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Review

Recent Trends in the Green Synthesis of Versatile Fused *N*-Heterocyclic Scaffolds *via* Multicomponent Reactions (MCRs): A Brief Review

Bhavesh S Hirani[1, 2]*, Sevak B Gurubaxani[2]

1. Department of Chemistry, Veer Narmad South Gujarat University, Surat-395007, Gujarat, **INDIA.**
2. Department of Chemistry, Government Science College, Pardi, Valsad-396125, Gujarat, **INDIA.**

Email: bshirani.chemresearch@gmail.com

Tel.+91-7874281527

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ABSTRACT

Nitrogen containing five, six and seven membered heterocycles have specific properties due to which they can be used as a potential material in a different type of industries such as medicinal or pharmaceutical, paint, packing and textile, required for various chemical, physical operations and their use as products. Especially dyes, paint, agrochemicals, medicine, etc. make them more significant. In present days, Nitrogen containing heterocycles are repeatedly attracting the interest of chemists due to their exceptional bioactive behaviour. There is a need to develop more sustainable and eco-friendlier MCR strategies, including catalyst-free and solvent-free reactions. The integration of MCRs with emerging technologies, such as flow chemistry, computational modelling, and machine learning offers exciting prospects for enhancing reaction efficiency and product diversity. The present study is a review of the work carried out by a chemist in the discovery of new, effective, medicinally important heterocyclic compounds. Here, we have reviewed the recent advancements in the synthesis of nitrogen containing five, six and seven membered heterocycles via multicomponent reactions (MCRs). Basically focused on nitrogen heterocycles of potential therapeutic interest, especially with benzofuran-fused piperidines, indole-fused oxadiazepines, indole-fused thiadiazepines, tetrazole-fused indole, quinazolinones, benzo[d]azepines, azolopyrimidine, pyrrole, thiazine, pyrimidine, morpholine, piperazine, benzothiazines, pyrazole-fused benzothiazines, morpholine-fused benzothiazines, piperazine-fused benzothiazines mainly due to their unique structural features, which enable them to exhibit a number of biological and pharmacological activities. Due to a novel mode of action, a broad spectrum of activity, lesser toxicity towards mammalian cells, and suitable profiles towards humans have triggered the use of Nitrogen containing heterocycles in designing and synthesizing their derivatives with better properties. The overall objective of the review is to brief discuss recently advanced multicomponent reaction to the synthesis of nitrogen heterocycles and importance of novel biodynamic structurally diverse compounds of potential therapeutic interest in specially fused N-heterocyclic compounds order to have access to important commercial molecules for the search of better future.

Keywords: Green synthesis, Multicomponent reactions (MCRs), N-heterocyclic compounds, Medicinal chemistry.

INTRODUCTION

In medicinal chemistry, the thiazole ring system is a significant class of molecules. This structure has been used in the development of medications to treat a variety of conditions, including cardiotonic, fungicidal, HIV infection, childhood mental retardation, age-related brain damage, and neurodegenerative diseases including Parkinson's and Alzheimer's. Despite their significance from a pharmacological and synthetic perspective, relatively few preparation techniques have been documented in the literature. In 1887, Hantzch synthesized thiazoles by condensing α-haloketones with thioureas or thioamides in refluxing alcohol under extreme circumstances [**1**]. Nevertheless, these techniques have a number of drawbacks, including a lengthy reaction time (24–25 hours) and challenging reaction conditions. The modified procedures of King and Dadson, in collaboration with some other works, have also been described for the synthesis of thiazole compounds. However, these procedures suffer from one or more limitations such as severe reaction conditions, disappointing yields, complex product isolation procedure and usage of volatile organic solvents [**2**]. Therefore, the development of more cost-effective and ecologically friendly conversion processes is highly desirable. The development of environmentally benign organic reactions has become an important and challenging research area in contemporary organic chemical research due to the increased regulatory constraints concentrated in the chemical and pharmaceutical industries. As a result, an increasing number of chemists are focusing their synthetic efforts on "green synthesis," which refers to reagent, solvent, and catalyst reactions that are solvent-free or ecologically benign [**3**]. The transdisciplinary idea of "clean chemistry" encourages the prudent application of chemical reactions while preventing contamination. It entails creating chemical products utilizing ecologically friendly processes that lower costs and the production of dangerous compounds. With several benefits, including gentle reaction conditions, ease of separation and purification, high efficiency and selectivity, and environmental acceptability, grinding procedures are attractive eco-friendly strategies for efficient organic synthesis [**4**]. Meanwhile, hydrazine-containing molecules (R_1R_2C=NNH-R_3) have a variety of biological actions, including anti-inflammatory, anti-viral, antifungal, anti-tubercular, analgesic, muscle relaxants, and antihistamines, making hydrazone an effective nucleus. An important family of chemicals for the creation of novel drugs are hydrazones with an azometine -NHN=CH- proton. The hydrazine group's two nitrogen atoms are nucleophilic, while the hydrazone group's carbon atom possesses both electrophilic and nucleophilic characteristics (Figure 1). The physical and chemical characteristics of hydrazones are mostly caused by these structural pieces. As a result, numerous scientists have created these substances as target structures and assessed their biological properties. These observations have been influencing the development of novel hydrazones that feature different biological function [**5, 6**].

Similarly, pyrazoline derivatives are extensively found in nature as colors, vitamins, alkaloids, and animal cells. Many researchers have found pyrazolines to be appealing synthetic targets due to their distinct structural array and strong pharmacological activity. In keeping with our focus in environmentally friendly heterocycle synthesis, we provide here a simple, effective solid-state grinding technique for hydrazone preparation [**7**]. This technique can also be applied to hyrazide reactions with anhydride and active methylene compounds. The century's greatest threat to humankind is SARS-CoV-2. It is the main cause of the new, deadly COVID-19 pandemic that is sweeping the globe. Because the major viral protease (Mpro) of SARS-CoV-2 is essential to the virus's survival, medication designers lose interest in it. Mpro is an essential enzyme for the conversion of viral polypeptides into several enzymes that sustain the SARS-CoV-2 life cycle. Therefore, preventing Mpro activity is essential in the fight against COVID-19. Different substances, both synthetic and natural, are employed as prospective treatments for SARS-CoV-2 Mpro. In this work, we examined a few derivatives of hydrazones, pyarzoles, and pyrazines that were created by a clean grinding method [**8**]. A great way to assess chemical reactivity in silico is through molecular modeling. For drug designers, molecular modeling has become second nature due to the rapid advancements over the past 20 years. It facilitates the drug design process by saving time, money, and effort. Strong antiviral drugs against a variety of viruses, including the Hepatitis C virus (HCV) and the Human Immunodeficiency Virus (HIV), were successfully discovered thanks to it [**9**]. Additionally, computer-aided drug design is employed to identify the potency of medications and natural products

against SARS-CoV-2 proteins throughout the last few months. This study tests various drugs against SARS-CoV-2 Mpro using a combination of molecular docking and molecular dynamics modelling [**10**].

MCRs are superior to traditional multistep synthetic approaches in a number of ways. These include: i) the potential for convergent synthesis due to the use of multiple starting materials in a single step; ii) high atom-economy and pot-economy; iii) the construction of complex molecules from simpler starting materials; iv) access to a diverse compound library through the use of different building blocks; v) the potential for post-MCR modifications to create novel ring systems and substitution patterns; and vi) convenient and mild reaction conditions leading to a greener approach [**11, 12**]. Because of these benefits, MCRs are especially well-suited for drug discovery scenarios, where access to huge chemical libraries can frequently be a bottleneck. Early medicinal chemistry efforts can be made more affordable by using MCRs to quickly produce several analogues of a hit molecule. Designing MCR-based synthetic methods for authorized medications provides the potential to provide affordable medications and reduce overall production costs [**13**].

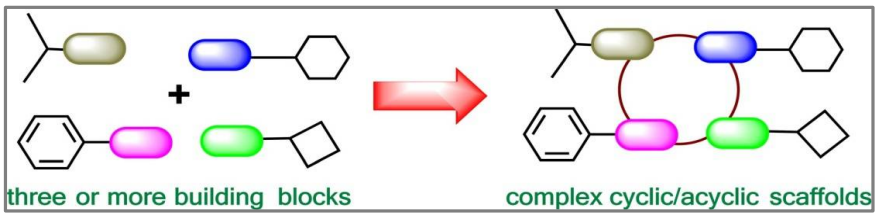

Figure 1. MCR approach in synthetic chemistry**.**

Nitrogen Heterocycles: Many medicinal compounds and natural medicines have structural motifs that comprise nitrogen-containing heterocycles. Tetrahydropyridines (THPs) and piperidines are particularly significant among the various N-heterocycles because they provide the molecules more three dimensions and aid in their escape from the "flatland." THPs and piperidines are often produced by intra-molecular cyclization, which frequently produces waste, and the reduction of matching pyridine rings [**14**]. Therefore, it is very desired to synthesize these aza-heterocyclic rings using convenient and environmentally friendly methods. Described a mild method for producing poly-substituted 1,2,5,6-THPs using an MCR catalyzed by copper [**15**]. Trimethylsilyl cyanide (TMSCN) (3), an alkene (2), and an F-masked benzene-sulfonamide allene (1) participate in a cascade Radical cyclization event that yields THPs with unusual C3 or C5 substituents (e.g. 4a, Figure 2**)** [**16**]. After screening the reaction conditions, it was discovered that the best combination was tetrakis (acetoni-trile) copper (I) hexafluorophosphate [Cu(CH3CN)4PF6] with a bisoxazoline (BOX) ligand and fluorobenzene as solvent **(**Figure 2**)**. The model compound 4a was thus synthesized at a yield of 65% under these perfect conditions. Although the BOX ligand provided high regioselectivity and installed the cyanide group at the primary carbon with the least steric hindrance, stereoselectivity was not observed despite using a chiral ligand.Under the ideal conditions, a range of alkenes with one or more aromatic ring substituents successfully reacted to produce a variety of C5-substituted THPs (e.g., 4b–4h). It is also possible to couple the heterocyclic rings and heteroatom substituents at C5. Similarly, the aryl ring of the F-masked sulfonamides tolerated a range of electron-donating groups (EDGs) and electron-withdrawing groups (EWGs), producing a range of C3 substituents (e.g., 4i–4m). However, the main drawback of this MCR is that alkyl groups (like 4n) could not be inserted at C3. Apart from TMSCN, the equivalent products (like 4o–4q) were also produced in good yields by other nucleophiles such azidotrimethylsilane (TMSN3), TMSSCN, and silver(I) trifluoromethanethiolate (AgSCF3) [**17**]. Additionally, the reaction proceeded smoothly using different alkynyl-trimethoxysilanes as nucleophiles to produce the matching THPs (such as 4r–4t), demonstrating the reaction's flexibility. By creating several derivatives of the THP products and scaling the reaction to a gram scale, the synthetic value of this reaction was further proven.

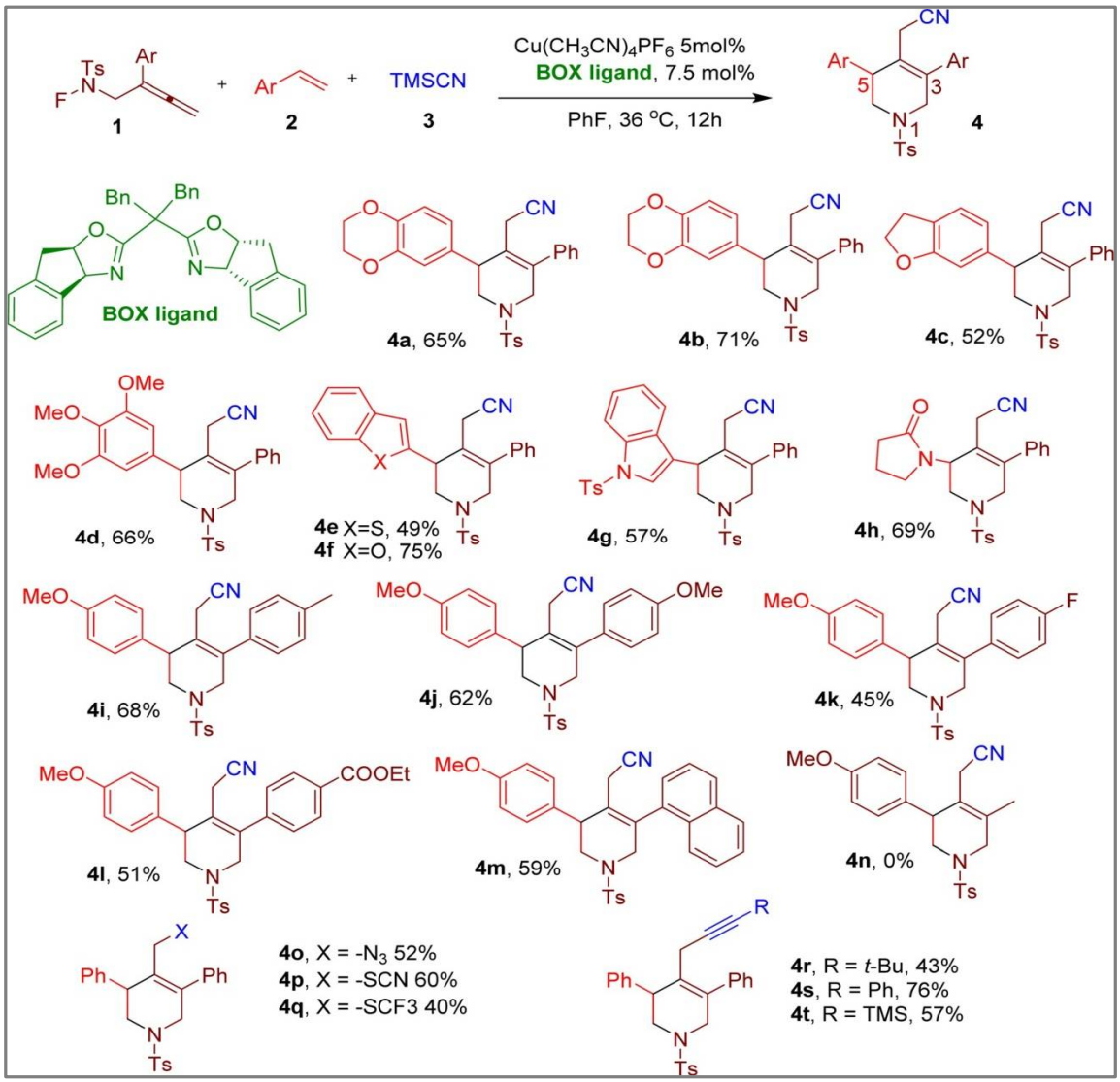

Figure 2. MCR for the synthesis of diversely substituted tetrahydropyridine derivatives.

