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Recent advances in zirconium-based catalysis and its applications in organic synthesis: a review

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In recent years, transition metal-catalysed organic synthesis has received great importance. Zirconium, a second-row transition metal, has gained prominence owing to its luster and abundance, but it is more expensive than other transition metals because it is difficult to refine and process. In particular, active zirconia-based catalysts have fascinated researchers owing to their low toxicity, affordability, flexibility and excellent dispersion. This review focuses on the latest zirconium catalysts used in the manufacturing of medicinal compounds, bioactive molecules and pertinent synthesis mechanisms reported since 2020. In this review, the synthesis of various heterocycles such as imidazoles, pyrazole, pyrimidinones, quinolines, quinazolinones, pyridines, pyrroles, benzopyrans, substituted amides and triazolidine-based bioactive molecules is discussed in detail. Future research in this area is based on further understanding the scope of zirconium catalysed sustainable and approachable synthesis of biologically active compounds.

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1 Introduction

The second-row transition metal zirconium (Zr) is very lustrous and abundant and may be used in dental implants, prosthetic limbs, knee and hip replacements, and nuclear medicine. It is also suitable for use in these devices as a biomaterial.[1–3] In the areas of chemical reactions, electrical fields, catalysis, electrochemical sensors and proton conduction, it exhibits encouraging outcomes.[4–7] Zr has been the focus of a great deal of research since the middle of the 20th century because it is an extremely reactive metallic compound. Because zirconium is just as biocompatible as titanium, it can be used in orthopaedic and dental applications. It has low ionic cytotoxicity and is highly osteocompatible.[8] Zr-containing sorbents have been applied to hemofiltration, haemodialysis, peritoneal dialysis and wearable kidney development in the field of nephrology.[9–13] Zr is not considered a material that is harmful to human health.[14]

A tris(hydroxymethyl)aminomethane-zirconium complex (SBA-15@n-Pr-THMAM-ZrO) (**1**) supported on modified SBA-15 is a novel mesoporous catalyst, effectively catalysing the multicomponent synthesis of industrially significant six-membered N-containing heterocyclic compounds.[15] The hexagonal mesoporous silica-based catalyst HMS/Pr-Rh-Zr (**2**) features a large surface area, large pore volume, and wormhole pores, making it an ideal support for heterogeneous catalyst synthesis. The HMS/Pr-Rh-Zr catalyst, prepared by immobilizing a Zr-rhodanine complex on functionalized hexagonal mesoporous silica (HMS), efficiently catalyzes the synthesis of tetrahydrobenzo[*b*]pyran derivatives and is reusable without significant loss of activity.[16] The synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones *via* the Biginelli reaction was used to test the catalytic activity of Zr(IV) porphyrin graphene oxide, a cross-linked catalyst that can catalyze reactions in a short time with good to excellent yields. The catalyst was created *via* the nucleophilic reaction of Zr(IV) coordinated 5,10,15,20-tetrakis(aminophenyl)porphyrin (ZrPPh) with carboxyl groups of the edges of GO (GO-ZrPPh) (Fig. 5).[17] Fe_3O_4@MCM-41@$ZrCl_2$ (**3**) is a core–shell magnetic mesoporous nanocomposite that was investigated for synthesizing naphthols *via* a multicomponent reaction. The favorable efficiency of the targeted nanocomposite in the synthesis was induced by the combination of special qualities of MCM-41 as a unique mesoporous compound, the pleasing magnetic nature of Fe_3O_4 magnetic nanoparticles, and significant catalytical applications of zirconium.[18] The catalytic activity of SPVAZP, a hybrid catalyst composed of sulfonated polyvinyl alcohol dispersed in Al-pillared α-zirconium phosphate, was investigated for one-pot synthesis of multicomponent 4,6-diarylpyrimidin-2(1*H*)-ones. ZP and AZP materials served as the host lattice for sulfonated polyvinyl alcohol dispersion.[19] The α-zirconium phosphate-based nanocatalysts BSA@α-ZrP **4** and α-ZrP/uracil/Cu^{2+} demonstrated promising catalytic activity in synthesizing 2-substituted benzimidazoles. α-ZrP is employed as a stable support for green organic molecules such as butane sulfonic acid (BSA) and uracil as well as to tune the metal

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interactions.[20] The mesoporous catalyst $FeCl_4$@[Zr-UiO-66-PDC-SO_3H] **5** is used for synthesizing biologically significant dihydrobenzo[*g*]pyrimido[4,5-*b*]quinoline derivatives incorporating uracil and henna moieties.[21] With ZrO_2 supported on a magnetic charcoal material, $CoFe_2O_4$/BC-ZrO_2 is an effective catalyst that can be retrieved by an external magnetic field and recycled at least five times without noticeably losing its activity. For the one-pot synthesis of spiro[furo[3,4-*b*]quinoline], it exhibits high catalytic activity.[22] The primary benefit of nano-ZrO_2 is that it demonstrated moderate recyclability and could be recovered using a decantation approach or basic filtration, in addition to its selectivity. The primary benefits of nano-ZrO_2 are its high reproducibility, ease of handling, recyclable nature, low mole percentage, and lack of leaching effect during organic conversions. Excellent recyclability of up to five cycles in dry ethanol was demonstrated by the nano-ZrO_2 catalyst. Catalytic activity in the synthesis of benzimidazoles,[23] dihydropyrimidinones,[24] imidazoles,[25] and pyranopyrazoles[26] is being studied. A cobalt-incorporated sulphated zirconia, (ZrO_2/SO_4^{2-}/Co), is an effective heterogeneous recyclable multifunctional nanocatalyst. The catalyst's heterogeneous nature with nearly minimal metal leaching was demonstrated by a hot filtration test. With minimal efficiency loss, the catalyst was recycled for at least eight runs in a row. The catalyst's ability to catalyze the production of 1,8-dioxo-octahydroxanthene was investigated.[27] Zr-KIT-6 is an inexpensive, environmentally friendly Lewis acid catalyst, investigated for synthesizing *N*-aryl pyrroles. Since adding Zr to the KIT-6 framework improved its dispersion, it exhibits better activity than ZrO_2. KIT-6 was chosen because of its high surface area and distinctive Ia3d cubical porous network, which improve mass transport for reactants and large product molecules (Fig. 1).[28]

Zirconium catalyst is used in the synthesis of organic compounds that are important to biology in a variety of forms. Two naturally occurring pyranone derivatives with medical significance were synthesized quickly and efficiently using chiral zirconium complexes and the asymmetric hetero-Diels–Alder reaction: (+)-prelactone C **6** (ref. 29–32) and (+)-9-deoxygoniopypyrone 7.[30,33] Pyridopyrimidine **8** derivatives are very desirable because of their many biological applications,[34] including antiaggressive,[35] antihypertensive,[36] antiasthmatic,[37] tuberculostatic,[38] antimicrobial,[39] calcium channel antagonists,[40] antileishmanial,[41] anticonvulsants,[42] antibacterial,[43] diuretic and potassium-sparing,[44] anti-inflammatory and analgesic[45] as well as antiallergic and antifolate[46] properties. Furthermore, pyridines are known to function as herbicides, insecticidal agents, antagonists and inhibitors.[47–50] The synthesis of β-amino carbonyl derivatives **10** and benzylamino coumarin derivatives **11** is facilitated by ZrO_2, a magnetic heterogeneous nanocatalyst.[51] The Mannich reaction yields β-amino carbonyl compounds, which are crucial synthetic intermediates found in numerous natural and pharmaceutical products. Benzylamino coumarins are significant members of the heterocyclic chemical family with antioxidant, anti-HIV and anticoagulant properties.[52–54] Coumarins catalysed by nanocrystalline sulfated zirconia (benzo-2-pyrone derivatives)[55] are significant coumarin compounds with a range of bioactivities and other uses.[56] β-Methylumbelliferone, or 7-hydroxy 4-methyl coumarin **9**, is a useful laser dye and fluorescent brightener that can be used as a raw material to make insecticides and furano coumarins.[57–59] Similarly, the main applications for 7-amino 4-methyl coumarin are as an intermediate in the synthesis of bioactive compounds and as a laser dye.[60]

One of the primary nanomaterials used in the manufacturing of ceramics, foundry sands and refractories is zirconia (ZrO_2) NPs. They are helpful in the biomedical domains of implants, cancer treatment, dentistry and biosensors, among others, because of their robust mechanical qualities. It works well as a catalyst for chemical processes like oxidation, hydrogenation, dehydration and elimination because of its unique chemical properties. Zirconium catalyst is used to combine heterocyclic spiroindoles, quinoxaline, quinoline, and furan-2,4[2*H*,5*H*]-dione to create a variety of unique compounds with biological and structural activity. Derivatives of tetrahydropyridines acted as a favourable scaffold for a variety of naturally occurring and artificially produced bioactive compounds, including ciprofloxacin **15**, arecoline **14**, awaine **13**, homoclausenamide **12** and Lapadin B.[61,62] *N*-Aryl pyrroles are a significant part of certain drugs such as pyrrolylimide **16** (antimycobacterial), lamellarin **17** (antiviral), pyrvinium **18** (anthelmintic), and BM212 **19** (anti-microbial) (Fig. 2).

A vast variety of heterocyclic compounds are synthesized using zirconium catalyst. Zirconium in various forms such as ZrO_2, Zr(IV), zirconium silicates, zirconium inorganic salts, organozirconium complexes, zirconium bimetal oxides and zirconium based MOFs are employed in synthesis of bioactive organic compounds. This review covers the catalytic applications of zirconium-mediated multicomponent reactions, C–H functionalization (Fig. 3), hydroaminoalkylation, *etc.*

Considering the synthetic utility of zirconium catalysis, significant research groups have summarized its remarkable applications. However very few reports have been published to emphasize the use of zirconium catalysis towards organic synthesis. In 2022, Peng's research group[63] summarized the zirconium catalysis in organic synthesis. This work emphasizes the application of inorganic zirconium catalysts—both those incorporating cyclopentadienyl (Cp) ligands and those

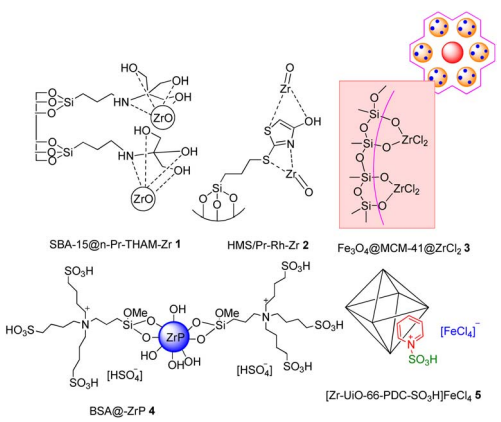


Fig. 1 Important zirconium-based complexes.

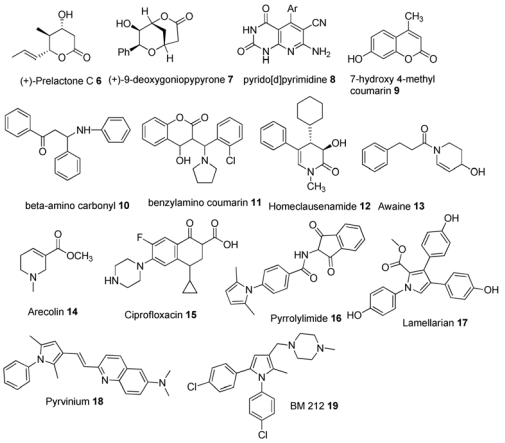


Fig. 2 Some biologically important Zr-based compounds.

