Review

Multicomponent reactions as an efficient and facile alternative route in organic synthesis and applications

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Abstract: Multicomponent reactions **(**MCRs) have been used for more than a century; since their discovery in 1850 by Strecker. To date, MCRs route is regarded as a beneficial strategy due to its capacity to quickly produce molecular diversity and structural complexity of interest for a variety of applications. Despite having famous MRCs such as the Ugi, Passerini, Biginelli, and Hantzsch, this review portrays the importance of MCRs in the synthesis of desired products towards applications such as medicinal purposes, sustainable chemistry, and polymerisation. MCRs provide advantages such as reducing the number of sequential multiple reactions to one step, atom economy, recyclable catalysts, mild conditions, preventing waste and reduce solvent use.

Keywords: Multicomponent reactions; medicinal chemistry; green chemistry; polymerization; synthesis

1. Introduction

Multicomponent reactions (MCRs), also known as one-pot reactions, that involve at least three or four reactants of interest to produce the desired single product that contains the building blocks of atoms from each of the reactants [1,2,3]. Figure 1, represents the overall practical idea of linear synthesis compared to MCRs, which depict at least four separate reactants (building blocks) coming together to generate a single product. MCRs are viewed as a practical strategy in synthetic chemistry and offer several advantages over conventional one- or two-component reactions by minimising the number of sequential multiple reactions necessary and frequently resulting in better yields [4,5,6]. The use of MCRs in organic synthesis towards medicinal chemistry, drug discovery, green chemistry, polymerisation and other related applications remains one of the better alternative routes for the synthesis and preparation of desired products.

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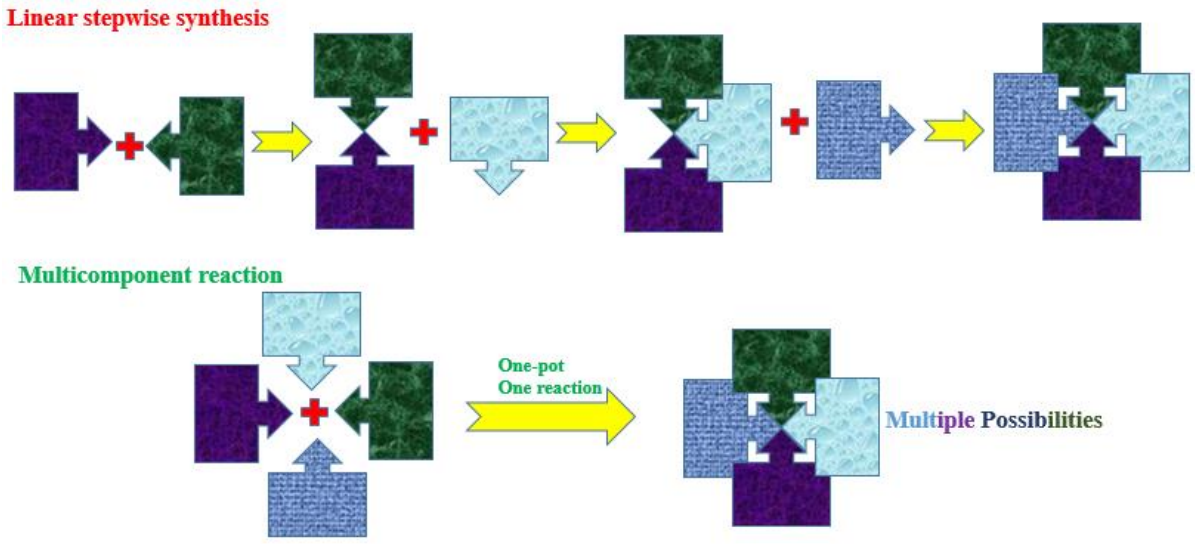

Figure 1. Linear stepwise synthesis *vs* multicomponent reactions.

Medicinal chemistry and drug development applications continue to gradually rely on the MCRs approach due to the ease and accessibility of preparing and synthesising desirable heterocyclic frameworks [7]. By producing complex compounds in a single step, MCRs have the interesting extra potential to significantly contribute to environmentally friendly pharmaceutical production methods and procedures [8]. MCRs greatly contribute to the reduction of the enormous amount of waste produced daily in pharmaceutical and industrial manufacturing as compared to sequential multistep reactions [9,10,11,12]. One of the recognised methods for enhancing "greenness" is the use of MCRs in the production of desired products in the pharmaceutical and industrial fields. The groundbreaking concept of alternative synthetic reaction schemes to reduce pollution and environmental risks that result from the conventional synthesis technique is conceptualised as green chemistry or sustainable chemistry. MCRs offer a feasible opportunity for the implementation of safe procedures and environmentally friendly manufacturing methods. In addition, multicomponent polymerisations (MCPs) have evolved from MCRs, and these processes produce polymers with well-defined structures, ordered sequences of monomer units, and several functions. MCRs continue to make wonders in synthetic chemistry since they are featured in interesting topics such as solid-phase synthesis, asymmetric catalysis, C-H functionalisation, and peptide synthesis. This review portrays organic synthesis, applications, and the elegant chemistry of MCRs in medicinal chemistry, sustainable chemistry, polymerisation, asymmetric catalysis, C-H functionalisation, and solid-phase peptide synthesis in the past six years (2018-2023).

2. Multicomponent reactions in synthesis and applications

2.1. Medicinal chemistry

Medicinal chemistry, biology and pharmacology play an important role in the intricate process of finding new medicines. Nevertheless, it inescapably depends on a crucial organic synthesis base to guarantee the availability of the necessary molecules. Since, from hit discovery through manufacture, this synthetic activity permeates all aspects of drug discovery/medicinal chemistry and has recently made tremendous strides [13,14]. A different approach to target synthesis is offered by MCRs, which are characterised by their "one-pot" reaction, the promotion of a very broad chemical space based on readily available basic building blocks, and the ability to tackle difficult sustainability-related issues. Consequently, MCR has the potential to be highly helpful in the identification and syn-

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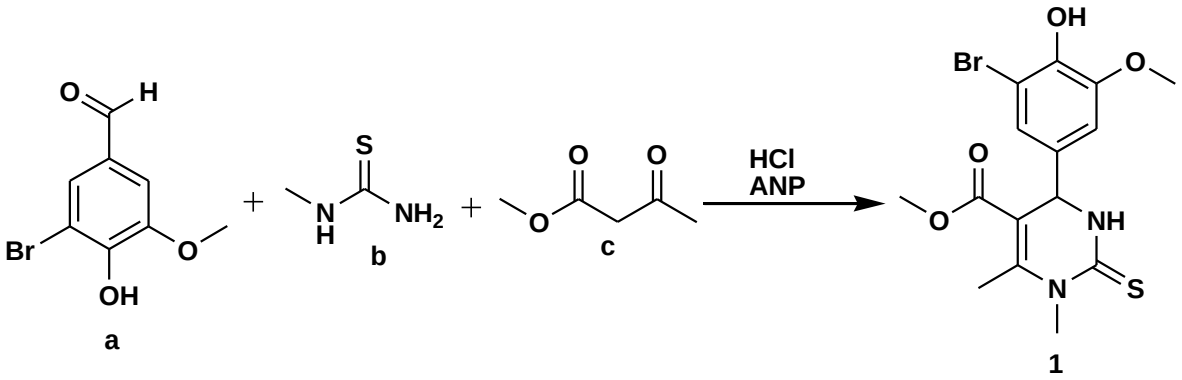
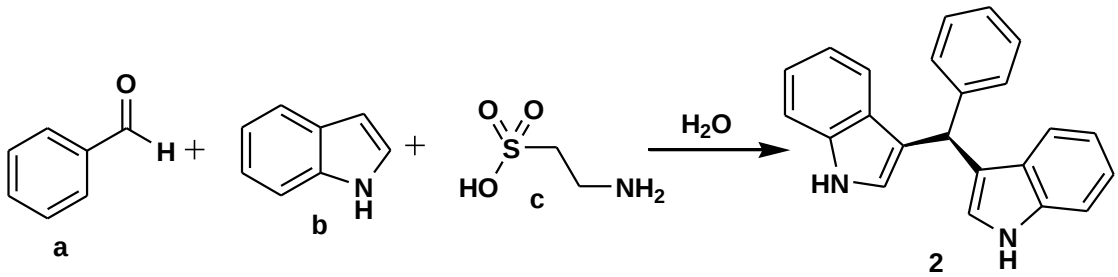
thesis of biologically active "drug-like" compounds. In a way, the interest is to cover specific instances of how MCR has been used in medicinal chemistry, including drug discovery, drug synthesis, screening libraries, and biopharmaceutical applications.

The biologically active tetrahydropyrimidines (THPMs) (**1**) derivatives were discovered after the three-component reaction (3CR) of vanillic aldehydes (**a**) with *N*-methylthiourea (**b**) and methyl acetoacetate (**c**) using 2-amino-1-(4-nitrophenyl)-1,3-propanediol (ANP) and hydrochloric acid, as demonstrated in Scheme 1[15]. It has been reported that these bioactive tetrahydropyrimidines (THPMs) exhibit good biological activities such as antimicrobial, anticancer, and glucosidase inhibitory effects. These compounds were further evaluated against five strains of bacteria and fungi, and the results were found to be effective.