Using an electron-rich benzofuran ring (5), primary amine (6), and formaldehyde (7, Figure 3), Cui and colleagues developed an MCR approach to produce benzofuran-fused piperidines. The benzofuran ring's position-2 C(sp2)–H and unactivated benzylic C(sp3)–H bonds serve asNucleophilic sites in a double Mannich reaction [**18**]. As a result, N-substituted piperidine fused with benzofuran at positions 2 and 3 makes up the newly created molecules. Acetic acid was the most effective solvent for the model reaction between 6-methoxy-3-methylbenzofuran, formaldehyde (4 equiv.), and glycine methyl ester hydrochloride (2 equiv.) that produced model chemical 8a.A variety of amino acids reacted well under the ideal circumstances, producing the matching benzofuran-fused piperidines (such as 8b–8h) in good yields with the retention of configuration on a-carbons. Furthermore, different primary amines with a variety of functions (such as 8i–8o) were also well tolerated, indicating the adaptability of the MCR [**19, 20**]. The potential application of this one-pot MCR in medicinal chemistry is demonstrated by the late-stage modification of several drug compounds with amine functionalities. The comparable piperidine products (e.g., 8p–8s) were also produced in good yields by the benzofuran derivatives with different EDGs. By using benzofurans with substituents on the benzyl carbon, a variety of multi-substituted piperidines could also be produced, giving compounds (like 8t and 8u) a variety of physico-chemical characteristics. Further diversity of piperidine-containing compound libraries for medicinal chemistry projects is also made possible by the presence of boronate and alkyne functionalities in some of the final products. Numerous intermediates produced by Mannich, retro-Mannich, and nucleophilic

substitution processes were implicated, according to mechanical studies and density functional theory (DFT) calculation [21].

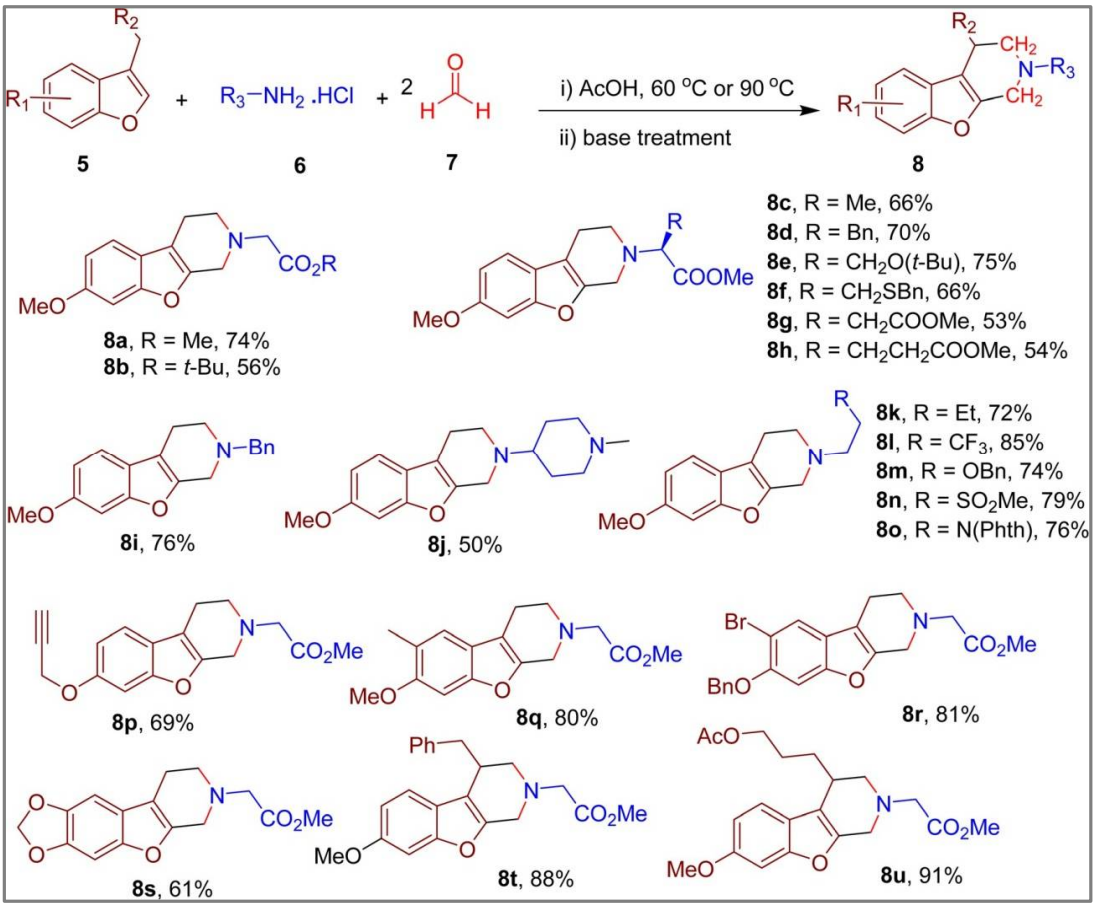

Figure 3: MCR for the synthesis of diverse benzofuran-fused piperidines**.**

The same group also reported synthesizing a piperidine-fused indole chemotype similar to natural alkaloids by substituting 2-methyl indole for benzofuran, which typically necessitates multistep synthesis. Notably, one of the most significant heterocycles of many medications and therapeutic prospects is indole.G-tetrahydrocarboline 10a was produced in an excellent yield by carrying out the model reaction in dimethylformamide (DMF) solvent using N-benzyl-2-methyl indole (9), methyl glycine ester, and formaldehyde **(**Figure 4**)** [22**]**.

The substrate scope showed that different amino acids (such as 10a–10f) and aliphatic amines with different functional groups and rings (such as 10g–10p) were compatible. Numerous indole ring replacements, such as 10q–10u, were also accepted. However, substituting H-atom or EWGs (like Boc, e.g., 10v) for the N-alkyl substitution decreased yields, indicating the significance of electron density on indole nitrogen. Interestingly, by choosing appropriate starting materials, this MCR might also produce azaindole (e.g., 10w) and pyrrole fused piperidines (e.g., 10x). By substituting 3-methyl indoles (13, Figure 5) for 2-methyl indoles (9), the authors further broadened the reaction's scope and reported the synthesis of a similar b-tetrahydrocarboline chemotype. In this instance, acetonitrile (CAN) as a solvent and the N-tert-butoxycarbonyl (N-Boc) group were discovered to be optimal for the high reaction yields. Once more, a variety of amines were acceptable in the conditions described (e.g., 14a–14j). However, altering the dimethoxy substitution pattern in indole to disrupt electron density led to low yields of the resultant products (e.g., 14k–14u). In a similar vein, yields were reduced by N-substitutions other than the Boc group (e.g., 14v). A few indole-based medications and clinical candidates were synthesized to show the usefulness of the MCR.

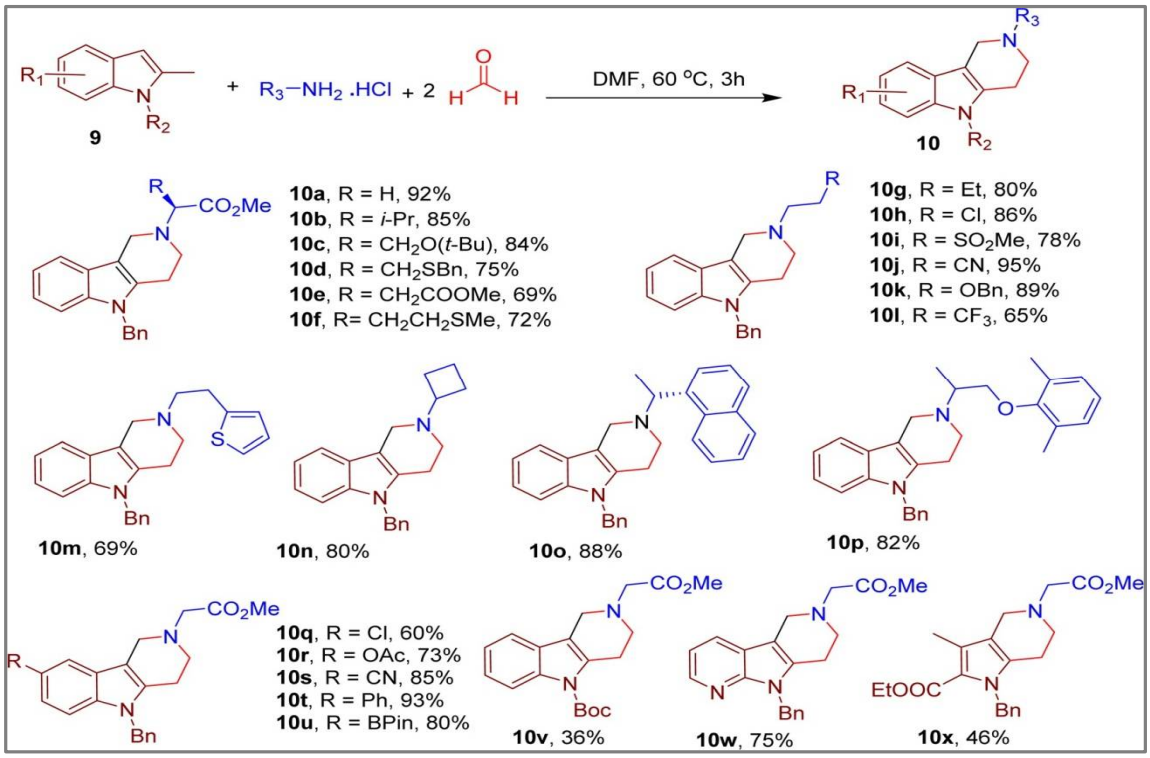

Figure 4. M C R for the synthesis of diverse g-tetrahydro carbolines.

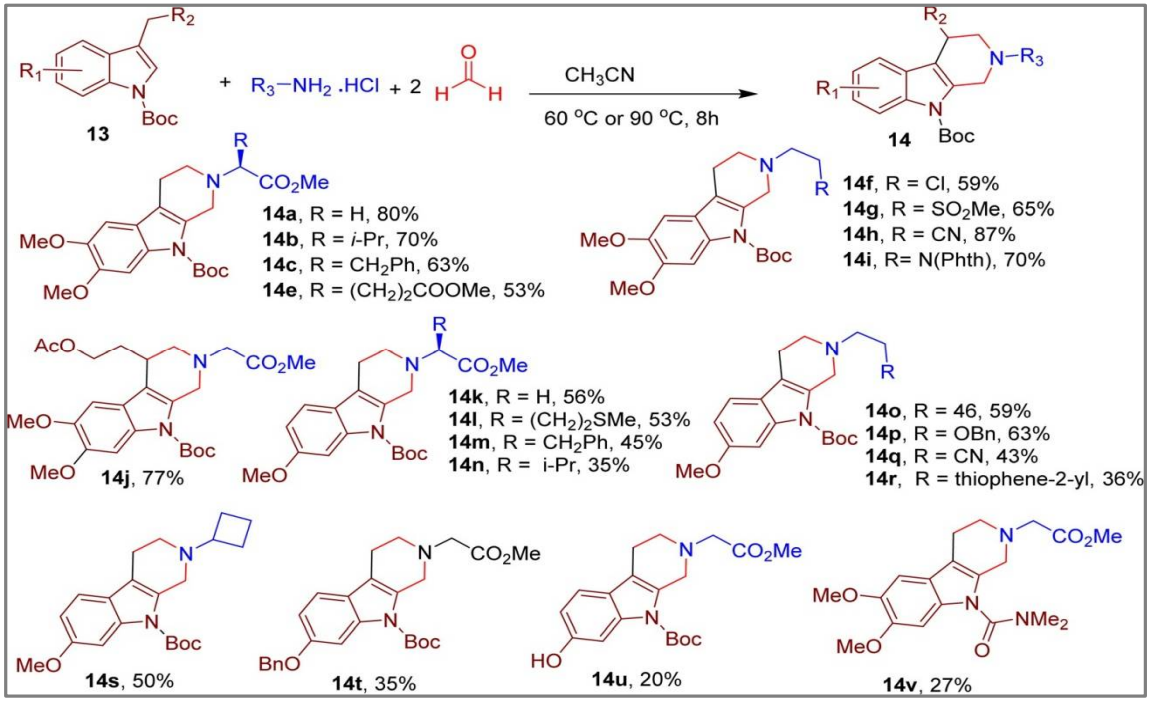

Figure5. MCR for the synthesis of diverse b-tetrahydrocarbolines.

Cui and colleagues reported the synthesis of indole-fused seven-membered heterocycles in addition to their indole-based MCRs. Indole-NH and carbon at position 2 participated in the reaction. The MCR produces an indole-fused oxadiazepine derivative by reacting 3-methylindole, excess formaldehyde, and amine hydrochloride salt in tetrahydrofuran (THF) (Figure 6) [23]. The corresponding oxadiazepines were obtained in moderate to good yields from various amino acids (e.g., 15a–15c) and

other aliphatic amines (e.g., 15d–15k). Under the ideal circumstances, the amino acids' chiral center integrity was likewise preserved. The generality of the MCR was demonstrated by the tolerance of a variety of EWGs and EDGs, including halogens, methoxy, alkene, and alkyne, on the indole ring (e.g., 15l–15r).

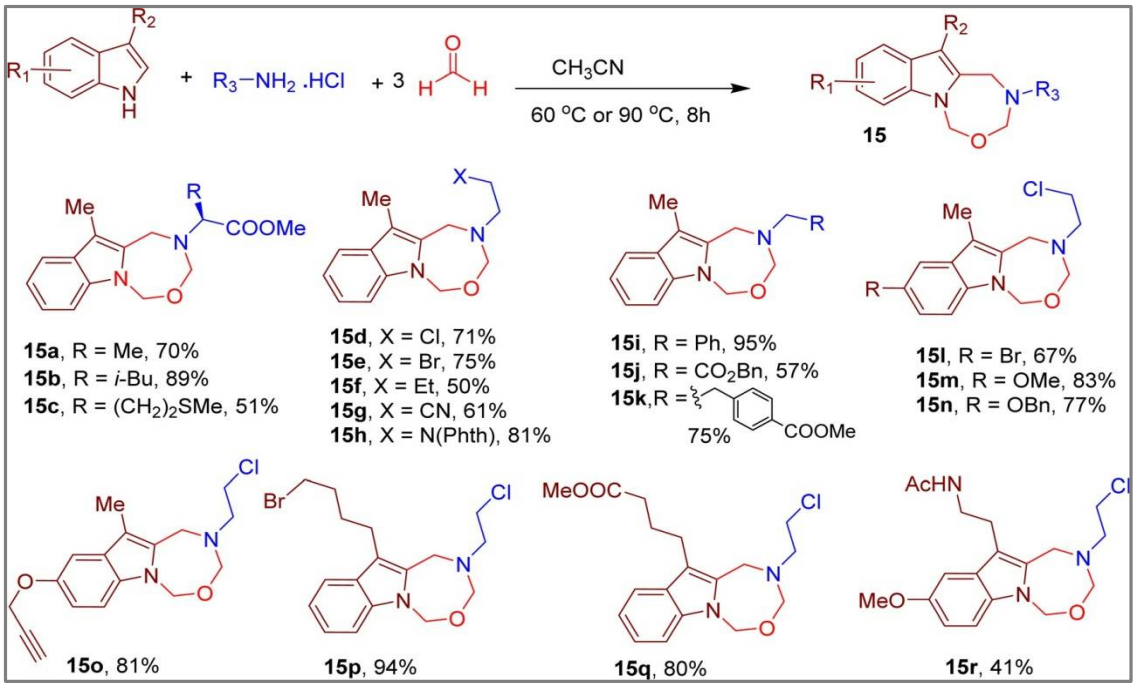

Figure 6. MCR for the synthesis of indole-fused oxadiazepines.

