A review on green synthesis and biological activities of nitrogen and oxygen containing heterocycles

Susheel Gulati*, Rajvir Singh and Suman Sangwan

[1]Department of Chemistry, Chaudhary Charan Singh Haryana Agricultural University, Hisar, 125004, India

***Corresponding author Email: sgbhuna@hau.ac.in**

Abstract

Heterocycles are unique precursors for the synthesis of various pharmaceuticals and agrochemicals particularly those possessing N- or O- moieties. The development of methods to prepare heterocycles is of great importance in synthesis of organic compounds, especially the heterocycles which can be found in natural products. The synthesis of nitrogen and oxygen containing heterocycles *viz*. coumarins, dihydropyrimidinones, imidazoles, isoxazoles and benzimidazoles represented an attractive and demanding work for chemists as these nucleus has found extensive applications in several fields such as material science, analytical chemistry and most importantly in medicinal chemistry. Organic synthesis has been attracted towards the development of new environmental friendly procedures to achieve the goals of green chemistry. The fundamental aspects of green chemistry are use of biocatalysts and environmental benign solvents under mild conditions. The present review article summarized the green synthetic methods and biological activities of nitrogen and oxygen containing heterocycles.

Keywords: Heterocycles, Coumarins, Dihydropyrimidinones, Imidazoles, Isoxazoles, Benzimidazoles and Green chemistry

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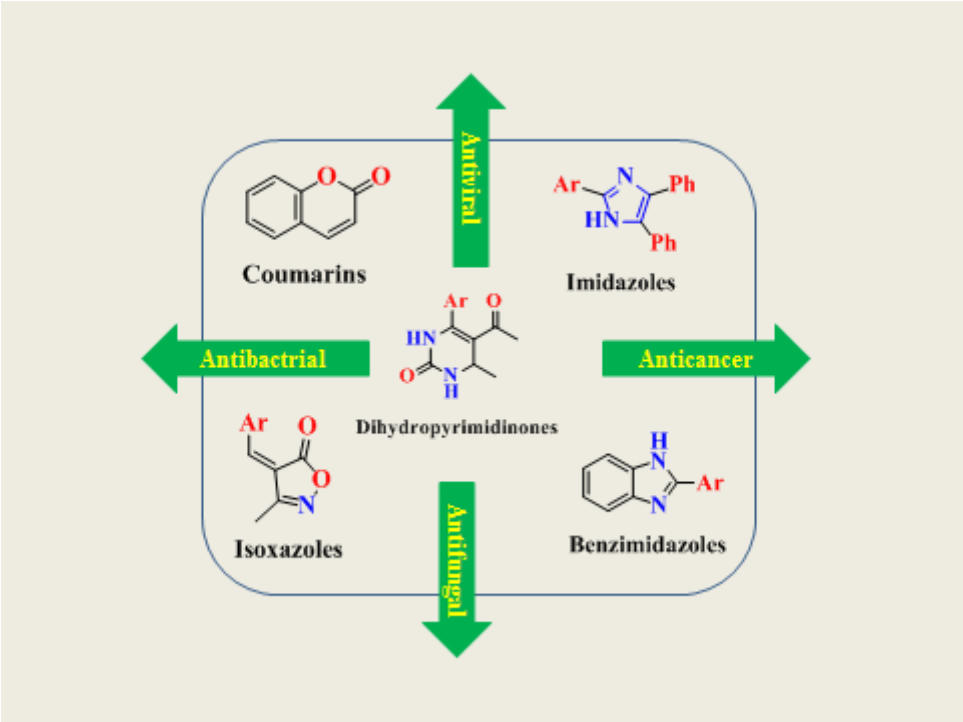
Graphical abstract



Introduction

Nowadays application of green chemistry for the formation of potentially bioactive heterocyclic molecules has turned out key area of research for organic chemist due to increasing concern over environmental issues. Therefore, the development of non-hazardous synthetic procedures gained the particular attention of synthetic chemist as frontier task in present scenario. Heterocyclic compounds specially containing nitrogen and oxygen atoms have been the major molecules in organic chemistry because of their extraordinary biological activities, particularly their anticancer activity. Coumarins are a supreme class of benzopyranes which have benzene ring linked to pyrane ring.[1] They are extensively used as food additives, perfumes, agrochemicals, cosmetics, pharmaceuticals and also in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers.[2] They also have broad range of biological activities *viz*. antibacterial, anticancer, inhibitory of HIV-1 protease, inhibitory of platelet aggregation.[3-6] Dihydropyrimidinones derivatives belong to fascinating class of heterocyclic molecules which have wide range of biological activities, such as

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antiviral, antitumour, antibacterial and calcium channel modulating activity.[7-10] Imidazole is an five membered aromatic ring acts as an important pharmacophore in drug discovery. Imidazole ring is present in many natural and synthetic bioactive compounds such as biotin, essential amino acids, histidines, histamine, fungicides and herbicides. They have also broad range of biological activities such as anticancer, antifungal, antiviral, antibacterial, antitubercular, anti-parasitic, antihistaminic, anti-inflammatory, anti-neuropathic, anti-obesity and antihypertensive.[11-20] Isoxazole scaffolds are influential class of heterocyclic compounds and display broad spectrum of biological and pharmaceutical activities such as β-adrenergic receptor antagonists, immunosuppressive, anti-inflammatory, antibacterial, HDAC inhibitors, antifungal, antitumor, antioxidant, antiprotozoal, antiviral, anti-tubercular, anti-HIV, analgesic and anti-androgens (II).[21-35] Benzimidazoles and its derivatives constitute one of most biologically active class of compounds, possessing a broad spectrum of activities such as neuropeptides YY_1 receptor antagonists, potent inhibitors of TIE-2 and VEGFER-2 tyrosine kinase receptors, antitumour agents, gamma-amino butyric acid (GABA) agonists and 5-HT_3 antagonists.[36-39] Recently, waste minimized synthesis of these heterocycles gaining more importance. Therefore, in this review paper we describe green synthesis and biological activities of these heterocyclic compounds. We hope that this paper will open new opportunities for organic chemist to design future generation novel and potent nitrogen and oxygen containing heterocycles.

Green synthetic methods for the preparation of substituted coumarins

Khan *et al*. reported eco-friendly method for the synthesis of novel substituted chromene-3-carboxamide derivatives **(3)** by condensation reaction between substituted salicyaldehyde **(2)** with N-(Substitiuted) phenyl malonic acid **(1)** in presence of basic catalyst ***viz***. piperidine (Scheme 1).[40]

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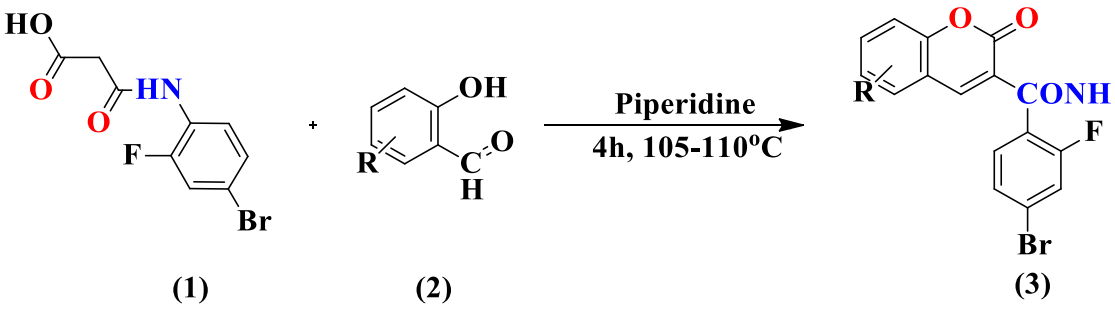
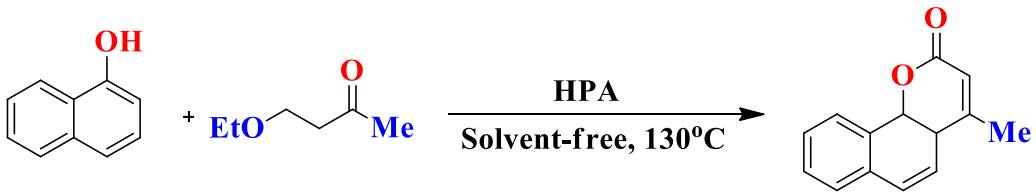


(1) (2) (3)

Scheme 1: Synthesis of substituted chromene-3-carboxamide derivatives

Synthesis of 4-methylnaphtho-(1,2-*b*)-pyran-2-one **(6)** from the condensation reaction between *α*-naphthol **(4)** and *β*-ketoester **(5)** in presence of green and reuseable catalyst *viz*. sodium30-tungsto pentaphosphate in a solvent-free medium and under thermal conditions reported by Heravi and his coworkers (Scheme 2).[41]



(4) (5) (6)

Scheme 2: Synthesis of 4-methylnaphtho-(1,2-*b*)-pyran-2-one

Hussien and his colleagues synthesized coumarins derivatives **(6)** *via* Pechmann condensation reaction of naphthol **(4)** and *β*-ketoester **(5)** using Amberlyst-15 as a green and efficient catalyst (Scheme 3).[42] For standardization of reaction conditions, a mixture of *α*-naphthol and ethylacetoacetate was used as model substrate for examine the reaction conditions such as temperature, time of completion of reaction, solvents molar ratio of catalyst and type of catalysts. They found that best result was obtained when the model reaction was explored in the presence of Amberlyst-15 at 110°C for 150 min under solvent-free conditions with an excellent yield i.e. 85% of **(6)**.

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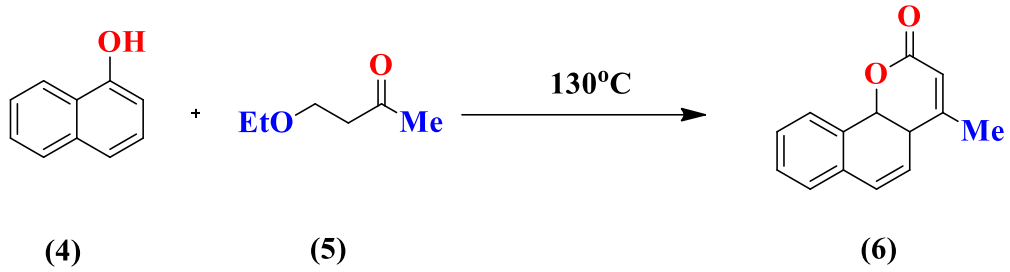
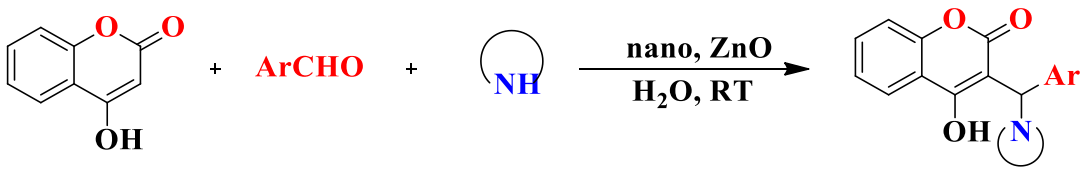


(4) (5) (6)

Scheme 3: Synthesis of coumarins derivatives

Ghosh and Das reported an green efficient and facile method for the synthesis of substituted benzyl amino coumarin derivatives **(10)** by the reaction of 4-Hydroxycoumarin **(7)**, cyclic secondary amine **(9)** and substituted aldehydes **(8)** in aqueous media in presence of nano crystalline ZnO at room temperature (Scheme 4).[43] Initially, *m*-nitrobenzaldehyde, 4-Hydroxycoumarin and piperidine were employed as reactant for the model reaction to synthesize benzyl amino coumarin derivatives in the presence of catalytic amount of zinc oxide. For optimization of reaction conditions, they performed the reaction in presence of polar and non-polar solvents *viz*. DMSO, ethanol, methanol, toluene, tetrahydrofuran and acetonitrile. They found that polar protic solvents produced better yield than other solvent and excellent catalytic activity of nano ZnO was observed in aqueous medium. Then, they explored the same model reaction in aqueous medium at room temperature in presence of different catalyst *viz*. nano aluminium oxide, *L*-Proline, alum zeolites, Tetrabutylammonium bromide and commercial ZnO. They found that in presence of ZnO, the desired product **(10)** was obtained in 93% within 15 min.



(7) (8) (9) (10)

Scheme 4: Synthesis of benzyl amino coumarin derivatives catalysed by nanocrystalline ZnO at room temperature

Halder *et al*. reported simple, novel and effortless synthesis of biscoumarins **(11)** and pyranocoumarins **(13)** in presence of both electrons donating and withdrawing substituted aldehydes

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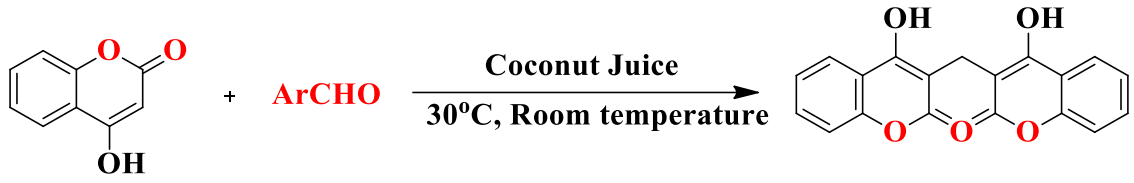
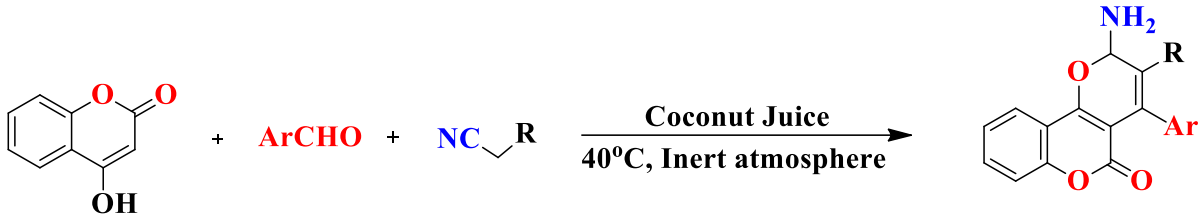
(8) using coconut juice as green catalyst. High yields, no work-up and no need of column chromatography are some beauties of present methodology (Scheme 5 and Scheme 6).[44]



(7) **(8)** **(11)**

Scheme 5: Synthesis of substituted biscoumarins



(7) **(8)** **(12)** **(13)**

R = CN; CO_2Et

Scheme 6: Synthesis of substituted pyranocoumarins

Kovvuri and his colleagues synthesized pyrazole-aniline linked coumarin derivatives **(16)** from reaction between aniline **(14)**, pyrazole aldehyde **(15)** and 4-Hydroxy coumarin **(7)** in presence of methanol (Scheme 7).[45] For optimization of reaction conditions a model reaction using above substrate was performed without solvent and also in presence of various solvents *viz*. acetonitrile, methanol, ethanol, water and chloroform. Among all the solvents used, it was found out that the reaction in methanol afforded 15% of product. Further, they performed the same model reaction under refluxed condition and observed that using methanol as solvent resulted in a product yield up to 91% within 5h. Poor yields of product were obtained without solvent and the environmentally benign solvents *viz*. ethanol and water resulted in moderate yield. After standardisation of reaction conditions they examined the substrate scope of substituted pyrazole synthesized along with anilines. They found that the method worked well with both electron rich and electron deficient substrate. However aniline with electron rich substituents gave lower yield as compared to electron deficient substituents on aniline. The plausible mechanism for the formation of pyrazole aniline linked coumarin is shown in

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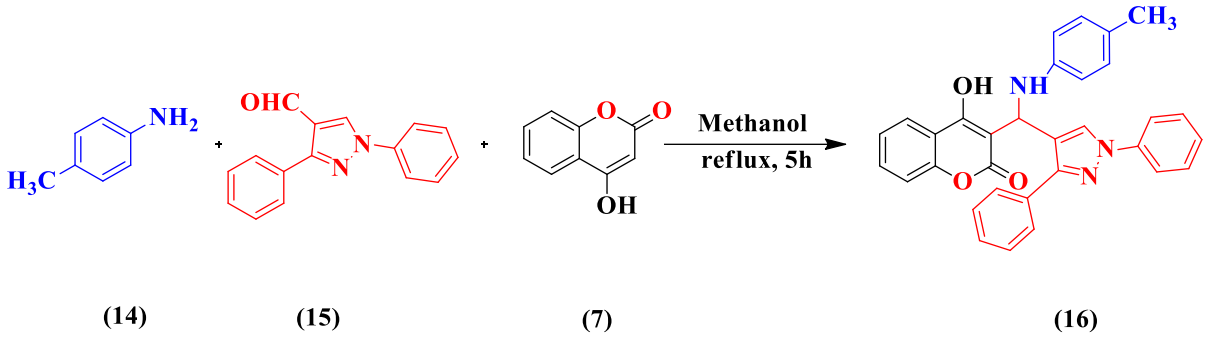
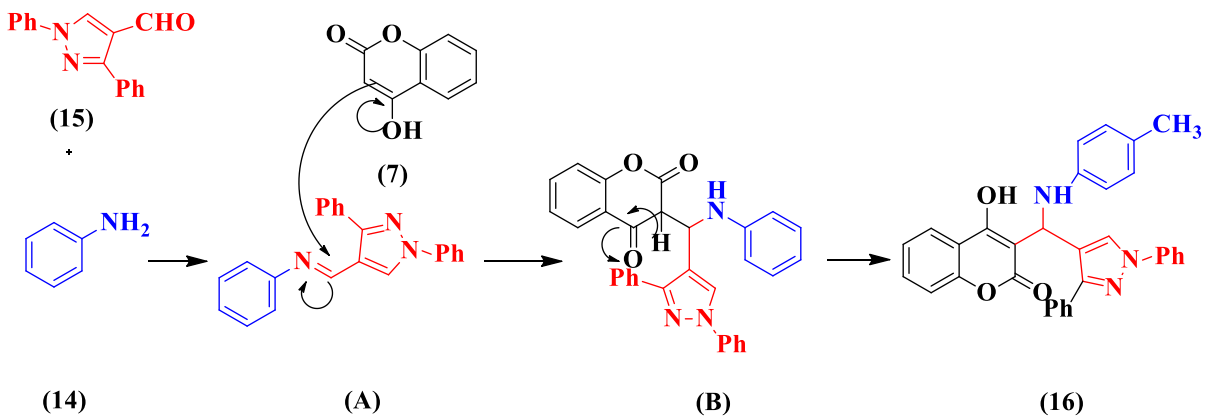
Fig 1, wherein initially the aniline and pyrazole aldehyde undergo condensation resulting in formation of imine **(A)**, by the nucleophilic attack of coumarin on imine gave the intermediates **(B)**, which undergoes rearrangement to give desired product.



(14) (15) (7) (16)

Scheme 7: Synthesis of pyrazole-aniline linked coumarin derivatives



(14) (A) (B) (16)

Fig 1: Plausible reaction mechanism

A simple, efficient and environmentally friendly method for the synthesis of 3-carboxycoumarins **(18)** *via* Knoevenagel condensation of Meldrum's acid **(17)** with salicyaldehyde **(1)** using aqueous extract of pods of *Acacia concinna* as a green and cost-effective catalyst was reported by Chavan and his coworkers (Scheme 8).[46] In the starting, a model reaction using 2-Hydroxybenzaldehyde and Meldrum's acid in 5mL 10% (*w/v*) aqueous extract of *Acacia concinna* pods at room temperature was explored and they observed excellent yield of desired product (92%) after 3h. The same model reaction was also performed using different concentration of catalyst and it

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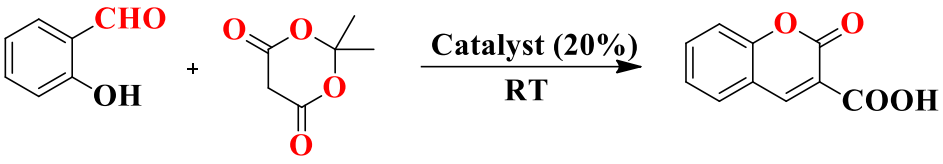
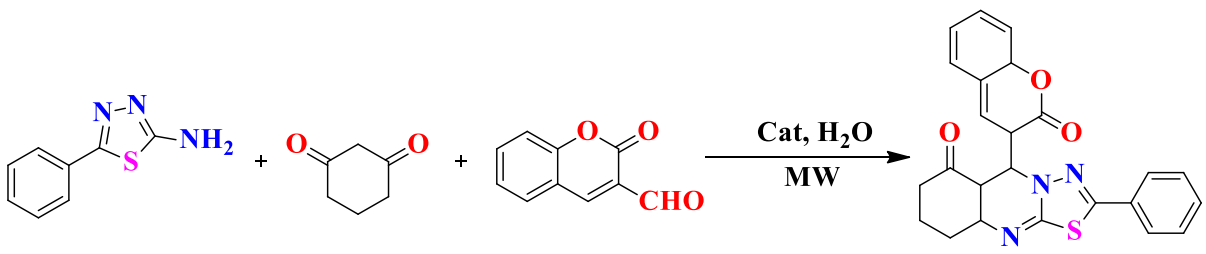
was observed that 20% of catalyst shows maximum yield (98%) and time of completion of reaction is also reduced.



(1) **(17)** **(18)**

Scheme 8: Synthesis of 3-Carboxycoumarins

Wadhwa *et al*. reported the synthesis of novel biofunctional coumarin-thiadiazoloquinazolinone **(21)** containing heterocycles *via* one-pot, three component reaction between 5-aryl-1,3,4-thiadiazol-2-amines **(19)**, 1,3-dicarbonyls **(5)** and 2-oxo-2*H*-chromene-3-carbaldehyde **(20)** under microwave irradiation in water (Scheme 9)[47]. For optimization of reaction condition a model reaction was carried out between 5-phenyl-1,3,4-thiadiazol-2-amines, 1,3-cyclohexanedione and 2-oxo-2*H*-chromene-3-carbaldehyde to yield 5-(2-oxo-2*H*-chromen-3-yl)-2-phenyl-8,9-dihydro-5*H*-[1,3,4]thiadiazolo[2,3-b]quinazolin-6(7*H*)-one in water. Further, the model reaction was also studied in presence of acids such as AcOH, $Sc(TOf)_3$, $Bi(NO_3)_3.5H_2O$ and bases include DABCO and TEA. Amongst all, they found that $Bi(NO_3)_3.5H_2O$ was found to be most suitable catalyst. A possible mechanism for $Bi(NO_3)_3.5H_2O$ mediated multicomponent reaction is shown in Fig 2. First, there is decomposition of $Bi(NO_3)_3.5H_2O$ into $Bi(OH)_3$ and HNO_3. Both species enhance Knoevenagel condensation reaction between cyclic-1,3-diketones and 2-oxo-2*H*-chromene-3-carbaldehyde to obtain *α,β*-unsaturated diketone intermediate **I**. Than Michael addition of 5-aryl-1,3,4-thiadiazol-2-amines into intermediate **I** would form intermediate II. Finally, intermolecular cyclization followed by removal of water molecule to give the final product.



(19) **(5)** **(20)** **(21)**

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Scheme 9: Synthesis of 5-(2-oxo-2*H*-chromen-3-yl)-2-phenyl-8,9-dihydro-5*H*-[1,3,4]thiadiazolo[2,3-b]quinazolin-6(7*H*)-one in water

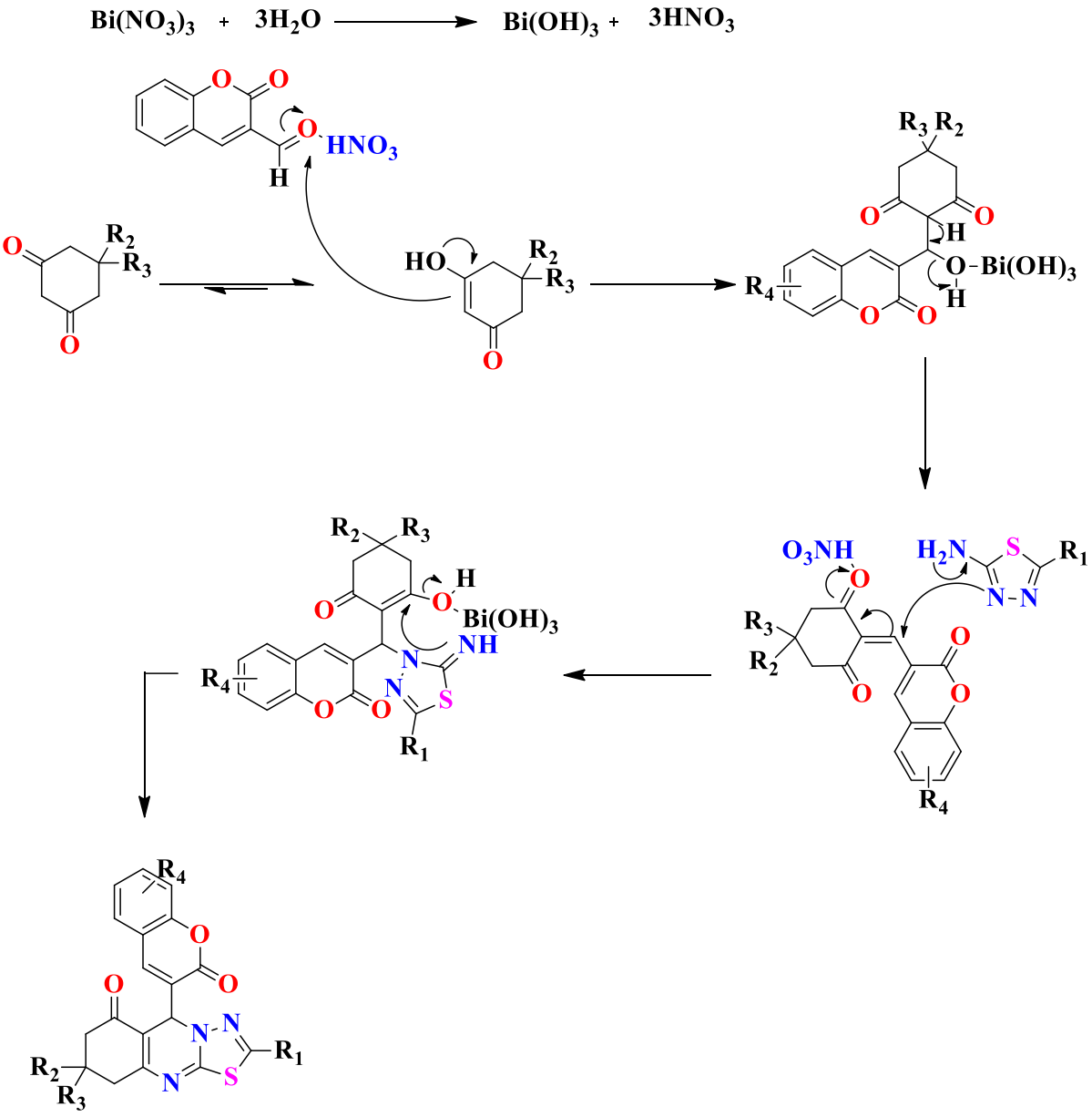

Fig 2: Plausible mechanism for $Bi(NO_3)_2.5H_2O$ catalyzed synthesis of 8-alkyl 5-(2-oxo-2*H*-chromen-3-yl)-2-aryl-8,9-dihydro-5*H*-[1,3,4]thiadiazolo[2,3-b]quinazolin-6(7*H*)-ones

Keri *et al*. reported solvent-free synthesis of substituted coumarins **(23)** using Phosphotungstic acid as a green catalyst *via* von Pechmann condensation reaction of substituted phenols **(22)** and *β*-keto esters **(5)** (Scheme 10)[48]. The present methodology offers significant

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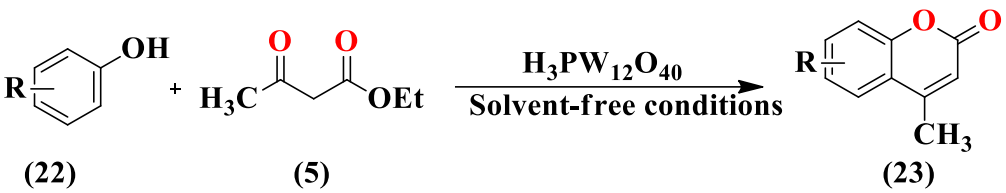
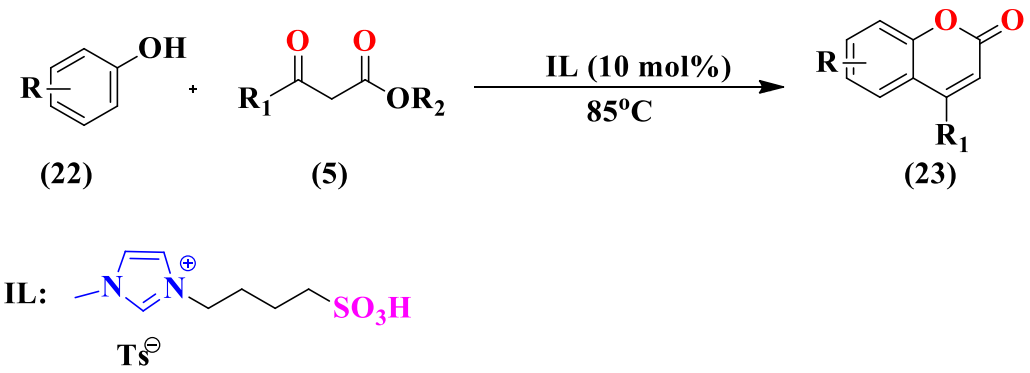
advantages for the synthesis of coumarins with respect to yield of products, simplicity in reaction operation and green aspects by avoiding toxic conventional catalysts and solvents.



(22) (5) (23)

Scheme 10: Synthesis of substituted coumarins using Phosphotungstic acid

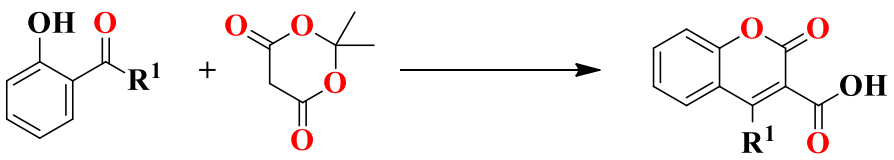
An efficient and facile method has been reported for the synthesis of substituted coumarin derivatives **(23)** using a Bronsted acidic ionic liquid as catalyst under solvent-free conditions *via* condensation reaction between substituted phenols **(22)** and *β*-keto esters **(5)** by Das and his coworkers (Scheme 11)[49].



(22) (5) (23)

Scheme 11: Synthesis of substituted coumarins using Bronsted acidic ionic liquid

Fiorito *et al*. reported the synthesis of coumarin-3-carboxylic **(18)** *via* Knoevenagel condensation reaction between salicyaldehyde **(1)** and Meldrum's acid **(17)** using juices from edible fruits and vegetables (Scheme 12)[50]. The main advantages of this method are simple work-up, mild reaction conditions, short reaction time and excellent yield of products.



(1) (17) (18)

R^1 = H; CH_3

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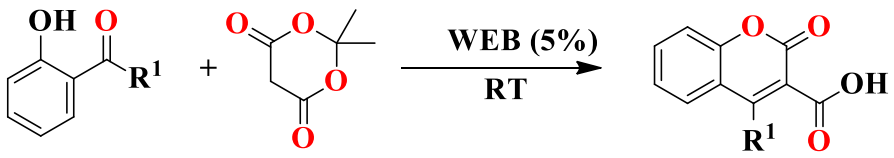
Scheme 12: Synthesis of coumarin-3-carboxylic

Bagul and his coworkers reported the synthesis of 3-carboxycoumarins **(18)** by one-pot Knoevenagel condensation and intramolecular cyclization of substituted salicyaldehyde **(1)** with Meldrum's acid **(17)** using water extract of banana (Scheme 13)[51]. Initially, the model reaction between salicyaldehyde and Meldrum's acid using water extract of banana peels was explored for synthesis of 3-carboxycoumarin derivatives at room temperature. The reaction was found to complete within 420 min to give the 2-oxo-2*H*-chromene-3-carboxylic acid as product in excellent yield. Inspired by these results, they studied the effect of various solvents *viz*. ethanol, methanol, acetonitrile and dichloromethane etc. They found that ethanol was efficient solvent for synthesis of desired product in in high yield (94%) in 420 min. Furthermore, concentration of catalyst was also standardized through the reaction of salicyaldehyde and Meldrum's acid at various concentrations of banana peels extracts i.e. 0, 1, 5, 10, 20, 50%. The result revealed that, water extract of banana showed highest yield in lowest time (420 min) at 5% of catalyst concentration. Therefore, the best and most favourable reaction condition for the model reaction is 5% (*w/v*) of 5 mL water extract of banana as the catalyst in ethanol at room temperature.



(1) **(17)** **(18)**

R^1 = H; CH_3

Scheme 13: Knoevenagel condensation routes to coumarin-3-carboxylic using water extract of banana peels

Peter *et al*. reported an efficient, mild and eco-friendly method for the synthesis of substituted coumarins **(23)** *via* Pechmann condensation reaction of substituted phenols **(22)** and *β*-ketoesters **(5)** in the presence of Polyvinyl sulfonic acid as a catalyst (Scheme 14)[52].

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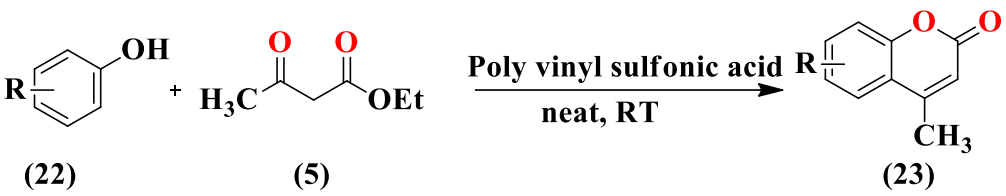
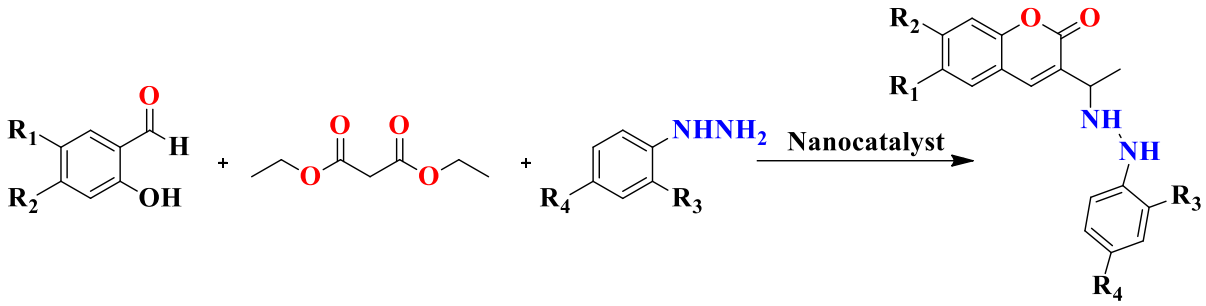


(22) (5) (23)

Scheme 14: Synthesis of substituted coumarins using polyvinyl sulfonic acid

Maleki *et al*. reported synthesis of novel coumarin derivatives **(26)** *via* one-pot reaction of salicyaldehyde **(1)**, diethylmalonate **(24)** and phenyl hydrazine **(25)** in the presence of core/shell nanocatalyst in EtOH (Scheme 15)[53].



(1) (24) (25) (26)

Scheme 15: Synthesis of substituted coumarins using nanocatalyst

Farahi *et al*. reported the synthesis of novel pyrano coumarins **(28, 29)** *via* three-component reactions of substituted aldehydes **(8)**, malononitrile **(12)** and hydroxycoumarin **(7, 27)** using silica sodium carbonate as catalyst (Scheme 16)[54]. The plausible mechanism for the formation of pyrano coumarin is shown in Fig 3. The major benefits of present methods over existing methods can be realized by comparing our results with those of some reported methods as shown in Table 1.

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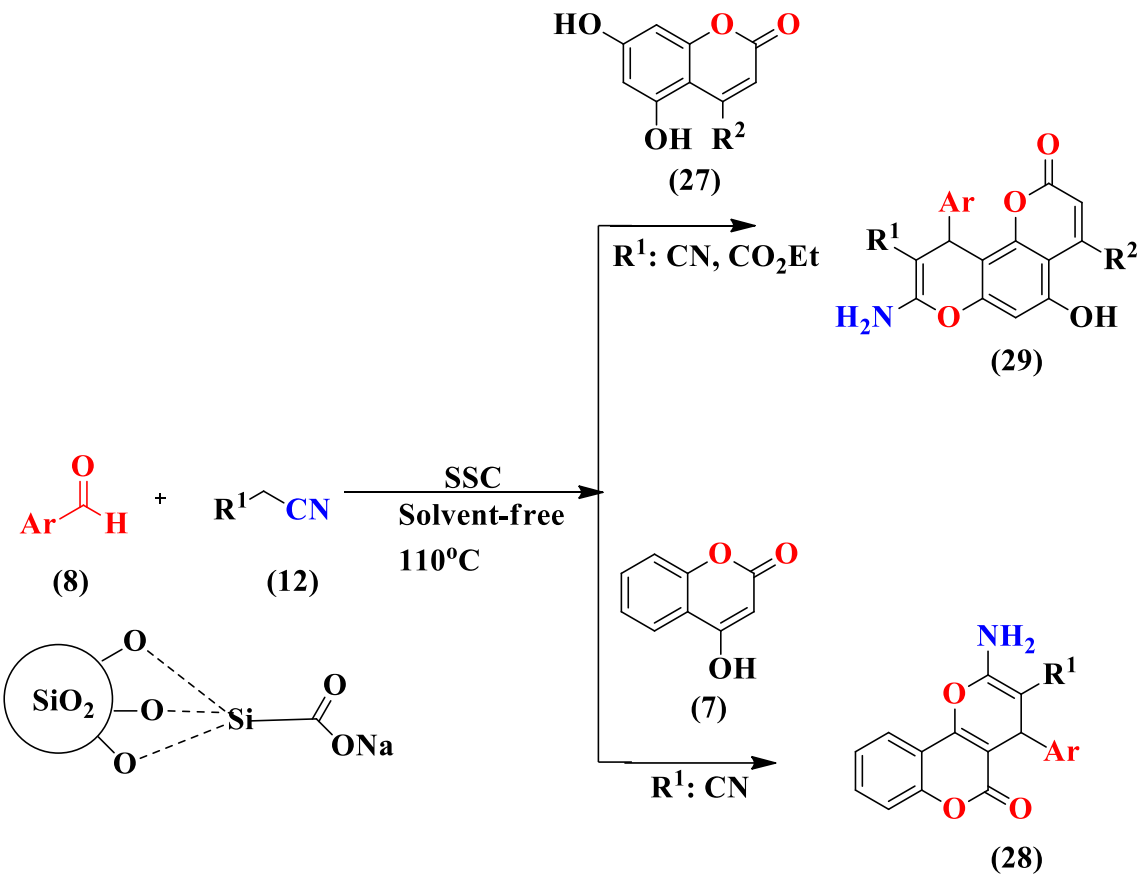

Scheme 16: Synthesis of pyrano coumarins in presence of silica sodium carbonate

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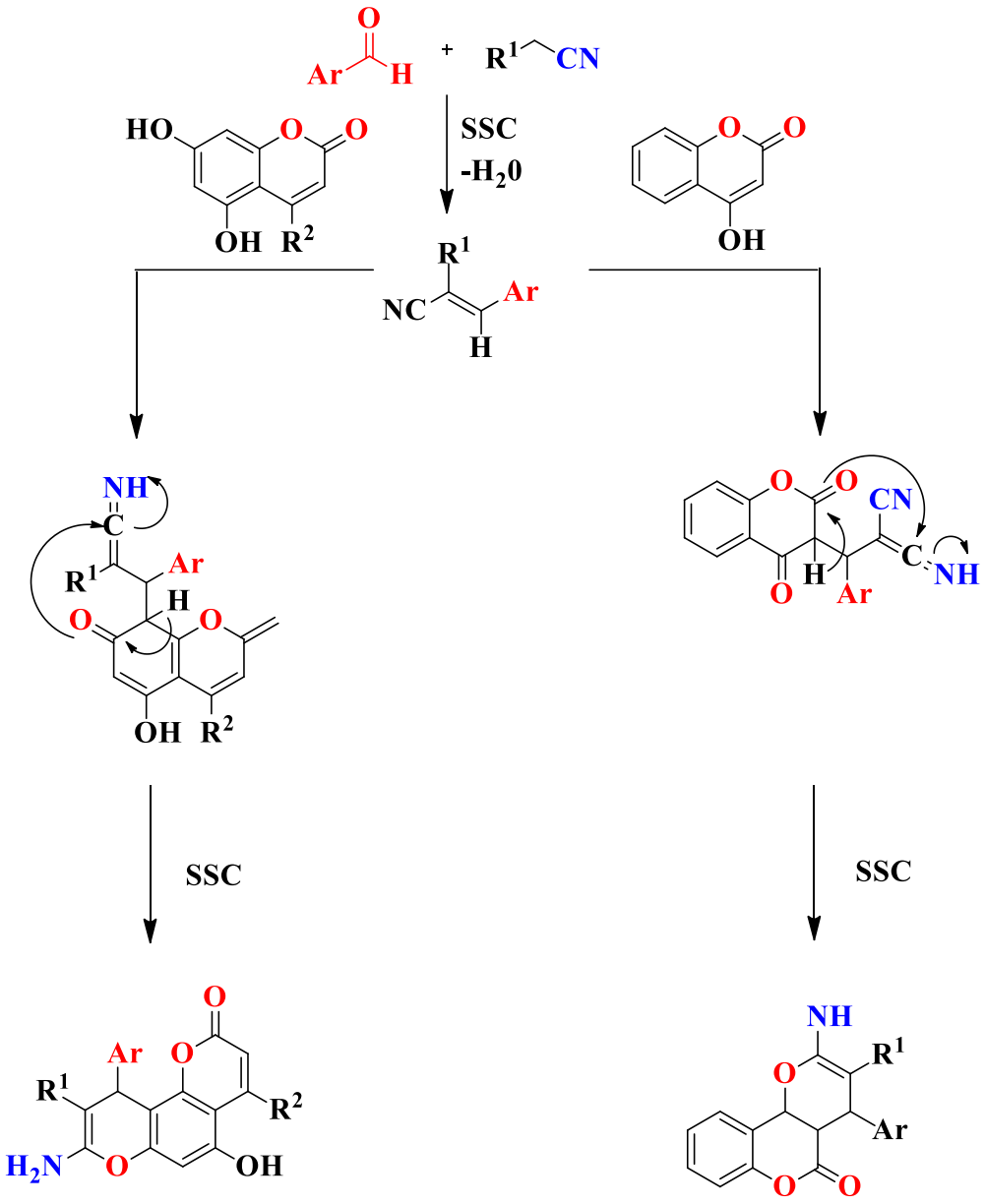

Fig 3: Plausible mechanism for SSC-catalyzed synthesis of pyrano coumarins

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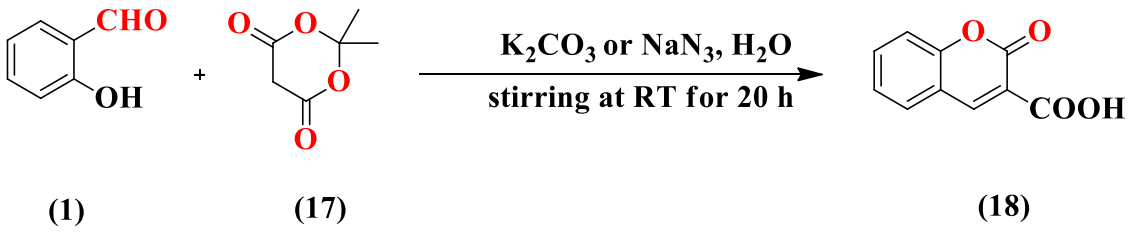
Table 1: Comparison of current work with other reported methods

Entry	Conditions	Time (min)	Yield (%)	References
1	Piperidine, EtOH, Reflux	30	70	55
2	SDS, H_2O, 60°C	120	85	56
3	DABCO, 100°C	30	94	57
4	TBBDA, EtOH:H_2O, Reflux	150	88	58
5	DAHP, EtOH:H_2O, Room temperature	180	81	59
6	KF-Al_2O_3, EtOH, reflux	240	90	60
7	TEBA, H_2O, 90°C	420	96	61
8	**SSC, solvent-free, 110°C**	**30**	**85**	**Current work**

Goutam Brahamchari reported a simple, efficient and facile method for the room temperature one-pot synthesis of potentially biologically active coumarin-3-carboxylic acids **(18)** in water *via* Knoevenagel condensation and intramolecular cyclization of diverse 2-hydroxybenzaldehydes **(1)** with Meldrum's acid **(17)** using either potassium carbonate or sodium azide as commercially available, cheap and eco-friendly catalyst (Scheme 17)[62]. Mild reaction conditions, good to excellent yields, high atom-economy, easy isolation of products, no need of column chromatography, clean reaction profiles and applicability towards large-scale synthesis are some merits of present methodology. The proposed mechanism for the formation of coumarin-3-carboxylic acids is shown in Fig 4.



Scheme 17: One-pot synthesis of coumarin-3-carboxylic acids in water at room temperature

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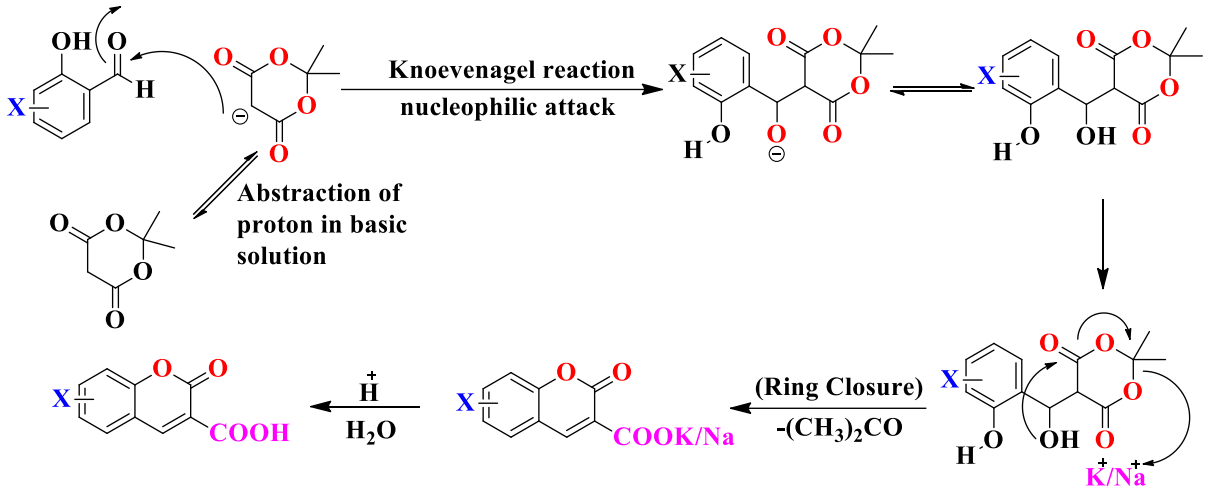
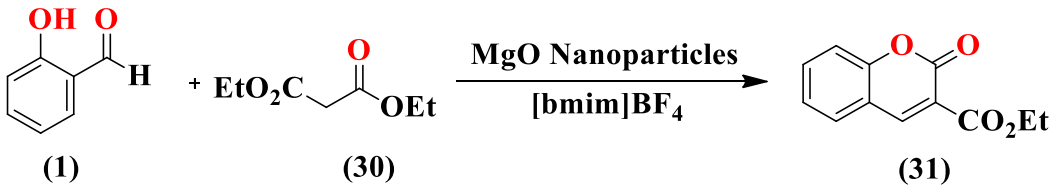


Fig 4: Proposed mechanism for base-catalyzed one-pot synthesis of coumarin-3-carboxylic acids in water

Dinparast and Valizadeh synthesized coumarin derivatives **(31)** through one-pot reaction between salicyaldehyde **(1)** and diethylmalonate **(30)** using MgO nanoparticles as a highly efficient reusable heterogeneous base catalyst in ionic liquid [bmim]BF_4 (Scheme 18)[63]. Good yields of reaction products, short reaction times, solvent-free and mild reaction condition, operational simplicity and use of inexpensive and non-toxic catalyst are some advantages of present methodology. The plausible mechanism for the formation of coumarin is shown in Fig 5.



Scheme 18: One-pot synthesis of substituted coumarins using MgO nanoparticles

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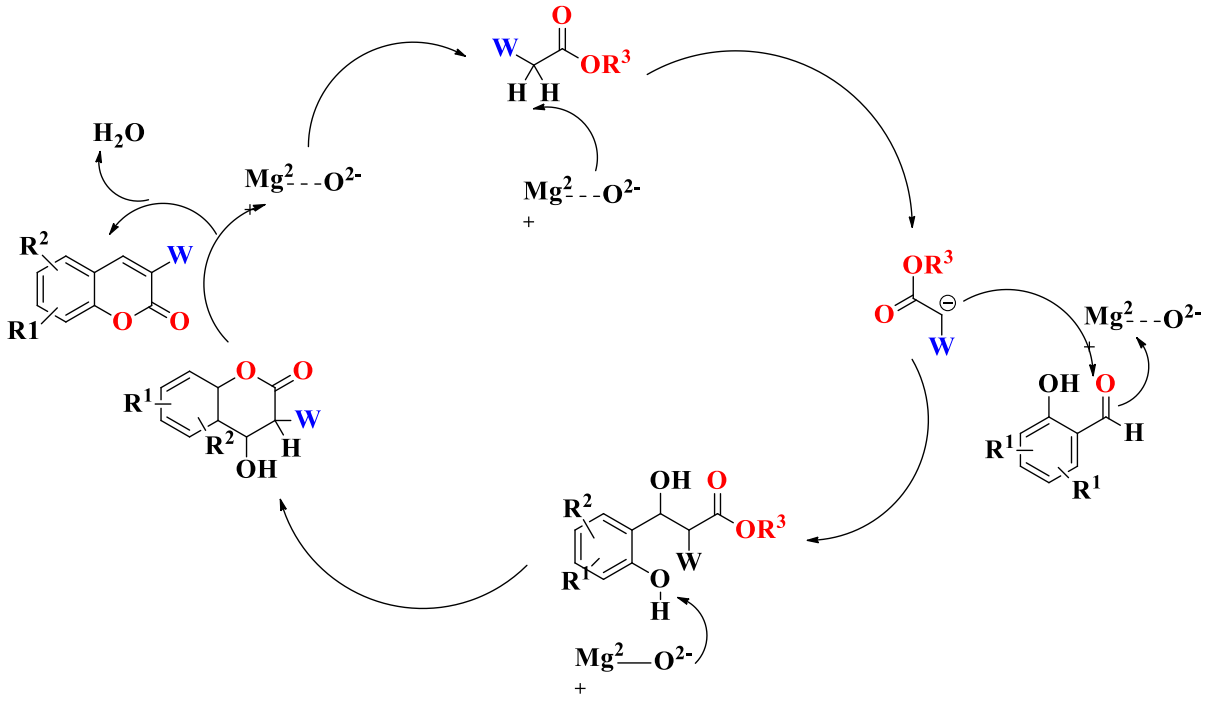
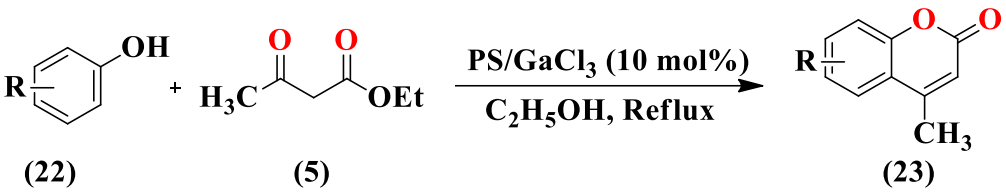


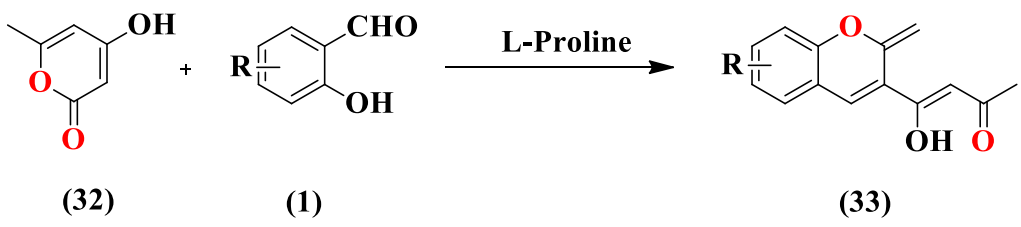
Fig 5: Plausible mechanism for the synthesis of coumarins in the presence of MgO nanoparticles

An eco-friendly Pechmann condensation method for the one-pot synthesis of 4-substituted coumarins **(23)** through the reactions between substituted phenols **(22)** with *β*-ketoesters **(5)** using polystyrene-supported $GaCl_3$ as a highly active and reuseable solid lewis acid catalyst in good to excellent yields was reported by Rahamatpour and his coworkers (Scheme 19)[64].