Scheme 1. Synthesis of bioactive tetrahydropyrimidines (THPMs) derivatives.

The 3CR of *p*-methoxybenzaldehyde (**a**) and indole (**b**) in the presence of taurine (**c**) using water as a solvent under sonification gave rise to potential bioactive 3,3-bis(indolyl)methanes (BIMs) (**2**) and their derivatives as shown in Scheme 2 [16]. The in silico-based structure activity of 3,3-bis(indolyl)methanes (**2**) derivatives reveals their potential ability to bind antineoplastic drug targets and spindle motor protein kinesin Eg5.



Scheme 2. Synthesis of 3,3-bis(indolyl)methanes (BIMs).

Mali and co-workers reported the four-component reaction (4CR) of benzaldehyde (**a**) with malononitrile (**b**) in the presence of hydrazine hydrate (**c**) and ethyl acetoacetate (**d**) using taurine as catalyst with solvents such as water, ethanol, acetonitrile, and toluene for the synthesis of therapeutic dihydropyrano[2,3-*c*]pyrazoles (**3**), as shown in Scheme 3 [17]. The in silico analysis of dihydropyrano[2,3-*c*]pyrazoles demonstrated their potential to bind variants of dihydrofolate reductase in pathogenic *Staphylococcus aureus* strains.

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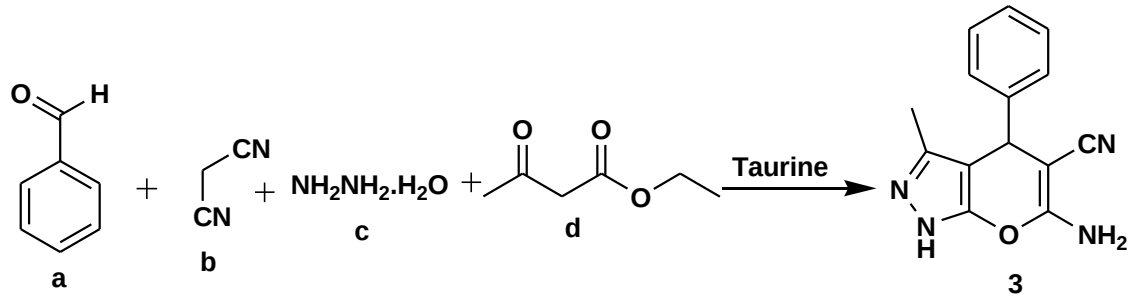
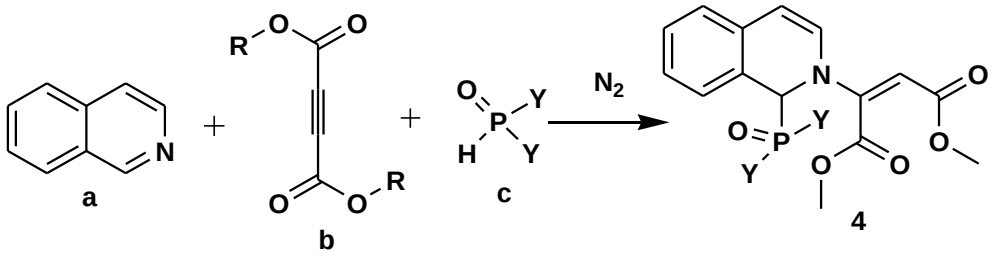


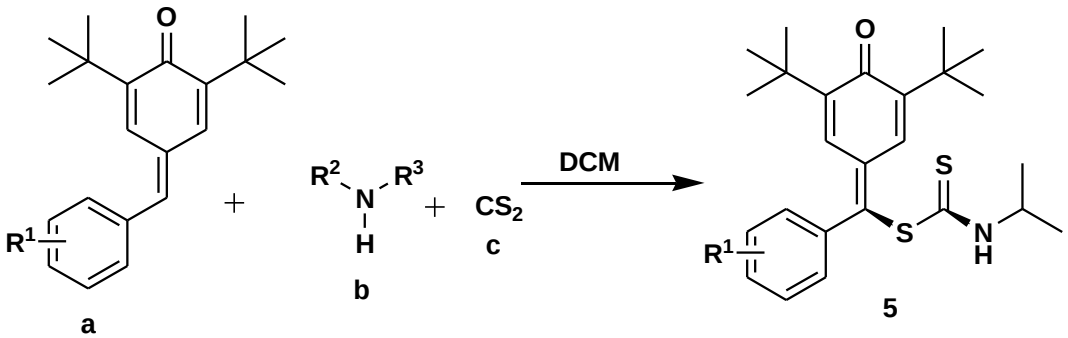
Scheme 3. Synthesis of therapeutic dihydropyrano[2,3-*c*]pyrazoles.

The biologically active arylphosphinoyl-functionalised dihydroisoquinoline (**4**) derivatives were synthesised by the 3CR of isoquinoline (**a**) with dialkyl acetylenedicarboxylates (**b**) and phosphine oxides (**c**) or ethyl phenyl-*H*-phosphinate under nitrogen atmosphere using acetonitrile as a solvent, as shown in Scheme 4 [18]. This set of compounds showed good activity against human promyelocytic leukemia (HL-60) cells and against *Bacillus Subtilis* gram-positive bacteria.



Scheme 4. Synthesis of arylphosphinoyl-functionalised dihydroisoquinoline derivatives.

Venkatesh and co-workers reported the 3CR of *para*-quinone methides (**a**) with amines (**b**) and carbon disulphide (**c**) using dichloromethane (DCM) as a solvent from 0 °C to room temperature for the synthesis of biologically active *S*-benzyl dithiocarbamates (**5**), as shown in Scheme 5 [19]. The biologically active compounds were attained in excellent yields and were reported to have some acetylcholinesterase (AChE) inhibitory and antioxidant activities.



Scheme 5. Synthesis of biologically active *S*-benzyl dithiocarbamates.

Groebke-Blackburn-Bienaymé 3CR (GBB-3CR) of the aminopyridine component (**a**) with aldehyde (**b**), and isocyanide (**c**) in dichloromethane and methanol as solvents under microwave at 120 °C in the presence of scandium triflate gave rise to the imidazo[1,2-*a*]pyridine-based (**6**) inhibitors as shown in Scheme 6 [20]. The synthesised imidaz-

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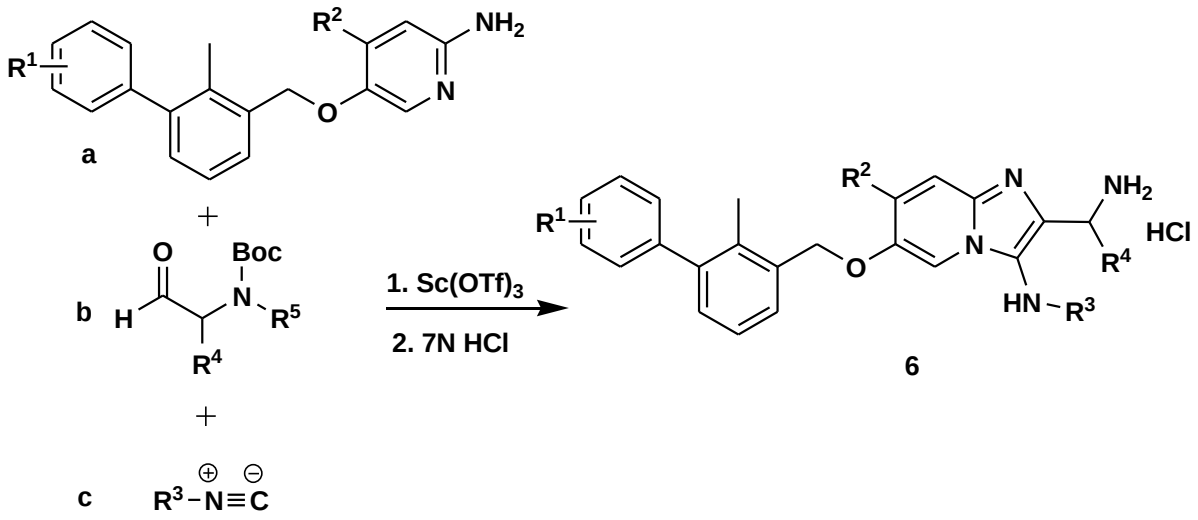
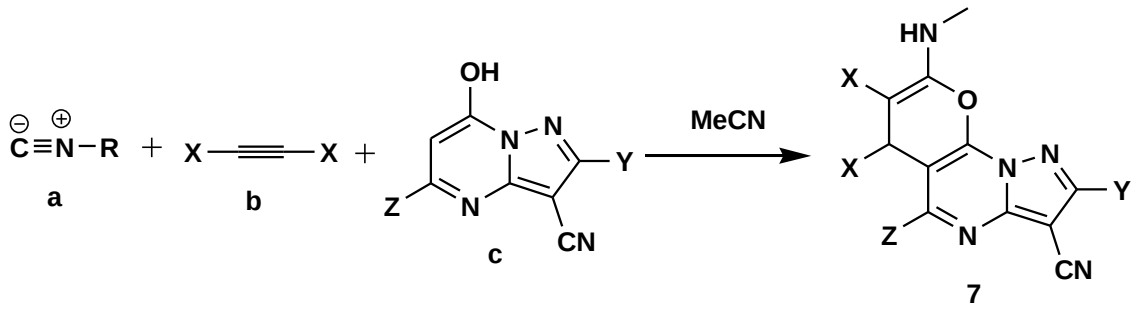
opyridine inhibitors showed potential as candidates with low micromolar PD-L1 affinities, and the result paves way for biologically active scaffold leading to a class of PD-L1 antagonists.



