed strong anxiolytic, sedative, muscle relaxant, and anticonvulsant properties with comparatively lower toxicity than barbiturates. The compound was clinically introduced under the trade name Librium, in 1960.[6] Their discovery significantly advanced the understanding of GABAergic neurotransmission and remains a landmark achievement in heterocyclic and medicinal chemistry.

Benzodiazepine-based structures have been essential to pharmaceutical chemistry over the years, acting as scaffolds for a variety of drug classes. These include anti-inflammatory,[9] antihypertensive,[10] antimalarial,[11,12] anti- depressant,[13,14,15] anticancer,[16,17] anticonvulsant,[18,19] antibacterial,[20] antitubercular,[21,22] anti-proliferative,[23] antifungal[24,25] and related neurological disorders.

1.1.2 Natural occurrence of Benzodiazepines

Originally, benzodiazepines were thought to exist only as synthetic pharmaceutical compounds. However, Subsequent scientific studies, identified several naturally occurring benzodiazepine-like substances in many biological systems. Small amounts of these compounds have been isolated from plants, microbes, animals, and even in human tissues. These naturally occurring receptor-binding compounds are collectively referred to as "endozepines." [Braestrup, C.; Squires, R. F. "Endogenous Benzodiazepine Receptor Ligands in Brain." *Nature*, 1977, **266**, 732–734.]

Naturally occurring benzodiazepine derivatives have been identified in both plants and microorganisms. Benzodiazepine motifs are found in trace amount in Carod plants (Ceratonia siliqua) and are used as anxiolytics, hypnotics and as chemo-anticipatory agents (Avallone,

Cosenza, Farina, Baraldi, & Baraldi, 2002). Benzodiazepines can also be found in Mimosa pudica (touch me not leaves). In addition, they can also be extracted from biological fluid (Westland & Dorman, 2013) and Erythrina velutina Willd (Fabaceae plant) (Danta et al., 2004; Ribeiro, Onusic, Poltronieri, & Viana, 2006; Teixeira-Silva et al., 2008). However, in 1986, benzodiazepine was first established in mammalian tissues (Burman et al., 2019; Sand et al., 2000). [Olayinka O. Tolu-Bolaji, Samuel O. Sojinu, Adebola P. Okedere & Olayinka O. Ajani (2022) A review on the chemistry and pharmacological properties of benzodiazepine motifs in drug design, Arab Journal of Basic and Applied Sciences, 29:1, 287-306, DOI: 10.1080/25765299.2022.2117677]. Several *Streptomyces* species produce secondary metabolites containing benzodiazepine frameworks. One of the most important examples is anthramycin isolated from Streptomyces refuineus. Ability to bind covalently with DNA, Anthramycin exhibits potent antitumor and antimicrobial activity. These findings suggest that benzodiazepine-related structures may occur naturally in biological systems, although the isolated concentrations are extremely low. The exact biosynthetic origin of these compounds remains under investigation, but microbial metabolism and endogenous biochemical pathways are considered possible sources. [* Möhler, H.; Okada, T. "Benzodiazepine Receptor: Demonstration in the Central Nervous System." *Science*, 1977, **198**, 849–851. *Ferrarese, C.; Appollonio, I.; Frigo, M.; et al. "Diazepam-Like Compounds in the Human Brain." *Brain Research*, 1989, **483**, 339–344. *Leimgruber, W.; Batcho, A. D.; Schenker, F.; et al. "Anthramycin, a New Antitumor Antibiotic." *Journal of the American Chemical Society*, 1965, **87**, 5791–5793. * Thurston, D. E. "Chemistry and Pharmacology of Pyrrolo[2,1-c][1,4]benzodiazepines." *Chemical Reviews*, 1993, **93**, 943–970]

1.1.3 Physical properties of Benzodiazepines.

The physical properties of benzodiazepines vary depending on the nature and position of substituents attached to the benzodiazepine nucleus. Most benzodiazepines exist as white or pale-yellow crystalline solids with a slightly bitter taste. They are generally odorless and exhibit good stability under normal storage conditions. They are weakly basic in narture because of the presence of nitrogen atoms in the diazepine ring and most of them possess relatively high melting points due to their aromatic and heterocyclic structures. Benzodiazepines are generally insoluble or sparingly soluble in water due to hydrophobic aromatic ring system

but readily soluble in organic solvents such as ethanol, methanol, chloroform, acetone, and dimethyl sulfoxide (DMSO). The lipophilic nature of benzodiazepines along with electron-

withdrawing groups such as chlorine or nitro substituents also influences their physicochemical properties, receptor affinity, and biological potency.

The general physicochemical behavior of benzodiazepines, including melting point, solubility, lipophilicity, and spectral characteristics, is highly important in drug design, pharmaceutical formulation and medicinal chemistry, as these properties directly influence absorption, distribution, metabolism, and therapeutic activity.

[*Sternbach, L. H. "The Benzodiazepine Story." *Journal of Medicinal Chemistry*, 1979, **22**(1), 1–7. * Mandrioli, R.; Mercolini, L.; Raggi, M. A. "Benzodiazepine Metabolism: An Analytical Perspective." *Current Drug Metabolism*, 2008, **9**, 827–844. * Katzung, B. G. *Basic and Clinical Pharmacology*, 14th ed.; McGraw-Hill Education: New York, 2018.

*Moffat, A. C.; Osselton, M. D.; Widdop, B. *Clarke's Analysis of Drugs and Poisons*, 4th ed.; Pharmaceutical Press: London, 2011. * Rang, H. P.; Dale, M. M.; Ritter, J. M.; Flower, R. J. *Rang and Dale's Pharmacology*, 8th ed.; Elsevier: London, 2016.]