Scheme 19: PS–$GaCl_3$-catalyzed synthesis of substituted coumarins

A series of chromen-2-one derivatives **(33)** was synthesized by reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one **(32)** with substituted 2-hydroxybenzaldehydes **(1)** catalysed by *L*-proline (Scheme 20)[65]. This method has the advantages of easy work-up, mild reaction conditions and high yields of desired product.



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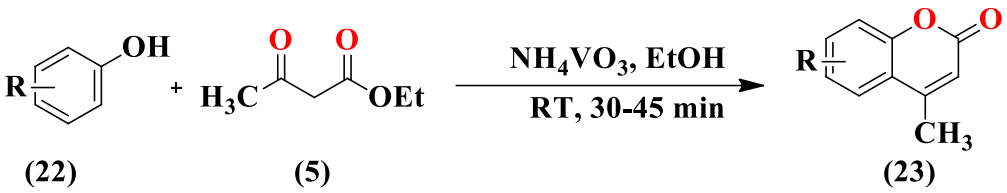
Scheme 20: One-pot synthesis of substituted coumarins

Mandhane *et al*. reported an efficient and facile method for the synthesis of substituted coumarins *via* condensation reaction between substituted phenols **(22)** with *β*-ketoesters **(5)** in the presence of catalytic amount of ammonium metavanadate (10 mol%) at room-temperature (Scheme 21)[66].



(22) (5) (23)

Scheme 21: Synthesis of substituted coumarins using ammonium metavanadate

A simple, efficient and green procedure for the synthesis of a wide range of pyrazoles bearing a coumarin unit **(36)** has been reported using multicomponent reaction of salicyaldehyde **(1)**, 4-hydroxy-6-methyl-2*H*-pyran-2-one **(34)** and hydrazine **(35)** using meglumine as a catalyst in aqueous-ethanol media reported by Li *et al*. (Scheme 22)[67]. This new method offers several advantages such as include the use of a biodegradable and inexpensive catalyst, short reaction time, high yields and simple work-up procedure. Firstly, salicyaldehydes, 1,4-hydroxy-6-methyl-2*H*-pyran-2-one and phenylhydrazine served as model substrates for optimization of reaction conditions. They observed that, no product was formed in absence of catalyst. Less amount of product was obtained when the reaction was performed using Fe_2O_3 or *L*-proline as catalyst in a mixture of EtOH-H_2O. They also observed that meglumine was the best catalyst for this multicomponent reaction and afforded the desired product in excellent yield of 80% in 1.5 h. They also found that aqueous-ethanol (1:1, *v/v*) was the best choice of solvent for this reaction. A plausible mechanism for the synthesis of 3-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-2*H*-chromen-2-one from salicyaldehyde, 4-hydroxy-6-methyl-2*H*-pyran-2-one and phenyl hydrazine catalysed by meglumine is shown in Fig 6. Firstly, Knoevenagel condensation reaction between salicyaldehyde and 4-hydroxy-6-methyl-2*H*-pyran-2-one would occur to give the intermediate **I**. The intermediate **I** then undergo intramolecular cyclization by the nucleophillic addition reaction between resonance stabilized enolate oxygen and carbon atom of carbonyl group to give intermediate **II**. The intermediate **II** further react with phenylhydrazine to form

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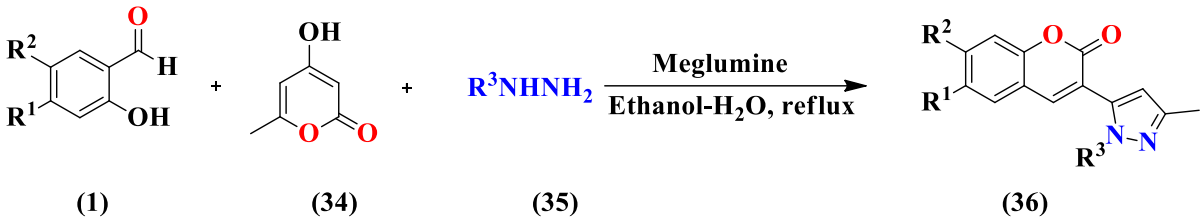
the intermediate **IV**, which then tautomerized to intermediate **IV**. Finally, an intramolecular cyclization of intermediate **IV** promoted by meglumine to give desired product *via* dehydration.



(1) **(34)** **(35)** **(36)**

Scheme 22: One-pot three-component synthesis of pyrazolylcoumarins catalysed by meglumine

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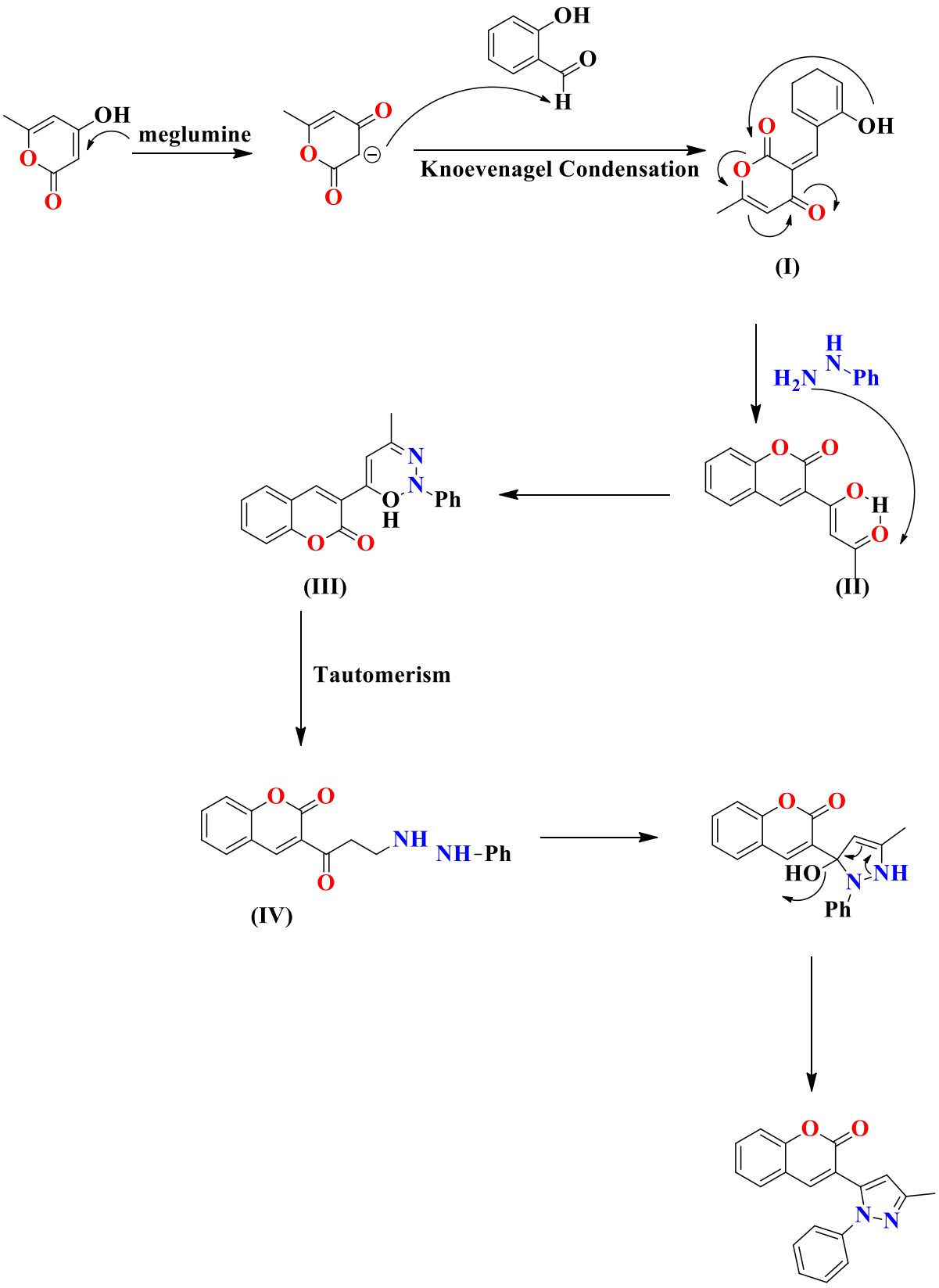

Fig 6: Plausible mechanism for synthesis of pyrazolylcoumarins catalysed by meglumine

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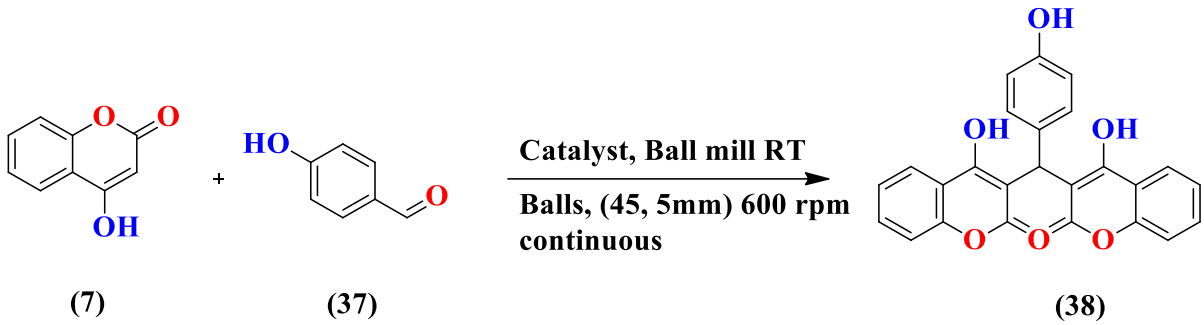
Mayank *et al*. reported a convenient, solvent-free synthesis of bis-coumarins **(38)** *via* reaction between 4-hydroxycoumarin **(7)** and 4-hydroxybenzaldehyde **(37)** using zwitterionic liquid coated copper oxide and mechanical ball milling (Scheme 23)[68]. The plausible mechanism for the formation of bis-coumarin is shown in Fig 7.



Scheme 22: Synthesis of bis-coumarins using zwitterionic liquid coated copper oxide

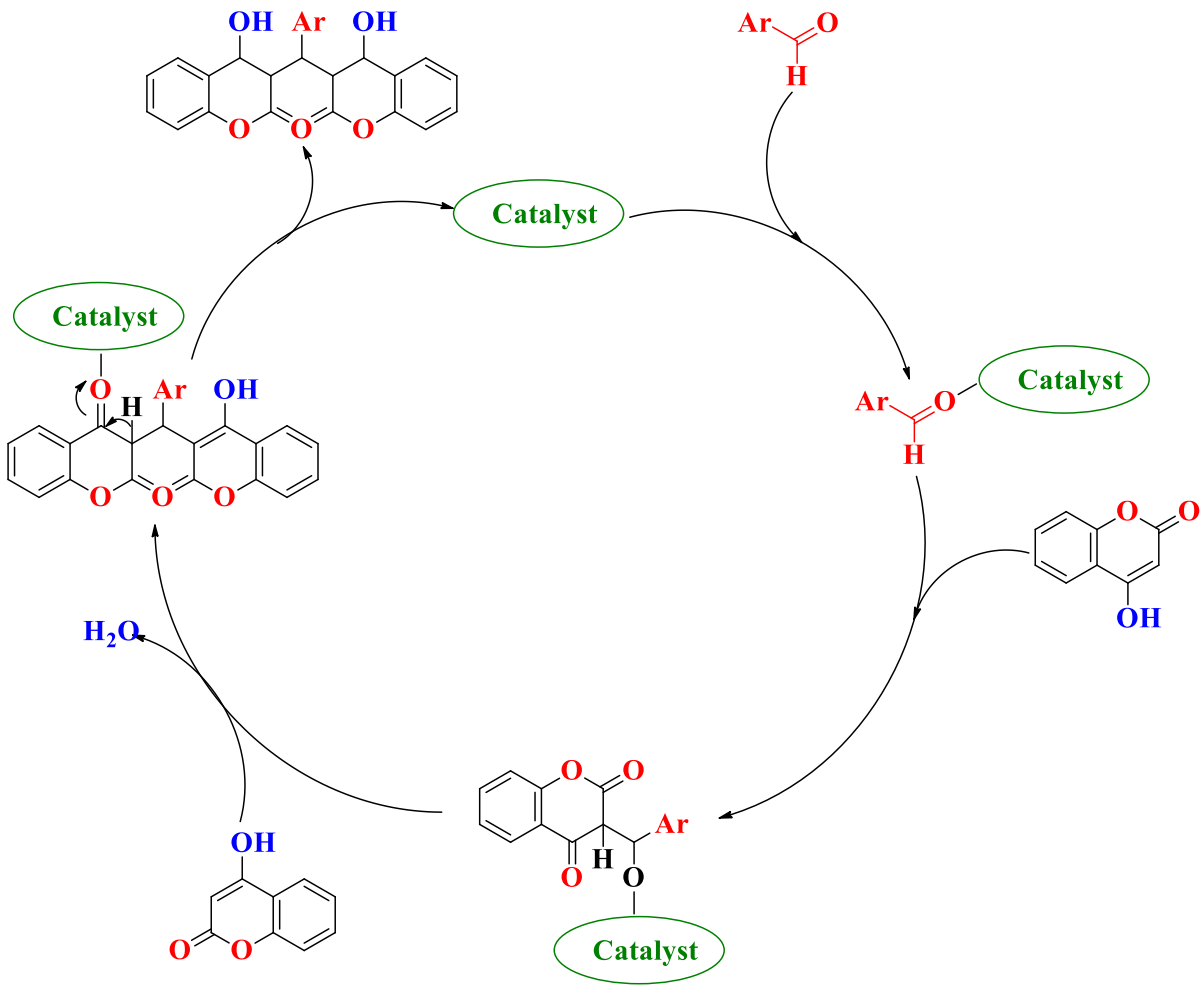


Fig 7: Plausible mechanism for synthesis of bis-coumarins using zwitterionic liquid coated copper oxide

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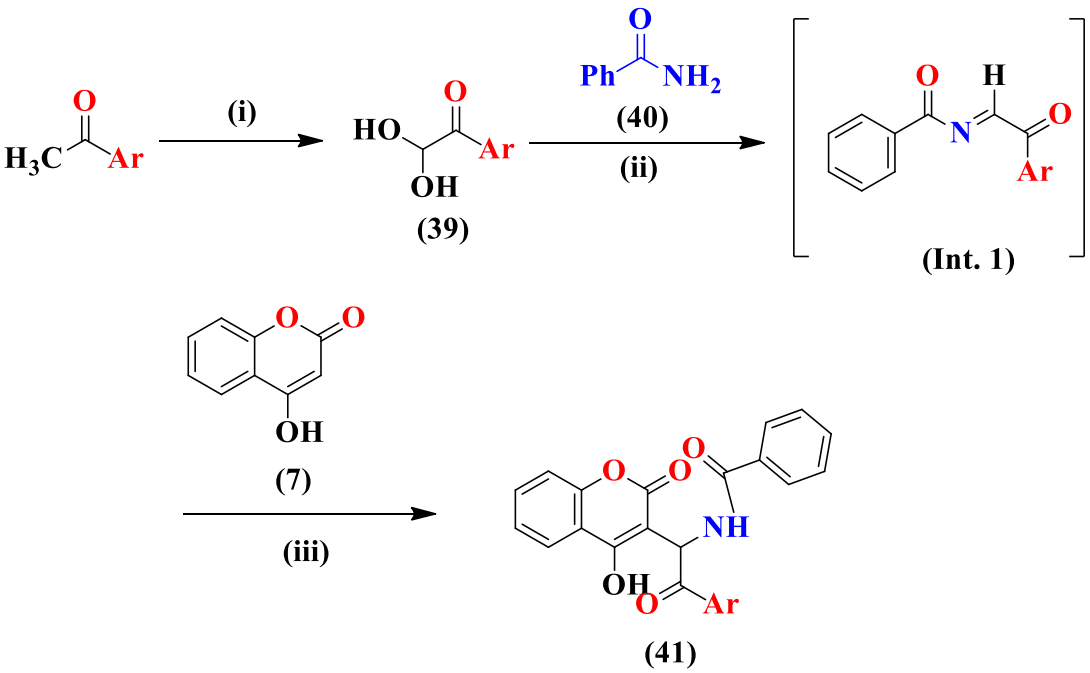
Khodabakhshi *et al*. reported effortless synthesis of new aryloylamido coumarins **(41)** *via* one-pot three components reaction between aryl glyoxal **(39)**, benzamide **(40)** and 4-hydroxycoumarin **(7)** in the presence of molybdate sulphuric acid as catalyst under solvent-free conditions (Scheme 23)[69].



Scheme 23: Synthesis of aryloylamido coumarins using MSA

A green and facile multicomponent synthesis of benzylamino coumarin derivatives **(10)** was reported *via* condensation reaction between 4-hydroxycoumarin **(7)**, cyclic secondary amine **(9)** and substituted aldehydes **(8)** in presence of CuO nanoparticles as heterogeneous catalyst in water at room temperature by Ardakani and his coworkers (Scheme 24)[70]. Initially, in order to standardize the reaction conditions, a model reaction was carried out using 4-bromobenzaldehyde, 4-hydroxycoumarin and piperidine in water at room temperature in the presence of different nanoparticle as catalysts *viz*. Fe_3O_4 nanoparticles, MgO nanoparticles, NiO nanoparticles and CuO nanoparticles. They were found that CuO nanoparticle was most efficient catalyst for the reaction in aqueous medium. Afterward, standardization of catalyst amounts was carried out by exploring same model reaction by using different amounts of CuO NPs. They found that excellent yield was obtained

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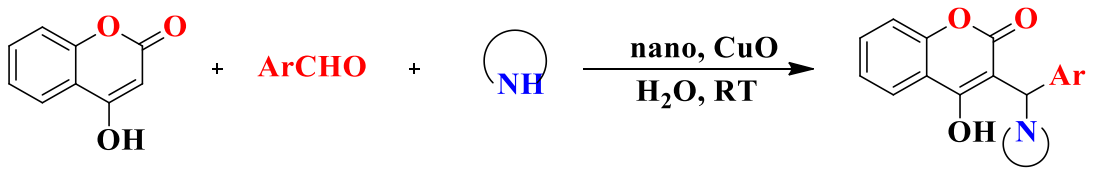
with increasing the amount of catalyst from 5 mol% to 20 mol%. Hence, the optimum concentration of CuO NPs was chosen 20 mol% in the model reaction. The possible mechanism for reaction is shown in Fig 8. According to mechanism first of all, imine intermediate was formed by the reaction of aldehyde with secondary amine. Then nucleophillic addition of 4-hydroxycoumarin to this intermediate afford the formation of desired product in excellent yield.



(7) (8) (9) (10)

Scheme 24: Synthesis of benzylamino coumarin derivatives catalysed by CuO nanoparticles (NPs) at room temperature

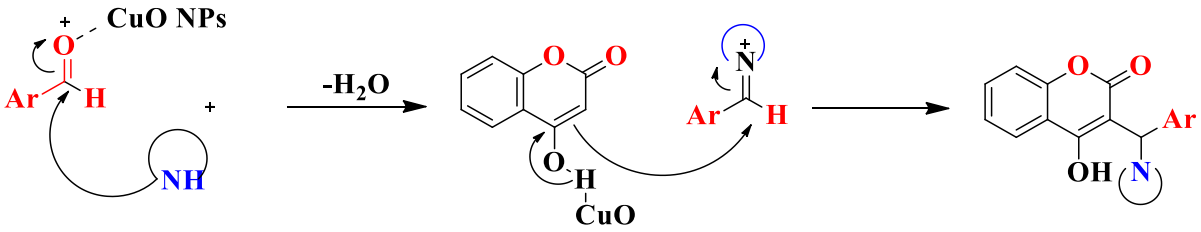
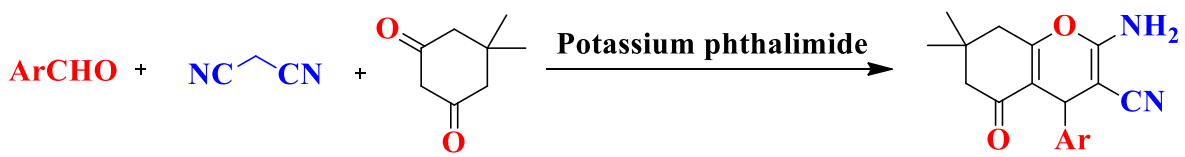


Fig 8: Possible reaction mechanism for the formation of benzyl amino coumarin

Kiyani and Ghorbani reported one-pot, green and eco-friendly multicomponent synthesis of substituted 5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromenes **(43)** derivatives *via* Knoevenagel-cyclocondensation reaction between substituted aldehydes **(8)**, malononitrile **(12)** and 5,5-dimethylcyclohexane-1,3-dione **(42)** in presence of green, low-cost, mild, efficient and commercially available potassium phthalimide as catalyst (Scheme 25)[71]. Short reaction times, high yields, simple work-up and no use of hazardous organic solvents are some merits of present methodology.



(8) (12) (42) (43)

Scheme 25: Synthesis of substituted 5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromenes derivatives

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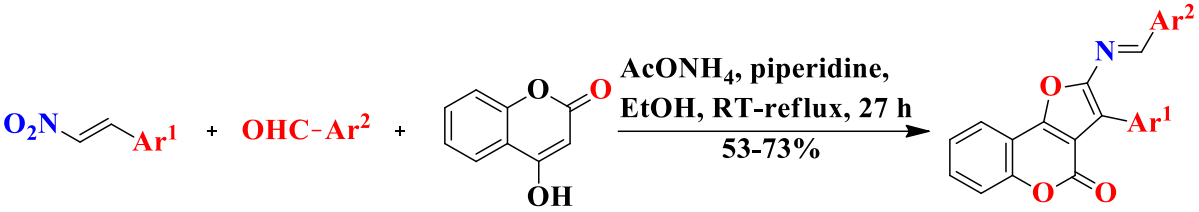
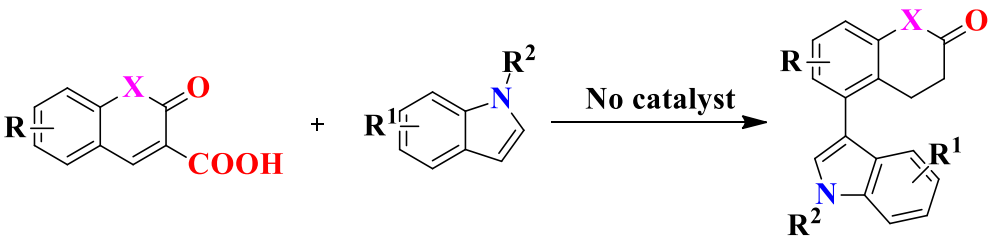
An efficient and novel synthesis of 2-arylideneamino-3-ary-4*H*-furo [3,2-c] chromen-4-ones **(45)** has been reported *via* four-component reaction between substituted nitrostyrenes **(44)**, substituted aldehydes **(8)**, 4-hydroxycoumarin **(7)** and ammonium acetate under very mild conditions by Zhou *et al*. (Scheme 26)[72].



(44) **(8)** **(7)** **(45)**

Scheme 26: Synthesis of 2-arylideneamino-3-ary-4*H*-furo [3,2-c] chromen-4-ones

Shao and his coworkers synthesized indole-3-substituted dihydrocoumarins **(48)** in good to excellent yield under catalyst-free conditions *via* tandem Michael addition/decarboxylation of (thio) coumarin-3-carboxylic acids **(46)** with indoles **(47)** (Scheme 27)[73]. The plausible mechanism for reaction is shown in Fig 9.



(46) **(47)** **(48)**

X = O, S

Scheme 27: Tandem Michael addition/decarboxylation of indoles with (thio) coumarin-3-carboxylic acids

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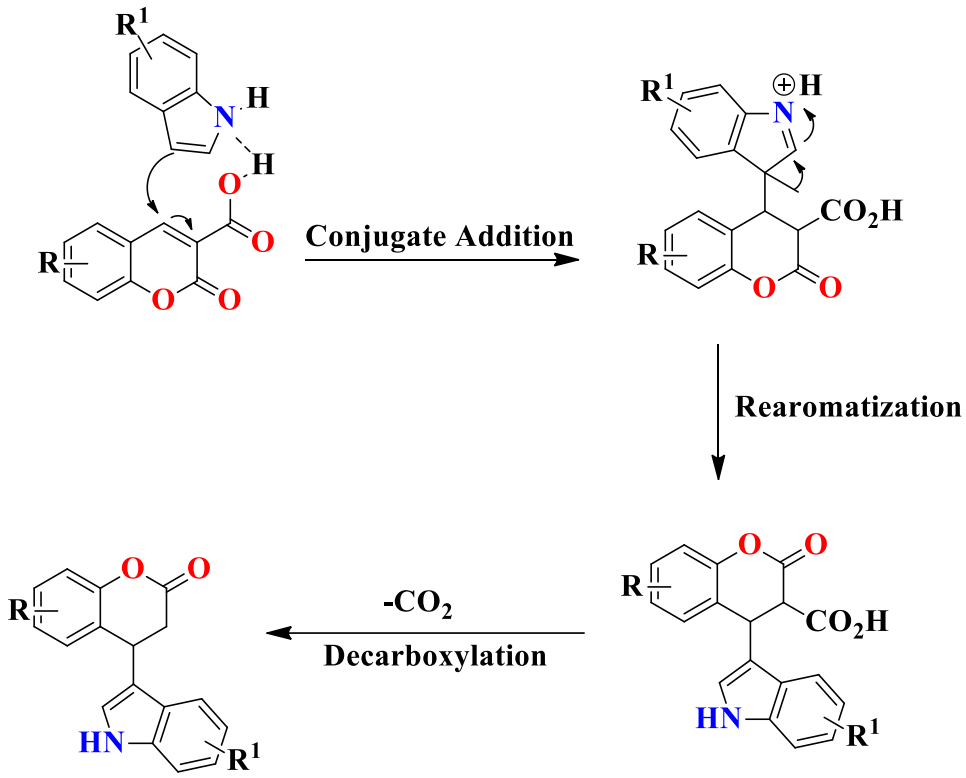
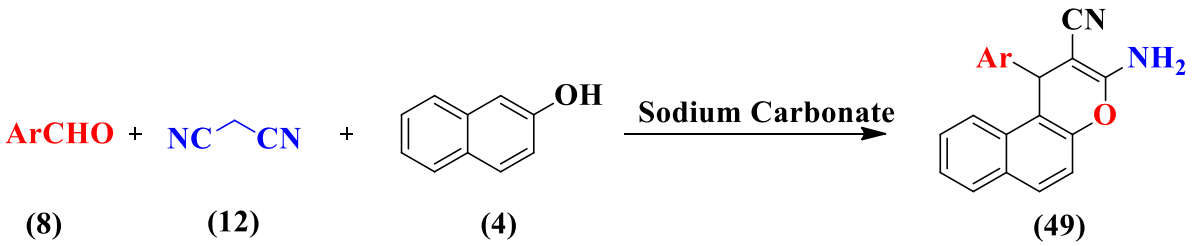


Fig 9: Plausible mechanism for synthesis of indole-3-substituted dihydrocoumarins

Solvent-free multicomponent synthesis of 2-amino-4*H*-chromene derivatives **(49)** was reported in a very simple, efficient and eco-friendly method using sodium carbonate as a cheap and non-toxic catalyst *via* one-pot reaction between substituted aldehydes **(8)**, malononitrile **(12)** and *β*-naphthol **(4)** by Jamal and his coworkers (Scheme 28)[74]. The plausible mechanism for reaction is shown in Fig 10.



Scheme 28: One-pot synthesis of 2-amino-4*H*-chromene derivatives

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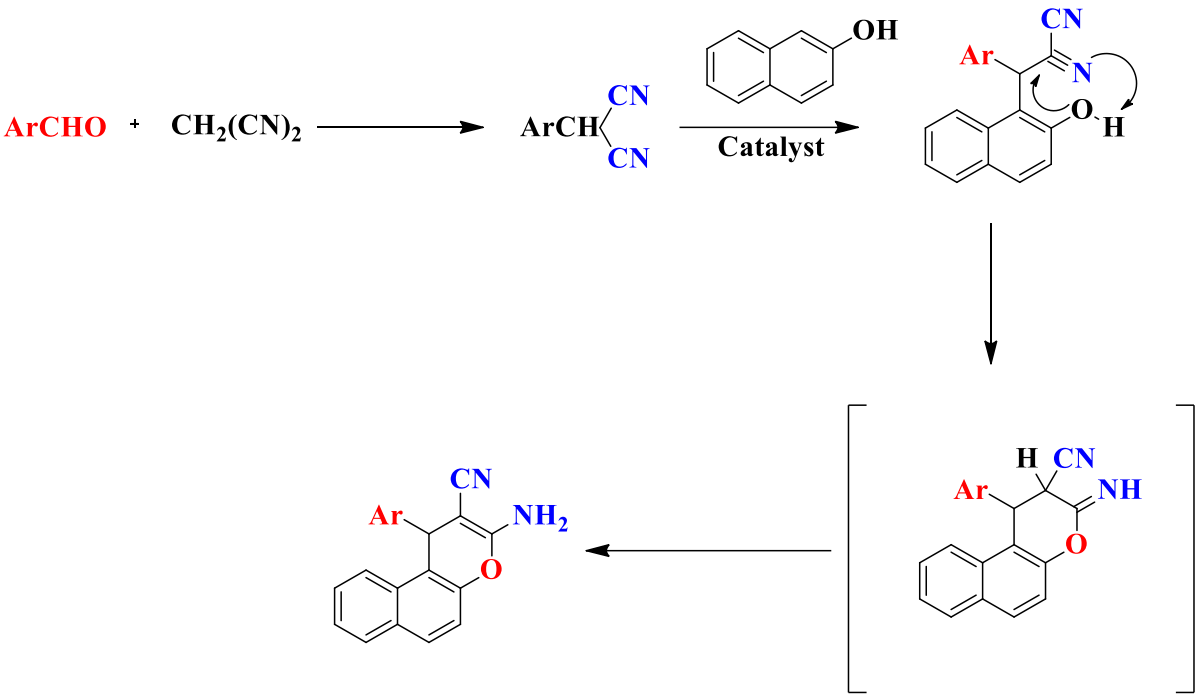
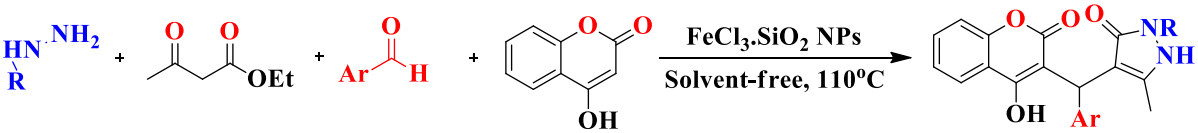


Fig 10: Plausible mechanism for synthesis of indole-3-substituted dihydrocoumarins

Piruzmand *et al*. synthesized benzylpyrazolyl coumarin derivatives **(51)** *via* four component reaction between aryl hydrazine/hydrazine hydrate **(50)**, ethylacetoacetate **(5)**, substituted aldehydes **(8)** and 4-hydroxycoumarin **(7)** in presence of $FeCl_3/SiO_2$ as an efficient and green catalyst (Scheme 29)[75]. The plausible mechanism for reaction is shown in Fig 11.



(50) **(5)** **(8)** **(7)** **(51)**

Scheme 29: One-pot synthesis of benzylpyrazolyl coumarin derivatives

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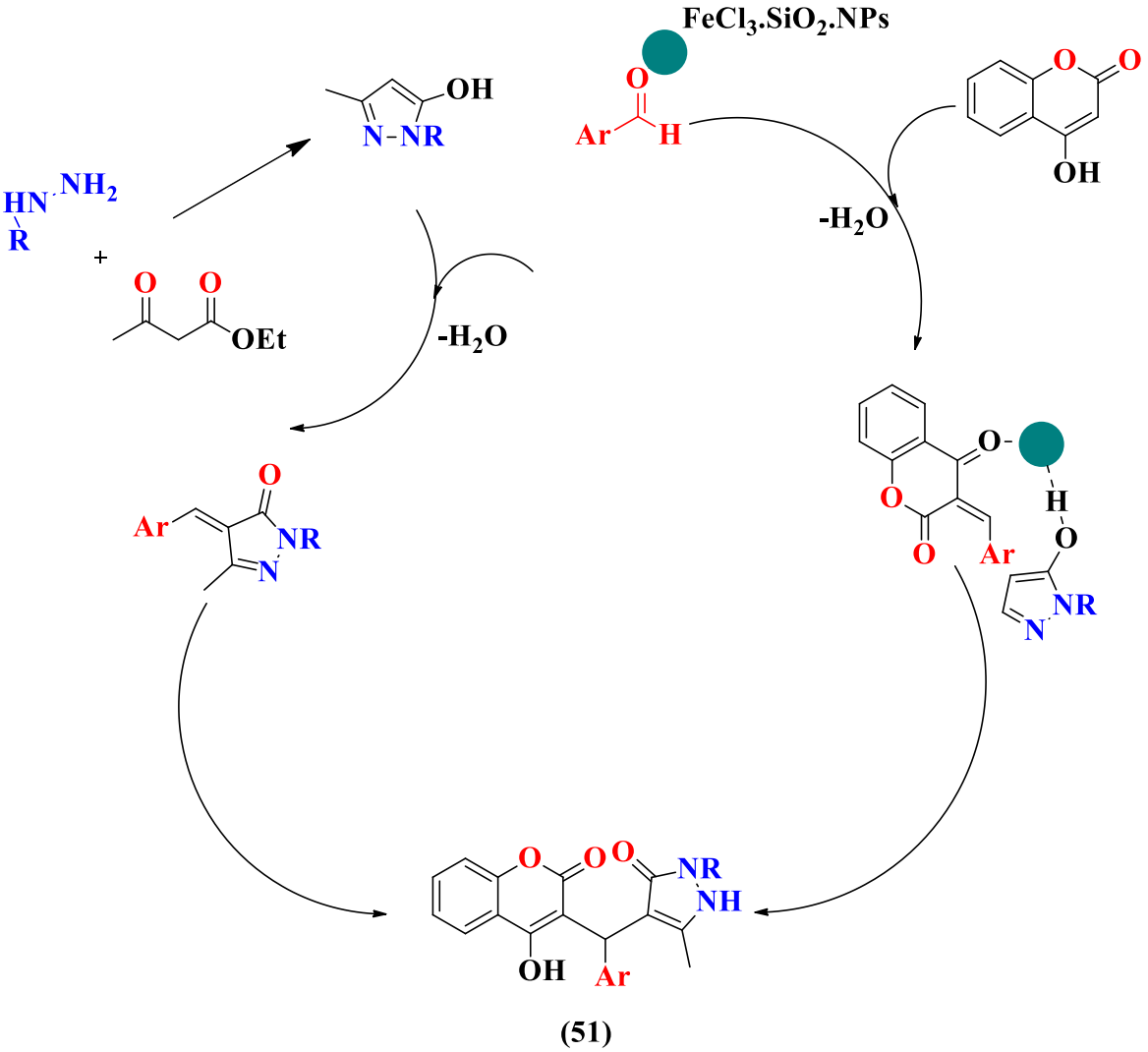

Fig 11: Plausible mechanism for the formation of benzylpyrazolyl coumarins

A green and highly efficient method has been reported for one-pot synthesis of tetrahydrobenzo[b]pyrans **(53)** *via* three components condensation reaction between substituted aldehydes **(8)**, 1,3-cyclic diketones **(52)** and malononitrile **(12)** under MW irradiation without using any catalyst and solvent by Santra and his coworkers (Scheme 30)[76]. Operational simplicity, solvent and catalyst-free conditions, the compatibility with various functional groups, no need of chromatographic purification technique, and excellent yields are the some advantages of current protocol. The plausible mechanism for reaction is shown in Fig 12.

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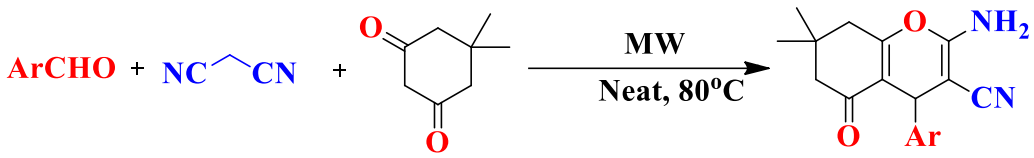

(8) (12) (52) (53)

Scheme 30: Synthesis of 4*H*-benzo[b]pyran derivatives under MW irradiation

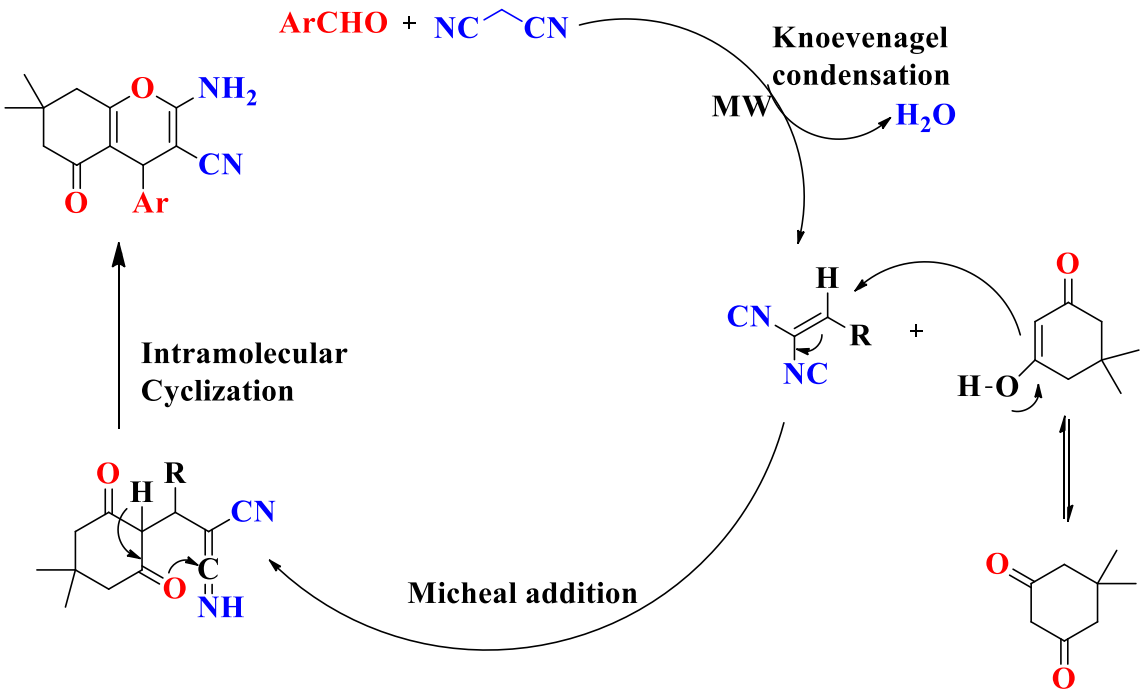

Fig 12: Plausible reaction mechanism

Green synthetic methods for the preparation of substituted dihydropyrimidinones

Pramanik *et al*. reported the synthesis of dihydropyrimidinone derivatives **(55)** *via* microwave assisted Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of fruit juices (Scheme 31)[77].

(5) (54) (8) (55)

Scheme 31: Synthesis of DHPM under MW in fruit juice

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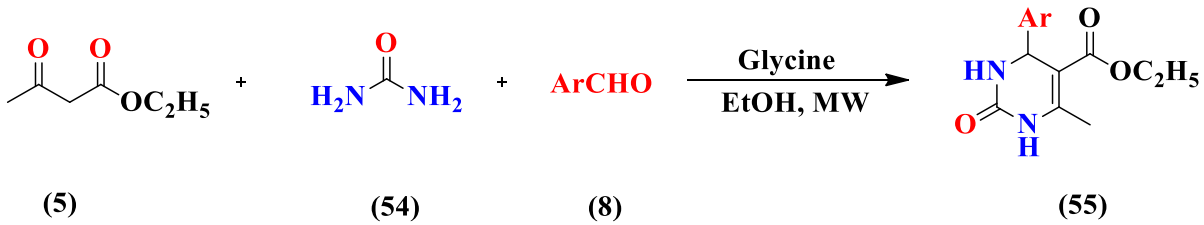
Sharma and his coworkers reported the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **(55)** *via* one-pot three component reaction between substituted aldehydes **(8),** *β*-ketoester **(5)** and urea **(54)** in presence of amino acid ionic liquid as a green catalyst (Scheme 32)[78]. The plausible mechanism for reaction is shown in Fig 13.



(5) **(54)** **(8)** **(55)**

Scheme 32: Synthesis of DHPM under MW in Glycine

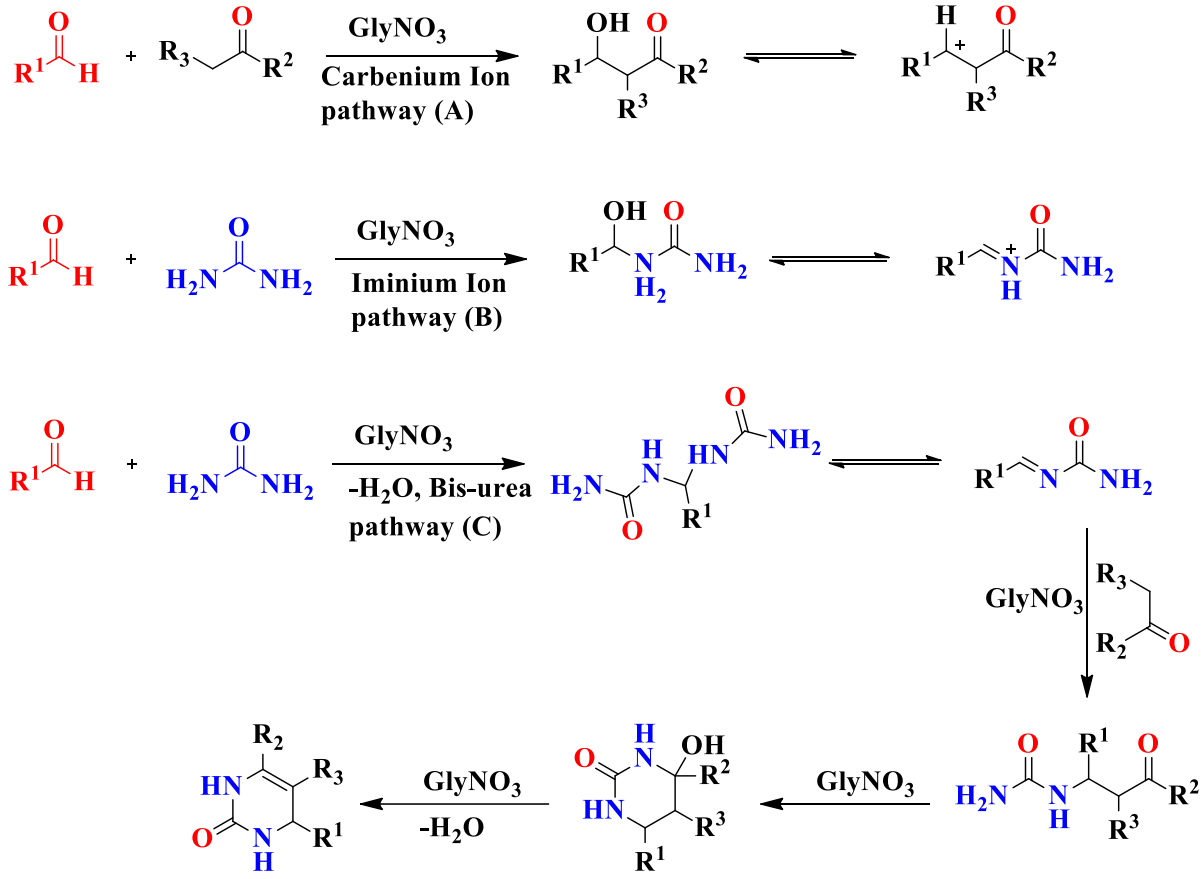


Fig 13: Plausible reaction mechanism for Biginelli reaction

An efficient and facile method for the synthesis of curcumin 3,4-dihydropyrimidinones **(57)** has been reported by simple one-pot condensation of curcumin **(56)**, substituted aldehydes **(8)** and urea/thiourea **(54)** in the presence of commercially available chitosan in 2% acetic acid in aqueous medium at 60°C for 80-90 min by Lal and his coworkers (Scheme 33)[79].

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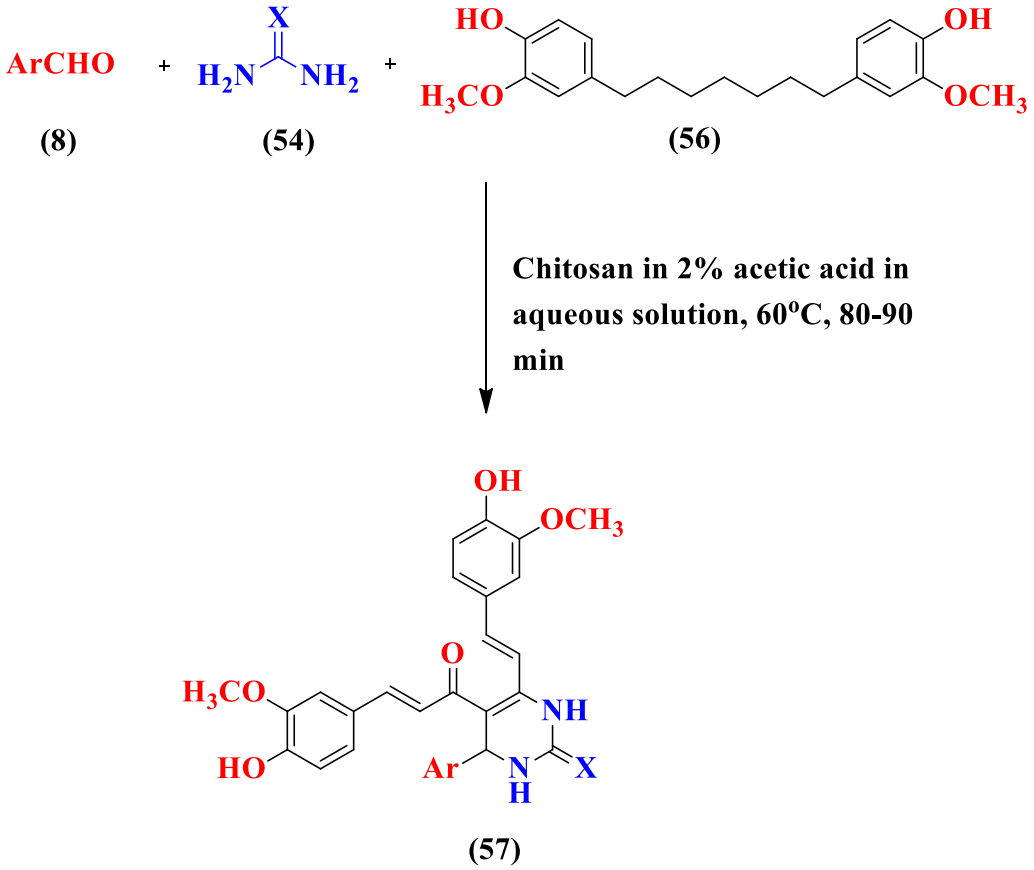

Scheme 33: Synthesis of curcumin 3,4-dihydropyrimidinones

A simple, efficient, green and cost-effective method has been developed for the synthesis of substituted dihydropyrimidinones **(55)** by solvent and catalyst free Biginelli's condensation of 1,3-dicarbonyl compound **(5)**, substituted aldehydes**(8)** and urea **(54)** by Ranu *et al*. (Scheme 34)[80].

Scheme 34: Synthesis of substituted dihydropyrimidinones

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Rafiee and Jafri reported the synthesis of substitiuted dihydropyrimidinones **(55)** using heteropoly acid mediated cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** (Scheme 35)[81].

(5) **(54)** **(8)** **(55)**

Scheme 35: Synthesis of substituted dihydropyrimidinones using heteropoly acid

Patil *et al*. reported an efficient and facile multicomponent synthesis of dihydropyrimidinones **(55)** under solvent-free conditions from substitiuted aldehydes **(8)**, 1,3-dicarbonyl compounds **(5)** and urea **(54)** at room temperature using extract of lemon juice as natural catalyst (Scheme 36)[82]. They found that this new method using lemon juice offers better yield of desired products, non-polluting and green approach to this bicyclocondensation reaction.

(5) **(54)** **(8)** **(55)**

Scheme 36: Three-component synthesis of dihydropyrimidinones catalyzed by lemon juice

Pramanik and Padan reported the synthesis of dihydropyrimidinone derivatives **(55)** *via* microwave assisted Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of fruit juices *viz*. apple juice, pomegranate juice and grape juice (Scheme 37)[83].

(5) **(54)** **(8)** **(55)**

Scheme 37: Synthesis of DHPM *via* Biginelli reaction

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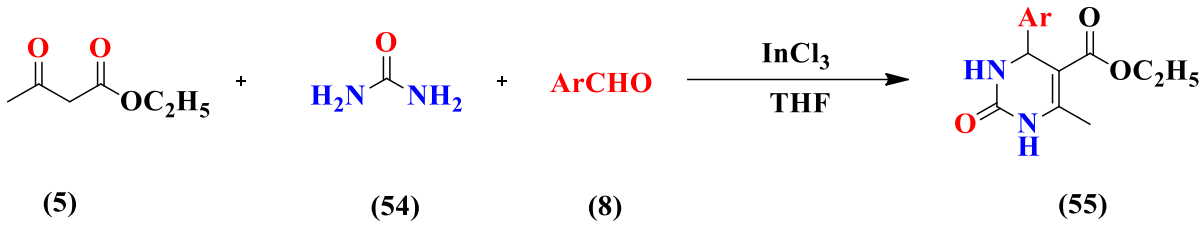
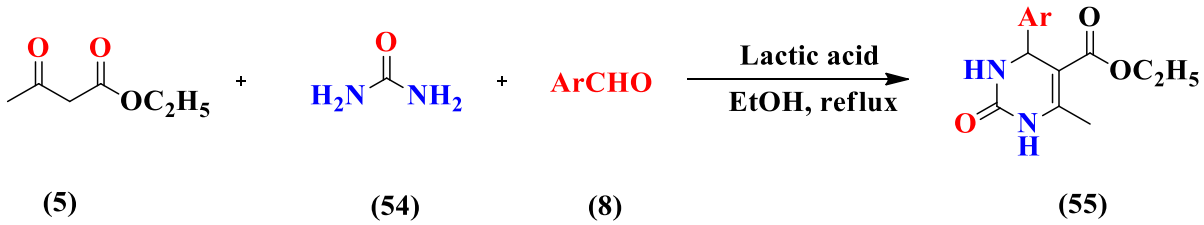
Ranu *et al*. reported the synthesis of dihydropyrimidinones **(55)** by a three-component coupling of substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** catalyzed by Indium(III) Chloride (Scheme 38)[84].



(5) (54) (8) (55)

Scheme 38: $InCl_3$-catalyzed Synthesis of dihydropyrimidinones

Suresh and his colleagues reported the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones **(55)** in excellent yields *via* eco-friendly reaction between of substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** catalyzed by lactic acid (Scheme 39)[85]. The plausible mechanism for reaction is shown in Fig 14.