Interestingly, the scope of this MCR was further expanded by using aqueous hydrochloric acid (HCl) and sodium thiosulfate (16) in the same process, which produced indole-fused thiadiazepine analogues (e.g., 17a–17n) **(**Figure 7**).**

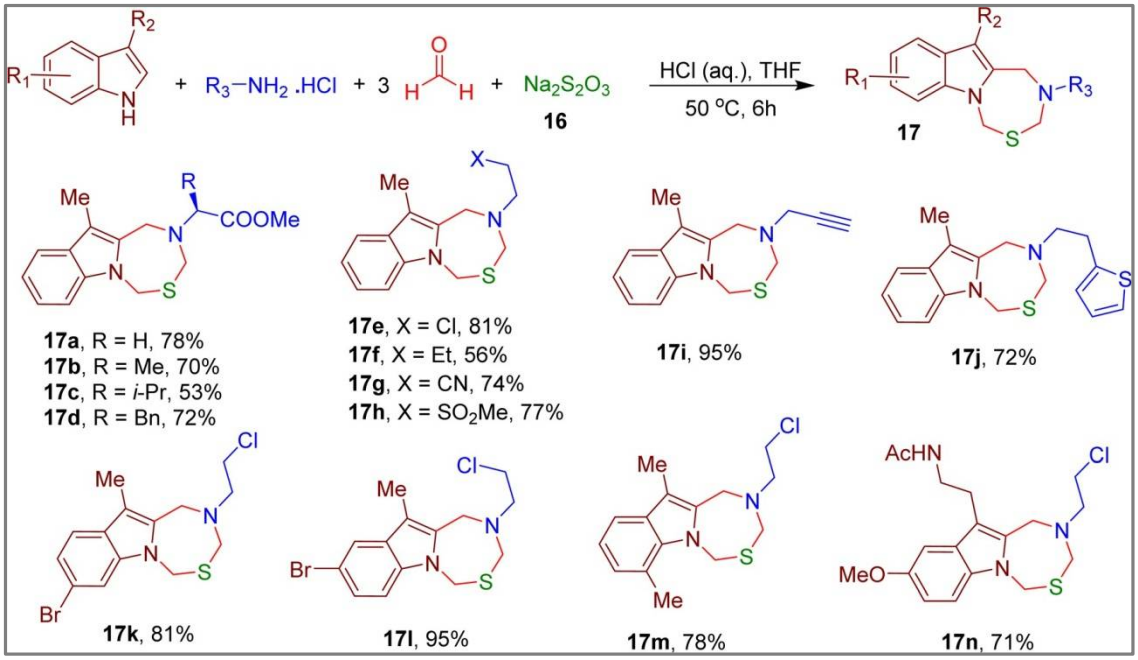

Figure 7. MCR for the synthesis of indole-fused thiadiazepines.

The liver (BEL7402) and breast cancer (MDA-MB-231) cell lines were inhibited in the micromolar (mM) range by a number of recently synthesized oxadiazepine and thiadiazepine analogues. Additionally, it was demonstrated that the indole ring of tryptophan (Trp) and Trp-bearing peptides participated in this reaction, indicating the possibility of using this MCR for peptide and protein modification. Fischer indole synthesis, which uses dangerous phenylhydrazine and is carried out in highly acidic environments, is frequently used to create the indole ring. There are very few MCR-based methods for synthesizing indole and its derivatives, despite the abundance of research centered on indole molecules.Using the Ugi-tetrazole four-component reaction, Domling and colleagues reported the simple synthesis of tetrazole indoles **(**Figure 8**)**. In this two-step process, MCR, a substituted arylamine (18), dimethoxyacetaldehyde (19), isocyanide (20), and TMSN3 (21) were reacted at room temperature to produce the Ugi-tetrazole adducts (22), which are then further cyclized to indole derivatives (23) in an acidic environment.Fifty A wide range of EWGs and EDGs on isocyanide and aniline building blocks (e.g., 23a–23h) were tolerated by the established approach. Methane sulfonic acid (MSA) had the highest yields when used for cyclization. The authors determined the ideal temperature for the selective precipitation of the principal regioisomer in unsymmetrical amines [**24**]. In the end, this two-step MCR was converted into a one-pot process that produced 23b in an overall yield of 49%. The synthetic protocol's scalability and ease are demonstrated by the reaction's capacity to be conducted at a gram scale without the need for chromatographic separation. To increase the variety of indole derivatives, the final products could be further functionalized. The yields of the first and second steps are reported, respectively. In cases where a mixture of Regio isomers is obtained, the structure of the major isomer is provided. Therefore, this MCR is a moderate and simple one-pot synthesis of the favoured indole core.

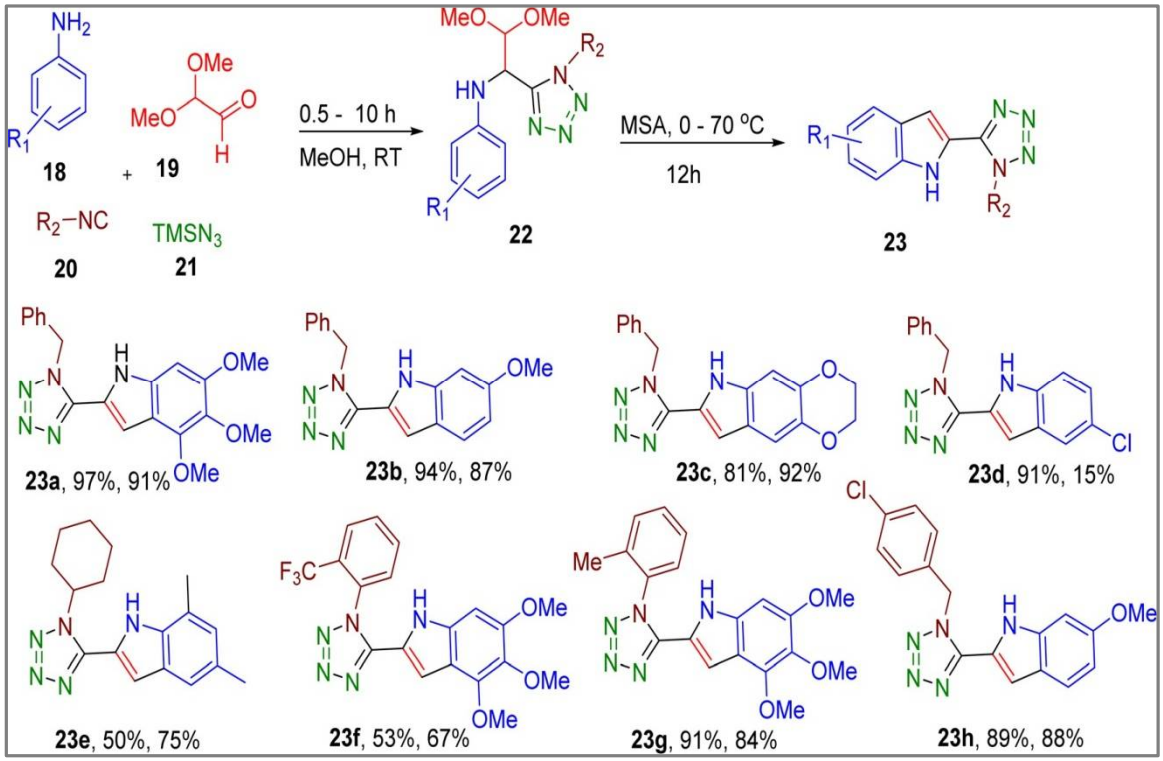

Figure 8. MCR reported for the synthesis of tetrazole-indole derivatives.

A comparable method for obtaining highly substituted indole-2-carboxamide derivatives was also disclosed by the group (Figure 9). First, substituted aniline, glyoxal dimethyl acetal, isocyanide, and formic acid were used to create Ugi adducts (24), which were then further cyclized using MSA to produce the indole carboxamides (26). While electron-deficient anilines either did not undergo cyclization or reacted inefficiently (e.g., 26g–26i), this two-step method worked effectively with

anilines with EDGs (e.g., 26a–26f). On the other hand, a variety of isocyanides produced the matching compounds in good yields, resulting in a library of indole carboxamides with a range of physiochemical characteristics [25]. The single-pot, two-step process was created by the authors, who also demonstrated the methodology's scalability to the gram scale. The authors used this practical and gentle MCR technique to synthesize two anti-tuberculosis drugs (e.g., 26j and 26k) and a SET domain containing 2 (SETD2) inhibitor (e.g., 26l) in a short amount of time, further demonstrating the efficacy of their proposed process. The yields of the first and second steps are reported, respectively. Single yields are reported for the compounds synthesized in one-pot operation.

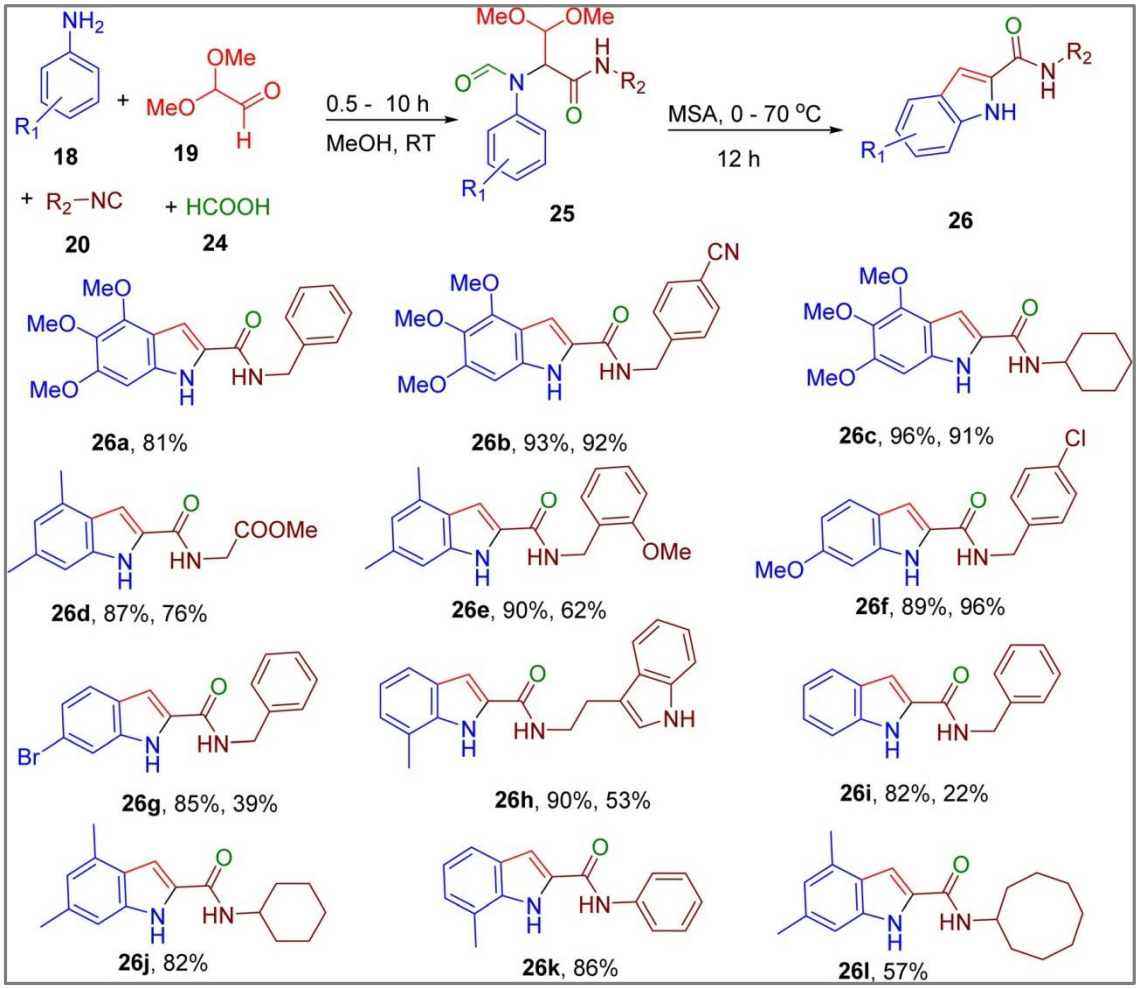

Figure 9. MCR for the synthesis of indole-2-carboxamide derivatives.

Derivatives of quinazolinone exhibit a variety of pharmacological characteristics, including as antibacterial, anticancer, antidiabetic, and antihypertensive effects. N1, N3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones can be synthesized using a variety of techniques. Nevertheless, the majority of these multi-step approaches restrict the variety of N1-substituents and may necessitate specific catalysts and laborious conditions. A Pd(II)-catalysed cascade reaction between an o-aminobenzoic acid (27), amine (28), aldehyde (29), and carbon monoxide was used by Zhang et al. to synthesize N-substituted quinazolinones (Figure 10) [26]. In this one-pot process, o-aminobenzoic acid was carbonylated by Pd, and the resulting is atoic anhydrides reacted with the amine and aldehyde components to produce N1,N3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones. Using copper(II) acetate [Cu(OAc)2] as the oxidant, along with the additives potassium iodide (KI), acetic acid (AcOH), and ACN solvent at 65°C, favored the model reaction.

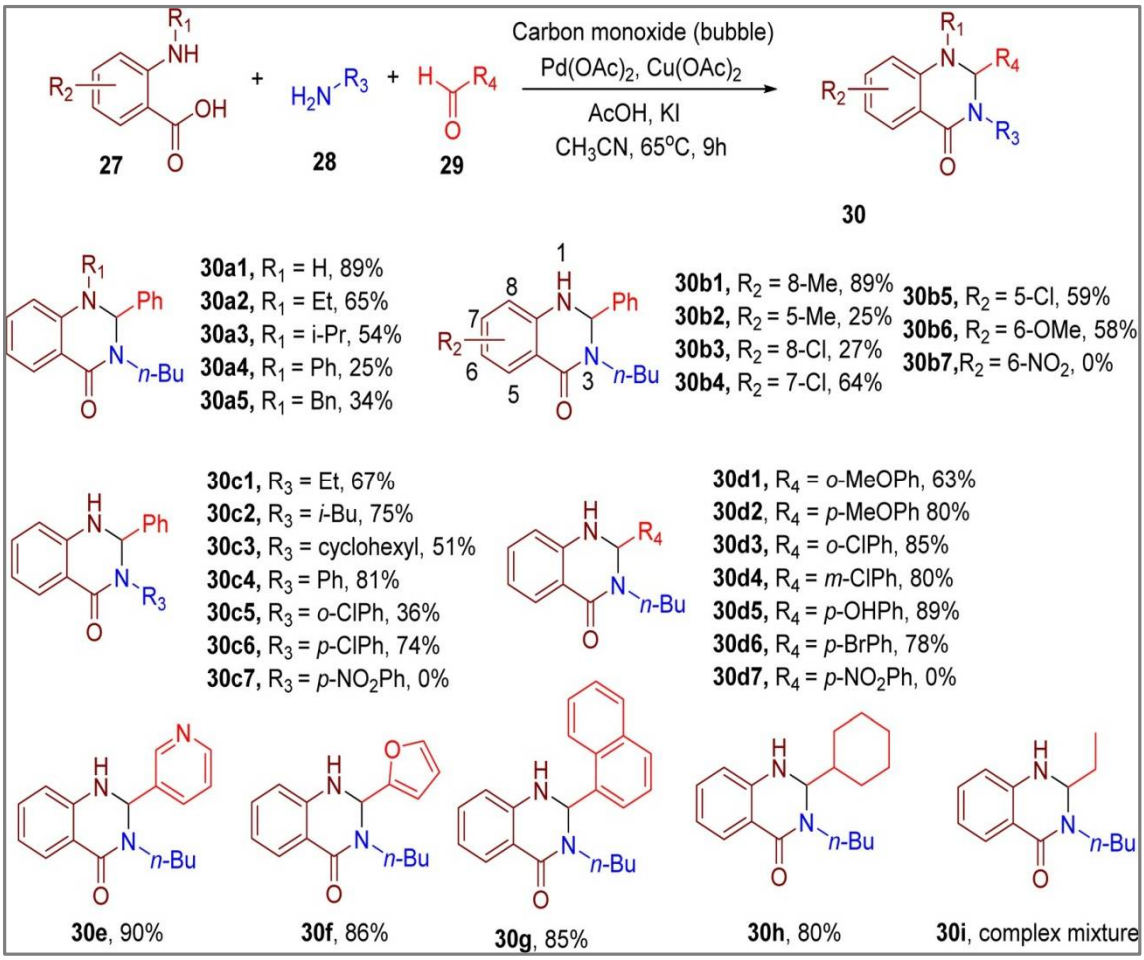

Figure 10. MCR for the synthesis of N_1, N_3-substituted quinazolinones.

