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Beyond Traditional Methods: Facile Multicomponent Reactions as Cornerstones of Drug Development

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Abstract:- Multicomponent reactions (MCRs) have emerged as transformative cornerstones in modern drug development, revolutionizing the synthesis of complex molecular architectures. Beyond traditional methods, MCRs offer unparalleled advantages by enabling the concurrent assembly of multiple reactants into intricate structures through a single, streamlined process. This abstract delves into the significance of MCRs in drug development, highlighting their facile nature and diverse applications. Traditional drug synthesis methods often involve a series of stepwise reactions, resulting in prolonged timelines, lower yields, and increased costs. In contrast, MCRs expedite synthesis by condensing several reactions into a single step, thereby accelerating drug discovery and development. Their inherent atom- and step-economy fosters efficiency, while the reduced number of purification steps minimizes resource consumption. The versatility of MCRs facilitates the creation of structurally diverse compounds, critical for exploring new biological targets and pathways. The broad scope of reactants allows the integration of various functional groups into a single molecule, enhancing drug potency, selectivity, and bioavailability. Furthermore, MCRs enable the incorporation of privileged scaffolds, expediting the optimization of lead compounds and the generation of focused compound libraries. The review also underscores the impact of MCRs on addressing medicinal chemistry challenges. Their application in fragment-based drug design and diversity-oriented synthesis presents innovative strategies for hit identification and lead optimization. MCRs have been pivotal in producing bioactive molecules with intricate 3D architectures, targeting protein-protein interactions and challenging binding pockets that were once deemed undruggable. However, the successful application of MCRs in drug development demands a profound understanding of reaction mechanisms, substrate compatibility, and stereochemistry. Computational tools and predictive models have aided in rationalizing reaction outcomes, enabling efficient reaction design and optimization. In conclusion, multicomponent reactions stand as powerful tools beyond traditional methods, reshaping the landscape of drug development. Their facile execution, synthetic efficiency, and structural diversity capabilities position them as pivotal techniques in the creation of innovative therapeutic agents. As research in this field continues to evolve, the seamless integration of multicomponent reactions into the drug development process holds the promise of accelerating the discovery of novel treatments for a myriad of diseases.

Keywords:- *Multicomponent reactions; Drugs; Biological activity; Isocyanide; Anticancer; Anti-inflammatory*.

I. INTRODUCTION

Multicomponent reactions (MCRs) hold substantial significance in the domains of synthetic organic chemistry and drug discovery [1]. They are bifurcated into isocyanide-based multicomponent reactions (IMCRs) and non-isocyanide-based multicomponent reactions (NIMCRs), both offering efficient avenues to construct molecular libraries with commendable yields [2]. Notably, the Gewald 3-component reaction (3-CR) emerges as a widely adopted technique within drug discovery [3]. In the current scenario, isocyanide-based MCRs, particularly the classical Passerini and Ugi reactions, stand at the forefront of multicomponent methodologies [4]. A pivotal application of MCRs is evident in the synthesis of kinase inhibitors, streamlining the production of potential drug candidates [5].

MCRs demonstrate robust utility in the synthesis of intricate molecules and drug-like heterocycles [6]. Their capacity to engender diverse chemical structures renders them indispensable for traversing expansive chemical landscapes. The paradigm of library screening has catalyzed a transformation in drug development, expediting the identification and optimization of bioactive lead molecules [7]. Notably, small organic molecule libraries possess heightened bioavailability compared to peptides and oligonucleotides, amplifying their worth as potential drug candidates. MCRs expedite the generation of substantial libraries, thereby constituting a valuable asset for medicinal substance research [8]. Although MCRs previously held limited appeal for around five decades, their resurgence in drug discovery has been fueled by the integration of high-throughput biological screening techniques. This revitalized interest stems from the considerable therapeutic potential inherent in diverse heterocyclic compounds [9]. Furthermore, the well-defined and rigid structures of heterocycles have proven pivotal in numerous structure-activity relationship studies.

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II. MULTICOMPONENT REACTION IN ISOCYANIDE-BASED DRUG DISCOVERY

Multicomponent reactions (MCRs) are influential techniques that combine multiple starting materials to generate novel compounds through chemical transformations. The complexity of products formed in an MCR is contingent on the number of reactants involved. Isocyanide-based multicomponent reactions (IMCRs) have gained prominence owing to the wide array of available starting materials [10]. Over the past two decades, classical Passerini and Ugi IMCRs have experienced substantial growth [11]. Furthermore, the integration of IMCRs with other reactions has expanded, leading to increased structural diversity [12]. IMCRs are characterized by their convenience, utilizing readily accessible starting materials and accommodating various functional groups. They allow for numerous subsequent transformations, facilitating the synthesis of diverse molecules that would otherwise require lengthy synthetic routes. IMCRs are valuable tools for exploring diverse chemical space, particularly in the context of combinatorial chemistry, where they aid in constructing libraries of hybrid molecules [13]. Both academia and pharmaceutical companies recognize the environmentally friendly nature of MCRs in developing biologically active compounds. In 2006, Domling's group extensively outlined the applications of IMCRs in drug discovery [14].

Currently, Isocyanide-Based Multicomponent Reactions (IMCRs) are extensively applied in the domain of drug discovery, fulfilling crucial prerequisites for the synthesis of intermediary drug compounds. These requisites encompass factors such as simplicity in execution, efficient use of time, adaptability, and a diverse array of structural frameworks. These characteristics render IMCRs particularly appealing to professionals in the pharmaceutical sector. Another captivating facet of Multicomponent Reactions (MCRs) in drug discovery pertains to their ability to generate intricate frameworks from smaller molecular fragments. This attribute introduces an innovative angle to fragment-based drug discovery, facilitating the exploration of varied MCR frameworks. It also allows for the integration of fragment-based initial materials upon the identification of suitable fragments. For a visual compilation of recent instances gleaned from patents and scholarly literature in the field of drug discovery, please refer to Figure 1.

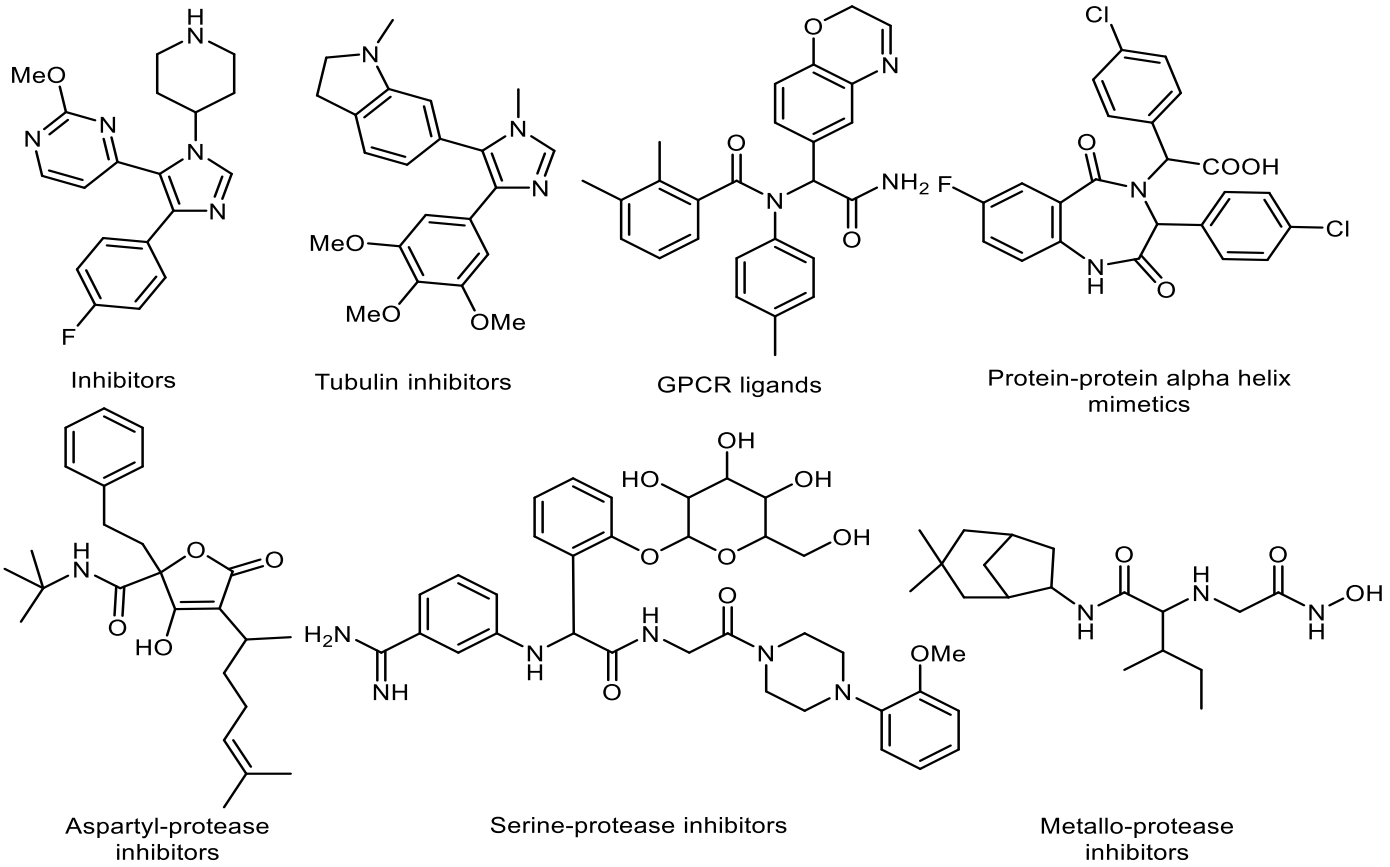
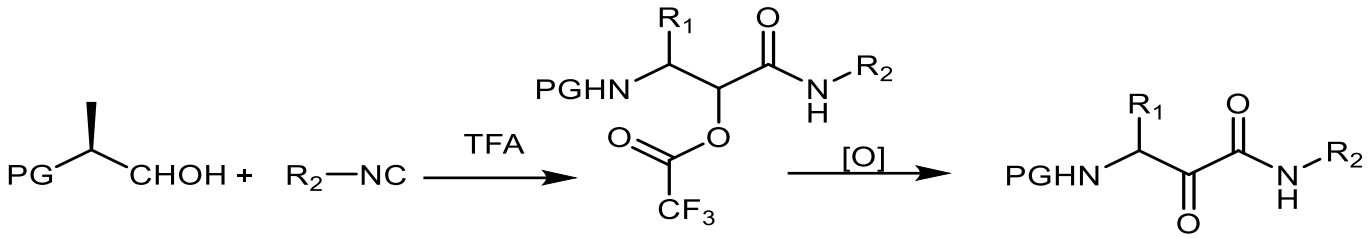


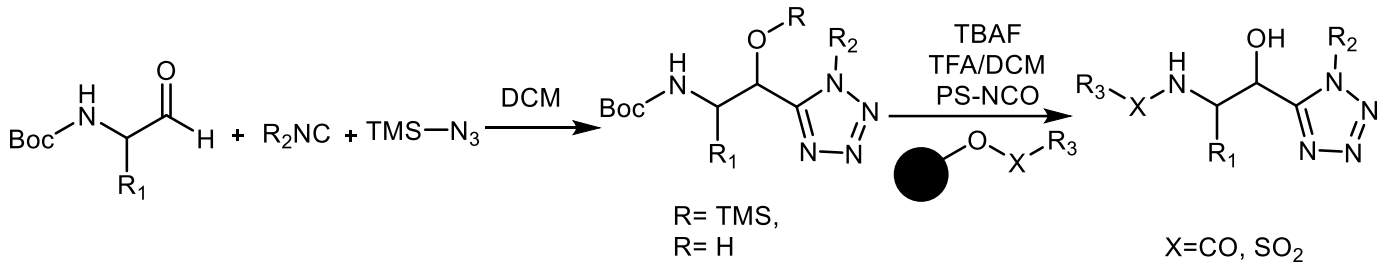
Fig 1 MCR in Drug Discovery.

The origins of IMCRs trace back to 1921 when Passerini first introduced them, and the term is derived from his name [15]. Isocyanides themselves have historical roots dating back to the 1850s, with Lieke making a noteworthy discovery in 1859. Much like contemporary chemists, Lieke was intrigued by their distinctive odor, one of the few drawbacks associated with this branch of chemistry. Fortunately, among commercially available reagents, most higher molecular weight isocyanides are odorless and solid [16, 17]. Conducting reactions involving isocyanides usually requires routine safety precautions.



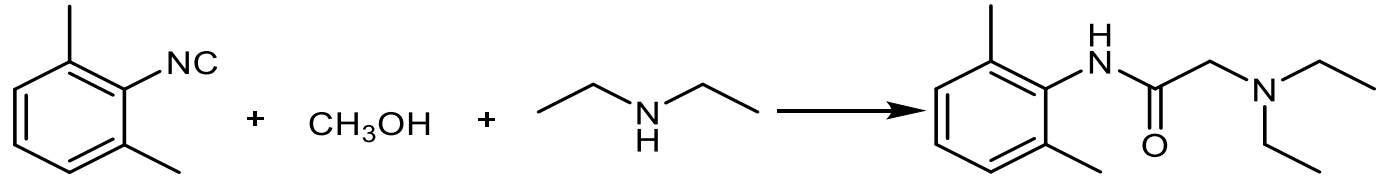
Scheme 1 Synthesis of Ketoamides by Passerini Reaction.

Peptidomimetics often offer a strategy to enhance the pharmacological attributes of molecules by substituting amide bonds [23]. The significance of cis-amide conformation in receptor recognition finds robust support in the notable biological efficacy of tetrazole-substituted analogs. This structural constraint proves particularly illuminating in deciphering enzyme-substrate interactions. A pioneering approach by Abell and colleagues involves the synthesis of cis-constrained hydroxyethyl amine isosteres based on tetrazole, ushering in a contemporary category of constraints for inhibiting HIV-1 protease [24]. Likewise, Nixey et al. introduced an innovative variation of the Passerini reaction, leveraging TMSN3, to target proteases utilizing cis-constrained norstatine-tetrazole transition state mimetics. This inventive strategy involves replacing the carboxylic acid in the Passerini reaction with TMSN3, amalgamating it with N-Boc-α-amino aldehydes and isocyanides to generate tetrazole intermediates. Subsequent treatment with TBAF, acid deprotection, and N-capping culminate in the synthesis of the desired cis-constrained norstatine-tetrazole mimetic (refer to Scheme 2) [25].



Scheme 2 Synthesis of Tetrazole Derivatives.

Ugi and his collaborators also recognized the potential of using a one-pot reaction involving isocyanide, aldehyde, and amine for drug discovery applications. This method was employed to synthesize the widely used local anesthetic Xylocaine (refer to Scheme 3). As a result, numerous local anesthetics based on the α-amino carboxamide scaffold have been uncovered by various pharmaceutical companies. All of these compounds are accessible through a single reaction, as depicted in Figure 2 [26].



Scheme 3 Synthesis of Xylocain.

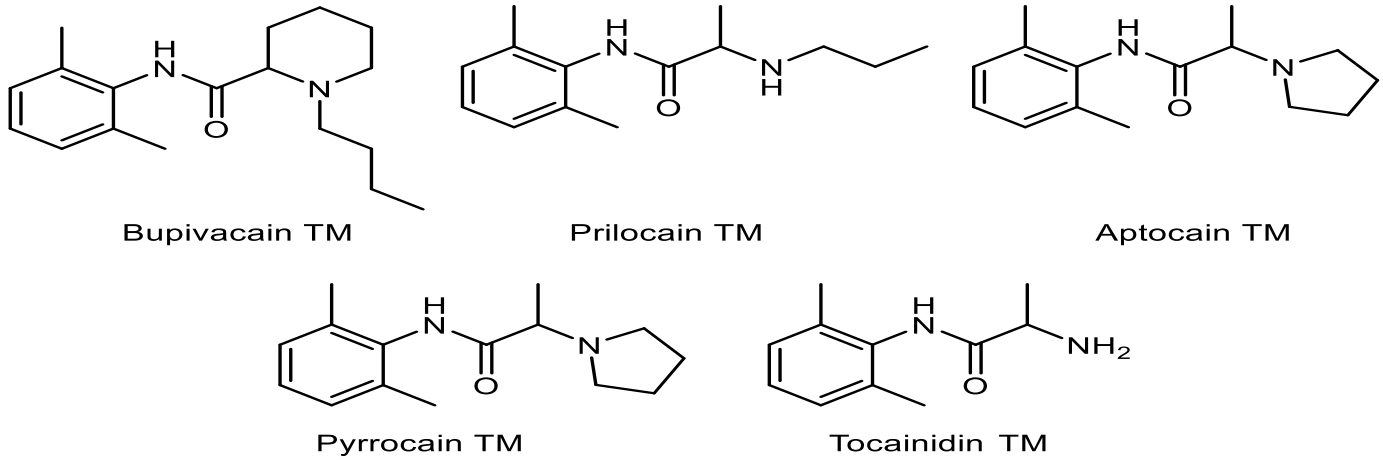


Fig 2 Local Anesthetic Marketed by Pharmaceutical Companies.

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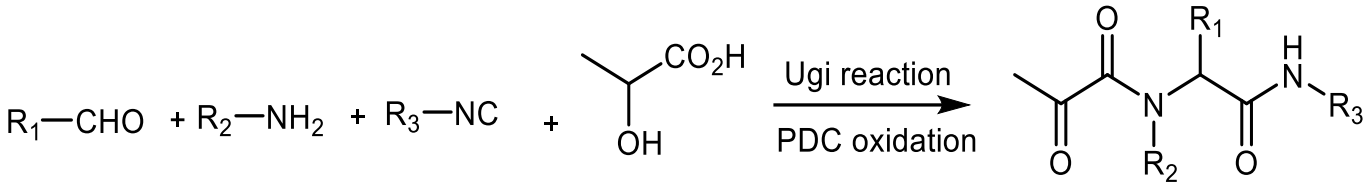
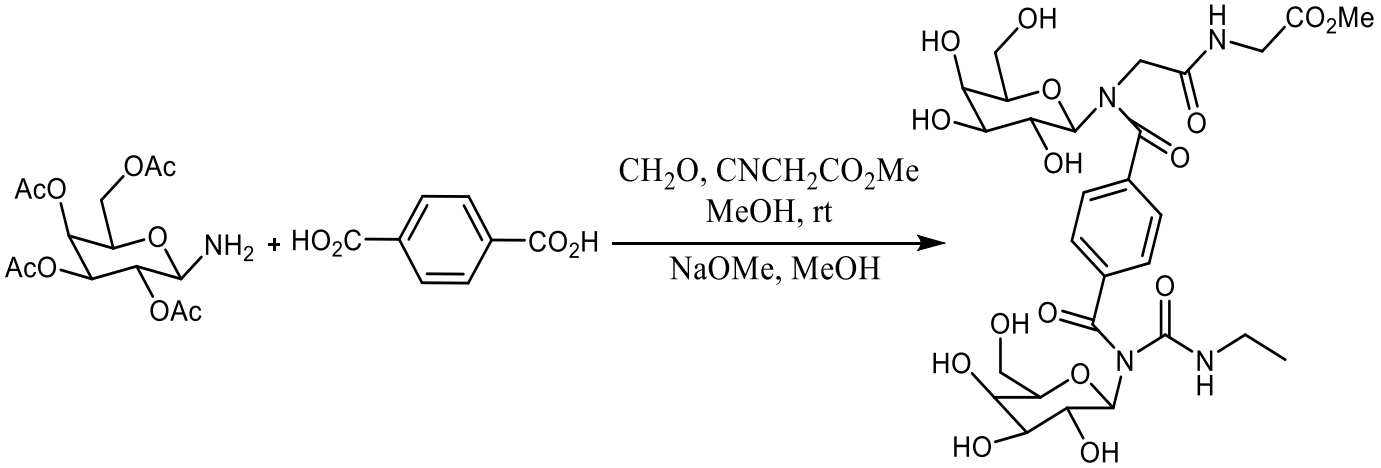
Nakamura *et. al.* pioneered the synthesis of cysteine protease inhibitors utilizing the Ugi reaction [27]. Cysteine proteases hold pivotal roles in the pathogenesis of diverse diseases, including osteoporosis [28], muscular dystrophy [29], and various central nervous system disorders [30]. Employing a three-component reaction followed by pyridinium dichromate (PDC) oxidation, they generated a library of 100 α-ketoamides in a one-pot synthesis (Scheme 4).



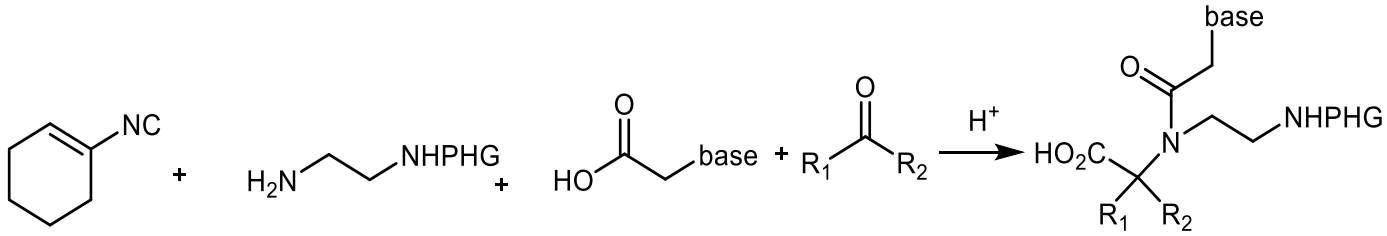
Scheme 4 Synthesis of α-ketoamides.

The extensive applicability of the Ugi reaction has garnered recognition from numerous research groups, finding utility in carbohydrate chemistry and biology [31]. Recently, Murphy and his research team demonstrated the utilization of the Ugi reaction in the synthesis of dimeric galactose derivatives [32]. As depicted in Scheme 5, a terephthaloyl-bridged neoglycoconjugate was successfully synthesized. This inventive approach has now been harnessed for crafting diverse libraries of divalent carbohydrate derivatives, significantly contributing to the development of innovative and potent carbohydrate-based therapeutics.



Scheme 5 Synthesis of Dimeric Galactose Derivatives by Ugi Reaction.

In the realm of structurally modified oligonucleotides, which have emerged as promising candidates for antisense and anti-gene therapy, Nielsen and his team introduced Peptide Nucleic Acids (PNAs). These PNAs incorporate a peptide moiety that entirely replaces the sugar-phosphate backbone [33]. Building upon this foundation, Martens et al. employed the classical Ugi condensation in conjunction with an innovative convertible isocyanide (cyclohexanylisocyanide) to synthesize an array of PNA monomers (refer to Scheme 6).



Scheme 6 Synthesis of Peptide Nucleic Acid.

Similarly, Ugi and colleagues employed a similar strategy for the synthesis of carbapenems and cephalosporin derivatives. In a parallel manner, Astra and their collaborators explored diverse *β*-lactam analogs of nocardicin, as outlined in Scheme 7 [35]. Nocardicin A, first synthesized in 1975, marked the initial instance of a monocyclic *β*-lactam with potential antibacterial activity [36]. Their approach involved utilizing chiral *β*-amino acids, aldehydes, isocyanides, and the transformation of the carboxylic acid into an N-diphenylmethane moiety through N-nitroso amide formation and subsequent conversion into the corresponding ester. This instance underscores an early application of a convertible isocyanide.

