

Recent advances in synthesis of aminopyrazole carbonitriles and applications

Received: 9 May 2026

Accepted: 10 August 2026

Published online: 23 August 2026

Cite this article as: Farooq S. & Ngaini Z. Recent advances in synthesis of aminopyrazole carbonitriles and applications. *Discov Appl Sci* (2026). <https://doi.org/10.1007/s42452-026-09395-2>

Saba Farooq & Zainab Ngaini

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

Recent Advances in Synthesis of Aminopyrazole Carbonitriles and Applications

Saba Farooq^{1*} , Zainab Ngaini^{1*} 

¹ Faculty of Resource Science and Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia.

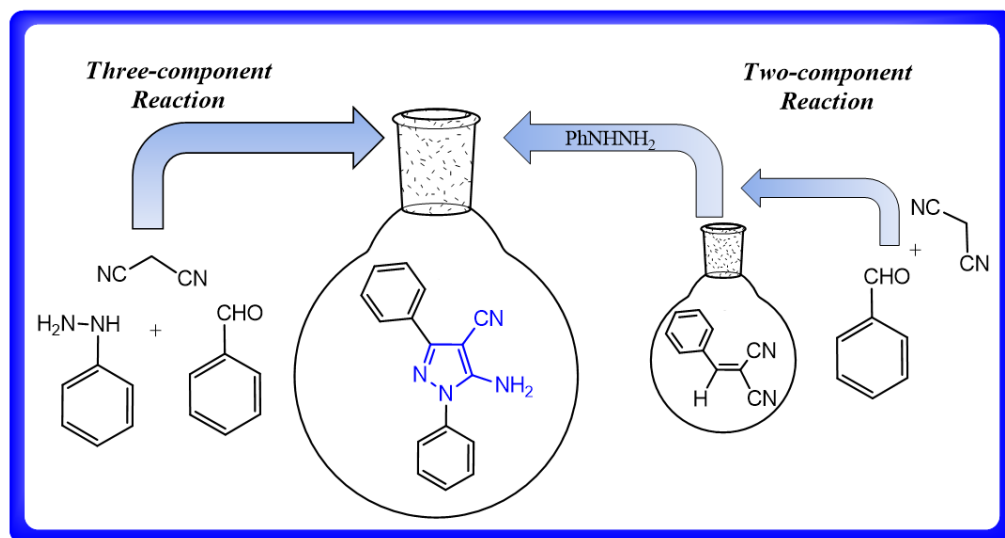
*Corresponding author: sabafarooq61@yahoo.com & nzainab@unimas.my

Abstract

Heterocyclic nitrogen-based compounds, particularly aminopyrazole carbonitriles, have gained significant research interest due to their diverse applications in pharmaceuticals, electronics, and other fields. The synthesis is facilitated by the availability of reagents through one-pot and two-pot approaches. The one-pot synthesis follows a three-component reaction in a single step, yielding the desired product efficiently with high atom economy and significantly reduced reaction times. In contrast, the two-pot synthesis involves formation of intermediate arylidenemalononitrile *via* Knoevenagel condensation, which is subsequently treated with hydrazine derivatives to generate pyrazole derivatives. This review provides a comprehensive analysis of the recent synthesis advances (2013-2026) in the synthesis of aminopyrazole carbonitriles focusing on one-pot multicomponent reactions and sequential two-pot strategies under mild catalytic or non-catalytic conditions, including solvent and solvent-free systems. We evaluate a range of synthetic media from solvent-free to aqueous media exploiting the salting-out effect. The scope of applications is extensively discussed, from documented anti-HIV, antimicrobial and cytotoxic activities to industrial roles in crop protection and steel corrosion inhibition. The review highlights the trend towards sustainable high-yield protocols and identifies challenges remaining in the field.

Keywords: Amine, Condensation, Hydrazine, Knoevenagel, Pyrazole, Solvent-free

Graphical Abstract



Introduction

Multicomponent reactions (MCRs) are distinctive to design versatile heterocyclic structures *via* multicomponent synthesis [1–4]. Five-membered heterocyclic ring compounds of pyrazoles having two nitrogen atoms [5],[6],[7],[8],[9], and two double bonds were first time reported by the German chemist Ludwig Knorr in 1883 [10]. Pyrazole and its derivatives have attained significant attention because of their broad applications [11],[12],[13] as antioxidant [14],[15],[16],[17], antimicrobial[18],[19], antiviral [20], anti-inflammatory [21], antibacterial [22], anticancer [23],[24],[25], acaricidal [26], herbicidal and insecticidal activities [27],[28]. Pyrazoles are also used in coordination and material chemistry due to their optical and elastic properties [29]. Aminopyrazole carbonitriles is one of the commonly reported pyrazoles with alternative names of enaminonitrile pyrazole [30], 5-aminopyrazole-4-carbonitriles, 3-amino-4-cyanopyrazole, 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile, 5-amino-1,3- diphenylpyrazole-4-carbonitrile and 5-amino-1-phenyl-3-phenyl-1H-pyrazole-4-carbonitrile and fascinating properties in biological and catalytic properties. Aminopyrazoles are the main reagents that lead to fused pyrazoles [31],[32].

Pyrazoles [33],[34],[35] are conveniently prepared from the multi-component reaction of malononitrile, aromatic aldehydes and phenylhydrazine derivatives [36],[37]. The multi-component reaction procedure was deemed noteworthy for its advantageous features, including easy one-step execution without byproducts, a short reaction time, energy conservation, and solvent provision, resulting in a high yield of synthesised products [38],[39]. Multi-component

synthesis of 5-amino-1H-pyrazole-4-carbonitriles has been conveniently reported using numerous catalysts such as $\text{Glu@Fe}_3\text{O}_4$ [40], $[\text{4CSPy}]\text{ZnCl}_3$ [41], $(\text{Bim})\text{OH}$ [38], BNPs-sulfamic acid [42], CPS-CDMNP [43], $[\text{HMIM}]\text{C}(\text{NO}_2)_3$ [44] and sodium ascorbate [45]. Due to the medical, industrial, and biological applications of 5-amino-1H-pyrazole-4-carbonitrile derivatives, improvements to their preparation procedures and the synthesis of derivatives using alternative reagents or methods remain valuable. Rimobant, celecoxib [46],[47], fomepizole, betazole [48] and fezolamine are a few examples of marketed pyrazole medications (**Figure 1**). Additionally, aminopyrazoles and their derivatives have been utilised in pesticides, insecticides [49], CRF-1 Antagonists, GABA inhibitors, and antifungal drugs [50].

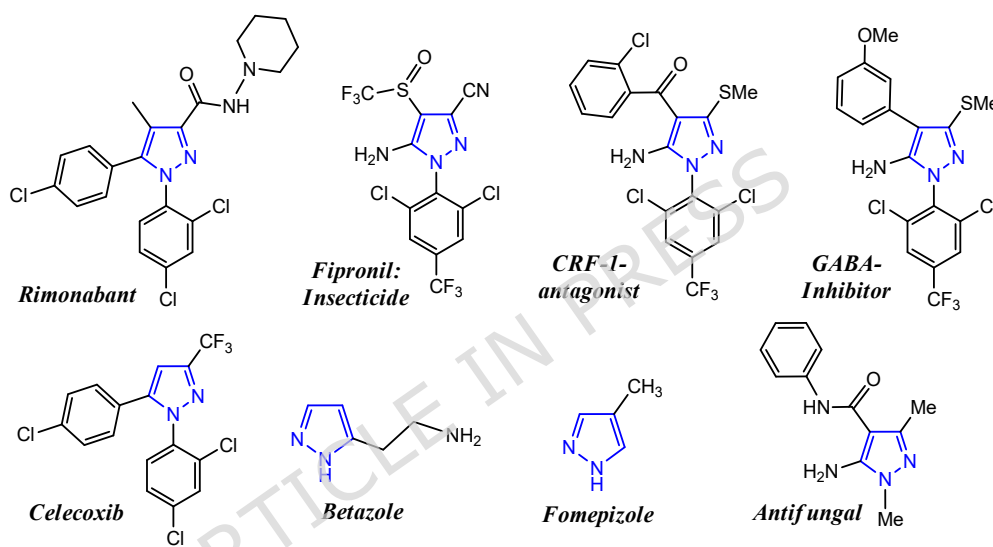


Figure 1: Pyrazole derivatives as commercial drugs [50]

A complete literature search was conducted to explore the aminopyrazole carbonitrile synthesis and biological applications. A systematic search of databases including Scopus, Reaxys, PubMed, SpringerLink, and Google Scholar was conducted. The search utilised specific keywords including “5-aminopyrazole-4-carbonitrile”, “5-aminopyrazole carbonitrile”, “aminopyrazole carbonitrile”, “aminopyrazole carbonitrile derivatives,” and “applications of aminopyrazole carbonitrile”. The search generated an estimated 200 peer-reviewed articles related to synthesis and applications of aminopyrazole carbonitrile, with 118 articles cited in the final review. Whereas focused books on aminopyrazole carbonitrile were limited, journal publications delivered broad insights into their synthesis and applications. The exclusion criteria covered review articles, non-peer-reviewed studies, conference abstracts and irrelevant publications to the primary topic.

The synthesis and application of generic pyrazole derivatives have been extensively discussed in earlier publications [51],[52],[53]. In general, **Figure 2** shows that two-component approaches have also been reported for the synthesis of multisubstituted pyrazoles. Among these, the three-component approach is preferred due to the use of stable, commercially available reagents [54],[55],[56],[57],[58]. In the literature, numerous methods have been reported for the synthesis of substituted pyrazole [59] by using three components of substituted aldehyde, malononitrile, and phenylhydrazine [60] in different conditions [61],[62],[63] and applications [64],[65],[66]. This review encompasses the recent advanced 5-amino-1H-pyrazole-4-carbonitriles synthesis utilising various reagents or methods, derivatization and their application. This information was not previously addressed and is crucial for transforming organic molecules into stable products and reagents for the synthesis of new derivatives.

