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REVIEW

# Review on advancements of pyranopyrazole: synthetic routes and their medicinal applications

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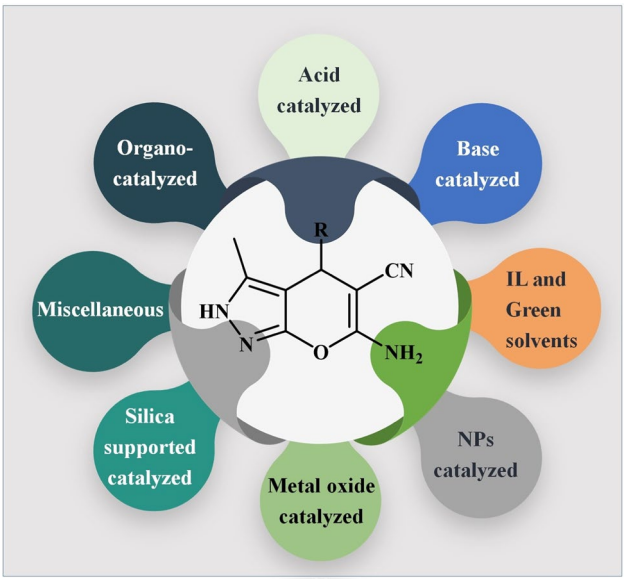
## Abstract

Pyranopyrazoles are among the most distinguished, biologically potent, and exciting scaffolds in medicinal chemistry and drug discovery. Synthesis and design of pyranopyrazoles using functional modifications via multicomponent reactions (MCRs) are thoroughly found in synthetic protocols by forming new C–C, C–N, and C–O bonds. This review aims to focus on the biological importance of pyranopyrazoles as well as on a diverse synthetic approach for their synthesis using various catalytic systems such as acid-catalyzed, base-catalyzed, ionic liquids and green media-catalyzed, nano-particle-catalyzed, metal oxide-supported catalysts, and silica-supported catalysts. In this review, we have summarized data on the advancements in synthesizing pyranopyrazole from the last two decades to the mid-2023 and research papers describing the importance of these scaffolds. This review will be significant for synthetic organic chemists and researchers working in organic chemistry.

### Graphical abstract




**Keywords** Pyranopyrazoles · Multicomponent reactions (MCRs) · Ionic liquids catalyzed · Nano-particles catalyzed · Silica-supported catalyst

Extended author information available on the last page of the article

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## Introduction

Heterocyclic nuclei have the potential to gain interest in a pharmacological activity for their application as a scaffold in the intent of biologically potent compounds [1, 2]. Multicomponent reaction (MCR) is a process contained in a chemical reaction; the combination of three or more reactants results in products in which all the reactions are essential parts of substantial chemistry. MCRs comply with several of the strict requirements of good for organic synthesis. These protocols are valuable and efficient organic synthesis from easily offered starting compounds in a single phase with the intrinsic flexibility to create molecular complexities, and diversification by reducing time, cost, and waste material [3–5]. Pyranopyrazoles are privileged motifs with two nitrogen atoms in 1, 2-positions and because of its structurally diverse biological range, one oxygen has received a lot of interest in medicinal chemistry [6]. Therefore, the progress of MCR in synthetic chemistry and methods for producing heterocyclic molecules have received Excellent focus. Pyranopyrazole is present in four isomeric forms such as pyrano[2,3-*c*] pyrazole (**I**), pyrano[3,2-*c*] pyrazole (**II**), pyrano[3,4-*c*] pyrazole (**III**), pyrano[4,3-*c*] pyrazole (**IV**), out of this isomeric form isomer pyrano[2,3-*c*] pyrazole (**I**) is broadly explored as it has high medicinal and industrial prominence in Fig. 1**.**

Pyranopyrazole rings possess broadly a variety of biological processes, including antimicrobial [7], anti-inflammatory [8, 9], and anticancer [10]. In particular, pyranopyrazole is regarded as a scaffold in the therapy of inhibitors of human Chk1 kinase [11]. Some of these biologically active molecules are shown in Fig. 2.

Using pyrazole-5-ones and tetracyanoethylene compounds, in 1973, Junek and Aigner synthesized pyrano [2,3-*c*] pyrazole motifs (**5**) [12]. Later on, in the subsequent years, there was an overwhelming response to the development of (**5**), and several experimental pyrazoles on heterocyclic compounds were performed up to mid-2023. Earlier reviews and book chapters are fascinating, mainly focused on the synthesizing and therapeutic application of pyranopyrazole motifs and suggesting potential heterocyclic compound [13–16]. In recent years, efforts have focused on significant pyranopyrazole candidates with extensive biological activities. However, to our knowledge in recent years, the correlation between pyranopyrazole derivatives and their biological activities has yet to be reviewed. Thus, the idea of the current review is to sum up pyranopyrazole development strategies and biological activities for those committed to designing novel compounds in the near future. Herein, we summarized the synthesis of pyranopyrazole heterocyclic compounds, based on the classification of the nature of catalysts Fig. 3**.**

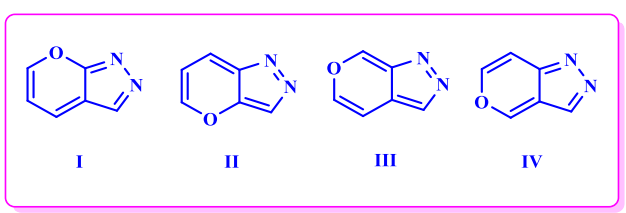



**Fig. 1** Isomeric of pyranopyrazole

## General method for synthesis pyranopyrazole

Pyranopyrazole (**5**) synthesized using multicomponent reaction (MCR) carried out four-component transformations. Ethyl acetoacetate (**1**) and hydrazine hydrates (**2**) were mixed into a round bottom flask and then aromatic aldehydes (**3**) and malononitrile (**4**) were added in the presence of a catalyst to offer a product. The general representation of (Scheme 1) and mechanism is given in Fig. 4.

### Acid-catalyzed reaction

Chaudhari et al. introduced an expedient and utilizing p-toluene sulfonic acid-supported polystyrene as a reusable and active heterogeneous catalyst in an aqueous solution as part of a green one-pot synthesis method (**5**). Essential aspects of the current methodology are admirable yields, a wide range of substrates, a simple workup procedure, and an inexpensive approach synthesis of (**5**) (Scheme 2) [17]. Later, Moosavi-Zare et al. efficiently used boric acid in aqueous form, a green system for tandem reaction of (**1**), (**2**), (**3**), and (**4**) to offer (**5**), $B(OH)_3$ catalyst in aqueous medium at 70 °C, and economical catalyzed reaction under mild condition (Scheme 2) [18]. Further, Abdolkarim Zare and co-workers did a synthesis of (**5**) employing the heterogeneous catalyst disulfonic acid imidazolium chloroaluminate [(Dsim)$AlCl_4$], the accessible protocol is efficient, good-to-excellent yield, comparatively less time, and finally adherence to green protocol (Scheme 2) [19].

Ahad et al. have achieved a heterocyclic synthesis of compound (**5**) by using (**1**), with (**2**), (**3**), and (**4**) produced in situ were successfully used in a process via an effective organocatalyst aspartic acid-catalyzed Knoevenagel reaction. A mixture of aqueous ethanol as a green medium, at room temperature offers good yields of reaction (Scheme 3) [20]. Zolfigol et al. introduced a straightforward and effective process for the preparation of (**5**) using condensation reactions of (**1**), (**2**) with 3-methyl-1*H*-pyrazol-5(4*H*)-one (**6**) in isonicotinic acid was used in the reaction as a biological and dual organocatalyst at 85 °C in neat condition to offer lesser reaction time of reaction (Scheme 3) [21].

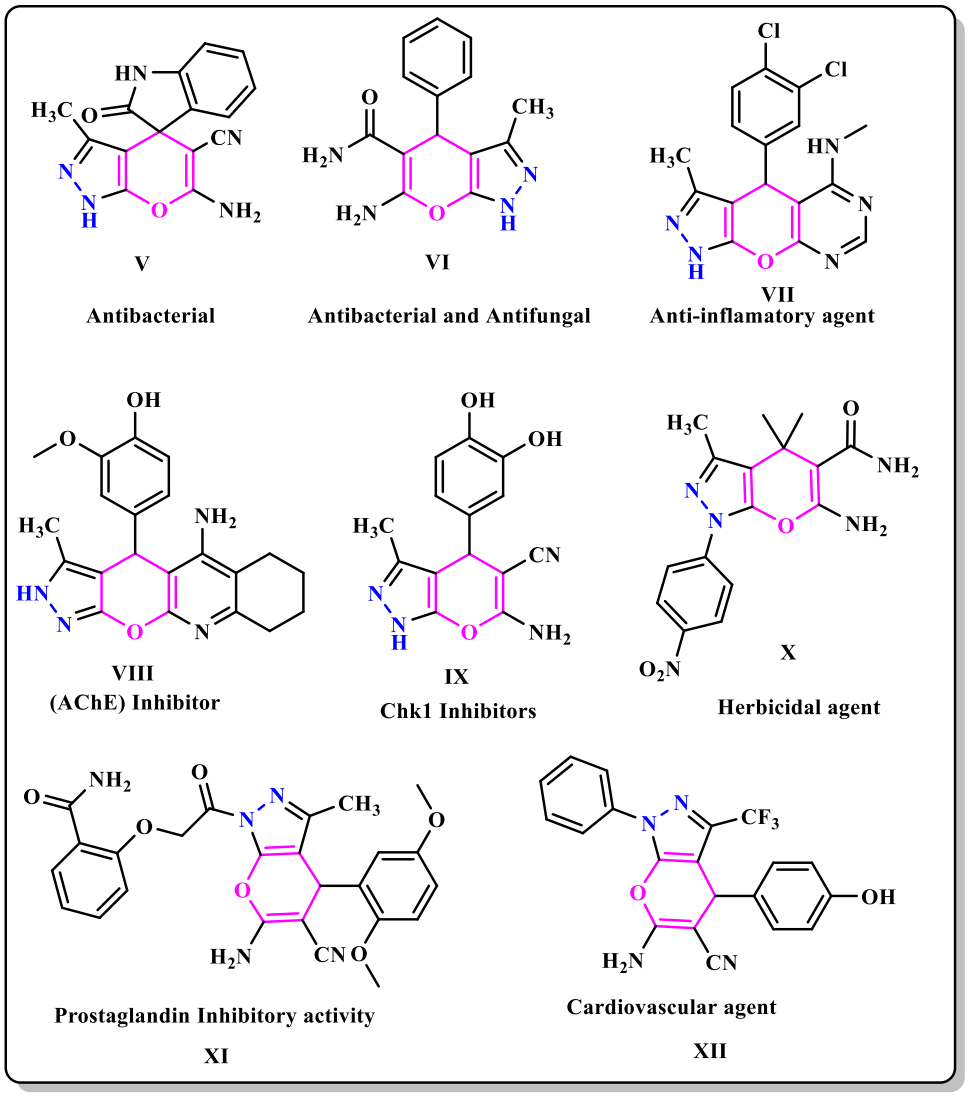



**Fig. 2** Some bioactive pyrano[2,3-*c*]pyrazole motifs

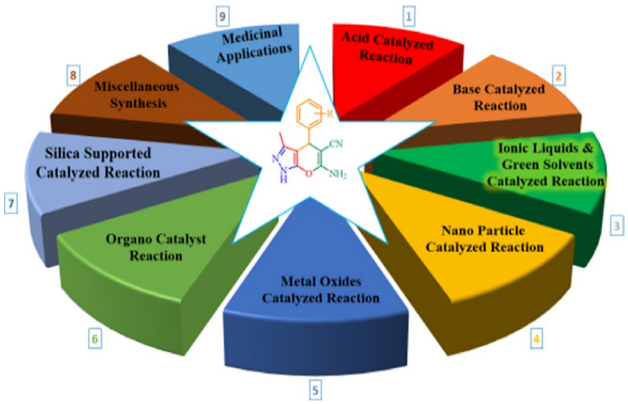
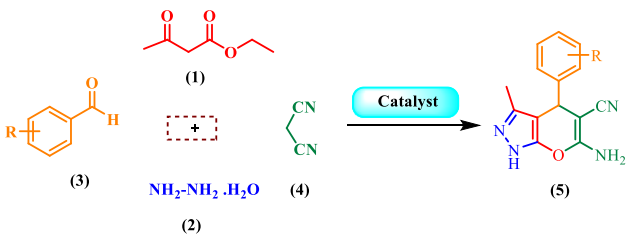



**Fig. 3** Classification following the nature of catalysts




**Scheme 1.** Synthesis of (**5**) derivatives

A series of (**5**) was effectively synthesized in 2011 by Chavan et al. by using (**1**) with (**2**), and (**3**), with (**4**) in silicotungstic acid [$H_4(SiW_{12}O_{40})$] catalytic quantity at 60 °C it gives in clean reaction condition (Scheme 4) [22]. Javid et al. looked at using preyssler HPA supported [$NiFe_2O_4$@$SiO_2$-Preyssler, (NFS-PRS)] for an effective synthesis of (**5**) via condensation of (**1**), (**2**), (**3**), and (**4**) at RT in an aqueous

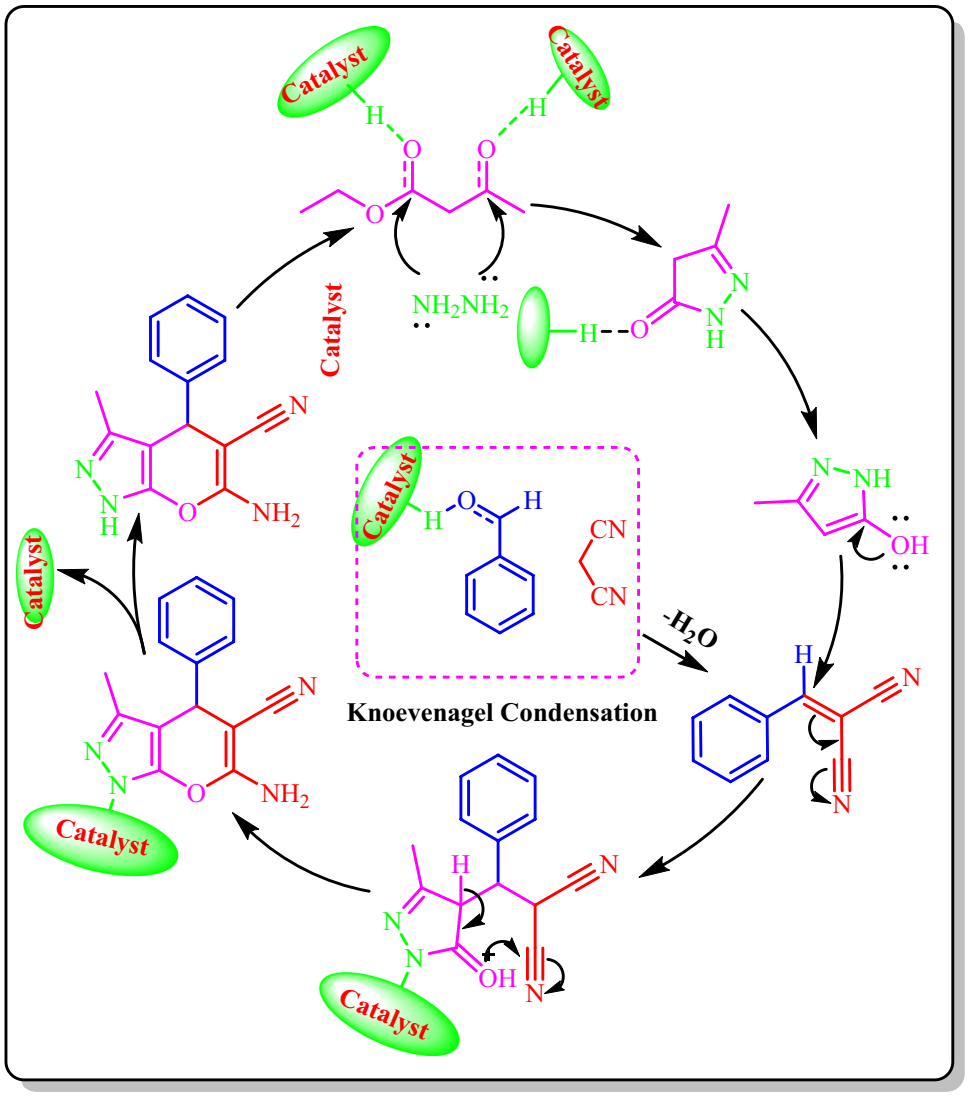



**Fig. 4** Propose mechanism of (**5**)

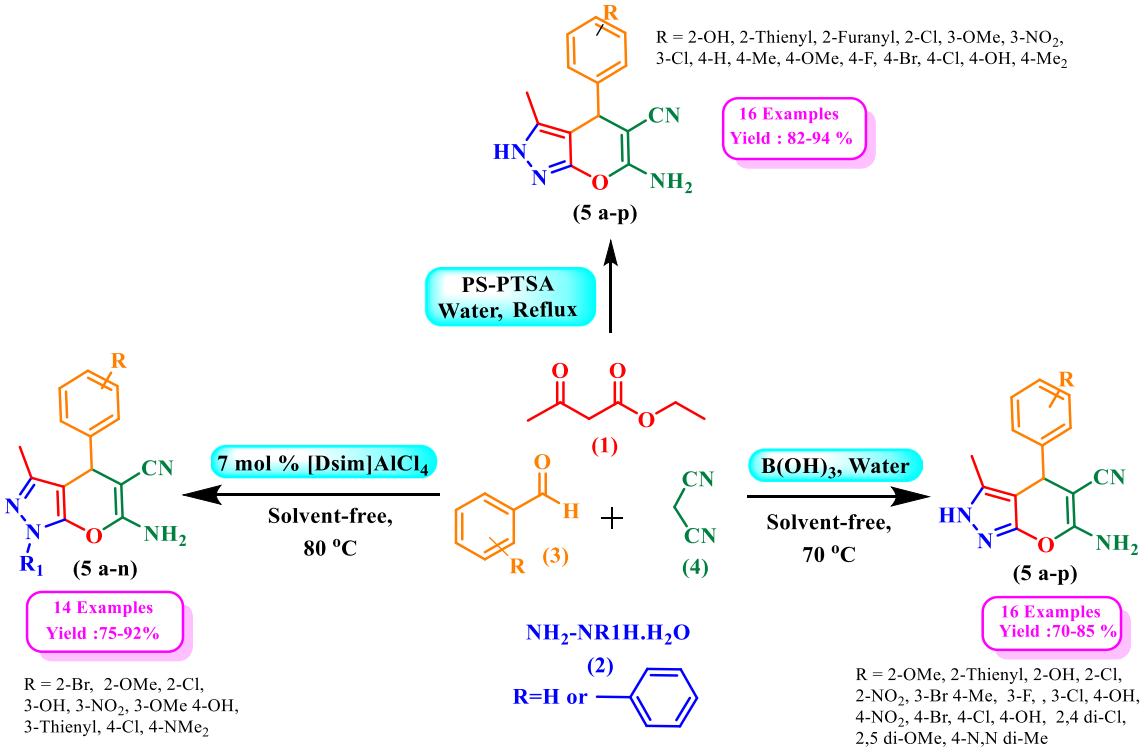
condition gives superior yields, accelerated reaction times, and reusable catalyst, which are key feature of this protocol (Scheme 4) [23]. Moosavi-Zare, et al. investigated in acetic acid-based [(cmpy)I] for the environmentally friendly one-pot synthesis of (**5**) by reacting (**3**) with (**1**), (**2**), and (**4**) at 100 °C under neat condition and catalyst was reusable eight runs for the reaction (Scheme 4) [24]. S. Kondabanthini et al. developed synthesis (**5**), the reaction was carried out in Wang resin (Wang-$OSO_3H$) acid catalyst by employing four components (**1**) (**2**) (**3**), and (**4**) in demineralized water under ultrasound irradiation with good yield. In silico interactions between compounds **5a** and **5b** and the residues GLN345 and ASN346 resulted in two significant H-bond interactions, which were reflected in their estimated total energy. Evaluation of **5a** and **5b** against SIRT1 revealed promoter inhibitory activity in agreement with docking study findings in vitro. Compounds **5a** and **5b** were discovered to be the most active in this series (Scheme 4) [25].

Gein et al. have designed (**5**) through diethyl oxaloacetate sodium salt reacts with (**1**), (**3**), and (**4**) in a four-component reaction using acetic acid in EtOH to produce (**5**) with high yield of products (Scheme 5) [26].

Nguyen et al. developed a new synthetic protocol for the synthesis of (**8**) derivatives from **(5)** and aniline **(7)** at RT in ethanol and the presence of the catalyst which is amorphous carbon-supported sulfonic acid (AC-$SO_3H$). This protocol AC-$SO_3H$ has many significant applications like good yield and cost-effective, non-poisons, and stability of catalyst (Scheme 6) [27].

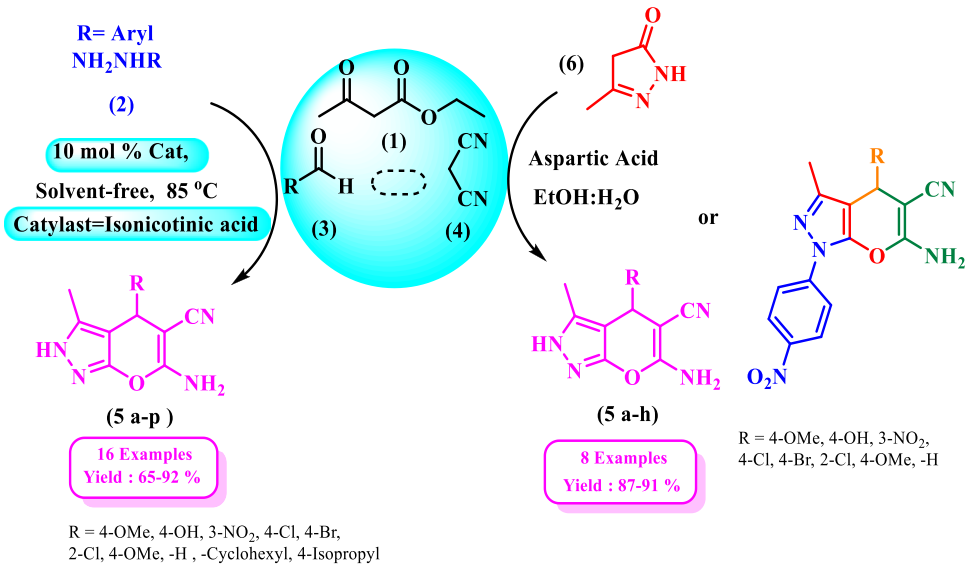
### Base-catalyzed reaction

Darandale et al. introduced a convenient method using diversified substitution (**1**), with (**2**) and (**3**) with (**4**) diverse synthesis of (**5**) using mild $NaHSO_3$ in ultrasound irradiations in neat condition. This approach showed an



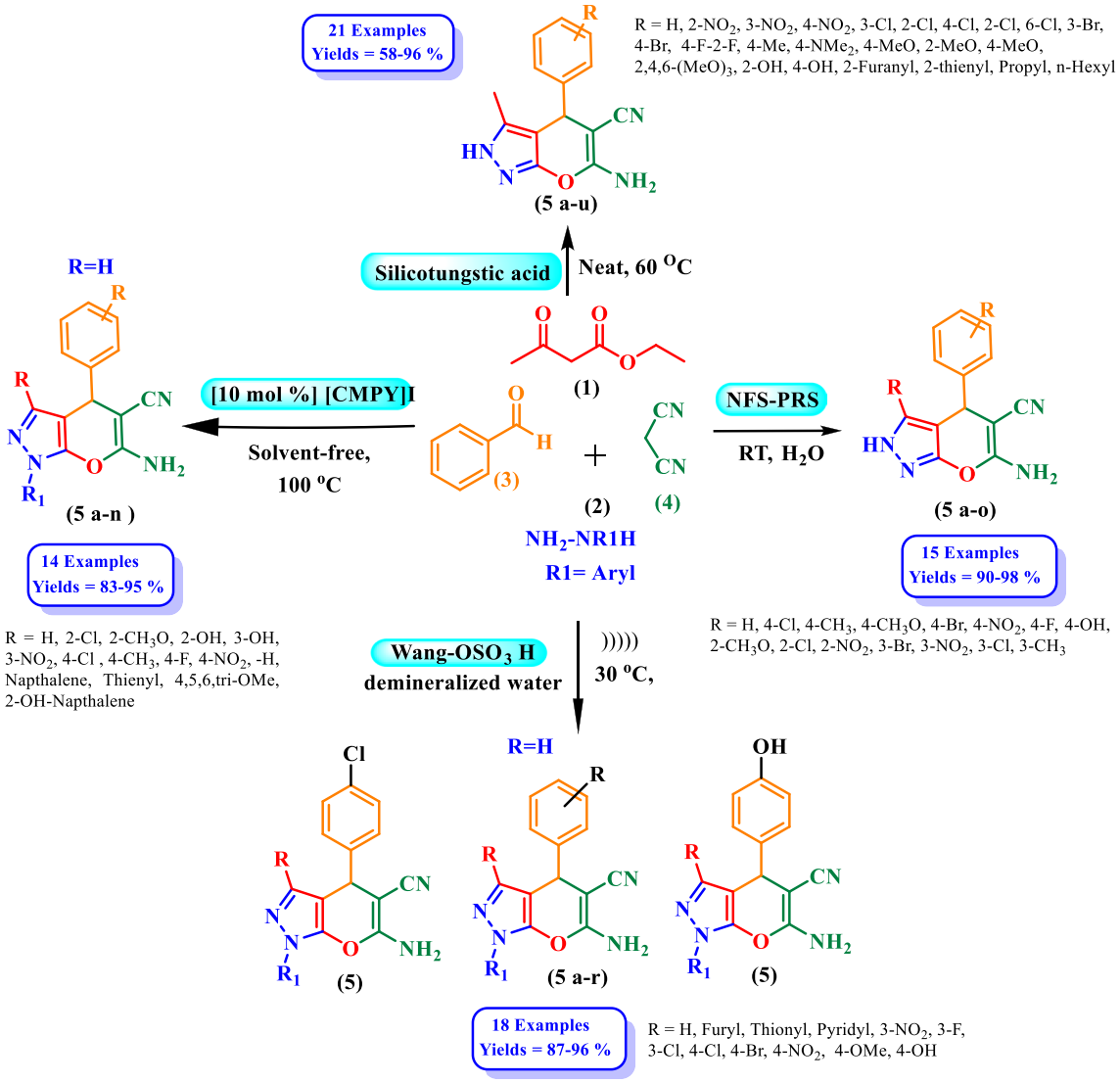

**Scheme 2.** Synthesis of (**5**) using PS-PTSA, $B(OH)_3$, and $[(Dsim)AlCl_4]$

**Scheme 3.** Aspartic acid and isonicotinic acid-catalyzed synthesis of (**5**)



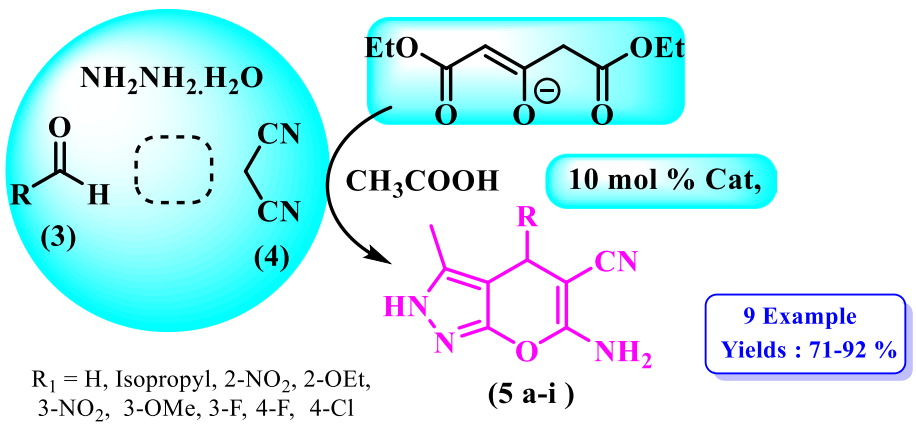

environmentally benign effect with reaction time with high yields of reaction (Scheme 7) [28]. Siddekhab et al. showed synthesis of (**5**) from (**1**), (**2**), (**3**), and (**4**) and mild organic base imidazole in aqueous media. Authors highlighted many advantages such as simple workup producers, and high yield of reaction (Scheme 7) [29]. Anatoliy M. Shestopalov and co-workers describe the synthesis of substituted (**5**) by using (**1**), (**2**), (**3**), and (**4**) protocol is an expedient toward (**5**) using $Et_3N$ as a catalyst for reaction (Scheme 7) [30].