Scheme 6. Synthesis imidazo[1,2-*a*]pyridine-based inhibitors.

Vahedi and co-workers reported the 3CR of alkyl isocyanides (**a**) with dialkyl acetylenedicarboxylates (**b**), and 7-hydroxy pyrazolo[1,5-*a*]pyrimidines (**c**) at room temperature using acetonitrile as a solvent to afford biologically active pyrano[3,2-*e*]pyrazaolo[1,5-*a*]pyrimidine (**7**) in good yields, as shown in Scheme 7 [21]. One of the reported synthesised compounds exhibited excellent potential as an anti-cancer agent with an IC_{50} value of 19.70 ±0.89 μM, comparable to the standard drug etoposide (IC_{50} = 18.71 ±1.09 μM). Additionally, one of the derivative compounds demonstrated promising antioxidant characteristics by having a high free radical scavenging effect (IC_{50} = 12.12 ±0.40 μM), which was equivalent to the ascorbic acid (IC_{50} = 11.85 0.30 μM) benchmark for antioxidants.



Scheme 7. Synthesis of pyrano[3,2- *e*]pyrazolo[1,5- *a*]pyrimidines.

Yanga and co-workers. reported the synthesis of biologically active 2-amino-4*H*-pyrans (**7**) in a 3CR of aldehyde (**a**) with malononitrile (**b**) and ethyl acetoacetate (**c**) using lipases as catalysts and different solvent media, as illustrated in Scheme 8 [22]. The synthesised compounds were subjected to in vitro antitumor activities against three cell lines (A549, Hela, and HepG2) and displayed good activity against tumour cells. One of the compounds was reported to have an IC_{50} of 0.0517 μM in A549 cells as an antitumor agent.

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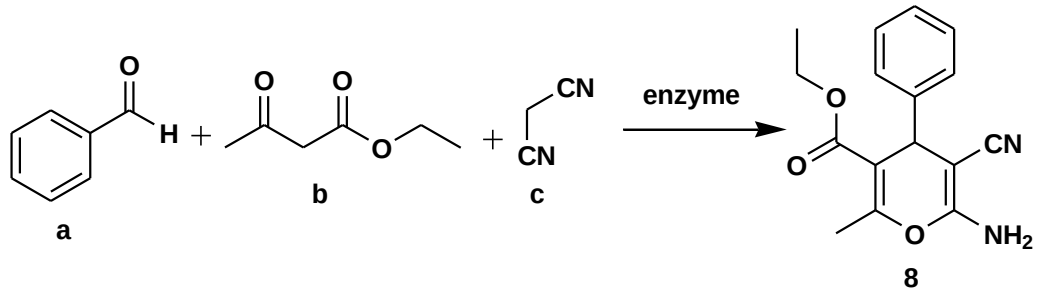
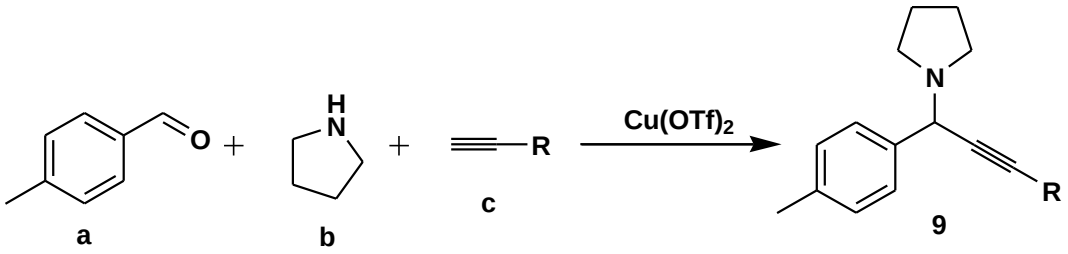


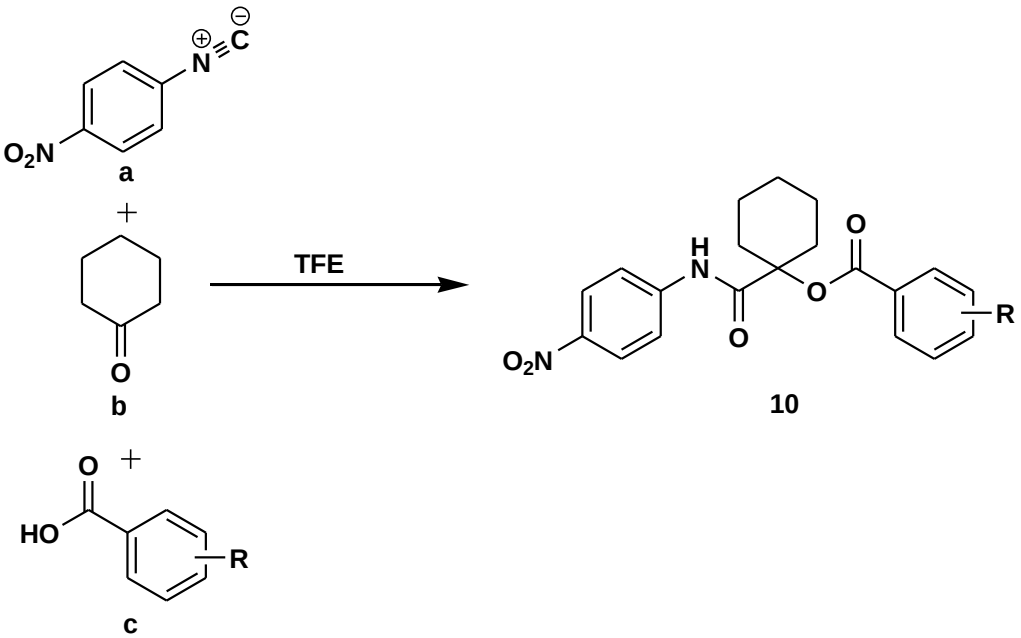
Scheme 8. Synthesis biologically active 2-amino-4*H*-pyrans.

The anticancer propargylamines (**9**) were prepared by 3CR of an aldehyde (**a**), amine (**b**), and alkyne (**c**) in toluene in the presence of $Cu(OTf)_2$ as a catalyst, as presented in Scheme 9 [23]. This set of compounds showed a high degree of selectivity, with an index higher than 3 for triple-negative breast cancer cells and a very interesting selectivity of 41.17 for pancreatic cancer cells.



Scheme 9. Synthesis of anticancer propargylamines.

The caspase-dependent apoptotic inducers *a*-acyloxycarboxamides (**10**) were prepared from *p*-nitrophenyl isonitrile (**a**), cyclohexanone (**b**), and various carboxylic acids (**c**) using 2,2,2-trifluoroethanol (TFE) as catalyst under reflux in ethanol, as illustrated in Scheme 10 [24]. This set of compounds presented potential and safety compared to doxorubicin based on IC50 values during cytotoxicity against normal human fibroblasts and anticancer activities against MCF-7 breast, NFS-60 myeloid leukemia, and HepG-2 liver utilising MTT assay.



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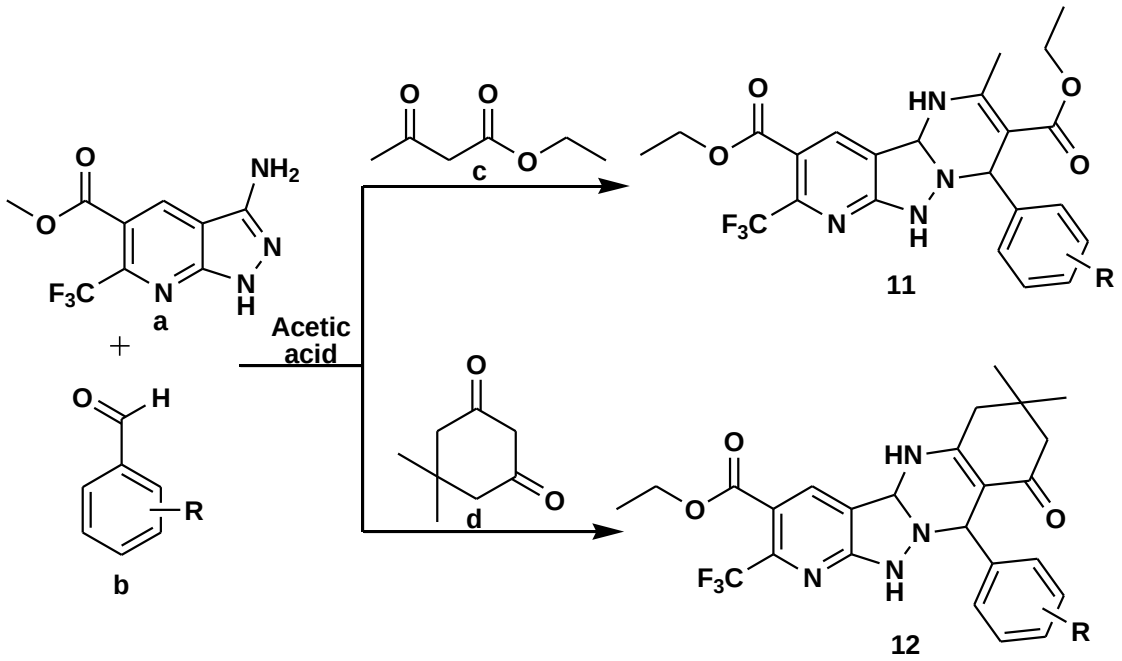
Scheme 10. The synthesis of *a*-acyloxycarboxamides.