Under ideal circumstances, various o-aminobenzoic acids with or without N-substituents often interacted easily to produce the desired products (e.g., 30a1–30a5). However, compared to substrates with smaller N-substituents (e.g., 30a3–30a5), sterically hindered substrates with bulky N-substituents produced lower yields. With the exception of the nitro group-bearing aminobenzoic acid (e.g., 30b7), which produced no product, different substituents on the phenyl ring of o-aminobenzoic acids generally produced moderate to good yields (e.g., 30b1–30b6). Using a range of aliphatic and aromatic amines (such as 30c1–30c7), the authors illustrated the reaction's universality. However, reduced product yields (e.g., 30c3) were caused by bulky amines. With the exception of those with EDGs, arylamines with ortho-substituents (such as 30c5) likewise showed the negative impact of a steric factor. On the other hand, the reaction failed when strong EWGs like nitro were present on the arylamine (such as 30c7) [27].

Additionally, the reaction was effective with a wide range of aromatic aldehydes, including 30d1–30d6, regardless of whether the substituents were steric or electronic. Nevertheless, the comparable product (such as 30d7) was not obtained via the reaction with 4-nitrobenzaldehyde, which has a strong EWG like NO_2. The products were also produced in good yields from a range of aromatic heterocyclic (e.g., 30e, 30f) and polycyclic aldehydes (e.g., 30g), demonstrating the broad substrate breadth of this MCR. It's interesting to note that when it came to aliphatic aldehydes, those with branched chains produced higher yields (like 30h), but those with linear chains produced an intractable mixture (like 30i). Fluorine and trifluoromethyl groups are commonly employed in medicinal chemistry to enhance a variety of pharmacological characteristics, including target potency, metabolic stability, and bioavailability. 57. One important tool for accessing various trifluoromethylated heterocycles is the

trifluorodiazoethane reagent. In order to create the pharmaceutically significant benzo[d]azepine motif (35, Figure 11) [**28**].

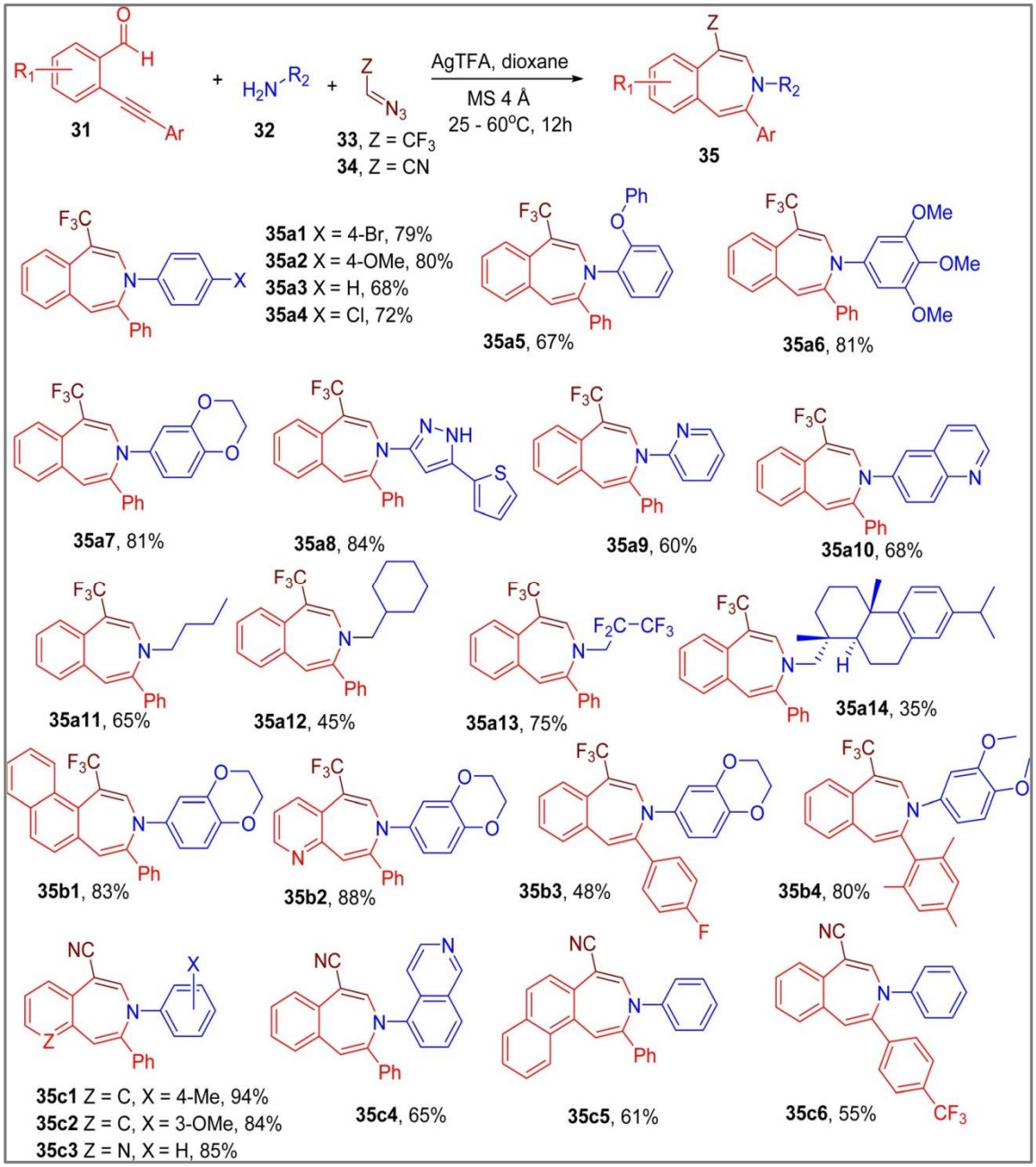

Figure 11. MCR for the synthesis of trifluoromethyl-orcyano-functionalized benzo[*d*]azepines.

Chandrasekharan *et al.*, developed an MCR between o-alkynyl benzaldehyde (31), amine (32), trifluorodiazoethane (33), or diazoacetonitrile (34).62. Silver trifluoroacetic acid (AgTFA) was discovered to provide the best yield of the model chemical (e.g., 35a1) after a variety of catalysts were examined during the reaction optimization. It was also discovered that using 1,4-dioxane solvent, 4 Å molecular sieves, and a moderate temperature enhanced the yields. The wide range of amine substrates was demonstrated by the fact that a number of arylamines (35a1–35a7), heteroarylamines (35a8–35a10), and alkylamines (35a12–35a14) produced the corresponding azepine products. Under the specified conditions, various o-akynylarylaldehydes were also tolerated to produce intriguing azepine derivatives (35b1–35b4). It's interesting to see that diazoacetonitrile (34) produced similar cyano-

substituted azepine products rather than trifluoromethylated ones when trifluorodiazoethane (33) was substituted. Therefore, it was demonstrated that a range of amines and akynylarylaldehydes may provide the cyano-functionalized azepines (35c1–35c6), expanding the range of the reaction. This MCR may give access to a varied library of azepine derivatives for drug discovery because nitrile function is open to additional synthetic alteration [**29**].

In medicinal chemistry, highly substituted pyrrole rings are very important. It has been demonstrated that a number of pyrrole-based compounds have antiviral, anticancer, antibiotic, and antifungal qualities. MCRs between a thioamide-enol (36), an aldehyde (37), and an ammonia source were recently reported by Afratis et al. to produce an intermediate (38) that, upon extrusion of sulfur, produced the substituted pyrrole product (39, Figure 12) [**30**]. At first, significant levels of by-product enamine were also noted, and reaction conditions were adjusted to lessen its production and increase the reaction's overall yield. With the exception of electron-neutral and electron-rich aryl and alkyl aldehydes, the improved conditions generally performed well with a variety of heteroaromatic and aromatic aldehydes (such as 39a–39i). Various substitutions on the thioamide's aromatic ring, such as 39j–39l, were likewise accepted with no yield reduction. Additionally, changes to the lactam moiety (such as 39m) were also accepted, and the absence of the lactam moiety produced the cyclic alkyl fused pyrroles in high yields (such as 39n and 39o).

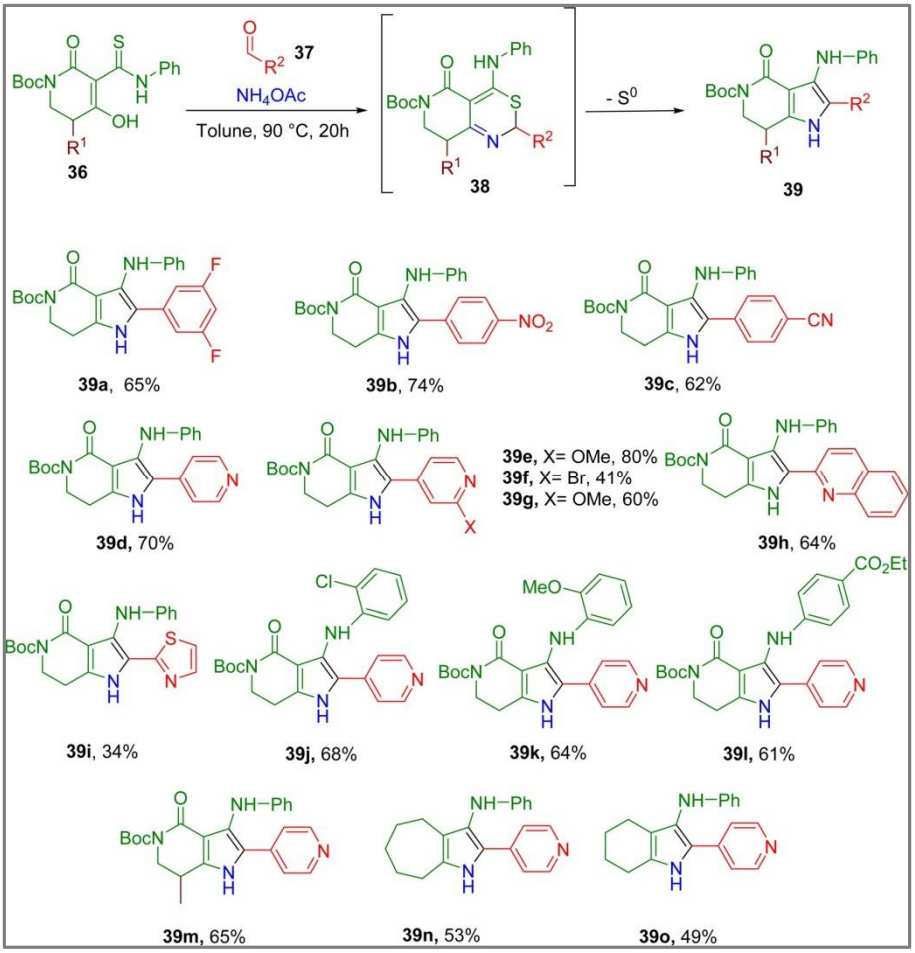

Figure 12. Synthesis of fully substituted fused pyrroles through an oxidant-free MCR.

A simple synthesis of 3-thio N-pyrrole ring (44) from thiol (42), amine (43), and cis-2-butene-1,4-dial (BDA) (41) was described by Wang et al. The latter was produced in situ by oxidizing pyrrole,

resulting in a two-step single-vessel procedure (Figure 13) [31]. The ideal conditions for this MCR were discovered to be a 5:1 mixture of acetone and water. Several N-pyrrole derivatives with different functional groups were produced using a range of thiols and amines (e.g., 44a–44g). The comparable compounds were also obtained in good yields by using alternative amino acids and less reactive aniline. Nevertheless, there is no information available regarding the substrate scope of heteroaromatic amines and thiols.

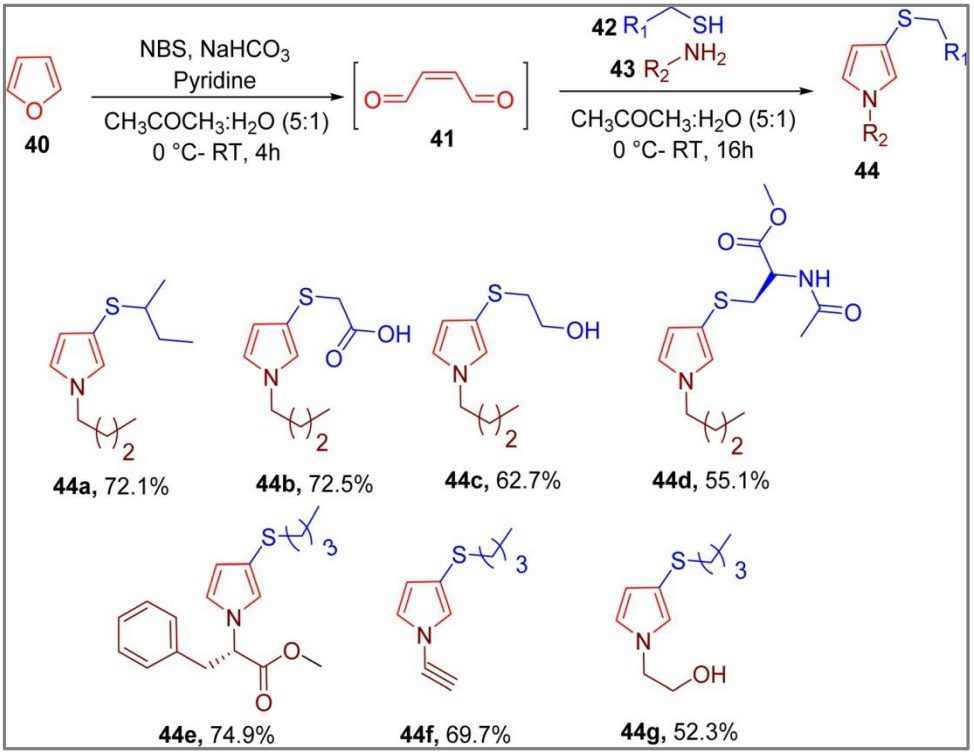

Figure 13. Development of one-pot furan-thiol-amine *via* MCR approach.

