Prayogik Rasayan

Medium Size Heterocyclic Ring Syntheses in Green Solvent: An Overview

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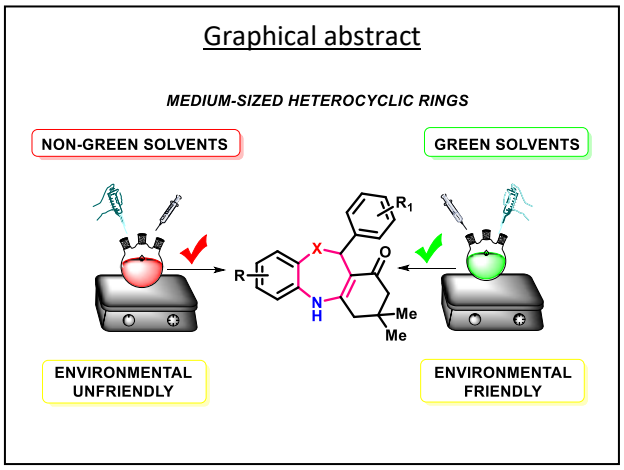
Abstract

Medium sized heterocyclic rings, an important class of organic molecules find their application in various biological arenas. They position themselves in the plethora of medicinally important molecules due its myriad properties, ranging from anti-microbial, anxiolytic, antituberculosis, antipsychotic, anticancer, anticonvulsant, and muscle relaxant. These pharmacologically important molecules fascinate chemists to devise a multitude of synthetic strategies over the past few decades, some of which use toxic, unsafe, harmful solvents. The urgency of this situation cannot be overstated thus immediate shift to green solvent is necessary. Green solvents play a pivotal role in marching towards the green chemistry as they are non-toxic, eco-friendly and ensures the entire life cycle of the product synthesized doesn't pose harm to the environment. Additionally, the use of green solvents can lead to safer working conditions in the laboratories and industrial settings, reducing the risk of chemical exposure and accidents. Thus, our review takes the extensive need for the synthesis of medium sized heterocyclic rings into consideration without leaving behind the ideology and vision for greener environment. Therefore, we have here summarized the relevant publications which aims at the heterocycle syntheses using green solvents over the past decade (2014-2023) and provided insights of the research development to pave way for the safe, eco-friendly, better and greener future.



Keywords: Green Solvents, Medium Size Heterocyclic ring, Benzodiazepine, Azepine, Anticancer, Antimicrobial.

1. Introduction

Solvents play a crucial role in chemical processing and reactions, often serving as catalysts. [1] They are an essential component of the 12 Green Chemistry principles, which have significantly influenced the practices of organic chemists over the past three decades. [2] Solvents have also become increasingly important for chemical process engineers who now design their processes with circularity in mind, following the "10R framework" which emphasizes principles such as recycling, reuse, repair, and remanufacture.[3]

It is even more important to use green solvent in heterocyclic ring synthesis, [4-7] as heterocyclic compounds are found in marine and terrestrial natural products as well as pharmaceutical compounds. Many approved drugs contain heterocyclic ring systems as an active pharmacophore. [8-9]

Many heterocyclic ring systems offer a unique advantage in the pharmaceutical industry for drug development as small

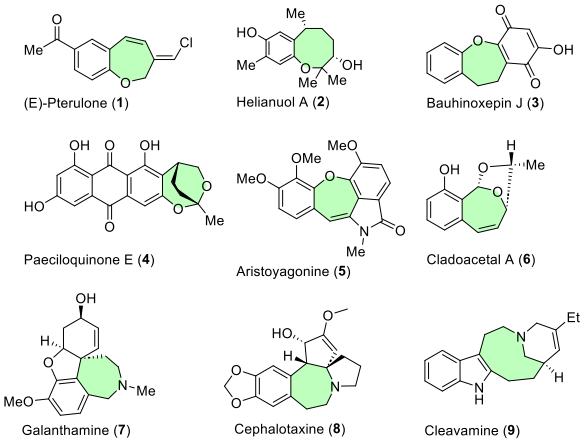


Figure 1: Medicinally significant medium sized benz-annulated heterocyclic ring compounds.

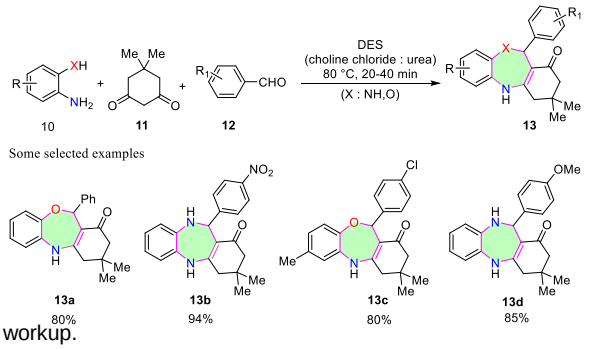
lead compounds.(**Figure 1**) Heterocyclic compounds, when coordinated with metals such as gold(I), rhodium(I), and iridium(I), form complexes with unique structural features and enhanced stability. [10] Recent studies have highlighted their potential antitumor activity, demonstrating significant cytotoxic effects against various cancer cell lines especially when coordinated with metals. [11]

Generally, heterocycles containing **7** to **9** members are frequently regarded as important structural components in pharmaceuticals and natural bio-active compounds.[12-13] They find application in compounds like fungicides, and herbicides.[14-15] Heterocyclic Compounds make up nearly half of all organic compounds that are known, and they also account for 90% of active pharmaceutical drugs.[16] However, the 7 to 9 membered medium-sized heterocyclic compounds have been acclaimed in recent decades as important biologically relevant heterocyclic structural motifs for drug development. Among them, ring systems such as azepine, oxepine, oxosine, azocine, diazepine, oxazepine, dioxepine, thiazepine and their benzofused analogues are found in compounds involved in many physiological activities.[17-21] Over 2000 structures of oxepine and over 350 structures of azepine have been documented to be associated with pharmacological actions.[22-23] Additionally, medium-sized systems with over two heteroatoms from various types have arisen as compounds with significant pharmacological value.

