Recent Advances in the Synthesis of 2-Hydroxy-1,4-naphthoquinone (Lawsone) Derivatives

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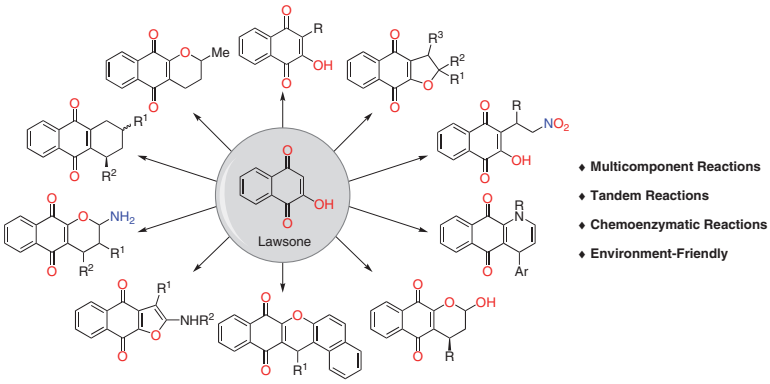
This work is dedicated to Prof. Srinivasan Chandrasekaran on his 78th birthday



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Abstract Lawsone, also known as 2-hydroxy-1,4-naphthoquinone, has been extensively studied and found to be a crucial precursor in the production of a diverse range of natural products such as molecular scaffolds, which are highly sought-after for biological research purposes. Due to its unique chemical composition, lawsone has been utilized for over a century as a starting material for the synthesis of numerous biologically active molecules and materials, and its intriguing properties have been showcased across a wide range of scientific and technological applications. Additionally, the various characteristics of lawsone have been widely used in organic synthesis processes. Recent advances in the synthesis of different scaffolds starting from lawsone, and their applications, are discussed in detail in the current review covering the period 2017 to 2023.

Key words multicomponent reactions, chemoenzymatic reactions, heterocyclic compounds, 2-hydroxy-1,4-naphthaquinone, magnetic nanoparticles, tandem reactions, green chemistry

1 Introduction

2-Hydroxy-1,4-naphthoquinone, also known as lawsone or hennotannic acid, is a naturally occurring naphthoquinone compound that has attracted significant interest in synthetic organic chemistry.[1–3] It is one of the simplest naturally occurring naphthoquinones and is primarily known for its presence in the leaves of the henna plant (*Lawsonia inermis*), where it imparts a red-orange color.[4] Henna extracts containing lawsone have been used for thousands of years as hair and skin dyes, highlighting its historical and cultural significance.[5,6]

Beyond its dyeing properties, 2-hydroxy-1,4-naphthoquinone exhibits a range of biological activities, including antibacterial, antifungal, anti-inflammatory, antiviral, and antineoplastic properties.[7,8] It has been found to inhibit tumor cell growth and to stimulate the production of reactive oxygen species (ROS).[9–12] These attributes make it a compelling target for synthetic development, as it serves as a starting material for the synthesis of diverse biologically active compounds and materials with intriguing properties.[13–15]

In the field of organic synthesis, 2-hydroxy-1,4-naphthoquinone has been employed in numerous reactions, where it plays a vital role in the construction of various molecular frameworks. Its hydroxyquinone structure is associated with the antibacterial activity of anthracycline and antibiotics such as daunomycin and doxorubicin.[16–19] The versatility of 2-hydroxy-1,4-naphthoquinone as a building block in organic synthesis has further expanded its potential for the development of novel compounds and therapeutic agents.[20–22]

Recent efforts have focused on the synthesis of new derivatives of 2-hydroxy-1,4-naphthoquinone.[23] The syntheses of such derivatives have been studied extensively, with many of the established methods involving multicomponent reactions. The versatile heterocyclic scaffolds have been used for further exploration and utilization in various synthetic transformations.[24–27]

In this review article, we aim to provide an overview of the recent advances in the synthetic developments in the use of 2-hydroxy-1,4-naphthoquinone. This review will

Biographical Sketches

Prof. Ram Sagar received his PhD in Organic Chemistry from the Central Drug Research Institute (CDRI) Lucknow and the University of Agra in 2006 under the supervision of Dr A. K. Shaw. After his PhD, he worked as a research associate with Prof. Y. D. Vankar at IIT Kanpur during 2006–2007. He pursued his first post-doctoral research at Seoul National University South Korea with Prof Seung Bum Park during 2007–2008. He moved to the University of Oxford and worked with Prof Benjamin G. Davis as a BBSRC postdoctoral fellow until August 2012. He returned to India in August 2012 and took up a faculty position at Shiv Nadar University (SNU). He moved to the Department of Chemistry, Banaras Hindu University (BHU) as Associate Professor in February 2018 and worked there until December 2020. He subsequently became Full Professor at 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 efficient chemical synthesis of natural-product-inspired small molecules, glycohybrids, and glycopeptides that are implicated in various diseases including tuberculosis and cancer.

Uma Shankar completed his MSc in 2017 from Kirori Mal College, University of Delhi, India. He joined the Glycochemistry laboratory of the School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a research scholar in 2022. He is currently pursuing his PhD degree under the supervision of Prof. Ram Sagar. His expertise lies in asymmetric catalysis with emphasis on C–C bond formation under mild and green conditions, organic synthesis, physical organic chemistry, synthesis of heterocyclic compounds, medicinal chemistry, and the development of new methods for the synthesis of bioactive glycohybrids.

Ashish Khanna completed his MSc at Kumaun University, Nainital, Uttarakhand, India in 2016. Since 2017, he has been part of the Department of Chemistry at the Institute of Science, Banaras Hindu University, as a research scholar in the Glycochemistry lab. He completed his PhD in March 2023 under the supervision of Prof. Ram Sagar. His expertise lies in organic synthesis, the development of carbohydrate-derived bioactive molecules and natural-product-inspired hybrid analogues. He is also focused on molecular modeling, especially in protein–ligand interactions via *in-silico* docking tools. He recently joined the Department of Chemistry, School of Physical Sciences, Dehradun Institute of Technology University, Dehradun as an Assistant Professor.

Kavita Singh completed her MSc at Deen Dayal Upadhyaya University, Gorakhpur, UP, India in 2019. She qualified as a CSIR-JRF then joined the Glycochemistry laboratory of the School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a junior research fellow in 2021. She is currently pursuing her PhD degree under the supervision of Prof. Ram Sagar. Her work is mainly focused on the development of new methods for the synthesis of carbohydrate-fused heterocyclic molecules as bioactive glycohybrids. She is also interested in medicinal chemistry and in the synthesis of natural-product-inspired bioactive scaffolds.

Ghanshyam Tiwari completed his MSc 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 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 natural-product-inspired glycohybrids.

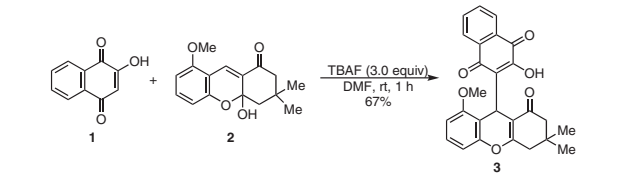
highlight the key synthetic methodologies employed for the preparation of 2-hydroxy-1,4-naphthoquinone derivatives, focusing on the advancements in reaction design, catalyst development, and the discovery of new reaction pathways. Furthermore, we will discuss the diverse applications of these synthesized compounds in medicinal chemistry, materials science, and other relevant fields.

By exploring the recent advances in synthetic strategies for 2-hydroxy-1,4-naphthoquinone, this review intends to offer valuable insights into the current state-of-the-art in this field and inspire further exploration of its synthetic potential. The development of efficient and sustainable synthetic routes to access 2-hydroxy-1,4-naphthoquinone derivatives hold great promise for the discovery of novel compounds with enhanced biological activities and potential therapeutic applications.

2 Synthetic Developments on 2-Hydroxy-1,4-naphthoquinone

2.1 2,3,4,9-Tetrahydro-9-(3-hydroxy-1,4-dioxo-1*H*-dihydronaphthalen-2-yl)-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one Derivatives

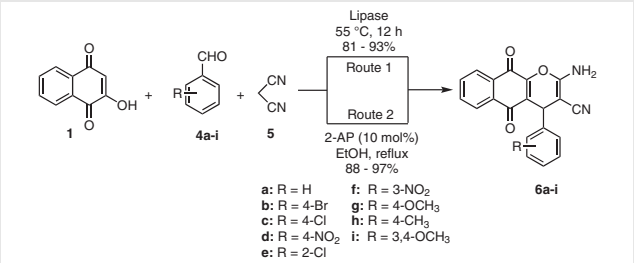
Yoshioka and co-workers[28] reported the synthesis of novel xanthene derivative **3** by the reaction of 2-hydroxy-1,4-naphthoquinone (**1**) and 2*H*-chromene derivative **2**. The authors synthesized **2** by a domino three-component coupling reaction of an aryne precursor with DMF and dimedone. Nucleophilic addition of **1** (1.1 equiv) in the presence of anhydrous TBAF (3 equiv), furnished 2,3,4,9-tetrahydro-9-(3-hydroxy-1,4-dioxo-1*H*-dihydronaphthalen-2-yl)-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one (**3**) with a good isolated yield of 67% (Scheme 1).[28]



Scheme 1 Synthesis of derivative **3**

2.2 Benzo[*g*]chromene Derivatives

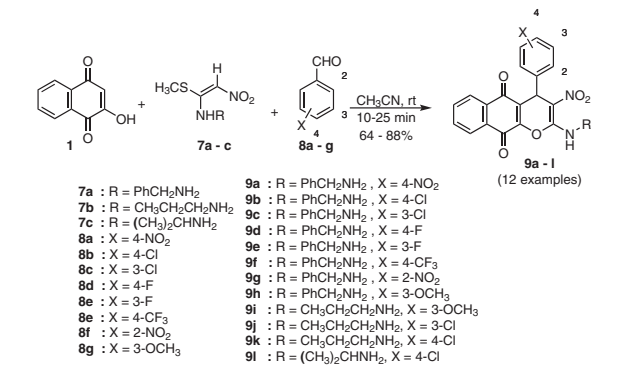
Benzo[*g*]chromene derivatives have received considerable attention in the field of medicinal chemistry because of their therapeutic potential. Additionally, they are used as intermediates in the synthesis of other organic compounds, making them significant building blocks in organic synthesis. In the field of organic synthesis, there are many different approaches that can be taken to achieve the desired product. Two examples of successful synthesis of benzo[*g*]chromene derivatives have been reported by Yang and Maheshwari and their respective research groups.[29,30] Yang and co-workers utilized *Candida sp.* lipase as an enzyme catalyst for a multicomponent reaction, while Maheshwari and co-workers used 2-aminopyridine as a reusable catalyst in a one-pot, three-component reaction. Both methods have been found to have their own unique advantages. Yang and co-workers reported a novel and efficient method for synthesizing benzo[*g*]chromene derivatives that provided numerous advantages, such as high yield, simple work-up, and eco-friendliness. The utilization of *Candida sp.* lipase as an enzyme catalyst was found to be particularly noteworthy, as it demonstrated the expanded versatility of the enzyme. The study developed the reaction of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **4a–i**, and malononitrile (**5**), using *Candida sp.* lipase as an enzyme catalyst in a multicomponent reaction to synthesize benzo[*g*]chromene derivatives **6a–i** (Route 1).[29] Maheswari and co-workers, on the other hand, were able to synthesize 2-amino-4*H*-benzo[*g*]chromene derivatives using a one-pot, three-component reaction with 2-aminopyridine as a catalyst. They employed a one-pot, three-component reaction that included malononitrile (**5**), aromatic aldehyde **4a–i**, and 2-hydroxy-1,4-naphthoquinone (**1**), using 10 mol% 2-aminopyridine(2-AP) as a reusable catalyst (Route 2).[30] The reaction was performed in ethanol at reflux, and the chosen catalyst proved to be effective in facilitating the desired reaction. The authors observed that the position of the substituent group on the aromatic aldehyde could affect the yield of the reaction, with those in the *para*-position providing excellent yields in short reaction times. These findings highlight the importance of careful consideration of reaction conditions and catalysts in organic synthesis, as the choice of catalyst and reaction conditions can have a significant impact on the outcome of the reaction. Overall, the successful synthesis of benzo[*g*]chromene derivatives using different approaches demonstrates the versatility and potential of enzyme-catalyzed and one-pot, multicomponent reactions in the synthesis of complex organic molecules (Scheme 2).



Scheme 2 Lipase-catalyzed synthesis of benzo[*g*]chromene derivatives **6a–i**

2.3 2-(Alkylamino)-3-nitro-4-(aryl)-4*H*-benzo[*g*]-chromene-5,10-dione Derivatives

Afsharnezhad et al.[31] successfully synthesized benzo[*g*]-chromene derivatives **9a–l** using a straightforward one-pot, multicomponent reaction. The reaction involved 2-hydroxy-1,4-naphthoquinone (**1**), *N*-alkyl-1-(methylthio)-2-nitroethenamine **7a–c**, and aromatic aldehydes **8a–g**, in acetonitrile (CH_3CN) at room temperature. Remarkably, the reaction was completed within a short timeframe of 10–25 minutes, without the need for a catalyst. The protocol offers several notable advantages in addition to not requiring a catalyst, including mild reaction conditions, a simple purification process that does not require chromatography, compatibility with various functional groups, and high product yields (Scheme 3).[31]



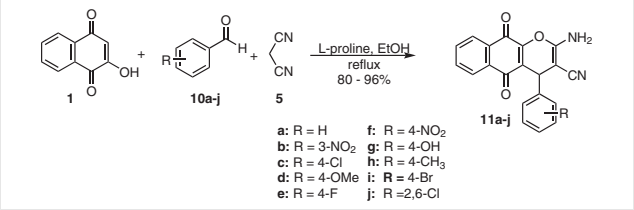
Scheme 3 2-(Alkylamino)-3-nitro-4-(aryl)-4*H*-benzo[*g*]chromene-5,10-dione derivatives **9a–l**

2.4 2-Amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile Derivatives

Daloee and co-workers[32] developed a green approach to synthesize 2-amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carbonitrile derivatives **11a–j**. The method involves the reaction of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **10a–j**, and malononitrile (**5**) in the presence of L-proline as an organocatalyst under reflux conditions in ethanol (Scheme 4). The approach offers several key benefits, including mild reaction conditions, the use of an environmentally friendly catalyst, a simple reaction work-up procedure, and the potential to produce novel derivative products. Overall, this new synthetic approach represents a promising step towards the development of more sustainable and eco-friendly methods for the production of important organic compounds.

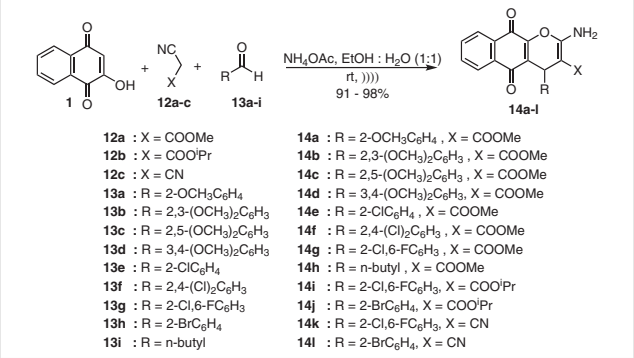
2.5 2-Amino-4*H*-benzo[*g*]chromene Derivatives

Gracious et al.[33] developed a highly efficient and environmentally friendly approach for the synthesis of dihydro-4*H*-benzo[*g*]chromene derivatives **14a–l** using ultrasonic



Scheme 4 2-Amino-5,10-dioxo-4-aryl-5,10-dihydro-4*H*-benzo[*g*]-chromene-3-carbonitrile derivatives **11a–j**

irradiation. The method involved a one-pot process that combined the Knoevenagel–Michael reaction of selected active methylene compounds **12a–c** and 2-hydroxynaphthalene-1,4-dione (**1**) with various substituted aldehydes **13a–i** in a mixture of water and ethanol at room temperature using ultrasonic irradiation. Ammonium acetate was used as a catalyst to facilitate the three-component condensation reaction. Remarkably, the reaction achieved high product yields (91–98%) within a short reaction time of 5–15 minutes. This study presents a promising strategy for the efficient synthesis of dihydro-4*H*-benzo[g]chromene derivatives through an environmentally benign approach utilizing ultrasonic irradiation (Scheme 5).

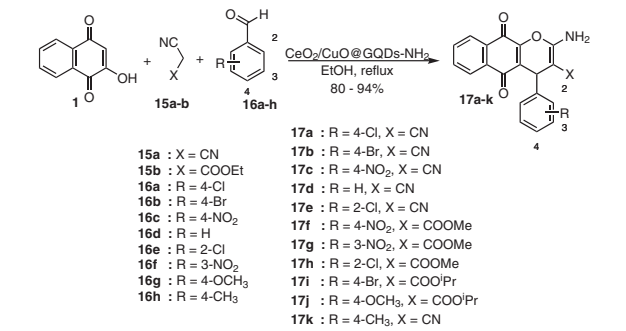


Scheme 5 2-Amino-4*H*-benzo[*g*]chromene derivatives **14a–l**

2.6 Synthesis of Benzo[*g*]chromene Derivatives by using Nanocomposite Catalysts

In their study, Safaei-Ghomi et al.[34] introduced a novel catalytic system consisting of a CeO_2/CuO@N-GQDs@NH_2 nanocomposite for the efficient synthesis of benzo[*g*]chromene compounds **17a–k**. By employing a one-pot, three-component reaction involving aromatic aldehydes **16a–h**, malononitrile (**15a**) or ethyl cyanoacetate (**15b**), and 2-hydroxy-1,4-naphthoquinone (**1**), the nanocomposite catalyst demonstrated remarkable performance. The chemical structures of the synthesized benzo[*g*]chromene products were confirmed through the utilization of ^{1}H NMR and Fourier transform infrared (FT-IR) spectroscopic techniques. This research highlights the potential of the

CeO_2/CuO@N-GQDs@NH_2 nanocomposite as an effective catalyst for the synthesis of benzo[*g*]chromenes (Scheme 6).



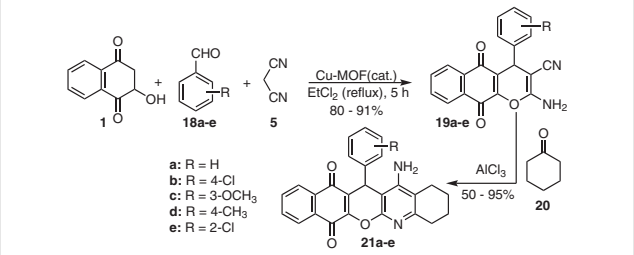
Scheme 6 Synthesis of benzo[*g*]chromenes using CeO_2/CuO@N-GQDs@NH_2 nanocomposite **17a–k**

2.7 Tacrine Derivatives

Tacrine, a drug known for its ability to enhance acetylcholine levels by inhibiting cholinesterase enzymes, has shown remarkable pharmacological properties and is commonly used as a reference compound in Alzheimer's disease (AD) research. The synthesis of tacrine analogues continues to be of interest to scientists studying AD. Various methods have been explored for the synthesis of tacrine and its analogues. Mollabagher et al.[35] introduced a novel procedure for the synthesis of tacrine derivatives **21a–e**, utilizing 2-hydroxynaphthalene-1,4-dione (**1**), malononitrile (**5**), aldehydes **18a–e**, and cyclohexanone (**20**) in a one-pot reaction, eliminating the need for intermediate separation. The use of Cu-MOF as a heterogeneous catalyst facilitated the formation of pyranic intermediates, followed by the addition of aluminum chloride in the Friedländer quinoline reaction, without interfering with the two catalysts involved. The presence of active Cu sites in Cu-MOF made it a suitable candidate for the synthesis of pyrene compounds. This work presents convenient methods for synthesizing tacrine derivatives starting from readily available starting materials. Furthermore, the process offers broad substrate compatibility, high yields (up to 93%), efficient atom-economy, utilization of readily available starting materials, and the advantage of a reusable nanocatalyst (Scheme 7).[35] Additionally, the process eliminates the need for column chromatography purification steps.