The MCR was also utilized for the late-stage modification (Figure 14) of the lysine (e.g., 47 from 45) and cysteine residues (e.g., 50 from 48) of peptides due to the chemo selectivity and robustness of the reaction in aqueous circumstances. Similarly, it was also shown that peptides (such as 52 from 51) with both free thiols and amino groups might undergo macrocyclization. Additionally, it was demonstrated that the amine and thiol groups of a number of proteins participated in this reaction in a complex cell lysate combination, indicating the use of this MCR for protein labelling and amino acid profiling. A number of organoselenium compounds have shown biological characteristics in recent years. Therefore, in medicinal chemistry, the easy synthesis of organoselenium compounds is crucial.

Recently, Peglow *et al.*, used MCR to synthesize pyrrole rings with mono- or di-substituted selanyl groups (Figure 15). Using amine (53, 0.5 mmol), diselenide (54, 0.25 mmol), and 2,5-hexanedione (55, 0.5 mmol), the authors attempted to construct a one-pot process to produce selenium-substituted pyrroles (e.g. 56 or 57), building on their earlier work.67. After screening under various conditions, CuI catalyst in dimethysulfoxide (DMSO) with ultrasound (US) (60% ampli-tude) as the energy source produced the highest yields of monoselenylated pyrrole [32]. It was also discovered that the final yields were influenced by the molar ratio of the starting components to diphenyl diselenide. With a range of alkyl, aryl, and heteroaryl diorganyl diselenides and amines, the reaction produced pyrroles in moderate to good yields (e.g., 56a–56i). In contrast to diaryl diselenides with EDG (e.g., 56h and 56i), those with EWG (e.g., 56f and 56g) needed more time to get moderate yields of theproducts. With dibutyl diselenide, the reaction performed poorly, yielding just 14% of the relevant product (e.g. 56c). The procedure generated pyrroles in moderate to good yields using a variety of alkyl,

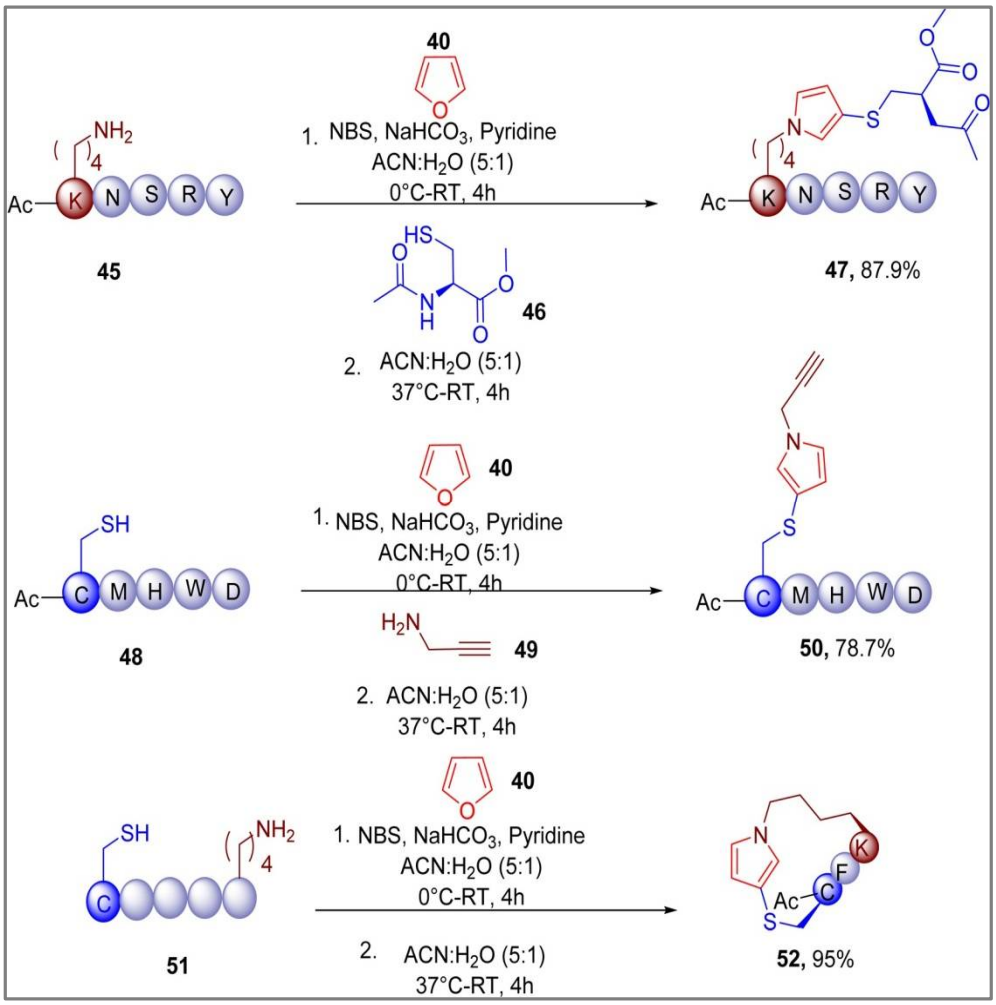

Figure14. Chemo selectivemodificationoflysineandcysteineresiduesbyone-potfuran-thiol-amineMCR.

aryl, and heteroaryl diorganyl diselenides and amines (e.g., 56a–56i). Diaryl diselenides with EWG (e.g., 56f and 56g) required longer time to obtain moderate yields of the products than those with EDG (e.g., 56h and 56i) [**33**]. The reaction behaved badly with dibutyl diselenide, producing just 14% of the necessary product (e.g. 56c).

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) bases are two examples of natural products and biomolecules that include pyrimidine rings. The literature reports a number of pyrimidine-based compounds with a wide range of biological features. Pyrimidines and their derivatives can be synthesized using a variety of methods [**34, 35**]. The synthesis of asymmetric bipyrimidines, such as 4,50- and 3,50-bipyrimidines, is, nevertheless, extremely difficult.

An MCR cascade that led to the synthesis of [4,50-bipyrimidin]-6(1H)-one, a highly functionalized asymmetric bipyrimidine scaffold, was accidentally found by Chen *et al.* (62, Figure 16) [**36**]. The authors investigated the condensation of 3-formylchromone (58) in the presence of dinucleophiles like amidine hydrochlorides (61) and 2-(pyridine-2-yl) acetate (59), which, depending on the solvent and temperature, produced (62 or 620) via intermediate (60). The chromone ring's EWGs and EDGs groups, such as 62a–62h and 620a–620d, were both well tolerated. To obtain the desired products, several benzamidines with differently substituted aromatic rings or alkyl groups could also be used (e.g., 62g and 62h).

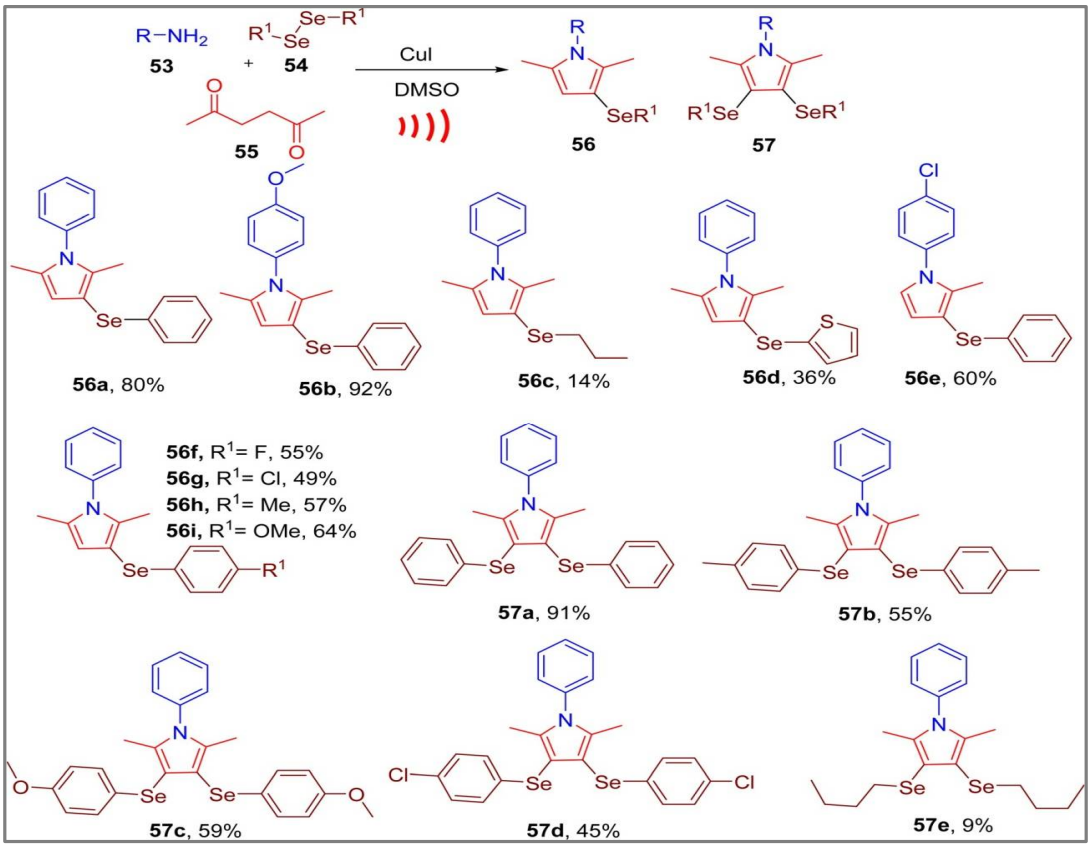

Figure 15. US-assistedone-potsynthesisofmono-orbis-substitutedorganylselanylpyrroles.

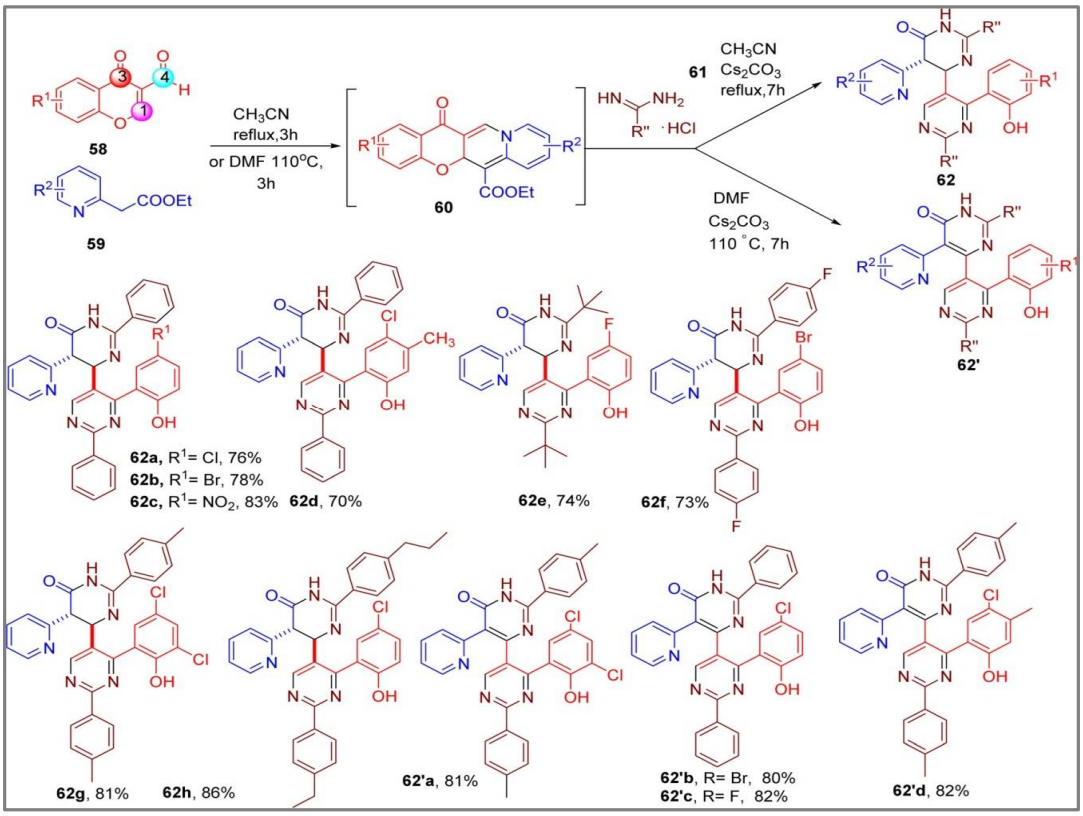

Figure16. MCR for the synthesis of asymmetric 4,5^0-bipyrimidine.

It was suggested that a series of Michael addition, cyclization, intra- and intermolecular ring opening, and dehydrogenative aromatization events would result in the synthesis of the bipyridines, with a total of five bonds formed and one bond cleaved.

The unexpected synthesis of a novel azolopyrimidine scaffold (66, Figure 17) from MCR involving nitroenamine (63), aminoazoles (64), and aromatic aldehyde (65)[37] was reported by Lyapustin *et al.* In order to obtain the model compound 66a in a good yield, the reaction optimization recommended using butanol solvent and boron trifluoride etherate (1.5 equiv.). Although other azolopyrimidines were produced by changing the building blocks (e.g., 66a–66f, Figure 17), the reaction's scope appears to be restricted because the majority of the derivatives only contain p-nitro and p-methoxy benzaldehydes. To demonstrate the universality of the reaction, a few products using other aminotriazoles are also described (66g–66j) in place of aminoazole (64). This scaffold can be diversified for other drug discovery applications by taking use of the nitro and ester groups.

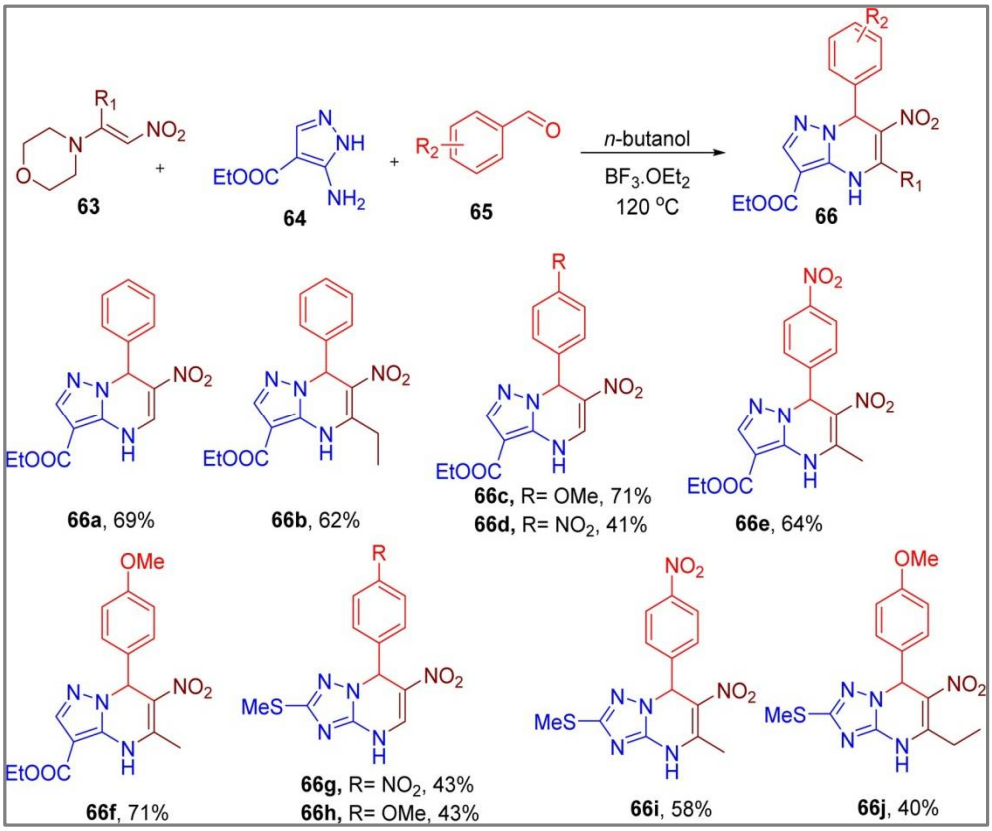

Figure 17. CR for the synthesis of azolopyrimidine scaffold.