The 3CR of 3-amino-5-carbethoxy-6-trifluoromethyl pyrazolo[3,4-*b*] pyridine (**a**) with aldehyde (**b**), and ethylacetoacetate (**c**)/dimedone (**d**) using acetic acid resulted in the biologically active pyrimidine fused pyrazolo[3,4-*b*]pyridine (**11**) derivatives and hexahydroquinazoline-fused pyrazole [3,4-*b*] pyridine (**12**) derivatives, as displayed in Scheme 11 [25]. These sets of compounds exhibit very good antibacterial, antifungal and antibiofilm activity against gram-positive and gram-negative bacterial strains.



Scheme 11. The synthesis of pyrimidine-fused pyrazolo[3,4-*b*]pyridine derivatives and hexahydroquinazoline-fused pyrazole [3,4-*b*] pyridine derivatives.

Vasava and co-workers synthesised biologically active 6-amino-1-(2,4-dinitrophenyl)-4-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (**13-14**) derivatives *via* 4CR of 2, 4-dinitrophenyl hydrazine (**a**), malononitrile (**b**), ethyl acetoacetate (**c**), and aromatic aldehyde (**d**) derivatives using $SnCl_2$ as a catalyst under neat microwave irradiation and conventional heating, as demonstrated in Scheme 12 [26]. The compounds performed well in vitro biological evaluations as antibacterial and antituberculosis agents.

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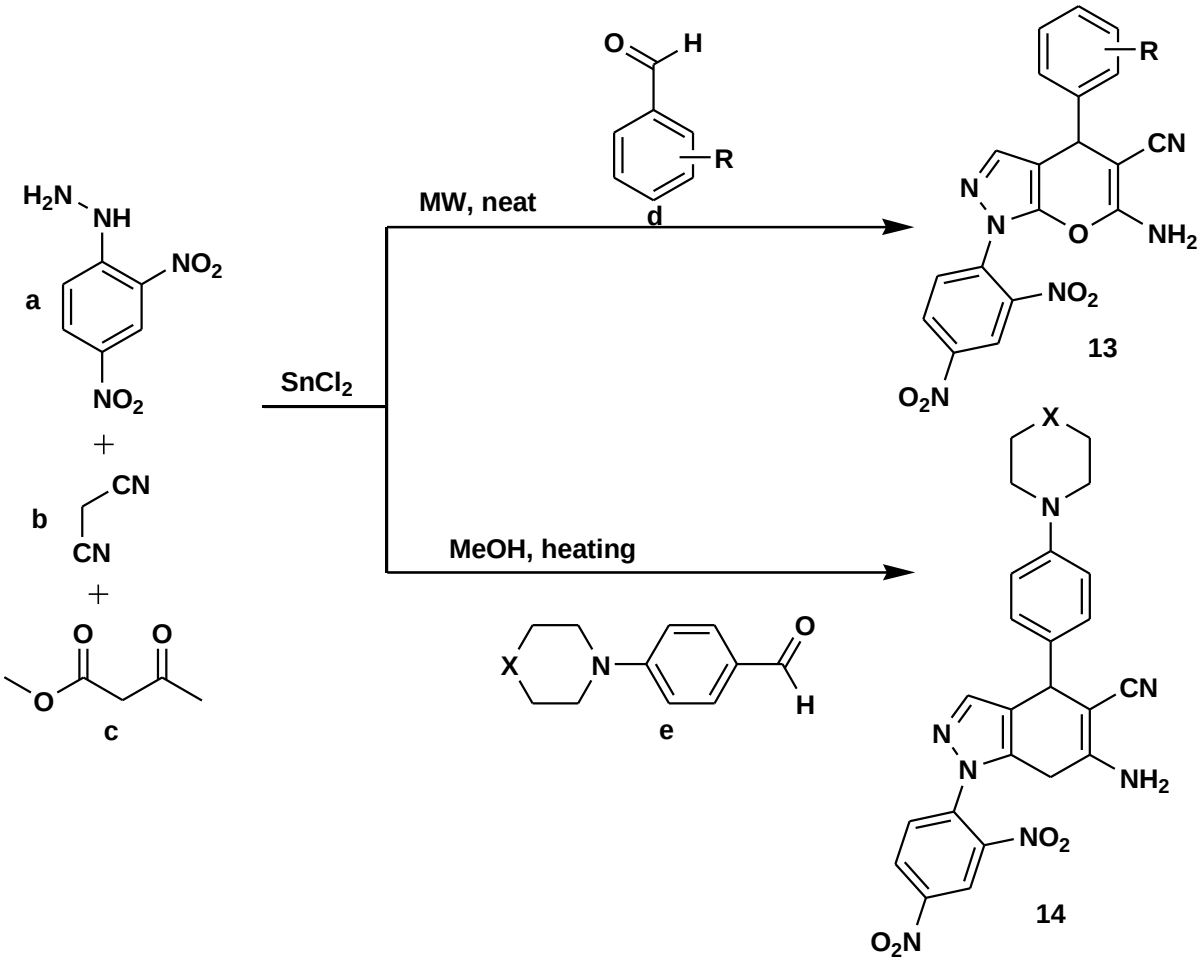
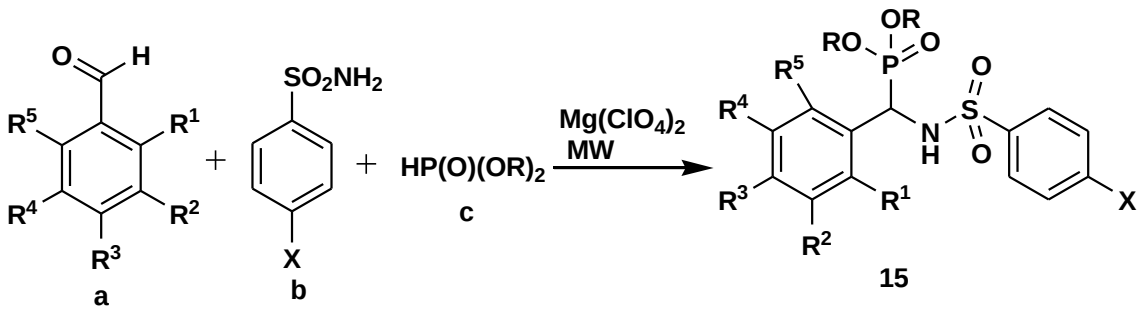


Scheme 12. The synthesis of biologically active 6-amino-1-(2,4-dinitrophenyl)-4-phenyl- 1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile derivatives.

Bhagata and co-workers reported the α-sulfonamidophosphonates (**15**) as anti-*Mycobacterium tuberculosis* H37Rv agents [27]. The α-sulfonamidophosphonates (**15**) were achieved after treating 4-methoxybenzaldehyde (**a**) with 4-methylbenzenesulphonamide (**b**) and dimethyl phosphite (**c**) using magnesium perchlorate under microwave irradiation, as demonstrated in Scheme 13. This class of compounds exhibited good MIC values of 1.56 µg/mL and 3.125 µg/mL. In addition, some of the active compounds are non-toxic to RAW 264.7 (mouse leukemic monocyte macrophage) cell lines.



Scheme 13. The synthesis biologically active α-sulfonamidophosphonate derivatives.