By utilizing isatin (**9**), (**4**), (**2**), and dialkyl acetylenedicarboxylates (**10**) in $Et_3N$, Pal et al. developed the synthesis of derivatives of (**5**). The authors screened numerous bases for experimental conditions to increase the reaction yield. $Et_3N$ was effective in terms of yields and less time and one step to formed one C–O two C–C and two C–N bonds (Scheme 8)

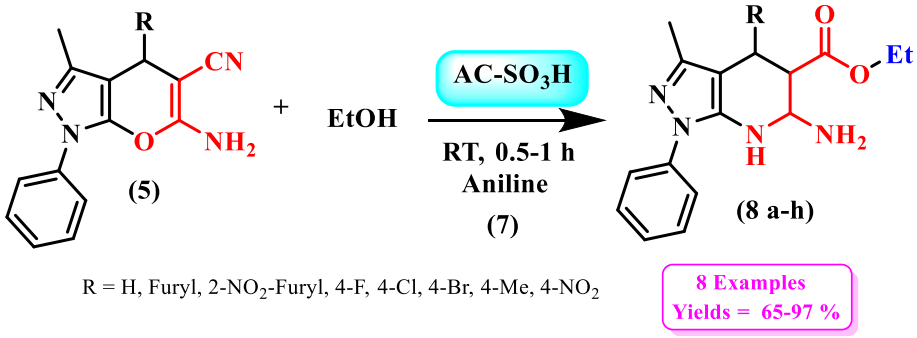



**Scheme 4.** $[H_4(SiW_{12}O_{40})]$, NFS-PRS, [(CMPY)I], and Wang-$OSO_3H$-catalyzed synthesis of (**5**)

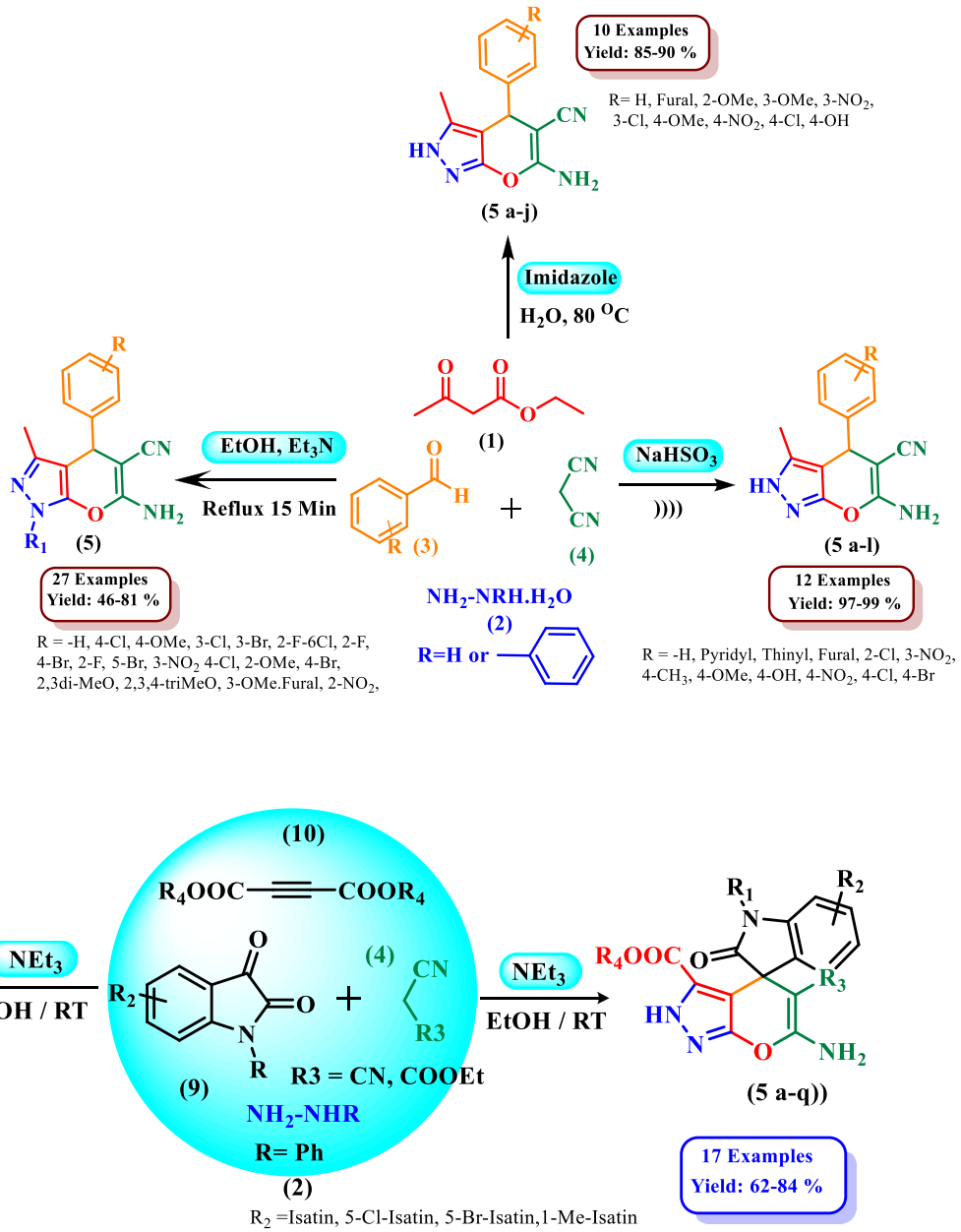
**Scheme 5.** Synthesis of (**5**) using acetic acid



**Scheme 6.** Synthesis of (**5**) catalyzed by AC-$SO_3H$



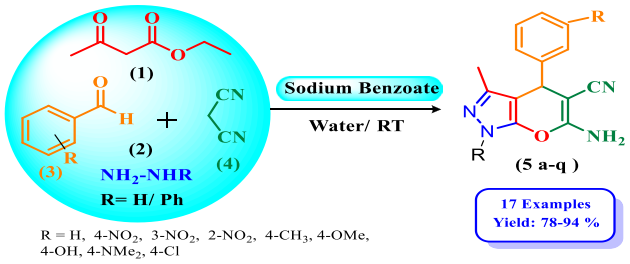

**Scheme 7.** Synthesis of (**5**) using $NaHSO_3$, Imidazole, and $Et_3N$







**Scheme 8.** $Et_3N$-Catalyzed synthesis of (**5**)

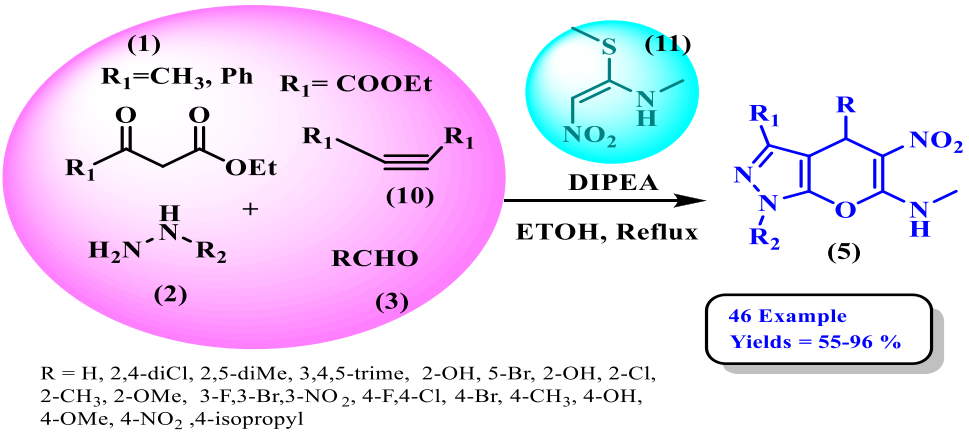


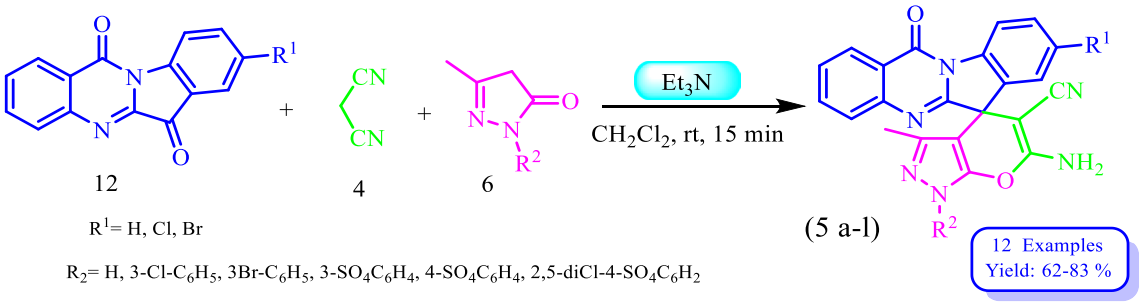

**Scheme 9.** Synthesis of (**5**) using sodium benzoate

[31]. Kiyani et al. prepared (**5**) making a mild base using sodium benzoate, the condensation reaction of (**1**), (**2**), (**3**), and (**4**), in $H_2O$ at RT for reaction to give good yields of reaction (Scheme 9) [32]. Kanchithalaivan et al. investigated aliphatic base [DIPEA] for the synthesis of newer protocol for diversified (**5**) domino reactions of (**1**), DMAD (**10**) with (**2**), (**3**), and (*E*)-N-methyl-1-(methylthio)-2-nitroethenamine (**11**) in ethanol. Synthesized derivatives have diversified to synthesizing previous compounds (**5**) for the same reaction condtion (Scheme 10) [33].

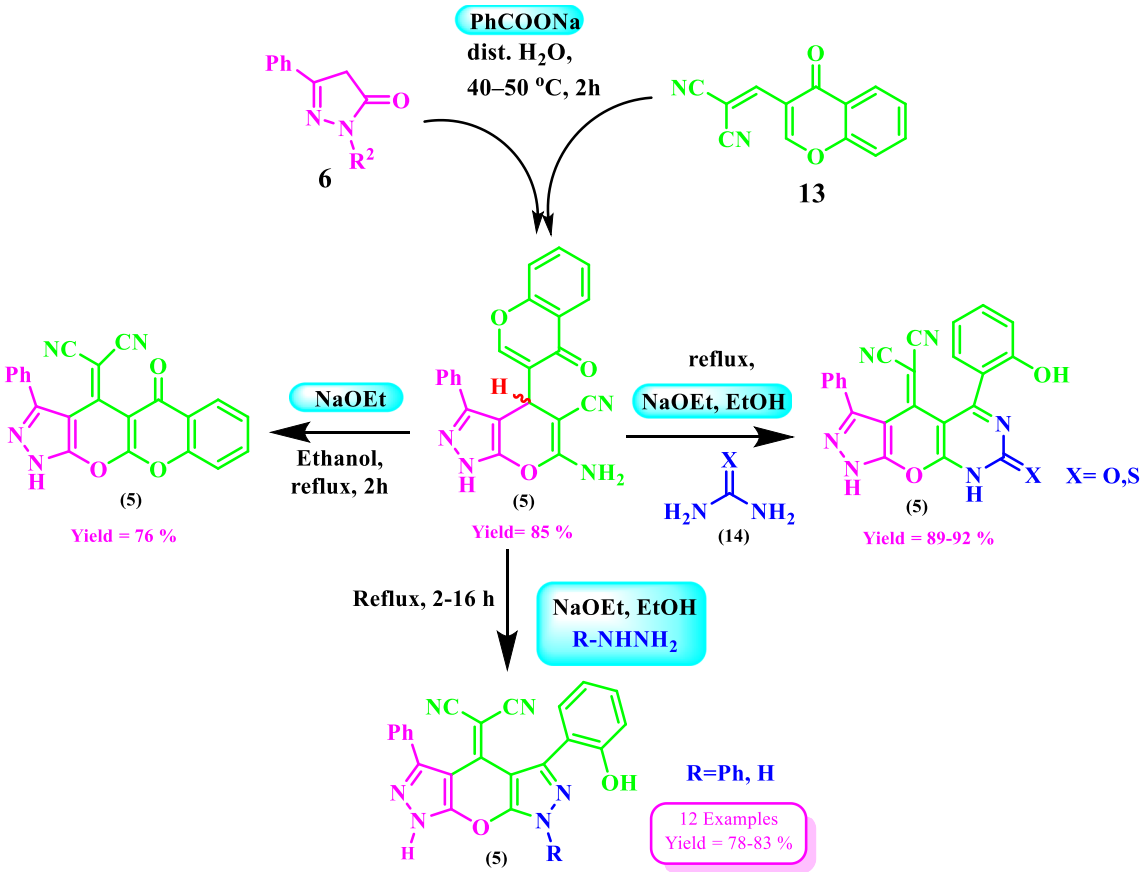
Sadeghian et al. have developed a simple and quick method for varied synthesis of (**5**). Compounds (**12**) with sequential multicomponent reactions of isotonic anhydride/isatin (**9**) and (**2**), 3-methyl-pyrazolones (**6**) by employing $Et_3N$ as basic catalyst in $CH_2Cl_2$ at RT. This approach offers various benefits including faster reaction times and good yields of reaction (Scheme 11) [34] D. A. Bakhotmah et al. developed a base-catalyzed heterocyclization reaction, which produces potentially bioactive (**5**). These compounds in both the one and two heterocyclic systems are combined on a single molecular scaffold. Additionally, the stated protocol has certain noticeable applications, such as quick response times and simple workup procedure (Scheme 12) [35]. Bania et al. developed a domino the Rauhut–Currier cyclization reaction within the unsaturated pyrazolones (**15**) and nitro-olefins (**16**) in the presence of DMAP catalytic asymmetric synthesis of (**5**) with yields ranging from moderate to good, along with excellent diastereoselectivities, formation of homocoupled product. First-time use of nitrostyrene in the Rauhut–Currier cyclization reaction, these are some salient features of this reaction (Scheme 13) [36]. According to Prabhakaran et al., a three-component reaction in one pot involving (**3**), N-methyl-1-(methylthio)-2-nitroethamine (NMSM) (**11**), and thiazolidinedione (**17**) are catalyzed by piperidine and results in the production of derivatives of phenyl-pyrano-thiazol-2-one (**17**) formed. A simple and quick synthesis method using intramolecular O-cyclization

**Scheme 10.** Preparation of (**5**) using DIPEA



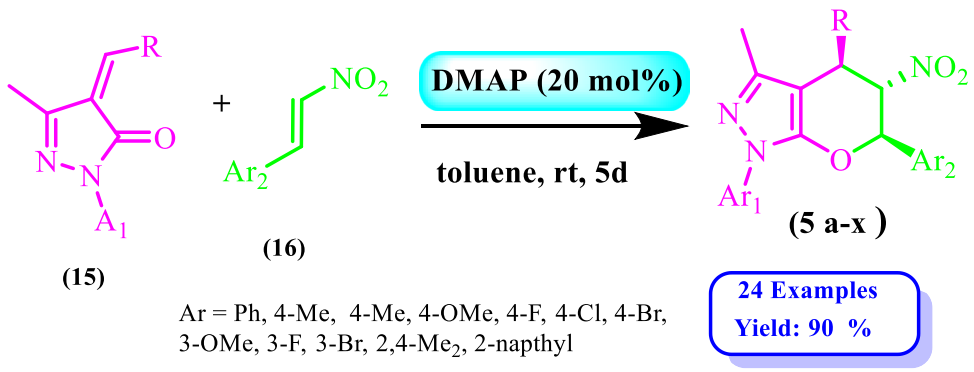




**Scheme 11.** Preparation of (**5**) using $Et_3N$



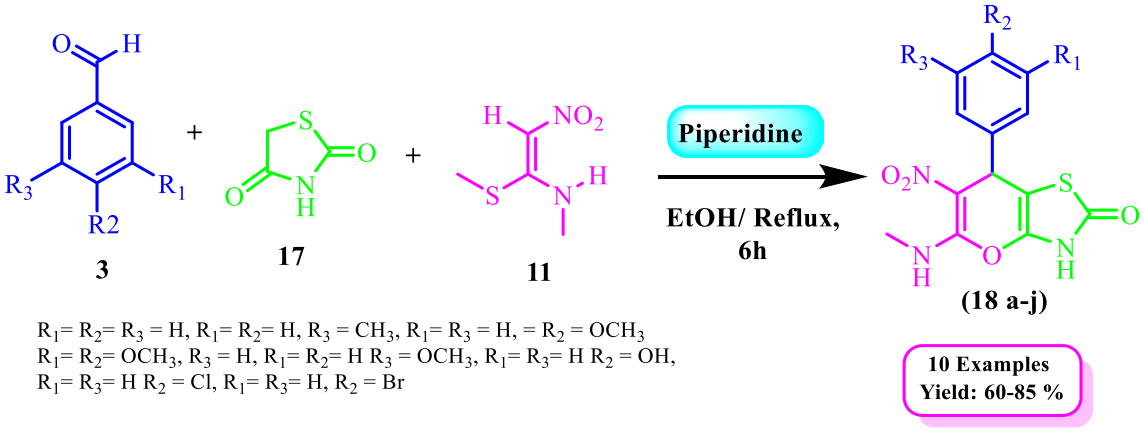

**Scheme 12.** Preparation of (**5**) using NaOEt

**Scheme 13.** DMAP-catalyzed synthesis of (**5**)



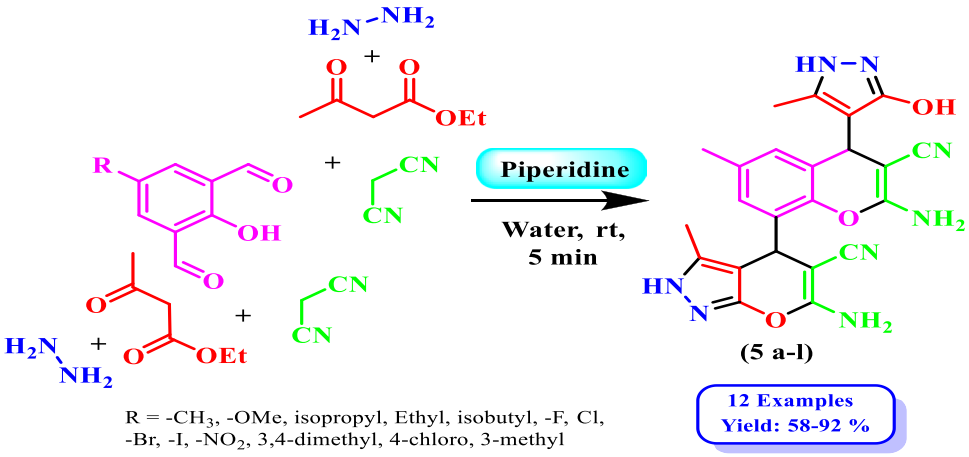

and domino Knoevenagel condensation results in a series of phenyl-pyrano-thiazol-2-one (**18**) derivatives with a moderate-to-good yield of product. It makes it easier to use multicomponent reactions in ways like lesser reaction times, being cost-effective, increasing structural diversity, and, most remarkably, purifying compounds using easy filtration (Scheme 14) [37]. Kumaravel et al. demonstrated an exact combination of MCRs from facile components in an aqueous medium within one step at room temperature. For the synthesis of pyranopyrazole-4*H*-chromene hybrid motif (**5**), two equivalents of (**1**), (**2**), (**3**), and (**4**) were treated with piperidine-catalyzed aqueous medium at RT offering good yields of product (Scheme 15) [38].

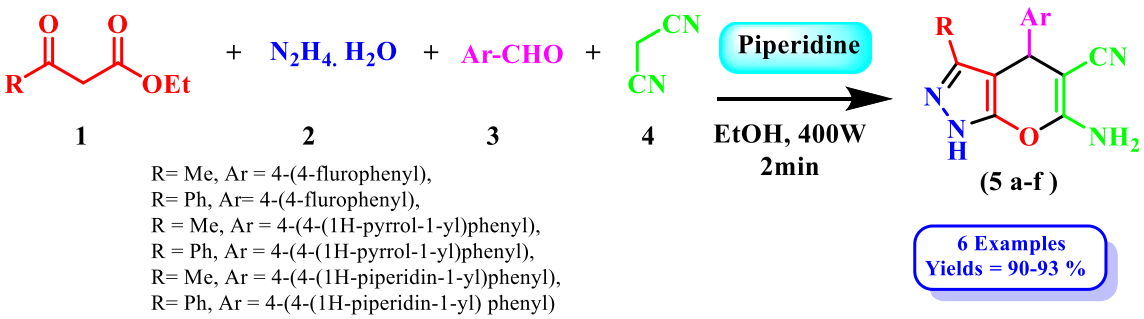
Fouda and colleagues synthesized a series of (**5**) motifs, the reaction was carried out (**1**), (**2**), (**3**), and (**4**) in the presence of secondary cyclic amine as piperidine in ethanol via non-conventional approach like Microwave Irradiation at 400 W (Scheme 16) [39].




**Scheme 14.** Piperdine-catalyzed synthesis of (**5**) derivatives

**Scheme 15.** Synthesis of (**5**) using piperidine

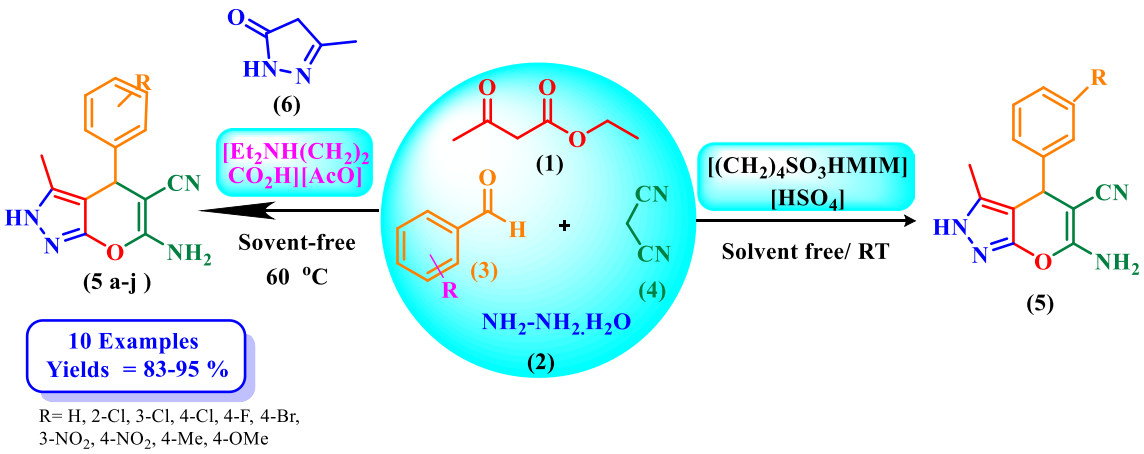



**Scheme 16.** Synthesis of (**5**) using piperidine

### Ionic liquids- and green solvents-catalyzed reaction

Ebrahimi et al. introduce a simple synthesis of (**5**) using various (**1**), (**2**), (**3**), and (**4**) in Ionic liquids as 3-methyl-1-(4-sulphonicacid)butylimidazolium hydrogen sulfate [$(CH_2)_4SO_3HMIM][HSO_4$]. The main features of the reaction are good yields, lesser reaction times, without chromatographic techniques and the reaction's catalyst's ability to be used again for reaction (Scheme 17) [40]. In brief, Syed Abed and co-workers have introduced an entirely new task-specific ionic liquid (TSIL), 2-carboxy-*N*,*N*-diethylethanaminium acetate denoted [$Et_2NH(CH_2)_2CO_2H$][ACO], as an eco-friendly catalyst. In situ-produced arylidenemalononitriles were used in the Knoevenagel reaction under neat



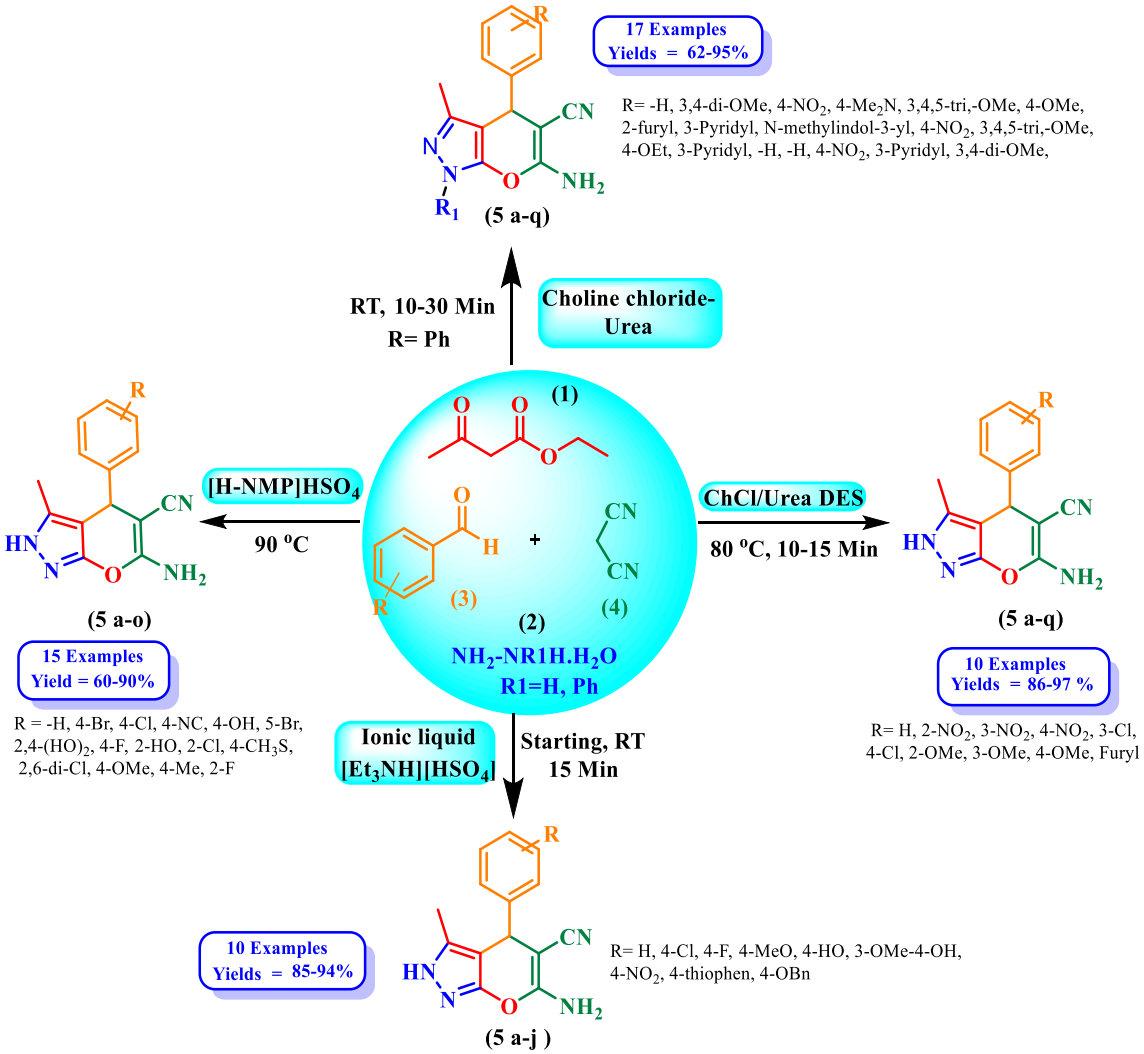

**Scheme 17.** $[(CH_2)_4SO_3HMIM]$ $[HSO_4]$, $[Et_2NH(CH_2)_2CO_2H][AcO]$-catalyzed synthesis of (**5**)

conditions to produce (**5**) and another dihydropyrano[3,2-*c*]chromene. The proposed methodology was highlighted for its sustainable process, good-to-exceptional yields, no chromatographic purification, and the catalyst can be reused for up to six reaction cycles without losing activity (Scheme 17). [41]

Zonouz et al. developed a straightforward method for synthesizing (**5**) derivatives, an environmentally friendly reaction media, and a deep eutectic solvent. A simple operational methodology avoids using potentially hazardous solvents and catalysts in the reaction, allowing for shorter reaction durations and higher yields of the target molecules (Scheme 18) [42]. Hajipour and colleagues developed a four-component synthesis of (**5**) using a new approach by [H-NMP]$HSO_4$] and [ChCl][$ZnCl_2$]$_2$. IL has low-cost and reusable acidic ionic liquids with good-to-excellent yield of product. Using both an environmentally friendly safe IL findings indicated that ionic liquids in terms of their lack of by-products, and capacity to be reused for reaction (Scheme 18) [43]. In summary, Toreshettahally et al. have developed a rapid, green procedure for the four-component reaction of (**2**), (**3**), (**4**), and (**1**) Choline chloride–urea catalyzed synthesis as an ecologically safe RT-IL for the production of substituted (**5**) (Scheme 18) [44]. The condensation processes of four components in one-pot are (**1**), (**2**), (**3**), and propanedinitrile (**4**). Nimbalkar et al. reported the utilization of [$Et_3NH$][$HSO_4$] from the Bronsted acid ionic liquid (BAIL) catalyst for the multicomponent synthesis of (**5**) under solvent-free conditions. Over currently employed reaction techniques, the innovative methodology has several benefits, providing high yields, a shorter reaction time, gentle reaction conditions, and a reusable catalyst as a catalyst for multicomponent synthesis (Scheme 18) [45].

