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# Recent advances in the synthesis of pyrazolo[1,2-*b*]phthalazines

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ABSTRACT

The remarkable ability of pyrazolo[1,2-*b*]phthalazines as a nitrogen-containing heterocycles with fused scaffold of bridgehead hydrazine and pyrazole moieties have generated substantial interest in the pharmaceutical industry and in the diversified field of synthetic chemistry. The present mini-review focuses on current progress in the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives using multi-component reaction of phthalhydrazide, aldehyde and malononitrile and covers publications from 2015 up to now.

## 1. Introduction

Heterocyclic compounds are one of the most attractive sections of chemistry, especially nitrogen-containing heterocyclic compounds which are distinguished in nature and their applications are becoming more and more important in biologically active pharmaceuticals, agrochemicals and functional materials [1]. Among diverse classes of nitrogen-containing heterocyclic compounds, pyrazole is a privileged motif in the design of drug candidates exhibiting biological activity, including Sildenafil, Phenazone, Celecoxib, Rimonabant (Scheme 1) and many others [2-4]. On the other hand, pyrazole derivatives have shown wide spectra of biological activities such as anticancer [5-7], anti-inflammatory [8], analgestic [9], antibacterial [10], anti-alzheimer [11], antifungal [12], anticoagulant [13] and antihypoglycemic [14]. Similarly, phthalazine derivatives including drugs such as Luminol, Olaparib and Talazoparib (Scheme 1) are acknowledged to possess antimicrobial, antifungal, anti-inflammatory, anticancer, anticonvulsant, antidiabetic, antipyretic, vasorelaxant, cardiotonic and cytotoxic activities [15-21]. As a result, molecules containing polyfunctionalized heterocycles like pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives, fused scaffold of pyrazole and phthalazine moieties, are of current interest due to their multiple pharmacological activities such as antimicrobial, antiflammatory, anticancer and anticonvulsant and play considerable roles in drug discovery [22-24]. In light of this background, the synthesis of pyrazolo[1,2-*b*]phthalazine analogs has attracted the attention of the research community by employing various interesting approaches. Literature survey reveals that the best strategies for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (PPDs) are three-component reaction including phthalhydrazide, aldehyde and active methylene compound like malononitrile, or four-component reaction involving phthalic anhydride/ phthalhydrazide, hydrazine, aldehyde and active methylene compound. These multi-component condensations affiliate the formation of C–C and C–N bonds to afford PPDs and are important area in the organic synthesis (Scheme 2) [15, 25]. The reaction proceeds through the Knoevenagel condensation, Michael type addition, intramolecular concerted cyclization followed by tautomerization to give the corresponding products [26, 27]. The present review summarizes the latest developments in these multi-component reactions, which have been accelerated by incorporating various catalysts.

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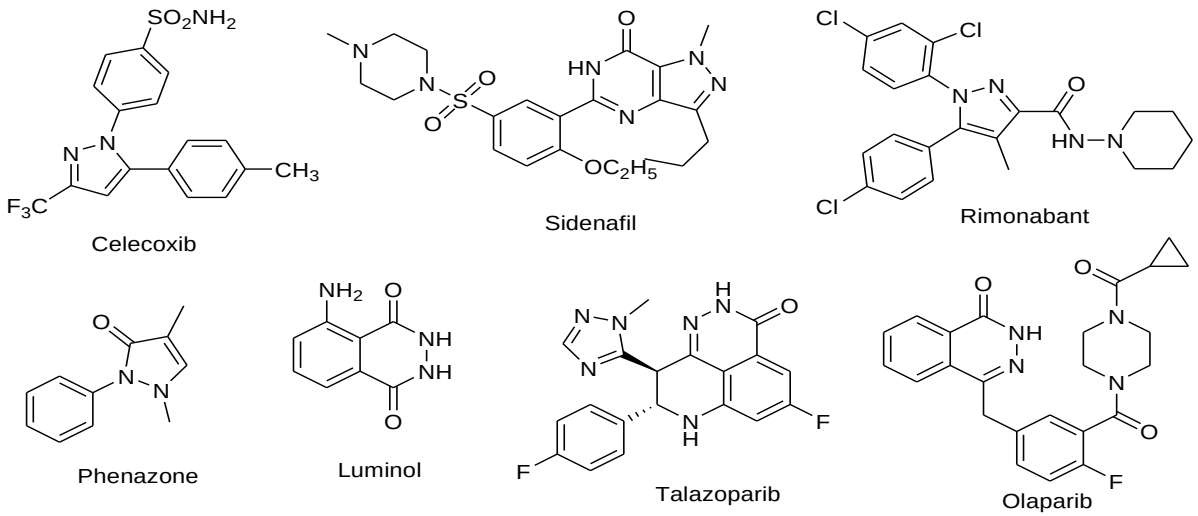
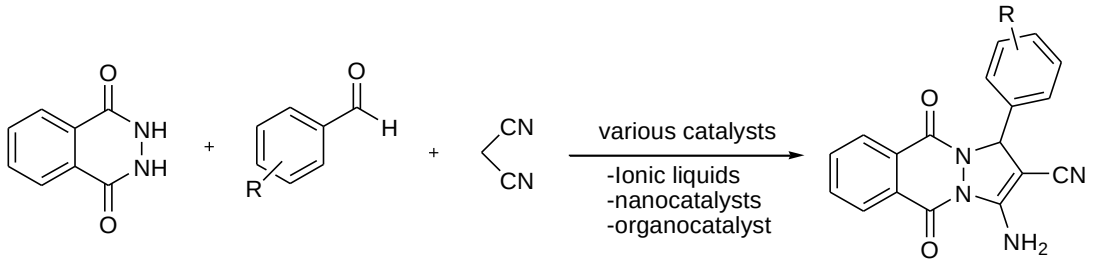



**Scheme 1.** Structures of drugs containing a pyrazole or phthalazine skeleton.




**Scheme 2.** Three-component synthesis of pyrazolo[1,2-*b*]phthalazines.

## 2. Multi-component synthesis of pyrazolo[1,2-*b*]phthalazines

### *2.1. Using Ionic Liquids*

Currently, usage of ionic liquids has drawn remarkable interest as environment-friendly reaction media or catalyst in diverse fields of the synthetic chemistry. It provides large number of convenient properties including nonflammability, high ionic conductivity, low vapor pressure, negligible volatility and excellent chemical stability which offers better alternatives to other catalysts [28, 29].

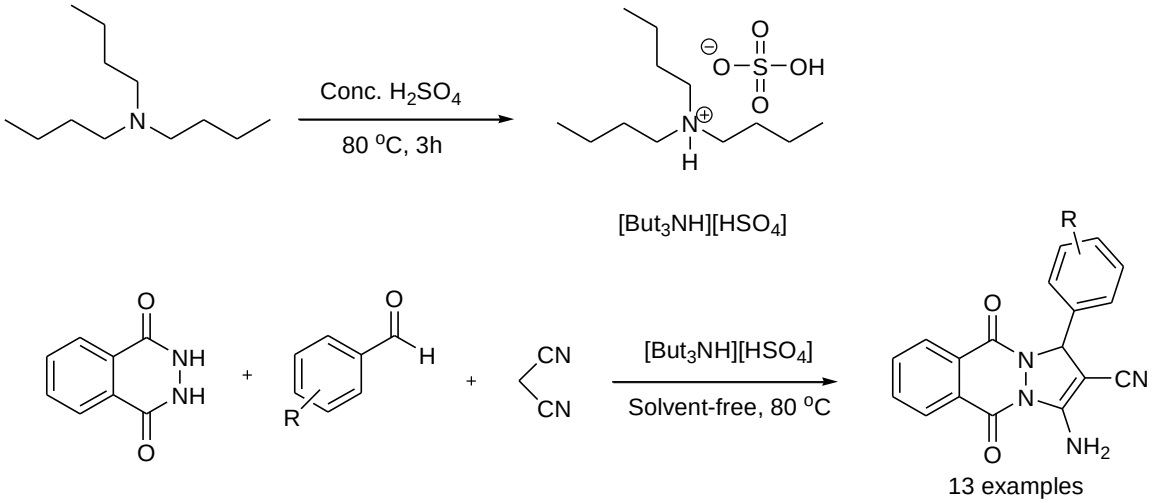
Basic ionic liquids 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH) has been utilized for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones (PPDs) by Wang *et al*. [30] through the one-pot, three-component condensation of aromatic aldehydes, malononitrile or ethyl cyanoacetate, and phthalhydrazide in EtOH. The results have been revealed that 10 mol% of [bmim]OH at 60 °C made the corresponding products (12 examples) in 0.8-3 h and excellent yields (86-97%).

Shaikh and colleagues [31] prepared a Brønsted acidic ionic liquid [$Bu_3NH$][$HSO_4$] *via* the neutralization reaction of *n*-tributylamine and concentrated sulfuric acid. This ionic liquid was explored in one-pot reaction of phthalhydrazide, various aldehyde and malononitrile for the synthesis of PPDs (Scheme 3). In this synthetic protocol 20 mol% of [$Bu_3NH$][$HSO_4$] has been utilized at 80 °C and offered excellent yields of the products (83–95%) in short reaction times (9–30 min).

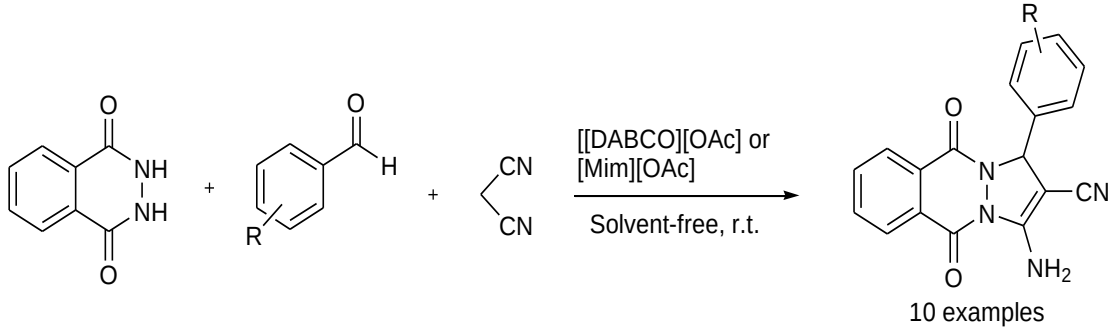
1,4-Diaza bicyclo[2.2.2]octanium acetate [DABCO][OAc] and 1-methylimidazolium acetate ([Mim][OAc] have also been used as a protic ionic liquids for the synthesis of PPDs through three-component reaction at ambient temperature under solvent-free conditions (Scheme 4) [32].

Raghavendra and Siddaiah [33] developed DBU acetate ionic liquid [DBUH][OAc] for the synthesis of 3-amino-1-(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine derivatives by one-pot, four component reaction of phthalic anhydride, hydrazine hydrate, malononitrile/ethyl cyanoacetate and indole-3-carboxaldehydes at 60–65°C (Scheme 5).

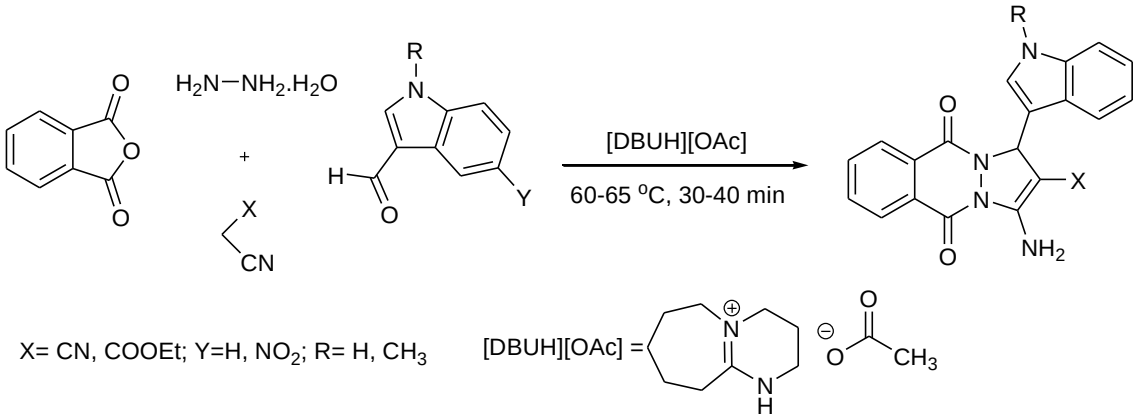
In other research [34], DBU-based ionic liquid [Bn-DBU][TFA] has been reported for the synthesis of PPDs *via* the three-component reaction of phthalhydrazide, aromatic aldehydes, and active α-methylene compounds. Benzylation of DBU followed by anion exchange of the resulting salt with trifluoroacetate gave nearly quantitatively the ionic liquid [Bn-DBU][TFA].