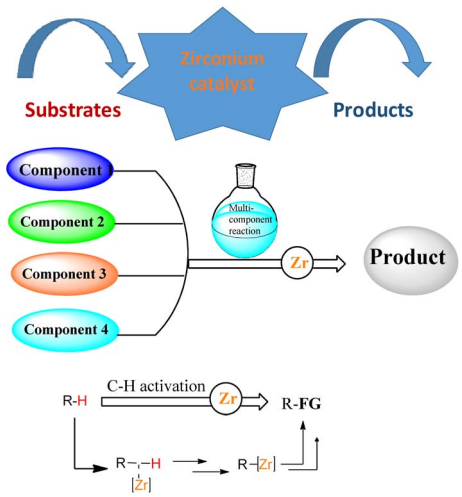


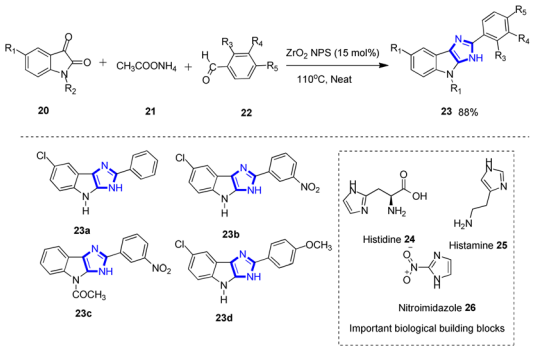
Fig. 3 Generalized scheme of zirconium-mediated reactions.

without—in facilitating diverse organic transformations. In 2024, Chattopadhyay provided a comprehensive review of zirconium-based metal–organic frameworks (MOFs), detailing their synthesis and highlighting their potential in biomedical applications.[64] In 2011, Zhang reviewed the applications of zirconium catalysts in organic synthesis that cover the zirconium mediated organic named reactions.[65] An overview of zirconia based solid acids for organic synthesis, which is restricted to their usage, was provided by the K. Patil research group in 2011.[66] Zirconium mediated synthesis of heterocyclic bioactive organic compounds and their intricate reaction mechanisms is the main topic of our review. Since 2022, there have been no comprehensive reviews published on zirconium-mediated organic synthesis. This represents a significant research gap that our review aims to address.

2 Literature review

2.1. Synthesis of substituted imidazoles

Imidazole is a 1,3-diazole that is a member of the alkaloid class. Heterocycles in the imidazole class have different substitutions

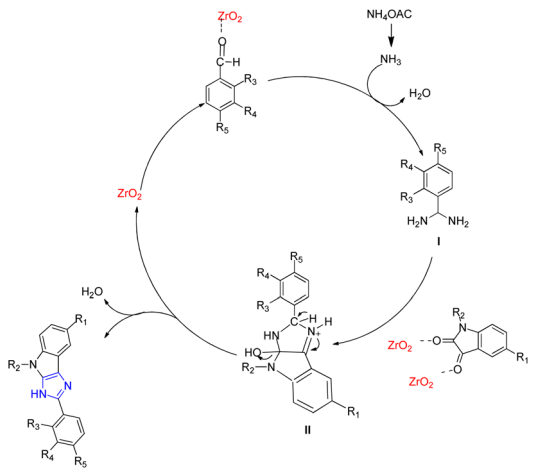


Scheme 1 Synthesis of imidazole derivatives from ZrO_2.

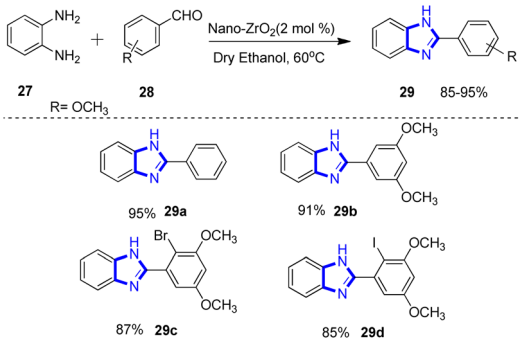
but an analogous ring structure. Important cellular architectures like histidine **24** and histamine **25** hormone have this ring system. The imidazole ring is also present in antifungal medications and nitroimidazole **26**.[67–70] Imidazole derivatives **23** were created by Singh and colleagues in a one pot at 110 °C without the use of solvents, wherein isatin derivatives **20** reacted with ammonium acetate **21** and substituted benzaldehydes **22** (Scheme 1).[25]

Scheme 2 provides the efficient mechanism for the synthesis of substituted imidazoles. Diamine intermediate **I** speeds up the process. Condensing diamine with derivatives of isatin, dehydrating it, and then rearranging it through imine intermediate **II** produced the desired result.

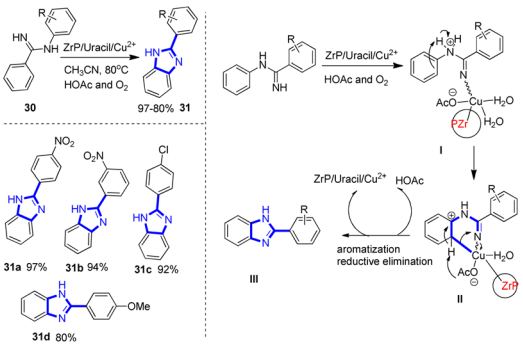
Benzimidazoles are essential synthetic intermediates in drug discovery. Many biological activities including antitumor, antibacterial, antifungal, anti-inflammatory, antiviral and analgesic effects are exhibited by benzimidazoles and their derivatives.[71] Rao and colleagues produced novel benzimidazole derivatives with antifungal and antibacterial properties using a simple, highly productive and environmentally safe catalyst. Using dry ethanol as a solvent, *O*-phenylenediamine (*o*-PDA) **27** and aromatic aldehydes **28** react with ZrO_2 at 60 °C to produce 2-



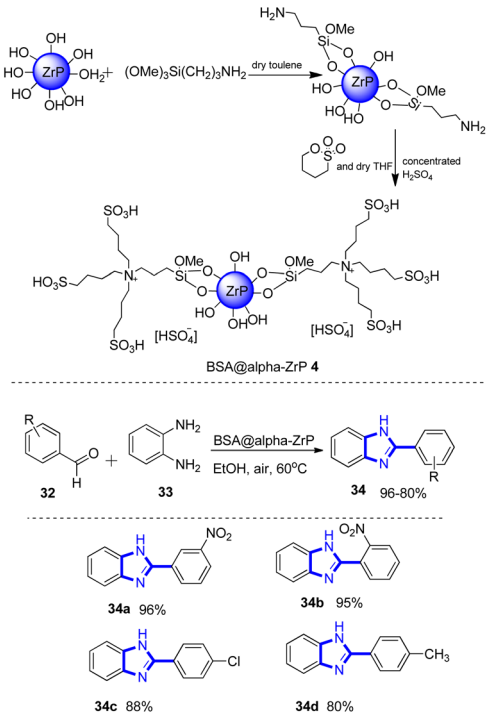
Scheme 2 Feasible mechanism for the synthesis of substituted imidazole derivatives.



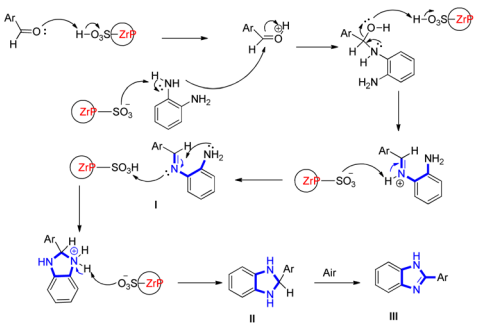
Scheme 3 One-pot synthesis of benzimidazole derivatives catalysed by Zr.



Scheme 4 Functionalization of the C–H bond and mechanism of benzimidazole synthesis.



Scheme 5 Scheme for the synthesis of the BSA@α-ZrP catalyst and benzimidazoles.



Scheme 6 Mechanism of benzimidazole synthesis.

arylbenzimidazoles **29**. The highest active potency of benzimidazole derivatives **29a–c** is against *Escherichia coli* bacterium. These derivatives are all extremely effective substances with antifungal properties (Scheme 3).[23]

Benzimidazole derivatives are a specific category of heterocyclic compounds in chemical[72–78] and pharmaceutical settings.[79–83] Using benzamidine **30**, HOAc, and ZrP/uracil/Cu^{2+} in CH_3CN refluxing at 80 °C under direct O_2 flow, Hajipour and colleagues synthesized benzimidazoles **31**.

A proposed mechanism for the synthesis of benzimidazole is shown in Scheme 4 along with background information from earlier literature.[20,84,85] This mechanism suggests that the reaction of benzamidine **30** with Cu(II) in α-ZrP/Uracil/Cu^{2+} results in **I**, where HOAc aids in the coordination of nitrogen and copper. The transfer of the ring bond generates a positive charge on the aromatic ring, which is promptly offset by the bond shift, and a metal cycle with the copper centre is formed **II**. The processes of aromatization and reductive elimination lead to the formation of the benzimidazole product **III**. Both the catalyst and the HOAc were eventually recovered. Hajipour and colleagues made benzimidazoles **34** by dissolving 1,2-phenylenediamine **33** (1 mmol) in 3 mL of ethanol. BSA@α-ZrP (15 mg) and aromatic aldehyde **32** (1.1 mmol) were added to the solution that was previously prepared (Scheme 5).

A feasible process for the synthesis of benzimidazoles is shown in Scheme 6. BSA@α-ZrP first activates the aromatic aldehyde. An aldehyde containing the amino group of 1,2-phenylenediamine condenses to form imimine **I**. Intermediate **II** is created when a nucleophile targets the leftover NH_2 in the presence of a catalyst. In the end, intermediate **II** was oxidatively aromatized at room temperature to create the benzimidazole product **III**. To ensure that air and oxygen played a critical role in the final step, the reaction was conducted in an argon atmosphere; no product was synthesized.[20]

2.2. Synthesis of substituted pyrazole derivatives

The two nitrogen atoms in pyrazole and its derivatives make them heterocyclic compounds with a variety of biological activities. These properties include antioxidant, antidiabetic, anticancer, and antimicrobial effects.[86–91] Zirconium magnetic

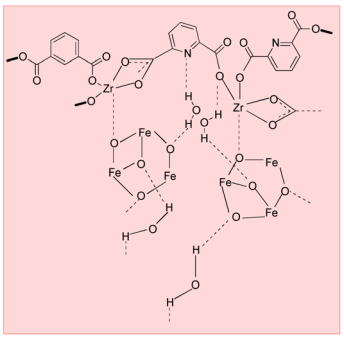


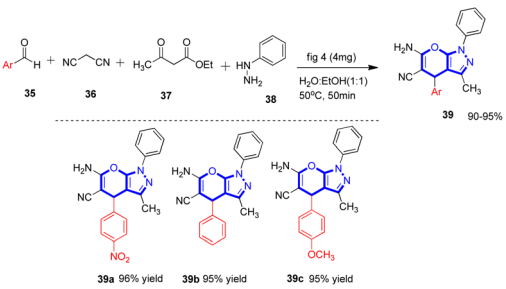
Fig. 4 Zirconium magnetic nanocomposite's proposed structure.

nanocomposite is a green catalyst employed in the production of derivatives of pyrazole. It can be reused without losing any of its effectiveness. Because of its large specific surface area, the zirconium magnetic nanocomposite (Fig. 4) exhibited effective biological activity against Gram-positive and Gram-negative fungal species. Asiri and colleagues produced pyrazole derivatives by a one-pot component reaction involving aromatic aldehyde derivatives, malononitrile, phenyl hydrazine and ethyl acetoacetate using a zirconium magnetic nanocomposite as a catalyst.[92]

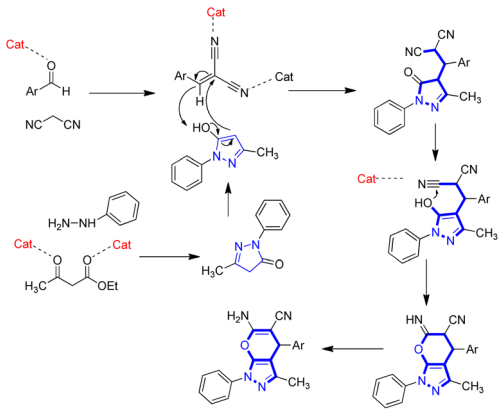
Aldehyde **35**, malononitrile **36**, ethyl 3-oxobutanoate **37**, phenylhydrazine **38** and zirconium magnetic nanocomposite (Fig. 4) are combined in a one pot reaction to synthesize 1,4-dihydropyrano pyrazole **39** in excellent yield (Scheme 7).

Using a zirconium magnetic nanocomposite, Scheme 8 provides a believable reaction mechanism for the synthesis of (*R*)-6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile **34**.

Using multi-component reactions (MCRs), Basappa and colleagues synthesized environmentally friendly nano-ZrO_2 catalysed pyranopyrazoles **44**. Compared to well-known synthetic methods, this method produced a good yield of products with fewer by-products while reducing the cost, time and energy required for the synthesis. The five-component reaction involving benzaldehyde **40**, substituted hydrazine **41**, malononitrile **42**, ethyl 3-oxobutanoate **43** and nano-ZrO_2 20 mol% in an H_2O–EtOH mixture produced a noteworthy yield of 75% in 50 minutes. MCF-7 cell viability is lost by



Scheme 7 Zr-catalysed one pot synthesis of (*R*)-6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile.