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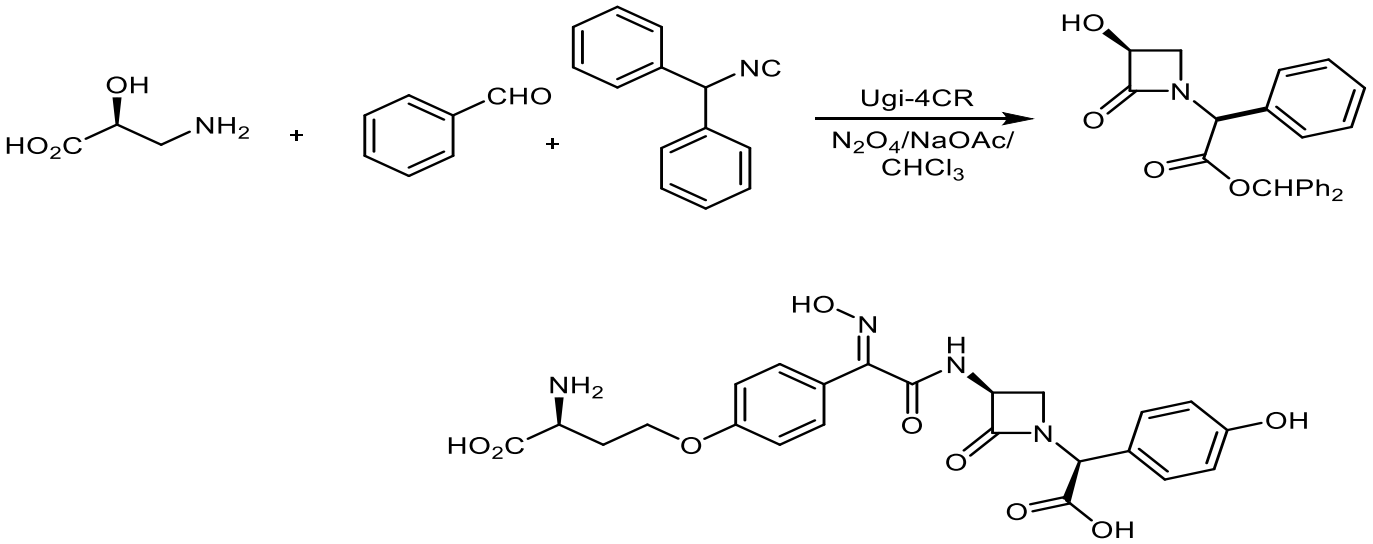
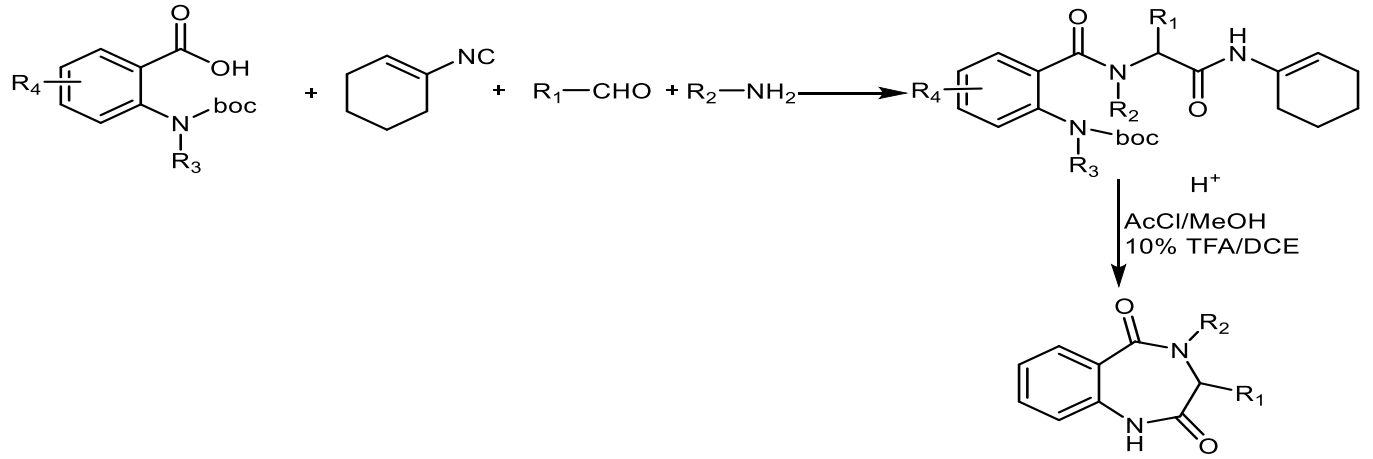


Scheme 7 Synthesis of Nocardicin A.

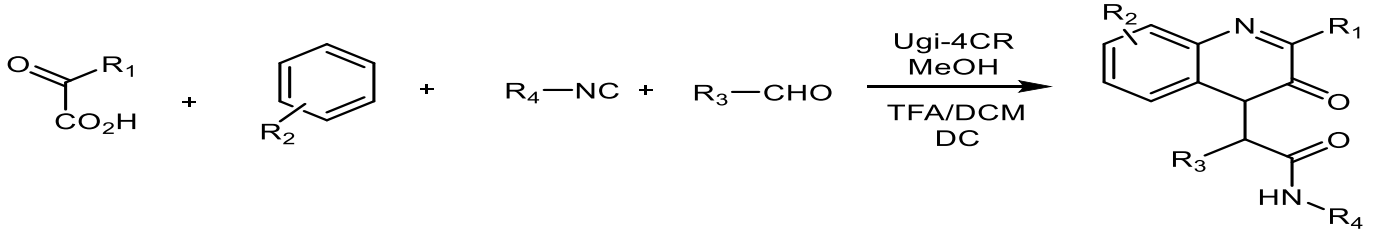
Benzodiazepines have garnered considerable pharmacological interest in recent decades and stand as a challenging heterocyclic template within drug therapeutics. Notably, 1,4-benzodiazepine-2,5-diones have found diverse biological applications, including their utilization as platelet glycoprotein IIb-IIIa antagonists [37] and anti-convulsant agents [38]. Armstrong and Keating [39] synthesized such compounds through the Ugi multicomponent reaction employing anthranilic acids, 1-isocyanocyclohexene, aldehydes, and amines (Scheme 8) [40].



Scheme 8 Synthesis of Benzodiazepines.

Imidazolines exhibit notable biological activity, including their role as antidepressants. Imidazoline ligands have been acknowledged for their interaction with receptors present in both the peripheral and central nervous systems [41]. Furthermore, the imidazoline moiety has been extensively studied as a substitute for amide bonds in biologically active peptides [42]. Benzimidazoles also have diverse organic applications, such as Xa inhibitors, NPY1 antagonists, and proton pump inhibitors [43].

In a recent investigation, Nixey et al. conducted the synthesis of quinoxalinone derivatives using a Ugi-4CR reaction involving glyoxylic acids, N-Boc-phenylenediamines, isocyanides, and aldehydes (refer to Scheme 9) [44]. Quinoxalinones exhibit a wide range of biological functions, including their role as kinase inhibitors [45]. Figure 3 displays four representative instances of quinoxalinone derivatives.



Scheme 9 Synthesis of Quinoxalinones.

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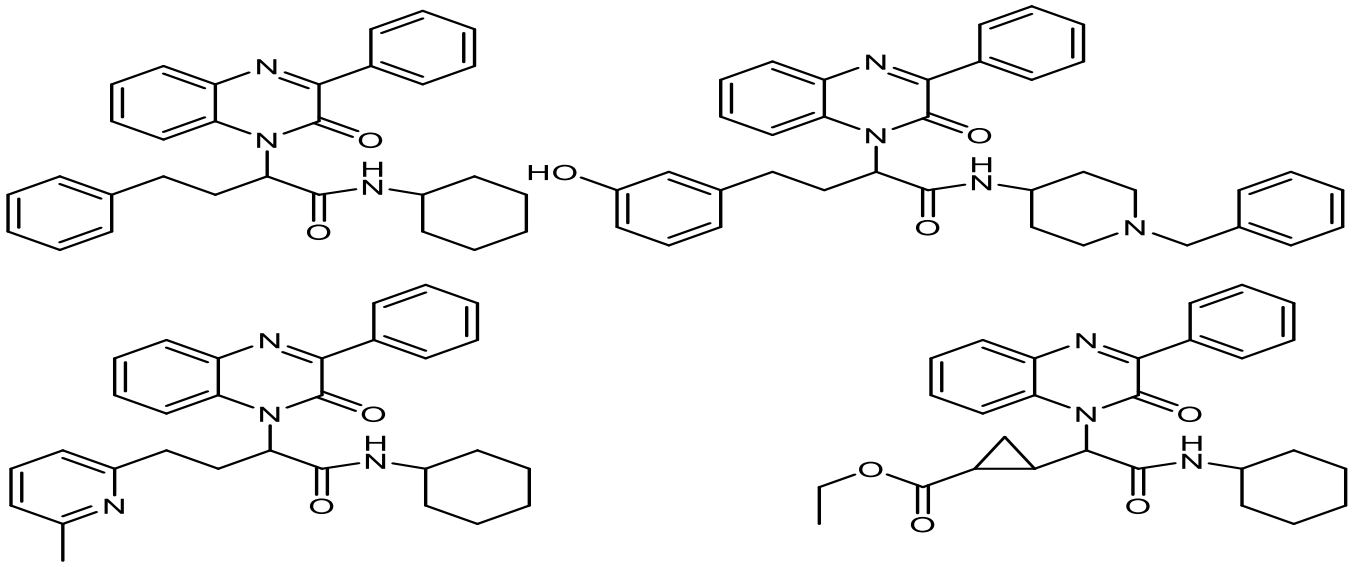
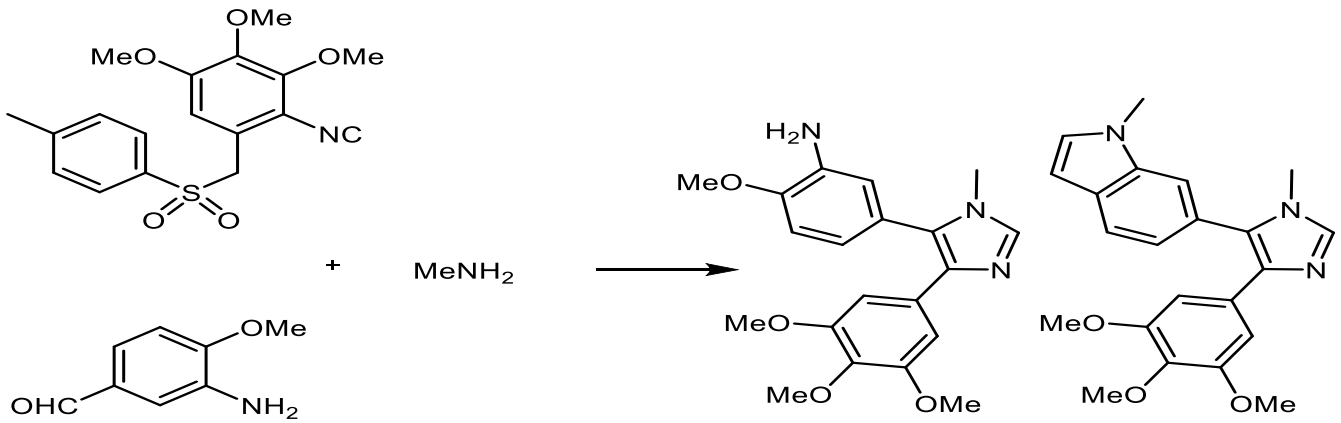


Fig 3 Quinoxalinones Derivatives.

Researchers have outlined the development of potent and orally available tubulin inhibitors for potential application in cancer therapy [46]. Their strategy involved the reaction of R-substituted tosylmethyl isocyanides with primary amines and aldehydes, resulting in 1,4,5-trisubstituted imidazoles (refer to Scheme 10) [47]. These promising tubulin inhibitors align well with the pharmacophore model of colchicine site binders, akin to compounds like colchicine, combretastatin, and podophyllotoxin.



Scheme 10 Synthesis of Potent Tubulin Derivatives.

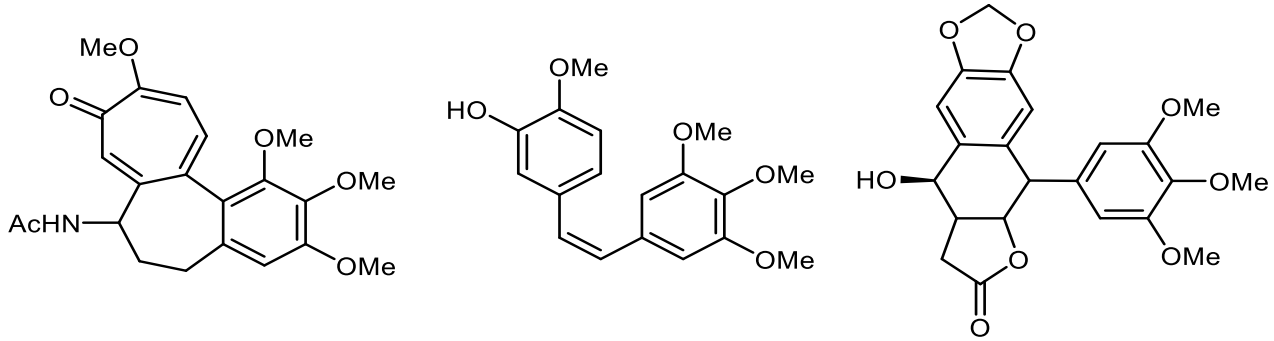


Fig 4 Examples of Potent Tubulininhibitors.

Heterocycles containing nitrogen are a prevalent structural feature found in pharmaceuticals and agrochemicals [48, 49]. Of these, tetrazole and hydroisoquinoline structural motifs have garnered substantial attention and are among the top 25 frequently employed nitrogen heterocycles in pharmaceutical compounds [50]. The tetrazole motif finds extensive use across diverse fields, including medicine, biochemistry, pharmacology, and various industries such as photography, imaging chemicals, and the military [51-56]. Table 1 presents various tetrazole derivatives showcasing potent biological activities.

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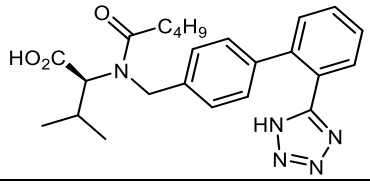
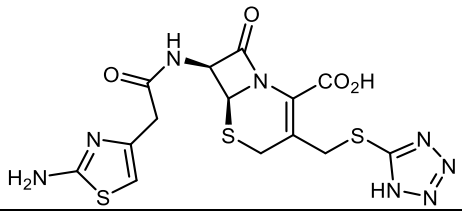
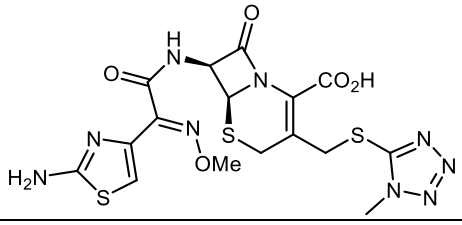
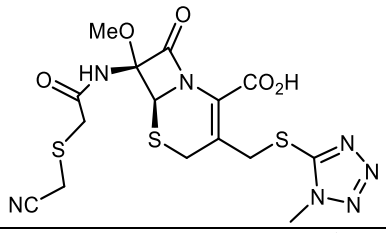
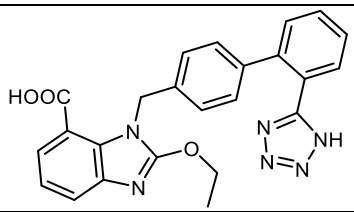
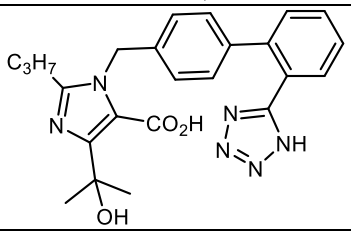
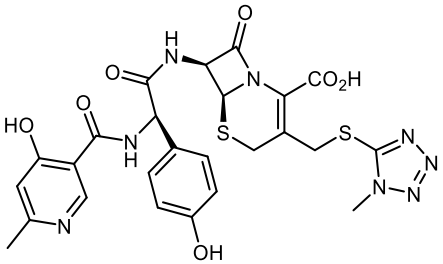
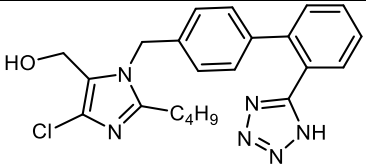
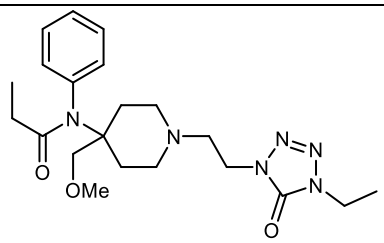
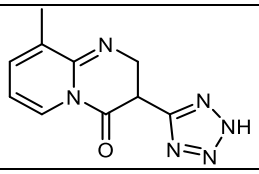
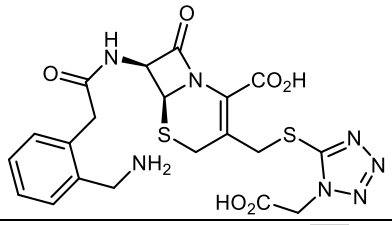
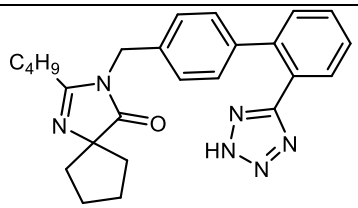
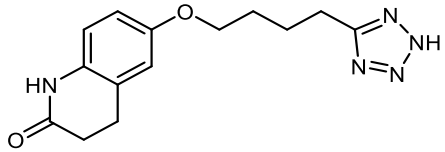
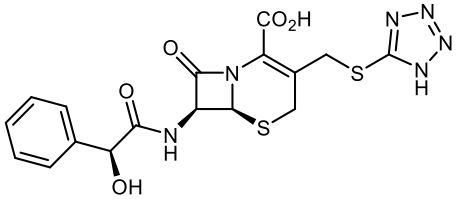
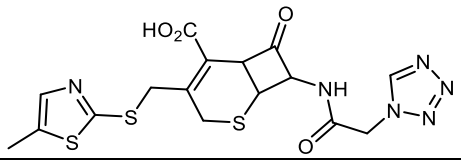
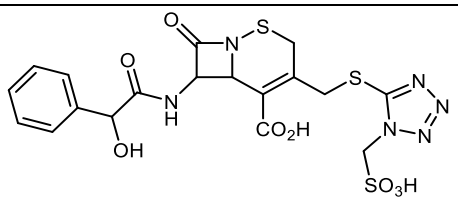
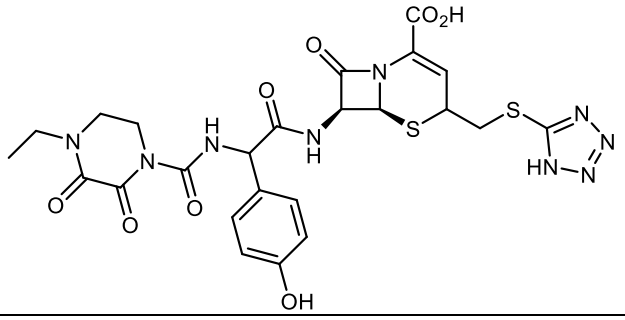
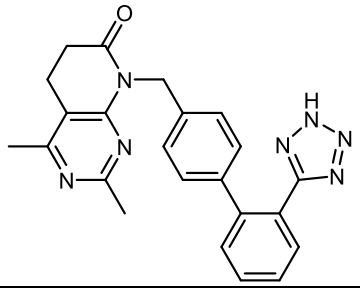
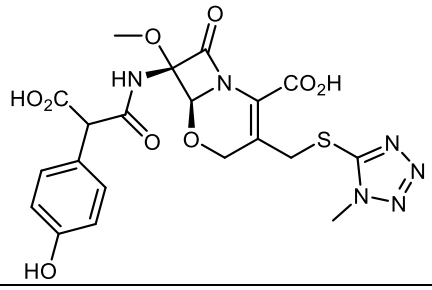
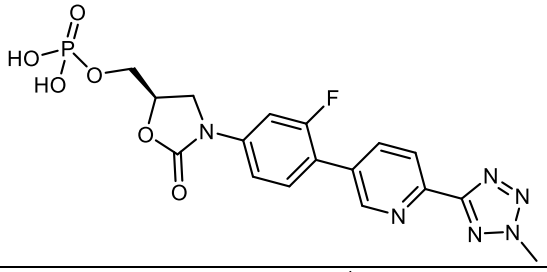
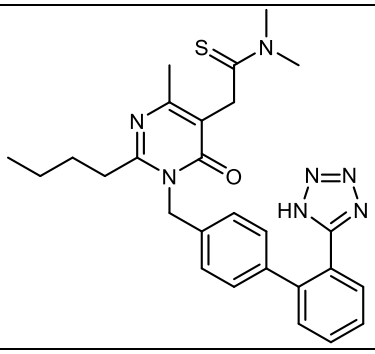
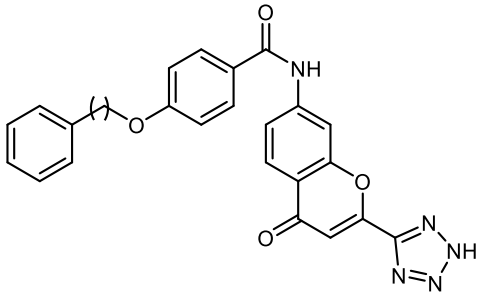
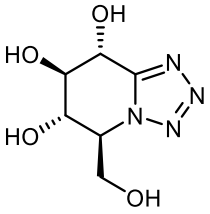
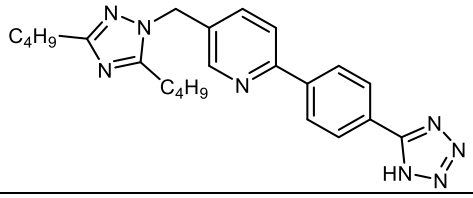
Table 1 Different Tetrazole Derivatives with Biological Activities**:**

Name	Structure	Activities
Valsartan		Antihypertensive agent angiotenin II receptor
Cefotiam		A broad-spectrum antibiotic against both gram-positive and gram-negative microorganisms
Cefmenoxime		A third-generation cephalosporin antibiotic
Cefmetazoic		A broad-spectrum antibiotic againstboth gram-positive and gram-negative microorganisms.
Candesartan		Antihypertensiv agent angiotensin II receptor
Olmesartan		Antihypertensiv agent angiotensin II receptor
Cefpiramide		A third-generation cephalosparin antibiotic
Losartan		Antihypertensiv agent angiotensin II receptor

Alfentanil		A short-acting opioid anesthetic and analgesic of fentanyl
Pemirolast		A mast cell stabilizer that acts as an antiallergic agent
Ceforanide		A second generation parenteral cephalosporin antibiotic
Irbesartan		Broadly used as medicament of hypertension
Cilostazol		Irregular limping in Individuals along surrounding vascular diseases
Cefamandole		Broad spectrum of cephalosporin antibiotic
Cefazolin		A broad-spectrum antibiotic
Cefonicid		Asecond generation cephalosporin

Cefoperazone		Semisynthetic broad-spectrum cephalosporin
Tasosartan		A long-acting angiotensin II (Angll) receptor blocker
Latamoxef		Broad-spectrum beta-lactam antibiotic
Tedizolid phosphate		oxazolidinone class antibiotic prodrug
Firmasartan		non-peptide angiotensin II receptor antagonist (ARB)
Pranlukast		A cysteinyl leukotriene receptor-1 antagonist to antagonize or reduce bronchospasm

Nojirimycin Tetrazole		Experimental target: Glycogen phosphorylase, muscle pain
Forasartan		Experimental, target: angiotensin II antagonist

Tetrazoles are noteworthy for their ample nitrogen content, rendering them favorable components in environmentally friendly gas generators that offer both high burn rates and a level of stability [57]. Within the DrugBank database, drugs incorporating 1H- or 2H-tetrazole substituents can be found, with 23 of these compounds having received FDA approval. This group of molecules showcases a wide array of biological activities, encompassing antihypertensive, antimicrobial, antiviral, antiallergic, cytostatic, and nootropic properties [58, 59].

The hydroisoquinoline motif holds a recurring presence in bioactive alkaloids such as jamtine, haiderine, and crystamidine (refer to Figure 4) [60-62]. Consequently, the establishment of a synthetic route for both tetrazole and reduced isoquinoline derivatives, particularly enantioenriched compounds featuring diverse peripheral functional groups, emerges as a crucial pursuit. This endeavor assumes significance in the exploration and tailoring of novel bioactive drug candidates.

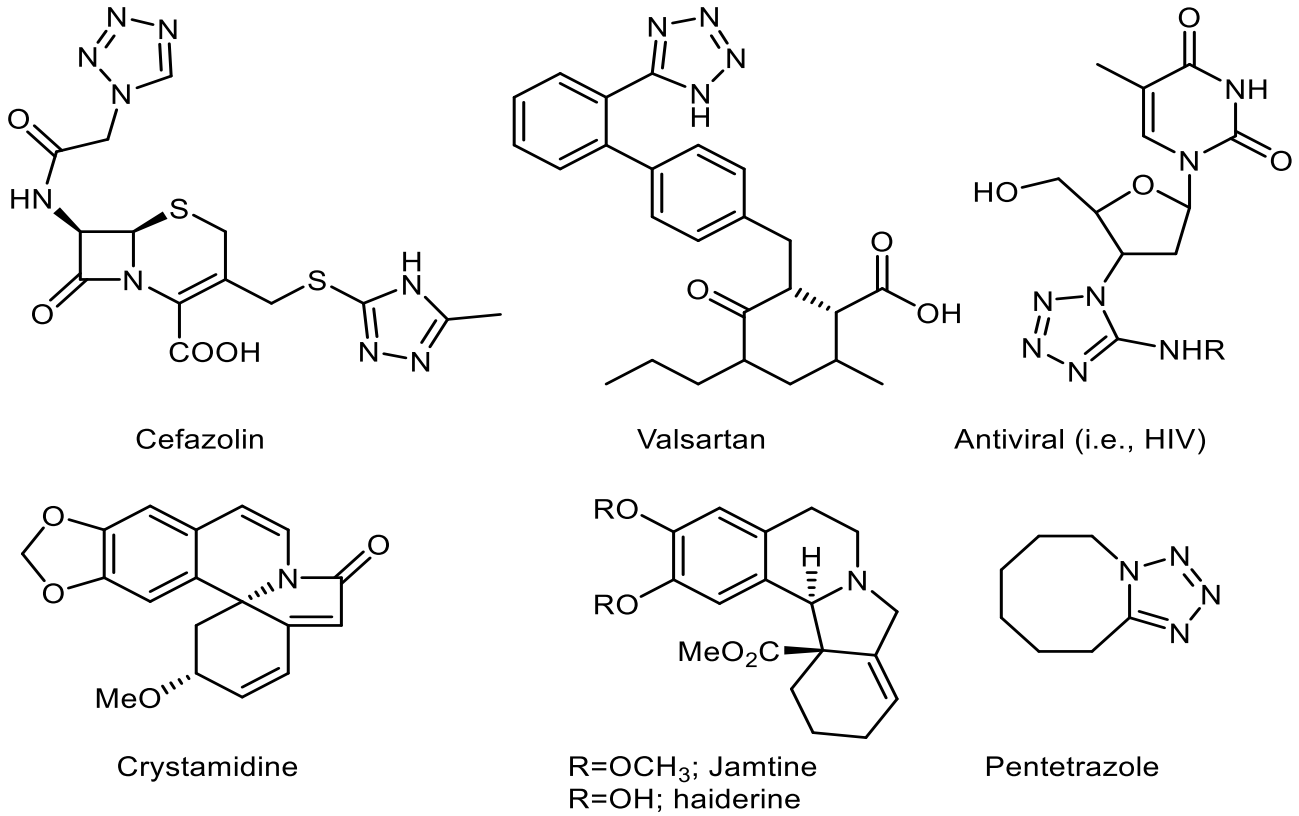


Fig 5 Biologically Active Molecules Containing Tetrazole and Hydroisoquinoline Moiety.