**Scheme 3.** Synthesis of PPDs using Brønsted acidic ionic liquid.




**Scheme 4.** Synthesis of PPDs using Brønsted acidic ionic liquid.



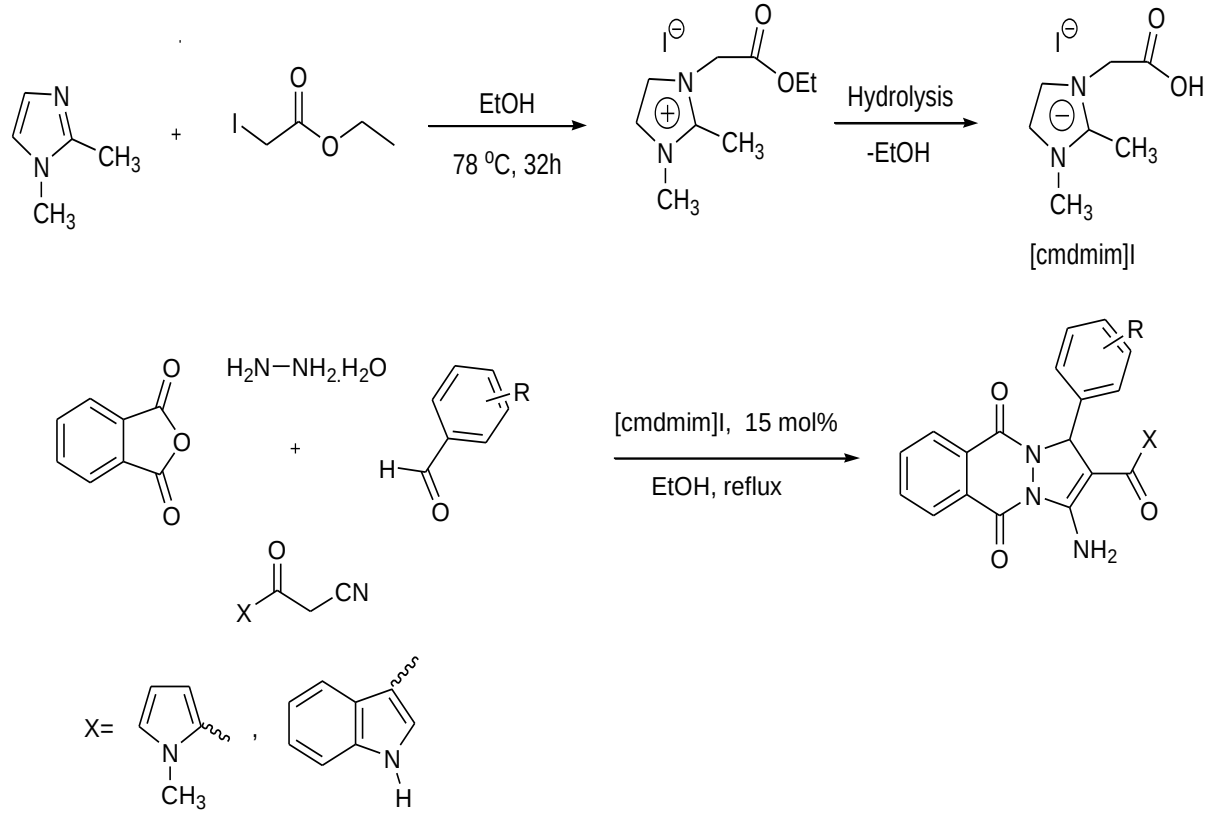

**Scheme 5.** Synthesis of PPDs in the presence of DBU acetate ionic liquid.

Jahanshahi and Mamaghani [35] described acetic acid functionalized imidazolium salt (1-carboxymethyl-2,3-dimethylimidazolium iodide, [cmdmim]I) as a Brønsted acidic ionic liquid catalyst for the synthesis of PPD derivatives. The reaction occurs through one-pot four-component cyclocondensation of phthalic anhydride, hydrazine hydrate, aromatic aldehydes and 3-(1-methyl-1*H*-pyrrol-2-yl)-3-oxopropanenitrile (or 3-(1*H*-indol-3-yl)-3-oxopropanenitrile) in ethanol under reflux conditions for 4-6 h and 71-89% yields in the presence of 15 mol% of catalyst. However, the catalyst has been prepared by the reaction of 1,2-dimethylimidazole with ethyl iodoacetate according to Scheme 6.

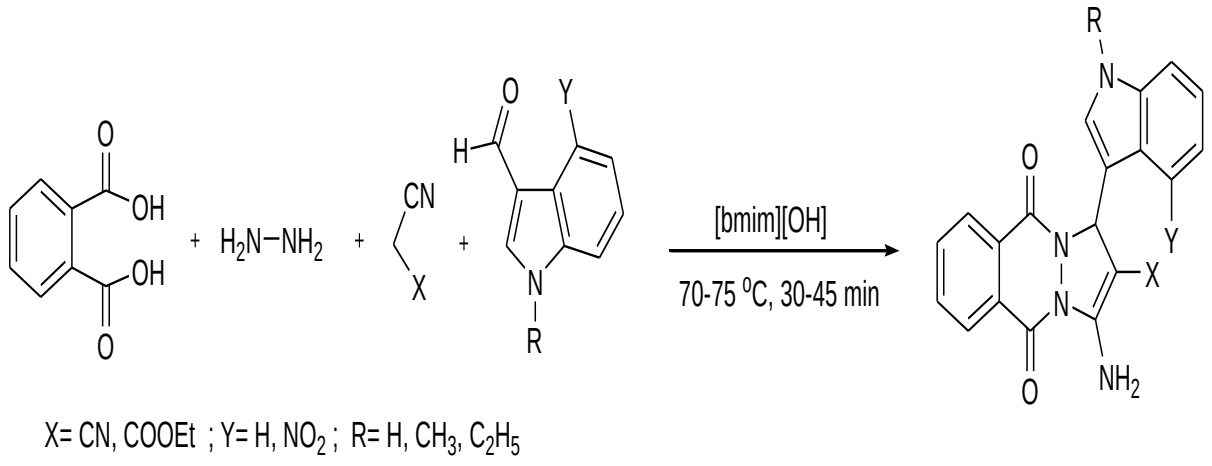
Hasthavaram *et al*. [36] used [bmim]OH ionic liquid for the synthesis of some pyrazophthalazine having indol moiety. The four-component reaction is initiated with phthalic acid and hydrazine hydrate to produce phthalhydrazide intermediate in the presence of ionic liquids. To this reaction mixture, indole-3-carbaldehyde and malononitrile have been added to afford 3-amino-1-

(5-nitro-1*H*-indol-2-yl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile derivatives (Scheme 7). The products have been synthesized at 70-75 °C for 30-45 min in 85-89 % yields. Moreover, the anti-cancer assessment and molecular modeling studies offered an insight into their potential anti-cancer agents and binding pattern with the protein respectively.

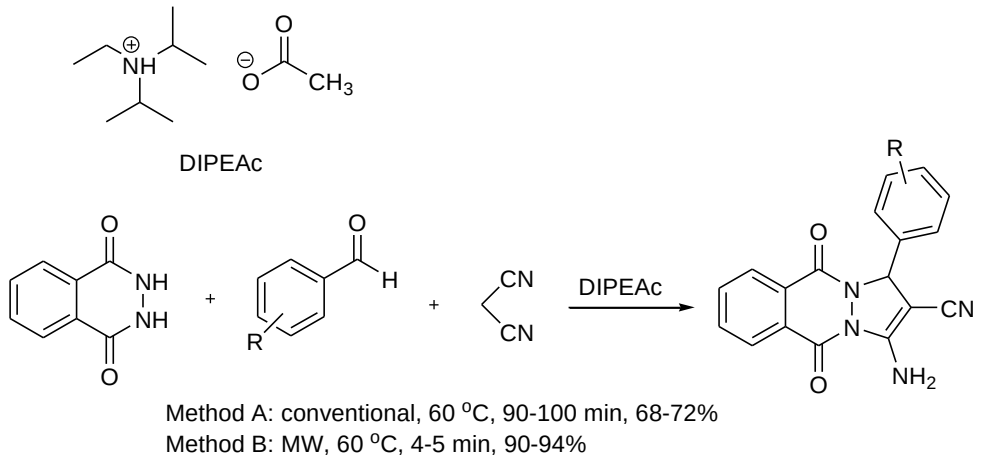
Jadhav and coworkers [37] reported the efficiency of diisopropyl ethyl ammonium acetate (DIPEAc) ionic liquid under controlled microwave irradiation or conventional heating in the reaction of phthalhydrazide, substituted aldehydes and malononitrile. The best results produced PPDs in 4–5 min with excellent yields (90-94%) (Scheme 8).




**Scheme 6.** Four-component synthesis of PPD derivatives in the presence [cmdmim]I.



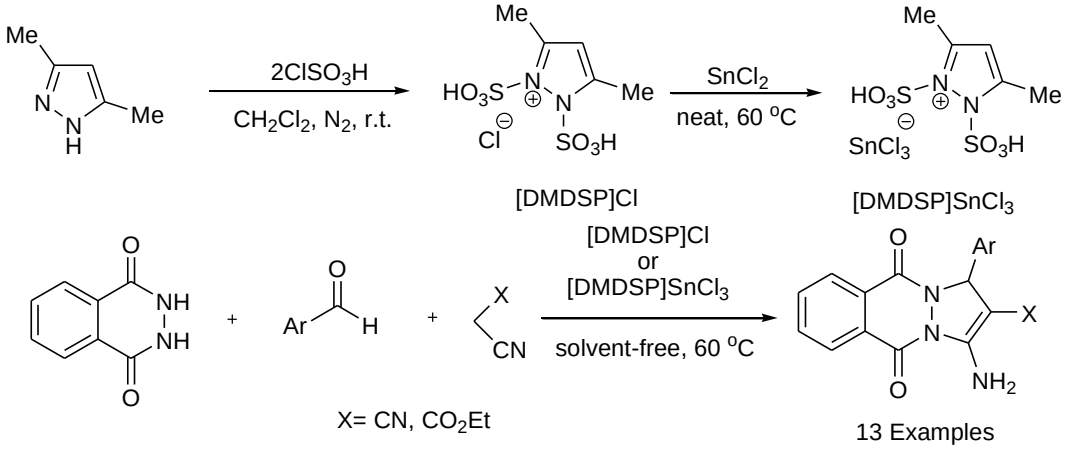

**Scheme 7.** Four-component reaction using [bmim]OH.




**Scheme 8.** Using diisopropyl ethyl ammonium acetate (DIPEAc) ionic liquid.

Kour and coworkers [38] prepared ionic liquid coated sulfonated carbon@titania composites (C@$TiO_2$-$SO_3$H-ILs) and used for the three-component condensation of phthalhydrazide, aromatic aldehydes and malononitrile to afford PPDs in aqueous medium at 100 °C.

Davoodniaa *et al*. [39] reported the synthesis of two disulfonic acid functionalized ionic liquids, 3,5-dimethyl-1,2-disulfonic acid-1*H*-pyrazolium chloride [DMDSP]Cl and 3,5-dimethyl-1,2-disulfonic acid-1*H*-pyrazolium trichlorostannate [DMDSP]$SnCl_3$. Their activity as homogeneous and green catalysts have been studied in the synthesis of PPDs by the reaction of phthalhydrazide with an aromatic aldehyde and malononitrile or ethyl cyanoacetate (Scheme 9) using 5 mol% catalyst at 60 °C for 10–30 min.




**Scheme 9.** Disulfonic acid functionalized ionic liquids in the synthesis of PPDs.

*2.2. Using nanocatalysts*

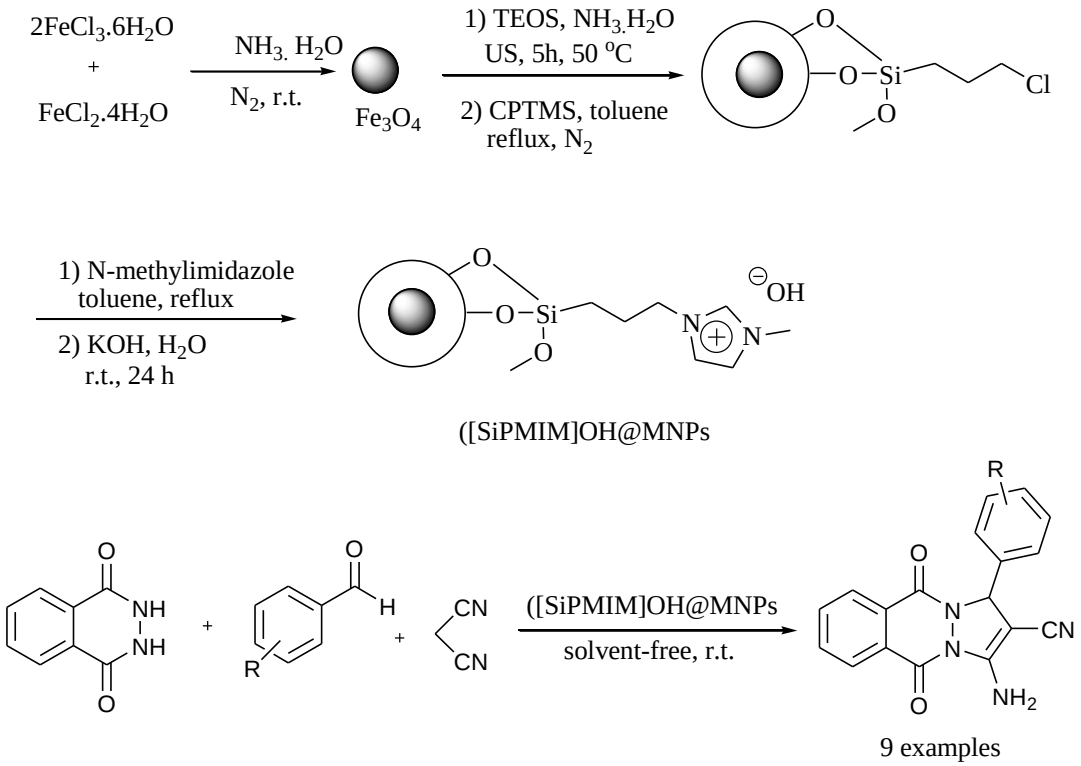
Nowadays, magnetic nanoparticles have attracted growing research attention due to some notable advantages such as simple separation using an external magnet, easy synthesis, reusability, high catalytic activity and excellent thermal and chemical stability in various organic solvents and chemical processes [40-42]. The majority of the novel heterogenized catalysts are based on magnetic nanoparticles $Fe_3O_4$ supports [43]. In recent years, some catalysts immobilized on magnetic nanoparticles have been prepared and utilized as catalysts [44].

Sabour *et al*. [45] described (3-propyltrimethoxysilane) imidazolium hydroxide supported on magnetic nanoparticles ([SiPMIM]OH@MNPs) as a recoverable catalyst for one-pot reaction of aromatic aldehydes, phthalhydrazide and malononitrile to offer PPDs in good to excellent yields (82-96%) in 12-20 min at ambient temperature and solvent-free media. Scheme 10 shows the preparation procedure of (3-propyltrimethoxysilane) imidazolium hydroxide supported on silicacoated magnetic nanoparticles ([SiPMIM]OH@MNPs) in multiple steps. Firstly, magnetic nanoparticles (MNPs) $Fe_3O_4$ were prepared form $FeCl_3{\cdot}6H_2O$ and $FeCl_2{\cdot}4H_2O$. Then the coating of a layer of silica on the surface of the

naked $Fe_3O_4$ (MNPs) was obtained using tetraethoxysilane (TEOS) by the sol–gel method. The product has been reacted with 3-chloropropyltrimethoxysilane (CPTMS), then *N*-methylimidazole and finally potassium hydroxide was added to get the (3-propyltrimethoxysilane) imidazolium hydroxide supported on magnetic nanoparticles.

Arora and Rajput [46] reported preparation of silicotungstic acid (STA, $H_4[W_{12}SiO_{40}]$) supported on amino-functionalized Si–magnetite nanoparticles. To improve the catalytic properties of heteropoly acid, STA has been coated over aminopropyltrimethoxysilane (APTMS)-functionalized silica-coated magnetite nanoparticles (STA-Amine-Si-Magnetite). The catalytic activity and recyclability of the STA–amine–Si–magnetite nanoparticles were investigated in the synthesis of PPD derivatives through the reaction of phthalhydrazide, malononitrile and aromatic aldehyde in $CH_3OH$ at 70 °C for around 16–330 min. The products (27 examples) have been obtained in 75-99% yields.