1.1.4 Chemical structure of Benzodiazepines and its applications

Benzodiazepines are two ring systems containing a benzene ring fused with a seven-membered diazepine ring with two nitrogen atoms at different positions resulting in different moiety structure along with their names.[7] Based on the position of nitrogen atoms in the ring, benzodiazepines can be classified into six major structural forms: 5H-1,2-benzodiazepine (1), 1H-1,3-benzodiazepine (2), 3H-1,5-benzodiazepine (3), 3H-1,4-benzodiazepine (4), 5H-2,3-benzodiazepine (5), and 1H-2,4-benzodiazepine (6) (Figure 1).[8]

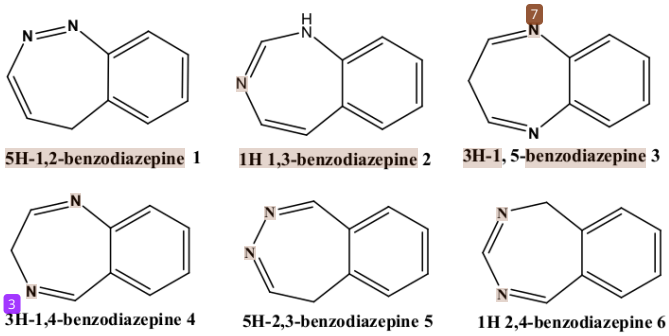


Figure 1. Six major ring structures of BZDs with respect to their nitrogen positions.

Owing vast pharmacological importance these compounds extensively investigated from recent years. Some of the psychotropic properties[6] such as hypnotics, anxiolytics, anticonvulsants, and muscle relaxants. The pharmacological effects of benzodiazepines can be understood by considering the role of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Currently, over 21 of the nearly 40 Benzodiazepines, have received global approval, some of them are **Clobazam 7, C1414S 8, Navirapine 9, Diazepam 10, Lorazepam 11, Temazepam 12, Oxazepam 13, Clorazepate 14** (Figure 2).[42]

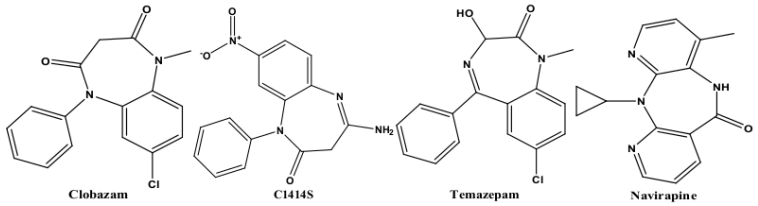


Figure 2. Some selected commercial benzodiazepine-based drug.

1.2 Importance of sustainable chemistry in synthesis

Sustainable chemistry is very important in today's world, and when we use it in the synthesis of benzodiazepine derivatives, it makes the process much more efficient. At the same time, it reduces the reaction time, requires less energy, and does not produce toxic by-products. Therefore, there is no need for extensive waste management. In this way, we are following the principles of green chemistry, which makes the overall synthesis more sustainable and efficient.

Earlier, traditional approaches were widely used, in which large amounts of toxic substances were involved, high energy input was required, and many unnecessary by-products were generated. These factors made the entire process expensive and environmentally harmful. However, since we have started employing sustainable methods, our approaches have become more environmentally friendly. We are placing greater emphasis on atom economy and the use of renewable raw materials, which helps prevent pollution at its source rather than treating it afterwards. Although many developments have already been made, there are still numerous advancements expected in the future.

- **Environmental and Economic Benefits**

- **Pharmaceutical Applications**
- **Catalytic Innovations**
- **Synthetic Efficiency**
- **Future Directions**

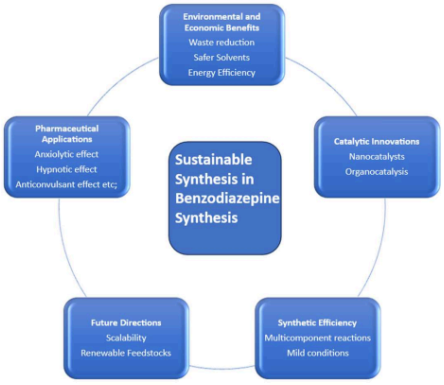


Figure 1: Major areas Highlighting the Importance of Sustainable Chemistry in the Synthesis of Benzodiazepine Derivatives.

1.2.1 Environmental and Economic Benefits

Waste minimization: Methods such as microwave-assisted synthesis and solvent-free synthesis for benzodiazepine production reduce waste to almost nothing.

Biomass-derived solvents such as ethanol, clean organic solvents, and particulates from MCRs, are non-toxic solvents. The elimination of solvent frees up waste as well.

Energy efficiency: Using the techniques such as microwave-assisted and ultrasonication reduces the requirement of excessive energy along with reduction in reaction time such as Microwave-assisted synthesis of 1,5-benzodiazepines Using MCM-41, reaction afforded excellent yields (90–98%) within 5–8 minutes under solvent free condition.

1.2.2 Catalytic Innovations

Nanocatalysts: Use of catalyst like Fe-MCM-41-IL and copper-(ll) clay as reusable nanoparticles leads to rapid reactions (5 to 15 minutes) and a high-end product (up to 95%). These catalysts can be used many times, which saves on cost and has the added benefit of damage reduction to the earth.

Natural catalyst: Use of Volcanic ash and FC/AC (ferrocene supported activated carbon) and Volcanic ash for the synthesis leads high yield upto 86% at 130^0C for 20 min and 90% at 90^0C respectively.