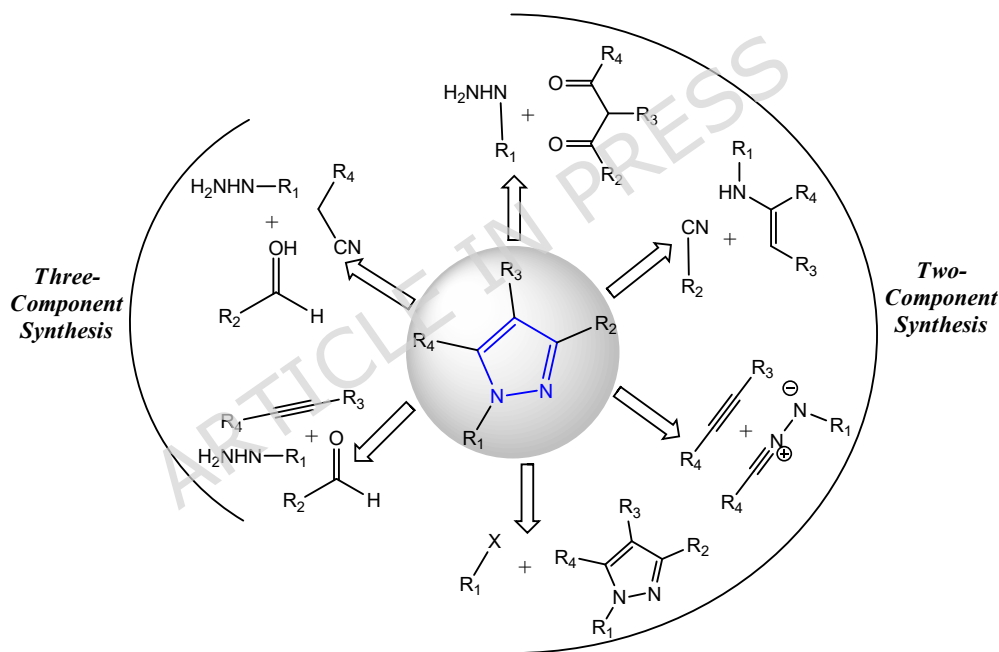


Figure 2: Aminopyrazole carbonitriles as multi-substituted pyrazoles synthesis [54]

This review specifically focuses on the recent synthetic strategies and the pharmacological/industrial roles of these derivatives in antimicrobial, antiviral, anticancer, crop protection, and corrosion inhibition fields.

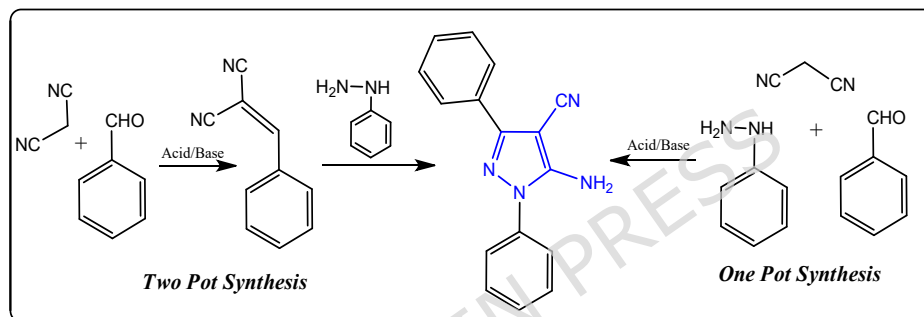
Synthesis of Aminopyrazole Carbonitriles

Plausible Reaction Mechanism

The synthesis of aminopyrazole carbonitrile derivatives has been reported in the presence of acidic [67] and basic catalysts *via* one-pot synthesis and two-pot synthesis [68] (**Scheme 1A**).

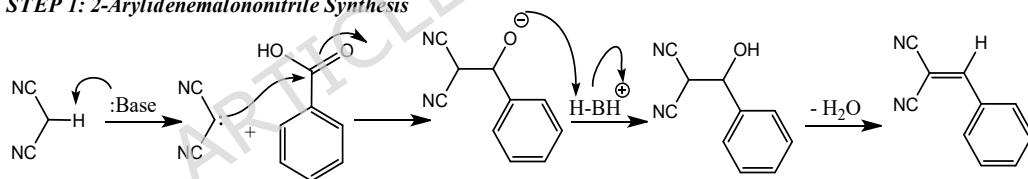
In general, the plausible reaction mechanism for 5-amino-1H-pyrazole-4-carbonitriles involves a two-step synthesis (**Scheme 1B**). The first step involved deprotonating the methylene nitrile, followed by its conversion to a malonate carbanion [36]. The carbanion acted as a nucleophile and reacted with the aldehyde *via* Knoevenagel condensation to form a 2-arylidene malononitrile intermediate as a Knoevenagel adduct [69]. Finally, hydrazine hydrate or phenylhydrazine reacted with the Knoevenagel adduct to form the corresponding cyclic pyrazole (**1**) *via* Michael addition [43].

A) Synthesis of Aminopyrazole-4-carbonitriles

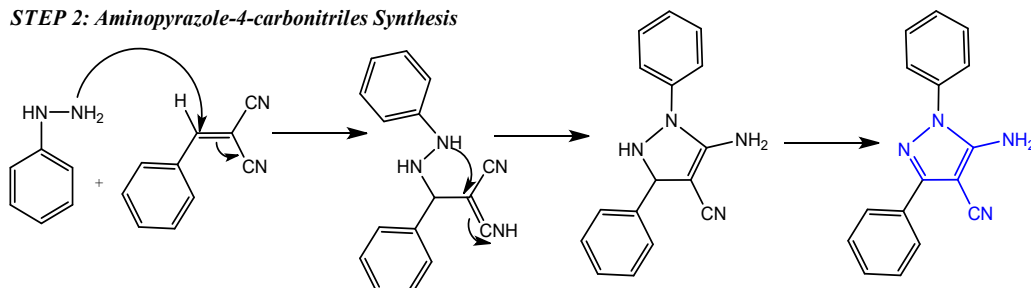


B) Proposed Mechanism for Aminopyrazole-4-carbonitriles Synthesis

STEP 1: 2-Arylidene malononitrile Synthesis



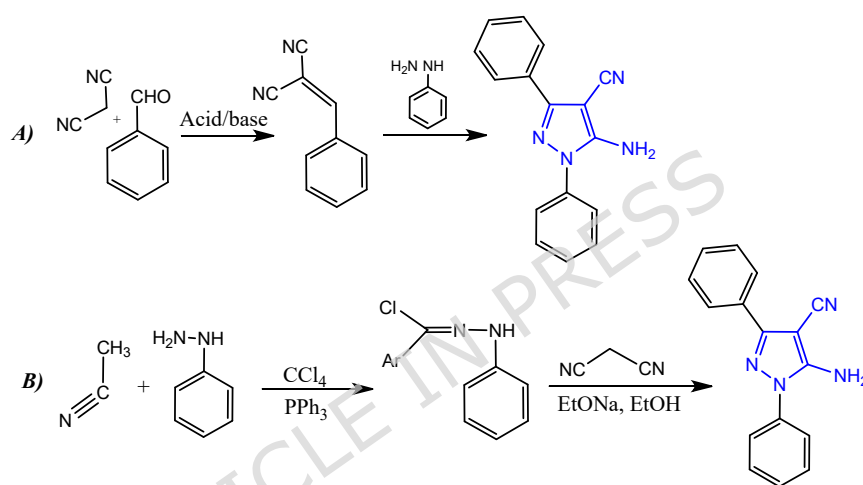
STEP 2: Aminopyrazole-4-carbonitriles Synthesis



Scheme 1: General one-pot and two-pot synthesis of aminopyrazole carbonitriles (**A**) and its plausible reaction mechanism (**B**)

Besides one-pot synthesis, aminopyrazole carbonitrile derivatives have also been widely synthesised *via* two-pot synthesis. The strategy involves forming arylidenemalononitrile from an

aldehyde and malononitrile, which is then further reacted with hydrazine derivatives to yield pyrazole derivatives. The formation of benzylidene malononitrile [70] led to a reaction with phenylhydrazine (**Route A, Scheme 2**) [48] in a different solvent and catalyst to achieve a good yield of pyrazole. Hassaneen *et al.* (2019) have reported another method that uses two pot synthesis from hydrazine, triphenylphosphine and carbon tetrachloride in acetonitrile to achieve *N*-phenyl-substituted benzenecarbohydrazonoyl chlorides [71], which were further treated with malononitrile with the aid of sodium ethoxide in ethanol to form 5-amino-1,3-diphenyl-pyrazole-4-carbonitrile (**Route B, Scheme 2**) [68],[72]. Both strategies are effective in achieving a high pyrazole yield.



Scheme 2: Synthesis of pyrazole *via* malononitrile (**A**) and hydrazine derivatives (**B**)

Three-Component Reaction

A wide variety of protocols have been employed for one-pot synthesis utilizing diverse acidic and basic catalysts in different reaction media, times, and temperatures. An example of an acidic-catalysed protocol involved the synthesis of pyrazole derivatives of benzylidene malononitrile. The synthesis was intriguingly produced *in situ* by employing aldehyde, hydrazine, and malononitrile in a one-pot synthesis [42]. A wide variety of protocols have been employed for one-pot synthesis in different reaction media, times, and temperatures, as detailed in **Table 1**. Ghorbani *et al.* reported a solvent-free three-component condensation reaction of benzaldehyde, phenylhydrazine, and malononitrile at different temperatures using various solvents and varying amounts of catalyst. The best yield was achieved (95% in 7 min) in an equivalent mole ratio of phenylhydrazine, benzaldehyde, and malononitrile (1:1:1) using an acidic catalyst

[Fe₃O₄@CQDs@Si(CH₂)₃NH@CC@TET@SO₃H] at 70°C in solvent-free conditions. Both homogeneous and heterogeneous catalysts are available in the synthesis of pyrazoles. The latter is known for being extremely soluble, stable, and active during the reaction [73]. Magnetic nanoparticles (NPs) offer several advantages for organic reactions, including the ability to remove catalysts quickly *via* filtration or magnets. The production is cheap, simple, cost-effective, controllable, and scalable. Stable catalytic bonds enable the utilisation of eco-friendly solvents [74].

Table 1: Synthesis of aminopyrazole carbonitriles under various reaction conditions

Synthesis approach	Catalysts	Time (min)	Solvent	Temperature (°C)	Yield (%)	Reference
One-Pot	[Dsim][TFA]	5		80	90-95	[75]
	Fe ₃ O ₄ @CQDs@Si(CH ₂) ₃ NH@CC@TET@SO ₃ H	7		70	95	[73]
	-	5-7		rt	85	[76]
	[HMIM]C(NO ₂) ₃	10		rt	95	[44]
	[Msim]CuCl ₃	10		60	83	[77]
	[CSPy]ZnCl ₃	30	Solvent-free	80	60-98	[41]
	m-SABNPs	45		80	95	[42]
	-	60		-	95	[39]
	Fe ₃ O ₄ @SiO ₂ @Tannic acid MNPs	120-150		rt	87-95	[78]
	Fe ₃ O ₄ @SiO ₂ /NH/CC/2APy/CuII	7		30	90	[79]
	SPVA	180		90	89	[37]
	Alumina-MnO ₂ /SDBS	3-12		30	91	[80]
	Alum: H ₂ O (10%)	60-180		rt	93	[81]
	I ₂	7		60	91	[82]
	(Bmim)OH	15		-	96	[38]
	NaCl-H ₂ O	18-20		rt	95	[83]
	CuO/ZrO ₂	90	H ₂ O	40	92	[84]
	GO-TiO ₂	10-20		rt	96	[85]
	NaPTS	30		24	92	[86]
	Glut@Fe ₃ O ₄	60		rt	95	[40]
	PEG-400	20		rt	99	[87]
	DABCO	10		rt	93	[36]
	Sodium ascorbate (SA)	10		50	98	[45]
	Pec-DAP-BS	30		50	96	[46]
	PPI	5	EtOH: H ₂ O	50	95	[50]
	TA-DAP@PMA	15		55	95	[88]
	Biochar/ZnO	5		50	97	[89]
	Calcined Mg-Fe Hydrotalcite	8		rt	96	[90]
	Fe ₃ O ₄ @Alg@CPTMS@Arg	10		70	95	[91]
	Eosin Y/ visible light, air,	5-15	EtOH	rt	95	[92]
	Fe ₃ O ₄ @SiO ₂ -NH ₃ [W ₆ O ₁₉]	25		rt	94	[93]
	NiFe ₂ O ₄	8		29	96	[94]
Two-Pot	CPS-CDMNPs	1	MeOH	rt	81.45	[43]
	AlCl ₃	30	DCE	80	83	[34]
	-	10	Glucose/urea (1:5)	rt	85	[95]
	CAN	5	PEG-400:H ₂ O (4:1)	rt	89-95	[96]
	-	10	H ₂ O	rt	89	[48]
	EtONa	15	EtOH	20	80	[68],[72]