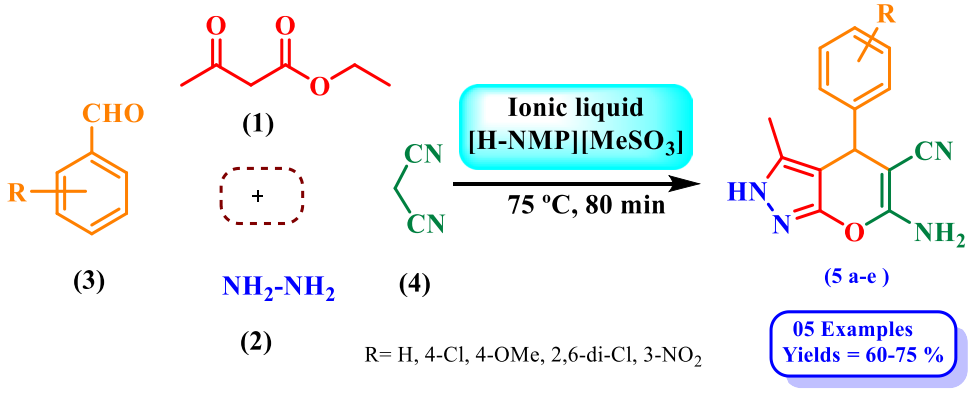
Four-component, one-pot synthesis of (**5**) was described by Deshmukh et al. with (**1**), (**2**), (**3**), and (**4**) in ethanol and [H-NMP][$MeSO_3$] ionic liquid catalyst. It is an environmentally benign protocol, clean, quick, high-yielding, and easily purifiable. Additionally, the reaction process is fairly straightforward to workup. Consequently, it can be applied to large-scale manufacture of (**5**) (Scheme 19) [46].

Bihani et al. showed a completely eco-friendly and enhanced procedure for producing (**5**) by a four-component reaction comprising a combination of (**1**), (**2**), (**3**), and (**4**) in boiling water (1:1) at reflux. A similar synthesis was started from aliphatic aldehydes while performed without the use of a catalyst (Scheme 20) [47]. Dekamin et al. produced (**5**) using a four-component, one-pot reaction of (**1**), (**2**), (**3**), and (**4**). The intended medicinally significant (**5**) derivatives are produced utilizing the ball milling process at room temperature without using a catalyst or solvent. This approach has several advantages including mild reaction conditions, high quantitative yields, low cost, and easy set-up. It also does not use any hazardous catalysts or solvents (Scheme 20) [48]. Moosavi-Zare et al. use an acetic acid functionalized pyridinium salt, 1-(carboxymethyl) pyridiniumiodide [CMPY]I, as a reusable catalyst for the one-pot tandem four-component condensation process of (**5**), a simple, an efficient, and an environmentally friendly synthetic process using (**1**), (**2**), (**3**), and (**4**) at 100 °C under neat condition (Scheme 20) [24]. Ramin Ghahramanzadeh and co-workers developed (**5**) using sulfonated carboxymethylcellulose (SCMC) heterogeneous catalysts. Sulfonated carboxymethyl cellulose was done using a novel, eco-friendly process. CMC demonstrated the catalytic activity for multicomponent one-pot synthesis of (**5**), the biopolymer-derived solid acid catalyst derivatives using the reaction of (**1**), (**2**), and various (**3**) and (**4**) in EtOH. Some significant application of the reported protocol includes the usage of a stable, recoverable, and non-toxic catalyst, a non-chromatographic product of purification, and an environmentally friendly reaction (Scheme 20) [49].

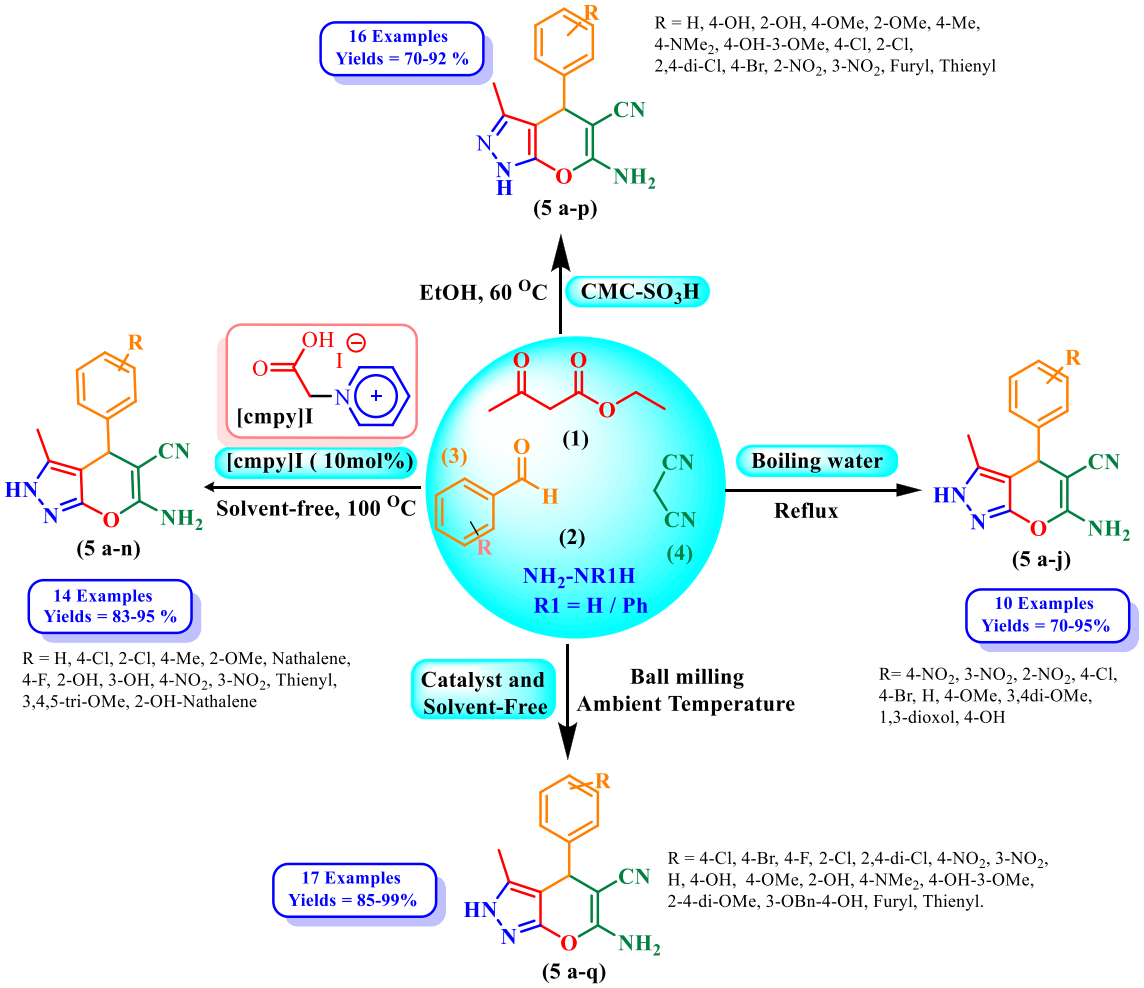



**Scheme 18.** Synthesis of (**5**) using deep eutectic, [H-NMP]$HSO_4$, choline chloride–urea, and [$Et_3NH$][$HSO_4$]

**Scheme 19.** [H-NMP][$MeSO_3$]-catalyzed synthesis of (**5**)



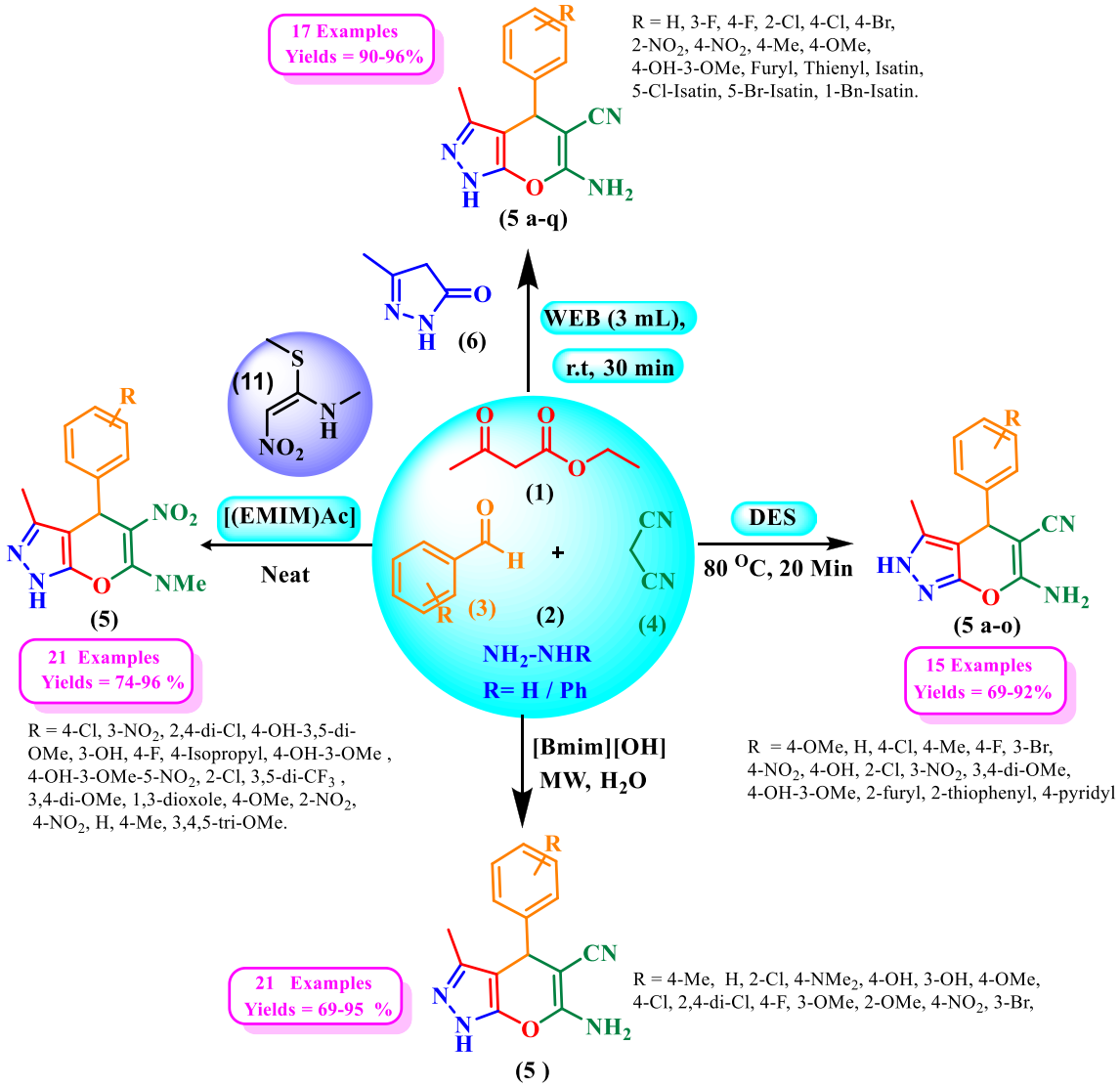

M.R. Bhosle et al. developed a simple protocol for synthesis (**5**) by one-pot cyclocondensation of (**1**), (**2**), (**3**), and (**4**) in DES. This method has facilitated the production of (**5**) in a shorter amount of time with higher yields (Scheme 21) [50]. Herein, Dwivedi et al. have formed a brand-new, straightforward, an effective, synthesis of (**5**) using aryliden-emalononitrile (**19**) and pyrazolone (**6**) in aqueous extract of Banana Peels (WEB) as a reaction medium at room




**Scheme 20.** Preparation of (**5**) using catalyst-free, boiling water, [CMPY][I], and [CMS-$SO_3H$]

temperature. Benefits of this protocol include an environmentally benign with high-to-outstanding yields including quick reactions, and simple product isolation without the need for column chromatography. The method displays a green matrix, a high atom economy for reaction (Scheme 21) [51]. Ashishkumar katariya et al. developed regioselective synthesis of fully functionalized (**5**) in one-pot condensation of (**6**) or (**1**) and (**2**), (**3**) with NMSM (**11**) in [(EMIM)Ac] IL neat condition. Domino protocol involves Knoevenagel condensation followed by Michael addition and *O*-cyclization with an eradication of the methanethiol group, which created C–C, C–N, and C–O, bonds. Strategy's noteworthy features include excellent yield with rapid reaction times (Scheme 21) [52]. To produce (**5**) Sharifi Aliabadi et al. used the imidazole-based IL, 1-butyl-3-methylimidazolium hydroxide [Bmim][OH] as a catalyst. Synthesis of (**5**) was carried out using this organo-solid catalyst in a microwave at 230 W (Scheme 21) [53].

Katariya et al. (**1**) (**2**) (**3**), and (**4**) in ethanol at reflux condition and [(EMIM)Ac)] as IL. This reaction has green, an efficient, and simple method for the synthesis of (**5**) derivatives. This reaction offers outstanding yield. Conditions apply to a wide range of substrates and take less time to react to form compounds (**5**) (Scheme 22) [54]. Mali et al. investigated taurine-catalyzed green catalyst and prepared a new series of **(5)** containing isonicotinamide **(20)** spirooxindole, and indole moieties, for synthesis of (**5**) derivatives, authors took four components **(1), (2)**, **(3)**, and **(4)** coupled together in the presence of ionic liquids taurine in water with good-to-excellent yield of reaction (Scheme 22) [55]. Amiri-Zirtol et al. reported a borax-catalyzed rapid and green synthesis protocol of **(5)** and xanthene-1,8-dione derivatives in an aqueous medium. The reported method displayed some prominent advantages like an inexpensive and easy-to-handle catalyst, high efficiency concerning time and yield, green solvent, and simple reaction set-up (Scheme 22) [56]. Chakraborty and co-workers reported a facile, productive, and green method for the synthesis of (**5**) compounds by using water-SDS-ionic liquid with a sequential multicomponent approach using (**3**), (**4**), and pyrazolin-5-one

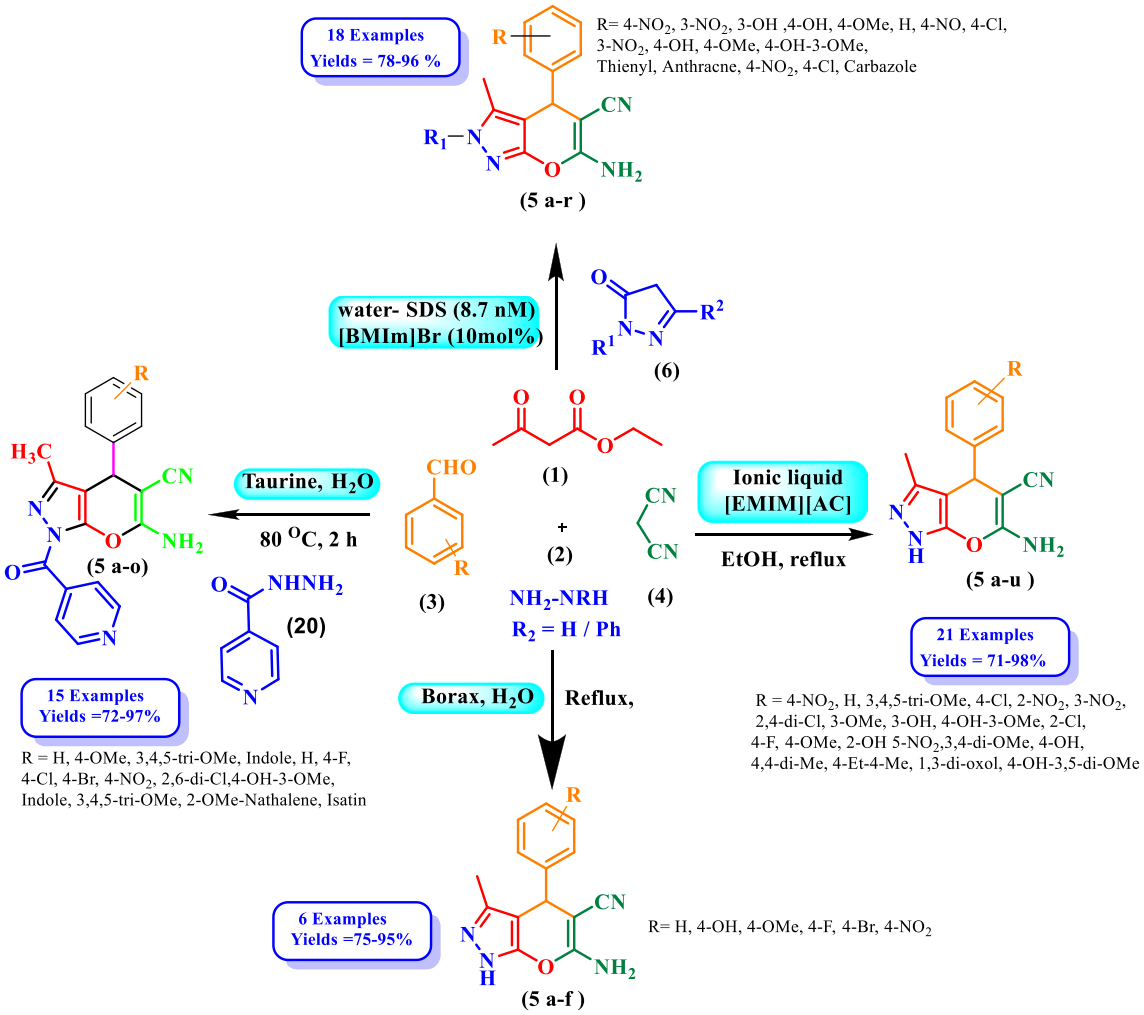



**Scheme 21.** DES, WEB, [EMIM][Ac], and [BMIM][OH]-catalyzed synthesis of (**5**)

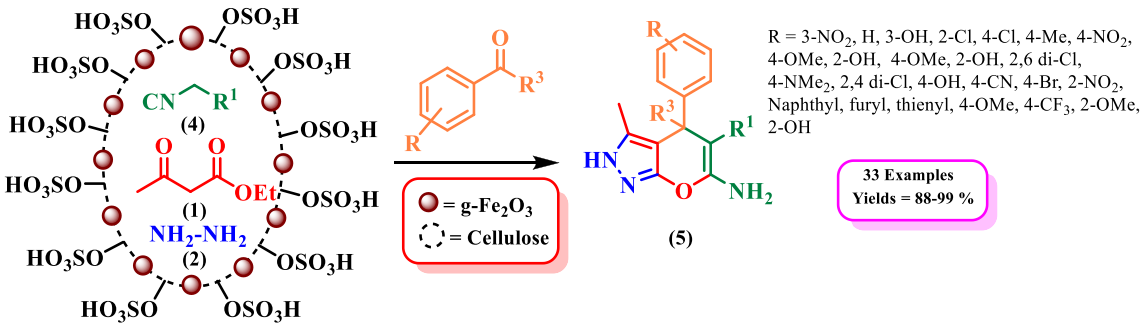
(**6**). This protocol has some key applicability such as high yield, environmentally friendly conditions, recyclability of the reaction medium, and chromatography-free purification (Scheme 22) [57].

### Nano-catalyzed reaction

Maleki and colleagues looked into the synthesis of (**5**) using isatin or acetophenones (**9**), (**1**), (**2**), and (**3**). This protocol offers mild conditions, quick reaction time, and high yields. They also provided a straightforward procedure for forming a brand-new functionalized magnetic NPs catalyst based on cellulose. The nanocomposite was easily separated using a magnet, and it was reused several times with no deterioration significantly in performance (Scheme 23) [58]. Unique features include an environmentally friendly, and biological approach for silver nanoparticles that have been designed by Jitender M. Khurana and co-workers using an easily accessible aqueous leaf extract of *Cinnamomum tamala* as their stabilizing and reducing agent with the aid of these Ag NPs the production of (**5**). This technique is appealing and practical because of the catalysts, eco-friendliness simplicity of recovery, and capacity to be reused many times (Scheme 24) [59]. In an aqueous environment with a catalytic amount of CuI NPs, Safaei-Ghomi et al. investigated a unique process for highly functionalized (**5**) from (**2**), (**3**), (**4**), Meldrum's acid (**21**), and acid chlorides (**22**). The approach has several advantages including in situ synthesis of (**1**) gentle reaction conditions, and an easy workup procedure with excellent yields. Moreover, the catalyst was recoverable and could be used repeatedly with nearly constant catalytic activity (Scheme 25) [60].

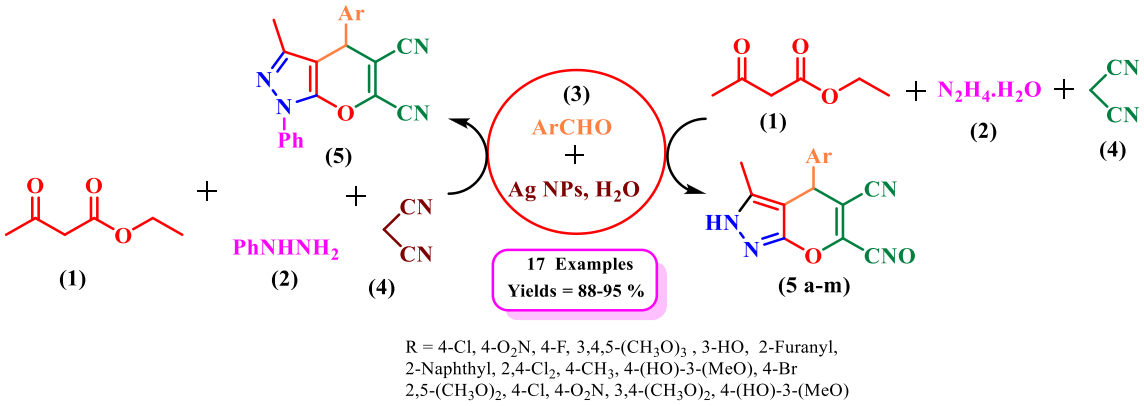



**Scheme 22.** [(EMIM)Ac)], Taurine, Borax, [BMIM]Br, catalyzed synthesis of (**5**)

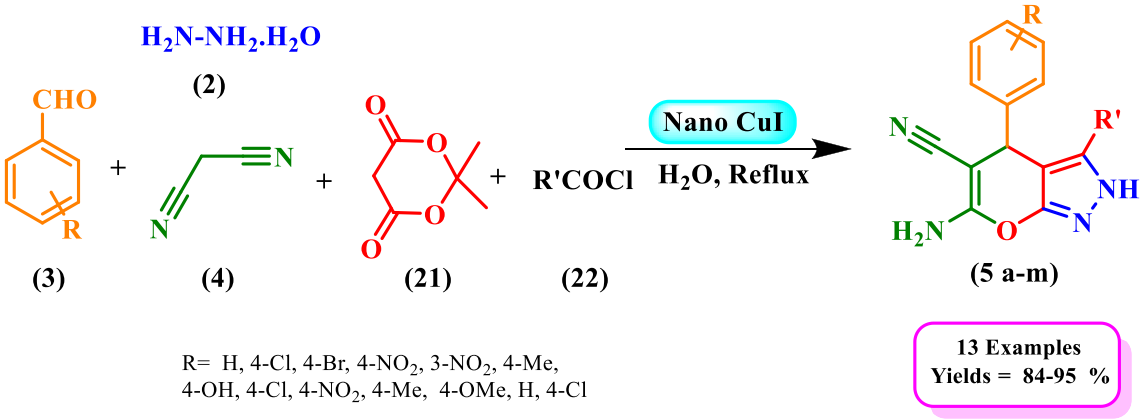



**Scheme 23.** Synthesis of (**5**) by nano-$Fe_2O_3$ cellulose

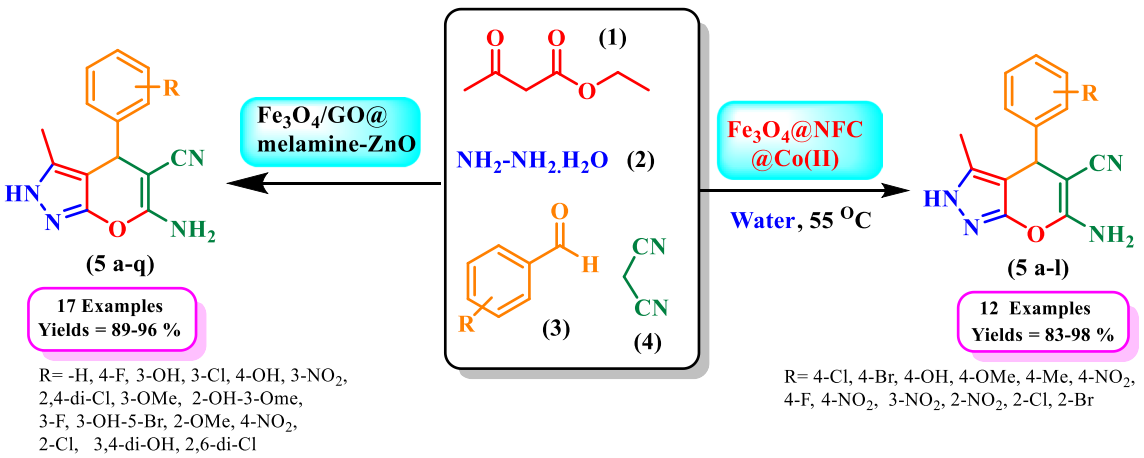
In this study, Kargar et al. controlled the interaction between the inorganic complexes and the support material to combine an excellent activity magnetic NPs $Fe_3O_4$@NFC@Co (II) ending complex as a multi-nuclear catalyst. This treatment employs cobalt acetate, a technique that is favorable to the environment. It is possible to form (**5**) and the magnetic $Fe_3O_4$@NFC@Co (II) as an eco-friendly, revolutionary, and effective catalyst that has a high yield, rapid reaction time, and simple procedure (Scheme 26) [61]. Here, graphene oxide nanosheets (GO@melamine) on (ZnO NPs), and $Fe_3O_4$ NPs were combined by Rezza et al. to make effective, multifunctional NPs ($Fe_3O_4$ NPs). Additionally, two




**Scheme 24.** Synthesis of (**5**) using of Ag NPs




**Scheme 25.** CuI-catalyzed synthesis of (**5**)




**Scheme 26.** $Fe_3O_4$/GO@melamine-ZnO and $Fe_3O_4$@NFC@Co (II) NPs-catalyzed synthesis of (**5**)

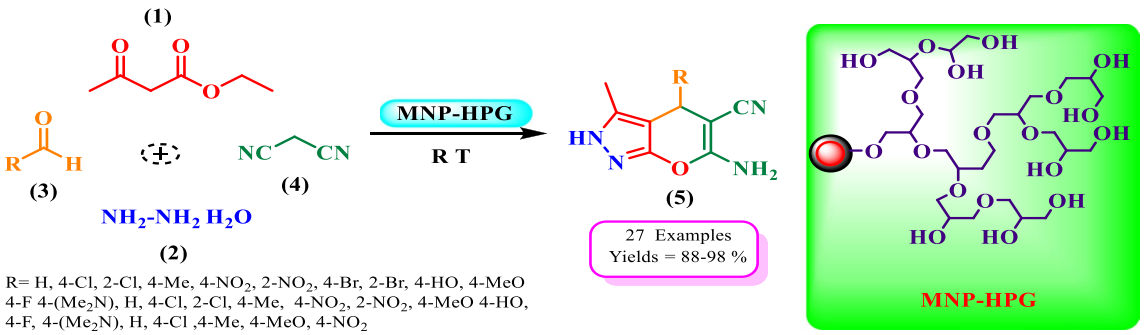
applications for the prepared $Fe_3O_4$/GO@melamine-ZnO nanocomposites have been used for the first time as a catalyst for the rapid synthesis of (**5**) derivatives with high yields (Scheme 26) [62].

