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Recent developments on microwave-assisted organic synthesis of nitrogen- and oxygen-containing preferred heterocyclic scaffolds†

Ghanshyam Tiwari,[a] Ashish Khanna,[a] Vinay Kumar Mishra[a] and Ram Sagar *[ab]

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In recent decades, the utilization of microwave energy has experienced an extraordinary surge, leading to the introduction of innovative and revolutionary applications across various fields of chemistry such as medicinal chemistry, materials science, organic synthesis and heterocyclic chemistry. Herein, we provide a comprehensive literature review on the microwave-assisted organic synthesis of selected heterocycles. We highlight the use of microwave irradiation as an effective method for constructing a diverse range of molecules with high yield and selectivity. We also emphasize the impact of microwave irradiation on the efficient synthesis of N- and O-containing heterocycles that possess bioactive properties, such as anti-cancer, anti-proliferative, and anti-tumor activities. Specific attention is given to the efficient synthesis of pyrazolopyrimidines-, coumarin-, quinoline-, and isatin-based scaffolds, which have been extensively studied for their potential in drug discovery. The article provides valuable insights into the recent synthetic protocols and trends for the development of new drugs using heterocyclic molecules.

1. Introduction

A natural product is a substance found in the nature, and can be in the form of heterocycles or other moieties.[1] Natural products have had a great influence on the developments of medicines and materials for treatment of cancer, bacterial infections, autoimmune diseases and inflammation.[2] Nature is a major source for organic molecules in the form of secondary metabolites, which can be used for the development of novel therapeutics. Most of the drugs based on chemical scaffolds isolated from plants, marine organisms, microbes and other natural sources serve as treatments of various diseases. Natural products have also been used for commercial purposes such as

[a]Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi 221005, India

[b]Glycochemistry Laboratory, School of Physical Sciences, Jawaharlal Nehru University, New Delhi 110067, India. E-mail: ram.sagar@jnu.ac.in

† This review is dedicated to Arun K. Shaw on his 68th birthday.

Ghanshyam Tiwari

Ghanshyam Tiwari completed his M.Sc. at Mahatma Gandhi Kashi Vidyapith, Varanasi, Uttar Pradesh, India. He joined the Glycochemistry lab of the Department of Chemistry at the Institute of Science, Banaras Hindu University, as a research scholar in year 2018. He completed his PhD in April 2023 under the supervision of Prof. Ram Sagar. His expertise lies in glycoscience, microwave-assisted synthesis, organic synthesis, and the development of new methods for synthesis of natural product inspired glycohybrids.

Ashish Khanna

Ashish Khanna completed his M.Sc. at Kumaun University, Nainital, Uttarakhand, India, in 2016. He joined the Department of Chemistry at the Institute of Science, Banaras Hindu University, as a PhD research scholar in the Glycochemistry lab in the year 2017. He completed his PhD in March 2023 under the supervision of Prof. Ram Sagar. Currently he is working as Assistant Professor in Department of Chemistry, SOPS, DIT University, Dehradun. His expertise lies in organic synthesis, the development of carbohydrate-derived bioactive molecules, natural product-inspired hybrid analogues and molecular modeling, especially protein–ligand interactions via in silico docking tools.

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cosmetics, dietary supplements, and many other edible products.[3,4]

New pharmaceuticals and many effective medications were initially developed as semi-synthetic analogues of compounds found in nature.[5] Natural products are very diverse in terms of three-dimensional (3D) chemical space and exhibit unique biological functions. This is inferred from the idea that virtually all natural compounds have some capability for receptor binding.[6,7]

Thus, the design and synthesis of natural products and natural product-inspired heterocyclic molecules have been of interest to medicinal chemists and chemical biologists because these molecules have significant roles in the drug-development process.[8–10] Common heterocycles are found in natural products, especially in alkaloids, polyketals, vitamins and propanoids.[11] Isatin, coumarin, quinoline, isoquinoline, pyrimidine, pyrazole, and pyrazolopyrimidine are heterocyclic motifs found widely in bioactive natural products as well as in pharmaceutical agents. Molecules derived from these scaffolds, such as coumarin derivatives, show various biological activities. Calanolide A is a coumarin based anti-HIV drug.[12] Warfarin is a coumarin-based anticoagulant drug which is mainly used to prevent blood clots.[13] Chloroquine is a quinoline-based antimalarial drug and recently used to treat COVID-19.[14] Hydroxychloroquine is also a quinoline-based antimalarial drug.[15] Nintedanib is an isatin derivative, currently used as an anticancer drug.[16] The pyrazolopyrimidine derivative zaleplon is used as treatment of insomnia in humans by decreasing the activity of the brain.[17] Sildenafil is a pyrazolopyrimidine-based drug mainly used in the treatment of erectile disfunction in humans[18] (Fig. 1).

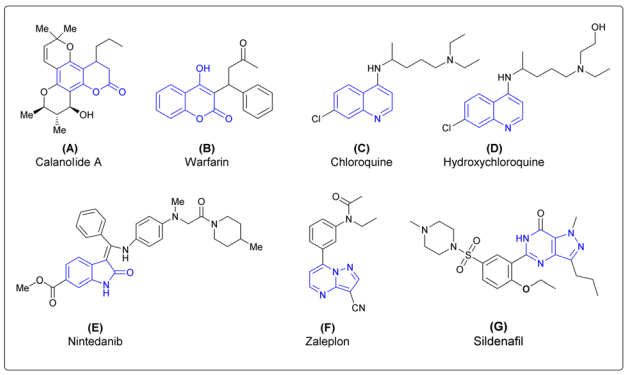

Fig. 1 Heterocycles derived bioactive molecules (A–D): (A) calanolide A, a coumarin-based anti-HIV drug, (B) warfarin, a coumarin-based anticoagulant, (C) chloroquine, a quinoline-based antimalarial drug, (D) hydroxychloroquine, a quinoline-based antimalarial drug, (E) nintedanib, an isatin-based anticancer drug, (F) zaleplon, a pyrazolopyrimidine-based anti-insomnia drug, and (G) sildenafil, a pyrazolopyrimidine-based drug.

Various techniques are available to efficiently synthesize these heterocyclic scaffolds and derivatives, including electrochemical synthesis, metal-free synthesis, photochemical

Vinay Kumar Mishra

Vinay Kumar Mishra completed his M.Sc. at Dr Ram Manohar Lohia Avadh University UP, India, in 2014. He joined the Glycochemistry lab at the Department of Chemistry, Institute of Science, Banaras Hindu University in 2019 to pursue his PhD. He completed his PhD in September 2023 under the supervision of Prof. Ram Sagar. His work is mainly focused on the development of new methods for the synthesis of carbohydrate-fused heterocyclic molecules as glycohybrids. He is also interested in the synthesis of natural product inspired bioactive scaffolds.

Ram Sagar

Prof. Ram Sagar received his PhD in Organic Chemistry from Central Drug Research Institute (CDRI), Lucknow, and University of Agra in 2006 under the supervision of Dr A. K. Shaw. After his PhD, he was a Research Associate under Prof. Y. D. Vankar at IIT Kanpur during 2006–2007. He pursued his first postdoctoral research at Seoul National University, South Korea, with Prof Seung Bum Park during 2007–2008. He then moved to the University of Oxford and worked with Prof Benjamin G. Davis as a BBSRC postdoctoral fellow up to August 2012. He then returned to India in August 2012 and held a faculty position at Shiv Nadar University (SNU). He moved to the Department of Chemistry, Banaras Hindu University (BHU) as an Associate Professor in February 2018 and worked there till December 2020. He subsequently moves as full professor to Jawaharlal Nehru University (JNU), New Delhi, in December 2020 and is presently working there as Professor of Chemistry in the School of Physical Sciences. His current research interests include devising new ways for the efficient chemical synthesis of natural product inspired small molecules, glycohybrids and glycopeptides implicated in various diseases, including tuberculosis and cancer.

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synthesis, solvent-free synthesis, ultrasonication, solvothermal synthesis, ball milling, and many more.[19–21] Some reactions under thermal conditions can take from a few hours to a few days.[22] In recent times, various techniques and methods have enabled chemical reactions to be undertaken efficiently and in less time. As a result, a new approach has been developed to serve as an energy source for performing efficient chemical synthesis.[23–26] This approach involves the use of microwave energy, which is harnessed through a microwave reactor.

A microwave reactor is an apparatus designed for carrying out microwave-assisted organic synthesis. It is important to note that this type of reactor is slightly different from the conventional household microwave oven.[27] The microwave reactor comprises a microwave emitter, a pressure controller, and a rotor with safety controls that are fitted with the reactor.[28] The microwave emitter in the reactor emits microwave energy, which is absorbed by the reactants in the reaction vessel, leading to a heating effect.[29] The pressure controller is responsible for regulating the pressure within the reactor, ensuring that it remains at the desired level. The rotor helps to distribute the reactants evenly within the reactor, enhancing the efficiency of the reaction.[30]

Over the past few decades, there has been a remarkable surge in the utilization of microwave energy. This had led to the introduction of novel and revolutionary applications in various fields, such as organic synthesis, heterocycle synthesis, polymer chemistry,[31,32] material sciences,[33] nanotechnology, and biochemical processes.[34,35] Notably, microwave irradiation has displayed the potential to significantly reduce processing time, amplify the reaction yield, as well as enhance the purity and properties of products, thereby surpassing traditional methods.[36] This advancement, known as microwave-assisted organic synthesis (MAOS), relies on the efficient heat transfer achieved through dielectric heating, and is primarily dependent on the absorption capacity of the solvent or reagents for microwave energy.[37]

Dielectric heating provides a crucial advantage over conventional heating methods as microwaves directly interact with dipoles or ionic molecules present in the reaction mixture, allowing energy transfer to occur in less than a nanosecond (10^{-9} s), leading to an instantaneous temperature rise.[38–40] Additionally, microwave irradiation facilitates volumetric heating by directly coupling the electromagnetic field with molecules in the reaction mixture, thereby minimizing or completely avoiding wall effects.[41] This introduction outlines the promising and transformative possibilities that microwave energy offers in advancing research and development across various scientific domains.[42]

Overall, the microwave reactor is an essential tool for conducting MAOS, providing a reliable and efficient energy source for various chemical reactions. Therefore, this approach has proven to be useful in obtaining a diverse library of heterocyclic molecules inspired by natural products that exhibit improved pharmacological properties. Thus, microwave irradiation has been identified as a crucial technique in organic synthesis and drug-discovery processes. This review highlights recent advancements in the synthesis of quinoline, pyrazolopyrimidine, coumarin, isatin and their derivatives under MAOS.

The review covers a wide range of microwave-assisted synthetic reactions, including Suzuki–Miyaura cross-coupling, Friedlander synthesis, copper-catalyzed four-component synthesis, and the synthesis of isatin-β-thiocarbohydrazones and quinoline fused 1,4-benzodiazepines. This breadth of coverage allows readers to gain insight into the diverse applications of microwave-assisted synthesis in different chemical transformations. We provide specific examples of successful reactions, the catalysts used, reaction conditions, and isolated yields. These examples enable researchers to understand the practical aspects of microwave-assisted synthesis. It highlights the advantages of microwave-assisted synthesis over conventional heating methods. It emphasizes the significant time savings, improved yields, and higher selectivity achieved through microwave irradiation, making it a more attractive option for various chemical reactions. The review offers valuable perspectives on the potential areas of research and improvement in microwave-assisted synthesis and discusses the need for a deeper mechanistic understanding, exploration of new reactions, "green" and sustainable chemistry applications, scale-up challenges, and the combination of microwave technology with other techniques.

Thus, this review offers a comprehensive, well-referenced, and forward-looking perspective on microwave-assisted synthesis. It goes beyond theoretical discussions and provides concrete examples and practical benefits, making it a valuable resource for researchers and practitioners in the fields of synthetic chemistry and materials science.

2. MAOS of N- and O-containing heterocycles

Nitrogen-containing heterocyclic motifs are abundant in natural products and natural product-derived drug molecules.[43,44] Therefore, chemical synthesis of these scaffolds has been of interest among organic synthesis and medicinal-chemistry research groups. Oxygen-containing molecules such as coumarins are also present in nature and display various biological functions.[45–47] Chemical modification of these secondary metabolites is needed to obtain diverse derivatives that can fulfill 3D chemical space. Thus, microwave-assisted synthetic modification evolved is a powerful tool which can complete reactions in a shorter time and furnish the desired products in high yields.

2.1. Quinolines and their derivatives

Quinoline is a heterocyclic organic compound consisting of a benzene ring fused to a pyridine ring. It is a fundamental building block in the synthesis of various pharmaceuticals and agrochemicals.[48–50] It is found in some plants, and is also a component in the flavour of tobacco.[51,52] Quinoline serves as a precursor for numerous derivatives with diverse properties. Many quinoline derivatives exhibit potent pharmacological activities,[53] including anti-malarial drugs such as chloroquine[54]

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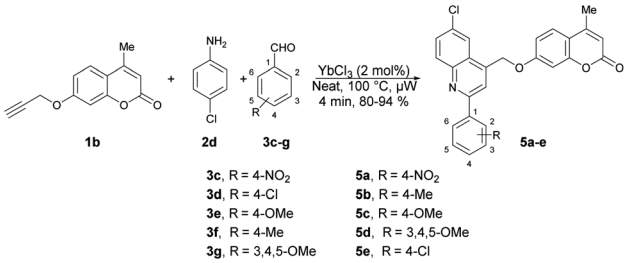
and anti-cancer agents such as camptothecin.[55] Its derivatives have been studied for their potential in treating neurodegenerative diseases because they can interact with specific receptors in the brain.[56] Certain quinoline derivatives are used in agriculture as pesticides and herbicides due to their ability to control plant diseases.[57] In summary, quinoline and its derivatives have pivotal roles in various fields, from medicine and chemistry to agriculture and materials science, owing to their versatile chemical properties and wide-ranging applications. Therefore, researchers have keen to synthesize quinoline-based pharmacophores for the development of new drugs. In this review, recent developments on the microwave-assisted synthesis of quinolines and their derivatives has been summarized.

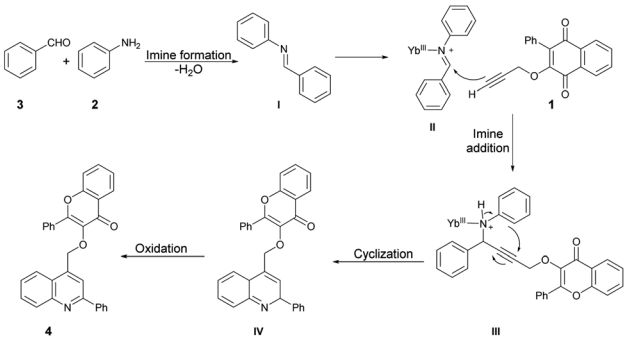
Ahmed and co-workers reported a one-pot, three-component domino reaction of propargylated-flavone or coumarin **1a–1b** with aldehydes **3a–g** and anilines **2a–e**.[58] The reaction was carried out under solvent-free and microwave conditions using $YbCl_3$ as a catalyst. It resulted in an efficient and highly eco-friendly synthesis of diverse and functionalized quinolin-4-ylmethoxychromen-4-ones **4a–n** (Scheme 1) and quinolin-4-ylmethoxychromen-2-ones **5a–e** (Scheme 2). The desired products (**4a–n** and **5a–e**) were obtained in excellent yields (80–95%) at 100 °C within 4 min. The reaction was also performed in an oil bath under heating conditions but it furnished a lower yield of product and longer reaction time (60 min) as compared to under microwave-assisted conditions (4 min). Hence, it is evident that the microwave approach offers several advantages, such as high yields, mild reaction conditions that are free of solvents, tolerance of functional groups, 95% atom-economy, and recyclability of the catalyst.

Scheme 3 illustrates a proposed mechanism for the one-pot synthesis of quinolin-4-ylmethoxychromen-4-ones based on the aforementioned results. This one-pot three-component reaction involves a series of steps. First, it includes domino imine formation, followed by imine addition and cyclization and, finally, oxidation. The high reactivity of $YbCl_3$ can be attributed to the smaller radius of Yb^{3+}. Importantly, the presence of H_2O in the reaction system does not deactivate or decompose the catalyst. The coordination of the hard Lewis-base site of the nitrogen lone pair with the hard Lewis-acid Yb^{3+} is supported by the HSAB theory. This coordination enhances the electrophilicity of the imine, leading to subsequent cyclization and aromatization. Notably, Yb^{3+} plays a significant role in both the imine addition and cyclization processes.

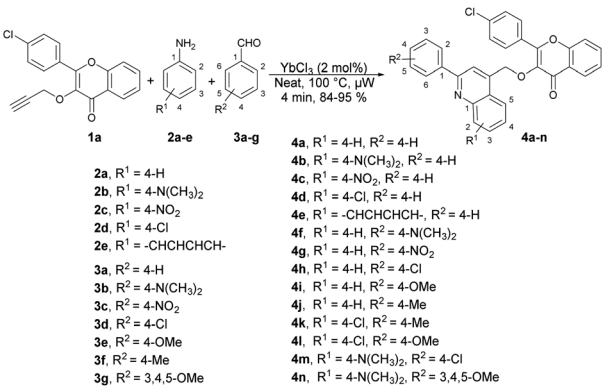
Frank and co-workers efficiently produced D- and A-ring fused novel quinolines in an estrone series.[59] They synthesized the desired molecules **9a–c** and **13a–g** using various arylamines **8a–c** and **12a–g** with the corresponding β-chlorovinyl aldehydes **7a** and **11a** in DMF under microwave irradiation. However, they discovered that the electronic and steric characteristics of the substituents of anilines, as well as the distinct reactivities of rings D and A of the sterane skeleton, had significant impacts on the rates and yields of the one-pot, catalyst-free synthesis. They found poor-to-moderate yields (47–53%) of D-fused quinolines **9a–c** applying microwave conditions at 140 °C, and A-fused quinolines (Scheme 4) **13a–g** were obtained in moderate-to-good isolated yields (43–92%) at 100 °C for 2–10 min (Scheme 5). To explore the benefits of



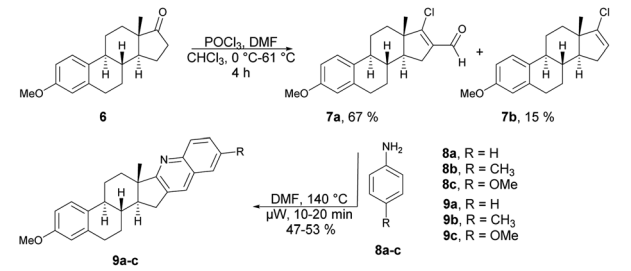
Scheme 2 Synthesis of quinolin-4-ylmethoxychromen-2-ones **5a–e**.



Scheme 3 A proposed mechanism of the one-pot synthesis of quinolin-4-ylmethoxychromen-4-ones catalyzed by $YbCl_3$.



Scheme 1 Synthesis of quinolin-4-ylmethoxychromen-4-ones **4a–n**.



Scheme 4 Synthesis of steroidal ring D-fused quinolines **9a–c**.

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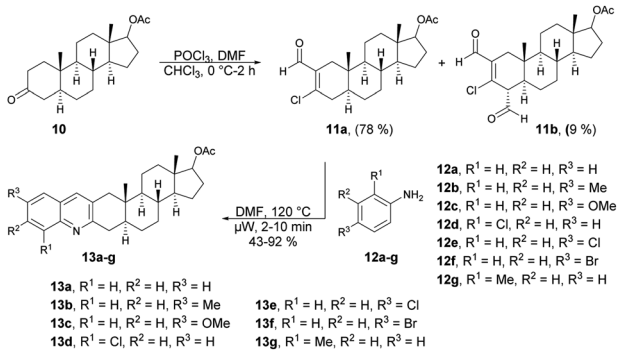


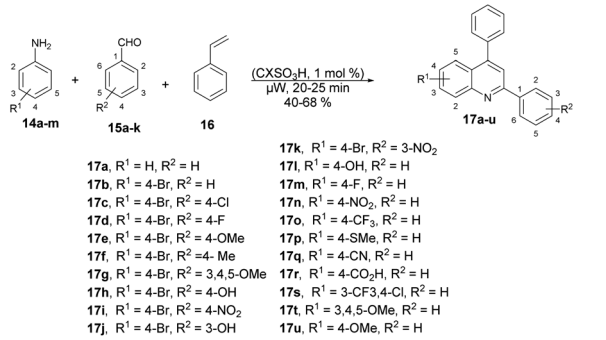
Scheme 5 Synthesis of steroidal ring A-fused quinolines **13a–g**.

microwave irradiation, the reaction between **11a** and **12b** (1 equiv.) was additionally conducted using conventional heating (120 °C, DMF) but it required an extended reaction time (4 h instead of 2 min) for production of the desired quinoline **13b**. Moreover, the yield achieved with conventional heating was lower, reaching 75%, as opposed to the 91% yield obtained with microwave irradiation.

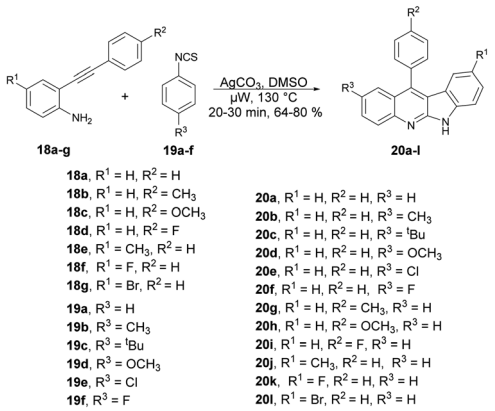
Fernandes and co-workers reported an efficient and environmentally friendly method to synthesize various derivatives of quinolines **17a–u** using microwave irradiation.[60] They optimized the reaction conditions using various solvents such as ethanol, water, and acetonitrile, as well as without a solvent. The microwave-assisted neat condition performed better for the synthesis of various derivatives of quinolines **17a–u** with moderate-to-good isolated yields (40–68%). All the reactions were carried out using various anilines **14a–m**, aryl aldehydes **15a–k** and styrene **16** in the presence of *p*-sulfonic acid calix[4] arene ($CX4SO_3H$) at neat conditions under microwave irradiation at 200 °C for 20–25 min (Scheme 6). For comparison purposes, the classical thermal method employing acetonitrile and 12 of reflux was used to obtain **17b–17h**. In contrast, the utilization of microwave irradiation with various aniline substrates resulted in improved yields of quinolines, as evidenced by the results obtained for the synthesis of **17i–17u**. Remarkably, microwave irradiation proved to be 11–19% more efficient than conventional heating for producing quinolines **17n**, **17p** and **17s**. The yield of the tri-methoxy-substituted product was twice as high when using microwave irradiation compared with that using conventional heating. Additionally, reactions under microwave irradiation allowed for faster formation of the desired quinolines in comparison with using thermal heating and solvent-free conditions.

An elegant cascade approach was developed by Patel and co-workers to synthesize indoloquinolines. This approach enabled the synthesis of numerous valuable indoloquinoline alkaloids through the Ag_2CO_3-mediated cascade annulation of internal alkynes under microwave heating.[61] They performed the Ag_2CO_3-mediated reaction with 2-(phenylethynyl)aniline **18** and phenyl isothiocynate **19** in DMSO using a conventional method, and observed the poor isolated yield (47%) of the desired product. They also carried out the reaction without using Ag_2CO_3 but only a trace amount of the product was formed, which indicated the significant role of Ag_2CO_3 in the reaction medium. Thus, to improve the yields of desired products **20a–l**, all Ag_2CO_3-mediated reactions of 2-(phenylethynyl)anilines **18a–g** with phenyl isothiocyanates **19a–f** were carried out in microwave conditions at 130 °C for 20–30 min and afforded good isolated yields (64–80%) (Scheme 7). This methodology offers several benefits, including good functional-group tolerance, mild microwave conditions, and short reaction times.

