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Two decades of recent advances of Ugi reactions: synthetic and pharmaceutical applications

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Multicomponent reactions (MCRs) are powerful synthetic tools in which more than two starting materials couple with each other to form multi-functionalized compounds in a one-pot process, the so-called "tandem", "domino" or "cascade" reaction, or utilizing an additional step without changing the solvent, the so-called a sequential-addition procedure, to limit the number of synthetic steps, while increasing the complexity and the molecular diversity, which are highly step-economical reactions. The Ugi reaction, one of the most common multicomponent reactions, has recently fascinated chemists with the high diversity brought by its four- or three-component-based isonitrile. The Ugi reaction has been introduced in organic synthesis as a novel, efficient and useful tool for the preparation of libraries of multifunctional peptides, natural products, and heterocyclic compounds with stereochemistry control. In this review, we highlight the recent advances of the Ugi reaction in the last two decades from 2000–2019, mainly in the synthesis of linear or cyclic peptides, heterocyclic compounds with versatile ring sizes, and natural products, as well as the enantioselective Ugi reactions. Meanwhile, the applications of these compounds in pharmaceutical trials are also discussed.

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1 Introduction

Multicomponent reactions (MCRs) are powerful synthetic tools, in which more than two starting materials react with each other to form multi-functionalized compounds in a one-pot experimental procedure. Nowadays, MCRs are an exceptional strategy to synthesize many pharmaceutical and drug-like structure compounds due to their atom economy, high efficiency, low cost and simple experimental procedure.^{1,2} Isonitrile-based multicomponent reactions (IMCRs) have attracted the attention of organic chemists since the development of the first one by Mario Passerini 1921,³ which is known as the Passerini-three component reaction (P-3CR), where the coupling between aldehyde, carboxylic acid and isonitrile affords α -acyloxycarboxamide.^{4,5} In 1959, a new era of isonitrile chemistry started when Ugi discovered that the reaction between primary amine, carbonyl compound (aldehyde or ketone), carboxylic acid and isonitrile formed highly substituted α -aminoacyl amides with high biological activity and structural diversity.⁶ The Ugi-four component reaction (U-4CR) gives peptide-like structure known as bis-amides or peptomers, which are classified as peptidomimetics and have promising pharmacological properties.⁷ Furthermore, U-4CR is an economic and environmentally friendly reaction since it can also be performed in water as the solvent.⁸ Moreover, the optimization of the conditions of the Ugi reaction by stirring the reactants in

a concentrated solution of polar protic solvents such as methanol, ethanol or 2,2,2-trifluoroethanol (TFE) has been investigated.^{9,10} Due to the high flexibility of the Ugi reaction with different functional groups, a wide range of linear bis-amides and pseudo-peptides (linear or cyclic) can be obtained and post-modifications can be achieved to synthesize versatile heterocyclic compounds with unusual structures and a wide range of biological activity.¹¹ Furthermore, U-4CR has become increasingly efficient in the synthesis of many natural products and macro-cyclic molecules.^{12–14} It has been proven that many important compounds and natural products studied for their biological efficiency can be synthesized simply *via* U-4CR, which had led to the emergence of many important drugs for the treatment of several diseases. For instance, Crixivan® **I** (Indinavir™, MK 639) made by Merck is an important HIV protease inhibitor (Fig. 1), where the Ugi reaction contributes to the short synthesis of the piperazine derivative that is the main starting compound in production of Crixivan® **I**.^{12,15} Also, philanthotoxin-12 analogues that show potential noncompetitive inhibitory effects on various types of ionotropic receptors in the central nervous system have been synthesized *via* the Ugi reaction.¹⁶

The Ugi reaction is considered a key step in the synthesis of many natural products, for example, the naturally potent α -amino acid antibiotic (+)-furanomycin **II** isolated from *Streptomyces threomyceticus* was synthesized using U-4CR.¹⁴ Also, the natural product (+)-demethyldysidenin **III** and its epimer (–)-demethylisodysidenin, which is an antihypertensive, which was demonstrated by Williard and co-workers,¹⁷ was

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Fig. 1 Structure of Crixivan I, furanomycin II and demethyldysidenin III.

synthesized through the condensation of the traditional four components.¹⁴

In this review, highlighted the recent advances of the Ugi reaction in the last two decades from 2000–2019, mainly in the organic syntheses of linear and cyclic peptides, heterocyclic compounds, natural products, asymmetric Ugi reaction, and the valuable applications of these compounds in pharmaceuticals trials.

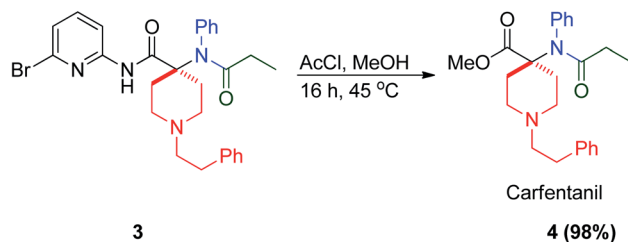
2 The synthetic and pharmaceutical applications of peptide and natural products

2.1 Synthetic and pharmaceutical applications of linear peptides

Recently, in the last two decades, chemists have become more interest in the synthesis of peptidomimetics and naturally occurring peptides *via* the Ugi reaction due to their special biological characters, great applicability and use in drug discovery.¹⁸ U-4CR reactions have proven their efficiency in the synthesis of these structures with the least number of steps and lowest cost, ensuring the synthesis of the target structure using different aliphatic or aromatic isocyanides, with carboxylic acid,

carbonyl compound or amine derivatives with structural diversity to synthesize α -aminoacyl amides (Scheme 1).^{7,18}

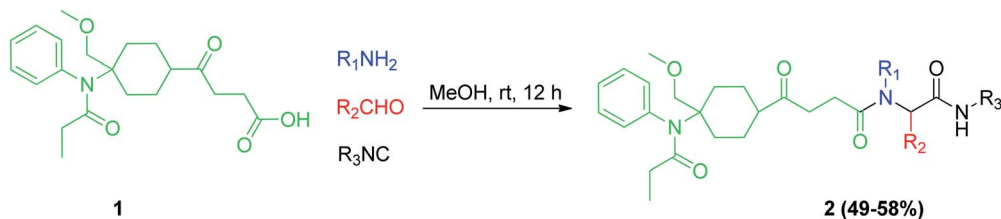
Fentanyl or fentanil is a synthetic opioid analgesic used as a pain medication to relieve pain after different treatments. Novel substituted amino acid-tethered norsufentanil derivatives **2** were synthesized by Ugi reaction utilizing the carboxylic acid-tethered norsufentanil **1** with a variety of aldehydes, amines, and isocyanides to produce a library of the desired norsufentanil derivatives compounds **2**. The *in vivo* analgesic activity of the synthesized compounds was evaluated by a tail flick test. Some of the synthesized compounds were found to be more potent than sufentanil, sufentanil citrate, and norsufentanil (Scheme 2).¹⁹



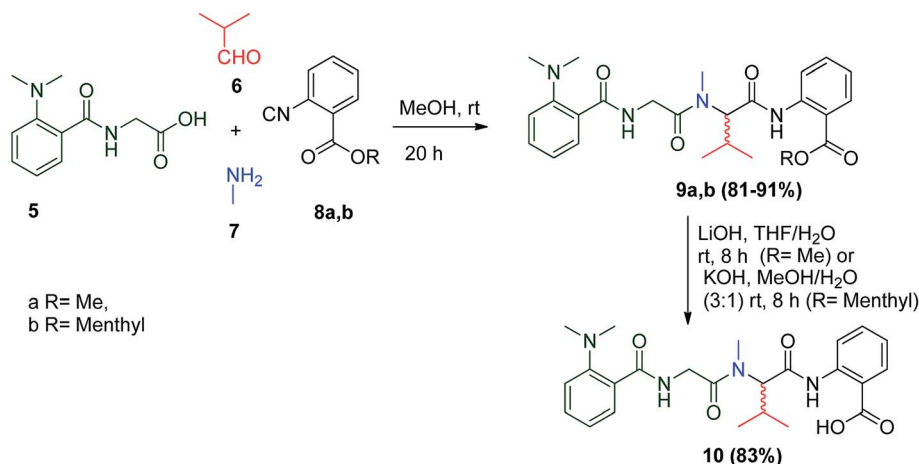
Scheme 3 Synthesis of carfentanil **4**.



Scheme 1 Synthesis of α -aminoacyl amides *via* (U-4CR).



Scheme 2 Synthesis of a synthetic opioid analgesic norsufentanil derivative **2**.



Scheme 4 Synthesis of (±)-viridic acid **10** using anthranilate-derived isonitriles **8a** and **b**.

Alternatively, the convertible isocyanide 2-bromo-6-isocyanopyridine was reported in MCR, where it is good leaving group when it is attacked by the nucleophile of the resulting Ugi bis-amide moiety under both basic and acidic conditions. This reaction sequence was used to prepare the potent opioid carfentanil **4** *via* acidic methanolysis of Ugi product **3** to give carfentanil **4** in near-quantitative yield (98%) (Scheme 3).²⁰ Carfentanil **4** is an opioid analgesic belong to the fentanyl class, which is ~100 000 times more potent than morphine.²⁰

(–)-Viridic acid is a tetrapeptide generated by many fungi of the *Penicillium* group,²¹ which was first isolated from *P. viridicatum*.²² Wessjohann and co-workers used the Ugi reaction to prepare the racemate mixture of viridic acid **10** to shorten the

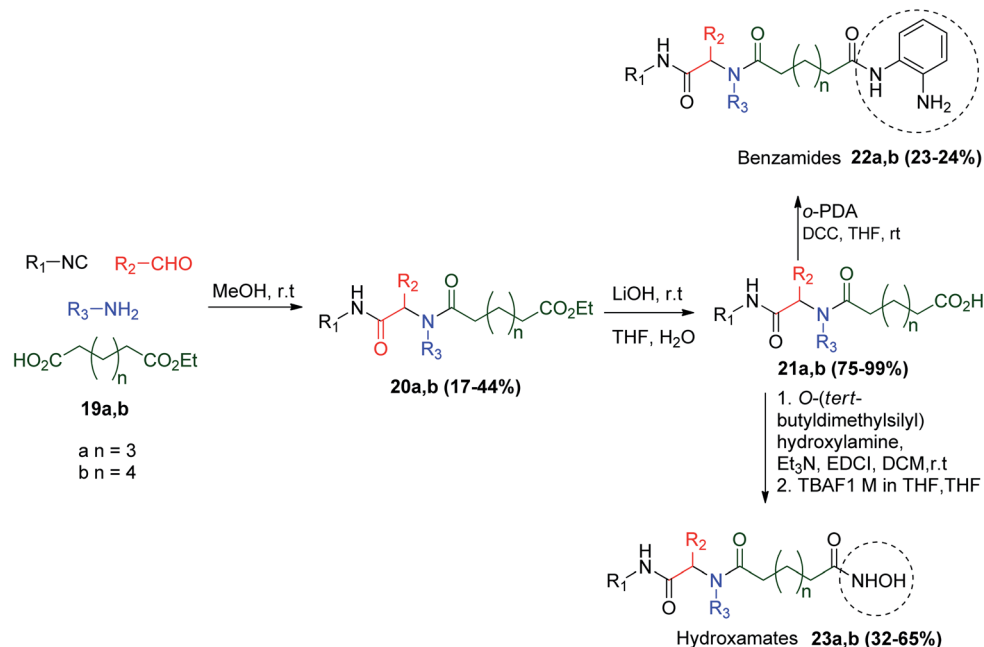
pathway of other conventional methods. U-4CR between dipeptide **5**, isobutyraldehyde **6**, methylamine **7** and the anthranilate-derived isonitrile **8a** and **b** were formulated to give **9a** and **b**, and saponification of **9a** and **b** afforded the racemic (±)-viridic acid **10** in 83% yield (Scheme 4).²³ Furthermore, as a result of the unsuccessful separation of the epimers by the classical separation methods, the racemic mixture of viridic acid was investigated as an antibacterial agent against the Gram-negative bacterium *Aliivibrio fischeri*. Compounds (–)-**10** and (±)-**10** were the most potent ones with IC₅₀ values of 45.0 ± 4.4 and 38.4 ± 5.8 μM, respectively.²³

The Ugi reaction presents a rapid and simple method to synthesize highly biologically active phosphonic pseudo-peptides using a special type of isonitriles, which is 1-



Scheme 5 Synthesis of phosphonic pseudo-peptides *via* Ugi reaction.





Scheme 6 Synthesis of bis-peptides containing benzamides **22a** and **b** or hydroxamate **23a** and **b** via Ugi reaction.

isocyanidealkylphosphonate diaryl ester derivatives.²⁴ The structural features of the synthesized phosphonic pseudo-peptides were designed to act as inhibitors to target human neutrophil elastase, a serine protease, which can be inactivated through exclusive reaction with the aromatic ester and hydroxyl group of serine protease.^{25,26} This may lead to the development of many pathophysiological states such as cystic fibrosis and rheumatoid arthritis, or tumor growth and invasion.²⁴

Two different types of phosphonic pseudo-peptides were prepared *via* the Ugi reaction using 1-isocyano-2-methylpropanephosphonic acid di(4-*S*-methylphenyl)ester (**11**) with butyl amine **14**, *Z*-Gly **13**, and aldehyde **12a** and **b**, or piperazine **16**, aliphatic acid **17** with aldehyde **12a** and **b** to afford phosphonic pseudo-peptides **15a** and **b** and **18a** and **b**, respectively. Higher ability to inhibit the proteolytic activity of human neutrophil elastase was observed when 1-isocyano-2-methylpropanephosphonic acid di(4-*S*-methylphenyl)ester derivative (**11**) was used to obtain a series of Ugi products with different activity against examined serine protease (Scheme 5).²⁴ According to Sienczyk, the most active Ugi products against the examined serine protease were when $R = \text{-CH}_2\text{Bn}$ ($k_{\text{obs}}/[\text{I}] = 1415 \text{ M}^{-1} \text{ s}^{-1}$) and when $R = \text{Bn}$ ($k_{\text{obs}}/[\text{I}] = 1360 \text{ M}^{-1} \text{ s}^{-1}$). It is worth mentioning that both products showed high potency for the inhibition of human neutrophil elastase.²⁴

Alternatively, a series of Ugi compounds containing a zinc-chelating moiety were found to act as histone deacetylase (HDAC) inhibitors, where HDACs are potential compounds that inhibit the growth of tumor and are in clinical trials as promising antitumor agents.²⁷ The Ugi reaction is the key step in the synthesis of target HDAC inhibitors, giving the Ugi products with an ester function **20a** and **b**, which are subsequently transformed into benzamides **22a** and **b** or hydroxamate **23a**

and **b** *via* the carboxylic acid intermediate **21a** and **b** (Scheme 6).²⁸

Alternatively, another interesting strategy was applied to synthesize Ugi products that could disturb protein–protein interaction. These compounds were designed to be planar, aromatic and functionalized with four points of diversity to easily recognise protein surfaces. The strategy was based on 6-alkyloxy-naphthalene-2-carbaldehyde hydrolysis of Ugi product **24** when ($R_1 = \text{CH}_2\text{COOt-Bu}$), with trifluoroacetic acid to give the corresponding acid **25** (Scheme 7).²⁹

Furthermore, the Ugi reaction was employed in the synthesis of a targeted library of C-capped dipeptide efflux pump inhibitors, where C-capped dipeptides BU-005 **27** were prepared *via* Ugi four-component reaction *via* the full deprotection of Boc and DMB of Ugi product **26** using TFA (Scheme 8).³⁰ Inhibitors of drug efflux pumps have great potential as pharmacological agents, which restore the drug susceptibility of multidrug resistant bacterial pathogens. C-capped dipeptides BU-005 **27** inhibit two chloramphenicol-specific efflux pumps in *Streptomyces coelicolor*, a Gram-positive bacterium, which is a relative of the human pathogen *Mycobacterium tuberculosis*.³⁰



Scheme 7 Synthesis of bis-amides **24** and **25** *via* Ugi reaction.



Scheme 8 Synthesis of C-capped dipeptides BU-005 27.