2.8 Benzo[*a*]pyrano[2,3-*c*]phenazine and Benzo[*a*]chromeno[2,3-*c*]phenazine Derivatives

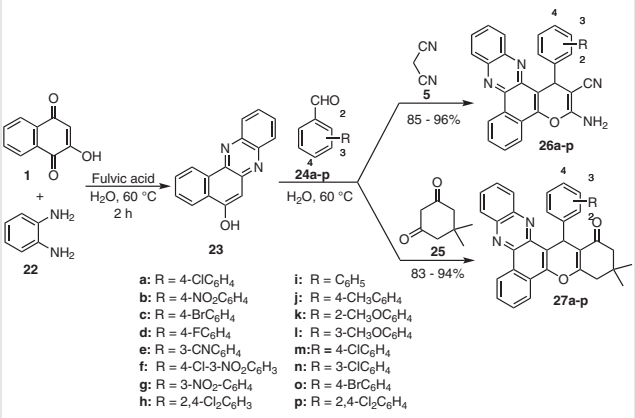
Benzophenazine belongs to the heterocyclic aromatic class of compounds, and is characterized by a fused benzene and phenazine ring system. In medicinal chemistry, benzophenazines have exhibited diverse biological activities, such as anticancer, antimicrobial, and antioxidant



Scheme 7 Synthesis of tacrine derivatives **21a–e**

properties. Researchers have explored their potential as therapeutic agents for various diseases and conditions. The structural versatility of benzophenazines allows for the design and synthesis of derivatives with optimized pharmacological properties and target selectivity. Furthermore, in materials science, benzophenazines have been investigated for their optical and electronic properties. These compounds possess conjugated π-electron systems, making them suitable for applications in organic electronic devices, such as organic light-emitting diodes (OLEDs) and organic photovoltaic cells (OPVs). The tunability of their electronic properties through structural modifications offers opportunities for tailoring their performance in these devices. Synthetic methodologies for the preparation of benzophenazines have been developed, involving multicomponent reactions, transition-metal catalysis, and other synthetic strategies. These methods enable the synthesis of diverse benzophenazine derivatives with varying substituents and functional groups, expanding the scope of their applications. Recently, Olyaei and co-workers[36] presented a detailed review on the synthesis and biological importance of various lawsone-derived benzo[*a*]phenazinols, which serves as precursors for the development of various five- and six-membered fused heterocycles such as furophenazines and pyranophenazines.[36]

In a continuation of this study Yazdani-Elah-Abadi et al.[37] demonstrated the use of fulvic acid as a convenient and efficient catalyst for the efficient synthesis of benzophenazine derivatives. In their study, they performed a four-component assembly of aromatic aldehydes **4**, various C–H acids (malononitrile **5** or dimedone **25**), 2-hydroxy-1,4-naphthoquinone (**1**), and *o*-phenylenediamine (**22**) in water at a temperature of 60 °C, resulting in excellent yields of benzo[*a*]pyrano[2,3-*c*]phenazine **26a–p** and benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **27a–p**. The catalyst, fulvic acid, offers several advantageous features; it is easily obtained, clean and easy to handle, safe and non-toxic, and it is also cost-effective (Scheme 8). Furthermore, the catalyst can be reused multiple times without significant loss of activity. This procedure delivers high yields of the desired products while maintaining clean reaction conditions. It offers operational simplicity, making it straightforward to perform. Additionally, the method has minimal

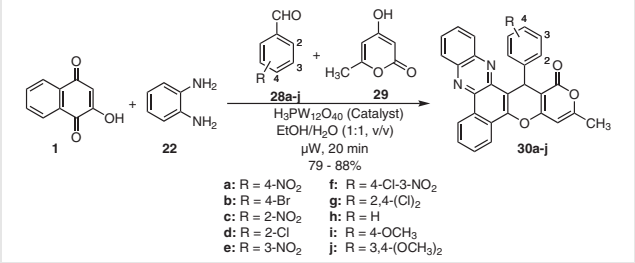


Scheme 8 Synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine **26a–p** and benzo[*a*]chromeno[2,3-*c*]phenazine derivatives **27a–p**

environmental impact, aligning with the principles of green chemistry.[37]

2.9 Benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazines

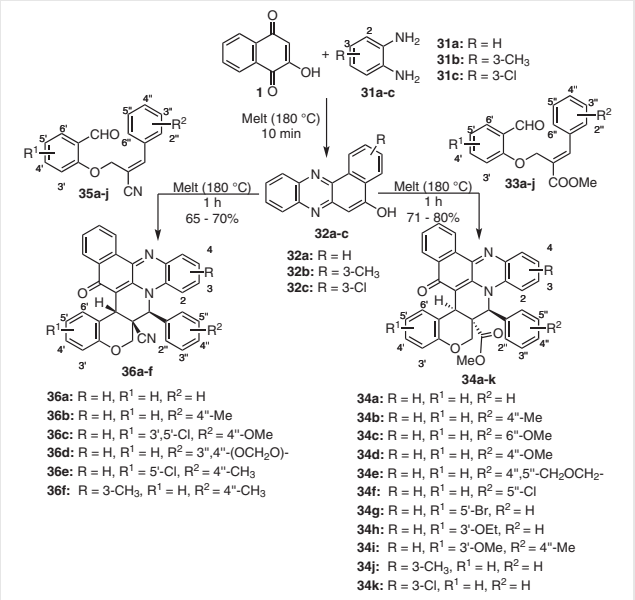
Mohammadrezaei et al.[38] presented an efficient method for the domino synthesis of benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazines. This synthesis involves a one-pot, four-component condensation reaction between 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **28a–j**, and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**29**). The catalyst employed in this reaction is phosphotungstic acid ($H_3PW_{12}O_{40}$). The use of $H_3PW_{12}O_{40}$ as a solid heteropolyacid catalyst in conjunction with microwave irradiation (180 W, maximum 70 °C) in a mixture of EtOH and H_2O (1:1) proved to be highly effective, environmentally friendly, and recyclable. The catalyst exhibits remarkable catalytic activity, facilitating the synthesis of benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazines **30a–j** with excellent yields (Scheme 9).[38] This method offers several advantages, including simplicity and the ability to perform the entire synthesis in a single pot. Additionally, the use of microwave irradiation enables rapid reaction times. Furthermore, the $H_3PW_{12}O_{40}$ catalyst can be easily recovered and reused, contributing to the overall efficiency and sustainability of the process.



Scheme 9 Benzo[*a*]pyrano[3′,4′:5,6]pyrano[2,3-*c*]phenazine derivatives **30a–j**

2.10 Chromene/Bicyclic Fused Benzo[*a*]phenazinone Derivatives

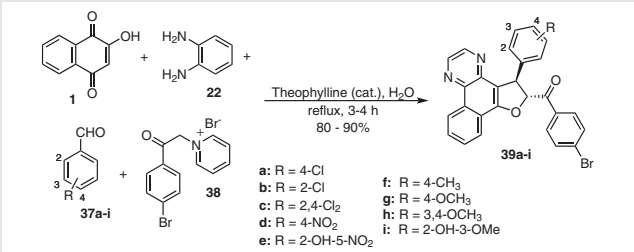
Bakthadoss et al.[39] developed a novel one-pot assembly method for the synthesis of highly functionalized benzo[*a*]phenazinone fused chromene/bicyclic scaffolds 34a–k and 36a–f. This approach involves the solid-state melt reaction of 2-hydroxynaphthalene-1,4-dione (1), *o*-phenylenediamine derivatives 31a–c, and *o*-allyl salicylaldehyde derivatives 33a–j and 35a–j, followed by a domino Knoevenagel intramolecular hetero-Diels–Alder reaction. In this single-pot reaction, three six-membered rings, three stereogenic centers, and five new bonds (two C–C bonds and three C–O bonds) are formed, resulting in the desired benzo[*a*]phenazinone fused chromene/bicyclic scaffolds. This synthesis strategy is particularly appealing due to its simplicity, rapidity, high yields, and the generation of only water as waste product. Furthermore, the method does not require extensive workup procedures. The innovative features of this approach make it highly attractive for the efficient synthesis of complex and functionalized benzo[*a*]phenazinone fused chromene/bicyclic scaffolds. The ability to achieve multiple ring formations and bond constructions in a single pot, along with the use of water as the only waste product, highlight the advantages of this method (Scheme 10).[39]



Scheme 10 Chromene/bicyclic fused benzo[*a*]phenazinone derivatives **34a–k** and **36a–f**

2.11 *trans*-1,2-Dihydrobenzo[*a*]furo[2,3-*c*]phenazine Derivatives

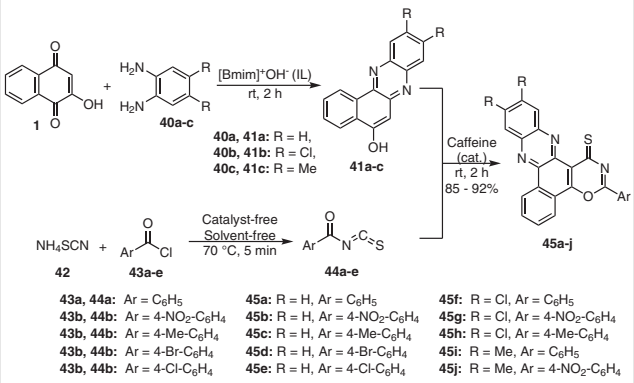
Yazdani-Elah-Abadi et al.[40] introduced a novel and efficient domino four-component coupling process for the synthesis of 1,2-dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives **39a–i**. This selective and highly productive method utilizes readily available starting materials 2-hydroxy-1,4-naphthquinone (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **37a–i**, and pyridinium ylide **38**, and the reaction occurs in the presence of a catalytic amount of theophylline in aqueous medium (Scheme 11). The reaction involves a sequence of condensation, Knoevenagel, Michael, and annulation steps, resulting in the formation of two C–C bonds, two C=N bonds, one C–O bond, and two new rings in a single operation. This protocol offers several advantages. Firstly, it enables an easy one-pot operation, simplifying the synthetic procedure. Additionally, the reaction exhibits a high atom-economy by efficiently utilizing the starting materials. The use of theophylline as a catalyst is noteworthy, as it is non-toxic, affordable, and easily accessible. Furthermore, the method eliminates the need for conventional volatile organic solvents, contributing to its environmental compatibility.[40]



Scheme 11 *trans*-1,2-Dihydrobenzo[*a*]furo[2,3-*c*]phenazine derivatives **39a–i**

2.12 Benzo[*a*][1,3]oxazino[6,5-*c*]phenazine Derivatives

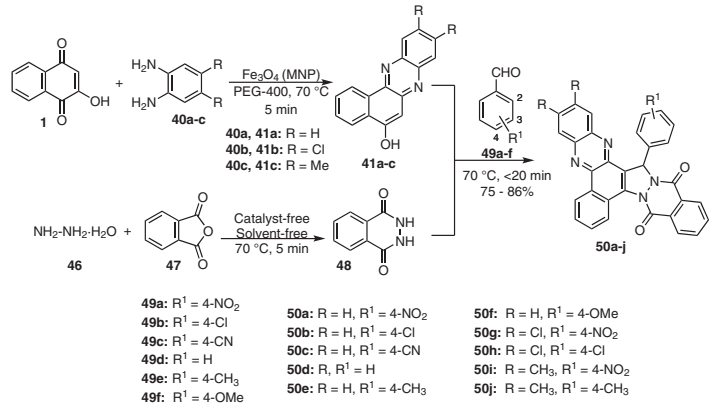
Mohebat and co-workers[41] successfully synthesized benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **45a–j** using a one-pot, four-component sequential condensation reaction. In this environmentally friendly approach, caffeine was employed as a natural catalyst. The reaction involved the condensation of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic 1,2-diamines **40a–c**, ammonium thiocyanate (**42**), and aryl-acid chlorides **43a–e**, in the presence of a basic ionic liquid (1-butyl-3-methylimidazolium hydroxide). This one-pot reaction enables the formation of five bonds and two additional rings, offering a highly efficient synthetic route. The reaction proceeds in three steps. Initially, 2-hydroxy-1,4-naphthoquinone and 1,2-diamines are mixed at room temperature in [Bmim]$^+$OH$^-$ (ionic liquid), resulting in the formation of benzo[*a*]phenazines within a short time (<30 min). In the second step, ammonium thiocyanate and acid chlorides are combined at 70 °C under solvent-free conditions, leading to the generation of solid aroyl isothiocyanate derivatives **44a–e**. Finally, the products from the first step react with the aroyl isothiocyanate derivatives in the presence of caffeine in [Bmim]$^+$OH$^-$ to yield the desired benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **45a–j** (Scheme 12). This methodology offers several advantages, including its user-friendly nature, excellent yields of the desired products, avoidance of toxic or hazardous catalysts, high chemo- and regioselectivity, and operational simplicity. The use of caffeine as a catalyst adds to the environmentally benign nature of the approach.[41]



Scheme 12 Synthesis of benzo[*a*][1,3]oxazino[6,5-*c*]phenazine derivatives **45a–j**

2.13 Benzo[*a*]phthalazino[2,3:1,2]pyrazolo[3,4-*c*]-phenazines

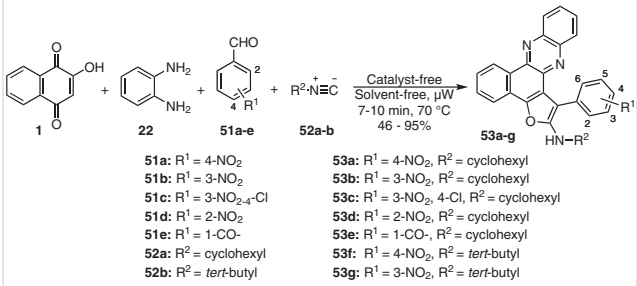
Yazdani-Elah-Abadi et al.[42] successfully synthesized benzo[*a*]phthalazino[2,3:1,2]pyrazolo[3,4-*c*]phenazines **50a–j**, which possess both biologically active benzophenazine and pyrazolophthalazine templates. These compounds were synthesized in a single-pot, five-component reaction using 2-hydroxynaphthalene-1,4-dione (**1**), aromatic 1,2-diamines **40a–c**, hydrazine hydrate (**46**), phthalic anhydride (**47**), and aromatic-aldehydes **49a–f**. The reaction was catalyzed by magnetic iron(III) oxide nanoparticles (Fe_3O_4 MNPs) in polyethylene glycol (PEG-400) as the reaction medium. The use of Fe_3O_4-MNPs as catalyst offered several advantages, including their ready availability, high efficiency, and recyclability. PEG-400 served as an affordable, safe, and effective medium, eliminating the need for additional organic co-solvents. Furthermore, PEG-400 is non-toxic and reusable, making it an environmentally friendly choice. The synthesis was carried out at a temperature of 70 °C, providing suitable reaction conditions. The combination of Fe_3O_4-MNPs catalyst and PEG-400 medium enabled a straightforward and efficient synthesis of the target compounds, offering a practical and sustainable synthetic approach (Scheme 13).[42]



Scheme 13 Benzo[*a*]phthalazino[2,3:1,2]pyrazolo[3,4-*c*]phenazine derivatives **50a–j**

2.14 Benzo[*a*]furo[2,3-*c*]phenazine Derivatives

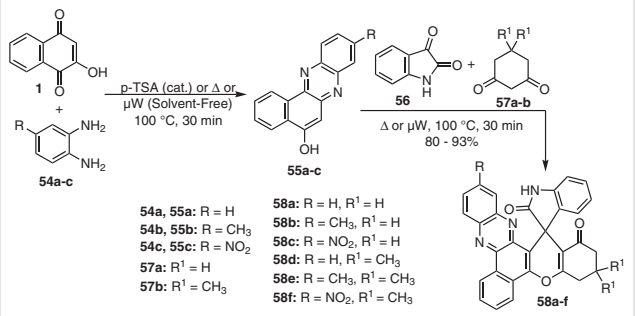
In a continuation of the work by Abadi et al. discussed in Section 2.13, the same group[43] reported a one-pot, four-component synthesis of benzo[*a*]furo[2,3-*c*]phenazines **53a–g** under microwave conditions. This method has proven to be effective, mild, and rapid. By combining 2-hydroxynaphthalene-1,4-dione (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **51a–e**, and substituted isocyanides **52a–b**, in a solvent-free and catalyst-free microwave environment, furan annulated heterocycles were successfully synthesized. The convenience of this methodology lies in its straightforward one-pot procedure, allowing for easy handling and manipulation. Furthermore, the work-up process is simplified, saving time and effort. The reaction times were relatively short, enabling rapid access to the desired benzo[*a*]furo[2,3-*c*]phenazines. Importantly, the products were obtained in high yields, highlighting the efficiency of this microwave-assisted synthetic approach (Scheme 14).[43]



Scheme 14 Benzo[*a*]furo[2,3-*c*]phenazine derivatives **53a–g**

2.15 Spiro[benzo[*a*]chromeno[2,3-*c*]phenazine] Derivatives

Mohebat et al.[44] conducted a synthesis of spiro[benzo[*a*]chromeno[2,3-*c*]phenazine] derivatives **58a–f** using a one-pot, four-component condensation reaction. The reaction involved 2-hydroxy-1,4-naphthoquinone (**1**), benzene-1,2-diamine **54a–c**, cyclic-1,3-dicarbonyl compounds **57a–b**, and isatin (**56**). The reaction was facilitated by *p*-toluenesulfonic acid, which served as an effective, non-toxic, and solid acid catalyst. The synthesis of these derivatives was achieved through a novel two-step domino protocol, employing either conventional heating or microwave irradiation. This solvent-free process resulted in the formation of five new bonds (two C–C, two C=N, and one C–O) and two new rings, leading to the generation of biologically significant heterocycles. The advantages of this reaction method include its operational simplicity, rapid reaction time, excellent yield of the desired products, elimination of time-consuming purification steps, and avoidance of potentially hazardous chemicals and solvents (Scheme 15).[44]

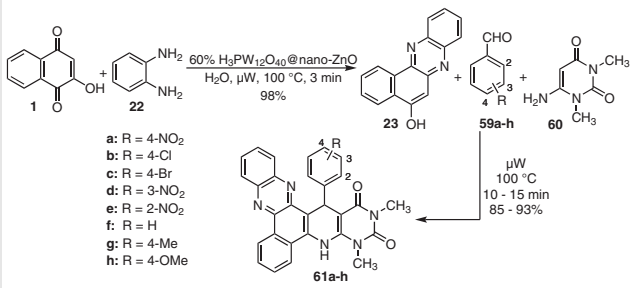


Scheme 15 Spiro[benzo[*a*]chromeno[2,3-*c*]phenazine] derivatives **58a–f**

2.16 Dihydrobenzo[*a*]pyrimido[50,40:5,6]pyrido-[2,3-*c*]phenazine Derivatives

Dehghan et al.[45] reported the development of a rapid, efficient, and environmentally friendly procedure for synthesizing novel heteroaryl-substituted dihydrobenzo[*a*]pyrimido[5,4:5,6]pyrido[2,3-*c*]phenazines **61a–h**. This synthesis involves condensation, Knoevenagel, Michael, and heterocyclization reactions of *o*-phenylenediamine (**22**), 2-hydroxynaphthalene-1,4-dione (**1**), aromatic aldehydes **59a–h**, and 6-amino-1,3-dimethyluracil (**60**). The reactions take

place in the presence of a recyclable heterogeneous catalyst, $H_3PW_{12}O_{40}$@nano-ZnO, under microwave irradiation in an aqueous medium. The current approach offers several advantages: It proceeds in short reaction times, gives high yields of the desired products, has excellent atom-economy, and exhibits remarkable chemoselectivity (Scheme 16).[45]

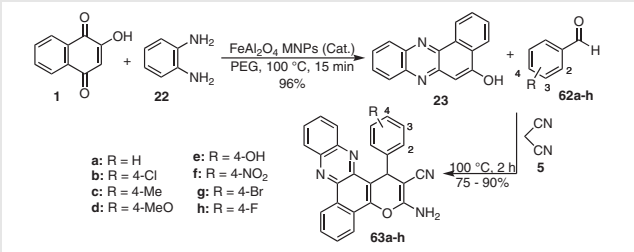


Scheme 16 Dihydrobenzo[*a*]pyrimido[50,40:5,6]pyrido[2,3-*c*]phenazine derivatives **61a–h**