Huigens and co-workers developed a catalyst-free microwave-assisted Friedländer synthesis which provided a single-step conversion of various derivatives of 8-hydroxyquinolines with higher yield (72%) over that achieved with conventional heating (34% yield).[62] Initially, they performed the reaction with generation of 2-amino-3-hydroxybenzaldehyde **21** which, upon condensation with ketones using conventional heating, afforded 8-hydroxyquinolines in low-to-moderate yields. Thus, to increase the product yields they also performed the condensation reaction with 2-amino-3-hydroxybenzaldehyde **21** and ketones **22a–g** in ethanol. Using a microwave-irradiated technique, they heated the reaction mixture at 130 °C for 30–40 min to afford good isolated yields (48–84%) of designed products **23a–g** (Scheme 8). They conducted additional analysis on the microwave-assisted Friedländer reaction using different substrates: significant enhancements in yields were observed for most of the quinoline library. The average yield, which was previously 34% using



Scheme 6 Synthesis of various derivatives of quinolines **17a–u**.



Scheme 7 Synthesis of various indoloquinolines **20a–l**.

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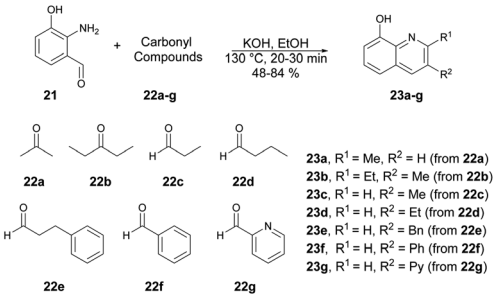
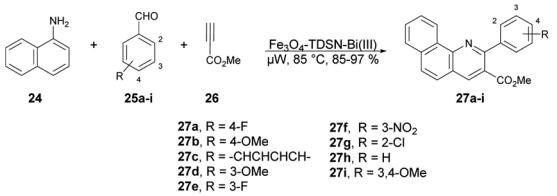


Scheme 8 Friedländer synthesis of 8-hydroxyquinolines **23a–g**.

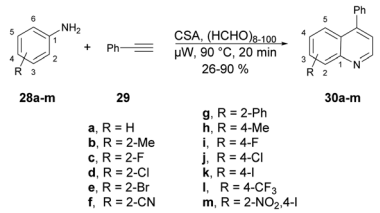


Scheme 9 Synthesis of various quinolines **27a–i**.

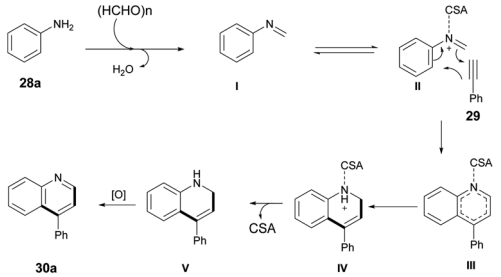
traditional oil-bath heating, improved to 72% with microwave irradiation.

Baltork and co-workers developed an efficient and reusable catalyst to synthesize quinoline derivatives using microwave irradiation. They utilized Fe_3O_4-TDSN-Bi(III) as a catalyst in solvent-free conditions using microwaves for the regioselective synthesis of quinolines.[63] They carried out the reaction with arylamine **24**, arylaldehydes **25a–i** and methyl propiolate **26** in the presence of Fe_3O_4-TDSN-Bi(III) as a catalyst under microwave irradiation at 80 °C to afford good-to-excellent yields (85–97%) of the designed products **27a–i** (Scheme 9). They also performed the reaction without using a catalyst (Fe_3O_4-TDSN-Bi(III)) but there was no conversion in product, and they used a conventional method for quinoline synthesis but obtained a very low yield (40%) of the designed product **27**. Thus, it was discovered that a catalyst and microwave irradiation were equally important to obtain desired products in high yields.

A microwave-assisted development of a Povarov-type multicomponent reaction to synthesize quinolines was reported by Sharma and co-workers.[64] They performed the reaction with anilines **28a–m**, an alkyne and paraformaldehyde in the presence of (±)camphor-10-sulfonic acid (CSA; used as a promotor) and heated the reaction mixture at 90 °C for 20 min to afford poor-to-good yields (26–90%) of designed quinolines **30a–m** (Scheme 10). The Povarov-type reaction involved [4 + 2]



Scheme 10 Synthesis of quinoline derivatives **30a–m**.

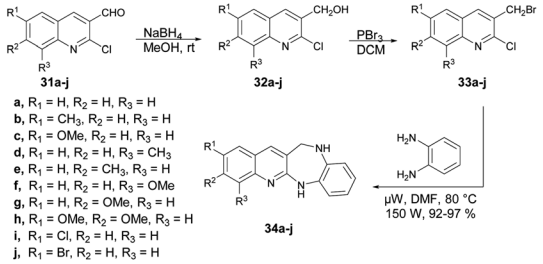


Scheme 11 A plausible mechanism for quinoline synthesis.

cycloaddition of imine (formed *in situ* with an aldehyde and aniline) and alkyne to afford various derivatives of quinolines **30a–m**.

The Povarov-type multicomponent reaction could proceed through the formation of *in situ*-generated intermediate **I** from the condensation of paraformaldehyde and aniline. Cycloaddition of **29** with CSA activated imine (**II**) *via* a Povarov-type multicomponent cycloaddition reaction to afford intermediate **III**. The latter was converted to intermediate **IV** which, upon further removal of CSA and spontaneous oxidation, yielded the final product **30a** (Scheme 11).

Kamble and co-workers reported an efficient microwave-assisted protocol for the synthesis of quinoline fused 1,4-benzodiazepine.[65] They performed the reduction reaction with 2-chloro,6,7,8-substituted quinoline-3-carbaldehydes **31a–j** to afford compounds **32a–j** which, on further bromination and condensation with 1,2-phenylenediamine, afforded the final products quinoline-fused 1,4-benzodiazepines **34a–j**. The condensation reaction was performed using brominated products 6,7,8-substituted 3-bromomethyl-2-chloro-quinolines **33a–j** in a microwave reactor at 80 °C to afford excellent isolated yields (92–97%) of quinoline-fused 1,4-benzodiazepines **34a–j** (Scheme 12). To compare the conventional and microwave irradiation methods, substituted quinoline derivatives were synthesized using a conventional method, resulting in final products **33a–j** with satisfactory yields of 62–65%. Researchers reported a microwave-assisted synthesis of benzimidazoles using amides and observed improved yields. This observation prompted them to investigate further by reacting substituted 3-bromomethyl-2-chloroquinolines (**33a–j**) with 1,2-phenylenediamine under microwave conditions to obtain **33a–j**. Remarkably, they achieved a significant increase in yield, ranging from



Scheme 12 Synthesis of quinoline-fused 1,4-benzodiazepines **34a–j**.

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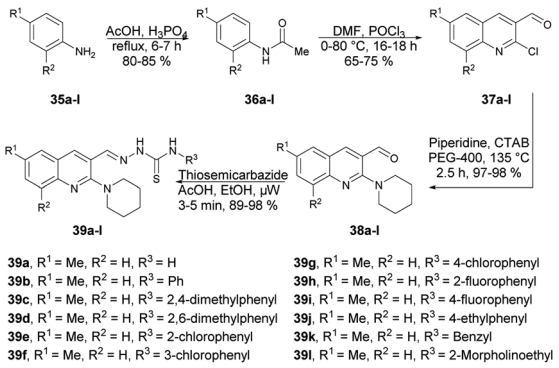
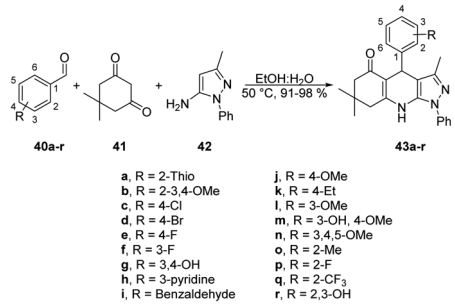
92% to 97%, within a very short time duration of 5 min using 150 W of microwave irradiation. Hence, microwaves produced good results in the form of higher yields, less time as well as atom-economy as compared with the traditional heating method.

Munir and co-workers reported a microwave-assisted synthesis of 2-((6/8-methyl-2-(piperidin-1-yl)quinolin-3-yl)methylene)hydrazinecarbothioamides.[66] They developed a new series of piperidine-containing quinolinyl thiosemicarbazones using commercially available anilines. Initially, they performed the acetylation of anilines **35a–l**, produced acetanilides **36a–l** which, on further Vilsmeier–Haack formylation using dimethylformamide and phosphoryl chloride, afforded 2-chloroquinoline-3-carbaldehydes **37a–l**. Subsequently, cetyltrimethylammonium bromide (CTAB)-catalyzed nucleophilic aromatic substitution of **37a–l** with piperidine in polyethylene glycol-400 (PEG-400) produced 2-(piperidin-1-yl)quinoline-3-carbaldehydes **38a–l** in 97–98% yields. Finally, microwave-assisted condensation of **38a–l** with thiosemicarbazides afforded the desired hybrid compounds **39a–l** in excellent yields (89–98%) within 3–5 min (Scheme 13). They investigated the reactions for comparative study between conventional and microwave irradiation and found a 10% fall in the yield using the conventional method instead of microwave irradiation.

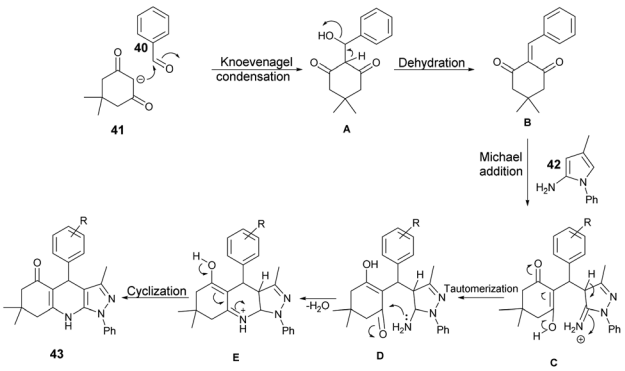
Jonnalagadda reported a new method for synthesizing pyrazolo-[3,4-*b*]-quinolines in an eco-friendly, fast, and convenient way using a microwave-assisted multi-component/one-pot protocol.[67] This method was conducted in aqueous ethanol at 50 °C for 5 min. This process resulted in a new series of pyrazolo-[3,4-*b*]-quinoline derivatives **43a–r** with excellent yields ranging from 91% to 98%. These derivatives were produced by the reaction with aryl aldehydes **40a–r**, dimedone **41**, and 5-amino-3-methyl-1-phenylpyrazole **42** applying microwave conditions (Scheme 14). Furthermore, during optimization of the reaction, they observed a significant decrease in the yield (15%) when varying the reaction temperature from 50 °C to 30 °C. They also noticed that increasing the reaction temperature resulted in a lower product yield. This result provided evidence that maintaining a constant temperature was crucial for this reaction, making microwave heating a superior choice compared with traditional heating methods.



Scheme 13 Synthesis of quinolinyl-hydrazinecarbothioamides **39a–l**.



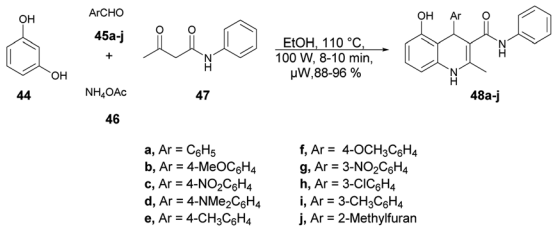
Scheme 14 Synthesis of pyrazolo-[3,4-*b*]-quinoline derivatives **43a–r**.



Scheme 15 Plausible mechanism for the synthesis of pyrazolo-[3,4-*b*]-quinoline derivatives.

Scheme 15 illustrates a plausible mechanism for the synthetic reaction. Initially, there is a Knoevenagel condensation reaction between dimedone **41** and an aryl aldehyde **40**, leading to the formation of adduct **A**. The adduct **A** undergoes dehydration to produce intermediate **B**. Subsequently, a Michael-type addition reaction occurs between 5-amino-3-methyl-1-phenylpyrazole **42** and intermediate **B**, yielding a new intermediate, **C**. This intermediate **C** then undergoes tautomerisation to form an intermediate **D**. Finally, through cyclization and dehydration reactions, the product **43** is obtained.

Jonnalagadda and co-workers reported an efficient and environmentally benign approach for the synthesis of substituted 1,4-dihydroquinolines.[68] The one-pot multicomponent reaction was performed using resorcinol **44**, aromatic aldehydes **45a–j**, ammonium acetate **46** and acetoacetanilide **47** under microwave conditions (100 W) at 110 °C for 8–10 min to



Scheme 16 Synthesis of 1,4-dihydroquinolines **48a–j**.

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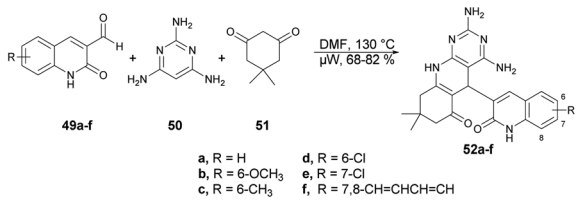
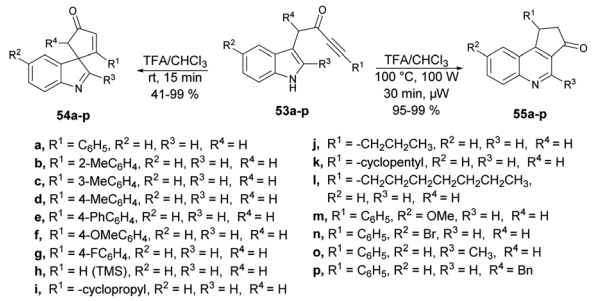
afford good isolated yields (88–96%) of compounds **48a–j**. The reaction proceeded through the Knoevenagel condensation, Michael addition followed by intramolecular cyclization (Scheme 16). To validate the advantage of microwaves, the reaction was conducted by heating a simple mixture of resorcinol, benzaldehyde, acetoacetanilide, and ammonium acetate in ethanol under reflux conditions, which led to completion of the reaction in 6 h and provided **48a** at a yield of 79%. Recognizing the advantages associated with microwave irradiation for conducting reactions, researchers investigated the same reaction under microwave irradiation at 100 W and 110 °C in ethanol. Surprisingly, this microwave-assisted reaction reached completion in just 10 min, resulting in a higher yield of **48a** (92%) compared with that using the traditional thermal reaction. Thus, microwaves are a better choice to proceed this type of reaction and obtain a maximum yield in a shorter time.

Abonia and co-workers developed a catalyst-free and one-pot three-component protocol to synthesize dihydropyrido[2,3-*d*]pyrimidines and dihydro-1*H*-pyrazolo[3,4-*b*]pyridines containing a quinoline pharmacophore.[69] They performed the microwave-assisted synthesis with formyl-quinoline derivatives **49a–f**, primary heterocyclic amine **50** and cyclic 1,3-diketone **51** in DMF at 150 °C for 8 min, which afforded the good isolated yields (68–82%) of target compounds **52a–f** (Scheme 17). The reaction proceeded *via* aldol condensation, Michael addition and intramolecular addition of an amine to a carbonyl group.

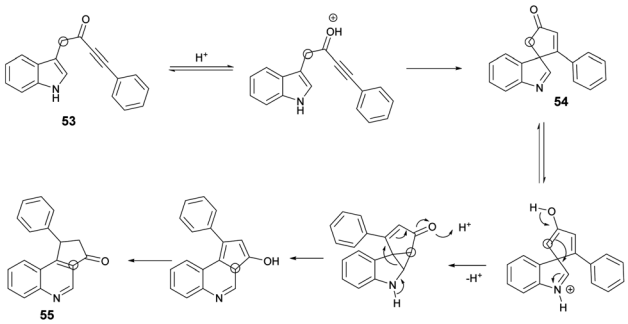
A microwave-assisted, temperature-variable, metal-free and acid-mediated procedure to prepare spiro-indolenines and quinolines was established by Eycken and co-workers.[70] They discovered that indolyl-ynones **53a–p** treated with TFA and continuous stirring at room temperature for 15 min afforded spiro-indolenines **54a–p** in good isolated yields (41–99%) whereas, upon heating the reaction mixture at 100 °C for 30 min under microwave conditions (100 W) afforded the quinolines **55a–p** in excellent yields (95–99%). For the synthesis of spiro-indolenine, the reaction proceeded through acid-catalyzed intramolecular Michael addition and double-protonation of the spiro-indolenine, rearrangement with the formation of cyclopropane ring, followed by expansion and restoration of aromaticity (Scheme 18). Thus, in this protocol, two types of product were noticed while using the same reactant in both cases. When the reaction was performed at room temperature using the conventional method, it generated spiro-indolenines and applying microwave conditions led to quinoline being formed as a major product. Hence, in some cases, microwave-assisted synthesis produces different products compared with those using traditional heating methods.



Scheme 17 Synthesis of dihydropyrido[2,3-*d*]pyrimidines **52a–f**.

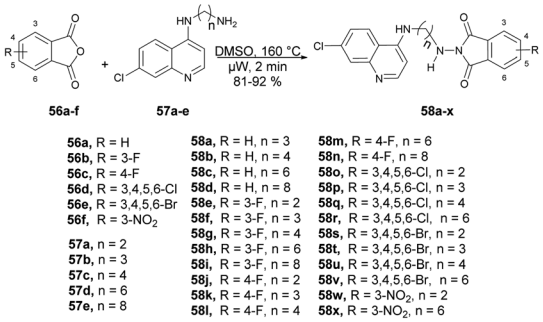


Scheme 18 Synthesis of spiro-indolenines **54a–p** and quinoline analogs **55a–p**.



Scheme 19 Plausible mechanism for the synthesis of spiro-indolenines and quinolines.

Scheme 19 illustrates a plausible mechanism. Initially, an intramolecular Michael addition is catalyzed by a Brønsted acid, involving the C-3 carbon of the indole and the ynone, resulting in the formation of spiro-indolenine **54**. The activation energy for the formation of 3a is notably higher than that for **54**, as evidenced by the requirement of a higher temperature for the rearrangement process. Under elevated temperature conditions, the second step involves double-protonation of the spiro-indolenine, leading to ketone tautomerization and the generation of an electrophilic iminium ion. This iminium ion is then attacked by the enol, followed by a rearrangement that forms a cyclopropane ring, leading to ring expansion and the restoration of aromaticity. Consequently, this series of reactions culminates in the formation of the quinoline core **55**.



Scheme 20 Synthesis of 4-aminoquinoline-phthalimides **58a–x**.

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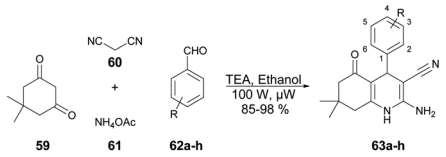


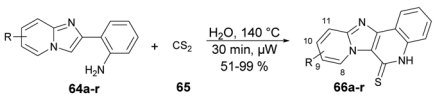
a, R = 4-Br
b, R = 2-Cl
c, R = 2,3-dimethoxy
d, R = 2-Br
e, R = 4-methoxy
f, R = 2,5-dimethoxy
g, R = 3,4-dimethoxy
h, R = 2,4,6-trimethoxy

Scheme 21 Synthesis of quinoline derivatives **63a–h**.

Kumar and co-workers reported a microwave-assisted synthesis of a series of quinoline derivatives having antitubercular properties.[71] To synthesize 4-aminoquinoline-phthalimides **58a–x**, they performed the reaction with various phthalic anhydrides **56a–f** and 4-aminoquinoline-diamines **57a–e** in DMSO, heated at 160 °C for 2 min in microwave obtained good isolated yields (81–92%) (Scheme 20). They have also evaluated the antitubercular potential of synthesized compounds against mc^{2}6230 strain of *Mycobacterium tuberculosis* and compound **58d** found the most potent (MIC_{99} value of 13.7 μM) among all the derived compounds.

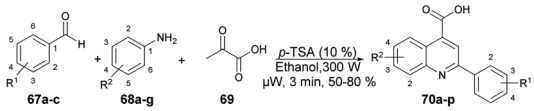
Jonnalagadda and co-workers developed a series of quinoline derivatives in ethanol under microwave conditions.[72] They performed the TEA-catalyzed reaction between 5,5-dimethylcyclohexane-1,3-dione, aromatic aldehydes, malononitrile and ammonium acetate in ethanolic solvent under microwave conditions at 100 W for 12 min to afford excellent yields (85–98%) of quinoline derivatives **63a–h** (Scheme 21).

Yu and co-workers reported a microwave-assisted development of polyheterocyclic-fused quinoline-2-thiones through catalyst-free annulation of various hetero anilines and carbon disulphide using green solvent.[73] In order to synthesize imidazopyridine-fused quinoline-2-thiones **66a–r**, they performed the reaction with various substituted 2-(imidazo[1,2-*a*]pyridin-2-yl)anilines **64a–r** and carbon disulfide **65**, heated at 140 °C for 30 min in water using microwave and obtained good isolated yields (51–99%). The reaction proceeds through 6π-electrocyclization followed by the aromatization of the intermediate (Scheme 22). This represents the first example of synthesizing polyheterocyclic-fused quinoline-2-thiones, showcasing several advantageous aspects, such as a catalyst-free process, a short reaction duration, a reusable and environmentally friendly solvent system, and easy isolation *via* simple filtration, thereby avoiding the need for column chromatography.



a, R = H
b, R = 9-Me
c, R = 9-OMe
d, R = 9-(4-methylpiperazine)
e, R = 9-Ph
f, R = 9,11-dimethyl
g, R = 9-CN
h, R = 9-CF3
i, R = 9-F
j, R = 9-Cl
k, R = 9-Br
l, R = 10-Me
m, R = 10-OMe
n, R = 10-CF3
o, R = 11-Me
p, R = 11-OMe
q, R = 11-CF3
r, R = 8-Me

Scheme 22 Synthesis of imidazopyridine fused quinoline-2-thiones **66a–r**.

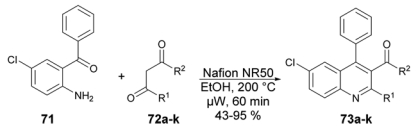


67a, R1 = H
67b, R1 = 4-Cl
67c, R1 = 2-Cl,
68a, R2 = H
68b, R2 = 4-NO2
68c, R2 = 4-OCH3
68d, R2 = 4-Cl
68e, R2 = 4-CH3
68f, R2 = 4-OH
68g, R2 = 4-F
70a, R1 = H, R2 = H
70b, R1 = H, R2 = 4-NO2
70c, R1 = H, R2 = 4-OCH3
70d, R1 = H, R2 = 4-Cl
70e, R1 = H, R2 = 4-CH3
70f, R1 = H, R2 = 4-OH
70g, R1 = H, R2 = 4-F
70h, R1 = 2-Cl, R2 = H
70i, R1 = 2-Cl, R2 = 4-OCH3
70j, R1 = 4-Cl, R2 = H
70k, R1 = 4-Cl, R2 = 4-NO2
70l, R1 = 4-Cl, R2 = 4-OCH3
70m, R1 = 4-Cl, R2 = 4-Cl
70n, R1 = 4-Cl, R2 = 4-CH3
70o, R1 = 4-Cl, R2 = 4-OH
70p, R1 = 4-Cl, R2 = 4-F

Scheme 23 Synthesis of quinoline derivatives **70a–p**.

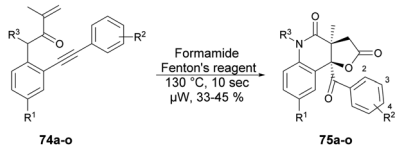
Patel and co-workers developed a green and efficient approach to synthesize a series of quinoline-4-carboxylic derivatives using an organocatalyst under microwave irradiation.[74] They carried out the three-component reaction of aromatic aldehydes **67a–c**, substituted anilines **68a–g**, and pyruvic acid **69** in ethanol using *p*-TSA as a catalyst under microwave conditions at 80 °C for 3 min, which furnished good isolated yields (50–80%) of quinoline derivatives **70a–p** (Scheme 23). They also performed the reaction using a conventional method but it required longer (3 h to overnight) instead of 3–4 min under microwave conditions. They also observed a lower yield in the conventional method as compared with the microwave method.