Caesium carbonate supported on hydroxyapatite-coated magnetic nanoparticles ($Ni_{0.5}Zn_{0.5}Fe_2O_4$@HAP-$Cs_2CO_3$) was prepared by Maleki *et al*. [47] and the catalytic activity of this catalyst was investigated in the synthesis of PPD derivatives through the three-component reaction of aldehydes, malononitrile and phthalhydrazide at 110 °C under solvent-free conditions. The products (16 examples) have been obtained in 10-30 min with 76-98%. The catalyst has been prepared in three steps. Firstly, $Ni_{0.5}Zn_{0.5}Fe_2O_4$ (NZF) was prepared from $FeCl_3$, $NiCl_2$ and $ZnCl_2$. Then a layer of hydroxyapatite on the surface of the NZF nanoparticles has been coated and finally caesium carbonate has been added to afford the catalyst.

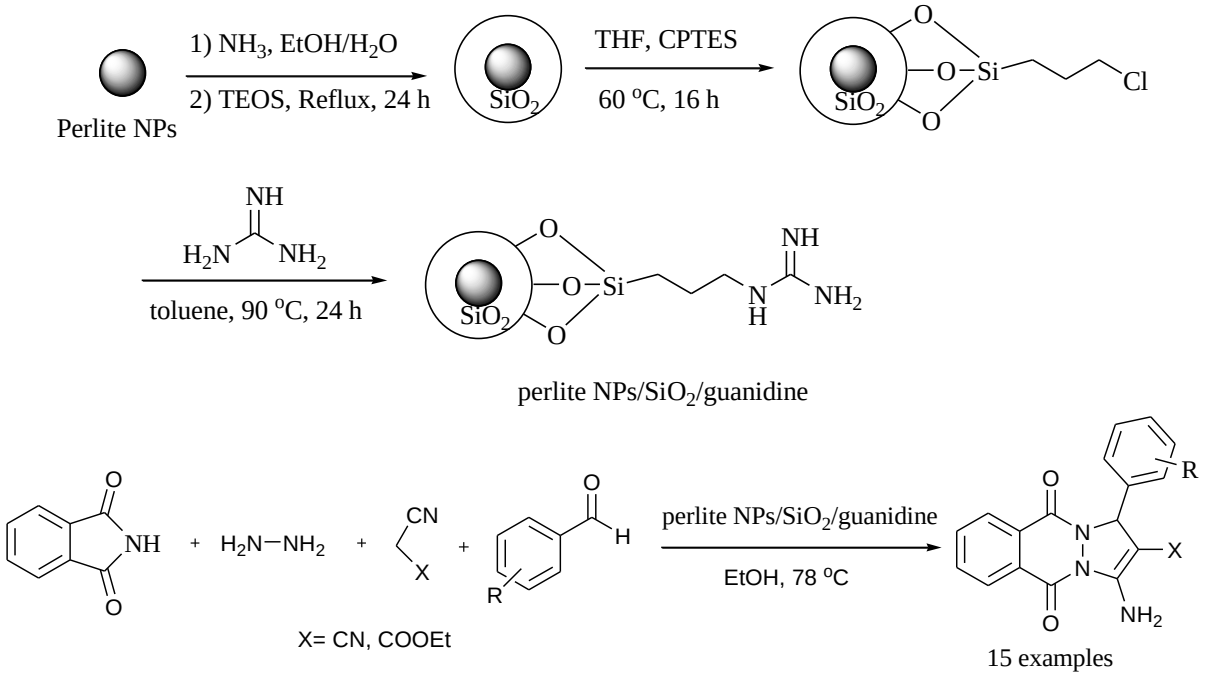



**Scheme 10.** Synthesis of PPDs in the presence of basic ionic liquid supported on silica-coated magnetic nanoparticles.

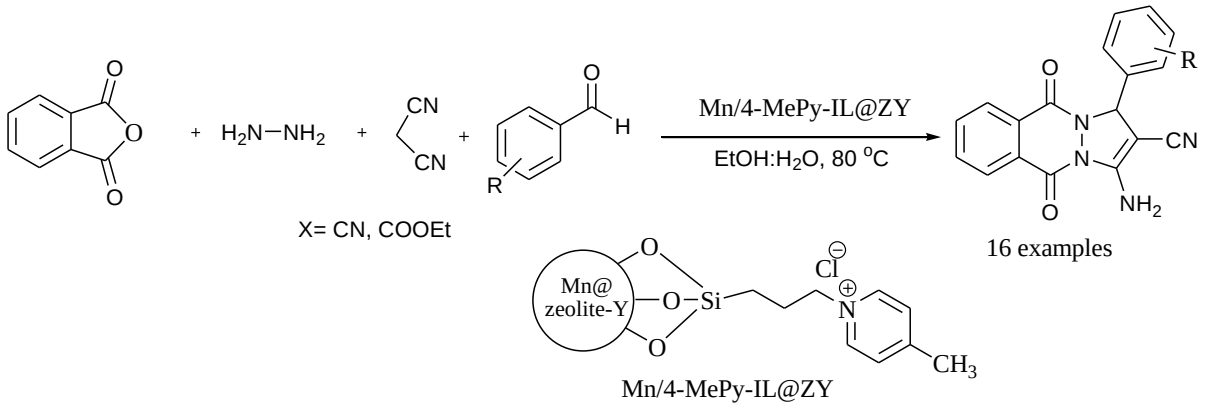
Moradi and her co-workers [48] described the synthesis of PPDs in the presence of modified perlite nanoparticles (perlite NPs/$SiO_2$/guanidine) as a heterogeneous catalyst through the four-component condensation of phethalimide, hydrazine hydrate, malononitrile (or ethylcyanoacetate) and aldehyde derivatives. The catalyst was prepared and characterized according to Scheme 11. Firstly perlite nanoparticles (NPs) have been prepared, then tetraethyl orthosilicate (TEOS) was added to obtain perlite NPs/$SiO_2$, then perlite NPs/$SiO_2$ /CPTES was prepared by the reaction with 3-chloropropyltriethoxysilane (CPTES). Finally, guanidine was added to afford the perlite NPs/$SiO_2$ /guanidine). This catalyst has been utilized for the four-component condensation and the best efficiency (82-97% yield) was obtained using 0.009 g of perlite NPs/$SiO_2$ /guanidine at 78 °C in ethanol as solvent over 150-235 min.

Kalhor and colleagues [49] prepared 4-methylpyridinium chloride ionic liquid manganese nanocomposite (Mn/4-

MePy-IL@ZY). First, Mn@zeolite-Y nanostructure was prepared by the metal exchange reaction of manganese (II) chloride with zeolite-NaY. This nanomaterial was then reacted consecutively with trimethoxysilylpropyl chloride and 4-methylpyridine to obtain the catalyst (Mn/4-MePy-IL@ZY). To evaluate the catalytic performance, the catalyst has been employed (10 wt.%, 0.01 g) in the synthesis of PPDs through the four-component reaction of phthalic anhydride, hydrazine hydrate, malononitrile and arylaldehydes in aqueous ethanol (50%) at 80 °C in 8-12 min with 88-98 % yields (Scheme 12).




**Scheme 11.** Four-component synthesis of PPDs using perlite NPs/$SiO_2$/guanidine.




**Scheme 12.** Application of 4-methylpyridinium chloride ionic liquid grafted on Mn@zeolite-Y in the synthesis of PPDs.

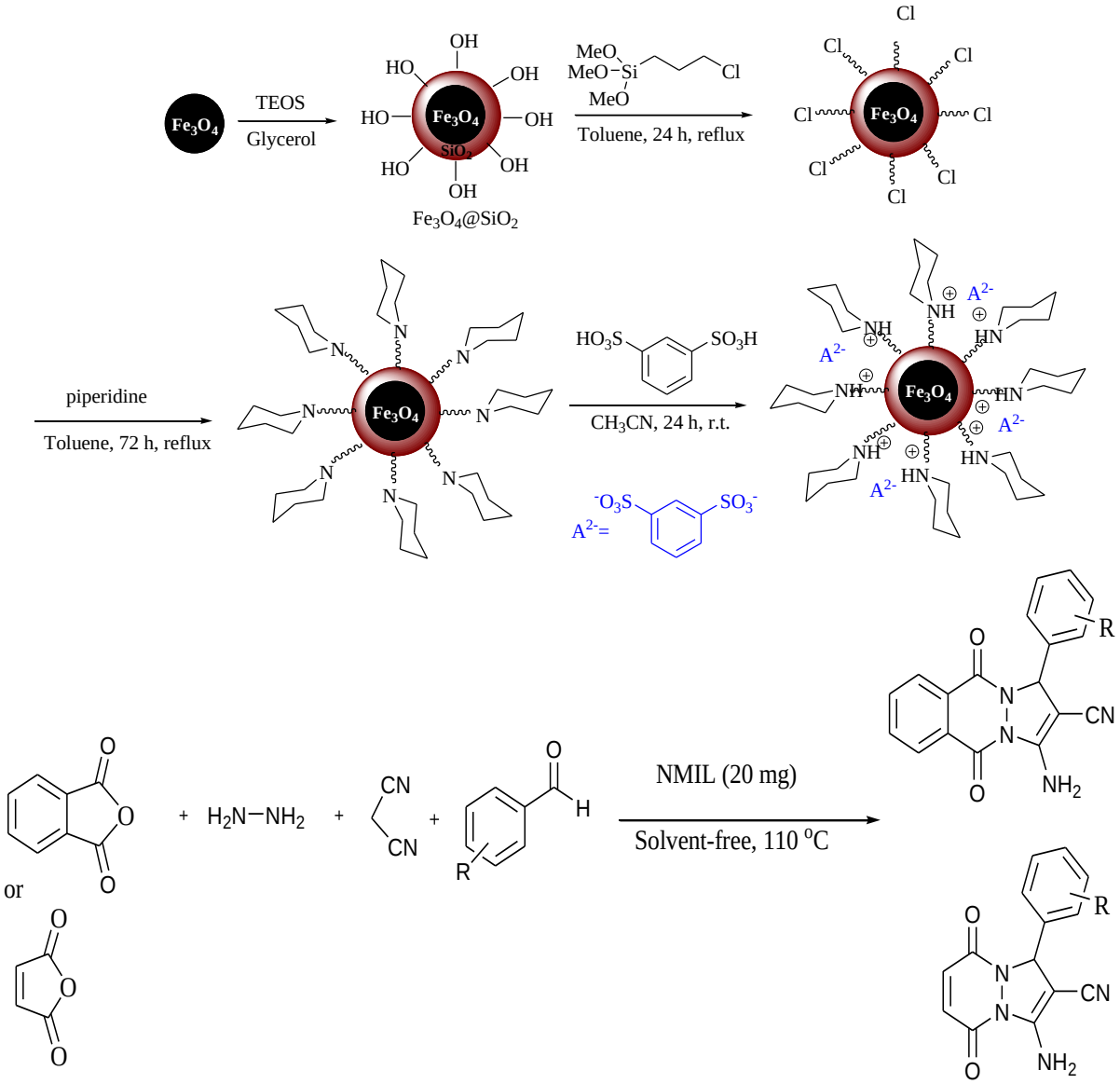
Hamidinasab and colleagues [50] described one-pot three-component condensation reaction of malononitril, phthalhydrazide and various aldehydes using heterogeneous magnetic nanocatalyst ($NiFe_2O_4$@$TiO_2$-Pip NPs) in PEG400 at 80 °C for approximately 60 min in 70-98% yields. For the preparation of the nanocatalyst, nickel ferrite magnetic nanoparticles ($NiFe_2O_4$) have been prepared, coated with $TiO_2$ and finally decorated with piperazine with the aid of the silane coupling agents. In addition, the cytotoxic activities of all PPD derivatives have been evaluated. In the same manner, *N*,*N*,2,2,6,6-hexamethyl-*N*-(3- (trimethoxysilyl)propyl) piperidin-4-amonium iodide was grafted onto titana-coated $NiFe_2O_4$ nanoparticles have been prepared and used as bifunctional base–ionic liquid hybrid magnetic nanocatalyst (nano-$NiFe_2O_4$@$TiO_2$–ILPip) for the synthesis of PPDs by these authors [51].

In other research, Khaleghi and Azarifar [52] reported a synthesis of magnetic *β*-alanine-functionalized-graphene oxide quantum dots $Fe_3O_4$@GOQDs-*N*-(*β*-alanine) as a

recyclable heterogeneous nanocatalyst for the one-pot three-component synthesis of various PPD derivatives. The reactions proceeded at room temperature for 10-20 min under mild and green conditions to afford the respected products in excellent yields (90-98%).

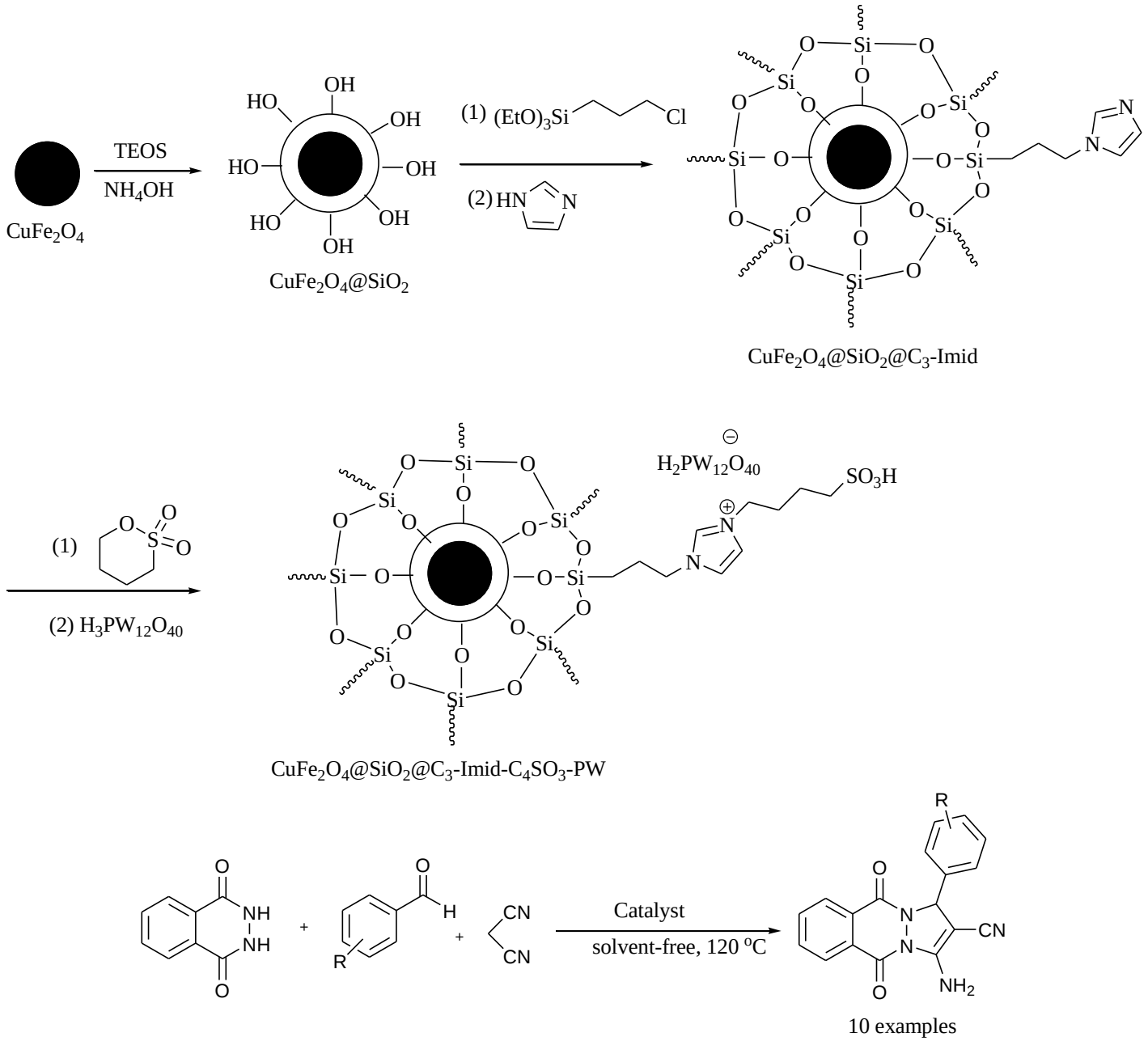
The catalytic activity of the superparamagnetic poly(aniline-com-phenylenediamine)@$Fe_3O_4$ nanocomposite was investigated in the synthesis of PPDs by MiraniNezhad *et al*. [53] through one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehyde derivatives and malononitrile at 80 °C under solvent free conditions, whereby the reaction was complete within 30 min. The antibacterial activity of some derivatives, according to the data (inhibition zone%), exhibited good activity against *Staphylococcus aureus* and *E. coli*.

