

Reminiscing the microwave-assisted chemistry of 5- and 6-membered benzene-fused N-heterocycles

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This article is dedicated to Prof. Dr. Ahmad Kamal for his outstanding contribution to organic synthesis, biocatalysis, and medicinal chemistry

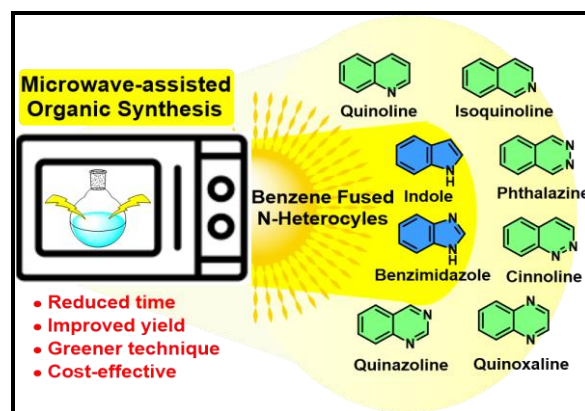
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Abstract

The dominance of *N*-Heterocycles' in chemical sciences, especially in drugs and pharmacological agents, makes them fascinating to advance their sustainable chemistry. Besides, the microwave technique enables functioning at higher temperatures beyond the boiling point of the reaction medium to offer adequate chemical transformations, which tend to be hassled with the classical approach. Herein, we have discussed microwave-assisted chemical transformations of paramount *N*-heterocycles (five- and six-membered) from the past decade. The role of microwave technique and its benefits has been emphasized in terms of reaction time, product yields, neat and clean reaction products, chemo/regio/enantioselectivity, and mild reaction conditions to achieve efficient transformations.



Keywords: Microwave-assisted organic synthesis, *N*-heterocycles, indole, benzimidazole, quinoline

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1. Introduction

Advancements in synthetic technologies through efficient and sustainable methods benefit the construction and diversification of organic frameworks.¹⁻³ A concern among the scientific community is to minimize toxic and hazardous reagents in chemical syntheses and find sustainable, greener approaches.^{3,5} The approach towards microwave chemistry with the advancement of safe instrumentations marked the beginning of an era for organic synthesis with reduced energy consumption and accelerated chemical synthesis.⁶⁻⁹ The transformation of electromagnetic energy in the form of heat by organic compounds during microwave irradiation raises the system's temperature (which may be higher than the reaction medium) more efficiently than conventional heating (conduction and convection).¹⁰⁻¹³ The microwave-assisted syntheses offer sustainable outputs like minimal waste/by-product formation, highly efficient heating, increased process speed, nominal use of toxic chemicals, higher purity, atom economy, solvent-free reactions with improved yields, and reduced reaction time.^{14,15}

Nevertheless, the application of microwave-assisted transformations in the chemical laboratory has been appraised previously. Reviews encompassing the synthesis of various heterocycles through microwave technology have been published by Kaur *et al.*, followed by a study by Frecentese *et al.* answering the importance of microwave reactions in combinatorial chemistry.^{16,17} Henary *et al.*, described the microwave-assisted synthesis of therapeutically active heterocycles.¹⁸ Banerjee *et al.*, published a summary of catalyst-free microwave-assisted synthesis of heterocycles.¹⁹⁻²¹ We have recently outlined the syntheses of five-/six-membered poly-*aza*-heterocycles (e.g., triazole, triazine, tetrazine, triazine), as well as non-(benzo)-fused azaheterocycles (e.g., aziridine, azetidine, pyrrole, pyridine, azepine) using microwave technologies.²²⁻²³ Herein, we aim to collate the literature of microwave-assisted chemical transformations associated with the class of benzo-fused N-heterocycles like indole, benzimidazole, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, and their analogues. This review emphasizes comparative analysis and the benefits of microwave-assisted transformations over classical heating. Eventually, such heterocycles are part of different synthetic or natural complex organic frameworks with excellent applications in various scientific domains.

Organic frameworks containing N-heterocycles are the principal component of various natural and synthetic compounds with particular applications in multiple research fields. The N-heterocycles mentioned above are abundant in natural products like tryptophan, reserpine, quinine, morphine, rutaecarpine, vincristine, histamine, etc. The synthetic derivatives of such heterocycles possess a broad spectrum of

pharmacological activities such as anticancer, antiviral, antibacterial, anti-inflammatory/analgesic, antifungal, antihypertensive, antiprotozoal, neuroprotective, antituberculosis, antihistaminic and other.²⁴ These heterocycles are an integral part of top prescription drugs, e.g., indomethacin, roxindole, indalpine, ondansetron, telmisartan, albendazole, chloroquine, amodiaquine, fasudil, gefitinib, afloqualone, azelastine, hydralazine, varenicline, quinacillin, and many others.²⁵ Moreover, these heterocycles have applications in pesticides, organic-electric devices, versatile building blocks, ionic-liquid, metal-ion coordination, fluorescent probes, and diagnostic agents (Figure 1). These significant and diverse applications prompted the researcher to develop a rapid and efficient protocol for various chemical transformations associated with such heterocycles.

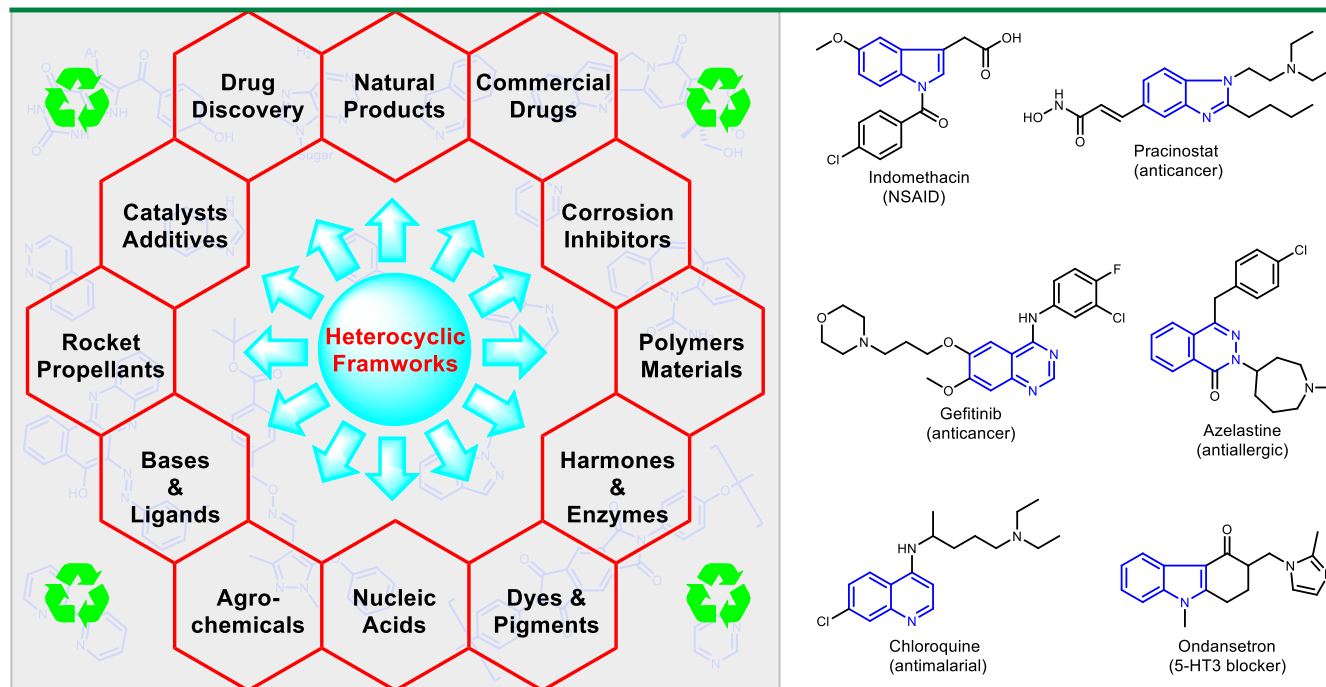
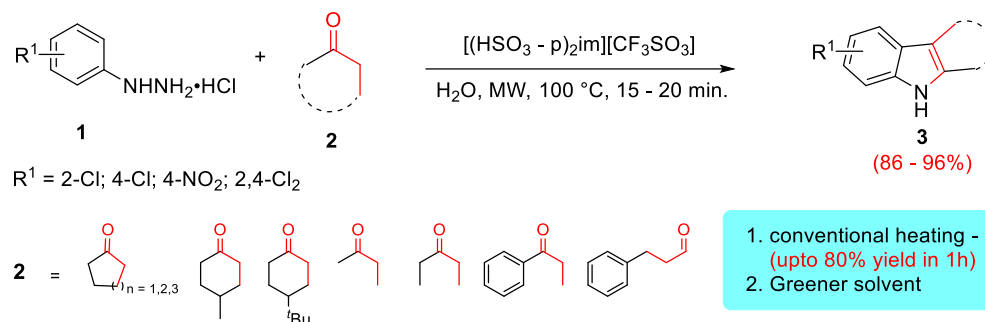


Figure 1. Applications of N-heterocycles in different scientific domains and representative examples of drugs containing N-heterocyclic moiety.

2. Benzene-fused five-member N-heterocycles

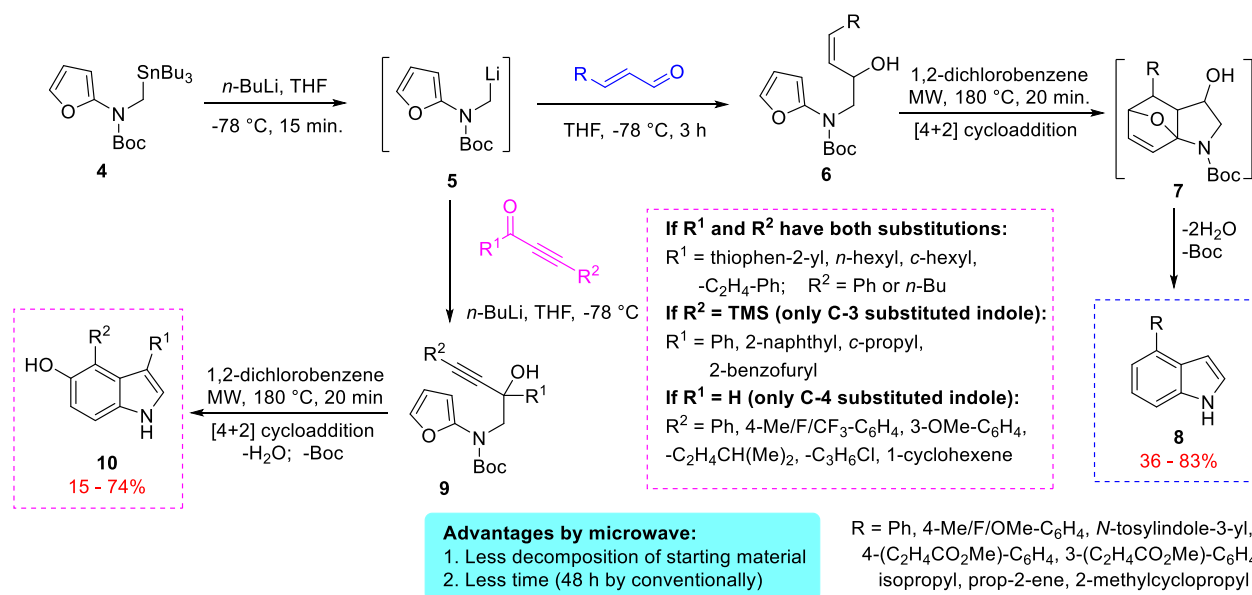
2.1. Indole

Fischer indole synthesis has given access to aromatic indoles from phenylhydrazine with aldehyde/ketone in the presence of Brønsted and Lewis acids which are unstable and hazardous. The use of SO₃H-functionalized ionic liquids was reported for synthesizing indole in an aqueous medium under microwave irradiation. This protocol uses arylhydrazine hydrochloride salts **1**, (readily available and low-toxic) with various aliphatic cyclic/acyclic ketones, aromatic ketone, aliphatic aldehyde yielded indole **3**, up to 96% in 15 min (Scheme 1).²⁶ The use of ruthenium catalyst allowed the replacement of the carbonyls with 1° or 2° alcohols having benefits such as easy handling, low toxicity, more stability, and commercial availability.²⁷ However, the heterogeneous catalyst Amberlyst-15 was also found to be useful, avoiding the use of costly metal catalysts.²⁸ The use of microwave heating in these protocols produced the best yield in shorter time than conventional overnight heating.

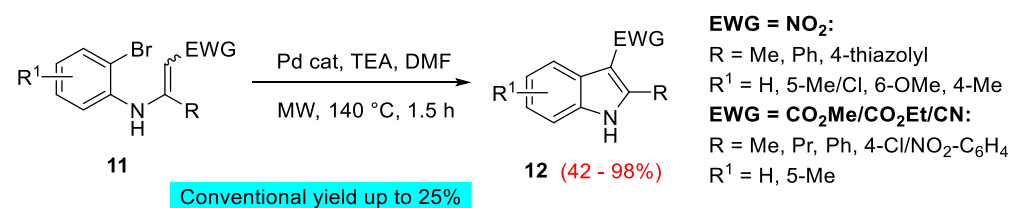


Scheme 1. Microwave-assisted Fischer indole synthesis.

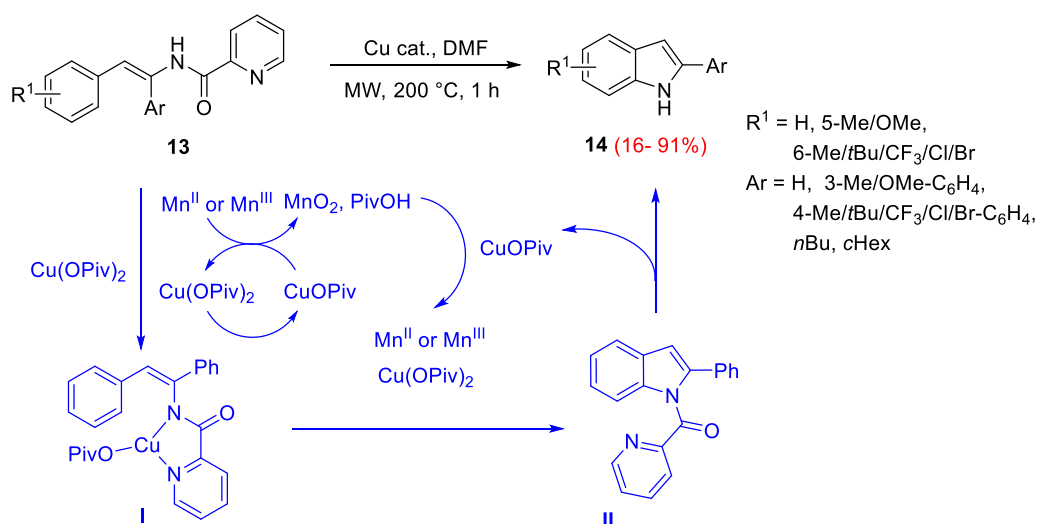
Peter Wipf's research group reported the convergent synthesis of 4-substituted indoles (**8**) by adding an α -lithiated alkylaminofuran **5** to α,β -unsaturated aldehydes followed by microwave-initiated intramolecular Diels–Alder furan (IMDAF) cycloaddition and *in situ* dehydrative aromatization reaction. The addition of α,β -unsaturated aldehydes to *in situ* generated α -lithiated alkylaminofuran in anhydrous THF at -78°C resulted in the corresponding hydroxyl homoallylic furanyl amines. Subsequently, the intramolecular cyclization followed by aromatization to furnish the desired product was initially conducted under conventional heating in toluene at reflux. In the reaction, gradual decomposition of starting material was observed without detection of desired outcome up to 48 h. However, further trials under microwave heating at 180°C for 20 min in 1,2-dichlorobenzene furnished the desired product **8** with good yields.²⁹ Later, they reported the synthesis of 5-hydroxy-4-substituted indole **10** by replacing the carbonyls with substituted alkynols based on the same IMDAF approach, which helps in the aromatization of intermediate at an earlier stage with the elimination of only two molecules of water. The reaction is well tolerated with branched/cyclic aliphatic/aromatic/heteroaromatic alkynols. Sterically bulky groups promote product formation and provide better yields than aliphatic substituents (Scheme 2).³⁰

Scheme 2. Microwave-assisted synthesis of 4-substituted indole (**8/10**).

N-Aryl- β -nitroenamines **11** along with other β -electron-withdrawing substituents such as carboxyl ester ($-\text{CO}_2\text{R}$) or cyanide ($-\text{CN}$) were transformed into 3-substituted indoles **12** (nitro, cyano or ester) in the presence of palladium catalyst *via* intramolecular arene-alkene coupling with complete regio-selectivity in microwave heating. As classic indole nitration uses harsh acidic conditions, sometimes expensive rhodium catalysts, and is limited by low functional group tolerance, lower yields, and lack of regio-selectivity are often observed. In the protocol, the initial trial with conventional heating produced only about 25% yield after 48 h at 140 °C. In contrast, microwave heating reduced the reaction time to 1.5 h with product formation up to 98%. A wide variety of electron-rich, electron-deficient, or neutral α -substituted aryl enamines or aliphatic enamines were tolerated with good outcomes. In contrast, heterocyclic enamines gave lower yields due to catalyst poisoning (Scheme 3).³¹ An amide-directed intramolecular C-H amination of *N*-picolinoyl enamide **13** in the presence of a copper catalyst under microwave irradiation also produced 2-arylindoles **14** with good yield (Scheme 4).³² The mechanism involves ligand exchange of $\text{Cu}(\text{OPiv})_2$ with **13** to form *N,N*-bidentate complex **I**, followed by C-H activation and subsequent reductive elimination to form **IV**. The hydrolysis of **IV** results in the formation of product **14**.



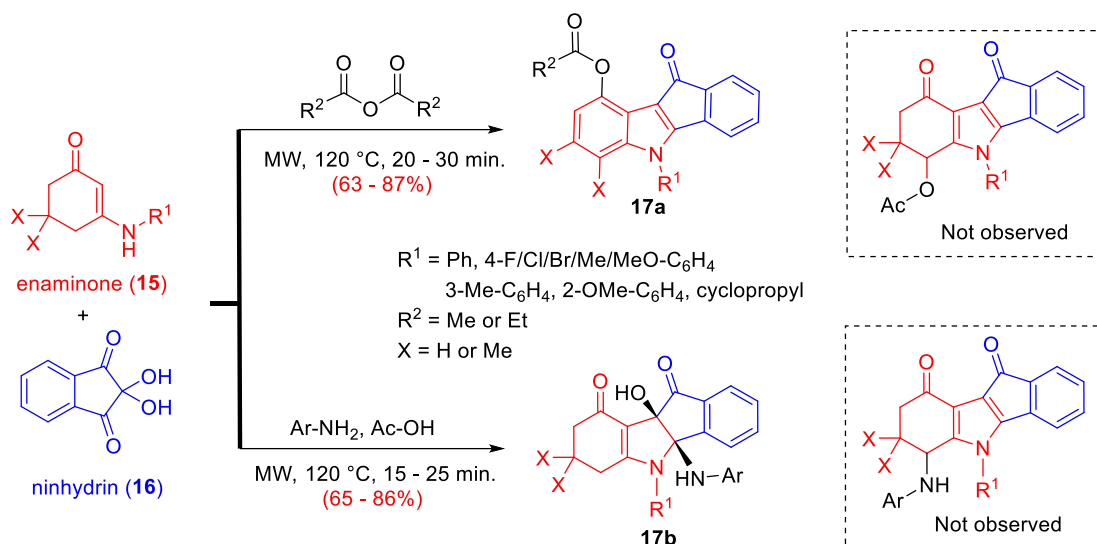
Scheme 3. Microwave-assisted synthesis of 3-substituted indoles **12**.



Scheme 4. Microwave-assisted synthesis of 2-substituted indoles **14** and its mechanism.

A one-pot three-component domino reaction of enaminones **15** was reported, resulting in multi-functionalized tetracyclic indeno-indole derivatives **17** under mild microwave reaction conditions. In the protocol, substituted cyclic enaminones were reacted with ninhydrin and aryl amines or acid anhydride, which also serves the purpose of solvent. The reaction with aryl amines in acetic anhydride follows sequential methyl migration, aromatization, and esterification steps, whereas the presence of AcOH has high *syn*-

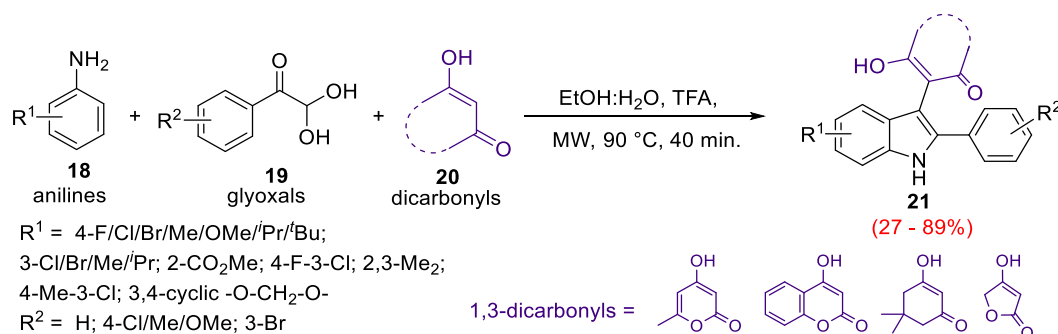
diastereoselectivity. The use of microwave heating significantly improved the product yield by 87% with different *N*-aryl enaminones having electron-withdrawing or releasing substituents (Scheme 5).³³



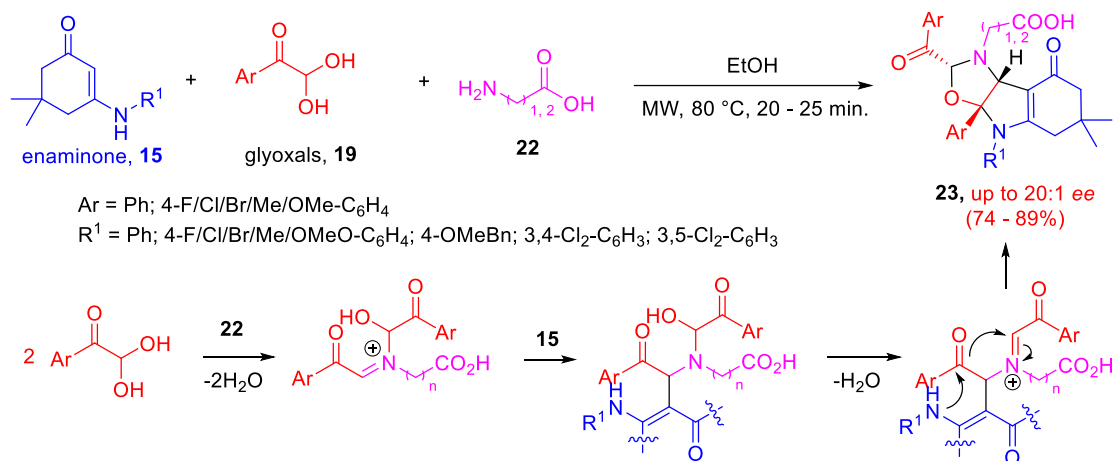
Scheme 5. Microwave-assisted one-pot domino synthesis of indeno-indoles **17**.

