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REVIEW **Open Access**

Two pot and one pot synthesis of dipyrazolopyridines derivatives and applications

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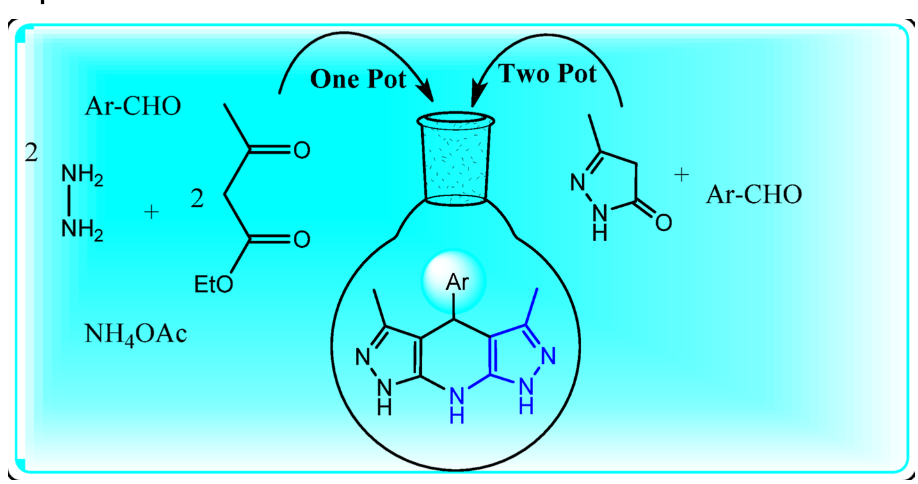
Abstract
Dipyrazolopyridines (DPPs) are distinctive heterocyclic compounds with broad applications in pharmaceutical and industrial fields. DPPs can be conveniently synthesised using commonly available reagents such as ethyl acetoacetate, hydrazine derivatives, ammonium hydroxide, and aldehyde derivatives. This review article explores the synthesis of DPP derivatives, highlighting various synthetic methods. Two-pot and one-pot synthesis of DPPs and their extensive applications in pharmaceuticals, material synthesis and environmental chemistry have also been comprehensively discussed. The current challenges and prospects of DPPs in various fields have also been emphasised due to the potential technological advancements and demand.

Keywords Ammonium, Condensation, Chemical reactions, Ethyl acetoacetate, Reflux

Graphical abstract



1 Introduction

Multicomponent reactions (MCRs) have attracted great attention among researchers to design biologically active heterocyclic compounds with advantages such as high functional group, efficient preparation, high flexibility and tolerance [1–3]. Heterocycles containing pyrazole rings are a significant target moiety in medicinal and synthetic chemistry [4–14]. Pyrazole is an important scaffold in diverse bio-active products [15], optical [16] and electroluminescent properties [17, 18]. One of the most attractive nitrogenous heterocyclic compounds is dipyrazolopyridines (DPPs). DPP is a fused-nitrogen heterocyclic scaffold containing pyrazole rings with extensive pharmacological properties [19, 20]. Besides DPPs, bispyrazolopyridine [21], bispyrazolo[3,4-b;4',3'-e]pyridine [22], tetrahydrodipyrazolopyridine (THDPPs) or dipyrazolo-1,4-dihydropyridines [23] are its alternative names. DPPs are bioactive compounds [24, 25] that are actively used in pharmaceutical drugs as cartazolate, etazolate and tracazolate (Fig. 1A) [26, 27]. DPPs are typically exhibited a wide range of biological activities including antiviral [28, 29], antiarthritic, anti-inflammatory [30, 31] protein kinase inhibitors [32], indoleamine-2,3-dioxy-genase inhibitors [33], antagonists [34], anticancer [35], antiasthmatic [36], hypoglycemic, anxiolytic, antileishmania, antiherpetic and antiallergic [37]. Moreover, DPPs are also used in LED [38], organic polymers [39], chemosensors as Ca^{2+} indicator [40] for fluorescent applications [41].