(5) (54) (8) (55)

Scheme 39: Synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones

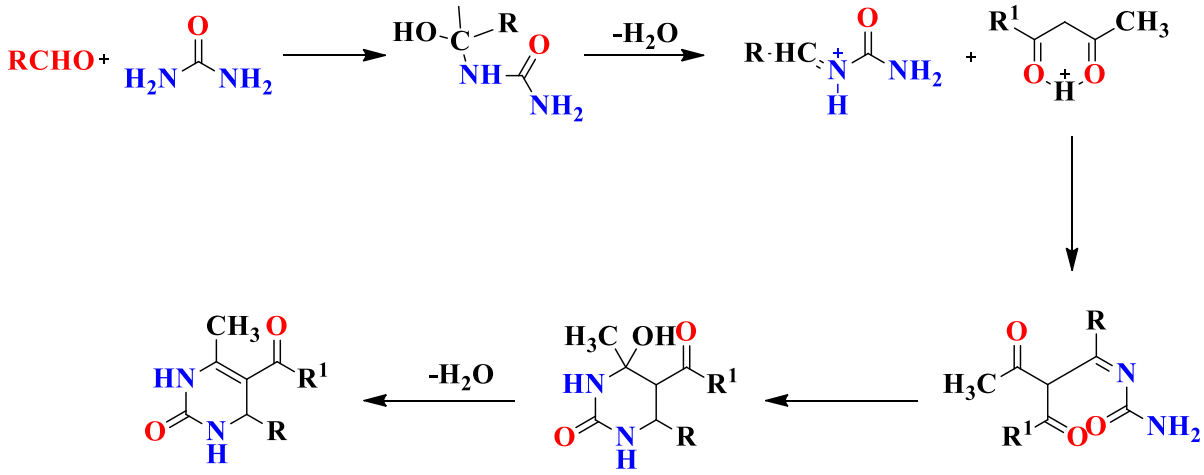


Fig 14: Plausible reaction mechanism for synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones

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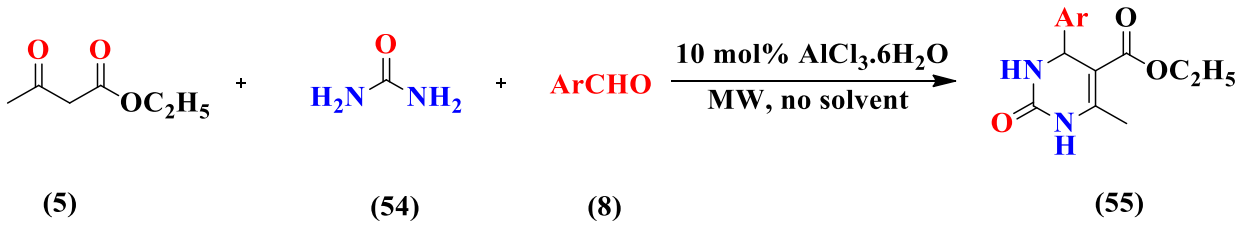
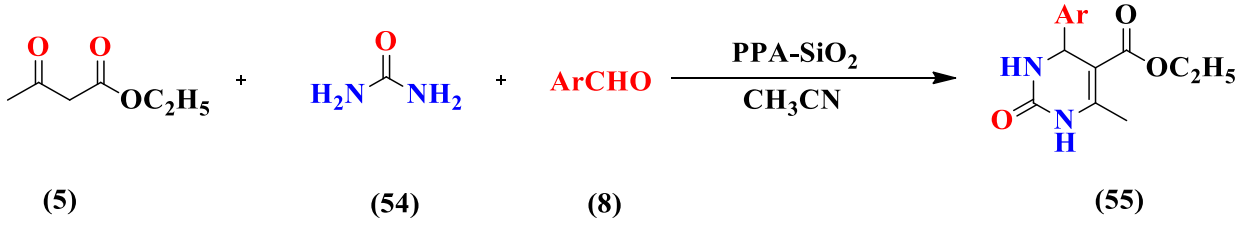
3,4-Dihydropyrimidine-2-(1*H*)-ones **(55)** were synthesized *via* a multicomponent reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** catalyzed by 10 mol% $AlCl_3.6H_2O$ by Kumar and his coworkers (Scheme 40)[86]. The catalyst reported here is non-expensive, easy to handle and whole method is eco-friendly.



Scheme 40: Synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones

A green and efficient method for the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones **(55)** and thiones through multicomponent reaction of ethyl acetoacetate **(5)**, substituted aldehydes **(8)** and urea or thiourea **(54)** in acetonitrile using silica gel-supported polyphosphoric acid (PPA-SiO_2) as catalyst reported by Dastmalbaf *et al*. (Scheme 41)[87]. Excellent yields, short reaction times, mild reaction conditions, reuse of catalyst and easy work-up are some merits of present methodology.



Scheme 41: Synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones

An facile and simple one-pot synthesis of 3,4-dihydropyrimidine-2-(1*H*)-thione derivatives **(55)** was reported in excellent yields by reaction of substituted aldehydes **(8)**, *β*-ketoester **(5)** and thiourea **(54)** in aqueous ethanol (50%) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a reusable catalyst by Sekhar and his coworkers (Scheme 42)[88].

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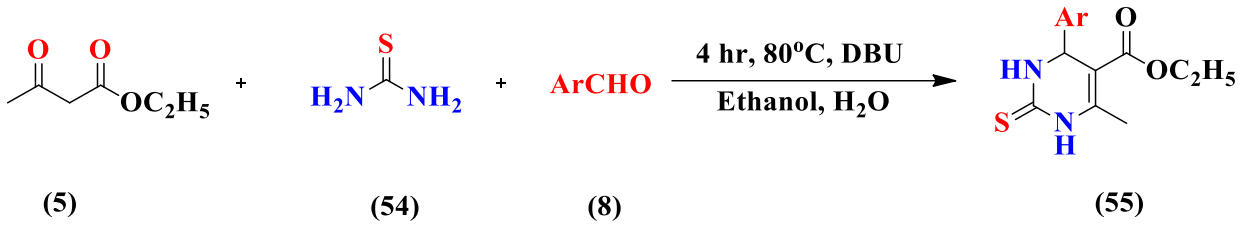
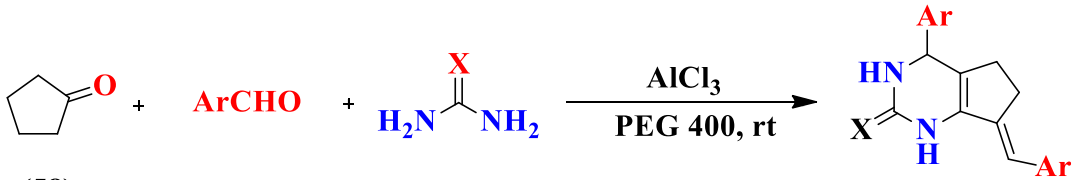


(5) (54) (8) (55)

Scheme 42: Synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-thione

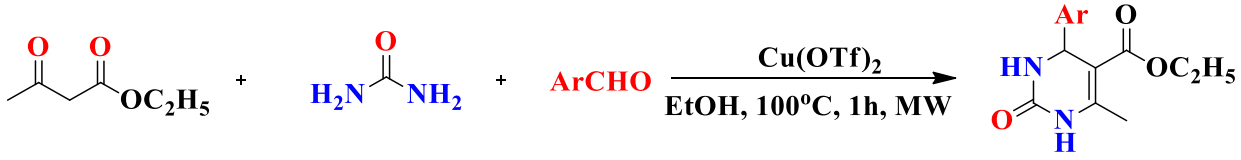
Biginelli condensation of substituted aldehydes **(8)**, cyclopentanone **(58)** and urea or thiourea **(54)** in poly (ethylene) glycol 400 at 45°C in the presence of aluminium chloride as a highly efficient catalyst has been reported for synthesis of pyrimidinone derivatives **(59)** by Amoozadeh *et al.* (Scheme 43)[89].



(58) (8) (54) (59)

Scheme 43: Synthesis of substituted pyrimidinone

The synthesis of dihydropyrimidinones **(55)** *via* clean multicomponent Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** under microwave irradiation catalysed by copper reported by Pasunooti *et al.* (Scheme 44)[90]. They observed that this method is simple, efficient, economical and environmentally friendly.



(5) (54) (8) (55)

Scheme 44: Synthesis of substituted dihydropyrimidinone

Moradi and Tadayon reported the one-pot multicomponent synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones *via* multicomponent Biginelli reaction between substituted

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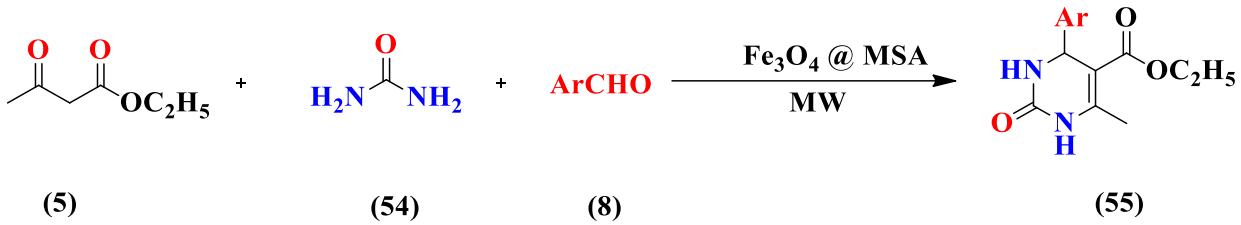
aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of nano Fe_3O_4@meglumine sulfonic acid as a new solid acid catalyst (Scheme 45)[91]. The plausible mechanism for reaction is shown in Fig 15.



Scheme 45: Synthesis of substituted dihydropyrimidinones using Fe_3O_4@MSA under microwave irradiation

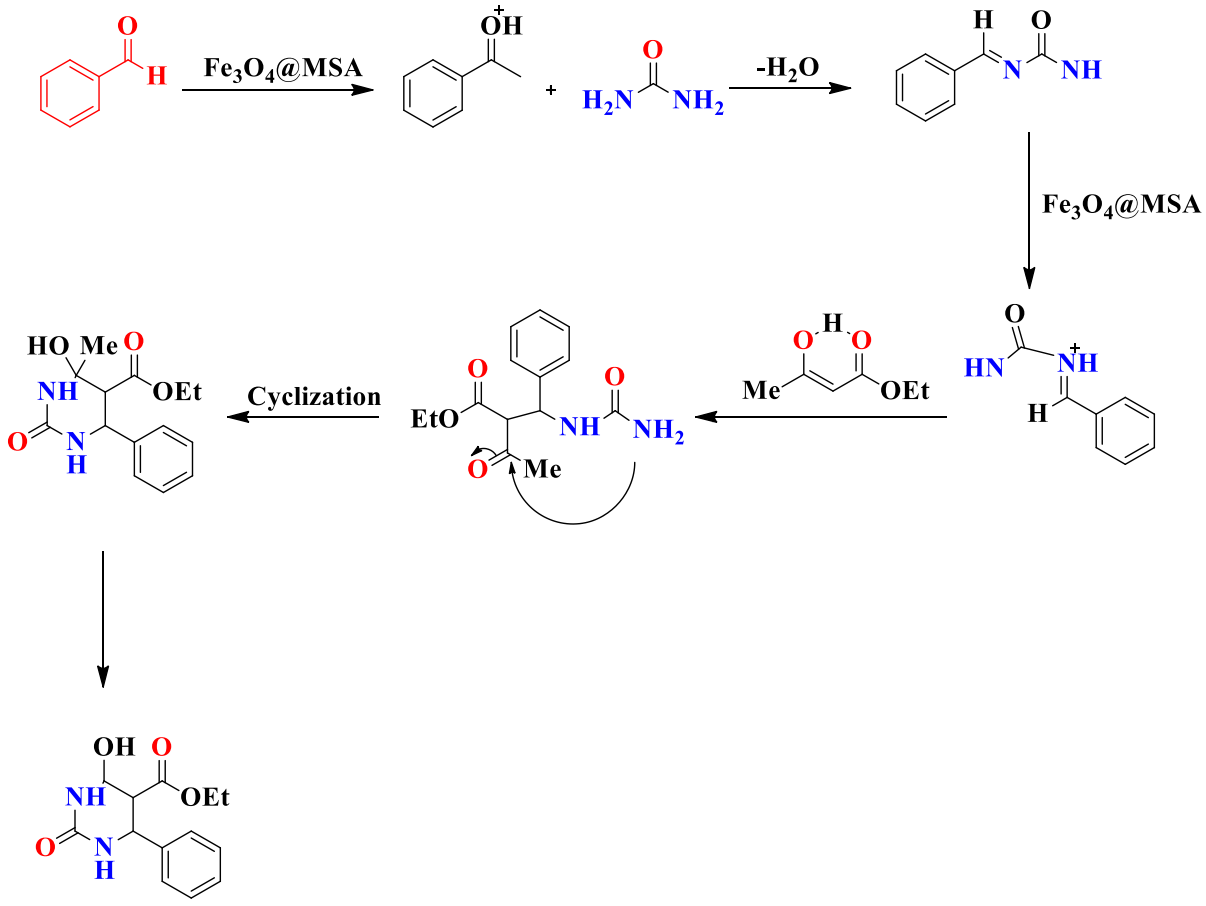


Fig 15: A plausible mechanism for the Biginelli reaction in the presence of Fe_3O_4@MSA

An efficient and green synthesis of a series of dihydropyrimidinones derivatives **(55)** were reported *via* three components one-pot cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of pineapple juice by Patil and his coworkers (Scheme 46)[92].

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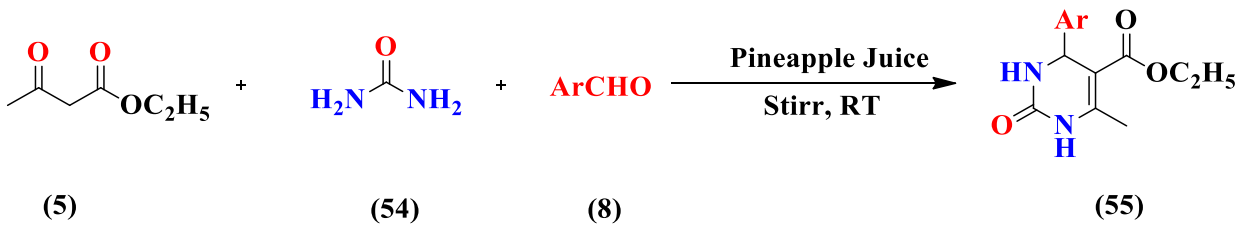
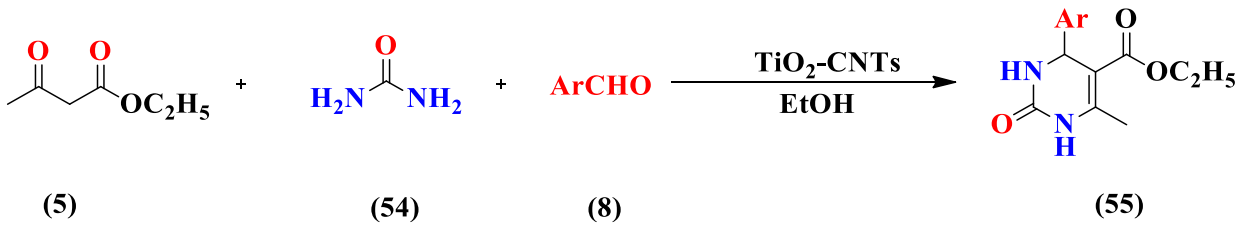
Solvent-free, shorter reaction time, mild reaction conditions, simple work-up and reduced environmental impact are some advantages of current methodology.



(5) (54) (8) (55)

Scheme 46: Synthesis of substituted dihydropyrimidinones

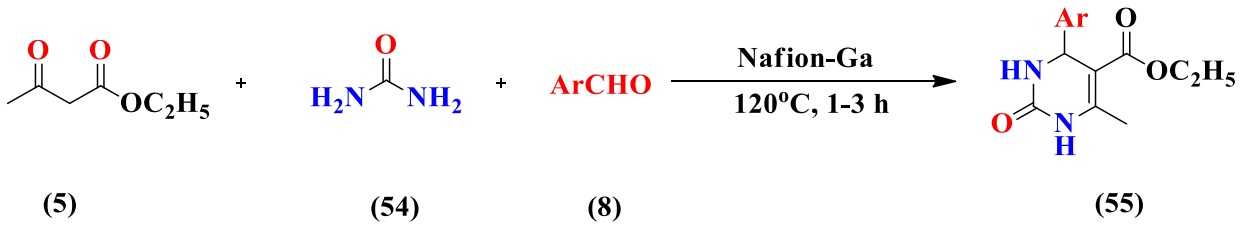
Safari and his coworkers synthesized substituted dihydropyrimidinones **(55)** *via* three components one-pot cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of carbon nanotubes supported by titanium dioxide nanoparticles as recyclable and green catalyst (Scheme 47)[93].



(5) (54) (8) (55)

Scheme 47: Synthesis of substituted dihydropyrimidinones

Prakash *et al*. reported the one-pot multicomponent synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones/thiones *via* green multicomponent Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of Nafion-Ga as a new solid acid catalyst (Scheme 48)[94].



(5) (54) (8) (55)

Scheme 48: Synthesis of substituted dihydropyrimidinones

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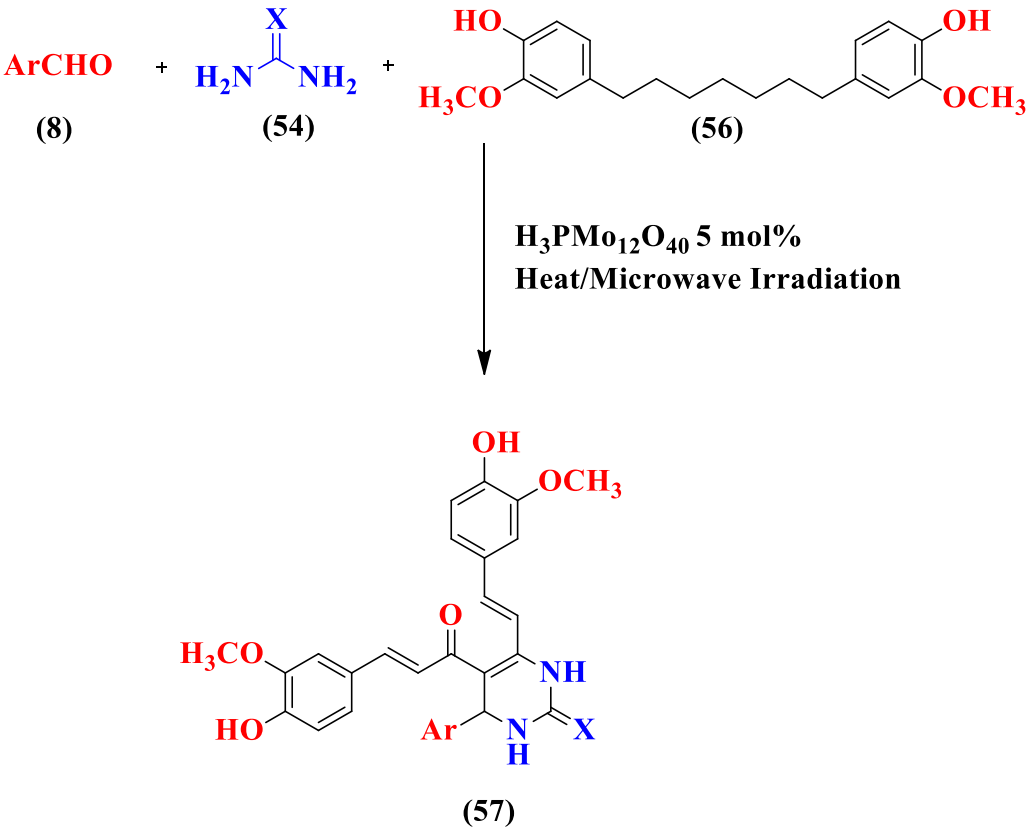
Khellafi *et al*. synthesized 3,4-Dihydropyrimidin-2(1*H*)-one/thione analogs of curcumin **(57)** in good yield by a one-pot multi-component cyclocondensation reaction between curcumin **(56)**, substituted aldehydes **(8)** and urea/thiourea **(54)** in less volume of ethanol catalysed by commercial heteropolyacide Keggin type $H_3PMo_{12}O_{40}$ as a recyclable and nontoxic catalyst under conventional heating and microwave irradiation (Scheme 49)[95]. The plausible mechanism for reaction is shown in Fig 16.



Scheme 49: Synthesis of 3,4-dihydropyrimidinones/thiones of curcumin under conventional reflux or MW irradiation

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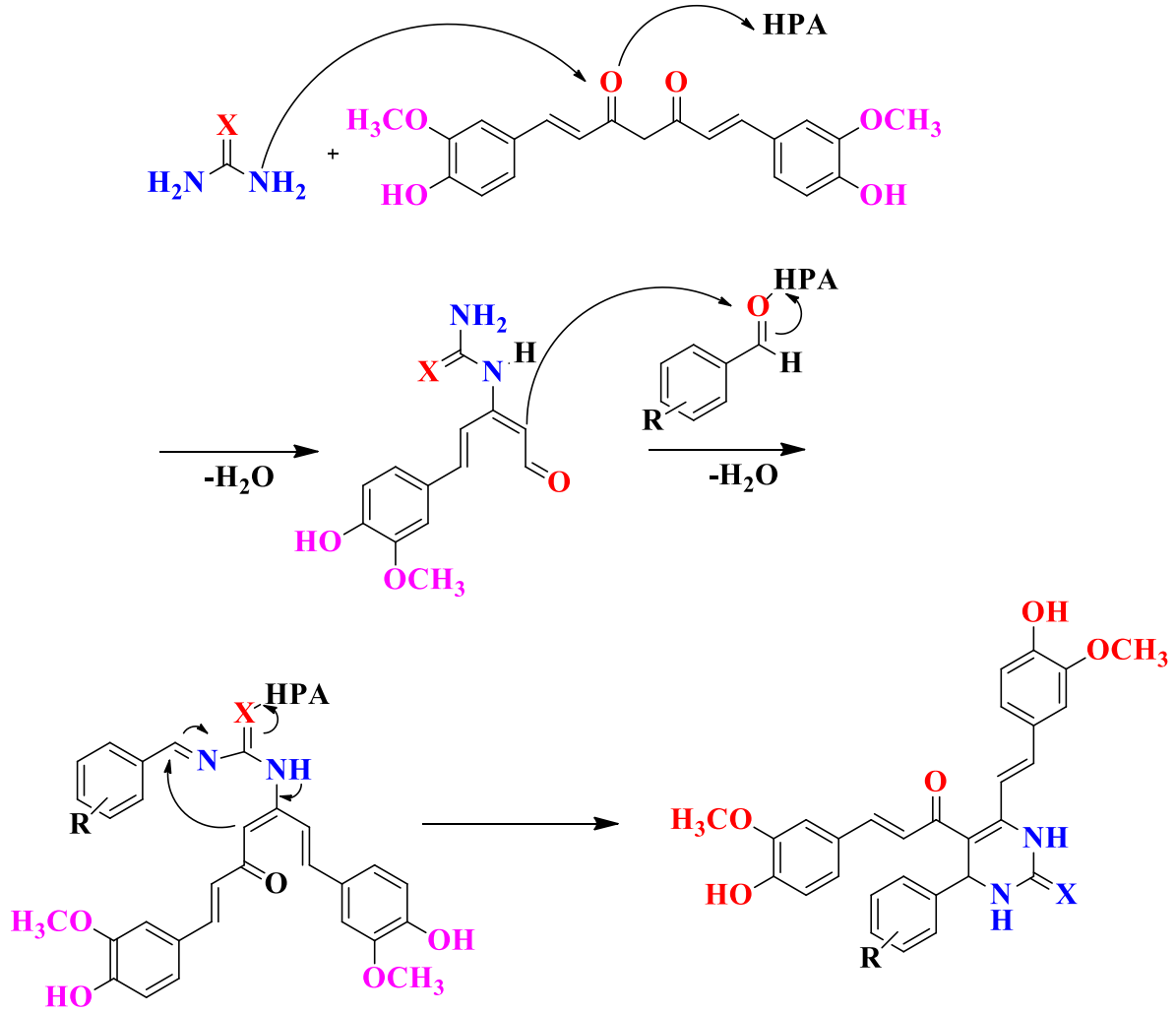
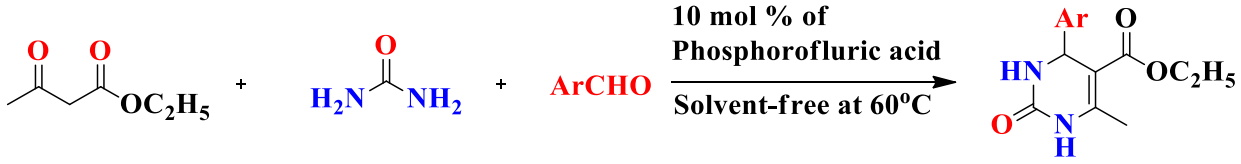


Fig 16: Plausible mechanism for the synthesis of 3,4-dihydropyrimidin-2(*H*)-one/thione analogs of curcumin catalysed by $H_3PMo_{12}O_{40}$ (HPA)

An efficient and simple method has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) **(55)** *via* one-pot three components reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of phosphorofluridic acid as the catalyst under solvent-free conditions by Mathapati *et al*. (Scheme 50)[96]. Excellent catalytic activity, eco-friendly, easy work-up process, high yields and short reaction times are some beauties of present methodology.



(5) **(54)** **(8)** **(55)**

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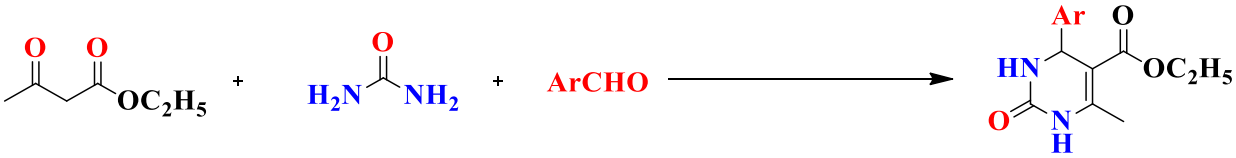
Scheme 50: Synthesis of substituted 3,4-dihydropyrimidine-2-(1*H*)-ones

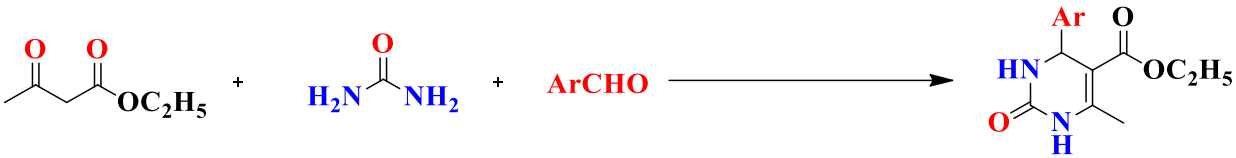
Elhamifar and his coworkers synthesized substituted dihydropyrimidinones **(55)** *via* one-pot three components cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of novel magnetic iron oxide supported copper/Schiff-base complex (Cu/SB-Fe_3O_4) as recyclable and green catalyst (Scheme 51)[97].



(5) **(54)** **(8)** **(55)**

Scheme 51: Synthesis of substituted dihydropyrimidinones

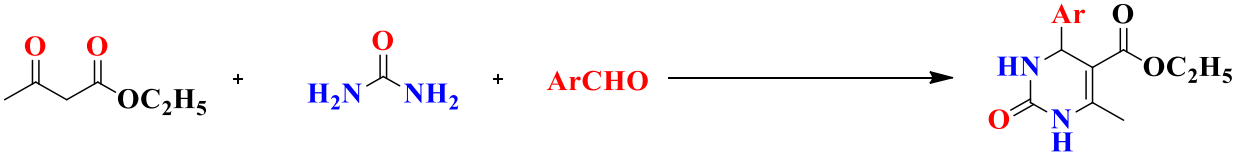
Sharma and Rawat synthesized substituted dihydropyrimidinones **(55)** *via* multicomponent cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of covalently anchored nickel complex on silica as catalyst in microwave irradiation under solvent-free conditions (Scheme 52)[98].



(5) **(54)** **(8)** **(55)**

Scheme 52: Synthesis of substituted dihydropyrimidinones

Lal and his coworkers synthesized substituted dihydropyrimidinones **(55)** *via* one-pot cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of Mg–Al–$CO_3$and Ca–Al–CO_3 hydrotalcite as a reusable solid catalyst (Scheme 53)[99].



(5) **(54)** **(8)** **(55)**

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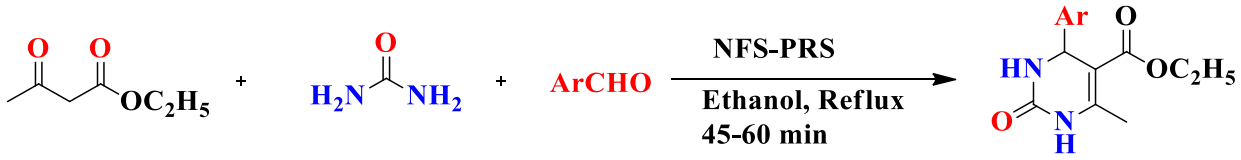
Scheme 53: Synthesis of substituted dihydropyrimidinones

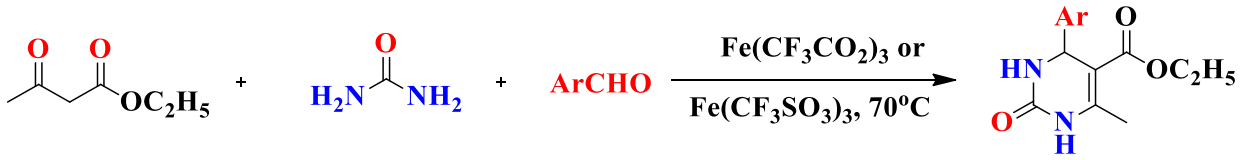
An efficient and simple procedure has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) **(55)** *via* multicomponent Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of novel magnetic acidic catalyst comprising Preyssler ($H_{14}[NaP_5W_{30}O_{110}]$) heteropoly acid supported on silica coated nickel ferrite nanoparticles ($NiFe_2O_4@SiO_2$) by Eshghi *et al*. (Scheme 54)[100].



(5) **(54)** **(8)** **(55)**

Scheme 54: Synthesis of substituted dihydropyrimidinones

Adibi and his coworkers synthesized substituted dihydropyrimidinones **(55)** *via* one-pot cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea/thiourea **(54)** in presence Iron(III) trifluoroacetate [$Fe(CF_3CO_2)_3$] or trifluoromethanesulfonate [$Fe(CF_3SO_3)_3$] as a reusable catalyst (Scheme 55)[101]. The possible mechanism for reaction is shown in Fig 17.



(5) **(54)** **(8)** **(55)**

Scheme 55: One-pot synthesis of DHPMs catalyzed by $Fe(CF_3CO_2)_3$ or $Fe(CF_3SO_3)_3$

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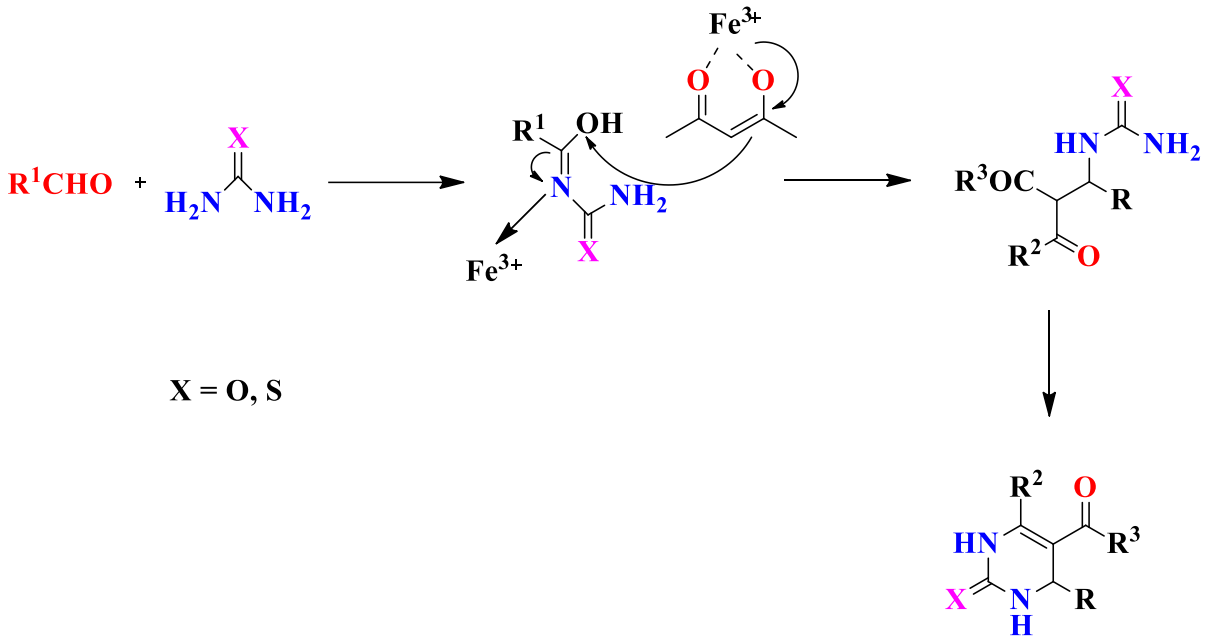
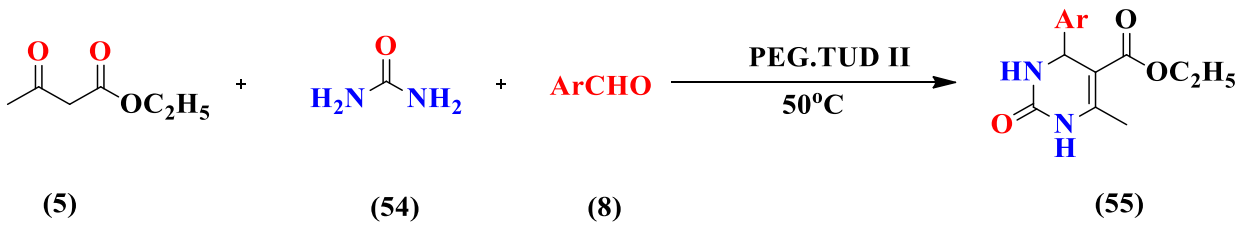


Fig 17: Possible mechanism for one-pot synthesis of DHPMs *via* Biginelli condensation protocol

An effortless method has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones (DHPMs) **(55)** *via* multicomponent Biginelli reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in presence of PEG-embedded thiourea dioxide (PEG.TUD) as a novel organocatalyst by Verma *et al*. (Scheme 56)[102]. According to mechanism, firstly reaction may involve the activation *via* the strong hydrogen bonding ability of the PEG.TUD II with oxygen of the carbonyl group as shown in Fig 18. This activation will be promoting the formation of acylimine intermediate by the reaction of aldehyde with urea/thiourea. In analogy to the well-established mechanism, the generation of acylimine intermediate is the key step, which subsequently reacts with *β*-dicarbonyl compound followed by cyclodehydration to give corresponding 3,4-dihydropyrimidinones.



Scheme 56: Biginelli condensation by using PEG.TUD II

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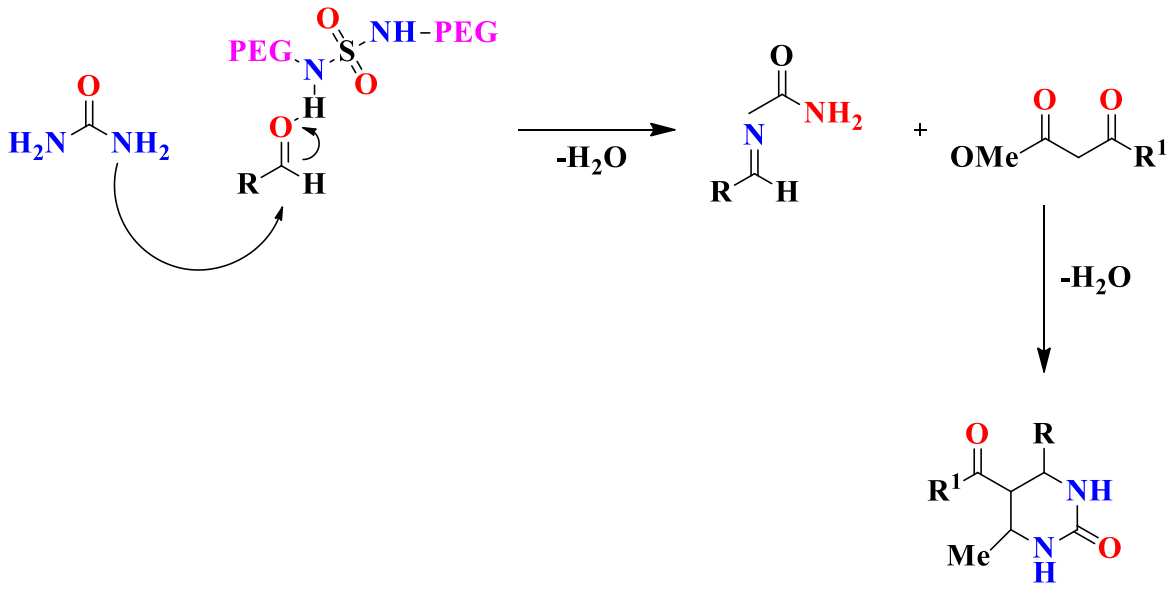
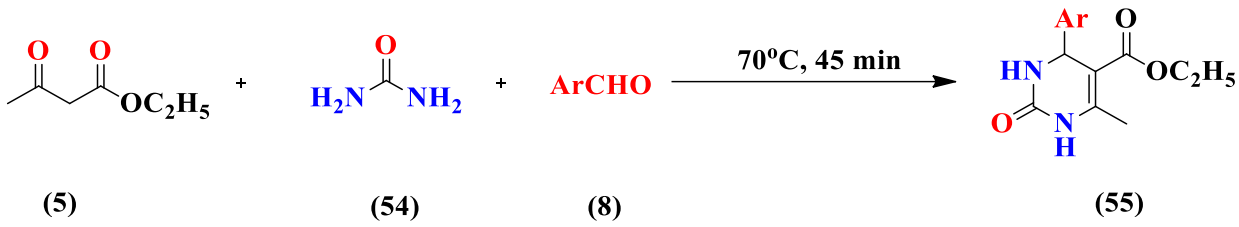


Fig 18: Plausible mechanistic pathway

A mild and efficient catalytic method has been developed to synthesize 3,4-dihydropyrimidinones **(55)** in excellent yield by one-pot three component Biginelli condensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54)** in the presence of triethylammonium acetate (TEAA) which acts as catalyst in reaction medium by Attri and his coworkers (Scheme 57)[103]. The plausible mechanism for reaction is shown in Fig 19.



Scheme 57: Synthesis of 3,4-dihydropyrimidinones from aldehyde, urea, *β*-dicarbonyl compound catalyzed by TEAA for 45 min at 70°C

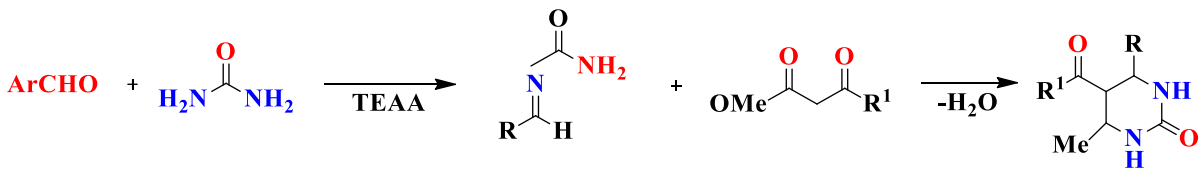


Fig 19: Mechanism for Biginelli condensation for the synthesis of 3,4-dihydropyrimidinones using triethylammonium acetate

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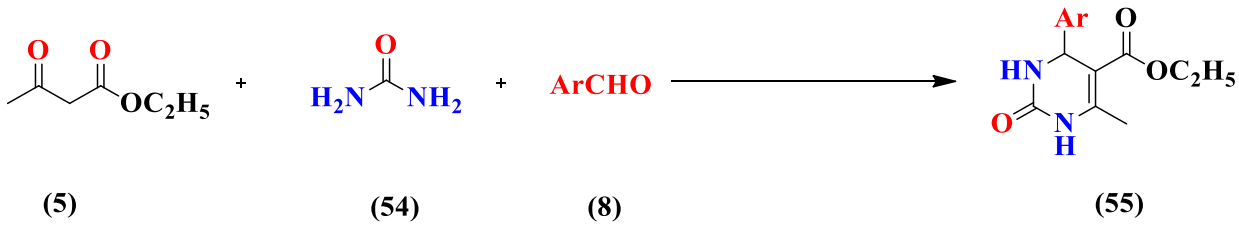
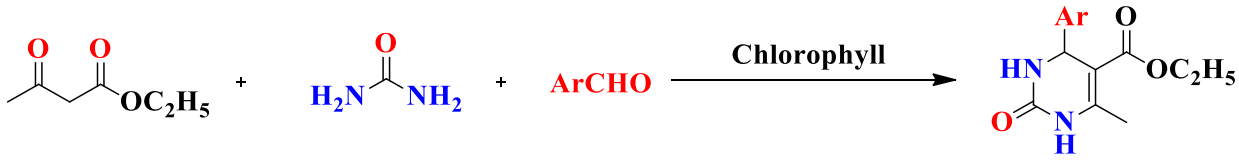
Gupta *et al*. synthesized substituted 3,4-dihydropyrimidinones **(55)** *via* multicomponent reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea/thiourea **(54)** in presence of novel covalently anchored sulfonic acid onto the surface of silica as a heterogeneous reusable catalyst (Scheme 58)[104].



(5) **(54)** **(8)** **(55)**

Scheme 58: Synthesis of substituted 3,4-dihydropyrimidinones

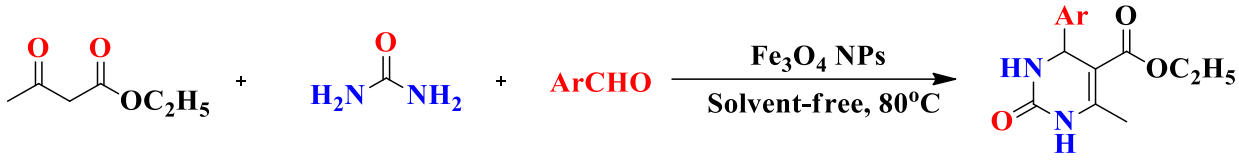
An effortless catalytic method has been developed to synthesize 3,4-dihydropyrimidinones **(55)** in good yield by one-pot three component Biginelli condensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea **(54),** which involves a photo induced electron transfer (PET) mechanism by Harsh and his coworkers (Scheme 59)[105].



(5) **(54)** **(8)** **(55)**

Scheme 59: Synthesis of substituted 3,4-dihydropyrimidinones

Esfahani *et al*. synthesized substituted 3,4-dihydropyrimidinones **(55)** *via* one-pot three components cyclocondensation reaction between substituted aldehydes **(8)**, *β*-ketoester **(5)** and urea/thiourea **(54)** in presence of Fe_3O_4 nanoparticles (NPs) as reusable catalyst (Scheme 60)[106].



(5) **(54)** **(8)** **(55)**

Scheme 60: Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones) using Fe_3O_4 NPs

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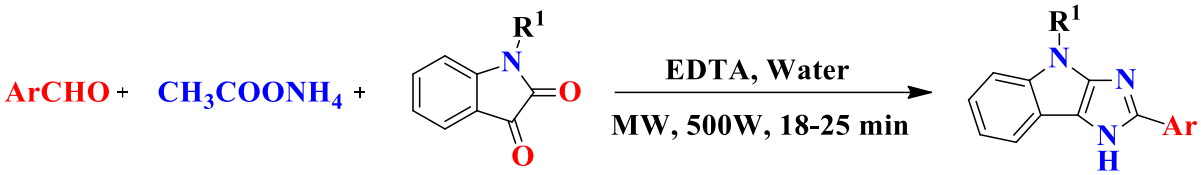
Green synthetic methods for the preparation of substituted imidazoles

Bajpai and Singh reported the synthesis of substituted imidazoles **(60)** under controlled microwave irradiation in water *via* multicomponent reaction of *N*-substituted isatin derivatives **(58)** with ammonium acetate **(59)** and substituted aldehydes **(8)** in the presence of catalytic amount of EDTA (Scheme 61)[107]**.** They observed that present method is mild, environmentally friendly, inexpensive and highly effective to give the desired products in significant yield.



(8) **(59)** **(58)** **(60)**

Scheme 61: Synthesis of substituted imidazoles

Ali Akbari reported the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles **(63)** *via* the condensation reaction between benzil **(61)**, substituted aldehydes **(8)**, aniline **(62)** and ammonium acetate **(59)** in presence of magnetic ionic liquid, tri(1-butyl-3-methylimidazolium) gadolinium hexachloride, ([bmim]$_3$[GdCl$_6$]) used as an catalyst (Scheme 62)[108].

(61) **(8)** **(62)** **(59)** **(63)**

Scheme 62: Synthesis of substituted imidazoles

An efficient method for the synthesis of imidazole derivatives **(64)** *via* three-component condensation reaction between benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** using supported ionic liquid like phase (SILLP) catalyst under ultrasonic irradiation or classical heating conditions was reported by Jourshari *et al*. (Scheme 63)[109]. The current method offers several advantages, such as excellent yields, simple procedures, less reaction times, simple work-up and mild reaction conditions.

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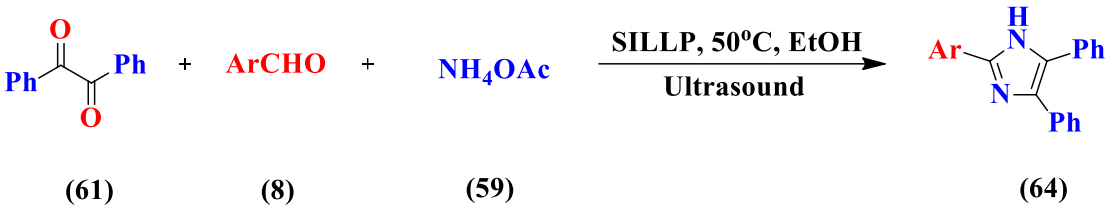
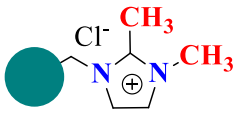


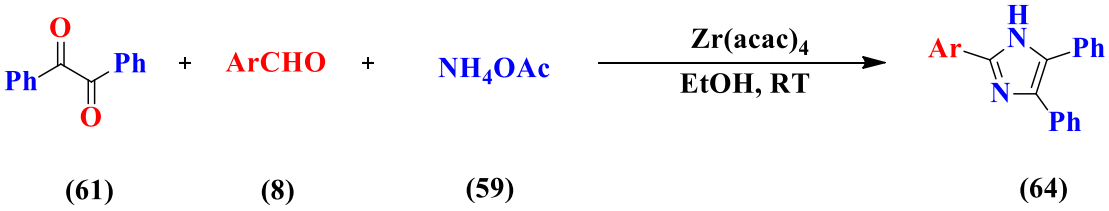
(61) (8) (59) (64)

SILLP:



Scheme 63: Synthesis of substituted imidazoles

A simple, efficient and green protocol has been developed for the synthesis of 2,4,5-trisubstituted imidazoles **(64)** *via* multicomponent reaction between benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** catalyzed by zirconium (IV) acetylacetonate using ultrasonic irradiation by Ahmad Khosropour (Scheme 64)[110]. The present method offers several advantages such as excellent yields, simple procedure, short reaction times and mild reaction conditions.



(61) (8) (59) (64)

Scheme 64: Synthesis of substituted imidazoles

Ziarani and his colleagues reported one-pot synthesis of 2,4,5-trisubstituted **(64)** and 1,2,4,5-tetrasubstituted imidazoles **(63)** under solvent-free conditions using sulfonic acid functionalized SBA-15 nanoporous material as green and efficient solid acid catalyst (Scheme 65 & Scheme 66)[111]. The plausible mechanism for the synthesis of 2,4,5-trisubstitued imidazoles are shown in Fig 20. Initially, the solid acid catalyst can activate the carbonyl groups of aldehyde **2** and benzil **1** to decrease the energy of transition state. Then nucleophilic attack of the nitrogen of ammonia, obtained from NH_4OAc on the protonated carbonyl group **7**, resulted in the formation of diamine intermediate **8**. This intermediate in the presence of SBA-Pr-SO_3H, condenses with benzil **9** to form intermediate **11** which in turn rearranges to the trisubstituted imidazoles by a [1,5]-H shift. Similarly, a plausible mechanism for the synthesis of 1,2,4,5-tetrasubstitued imidazoles was presented in Fig 21. After the

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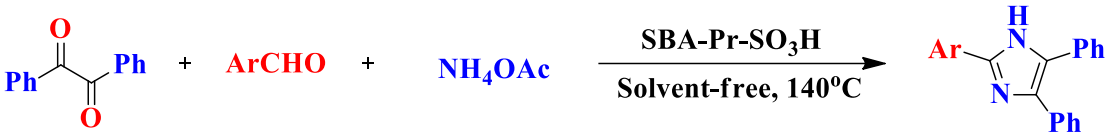
protonation of the carbonyl group of the substituted aldehyde **2** and the nucleophilic attack of the nitrogen atoms of ammonia, obtained from NH_4OAc, and aniline **5** to it, intermediate **12** is formed. In the presence of SBA-Pr-SO_3H, intermediate **12** condenses with benzil **9** to form intermediate **14** which in turn forms tetrasubstituted imidazoles by removal of water molecule.



(61) **(8)** **(59)** **(64)**

Scheme 65: Synthesis of 2,4,5-trisubstituted imidazoles in the presence of SBA-Pr-SO_3H

(61) **(8)** **(62)** **(59)** **(63)**

Scheme 66: Synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of SBA-Pr-SO_3H

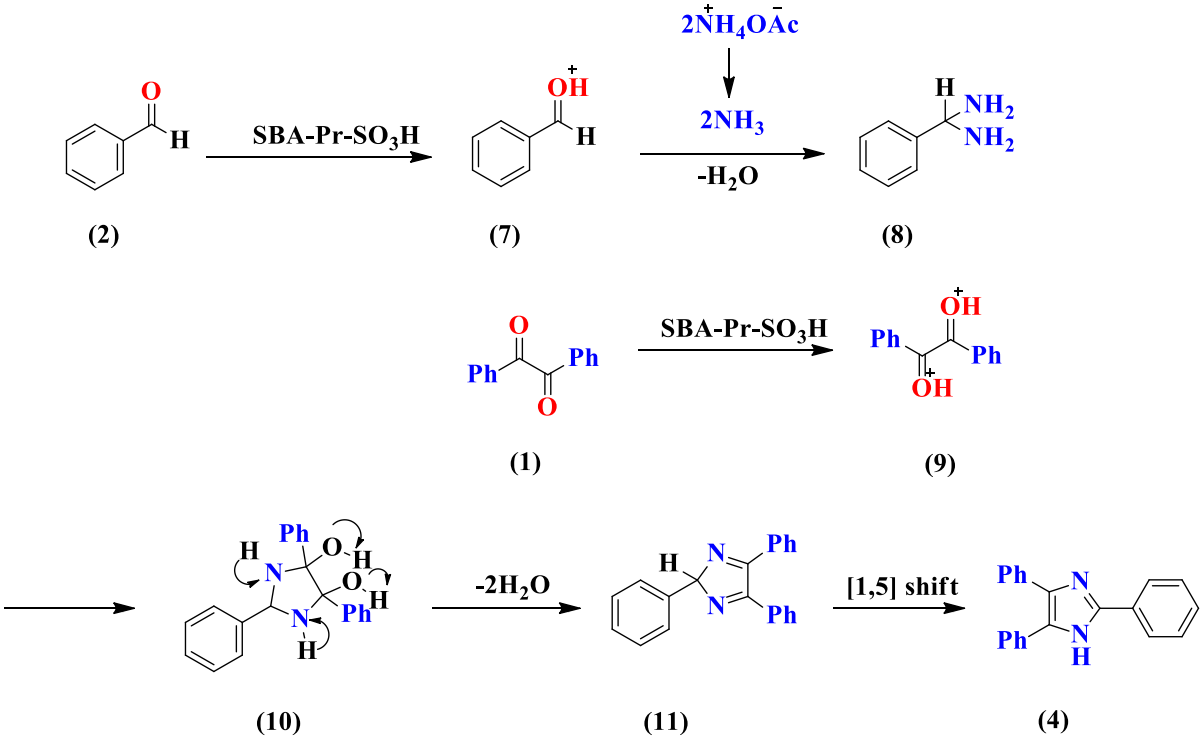


Fig 20: Plausible mechanism for the synthesis of 2,4,5-trisubstituted imidazoles

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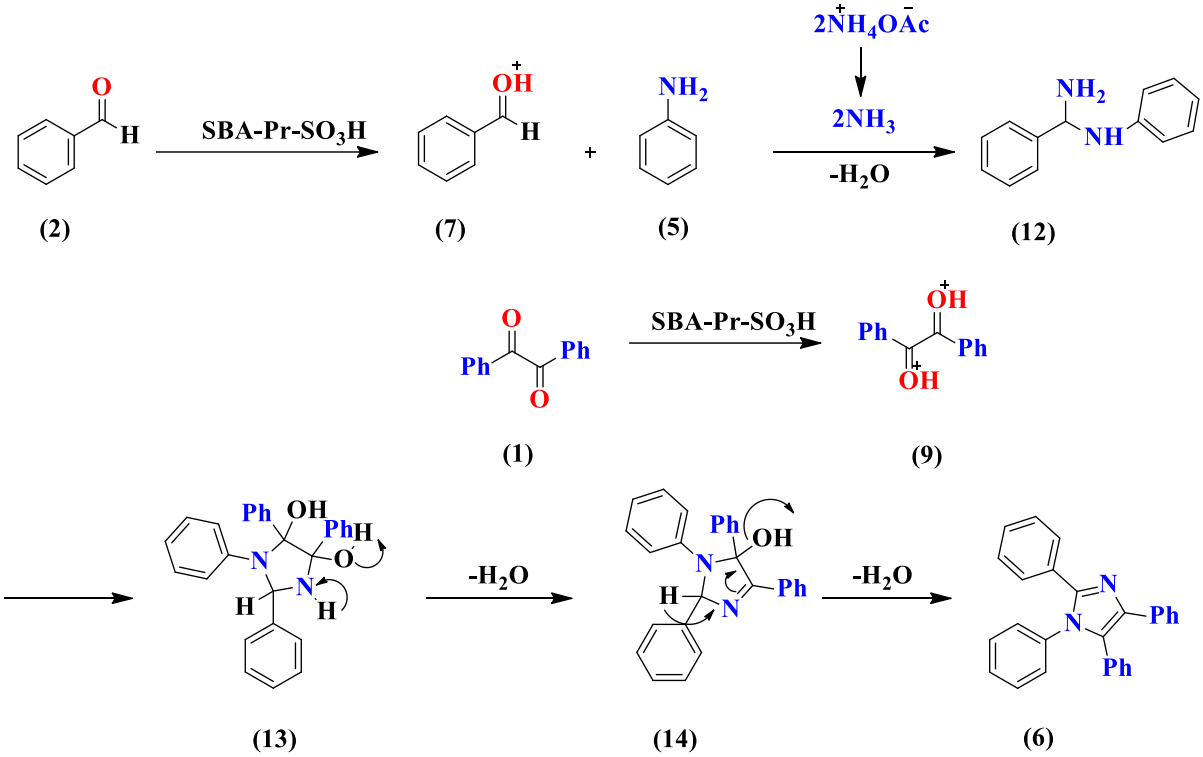
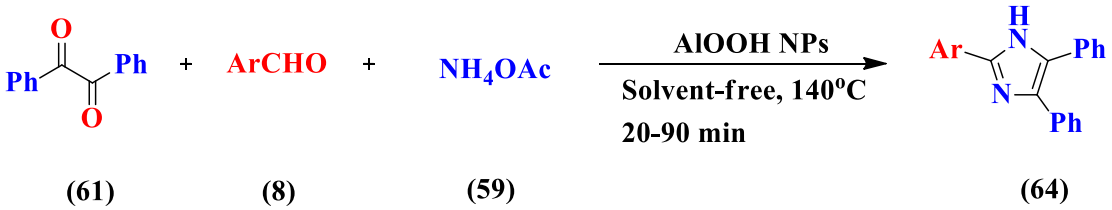


Fig 21: Plausible mechanism for the synthesis of 1,2,4,5-tetrasubstituted imidazoles

Keivanloo *et al*. reported the synthesis of substituted imidazoles **(64)** by a three-component condensation reaction between benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** using Boehmite nanoparticles (Scheme 67)[112]. They found that this one-pot procedure is very simple, and affords good to excellent yields. Furthermore, the catalyst shows good thermal stability and recyclability. They also observed that catalyst was recycled for five runs without an appreciable loss in its catalytic activity.