Wang and co-workers discovered a novel, environmentally friendly synthetic route for the Friedländer quinoline synthesis of various substituted quinolines.[75] They performed the reaction with 2-aminobenzophenone **71** and various dicarbonyl moieties **72a–k** using Nafion NR50 as a catalyst in ethanolic solvent under microwave conditions at 200 °C for 60 min to



a, R1 = CH3, R2 = -CH2CH(CH3)2
b, R1 = CH3, R2 = Ph
c, R1 = Ph, R2 = Ph
d, R1, R2 = -COCH2CH2-
e, R1, R2 = -COCH2CH2CH2-
f, R1, R2 = -COCH2CH(CH3)2CH2-
g, R1 = CH3, R2 = OMe
h, R1 = CH3, R2 = OEt
i, R1 = Ph, R2 = OEt
j, R1 = 4-OMeC6H4, R2 = OEt
k, R1 = 4-NO2C6H4, R2 = OEt

Scheme 24 Synthesis of polysubstituted quinolines **73a–k**.



a, R1 = H, R2 = H, R3 = CH3
b, R1 = H, R2 = 4-Me, R3 = CH3
c, R1 = H, R2 = 2-Me, R3 = CH3
d, R1 = H, R2 = 4-F, R3 = CH3
e, R1 = CH3, R2 = H, R3 = CH3
f, R1 = CH3, R2 = 4-Me, R3 = CH3
g, R1 = CH3, R2 = 2-Me, R3 = CH3
h, R1 = Cl, R2 = H, R3 = CH3
i, R1 = Cl, R2 = 4-Me, R3 = CH3
j, R1 = Cl, R2 = 2-Me, R3 = CH3
k, R1 = Cl, R2 = 4-F, R3 = CH3
l, R1 = F, R2 = H, R3 = CH3
m, R1 = F, R2 = 2-Me, R3 = CH3
n, R1 = F, R2 = 4-Me, R3 = CH3
o, R1 = H, R2 = H, R3 = Bn

Scheme 25 Synthesis of tetrahydrofuro quinoline-diones **75a–o**.

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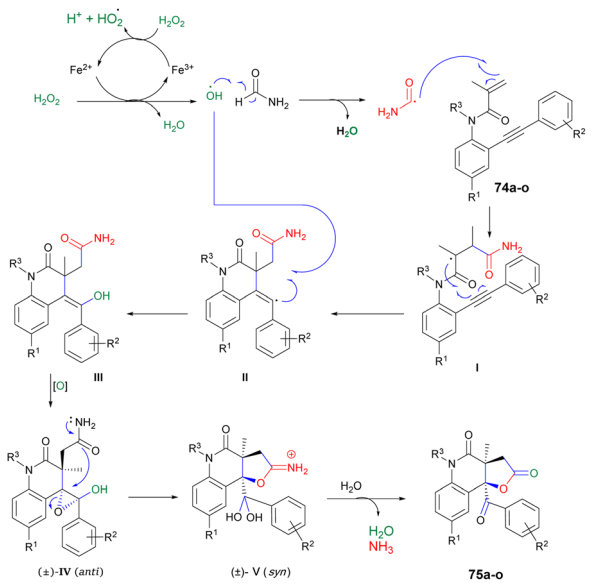
afford good isolated yields (43–95%) of polysubstituted quinolines **73a–k** (Scheme 24).

Andrade and co-workers reported a new method to synthesize poly-functionalized 2-quinolinones from *N*-(*o*-ethynylaryl)-acrylamides (1,7-enynes).[76] They discovered the microwave-assisted synthesis of 2-quinolinone-fused γ-lactones using Fenton's reagent within 10 s. They performed the reaction with various derivatives of compound **74a–o** and ^{t}BuOH/formamide using Fenton's reagent heated in microwave-irradiated conditions at 130 °C for 10 s to afford the desired compounds **75a–o** in isolated yields of 33–45% (Scheme 25). A similar reaction was also performed using a conventional method, but took (4 h) instead of 10 s in microwave conditions.

Scheme 26 illustrates the possible mechanism for the synthesis of 2-quinolinone-fused γ-lactones **75a–o**. The initial phase involves the generation of hydroxyl radicals using Fenton's reaction. In an acidic environment, $6H_2O_2$ and Fe(II) facilitate the production of hydroxyl radicals, water, and Fe(III). The reaction also allows for the regeneration of Fe(II) from the reaction between Fe(III) and H_2O_2. Subsequently, formamide is transformed into the carbamoyl radical by the action of the hydroxyl radical. This carbamoyl radical then attacks the carbon–carbon double bond of the acrylic amide moiety and undergoes cyclization with the carbon–carbon triple bond, resulting in the formation of vinyl radical **II**. The recombination of hydroxyl and vinyl radicals **II** leads to the formation of enol **III**. Enol **III** is then converted into racemic epoxide **IV** through an epoxidation reaction. Studies have shown that peroxides, in the presence of iron, can oxidize C–C double bonds that are conjugated to aromatic rings, resulting in the formation of epoxides. The pathway for the construction of lactone involves a selective epoxide-opening reaction *via* an SN_2-type mechanism, which explains the observed maximum yield (50%) in this process. Once intermediate **IV** is formed with the appropriate stereochemistry (anti), 5-*exo*-tet cyclization can take place. This involves a nucleophilic attack of the amide group from the backside of the epoxide through an SN_2-type mechanism, leading to the formation of intermediate **V** (geminal diol). After simple hydrolysis and dehydration of **V**, product **75a–o** is obtained with the release of ammonia.



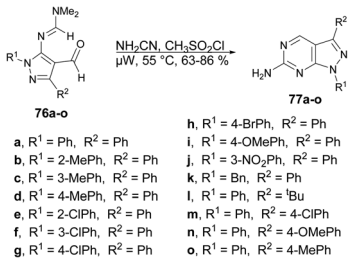
Scheme 26 Proposed mechanism for the synthesis of 2-quinolinone-fused γ-lactones **75a–75o**.

2.2. Pyrazolopyrimidines and their derivatives

The pyrazolopyrimidine scaffold is an important class of N-heterocycles in the realm of drug discovery.[77] It comprises fusion between a pyrazole ring and a six-membered pyrimidine ring. Pyrazolopyrimidines exist in several isomeric forms, including pyrazolo [3,4-*d*]pyrimidines, pyrazolo [4,3-*d*]pyrimidines, pyrazolo [5,1-*b*]pyrimidines, and pyrazolo [1,5-*a*]pyrimidines, all of which hold scientific importance.[78] The pyrazolopyrimidine structure is particularly alluring due to its synthetic feasibility and profound pharmacological significance. Several well-known drugs in the market incorporate the pyrazolopyrimidine nucleus, including zaleplon,[79] indiplon,[80] allopurinol,[81] dinaciclib,[82] ocinaplon,[83] pyrazophos,[84] and sildenafil.[85] Pyrazolopyrimidines showcase a diverse range of pharmacological properties, serving as cyclin-dependent kinase (CDK) inhibitors,[86] antibacterial agents,[87] antifungal agents,[88] anti-proliferative compounds,[89] as well as anti-leishmanial[90] and antiviral agents.[91] Therefore, the synthesis of these types of scaffolds and investigation of their biological potential are of keen interest to researchers. Herein, we have compiled the microwave-assisted synthetic developments on pyrazolopyrimidines and their derivatives.

An acid-promoted one-pot development of 6-amino-pyrazolopyrimidines was reported by Wong and co-workers.[92] The reaction was carried out with 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines or 5-amino-1*H*-pyrazole-4-carbaldehydes **76a–o** and cyanamide (NH_2CN) in an acid-mediated solution applying microwave conditions at 55 °C to afford good isolated yields (63–86%) of desired compounds **77a–o** (Scheme 27). The overall reaction involves deprotection, imination, acid promoted heterocyclization and aromatization. For comparative experiments, conventional heating was conducted using a standard hot plate/magnetic stirrer. However, this method resulted in a lower yield compared with that obtained using microwave irradiation.

A protocol for microwave-assisted Suzuki–Miyaura cross-coupling reaction of 3-bromo pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-



Scheme 27 Synthesis of 6-amino-pyrazolopyrimidines **77a–o**.

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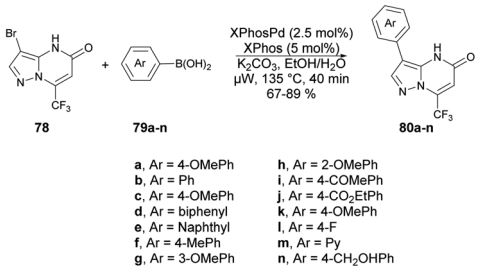
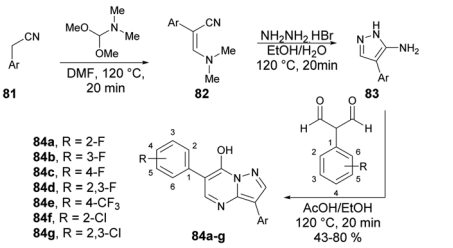


Scheme 28 Synthesis of arylated pyrazolo[1,5-*a*]pyrimidin-5-ones **80a–n**.

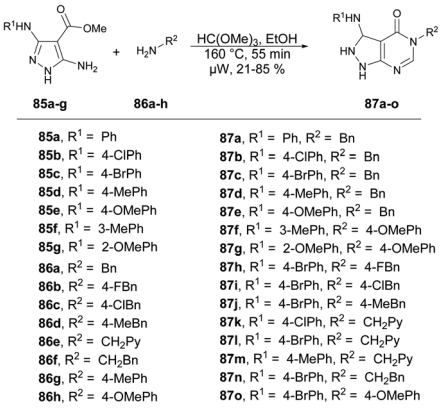
one was reported by Ababri and co-workers.[93] They optimized arylation reactions using various aryl and heteroaryl boronic acids **79a–n** with a catalyst XPhosPdG2/XPhos to avoid the debromination reaction. The improved conditions were effectively utilized to synthesize various arylated pyrazolo[1,5-*a*]pyrimidin-5-ones **80a–n** from their respective brominated starting material **78**. In addition, the Suzuki–Miyaura cross-coupling conditions were used to perform the second C-5 arylation of C-3-arylated pyrazolo[1,5-*a*]pyrimidin-5-ones. By utilizing microwave irradiation at 135 °C instead of conventional thermal heating, only the coupled product **80a–n** was generated, with a yield of 67–89% (Scheme 28). The most noteworthy aspect was that the reaction duration was shortened from 12 h to 40 min, and there was no indication of the debrominated product in the crude material.

Peterson and co-workers reported a straightforward synthesis of 3-substituted pyrazolo[1,5-*a*]pyrimidines using microwave-assisted synthesis.[94] The synthesis of pyrazolo[1,5-*a*]pyrimidines **84a–g** involved sequential treatment of commercially available acetonitrile derivative **81** with DMF-dimethylacetal (120 °C, 20 min), followed by treatment with $NH_2NH_2 \cdot HBr$ (120 °C, 20 min), and 1,1,3,3-tetramethoxypropane or 2-aryl-substituted malondialdehdyes (120 °C, 20 min) (Scheme 29).

Dolzhenko and co-workers developed a microwave-assisted three-component protocol for the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones **87a–o**.[95] They carried out the microwave-assisted one-pot reaction using methyl 5-aminopyrazole-4-carboxylates **85a–g**, trimethyl orthoformate and primary amines **86a–h** to afford poor-to-good isolated yields of desired products **87a–o**. The reaction mixture was heated at 160 °C for 55 min in ethanolic conditions (Scheme 30). The method that



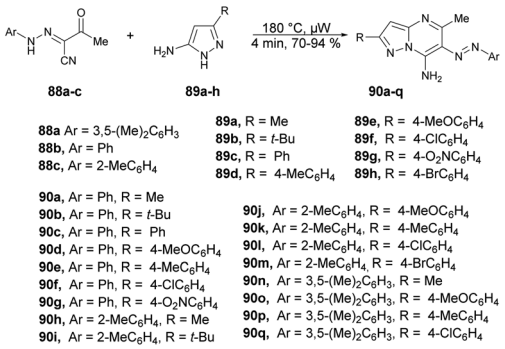
Scheme 29 Synthesis of 3-substituted pyrazolo[1,5-*a*]pyrimidines **84a–g**.



Scheme 30 Synthesis of pyrazolo[3,4-*d*]pyrimidin-4-ones **87a–o**.

was optimized for benzylamine proved to be effective in producing pyrazolo[3,4-*d*]pyrimidin-4-ones with substituted benzylamines and their analogues, resulting in yields of 60–85%. Nevertheless, when aromatic amines were utilized as substrates, the yields dropped to 21–53%. To compare conventional and microwave methods, the reaction was also attempted under conventional heating with reflux in EtOH. However, even after 3 days of heating, the desired product was not obtained. Thus, the developed microwave protocol offers several advantages, including a shorter reaction time, efficient utilization of materials and steps, and the convenience of isolating the product without the need for chromatography.

A palladium-catalyzed microwave-assisted development was reported by Portilla and co-workers for the synthesis of functionalized 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amines **90a–q** from the cyclization of 3-oxo-2-(2-arylhydrazinylidene) butanenitriles and 5-amino-1*H*-pyrazoles in neat conditions.[96] They performed the reaction with 2-arylhydrazinyliden-3-oxobutanenitriles **88a–c** and various substituted 5-amino-1*H*-pyrazoles **89a–h** without a solvent under microwave conditions at 180 °C for 4 min to afford yields of 70–94% of 6-(aryldiazenyl) pyrazolo[1,5-*a*]pyrimidin-7-amines **90a–q** (Scheme 31). In order to validate the efficiency and advantage of microwaves, the reaction was also carried out using a conventional heating method with variation of solvent and temperature. When the



Scheme 31 Synthesis of 6-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidin-7-amines **90a–q**.

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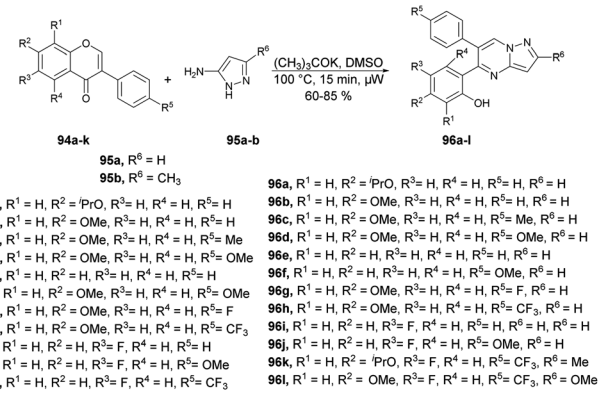
reaction was carried out in ethanol or toluene, it did not favour the desired product. Interestingly, they observed that a high-boiling-point solvent such as DMSO and DMF favoured the product at high temperature, but the yield was not satisfactory. Thus, to retain the high temperature with low-boiling-point solvent was not possible, which is why microwaves were the best choice to perform the reaction in ethanol while using high temperature and pressure.

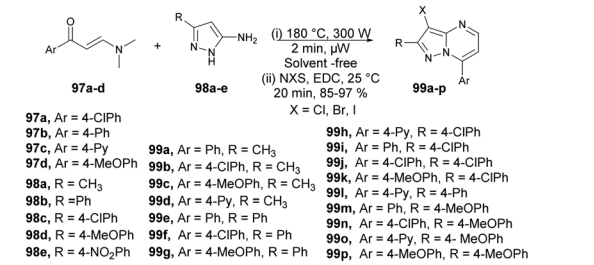
Raboin and co-workers reported microwave-assisted developments of 7-substituted pyrazolo[1,5-*a*]pyrimidines. They developed a one-pot two-step reaction through palladium-catalyzed CH-activation and saponification–decarboxylation reaction.[97] The reaction was carried out between 7-ethoxycarbonylmethyl-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine **91**, aryl or heteroaryl halides **92a–l** and 2-dicyclohexylphosphino-20-(*N*,*N*-dimethylamino) biphenyl (DavePhos) in the presence of a palladium catalyst and toluene as a solvent under microwave irradiation at 150 °C for 30 min which, upon further saponification–decarboxylation, afforded moderate-to-good isolated yields (48–80%) of 7-substituted pyrazolo[1,5-*a*]pyrimidines **93a–l** (Scheme 32). In contrast to the classical method, this novel approach offers several consistent advantages, such as achieving good yields, shorter reaction times, a reduced number of steps, and the utilization of commercially available and relatively non-toxic compounds.

Zhang and co-workers reported a microwave-assisted chemoselective synthesis of 5,6-pyrazolo[1,5-*a*]pyrimidines **96a–l** and their antifungal properties against *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani*, and *Fusarium solani*.[98] They performed the reaction between various isoflavones **94a–k** and substituted 3-aminopyrazole **95a–b** in DMSO using potassium *tert*-butoxide as a base under microwave conditions at 100 °C for 15 min to yield 60–85% isolated yields of 5,6-pyrazolo[1,5-*a*]pyrimidines **96a–l** (Scheme 33).

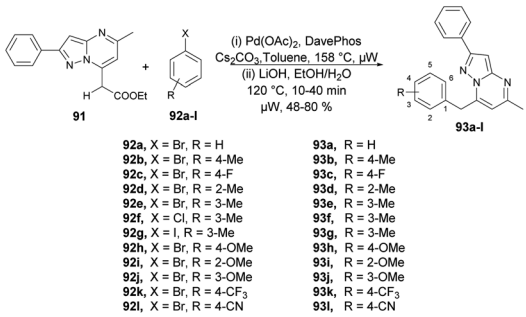
An efficient, microwave-assisted route to synthesize various substituted 3-halo and 3-nitropyrazolo[1,5-*a*]pyrimidines was reported by Portilla and co-workers.[99] They performed the reaction between various β-enaminones **97a–d** and NH-5-aminopyrazoles **98a–e** under microwave conditions at 180 °C and 300 W for 2 min to afford good isolated yields (85–97%) of 3-halo and 3-nitropyrazolo[1,5-*a*]pyrimidines **99a–p** (Scheme 34). The reaction proceeds through condensation of β-enaminones and NH-5-aminopyrazole followed by regioselective electrophilic substitution using electrophilic reagents. During the optimization process, the researchers explored various factors such as temperature, solvent, and the impact of conventional heating *versus* microwave irradiation. Refluxing the reaction in ethanol or toluene for 12 h did not result in the formation of the desired product. When they attempted the reaction in DMF at a higher temperature, the yield of the desired product remained poor. It became evident that higher temperatures were necessary for completion of the product. Consequently, the conventional heating method was not sufficient to achieve the maximum yield in high-temperature reactions. Microwave irradiation proved to be a crucial technique in



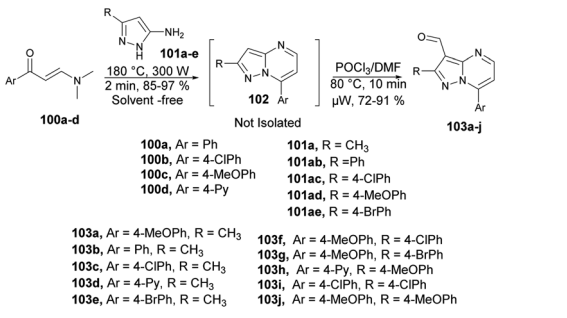
Scheme 33 Synthesis of 5,6-pyrazolo[1,5-*a*]pyrimidines **96a–l**.



Scheme 34 Synthesis of 3-substituted pyrazolo[1,5-*a*]pyrimidines **99a–p**.



Scheme 32 Synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidines **93a–l**.



Scheme 35 Synthesis of diverse 3-formylpyrazolo[1,5-*a*]pyrimidines **103a–j**.

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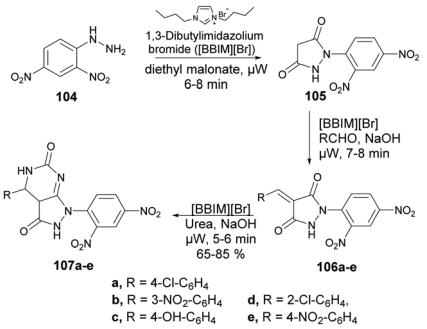
attaining higher yields, especially when using high-boiling-point solvents.

Portilla and co-workers developed a new microwave-assisted route for the regioselective development of 3-formylpyrazolo[1,5-*a*]pyrimidines.[100] They carried out the cyclocondensation reaction between β-enaminones **100a–d** and NH-3-aminopyrazoles **101a–e** under microwave conditions at 180 °C for 2 min to afford an intermediate **102**, which was not isolated and reaction was continued by the formylation of an iminium salt using Vilsmeier–Haack reagent under microwave conditions at 80 °C for 10 min to afford good to excellent isolated yields (72–91%) of 3-formylpyrazolo[1,5-*a*]pyrimidines **103a–j** (Scheme 35).

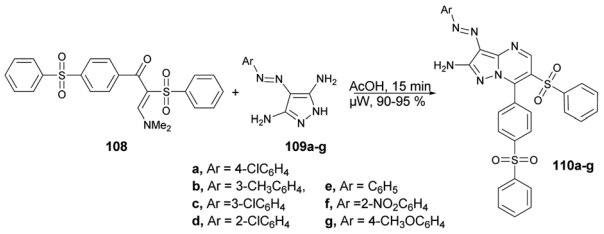
To investigate the specific effect of microwave heating compared with conventional heating on reaction acceleration, a preheated sand bath was employed as a heat source for comparative experiments. Encouragingly, the heteroaryl aldehyde was obtained using conventional heating at 80 °C for 60 min. However, this method was not entirely satisfactory because there was a loss of intermediate mass during the transfer from the microwave tube to the round-bottom flask. The validity of their hypothesis was confirmed by performing a reliable cyclocondensation-formylation sequence directly in the same microwave tube without the need for further isolation steps.

Ameta and co-workers reported an efficient and environmentally friendly method to synthesize pyrazolo[3,4-*d*]pyrimidine-3-ones using microwave irradiation.[101] The reaction was carried out between 2,4-dinitrophenylhydrazine **104** and diethyl malonate in 1,3-dibutylimidazolium bromide ionic liquid under microwave irradiation for 5–8 min to afford compound **105** which, on further treatment with base and 1,3-dibutylimidazolium bromide ionic liquid under microwave irradiation for 7–8 min, afforded compound **106a–e**. The latter, on further reaction with urea under similar conditions, afforded desired compounds **107a–e** in moderate-to-good isolated yields (65–85%) (Scheme 36).

A microwave-assisted synthesis was reported by Shaaban and co-workers for the preparation of a series of pyrazolo[1,5-*a*]pyrimidines through the reaction of 2-(phenylsulfonyl)-1-(4-(phenylsulfonyl)phenyl)ethan-1-one, 2-benzenesulfonyl-1-(4-benzenesulfonyl-phenyl)-3-dimethylamino-propenone and 3-(dimethylamino)-1-(4-(phenylsulfonyl)phenyl)prop-2-en-1-



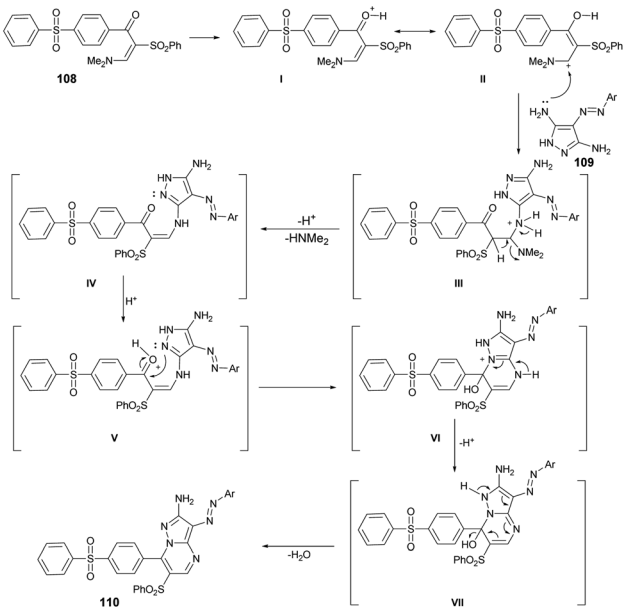
Scheme 36 Synthesis of pyrazolo[3,4-*d*]pyrimidin-3-ones **107a–e**.