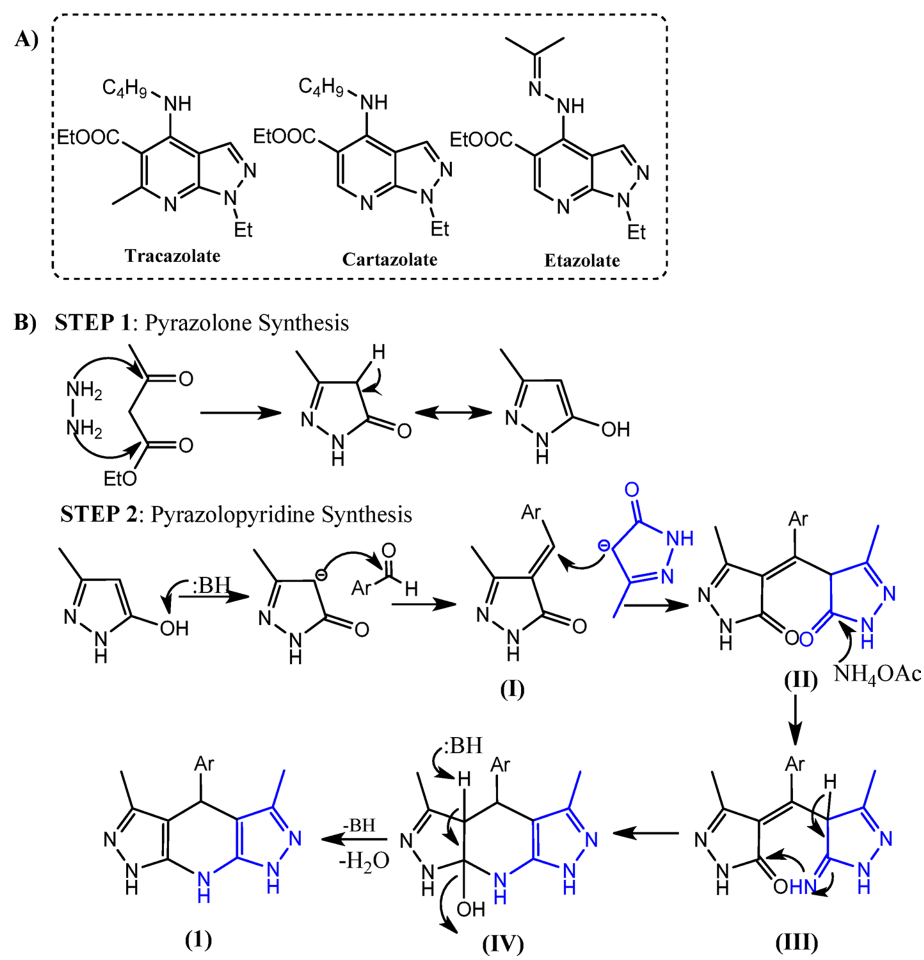
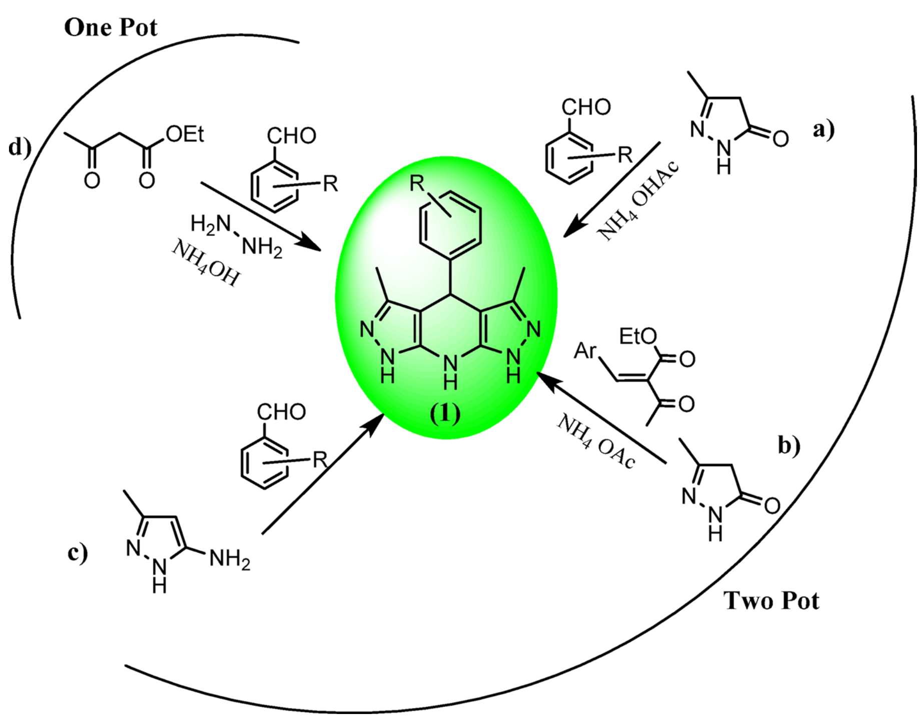


Fig. 1 DPP derived drugs [27] and proposed mechanism

The proposed mechanism has been reported for DPPs (Fig. 1B). It consists of two-step reactions, such as pyrazolone synthesis and pyrazolopyridine formation [42]. In the first step, the lone pairs of hydrazine hydrate act as intramolecular nucleophiles and react with the carbonyl carbon of ethyl acetoacetate for the successful formation of pyrazolone *via* tautomerization [2]. The next step involved Knoevenagel condensation [43] between pyrazolone and activated aldehyde to form intermediate (I), which then reacted with the second pyrazolone *via* Michael reaction to form intermediate (II). Lastly, the ammonium salt acts as nucleophilic and forms a reaction with the intermediate (II) in the presence of a catalyst following intramolecular cyclisation and tautomerization to form the desired product **(1)** [44].

Generally, DPPs have been synthesised *via* four different strategies mentioned in Scheme 1a-**d**. In two pot strategies, pyrazolone [45] and aminopyrazole derivatives [46, 47] have been used to achieve the targeted DPP derivatives **(1)** Scheme 1a–c. In Scheme 1a, ammonium salts are utilised with pyrazolone and aldehyde derivatives under catalytic conditions. In contrast, the Scheme 1c strategy is not dependent upon salts due to the usage of amino pyrazolone and aldehyde derivatives as reagents. Moreover, in Scheme 1b, pyrazolone and ethyl-2-benzylidenacetoacetates are used to achieve compound **(1)** [23]. The Moshtaghi-Zonouz and Forghani-Basmenj have also reported a similar DPP product **(1)** from the easily accessible three-component reaction of ammonium acetate, pyrazolone and ethyl-2-benzylidenacetoacetate in ethanolic reflux. This DPP, as an unexpected product, was achieved instead of fused pyrazolo-1,4-dihydropyridines [23].

The one-pot method or pseudo-six component method is commonly reported under optimum conditions due to readily available reagents ethyl acetoacetate, aldehydes, hydrazine hydrate and ammonium salts (Scheme 1d and Table 1) [48, 49].