In recent developments, Qian and his research team have explored asymmetric IMCRs triggered by the enantioselective addition of basic isocyanides to olefins [63]. Their method involves a single-step reaction combining alkylidene malonates, isocyanides, and TMSN3 to yield a mixture of two enantioenriched tetrazole derivatives with high efficiency (Scheme 11). Similarly, when dihydroisoquinoline is subjected to the reaction with alkylidene malonates and isocyanides, it affords the desired 1,2-dihydroisoquinolines in remarkable yields (Scheme 12).

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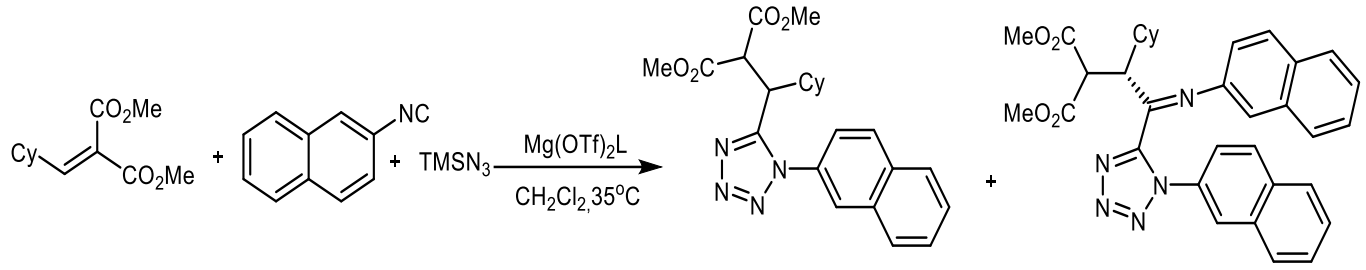
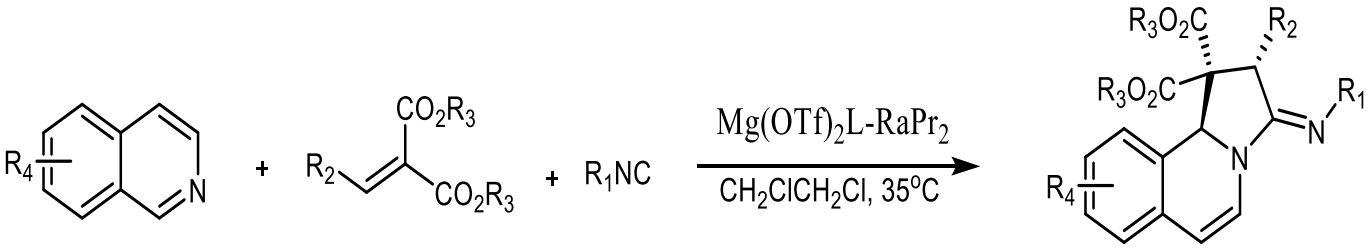
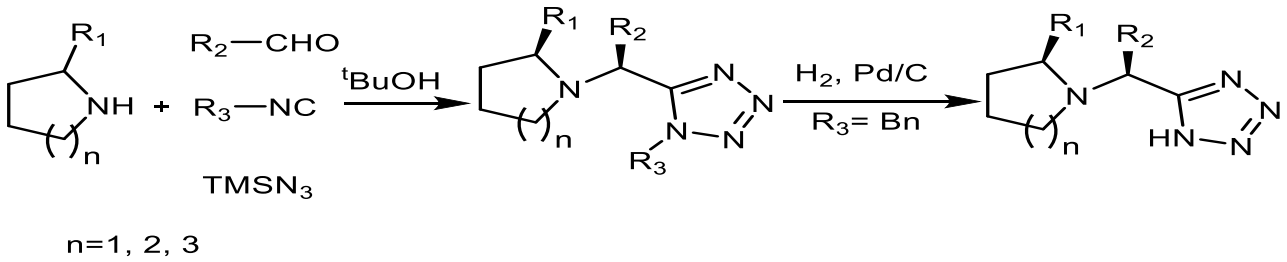


Scheme 11 Asymmetric Synthesis of Tetrazole Derivatives by IMCRs.



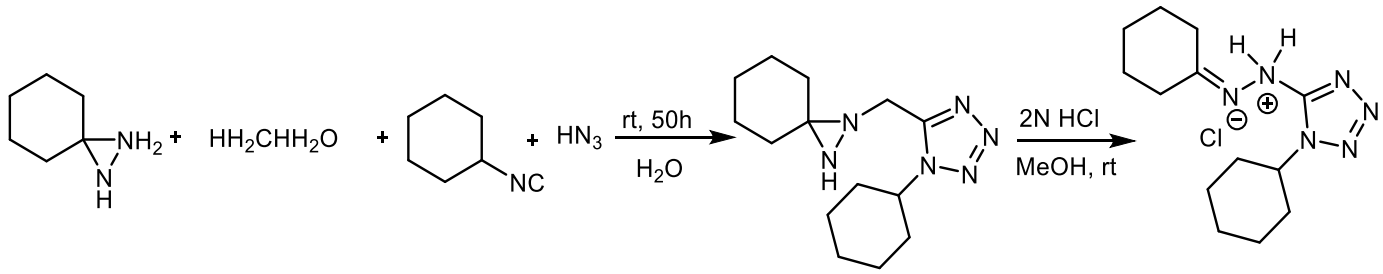
Scheme 12 Asymmetric Synthesis of Dihydro Isoquinoline Derivatives by IMCRs.

Nenajdenko and collaborators have documented the diastereoselectivity inherent in the UT-4CR when combined with cyclic amines, leading to the creation of tetrazole derivatives via a one-pot four-component reaction (depicted in Scheme 13) [64, 65]. Their research exemplifies how the reaction involving α-substituted five- to seven-membered cyclic amines effectively manages significant diastereoselectivity control even under mild reaction conditions.



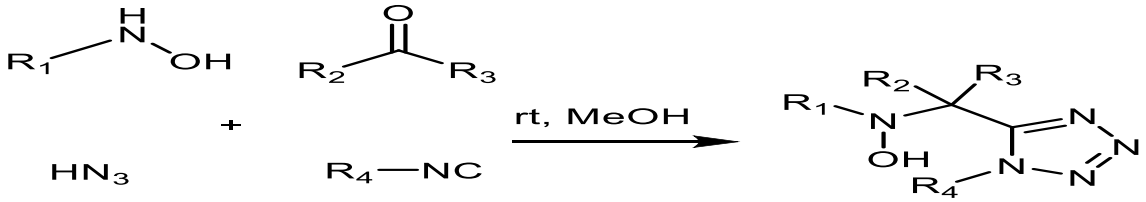
Scheme 13 Stereoselective Synthesis of Tetrazole Derivatives.

In 1972, Zinner et al. investigated the UT-4CR employing a range of amines. In their methodology, the corresponding diaziridine engaged with formaldehyde, cyclohexylisocyanide, and HN3 to yield diaziridine tetrazole derivatives. Subsequent treatment with acid induced the opening of the diaziridine ring, leading to the formation of the hydrazone derivative (depicted in Scheme 15) [66].



Scheme 14 Synthesis of Diaziridine Tetrazole UT-4CR.

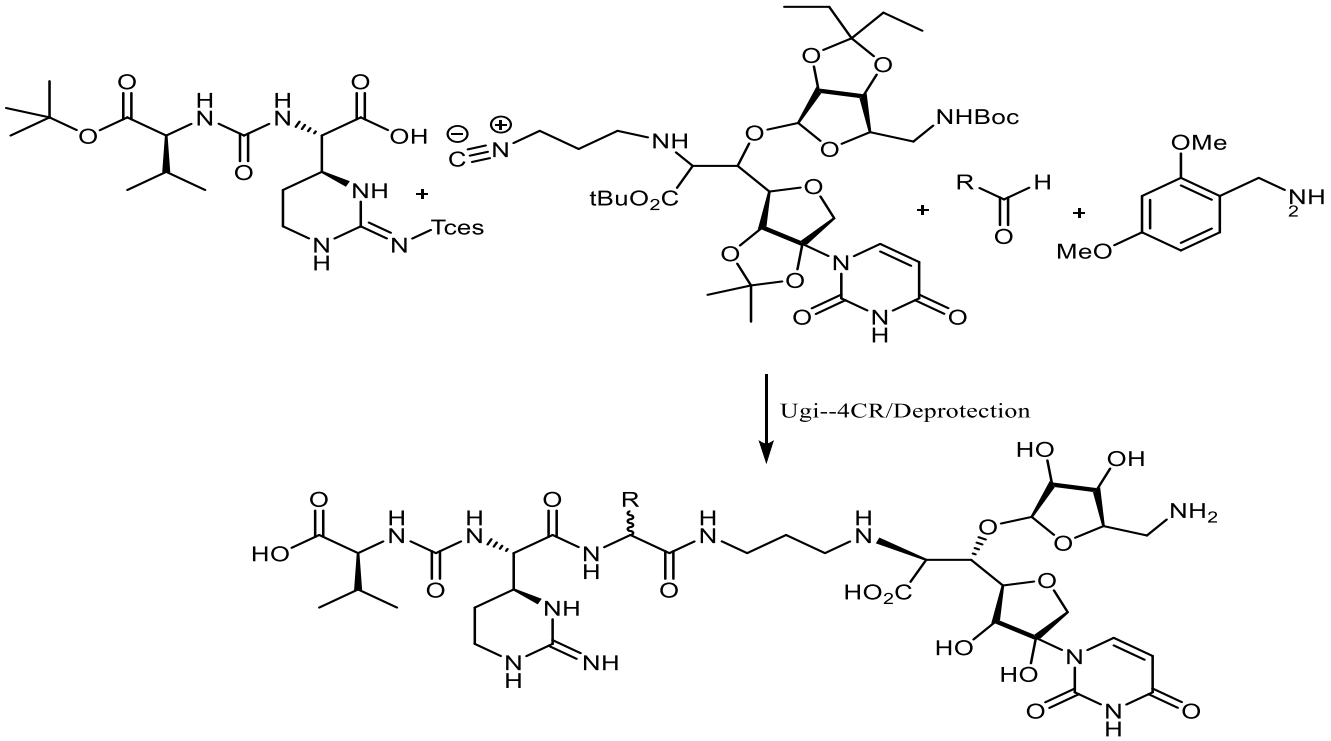
In an independent investigation, Zinner and co-researchers [67] introduced a distinct UT-4CR strategy for the synthesis of 1,5-disubstituted tetrazoles. This approach utilized hydroxylamines as amine components, which engaged with formaldehyde in the presence of cyclohexylisocyanide and hydrazoic acid (HN3) to yield the targeted 1,5-disubstituted tetrazole methylene hydroxylamines (depicted in Scheme 16).



Scheme 15 UT-4CR Approach to Synthesize 1,5-Disubstituted Tetrazoles.

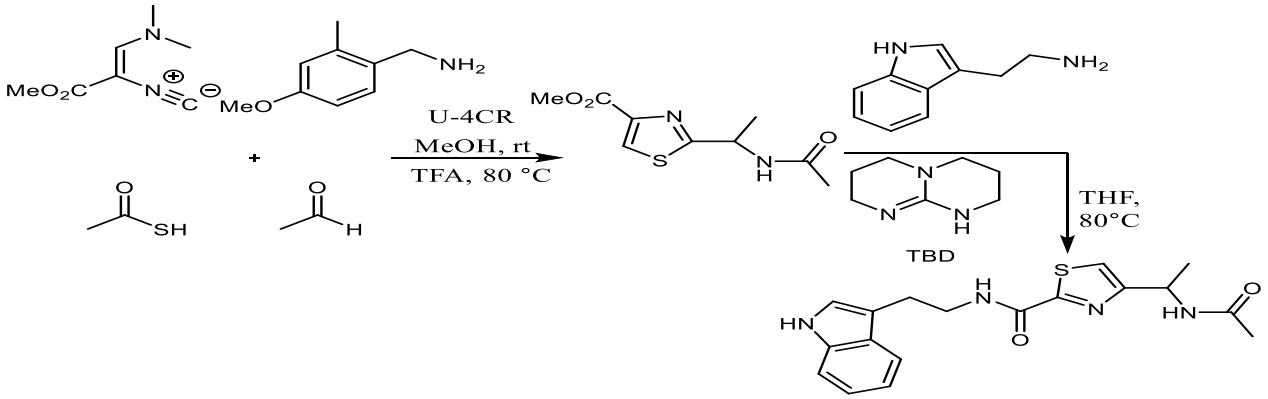
III. MULTICOMPONENT REACTION IN NATURAL PRODUCTS-BASED DRUG DISCOVERY

MCRs have made substantial contributions to the synthesis of intricate biologically active molecules. Within the realm of organic chemistry, the total synthesis of natural peptides has garnered significant attention due to their diverse applications. MCRs present an efficient approach for generating natural peptides in a streamlined manner. In the pharmaceutical domain, the extraction of natural products holds paramount importance [68, 69], with approximately 60% of anticancer drugs originating from natural sources [70]. The significance of natural products in the sphere of drug development spans various therapeutic areas, and in recent years, combinatorial techniques have gained widespread adoption for the synthesis of these compounds.



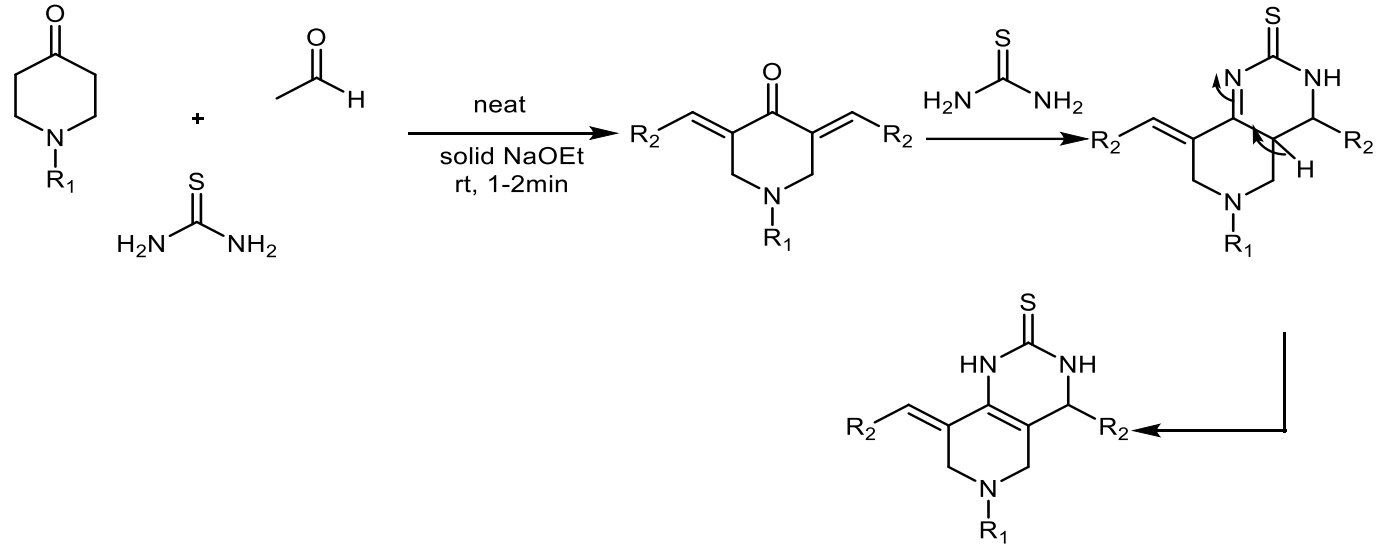
Scheme 16 Synthesized the Muraymycin D2.

Moreover, novel natural compounds featuring a tryptamidethiazole motif, including Bacillamide C, have been synthesized, showcasing robust algicidal and antibacterial properties [72]. An innovative approach for the synthesis of Bacillamide C and its derivatives was established by Domling and his research team (refer to Scheme 17) [73], effectively utilizing a Ugi-type strategy.



Scheme 17 Synthesis of Bacillamide C by U-4CR.

Concurrently, Perumal and collaborators documented the synthesis of pyridopyrimidine-2-thiones through a multicomponent reaction, delving into their anti-tubercular properties [74]. Their methodology hinged on a Biginelli-type interaction, involving the bi-aldol condensation of N-substituted piperidones with two identical aldehydes. This sequence generated intermediate products that subsequently underwent a tandem Michael addition/imine formation, succeeded by tautomerization, resulting in the rapid formation of pyridopyrimidine-2-thiones (as depicted in Scheme 18). The synthesized compounds were systematically assessed for their potential inhibition against M. tuberculosis (H37rv strain).



Scheme 18 Preparation of Pyridopyrimidine-2-Thiones.

Malaria remains a significant global health challenge, affecting millions annually. Parasites, particularly in tropical regions, contribute significantly to the disease burden, with over 40% of the world's population residing in malaria-endemic areas [75]. Plasmodium falciparum stands out among the various parasites causing malaria due to its aggressive nature. In the pre-synthetic drug era, quinine, a natural product, was the sole treatment for malaria (refer to Figure 6). Although effective chloroquine-based drugs were developed, Chibale and his colleagues introduced diverse synthetic methods to generate chloroquine analogues. Utilizing a moiety-based approach, they employed chloroquine-like amines as starting materials in multiple MCRs to synthesize a range of chloroquine derivatives. The Ugi reaction was employed between amines, formaldehyde, various carboxylic acids, and isocyanides to achieve the synthesis of chloroquine derivatives (refer to Scheme 19) [76].

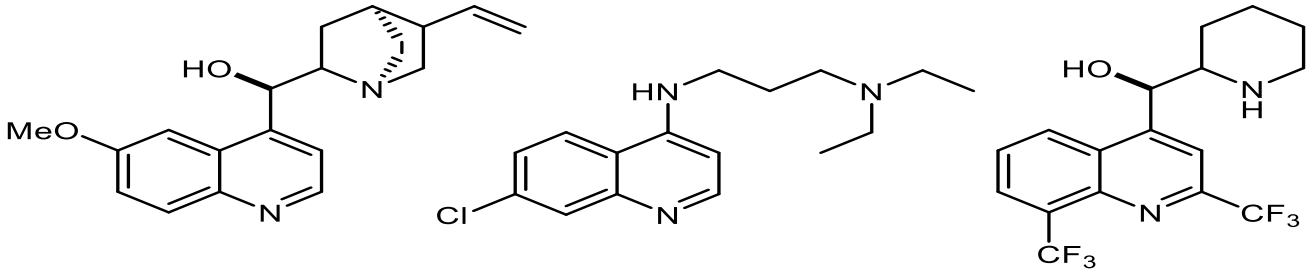
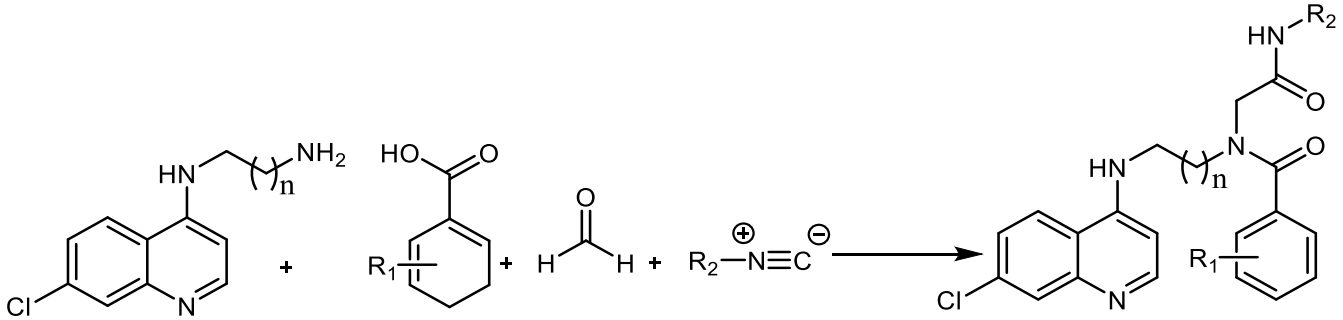


Fig 6 Antimalarial Drug having Quinoline as Parent Structural Motif.



Scheme 19 Synthesis of Chloroquine Derivatives.

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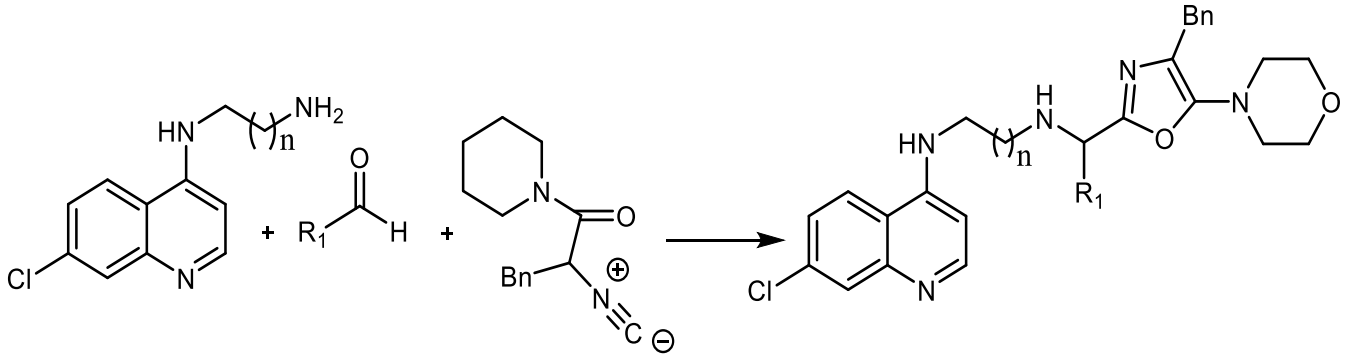
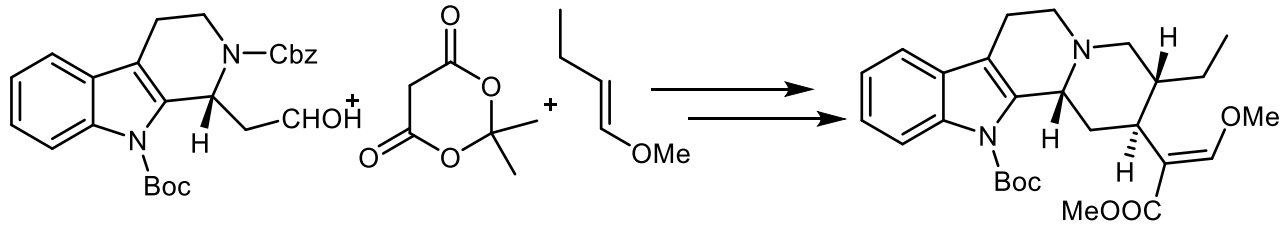
In 2007, Zhu et al. presented an isocyanide-based three-component reaction involving an isocyanoamide, an aldehyde, and an amine to produce chloroquine analogues (Scheme 20) [77]. These analogues were tested against chloroquine-resistant strains of P. falciparum, and many exhibited chloroquine-like activity.



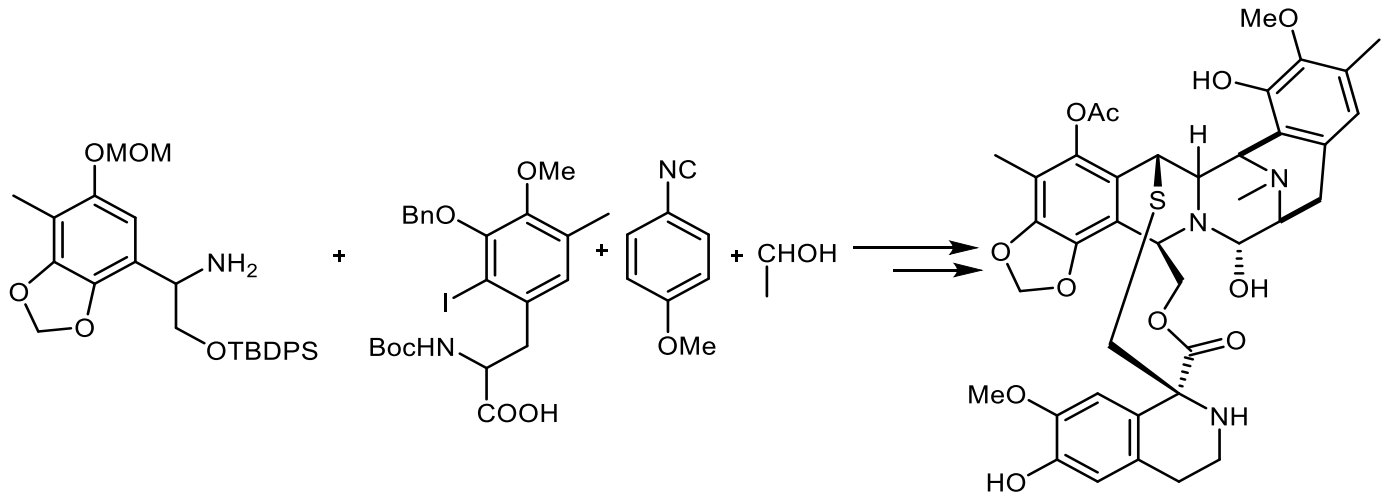
Scheme 20 Synthesis of Chloroquine Analogues.