Greener Solvents

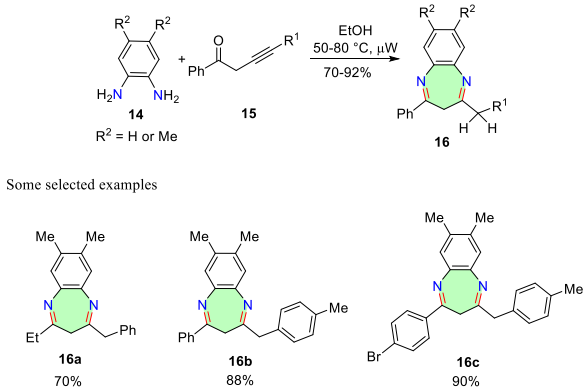
Considerable recognition has been gained by deep eutectic solvents (DESs) in the last decade. DESs reduce the aptness of precursors to crystallize, as they are a combination of high melting-point components that possess strong hydrogen-bonding in liquid form. [24-25] DESs are easy to make, needs inexpensive starting materials, need no purification, exhibit high atom economy features,

Shaabani *et al* have reported the successful synthesis of benzo-fused seven-membered heterocycles using a deep eutectic solvent consisting of a mixture of urea and choline chloride (**Scheme 1**). This method was allowed to produce tricyclic 1,4-benzodiazepines **13b** and **13d** and 1,4-benzoxazepines **13a** and **13c** through a three-component, single enclosure reaction. [27] The reaction conditions were mild, and no additional metals, acid catalysts, or organic solvents were required. The eco-friendly method resulted in rapid completion of the reaction, excellent yields, and easy workup.



Scheme 1. Synthesis of benzo-fused seven-membered heterocycles *via* a three-component reaction in DES.

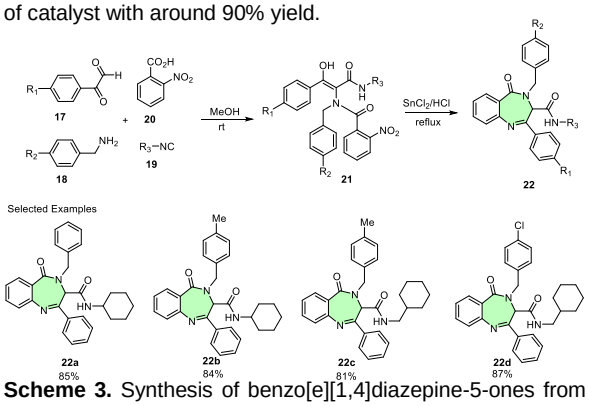
According to Dembinski and colleagues, a condensation reaction between alk-3-yn-1-ones **15** and o-phenylenediamines **14** produced a variety of 2,4-disubstituted 1,5 benzodiazepines 16 with moderate to high yields (70–92%) (Scheme 2).[28] This method allowed for the addition of benzyl-type substituents at the C-2 position of the benzodiazepine. The use of a catalyst-free process made this approach more appealing, as it only involved the formation of two C=N bonds and did not require the separation of enaminone. Generally, the amination reaction proceeded with anti-Markovnikov regio-chemistry with respect to the initial alkyne bond.



Scheme 2. The Synthesis of 1,5-diazepine in ethanol.

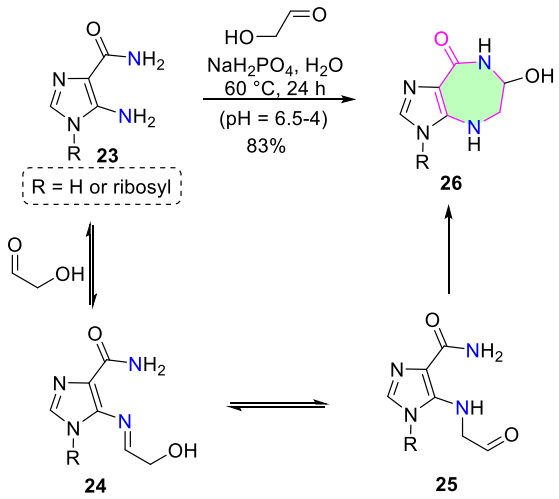
Aromatic starting materials and products were found to be soluble in ethanol, making it the most environmentally friendly solvent for the reaction. With reagent -grade ethanol, which can be easily recovered and recycled, there is no need for moisture-free reaction conditions, and microwave radiation can be used at moderate temperatures.

A Simple and straightforward method has been developed by Valverde and their co-workers to synthesize benzodiazepines **22**. This procedure highlighted the Ugi and cyclization reactions being carried out to form the heterocyclic rings. [29] The imine formation was carried out using substituted benzylamine **18** mixed with arylglyoxal **17** in MeOH. Addition of Alkyl isocyanide**19** and 2-nitrobenzoic acid **20** produced **21,** which on reduction along with subsequent cyclization produced **22** in good yields. This protocol depicts both theoretical and experimental studies of heterocycles and especially over the regio-isomeric benzodiazepines **(22a-22d)** which has been developed through two steps in an economical method, using green solvent such as methanol and easily available reagents (**Scheme 3**). Their regio-isomeric behaviours led them to evaluate their potent drug activities. This method carried out around 70 ˚C exposed good yields, favourable time of reaction, and eco-friendliness of catalyst with around 90% yield.



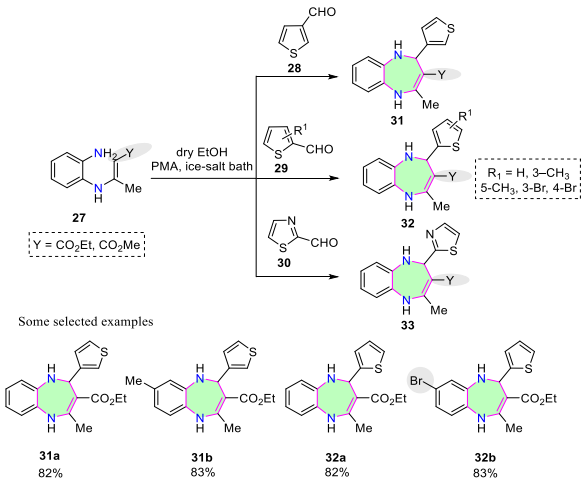
Scheme 3. Synthesis of benzo[e][1,4]diazepine-5-ones from 2-nitrobenzoic acid.