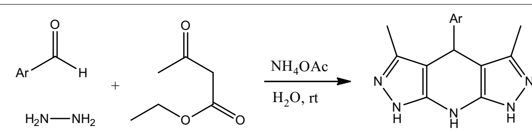


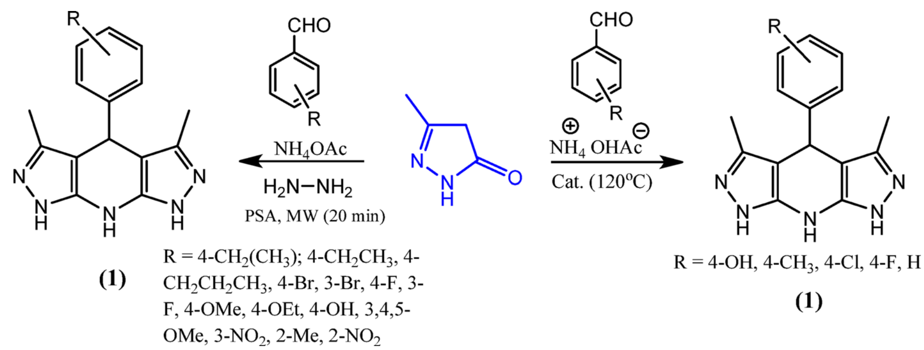
Scheme 1 General synthesis of DPPs **(1)**

Various ammonium salts such as NH_4Cl, NH_4NO_3, NH_4VO_3, NH_4HCO_3, $NH_4OC(O)H$, $(NH_4)_2CO_3$, and $[(NH_4)OC(O)_2]$ have been used as nitrogen sources at room temperature in water for DPP synthesis. Among these salts, ammonium acetate is moisture sensitive due to its hygroscopic nature and is commonly replaced by ammonium carbonate. Ammonium carbonate is a sublimable solid, non-hygroscopic, less-toxic and safer nitrogen source *via* ammonia for DPP formation in water with high yield [50].

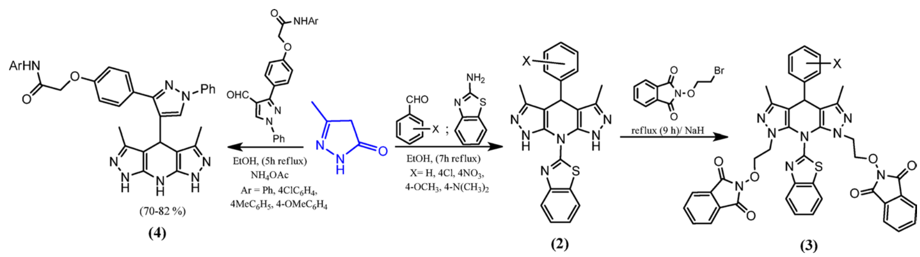
Whereas previous reviews have extensively covered general pyridine synthesis and various catalysed one-pot syntheses involving ethyl acetoacetate, aldehyde, hydrazine hydrate and ammonium [65], there remains a lack of comprehensive studies on the impact of different catalysts and reaction conditions on the efficiency and yield of these syntheses. Additionally, the mechanistic pathways of these reactions under varying conditions have not been fully elucidated, presenting an opportunity for further investigation to optimise and understand these processes better.

Table 1 One-pot synthesis of DPP

Catalyst	Conditions	Time	Yield (%)	Ref
				
AG-g-PAO/$CuFe_2O_4$	EtOH/rt	20 min	97	[48]
Alg@sba-15/ Fe_3O_4	EtOH/ r.t	20 min	93	[19]
Cu(II)/Schiff-base @MWCNT-Fe_3O_4/SiO_2	Solvent free/r.t	75 min	90	[49]
$CuCr_2O_4$NPs	EtOH (25 °C)	50 min	93	[51]
$CuFe_2O_4$@HNTs	EtOH/rt	20 min	96	[43]
Co_4ChDES	H_2O, rt	0.25 h	94	[52]
Fe_3O_4@SiO_2@$(BuSO_3H)_3$	Solvent-free (120 °C)	8 min	81	[45]
Fe_3O_4@NAC	H_2O, rt	5 min	97	[53]
Fe_3O_4@KCC-1-nPr-NH_2	EtOH /reflux	30 min	90	[54]
Fe_3O_4/KCC-1/IL/HPW MNPs	H_2O (60 °C)	30 min	96	[55]
$FeNi_3$-IL	EtOH/Reflux	44 min	90	[56]
Fe_3O_4@SiO_2-SO_3H	EtOH (500 W, MW)	15 min	92	[57]
FGO@dextrin	EtOH/r.t	15 min	98	[58]
HANCD@urease	H_2O (70 °C)	80 min	96	[59]
$MgFe_2O_4$@Tris	H_2O/r.t	10 min	98	[42]
$Mg_{0.5}Zn_{0.375}Ni_{0.125}Fe_2O_4$	H_2O/r.t	5 min	98	[60]
$MnCoFe_2O_4$@Niacin-$SO_3H)^+Cl^-$	EtOH /reflux	30 min	95	[61]
Nano-$CdZr_4(PO_4)_6$	EtOH/reflux (25 °C)	43 min	88	[62]
Nano-ovalbumin	H_2O/55 °C	35 min	94	[44]
Pseudopolymeric MNPs	EtOH/r.t	60 min	63	[63]
TEA: SA	Deep eutectic solvents (DES)	3 min	98	[37]
White LEDs (30 W)/ Eosin Y	MeOH, rt	23 min	93	[25]
[Zn-2BSMP]Cl_2	Water /reflux (80 °C)	65 min	90	[20]
-	H_2O, rt	45 min	98	[27]
-	H_2O, r.t.	15 min	97	[50]
-	H_2O (50 °C)	7 h	64	[64]
-	H_2O (ultrasound)	2 h	95	[64]



Scheme 2 Synthesis of DPPs from pyrazolone



Scheme 3 Synthesis of DPP derivatives

2 Synthesis of DPP derivatives

DPPs can generally be synthesised via either two-pot and one-pot methodologies, as illustrated below:

2.1 Two pot synthesis

A two-pot synthesis of DPPs has been reported via a three-component (pseudo-five component) reaction involving pyrazolone, aldehyde and ammonium derivatives. This solvent-free process, conducted at 120 °C, yields excellent product efficiency (81–98%) within a remarkably short reaction time of 1–8 min [45]. DPPs have also been synthesised *via* green and efficient microwave-assisted (MW) method at 70 °C under solvent-free conditions employing aldehydes, 3-methyl-1Hpyrazol-5(4 H)-one, ammonium acetate and solid catalyst phospho sulfonic acid (PSA) as key starting materials. The MW-assisted strategy offers a straightforward and efficient approach enabling excellent yields under mild, solvent-free conditions (Scheme 2).