L.F. Tietze and his co-workers achieved the synthesis of the indole alkaloid hirsutine, a potent inhibitor of the influenza A virus, using a domino multi-component reaction, involving only 5 steps (refer to Scheme 21) [78].



Scheme 21 Domino Multi-Component Reaction Towards the Synthesis of Hirsutine.

Fukuyama and his team recently employed MCRs in the total synthesis of Ecteinascidin, a marine natural product being developed by Pharma Mar as an anti-cancer treatment. They incorporated a Ugi-4CR as a crucial step, streamlining the procedure initially developed by Corey (refer to Scheme 22) [80].



Scheme 22 Total Synthesis of Ecteinascidin.

In 2010, Ichikawa and his research team accomplished the total synthesis of (–)-muraymycin D2 and its epimer through the implementation of the Ugi reaction (depicted in Scheme 23) [81]. These muraymycins fall within the category of 6′-N-alkyl-5-α-O-aminoribosyl-C-glycyluridine antibiotics, showcasing a distinctive core structure. Initially isolated from Streptomyces sp. culture broth by McDonald and colleagues, these compounds exhibited antimicrobial efficacy against Gram-positive bacteria like Staphylococcus aureus and displayed potent activity against E. coli translocase.

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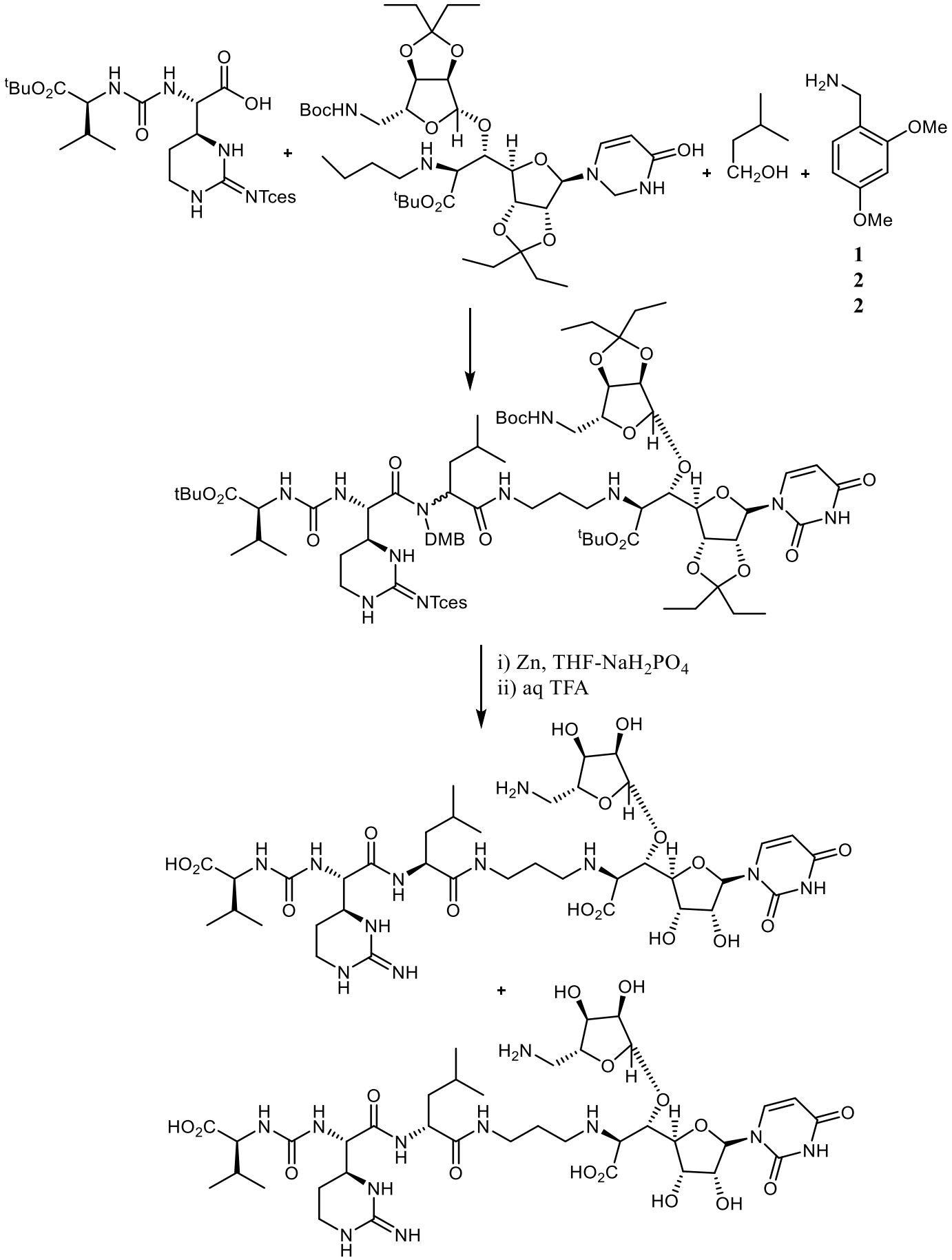
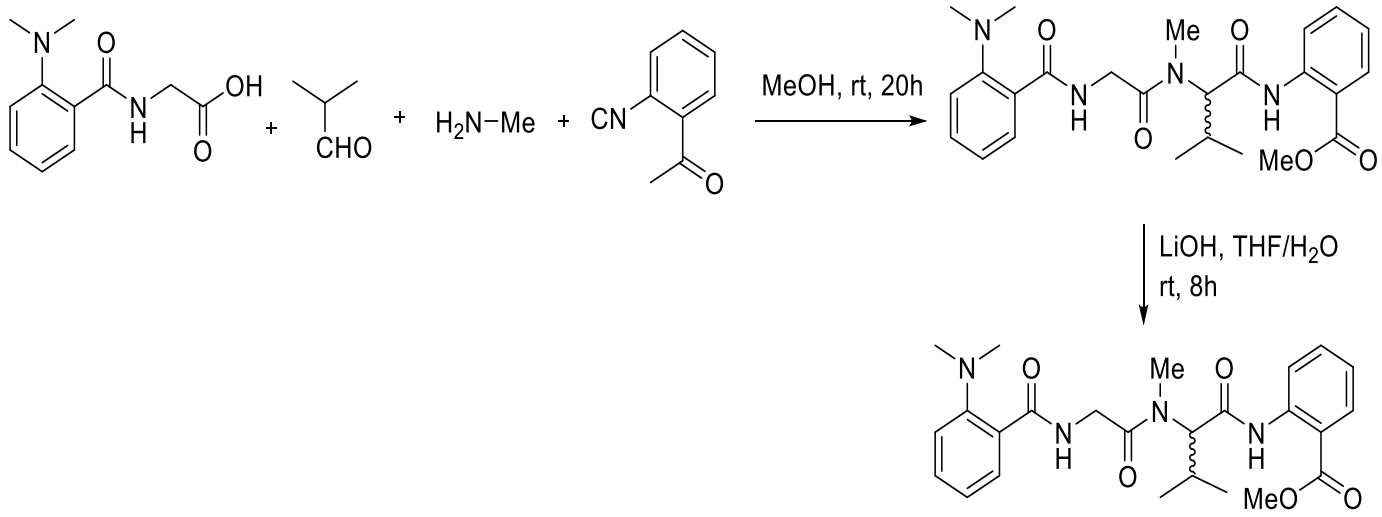


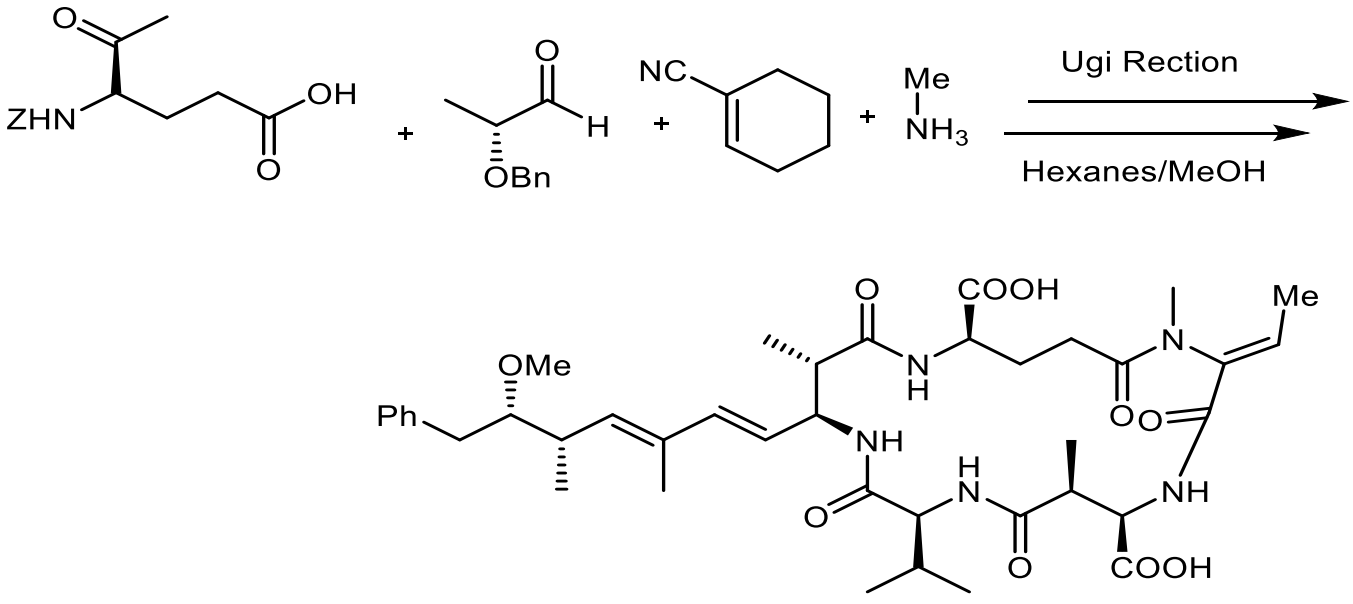
Scheme 23 Total Synthesis of (–)-Muraymycin D2 and its Epimer.

In another scientific endeavor, Wessjohann and his team introduced a method for the comprehensive synthesis of the antibacterial drug viridic acid utilizing the Ugi reaction (as depicted in Scheme 24) [83]. This tetrapeptide mycotoxin was extracted from Penicillium viridicatum Westling (CSIR strain No. 354) [84]. The synthesis process encompassed condensation reactions involving the dipeptide carboxylate, isobutyraldehyde, methylamine, and anthranilic isonitrile through the Ugi reaction. Subsequent saponification with LiOH at room temperature yielded viridic acid.



Scheme 24 Synthesis of Viridic Acid.

In 1999, Armstrong and his research team delineated a methodology for the complete synthesis of motuporin, leveraging the Ugi reaction and Matteson's dihalomethyl lithium insertion technique (illustrated in Scheme 25). Derived from the marine sponge Theonella swinhoei [85], motuporin exhibited in vitro cytotoxicity against various cancer cell lines. Their synthesis process involved the reaction of the carboxylbenzyloxy (Z)-protected glutamate ester with aldehyde, cyclohexenyl isocyanide, and methylamine under the Ugi reaction.



Scheme 25 Synthesis of Motuporin

In a more contemporary context, Rivera and Wessjohann combined the Ugi reaction with peptide-coupling and macrocyclic-ring-closing (MRC) reactions to achieve the comprehensive synthesis of cordyheptapeptide A (depicted in Scheme 26) [86]. This specific compound originates from the insect pathogenic fungus Cordyceps sp. BCC 1788 [87], demonstrating notable cytotoxic effects against various cancer cell lines. The synthesis process involved the reaction between L-Boc-Pro-OH, paraformaldehyde, methylamine, and isonitrile 4-isocyanopermethylbutane-1,1,3-triol (IPB). Subsequently, HATU and DIPEA in DMF at room temperature were utilized to complete the synthesis.

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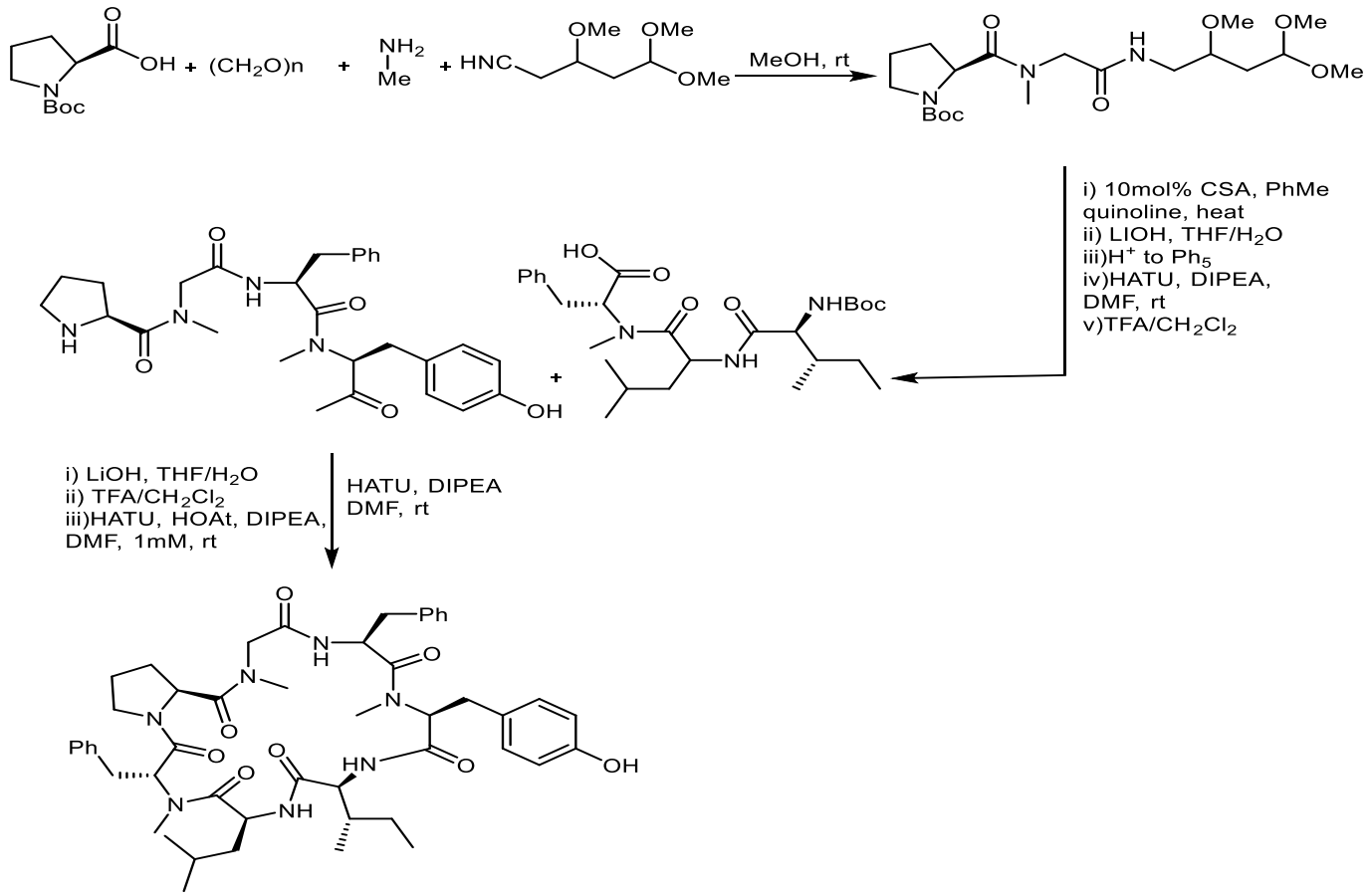
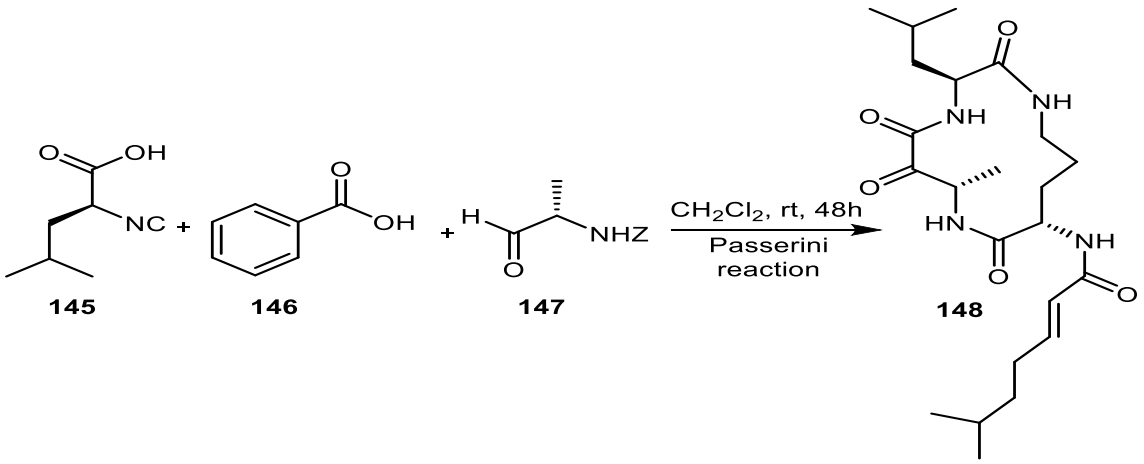


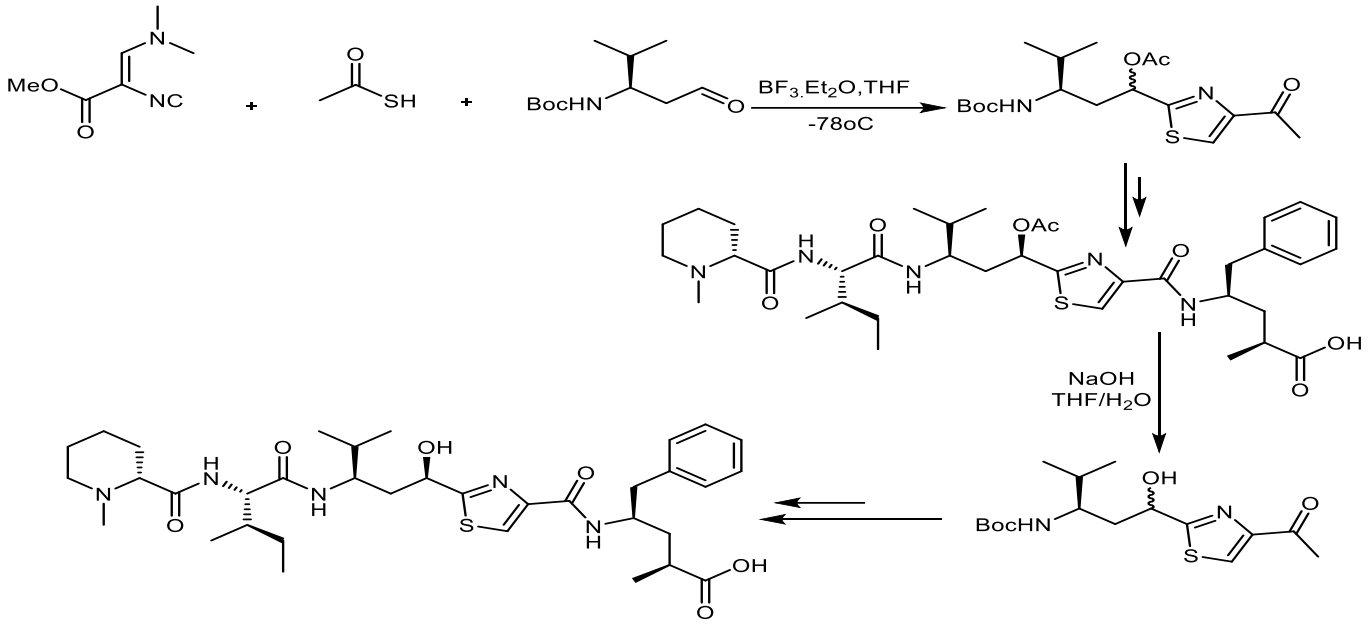
Scheme 26 Total Synthesis of Cordyheptapeptide A by Ugi Reaction.

In 1994, Schmidt and Weinbrenner detailed a procedure for the complete synthesis of the 13-membered macrocycle eurystatin A employing the Passerini reaction (as illustrated in Scheme 27) [88]. Isolated from Streptomyces eurythermus R353-21 by Toda and colleagues, this natural product exhibited potent inhibitory effects against the serine protease prolyl endopeptidase (PEP). The synthesis of eurystatin A was accomplished by reacting methyl (S)-2-isocyano-4-methylpentanoate, benzoic acid, and N-protected (S)-Z-alaninal via the Passerini reaction.



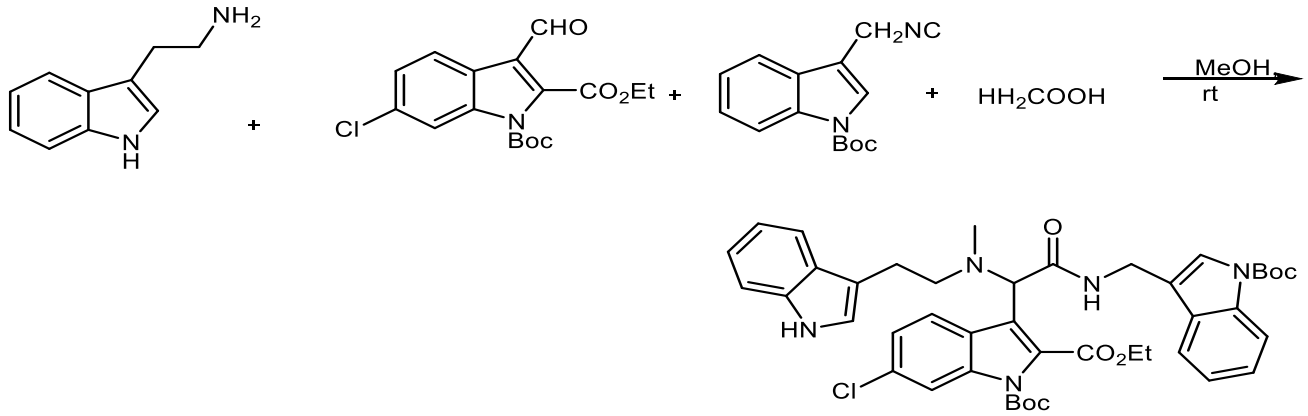
Scheme 27 Total Synthesis of Eurystatin A.

Dömling and his research team introduced an approach for the comprehensive synthesis of tubulysin U and tubulysin V. The procedure was initiated with a multicomponent reaction, involving readily available Schöllkopf isocyanide, thioacetic acid, and Boc-protected L-homovaline aldehyde in the presence of BF3·Et2O in THF. This produced an intermediate that underwent subsequent transformations leading to tubulysin U. An alternative pathway resulted in tubulysin V through a sequence of steps, starting with the hydrolysis of an acetate to an alcohol using NaOH (depicted in Scheme 28) [90]. Significantly, these natural compounds demonstrate considerable activity against mammalian cell lines [91].



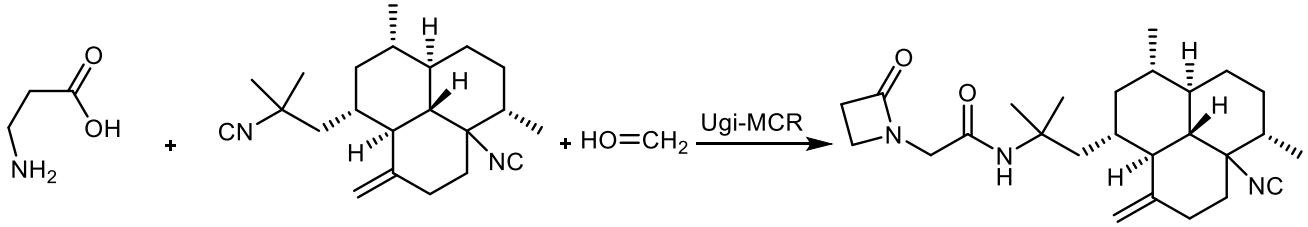
Scheme 28 Total Synthesis of Tubulysin U and Tubulysin V.

Rawat and colleagues presented a method for synthesizing a tris-indole alkaloid-like structure utilizing a Ugi-4C reaction. Their approach involved the reaction of an unprotected tryptamine with a protected indole aldehyde and a protected indole isocyanide, along with formic acid. This process resulted in the formation of the tris-indole component (illustrated in Scheme 29) [92].



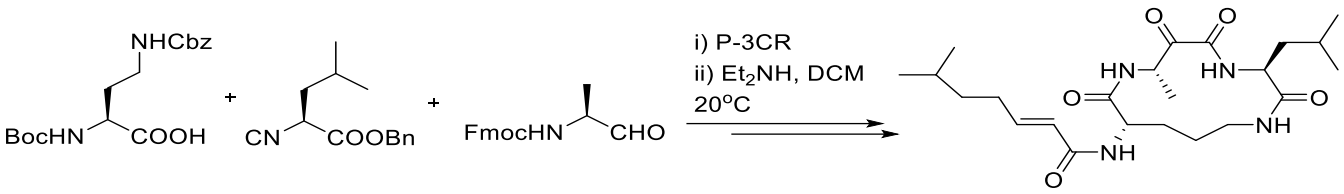
Scheme 29 Development of Tris-Indole Alkaloid Component.