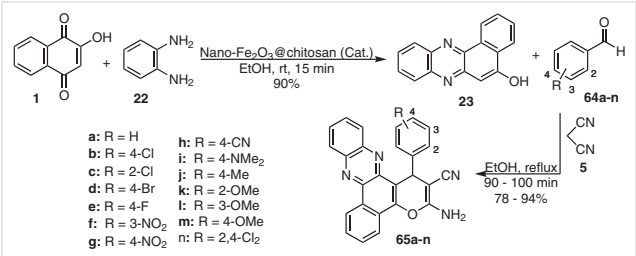
2.17 Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives

Ghorbani-Choghamarani et al.[46] developed a catalytic system utilizing spinel ferrite $FeAl_2O_4$ (hercynite) magnetic nanoparticles (MNPs) for the efficient one-pot synthesis of benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **63a–h** through a multicomponent reaction under environmentally friendly reaction conditions. This method involves a one-pot, four-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **62a–h**, and malononitrile (**5**) using $FeAl_2O_4$ MNPs as a catalyst (Scheme 17). The structure of the synthesized nanocatalyst was thoroughly characterized using XRD, FTIR, SEM, EDS, BET, and VSM techniques. The $FeAl_2O_4$ MNPs exhibit Lewis acid behavior and offer numerous advantages, including high product yields, short reaction times, and easy workup procedures. Additionally, the nanocatalyst could be recycled and reused up to four times without significant loss of activity.[46]

In a separate study, Safaei-Ghomi et al.[47] presented a simple and rapid method for the preparation of benzo[*a*]pyrano[2,3-*c*]phenazine **65a–n**. This method also involves a one-pot, four-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **64a–n**, and malononitrile (**5**) using nano-Fe_3O_4@chitosan as an efficient heterogeneous solid acid catalyst under reflux conditions in ethanol (Scheme 18). The catalyst was characterized using various techniques including powder X-ray diffraction (XRD), scanning electron microscopy (SEM), magnetic susceptibility measurements, energy-dispersive X-ray spectroscopy (EDS), and Fourier transform infrared (FTIR) spectroscopy. Key features of this method include high atom-economy, excellent catalytic activity, a broad range of products, high yields in short reaction times, and low catalyst loading.[47]



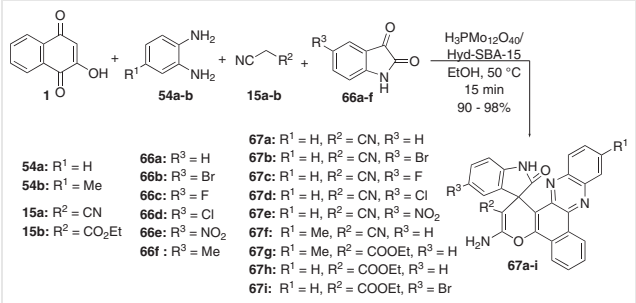
Scheme 17 Benzo[*a*]pyrano[2,3-*c*] phenazine derivatives **63a–h**



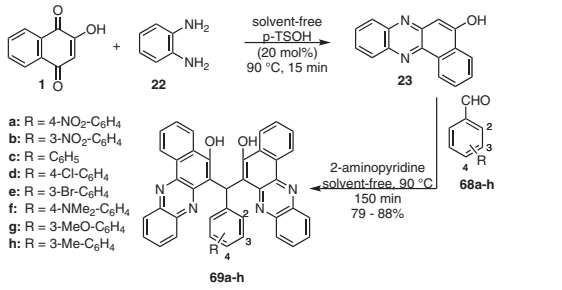
Scheme 18 Benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **65a–n**

2.18 3-Amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]-phenazine-1,3′-indoline]-2-carbonitrile/carboxylate Derivatives

Safaei-Ghomi et al.[48] developed an innovative approach using an inorganic–organic hybrid catalyst for the efficient synthesis of 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **67a–i** through a domino multicomponent reaction (MCR). This method also involves a one-pot, four-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine **54a–b**, substituted isatin derivative **66a–f**, and malononitrile (**15a**) or ethyl cyanoacetate (**15b**) in EtOH (Scheme 19). This methodology addresses the issue of employing harsh catalysts and offers significant advancements by utilizing $H_3PMo_{12}O_{40}$/Hyd-SBA-15 as a catalyst. The key features of this approach are the remarkably low reaction times and high yields of the products, making it



Scheme 19 3-Amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile/carboxylate derivatives **67a–i**



Scheme 20 6,6′-(Arylmethylene)bis(benzo[*a*]phenazin-5-ol) derivatives **69a–h**

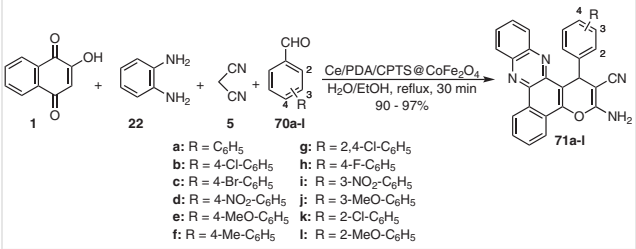
both impressive and environmentally beneficial. The synthesis of the $H_3PMo_{12}O_{40}$/Hyd-SBA-15 catalyst is straightforward, providing a solution to the problem associated with the use of harsh catalysts. Overall, this novel inorganic–organic hybrid catalyst demonstrates excellent efficiency, while also being environmentally friendly due to its low reaction times and high product yields.[48]

2.19 Synthesis of 6,6′-(Arylmethylene)bis(benzo[*a*]phenazin-5-ol) Derivatives

Olyaei et al.[49] developed a straightforward and effective method for the synthesis of novel 6,6′-(arylmethylene)bis(benzo[*a*]phenazin-5-ol) derivatives **69a–h**. This was achieved through a sequential one-pot, two-step, pseudo-five-component tandem reaction using 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), and aromatic aldehydes **68a–h**. The reaction took place under solvent-free conditions at 90 °C, in the presence of 2-aminopyridine as a co-catalyst and *p*-TsOH as a catalyst (Scheme 20). This green sequential method offers several advantages, including low cost, clean reactions, high yield, operational simplicity, easy handling, and the absence of any tedious work-up or purification using non-chromatographic methods.[49]

2.20 Benzo[*a*]pyrano[2,3-*c*]phenazine Derivatives

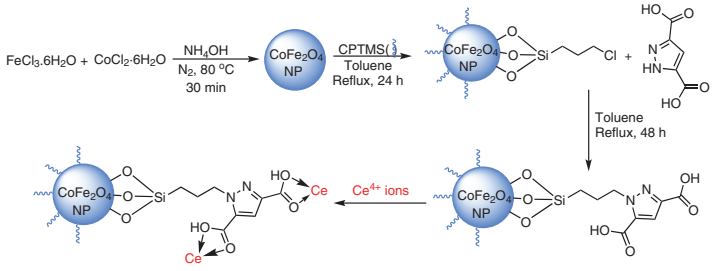
In the context of sustainable chemical processes, the utilization of modern nanotechnology has gained significant attention in the development of functionalized eco-friendly materials. These nanomaterials show great promise as heterogeneous catalysts in various chemical synthesis reactions. Spinel ferrites, with a general molecular formula of MFe_2O_4 (where M = Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}), exhibit unique structural and electronic properties, making them highly valuable in catalytic applications. In this regard, Daraie et al.[50] successfully synthesized a Ce/PDA/CPTMS@$CoFe_2O_4$ nanocomposite that was employed as a catalyst (Scheme 21). Under green conditions, a range of biologically important benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **71a–l** were synthesized by condensing 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), malononitrile (**5**), and various aryl aldehydes **70a–l** (Scheme 22). This approach yielded a diverse set of products with remarkable yields in short reaction times.[50]



Scheme 22 Benzo[*a*]pyrano[2,3-*c*]phenazine derivatives **71a–l**

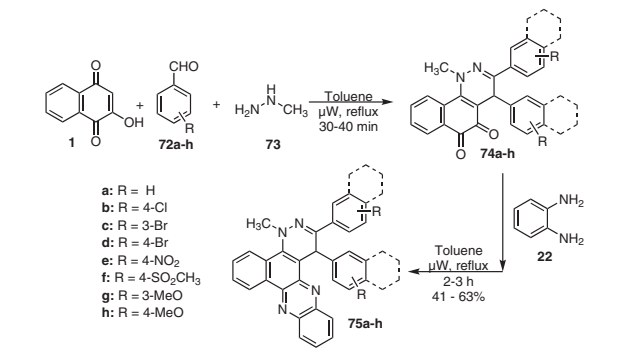
2.21 Benzo[*a*]pyridazino[3,4-*c*]phenazine Derivatives

The remarkable biological properties exhibited by nitrogen-containing heterocyclic molecules have positioned them as significant targets in the fields of synthetic organic and medicinal chemistry. Among these, phenazines represent a highly abundant class of synthesized and naturally occurring nitrogen-containing heterocycles, known for their broad-spectrum antibiotic, fungicidal, and antimalarial activities. To access novel functionalized benzo[*a*]pyri-



Scheme 21 Preparation of Ce/PDA/CPTMS@$CoFe_2O_4$ nanocomposite

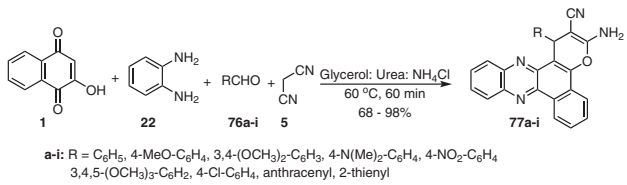
dazino[3,4-*c*]phenazine derivatives **75a–h**, Le-Nhat-Thuy et al.[51] developed a convenient one-pot, microwave-assisted, four-component synthetic approach. The reaction involved the utilization of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **72a–h**, methyl hydrazine (**73**), and *o*-phenylenediamine (**22**) as starting materials (Scheme 23). This innovative method offers an efficient and expedient route to obtain diverse and functionalized benzo[*a*]pyridazino[3,4-*c*]phenazine derivatives, broadening the scope for their potential applications in various fields.[51]



Scheme 23 Benzo[*a*]pyridazino[3,4-*c*]phenazine derivatives **75a–h**

2.22 Benzopyranophenazine Derivatives

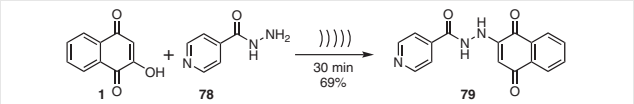
Theresa et al.[52] achieved an efficient synthesis of benzopyranophenazine carbonitrile **77a–i** that improved the safety and cost-effectiveness, and reduced the reliance on organic solvents in the reaction. The reaction involved the effective combination of 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), malononitrile (**5**), and aryl aldehyde **76a–i**, resulting in good to excellent yields (Scheme 24). The synthesis of benzopyranophenazine derivatives involved a two-step process: Knoevenagel condensation reaction followed by Michael addition reaction. Initially, aldehydes and malononitrile underwent condensation via the Knoevenagel reaction. The condensation of 2-hydroxy-1,4-naphthoquinone and *o*-phenylenediamine led to the formation of a benzophenazine intermediate. Subsequently, the intermediate underwent Michael addition followed by cyclization, yielding benzopyranophenazine carbonitrile derivatives. To facilitate the reaction, a low-melting mixture of glycerol, urea, and NH_4Cl was utilized as both the reaction medium and catalyst, further enhancing the efficiency of the synthesis of benzopyranophenazine carbonitrile.[52]



Scheme 24 Benzopyranophenzine carbonitrile derivatives **77a–i**

2.23 *N′*-(1,4-Naphthoquinone-2-yl) Isonicotinohydrazide (NIH) Derivatives

Rani et al.[53] conducted a study in which they employed ultrasonic irradiation to react 2-hydroxy-1,4-naphthaquinone (**1**) with isonicotinoyl hydrazine (**78**) in methanol, resulting in the synthesis of *N′*-(1,4-naphthoquinone-2-yl)isonicotinohydrazide (NIH, **79**) (Scheme 25). Lawsone, extracted from henna leaves (*Lawsonia inermis*), serves as a primary dye. To enhance the compound's activity, its structure was modified. The structural characteristics of both the parent compound and the derivative were evaluated through elemental analysis, IR, electronic, ^{1}H and ^{13}C NMR, and GC-MS spectroscopy. Cytotoxicity experiments were performed using the MTT test on human breast adenocarcinoma (MCF-7) and colon cancer (HCT-15) cell lines to assess the potential of NIH as a therapeutic agent.[53]



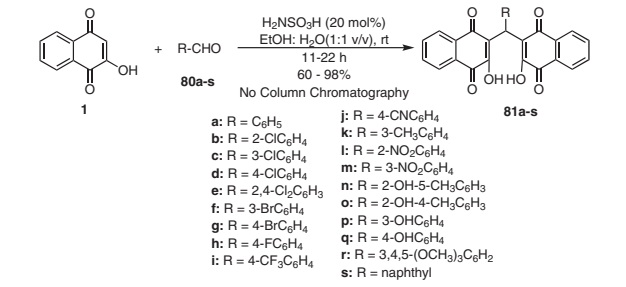
Scheme 25 *N′*-(1,4-Naphthoquinone-2-yl)isonicotinohydrazide (NIH) derivative **79**

2.24 Bis-Lawsone Derivatives

Brahmachari et al.[54] introduced a straightforward and environmentally friendly synthesis method for various functionalized bis-lawsones; specifically, 3,3′-(aryl/alkylmethylene)bis(2-hydroxynaphthalene-1,4-dione) derivatives **81a–s**. The synthesis was accomplished by using sulfamic acid as a benign organocatalyst in a one-pot, pseudo-multicomponent reaction conducted at room temperature with 2-hydroxy-1,4-naphthaquinone (**1**) and aryl aldehyde **80a–s** (Scheme 26). This protocol offers several noteworthy features, including mild reaction conditions, good to excellent product yields, simplicity in operation, energy efficiency, high atom-economy, environmental friendliness, easy product isolation, and the absence of column chromatographic separation.[54]

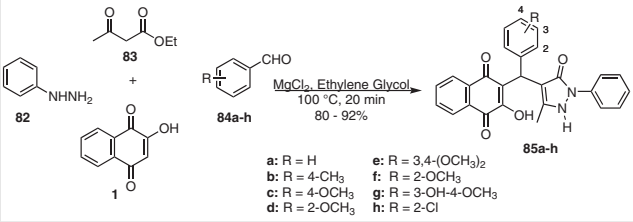
2.25 2-Hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione Derivatives

Multicomponent reactions (MCRs) have emerged as valuable tools for the synthesis of biologically active compounds, offering numerous advantages compared to conventional synthetic approaches. These advantages include shortened reaction times, reduced waste generation, ener-



Scheme 26 Bis-lawsone derivatives **81a–s**

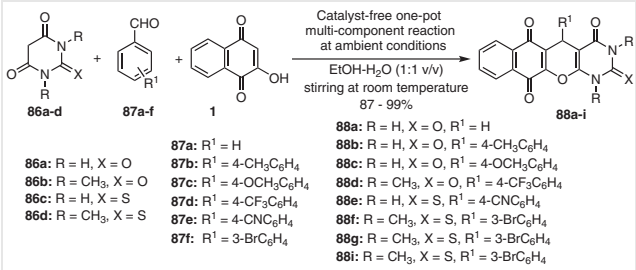
gy conservation, and efficient utilization of starting materials. Fu et al.[55] developed an efficient and practical method for synthesizing 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives **85a–h**. This was achieved through a one-pot, four-component reaction involving aromatic aldehydes **84a–h**, β-keto esters **83**, phenylhydrazine hydrate (**82**), and 2-hydroxy-1,4-naphthoquinone (**1**), catalyzed by $MgCl_2$ in ethylene glycol (EG) at 100 °C (Scheme 27). The protocol offers appealing features such as a simple work-up procedure, short reaction time, high yield, and the use of an eco-friendly catalyst, making it a valuable and attractive strategy in the field of synthetic organic chemistry.[55]



Scheme 27 2-Hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives **85a–h**

2.26 1*H*-Benzo[6,7]chromeno[2,3-*d*]pyrimidine Derivatives

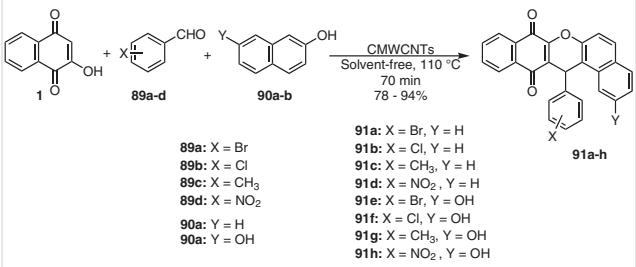
Brahmachari et al.[56] devised a catalyst-free, energy-efficient, and practical method for the synthesis of a wide range of biologically significant 5-aryl-2-oxo-/thioxo-2,3-dihydro-1*H*-benzo[6,7]chromeno[2,3-*d*]pyrimidine-4,6,11(5*H*)-trione derivatives **88a–i**. These derivatives were obtained through a one-pot multicomponent reaction (MCR) in aqueous ethanol at room temperature, involving barbituric/2-thiobarbituric acids **86a–d**, aromatic aldehydes **87a–f**, and 2-hydroxy-1,4-naphthoquinone (**1**). The protocol offers several notable features, including mild reaction conditions at room temperature, the absence of catalyst, operational simplicity, and clean reaction profiles. Moreover, the methodology provides excellent yields and high atom-economy. The use of commercially available and inexpensive starting materials, along with the ease of product isolation and purification without the need for time-consuming column chromatography, further adds to the advantages of this approach (Scheme 28).[56]



Scheme 28 5-Aryl-2-oxo-/thioxo-2,3-dihydro-1*H*-benzo[6,7]chromeno[2,3-*d*]pyrimidine-4,6,11(5*H*)-trione derivatives **88a–i**

2.27 5-Oxatetracene Derivatives

Khodabakhshi et al.[57] successfully synthesized 5-oxatetracene derivatives **91a–h**, which consist of five fused rings, using carboxylated multiwall carbon nanotubes (CMWCNTs) as efficient nanocatalysts. A mixture of lawsone (**1**), aromatic aldehyde **89a–d**, and β-naphthol (**90**) was heated at 110 °C to give the desired product (Scheme 29). The CMWCNTs exhibited high efficiency and good recyclability under solvent-free conditions. The method offers several significant advantages, including short reaction times, utilization of a readily available catalyst, simple work-up procedure, high product yield, and elimination of toxic organic solvents.[57]

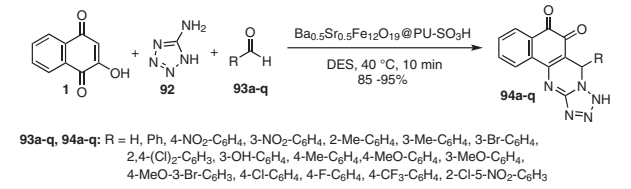


Scheme 29 Synthesis of 5-oxatetracene derivatives **91a–h** using CMWCNTs

2.28 7-Arylbenzo[*h*]tetrazolo[5,1-*b*]quinazoline-5,6-dione Derivatives

Maleki et al.[58] achieved the successful synthesis of a magnetic polymeric nanocomposite, $Ba_{0.5}Sr_{0.5}Fe_{12}O_{19}$@PU-$SO_3H$, functionalized with Brönsted acid groups. The catalytic performance of this nanocomposite was investigated in a deep eutectic solvent (DES) based on choline chloride and urea, which is environmentally friendly and recyclable. The nanocomposite exhibited remarkable catalytic activity in the regioselective synthesis of 7-aryl-benzo[*h*]tetrazolo[5,1-*b*]quinazoline-5,6-diones **94a–q** from lawsone (**1**),