Microwave-assisted regioselective synthesis of 2-aryl-3-functionalized indole derivatives **21** was reported *via* a three-component domino reaction between anilines, arylglyoxal monohydrates, and cyclic 1,3-dicarbonyl compounds. The protocol uses green solvent and mild reaction conditions; produced good results with electron-rich or electron-deficient anilines as well as arylglyoxals in short reaction times (Scheme 6). Apart from the superior tolerance achieved over both electron-withdrawing and electron-donating substituents, substitution at *ortho*-position of aniline resulted in steric hinderance, thus reducing the reaction outcome.³⁴

A catalyst-free multi-component bicyclization from arylglyoxals, cyclic enaminones, and amino acids resulted in diastereo-enriched oxazolo-indoles **23** under microwave irradiation with high yields and high diastereoselectivity. This environment-friendly approach (only water as a by-product) was compatible with electron-rich, neutral, and electron-deficient substituents; notably, a single diastereomer was obtained with β -alanine as substrate (Scheme 7). Increment in the length between carboxylic group and amine in the amino acid favored the higher diastereoselectivity and electron donating groups in the enaminone favored the reaction compared to enaminones substituted with electron-donating groups.³⁵



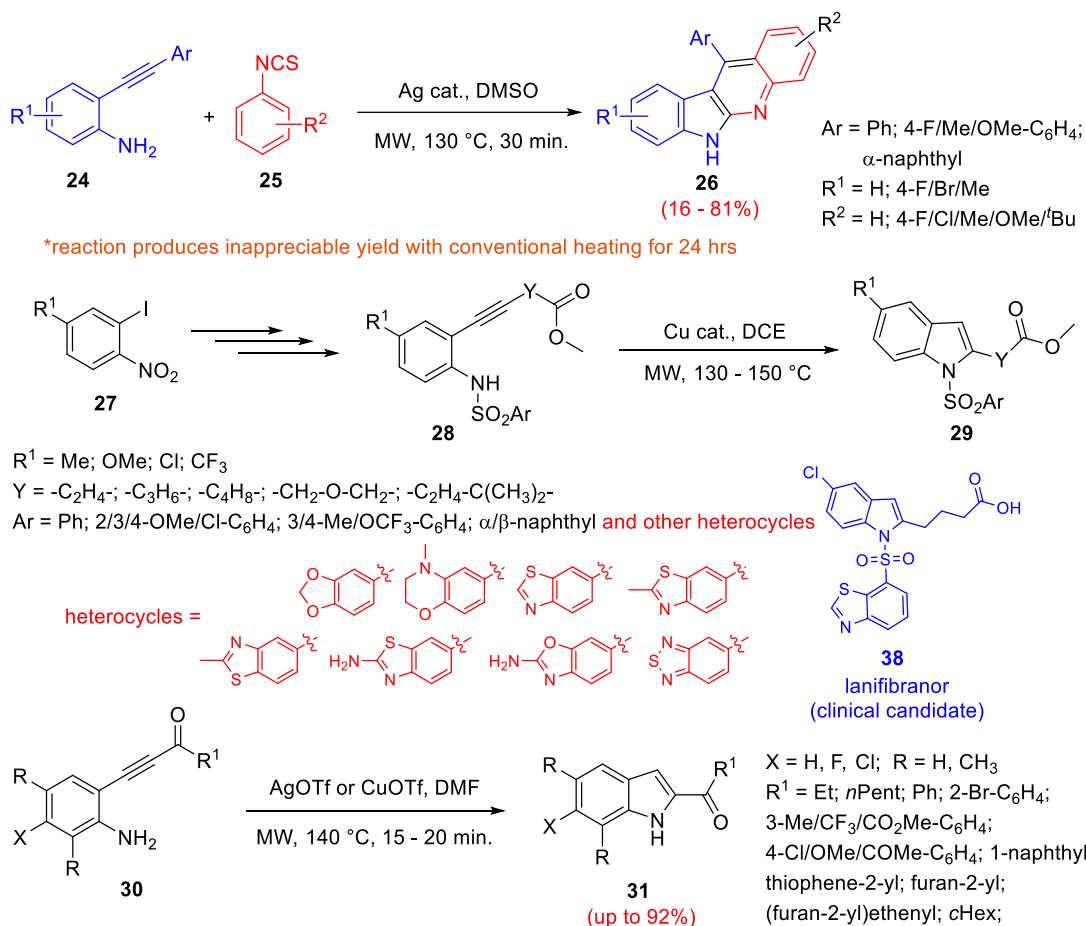
Scheme 6. Microwave-assisted synthesis of 2-aryl indoles **21**.



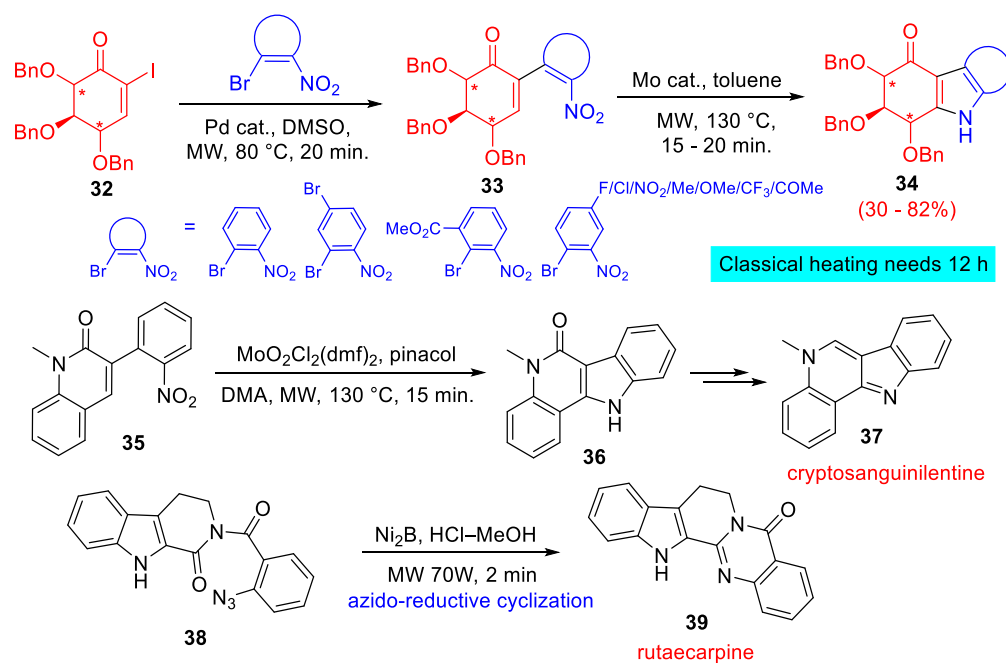
Scheme 7. Synthesis of diastereo-enriched oxazolo-indoles **23** under microwave irradiation.

Microwave-assisted cascade strategy was applied for synthesizing quinolone fused indoles **26** starting from 2-(phenylethynyl)anilines and aryl isothiocyanates in the presence of a silver catalyst. Due to the failure of conventional heating to produce good yields with various catalysts, solvents, and temperatures for 24 h, the author shifted to microwave heating, where a significant yield improvement of 81% was observed in a short reaction time (only 30 min). The protocol has good substrate scope with substituted anilines and aryl isothiocyanates.³⁶ In an expedition to synthesize *N*-aryl sulphonyl indoles as $\alpha/\gamma/\delta$ PPAR triple activators, including clinical candidate lanifibranor from 2-iodo-nitrobenzene (**27**), the central indole framework was prepared through a microwave-assisted reaction. Out of five steps, intramolecular cyclization was performed under microwave irradiation in the presence of a copper catalyst resulting in a good yield of *N*-sulfonamide indole derivatives **29**, which upon further ester hydrolysis, led to the desired compounds.³⁷ Similarly, another silver/copper-catalyzed selective anti-Michael hydroamination of β -(2-aminophenyl)- α,β -ynones **30** furnishing 2-acylindoles **31** was reported under microwave irradiation. The extensive screening for suitable catalysts, solvents, and temperatures showed that these reactions produced inappreciable yields (32%) along with the remaining 60% starting material in conventional heating for 16 h at 100 °C. The application of microwave heating in this conversion produced a good yield (up to 92%) with complete conversion in 15 – 20 min under the same catalytic system. In the protocol, a wide range of substrates produced satisfactory yields except for thienyl and cyclohexyl substitutions (Scheme 8).³⁸

Narayana *et al.*, (2018) reported the regioselective synthesis of chiral-enriched tetrahydrohexanone-fused indoles *via* nitro-reductive cyclization of Ullmann products **33** (a chiral-rich synthon) under microwave irradiation. The Ullmann products were synthesized under microwave heating, producing a good yield within 20 min. Further, the reductive cyclization was optimized with a molybdenum-based catalyst under microwave conditions for 15 - 20 min, resulting in tetrahydrohexanones **34** with satisfactory outcomes. In contrast, this transformation required about 12 h in classical reflux. The strategy was applied in synthesizing the precursor for indoloquinoline alkaloid cryptosanguinilentine (**37**), possessing antimicrobial and cytotoxic activity (Scheme 9).³⁹ The various substitutions over the phenyl group did not affect the reaction significantly and halogen/keto moieties in the substrates did not undergo any change during the conversion. Moreover, in our laboratory, we have developed an intramolecular azido-reductive cyclization method by employing TPP or Ni₂B in HCl–MeOH (1M) using microwave irradiation for the synthesis of naturally occurring rutaecarpine (**39**) and their derivatives (Scheme 9).⁴⁰

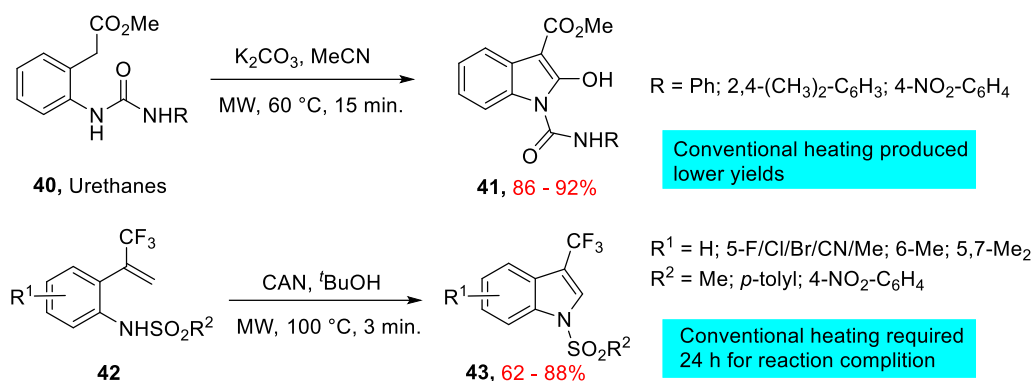


Scheme 8. Microwave-assisted synthesis of indoles from 2-ethynylanilines.



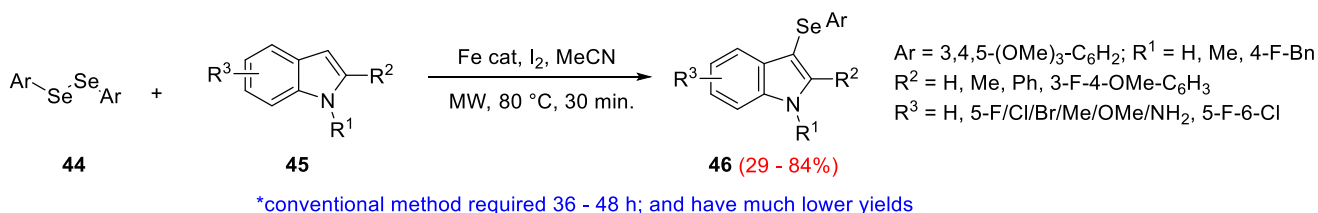
Scheme 9. Microwave-assisted synthesis of hexanone-fused indoles, cryptosanguinilentine, and rutaecarpine.

Similarly, an environmentally benign synthesis of bioactive indole derivatives **41** from respective urethanes was reported in the presence of a base. The reactions use mild conditions with a significantly improved yield up to 92% under microwave compared to the conventional result of 62%.⁴¹ The oxidative cyclization of 2-substituted- α -(trifluoromethyl) styrenes **42** in the presence of ceric ammonium nitrate (CAN) under microwave irradiation produced the corresponding 3-(trifluoromethyl) indoles **43**. The transformation furnished good yields with desired products in a short reaction time of 3 min under microwave while about 24 h is taken in conventional reflux (Scheme 10).⁴² A variety of substitutions on the phenyl ring were tolerated in the protocol along with different N-H protections such as mesyl and tosyl groups.



Scheme 10. Synthesis of 2-acylindoles, indole-2-carboxylates and 3-(trifluoromethyl)indoles.

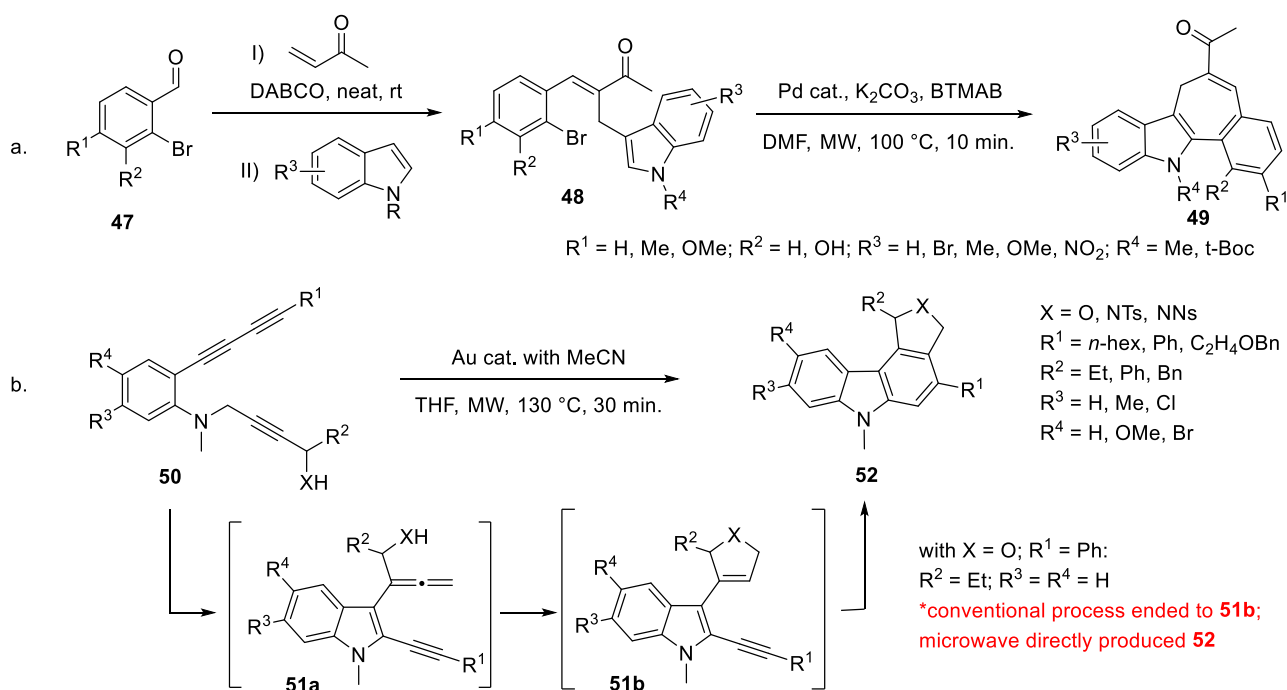
In pursuit of further diversification, various chemical functionalization of indoles under the microwave technique was reported. Diselenide **44** was reacted under microwave conditions with N-1 or C-2/5/6 substituted indoles **45** resulting in combretastatin A-4 analogues of 3-(3,4,5-trimethoxyphenylselenyl)-1*H*-indoles **46**. The microwave-assisted synthesis of 3-selenyl indole was reported with the best results obtained in 30 min with the isolated yield up to 84% as they already reported conventional protocol by Fang *et.al.*,⁴³ involved long reaction time of around 36 to 48 h and with the same condition use of other substrate produced only 47% of the desired product after 48 h reflux. The reaction was reproduced with different C-2 alkyl or aryl or C-5/6 electron-withdrawing or donating substituents over indoles; although C-5-NH₂ has not produced satisfactory results (Scheme 11).⁴⁴



Scheme 11. Microwave-assisted synthesis of 3-(trimethoxyphenylselenyl)-1*H*-indoles (CA-4 analogues)

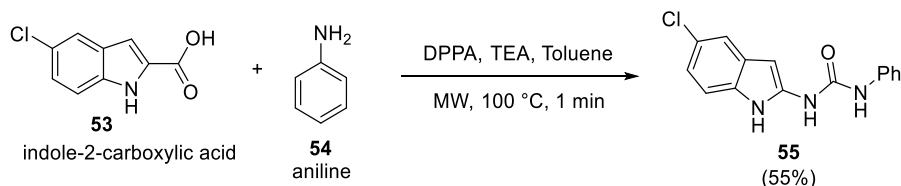
The structural analogues of ervatamine-silicine alkaloids having cycloheptaindole scaffold were synthesized starting from substituted 2-bromobenzaldehyde **47** in three steps. The final Heck coupling was performed with microwave irradiation in which *N*-boc protected-bromoindole was used in the presence of palladium catalyst with base producing satisfactory yields of products **49** in 10 min, although unprotected free N-H had lower yields.⁴⁵ A direct approach for synthesizing tetracyclic fused carbazoles by tricyclization of *N*-

propargylanilines **50** bearing conjugated diynes was reported *via* cascade reaction through allenylindole intermediate **51a** and rearrangement of *N*-propargyl group followed by intramolecular nucleophilic addition and subsequent hydroalkenylation. The electron donating substituents (5-OMe) hindered the product formation, attributed to the decreased stability of the product due to high electron density or due to competitive nucleophilic attacks. The report shows that reaction performed under conventional heating could not produce desired results even after a longer reaction time. In contrast, microwave heating produced good results with 100% atom economy from various diversified substrates having yields up to 86%. Further, the compound formed in the conventional method **51b**, has been reacted under microwave heating which furnished the titled compounds **52**; indicating that the conventional method was unable to cross the energy barrier for the transformation and justified the importance of microwave technology (Scheme 12).⁴⁶



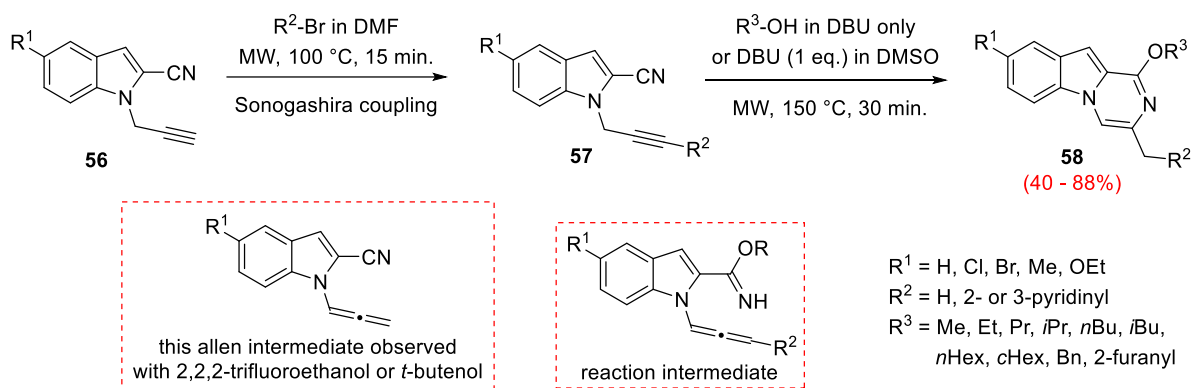
Scheme 12. Microwave-assisted synthesis of benzocycloheptaindoles (a) and tetracyclic fused carbazoles (b).