Nesseri et al. rapidly developed a magnetic NPs-based hyper-branched polyglycerol catalyst in an aqueous solution from affordable starting materials, effectively catalyzing the synthesis of (**5**) in a neat environment at room temperature.

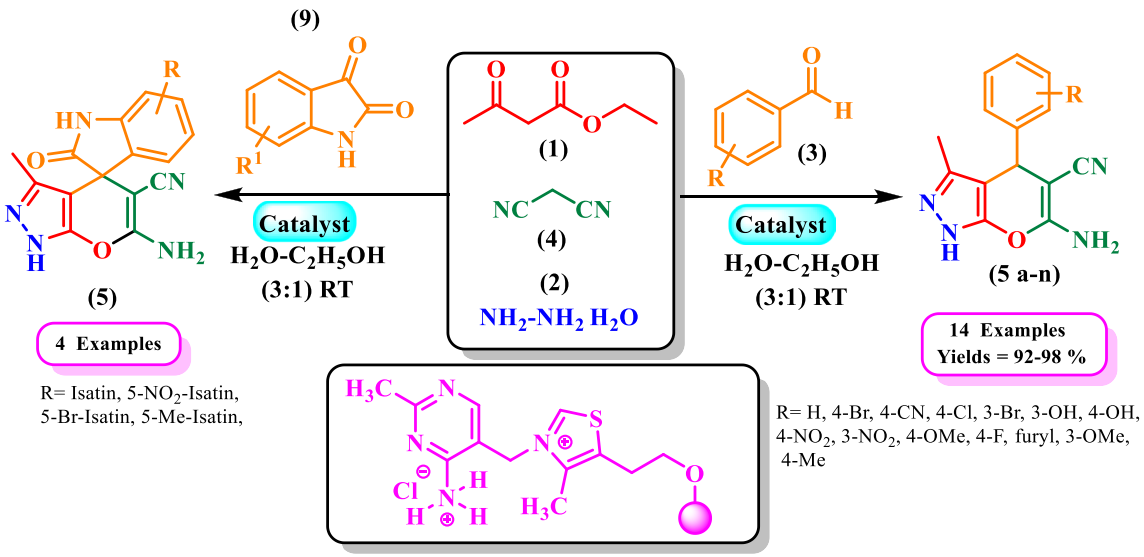
These catalytics are simplicity of recovery from the reaction using a magnet, and ability to be reused numerous times without appreciably deteriorating performance are further environmentally favorable qualities of the catalyst (Scheme 27) [63]. In the present study, Rahman et al. concentrated on the synthesis of an organo-nanocatalyst and using it to synthesis (**5**) derivatives as a magnetic organo-nanocatalyst, vitamin B1 supported by $Fe_2O_3$@$SiO_2$ NPs was employed to synthesize (**5**) derivatives from (**1**), (**2**), (**3**), and (**4**) in a water–ethanol mixture at RT. The coordination of carbonyl oxygen and nitrile nitrogen by vitamin B1 supported by $Fe_2O_3$@$SiO_2$ NPs increases the electrophilic character of the corresponding carbons for simple nucleophilic attack. In this work, the catalyst was recycled and used again up to 6 times after the reaction had ended without significantly losing any of its activity (Scheme 28) [64].

In this study, Babaei et al. synthesized (**5**) in $H_2O$:ethanol under reflux conditions with nano-$Al_2O_3$/$BF_3$/$Fe_3O_4$ acting as a catalyst. The catalyst was removed from the reaction mixture by an external magnet, allowing it to be reused numerous times, without losing its activity. The benefits of this strategy include a straightforward purification process and a clean, practical procedure (Scheme 29) [65]. Ghorbani et al. designed and prepared nanocatalysts (PhAzLa = $Fe_3O_4$@$SiO_2$@CPTES@PhAzPhDA@La) and characterized them with different spectroscopic methods.The prepared nanocatalyst was used for the synthesis of a wide range of (**5**) from the reaction of (**1**), (**2**), (**3**), and (**4**) at 110 °C with 64–97% yields at neat condition (Scheme 29) [66].

Khadijeh Saki and colleagues reported condensation reactions within (**1**), (**2**), (**3**), and (**4**) to produce derivatives (**5**). This derivative was reacted with salicylaldehyde to produce nano-Fe-[phenylsalicylaldiminemethylpyranopyrazole]$Cl_2$ (**23**) (nano[Fe-PSMP]$Cl_2$). Compounds (**5**) were produced using the completely characterized nano-Schiff base complex, which also served as an effective catalyst (Scheme 30) [67].

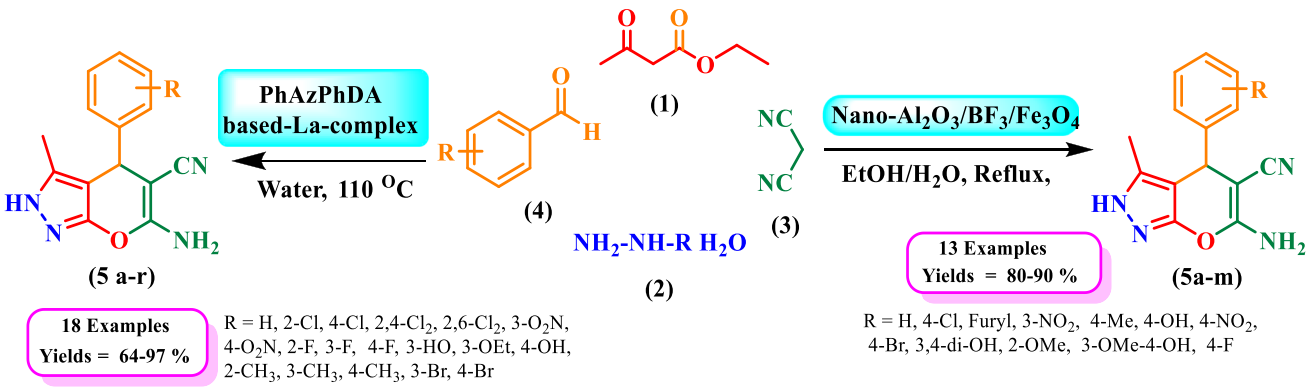



**Scheme 27.** Synthesis of (**5**) using MNP-HPG

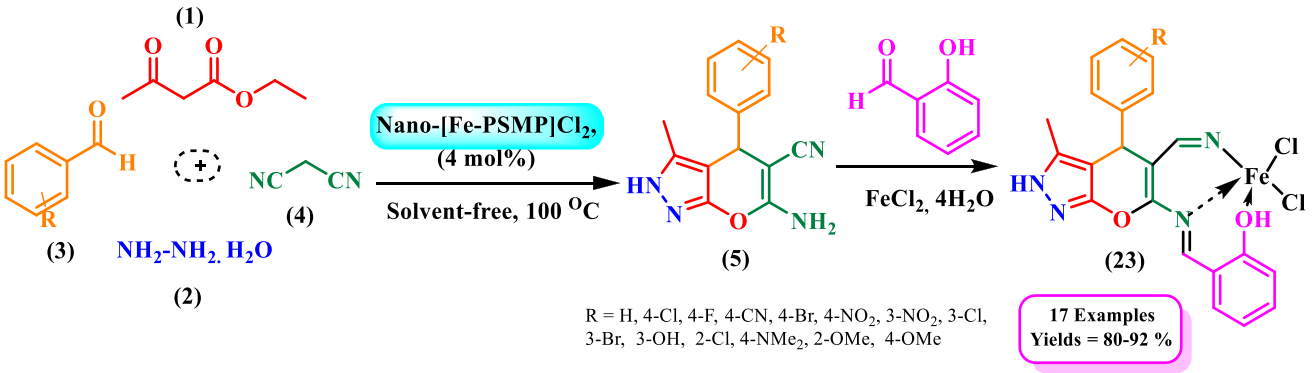



**Scheme 28.** Preparation (**5**) catalyzed by vitamin B1 supported by $Fe_2O_3$@$SiO_2$ NPs

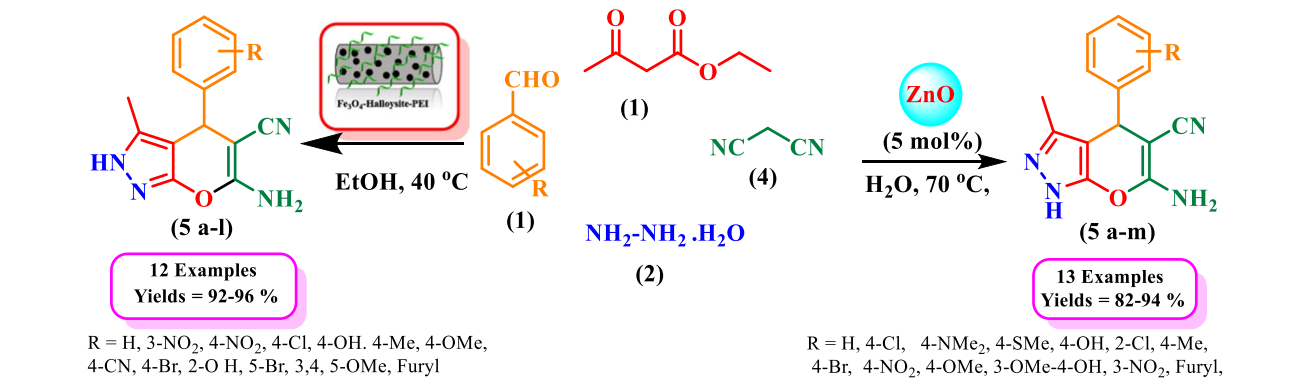
Sunil Tekale et al. described ZnO NPs-catalyzed synthesis of (**5**) from (**1**), (**2**), (**3**), and (**4**) in an aqueous reaction medium, making it an environmentally friendly way to synthesis (**5**). In an aqueous medium, a reusable heterogeneous nano-ZnO catalyst is used. This protocol was used without chromatographic method for purification that consumes minimum time are few of the noticeable applications of the current protocol. It successfully used nanocatalysis as green chemistry and synergistic effects (Scheme 31) [68]. In this study, Ali Maleki and co-workers fabricated a clay-based natural green magnetic nanocatalyst. Halloysite nanotubes (HNTs) were covalently grafted onto poly(ethylene imine), which were then loaded with magnetic NPs. For the production of (**5**) derivatives, $Fe_3O_4$@HNTs-PEI catalytic activity was evaluated. This heterogeneous catalyst demonstrated good efficacy in green media at RT and is readily recoverable




**Scheme 29.** Synthesis of (**5**) using (PhAzLa = $Fe_3O_4$@$SiO_2$@CPTES@PhAzPhDA@La) and $Al_2O_3/BF_3/Fe_3O_4$




**Scheme 30.** Nano[Fe-PSMP]$Cl_2$-catalyzed synthesis of (**5**)



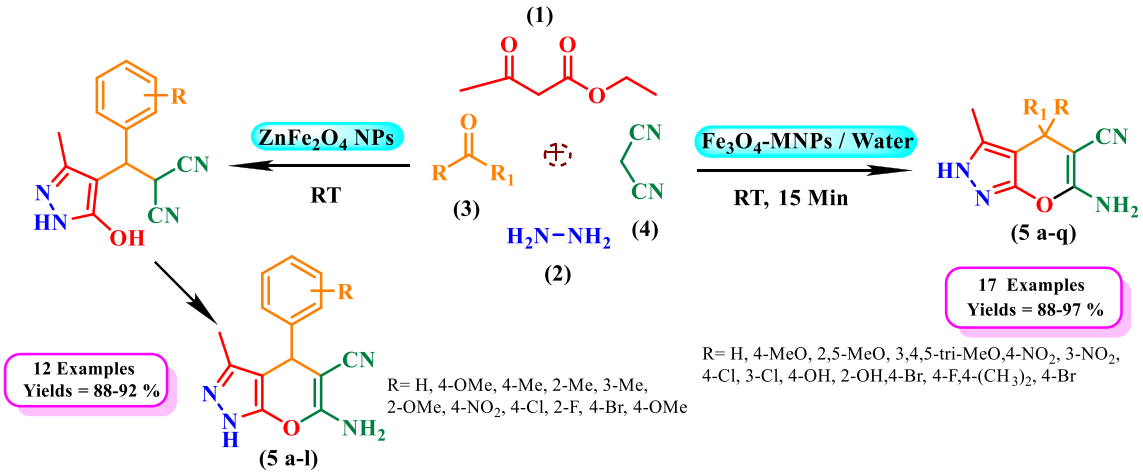

**Scheme 31.** Synthesis of (**5**) using $Fe_3O_4$@HNTs-PEI and ZnO NPs

from the reaction mixture using an external magnet, allowing for reuse at least 8 times without loss in catalytic activity (Scheme 31) [69].

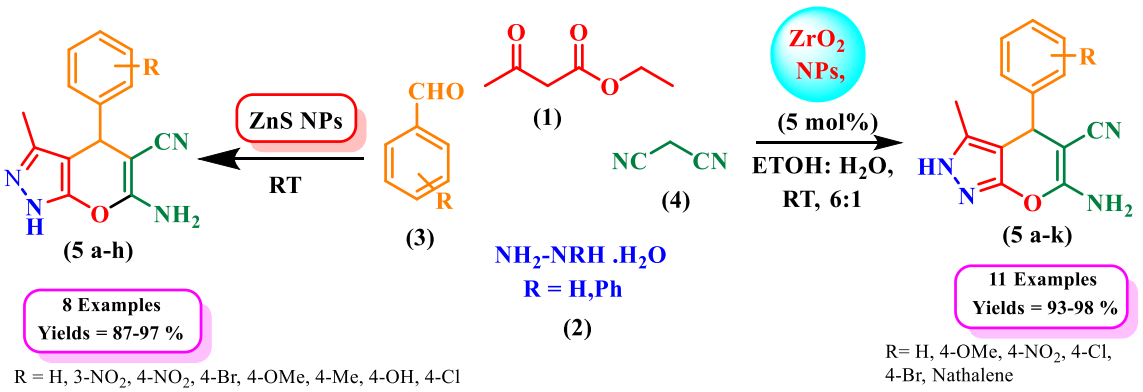
According to Abd El Aleem et al. magnetic $Fe_3O_4$ NPs worked well as a heterogeneous catalyst and combination of (**1**), (**2**), (**3**), and (**4**) in water at RT to produce a series of (**5**). Accordingly, results were attributed to the catalyst's ability to function as a nano-size of nearly 16 nm. The advantages of this reaction are rapid reaction times, clean, simple purification, high yields, and affordable catalyst availability (Scheme 32) [70]. Safaei-Ghomi et al. developed a simple method for the synthesis of (**5**) derivatives using a one-pot, four-component condensation process of (**1**), (**2**), (**3**), and (**4**) using $ZnFe_2O_4$ NPs in a solvent-free and eco-friendly. Benefits of this approach include short reaction times, high yields, simplicity of set-up, and environmental friendliness (Scheme 32) [71].

Borhade et al. investigated ZnS NPs in the RT for synthesis of (**5**) as a heterogeneous catalyst utilizing the grinding process, hydrothermal process was utilized to synthesis the ZnS nanoparticles, and they are easily recoverable and reusable for up to 5 runs no significantly losing their catalytic activity (Scheme 33) [72]. Parallel, Saha et al. synthesized (**5**) using $ZrO_2$ NPs used for reaction at room temperature, active hydroxyl, oxide, and $Zr^{4+}$ may be present on the surface of $ZrO_2$ NPs, functioning as Lewis's acids or bases after the $10^{th}$ cycle, the $ZrO_2$ NPs tetragonal plane and catalytic activity remained unaltered (Scheme 33) [73].

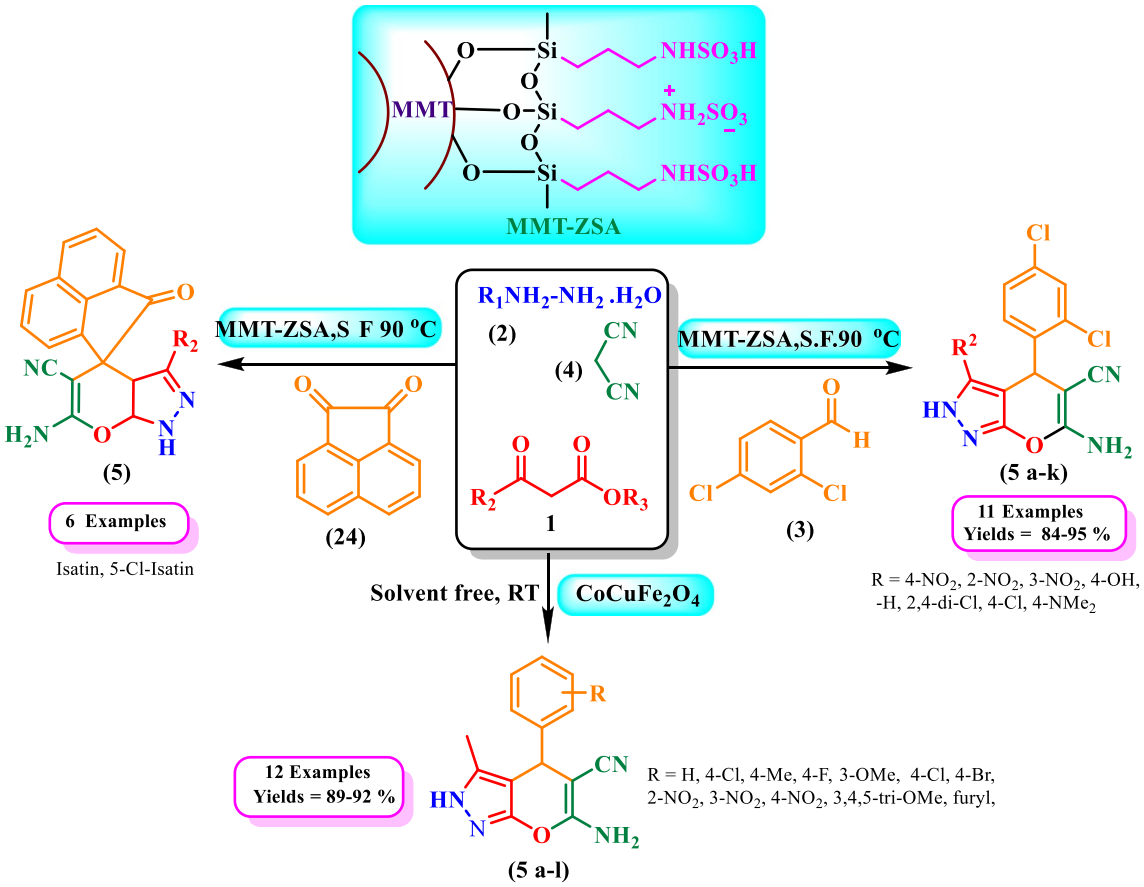
Safari et al. used montmorillonite K-10 as the template, 3-aminopropyltriethoxysilane as the linker, and chlorosulfonic acid as the source of $SO_3H$ to generate zwitterionic sulfamic acid functionalized nano-clay MMT-ZSA. Catalyst was investigated in the multicomponent reaction involving (**2**), (**4**), (**1**) and carbonyl compounds (1,2-di ketones and benzaldehyde derivatives) (**24**) to produce (**5**) derivatives under clean circumstances. Compounds listed above were synthesized using this approach with quick reaction times and high-to-exceptional yields. Mild process, heterogeneous reaction conditions, a wide range of functional group tolerance, and catalyst reusability are significant features of the




**Scheme 32.** $ZnFe_2O_4$ and $Fe_3O_4$ NPs-mediated synthesis of (**5**)




**Scheme 33.** ZnS and $ZrO_2$ NPs-catalyzed synthesis of (**5**)

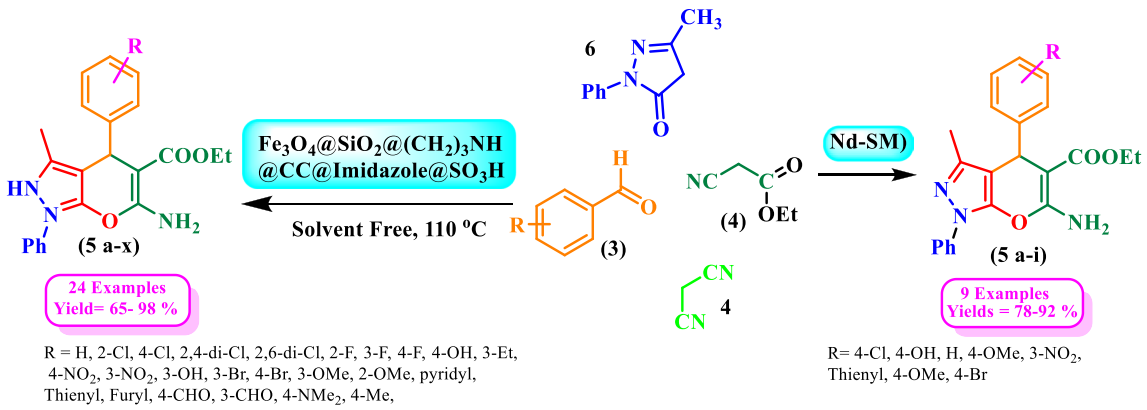



**Scheme 34.** Preparation of (**5**) mediated by MMT-ZSA and $CoCuFe_2O_4$ NPs

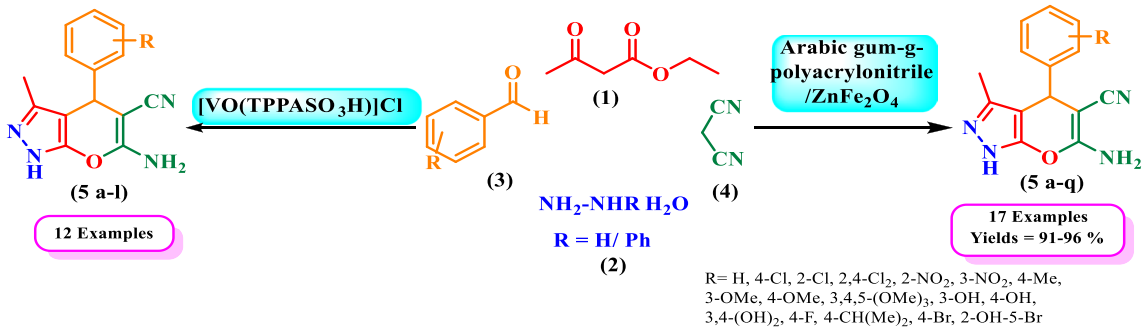
reaction (Scheme 34) [74]. Parallelly Dadaei et al. showed an efficient method for the synthesis of (**5**) derivatives by using $CoCuFe_2O_4$ silica-supported behavior melamine as a magnetic nanocatalyst. On the surface of a nanostructure, a catalyst potential active site has functionalized. These magnetic nanocatalyst key advantages are its efficiency as a heterogeneous catalyst, ease of application, minimal catalyst use, non-toxicity, high yields and simple set-up of the end products, rapid reaction times, and repeatability. Excellent magnetic and chemical stability can be found in the central core nanoparticles. As a result, cobalt ferrite's magnetic moment relaxes far more slowly than magnetite with a similar particle size (Scheme 34) [75].

The distinctive Nd-Salen Schiff base complex immobilized mesoporous silica was produced by Rather et al. using a catalyst to adsorb $NdCl_3$ on mesoporous-$SiO_2$ (Nd-SM). It was employed as a catalyst for the synthesis of (**5**) at 70 °C in a neat condition. The catalyst was recycled up to six times for the reaction (Scheme 35) [76]. An IL-based nanocatalyst ($Fe_3O_4$@$SiO_2$@$(CH_2)_3NH$@CC@Imidazole@$SO_3H$) was claimed to have been synthesized by Akbarpour et al. while the activity of the catalyst was investigated in the synthesis of (**5**) derivatives, the prepared catalyst was characterized using a variety of spectroscopic techniques. The reaction was carried out within a minimum time and high yield using starting materials (**3**), (**6**), and (**4**) in the presence of the catalyst in solvent-free condition at 110 °C (Scheme 35) [77].

Mahtab Moeinimehr et al. studied the novel heterogeneous and recyclable catalyst Nano-N-sulfonated ($SO_3H$) phthalocyanine molten salt (vanadium-oxo pyridiniumporphyrazinato sulfonic acid) [VO(TPPA$SO_3H$)]Cl. The catalyst, which has two active sites, is used for synthesis of (**5**) and its different derivatives. Protocol provides significant advantages such as shorter reaction times, high yields, simple set-up, and moderate reaction conditions (Scheme 36) [78]. According to Fereshte et al., the catalyst used hydrolyzed Arabic gum-g-polyacrylonitrile/$ZnFe_2O_4$ (Hyd AG-g-PAN/$ZnFe_2O_4$) for efficient production of (**5**) from (**4**), (**3**), (**2**), and (**1**). Zinc ferrite magnetic particles, Arabic gum (AG) as the support, N, N-methylene bisacrylamide crosslinking with ammonium persulfate as an initiator, and alkaline solution for hydrolyzation, which has distinct acidic and basic sites and a soft three-dimensional cross-linked framework, could be used as an effective catalyst for the synthesis of (**5**). Additionally, before losing its effectiveness the catalyst can




**Scheme 35.** Preparation of (**5**) using Nd-SM and ($Fe_3O_4$@$SiO_2$@$(CH_2)_3$NH@CC@Imidazole@$SO_3H$)

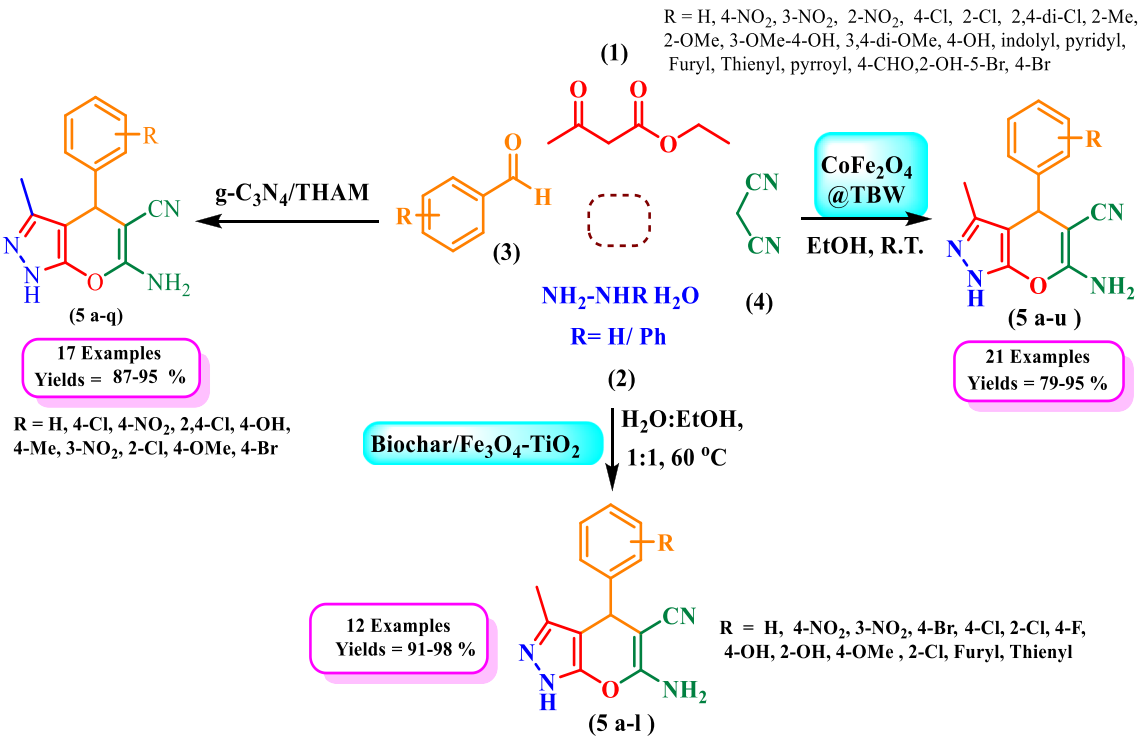



**Scheme 36.** Synthesis of (**5**) using [VO(TPPASO$_3$H)]Cl and [AG-g-PAN/Z$nFe_2O_4$]

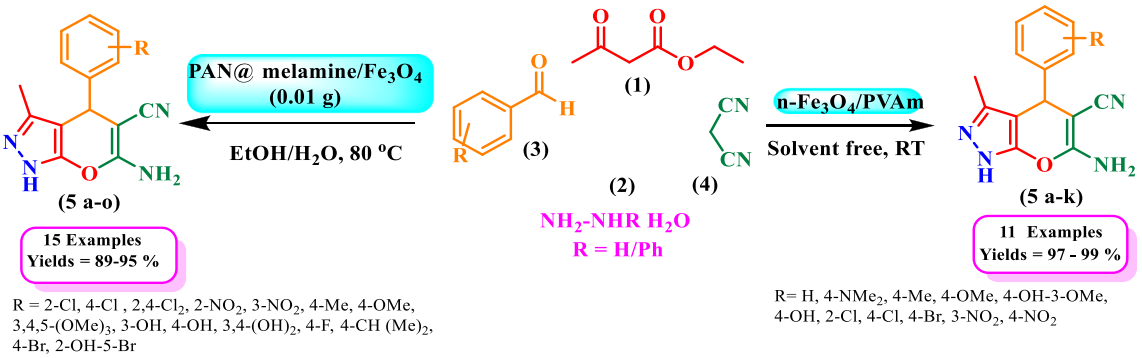
be used at least 6 more times in subsequent reaction cycles at 80 °C was reusability (Scheme 36) [79].