Scheme 37 Synthesis of pyrazolo[1,5-*a*]pyrimidines **110a–g**.

one.[102] They performed the reaction between a mixture of enaminosulfone **108** with arylazodiaminopyrazole **109a–g** in acetic acid under microwave conditions for 15 min to afford good isolated yields (90–95%) of pyrazolo[1,5-*a*]pyrimidines **110a–g** (Scheme 37). Furthermore, a comparative study between conventional and microwave methods was carried out, revealing a 10% decrease in yield when using conventional heating as opposed to microwave heating. Consequently, in order to achieve a superior yield with fewer impurities, the researchers opted to employ microwave heating for all reactions.

From a mechanistic perspective, it was anticipated that the multi-component synthesis of compounds **110a–g** would occur through Michael-type addition under acidic conditions. Scheme 38 illustrates the process leading to the formation of pyrazolo[1,5-*a*]pyrimidine derivatives **110a–g**. This process involves Michael-type addition, resulting in the formation of a non-isolable Michael adduct **IV**, which then undergoes cyclocondensation with the loss of dimethylamine, leading to the formation of three additional non-isolable intermediates **V–VII**. Subsequently, a water molecule is eliminated to yield the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **110a–g**.



Scheme 38 General mechanism for the synthesis of compound **110a–g**.

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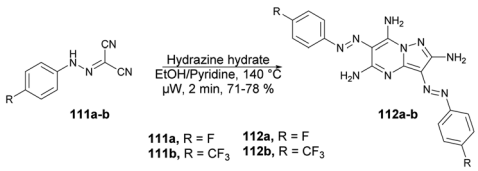
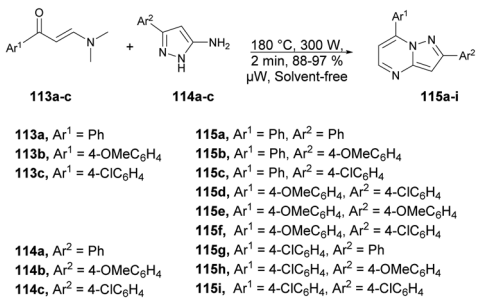


Scheme 39 Synthesis of diarylazo-2,5,7-triaminopyrazolo[1,5-*a*]pyrimidines **112a–b**.

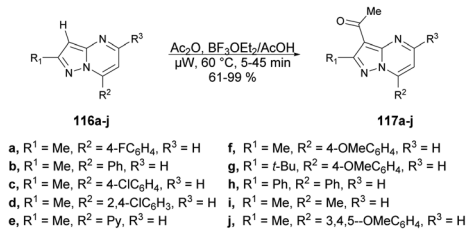
Abbas and co-workers reported a microwave-assisted procedure for the synthesis of a series of pyrazolo[1,5-*a*]pyrimidine derivatives. They developed various symmetrical and asymmetrical 3,6-diarylazo-2,5,7-triaminopyrazolo[1,5-*a*]pyrimidines by applying microwave conditions.[103] The reaction was carried out between hydrazone **111** and hydrazine hydrate in ethanol/pyridine, heated under microwave conditions at 140 °C for 2 min to afford a good isolated yield (71–78%) of desired compounds **112a–b** (Scheme 39). Additionally, a comparative study encompassing conventional, microwave, and ultrasound techniques was undertaken. The results revealed a 10% reduction in yield when utilizing the conventional method over 4–7 h compared with a mere 2 min with microwave irradiation. Furthermore, the ultrasound technique also exhibited a decline in yield (10–15%) in comparison with the microwave-assisted approach. These findings clearly indicate that microwave irradiation is the preferred choice for conducting such experiments.

A microwave-assisted development of a series of 2,7-diarylpyrazolo[1,5-*a*]pyrimidine derivatives and investigation of their antitumor activity against a colorectal carcinoma cell line was reported by Miscione and co-workers.[104] They performed the reaction between various β-enaminones **113a–c** and NH-5-aminopyrazole **114a–c** under microwave conditions at 180 °C and 300 W for 2 min to afford good isolated yields (88–97%) of pyrazolo[1,5-*a*]pyrimidines **115a–i** (Scheme 40). The reaction proceeds through condensation of β-enaminones and NH-5-aminopyrazole followed by regioselective electrophilic substitution.

Portilla and co-workers described a straightforward microwave-assisted BF_3-mediated acetylation reaction of pyrazolo[1,5-*a*]pyrimidines.[105] The synthesis of this fundamental building block was reported in good yield, even with substrates containing electron-deficient or strongly hindered groups under mild reaction conditions. Importantly, several N-hetero aromatic substrates were effectively used for acetylation using a newly found technique. They performed the Lewis acid (BF_3OEt_2)-promoted acetylation reaction with pyrazolo[1,5-*a*]pyrimidines **116a–j** using acetic acid as a solvent under microwave conditions at 60 °C for 5–45 min, which furnished good to excellent isolated yields (61–99%) of acetylated products **117a–j** (Scheme 41).



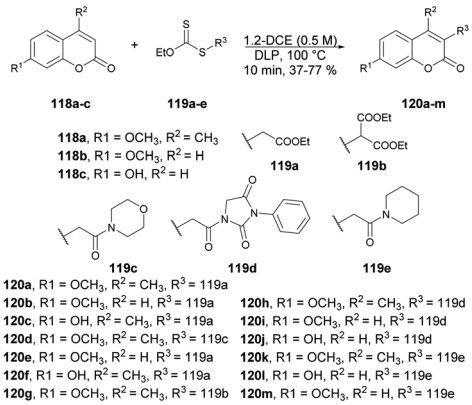
Scheme 40 Synthesis of diverse substituted pyrazolo[1,5-*a*]pyrimidines **115a–i**.



Scheme 41 Synthesis of diverse acetylated pyrazolo[1,5-*a*]pyrimidines **117a–j**.

2.3. Coumarin and its derivatives

Coumarin derivatives have gained recognition for their diverse range of biological activities, such as antimicrobial,[106,107] antioxidant and anti-inflammatory properties.[108] Coumarin derivatives, with their unique and versatile oxygen-containing heterocyclic structure, are widely distributed in nature and can be found in numerous naturally occurring and synthetic bioactive molecules.[109] This structure makes them a privileged scaffold in medicinal chemistry. Consequently, many coumarin derivatives have been extracted from natural sources, designed, synthesized, and assessed for various pharmacological targets.[110] Furthermore, coumarin-based ion receptors,[111] fluorescent probes,[112–114] and biological stains are experiencing rapid growth, with extensive applications in monitoring enzyme activity, complex biological events, and precise pharmacological and pharmacokinetic properties within living cells.[115] As a result, the extraction, synthesis, and biological evaluation of coumarins have become highly attractive and rapidly evolving



Scheme 42 C-3 radical alkylation of coumarins and formation of alkylated products **120a–m**.

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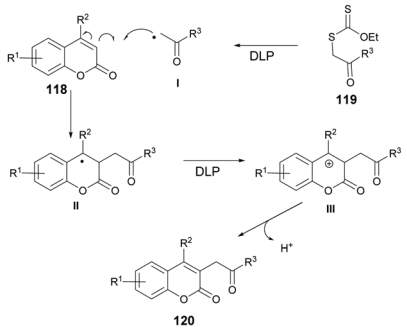


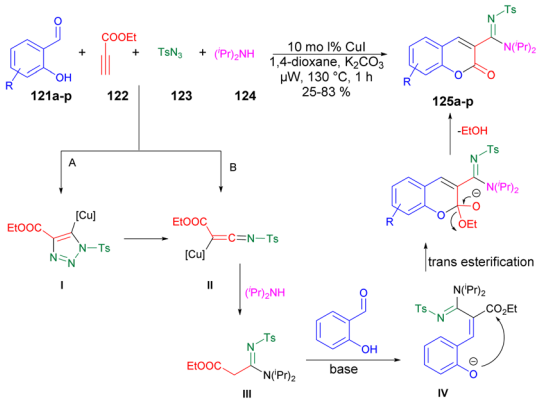
Scheme 43 Proposed mechanism for the oxidative radical addition products 120a–m.

areas of research.[116–118] Thus, we have highlighted the latest synthetic pathways that use microwave-irradiated techniques and theoretical studies. This special issue places a strong emphasis on exploring the diverse facets of coumarin derivatives.

Miranda and co-workers developed an efficient, microwave-assisted xanthate-based direct alkylation of the coumarin ring system.[119] They carried out the C-3 radical alkylation of various derivatives of coumarin **118a–c** and xanthate of ethyl acetate **119a–e** using dilauril peroxide in toluene at 100 °C for 10 min under microwave irradiation to afford the desired products **120a–m** in low-to-moderate isolated yields (Scheme 42). Furthermore, a comparative study between conventional and microwave methods was carried out, revealing a 5% decrease in yield when using conventional heating as opposed to microwave heating.

According to the suggested mechanism depicted in Scheme 43, the addition of radical **I** (formed from xanthate **119** through the action of dilauroyl peroxide (DLP)) to the coumarin system **118** could result in the formation of stabilized benzyl radical **II**. In the presence of an appropriate amount of DLP in the reaction medium, radical intermediate **II** might undergo oxidation, leading to the formation of benzyl carbocation **III**. The deprotonation of carbocation **III** would subsequently restore the double bond, ultimately yielding the alkylated product **120**.

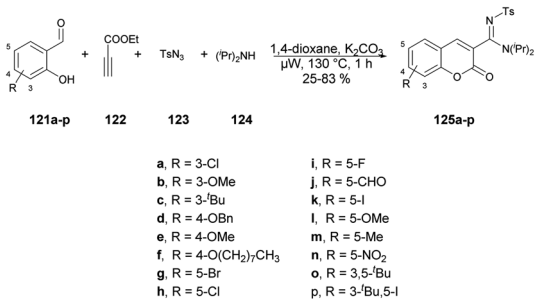
A copper-catalyzed four-component synthesis of 3-*N*-sulfonylamidine coumarins using microwaves was reported by Punniyamurthy and co-workers.[120] They performed the coupling reaction with salicylaldehydes **121a–p**, propiolate **122**, sulfonyl



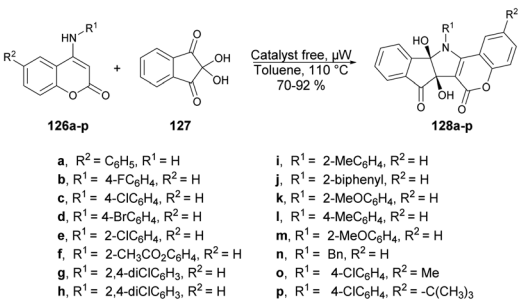
Scheme 45 Catalytic cycle for the synthesis of 3-*N*-sulfonylamidine coumarins 125a–p.

azides **123**, and secondary amines **124**. Using a copper source along with a basic solvent under microwave conditions at 130 °C for 1 h afforded poor-to-good isolated yields of desired products **125a–p** (Scheme 44). They found microwaves a more effective tool for these chemical reactions compared with traditional heating processes. This was due to the ability to produce higher reactivity, operate under milder conditions, and yield greater selectivity, all of which offer significant practical benefits. The results of that study suggest that use of microwave irradiation may lead to new opportunities for advancing the synthesis of highly functionalized coumarin derivatives through multiple components. Moreover, microwave-assisted organic synthesis offers the benefits of increased reactivity, gentle reaction conditions, and enhanced selectivity. The catalytic cycle depicted in Scheme 45 implies that the reaction could proceed through intermediates **III** and **IV** to generate the desired heterocycle **125a–p**. It means that the combination of **122** and **123** in a cycloaddition reaction may lead to the formation of ketenimine **II** through **I**. The nucleophilic addition of amine to intermediate **II** could give rise to intermediate **III**, which, in turn, may react with the aldehyde to form intermediate **IV**. Further intermediate **IV** may subsequently undergo cyclization through transesterification, ultimately resulting in the synthesis of the target compound **125a–p** as illustrated in Scheme 45.

A facile and catalyst-free protocol was reported by Chen and co-workers to synthesize pentacyclic compounds containing



Scheme 44 Synthesis of 3-*N*-sulfonylamidine coumarins 125a–p.



Scheme 46 Catalyst free synthesis of coumarin derivatives 128a–p.

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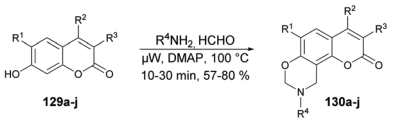


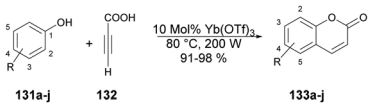
a, R^1 = H, R^2 = Me, R^3 = H, R^4 = Ph
b, R^1 = Cl, R^2 = Me, R^3 = H, R^4 = Ph
c, R^1 = Ph, R^2 = Me, R^3 = H, R^4 = Ph
d, R^1 = Cl, R^2 = CF_3, R^3 = H, R^4 = Ph
e, R^1 = Cl, R^2 = Me, R^3 = Me, R^4 = Ph
f, R^1 = H, R^2 = Me, R^3 = H, R^4 = 4-MeC_6H_4
g, R^1 = Cl, R^2 = Me, R^3 = H, R^4 = 4-MeC_6H_4
h, R^1 = Ph, R^2 = Me, R^3 = H, R^4 = 4-MeC_6H_4
i, R^1 = Cl, R^2 = CF_3, R^3 = H, R^4 = 4-MeC_6H_4
j, R^1 = Cl, R^2 = Me, R^3 = Me, R^4 = 4-MeC_6H_4

Scheme 47 Synthesis of coumarin[8,7-*e*][1,3]oxazine derivatives **130a–j**.

coumarin, pyrrole and indene.[121] They carried out the reaction with *N*-substituted 4-aminocoumarins **126a–p** and ninhydrin **127** using toluene as a solvent under microwave heating at 110 °C. All reactions were carried out in a catalyst-free and regioselective manner, which afforded good-to-excellent yields (70–92%) of designed products **128a–p** (Scheme 46). Microwave heating offers several advantages over conventional heating, including accelerated reaction rates, reduced energy consumption, and the production of cleaner products with fewer impurities. As a result of these benefits, microwave-assisted organic synthesis has garnered significant attention in the scientific community.

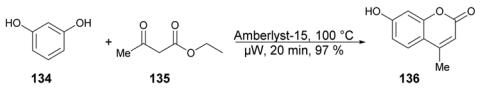
Zhang and co-workers reported a microwave-assisted synthesis of coumarin[8,7-*e*][1,3]oxazine derivatives and evaluation of their antifungal activity.[122] They accomplished a one-pot three-component Mannich reaction in this synthesis. Thus, they initially synthesized the various coumarin derivatives *via* a Pechmann condensation reaction. Then, using their designed 7-hydroxycoumarins **129a–j**, they carried out the reaction with various amines in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) using 1,4-dioxane as a solvent under microwave irradiation at 100 °C to afford the coumarin[8,7-*e*][1,3]oxazine derivatives **130a–j** in good isolated yields (57–80%) (Scheme 47). The antifungal activities of derived compounds were evaluated against *Alternaria mali*, *Rhizoctonia solani*, *Alternaria solani*, *Gibberella zeae*, *Colletotrichum capsica* and *Botrytis cinerea*. It was found that the most active compound was **130i** with an EC_{50} value of 0.0021 μM against *Botrytis cinerea*. In their initial study, they employed microwave irradiation for the synthesis of the designed coumarin–oxazines instead of conventional heating. The results indicated that the reaction times could be significantly reduced, from approximately 6 h to just 30 min.

Genovese and co-workers reported a microwave-assisted development of coumarin derivatives using $Yb(OTf)_3$ as a catalyst.[123] They performed the reaction with various substituted phenols **131a–j** and propiolic acid **132** using $Yb(OTf)_3$ as a catalyst under microwave irradiation at 80 °C and 200 W for 2 min to afford excellent yields (91–98%) of designed coumarin derivatives **133a–j** (Scheme 48). Instead of microwave-assisted synthesis they carried out the reactions *via* a traditional heating method but, due to the poor yields of designed compounds, they opted for the microwave-irradiated technique.



a, R = H
b, R = 3-OH
c, R = 3-OH,5-Me
d, R = 3-OMe
e, R = 2,3-OH
f, R = 2,5-OH
g, R = 3-Me
h, R = 2-F
i, R = 4-Cl
j, R = 3-NO2

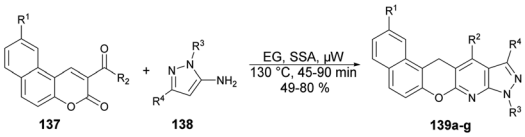
Scheme 48 $Yb(OTf)_3$-catalyzed synthesis of various coumarins **133a–j**.



Scheme 49 Synthesis of 7-hydroxy-4-methylcoumarin **136**.

A solvent-free microwave-assisted methodology for the synthesis of 7-hydroxy-4-methylcoumarin was reported by Bouasla and co-workers.[124] They selected phenol, resorcinol and ethyl acetoacetate as reactants for a Pechmann condensation reaction. The catalytic activity of various heterogenous acid catalysts, including Amberlyst-15, zeolite, and hybrid silica functionalized with sulfonic acid, was examined in the solvent-free microwave-assisted synthesis of corresponding coumarin derivatives. They found that Amberlyst-15 to be the most active catalyst in microwave conditions and yielded 7-Hydroxy-4-methylcoumarin **136** in 97% yield (Scheme 49). The Pechmann reaction was also conducted using conventional thermal heating. However, even after 20 min, the phenol conversion did not exceed 18%. This outcome underscores the potential of microwave irradiation as a viable alternative to conventional heating methods for this type of reaction.

A facile and efficient protocol for the synthesis of hetero[5]helicene-like molecules and coumarin derivatives was reported by Lin and co-workers. They used silica sulfuric acid (SSA) as a catalyst with various solvents and reaction temperatures for reaction selectivity to afford coumarin derivatives or hetero[5]helicene-like molecules.[125] They found the best results when they carried out the reaction with coumarin and 3-aminopyrazole using SSA as a catalyst in ethylene glycol (EG) under microwave conditions at 130 °C (Scheme 50). After optimising the reaction conditions, various substrates with substituted functional groups were investigated. The results indicated that incorporating an electron-withdrawing group as the substituent R^3 led to higher yields and a shorter reaction time. Conversely, when an electron-donating group was utilized as the R^3



139a, R^1 = H, R^2 = $CH_2CH_2CH_3$, R^3 = Ph, R^4 = CH_3
139b, R^1 = OCH3, R^2 = $CH_2CH_2CH_3$, R^3 = Ph, R^4 = CH_3
139c, R^1 = OCH_2CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = Ph, R^4 = CH_3
139d, R^1 = H, R^2 = CH_3, R^3 = Ph, R^4 = CH_3
139e, R^1 = OCH_3, R^2 = CH_3, R^3 = Ph, R^4 = CH_3
139f, R^1 = OCH_3, R^2 = $CH_2CH_2CH_3$, R^3 = Ph, R^4 = Ph
139g, R^1 = H, R^2 = $CH_2CH_2CH_3$, R^3 = CH_3, R^4 = Ph

Scheme 50 Synthesis of coumarin derivatives **139a–g**.

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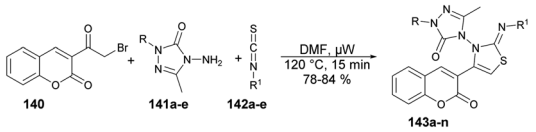
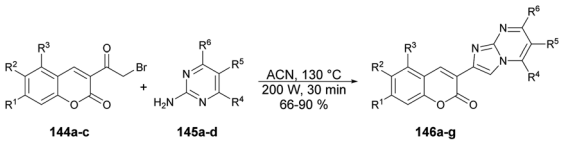


143a, R = R^1 = Ph
143b, R = R^1 = 4-OMeC_6H_4
143c, R = R^1 = 4-MeC_6H_4
143d, R = R^1 = 4-BrC_6H_4
143e, R = R^1 = 4-ClC_6H_4
143f, R = Ph, R^1 = 4-OMeC_6H_4
143g, R = Ph, R^1 = 4-ClC_6H_4
143h, R = Ph, R^1 = 4-BrC_6H_4
143i, R = 4-MeC_6H_4, R^1 = 4-OMeC_6H_4
143j, R = 4-OMeC_6H_4, R^1 = 4-ClC_6H_4
143k, R = 4-MeC_6H_4, R^1 = 4-ClC_6H_4
143l, R = 4-BrC_6H_4, R^1 = 4-ClC_6H_4
143m, R = 4-ClC_6H_4, R^1 = 4-BrC_6H_4
143n, R = 4-OMeC_6H_4, R^1 = 4-MeC_6H_4

Scheme 51 Synthesis of 5-methyl-4-[(2*Z*)-4-(2-oxo-2*H*-chromen-3-yl)-2-(4-arylimino)thiazol-3(2*H*)-yl]-2-(4-aryl)-2*H*-1,2,4-triazol-3(4*H*)-ones **143a–n**.



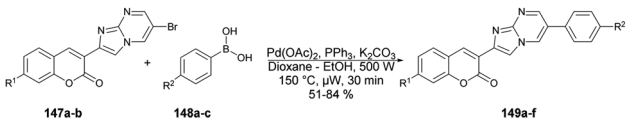
144a, $R^1 = R^2 = R^3$ = H
144b, R^1 = NEt_2 $R^2 = R^3$ = H
144c, $R^1 = R^2 = R^3$ = -CHCHCHCH-
145a, $R^4 = R^5 = R^6$ = H
145b, R^4= Me $R^5 = R^6$ = Me
145c, R^4= Me R^5 = H, R^6 = Morpholinyl
145d, R^4= H, R^5 = Br, R^6 = H
146a, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6$ = H
146b, R^1 = NEt_2, $R^2 = R^3 = R^4 = R^5 = R^6$ = H
146c, R^1 = H, $R^2 = R^3$ = -CHCHCHCH-, $R^4 = R^5 = R^6$ = H
146d, $R^1 = R^2 = R^3$ = H, R^4= Me $R^5 = R^6$ = Me
146e, R^1 = NEt_2 $R^2 = R^3 = R^4$= Me, R^5 = H, R^6 = Me
146f, R^1 = NEt_2 $R^2 = R^3$ = H, R^4= H, R^5 = Br, R^6 = H
146g, $R^1 = R^2 = R^3$ = H, R^4= Me, R^5 = H, R^6 = Morpholinyl

Scheme 52 Synthesis of 2-coumarin-3-yl-imidazo[1,2-*a*]pyrimidines **146a–g**.

substituent, lower yields were observed, and the reaction time was prolonged.

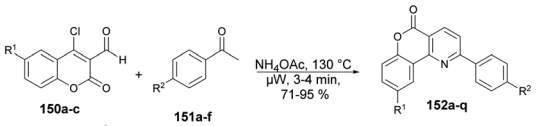
Inamdar and co-workers synthesized 5-methyl-4-[(2*Z*)-4-(2-oxo-2*H*-chromen-3-yl)-2-(4-arylimino)thiazol-3(2*H*)-yl]-2-(4-aryl)-2*H*-1,2,4-triazol-3(4*H*)-ones using a microwave-assisted technique.[126] They performed the one-pot multi-component reaction with 3-(2-Bromoacetyl)-2*H*-chromen-2-one, various substituted triazoles **141a–e** and diverse isothiocyanatobenzenes **142a–e** in DMF under microwave irradiation at 120 °C for 15 min to afford good-to-excellent isolated yields (78–84%) of designed products **143a–n** (Scheme 51). This microwave-assisted approach was solvent-free and catalyst-free, which provides environmentally friendly conditions to develop various derivatives of coumarin. Thus, this is one of the best green approaches for a complex synthesis.