Ghorbani-Vaghei and coworkers [54] used piperidinium benzene-1,3-disulfonate nanomagnetic ionic liquid (NMIL) as a reusable catalyst for the one-pot four-component synthesis of PPDs and 1*H*-pyrazolo[1,2-*a*] pyridazine-5,8-diones from the reaction of aldehydes, malononitrile, hydrazine hydrate and phthalic anhydride or maleic anhydride at 110 °C in 40-85 min with 75-94 % yields. For the preparation of NMIL Catalyst, firstly, magnetite-phase $Fe_3O_4$ was prepared and treated with tetraethylorthosilicate (TEOS) under reflux to achieve $Fe_3O_4$@$SiO_2$. Subsequently, $Fe_3O_4$@$SiO_2$ reacted with (3-chloropropyl)triethoxysilane to obtain $Fe_3O_4$@$SiO_2$@$(CH_2)_3Cl$. Then reacted with piperidine followed by adding benzene-1,3-disulfonic acid to afford the catalyst (Scheme 13).




**Scheme 13.** Four-component synthesis of PPDs using perlite NPs/$SiO_2$/guanidine.

Davoodnia *et al*. [55] reported phosphotungstic acid-containing ionic liquid immobilized on $CuFe_2O_4@SiO_2$ magnetic nanoparticles in the synthesis of PPDs by reaction of phthalhydrazide with an aromatic aldehyde and malononitrile under solvent-free conditions in 10-15 min with 88-95 % yields. $CuFe_2O_4$ has been prepared by a chemical co-precipitation method using $Cu(NO_3)_2{\cdot}3H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$ as precursors and were coated with a layer of $SiO_2$ *via* sol-gel method with tetraethyl orthosilicate (TEOS) that led to $CuFe_2O_4@SiO_2$. These magnetic nanoparticles (MNPs) reacted with (3-chloropropyl) triethoxysilane and then with an excess of imidazole to give $CuFe_2O_4@SiO_2@C_3$-Imid MNPs. Finally, interaction of obtained $CuFe_2O_4@SiO_2@C_3$-Imid MNPs with 1,4-butane sultone followed by reaction with phosphotungstic acid ($H_3PW_{12}O_{40}$, denoted as PW) gave the final PW-containing IL immobilized on $CuFe_2O_4@SiO_2$ MNPs which is denoted as $CuFe_2O_4@SiO_2@C_3$-Imid-$C_4SO_3$-PW (Scheme 14).




**Scheme 14.** Phosphotungstic acid-containing IL immobilized on $CuFe_2O_4@SiO_2$ magnetic nanoparticles in the synthesis of PPDs.

CuO nanoparticles was successfully utilized as a reusable catalyst for the synthesis of PPD derivatives by Patil *et al*. [56] using one-pot three-component reaction of phthalhydrazide, malononitrile and aromatic aldehydes at

70 °C under solvent-free conditions. Sixteen derivatives have been obtained in 15-35 min with 86-94% yields.

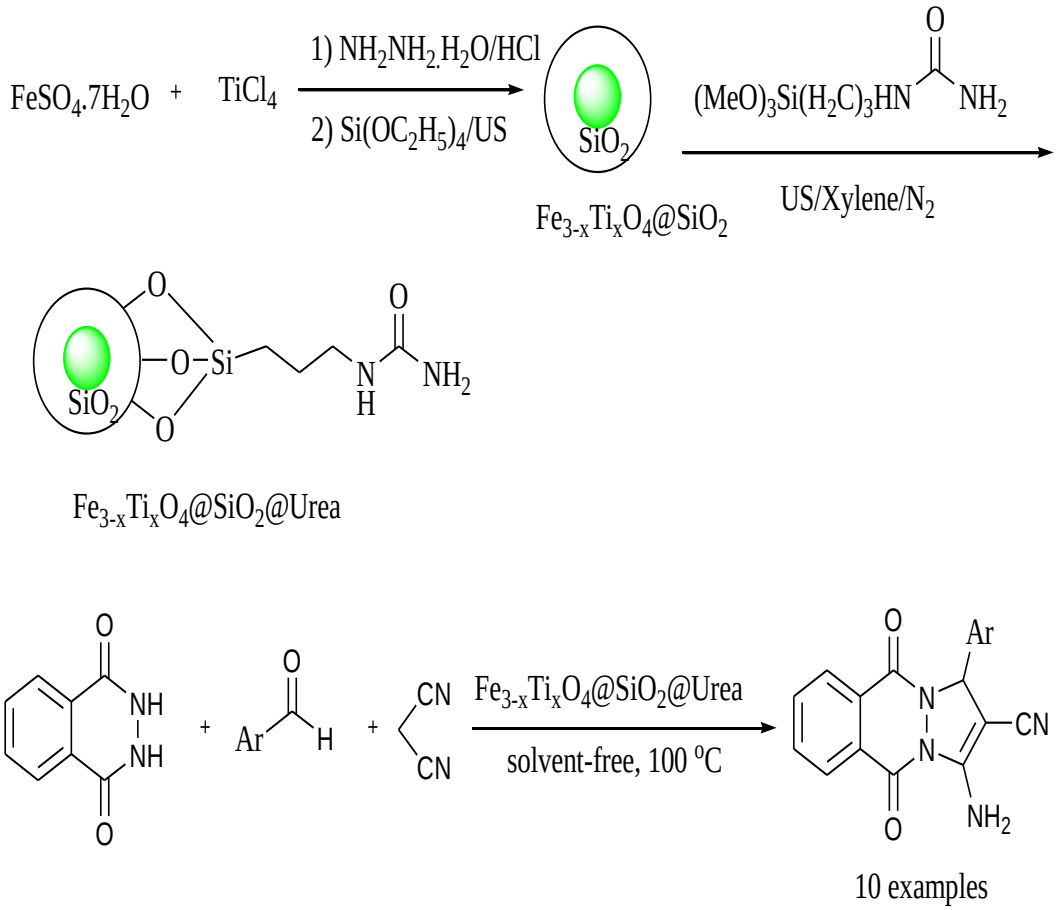
In other research, Cu-doped ZnO hollow sphere nanostructures have been used as a recyclable catalyst in the synthesis of PPDs from the three-component reaction of phthalhydrazide, malononitrile and aldehydes at 100 °C under solvent-free condition [57].

Chalaki and Akhlaghinia [58] prepared $Cu^{II}$ anchored onto the magnetic talc (γ-$Fe_2O_3$/ talc /$Cu^{II}$ NPs) as a magnetically heterogeneous nanocatalyst for the one-pot gram-scale synthesis of PPD derivatives through the reaction between phthalhydrazide, malononitrile and aldehydes in 10-25 min with 85-96% yields. The catalyst has been prepared in multiple steps. Firstly, the reaction of a mixed salt-solution of ferrous and ferric ions and NaOH in the presence of talc powder as supporting material. Afterward, the obtained $Fe_3O_4$/talc has been heated at 220 °C for 3 h to produce γ-$Fe_2O_3$/talc NPs. Subsequently, the treatment of γ-$Fe_2O_3$/talc NPs with refluxing solution of $Cu(OAc)_2.H_2O$ in methanol gave γ-$Fe_2O_3$/talc/$Cu^{II}$ NPs.

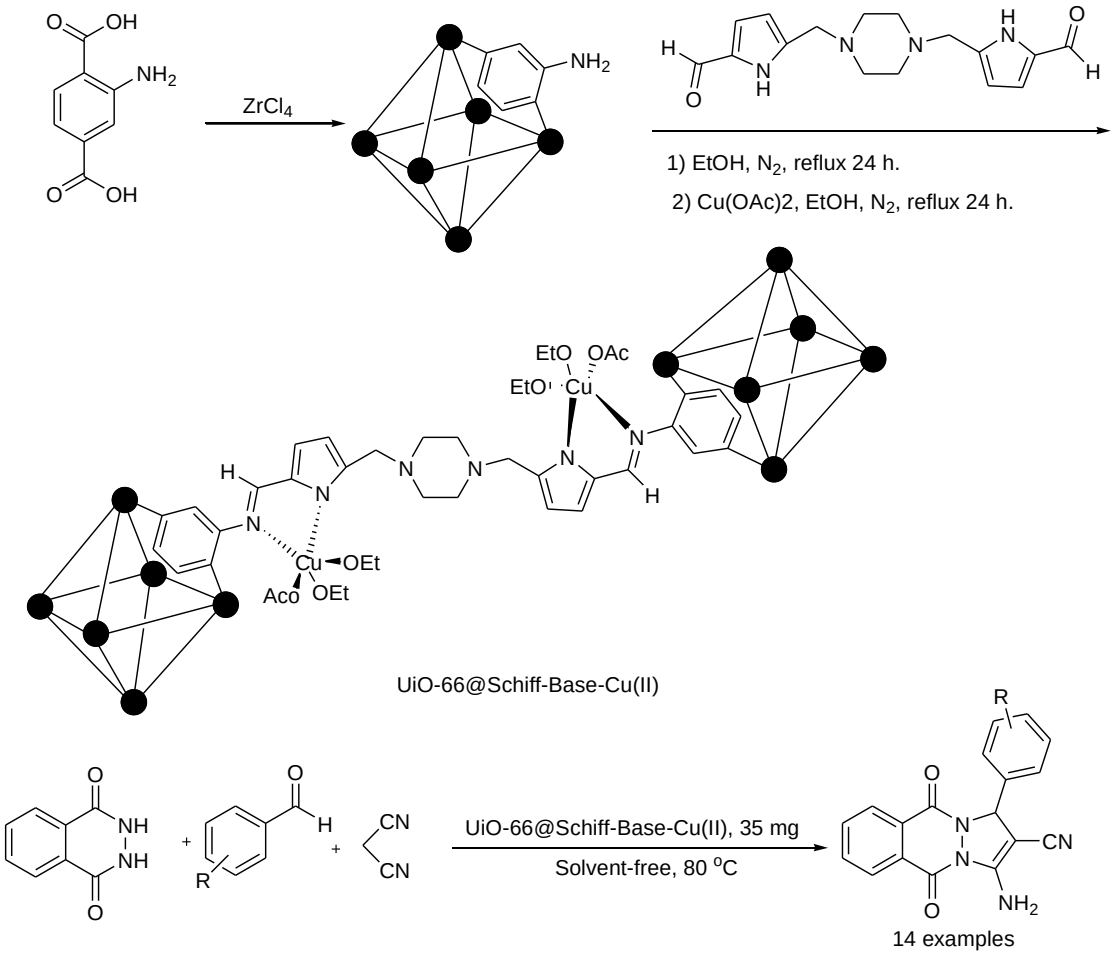
PbO nanoparticles were explored by Tayebee *et al*. [59] as a recyclable catalyst for the fast synthesis of PPD derivatives (11 examples) through a one-pot three-component reaction of phthalhydrazide, aromatic aldehyde and malononitrile under solvent-free conditions at 80 °C for 15 min with 69-99 %.

Piltan [60] reported zirconium oxide nanoparticles for the three-component reaction between phthalhydrazide, malononitrile and aromatic aldehydes. In this study, PPDs have been obtained with good yields (87-96%) using $ZrO_2$ nanoparticles (15 mol%) at 100 °C under solvent-free conditions for 35–45 min.

Azarifar and coworkers [61] prepared urea-functionalized silica-coated magnetic core–shell $Fe_{3-x}Ti_xO_4$ nanoparticles as illustrated in scheme 15. This catalyst has been utilized as a heterogeneous nanocatalyst for the synthesis of PPDs from three-component reaction between aromatic aldehydes, malononitrile, and phthalhydrazide at 100 °C under solvent-free conditions in 10-25 min and high yields (87-98%).




**Scheme 15.** Synthesis of PPDs using urea-functionalized silica-coated magnetic core–shell $Fe_{3-x}Ti_xO_4$ nanoparticles.