Bread waste from $CoFe_2O_4$@TBW was used by Firouz Matloubi Moghaddam et al. to produce core–shell magnetic NPs. The required technique was used to characterize the prepared heterogeneous catalyst. Synthesis of (**5**). Additionally, the new heterogeneous magnetic catalyst is easily recoverable with a magnet and reused up to 10 times with no significant loss of catalytic activity, making it both environmentally safe and financially feasible to carry out the desired transformations (Scheme 37) [80]. Heterogeneous catalytic system developed by Bagherian Jamnani et al. used g-$C_3N_4$/THAM. To design the derivatives of (**5**) and in multicomponent reactions (MCRs), the innovative g-$C_3N_4$/THAM NPs were characterized and appropriately examined. Relevant reaction products were generated with exceptional efficiency by tuning the previously reported NPs, and the reversibility process was afterwards examined. The ecologically friendly g-$C_3N_4$/THAM nanocatalyst was used to catalyze the processes using ethanol (Scheme 37) [81]. The special $Fe_3O_4$-$TiO_2$ nanocatalyst made of naturally occurring magnetic biochar was synthesized by Dharmendra et al. that characterized it and used to synthesize physiologically active (**5**) derivatives using (**1**), (**2**), (**3**), and (**4**) operated at 60 °C, the reaction was conducted with good yield while using $H_2O$: EtOH as the solvent. This operationally easy technology has many benefits such as simple workup and purification methods, a short reaction time, high atom efficiency, cheap cost, and magnetically separable NPs. Testing for antimicrobial activity was done on the final products (**5**). Studies show that the synthesized compounds exhibit significant antibacterial activity against the fungus *Candida albicans*, the Gram-positive and Gram-negative bacteria (Scheme 37) [82].

According to Arghan et al. introducing n-$Fe_3O_4$/PVAm as a catalyst, the authors used the developed mixed nanocomposite in the orderly synthesis of (**5**) derivatives at RT. With its free primary amino groups, the n-$Fe_3O_4$/PVAm nanocomposite acts as a base catalyst in the process and reused up to 9 times without any loss of catalytic activity (Scheme 38) [83]. Afruzi et al. reported the preparation of PAN@melamine/$Fe_3O_4$ organometallic nanocomposite $Fe_3O_4$ MNPs, the synthesis nanocomposite was used to synthesize (**5**) as a heterogeneous catalyst. With a straightforward workup procedure, corresponding compounds were produced in excellent yields. Additionally, there was




**Scheme 37.** Preparation of (**5**) using g-$C_3N_4$/THAM, $CoFe_2O_4$@TBW, and Biochar/$Fe_2O_4$-$TiO_2$

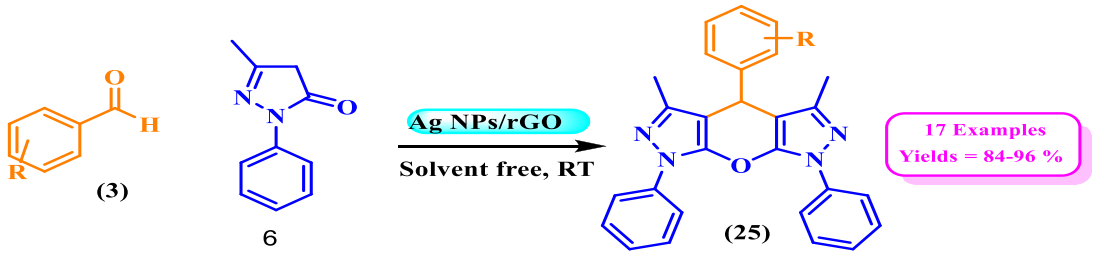



**Scheme 38.** Preparation of (**5**) using PAN@melamine/$Fe_3O_4$ and n-$Fe_3O_4$/PAM

no loss of catalytic activity when the produced NPs were recycled and utilized repeatedly in both multicomponent reactions (Scheme 38) [84].

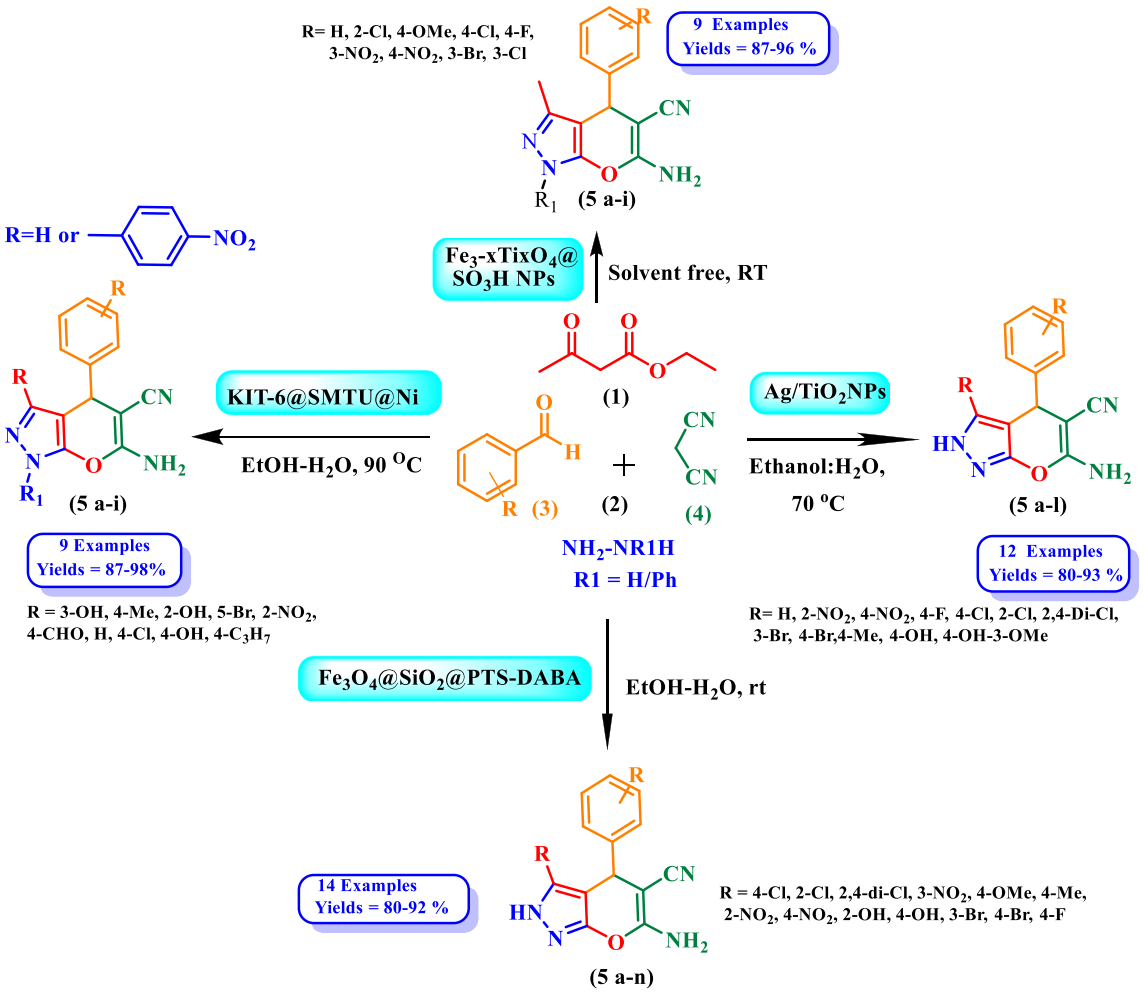
In 2017, Dandia et al. synthesized (**5**) derivatives via reaction of different (**1**) with (**6**) at RT. The greater and widely spread Lewis's acid sites of the composite Ag NPs/GO used in this study increase the reactant and intermediates reactivity towards the Knoevenagel–Michael addition process by subsequent cyclization. According to this technique, aryl methylene bis-pyrazolols and aryl methylene pyrazolones (**6**) are significantly less selective than pyranodipyrazolones (**25**) at least 7 repetitions of recovery and reuse of the catalyst were possible without losing any catalytic activity (Scheme 39) [85].

Azarifar et al. have carried out the fabrication of a magnetic acidic catalyst supported by titanomagnetite nanoparticles ($Fe_3$-x$TixO_4$). The $Fe_3$-x$TixO_4$@$SO_3H$ nanoparticles were synthesized by functionalizing these NPs with sulfonic acid groups and a catalyst was used for the synthesis of (**5**). Catalysts having certain advantages such as reusable nanoparticles were employed for the reaction (Scheme 40) [86]. Fatahpour, et al. derivatives of (**5**) were made in EtOH:$H_2O$ at 70 °C using Ag/$TiO_2$ nano-thin sheets as a strong, environmentally friendly, and recyclable




R = H, 4-OMe, 4-Me, 4-Cl, ,4,5-$(OMe)_3$, 4-Br, 4-F, 4-$NO_2$, 3-OPh, indolyl, Thienyl Furyl, H, 4-Cl, 4-Me, 4-F, 3-OMe, 4-Cl, 4-Br, 2-$NO_2$, 3-$NO_2$, 4-$NO_2$, 3,4,5-tri-OMe, furyl, Isatin, 5-Me-Isatin, 5-Br-Isatin, 5-Cl-Isatin, 5-$NO_2$-Isatin

**Scheme 39.** Ag NPs/GO-catalyzed synthesis of (**5**)




**Scheme 40.** Synthesis of (**5**) mediated $Fe_3$-x$TixO_4$@$SO_3H$, Ag/$TiO_2$, ($Fe_3O_4$@$SiO_2$@PTSDABA), and KIT-6@SMTU@Ni

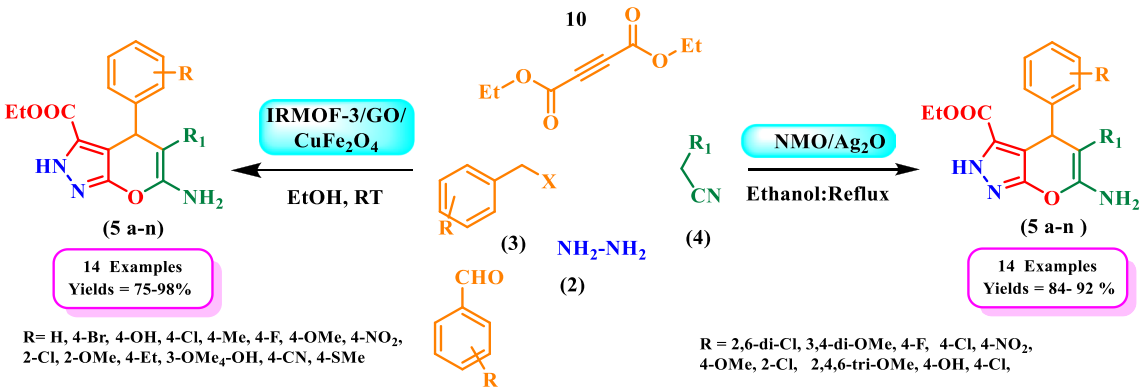
catalyst (Scheme 40) [87]. Karami et al. developed a new and efficient silica-coated magnetite nanocatalyst ($Fe_3O_4$@$SiO_2$@PTSDABA) that was synthesized and confirmed by different spectroscopic methods. Successfully employed for biologically potent (**5**) derivatives with excellent yield, the catalyst was recovered by magnetic separation method. The prepared catalysts can be used repeatedly without significantly losing their catalytic activity (Scheme 40) [88]. Darabi et al. reported that KIT-6@SMTU@Ni was synthesized as a novel and green heterogeneous catalyst via

a new technique of Ni (II) complex stabilization on modified mesoporous KIT-6, while confirmed by various spectroscopic techniques. Synthesis of (**5**) was successfully carried out by employing nanocatalyst (KIT-6@SMTU@Ni). Moreover, synthesizing (**5**) via the condensation reaction of (**3**) with (**4**), (**2**), and (**1**) with high and excellent yields, simple workup, and prominent highlight of this protocol, KIT-6@SMTU@Ni can be excellent separation (Scheme 40) [89].

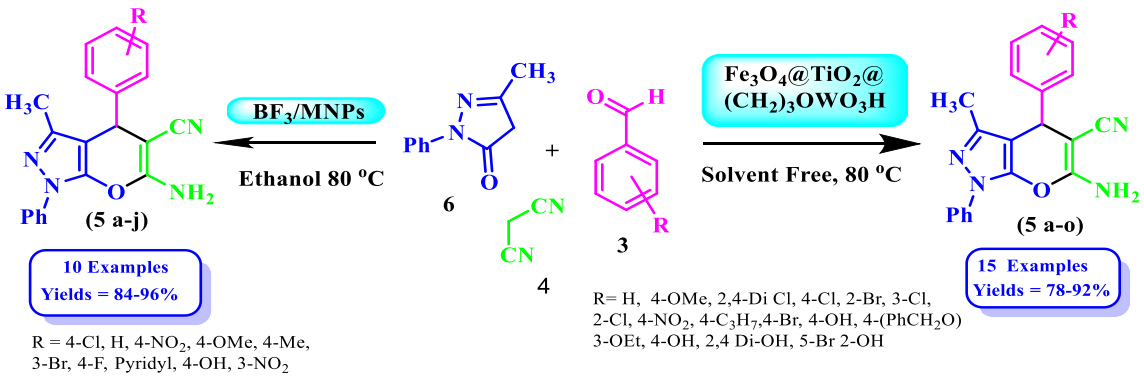
In a four-component reaction involving benzyl halide, (**4**), (**10**)/(**1**), and (**2**), Beerappa et al. employed silver oxide ($Ag_2O$) and n-methyl morpholine N-oxide (NMO) as catalysts to synthesize (**5**) (Scheme 41) [90]. Ghasemzadeh et al. reported a simple and worthwhile protocol for synthesizing copper ferrite NPs supported on IRMOF-3/GO[IRMOF-3/GO/$CuFe_2O_4$]. Synthesized NPs IRMOF-3/GO/$CuFe_2O_4$ were fully characterized by different techniques. Prepared NPs were employed in the synthesis of (**5**) through **(2)**, **(1)**, **(3)**, and **(4)** placed in ultrasonication irradiation furnishing the good-to-excellent yield of the desired product. A significant application of NPs displays high catalytic activity, compatibility, short reaction times, and high efficiency (Scheme 41) [91].

Masoomi, a co-worker in 2015 used $BF_3$ bound nano-$Fe_3O_4$ ($BF_3$/MNPs) as a versatile catalyst for the synthesizing of (**5**), synthesized $BF_3$/MNPs NPs at three calcination temperatures, and used synthetic application. A variety of techniques were used to characterize this catalyst (Scheme 42) [92]. Gholtash et al. reported newer magnetic NPs based on the immobilization of tungstic acid on to $TiO_2$-coated $Fe_3O_4$ NPs that have had 3-chloropropyl grafted onto them ($Fe_3O_4$@$TiO_2$@ $(CH_2)_3OWO_3H$) was synthesized, fully characterized, and used for the preparation of series of (**5**). Using (**6**) and (**3**), the mixture was stirred in the presence of a novel catalyst under neat conditions at 80 °C for the required time. This methodology provides excellent yields, non-toxic, and thermally stable catalysts that exhibit good catalytic activity and can be reused for five catalytic cycles without any loss (Scheme 42) [93].

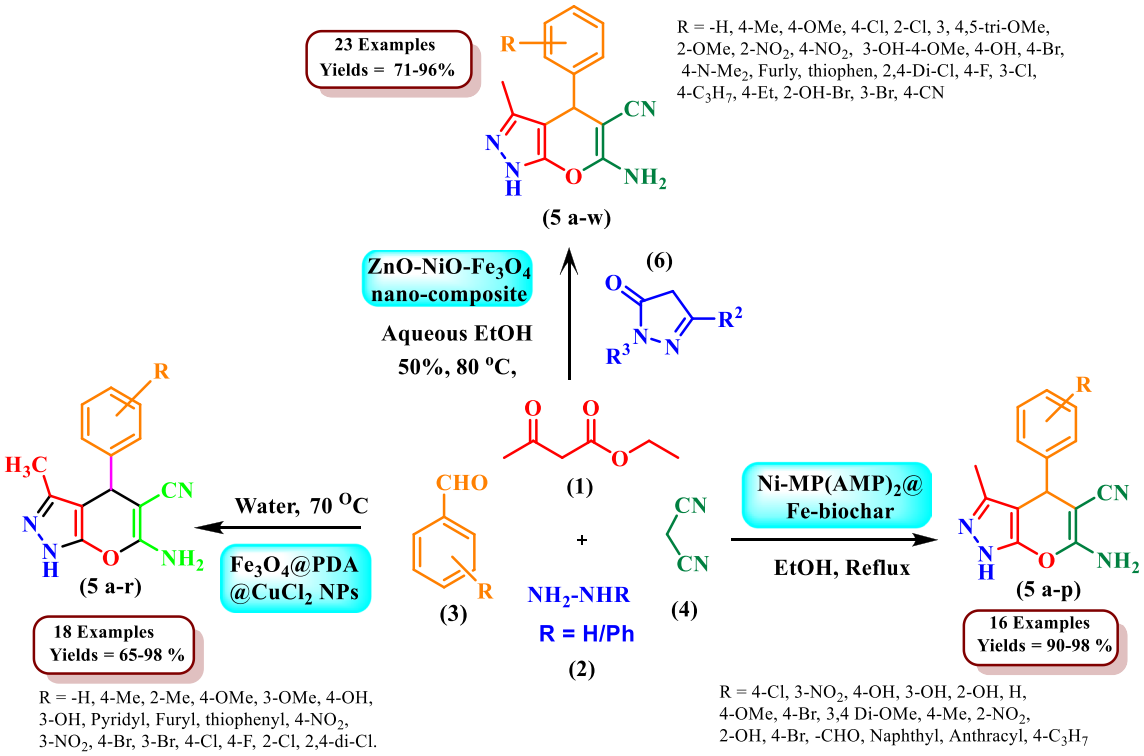
Moradi et al. reported the synthesis of biochar NPs (Ni-MP(AMP)$_2$@Fe-biochar) from chicken manure, and the prepared biochar NPs were magnetized through an environmentally benign method. Synthesis of series of (**5**) from four-component condensation of (**1**), (**2**), (**3**), and (**4**) was in EtOH under reflux. Using magnetically reusable catalysts with excellent yield, the feature of this reaction is easy




**Scheme 41.** Preparation of (**5**) using IRMOF-3/GO/$CuFe_2O_4$ and $Ag_2O$/NMO




**Scheme 42.** $BF_3$/MNPs and ($Fe_3O_4$@$TiO_2$@$(CH_2)_3OWO_3H$) catalyzed by synthesis of (**5**)




**Scheme 43.** Synthesis of (**5**) using Ni-MP(AMP)$_2$@Fe-biochar, $Fe_3O_4$@PDA/$CuCl_2$, and ZnO-NiO-$Fe_3O_4$

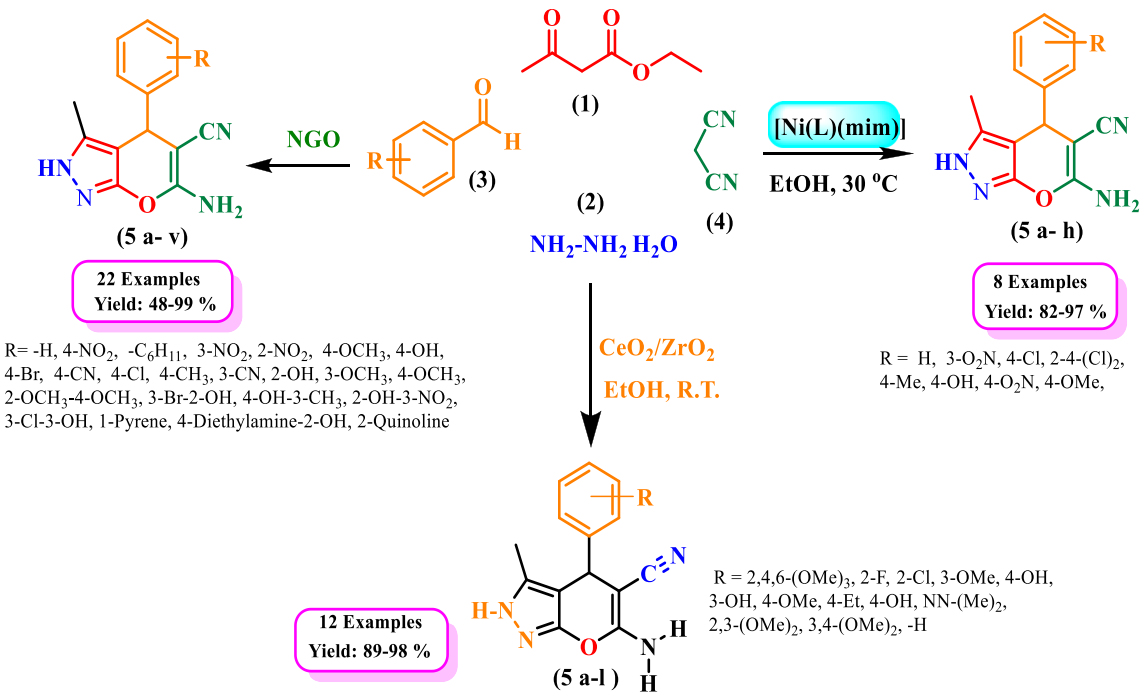
workup and chromatographic separation is not required for purification. Catalyst (Ni-MP(AMP)$_2$@Fe-biochar) can be retrieved and reused for up to 9 runs with no prominent loss in its catalytic activity (Scheme 43) [94]. Copper NPs supported by magnetite were created by Badbedast et al. using a straightforward co-precipitation method, and they were then characterized using a variety of spectroscopic methods. In the synthesis of (**5**), the catalytic activity of the $Fe_3O_4$@PDA/$CuCl_2$ combination was investigated. The catalyst's ability to generate (**5**) with high to acceptable yields at low loadings without the use of an external reducing agent is illuminating. In addition, the created heterogeneous catalyst can be recycled an additional six times with little to no loss of catalytic activity (Scheme 43) [95]. Lashkari et al. reported the synthesis of (**5**). The reactions of (**6**) and (**4**) were placed under ultrasonic irradiation in the presence of ZnO-NiO-$Fe_3O_4$ nanocomposite catalyst in aqueous ethanol solvent medium at an appropriate time to offer the corresponding (**5**) with good-to-excellent yield (Scheme 43) [96].

### Metal oxide-catalyzed reaction

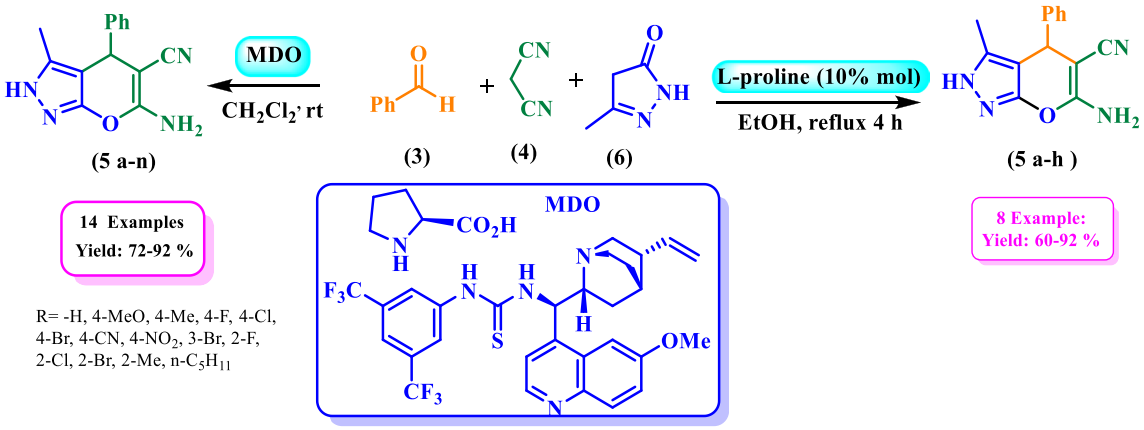
Maddila et al. described ceria-doped zirconia ($CeO_2$/$ZrO_2$)-catalyzed synthesis of (**5**) via four-component reactions of (**1**), (**2**), (**3**), and (**4**). Catalytic material $CeO_2$/$ZrO_2$ was synthesized, characterized, and used for the synthesizing of (**5**). This protocol was good-to-outstanding yield, eco-friendly of this development consists of a simple workup, less reaction time, avoidance of chromatographic separation and elimination of toxic solvents, less expensive, and is a highly reusable catalyst (Scheme 44) [97]. A novel mixed-ligand Ni (II) complex, [Ni(L)(mimi)], was synthesis by Ebrahimipour et al. by reacting 4-bromo-2-[(2-hydroxy-5-methylphenyl] iminomethyl] phenol [$H_2$L], Ni(OAc)$_2$ $4H_2O$, and 1-methylimidazole in two forms of NPs and bulk sizes, respectively. The four-component synthesis of (**5**) from a stoichiometric combination of (**1**), (**2**), (**3**), and (**4**) in ethanol was found to be successfully catalyzed by [Ni(L)(mimi)] in both its bulk and nano forms. Additionally, the complex nano form has a higher catalytic activity (Scheme 44) [98]. In the present work, using nitrogen-doped graphene oxide (NGO) as a catalyst, Palaniswamy Suresh and colleagues have established a simple and sustainable approach for the one-pot production of the compound (**5**). Currently, available carbonaceous NGO facilitates the synthesis of (**5**) from various (**3**) and ketones in the absence of solvents and with simple grinding procedures (Scheme 44) [99].

