doi:10.20944/preprints202204.0151.v1

The Discovery of Novel Antimicrobial Agents by The Application of Isocyanide Based Multicomponent Reactions

Sameer Quazi[1,2,*], Shreelaxmi Gavas[1], Bahareh Farasati Far[3], Javid Ahmad Malik[1,4], Maliha Tabassum Rashid[5,6]

1. GenLab Biosolutions Private Limited, Bangalore, Karnataka, India. (560043)
2. Department of Biomedical Sciences, School of Life Science, Anglia Ruskin University, United Kingdom.
3. Department of Chemistry, Iran University of Science and Technology, Tehran, Iran.
4. Department of Zoology, Guru Ghasidas University, Bilaspur, Chhattisgarh, India.
5. Research Fellow, Asian Network of Research on Antidiabetic Plants, Bangladesh.
6. Department of Pharmacology, University of Health Sciences, Dhaka, Bangladesh.

*Corresponding author: colonel.quazi@gmail.com

Abstract:

Multicomponent reactions (MCR) have been used to synthesis a wide range of analogs from several classes of heterocyclic compounds, with multifaceted medicinal uses. The synthesis of highly functionalized molecules in a single pot is a unique property of MCR, allowing researchers to quickly assemble libraries of compounds of biological interest and uncover novel leads as possible therapeutic agents. Isocyanide-based multicomponent reactions have proven to be extremely effective at swiftly specifying members of compound libraries, particularly in discovery of drug . The understanding of structure-activity correlations that drive the development of new goods and technology, requires structural variety in these libraries. In current world, antibiotic resistance is a major ongoing problem which is developing a problematic scenario in public health. The implementation of isocyanide based multicomponent reactions uphold a significant potential in this regard. By utilizing such reactions, new antimicrobial compounds can be discovered and fight against such concerns. This study discusses recent developments in antimicrobial medication discovery using isocyanide-based multicomponent reactions (IMCRs). Furthermore, the article emphasizes the potential of IMCRs in the near future.

Keywords: Isocyanide-based multicomponent reactions; Antimicrobial Discovery; Antibiotic Resistance; Public Health

Highlights:

1. Multicomponent Reaction has distinct variety.
2. The isocyanide based multicomponent reactions are three types.
3. Isocyanide based multicomponent reactions has significant potential in drug discovery.
4. The Groebke-Blackburn-Bienaymé reaction can be applied to increase the potency of drugs.
5. Along with antimicrobials agents, isocyanide based multicomponent reactions has been found to be very efficacious in anti-HIV, anti-cancer agents.

Introduction:

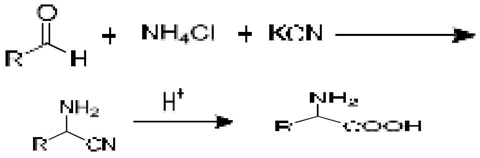
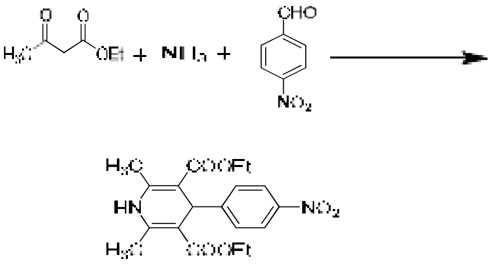
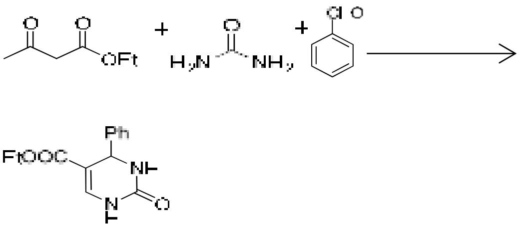
Multicomponent based reactions are mainly chemical reactions where three or more compounds are used to make a final product. It has been almost 150 years since multicomponent reactions are known to the world of chemistry. Multicomponent reactions are a fascinating family of organic chemistry transformations [1]. Traditional bimolecular reactions are outperformed by such reactions, which combine 3 or more reactants into one reaction product [2]. Multicomponent reactions speed up chemical space exploration by minimizing the quantity of synthesis and refinement steps needed to create a particular target[3]. The associated atom economy of multicomponent reactions improves the chemical enterprise's long-term viability even further. Our knowledge of delicate reactivity principles is likewise' challenged by the mechanics of multicomponent reactions. Aside from the benefits of mechanistic beauty and green chemistry , a crucial characteristic of multicomponent reactions that has yet to be completely appreciated is the ease with which functional materials can be built. Affinity ligands for immunoglobulin purification, imaging compounds in biological systems, proteome-wide mapping of protein-protein interactions, molecular machines, and molecular keys for utilization in advanced encryption standard cryptography with molecular steganography are just some of the functions that can be performed [4-7]. Multicomponent reactions (MCRs) are a valuable method for creating small-molecule compound libraries and are essential for studying structure–activity relationships (SARs). Since, a number of MCRs produce exceptional, if not unique, scaffolds, the capacity to further qualify or functionalize them is critical for determining the scaffold's biological value. Many of these scaffolds have a distinctive structure that allows them to investigate biological targets that regular scaffolds cannot. As infections change to become unsusceptible to conventional treatments, and anti-aging compounds are required to combat diseases like Parkinson's, diabetes, Alzheimer's and cancer, novel scaffolds are becoming increasingly sought for.

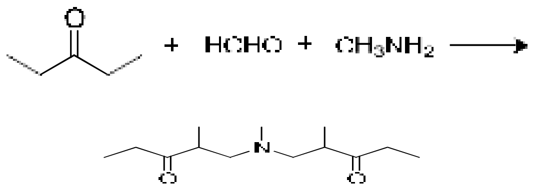
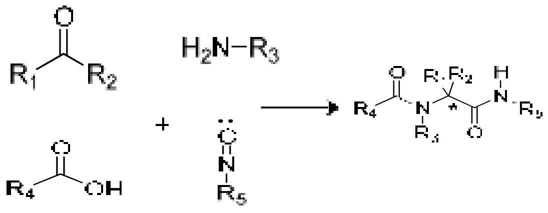
Previously, the majority of medications were found by coincidence or by identifying the active compounds in traditional cures. Modern drug development faces the difficulty of engineering chemical reactions capable of giving the majority of functional complexness and diversity with the fewest possible artificial steps for a specific target with fascinating attributes [8-10]. Combinatorial chemistry has recently been hailed as a strong method for rapidly developing lead molecules in the drug development process [11,12]. Thus, the necessity to find and produce novel chemical entities with desirable qualities in a more efficacious and cost-efficient manner, and most crucially, within a short time, it has been a

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 April 2022 doi:10.20944/preprints202204.0151.v1

primary dynamic power behind the rising interest in this subject. The majority of medications on the market today are tiny chemical molecules with heterocyclic rings[8]. Furthermore, there are several restrictions to the availability and accessibility of properly functionalized heterocyclic building blocks for the synthesis of diverse libraries in combinatorial chemistry. Consequently, chemists continue to face a significant difficulty in developing innovative, efficient, and clean synthetic processes [13]. There has been a numerous multiplecomponent reaction in organic chemistry . In the following table 1, several types of multicomponent reactions are listed below :

Table 1: Different types of multicomponent reactions

Names of Researcher	**Invention Year**	**Reaction**	**Reaction Litterateur**
Strecker	1850		An aldehyde is condensed with ammonium chloride in the presence of potassium cyanide to generate an a-amino nitrile, which can be hydrolyzed to give the a-amino acid [14]
Hantzsch	1882		An ammonia, two equivalents of ethyl acetoacetate and an aldehyde has developed adihydropyridine from this synthesis [15].
Biginelli	1891		Synthesis of an ethyl acetoacetate, ,urea and an aryl aldehyde (benzaldehyde) has developed 3,4-dihydropyrimidin-2(1H) [16-19].

Mannich	1912		An amino alkylation of an enol with an amine and an aldehyde is used in this reaction [20]
Ugi	1960		A ketone or aldehyde, an amine, an isocyanide, and a carboxylic acid are used in this multicomponent process to generate a bis-amide [21-24]

The inclusion of an isocyanide including, isonitrile reagent in the result is one of the most well-known and diversified types of multicomponent reactions. Multicomponent reactions based on isocyanide were among the first MCRs found in organic chemistry. Nearly a century ago, Mario Passerini reported the first isocyanide-based 3CRs including an aryl isocyanide, carboxylic acids and ketones [25]. Nearly 40 years later, Ugi announced the first isocyanide-based 4CRs [26]. Many reaction variants have been discovered as a result of Ugi's visual percept into the processes of these MCRs. Multicomponent reactions also have the potential to facilitate combinatory collection synthesis and serve as platforms for diversity-oriented synthesis, according to Ugi. More than 150 years of study into IMCRs has been supported by these pillars. Since synthetic organic chemists use IMCRs to solve difficulties in biology, polymers, and materials science, these themes remain ubiquitous as we indicate on the state-of-the-art in the area [27-29]. In this review article, the invention of novel antibiotics by the application of isocyanide based multicomponent reactions are being elucidated.

Isocyanides and the types of Isocyanides Based Multicomponent Reactions:

Isocyanides (isonitriles) were the only stable organic molecules containing a formally divalent carbon for a long period of time. The group isocyanides are distinguished from other functional groups by their reactivity. All isocyanides which are found commercially are volatile and emit a foul, harsh, and repulsive odor. It has been examined as potential non-lethal weapon as a result of this type of odor. There are a number of isocyanides based multicomponent reactions among which the maximum number of reported chemical synthesis

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 18 April 2022 doi:10.20944/preprints202204.0151.v1

use UGI's 4 component-based reaction. Though, in the following context, the distinct types of isocyanides based multicomponent reactions are described .

In1859. Lieke discovered isocyanides from the random reaction of silver cyanide and allyl iodide [30].Later, Gautier and Hoffmann coined the word "isonitrile" after synthesizing these compounds by experimenting primary amines with alkali and chloroform [31]. Passerini presented the first IMCRs around half a century later, in 1921. The P-3CR Passerini 3CR between an isocyanide, a carbonyl molecule and a carboxylic acid resulted in the formation of α-acyloxy carboxamide 4. Although attempts have been made to produce isocyanides in a more practical manner since 1950s[32].

Finally, U-4CR began in the middle of 19th century, when Ivar Karl Ugi (1930–2005) synthesized α-acylamido carboxamide 9 by a single reaction of amine, carbonyl molecule, isocyanide, and acid [33-35]. The reaction has been known to as the Ugi response since 1962. Around 20 later, the modification was carried out on a solid phase as well [36]. A research team has achieved the first stereoselective Ugi reaction on the solid phase in 2000 [37]. Finally,GBB-3CR, product 13 was discovered as the most recent MCR [38-40].

The reactions of Passerini:

Mario Passerini, discovered the Passerini reaction in 1921. It is the first MCR founded on isocyanide and continues to play a significant role in combinatorial chemistry today. It entails the use of an aldehyde or ketone, an isocyanide, and a carboxylic acid, and provides direct access to -hydroxy carboxamides (Reaction 1 Figure 1). Ugi's hypothesis indicates a non-ionic pathway, as the reaction is expedited in aprotic solvents (Figure 1 : Reaction 2) [41]. The isocyanide's nucleophilic attack follows the electrophilic activation of the carbonyl group . This produces a nitrilium intermediate, which is later targeted by carboxylate.