Powner *et al* traced a cost-effective, high-productivity, chromatography-free, and protecting-group-free approach of water-based synthesis of azepinomycin **26**. [30] This approach revealed how binding of amino-imidazole depends on the pH using amadori rearrangement, by which coupling between glycolaldehyde and 5-amino-imidazole-4-carboxamide (AICA) **25** took place, which results in azepinomycin formation (**Scheme 4**). This methodology gave highly efficient sugar-C2′-(5-amino)-imidazole binding of carbohydrates and 5-aminoimidazoles, which are the major precursors for purine nucleobase which is the origin of life and evolution of biospheres.



Scheme 4. Synthesis of Azepinomycin (R = H) azepinomycin riboside (R = ribofuranosyl) in aqueous medium.

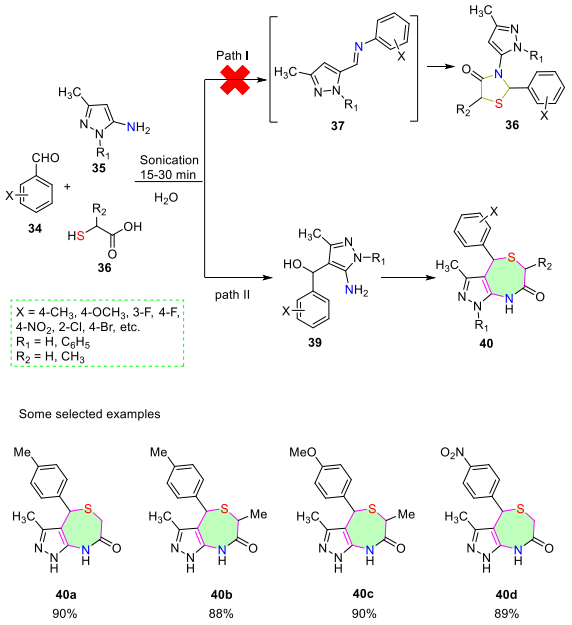
Wang and his colleagues described a method for producing benzodiazepines with a yield of 80-90% by efficiently converting **27** to 1,5-benzodiazepine derivatives (**Scheme 5**). This was achieved by conducting a reaction in ethanol at 0 °C using substituted thiophene aldehyde **28 or 29** or thiazole aldehyde **30** in the presence of phosphomolybdic acid (PMA) as the catalyst. The synthesized 1,5-benzodiazepine derivatives were then tested for in vitro antimicrobial activity against *C. neoformans, C. neoformans clinical isolates*, *C. albicans*, *E. coli,* and *S. aureus.* The majority of the derivatives displayed significant biological activity and demonstrated appreciable strength against all of the tested strains. [31]



Scheme 5. Synthesis of benzodiazepine.

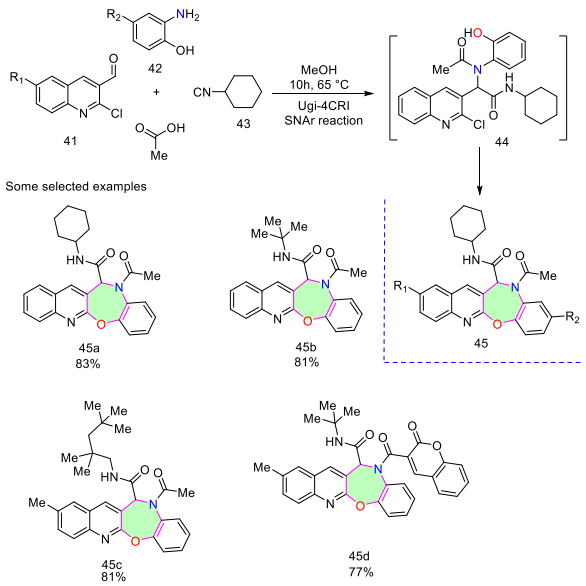
Dandia *et al.* achieved another successful synthesis using ultrasound irradiation to produce pyrazolo[3,4-e][1,4]-thiazepine derivatives **40** (**Scheme 6**). This resulted in a new heptacyclic ring system, rather than the expected pentacyclic

ring system, in a chemo-selective manner without the use of any catalyst in water. The procedure had a shorter reaction time, was easy to operate, and yielded higher results. [32]



Scheme 6. Synthesis of pyrazole[3,4-e][1,4]thiazepine.

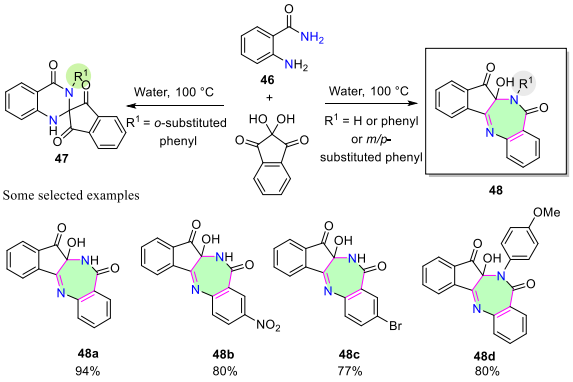
A more suitable and simple method for the synthesis of functionalized diverse quino[2,3-b][1,5]benzoxazepines **45** was provided by Ghandi *et al.* [33]



Scheme 7. Synthesis of quino[2,3-b][1,5]benzoxazepine.

Moderate to good yields may be achieved for these new compounds via single enclosure sequential base-free Ugi-4CR intramolecular aromatic nucleophilic substitution (SN-Ar) reaction from easily accessible starting materials. The reaction begins with the treatment of 2-chloroquinoline-3-carbaldehydes **41** with 2-aminophenol **42**, acetic acid, and cyclohexyl isocyanide 43. This immediately procures quino[2,3-][1,5]benzoxazepine **45** uniquely in good to excellent yield, including refluxing with methanol within 10 hours (**Scheme 7**).

11a-hydroxy-11,11a-dihydrobenzo[e]indeno[2,1-b][1,4]diazepine-10,12-dione derivatives **48** were effectively formed a condensation reaction with ninhydrin, resulting in the expected 3′-phenyl-1′H-spiro[indene-2,2′-quinazoline]-1,3,4′(3′H)-triones **47** (**Scheme 8**). This reaction is environmentally friendly, simple, and does not require a catalyst, and the product can be easily recovered. [34] The reaction proceeds through a nucleophilic attack to the ortho-substituted 2-amino-N-phenylbenzamide derivative's N-phenyl group at the C-2 position. The potential for the creation of biologically and pharmacologically hit molecules from commercially available starting materials was offered by the 1,4-benzodiazepine framework During the reaction, ninhydrin undergoes a nucleophilic attack on C-1 rather than on C-2, demonstrating the remarkable "ortho effect".