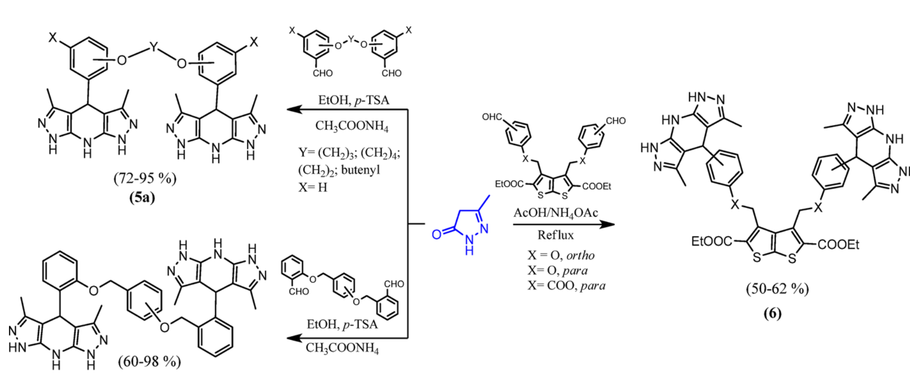
Benzothiazole-derived DPPs **(2)** have been reported *via* a multicomponent reaction involving 5-methyl-2,4-dihydro-3 H-pyrazol-3-one, phenylenediamine, benzaldehyde, and sodium ethoxide (C_2H_5ONa) under reflux in ethanol for 7 h. Compound **(2)** was further treated with phthalimidoxyethylbromide in ethanol under reflux (9 h) in the presence of NaH to achieve the targeted compound **(3)** with good yield [66]. Acetamide derivatives-based DPP derivative **(4)** were achieved from ammonium acetate and an acetamide-based aldehyde and pyrazolone mixture to achieve 70–82% yield [67] (Scheme 3).

DPPs have also been synthesised *via* microwave (MW) irradiation, offering higher yields and significantly reduced reaction time compared to conventional methods. For instance, the synthesis of **5a** and **5b** has been comparatively performed under conventional heating (3 h reflux) and MW irradiation at 100 °C (250 W, 10 min) in absolute ethanol using *p*-toluenesulfonic acid (*p*-TSA) as a catalyst. Both methods yielded good results with product yields ranging from 60 to 98% [68]. The reaction of *bis*(aldehyde), pyrazolone and ammonium acetate led to the formation of the targeted **(5a** and **5b)**. MW irradiation methodology gave a better yield (70–98%) than the conventional method (60–88%). Under MW irradiation, the synthesis of targeted *bis*-DPPs **(5a** and **5b)** was achieved through an efficient, straightforward, and eco-friendly process [68]. *Bis*(heterocycles) **(6)** have also been synthesised in acidic media by using acetic acid for the reaction of ammonium acetate, pyrazolone and phenoxymethyl linker thieno[2,3-b] thiophene scaffold having *bis*(aldehydes) under 5 h reflux to achieve Hantzsch-like product **(6)** with 50–62% yield [69] (Scheme 4).

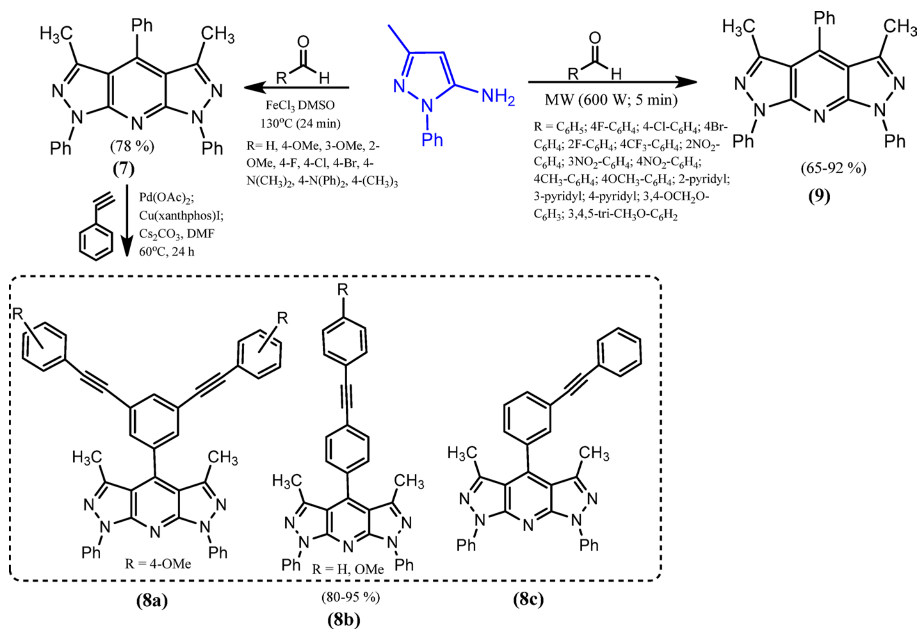
Apart from pyrazolone, DPPs have also been synthesised from 5-amino-3-methyl-1-phenylpyrazole [70] with aldehyde in a ratio (2:1) employing ionic liquids and organic solvents ([bmim]Br, [bmim]BF_4, [bmim]PF_6, CH_3COOEt, CH_3COCH_3, DMF, EtOH, CH_3CN) [71]. *Bis*-pyrazolo-pyridine derivatives **(7** and **8)**, for example, have been conveniently prepared using iron chloride as a catalyst at lower heating (130 °C, 24 h) compared to other methods (220–250 °C) [72]. Nevertheless, the facile synthesis of *bis*-DPPs **(9)** has also been reported in solvent-free microwave-assisted synthesis in a higher yield and shorter time (5 min) to produce 65–92% yield [73] (Scheme 5). MW irradiation has been shown to enhance reaction kinetics, resulting in increased yields and significantly reduced reaction times.