Karypidou and co-workers reported the synthesis of biologically active 1,2,3-triazole (**16**) from 3CR of oxopiperidine carboxylate (**a**) with primary amines (**b**) and 4-nitrophenyl

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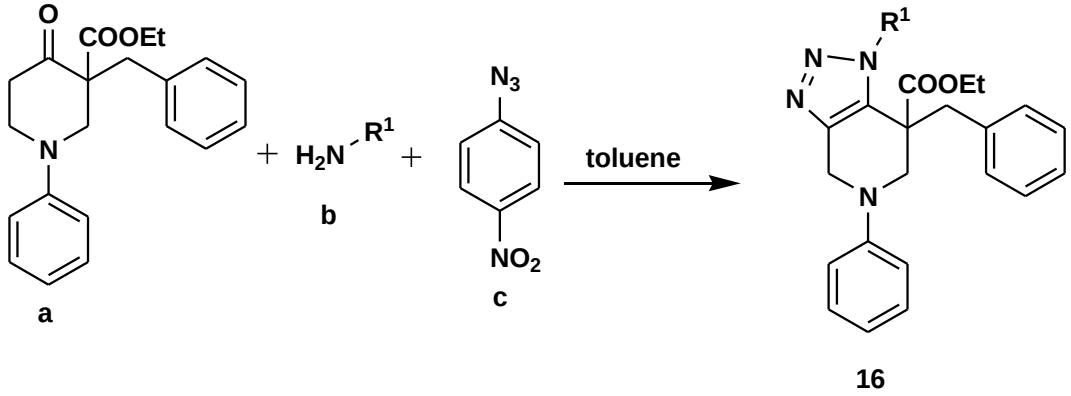
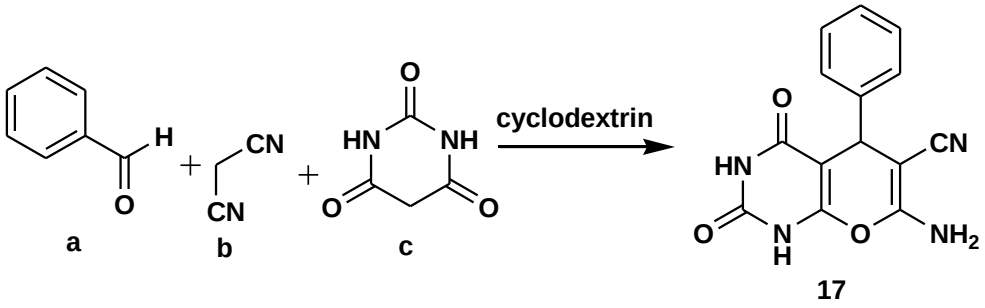
azide (**c**) using toluene as a solvent at 100 °C, as shown in Scheme 14 [28]. This set of compounds demonstrated promising antiviral activity against human coronavirus 229E.



Scheme 14. 3CR for the synthesis of biologically active 1,2,3-triazole.

The 3CR of benzaldehyde (**a**) with malonitrile (**b**) and barbituric acid (**c**) gave rise to biologically active pyrano[2,3-*d*]-pyrimidinone (**17**) derivatives using *β*-cyclodextrin as a catalyst and water as a solvent, as shown in Scheme 15 [29] The in vitro antimicrobial activity evaluations exhibited good results compared to ciprofloxacin, used as the reference drug.



Scheme 15. 3CR for the synthesis of pyrano[2,3-*d*]-pyrimidinone derivatives.

2.2. Green chemistry

Green chemistry refers to the development of chemical products and procedures that lessen or do away with the usage or production of hazardous materials. Green chemistry covers all aspects of a chemical product's life cycle, including its formation, usage, and final disposal. Green sustainable chemistry practices provide a safe environment in laboratories. The use of efficient and economical chemical processes is highly recommended for the synthesis and preparation of desired products. One of the recognisable methods for enhancing "greenness" is the use of MCRs in the production of medicinal and industrial products. MCRs offer a great chance to implement safe practices and environmentally safe methods. The use of green solvents, solvent-free reactions, working at modestly safe temperatures, utilising biocatalysts, photocatalysis's, safe catalysts, and the use of catalyst-free reactions are some of the most well-known suggested practices and conditions for a green production process. The significant benefit of green chemistry is undeniable, according to regulatory bodies, federal, state governments, and scientific societies. The Twelve Principles of Green Chemistry, first outlined by Anastas and Warner [30] in 1998 and later revised by Nigist and colleagues [31] as well as Anastas and Eghbali [32] serve as the norm for green chemistry practice and sustainable production (Figure 2).

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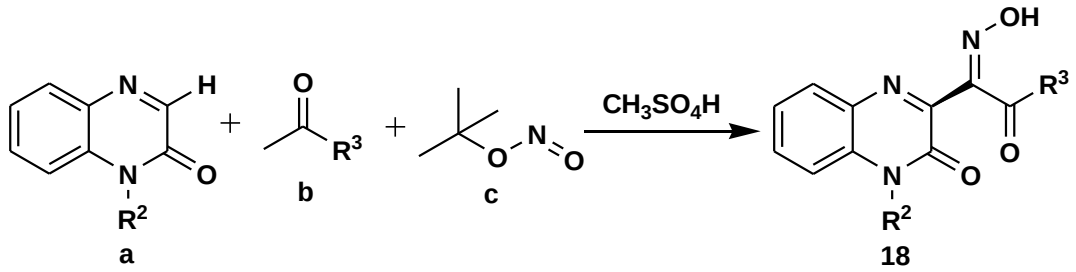
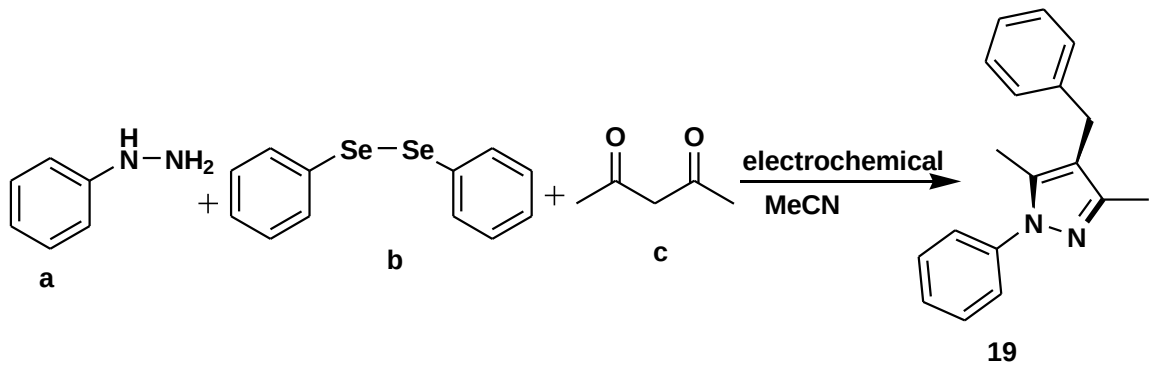
Figure 2. Conditions and benefits of green chemistry practices.

The 3CR of quinoxalinones (**a**) with methyl ketones (**b**) and *tert*-butyl nitrite (**c**) in the presence of methanesulfonic acid at ambient temperature gave rise to the (*E*)-quinoxalinone oximes (**18**) [33]. The reactions occurred under green chemical production with transition-metal-free conditions to afford moderate to good products as demonstrated in Scheme 16.



Scheme 16. Green chemical synthesis of (*E*)-quinoxalinone oximes.

Wu and co-workers [34] reported the electrochemical multicomponent reaction of phenylhydrazine (**a**) with diphenyl diselenide (**b**) and 2,4-pentanedione (**c**) using a reticulated vitreous carbon (RVC) anode/Pt plate cathode system in acetonitrile as a solvent to afford 4-selanylpyrazoles (**19**). This method requires no catalyst or oxidant, and it proceeds under mild conditions to afford good to excellent yields, as shown in Scheme 17.



Scheme 17. Electrochemical multicomponent reaction for the synthesis of 4-selanylpyrazoles.

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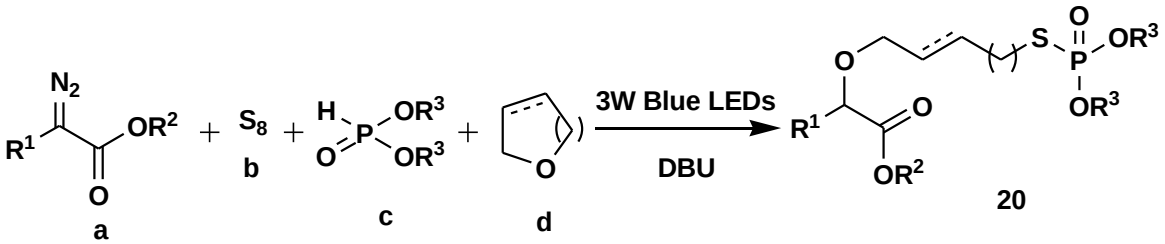
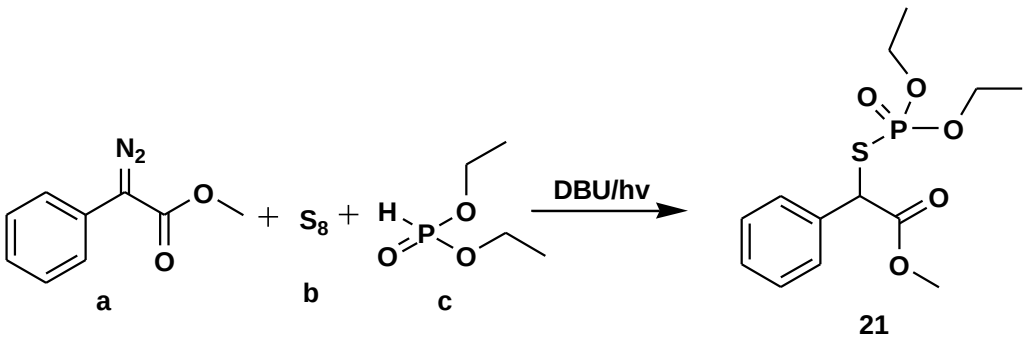
The 4-CR of α-diazoesters (**a**), elemental sulfur (**b**), *H*-phosphonates (**c**), and cyclic ethers (**d**) gave rise to *S*-alkyl phosphorothioates (**20**), as represented in Scheme 18 [35]. The reaction to achieve the products was done through visible light using 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as an additive under mild conditions.