Additionally, Zhang *et al.* described a simple three-component reaction for the synthesis of chromone-fused pyrimidine derivatives. Heating 3-formylchromone (67), p-toluidine (68), and para-formaldehyde (69) under microwave (MW) irradiation without solvent produced the maximum yield (98%) of the model chemical 5H-chromeno[2,3-d]pyrimidin-5-one (e.g. 70) (Figure 18) [**38**]. Substrate scope tests show that the halide-substituted chromones produced a higher yield of the final products than the methyl, hydroxy, or methoxy EDGs (e.g., 70a–70g). In a similar vein, naphthalene-fused chromone (70h) showed reduced conversion to the matching product. The intended pyrimidine-fused derivative (70i) was also produced in good yield by the estrone-based chromone, indicating this MCR's potential for late-stage derivatization. On the aryl amines, a range of EWGs and EDGs were likewise tolerated without significantly altering the final product yields (e.g. 70j–70n). Alkyl amines, however,

produced the corresponding compounds in comparatively lower yields, particularly those that provided steric hindrance around the amino group (e.g., 70u).

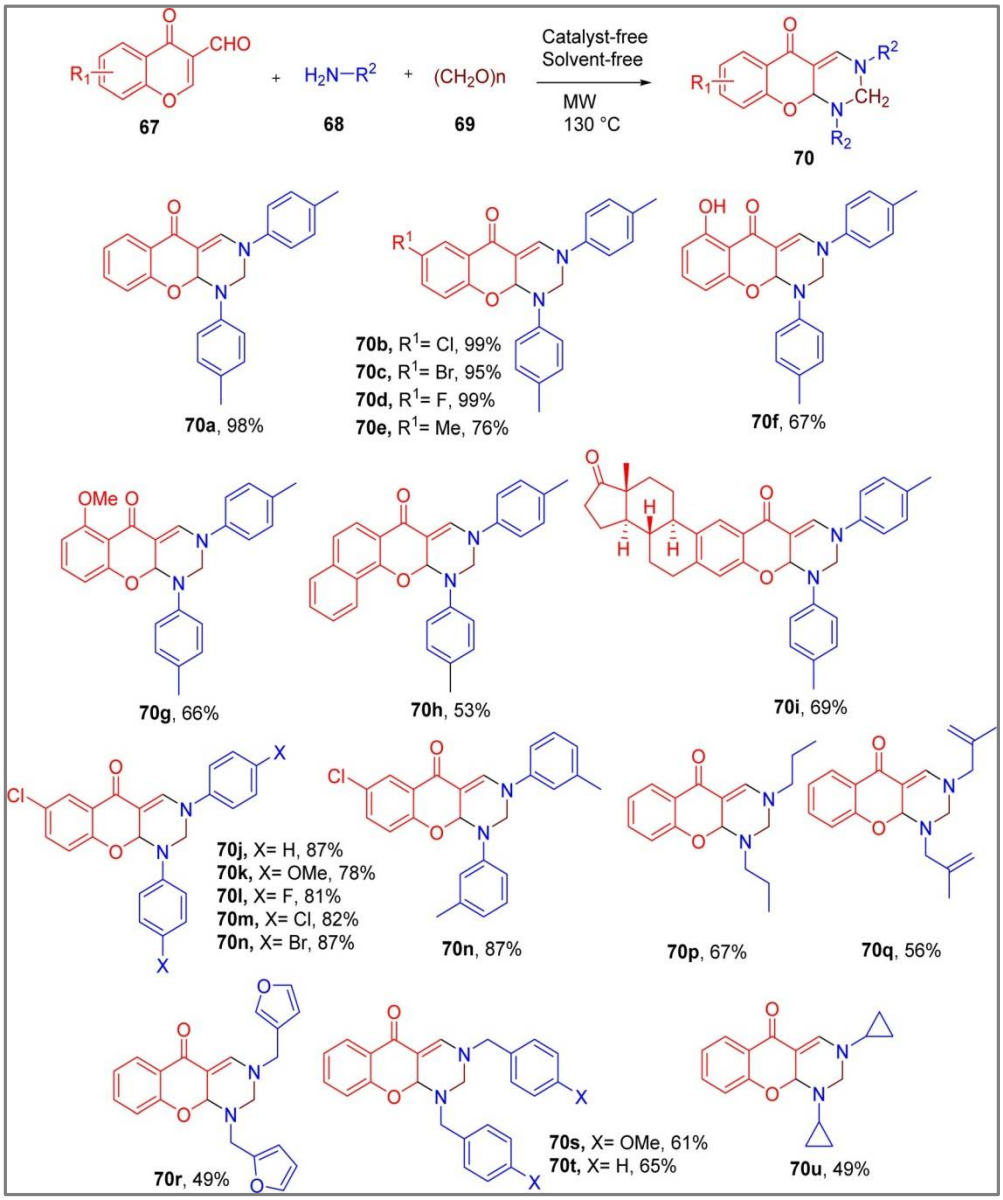

Figure 18. MCR for the synthesis of chromone-fused pyrimidines.

All things considered, this MCR is a significant one-pot method for creating a chromone-fused pyrimidine scaffold without the need for a solvent or catalyst. Tan and Wang reported a one-pot MCR that produced a tetra-substituted hexahydroimidazo[1,2-a]pyridine ring system (74, Figure 19) [**39**]. using easily accessible ethylenediamine (71), cinnamonaldehydes (72), and 1,3-dicarbonyl compounds (73). The best method for synthesizing the model chemical 74a, according to the screening of several reaction conditions, is to use an AcOH catalyst (0.2 equiv.) in methanol solvent. Single-crystal X-ray analysis verified that the MCR produced 74a at 84% at room temperature with good trans-selectivity (dr > 99: 1).Except for those with the ortho-substituents, a wide range of cinnamaldehydes with various EWGs and EDGs produced good yields of the respective products (e.g., 74a–74c). The required compounds were also produced in good quantities by substituting alkyl, phenyl, or benzyl groups at one end of ethylenedi-amine (e.g., 74d–74f). Similarly, indanedione and other 1,3-dicarbonyl beginning materials provided the goal chemicals with high yields, indicating the reaction's universality (e.g., 74g–

74i). It's interesting to note that using aminoethanol in place of ethylenediamine produced oxazolo[3,2-a] pyridine (such as 74j and 74k), a fragment that resembles a natural product.

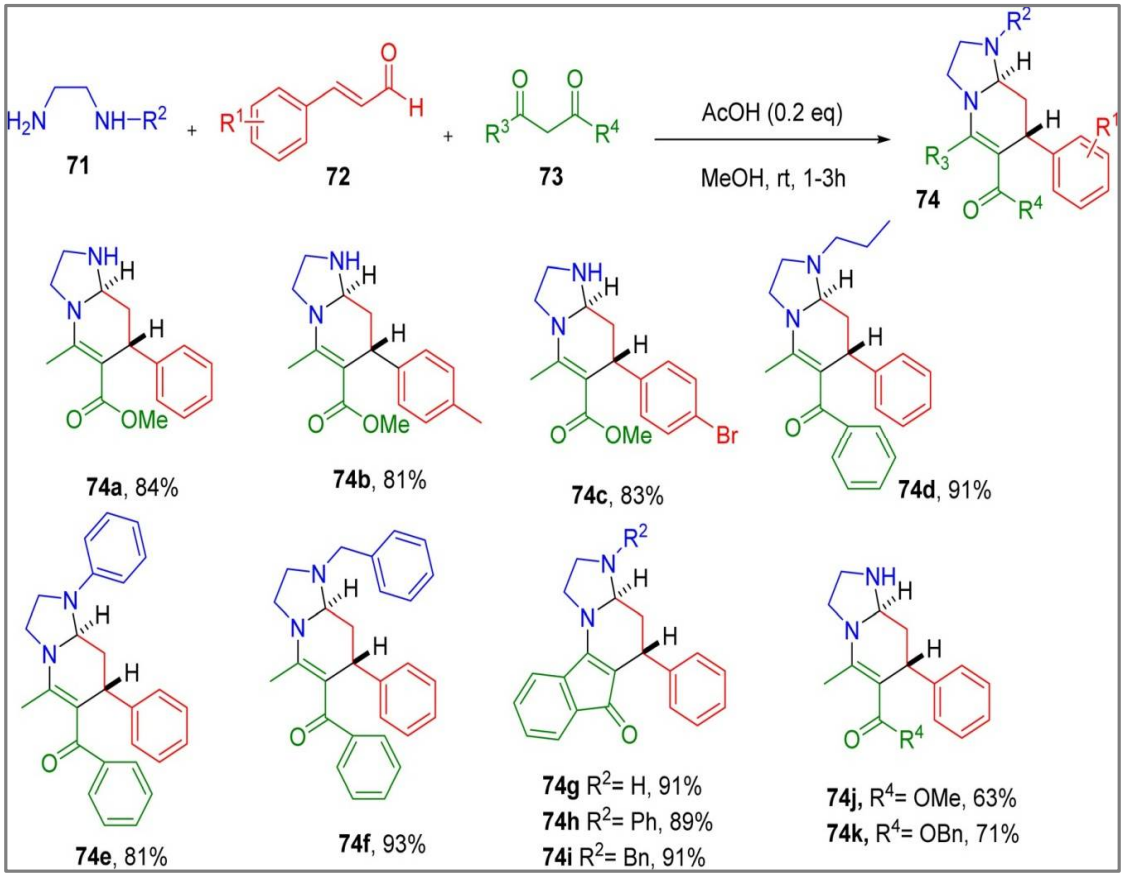

Figure 19. MCR for the synthesis of novel hexahydroimidazo[1,2-*a*] pyridine derivatives.

All things considered, this MCR is an essential tool for producing compounds that resemble natural products, beginning with the commercially available building blocks. High atom economy, mild conditions, high diastereo selectivity, and the use of inexpensive catalysts are the main characteristics of this MCR. Numerous manufactured and naturally occurring compounds with significant biological applications contain the heterocyclic ring 1,3,5-triazines and its derivatives. Specifically, 2,4-diamino-1,3,5-triazines exhibit strong antibacterial and anti-cancer properties. Under challenging circumstances, biguanide and one-carbon synthons are typically used to create this heterocyclic chemotype. A one-pot MCR technique for the synthesis of 2,4-diamino-1,3,5-triazines (78) from methyl ketones (75), anilines (76), and cyanamides (77) was recently devised by Zhao *et al.*, (Figure 20) [**40**]. The greatest yields of the model product 78a substituted with an iodine atom at the ortho-position of the aromatic amine were obtained by combining molecular iodine (2 equiv.) with TFA (1 equiv.) as an additive.

It was discovered that methyl ketones with various EWGs and EDGs were compatible with the ideal conditions (e.g., 78b–78i). The comparable compounds were also produced in good yields from electron-rich and halogen-substituted aniline substrates (e.g., 78j–78o). The products without an iodo-substituent at the ortho position (such as 78p and 78q) were produced by electron-deficient anilines with numerous halogens, which is consistent with the low nucleophilicity of such anilines at the ortho position. Quinoline-based amines or ketones were also used to obtain medically significant bi-heterocyclic compounds (such as 78r).

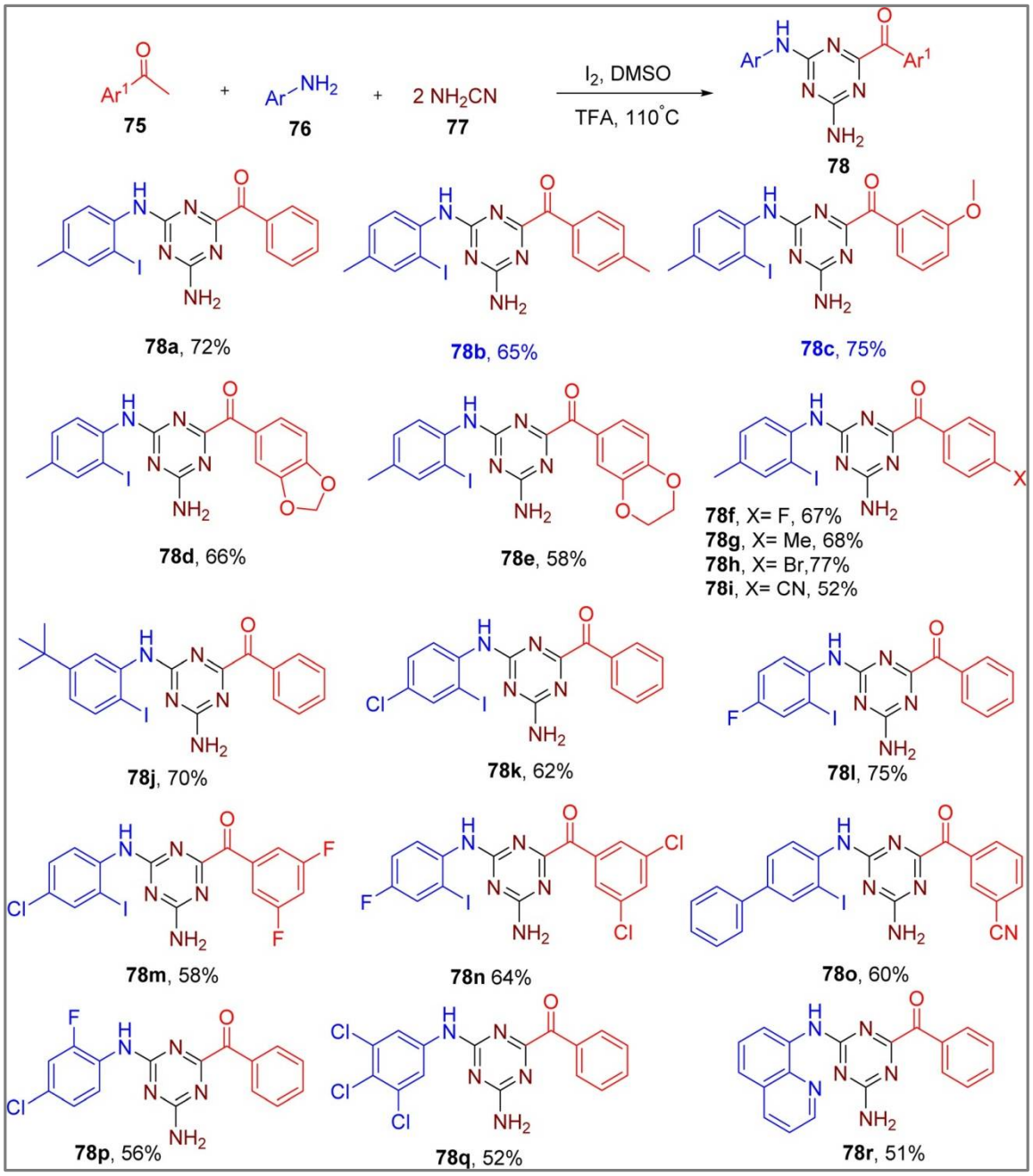

Figure 20. Synthesis of 2,4-diamino-1,3,5-triazines via MCR.