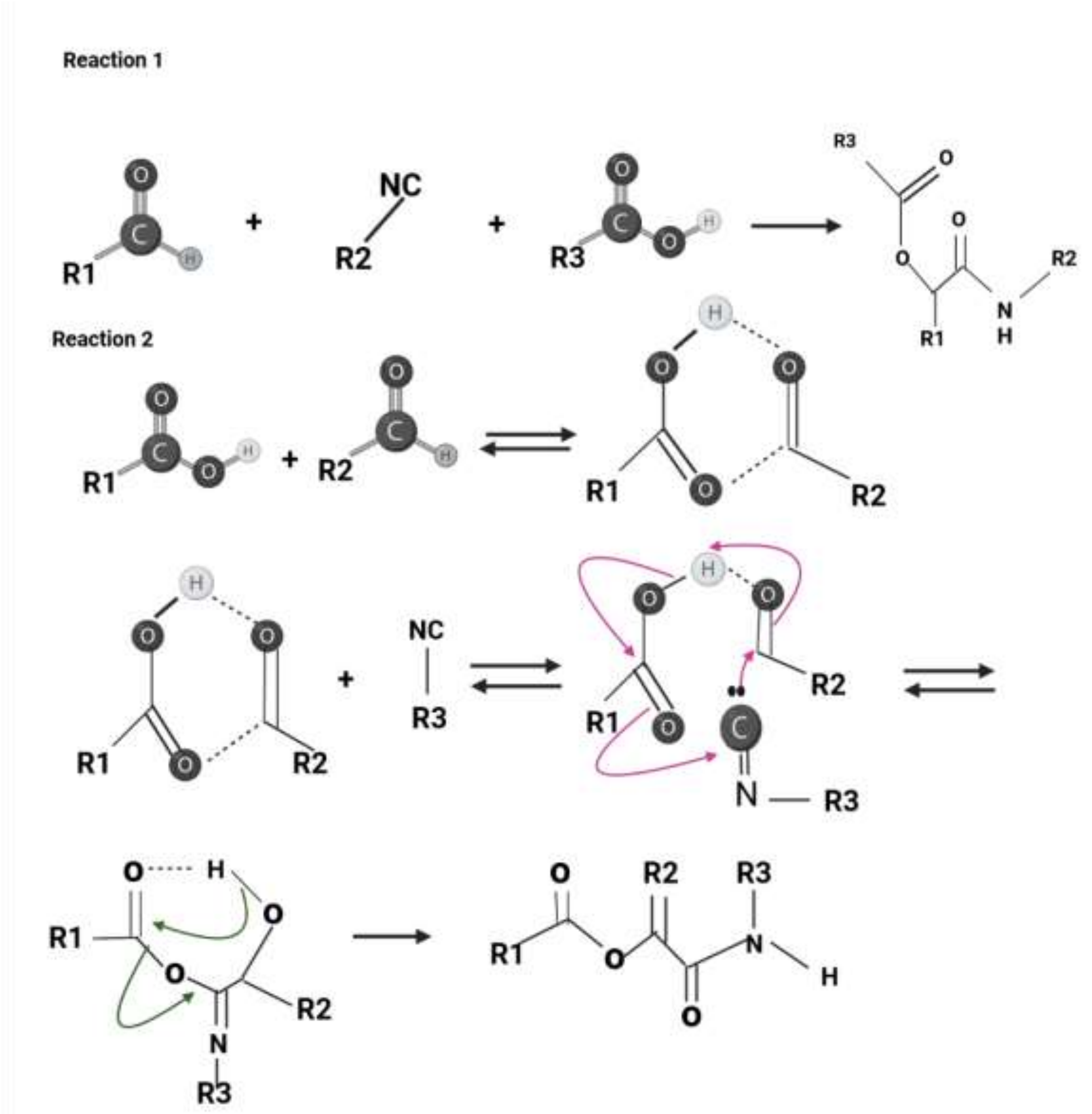


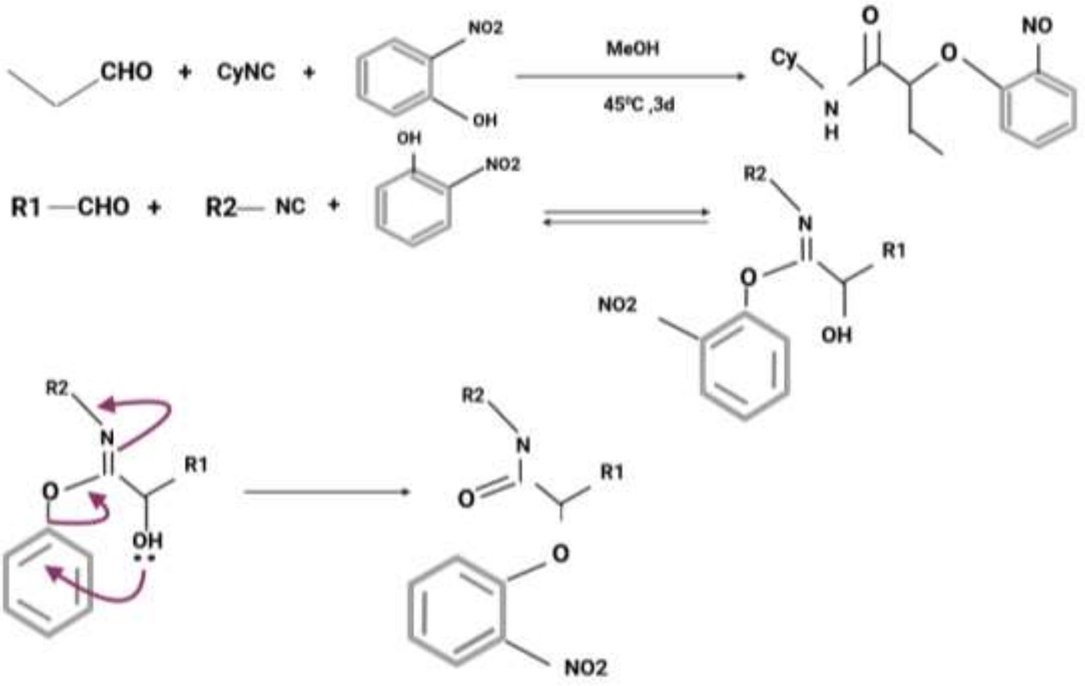
Figure 1 : Reaction 1 : A general Passerini reaction yielding an α-acyloxy amide , Reaction 2: The mechanism of Passerini.

After Passerini's general reaction , many scientists have experimented with different compounds such as Wang et al. Wang et al. recently demonstrated asymmetric reactions using widely available chiral Lewis acids [42]. The Zhu lab has documented Passerini reactions with alcohols, isocyanides, and carboxylic acids, broadening the reaction's potential utility beyond carbonyl-containing molecules. The process employs catalytic TEMPO, CuCl2, and NaNO2 to convert an alcohol to an aldehyde [43].

Passerini-type reactions between free alcohols (isopropanol), aldehydes (unsaturated and aryl), and isocyanides such as t-butyl isocyanide have been reported in the presence of In(III)

[44]. El Kam and Grimaud's pioneering study resulted in the revelation of what is now renowned as the Smiles reaction of Passerini.

In this situation, the carboxylic acid is replaced by an electron-deficient phenol such as 2-nitrophenol (or other nitrogen heteroaromatic but electron-deficient phenols). The method is thought to include stimulation of the aldehyde by the frail acidic phenol (pKa~ 4.2), rendering the carbonyl electrophilic and susceptible to attack by the isocyanide. The phenol attacks the incipient nitrilium ion, followed by a SNAr, forming a -aryloxy amide. The critical step, according to current thinking, is the irreversible Smiles rearrangement of the intermediate phenoxyimidate adduct (figure 2) [45].



Smiles reaction of Passerini and its possible mechanism.

Figure 2 : The Passerini Smiles reaction

A relatively recent but significant addition made by Soeta et al. is the substitution of silanols for carboxylic acids in the Passerini Reaction, allowing for the production of α--siloxyamides. The mechanism involves the coordination of the silyl group to the carbonyl's oxygen. This makes it vulnerable to nucleophilic attack by an isocyanide, which is followed by intramolecular trapping of the nitrilium ion by the silanol's alcoholic functional group [46] (Figure 3).

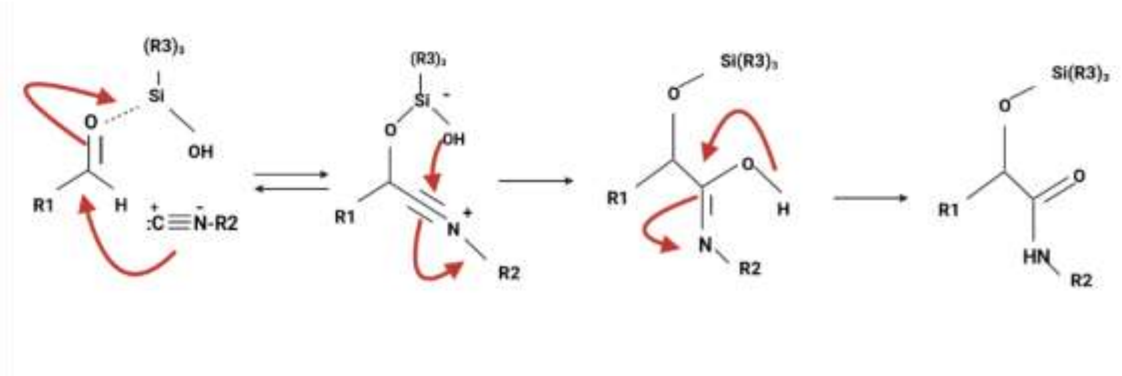


Figure 3 : Passerini reaction yielding α-(sulfonyloxy)amides

Ugi-4C Reaction:

A ketone or aldehyde, a carboxylic acid, an isocyanide, and an amine are used in a traditional Ugi four component reaction (U4CR).Typically, the reaction is carried out in high concentrations of methanol or 2,2,2-trifluoroethanol.The first step is to create an imine by reacting the amine with the carbonyl compound. Following by the isocyanide's nucleophilic attack, which produces the highly reactive nitrilium intermediate. The carboxylic acid then attacks the nitrilium, resulting in the formation of a central bis-amide via intramolecular Mumm rearrangement (figure 4).

Post-Ugi reactions have been reported depending on the R groups. Among the most notable are the Ugi-Heck , Ugi-Diels-Alder , Ugi-click , and Ugi-Buchwald-Hartwig reactions, in which a Ugi bis-amide containing reactive functional groups undergoes secondary reactions to form a ring.On the other hand, linear bis-amides are useful for the synthesis of peptides (both linear and cyclic) and peptidomimetics (figure 4) [47-51].