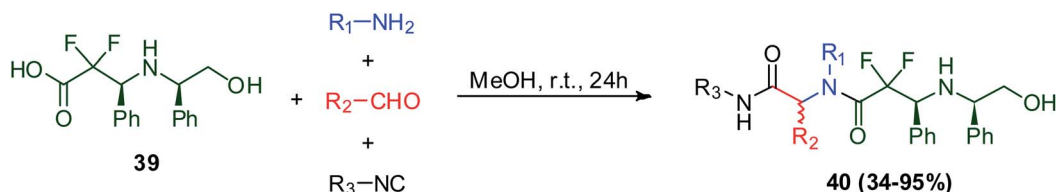
Scheme 9 Synthesis of Ugi nucleosides using 5-formyl-2'-deoxyuridine 29.

N-Nucleosides have also been synthesized *via* the U-4CR protocol. A protocol was developed to afford 5-substituted pyrimidine nucleoside *N*-acylamino acid amide scaffolds **30**, which show promising anti-leishmanial activity in the 10^{-5} M range. The reaction was based on utilizing aniline derivatives **28**, 5-formyl-2'-deoxyuridine (**29**), carboxylic acid and isonitrile to afford the desired 5-position-substituted product **30**. In contrast, using trimethylsilylazide **31** instead of an ordinary

carboxylic acid gave tetrazolo compounds **32**, which show more flexibility than **30** and show striking antiviral and anti-leishmanial activities (Scheme 9).³¹ It should be noted that pyrimidine derivatives show potential biological activities and wide clinical use in the few last years.^{32,33}

Linderman and co-workers prepared convertible isonitrile **35**,³⁴ which was subsequently used for the synthesis analogues of uracil polyoxin C (UPOC) methyl ester **38** *via* the Ugi reaction. The

Scheme 10 Synthesis of (UPOC) methyl ester **38** *via* Ugi reaction.

Scheme 11 Synthesis of *gem*-di-fluorinated pseudo-peptides via Ugi reaction.Scheme 12 Synthesis of tertiary glycosyl amides **45** via Ugi reaction.

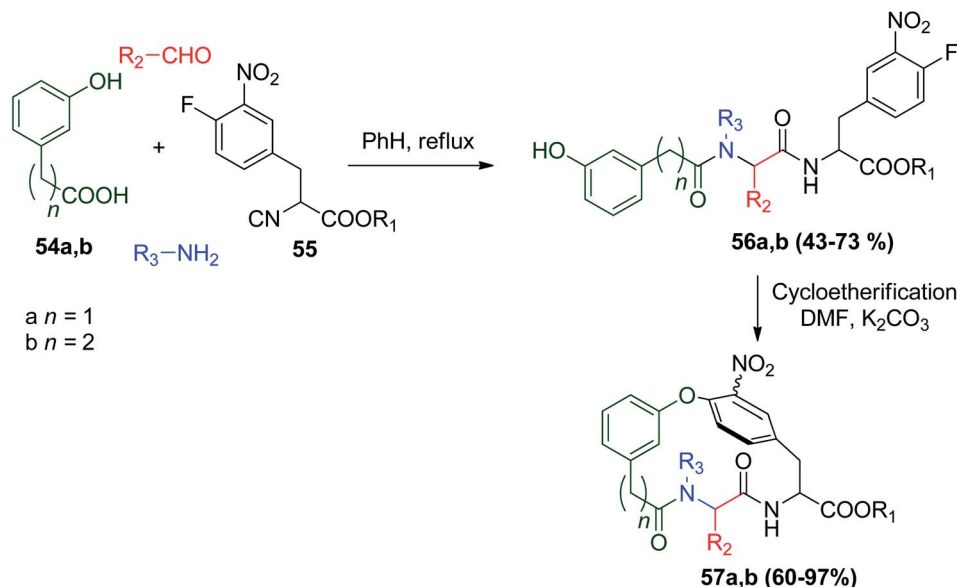
polyoxins are group of nucleoside antibiotics that have found use as agricultural fungicides. Because of their antimicrobial activities, polyoxins that play a crucial biological role against chitin synthase (CS) were obtained from *Saccharomyces cerevisiae* and *Candida albicans*.³⁵ Chitin synthases are tempting targets for inhibition in fungi and insects.³⁶ The synthesis of the polyoxins and the structurally related nikkomycins was achieved by Ugi reaction using 2',3'-isopropylidene-protected uridine-5'-aldehyde (**33**), 2,4-dimethoxybenzylamine (**34**), isoxazolecarboxylic acid derivative **36**, and the convertible isocyanide **35**. Subsequently, acidic hydrolysis achieved complete deprotection of the isopropylidene group and DMB group, and conversion of the isocyanide-derived amide into the corresponding uracil polyoxin C (UPOC) methyl ester **38** (Scheme 10).³⁶

Fluorinated peptides have attracted significant interest because the insertion of fluorine into peptides can modulate their acidity, basicity, hydrophobicity, geometry, conformation, reactivity, and biological activity.^{9,37-39} The Ugi reaction was used to synthesize bis-amide with exceptional structural features such as *gem*-di-fluorinated pseudo-peptides. The Ugi reaction using 2,2-difluoro-3-(2-hydroxy-1-phenylethylamino)-3-phenylpropionic acid (**39**), isocyanide, aldehyde, and primary amine afforded di-fluorinated pseudo-peptides derivatives **40** in methanol with up to 95% yield (Scheme 11).⁴⁰

Alternatively, tertiary glycosyl amide derivatives **45** were prepared *via* the Ugi reaction using β -galactopyranosyl pentaacetate amine (**41**) with formaldehyde **42**, methyl isocynoacetate (**43**) and terephthalic acid (**44**) followed by



Scheme 13 Synthesis of cyclic peptide via Ugi reaction.



Scheme 14 Two-step synthesis of biaryl ether-containing macrocycles.

deacetylation. The applications of tertiary glycosyl amides are as frameworks for the design and preparation of ligands that will facilitate protein–protein or other receptor–receptor interactions. The partiality of limited divalent ligands (or higher order) planned to bind to protein that recognize carbohydrates would encourage clustering and associatively advance protein–protein interactions, which may be essentially higher than monovalent partners or multivalent ligands without these properties. This may be valuable as a modern methodology within the advancement of therapeutics dependent on carbohydrates (Scheme 12).⁴¹

The Ugi reaction differs from other traditional peptide coupling techniques, where it represents a short and efficient

pathway to design and synthesize linear bis-amides in a one-pot reaction, which can provide pharmaceutical applications.

2.2 Synthetic and pharmaceutical applications of macro and cyclic peptides

Cyclic peptides are widely found in marine organisms and fungi.⁴² Many of these peptides show particular biological activity, and therefore are highly interesting from a pharmaceutical point of view.^{42,43} Cyclic peptides show interesting biological activity, putting them on the map of organic chemists to create new methods with minimal steps, which is beneficial for the synthesis of cyclic peptides with exceptional structural features. U-4CR is a promising strategy to synthesize these cyclic



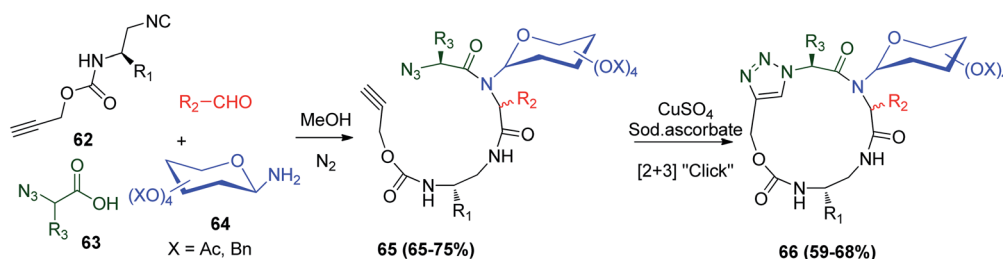
Scheme 15 Sulfur-switch Ugi reaction for the synthesis of disulfide-bridged peptides 61.



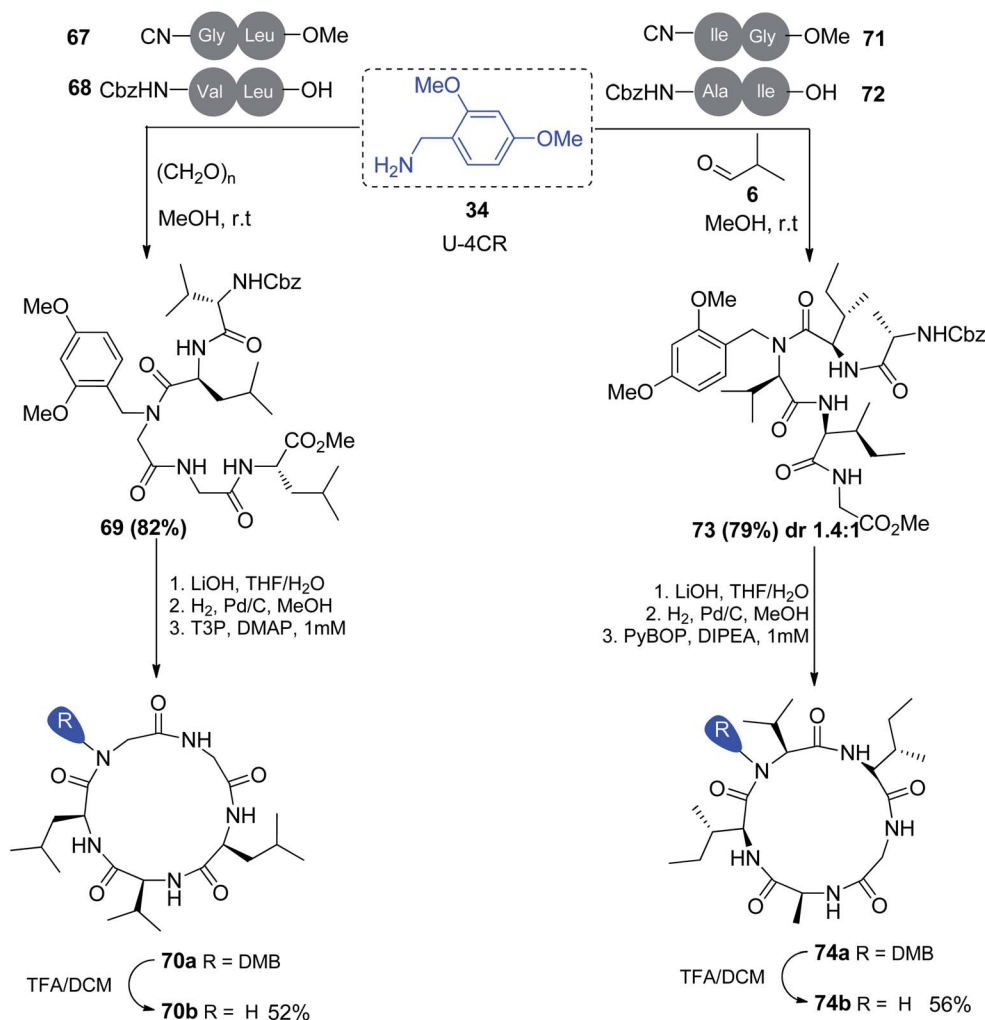
peptides through the ring-closing metathesis (RCM) approach.⁴⁴ It was shown that not only the length or the sequence of the peptide chain is responsible for the success of RCM, but also the synthetic approach. Moreover, the Ugi reaction using allyloxycarbonyl (Alloc)-protected isonitrile **46** and Alloc-protected carboxylic acids **48** and **51**, 1-(3-methoxyphenyl) ethanamine (**47**), and isobutyraldehyde (**6**) gives Ugi adducts **49** and **52** in excellent yields, respectively. The peptides formed *via* U-4CR undergo the RCM to form cyclic peptides **50** and **53** in the

presence of Ru-catalyst under different reaction conditions, respectively (Scheme 13).⁴⁴

Another interesting example reported was the synthesis of biaryl ether-containing macrocycle amide *via* a two-step reaction starting with U-4CR using α -(4'-fluoro-3'-nitro)phenethyl isocyanoacetate (**55**) with *m*-hydroxy phenyl alkylcarboxylic derivatives **54a** and **b** followed by intramolecular S_NAr-based cycloetherification to give products **57a** and **b**, respectively. The two-step synthesis increased the molecular complexity and



Scheme 16 Synthesis of triazole-linked cyclic glycopeptidomimetics *via* Ugi reaction.



Scheme 17 Macrocyclization of pentapeptides assisted by a traceless turn-inducing core derived from the Ugi reaction.



points of diversity, where the presence of the nitro group in macrocycles facilitates macrocyclization and provides functional groups in the existing macrocycles, and accordingly increases the molecular diversity (Scheme 14).⁴⁵

Furthermore, a general strategy for the effective synthesis of artificial disulfide-linked macrocycles *via* U-4CR after oxidative cyclization was introduced. The Ugi reaction using cysteine isocyanide **58** and Fmoc-Cys(Trt)-OH acid **59** with a variety of amine or aldehyde yielded diastereoisomeric combinations **60** in MeOH/THF/DMF (1 : 1 : 0.1, 0.2 M). This protocol was used to generate the novel isolated disulfide-bridged peptides **61** by Ugi cyclization using I₂/MeOH/DCM (Scheme 15).⁴⁶

A successive combination between the Ugi reaction and click reaction was utilized for the synthesis of triazole connected to cyclic glycopeptidomimetics. This combination mixed the usual four Ugi reactants, protected glycosyl amine **64**, propargyloxycarbonyl Poc-amino alkyl isonitriles derivatives **62**, α -azido carboxylic acid **63**, and aldehydes in methanol afford Ugi products **65** with a terminal alkyne and azido group. It is worth mentioning that the double nature of the propargyloxycarbonyl (Poc) group was investigated for amine protection and the catalytic cycloaddition with an azide in the presence of CuSO₄·5H₂O/sodium ascorbate in *t*BuOH/water, giving **66** as a mixture of two diastereomers (Scheme 16).⁴⁷

On the other hand, the macrocyclization of pentapeptides was performed using the Ugi reaction through a three-step protocol to obtain the expected biologically active compounds **70a** and **b** and **74a** and **b** in good yield. This methodology was based on the use of 2,4-dimethoxybenzylamine (**34**) in MCR of dipeptide acids **68** and **72** and isocyanides **67** and **71** with aldehyde to afford *N*-alkylated pentapeptides **69** and **73**,

respectively. The deprotection of both pentapeptides followed by macrolactamization by propanephosphonic acid anhydride (T3P) or benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) afforded cyclic peptides **70a** and **74a**, respectively. Treatment of **70a** and **74a** with TFA in the presence of DCM easily removed the DMB *N*-substituent to afford **70b** and **74b** in good yield (Scheme 17).⁴⁸

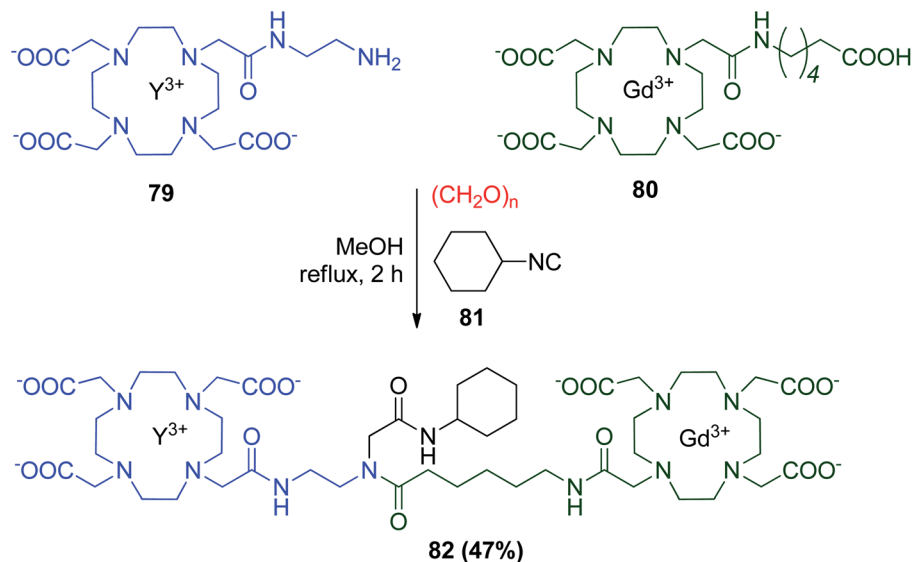
Ditopic bifunctional chelating agents **78a** and **b** were synthesized *via* U-4CR in a single synthetic step utilizing 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid DOTA and DOTA monoamide (DOTAMA) analogues as amine **75a** and **b** and acid **76** input. Different aldehydes and isocyanides afforded Ugi products **77a** and **b** using methanol with ultrasound irradiation. Hydrolysis of the *t*-butyl esters of **77a** and **b** was successfully carried out by TFA, and the dimeric ligands **78a** and **b** were obtained as analytically pure white solids by precipitation with ether (Scheme 18).⁴⁹

The wide applicability of optical and nuclear properties of yttrium (Y) and gadolinium (Gd) cations can be used in the synthesis of homo- and heterodimetallic systems for diagnostic and therapeutic applications. The Y(III) complex of DOTAMAEEn **79** and the Gd(III) complex of DOTAMAC6OH **80** were then reacted together with paraformaldehyde and cyclohexyl isocyanide **81** to give heteroditopic Y-Gd complex **82** (Scheme 19). One of the Gd(III) lipophilic complexes (R₁ = H, R₂ = C₁₈H₃₇) forms micelles at concentrations <0.1 mM and bind to human serum albumin (HSA) and has been studied by proton relaxometry, and the affinity constant of the complex and the relaxivity of the macromolecular adduct (rb1p = 38.1 mM⁻¹ s⁻¹; 20 MHz and 310 K, respectively) were derived.⁴⁹



Scheme 18 General synthesis of ditopic bifunctional chelating agents **78a** and **b** *via* U-4CR.