Microwave-accelerated one-pot tandem synthesis of unsymmetrical urea was reported *via* Curtius rearrangement from (hetero)aromatic acids and aryl amines in the presence of diphenylphosphorylazide (DPPA). This method enabled highly rapid (1 - 5 min) construction of an array of unsymmetrical urea with excellent yields and applicable to the gram-scale synthesis of key biologically active congeners. In the same course of reactions, 5-chloro indole-2-carboxylic acid with aniline furnished an acceptable yield of indole containing urea **55** just in 1 min under microwave condition (Scheme 13).⁴⁷



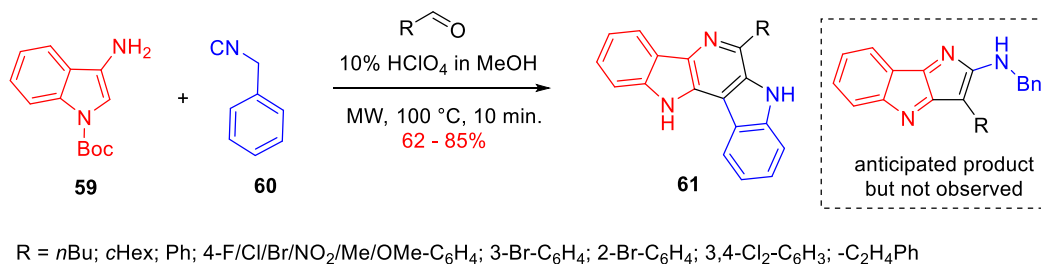
Scheme 13. Microwave-accelerated synthesis of unsymmetrical urea **55**.

1-Alkoxyprazino-indoles **58**, were synthesized from the corresponding *N*-(propargyl)indol-2-carbonitriles **56** with primary/secondary alcohol or thiols in the presence of a base under microwave condition *via* domino process; proceeds through an alkyne-allene rearrangement followed by nucleophilic cyclization. The reaction optimization shows about 50% yield under conventional heating at 80 °C in DMSO for 18 h; the yield reached 80% when the reaction was refluxed in DBU for 18 h without using any other solvent. Moreover, reaction time dropped down to 30 min by using microwave heating at 150 °C with comparable yields. This protocol offers substrate scope with a phenyl ring of indole as well as over alkyne moiety, although the allenyl intermediates were observed when 2,2,2-trifluoroethanol or *t*-butanol was used (Scheme 14).⁴⁸ The use of secondary alcohols such as isopropanol and cyclohexanol did not yielded the desired products.



Scheme 14. Microwave-assisted base-promoted synthesis of 1-alkoxyprazino-indoles.

A one-pot metal-free atom-economic three-component cascade condensation of *N*¹-*boc*-3-amino indole **59**, benzyl isocyanide and various aldehydes resulted in pyridobiindole **61** by microwave-assisted reaction in an acidic medium. The work aimed to synthesize pyrrolo-indoles *via* Schiff base formation and subsequent cyclization under thermal conditions. However, the result was knocked out as an expanded pyridobiindole ring demonstrating decent anticancer activity. The reaction produced the best results with microwave heating (100 °C, 10 min) in an acidic medium for various aliphatic or aromatic aldehydes with electron-donating/withdrawing substituents (Scheme 15).⁴⁹

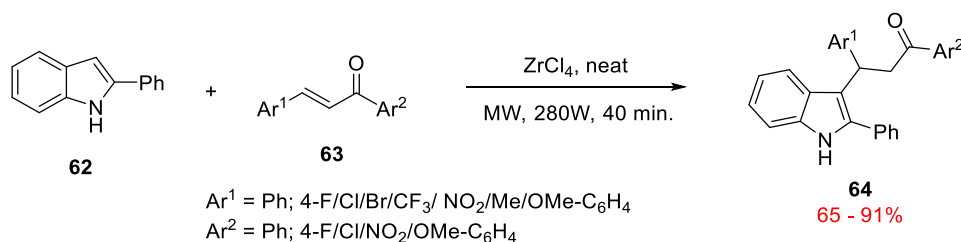


Scheme 15. Microwave-assisted one-pot metal-free synthesis of pyridobiindoles.

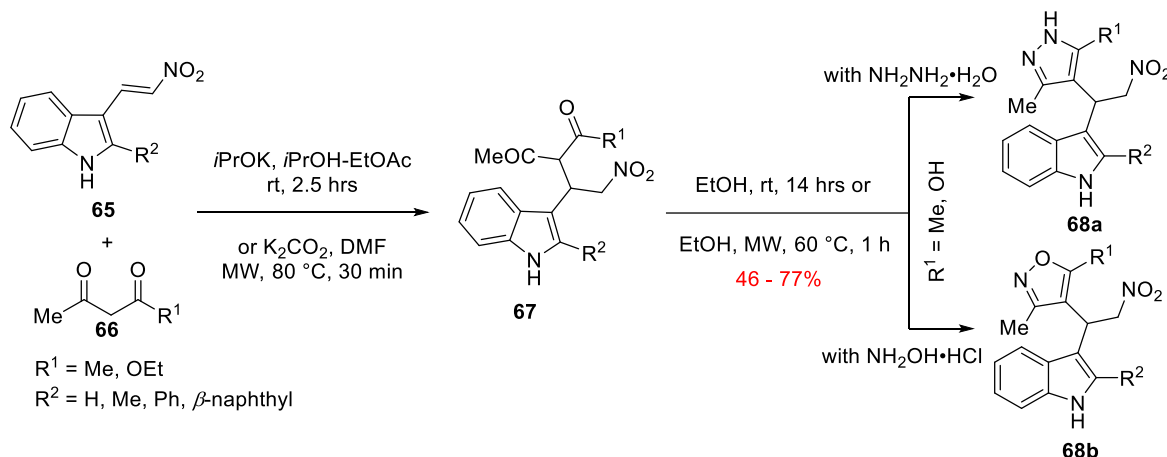
Michael's addition of 2-aryl-indole **62** with various chalcones substituted with electron-withdrawing/donating groups using ZrCl_4 as Lewis acid catalyst resulted in cytotoxic agents such as 1,3-diaryl-3-(2-(phenyl-1*H*-indol-3-yl)propan-1-ones **64**. The reaction was performed under microwave heating in neat

conditions and notably improved yield up to 91% with exclusive single product formation observed just in 40 min compared to 73% yield after 8 h reflux in acetonitrile (Scheme 16).⁵⁰ Moreover, exclusive product formation was observed in all the substrates and electron-withdrawing substituents on the chalcones favored the reaction.

Indoles bearing 2-nitroethyl and polar azole moiety were synthesized by conjugate Michael addition of 1,3-dicarbonyl compounds to 3-(2-nitrovinyl)-1*H*-indoles **65** followed by cyclo-condensation with hydrazine or hydroxyl amine to generates pyrazole (**68a**) or isoxazole (**68b**) ring respectively. The Michael addition reaction has been performed at room temperature and under microwave heating, and the latter technique gave better results, especially with C-2 bulky substituted indoles, which produced unsatisfactory results at ambient temperature. Similarly, the next cyclization step with hydrazine or hydroxyl amine under microwave heating had excellent results, completed in 1 h while in the ambient condition needed 14 h (Scheme 17).⁵¹

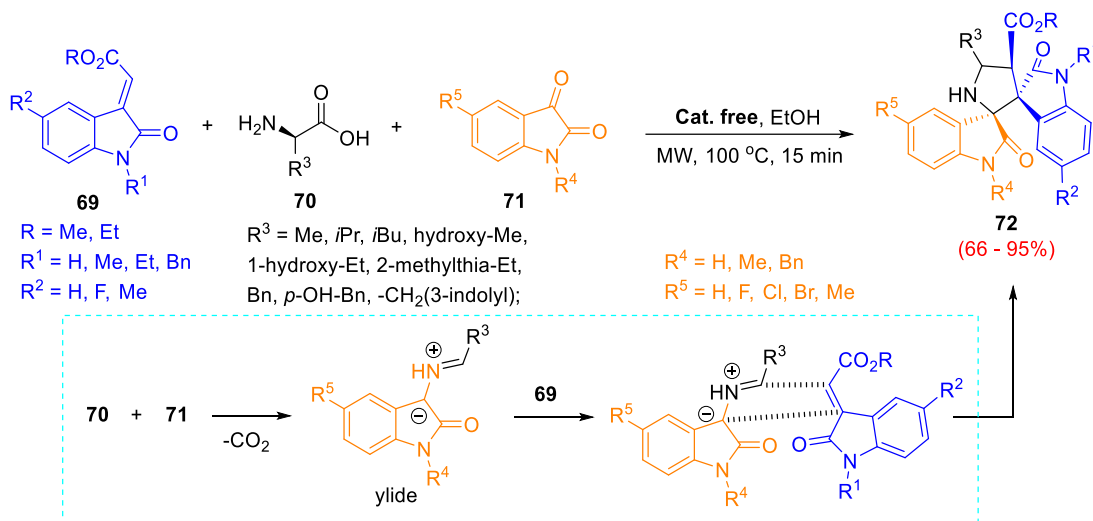


Scheme 16. Microwave-assisted synthesis of 1,3-diaryl-3-(2-phenyl-1*H*-indol-3-yl) propan-1-one.



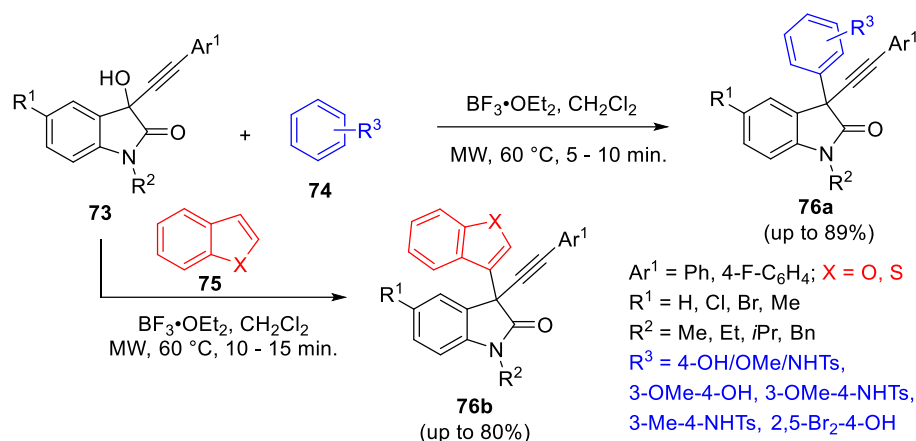
Scheme 17. Microwave-assisted synthesis of indoles bearing 2-nitroethyl and polar azole moiety.

Microwave-assisted protocols have been utilized in our endeavor to synthesize various heterocycles of potential biological interest.^{52,53} Pyrrolidine fused bis-spirooxindoles were constructed from the reaction of 3-alkenyloxindoles with *in situ* generated azomethine ylide *via* [3+2] cycloaddition. The catalyst-free one-pot reaction of alkenyloxindoles **69**, α -amino acids **70**, and isatin **71** efficiently yielded the products **72** under microwave irradiation at 100 °C for 15–20 min. The reaction kinetics was effectively improved under microwave irradiation without using any additive or catalyst and enabled high yields (66–95%) in short reaction time with broader substrates scope (Scheme 18).⁵²



Scheme 18. Microwave-assisted synthesis of pyrrolidine fused bis-spirooxindoles.

Another regioselective Friedel–Crafts arylation of 3-hydroxy-3-phenylethynyl oxindoles **73** with different electron-rich nucleophiles was established to construct a new C–C bond. The reaction of 3-hydroxy-3-(arylethynyl)oxindole with nucleophiles such as phenols, sulphonamides, anisole, benzofuran, and benzothiophene employing $\text{BF}_3 \cdot \text{OEt}_2$ under microwave was performed. The reaction furnished high yields of densely substituted 3-substituted-3-propargyloxindoles **76a** (up to 89%) in 5 - 10 min at 60 °C (Scheme 19).⁵³

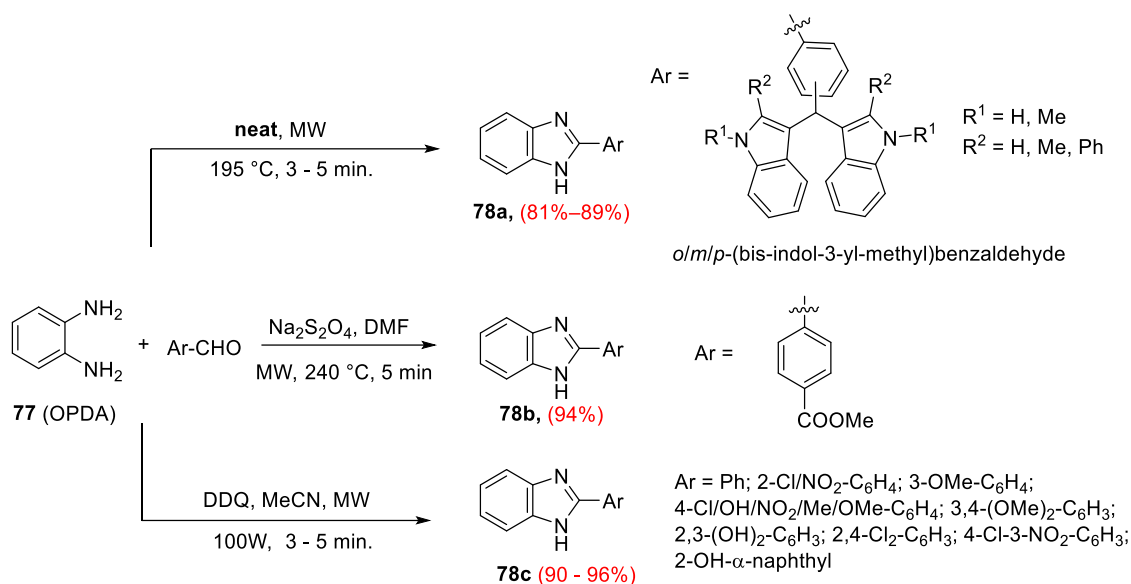


Scheme 19. Microwave-assisted regioselective Friedel–Crafts arylation and new C–C bond formation.

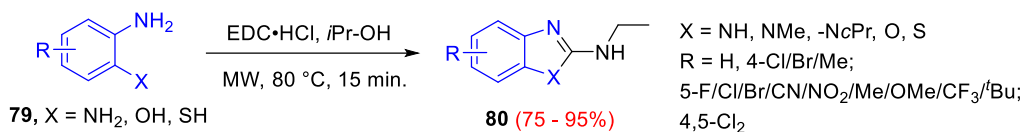
2.2. Benzimidazole

Kahveci *et al.*, (2017) provided a comprehensive review of the microwave-assisted synthesis of benzimidazole and its derivatives from 1994 – 2016.⁵⁴ In this section; we aimed to discuss reports hereafter for the synthesis and functionalization of benzimidazoles. *Ortho*-phenylenediamine **77** (OPDA) with aldehydes is the most common precursor; 2-(bis-indolyl)methyl benzimidazoles **78a** were prepared by solvent and catalyst-free green protocol in neat conditions. The reaction of OPDA with bis-indolylmethane-based aryl aldehydes under microwave irradiation afforded benzimidazoles with yields ranging between 86-94% within 3-5 min.⁵⁵ DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) has been efficiently used as an oxidant in similar reaction for chemoselective one-pot synthesis of 2-arylbenzimidazoles **78c** from OPDA with substituted benzaldehydes

under microwave heating, where electron-withdrawing group substituted aldehydes were more favourable.⁵⁶ OPDA **77** and methyl 4-formylbenzoate also reacted in the presence of Na₂S₂O₄ in DMF under microwave for 5–10 min furnished imidazoles **78b**. Product **78b** was engaged in a series of transformations to afford the compounds with anticandidal, cytotoxic/anticancer, intestinal antiseptic, antimicrobial, COX inhibition, and antifungal profiles (Scheme 20).⁵⁷ The OPDA has also been replaced with 2-hydroxy/mercapto-anilines **79** in the presence of EDC·HCl to synthesize 2-ethylaminobenzimidazole **80** under microwave for 15 min (Scheme 21). Electron-donating substituents on the OPDA achieved higher yields compared to electron-withdrawing substituents as a resultant effect on the basicity of OPDA.⁵⁸

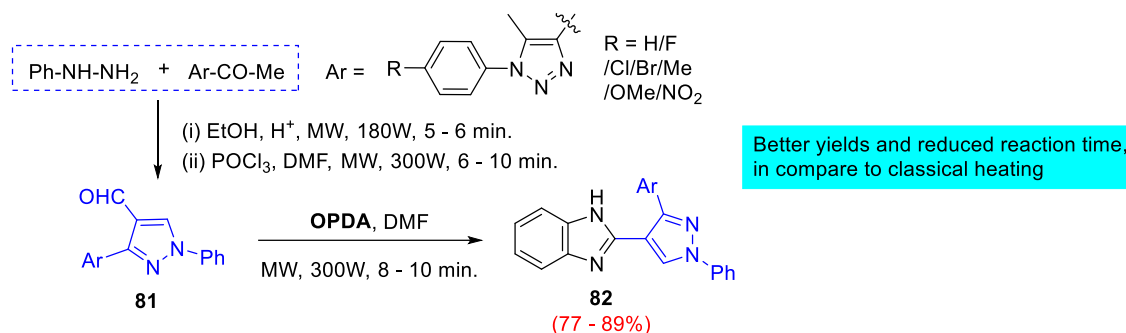


Scheme 20. Microwave-assisted synthesis of 2-(bis-indolyl)methyl benzimidazoles.

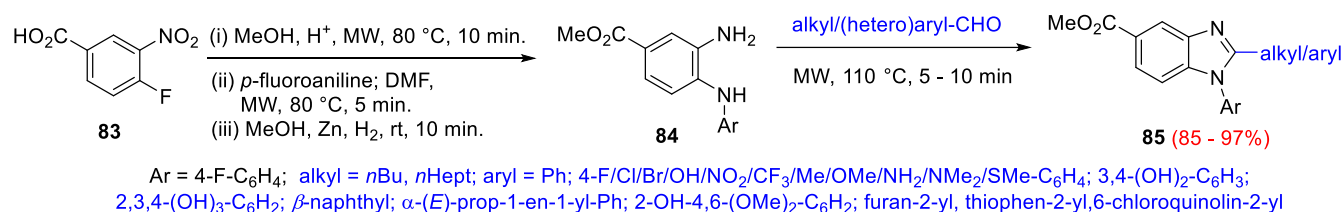


Scheme 21. Synthesis 2-aminoethylbenzimidazoles using EDC·HCl with OPDA or its analogues.

Many pharmacologically active agents were synthesized in a very efficient manner with the help of microwave-assisted chemistry. Pyrazole-aldehydes **81** on reaction with OPDA, produced anti-proliferative benzimidazole derivatives **82** tethered with triazole and pyrazole under microwave irradiation. The conventional synthesis of these compounds needed about 8–10 h producing 60–65% yields, whereas the application of microwave took about 15–25 min to complete protocol (2-steps) with improved outcomes up to 89% (Scheme 22).⁵⁹ Antimicrobial agents like methyl 1-(4-fluorophenyl)benzimidazole-5-carboxylates **85**, were prepared from 2-(*p*-fluorophenyl)amino-aniline **84** (instead of OPDA) upon reaction with various alkyl/aryl/heteroaryl aldehydes under solvent and catalyst-free microwave heating. The results were compared with mechanochemical (grinding) and conventional process; grinding yielded only 10–56% of products, the traditional process improved yields to 60–90% in 12–18 h, whereas microwave reaction afforded excellent yields ranging from 85 to 97% in 5–8 min (Scheme 23).⁶⁰

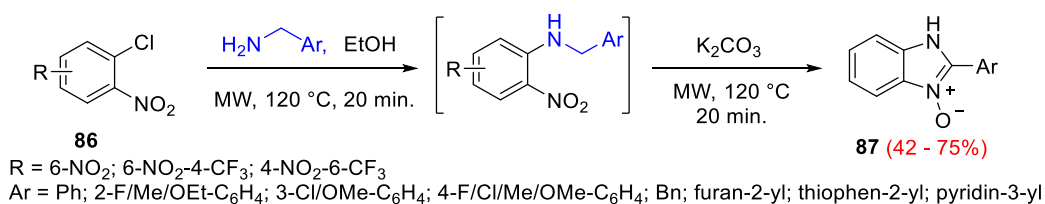


Scheme 22. Synthesis of triazole and pyrazole tethered benzimidazole derivatives.



Scheme 23. Synthesis of 2-substituted methyl 1-(4-fluorophenyl)benzimidazole-5-carboxylates.

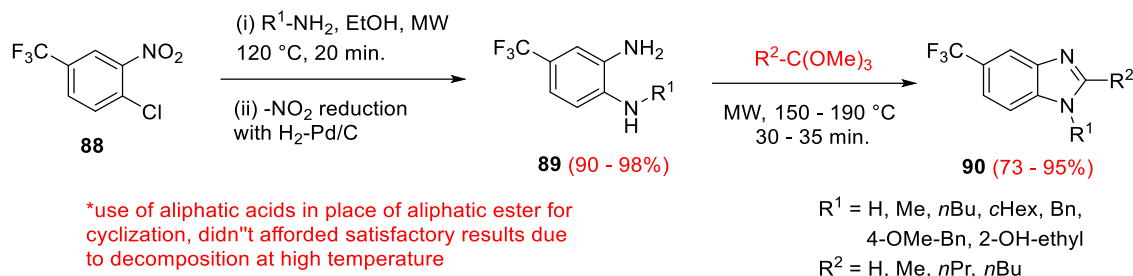
The one-pot two-step reaction of OPDA precursor/analogue *o*-nitrochlorobenzene **86** with substituted (hetero)aryl amines under microwave resulted in 2-aryl benzimidazole-*N*-oxides **87**. The isolation of these coordination compounds (with push-pull electron donor/acceptor group) was a significant challenge during conventional heating (yield 20–30%), whereas 40 min microwave heating yielded product in pure form with >75% yield (Scheme 24).⁶¹ The presence of strong electron withdrawing groups in the substrate facilitate the cyclization through deprotonation of amine group in the intermediate.