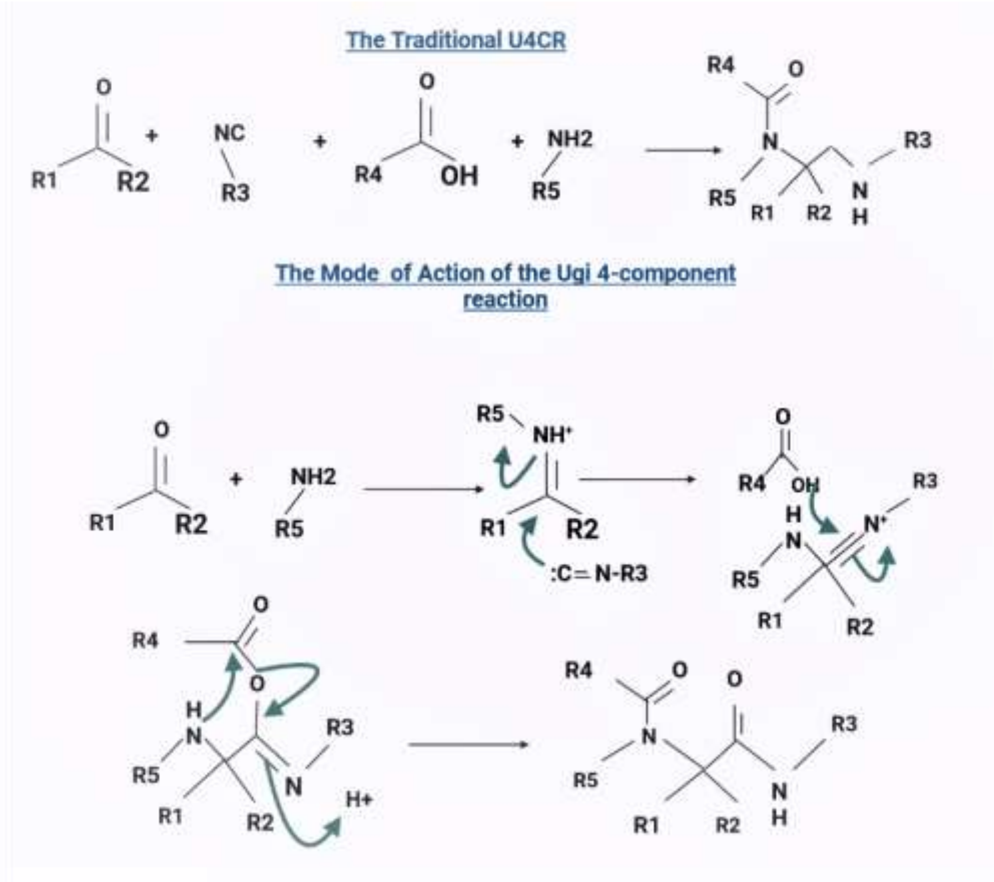


Figure 4: The Traditional Ugi-4C Component Reaction and The mode of action of the Ugi 4C Reaction

Groebke-Blackburn-Bienaymé reaction:

In a non-concerted [4 + 1] reaction between an imine generated through the reaction between an aldehyde and an amine and an isocyanide, the reaction gives 3-aminoimidizoles [52-54].This is called the Groebke-Blackburn-Bienaymé reaction. The nitrilium ion is trapped by the heterocyclic nitrogen, resulting in the production of an imidazole ring after a rearrangement [55,56]. Kinase inhibitors, topoisomerase II inhibitors, antibacterial efficient against methicillin-resistant *Staphylococcus aureus*, fluorescence probes, and HIV-1 reverse transcriptase inhibitors are among the bioactive molecules created using this method [57-62].

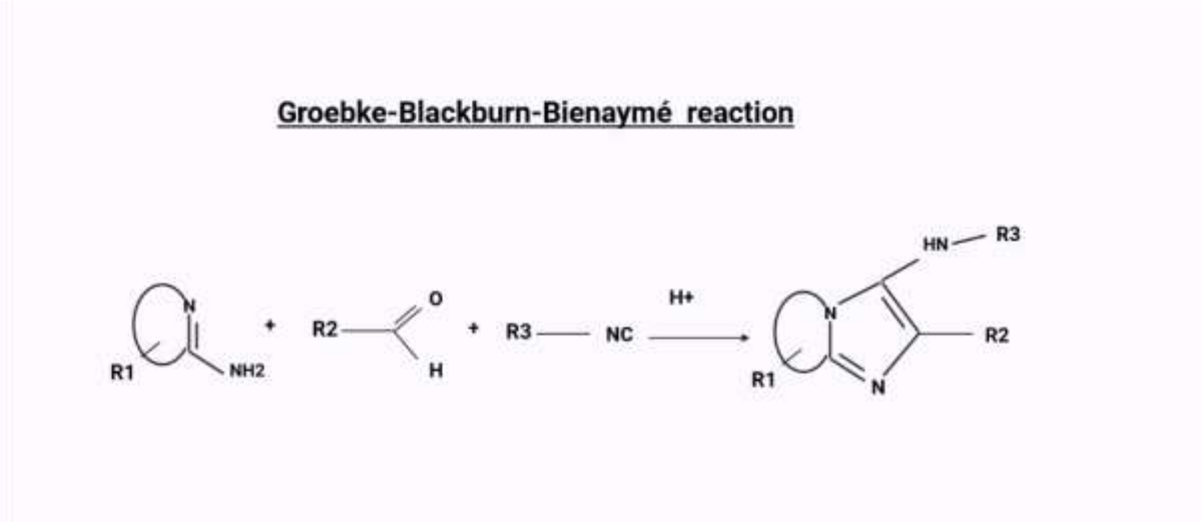


Figure 5: Groebke-Blackburn-Bienaymé reaction

Groebke-Blackburn-Bienaymé reaction in the discovery of modified antibiotic :Trimethoprim

Antibiotic Resistance is the new concern of public health currently in world. It does not only have high morbidity ; it also has high mortality rates. Trimethoprim is a known antibiotic in the medicine field which is generally used with Sulfamethoxazole to treat infection of urinary tract , infections caused by *Staphylococcus aureus* in cystic fibrosis patients, acute or severe bacterial diarrhea or dysentery and to prevent infected area from the opportunistic bacteria *Pneumocystis carinii*, which causes pneumonia in AIDS patients [63]. Combined medications of Trimethoprim and Sulfamethoxazole used to work by blocking two enzymes involved in the biosynthesis of folic acid: dihydropteroate synthetase and dihydrofolate reductase (DHFR), respectively [64]. Folate is produced by bacteria and is required for the biosynthesis of thymidine, which is required for DNA synthesis. As a result, when these antibiotics are taken together, they have a synergistic impact, limiting the growth of bacteria and eventually forwarding towards cell death. Later, when bacteria developed resistance to this treatment, determining progressive drugs to combat multidrug-resistant infections and organisms became increasingly difficult, as is the scenario with multidrug-resistant *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) . Combined medication of the two antibiotics has been found to be ineffective in treating infections caused by bacteria that have TMP-resistant DHFR enzymes. Many research teams have presented chemical variability at the residue of trimethoxybenzyl of the trimethoprim for the optimization of the medicine's characteristics, overall activity, and address trimethoprim resistance issues , resulting in the discovery of potential compounds against *E.*

coli and *S. aureus* [65-68].

In the year of 2019, Pedrola and her research has published a study where they have modified the 2,4-diaminopyrimidine moiety of the drug Trimethoprim by the application of Groebke-Blackburn-Bienaymé reaction. In their study, they have planned to use the GBBR to create a series of TMP derivatives by interacting the trimethoprim with a distinct types of ketones aldehydes and isocyanides and then analyze the sequent MCR compound as new antibacterial agents, determining their efficiency and potency while also taking into account their possible effect on resistant bacteria [69].

TMP has undergone chemical alterations based on their new discovery of GBBRs on diaminopyrimidines, which entail selective and numerous MCRs [70]. The trimethoprim analogs therefore comprised of a regioselective mono Groebke-Blackburn-Bienaymé reaction with an isocyanide/aldehyde pair, yielding by products; it is worth noting that the advantageous production of the discovered isomer is justified by a kinetic control. Double GBBR procedures on TMP also result in two secondary by-products, with both of them are equivalents to each reactant class. To adequately produce and initiate the imine intermediate and obtain a decent yield, a range of Lewis acids catalysts was used. In addition, to obtain the pure product, conventional flash chromatography purification was usually required. The TMP reactant's imidazo-azine scaffolds (N-fused bicyclic) , were employed in the analogs which showed the variance points at R1, which came from the isocyanide input, and from the aldehyde reactant R2 came (figure 6).

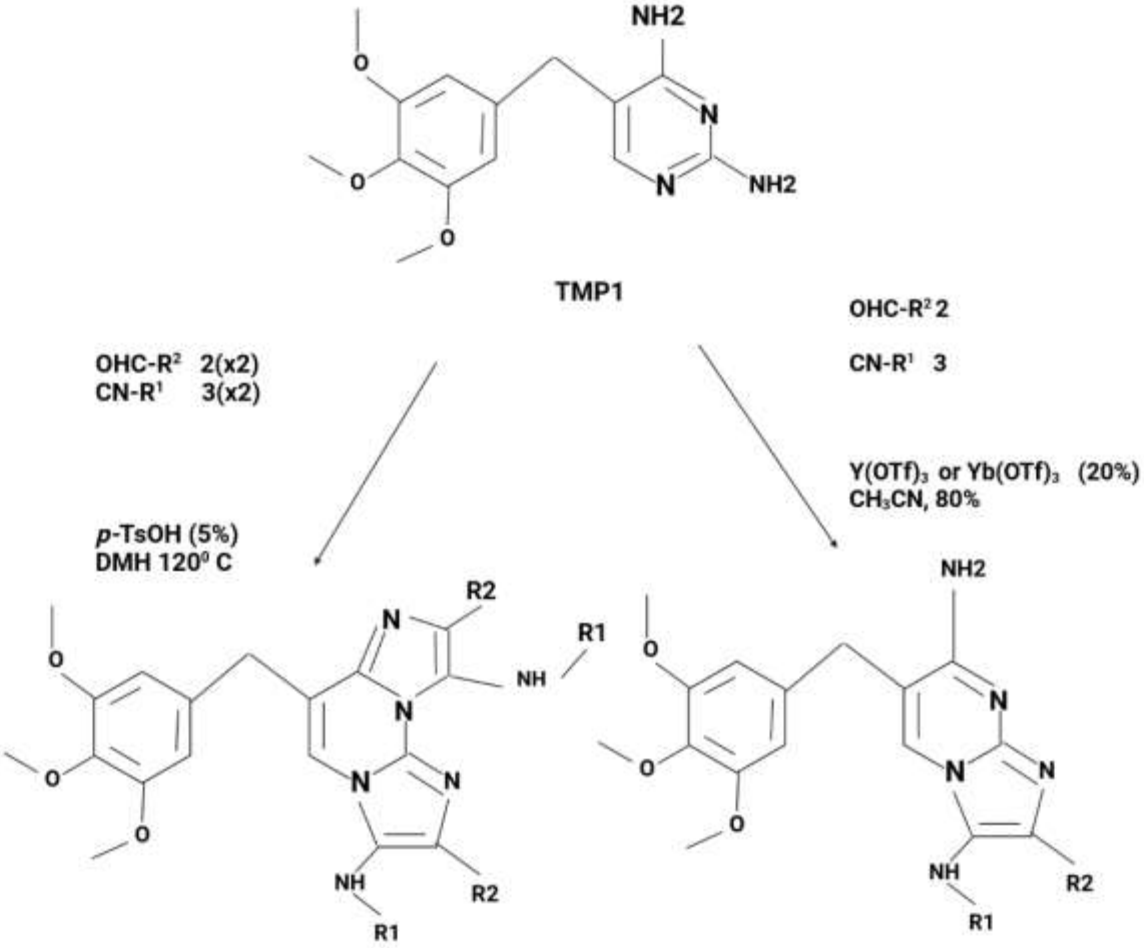


Figure 6:The chemical chemical action of mono and double Trimethoprim GBBR compounds.