DPP derivatives **(10)** and **(11)** have also been conveniently synthesised *via* a two-pot strategy, affording yields of 40–83% and 17% respectively, for the targeted compounds. In the synthesis of **10**, 2-(iodomethyl)quinoline was produced by reacting methylquinoline with iodine. This compound was then transformed into quinolin-2-carboxaldehyde, which served as a reactive intermediate. Subsequently, it was reacted with pyrazoloamine, yielding a product in the range of 40–83%. This reaction protocol is a convenient, metal-free approach that leads to high functional-group compatibility and a wide range of substrate scope [74]. However, compound **11**, synthesised from aldehyde and amino-3-methyl-1-phenylpyrazole, was obtained in a relatively low yield of 17%. This reduced yield has been attributed to the formation of an intramolecular Claisen-type condensation between acetate groups [40] (Scheme 6).

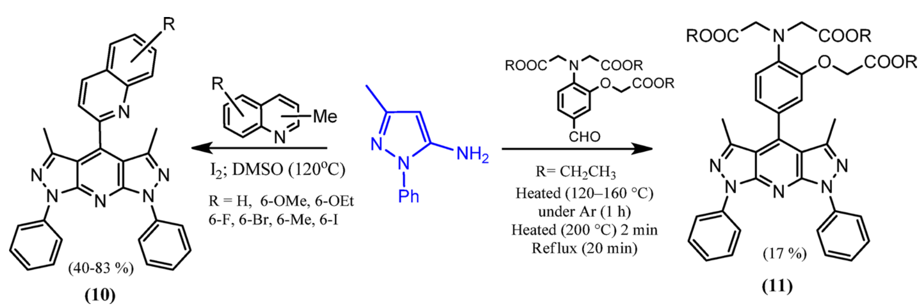
In the one-pot synthesis of DPPs, pseudo-six-component strategies have also been reported, carried out at room temperature in ethanol over a 60-minute reaction period, to yield DPPs in 42–92%.



Scheme 4 Synthesis of DPP derivatives



Scheme 5 Synthesis of DPPs from pyrazolone

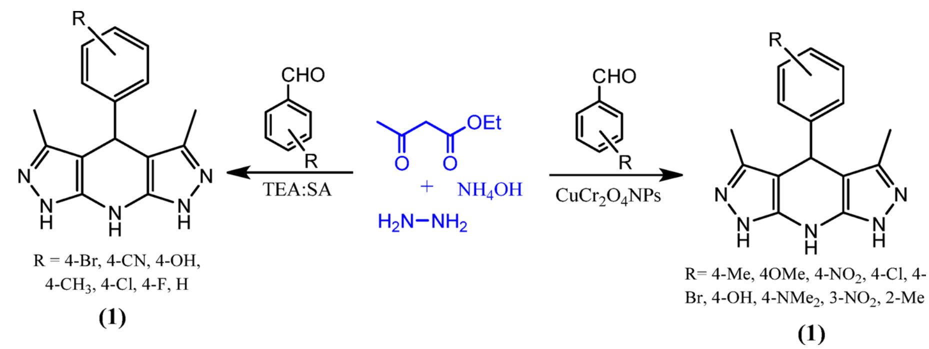


Scheme 6 Synthesis of DPPs from pyrazolone

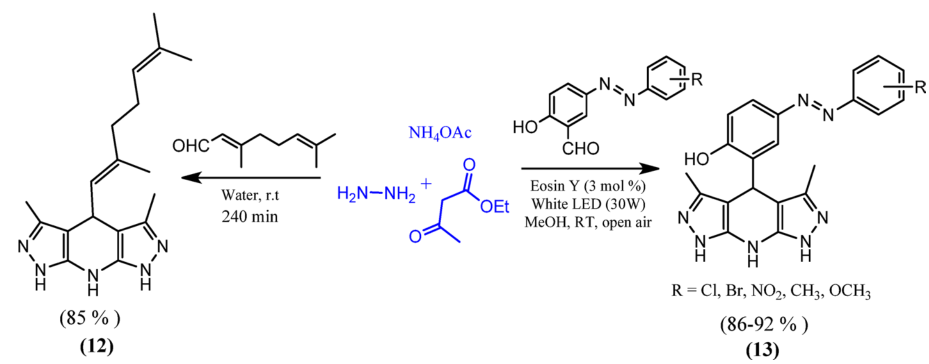
2.2 One pot synthesis

In the one-pot synthesis of DPPs, pseudo-six-component techniques have also been reported at room temperature in ethanol for a 60-minute reaction period, yielding the desired DPPs in 42–92% [63]. Moreover, under microwave conditions for 3 min, the targeted product DPP yielded 98% with the aid of triethanolamine–sodium acetate (TEA: SA) as eutectic solvent [37]. Alternative catalysts, such as $CuCr_2O_4$ nanoparticles ($CuCr_2O_4$NPs), have also been employed in the synthesis of DPPs, yielding 45–60% of the desired products [51] (Scheme 7). Numerous other catalysts have been reported and are summarised in Table 1.