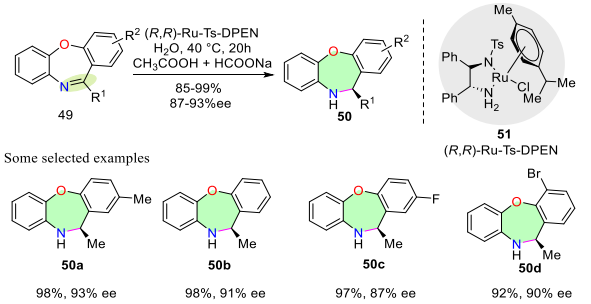


Scheme 8. Synthesis of diazepine dione in water.

Enantiopure amines can be directly accessed through the asymmetric hydrogenation of imines. Aqueous medium asymmetric transfer hydrogen (ATH) reactions are considered to be greener, economically reliable, and simpler to operate compared to molecular hydrogenation. There is no need to maintain an inert atmosphere, and they offer excellent selectivity. These aqueous mediated ATH methods have several advantages, including the fact that there is no need to maintain an inert atmosphere and that the product is obtained with excellent selectivity.

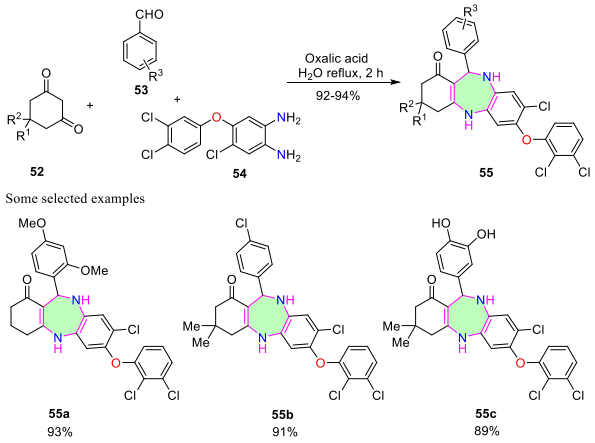
Bhanage *et al* highlighted an additive-free, catalytic, phosphine-free ATH procedure in an aqueous medium for dibenzo[b,f][1,4]oxazepine **50** and its derivatives using an unchanged (R,R)-Ru-TsDPEN complex **51**. The resulting cyclic amines exhibited remarkable enantioselectivities (up to 93% ee) and excellent yields (up to >99%) at 40 °C in 12 hours (**Scheme 9**). This method

follows a greener approach, utilizing a green hydrogen source HCOOH–HCOONa, enabling cost effective synthesis, and employing water as an environmentally friendly solvent.[35]



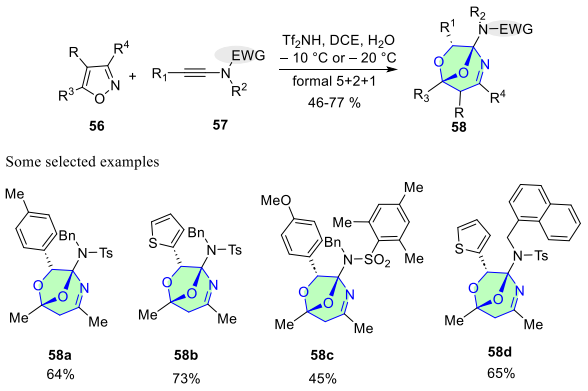
Scheme 9. Benzo[b,f][1,4]oxazepine in water.

Sangshetti and his co-workers proposed a more environmentally friendly method to synthesize a certain fresh dibenz[1,4]-diazepine-1-one derivative **55**.[36] This procedure involved a single enclosure three-component condensation of 1,3-diketones derivative **52** , aromatic aldehydes derivative **53**, and diamines **54** to form dibenz[1,4]-diazepine-1-one **55** with oxalic acid as the catalyst in water as the medium (**Scheme 10**). This method was environmentally sound, economical, and utilized ample amounts of oxalic acid. It also resulted in a satisfactory yield (92–94%), excellent reaction speed, easy work-up, and was simple to operate greener Eco-friendly solvents, moderate reaction conditions added further perks to this methodology.



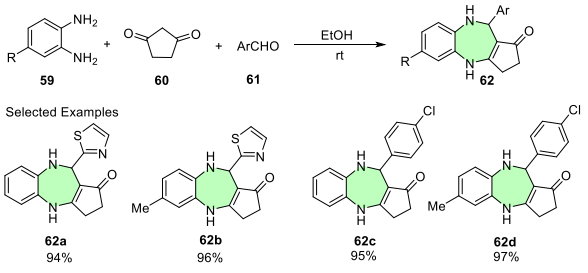
Scheme 10. Dibez[1,4]-diazepine-1-one Synthesis catalysed in Water by Oxalic acid.

Recently, Wan and colleagues presented a more traditional method for the [5+2+1] cycloaddition of ynamides **57** and isoxazoles **56** in water using bronsted acid as the catalyst. This approach offered a cost-effective way to produce oxygen-bridged tetrahydro-1,4- oxazepines **58**, with the oxygen atom originating from water forming the bridge (**Scheme 11**). In addition to advancing ynamides chemistry, this method also focused on designing and developing acid-catalyzed cycloadditions with varying selectivity. [37]



Scheme 11. The reaction of ynamides with 3,5-dimethylisoxazole in water.