Seferoğlu and co-workers reported that a range of fluorescent compounds were produced by synthesizing a novel series of 2-coumarin-3-yl-imidazo[1,2-*a*]pyrimidines **146a–g** using



147a, R^1 = H
147a, R^1 = NEt_2
148a, R^2 = H
148b, R^2 = NEt_2
148c, R^2 = OMe
149a, R^1 = H, R^2 = H
149b, R^1 = H, R^2 = NEt_2
149c, R^1 = H, R^2 = OMe
149d, R^1 = NEt_2, R^2 = H
149e, R^1 = NEt_2, R^2 = NEt_2
149f, R^1 = NEt_2, R^2 = OMe

Scheme 53 Synthesis of 6-aryl-2-coumarin-3-yl-imidazopyrimidines **149a–f**.



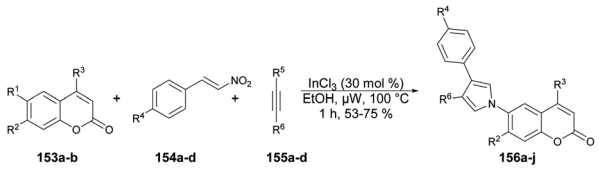
150a, R^1 = H
150b, R^1 = Me
150c, R^1 = Br
151a, R^2 = H
151b, R^2 = Me
151c, R^2 = OMe
151d, R^2 = Cl
151e, R^2 = Br
151f R^2 = NO_2
152a, R^1 = H, R^2 = H
152b, R^1 = H, R^2 = Me
152c, R^1 = H, R^2 = OMe
152d, R^1 = H, R^2 = Cl
152e, R^1 = H, R^2 = Br
152f, R^1 = H, R^2 = NO_2
152g, R^1 = Me, R^2 = H
152h, R^1 = Me, R^2 = Me
152i, R^1 = Me, R^2 = OMe
152j, R^1 = Me, R^2 = Cl
152k, R^1 = Me, R^2 = Br
152l, R^1 = Me, R^2 = NO_2
150m, R^1 = Br, R^2 = H
150n, R^1 = Br, R^2 = Me
150o, R^1 = Br, R^2 = OMe
150p, R^1 = Br, R^2 = Br
150q, R^1 = Br, R^2 = NO_2

Scheme 54 Synthesis of diverse pyrido[3,2-*c*]coumarins **152a–q**.

functionalized coumarin and pyrimidine units with different substitutions (Scheme 52).[127] Another set of compounds, which included unsubstituted coumarin and 7-dialkylaminocoumarin **149a–f** as a fluorophore, were obtained through palladium-catalyzed cross-coupling reactions. This was achieved by coupling 6-bromo-2-coumarin-3-yl-imidazopyrimidine derivatives **147a–b** with various arylboronic acids **148a–c** (Scheme 53). Microwave irradiation was used in all the reaction steps and compared with the conventional method. It was observed that microwave synthesis was facile, productive and occurred in a short time (30 min) as compared with the conventional method (24 h).

Bhuyan and co-workers reported a microwave-assisted solvent-free synthesis of diverse functionalized pyrido[3,2-*c*]coumarins **152a–q** in excellent yields.[128] Initially, they started to optimize the reaction conditions with 4-chloro-3-formylcoumarin **150**, acetophenone **151** and ammonium acetate using various solvents at different temperatures under microwave conditions. The best condition obtained for completion of the reaction with a higher yield (84%) was a solvent-free condition at 130 °C and 3 min. Once the reaction conditions had been optimized, then various substrates were investigated, which afforded the diverse functionalized pyrido[3,2-*c*]coumarins **152a–q** in good-to-excellent yields (71–95%) (Scheme 54).

A microwave-irradiated multi-component synthesis of 6-(pyrrolyl) coumarin derivatives was reported by Ansary and co-workers.[129] They performed the initial model reaction with 6-



153a, $R^1 = NH_2$, $R^2 = R^3$ = H
153b, $R^1 = NH_2$, $R^2 = NH_2$, R^3 = Me
154a, R^4 = H, **154b**, R^4 = Me
154c, R^4 = OMe **154d**, R^4 = Cl
155a, $R^5 = R^6 = CO_2Et$
155b, $R^5 = R^6 = CO_2Me$
155c, $R^5 = R^6$ = Ph
155d, R^5 = ^{t}Bu, R^6 = H
156a, $R^2 = R^3$ = H, R^4 = Me, $R^5 = R^6 = CO_2Et$
156b, $R^2 = R^3$ = H, R^4 = H, $R^5 = R^6 = CO_2Me$
156c, $R^2 = R^3$ = H, R^4 = H, $R^5 = R^6$ = Ph
156d, $R^2 = R^3$ = H, R^4 = H, R^5 = ^{t}Bu, R^6 = H
156e, $R^2 = NH_2$, R^3 = Me, R^4 = Me, $R^5 = R^6 = CO_2Et$
156f, $R^2 = NH_2$, R^3 = Me, R^4 = Me, $R^5 = R^6 = CO_2Me$
156g, $R^2 = NH_2$, R^3 = Me, R^4 = Me, $R^5 = R^6$ = Ph
156h, $R^2 = NH_2$, R^3 = Me, R^4 = Me, R^5 = ^{t}Bu, R^6 = H
156i, R^2 = H, R^3 = H, R^4 = Cl, R^5 = ^{t}Bu, R^6 = H
156j, $R^2 = NH_2$, R^3 = Me, R^4 = OMe, R^5 = ^{t}Bu, R^6 = H

Scheme 55 Synthesis of 6-(pyrrolyl) coumarin derivatives **156a–j**.

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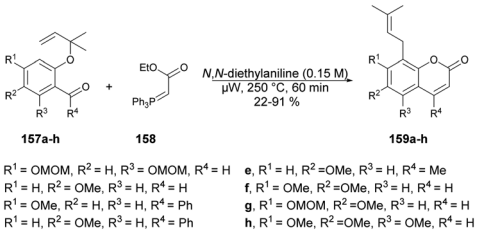
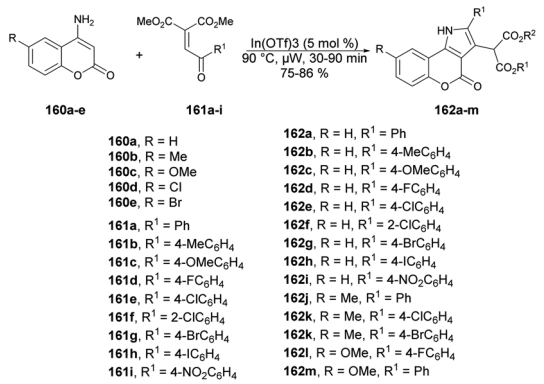


Scheme 56 Synthesis of 8-prenylcoumarins **159a–h**.

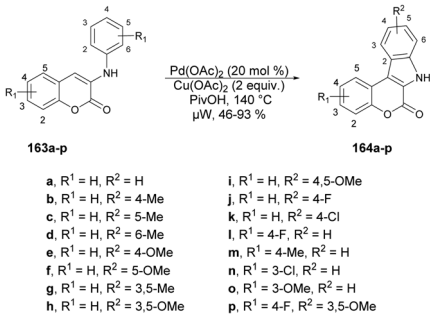
amino coumarin **153a**, β-nitrostyrene **154b** and diethyl acetylenedicarboxylate **155a** to form 6-(pyrrolyl) coumarin **156a**. They obtained best result (75% yield) when $InCl_3$ was used as a catalyst in ethanol under microwave conditions at 100 °C for 1 h. After investigation of reaction conditions, they synthesized a series of 6-(pyrrolyl) coumarin derivatives **156a–j** in 53–79% isolated yields using 6-amino coumarins **153a–b**, β-nitrostyrenes **154a–d**, and dialkyl acetylenedicarboxylates **155a–d** (Scheme 55). It was found that nitrostyrenes with an electron-donating substituent at the aryl ring afforded better yields as compared with an electron-withdrawing substituent.

Schmidt and co-workers reported microwave-assisted development of new methodology for one-pot synthesis of 8-prenylcoumarins **159a–h**.[130] They performed the reaction with 1,1-dimethylallylated salicylaldehydes **157a–h**, stabilized ylide [(ethoxycarbonyl)methylene]triphenylphosphorane **158** and *N*,*N*-diethylaniline under microwave conditions at 250 °C to afford poor-to-good isolated yields (22–91%) of designed products **159a–h** (Scheme 56).

Samanta and co-workers described a new class of diverse coumarins, dimedone, and naphthoquinone-fused pyrroles, which can be quickly synthesized through a one-pot, solvent-free annulation reaction.[131] The reaction was catalyzed by a superior Lewis acid and assisted by microwave energy, and it involved various carbo- and heterocyclic enaminones with α-aroyl/heteroaryl/acetylidene malonates and 3-aroylidene-2-oxindoles. Initially, they started the model reaction between 4-aminocoumarin **160a** as a C/N-binucleophile and benzoylidene malonate **161** as 1,2-bielectrophile. They investigated the reaction conditions using various solvent and neat conditions along



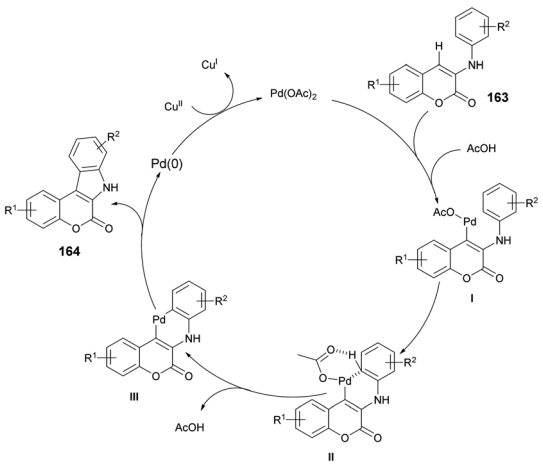
Scheme 57 Synthesis of various coumarin derivatives **162a–m**.



Scheme 58 Synthesis of indolo[2,3-*c*]coumarins **164a–p**.

with various acid catalysts under conventional and microwave conditions. Among all the tested conditions, the neat condition under microwave irradiation at 90 °C within 30 min provided a better yield (85%) of designed compound. After optimizing the reaction condition, they prepared a library of designed compounds **162a–m** using similar microwave and catalytic conditions (Scheme 57). In addition, they conducted the experiment using the conventional method and noted that the reaction remained incomplete with 60% yield even after 12 h. However, when employing microwave irradiation, the reaction was completed within just 30 min, achieving higher yields. This microwave-based methodology offers several advantages, such as its environmentally friendly nature, superior synthetic efficiency, easy handling, high reactivity, and accelerated procedures, resulting in good yields with high purity.

Xu and co-workers developed a new method for synthesizing a wide variety of indolo[2,3-*c*]coumarins and indolo[2,3-*c*]quinolinones with high yields (up to 93%).[132] They used a microwave-assisted base-free intramolecular cross dehydrogenative coupling (CDC) of 3-aniline substituted coumarins **163a–p** under palladium catalysis using microwave irradiation at 140 °C to afford indolo[2,3-*c*]coumarins **164a–p** (Scheme 58). This approach was considered to be one of the most convenient and uncomplicated ways to produce these fused polyheterocycles.



Scheme 59 A plausible mechanism for the synthesis of indolo[2,3-*c*] coumarins **164**.

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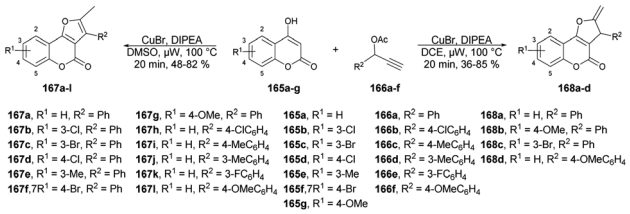
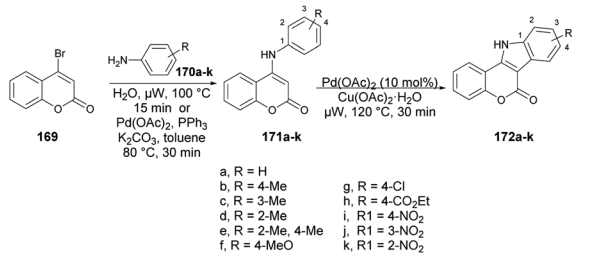


Scheme 60 Synthesis of furo[3,2-*c*]coumarins **167a–l** and isomeric series of 2-methylene-2,3-dihydrofuro[3,2-*c*]coumarins **168a–d**.

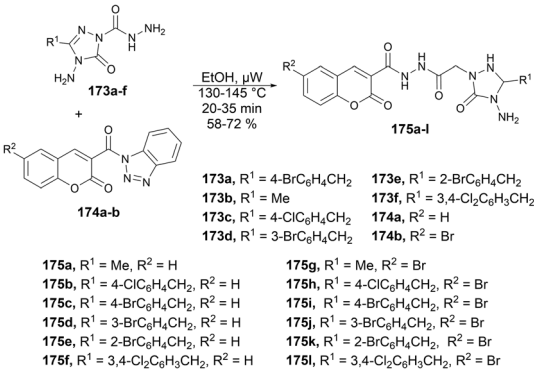
A reaction mechanism was proposed and is depicted in Scheme 59. It is hypothesized that the initial palladation occurs preferably at the coumarin nucleus and generates the intermediate **I**. The crucial intermediate **III** is likely formed through CeH activation in a concerted metalation–deprotonation process from the Pd(II) species **I**. Subsequently, reductive elimination leads to the formation of the desired indolo[2,3-*c*]coumarin product **164** and Pd(0). Finally, the oxidant Cu(II) salt serves to regenerate the active Pd(II) catalyst.

A new method for synthesizing 2-methylfuro[3,2-*c*]coumarins was developed by Cui and co-workers using a copper-catalyzed microwave-promoted propargylation and oxacyclization.[133] The starting materials for this reaction were readily available 4-hydroxycoumarins and terminal propargyl acetates. They obtained moderate-to-good yields (up to 82%) of furo[3,2-*c*]coumarins **167a–l** produced by this reaction. Interestingly, when they changed the solvent from dimethyl sulfoxide to 1,2-dichloroethane while retaining the conditions, the isomeric series of 2-methylene-2,3-dihydrofuro[3,2-*c*]coumarins **168a–d** was obtained in low-to-acceptable yields (up to 85%) (Scheme 60).

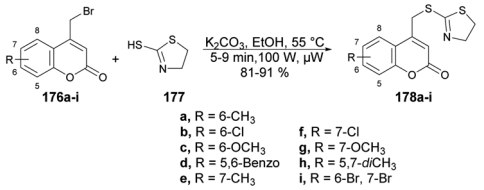
Litinas and co-workers developed a Pd-catalyzed oxidative coupling protocol for the synthesis of azacoumestans using microwave irradiation.[134] The Pd-catalyzed oxidative coupling of 4-(arylamino)coumarins was carried out using $Cu(OAc)_2$ in acetic acid under microwave irradiation. They synthesized azacoumestans, including those substituted with electron-withdrawing groups, with almost quantitative yield. The arylamines **170a–k** were reacted with 4-bromocoumarin **169** in water or through Pd-catalyzed C–N coupling under microwave heating to achieve intermediate product **171a–k**, which was again catalyzed by copper and Pd catalysts to afford the designed products **172a–k** in good-to-excellent yields (85–99%) (Scheme 61).



Scheme 61 Synthesis of azacoumestans **172a–k**.



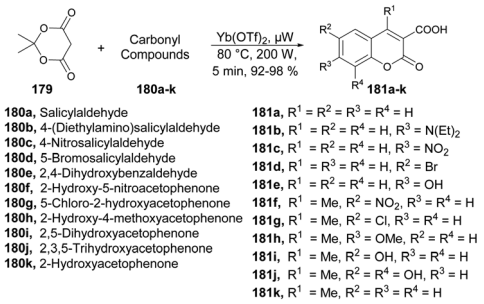
Scheme 62 Synthesis of *N*-[(1,2,4-triazol-1-yl)acetyl]coumarin-3-carbohydrazides **119a–l**.



Scheme 63 Synthesis of coumarin–thiazoline hybrids **178a–i**.

A microwave-assisted environmentally benign protocol to synthesize coumarin derivatives was developed by Mentese and co-workers.[135] In order to synthesize designed molecules *N*-[(1,2,4-triazol-1-yl)acetyl]coumarin-3-carbohydrazides **175a–l**, they carried out the reaction between 2-(3-alkyl/aryl-4-amino-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetohydrazides **173a–f** and 3-(1*H*-benzotriazol-1-ylcarbonyl)-2*H*-chromen-2-ones **174a–b** in ethanol under microwave conditions at 130–145 °C for 20 ± 35 min to afford good isolated yields (58–72%) of designed products **175a–l** (Scheme 62).

Hosamani and co-workers reported a microwave-irradiated rapid development of coumarin–thiazoline hybrids and their antitubercular activity.[136] They performed the reaction between various substituted coumarins **176a–i** and 4,5-dihydrothiazole-2-thiol **177** using K_2CO_3 as a base in ethanol under microwave conditions at 55 °C and 100 W for 5–9 min to afford good isolated yields (81–91%) of coumarin–thiazoline hybrids **178a–i** (Scheme 63). After the synthesis, these compounds were



Scheme 64 Synthesis of coumarin-3-carboxylic acids **181a–k**.

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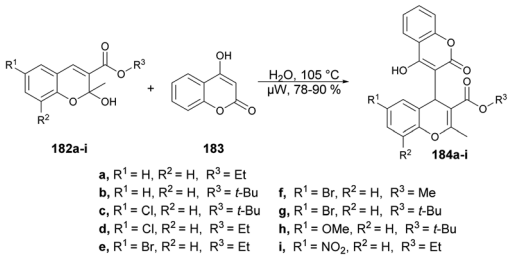
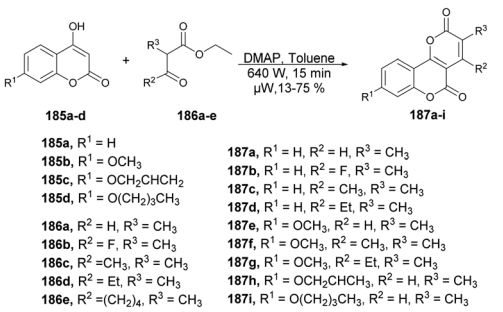


Scheme 65 Synthesis of chromene–coumarin derivatives **184a–i**.

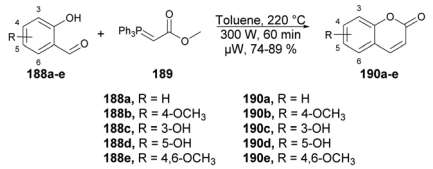
investigated for their antitubercular activity. Compound **178b** was found to be most potent antitubercular compound with an IC_{50} value of 280 μM. In order to compare the conventional method and microwave irradiation, various reactions were conducted. The conventional method produced 20% lower yields as compare with microwave irradiation. Thus, microwave irradiation was a better choice to perform this type of reaction.

A new microwave-irradiated development of coumarin-3-carboxylic acids was reported by Genovese and co-workers.[137] They performed the reaction between 2,2-dimethyl-1,3-dioxane-4,6-dione **179** and various carbonyl compounds **180a–k** using $Yb(OTf)_3$ as a catalyst with no solvent and microwave irradiation at 80 °C and 200 W for 5 min to afford a good isolated yield (92–98%) of coumarin-3-carboxylic acids **181a–k** (Scheme 64). It is important to emphasize that when the same reaction was conducted under conventional conditions, it resulted in a complex mixture of products, as evidenced by TLC. This mixture partly originated from the decomposition of Meldrum's acid and the air-oxidation of benzaldehyde. Under these experimental conditions, the estimated yield of coumarin-3-carboxylic acid, as determined by GC, was ∼15%. Furthermore, attempts to use other β-dicarbonyl compounds (*e.g.*, diethyl malonate) also yielded unsatisfactory results.

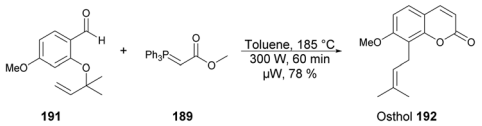
Coumarin derivatives have gained recognition for their diverse range of biological activities, such as antimicrobial, antioxidant and antitumor properties. In light of this, Rao and co-workers introduced a new method for developing hybrid chromene–coumarin derivatives **184a–i** through an environmentally friendly and catalyst-free synthesis.[138] Formation of the key C–C bond occurred in an aqueous medium using microwave irradiation at 105 °C, and resulted in a rapid reaction time, high conversion and exceptional regioselectivity (Scheme 65). Various solvents were tested but "in water" reactions proved to be the most efficient in terms of time and yields, achieving yields of 78–90% at 105 °C.



Scheme 66 Synthesis of pyrano [3,2-*c*]chromene-2,5-diones **187a–i**.



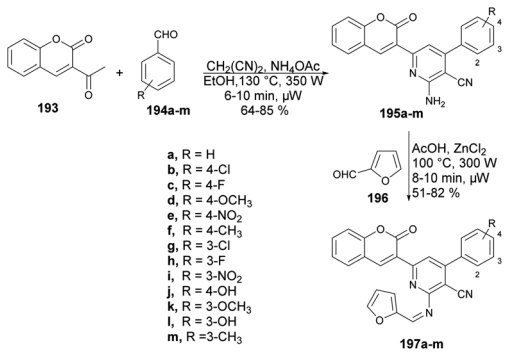
Scheme 67 Synthesis of coumarin derivatives **190a–e**.



Scheme 68 Synthesis of natural product osthol **192**.

Zhang and co-workers developed a novel protocol for the synthesis of a group of pyrano [3,2-*c*]chromene-2,5-diones through microwave irradiation and also investigated their antifungal activity against *Botrytis cinerea*, *Colletotrichum capsica*, *Alternaria solani*, *Gibberella zeae* and *Rhizoctonia solani*.[139] In order to synthesize pyrano[3,2-*c*]chromene-2,5-diones **187a–I**, a reaction was carried out between various 4-hydroxycoumarin **185a–e** and ethyl 2-methylacetoacetate **186** in the presence of DMAP as a catalyst in toluene under microwave irradiation at room temperature and 640 W for 15 min to afford 13–75% yield of desired products **187a–i** (Scheme 66). Among all the derived compounds of pyrano [3,2-*c*]chromene-2,5-diones, compound **187g** was found to be the most potent for antifungal activity with an EC_{50} value of 0.082 μM. Additionally, when compared with conventional heating, it was observed that the reaction times for target compounds could be significantly reduced from ∼6 h to just 15 min. Moreover, the isolated yields could be enhanced, reaching a maximum of 76% (compound **187a**) as opposed to the previous 30%.

A microwave-assisted regioselective method for the synthesis of coumarin derivatives was developed by Pospisil and co-workers.[140] They discovered an efficient and protecting group-



Scheme 69 Synthesis of coumarin derivatives **197a–m**.

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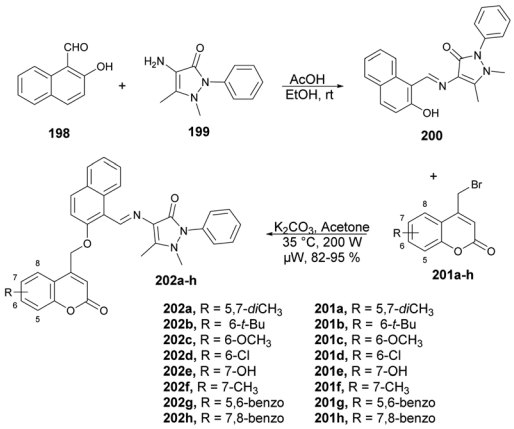


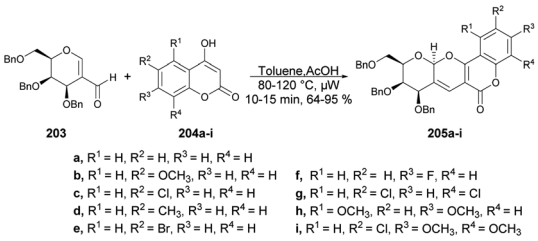
Scheme 70 Synthesis of various substituted coumarin pyrazolone hybrids **202a–h**.

free synthesis of coumarins. The reaction was carried out between various unprotected aldehydes **188a–e** and stabilized Wittig ylide **189** in the presence of toluene in microwave conditions at 220 °C and 300 W for 60 min to afford a good isolated yield (74–89%) of coumarin derivatives **190a–e** (Scheme 67). For the synthetic applications of the developed method, they also performed the reaction using a similar approach to develop natural product osthol **192** (Scheme 68).