* Units standardized; Solvent free catalyst free denoted with (-)

Khazaei *et al.* (2022) reported a one-pot synthesis of pyrazoles utilising aromatic aldehyde, malononitrile and $[\text{Msim}]\text{CuCl}_3$ as acid catalyst (2 mol%) at 60°C for 3 min after reflux. Phenylhydrazine was added and allowed to sit at 60 °C for 10-15 min under solvent-free conditions [77]. Bakhtiarinet *et al.* (2024) reported that in some cases, solvent- and catalyst-free conditions are not significantly effective for pyrazole synthesis even after prolonged reaction time. Acid catalysts, namely Pec-DAP-BS and a solvent mixture of EtOH/H₂O (1:1), are nevertheless required to achieve the highest yield within 30 min [46]. Other catalysts, such as DABCO, have also been used in a one-pot synthesis in the same solvent EtOH/H₂O [36]. Additionally, another effective acidic system includes sulfonic acid-functionalized polyvinyl alcohol (SPVA), which facilitates the reaction at 90°C with benzaldehyde and malononitrile to produce a solid product, which was then treated with phenylhydrazine to produce 89% yield [37].

Another acid-catalysed reaction has been reported on the synthesis of pyrazole 4-carbonitrile. Bioorganic catalysts (*i.e.*, vitamin B1, glycine), acidic or phase-transfer catalysts (*i.e.*, HCl, PTSA, $\text{SO}_4^{2-}/\text{ZrO}_2$, K_2CO_3) and nonacidic salts (*i.e.*, NaCl, NaBr, NaI) have been reported to produce higher yields. Higher yields were obtained with NaCl in water than with DMF, ethanol, or methanol. The NaCl selectivity was due to the sodium ion's smaller size compared to the potassium ion, thereby resulting in a larger hydration sphere and higher cohesive energy through interaction with water dipoles, which in turn affects the structure and increases the viscosity of the medium [83]. Moreover, the hydrophobic interaction increases due to collisions and interactions between the aqueous medium and organic components [97]. The presence of NaCl in water leads to stronger solute-solute interactions than solute-solvent interactions, altering the hydration spheres of Na^+ and Cl^- ions and reducing the availability of water molecules for organic components. Consequently, this salting-out effect is more pronounced with NaCl [98].

The use of base catalysts has been well documented for the one-pot synthesis of aminopyrazole carbonitriles with rapid reactions under relatively mild conditions (**Table 1**). A striking example is potassium phthalimide (PPI), which is a very efficient promoter producing 95% yield in only 5 min at 50°C. Other simple systems such as DABCO have been successfully employed in ethanol-water mixtures at room temperature to afford 93% yields. Several other bases of different nature such as Et_3N , NaOH, DBU and K_2CO_3 were also reported. Nevertheless, they often give similar yields at room temperature with no significant change in efficiency. In some solvent-free grinding

approaches, it is interesting to note that the phenylhydrazine reagent can play a dual role as a nucleophile and a Brønsted base catalyst in situ, promoting the cyclisation reaction without the requirement of any extra basic additives. Moreover, non-acidic salts such as NaCl have been reported to improve the yields (up to 95%) in aqueous media by increasing the interaction between solutes due to the salting-out effect, which is crucial for the collision of molecules required for the formation of products.

Bale *et al.* (2014) attempted to form aminopyrazoles *via* a simple grinding method using a three-component reaction of aliphatic and aromatic aldehydes, phenylhydrazine, and malononitrile, without a basic catalyst to achieve excellent yields within 5-7 min. The phenylhydrazine functions as both a nucleophile [99] and a catalyst for Brønsted base reaction. Moreover, with the aid of different base catalysts of varying natures, i.e., Et₃N, NaOH, DBU, DABCO, and K₂CO₃, at room temperature, no significant effect was observed on the yield of pyrazole. Additionally, aliphatic aldehydes are less reactive than aromatic aldehydes and do not yield a product in this nucleophilic addition [76].

Various magnetic nanoparticles of heterogeneous catalysts have been successfully used to synthesise pyrazoles with high yields under different conditions. Fe₃O₄@-SiO₂@vanillin@thioglycolic acid MNPs, for instance, have been used as a catalyst to achieve 91-96% yield of azo-pyrazole series [100], while Fe₃O₄@SP@TA catalyst was used to achieve *bis*-pyrazole derivatives [101]. The one-pot synthesis of aminopyrazole carbonitrile derivatives has also been reported under green conditions at room temperature, utilising a grinding method and ultrasound irradiation. Employing the same reagents in water as a solvent for a reaction duration of 15 min to 1 h. The synthesis is reported to yield 95-99% of the desired product.

Two-Component Reaction

The synthesis of 5-amino-1H-pyrazole-4-carbonitriles is most efficiently achieved through a one-pot multicomponent reaction involving hydrazine, malononitrile, and aldehydes [102]. This method is widely preferred over traditional two-step approaches due to its streamlined process, reduced reaction time and elimination of intermediate isolation steps. Two-pot synthesis is based upon the formation of arylidenemalononitrile from aldehyde and malononitrile, which is further treated with hydrazine derivatives to achieve the pyrazole derivatives. While both synthetic strategies can achieve comparable yields under optimised conditions, the one-pot approach offers

practical advantages in terms of operational simplicity and scalability. The two-pot approach is limited by increased reaction times, higher operational complexity, lower efficiency [68],[72] and yields, greater environmental impact, and higher costs due to the need for intermediate isolation and purification steps. Recent advancements have demonstrated that Ultrasound-assisted synthesis further enhances this methodology, improving reaction efficiency, product selectivity and overall yields in the one-pot strategy.

A comparative analysis of the reported synthetic protocols reveals that one-pot multicomponent approaches generally outperform traditional methods in terms of efficiency and yield, with many systems reaching more than 90% yield within significantly reduced reaction times. For instance, the conventional acid catalysts such as SPVA require 180 min at 90°C to give an 89% yield, while advanced nanocatalysts such as CPS-CDMNPs give 81.45% yield in only 1 min at room temperature. The reaction temperatures range from room temperature to 90 °C. Green methodologies such as grinding and ultrasound irradiation suggest that high efficiency (95-99% yield) can be achieved under mild conditions. Solvent effects are also important. The use of NaCl in aqueous media significantly enhances yields *via* the salting-out effect, which increases hydrophobic interactions between organic components.

In contrast, solvent-free conditions such as [Dsim][TFA]) are preferred for their high yields (90–95%) with simple operation. A clear trend is observed in the substrate scope, where aromatic aldehydes are highly reactive whereas aliphatic aldehydes exhibit lower reactivity and often fail to yield products in these nucleophilic additions. Moreover, the method is sufficiently flexible to allow for the use of dialdehydes in the synthesis of *bis*-poly-substituted pyrazoles, and a range of electronic effects are tolerated, as demonstrated by the successful synthesis of both methoxy- (electron-donating) and chloro- (electron-withdrawing) substituted derivatives with potent biological activities. Although specific parameters such as TON/TOF were not consistently reported in the reviewed primary literature, the overall data set points to a shift towards rapid, high-yield and green protocols.

Sustainability and Green Chemistry Assessment

In a detailed sustainability assessment of the reported methodologies, a strategic shift to greener synthetic protocols is currently emphasised. The one-pot three-component approach exhibits more sustainable for synthesis of aminopyrazole carbonitriles scaffold, with water as the main

byproduct. Another two-component approach *via* two-pot strategy, which generates considerable waste in the isolation and purification of the 2-arylidene malononitrile intermediate. Recent literature shows a clear trend in the solvent hierarchy toward the use of solvent-free conditions or aqueous media, instead of hazardous organic solvents. In particular, the use of NaCl in water takes advantage of the salting-out effect, which favours stronger solute-solute interactions and enhances the reaction efficiency without the use of toxic catalysts or solvents. Mechanochemical methods like ball milling and ultrasound irradiation lower energy inputs, yielding high yields (95-99%) at room temperature and considerably decreasing the carbon footprint of the conventional high-temperature reflux (*e.g.*, 90 °C for 180 min). The use of hydrazine derivatives is inherently hazardous, but the change to mild catalytic or non-catalytic conditions reduces the hazards of high-pressure or high-temperature handling. Moreover, the hybridisation of heterogeneous magnetic nanocatalysts allows effective separation by external magnets, thus supporting the recyclability and reducing the catalyst leaching into the environment.

Derivatives and Applications of Aminopyrazole Carbonitriles

The derivatives of 5-aminopyrazole-4-carbonitriles (**1**) were prepared by reacting with dimedone in acidic catalyst trichloroacetic acid *via* the Friedlander-type reaction to achieve pyrazole quinolone (**2**) under solvent-free conditions. Moreover, pyrazole-2-cyanoacetamides (**3**) are achieved from the reaction of 5-aminopyrazole-4-carbonitriles (**1**) and acetic 2-cyanoacetic anhydride. This obtained compound (**3**) was further treated with acetylacetone under reflux in ethanol and catalytic piperidine to form pyrazole pyridine derivatives (**4**) [103]. These derivatives have significant biological and pharmaceutical properties. The fused pyrazole derivatives have attracted the attention of researcher due to their wide applications in medicinal chemistry in recent years [104]. The cyanoamino pyrazole is a unique and versatile scaffold for the synthesis of fused pyrazole heterocycles *via* multicomponent reactions owing to the fascinating reactivity of the reagents. From aminopyrazole, the preparation of aminopyrimidine (**5**) is commonly reported, with numerous protocols utilising malononitrile, trimethylamine, and ethanol, yielding 77% of the product under reflux [105]. Fused pyrimidines (**6 & 7**) have been achieved from the enaminonitrile reaction with pyrazole derivatives in acetic acid under reflux for a long time to achieve 86-89% yield [106]. Another fused pyrazole-imidazole derivative (**8**) was also achieved after a multistep reaction where aminopyrazole carbonitrile and bromoacetophenone reacted to form a protected

pyrazole, which then underwent intramolecular interaction-mediated cyclocondensation of carbonyl and amine groups to form compound **(4)** with 78-90% yield [107] (**Figure 3**).