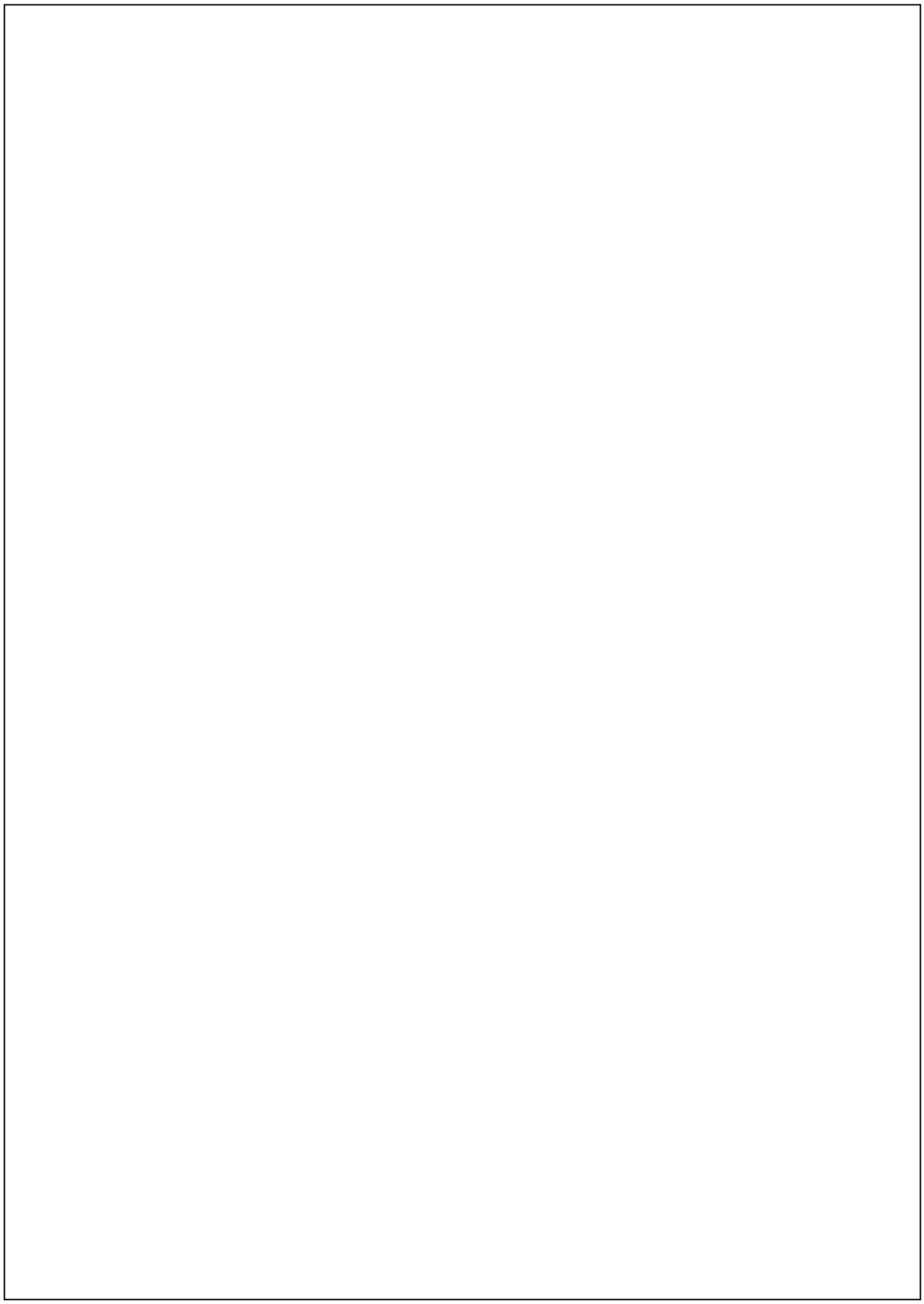
1.2.3 Synthetic Efficiency

Multicomponent reactions: More efficient use of resources (Convergent MCRs) improve physical economy, such as synthesis of 1,5 benzodiazepines in presence of DABCO- diacetate as a catalyst gives 93 - 98% product yield in 8 -15 min at room temperature.

1.2.4 Pharmaceutical Applications

High medicinal importance and large-scale demand for benzodiazepines require environmentally safer and sustainable production methods to ensure sustainable pharmaceutical development. The development of green synthetic strategies that align with the principles of sustainable and environmentally benign chemistry is the requirement of today.

1.3 Brief comparison of traditional and green synthesis methods



CHAPTER 2

LITERATURE REVIEW

2.1 Overview of Conventional synthesis methods

Benzodiazepines are the one of the most widely known class of psychoactive compounds and significant class of heterocycle compound, which is traditionally synthesized by using classical organic route that is condensation, cyclisation and rearrangement processes. These reaction were often useful but carried out under extreme reaction condition that is require strong acidic or basic medium and sometimes elevated temperature. Although method provide the discovery of important therapeutic drug such as chlordiazepoxide and diazepam but these methods remain limited due to severe impact on environment, higher reaction time, provide poor yield.

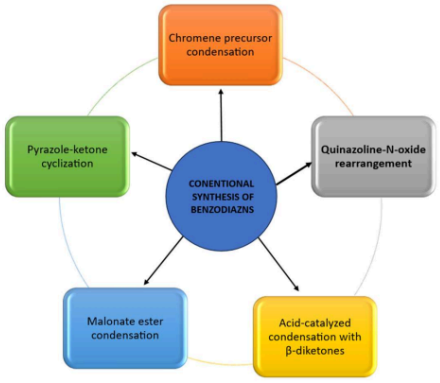
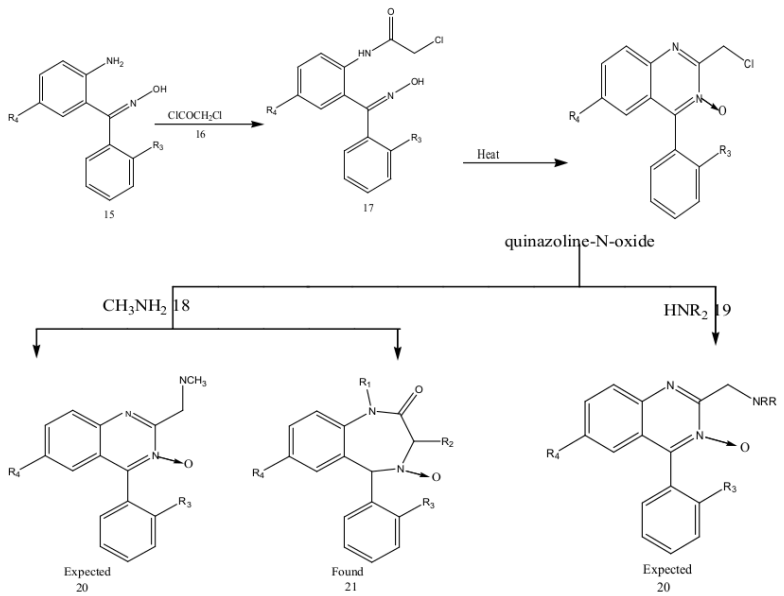


Figure 2: Major Conventional Benzodiazepines synthesis methods.