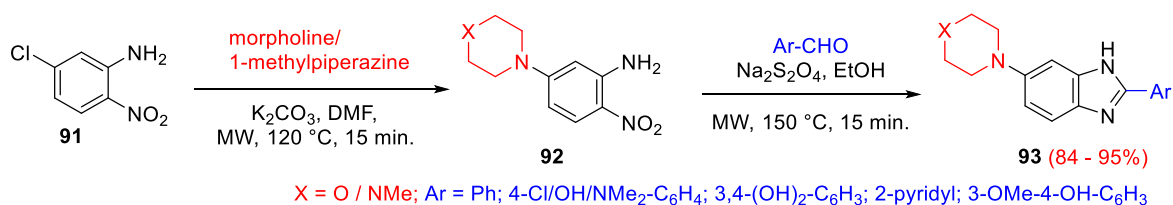
Scheme 24. Microwave-assisted synthesis of 2-arylbenzimidazole-*N*-oxides.

In another three-step protocol, *o*-nitro-*p*-trifluoromethylchlorobenzene **88** with various amines under microwave transformed to OPDA analogues followed by NO₂-reduction to **89**, and used for the synthesis of 1,2-dialkyl-5-trifluoromethylbenzimidazoles **90**. Initially, only 48% yield was observed under conventional reflux, whereas a remarkable yield improvement to 93% was observed with microwave heating at 120 °C. Further, cyclization with aliphatic *ortho*-esters (instead of aliphatic acids - prone to decomposition) was optimized under solvent and catalyst-free microwave heating at 150–190 °C with >95% overall yields. These substrates are helpful in synthesizing miconazole/fluconazole analogues (Scheme 25).⁶² Microwave-assisted reductive cyclization of 5-piperazino/morpholino-2-nitroaniline **92** (constructed from 5-chloro-2-nitroaniline) with aldehydes afforded piperazine/morpholine containing 2-arylbenzimidazoles **93**. The S_NAr and cyclization

both steps took 15 min each under microwave heating; whereas conventional heating at the same temperature required 24 h and 6 h, respectively, for two steps (Scheme 26).⁶³



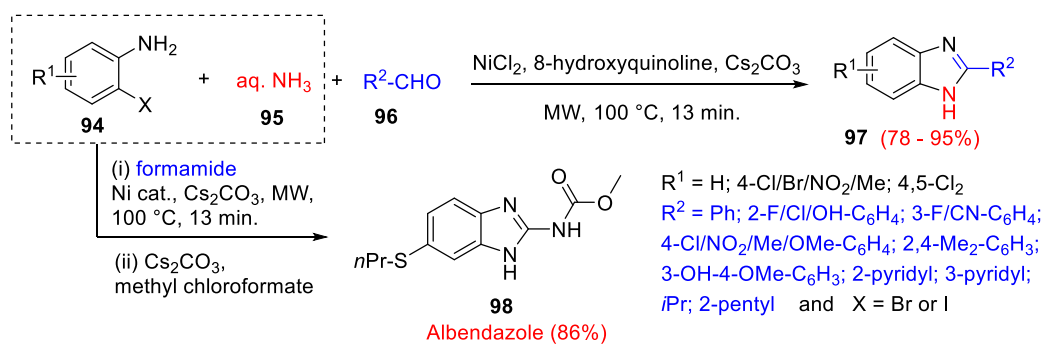
Scheme 25. Microwave-assisted synthesis of 1,2-dialkyl-5-trifluoromethylbenzimidazoles.



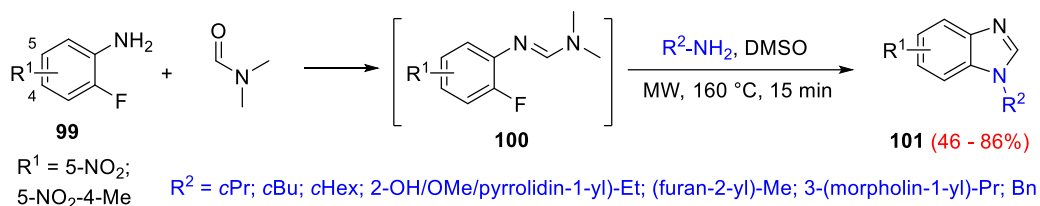
Better yield in shorter reaction time in compare to classical heating

Scheme 26. Synthesis of piperazine/morpholine containing 2-arylbenzimidazoles.

ortho-Haloanilines with cheap, non-toxic aqueous ammonia (as nitrogen source) and different aldehydes resulted in 2-alkyl/aryl substituted benzimidazoles **97** under solvent-free microwave heating at 100 °C with appreciable yields up to 95% within 15 min. Aldehydes containing electron-donating substituent enhanced the formation of *N*-phenylformimine, a key intermediate of reaction. Moreover, this protocol has been useful for the efficient synthesis of anthelmintic albendazole and mebendazole (Scheme 27).⁶⁴ The reaction of *o*-fluoroarylformamidines **100** with alkyl/benzyl amines (primary amine) by microwave irradiation furnished *N*¹-alkyl-2-unsubstituted benzimidazoles **101** without using any catalysts. Although in this protocol, aryl/heteroaryl amines were not producing the desired results or satisfactory yields, various aliphatic, benzyl, and hydroxyl substituted amines (strong nucleophiles) were well tolerated. Moreover, electron-withdrawing solid groups over *o*-fluoroarylformamidines favoured the regio-selective results in a short time (Scheme 28).⁶⁵

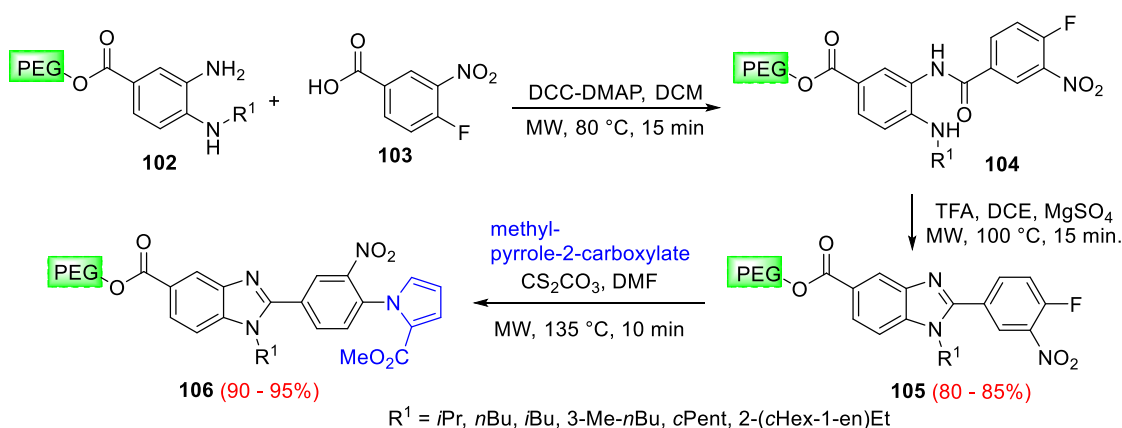


Scheme 27. Microwave-assisted Ni-catalyzed synthesis of benzimidazoles.



Scheme 28. Microwave-assisted metal-free synthesis of N^1 -alkyl-2-unsubstituted benzimidazoles.

Polymer bound N^1 -substituted OPDA **102** with 4-fluoro-3-nitrobenzoic acid produced N^2 -amide coupled intermediate **104** in 15 min; followed by acid-catalyzed intramolecular cyclization under microwave afforded good yields of polymer immobilized N^1 -substituted 2-(4-fluoro-3-nitrophenyl)benzimidazoles **105** at 100 °C for 15 min. Further, this aryl fluoride was subjected to S_NAr with pyrrole-2-carboxylate in presence of base under microwave heating for 10 min offering efficient access to **106**; whereas conventional protocol required about 18 h due to less reactivity of fluorides towards aromatic nucleophilic substitutions (Scheme 29).⁶⁶

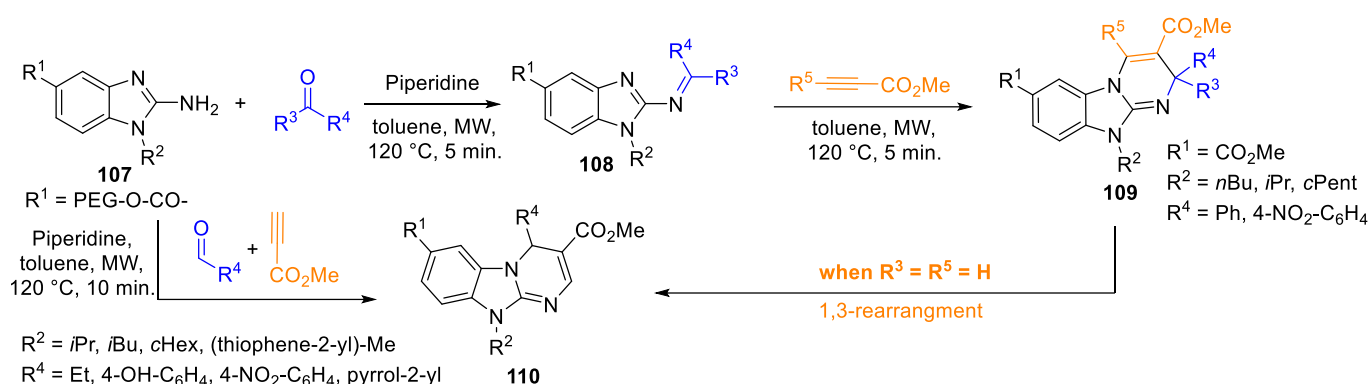


Scheme 29. Synthesis of polymer immobilized N^1 -substituted 2-(4-fluoro-3-nitrophenyl)benzimidazoles.

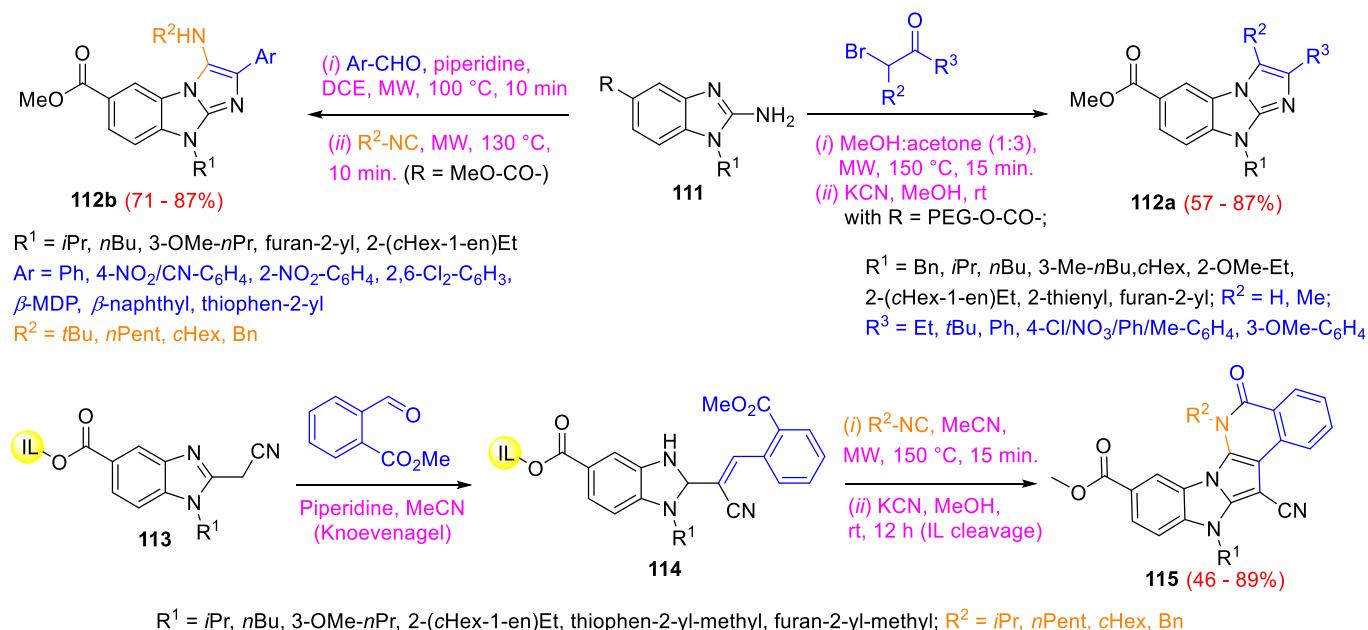
The various chemical modifications of benzimidazole were efficiently accessed under microwave conditions to produce the most desirable molecules. The first report of base-catalyzed one-pot multicomponent Povarov reaction of 2-aminobenzimidazole with aldehydes and electron-deficient dienophiles (alkynes) afforded a library of dihydropyrimido-benzimidazole **110** with an unusual 1,3-sigmatropic rearrangement under microwave heating for 10 min. Moreover, the 1,3-sigmatropic rearrangement was not observed with ketones, disubstituted alkynes, and with the rigid configuration of Povarov product like in the case of 2,3-dihydrofuran as dienophiles. The reaction was also tried with conventional reflux or excessive heating in a sealed tube took a longer reaction time of 24 h (Scheme 30).⁶⁷

C. M. Sun and their group explored various reactions of 2-aminobenzimidazole and similar analogues for cycloaddition reactions under microwave heating.⁶⁸⁻⁷⁰ The regioselective condensation of soluble polymer-supported 2-aminobenzimidazoles **111** with α -bromoketones followed by subsequent intramolecular cyclization promoted by microwave heating afforded imidazobenzimidazoles **112a** at 150 °C for 15 min. The methodology was well-tolerated among aliphatic and aromatic ketones with an exception for heteroaromatic aldehydes. In contrast to prolonged conventional Ugi reaction for synthesizing the desired product, microwave-assisted protocol quickly afforded a high yield of guanidine implanted heterocyclic library.⁶⁸ Similarly, a one-pot three-component reaction of **111** with aryl aldehydes and isocyanides afforded the same

kind of heterocycles **112b** with good yields. In this protocol, it was observed that initial imine formation with aldehyde and cycloaddition with isocyanides were promoted by microwave heating. Also, all the three reactants irrespective of their stereo-electronic nature resulted the products in good yields. In contrast, a sealed tube reaction at a similar temperature for 12 h produced lower yields (Scheme 31).⁶⁹ Aza-pentacyclic benzimidazo-pyrrolo-isoquinolones **115** were prepared in the two-step, three components coupling of ionic liquid supported 2-cyanomethylbenzimidazoles with methyl 2-formyl benzoate followed by cycloaddition with isocyanides promoted under microwave conditions. In this protocol, the synergy of ionic liquid (IL) with microwave heating was observed, where microwave activated both steps (Knoevenagel followed by cycloaddition). The cycloaddition under conventional sealed tube heating (180 °C, 12 h) has a significantly reduced yield; whereas microwave heating resulted in a better yield in a shorter time and at a lower temperature (150 °C, 15 min) (Scheme 31).⁷⁰



Scheme 30. Microwave-assisted base-mediated Povarov reaction of 2-aminobenzimidazole.

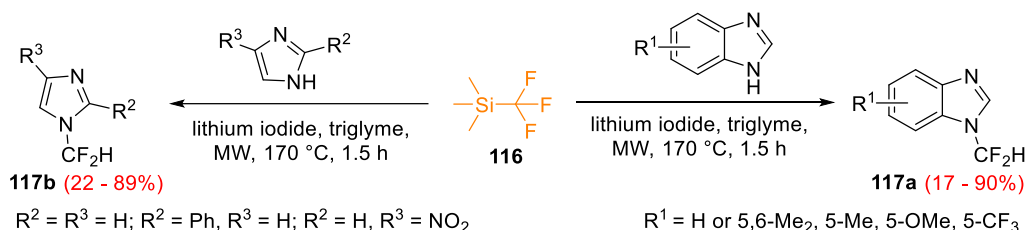


Scheme 31. Microwave-promoted synthesis of imidazobenzimidazoles and benzimidazo-pyrrolo-isoquinolones.

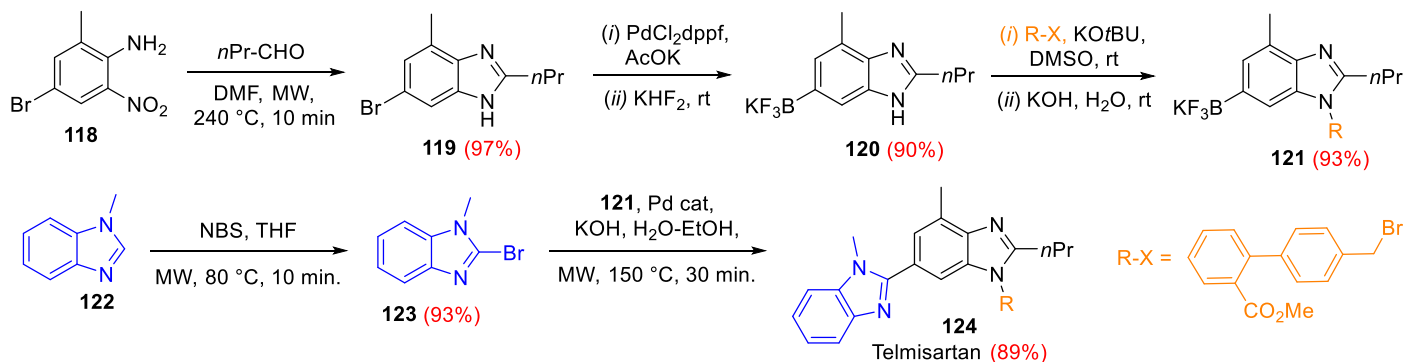
N-Difluoro methylated benzimidazoles and imidazoles **117**, were synthesized directly using inexpensive, commercially available TMS-CF₃ (Ruppert-Prakash reagent) under microwave conditions in relatively shorter

reaction time. Moreover, this protocol also works with conventional heating but requires a longer time (3–8 h). The earlier report used chlorodifluoromethane (ozone-depleting) or TMSCF_2Br (commercially not available) under strongly acidic conditions (conventional approaches).^{71,72} Benzimidazoles and imidazoles with electron-withdrawing/donating substituents showed similar reactivity (Scheme 32). Further, this protocol was extended for the difluoromethylation of theophylline and 8-(1*H*-benzimidazol-2-yl)quinoline as amyloid β -peptide inhibitor.⁷³

Telmisartan is a widely prescribed antihypertensive drug containing two benzimidazole moieties. A new convergent synthetic route was developed with some key steps under the microwave, significantly improving yield and reducing total reaction time. The previous approach was limited in terms of low overall yield (about 21%) and harsh reaction conditions (high temperature and acidic medium), which impacted yield and purity. The new protocol combines two functionalized benzimidazoles (**121** and **124**) by a high-yielding Suzuki reaction catalyzed by a homogeneous palladium source or graphene-supported palladium nanoparticles. This protocol produced high yields of commercial drug telmisartan (Scheme 33).⁷⁴



Scheme 32. Microwave-assisted *N*-difluoromethylation of benzimidazoles and imidazoles.

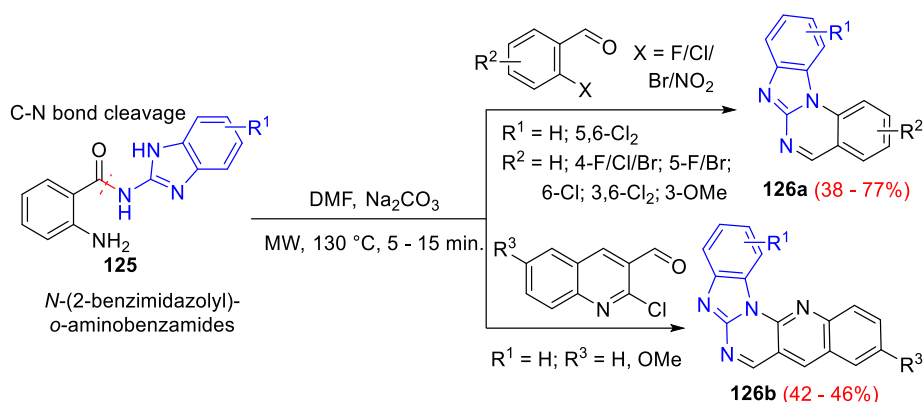


Scheme 33. Microwave-assisted convergent synthesis of telmisartan avoiding harsh reaction conditions.