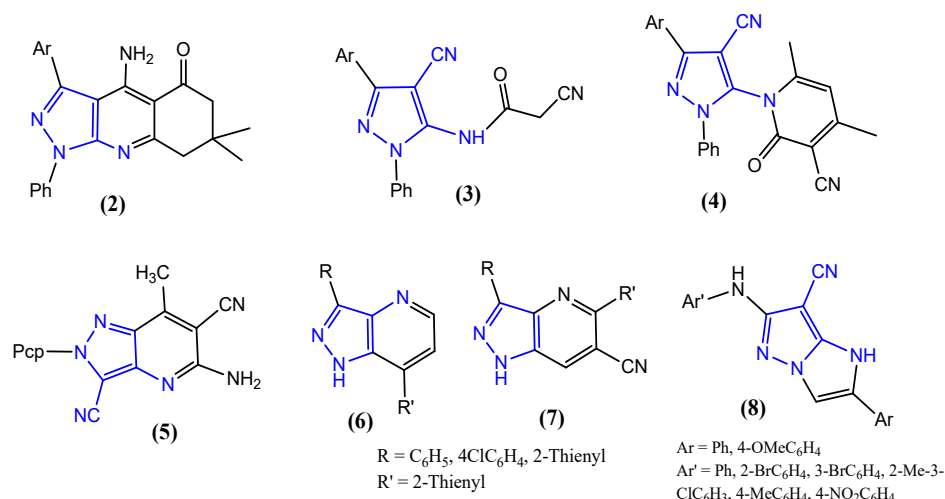


Figure 3: Aminopyrazole-based fused pyrimidines and imidazoles derivatives

Antimicrobial Activities

Hydroxy pyrazoles **(9)** were found to be more potent antifungals, with results of 29.37 mm and 30.67 mm, than the reference standards against the fungal strains *C. albicans* (NCIM 3471) and *A. niger* (NCIM 1028) [48]. Antimicrobial activities against *A. fumigatus*, *C. albicans*, *S. aureus*, *B. subtilis*, *E. coli*, and *P. vulgaris* have been reported for pyrazole derivatives **(10-15)**. Most compounds showed very broad-spectrum inhibitory activity against *S. aureus* (12-20 mm) and *B. subtilis* (8-17 mm), compared to *E. coli* (0-14 mm) [30]. Furthermore, Hassaneen *et al.* (2019) explored the compound **(16)** against *C. albicans*, *A. flavus*, *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*, and reported significant antimicrobial activity for chloro-substituted pyrazole-pyrimidine **(16)** [68].

Multi-substituted amino pyrazoles, including *mono*- and *bis*-pyrazole derivatives **(17-18)**, have also been prepared under green conditions. Similarly, dialdehydes were successfully employed to give *bis*-poly-substituted pyrazoles in excellent yields [54]. Furthermore, pyrazolopyrimidine **(19)** has been prepared and exhibits superb activity against microbes and cancer cells, similar to that of anthracene. The anthracene-substituted compound **(19)** showed better activity against the standard drug ampicillin against *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. subtilis*. Methoxy-substituted compounds **(19)** exhibited potent cytotoxic activity against human skin cancer cells HFB4

[108],[109]. Under microwave, triazine derivatives (**20**) have also been designed [56] (**Figure 4**). One-pot synthesis reported for compound (**21**) by Beyzaei *et al.* in 2017, by the glycerol/K₂CO₃ (4:1) as deep eutectic solvent (DES): H₂O (2:1) used to achieve 84-91% yield of product [110]. Compound **21** exhibited antimicrobial activity against *S. pyogenes* and *P. vulgaris*, among which the *p*-methoxy derivative (**21**) showed effective outcomes [110]. The dichloromethane derivative (**21**) exhibited antifungal activity.

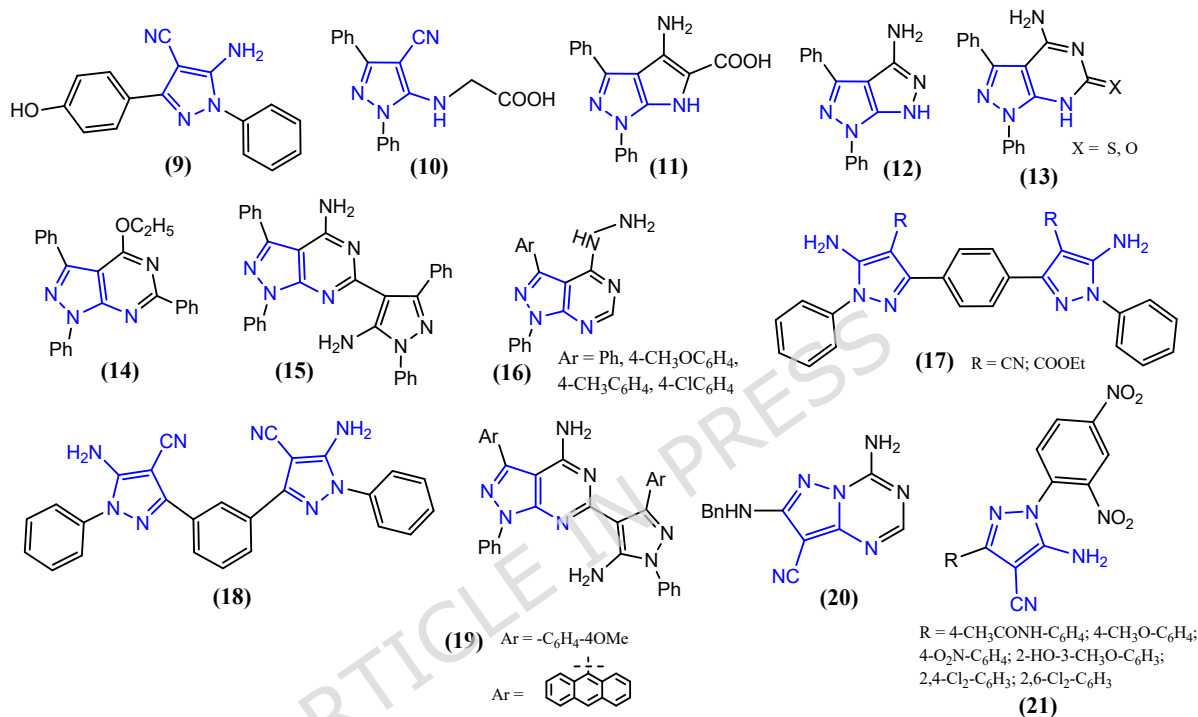


Figure 4: Aminopyrazole derivatives as antimicrobial agents

Crop Protection and Steel Erosion Activities

In 2015, Pelin and coworkers designed the pyrazole using (ethoxymethylene)malononitrile in absolute ethanol and refluxed the mixture for 0.5-4 h to yield 47-84% of the product. Compound (**1**) exhibited crop protection [111] and biological applications [112]. 4-Cyano-5-aminopyrazole derivatives were converted to Schiff base derivatives (**22**) with benzaldehyde in acidic media at room temperature under stirring to achieve 40-67% yield. Furthermore, the 1,2,4-triazine derivatives (**23**) were synthesised *via* a Diels-Alder reaction that reacted with Schiff-based derivatives and diarylidene hydrazine under microwave irradiation (700 W) within 5-10 min to obtain higher 55-89% yield (**22** and **23**) [113]. The corrosion inhibition efficiency of compounds

24, 25, and 26 has been evaluated through gravimetric measurements, which revealed high inhibition efficiencies of 90.34%, 92.04%, and 95.45%, respectively, at a concentration of 7.69×10^{-4} M. Pyrazole derivatives **24-26** contributed to increased charge-transfer resistance as corrosion inhibitors for the corrosion process. Surface morphological studies have shown the formation of a protective surface film that inhibits corrosion in aggressive solutions [114] (**Figure 5**).

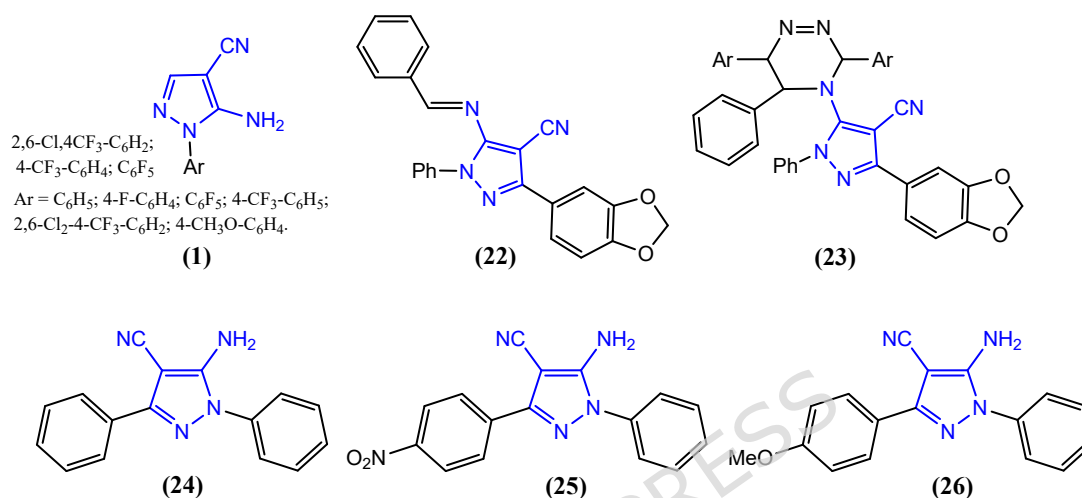


Figure 5: Aminopyrazole derivatives as crop protection and steel erosion agent

Anti-HIV, Anti-influenza and Cytotoxic Activities

Mizuhara *et al.* (2013) have also prepared a series of aminopyrazole derivatives, **27**, **28**, and **29**, which exhibited anti-HIV activity. Diazo compound (**27**) can be metabolised broadly by both extra- and intracellular enzymatic modules of intestinal bacteria. The diazenyl group was replaced with aminomethylene groups, yielding the compounds **28** and **29**, which contributed to an increase in activity. The substituents on the pyrazole and phenolic rings are important for potent anti-HIV activity. This optimisation contributed to a six-fold increase in the anti-HIV activity of the compound (**29**) compared to the lead compound (**27**) [115]. The aminopyrazole derivatives **30** and **31** were reported and analysed for their anti-influenza activity against the A virus (subtype H5N1) *in vitro*. Viral reductions were observed with compounds **30** and **31**, which exhibit essential antiviral activity against H5N1 avian influenza, resulting in 85-65% reduction in viral load [116]. While aminopyranopyrazole nitriles (**32a** & **32b**), obtained from 5-aminopyrazole with a chloro substituent, exhibited cytotoxic activities against breast cancer cells, antibacterial activities against *S. aureus*, *S. epidermidis*, and *P. aeruginosa*, and antifungal activities against *A. niger* and *A.*

brasiliensis. Among all compounds, **32a** showed the most promising results, with a CC_{50} of $7.5 \pm 2.04 \mu\text{g/mL}$ against breast cancer cells (MCF-7) [117],[118] (**Figure 6**).