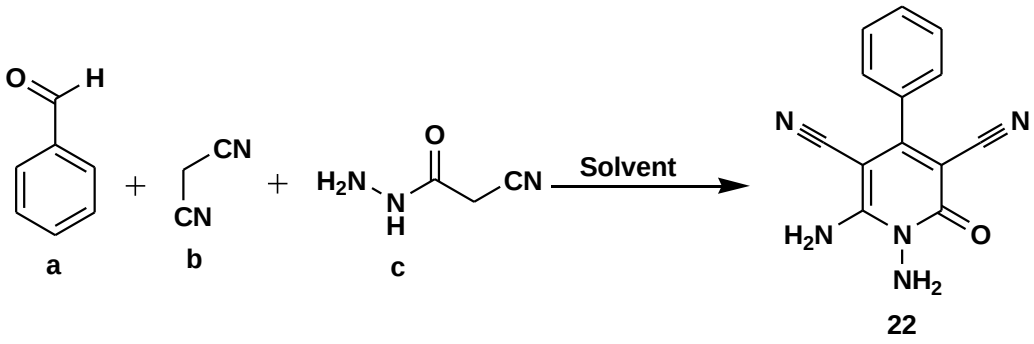
Scheme 18. The 4CR for synthesis of *S*-alkyl phosphorothioate.

Furthermore, Qu and colleagues studied the 3CR of α-diazoesters (**a**), elemental sulfur (**b**), and *H*-phosphonates (**c**) to generate *S*-alkyl phosphorothioate (**21**) in moderate to good yields using visible-light and base DBU, as demonstrated in Scheme 19. Despite using other solvents, recommended green solvents such as dimethyl sulfoxide, tetrahydrofuran, and acetonitrile were employed.



Scheme 19. The 3CR for synthesis of *S*-alkyl phosphorothioate.

The 3CR of aldehydes (**a**) with cyanoacetohydrazide (**b**) and malononitrile (**c**) or ethyl cyanoacetate gave rise to functionalised *N*-amino-3-cyano-2-pyridone (**22**) using a biodegradable green solvent PEG-200 and other solvents such as water, ethanol, glycerine, and neat conditions with temperatures ranging from room temperature to 100 °C (Scheme 20) [36]. PEG-200 is one of the good solvents considered for sustainable chemistry synthesis since is non-toxic, economical, easily available and robust to promote this cascade method.



Scheme 20. Synthesis of functionalised *N*-amino-3-cyano-2-pyridone.

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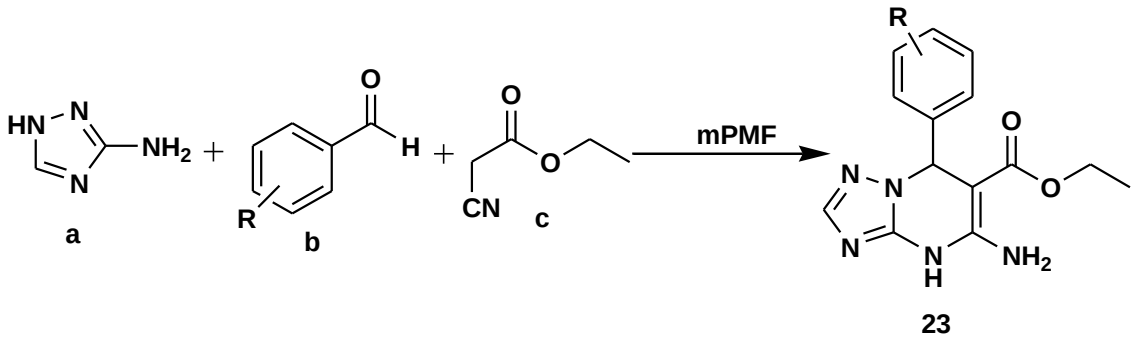
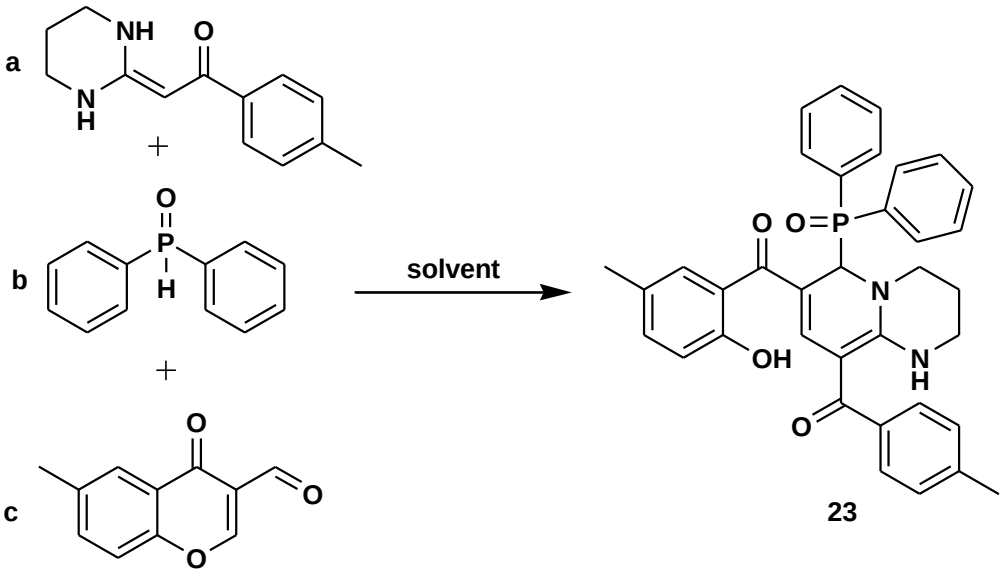
The 3CR of 3-amino-1,2,4-triazole (**a**), aldehyde (**b**), and ethyl cyanoacetate (**c**) gave rise to dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidines (**23**) under green chemical production using poly-melamineformaldehyde (mPMF) as catalyst (Scheme 21) [37]. The reactions were performed at room temperature under solvent-free conditions. The catalyst was reported to be recyclable for at least five runs while still providing good efficiency.



Scheme 21. 3CR for the synthesis of dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidines.

Li and colleagues [38] reported a 3CR reaction of heterocyclic ketene aminals (**a**), phosphine oxides (**b**), and 3-formylchromones (**c**) to afford highly functionalised 2-(diarylphosphoryl)-1,2-dihydropyridine (**24**) derivatives as demonstrated in Scheme 22. The investigation revealed that when the reactions were performed using propylene carbonate (PC) as a solvent and trimethylamine as a promoter, the highest yields were achieved.



Scheme 22. Synthesis of highly functionalised 2-(diarylphosphoryl)-1,2-dihydropyridine derivatives.

Paul and co-workers [39] developed a sustainable and eco-friendly method for the synthesis of pyrrolidine-2-one (**24**) using a water-soluble supramolecular β-cyclodextrin as a catalyst. The 3CR of aldehydes (**a**) with amines (**b**) and dimethylacetylenedicarboxylate (DMAD) (**c**) was done at room temperature using water-ethanol medium to afford the products, as shown in Scheme 23.

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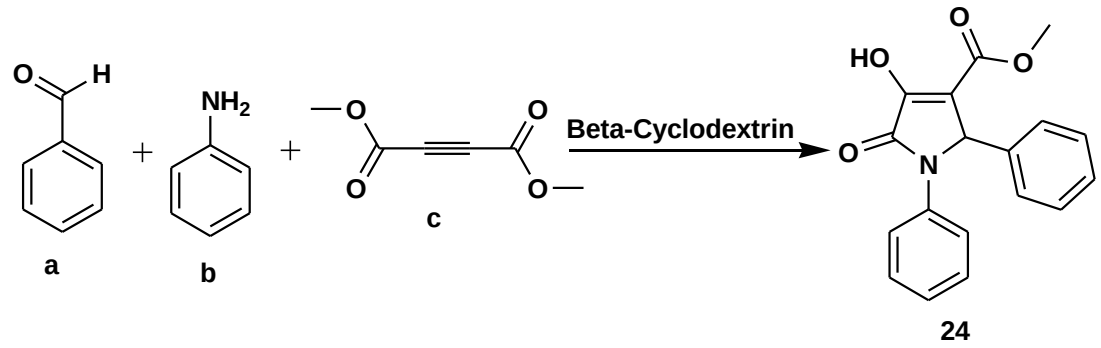
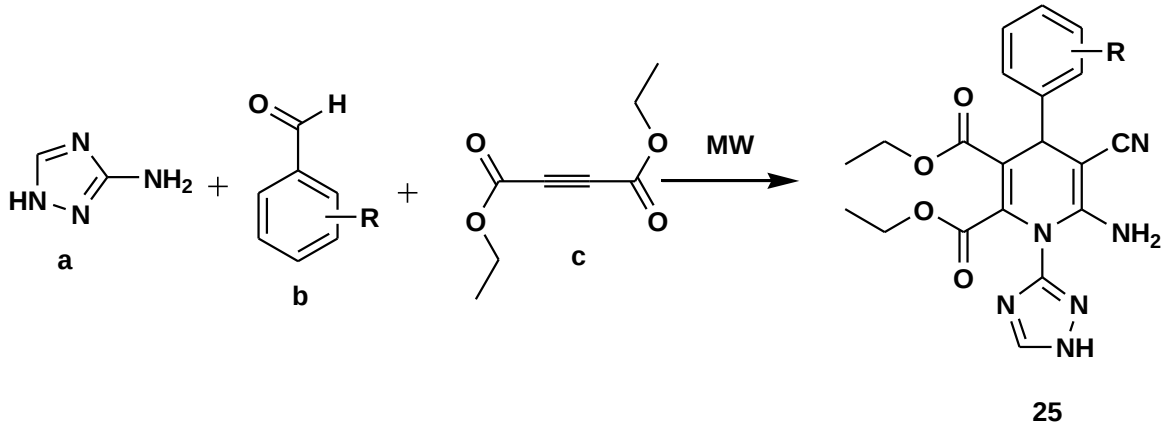