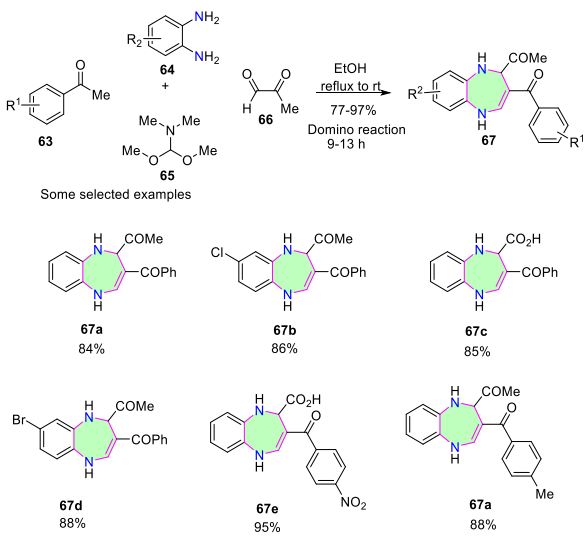
Wang et al have reported the novel protocols for the domino reactions or three component reactions that lead to different heterocyclic systems **(62a-62d)**. One-pot is the strategy used by the group to provide an efficient synthesis of benzodiazepines **62** with tetracyclic and tricyclic system possessing various functional groups. Their work has started with 1,2-phenylenediamine **59**, β-cyclodione **60**, different aldehydes **61**, $CeCl_3$ as promising mild catalyst and the application of ethanol as green solvent, leading to the sustainability concept (**Scheme 12**). [38] This procedure possesses various pros that include, easy availability of materials, simple operation, non-toxicity nature of solvent-EtOH as green solvent etc. They have showcased a greater number of examples with this protocol thus proving the reliability of the procedure.



Scheme 12. Design strategy for the synthesis of benzodiazepines.

To synthesize exceptional 3-acyl-1,5-benzodiazepines **67** that involves a domino reaction of aromatic ketones **63**, N,N-dimethylformamide dimethyl acetal **65**, aldehyde derivatives **66**, and 1,2-phenylenediamine derivative **64** in a single step Wang and co-workers have established an extraordinary approach that is free from any catalyst (scheme 13).[39] Additionally, the formation of four new bonds (one C–

C, two C–N, and one C=C) and one new cycle was achieved through cyclization, nucleophilic substitution, nucleophilic addition, and dehydration reactions via H+ shift, resulting in the development of 3-acyl-1,5-benzodiazepines containing functional groups such as ester, carboxyl, and acyl groups at position-2.

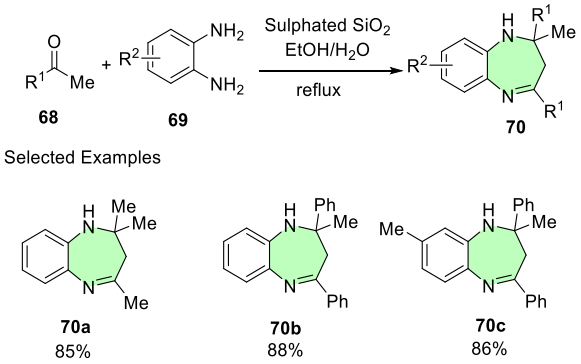


Scheme 13. Synthesis of 3-acyl-1,5-benzodiazepine using ethanol.

The best aspect of this procedure is the use of economical and readily available starting materials, which can be conveniently operated in a single step, and the product can be easily purified with high yields. Remarkably, the procedure offers a wide substrate scope and can yield excellent reactions with many functional groups. The 1,5-benzodiazepines facilitate the formation of compounds with diverse structures for future bioassays and medicinal uses.

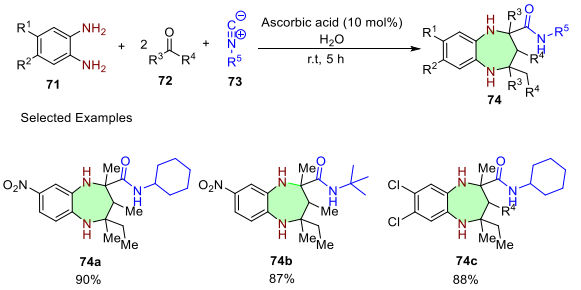
A moderate procedure developed by Munde and co-workers included ethanol/water (1:1) refluxing to synthesize 1,5-benzodiazepines derivatives **70**. [40] This procedure highlighted the use of a solid acid heterogeneous catalyst of sulphated tin oxide which was first produced and put into use for catalysed scheming. Also, this protocol involved a sulphated tin oxide catalysed condensation reaction between phenelenediamine derivative **69** and various ketones **68**, and 1,5-benzodiazepines were formed in 80-90% yield in ethanolic aqueous medium and refluxing using 25 mol% of catalyst (**Scheme 14**). The catalyst used can be recovered by carrying out simple filtration.

Ahmad Shaabani *et al* recently developed a strategy for the synthesis of benzodiazepines from a complete green chemistry perspective utilising environmentally friendly bio-degradable non-toxic, catalysts, and solvent. They proposed a synthetic strategy for a number of benzodiazepines using Vitamin C as catalyst and water as solvent.



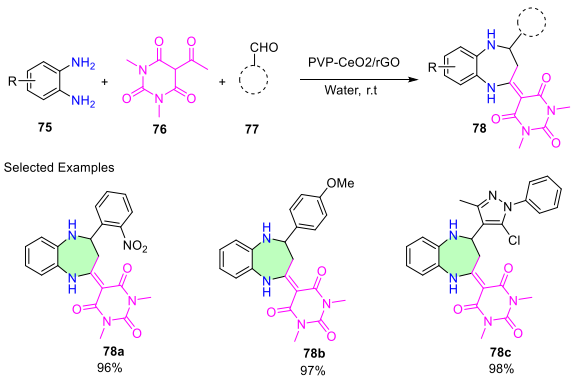
Scheme 14. Synthesis of 1,5-benzodiazepines.