Scheme 19 Synthesis of a heteroditopic Y-Gd complex by U-4CR.

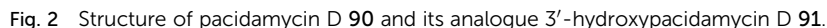
2.3 Synthetic and pharmaceutical application of natural products

Furthermore, the Ugi reaction considered as a key step in the synthesis of many natural products, where not only bacteria contain attractive natural biologically active compounds, but also marine organisms contain interesting natural products.⁵⁰ Exigurin **89** was isolated from the marine sponge *Geodia exigua* collected in Oshima Island, and boneratamide A **83** isolated from the marine sponge *Axinyssa aphysinoides* collected in Indonesia.⁵¹ Boneratamide A **83** has an extraordinary structure, which contains terpene and amino acid units connected through an amide linkage. Despirocyclic boneratamide A analogue **86** was simply prepared *via* the Ugi reaction of terpene isocyanides **84** with α -methyl L-glutamate **85** in yield 43%.⁵²

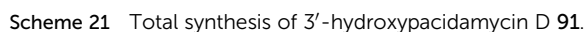
Moreover, the synthesis of exigurin **89** originated from four building blocks including (–)-10-*epi*-axisonitrile-3 **87**, and the simple substances formaldehyde **42**, sarcosine **88** and methanol. Similarly, the Ugi reaction between axisonitrile-3 **83** acetone **85** and glutamic acid **84** was the key step in the biosynthesis of boneratamide A **83** (Scheme 20).^{13,53,54}

Pacidamycin D **90**, a member of a class of uridylpeptide antibiotics, was first isolated from *Streptomyces coeruleorubidus* AB 1183F-64 in 1989.⁵⁵ The analogues of pacidamycin D **90** are 3'-hydroxypacidamycin D **91** (Fig. 2), a type of uridylpeptide antibiotics, which are selective antibacterial agents against *Pseudomonas aeruginosa*, and also act as inhibitors of phospho-MurNAC-pentapeptide transferase (MraY). Their IC₅₀ for MraY is 42 nM and MIC for different types of *P. aeruginosa* range

Scheme 20 Total synthesis of a despirocyclic boneratamide A analogue **86** and exigurin **89** via the Ugi reaction.



The glutarimide moiety (2,6-piperidinedione) is present in natural product scaffolds that showed diverse biological activities.^{58,59} This scaffold is present in the structure of julocrotine **105**, which has shown antiproliferative effects *in vitro* against the promastigote and amastigote forms of *Leishmania amazonensis*. The glutarimide alkaloid julocrotine **105** was prepared through the reaction between (*R*)-(+)-1-(4-methoxyphenyl)ethylamine (**100**) as a chiral auxiliary and the usual Ugi reactants to give **102a**, followed by ester basic hydrolysis to give the corresponding carboxylic acid **102b**. Subsequently, intermolecular cyclization was carried out with acetic anhydride and



Scheme 22 Synthetic route for julocrotine **105**.

sodium acetate to yield the natural julocrotine **105** and its diastereomer **106** (Scheme 22).⁶⁰

biological activity, attracting valuable attention from organic and medicinal chemists.

3 Synthetic and pharmaceutical applications of heterocyclic compounds

Versatile methods have been reported for the synthesis of different heterocycles, but most of them depend on multi-step systems, which result in high costs and long reaction time.⁶¹ On the other hand, isocyanide-based multicomponent reactions (IMCRs) guarantee a one-pot procedure, shorter time and products with high functionality and high yields. U-4CR is one of the most common reactions used in the synthesis of heterocyclic compounds through several routes, including post-modification reactions (from linear adduct to heterocyclic compound) or the UDC strategy (Ugi/deprotect/cyclize), where the final step of ring closing is mediated through amide bond formation.⁶² Due to the extreme importance of different heterocycles as biologically active compounds,^{63,64} this review will present the most efficient synthetic routes of U-4CR to synthesize different heterocyclic systems with interesting

3.1 Synthesis of five-membered heterocyclic compounds

Dihydropyrrolidines are nitrogen-based five-membered heterocyclic compounds, which are found in many natural occurring compounds that have promising biological activities. For instance, some alkaloids contain dihydropyrrolidine moieties such as swainsonine **107**,⁶⁵ hyacinthacine **108**,⁶⁶ and uniflorine A **109**⁶⁷ (Fig. 3), which are used as anticancer or antidiabetes compounds.

The synthesis of 1,2-disubstituted-*cis*-3,4-dihydropyrrolidine derivatives **114a** was reported using the Ugi reaction protocol. Polindara-García and co-workers synthesized different Ugi products in TFE/InCl₃ under microwave

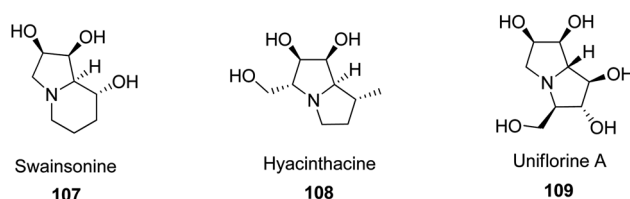


Fig. 3 Structures of some biologically active dihydropyrrolidines.



Scheme 23 Synthesis of 1,2-disubstituted-*cis*-3,4-dihydropyrrolidine derivatives **114a** and **b**.

irradiation using propargyl amine **110** and glyoxal derivatives **111** to afford Ugi product **112**. Subsequently, cesium carbonate and MWI facilitated the cyclization process to obtain 3-pyrroline derivatives **113**. Treatment of **113** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) was carried out to afford the medicinally dihydroxylated diastereoisomers **114a** (*cis*-isomer) and **114b** (*trans*-isomer) (Scheme 23).⁶⁸

The reaction between isocyanoalkyl carbonate **115** with the different Ugi components gave the usual Ugi products **116** in moderate to excellent yields. Compounds **116** gave *N*-acyloxazolidinones **117** in the presence of *t*-BuOK/THF and molecular sieves 4 Å (MS 4 Å).⁶⁹ On the other hand, upon treatment of *N*-acyloxazolidinones **117** with lithium thiolate derived from *n*-BuLi and *n*-dodecanethiol **118**, the conversion occurred effectively to afford *n*-dodecanethiol esters **119** (Scheme 24).⁶⁹

On the other hand, *N*-acylpyrroles building block scaffolds were prepared using 4-isocyanopermethybutane-1,1,3-triol

(IPB) **120** as a convertible isonitrile *via* the Ugi reaction to afford bis-amide **121**. Bis-amide **121** obtained from the Ugi reaction was converted into highly activated *N*-acylpyrroles **122** using TFA (Scheme 25).⁷⁰

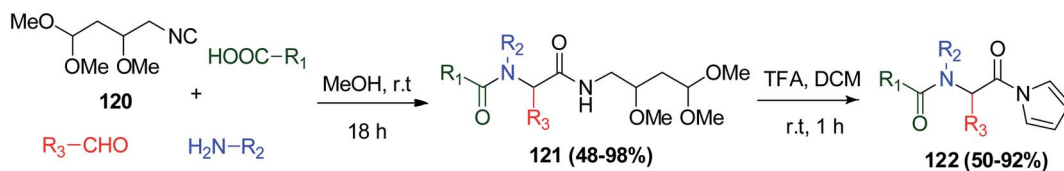
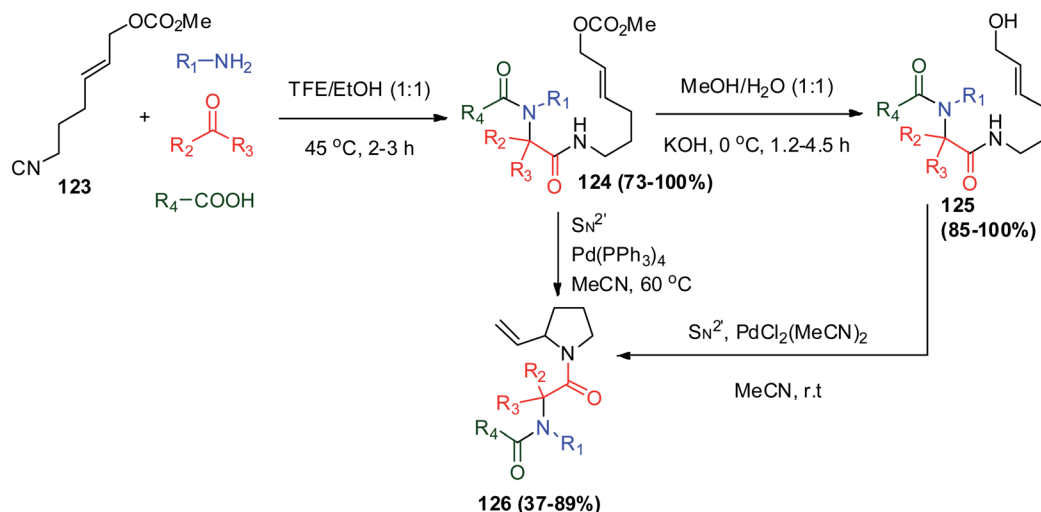
The functionalized *N*-acyl-2-vinylpyrrolidines derivatives **126** were prepared *via* the Ugi reaction using unsaturated isocyanide **123** together with a variety of carbonyl compounds, primary amines, and carboxylic acids for the preparation of Ugi derivatives **124**, followed by a second transformation involving different Pd catalysts and S_N2' cyclization to give **126**, where in most cases the Pd(0)-catalyzed reaction gave the final product in low yield (Scheme 26).⁷¹

Also, Ugi-Dieckmann reaction combination was utilized in the synthesis of the tetramic acid derivatives, which are an important class of nitrogen-containing heterocycles and considered as key structures in many natural products with interesting biological activity, including antiviral⁷² and



Scheme 24 Synthesis of *N*-acyloxazolidinones.



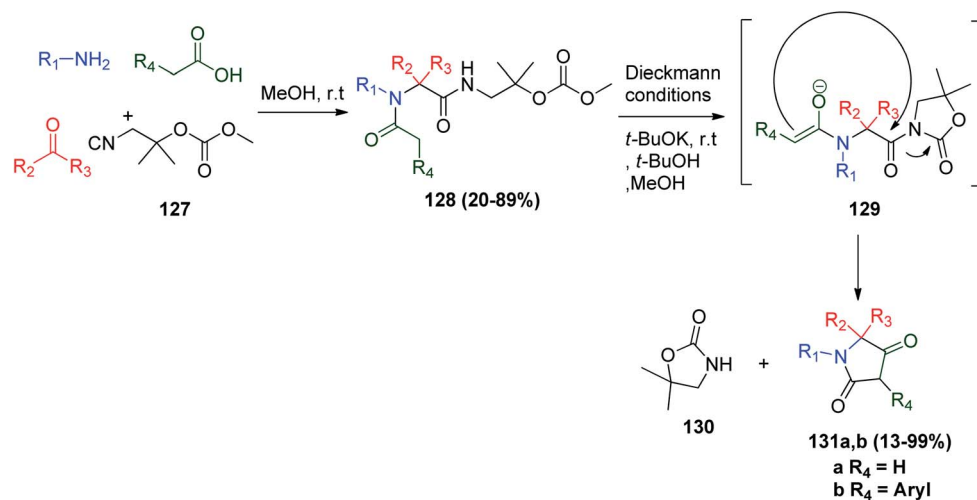
Scheme 25 Synthesis of *N*-acylpyrroles 122.Scheme 26 Synthesis of *N*-acyl-2-vinylpyrrolidines derivatives 126.

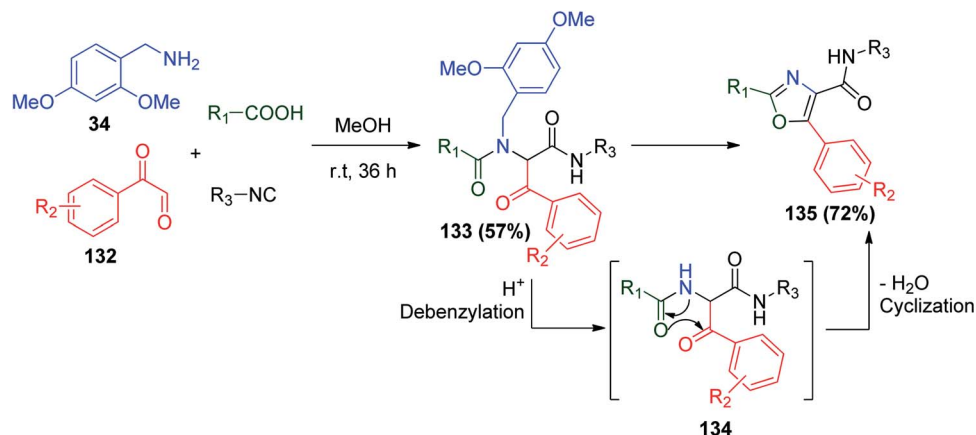
phytotoxic activities.⁷³ The convertible isocyanide 1,1-dimethyl-2-isocyano-ethyl-methylcarbonate (127) was condensed with other Ugi reactants to give 128, which was deprotonated and then cyclized to 129 *via* intramolecular attack of the enolized anion, allowing 5,5-dimethyloxazolidin-2-one to act as a leaving group and a Dieckmann-like cyclization to tetramic acid derivatives 131a and b occurred (Scheme 27).⁷⁴

On the other hand, a series of 2,4,5-trisubstituted oxazoles were synthesized through another Ugi combination *via* Ugi/

Robinson–Gabriel reactions, condensation of 2,4-dimethoxybenzylamine (34) with phenylglyoxal 132 and other Ugi reactants to afford bis-amide 133. The conversion of Ugi product 133 to oxazole 135 was subsequently carried out *via* a debenzylation/cyclodehydration protocol using (POCl₃), which led to the desired Robinson–Gabriel cyclodehydration reaction (Scheme 28).⁷⁵

In another interesting synthesis employing the Ugi reaction is the synthesis of aryloxazolone compounds, which are found in many potent non-steroidal drugs and found to be anti-

Scheme 27 Synthesis of tetramic acid derivatives 131a and b *via* Ugi–Dieckmann reactions.