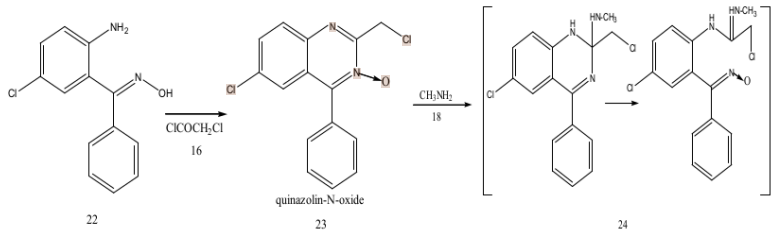
1. **Quinazoline-N-oxide rearrangement**

First benzodiazepine was accidentally discovered during the study of Quinazoline-N-oxide. This synthesis includes formation of an oxime and the intermediate chloroacetamide and intra-molecular cyclization. Though reaction has significant importance but it is environmentally and unfavourable involve complex reaction.

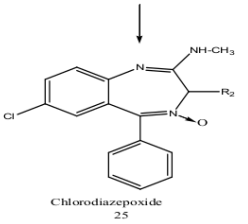


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Scheme 1(a): Synthesis of 1,4-BZDs.[47]



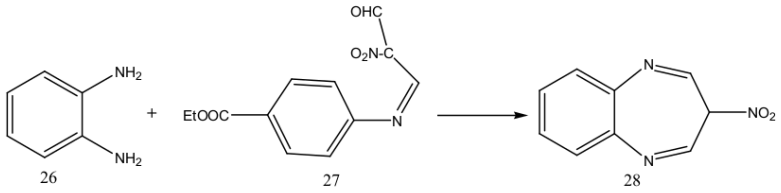
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Scheme 1(b): Synthesis of Chlordiazepoxide.[48]

2. Acid-catalysed condensation with β-diketones

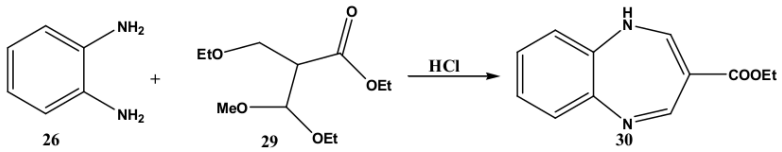
Formulated by Thiele and Stemming by acid catalysed condensation reaction of o-phenylenediamine with acetylacetone in acidic medium to provide 2,4-dimethyl-1,5 benzodiazepine as a primary product. However, this method was simple but required strong acidic condition.



Scheme 2. Synthesis of 2,4-dimethyl-1,5-benzodiazepine**.**

3. Malonate ester condensation

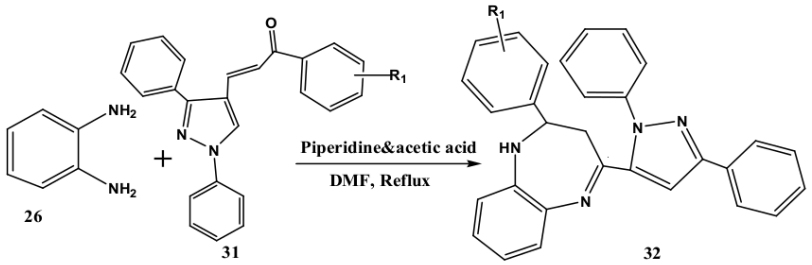
Demonstrated by Taka et al, through the condensation of o-phenylenediamine with malonate ester. Even though method was novel and expanded the structural diversity of benzodiazepines but it requires reflex in organic solvent and multi-step synthesis, protected intermediate, long reaction time also provide poor which highlights the method limitations.



Scheme 3. Synthesis of 3-ethoxycarbonyl-substituted benzodiazepine**.**

4. **Pyrazole-ketone cyclization**

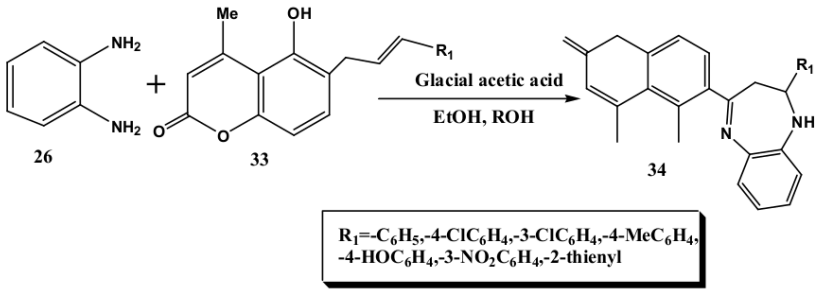
Demonstrated by Desai and co-workers. They synthesize pyrazole substituted Benzodiazepines using the reaction of o-phenylenediamine and α, β unsaturated ketone. Although reaction provide a structural variation of Benzodiazepines but require long reaction time and toxic reaction condition. however, product yield was moderate.



Scheme 4. Synthesis of pyrazole-bearing benzodiazepines.

5. **Chromene precursor condensation**

Toan et al, synthesized of chromene fused benzodiazepine using condensation reaction of o-phenylenediamine and chromene derived α, β unsaturated ketone. This method enables structural diversification but involves multistep process and provide poor product yield.



Scheme 5. Synthesis of chromene-containing 1H-1,5-benzodiazepines

Table 1: Conventional methods for synthesis of Benzodiazepines derivative and their Advantages and Disadvantages.