**Scheme 16.** Synthesis of PPDs catalyzed by the [UiO-66@Schiff-base-Cu(II)] nanocomposite.

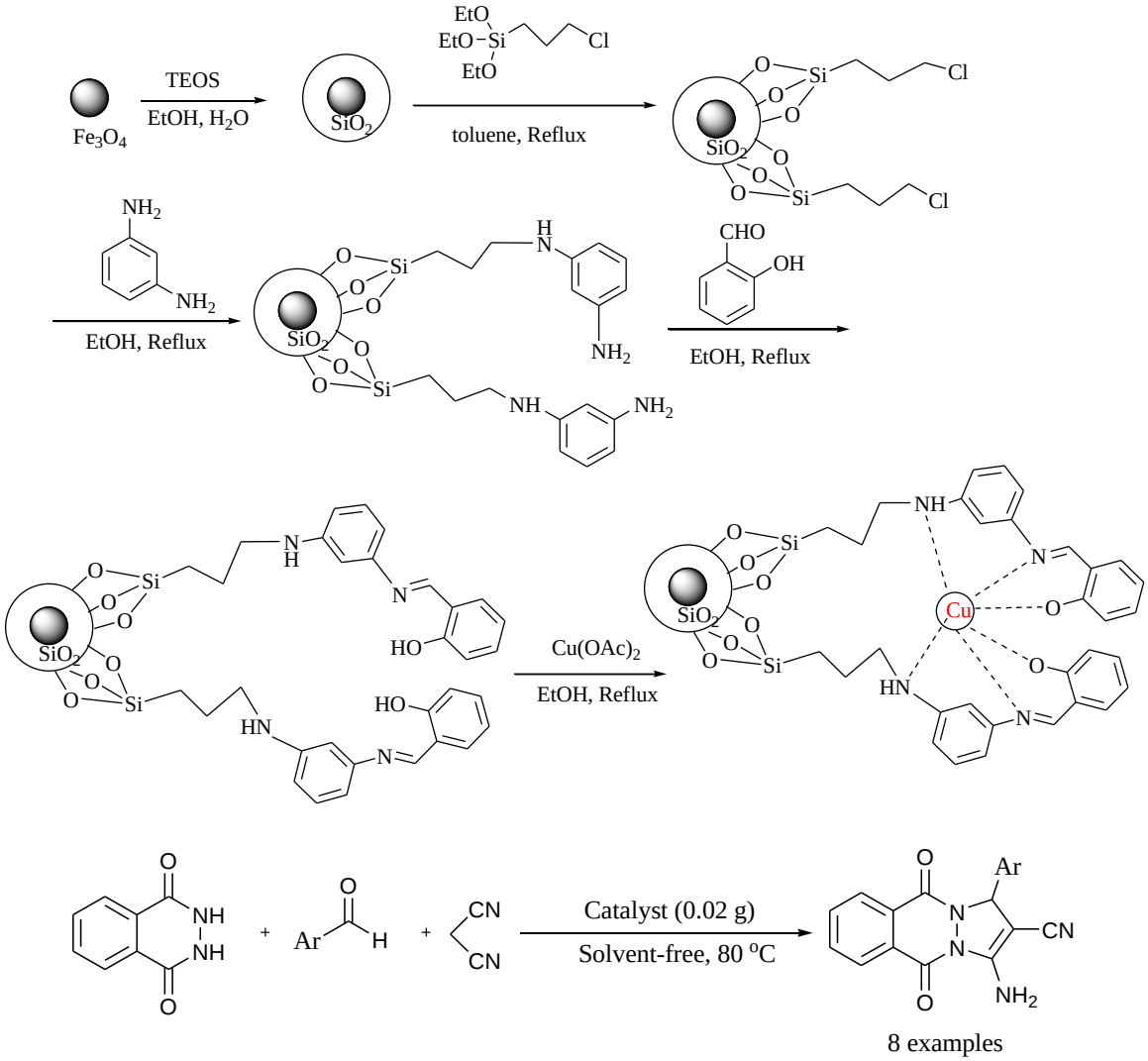
Ghobakhloo and colleagues [62] developed the one-pot three-component reaction of aromatic aldehydes, malononitrile, and phthalhydrazide to afford the corresponding PPDs using metal-organic framework-based supported Cu(II) nanocatalyst [UiO-66@Schiff-Base-Cu(II)] at 80 °C under solvent-free conditions. The procedure gave the products in 10-45 min with 38-93% yields. The catalyst has been prepared using the reaction of $ZrCl_4$ and 2-aminoterephthalic acid. Then the Schiff-base reaction of amine groups with the as-prepared aldehyde, containing a ligand, has been made in order to afford UiO-66@Schiff-Base, which was finally coordinated to copper ions to give the target [UiO-66@Schiff-Base-Cu(II)] catalyst as illustrated in Scheme 16.

Nesarvand *et al*. [63] utilized magnetite-silica core–shell nanoparticles modified with Cu-salen complex ($Fe_3O_4$@$SiO_2$-imine/phenoxy-Cu(II)) a heterogeneous catalyst in the synthesis of PPDs through the three-component reaction of phthalhydrazide, malononitrile and aldehydes at 80 °C under solvent-free conditions in 14-22 min and 88-96% yields. To prepare the catalyst, the $Fe_3O_4$@$SiO_2$ nanoparticles were first prepared and treated with (3-chloropropyl)triethoxysilane, yielding the $Fe_3O_4$@ $SiO_2$–$(CH_2)_3$-Cl MNPs. In the next step, the $Fe_3O_4$@$SiO_2$–$(CH_2)_3$-Cl nanoparticles were reacted with 1,3-phenylenediamine followed by further Schiff base reaction with salicylaldehyde and coordination with Cu(II) ion in order to give the catalyst (Scheme 17). In the same manner, a Schiff base Cu (II) complex immobilized on $Fe_3O_4$@$SiO_2$ nanoparticles has been reported for the synthesis of PPDs by Ebrahimiasl *et al*. [64]. The Schiff base ligand has been prepared from the reaction of 2-pyridinecarboxaldehyde and 2-((4-(2-aminobenzyl)-1,4-diazepan-1-yl)methyl)benzenamine.

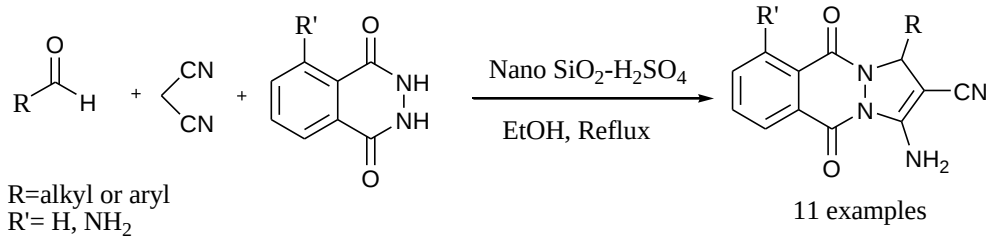
Bashti *et al*. [65] prepared dicationic 4,4′-bipyridine silica hybrid nanocomposite and utilized in the three-component reaction of phthalhydrazide, malononitrile and aromatic aldehyde at 100 °C under solvent-free conditions. The PPD products (10 examples) have been obtained in 30-60 min and 86-96% yields.

Shafe-Mehrabadi and colleagues [66] reported preparation of nanostructured silica-supported sulfuric acid ($SiO_2$–$H_2SO_4$) and used as a nanocatalyst for one-pot

synthesis of phtahalazines *via* three-component condensation of an aromatic or aliphatic aldehyde, malononitrile and 5-amino-2,3-dihydrophthalazine-1,4-dione in ethanol at reflux conditions in 10 min with 86-95% yields (Scheme 18). Nano $SiO_2$-$H_2SO_4$ was prepared form the reaction of chlorosulfonic acid and nanosilica gel powder at 0 °C.



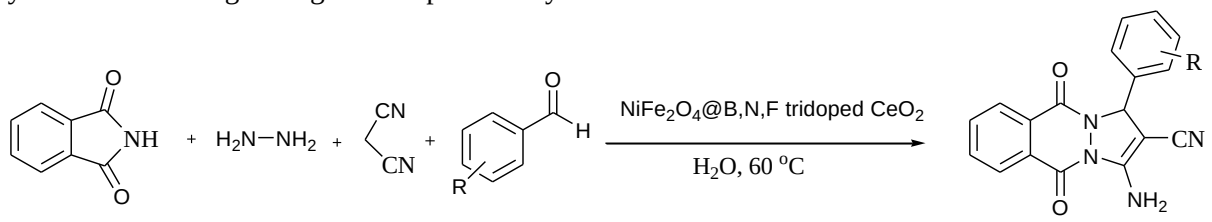

**Scheme 17.** Synthesis of magnetite-silica nanoparticles modified with Cu-salen complex and application for the synthesis of PPDs.




**Scheme 18.** Synthesis of PPDs in the presence of silica-supported sulfuric acid nanoparticles.

Nickel ferrite immobilized over B,N,F tridoped mesoporous cerium oxide ($CeO_2$) nanostructures have been prepared by Sharma *et al*. [67] and used as an heterogeneous nanocatalyst for the synthesis of PPD derivatives through the reaction of phthalimide, hydrazine monohydrate, aromatic aldehyde and malononitrile in $H_2O$ at 60 °C (Scheme 19). To prepare the mesoporous nanocatalyst, firstly, 1-butyl-4-

methylpyridinium tetrafloroborate ionic liquid has been added to the already prepared nanoceria in a silica crucible for tri-doping of ceria. This mixture was thoroughly mixed with grinding accompanied by calcination. Then $NiFe_2O_4$ nanopartiles and tri-doped nanoceria have been mixed in a silica crucible and heated at 650 °C for 3 h in a muffle furnace to afford the catalyst.

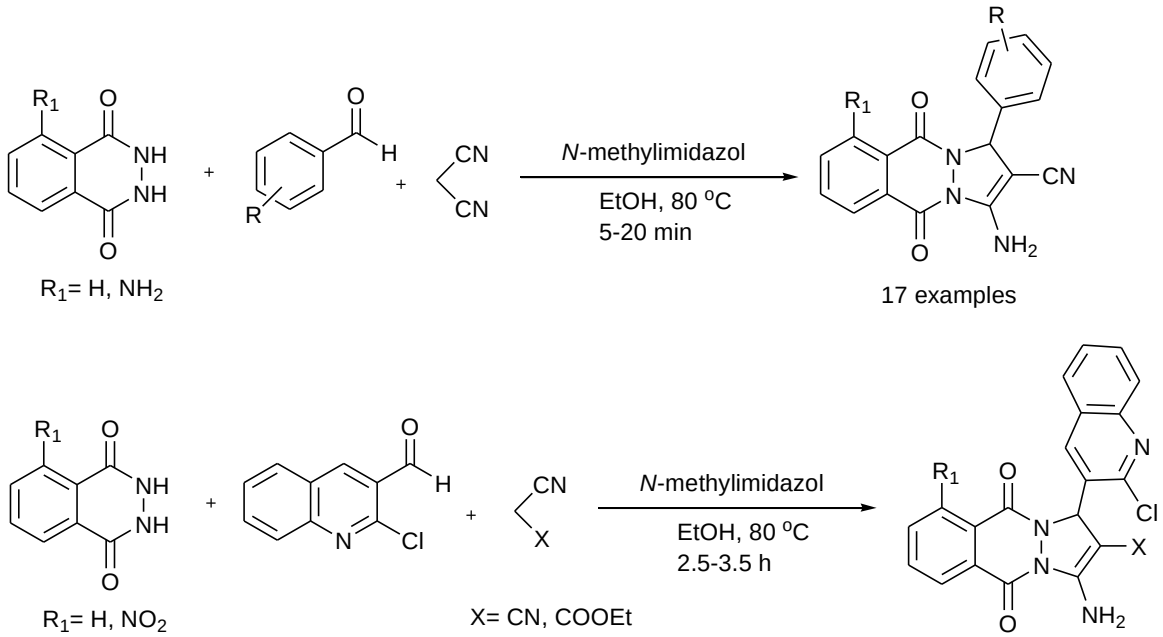



**Scheme 19.** Synthesis of PPDs using $NiFe_2O_4$@B,N,F tridoped $CeO_2$.

*2.3. Using Bio/organocatalysts*

In the last decade, organocatalysts have gained much interest because in many cases, they are usually more readily available, less expensive, more environmentally friendly and can be applied using less demanding reaction conditions [68].

The catalytic potential of organocatalyst *N*-methylimidazole (one drop, *ca*. 20 mol%) is explored in the multi-component reactions of aromatic aldehydes, malononitrile and 2,3-dihydro-phthalazine-1,4-dione in ethanol under reflux conditions. In this method, PPDs have been obtained in 5-20 min with 86-95% yields. In addition, *N*-methylimidazole has been used as a catalyst in the reaction of 2-chloro-3-formylquinoline, malononitrile or ethylcyanoacetate and 2,3-dihydrophthalazine-1,4-dione in ethanol. After 2.5-3.5 h the corresponding pyrazolophthalazinyl quinolines have been synthesized in 78-82% yields (Scheme 20) [69].




**Scheme 20.** Synthesis of PPDs using *N*-methylimidazole.

Bovine serum albumin was used as a biocatalyst for the synthesis of PPDs through a cyclocondensation reaction of malononitrile, phthal hydrazide and aryl aldehydes in water as a solvent. The reaction worked well and gave the products (10 examples) after 24 h with 73–93% yields. It was found that a wide range of aryl aldehydes can participate in this reaction and electron-withdrawing groups ($NO_2$, Br, Cl) gave higher yields than electron-donating groups (OH, Me). However, there is no product was observed when aliphatic aldehydes such as isobutyric aldehyde and acetaldehyde were tested [70].

Dalal *et al*. reported [71] the synthesis of PPD derivatives using lipase from the Aspergillus niger through multicomponent reaction of aldehydes, malononitrile, and phthalhydrazide in DMSO:$H_2O$ at 50 °C for 48 h to achieve the products with good yield (70-86%).

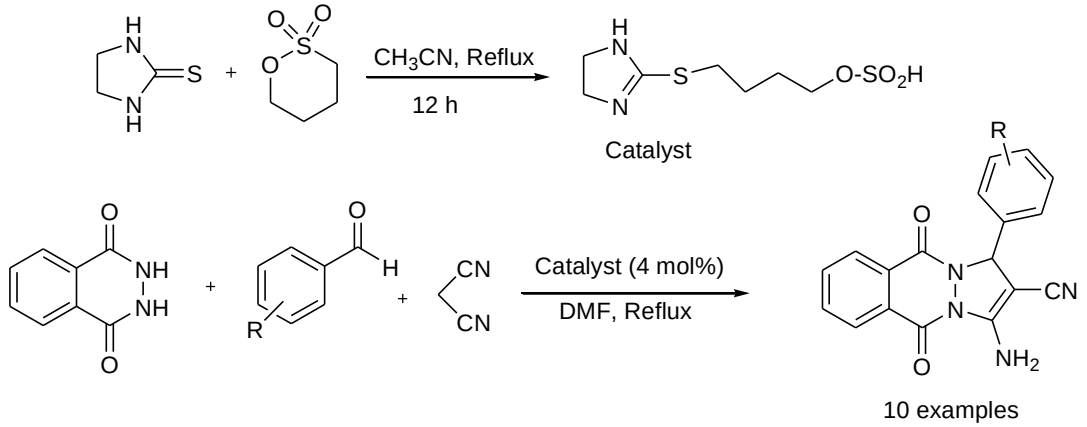
Mohamadpour [72] reported 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a bicyclic amidine catalyst for the synthesis of biologically active

PPD derivatives (19 examples) through one-pot four-component condensation reaction of phthalimide, hydrazine monohydrate, aryl aldehydes and malononitrile under solvent-free conditions at 70 °C for 2–4 h with 75-90% yields.

Lamera and coworkers [73] investigated 4-*N*,*N*-dimethylaminopyridin as Brønsted base catalyst for the synthesis of PPDs starting from phthalhydrazide, aromatic aldehydes and malononitrile. The procedure gave the products with good yields (88-97%) in 0.5-2 h using 20 mol% of catalyst in ethanol under reflux conditions.

Tayade and Dalal [74] developed the synthesis of PPD derivatives by employing 20 mol% β-cyclodextrin *via* a one-pot three-component reaction of aldehydes, malononitrile and phthalhydrazide in $H_2O$–EtOH (4:1) at 100 °C in 2.5-5 h with 82-93 % yields.