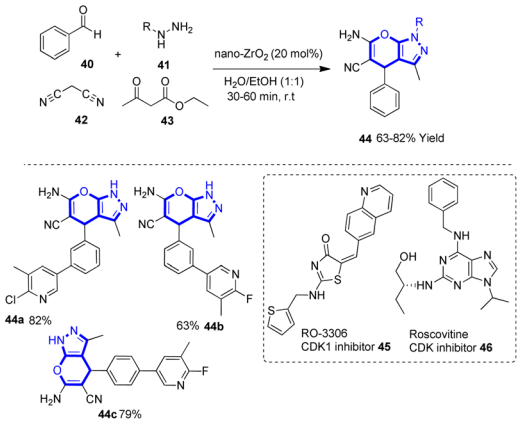


Scheme 8 Proposed mechanism for synthesizing (*R*)-6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]carbonitrile pyrazole-5.

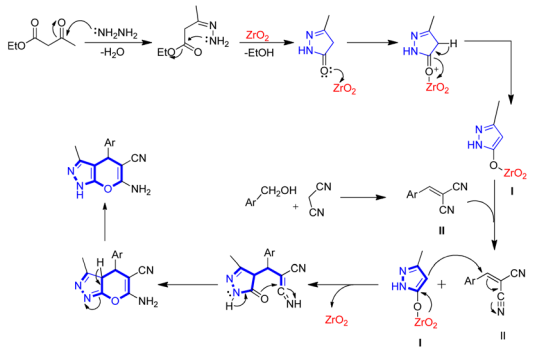
pyrazopyrazole derivatives **44a** and **44c**, with IC_{50} values of 17.83 and 23.79 μM, respectively. Research on the *in vitro* and *in silico* mechanisms of action of pyranopyrazoles has revealed that **44b** and **44c** derivatives have strong IC_{50} values and target the cyclin-dependent kinase (Cdk1) protein on human breast cancer cells (Scheme 9).

Scheme 10 shows a presumable mechanism for the synthesis of pyranopyrazoles, in which nano-ZrO_2 functions as both a base and a Lewis acid. Initially, ethyl-3-oxobutanoate and substituted hydrazine hydrate were condensed to create pyrazolone **I** derivatives. By absorbing an electron pair from the carbonyl oxygen, ZrO_2 functions as a Lewis acid, facilitating the reaction between hydrazine hydrate and ethyl acetoacetate. ZrO_2's base site can be activated by malononitrile **II** to produce an active methylene group. It initiates the benzaldehyde and malononitrile Knoevenagel condensation reaction, which yields arylidene malononitrile. After arylidene malononitrile and pyrazolone undergo the Michael addition reaction, cyclization and tautomerization take place to produce pyranopyrazoles **44**.[26]

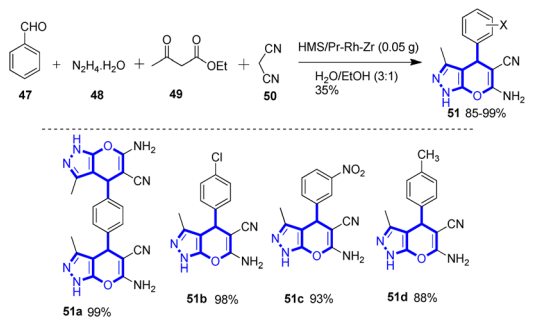
Aldehyde **47**, hydrazine hydrate **48**, ethyl acetate **49** and malononitrile **50** were mixed and heated to 35 °C. EtOH acts as



Scheme 9 Zr-catalysed synthesis of pyranopyrazole derivatives.



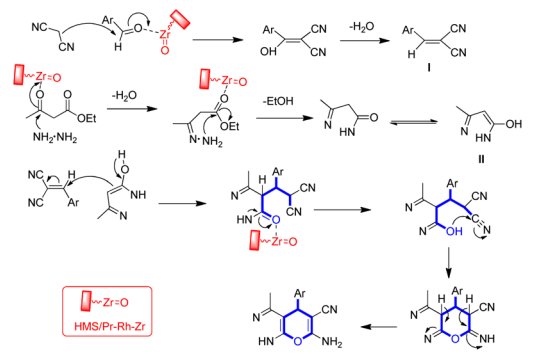
Scheme 10 Presumable mechanism for the multicomponent synthesis of pyranopyrazoles using ZrO_2.



Scheme 11 Scheme for the synthesis of (*R*)-6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile.

a catalyst for (*R*)-6-amino-3-methyl-4-phenyl-1,4-dihydropyrano [2,3-*c*] when combined with HMS/Pr-Rh-Zr (0.01 g) to synthesize 5-carbonitrile pyrazole **51** (Scheme 11).

A tenable process for 1,4-dihydropyrano pyrazole-5-carbonitrile **51** synthesis is illustrated in Scheme 12. With the use of a catalyst, malononitrile and activated aldehyde undergo Knoevenagel condensation, generating intermediate **I**, an arylidene malononitrile intermediate. Pyrazone (intermediate **II**) was formed from the condensation reaction that occurred among hydrazine and activated ethyl acetoacetate. Ultimately,



Scheme 12 Mechanism for the synthesis of (*R*)-6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile.

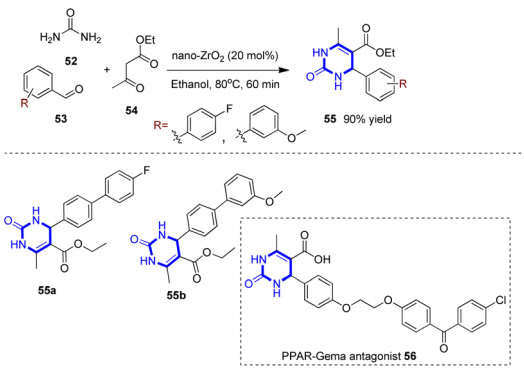
a Michael addition reaction was observed between the enolized pyrazolone and the arylidene malononitrile. The intermediate is then tautomerized to yield 1,4-dihydropyrano pyrazole-5-carbonitrile.[93]

2.3. Synthesis of substituted pyrimidinones

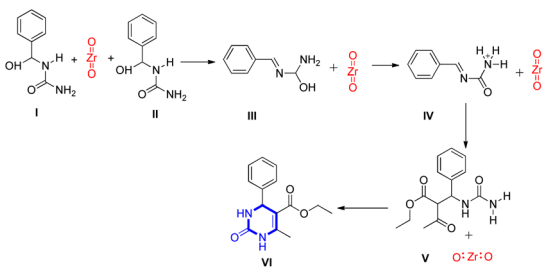
Deveshegowda and colleagues synthesised dihydropyrimidinones **55** using polarized surface nano-ZrO_2. Peroxisome proliferator-activated receptor (PPAR)-γ **56** was discovered to be the target of the DHPs; these ligands were observed to be toxic against MCF-7 cell proliferation, and compounds **55a** and **55b** inhibit proliferation, with IC_{50} values of 11.8 and 15.8 μM, respectively. By using nano-ZrO_2 as a catalyst, organic substrates and reagents can selectively form products due to the increased surface area of the nano-constituents. The Biginelli reaction was carried out by refluxing urea **52**, benzaldehyde **53**, ethyl acetoacetate **54** and 20 mol% nano-ZrO_2 catalyst in EtOH for 60 minutes, yielding 90% products (Scheme 13).

The Biginelli reaction mechanism (Scheme 14) begins with a condensation reaction between urea and benzaldehyde, which is then catalysed by a second urea molecule to add ethyl acetoacetate. It is carried out using a catalyst system decorated with sulfonic acid and imidazolium in a solvent-free environment.[24]

Recently, synthetic organic chemistry has been very interested in the pharmacological and therapeutic properties of 3,4-dihydropyrimidin-2(1*H*)-ones, which has led to their synthesis.[94] Fig. 5 shows the synthesis of GO-ZrPPh **57** catalyst that catalyse 3,4-dihydropyrimidin-2(1*H*)-one synthesis.



Scheme 13 Zr-catalysed synthesis of dihydropyrimidinone derivatives.



Scheme 14 Biginelli reaction intermediates and product mechanism for dihydropyrimidinone synthesis.

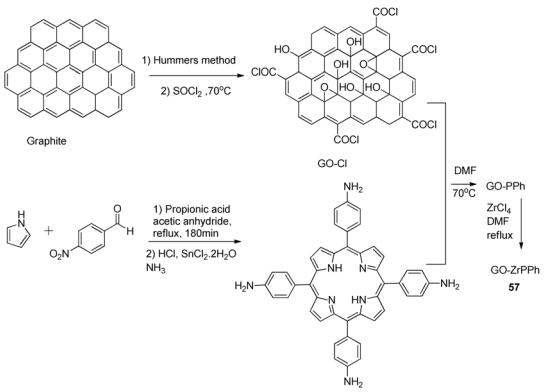
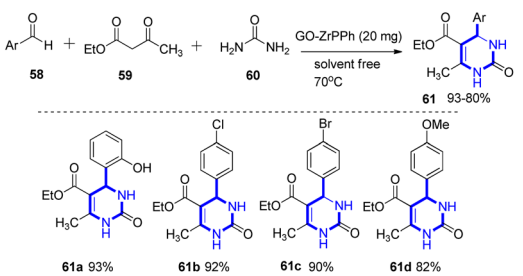


Fig. 5 Synthesis of the GO-ZrPPh catalyst.

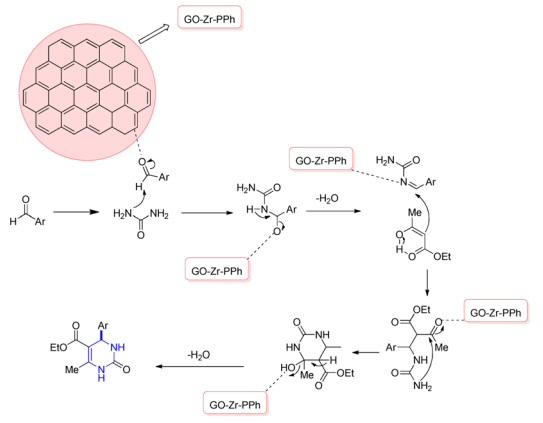
Ghadamyari and colleagues added GO-ZrPPh **57** catalyst to a solution of aromatic aldehydes **58**, ethyl acetoacetate **59** and urea **60** in a solvent-free environment at 70 °C for 35–60 minutes, yielding substituted (*R*)-ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **61**. The catalyst was sucked out of the reaction mixture and heated ethanol was added when the reaction was completed, with excellent yields of 80–93% observed for the various derivatives **61a–d** (Scheme 15).

Scheme 16 presents a plausible process for zirconium-coordinated porphyrin bonding to graphene oxide (GO), yielding 3,4-dihydropyrimidin-2(1*H*)-ones **61**. To produce the final product, urea must be attacked with a nucleophile, condensed with ethyl acetoacetate, water must be removed, and Zr IV Lewis acid must react to activate the carbonyl group of aromatic aldehydes.[17]

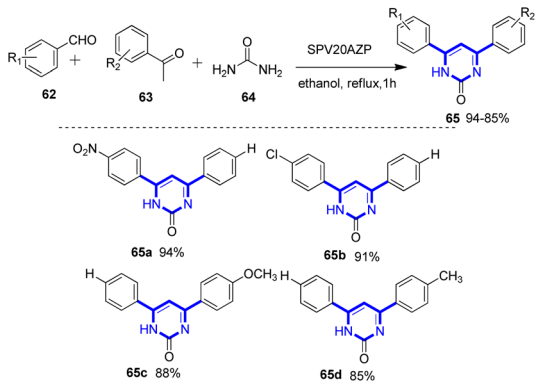
The pyrimidine moiety of organic compounds has attracted a lot of interest in synthetic chemistry due to its biological significance, potential as a therapeutic agent and frequent presence in a wide range of natural products.[95,96] The pyrimidine ring is a fundamental structural component of numerous synthetic and natural drug molecules, vitamins, chemotherapeutic agents, herbicides, and dyes. In recent decades, an enormous research has been conducted on the pharmacological actions of the structural analogues of pyrimidine, specifically 3,4-dihydropyrimidin-2(1*H*)-ones and 4,6-diarylpyrimidin-2(1*H*)-ones **60**.[95–97] The biological activities of these nitrogen-containing heterocycles are diverse and include antibacterial,



Scheme 15 Scheme for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives.