### Organo-catalyzed reaction

Hilmy Elnagdi et al. employed the multicomponent reaction (MCR) of (**1**) and (**4**) with active methylene (**27**) and L-proline to form (**5**). This protocol has stereo specifically, in good yields of reaction (Scheme 45) [100]. Muramulla




**Scheme 44.** Synthesis of (**5**) mediated $CeO_2/ZrO_2$, NGO, and [Ni(L)(mimi)]

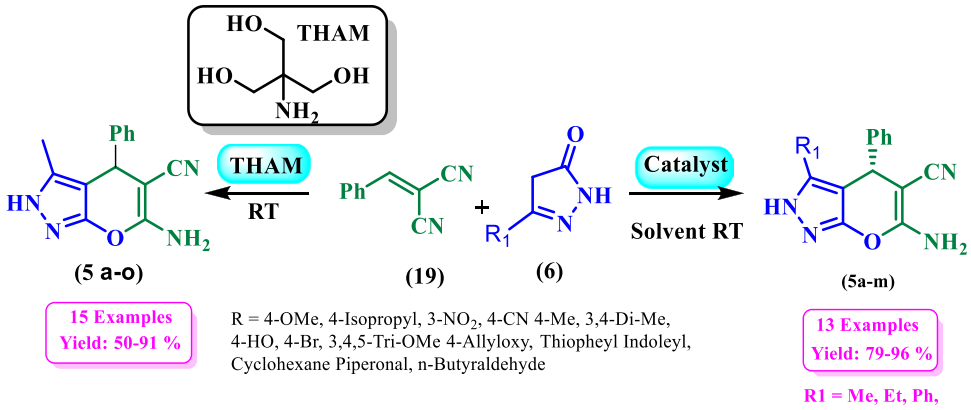



**Scheme 45.** Synthesis of (**5**) mediated L-proline and MDO

et al. established an important, entirely novel organocatalytic mode of the modularly constructed catalyst (MDOs) and used the investigation of the tandem Michael addition–cyclization reaction and benzylidenemalononitriles (**19**) to form (**5**) with high yields of enantioselectivities product (Scheme 45) [101].

Through a Thorpe–Ziegler type reaction and cinchona alkaloid-catalyzed tandem Michael addition reaction between (**19**) and 2-pyrazolin-5-ones (**6**), Gogoi et al. were able to produce the first enantioselective synthesis of (**5**). By synthesizing these two components on-site from basic, easily available starting materials, a reaction can likewise be carried out in a three- or four-component method with outstanding yields obtained for the intended products (**5**) (Scheme 46) [102]. Synthesis of medicinally important (**5**) using reasonably priced, non-toxic, and biodegradable tris-hydroxymethylaminomethane (THAM) catalyst, has been the subject, it is a very interesting article by Wadgaonkar and co-workers. The practical utility of this MCR process has been greatly enhanced at RT. It has broad scope, avoidance of conventional isolation and purification approaches, and the reusability of the catalyst for 5 successive runs for

**Scheme 46.** THAM-catalyzed synthesis of (**5**)

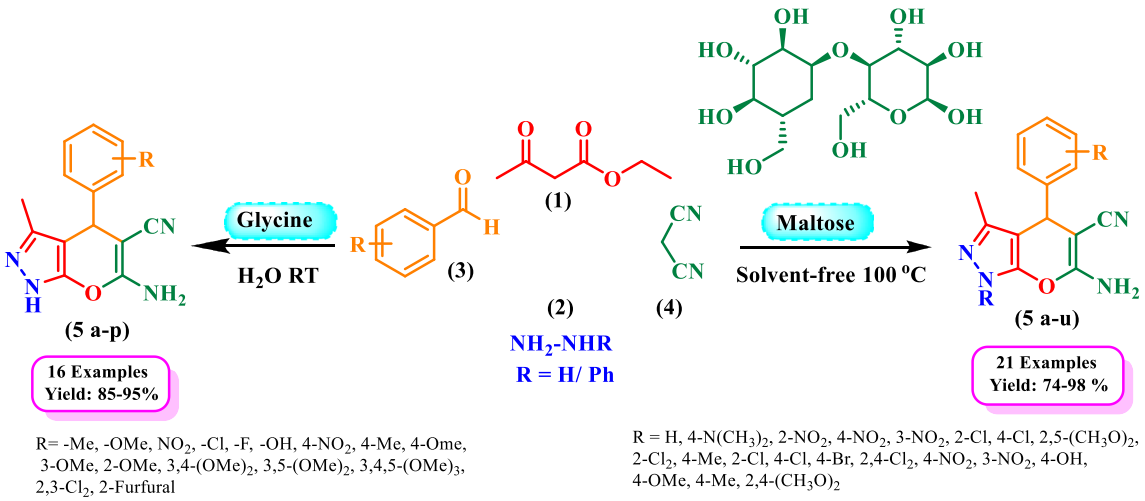



reaction (Scheme 46) [103]. In a study by Madhusudana Reddy et al. in 2010, the rapid and high-yielding synthesis of fused (**5**) from (**1**), (**2**), (**3**), & (**4**) in an aqueous medium at 25 °C was carried out using the amino acid as a glycine as an organocatalyst (Scheme 47) [104]. Kangani et al. introduced maltose which is used as an organocatalyst in a one-pot, four-component reaction with (**1**), (**2**), (**3**), & (**4**) under traditional, solvent-free with heating to synthesis (**5**) (Scheme 47) [105].

Organocatalyst ammonium triflate has been utilized in several processes. To synthesize (**5**), Zhou et al. described using (**1**), (**2**), (**3**), & (**4**). Authors optimized the look at several ammonium triflates. The effective one, MorT, provided the highest yield among the rest of the catalysts (Scheme 48) [106].

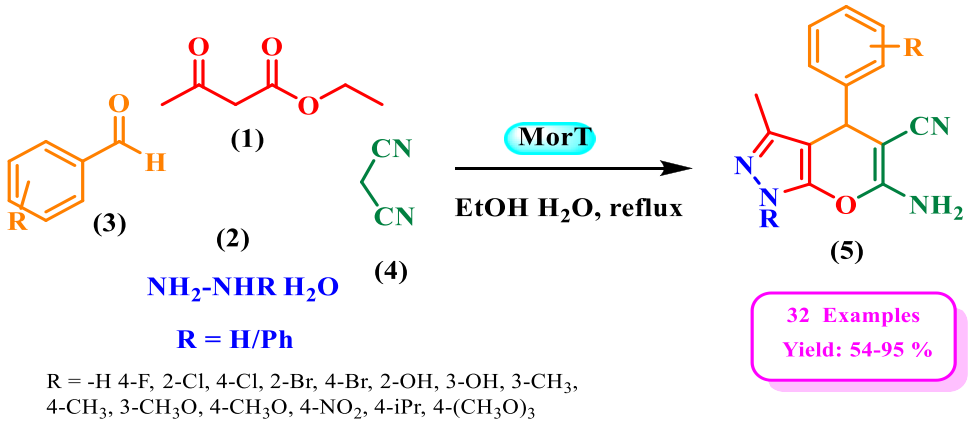
### Silica-supported catalyzed reaction

Atar et al. have developed for the first time a four-component, one-pot cyclocondensation process comprising (**1**), (**2**), (**3**), and (**4**) utilizing silica-supported tetramethylguanidine as a heterogeneous catalyst, which is an effective, and rapid method for making diversity-oriented (**5**) derivatives. Protocol showed to be an efficient protocol in terms of good yields, quite simple workup, and simplicity in the recovery of catalyst. Moreover, this method is better pertaining to the quantity of catalyst, green media, and less reaction time (Scheme 49) [107]. Khazdooz et al. used (**1**), (**2**), (**3**), and (**4**) as building blocks and $Ca_{9.5}Mg_{0.5}(PO_4)_{5.5}(SiO_4)_{0.5}F_{1.5}$ serves as a heterogeneous catalyst for the synthesis of (**5**). The reaction was carried out in a mild reaction condition, at 70 °C. By using this green procedure, the key benefits current process include a catalyst that produces products with high yields in a shorter time (Scheme 49) [108]. Sinija et al. described here a straightforward, green, and extremely effective method for (**5**) by developing a Ti-grafted polyamidoamine dendritic silica hybrid catalyst. Loading of low catalysts has high product yields, simple set-up, quicker reaction times, and the possibility to reuse the catalyst, and these are some of the main benefits of the current process




**Scheme 47.** Preparation of (**5**) mediated by glycine and maltose

**Scheme 48.** Synthesis of (**5**) using MorT




(Scheme 49) [109]. Here, (**1**), (**2**), (**3**), and (**4**) react in one pot in water at 60 °C and nano-magnetic piperidinium benzene-1,3-disulfonate, to synthesize (**5**) derivatives. Vaghei et al. developed a straightforward, effective protocol. It was fabricated to support IL with $Fe_3O_4$@$SiO_2$ NPs. The current protocol has many benefits including rapid and clean reactions, simplicity in a purification process, good-to-exceptional yields, and readily recoverable catalyst (Scheme 49) [110].

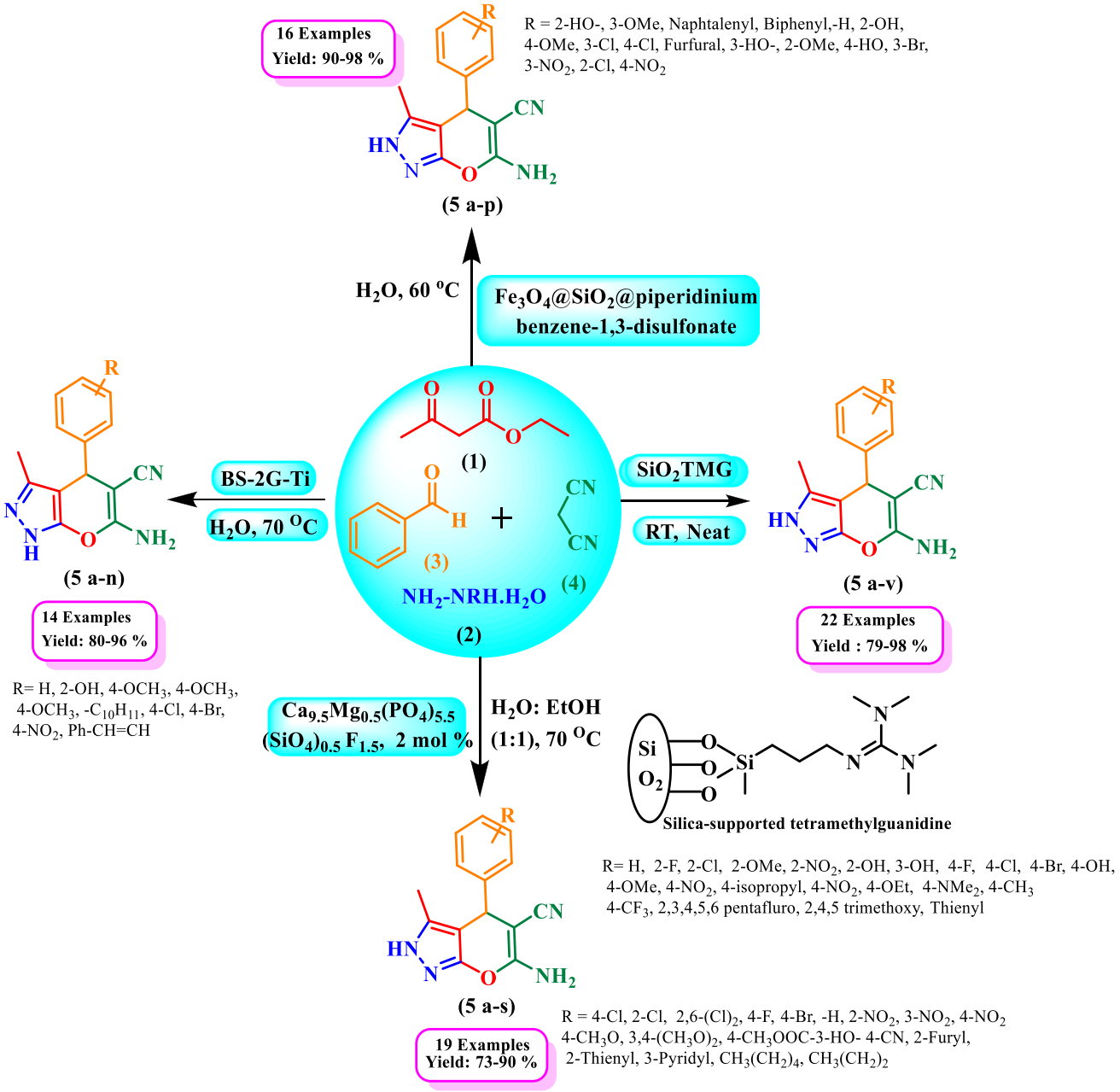
According to Shaterian et al., the four-component, solvent-free synthesis of (**5**) was done by using (**1**), (**2**), (**3**), and (**4**) in the presence of $P_2O_5/SiO_2$, $H_3PO_4/Al_2O_3$. This method has the advantages of using inexpensive, non-toxic components, simple and clean workup, short reaction times, and good reaction product yields (Scheme 50) [111]. Dadaei et al. reported efficient $CoFe_2O_4$ silica-supported bearing melamine as magnetic NPs for preparation (**5**) derivatives. The main benefits of these magnetic NPs are their ease of synthesis, effectiveness as heterogeneous NPs, mildness, minimal need for catalyst, high yields and rapid reaction, ease of workup, and reusability. It also displays excellent chemical and magnetic stability of the catalyst (Scheme 50) [112].

### Miscellaneous reactions

Bihani et al. developed an advantageous protocol for industry and academia for the synthesizing of a series of (**5**) by using an extremely efficient catalyst Amberlyst A21 by a four-component reaction in a mixture of (**1**), (**2**), (**3**), and (**4**) ethanol at RT. The catalysts have facile recovery and reuse, rapid reaction times, and no chromatographic purification with outstanding yields (Scheme 51) [113]. In a four-component one-pot reaction involving (**1**), (**2**), (**3**), and (**4**) plus a phase transfer catalyst, Ablajan et al. synthesize a series of (**5**). Products with high yield were obtained utilizing 30 mol% HDBAC as a catalyst (Scheme 51) [114]. Abdelmadjid Debache and colleagues present a simple and risk-free method for the synthesis of (**5**) using a four-component condensation of a different (**3**) and (**1**), (**2**), and (**4**). Triphenylphosphine catalyzes this condensation reaction (Scheme 51) [115].

Mecadon et al. developed an effective four-component synthesis of (**5**) involving (**1**), (**2**), (**4**) various (**3**) utilizing L-proline in aqueous conditions (10 mol %) in a mild reaction environment to produce high yields. Moreover, a comparison of L-proline and KF alumina was used (Scheme 52) [116]. Zhan-Hui Zhang and co-workers demonstrated the bio-based chemical meglumine, as a reusable and highly effective catalyst for a one-pot, four-component reaction of a sequence of (**5**) derivatives using (**2**), (**4**), carbonyl compound or isatin (**24**), and β-keto ester (**10**). This protocol offers short reaction times, a broad substrate range, good yields, the possibility to reuse the catalyst, a simple workup procedure, and the absence of potentially hazardous organic solvents is one of the best features of this revolutionary technique (Scheme 52) [117].

According to Mohammad Ali Ghasemzadeh et al., the efficient and quick synthesis of (**5**) was achieved using a novel and simple procedure in the 4-component condensation reaction of (**1**), (**2**), (**4**), and (**3**) using a metal–organic framework (MOF), MIL-53(Fe) as a catalyst in ethanol at room temperature. MIL-53 (Fe) can be simply recycled and used a minimum of 6 times without considerably losing any of its activity, according to recycling trials. The method offers various distinguishing characteristics, including simple set-up, rapid reaction durations, elimination of dangerous solvents, high yields, lack of chromatographic purification requirements, and recoverability of the catalyst (Scheme 53) [118]. For the four-component synthesis of (**5**), aspergillus niger lipase (ANL) was demonstrated to be a very effective catalyst from a stoichiometric combination of (**1**), (**2**), (**3**), and (**4**) in ethanol, as demonstrated by Bora et al., the enzymatic promiscuity of the lipase ANL towards various aliphatic and aromatic ketones as well as aldehydes is demonstrated. Some of the main characteristics of this technique

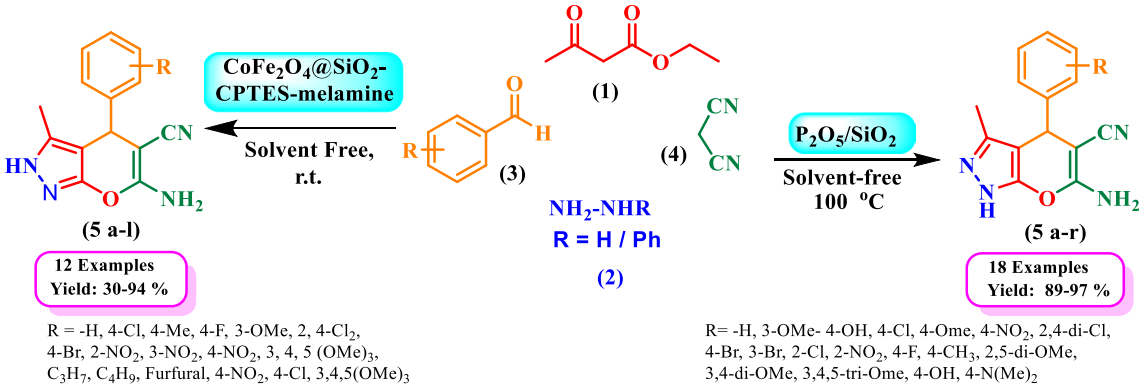



**Scheme 49.** Preparation of (**5**) by silica-supported tetramethylguanidine, $SiO_2$-TMG, BS-2-G-Ti, IL with $Fe_3O_4$@$SiO_2$

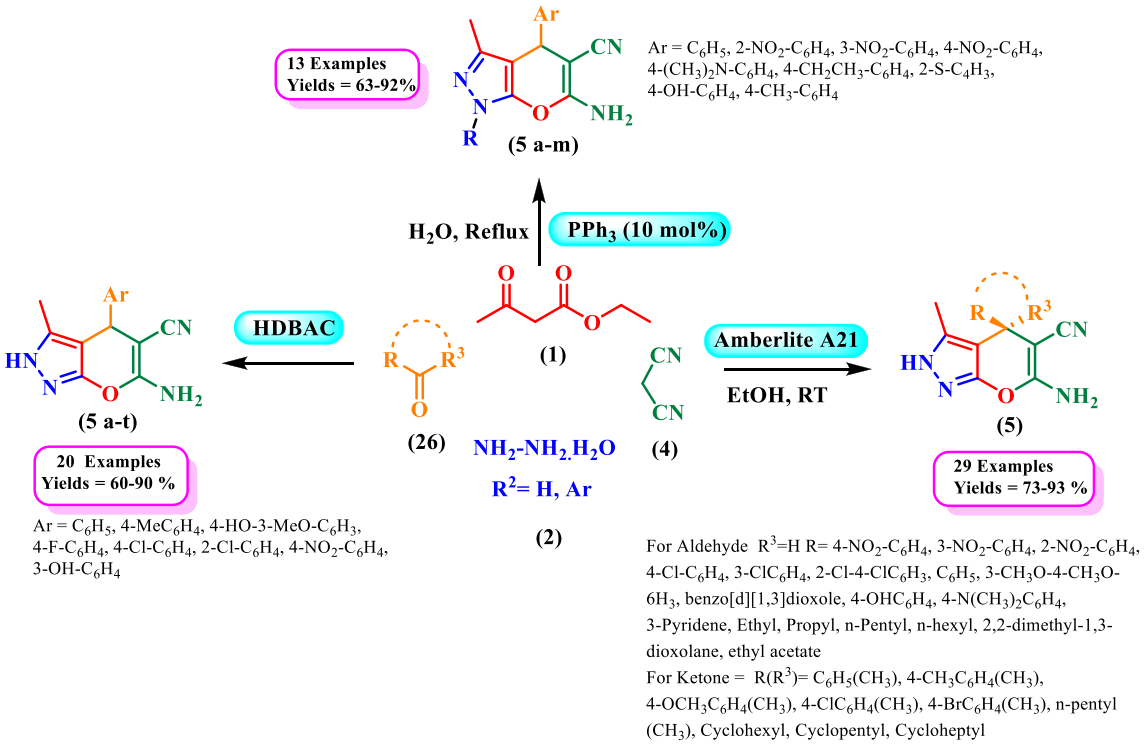
are the use of green bio-catalysts, the reusability of catalysts, good yields, and the absence of toxic solvents (Scheme 53) [119].

Khairnar et al. devised an approach for the efficient, rapid, and high-yielding synthesis of (**5**) derivatives employing PS-DABCO as a reusable green heterogeneous catalyst and a four-component one-pot, C–N and C–C bond-forming process of (**1**), (**2**), (**3**), and (**4**). With its broad applicability, a green synthesis that avoids toxic reagents, non-chromatographic purification method, improved operational simplicity, and reusable catalyst, this protocol is more practical, environmentally friendly, and affordable for commercial and academic uses (Scheme 54) [120]. Tetraethylammonium bromide (TEABr) has recently gained noticeable as a gentle, water-tolerant, cost-effective catalyst. This TEABr was utilized by Kumar et al. as a catalyst for the production of (**5**) (Scheme 54) [121].

The one-pot tandem reaction of (**3**) with (**1**), (**2**), and (**4**) at 60 °C in the presence of $Ph_3CCl$ under orderly, neutral, and silent conditions were detailed by Moosavi-Zare et al. in this study to generate the synthesis of (**5**) derivative (Scheme 55) [122]. MIL-101(Cr)-N($CH_2PO_3H_2$)$_2$ was



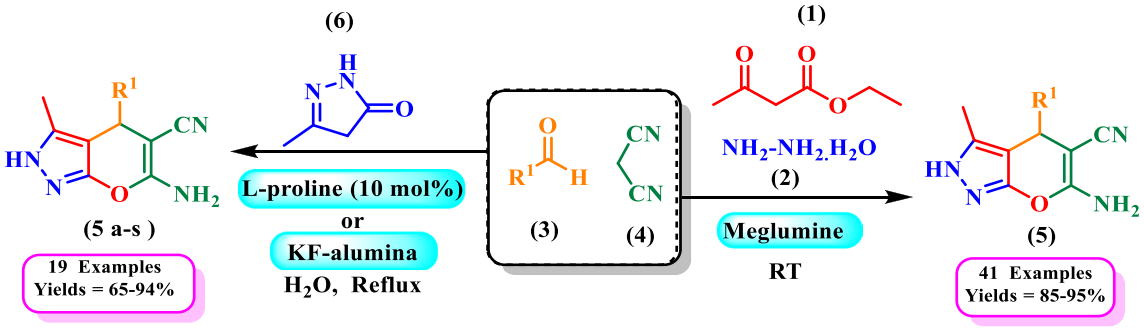

**Scheme 50.** Synthesis of (**5**) using $P_2O_5/SiO_2$ and $CoFe_2O_4$




**Scheme 51.** Amberlyst A21, HDBAC, and $PPh_3$-mediated synthesis of (**5**)

designed and formed by Babaee et al. when producing (**5**) compounds through the reaction of (**3**) with (**1**), (**2**), and (**4**), developed metal–organic frameworks were first tested for their suitability as a heterogeneous multifunctional and nano-porous catalyst. In the final stage, the cooperative vinylogous anomeric-based oxidation was carried out. The reported approach has noticeable applications including quick reaction times, good yields, catalyst recycling, and reusability (Scheme 55) [123].

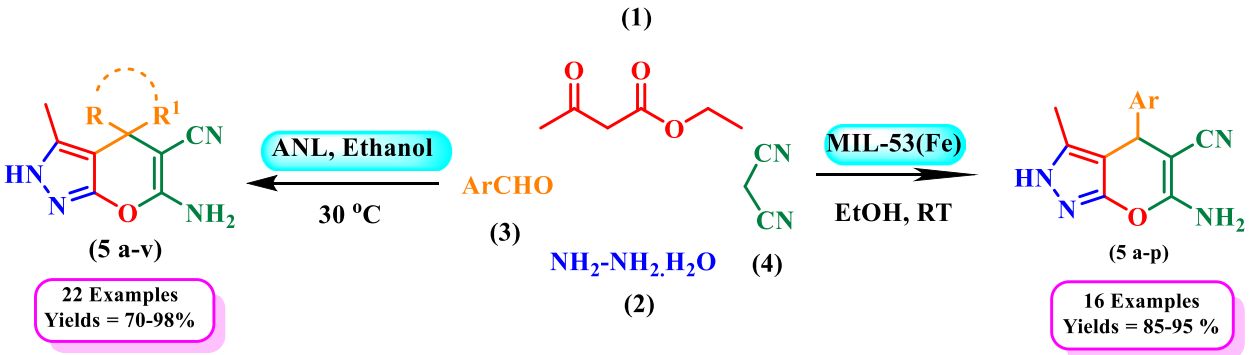
In a four-component, one-pot, solvent-free synthesis of (**5**) using (**1**), (**2**), (**3**), and (**4**), Govindan et al. successfully synthesized a novel poly-3,3-bis(chloromethyl) oxetane (PBCMO amine) dendritic polymer with a porphyrin-started amine-functionalized and employed as a catalyst. Due to PBCMO amine's water solubility, the catalyst may be easily detached and reused without losing any of its behavior (Scheme 56) [124]. In the current study, Agarwal et al. formed a papain enzyme immobilized on a polymer support called chitosan using a glutaraldehyde linkage to create [Pap-Glu@Chi] biocatalyst, which was then used for the four-component synthesis of (**5**) derivatives using (**1**), (**2**), (**3**), and (**4**) to provide outstanding yields in fewer reaction times (Scheme 56) [125].