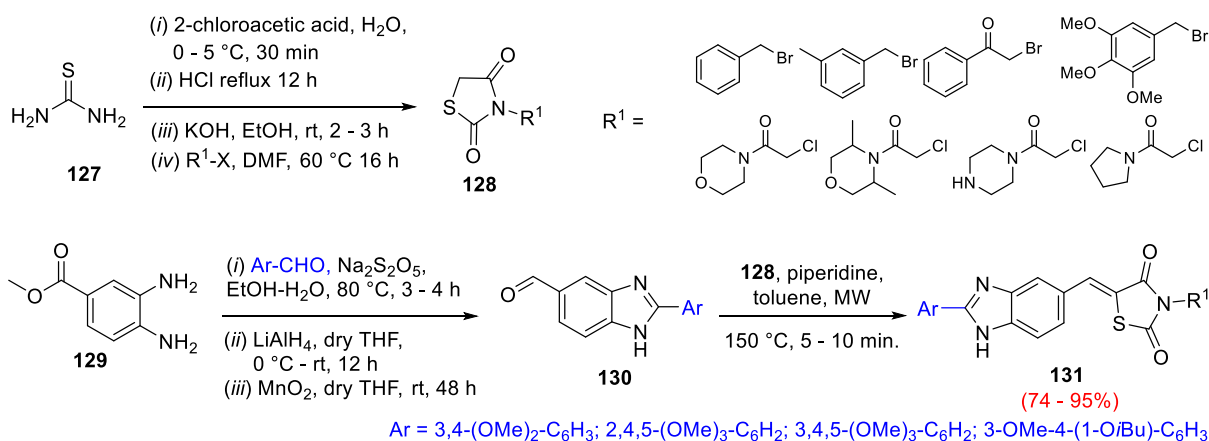
Another significant result for the influence of microwave was observed in one-pot metal-free C–N bond formation/cleavage in the synthesis of benzimidazoquinazolines **126** from *N*-(2-benzimidazolyl)-*o*-aminobenzamides and *ortho*-halogenated aldehydes under basic medium. The conventional protocol uses transition-metal catalysis with expensive ligands and additives. This metal-free microwave-promoted method furnished the designed product in 5–15 min at 130 °C with appreciable yields up to 77%; whereas conventional heating to the same temperature for 16–18 h produced only 36% yield (Scheme 34).^{75,76}

We have published gratifying results from the Knoevenagel condensation between *N*-substituted thiazolidine-2,5-dione **128** and 2-substituted benzimidazole-5-carboxaldehyde **130** under the microwave. The reaction furnished the corresponding benzimidazole-thiazolidinedione derivatives **131** as potential anticancer scaffolds. The comparative results from conventional and microwave protocols; showed better yields up to

95% in 5–10 min for microwave-assisted synthesis. The conventional protocol has significantly lower products of all the analogues (up to 79%) in 6–12 h (Scheme 35).⁷⁷



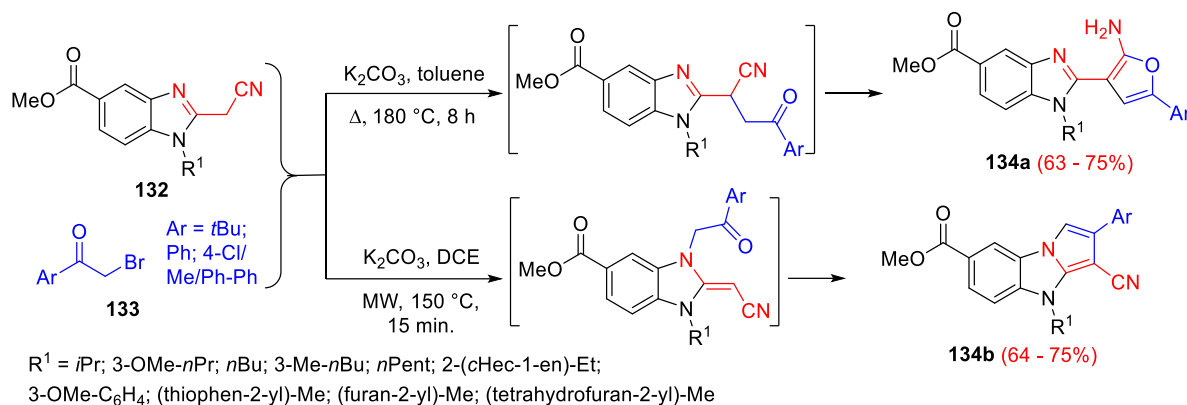
Scheme 34. Microwave-accelerated one-pot metal free synthesis of benzimidazoquinazolines.



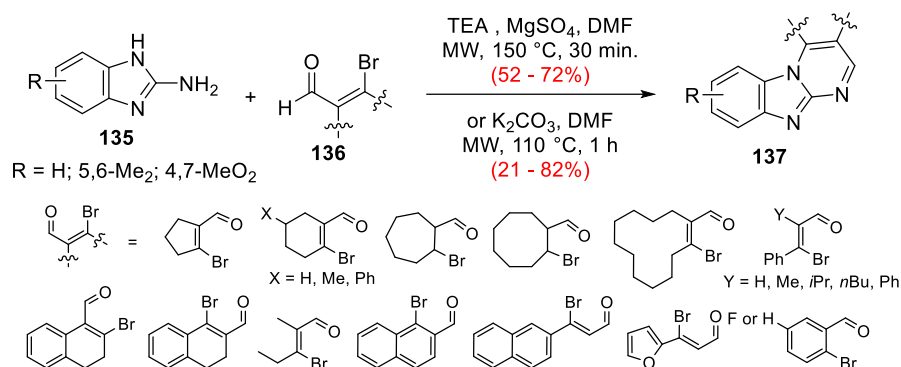
Scheme 35. Microwave-assisted synthesis of benzimidazole-thiazolidinediones as anticancer scaffolds.

A pleasant explanation of condition-based scaffold divergence for condensing 2-cyanomethyl benzimidazole **132** with α -bromoketone was accomplished, where regio-selective *C*- vs. *N*-alkylation was observed under conventional and microwave conditions, respectively. Owing to the fact, two non-equivalent nucleophilic centers (*C*- or *N*- of **132**) react selectively under conventional and microwave heating affording 2-amino-5-aryl furan-3-yl-benzimidazoles **134a** or 3-cyano-4-aryl-pyrrolo-benzimidazoles **134b** as a result of intramolecular cyclization of corresponding *C*- or *N*- alkylated intermediates respectively (Scheme 36).⁷⁸

Cho and co-workers explored the condensation of 2-aminobenzimidazoles with β -bromo- α,β -unsaturated aldehydes under microwave-assisted transition-metal free basic medium furnishing polycyclic benzimidazo-pyrimidines **137**. The protocol used organic (TEA) or inorganic (K₂CO₃) bases in DMF with various aliphatic, alicyclic, and aromatic aldehydes and furnished the corresponding *N*-fused benzimidazoles (Scheme 37).^{79,80} Cyclic β -bromo- α,β -unsaturated aldehydes produced better yields (72–82%) compared to benzo-fused β -bromo- α,β -unsaturated aldehydes (61% in 2 hours). Other reactions reported with benzimidazole include Knoevenagel condensation,⁸¹ and microwave-enhanced Suzuki-Miyaura coupling with improved functional group tolerability.⁸²



Scheme 36. Conventional or microwave condition-based regio-selectivity in 2-cyanomethyl benzimidazole.

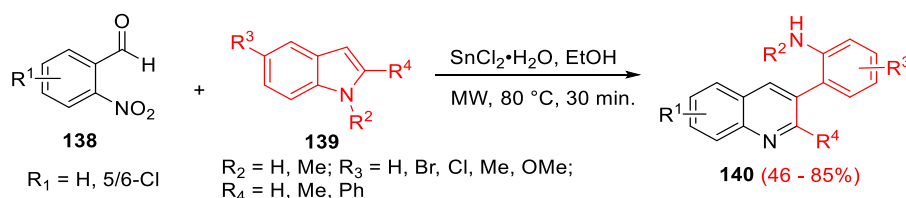


Scheme 37. Microwave-assisted synthesis of pyrimidine/quinazoline fused benzimidazoles.

3. Benzene-fused six-membered N-heterocycles

3.1. Quinoline and isoquinoline

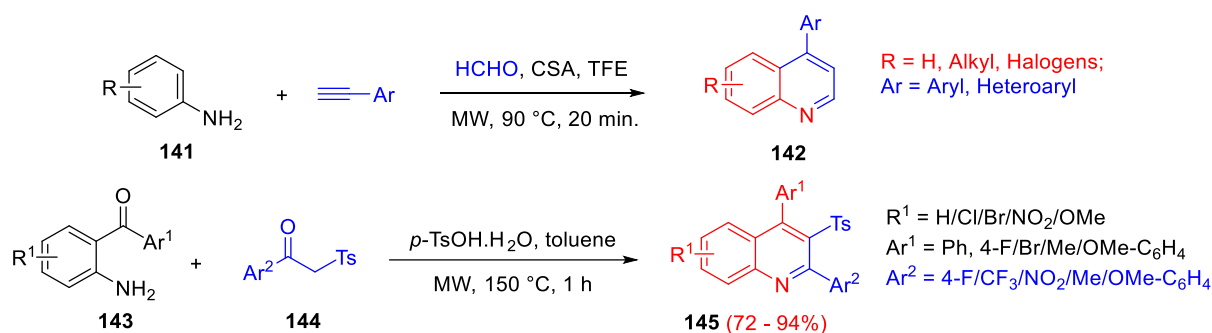
The sustainable synthesis of quinoline heterocycle using microwave was suitably collected in early 2019,⁸³ new synthetic approaches that appeared afterward are discussed in this section. The one-pot reaction of 2-nitrobenzaldehyde and indole was reported as a new variant of Friedlander synthesis for constructing 3-(*o*-aminoaryl)quinoline **140**. This robust reaction involved the reduction of 2-nitrobenzaldehyde in the presence of SnCl_2 , which provides an acidic medium to the reaction and leads to the formation of products **140** (Scheme 38).⁸⁴



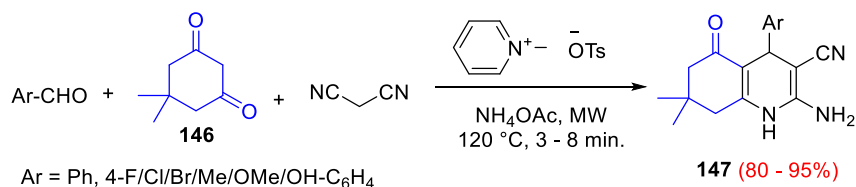
Scheme 38. Microwave-assisted one-pot synthesis of 3-(*o*-aminoaryl)quinoline.

Microwave-assisted metal-free synthesis of C-4 arylated quinolines **142** using multicomponent Povarov reaction with (\pm) camphor sulphonic acid (CSA) catalyst was reported. The reaction involved [4+2]

cycloaddition of *in situ* generated imine with alkynes without any observation of Troger's base formation, which was inhibited by CSA. The earlier reported synthesis of 4-arylated quinoline involved longer heating with metal catalysts, thus the microwave-assisted reactions are energy efficient which were completed within 20 min without any metal catalyst.⁸⁵ Similarly, metal-free synthesis of 2,4-diarylquinolines **145** from 2-aminobenzophenones and β -ketosulphones was also reported. This microwave-assisted Friedlander reaction was catalyzed by *p*-TsOH·H₂O and had good atom economy with improved product yields (Scheme 39).⁸⁶ The four-component metal-free microwave-assisted reaction between arylaldehydes, dimedone, malononitrile, and ammonium acetate in the presence of a recyclable homogenous catalytic amount of *N*-methylpyridinium tosylate (ionic liquid) furnished appreciable yields of titled products. This protocol has been featured with operational simplicity, short reaction time (3–8 min), excellent product yields, and high energy efficiency (Scheme 40).⁸⁷

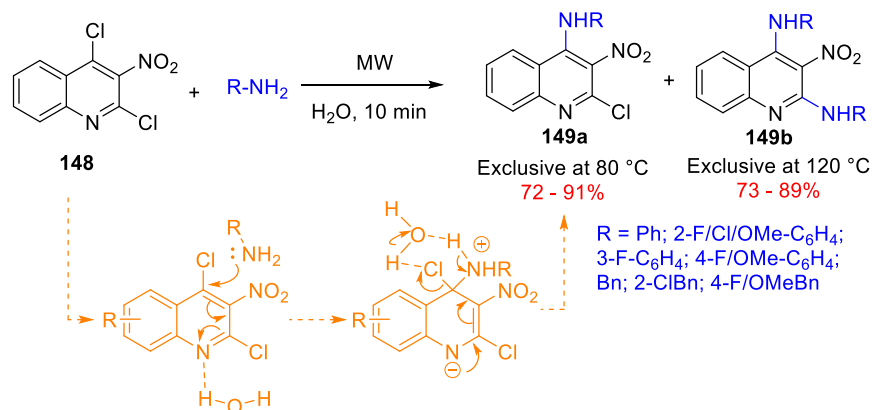


Scheme 39. Microwave-assisted metal-free synthesis of 4-arylquinolines.



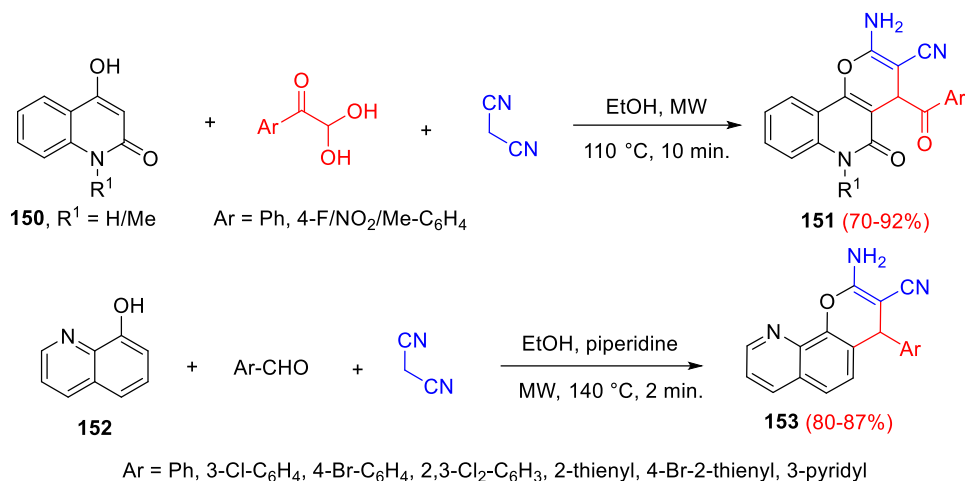
Scheme 40. Microwave-assisted metal-free synthesis of 4-aryl hexahydroquinoline.

Apart from these recent synthetic reports, several reactions and applications regarding quinoline derivatives have been explored under microwave conditions, including nucleophilic substitution reactions,⁸⁸⁻⁹⁰ multicomponent reactions,⁹¹⁻⁹⁴ C-H functionalization^{95,96} and others.^{97,98} Regio-selective nucleophilic substitution reaction of 2,4-dichloro-3-nitroquinoline **148** with different aryl/alkyl amines was explored. The reaction yielded only traces of products in conventional heating, whereas 10-15% of the product was obtained in neat microwave heating. Further, using water as a solvent with microwave heating led to the temperature-dependent regio-selective formation of products **149a** and **149b**. Moreover, with organic polar/nonpolar solvents, regio-selectivity was not observed. The regio-selectivity of the reaction was attributed to the solvent-assisted electron delocalization towards nitrogen and increased electrophilicity at C-4 position of the quinoline. The water can also stabilize the Meisenheimer complex *via* 'ambiphilic dual activation', which is less likely to happen at C-2 position of the quinoline (Scheme 41).⁹⁰



Scheme 41. Regio-selective nucleophilic substitution of 2,4-dichloro-3-nitroquinoline.

The catalyst-free one-pot multicomponent reaction of 4-hydroxy-2-quinolone **150** (1,3-dicarbonyl precursor) with malononitrile and arylglyoxal furnished fused pyrano-quinolines derivatives **151**. The reaction was assisted by microwave heating at 110 °C in ethanol producing good yields of 72-92%. The protocol featured catalyst-free, atom-efficient, use of greener solvent, short reaction time, easy purification, and applicability to a wide range of substrates, including naphthoquinones, coumarins, and pyrans.⁹¹ Similarly, the one-pot, three-component condensation of 8-hydroxyquinolines **152** with aryl/heteroaryl aldehydes and malononitrile also furnished pyranoquinolines **153** under microwave irradiation just in 2 min (Scheme 42).⁹²

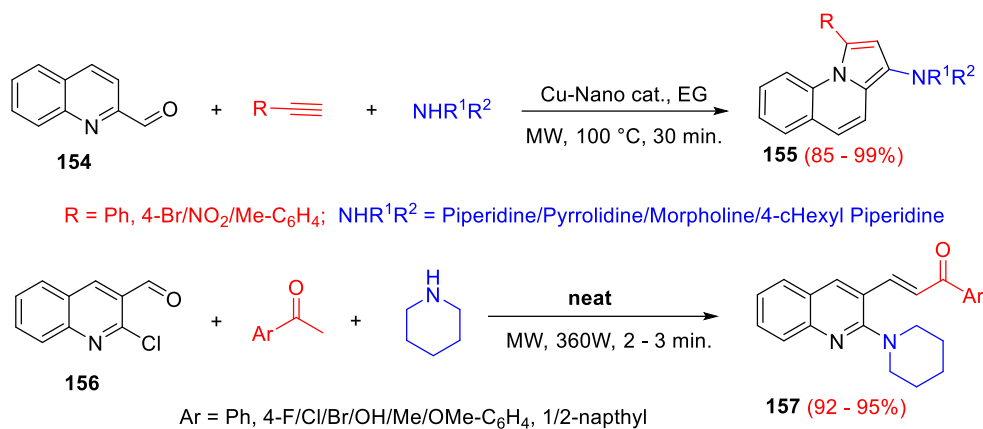


Scheme 42. Multi-component reactions of quinoline derivatives furnishing pyranoquinolines.

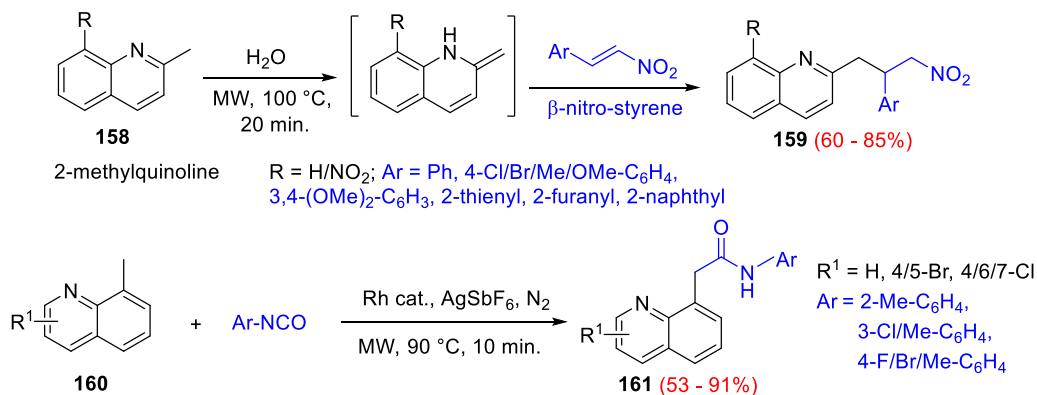
The one-pot multicomponent reaction of quinoline-2-carboxaldehyde **154** with substituted phenylacetylenes and secondary amines furnished the pyrrolo[1,2-*a*]quinolines **155**. The reaction performed in the presence of copper nanoparticles as a heterogeneous catalyst under microwave conditions in a recyclable green solvent like ethylene glycol at 100 °C for 30 min produced the desired products with only water as by-product.⁹³ Another multicomponent reaction of 2-chloroquinoline-3-carboxaldehyde **156** with acetophenone and piperidine under solvent-free microwave condition furnished quinoline-chalcone derivative **157** *via* a cascade of aldol condensation and nucleophilic substitution (Scheme 43).⁹⁴

Michael's addition of 2-methylquinoline with β -nitro-styrene furnished the product **159** *via* water-mediated catalyst-free benzylic C-H functionalization. Interestingly, among the solvents screened, water gave

the best result without any catalyst under microwave irradiation (no effect was detected with iodine as a catalyst in organic solvents). The developed protocol is advantageous in using green solvents, energy efficient, easy work-up and isolation. The reactions were tolerated with 8-nitroquinoline and various nitrostyrene-bearing electron-releasing/withdrawing groups in which electron-releasing groups offered better yields.⁹⁵ Microwave-assisted solvent-free Rh-catalysed C(sp³)-H activation of 8-methylquinoline was reported with phenyl isocyanates providing the corresponding C-C coupled products **161**, in 10 min with appreciable yields and purity (Scheme 44).⁹⁶

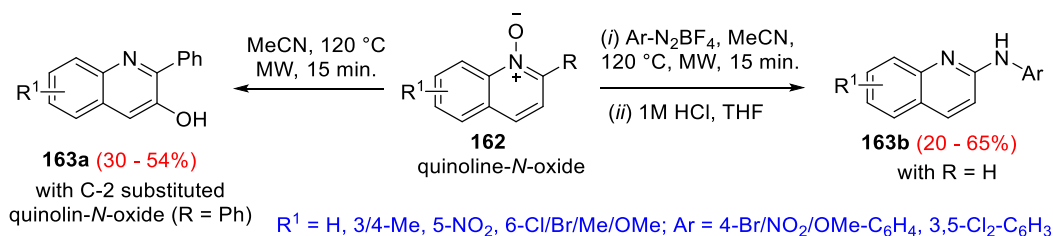


Scheme 43. Reactions of quinolines forming pyrroloquinolines or quinoline-chalcones.



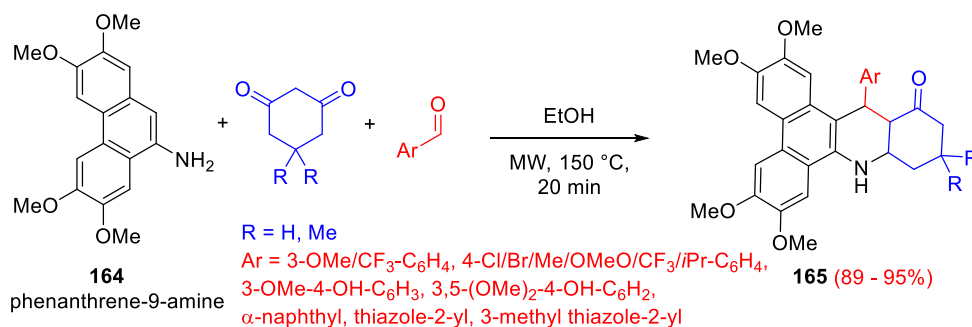
Scheme 44. C-H functionalization of quinoline derivatives under microwave conditions.

Quinoline *N*-oxide with aryldiazonium salts in a catalyst-free regio-selective reaction under microwave irradiation furnished two products, namely 3-hydroxyquinolines **163a** and 2-anilinoquinolines **163b**, in which acetonitrile (solvent) act as single nitrogen source forming two new C-N bonds. The conventional approaches required copper/silver catalysts or diethyl hydrogen phosphonate with prolonged reaction time (>20 h) at elevated temperatures using arylisothiocyanates or arylamines as nitrogen sources. The microwave heating at 120 °C enabled the reaction without any metal catalysts, which upon further acid hydrolysis, led to the formation of 2-anilinoquinolines **163b** within 15 min up to 65% yield. Interestingly, when the reaction was performed with C-2 substituted quinoline *N*-oxide, the product was 1,3-oxygen shifted C-2 substituted 3-hydroxyquinolines **163a** (Scheme 45).⁹⁸



Scheme 45. Regioselective synthesis of 2-anilinoquinolines and 3-hydroxyquinolines.