Scheme 67: Synthesis of substituted imidazoles

Heravi *et al*. reported the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles **(63)** *via* the condensation reaction between benzil **(61)**, substituted aldehydes **(8)**, aniline **(62)** and ammonium acetate **(59)** in presence of Keggin-type heteropolyacid (HPA) as reuseable catalyst (Scheme 68)[113].

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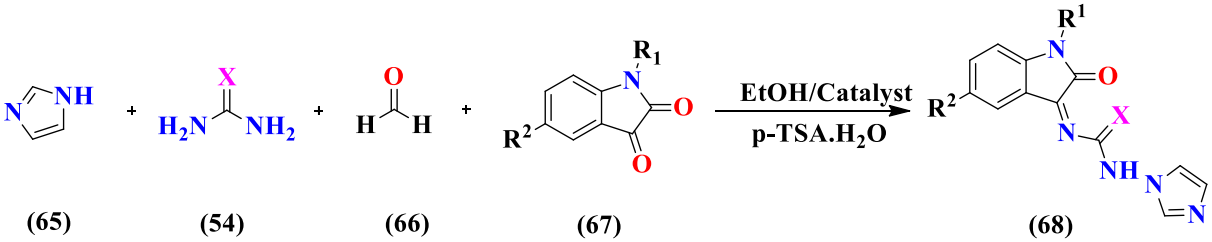
(61) (8) (62) (59) (63)

Scheme 68: Synthesis of substituted imidazoles

A novel one-pot multicomponent reaction was carried out to synthesize isatin-based imidazole derivatives **(68)** *via* imidazole/benzotriazole **(65)**, thiourea/urea **(54)**, formaldehyde **(66)**, and isatins **(67)** using *p*-TSA. H_2O as catalyst (Scheme 69)[114].



(65) (54) (66) (67) (68)

R^1 = H, -CH_3, -ClC_6H_4, -CH_2COOH, -CH_2CH_3, -C_2H_4Br
R^2 = H, Br, X = O,S

Scheme 69: General route of synthesis of isatin-based imidazole derivatives

Kerru and his coworkers reported an efficient and facile one-pot method for the synthesis of tetrasubstituted imidazole-chromenone analogs **(63)** *via* multicomponent reaction between benzil **(61)**, substituted aldehydes **(8)**, aniline **(62)** and ammonium acetate **(59)** in presence of NiO/FAp, as a reusable heterogeneous catalyst (Scheme 70)[115].

(61) (8) (62) (59) (63)

Scheme 70: Multicomponent synthetic route for novel 1,2,4,5-tetrasubstituted imidazoles

A simple, efficient and eco-friendly method has been developed using Selectfluor™ (15% mol) as a novel catalyst under ultrasound irradiation and solvent-free conditions for the synthesis of

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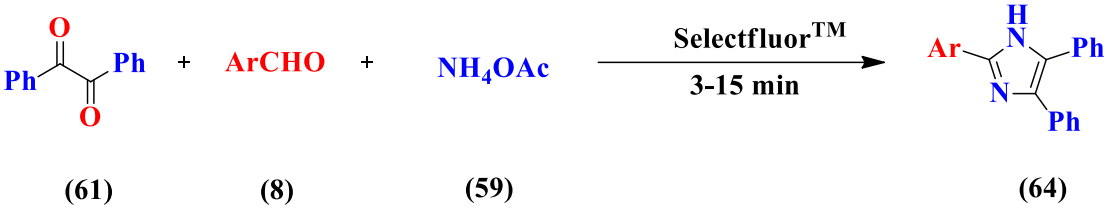
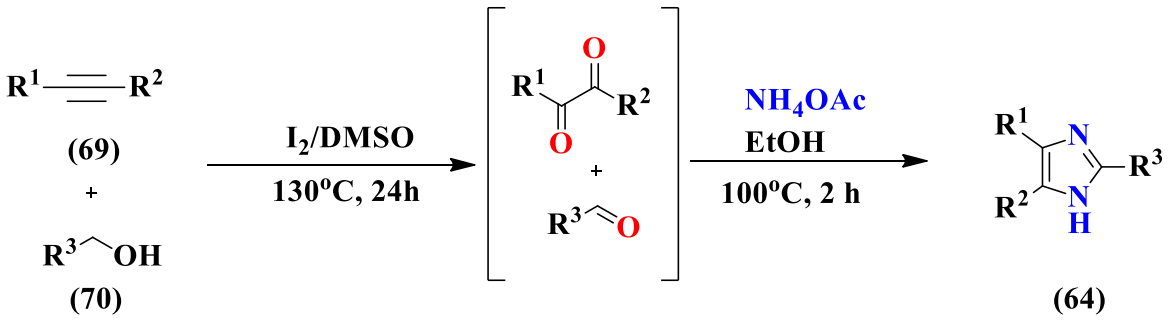
2,4,5 triaryimidazole **(64)** *via* multicomponent condensation reaction between benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** by Heravi and his coworkers (Scheme 71)[116].



(61) **(8)** **(59)** **(64)**

Scheme 71: Synthesis of 2,4,5-trisubstituted imidazoles catalysed by Selectfluor™ under ultrasound irradiation

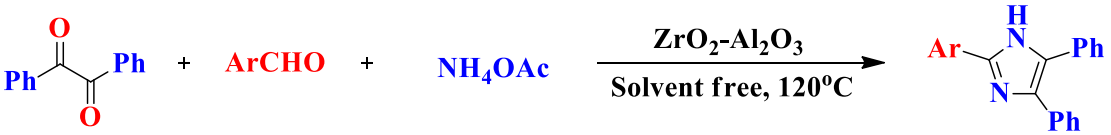
An efficient, eco-friendly and practical oxidation of internal alkynes **(69)** and primary alcohols **(70)** as key steps towards the synthesis of 2,4,5-trisubstituted imidazoles **(64)** was reported by Naidoo and Jeena by using metal-free molecular iodine/DMSO system (Scheme 72)[117].



(64)

Scheme 72: Synthesis of 2,4,5-trisubstituted imidazoles

Thimmaraju and Shamshuddin reported the synthesis of 2,4,5-trisubstituted imidazoles **(64)** by one-pot three-component condensation reaction between benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** using eco-friendly and highly efficient ZrO_2-Al_2O_3 as catalyst (Scheme 73)[118]. The present method is experimentally simple, non-toxic and involves cost-effective reagents, clean reaction pathways and eco-friendly catalyst.



(61) **(8)** **(59)** **(64)**

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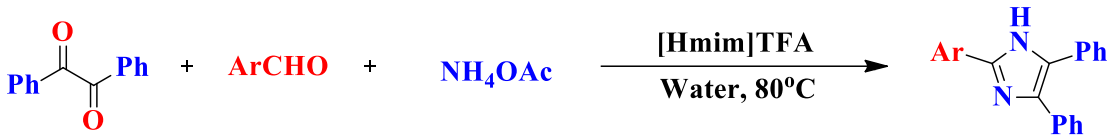
Scheme 73: Cyclo-condensation of benzil, aldehydes and ammonium acetate with ZrO_2-Al_2O_3 catalytic materials

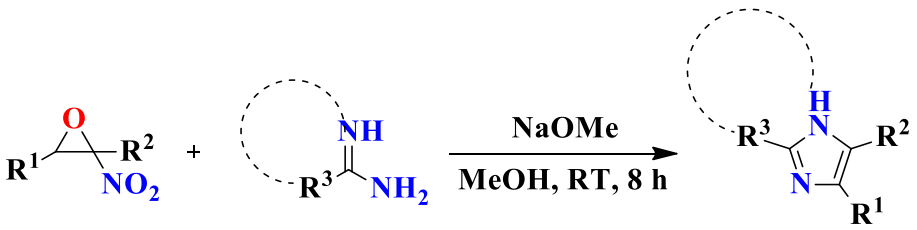
Highly efficient one-pot reactions of benzil **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** were carried out in water in the presence of 1-methylimidazolium trifluoroacetate ([Hmim]TFA) under mild and green conditions for the synthesis of 1,4,5-trisubstituted imidazoles **(64)** in excellent yields by MaGee *et al*. (Scheme 74)[119].



(61) **(8)** **(59)** **(64)**

Scheme 74: Synthesis of 2-aryl-4,5-diphenyl-1*H*-imidazoles in water using [Hmim]TFA as a catalyst

A simple and direct synthesis of functionalized imidazoles **(73)** from *α*-nitro-epoxides **(71)** and amidines **(72)** was developed by Guo and his coworkers. They observed that reaction could proceed smoothly in a highly efficient and eco-friendly manner and moderate to excellent yields of desired products were obtained (Scheme 75)[120]. The plausible mechanism for reaction is shown in Fig 22.



(71) **(72)** **(73)**

Scheme 75: Synthesis of functionalized imidazoles

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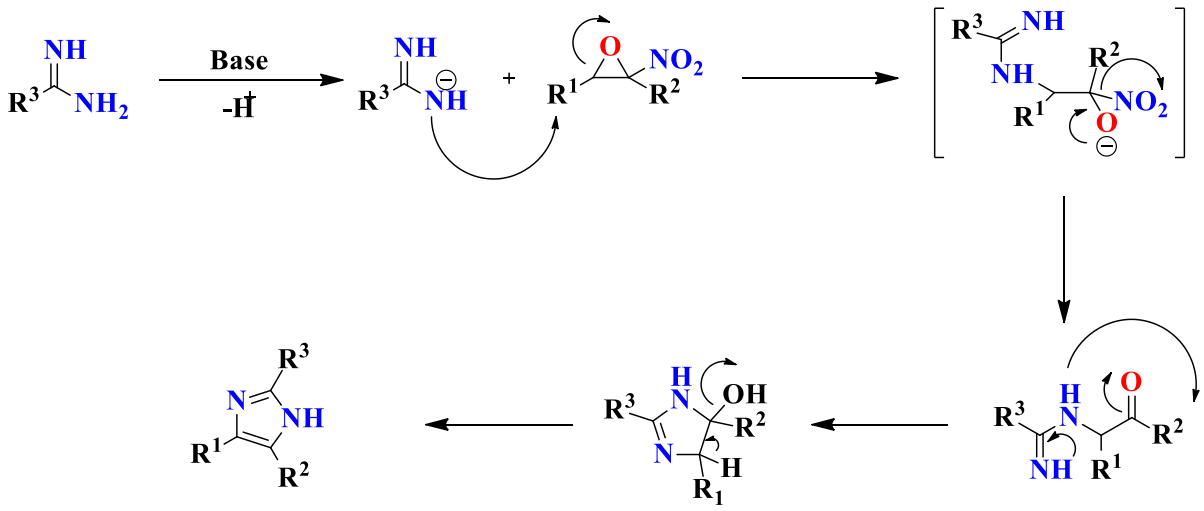
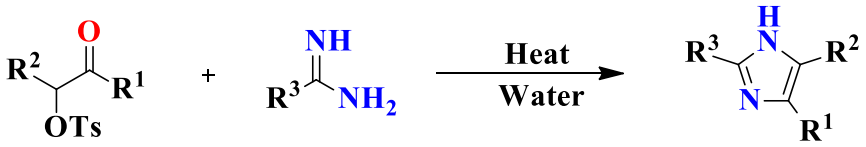


Fig 22: Plausible Mechanism for the Tandem Reaction

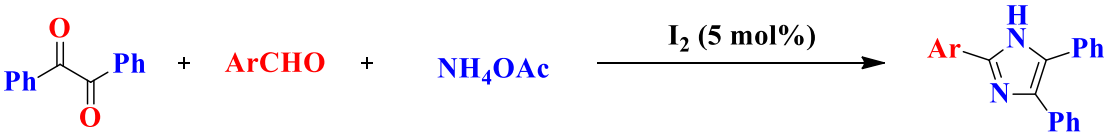
A simple, efficient and green method for the synthesis of substituted imidazoles **(75)** was reported *via* reaction of easily available *α*-tosyloxy ketones **(74)** with variety of thioamides/amidines **(72)** in water by Kumar and his coworkers (Scheme 76)[121].



(74) **(72)** **(75)**

Scheme 76: Synthesis of substituted imidazoles

Molecular iodine has been used an efficient catalyst for multicomponent synthesis of 2,4,5-trisubstituted **(64)** and 1,2,4,5-tetra substituted imidazoles **(63)** in good yields by Kidwai *et al.* (Scheme 77 & Scheme 78)[122].



(61) **(8)** **(59)** **(64)**

Scheme 77: Iodine catalyzed synthesis of 2,4,5-triarylimidazoles

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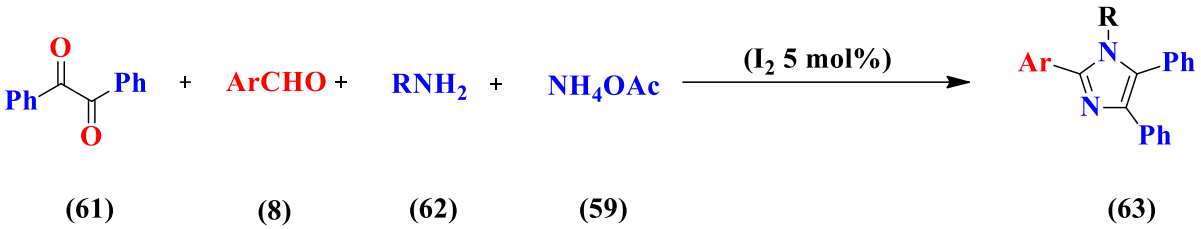
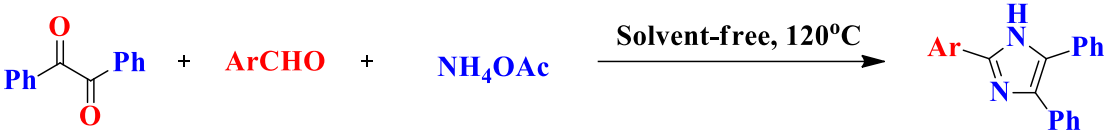


(61) (8) (62) (59) (63)

Scheme 78: Iodine catalyzed synthesis of 1,2,4,5-tetraarylimidazoles

A simple, effortless and eco-friendly method for the synthesis of 2,4,5-trisubstituted-1*H*-imidazoles **(64)** *via* one-pot three component condensation reaction between benzil **(61)** , substituted aldehydes **(8)** and ammonium acetate **(59)** under solvent-free conditions has been carried out utilizing Brønsted acidic ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl) phosphonium hydrogen sulfate as catalyst by Banothu and his coworkers (Scheme 79)[123].



(61) (8) (59) (64)

Scheme 79: Synthesis of 2,4,5-trisubstituted-1*H*-imidazoles catalyzed by (4-SB)T(4-SPh)PHSO$_4$

An efficient synthesis of various tetrasubstituted imidazoles **(63)** using silica gel-supported sodium bisulfate as a catalytic support by four component condensation reaction between benzil **(61)**, substituted aldehydes **(8)**, amines **(62)**, and ammonium acetate **(59)** under microwave irradiation or classical heating conditions was reported by Karimi *et al*. (Scheme 80)[124].

(61) (8) (62) (59) (63)

Scheme 80: Synthesis of tetrasubstituted imidazoles

A simple, efficient and eco-friendly protocol has been developed using tetrabutylammonium bromide (TBAB, 10 mol%) as novel neutral ionic liquid catalyst for the synthesis of 2,4,5-triaryl imidazoles **(64)** *via* multicomponent condensation reaction between benzil **(61)**, substituted aldehydes

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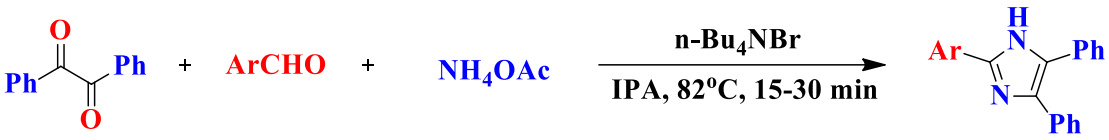
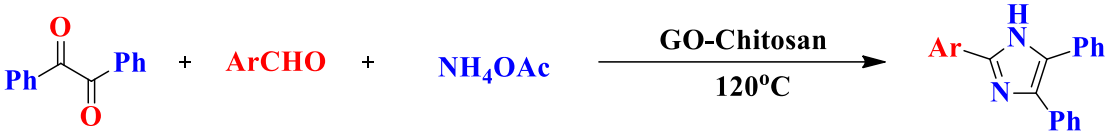
(8) and ammonium acetate **(59)** with refluxing in isopropanol by Chary and his coworkers (Scheme 81)[125]. Excellent yields, short reaction time, eco-friendly and mild reaction conditions are some beauties of present methodology.



(61) **(8)** **(59)** **(64)**

Scheme 81: Synthesis of 2,4,5-triarylimidazoles

Maleki and Paydar reported the green, rapid and convenient method for synthesis of 2,4,5-trisubstituted imidazoles **(64)** *via* one-pot three component condensation reaction between benzil **(61)** , substituted aldehydes **(8)** and ammonium acetate **(59)** in the presence of graphene oxide–chitosan bionanocomposite (Scheme 82)[126]. This procedure has many advantages such as short reaction time, high yield, easy separation of the catalyst and solvent-free condition.



(61) **(8)** **(59)** **(64)**

Scheme 82: GO–chitosan-catalyzed synthesis of substituted imidazoles

Silica-supported boron trifluoride ($BF_3.SiO_2$) is an efficient, readily available and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **(63)** using benzil **(61)**, substituted aldehyde **(8)** and amine **(62)** in the presence of ammonium acetate **(59)** reported by Sadeghi *et al*. (Scheme 83)[127]. This one-pot procedure is very simple, affording good to excellent yield of desired products.

(61) **(8)** **(62)** **(59)** **(63)**

Scheme 83: BF_3/SiO_2-catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles

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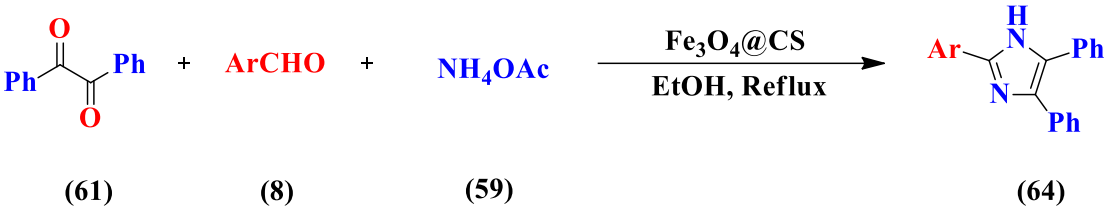
Zarnegar and Safari reported the synthesis of 2,4,5-trisubstituted imidazoles **(64)** by one-pot condensation reaction between benzil derivatives **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** in EtOH in presence of Chitosan-coated Fe_3O_4 nanoparticles (Scheme 84)[128]. This novel method offers several benefits compared to those reported in the previous literature, including avoiding the use of harmful reagents, easy and quick isolation of the products, excellent yields, mild reaction conditions, and simplicity of the methodology. High catalytic activity and ease of recovery using an external magnetic field are additional eco-friendly attributes of this catalytic system. The plausible mechanism for reaction is shown in Fig 23.



Scheme 84: One-pot synthesis of 2,4,5-trisubstituted imidazoles catalyzed by Fe_3O_4@CS

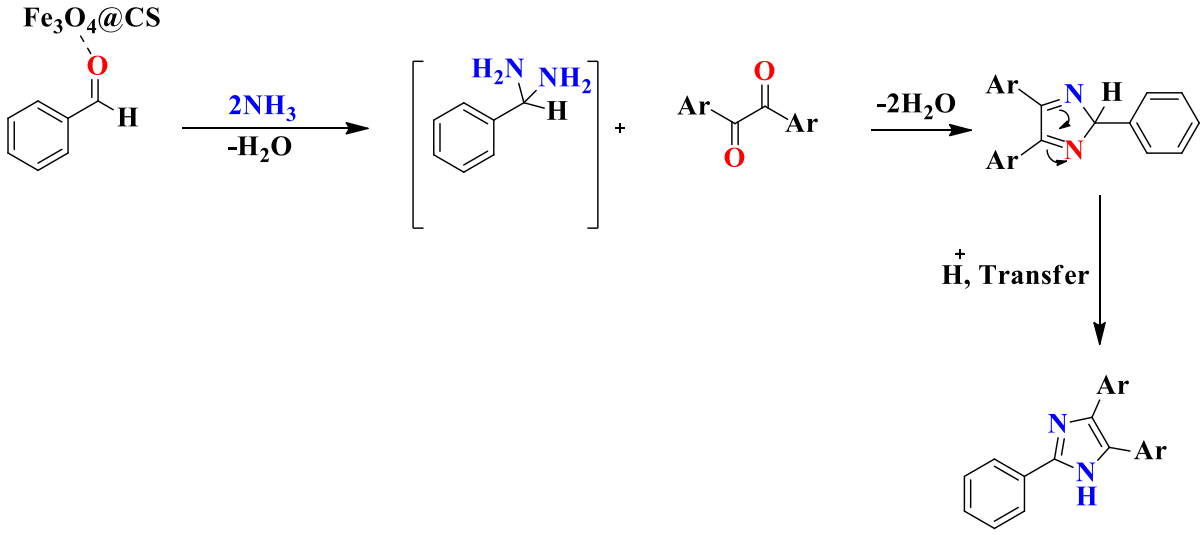


Fig 23: Plausible mechanism for the reaction

Varzi and Maleki reported the synthesis of 2,4,5-trisubstituted imidazoles **(64)** by one-pot condensation reaction between benzil derivatives **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** in presence of ZnS-$ZnFe_2O_4$ an efficient hybrid nanocatalyst (Scheme 85)[129].

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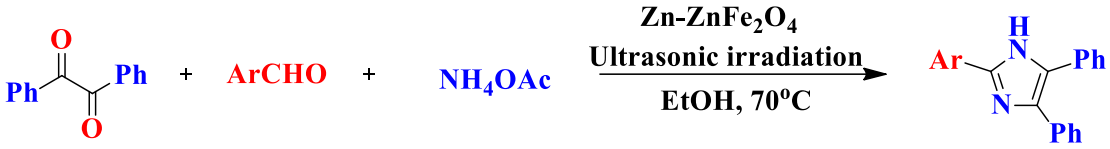
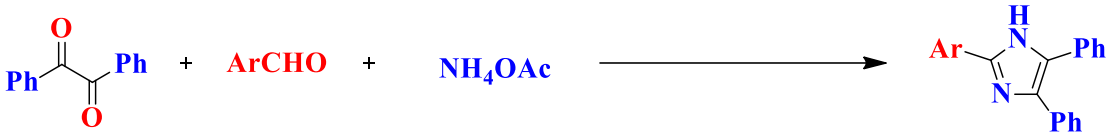


(61) **(8)** **(59)** **(64)**

Scheme 85: Synthesis of 2,4,5-triaryl-1*H*-imidazoles in the presence of ZnS-$ZnFe_2O_4$

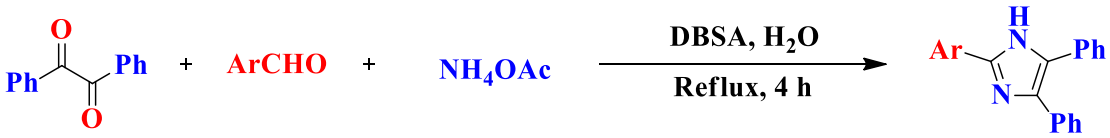
Safari and Zarnegar reported the synthesis of 2,4,5-trisubstituted imidazoles **(64)** by one-pot condensation reaction between benzil derivatives **(61)**, substituted aldehydes **(8)** and ammonium acetate **(59)** in presence of Magnetic Fe_3O_4 nanoparticles an efficient hybrid nanocatalyst (Scheme 86)[130].



(61) **(8)** **(59)** **(64)**

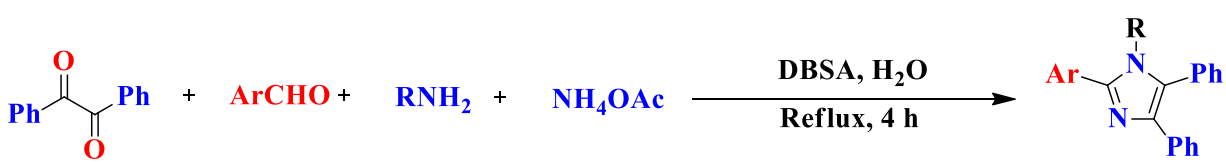
Scheme 86: One-pot synthesis of 2,4,5-trisubstituted imidazoles catalyzed by MNPs under ultrasound irradiation at ambient temperature

p-dodecylbenzenesulfonic acid has been used an efficient catalyst for one-pot synthesis of 2,4,5-trisubstituted **(64)** and 1,2,4,5-tetra substituted imidazoles **(63)** in excellent yields by Das *et al.* (Scheme 87 & Scheme 88)[131].



(61) **(8)** **(59)** **(64)**

Scheme 87: Synthesis of 2,4,5-trisubstituted imidazole derivatives



(61) **(8)** **(62)** **(59)** **(63)**

Scheme 88: Synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives

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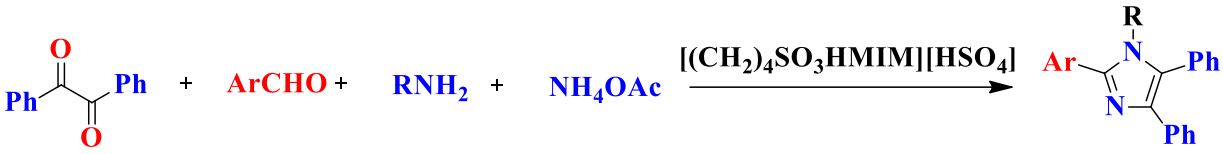
Niloofar and Abolghasem reported the synthesis of 1,2,4,5-tetrasubstituted imidazoles **(63)** using benzil **(61)**, substituted aldehyde **(8)**, amine **(62)** and ammonium acetate **(59)** in the presence of carbon based solid acid catalyst (Scheme 89)[132]. The present methodology offers several advantages, such as high yields, less reaction time, mild reaction condition and a recyclable catalyst with very easy work-up.

(61) **(8)** **(62)** **(59)** **(63)**

Scheme 89: Synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives

3-Methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate $[(CH_2)_4SO_3HMIM][HSO_4]$, a Brønsted acidic ionic liquid, has been used as an efficient, green, and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles *via* condensation reaction between benzil **(61)**, substituted aldehydes **(8)**, amine **(62)** and ammonium acetate **(59)** under solvent-free conditions by Davoodnia and his coworkers (Scheme 90)[133].



(61) **(8)** **(62)** **(59)** **(63)**

Scheme 90: Synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives

Green synthetic methods for the preparation of substituted isoxazoles

A facile and efficient microwave assisted synthesis of 3,5-disubstituted isoxazoles **(78)** was reported by Meena and his coworkers in green reaction medium *via* the reaction of N-hydroxyl imidoyl chlorides **(76)** with substituted alkynes **(77)** in aqueous medium using 2 mol% of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst (Scheme 91)[134].

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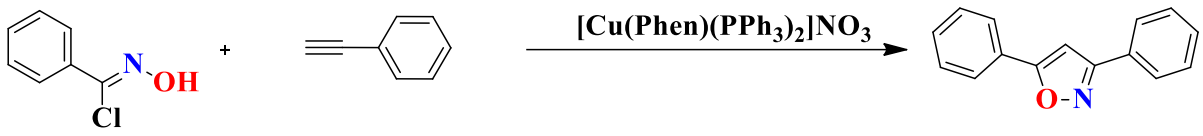
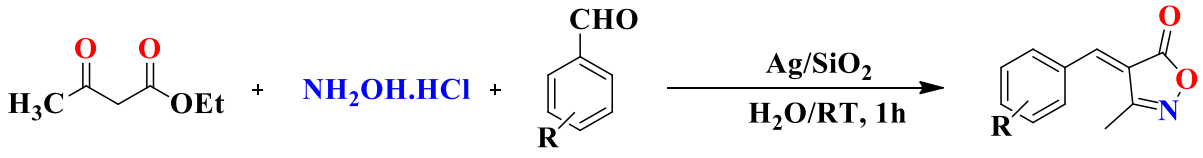


(76) (77) (78)

Scheme 91: Telescoped approach to 3,5-diphenylisoxazole

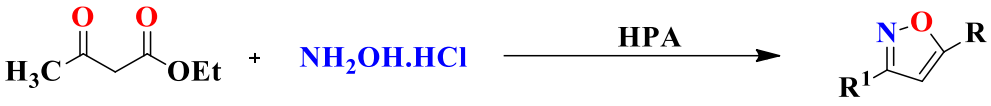
A green method for synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one **(80)** *via* room temperature reaction of hydroxylamine **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** is designed, using Ag/SiO_2 as catalyst with water as solvent reported by Maddila and his coworkers (Scheme 92)[135].



(5) (79) (8) (80)

Scheme 92: Synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives

Heravi *et al*. reported the synthesis of isoxazole derivatives **(81)** from the condensation reaction between *β*-dicarbonyl compound **(5)** and hydroxylamine hydrochloride **(79)** in different solvents and under heating conditions in presence of heteropolyacid $H_3PW_{11}CuO_{40}$ as catalyst (Scheme 93)[136].



(5) (79) (81)

Scheme 93: Synthesis of isoxazole derivatives

A series of 5-arylisoxazole derivatives **(83)** were synthesized *via* the reaction of 3-(dimethyl-amino)-1 arylprop-2-en-1-ones **(82)** with hydroxylamine hydrochloride **(79)** in aqueous media without using any catalyst by Dou *et al*. (Scheme 94)[137]. Easy work-up, mild reaction conditions, high yield and eco-friendly method are some merits of present methodology. The plausible mechanism for reaction is shown in Fig 24.

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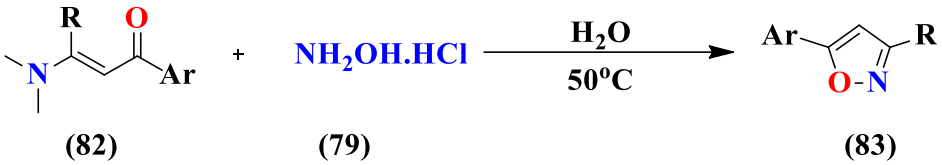


(82) (79) (83)

Scheme 94: Synthesis of isoxazole derivatives

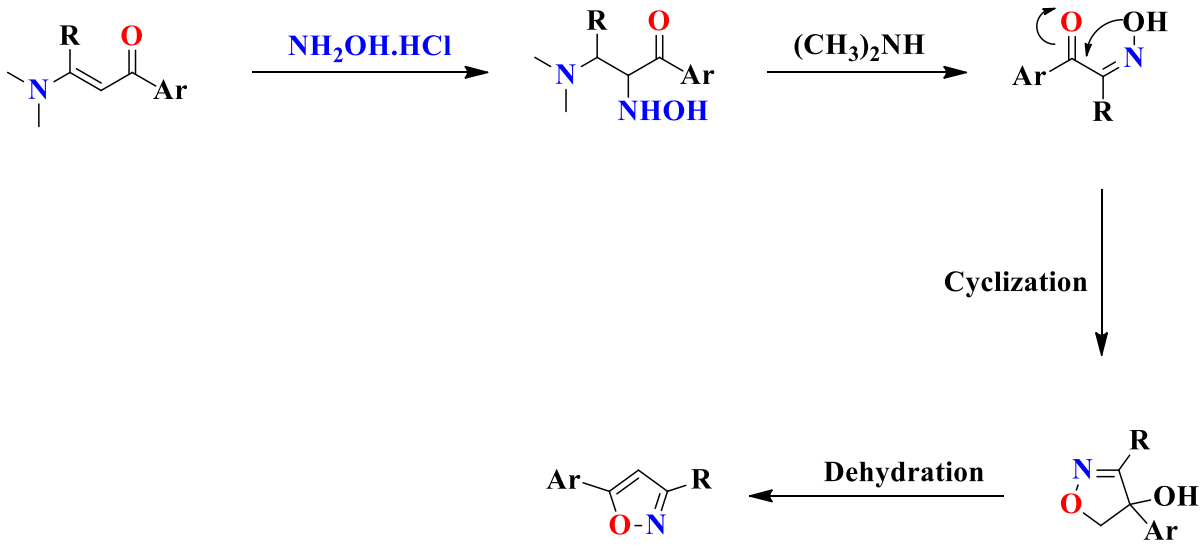
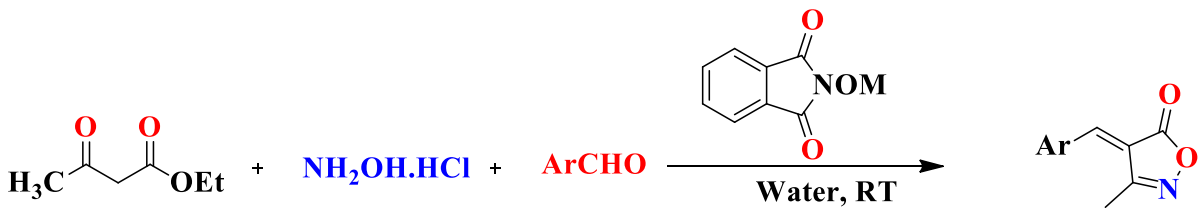


Fig 24: Plausible mechanism for the reaction

Dekamin and Peyman reported the synthesis of (*Z*)-3-methyl-4-(arylmethylene)-isoxazole-5(4*H*)-one derivatives **(80)** in water *via* multicomponent reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in the presence of tetrabutylammonium or potassium salts of phthalimide-N-oxyl (Scheme 95)[138]. This method offers many advantages including clean reaction profiles, mild reaction conditions, short reaction time, high yield of desired products, and easy work-up.



(5) (79) (8) (80)

Scheme 95: Synthesis of isoxazole derivatives

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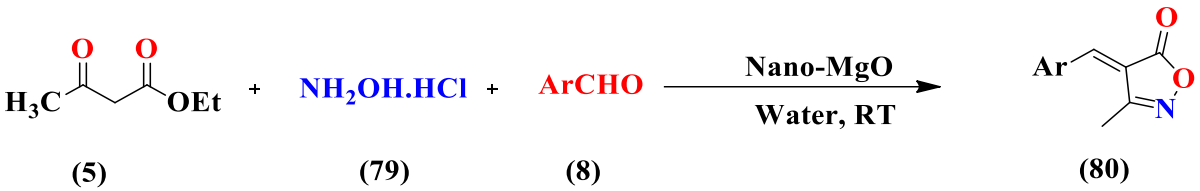
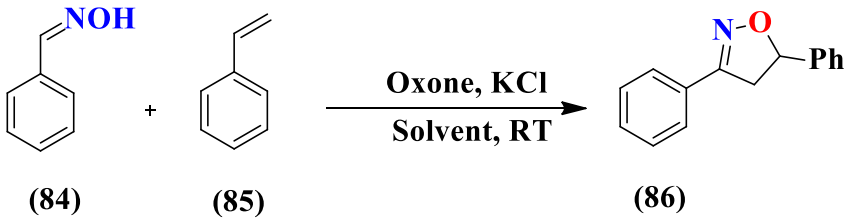
Kiyani and Ghorbani reported the synthesis of 3,4-disubstituted isoxazole-5(4*H*)-ones **(80)** *via* one-pot three-component reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in the presence of nano-MgO as catalyst (Scheme 96)[139].



Scheme 96: Synthesis of substituted 3,4-disubstituted isoxazole-5(4*H*)-ones

An effective and environmentally benign protocol for the synthesis of isoxazolines and isoxazoles **(86)** has been developed by cycloaddition of nitrile oxides **(84)** with alkenes or alkynes **(85)** in water by Han and his coworkers (Scheme 97)[140]. The plausible mechanism for reaction is shown in Fig 25.



Scheme 97: Synthesis of substituted isoxazole

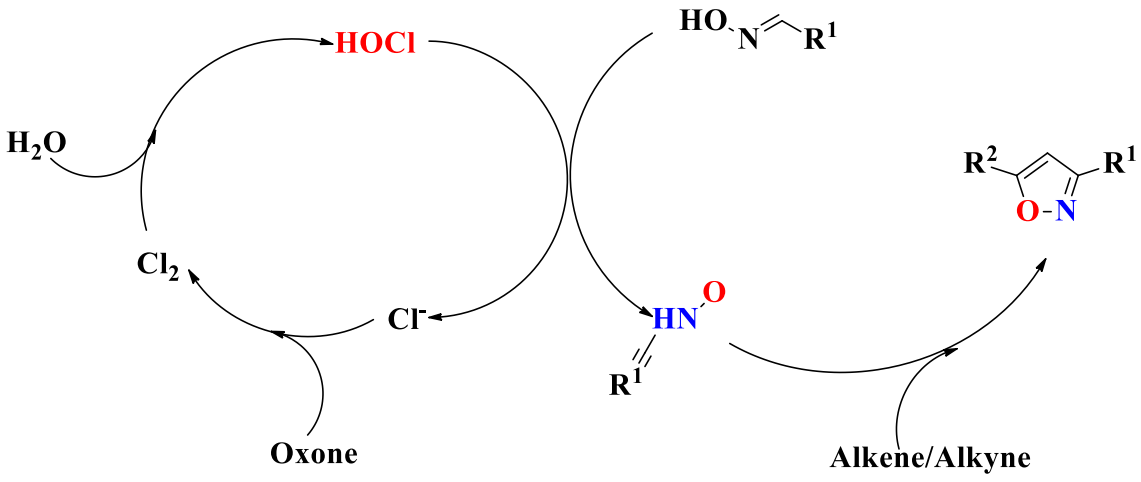


Fig 25: Plausible mechanism for the synthesis of isoxazolines and isoxazoles

Patil and his coworkers reported the rapid and highly efficient method for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones **(80)** *via* multicomponent reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in presence of

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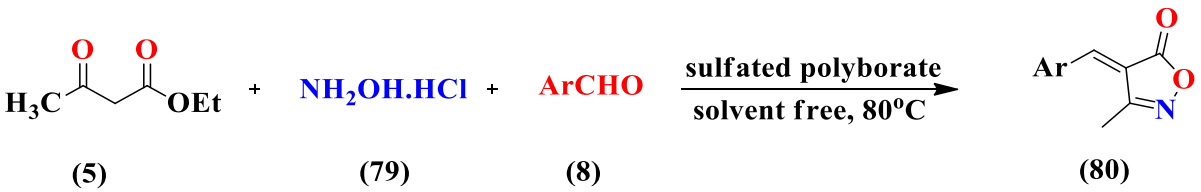
sulfated polyborate as a catalyst (Scheme 98)[141]. The plausible mechanism for reaction is shown in Fig 26.



Scheme 98: Synthesis of various 3-methyl 4-phenylmethylene isoxazol-5(4*H*)-one catalyzed by sulfated polyborate

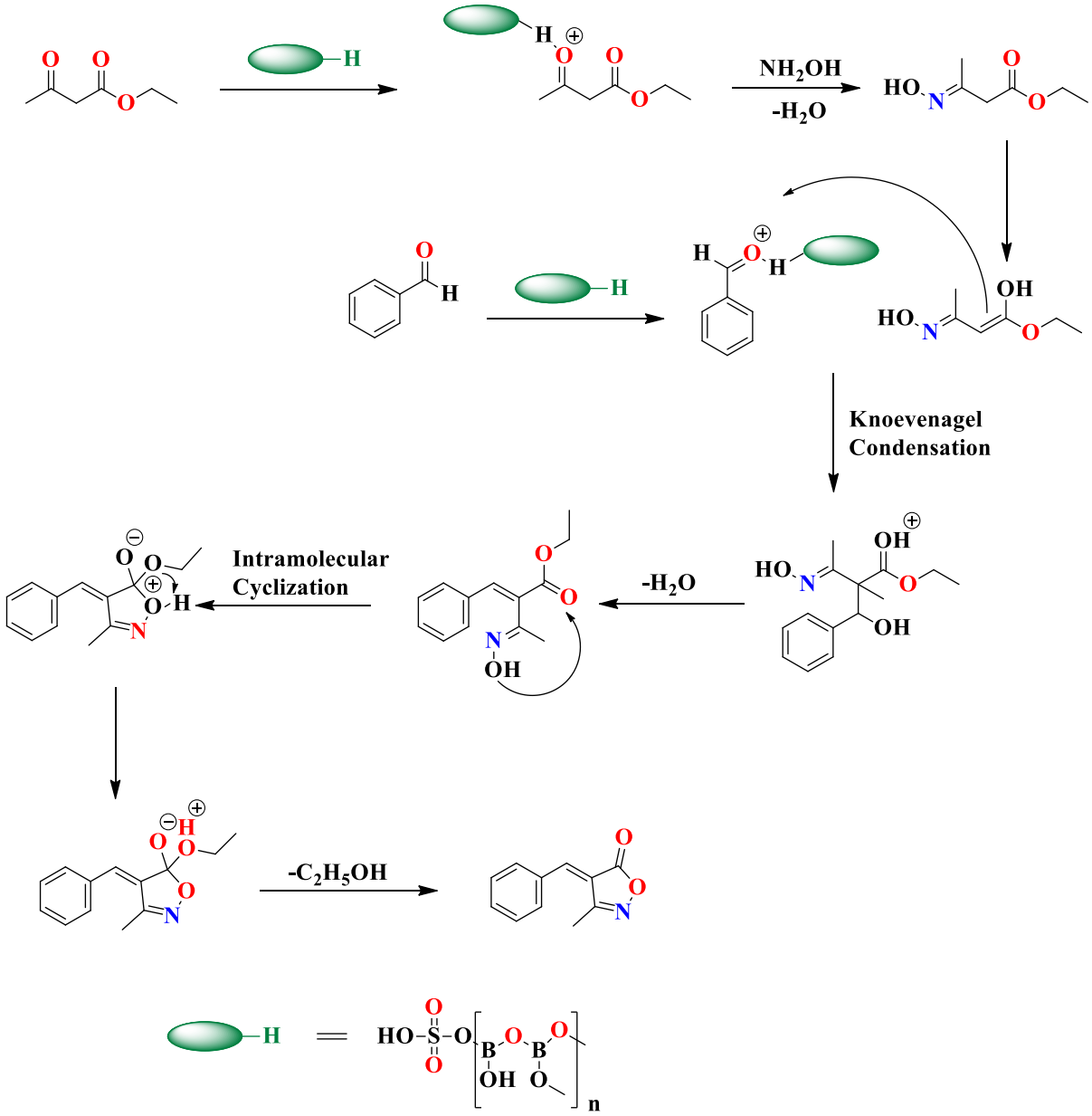


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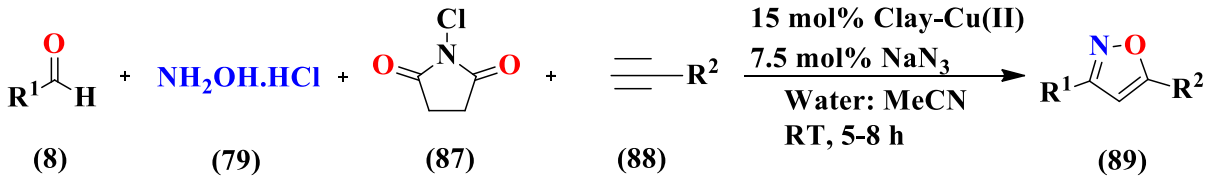
Fig 26: A plausible mechanism for sulfated polyborate catalyzed synthesis of 3-methyl-4 phenylmethylene isoxazole-5(4*H*)-ones

Bharate *et al*. reported effortless one-pot multicomponent synthesis of 3,5-disubstituted isoxazoles **(89)** from substituted aldehydes **(8)** and terminal alkynes **(88)** using recyclable montmorillonite clay supported Cu(II)/NaN_3 as catalyst (Scheme 99)[142]. The method is operationally simple, regioselective, economical and possesses excellent functional group compatibility to synthesize structurally diverse isoxazoles in good yields. The plausible mechanism for reaction is shown in Fig 27.



Scheme 99: Clay-Cu(II)-catalyzed one-pot synthesis of 3,5-disubstituted isoxazoles

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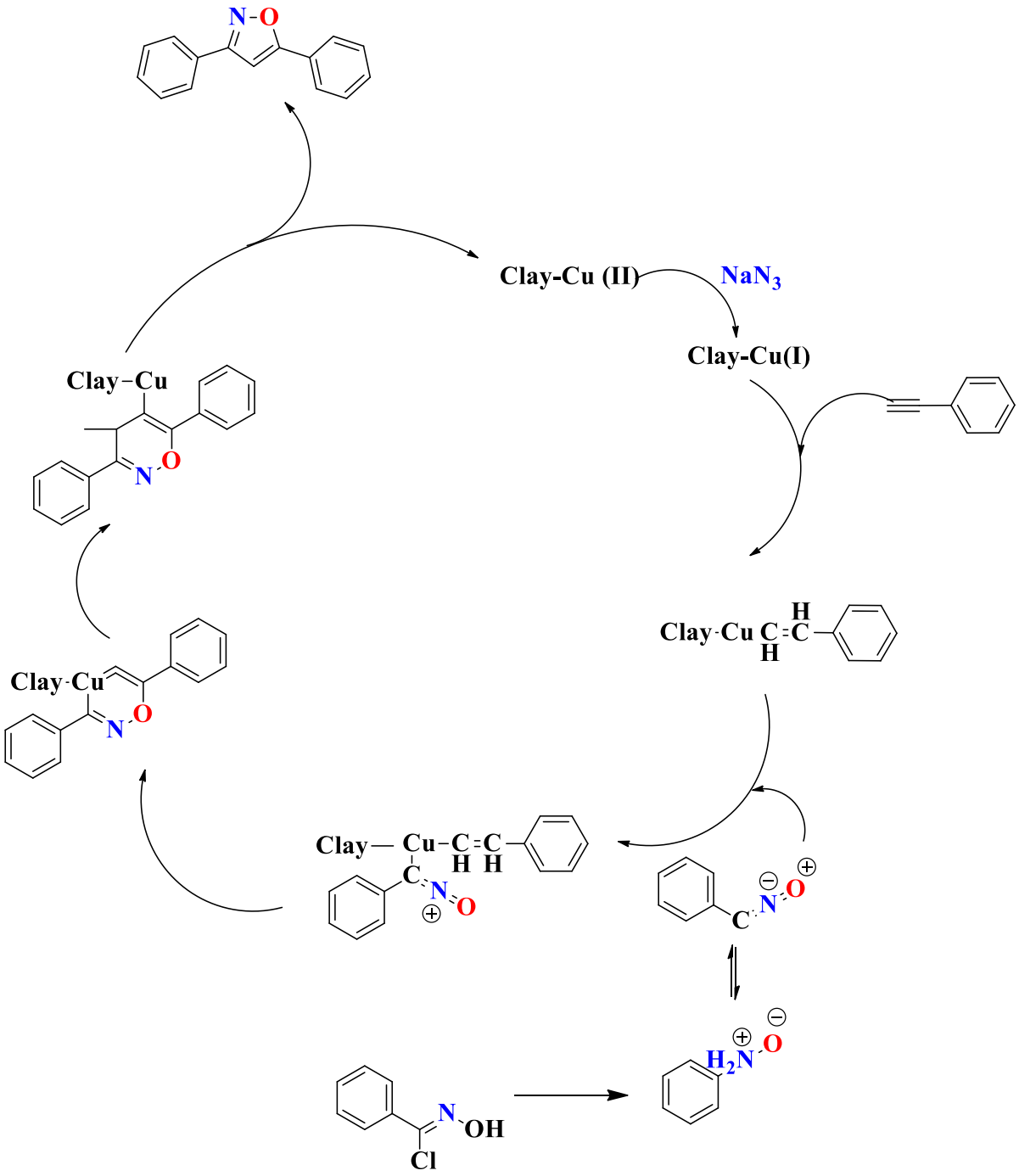

Fig 27: Plausible mechanism of one-pot multicomponent protocol for synthesis of 3,5-disubstituted isoxazole using clay-Cu(II)/NaN_3 catalyst

Beyzaei *et al*. reported the synthesis of novel 5-amino-isoxazole-4-carbonitriles **(90)** *via* multicomponent reaction between malononitrile **(12)**, hydroxylamine hydrochloride **(79)** and substituted aldehydes **(8)** in excellent yield in presence of deep eutectic solvent K_2CO_3/glycerol as catalyst (Scheme 100)[143].

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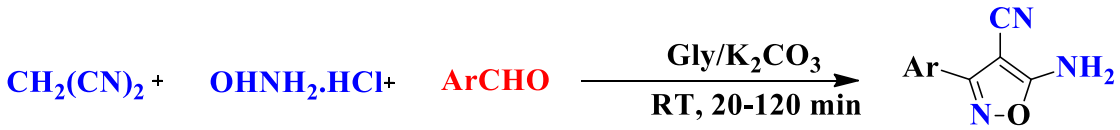

(12) (79) (8) (90)

Scheme 100: One-pot synthesis of 3,5-disubstituted isoxazoles

Ahmadzadeh and his coworkers reported the synthesis of 3-methyl-4-arylmethylene isoxazole-5 (4*H*)-ones **(80)** *via* one-pot multicomponent cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in water under ultrasound irradiations in presence of Sn^{II}-Mont K10 as a recoverable solid catalyst (Scheme 101)[144]. A plausible mechanism for the one-pot cyclocondensation of substituted aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride, in the presence of Sn^{II}-Mont K10, is shown in Fig 28.