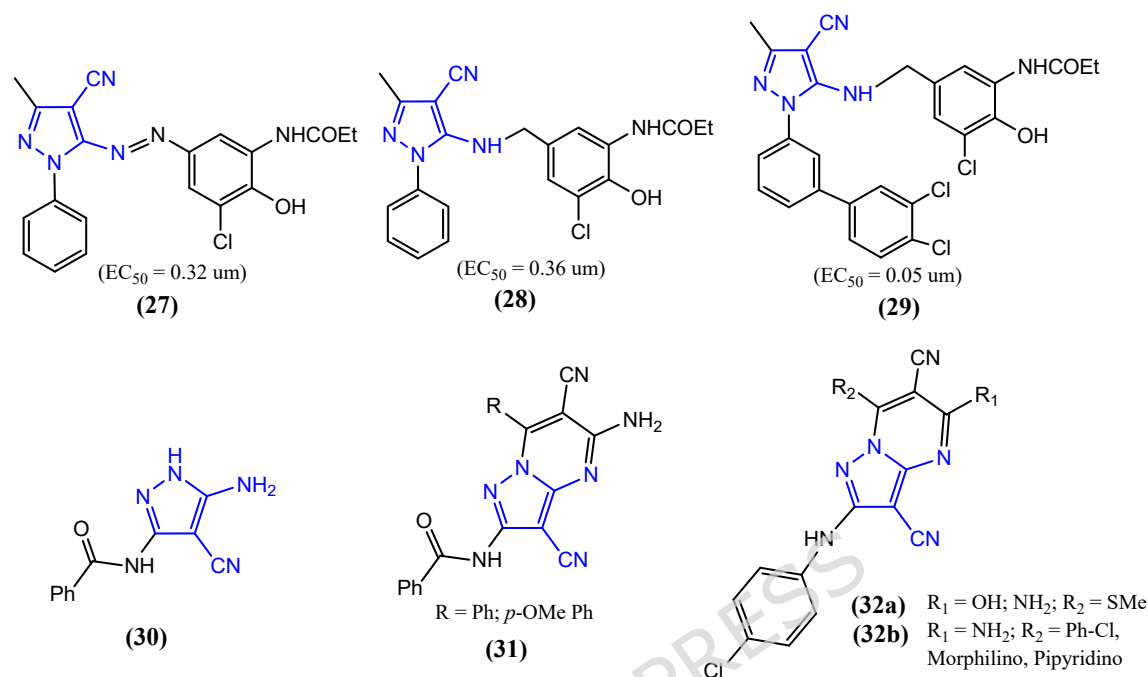


Figure 6: Aminopyrazole derivatives as anti-HIV, anti-influenza and cytotoxic agent

Limitations and Future Outlook

Although the synthesis of aminopyrazole carbonitriles has made considerable progress, some limitations still exist in the present literature. A major gap is the lack of standardised quantitative data. Many studies do not include key green chemistry metrics such as E-factors, atom economy, and turnover number/frequency (TON/TOF), which prevents rigorous cross-protocol comparisons. MNPs and bio-organic catalysts such as Vitamin B1 are simple and scalable in recovery procedures for reproducibility and scalability, however the performance of these systems can be sensitive to specific reaction conditions. Another limitation is the substrate scope as most successful protocols are optimised for aromatic aldehydes while aliphatic aldehydes usually exhibit poor reactivity or do not afford products at all. Future directions include designer catalysts capable of accommodating a wider range of aliphatic and heteroaryl substrates. In addition, more robust Structure-Activity Relationship (SAR) studies are necessary to bridge the gap between initial biological screening (e.g., MIC values) and more advanced drug development. Improving the reducibility of complex nanocatalysts and increasing the employment of solvent-free

mechanochemistry approaches is essential for translating these laboratory successes to viable industrial and pharmaceutical applications

Conclusion

Pyrazole-based scaffolds have garnered substantial interest in medicinal chemistry due to their broad pharmacological relevance. Among them, aminopyrazole carbonitriles are versatile and widely used for the synthesis of heterocyclic compounds. Recent advances highlight one-pot and two-pot strategies employing malononitrile, benzaldehyde, and phenylhydrazine as key building blocks. These methods afford efficient, high-yield syntheses of aminopyrazole carbonitrile derivatives with enhanced drug-like potential. This review compiles contemporary synthetic approaches and their relevance in drug discovery. Notably, several derivatives exhibit promising biological activities and structural adaptability. Beyond pharmaceuticals, these compounds hold potential in catalysis, materials chemistry, and molecular functionalization. Their reactivity and modular synthesis position them as valuable leads for future therapeutic development.

List of Abbreviations

(Bmim)OH	1-Methyl-3-butylimidazolium hydroxide
[4CSPy]ZnCl₃	4-Carboxy-1-sulfonylpyridin-1-ium monozinc(II)trichloride
[Dsim][TFA]	1,3-Disulfonic Acid Imidazolium Trifluoroacetate
[HMIM]C(NO₂)₃	1-methylimidazolium trinitromethanide
[Msim]CuCl₃	3-Methyl-1-sulfonic acid imidazolium trichlorido copper (II)
AlCl₃	Aluminium chloride
Alumina–MnO₂/SDBS	Alumina–silica-supported MnO ₂ /sodium dodecyl benzene sulphonate
Biochar/ZnO	Biochar zinc oxide nanocomposite
CAN	Ceric ammonium nitrate
CQDs	Carbon quantum dots
CPS-CDMNP s	Capsaicin coated cyclodextrin
CuO/ZrO₂	Copper (II) oxide / Zirconium dioxide
DABCO	1,4-diazabicyclo[2.2. 2]octane
DCE	1,2-Dichloroethane
Fe₃O₄@Alg@CPTMS@Arg	Alginate iron oxide NPs with 3-chloropropyltrimethoxysilane coated with amino acid L-arginine
Fe₃O₄@SiO₂-NH₃[W₆O₁₉]	Magnetic silica-supported hexatungstate;

Fe₃O₄@SiO₂@Tannic acid MNPs	Tannic acid-functionalized silica-coated Fe ₃ O ₄ nanoparticles
or Fe₃O₄@SP@TA	
Fe₃O₄@SiO₂/NH/CC/2APy/CuII	copper-based nano-magnetic
GO-TiO₂	Graphene oxide-Titanium dioxide
Glu@Fe₃O₄	Glucose-coated iron oxide nanoparticles
I₂	Iodine
m-SABNPs	Boehmite silylpropyl amine sulfamic
NaCl-H₂O	Sodium chloride-water
NaPTS	Sodium <i>p</i> -toluenesulfonate
NiFe₂O₄	Nickel iron oxide nanoparticles
SPVA	Sulfonic acid-functionalized polyvinyl alcohol
SA	Sodium ascorbate
PEG 400	Polyethylene glycol 400
Pec-DAP-BS	Pectin-2,6-diamino pyridine-1,4-butane sultone
PPI	Potassium phthalimide
TA-DAP@PMA	Terephthalaldehyde - 2,6-diaminopyridine based polymeric immobilized phosphomolybdic acid

Acknowledgement

None

Authors Contribution Statement

S.F. conceptualised and wrote the original manuscript. Z.N reviewed the manuscript.

Funding

The authors would like to thank the Ministry of Higher Education Malaysia for financial support through FRGS/1/2025/STG01/UNIMAS/01/1.

Data Availability Statement

Not applicable

Declarations

Ethical approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Competing interests

The authors declare no competing interests

References

1. Javahershenas R, Nikzat S (2024) Recent developments using malononitrile in ultrasound-assisted multicomponent synthesis of heterocycles. *Ultrasonics Sonochemistry* 102:106741. <https://doi.org/10.1016/j.ultsonch.2023.106741>
2. Javahershenas R, Han J, Kazemi M, Jervis PJ (2024) Recent Advances in the Multicomponent Synthesis of Heterocycles using Thiosemicarbazide. *ChemistrySelect* 9:e202401496. <https://doi.org/10.1002/slct.202401496>
3. Javahershenas R, Mei H, Koley M, Soloshonok VA, Makarem A (2024) Recent Advances in the Multicomponent Synthesis of Heterocycles Using 5-Aminotetrazole. *Synthesis* 56:2445–2461. <https://doi.org/10.1055/s-0042-1751526>
4. Javahershenas R, Han J, Kazemi M, Jervis PJ Recent Advances in the Application of 2-Aminobenzothiazole to the Multicomponent Synthesis of Heterocycles. 13:e202400185. <https://doi.org/10.1002/open.202400185>
5. Kachhadiya R, Shah D, Prajapati A, Patel A (2025) Green Synthetic Strategies for Pyrazole Derivatives: A Comprehensive Review. *Archiv der Pharmazie* 358:e70055. <https://doi.org/10.1002/ardp.70055>
6. Khan MF, Alam MM, Verma G, Akhtar W, Akhter M, Shaquiquzzaman M (2016) The therapeutic voyage of pyrazole and its analogs: A review. *European Journal of Medicinal Chemistry* 120:170–201. <https://doi.org/10.1016/j.ejmech.2016.04.077>
7. Annes SB, Saritha R, Chandru K, Mandali PK, Ramesh S (2021) Metal- and Solvent-Free Cascade Reaction for the Synthesis of Amino Pyrazole Thioether Derivatives. *J Org Chem* 86:16473–16484. <https://doi.org/10.1021/acs.joc.1c01846>
8. Becerra D, Abonia R, Castillo J-C (2022) Recent Applications of the Multicomponent Synthesis for Bioactive Pyrazole Derivatives. *Molecules* 27:4723. <https://doi.org/10.3390/molecules27154723>
9. Elbastawesy MAI, Aly AA, El-Shaier YAMM, Brown AB, Abuo-Rahma GE-DA, Samir M, Ramadan M (2023) Facile synthesis of 5-aminopyrazolo-quinolones. *Monatsh Chem* 154:1197–1204. <https://doi.org/10.1007/s00706-023-03112-0>
10. Shaabani A, Nazeri MT, Afshari R (2019) 5-Amino-pyrazoles: potent reagents in organic and medicinal synthesis. *Mol Divers* 23:751–807. <https://doi.org/10.1007/s11030-018-9902-8>
11. Padmini T, Bhikshapathi D, Suresh K, Kulkarni R, Kamal BR (2021) Novel Aminopyrazole Tagged Hydrazones as Anti-Tubercular Agents: Synthesis and Molecular Docking Studies. *Medicinal Chemistry* 17:344–351. <https://doi.org/10.2174/1573406416666200514084747>
12. Lusardi M, Wehrle-Haller B, Sidibe A, Ponassi M, Iervasi E, Rosano C, Brullo C, Spallarossa A (2023) Novel 5-aminopyrazoles endowed with anti-angiogenetic properties: Design, synthesis and biological evaluation. *European Journal of Medicinal Chemistry* 260:115727. <https://doi.org/10.1016/j.ejmech.2023.115727>
13. Naglah AM, Almehizia AA, Al-Wasidi AS, Alharbi AS, Alqarni MH, Hassan AS, Aboulthana WM (2024) Exploring the Potential Biological Activities of Pyrazole-Based Schiff Bases as Anti-