In 2010, Rodriguez and colleagues presented a technique for synthesizing monamphilectine A using the Ugi reaction [93]. The researchers showcased the process involving bioassay-guided and mass-directed fractionation of an extensive organic extract obtained from the sponge Svenzeaflava, leading to the production of monamphilectine A (depicted in Scheme 30) [94].



Scheme 30 Synthesis of monamphilectine A

Vassilev and his research group investigated the synthesis of Eurystatins A and B, both being 13-membered macrocyclic natural compounds. The synthesis process involved the reaction of leucine, ornithine, and R-ketoalaninamide. These compounds exhibit potent inhibition against the serine protease prolyl endopeptidase (PEP). Due to their relatively straightforward structures, they serve as attractive targets for the development of novel R-hydroxy-α-amino amides and R-ketoamides (depicted in Scheme 31) [95].



Scheme 31 Synthesis of Eurystatins A and B.

IV. MULTICOMPONENT REACTION IN SYNTHESIS OF SMALL BIOACTIVE MOLECULES

Multicomponent reactions play a pivotal role in drug discovery processes, relying on synthetic chemistry to generate libraries of small molecules. To achieve diverse and complex small molecule libraries, the incorporation of multicomponent reactions with elaboration or cyclization steps has demonstrated effectiveness. In the current scientific landscape, multicomponent reactions have explored a range of mechanistic pathways in synthetic organic chemistry, encompassing organocatalytic transformations, cycloadditions, and protocols mediated by transition metals or radicals [97]. The inherent advantages of multicomponent reactions arise from their capacity to rapidly enhance molecular complexity, thereby bolstering synthetic efficiency. A notable characteristic involves the independent manipulation of multiple starting materials to yield a diverse array of hybrid molecules. Medicinal chemists have extensively harnessed multicomponent reactions for the construction of expansive libraries of hybrid molecules, pertinent to biological screening and drug discovery [98]. More recently, diversity-oriented synthesis (DOS) has significantly contributed to the advancement of novel multicomponent reactions [99]. The evolution and application of multicomponent reactions have reached an advanced stage, with numerous comprehensive reviews highlighting their utility in diverse domains such as the synthesis of bioactive molecules [100], diversity-oriented synthesis [101], heterocycle synthesis [102], and the creation of polycyclic structures resembling natural products [103]. Figure 7 visually presents several instances encompassing bioactive natural products, pharmaceutical drugs, and synthetic compounds with noteworthy biological activities, all of which feature heterocycles.

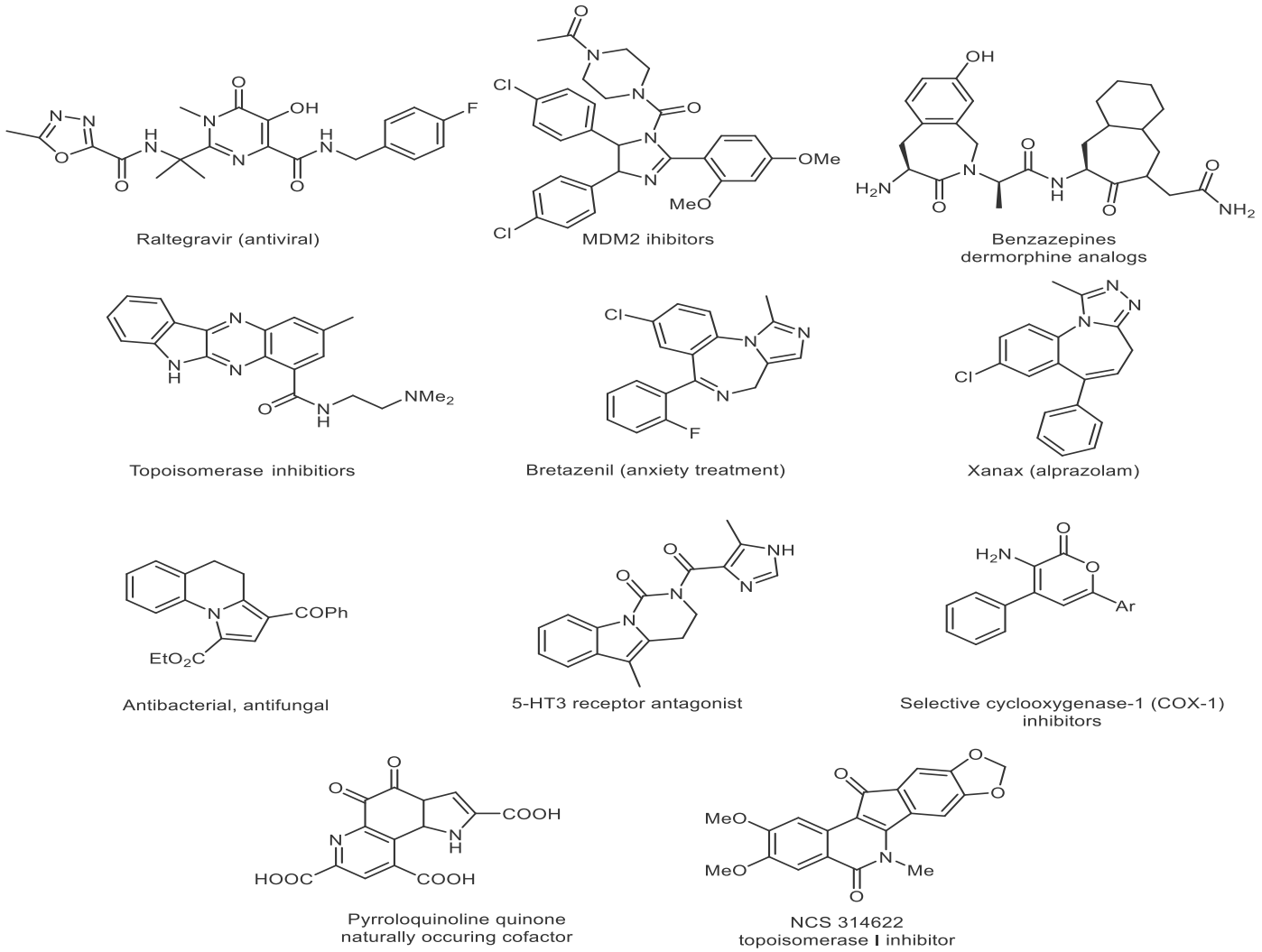


Fig 6 Examples of Bioactive Natural Products, Pharmaceutical Drugs, and Synthetic Compounds with Significant Biological Activities.

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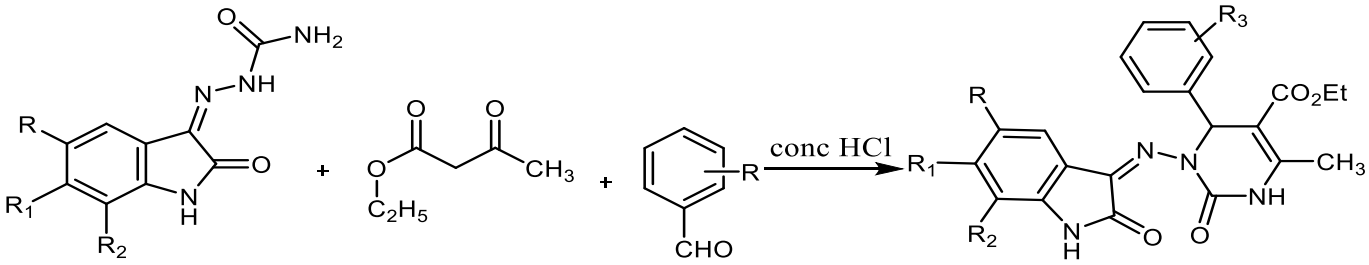
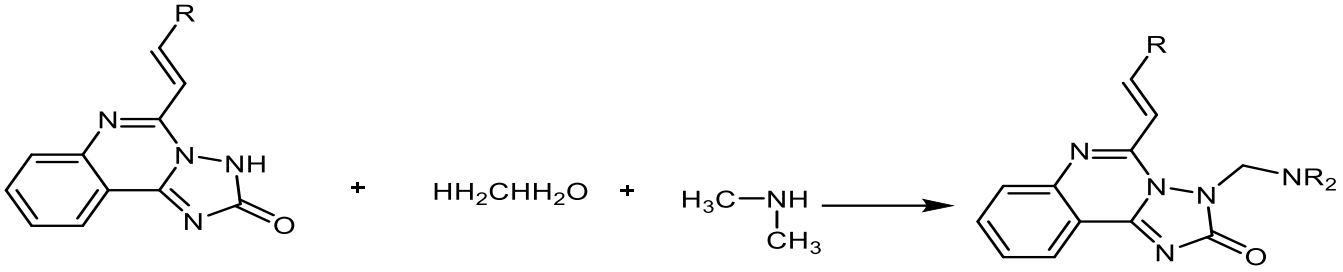


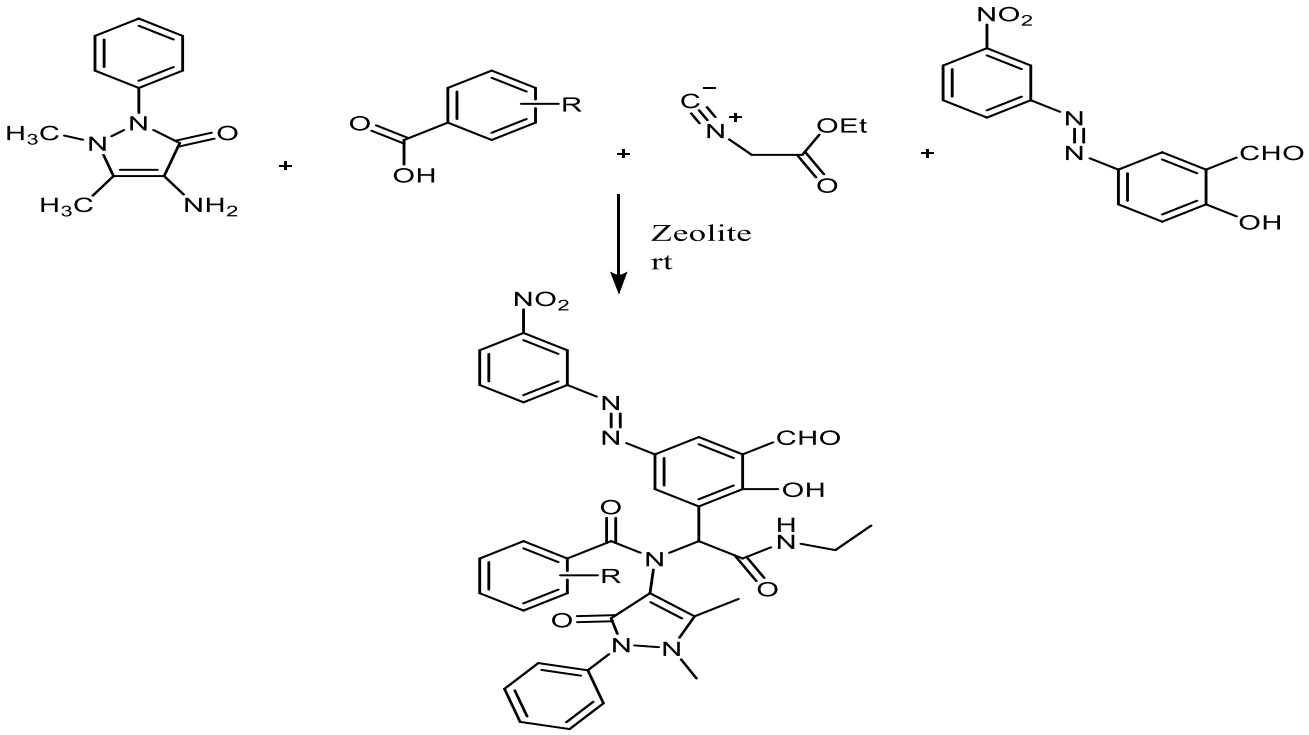
Scheme 32 Synthesis of 3-Substituted [3, 4-Dihydropyrimidinones]-Indolin-2-Ones.

Chaudhary and colleagues devised an efficient approach to prepare novel substituted-[1,2,4]triazolo[1,5c]quinazolinone derivatives by employing the Mannich reaction with formamide and various secondary amines (Scheme 37) [133]. These compounds demonstrated diverse biological activities such as anticancer, anticonvulsant, anti-inflammatory, antihelminthic, and antimicrobial effects.



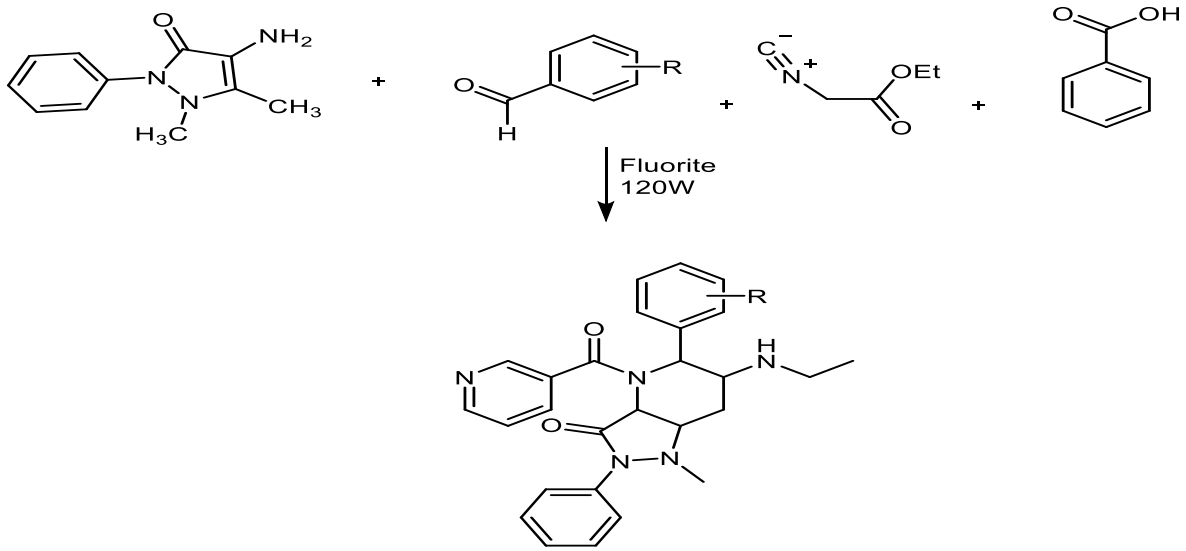
Scheme 33 Synthesis of Substituted Quinazolinone Derivative.

Mohanram and colleagues conducted the synthesis of Ugi 4CR derivatives through a one-pot reaction involving 4-aminoantipyrine, substituted carboxylic acid, ethyl isocyanoacetate, and 2-hydroxy-4-((3-nitrophenyl)diazenyl)benzaldehyde in a mixture of ethanol and zeolite under ambient conditions [135]. The synthesized compound exhibited activity against analgesic and anti-inflammatory activities (Scheme 38) [134].



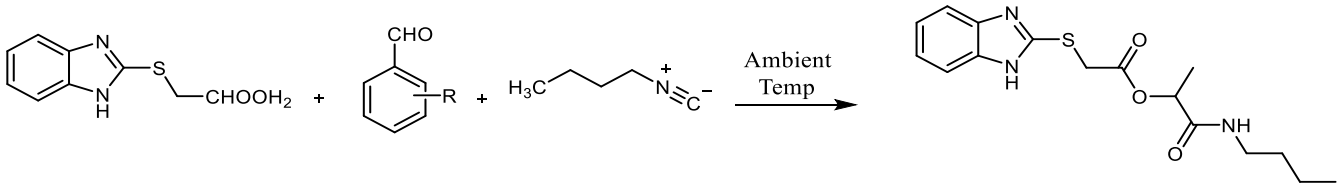
Scheme 34 Synthesis of Ugi Derivatives.

Additionally, Mohanram et al. introduced an effective method for producing novel anti-inflammatory and antimicrobial agents. By utilizing fluorite-catalyzed Ugi four-component reactions of 4-aminoantipyrine, nicotinic acid, ethyl isocyanoacetate, and substituted aldehydes under microwave irradiation, they generated the desired anti-inflammatory and antimicrobial agents (Scheme 39).



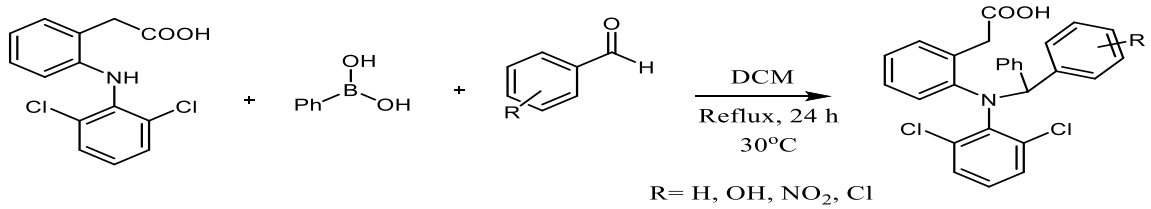
Scheme 35 Synthesis of Novel Anti-Inflammatory and Antimicrobial Agents by Ugi-4CR.

Shaikh and associates synthesized a series of carbonyl-amide linkage-based benzimidazole derivatives through the Passerini reaction involving acids, aldehydes, and isocyanides at ambient temperature. These newly prepared compounds were subjected to screening for potential anti-inflammatory, antidiabetic, and anticonvulsant properties (Scheme 40) [136].



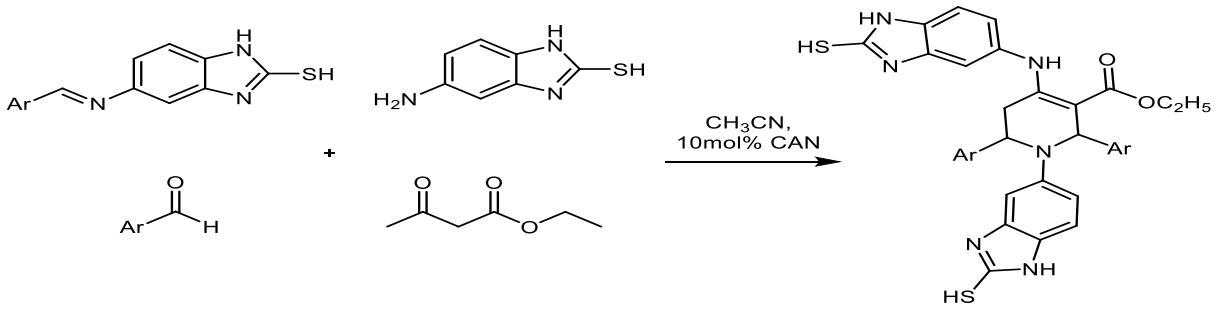
Scheme 36 Synthesis of Benzimidazole Derivative.

Osman and colleagues presented a series of diclofenac derivatives synthesized through a reaction involving aldehyde, diclofenac, and phenyl boronic acid in a 1:1:1 molar ratio, utilizing the Petasis reaction. The resulting compounds were subjected to anti-inflammatory activity evaluation using the carrageenan-induced paw edema method (Scheme 41) [137].



Scheme 37 Synthesis of Diclofenac Derivatives.

Ravindernath et al. introduced an efficient and environmentally friendly approach for synthesizing benzo[d]imidazolyltetrahydropyridine carboxylates derivatives. This involved a ceric ammonium nitrate catalyzed one-pot multicomponent reaction of (E)-5-(benzylidene amino)-1H-benzo[d]imidazole-2-thiol, 5-amino-2-mercapto-benzimidazole, aromatic aldehyde, and ethyl acetoacetate in acetonitrile. The resulting compounds were optimized for their anti-inflammatory, antioxidant, antibacterial, and antifungal activities (Scheme 42) [138].



Scheme 38 Synthesis of Benzo[d]Imidazolyltetrahydro Pyridine Carboxylates.

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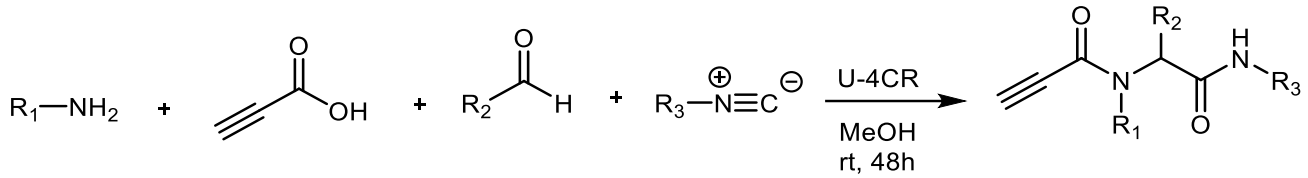
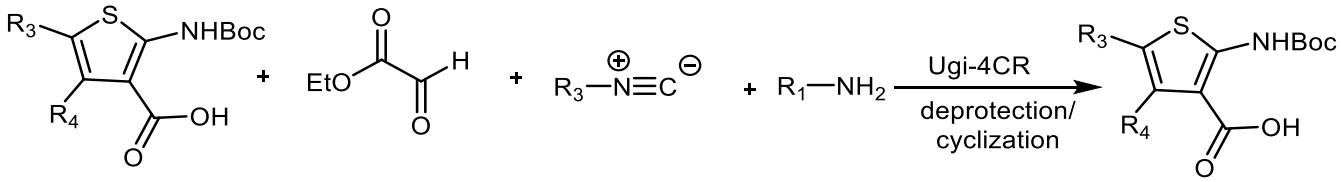
Petasis and co-workers designed a library of anticancer compounds using the Ugi-4CR methodology (Scheme 43) [139]. By varying substituents on different components, the propiolic acid was applied as a common alkyne moiety. This approach yielded a series of 19 molecules intended for combating human cancer cell lines.



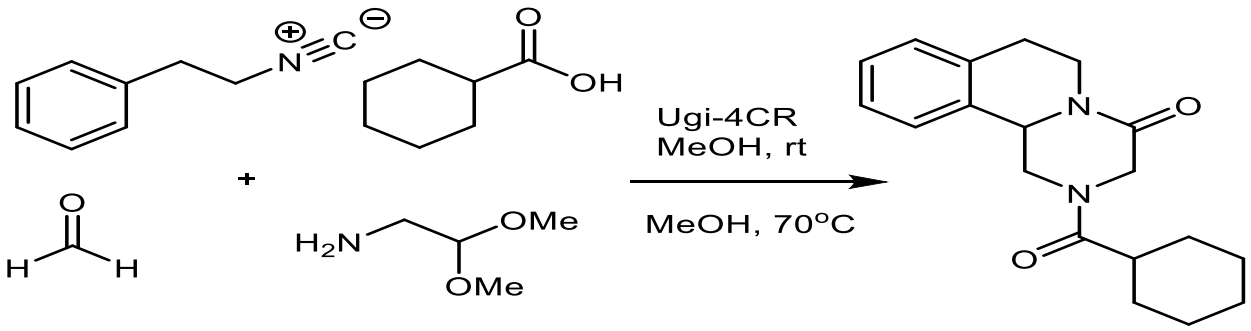
Scheme 39 Synthesis of Library of Anticancer Compound.

Dömling and his team devised a novel strategy for preparing 1,4-thienodiazepine-2,5-diones through the Ugi-Deprotection-Cyclization (UDC) approach. These components were identified as inhibitors of the p53–MDM2 reaction (Scheme 44) [140].



Scheme 40 Development of 1,4-Thienodiazepine-2,5-Diones.

In a separate study, Domling and his team introduced an efficient method for synthesizing praziquantel using the Ugi reaction followed by Pictet–Spengler cyclization (Scheme 45) [141]. Praziquantel, an anti-schistosomiasis drug, is active against Schistosomiasis, a type of snail fever that is a common tropical disease causing various health issues such as cancer, HIV infection, organ failure, and growth disorders in children [142]. Praziquantel is the primary medication effective for treating this disorder.



Scheme 41 Synthesis of Praziquantel.

Ross and his team demonstrated the capability of MCRs in developing therapeutic drugs that are already in the market. They synthesized clopidogrel (Plavix) and bicalutamide (Casodex) using MCR approaches (Figure 9) [143].