Scheme 16 Plausible mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.



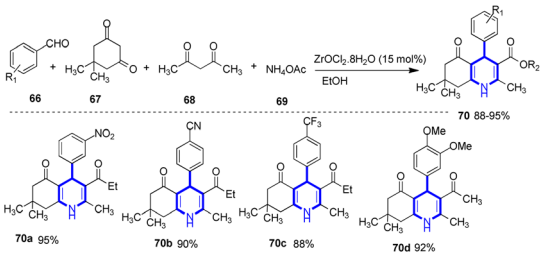
Scheme 17 Scheme for the synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones.

anti-inflammatory, anti-hypertensive, antiviral, and anti-tumour properties.[95–98] Majhi and colleagues synthesized 4,6-diarylpyrimidin-2(1*H*)-ones **65** shown in Scheme 17. For the one-pot synthesis of 4,6-diarylpyrimidin-2(1*H*)-ones, the catalytic activities of the SPVxZP and SPVxAZP materials have been assessed. This was achieved by condensation of aryl aldehydes **62**, ketones **63**, and urea **64** in an ethanolic medium under reflux conditions.[19]

2.4. Synthesis of substituted quinolines and quinazolinone

Quinolines possess various pharmacological properties such as antimalarial,[99] antitubercular,[100] antifungal,[101] anthelmintic, cardiotonic, anticonvulsant, analgesic,[102] anti-inflammatory, antibacterial and anticancer[103] activities. Tasqeeruddin and colleagues synthesized hexahydroquinoline derivatives **70** *via* one pot reaction of benzaldehyde **66**, 5,5-dimethylcyclohexane-1,3-dione **67**, pentane-2,4-dione **68**, ammonium acetate **69** and 10 mol% $ZrCl_2 \cdot 8H_2O$ conducted in a variety of solvents, including EtOH, DMF, CH_2Cl_2, and MeCN (Scheme 18).[104]

Fig. 6 illustrates potential biological and pharmacological uses for 1,4-dihydropyridine structures containing uracil and henna (2-hydroxynapthalene-1,4-dione).[105,106] Frameworks



Scheme 18 Zr-catalysed synthesis of hexahydroquinoline derivatives.

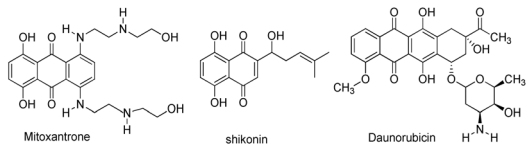
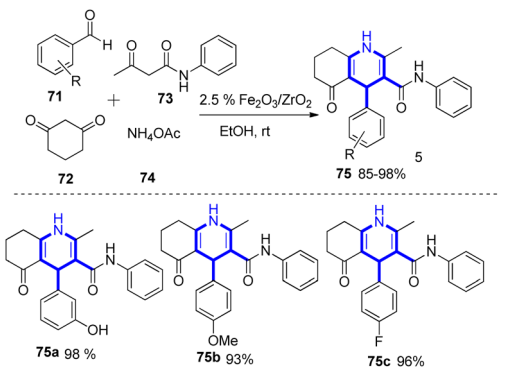


Fig. 6 Biological substances with moieties of dihydropyridine, henna, and uracil in their structure.

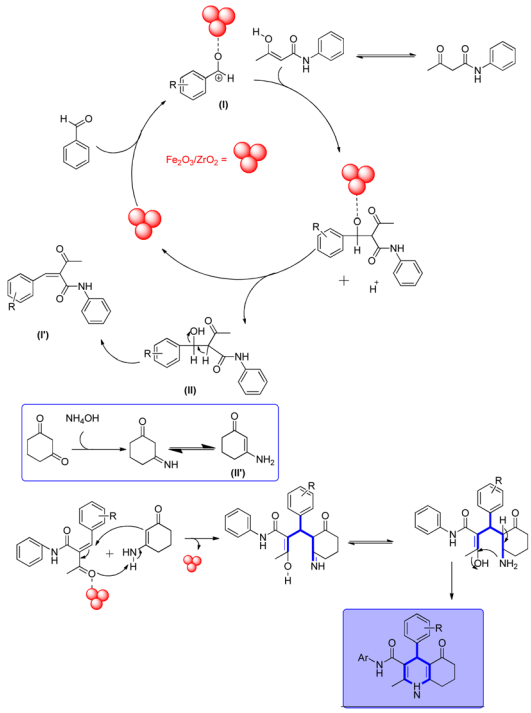
containing uracil moieties have antitumor,[107] cardiotonic,[108] heptaprotactive,[109] anticoagulants,[110] antibronchitic[111] and antifungal activity.[112]

Substituted hexahydroquinoline carboxamide shows a variety of bioactivities such as antitubercular[113] and anti-cancer[114] and is also used for the blockage of calcium channels. Sandeep and colleagues synthesized 1,4-dihydropyridine **75** using aromatic aldehyde **71**, 1,3-cyclohexadione **72**, acetoacetanilide **73** and ammonium acetate **74** (Scheme 19).

The catalyst's Lewis acidic patches will help the reaction proceed more smoothly overall. Lewis acidic sites and carbonyl oxygen have to coordinate to form a Knoevenagel condensation product. As a result, an intermediate **I** carbonium ion formed. Then, there was an interaction between the intermediate **I** and the active methylene group of the acetoacetanilide. After the intermediate separates from the catalyst surface, it becomes intermediate **II** by absorbing a proton from the EtOH. The crucial intermediate **I′** is then produced by intramolecular



Scheme 19 Scheme for the synthesis of hexahydroquinoline carboxamide.



Scheme 20 Proposed mechanism for 1,4-dihydropyridin synthesis.

dehydration, and the target molecules are obtained by condensation of intermediate **II′** (Scheme 20).

Metal–organic frameworks, or MOFs, are coordinating networks with an open structure made up of organic linkers and inorganic nodes that may have voids.[115–117] Zr-based MOFs are interesting materials for biological applications like drug administration and bio imaging because of their low toxicity, adaptable surface properties, and structural stability under physiological conditions.[118] For instance, it has been shown that Zr-based MOFs may effectively encapsulate azo chemicals with anticancer properties that are soluble in water, especially in the hypoxic environments linked to pancreatic cancer.[119] Since zirconium has low toxicity,[120] zirconium-based metal–organic frameworks (MOFs) are probably one of the most studied classes of materials in MOF chemistry because they are easily obtainable and reasonably priced. This stability is consistent with the hard and soft acids and bases (HSAB) principle and results from the robust coordination link between the strongly

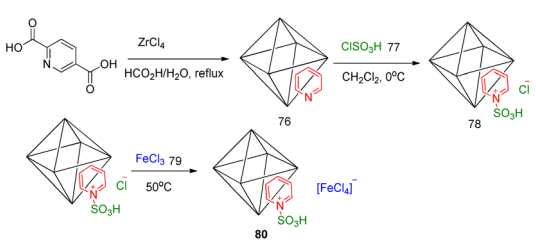


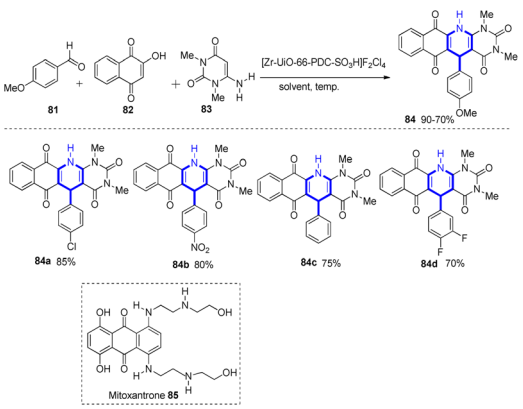
Fig. 7 Scheme for synthesis of the [Zr-UiO-66-PDC-SO_3H]$FeCl_4$ catalyst.

Lewis acidic Zr^{4+} ions and the strongly Lewis basic oxygen anions from the ligand molecules.[121] MOFs with large surface areas and stability are typically favoured for potential uses such as catalysis, gas storage, heat transformation, and medical programs.[122,123] Initially, the MOFs [Zr-UiO-66-PDC] were made by a previously established method.[124] A mixture of $ClSO_3H$ **77** and [Zr-UiO-66-PDC] **76** in dry CH_2Cl_2 at 0 °C was stirred for two hours in a 50 mL round-bottom flask. Following that, a white precipitate developed and was vacuum-dried after being separated by centrifugation. Next, a mixture of [Zr-UiO-66-PDC-SO_3H]Cl **78** and $FeCl_3$ **79** was stirred in a mortar for two hours at 50 °C using the anion exchange method. The reaction mixture was allowed to cool to room temperature once the reaction was finished. Lastly, [Zr-UiO-66-PDC-SO_3H]$FeCl_4$ **80** was triturated in acetone to purify it (Fig. 7).

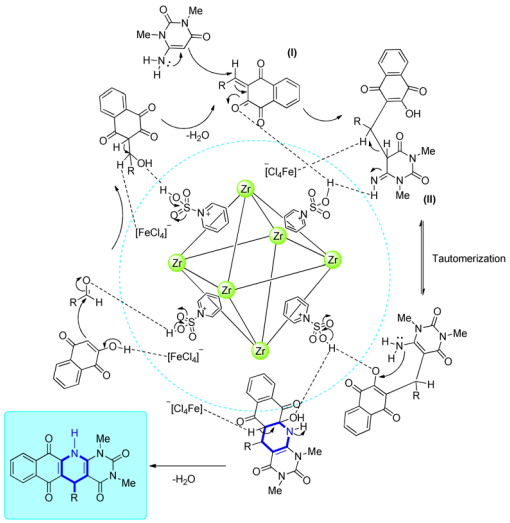
Combining [Zr-UiO-66-PDC-SO_3H]$FeCl_4$ **80** with aldehyde **81**, 2-hydroxynaphthalene-1,4-dione **82**, and 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **83**, Jalili and colleagues synthesized the compound (*S*)1,3-dimethylbenzo[*g*]-5-(4-methoxyphenyl)2,4,6,11 pyrimido[4,5-*b*]quinoline (1*H*,3*H*,5*H*,12*H*)tetraone **84** (Scheme 21).

According to the suggested mechanism, the aldehyde's carbonyl functional group is activated by the [Zr-UiO-66-PDC-SO_3H]$FeCl_4$ **80** catalyst. 4-Methoxy benzaldehyde **81** was reacted with [Zr-UiO-66-PDC-SO_3H]$FeCl_4$ **80** at room temperature to examine the activation of the aldehyde. One H_2O molecule is then extracted from the aldehyde by the henna (2-hydroxynaphthalen-1,4-dione) **82** moiety when it combines with the carbonyl to form intermediate **I**. The next step is to react intermediate **I** with 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **83** to create intermediate **II**. After intramolecular cyclization and the loss of an additional H_2O molecule, intermediate **II** produces the desired product in two steps (Scheme 22).[21]

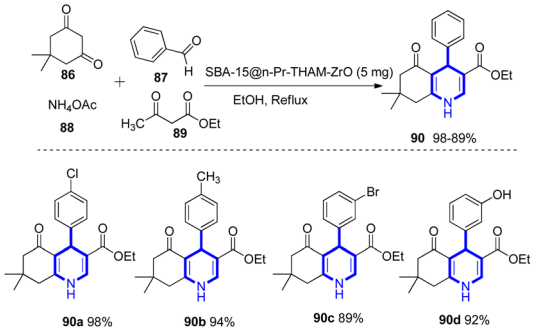
Polyhydroquinolines, which are heterocyclic compounds, are mostly present in a variety of natural products and are crucial for the creation of novel medications and synthetic organic chemistry.[125–131] Arash and colleagues utilized the



Scheme 21 Synthetic procedure for (*S*) derivatives of 1,3-dimethylbenzo[*g*]-5-(4-methoxyphenyl)pyrimidine[4,5-*b*] 2,4,6,11(1*H*,3*H*,5*H*,12*H*)-quinoline-tetraone.