The phthalimide heterocycle is a crucial pharmacophore found in numerous pharmaceuticals that are utilized in clinical settings, physiologically active compounds, natural products, and the developing field of proteolysis. focusing on chimeras (PROTACs). Phthalimides and their analogues must be synthesized in multiple steps employing metal catalysts, unique building blocks, and reagents.[**41, 42**].

The US-mediated MCR process for the synthesis of a phthalimide skeleton was described by Alizadeh et al. First, they used an amine (79), CS2 (80), and dimethyl acetylene dicarboxylate (81, Figure 21**)** **[43**] to create the intermediate methyl 2-(3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene) acetate (82). The required functionalized phthalimide skeleton (85 and 86) was obtained by further reacting the latter with the malononitrile derivative (83 and 84) in the same pot. The best outcomes in terms of reaction time and ultimate yields were obtained with an 80% amplitude US irradiation with

triethylamine (Et3N) as the base. containing the exception of those containing EWGs like nitro, the reaction produced products in good yields with a variety of 84 derivatives (e.g., 85a–85d). The equivalent phthalimide products (86) with the fused bicyclic indene ring were also produced in good yields (e.g., 86a–86c) by switching to the 2-(3-oxo-2,3-dihydro-1H-inden-1-ylidene) malononitrile (83), indicating the reaction's universality.

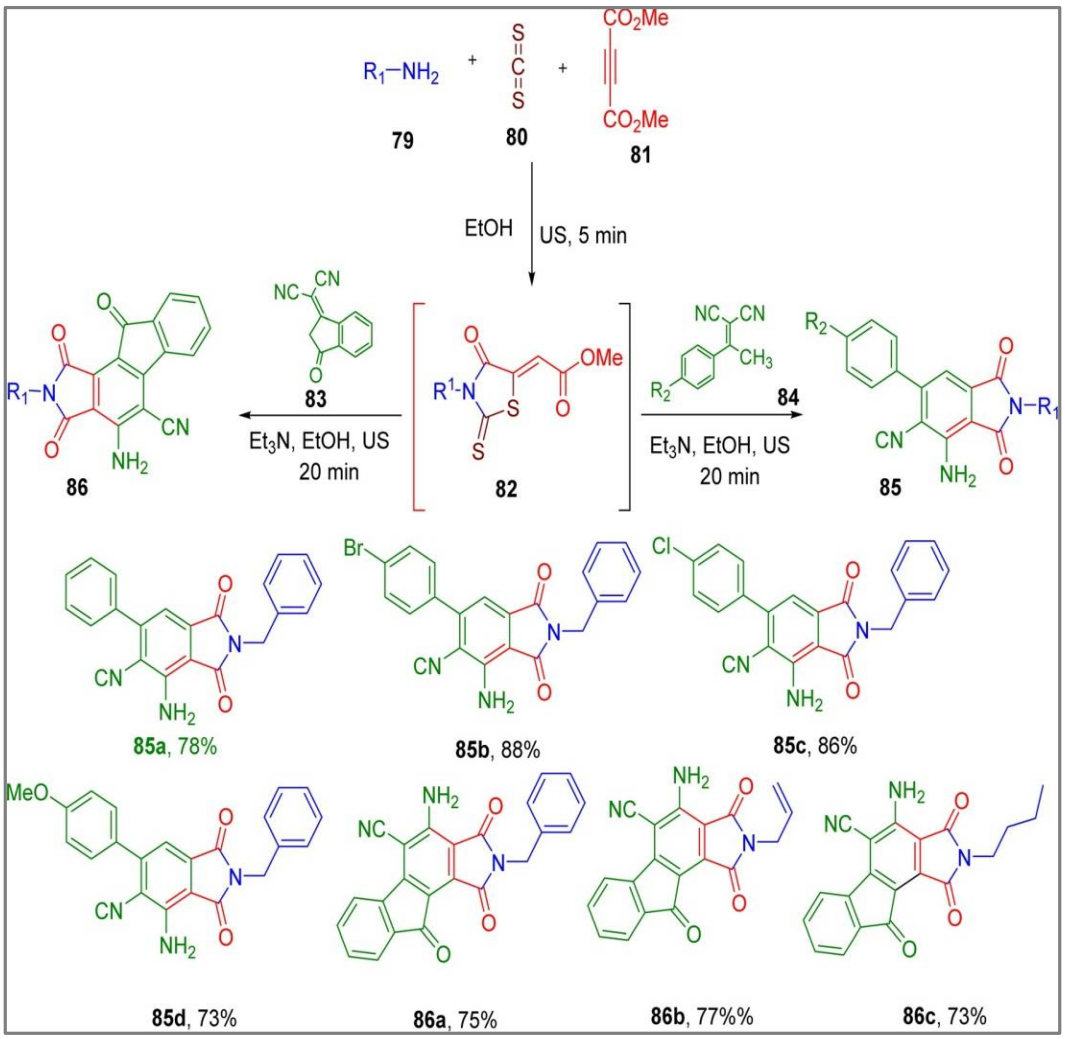

Figure 21. US-mediated MCR for the synthesis of substituted phthalimides *via* one-pot MCR.

Similar to podophyllotoxin, 4-azapodophylolotoxins have good tubulin polymerization inhibitory qualities and strong anticancer action. By coupling the pharmacophore of 4-aza-podophylolotoxins with aza-anthraquinones, Thi *et al.*, achieved an efficient synthesis of hybrid compounds. By intercalating DNA, the latter are also known to exhibit cytotoxicity. MCR between 2-hydroxy-1,4-naphthoquinone (87), tetronic acid (88), benzaldehyde derivative (89), and ammonium acetate (90) under MW irradiation produced the hybrid molecules (Figure 22) [44]. The best yield of the model chemical 91a was obtained by using molecular sieves, glacial acetic acid as a solvent, and heating at 120°C. It was discovered that a variety of aldehyde derivatives with different EDGs and EWGs produced the corresponding compounds with good to exceptional isolated yields (e.g., 91a–91k). Some of these novel substances showed strong cytotoxicity against various cancer cell lines, as was to be predicted.

Aminopyrazoles are important heterocycles in medicinal chemistry and serve as essential building blocks for the synthesis of other fused heterocycles. Annes *et al.*, described a metal-free synthesis of aminopyrazole derivatives (94, Figure 23) [45]. with a thioether substitution via an MCR between

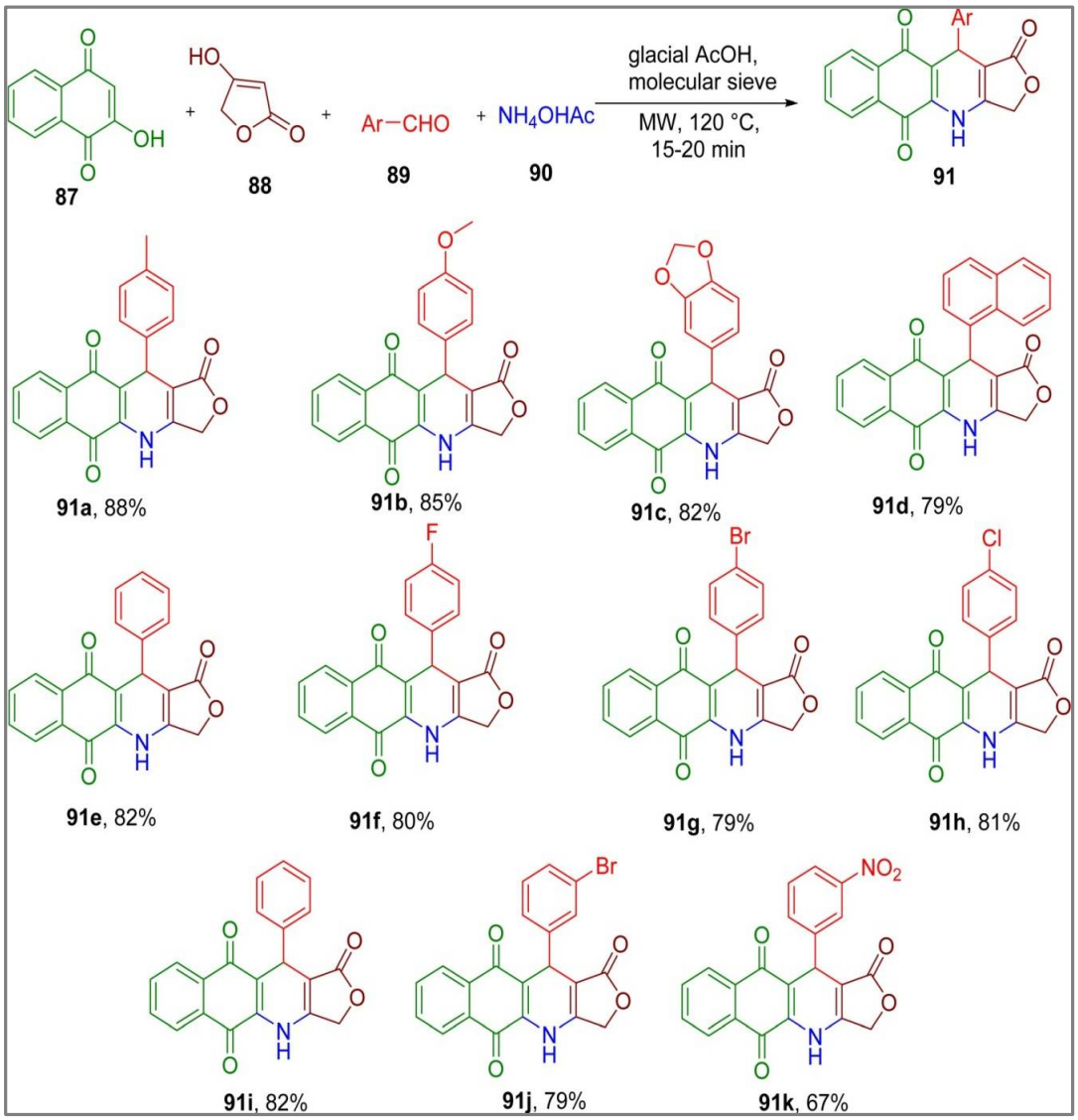

Figure 22. Synthesis of dihydrobenzo[*g*]furo[3,4-*b*] quinoline-1,5,10(3*H*)-triones derivatives.

phenylhydrazine (92), aryl thiol (93), and aminocrotononitrile (Figure 25). 90 When a solventless combination of all components was cooked in the presence of 1 equiv. iodine, the model product (95a) yielded well. A range of phenylhydrazines and thiols were utilized to produce the appropriate pyrazole compounds (95a-95z). Overall, both phenylhydrazines and thiols demonstrated similar steric and electrical effects. In both cases, EWGs or halide replacements resulted in lower product yields (e.g., 95c-95h; 95m-95p) than those containing EDGs. Ortho-substitution resulted in reduced yields of the respective pyrazoles (95i and 95j), possibly due to the steric effect. Interestingly, in the instance of tosyl hydrazide, the tosyl group remained intact in the resulting product (95k), albeit at a lower yield. Benzyl and aliphatic thiols (95s and 95u) performed less efficiently than phenylthiols under optimum conditions. Using different aryl-substituted aminonitriles instead of aminocrotononitrile resulted in lower yields (e.g. 95v-95z), limiting the scope of b-enaminonitriles.

Overall, this one-pot MCR produced a wide variety of aminopyrazoles. End products containing halide substituents are especially helpful for further alterations.

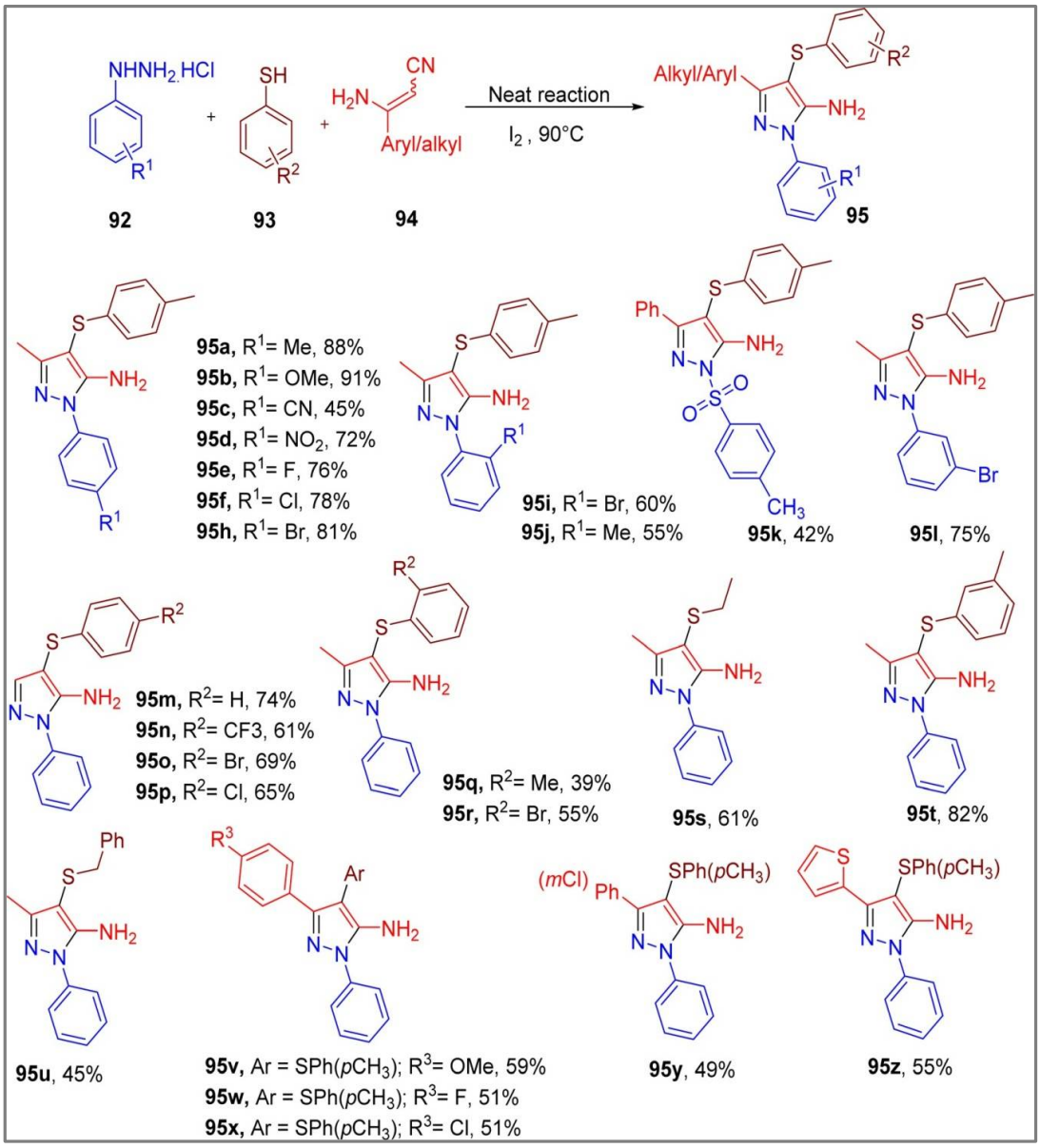

Figure 23. Synthesis of aminopyrazole thioether derivatives *via* solvent-free cascade reaction.