(5) (79) (8) (80)

Scheme 101: Sonochemical synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones using Sn^{II}-Mont K10

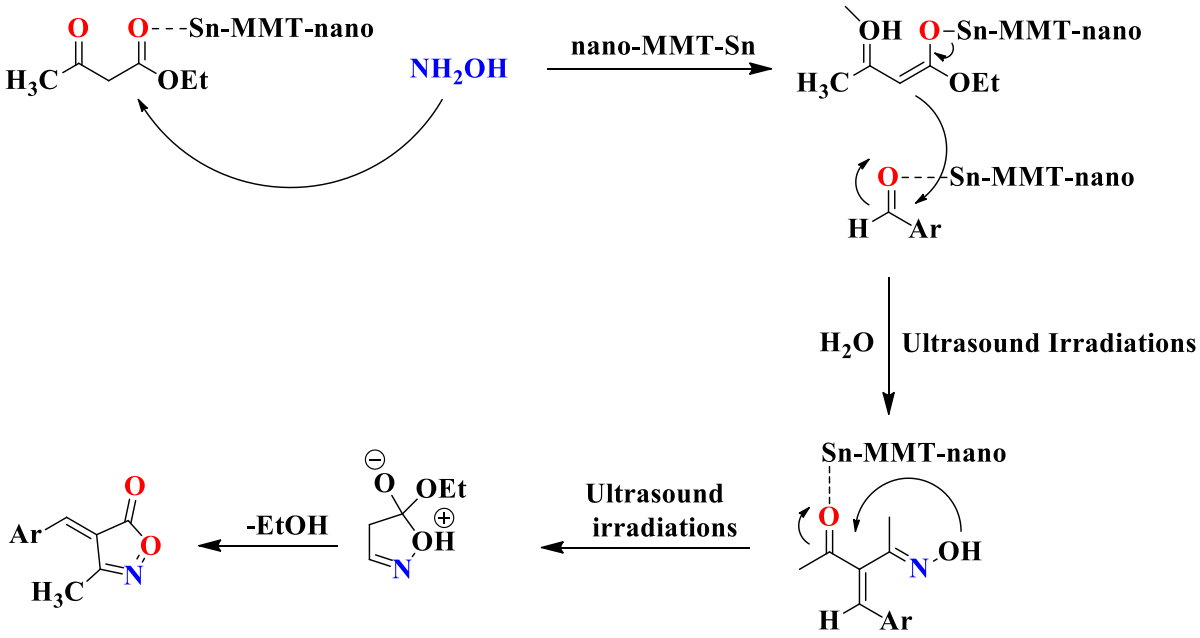

Fig 28: Plausible mechanism for synthesis of 3-methyl-4-arylmethylene isoxazole-5(4*H*)-ones by Sn^{II}-Mont K10

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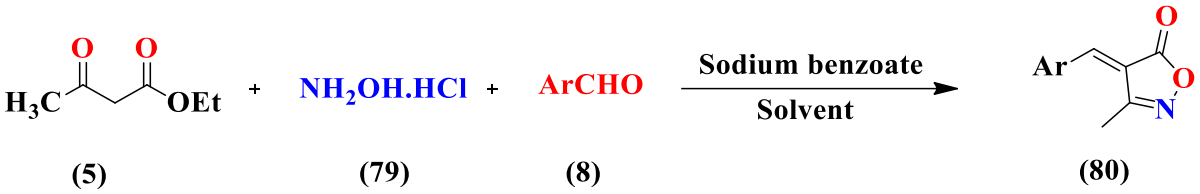
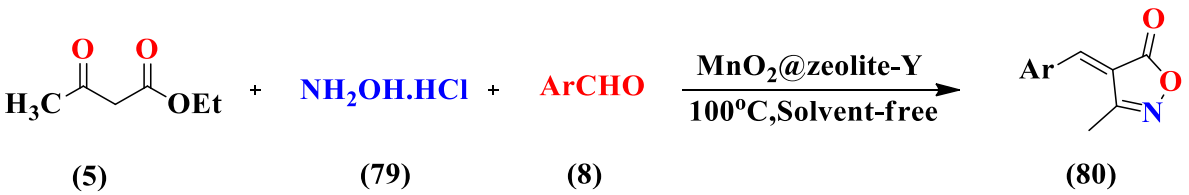
Liu and Zhang reported multicomponent synthesis of 3-Methyl-4-arylmethylene-isoxazol-5(4*H*)-ones **(80)** *via* cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** catalysed by Sodium benzoate in aqueous media (Scheme 102)[145].



(5) **(79)** **(8)** **(80)**

Scheme 102: Synthesis of substituted isoxazoles

Kalhor and his coworkers reported the preparation of 3,4-disubstituted isoxazole-5(4*H*)-one **(80)** scaffolds *via* one-pot multicomponent cyclocondensation reaction between hydroxylamine hydrochloride (79), ethylacetoacetate **(5)** and substituted aldehydes **(8)** catalysed by MnO_2@Zeolite-Y nanoporous (Scheme 103)[146]. The plausible mechanism for reaction is shown in Fig 29.



(5) **(79)** **(8)** **(80)**

Scheme 103: Synthesis of isoxazole-5(4*H*)-ones using MnO_2@zeolite-Y

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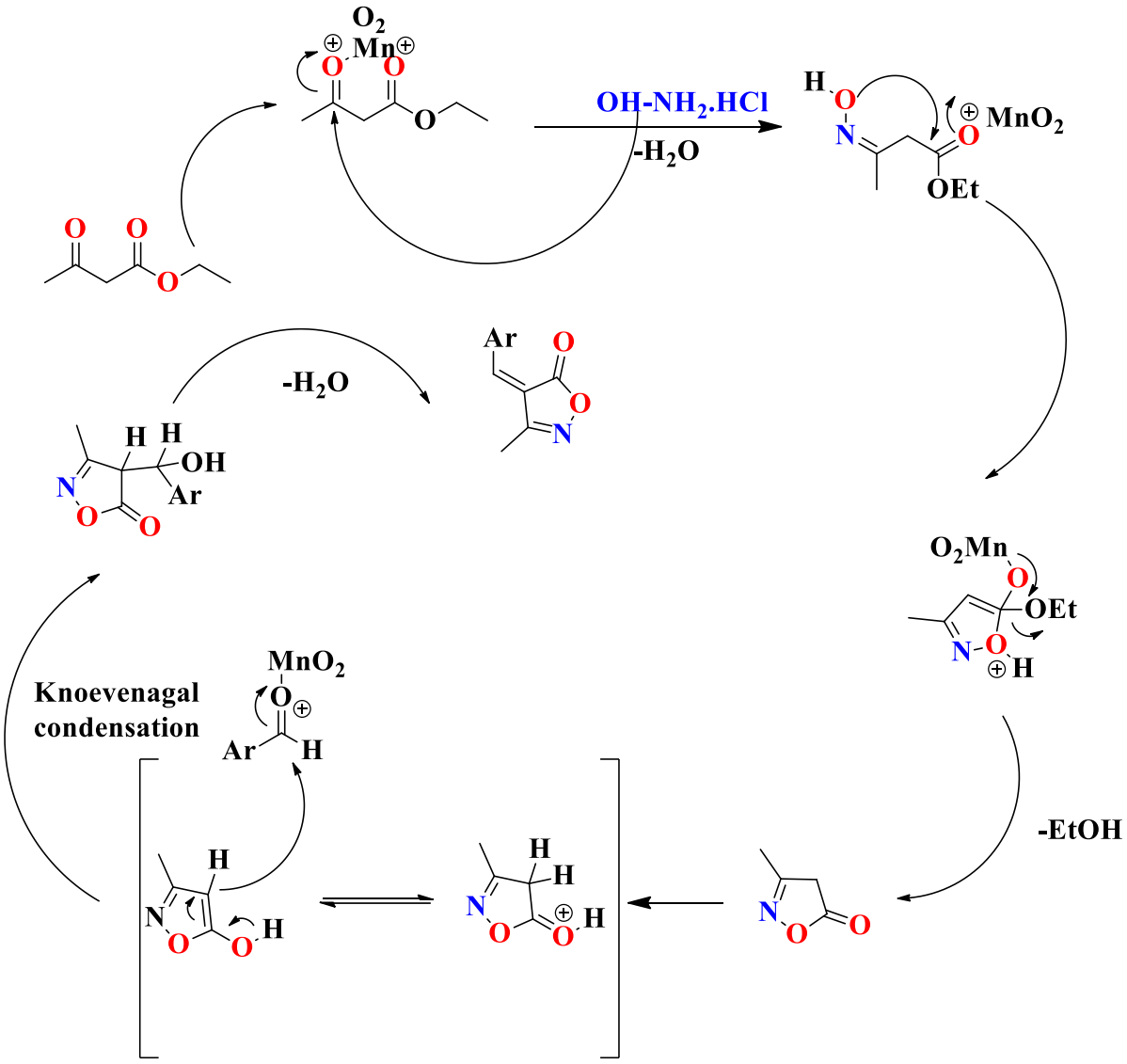
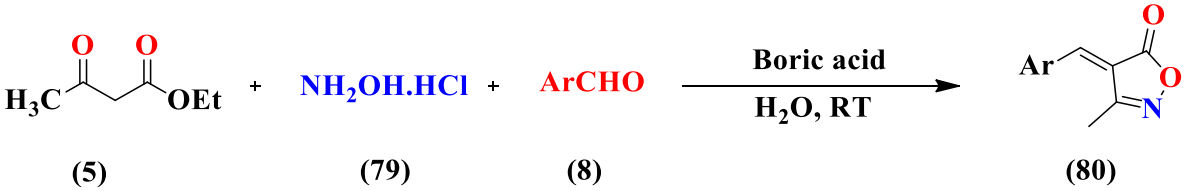


Fig 29: Plausible mechanism for the synthesis of compounds

The one-pot three component reaction of substituted aldehydes **(8)** with hydroxylamine hydrochloride **(79)** and ethylacetoacetate **(5)** for synthesis of 4*H*-isoxazol-5(4*H*)-ones **(80)** in high yields in presence of boric acid, H_3BO_3 reported by Kiyani and Ghorbani (Scheme 104)[147]. The plausible mechanism for reaction is shown in Fig 30.



(5) **(79)** **(8)** **(80)**

Scheme 104: One-pot three-component condensation of substituted aldehydes, hydroxylamine hydrochloride and *β*-ketoesters using boric acid

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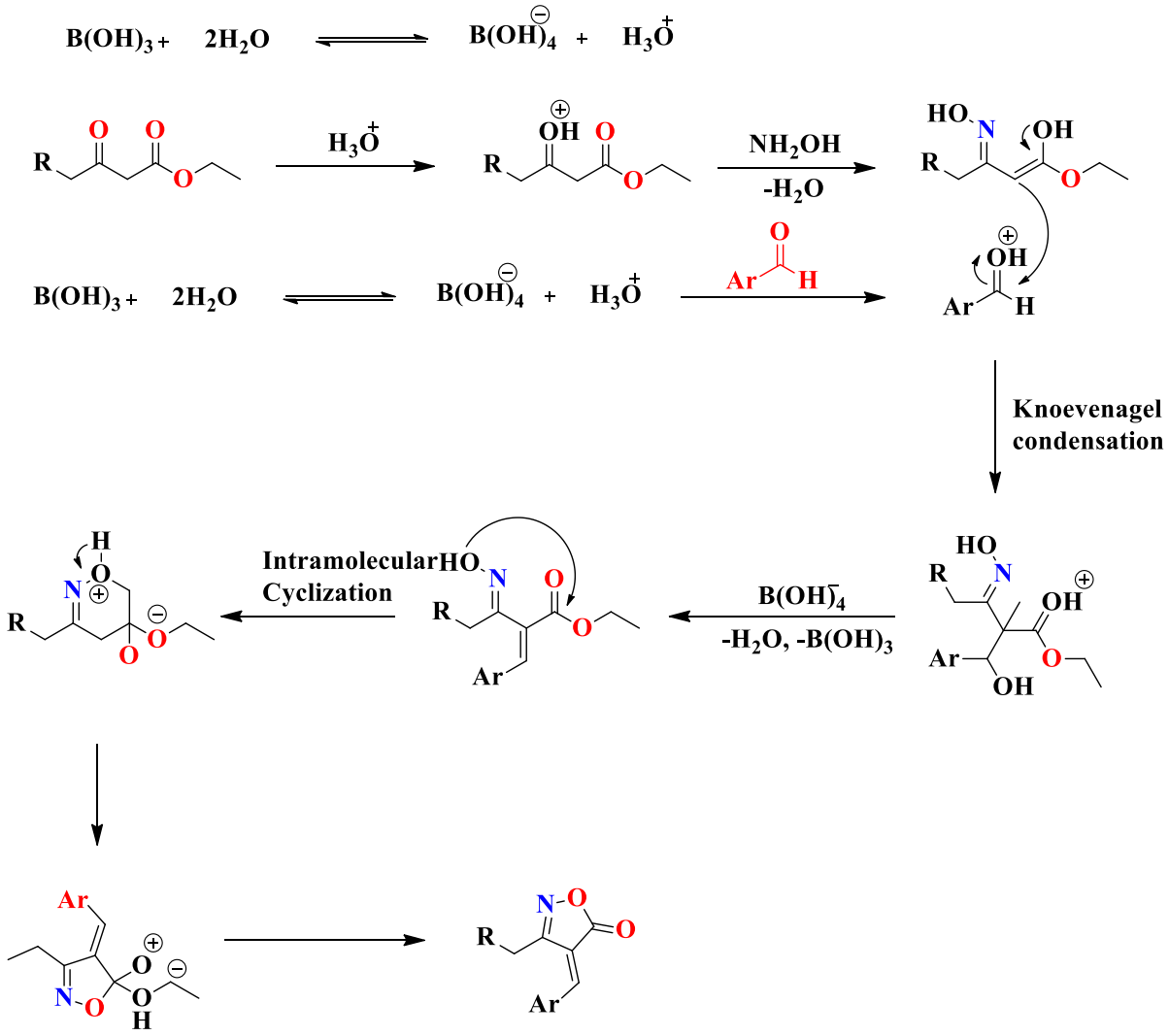

Fig 30: Plausible mechanism for synthesis of 4*H*-isoxazol-5(4*H*)-ones

Ceric ammonium nitrate (CAN) acts as an efficient catalyst for the synthesis of 2,4,5-triphenyl-1*H*-1-imidazolyl isoxazoles **(91)** in multicomponent reaction between benzil **(61)**, substituted aldehydes **(8)**, isoxazole amine **(9)** and ammonium acetate **(59)** by Rajanarendar *et al.* (Scheme 105)[148]. The plausible mechanism for reaction is shown in Fig 31.

(61) **(8)** **(9)** **(59)** **(91)**

Scheme 105: Synthesis of 2,4,5-triphenyl-1*H*-1-imidazolyl isoxazoles

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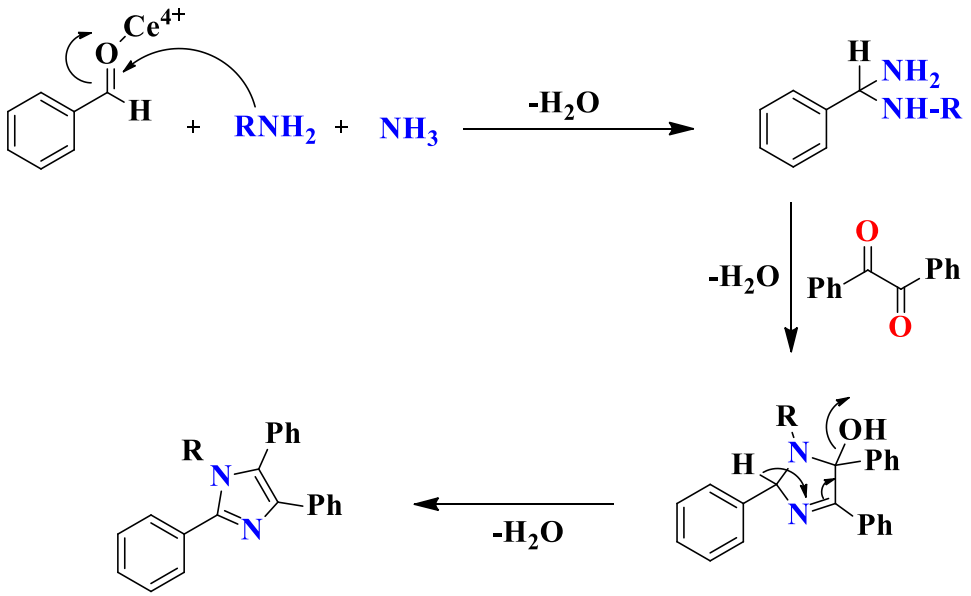

Fig 31: Plausible mechanism for the formation of title compounds

Kiyani and Ghorbani reported the synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones **(80)** in excellent yields *via* one-pot cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** catalysed by Potassium phthalimide (PPI) as an efficient and effective basic organocatalyst (Scheme 106)[149]. The plausible mechanism for reaction is shown in Fig 32.

(5) **(79)** **(8)** **(80)**

Scheme 106: Synthesis of 3,4-disubstituted isoxazol-5(4*H*)-ones catalyzed by PPI

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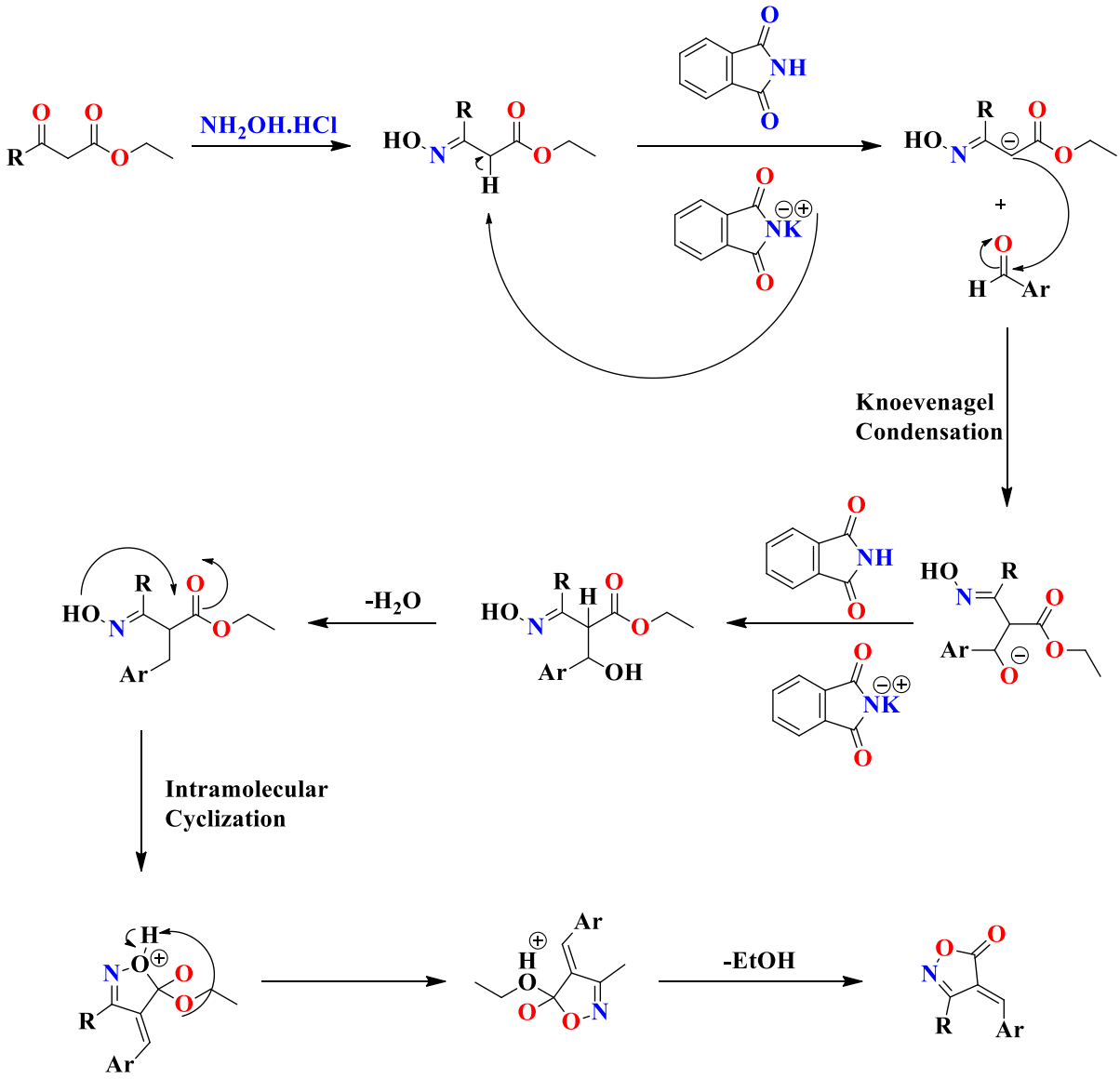

Fig 32: Plausible mechanism for the formation of isoxazol-5(4*H*)-ones

An effective and eco-friendly method for the synthesis of isoxazol-5(4*H*)-one **(80)** derivatives has been developed *via* one-pot three component reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** using ZnO@Fe_3O_4 core-shell nanocatalytic system (Scheme 107)[150]. The plausible mechanism for reaction is shown in Fig 33.

(5) **(79)** **(8)** **(80)**

Scheme 107: Synthesis of 3,4-disubstituted isoxazole-5(4*H*)-ones catalyzed by ZnO@Fe_3O_4

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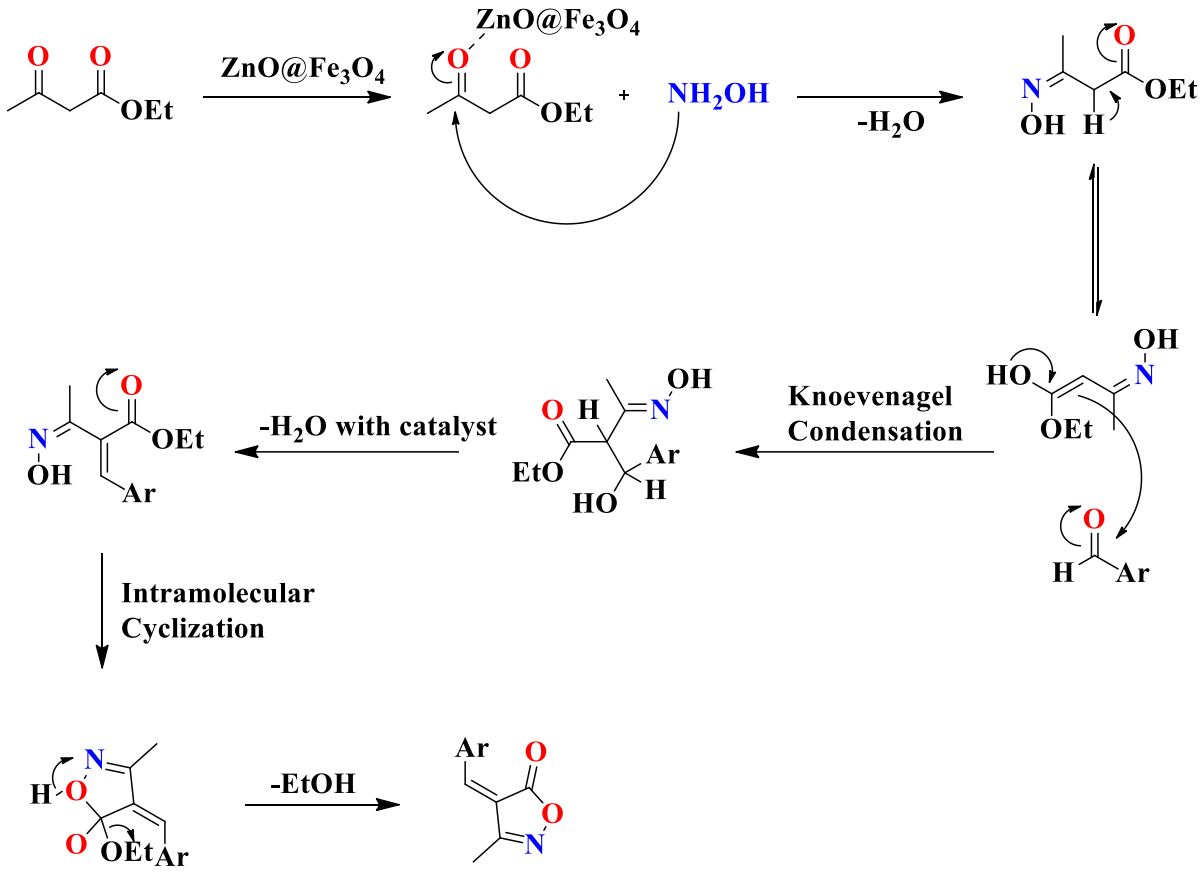
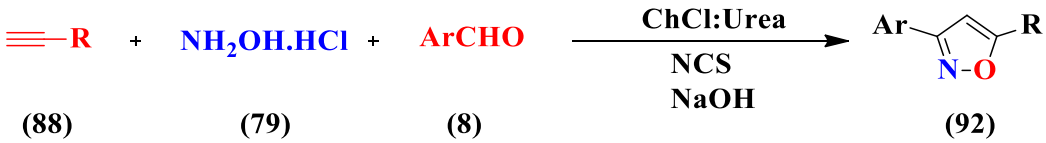


Fig 33: A plausible mechanism for the synthesis of 3,4–disubstituted isoxazol–5(4*H*)–ones catalyzed by ZnO@Fe_3O_4

Perez and Ramon reported the synthesis of 3,5-disubstituted isoxazoles **(92)** and related isoxazolines using choline chloride: urea as deep eutectic solvent (DES) *via* one-pot three component reaction between substituted aldehydes **(8)**, hydroxylamine hydrochloride **(79)** and terminal alkynes **(88)** (Scheme 108)[151].



(88) **(79)** **(8)** **(92)**

Scheme 108: Synthesis of 3,4-disubstituted isoxazole-5(4*H*)-ones catalyzed by ZnO@Fe_3O_4

Zhang and his coworkers reported the efficient synthesis of medicinally important isoxazole substituted 3-hydroxy-2-oxindole derivatives **(94)** *via* Henry addition of 3,5-dialkyl-4-nitroisoxazoles **(93)** to isatins **(67)** in presence of water at room temperature (Scheme 109)[152].

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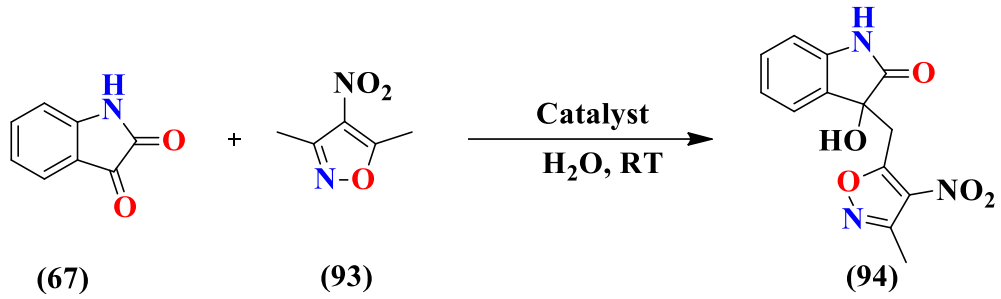

(67) (93) (94)

Scheme 109: Henry reactions of 3,5-dimethyl-4-nitroisoxazole with isatins

Tayade *et al*. reported the one-pot three component synthesis of 4-aryl-3-methylisoxazole-5(4*H*)-one derivative *via* one-pot multicomponent cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** using sodium hypophosphite as catalyst (Scheme 110)[153].

(5) (79) (8) (80)

Scheme 110: One-pot three component condensations of ethyl acetoacetate, hydroxylamine hydrochloride and aldehyde with sodium hypophosphite give isoxazole

A novel dicationic ionic liquid, N,N,N^1,N^1-tetramethyl-N,N^1-bis(sulfo)ethane-1,2-diaminium mesylate [TMBSED][OMs]$_2$) has been used under solvent-free conditions for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones *via* one-pot reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** by Gheshlaghchaei and his coworkers (Scheme 111)[154].

(5) (79) (8) (80)

Scheme 111: Synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4*H*)-ones

A simple and efficient method has been reported for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones *via* multicomponent cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in presence of

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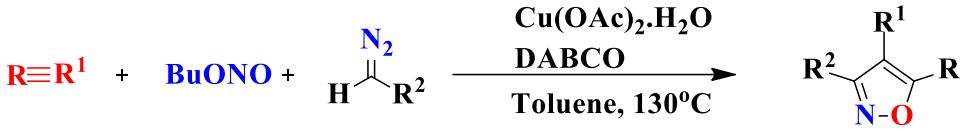
sulfonated graphene-oxide as metal-free efficient carbocatalyst by Basak *et al*. (Scheme 112)[155]. Metal free synthesis, good to excellent yield, high atom economy, use of easily available starting material, operational simplicity, easy workup, and recyclable catalyst are merits of present protocol.



(88) **(94)** **(93)** **(95)**

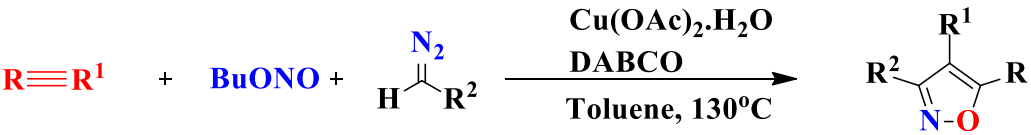
Scheme 112: Synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones

An efficient and magnetically recoverable catalyst consisting of 6-methylguanamine supported on $CoFe_2O_4$ nanoparticles for the preparation of isoxazol-5(4*H*)-one derivatives **(80)** has been synthesized by Moshtaghin and his coworkers for one-pot multicomponent cyclocondensation reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** (Scheme 113)[156]. The present method possesses some advantages such as mild reaction conditions, excellent yields, short reaction time, avoid of use organic solvents, and easy work-up.

(5) **(79)** **(8)** **(80)**

Scheme 113: Preparation of isoxazol-5(4*H*)-one derivatives

A novel copper-catalyzed [3+2] cycloaddition reaction of alkynes **(88)** with nitrile oxides **(93)** generated *in situ* from the coupling reaction of copper carbene and nitroso radical **(94)** has been developed by Wang and his coworkers for the synthesis of substituted isoxazoles **(95)** in a highly regioselective manner (Scheme 114)[157].



(88) **(94)** **(93)** **(95)**

Scheme 114: Preparation of substituted isoxazoles

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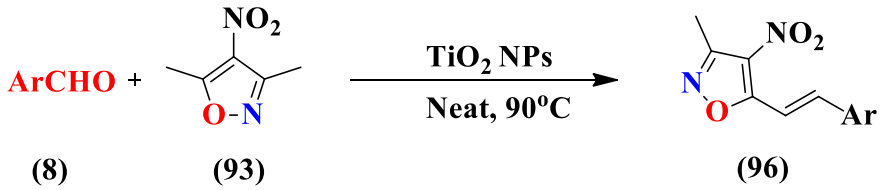
An efficient and solvent-free method for the synthesis of 3-methyl-4-nitro-5-styrylisoxazoles **(96)** using nano-titania as solid supported and recyclable catalyst was reported by Dwivedi and his coworkers with reaction between substituted aldehydes **(8)** and 3,5-dimethyl-4-nitroisoxazole **(93)** (Scheme 115)[158].



(8) **(93)** **(96)**

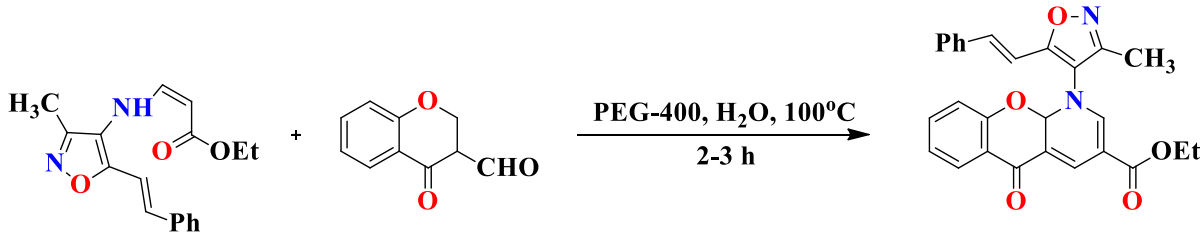
Scheme 115: Preparation of 3-methyl-4-nitro-5-styrylisoxazoles

Kiyani and Ghorbani reported the synthesis of 4-arylidene-3-methylisoxazol-5(4*H*)-ones **(80)** *via* one-pot three-component reaction between hydroxylamine hydrochloride **(79)**, ethylacetoacetate **(5)** and substituted aldehydes **(8)** in presence of sodium saccharin as a catalyst in water (Scheme 116)[159].

(5) **(79)** **(8)** **(80)**

Scheme 116: Synthetic route for the 4-arylidene-3-methylisoxazol-5(4*H*)-ones

A green, simple and efficient method for the synthesis of new series of isoxazolyl chromeno[2,3-b]pyridine-3-carboxylate derivatives **(99)** have been reported by one-pot reaction between isoxazolyl enamine esters **(97)** and 3-formylchromones **(98)** by using water as reaction medium and polyethylene glycol-400 (PEG-400) as green catalyst (Scheme 117)[160]. The superiority of this procedure is environmentally benign, simple operation, metal-free, good yields, less reaction time. The plausible mechanism for reaction is shown in Fig 34.



(97) **(98)** **(99)**

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Scheme 117: Synthetic route for the isoxazolyl chromeno[2,3-b]pyridine-3-carboxylate derivatives

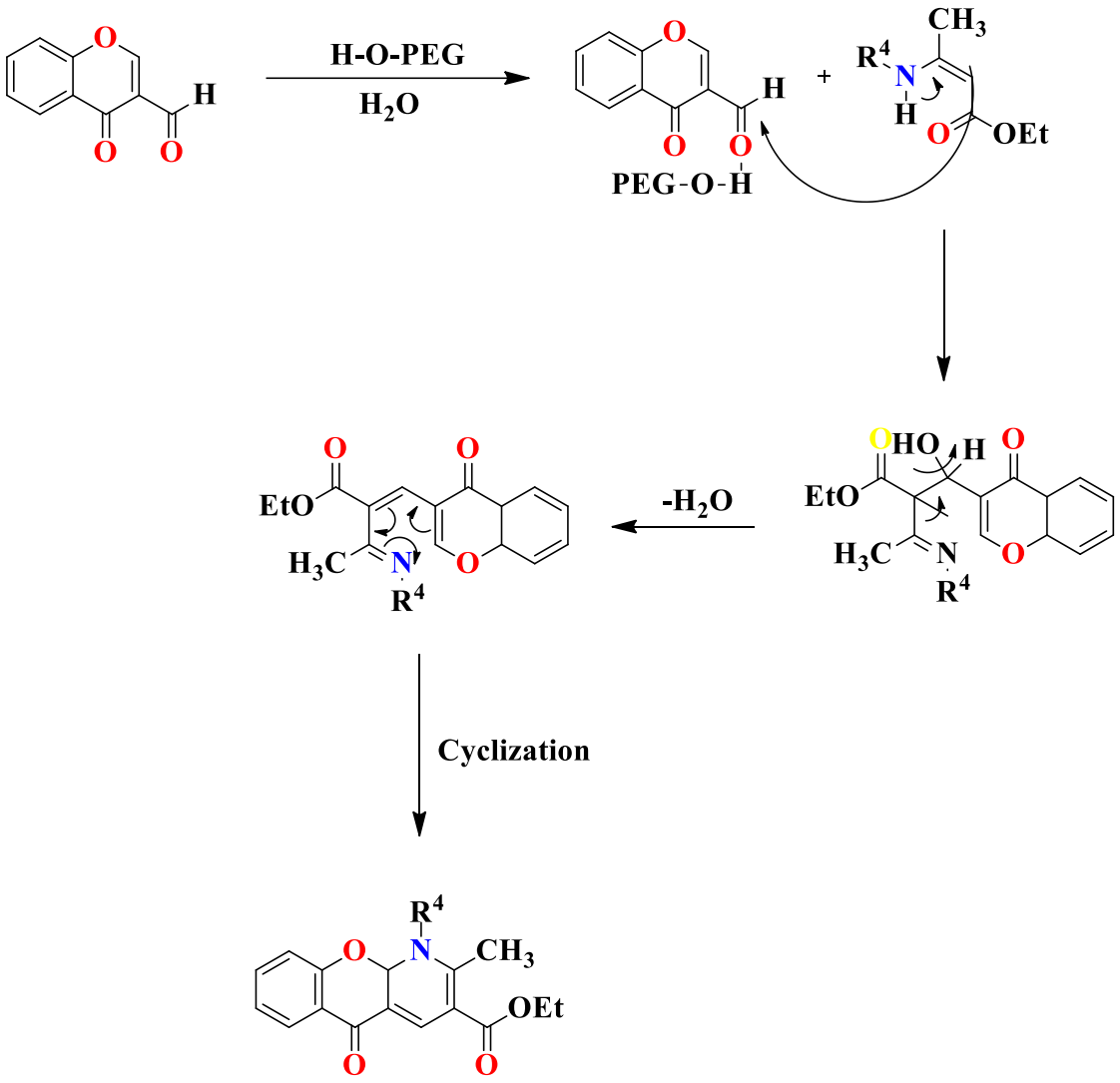
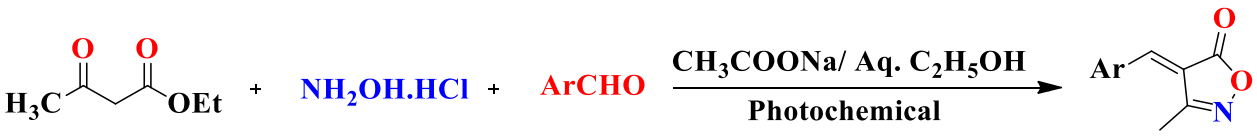


Fig 34: Plausible mechanism

A highly efficient method for the synthesis of 3-methyl-4-arylmethylene-isoxazole 5(4*H*)-ones **(80)** has been developed *via* visible light induced multicomponent reaction between substituted aldehydes **(8)**, ethyl acetoacetate **(5)**, hydroxylamine hydrochloride **(79)** and sodium acetate in aqueous ethanol by Saikh *et al*. (Scheme 118)[161].



(5) **(79)** **(8)** **(80)**

Scheme 118: Photochemical synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones

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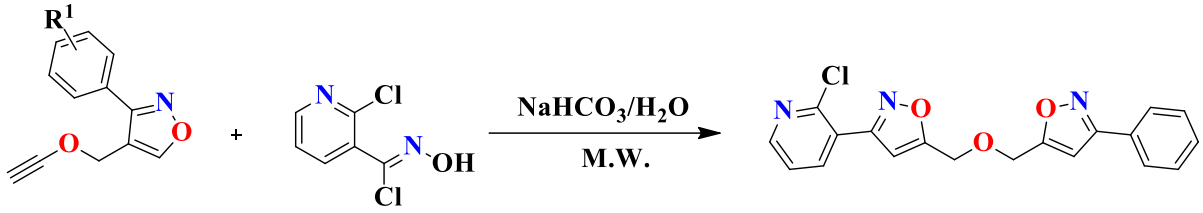
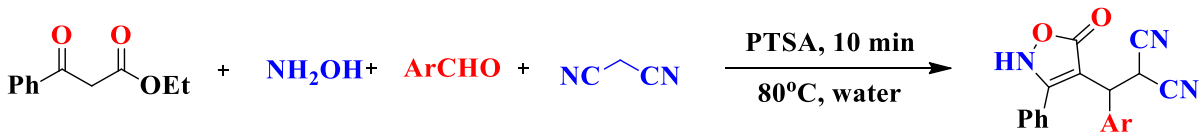
An efficient synthesis of 3-substituted bis-isoxazole ethers **(102)** *via* 1,3-dipolar cycloaddition reaction starting from 3-substituted phenyl-5-((prop-2-yn-1-yloxy))methyl)isoxazoles **(100)** and (*Z*)-2-chloro-N-hydroxynicotinimidoyl chloride **(101)** using $NaHCO_3$ as an acid-binding agent in THF solvent-dissolved trace water under catalyst-free microwave-assisted conditions reported by Zheng and his coworkers (Scheme 119)[162].



(100) **(101)** **(102)**

Scheme 119: Synthesis of 3-substituted bis-isoxazole ethers

Yaghoub and Mohammad reported the synthesis of isoxazol-5(2*H*)-ones **(104)** *via* multicomponent reaction between ethyl benzoylacetate **(103)**, hydroxylamine hydrochloride **(79)**, substituted aldehydes **(8)** and malononitrile **(12)** in the presence of PTSA (Scheme 120)[163]. The plausible mechanism for reaction is shown in Fig 35.



(103) **(79)** **(8)** **(12)** **(104)**

Scheme 120: Four-component synthesis of isoxazol-5(2*H*)-one

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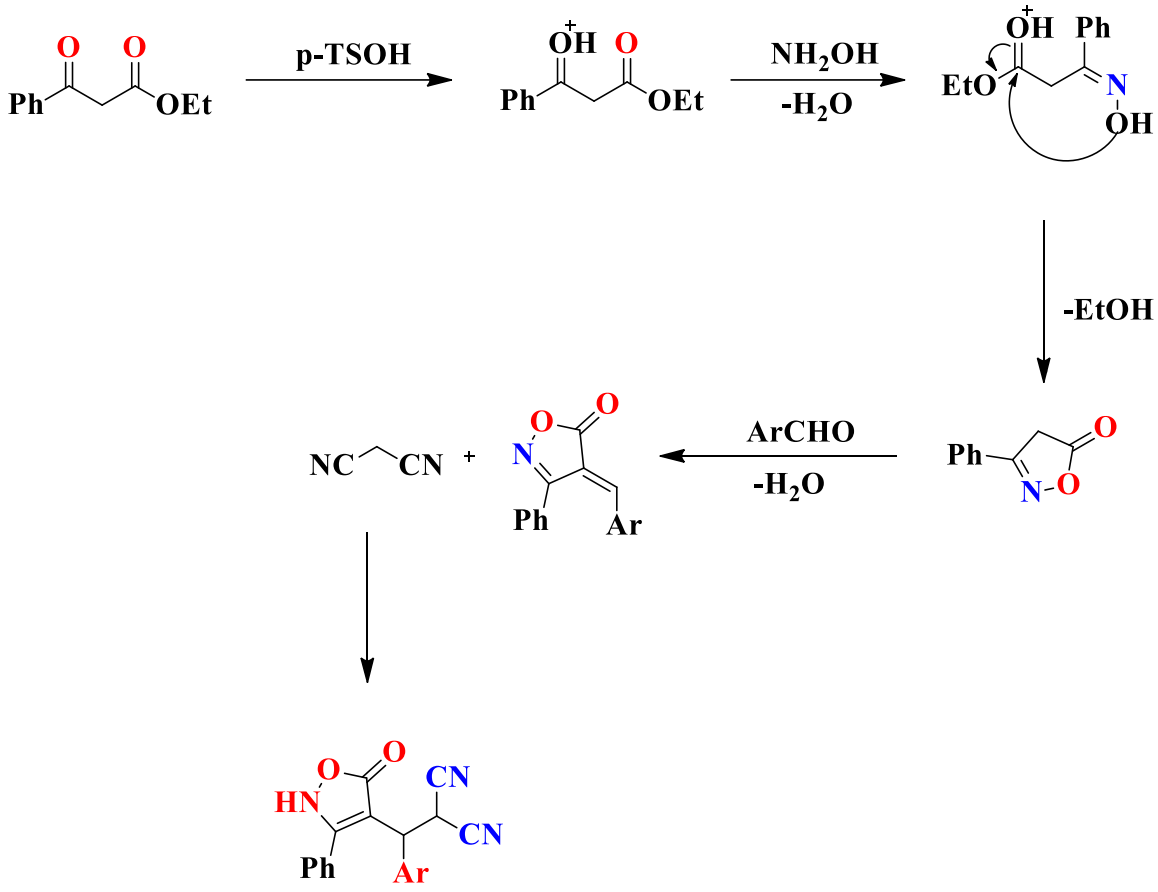

Fig 34: Plausible mechanism

Green synthetic methods for the preparation of substituted benzimidazoles

An efficient and facile synthesis of substituted novel benzimidazole **(106)** mediated by fruit juices *viz*. *Cocos nucifera* L. juice, *Citrus limetta* juice and *Citrus sinensis* L. juice *via* condensation reaction between substituted aldehydes **(8)** and *o*-phenylenediamine **(105)** under solvent-free condition at ambient temperature was reported by Gulati and his coworkers (Scheme 121)[164]. The present method offers an attractive option because of its ecological safety, environmental acceptance, cost effective and easy workup process. The plausible mechanism for the formation of substituted benzimidazoles is shown in Fig 35. From mechanism, it was found that carbonyl group is activated by acidity of natural catalyst viz. *Cocos nucifera* L. juice, *Citrus limetta* juice and *Citrus sinensis* L. juice for nucleophilic attack that led to formation of intermediate (I). The intermediate (I) undergo intramolecular cyclization proceeds to form desired products.

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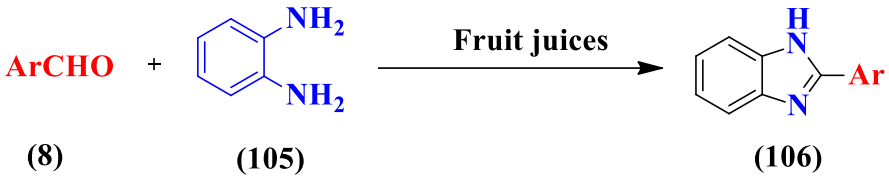


Scheme 121: Synthesis of substituted benzimidazole derivatives

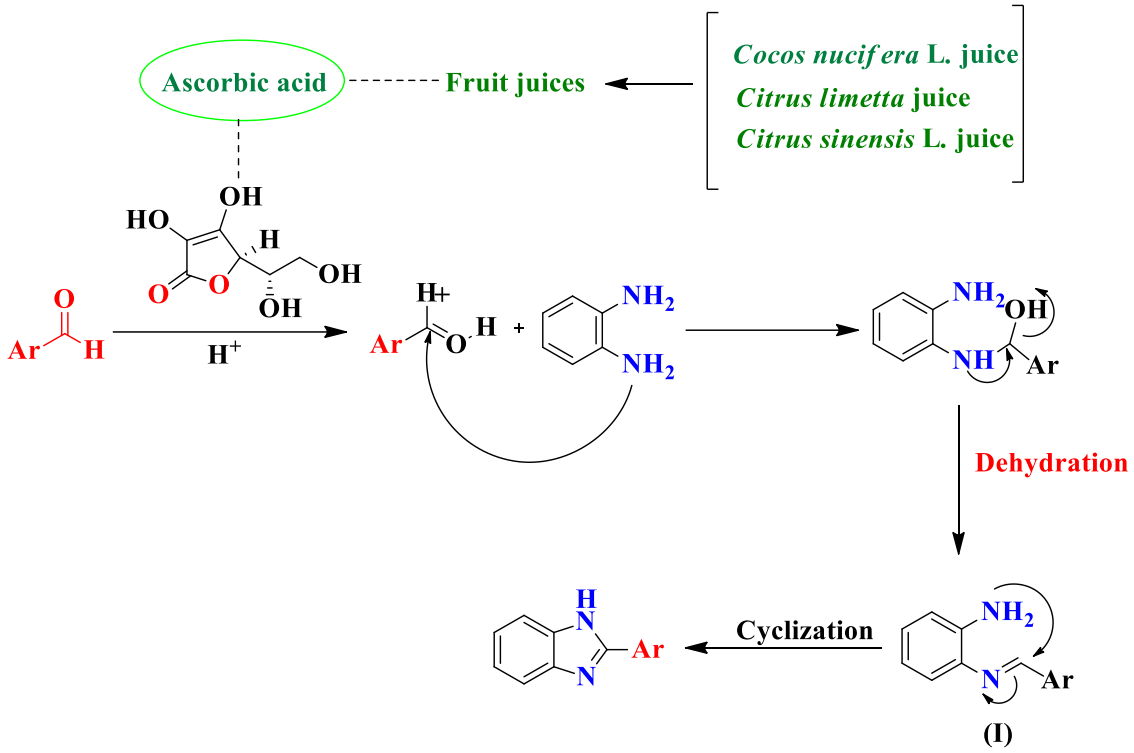
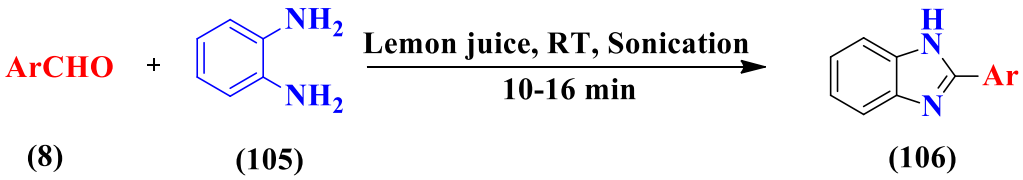


Fig 35: The plausible mechanism for synthesis of substituted benzimidazoles

Gulati *et al*. prepared a series of substituted benzimidazoles **(106)** *via* one-pot reaction of *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** in the presence of lemon juice as a catalyst under solvent-free conditions (Scheme 122)[165]. There is a substantial effect of substituents on yields and times of reaction. Substituted aldehydes substituted with electron withdrawing groups resulted in a faster reaction than aldehydes substituted with electron-donating groups. Moreover, substitutions at the ortho position of the aldehydes also retarded the rate of reaction.



Scheme 122: Preparation of substituted benzimidazoles

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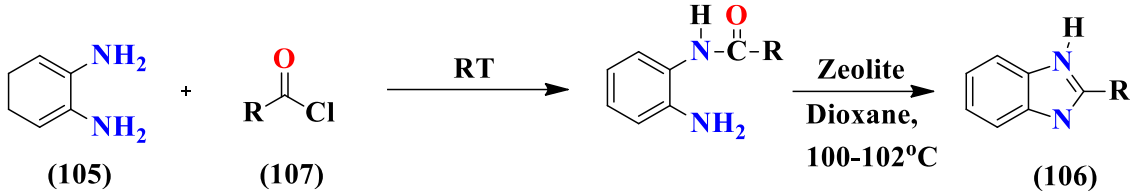
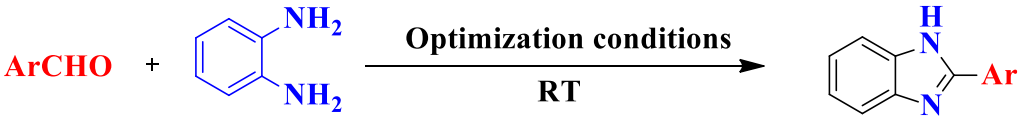
Heravi and his coworkers reported the synthesis of 2-substituted benzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** with acid chlorides **(107)** in the presence of Zeolite as heterogeneous catalyst (Scheme 123)[166].



(105) (107) (106)

Scheme 123: Synthesis of 2-substituted benzimidazoles

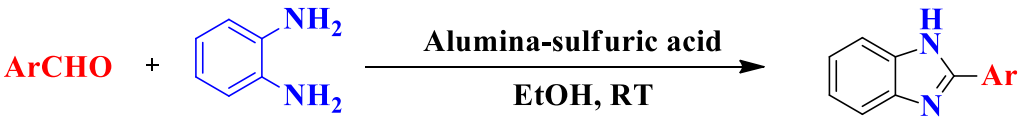
A simple, eco-friendly method for the synthesis of 2-substituted benzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** using continuous bubbling of air in absolute ethanol at room temperature reported by Chen *et al*. (Scheme 124)[167]. The simplicity of the system, mild reaction conditions, involvement of a non-toxic and practically inexhaustible oxidant, easy and quick isolation of the products, and moderate to good yields are the main advantages of current method.



(8) (105) (106)

Scheme 124: Room temperature synthesis of 2-phenyl-1*H*-benzimidazole using air as the oxidant

A cost-effective and eco-friendly synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles **(106)** has been developed through the condensation reaction between substituted aldehydes **(8)** and *o*-phenylenediamine **(105)** using alumina-sulfuric acid as a recyclable heterogeneous solid acid catalyst by Pramanik and his coworkers (Scheme 125)[168].



(8) (105) (106)

Scheme 125: Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from 1,2-diamine and aryl aldehydes

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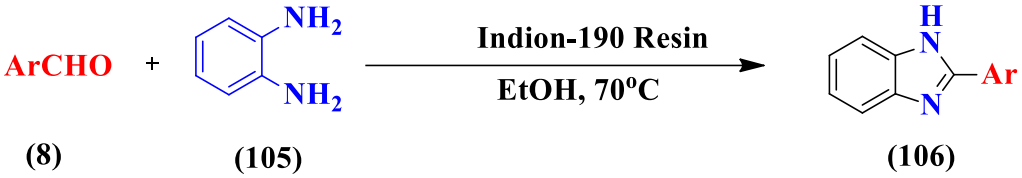
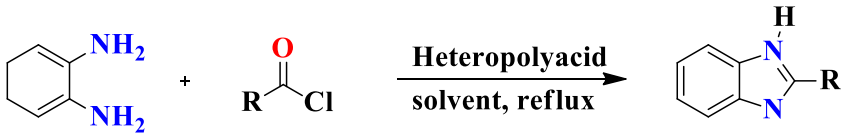
An efficient and facile method has been developed for the preparation of benzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of catalytic amount of Indion 190 resin (Scheme 126)[169]. Short reaction time, ambient conditions, simple work-up procedure, high yield, easy availability, reusability, and use of an eco-friendly catalyst are some of the striking features of the present protocol.



(8) **(105)** **(106)**

Scheme 126: Synthesis of benzimidazoles

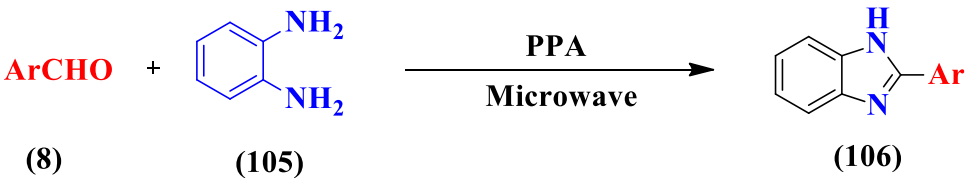
Synthesis of benzimidazoles **(106)** from the condensation reaction between phenylenediamine (*o*-PDA) **(105)** and acyl chlorides **(107)** in the presence of a catalytic amount of various heteropolyacids (HPAs) is reported by Heravi and his coworkers (Scheme 127)[170].



(105) **(107)** **(106)**

Scheme 127: Synthesis of benzimidazoles

An efficient microwave irradiation synthesis of 2-substituted benzimidazoles **(106)** using polyphosphoric acid as a catalyst from one-pot reaction between *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** under solvent-free conditions reported by Lu and his coworkers (Scheme 128)[171].