The combination of *o*-phenylenediamine derivative **71** ketone **72**, isocyanide **73** and catalyst (10 mol %) was used in appropriate reaction of water as solvent and allowed for 5 hours to yield the desired products (**Scheme 15**). The multi-component synthesis was successfully carried out using vitamin C as highly efficient H-bond donor organo-catalyst. The maximum yield of 90% was observed when 4-nitro-1,2-phenylenediamine produced using Acetone, Cyclohexyl isocyanide in water and ascorbic acid at room temperature for 5 hours. [41]



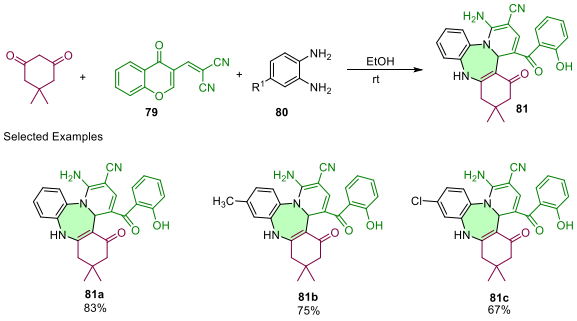
Scheme 15. Synthesis of Benzodiazepine derivatives using water and ascorbic acid

Shaheen *et al* have recently developed a protocol for the synthesis of biologically important benzodiazepine derivatives from a greener perspective.[42] The synthetic strategy used hetero-aromatic/aromatic aldehydes **77**, 5-acetyl-1,3-dimethylbarbi-turic acid **76** and 1,2-diamines **75** for the multicomponent synthesis (**Scheme 16**). They observed that the yield was comparatively lesser in the presence of aprotic solvents than the protic and concluded that the maximum was in water (96%). The reaction carried out in room temperature with the synthesized PVP–CeO_2/ rGO heterogenous catalyst for various time points and checked for carbon efficiency, reaction mass efficiency and overall efficiency (scheme 14). The maximum yield and overall efficiency were reported in **78c** and the strategy qualified to be eco-friendly.



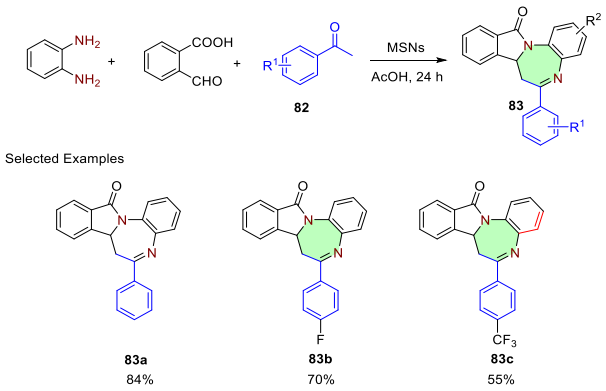
Scheme 16. Synthesis of Benzodiazepine using water as solvent.

Abdolali Alizadeh *et al* recently developed a chemo-selective protocol for the synthesis of Dibenzo[b,f]pyrido[1,2-d][1,4]diazepine **81**.[43] Dimedone, 1,2-diamines **80,** and condensation product of 3-formyl-chromones and malononitrile **79** undergoes a three- component cascade reaction to form the Tetracyclic Seven-membered ring 70 (**Scheme 17**). It generated a Knoevenagel adduct that acts as a soft electrophile which will eventually follow the cascade in the absence of catalyst. They observed that the best yield (70-90%) was in ethanol at room temperature.



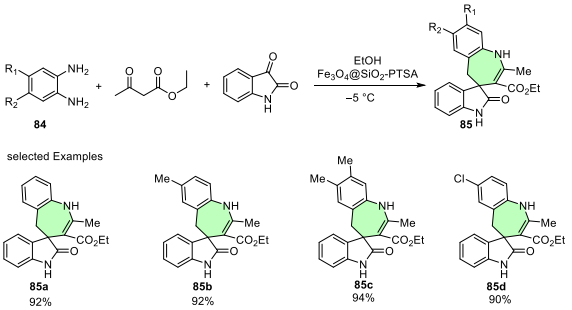
Scheme 17. Synthesis of Dibenzo[b,f]pyrido[1,2-d][1,4]diazepine using ethanol.

Shuo Yuan *et al* recently demonstrated a multi-component reaction using MSN (Mesoporous Silica Nanoparticles) as catalyst for the efficient synthesis combining benzodiazepine and isoindolininone NP to yield benzodiazepine-fused isoindolinone **83** pseudo natural products (**Scheme 18**).[44] The reaction proceeded by forming one C–C bond, three C–N bonds and two heterocycle ring systems like 6-aryl-7,7a-dihydro-12H-benzo[2,3][1,4]diazepino-[7,1-a]isoindol-12-ones. The organic synthesis encompassed the reactants with acetic acid and MSNs at room temperature for 24hrs. Among the substituents, the maximum yield (91%) was observed when the R group was a halogen. The protocol developed by them was advantageous as it was metal- free, used recyclable and efficient catalyst with a non-toxic green solvent.



Scheme 18. Multi component-synthesis of Benzodiazepine using MSN and acetic acid.

Wang *et al.* has developed several strategies involving domino reactions in the synthetic approach towards heterocyclic systems. The group 's protocol included four novel approaches that tend to be atom-economical, providing higher yields etc for the successful synthesis of heterocycles.[45] The approaches included domino reactions containing three-component, four-components to yield 1,5-Benzodiazepines (**85**) containing indole with the aid of catalytic number of magnetic nanoparticles ((Fe_3O_4@SiO_2-PTSA) as catalyst (**Scheme 19**). The solvent used was ethanol, justifying the greener solvent system along with higher yields. This provides the efficacy of the synthesis of the benzodiazepines made through one-pot with varying functional groups and multi-ring substituents.

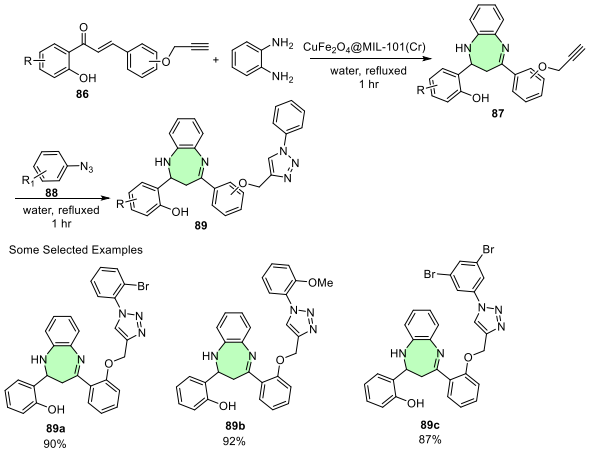


Scheme 19. Reaction of three-component synthesis of 1,5-benzodiazepines

The three component reactions were started with phenylenediamine **84**, ethyl acetoacetate and isatin as the starting materials and the investigation results provided the electron rich centres in diamine had higher yields with lesser reaction time. Similar reactions were carried out for three-component domino reactions. Further novel four-component reactions were also successful with the green solvent using Fe_3O_4@SiO_2-PTSA catalyst showing higher yields up to 97% with good feasibility **(85a-85d)**. This method relies on its method of simplicity, simple purification methods, less