Pyrazole rings are frequently found in compounds that are useful to medicine and other fields of chemical study.91–93 Barroso et al. created a three-component reaction combining alkyne (96), hydrazone (97), and N-heterocycle (98) to produce multi-substituted pyrazole scaffold (99) (Figure 24), [**46**] building on their previous work.95. Heating the building blocks in ACN with extra potassium carbonate (K_2CO_3) (5 equiv.) produced the maximum yield of the model compound (99a). Different trisubstituted pyrazole compounds were produced in good to moderate yield (99b–99h) by combining nucleophilic N-heterocycles such imidazole and benzotriazole with a range of terminal alkynes linked to aryl and heteroaryl rings.

For this MCR, the scientists also developed a two-stage, four-component approach in which alkyne and azole components were added after N-tosyl hydrazones were obtained from a-bromoketones and tosylhydrazide in the first phase. The MCR became simpler as a result of this procedure, increasing its promise in medicinal chemistry. A crucial component of medications, catalyst ligands, and other compounds is the pyridine ring.27, 96 However, metal-free, inexpensive, and ecologically benign ways to build 2-substituted pyridines are missing.

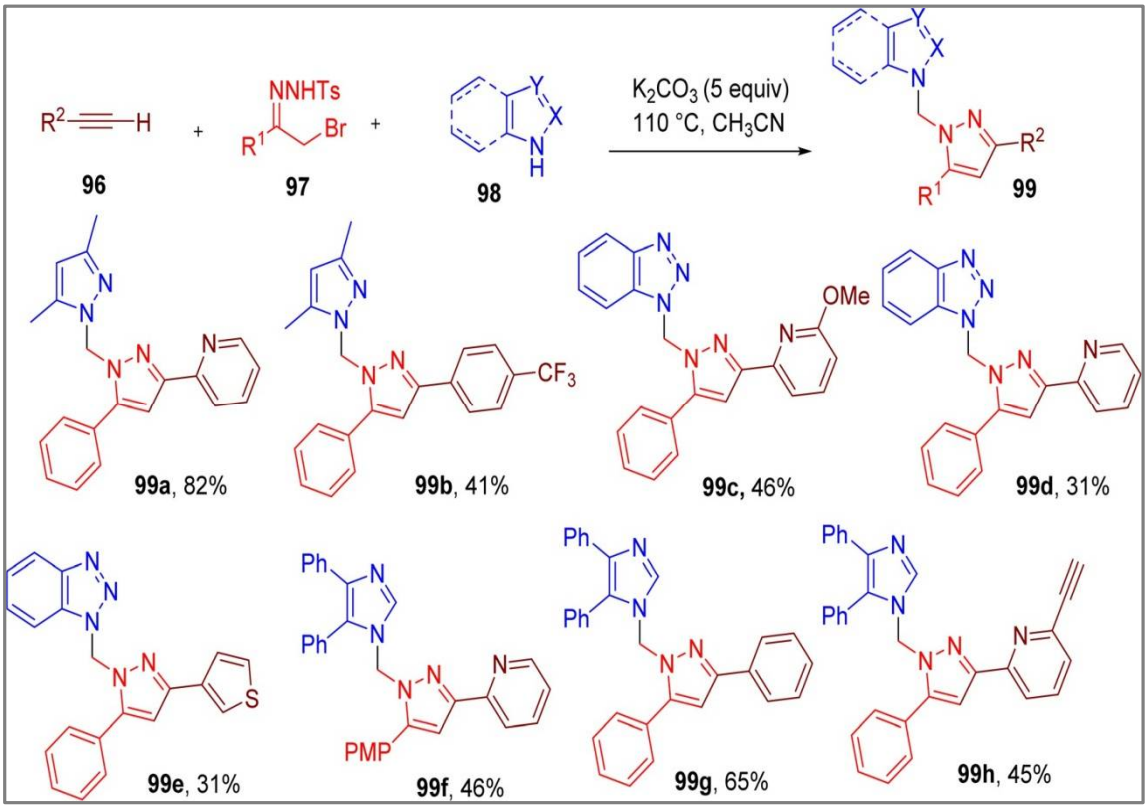

Figure 24. MCR approach for the synthesis of the trisubstituted pyrazoles.

For the production of pyridine derivatives under mild circumstances, Zhu *et al*., found an MCR between ynals (100), isocyanides (101), and amines/alcohols (102) **(**Figure 25) [**47**]. A hundred THF solvent and diisopropylethylamine (DIPEA) base at 50°C were the ideal reaction conditions (Figure 25). In these circumstances, the intended pyridine derivatives (such as 103a and 103b) were obtained in good yields from secondary and primary amines. The corresponding intended products with good to moderate yields (e.g., 103c–103h) were likewise formed by the aniline derivatives with different EDGs and EWGs. The equivalent 2-O-substituted pyridine derivatives (such as 103i–103l) were also produced by substituting other alcohols for an amine, demonstrating the wide range of applications of this MCR.[48]

Methyl and methoxy groups could be substituted on the phenyl ring (e.g., 103m and 103n), even though the majority of the analogues were derived from phenylpropiolaldehyde as an ynal component. Additionally, the reaction proceeded effectively using oct-2-ynal (103o) and 3-(thiophen-3-yl) propionaldehyde (103p). Moving away from the model substrate ethyl isocyanoacetate did not produce the equivalent pyridines in the case of isocyanides, indicating a limited substrate scope [**49**].

It is well recognized that the imidazolopyridine scaffold has significant medicinal qualities. The creation of this scaffold has previously been reported using either multistep synthesis or the use of metal catalysts and toxic organic solvents. Equimolar amounts of phenylglyoxal (104), 2-aminopyridine (105), and barbituric acid (106) reacted to produce imidazolopyridine functionalized at C-3 with a pyrimidine ring (107, Figure 26) [**50**]. according to Brahmachari et al. Reaction optimization studies revealed that water under reflux conditions was the optimal solvent for this MCR, producing 93% of the model product (107a). These catalyst-free conditions also produced good yields of the target compounds (e.g., 107b–107f) when used with additional phenylglyoxals replaced with halides, methoxy, and nitro groups. The necessary products (e.g., 107g) were likewise obtained in good yields

Figure 25. MCR for the synthesis of tri-substituted pyridines.

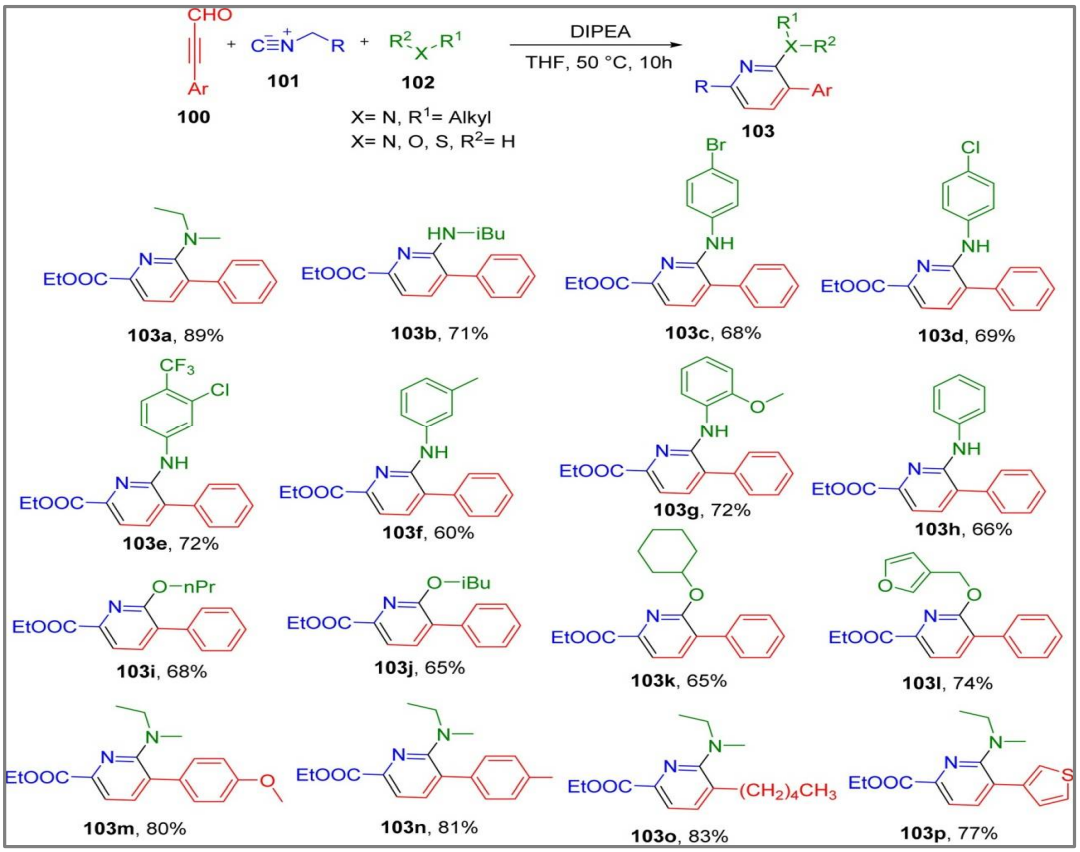

Figure 25. MCR for the synthesis of tri-substituted pyridines.

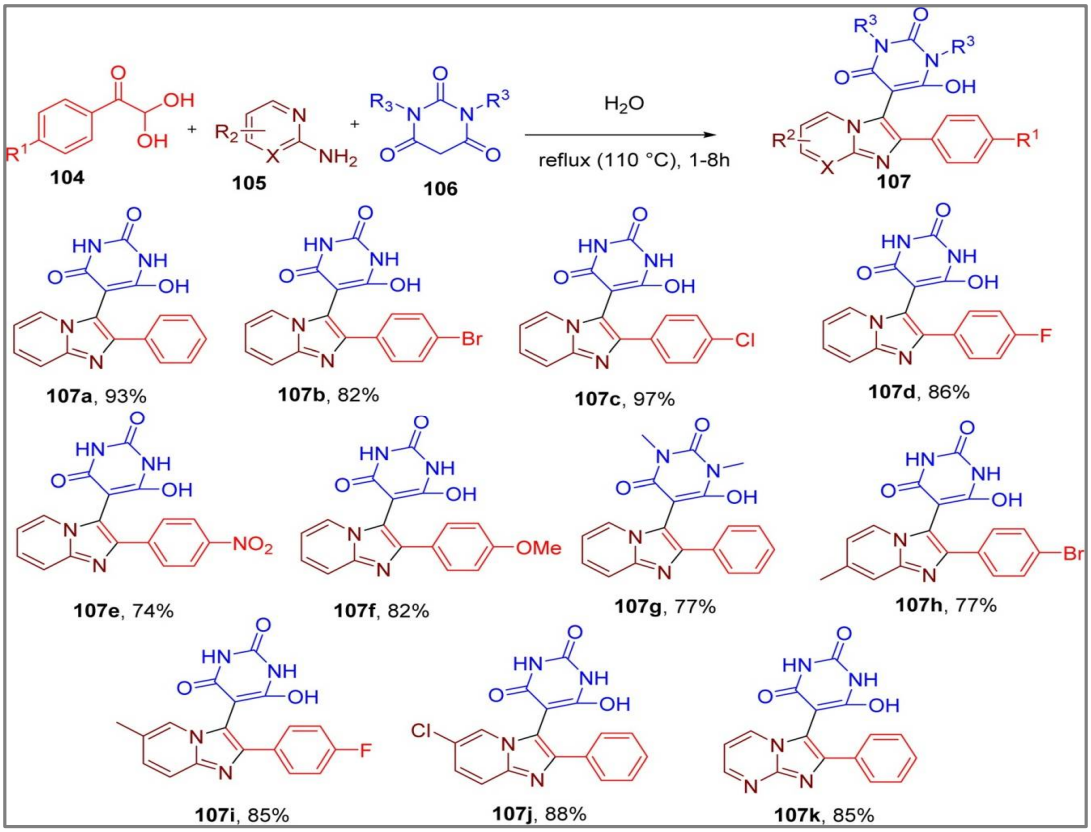

Figure 26, MCR for the synthesis of substituted imidazolopyridines

when barbituric acid was substituted with N, N-dimethyl barbituric acid. Likewise, methyl and halide replacements on the aminopyridine component were also accepted (e.g., 107h–107j). The equivalent products (such as 107k) were likewise produced in good yields when 2-aminopyrimidine was substituted for aminopyridine, indicating the wide range of this MCR.

After filtration, all of the products that precipitated from the reaction mixture could be collected with high purity. All things considered, this MCR is an easy catalyst-free green technique with a very low E-factor and a great atom economy.

CONCLUSION

The most up-to-date sources and procedures for the synthesis of a wide range of fused n-heterocyclic derivatives using modern-day multicomponent reactions (MCRs) are presented. This method predominates the other instrumental practices because of its easy workup and more efficient processes. The present research scenario uses greenery and eco-friendly instrumental setups to generate novel derivatives. There has been a lot of progress in N-heterocyclic skeleton synthesis and application in medicinal chemistry, which is possible only due to their greater bioavailability, easy manufacturing, lower toxicity, lesser drug resistance, higher biocompatibility, etc. Therefore, the synthesis method depends on the characteristics of these scaffolds in the present system of drug discovery and design. The study dealt extensively with the fused N-based heterocyclic compounds, including benzofuran-fused piperidines, indole-fused oxadiazepines, indole-fused thiadiazepines, tetrazole-fused indole, quinazolinones, benzo[*d*]azepines, azolopyrimidine, pyrrole, thiazine, pyrimidine, morpholine, piperazine, benzothiazines, pyrazole-fused benzothiazines, morpholine-fused benzothiazines, piperazine-fused benzothiazines along with extremely promising biological properties such as antimicrobial, anticancer, anti-inflammatory, and other therapeutic properties. There is a need to develop more sustainable and eco-friendlier MCRs strategies, including catalyst-free and solvent-free reactions. The integration of MCRs with emerging technologies, such as flow chemistry, computational modelling, and machine learning, offers exciting prospects for enhancing reaction efficiency and product diversity. Continued research into overcoming the current limitations of MCRs, especially in terms of selectivity and scalability, will be essential for fully realizing their potential in both academic and industrial settings.

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