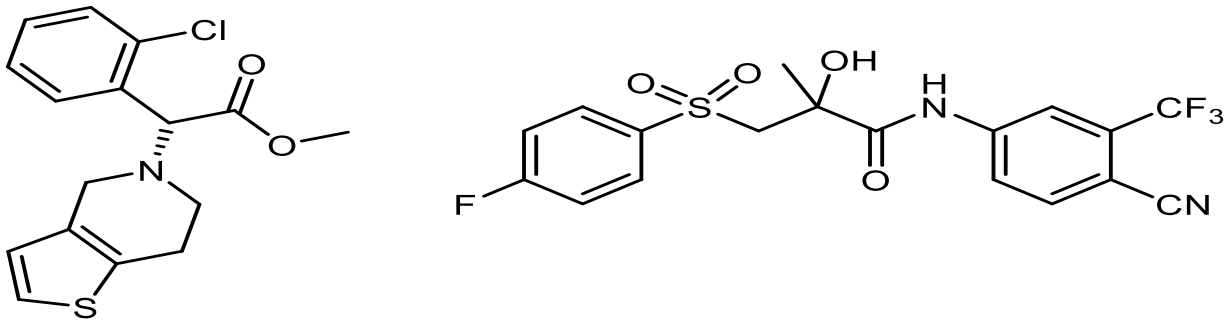
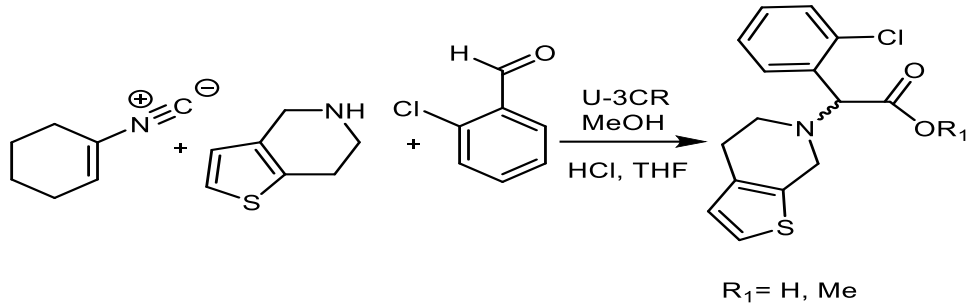


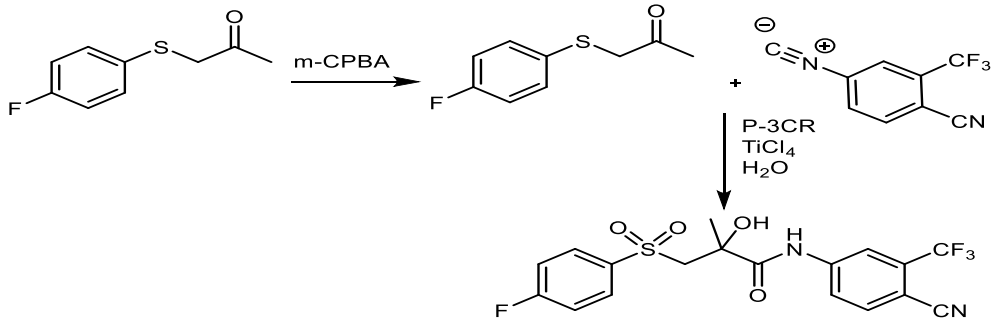
Fig 7 Structure of Clopidogrel (Plavix) and Bicalutamide (Casodex).

Plavix, an anti-platelet factor used to inhibit blood clot formation in coronary artery disease and related conditions, can be synthesized via Ugi-3CR employing readily available starting materials (Scheme 46).



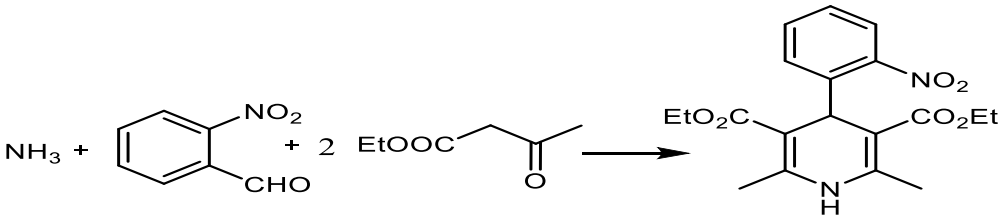
Scheme 42 Synthesis of Clopidogrel.

Casodex, the drug is used in cure of prostate cancer through inhibiting the androgen receptor, and it is produced from $TiCl_4$-mediated Passerini-type method (Scheme 47).



Scheme 43 Synthesis of Bicalutamide.

The cardiovascular drug Nifedipin is one of the prompt examples of MCRs with the Hantzsch synthesis (Scheme 48).



Scheme 44 Hantzsch Synthesis Towards Nifedipin.

Bayer chemists constructed a compound library by modifying the amine, aldehyde, and β-keto acid ester parts, although this was done only after Nifedipine had already been introduced as a blood pressure-lowering agent. Similarly, diverse local anesthetics can be generated using the Ugi-3 component reaction, involving various isocyanides, aldehydes, and secondary amines (Figure 10).

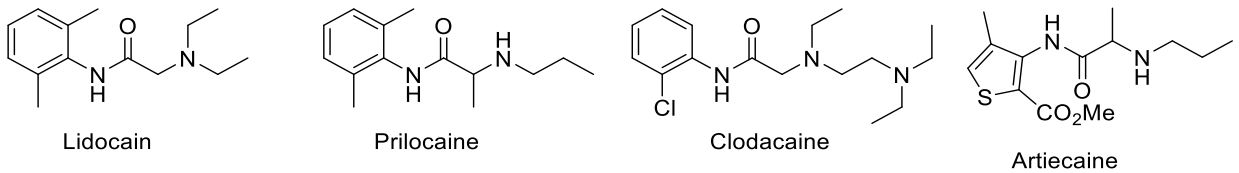
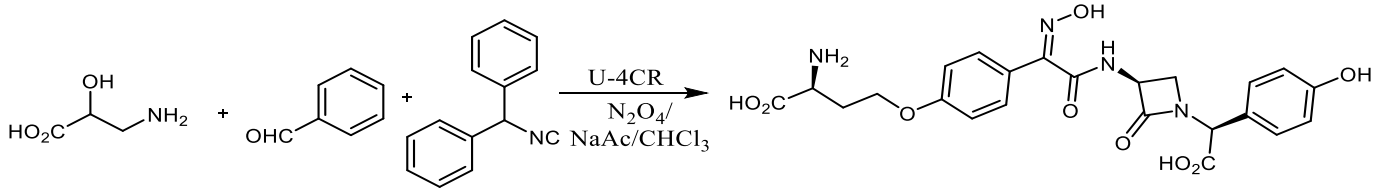


Fig 8 Marketed Products Obtained Through MCRs.

Hofheinz and his team generated a library of Nocardicine A analogues using MCR chemistry. In their approach, the reaction of β-amino acids, diphenylmethyl isocyanide, and aldehydes led to the synthesis of Nocardicine A derivatives (Scheme 49) [147].



Scheme 45 Synthesis of Nocardicine A.

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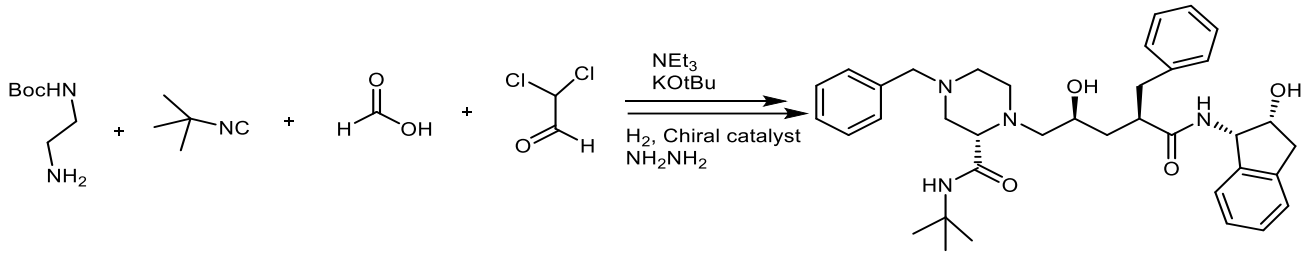
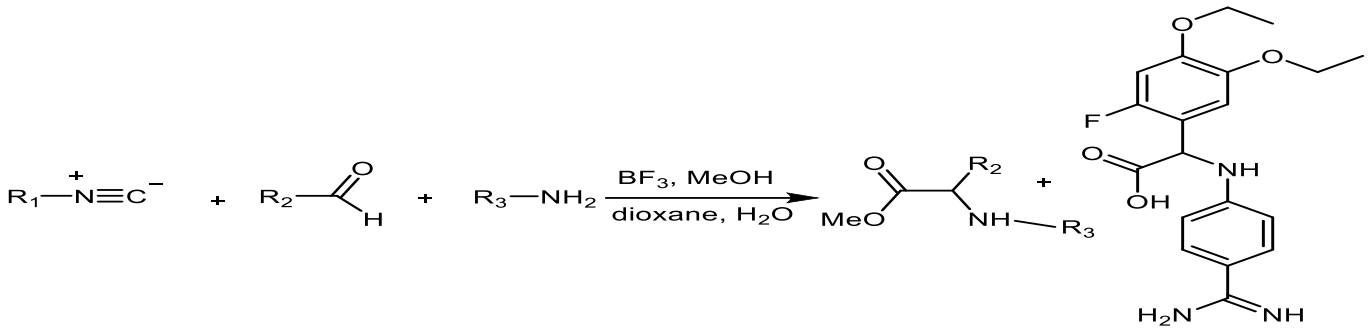
HIV protease inhibitors are known for their complex synthesis, typically involving over 15 synthetic steps and leading to high-cost production. Merck & Co. developed a synthesis route for Crixivan utilizing Ugi-MCR as a key step (Scheme 50) [148].



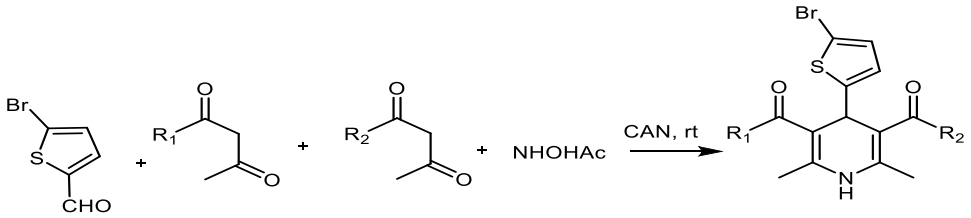
Scheme 46 Ugi-type MCR in the synthesis of Crixivan.

Hoffmann et al. in 2001 introduced an efficient variation of Ugi-MCR for synthesizing inhibitors of the serine protease factor VIIa. Their strategy involved the use of boron trifluoride as a catalyst for a Ugi-3CR with N-substituted glycine esters (Scheme 51) [149].



Scheme 47 Ugi-Type Variation in the Synthesis of Serine Protease Factor VIIa Inhibitors.

A novel protocol for synthesizing certain thiophene-based 1,4-DHP derivatives using ceric ammonium nitrate (CAN) as the catalyst was developed by Sharma and his team. In their method, the reaction between 1,3-diones, 5-bromothiophen-2-carboxaldehyde, and ammonium acetate under room temperature and solvent-free conditions resulted in the desired compounds (Scheme 52) [150].

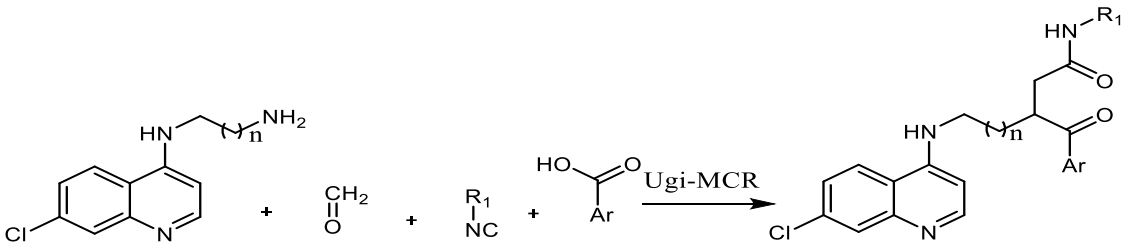


R_1= OCH_3, OC_2H_5, CH_3
R_2= OCH_3, OC_2H_5, CH_3

Scheme 48 Synthesis of1,4-DHP Derivatives.

1,4-DHPs are gaining significant importance due to their pharmacological and biological activities, including roles as antihypertensive, anti-anginal, and calcium channel blockers for cardiovascular diseases [151]. As a result, several clinically important drugs have entered the market with varying new active functional groups in their main skeleton. Notable examples include Nicardipine, Nifedipine, Nimodipine, Felodipine, Isradipine, and Amlodipine [152-155].

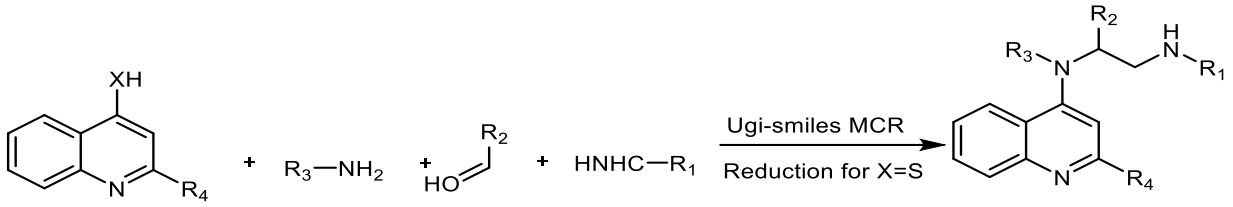
In the synthesis of aminoquinoline-based antimalarial compounds, Chibale's research group employed the Ugi reaction [156]. This approach was selected to establish structure-activity relationships (SAR) around a specific therapeutic class by using components with known pharmacophoric moieties of drugs. The 7-chloro-4-aminoquinoline scaffold is found in several antimalarial drugs, including chloroquine, where it enables inhibition of Plasmodium falciparum hemozoin formation. To incorporate this pharmacophore, the Chibale group utilized a 4-aminoquinoline moiety in the amine input of the Ugi reaction. Hydroxyl groups and protonatable basic nitrogen atoms were added to the carboxylic acid input to confer iron-chelating properties and facilitate drug accumulation within the acidic parasitic food vacuole of P. falciparum (Scheme 53).



R_1= Cyclohexyl, t-Bu
Ar= 2-pyrazinyl, 4-pyridyl, 4-pyridyl

Scheme 49 Ugi MCR Synthesis of Antimalarial 4-Aminoquinoline-Based α-Acylamino Amides.

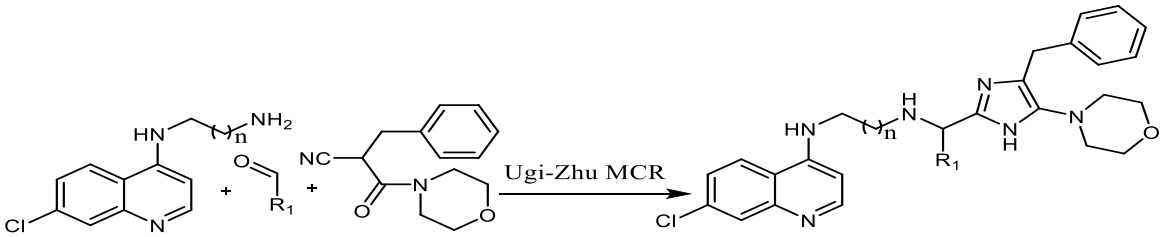
El Kaim and Grimaud developed a series of chloroquine analogues using the Ugi-Smiles MCR, incorporating 4-hydroxyquinolines or 4-mercaptoquinolines as the acidic component (Scheme 54) [157].



X= O, S

Scheme 50 Synthesis of Chloroquine Analogues.

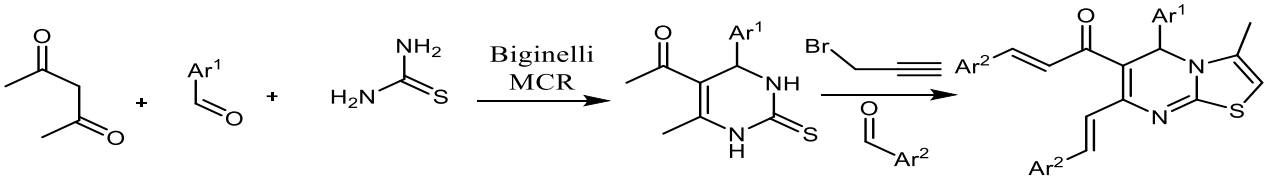
Similarly, isocyanide-based MCRs have been employed to design new drug moieties against infectious tropical diseases. Zhu et al. synthesized a novel class of antimalarial 7-chloro-4-aminoquinolines with a substituted oxazole ring in the side chain [159]. In their method, a 3-component reaction involved an amine with the 7-chloro-4-aminoquinoline pharmacophore of chloroquine, an aldehyde, and an isocyanoacetamide (Scheme 55).



R_1= Me, H

Scheme 51 Synthesis of Antiplasmodial Aminoquinolines.

Tripathi and colleagues devised an effective protocol for synthesizing styrylthiazolo[3,2-a]pyridimines by employing two one-pot Biginelli reactions involving acetylacetone, thiourea, and an aromatic aldehyde. The synthesized compounds exhibited potent antimalarial activity (Scheme 56) [160].



Ar_1= Ph, 4-Cl-Ph

Ar_2= 2-Cl-Ph, Ph

Scheme 52 Synthesis of Antimalarial Styrylthiazolo[3,2-a]Pyrimidines.

In light of the significant anti-plasmodial activity demonstrated by certain chloroquine analogues incorporating thiazolidinone moieties in the side chain, Cunico and his team adopted a molecular hybridization strategy from the primaquine drug. They utilized a three-component reaction to generate primaquine–thiazolidinone hybrids, potentially serving as novel antiplasmodial agents (Scheme 57) [161].

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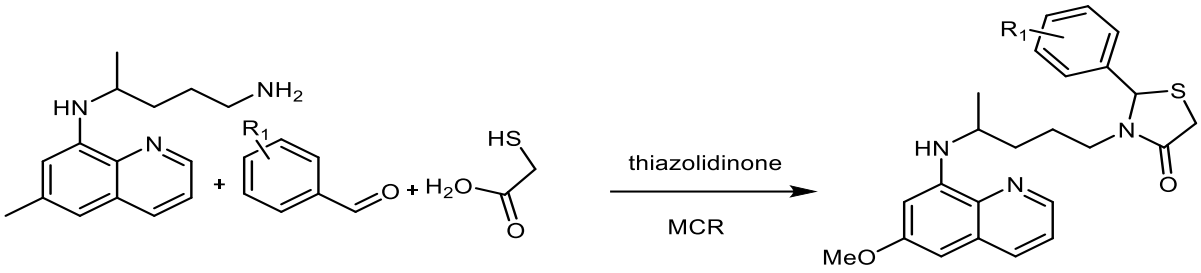
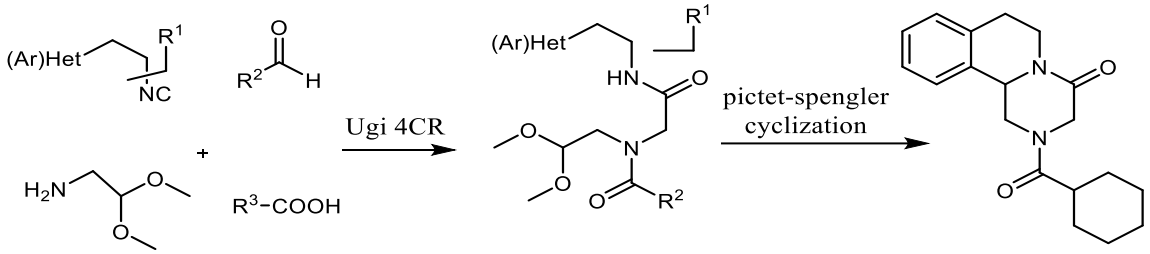


Scheme 53 Synthesis of New Primaquinethiazolidinone Derivatives.

Domling and colleagues [162] synthesized the praziquantel drug using the Ugi multicomponent reaction. The one-pot condensation of isocyanide, carbonyl component, amine, and carboxylic acid yielded a substituted acylamino carbonamide product, followed by a Pictet–Spengler cyclization under acidic conditions, ultimately leading to the formation of praziquantel under mild conditions (Scheme 58) [163-165].

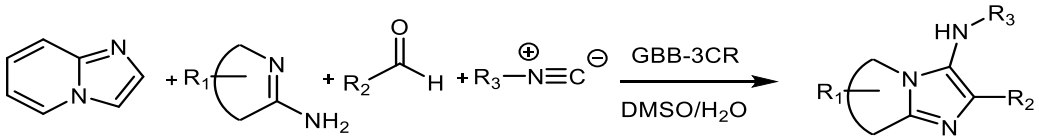


Scheme 54 Synthesis of Drug Praziquantel.

V. MISCELLANEOUS

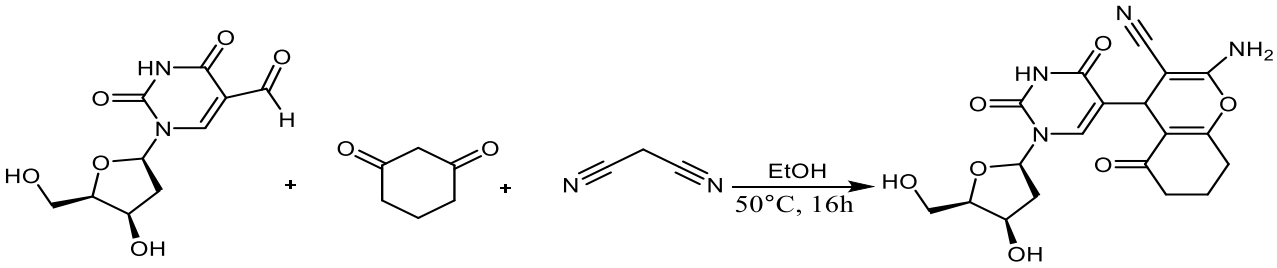
The pivotal role of MCRs extends beyond the marketing of synthesized drugs, as they have made significant contributions to clinical chemistry and chemical biology. This section highlights some important examples. MCRs have been instrumental in the field of bio-imaging, particularly in the development of new fluorescent pharmacophores [166]. Fluorescent labeling of bioactive compounds has enabled cell analysis [167]. While several fluorescent dyes are available in the market for medical applications, the creation of novel compounds with similar properties remains challenging due to high demands.

In 2011, Balakirev et al. discovered autofluorescence substrates for screening inhibitors of serine proteases. They utilized the GBB-3CR reaction to synthesize the scaffold imidazo[1,2-a]pyridine, which served as the starting substrate (Scheme 59) [168].



Scheme 55 GBB-3CR Reaction.

Torrence *et. al*. reported the synthesis of an unconventional nucleoside structure possessing antiviral properties. They employed a one-step 3CR involving a nucleoside, 1,3-cyclohexadione, and malonitrile to generate the hybridized structure (Scheme 60) [169]. The resulting component was tested against various viruses, revealing its impact on cowpox virus.



Scheme 56 Hybridisation of a Nucleoside and Chromene Scaffold.

In 2008, the Giralt group synthesized several compounds acting as POP inhibitors using the Povarov method. They utilized anilines, aldehydes, and cyclic enol ethers to produce fused quinolines of the Povarov products through DDQ oxidation followed by methylation (Scheme 61) [171].

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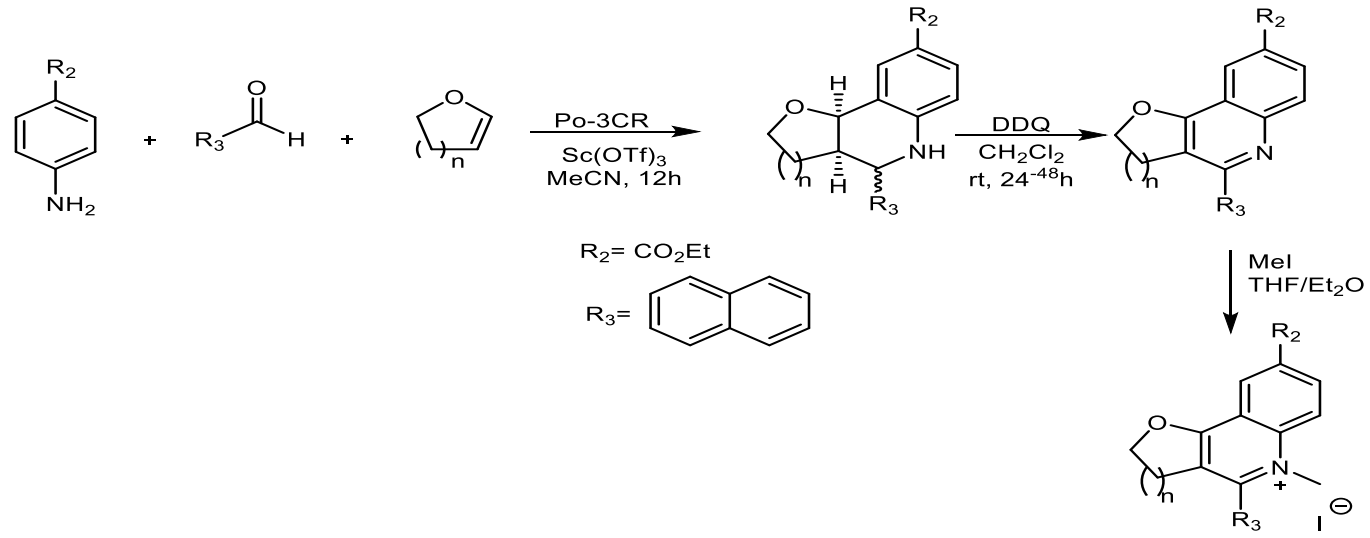
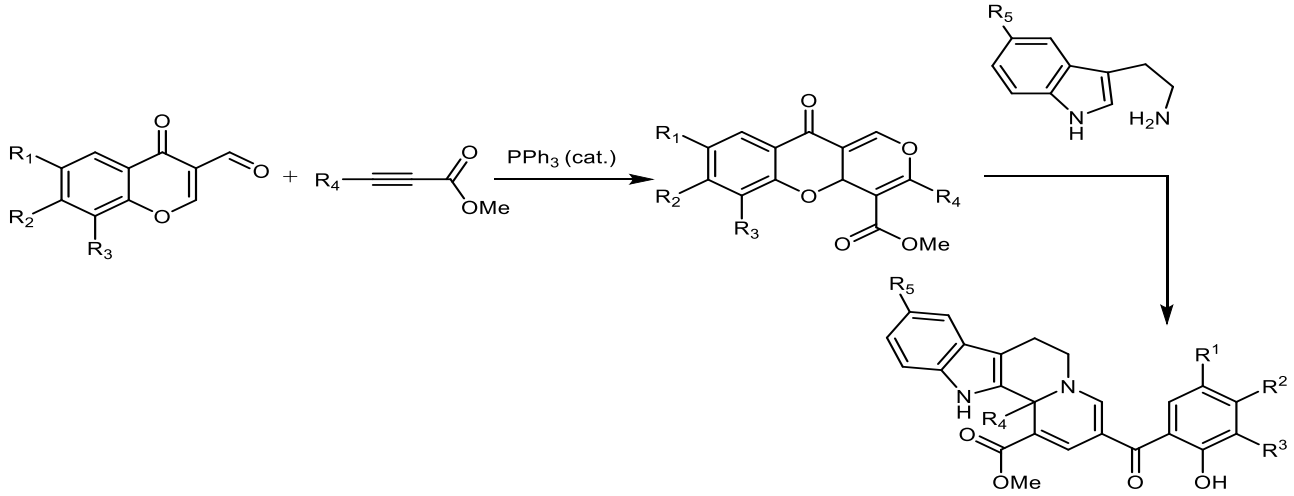


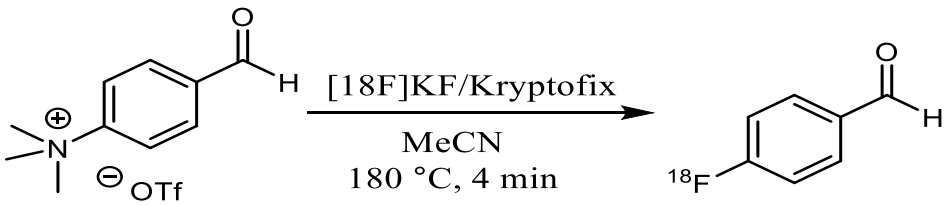
Scheme 57 Synthesis of POP Inhibitors.