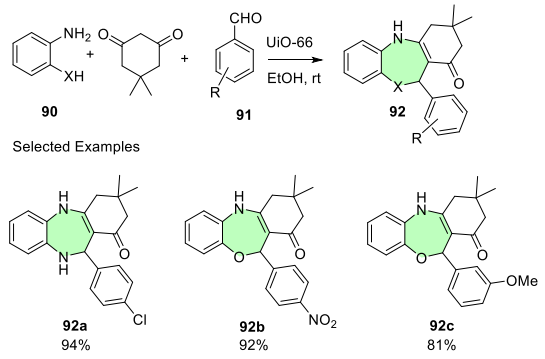
reaction times, mild conditions, greener approach and good product yields.

Pal and their co-workers traced a protocol possessing good yields, reusage of catalyst and large-scale synthesis of development of heterocyclic ring systems through metal organic framework. The protocol included substituted azides **86** and chalcones as starting material and a metal organic framework as the catalyst ($CuFe_2O_4$ @MIL-101(Cr)) yielding the benzodiazepine **87** which when treated with azide **88** formed the benzodiazepine containing triazole scaffold **89** in it (**Scheme 20**).[46] The whole reaction was carried out in green solvent system such as water and achieved higher yields which explained the sustainability of the protocol. The demonstration of the gram scale synthesis proved the reliability of the protocol and also the reusability, greener approach of the process.



Scheme 20. Reaction for the synthesis of benzodiazepine triazole scaffolds.

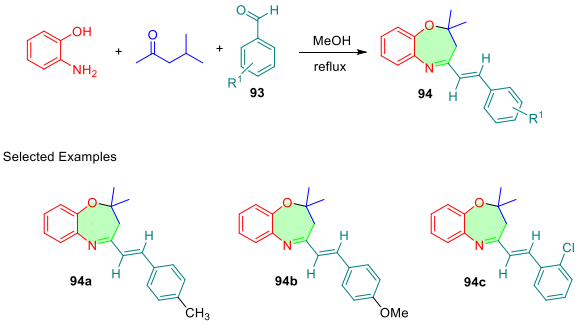
Ghasemzadeh and their group depicted a simplified approach for the synthesis of benzo-fused seven-membered heterocyclic compounds catalysed by UiO-66 MOF with the aid of ethanol as a green solvent. This technique ensured a straightforward procedure, a brief reaction time, a cost-effective catalyst and gentle reaction conditions.



Scheme 21. Synthesis of tricyclic 1,4-benzoxazepines using & 1,4-benzodiazepines.

This approach revealed the use of derivatives of benzaldehyde 91, dimedone and o-phenylenediamines 90 to give 1,4-benzodiazepines 92a and 1,4-benzoxazepines 92b-92c (**Scheme 21**). [47] They also proved the reusability of the catalyst with better catalytic performance owing to the eco-friendly nature of the procedure. Thus, showcasing the pharmacological properties of the heterocyclic compounds with simple and mild conditions resulting in 94% yield.

Felix *et al* recently synthesized and characterized various benzodiazepine derivatives and contemplated their unique anticancer and cytotoxic activities in metastatic cancer cells.[48]

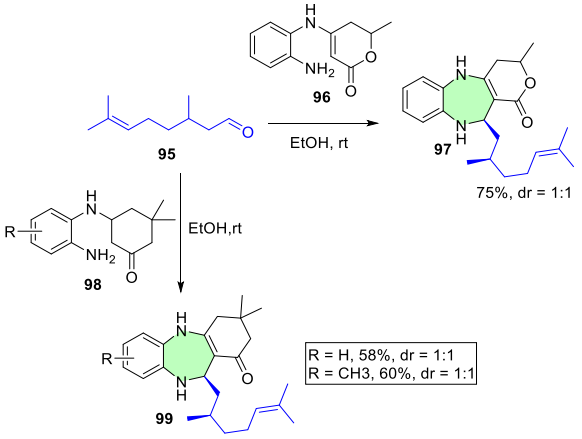


Scheme 22. Synthesis of Benzodiazepine derivatives using ethanol

This included a number of novel 2,3-dihydro-1,5-benzoxazepine derivatives **94**, some of which showed potential anticancer activity by interacting the polar group with microtubules at G2/M phase. The compounds were obtained by the combination of several ortho substituted aniline and methyl isobutyl ketones in the presence of methanol as the solvent for 8 hours under reflux (**Scheme 22**). This resulted in a series of 2,3-dihydro-1,5-benzoxazepine derivatives **94**, benzothiazole derivatives, and benzimidazole. Among these, 2,2- dimethyl-4-[(E)-2-(4-methylphenyl)ethenyl]-2,3-dihydro-1,5- benzoxazepine in complete green synthesis showed the cell cycle arrest at G2/M phase.

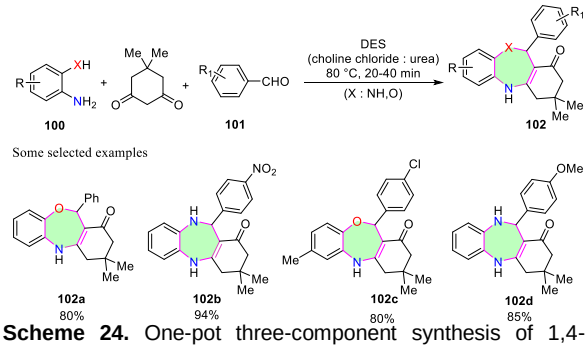
Very recently, Brahim Cherfaoui *et al* devised an efficient hemi-synthesis method that follows a complete green strategy of using green solvent and greener starting material.[49] The synthesis of benzodiazepine used eucalyptus citriodora essential oil in the presence of ethanol as the solvent at room temperature. The reaction forged through the formation of imine bond by the condensation of amines 4-((2-aminophenyl)amino)-6-methyl pyran −2-one) **96**, 3-[(2-aminoaryl)amino]dimedone 98, and CH_3-3-[(2-aminoaryl)amino]dime-done with citronellal aldehyde **95**. The yield was good ranging from 58 to 75% (**Scheme 23**). The formed product, chiral benzodiazepine was a diastereomeric mixture. The technique thus proved to be a part of future

green organic chemistry promising the effective use of chemical synthesis using green solvents.