Scheme 23. Synthesis of pyrrolidine-2-one using β-cyclodextrin.

Kerru and colleagues [40] developed an efficient and sustainable method after setting a 4CR reaction of 1*H*-1,2,4-triazol-3-amine (**a**) with aldehydes (**b**), methylene compounds (**c**), and diethyl acetylenedicarboxylate (**d**) using water as solvent under microwave irradiation conditions to afford 1,2,4-triazole-tagged 1,4-dihydropyridine (**25**) derivatives (Scheme 24). The desired products were achieved in excellent yields ranging from 94 to 97 % with high selectivity at room temperature. The solvent effect was investigated by testing polar-aprotic (acetonitrile, dichloromethane, and tetrahydrofuran), which gave lower yields compared to polar-protic (acetic acids, water, methanol and ethanol), which gave better and excellent yields.



Scheme 24. 4CR for the synthesis of 1,2,4-triazole-tagged 1,4-dihydropyridine derivatives.

Ma and associates [41] reported the green chemical diastereoselective synthesis of tetrahydropyrrolo[1,2-*d*][1,4]benzodiazepines (**26**) and tetrahydropyrrolo[1,2-*d*][1,4]diazepinones (**27**), as shown in Scheme 25. The 4CR of L-alanine ethyl ester hydrochloride (**a**) with *N*-ethylmaleimide (**b**), and 2-azidobenzaldehyde (**c**) in the presence of phenacyl bromide or phenylglyoxylic acid using acetonitrile as a solvent under microwave gave good yields.

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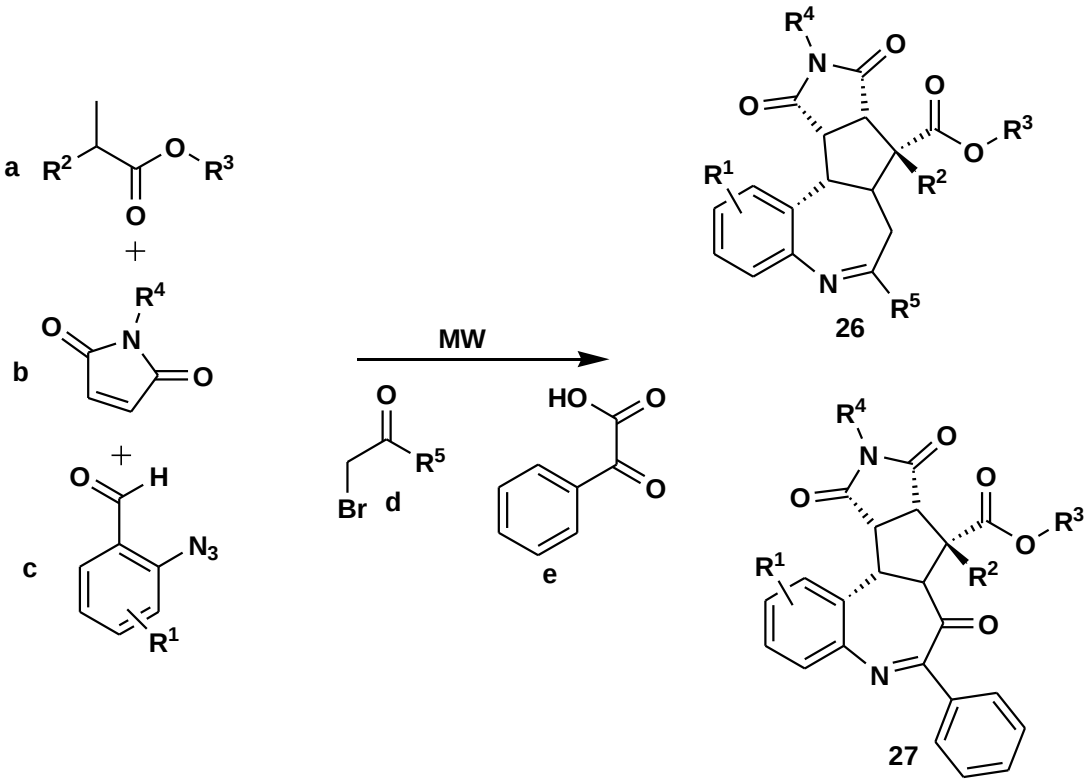
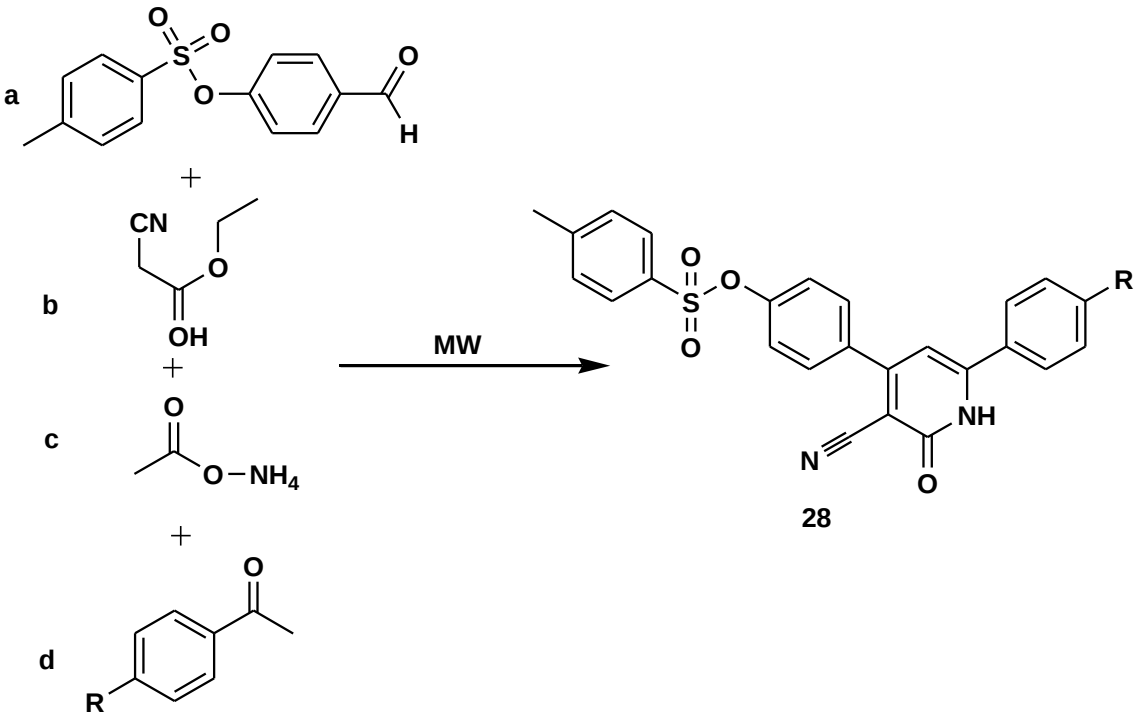


Scheme 25. Synthesis of tetrahydro-pyrrolobenzodiazepine derivatives.

El-Lateef and co-workers [42] reported an efficient and sustainable method by setting a FF4CR of *p*-formylphenyl- 4-toluenesulfonate (**a**) with ethyl cyanoacetate (**b**), ammonium acetate (**c**) and acetophenone derivatives (**d**) using ethanol as a solvent under microwave irradiation to afford pyridine (**28**) (Scheme 26). This method gave even better yields with good atom economy and pure products at a short reaction time.



Scheme 26. Synthesis of 3-Cyanopyridines.