Scheme 22 Proposed mechanism for the synthesis of (*S*)1,3-dimethylbenzo[*g*]-5-(4-methoxyphenyl)pyrimidine[4,5-*b*] 2,4,6,11(1*H*,3*H*,5*H*,12*H*) quinolinetetraone.

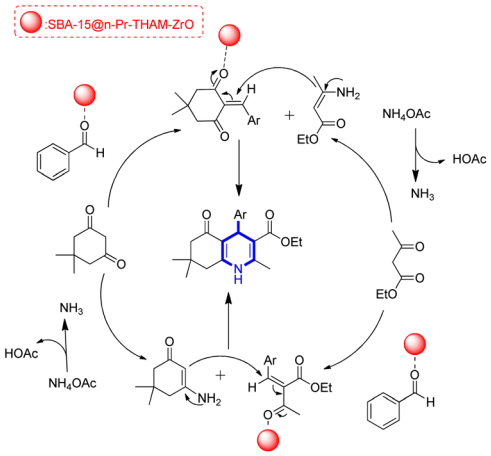


Scheme 23 Scheme for polyhydroquinoline synthesis.

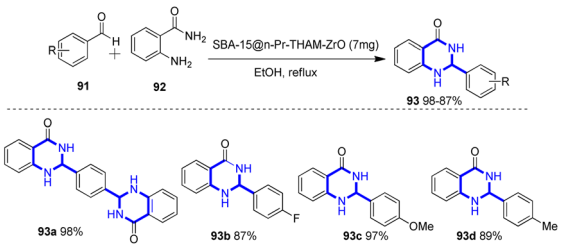
tris(hydroxymethyl)aminomethane-ZrO complex to fill the SBA-15's pores and produce a new type of heterogeneous mesoporous catalyst. It was shown that the mesopore material may be used to combine several components to create a broad range of industrially important six-membered N-containing heterocyclic compounds, such as (*S*)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one and polyhydroquinolines (Scheme 23).

Arash and colleagues synthesized polyhydroquinolines **90** by dissolving a mixture of dimedone **86**, aryl aldehyde **87**, ammonium acetate **88**, ethyl acetate **89** and ZrO catalyst in ethanol and stirring it under reflux conditions for the necessary amount of time. The reaction mechanism for the synthesis of polyhydroquinolines **90** is shown in Scheme 24.

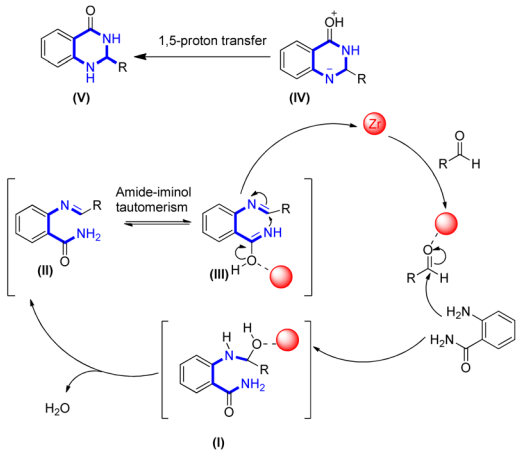
Arash and colleagues prepared (*S*)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **93** by filling the flask with ZrO catalyst, swirling the mixture during reflux and dissolving the combination of aromatic aldehyde **91** and anthranilamide **92** in three millilitres of ethanol (Scheme 25).[15] Scheme 26 presents the plausible reaction mechanism for the synthesis of (*S*)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **93**.



Scheme 24 Mechanism for the synthesis of polyhydroquinolines.

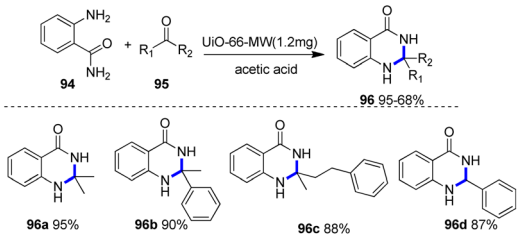


Scheme 25 Scheme for the synthesis of (*S*)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one.

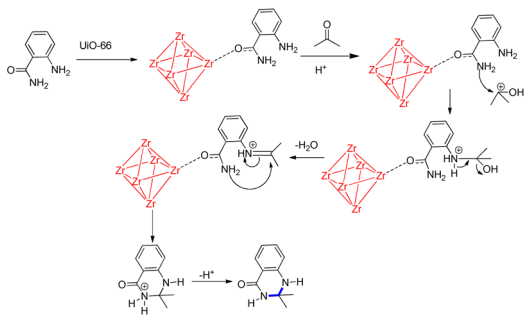


Scheme 26 Mechanism for the synthesis of (*S*)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one.

Because of its biological and pharmaceutical properties, quinazolinone and its derivatives are a significant class of heterocycles that contain nitrogen.[132–135] These substances are also useful starting points for the synthesis of several pharmaceuticals that are sold commercially.[136] Quinazolinone **96** are synthesized by the reaction of 2-aminobenzamide **94** and



Scheme 27 Synthesis of quinazolinones.

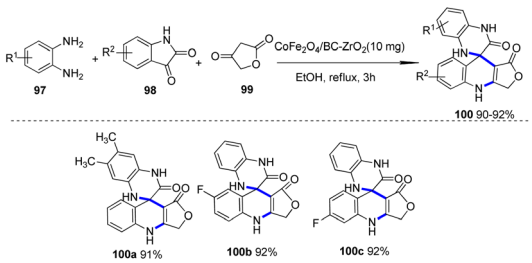


Scheme 28 Proposed mechanism for the synthesis of quinazolinones.

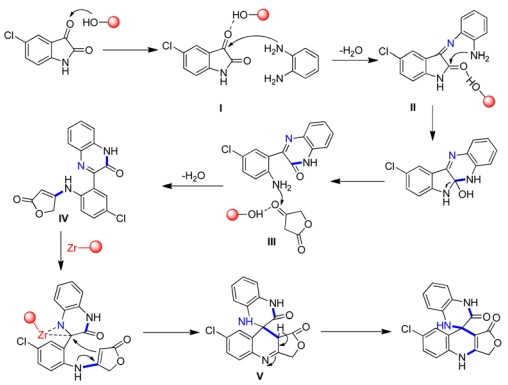
ketone **95** in the presence of acetic acid and UiO-66-MW Zr complex (Scheme 27). The possible reaction mechanism for quinazolinone synthesis is shown in (Scheme 28).

Polyheterocyclic compounds are extensively used in food, medicine, building materials and fine chemicals.[137] Many natural alkaloids and pharmaceuticals contain heterocyclic spiroindoles, which are also used as building blocks in synthetic organic chemistry.[138] Quinoxaline derivatives have a variety of pharmacological characteristics, such as anti-hyperglycemic, anticonvulsant, analgesic, anti-HIV, antidepressant and anticancer effects.[22,139] Furan-2,4[3*H*,5*H*]-dione, a heterocyclic tetronic acid, exhibits antibacterial, fungicidal, and insecticidal properties.[140,141] Biochar (BC) is a biomass carbon based material that is obtained from agricultural waste, pyrolysis of sediments and biomass in a hypoxic environment. BC qualities include a large surface area, high permeability, potent adsorption capability, good stability, and modifiable functional groups.[142,143] Conversely, ZrO_2 is a commonly utilized catalyst in organic reactions.[63] Zhang and colleagues designed an effective magnetic recyclable catalyst ($CoFe_2O_4$/BC-ZrO_2) supported on magnetic BC for the synthesis of bioactive organic compounds. By using benzene-1,2-diamine **97**, tetronic acid **98** and indoline-2,3-dione **99** as three separate components in a three-component reaction, spiro[furo[3,4-*b*]quinolones] **100** were synthesized. Yields are adjusted by varying the reaction parameters and the neutral, electron-donating or electron-withdrawing R groups (Scheme 29).

A possible mechanism (Scheme 30) for this reaction is that enormous number of hydroxyl groups present on catalyst surface form hydrogen bonding with the indoline-2,3-dione



Scheme 29 Zr-catalysed synthesis of 1*H*,1′*H*-spiro[furo[3,4-*b*]quinoline-9,2′-quinoxaline]-1,3′(3*H*,4*H*,4′*H*)-diones.

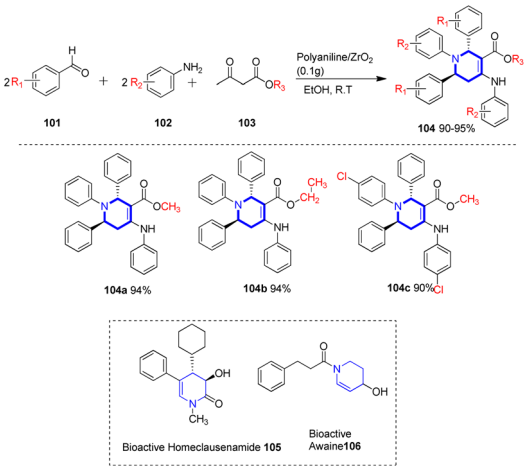


Scheme 30 Mechanism for the formation of 7-chloro-1-*H*-spiro[furo[3,4-*b*]quiloxaline-9,2′-quinoline]-1,3′(3*H*,4*H*,4′*H*)-dione.

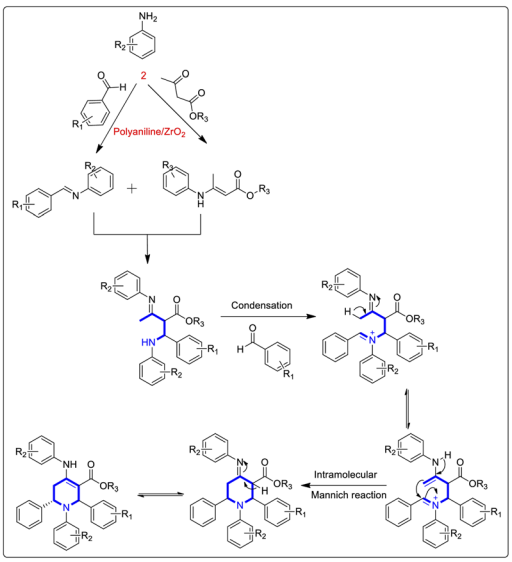
carbonyl group to produce intermediate **I**. Intermediate **II** is synthesized when the amino groups of benzene-1,2-diamine undergoes an aldoamine condensation reaction with intermediate **I**. Attack of amino groups of intermediate **II** on the activated carbonyl group generates intermediate **III**. The catalyst activates the tetronic acid carbonyl position by forming a hydrogen bond with the OH group, resulting in the production of intermediate **IV**. With the help of the catalyst, intermediate **IV** is formed into σ–π. Intermediate **V** is then produced by intramolecular cyclization, and its tautomerization yields the final products **100**.[22]

2.5. Synthesis of substituted pyridines

Tetrahydropyridine derivatives are favourable scaffolds for a variety of naturally occurring and artificially produced bioactive compounds, including ciprofloxacin, arecoline, homoclausenamide **105**, awaine **106**, and lapadin B.[61,62] Tetrahydropyridines are interesting target molecules for synthesis due to their varied pharmacological activities such as analgesic,[144] hyperglycemic,[145] anticonvulsant,[146] antitumor,[147] vasodilators,[148] antioxidant[149] and HIV protease inhibitor.[150] Yelwande and colleagues used a polyaniline zirconium oxide catalyst to synthesize tetrahydropyridines **104** in a one-pot manner by condensation of aldehydes **101**, anilines **102**, and β-keto esters **103** (Scheme 31).



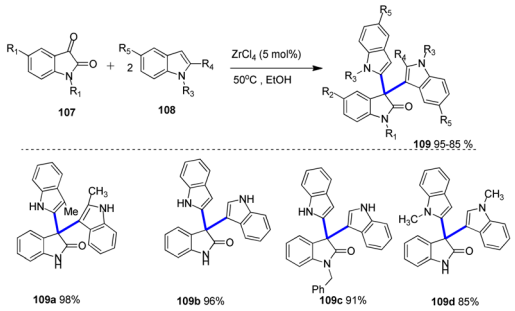
Scheme 31 Zr-catalysed synthesis of tetrahydropyridine derivatives.