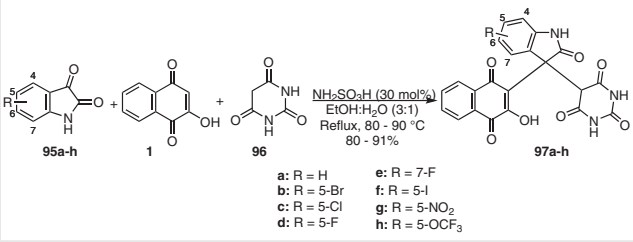
tetrazoloamine, and aromatic aldehyde **93a–q** (Scheme 30). This methodology offers several advantages, including high yields, short reaction times, the use of environmentally acceptable reaction media, straightforward product isolation, and an easy method for synthesizing nanocatalysts. Furthermore, the synthesized catalyst can undergo up to six recycling cycles with the use of an external magnetic field, all while maintaining its activity and mass without substantial degradation.[58]



Scheme 30 7-Arylbenzo[*h*]tetrazolo[5,1-*b*]quinazoline-5,6-diones derivatives **94a–q**

2.29 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidine Derivatives

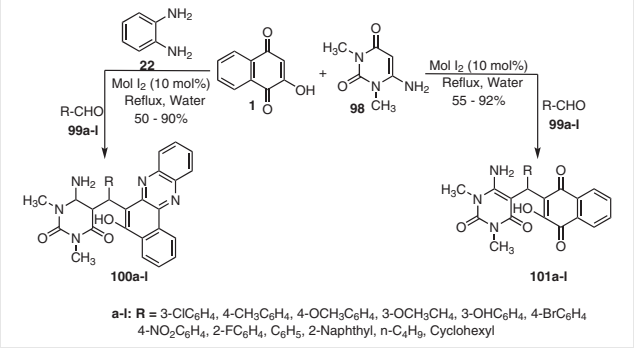
Brahmachari et al.[59] developed a straightforward and highly efficient one-pot, three-component synthesis of diverse and functionalized 5-((1*H*-indol-3-yl)(aryl)methyl)-6-aminopyrimidine-2,4(1*H*,3*H*)-dione derivatives **97a–h** based on a molecular hybridization approach. The target molecules were obtained through a tandem reaction involving 6-aminouracils **96**, 2-hydroxy-1,4-naphthoquinone (**1**), and indoles **95a–h** in the presence of sulfamic acid as a low-cost and environmentally friendly organocatalyst, utilizing water as the reaction medium at room temperature. The developed protocol offers high atom-economy, energy efficiency, excellent yields, metal-free synthesis, eco-friendliness, and operational simplicity (Scheme 31).[59]



Scheme 31 1,4-Naphthoquinonyl-2-oxoindolinylpyrimidine derivatives **97a–h**

2.30 Aminouracil-Tethered Trisubstituted Methane Derivatives

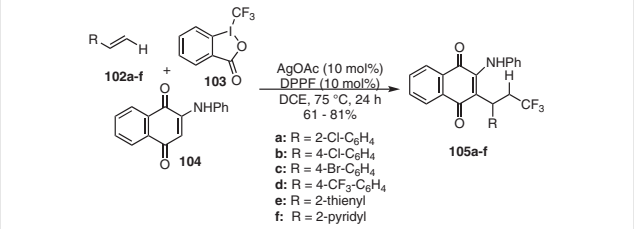
Kumari et al.[60] successfully achieved the synthesis of aminouracil-tethered tri-substituted methane derivatives using a mild, efficient, and environmentally friendly approach. The three-component reaction of 6-amino-1,3-dimethyluracil (**98**), aldehydes **99a–l**, and 2-hydroxy-1,4-naphthaquinone (**1**), with molecular iodine as the catalyst under reflux conditions, resulted in the formation of aminouracil-tethered tri-substituted methane derivative **101a–l**, respectively, in aqueous medium. Similarly, employing the same reaction conditions, the four-component reaction involving 2-hydroxy-1,4-naphthaquinone (**1**), *o*-phenylenediamine (**22**), aminouracil (**98**), and aldehyde derivatives **99a–l** yielded aminouracil-tethered tri-substituted methane derivatives **100a–l** (Scheme 32).[60]



Scheme 32 Aminouracil-tethered tri-substituted methane derivatives **100a–l** and **101a–l**

2.31 CF_3-Functionalized Alkyl-Substituted 2-Amino- and 2-Hydroxy-1,4-naphthoquinone Derivatives

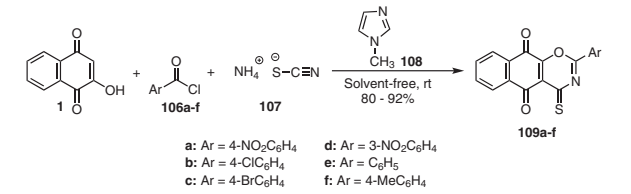
The three-component difunctionalization of alkenes through radical pathways has emerged as a highly efficient strategy for constructing polyfunctionalized molecules and has garnered significant attention in recent years. In this regard, the development of new radical trapping reagents has been an actively explored area, leading to the discovery of oxygen-based, nitrogen-based, carbon-based, and other types of radical trapping reagents. Wang et al.[61] conducted a study in which they utilized 2-amino-1,4-naphthoquinone derivative **104** as radical-trapping agent in a silver-catalyzed three-component difunctionalization of alkenes. The reaction employed various alkenes **102a–f** and 2-amino-1,4-naphthoquinone **104** with diverse structures and electronic properties. This methodology offers an alternative approach for accessing CF_3-functionalized alkyl-substituted quinone derivatives **105a–f**, which are commonly found in bioactive molecules (Scheme 33).[61]



Scheme 33 2-Amino-1,4-naphthoquinone derivatives **105a–f**

2.32 2-Aryl-4-thioxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione Derivatives

In the field of biological sciences, 1,3-oxazine derivatives have gained significant attention as antibacterial agents and cancer screening agents. Additionally, the thio-derivatives of pyrano-1,3-benzoxazine have shown promising anti-inflammatory and antipyretic properties. In their study, Balouchzehi et al.[62] developed a selective one-pot method for synthesizing biologically active 2-aryl-4-thioxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones **109a–f**. This method involves the condensation of ammonium thiocyanate **107** and aromatic acyl chlorides **106a–f** with 2-hydroxy-1,4-naphthoquinone (**1**) in the presence of catalytic amounts of N-methylimidazole **108** under solvent-free conditions at ambient temperature, resulting in excellent yields (Scheme 34). The advantages of this new protocol include mild reaction conditions, short reaction time, utilization of an inexpensive and non-toxic catalyst, high yields of biologically active products, and the absence of hazardous solvents. The discovery of these novel oxazine compounds holds promise because of their diverse pharmacological properties.[62]



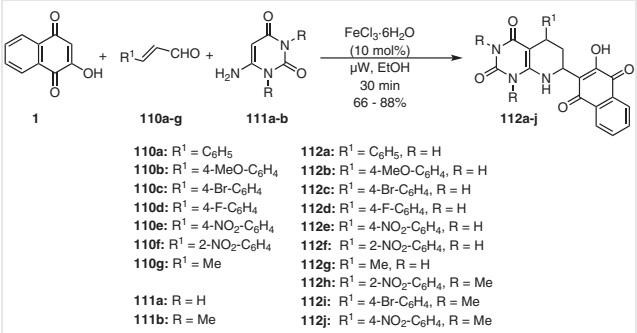
Scheme 34 2-Aryl-4-thioxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione derivatives **109a–f**

2.33 Pyrimidine-Fused Tetrahydropyridine Derivatives

Kumari and co-workers[63] conducted a study on the synthesis of regioselective pyrimidine-fused tetrahydropyridines through a one-pot, three-component reaction. The researchers employed $FeCl_3{\cdot}6H_2O$ as a catalyst under microwave irradiation to achieve the regioselective three-component reaction. By combining α,β-unsaturated aldehydes (cinnamaldehyde/crotonaldehyde) **110a–g**, 2-hydroxy-1,4-naphthaquinone (**1**), and 6-aminouracils **111a–b**, they successfully obtained pyrimidine-fused tetrahydropyridine-linked cyclic 1,3-diketones **112a–j** (Scheme 35).[63]

2.34 Benzylpyrazolyl Naphthoquinone Derivatives

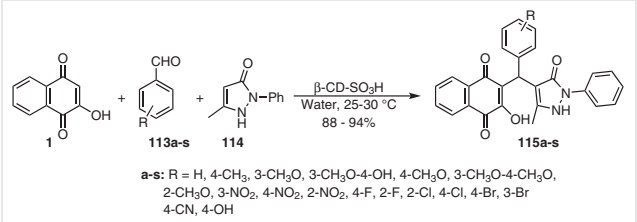
In recent decades, there has been a growing interest in the synthesis of complex biologically active scaffolds using one-pot multicomponent reactions (MCRs). To enhance the synthetic efficiency of such protocols, there has been a focus on utilizing green solvents and effective heterogeneous



Scheme 35 Pyrimidine-fused tetrahydropyridine derivatives **112a–j**

catalysts. Benzylpyrazolyl naphthoquinone derivatives hold significant importance as they are found in numerous natural products including atovaquone, lapachol, parvaquone, and buparvaquone.[64] These derivatives have demonstrated diverse biological activities such as antibacterial, anti-HIV, antiviral, anticoagulant, antioxidant, and anticancer properties.[65]

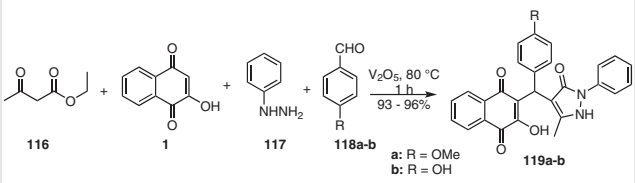
Patil et al.[66] presented a green and cost-effective method for synthesizing benzylpyrazolyl naphthoquinone in water at room temperature, utilizing β-CD-SO_3H as a catalyst. This protocol demonstrates environmental friendliness by employing a heterogeneous and reusable catalyst in a green reaction medium. The methodology offers numerous advantages, including excellent product yield, short reaction time at room temperature, simple workup procedure, and the elimination of column chromatographic separation. The significance of pyrazolyl derivatives lies in their presence as a crucial component in many biologically active compounds. To synthesize dihydro-1*H*-pyrazolyl naphthalene-1,4-dione derivatives **115a–s**, a mixture containing 3-methyl-1-phenyl-1*H*-pyrazol-5-ol **114** (1 mmol), substituted aldehyde **113a–s** (1 mmol), and 2-hydroxy naphthoquinone **1** (1 mmol) in water (5 mL), along with 10 mol% β-CD-SO_3H catalyst, was stirred at room temperature (Scheme 36).[66]



Scheme 36 Synthesis of dihydro-1*H*-pyrazolyl naphthalene-1,4-dione derivatives **115a–s**

Vairaperumal and co-workers[67] developed a synthetic route for the production of a series of potential cytotoxic agents **119a–b** that incorporate a pyrazolyl naphthoquinone framework. The synthesis involves the one-pot, four-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**),

ethyl acetoacetate (**116**), phenylhydrazine (**117**), and aromatic aldehydes **118a–b**. Different catalysts, including metal triflates, Lewis acids, and metal oxides, were evaluated for their effectiveness in this multicomponent reaction. While metal triflates demonstrated good catalytic activity, their high cost, sensitivity to moisture, and non-recyclability posed challenges. Consequently, the researchers sought alternative catalysts, and V_2O_5 emerged as a suitable candidate. V_2O_5 offers advantages such as abundance, affordability, and ease of handling (Scheme 37).[67]



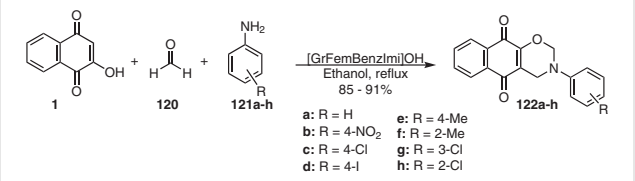
Scheme 37 Benzylpyrazolyl naphthoquinone derivatives **119a–b**

2.35 3,4-Dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione Derivatives

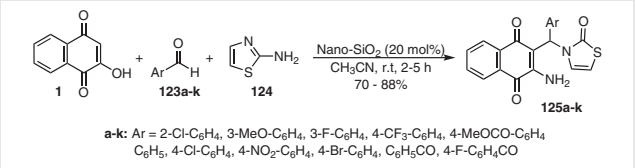
[GrFemBenzImi]OH was employed as a highly effective heterogeneous catalyst in the synthesis of bioactive 3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones **122a–h** through the reaction of 2-hydroxy-1,4-naphthoquinone (**1**) and formaldehyde (**120**) with various aromatic anilines **121a–h** (Scheme 38). To synthesize a graphene oxide-supported ionic liquid phase catalyst ([GrFemBenzImi]OH), Gajare et al.[68] followed a two-step process. First, covalent grafting of 1-*N*-ferrocenylmethyl benzimidazole into the functionalized matrix of graphene oxide was performed, followed by an anion metathesis reaction. The resulting catalyst was characterized using various analytical techniques, including Fourier transform infrared (FT-IR), Fourier transform Raman (FT-Raman), CP-MAS ^{13}C NMR spectroscopy, thermogravimetric analysis (TGA), transmission electron microscopy (TEM), X-ray diffraction (XRD), energy-dispersive X-ray (EDX) analysis, and Brunauer–Emmett–Teller (BET) surface area measurements.[68]

2.36 2-Amino-3-(2-oxothiazolmethyl)-Substituted 1,4-Naphthoquinone Derivatives

Farahani et al.[69] utilized silica-based materials to develop an environmentally friendly approach for the synthesis of potentially biologically active molecular scaffolds. They employed a one-pot, three-component reaction involving 2-hydroxy-1,4-naphthoquinone (**1**), 2-aminothiazole (**124**), and aromatic aldehydes **123a–k**, facilitated by nano-SiO_2 (20% mol) as a Lewis acid and heterogeneous nanocatalyst in acetonitrile at room temperature. This reaction led to the synthesis of a series of 2-amino-3-(2-oxothiazolmethyl)-substituted 1,4-naphthoquinone compounds **125a–k** with reaction times ranging from 2 to 5 hours. The structures of the synthesized molecules were determined using spectroscopic techniques (Scheme 39).[69]



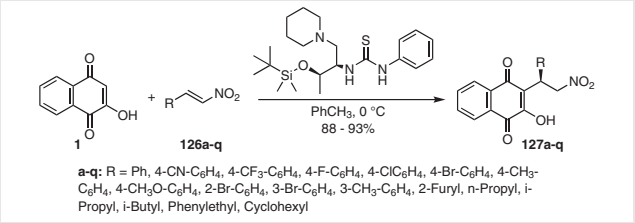
Scheme 38 3,4-Dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones derivatives **122a–h**



Scheme 39 2-Amino-3-(2-oxothiazolmethyl)-substituted 1,4-naphthoquinone derivatives **125a–k**

2.37 Chiral Nitroalkylated Naphthoquinone Derivatives

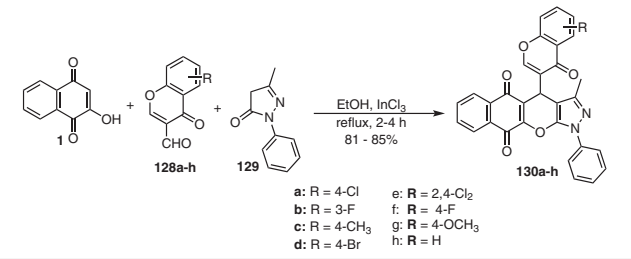
Threonine-based thiourea catalysts were developed by Zheng et al. by modifying the chiral framework of L-threonine. They successfully synthesized chiral nitroalkylated naphthoquinone derivatives **127a–q** through reactions involving 2-hydroxy-1,4-naphthoquinone (**1**), nitroalkenes **126a–q**, and toluene. The reactions were carried out with a low catalyst loading, resulting in high yields (up to 93%) and excellent enantioselectivities (up to 99% ee). By modifying the chiral scaffold of L-threonine, a series of thiourea derivatives were developed and tested for their enantioselective efficiency in the catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes. This reaction yielded chiral nitroalkylated naphthoquinone derivatives with high yields (up to 93%) and enantioselectivities (up to 99% ee) using a low catalyst loading of 3 mol% (Scheme 40).[70]



Scheme 40 Chiral nitroalkylated naphthoquinone derivatives **127a–q**

2.38 Quinone-Based Chromenopyrazole Derivatives

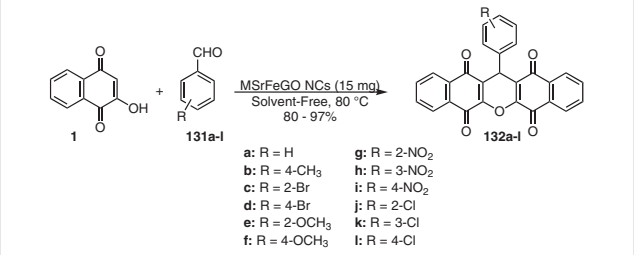
Kandhasamy and co-workers[71] developed a novel approach aimed at combining naphthoquinone, chromene, and pyrazolone to create chromenopyrazole derivatives **130a–h** based on a highly active heterocyclic moiety, with potential therapeutic applications. In this study, the authors focused on the synthesis and fabrication of a unique scaffold composed of quinone-based chromenopyrazole (QCP) loaded onto silk fibroin (SF) electrospun nanofibers for use in tissue engineering. To achieve this, the researchers employed a one-pot, three-component coupling reaction involving 2-hydroxy-1,4-naphthoquinone (**1**), chromene-3-carbaldehyde **128a–h**, and phenyl-3-methylpyrazol-5-one (**129**). Ethanol was used as the solvent, and $InCl_3$ served as the catalyst. Remarkably, the reaction was completed within 3–4 hours, and the pure synthetic products were easily isolated through filtration, followed by ethanol washing and drying. The synthesized compounds were thoroughly characterized using various techniques, including ^1H and ^{13}C NMR spectroscopy, Fourier-transform infrared (FT-IR) spectroscopy, and electrospray ionization mass spectrometry (ESI-MS) (Scheme 41).[71]



Scheme 41 Quinone-based chromenopyrazole derivatives **130a–h**

2.39 13-Aryl-5*H*-dibenzo[*b*,*i*]xanthenes-5,7,12,14-(13*H*)-tetraone Derivatives

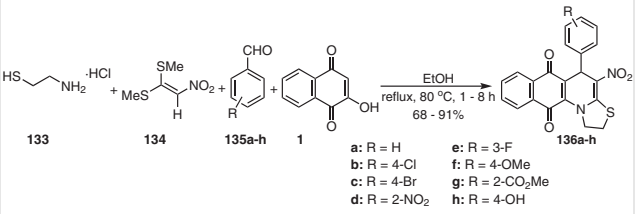
Mousavi et al.[72] developed a highly efficient and cost-effective approach using graphene oxide/strontium nanocatalyst for a pseudo-three-component, one-pot cyclocondensation reaction. This reaction involved the combination of aromatic aldehydes **131a–l** and lawsone (**1**) to produce the corresponding 13-aryl-5*H*-dibenzo[*b*,*i*]xanthenes-5,7,12,14(13*H*)-tetraones **132a–l** under solvent-free conditions (Scheme 42). One of the notable features of this study was the recyclability of the nanocatalyst, which was easily separated from the reaction mixture using an external magnet and reused for up to six cycles without any notable decrease in catalytic activity. The use of this catalyst offered several advantages, including high product yields, fast reaction times, simple experimental setup, the ability to recycle the catalyst, and tolerance towards various functional groups. These aspects not only benefit the environment but also contribute to the economic feasibility of the process.[72]



Scheme 42 13-Aryl-5*H*-dibenzo[*b*,*i*]xanthenes-5,7,12,14(13*H*)-tetraone derivatives **132a–l**

2.40 Benzo[*g*]thiazolo[3,2-*a*]quinolone Derivatives

Bayat et al.[73] presented an efficient one-pot synthesis method for the production of chemoselective derivatives of 4-nitro-5-phenyl-1,2-dihydro-5*H*-benzo[*g*]thiazolo[3,2-*a*]quinoline-6,11-dione **136a–h**. This synthesis involved the reaction of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **135a–h**, and the condensation of the enamine analog of β-nitrothiazolidine **134** in ethanol (Scheme 43). Ethanol was chosen as the solvent due to its environmentally benign nature and low cost, as well as its miscibility with water. The β-nitrothiazolidine used in the reaction was derived from the addition of cysteamine hydrochloride to 1,1-bis(methylthio)-2-nitroethene. To assess the cytotoxic effects of the synthesized products, an in-vitro analysis was also performed to assess their impact on lung, breast, and prostate cancer cells.[73]