A pseudo-six-component reaction involving an aliphatic aldehyde, ethyl acetoacetate, hydrazine hydrate, and ammonium acetate has been employed for the catalyst-free multicomponent synthesis of DPPs in water at room temperature. This method offers a straightforward work-up and yields a compound **12** in 85% yield [27]. While DPP **13** has also been prepared from the pseudo-six component of ammonium acetate, multifarious aldehydes, hydrazine hydrate and ethyl acetoacetate under visible light and eosin Y dye under simple and metal-free conditions at room temperature to achieve the targeted compounds in 86–92% yield [25] (Scheme 8).



Scheme 7 Synthesis of DPPs from pyrazolone



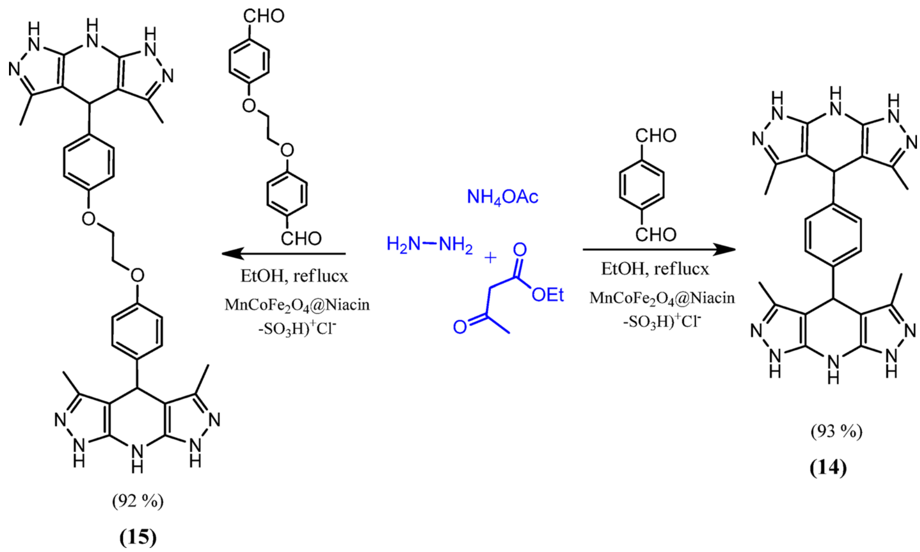
Scheme 8 Catalysed DPP derivatives synthesis

Bis-DPP derivatives **(14** and **15)** were synthesised *via* a multi-component reaction involving aldehyde derivatives, hydrazine, ammonium acetate and ethyl acetoacetate in a 1:4:6:4 molar ratio. Under optimised conditions, the reaction proceeded efficiently at room temperature within 40 min, affording excellent yields of 92–93%. This procedure offers several advantages, including the use of green solvent, easy separation of MnCo-Fe_2O_4@Niacin-$SO_3H)^+Cl^-$ catalyst from the reaction medium, straightforward catalyst recovery, high product purity and the accessibility of the final products [61] (Scheme 9). Moreover, some other catalysts have also been used for the synthesis of *bis*-DPPs, such as nano-$CuCr_2O_4$ [51], $FeNi_3$-IL [56], Fe_3O_4@SiO_2-SO_3H [57], nano-$CdZr_4(PO_4)_6$ [62].

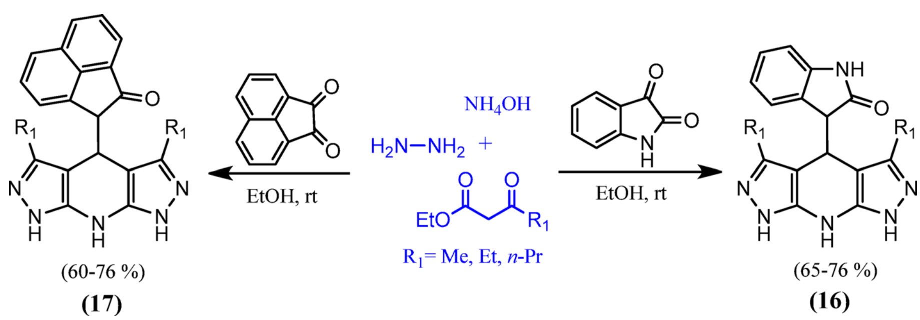
The isatin and acenaphthenquinone-derived DPPs **(16** and **17)** have also been designed *via* the same pseudo-six-component approach in ethanolic medium to produce 60–76% yield of product. Isatin and acenaphthenquinone were used instead of the aldehyde to form spiro-products **(16** and **17)**. It was observed that both aldehydes and activated α-diketones effectively participated in the reaction, yielding the desired products in good yields [75] (Scheme 10). However, lower product yields were observed when using *p*-toluenesulfonic acid (*p*-TSA), potassium carbonate (K_2CO_3) and piperidine as catalysts in aqueous media [75].

2.3 Advantages and challenges in multi-step vs. one-pot DPPs synthesis

DPPs can be synthesised using either one-pot or two-pot methodologies, each offering distinct advantages and limitations. The two-pot approach provides greater flexibility, allowing for the independent optimisation of each reaction step, which can be beneficial for improving yield, purity, and selectivity. This approach ensures higher product purity



Scheme 9 *Bis*-DPP derivatives synthesis *via* $MnCoFe_2O_4$@Niacin-$SO_3H)^+Cl^-$



Scheme 10 Synthesis of spiro-DPP derivatives

due to the possibility of intermediate purification between reaction steps. By allowing the isolation and purification of intermediates, the two-pot synthesis procedure contributes to improved overall product purity. Nevertheless, the two-pot method is time-consuming and incurs higher costs due to the increased consumption of solvents and reagents.

In contrast, the one-pot synthesis of DPPs is time-saving, cost-effective, and environmentally friendly. All reaction steps occur within a single vessel, reducing the need for intermediate purification steps and minimising solvent usage. This method is increasingly preferred in synthetic chemistry due to its ability to deliver high yields and purity while aligning with green chemistry principles.