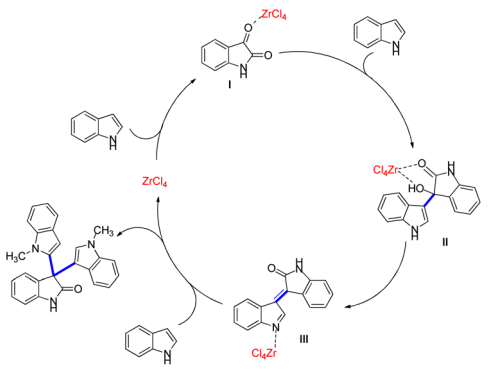
Scheme 32 Plausible mechanism for the synthesis of tetrahydropyridines derivatives.

Scheme 32 illustrates a reasonable process for the synthesis of tetrahydropyridines **104**. ZrO_2 functions as a Lewis acid catalyst when aniline and methyl acetoacetate or benzaldehyde react, resulting in the production of β-enaminone or imine. The steps involved in forming a product are intermolecular Mannich reaction, condensation, tautomerism, intramolecular Mannich reaction and tautomerism at the last step.[151]

Indole derivatives are substances with biological and pharmacological activity that are used as intermediate products in the synthesis of organic compounds.[152,153] The pharmacological activities of indole derivatives [2,3′:3′,3″-terindolin]-2′-one include antiproliferative,[154] antibacterial,[155] anti-inflammatory,[156] laxative[157] and anticonvulsant qualities.[158] Hojati and colleagues synthesized indole derivatives **109**, when isatin **107**



Scheme 33 Indole derivative synthesis using zirconium(IV).

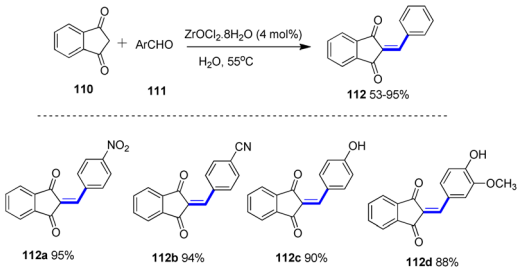


Scheme 34 Plausible mechanism for the synthesis of indole derivatives.

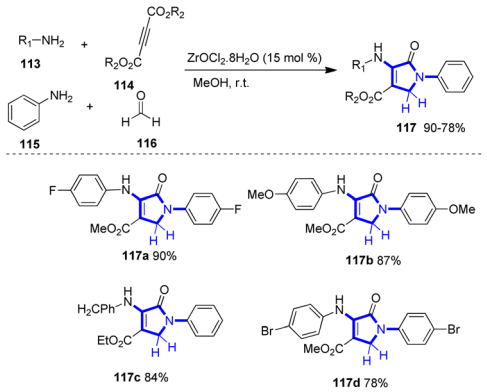
and indole **108** in EtOH were reacted in the presence of $ZrCl_4$ at 50 °C, resulting in a 95% yield (Scheme 33).

Scheme 34 provides a feasible mechanism for indole derivative synthesis. It is plausible that $ZrCl_4$ will coordinate with isatins non-amidic carbonyl group and activate intermediate **I**. Then, (*S*)-3-hydroxy-3-(1*H*-indol-3-yl)indolin-2-one **II** is produced as a critical intermediate by nucleophilic attack of indole at position **I**, and this is converted into **III** as a result of H_2O loss. N-activated **III** is combined with the second indole to create the analogous product, and $ZrCl_4$ proceeds to the subsequent catalytic cycle.[159]

The *Flavivirus* genus includes a family of encased RNA arthropod-borne viruses, which cause a number of serious diseases in humans and animals, such as the Kyasanur Forest disease virus (KFDV), (JEV), (WNV), Dengue virus (DENV), Zika virus (ZIKV), and Yellow fever virus. 2-Benzylidene-1*H*-indene-1,3(2*H*)-dione derivatives exhibit flavivirus protease inhibitory activity.[160] 2-Benzylidene-1*H*-indene-1,3(2*H*)-dione **112** was designed using a simple and efficient Knoevenagel method. $ZrOCl_2.8H_2O$ was used as a catalyst in the reaction between indan-1,3-dione **110** and various aromatic aldehydes **111** to create these moieties, with water acting as a solvent. The generated compounds were evaluated for their capacity to inhibit the NS2B-NS3 protease of the West Nile virus (WNV) (Scheme 35).[161]



Scheme 35 Synthesis of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione derivatives catalysed by Zr.

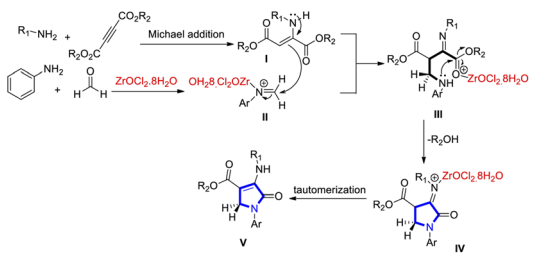


Scheme 36 Zr-catalysed synthesis of derivatives of substituted dihydro-2-oxopyrroles.

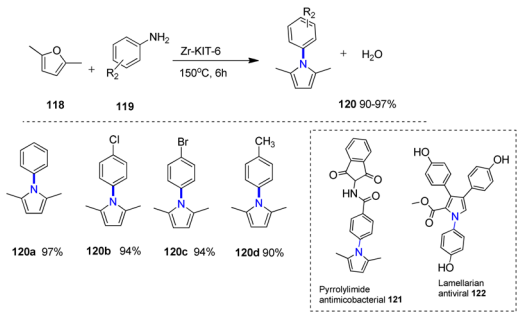
2.6. Synthesis of substituted pyrrole derivatives

Pyrroles rings have gained considerable devotion because of their advantages in biological and pharmaceutical products, such as cytomegalovirus protease,[162] CD45 protein tyrosin-phoshate,[163] anticancer,[164] thiomarinol A3 antibiotic,[165] alkaloids,[166] UCS1025A,[167] and oteromycin.[168] These rings show herbicidal activities[169] and are a component of HIV integrase.[170]

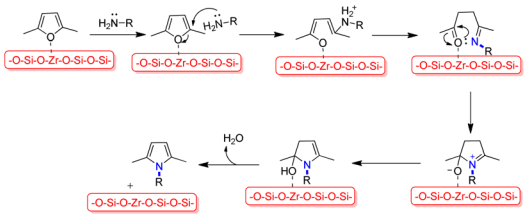
Using a mixture of amine **113** and dialkyl acetylenedicarboxylate **114**, which was stirred in MeOH for 15 minutes, Mohamadpour synthesized substituted dihydro-2-oxopyrroles **117** by adding $ZrOCl_2 \cdot 8H_2O$ (15 mol%), amine **115** and formaldehyde **116**, and stirring the reaction for the appropriate amount of time (Scheme 36).



Scheme 37 Feasible process of synthesizing substituted dihydro-2-oxopyrroles.



Scheme 38 Zr-KIT catalysed synthesis of pyrrole derivatives.



Scheme 39 A conceivable process for the synthesis of *N*-aryl pyrrole in the presence of Zr-KIT-6.

Scheme 37 depicts the suggested procedure for producing highly substituted dihydro-2-oxopyrroles **117** when $ZrOCl_2 \cdot 8H_2O$ is present. To produce intermediate **I**, dialkyl acetylenedicarboxylate **114** and an amine **113** first react. Second, imine is produced by the condensation of amine and formaldehyde **116** in the presence of $ZrOCl_2 \cdot 8H_2O$. Because of its enamine nature, intermediate **I** can easily react with imine **II** in $ZrOCl_2 \cdot 8H_2O$ to produce intermediate **III**. The final step involves tautomerizing intermediate **IV** to the corresponding highly substituted dihydro-2-oxopyrroles **V** after intermediate **IV** is cyclized.[171]

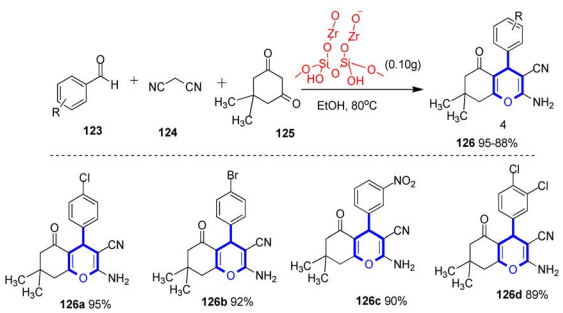
Pyrroles are needed to make agrochemicals, drugs, dyes, and molecular materials for electronics and transmission applications.[172–174] *N*-Aryl pyrroles exhibit noteworthy biological properties such as anticancer,[175] antitumor,[176] antifungal,[177] anti-tubular,[178] anti-mycobacterial,[179] anti-HIV,[180] and anti-inflammatory.[181] Currently, the pharmaceutical, polymer, and other chemical-based industries require more than 10 000 tons of pyrroles per year to meet their needs. A low-cost, easily scalable Lewis acid catalyst based on zirconium is called Zr-KIT-6. Using Zr-KIT-6 catalyst, condensation of 2,5 DMF **118**, and aniline **119** under ideal reaction conditions, Manal and Srivastava produced *N*-aryl pyrrole **120** (Schemes 38 and 39).[28]

2.7. Synthesis of substituted benzopyran

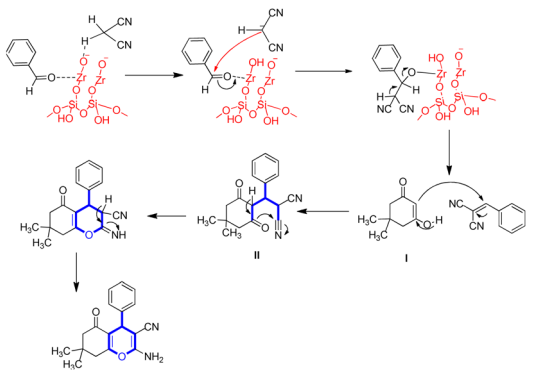
Zirconium silicates are abundant in nature and have received an abundance of intrigue, mostly involving the resolution of general geophysical and mineralogical issues, due to their creation under hydrothermal circumstances (between ≈300 and ≈550 °C).[182] Approximately one-third of the known zirconium silicates, both natural and manufactured, have crystal structures that have been determined. Maurice conducted some of the earliest hydrothermal synthesis of zirconium silicates in 1949.[183,184] Derivatives of tetrahydro-1-benzopyran show various effects on biological processes, such as anti-anaphylactic, anti-cancer, diuretic, spasmolytic and anticoagulant properties.[185] They are also used to treat AIDS, amyotrophic lateral sclerosis, neurodegenerative diseases and cognitive enhancers.[186] Mishra and colleagues used multicomponent condensation of different aldehydes **123** with malononitrile **124** and dimedone **125** to create bioactive tetrahydro-1-benzopyran derivatives **126**. Many benefits are provided by this protocol, including high yields, an easy-to-follow experimental work-up process, a quick reaction time, absence of by products, affordability, simple reliability of catalysts and detoxification (Scheme 40).

Scheme 41 provides a tenable mechanism for tetrahydro-1-benzopyran synthesis **126**. ZrRHSi activates aldehyde **123** in the reaction, which is then attacked by dicyanomethanide to form Knoevenagel adduct **I**. This adduct then combines with the enol form of dimedone **125** to produce intermediate **II**. Later, it is cyclized to produce tetrahydro-1-benzopyrans.[187]

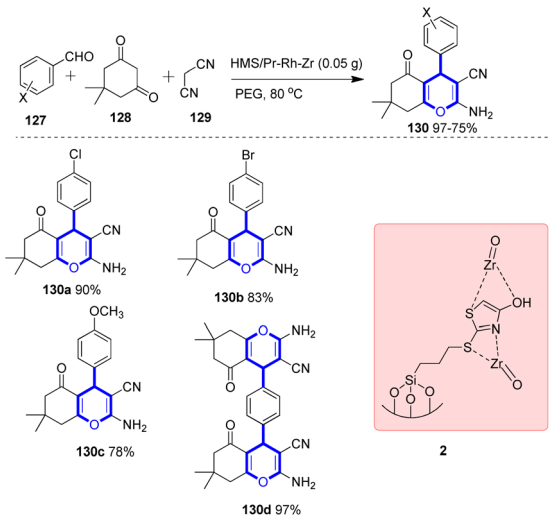
Benzopyran and pyrano[2,3-*c*] pyrazole are extensively used in pharmaceutical chemistry and biosciences. They are used as antibacterial,[188,189] anticancer,[190] anti-inflammatory[191,192] and antioxidants.[193,194] Abdolahi and colleagues synthesized



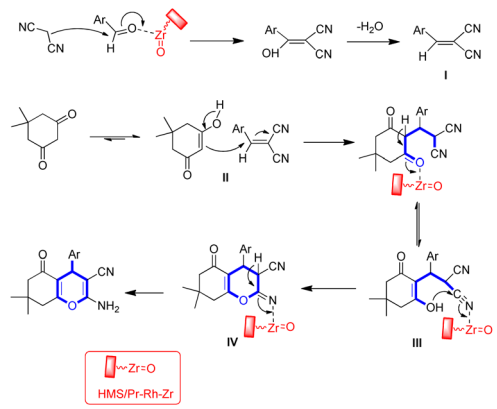
Scheme 40 Tetrahydro-1-beznopyran synthesis using silicated zirconium.