The procedures performed as expected in their TMP system, generating the desired compounds and exhibiting the similar reactivity and selectivity trends as the unsubstituted diaminopyrimidine experiments [70]. For primary screening, they have created a order of trimethoprim analogs with a distinct kinds of options on the imidazole amino group (R1 is 4-methoxyphenyl,ethoxycarbonylmethyl and cyclohexyl,tert-butyl,), and a distinct variety of aromatic or alkyl substituents at the carbon position (R2 being methyl, α-, β-, or γ-pyridinyl, 4-chlorophenyl, isopropyl and α-thienyl,). These reactions were prosperous, providing acceptable yields of mono-Groebke-Blackburn-Bienaymé by-products, and doubly substituted-Groebke-Blackburn-Bienaymé adducts. As a result, 12 novel compounds were derived and the appropriate aldehyde/isocyanide combined mixture were synthesized as pure materials in this manner. Later, they determined to add an unsubstituted amino group to the imidazole ring of the new derivatives to help them be recognized by the DHFR function region, as the native substrate does. They then went about making such compounds by acidically removing a tert-butyl group from a suitable precursor adduct derived from MCRs involving tert-butyl isocyanide.

Though all of the abducts had MIC values greater than TMP against *S. aureus* ATCC 29213 and *E. coli* ATCC 25922, some of them were almost as efficacious as TMP (Figure 7: 1,2,3,4,5,6,7). TMP, as well as all novel compounds, proved to be completely ineffective against *P. aeruginosa* PAO1 [71]. Almost all of the novel compounds, like the control drug TMP, responded synergistically with SMX against *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 with the other species being substantially more sensitive to the SMX combination than to the TMP-GBBR analogs alone . It was also discovered that nearly all of the novel compounds had high efficacy against a collection of MRSA clinical isolates recovered from hospitalized or CF patients. The greatest challenge of antibiotic therapy in CF patients is Staphylococcus aureus (and specifically MRSA) infection, because this bacterium's persistent infection is significantly linked to increasing rates of respiratory function loss and high mortality. As a result, new ways to combating this type of bacterium are required, and they should be based on new antimicrobials, most likely in combination with existing ones [72,73].

On the SMX combination, there was a significant potency (Figure 8: 6) (Figure 9: 8,9,10,11). Unfortunately, no effect of adducts alone or in conjunction with SMX on *Pseudomonas aeruginosa* was seen in any circumstance, despite the presence of TMP activity.

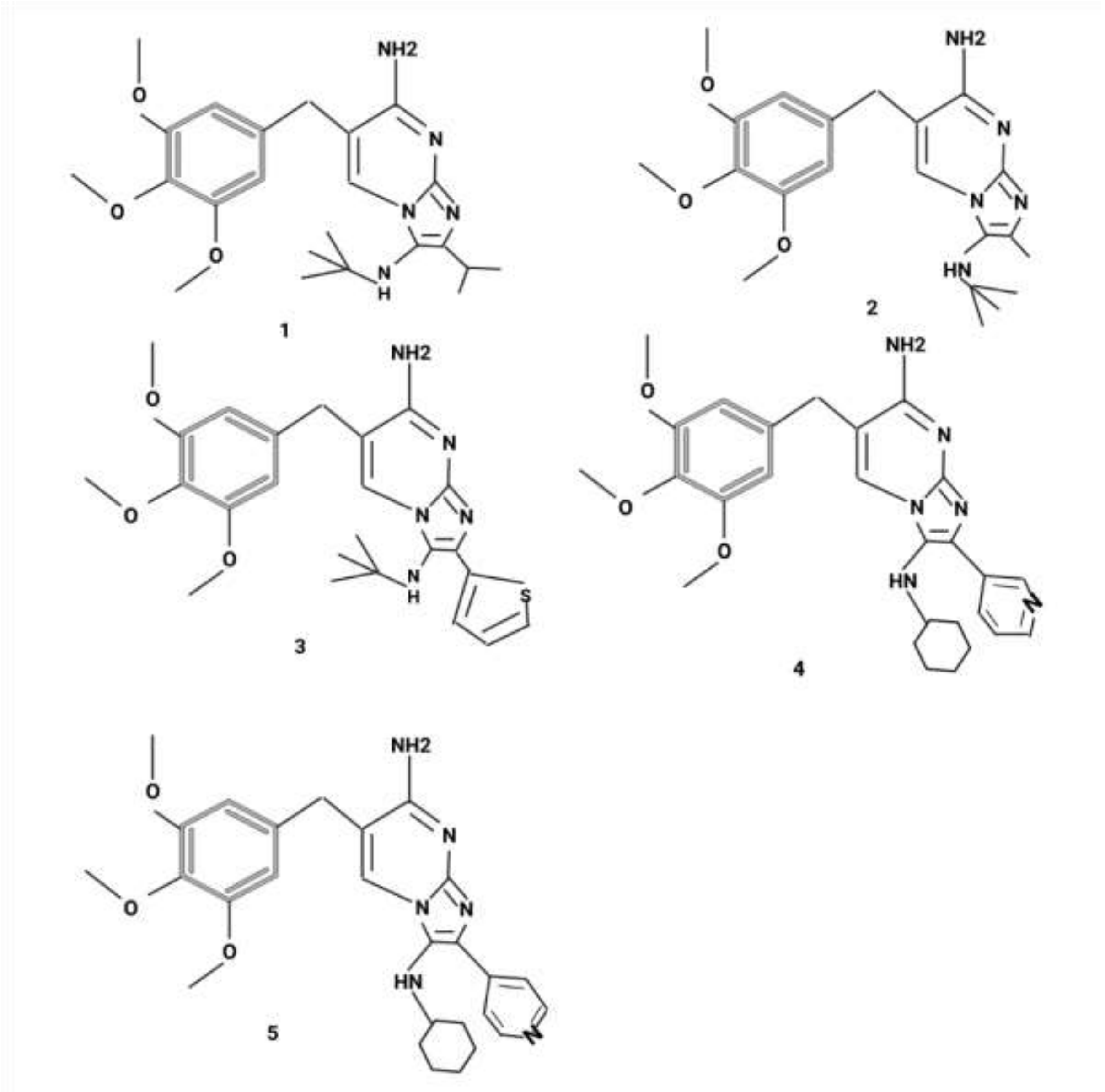
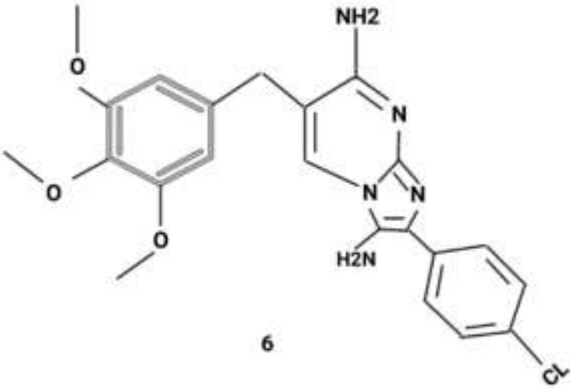
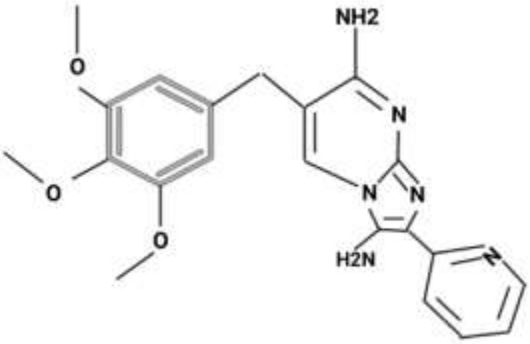


Figure 7: Some of novel compound of TMP which have potential activity against bacterium



6



7

Figure 8: Some of the derivatives of TMP which has shown potential activity against bacterium

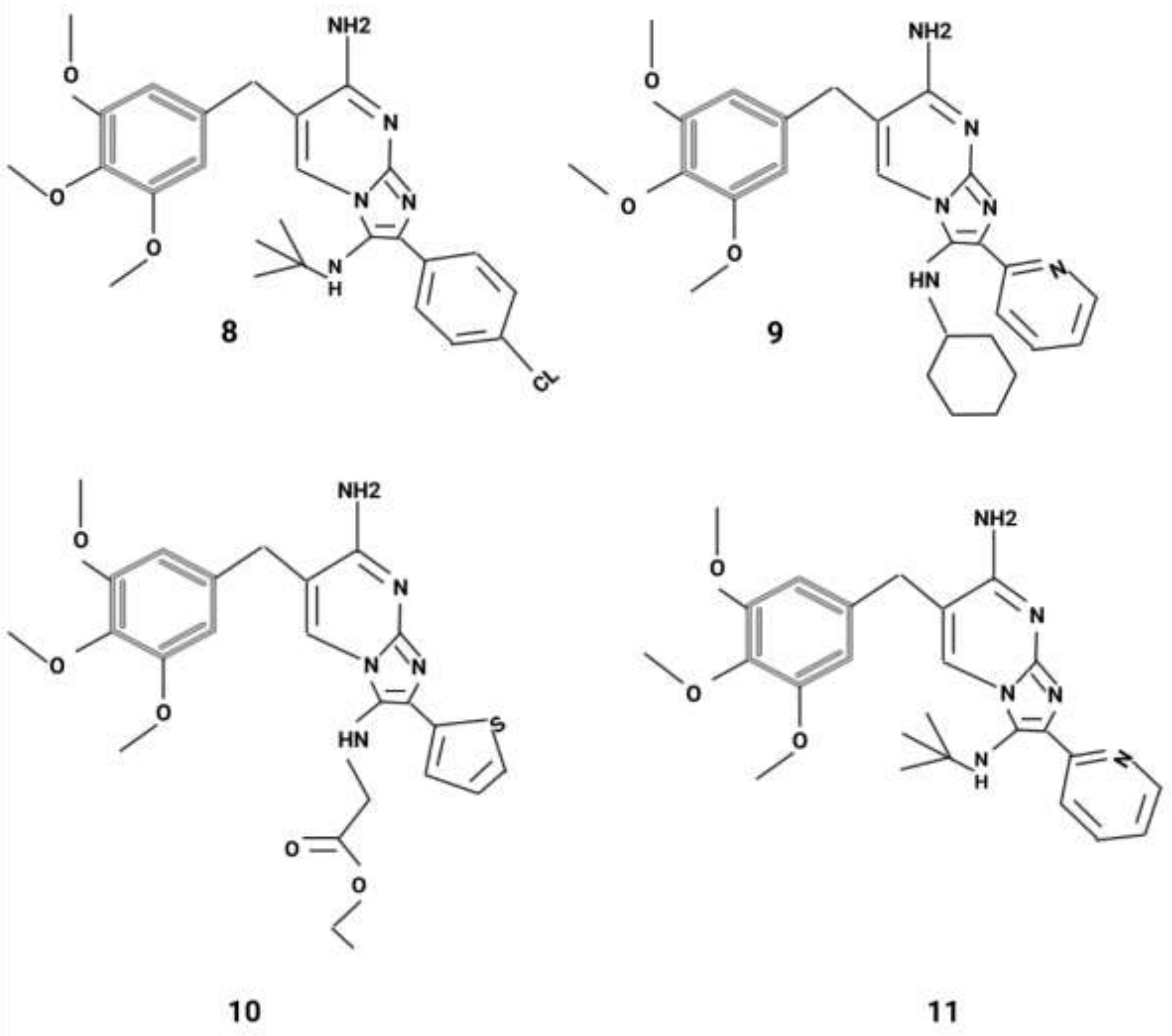


Figure 9: Some of the TMP derivatives which has shown potential activity against bacteria with combined therapy with SMX.