In a recent study, Kumar and Waldmann's research group introduced an efficient 3-component reaction (3CR) for the synthesis of indoloquinolizines, centrocountins. They employed a PPh3-catalyzed formal [4+2] cycloaddition between 3-formylchromones and propiolate derivatives, leading to the formation of fused 4H-pyrans. These pyran intermediates then reacted with tryptamines, followed by nucleophilic ring-opening to yield a variety of indoloquinolizine derivatives (Scheme 62) [172].



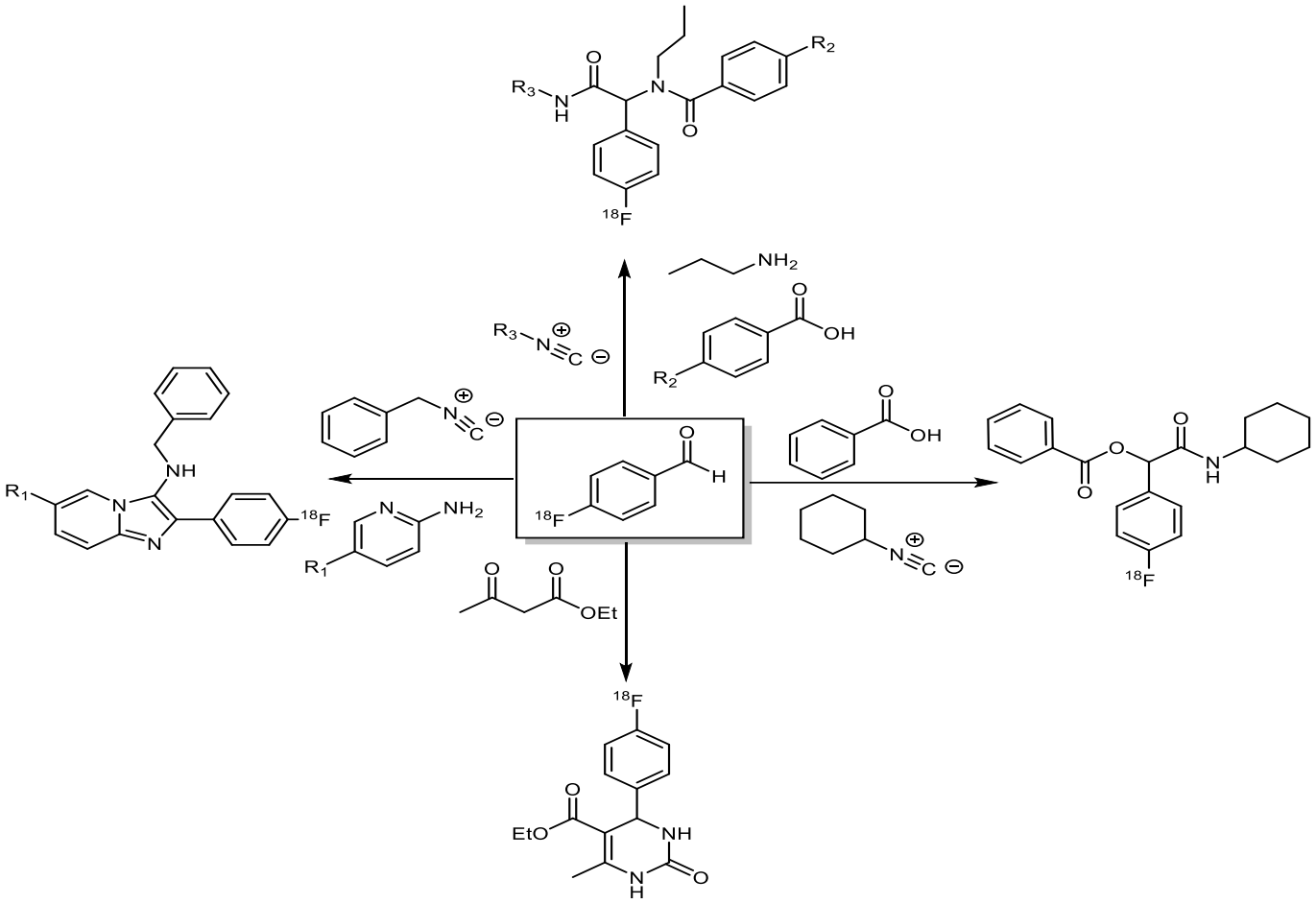
Scheme 58 Synthesis of Indoloquinolizines and Centrocountins.

Another distinctive application in drug discovery was explored by Gouverneur et al. in the synthesis of radiolabeled compounds using MCRs [173]. Radiolabeled probes are essential for positron emission tomography (PET) imaging analysis. Radiolabeled drugs are administered to assess their distribution and activity [174]. However, conventional synthesis methods for radiolabeled compounds are often time-consuming due to the limited half-life of radiolabeled isotopes. Gouverneur's team developed a method for synthesizing various molecules from radiolabeled 18F-benzaldehyde, generated through nucleophilic fluorination (SNAr), and correlated it with 4-trimethylammonium aryl triflate using [18F]KF/Kryptofix in a multicomponent reaction (Scheme 63) [175].



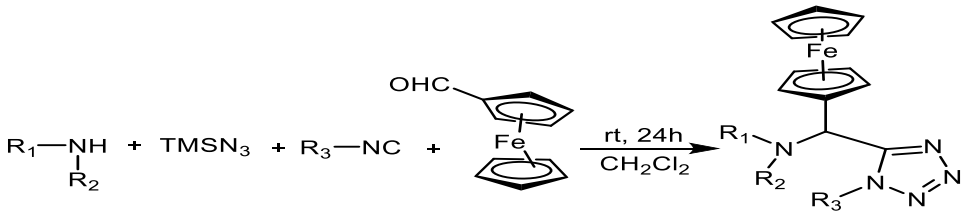
Scheme 59 Synthesis of Radiolabeled ^{18}F-Benzaldehyde.

The generated aldehydes from this process find utility in various multicomponent approaches for synthesizing diverse products. Scheme 64 illustrates the versatility of multicomponent reactions in radiolabeling.



Scheme 60 Radiolabelling Multicomponent Reactions with [18F] p-fluorobenzaldehyde.

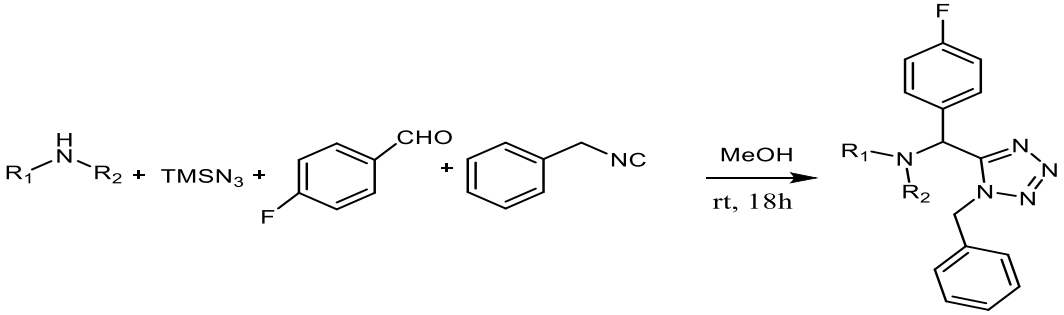
In 2012, Bazgir and his team reported a method for synthesizing a series of ferrocenyl dialkylamino tetrazoles and ferrocenyl arylamino tetrazoles using a UT-4CR without the need for a catalyst (Scheme 65) [176].



R_1, R_2= H, alkyl, aryl

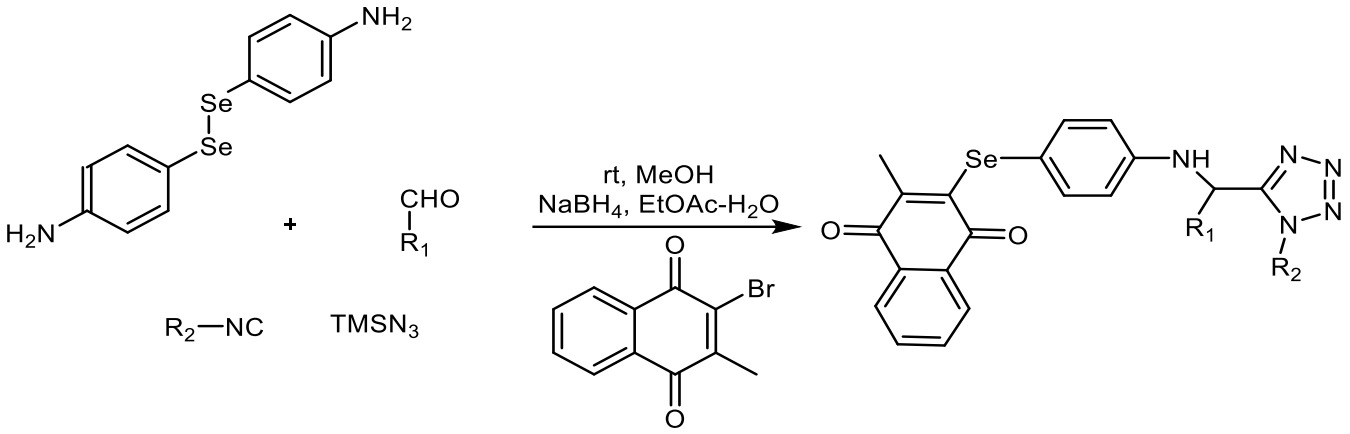
Scheme 61 Synthesis of Ferrocenyl 1,5-Disubstituted Tetrazoles.

In another study, Davenport et al. developed a method to synthesize a series of potent and subtype-selective H3 receptor antagonists with a novel tetrazole core and diamine motif (Scheme 66) [178].



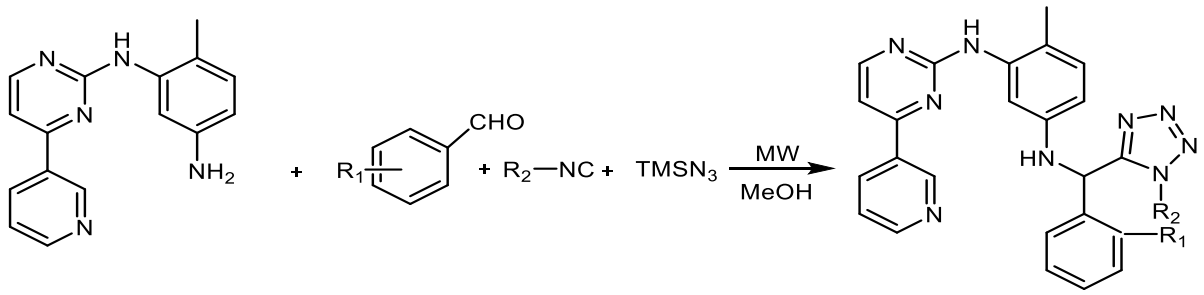
Scheme 62 Synthesis of substituted benzyl tetrazole.

In 2016, Wessjohann and his research group synthesized tetrazole-based diselenides and selenoquinones through a UT-4CR followed by nucleophilic substitution. The resulting compound was evaluated for its activity against hepatocellular carcinoma. Cytotoxicity tests were conducted using hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MCF-7) cancer cells, and the cytotoxicity was compared with fibroblast (WI-38) cells (Scheme 67) [179].



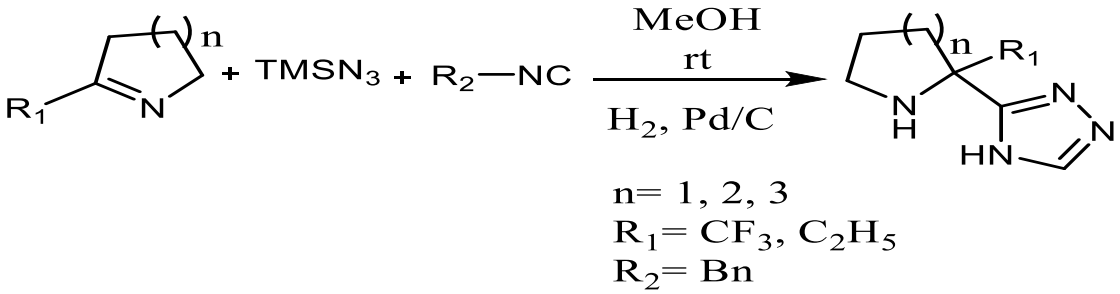
Scheme 63 Synthesis of Tetrazole-Based Diselenides and Selenoquinones.

Imatinib, an anticancer drug, was synthesized by Gámez-Montano's group in 2016 using a UT-4CR involving aldehydes, amines, and two isocyanides under microwave irradiation (Scheme 68) [180].



Scheme 64 Synthesis of Imatinib.

Organofluoride compounds have gained significant interest due to their diverse effects in pharmaceutical applications and materials science [181]. Nenajdenko and colleagues reported the use of trifluoroalkylated cyclic imines in UT reactions. Their approach involved various five, six, and seven-component trifluoroalkylated cyclic amines to generate tetrazole analogs of saturated nitrogen heterocycles carrying the trifluoroalkyl moieties (Scheme 69) [182].



Scheme 65 Synthesis of *N*-unsubstituted Tetrazoles.

Furthermore, endoperoxide linkages are present in various natural products such as artemisinin and its derivatives (artemether, arteether, artesunic acid, artelinic acid) and yingzhaosu A, which belong to the class of antimalarial agents. Artemisinin contains the trioxane system, while yingzhaosu A contains a 2,3-dioxabicyclo [3.3.1] nonane scaffold. Bachi and his research team synthesized endoperoxides containing this bicyclic scaffold by utilizing a sequential, free-radical, thiol-olefins co-oxygenation (TOCO) MCR followed by a post-condensation reaction [183] (Scheme 70).

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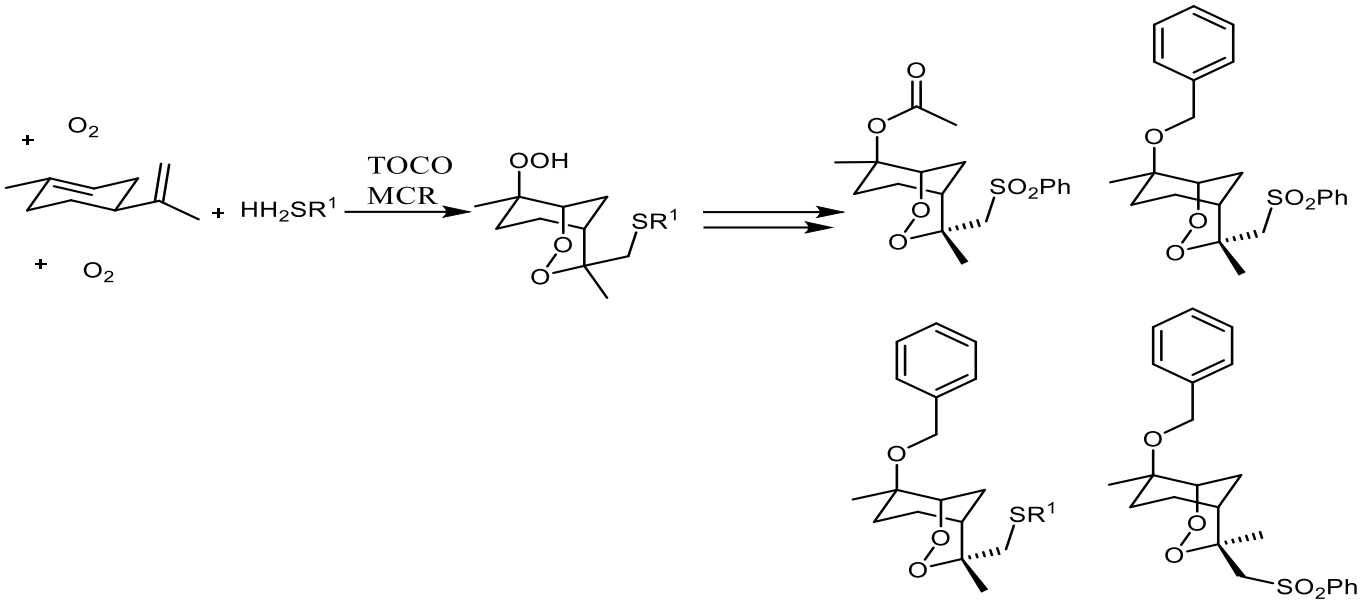
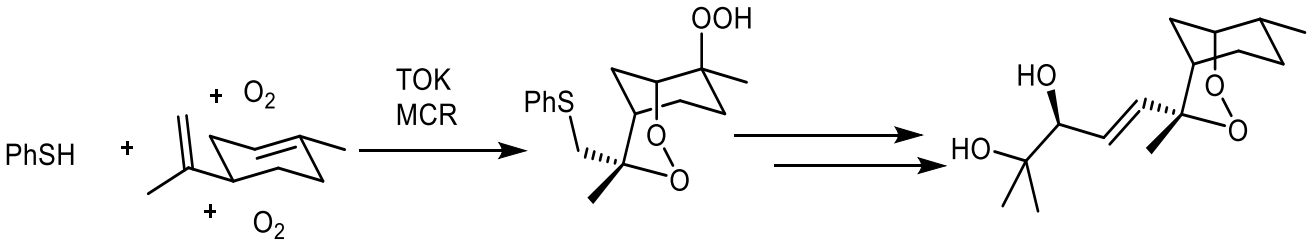


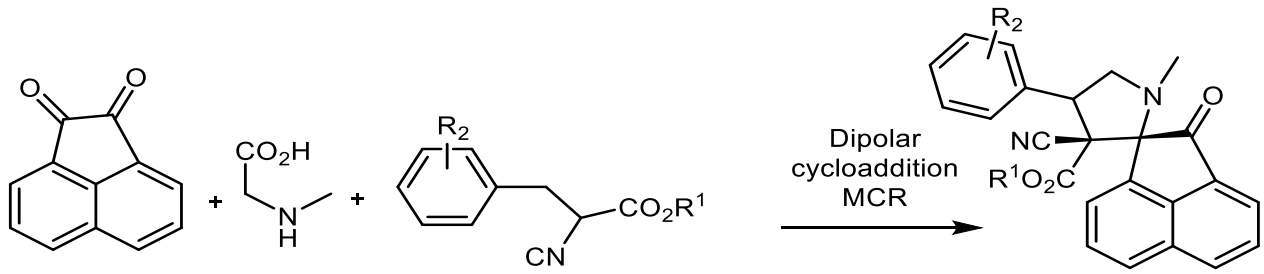
Scheme 66 Synthesis of Bicyclic Endoperoxide.

Soon thereafter, the same group utilized the aforementioned MCR procedure for the synthesis of the naturally occurring endoperoxide yingzhaosu A (Scheme 71) [184].



Scheme 67 Synthesis of Yingzhaosu A.

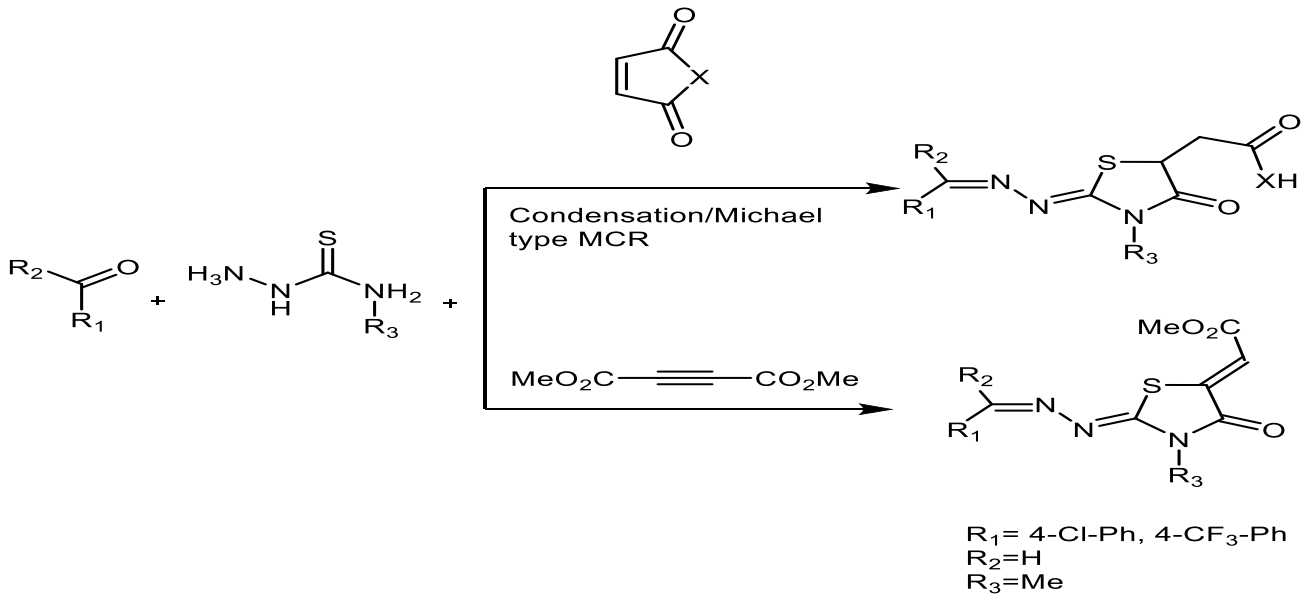
In another instance, Dandia et al. reported an efficient protocol for the synthesis of analogs of spiro[acenaphthylene-1,20-pyrrolidine] moieties. Their strategy involved the reaction between acenaphthene quinone, the amino acid sarcosine, and methyl or ethyl cyanoacetate through the use of dipolar cycloaddition MCR to produce the desired compound (Scheme 72) [185].



R_1= Me
R_2= 4-Cl, 4-Br, 4-OMe

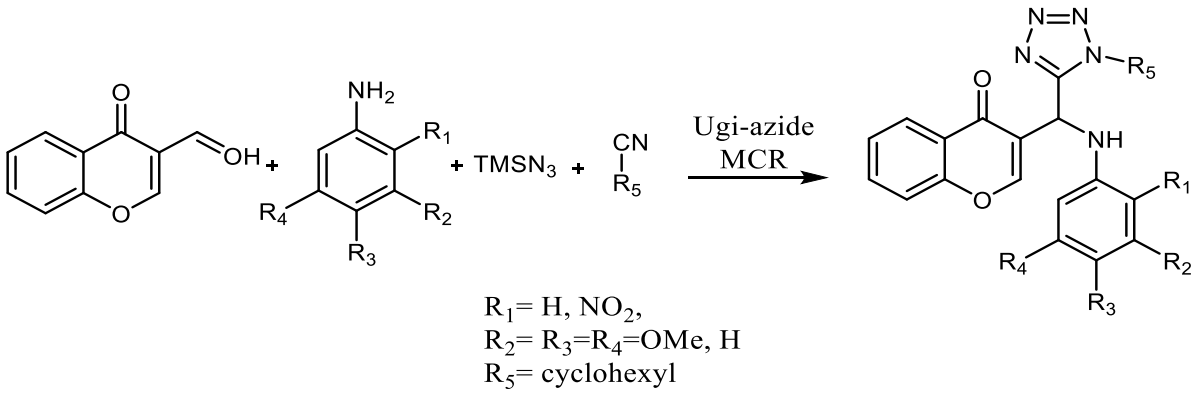
Scheme 68 Synthesis of Spiro[Acenaphthylene-1,20-Pyrrolidine].

Cruzipain, also recognized as Cruzain, serves as a cysteine protease pivotal to the proteolytic function within the parasite T. cruzi. This parasite is accountable for inducing Chagas disease. This enzyme's significance lies in its necessity for the parasite's viability within host cells, rendering it a prime target for the exploration of drugs to combat Chagas disease. In light of its critical role, Mahler and colleagues introduced a technique to synthesize hydrazolyl-4-thiazolidinone. This was accomplished through the reaction of a carbonyl compound, a thiosemicarbazide, and a potent Michael acceptor (such as maleic anhydride, N-methylmaleimide, or dimethyl acetylenedicarboxylate) utilizing a microwave-assisted three-component reaction approach (delineated in Scheme 73).