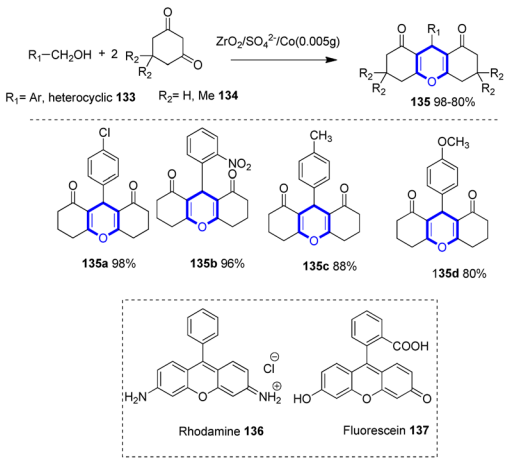
Scheme 41 Plausible process for synthesizing tetrahydro-1-beznopyrans.



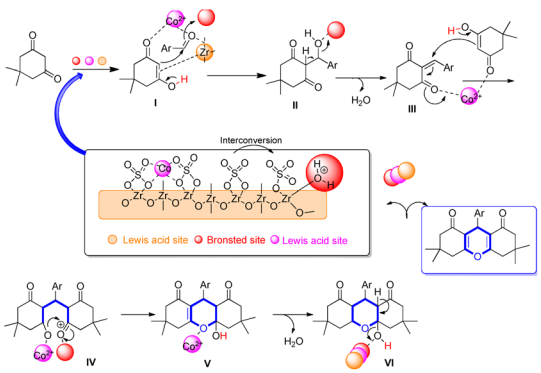
Scheme 42 Synthesis of (*S*)-2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives.



Scheme 43 Plausible mechanism for the synthesis of (*S*)-2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile.



Scheme 44 Scheme for the synthesis of 3,3,6,6,9-pentamethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives.



Scheme 45 Suggested process for synthesizing derivatives of 3,3,6,6,9-pentamethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione.

tetrahydrobenzo[*b*]pyran **130** using HMS/Pr-Rh-Zr added to a mixture of aldehyde **127**, malononitrile **129** and dimedone **128** in polyethylene glycol (PEG) at 80 °C (Scheme 42).

Tetrahydrobenzo[*b*]pyran formation in the presence of HMS/Pr-Rh-Zr is shown to be a likely reaction mechanism in Scheme 43. When activated aldehyde **127** and malononitrile **129** react, arylidene malononitrile intermediate **I** is produced, marking the start of the reaction. Arylidene malononitrile intermediate **I** produced in the preceding step reacts with enolized dimedone **128 II** in the subsequent step. Ultimately, tetrahydrobenzo[*b*]pyran **130** is created because of rearranging and intramolecular cyclization.[16]

The core xanthene structure can be efficiently synthesized using ZrO_2/SO_4^{2-}/Co catalyst. Further functionalization of this core structure lead to the formation of various artificial dyes, such as rhodamine, fluoresceins and eosins, which have diverse applications (Fig. 8).

Nasseri and colleagues[195] synthesized 1,8-dioxo-octahydroxanthene **135** using aldehyde **133** (1 equiv.), 1,3-cyclohexadione **134** (2.1 equiv.) and water as solvent. After adding the catalyst (0.005 g), the mixture was agitated for the required time at 25 °C (Scheme 44).

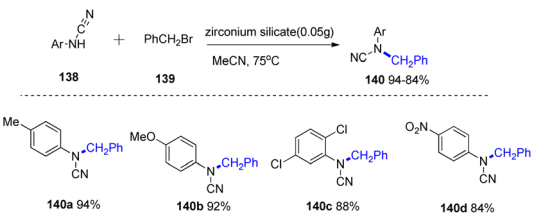
A plausible mechanism was proposed in Scheme 45.[196–199] At first, the catalyst's Co and Zr Lewis acid sites activated aldehyde and cyclohexadione derivatives. A cyclohexadione is attacked nucleophilically to initiate the reaction, which is then followed by an aldehyde capturing a proton with the catalyst's Brønsted acid (Scheme 45 **I** and **II**). Once more, a water molecule is eliminated by Brønsted acid to create a Knoevenagel product **III** (Scheme 45). The cyclic intermediate **IV** is produced by the reaction continuing with another nucleophilic assault of cyclohexadione to **III**. Lewis and Brønsted acid mediators are used in the catalyst to facilitate the cyclization process **V**. Ultimately, the process of dehydrating **VI** yields the required 1,8-dioxo-octahydroxanthene product and regenerates the ZrO_2/SO_4^{2-}/Co catalyst for the subsequent cycle (Scheme 45).[27]

2.8. Synthesis of substituted amides

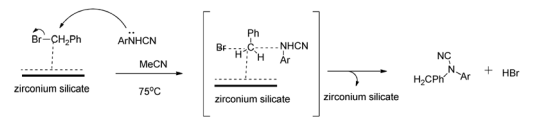
In synthetic organic and coordination chemistry, cyanamides are a prominent class of reactive organic molecules with a wide variety of uses.[200–203] It is known that compounds based on cyanamide have a range of intriguing biological properties, including antiviral and anticancer properties.[204,205] The suggested method for using zirconium silicate to *N*-benzylate arylcyanamides is depicted in Scheme 46. The Lewis acidity of the zirconium silicate nanocomposite material in the *N*-benzyl-*N*-phenylcyanamide is probably going to play a significant part in this. It was proposed that using a zirconium silicate nanocomposite to activate the C–Br bond of benzyl bromide would enable the synthesis of *N*-benzyl-*N*-phenylcyanamide *via* an SN_2-type mechanism in an aprotic solvent of MeCN with nucleophile attack of the phenylcyanamides (Scheme 47).[206]

Aromatic nitro compounds **141** reduction: The catalytic transfer hydrogenation of aromatic nitro compounds **141** to the corresponding amines **142** is an important step in the commercial synthesis of colours, physiologically active compounds, medications, rubber chemicals, photography, and agricultural chemicals.[207] Numerous techniques have been created for this aim (Scheme 48).[208]

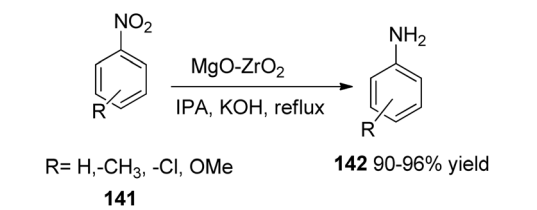
Creating derivatives of (*S*)-*N*-(1-(2-hydroxynaphthalen-1-yl) ethyl)acetamide is an interesting use for these MCRs. A lot of attention has focused on derivatives of 1-amidoalkyl-2-naphthols with 1,3-amino functional groups that are oxygenated because they are essential parts of many potent drugs, synthetic pharmaceuticals and bioactive natural products, including HIV protease inhibitors and several nucleoside antibiotics.[209] Dipake and colleagues synthesized 1-aminoalkyl naphthols **146** by combining benzamide **145**, aldehyde **144** and naphthol **143** at 110 °C with zirconium silicate catalyst without the use of a solvent (Scheme 49).



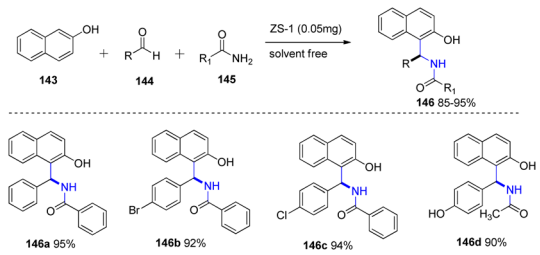
Scheme 46 Zirconium silicate catalysed *N*-benzylation of arylcyanamides.



Scheme 47 Proposed mechanism for *N*-benzyl-*N*-phenylcyanamide synthesis.



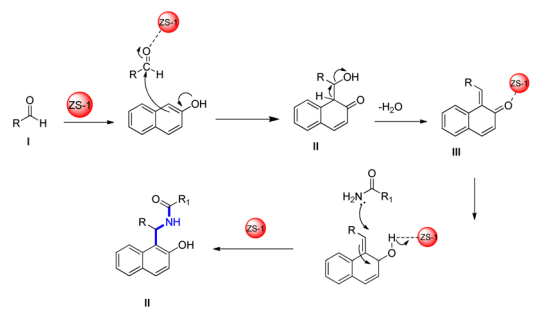
Scheme 48 Utilization of $MgO–ZrO_2$ for reduction of an aromatic nitro compound.



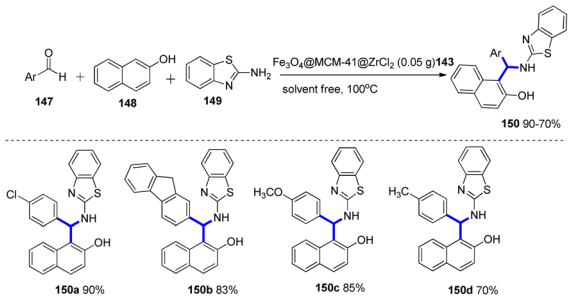
Scheme 49 Scheme for the synthesis of (*S*)-*N*-(1-(2-hydroxynaphthalen-1-yl)ethyl)acetamide.

Scheme 50 illustrates the suggested reaction mechanism for the ZS-1 catalyst-mediated synthesis of (*S*)-*N*-(1-(2-hydroxynaphthalen-1-yl)ethyl)acetamide.[210,211] Because of the characteristics of the ZS-1 catalyst, the carbonyl group of aldehydes has a lower electron density. B-naphthol's nucleophilic attack on the carbonyl group of activated aldehydes forms intermediate **II**. Next, the water molecule condensed to form the *ortho*-quinone methide **III** intermediate. After that, the ZS-1 catalyst activates the *ortho*-quinone methide **III** intermediate, which then allows the Michael addition of amide to yield (*S*)-*N*-(1-(2-hydroxynaphthalen-1-yl)ethyl)acetamide **IV** as expected.[212]

It is certain that the 2-aminobenzothiazole core plays a wide and important role in industrial, biological, and pharmaceutical chemistry as a preferred scaffold.[213–221] Among these kinds of compounds, benzo[*d*]thiazol-2-amine and a Betti base are the two biologically active components of ((benzo[*d*]thiazol-2-ylamino)methyl)naphthalen-2-ol. The molecule known as 1-(amino(phenyl)methyl)naphthalen-2-ol, which has two active amino and hydroxyl groups, is called a Betti base and is essential in synthetic chemistry because it can create C–C bonds



Scheme 50 Mechanism for the synthesis of (*S*)-*N*-(1-(2-hydroxynaphthalen-1-yl)ethyl)acetamide.

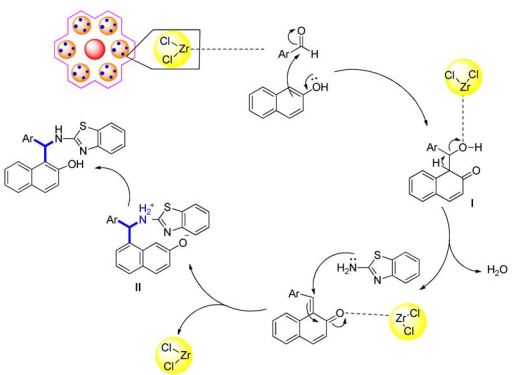


Scheme 51 Scheme for the synthesis of ((benzo[*d*]thiazol-2-ylamino) methyl)naphthalen-2-ol.