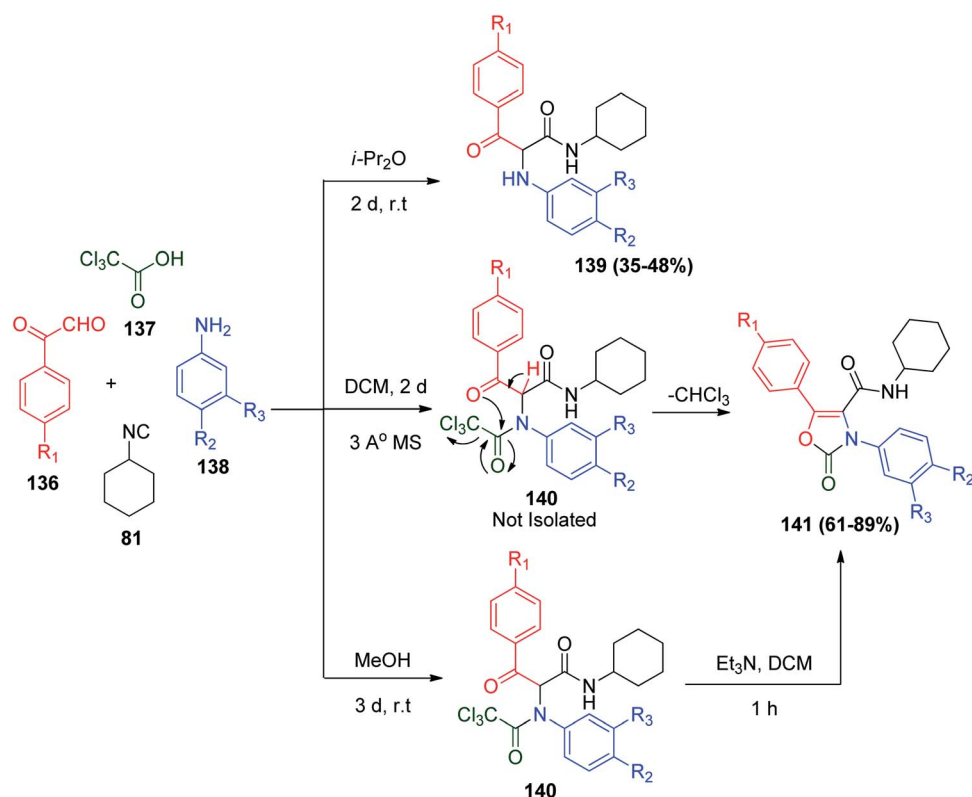
Scheme 28 Synthesis of 2,4,5-trisubstituted oxazoles via Ugi/Robinson–Gabriel reactions.

inflammatory and selective COX-2 inhibitors.⁷⁶ The reaction of different derivatives of arylglyoxals **136** and anilines **138** with cyclohexyl isocyanide (**81**) and trichloroacetic acid in dichloromethane in the presence of molecular sieves gives aryloxazolones **141** in single synthetic steps, where the formed Ugi bis-amide is not isolated and spontaneously cyclized with elimination of chloroform to irreversibly afford the target product (Scheme 29). The same reaction under the classical Ugi reaction conditions (MeOH, rt) gives bis-amide **140**, which is converted to **141** after treatment with Et₃N/DCM. Also, the same Ugi reactants can afford deacylated Ugi products **139** in isopropyl ether at room temperature (Scheme 29).⁷⁷

A series of benzene/imidazole systems with more than three connected aromatic rings was synthesized using U-4CR through the condensation of terephthalic acid **44**, *c*-hexylisocyanide **81** with *n*-butylamine **14**, and phenylglyoxal hydrate **142** to afford Ugi adduct **143** followed by condensation with ammonia **144** to give the target compound **145** (Scheme 30).⁷⁸

3.2 Synthesis of fused five-membered heterocyclic compounds

As mentioned before, nitrogen-containing heterocycles are an important class of organic compounds, which represent a wide section of drugs and medicinal chemistry.^{79,80} A series of fused



Scheme 29 Synthesis of aryloxazolone derivatives utilizing trichloroacetic acid via Ugi reaction.





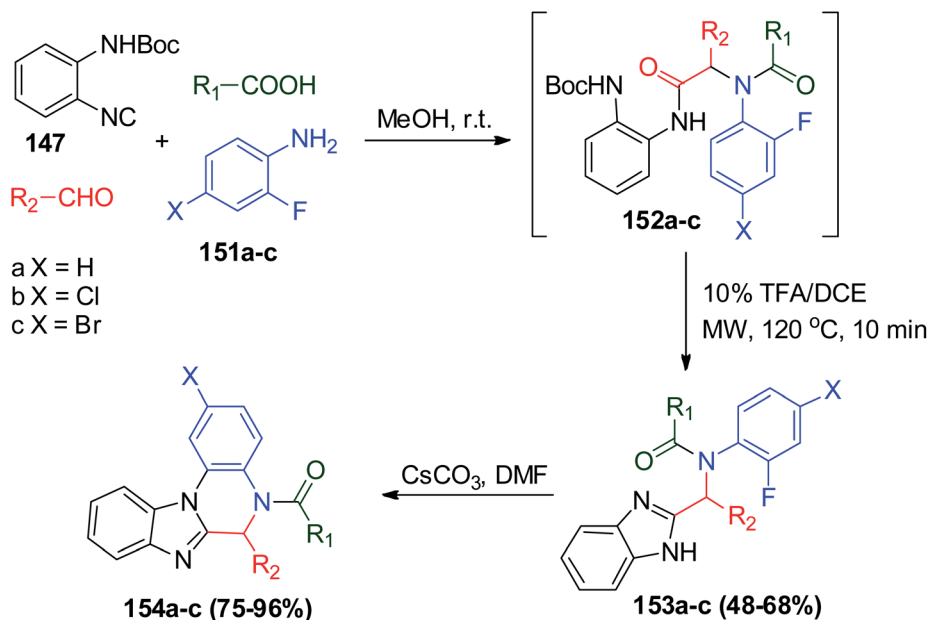
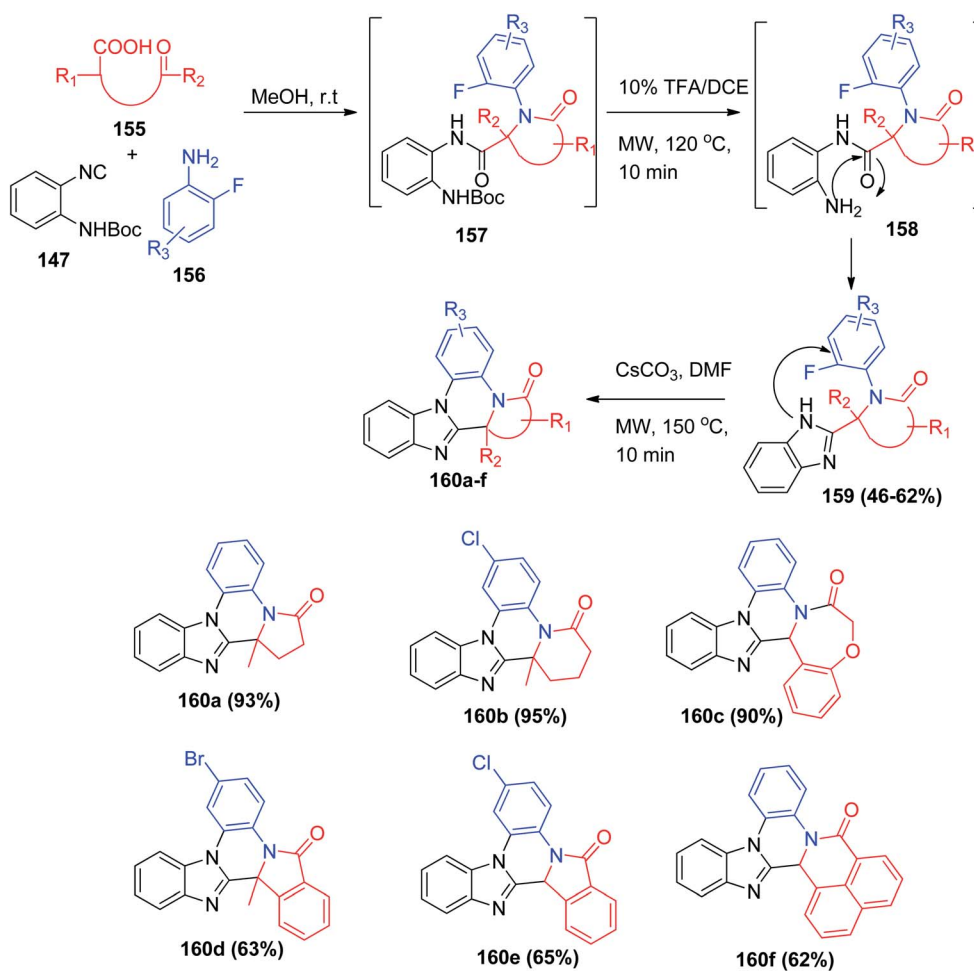
Scheme 30 Two-pot synthesis of benzene/imidazole systems.

benzimidazole-isoquinolinones (BIDs) was prepared *via* Ugi reaction utilizing *N*-Boc-2-aminophenylisocyanide **147**, methyl 2-formylbenzoate **146**, amine and carboxylic acid in methanol. The observed Ugi products **148** were deprotected and then cyclized using 10% TFA/DCE, MW to afford the desired biologically active BIDs **150** (Scheme 31). The obtained BIDs were screened against human colorectal cancer (CRC), which showed anti-cancer activity against the SW620 and HT29 CRC lines. It was found that $\text{R}_1 = \text{i-Bu}$ and $\text{R}_2 = 3\text{-pyridyl}$ gave the most potent compound with the lowest growth inhibition (GI_{50}) values among the other observed BIDs for both CRC cell lines ($\text{GI}_{50} = 23.78 \mu\text{M}$ for SW620 and $24.13 \mu\text{M}$ for HT29). Also, the compound molecular mechanism was explored and the result

showed that it suppresses CRC proliferation, growth and survival, and addition, it induces mitochondrial-mediated apoptosis through prohibition of the PI3K/AKT/mTOR signaling cascade (Scheme 31).⁸¹

Alternatively, the UDC (Ugi/deprotection/cyclization) strategy was used in the synthesis of fused benzimidazole-quinoxalines scaffolds in good yields using *N*-Boc-2-aminophenylisocyanide (**147**) with different 2-fluoroaniline derivatives **151a-c** and other Ugi reactants after stirring in methanol at room temperature. After deprotection and cyclization occurred in TFA/DCE to afford **153a-c**, a nucleophilic substitution reaction of **153a-c** was carried out in DMF and

Scheme 31 Synthesis of fused benzimidazole-isoquinolinones **150** *via* Ugi reaction.

Scheme 32 Synthesis of fused benzimidazole-quinoxalinones **154a-c** via UDC reaction.Scheme 33 Synthesis of fused BID polycyclic **160a-f** via UDC reaction.



Scheme 34 Synthesis of piperazine-benzimidazoles **164** via Ugi reaction.

catalyzed by cesium carbonate, affording benzimidazole-quinoxalinones **154a-c** (Scheme 32).⁸²

Using the same UDC (Ugi/deprotection/cyclization) strategy, the polycyclic heterocycles benzimidazole-quinoxalinones **160a-f** were synthesized utilizing a range of tethered ketone acids **155**. This strategy will accelerate the preparation of a large number of compounds in high through-put screening in pharmaceutical studies (Scheme 33).⁸²

In another application of the UDC strategy, two series of fused piperazine-benzimidazole compounds were prepared using the same isonitrile **147** under similar reaction conditions, followed by intermolecular nucleophilic substitution reaction to give the target compounds, which have great applicability in medicinal chemistry (Scheme 34).⁸³

Furthermore, the same strategy was used to synthesize a wide range of more complex piperazine-benzimidazole compounds, where isonitrile **147**, bromoacetic acid **161**, *N*-Boc-protected *o*-phenylenediamine derivatives **165** and aldehydes react with each other to give **166** followed by deprotection to

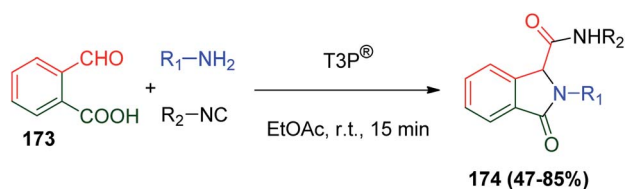
finally give **169** through intermediates **167** and **168** (Scheme 35).⁸³

Oxindoles are important nitrogen-containing heterocycles that are found in a large number of natural products and pharmaceuticals.^{84,85} An important two-step synthesis of oxindoles **172** was achieved by Ugi reaction in the first key step using 2-iodobenzaldehyde derivatives **170** followed by efficient intramolecular Pd(II)-catalyzed Buchwald-Hartwig reaction in the presence of microwave heating to advance the second step reaction (Scheme 36).⁸⁶

Furthermore, oxoisindoles **174** are an important class of heterocyclic compounds that represent valuable building blocks for the synthesis of pharmaceutical compounds and natural products.⁸⁷ They were synthesized *via* a Ugi four-center, three-component reaction (Ugi-4C-3CR) by condensation between 2-formylbenzoic acid (**173**), amines and isonitriles. The reaction was promoted by propylphosphonic anhydride (T3P®) to avoid the problem of long reaction time (Scheme 37).⁸⁸



Scheme 35 Synthesis of piperazine-bis-benzimidazoles **169** via Ugi reaction.

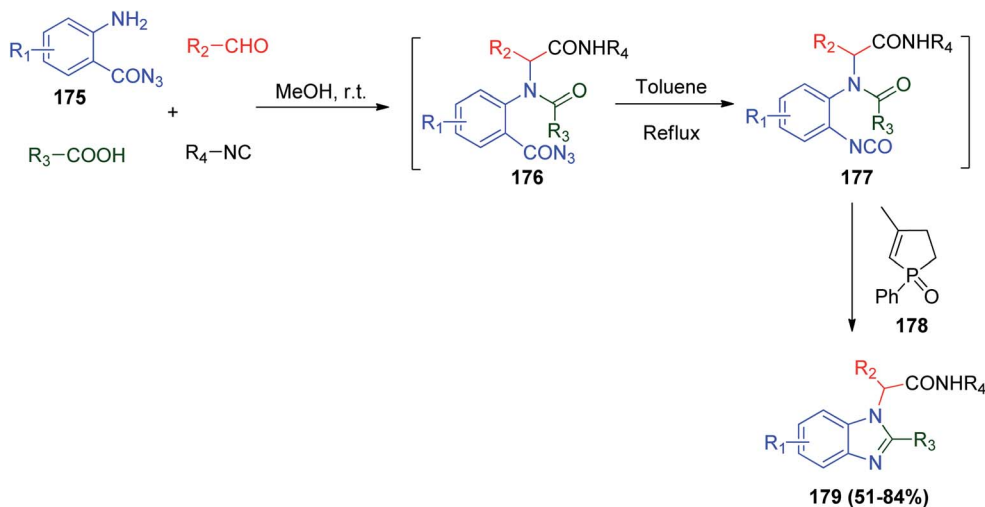
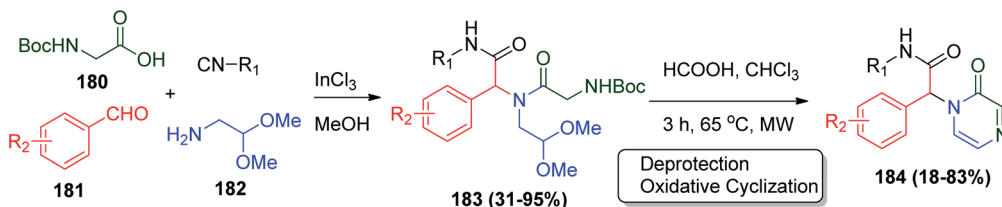
Scheme 36 Synthesis of oxindoles **172** via Ugi/Buchwald-Hartwig reaction.Scheme 37 Synthesis of oxoisindoles **174** via Ugi reaction.