- Diabetic, Anti-Alzheimer's, Anti-Inflammatory, and Cytotoxic Agents: In Vitro Studies with Computational Predictions. *Pharmaceuticals* 17:655. <https://doi.org/10.3390/ph17050655>
14. Burgart YV, Makhaeva GF, Krasnykh OP, Borisevich SS, Agafonova NA, Kovaleva NV, Boltneva NP, Rudakova EV, Shchegolkov EV, Triandafilova GA, Gazizov DA, Serebryakova OG, Ulitko MV, Khursan SL, Saloutin VI, Richardson RJ (2022) Synthesis of 4-Aminopyrazol-5-ols as Edaravone Analogs and Their Antioxidant Activity. *Molecules* 27:7722. <https://doi.org/10.3390/molecules27227722>
 15. Fekri A, Keshk EM, Khalil A-GM, Taha I (2022) Synthesis of novel antioxidant and antitumor 5-aminopyrazole derivatives, 2D/3D QSAR, and molecular docking. *Mol Divers* 26:781–800. <https://doi.org/10.1007/s11030-021-10184-9>
 16. Toni NPD, Azra F, Maahury MF (2022) Modeling the Relationship of Net Atomic Charge with the Activity of 5-Aminopyrazole Derivative Compounds as Antioxidants with AM1 Method. *EKSakta* 23:242–254. <https://doi.org/10.24036/eksakta/vol23-iss04/334>
 17. Sanghavi KN, Kher MN, Kapadiya KM (2023) An efficient protocol for the synthesis of substituted 5-amino pyrazole bearing benzo[d]imidazolone Core and their antioxidant activity. *Journal of Heterocyclic Chemistry* 60:993–1003. <https://doi.org/10.1002/jhet.4644>
 18. Mukhtar SS, Hassan AS, Morsy NM, Hafez TS, Saleh FM, Hassaneen HM (2021) Design, synthesis, molecular prediction and biological evaluation of pyrazole-azomethine conjugates as antimicrobial agents. *Synthetic Communications* 51:1564–1580. <https://doi.org/10.1080/00397911.2021.1894338>
 19. Helal MH, Salem MA, Aly HM (2017) Synthesis, Antimicrobial Activity and Molecular Modeling of Some Novel 5-Aminopyrazole, Pyrazolo[1,5-a]pyrimidine, Bispyrazole and Bispyridone Derivatives Containing Antipyrinyl Moiety. *Journal of Heterocyclic Chemistry* 54:2614–2626. <https://doi.org/10.1002/jhet.2858>
 20. Taha I, Keshk EM, Khalil A-GM, Fekri A (2024) Synthesis and Molecular Docking Simulation of Some Novel N-Heterocycles Based on 4-Aminobenzohydrazide with Anti-Viral Potency
 21. Khadri MJN, Ramu R, Simha NA, Khanum SA (2024) Synthesis, molecular docking, analgesic, anti-inflammatory, and ulcerogenic evaluation of thiophene-pyrazole candidates as COX, 5-LOX, and TNF- α inhibitors. *Inflammopharmacol* 32:693–713. <https://doi.org/10.1007/s10787-023-01364-0>
 22. Sofan M, El-Taweel F, Abdel-Rahman A, Salman H, Negm E (2024) Synthesis of novel azo pyrazole disperse dyes for dyeing and antibacterial finishing of PET fabric under supercritical carbon dioxide. *Sci Rep* 14:1121. <https://doi.org/10.1038/s41598-023-48740-y>
 23. Rapetti F, Spallarossa A, Russo E, Caviglia D, Villa C, Tasso B, Signorello MG, Rosano C, Iervasi E, Ponassi M, Brullo C (2024) Investigations of Antioxidant and Anti-Cancer Activities of 5-Aminopyrazole Derivatives. *Molecules* 29:2298. <https://doi.org/10.3390/molecules29102298>
 24. Holló B, Leovac VM, Bombicz P, Kovács A, Jovanović LS, Bogdanović G, Kojić V, Divjaković V, Joksović MD, Szécsényi KM (2010) Synthesis, Structural, DFT, and Cytotoxicity Studies of CuII and NiII Complexes with 3-Aminopyrazole Derivatives*. *Aust J Chem* 63:1557–1564. <https://doi.org/10.1071/CH10210>

25. Hossan A, Aljohani M, Alrefaei AF, Althumayri K, Bayazeed A, Saad FA, Abumelha HM, El-Metwaly NM (2023) Synthesis of functionalized aminopyrazole and pyrazolopyrimidine derivatives: Molecular modeling and docking as anticancer agents. *Arabian Journal of Chemistry* 16:104645. <https://doi.org/10.1016/j.arabjc.2023.104645>
26. Ma Y-D, Zhou H, Lin G-T, Wu K-H, Xu G, Liu X, Xu D (2024) Design, Synthesis, and Fungicidal Activities of Novel N-(Pyrazol-5-yl)benzamide Derivatives Containing a Diphenylamine Moiety. *J Agric Food Chem* 72:6691–6701. <https://doi.org/10.1021/acs.jafc.3c07567>
27. Sayed GH, Negm NA, Azab ME, Anwer KE (2016) Synthesis, Characterization and Biological Activity of Some Pyrazole-Pyrazolone Derivatives. *Egypt J Chem* 59:663–672. <https://doi.org/10.21608/ejchem.2016.1442>
28. Jha NN, Thorat BR, Yadav S, Mali SN, Tawade SA, Yamgar RS (2024) Catalyst-Free, One-Pot, Three-Component Synthesis of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitriles in Green Media, and Evaluation of Their Biological Activities. *Russian Journal of Bioorganic Chemistry* 50:949–961
29. Elnagdy HMF, Sarma D (2019) FeCl₃/PVP as Green Homogeneous Catalyst to Synthesize 5-Amino-1H-Pyrazole-4-Carbonitriles from Malononitrile Derivatives. *ChemistrySelect* 4:783–787. <https://doi.org/10.1002/slct.201802919>
30. Mohamed S, Dawoud N, Nabil S, Fathall N, Hosni G, Anwer K (2021) Synthesis and biological activity of a new class of enamionitrile pyrazole. *Egypt J Chem* 64:3187–3203. <https://doi.org/10.21608/ejchem.2021.62916.3350>
31. Aggarwal R, Kumar S (2018) 5-Aminopyrazole as precursor in design and synthesis of fused pyrazoloazines. *Beilstein J Org Chem* 14:203–242. <https://doi.org/10.3762/bjoc.14.15>
32. Odeh DM, Odeh MM, Hafez TS, Hassan AS (2025) Bioactive Fused Pyrazoles Inspired by the Adaptability of 5-Aminopyrazole Derivatives: Recent Review. *Molecules* 30:366. <https://doi.org/10.3390/molecules30020366>
33. Abdel-Motaleb RM, Makhloof AA, Ibrahim HM, Elnagdi MH (2006) Studies with 3-functionally substituted 2-arylhydrazononitriles: A new route to 3-substituted-2-arylhydrazononitriles, 4-amino-pyrazole-5-carbonitriles, azadienes and cinnolines. *Journal of Heterocyclic Chem* 43:931–934. <https://doi.org/10.1002/jhet.5570430418>
34. Zhang Q, Tang M (2019) Regioselective Synthesis of Highly Functionalized Pyrazoles from N-Tosylhydrazones. *Org Lett* 21:1917–1920. <https://doi.org/10.1021/acs.orglett.9b00561>
35. Medrasi H, Al-Sheikh M, Salaheldin A (2013) Enaminonitriles in Heterocyclic Synthesis: A Route to 1,3-Diaryl-4-aminopyrazole Derivatives. *Molecules* 18:535–544. <https://doi.org/10.3390/molecules18010535>
36. Singh N, Pandey J (2021) DABCO catalyzed, green and efficient, one-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile. *Current Research in Green and Sustainable Chemistry* 4:100134. <https://doi.org/10.1016/j.crgsc.2021.100134>
37. Patki AS, Patil KN, Kusuma S, Muley DB, Jadhav AH (2021) One-pot synthesis of multicomponent pyrazole-4-carbonitrile derivatives under solvent-free condition by using engineered polyvinyl alcohol catalyst. *Res Chem Intermed* 47:2751–2773. <https://doi.org/10.1007/s11164-021-04450-6>

38. Srivastava M, Rai P, Singh J, Singh J (2013) An environmentally friendlier approach—ionic liquid catalysed, water promoted and grinding induced synthesis of highly functionalised pyrazole derivatives. *RSC Adv* 3:16994. <https://doi.org/10.1039/c3ra42493f>
39. M'hamed MO, Alduaij OK (2016) Green and Effective One-Pot Synthesis of 5-Oxo-pyrazolidine and 5-Amino-2,3-dihydro-1H-Pyrazole Derivatives through Ball Milling Under Catalyst-Free and Solvent-Free Conditions. *Asian J Chem* 28:543–547. <https://doi.org/10.14233/ajchem.2016.19397>
40. Esfandiary N, Nakisa A, Azizi K, Azarnia J, Radfar I, Heydari A (2017) Glucose-coated superparamagnetic nanoparticle-catalysed pyrazole synthesis in water. *Applied Organomet Chem* 31:e3641. <https://doi.org/10.1002/aoc.3641>
41. Moosavi-Zare AR, Rezaei-Gohar M, Tavasoli M, Goudarziafshar H (2021) The synthesis of 5-amino-1H-pyrazole-4-carbonitriles by anomeric based oxidative aromatization over [CSPy]ZnCl₃ as a new catalyst. *Res Chem Intermed* 47:2689–2700. <https://doi.org/10.1007/s11164-021-04437-3>
42. Doosti R, Bakherad M, Mirzaee M, Jadidi K (2017) Boehmite Silylpropyl Amine Sulfamic Acid as an Efficient and Recyclable Catalyst for the Synthesis of some Pyrazole Derivatives. *LOC* 14:. <https://doi.org/10.2174/1570178614666170505113009>
43. Arora P, Rajput JK (2017) One-pot multicomponent click synthesis of pyrazole derivatives using cyclodextrin-supported capsaicin nanoparticles as catalyst. *J Mater Sci* 52:11413–11427. <https://doi.org/10.1007/s10853-017-1304-2>
44. Zolfigol MA, Afsharnadery F, Bagheri S, Salehzadeh S, Maleki F (2015) Catalytic applications of {[HMIM]C(NO₂)₃}: as a nano ionic liquid for the synthesis of pyrazole derivatives under green conditions and a mechanistic investigation with a new approach. *RSC Adv* 5:75555–75568. <https://doi.org/10.1039/C5RA16289K>
45. Kiyani H, Bamdad M (2018) Sodium ascorbate as an expedient catalyst for green synthesis of polysubstituted 5-aminopyrazole-4-carbonitriles and 6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles. *Res Chem Intermed* 44:2761–2778. <https://doi.org/10.1007/s11164-018-3260-0>
46. Bakhtiarian M, Khodaei MM (2022) Pyridinium-based dual acidic ionic liquid supported on the pectin for efficient synthesis of pyrazoles. *Journal of Molecular Liquids* 363:119883. <https://doi.org/10.1016/j.molliq.2022.119883>
47. Mitchell D, Luo Y, McNulty L, Buser J, McFarland A (2014) A Convenient and Practical Synthesis of Aminopyrazoles. *Synthesis* 47:235–241. <https://doi.org/10.1055/s-0034-1379474>
48. Koli BP, Gore RP (2023) Catalyst-free On-Water Synthesis of 5-Aminopyrazole-4-carbonitriles as Potential Antifungal Agents. *Organic Preparations and Procedures International* 55:351–357. <https://doi.org/10.1080/00304948.2022.2153640>
49. Jagath Reddy G, Sailaja S, Manjula D, Srinivasa Rao K (2005) A clean and rapid synthesis of 5-aminopyrazole-4-carboxylic acid esters and nitriles using montmorillonite K10. *Heterocyclic Communications* 11:. <https://doi.org/10.1515/HC.2005.11.5.385>
50. Kiyani H, Bamdad M (2017) One-Pot and Efficient Synthesis of 5-Aminopyrazole-4-carbonitriles Catalyzed by Potassium Phthalimide. *HETEROCYCLES* 94:276. <https://doi.org/10.3987/COM-16-13623>