2.4 Applications of DPPs

DPPs have been widely used in many applications, such as antiwear and antifriction in the steel industry, as well as anticancer and pharmaceutical agents and chemosensors.

2.5 Antiwear and antifriction agents

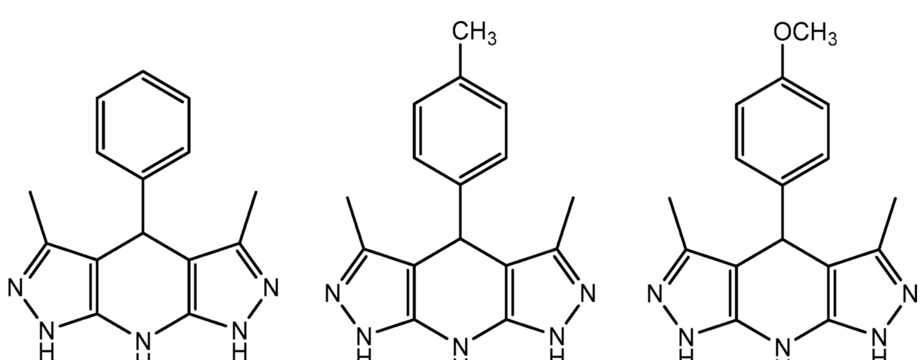
DPPs having electron-donating groups such as methoxy (OMe-DPP) and methyl (Me-DPP) that were prepared *via* one-pot multi-component reaction showed high tribological activity with zero sulfated ash, phosphorus and sulfur (SAPs) additive contents. It also depicted a low concentration (0.25% w/v) of maximum activity. The loading ramp and antiwear tests (conc. 0.25% w/v) follow the trend of OMe-DPP **(1b)** >Me-DPP **(1a)** >H-DPP **(1)**. Moreover, the wear-scar surface is authenticated in morphology for tribiological activity. EDX-analysis displayed tribiochemical film wear-scar surface showed adsorption on steel due to the presence of oxygen and nitrogen heteroatoms [37] (Fig. 2).

2.6 Cytotoxic agents

The synthesis of DPPs *via* Fe_3O_4@KCC-1-*n*Pr-NH_2 has also been reported under moderate conditions. A series of DPPs **(18a-f)** was evaluated for their cytotoxic activity against HT29 and MCF7 cancer cell lines. Among them, **18a**, **18c** and **18f** exhibited notable cytotoxic effects. Additionally, compound **18e** showed promising activity against MCF7 cells, while **18b** displayed significant efficacy against HT29 cells. DPPs **18a**, **18c** containing indole and **18f** hydroxide moieties displayed remarkable cytotoxic activity and have also been documented as the most potent against HT29 and MCF7 cell lines [54]. Evaluating DPPs for otherpotential anticancer agents has also been reported using **(19a-d)** against HeLa and SK-BR-3 cancer cell lines. Among the series, DPPs **19b** and **19c** exhibited strong interactions with receptors to inhibit the anticancer cells' growth [35] (Fig. 3).

2.7 Antibacterial, antifungal and anti-inflammatory activities

Phenyl-substituted DPPs **(20 & 21)** were synthesised with the aid of *p*-TSA under acetonitrile reflux to afford a 92% yield. The compounds were evaluated for antibacterial and antifungal activity against bacteria (*K. pneumonia*, *P. aeruginosa*, *E. coli*, *S. aureus*, *B. subtilis*, and *S. pyogenes*) and fungi (*A. janus*, *P. glabrum*, *A. sclerotiorum*, and *A. niger*). Unsubstituted THDPP **20** exhibited significant activities of MIC (8 µg/ml) against *(A) niger*, *P. aeruginosa*, *K. pneumonia*, *S. aureus* and *(B) subtilis*. In comparison, methoxy-substituted DPP **20** displayed activity against *A. janus*, *E. coli* and *S. aureus*. Furthermore, dimethoxy substituted DPP **13** presented significant activity against *A. sclerotiorum*, *A. niger*, *E. coli*, and *P. aeruginosa* [76]. Compound **(22)** showed superb anti-inflammatory activities due to nitrogenous-nucleus and reactive substituents [77] (Fig. 4).