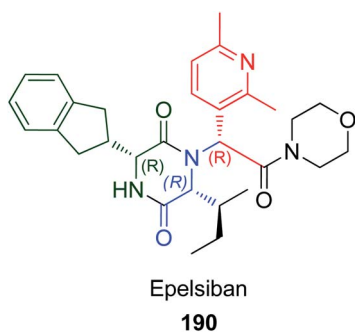
A series of benzimidazole derivatives were synthesized by Ding *et al.*, where they extended their study on Ugi and aza-Wittig reactions to synthesize more valuable heterocycles. They developed Ugi reaction combined with catalytic aza-Wittig reaction to synthesize multi-substituted benzimidazoles under the classical Ugi reaction conditions in the presence of

a catalytic amount of 3-methyl-1-phenyl-2-phospholene 1-oxide (**178**), 2-aminobenzoyl azide derivatives **175**, aldehydes, carboxylic and isocyanides a one-pot reaction proceeds easily to give the target poly-substituted benzimidazoles **179** (Scheme 38).⁸⁹ On the other hand, benzimidazoles act as antibacterial,⁹⁰ anti-HIV-1,⁹¹ anti-inflammatory,⁹² and anticancer agents.⁹³

3.3 Synthesis of pyrazinone or diketopiperazine compounds

On the other hand, the UDC strategy was applied to achieve a series of anti-inflammatory peptidic pyrazinones **184** in a two-step methodology starting with the usual Ugi reaction using *N*-Boc glycine **180**, aromatic aldehyde **181**, aminoacetaldehyde dimethyl acetal **182** and isocyanide, followed by microwave-assisted deprotection and oxidative cyclization step (Scheme 39).⁹⁴ The synthesized pyrazinones were evaluated using *in vivo*

Scheme 38 Synthesis of benzimidazoles derivatives **179** via Ugi reaction/catalytic aza-Wittig cyclization.Scheme 39 Synthesis of peptidic pyrazinones **184** via Ugi reaction.

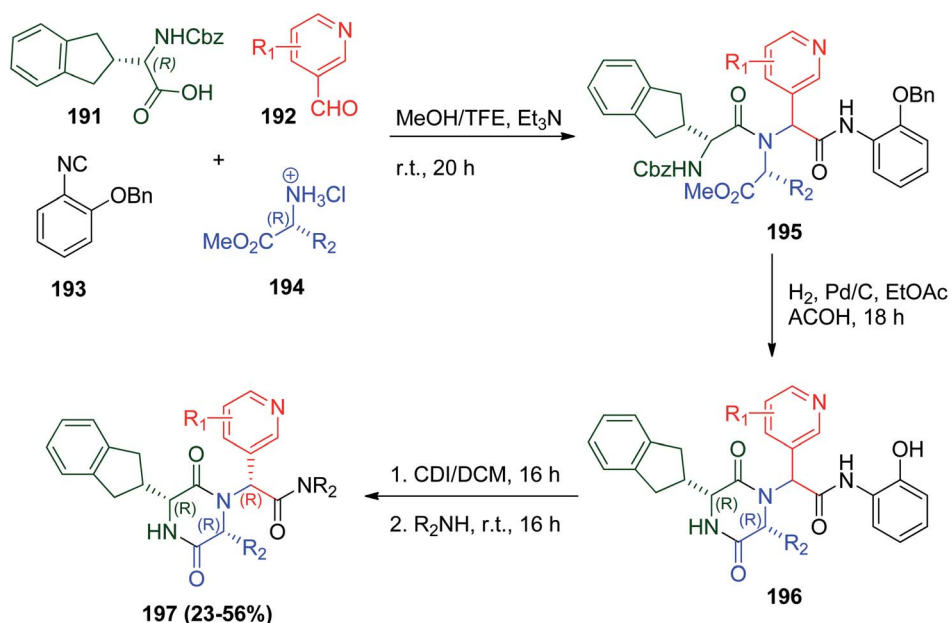
Scheme 40 Synthesis of pyrazin derivatives **188** and **189** via Ugi reaction.Fig. 4 Structure of epelsiban **190**.

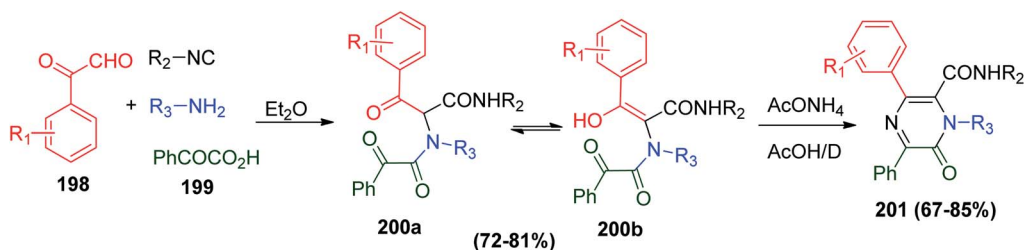
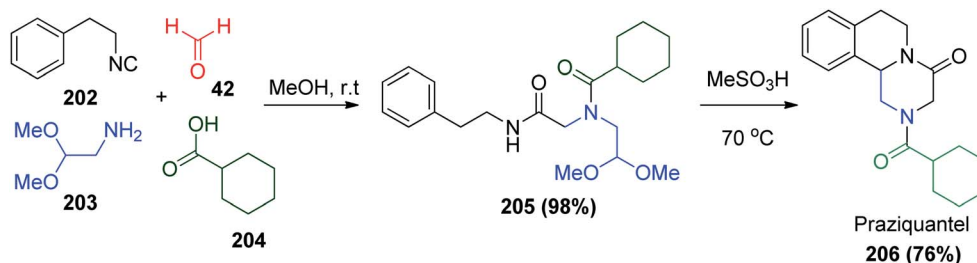
topical anti-inflammatory model using tetradecanoylphorbol acetate (TPA) as an inducer of mouse ear edema, and all the compounds showed interesting results. The most potent compounds were obtained when $R_1 = c\text{-Hex}$ and $R_2 = \text{Me}$ or CF_3 and their infective dose ID_{50} values were determined to be 0.45

and $0.46 \mu\text{mol}$ per ear, respectively, where both compounds were more active than the selective COX-2 inhibitor celecoxib.⁹⁴

Moreover, a methodology based on the Ugi reaction was applied to obtain pyrazin-2(1H)-one analogues, which are precious moieties in drug discovery and many therapeutic agents.⁹⁵ α -Ketoaldehyde **185**, *N*-Boc-amino acid **186**, amine, and isonitrile were utilized to afford Ugi bis-amide **187**, followed by deprotection-cyclization via HCl/ether at 0°C to obtain 3,4-dihydropyrazin-2(1H)-ones (**188**) or via TFA/DCE at 80°C to obtain pyrazin-2(1H)-ones (**189**) (Scheme 40).⁹⁶

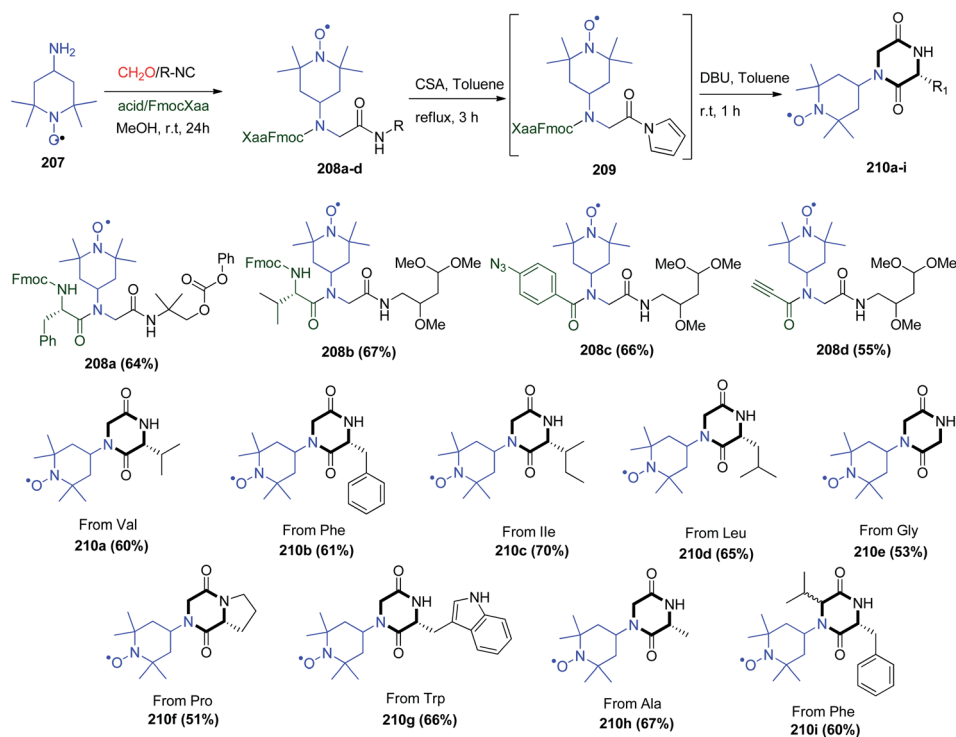
Epelsiban **190** is one of the most important orally bioavailable drugs, which is a powerful and selective oxytocin receptor (OXTR) antagonist (Fig. 4).⁹⁷ The synthesis of epelsiban and its derivatives could be achieved through U-4CR by condensation of *N*-benzyloxycarbonyl-*R*-indanylglycine **191**, pyridylaldehydes **192**, *o*-benzyloxy phenylisonitrile (**193**) and *R*- α -amino acid esters **194** to give tri-peptide product **195** followed by hydrogenolysis to eliminate the *Z* and benzyl groups to give **196**, and subsequent treatment of **196** with carbonyldiimidazole CDI and

Scheme 41 Synthesis of epelsiban derivatives **197** via Ugi reaction.

Scheme 42 Synthesis of 6-oxypyrazine-2-carboxamide derivatives **201** via Ugi reaction.Scheme 43 Synthesis of anti-schistosomal praziquantel drug **206** via Ugi reaction.

a variety of secondary amines gave the desired RRR amides (epelsiban derivatives) **197** (Scheme 41).⁹⁸ Investigation of the pharmacokinetic profile in rats, dogs, and cynomolgus monkeys of these derivatives showed that 2',6'-dimethyl-3'-pyridyl *R*-*sec*-butyl morpholine amide epelsiban **190** is a significantly powerful oxytocin antagonist ($pK_i = 9.9$) with >31 000-fold selectivity with no significant P450 inhibition.⁹⁸

Another protocol was used to prepare derivatives of heterocycles with a pyrazine moiety utilizing a two-step synthesis including U-4CR followed by [5 + 1] cyclization to obtain the target 1,6-dihydro-6-oxypyrazine-2-carboxylic acid derivatives **201**. Product **201** was prepared *via* the reaction between arylglyoxals **198**, benzoylformic acid **199**, amines and isonitrile to afford the usual Ugi adduct **200a** and its tautomer **200b**, which

Scheme 44 Synthesis of DKPs **210a-i** with spin-labels attached.

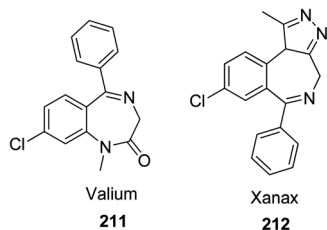


Fig. 5 Structure of Valium 211 and Xanax 212.

cyclized in the next step in the presence of ammonium acetate in acetic acid to obtain **201** in good yields (Scheme 42).⁹⁹

Moreover, a wide range of heterocyclic compounds are commercially available drugs to treat many infections. Praziquantel (PZQ) **206**¹⁰⁰ is a drug containing a pyrazino isoquinoline ring system as its core structure, which can be synthesized *via* the Ugi reaction under mild conditions (MeOH, rt) (Scheme 43).^{101,102} PZQ **206** is widely used in the treatment of schistosomiasis, which is disease also known as bilharzia or silent pandemic.^{103,104} Indeed, PZQ **206** showed activity against trematode and cestode infections in humans and animals.¹⁰⁵

Additionally, the Ugi strategy can be applied to synthesize many complex spin-labeled structures for EPR analysis for screening methods in biomedically significant ligand binding investigations. Labelled diketopiperazines (DKPs) and peptide-peptoid chimera were synthesized through the reaction between 4-amino-2,2,6,6-tetramethylpiperidinyloxy (4-amino TEMPO) (**207**) and the other Ugi reactants to form Ugi products

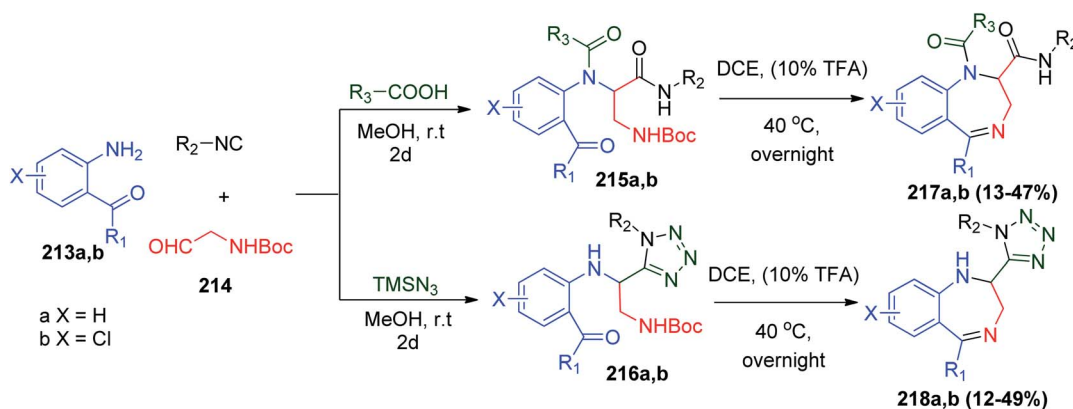
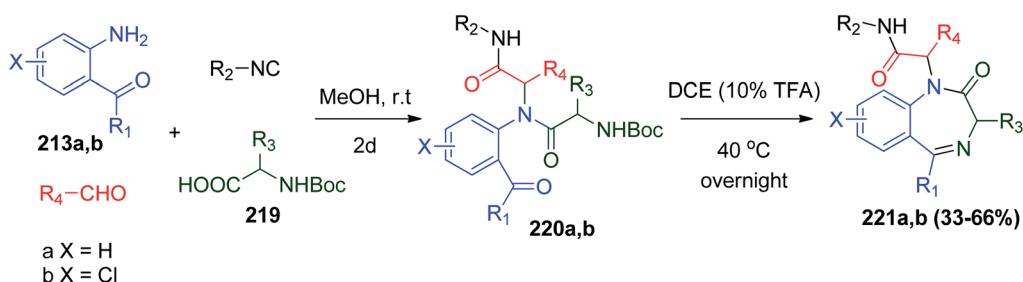
208a–d. After the formation of Ugi products **208a–d**, the corresponding acylpyrroles **209** were obtained in the presence of camphorsulfonic acid (CSA) under reflux. Similarly, the basic cleavage of the Fmoc group by DBU led to the formation of the desired spin-labeled DKPs **210a–i** (Scheme 44).¹⁰⁶

3.4 Synthesis of seven-membered heterocyclic compounds

Benzodiazepines (BDZs) show a wide range of applicability as biologically active structures, where they are used as anti-anxiety drugs due to their ability to slow the central nervous system. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA_A receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties¹⁰⁷ or antitumor drugs.¹⁰⁸ Both Valium **211** and Xanax **212** are the best known biologically active BDZs (Fig. 5).¹⁰⁹

Also, several 1,4-benzodiazepine (BDZ) scaffolds **217a** and **b** and **218a** and **b** were synthesized using anthranilate **213a** and **b** as an amine component for Ugi-4CR together with the isocyanide Boc-glycinal **214**, and a carboxylic acid with the UDC protocol followed by deprotection of the Boc group by TFA in 1,2-dichloroethane (DCE), respectively. Subsequently, the free amine group is condensed with the orthogonal ester group to form the 1,4-diazepine ring in the third step (cyclization) (Scheme 45).¹¹⁰ Alternatively, using trimethylsilylazide instead of carboxylic acid affords 2-tetrazolo substituted 1,4-benzodiazepines **218a** and **b**.¹¹⁰

Subsequently, a series of *N*-Boc-amino acids **219** were subjected to the same protocol for the synthesis of 1,4-

Scheme 45 Synthesis of 1,4-benzodiazepines derivatives **217a** and **218b** using Boc-glycinal **214**.Scheme 46 Synthesis of 1,4-benzodiazepine-2-one derivatives **221a** and **b** using *N*-Boc-amino acids **219**.