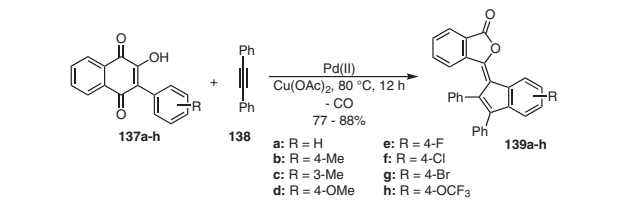


Scheme 43 Benzo[*g*]thiazolo[3,2-*a*]quinolone derivatives **136a–h**

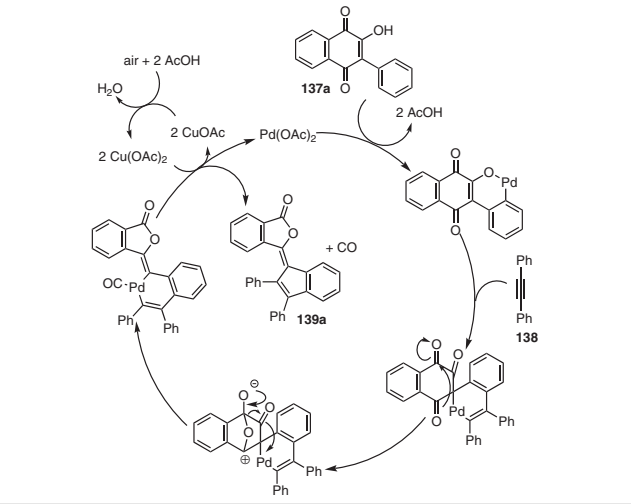
2.41 Alkyne Insertion on 2-Hydroxy-1,4-naphthaquinone

Borthakur et al. introduced a novel approach involving a Pd(II)-catalyzed decarbonylative alkyne insertion reaction for six-membered ring compounds. Annulation reaction between 2-hydroxy-1,4-naphthoquinones derivative **137a–h** and disubstituted alkynes **138** led to the formation of alkylidene phthalides **139a–h** in good yields; these products serve as crucial intermediates in the synthesis of biologically significant compounds (Scheme 44). This reaction en-

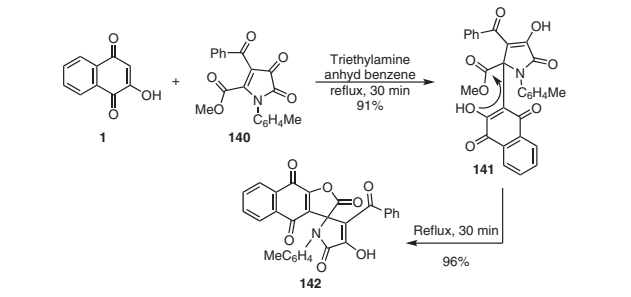
compasses multiple steps, including C–H/C–C activation, alkyne insertion, intramolecular cyclization, and decarbonylation (Scheme 45).[74]



Scheme 44 Alkyne insertion on 2-hydroxy-1,4-naphthaquinone **139a–h**



Scheme 45 Probable mechanism



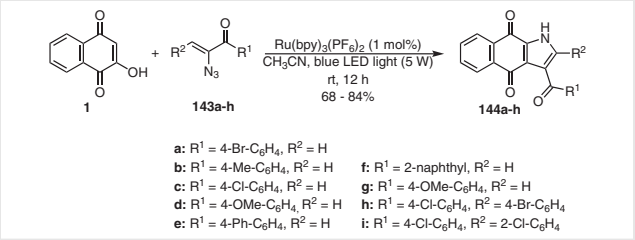
Scheme 46 3′-Benzoyl-4′-hydroxy-1′-(4-methylphenyl)-2*H*-spiro[naphtho[2,3-*b*]-furan-3,2′-pyrrole]-2,4,5′,9(1′*H*)-tetraone derivative **142**

2.42 3′-Benzoyl-4′-hydroxy-1′-(4-methylphenyl)-2*H*-spiro[naphtho[2,3-*b*]-furan-3,2′-pyrrole]-2,4,5′,9(1′*H*)-tetraone Derivatives

Dubovtsev et al.[75] successfully carried out a study in which methyl 3-benzoyl-1-(4-methylphenyl)-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylate (**140**) was reacted with 2-hydroxy-1,4-naphthoquinone (**1**). This reaction resulted in the formation of 3′-benzoyl-4′-hydroxy-1′-(4-methylphenyl)-2*H*-spiro[naphtho[2,3-*b*]furan-3,2′-pyrrole]-2,4,5′,9(1′*H*)-tetraone (**142**). During this spiro heterocyclization process, an intermediate product known as the Michael adduct, specifically methyl 3-benzoyl-4-hydroxy-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(4-methylphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (**141**), was isolated for the first time (Scheme 46).[75]

2.43 2,3-Fused Pyrrole Derivatives

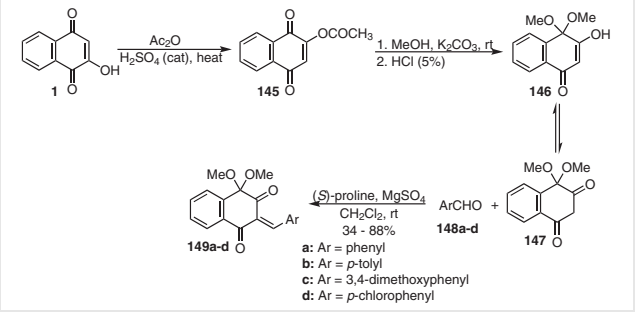
Borra et al.[76] successfully synthesized 2,3-fused pyrroles **144a–h** through the coupling of α-azidochalcones **143a–h** with 2-hydroxy-1,4-naphthoquinone (**1**), employing $Ru(bpy)_3$–$(PF_6)_2$ as a photocatalyst under blue LED light irradiation. This synthetic process involves the photosensitized breakdown of α-azidochalcones, leading to the formation of highly reactive 2*H*-azirines. These reactive intermediates are subsequently captured by 2-hydroxy-1,4-naphthoquinone, resulting in the formation of one new C–C bond and two new C–N bonds (Scheme 47).[76]



Scheme 47 2,3-Fused pyrrole derivatives **144a–h**

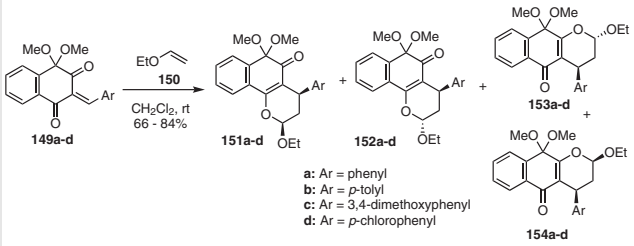
2.44 Hetero-Diels–Alder Reactions of Methylidene Derivatives of Lawsone

Tsanakopoulou et al.[77] conducted a study involving the synthesis, isolation, and utilization of an acetal derivative of lawsone **147** in tandem Knoevenagel/hetero-Diels–Alder reactions catalyzed by (*S*)-proline (Scheme 48). This re-



Scheme 48 Preparation of the starting acetal and stable 2-arylidene-1,3-diones **149a–d**

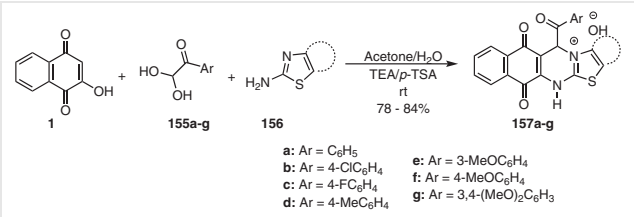
search aimed to explore the reactivity of hydroxyquinones, providing new insights and perspectives. The in-situ formation of intermediate alkylidene-1,3-diones **149a–d**, derived from lawsone (**1**), underwent reactions with electron-rich alkenes **150**. This resulted in the predominantly high-yield formation of pyrano-1,2-naphthoquinone (β-lapachone) derivatives, as well as the isomeric pyrano-1,4-naphthoquinone (α-lapachone) derivatives **151–154(a–d)** (Scheme 49).[77]



Scheme 49 Reactions of the in situ generated alkylidene-1,3-diones **149a–d** with alkyl vinyl ethers **150**

2.45 Benzo[g]thiazolo[2,3-*b*]quinazolin-4-ium and Benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazolin-14-ium Hydroxide Derivatives

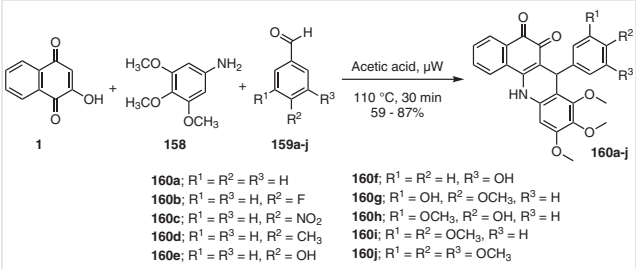
Nouri et al.[78] developed a novel series of benzo[g]thiazolo[2,3-*b*]quinazolin-4-ium and benzo[g]benzo[4,5]thiazolo[2,3-*b*]quinazolin-14-ium hydroxide derivatives **157a–g**. These derivatives were synthesized through a one-pot, three-component reaction involving aryl glyoxal monohydrates **155a–g**, 2-hydroxy-1,4-naphthoquinone (**1**), and 2-aminothiazole **156**. The reaction took place in the presence of triethylamine and *p*-toluenesulfonic acid, which served as organocatalysts, in a mixture of water and acetone (2:1) at room temperature (Scheme 50). This synthetic approach offers several advantages. Firstly, it provides mild reaction conditions, ensuring that the reaction proceeds under relatively gentle circumstances. Additionally, the method yields excellent product yields, indicating the efficiency of the reaction. The workup process is also simple and straightforward. Moreover, the starting materials and catalysts used in the reaction are readily accessible, contributing to the convenience and accessibility of the method.[78]



Scheme 50 Benzo[*g*]thiazolo[2,3-*b*]quinazolin-4-ium and benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazolin-14-ium hydroxide derivatives **157a–g**

2.46 Benzo[*c*]acridine-dione Derivatives

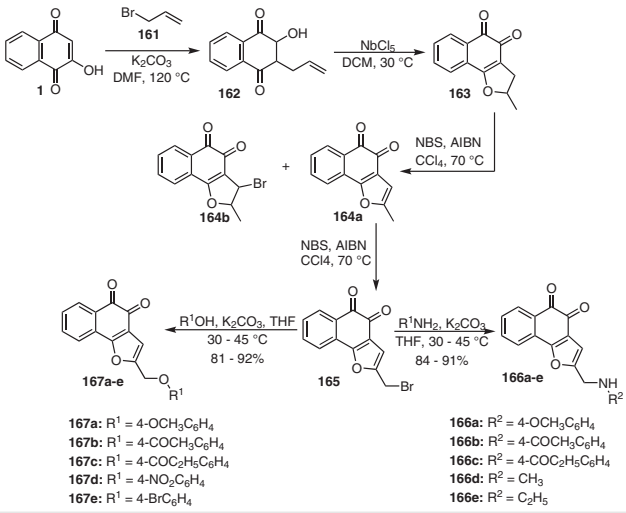
Behbahani et al.[79] undertook the synthesis of a novel series of benzo[*c*]acridine-diones that incorporate pharmacophoric elements found in anti-tubulin compounds. These compounds were designed and synthesized with a central dihydropyridine bridge, aiming to develop potential anticancer agents and tubulin polymerization inhibitors. The synthesis process involved the reaction of 2-hydroxy-1,4-naphthoquinone (**1**), 3,4,5-trimethoxyaniline (**158**), and substituted benzaldehydes **159a–j** in the presence of acetic acid under microwave irradiation. The reaction mixture was stirred until completion, resulting in the formation of the desired benzo[*c*]acridine-dione derivatives **160a–j** (Scheme 51).[79]



Scheme 51 Benzo[*c*]acridine-dione derivatives **160a–j**

2.47 Naphtho[1,2-*b*]furan-4,5-diones

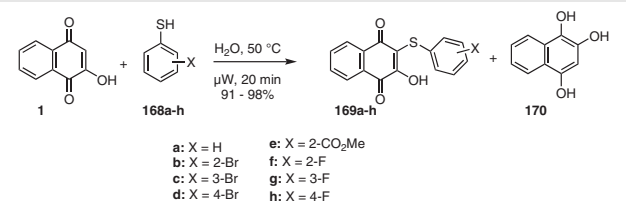
Li et al.[80] conducted a study involving the synthesis of two substituted naphtho[1,2-*b*]furan-4,5-diones (**166a–e** and **167a–e**) derived from lawsone (**1**). The synthesis involved the treatment of lawsone (**1**) with allyl bromide (**161**), followed by a subsequent Claisen rearrangement to yield 2-allyl-3-hydroxynaphthene-1,4-dione (**162**). This intermediate was further cyclized to obtain *ortho*-quinone **163** using Lewis acid $NbCl_5$ at room temperature. The *ortho*-quinone **163** was then subjected to a reaction with N-bromosuccinimide (NBS) and 2,20-azobis(2-methylpropionitrile) (AIBN), resulting in its conversion into 2-(bromomethyl)naphtha[1,2-*b*]furan-4,5-dione **165** through a bis-radical reaction. The brominated intermediate **165** was subsequently reacted with substituted phenol or amine to yield the desired *ortho*-quinone derivatives **166a–e** and **167a–e** (Scheme 52). The structures of these derivatives were characterized using ^{1}H NMR, ^{13}C NMR spectroscopy, and high-resolution mass spectrometry (HRMS). The cytotoxicity activities of the synthetic derivatives were investigated against human leukemia cells K562, prostate cancer cells PC3, and melanoma cells WM9. The results of the study were used to evaluate the potential of these *ortho*-quinone derivatives as cytotoxic agents against these specific cancer cell lines.[80]



Scheme 52 Naphtho[1,2-*b*]furan-4,5-dione derivatives **167a–e**

2.48 Thio-Derivatives of 2-Hydroxy-1,4-naphthoquinone

In a recent study conducted by Monroy-Cardenas et al.,[81] a novel series of thio-derivatives **169a–h** of 2-hydroxy-1,4-naphthoquinone (**1**) was synthesized using microwave irradiation in an aqueous medium (Scheme 53). The objective of this synthesis was to enhance the antiplatelet activity of 2-hydroxy-1,4-naphthoquinone derivatives. Furthermore, the position and nature of the substituent on the phenyl ring played a pivotal role in determining the observed biological activity. This research highlights the potential of modifying lawsone to generate thio-derivatives **168a–h** with improved antiplatelet properties. By exploring the structural variations and their impact on biological activity, the study provided valuable insights for further development and optimization of lawsone-based compounds with enhanced therapeutic potential. Overall, lawsone's versatility as a starting material opens up promising avenues for synthesizing biologically active compounds, while investigations into its structure–activity relationship pave the way for the design and development of novel agents with targeted effects against specific diseases and pathogens.[81]

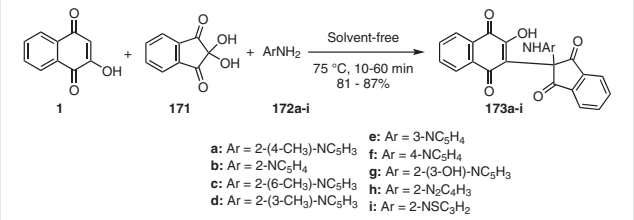


Scheme 53 Thio-derivatives of 2-hydroxy-1,4-naphthoquinone derivatives **169a–h**

2.49 Aminonaphthoquinone Derivatives

Aminonaphthoquinone Mannich bases, specifically 3-(aminomethyl)-2-hydroxy-1,4-naphthoquinones, constitute an intriguing class of compounds. These compounds, along with their metal complexes, have shown diverse biological properties such as antimalarial, leishmanicidal, antibacterial, anticancer, antifungal, antimolluscicidal, cholinesterase inhibitory, antiparasitic, and antiviral activities. Researchers have primarily focused on the synthesis of aminonaphthoquinone derivatives.

In a recent study, Olyaei et al.[82] employed a convenient one-pot, three-component condensation method to synthesize aminonaphthoquinone derivatives **173a–i**. The reaction involved the catalyst and solvent-free condensation of 2-hydroxy-1,4-naphthoquinone (**1**), ninhydrin (**171**), and heteroaryl amines **172a–i** at 75 °C. The imines, formed in situ as intermediates from the addition of 2-hydroxynaphthalene-1,4-dione to the imine, followed by the condensation reaction of ninhydrin with heteroaryl amines, yielded the desired products. This synthetic approach offers advantages such as shorter reaction times, simplicity, clean reactions, environmentally friendly conditions, simple workup procedures, high yields, and easy purification of products using non-chromatographic methods (Scheme 54).[82]

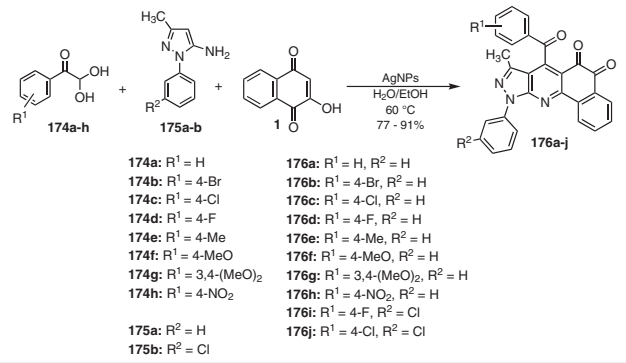


Scheme 54 Amino naphthoquinones derivatives **173a–i**

2.50 Benzo[*g*]pyrazolo[3,4-*b*]quinoline Derivatives

Pyrazoloquinoline derivatives have garnered significant attention due to their pharmaceutical and biological properties. Researchers have developed innovative nanocatalysts and durable multicomponent reactions (MCRs), which have transformed this approach into a noteworthy tool. The most notable features of nanocatalysts include high catalytic activity, stability, reusability, selectivity, and adherence to green chemistry principles. Among them, noble metal nanocatalysts, such as silver nanoparticles (AgNPs), have been extensively investigated due to their superior physicochemical, environmentally benign, biological properties, and low cost. Further, following a similar approach, Khalafy et al.[83] synthesized benzo[*g*]pyrazolo[3,4-*b*]quinolines **176a–j** using AgNPs as a high-performance nanocatalyst in a one-pot, three-component reaction of aryl glyoxal monohydrates **174a–h**, 5-amino-1-aryl-3-methylpyrazoles **175a–b**, and 2-hydroxy-1,4-naphthoquinone (**1**) in H_2O/EtOH at 60 °C (Scheme 55). The structures of ben-

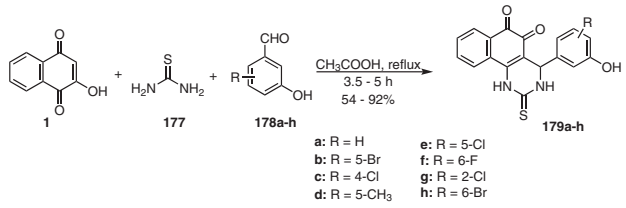
zo[g]pyrazolo[3,4-*b*]quinolines were confirmed using Fourier transform infrared, ^{1}H, and ^{13}C NMR spectral data and microanalysis.[83]



Scheme 55 Benzo[*g*]pyrazolo[3,4-*b*]quinolines derivative **176a–j**

2.51 β-Lapachone–Monastrol Hybrids

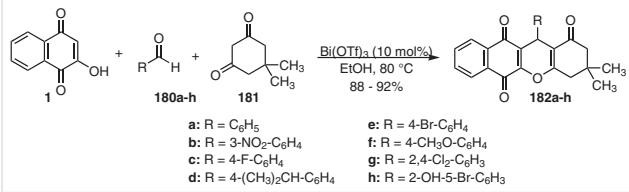
Wu et al.[84] synthesized a novel series of β-lapachone analogs **179a–h** by incorporating the tetrahydropyrimidinethione moiety of monastrol in place of the pyran ring. The hybrid molecules were conveniently prepared via a multicomponent reaction involving the condensation of 2-hydroxy-1,4-naphthoquinone (**1**), thiourea (**177**), and 3-hydroxybenzaldehydes **178a–h**. This strategy presents a promising approach for the development of new β-lapachone derivatives with potential biological activities (Scheme 56).[84]