Oliaei and coworkers [75] reported the unexpected synthesis of 4-(4,5-dihydro-1*H*-imidazol-2-ylsulfanyl) butyl hydrogen sulfite through the reaction of imidazolidine-2-thione and 1,4-butane sultone in acetonitrile at reflux conditions (Scheme 21). Then, it has been applied as a catalyst for the synthesis of PPDs by means of the one-pot three-component condensation reaction of phthalhydrazide, malononitrile and aromatic aldehydes in DMF at reflux conditions in 10-30 min with 89-98% yields (Scheme 21).




**Scheme 21.** Synthesis of 4-(4,5-dihydro-1*H*-imidazol-2-ylsulfanyl) butyl hydrogen sulfite and using for the synthesis of PPDs.

Unnikrishnan *et al*. [76] prepared inositol cored primary amine-functionalized G0 dendritic polymer (INO-G0) and used for the synthesis of PPDs as the catalyst. The products have been prepared through the reaction of aldehydes, phthalhydrazide and malononitrile in the presence of 0.3 mol% of polymer catalyst INO-G0 within 15 min and 89- 95% yields in ethanol medium under ultrasonic irradiation. According to Scheme 22, the polymer catalyst has been synthesized firstly by the ring opening polymerization of epichlorohydrin initiated by inositol, in the presence of $BF_3OEt_2$. Then it has been subjected to azidation reaction using sodium azide and finally, reduced to inositol cored dendritic amino polymer (INO-G0) by $LiAlH_4$.

The diethylenetriamine (DETA) covalently immobilized on the surface of the Zeolite HY and used as an organic-inorganic hybrid catalyst (Zeolite HY@DETA) for the synthesis of PPD derivatives by Hamidinasab et al. [77] The products (16 examples) have been achieved in ethanol under reflux conditions after 20-30 min. with 85-95% yields.

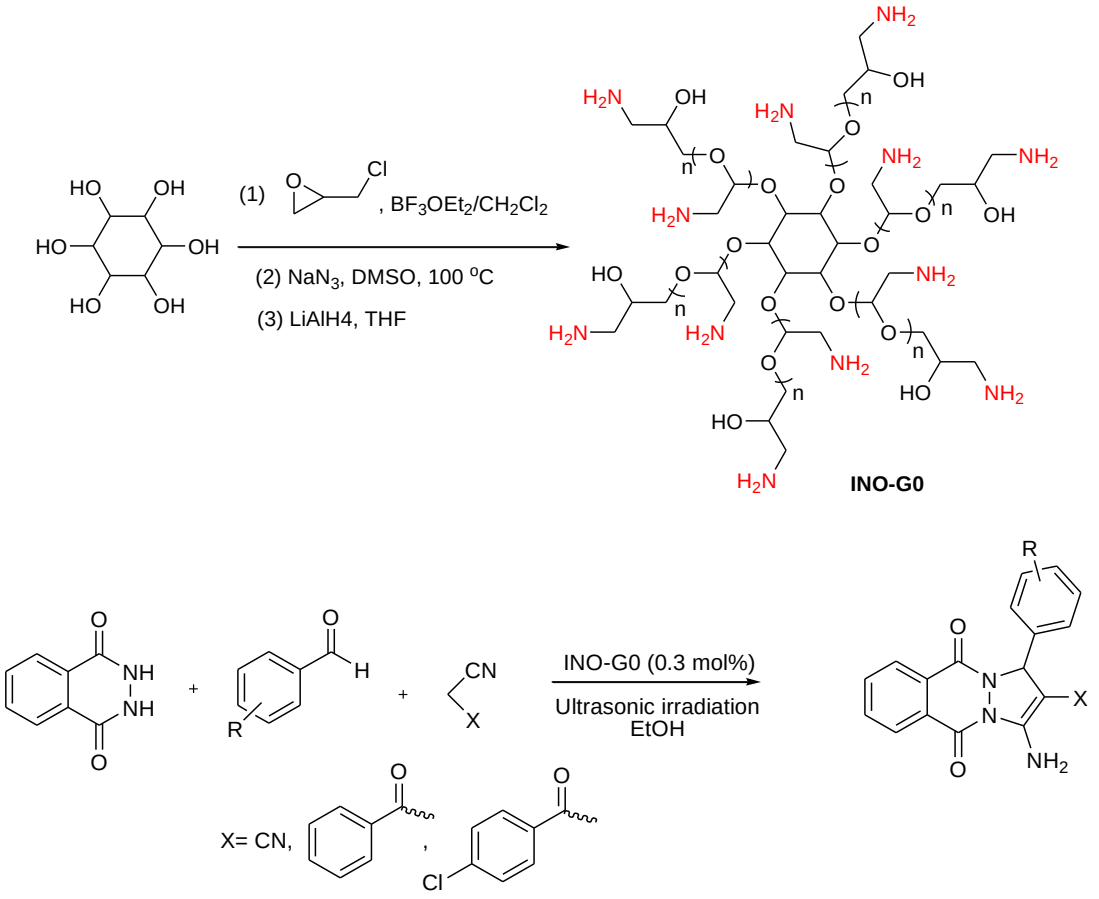
Zaky *et al*. [78] described glycerol as a cheap, biodegradable, and commercially available promoting solvent and catalyst for the one-pot, multi-component synthesis PPDs under controlled microwave irradiations. Saccharin has also been reported as a green catalyst for four-component reaction of phthalimide, hydrazine monohydrate, aromatic aldehydes and malononitrile at 90 °C under solvent-free condition [79].

### *2.4. Using miscellaneous methods*

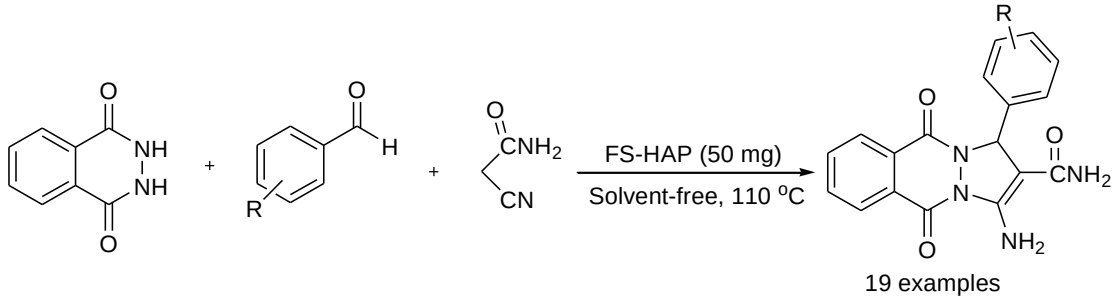
An efficient protocol was demonstrated for the synthesis of PPDs by employing catalytic amount of zinc–proline complex (Zn[L-proline]$_2$) *via* one-pot three-component reaction of phthalhydrazide, aldehyde and malononitrile in the solvent of $H_2O$:PEG400= 6:4 at 80 °C. After 0.5-1 h the products (18 examples) have been prepared with 85-98% yields. The zinc–proline complex was prepared by adding $Et_3N$ to L-proline in MeOH, followed by the addition of zinc acetate [80].

Hiremath and Kamanna [81] described an interesting catalyst for one-pot multicomponent synthesis of PPDs through condensation of aldehyde, malononitrile and phthalhydrazide catalyzed by water extract of mango peel ash under microwave irradiation in ethanol in short reaction time (6–8 min) and good yields (83%–89%).

Maheswari and coworkers[82] reported a one-pot three-component synthesis of PPD derivatives from the aromatic aldehyde, cyanoacetamide and phthalhydrazide using fish scale hydroxyapatite (FS-HAP) as a reusable heterogeneous catalyst at 110 °C under solvent-free condition (Scheme 23). The products have been achieved with remarkable yields (88-96%) in short reaction time (5-12 min).




**Scheme 22.** Synthesis of PPDs using inositol cored primary amine-functionalized G0 dendritic polymer (INO-G0).

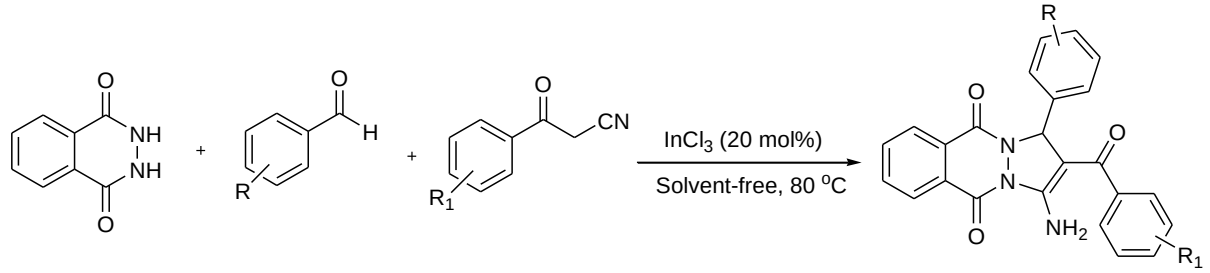



**Scheme 23.** Synthesis of PPDs using fish scale hydroxyapatite.

Synthesis of PPD derivatives *via* one-pot four-component condensation reaction of phthalimide, hydrazine monohydrate, aromatic aldehyde derivatives and malononitrile in the presence of a catalytic amount of zirconium tetrachloride (20 mol%, $ZrCl_4$) as a Lewis acidic catalyst at 80 °C and solvent-free conditions has been developed by Lashkari *et al*. [83]. However in this method, firstly, a mixture of hydrazine monohydrate, phthalimide and $ZrCl_4$ (20 mol%) was heated at 80 °C for 2 h. Then, malononitrile and aromatic aldehyde were added and the mixture was heated for 2-5 h to afford the products with good yields (79-94%).

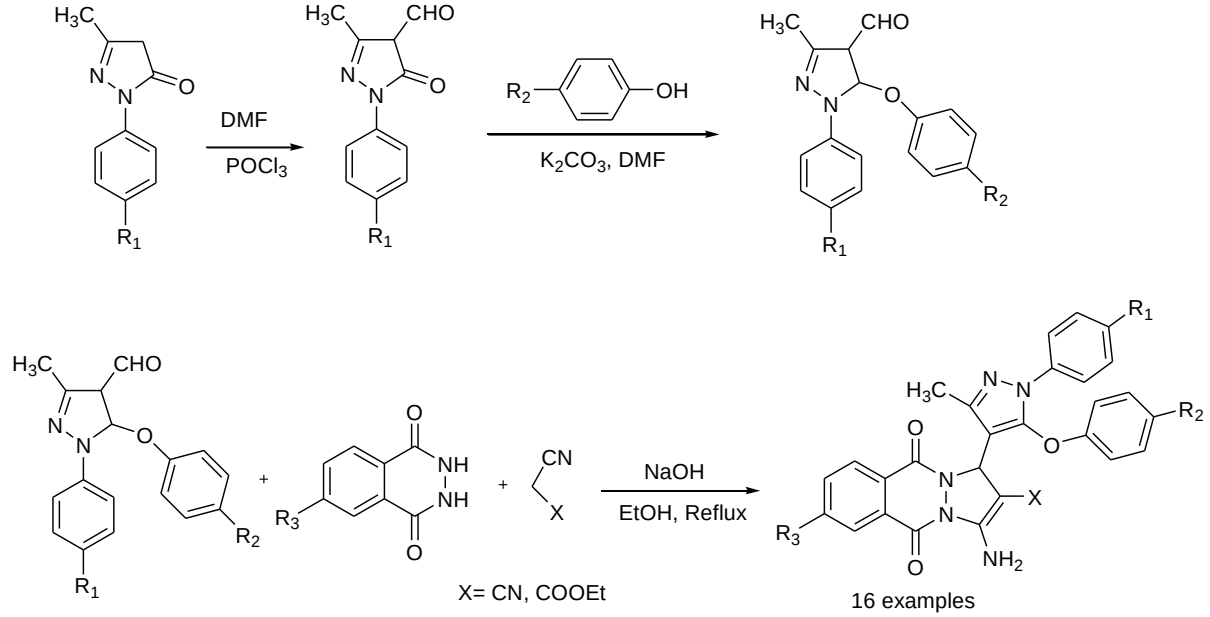
Jadhav and coworkers [84] described synthesis of 3-amino-2-benzoyl-1-aryl PPDs *via* one-pot three-component reaction between phthalhydrazide or maleic hydrazide, aldehydes and arylacetonitrile in the presence

of 20 mol% of indium (III) chloride ($InCl_3$) as a Lewis acid catalyst at 80 °C under solvent-free conditions in 25-40 min and 86-94% yields (Scheme 24).




**Scheme 24.** Synthesis of PPDs in the presence of indium (III) chloride.

Sangani *et al*. [85] reported the synthesis of a series of PPD derivatives using one-pot, three-component base-catalyzed cyclocondensation reaction of 3-methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehyde, malononitrile or ethyl cyanoacetate and 2,3-dihydro-1,4-phthalazinedione in ethanol containing NaOH under reflux for 3.5–4 h in good yields (70-89%). The required starting material was prepared according to scheme 25. However, the antimicrobial, antituberculosis and antioxidant activity of products have been investigated.



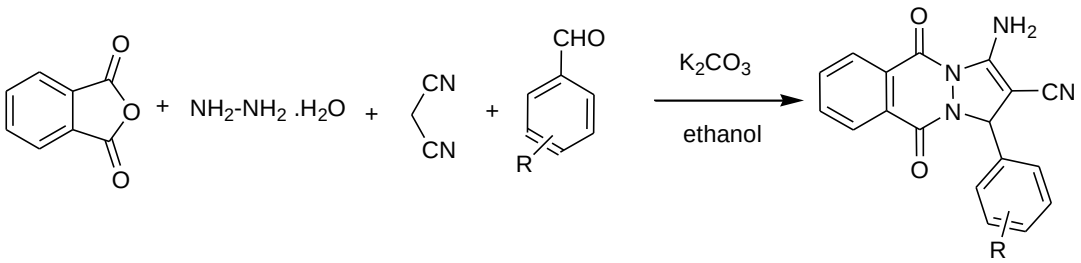

**Scheme 25.** Synthesis of PPDs in the presence of NaOH.

Kerru and colleagues [86] used eggshell powder as an inexpensive, biodegradable and heterogeneous catalyst for the four-component one-pot condensation reaction through the reaction of different chosen active methylene compounds, phthalic anhydride, and hydrazine hydride with aromatic aldehydes in the water at 60 °C and provided the high yields of products (93–98%) in short reaction time of 28 to 45 min. The eggshell powder has been characterized and composed of the high percentage of calcium oxides and carbonates.