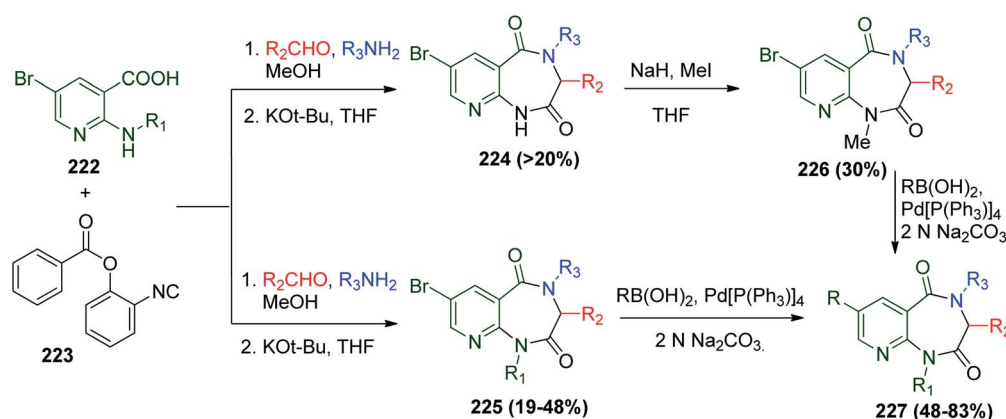
benzodiazepines-2-one derivatives **221a** and **b**, which are abundant in the protein–protein interaction interface (Scheme 46).¹¹⁰

On the other hand, another protocol was reported to synthesize pyridodiazepinediones by utilizing the Ugi reaction as a key step using 2-isocyanophenyl benzoate **223** and nicotinic acid derivatives **222**. The Ugi bis-amide was obtained in poor yield using this method, and thus the pyridodiazepinediones **224** and **225** were formed after treatment of the crude mixture of Ugi reaction with KOt-Bu in dry THF. When R₁ is a butyl or benzyl group, another step including Suzuki cross-coupling reaction is needed to afford product **227**. In the case of **224**, methylation of the NH– group was necessary to obtain **226**, which in turn may engage to Suzuki reaction to obtain the tetra-substituted pyridodiazepinedione scaffolds **227** (Scheme 47).¹⁰⁹

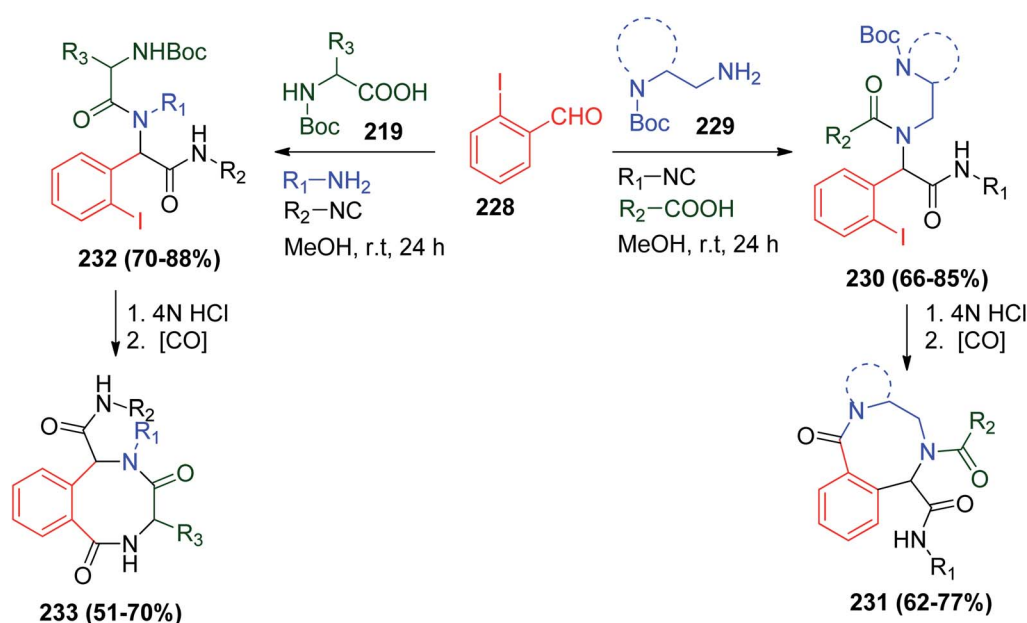
A different series of novel bicyclic and tricyclic macrolactams were synthesized using a methodology similar to the UDC

method known as Ugi-deprotection–carbonylation/intramolecular amidation. This strategy based on the use of bi-functional acids **219** or bi-functional amines **229** with *o*-iodobenzaldehyde **228** and different isocyanides to afford Ugi-protected bis-amides **230** and **232**, which are transformed into macrolactams **231** or **233** *via* Boc deprotection followed by carbonylation/intramolecular amidation sequential reactions (Scheme 48).¹¹¹

Further, the interesting synthesis of BDZs was applied by combining the Ugi reaction and S_NAr chemistry. In the U-4CR of *N*-Boc- α -aminoaldehydes **234**, 2-fluoro-5-nitrobenzoic acid (**235**) as an electrophilic component with amines and isocyanides were used to give Ugi product **236**. Notably, the scavenging resins PS-tosylhydrazine (PS-TsNHNH₂) and PS-diisopropylethylamine (PS-DIEA) were utilized for purification, where they could remove excess aldehyde or unreacted acid, while PS-morpholine acted as a proton scavenger. Indeed, this protocol represents an



Scheme 47 Synthesis of tetra-substituted pyridodiazepinedione 224–227.



Scheme 48 Synthesis of macrolactams **231** and **233**.



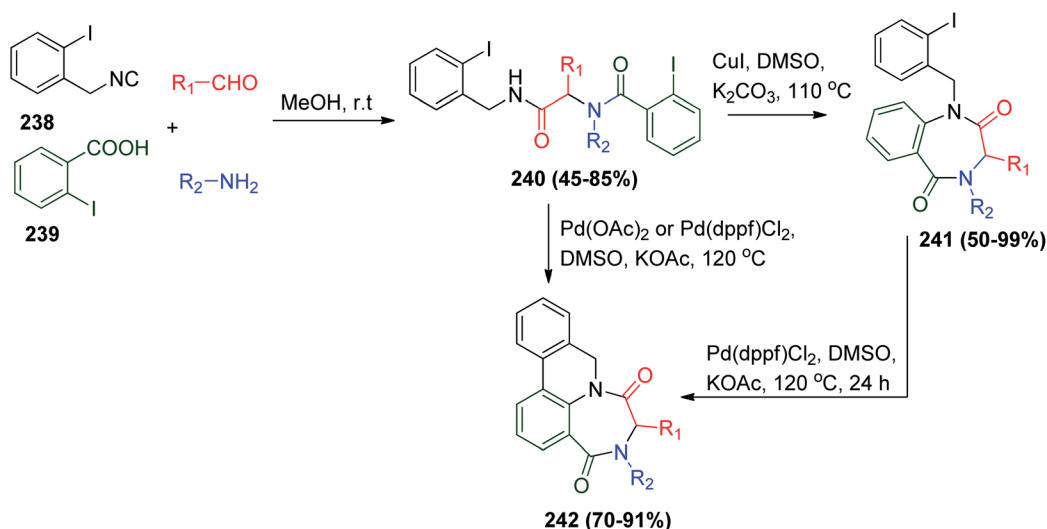
Scheme 49 Synthesis of BDZs **237** via UDC/ S_NAr strategy.

additional instance of the UDC strategy, and hence, after Boc group removal by TFA, with aid of PS-morpholine, cyclization occurs to give desired benzodiazepines **237** by elimination of HF (Scheme 49).¹¹²

On the other hand, transition metal catalysis plays an important role in the Ugi reaction, affording different strategies to obtain an increasing number of novel structures.^{113,114} Zhu and co-workers reported the palladium- and copper-catalyzed synthesis of 1,4-benzodiazepine-2,5-diones **241** and ring-fused dihydroazaphenanthrenes **242** via U-4CR as a key step using *o*-iodophenylisocyanide **238** and *o*-iodobenzoic acid **239** with other Ugi starting materials followed by catalytic treatment of the bis-amide **240** with Cu(I)-catalyst to give 1,4-benzodiazepine-2,5-dione **241** or using Pd(II)-catalyst to give ring-fused dihydroazaphenanthrenes **242**. Also, the conversion of **241** to **242** could be achieved easily through Pd(II) catalysis (Scheme 50).¹¹⁵

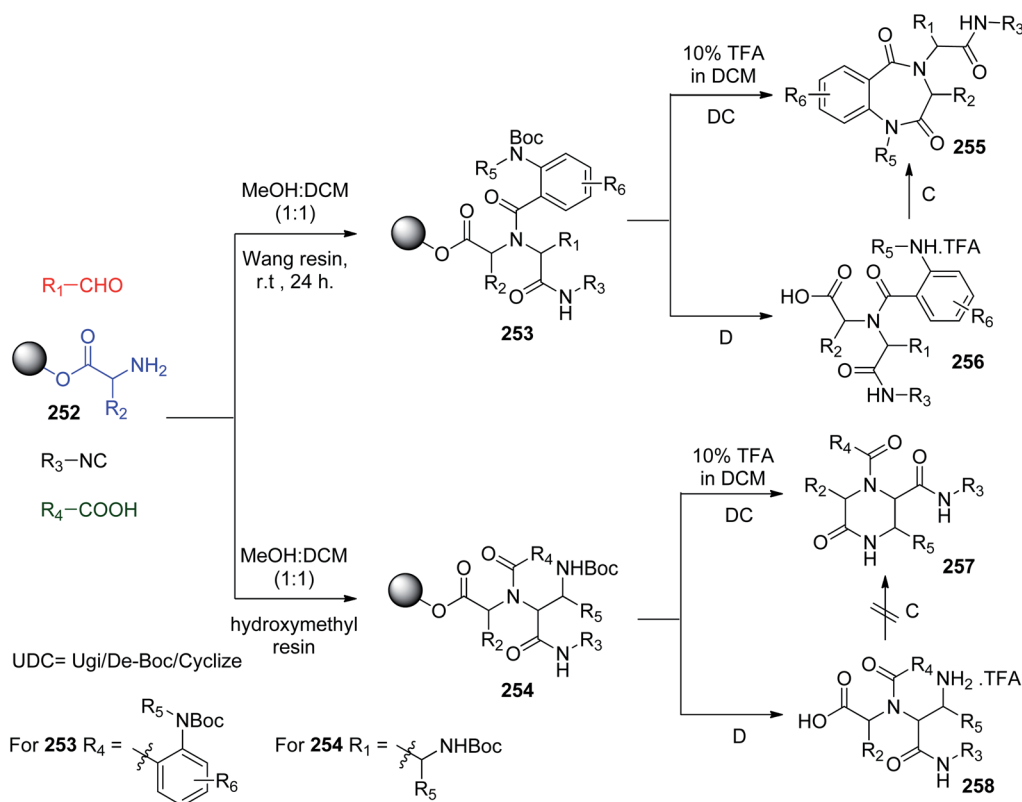
In another strategy to synthesize the biologically active BDZ derivatives, a series of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones **244** or **245** using the Ugi reaction in the presence of the two-electron reducing agent Fe(0)/NH₄Cl with *E*- α,β -unsaturated carboxylic acid **243** and microwave irradiation afforded the target products **244** or **245** without obtaining the Ugi linear bis-amide (Scheme 51).¹¹⁶ However, in the absence of microwave irradiation or any heat sources in the one-pot protocol, only the linear bis-amide Ugi product was obtained.¹¹⁶

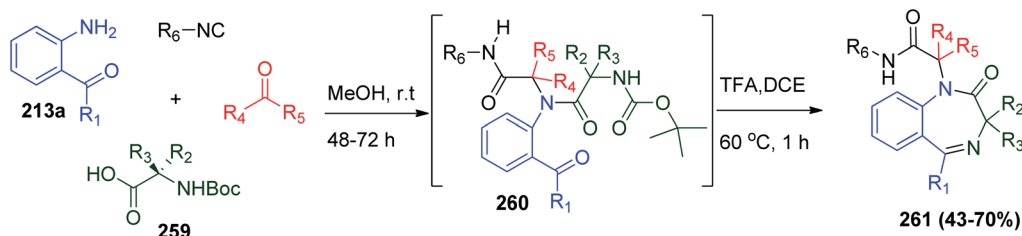
A post-Ugi reductive aza-Michael reaction was performed using isopropyl aldehyde **6**, *o*-nitrobenzylamine **246**, benzyl isocyanide **247** and (*E*)-fumaric acid monoethyl ester **248**. It is worth mentioning that at high microwave intensity, a one-pot 6-*exo* aza-Michael cyclization occurred to afford 2,5-diketopiperazines **249** and **250**, while in the case of a decreasing microwave intensity, only BDZ **251** was formed, as illustrated in Scheme 52.¹¹⁶ Moreover, Ugi reaction using (*E*)-fumaric acid monoethyl

Scheme 50 Synthesis of 1,4-benzodiazepine-2,5-diones **241** and ring-fused dihydroazaphenanthrenes **242** via U-4CR.

Scheme 51 Synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-one **244** or **245**.

Scheme 52 Microwave intensity controls the pathway selectivity of aza-Michael cyclization.

Scheme 53 Synthesis of BDZs **255** and ketopiperazines **257** in the solid phase via UDC.



Scheme 54 Synthesis of 1,4-benzodiazepin-2-one derivatives **261** using *N*-Boc amino acid **259** via UDC.

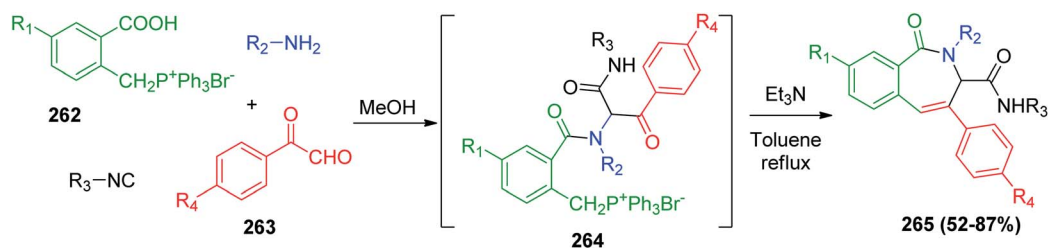
ester **248** gives a series of 2,5-diketopiperazines or 2-azaspiro [4.5]deca-6,9-diene-3,8-diones derivatives in a single synthetic operation under the influence of microwaves with complete control of pathway selectivity.¹¹⁷

Some resins such as Wang resin and hydroxymethyl resin have been utilized in the two-step solid phase synthesis of the biologically active ketopiperazines and BDZs through the UDC (Ugi/Boc-deprotect/cyclize) strategy. The reaction of *N*-Boc-anthranilic acids or *N*-Boc- α -amino aldehydes with resin-bound α -amino acids **252** for the synthesis of 1,4-benzodiazepine-2,5-diones **255** and ketopiperazines **257** via both Wang resin and hydroxymethyl resin, respectively, as illustrated in Scheme 53,¹¹⁸ was performed via the deprotection/cyclization of resin-bound Ugi products **253** and **254**.¹¹⁸

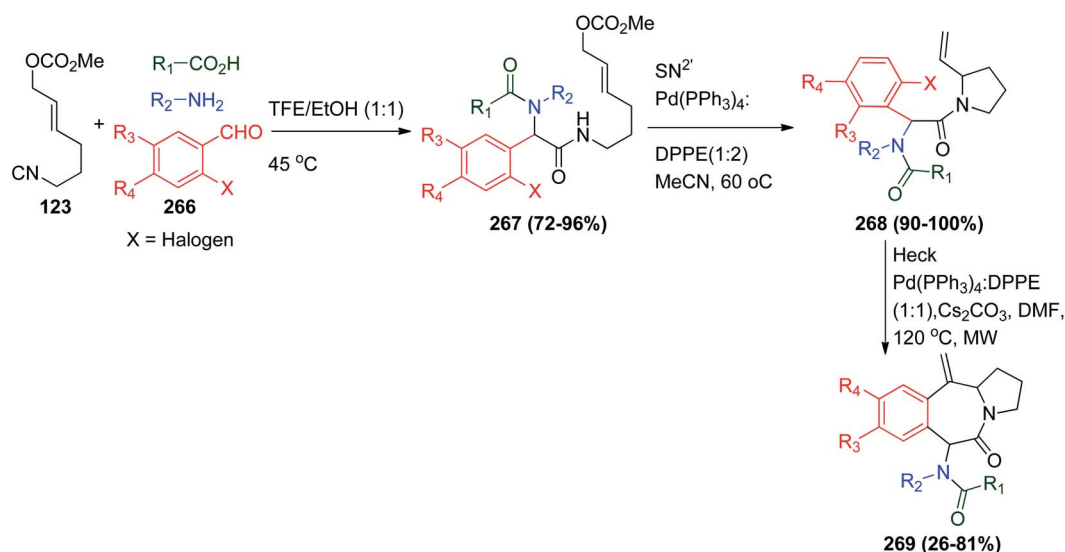
Furthermore, the UDC strategy dependent on the use of *N*-Boc-protected amino acid **259** with 2-aminobenzoyl derivatives **213a** to obtain linear Ugi bis-amide **260** in methanol, and subsequent deprotection-cyclization process to obtain functionalized BDZ scaffolds **261** was reported (Scheme 54).¹¹⁹

The one-pot synthesis of substituted 2,3-dihydro-1*H*-2-benzazepin-1-ones **265** via U-4CR/Wittig reaction was developed, where phosphonium salt **262** was introduced into U-4CR as the acidic partner with *p*-substituted arylglyoxals **263**, amine and isonitrile to afford **264**, which were converted to 2,3-dihydro-1*H*-2-benzazepin-1-ones (**265**) via the intramolecular Wittig reaction in the presence of triethyl amine Et_3N (Scheme 55).¹²⁰

The combination of the Ugi reaction, S_N2' cyclization and intramolecular Heck reaction gave natural product-like



Scheme 55 One-pot synthesis of 2,3-dihydro-1*H*-2-benzazepin-1-ones **265**.