(1) **(1a)** **(1b)**

Fig. 2 DPPs as antiwear and antifriction agents

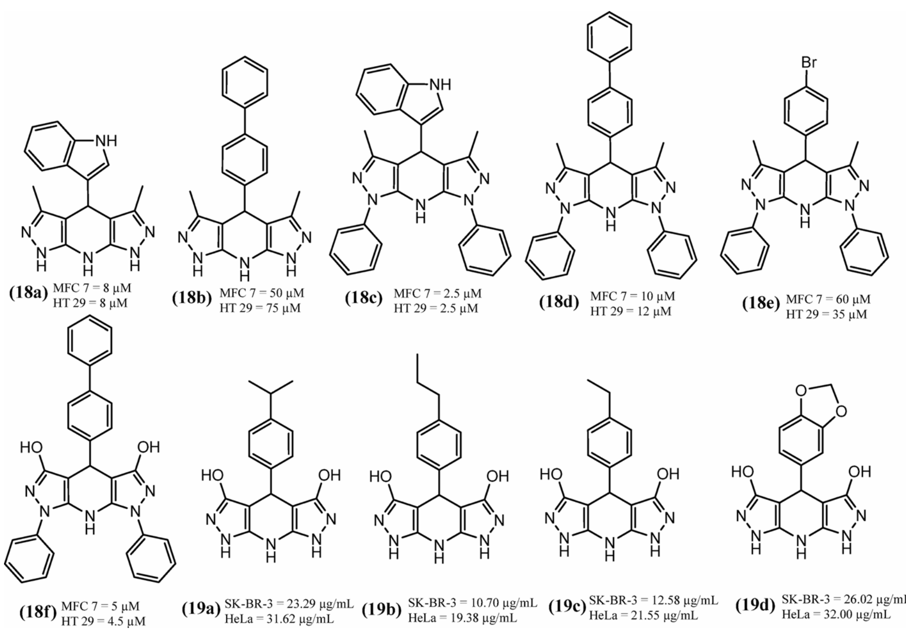


Fig. 3 DPP derivatives as a cytotoxic agent

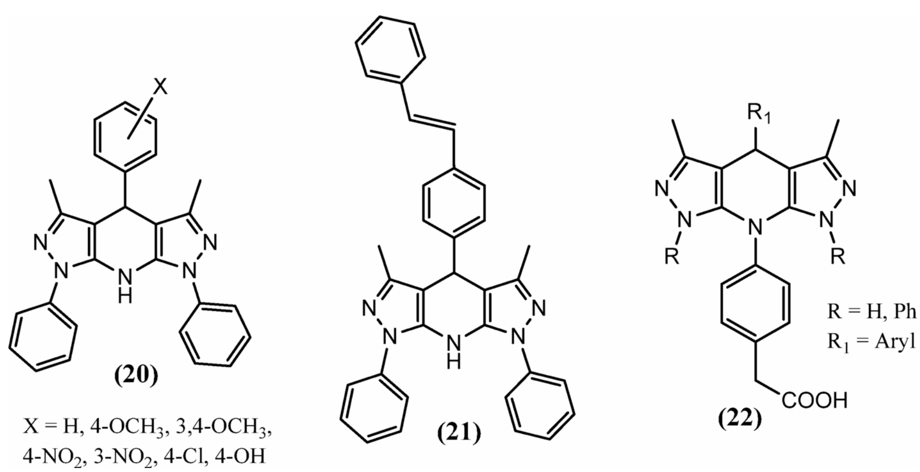


Fig. 4 DPPs as antibacterial, antifungal and anti-inflammatory agents

2.8 Chemosensors for metal detection activities

Metal detection using chemosensor of DPPs **(23)** has also been carried out *via* colourimetric method for Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Ag^{+}, Hg^{2+}, Al^{3+}, Cu^{2+}, Cr^{3+}, Ni^{2+}, Mn^{2+}, Cd^{2+}, Zn^{2+}, Pb^{2+}, Co^{2+}, Fe^{3+} and Fe^{2+} ions with their nitrate salts solutions [45]. Metal detector monitoring *via* the chemical method is supported to prevent several risks at irregular levels or theoretically harmful metals. This procedure holds potential for the investigation of various disease treatments, including cancer, anaemia, Alzheimer's disease, and diabetes. Notably, the interaction of DPPs with iron ions (Fe^{3+}) has demonstrated strong analytical capabilities, exhibiting a maximum absorption wavelength at 468 nm and an ion detection limit as low as 8.1×10^{-9} M. The organic chemosensor DPP (**23**) demonstrated excellent detection capabilities for Fe^{3+} ions, including a low detection limit, high selectivity, and compatibility with various solvents [45] (Scheme 10). Notably, the hydroxyl-substituted DPP **23** exhibited strong interactions with Fe^{3+} ions, forming stable

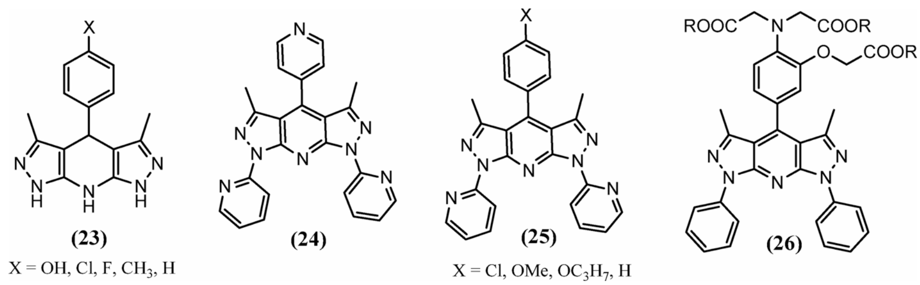


Fig. 5 DPP derivatives as metal detection agent

complexes. It is proposed that this coordination occur via the NH moiety of the pyrazole ring, facilitating effective binding and signal response.

DPPs (**24** & **25**) have also been used for metal detection (Cu^{2+}, Hg^{2+}, Co^{2+} and Ni^{2+}). However, only the 4-phenyl-substituted probe **(25)** without a substituent was potent by fluorescence quenching phenomena due to the presence of ethylenediamine. Unsubstituted probe **(25)** showed a significant sensitivity for Cu^{2+} in low concentrations (26 nM) *via* “on – off – on” fluorescent switching [78]. DPP **(26)** has also shown potential for fully conjugated low-affinity fluorescent Ca^{2+} indicators [40] (Fig. 5).

3 Conclusion

This review expresses that the DPP derivatives belong to the heterocyclic class that has attained attention because of their diverse biological activities and potential applications in catalysis, medicinal chemistry and materials science. DPPs are typically synthesised *via* two-pot and one-pot cyclisation reactions through condensation and multicomponent reactions under acidic or basic conditions. DPPs represent a versatile class of compounds with significant potential in various fields. Continued research into their synthesis and applications can lead to the development of new drugs, advanced materials, and innovative technologies. The DPP’s applications in medicinal chemistry as chemical sensors and organic electronics, including OLEDs and photovoltaic devices, anticancer agents, and antimicrobial activity exhibit significant antibacterial, antifungal, and antiviral properties.

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None.

Author contributions
S.F conceptualized and SF and Z.N both write the original manuscript and reviewed it.

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None.

Data availability
The data generated during this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competinginterests
The authors declare no competing interests.

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