Kefayati and colleagues [87] used tetrabutylammonim fluoride as phase-transfer catalyst for the synthesis of PPD derivatives in one-pot three-component reaction of phthalhydrazide, aromatic aldehydes or isatin derivatives and malononitrile in water at 75 °C under ultrasonic irradiation. The products (12 examples) have been synthesized for 20-45 min with 86-95% yields.

Synthesis of PPDs has also been reported in the presence of copper(II) acetate monohydrate as a catalyst by means of four-component reaction using phthalic anhydride [88].

Abdesheikhi and Karimi-Jaberi [89] reported an efficient method to synthesize PPD derivatives through one-pot, four-component cyclocondensation of phthalic anhydride, hydrazine hydrate, aromatic aldehydes and malononitrile in the presence of potassium carbonate ($K_2CO_3$). The reaction was performed in ethanol under reflux conditions gave the corresponding products in 85-96% yield after 50-80 min (Scheme 26).




**Scheme 26.** Four-component synthesis of PPDs in the presence of potassium carbonate.

## 3. Conclusion

This review presented a brief overview of the recent methods and catalysts leading to pyrazolo[1,2-*b*]phthalazines as biologically or pharmaceutically active compounds. As is evident from the several approaches outlined in this review article, these synthetic procedures offered access to pyrazolo[1,2-*b*]phthalazine-5,10-diones from three-component reaction including phthalhydrazide, aldehydes and malononitrile, or four-component reaction of phthalic anhydride/ phthalhydrazide, hydrazine, aldehydes and malononitrile. Now that the useful methods and catalysts like ionic liquids, organic acids, metal nanoparticles, biocatalysts and so on which have been utilized in the multi-component reaction have been summarized in one source, we hope that this review could be of interest in medicinal, natural products and organic synthesis.

**References**


[1] B. Eftekhari-Sis, M. Zirak and A. Akbari, Arylglyoxals in Synthesis of Heterocyclic Compounds. *Chem. Rev.*, 113 (2013) 2958-3043.

[2] K. Karrouchi, S. Radi, Y. Ramli, J. Taoufik, Y. N. Mabkhot, F. A. Al-Aizari and M. h. Ansar, Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules*, 23 (2018) 134-220.

[3] M. Faisal, A. Saeed, S. Hussain, P. Dar and F. A. Larik, Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. *J. Chem. Sci.*, 131 (2019) 70.

[4] M. Li and B.-X. Zhao, Progress of the synthesis of condensed pyrazole derivatives (from 2010 to mid-2013). *Eur. J. Med. Chem.*, 85 (2014) 311-340.

[5] K. M. Dawood, T. M. Eldebss, H. S. El-Zahabi, M. H. Yousef and P. Metz, Synthesis of some new pyrazole-based 1, 3-thiazoles and 1, 3, 4-thiadiazoles as anticancer agents. *Eur. J. Med. Chem.*, 70 (2013) 740-749.

[6] K. Kula, J. Dobosz, R. Jasiński, A. Kącka-Zych, A. Łapczuk-Krygier, B. Mirosław and O. M. Demchuk, [3+ 2] Cycloaddition of diaryldiazomethanes with (E)-3, 3, 3-trichloro-1-nitroprop-1-ene: An experimental, theoretical and structural study. *J. Mol. Struct.*, 1203 (2020) 127473.

[7] K. Kula, A. Łapczuk, M. Sadowski, J. Kras, K. Zawadzińska, O. M. Demchuk, G. K. Gaurav, A. Wróblewska and R. Jasiński, On the Question of the Formation of Nitro-Functionalized 2,4-Pyrazole Analogs on the Basis of Nitrylimine Molecular Systems and 3,3,3-Trichloro-1-Nitroprop-1-Ene. *Molecules*, 27 (2022) 8409-8421.

[8] J.-J. Liu, M.-y. Zhao, X. Zhang, X. Zhao and H.-L. Zhu, Pyrazole derivatives as antitumor, anti-inflammatory and antibacterial agents. *Mini Rev. Med. Chem.*, 13 (2013) 1957-1966.

[9] A. Vijesh, A. M. Isloor, P. Shetty, S. Sundershan and H. K. Fun, New pyrazole derivatives containing 1, 2, 4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. *Eur. J. Med. Chem.*, 62 (2013) 410-415.

[10] R. Verma, S. K. Verma, K. P. Rakesh, Y. R. Girish, M. Ashrafizadeh, K. S. S. Kumar and K. S. Rangappa, Pyrazole-based analogs as potential antibacterial agents against methicillin-resistance staphylococcus aureus (MRSA) and its SAR elucidation. *Eur. J. Med. Chem.*, 212 (2021) 113134.

[11] M. F. Khan, M. M. Alam, G. Verma, W. Akhtar, M. Akhter and M. Shaquiquzzaman, The therapeutic voyage of pyrazole and its analogs: a review. *Eur. J. Med. Chem.*, 120 (2016) 170-201.

[12] H. Aziz, A. F. Zahoor and S. Ahmad, Pyrazole bearing molecules as bioactive scaffolds: A review. *J. Chil. Chem. Soc.*, 65 (2020) 4746-4753.

[13] J. V. Faria, P. F. Vegi, A. G. C. Miguita, M. S. Dos Santos, N. Boechat and A. M. R. Bernardino, Recently reported biological activities of pyrazole compounds. *Biorg. Med. Chem.*, 25 (2017) 5891-5903.

[14] O. Ebenezer, M. Shapi and J. A. Tuszynski, A review of the recent development in the synthesis and biological evaluations of pyrazole derivatives. *Biomedicines*, 10 (2022) 1124.

[15] J. Sangshetti, S. K. Pathan, R. Patil, S. A. Ansari, S. Chhajed, R. Arote and D. B. Shinde, Synthesis and biological activity of structurally diverse phthalazine derivatives: A systematic review. *Biorg. Med. Chem.*, 27 (2019) 3979-3997.

[16] S. Zaib and I. Khan, Synthetic and medicinal chemistry of phthalazines: Recent developments, opportunities and challenges. *Bioorg. Chem.*, 105 (2020) 104425.

[17] Y. Taek Han, J.-W. Jung and N.-J. Kim, Recent advances in the synthesis of biologically active

cinnoline, phthalazine and quinoxaline derivatives. *Curr. Org. Chem.*, 21 (2017) 1265-1291.

[18] J. Aswathy, A concise review on phthlazine derivatives and its biological activities. *J. Pharm. Sci. Res.*, 11 (2019) 2526-2532.

[19] M. Asif, Some recent approaches of biologically active substituted pyridazine and phthalazine drugs. *Curr. Med. Chem.*, 19 (2012) 2984-2991.

[20] S. Dubey and P. A. Bhosle, Pyridazinone: an important element of pharmacophore possessing broad spectrum of activity. *Med. Chem. Res.*, 24 (2015) 3579-3598.

[21] H. Almahli, E. Hadchity, M. Y. Jaballah, R. Daher, H. A. Ghabbour, M. M. Kabil, N. S. Al-Shakliah and W. M. Eldehna, Development of novel synthesized phthalazinone-based PARP-1 inhibitors with apoptosis inducing mechanism in lung cancer. *Bioorg. Chem.*, 77 (2018) 443-456.

[22] D.-Q. Xue, X.-Y. Zhang, C.-J. Wang, L.-Y. Ma, N. Zhu, P. He, K.-P. Shao, P.-J. Chen, Y.-F. Gu and X.-S. Zhang, Synthesis and anticancer activities of novel 1, 2, 4-triazolo [3, 4-a] phthalazine derivatives. *Eur. J. Med. Chem.*, 85 (2014) 235-244.

[23] L. Jalili-Baleh, H. Nadri, A. Moradi, S. N. A. Bukhari, M. Shakibaie, M. Jafari, M. Golshani, F. H. Moghadam, L. Firoozpour and A. Asadipour, New racemic annulated pyrazolo [1, 2-b] phthalazines as tacrine-like AChE inhibitors with potential use in Alzheimer's disease. *Eur. J. Med. Chem.*, 139 (2017) 280-289.

[24] P. Taslimi, K. Turhan, F. Türkan, H. S. Karaman, Z. Turgut and I. Gulcin, Cholinesterases, α-glycosidase, and carbonic anhydrase inhibition properties of 1H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives: Synthetic analogues for the treatment of Alzheimer's disease and diabetes mellitus. *Bioorg. Chem.*, 97 (2020) 103647.

[25] T. Mathew, A. Á. Papp, F. Paknia, S. Fustero and G. S. Prakash, Benzodiazines: recent synthetic advances. *Chem. Soc. Rev.*, 46 (2017) 3060-3094.

[26] M. V. Reddy and Y. T. Jeong, $InCl_3$-catalyzed green synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones under solvent-free conditions. *Tetrahedron Lett.*, 54 (2013) 3546-3549.

[27] R. Ghahremanzadeh, G. I. Shakibaei and A. Bazgir, An efficient one-pot synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-dione derivatives. *Synlett*, 2008 (2008) 1129-1132.

[28] G. Kaur, H. Kumar and M. Singla, Diverse applications of ionic liquids: A comprehensive review. *J. Mol. Liq.*, 351 (2022) 118556.

[29] H. R. Shaterian and M. Mohammadnia, Mild basic ionic liquids catalyzed new four-component synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-diones. *J. Mol. Liq.*, 173 (2012) 55-61.

[30] W. Wang, L. Cong-Hao, Y. Yi, L. Xiao-Jun and G. Hong-Yun, An Improved Procedure for the Three-Component Synthesis of 1 H-Pyrazolo [1, 2-B] Phthalazine-5, 10-Dione Derivatives Using Basic Ionic Liquid. *J. Chem. Research*, 40 (2016) 354-357.

[31] M. A. Shaikh, M. Farooqui and S. Abed, [Bu3NH][HSO4] catalyzed: an eco-efficient synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones and 2H-indazolo[2,1-b]phthalazine-triones under solvent-free conditions. *Res. Chem. Intermed.*, 44 (2018) 5483-5500.

[32] A. G. Mulik, D. R. Chandam, D. R. Patil, P. P. Patil, G. N. Mulik, S. T. Salunkhe and M. B. Deshmukh, Protic ionic liquids: a lucid, rational tool for synthesis of phthalazinediones, quinoxalines and benzopyrans. *Res. Chem. Intermed.*, 41 (2015) 10085-10096.

[33] G. Jeevan Raghavendra and V. Siddaiah, One-Pot Four Component Synthesis of 3-Amino-1-(1H-indol-2-yl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine Derivatives Mediated by [DBUH][OAc]. *Russ. J. Gen. Chem.*, 88 (2018) 1892-1898.

[34] S. Fallah-Ghasemi Gildeh, M. Mehrdad, H. Roohi, K. Ghauri, S. Fallah-Ghasemi Gildeh and K. Rad-Moghadam, Experimental and DFT mechanistic insights into one-pot synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones under catalysis of DBU-based ionic liquids. *New J. Chem.*, 44 (2020) 16594-16601.

[35] P. Jahanshahi and M. Mamaghani, Chemodivergent, multicomponent-tandem facile synthesis of novel 1 H-pyrazolo [1, 2-b] phthalazine-5, 10-dione using acetic acid functionalized imidazolium salt {[cmdmim] I} as a recyclable catalyst. *New J. Chem.*, 43 (2019) 8266-8278.

[36] S. Hasthavaram, N. A. Reddy, K. Kamala, R. Dayam and K. Saritha, One-pot synthesis of phthalazinyl-2-carbonitrile indole derivatives via [bmim][OH] as ionic liquid and their anti cancer evaluation and molecular modeling studies. *Eur. Chem. Bull.*, 9 (2020) 154-159.

[37] C. K. Jadhav, A. S. Nipate, A. V. Chate, M. V. Kulkarni and C. H. Gill, Microwave-Assisted Chemistry: New Synthetic Application for the Rapid Construction of 1H-Pyrazolo[1,2-b]Phthalazine-5,10-Dione Derivatives in Diisopropyl Ethyl Ammonium Acetate. *Polycyclic Aromat. Compd.*, 43 (2023) 895-914.

[38] M. Kour, M. Bhardwaj, H. Sharma, S. Paul and J. H. Clark, Ionic liquid coated sulfonated carbon@titania composites for the one-pot synthesis of indeno[1,2-b]indole-9,10-diones and 1H-pyrazolo[1,2-b]phthalazine-5,10-diones in aqueous media. *New J. Chem.*, 41 (2017) 5521-5532.

[39] A. Vafaee, A. Davoodnia, A. Nakhaei, S. Yadegarian and M. Nejatianfar, Two Novel Pyrazole Derived Ionic Liquids Based on Chloride and Trichlorostannate Anions: Preparation, Characterization, and Evaluation of Their Catalytic Activity in the Synthesis of 1H-Pyrazolo[1,2-b]phthalazine-5,10-diones. *Russ. J. Gen. Chem.*, 91 (2021) 273-278.

[40] D. Xiao, T. Lu, R. Zeng and Y. Bi, Preparation and highlighted applications of magnetic microparticles and nanoparticles: a review on recent advances. *Microchim. Acta*, 183 (2016) 2655-2675.

[41] M. Khatami, H. Q. Alijani, M. S. Nejad and R. S. Varma, Core@ shell nanoparticles: greener synthesis using natural plant products. *Appl. Sci.*, 8 (2018) 411.

[42] M. A. Abarghooei, R. Mohebat, Z. Karimi-Jaberi and M. H. Mosslemin, An efficient synthesis of naphtho[2,1-b]furan-2(1H)-ones catalysed by Nafion-H supported on silica-coated super paramagnetic iron oxide nanoparticles. *J. Chem. Research*, 41 (2017) 408-412.

[43] S. Liu, B. Yu, S. Wang, Y. Shen and H. Cong, Preparation, surface functionalization and application of Fe3O4 magnetic nanoparticles. *Adv. Colloid Interface Sci.*, 281 (2020) 102165.

[44] S. Sayyahi, M. Fallah-Mehrjardi and S. J. Saghanezhad, Synthesis of Heterocyclic Compounds by Catalysts Supported on Nano-Magnetite (Fe3O4)-An Update. *Mini-Rev. Org. Chem.*, 18 (2021) 11-26.

[45] F. Hatami Sabour, M. Nasr-Esfahani, I. Mohammadpoor-Baltork, S. Tangestaninejad, M. Moghadam and V. Mirkhani, A convenient approach for the synthesis of various derivatives of pyrazolo[1,2-b]phthalazinediones in the presence of an efficient supported basic ionic liquid at ambient temperature and solvent-free media. *J. Iran. Chem. Soc.*, 15 (2018) 671-683.

[46] P. Arora and J. K. Rajput, Amelioration of H4[W12SiO40] by nanomagnetic heterogenization: For the synthesis of 1H–pyrazolo[1,2-b]phthalazinedione derivatives. *Appl. Organomet. Chem.*, 32 (2018) e4001.