Scheme 56 Synthesis of benzo[d]pyrrolo[1,2-*a*]azepin-5(6*H*)-ones **269** via Ugi-Heck reactions.



Scheme 57 Synthesis of amino-triazoloazepinone (Ata) 272 via Ugi/Huisgen cycloaddition.

compounds of polycyclic heterocyclic-containing benzo[*d*]pyrrolo[1,2-*a*]azepin-5(6*H*)-one analogues **269** in excellent yields. The protocol was achieved using unsaturated isonitrile **123**, which carries a methyl carbonate that acts as a leaving group in the cyclization, and several *o*-halobenzaldehydes **266** suitable for the Heck step were obtained. It is important to note that the Ugi conditions were different from the classical conditions, where the solvent mixture of trifluoroethanol (TFE) and ethanol was used in an equivalent ratio at 45 °C, while both the S_N2' cyclization and intramolecular Heck steps were carried out using the optimized Pd(0)-catalyzed conditions in the presence of 1,2-diphenylphosphinoethane (DPPE) as the ligand (Scheme 56).¹²¹

In the last decades, several methods have been reported for the synthesis of amino-triazoloazepinone (Ata) analogues, including the use of ruthenium catalyst followed by lactimization process or heating in the presence of DMF as a solvent.¹²² It was investigated if amino-triazoloazepinone could be synthesized *via* U-4CR followed by [3 + 2] Huisgen thermal cycloaddition. This procedure has the advantages of the minimum number of synthetic steps, no additives or catalysts, high yield

and low-cost solvents.¹²³ Condensation between azidoamino acid **270**, aldehydes, propargylamine **110** and several aliphatic and aromatic isonitriles gave the desired (Ata) **272** (Scheme 57).¹²³

3.5 Synthesis of fused six-membered heterocyclic compounds

A series of coumarin-based structures was synthesized by coupling the Ugi and Knoevenagel reactions to report a powerful pathway to one-pot five-component Knoevenagel–Ugi adducts. Coumarin derivatives have been reported to exhibit valuable biological behaviors, for instance, anticancer,¹²⁴ antiviral,¹²⁵ anti-Alzheimer's,¹²⁶ and anti-HIV activities.¹²⁷ The synthesis of coumarin-based α -acyl amino amides **277** in a one-pot five-component Knoevenagel–Ugi approach was achieved by the reaction among 2,2-dimethyl-1,3-dioxane-4,6-dione (**273**), which known as Meldrum's acid, salicylaldehyde, **274**, aniline **275**, benzaldehyde derivatives **276** and isonitrile in ethanol (Scheme 58).²

As mentioned before, the Ugi reaction is an efficient route to synthesize several heterocyclic compounds. Another fruitful

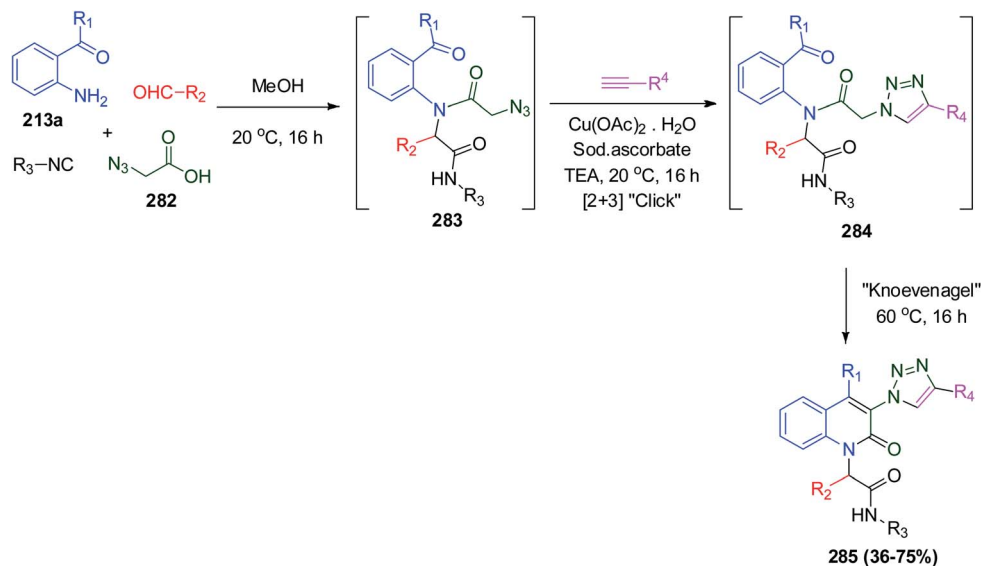


Scheme 58 Synthesis of coumarin-based α -acyl amino amides **277** via Knoevenagel–Ugi strategy.



Scheme 59 Synthesis of benzoxazinones **281** via U-4CR/Mitsunobu cyclization.





Scheme 60 Synthesis of 1,2,3-triazolo-quinolinone **285** via Ugi "click"–Knoevenagel condensations.

strategy represents the synthesis of benzoxazinone analogues via U-4CR/Mitsunobu cyclization starting from *o*-amino phenols **278**, α -hydroxy acids **279**, aldehydes and isocyanides to give Ugi product **280** followed by Mitsunobu cyclization using DEAD/ PPh_3 protocol to afford benzo[*b*][1,4]oxazin-3-ones **281** in two high yielding steps (Scheme 59).¹²⁸ It is worth mentioning that benzo[*b*][1,4]oxazin-3-ones **281** represent a drug-like structure involved in many pharmaceutical compounds.^{129,130}

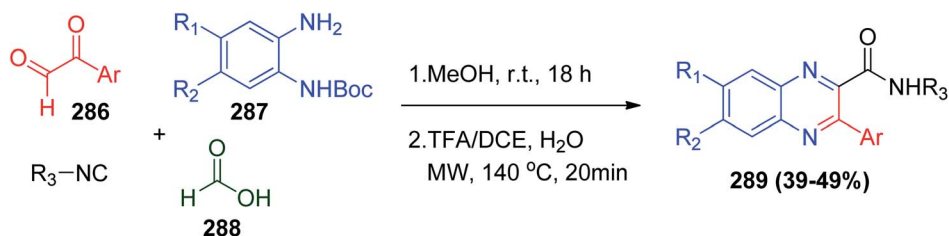
Moreover, the preparation of 3-triazolyl-quinolin-2-(1*H*)-one analogues was carried out via the combination of Ugi, click and Knoevenagel reactions. The Ugi reaction between *o*-acylanilines **213a**, 2-azidoacetic acid **282**, and different aldehydes and isocyanides affords azido-decorated Ugi products **283**, which are subsequently reacted with terminal alkyne derivatives under the influence of Cu(I)-catalysis via [3 + 2] cycloaddition to give 1,2,3-triazolo derivatives **284**, followed by intramolecular Knoevenagel fashion to afford the 1,2,3-triazolo-quinolinone scaffold **285** (Scheme 60).¹³¹

The first synthesis of quinoxaline derivatives via the Ugi reaction was reported by Ayaz and co-workers utilizing aryl glyoxal derivatives **286**, *N*-Boc-*o*-phenylenediamine derivatives **287**, and formic acid **288**, where the reaction proceeds smoothly in methanol at room temperature to obtain the linear Ugi product, which is easily cyclized in the presence of TFA/DCE solution and a catalytic amount of water with microwave

irradiation at 140 °C for 20 min to afford quinoxalines **289** (Scheme 61).¹³²

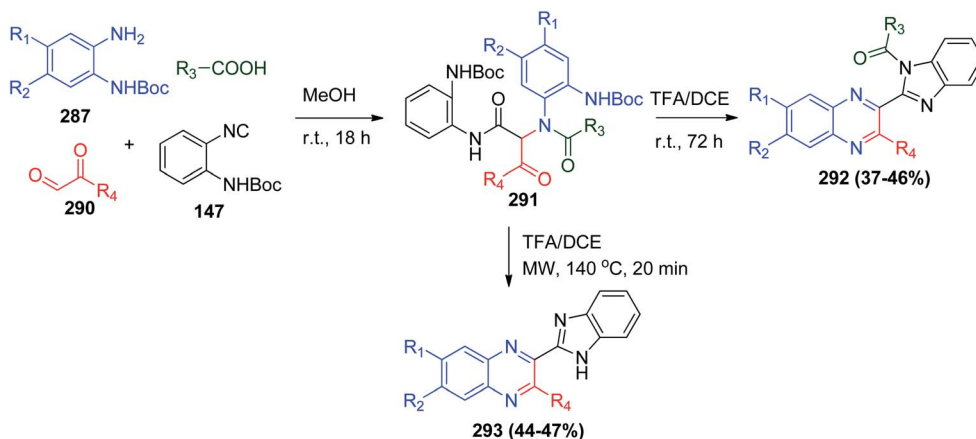
Searching for expansion of the structural diversity under the same reaction conditions, it was reported that the use of *o*-*N*-Boc-phenylisocyanide (**147**) facilitates access to 2-benzimidazolylquinoxalines **292** and **293**, in which the combination between the benzimidazole and quinoxaline ring can give an opportunity to improve their biological activity. Also 2-benzimidazolylquinoxalines **292** can be obtained during this reaction when *ortho*-substituted aromatic carboxylic acids are used (Scheme 62).¹³²

Through the same one-pot protocol, Yan, Ding and co-workers successfully synthesized multi-substituted quinoxalin-2(1*H*)-ones via a U-4CR/catalytic aza-Wittig reaction. They developed a new strategy to synthesize their target compounds through the Ugi reaction between 2-aminobenzoyl azides **175**, aldehydes, ketoacids **294**, and isocyanides in the presence of a catalytic amount of the same phosphorus catalyst they used before, 3-methyl-1-phenyl-2-phospholene 1-oxide (**178**), to produce quinoxalin-2(1*H*)-ones **297** as the target product (Scheme 63).¹³³ With regard to other heterocycles, quinoxalin-2(1*H*)-one derivatives are classified as crucial pharmacologically active compounds,¹³³ where they act as antidiabetic agents,¹³⁴ anti-inflammatory agents¹³⁵ and antibacterial agents.¹³⁶ It has been noted that Ding's protocol guarantees high atom



Scheme 61 Synthesis of quinoxaline derivatives **289** via Ugi reaction.





Scheme 62 Synthesis of 2-benzimidazolylquinoxalines derivatives **292** and **293** via Ugi reaction.

efficiency, mild reaction conditions, ready availability of starting materials and yield of up to 90%.^{89,133}

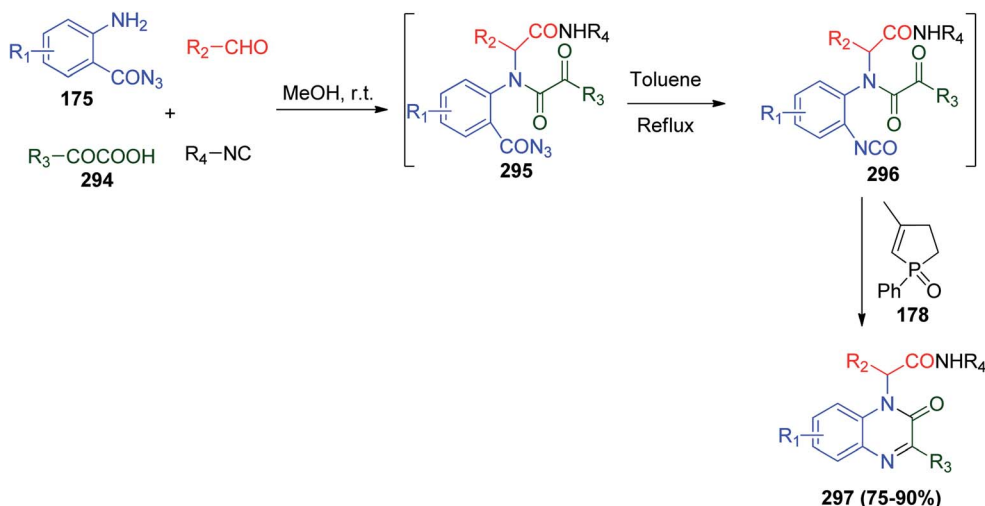
Several bioactive natural products contain quinazolinone moieties, which have promising biological properties such as antibacterial,¹³⁷ antileishmanial,¹³⁸ anti-HIV,¹³⁹ anti-inflammatory,¹⁴⁰ and antifungal¹⁴¹ activities. Balalaie and co-workers successfully synthesized pseudo-peptides containing a quinazolinone moiety *via* U-4CR¹⁴² using 3-amino-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic acid derivatives **298**.¹⁴² The Ugi reaction using **298** with different aromatic aldehydes, primary amines and isonitriles gave the desired pseudo-peptides, which contain quinazolinone moiety **299** (Scheme 64).¹⁴² Notably, the major diastereoisomer was observed in crystalline form and the minor one remained dissolved in ethanol.

A two-step solution phase protocol for the synthesis of dihydroquinazoline scaffolds was reported, where the method is based on the *trans*-modification of the Ugi products with acid treatment to obtain new highly functionalized drug-like dihydroquinazolines.^{129,143} The Ugi reaction with isonitrile, carboxylic acid, aldehyde and mono-Boc protected 2-

aminobenzylamines afford Ugi product **302**, which can be treated by acid to obtain the target products **304** (Scheme 65, Path A).¹⁴⁴ Notably, changing the position of the Boc protecting group in the used amine can modify the resulting product from 1,4-dihydroquinazoline **304** to 3,4-dihydroquinazoline **305** (Scheme 65, Path B).¹⁴⁴

3.6 Synthesis of polycyclic heterocyclic compounds

In the same context, the aza-Wittig reactions have received considerable attention as a powerful tool to synthesize heterocycles.^{145,146} Recently, the Ugi reaction followed by a post-condensation Staudinger-aza-Wittig reaction was proven to be beneficial in the synthesis of several biologically active heterocycles.^{147,148} Ding and co-workers reported the first cyclization of the Ugi product to afford an indolo[1,2-*c*]quinazoline ring system *via* the nucleophilic addition of the methine group to the carbonyl group or what it is known as the Staudinger-aza-Wittig-nucleophilic addition reaction,¹⁴⁹ and the Ugi reaction using *o*-acylaniline **213a**, *o*-azidobenzaldehyde **306**, carboxylic acid



Scheme 63 Synthesis of quinoxalin-2(1*H*)-ones **297** via a U-4CR/catalytic aza-Wittig reaction.