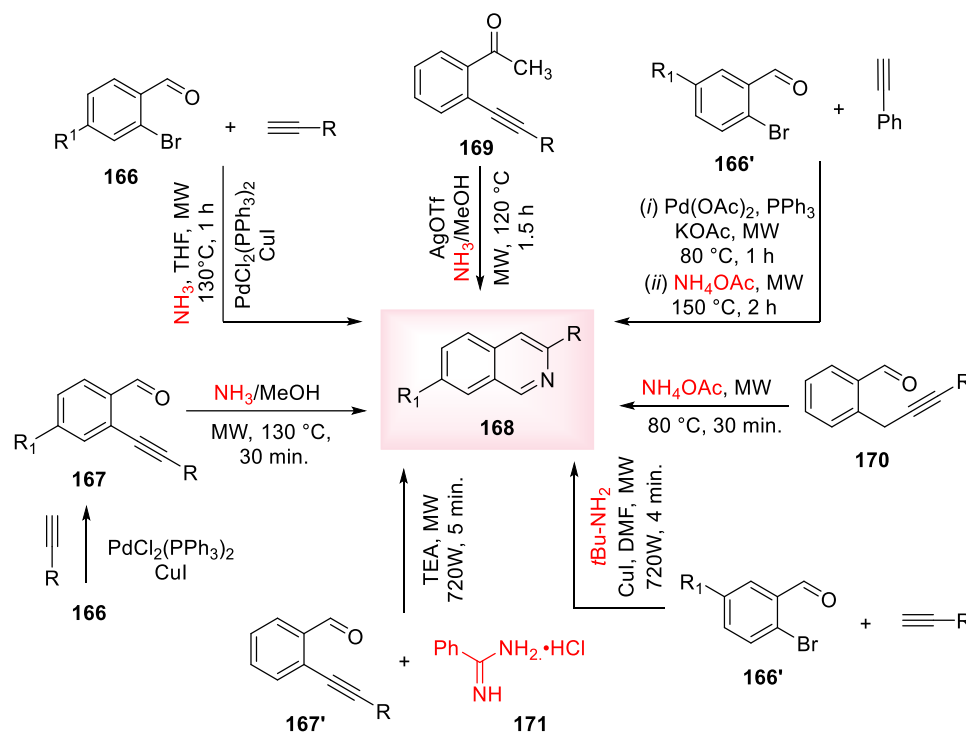
We also synthesized hexahydroquinolin-5-one fused with phenanthrene **165** in a one-pot single-step conversion of phenanthrene-9-amine **164**, arylaldehydes, and 1,3-dicarbonyl compounds. The microwave-assisted catalyst-free protocol offered broad substrate scope with high product yields (89 – 95%) within 20 min at 150 °C (Scheme 46). The prepared series displayed significant *in vitro* cytotoxicity profiles in sub-micromolar concentration against various cancer cells and were safer to normal cell line.⁹⁹



Scheme 46. Microwave-assisted synthesis of hexahydroquinolin-5-one fused with phenanthrene.

Isoquinoline is equally important, being a structural isomer of quinoline.¹⁰⁰ Isoquinoline is a core part of several drugs such as dimethisoquin, quinapril, debrisoquine, sequinavir, papavarine etc.¹⁰¹⁻¹⁰³ It has also been used as an organic catalyst in several reactions alone or along with metal catalysts as a ligand.¹⁰⁴ Past decade witnessed several reports on microwave-assisted synthesis of isoquinolines and their derivatives. The basic reaction course involved C-C coupling between 2-halobenzaldehydes with alkynes in generating 2-alkynyl benzaldehydes, which upon reaction with different nitrogen sources, converted to imines, followed by annulation to furnish 3-substituted isoquinolines. The reaction of 2-bromobenzaldehydes **166** with various alkynes under palladium catalyst and copper additive (Sonogashira coupling) resulted in the corresponding alkynyl aldehyde **167**, which upon treatment with ammonia (nitrogen source) under microwave heating for 30 min at 130 °C furnished isoquinolines **168** with moderate yields over two steps.¹⁰⁵ The reaction produced the same results in three component single-step reaction with slightly prolonged heating under microwave irradiation.¹⁰⁶ The propargylated ketone derivatives **169** have been implemented with good results (in place of aldehyde) by replacing the catalytic system with silver triflate.¹⁰⁷ The key steps in these reactions were imination of the carbonyl group, replacement of ammonia with ammonium acetate under palladium catalysis without any additive, improved the product yields up to 80% from <60% (in the case of ammonia). Thus, it indicates better efficiency of ammonium acetate as a nitrogen source and for imination.¹⁰⁸ 2-Propargyl benzaldehydes **170** were employed with ammonium acetate, and good yields of isoquinoline derivatives **168** were observed.¹⁰⁹ *t*-Butyl amine was used to have a more effective nitrogen source. Interestingly, the reaction furnished anticipated quinolines **168** within 4 min under microwave conditions only with economical copper-

catalyst and avoided the uses of expensive palladium catalysts. Pleasingly, 2-chloro arylaldehydes also gave isoquinoline in good yields when used in place of 2-bromobenzaldehydes. It was also found that the use of benzamidine **171** (as nitrogen source) furnished the product without any metal catalyst in 5 min using microwave heating.¹¹⁰ All the results together indicate the imination efficiency of different nitrogen sources as ammonia < ammonium acetate < *tert*-butyl amine < benzamidine, which was followed by intramolecular cyclization obtained isoquinoline with appreciable yields in a short reaction time (Scheme 47).

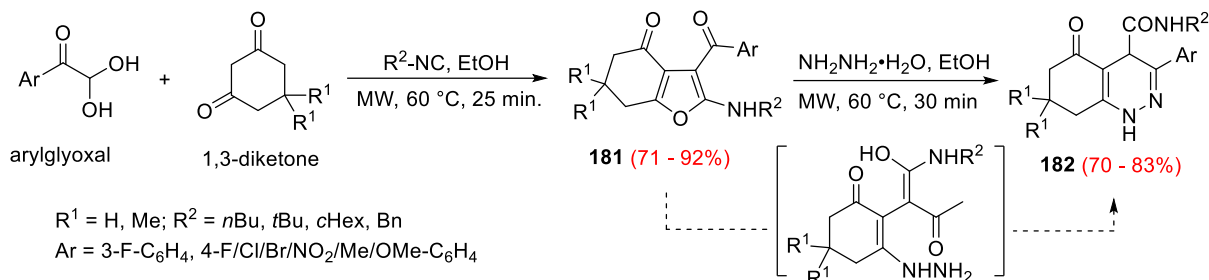


Scheme 47. Synthesis of isoquinolines *via* aldehydes – alkynyl coupling followed by cyclization.

Vinyl isocyanides **172** were efficiently used in the synthesis of isoquinolines; hydroxyl-containing isoquinolines **173** were prepared by the reaction of vinyl isocyanides with alcohols under metal-free microwave conditions *via* radical cyclization.¹¹¹ Radical insertion/cyclization of vinyl isocyanides with C(sp³)-H bond adjacent to a heteroatom in the presence of iron catalyst was also reported to generate isoquinoline **174**.¹¹² Isooxazoline-functionalized isoquinolines **175** were prepared *via* radical cascade cyclization of vinyl isocyanides with β,γ -unsaturated ketoximes using *n*-Bu₄NI (TBAI) catalyst under microwave condition (Scheme 48).¹¹³ These microwave-assisted reactions have been advantageous in terms of high yields, short reaction time, eco-friendly, broad substrate scope, good functional group tolerance, and the use of cheaper metal-catalyst or free of catalysts.

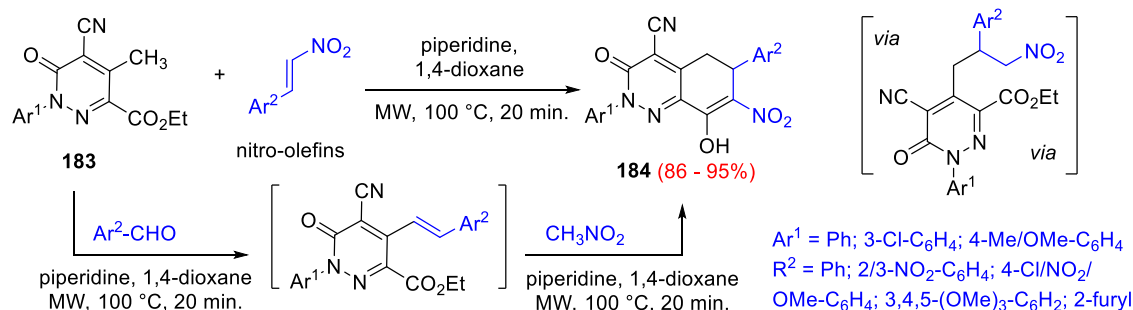
Dibenzoylhydrazine (ketazine, **176**) was used for annulation with internal alkynes in the presence of ruthenium catalyst and resulted in isoquinoline derivatives **177** *via* C-H/N-N activation under microwave condition for 10 min. The protocol fulfills the need for sustainability in terms of green chemistry principles and applies to gram-scale synthesis.¹¹⁴ Another ruthenium-catalyzed reaction of aryl ketones/ α,β -unsaturated ketones **178**, alkynes, and ammonium acetate resulted in the isoquinoline or substituted pyridines **179**. The three-component reaction preceded *via* C–H activation \rightarrow *N*-annulation sequence under microwave resulted in appreciable yields of isoquinolines in 10 min (Scheme 49).¹¹⁵ We have accomplished an efficient microwave-assisted protocol for the direct oxidative coupling of acetophenones with secondary amines such as

A microwave-assisted domino strategy was implemented with benzofuran derivatives to access cinnoline-4-carboxamides efficiently. The microwave-promoted reaction between arylglyoxals, isocyanides, and cyclic 1,3-dicarbonyl compounds resulted in high yields of multi-functionalized 6,7-dihydrobenzofuran-4-ones **181** (EtOH, 60 °C, 25 min; 71–92%). The regioselective ring-opening of **181** in the presence of hydrazine hydrate under the same reaction condition afforded the corresponding hexahydrocinnoline-4-carboxamides **182** with good yields of 70–83% (Scheme 51).¹¹⁷



Scheme 51. Synthesis of cinnoline-4-carboxamides **182**, from benzofuran derivatives.

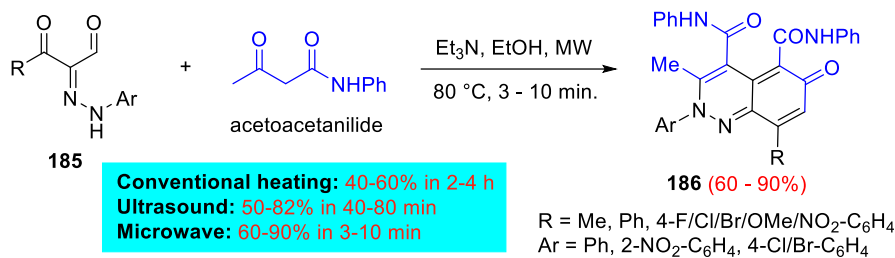
Unsymmetrical benzo[*c*]cinnolines have been synthesized from 2,2'-dinitro-1,1'-biphenyls by a domino partial nitro group reduction followed by intramolecular diazo bond formation.¹¹⁸ A short, metal-free, green and efficient approach using 4-methyl-pyridazine-3-carboxylate **183** with nitro-olefins was presented to synthesize poly-functionalized cinnolines **184**. The controlled microwave heating at 100 °C for 20 min in the presence of piperidine afforded high yields (86–93%) of expected cinnoline derivatives without detecting possible phthalazine formation (Scheme 52).¹¹⁹ This synthetic strategy was implemented for reaction inside natural *Lycopodium clavatum* sporopollenin (LCS) microcapsules for the first time and synthesized cinnoline-loaded microcapsules along with pure cinnoline and were evaluated for antibacterial potential against gram-positive and gram-negative bacteria.¹²⁰ Alternatively, these molecules have also been constructed with aryl aldehyde and nitromethane instead of nitroolefins under similar microwave-assisted reaction conditions.¹²¹



Scheme 52. Synthesis of poly-functionalized cinnolines from 4-methyl-pyridazine-3-carboxylate.

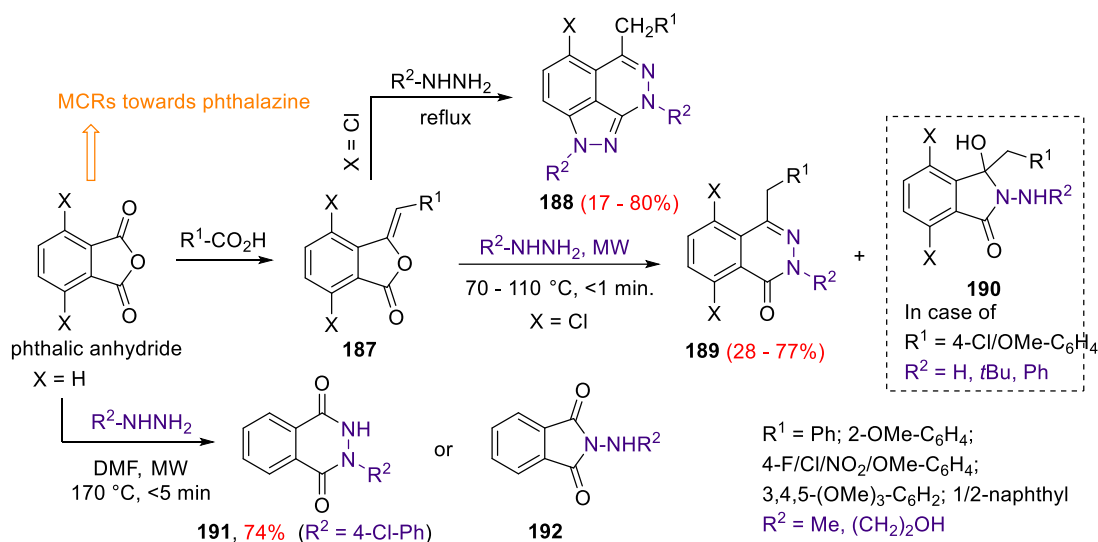
Tandem one-pot annulation (aldol-condensation followed by Michael-type addition) of 3-oxo-2-arylhydrazonopropanals **185** with aceto-acetanilide in the presence of mild base gave access to 2-arylcinnolin-6-one derivatives **186**. The initial screening of the reaction condition revealed ethanol with triethylamine as the best combination offering the highest yields. The reaction was performed under different heating modes: conventional reflux, ultrasound waves, and microwave heating. The conventional reflux was inefficient with low yield and long reaction time (45–75%; 2–4 h), whereas the application of ultrasound improved the

reaction efficiency to an extent (50–82%; 40–80 min). The application of microwave heating enhanced the reaction rate and furnished the highest yields (60–90%) within 3–10 min (Scheme 53).¹²² In addition, some cinnoline has also been reported to be used in the Stille-coupling under microwave condition.¹²³



Scheme 53. One-pot annulation of 3-oxo-2-arylhydrazonopropanals with aceto-acetanilide.

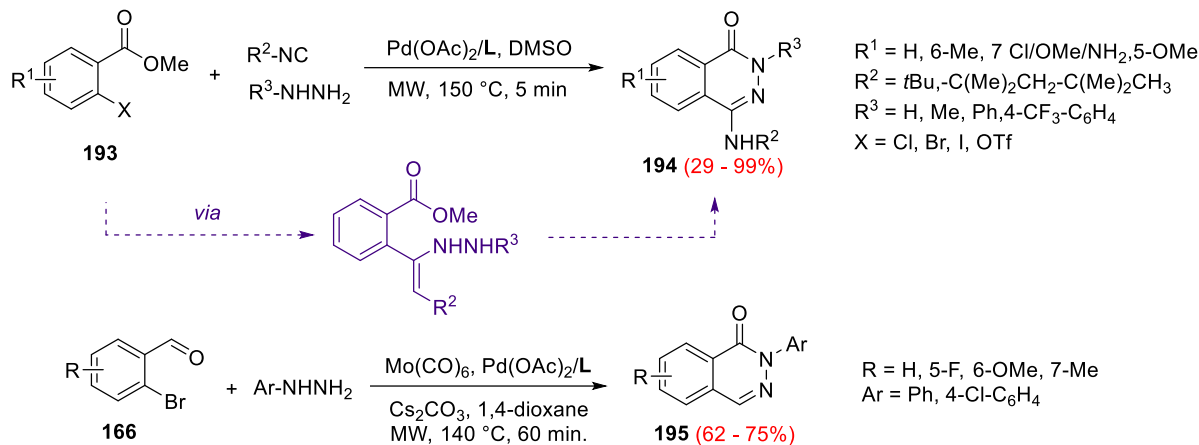
In an attempted reaction of 4,7-dichlorobenzalphthalides **187** with methylhydrazine, a new scaffold pyrazolo[3,4,5-*d,e*]phthalazine **188** was confirmed under classical reflux (*via* a phthalazinone intermediate); even with an equimolar amount of substrates (1:1) and mild heating. The reaction cannot be stopped at phthalazinone intermediate stage under reflux. Interestingly, this transformation has been controlled by microwave heating, where exclusively phthalazinone products **189** were obtained even with an excess of hydrazine. Although some hydrazine derivatives led to the formation of other heterocyclic isoindolinone **190** as a significant or exclusive product.¹²⁴ Alternatively, dihydrophthalazine-1,4-dione(s) **191** can be prepared by direct reaction of phthalic anhydride with a variety of substituted hydrazines/amines under microwave heating for a short reaction time (<5 min) at 160–170 °C. Although with electron-deficient hydrazine, the reaction ended with isoindol-1,3-diones **192**, which were subjected to ring expansion in a subsequent step towards preparing phthalazine derivatives (Scheme 54).¹²⁵ However, there is no report for the conversion of **190** to **189**; unlike **192** to **191**.



Scheme 54. Microwave-controlled synthesis of phthalazines (pyrazolo-phthalazine with classical heating).

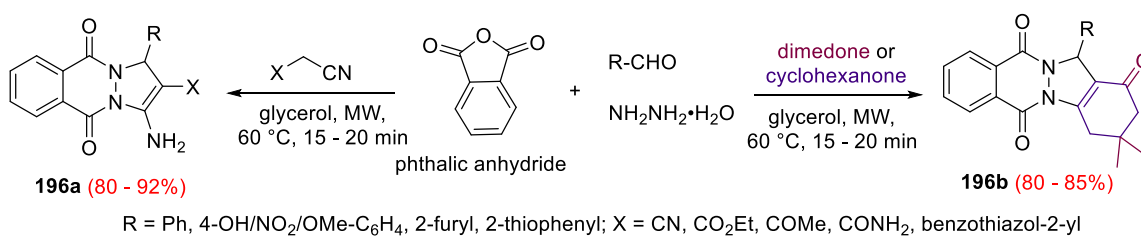
Regioselective isocyanide insertion was observed in the synthesis of phthalazines in the presence of a Pd(0) catalyst. The reaction of *ortho*-(pseudo) halobenzoate **193** with hydrazine and isocyanide under

microwave heating for 5 min progress by isocyanide insertion to the *ortho*-halogen-carbon bond followed by amine attachment and lactomization to 4-aminophthalazin-1(2*H*)-ones **194** with the high yield up to 99%.¹²⁶ Another palladium-catalyzed reaction of *ortho*-bromobenzaldehyde with arylhydrazines yielded *N*-arylphthalazinone **195**. In the reaction, Mo(CO)₆ was employed (avoided use of toxic carbon monoxide), which furnished appreciable yields up to 75% with microwave heating at 140 °C for 60 min (Scheme 55).¹²⁷



Scheme 55. Microwave-assisted synthesis of phthalazines from *ortho*-halo-benzoate/benzaldehyde and hydrazine.

A catalyst-free synthesis of pyrazolo/indazolo[1,2-*b*]phthalazine-diones **196** under controlled-microwave irradiation was achieved in a benign reaction media. The one-pot MCR reaction of phthalic anhydride, hydrazine hydrate, arylaldehyde, and active methylene reagents (malononitrile, ethylcyanoacetate, cyclic diones etc.) in glycerol under microwave heating at 60 °C for 15–20 min, furnished the high yields of phthalazinones **196a-b** respectively, with nitriles or diketones (Scheme 56). The reaction under conventional heating up to 4 h produced poor yields of 60% only.¹²⁸

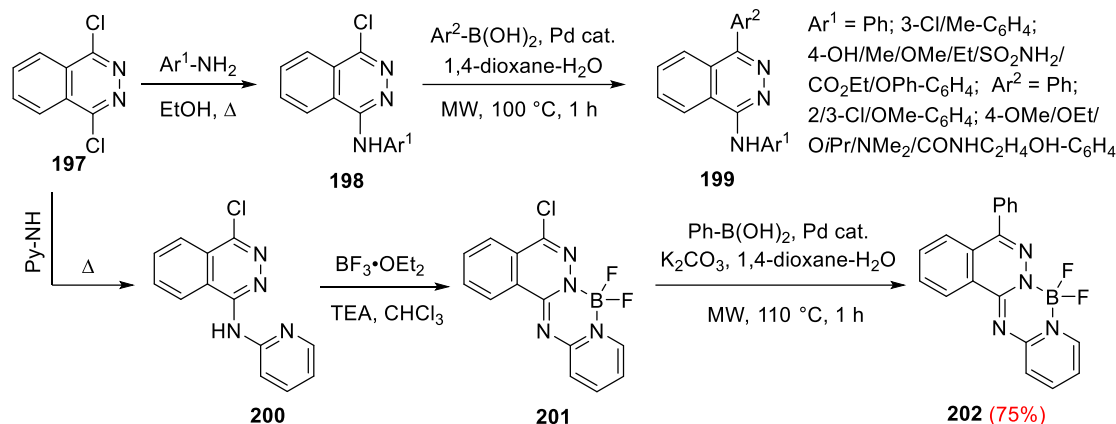


Scheme 56. Synthesis of pyrazolo/indazolo[1,2-*b*]phthalazine-diones.