Scheme 56 β-Lapachone-monastrol hybrids **179a–h**

2.52 3,4-Dihydro-12-aryl-1*H*-benzo[*b*]xanthene-1,6,11-(2*H*,12*H*)trione

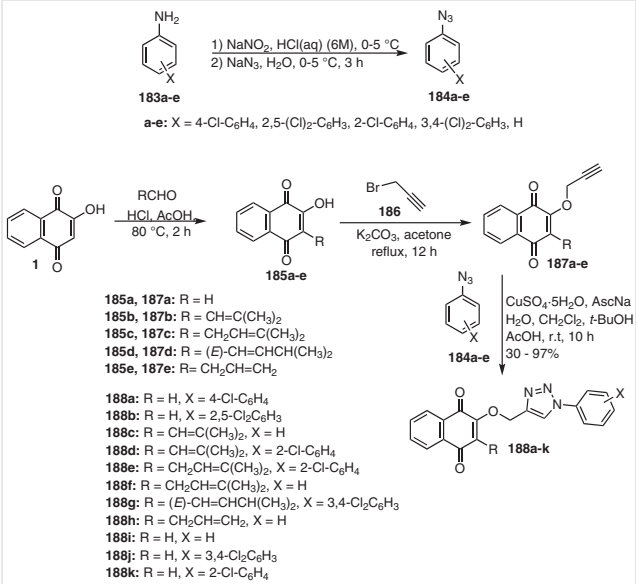
In their study, Turhan et al.[85] synthesized 3,4-dihydro-12-aryl-1*H*-benzo[*b*]xanthene-1,6,11-(2*H*,12*H*)trione compounds **182a–h** using a one-pot condensation reaction of various substituted aromatic aldehydes **180a–h**, 2-hydroxy-1,4-naphthoquinone (**1**), and dimedone (**181**) in the presence of a green and reusable catalyst, $Bi(OTf)_3$.The novel substituted benzo[*b*]xanthenes were characterized using various spectroscopic methods, and their inhibitory actions against butyrylcholinesterase (BChE), acetylcholinesterase (AChE), and glutathione S-transferase (GST) were investigated. The one-pot method was utilized for the synthesis of benzoxanthene compounds to promote green chemistry, using ethanol as a solvent and recycled $Bi(OTf)_3$ (Scheme 57).[85]



Scheme 57 3,4-Dihydro-12-aryl-1*H*-benzo[*b*]xanthene-1,6,11-(2*H*,12*H*)trione derivatives **182a–h**

2.53 1,4-Naphthoquinones Tethered to 1,2,3-1*H*-Triazoles

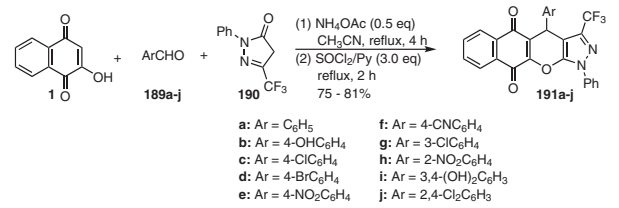
Chipoline et al.[86] synthesized 1,4-naphthoquinones tethered to 1,2,3-1*H*-triazoles **188a–k** using a sequence of reactions that involved C-3 alkylation by Knoevenagel condensation or [3.3]-sigmatropic rearrangement. The quinones were treated with propargyl bromide, K_2CO_3, and refluxing acetone to obtain the propargylated quinines **187a–e** in yields ranging from 50 to 84%. In addition, arylazides **184a–e** were prepared from commercial anilines **183a–e** via treatment with sodium nitrite in hydrochloric acid at 0–5 °C followed by aromatic electrophilic substitution with sodium azide. The arylazides were obtained in quantitative yields. The reaction between the arylazides **184a–e** and *O*-propargyl quinones **187a–e** was catalyzed by Cu(I) and produced only the 1,4-disubstituted regioisomer through a Huisgen 1,3-dipolar cycloaddition CuAAC in yields ranging from 30 to 97% (Scheme 58).[86]



Scheme 58 1,4-Naphthoquinones tethered to 1,2,3-1*H*-triazoles derivatives **188a–k**

2.54 Trifluoromethylated Benzo[6,7]chromeno-[2,3-*c*]pyrazoles

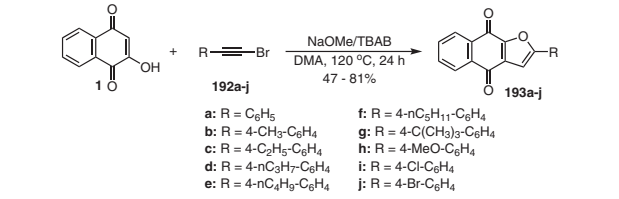
Duan and co-workers[87] successfully synthesized trifluoromethylpyrazolone-tethered trisubstituted methane derivatives **191a–j** with high yields. The synthesis involved a one-pot, three-component reaction using 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **189a–j**, and 1-aryl-3-trifluoromethyl-5-pyrazolone (**190**) in the presence of acetonitrile solvent and NH_4OAc. The authors then combined these derivatives with $SOCl_2$/pyridine as a dehydration agent in acetonitrile to produce appropriate annulated fused polyheterocyclic trifluoromethylated benzo[6,7]chromeno[2,3-*c*]pyrazole-5,10-dione derivatives **191a–j** (Scheme 59).[87]



Scheme 59 Trifluoromethylated benzo[6,7]chromeno[2,3-*c*]pyrazoles derivatives **191a–j**

2.55 Naphthoquinonefuran Derivatives

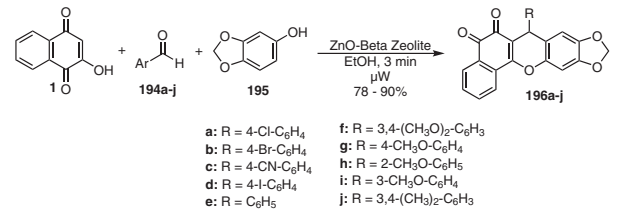
Naphthofuroquinone is a well-known pharmacophoric unit with a broad range of biological activities, including cytotoxic, anti-inflammatory, antitumor, trypanocidal, and antileukemic activity, that is commonly found in natural products and drugs. Due to their wide spectrum of biological activities, there has been significant interest in synthesizing derivatives of naphthofuroquinone. To this end, Li et al.[88] developed a transition-metal-free, tandem one-pot approach for the synthesis of naphthoquinonefuran derivatives **193a–j** using 2-hydroxynaphthoquinones as starting materials. The process involves an intermolecular alkynylation of the sp^2-carbon at the 3-position of 2-hydroxy-1,4-naphthoquinone (**1**) with arylethynyl bromides **192a–j**, followed by a base-promoted intramolecular nucleophilic annulation reaction (Scheme 60). This method is compatible with a wide range of functional groups, and various naphtho[2,3-*b*]furan-4,9-diones can be produced with excellent regioselectivity and good yields.[88]



Scheme 60 Naphthoquinonefuran derivatives **193a–j**

2.56 Benzodioxolo[4,5-*b*]xanthenedione Derivatives

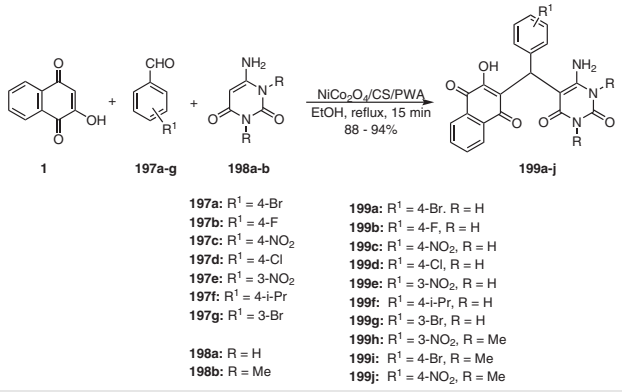
Lambat et al.[89] reported the use of ZnO-β zeolite nanoparticles as a cost-effective and highly effective heterogeneous catalyst for the one-pot multicomponent synthesis of 7-benzodioxolo[4,5-*b*]xanthenedione derivatives **196a–j** under microwave (μW) irradiation using 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehyde **194a–j**, and 3,4-methylenedioxyphenol (**195**) as starting material. The method presents numerous advantages, including fast reactions, simple work-up procedures, excellent product yields of over 90%, and the reuse of the catalyst (Scheme 61).[89]



Scheme 61 Benzodioxolo[4,5-*b*]xanthenedione derivatives **196a–j**

2.57 Pyrimido[4,5-*b*]quinoline-tetraone Derivatives

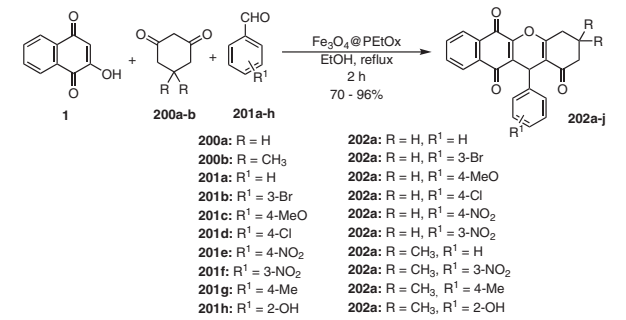
Safari and co-workers[90] successfully carried out a multicomponent reaction under reflux conditions using aromatic aldehydes **197a–g**, 6-aminouracil, or 6-amino-1,3-dimethyluracil **198a–b**, and 2-hydroxy-1,4-naphthoquinone (**1**) with the aid of a magnetic nanocomposite. Specifically, the researchers employed 12-phosphotungstic acid functionalized chitosan@$NiCo_2O_4$ NPs (PWA/CS/$NiCo_2O_4$) as the heterogeneous nanocatalyst to produce pyrimido[4,5-*b*]quinoline-tetraones **199a–j** (Scheme 62). The approach utilized green solvents, offered a simple procedure, gave excellent product yields, involved simple purification methods, and had short reaction times. Moreover, the reaction products were obtained with ease and in good-to-excellent yields without requiring column chromatography.[90]



Scheme 62 Pyrimido[4,5-*b*]quinoline-tetraone derivatives **199a–j**

2.58 Benzo[*b*]xanthene-trione Derivatives

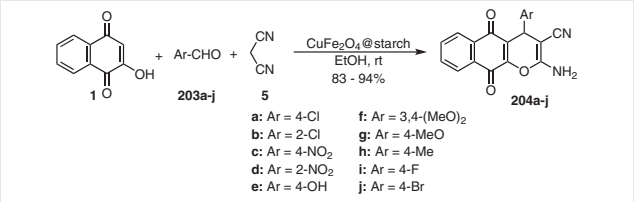
In the study, Rahnamafar et al.[91] developed a one-pot, three- or pseudo-five-component reaction between 2-hydroxy-1,4-naphthoquinone (**1**), aldehyde **201a–h** and dimedone or 1,3-cyclohexanedione **200a–b** to synthesize benzo[*b*]xanthenetrione derivatives **202a–j**. The reaction was conducted under reflux conditions in ethanol by using Fe_3O_4@SiO_2/PEtOx as a nanocatalyst (Scheme 63). This new, heterogeneous, efficient, and recyclable nanocatalyst was generated by immobilizing poly(2-ethyl-2-oxazoline) (PEtOx) on Fe_3O_4 nanoparticles. The nanocatalyst was characterized using various techniques, including scanning electron microscopy (SEM), Fourier transform infrared (FTIR), powder X-ray diffraction (XRD), vibrating-sample magnetometer (VSM), and energy-dispersive X-ray spectroscopy (EDS) analysis. One of the advantages of this catalyst was its ability to be easily separated and recycled several times without significant loss of activity. The reaction used a clean methodology with mild reaction conditions, easy work-up, short reaction time, and gave good-to-excellent yields. Additionally, the preparation of the catalyst was simple, making it a promising approach for the synthesis of benzo[*b*]xanthene-trione derivatives.[91]



Scheme 63 Benzo[*b*]xanthene-trione derivatives **202a–j**

2.59 4*H*-Pyran Derivatives

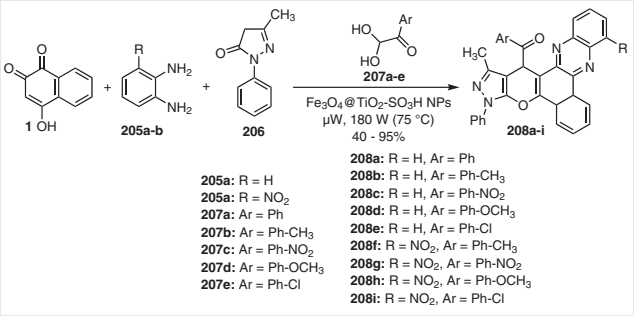
Kamalzare et al.[92] reported the synthesis of a novel, green, heterogeneous bio-nanocatalyst from natural, inexpensive and readily available materials. This catalyst exhibits distinctive properties such as environmental compatibility and low-cost, and is highly efficient for the synthesis of 4*H*-pyran derivatives **204a–j**. The synthesis of 4*H*-pyran derivatives was achieved through the mixing of aryl aldehyde **203a–j**, enolizable C–H activated acidic compounds (2-hydroxy-1,4-naphthaquinone; **1**), and malononitrile (**5**) in the presence of $CuFe_2O_4$@starch as a catalyst in ethanol solvent. The reaction was stirred for an appropriate amount of time at room temperature (Scheme 64). The green heterogeneous bio-nanocatalyst is composed of natural materials, which provides a more sustainable and eco-friendly approach to the synthesis of 4*H*-pyran derivatives. The use of this catalyst offers advantages such as low cost, good availability, and high efficiency. Furthermore, ethanol was used as the solvent of the reaction, providing an additional eco-friendly benefit to the synthesis. The $CuFe_2O_4$@starch catalyst was found to exhibit excellent catalytic activity and could be reused for subsequent reactions without significant loss of activity. The synthesis conditions were mild and required no additional harmful catalysts, which is a further benefit in terms of the safety and environmental impact of the reaction.[92]



Scheme 64 2-Amino-5,10-dihydro-5,10-dioxo-4*H*-benzo[*g*]chromene-3-carbonitrile derivatives **204a–j**

2.60 Pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazin-15-yl Methanone Derivatives

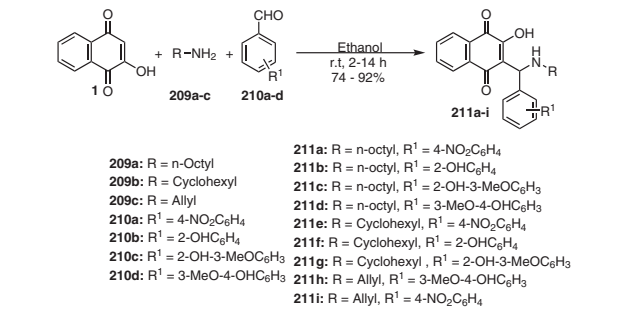
A novel method for synthesizing the four-component pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazin-15-yl methanone **208a–i** was developed by Taheri et al.[93] The reaction involved the use of 2-hydroxy-1,4-naphthaquinone (**1**), benzene-1,2-diamine **205a–b**, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**206**), and arylglyoxals **207a–e**, followed by the addition of Fe_3O_4@TiO_2-SO_3H nano-composite catalyst under microwave conditions and in a solvent-free environment at 180 W (Scheme 65). One notable advantage of using this catalyst was its ability to be reused in subsequent reaction phases without significant loss of activity. The synthesis process provided several benefits, including mild reaction conditions, a solvent-free environment, no harmful catalysts in the laboratory, low energy consumption, and economical feasibility.[93]



Scheme 65 Pyrazolo[4′,3′:5,6]pyrano[2,3-*c*]phenazin-15-yl methanone derivatives **208a–i**

2.61 Aminonaphthoquinone Derivatives

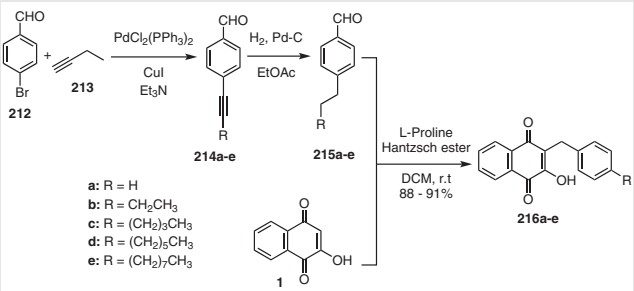
A clean and facile one-pot, three-component protocol was developed by Nariya et al.[94] for the synthesis of a diverse library of derivatives of aminonaphthoquinones **211a–i** using different amines **209a–c**, aromatic aldehydes **210a–d**, and lawsone (**1**), for potential anticancer applications (Scheme 66). The synthesized compounds were characterized using various spectroscopic techniques, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy, mass spectrometry, and elemental analysis. The compounds exhibited moderate-to-good anticancer activity, and their hemocompatibility was established.[94]



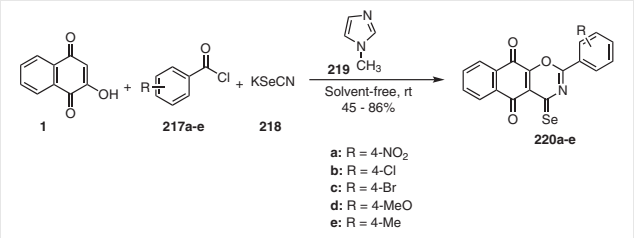
Scheme 66 Aminonaphthoquinone derivatives **211a–i**

2.62 3-Aryl-Substituted Lawsone Derivatives

In their study, Song et al.[95] reported on the synthesis of a lawsone-based compound as an antimicrobial agent against methicillin-resistant *Staphylococcus aureus* (MRSA), which has become increasingly difficult to treat due to multidrug resistance. The authors synthesized a series of lawsone-derived compounds **216a–e** with varying lipophilicity and screened them for minimum inhibitory concentrations against MRSA to identify a potent candidate. The identified compound showed significantly improved drug resistance profiles compared to conventional antibiotics and was validated for therapeutic efficacy using murine models of wound infection and non-lethal systemic infection induced by MRSA. In addition, the synthesis of lawsone derivatives **216a–e** was achieved by incorporating aromatic rings with different lengths of carbon chains into the C3 position of lawsone (**1**) via an organocatalytic three-component reductive alkylation (TCRA) reaction (Scheme 67). The entire series of lawsone derivatives was characterized using ^{1}H NMR spectroscopy, mass spectrometry (MS), and single-crystal X-ray structural analysis to determine their structural properties.[95]



Scheme 67 3-Aryl-substituted lawsone derivatives **216a–e**



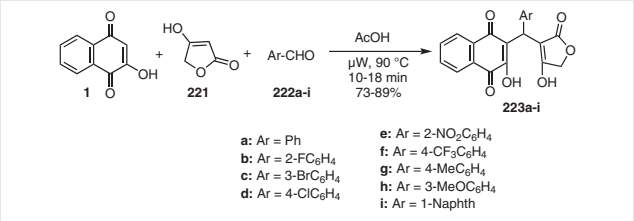
Scheme 68 2-Aryl-4-selenoxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione derivatives **220a–e**

2.63 2-Aryl-4-selenoxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-dione Derivatives

A facile and efficient one-pot method for the synthesis of 2-aryl-4-selenoxo-4*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones **220a–e** was reported by Keykha et al.[96] This method involves the condensation reaction of 2-hydroxy-1,4-naphthoquinone (**1**) and aroyl chlorides **217a–e** with potassium selenocyanate (**218**) in the presence of catalytic amounts of N-methylimidazole (**219**) under solvent-free conditions (Scheme 68). The proposed method offers several benefits such as mild reaction conditions, short reaction time, straightforward experimental setup, and high yields of bioactive compounds.[96]