$R^1$ = $C_6H_5$, 4-$CH_3$-$C_6H_4$, 4-$CH_3O$-6$H_4$, 2-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 3-Br-$C_6H_4$, 4-Br-$C_6H_4$, 4-HO-$C_6H_4$, 4-N($CH_3$)$_2$-$C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2$-$C_6H_4$, 3-$CH_3O$-4-HO$C_6H_3$, 3,4-($CH_3O$)$_2$ $C_6H_3$, 2,5-($CH_3O$)$_2C_6H_3$, 3,4,5-($CH_3O$)$_3$-$C_6H_2$, 1-Naphthyl, 9-Anthranyl, Butyl

$R^1$ = $C_6H_5$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4$CH_3(CH_2)_2OC_6H_4$, 4-$CH_3(CH_2)_4OC_6H_4$, 2-OMe-5-CH($CH_3$)$_2C_6H_3$, 2,3,4-(OMe)$_3$ $C_6H_2$, 3-$CH_3C_6H_4$, 4-C($CH_3$)$_3C_6H_4$, 4-$SCH_3C_6H_4$, 4-$OHC_6H_4$, 2-$FC_6H_4$, 3-$FC_6H_4$, 4-$FC_6H_4$, 2-$ClC_6H_4$, 3-$ClC_6H_4$, 4-$ClC_6H_4$, 2,4-$Cl_2C_6H_3$, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-$CF_3C_6H_4$, 4-$CF_3$ $C_6H_4$, 4-((4-Nitrobenzyl(oxy)-Ph, 2- Furyl, 2-Thienyl, 4-Pyridine, 1-Naphthyl, Decyl, Cyclohexyl, $C_2H_6(CH_3)_2$, Cyclonutyl, Cyclopentyl, Cyclohexyl, 4-Meethyl-Cyclohexyl, 5-methylisatin, 5-Nitroisatin, 5-Bromoisatin, 5-Floroisatin, 5-Chloroisatin, Isatin

**Scheme 52.** Preparation of (**5**) using L-proline and meglumine




Ar-CHO = 3-$NO_2$-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2-$NO_2$-$C_6H_4$ 4-F $C_6H_4$, 2,4-Cl-$C_6H_3$, $C_6H_5$, 4-$CH_3$-$C_6H_4$, 3-OH-$C_6H_4$, 4-$OCH_3$-$C_6H_4$, 5-benzo[d][1,3]dioxole, nicotin, n-butyl, n-hexyl, n-Heptyl, 2,2-dimethyl-1,3dioxolane
For Ketone R ($R^1$) = $C_6H_5$($CH_3$), 4-Cl-$C_6H_5$-($CH_3$), 4-$CH_3$-$C_6H_5$-($CH_3$), Pentyl-($CH_3$), Cyclopentyl, Cyclohexyl, Cyclohexyl

Ar = $C_6H_5$, 4-$ClC_6H_4$, 4-$NO_2C_6H_4$, 4-$BrC_6H_4$, 4-F $C_6H_4$, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$, 4-$SCH_3C_6H_4$, 2-$ClC_6H_4$, 2-$FC_6H_4$, 4-Et $C_6H_4$, 2,3-($OMe$)$_2C_6H_3$, 4-$OHC_6H_4$, 4-$CNC_6H_4$, 5-Br-2$OHC_6H_3$, 5-OH-2-$NO_2$ $C_6H_3$

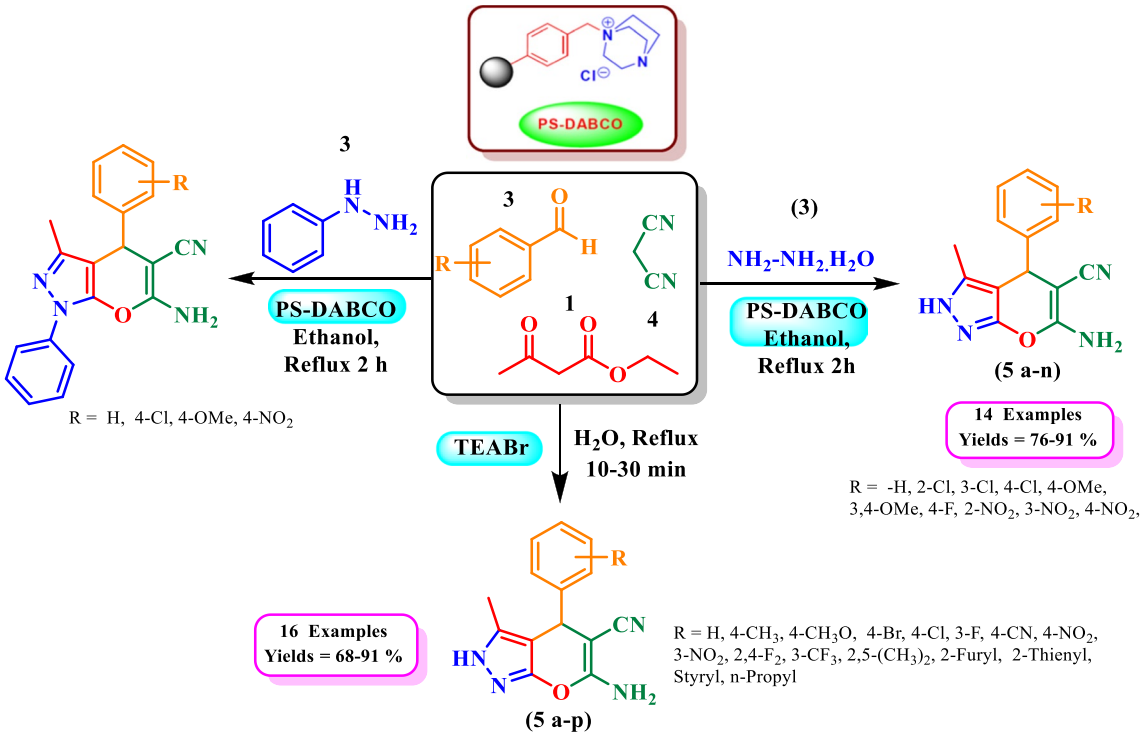
**Scheme 53.** MIL-53(Fe) and ANL catalyzed by (**5**)

Under completely non-catalytic conditions, Mandha et al. developed an environmentally acceptable approach for the one-pot multicomponent production of substituted (**5**) in aqueous EtOH medium. Synthesized compounds were assessed for their cytotoxic activities (Scheme 57) [126].

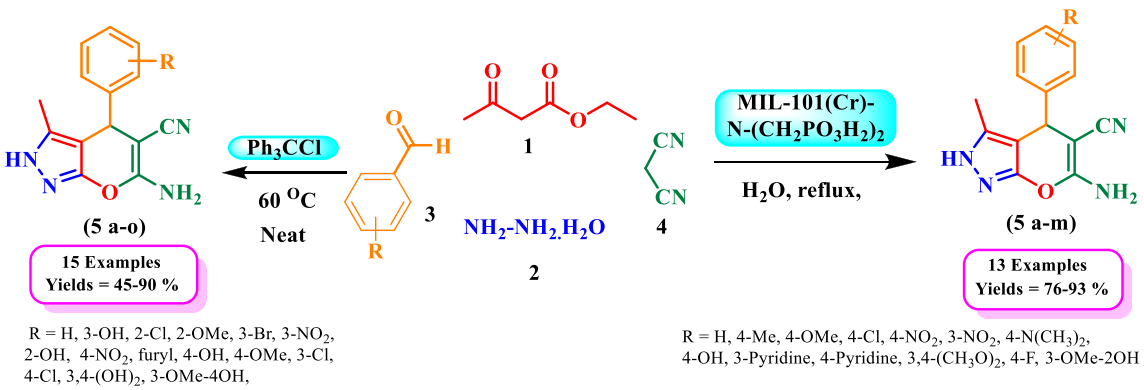
Dalal and co-workers used bovine serum albumin (BSA) biocatalyst. Using a three-component, one-pot reaction with (**1**) or (**9**), (**4**), and (**6**) in $H_2O$-EtOH (7:3) at RT, BSA catalytic synthesis of (**5**) (Scheme 58) [127].

For the synthesis of (**5**) derivatives, Lu Zh described a one-pot, five-component approach in 2015 that involves Suzuki coupling of 4-bromobenzaldehyde (**27**) and arylboronic acids (**28**), followed by a four-component reaction (**1**), (**2**), (**3**), & (**4**). In this study, the authors optimized the effects of temperature a Pd/C catalytic quantity. The solvent was based on the findings in aqueous. The aromatic ring substituents of the aryl boronic acids (**28**) had a substantial impact on product yields. The reactivity of aryl boronic acids was stronger when an EDG substituent was present in the para-position of an aromatic ring than the EWG substituent (Scheme 59) [128].

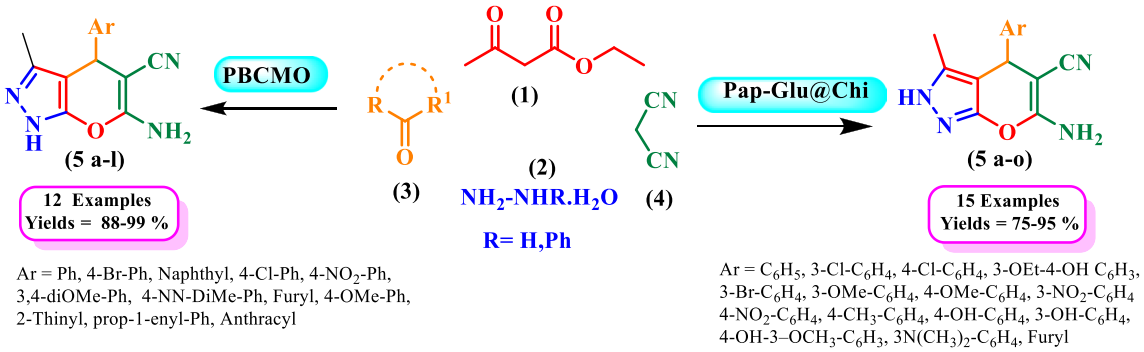
A four-component condensation of (**2**), (**3**), (**4**), & (**10**) in ethanol was used by Gangu et al. in 2017 to produce (**5**), with high yields and rapid reaction durations. Using the



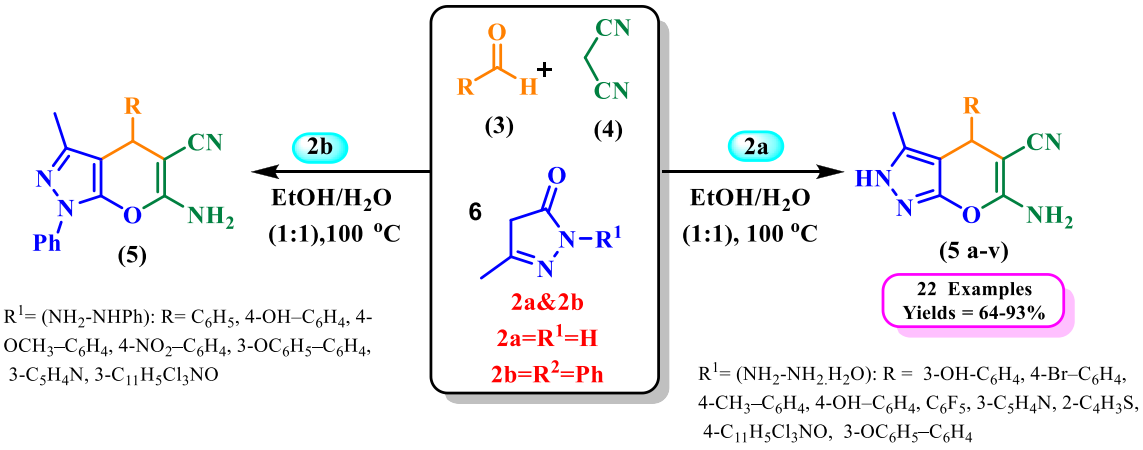

**Scheme 54.** Synthesis of (**5**) mediated by PS-DABCO and (TEABr)



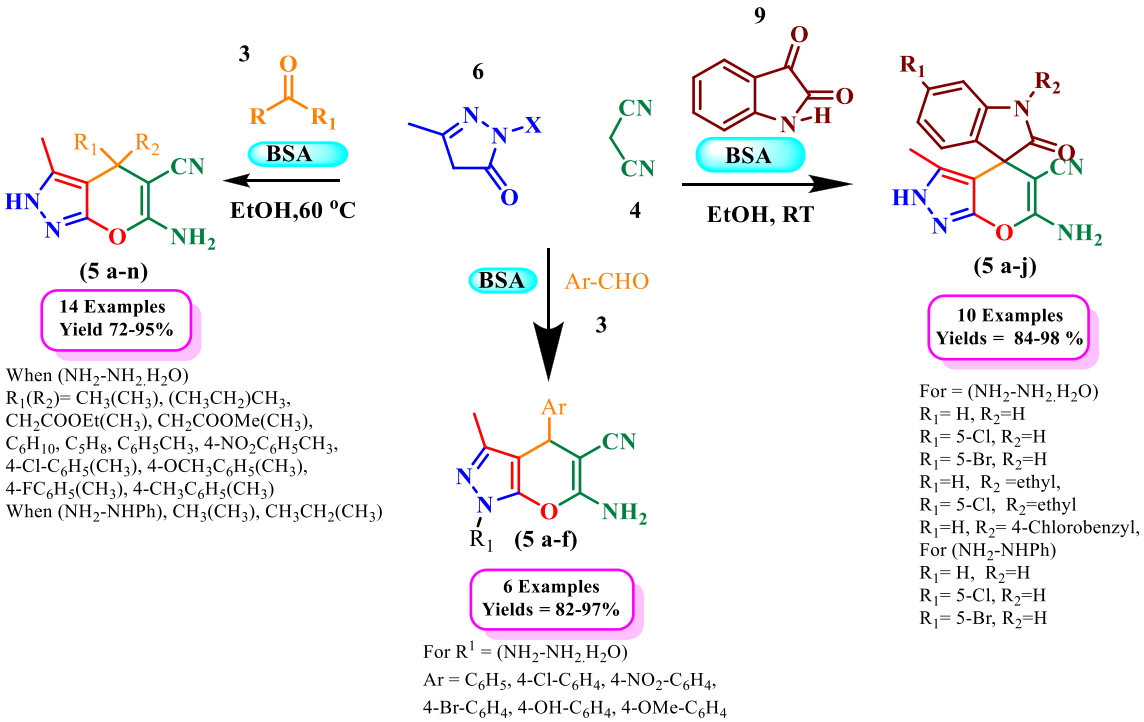

**Scheme 55.** Preparation of (**5**) using MIL-101(Cr)-N($CH_2PO_3H_2$)$_2$ and $Ph_3CCl$




**Scheme 56.** PBCMO and [Pap-Glu@Chi] mediated by (**5**)




**Scheme 57.** Synthesis of (**5**) in ethanol medium

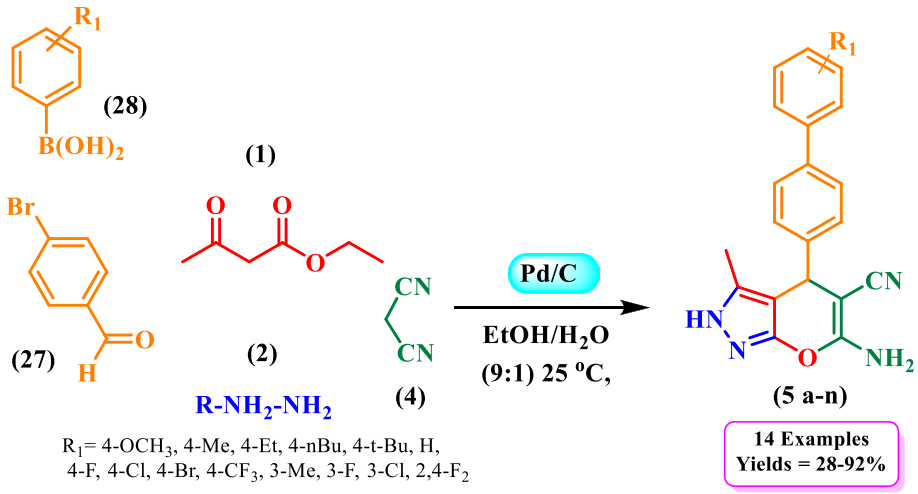


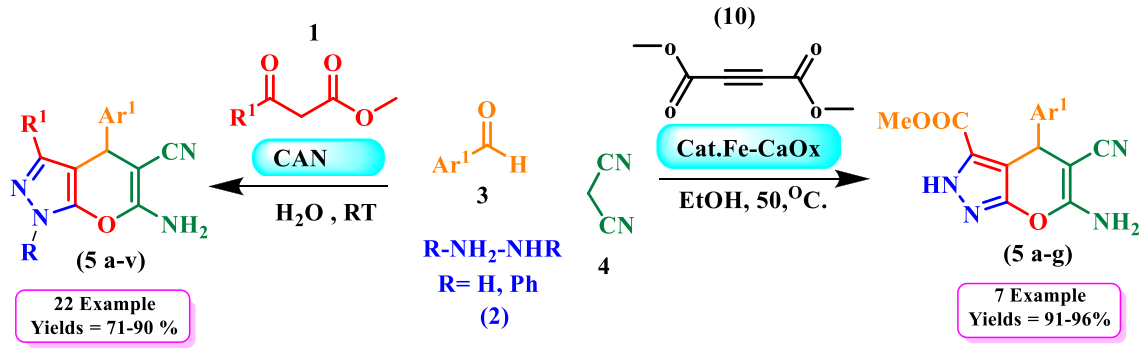

**Scheme 58.** BSA catalyzed by Synthesis of (**5**)

co-precipitation technique and glutamic acid (GA) as a crystal growth inhibitor addition, the authors produce Fe-CaOx catalysts. Glutamic acid stimulated the formation of well-controlled Fe-CaOx crystals while leaving the thermally stable calcium oxalate monohydrate (COM) phase unchanged. According to the characterization results, the CaOx crystal's interstitial regions are occupied by doped iron. The Knoevenagel condensation between (**3**) & and (**4**) is made possible by the doping of Fe in CaOx, which increases many catalytic sites and allows for the quick synthesis of (**5**) (Scheme 60) [129]. In a study by Ablajan et al. in 2013, the synthesis of multi-substituted derivatives of (**5**) via four-component reaction of **(3), (4), (10)** and 4-hydrazinobenzoic acid (**26**) was reported CAN in ultrasonic irradiation (Scheme 60) [130].

Gujar et al. documented the synthesis of (**5**) using molecular sieves MS4 as a catalyst in ethanol under reflux. The authors compared the catalyst's efficiency to other aluminates and silicate-based catalysts. Repeatedly using MS 4 as a catalyst with the (**1**), (**2**), (**3**), and (**4**) reactants was examined. Catalyst recovered and continued to operate as efficiently as the first three runs, but that product yield somewhat decreased in runs four and five (Scheme 61) [131].

**Scheme 59.** Preparation of (**5**) by using Pd/C

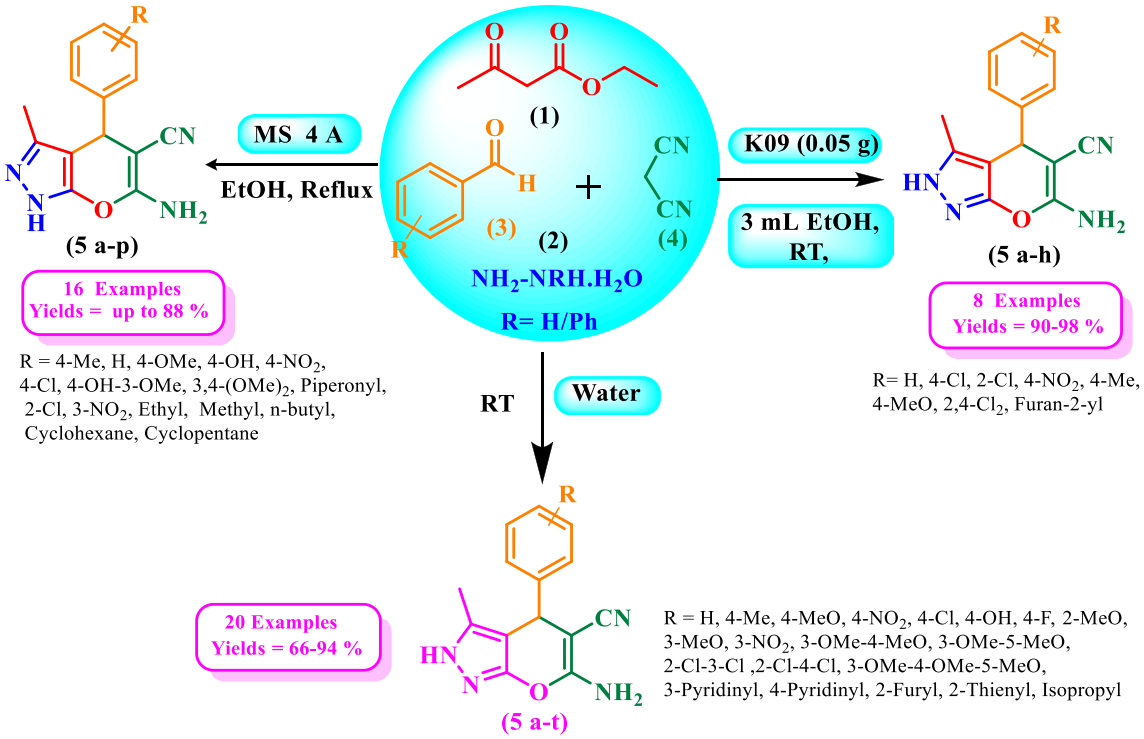



**Scheme 60.** CaOx- and CAN-catalyzed synthesis of (**5**)

In this study, El Mejdoubi et al. reported the natural phosphate K09 as a mild and effective heterogeneous catalyst, a straightforward, effective, and green method for synthesizing derivatives of (**5**). For this conversion, it was discovered that K09 had the best catalytic efficiency compared to other heterogeneous catalysts. This approach's critical characteristics are simple catalyst recovery and reusability, RT condition, quick reaction times, and outstanding yields (Scheme 61) [132]. To synthesize (**5**), Vasuki et al. used a four-component (**1**), (**2**), (**3**), and (**4**) reactants reaction, a green process in water at room temperature for the synthesis of (**5**) (Scheme 61) [133].

Per-6-amino-b-cyclodextrin (per-6-ABCD), which performs dual roles as a solid base catalyst and supramolecular host for the neat synthesis of various (**5**), was used by Kanagaraj et al. in a straightforward, environmentally friendly, and an effective approach. This atom-economical process, which was (**1**), (**2**), (**3**), and (**4**) with ketones as well, contains a much milder procedure, requires no time-consuming work-up or purification, stays clear of unsafe reagent by-products, and provides almost quantifiable amounts. At least six re-uses of the catalyst are possible without any deterioration in its catalytic activity (Scheme 62) [134]. In these circumstances, Nagarajan et al. describe a straightforward and effective synthesis of (**5**) neat conditions with high yield using a four-component reaction between (**1**), (**2**), (**3**), and (**4**) (Scheme 62) [135]. With the help of sulfuric acid, Nguyen et al. produced sulfonated amorphous carbon (AC-$SO_3H$) from rice husks. A cheap and easily accessible substance was used to synthesize a deep eutectic solvent




**Scheme 61.** MS, Phosphate K09, and water mediated by (**5**)

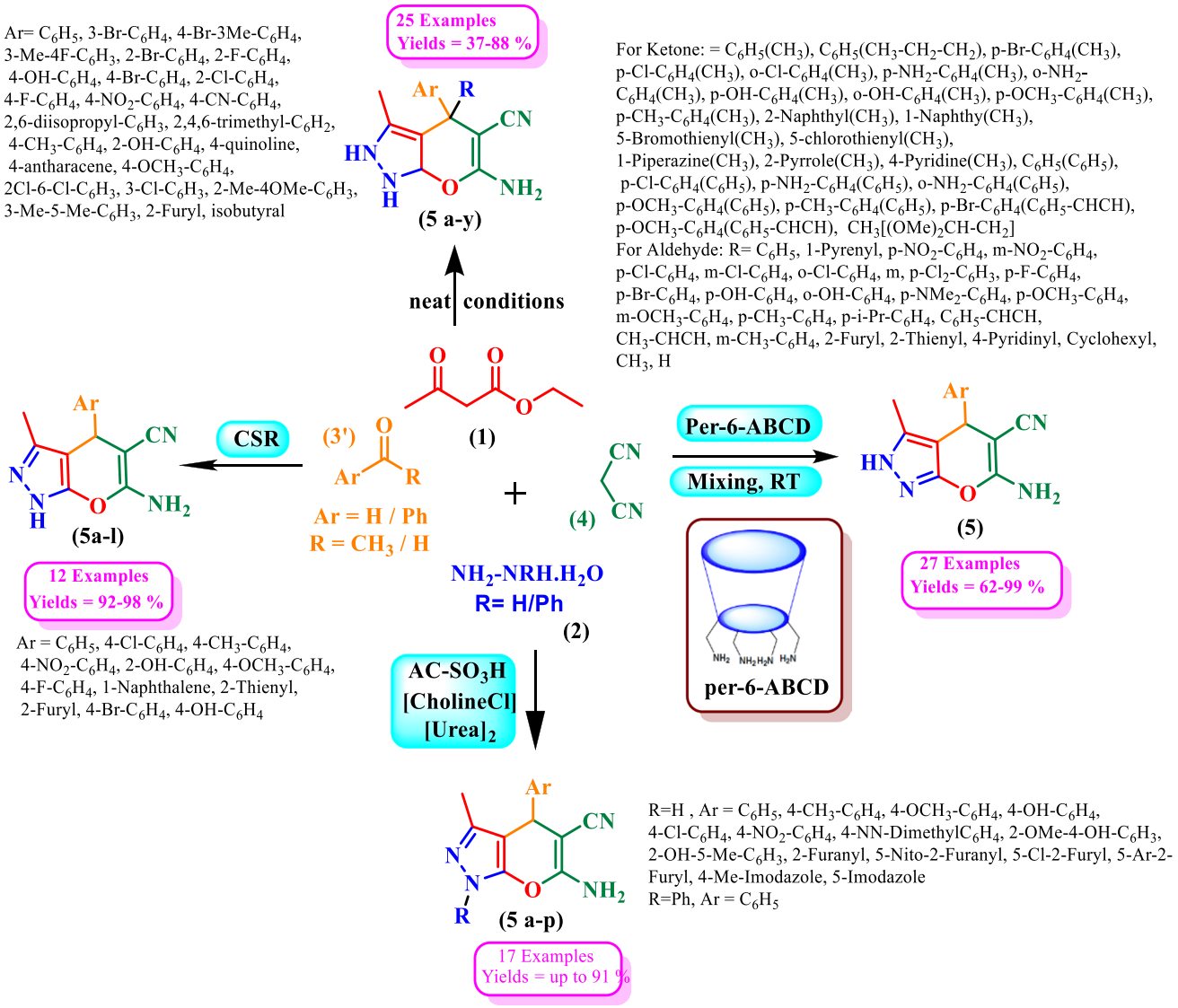
between choline chloride and urea. Through a four-component reaction of (**1**), (**2**), (**3**), and (**4**) with good yields in a deep eutectic solvent at RT, the as-synthesized AC-$SO_3H$ was used to make (**5**). A catalytic system was simply created using a non-toxic, low-cost, eco-friendly, approach that could be used in large-scale processes (Scheme 62) [136]. Gadkari et al. reported using the current methods of concentrated sun radiation (CSR) to assist in synthesizing (**5**) under solvent and neat conditions. Final required compounds (**5**) are produced in a good yield by one-pot multicomponent synthesis (**5**) from components (**1**), (**2**), (**3**), and (**4**). This technologically simple process has a variety of advantages, such as a clean and environmentally friendly reaction profile, simple workup and purification procedures, quick reaction time, and effectiveness and atom efficiency; compared to traditional approaches, the present energy and efficient technique saves about 98% of energy (Scheme 62) [137].

Shinde et al. used bael fruit ash (BFA) as an unconventional natural catalyst in water at RT to carry out a clean and more economical approach for the production of (**5**) and pyrazolyl-4*H*-chromenes (**21**). It was discovered that the BFA catalyst was environmentally friendly, quickly biodegradable, recyclable, and highly active, with no activity loss up to the 6 runs. The approach offers an alternative to the traditional catalyzed technique (Scheme 63) [138].

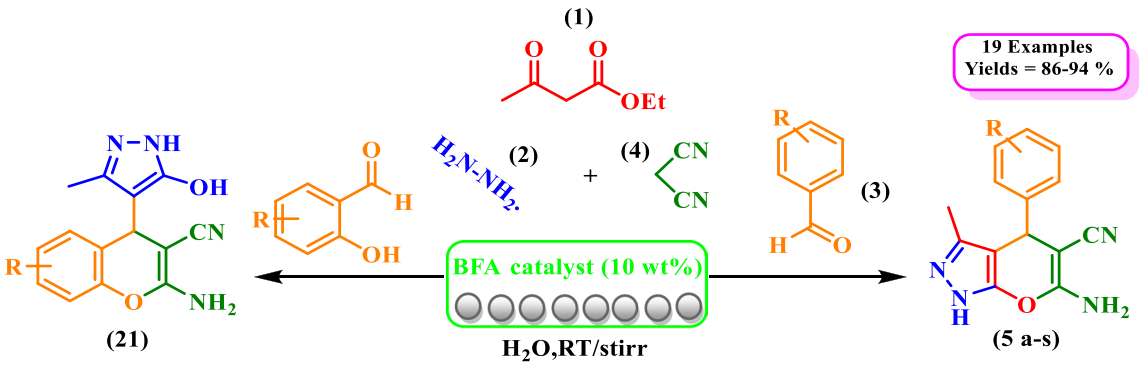
Yang and co-workers reported a very interesting article on enantiomer and diastereoselective [2 + 4] cycloaddition reactions of various substituted propionic aldehyde (**29**) and the oxindole-derived pyrazolone (**30**) by using NHC as carbene catalyst furnishes the quick and efficient access to structurally complex multicyclic (**5**) scaffold. Reaction facilitates a wide range of substrates mounted with different substitution patterns, with the multicyclic (**5**) derivative producing good-to-excellent yields along with good enantiomeric excess, moreover, this provides sophisticated spiro & fused cyclic products (Scheme 64) [139].

According to Nguyen et al., a four-component reaction including the benzyl alcohols (**31**), (**1**), (**2**), and (**4**), in the presence of sulfonated amorphous carbon and eosin Y catalyzed a novel method to synthesize (**5**) and their role as p38 MAP Kinase inhibitors. This methodology makes it possible to synthesize new compounds (**5**) and confirm using bioinformatics that they have the biological potential to inhibit p38 MAP kinase pockets, which is advantageous from a pharmaceutical perspective for cancer or immune treatments (Scheme 65) [140].