The discovery of antimicrobial compounds against Infectious diseases by Ugi's Reaction

Multicomponent reactions have been used by a number of institutions and pharmaceutical businesses to produce medications to combat infectious diseases caused by bacteria, viruses, and parasites. Morphochem created a series of antituberculosis compounds based on the structure of isoniazid and pyrazinamide [74]. Two libraries of 192 new compounds each were created using the pyridine-4- carboxy and pyrazine carboxy pharmacophores present in isoniazid and pyrazinamide as part of the carboxylic acid component in the Ugi reaction . The libraries were made up of individual compounds in 96-well plates, and the raw materials were evaluated against *M. tuberculosis* after the reaction solvent had evaporated. Compounds that inhibited *M. tuberculosis* H37Rv by more than 90% were resynthesised and purified, and their minimum inhibitory activity (MIC) and cytotoxicity (IC50) were assessed against the H37Rv strain of M. tuberculosis. The preliminary findings were promising, as numerous compounds from each library had cellular activity similar to isoniazid.

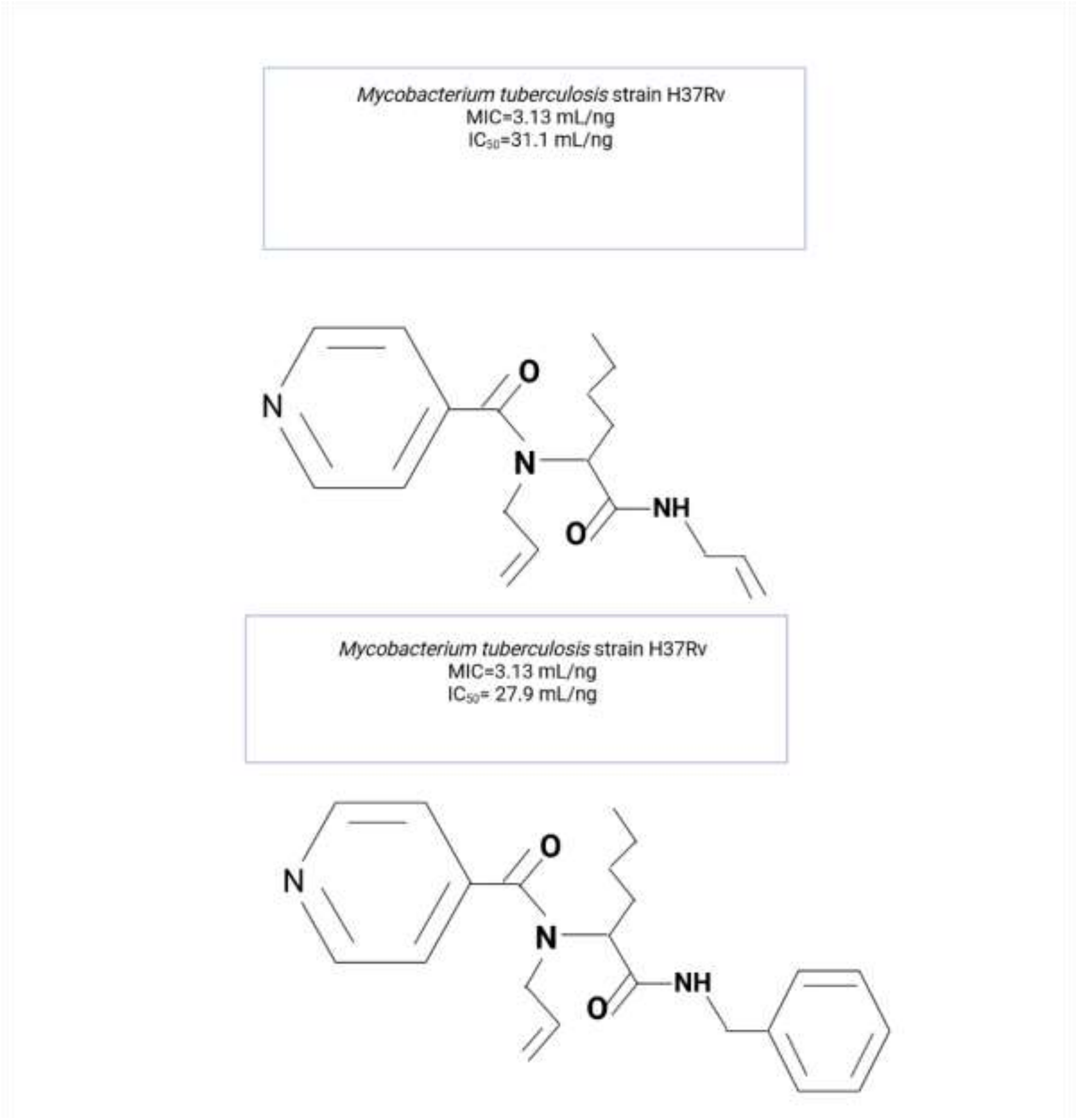


Figure 10: Antituberculosis agents made by the synthesis of Ugi's Reaction

The Ugi/Joullie' reaction [75] was used to make a library of pyrrolidones (Figure 11), which were evaluated against a range of targets and found to be active against the bovine diarrhea virus (BVDV), which is used as a surrogate for the human hepatitis C virus [76]. The compounds were found to be inactive in a variety of glycosidase assays and against the hepatitis B virus, indicating a novel and specific mechanism of action.

Early findings on the preparation and testing of a small library of 25 2´-deoxyuridine analogs as antiviral and antileishmanial drugs were reported by Torrence et al. (Figure 12)[77]. The compounds were isolated and evaluated as single diastereomers against cowpox virus, a surrogate for smallpox virus, and the parasite *Leishmania donovani*, which were produced as diastereomeric mixtures by the Ugi reaction using 5-formyl-2´- deoxyuridine as the aldehyde component. Several compounds, particularly as antileishmanial agents, showed potential. The quinoline substructure seen in many antimalarial medications was integrated into an amine component for the Ugi reaction using a technique similar to that used in antituberculosis libraries [78]. Despite the fact that several compounds from these libraries had antimalarial activity, the initial libraries' flexibility and peptidic nature, as well as their low activity, prompted the researchers to pursue a variant of the Ugi reaction that employs two functional groups in one molecule, resulting in heterocyclic structures [79]. A library of 16 4-aminoquinoline γ and δ lactams was synthesized and evaluated against parasite cells of the chloroquine-resistant *P. falciparum* W2 strain as well as enzymatic activity against recombinant falcipain-2. The compound was found to be more effective against the resistant *P. falciparum* strain than the antimalarial medication chloroquine [80].