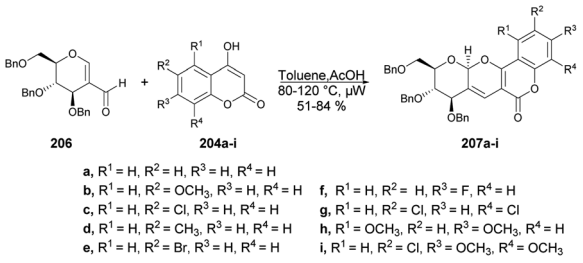
Desai and co-workers reported a microwave-assisted rapid and efficient method for the synthesis of novel coumarin derivatives and evaluation of activity against various bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*) and fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*).[141] To synthesize coumarin derivatives, the reaction was carried out between 3-acetyl-2*H*-chromen-2one **193**, aromatic aldehydes **194a–m**, malononitrile and ammonium acetate in microwave conditions using ethanol as a solvent to yield products **195a–m**, which were again microwave-irradiated with another aldehyde **196** at 300 W and 100 °C for 8–10 min to afford a good isolated yield of desired products **197a–m** (Scheme 69).

Chavan and co-workers reported an expedient and high-yielding method for synthesizing coumarin, pyrazolone hybrids containing Schiff-base structures using microwave irradiation.[142] For the synthesis of Schiff base analogues **200**, the reaction was carried out between 2-hydroxy-1-naphthaldehyde **198** and 4-aminoantipyrene **199** in the presence of acetic acid in ethanol. On a condensation reaction with substituted 4-bromomethyl coumarins **201a–h** in microwave conditions at 35 °C and 200 W for 8–12 min, a good isolated yield (82–95%) of various substituted coumarin, pyrazolone hybrids **202a–h** were obtained (Scheme 70). The synthesized compounds were evaluated for their antibacterial and anti-inflammatory properties using the agar well-diffusion and egg albumin-denaturation methods, respectively. It was found that compound **202d** and **202h** exhibited antibacterial effects with a minimum inhibitory concentration (MIC) of 1.420 μM and MIC of 2.33 μM, respectively, against the Gram-positive *Staphylococcus aureus* strain, which was better than the standard drug (ciprofloxacin).

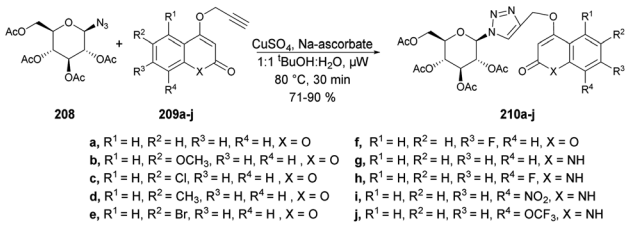
The pyrano[3,2-*c*]pyranone structure is a crucial structure found in various natural products with different biological activities. Sagar and co-workers reported the efficient and rapid synthesis of two sets of pyrano[3,2-*c*]pyranone derivatives (**205a–i** and **207a–i**) fused with carbohydrates utilizing 2 *C*-formyl galactal **203** and 2-*C*-formyl glucal **206**. They were reacted with diverse 4-hydroxycoumarins **204a–i** in a short time (10 min) using microwave-assisted conditions (Schemes 71 and 72).[143] They also evaluated the anticancer potential of the newly derived pyrano[3,2-*c*]pyranones against MCF-7 (breast), MDA-



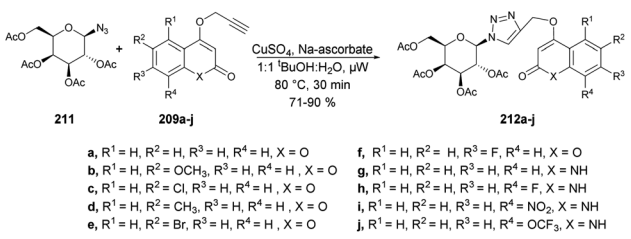
Scheme 71 Synthesis of pyrano[3,2-*c*]pyranone derivatives **205a–i** fused with 2-*C*-formyl galactal.



Scheme 72 Synthesis of pyrano[3,2-*c*]pyranone hybrids **207a–i** fused with 2-*C*-formyl glucal.



Scheme 73 Synthesis of triazole-linked *N*-glucopyranosides **210a–j**.



Scheme 74 Synthesis of triazole linked *N*-galactopyranosides **212a–j**.

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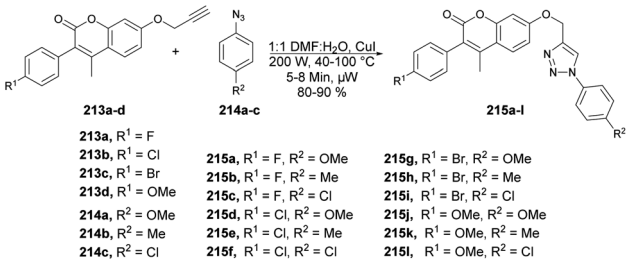
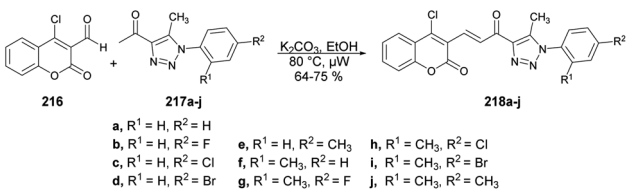


Scheme 75 Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives of coumarin **215a–l**.

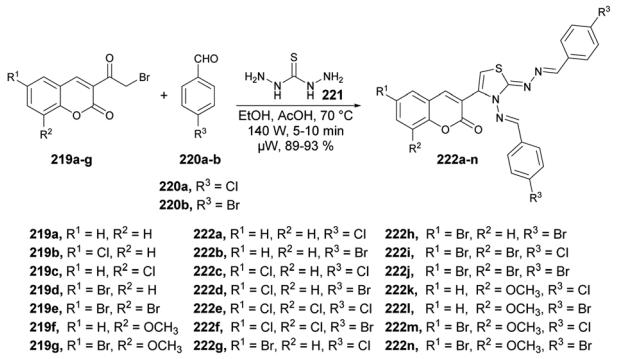
MB-231 (breast), and HepG2 (liver) cancer cell lines *via* cellular assays and examined their ability to inhibit the growth and viability of MCF-7, MDA-MB-231, and HepG2 cell lines. It was found that compound **205d** showed considerable growth-inhibitory effects with a MIC_{50} value of 10.9 μM.

Sagar and co-workers also reported the synthesis of two series of triazole-linked *N*-glycosides of coumarins and quinolones using 1-azido-2,3,4,6-tetra-*O*-acetyl-β-D-glucose **208** and 1-azido-2,3,4,6-tetra-*O*-acetyl-β-D-galactose **211** as starting materials.[144] The reactions were performed under microwave-assisted conditions *via* click chemistry and resulted in a good isolated yield of triazole-linked *N*-glycosides of coumarins and quinolones (Schemes 73 and 74). They also evaluated the biological activity of diverse synthesized compounds against several cancer cell lines, and one of the library members **212d** was found to have low micromolar IC_{50} (10.97 μM) and selective toxicity against the breast cancer cell line (MCF-7).

A highly efficient and environmentally friendly method was reported by Ashok and co-workers to synthesize 1,4-disubstituted 1,2,3-triazole derivatives **215a–l** based on coumarin scaffolds.[145] The synthesis involved a copper(I)-catalyzed click reaction between various substituted arylazides **214a–c** and terminal alkynes **213a–d**. It was carried out under microwave irradiation at 200 W and 40–100 °C for 5–8 min to afford the designed products **215a–l** in excellent yields (Scheme 75). They also evaluated the synthesized compounds for their antimicrobial, antioxidant, and anti-inflammatory activities. Compounds **215g** and **215l** exhibited better anti-inflammatory activity with an IC_{50} value of 13.16 μM and 15.35 μM, respectively, than the standard drug diclofenac. In order to compare the synthesis of alkyne-substituted 3-aryl coumarin intermediates and coumarin-based 1,2,3-triazole the reaction was performed using conventional and microwave irradiation methods. In comparison, the microwave irradiation method yielded better results,



Scheme 76 Synthesis of chalcone-linked coumarin-triazole hybrids **218a–j**.



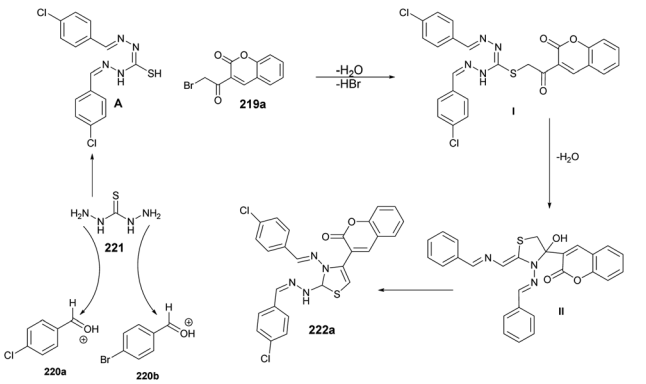
Scheme 77 Synthesis of coumarin-based thiazoles **222a–n**.

with good-to-excellent yields ranging from 80% to 90%, while the conventional method resulted in yields of 68% to 79%.

A synthesis and evaluation of anticancer activity of α,β-unsaturated carbonyl-linked coumarin-triazole hybrids **218a–j** using microwave assistance have been reported by Kumar and co-workers.[146] The base-catalyzed reaction was carried out between 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **216** and diverse aryl azides **217** in microwave conditions at 80 °C for 15–30 min afforded the α,β-unsaturated carbonyl-linked coumarin-triazole hybrids **218a–j** (Scheme 76). Out of the series, compound **218d** demonstrated greater potential for fighting cancer against PC-3 and DU-145 cell lines, exhibiting an IC_{50} value of 10.538 ± 0.3 μM and 9.845 ± 0.6 μM, respectively. Moreover, it had very low toxicity (10 μM) against normal cells.

Microwave-induced synthesis frequently leads to lower reaction temperatures and shorter reaction times. Target compounds were synthesized using conventional reflux and microwave irradiation methods. The optimization of reaction conditions demonstrated that microwave-assisted synthesis required significantly less reaction time compared with conventional heating methods.

Vedula and co-workers reported microwave irradiation of thiocarbohydrazide **221**, aldehydes **220a–b**, and 3-(2-bromoacetyl) coumarins **219a–j** to synthesize a sequence of novel



Scheme 78 A plausible mechanism for the synthesis of coumarin-based thiazoles **222a–n**.

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coumarin-based thiazoles **222a–n**.[147] The reaction was carried out under microwave conditions at 70 °C and 210 W for 5–10 min in ethanol/acetic acid to afford a good isolated yield of coumarin-based thiazoles **222a–n** (89–93%) (Scheme 77). They evaluated the activity of synthesized compounds **222a–n** against the Gram-positive bacterium *Staphylococcus aureus* (ATCC-12600). Compound **222e** was discovered to exhibit good antibacterial activity with an IC_{50} value of 5.09 μM. They also performed the reactions using a conventional method and observed a lower yield of desired compounds as compared with use of microwave irradiation.

In Scheme 78, a plausible mechanism for the formation of the target compound **222a–n** is illustrated. Initially, two equivalents of aldehydes react with one equivalent of thiocarbohydrazide in the presence of acetic acid, resulting in the formation of bis-thiocarbohydrazone **A**. Subsequently, a SN_2-type attack occurs, with the sulfur from bis-thiocarbohydrazone attacking the C–Br of 3-(2-bromoacetyl) to form intermediate **II**. This intermediate then undergoes acid-catalyzed dehydration, leading to the formation of the titled coumarin-based thiazole **222a**.

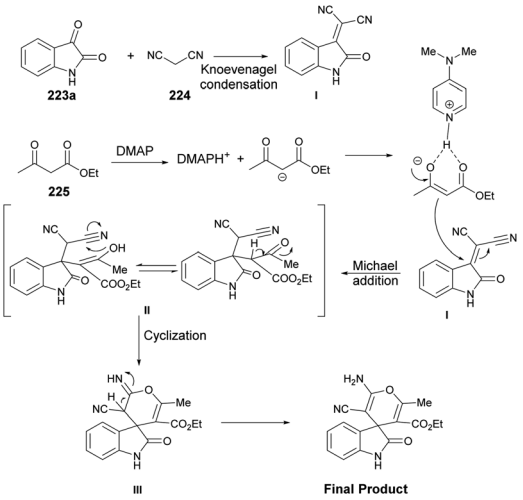
2.4. Isatins and their derivatives

Isatin is a heterocyclic compound used extensively as a foundational component in the synthesis and advancement of novel drug candidates.[148–150] The remarkable versatility of isatins, which can serve as electrophiles and nucleophiles, coupled with their ready availability, positions them as highly prized building blocks in organic synthesis.[151–153] They participate in a range of transformations, including electrophilic aromatic substitution at the C-5 and C-6 positions of the phenyl ring,[154] N-substitutions,[154] nucleophilic additions to the C-3 carbonyl group,[154] selective oxidations, reductions, ring expansions, spiro-annulations, and more reactions.[155] Using isatins as starting materials, various heterocyclic frameworks of significant biological importance, such as pyrrolidines, indoles, quinolines, β-lactams, and 2-oxindoles, have been synthesized.[156–158]

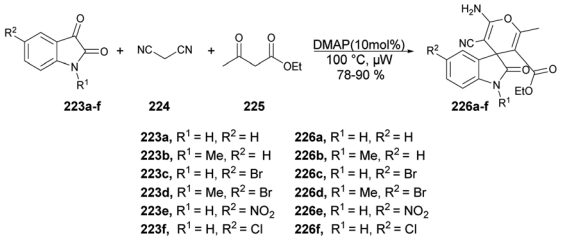
Recent literature reflects a renewed interest in the chemistry and bioactivity of isatin derivatives, leading to advancements in established reaction procedures and the development of selective methods for producing isatin derivatives through microwave irradiation techniques.

Zakeri and co-workers have discovered microwave-assisted eco-friendly methods for producing spiro-4*H*-pyrans **226a–f** through a one-pot, three-component condensation reaction using a domino Knoevenagel/Michael/cyclization sequence.[159] These approaches were tested using various organocatalysts in water and solvent-free conditions under microwave irradiation and ball-milling conditions. The research team conducted numerous experiments to optimize the reaction parameters, such as catalyst type/amount, reaction temperature, and time. The most effective procedure was observed to be microwave irradiation in the presence of 4-dimethylaminopyridine (DMAP), resulting in good yields (78–90%) of final products **226a–f**, in a short reaction time, environmentally sustainable and ease-of-operation manner (Scheme 79). Microwave-induced synthesis frequently leads to lower reaction temperatures and shorter reaction times. Target compounds were synthesized using conventional reflux and microwave irradiation methods. The optimization of reaction conditions demonstrated that microwave-assisted synthesis required significantly less reaction time compared with conventional heating methods.

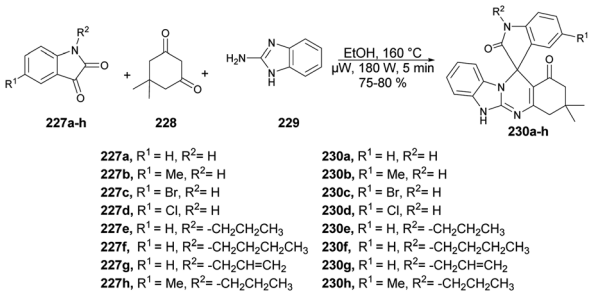
Spiro-4*H*-pyrans can be formed through a series of chemical reactions, as depicted in Scheme 80. This scheme illustrates a plausible mechanism for the reaction between isatin and malononitrile with ethyl acetoacetate to yield **226** derivatives. The process involves a typical cascade reaction. First, isatin **223a** undergoes a Knoevenagel condensation with malononitrile in the presence of DMAP, leading to the formation of an



Scheme 80 Plausible mechanism for the synthesis of spiro-4*H*-pyrans.



Scheme 79 Synthesis of spiro-4*H*-pyrans **226a–f**.



Scheme 81 Synthesis of spiro-benzimidazoquinazolinones **230a–h**.

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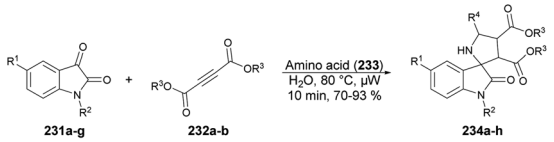


231a, R^1 = H, R^2 = H
231b, R^1 = Cl, R^2 = H
231c, R^1 = F, R^2 = H
231d, R^1 = Me, R^2 = H
231e, R^1 = OMe, R^2 = H
231f, R^1 = NO_2, R^2 = H
231g, R^1 = H, R^2 = Ph
232a, R^3 = Me
232b, R^3 = Et

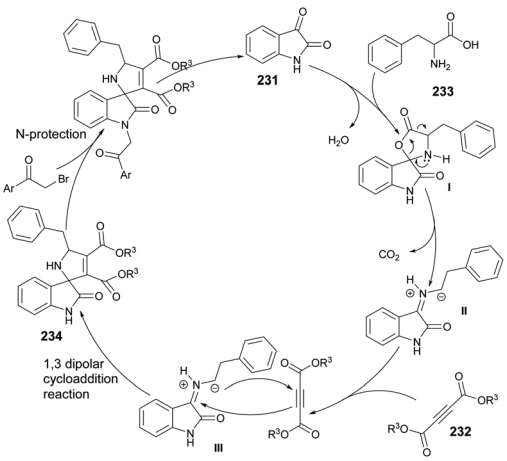
Amino acid = Proline, 4-hydroxyproline
234a, R^1 = H, R^2 = H, R^3 = Me, R^4 = $-CH_2CH_2CH_2-$
234b, R^1 = Cl, R^2 = H, R^3 = Me, R^4 = $-CH_2CH_2CH_2-$
234c, R^1 = F, R^2 = H, R^3 = Me, R^4 = $-CH_2CH_2CH_2-$
234d, R^1 = Me, R^2 = H, R^3 = Me,R^4 = $-CH_2CH_2CH_2-$
234e, R^1 = H, R^2 = H, R^3 = Et,R^4 = $-CH_2CH_2CH_2-$
234f, R^1 = H, R^2 = H, R^3 = Me,R^4 = $-CH_2CHOHCH_2-$
234g, R^1 = NO_2, R^2 = H, R^3 = Me,R^4 = $-CH_2CH_2CH_2-$
234h, R^1 = F, R^2 = H, R^3 = Et, R^4 = $-CH_2CH_2CH_2-$

Scheme 82 Synthesis of isatin based spiro compounds **234a–h**.

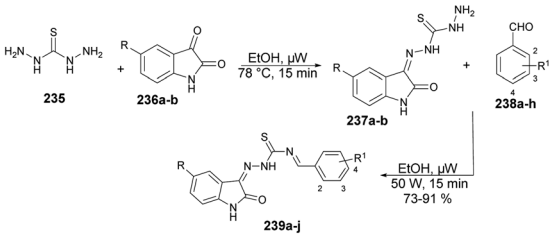
isatylidenemalononitrile derivative (intermediate **I**). Subsequently, the treatment of a β-keto ester with DMAP generates the major thermodynamic enolate product. Next, intermediate **I** is subjected to Michael addition, wherein the thermodynamic ethyl acetoacetate enolate attacks intermediate **I**, giving rise to the formation of intermediate **II**. Finally, the hydroxyl group participates in a cycloaddition reaction with the cyano moiety, resulting in the exclusive formation of the desired **226a** product. Notably, the kinetic product was not observed in this process.

Pardasani and co-workers developed a new catalyst-free method for synthesizing spiro-benzimidazoquinazolinones using multiple components under microwave irradiation.[160] The method involves a one-pot three-component reaction of acenaphthoquinone or isatin **227a–h**, 1,3-diketone **228**, and 2-aminobenzimidazole **229** in ethanol at 160 °C and 180 W afforded good isolated yields (75–80%) of spiro-benzimidazoquinazolinones **230a–h** (Scheme 81). One of the most attractive features of this method is the mild reaction conditions it employs, along with operational simplicity.

A microwave-assisted multicomponent reaction was developed by Meshram and co-workers to synthesize a series of isatin derivatives.[161] The three-component reaction was performed between isatins **231a–g**, amino acid **233** and but-2-ynedioates **232** in an aqueous medium, under microwave irradiated



Scheme 83 Plausible mechanism for the formation of pyrrolizine-1,2-dicarboxylate.



239a, R = Br, R^1 = 2-Br
239b, R = Br, R^1 = 4-Cl
239c, R = Br, R^1 = 2-Cl,5-F
239d, R = Br, R^1 = 2,5-Cl
239e, R = CH_3, R^1 = 2-F
239f, R = CH_3, R^1 = 2-OMe
239g, R = CH_3, R^1 = 2-Me
239h, R = CH_3, R^1 = 3-Me,6-OH
239i, R = Br, R^1 = 2-OMe
239j, R = CH_3, R^1 = 2-OMe

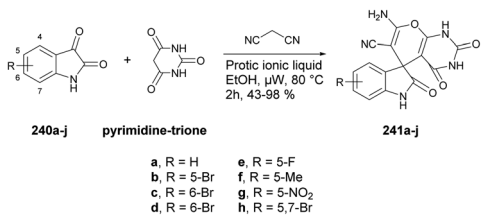
236a & 237a, R = Br
236b & 237b, R = CH_3
238a, R^1 =,2-Br
238b, R^1 = 4-Cl
238c, R^1 = 2-Cl,5-F
238d, R^1 = 2,5-Cl
238e, R^1 = 2-F
238f, R^1 = 2-OMe
238g, R^1 = 2-Me
238h, R^1 = 3-Me,6-OH

Scheme 84 Synthesis of isatin-β-thiocarbohydrazones **239a–j**.

conditions at 80 °C for 10 min afforded a good isolated yield (70–93%) of the target compounds **234a–h** (Scheme 82). The synthesis of other diverse functionalized spirooxindole derivatives can be achieved by utilizing this synthetic protocol. This reaction offers numerous benefits, including: (i) utilizing water as the reaction solvent; (ii) achieving a high atom economy; (iii) eliminating the need for a catalyst; (iv) accommodating a wide range of substrates.

A plausible mechanism for the three-component reaction is proposed and depicted in Scheme 83. The reaction begins with the condensation of α-amino acid **233** and isatin **231**, leading to the formation of imine intermediates **II** through the elimination of CO_2. Subsequently, a 1,3-dipolar cycloaddition reaction (III) occurs between the imine intermediates and but-2-ynedioates **232**, then undergoes cyclization, yielding the spiro compound **234**. In the case of the four-component reaction, the spiro compound 234 undergoes a further reaction with phenacyl bromide, leading to the formation of a N-protected product.

Gohary and co-workers developed a microwave-assisted new range of isatin-β-thiocarbohydrazones by utilizing the key features required for metal chelation found in triapine.[162] Their approach involved modifying the basic structure of triapine by substituting the pyridinyl group with isatin, which retained the three-pronged feature necessary for metal chelation. The reaction carried out between thiocarbohydrazide **235** and isatin derivatives **236a–b** in ethanol under microwave irradiation afforded good isolated yields (73–91%) of **237a–b** which, on further treatment with aryl aldehydes **238a–h**, afforded the



a, R = H
b, R = 5-Br
c, R = 6-Br
d, R = 6-Br
e, R = 5-F
f, R = 5-Me
g, R = 5-NO_2
h, R = 5,7-Br

Scheme 85 Synthesis of isatin derivatives **241a–h**.