Scheme 23. Synthesis of Benzodiazepine from Eucalyptus citriodora essential oil.

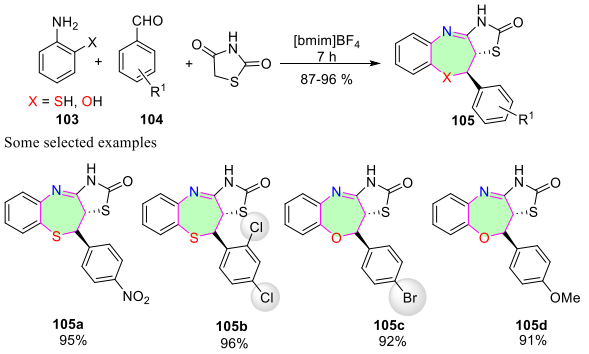
Zeynizadeh developed a protocol for the construction of benzodiazepines that is greener, effortless and one- pot eco-friendly. This group developed a nanocomposite material owing to its reusable catalytic nature paving a newer ecological appealing approach for the synthesis of heterocyclic compounds. They developed a nickel-based nanocomposite material employing it for the synthesis of benzodiazepines **102a-102d** in one-pot. Synthesis of the compound started with the dimedone, different aldehydes **101** and o-phenylenediamine **100** with various green solvents such as water, PEG-400 and ethanol (**Scheme 24**). [50] This method carried out in 60 ℃ exposed good yields, favourable time of reaction, and eco-friendliness of catalyst.



Scheme 24. One-pot three-component synthesis of 1,4-benzodiazepines catalysed by Fe_3O_4/f-MWCNT/Ni_2B.

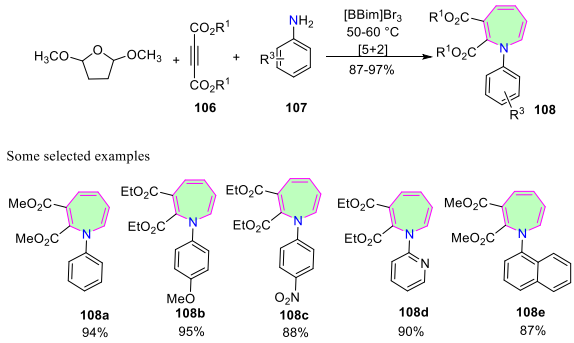
Ionic Liquids

Another demonstration from Kommidi and co-workers includes greener protocols for the productive synthesis of thiazepines and oxazepines of thiazolidine 2,4-dione **105** (**Scheme 25**) as a single diastreomer after recrystallization. [51] The reaction was a single enclosure three-component reaction at room temperature between fused cyclic thiazolidine dione, substituted aromatic aldehyde **104**, 2-amino phenol, or 2-amino thiophenol. So, the synthesis by this Ionic liquid [bmib]BF_4 endorsed method increases not only the productivity of the reaction but also considerably reduces the time taken to complete the reaction.



Scheme 25. Synthesis of 1,5-benzodiazepine and 1,5-benzodiazepine.

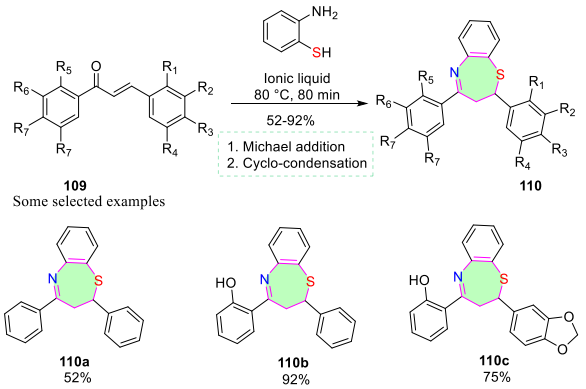
An eco-friendly, ionic liquid-assisted multi-component approach to N-substituted azepines can be furnished by coupling aromatic amines **107**, dimethyl acetylene dicarboxylate **106**, 2,5-dimethoxytetrahydrofuran using 1,3-Di-n-butylimidazolium tribromide [BBim]Br_3 (**Scheme 26**). [52] The main benefit to use this type of catalyst is that it can be recycled and reused for subsequent reactions.



Scheme 26. Synthesis of N-substituted azepine derivative.

Currently. Sakirolla and co-workers demonstrated an effective, new and eco-friendly protocol to reacto-aminothiophenol with different chalcones **109** providing the moderate reaction conditions with di-cationic liquid that acts more as a catalyst and not as a solvent gave 1,5-benzothiazepines **110** and as the products finally [53] 1,5-

benzothiazepines were obtained as the products by 1,4-conjugate Michael addition of or o-amino thiophenol with chalcone which proceeded a cyclo-condensation reaction



(scheme 27).

Scheme 27. Synthesis of 1,5-benzodiazepine and 1,5-benzodiazepine.

2. Conclusions

Thus, the pharmacologically important medium size heterocyclic ring synthetic strategies have been summarized highlighting the use of green solvents like DES, water, ethanol, etc. Over the past decade, the strategies have flourished towards the green syntheses. Various reactants, catalysts and mechanisms have been exploited for the synthesis only by using green solvents. We hope that this article allows its readers to understand the dynamic methodologies used and leaves with the essence of encouragement to work towards syntheses ensuring eco-friendly environment.

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Pooja Sivaganesan completed her Undergraduate studies in Chemistry at PSG College of Arts and Sciences, Coimbatore in 2022 and earned her Master's degree in Chemistry from Vellore Institute of Technology, Vellore in 2024. During her master's program, she completed her thesis work under the supervision of Dr. Saikat Chaudhuri, CSIR-Central Leather Research Institute, Chennai. She is currently engaged in a research project at the CSIR-Central Leather Research Institute, continuing to work under Dr. Saikat Chaudhuri's guidance. Her research interests focus on the development of new organic methodologies and the total synthesis of natural molecules.

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