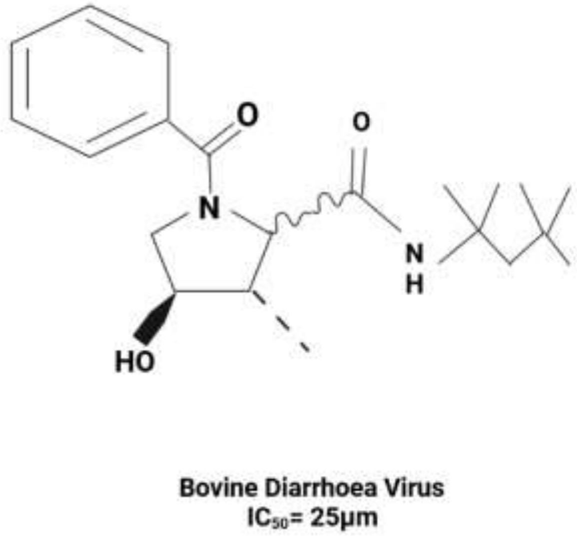


Figure 11:Hepatitis agents synthesized by the Ugi or Joullie reaction

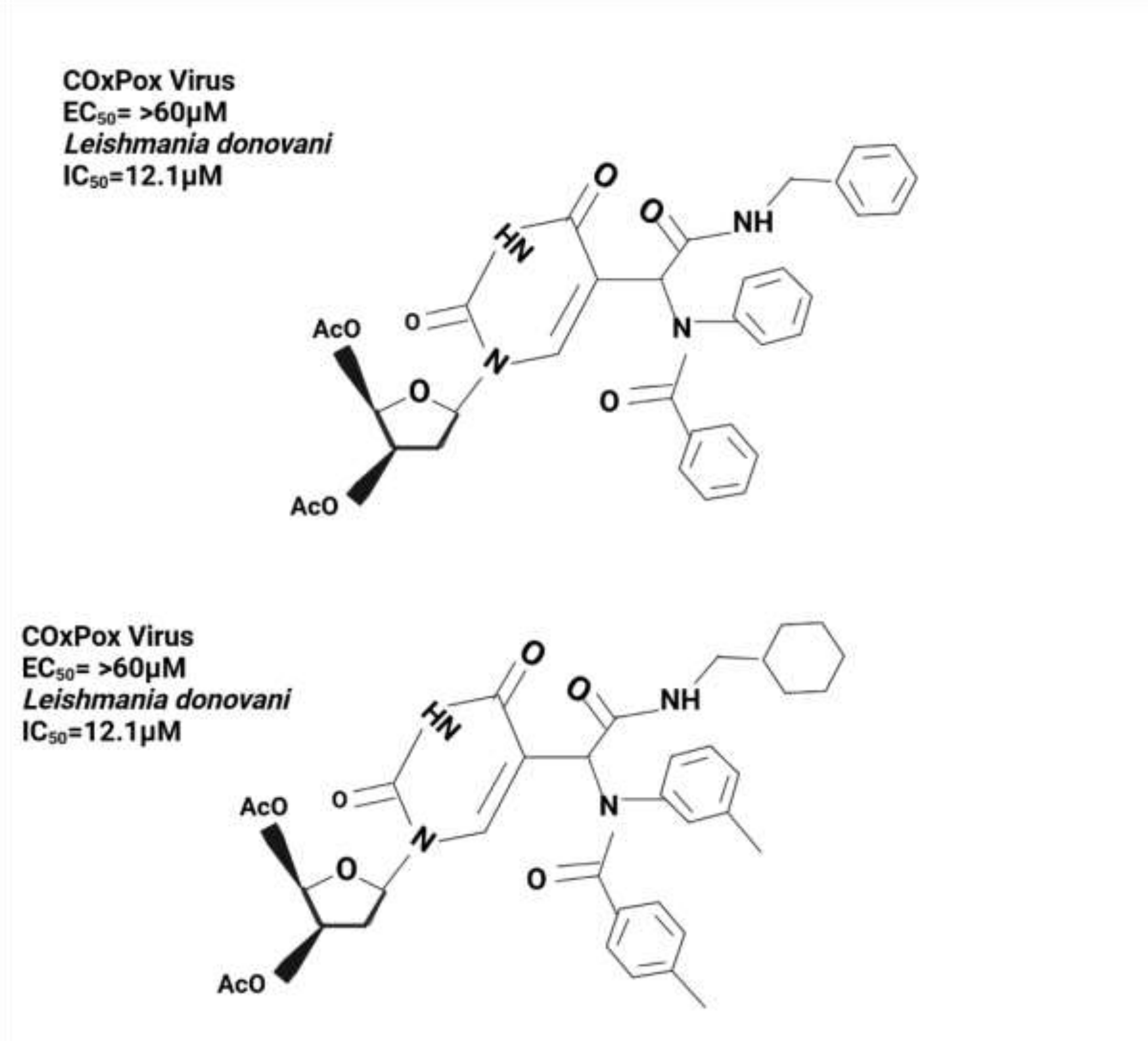


Figure 12: Antiviral agents synthesized by the Ugi reaction

Linderman and colleagues synthesized convertible isonitrile, which was then employed in the Ugi process to make analogues of (UPOC) methyl ester which is also known as uracil polyoxin C [81] . Polyoxins are a class of nucleoside antibiotics that have been used as fungicides in agriculture. It acts as a critical natural function in oppose to chitin synthase (CS) which were isolated from *Saccharomyces cerevisiae* and *Candida albicans* due to their antibacterial properties [82]. In fungi and insects, chitin synthases are attractive targets for inhibition. The polyoxins and structurally related nikkomycins were synthesized using the Ugi process, which included, convertible isonitrile, 2′,3′-isopropylidine-protected uridine-5′-aldehyde ,isoxazolecarboxylic acid derivative, and 2,4-dimethoxybenzylamine, [83]

.

Acidic hydrolysis then resulted in full deprotection of the isopropylidene and DMB groups, as well as transition of the isonitrile-extracted amide to the equal UPOC methyl ester. Viridic acid is a tetrapeptide produced by numerous *Penicillium* species and was initially isolated from *P. viridicatum*. To shorten the pathway of other standard procedures, Wessjohann and colleagues applied the reaction of Ugi to create the racemate combination of viridic acid. The chemical U-4CR was created by combining dipeptide, isobutyraldehyde, methylamine, and the anthranilate-derived isonitrile, and saponification of that product yielded the racemic viridic acid in 83 percent yield. In addition, after traditional separation procedures failed to separate the epimers, combined acid was tested as an antimicrobial drug in the opposition of a bacteria called *Aliivibrio fischeri* (Gram negative). With the half-maximal inhibitory concentration values of 45.0 ± 4.4 and 38.4 ±5.8 M, respectively, the compounds were the most powerful [84-87].

The Ugi process was used to make a targeted collection of C-capped dipeptide efflux pump inhibitors, with C-capped dipeptides BU-005 being made using the Ugi 4C reaction and full deprotection of Boc and DMB of the product using TFA. Drug efflux pump inhibitors have a lot of promise as pharmacological treatments for restoring drug sensitivity in multidrug-resistant bacterial infections. In *Streptomyces coelicolor*, a Gram-positive bacterium that is related to the human pathogen *Mycobacterium TB*, C-capped dipeptides BU-005 was able to inhibit two chloramphenicol-specific efflux pumps [88].

Pacidamycin D is a uridylpeptide antibiotic that was initially discovered in 1989 from Streptomyces coeruleorubidus AB 1183F-64. 3′-hydroxypacidamycin D and its analogues are uridylpeptide antibiotics that are selective antimicrobial drugs against *Pseudomonas aeruginosa* and also work to inhibit phospho-MurNAc-pentapeptide transferase (MraY). The half-maximal inhibitory concentration value is 42 nM, and their MIC for different strains of *P. aeruginosa* is 8–32 μg mL1. MraY is an essential enzyme in bacteria, where it is responsible for the creation of lipid I in the peptidoglycan biosynthesis pathway [89,90].

Ding et al. synthesized a variety of benzimidazole derivatives, expanding on their previous work on the processes of Ugi and aza-Wittig to create useful heterocycles than before for which the scientist team has developed a one-pot reaction that combines the reaction of Ugi with a catalytic reaction of aza-Wittig to synthesize multi-substituted benzimidazoles. In the presence of a catalytic amount of 2-aminobenzoyl azide derivatives,3-methyl-1-phenyl-2-phospholene 1-oxide, carboxylic,aldehydes and isonitriles, a single reaction yields easily to give benzimidazoles which have antibacterial,anti-inflammatory, anti-HIV-1 and anticancer properties [91-94].

Other than as antimicrobial agents, Isocyanide based multicomponent reactions has varied application in the area of medicine field.

Another area where IMCRs have proven useful is in the treatment of HIV. Three different groups described a method to access fused bicyclic imidazoles at the same time, which was combined with a further cyclization to produce tetracyclic pyridinones that were active against the wild-type HIV-IIIB strain. Domling and coworkers and Sperka et al. previously observed MCR-mediated inhibition of the HIV-1 protease. They recently reported the synthesis of a new library of aspartyl protease inhibitors based on the van Leusen reaction, which is currently being tested for biological activity [38-40].

The creation of strong C-C Motif Chemokine Receptor 5 antagonists for the treatment of HIV infection exemplifies the potency of MCRs in drug discovery. Ono researchers [95] employed a method called UDC (Ugi/deBoc/cyclization) established by Hulme et al. [96] to synthesis libraries of spirodiketopiperazines based on the idea that spiropiperidines are known favored structures for G protein coupled receptors. The first libraries were screened against a variety of chemokine targets, and several compounds were discovered to be active in CCR5. Rapid follow-up libraries allowed the original hits to be optimized into compounds that were very powerful against CCR5 functional (IC50 = 0.02 mM) and binding tests (IC50 = 0.002 mM) as well as selective over other GPCRs. GlaxoSmithKline produced clinical candidate Aplaviroc [97] for the treatment of HIV infection [98] after further refining of pharmacokinetic properties. The advancement of an MCR-derived molecule to late clinical phase trials shows the significance of the technique for drug development, despite the fact that further development of this clinical candidate was halted due to liver issues [99].

The creation of diketopiperazines as oxytocin-receptor antagonists has been a continuing success story for MCRs and early combinatorial chemistry efforts. GlaxoSmithKline tried solid-phase libraries generated by Affymax scientists against the oxytocin receptor at first, and numerous hits were found. Potent, selective, and orally bioavailable Oxytocin antagonists were developed from these hits. GSK221149A was identified as a clinical candidate after further optimization. Due to the chirality of the starting components, this chemical is produced in four steps, mostly as the desired single diastereoisomer. GSK221149A is currently in Phase II clinical trials for the treatment of pre-term labor, according to reports[100-103].

There have been two recent publications on the usage of IMCRs to reach Class C metabotropic glutamate receptors. The Ugi process was utilized to make diastereomeric mixes of 2-(3´ -phosphonobicylo[1.1.1]pentyl)- glycines in the first case. Both diastereomers were 16-fold more active against mGluR4 after separation and testing [104-105] Furthermore, the chemical was selective for mGluR4 over most other mGlu receptors, suggesting that it could be a useful tool for researching the role of mGluR4 in a range of diseases. A library of imidazo[2,1-B]thiazoles prepared by the Blackburn/Groebke/Bienayme' reaction was used to identify powerful mGluR5 binders in the second scenario [38-40]. From adequate starting materials, the bulk of the compounds might be synthesized in one or two steps. In a rat pain formalin paradigm, the compound was orally effective, resulting in a 66 percent reduction in nociceptive pain when compared to a control at 10 mg/kg.

Conclusion and Future Perspectives:

IMCRs continue to provide speedy access to novel chemotypes while also enabling for large-scale chemical investigation. Although various uses of MCRs in drug development have emerged in the last decade, the potential benefits of MCR chemistry have yet to be fully realized. Variations and postMCR techniques for accessing more constrained scaffolds, in particular, remain relatively unexplored areas for investigating biological space.

The use of a multicomponent reaction approach offers a wide range of applications in the synthesis of heterocyclic compounds with biological potential. MCR has gained a lot of traction in organic synthesis for synthesizing highly functionalized compounds and testing them against various biological targets to find novel therapeutic leads. The three or four multicomponent reactions have been extensively investigated for synthesizing various heterocyclic compounds in order to investigate their biological potential and develop new/novel therapeutic medicines. Most MCR reactions may be carried out in a single pot without the use of common volatiles, allowing eco-friendly chemistry to be developed.

The MCR has a lot of flexibility when it comes to generating libraries of compounds with various functional groups for screening purposes against biological targets of interest. The use of diversity-oriented synthesis to create compounds or intermediates in the hunt for new/novel medicinal molecules is gaining popularity. There were strategies disclosed that exploited a wide range of mechanistic types of MCRs, including those based on classic carbonyl condensations, isocyanide-based MCRs, cycloaddition-based MCRs, and transition metal-catalyzed MCRs.

doi:10.20944/preprints202204.0151.v1

Identifying more selective catalysts and optimal reaction conditions that would enhance functional group tolerance and hence variety in the products of the earliest MCRs is one of the issues that must be tackled. Divergent sequential methods, where divergent reaction paths could arise owing to variation in reaction conditions, catalysts utilized, or a slight structural variation in the building blocks, need to be developed further in order to construct libraries with significant structural diversity.

Finally, great work must be put into the creation of sequential protocols that can be executed as one-pot operations in order to enable the generation of different libraries both environmentally and economically viable. According to the current state of the art, all of these problems can be overcome, and one-pot sequential methods including an MCR and successive elaborations are likely to become a major tool for drug development. Furthermore, MCR techniques aid research teams with limited personnel and financial resources by allowing them to advance their programs more effectively. We should anticipate to see even more examples of MCR chemistry in drug discovery in the coming years as compounds from a variety of robust techniques make their way into compound collections and deliver valuable hits for drug development programs.