Method	Reaction Type	Major Reactants	Advantages	Disadvantages	Ref.
Quinazoline-N-oxide rearrangement	Rearrangement	2-amino benzophenone, oxime, chloroacetamide	Historical importance (first benzodiazepine, chlordiazepoxide)	Complex, multistep reaction moderate yield	
Acid-catalysed condensation with β-diketones	Condensation	*o*-phenylenediamine, β-diketones (e.g. acetylacetone)	Simple, direct synthesis of 1,5-Benzodiazepines		
Malonate ester condensation	Condensation	*o*-phenylenediamine, functionalized malonate esters	Introduces ester at 3-position, expands structural diversity		
Pyrazole-ketone cyclization	Cyclization	*o*-phenylenediamine, α,β-unsaturated ketones (pyrazole-substituted)	Expanded the structural diversity of benzodiazepines		
Chromene precursor condensation	Condensation	Chromene-derived α,β-unsaturated ketones, *o*-phenylenediamine	Enables structural diversification		

2.2 Green Synthesis Approaches

in recent years, the diverse nature of chemical synthesis required the development of greener pathways to achieve sustainability, since the concept is totally based on the 12 principles of Green Chemistry, which focus mainly on waste minimization, atom economy, safe solvents, and energy minimization. Recently, green techniques gained significant importance in the synthesis of heterocyclic chemistry. Therefore, the synthesis of benzodiazepines has majorly shifted towards green methodology. Conventional synthesis of benzodiazepines is frequently associated with the use of toxic solvents, extreme reaction conditions, prolonged heating, and multiple steps, which ultimately cause environmental damage. To conquer this problem, researchers introduced multiple greener methodologies, including microwave-assisted synthesis, ultrasound-free protocols, and use of green catalysts and solvent such as Deep eutatic solvent



Figure 3: Green synthesis approaches for Benzodiazepines derivatives

1. Microwave-Assisted Synthesis

Microwave-assisted synthesis plays a vital role and is one of the most widely accepted green methodologies in organic synthesis. It delivers microwave irradiation to the chemical reaction, providing direct energy to the reactants resulting in a significant reduction in reaction time and enhanced reaction rates. Compared to conventional heating, microwave-assisted synthesis requires less energy consumption and delivers higher product yields. The uniform and rapid heating conditions also allow specific temperature control. Additionally, microwave-assisted synthesis can facilitate solvent-free conditions and the use of recyclable catalytic systems, thereby reduce the use of toxic solvents and increasing overall efficiency. Ultimately microwave-assisted synthesis provides an environmentally friendly approach to chemical synthesis. Microwave-assisted synthesis has been widely used in benzodiazepine synthesis. For instance, Young et al. and Shaikh et al. reported efficient microwave-assisted protocols for benzodiazepine synthesis under microwave irradiation, affording the better yield of desired products in lesser reaction times [Ref]. Their studies highlight the emerging application of microwave technology for the green synthesis of benzodiazepines.

2. Solvent-Free Reactions

Solvent-free synthesis has become a prominent green synthesis technique in modern organic chemistry. Earlier, it was believed that no reaction would be possible without the use of solvents. The use of volatile solvents and hazardous reagents is considered highly toxic to the environment, and solvents contribute a major portion of chemical waste during the synthesis process. However, under solvent-free conditions, reactants interact directly without any medium, often resulting in an increased reaction rate, improved atom economy, and reduced energy consumption. Furthermore, avoiding volatile and toxic solvents protects the environment from solvent related toxicity. Therefore, solvent-free techniques are widely popular in heterocyclic synthesis. They also have representative applications in the synthesis of a very well-known heterocycle that is benzodiazepines. For example, Jamatia et al. reported a condensation reaction using graphite oxide as a catalyst under solvent-free conditions, achieving excellent yields [Ref]. This study highlights the advantages of solvent-free methodology in efficient green benzodiazepine synthesis.

3. GREEN SOLVENT

The development of sustainable organic synthetic strategies with the least use of hazardous organic solvents is a major concern of green chemistry researchers. In recent years, various approaches have been developed to synthesize organic compounds using minimal or even no hazardous solvents. One of the best methods is the use of **green solvents**, which are environmentally friendly and have minimal impact on the environment. Green solvents such as water, ethanol, glycerol, ionic liquids, and eutectic solvents are considered less toxic and biodegradable. Among these, water and ethanol are more popular and are considered versatile solvents since they are abundant, low-cost, and environmentally favourable.

The purpose of using green solvents is not limited to reducing toxicity but also to enhance reaction rates, decrease reaction time, and improve product yield. Hence, this method is widely used in the synthesis of heterocycles, including benzodiazepines. For instance, **Taha and Rashid** carried out a microwave-assisted synthesis of 1,5-benzodiazepine derivatives using ethanol as the reaction solvent. This protocol was environmentally benign and produced better yields compared to other solvents [Ref]. This study demonstrates the advantages of green solvents in green benzodiazepine synthesis.

4. **Green catalyst**

Catalysts play an important role in the synthesis of organic compounds. Meanwhile, using toxic catalysts that involve hazardous reagents, non-reusable systems, and heavy metals often give rise to environmental problems. Therefore, the development of **green catalysts** has become a major aspect for green chemistry researchers.

A green catalyst is designed as a catalytic system that minimizes environmental problems by reducing chemical waste and enabling recycling processes. Basically, it is strongly aligned with the 12 principles of Green Chemistry**.**

In benzodiazepine synthesis, multiple types of green catalysts have been explored. For instance, nanostructured catalysts developed by **Ghalavand and co-workers** offer several advantages, including high catalytic efficiency, short reaction time, and excellent yields under mild reaction conditions [Ref]. This example highlights the importance of green catalysts in heterocyclic chemistry, particularly benzodiazepine synthesis.

5. Ultrasonication

In organic synthesis, ultrasonication has appeared as an important green methodology for the synthesis of organic molecules, particularly heterocycles. The application utilizes high-frequency sound waves in the reaction system, resulting in an increased reaction rate and providing better yields through acoustic cavitation. It also offers better selectivity compared to conventional thermal methods.

Additionally, this method becomes more powerful when combined with green solvents and recyclable catalytic systems. Moreover, ultrasonication has multiple advantages, including applications in pharmaceuticals and heterocyclic compound synthesis. An important example in benzodiazepine synthesis was demonstrated by Vajiha Najadshafiee et al**.**, who used **Fe-MCM-41 catalyst under ultrasonic irradiation** for the sustainable synthesis of benzodiazepines. This protocol delivered shorter reaction times and highlighted the advantages of ultrasonication in chemical synthesis.

2.3 Deep Eutectic Solvent

Deep eutectic solvents are one of the classes of eutectic solvents and are considered a new and better type of green solvent. They are typically formed by the combination of a hydrogen bond acceptor, usually a quaternary ammonium salt, with a hydrogen bond donor such as urea, glycol, amide, etc., in a specific ratio. In these solvents, the components are associated through hydrogen bonding, which results in a substantial decrease in lattice energy and a melting point significantly lower than those of the individual components, allowing them to exist in the liquid state at room temperature. Deep eutectic solvents offer several advantages, such as low toxicity, volatility, and cost. They also have high thermal stability and are biodegradable in nature, making them safer and important alternatives to conventional and ionic liquid solvents.