2.64 3-Arylated 2-Hydroxy-1,4-naphthoquinone Derivatives

In their study, Thi and co-workers[97] efficiently synthesized novel naphthoquinone derivatives **223a–i** using a microwave-assisted three-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**), tetronic acid (**221**), and various aromatic aldehydes **222a–i** in AcOH. The multicomponent domino reaction proceeds through Knoevenagel condensa-

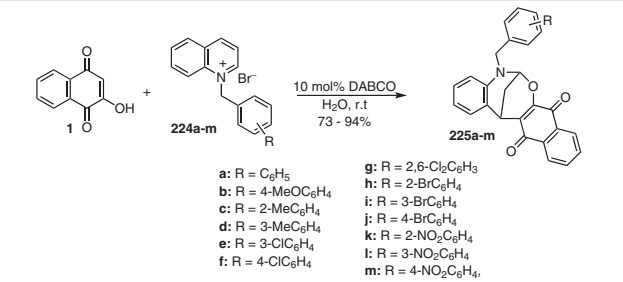


Scheme 69 3-Arylated-2-hydroxy-1,4-naphthoquinone derivatives **223a–i**

tion, Michael addition, deprotonation, and 1,3-H shift steps (Scheme 69). The researchers also evaluated the influence of electron-donating and electron-withdrawing substituents on the phenyl moieties on the reaction outcome. The synthesized compounds were tested for their cytotoxic activity against KB and HepG2 cancer cell lines, revealing the potential importance of 3-alkylated 2-hydroxy-1,4-naphthoquinones for the development of anticancer agents.[97]

2.65 Benzo[*d*]naphtho[2,3-*g*][1,3]oxazocine-8,13(6*H*,14*H*)-diones

Privileged N,O-acetal heterobicyclic compounds featuring medium-sized rings have garnered considerable interest in both organic chemistry and biology. These frameworks have been widely observed among diverse natural products that exhibit antiproliferative, antimicrobial, antiallergic, anti-inflammatory, and cytotoxic activity. Oxazocine, in particular, represents one of the most significant N,O-acetal heterobicyclic compounds. The synthesis of functionalized polycyclic naphthooxazocines 225a–m was achieved by Madani Qamsari and co-workers via a tandem reaction between 2-hydroxy-1,4-naphthoquinone (1) and quinolinium salts 224a–m in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) in an aqueous medium (Scheme 70). This method for preparing oxazocine boasts good-to-excellent yields of products, along with an operationally simple procedure. Furthermore, the products are obtained without the need for column chromatography. To minimize the hazards of chemicals and solvents, the reaction was conducted in water, a green solvent. All newly synthesized compounds were subjected to characterization using various methods, including IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.[98]



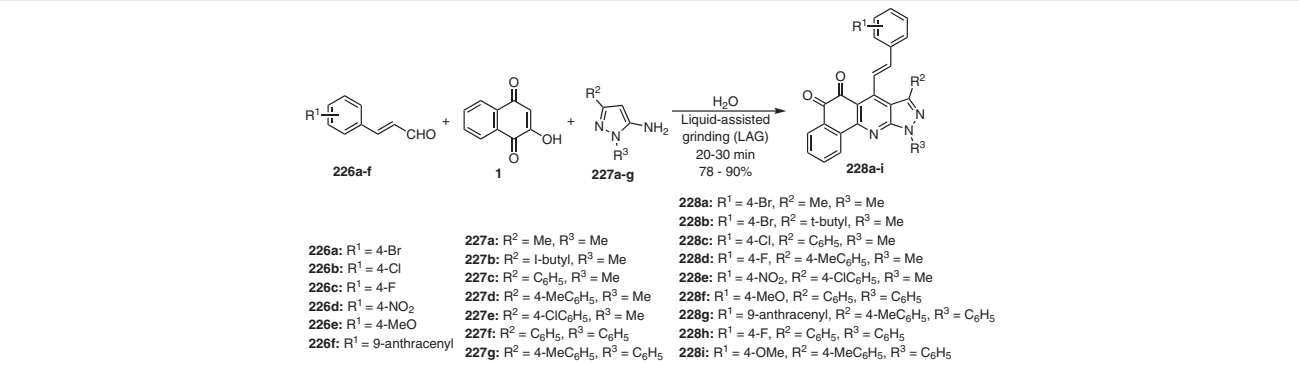
Scheme 70 Benzo[*d*]naphtho[2,3-*g*][1,3]oxazocine-8,13(6*H*,14*H*)-dione derivatives **225a–m**

2.66 Styryl-Linked Benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione Derivatives

Pyrazoles represent a widely researched class of aromatic N-heterocycles with a significant presence in synthetic bioactive scaffolds and natural products, offering an extensive range of bioactivities. Pyrazole-based moieties have been successfully combined with other bioactive molecules such as pyridine and naphthoquinone, resulting in applications with multiple uses. For instance, combining pyrazoles with quinoline may yield compounds with potential antibacterial, antitumor, antifungal, antimicrobial, anticancer, and antiangiogenic activities. Recently, Yadav et al.[99] reported an interesting multicomponent reaction involving unsaturated aldehydes **226a–f**, 2-hydroxy-1,4-naphthoquinone (**1**), and 5-aminopyrazoles **227a–g**. The reaction proceeded by liquid-assisted grinding of the three components for a period of 20–30 minutes in the presence of water, leading to the formation of styryl-linked benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-diones **228a–j** (Scheme 71). The resulting three-component product contains four bioactive moieties, namely 1,2-naphthoquinone, pyridine, pyrazole, and styryl. This methodology has several notable features, including short reaction time, green reaction conditions, good yields, and a simplified purification process.[99]

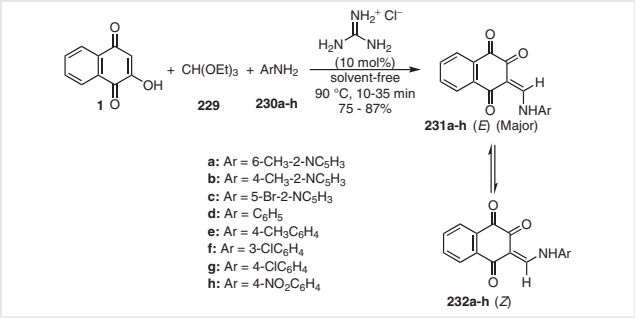
2.67 Lawsone Enaminones Derivatives

Enaminone derivatives are widely used in the synthesis of bioactive compounds and natural products with diverse therapeutic activities such as antitumor, anti-inflammatory, antiepileptic, and antibacterial properties. Olyaei et al.[100]



Scheme 71 Styryl-linked benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(10*H*)-dione derivatives **228a–j**

developed a new method to synthesize enaminone derivatives **231a–h** and **232a–h** using lawsone (**1**), triethyl orthoformate (**229**), and aromatic amines **230a–h** in the presence of guanidinium chloride under solvent-free conditions. The ^{1}H NMR spectra of the resulting lawsone enaminones indicate that they exist in the keto–enamine tautomeric form and undergo *Z*/*E*-isomerization with respect to the C=C bond in DMSO-d_6 at room temperature. This method offers high-to-excellent yields, short reaction times, easy purification of products without chromatographic methods, and a simple work-up procedure (Scheme 72).[100]



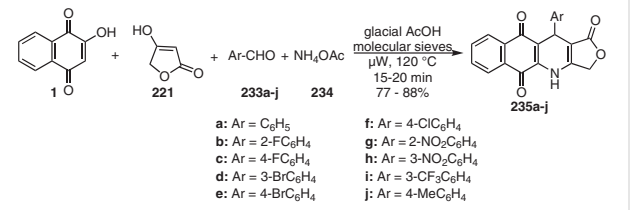
Scheme 72 Lawsone enaminone derivatives **232a–h**

2.68 Dihydrobenzo[*g*]furo[3,4-*b*]quinoline-1,5,10(3*H*)-trione Derivatives

Multicomponent reactions (MCRs) conducted in a single synthetic step are highly efficient and offer a convenient way to access a diverse range of complex compounds while maintaining excellent selectivity and atom economy. Microwave-assisted chemistry is a cutting-edge method that is frequently employed in green chemistry since it can reduce reaction times and boost yields. Thi et al.[101] utilized this approach to synthesize dihydrobenzo[*g*]furo[3,4-*b*]quinoline-1,5,10(3*H*)-triones (podophyllotoxin naphthoquinone) **235a–j** with good yields via a four-component reaction of 2-hydroxy-1,4-naphthoquinone (**1**), aromatic benzaldehydes **233a–j**, tetronic acid (**221**), and ammonium acetate (**234**) (Scheme 73).[101]

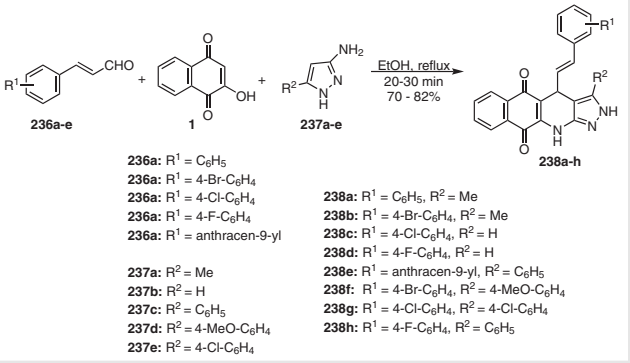
2.69 Styryl-Linked Fused Dihydropyridine Derivatives

Yadav et al.[102] described a simple and rapid method for the synthesis of styryl-linked dihydropyridines fused with naphthoquinone and pyrazole moieties using a catalyst-free three-component reaction. The reaction was carried out in ethanol under reflux conditions and involved the use of 2-hydroxy-1,4-naphthoquinone (**1**), cinnamaldehydes **236a–e**, and 3-aminopyrazoles **237a–e**. A wide range of cinnamaldehyde derivatives and 3-aminopyrazoles were found to be suitable for this reaction, and the products were



Scheme 73 Dihydrobenzo[*g*]furo[3,4-*b*]quinoline-1,5,10(3*H*)-trione derivatives **235a–j**

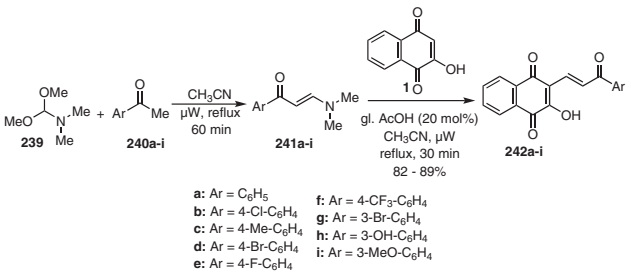
fully characterized using spectroscopic tools (Scheme 74). Single-crystal XRD was used to characterize one of the products. The methodology has notable features such as catalyst-free reaction conditions, short reaction time, good yields of the products, easy purification process, formation of three new bonds (two C–C and one C–N) in one-pot, and products with four different bioactive moieties.[102]



Scheme 74 Multicomponent synthesis of styryl-linked fused dihydropyridines derivatives **238a–h**

2.70 Naphthoquinone Chalcone Hybrid Derivatives

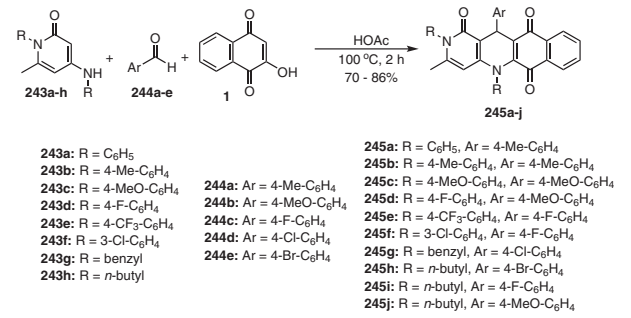
Chalcones are compounds found in nature that consist of an α,β-unsaturated ketone and two aromatic rings. The α,β-unsaturated ketone group in chalcones acts as a Michael acceptor for a variety of biological nucleophiles. Chalcones, whether naturally occurring or synthetic, possess a variety of pharmacological properties due to their small structures and Michael acceptor features. These properties include antibacterial, anticancer, antileishmanial, antifungal, antiviral, antitubercular, and antimalarial activities. Nguyen and co-workers[103] reported a facile and efficient method to synthesize new naphthoquinone-based chalcone hybrids **242a–i** via microwave-assisted one-pot, three-component reaction of 2-hydroxy-1,4-naphthoquinones (**1**), *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA; **239**), and acetophenone derivatives **240a–i**. The synthesis of the naphthoquinone-based chalcone hybrids involved a sequence of steps, including condensation, 1,4-addition, rotation, elimination, and [1,3]-H shift (Scheme 75).[103]



Scheme 75 Naphthoquinone-based chalcone hybrids **242a–i**

2.71 Naphtho[2,3-*b*][1,6]naphthyridine Derivatives Promoted by Acetic Acid

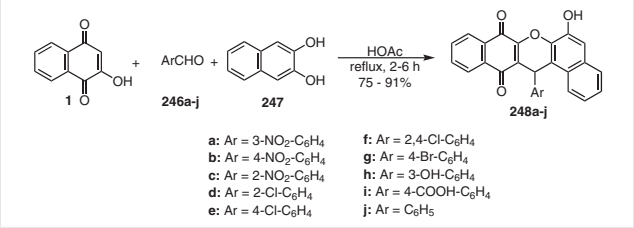
Naphthyridine derivatives have a wide range of applications in various fields such as pharmaceuticals, animal husbandry, industrial lubricants, and analytical chemistry. These compounds have been found in natural alkaloids as bipyridine scaffold molecules with significant chemical and biological importance. 1,6-Naphthyridines are particularly important due to their unique therapeutic and pharmacological properties in organic and biological chemistry. Shen and co-workers[104] synthesized naphtho[2,3-*b*][1,6]naphthyridine derivatives **245a–j**. A three-component domino reaction was employed, which demonstrated excellent substrate scope, including 2-hydroxy-1,4-naphthoquinone (**1**), various enaminones **243a–h**, and aldehydes **244a–e**, and yielded a series of multi-functionalized naphtho[2,3-*b*][1,6]-naphthyridine derivatives **245a–j** with 70–86% yields (Scheme 76). The advantages of this strategy are its bond-forming efficiency, the sole byproduct being water, and the accessibility of starting materials, which provide a valuable means of accessing biological 1,6-naphthyridines.[104]



Scheme 76 Naphtho[2,3-*b*][1,6]naphthyridines derivatives **245a–j**

2.72 6-Hydroxy-14-aryl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-diones

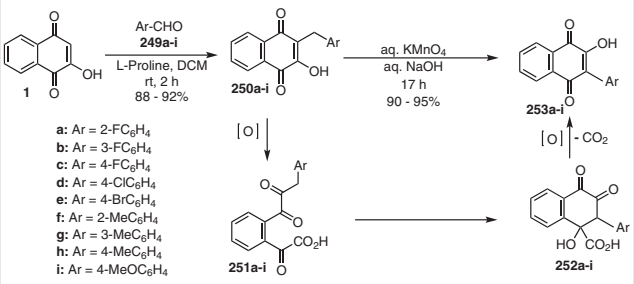
Olyaei and co-workers[105] investigated the synthesis of xanthenes and their derivatives, specifically benzo-fused xanthenes, which have been extensively studied for their diverse range of biological and pharmacological properties, including antibacterial, antiviral, anti-inflammatory, phototoxicity, antitumor, and anti-HIV properties. They utilized a one-pot, three-component condensation reaction in glacial acetic acid under reflux conditions to synthesize novel 6-hydroxy-14-aryl-8*H*-dibenzo[*a*,*i*]xanthene-8,13(14*H*)-dione derivatives **248a–j** by combining 2-hydroxy-1,4-naphthoquinone (**1**), aromatic aldehydes **246a–j**, and 2,3-naphthalenediol (**247**). This reaction involved Knoevenagel condensation, intramolecular cyclization, Michael addition, and dehydration. The reaction offers several benefits, such as operational simplicity, a clean process, easy handling, a simple purification process, high yields of the products, and direct precipitation of the products from the reaction medium, thereby avoiding a tedious workup procedure (Scheme 77).[105]



Scheme 77 6-Hydroxy-14-aryl-8*H*-dibenzo[*a*,*i*] xanthene-8,13(14*H*)-dione derivatives **248a–j**

2.73 Synthesis of Biologically Important 3-Aryl-lawsones

In medicinal chemistry, 3-aryl-lawsones are recognized for their various applications. Krishna and co-workers[106] conducted a study to synthesize different 3-aryl-lawsones **253a–i** with high regioselectivity using simple lawsone (**1**) and aldehydes **249a–i** in a seven-step, double-cascade, one-pot reaction (Scheme 78). This was achieved by combining organocatalytic Ramachary reductive coupling and Hooker oxidation reactions. The work's main attractions include the commercial availability of starting materials, a diverse substrate scope, the possibility of a one- or two-pot approach, regioselectivity of alkyl transfer, and the numerous medicinal applications of 3-aryl-lawsones.[106]



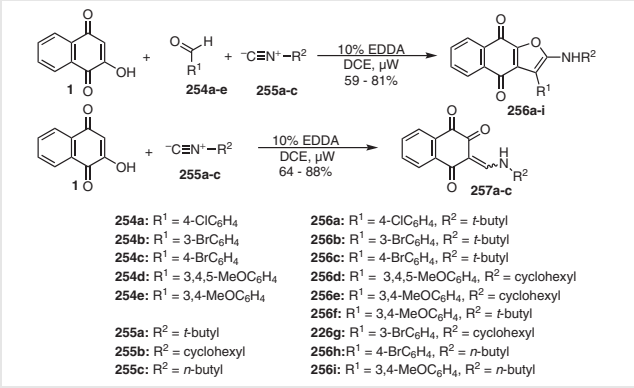
Scheme 78 3-Aryl-lawsone derivatives **253a–i**

2.74 Lawsone in a Three-Component Reaction with Aldehydes and Isocyanides

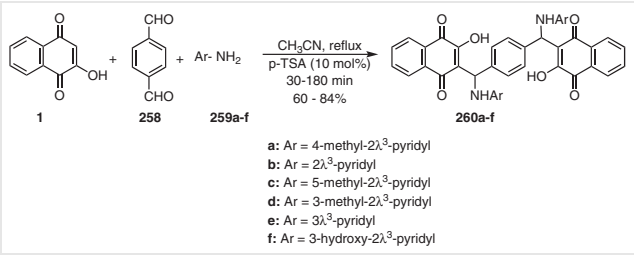
In medicinal chemistry and synthetic chemistry, 2-hydroxy-1,4-naphthoquinone (**1**) is a highly sought-after structure due to the presence of the quinone fragment in numerous natural products with vital biological functions in plants, animals, and humans. Thus, Koumpoura et al.[107] synthesized a range of non-natural molecules containing the quinone scaffold and evaluated their biological activities, including anticancer, antifungal, and antimalarial properties. The first efficient synthetic method for the production of naphthofuroquinones **256a–i** was achieved through a microwave-assisted reaction between lawsone (**1**), various aldehydes **254a–e**, and three isocyanides **255a–c**, yielding derivatives in moderate-to-good yields. Additionally, two naphtho-enaminodione quinines **257a–c** were obtained for the first time by condensing lawsone (**1**) and isocyanides **255a–c** for less-reactive aldehydes (Scheme 79). All synthesized compounds were evaluated for their anti-infectious activities.[107]

2.75 Bis-heteroarylaminomethylnaphthoquinone Derivatives

Olyaei et al.[108] developed a facile and effective one-pot, pseudo-five-component reaction utilizing *p*-TSA as a catalyst in CH_3CN under reflux conditions, to produce a series of bis-heteroarylaminomethylnaphthoquinones **260a–f** Mannich bases. Lawsone (**1**), various heteroaryl amines **259a–f**, and terephthalaldehyde (**258**) were employed as readily available starting materials. This synthetic approach offers several advantages, such as high product yields, easy operation, high atom-economy, simple workup procedure, and the ability to isolate/purify target products without chromatography (Scheme 80).[108]



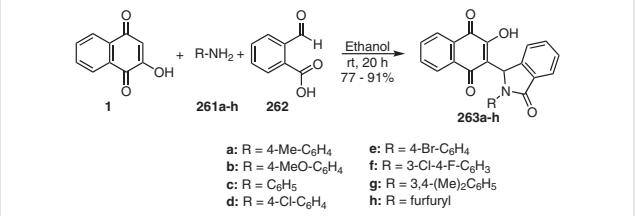
Scheme 79 Synthesis of naphthofuroquinones **256a–i** and **257a–c**