Metwally and his co-workers have designed 4-formylphenyl benzoates, (**32**), and (**6**) with the help of pepsin as a biocatalyst and the preparation of the corresponding reactants in a mortar for 0.5 to 3 h at RT result in excellent yields of the corresponding derivatives (**5**). Among the synthesized compounds screened for *K. pneumonia* and *S. aureus* strains with inhabitation zones of 29.6–30.3 mm

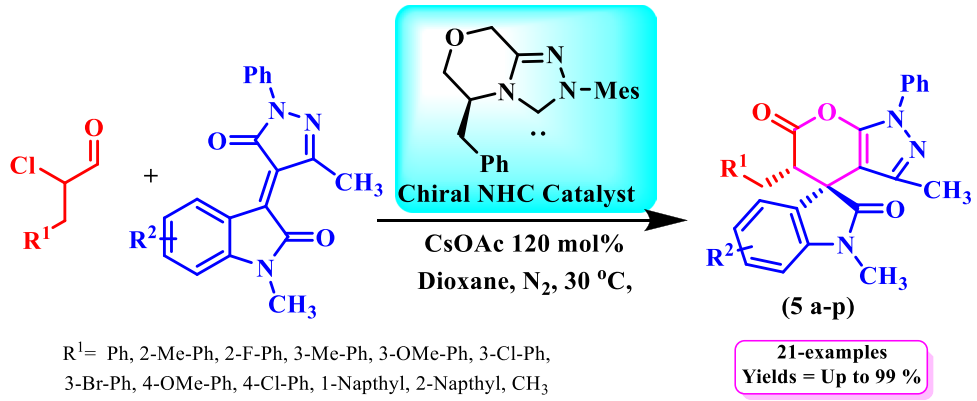


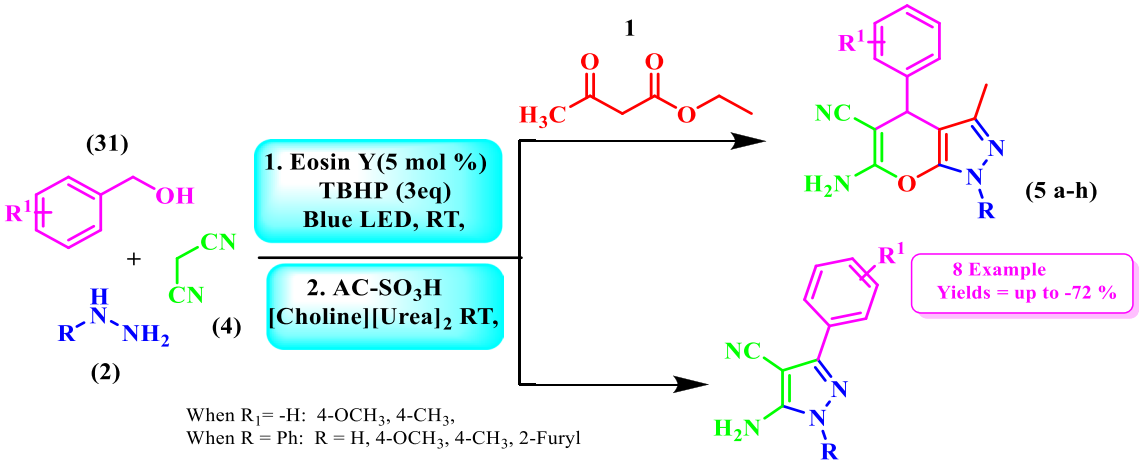

**Scheme 62.** Preparation of (**5**) using per-6-ABCD, CSR, AC-$SO_3H$, and neat conditions



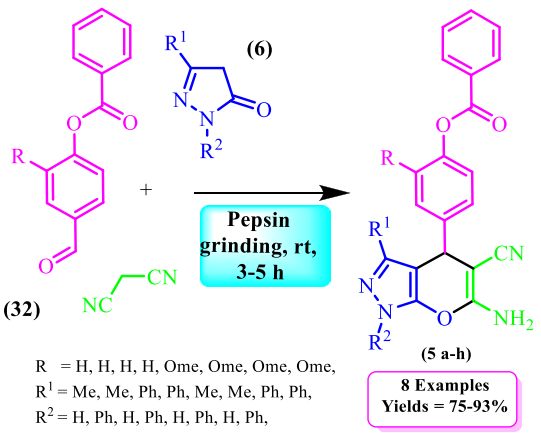

**Scheme 63.** Bael fruit ash (BFA) catalyzed by (**5**)

**Scheme 64.** Synthesis of (**5**) using NHC




**Scheme 65.** Eosin Y and AC-$SO_3H$ medicated by synthesis of (**5**)




**Scheme 66.** Preparation of (**5**) by using pepsin

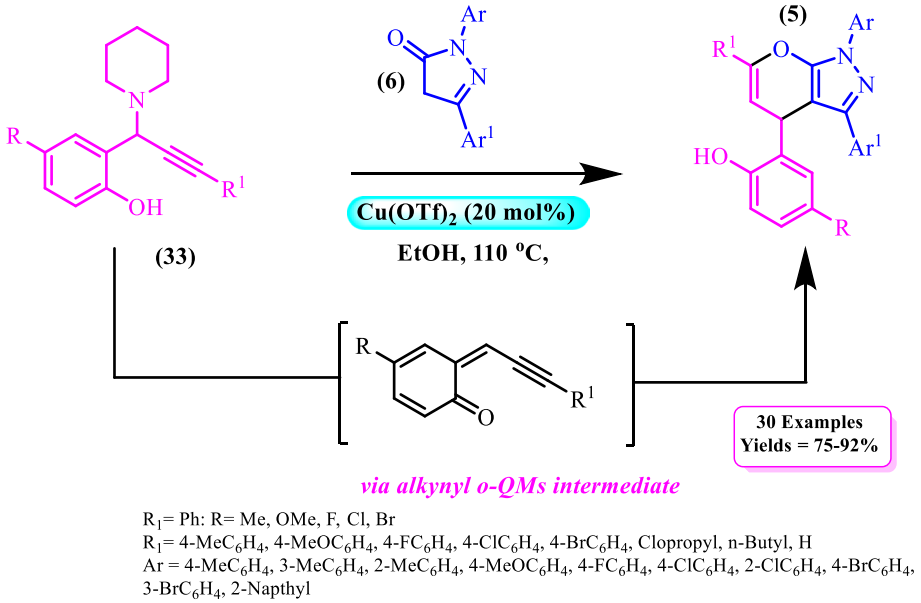
and MIC = 125–250 lg/mL showed moderate antibacterial activity (Scheme 66) [141].

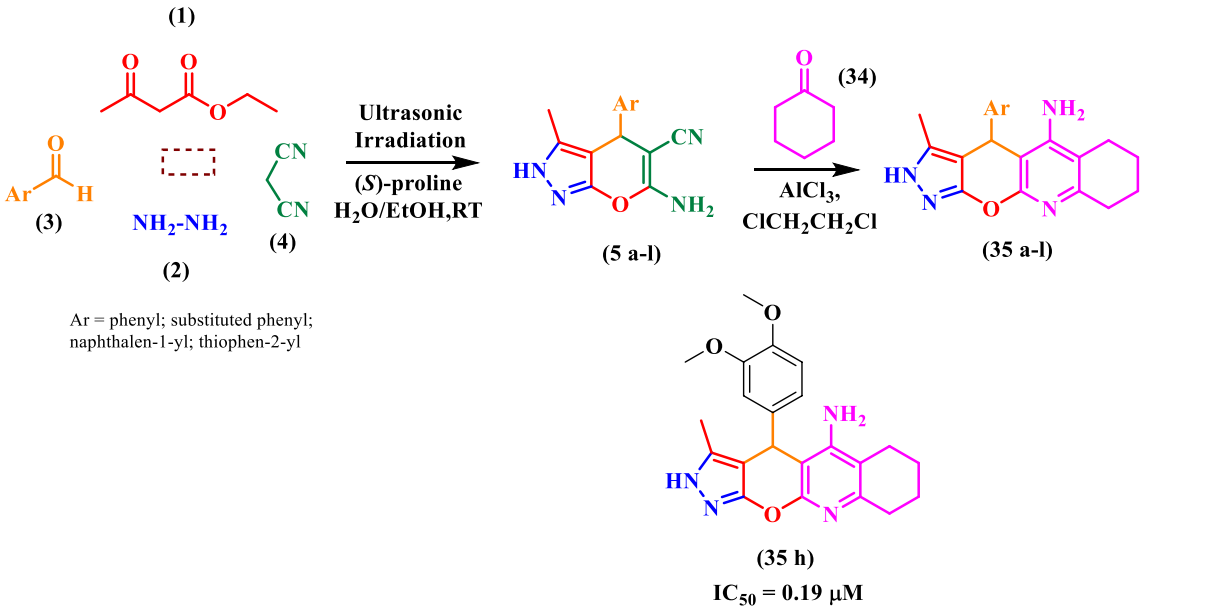
Yi et al. reported the synthesis of *o*-hydroxyphenyl propargylamines (**33**) and (**6**) via productive copper-catalyzed cascade annulation. Using a straightforward approach, this protocol is applied to prepare a wide range of rapid assembly of several worthwhile (**5**) derivatives with better yields. This novel reaction includes the formation of alkynyl ortho-quinone methides, a 1,4-conjugate addition, and a sequel 6-endocyclization process (Scheme 67) [142].

## Medicinal applications

To synthesize the final compound (**35**) derivatives, Khoobi et al. developed a series of tacrine-base compounds using an $AlCl_3$-catalyzed Friedlander reaction to obtain (**5**)

**Scheme 67.** Cu $(OTf)_2$ catalyzed by (**5**)



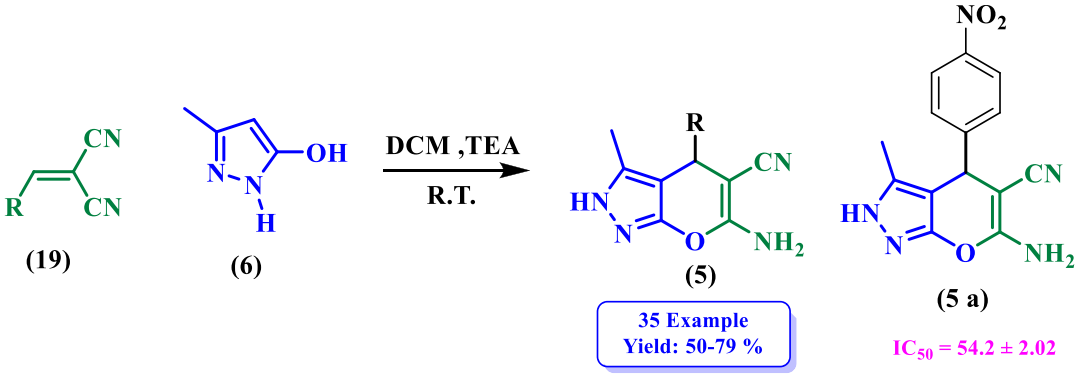




**Scheme 68.** $AlCl_3$-catalyzed synthesis of (**5**)

and cyclohexanone (**34**). All synthesized compounds are tested for sub-micromolar AChE antagonist activity. The 3,4-dimethoxyphenyl derivative of (**35 b**), with $IC_{50} = 0.19$ µM, is the most promising. Its anti-AChE activity outperformed that of the standard treatment tacrine (Scheme 68) [143].

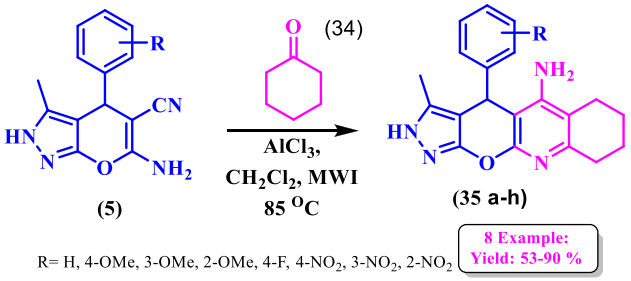
Iqbal Choudhary and co-workers synthesized derivatives of (**5**) and explored the activity of controlling the associated risk factors for postprandial hyperglycemia by inhibiting the enzyme-glucosidase activity. Compound (**5**), i.e., P-$NO_2$ substituted aromatic most promising and facilitated its interaction with the enzyme. It was discovered that some of these substances were significant yeast glucosidase enzyme inhibitors (Scheme 69) [144].

Mourad Chioua et al. reported a renewed search for multipotent, non-hepatotoxic tacrines due to the complexity of Alzheimer's disease. Pyranopyrazolotacrines (**35**) were synthesized, and screened for non-hepatotoxic multipotent




R= 4-$NO_2$-$C_6H_4$, 3$NO_2$-$C_6H_4$, 2$NO_2$-$C_6H_4$, 2,4-diCl-$C_6H_4$, 2-Cl-$C_6H_4$, 2-Br-$C_6H_4$,3-Br, 6-OMe-$C_6H_4$,3-Br-$C_6H_4$, 4-Br, 2,6-di-OMe-$C_6H_4$, 3-Br, 4-OMe-$C_6H_4$, 2,6-di-OMe-$C_6H_4$, 3-OMe,4-OEt-$C_6H_4$, 3,4-di-OMe-$C_6H_4$, -$C_6H_5$, -Napthyl, 4-$SCH_3$-$C_6H_4$, 2-methyl-Fural, -phenol, 2,5-di-OMe-$C_6H_4$, 2,6-diOMe-$C_6H_4$, 3-OMe-4-OH-$C_6H_4$, 3-Br-4-OMe-$C_6H_4$, 3,4,5-tri-OMe-$C_6H_2$, 2,4-di-OMe, 4-Cl-$C_6H_2$, 3-OMe, 4-$OCOCH_3$-$C_6H_2$, 2,5-di-OMe,4-Br-$C_6H_2$, 3,5-di-OMe, 4-Br-$C_6H_2$, 2-Cl-3-OMe-$C_6H_3$, 4-$OCH_2$-$C_6H_5$--3OMe-$C_6H_3$, 4-$CF_3$-$C_6H_4$, 4-$OCH_2$-$C_6H_5$--$C_6H_4$, 2-$OCH_2$-$C_6H_5$--$C_6H_4$, 2-Cl-3,4-di-OMe-$C_6H_4$, 3-$NO_2$-5-OH-$C_6H_4$

**Scheme 69.** Synthesis of (**5**) using TEA




R= H, 4-OMe, 3-OMe, 2-OMe, 4-F, 4-$NO_2$, 3-$NO_2$, 2-$NO_2$

**Scheme 70.** Synthesis of (**5**) by using $AlCl_3$ catalyst

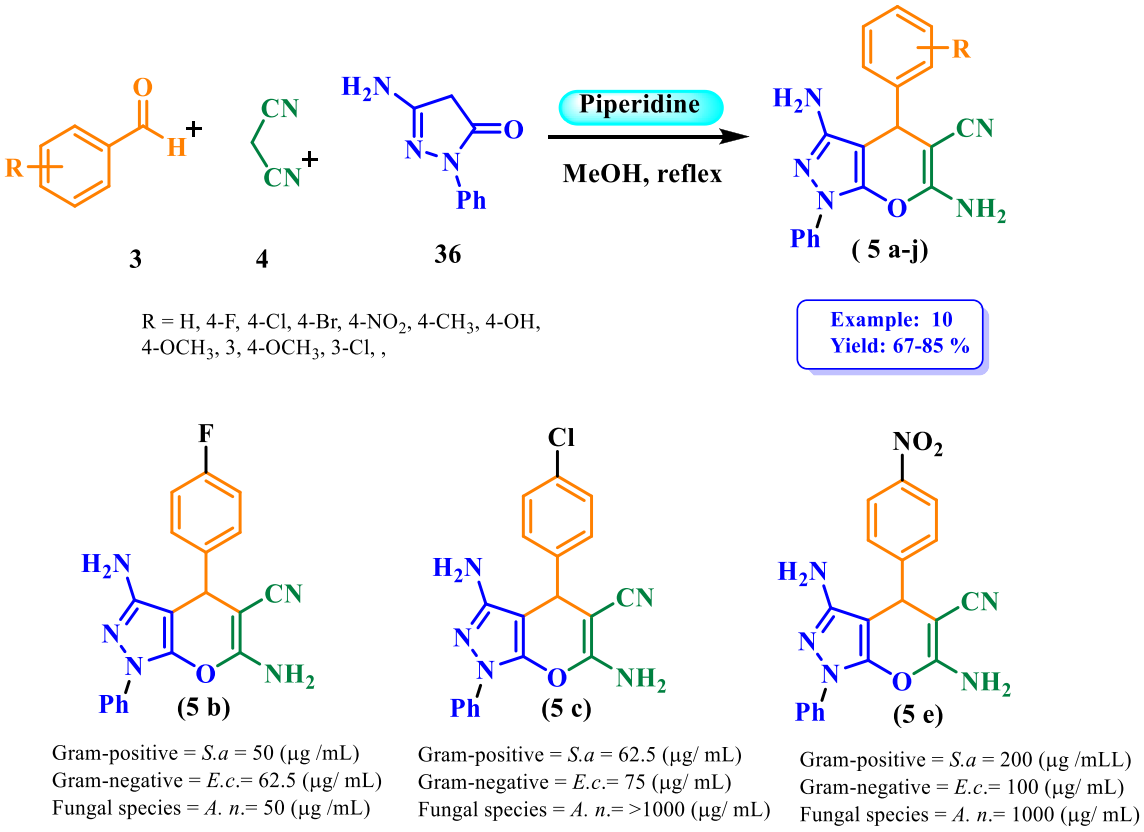
tacrine analogs. This family of permeable tacrine analogs may be used to treat Alzheimer's disease effectively (Scheme 70) [145].

Ranmal et al. used piperidine as a catalyst that successfully synthesized a wide range of (**5**). Synthetic chemicals were put through several antimicrobial tests, including bactericidal and antifungal activity. All synthesized derivatives screen for the antibacterial and antifungal activity of two Gram-positive, and Gram-negative bacteria and three fungal strains. The compounds **5b, (5c)**, and (**5e)** displayed significant antibacterial and antifungal activity (Scheme 71) [146].

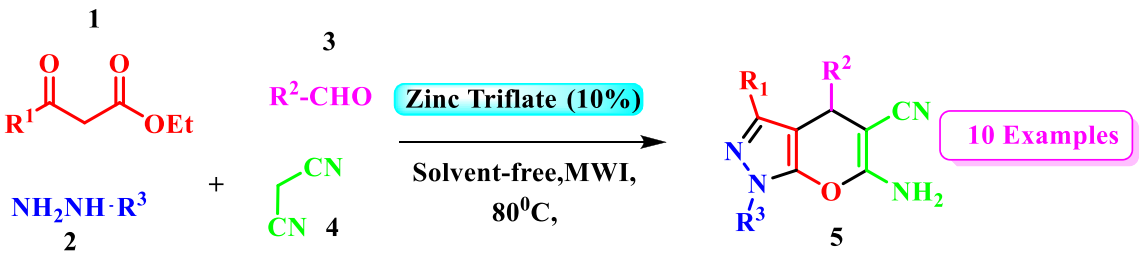
Parikh et al. reported the solvent-free synthesis of a novel biologically potent motif **(5)**, the zinc triflate catalyzed using (**1**), (**2**), (**3**), and (**4**) under (MWI). Synthesized derivatives examined different activities. Specifically, derivatives showed good activity against all compound **4** and **8** bacterial strains. Unexpectedly, compounds 3 and 4 demonstrated marked anti-malarial activity with $IC_{50}$ = 0.027–0.26 µg/mL. Lastly, compounds screen for anticancer and against all four investigated cancer cell lines. Compound (**8**) inhibits cell growth of cell line with an $IC_{50}$ = 9.9 µg/mL (Scheme 72) [147].

Nagasundaram et al. developed a catalyst-free ultrasonication method for the preparation of a series of (**5**) compounds using (**1**), (**2**), (**3**), and (**4**). Synthesized derivatives display an excellent binding affinity towards the target of *E. coli* MurB and EGFR domains by forming strong interactions with amino acids confirmed by molecular docking analysis. In vitro antimicrobial activity against human pathogenic bacterial and fungal strains was examined for all prepared compounds; among them, one molecule displays an excellent MIC = 0.19 µg/mL against *B. cereus*, whereas the selected compounds were examined for their anticancer activity against (HeLa) and live/dead cells were determined by AO/EtBr staining (Scheme 73) [148].

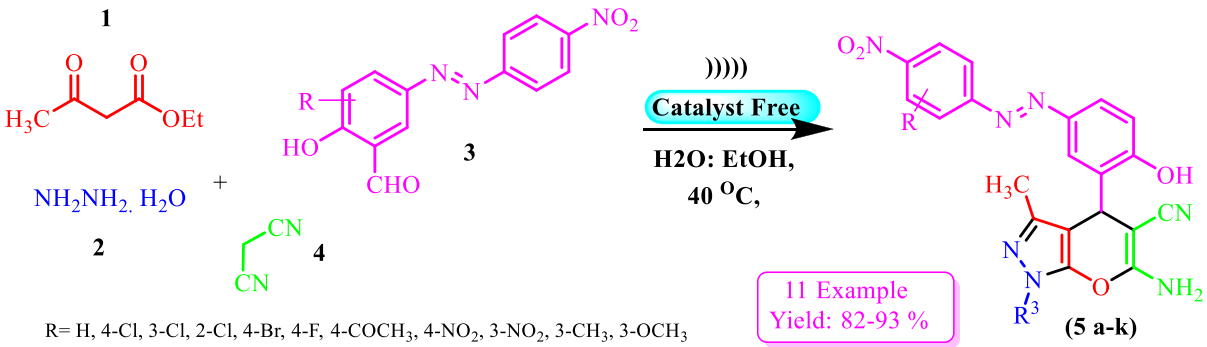
Messaad and co-workers reported the synthesis of (**5**) derivatives as acetylcholinesterase inhibitors; the condensation reaction was carried out using various catalytic conditions within thiosemicarbazide (**37**) and tosylhydrazine with (**1**). All synthesized compounds were examined for their inhibitory effect against AChE implicated in the development of Alzheimer's disease using the *in-silico* study. In vitro Acetyl-cholinesterase (AChE) inhibition confirmed that the compounds (**8**) and (**7**) showed, respectively, low and moderate activity against AChE, while (**5**) displayed sound inhibitory activity against AChE IC50 value of 0.38 ± 0.019 mg/mL(Scheme 74) [149].



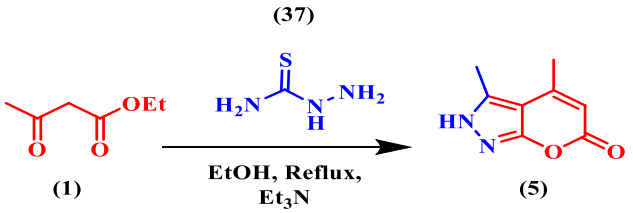

**Scheme 71.** Synthesis of (**5**) using piperidine




**Scheme 72** Zinc triflate catalyzed by (**5**)




**Scheme 73.** Synthesis of (**5**) in ethanol



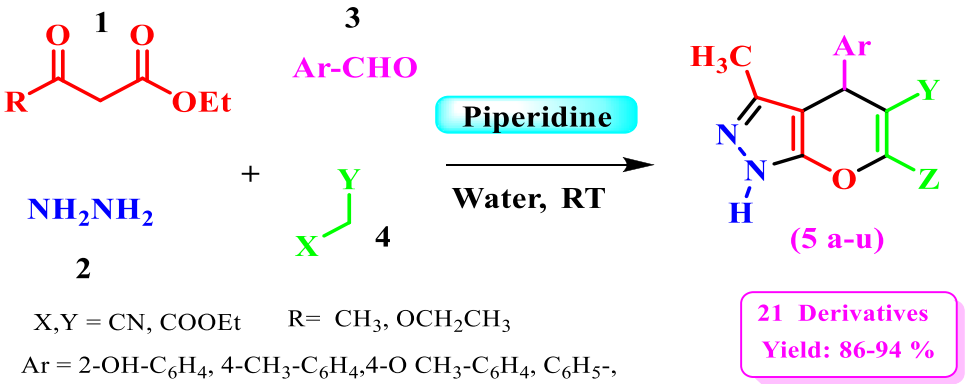

**Scheme 74.** Synthesis of (**5**) using $Et_3N$

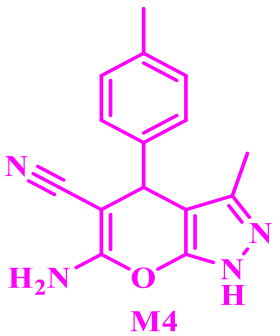
Abouelenein et al. designed a protocol for the synthesis of a series of (**5**), the one-pot reaction of (**1**), (**2**), (**3**), and (**4**). Furthermore, all synthesized compounds were examined for their antimicrobial, antioxidant, and anticancer activities. Fortunately, most of the derivatives displayed encouraging biological activities. At the same time, an *in-silico* study was carried out for synthesized compounds. Among these compounds, (**5a)** displayed the most promising antibacterial activity, whereas (**5b)** showed the most cytotoxic agent (Scheme 75) [150].

## Conclusion

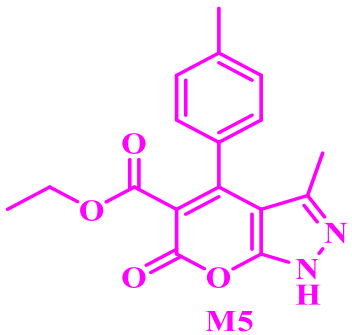
In this review, we have sincerely tried to summarize data on the synthetic approaches and therapeutic significance of the pyranopyrazoles scaffold. We have systematically represented the work done on pyranopyrazoles in conventional and non-conventional methods, along with a systematic summary of all reported protocols based on the nature of the catalyst used for synthesis (Fig. 5). These diverse protocols using different catalytic systems for these valuable nuclei will benefit organic chemists working in these fields and encourage the upcoming researchers who wish to work on these scaffolds. The present review anticipates significant

**Scheme 75.** Synthesis of (**5**) using piperidine




$IC_{50}$ (mM) of the studied compounds versus A549 cell lines. $IC_{50}$ ( mM) = 54.50 ( mM )




$IC_{50}$ (mM) of the studied compounds versus HepG2 cell line. $IC_{50}$ (mM) M5 = 32.43 mM

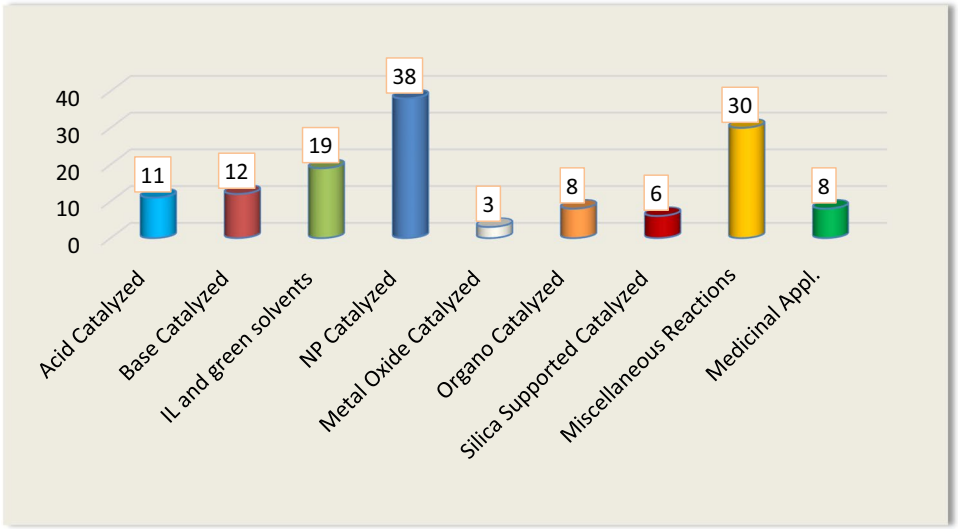



**Fig. 5** Number of synthetic protocols as per the nature of catalyst

advancement in ongoing research in pyranopyrazoles heterocyclic compounds.

**Author contributions** Ashok R. Yadav: Primary data collection; Ashishkumar P. Katariya: Drawing mechnaism; Anant B. Kanagare: Review writing and Scheme Drawing; Pramod D. Jawale Patil: Scheme Drawing; Chandrakant K. Tagad: Preparation Graphical Abstract; Satish A. Dake: Review checking; Pratik A. Nagwade: Grammatical checking; Satish U. Deshmukh: Review writing and Scheme Drawing.

## Declarations

**Competing interests** The authors declare no competing interests.

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