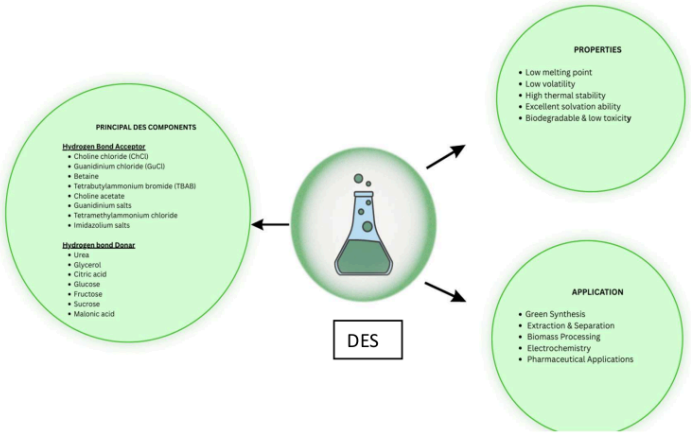


Figure 4: Properties, Principles, and Applications of Deep Eutectic Solvents (DES)

Key mechanism:

- Hydrogen Bond Network Formation: A hydrogen bond donor and the halide anion (X^-) of the hydrogen bond acceptor, often a halide salt, form hydrogen bonds with donor groups such as –OH, –COOH, and $–NH_2$. Because of these interactions, there

is creation of a strong hydrogen bonding network which causes stabilization of the liquid state.

- Charge Delocalization and Lattice Disruption: The interaction between ionic species, donor–acceptor interaction, disperses charge across the network. This causes disruption in the ordered crystal lattice, leading to lowering of the lattice energy.

- Lowering of Melting Point and Liquid Stabilization: Due to reduced lattice energy and strong hydrogen bonding, the mixture shows a significantly lower melting point than those of its pure components. This results in the Deep Eutectic Solvent existing in the liquid state at room temperature even though the individual components were solids. Ref

General formula of Deep Eutectic Solvent:

$$Cat^{+}X^{-}.zY$$

Cat^{+}: Stand for all quaternary ions (Phosphonium, ammonium and sulfonium)
X^{-}: Indicates Lewis Base Specifically halide anion(X^{-}).
Y: Stand for Lewis or Bronsted acid.
z : Represents the number of X molecule

TYPE	GENERAL FORMULA	EXAMPLE	MAJOR APPLICATIONS
Type I	$Cat^{+}X^{-}\cdot zMCl_x$	Choline chloride/$ZnCl_2$	Metal processing, Catalysis
Type II	$Cat^{+}X^{-}\cdot zMCl_x\cdot yH_2O$	Choline chloride/$CrCl_3\cdot 6H_2O$	Electroplating, industrial processing
Type III	$Cat^{+}X^{-}\cdot zRZ$	Choline chloride/Urea (Reline)	Green synthesis, Extraction, biomass processing, Pharmaceuticals
Type IV	$MCl_x + RZ \rightleftharpoons MCl_{x-1}^{+}\cdot RZ + MCl_{x+1}^{-}$	$ZnCl_2$/Urea	Nanomaterial synthesis, metal oxide processing
NADES	HBA + Natural HBD	Choline chloride/Citric acid	Natural product extraction, food, cosmetics, drug delivery

Figure 5: Classification of DESs and its Applications

2.4 Research Gap

Synthesis of benzodiazepines is important because of its large application in medicinal chemistry. Several synthetic routes, both conventional and green, were reported. Among these, conventional synthesis usually involves toxic solvents, hazardous reagents, and elevated temperature, while green synthesis approaches such as Deep Eutectic Solvent, microwave-assisted synthesis, solvent-free method, green catalyst, and ultrasonification were highly effective and offered numerous advantages. Among these, Deep Eutectic Solvents were not much explored as reaction solvents for benzodiazepine synthesis. Deep Eutectic Solvents stand out due to their eco-friendly nature, tunable properties, and adjustable characteristics. Therefore, our work is to study the Deep Eutectic Solvent as a reaction medium for the synthesis of benzodiazepines.

Possible advantages of this study:

- Non-toxic medium: Deep Eutectic Solvents are eco-friendly, biodegradable, and recyclable. They can reduce toxicity caused by solvents.
- Dual role(Solvent and Catalyst): The large hydrogen bonding network in Deep Eutectic Solvents may stabilize the intermediate. They can act as both solvent and catalyst.
- Improved efficiency: Deep Eutectic Solvents can improve selectivity and also provide higher yield in shorter reaction time.
- Cost reduction: Deep Eutectic Solvents are inexpensive and very easy to prepare.

Our work tries to overcome this gap and lead to a more sustainable method for the synthesis of benzodiazepine and its derivatives.

EXPERIMENTAL WORK:

Green Synthesis of Benzodiazepines Derivatives Using Deep Eutectic Solvents (Des)

Common method of synthesis of Deep Eutectic Solvent is mixing of hydrogen bond acceptors and hydrogen bond Donar using general method like heating, evaporation and freeze-drying.

3.1 Materials and Methods

The chemical structures of the hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) used in this study are presented in Fig. 8. All chemicals were purchased from local suppliers and used as received, without any additional purification.

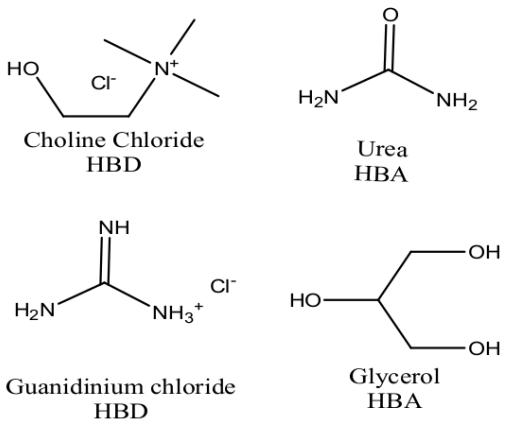


Figure 5: Structures of the HBAs and HBDs used for deep eutectic solvent formation

3.2 Preparation of DES

The Deep Eutectic Solvent used in this work was prepared and reported previously. For this DES combination, the required amounts of HBD and HBA were weighed carefully and placed in a clean, dry vial. The solution mixture was stirred and heated gently until a clear, uniform liquid was formed and then cooled at room temperature. After that, the DES was stored in sealed vials.