Scheme 80 Bis-heteroarylaminomethylnaphthoquinone derivatives **260a–f**

2.76 Isoindolinone Derivatives

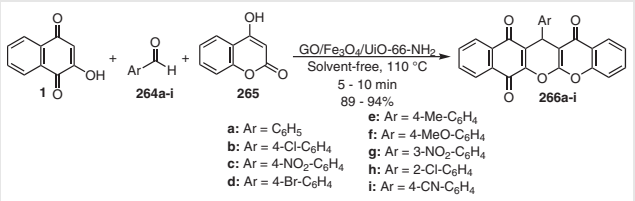
The isoindolinone framework can be found in numerous natural and synthetic compounds, possessing diverse biological activities such as antihypertensive, anti-inflammatory, anesthetic, antiviral, and anticancer properties. Nariya et al.[109] introduced a successful Mannich-type multicomponent reaction strategy to create a range of new substituted isoindolinones **263a–h** derived from 2-hydroxy-1,4-naphthaquinone (**1**), 2-formyl benzoic acid (**262**), and primary amines **261a–h** of various kinds. This metal-free approach directly forms C–N and C–C bonds at room temperature, employing an environmentally friendly solvent. Synthetic isoindolinones were characterized using ^{1}H NMR, ^{13}C NMR, FT-IR, and ESI-MS techniques (Scheme 81).[109]



Scheme 81 Isoindolinones derivatives **263a–h**

2.77 Chromene Derivatives

Basir et al.[110] developed a magnetically recoverable heterogeneous catalyst, $GO/Fe_3O_4/UiO\text{-}66\text{-}NH_2$, which was used to synthesize chromene derivatives **266a–i** via a one-pot, three-component condensation reaction of 2-hydroxy-1,4-naphthaquinone (**1**), 4-hydroxycoumarin (**265**), and aromatic aldehydes **264a–i**. The reaction was carried out at 110 °C in a solvent-free environment, and the new process offered several advantages, such as reduced catalyst loading, excellent yields (88–98%), short reaction times (5–10

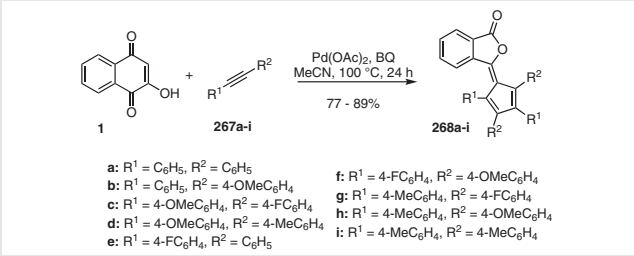


Scheme 82 Chromene derivatives **266a–i**

min), a simple work-up procedure, and straightforward recovery using a standard magnet. The catalyst was characterized using SEM, XRD, EDX, BET, TGA, and FT-IR analyses. Overall, the GO/Fe_3O_4/UiO-66-NH_2 catalyst showed promise for use in other catalytic reactions due to its excellent catalytic activity and magnetic recoverability (Scheme 82).[110]

2.78 Phthalide–fulvene Derivatives

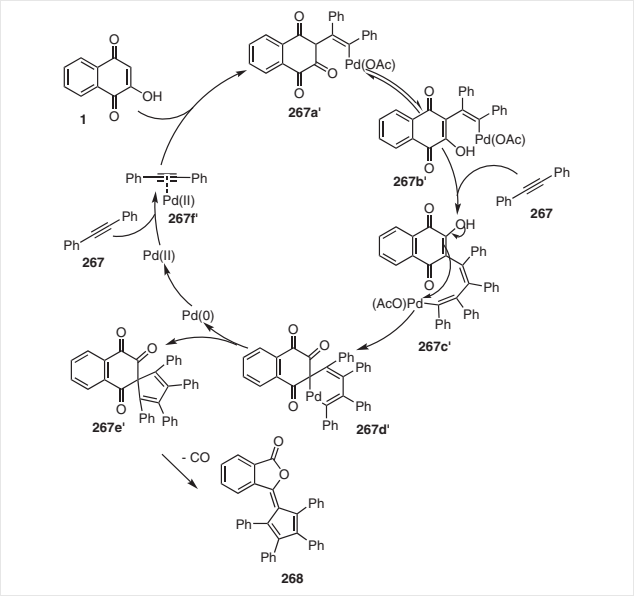
Wang et al.[111] presented a novel approach involving palladium-catalyzed ring-contraction reactions of naphthoquinones with alkynes. This methodology enabled the efficient synthesis of a diverse range of phthalides with excellent yields and regioselectivity. The resulting phthalides serve as valuable intermediates for the synthesis of various other important building blocks. The initial investigation focused on optimizing the reaction conditions using 2-hydroxy-1,4-naphthoquinone (**1**) and diphenylacetylene **267a–i** as model substrates, along with benzoquinone as an oxidant. $Pd(OAc)_2$ was identified as the catalyst of choice, and the addition of 2.0 equivalents of 1,4-benzoquinone (BQ) significantly enhanced the conversion of the reaction. The desired phthalide fulvene derivatives **268a–i** were obtained in good yield from the ring contraction of naphthoquinone (Scheme 83). A plausible mechanism for the ring contraction of six-membered naphthoquinone through various intermediates **267a′–f′** have also been discussed (Scheme 84).[111]



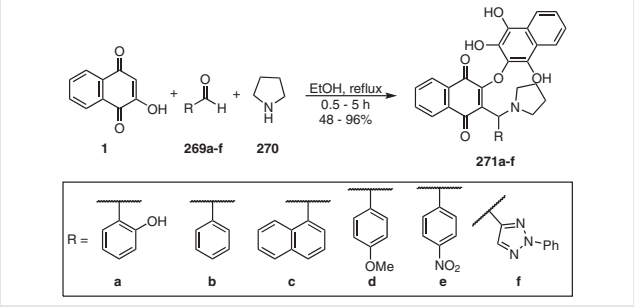
Scheme 83 Phthalide–fulvene derivatives **268a–i**

2.79 Naphthoquinone-Polyphenol Derivatives

Filho et al.[112] developed an innovative, fast, and simple method for the one-step synthesis of naphthoquinone-polyphenols **271a–f** using a multicomponent domino Mannich–Michael reaction with lawsone (**1**). The reaction involved the use of aromatic aldehyde **269a–f** and pyrrolidine (**270**), and yielded good to excellent results (48 to 96% yield). The resulting polyphenols were analyzed by IR and NMR spectroscopy, and mass spectrometry (Scheme 85). Antiproliferative activities of the polyphenols against four cancer cell lines (HCT116, PC3, HL60, and SNB19) were also observed. This method offers a simple and efficient way to synthesize naphthoquinone-polyphenols with potential pharmacological applications.[112]



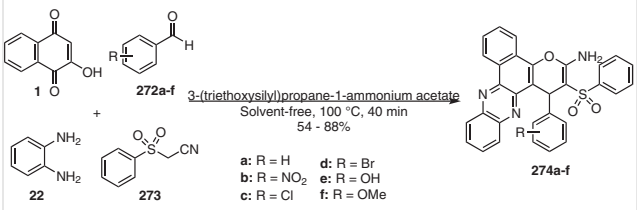
Scheme 84 Plausible mechanism



Scheme 85 Naphthoquinone-polyphenol derivatives **271a–f**

2.80 2-(Phenylsulfonyl)-1*H*-benzo[*a*]pyrano[2,3-*c*]-phenazin-3-amine Derivatives

Shirzaei and co-workers[113] developed an efficient and eco-friendly method for synthesizing 2-(phenylsulfonyl)-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-3-amine derivatives **274a–f**. The method involves a one-pot, four-component condensation reaction of 2-hydroxy-1,4-naphthoquinone (**1**), *o*-phenylenediamine (**22**), aromatic aldehydes **272a–f**, and (phenylsulfonyl)acetonitrile (**273**) in the presence of a novel basic ionic liquid catalyst, $[(EtO)_3Si(CH_2)_3NH_3^+][CH_3COO^-]$, under solvent-free conditions (Scheme 86). The protocol offers several advantages, including simplicity, high yields, short reaction times, and ecological friendliness. Additionally, the catalyst used in the reaction, $[(EtO)_3Si(CH_2)_3NH_3^+][CH_3COO^-]$,can be recovered and reused multiple times without loss of activity. Overall, this method provides a promising route for the synthesis of these important organic compounds while

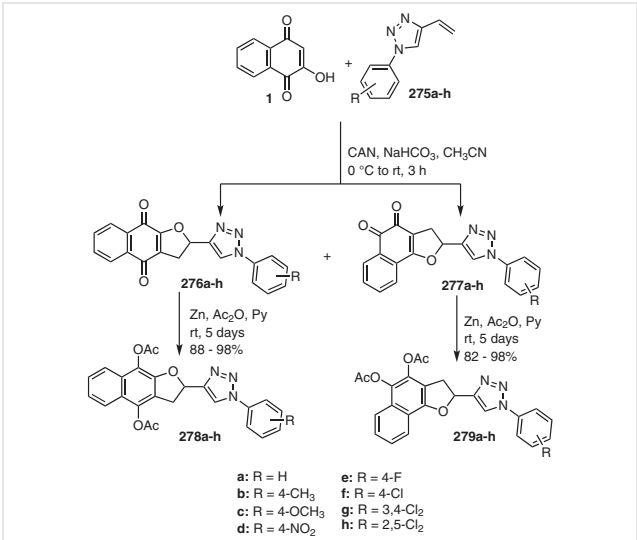


Scheme 86 2-(Phenylsulfonyl)-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-3-amine derivatives **274a–f**

also promoting sustainability and efficiency in the chemical industry.[113]

2.81 Acetylated 1,2,3-Triazole-quinoidic Derivatives

Costa and co-workers[114] utilized an oxidative cycloaddition reaction, promoted by ceric ammonium nitrate (CAN) in an alkaline medium, to obtain 1,2,3-triazole-naphthoquinodoic acetyl derivatives **278a–h** and **279a–h** from lawsone (**1**) and 4-vinyl-1*H*-1,2,3-triazoles **275a–h**. The resulting compounds were then subjected to reductive acetylation of the quinones using excess metallic zinc and acetic anhydride, with yields exceeding 98%. Interestingly, it has been observed that acetylated naphthoquinone derivatives have the potential to act as a prodrug against tumors, making these compounds an attractive target for further investigation in the development of new therapeutic agents (Scheme 87).[114]



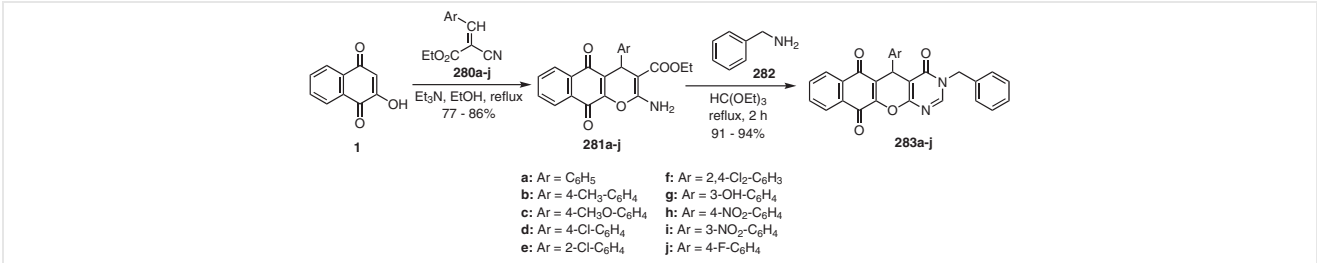
Scheme 87 Acetylated 1,2,3-triazoles-quinoidic derivatives **278a–h** and **279a–h**

2.82 Benzochromenopyrimidine Derivatives

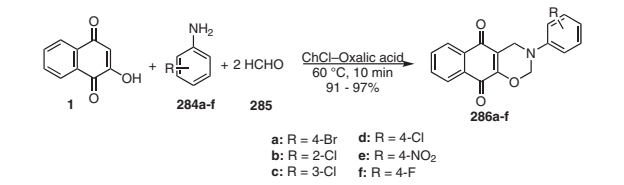
Using a straightforward and cost-effective method, Choura et al.[115] produced 3-benzyl-5-aryl-3,5-dihydro-4*H*-benzo[6,7]chromeno[2,3-*d*]pyrimidin-4,6,11-triones **283a–j** through a one-pot, three-component reaction. The reaction involved readily available 2-hydroxy-1,4-naphthoquinone (**1**) heated at reflux with aryl 2-cyano-3-arylacrylates **280a–j** in the presence of a catalytic amount of triethylamine to form intermediate 2-amino-4-aryl-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene-3-carboxylates **281a–j**. The intermediate further reacts with benzylamine (**282**), and triethyl orthoformate under solvent- and catalyst-free conditions to obtain benzochromenopyrimidine derivatives (Scheme 88). The researchers tested the antiproliferative activity of all synthesized compounds against two colorectal-cancer-cell lines: human LoVo and HCT-116.[115]

2.83 1,3-Oxazine Derivatives

Chaudhary and co-workers[116] established a straightforward, efficient, and environmentally friendly technique for producing 1,3-oxazine derivatives (3-aryl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-5,10-diones) **286a–f**. The method involved a one-pot multicomponent condensation reaction of 2-hydroxy-1,4-naphthoquinone (**1**) with various amines **284a–f** and formaldehyde (**285**), catalyzed by a choline chloride–oxalic acid deep eutectic solvent (Scheme 89). The benefits of this method include mild reaction conditions, a simple operating protocol, a catalyst that is both reusable and biodegradable, high yields, and rapid reaction times.[116]



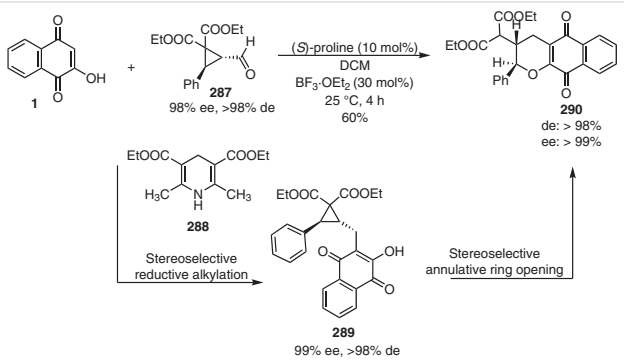
Scheme 88 Benzo[*g*]chromeno pyrimidine derivatives **283a–j**



Scheme 89 1,3-Oxazine derivative **286a–f**

2.84 Chiral Naphthoquinone-pyran Derivative

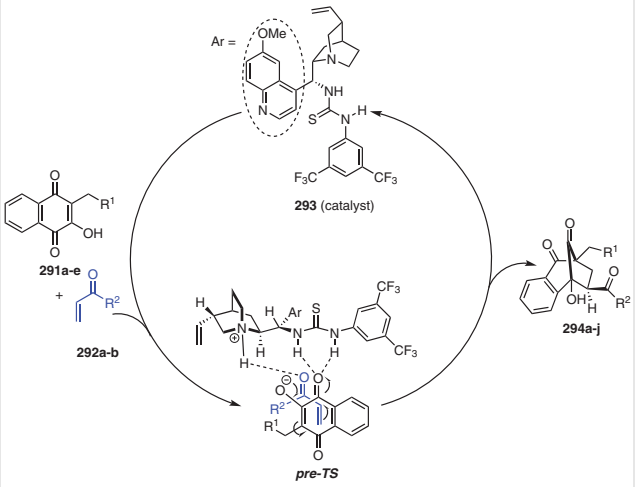
In earlier reports it has been discussed that lawsone and its derivatives serve as synthons for several asymmetric synthesis of biologically active molecules.[117] Among these, recently, Ramachary and co-workers[118] developed a protocol for the synthesis of chiral naphthoquinone-fused pyran derivative **290**. The synthesis involves the stereoselective Knoevenagel condensation or Ramachary reductive coupling between the starting material lawsone (**1**) and chiral formylcyclopropane (**287**) in the presence of Hantzsch ester (**288**). This results in coupling product (**289**), which undergoes Lewis acid mediated annulative ring-opening of the chiral cyclopropane to furnish chiral naphthoquinone-fused 3,4-dihydro-2*H*-pyran **290** in good yield with ee >99% (Scheme 90). This chiral naphthoquinone based pyran derivative has several pharmacologically important activities.[118]



Scheme 90 Tandem protocol for organocatalytic synthesis of chiral naphthoquinone-pyran derivative **290**

2.85 Synthesis of Chiral Tandem Michael/Aldol Product of Naphthoquinone

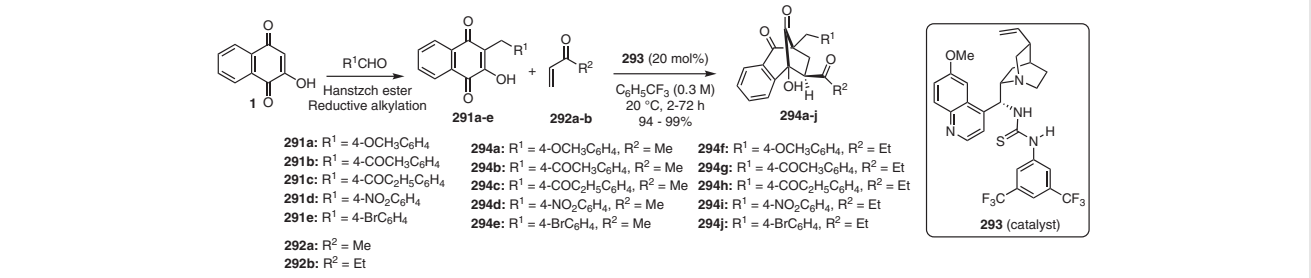
Ramachary and co-workers[119] reported [3+2] annulation of naphthoquinone derivatives **291a–e** and aryl vinyl ketones **292a–b** to furnish chirally enriched Michael/aldol product methanobenzo[7]annulenes **294a–j** as a biologically and pharmaceutically active product. This reaction proceeds with the formation of 3-aryl-lawsone derivatives **291a–e** through Ramachary reductive coupling reaction. Further, in the presence of quinine thiourea **293** as a catalyst, stereoselective annulation with aryl vinyl ketones **292a–b** furnished the desired product **294a–j** in excellent yields with enantio- and diastereoselectivities up to 99%. The authors reported the reaction followed 5-(enolexo)-*exo-trig* annulation reaction (Scheme 91).[119] A plausible mechanism involved concerted annulation of the ring, promoted by the catalyst (Scheme 92).



Scheme 92 Ramachary tandem Michael/aldol: plausible mechanism for catalytic asymmetric synthesis of methanobenzo[7]annulenes

3 Conclusions

Naphthoquinone is a highly important heterocyclic compound in the fields of medicinal, material, and synthetic chemistry, with a wide range of pharmacological activi-



Scheme 91 Tandem Michael/aldol for chiral methanobenzo[7]annulenes **294a–j**

ties. Despite this, some naphthoquinone compounds are found to have low toxicity towards host cells, making them attractive targets for in-vivo investigation. Over the years, researchers have synthesized and investigated many different naphthoquinone compounds that have displayed promising biological activity. As a result, the study of naphthoquinone derivatives continues to attract significant attention in both academic and industrial settings, with a particular focus on the development of new drugs and therapeutic agents. This review has described the recent strategies used to synthesize diverse 2-hydroxy-1,4-naphthoquinone derivatives. The review highlighted the elegant strategies developed by various research groups in academia and in the pharma industry around the globe to construct diverse derivatives of lawsone. Tandem reactions, chemoenzymatic, metal catalysis, one-pot multicomponent reactions, and environmentally friendly approaches have been employed for the efficient synthesis. This review has provided a broad overview on recent synthetic strategies employed to prepare 2-hydroxy-1,4-naphthoquinone derivatives. We hope it will be helpful for the preparation of new hybrid analogs of these bioactive molecules with enhanced properties.

Conflict of Interest

The authors declare no conflict of interest.

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