Declarations

- **Acknowledgements: None**
- **Availability of Data and Materials: N/A**
- **Conflict of Interest: None**
- **Funding: None**
- **Informed Consent: N/A**
- **Research involvement of Human or animals: N/A**

References:

1. Zarganes-Tzitzikas, T.; Chandgude, A. L.; Dömling, A. Multicomponent Reactions, Union of MCRs and Beyond. *Chem. Rec.* **2015**, *15* (5), 981–996. https://doi.org/10.1002/tcr.201500201.
2. Afshari, R.; Shaabani, A. Materials Functionalization with Multicomponent Reactions: State of the Art. *ACS Comb. Sci.* **2018**, *20* (9), 499–528. https://doi.org/10.1021/acscombsci.8b00072
3. Kruljec, N.; Bratkovič, T. Alternative Affinity Ligands for Immunoglobulins. *Bioconjug. Chem.* **2017**, *28* (8), 2009–2030. https://doi.org/10.1021/acs.bioconjchem.7b00335.
4. Lin, W.; Zhang, W.; Sun, T.; Liu, S.; Zhu, Y.; Xie, Z. Rational Design of Polymeric Nanoparticles with Tailorable Biomedical Functions for Cancer Therapy. *ACS Appl. Mater. Interfaces* **2017**, *9* (35), 29612–29622. https://doi.org/10.1021/acsami.7b10763.
5. Kambe, T.; Correia, B. E.; Niphakis, M. J.; Cravatt, B. F. Mapping the Protein Interaction Landscape for Fully Functionalized Small-Molecule Probes in Human Cells. *J. Am. Chem. Soc.* **2014**, *136* (30), 10777–10782. https://doi.org/10.1021/ja505517t.
6. García-González, M. C.; Aguilar-Granda, A.; Zamudio-Medina, A.; Miranda, L. D.; Rodríguez-Molina, B. Synthesis of Structurally Diverse Emissive Molecular Rotors with Four-Component Ugi Stators. *J. Org. Chem.* **2018**, *83* (5), 2570–2581. https://doi.org/10.1021/acs.joc.7b02858.
7. Boukis, A. C.; Reiter, K.; Frölich, M.; Hofheinz, D.; Meier, M. A. R. Multicomponent Reactions Provide Key Molecules for Secret Communication. *Nat. Commun.* **2018**, *9* (1). https://doi.org/10.1038/s41467-018-03784-x.
8. Domling, A. Recent Advances in Isocyanide-Based Multicomponent Chemistry. *ChemInform* **2003**, *34* (1), no-no. https://doi.org/10.1002/chin.200301251.
9. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. *J. Med. Chem.* **1994**, *37* (10), 1385–1401. https://doi.org/10.1021/jm00036a001.
10. Golisade, A.; Wiesner, J.; Herforth, C.; Joma, H.; Link, A. Med. *Bioorg.Med. Chem* **2002**, *10*, 769–777.
11. Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. The Design of Leadlike Combinatorial Libraries. *Angew. Chem. Int. Ed Engl.* **1999**, *38* (24), 3743–3748.

https://doi.org/10.1002/(sici)1521-3773(19991216)38:24<3743::aid-anie3743>3.0.co;2-u.

12. Obert, R.; Armstrong, W.; Combs, A. P.; Tempest, P. A.; Brown, S. D. *Multiple-Component Condensation Strategies for Combinatorial Library Synthesis*.
13. Orru, R. V. A.; de Greef, M. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. *ChemInform* **2003**, *34* (40). https://doi.org/10.1002/chin.200340290.
14. Li, J. J. Strecker Amino Acid Synthesis. In *Name Reactions*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2003; pp 399–400.
15. Hantzsch, A. Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak. *Justus Liebigs Ann. Chem.* **1882**, *215* (1), 1–82. https://doi.org/10.1002/jlac.18822150102.
16. Biginelli, P. Ueber Aldehyduramide Des Acetessigäthers. II. *Ber. Dtsch. Chem. Ges.* **1891**, *24* (2), 2962–2967. https://doi.org/10.1002/cber.189102402126.
17. Biginelli, P. Aldehydureidderivate Des Acet-Und Oxalessigäthers. *Ber Deutsch Chem Ges* **1893**, *26*, 447–450.
18. Kappe, C. O. 100 Tetrahedron 1993, 49, 6937.(b) Kappe, CO. *Acc. Chem. Res* **2000**.
19. Kappe, C. O. (1997). A reexamination of the mechanism of the Biginelli dihydropyrimidine synthesis. Support for an N-Acyliminium ion intermediate1. *The Journal of organic chemistry*, *62*(21), 7201-7204.
20. Sotiri, K.; Hilgert, S.; Mannich, M.; Bleninger, T.; Fuchs, S. Implementation of Comparative Detection Approaches for the Accurate Assessment of Sediment Thickness and Sediment Volume in the Passaúna Reservoir. *J. Environ. Manage.* **2021**, *287* (112298), 112298. https://doi.org/10.1016/j.jenvman.2021.112298.
21. Ugi, I. Versuche Mit Isonitrilen. In *Angewandte Chemie-International Edition*; BERLIN, GERMANY, 1959; Vol. 71, pp 386–386.
22. Ugi, I.; Steinbrückner, C. Über Ein Neues Kondensations-Prinzip. *Angew. Chem. Weinheim Bergstr. Ger.* **1960**, *72* (7–8), 267–268. https://doi.org/10.1002/ange.19600720709.
23. Ugi, I. (1962). The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions. *Angewandte Chemie International Edition in English*, *1*(1), 8-21.
24. Gokel, G.; Lüdke, G.; Ugi, I. *Isonitrile Chemistry”*; Ugi, I., Ed.; Academic Press: New York.

25. Passerini, M. Composto Del P-Isontril-Azobenzolo Con Acetone Ed Acido Acetico. *Gazz. Chim. Ital* **1921**, *51*, 126–129
26. Ugi, I.; Steinbrückner, C. Über Ein Neues Kondensations-Prinzip. *Angew. Chem. Weinheim Bergstr. Ger.* **1960**, *72* (7–8), 267–268. https://doi.org/10.1002/ange.19600720709.
27. Neochoritis, C. G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119* (3), 1970–2042. https://doi.org/10.1021/acs.chemrev.8b00564.
28. Kakuchi, R. The Dawn of Polymer Chemistry Based on Multicomponent Reactions. *Polym. J.* **2019**, *51* (10), 945–953. https://doi.org/10.1038/s41428-019-0209-0.
29. Quazi, S.; Gavas, S.; Malik, J. A.; Suman, K. S.; Haider, Z. In-Silico Pharmacophore and Molecular Docking Based Drug Discovery against Marburg Virus's Viral Protein 35; A Potent of MAVD. *bioRxiv*, 2021. https://doi.org/10.1101/2021.07.01.450693.
30. Lieke, W. Ueber Das Cyanallyl. Justus Liebigs Ann. *Justus Liebigs Ann. Chem 1859*, 316–321.
31. Gautier, A. Ueber die Einwirkung des Chlorwasserstoffs u. a. auf das Aethyl- und Methylcyanür. *Ann. Chem. Pharm.* **1867**, *142* (3), 289–294. https://doi.org/10.1002/jlac.18671420304.
32. Ugi, I.; Dömling, A.; Gruber, B.; Almstetter, M. Multicomponent Reactions and Their Libraries-A New Approach to Preparative Organic Chemistry. *Croat. Chem. Acta* **1997**, *70*, 631–647.
33. Ugi, I. Neuere Methoden Der Präparativen Organischen Chemie IV: Mit Sekundär-Reaktionen Gekoppelte α-Additionen von Immonium-Ionen Und Anionen an Isonitrile. *Angew. Chem* **1962**, *74*, 9–22.
34. Ugi, I. The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions. *Angew. Chem. Int. Ed. Engl* **1962**, *1*, 8–21.
35. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. Versuche Mit Isonitrilen. *Angew. Chem* **1959**.
36. Arshady, R.; Ugi, I. Solid Phase Peptide Synthesis by Four Component Condensation: Peptide Formation on an Isocyano Polymer Support. *Z. Naturforsch. B J. Chem. Sci.* **1981**, *36* (9), 1202–1203. https://doi.org/10.1515/znb-1981-0933.
37. Oertel, K.; Zech, G.; Kunz, H. Stereoselective Combinatorial Ugi-Multicomponent Synthesis on Solid Phase This Work Was Supported by the Deutsche Forschungsgemeinschaft and by the Fonds Der Chemischen Industrie. *Angew. Chem. Int.*

Ed Engl. **2000**, *39* (8), 1431–1433. https://doi.org/10.1002/(sici)1521-3773(20000417)39:8<1431::aid-anie1431>3.0.co;2-n.

38. Bienaymé, H.; Bouzid, K. A New Heterocyclic Multicomponent Reaction for the Combinatorial Synthesis of Fused 3-Aminoimidazoles. Angew. *Angew. Chem. Int. Ed* **1998**, *37*, 2234–2237.
39. Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. Parallel Synthesis of 3-Aminoimidazo[1,2-a]Pyridines and Pyrazines by a New Three-Component Condensation. *Tetrahedron Lett.* **1998**, *39* (22), 3635–3638. https://doi.org/10.1016/s0040-4039(98)00653-4.
40. Groebke, K.; Weber, L.; Mehlin, F. ChemInform Abstract: Synthesis of Imidazo[1,2-a] Annulated Pyridines, Pyrazines, and Pyrimidines by a Novel Three-Component Condensation. *ChemInform* **2010**, *29* (39), no-no. https://doi.org/10.1002/chin.199839120.
41. Ugi, I.; Meyr, R. Isonitrile, V. Erweiterter Anwendungsbereich Der Passerini-Reaktion. *Chem. Ber.* **1961**, *94* (8), 2229–2233. https://doi.org/10.1002/cber.19610940844.
42. Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. Catalytic Enantioselective Passerini Three-Component Reaction. *Angew. Chem. Int. Ed Engl.* **2008**, *47* (2), 388–391. https://doi.org/10.1002/anie.200704315.
43. Brioche, J.; Masson, G.; Zhu, J. Passerini Three-Component Reaction of Alcohols under Catalytic Aerobic Oxidative Conditions. *Org. Lett.* **2010**, *12* (7), 1432–1435. https://doi.org/10.1021/ol100012y.
44. Yanai, H.; Oguchi, T.; Taguchi, T. Direct Alkylative Passerini Reaction of Aldehydes, Isocyanides, and Free Aliphatic Alcohols Catalyzed by Indium(III) Triflate. *J. Org. Chem.* **2009**, *74* (10), 3927–3929. https://doi.org/10.1021/jo900354e.
45. El Kaim, L.; Gizolme, M.; Grimaud, L. O-Arylative Passerini Reactions. *Org. Lett.* **2006**, *8* (22), 5021–5023. https://doi.org/10.1021/ol0617502.
46. Soeta, T.; Kojima, Y.; Ukaji, Y.; Inomata, K. O-Silylative Passerini Reaction: A New One-Pot Synthesis of α-Siloxyamides. *Org. Lett.* **2010**, *12* (19), 4341–4343. https://doi.org/10.1021/ol101763w.
47. Sunderhaus, J. D.; Martin, S. F. Applications of Multicomponent Reactions to the Synthesis of Diverse Heterocyclic Scaffolds. *Chemistry* **2009**, *15* (6), 1300–1308. https://doi.org/10.1002/chem.200802140.