51. Gulati S, Singh R (2018) Synthesis and bioevaluation of novel pyrazole by different methods: A review. *Journal of Pharmacognosy and Phytochemistry* 7:3401–3406
52. Medjahed N, Kibou Z, Berrichi A, Choukchou-Braham N (2023) Advances in Pyrazoles Rings' Syntheses by Heterogeneous Catalysts, Ionic Liquids, and Multicomponent Reactions - A Review. *Current Organic Chemistry* 27:471–509. <https://doi.org/10.2174/1385272827666230602121855>
53. Farooq S, Ngaini Z (2020) Chalcone Derived Pyrazole Synthesis via One-pot and Two-pot Strategies. *COC* 24:1491–1506. <https://doi.org/10.2174/1385272824999200714101420>
54. Hasaninejad A, Firoozi S (2013) Catalyst-free, one-pot, three-component synthesis of 5-amino-1,3-aryl-1H-pyrazole-4-carbonitriles in green media. *Mol Divers* 17:459–469. <https://doi.org/10.1007/s11030-013-9445-y>
55. Liu P, Pan Y-M, Xu Y-L, Wang H-S (2012) PTSA-catalyzed Mannich-type-cyclization-oxidation tandem reactions: one-pot synthesis of 1,3,5-substituted pyrazoles from aldehydes, hydrazines and alkynes. *Org Biomol Chem* 10:4696–4698. <https://doi.org/10.1039/C2OB25487E>
56. Lim FPL (2015) A one-pot, three-component, microwave-assisted synthesis of novel 7-amino-substituted 4-aminopyrazolo[1,5-a][1,3,5]triazine-8-carbonitriles
57. Rai P, Srivastava M, Singh J, Singh J (2014) Molecular iodine: a green and inclusive catalyst for the synthesis of highly functionalized 1,3,5-trisubstituted pyrazoles in aqueous medium. *RSC Adv* 4:779–783. <https://doi.org/10.1039/C3RA44315A>
58. Kiyani H, Bamdad M (2014) Three-Component Reaction of Malononitrile with Phenyl hydrazine and Aryl Aldehydes Promoted by Sodium Ascorbate. *The 22nd Iranian Seminar of Organic Chemistry*
59. Neto JSS, Zeni G (2020) Alkynes and Nitrogen Compounds: Useful Substrates for the Synthesis of Pyrazoles. *Chemistry – A European Journal* 26:8175–8189. <https://doi.org/10.1002/chem.201905276>
60. Mishra D, Singh R, Rout C (2017) Synthesis of Highly Functionalized Pyrazoles Using AlCl₃ as Catalyst
61. Anwar HF, Elnagdi MH (2009) Recent developments in aminopyrazole chemistry. *Arkivoc* 2009:198–250. <https://doi.org/10.3998/ark.5550190.0010.107>
62. Hassaneen HME (2007) New Approach to 4- and 5-Aminopyrazole Derivatives. *Synthetic Communications* 37:3579–3588. <https://doi.org/10.1080/00397910701557564>
63. Manojmouli C, Bharath S, Khaleel M, Pasha T, Ramesh B, Koppuravuri NP (2022) Recent Updates on Green Synthesis of Pyrazole Derivatives: A Review. *Indian Journal of Natural Sciences* 13:50148–50154
64. Marinozzi M, Marcelli G, Carotti A (2015) N-Aryl-5-aminopyrazole: A Versatile Architecture in Medicinal Chemistry. *Mini Reviews in Medicinal Chemistry* 15:272–299
65. El-Gaby MSA, Atalla AA, Gaber AM, Abd Al-Wahab KA (2000) Studies on aminopyrazoles: antibacterial activity of some novel pyrazolo[1,5-a]pyrimidines containing sulfonamido moieties. *Il Farmaco* 55:596–602. [https://doi.org/10.1016/S0014-827X\(00\)00079-3](https://doi.org/10.1016/S0014-827X(00)00079-3)

66. Yu M, Lizarzaburu M, Motani A, Fu Z, Du X, Liu J (Jim), Jiao X, Lai S, Fan P, Fu A, Liu Q, Murakoshi M, Nara F, Oda K, Okuyama R, Reagan JD, Watanabe N, Yamazaki M, Xiong Y, Zhang Y, Zhuang R, Lin DC-H, Houze JB, Medina JC, Li L (2013) Aminopyrazole–Phenylalanine Based GPR142 Agonists: Discovery of Tool Compound and in Vivo Efficacy Studies. *ACS Med Chem Lett* 4:829–834. <https://doi.org/10.1021/ml4000854>
67. Dooley MJ, Quinn RJ, Scammells PJ (1989) Synthesis of 5-Aminopyrazole-4-carbonitriles. *Aust J Chem* 42:747–750. <https://doi.org/10.1071/ch9890747>
68. Hassaneen HM, Saleh FM, Abdallah TA, Mohamed YSh, Awad EM (2020) Synthesis, reactions, and antimicrobial activity of some novel pyrazolo[3,4-d]pyrimidine, pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine, and pyrazolo[4,3-e][1,2,4]triazolo [3,4-c]pyrimidine derivatives. *Journal of Heterocyclic Chem* 57:892–912. <https://doi.org/10.1002/jhet.3835>
69. Farooq S, Ngaini Z (2024) Recent Synthesis of Mono- & Bis-Pyranopyrazole Derivatives. *ChemistrySelect* 9:e202400028. <https://doi.org/10.1002/slct.202400028>
70. Deb ML, Bhuyan PJ (2005) Uncatalysed Knoevenagel condensation in aqueous medium at room temperature. *Tetrahedron Letters* 46:6453–6456. <https://doi.org/10.1016/j.tetlet.2005.07.111>
71. Wolkoff P (1976) Fragmentation paths of hydrazonyl halides upon electron impact; simulation of nitrilimine formation. *J Chem Soc, Perkin Trans 2* 921. <https://doi.org/10.1039/p29760000921>
72. Fahmi AA, Mekki ST, Albar HA, Shawali AS, Hassaneen HM, Abdelhamid H (1994) ChemInform Abstract: A Facile Synthesis of Some Pyrazolo Analogues of Tricyclic Purine Derivatives via Hydrazonoyl Halides. *ChemInform* 25:chin.199426193. <https://doi.org/10.1002/chin.199426193>
73. Ghorbani S, Habibi D, Heydari S, Ebrahimiasl H (2023) The acid modified magnetic carbon quantum dots as a capable nano-catalyst for the synthesis of pyridines and pyrazoles. *Inorganic Chemistry Communications* 156:111258. <https://doi.org/10.1016/j.inoche.2023.111258>
74. Ali A, Shah T, Ullah R, Zhou P, Guo M, Ovais M, Tan Z, Rui Y (2021) Review on Recent Progress in Magnetic Nanoparticles: Synthesis, Characterization, and Diverse Applications. *Front Chem* 9. <https://doi.org/10.3389/fchem.2021.629054>
75. Abshirini Z, Lotfifar N, Zare A (2020) A Highly Effectual and Rapid Protocol for the Synthesis of 5-Amino-1,3-diaryl-1 H -pyrazole-4-carbonitriles Using 1,3-Disulfonic Acid Imidazolium Trifluoroacetate as a Dual-Functional Catalyst. *Organic Preparations and Procedures International* 52:428–433. <https://doi.org/10.1080/00304948.2020.1780884>
76. Bhale PS, Dongare SB, Chanshetti UB (2014) Simple Grinding, Catalyst-free, One-Pot, Three-Component Synthesis of Polysubstituted Amino Pyrazole. *Res J Chem Sci* 4:16–21
77. Khazaei A, Moosavi-Zare AR, Goudarzi H, Tavasoli M (2022) [Msim]CuCl₃ : as an efficient catalyst for the preparation of 5-amino-1H-pyrazole-4-carbonitriles by anomeric based oxidation. *Zeitschrift für Naturforschung B* 77:87–93. <https://doi.org/10.1515/znb-2021-0153>
78. Pashaki FS, Nikpassand M (2021) Synthesis of Novel Azo-Linked 5-Amino-Pyrazole-4-Carbonitrile Derivatives Using Tannic Acid–Functionalized Silica-Coated Fe₃O₄ Nanoparticles as a Novel, Green, and Magnetically Separable Catalyst. *Front Chem* 9:724745. <https://doi.org/10.3389/fchem.2021.724745>