3.2.1 Synthesis of Choline Chloride and Urea DES

The Choline Chloride–Urea Deep Eutectic Solvent was synthesized carefully by taking Choline Chloride and Urea according to molar ratios of 1:2, 1:3, and 1:4. Choline chloride (0.13 g) with Urea (0.12 g) were weighed for 1:2; similarly, for 1:3 and 1:4, Urea was weighed 0.18 g and 0.24 g respectively. The weighed compounds were transferred to clean glass vials, and a magnetic bead was added to each vial to ensure uniform mixing. A magnetic stirrer was introduced, and the vials containing the mixtures were securely placed on a heating plate fitted with a temperature controller and magnetic stirrer operating at 600 rpm.

For the 1:2 molar ratio and 1:3 molar ratio, the mixtures were heated and stirred at 60 °C for 60 minutes.

For the 1:4 molar ratio, the mixture was heated and stirred at three different temperatures: 60 °C, 80 °C, and 100 °C, each for 120 minutes. After each cycle of heating, the molten mixture of solids was allowed to cool naturally at room temperature, which resulted in the formation of a homogeneous liquid Deep Eutectic Solvent. After that, the DES was carefully evaluated for yield.



Figure 6: Choline Chloride-Urea DES prepared via heating and mixing

3.2.2 Synthesis of Choline Chloride and Glycerol DES

The Choline Chloride–Glycerol Deep Eutectic Solvent was synthesized carefully by taking Choline Chloride and Glycerol according to molar ratios of 1:1, 1:2, and 1:3. Choline chloride (0.13 g) with Glycerol (0.092 g) were weighed for 1:1 ratio; similarly, for 1:2 and 1:3, Glycerol was weighed 0.184 g and 0.276 g respectively. The weighed compounds were transferred to clean glass vials; a magnetic bead was added to each of the vials to ensure uniform mixing. Also, a magnetic stirrer was introduced, and the vials containing the mixtures were securely placed on a heating plate fitted with a temperature controller and magnetic stirrer operating at 500 rpm.

For the 1:1 molar ratio and 1:3 molar ratio, the mixtures were heated and stirred at 80 °C for 45 minutes.

For the 1:2molar ratio, the mixture was heated and stirred at three different temperatures: 80 °C, 100 °C, and 120 °C, each for 60 minutes. After each cycle of heating, the molten mixture of solids was allowed to cool naturally at room temperature, which resulted in the formation of a homogeneous liquid Deep Eutectic Solvent. After that, the DES was carefully evaluated for yield.



Figure 7: Choline Chloride–Glycerol DES preparation via heating and mixing

3.2.3 Synthesis of Guanidinium Chloride–Urea DES

The Guanidinium Chloride–Urea Deep Eutectic Solvent was synthesized carefully by taking Guanidinium Chloride and Urea according to molar ratios of 1:1, 1:2, and 1:3. Guanidinium chloride (0.13 g) with Urea (0.12 g) were weighed for 1:1; similarly, for 1:2 and 1:3, Urea was weighed 0.18 g and 0.24 g respectively. The weighed compounds were transferred to clean glass vials, and a magnetic bead was added to each vial to ensure uniform mixing. A magnetic stirrer was introduced, and the vials containing the mixtures were securely placed on a heating plate fitted with a temperature controller and magnetic stirrer operating at 500 rpm.

For the 1:1 molar ratio and 1:3 molar ratio, the mixtures were heated and stirred at 60 °C for 40 minutes.

For the 1:2 molar ratio, the mixture was heated and stirred at three different temperatures: 60 °C, 80 °C, and 100 °C, each for 60minutes. After each cycle of heating, the molten mixture of solids was allowed to cool naturally at room temperature, which resulted in the formation of a homogeneous liquid Deep Eutectic Solvent. After that, the DES was carefully evaluated for yield.



Figure 8: Guanidinium Chloride–Urea DES prepared via heating and mixing

3.3 Optimization of DES

The synthesis conditions, including the molar ratio of Choline Chloride–Urea DES, reaction temperature, and time, were optimized. The investigated parameters are summarized in Table 3.

Table 2 Optimization studies Choline Chloride–Urea for DES

S. No.	Choline Chloride-Urea	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:2	60	600	60	58
2.	1:3	60	600	60	66
3.	1:4	120	600	60	82
4.	1:4	120	600	80	90
5.	1:4	120	600	90	85

The optimization of molar ratio, reaction temperature, and time was carried out for the synthesis of the Choline Chloride–Glycerol DES system as shown in Table 4.

Table 3 Optimization studies for Choline Chloride- Glycerol DES

S. No.	Choline Chloride–Glycerol	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:1	40	600	80	55
2.	1:3	45	600	80	72
3.	1:2	60	600	80	80
4.	1:2	60	600	100	90
5.	1:2	60	600	120	86

The optimization of molar ratio, reaction temperature, and time was carried out for the synthesis of the Guanidinium Chloride- Urea DES system as shown in Table 5.

Table 5 Optimization studies Guanidinium Chloride- Urea DES

S. No.	Guanidinium Chloride–Urea	Reaction time (min)	Magnetic rotation speed (rpm)	Temperature (°C)	Yield (%)
1.	1:1	40	600	60	60
2.	1:3	40	600	60	76
3.	1:2	60	600	60	84
4.	1:2	60	600	80	92
5.	1:2	60	600	100	85

CHAPTER 4

RESULTS & DISCUSSION

The optimisation table has provided valuable insights regarding the synthesis conditions for three different deep eutectic solvents DES; Choline Chloride-Urea DES, Choline Chloride-Glycerol DES, and Guanidinium Chloride- Urea DES. By analysing the data mentioned in the table optimum conditions for achieving the high yield of each DES can be identified.