(8) **(105)** **(106)**

Scheme 128: Synthesis of substituted benzimidazoles

A very simple, green and efficient method is developed in which zinc chloride-exchanged K10-montmorillonite (clayzic) is employed as a Lewis acid catalyst in aqueous media at room

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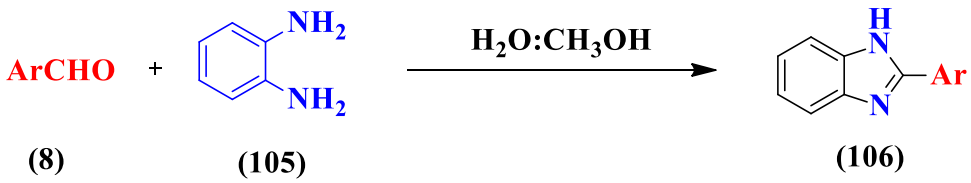
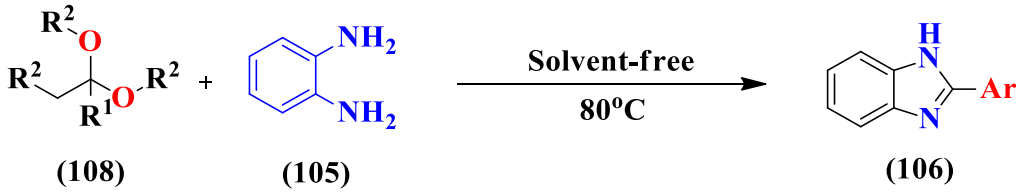
temperature for the synthesis of various benzimidazoles **(106)** from one-pot reaction of *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** by Dhakshinamoorthy *et al*. (Scheme 129)[172].



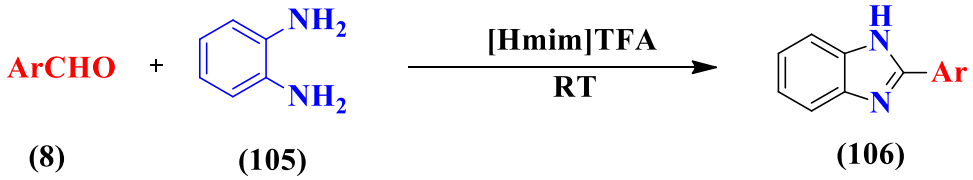
Scheme 129: Synthesis of substituted benzimidazoles

A novel silica tungstic acid (STA) as a highly efficient catalyst has been synthesized and employed for the cyclocondensation reaction between *o*-phenylenediamine **(105)** and orthoesters **(108)** under solvent-free conditions to give high yields of benzimidazoles **(106)** at 80°C reported by Karami and his coworkers (Scheme 130)[173].



Scheme 130: Synthesis of benzimidazole derivatives using STA 2 under solvent-free conditions

An environmentally benign method for the synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles **(106)** by the reaction of *o*-phenylenediamines **(105)** and substituted aldehydes **(8)** in the presence of 1-methylimidazolium triflouroacetate ([Hmim]TFA) at room temperature under aqueous conditions was reported by Dabiri *et al*. (Scheme 131)[174].



Scheme 131: Synthesis of 2-substituted benzimidazoles

Kidwai *et al*. reported the synthesis of benzimidazole derivatives **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in PEG (Polyethylene Glycol) using Ceric ammonium nitrate (CAN) as catalyst (Scheme 132)[175]. The plausible mechanism for the formation of substituted benzimidazoles is shown in Fig 36.

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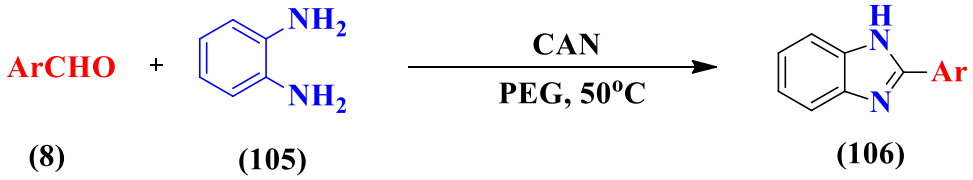


Scheme 132: Synthesis of 2-substituted benzimidazoles

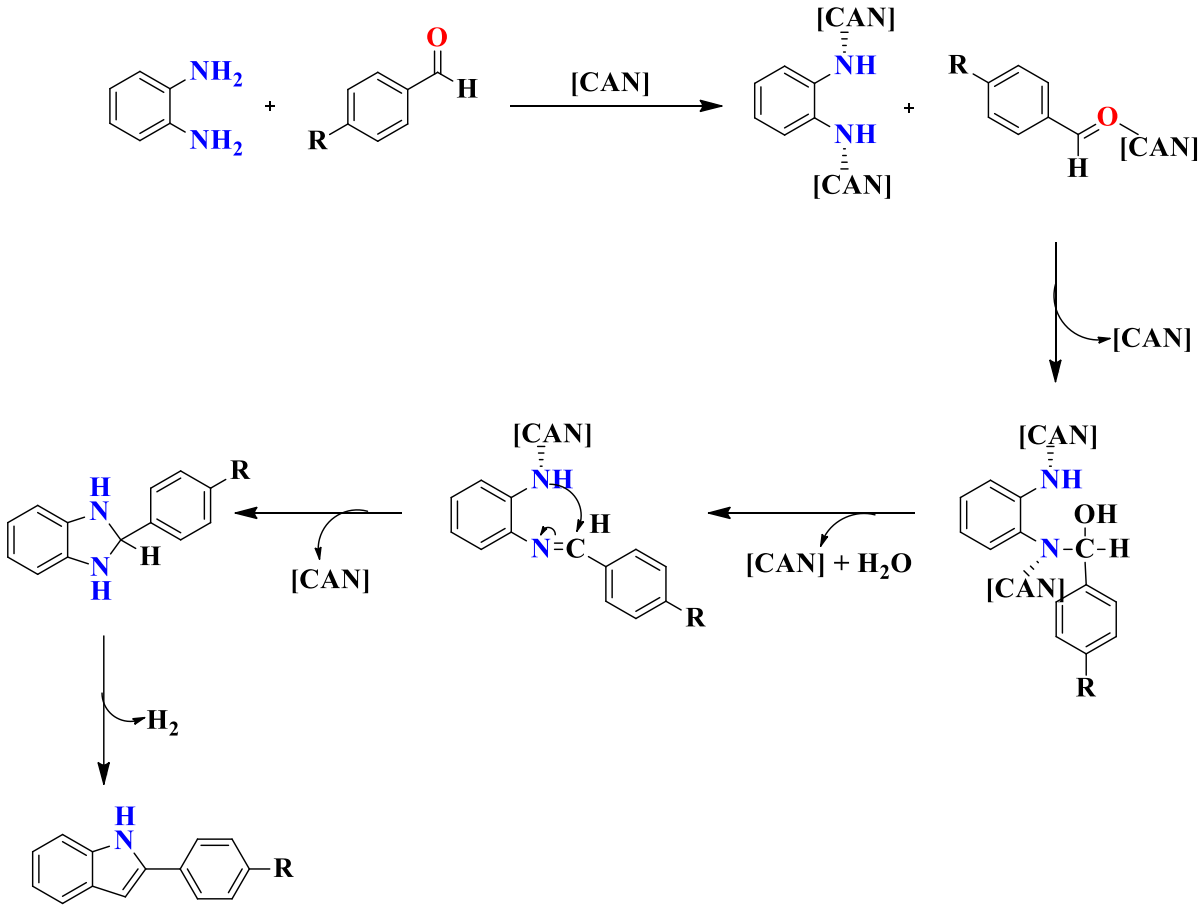
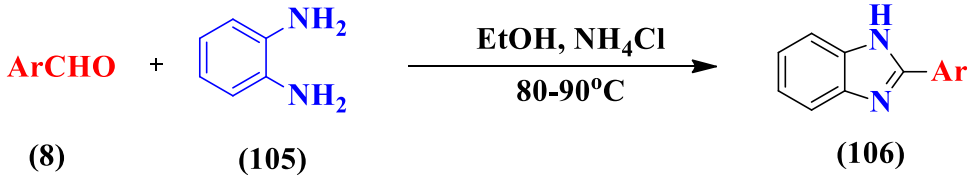


Fig 36: The plausible mechanism for synthesis of substituted benzimidazoles

Kathirvelan *et al*. reported the green synthesis of 2-substituted benzimidazoles **(106)** in one-pot by condensation reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of ammonium chloride as a catalyst at 80-90°C (Scheme 133)[176].



Scheme 133: Synthesis of 2-substituted benzimidazoles

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Silica boron sulfonic acid (SBSA) used as efficient solid acid catalyst for the synthesis of benzimidazole derivatives with high yields *via* one-pot reaction of *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** by Sajjadifar and his coworkers (Scheme 134)[177]. The possible mechanism for the formation of substituted benzimidazoles is shown in Fig 37.

Scheme 134: Synthesis of benzimidazole derivatives

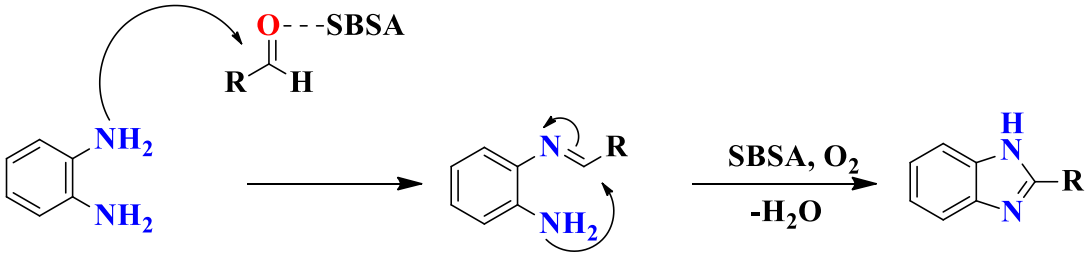
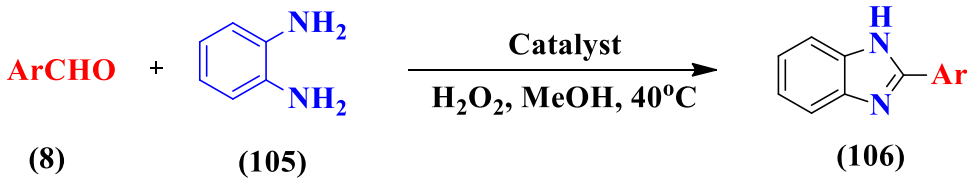


Fig 37: The plausible mechanism for synthesis of substituted benzimidazoles

Chen *et al*. reported the synthesis of 2-arylbenzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of biomass-derived N-Doped carbons with silica supported ultrasmall ZnO nanoparticles as catalyst (Scheme 135)[178].



Scheme 135: Synthesis of benzimidazole derivatives

The one-pot synthesis of benzimidazole derivatives **(106)** *via* oxidative condensation of substituted aldehydes **(8)** with *o*-phenylenediamines **(105)** under mild conditions was reported using cobalt (II) supported on mesoporous silica-type material by Rajabi and his coworkers (Scheme 136)[179].

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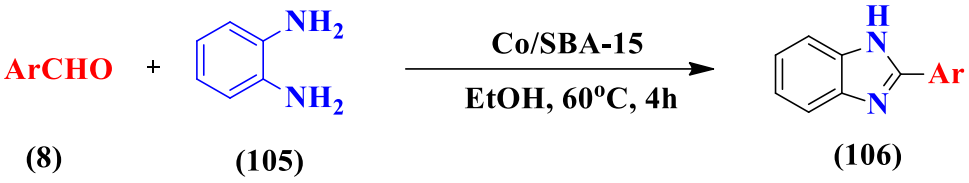
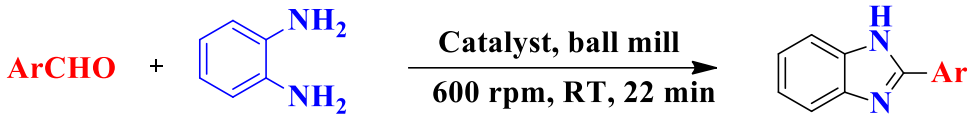


(8) (105) (106)

Scheme 136: Synthesis of benzimidazole derivatives

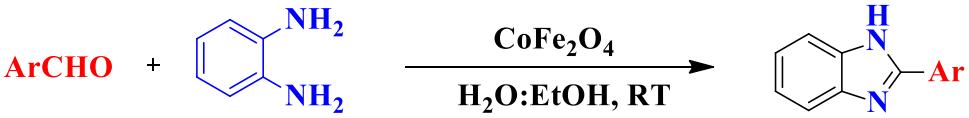
A solvent-free green synthesis of 1,2-disubstituted benzimidazoles **(106)** was developed using ball-milling technique *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of recyclable ionic liquid-coated ZnO-nanoparticles as catalyst by Sharma *et al*. (Scheme 137)[180].



(8) (105) (106)

Scheme 137: Synthesis of 1,2-disubstituted benzimidazoles

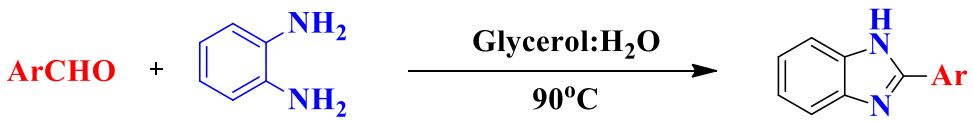
Borade *et al*. reported the synthesis of substituted benzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of highly efficient magnetically recoverable cobalt ferrite nano-catalyst (Scheme 138)[181].



(8) (105) (106)

Scheme 138: Synthesis of substituted benzimidazoles

A simple, efficient and more sustainable catalyst-free method has been developed for the synthesis of benzimidazoles **(106)** in presence of glycerol-water system *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** by Bachhav and his coworkers (Scheme 139)[182].



(8) (105) (106)

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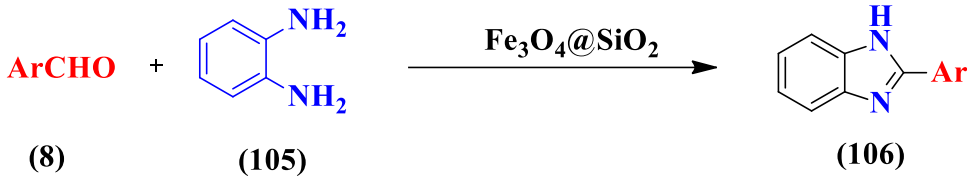
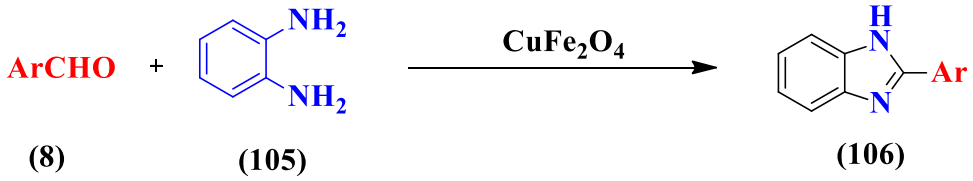
Scheme 139: Preparation of 2-arylbenzimidazole

An ammonium molybdate deposited amorphous silica coated iron oxide (Fe_3O_4@SiO_2) magnetic core-shell nanocomposite was prepared and tested for the synthesis of 2-benzimidazoles *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** using hydrogen peroxide as an oxidant at room temperature by Bai and his coworkers (Scheme 140)[183].



Scheme 140: Synthesis of 2-benzimidazoles

A green and efficient protocol for the synthesis of substituted benzimidazoles **(106)** has been developed by using cost-effective, readily available, dioxygen-stable and recyclable $CuFe_2O_4$ as nanocatalyst *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** by Yang *et al*. (Scheme 141)[184]. The plausible mechanism for the formation of substituted benzimidazoles is shown in Fig 38.



Scheme 141: Synthesis of substituted benzimidazoles

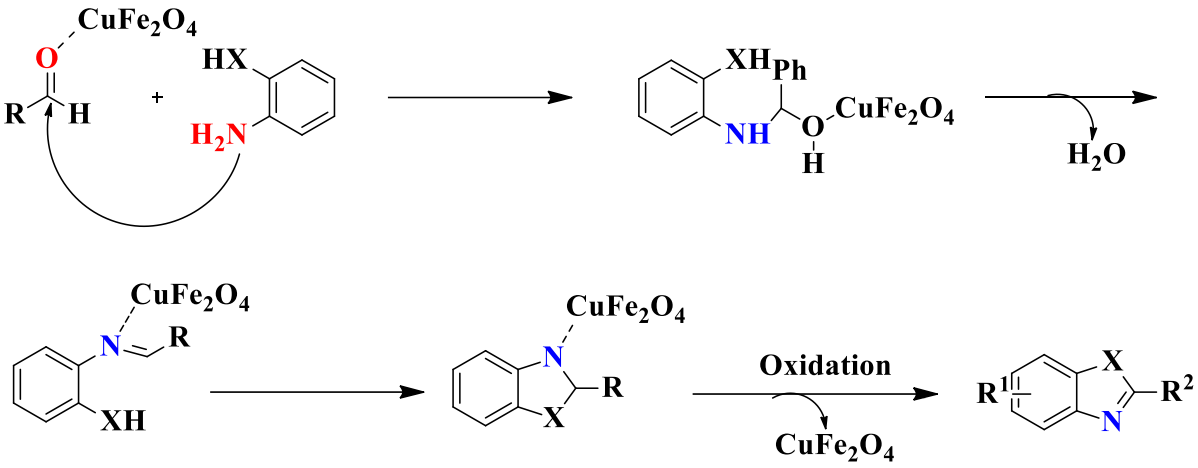


Fig 38: The plausible mechanism for synthesis of substituted benzimidazoles

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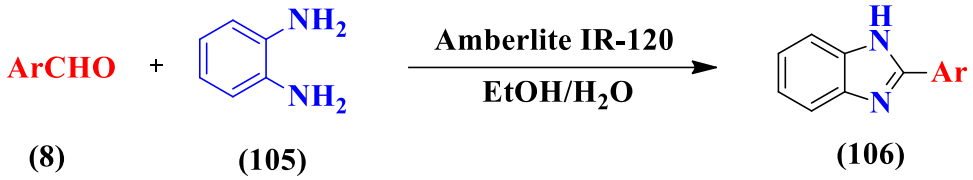
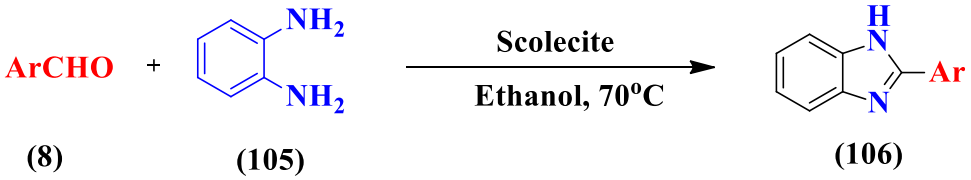
A simple, efficient and eco-friendly method has been developed for the synthesis of biologically significant 2-aryl-1-arylmethyl-1*H*-benzimidazoles **(106)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of Amberlite IR-120 as heterogeneous catalyst in aqueous media by Sharma and Konwar (Scheme 142)[185].



(8) **(105)** **(106)**

Scheme 142: Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles

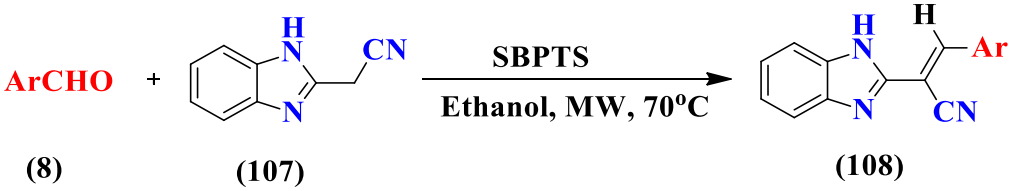
A series of benzimidazole derivatives **(106)** were synthesized in excellent yields by condensation reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of solid acid scolecite catalyst by Gadekar *et al*. (Scheme 143)[186]. Easy handling, reuseability of catalyst, higher yields and shorter reaction times are some merits of present protocol.



(8) **(105)** **(106)**

Scheme 143: Synthesis of benzimidazole derivatives

Ahmad and Parveen reported highly efficient and green approach for the synthesis of benzimidazole-acrylonitrile derivatives **(108)** *via* Knoevenagel condensation reaction between benzimidazole-2- acetonitrile **(107)** and substituted aldehydes **(8)** in absolute ethanol in presence of SBPTS catalyst (Scheme 144)[187]. The salient features of the present protocol includes simple operational procedure, short reaction time, mild reaction conditions, economic viability, high yield of desired products.



(8) **(107)** **(108)**

Scheme 144: Synthetic route for the synthesis of benzimidazole-acrylonitrile derivatives

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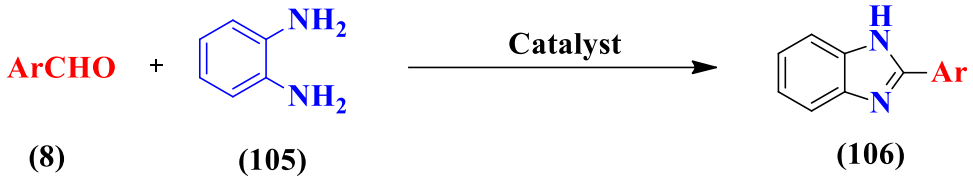
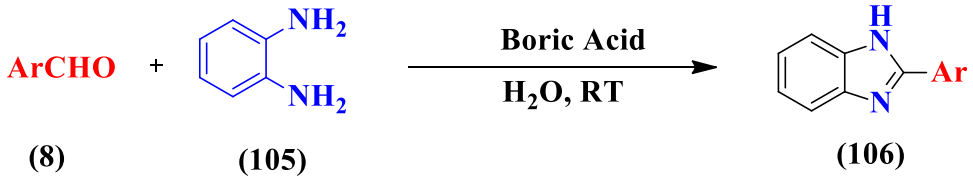
Sadeghi and Nejad reported the synthesis of benzimidazole derivatives **(106)** under reflux in ethanol *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** in presence of Silica sulfuric acid (SiO_2-OSO_3H) as an eco-friendly, readily available, and reusable catalyst (Scheme 145)[188].



Scheme 145: Acid-catalyzed synthesis of 2-(phenyl)benzimidazole

Jaberi and Amiri reported the efficient and inexpensive synthesis of 2-substituted benzimidazoles **(106)** in water using boric acid at room temperature *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** (Scheme 146)[189]. The method was proved to be eco-friendly, convenient and the products were obtained in good yields.



Scheme 146: Synthesis of 2-substituted benzimidazoles

Vernekar and his coworkers reported the synthesis of new Schiff-bases containing benzimidazole molecules **(110)** *via* one-pot reaction between *o*-phenylenediamine **(105)** and 3-amino-napthoic acid **(109)** in presence of $H_3PO_4.12WO_3.xH_2O$ as catalyst. The advantages of this environmental friendly and mild method are such as simplicity of the reaction procedure, the elimination of solvents, simple work-up, high product yields and less reaction time (Scheme 147)[190].

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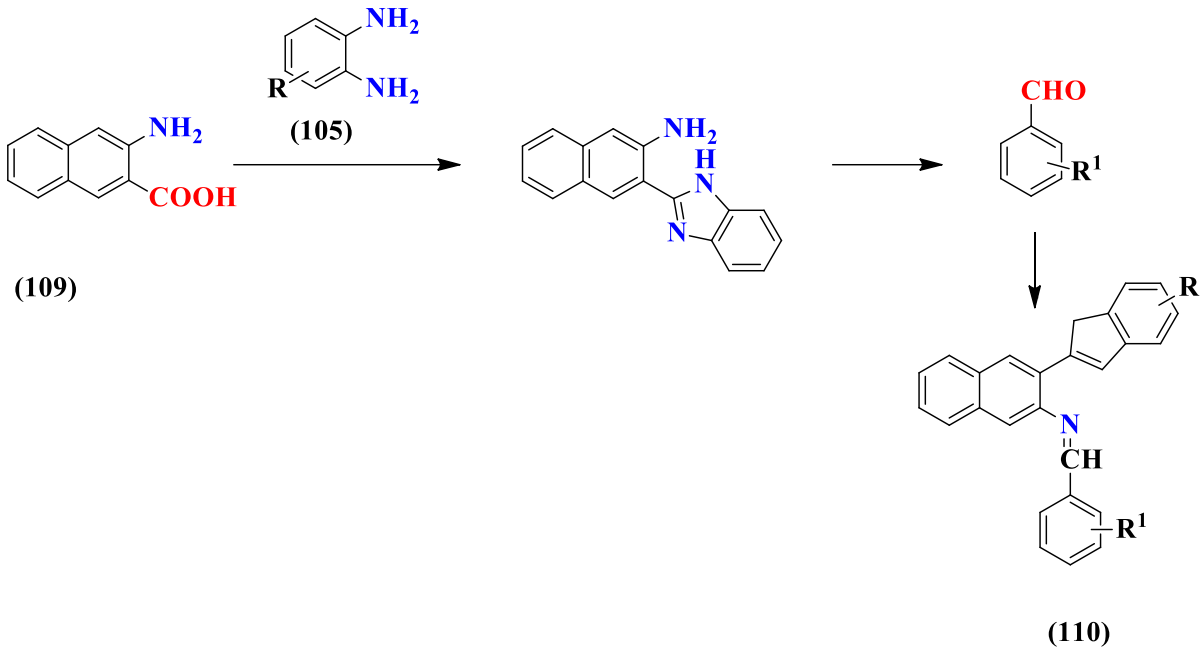
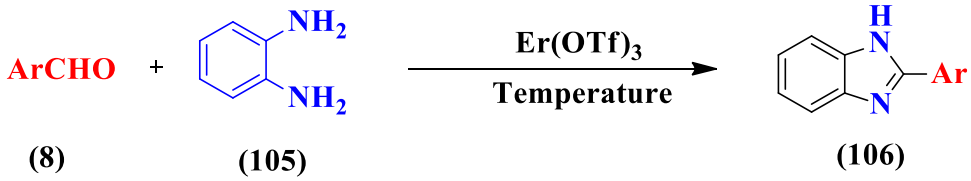


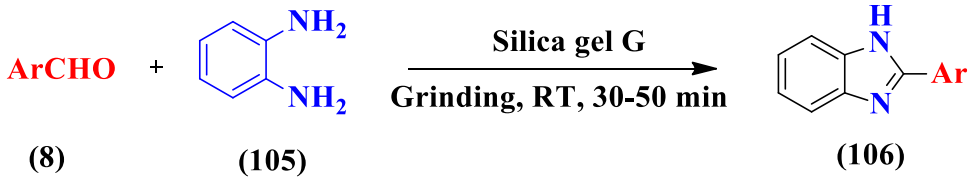
Scheme 147: Synthesis of new Schiff-bases containing substituted benzimidazole

An improved and greener method for the synthesis of benzimidazole derivatives reported by Cano *et al*. starting from *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** in presence of $Er(OTf)_3$ as catalyst (Scheme 148)[191]. One of the major advantages of these reactions was the formation of a single product and avoids extensive isolation and purification of products.



Scheme 148: Formation of the substituted benzimidazoles

An efficient and eco-friendly method for synthesis of 2-arylbenzimidazoles **(106)** has been reported simply by grinding intimate mixtures of *o*-phenylenediamine **(105)** with substituted aldehydes **(8)** in presence of TLC grade silica gel at room temperature for 30-50 minutes by Samanta and his coworkers (Scheme 149)[192].



Scheme 149: Synthesis of benzimidazoles from of *o*-phenylenediamine and substituted aldehydes

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A simple and eco-friendly montmorillonite K10 (MK10) catalyzed method for the synthesis of benzimidazole derivatives **(106)** has been developed *via* one-pot reaction between *o*-phenylenediamine **(105)** and substituted aldehydes **(8)** by Bonacci and his coworkers (Scheme 150)[193].

Scheme 150: Synthesis of benzimidazole derivatives

Biological potential of substituted coumarins

Wu *et al*.[194] found that 3-benzyl substituted coumarins showed broad range of biological activities and these moieties were part of various natural products *viz*. warfarin, phenprocumene and coumatetralyl which showed antibacterial, anti-HIV, antiviral, anticoagulant, antioxidant and anticancer activities (Fig 39).

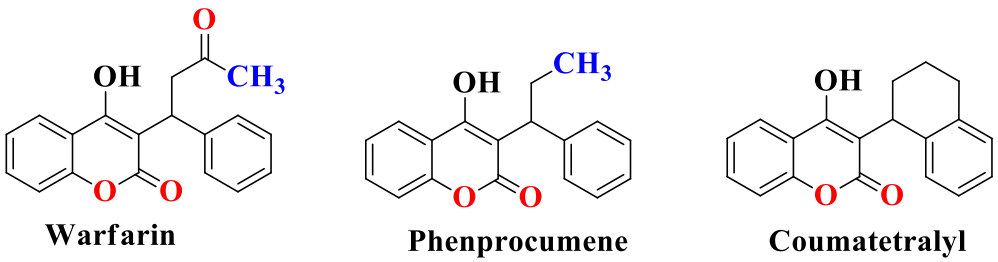

Fig 39: Some bioactive 3-benzyl substituted coumarins

Fylaktakidou and his coworkers[195] found various natural and synthetic coumarin derivatives as anti-inflammatoy and antioxidant molecules. Curini *et al*[196] also found biological potential of prenyloxycoumarins and prenyloxyfuranocoumarins which are generally considered as family of secondary plant metabolites. Maddi and his coworkers[197] reported series of substituted 3-(benzylideneamino)coumarins and evaluated for anti-inflammatory activity at an oral dose of 100 mg/kg. They found that compounds **111** and **112** (Fig 40) exhibited 75 and 60% inhibitions of carrageenan-induced paw edema (CPE). These compounds also showed significant analgesic activity in acetic acid-induced writhing model in mice.

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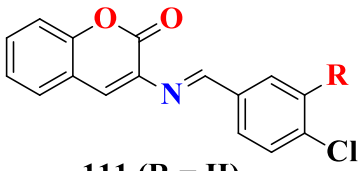
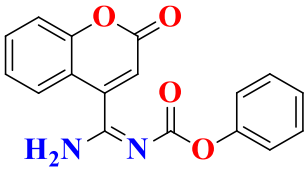


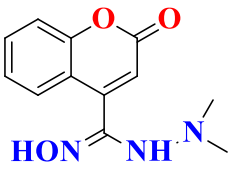
111 (R = H)
112 (R = Cl)

Fig 40: Series of substituted 3-(benzylideneamino)coumarins

Nicoladies *et al.*[198] synthesized various coumarin-4-carboxamidoximes and 4-oxadiazolyl coumarins and found that compounds **113** and **114** (Fig 41) produced maximum inhibition of CPE (more than 80%), whereas the compounds **115** and **116** (Fig 42) inhibited lipoxygenase with IC_{50} value of 76 and 77% respectively.

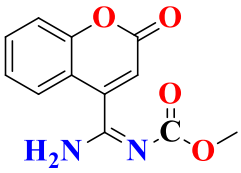


(113)

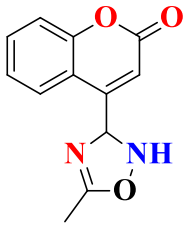


(114)

Fig 41



(115)



(116)

Fig 42

Mazzeia and his coworkers[199] synthesized series of 2-oxo-2*H*-1-benzopyran-3-carboxamides and reported that compound **117** reduced **54%** O_2^- production due to presence of acetoxy group at C-7 position in coumarin nucleus (Fig 43). Cheng *et al.*[200] synthesized series of carbamic acid esters of 7-coumarinol from which they found that compound **118** was reported as moderate TNF-α inhibitor (Fig 44)**.**

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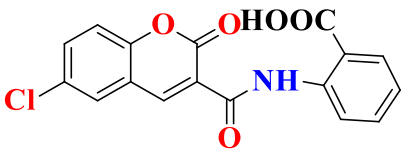
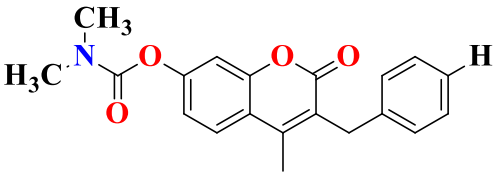


(117)

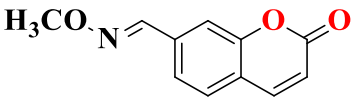
Fig 43



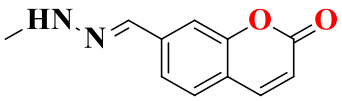
(118)

Fig 44

Kontogiorgis and Hadjipavlou-Litina[201] synthesized coumarin derivatives possessing azo-methine substituents at C-7 position and further evaluated for *in vivo* anti-inflammatory and *in vitro* antioxidant activities. They found that compounds **119** and **120** exhibited 54-58% inhibition of CPE, which conclude that minimum requirement for *in vivo* and *in vitro* activities include a coumarin ring having polar substitution at 7-position (Fig 45). They also explored various Mannich bases at C-8 position of 7-hydroxy coumarin and found that compounds **121** and **122** exhibited 75-77% inhibition of CPE in comparison to 47% inhibition by indomethacin (Fig 46). The compounds also inhibit LOX and exert good antioxidant activities.

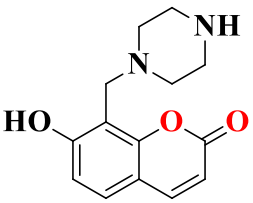


(119)

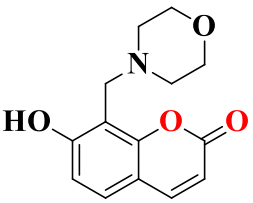


(120)

Fig 45



(121)



(122)

Fig 46

Ghate *et al.*[202] have synthesized various coumarinyl ethers and reported that benzofuranyl derivatives **(123)** have analgesic and anti-inflammatory activities comparable with indomethacin. They also found that chlorine substituent at C-6 further enhanced the activity (Fig 47). Khan and his coworkers[203] reported that compounds **124** and **125** showed anti-inflammatory activity with maximum

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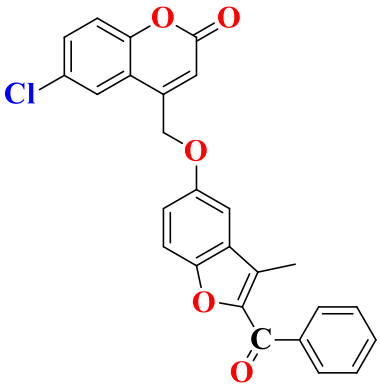
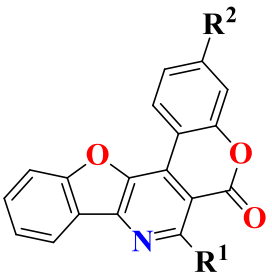
inhibition 97% at 300 mg/kg due to fusion of coumarin nucleus with benzofurans through pyridine ring (Fig 48). Jackson and his coworkers[204] reported that compound **126** having IC_{50} of 60 nM for inducible nitric oxide synthase inhibitor (Fig 49).



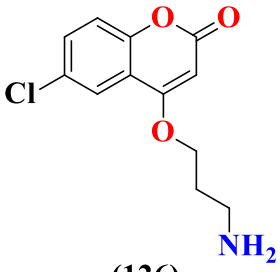
(123)

Fig 47



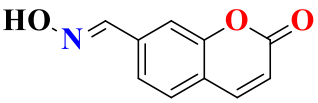
124 ($R^1 = CH_3$, $R^2 = Cl$
125 ($R^1 = C_2H_5$, $R^2 = OCH_3$

Fig 48



(126)

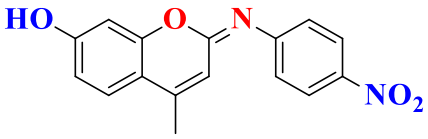
Fig 49



(127)

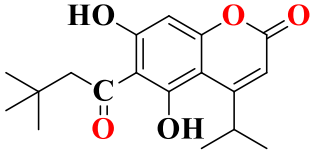
Fig 50

Kontogiorgis and his coworkers[205] synthesized a series of coumarin derivatives with 7-azomethine linkage and they found that compound **127** acts as most potent COX-1 inhibitor (78.6% inhibition) (Fig 50). Gacche *et al*[206] synthesized coumarin Schiff bases (CSBs) possessing different substituents and tested for their *in vitro* anti-inflammatory activity through inhibition of *β*-glucuronidase and reported that compound **128** was most potent having 39% inhibition (Fig 51).



(128)

Fig 51



(129)

Fig 52

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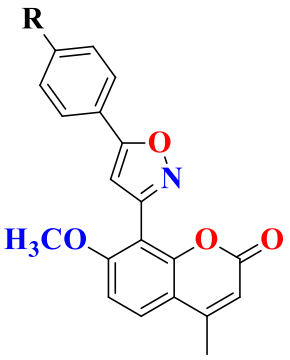
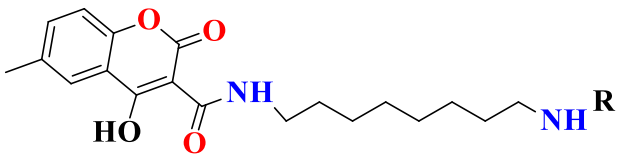
Lin *et al*[207] reported that polysubstituted coumarin derivatives **(129)** have potent anti-inflammatory activity with IC_{50} of 7.6 µM against NO production in LPS-induced at raw edema and to reduce hydroxyl radical production by 50% (Fig 52). Kalkhambkar and his coworkers[208] found that fluorescent zinc probes of coumarin exert anti-inflammatory activity *via* inhibition of soybean carbostyril and also presence of bromo substitution at C-6 and C-8 position in the coumarin ring increase the anti-inflammatory activity.

Sandeep and his coworkers[209] synthesized a series of substituted 7-methoxy-4-methyl-8-[5-(substituted aryl)isoxazol-3-yl]-coumarins and reported that compounds **130** and **131** possesed good anti-inflammatory activity with 72 and 68% inhibition of CPE, respectively (Fig 53). Melagraki *et al*.[210] have synthesized various coumarin-3-carboxamides as well as coumarin-lipoic acid conjugates to develop novel hybrid molecules for treatment of human diseases and reported that compounds **132** and **133** acts as most promising agents exhibited 100% hydroxyl radical scavenging activity (Fig 54).



130 (R = OCH_3
131 (R = Cl)

Fig 53



132 R = H

133 R =

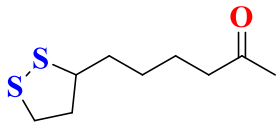


Fig 54

Bansal *et al*.[211] have synthesized coumarin derivatives having 5-phenyloxathiadiazol-4-yl moiety at C-4 of the nucleus on the basis of the pharmacological requirements for binding with p38 MAP kinase. They reported that compound **134** showed anti-inflammatory activity (55.28% inhibition) comparable with indomethacin (55.62%) (Fig 55). Reddy and his coworkers[212] synthesized 3-coumarinyl and reported that compound **135** exhibited 66.5% inhibition in acute inflammatory model in rats as compared to indomethacin (70.99%) (Fig 56). Roussaki *et al*.[213] synthesized 3-aryl

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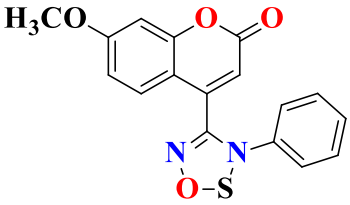
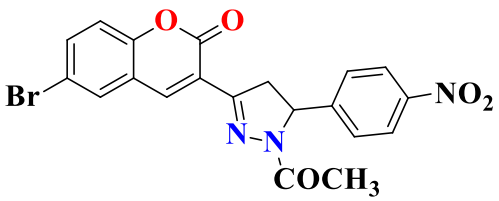
coumarin derivatives and screened for antioxidant and LOX inhibitory activities and they reported that compound **136** caused 86% LOX inhibition and prevent lipid peroxidation (Fig 57).



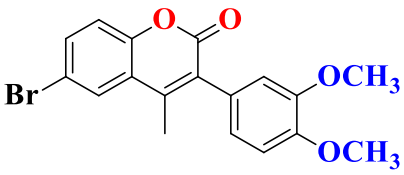
(134)

Fig 55



(135)

Fig 56

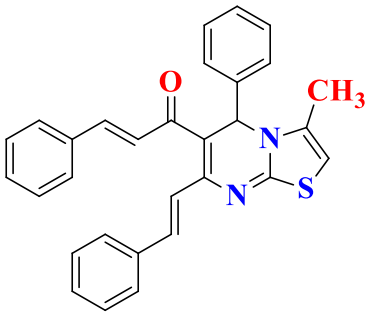


(136)

Fig 57

Biological potential of substituted dihydropyrimidinones

Fatima and his coworkers[214] synthesized a series of (*e*)-1-(3-methyl-5-aryl-7-styryl-5*H*-thiazolo[3,2-a]pyrimidin-6-yl)-3-arylprop-2-en-1-ones and reported that compound **137** having antimalarial activity against Plasmodium falciparum and HIV-RT inhibitors (Fig 58).



(137)

Fig 58

Brodsky *et al*.[215] reported that compounds **138**, **139** & **140,** a new class of Hsp70 modulators, could inhibit the replication of the pathogenic stages in human red blood cell (Fig 59).

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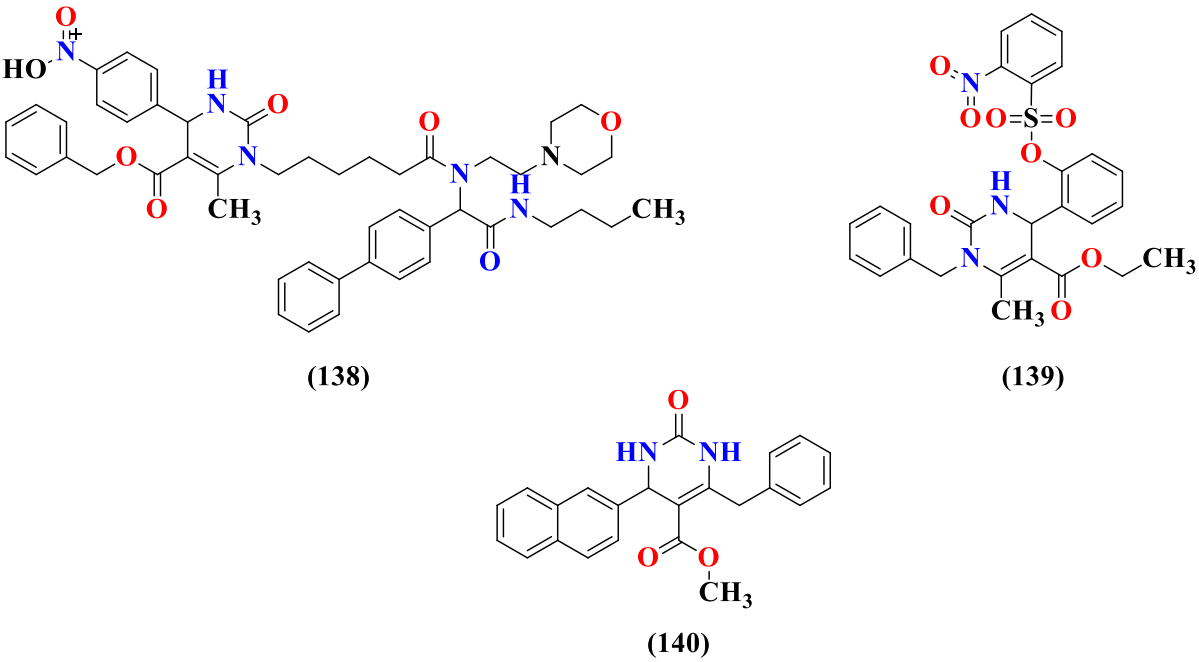
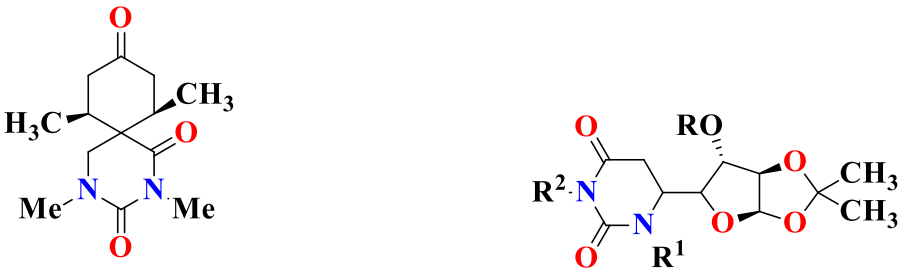


(138) (139) (140)

Fig 59: Dihydropyrimidinones reported as antimalarial agents

Islam and his coworkers[216] synthesized a series of dihydropyrimidinones derivatives and found that compound **141** have excellent *α*-glucosidase enzyme inhibition activity in comparison to standard drug acarbose and also showed *in vitro* cytotoxic activity against PC-3, HeLa and MCF-3 cancer cells lines and 3T3 mouse fibroblast cell line. Tripathi *et al*[217] synthesized some dihydropyrimidinones on cyclative amidation of glycosyl urea and tested for their *α*-glucosidase inhibitory activity and found that compound **142** exhibited strong inhibition against rat intestinal *α*-glucosidase (Fig 60).



(141) (142)

Fig 60: Dihyropyrimidinones reported as antidiabetic agents

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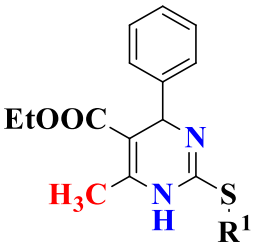
Rana *et al.*[218] synthesized various 6-methyl-4-substitutedphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters and 6-methyl-4-substitutedphenyl-2-S-alkyl(benzyl)-1,4-dihydropyrimidine-5-carboxylic acid ethyl esters and found that compound **143** have anti-ulcer activity (Fig 61).



(143)

Fig 61: Dihydropyrimidinones reported as antiulcer agents

Lal and his coworkers[219] synthesized 3,4-dihydropyrimidinones of curcumin by multi-component reaction and reported that compound **144** having *in vitro* cytotoxicity activity against three human cancer line Hep-g2, HCT-116 and QG-56. Hanan and his coworkers[220] reported that compound **145** acts as non-covalent inhibitors of EGFR, with excellent activity against the T790M resistance double mutants and initial single activating mutants. Tawtik *et al.*[221] synthesized dihydropyrimidines derivatives with multifunctional aromatic substitutions and they reported that compounds **146** and **147** having tumour antiinitiating activity (Fig 62)**.**

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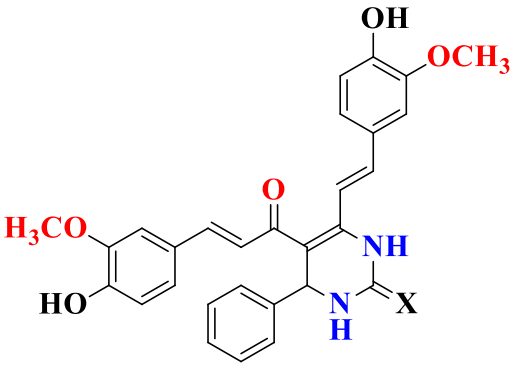
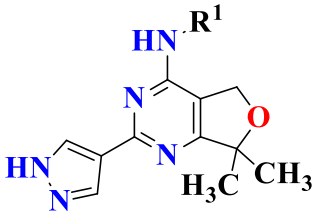
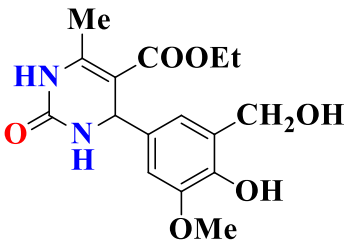


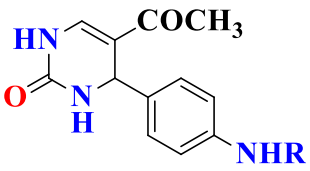
(144)



(145)



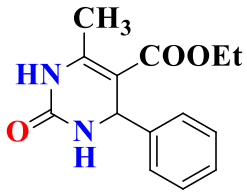
(146)



(147)

Fig 62: Dihydropyrimidinones reported as anticancer agents

Singh *et al.*[222] synthesized a series of dihydropyrimidinones by Biginelli reaction in presence of copper (II) chloride and found that compound **148** having antifungal activity against three fungal species *viz. Trichoderma hammatum*, *Trichoderma koningii* and *Aspergillus niger*. Ashok and his coworkers[223] synthesized a series of 2-(arylidene/5-arylfurfurylidene)-5-(4-methylthiophenyl)-6-carbethoxy-7-methyl-5*H*-thiazolo[2,3-b]pyrimidin-3(1*H*)ones by multicomponent reaction and found that compound **149** have antibacterial and antifungal activity (Fig 63).



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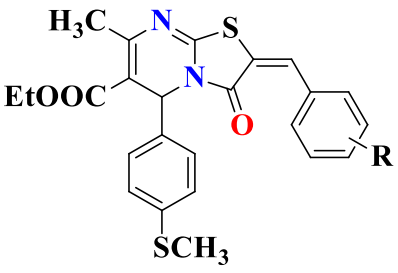

(149)

Fig 63: Dihydropyrimidinones reported as antimicrobial agents

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Kumar *et al.*[224] synthesized and evaluated novel [4,6-(4-subsituted aryl)-2-thioxo-1,2,3,4-tetrahydroyrimidine-5-yl]-acetic acid derivatives as potential anti-inflammatory agents on the basis of reference drug diclofenac sodium and reported that compounds **150**, **151** & **152** were found most active (Fig 64). They also found that presence of 4-methoxy group at C-4 position play an important role in the activity of compounds. It was observed that 4-methoxy phenyl increase the activity of synthesized compounds.

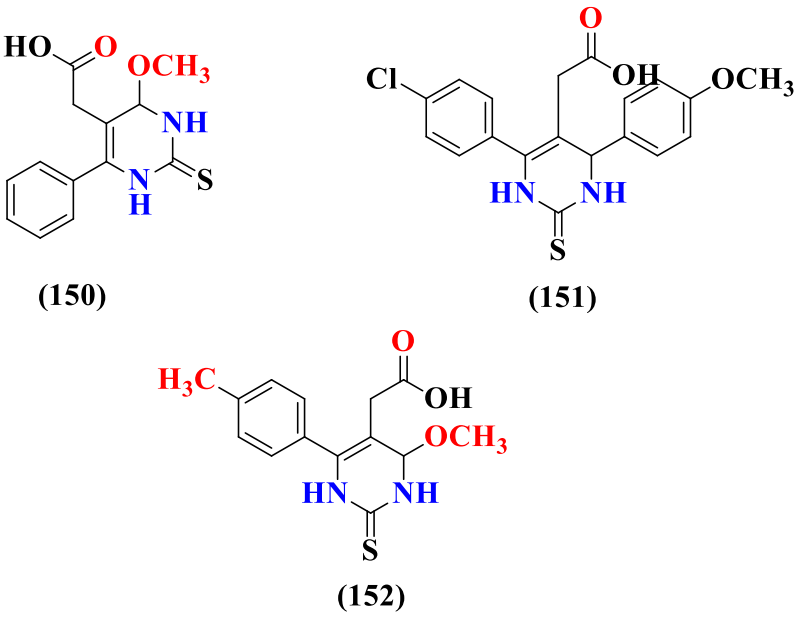

Fig 64: The structure of potent DHPMs having anti-inflammatory activity

Sari and his coworkers[225] synthesized dihydropyrimidines *α,γ*-diketobutanoic acid derivatives and reported that compounds **153**, **154**, **155** & **156** inhibited strand transfer and submicromolar activities (Fig 65). They also found that substitution at C-6 position responsible for activity of synthesized compounds.