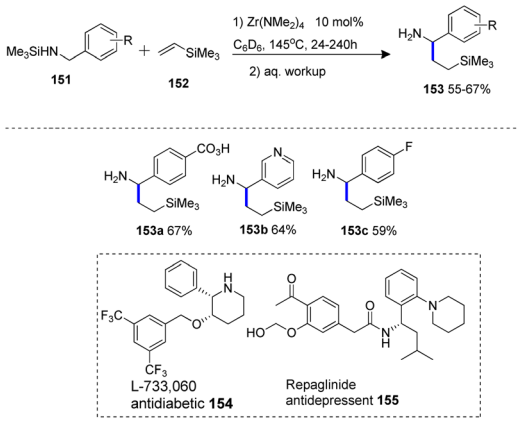
in mild laboratory settings.[221] The targeted nanocomposite exhibited favourable efficiency in the multicomponent condensation reaction of aromatic aldehydes **147**, naphthalen-2-ol **148** and benzo[*d*]thiazol-2-amine **149** in the absence of solvent, owing to the presence of zirconium. These reactions have excellent yields (70–90%) of ((benzo[*d*]thiazol-2-ylamino) methyl)naphthalen-2-ol **150** (Scheme 51).

The Lewis acidic catalyst Fe_3O_4@MCM-41@$ZrCl_2$ is said to initiate the reaction by activating the aldehyde's carbonyl group, according to the proposed mechanism. Next, 2-naphthol attacks the activated aldehyde nucleophilically, forming intermediate **I**. The next stage produces intermediate **II** and finally the main product by reacting this intermediate with 2-amino-benzothiazole (Scheme 52).[18]

α-Arylated amines are used as construction blocks to make medications like L-733-060 **154**, an antidepressant/anxiolytic and repaglinide **155**, an antidiabetic. A novel and cost-effective catalytic technique for creating Csp_3–Csp_3 bonds α-to nitrogen in primary and secondary amine substrates is hydroaminoalkylation.[222–226] The synthesis of (*R*)-1-phenyl-3-(trimethylsilyl)propan-1-amine **153** through zirconium catalysis was reported by Ana and colleagues. This involved using *N*-silylated benzyl amines **151** to hydroaminoalkylate activated and unactivated alkenes **152**. An easy-to-find commercially accessible $Zr(NMe_2)_4$ was discovered to catalyse the formation



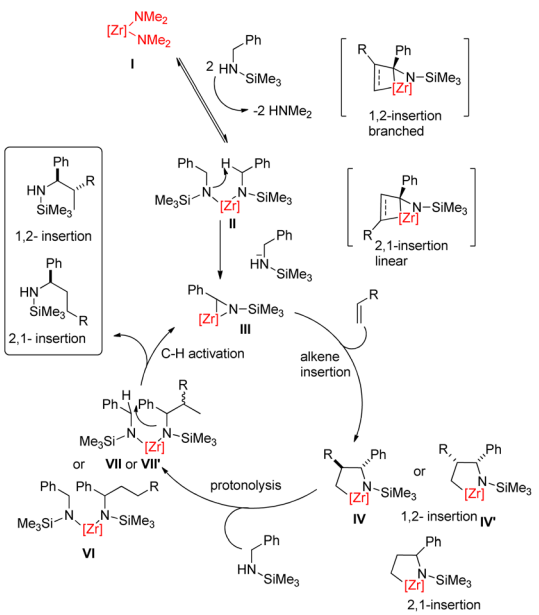
Scheme 52 Proposed mechanism for the synthesis of ((benzo[*d*] thiazol-2-ylamino)methyl)naphthalen-2-ol.



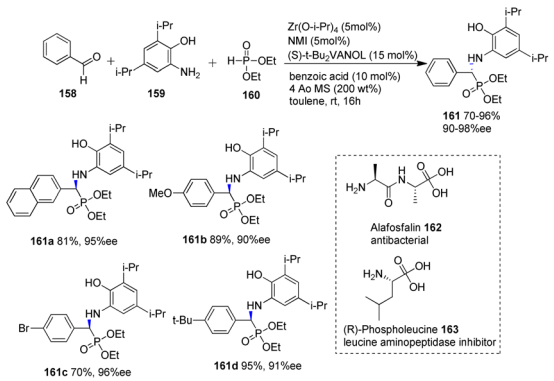
Scheme 53 (*R*)-1-phenyl-3-(trimethylsilyl)propan-1-amine synthesis using zirconium.

of Csp_3–Csp_3 bonds by activating the carbon–hydrogen bond α to nitrogen, resulting in the wanted products after aqueous workup (Scheme 53).

Scheme 54 presents a plausible mechanism for hydro-aminoalkylation catalysed by transition metals. After complex **I** formation, amido groups are transmuted with *N*-silylamine to form complex **II**, and the catalytically active zirconaaziridine **III** with its phenyl substituent is produced upon hydrogen removal. Complex **III** then undergoes alkene insertion into the more reactive carbon–carbon bond to form zirconapyrrolidine intermediates **IV** and **V**, where the steric bulk of the alkene affects the reaction's regioselectivity. Diastereomers **IV** and **IV′** may arise from the formation of intermediate **IV**, and the major



Scheme 54 Mechanism for (*R*)-1-phenyl-3-(trimethylsilyl)propan-1-amine synthesis.



Scheme 55 Synthesis of α-aminophosphonic acid using a zirconium metal complex.

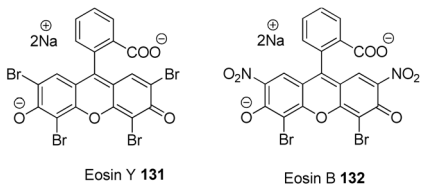
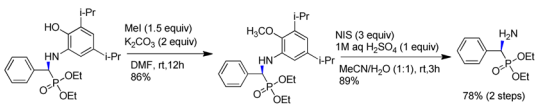


Fig. 8 Dyes with the xanthene core in their structure.



Scheme 56 Liberation of α-amino phosphonates.

diastereomer is obtained by *trans*-orienting the metallacyclic intermediates.[227,228]

2.8.1 Kabachnik-fields reaction. Alpha-aminophosphonic acids **161** are significant analogues of α-amino acids.[229,230] They can used as transition state correspondents of a tetrahedral intermediate formed during hydrolysis of carbonyl amide. Many of the bioactivities of aminophosphonic acid are associated with their capacity to inhibit enzymes that are capable of cleaving peptide bonds.[231] Bioactive α-aminophosphonic acids are alafosfalin **162** (antibacterial)[232,233] and phospholeucine **163** is a leucine aminopeptidase inhibitor.[234,235] It is crucial to the function of pepsin and penicillopepsin inhibitors.[236] Using the VANOL complex of zirconium catalyst **157**, Dai and colleagues synthesized α-aminophosphonic **161** acid through a one pot reaction involving aldehyde **158**, amine **159** and phosphite **160** (Scheme 55).[237]

Three VANOL **156** ligands encircle zirconium **157** (Fig. 9) and charge is balanced by two protonated *N*-methylimidazoles. Scheme 56 presents the liberation of α-amino phosphonates.

2.9. Synthesis of substituted triazolidine

N-heterocycles are essential components of many natural product analogues with a variety of biological functions and are basic components in the discipline of heterocyclic chemistry.

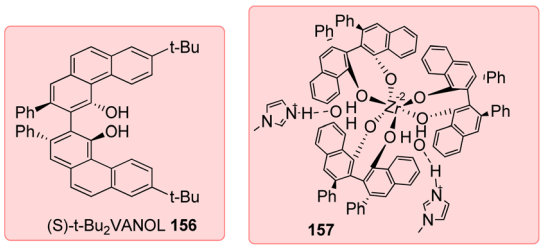
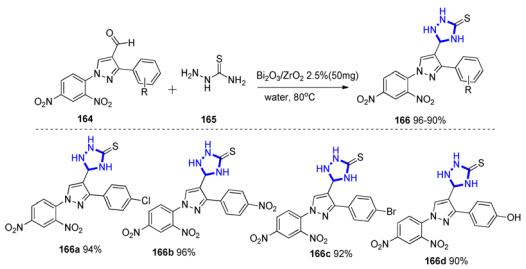


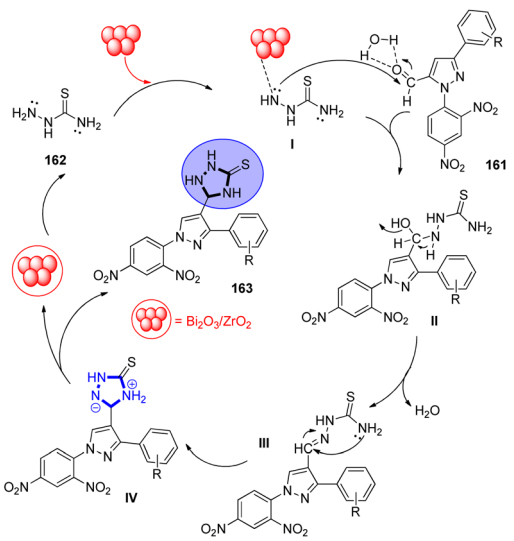
Fig. 9 Structure of a homoleptic VANOL complex of zirconium.



Scheme 57 Scheme for the synthesis of 1,2,4-triazolidine-3-thiones.

Numerous triazoles exhibit antibacterial, anticonvulsant,[238] anti-leishmanial,[239] anti-tubercular,[240] and anticancer[241] properties. Among them, triazoles with pyrazole groups stand out due to their potent PDE4 inhibitory properties.[242] Kerru and colleagues[243] used thiosemicarbazide **165** and water, an environmentally friendly solvent, to create 1,2,4-triazolidine-3-thiones **166** by heating 1-(2,4-dinitrophenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehyde **164** at 80 °C for 30 to 45 minutes (Scheme 57).

Active intermediate **I** is produced in the first reaction, which is the probable adsorption of thiosemicarbazide **165** onto the



Scheme 58 Mechanism for the synthesis of 1,2,4-triazolidine-3-thiones.

Bi_2O_3/ZrO_2 catalyst's active site. The reaction is made possible by the multiple Lewis acid catalytic centres that allow the active sites of bismuth and zirconia to cooperate. The two oxides' active sites working together synergistically results in the improved production of the product. Water may then form a hydrogen bond with the oxygen atom of the carbonyl group and the water molecule, increasing the electrophilicity of the second precursor, pyrazole-4-carbaldehyde **164** carbonyl carbon. Thus, hemiminal intermediate **II** was created.[244,245] The water molecule (H_2O) was eliminated to form thiosemicarbazone **III**, and the ring closed as a result of the free –NH_2 group III's intramolecular cyclization and tautomerization. The intended target compound was 5-(1-(2,4-dinitrophenyl)-3-phenyl-1*H*-pyrazol-4-yl)-1,2,4-triazolidine-3-thione **166** (Scheme 58).

3 Conclusion

The exploration of zirconium metal-based catalysis in synthesizing bioactive molecules has yielded significant potential for advancing pharmaceutical development and creating biologically active compounds. This research showcases the latest breakthroughs in zirconium catalysis, underscoring its effectiveness and versatility. Zirconium catalysis emerges as a sustainable, efficient and adaptable tool for the synthesis of various bioactive heterocyclic molecules such as imidazoles, pyrazole, pyrimidinones, quinolines, quinazolinones, pyridines, pyrroles, benzopyrans, substituted amides and triazolidine. This makes it easier to synthesize intricate chemical structures with excellent efficiency and encourages the formulation of novel proposals for modifying pharmacological compounds. Zirconium catalysis is a powerful synthetic tool, enabling complex reactions under mild conditions while promoting sustainability. Due to its cost-effectiveness, stability and recyclability, zirconium catalysts offers promising advantages for future applications. It is significant to use green and stable zirconium catalysts in pharmaceutical production instead of other metal catalysts. Developments of greener ligands, chiral zirconium catalysts and Zr-based MOFs as heterogeneous catalysts enhances future research. Since there is no comprehensive review on zirconium-mediated organic synthesis published after 2022, there is a significant research gap in this area. Our review aims to address and potentially fill this gap.

Data availability

No new data have been generated, and all data are present in the manuscript.

Author contributions

S. Bibi: wrote the manuscript. M. Zubair: supervised the project. R. Riaz: conducted literature survey and data analysis. A. Kanwal & S. A. A. Shah: review and editing. All the authors reviewed and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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