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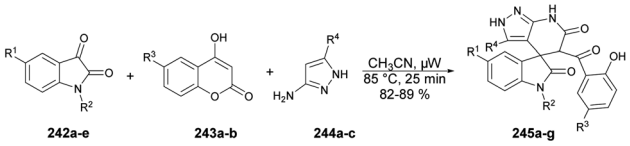


242a, R^1 = F, R^2 = CH_3
242b, R^1 = H, R^2 = H
242c, R^1 = Cl, R^2 = H
242d R^1 = OMe, R^2 = CH_3
242e, R^1 = Cl, R^2 = CH_3

243a, R^3 = H
243b, R^3 = CH_3

244a, R^4 = CH_3
244b, R^4 = Ph
244c, R^4 = 4-BrC_6H_4

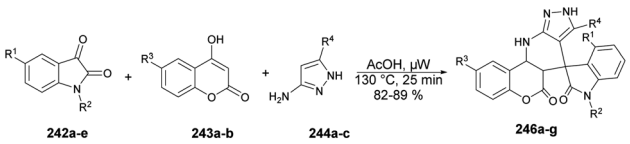
245a, R^1 = H, R^2 = H, R^3 = H, R^4 = CH_3
245b, R^1 = H, R^2 = H, R^3 = H, R^4 = 4-BrC_6H_4
245c, R^1 = F, R^2 = CH_3, R^3 = CH_3, R^4 = CH_3
245d, R^1 = H, R^2 = H, R^3 = H, R^4 = Ph
245e, R^1 = Cl, R^2 = H, R^3 = H, R^4 = CH_3
245f, R^1 = OMe, R^2 = CH_3, R^3 = H, R^4 = CH_3
245g, R^1 = F, R^2 = CH_3, R^3 = H, R^4 = CH_3

Scheme 86 Synthesis of spirooxindoles **245a–g**.

products **239a–j** (Scheme 84). The newly developed compounds were also evaluated for their effectiveness in fighting cervical cancer (HeLa) and kidney fibroblast cancer (COS-7) cell lines utilizing doxorubicin as a standard drug. Compound **239c** exhibited remarkable efficacy with an IC_{50} value of 1.51 μM against the HeLa cell line and 2.19 μM against the COS-7 cell line, among all the derived compounds.

Greco and co-workers introduced a microwave-assisted Knoevenagel/Michael/cyclization multicomponent domino approach for producing isatin-based spiro compounds **241a–h**, with ethanol serving as the solvent and 1-methylimidazolium chloride as a catalyst.[163] They undertook a thorough methodological investigation involving alterations to solvent, catalyst, amount of catalyst, temperature, and heating mode to identify optimal reaction conditions. Additionally, the scope of the reaction was examined by varying the starting materials (isatin, malononitrile, and barbituric acid), which resulted in the synthesis of 12 spiro compounds with good yields ranging from 43% to 98% (Scheme 85).

Choudhury and co-workers reported a microwave-irradiated three-component reaction that could be switched depending on the reaction solvent and temperature, leading to the synthesis of two types of fused spirooxindoles.[164] The reaction involves isatins **242a–e**, 4-hydroxycoumarins **243a–b**, and either aminopyrazole **244a–c** under microwave irradiation. When the reaction is performed in acetonitrile at 85 °C, the resulting spirooxindoles **245a–g** are fused with pyrazolo-tetrahydropyridinones due to the ring-opening of the hydroxycoumarin moiety (Scheme 86). On the other hand, when the reaction is performed in acetic acid at 130 °C, the resulting spirooxindoles **246a–g** are fused with a tetracyclic coumarin-



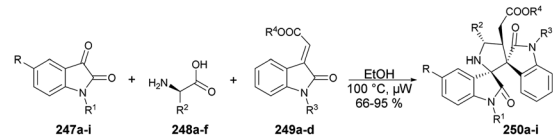
242a, R^1 = F, R^2 = CH_3
242b, R^1 = H, R^2 = H
242c, R^1 = Cl, R^2 = H
242d R^1 = OMe, R^2 = CH_3
242e, R^1 = Cl, R^2 = CH_3

243a, R^3 = H
243b, R^3 = CH_3

244a, R^4 = CH_3
244b, R^4 = Ph
244c, R^4 = 4-BrC_6H_4

245a, R^1 = H, R^2 = H, R^3 = H, R^4 = CH_3
245b, R^1 = H, R^2 = H, R^3 = H, R^4 = 4-BrC_6H_4
245c, R^1 = F, R^2 = CH_3, R^3 = CH_3, R^4 = CH_3
245d, R^1 = H, R^2 = H, R^3 = H, R^4 = Ph
245e, R^1 = Cl, R^2 = H, R^3 = H, R^4 = CH_3
245f, R^1 = OMe, R^2 = CH_3, R^3 = H, R^4 = CH_3
245g, R^1 = F, R^2 = CH_3, R^3 = H, R^4 = CH_3

Scheme 87 Synthesis of spirooxindoles **246a–g**.



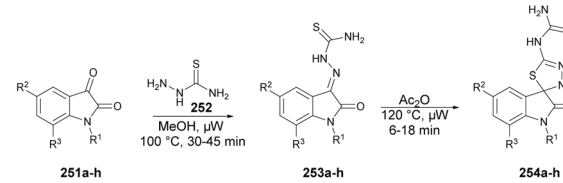
247a, R = H, R^1 = H
247b, R = H, R^1 = Me
247c, R = H, R^1 = Bn
247d, R = F, R^1 = Me
247e, R = Br, R^1 = Me
247f, R = Cl, R^1 = Me
247g, R = Me, R^1 = Me
247h, R = Cl, R^1 = H
247i, R = Me, R^1 = H

248a, R^2 = Bn
248b, R^2 = Me
248c, R^2 = CH_2CH_3
248d, R^2 = CH_2OH
248e, R^2 = -CHMeOH
248f, R^2 = -CH_2CHMe_2

249a, R^3 = CH_3, R^4 = CH_3
249b, R^3 = CH_3, R^4 = Et
249c, R^3 = H, R^4 = CH_3
249d, R^3 = H, R^4 = Et

250a, R = R^1 = H, R^2 = Bn, R^3 = R^4 = CH_3
250b, R = H, R^1 = Me, R^2 = Bn, R^3 = R^4 = CH_3
250c, R = H, R^1 = Bn, R^2 = Bn, R^3 = Me, R^4 = Et
250d, R = F, R^1 = Me, R^2 = Me, R^3 = Me, R^4 = Et
250e, R = Br, R^1 = Me, R^2 = CH_2OH, R^3 = Me, R^4 = Et
250f, R = Cl, R^1 = Me, R^2 = Me, R^3 = Me, R^4 = Et
250g, R = H, R^1 = Me, R^2 = Et, R^3 = H, R^4 = Me
250h, R = Cl, R^1 = H, R^2 = -CH_2CHMe_2, R^3 = Me, R^4 = Et
250i, R = Me, R^1 = H, R^2 = -CHMeOH, R^3 = Me, R^4 = Et

Scheme 88 Synthesis of pyrrolidine fused bisspirooxindoles **250a–I**.



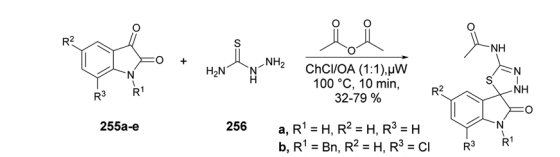
a, R^1 = H, R^2 = H, R^3 = H
b, R^1 = H, R^2 = Br, R^3 = H
c, R^1 = C_3H_5, R^2 = Cl, R^3 = Cl
d, R^1 = C_3H_5, R^2 = Br, R^3 = H
e, R^1 = C_7H_7, R^2 = Cl, R^3 = H
f, R^1 = CH_3, R^2 = Cl, R^3 = H
g, R^1 = CH_3, R^2 = Br, R^3 = H
h, R^1 = CH_3, R^2 = Cl, R^3 = Cl

Scheme 89 Synthesis of spiro 1,3,4-thiadiazolines from isatin-β-thiosemicarbazone **254a–h**.

dihydropyridine-pyrazole/isoxazole moiety spiro fused with oxindoles (Scheme 87). This switchable multicomponent reaction has been used to synthesize a series of medicinally important spiroxindole-fused pyrazolo-tetrahydropyridinones and spirooxindole-fused coumarin-dihydropyridine-pyrazole/isoxazole tetracycles under metal-free conditions.

Shankaraiah and co-workers devised an effective approach to synthesize pyrrolidine-fused bisspirooxindoles **250a–i** using a one-pot method assisted by microwaves.[165] The reaction was carried out under microwave-conditions at 100 °C. This method involves the generation of azomethine ylide through the decarboxylative condensation of isatins **247a–i** and primary α-amino acids **248a–f**, along with the [3 + 2] cycloaddition of 3-alkenyl oxindoles **249a–d** (Scheme 88). The use of microwave irradiation in ethanol solvent without any additives or catalyst facilitates these reactions, and results in a broad substrate scope, good yields, eco-friendliness, and atom-economy.

Microwave irradiation was used by Junior and co-workers to heat the reaction medium while synthesizing spiro 1,3,4-thiadiazolines from isatin-β-thiosemicarbazone acetylation.[166] To



a, R^1 = H, R^2 = H, R^3 = H
b, R^1 = Bn, R^2 = H, R^3 = Cl
c, R^1 = Me, R^2 = Cl, R^3 = H
d, R^1 = allyl, R^2 = H, R^3 = Cl
e, R^1 = Bn, R^2 = Br, R^3 = H

Scheme 90 Synthesis of spiro 1,3,4-thiadiazolines from isatin **257a–e**.

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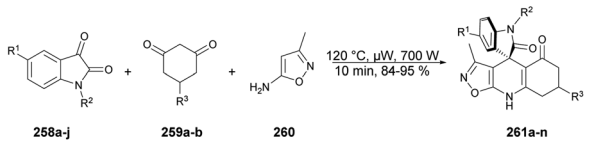
produce thiosemicarbazones **253a–h**, *N*-substituted isatin derivatives **251a–h** were used as substrates, and thiosemicarbazide **252** was added to the isatin ketone carbonyl. The final step in the synthetic process involved the reaction of thiosemicarbazones with acetic anhydride under microwave irradiation at 120 °C to produce the spiro 1,3,4-thiadiazolines **254a–h** within 6–18 min (Scheme 89). They also evaluated the antibacterial and antifungal activity of derived compounds and found that particularly spiro-thiadiazolines **254c** derived from allylated isatins showed promising activity with an IC_{50} value of 360 μM in biological assays.

In a one-pot process utilizing microwave irradiation and deep eutectic solvents (DES), Junior and co-workers discovered a simple and efficient alternative method for synthesizing 1,3,4-thiadialzolinic spiro compounds **257a–e**.[167] They explored a series of DES based on different acids as solvents in a three-component reaction which included isatin derivatives (monomeric and dimeric), thiosemicarbazide, and acetic anhydride. Of all the solvents screened, choline chloride (ChCl) and oxalic acid (in a 1 : 1 ratio) were the best, producing yields of up to 79%. The yields for most of the monomeric compounds were either very close to or higher than those reported in the literature for a two-step synthesis (Scheme 90).

Reddy and co-workers developed a series of oxazolo[5,4-*b*]quinoline-fused spirooxindoles using a microwave-assisted chemoselective synthesis.[168] The three-component Knoevenagel/Michael addition reaction was performed between isatin **258a**, β-diketone **259a** and 5-amino-3-methylisoxazole **260** in the absence of a catalyst using solvent-free conditions under microwave irradiation at 120 °C at 700 W for 10 min to afford the oxazolo[5,4-*b*]quinoline-fused spirooxindole **261a** in 95% yield. The optimized conditions were utilized to test the impact of altering the β-diketones and substituents in the isatin to determine the extent of this reaction. As a result, numerous derivatives of the intended compounds **261a–n** were synthesized with outstanding yields (84–95%) (Scheme 91).

Praveen and co-workers reported a gold-catalyzed microwave-assisted synthesis of spirooxindoles using double condensation between isatin and 4-hydroxycoumarin.[169] They

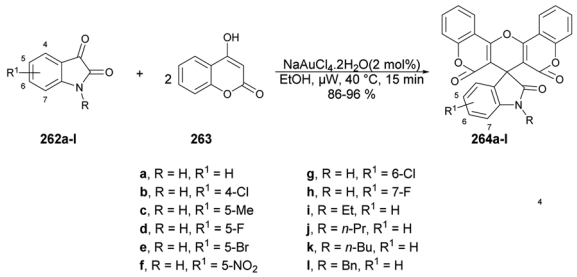


259a, R^3 = H
259b, R^3 = $(Me)_2$

258a, R^1 = H, R^2 = H
258b, R^1 = F, R^2 = H
258c, R^1 = Cl, R^2 = H
258d, R^1 = Br, R^2 = H
258e, R^1 = NO_2, R^2 = H
258f, R^1 = H, R^2 = Me
258g, R^1 = F, R^2 = Me
258h, R^1 = Cl, R^2 = Me
258i, R^1 = Br, R^2 = Me
258j, R^1 = NO2, R^2 = Me

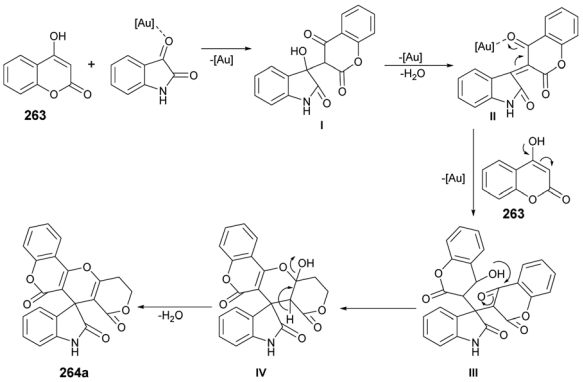
261a, R^1 = H, R^2 = H, R^3 = 259a
261b, R^1 = F, R^2 = H, R^3 = 259a
261c, R^1 = Cl, R^2 = H, R^3 = 259a
261d, R^1 = Br, R^2 = H, R^3 = 259a
261e, R^1 = NO_2, R^2 = H, R^3 = 259a
261f, R^1 = H, R^2 = Me, R^3 = 259a
261g, R^1 = F, R^2 = Me, R^3 = 259a
261h, R^1 = Cl, R^2 = Me, R^3 = 259a
261i, R^1 = Br, R^2 = Me, R^3 = 259a
261j, R^1 = NO2, R^2 = H, R^3 = 259b
261k, R^1 = NO2, R^2 = Me, R^3 = 259a
261l, R^1 = F, R^2 = Me, R^3 = 259b
261m, R^1 = H, R^2 = H, R^3 = 259b
261n, R^1 = Cl, R^2 = Me, R^3 = 259b

Scheme 91 Synthesis of oxazolo[5,4-*b*]quinoline-fused spirooxindoles **261a–n**.



a, R = H, R^1 = H
b, R = H, R^1 = 4-Cl
c, R = H, R^1 = 5-Me
d, R = H, R^1 = 5-F
e, R = H, R^1 = 5-Br
f, R = H, R^1 = 5-NO_2
g, R = H, R^1 = 6-Cl
h, R = H, R^1 = 7-F
i, R = Et, R^1 = H
j, R = *n*-Pr, R^1 = H
k, R = *n*-Bu, R^1 = H
l, R = Bn, R^1 = H

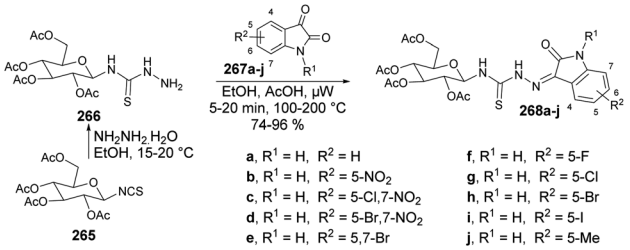
Scheme 92 Gold-catalyzed synthesis of spirooxindoles **264a–l**.



Scheme 93 A plausible mechanism for the synthesis of spirooxindole.

performed the condensation reaction with various derivatives of isatin **262a–l** and 4-hydroxy coumarin **263** using a gold catalyst ($NaAuCl_4 \cdot 2H_2O$) under microwave irradiation at 40 °C for 15 min to afford good-to-excellent yields (86–96%) of designed products **264a–l** (Scheme 92). They also observed that microwaves could lead to efficiently syntheses of these compounds as compared with a conventional heating method.

Based on the observed results, a tentative mechanism (Scheme 93) was proposed to explain formation of the representative compound **264a**. The process begins with 4-hydroxycoumarin undergoing nucleophilic addition at the carbonyl carbon of the [Au]-activated isatin, leading to the formation of intermediate **I**. Subsequently, dehydration of intermediate **I** takes place, resulting in the formation of intermediate **II**. The Lewis acidic [Au] species re-enters the catalytic cycle by interacting with the carbonyl oxygen of intermediate **II**. This interaction drives the addition of another molecule of 4-



a, R^1 = H, R^2 = H
b, R^1 = H, R^2 = 5-NO_2
c, R^1 = H, R^2 = 5-Cl,7-NO_2
d, R^1 = H, R^2 = 5-Br,7-NO_2
e, R^1 = H, R^2 = 5,7-Br
f, R^1 = H, R^2 = 5-F
g, R^1 = H, R^2 = 5-Cl
h, R^1 = H, R^2 = 5-Br
i, R^1 = H, R^2 = 5-I
j, R^1 = H, R^2 = 5-Me

Scheme 94 Synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones with isatin derivatives **268a–j**.

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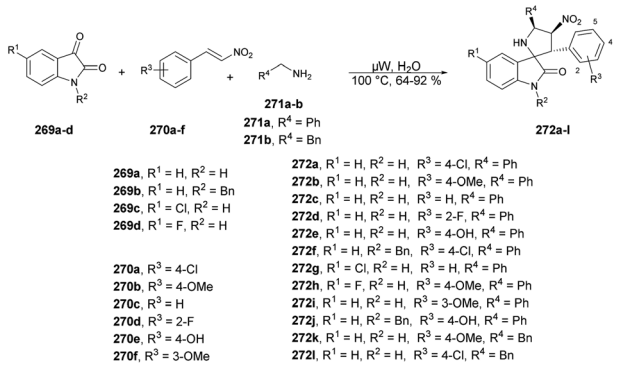
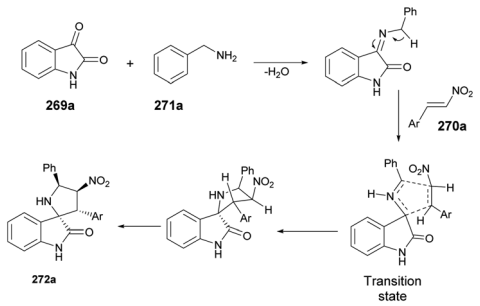


Scheme 95 Synthesis of functionalized spirooxindole derivatives 272a–l.

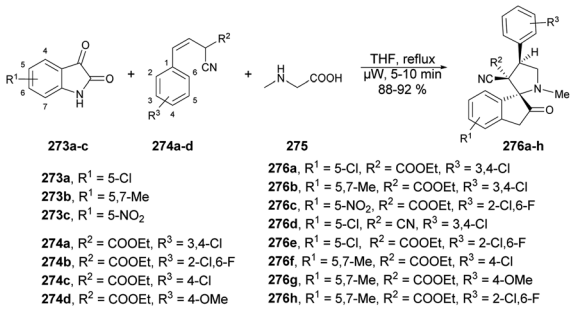
hydroxycoumarin, leading to the formation of intermediate **III**. Later, intramolecular cyclization occurs in intermediate **III**, resulting in the formation of intermediate **IV**. Through subsequent dehydration reactions, the final product **264a** is obtained.

A new microwave-assisted development was reported by Thanh and co-workers for the synthesis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones **268a–j** with various isatin derivatives.[170] Initially, they performed the reaction to convert *N*-(tetra-*O*-acetyl-β-D-glucopyranosyl)isothiocyanate **265** into the corresponding thiosemicarbazide **266** which, on further reaction with various isatin derivatives **267a–j** under microwave irradiation at 100–200 °C, afforded excellent yields (74–96%) of designed products (**268a–j**) (Scheme 94). They also investigated the cytotoxic effects of the derived compounds. Compound **268f** showed cytotoxic effects with an IC_{50} value of 0.78 μM against some cancer (LU-1, HepG2, MCF7, P338, SW480, KB) cell lines as well as a normal fibroblast cell line (NIH/3T3).

Meshram and co-workers developed a straightforward and environmentally friendly method that involves only one pot and three-components in an aqueous phase to synthesize functionalized spirooxindole derivatives.[171] They performed the reaction with isatin **269a–d**, β-nitrostyrene **270a–f**, and aryl amines **271a–b** in water under microwave irradiation. A library of spirooxindoles **272a–l** was easily constructed with good diastereoselectivity and in moderate-to-good yields (64–92%) (Scheme 95). This approach is especially beneficial because it



Scheme 96 Plausible mechanism for the synthesis of representative molecule 272a.

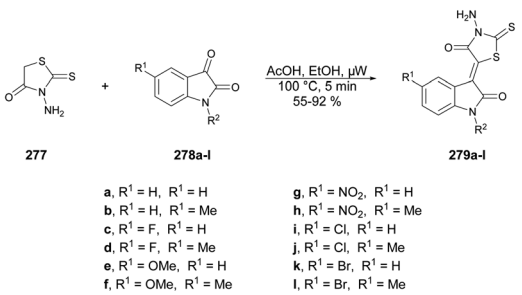


Scheme 97 Synthesis of spiropyrrolidine oxindole derivatives 276a–h.

employs readily available starting materials, a green solvent and can be completed in short period of time.

The α-amino acid or benzyl amine undergoes an initial reaction with isatin through a typical addition process, resulting in the formation of an imine. The formed imine then undergoes a reaction with β-nitrostyrenes, leading to a 1,3-cycloaddition reaction. During this cycloaddition, two nucleophilic carbons add to the electron-deficient carbon of the dipolarophile to form a transition state which, on transformation, is converted in compound **272a**. This can be explained based on the transition state, with the observed product being more stable. The transition state is preferred if the spiro carbon is *cis* to the carbonyl of the oxindole moiety and *trans* to the nitro group (Scheme 96).

Dandia and co-workers developed a microwave-assisted, one-pot method for synthesizing spiropyrrolidine/thiapyrrolizidine oxindole derivatives with antimicrobial properties.[172] The approach was simple, environmentally friendly, highly efficient, and involved two pharmacophoric groups (1,3-indanedione and pyrrolidine/thiapyrrolizidine) in a single molecule through a three-component 1,3-dipolar cycloaddition reaction. They carried out the reaction using substituted isatin **273a–c**, thiazoles-4-carboxylic acid **275** and either 2-cyano-3-phenylacrylic acid ethyl ester or 2-benzylidene-malononitrile **274a–d** reflux under microwave irradiation for 5–10 min to afford the desired products **276a–h** (Scheme 97). The methodology exhibits good tolerance for functional groups and a wide range of substrates, and demonstrates high levels of chemo-, regio-, and stereoselectivity with acceptable yields (88–92%) of designed products.



Scheme 98 Synthesis of isatin-aminorhodanine hybrids 279a–l.

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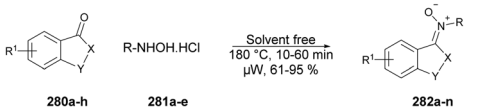


280a, R^1 = H
280b, R^1 = 5-Br
280c, R^1 = 5-NO_2
280d, R^1 = 5,7-Cl
280e, R^1 = 5-F
280f, R^1 = 4-Br,7-OH
280g, R^1 = 7-F
280h, R^1 = 6-OMe

281a, R = Bn
281b, R = Ph
281c, R = 3-Cl,Ph
281d, R = Me
281e, R = ^{t}Bu

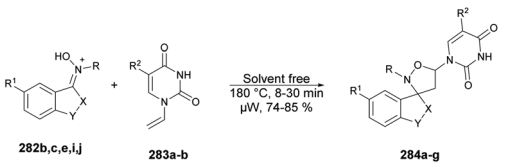
282a, R = Bn, R^1 = H, X = C=O, Y = NH
282b, R = Ph, R^1 = H, X = C=O, Y = NH
282c, R = 3-Cl,Ph, R^1 = H, X = C=O, Y = NH
282d, R = Me, R^1 = H, X = C=O, Y = NMe
282e, R = Bn, R^1 = H, X = C=O, Y = NMe
282f, R = Ph, R^1 = H, X = C=O, Y = NMe
282g, R = 3-Cl,Ph, R^1 = H, X = C=O, Y = NMe
282h, R = Me, R^1 = 5-Br, X = C=O, Y = NH
282i, R = Bn, R^1 = 5-Br, X = C=O, Y = NH
282j, R = Ph, R^1 = 5-Br, X = C=O, Y = NH
282k, R = Me, R^1 = 5-NO_2, X = C=O, Y = NH
282l, R = Bn, R^1 = 5-NO_2, X = C=O, Y = NH
282m, R = Ph, R^1 = 5-NO_2, X = C=O, Y = NH
282n, R = Bn, R^1 = R^1 = 5,7-Cl, X = C=O, Y = NH

Scheme 99 Synthesis of ketonitrones **282a–n**.