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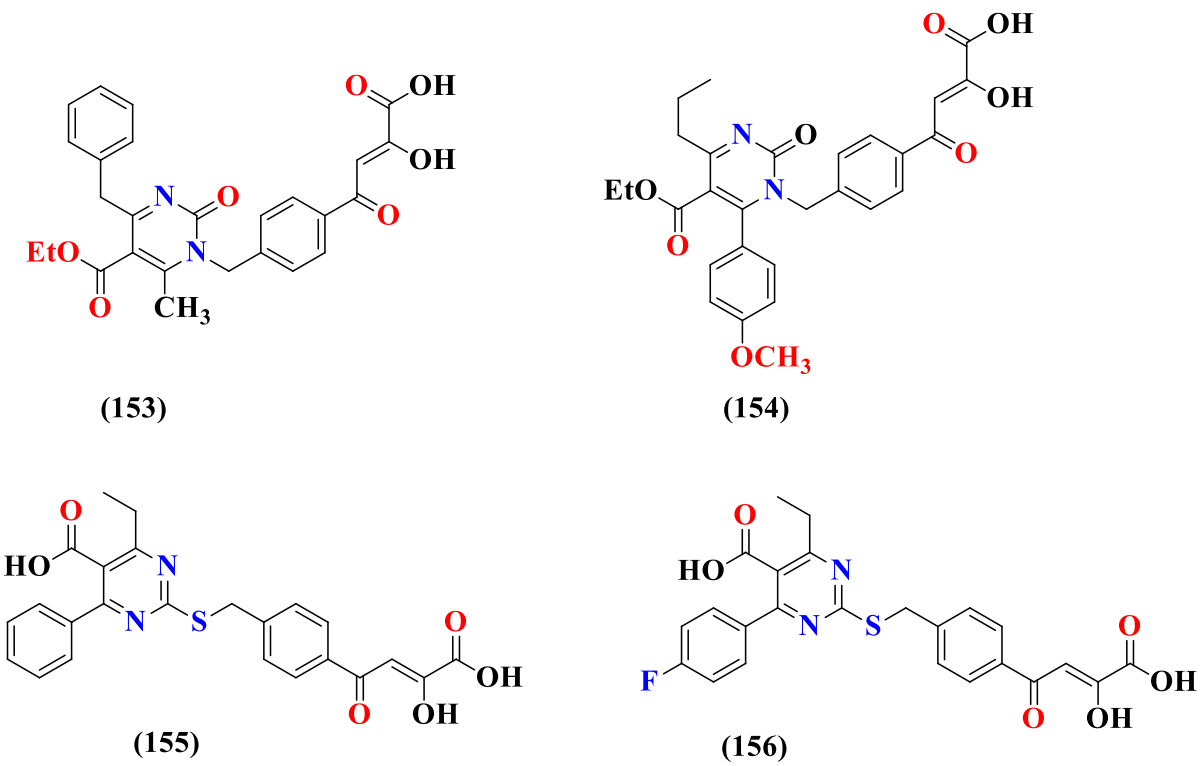

Fig 65: The structure of potent DHPMs having anti-HIV activity

Trivedi *et al.*[226] synthesized novel dihydropyrimidines as a potential new class of antitubercular agents and reported that compounds **157** and **158** most active against *Mycobacterium tuberculosis* strain having MIC of 0.02 µg/mL and SI > 500 (Fig 66).

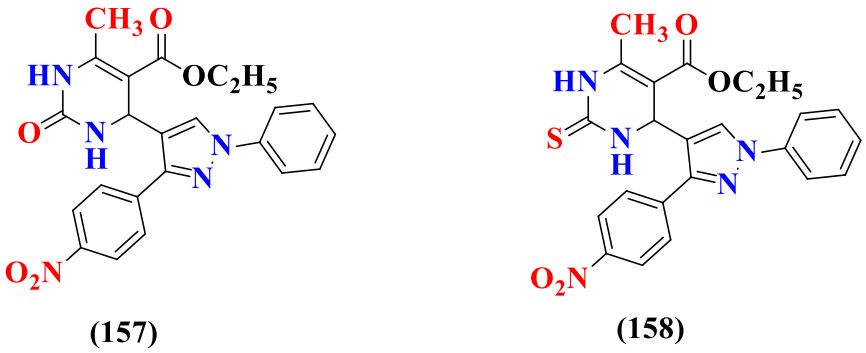

Fig 66: The structure of potent antitubercular compounds

Aly and Kamal[227] developed a novel fused chromeno [2,3-*d*] pyrimidine and pyrano [2,3-*d*] pyrimidine derivatives and tested for *in vitro* antifungal activity against two fungal species *viz*. *Aspergilus flavus* and *Candida albicans* and reported that compound **159** was more potent than the standard drug Amphotericin B against the *Aspergillus flavus* fungus (Fig 67).

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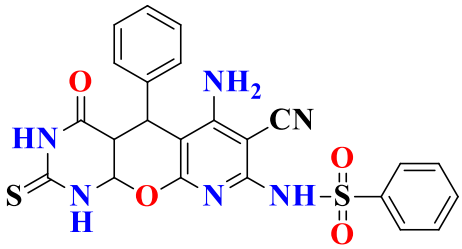
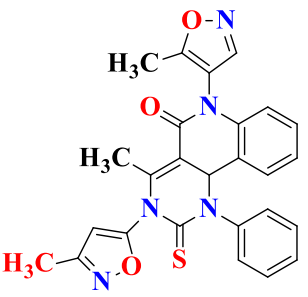


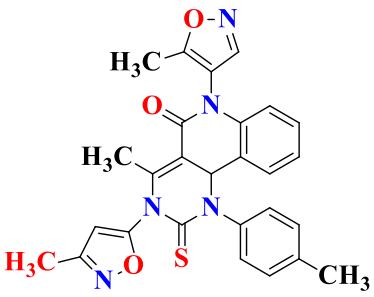
(159)

Fig 67: The structure of potent antifungal compounds

Rajanarendar *et al.*[228] synthesized the antibacterial novel piperazine and morpholine linked substituted pyrimidine derivatives as antimicrobial agents and reported that compounds **160**, **161** and **162** have excellent antibacterial activity compared to standard drug ciprofloxacin (Fig 68). They also found that when benzene ring is substituted by electron withdrawing group like chloro and bromo it enhanced activity of compounds. Attri and his coworkers[229] reported the antibacterial activity of synthesized compounds and found that compounds **163**, **164** and **165** showed the good antibacterial activity which is possibly due to presence of halogen atom. They also found that compound **165** was found to be effective against bacteria with lower MIC in comparison to compound **163** and **164**. This is due to substitution of two halogen atoms in compound **165** which is responsible for increase in the antibacterial activity (Fig 68).



(160)



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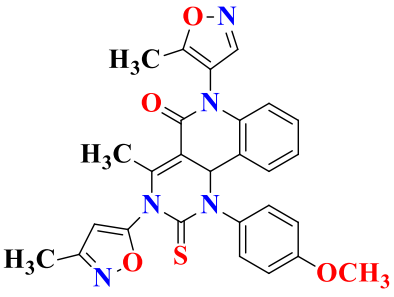
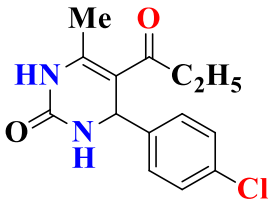


(162)



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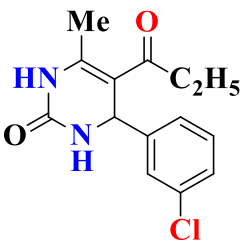

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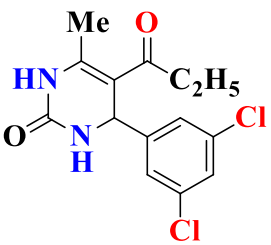

(165)

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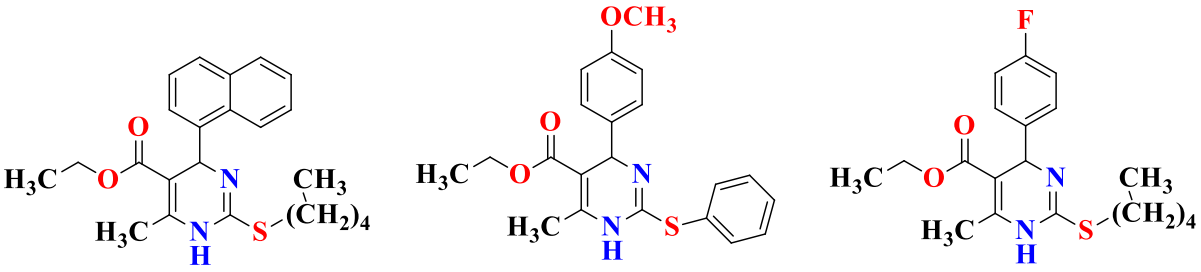
Fig 68: The structure of potent anti-bacterial compounds

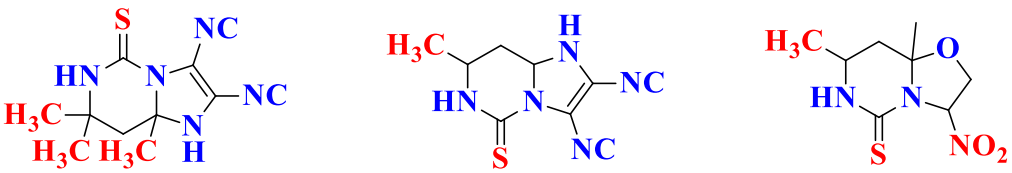
Singh *et al.*[230] synthesized 2-sulfanyl-6-methyl-1,4-dihydropyrimidines as a antiflarial agents against *Brugia malayi* and found that compounds **166**, **167** and **168** have excellent *in vitro* antiflarial activity (Fig 69).



(166) **(167)** **(168)**

Fig 69: The structure of potent anti-filarial compounds

Sondhi and his coworkers[231] synthesized mono, bi and tricyclic pyrimidine derivatives and screened for their analgesic activity and reported that compounds **169**, **170** and **171** exhibited 100, 70 and 75% activity at 100 mg/kg dose respectively (Fig 70).



(169) **(170)** **(171)**

Fig 70: The structure of potent analgesic compounds

Khange *et al.*[232] synthesized and evaluated some new pyrimidine derivatives containing 1,2,4-triazole for tested their anticonvulsant activity by maximal electroshock seizure method and reported that compounds **172**, **173**, **174**, **175** and **176** have excellent activity and they also found that electron withdrawing group substituted phenyl ring at sixth position of dihydropyrimidines showed marked increase in anticonvulsant activity (Fig 71).

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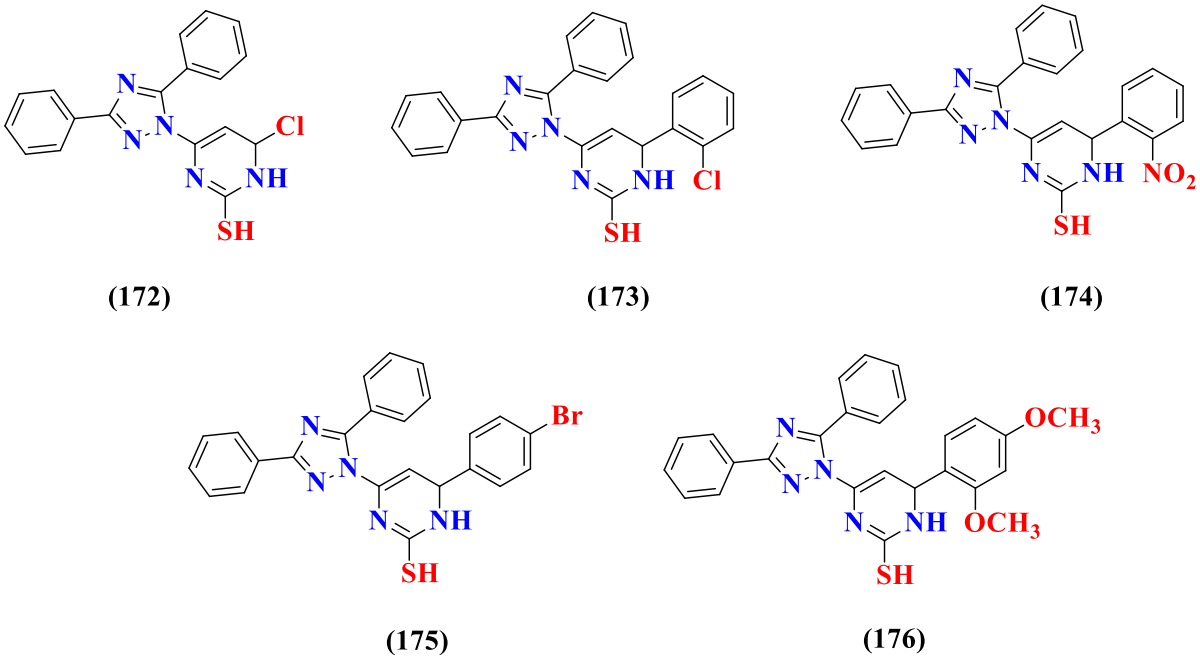

Fig 71: The structure of potent anticonvulsant compounds

Yadlapalli and his coworkers[233] synthesized diarylpyrazole ligated dihydropyrimidines and synthesized compounds were screened for *in vitro* anticancer activity against the MCF-7 human breast cancer cell line and they found that compound **177** showed more affinity to inhibition of cell growth with GI_{50} of 33.2 µM and also showed good dose response. They also conclude that presence of thio-urea functional group in DHPMs enhance the anticancer activity (Fig 72).

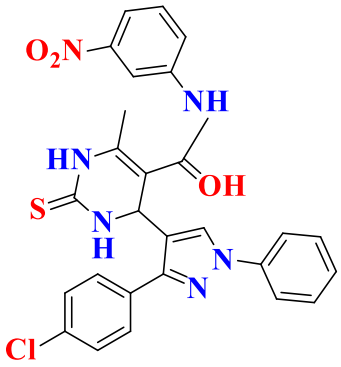

Fig 72: The structure of potent molecule against breast cancer

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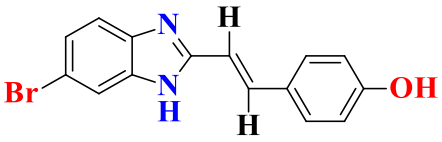
Biological potential of substituted imidazoles

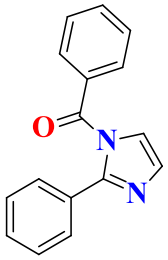
Shingalapur *et al*.[234] synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* and anti-fungal activity against *Candida albicans* and *Aspergillus fumigates* and reported that compound **178** was most active (Fig 73).



(178)

Fig 73: 4-((E)-2-(6-bromo-1*H*-benzo[d]imidazol-2-yl)vinyl)phenol

Sharma and his coworkers[235] synthesized 2-(substituted phenyl)-1*H*-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues and tested for antimicrobial activity against Gram positive, Gram negative, and fungal species and reported that compound **179** was most active (Fig 74). Zampieri *et al*.[236] synthesized bis-imidazole derivatives and tested for antifungal and anti-mycobacterial activity. They found that all compounds showed excellent activity against *Candidaalbicans* and *Candida glabrata* (Fig 75).



(179)

Fig 74

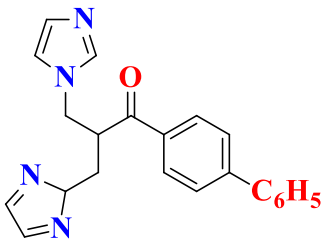


Fig 75

Olender *et al*.[237] synthesized nitroimidazole derivatives and tested for their antifungal activity using the standard nutrient method against *Sclerophoma pityophila* and reported that compound **180** showed more potent fungistatic activity (Fig 76)**.**

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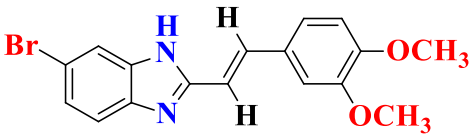
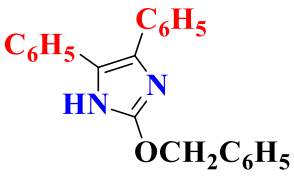


(180)

Fig 76: 2-(3,4-dimethoxystyryl)-6-bromo-1*H*-benzo[*d*]imidazole

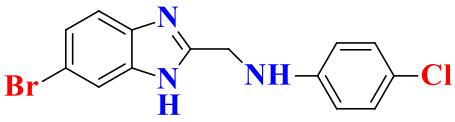
Puratchikody and his coworkers[238] studied on 2-substituted-4,5-diphenyl-1*H*-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. They reported that compound **181** showed maximum activity and indomethacin used as reference drug (Fig 77).



(181)

Fig 77: 2-(benzyloxy)-4,5-diphenyl-1*H*-imidazole

Achar *et al*.[239] has synthesized a series of 2-methylaminibenzimidazole derivatives and newly synthesized compounds were tested for analgesic and anti-inflammatory activities. They found that compound **182** showed good analgesic activities compared with standard nimesulide drug (Fig 78). This compound also showed potent anti-inflammatory activity compared with nimesulide.



(182)

Fig 78: *N*-((6-bromo-1*H*-benzo[*d*]imidazol-2-yl) methyl)-4-chlorobenzenamine

Gupta and his coworkers[240] described anti-mycobacterium tuberculosis activities of ring substituted-1*H*-imidazole- 4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against durg-sensetive and durg-resistent *M. tuberculosis* strains and reported that compound **183** was most potent compound (Fig 79).

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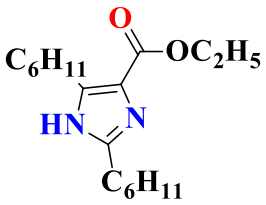
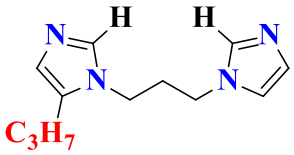


(183)

Fig 79

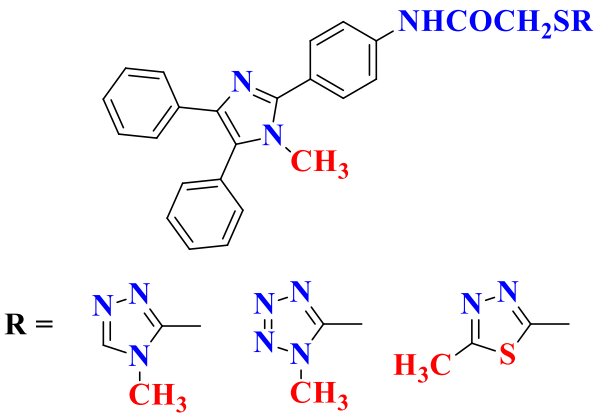
Pandey *et al*.[241] synthesized a series of imidazole derivatives and compounds were tested against *M .tuberculosis* and reported that compound **184** showed good antitubercular activity (Fig 80).



(184)

Fig 79: 1-(3-(1*H*-imidazol-1-yl)propyl)-5-propyl-1*H*-imidazole

Ozkay and his coworkers[242] synthesized many novel imidazole-(Benz) azole and imidazole epiperazine derivatives in order to investigate anticancer activity and reported that compound **185** was most active compound (Fig 80).



(185)

Fig 80

Refaat *et al*.[243] synthesized various 2-substituted benzimidazole and tested for anticancer activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma and they reported that compound **186** and **187** showed the highest activity against human hepatocellular carcinoma (Fig 81).

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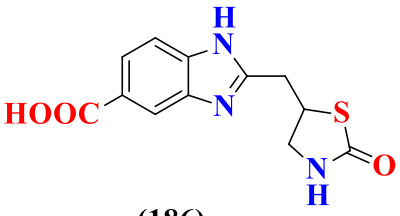

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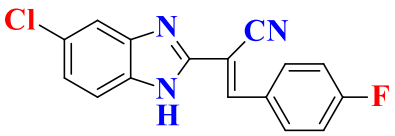
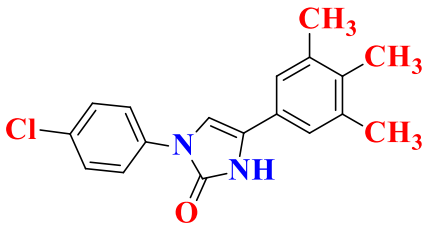


(187)

Fig 81

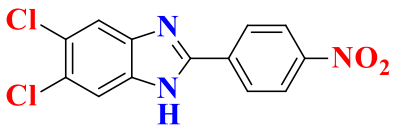
Congiu and his coworkers[244] synthesized a series of 1, 4-diarylimidazole-2(3*H*)-one derivatives and their 2-thione analogues and evaluated their antitumor activity and found that compound **188** showed potent antitumor activity (Fig 82).



(188)

Fig 82: 1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1*H*-imidazol-2(3*H*)-one

Tonelli *et al.*[245] synthesized 2-phenylbenzimidazole derivatives and evaluated for cytotoxicity and anti-viral activity against a panel of RNA and DNA viruses. They reported that compound **189** exhibited excellent activity resulting more potent than reference drugs smycophenolic acid and 6-azauridine (Fig 83).



(189)

Fig 83: 5,6-dichloro-2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole

Bhandari and his coworkers[246] synthesized a series of substituted aryloxy alkyl and aryloxy aryl alkyl imidazole and evaluated for *in vitro* as antileishmanial agents against *Leshmania donovani* and found that compound **190** exhibited 94-100% inhibition (Fig 84).

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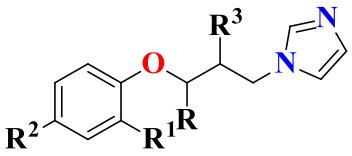
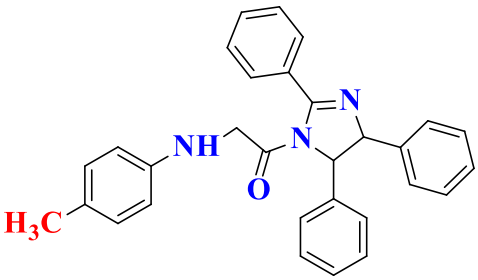


(190)

Fig 84

A series of 2,4,5-triphenyl-1*H*-imidazole-1-yl derivatives have been synthesized and tested for their anti-fungal activity against *Candida albicans* and antimicrobial activity against *B. Subtills* and *E. Coli* by Zara *et al*.[247]. They reported that compound **191** was found to be most active derivative (Fig 85).



(191)

Fig 85

A new series of 1-substituted imidazole derivatives have been synthesized by taking different anilines and sulphonamides as substitution by Prasanthy and his coworkers[248] and synthesized compounds were further tested for their anticancer and antimicrobial activities. They reported that compound **192** exhibited highest activity against cervical cancer. Compound **193** showed good antifungal activity while compound **194** showed good antibacterial activity (Fig 86).

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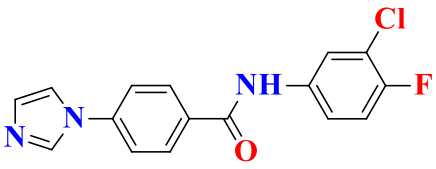

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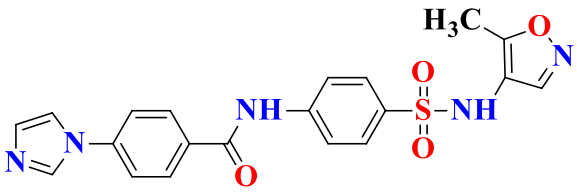

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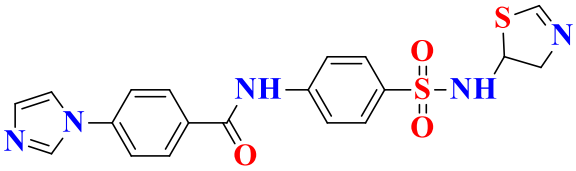
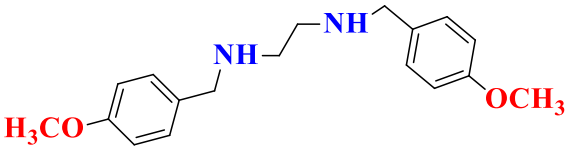


(194)

Fig 86

Carvalho *et al*.[249] synthesized series of N,N'-disubstituted ethylenediamine and imidazolidine derivatives and tested their *in vitro* biological activities against *Leishmania* species and reported that compounds **195** and **196** showed excellent activities on intracellular amastigotes with IC_{50} values of 2.0 and 9.4 µg mLG^{1}, respectively (Fig 87).



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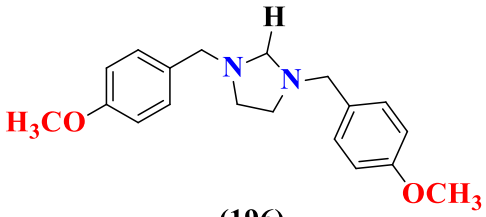

(196)

Fig 87

Gopinath and his coworkers[250] synthesized new series of imidazoles by the reaction of chrome-3-carboxylic acids with substituted acyl bromides in the presence of TEA followed by reflux with NH_4OAc in toluene and reported compounds were screened *in vitro* for the inhibition of KRAS/Wnt and their anti-angiogenesis properties. Based on angiogenesis inhibition mechanism, they conclude that compound **197** is potent anticancer and higher affinity with KRAS/Wnt and VEGF (Fig 88).

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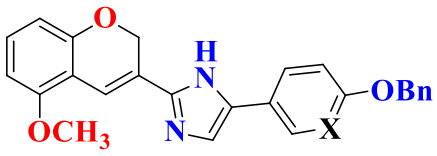
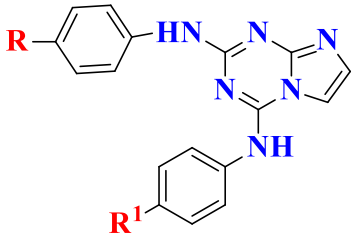


(197)

Fig 88: Imidazoles reported as antiangiogenic agents

Dao *et al*.[251] explained anticancer activity of imidazoles and explores their anti-angiogenic activities against human umbillcal vein endothelial cells and also evaluated *in vitro* enzymatic activities with reference to standard inhibitor TAE-226. They reported that compounds **198**, **199** and **200** showed good activity against four cancer cell lines (U87-MG, HCT-116, MDA-MB-231, and PC-3) (Fig 89).



198; R = 2-CONHCH$_3$ and R^1 = 3,4,5-trimethoxy
199; R = 2-CONHCH$_3$ and R^1 = 2-OCH$_3$-4-morpholino
200; R = 2-CONHCH$_3$ and R^1 = 4-CH$_2$NHAlloc

Fig 89: Potent antiangiogenic imidazoles

Sarkarzadeh and his coworkers[252] synthesized series of heterocyclic molecules containing imidazole moieties for their antiproliferative effects on cervical (HeLa), colon (LS180), breast (MCF-7) and Jurkat human cancer cell lines by MTT assay and they found that compounds **201**, **202** and **203** bearing imidazole-2-yl moiety on the C-11-position of the dihydropyridine ring exhibited superior antiproliferative activities compared to cis-platin, especially in the Jurkat cell line (Fig 90).

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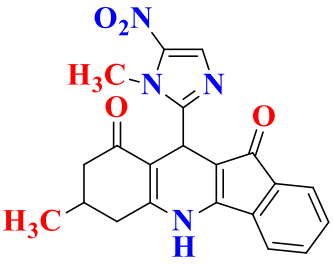

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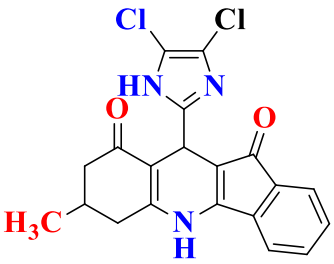

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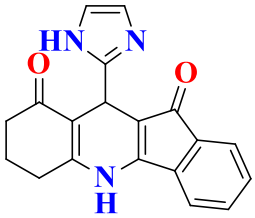
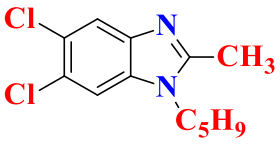


(203)

Fig 90: Potent antiproliferative imidazoles

Alkahtani *et al.*[253] synthesized series of benzo[*d*]imidazoles and evaluated their anticancer activities and reported that compounds **204**, **205** and **206** having chloro, cylopentyl, -CH_3, -$SOCH_3$ and –SO_2CH_3 substituents as potent antiproliferative agents in cancer cell lines (Fig 91).



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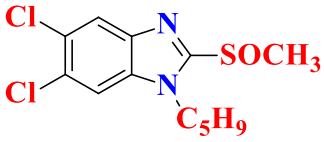

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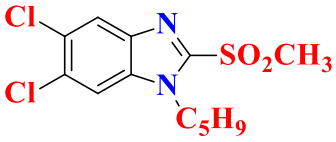

(206)

Fig 91

Biological potential of substituted isoxazoles

A series of new isoxazoles derivatives linked by alkynes were synthesized by Sun *et al*[254] and they found that compounds **207**, **208** and **209** exhibited anti-proliferative activity towards several human cancer cell lines with IC_{50} value in the low nanomolar range (Fig 92).

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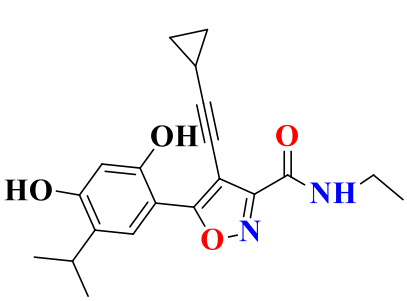
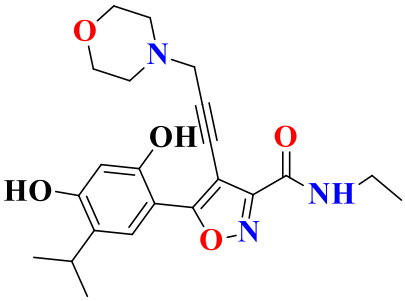
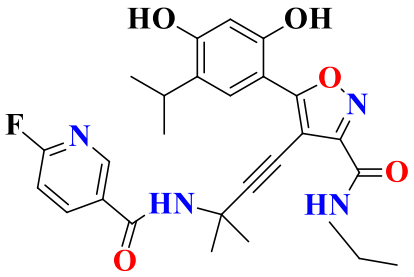


(207)



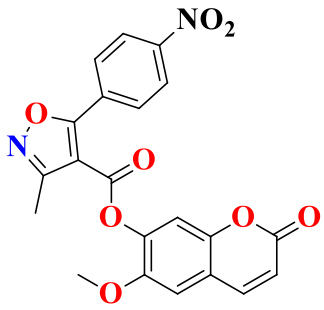
(208)



(209)

Fig 92: Isoxazole derivatives as anticancer agents

Shi and his coworkers[255] synthesized series of scopoletin-isoxazole and scopoletin-pyrazole hybrids and evaluated their anticancer activities against three human cancer cell lines including HCT-116, Hun7 and SW620 by MTT assay. They found that compound **210** exhibited significant anti-proliferative activity similar to sunitinib with IC_{50} values ranging from 8.76 µM to 9.83 µM and weak cytotoxicity on normal cells HFL-1 with IC_{50} value of 90.9 µM (Fig 93).



(210)

Fig 93

3,5-Disubstituted isoxazole derivatives were synthesized by Ananda *et al*[256] and screened for their antiproliferative properties against cancer cell lines such as MCF7 and HeLa. They found that

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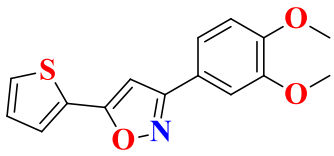
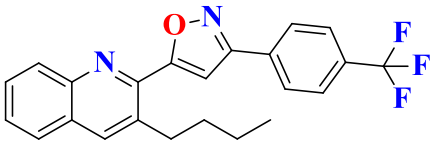
compound 3-(3,4-dimethox-yphenyl)-5-(thiophen-2-yl)isoxazole **(211)** displayed considerable inhibition of proliferation of MCF7 and HeLa cells (Fig 94).



(211)

Fig 94

A series of 5-(3-alkylquinolin-2-yl)-3-aryl isoxazole derivatives were synthesized and evaluated towards four human cancer cell lines (A549, COLO205, MDA-MB 231 and PC-3) by Rao and his colleague[257]. They found that compound **212** showed excellent cytotoxicity against all the tested cell lines with IC_{50} values lower than 12 µM. They also conclude that fluorine or trifluoromethyl group at the fourth position of phenyl in isoxazole ring was beneficial to the activity on the basis of structure-activity relationship (Fig 95).



(212)

Fig 95

Pedada and his coworkers[258] synthesized a series of novel indole containing isoxazole derivatives and tested for their sPLA2 inhibitory activity. They found that compound **213** showed more potent sPLA2 inhibition activity. This compound also exhibited *in vitro* antiproliferative activity against MCF-7 breast and DU145 prostate cancer cells (Fig 96).

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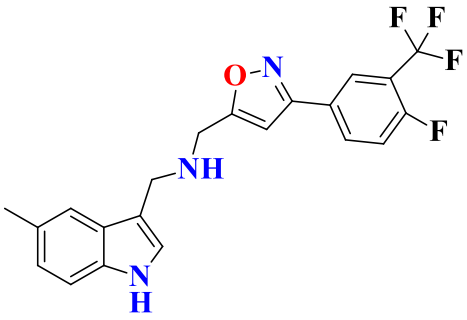
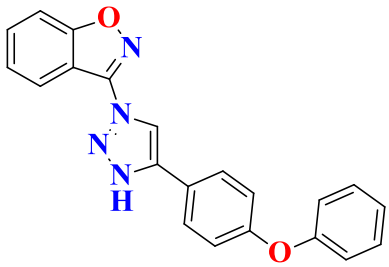


(213)

Fig 96

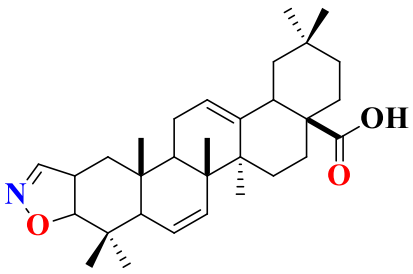
A novel series of 1,2,3-triazoles attached to third position of the 1,2-benzisoxazole heterocycles were synthesized by Ashwini *et al*[259] and further tested for their cytotoxic effect on cervical cancer and acute myeloid leukemia (AML) cells. They found that compound 3-(4-(4 phenoxyphenyl)-1*H*-1,2,3-triazol-1-yl)benzo[*d*]isoxazole (PTB) **(214)** was identified as most active antiproliferative against various AML cell lines (MOLM13, MOLM14 and MV4-11 cells) (Fig 97).



(214)

Fig 97

Pan and his coworkers[260] demonstrated that oleana-2,12-dieno[2,3-*d*]isoxazole-28-oic acid (Compound **215**) can efficiently inhibit cell proliferation and induce apoptosis in a human leukemia K562 cell. They also found that OA derivatives may be potential chemotherapeutic agents for treating human cancer (Fig 98).



(215)

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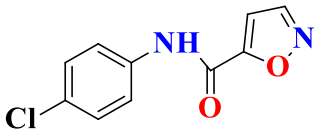
Fig 98

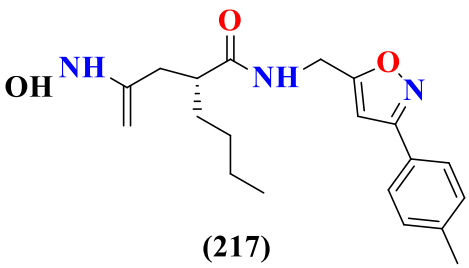
A new series of isoxazole derivatives, N-phenyl-5-carboxamidyl isoxazoles were tested for their anticancer activity using mouse colon carcinoma cells by Shaw *et al*[261] and they found that compound **216** was most active against colon 38 and CT-26 mouse colon tumor cells with an IC_{50} of 2.5 µg/mL for both cells and could be further investigated as a promising chemotherapeutic for treating colon cancer (Fig 99).



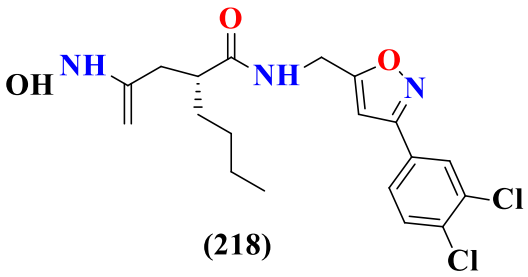
(216)

Fig 99

Zhang and his coworkers[262] designed two series of novel hydroxamates bearing aryl substituted isoxazole ring and evaluated for their antibacterial activity against *Klebsiellar pneumonia* and *Staphylococcus aureu*. They found that compounds **217** and **218** exhibited moderate activity against the two bacteria (Fig 100).



(217)



(218)

Fig 100

Hamada and his colleague[263] synthesized a series of novel heterocyclic compounds with isoxazole, pyrazole and oxadiazole ring and screened for their antibacterial activity and found that compound **219** showed maximum activity against *Staphylococcus aureus* ATCC6538P and *Escherichia coli* ATCC8739 (Fig 101).

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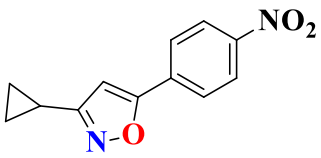
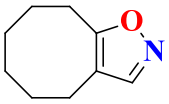


(219)

Fig 101

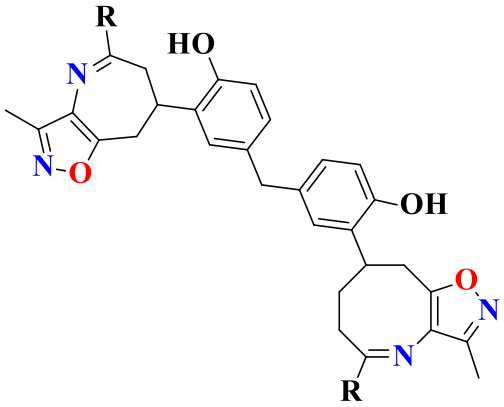
Ali *et al*.[264] synthesized some new cyclooctane-based heterocycles with pyrazole, isoxazole and pyrimidine and these compounds were further evaluated for their antimicrobial activities against *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*. They found that compound **220** showed good antibacterial activities against MRSA, which may be due to presence of isoxazole (Fig 102).



(220)

Fig 102

Rajanarendar and his coworkers[265] reported the synthesis and antimicrobial activity of novel methylene bis-isoxazolo[4,5-*b*]azepines and found that compounds **221** and **222** possess both remarkable antibacterial and antifungal activity (Fig 103).



221 (R = 2-furyl)
222 (R = 2-thienyl)

Fig 103

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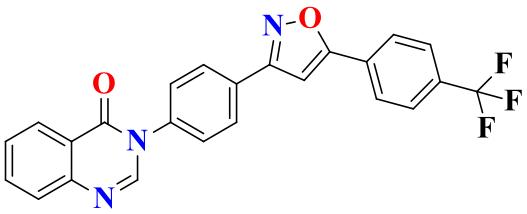
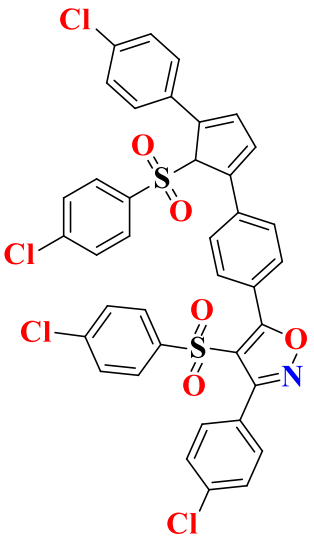
Saravanan *et al.*[266] synthesized a series of novel isoxazole quinazolin-4(3*H*)-one derivatives and screened for antimicrobial activity against four Gram-positive bacteria, three Gram-negative bacteria and two fungi. They found that compound **223** showed excellent antimicrobial activity against all pathogenic strains (Fig 104).



(223)

Fig 104

Lavanya and his coworkers[267] synthesized two series of novel compounds 1,4-phenylene bis-arylsulfonyl-pyrazole and isoxazole. The compounds with isoxazole ring showed better antimicrobial activity than compounds bearing pyrazole moiety. They found that compound **224** exhibited excellent antibacterial and antifungal activities, which was identified as promising antimicrobial agent (Fig 105).



(224)

Fig 105

A series of new diaziridinyl quinone isoxazole hybrids were synthesized and screened for antimicrobial, anti-biofilm and cytotoxic activities by Swapnaja and his coworkers[268]. They found that compound **225** showed excellent antibacterial activity against *S. aureus* MTCC 96, *S. aureus* MLS-16

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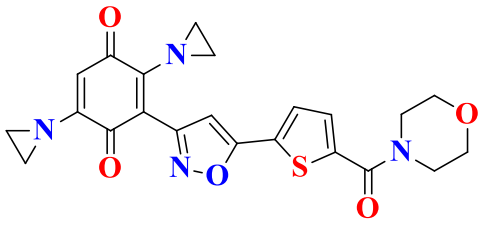
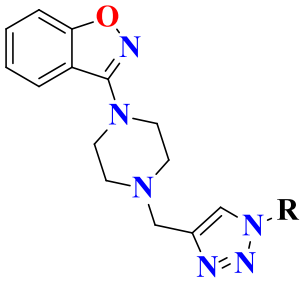
MTCC 2940 and *B. subtilis* MTCC 121 (MIC = 3.9 µg/mL) as well as *K. planticola* MTCC 530 (MIC = 7.8 µg/mL). This compound also showed potent antifungal activity against a range of *Candida* strains and also exhibited pronounced anti-biofilm activity against all the tested pathogens (Fig 106).



(225)

Fig 106

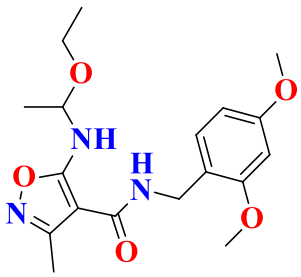
A series of benzo[*d*]isoxazole derivatives were synthesized and evaluated for their anti-TB activity by Naidu and his colleague[269] and they found that compound **226** having excellent anti-tubercular activity (Fig 107).



226 (R = 4-Br-3-CF_3Ph)

Fig 107

Maczynski *et al*.[270] synthesized a series of novel isoxazole as immunosuppressive agents and found that compound **227** was most potent. This compound strongly inhibited the carrageenan-induced foot pad inflammation in a dose-dependent manner and also serve as potential drug to ameliorate inflammatory process (Fig 108).



(227)

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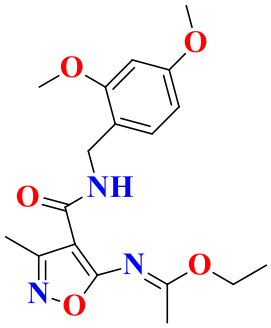
Fig 108

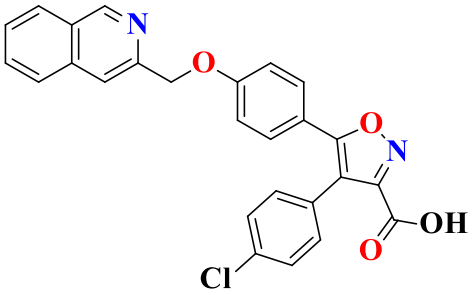
Rakesh and his coworkers[271] synthesized isoxazole derivatives and evaluated for their anti-inflammatory activity *via* LOX and COX inhibition. They found that compound **228** significantly inhibit the activity of LOX and COX. It also showed good inhibition on tumor growth *in vitro* and *in vivo* and also acts as promising agent against inflammation and cancer (Fig 109).



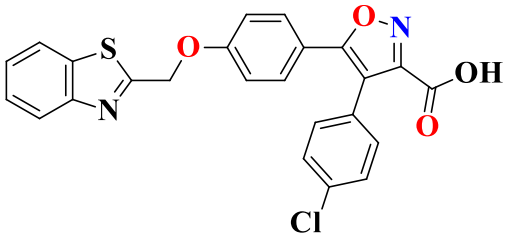
(228)

Fig 109

Banoglu *et al.*[272] synthesized new isoxazole compounds and found that compounds **229** and **230** having remarkable inhibitory activity against cellular 5-LO product formation. These compounds may also serve as lead for the development of anti-inflammatory drugs by leukotriene biosynthesis inhibition (Fig 110).



(229)



(230)

Fig 110

Perrone and his colleague[273] synthesized a new series of isoxazole and evaluated them for their COX inhibitory activity and selectivity and compound **231** was found to be a sub-micromolar selective COX-2 inhibitor (Fig 111).

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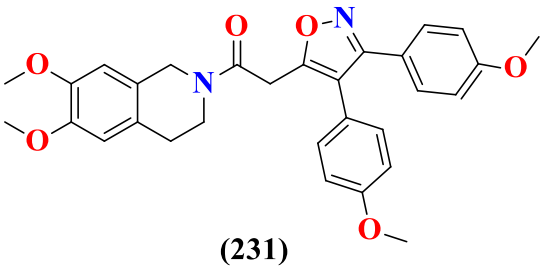
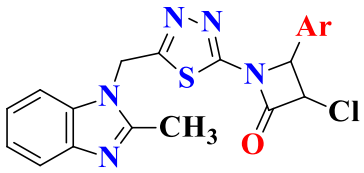


(231)

Fig 111

Biological potential of substituted benzimidazoles

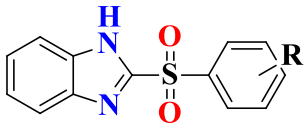
Ansari and Lal[274] synthesized novel azetidine-2-one **(232)** and evaluated for their antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, *Aspergillus niger* and *Aspergillus flavus*. They found that tested compounds are more effective against gram positive bacteria. They also conclude that strong lipophilic character of molecules plays an essential role in producing antimicrobial properties (Fig 112).



(232)

Fig 112

Ghoneim *et al.*[275] synthesized 2-[(4-aminophenyl)sulphonyl] derivative **(253)** of benzimidazole and evaluated the antimicrobial activity of compounds against *E. coli* using agar diffusion method. They found that all 4-amino and 2,4-diaminophenylsulphonyl derivatives showed antimicrobial activity (Fig 113).



(253)

Fig 113

Gupta and Rani[276] synthesized 2-thiohalogenonitrophenyl benzimidazole **(254)** by the condensation of halogenonitrobenzenes and sodium salt of 2-mercaptobenzimidazole and tested for

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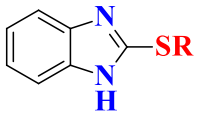
their antifungal activity against *Helmithosporium sativum*, *A. niger* and *Fusarium oxysporum* by spore germination method. The percentage inhibition of the spores at 10 ppm has been recorded (Fig 114).

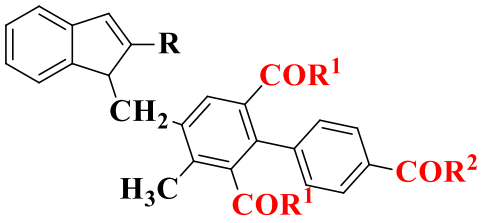


(254)

R = 2,4-DNP, 2,6-DNP, 2,4,6-TNP, 2-chloro 4,6-DNP, 2-methyl-4,6-DNP, 2-chloro-4-bromo-3,5-DNP (DNP = dinitrophenyl, TNP = trinitrophenyl

Fig 114

Mane and his coworkers[277] synthesized benzimidazole derivatives **(254)** and evaluated against *Alternaria brassicicola*, *Fusarium*, *Staphylococcus* (Gram +ve) and *E. coli* (Gram –ve) using filter paper disc method. They found that the compound having NO_2 and chloro substituent showed good activity against fungi as well as bacteria (Fig 115).



(254)

R = H, CH_3, C_2H_5, C_6H_5
R^1 = CH_3, OCH_3, OC_2H_5
R^2 = H, 4-CH_3, 4-OCH_3, 3-Cl, 3-NO_2, 4-NO_2, 4-OH

Fig 115

Kumar and his colleague[278] synthesized some novel 2-(6-flurochroman-2-yl)-1 alkyl/acy/aroyl-1-*H*-benzimidazoles **(255)** with different type of electrophiles and showed excellent antibacterial activity against *Salmonella typhimurium* and poor activity against *Staphylococcus aureus* (Fig 116).

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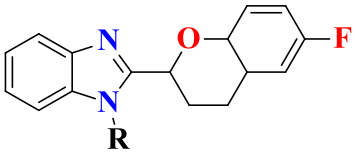
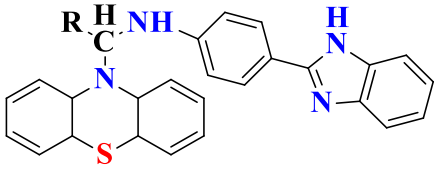


(255)

R = CH_3, C_2H_5, -CO-Phenyl, -SO_2-phenyl, Benzyl, *p*-fluorophenyl

Fig 116

Bishnoi and his coworkers[279] reported various 10-(*α*-*p*-benzimidazolyl-aminobenzyl)phenothiazines and found that compound **256** was active against *Fusarium solani* fungus (Fig 117).

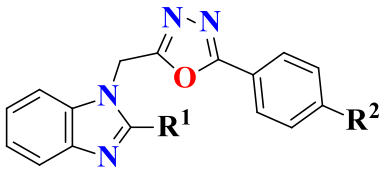


(256)

R = Phenyl and substituted phenyl

Fig 117

A new series of 2-substituted-1-[(5-substituted-phenyl-1,3,4-oxadiazole-2yl)methyl-1*H*-benzimidazole have been synthesized by Gowda *et al.*[280] and evaluated for their antibacterial activity by the serial dilution method. They found that compound **257** was active against Gram positive bacteria *viz*. *E. coli*, *S. aureus* and Gram negative bacteria namely *Pseudomonas aeruginosa* (Fig 118).



(257)

R^1 = Propyl, Benzyl

R^2 = H, Cl, Br, Me, OMe

Fig 118

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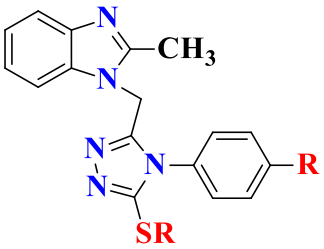
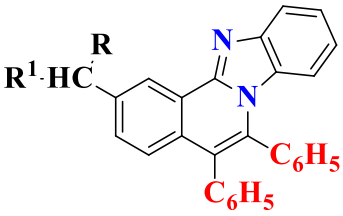
A series of 1-[(4-(40-substituted)phenyl-3-alkyl/aralkyl-thio-4*H*-1,2,4-triazoles have been prepared by Shetgiri and Kokitkar[281] and screened for their antimicrobial activity against pathogenic organisms *S. citrus*, *B. subtilis* and *E. coli* and antifungal against *A. fumigatus*, *C. albicans* and *F. heterosporum* by single disc method. They found that compound **258** was most active against all the organisms (Fig 119).



(258)

Fig 119

Pandey and Shukla[282] synthesized 7-(arylamidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]benzimidazoles and evaluated for their *in vivo* against influenza virus and found that compound **259** showed the maximum activity (Fig 120).



(259)

Fig 120

Kristina and his coworkers[283] synthesized 2-substituted-5-amidino-benzimidazole derivatives and tested for their antiviral activity towards *coxsackie viruses* and *echo viruses* They found that compound **260** was most active towards *coxsackie viruses* and *echo viruses* having pyridine ring at C-2 position (Fig 121).

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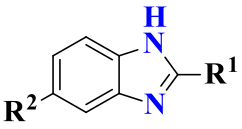


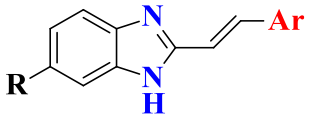
(260)

R^1 = Hterocyclic substituent

R^2 = Amidino substituent

Fig 121

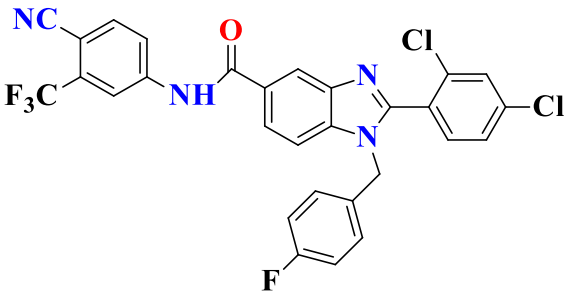
Hranjec *et al*.[284] synthesized novel series of benzimidazole Schiff bases *via* reaction between substituted aldehydes **and** 2-aminobenzimidazoles and screened for their antiproliferative activity *in vitro*. They found that compound **261** exerted non-specific antiproliferative activity on the tested cell lines at the highest tested concentration (Fig 122).



(261)

Fig 122

Thimmegowda and his colleague[285] synthesized a series of trisubstituted benzimidazoles and evaluated for inhibition against MDA-MB-231 breast cancer cell proliferation. They conclude that compound that N-(4-cyano-3-(trifluoromethyl)phenyl)-4-fluoro-3-nitrobenzamide **(262)** was most active (Fig 123).



(262)

Fig 123

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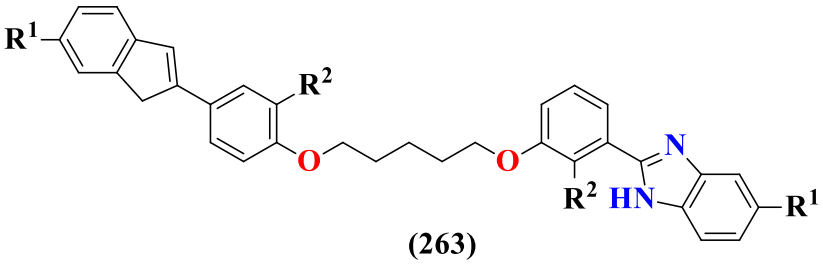
Gomez *et al.*[286] prepared a novel series of benzimidazole derivatives and further tested *in vitro* against the protozoa *viz. Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*, *Leishmania mexicana* and *Plasmodium berghei*. The tested compounds were compared with pentamidine and metronidazole and they found that compound **263** was most active (Fig 124).

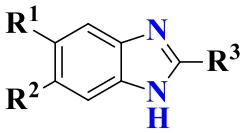


(263)

R^1 = H, OCH_3, CH_3, CF_3, $NO_2
R^2 = H, OCH_3

Fig 124

Valdez and his coworkers[287] synthesized 1-*H*-benzimidazoles and tested *in vitro* against the protozoa *G. lamblia*, *E. histolytica* and the helminth *T. spiralis*. The compounds were also screened for the inhibition of rat brain tubulin polymerization and compared with standard drug. They found that compound **264** was most active (Fig 125).