Scheme 64 Synthesis of pseudo-peptides containing quinazolinone moiety **299** via U-4CR.Scheme 65 Synthesis of dihydroquinazolines **304** and **305** via Ugi reaction.

and isocyanide was carried out in methanol at room temperature to give Ugi products **307** in fair yield. Ugi products **307** were further reacted with triphenyl phosphine followed by heating in toluene to give the desired indolo[1,2-*c*]quinazolines **310** (Scheme 66).¹⁴⁹

Furthermore, the synthesis of fused dihydroquinazoline-benzodiazepine tetracycles was reported by a similar route but with different conditions utilizing propyl aldehyde **311**, butyl isocyanide **312**, *N*-Boc-protected anthranilic acid **313** and 2-amino-*N*-Boc-protected benzylamines **300** to afford the Ugi product **314**, which was treated by acid to get the target products

Scheme 66 Synthesis of indolo[1,2-*c*]quinazolines **310** via the sequential (U-4CR)–Staudinger–aza-Wittig–nucleophilic addition reaction.



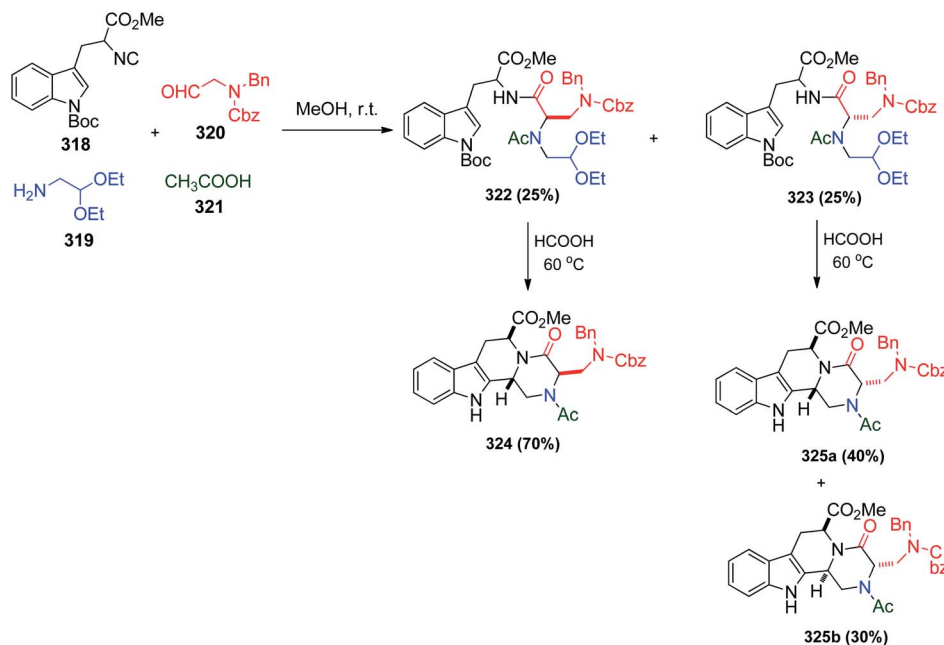
Scheme 67 Synthesis of dihydroquinazoline-benzodiazepines **316** and **317**.

(Scheme 67, Path A).¹⁴⁴ The imine was pre-formed in DCM in the presence of magnesium sulphate followed by microwave irradiation at 120 °C for 10 min to get the desired Ugi product, which was deprotected by an acid to form tetracyclic adduct **316**, and with the same steps and reactants **317** was afforded by utilizing amine **301** instead of **300** (Scheme 67, Path B).¹⁴⁴

In continuation of our study on the Ugi reaction and its post-condensations, Ugi reaction followed by the Pictet-Spengler reaction was used to synthesize useful heterocycles such as 1,2,3,4-tetrahydro- β -carboline (THBC), which are based on tetracyclic peptidomimetics and considered tryptophan analogues. These analogues (*e.g.* THBC) are known to bind with various receptor sites such as serotonin to cause inhibition of monoamine oxidase A enzyme.¹⁵⁰ Moreover, some of the tetracyclic β -carbolines were found to have antimalarial characters¹⁵¹

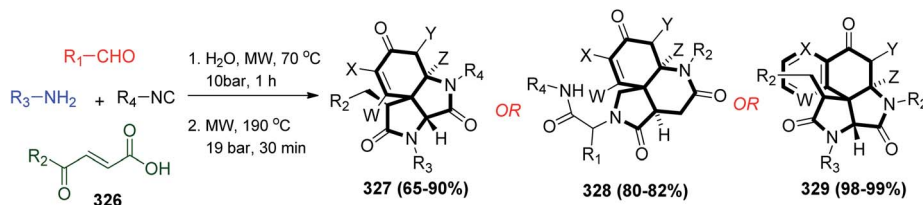
or act as selective inhibitors in the anticancer field.¹⁵² The use of 2-aminoacetaldehyde **320** as a carbonyl partner in the Ugi reaction was investigated for the first time by Lesma and co-workers. Their target was to condense *N*-protected tryptophan-derived isonitrile **318**, *N*-protected-2-aminoacetaldehyde **320**, aminoacetaldehyde diethylacetal **319** and acetic acid **321** as a carboxylate nucleophile to obtain the desired Ugi products **322** and **323**. The cyclization of both **322** and **323** was carried out smoothly in the presence of formic acid at 60 °C to afford **324** and **325a** and **b**, respectively (Scheme 68).¹⁵³

Furthermore, an unusual protocol was developed utilizing the Ugi reaction to synthesize azaspiro compounds, which are natural product-like compounds. The combination of the Ugi and Michael reaction afforded a unique protocol known as the Ugi/Michael/aza-Michael reaction (UMAM), which was used to

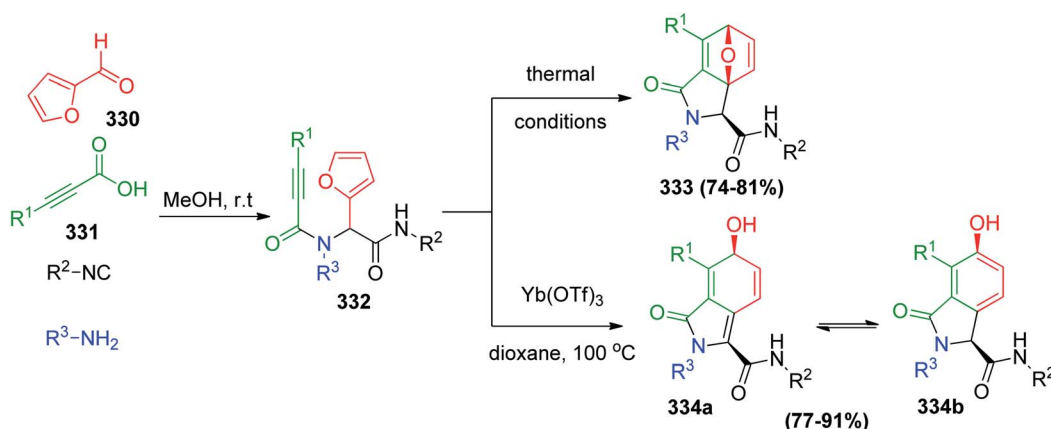


Scheme 68 Synthesis of 1,2,3,4-tetrahydro- β -carboline **324** and **325a** and **b** via U-4CR/Pictet-Spengler reaction.





Scheme 69 Synthesis of azaspiro compounds 327–329 via Ugi reaction.



Scheme 70 Ugi MCR reaction followed by the intramolecular Diels–Alder reaction of furan (IMDAF).

synthesize fused azaspiro tricycles and azaspiro tetracycles in good yield using γ -keto- α,β -unsaturated carboxylic acid and different types of acids amines, aldehydes and isocyanides under microwave irradiation, in the presence of water as the solvent (Scheme 69).¹⁵⁴

Paulvannan illustrated Ugi MCR reaction followed by intramolecular Diels–Alder reaction of furan (IMDAF)¹⁵⁵ to build natural product-like libraries. Ugi condensation of 2-furaldehyde 330, acetylenic acids 331 as dienophiles, isocyanides and amines generated acetylenic amides 332 (Scheme 70).¹⁵⁵ Transformation of 332 to the oxabicyclo[2.2.1]heptadiene derivatives 333 was accomplished under thermal conditions. However, it was observed that when the Ugi products were allowed to stand at room temperature, they were partially converted to the corresponding cycloadduct 333. In contrast, exposure of 332 to catalytic Yb(OTf)₃ in 1,4-dioxane at high temperatures cleanly converted it to isoindolinone 334a in tautomerism with 334b.¹⁵⁶

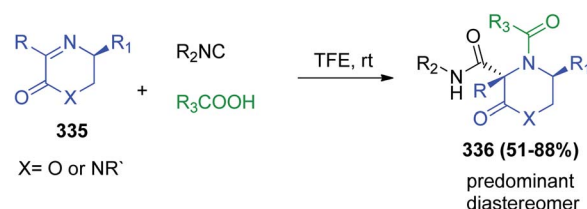
using chiral cyclic aldimines or ketoimines 335. The chiral imines showed promising stereo induction for the new chiral center of the Ugi products, and predominantly *trans*-isomers were obtained in most cases with good diastereoselectivity of the new stereocenter at C-3 in the products (Scheme 71).¹⁶⁰

The catalyzed enantioselective Ugi-4CR or Ugi-3CR with high optical purity was accomplished recently using chiral phosphoric acids (CPAs), which are diesters derived from the 1,1'-bi-2-naphthol (BINOL) or (*S*)-1,1'-spirobiindane-7,7'-diol (SPINOL) motifs possessing chiral backbones. CPA are used in asymmetric catalysis due to their enhanced acidity compared to carboxylic acids, which is perceived to accelerate the kinetics of the enantioselective Ugi reaction. Consequently, the chiral phosphoric acid CPA 338-catalyzed enantioselective Ugi four-center, three-component reaction of isocyanides, anilines, and 2-formylbenzoic acids 337 was employed for the synthesis of isoindolinones 339 in excellent yields. Chiral isoindolinone derivatives are considered a key structural motif in many bioactive natural products such as (*S*)-(+)-lennoxamine (340)

4 Enantioselective Ugi reaction

Enantioselective Ugi-4CR or Ugi-3CR with stereochemical control is appropriate for molecular diversity of α -acylaminoamide with applicable synthesis in drug discovery since it facilitates rapid access to diverse libraries of biologically important molecules and natural products, which demand multistep synthetic pathways.^{157–159}

A series of novel chiral morpholin-2-one-3-carboxamide derivatives or ketopiperazine-2-carboxamide compounds 336 was prepared *via* the asymmetric Ugi three-component reaction



Scheme 71 Synthesis of chiral morpholin-2-one-3-carboxamide derivatives 4 and ketopiperazine-2-carboxamide.



Scheme 72 Synthesis of chiral isoindolinones **339**.

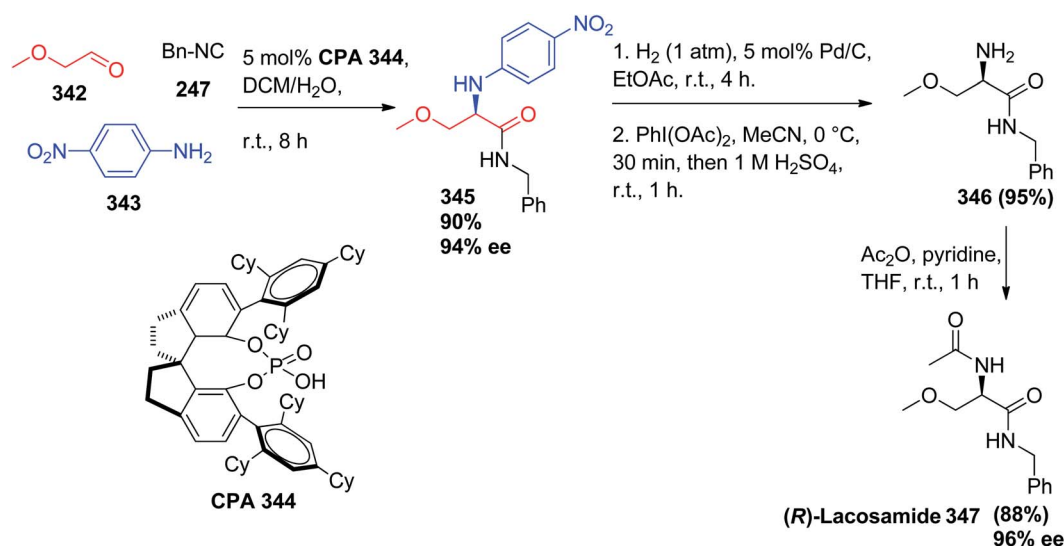
and medically relevant compounds such as (*R*)-pazinaclone (**341**), a sedative and anxiolytic drug (Scheme 72).^{161,162}

Alternatively, lacosamide is a medication used in the adjunctive treatment of partial-onset seizures and diabetic neuropathic pain. It is administered orally or intravenously and sold under the brand name Vimpat.¹⁶³ α -Amino amide derivatives were prepared *via* a catalytic enantioselective three-component Ugi reaction utilizing SPINOL-derived phosphoric acid with bulky 2,4,6-tricyclohexylphenyl groups at the 6,6' positions **344** in good to excellent yields (62% to 99%) and enantiocontrol (81% to >99% enantiomeric excess). This method was used to prepare the anticonvulsive drug (*R*)-lacosamide **347** using 2-methoxy acetaldehyde (**342**), 4-nitroaniline (**343**), and benzyl isocyanide **247**, affording the Ugi product **345** in 90% yield and 94% ee, which was transformed into **346** in 95% yield after dearylation *via* sequential reduction and

oxidation. Acylation of the chiral amine **346** afforded (*R*)-lacosamide **347** in 88% yield and 96% ee (Scheme 73).¹⁶⁴

Alternatively, the enantioselective synthesis of 2-(1-aminoalkyl)-5-aminooxazoles **350** from α -isocyanoacetamides (**348**), aldehydes, and anilines was accomplished using U-3CR (Scheme 74) and CPA catalyst by stirring a toluene solution of aldehydes, anilines, and α -isocyanoacetamides (**348**) ($c = 0.05$ M, -20 °C) in the presence of CPA **349** (20 mol%), affording the target oxazoles **350** in excellent yields with enantioselectivities of up to 90% ee.¹⁶²

Recently, Houk, Tan and coworkers constructed α -acylaminoamide compounds by combining the traditional starting materials in a one-pot reaction. Stereochemistry control of the enantioselective four-component Ugi reaction was achieved using a variety of chiral phosphoric acid derivative catalysts CPA **351** and **344** and the type of aldehyde (aryl or alkyl), providing

Scheme 73 Enantioselective synthesis of (*R*)-lacosamide (**347**) via Ugi-3CR.

Scheme 74 CPA 349-catalyzed enantioselective reaction of aldehydes, amines, and α -isocyanoacetamides.

Fig. 6 Stereochemistry control of enantioselective four-component Ugi reaction.

more than 80 examples of α -acylaminoamides in good to excellent enantiomeric excess, as illustrated in Fig. 6.^{165,166}

5 Conclusion

In this review, we summarized the preliminary applications of the Ugi reaction in organic synthesis and pharmaceutical research during the last 20 years from 2000 to 2019 due to the amazing properties of the Ugi reaction. We have highlighted the use of the Ugi reaction to prepare a variety of linear or cyclic peptides with multifunctional structures, which have promising

biological activities. Also, the application of the Ugi reaction was extended to the synthesis of fused or unfused heterocyclic compounds with 5, 6, and 7-membered rings. Furthermore, the Ugi reaction is considered as a magic tool to prepare natural products with complex structures or stereochemistry with high enantioselectivity. However, despite the successful application of the Ugi reaction in the preparation of functional peptides, heterocyclic compounds, and natural products in the last two decades, there are still some limitations of the Ugi reaction that must be illustrated. The intolerable odor, difficulty in synthesis, relatively high price and sensitivity in acidic medium of

isonitriles are the major disadvantages, which limit its application for large-scale synthesis. Additionally, the functional modification of isocyanide is difficult, which also limits the modification of functional groups of peptides, heterocyclic or natural products. Accordingly, other MCRs may be used to overcome the limitations of Ugi reactions, such as the Mannich reactions, Povarov MCRs, Petasis reaction, and Biginelli reaction, for applications with different purposes. A future challenge is to complete the isocyanide MCR by summarizing the applications of the Passerini reaction in a separate perspective.

Conflicts of interest

There are no conflicts of interest to declare.

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