Besbes and co-workers synthesized a series of isatin-aminorhodanine hybrids **279a–l** using a microwave-irradiated technique.[173] They performed the condensation reaction of isatin derivatives **278a–l** and 3-aminorhodanine **277** in a microwave condition at 100 °C for 5 min to afford moderate-to-acceptable yields (55–92%) of hybrid products **279a–l** (Scheme 98). This microwave approach is facile, effective for the development of various biologically important hybrid molecules, ecological, fast and energy efficient. Compared with the microwave method, the conventional method is slow, time-consuming and provides a low yielding product. When a similar reaction was carried out using the conventional heating method, it was completed in 24 h, compared with 5 min using microwaves.

The antiviral properties of spiro-oxindoles have led to their broad application. Initially, Nino and co-workers utilized a rapid and efficient synthetic method to produce ketonitrones using a solvent-free microwave-assisted reaction between various hydroxylamines and isatin or indanone derivatives.[174] This synthetic technique was simple, efficient, fast, clean, and stereoselective. Subsequently, they investigated the feasibility of generating spiro-isoxazolidines **284a–g** containing nucleobases with isatin and indanone nuclei through solvent-free microwave-assisted 1,3-dipolar cycloaddition, which yielded good outcomes in terms of yields (74–85%) of regio- and diastereoselective products (Schemes 99 and 100).

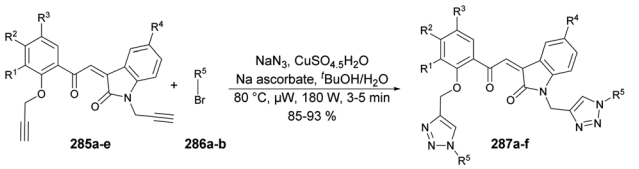
Ashok and co-workers developed a group of 2-indolinone-based bis-1,2,3-triazole derivatives *via* microwave irradiation.[175] They performed the copper-catalyzed azide–alkyne click reaction between various isatin derivatives containing terminal alkyne and azides under microwave irradiation at 80 °C for 3–5 min to afford excellent yields (85–93%) of designed products **287a–f**. The microwave-assisted method that was involved in this reaction completed the reaction in short period of time with higher yields (85–93%) as compared with yields using conventional heating (43–54%) (Scheme 101).



283a, R^2 = Me
283b, R^2 = H

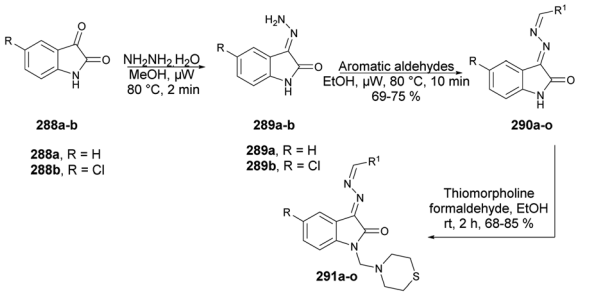
284a, R = Bn, R^1 = H, R^2 = H
284b, R = Ph, R^1 = H, R^2 = H
284c, R = Ph, R^1 = H, R^2 = Me
284d, R = Me, R^1 = H, R^2 = H
284e, R = Me, R^1 = Br, R^2 = Me
284f, R = Bn, R^1 = Br, R^2 = Me
284g, R = Bn, R^1 = NO_2, R^2 = Me

Scheme 100 Synthesis of spiro-isoxazolidines containing nucleobases with isatin **284a–g**.



287a, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = C_6H_{11}
287b, R^1 = H, R^2 = H, R^3 = H, R^4 = Br, R^5 = C_6H_{11}
287c, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = C_6H_{11}
287d, R^1 = H, R^2 = H, R^3 = Br, R^4 = Br, R^5 = C_6H_{11}
287e, R^1 = H, R^2 = Me, R^3 = Cl, R^4 = H, R^5 = C_6H_{11}
287f, R^1 = H, R^2 = Me, R^3 = Cl, R^4 = H, R^5 = Bn

Scheme 101 Synthesis of 2-indolinone-based triazole derivatives **287a–f**.



288a, R = H
288b, R = Cl

289a, R = H
289b, R = Cl

290a,291a, R = H, R^1 = 4-$OMeC_6H_4$
290b,291b, R = H, R^1 = 3,4-$OMeC_6H_3$
290c,291c, R = H, R^1 = 3-Py
290d,291d, R = H, R^1 = 2-thienyl
290e,291e, R = H, R^1 = 2-furyl
290f,291f, R = H, R^1 = 5-nitro,2-thienyl
290g,291g, R = H, R^1 = 4-Py
290h,291h, R = H, R^1 = 5-nitro,2-furyl
290i,291i, R = Cl, R^1 = 4-$OMeC_6H_4$
290j,291j, R = Cl, R^1 = 3,4-$OMeC_6H_3$
290k,291k, R = Cl, R^1 = 3-Py
290l,291l, R = Cl, R^1 = 2-thienyl
290m,291m, R = Cl, R^1 = 2-furyl
290n,291n, R = Cl, R^1 = 5-nitro,2-thienyl
290o,291o, R = Cl, R^1 = 4-Py

Scheme 102 Synthesis of isatin hydrazones **290a–290o** and their thiomorpholine-tethered analogues **291a–291o**.

To save the lives of patients infected with multidrug resistant-tuberculosis (MDR-TB), there is an urgent need for new chemotherapeutic agents. Karpoormath and co-workers addressed this issue by synthesizing and characterizing novel isatin hydrazones **290a–o** and their thiomorpholine-tethered analogues **291a–o**.[176] They started with isatins **288a–b** which, on reaction with hydrazine hydrate, afforded compounds **289a–b**. These compounds were again treated with various aromatic aldehydes under microwave irradiation at 80 °C to afford the designed compounds **290a–o**. After that, isatin hydrazones **290a–o** reacted with thiomorpholine and formaldehyde at room temperature to afford the designed products **291a–o** in good isolated yields (68–85%) (Scheme 102). They investigated the anti-mycobacterial activity of derived compounds against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis*. All of the synthesized compounds were initially screened for their anti-mycobacterial activity. Notably, five compounds (**290f**, **290h**,

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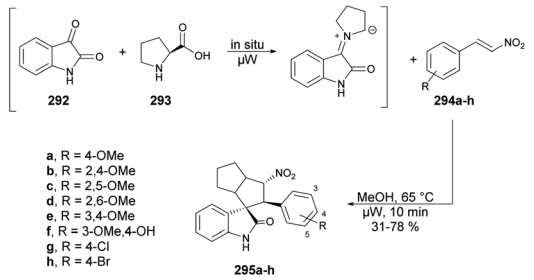
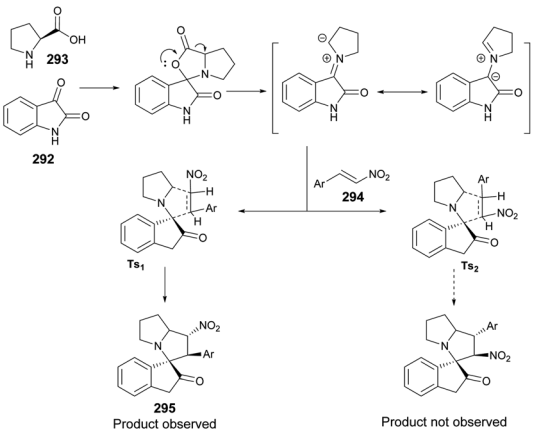


Scheme 103 Synthesis of Sox-pyrrolizidines **295a–h**.



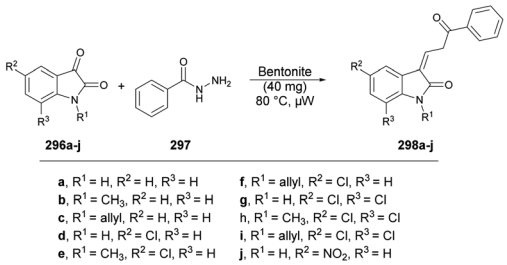
Scheme 104 Proposed mechanism for the synthesis of nitro-Sox compounds.

290n, **291f**, and **291m**) demonstrated high activity, with **290f** (IC_{50} = 1.9 μM) exhibiting the highest inhibition of H37Rv, indicating potential as effective treatment options.

Maniam and co-workers reported a microwave-assisted, one-pot, three-component, 1,3-dipolar cycloaddition approach to generate azomethine ylides from L-proline and isatin, followed by their reaction with various β-nitrostyrenes to rapidly synthesize a library of Sox-pyrrolizidines.[177] These compounds exhibited remarkable binding affinities to the intensely amyloidogenic regions of HEWL, leading to the prevention of fibril aggregation and prompting fibrillation to adopt a less structured form than β-sheets. Notably, the Sox molecules showed negligible cell toxicity, and compound **295b** was capable of safeguarding HEK cells against α,β-induced toxicity (Scheme 103).

The author of that study proposed a reaction mechanism involving two main steps. First, a condensation reaction takes place to form an intermediate (Scheme 104). Following this, a cycloaddition reaction occurs between the two nucleophilic carbons and electrophilic β-carbon of the β-nitrostyrene. This addition results in the formation of a spirocyclic structure involving three new C–C bonds and generating four contiguous stereocenters, including a quaternary carbon. Consequently, two potential regioisomers can be formed due to the different transition states, namely $\mathbf{TS_1}$ and $\mathbf{TS_2}$.

However, the sterically hindered nature of $\mathbf{TS_2}$ compared with $\mathbf{TS_1}$ leads to an unfavorable and less stable product, which is not observed experimentally. This observation was consistent with the exclusive formation of only one regioisomer from $\mathbf{TS_1}$. Despite the presence of four stereocenters, the reaction tends to favor the aromatic group attached to the pyrrolizidine moiety being *cis* to the carbonyl group of the oxindole and *trans* to the nitro group. This specific arrangement minimizes steric hindrance between the aryl group attached to the pyrrolizidine moiety and the benzo group of the oxindole moiety.



Scheme 105 Synthesis of *N*-(2-oxoindolin-3-ylidene)benzohydrazide derivatives **298a–j**.

Junior and co-workers developed a novel approach to synthesize *N*-(2-oxoindolin-3-ylidene)benzohydrazide derivatives, which are extensively explored in pharmacological research.[178] Conventionally, their production relies on organic solvents, leading to increased costs, the generation of residues and is a time-consuming process. To address these challenges, researchers developed a more environmentally friendly and cost-effective method utilizing bentonite clay as a catalyst and microwave irradiation. The study involved optimizing various parameters, such as the type and amount of catalyst, solvent, and heating method. Ultimately, the most favorable conditions were found to be a solvent-free reaction in the presence of bentonite as the catalyst, resulting in yields of up to 96% for isolated products and reaction times of 15–60 min. Remarkably, these outcomes were comparable to or even surpassed those reported in the literature, yet with the added advantage of a greener approach through heterogeneous catalysis using a microwave technique (Scheme 105).

Furthermore, researchers demonstrated that the bentonite catalyst could be recycled at least three times without significant loss in yields or reaction time, showcasing its practicality as a low-cost and sustainable alternative. This innovative methodology opens up new possibilities for the efficient and environmentally compatible synthesis of isatin-derived Schiff bases with potential implications in pharmacological applications.

Chaudhary and co-workers developed a novel series of functionalized spiro[indoline-3,20-pyrrolidin]-2-one/spiro[indoline-3,30-pyrrolizin]-2-one compounds (denoted as **302a–d**, **303a–e**, and **304a–d**).[179] These compounds were derived from pharmaceutically privileged bioactive sub-structures, namely isatins **299a–f**, various substituted chalcones **300a–f**, and **301a–c** amino acids, using 1,3-dipolar cycloaddition reactions. Microwave-assisted 1,3-dipolar cycloaddition reactions were carried out in MeOH at 80 °C for 5 min involving substituted

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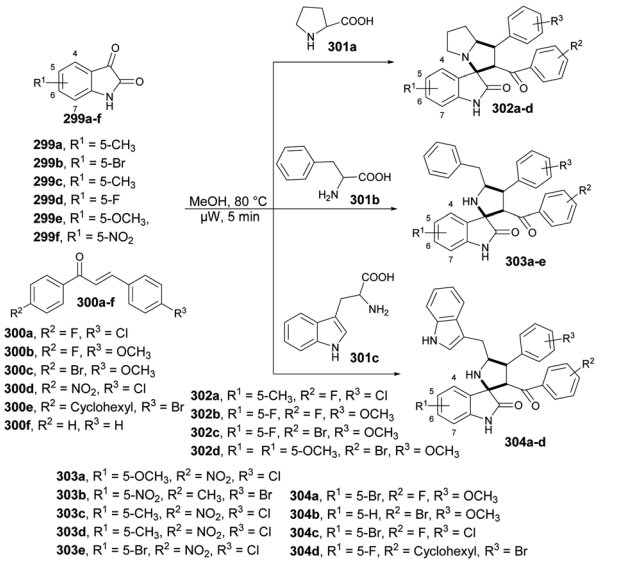
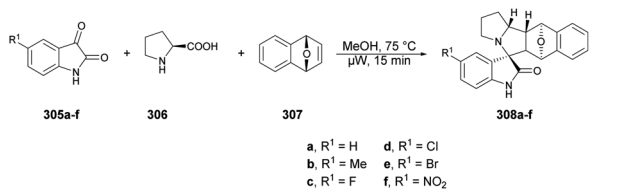


Scheme 106 Synthesis of spiro[indoline-3,20-pyrrolidin]-2-one/spiro[indoline-3,30-pyrrolizin]-2-one **302a–d**, **303a–e**, and **304a–d**.

isatins **299a–f**, substituted chalcones **300a–f**, and various amino acids **301a–c**. These reactions yielded the desired chalcone-isatin-amino acid-based spirooxindole compounds **302a–d**, **303a–e**, and **304a–d** in excellent yields of up to 98%, and the process displayed high diastereoselectivity. The reaction involved the [3 + 2] cycloaddition of substituted chalcones with *in situ*-generated azomethine ylides, which resulted from the microwave-assisted decarboxylative condensation of substituted isatins and various secondary amino acids. Compared with traditional methods, the microwave-assisted approach yielded higher quantities of compounds with improved quality, all while requiring less time for synthesis.

After the successful synthesis of derived molecules, researchers evaluated the *in vitro* antileishmanial activity against *Leishmania donovani* and performed structure–activity relationship (SAR) studies. Among the compounds tested, **302a**, **303e**, and **304d** demonstrated the most potent activity within the series, exhibiting IC_{50} values of 2.43 μM, 0.96 μM, and 3.55 μM, respectively, when compared with the standard reference drug amphotericin B (IC_{50} = 0.60 μM). Those findings suggest that the newly synthesized compounds hold promise as potential candidates with antileishmanial properties (Scheme 106).

Zhao and co-workers developed an environmentally friendly and efficient microwave-promoted multicomponent reaction involving isatins, α-amino acids, and 1,4-dihydro-1,4-epoxynaphthalene.[180] Within a remarkably short time of 15 min, the reaction produced oxygen-bridged spirooxindoles in good-to-excellent yields. Notably, the 1,3-dipolar cycloaddition process exhibited compatibility with various primary amino acids and showcased high efficiency due to its rapid reaction time (Scheme 107). Furthermore, they scaled up the reaction and performed synthetic transformations of spiropyrrolidine oxindole, showcasing its practical synthetic utility. The introduction of this new method expands the structural diversity of spirooxindoles, making them a promising scaffold for novel-drug discovery. With these attractive features and potential applications, that work presents a powerful approach to enhance the repertoire of spirooxindoles as a platform for exploring new drug candidates.



Scheme 107 Synthesis of oxygen-bridged spirooxindoles **308a–f**.

Initially, the reaction involves the condensation of isatin with proline, resulting in the formation of the ylide intermediate A through subsequent decarboxylation. This ylide intermediate A serves as a 1,3-dipole and reacts with 3a through two potential pathways, labeled as A and B. Path A leads to the production of the thermodynamically more stable *endo*-cycloadduct 4a, while the formation of the *exo*-cycloadduct 4a′ through path B is likely less favored.

3. Conclusions and perspectives

Based on the discussions stated above, it is evident that microwave-assisted organic synthesis is a highly effective method for conducting a diverse range of chemical reactions in a shorter reaction of time with high yield and selectivity. Ultimately, the use of microwave irradiation has greatly enhanced the process of drug discovery and contributed towards efficient synthesis of complex natural products and natural product-like molecules. This review presented the microwave-assisted organic synthesis of N- and O-containing heterocyclic compounds. Various quinoline derivatives with structural diversity could be prepared in shorter reaction time and high yields. Similarly, pyrazolopyrimidine derivatives have been synthesized under microwave irradiation which were otherwise difficult to prepare. Comarins, isatins and their diverse derivatives with structural complexity were prepared in efficient manners recently adopting microwave assisted-organic synthesis. Thus, this technique has scope to prepare various natural-product scaffolds, which are complex and filling 3D chemical space.

In conclusion, microwave-assisted synthesis has proven to be a game-changer in the field of organic synthesis and materials science. Its ability to accelerate reactions, improve yields, and reduce energy consumption has made it an invaluable tool for researchers. As we delve deeper into its mechanisms and explore new applications, microwave-assisted synthesis is poised to play an increasingly significant part in shaping the future of chemistry and materials research. The data provided showcase several successful applications of microwave-assisted synthesis in various chemical reactions, leading to enhanced yields, shortened reaction times, and improved selectivity. The examples presented highlight the effectiveness of microwave irradiation in different synthetic transformations.

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Suzuki–Miyaura cross-coupling reactions: Ababri and co-workers demonstrated an optimized microwave-assisted Suzuki–Miyaura cross-coupling reaction protocol. By utilizing microwave irradiation at 135 °C, the reaction time was significantly reduced from 12 h to just 40 min, and the yield of the coupled product was impressive (67–89%). Moreover, the unwanted debromination reaction was effectively avoided, resulting in high product purity. Friedlander synthesis of 8-hydroxyquinolines: Microwave-assisted Friedlander synthesis provided a single-step conversion of various derivatives of 8-hydroxyquinolines with a higher yield (72%) compared with conventional heating (34% yield). This demonstrates the efficiency and effectiveness of microwave-assisted synthesis in complex transformations. Copper-catalyzed four-component synthesis of 3-*N*-sulfonylamidine coumarins: Punniyamurthy and co-workers reported a copper-catalyzed four-component synthesis of coumarins using microwave irradiation. The use of microwave conditions resulted in higher reactivity, milder reaction conditions, and greater selectivity, leading to good isolated yields of the desired products. Microwave-assisted synthesis of isatin-β-thiocarbohydrazones: Gohary and co-workers developed a new range of isatin-β-thiocarbohydrazones using microwave irradiation. The approach utilized the key features required for metal chelation found in triapine and resulted in good isolated yields of the desired products. Moreover, some of the newly developed compounds showed promising efficacy against cancer cell lines. Microwave-assisted synthesis of quinoline fused 1,4-benzodiazepine: Kamble and co-workers reported an efficient microwave-assisted protocol for the synthesis of quinoline fused 1,4-benzodiazepines. The use of microwave irradiation at 80 °C afforded excellent isolated yields of the desired products, but the conventional method did not afford a good yield in a limited time. The Pechmann reaction was conducted using conventional thermal heating. However, even after 20 min, the phenol conversion did not exceed 18%. This outcome underscores the potential of microwave irradiation as a viable alternative to conventional heating methods for this type of reaction.

Continuous efforts are being made by different research groups across the globe using microwave irradiation techniques for the successful synthesis of a variety of biologically active compounds. This strategy shows great promises for its use in the near future as a powerful tool for constructing efficiently natural product-like scaffolds. Microwave-assisted synthesis has already demonstrated its potential as a powerful and efficient tool for chemical transformations. Looking ahead, this innovative technology holds promising future perspectives that could further revolutionize synthetic chemistry and materials research.

Despite the successful applications of microwave-assisted synthesis, further research is needed to gain deeper understanding of the underlying mechanisms responsible for its enhanced reactivity and selectivity. A deeper understanding of these mechanisms can guide the optimization of reactions and the development of new synthetic strategies. The success of microwave-assisted synthesis in various reactions encourages the exploration of new transformations that can benefit from this technique. Researchers can investigate unexplored reactions that can be accelerated and improved through microwave irradiation. Green and sustainable chemistry: the energy efficiency and reduced reaction times associated with microwave-assisted synthesis align well with the principles of green and sustainable chemistry. Microwave-assisted synthesis has shown its potential for promoting green chemistry principles. Future research should continue to explore environmentally friendly reaction conditions, such as solvent-free and catalytic microwave reactions, to reduce waste and energy consumption.

Researchers need to address scale-up challenges to make microwave-assisted synthesis more applicable to industrial processes. The development of scalable and economically viable methodologies is essential. Bridging the gap between laboratory-scale experiments and industrial applications is a critical aspect of future perspectives. Researchers should focus on developing scalable and economically viable microwave-assisted synthetic methodologies to facilitate the adoption of this technology in industrial processes. Researchers can explore the combination of microwave-assisted synthesis with other innovative techniques, such as flow chemistry, photochemistry, and catalysis, to achieve synergistic effects and expand the scope of synthetic possibilities. The development of advanced microwave reactors with precise control over power, frequency, and temperature will allow researchers to optimize and scale-up reactions effectively. Integration of automation and artificial-intelligence technologies in reactor design could lead to more efficient and autonomous synthesis processes. Multicomponent reactions: microwave irradiation has proven to be advantageous in multicomponent reactions, offering rapid access to complex molecules. Future efforts should focus on developing novel multicomponent reactions that take advantage of the enhanced reactivity and selectivity offered by microwave technology.

The pharmaceutical industry can benefit significantly from microwave-assisted synthesis for drug discovery and development. Integrating microwave technology in medicinal chemistry research can expedite the synthesis of potential drug candidates and facilitate the production of complex molecules. Microwave technology can be applied to the synthesis of advanced materials with "tailored" properties. Researchers should explore the use of microwave irradiation in the preparation of nanomaterials, catalysts, and functional materials for various applications. safety and standardization:

As microwave-assisted synthesis gains wider adoption, it is crucial to establish standardized safety protocols and guidelines for its use in laboratories and industrial settings. Safety training and awareness will ensure responsible and efficient operation.

These forward-looking perspectives provide valuable guidance to researchers interested in advancing this field. The review emphasizes the practical benefits of microwave-assisted synthesis, such as shorter reaction times, improved yields, and enhanced reactivity. It also highlights the applicability of microwave technology to complex reactions, which can lead to the synthesis of highly functionalized compounds. The review includes examples of microwave-assisted synthesis applied to

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drug discovery, showcasing its relevance and potential impact in the pharmaceutical industry.

The future perspectives of microwave-assisted synthesis hold great promise for advancing synthetic chemistry and materials science. With a focus on understanding mechanisms, developing green and sustainable methodologies, and exploring new applications, microwave-assisted synthesis is poised to become an indispensable tool in modern chemistry, paving the way for faster, cleaner, and more efficient chemical transformations.

Conflicts of interest

There are no conflicts to declare.

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