[47] B. Maleki, S. Barat Nam Chalaki, S. Sedigh Ashrafi, E. Rezaee Seresht, F. Moeinpour, A. Khojastehnezhad and R. Tayebee, Caesium carbonate supported on hydroxyapatite-encapsulated Ni0.5Zn0.5Fe2O4 nanocrystallites as a novel magnetically basic catalyst for the one-pot synthesis of pyrazolo[1,2-b]phthalazine-5,10-diones. *Appl. Organomet. Chem.*, 29 (2015) 290-295.

[48] L. Moradi, M. Mirzaei and H. R. Sasi, Preparation and characterization of perlite nanoparticles modified with guanidine as an efficient solid base catalyst for the multicomponent synthesis of 1H-pyrazolo [1,2-b] phthalazine-5,10-dione derivatives. *J. Mol. Struct.*, 1263 (2022) 133124.

[49] M. Kalhor, Z. Orouji and M. Khalaj, 4-Methylpyridinium chloride ionic liquid grafted on Mn@zeolite-Y: Design, fabrication and performance as a novel multi-functional nanocatalyst in the four-component synthesis of pyrazolophthalazine-diones. *Microporous Mesoporous Mater.*, 329 (2022) 111498.

[50] M. Hamidinasab, A. Ameri, A. Hekmat, H. Forootanfar, T. Mortezazadeh, M. A. Bodaghifard, F. Peytam, R. Esmaeili, A. Foroumadi, M. Sharifzadeh, A. Mobinikhaledi and M. Khoobi, Mono- and bis-pyrazolophthalazines: Design, synthesis, cytotoxic activity, DNA/HSA binding and molecular docking studies. *Biorg. Med. Chem.*, 30 (2021) 115944.

[51] M. Hamidinasab, M. A. Bodaghifard and A. Mobinikhaledi, Green synthesis of 1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile derivatives using a new bifunctional base–ionic liquid hybrid magnetic nanocatalyst. *Appl. Organomet. Chem.*, 34 (2020) e5386.

[52] M. Khaleghi Abbasabadi and D. Azarifar, β-Alanine-functionalized magnetic graphene oxide quantum dots: an efficient and recyclable heterogeneous basic catalyst for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione and 2,3-dihydroquinazolin-4(1H)-one derivatives. *Appl. Organomet. Chem.*, 34 (2020) e5872.

[53] S. M. Nezhad, S. A. Pourmousavi and E. N. Zare, Superparamagnetic Poly (aniline-co-m-phenylenediamine)@ Fe3O4 Nanocomposite as an Efficient Heterogeneous Catalyst for the Synthesis of 1H-pyrazolo [1, 2-a] pyridazine-5, 8-diones & 1H-pyrazolo [1, 2-b] phthalazine-5, 10-diones Derivatives. *Curr. Org. Synth.*, 19 (2022) 246-266.

[54] R. Ghorbani-Vaghei, J. Mahmoodi and Y. Maghbooli, Preparation and characterization of nanomagnetic piperidinium benzene-1,3-disulfonate ionic liquid as a novel, green and heterogeneous catalyst and its use in the synthesis of 1H–pyrazolo[1,2-b]phthalazine-5,10-diones and 1H–pyrazolo[1,2-a] pyridazine-5,8-diones under solvent-free conditions. *Appl. Organomet. Chem.*, 31 (2017) e3717.

[55] N. Hosseininasab, A. Davoodnia, F. Rostami-Charati and A. Khojastehnezhad, Preparation, characterization, and first catalytic application of a novel phosphotungstic acid-containing ionic liquid immobilized on CuFe2O4@SiO2 magnetic nanoparticles in the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones. *Russ. J. Gen. Chem.*, 87 (2017) 2436-2443.

[56] S. Patil, A. Mane and S. Dhongade-Desai, CuO nanoparticles as a reusable catalyst for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives under solvent-free conditions. *J. Iran. Chem. Soc.*, 16 (2019) 1665-1675.

[57] B. Maleki, R. Nejat, H. Alinezhad, S. M. Mousavi, B. Mahdavi and M. Delavari, Nanostructural Cu-Doped ZnO Hollow Spheres as an Economical and Recyclable Catalyst in the Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones and Pyrazolo[1,2-a][1,2,4]triazole-1,3-diones. *Org. Prep. Proced. Int.*, 52 (2020) 328-339.

[58] S. B. Chalaki and B. Akhlaghinia, CuII Anchored onto the Magnetic Talc: A New Magnetic Nanostructured Catalyst for the One-Pot Gram-Scale Synthesis of 1H-Pyrazolo[1,2-b]phthalazine-5,10-dione Derivatives. *ChemistrySelect*, 5 (2020) 11010-11019.

[59] R. Tayebee, B. Maleki and M. sabeti, A new simple method for the preparation of PbO nanoparticles and implementation of an efficient and reusable catalytic system for the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones. *J. Iran. Chem. Soc.*, 14 (2017) 1179-1188.

[60] M. Piltan, Preparation of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones using ZrO2 nanoparticles as a catalyst under solvent-free conditions. *Heterocycl. Commun.*, 23 (2017) 401-403.

[61] D. Azarifar, O. Badalkhani, Y. Abbasi and M. Hasanabadi, Urea-functionalized silica-coated Fe3−xTixO4 magnetic nanoparticles: as highly efficient

and recyclable heterogeneous nanocatalyst for synthesis of 4H-chromene and 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives. *J. Iran. Chem. Soc.*, 14 (2017) 403-418.

[62] F. Ghobakhloo, D. Azarifar, M. Mohammadi, H. Keypour and H. Zeynali, Copper(II) Schiff-Base Complex Modified UiO-66-NH2(Zr) Metal–Organic Framework Catalysts for Knoevenagel Condensation–Michael Addition–Cyclization Reactions. *Inorg. Chem.*, 61 (2022) 4825-4841.

[63] M. Nesarvand, D. Azarifar and H. Ebrahimiasl, One-pot and green synthesis 1H-pyrazolo[1,2-b]phthalazine-5,10-dione and dihydropyrano[3,2-c]chromene derivatives by Fe3O4@SiO2-imine/phenoxy-Cu(II) as an efficient and reusable catalyst. *Res. Chem. Intermed.*, 47 (2021) 3629-3644.

[64] H. Ebrahimiasl, D. Azarifar, M. Mohammadi, H. Keypour and M. Mahmood abadi, Synthesis of Fe3O4-supported Schiff base Cu (II) complex: a novel efficient and recyclable magnetic nanocatalyst for one-pot three-component synthesis of quinolin-5-one, chromene-3-carbonitrile and phthalazine-5,10-dione derivatives. *Res. Chem. Intermed.*, 47 (2021) 683-707.

[65] A. Bashti, A. R. Kiasat and B. Mokhtari, Synthesis and characterization of dicationic 4, 4′-bipyridinium dichloride ordered mesoporous silica nanocomposite and its application in the preparation of 1 H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives. *RSC Adv.*, 5 (2015) 25816-25823.

[66] S. R. Shafe-Mehrabadi, B. Sadeghi and A. Hassanabadi, SiO2–H2SO4 Nanoparticles: A Solid Phase Acidic Catalyst and an Efficient for One-Pot Synthesis of 3,9-Diamino-5,10-dioxo-1-aryl-5,10-dihydropyrazolo[1,2-b]phthalazine-2-carbonitrile Derivatives. *Polycyclic Aromat. Compd.*, 42 (2022) 574-581.

[67] N. Sharma, B. Chowhan, M. Gupta and M. Kouser, NiFe 2 O 4@ B, N, F-tridoped CeO 2 (NFTDNC): a mesoporous nanocatalyst in the synthesis of pyrazolopyranopyrimidine and 1 H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives and as an adsorbent. *Dalton Transactions*, 51 (2022) 13795-13807.

[68] T. Parvin, R. Yadav and L. H. Choudhury, Recent applications of thiourea-based organocatalysts in asymmetric multicomponent reactions (AMCRs). *Org. Biomol. Chem.*, 18 (2020) 5513-5532.

[69] M. Barge, G. Rashinkar, D. Kanase, S. Mohite and T. Lohar, One-drop organocatalyzed multicomponent synthesis of pyrazolo[1,2-b]phthalazine-diones and pyrazolophthalazinyl quinolines. *Res. Chem. Intermed.*, 48 (2022) 5045-5058.

[70] A. Farahanipour, H. Bavandi, M. Shahedi and Z. Habibi, Synthesis of 1H-Pyrazolo[1,2-b]Phthalazine-5,10-Dione and 1H-Pyrazolo[1,2-a]Pyridazine-5,8-Dione Derivatives by Bovine Serum Albumin in Water. *Polycyclic Aromat. Compd.* (2023) https://doi.org/10.1080/10406638.2022.2128829.

[71] K. S. Dalal, Y. A. Tayade, Y. B. Wagh, D. S. Dalal and B. L. Chaudhari, Lipase-mediated multicomponent synthesis of 1H-Pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives in a binary solvent medium. *Biotechnol. Appl. Biochem.*, 69 (2022) 2017-2027.

[72] F. Mohamadpour, 1, 8-Diazabicyclo [5.4. 0] undec-7-ene (DBU): as a highly efficient bicyclic amidine catalyst promoted solvent-free and one-pot synthesis of 1 H-pyrazolo [1, 2-b] phthalazine-5, 10-dione derivatives. *Indian J. Chem.*, 59B (2020) 1234-1242.

[73] E. Lamera, S. Bouacida, H. Merazig, A. Chibani, M. L. Borgne, Z. Bouaziz and A. Bouraiou, DMAP as a new efficient catalyst for the one-pot synthesis of condensed phthalazines. *Z. Naturforsch. B*, 72 (2017) 361-368.

[74] Y. A. Tayade and D. S. Dalal, β-Cyclodextrin as a Supramolecular Catalyst for the Synthesis of 1H-Pyrazolo[1,2-b]phthalazine-5,10-dione Derivatives in Water. *Catal. Lett.*, 147 (2017) 1411-1421.

[75] S. S. Oliaei, D. Habibi, S. Heydari, R. Karamian and S. Ghasemian Sorboni, Unexpected synthesis of 4-(4,5-dihydro-1H-imidazol-2-ylsulfanyl)butyl-H-sulfite as a catalyst for the synthesis of pyrazolophthalazines. *Mol. Divers.* (2023) https://doi.org/10.1007/s11030-022-10563-w.

[76] V. Unnikrishnan, G. Avudaiappan, S. Swathy, P. K. Shenoi and K. Sreekumar, Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives using dendritic polymer with amine-loaded catalytic capsules: computational approaches. *Polym. Bull.*, 80 (2023) 2835-2853.

[77] M. Hamidinasab, M. Ghasemi and M. A. Bodaghifard, Zeolite-based hybrid material as an efficient promoter in the green synthesis of mono/bis-phthalazinones. *Synth. Commun.*, 51 (2021) 3435-3448.

[78] O. S. Zaky, M. A. Selim, M. M. Ebied and K. U. Sadek, Glycerol: A Promising Benign Solvent for Catalyst-free One-pot Multi-component Synthesis of 1H-Pyrozolo[1,2-b]phthalazine-5,10-diones and 2H-Indazolo[2,1-b]phthalazine-triones Under Controlled Microwaves Irradiation. *J. Heterocycl. Chem.*, 56 (2019) 2796-2803.

[79] F. Mohamadpour, M. T. Maghsoodlou, R. Heydari and M. Lashkari, Saccharin: a green, economical and efficient catalyst for the one-pot, multi-component synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives and 1H-pyrazolo [1,2-b] phthalazine-5,10-dione derivatives and substituted dihydro-2-oxypyrrole. *J. Iran. Chem. Soc.*, 13 (2016) 1549-1560.

[80] S. Yan, X. Jiang, Z. Wang, S. He and W. Zhang, Zinc–proline complex as a novel and efficient catalyst for the green synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones. *Res. Chem. Intermed.*, 48 (2022) 2413-2427.

[81] P. B. Hiremath and K. Kamanna, Microwave-Accelerated Facile Synthesis of 1H-Pyrazolo[1,2-b]Phthalazine-5,10-Dione Derivatives Catalyzed by WEMPA. *Polycyclic Aromat. Compd.*, 42 (2022) 2162-2178.

[82] C. S. Maheswari, R. Ramesh and A. Lalitha, Antibacterial Evaluation of Some 3-Amino-1H-Pyrazolo[1,2-b]Phthalazine-2-Carboxamides by using

Fish Scale Hydroxyapatite as a Heterogeneous Catalyst. *Polycyclic Aromat. Compd.*, 41 (2021) 2221-2237.

[83] M. Lashkari, R. Heydari and F. Mohamadpour, A Facile Approach for One-Pot Synthesis of 1H-pyrazolo [1,2-b]phthalazine-5,10-dione Derivatives Catalyzed by ZrCl4 as an Efficient Catalyst Under Solvent-Free Conditions. *Iran. J. Sci. Technol. Trans. A: Sci.*, 42 (2018) 1191-1197.

[84] A. M. Jadhav, S. G. Balwe, J. S. Kim, K. T. Lim and Y. T. Jeong, Indium(III)chloride catalyzed synthesis of novel 1H-pyrazolo[1,2-b]phthalazine-5,10-diones and 1H-pyrazolo[1,2-a]pyridazine-5,8-diones under solvent-free condition. *Tetrahedron Lett.*, 60 (2019) 560-565.

[85] C. B. Sangani, J. A. Makwana, Y.-T. Duan, N. J. Thumar, M.-Y. Zhao, Y. S. Patel and H.-L. Zhu, Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives: assessment of their antimicrobial, antituberculosis and antioxidant activity. *Res. Chem. Intermed.*, 42 (2016) 2101-2117.

[86] N. Kerru, L. Gummidi, S. V. H. S. Bhaskaruni, S. N. Maddila and S. B. Jonnalagadda, One-pot green synthesis of novel 5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine derivatives with eco-friendly biodegradable eggshell powder as efficacious catalyst. *Res. Chem. Intermed.*, 46 (2020) 3067-3083

[87] H. Kefayati, A. Delafrooz and S. Homayoon, Ultrasound-assisted synthesis of pyrazolo[1,2-b]phthalazines and dihydrospiro[indoline-3,1'-pyrazolo[1,2-b]phthalazines] using TBAF as an efficient phase-transfer catalyst. *Russ. J. Gen. Chem.*, 86 (2016) 1735-1740.

[88] F. Mohamadpour, M. T. Maghsoodlou, R. Heydari and M. Lashkari, Copper(II) acetate monohydrate: an efficient and eco-friendly catalyst for the one-pot multi-component synthesis of biologically active spiropyrans and 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives under solvent-free conditions. *Res. Chem. Intermed.*, 42 (2016) 7841-7853.

[89] M. Abdesheikhi and Z. Karimi-Jaberi, Four-component synthesis of 3-amino-1-aryl-5,10-dioxo-1H-pyrazolo[1,2-b] phthalazine-2-carbonitrile derivatives promoted by potassium carbonate. *J. Chem. Research*, 39 (2015) 482-483.