4.1 Choline Chloride-Urea DES

Using Choline Chloride-Urea in molar ratio of 1:4 with a reaction time of 60 minute at 80^0C, the maximum yield of 90% has achieved by Choline Chloride-Urea DES. Subsequently, raising the temperature to 90^0C has caused the slight decrease in yield from 92% to 85%. Suggesting that extra heat given than required may have a detrimental effect on the stability or the formation of deep eutectic mixtures.
Using molar ratio of 1:2 and 1:3 at a lower temperature of 60^0C, produced lower yield of 58% and 66%, respectively. Observing the given pattern of results, implies that increasing the relative concentration of urea is quite essential for enhancing the effectiveness of DES synthesis.

4.2 Choline Chloride-Glycerol DES

From the analysis of the experimental results, the most appropriate conditions for synthesizing the Choline Chloride-Glycerol DES with excellent yield of 90% was

achieved by molar ratio of 1:2 with a reaction time of 60 minute at a temperature of 100^0C. Suggesting that the efficiency of DES formation greatly depends on these parameters. Raising the temperature from 100^0C to 120^0C minor decrease in the yield has seen, implying that higher temperatures decrease the DES stability as well as formation. The role of other parameter i.e; the concentration of glycerol and its importance in the promotion of DES synthesis has also been depicted from the molar ratio of 1:1 to 1:3 at a fixed temperature of 80^0C. Significantly increasing the yield from 55% to 72% but the excellent yield is obtained on the molar ratio of 1:2. These results highlights the importance of temperature and molar ratio in the effectiveness of Choline Chloride-Glycerol DES.

4.3 Guanidinium Chloride- Urea DES

At the molar ratio combination of 1:2 (guanidinium chloride-urea) with a reaction time of 60 minute at a temperature of 80^0C, maximum yield of 92% is achieved. Interestingly, on increasing the temperature from 80^0C to 100^0C, slight decrease in yield is observed from 92% to 85%. Suggesting the underline importance of temperature in the synthesis and formation of given DES systems. From the analysis of the molar ratio combinations of 1:1 to 1: 3 at a fixed temperature of 60^0C, it was found that the yield is increased with increasing the molar concentration of urea but the most excellent yield results are obtained from the combination of 1:2 molar ratio at 80^0C, as stated before. From this thorough analysis of experimental results the importance of these parameters can be understood and the identification of correct working condition for the synthesis and effectiveness of Guanidinium Chloride- Urea DES systems can be possible.

CHAPTER 5

FUTURE PROSPECTS, CONCLUSION & SOCIAL IMPACT

5.1 Future Prospects

Benzodiazepine derivatives have been an important class of compounds for a long time, especially since their applications in medicinal chemistry and their industrial demand have increased significantly. Researchers have been working extensively on these compounds and continue to explore new approaches to synthesize them with greater efficiency and sustainability. This work here highlights that these derivatives can be synthesized more efficiently through various green synthetic methods. Furthermore, numerous opportunities still exist for methodological improvements and the integration of emerging technologies, which may lead to more sustainable, efficient, and environmentally friendly synthetic strategies in the future. Some of the suggesting directions are;

Expansion of Deep Eutectic Solvents (DES): While our study demonstrates the efficiency of DES in benzodiazepine synthesis, future research can explore novel HBA–HBD combinations with tenable polarity, viscosity, and hydrogen-bonding capacity. This could open pathways for selective synthesis of diverse benzodiazepine derivatives.

Integration with Advanced Green Technologies: Combining DES with other methods such as microwave-assisted, ultrasound-assisted, or photocatalytic, may further reduce reaction times, enhance yields, and improve selectivity. Such hybrid approaches could become benchmarks for sustainable heterocyclic synthesis.

Biocatalysis and Enzyme-Compatible DES: Investigating DES systems which are compatible with enzymes could enable biocatalytic benzodiazepine synthesis for highly selective, mild, and eco-friendly processes.

Scalability and Industrial Application: Future work should focus on scaling DES-based protocols to pilot and industrial levels. Also addressing different challenges such as solvent recovery, recyclability, and cost-effectiveness will be crucial for real-world pharmaceutical manufacturing.

Computational and Mechanistic Studies: Using advanced computational modelling and mechanistic studies can help in predicting the DES behaviour, optimizing reaction conditions, and designing tailor-made solvent systems for specific benzodiazepine derivatives.

Policy and Sustainability Goals: Aligning the future research with global sustainability frameworks (UN SDGs, green chemistry principles) will ensure that the benzodiazepine synthesis contributes not only to scientific progress but also to environmental and societal well-being.

5.2 Conclusion

- With increasing use of Benzodiazepine and its derivative in medicinal chemistry, their synthesis also becomes crucial.
- From a long time, traditional methods are being used to meet the increasing industrial demands but these synthesis methods raise significant concerns as they rely on harsh conditions, toxic chemicals and solvents which further impact sustainability and environment.
- This thesis highlights current and environmentally friendly techniques for the synthesis of benzodiazepine derivatives.
- By using the methods which inclines with the "Principle of Green Chemistry" not only promotes safer synthetic routes for the researcher but also align with the essence of sustainability, which is the scientific and societal call of today.
- Despite of all the advancements till now, difficulties still exist:

  i. Various methods are still only convenient for small setup like laboratory not for bulk industrial production, reliable work in the industrial engineering setup still needed.
  ii. Researches are still going on numerous techniques and they are not yet been refined for general use.

5.3 Social Impact

During the synthesis of benzodiazepine derivatives, we replaced toxic and hazardous solvents with more eco-friendly alternatives particularly Deep Eutectic Solvents (DES). The use of DES not only reduces chemical waste, emissions, and ecological damage but also making the overall process greener and more sustainable. DES are inexpensive, reusable and easy to prepare, which lowers the production cost and ultimately making medicines more affordable for society.

The adoption of such methods also improves occupational and public health safety because workers are exposed to fewer hazardous chemicals ensuring a safer working environment. In addition, cleaner reaction pathways generate fewer by-products, reducing waste management requirements and making the process more cost-effective.

Furthermore, these approaches align with government sustainability policies and the principles of green chemistry. It also promotes societal awareness by encouraging industries and researchers to adopt innovative and environmentally responsible technologies.

Overall, implementing such novel and sustainable methodologies can drive further research with improved industrial efficiency contributing to a healthier environment.

Thesis

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