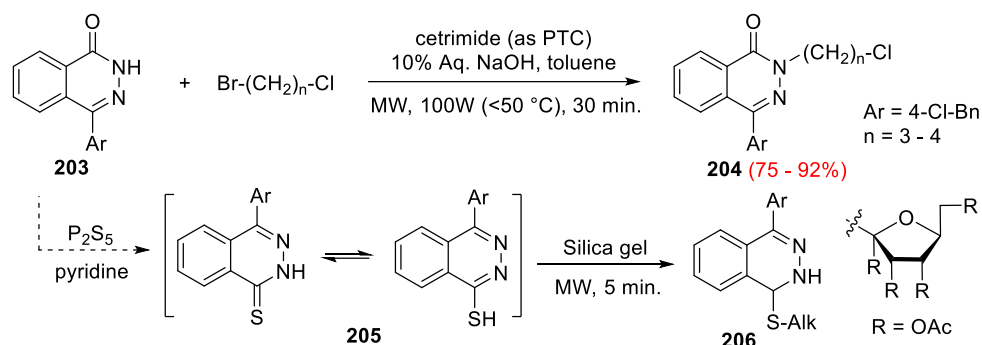
Microwave-assisted Suzuki-coupling of 1-arylamino-4-chlorophthalazine **198** gave access to 1-arylamino-4-(hetero)arylphthalazines **199**; capable of reducing the production of PGE₂.¹²⁹ Similarly, Suzuki-coupling employed with boron-difluoride complex of *N*-pyridyl-1-amino-4-chlorophthalazine **201** with phenylboronic acid under microwave heating; furnished the corresponding high blue fluorescent boron difluoride complexes **202** (Scheme 57).¹³⁰

4-Benzyl-phthalazin-1-one derivatives **203** were subjected to *N*³-alkylation (amidic-NH) in a biphasic reaction media using phase-transfer catalyst cetrimide *via* a microwave-promoted reaction which yielded up to 92% of *N*³-alkylated 4-benzyl-phthalazin-1-one derivatives **204** within 30 min at a temperature below 50 °C.

The reaction attempted under classical heating at 50 °C for 14 h, resulted in much lower yields.¹³¹ Microwave-assisted *S*-glycosylation of 4-arylphthalazine-2-thione **205** with par-acetylated ribose furnished phthalazine based *S*-glycosides **206**; having antiviral and antimicrobial potential (Scheme 58).¹³²

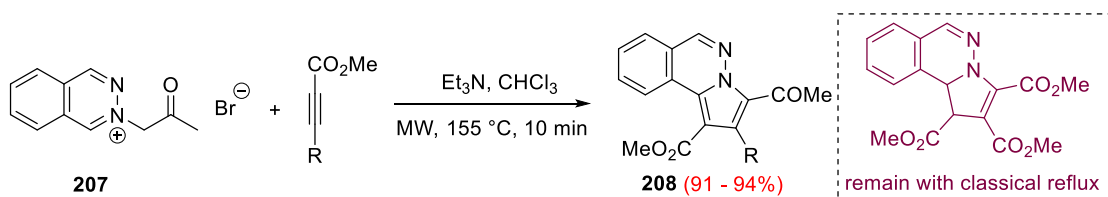


Scheme 57. Suzuki-coupling of 1-arylamino-4-chlorophthalazine under MWI.



Scheme 58. Microwave-assisted *N*³-alkylation and *S*-glycosylation of 4-aryl-phthalazin-1-one.

The [3+2] cycloaddition reaction of *N*-alkylated phthalazine **207** with methyl propionate or dimethyl acetylene dicarboxylate offered access to fluorescent building blocks pyrrolophthalazines **208**. Excellent yields were observed under microwave heating for 10 min (94% and 91%); while conventional approaches have compromised the yields with incomplete aromatization leading to non-aromatic side product (Scheme 59).¹³³

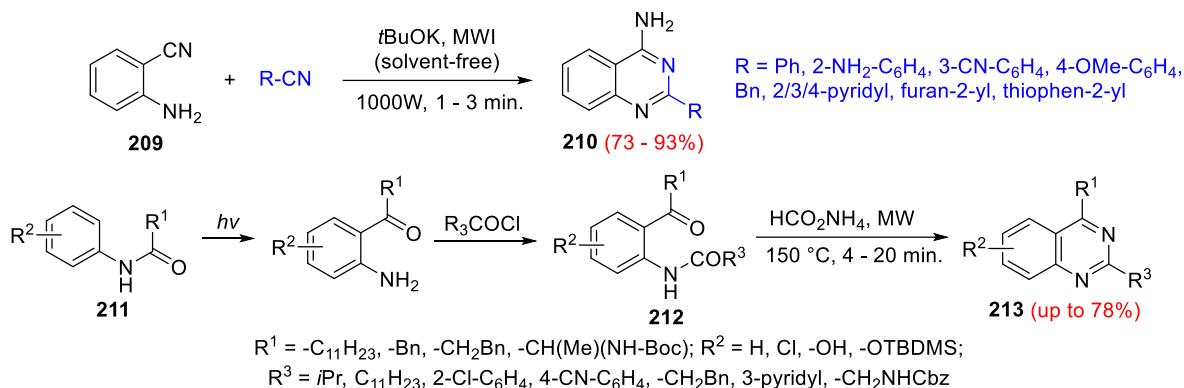


Scheme 59. Synthesis of pyrrolophthalazines – a fluorescent building block.

3.3. Quinazoline

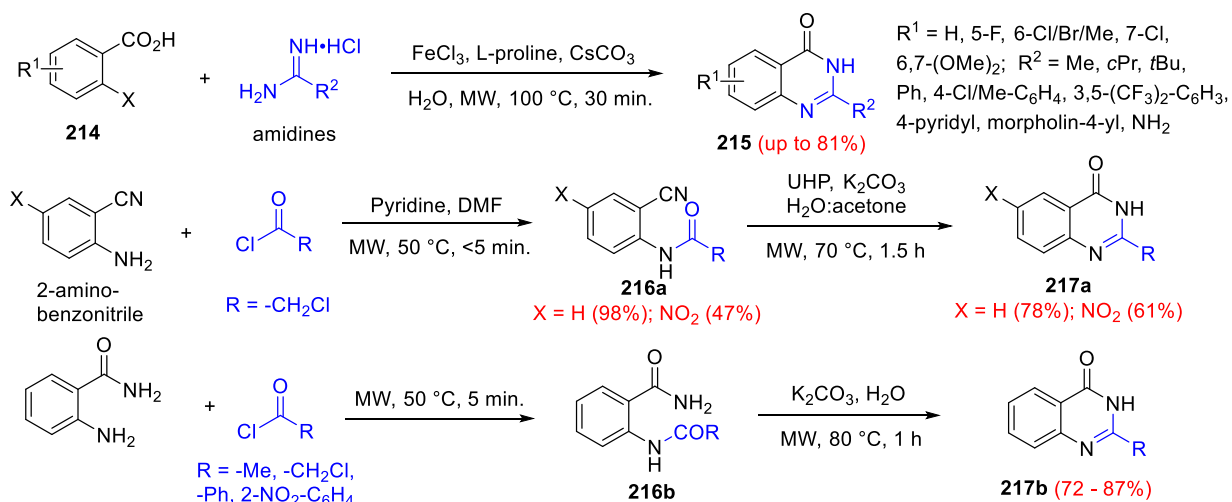
The rapid solvent-free reaction of *ortho*-aminobenzonitrile **209** with aryl nitriles under microwave irradiation (in a domestic oven) produced 2-substituted 4-aminoquinazolines **210** in high yields (up to 93%) in

the presence of potassium tertiary butoxide.¹³⁴ Another three-step conversion of anilids **211** to 2,4-disubstituted quinazolines **213** was reported via cascade of photochemical Fries-rearrangement to *ortho*-aminoacylbenzene followed by reaction with acyl chloride to an amide derivatives **212**. These amides were efficiently cyclized to quinazolines **213** using ammonium formate (as nitrogen source) under neat microwave-heating for 4–20 min (Scheme 60).¹³⁵



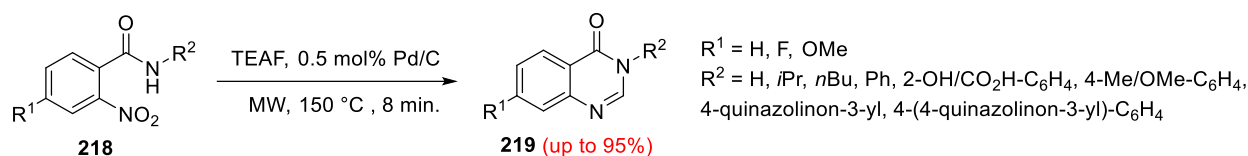
Scheme 60. Microwave-enhanced solvent-free synthesis of quinazolines.

ortho-Halobenzoic acids **214** with amidines efficiently produced 4-quinazolinone **215** in the presence of FeCl₃ under microwave conditions in aqueous media *via* C-N coupling followed by intramolecular cyclization. Although the reactions proceeded smoothly in dimethyl formamide (DMF) and Fe₂(acac)₃ with almost similar yields, the use of water and readily available cost-effective FeCl₃ catalyst with L-proline is considerably better due to the green and economic aspects of the method. This reaction produces good yield with electron-rich substrates and even non-active amidines like guanidines.¹³⁶ Similarly, *N*-(2-cyanophenyl)acetamide **216a** (obtained from 2-aminobenzonitrile) in mild oxidative condition using UHP (Urea Hydrogen Peroxide) under aqueous microwave condition furnished 2-chloromethyl-4-quinazolinone **217a** in 90 min (30 h in conventional heating, have poor yields). Alternatively, the one-pot reactions of *N*-acyl-2-aminobenzamides **216b** (from 2-aminobenzamides) in water under microwave heating have also been furnished quinazolinone **217b** with yields up to 87% (Scheme 61).¹³⁷



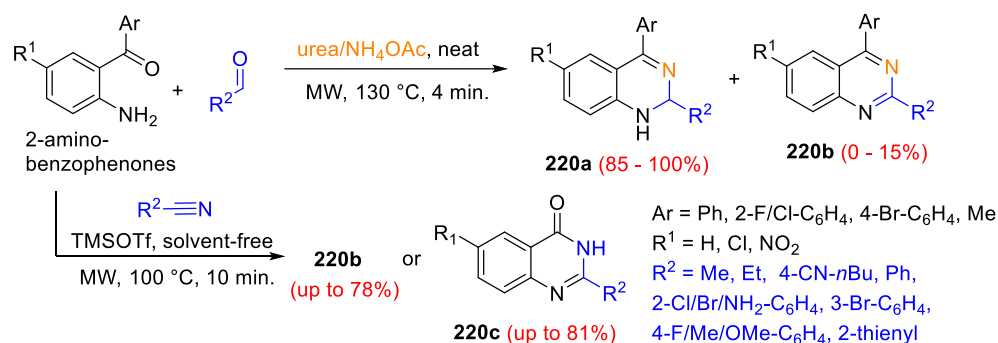
Scheme 61. Microwave-assisted green synthesis of 2-substituted-4-quinazolinone in aqueous media.

Apart from 2-aminobenzamide, its precursor, 2-nitrobenzamide **218** has been used to synthesize 4-quinazolinone **219** *via* a cascade of palladium-catalyzed hydrogen transfer followed by condensation, promoted by microwave-irradiation at 150 °C for <10 min.¹³⁸ This method was also used for the synthesis of benzimidazoles and 1,4-benzodiazepines by replacing *o*-nitrobenzamides with respective substrates (Scheme 62).¹³⁸



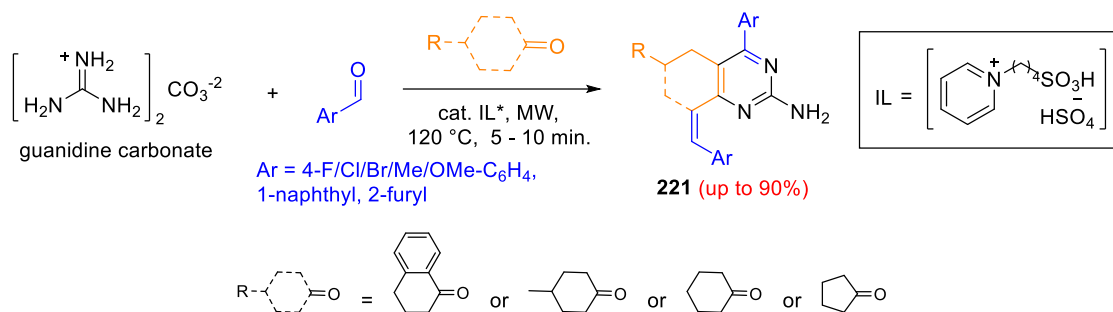
Scheme 62. Palladium-catalyzed one-pot synthesis of 4-quinazolinone from 2-nitrobenzamides.

A solvent and catalyst-free one-pot microwave-promoted strategy was developed to synthesize 4-aryl-dihydro-quinazolines. The reaction of 2-amino-benzophenones with different aldehydes and urea (as nitrogen source) furnished excellent yields of dihydroquinolines **220a** with little traces of aromatic counterpart **220b**, after microwave irradiation for 4 min at 130 °C. This clean and simple protocol has wide substrate scope for benzophenone derivatives and aldehydes; ammonium acetate has also been used effectively as a nitrogen source producing high yields 80–90%. These syntheses under the classical approach in acetic acid required continuous reflux for 10 h.¹³⁹ Another one-pot Lewis acid-mediated activation of aliphatic/aromatic nitriles with amino-benzophenone efficiently produced 4-aryl quinazolines **220b** *via in situ* amidine generation under solvent-free microwave conditions. The reaction produced high yields ranging from 72–81% under microwave heating at 100 °C for 10 min in the presence of TMSOTf. The protocol was equally effective with anthranilic acid; afforded good yields of 4-quinazolinones **220c** (Scheme 63).¹⁴⁰



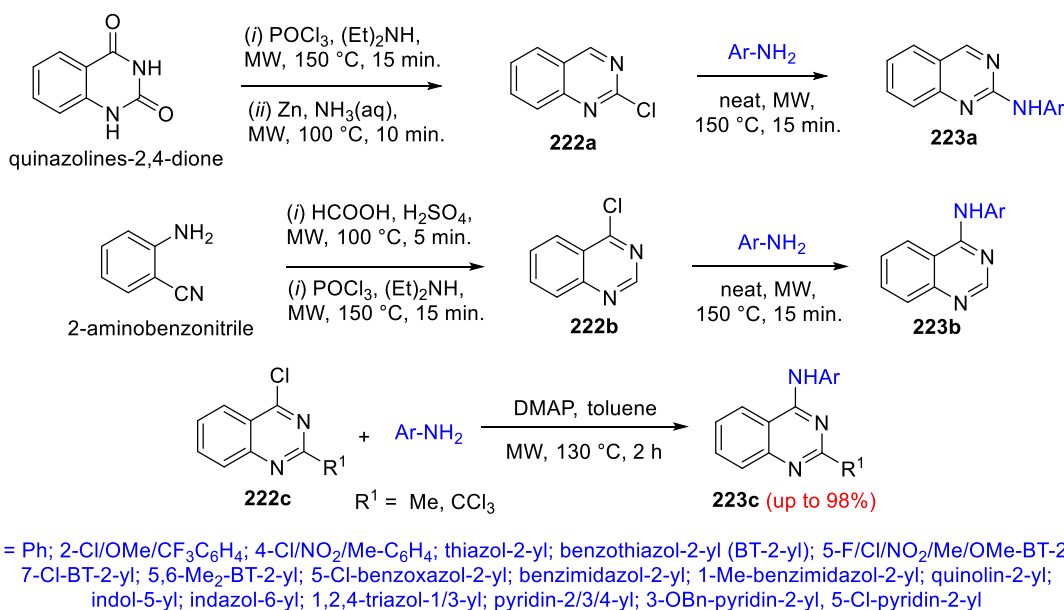
Scheme 63. Microwave-assisted solvent-free synthesis of 4-aryl quinazolines from benzophenones.

Tetrahydroquinazoline **221** has been prepared from a three-component one-pot reaction of guanidine carbonate, aldehydes, and cyclic ketones using an acidic ionic liquid catalyst under solvent-free microwave conditions. Although the reaction was also attempted with ultra-sounds using an excess of ionic liquid (as solvent and catalyst), the solvent-free microwave condition was proved more efficient in terms of chemical yields and reaction time (Scheme 64).¹⁴¹



Scheme 64. Microwave-assisted solvent-free IL-catalysed synthesis of tetrahydroquinazoline.

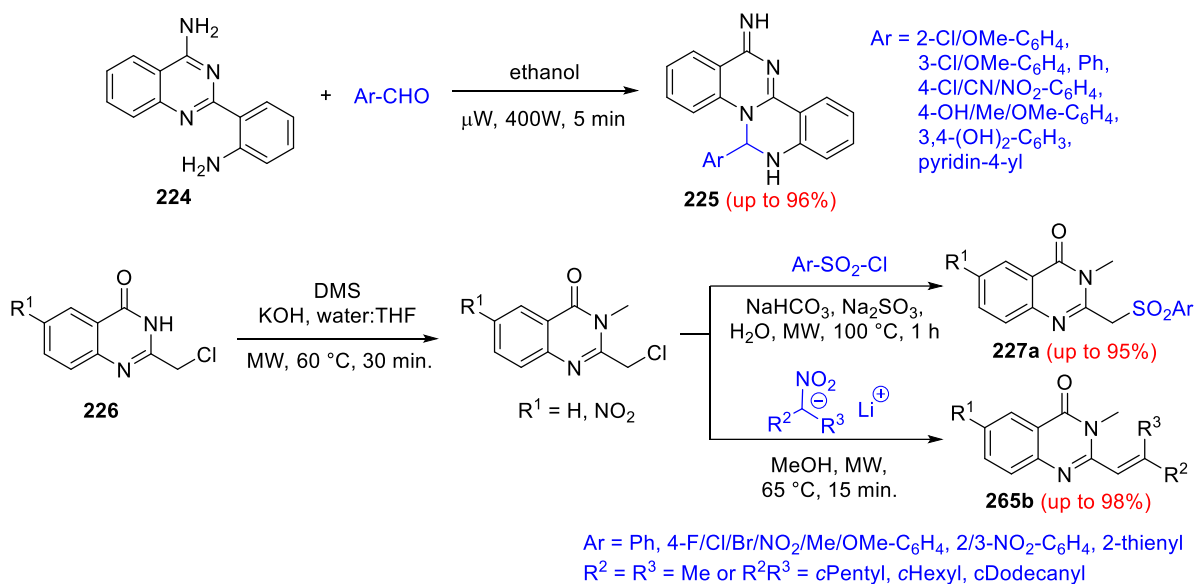
The chemical reactions of quinazolines include microwave-assisted synthesis of 2/4-arylaminoquinazolines **223a,b** by substituting 2/4-chloroquinazoline with aromatic amine to furnish biologically relevant molecules. Before that, 2-chloroquinazoline **222a** was prepared by chlorinating quinazolines-2,4-dione with phosphorous oxychloride, followed by selective dehalogenation with activated zinc and aqueous ammonia. Similarly, 4-chloroquinazoline **222b** was prepared from 2-aminobenzonitrile by condensation with formic acid followed by chlorination. Further, both 2- or 4-chloroquinazoline were subjected to nucleophilic substitution with arylamines under microwave at 150 °C for 15 min.¹⁴² A well-known C-N bond forming reaction, Buchwald-Hartwig cross-coupling uses palladium catalysts; as an alternate, DMAP-catalysed amination with microwave condition was reported. The reaction of 4-chloroquinazoline **222c** with different aryl/heteroaryl amines under microwave irradiation furnished considerable yields of **223c** up to 98% with a broad scope of anilines and other heterocyclic amines (Scheme 65).¹⁴³



Scheme 65. Microwave-assisted alternative Buchwald-Hartwig reaction for the synthesis of 2-/4-arylaminoquinazolines.

A simple and efficient cyclization of 2-(2-aminophenyl)quinazoline-4-amine **224** with various aryl aldehydes furnished tetracyclic dihydroquinazolines **225**. The microwave-assisted protocol produced high yields up to 96% within 5 min; while 2–4 h continuous reflux was required for comparable yields in the

classical approach.¹⁴⁴ 2-(Chloromethyl)-4-quinazolinone **226** subjected to amidic -NH methylation under microwave condition at 60 °C for 30 min followed by nucleophilic substitutions with arylsulfonyl chloride or nitroalkyl anions furnishing the corresponding sulfones **227a** or 2-ethylenic derivatives **227b**, respectively (Scheme 66).¹³⁷

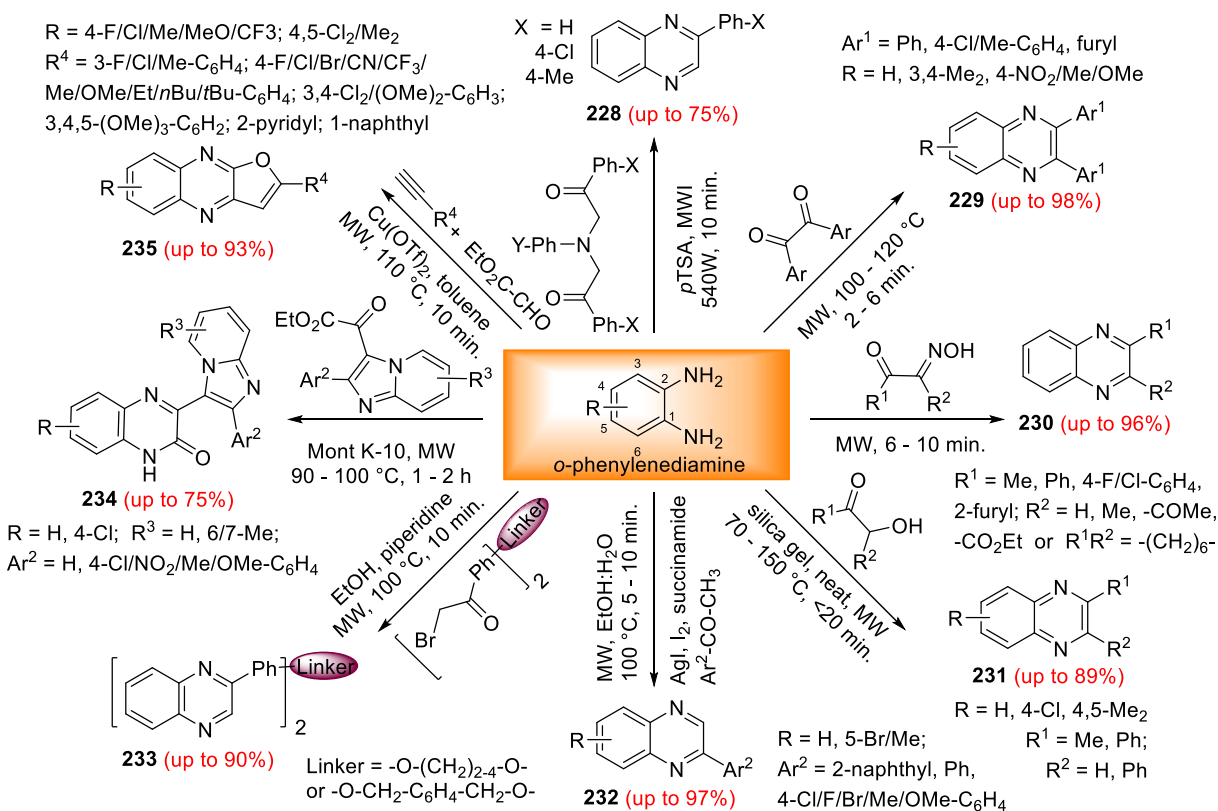


Scheme 66. Synthesis of tetracyclic dihydroquinazolins and 2-substituted 4-quinazolinone.