48. Paulvannan, K. Preparation of Tricyclic Nitrogen Heterocycles via Tandem Four-Component Condensation/Intramolecular Diels-Alder Reaction. *Tetrahedron Lett.* **1999**, *40* (10), 1851–1854. https://doi.org/10.1016/s0040-4039(99)00072-6
49. Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. Isocyanide-Based Multicomponent Reactions towards Cyclic Constrained Peptidomimetics. *Beilstein J. Org. Chem.* **2014**, *10*, 544–598. https://doi.org/10.3762/bjoc.10.50.
50. Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. Rapid Access to Oxindoles by the Combined Use of an Ugi Four-Component Reaction and a Microwave-Assisted Intramolecular Buchwald−Hartwig Amidation Reaction. *Org. Lett.* **2006**, *8* (19), 4351–4354. https://doi.org/10.1021/ol061755z.
51. White, C. J.; Yudin, A. K. Contemporary Strategies for Peptide Macrocyclization. *Nat. Chem.* **2011**, *3* (7), 509–524. https://doi.org/10.1038/nchem.1062.
52. Quazi, S.; Jangi, R. Artificial Intelligence and Machine Learning in Medicinal Chemistry and Validation of Emerging Drug Targets. *Preprints*, 2021. https://doi.org/10.20944/preprints202105.0567.v1.
53. Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. Parallel Synthesis of 3-Aminoimidazo[1,2-a]Pyridines and Pyrazines by a New Three-Component Condensation. *Tetrahedron Lett.* **1998**, *39* (22), 3635–3638. https://doi.org/10.1016/s0040-4039(98)00653-4.
54. Bienaymé, H.; Bouzid, K. A New Heterocyclic Multicomponent Reaction for the Combinatorial Synthesis of Fused 3-Aminoimidazoles. *Angew. Chem. Int. Ed Engl.* **1998**, *37* (16), 2234–2237. https://doi.org/10.1002/(sici)1521-3773(19980904)37:16<2234::aid-anie2234>3.0.co;2-r.
55. Hulme, C.; Lee, Y.-S. Emerging Approaches for the Syntheses of Bicyclic Imidazo[1,2-x]-Heterocycles. *Mol. Divers.* **2008**, *12* (1), 1–15. https://doi.org/10.1007/s11030-008-9072-1.
56. Devi, N.; Rawal, R. K.; Singh, V. Diversity-Oriented Synthesis of Fused-Imidazole Derivatives via Groebke–Blackburn–Bienayme Reaction: A Review. *Tetrahedron* **2015**, *71* (2), 183–232. https://doi.org/10.1016/j.tet.2014.10.032.
57. Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. Scaffold Oriented Synthesis. Part 4: Design, Synthesis and Biological Evaluation of Novel 5-Substituted Indazoles as Potent and Selective Kinase Inhibitors Employing Heterocycle Forming and Multicomponent Reactions. *Bioorg. Med. Chem. Lett.* **2011**, *21* (5), 1480–1483. https://doi.org/10.1016/j.bmcl.2011.01.001.

58. Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. N-Fused Imidazoles as Novel Anticancer Agents That Inhibit Catalytic Activity of Topoisomerase IIα and Induce Apoptosis in G1/S Phase. *J. Med. Chem.* **2011**, *54* (14), 5013–5030. https://doi.org/10.1021/jm200235u.
59. Shukla, N. M.; Salunke, D. B.; Yoo, E.; Mutz, C. A.; Balakrishna, R.; David, S. A. Antibacterial Activities of Groebke–Blackburn–Bienaymé-Derived Imidazo[1,2-a]Pyridin-3-Amines. *Bioorg. Med. Chem.* **2012**, *20* (19), 5850–5863. https://doi.org/10.1016/j.bmc.2012.07.052.
60. Burchak, O. N.; Mugherli, L.; Ostuni, M.; Lacapère, J. J.; Balakirev, M. Y. Combinatorial Discovery of Fluorescent Pharmacophores by Multicomponent Reactions in Droplet Arrays. *J. Am. Chem. Soc.* **2011**, *133* (26), 10058–10061. https://doi.org/10.1021/ja204016e.
61. Elleder, D.; Baiga, T. J.; Russell, R. L.; Naughton, J. A.; Hughes, S. H.; Noel, J. P.; Young, J. A. T. Identification of a 3-Aminoimidazo[1,2-a]Pyridine Inhibitor of HIV-1 Reverse Transcriptase. *Virol. J.* **2012**, *9* (1). https://doi.org/10.1186/1743-422x-9-305.
62. Bode, M. L.; Gravestock, D.; Moleele, S. S.; van der Westhuyzen, C. W.; Pelly, S. C.; Steenkamp, P. A.; Hoppe, H. C.; Khan, T.; Nkabinde, L. A. Imidazo[1,2-a]Pyridin-3-Amines as Potential HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors. *Bioorg. Med. Chem.* **2011**, *19* (14), 4227–4237. https://doi.org/10.1016/j.bmc.2011.05.062.
63. Urbancic, K. F.; Ierino, F.; Phillips, E.; Mount, P. F.; Mahony, A.; Trubiano, J. A. Taking the Challenge: A Protocolized Approach to Optimize Pneumocystis Pneumonia Prophylaxis in Renal Transplant Recipients. *Am. J. Transplant* **2018**, *18* (2), 462–466. https://doi.org/10.1111/ajt.14498.
64. Heaslet, H.; Harris, M.; Fahnoe, K.; Sarver, R.; Putz, H.; Chang, J.; Subramanyam, C.; Barreiro, G.; Miller, J. R. Structural Comparison of Chromosomal and Exogenous Dihydrofolate Reductase from Staphylococcus Aureus in Complex with the Potent Inhibitor Trimethoprim. *Proteins* **2009**, *76* (3), 706–717. https://doi.org/10.1002/prot.22383.
65. Zhou, W.; Scocchera, E. W.; Wright, D. L.; Anderson, A. C. Antifolates as Effective Antimicrobial Agents: New Generations of Trimethoprim Analogs. *Medchemcomm* **2013**, *4* (6), 908. https://doi.org/10.1039/c3md00104k.
66. Quazi, S.; Malik, J.; Suman, K. S.; Capuzzo, A. M.; Haider, Z. Discovery of Potential Drug-like Compounds against Viral Protein (VP40) of Marburg Virus Using

Pharmacophoric Based Virtual Screening from ZINC Database. *bioRxiv*, 2021. https://doi.org/10.1101/2021.05.13.444037.

67. Lombardo, M. N.; G-Dayanandan, N.; Wright, D. L.; Anderson, A. C. Crystal Structures of Trimethoprim-Resistant DfrA1 Rationalize Potent Inhibition by Propargyl-Linked Antifolates. *ACS Infect. Dis.* **2016**, *2* (2), 149–156. https://doi.org/10.1021/acsinfecdis.5b00129.
68. Rashid, U.; Ahmad, W.; Hassan, S. F.; Qureshi, N. A.; Niaz, B.; Muhammad, B.; Imdad, S.; Sajid, M. Design, Synthesis, Antibacterial Activity and Docking Study of Some New Trimethoprim Derivatives. *Bioorg. Med. Chem. Lett.* **2016**, *26* (23), 5749–5753. https://doi.org/10.1016/j.bmcl.2016.10.051.
69. Pedrola, M.; Jorba, M.; Jardas, E.; Jardi, F.; Ghashghaei, O.; Viñas, M.; Lavilla, R. Multicomponent Reactions upon the Known Drug Trimethoprim as a Source of Novel Antimicrobial Agents. *Front. Chem.* **2019**, *7*, 475. https://doi.org/10.3389/fchem.2019.00475.
70. Ghashghaei, O.; Caputo, S.; Sintes, M.; Revés, M.; Kielland, N.; Estarellas, C.; Luque, F. J.; Aviñó, A.; Eritja, R.; Serna-Gallego, A.; Marrugal-Lorenzo, J. A.; Pachón, J.; Sánchez-Céspedes, J.; Treadwell, R.; de Moliner, F.; Vendrell, M.; Lavilla, R. Multiple Multicomponent Reactions: Unexplored Substrates, Selective Processes, and Versatile Chemotypes in Biomedicine. *Chemistry* **2018**, *24* (54), 14513–14521. https://doi.org/10.1002/chem.201802877.
71. Dolce, D.; Neri, S.; Grisotto, L.; Campana, S.; Ravenni, N.; Miselli, F.; Camera, E.; Zavataro, L.; Braggion, C.; Fiscarelli, E. V.; Lucidi, V.; Cariani, L.; Girelli, D.; Faelli, N.; Colombo, C.; Lucanto, C.; Lombardo, M.; Magazzù, G.; Tosco, A.; Raia, V.; Manara, S.; Pasolli, E.; Armanini, F.; Segata, N.; Biggeri, A.; Taccetti, G. Methicillin-Resistant Staphylococcus Aureus Eradication in Cystic Fibrosis Patients: A Randomized Multicenter Study. *PLoS One* **2019**, *14* (3), e0213497. https://doi.org/10.1371/journal.pone.0213497.
72. Lo, D. K.; Muhlebach, M. S.; Smyth, A. R. Interventions for the Eradication of Meticillin-Resistant Staphylococcus Aureus (MRSA) in People with Cystic Fibrosis. *Cochrane Database Syst. Rev.* **2018**, *7*, CD009650. https://doi.org/10.1002/14651858.CD009650.pub4.
73. Xhemali, X.; Smith, J. R.; Kebriaei, R.; Rice, S. A.; Stamper, K. C.; Compton, M.; Singh, N. B.; Jahanbakhsh, S.; Rybak, M. J. Evaluation of Dalbavancin Alone and in Combination with β-Lactam Antibiotics against Resistant Phenotypes of Staphylococcus

Aureus. *J. Antimicrob. Chemother.* **2019**, *74* (1), 82–86. https://doi.org/10.1093/jac/dky376.

74. Dömling, A.; Achatz, S.; Beck, B. Novel Anti-Tuberculosis Agents from MCR Libraries. *Bioorg. Med. Chem. Lett.* **2007**, *17* (19), 5483–5486. https://doi.org/10.1016/j.bmcl.2007.04.066.
75. Nutt, R. F.; Joullie, M. M. Four-Component Condensation: A New Versatile Method for the Synthesis of Substituted Prolyl Peptides. *J. Am. Chem. Soc.* **1982**, *104* (21), 5852–5853. https://doi.org/10.1021/ja00385a080.
76. Akritopoulou-Zanze, I. Isocyanide-Based Multicomponent Reactions in Drug Discovery. *Curr. Opin. Chem. Biol.* **2008**, *12* (3), 324–331. https://doi.org/10.1016/j.cbpa.2008.02.004.
77. Fan, X.; Zhang, X.; Bories, C.; Loiseau, P. M.; Torrence, P. F. The Ugi Reaction in the Generation of New Nucleosides as Potential Antiviral and Antileishmanial Agents. *Bioorg. Chem.* **2007**, *35* (2), 121–136.