(264)

R^1 = R^2 = H, Cl
R^3 = H, CH_3, NH_2, $NHCO_2CH_3$, SH, SCH_3

Fig 125

Kazimierczuk and his colleague[288] prepared some thio-alkylated and thio-arylated derivatives of C-substituted benzimidazole and evaluated as antiprotozoal activity against nosocomial strains of *S. malthophilia* using metronidazole as standard. They found that compound 4,6,-dichloro-2-(4-nitrobenzylthio)-benzimidazole **(265)** showed the promising antiprotozoal activity (Fig 126).

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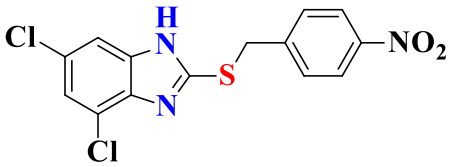
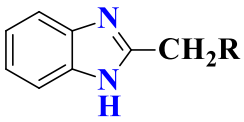


(265)

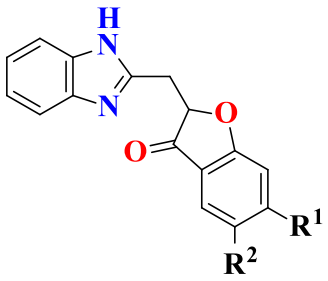
Fig 126

Khan and Nandan[289] synthesized 2-substituted benzimidazoles *via* condensation reaction between *o*-phenylenediamine and 2-maranonyl acetic acid derivatives and evaluated their anti-inflammatory and analgesic activities. They found that compounds **266** and **267** were found to have significant anti-inflammatory activity at 50 mg/kg dose (Fig 127).



(266)

R = indolyl, 3-skatolyl, 1-[2-(3-indolyl)-ethyl]

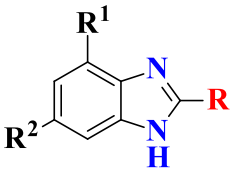


(267)

R^1= R^2 = H

Fig 127

Evans *et al.*[290] synthesized 1*H*-benzimidazole derivatives and evaluated their anti-inflammatory activity. The compounds were assessed on rat adjuvant arthritis screen and indomethacin as standard compound. They found that compound **268** was more active (Fig 128).



(268)

Fig 128

A series of novel 5-substituted-1-(phenylsulphonyl)-2-methylbenzimidazole derivatives have been synthesized by Gaba *et al*[291] and further screened for their anti-inflammatory and analgesic activities as well as gastric ulcerogenic effects by carrageenan-induced rat paw edema and acetic acid-

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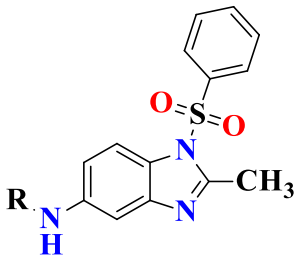
induced writhing in mice using indomethacin as standard. They found that compound **269** was more active (Fig 129).

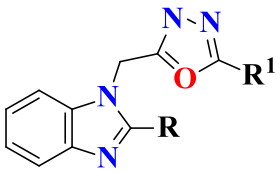


(270)

R = *o*-$NH_2C_6H_4$, *p*-$NH_2C_6H_4$, *p*-$NH_2C_7H_6$

Fig 129

Ansari and Lal[292] synthesized some derivatives of benzimidazoles and further evaluated toward Gram positive and Gram negative bacteria. They found that compound **270** showed moderate activity against tested fungi (Fig 130).



(270)

Fig 130

Mavrova and his coworkers[293] synthesized 1*H*-benzimidazole-2-yl thioacetylpiperazine derivatives and evaluated for their *in vitro* activity against *T. spiralis* as well as *in vivo* antinematode activity against *S. obvelata*. They found that compounds **271**, **272** and **273** were most active (Fig 131).

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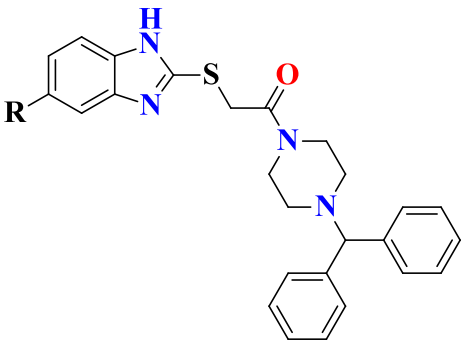
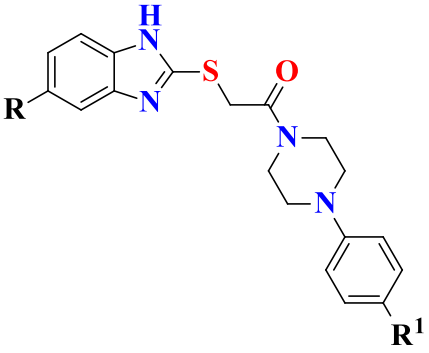


(271)

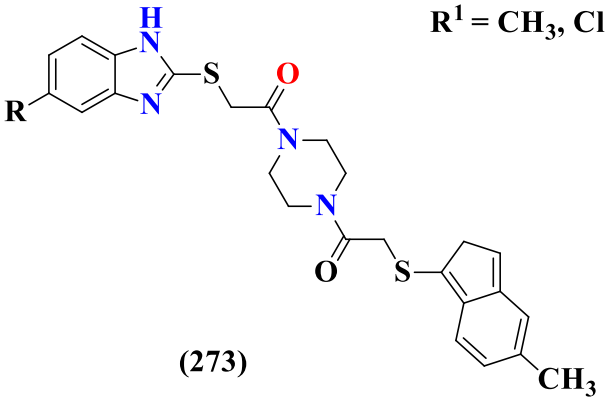
R = H, CH_3



(272)

R = H, CH_3, NO_2, Cl

R^1 = CH_3, Cl



(273)

R = H, CH_3

Fig 131

Conclusions

This review article demonstrates the green synthetic methods and biological activities of nitrogen and oxygen containing heterocycles. Benefits of these methods include clean reaction profiles, lack of side reactions, minimization of waste, efficient experimental procedures and cost-effective. This review is endeavouring to find potential future directions in the development of more potent and specific analogs of nitrogen and oxygen containing compounds for the biological target. The information illustrated in this review also encourage organic chemist for the design of novel molecules to identify many more biologically active heterocycles for the benefit of humanity.

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List of Abbreviations

RT Room temperature

IL Ionic liquid

MW Microwave irradiation

WEB Water extract of banana

SSC Silica sodium carbonate

MSA Molybdate sulphuric acid

PPA Polyphosphoric acid

SILLP Supported ionic liquid like phase

HPA Hteropolyacid

TFA Trifluoroacetate

TBAB Tetrabutylammonium bromide

DBSA Dodecylbenzenesulfonic acid

PPI Potassium phthalimide

SHP Sodium hypophosphite

SBSA Silica boron sulfonic acid

Conflicts of interest

Authors declared that there is no conflict of interest regarding the publication of this paper.

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References

1. R.O. Kennedy, R.D. Thornes, Coumarins: Biology, Applications and Mode of Action, John Wiley and Sons, Chichester, 1997.
2. M. Maeda, Laser Dyes, Academic Press, New York, 1984.
3. O. Kayser, H. Kolodziej, *Planta Med*., 1997, **63**, 508.

4. C.J. Wang, Y.J. Hsieh, C.Y. Chu, Y.L. Lin, T.H. Tseng, *Cancer Lett*., 2002, **183,** 163.
5. S. Kirkiacharian, D.T. Thuy, S. Sicsic, R. Bakhchinian, R. Kurkjian, T. Tonnaire, Il Farmaco, 2002, **57**, 703.
6. A.K. Mitra, A. De, N. Karchaudhuri, S.K. Misra, A.K. Mukopadhyay, *J. Indian Chem. Soc*., 1998, **75**, 666.
7. E.W. Hurst, R. J. Hull, *Med Chem*., 1961, **3**, 215-229.
8. E. Klein, S. DeBonis, B. Thiede, D.A. Skoufias, F. Kozielski, L. Lebeau, *Bioorg Med Chem*., 2007, **15**, 6474-6488.
9. B. Ramesh, C.M. Bhalgat, *Eur J Med Chem*., 2011, **46**, 1882-1891.
10. G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, *J Med Chem*., 1992, **35**, 3254-3263.
11. J. Cai, S. Li, C. Zhou and J. Wu, *Zhongguo Xinyao Zazhi*, 2009, **18**, 598–608.
12. G. Piérard, V. Vroome, M. Borgers, G. Cauwenbergh and C. Pierard-Franchimont, *Curr. Top. Pharmacol*., 2006, **10**(1), 59–65.
13. D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq and J. Balzarini, *Eur. J. Med. Chem*., 2009, **44**(6), 2347–2353.
14. S. Khabnadideh, Z. Rezaei, M. Motazedian and M. Eskandari, *Daru, J. Pharm. Sci*., 2007, **15**(1), 17–20.
15. C. K. Stover, P. Warrener, D. R. VanDevanter, D. R. Sherman, T. M. Arain, M. H. Langhorne, S. W. Anderson, J. A. Towell, Y. Yuan and D. N. McMurray, *Nature*, 2000, **405**(6789), 962–966.
16. M. Sánchez-Moreno, F. Gómez-Contreras, P. Navarro, C. Marín, I. Ramírez-Macías, F. Olmo, A. M. Sanz, L. Campayo, C. Cano and M. J. Yunta, *J. Antimicrob. Chemother*., 2012, **67**(2), 387–397.
17. D. Łażewska, M. Więcek, X. Ligneau, T. Kottke, L. Weizel, R. Seifert, W. Schunack, H. Stark and K. Kieć-Kononowicz, *Bioorg. Med. Chem. Lett*., 2009, **19**(23), 6682–6685.
18. S. C. Cherkofsky and T. R. Sharpe, *United States Pat*., US4190666, 1980.

19. G. Galley, H. Stalder, A. Goergler, M. C. Hoener and R. D. Norcross, *Bioorg. Med. Chem. Lett*., 2012, **22**(16), 5244–5248.

20. A. A. Hancock, Y. L. Bennani, E. N. Bush, T. A. Esbenshade, R. Faghih, G. B. Fox, P. Jacobson, V. Knourek-Segel, K. M. Krueger, M. E. Nuss and J. B. Pan, *Eur. J. Pharmacol*., 2004, **487**(1), 183–197.

21. P. Conti, M.D. Dallanoce, M.D. Amici, C.D. Micheli and K.N. Klotz, *Bioorg. Med. Chem*. 1998, **6**, 401.

22. M. Gordaliza, G.T. Faircloth, M.A. Castro, J.M. Corral, M.L. Vazque and A.S. Feliciano, *J. Med. Chem*. 1996, **39**, 2865.

23. T. Kwon, A.S. Heimann, E.T. Oriaku and K. Yoon, *J. Med. Chem*. 1995, **38**, 1048.

24. Y.K. Kang, K.J. Shin, K.H. Yoo, K.J. Seo, C.Y. Hong, C.S. Lee, S.Y. Park, D.J. Kim and S.W. Park, *Bioorg. Med. Chem. Lett*. 2000, **10**, 95.

25. A.P. Kozikowski, S. Tapadar, D.N. Luchini, K.H. Kim and D.D. Billadeau, *J. Med. Chem*. 2008, **51**, 4370.

26. C.V. Vicentini, C. Romagnoli, S. Manfredini, D. Rossi and D. Mares, *Pharm. Biol*. 2011, **49**, 545.

27. R.K. Reddy, S.P. Rao, J.G. Dev, Y. Poornachandra, G.C. Kumar, S.P. Rao and B.B. Narsaiah, *Bioorg. Med. Chem. Lett*. 2014, **24**, 1661.

28. A. Padmaja, C. Rajasekhar, A. Muralikrishna and V. Padmavathi, *Eur. J. Med. Chem*. 2011, **46**, 5034.

29. D.A. Patrick, S.A. Bakunov, S.M. Bakunova, E.V. Kumar, R.J. Lombardy, S.K. Jones, A.S. Bridges, O. Zhirnov, J.E. Hall, T. Wenzler, R. Brun, R.R. Tidwell, *J. Med. Chem*. 2007, **50**, 2468.

30. B. Loh, L. Vozzolo, B.J. Mok, C.C. Lee, R.J. Fitzmaurice, S. Caddick and A. Fassati, *Chem. Biol. Drug Des*. 2010, **75**, 461.

31. J. Mao, H. Yuan, Y. Wang, B. Wan, M. Pieroni, Q. Huang, R.B. Breemen, A.P. Kozikowski and S.G. Franzblau, *J. Med. Chem*. 2009, **52**, 6966.

32. B.L. Deng, M.D. Cullen, Z. Zhou, T.L. Hartman, R.W. Buckheit, C. Pannecouque, E. Declescq, P.E. Fanwick and M. Cushman, *Bioorg. Med. Chem*. 2006, **14**, 2366.

33. H. Kano, I. Adachi, R. Kido and K. Hirose, *J. Med. Chem*. 1967, **10**, 411.

34. T. Ishioka, A. Kubo, Y. Koiso, K. Nagasawa, A. Itaib, Y. Harshimotol, *Bioorg. Med. Chem*. 2002, **10**, 1555.

35. T. Ishioka, A. Tanatani, K. Nagasawa and Y. Hashimoto, *Bioorg. Med. Chem. Lett*. 2003, **13**, 2655.

36. H. Zarrinmayeh, A.M. Nunes, P.L. Ornstein, D.M. Zimmerman, M.B. Arnold and D.A. Schober, *J Med Chem*., 1998, **41**, 2709–2719.

37. M. Hasegawa, N. Nishigaki, Y. Washio, K. Kano, P.A. Harris and H. Sato, *J Med Chem*., 2007, **50**, 4453–4470.

38. M. Hranjec, M. Kralj, I. Piantanida, M. Sedic, L. Suman and K. Pavelic, *J Med Chem*., 2007, **50**, 5696–5711.

39. J. Falco, M. Pique, M. Gonzalez, I. Buira, E. Mendez and J. Terencio, *Eur J Med Chem*., 2006, **41**, 985–990.

40. M.S. Khan, R. Agrawal, M. Ubaidullah, M.I. Hassan and N. Tarannum, *Heliyon*, 2019, **5**, 1-12.

41. M.M. Heravi, M. Khorasani, F. Derikvand, H.A. Oskooie and F.F. Bamoharram, *Catal. Commun*., 2007, **8**, 1886-1890.

42. F.A. Hussien, J. Merza and A. Karam, *Chem. Material Res*., 2016, **8**, 16-20.

43. P.P. Ghosh and A.R. Das, *Tetrahedron Lett*., 2012, **53**, 3140-3143.

44. B. Halder, H.S Maity and A. Nag, *Curr. Organocatalysis*, 2019, **6**, 1-18.

45. J. Kovvuri, B. Nagaraju, C.G. Kumar, K. S. C. Chandrasekhar, A. Alarifi and A. Kamal, *J. of Saudi Chem. Soc*., 2018, **22**, 665-677.

46. H.V. Chavan and B.P. Bandgar, *ACS Sustain. Chem. Eng*., 2013, 1-8.

47. P. Wadhwa, A. Kharbana, S. Bagchi and A. Sharma, *ChemistrySelect*, 2018, **3**, 2837-2841.

48. R.S. Keri, K.M. Hosamani and H.R.S. Reddy, *Catal. Lett*., 2009, **131**, 321-327.

49. S. Das, A. Majee and A. Hajra, *Green Chem Lett and Rev*., 2011, **4**, 349-353.

50. S. Fiorito, V.A. Tddeo, S. Genovese and F. Epifano, 2016, **57**, 4795-4798.

51. S.D.Bagul, J.D. Rajput and R.S. Bendre, *Environ. Chem. Lett.*, 2017, **15**, 725-731.

52. B.S. Kuram, P.A. Crooks and B. Rajitha, *Int. J. Res. Pharm. and Biomed. Sci.*, 2012, **3**, 50-53.

53. A. Maleki, P. Ravaghi, H. Movahed and M. Aghaie, 2020, 1-7.

54. M. Farahi and M. Abdipur, *Org. Chem. Res.*, 2018, **4**, 182-193.

55. N.A. Greenwood, N. Earnshaw, Chemistry of the Elements, Pergamon, Oxford, 1984.

56. H. Mehrabi, H. Abusaidi, *J. Iran. Chem. Soc.*, 2010, **78**, 890.

57. S. Jain, D. Rajguru, B.S. Keshwal, A.D. Acharya, *Org. Chem*. 2013, 185120.

58. R. Ghorbani-Vaghaei, Z. Tghvaei-Semiromi, R. Karami-Nami, *J. Braz. Chem. Soc.*, 2011, **22**, 905.

59. S. Abdolmohammadi, S. Balalaie, *Tetrahedron Lett.*, 2007, **48**, 3299.

60. W. Xiang-Shan, Z. Zhao-Sen, S. Da-Qing, W. XianYong, Z. Zhi-Min, *Chin. J. Org. Chem.*, 2005, **25**, 1138.

61. S. Da-Qing, W. Jing, Z. Qi-Ya, W. Xiang-Shan, *Chin. J. Org. Chem.*, 2006, **26**, 643.

62. G. Brahamachari, *ACS Sustain Chem. & Eng.*, 2015, 1-34.

63. L. Dinparast and H. Valizadeh, *Iran. J. Org. Chem.*, 2014, **6**, 1341-1345.

64. A. Rahamatpour and S. Mohammadian, *C.R. Chimie*, 2013, **16**, 271-278.

65. C. Shi and D. Shi, *J Chem Res*., 2011, 585-586.

66. P.G. Mandhane, R.S. Joshi, A.R. Ghawalkar, G.R. Jadhav and C.H. Gill, *Bull. Korean Chem. Soc*., 2009, **30**, 2969-2972.

67. X.T. Li, Y. H. Liu, X. Liu and Z. H. Zhang, *RSC Adv*., 2015, **5**, 25625-25633.

68. Mayank, A. Singh, P. Raj, R. Kaur, A. Singh, N. Kaur and N. Singh, *New J. Chem.*, 2017, **41**, 3872-3881.

69. S. Khodabakhshi, B. Karami and K. Eskandari, *Res. Chem. Intermed*., 2014, 1-10.

70. H.A. Ardakani, B. Mirza and N. Mokhtarian, *J App Chem Res*., 2015, **9**, 103-110.

71. H. Kiyani and F. Ghorbani, *J Saudi Chem Soc*., 2014, 1-13.

72. Z. Zhou, H. Liu, Y. Li, J. Liu, Y. Li, J. Liu, J. Yao and C. Wang, *ACS Comb Sci*., 2013, 1-7.

73. Z. Shao, L. Xu, L. Wang, H. Wei and J. Xiao, *Org. Biomol. Chem.*, 2014, 1-3.

74. M.R.N. Jamal, S. Mashkouri and A. Sharifi, *Mol. Divers*., 2010, **14**, 473-477.

75. Z. Piruzmand, J.S. Ghomi and M.A. Ghasemzadeh, *Bul. Chem. Commun*., 2016, **48**, 619-623.

76. S. Santra, M. Rahman, A. Roy, A. Majee and A. Hajra, *Org. Chem. Int*., 2014, 1-8.

77. T. Pramanik and P. Maji, *Int. J. of Pharm. Pharm. Sci.*, 2015, **7**, 376.

78. N. Sharma, U.K. Sharma, R. Kumar, Richa and A.K. Sinha, *RSC Adv*., 2012, 1-4.

79. J. Lal, S.K. Gupta and D.D. Agarwal, *Catal commun*., 2012, **27**, 38-43.

80. B.C. Ranu, A. Hajra and S.S. Dey, *Org Process Res Dev.*, 2002, *6*, 817-818.

81. E. Rafiee and H. Jafari, *Bioorg. Med. Chem. Lett*., 2006, **16**, 2463-2466.

82. S. Patil, S. D. Jhadav and U. P. Patil, *Arch. Appl. Sci. Res.*, 2011, **3**, 203.

83. T. Pramanik and S.K. Padan, *Int. J. Pharm. Pharm. Sci*., 2016, **8**, 396-398.

84. B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem*., 2000, **65**, 6270-6272.

85. Suresh, A. Saini, D. Kumar and J.S. Sandhu, *Green chem lett rev.*, 2009, **2**, 29-33.

86. D. Kumar, Suresh and J.S. Sandhu, *Indian J. Chem.*, 2010, **49B**, 360-363.

87. M.Z. Dastmalbaf, A. Davoodnia, M.M. Heravi, N.T. Hoseini, A. Khojastehnezhad and H.A. Zamani, *Bull. Korean Chem. Soc*., 2011, **32**, 656-658.

88. T. Sekhar, P. Thriveni, M. Harikrishna and K. Murali, *Asian J. Chem*., 2018, **30**, 1243-1246.

89. A. Amoozadeh, S. Rahmani and F. Nemati, *Heterocycl. Commun*., 2013, **19**, 69-73.

90. K.K. Pasunooti, H. Chai, C.N. Jensen, B.K. Gorityala, S. Wang and X.W. Liu, *Tetrahedron Lett*., 2011, **52**, 80-84.

91. L. Moradi and M. Tadayon, *J. Saudi Chem. Soc*., 2018, **22**, 66-75.

92. S. Patil, S.D. Jadhav and S.Y. Mane, *Int. J. Org. Chem.*, 2011, **1**, 125-131.

93. J. Safari and S.G. Ravandi, *J. Mol. Struct*, 2014, 1-7.

94. G.K.S. Prakash, H. Lau, C.Panja, I. Bychinskaya, S.K.Ganesh, B. Zaro, T. Mathew and G. A. Olah, *Catal. Lett*. 2014, 1-9.

95. N.K. Khellafi, M.M. Chebli, D.O. Hikem, S.T. Bouaziz, K.O. Lamara, T. Idir, A.B. Touami and F. Dumas, *J. Mol. Struct*., 2019, **1181**, 261-269.

96. S.R. Mathapati, D. Prasad, A.B. Atar, B.M. Nagaraja, J.K. Dawle and A.H. Jadhav, *Mater Today*, 2019, **9**, 661–668.

97. D. Elhamifar, P. Mofatehnia and M. Faal, *J Colloid Interface Sci*., 2017, **504**, 268-275.

98. R.K. Sharma and D. Rawat, *Inorg Chem Commun*., 2012, **17**, 58-63.

99. J. Lal, M. Sharma, S. Gupta, P. Parashar, P. Sahu and D.D. Agarwal, *J Mol Catal A-Chem*., 2012, **352**, 31-37.

100. H. Eshghi, A. Javid, A. Khojastehnezhad, F. Moeinpour, F.F. Bamoharram, M. Bakavoli and M. Mirzaei, *Chinese J Catal.*, 2015, **36**, 299-307.

101. H. Adibi, H.A. Samimi and M. Beygzadeh, *Catal. Commun*., 2007, **8**, 2119-2124.

102. S. Verma, S.L. Jain and B. Sain, *Tetrahedron Lett*., 2010, 51, 6897-6900.

103. P. Attri, R. Bhatia, J. Gaur, B. Arora, A. Gupta, N. Kumar and E.H. Choi, *Arabian J. Chem*., 2017, **10**, 206-214.

104. R. Gupta, S. Paul and R. Gupta, *J. Mol. Catal. A Chem*., 2007, **266**, 50-54.

105. S. Harsh, S. Kumar, R. Sharma, Y. Kumar and R. Kumar, *Arabian J. Chem*., 2020, **13**, 4720-4730.

106. M.N. Esfahani, S.J. Hoseini and F. Mohammadi, *Chin. J. Catal*., 2011, **32**, 1484-1489.

107. S. Bajpai and S. Singh, *Mater Today.*, 2017, **4**, 10498-10503.

108. A. Akbari, *Tetrahedron Lett*., 2015.

109. M.S Jourshari, M. Mamaghani, F. Shirini, K. Tabatabaeian, M. Rassa and H. Langari, *Chinese Chem Lett.*, 2013, 1-4.

110. A.R. Khosropour, *Ultrason Sonochem.*, 2008, **15**, 659-664.

111. G. M. Ziarani, A. Badiei, N. Lashgari and Z. Farahani, *J Saudi Chem Soc*., 2016, **20**, 419-427.

112. A. Keivanloo, M. Bakherad, E. Imanifar and M. Mirzaee, *Appl Catal A: Gen*., 2013, 1-26.

113. M.M. Heravi, F. Derikvand and F. F. Bamoharram, *J Mol Catal A: Chem*., 2007, **263**, 112-114.

114. R. Kumar, V. Dhayabaran, N. Sudhapriya, A. Manikandan, D.A. Gideon and S. Annapoorani, *Bioorg. Chem.*, 2020, 1-56.

115. N. Kerru, L. Gummidi, S. N. Maddila, K.K. Gangu and S.B. Jonnalagadda, *Inorg Chem Commun*., 2020, **116**, 1-7.

116. M.R.P. Heravi, E. Vessally and G.R.R. Behbehani, *CR Chim*., 2014, **17**, 146-150.

117. S. Naidoo and V. Jeena, *Tetrahedron*, 2020, 76, 1-10.

118. N. Thimmaraju and S.Z.M. Shamshuddin, *RSC Adv*., 2016, 1-33.

119. D. I. MaGee, M. Bahramnejad and M. Dabiri, *Tetrahedron Lett*., 2013, 1-4.

120. X. Guo, J. Shao, H. Liu, B. Chen, W. Chen and Y. Yu, *RSC Adv*., 2015, 1-5.

121. D. Kumar, N.M. Kumar, G. Patel, S. Gupta and R.S. Verma, *Tetrahedron Lett*., 2011, **52**, 1983-1986.

122. M. Kidwai, P. Mothsra, V. Bansal, R.K. Somavanshi, A.S. Ethayathulla, S. Dey and T.P Singh, *J Mol Catal A: Chem*, 2007, **265**, 177-182.

123. J. Banothu, R. Gali, R. Velpula and R. Bavantula, *Arabian J. Chem*., 2017, **10**, 2754-2761.

124. A.R. Karimi, Z. Alimohammadi, J. Azizian, A.A. Mohammadi and M.R. Mohammadizadeh, *Catal Commun*., 2006, **7**, 728-732.

125. M.V. Chary, N.C. Keerthysri, S.V.N. Vupallapati, N. Lingaiah and S. Kantevari, *Catal Commun*., 2008, **9**, 2013-2017.

126. A. Maleki and R. Paydar, *RSC Adv*., 2015, **5**, 33177-33184.

127. B. Sadeghi, B.B.F. Mirjalili and M.M. Hashemi, *Tetrahedron Lett*., 2008, **49**, 2575-2577.

128. Z. Zarnegar and J. Safari, *RSC Adv*., 2014, **4**, 20932-20939.

129. Z. Varzi and A. Maleki, *Appl organomet Chem*., 2019, 1-11.

130. J. Safari and Z. Zarnegar, *Iran. J. Catal*., 2012, **2**, 121-128.

131. B. Das, J. Kashanna, R.A. Kumar and P. Jangili, *Montash Chem*., 2013, **144**, 223-226.

132. T.H. Niloofar and D. Abolghasem, *Chin. J. Chem*., **29**, 203-206.

133. A. Davoodnia, M.M. Heravi, Z. S. Rad and N.T. Hoseini, *Synth. Commun*., 2010, **40**, 2588-2597.

134. D.R. Meena, B. Maiti and K. Chanda, *Tetrahedron Lett*., 2016, **57**, 5514-5517.

135. S.N. Maddila, S. Maddila, W.E.V. Zyl and S.B. Jonnalagadda, *Res Chem Intermed*., 2015, 1-14.

136. M.M. Heravi, F. Derikvand, A. Haeri, H. A. Oskooie and F.F. Bamoharram, *Synth. Commun*., 2008, **38**, 135-140.

137. G. Dou, P. Xu, Q. Li, Y. Xi, Z. Huang and D. Shi, *Molecules*, 2013, **18**, 13645-13653.

138. M.G. Dekamin and S.Z. Peyman, *Monatsh Chem*., 2015, 1-6.

139. H. Kiyani and F. Ghorbani, *Res Chem Intermed*., 2016, **42**, 6831-6844.

140. L. Han, B. Zhang, M. Zhu and J. Yan, *Tetrahedron Lett*., 2014, **55**, 2308-2311.

141. M.S. Patil, C. Mudaliar and G.U. Chaturbhuj, *Tetrahedron Lett*., 2017, **58**, 3256-3261.

142. S.B. Bharate, A.K. Padala, B.A. Dar, R.R. Yadav, B. Singh and R.A. Vishwakarma, *Tetrahedron Lett*., 2013, 1-6.

143. H. Beyzaei, M.K. Deljoo, R. Aryan, B. Ghasemi, M.M. Zahedi and M.M. Manesh, *Chem Cent J*., 2018, **12**, 1-8.

144. M. Ahmadzadeh, Z. Zarenegar and J. Safri, Green *Chem Lett Rev*., 2018, **11**, 78-85.

145. Q. Liu and Y.N. Zhang, *Bull. Korean Chem. Soc*., 2011, **32**, 3559-3560.

146. M. Kalhor, S. Samiel and S.A. Mirshokraie, *Silicon*, 2020, 1-10.

147. H. Kiyani and F. Ghorbani, *Res Chem Intermed*., 2015, 41, 2653-2664.

148. E. Rajanarendar, K.R. Murthy and M. N. Reddy, *Indian J. Chem*., 2011, **50B**, 926-930.

149. H. Kiyani and F. Ghorbani, *J. Saudi Chem Soc*., 2017, **21**, S112-S119.

150. M. Shanshak, S. Budagumpi, J.G. Malecki and R.S. Keri, *Appl Organome Chem*., 2019, 1-6.

151. J.M. Perez and D.J. Ramon, *ACS Sustain Chem Eng*., 2015, 1-7.

152. Y. Zhang, B.W Wei, H. Lin, L. Zhang, J. X. Liu, H.Q. Luo and X. L. Fan, *Green Chem*., 2015, 1-6.

153. A.P. Tayade, R.P. Pawar, R.V. Khobare, C.B. Mane and N.P. Tayde, *Int J. Innov Sci Res Technol*., 2019, 4, 358-360.

154. N.I. Gheshlaghchaei, A. Zare, S.S. Sajadikhah and A. Banaei, *Res Chem Intermed*., 2018, 1-14.

155. P. Basak, S. Dey and P. Ghosh, *Chemistry Select*, 2020, **5**, 626-636.

156. H.R.S. Moshtaghin, B.Maleki, R.Tayebee, S. Kahrobaei and F. Abbasinohoji, *Polycycl Aromat Comp*, 2020, 1-13.

157. X.D. Wang, L.H. Zhu, P. Liu, X.Y. Wang, H.Y. Yuan and Y.L. Zhao, *J. Org. Chem*., 2019, **84**, 16214-16221.

158. K.D. Dwivedi, S.R. Marri, S.K. Nandigama and R.L. Chowhan, *J. Chem. Sci*., 2018, **130**, 1-6.

159. H. Kiyani and F. Ghorbani, *http://heteroletters.org*., 2013, **3**, 359-369.

160. R. Ponduri, P. Kumar, L.R. Vadali and N.R. Modugu, *ChemistrySelect*, 2018, **3**, 7766-7770.

161. F. Saikh, J. Das and S. Ghosh, *Tetrahedron Lett*., 2013, 1-15.

162. R. Zheng, F. Feng, Z. Zhang, J. Fu, Q. Su, Y. Zhang and Q. Gu, *Mol Divers*., 2019, 1-13.

163. S. Yaghoub and E. Mohammad, *Iran. J. Chem. Chem. Eng*., 2016, **35**, 9-13.

164. S. Gulati, R. Singh, S. Sangwan and S. Rana, *J. Iran. Chem. Soc*., 2020, 1-13.

165. S. Gulati, R. Singh, J. Sindhu and S. Sangwan, *Org. Prep. Proced. Int*., 2020, 1-16.

166. M.M. Heravi, M. Tajbakhsh, A.N. Ahmadi and B. Mohajerani, *Monatshefte f€ur Chemie*., 2006, **137**, 175-179.

167. G.F. Chen, H.D. Shen, H.M. Jia, L.Y. Zhang, H.Y. Kang, Q.Q. Qi, B.H. Chen, J.L. Cao and J.T. Li, *Aust. J. Chem*., 2013, **66**, 262-266.

168. A. Pramanik, R. Roy, S. Khan, A. Ghatak and S. Bhar, *Tetrahedron Lett*., 2014, **55**, 1771-1777.

169. V.S. Padalkar, V.D. Gupta, K.R. Phatangare, V.S. Patil, P.G. Umape and N. Sekar, *Green Chem Lett Rev*., 2011, **5**, 139-145.

170. M.M. Heravi, S. Sadjadi, H.A. Oskooie, R.H. Shoar and F.F. Bamoharram, *Catal Commun*., 2007, **9**,504-507.

171. J. Lu, B. Yang and Y. Bai, *Synth. Commun*., 2002, **32**, 3703-3709.

172. A. Dhakshinamoorthy, K. Kanagraj and K. Pitchumani, *Tetrahedron Lett*., 2011, **52**, 69-73.

173. B. Karami, V. Ghashghaee and S. Khodabakshshi, *Catal. Commun*., 2012, **20**, 71-75.

174. M. Dabiri, P. Salehi, M. Baghbanzadeh and M.S. Nikcheh, *Synth Commun*., 2008, **38**, 4272-4281.

175. M. Kidwai, A. Jahan and D. Bhatnagar, *J. Chem. Sci*., 2010, **122**, 607-612.

176. D. Kathirvelan, P. Yuvaraj, K. Babu, A.S. Nagarajan and B.S.R. Reddy, *Indian J. Chem*., 2013, **52B**, 1152-1156.

177. S. Sajjadifar, S.A. Mirshokraie, N. Javaherneshan and O. Louie, *American J. Org. Chem*., 2012, **2**, 1-6.

178. B. Chen, C. Zhang, L. Niu, X. Shi, H. Zhang, X. Lan and G. Bai, *Chem European J*. 1-9.

179. F. Rajabi, S. De and R. Luque, *Catal. Lett*, 2015, 1-5.

180. H. Sharma, N. Kaur, N. Singh and D.O. Jang, *Green Chem*., 2015, 1-18.

181. R.M. Borade, P.R. Shinde, S.B. Kale and R.P. Pawar, *AIP Conference Proceedings*, 2018, **1953**, 1-6.

182. H.M. Bachhav, S.B. Bhagat and V.N. Telvekar, *Tetrahedron Lett*., 2011, **52**, 5697-5701.

183. G. Bai, X. Lan, X. Liu, C. Liu, L. Shi, Q. Chen and G. Chen, 2014, *Green Chem*., **16**, 3160.

184. D. Yang, X. Zhu, W. Wei, N. Sun, Li. Yuan, M. Jiang, J. You and H. Wang, *RSC Adv*., 2014, **4**, 17832.

185. S.D. Sharma and D. Konwar, *Synth Commun*., 2009, **39**, 980-991.

186. L.S. Gadekar, B.R. Arbad and M.K. Lande, *Chinese Chem Lett*., 2010, **21**, 1053-1056.

187. F. Ahmad and M. Parveen, *New J. Chem*., 2018, 1-31.

188. B. Sadeghi and M.G. Nejad, *J. Chem*., 2013, 1-6.

189. Z.K. Jaberi and M. Amiri, *J. Chem*., 2012, **9**, 167-170.

190. V.U. Vernekar, K.M. Hosamani, I.N. Shaikh and K.C.S. Achar, *Arabian J. Chem*., 2011, 1-5.

191. N.H. Cano, J.G. Urenga, M. Nardi, A. Procopio, D.A. Wunderlin and A.N. Santiago, *Beilstein J. Org. Chem*., 2016, **12**, 2410-2419.

192. S. Samanta, C. Guha and A.K. Malik, *Eur. Chem. Bull.*, 2014, **3**, 396-399.

193. S. Bonacci, G. Iriti, S. Mancuso, P. Novelli, R. Paonessa, S. Tallarico and M. Nardi, 1-12.

194. T. W. Wu, L. H. Zeng, J. Wu and K. P. Fung, *Life Sci*., 2002, **71**, 2249.

195. K.C. Fylaktakidou, D.J.H. Litinas, K.E. Litinas and D.N. Nicolaides, *Curr. Pharm Des*. 2004, **10**, 3813-3833.

196. M. Curini, G. Cravotto, F. Epifano and G. Giannone, *Curr Med Chem*., 2006, **13**, 199-222.

197. V. Maddi, K.S. Raghu and M.N.A. Rao, *J Pharm Sci*., 1992, **81**, 964–966.

198. D.N. Nicolaides, K.C. Fylaktakidou, K.E. Litinas and D.H. Litina, *Eur J Med Chem*., 1998, **33**, 715–724.

199. M. Mazzeia, R. Donderoa, E. Sottofattoria, E. Mellonib and R. Minafrab, *Eur J Med Chem*., 2001, **36**, 851–861.

200. J.F. Cheng, M. Chen, D. Wallace, S. Tith, T. Arrhenius, H. Kashiwagi, Y. Ono, A. Ishikawa, H. Sato, T. Kozono, H. Satob and A.M. Nadzan, *Bioorg Med Chem Lett*., 2004, **14**, 2411–2415.

201. C.A. Kontogiorgis and D.J. Hadjipavlou-Litina, *Bioorg Med Chem Lett*., 2004, **14**, 611–614.

202. M. Ghate, R.A. Kusanur and M.V. Kulkarni, *Eur J Med Chem*., 2005, **40**, 882–887.

203. I.A. Khan, M.V. Kulkarni, M. Gopal, M.S. Shahabuddinb and C.M. Sun, *Bioorg Med Chem Lett*., **15**, 3584–3587.

204. S.A. Jackson, S. Sahini, L. Lee, Y. Luo, T.R. Nieduzak, G. Liang, Y. Chiang, N. Collar, D. Fink, W. He, A. Laoui, J. Merrill, R. Boffey, P. Crackett, B. Ress, M. Wong, J.P. Guilloteau, M. Mathieuc and S.S. Rabelloa, *Bioorg Med Chem*., **13**, 2723–2739.

205. C.A. Kontogiorgis, K. Savvoglou, D.J. Hadjipavlou-Litina, *J Enzyme Inhib Med Chem*., **21**, 21–29.

206. R.N. Gacche, D.S. Goud, N.A. Dhole and B.S. Dawane, *J Enzyme Inhib Med Chem*., **21**, 157–161.

207. C.M. Lin, S.T. Huang, F.W. Lee, H.S. Kuoa and M.H. Lin, *Bioorg Med Chem*., 2006, **14**, 4402–4409.

208. R.G. Kalkhambkar, G.M. Kukarni, H. Shivkumar and R.N. Rao, *Eur J Med Chem*., 2007, **42**, 1272–1276.

209. G. Sandeep, Y.S. Ranganath, S. Bhasker and N. Rajkumar, *Asian J Res Chem*., 2009, **2**, 155–160.

210. G. Melagraki, A. Afantitis, O.I. Markopoulou, A. Detsi, M. Koufaki, C. Kontogiorgis, D.J. Hadjipavlou-Litina, *Eur J Med Chem*., 2009, **44**, 3020–3026.

211. Y. Bansal, S. Ratra, G. Bansal, I. Singh, H.Y. Aboul-Eneinc, *J Iran Chem Soc*., 2009, **6**, 504–509.

212. C.P.K. Reddy, V.M. Goud, N. Sreenivasula and R. Prasad, *Int J Pharma World Res*., 2010, **1,** 1–19.

213. M. Roussaki, C.A. Kontogiorgis, D. Hadjipavlou-Litina, S. Hamilkis and A. Detsi, *Bioorg Med Chem Lett*., 2010, **20**, 3889–3892.

214. S. Fatima, A. Sharma, R. Saxena, R. Tripathi, S.K. Shukla, S.K. Pandey, R. Tripathi and R.P. Tripathi, *Eur J Med Chem*., 2012, **55**, 195–204.

215. J.L. Brodsky, A.N. Chiang, J.C. Valderramos, R. Balachandran, R.J. Chovatiya, B.P. Mead, C. Schneider, S.L. Bell, M.G. Klein, D.M. Huryn, X.S. Chen, B.W. Day, D.A. Fidock and P. Wipf, *Bioorg Med Chem*., 2009, **17**, 1527–1533.

216. M.S. Islam, A. Barakat, A.M. Al-Majid, H.A. Ghabbour, H.K. Fun, K. Javed, R. Imad, S. Yousuf, M.I. Choudhary and A.Wadood, *Bioorg Med Chem*., 2015, **23**, 6740–6748.

217. R.P. Tripathi, B.S. Srivastava, N. Tiwari, V.K. Tiwari, R.C. Mishra, A.K. Srivastava, R. Ahmad and R. Srivastava, *Bioorg Med Chem*., 2003, **11**, 2911–2922.

218. K. Rana, B. Kaur, G. Chaudhary, S. Kumar and S. Goyal, *Int J. Pharm. Sci Drug Re*s., 2011, **3**, 226-229.

219. J. Lal, S.K. Gupta, D. Thavaselvam and D.D. Agrawal, *Bioorg Med Chem Lett*., 2012, **22**, 2872–2876.

220. E.J. Hanan, M. Baurngardner, M.C. Bryan, Y. Chen, C. Eigenbrot, P. Fan, X. H. Gu, H. La, S. Malek, H.E. Purkey, G. Schaefer, S. Schmidt, S. Sideris, I. Yen, C. Yu and T.P. Heffron, *Bioorg Med Chem Lett*., 2016, **26**, 534–539.

221. H.A. Tawtik, F. Bassyouni, A.M.G-Eldeen, M.A.A. Zeid and W.S.E. Hamouly, *Pharmcol. Rep*., 2009, **61**, 1153-1162.

222. O.M. Singh, S.G. Lee, S.J. Singh, M.B. Devi, L.N. Devi, N.I. Singh and S.G. Lee, *Bioorg Med Chem Lett*., 2008, **18**, 6462–6467.

223. M. Ashok, B.S. Holla and N.S. Kumari, *Eur J Med Chem*., 2007, **42**, 380-385.

224. B.P. Kumar, G. Sankar, R.N. Baig and S. Chandrashekaran, *Eur J Med Chem*., 2009, **44**, 4192-4198.

225. O. Sari, V. Roy, M. Metifiot, C. Marchand, Y. Pommier, S. Bourg, P. Bonnet, R.F. Schinazi and L.A. Agrofoglio, *Eur J Med Chem*., 2015, **104**, 127-138.

226. A.R. Trivedi, V.R. Bhuva, B.H. Dholariya, D.K. Dodiya, V.B. Kataria and V.H. Shah., *Bioorg Med Chem Lett*., **20**, 6100–6102.

227. H.M. Aly and M.M Kamal, *Eur J Med Chem*., 2012, **47**, 18-23.

228. E. Rajanarendar, M.N. Reddy, K.R. Murthy. K.G. Reddy, S. Raju, M. Srinivas, B. Praveen and M.S. Rao, *Bioorg Med Chem Lett*., 2010, **20**, 6052–6055.

229. P. Attri, R. Bhatia, J. Gaur, B. Arora, A. Gupta, N. Kumar and E.H. Choi, *Arab. J. Chem*., 2017, **10**, 206-214.

230. B. Singh, M. Mishra, N. Saxena, G. Yadav, P. Maulik, M. Sahoo, R. Gaur, P. Murthy and R. Tripathi., *Eur J Med Chem*., **43**, 2717-2723.

231. S.M. Sondhi, R.N. Goyal, A.M. Lahoti, N. Singh, R. Shukla and R. Raghubir, *Bioorg Med Chem*., 2005, **13**, 3185–3195.

232. S.G. Khange, S.A. Raju, P.B. Mohite and R.B. Pandhare, *Adv. Pharm. Bull*., 2012, **2**, 213-222.

233. R.K. Yadlapalli, O. Chourasia and R.S. Perali, *Tetrahedron Lett*., 2012, **53**, 6725-6728.

234. R.V. Shingalapur, K. M. Hosamani and R.S. Keri, *Eur J Med Chem*., 2009, **44**, 4244-4248.

235. D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E.D. Clercq and J. Balzarini, *Eur J Med Chem*., 2009, **44**, 4244-4248.

236. D. Zampieri, M.G. Mamolo, L. Vio, E. Bnafi, G. Scialino, M. Fermeglia, M. Ferrone and S. Pricl, *Bioorg Med Chem*., 2007, **15**, 7444–7458.

237. D. Olender, J. Zwawiak, V. Lukianchuk, R. Lesyk, A. Kropacz, A. Fojutowaski and L. Zaprutko, *Eur J Med Chem*., 2009, **44**, 645-652.

238. A. Puratchikodya and M. Doble, *Bioorg Med Chem*., 2007, 15, 1083–1090.

239. K.C.S. Achar, K.M. Hosamani and H.R. Seetharamareddy, *Eur J Med Chem*., 2010, **45**, 2048-2054.

240. P. Gupta, S. Hameed and R. Jain, *Eur J Med Chem*., 2004, **39**, 805-814.

241. J. Pandey, T.K. Vinod, V.S. Shyam, C. Vinita, S. Bhatnagar, S. Sinha, A.N. Gaikwad and R.P. Tripathi, *Eur J Med Chem*., 2009, **44**, 3350-3355.

242. Y. Ozkay, I. Iskar, Z. Incesu and G.E. Akalin, *Eur J Med Chem*., 2010, 1-9.

243. H.M. Refaat, *Eur J Med Chem*., 2010, **45**, 2949-2956.

244. C. Congiu, M.T. Cocoo and V. Onnis, *Bioorg Med Chem*., 2008, **18**, 989–993.

245. M. Tonelli, M. Simone, B. Tasso, F. Novelli and V. Boido, *Bioorg Med Chem*., 2010, **20**, 2937–2953.

246. K. Bhandari, N. Srinivas, V.K. Marrapu, A. Verma, S. Srivastava and S. Gupta, *Bioorg Med Chem*., 2010, **20**, 291–293.

247. S.P. Zala, R. Badmanaban, D.J. Sen and C.N. Patel, *J. Applied Pharm. Sci*., 2012, **2**, 202-208.

248. G. Prasanthy, KV. Ramana, V.K. Reddy, K. Nirmala and N.R. Kumar, *Int. J. Pharma*, 2011, **1**, 92-99.

249. D. Carvalho, P.A. Machado, D.T.S. Paula, E.S. Coimbra and A.D. de Silva, *Scient. World J*., 2010, **10**, 1723-1730.

250. G. Gopinath, S. R. Sagurthi, S. Perugu, G. Achaiah and G. D. Krupadanam, *RSC Adv*., 2014, **4**, 56489–56501.

251. P. Dao, N. Smith, C. Tomkiewicz-Raulet, E. Yen-Pon, M. Camacho-Artacho, D. Lietha, J.-P. Herbeuval, X. Coumoul, C. Garbay and H. Chen, *J. Med. Chem*., 2014, **58**, 237–251.

252. H. Sarkarzadeh, R. Miri, O. Firuzi, M. Amini, N. RazzaghiAsl, N. Edraki and A. Shafiee, *Arch. Pharmacal Res*., 2013, **36**, 436–447.

253. H. M. Alkahtani, A. Y. Abbas and S. Wang, *Bioorg. Med. Chem. Lett*., 2012, **22**, 1317–1321.

254. J. Sun, C. Lin and X. Qin, *Bioorg. Med. Chem. Lett*., 2015, **25**, 3129–3134.

255. D. Chen, A. Shen and J. Li, *Eur J Med Chem*., 2014, **87**, 765–781.

256. H. Ananda, K.S.S. Kumar, M. Hegde and K.S. Rangappa, *Mol Cell Biochem*., 2016, **420**, 141-150.

257. S. Rao, C. Kurumurthy, B. Veeraswamy, Y. Poornachandra, G. Kumar and B. Narsaiah, *Bioorg. Med. Chem. Lett*., 2014, **24**, 1349–1351.

258. S.R. Pedada and N.S. Yarla and P.J. Tambade, *Eur J Med Chem*., 2016, **112**, 289–297.

259. N. Ashwini, M. Garg and C.D. Mohan, *Bioorg Med Chem*., 2015, **23**, 6157-6165.

260. S. Pan, J. Hu, T. Zheng, X. Liu, Y. Ju and C. Xu, Cytotechnology, 2015, **67**, 821-829.

261. J. Shaw, B. Chen and J.P. Bourgault, *Am. J. Biomed Sci*., 2012, **4**, 14-25.

262. D. Zhang, J. Jia, L. Meng, W. Xu, L. Tang and J. Wang, *Arch Pharm Res*., 2010, **33**, 831-842.

263. N.M. Hamada and E.M. Sharshira, *Molecules*, 2011, **16**, 2304-2312.

264. K.A. Ali, H.M. Hosni, E.A. Rageb and S.I. Moez, *Arch Pharm*., 2012, **345**, 231-239.

265. E. Rajanarendar, M.N. Reddy, S.R. Krishna, K.G. Reddy, Y.N. Reddy and M.V. Rajam, *Eur J Med Chem*., 2012, **50**, 344–349.

266. G. Saravanam, V. Alagarsamy and P. Dineshkumar, *Arch Pharm Res*., 2013.

267. G. Lavanya, L.M. Reddy, V. Padmavathi and A. Padmaja, *Eur J Med Chem*., 2014, **73**, 187–194.

268. K.J. Swapnaja, S. Yennam and M. Chavali, *Eur J Med Chem*., 2016, **117**, 85-98.

269. K.M. Naidu, S. Srinivasarao, N. Agnieszka, A.K. Ewa, M.M.K. Kumar and K.V.G. Chandra Sekhar, *Bioorg. Med. Chem. Lett*., 2016, **26**, 2245–2250.

270. M. Maczynski, J. Artym, M. Kocieba, I. Kochanowska, S. Ryng and M.Zimecki, *Pharmacol Rep*., 2016, **68**, 894-902.

271. K.S. Rakesh, S. Jagadish and K.S. Balaji, *Inflammation*, 2016, **39**, 269-280.

272. E. Banoglu, E. Celikoglu and S. Volker, *Eur J Med Chem*., 2016, **113**, 1-10.

273. M.G. Perrone, P. Vitale, A. Panella, S. Ferorelli, M. Contino, A. Lavecchia and A. Scilimati, *Chem Med Chem*., 2016, **11**, 1172-1187.

274. K.F. Ansari and C. Lal, *Eur J Med Chem*., 2009, **44**, 2294.

275. K.M. Ghoneim, M.Y.H. Essawi, M.S. Mohamed and A.M. Kamal, *Ind . J. Chem*., 1998, **37B**, 904.

276. S.P. Gupta and S. Rani, *J. Ind. Chem. Soc*., 1997, *LIV*, 478.

277. D.V. Mane, D.B. Shinde, S.N. Thore and M.S. Shingare, *Ind. J. Chem*., **34B**, 917.

278. B.V.S. Kumar, S.D. Vaidya, R.V. Kumar, S.B. Bhirud and R.B. Mane, *Eur J Med Chem*., 2006, **41**, 599.

279. A. Bishnoi, V.K. Pandey and R. Saxena, *Ind. J. Chem*., 2002, **41B**, 1978.

280. J. Gowda, A.M.A. Khadar, B. Kalluraya and N.S. Kumari, *Ind. J. Chem*., 2010, **49B**, 1130.

281. N.P Shetgiri and S.V. Kokitkar, *Ind. J. Chem*., 2001, **40B**, 163.

282. V.K. Pandey and A. Shukla, *Ind. J. Chem*., 1999, **38B**, 1381.

283. S. Kristina, M. Marijeta, E. Katja, S. Ivan, G. Magdalena, P. Kresimir and K.Z. Grace, *Bioorg Med Chem*., 2007, **15**, 4419.

284. M. Hranjec, K. Starcevic, S.K. Pavellic, P. Lucin, K. Pavellic and G.K. Zamola, *Eur J Med Chem*., 2011, **46**, 2274.

285. N.R. Thimmegowda, S.N. Swamy, C.S.A, Kumar, Y.C.S, Kumar, S. Chandrappa, G.W. Yip and K.S. Rangappa, Bioorg Med Chem Lett., 2008, 18, 432.

286. H.T. Gomez, E.H. Nunez, I.L. Rivera, J.G. Alvarez, R.C. Rivera, R.M. Puc, R.A. Ramos, M.C.R. Gutttirez, M.J.C. Baceb and G.N. Vazquez, *Bioorg Med Chem Lett*., 2008, **18**, 3147.

287. J. Valdez, R. Cedillo, A.H. Campos, L. Yepez, F.H. Luis, G.N. Vazquez, A. Tapia, R. Cortes, M. Hernandez and R. Castillo, *Bioorg Med Chem Lett*., 2008, **12**, 2221.

288. Z. Kazimierczuk, J.A. Upcroft, P. Upcroft, A. Gorska, B. Starosciak and A. Laudy, Acta Biochim Pol., 2002, **49**, 185.

289. S.A. Khan and S.A. Nandan, *Indian J. Heterocycl Chem*., 1997, **7**, 55.

290. D. Evans, T.A. Hicks, W.R.N. Williamson, S.C.R. Meacock and E.A. Kitchen, *Eur J Med Chem*., 1996, **31**, 635.

291. M. Gaba, D. Singh, S. Singh, V. Sharma and P. Gaba, *Eur J Med Chem*., 2010, **45**, 2245.

292. K.F. Ansari and C. Lal, *Eur J Med Chem*., 2009, **44**, 4028.

293. A.T. Mavrova, D. Vuchev, K. Anichina and N. Vassilev, *Eur J Med Chem*., 2010, **45**, 5856.