79. Liwal A, Akbarpour T, Khazaei A, Ghanbarpour A (2025) Magnetic 2-aminopyridine-functionalized $\text{Fe}_3\text{O}_4@\text{SiO}_2$ nanocatalyst for green production of new pyrazole carbonitrile and aryl methylene-pyrazole derivatives. *Materials Chemistry and Mechanics* 3:e233470. <https://doi.org/10.22034/mcm.2025.471516.1052>
80. Poonam, Singh R (2019) Facile one-pot synthesis of 5-amino-1H-pyrazole-4-carbonitriles using alumina–silica-supported MnO_2 as recyclable catalyst in water. *Res Chem Intermed* 45:4531–4542. <https://doi.org/10.1007/s11164-019-03847-8>
81. Ubale M, Shioorkar M (2016) An environmentally benign alum catalyzed approach for synthesis of polysubstituted amino pyrazole. *Heterocyclic Letters* 6:265–270
82. Srivastava M, Rai P, Singh J, Singh J (2014) Efficient iodine-catalyzed one pot synthesis of highly functionalised pyrazoles in water. *New J Chem* 38:302–307. <https://doi.org/10.1039/C3NJ01149F>
83. Khandebharad A, Sarda S, Soni M, Gill C, Kulkarni P, Agrawal B (2018) NaCl: a facile, environmentally benign catalyst for the synthesis of pyrazole 4- carbonitrile in aqueous media. *Current Chemistry Letters* 7:57–64
84. Maddila S, Rana S, Pagadala R, Kankala S, Maddila S, Jonnalagadda SB (2015) Synthesis of pyrazole-4-carbonitrile derivatives in aqueous media with CuO/ZrO_2 as recyclable catalyst. *Catalysis Communications* 61:26–30. <https://doi.org/10.1016/j.catcom.2014.12.005>
85. Kumari S, Shekhar A, Pathak DD (2016) Graphene oxide– TiO_2 composite: an efficient heterogeneous catalyst for the green synthesis of pyrazoles and pyridines. *New J Chem* 40:5053–5060. <https://doi.org/10.1039/C5NJ03380B>
86. Sapkal A, Kamble S (2020) Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for greener synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium. *Journal of Heterocyclic Chem* 57:3597–3604. <https://doi.org/10.1002/jhet.4077>
87. Nemati F, Nikkhah SH, Elhampour A (2015) An environmental friendly approach for the catalyst-free synthesis of highly substituted pyrazoles promoted by ultrasonic radiation. *Chinese Chemical Letters* 26:1397–1399. <https://doi.org/10.1016/j.cclet.2015.07.009>
88. Saki S, Khodaei MM (2025) Immobilized phosphomolybdic acid on a pyridine-based rigid polymeric as a heterogeneous catalyst for the synthesis of 5-aminopyrazole-4-carbonitrile
89. Nouri M, Hajjami M, Siahpour Z (2025) Zinc oxide on biochar waste-derived support as nanocomposite catalyzed synthesis of tetrahydrobenzo[a]xanthen-11-one and 5-aminopyrazole-4-carbonitrile derivatives. *J IRAN CHEM SOC* 22:1879–1892. <https://doi.org/10.1007/s13738-025-03264-2>
90. Badhe K, Dabholkar V, Kurade S (2018) One-pot Synthesis of 5-Amino-1H-pyrazole-4-carbonitrile Using Calcined Mg-Fe Hydrotalcite Catalyst. *COCAT* 5:3–12. <https://doi.org/10.2174/2213337205666180516094624>
91. Amirnejat S, Nosrati A, Javanshir S (2020) Superparamagnetic Fe_3O_4 @Alginate supported L-arginine as a powerful hybrid inorganic–organic nanocatalyst for the one-pot synthesis of pyrazole derivatives. *Applied Organomet Chemis* 34:e5888. <https://doi.org/10.1002/aoc.5888>

92. Yadav S, Rai P, Srivastava M, Singh J, Tiwari KP, Singh J (2015) Atmospheric oxygen mediated synthesis of pyrazole under visible irradiation. *Tetrahedron Letters* 56:5831–5835. <https://doi.org/10.1016/j.tetlet.2015.07.039>
93. Nemati R, Elhamifar D, Zarnegaryan A, Shaker M (2021) Core-shell structured magnetite silica-supported hexatungstate: A novel and powerful nanocatalyst for the synthesis of biologically active pyrazole derivatives. *Applied Organometallic Chemistry* 35:e6409. <https://doi.org/10.1002/aoc.6409>
94. Dabholkar VV, Kurade SK, Badhe KS, Karthik K, Anpat S (2018) Synthesis of Polysubstituted Amino Pyrazole via Multicomponent Strategy Using NiFe₂O₄ Nanocatalyst. *Der Pharma Chemica* 10:62–67
95. Aryan R, Beyzaei H, Nojavan M, Rezaei M (2017) Novel biocompatible glucose-based deep eutectic solvent as recyclable medium and promoter for expedient multicomponent green synthesis of diverse three and four substituted pyrazole-4-carbonitrile derivatives. *Res Chem Intermed* 43:4731–4744. <https://doi.org/10.1007/s11164-017-2908-5>
96. Kadu VD, Hublikar MG, Raut DG, Bhosale RB (2019) Water-Mediated Ceric Ammonium Nitrate Catalyzed C-C/C-N Bond Formation: Convenient Access to Polyfunctionalized Pyrazoles via Multicomponent Reaction. *Asian J Chem* 31:1189–1194. <https://doi.org/10.14233/ajchem.2019.21947>
97. Endo S, Pfennigsdorff A, Goss K-U (2012) Salting-Out Effect in Aqueous NaCl Solutions: Trends with Size and Polarity of Solute Molecules. *Environ Sci Technol* 46:1496–1503. <https://doi.org/10.1021/es203183z>
98. Hasseine A, Meniai A-H, Korichi M (2009) Salting-out effect of single salts NaCl and KCl on the LLE of the systems (water + toluene + acetone), (water + cyclohexane + 2-propanol) and (water + xylene + methanol). *Desalination* 242:264–276. <https://doi.org/10.1016/j.desal.2008.05.006>
99. Rosamilia AE, Aricò F, Tundo P (2008) Reaction of the Ambident Electrophile Dimethyl Carbonate with the Ambident Nucleophile Phenylhydrazine. *J Org Chem* 73:1559–1562. <https://doi.org/10.1021/jo701818d>
100. Nikpassand M, Fekri LZ, Varma RS, Hassanzadi L, Pashaki FS (2022) Green synthesis of novel 5-amino-bispyrazole-4-carbonitriles using a recyclable Fe₃O₄@SiO₂@vanillin@thioglycolic acid nano-catalyst. *RSC Adv* 12:834–844. <https://doi.org/10.1039/D1RA08001F>
101. Nikpassand M, Hassanzadi L, Fekri LZ (2023) The solid state synthesis of novel pyrazolyl-5-amino-pyrazole-4-carbonitrile derivatives using Fe₃O₄@SP@TA nanocomposites as a novel, green, and magnetically separable catalyst. *Inorganic and Nano-Metal Chemistry* 1–10. <https://doi.org/10.1080/24701556.2023.2166075>
102. Abdel-Megid M, Ibrahim MA, Badran A-S, El-Mahdy KM (2024) Synthetic Approaches and Biological Applications of Aminopyrazolecarbonitriles. *Synthetic Communications* 54:239–267. <https://doi.org/10.1080/00397911.2023.2292702>
103. Teleb MAM, Hassaneen HM, Abdelhamid IA, Saleh FM (2021) 5-Aminopyrazole-4-carbonitriles as precursors to novel 4-aminotetrahydropyrazolo[3,4-*b*]quinolin-5-ones and *N*-(4-cyanopyrazol-5-yl)pyridine-3-carbonitrile. *Synthetic Communications* 51:2357–2364. <https://doi.org/10.1080/00397911.2021.1936059>

104. Parvin T (2023) Multicomponent Reactions Using C,N-Binucleophilic Nature of Aminopyrazoles: Construction of Pyrazole-Fused Heterocycles. *Top Curr Chem (Z)* 381:19. <https://doi.org/10.1007/s41061-023-00427-8>
105. Salaheldin AM, Abdallah TA, Radwan NF, Hassaneen HM (2007) A Novel Route to 4-Aminopyrazoles and Aminopyrazolo[4,3-b]pyridines. *ChemInform* 38:chin.200703037. <https://doi.org/10.1002/chin.200703037>
106. Al-Qalaf F, Mandani F, Abdelkhalik MM, Bassam AA (2008) Synthesis of 5-Substituted 3-Amino-1H-Pyrazole-4-Carbonitriles as Precursors for Microwave Assisted Regiospecific Syntheses of Pyrazolo[1,5-a]Pyrimidines. *Molecules* 14:78–88. <https://doi.org/10.3390/molecules14010078>
107. Khalafy J, Poursattar Marjani A, Salami F (2014) A novel synthesis of new 2-aryl-6-(arylamino)-1H-imidazo[1,2-b]pyrazole-7-carbonitrile derivatives. *Tetrahedron Letters* 55:6671–6674. <https://doi.org/10.1016/j.tetlet.2014.10.061>
108. Sayed GH, Azab ME, Negm NA, Anwer KE (2018) Antimicrobial and Cytotoxic Activities of Some Novel Heterocycles Bearing Pyrazole Moiety. *Journal of Heterocyclic Chem* 55:1615–1625. <https://doi.org/10.1002/jhet.3196>
109. Sayed G, Azab M, Anwer K, Negm N (2016) Utility of enaminonitrile in the synthesis of novel heterocycles bearing pyrazole moiety and their antimicrobial and cytotoxic activity assessment. *Al-Azhar Bulletin of Science* 27:9–22. <https://doi.org/10.21608/absb.2016.24327>
110. Beyzaei H, Motraghi Z, Aryan R, Mehdi Zahedi M, Samzadeh-Kermani A (2017) Green One-pot Synthesis of Novel Polysubstituted Pyrazole Derivatives as Potential Antimicrobial Agents. *ACSi* 64:911–918. <https://doi.org/10.17344/acsi.2017.3609>
111. Plem SC, Müller DM, Murguía MC (2015) Key Intermediates: A Simple and Highly Selective Synthesis of 5-Amino-1-aryl-1H-pyrazole-4-carbonitriles for Applications in the Crop Protection. *ACES* 05:239–261. <https://doi.org/10.4236/aces.2015.53025>
112. Plem SC, Carrió MJ, Vaira SM, Müller DM (2016) Comparative study of biological activity of fluorinated 5-aminopyrazoles on *Spodoptera frugiperda*. *IJOEAR* 2:88–93
113. Quantology N, Sami MH, Younis SK (2022) Convenient methodology for Synthesis a New Series of Heterocyclic Compounds Including The Enamine Moiety 3676 Mustafa.H. Sami a, Shaymaa. K. Younis b. *Neuro Quantology* 20:3676–3683
114. Mishra A, Verma C, Chauhan S, Quraishi MA, Ebenso EE, Srivastava V (2018) Synthesis, Characterization, and Corrosion Inhibition Performance of 5-Aminopyrazole Carbonitriles Towards Mild Steel Acidic Corrosion. *J Bio Tribo Corros* 4:53. <https://doi.org/10.1007/s40735-018-0174-8>
115. Mizuhara T, Kato T, Hirai A, Kurihara H, Shimada Y, Taniguchi M, Maeta H, Togami H, Shimura K, Matsuoka M, Okazaki S, Takeuchi T, Ohno H, Oishi S, Fujii N (2013) Structure–activity relationship study of phenylpyrazole derivatives as a novel class of anti-HIV agents. *Bioorganic & Medicinal Chemistry Letters* 23:4557–4561. <https://doi.org/10.1016/j.bmcl.2013.06.026>
116. Hebishy AMS, Salama HT, Elgemeie GH (2020) New Route to the Synthesis of Benzamide-Based 5-Aminopyrazoles and Their Fused Heterocycles Showing Remarkable Antiavian Influenza Virus Activity. *ACS Omega* 5:25104–25112. <https://doi.org/10.1021/acsomega.0c02675>

117. Melad Al-Adiwish W (2017) Synthesis, Biological Activity and Cytotoxicity of New Fused Pyrazolo[1,5-a]pyrimidine from 5-Aminopyrazole Incorporated with p-Chloroaniline. *AJHC* 3:86–94. <https://doi.org/10.11648/j.ajhc.20170306.15>
118. Nesaragi AR, Kamat V, Chapi S, Guddappa H, T. M. S, Chandu A, Al-Zaqri N, Palem RR, Murugesan S, Kumbar VM (2025) WELPSA: A Green Catalyst Mediated Microwave Assisted Efficient Synthesis of Novel 5-Aminopyrazole-4-Carbonitrile Derivatives as Anticancer Agents (MCF-7, A-549) and In Silico Studies. *Archiv der Pharmazie* 358:e202500055. <https://doi.org/10.1002/ardp.202500055>

ARTICLE IN PRESS