3.4. Quinoxaline

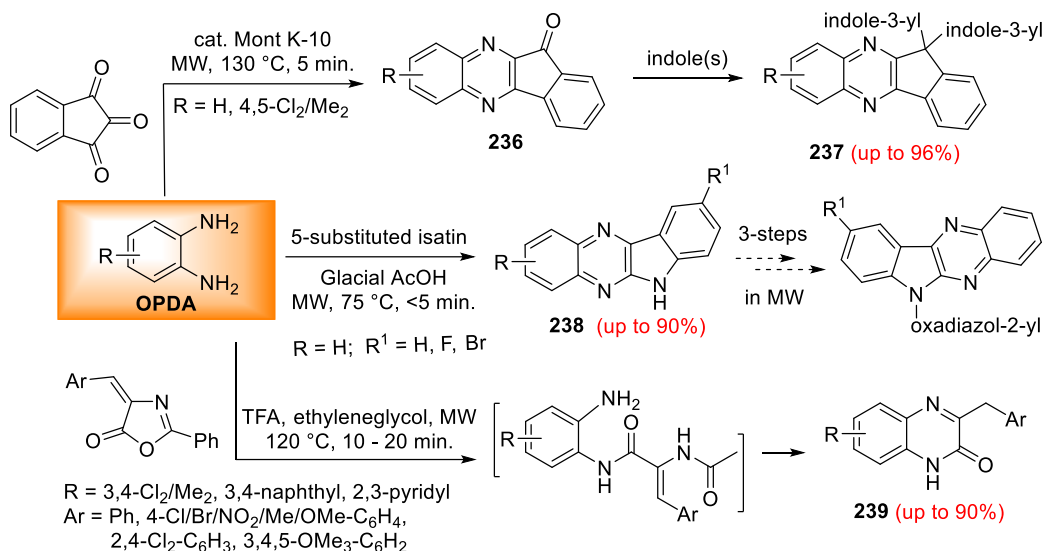
The most often adapted synthetic strategy is double condensation of 1,2-dicarbonyls with 1,2-diaminoaromatic compound.¹⁴⁵⁻¹⁵² A neat reaction of *N,N*-diphenacylaniline with *o*-phenylenediamine (OPDA) in the presence of *p*-TSA produced unexpected 2-arylquinoxaline **228** (presumably proceeded by tandem carbonyl addition → eliminative cyclization → air oxidation sequence) under microwave irradiation for 10 min in open vessel domestic microwave oven.¹⁴⁵ A efficient solvent and catalyst-free green protocol used for the reaction of various substituted OPDA with phenyl/furyl substituted 1,2-dicarbonyls under microwave afforded the corresponding quinoxalines **229** up to 98% in 2-6 min.¹⁴⁶ The replacement of 1,2-dicarbonyls with α -hydroxyimino ketones (easily prepared from corresponding α -CH₂-ketones) under neat microwave heating offered high yields (up to 96%) of respective quinoxalines **230** in 6–10 min.¹⁴⁷ Another replacement of dicarbonyl with a cost-effective α -hydroxy ketone (2-hydroxy acetophenone derivatives); in the presence of silica-gel afforded good yields of quinoxalines **231** under solvent-free microwave heating for <20 min. However, this reaction under conventional reflux or with various organic solvents offered poor conversion (yields <10%).¹⁴⁸ A fast multicomponent approach for the reaction of acetophenone derivatives in the presence of oxidants (AgI, iodine, and succinamide) was optimized towards synthesizing 2-arylquinoxalines **232**. The protocol used green reaction media ethanol:water or PEG400:water with microwave heating, in which *in situ* generated α -iodoacetophenone condensed with OPDA; resulted in a high yield of anticipated arylquinoxalines **232** within 5–10 min.¹⁴⁹ Bis-(α -bromoketone) *i.e.*, acetophenone derivatives, were employed under microwave heating to prepare quinoxalines **233**. Although the protocol attempted with various solvents, bases, and heating modes proceeded towards product formation. Still, the best yields of up to 90% were obtained in ethanol and piperidine under microwave heating for 10 min. The reaction of a simple *p*-OH derivative of acetophenone did not afford any expected product, whereas when 2,3-diaminopyridine was

employed, two regio-isomers were observed.¹⁵⁰ An efficient solvent-free protocol for synthesizing quinoxalines from sterically/bulky glyoxalate was optimized under microwave with the use of a Mont-K-10 catalyst. The Hinsberg hetero-cyclization of imidazo-pyridyl based α -ketoesters under conventional reflux did not proceed even after 48 h. Concurrently, the reaction with microwave activation resulted in effective transformation to the corresponding imidazo-pyridylquinoxalin-2-ones **234** with appreciable yields.¹⁵¹ A fascinating copper-catalyzed one-pot A^3 -coupling of OPDA with ethylglyoxalate and terminal alkyne was optimized towards the synthesis of furoquinoxalines **235**. The protocol has broad substrate scope for the reaction of various substituted OPDA and terminal alkynes in toluene under microwave heating at 110 °C for 10 min; affording high yields up to 93% (Scheme 67).¹⁵²



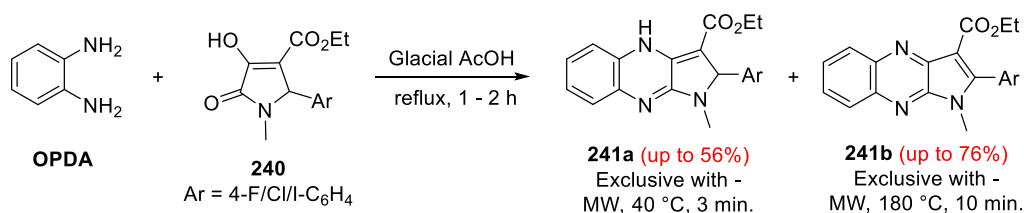
Scheme 67. Synthesis of quinoxalines by condensation of 1,2-dicarbonyls with 1,2-diaminoaryls.

The reaction of indane-1,2,3-trione with OPDA using a Mont-K-10 catalyst under solvent-free microwave irradiation for 5 min generated good yields of indenoquinoxalines **236**; which has been further treated with indole derivative to produce bis-indole-containing indeno[1,2-*b*]quinoxalines **237**.¹⁵³ Similarly, the reaction of OPDA and isatin in glacial acetic acid under microwave heating at 75 °C produced indolo[2,3-*b*]quinoxalines **238** in high yields up to 90% within 3–5 min. The quinoxaline **238** was further functionalized with oxadiazoles by sequential reaction with ethyl-2-chloroacetate, hydrazine, and carboxylic acids.¹⁵⁴ A solvent-dependent microwave-assisted approach for the chemoselective synthesis of 3-benzylquinoxalin-2-ones **239** was reported. The reaction of OPDA with 4-arylidene-2-phenyloxazol-5-ones under microwave heating at 120 °C, resulted in different products depending upon the choice of solvent made; ethylene glycol with a catalytic amount of TFA afforded high yields of **239** up to 90% in 10–20 min (Scheme 68). Moreover, the reaction in acetic acid or DMSO, respectively, resulted in benzimidazole and β -amino dipeptides.¹⁵⁵



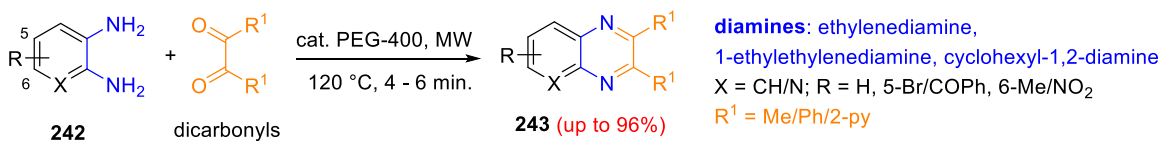
Scheme 68. Synthesis of quinoxalines by condensation of OPDs with different di-keto or its analogues.

The reaction of OPDA with *N*-methyl-4-hydroxy-5-oxo-pyrroles **240** in acetic acid furnished quinoxalines **241**. The reaction under conventional heating produced a mixture of 2,4-dihydro-pyrrolo-quinoxalines **241a** and aromatized pyrrolo-quinoxalines **241b**. In contrast, an attempt for the sole aromatized product could not be achieved even by extending the reaction time or by means of an oxidizing reagent (decomposition of starting material was observed). Later, the reaction with microwave heating exclusively produced **241a** after 3 min at 40 °C or exclusive aromatized products were afforded at 180 °C for 10 min (Scheme 69).¹⁵⁶



Scheme 69. Temperature-controlled microwave-assisted synthesis of pyrrolo-quinoxalines.

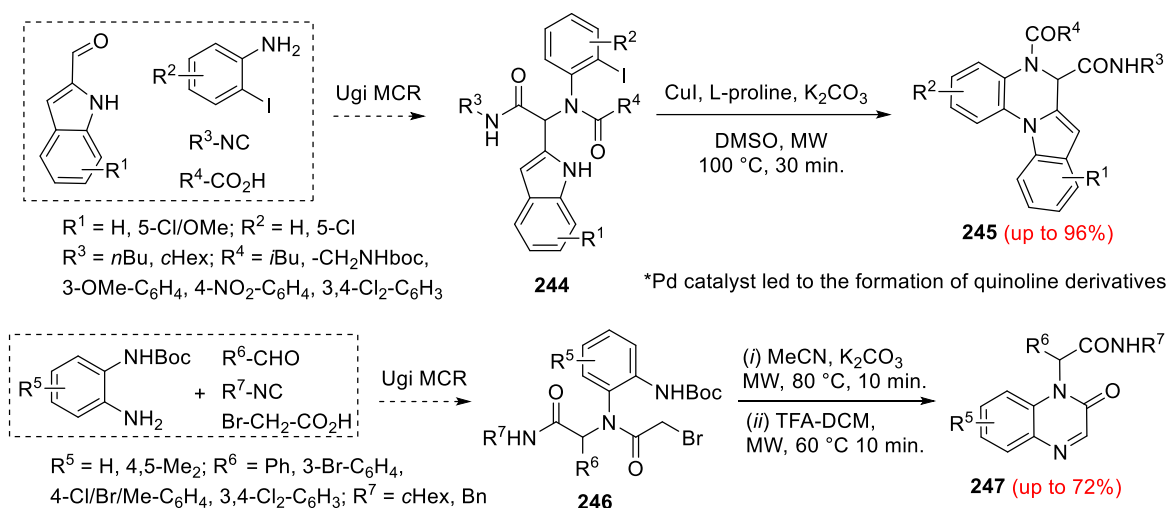
PEG-400 has been found as a catalyst for the reaction of 1,2-diamines with dicarbonyls in synthesizing quinoxalines. A protocol was optimized with microwave heating for 4–6 min at 120 °C afforded yields up to 96% for various aliphatic/aryl/hetero-aryl diamines with a catalytic amount of PEG-400 (Scheme 70).¹⁵⁷



Scheme 70. Microwave-assisted synthesis of quinoxalines catalyzed by PEG-400.

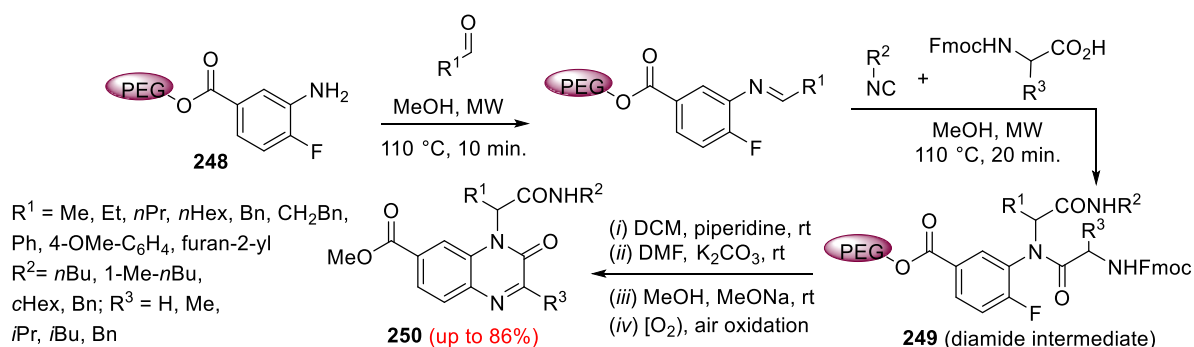
Isocyanide-based chemistry of coupling reactions was used for the preparation of quinoxalin-2-one. Ugi adduct (4C-MCR – isocyanide, aldehyde, amine, and acid) was effectively used to construct the quinoxalines.

The adduct **244** of indole-2-carboxaldehyde(s), 2-iodoanilines, isocyanides, and carboxylic acid derivatives were exclusively transformed into 5,6-dihydroindolo[1,2-*a*]quinoxalines **245** using a copper catalyst, through microwave-accelerated chemoselective C-N and C-C bond formation during intramolecular cyclization.¹⁵⁸ Another intramolecular cyclization of Ugi adduct **246** from *N*¹-*boc*-phenylenediamines, bromoacetic acid, arylaldehydes, and isocyanides in the presence of a mild base under microwave heating at 80 °C for 10 min afforded quinoxaline derivatives **247** in substantial yields after *Boc*-deprotection (Scheme 71). Moreover, the protocol has access to benzimidazopyrazinone derivatives when the reaction is performed in reverse order i.e., *Boc*-deprotection followed by intramolecular cyclization.¹⁵⁹



Scheme 71. Microwave-assisted intramolecular cyclization of Ugi-adducts to quinoxalines.

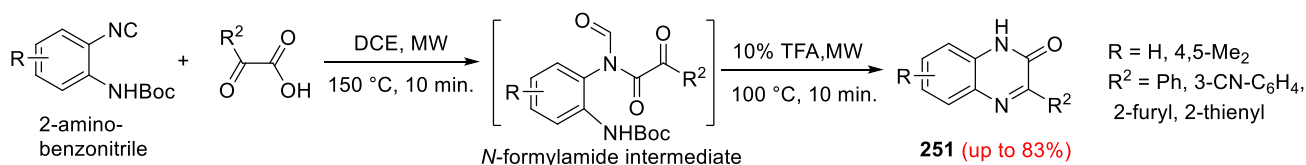
In the above-discussed intramolecular cyclizations, the generation of diamide intermediate/Ugi-adduct (particularly with the use of amino acids - in place of carboxylic acids) had a challenging issue. A stepwise synthetic strategy under microwave was implemented to address the diamide generation. PEG-bonded anilines and aldehydes were irradiated with microwave for 10 min at 110 °C followed by the addition of *N*-protected amino acids and isocyanides with further heating for 20 min at the same temperature, which resulted in crucial diamide intermediates **249**. The synthesis of Ugi adducts **249** under conventional reflux required 5–10 h with poor yields of <50%. Further, amine deprotection followed by selective intramolecular cyclization resulted in tetrahydroquinoxalin-2-ones in the presence of a base, which was cleaved from PEG followed by air oxidation to dihydroquinoxaline-2-one **250** (Scheme 72).¹⁶¹



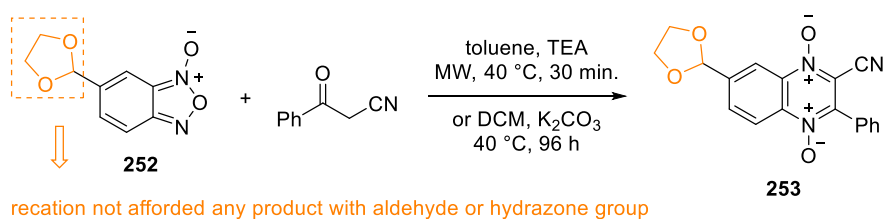
Scheme 72. Microwave-promoted stepwise synthesis of diamide intermediate to quinoxaline.

The one-pot two-component coupling of boc-protected 2-aminobenzonitrile with glyoxylic acids under microwave irradiation produced intermediate *N*-formylamide. The boc-deprotection (10% TFA-DCE) followed by intramolecular cyclization under microwave heating to 100 °C for 10–15 min afforded significant yields of quinoxalin-2-ones **251** (Scheme 73). This protocol also offered access to *N*¹-acylbenzimidazoles with the application of carboxylic acids in place of glyoxylic acids.¹⁶¹

The benzofuroxan derivatives **252** with 2-cyanoacetophenone gave quinoxaline-1,4-di-*N*-oxide **253**. The protocol aimed for a comparative study of conventional and microwave-assisted synthesis with different strategies to prepare the designed compounds, but the presence of aldehyde or hydrazone group in starting material did not afford any product. In contrast, with the alkyl group, poor yields were observed. Finally, the reaction of **252** with 2-cyanoacetophenone afforded satisfactory results in 30 min under microwave, whereas it took 96 h by conventional approach (Scheme 74). Further, it was modified as 2-(*N*-acylhydrazone) derivatives with anti-tubercular potential.¹⁶²



Scheme 73. Two-component coupling of 2-(*N*-boc-amino)phenylisocyanide with glyoxylic acids.



Scheme 74. Synthesis of quinoxaline 1,4-di-*N*-oxide from benzofuroxan derivatives.

Microwave-assisted reactions were also found beneficial in the synthesis of different functionalized quinoxalines such as triazolo-quinoxalines,¹⁶³ or imidazo/pyrazolo[1,5-*a*]quinoxalin-2-amines,^{164,165} avoiding harsh conventional reaction condition or metal catalyst. These compounds found their utility as anti-inflammatory agents by inhibiting IKK1, IKK2 or selective TLR7 antagonists.

Conclusions

In summary, the syntheses and reactions of nitrogen-containing 5- and 6-membered benzene-fused heterocycles by employing microwave-assisted technology from the past decade have been discussed. It was appealing to find that microwaves have played a significant role in the sustainable construction and chemical modification of various heterocycles. The use of microwave technique in a chemical laboratory benefits the chemist in a way or other. There is example where the improvement in the yields was not observed but the reaction produced completely new class of product which not even traced in conventional heating. Indeed, the occurrence of chemical reactions in a domestic oven and rapid acceleration; indicates the catalytic role of

microwaves. Moreover, the advancement in technology and the development of special instruments to perform a reaction under high pressure in closed vessels bring many opportunities to use the temperature beyond the boiling point of the reaction medium. Indeed, the use of microwave irradiation benefits reduced side products, chemo/regioselectivity concerns, and avoiding the use of several harsh/toxic/hazardous reagents or catalysts. The future of microwave technology in chemical laboratories thrives by developing surplus protocols for various chemical transformations. In our wisdom, large-scale industrial synthesis is still an obscure area for microwave techniques, and microwave-assisted flow chemistry can open a novel state-of-the-art. Developing special instruments/hyphenated techniques to apply microwaves for bulk synthesis is very much needed.

List of Abbreviations:

MW/ μ W	:	Microwave (heating)
MWI	:	Microwave irradiation
IMDAF	:	Intramolecular diels–alder furan
THF	:	Tetrahydrofuran
TEA	:	Triethylamine
DMF	:	Dimethylformamide
EWG	:	Electron withdrawing group
EDG	:	Electron donating group
TFA	:	Trifluoroacetic acid
PPAR	:	Peroxisome proliferator-activated receptor
TPP	:	Triphenylphosphine
DMSO	:	Dimethylsulphoxide
DCE	:	Dichloroethane
DMA	:	Dimethylacetamide
CAN	:	Ceric ammonium nitrate
DABCO	:	1,4-Diazabicyclo[2,2,2]octane
BTMAB	:	Benzyltrimethylammonium bromide
DPPA	:	Diphenylphosphorylazide
DBU	:	1,8-Diazabicyclo[5,4,0]undec-7-ene
OPDA	:	<i>Ortho</i> -phenylenediamine
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCC	:	Dicyclohexyl carbodiimide
TBAI	:	Tetra- <i>n</i> -butylammonium iodide
TEAF	:	Tetra- <i>n</i> -butylammonium fluoride
DMAP	:	4-(Dimethylamino)pyridine
NBS	:	<i>N</i> -Bromo succinimide
CSA	:	Camphor sulphonic acid
TFE	:	2,2,2-Trifluoroethanol
TBPB	:	Tertiary butyl peroxybenzoate
UHP	:	Urea hydrogen peroxide
MCR	:	Multicomponent reaction

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