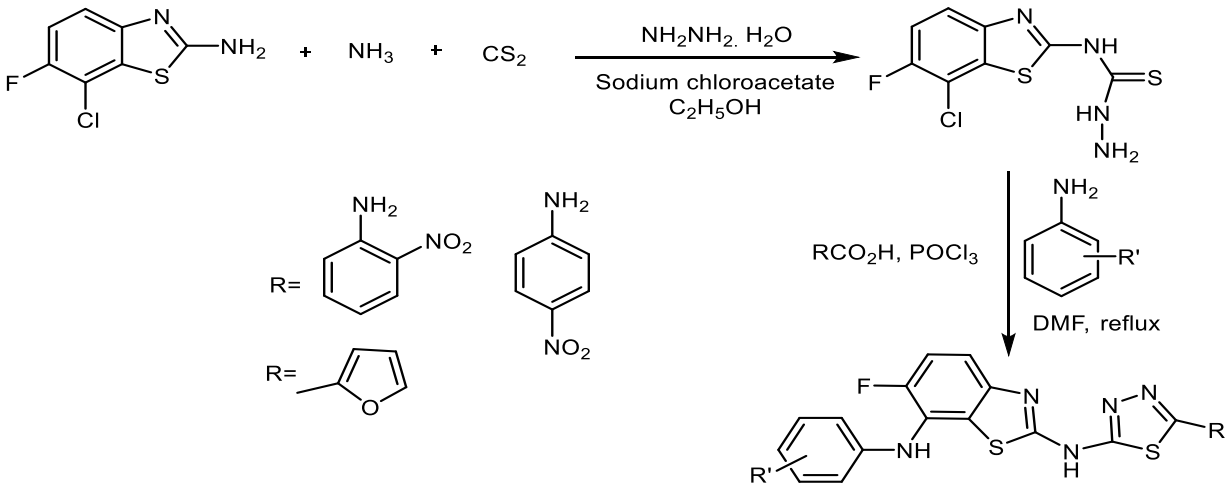
Scheme 69 Synthesis of 2-Hydrazolyl-4-Thiazolidinone.

The naturally occurring compound formononetin, characterized by a 3-substituted chromen-4-one structure, has displayed notable effectiveness against Giardia intestinalis, surpassing the potency of metronidazole. Expanding on this observation, the team led by Gamez-Montano undertook the synthesis of 3-tetrazolylmethyl-4H-chromen-4-ones utilizing an Ugi-azide multicomponent reaction strategy (depicted in Scheme 74) [188].



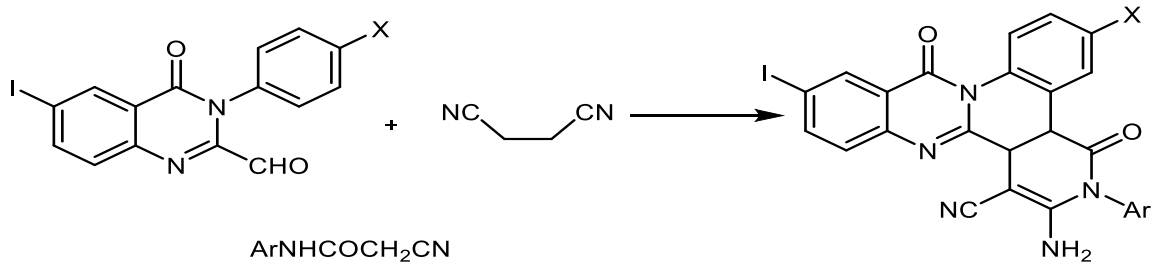
Scheme 70 Synthesis of 3-Tetrazolylmethyl-4H-Chromen-4-Ones.

In 2012, Sugumaran and his team synthesized a novel series of fluoro-benzothiazole-incorporated 1,3,4-thiadiazole compounds and evaluated their anti-inflammatory activity using the carrageenan-induced paw edema method (Scheme 75) [189].



Scheme 71 Synthesis of Flurobenzothiazole.

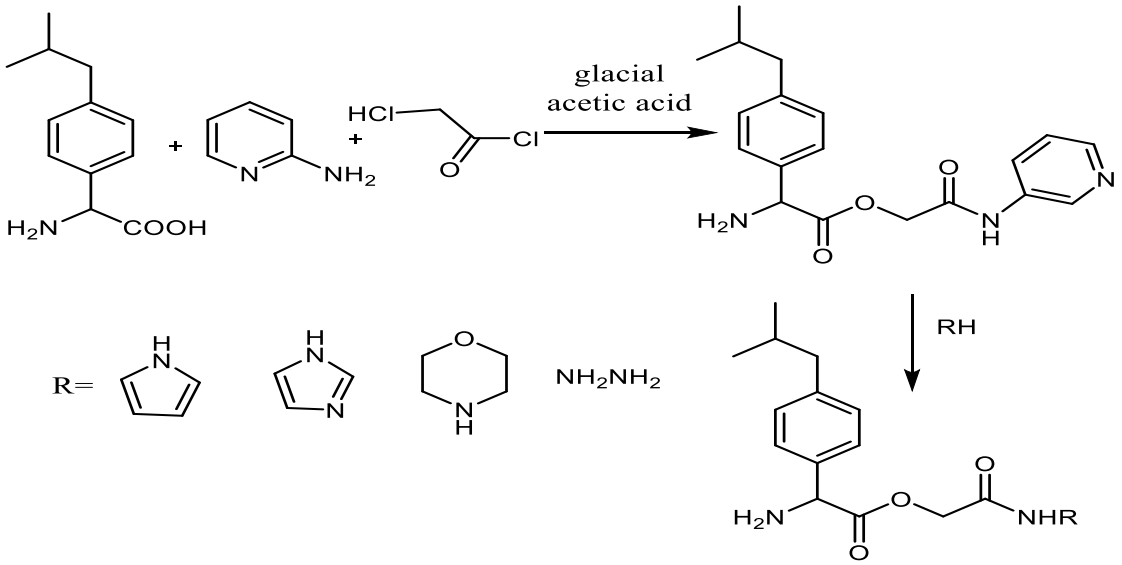
In 2013, Faragandhis co-workers reported a protocol to preparation pyridinone derivatives (Scheme 76) [190].



X= F, Cl, Ar= $C_6H_4(OC_2H_5)_2$

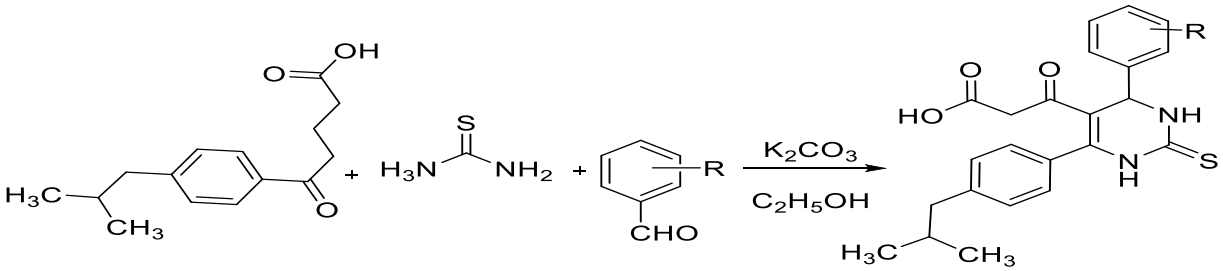
Scheme 72 Synthesis of Pyridinone Derivatives.

Gupta and his group synthesized 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-ylcarbamoyl methyl ester derivatives by refluxing Ibuprofen with 2-amino pyridine in chloroacetyl chloride in the presence of glacial acetic acid, resulting in 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-yl-carbamoyl methyl ester. This compound could be used as a prodrug for ibuprofen with enhanced anti-inflammatory potential (Scheme 77) [191]. The compounds were further treated with various cycloamino moieties like morpholine, pyrrolidine, hydrazine hydrate, and found to exhibit significant anti-inflammatory activity.



Scheme 73 Synthesis of 2-(4-sec-butyl-phenyl)-Propionic Acid-Pyrrolidin-2-Ylcarbamoyl Methyl Ester.

Osman et al. synthesized 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives through the condensation of 5-(4-isobutylphenyl)-5-oxopentanoic acid, thiourea, and substituted aldehydes using the Biginelli reaction (Scheme 78) [192].



Scheme 74 Synthesis of 3-(4, 6-Disubtituted-2-Thioxo-1,2,3,4-Tetrahydropyrimidin-5-yl) Propanoic Acid.

A report highlighted that inhibiting histone deacetylase (HDAC) plays a role in gene regulation correlated with cell cycle progression and carcinogenesis. Inhibitors of HDACs have been used in the treatment of T-cell lymphoma [193, 194]. In this context, Tron and his team developed a reaction involving α-isocyano amides, aldehydes, and secondary amines to synthesize substituted oxazoles via a Zhu-3CR, utilizing two distinct chemical approaches in combination to form the macrocycles (Scheme 79).

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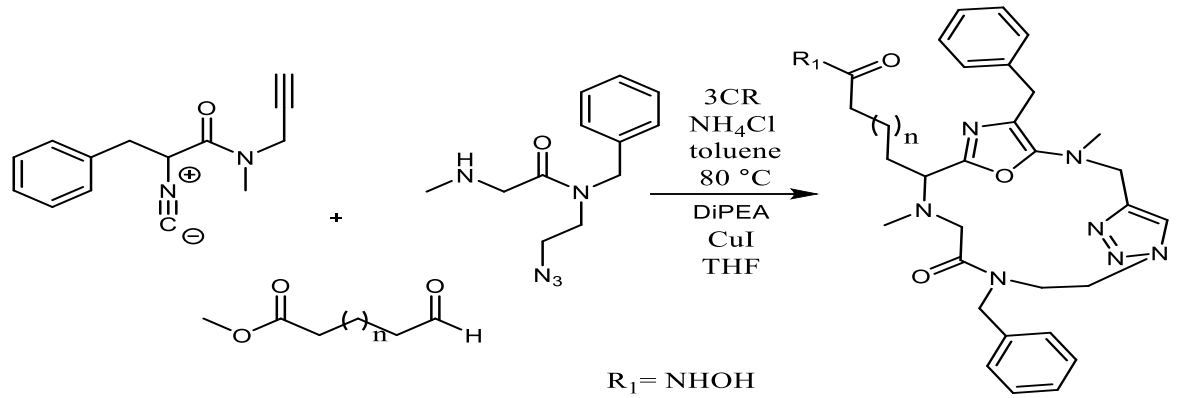
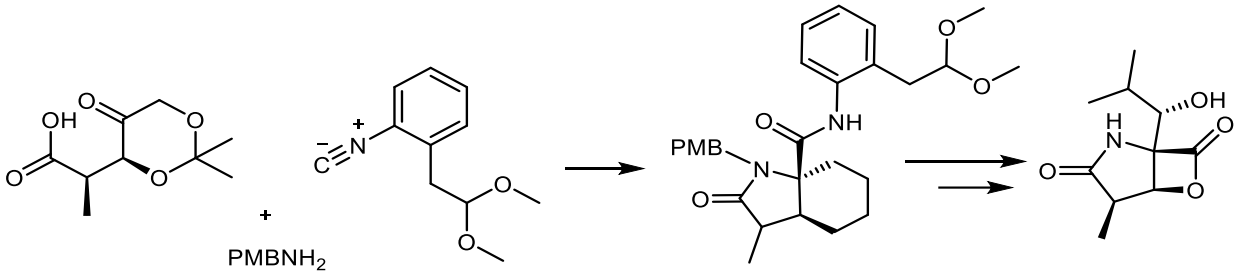


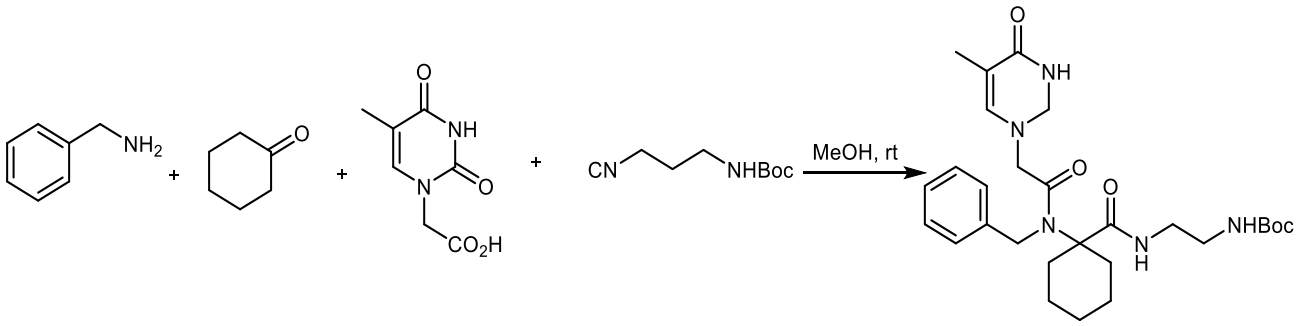
Scheme 75 Synthesis of Cyclic Peptide Composition.

In a recent study, the Kobayashi group successfully synthesized the proteasome inhibitor Omuralide using a Ugi reaction, incorporating 1-isocyano-2-(2,2-dimethoxyethyl) benzene as a convertible isocyanide (Scheme 80) [196].



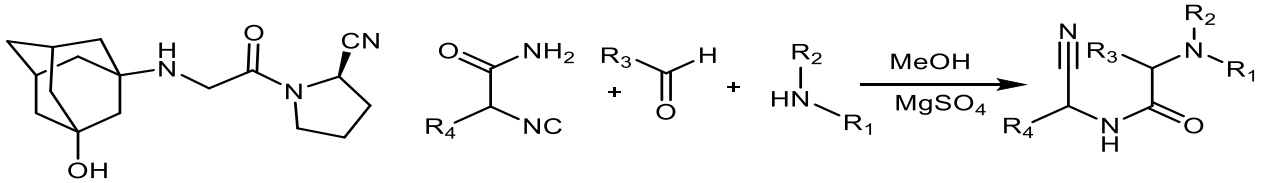
Scheme 76 Proteasome Inhibitors Synthesized by Ugi-3CR.

Moreover, Domling's group employed Ugi-MCR as a critical step in the synthesis of peptide nucleic acids (PNAs), which have applications in diagnostics and therapeutics (Scheme 81) [197].



Scheme 77 Synthesis of Peptide Nucleic Acids.

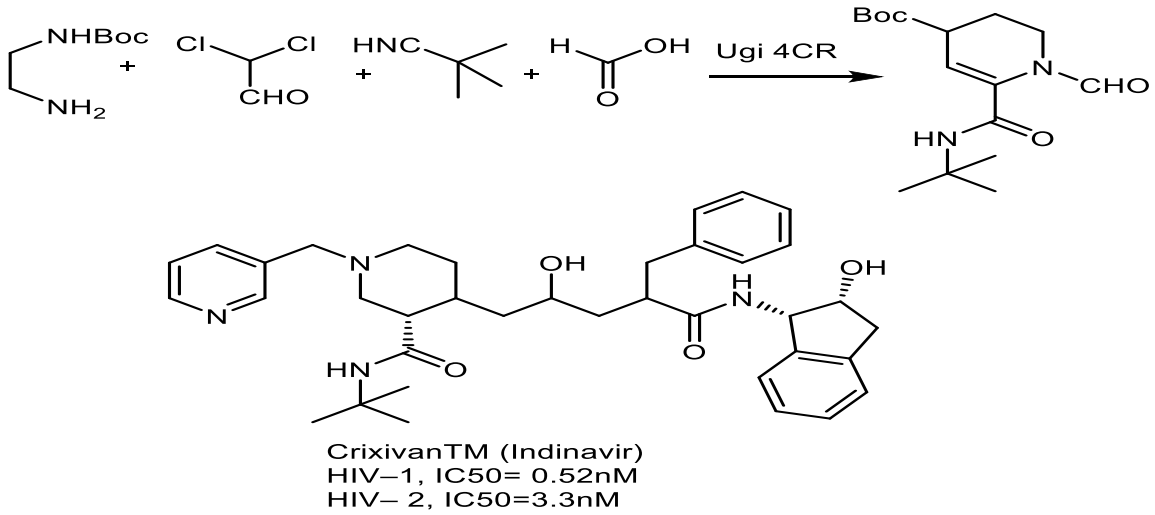
Vildagliptin, a medication for class II diabetes and a novel DPP-IV inhibitor, acts as an inhibitor for the serine protease dipeptidyl peptidase IV (DPP-IV). The α-aminonitrile structure of vildagliptin is accessible through various variations of the Ugi 4CR (Scheme 82) [198].



Vildagliptin

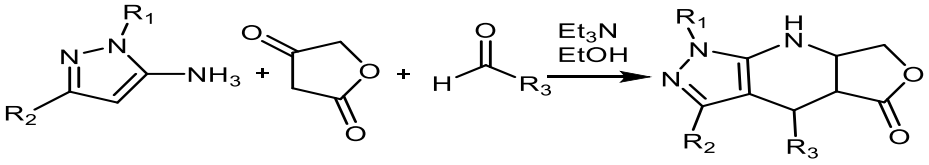
Scheme 78 Assembly of the α-aminonitrile nucleous of Vildagliptin.

Rossen and his team synthesized the piperazine nucleus of Crixivan TM, a protease inhibitor marketed for the treatment of HIV, through an Ugi 4CR (Scheme 83) [199].



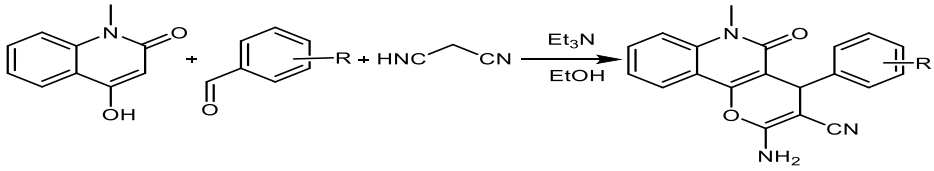
Scheme 79 Synthesis of Piperazine Core of Crixivan.

In 2007, Kornienko et al. developed a method for synthesizing the natural product podophyllotoxin, a tubulin polymerization inhibitor. Their strategy involved a 3CR between aminopyrazoles, tetramic acid, and an aldehyde via Knoevenagel condensation, followed by Michael addition/ring closure reaction to yield the desired product (Scheme 84) [200, 201].



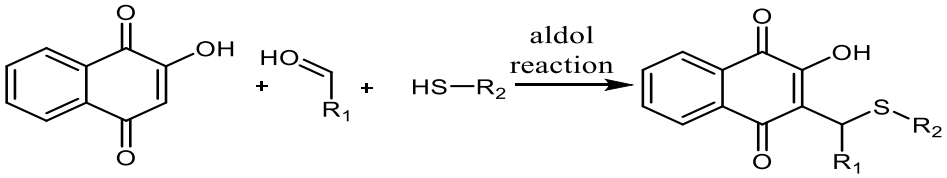
Scheme 80 Synthesis of the Natural Product Podophyllotoxin.

In another study, the same group utilized a 3CR reaction to synthesize antitubulin agents, such as pyrano [3,2-c] quinolones, through Knoevenagel condensation of pyridine, aldehyde, and malonitrile, followed by ring closure (Scheme 85) [202].



Scheme 81 Synthesis of Pyrano[3,2-c] Quinolones.

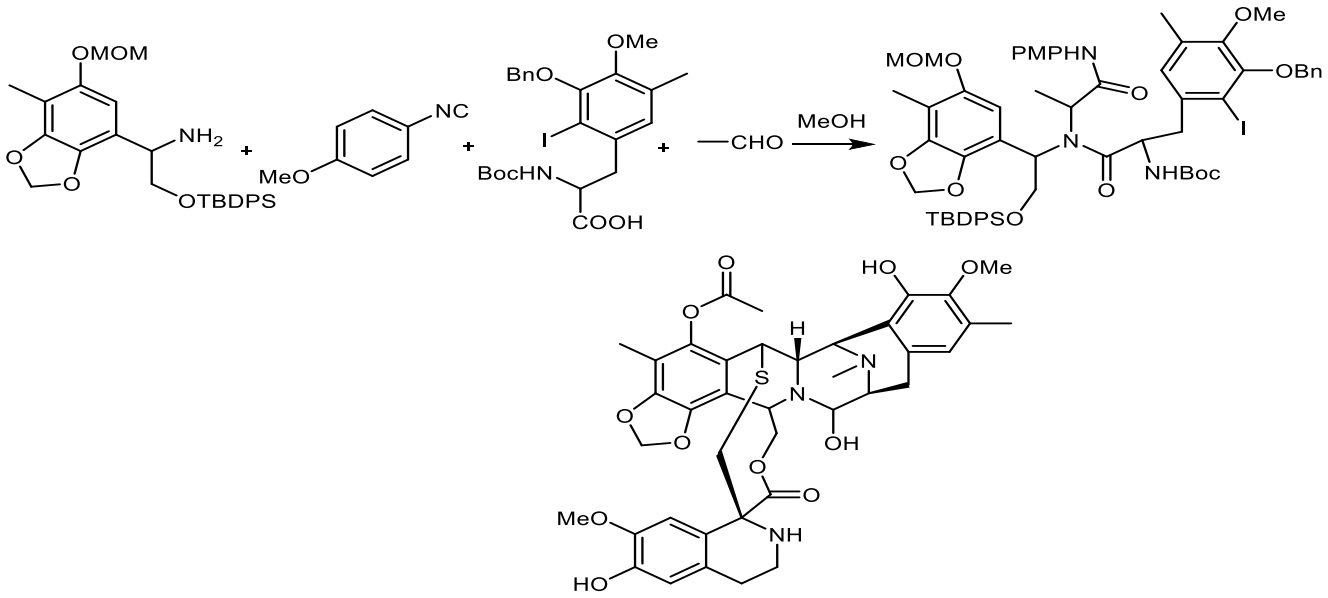
Lapachol, a naturally occurring compound characterized by a 3-substituted 2-hydroxy-1,4-naphthoquinone structure, has demonstrated antiplasmodial properties. This compound's properties have served as inspiration for the development of various antiparasitic drugs, including atovaquone, parvaquone, and buparvacone. In a significant advancement, the team led by Garcia introduced a methodology to synthesize a novel series of 2-hydroxy-3-phenylsulfanylmethyl [1,4] naphthoquinones, akin to lapachol, which hold potential as antimalarial agents. Their approach involved a reaction between lawsone (2-hydroxy-1,4-naphthoquinone), an aldehyde, and a thiol. This reaction was facilitated by microwave irradiation, employing an aldol-type multicomponent reaction technique (depicted in Scheme 86) [204].



R_1= 4-NO_2-Ph, H
R_2= 4-MeO-Phe, 4-Me-Ph

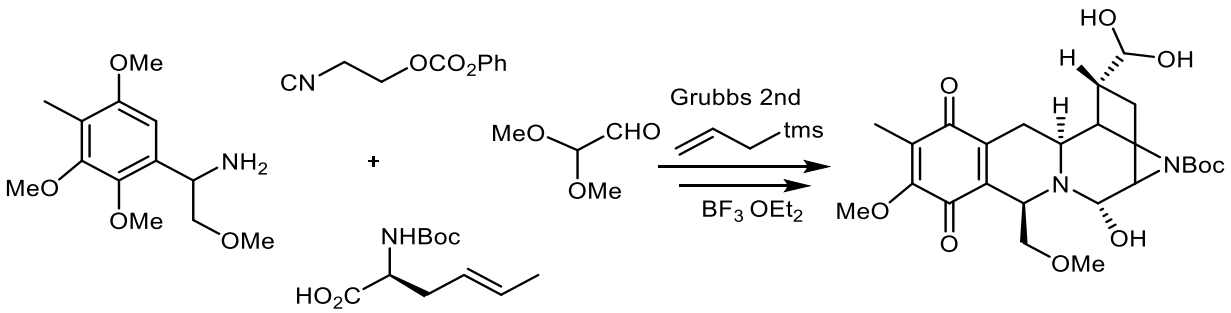
Scheme 82 Synthesis of 2-Hydroxy-3-Phenylsulfanylmethyl [1,4] Naphthoquinones.

Fukuyama and his research group accomplished a total synthesis of the antitumor antibiotic ecteinascidine 743, which is presently undergoing clinical trials by the application of Ugi-4CR (Scheme 87) [205].



Scheme 83 Synthesis of Ecteinascidine 743.

In 2004, Fukuyama and his group undertook synthetic studies toward the class of naphthyridin antibiotics, employing U-4CR [206]. The formation of the 3,8-diazabicyclo [3.2.1] moieties, an essential part of the tetrahydroisoquinoline alkaloid lemonomycin, was recently accomplished (Scheme 88). The U-4CR synthetic strategy involved the reaction of an amine, isocyanide, amino acid, and glyoxyaldehyde dimethylacetal in trifluoroethanol to synthesize the tetrahydroisoquinoline alkaloids



Scheme 84 Synthesis of Lemonomycin.

VI. CONCLUSION

In the field of drug discovery and development, multicomponent reactions (MCRs) have played a pivotal role. MCRs have been extensively used from lead identification to the generation of large analog libraries. They have proven to be valuable in cancer therapy and addressing various infectious diseases. Numerous protein-based drug candidates have been synthesized using MCRs. Additionally, several well-known natural products have been synthesized with potent pharmacological activities through the application of MCRs. The versatility of MCRs is also evident in the synthesis of complex drugs.

- *Conflict of Interest:* There is no conflict of interest.

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