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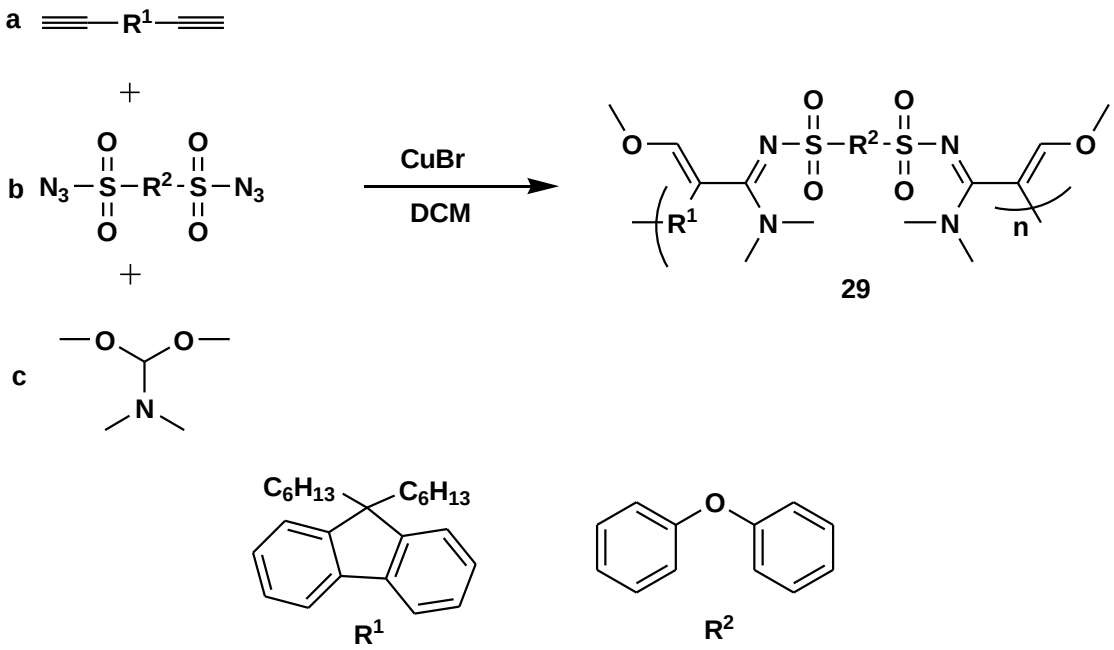
2.3. Polymerisations

The approach of MCR chemistry towards the production of functionalised polymers with good properties for advanced material use is not well exploited. Although, recently, the application of MCR in polymer chemistry is slowly gaining interest. This polymeric material possesses distinguishing and unique thermal, fluorescence sensing, mechanical, chemical, and optoelectronic properties, which enhance their practical chemical applications. Multicomponent polymerisation (MCP) has significantly accelerated the growth of the polymer science and advanced materials sectors. Some of the heteroatom polymers derived from MCP have been applied in various fields, including water treatment [43], flame retardants [44] and fluorescent sensors [45]. The interest in employing MCP for the production of polymers is gradually growing, and it brings some interesting benefits such as multiple sequential stepwise reductions, atom economy, and mild conditions.

The three-component reaction of alkyne (**a**), sulfonyl azide (**b**), and *N,N*-dialkyloxyformamide dialkyl acetal (**c**) gave rise to functional polymers (**29**), as shown in Scheme 27 [46]. The polymerizations leading to functional polymers were accomplished using copper bromide as a catalyst, bis(diphenylphosphino)ethane as a ligand, molecular sieves 4 Å, under N_2 with DCM as a solvent at room temperature for 1 hour. The facile method of polymerisation occurs under mild conditions, which provide high polymerisation efficiency and stereoselectivity. The multiple functional polymers produced show good activity in acid-base responsive fluorescence, visualisation of food spoilage, efficient gold enrichment and recovery, lysome-specific cell imaging, and are also highly selective with a sensitive Au^{3+} sensor.



Scheme 27. Amidine-containing polymers.

Xu and co-workers treated an alkyne (**a**), sulfonyl azide (**b**), and 2-hydroxybenzonitrile (**c**) in the presence of copper chloride and trimethylamine under N_2 using dichloromethane as a solvent to achieve functional polymers (**30**), as shown in Scheme 28 [47]. The iminocoumarin/quinolone-containing poly(N-sulfonylimine)s obtained gave molecular weights up to 37700 g/mol and a 96% yield. The fluorescence poly(N-sulfonylimine) (**30**) shows good activities such as sensitivity and detection of Ru^{3+} and some antibacterial properties.

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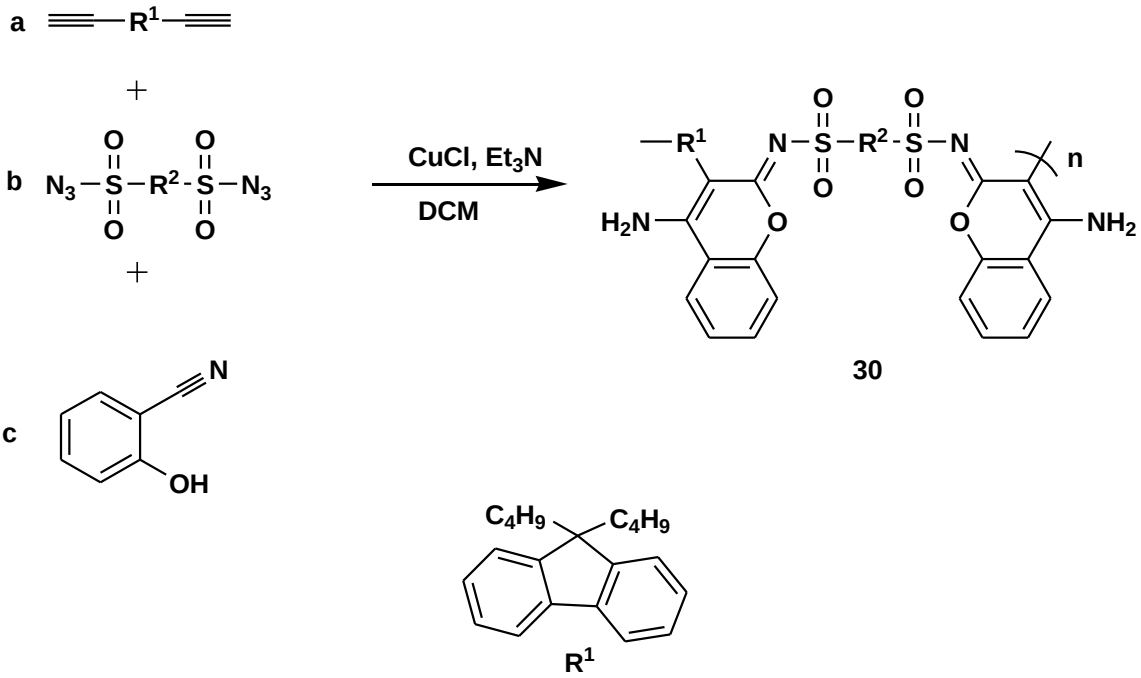
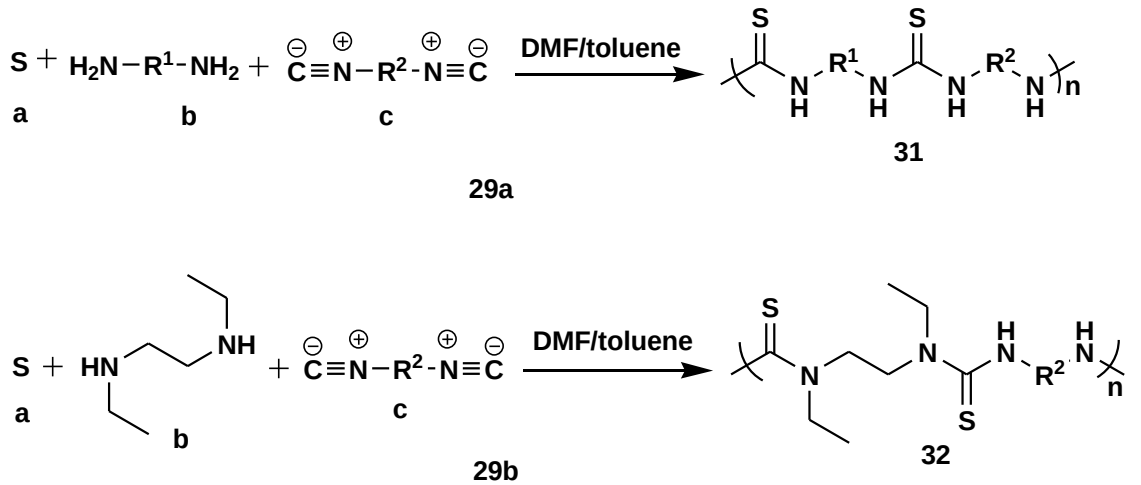


Scheme 28. Poly(*N*-sulfonylimine)s functional polymers.

The reaction of sulfur (**a**), diamines (**b**), and diisocyanides (**c**) at room temperature using dimethylformamide and toluene as solvents gave rise to functional polythioureas (**31-32**) under catalyst-free conditions in air with 100% atom economy, as shown in Schemes 29a-b [48]. The scope of this polymerisation was explored to give more products of polythioureas that are well characterised. The polythioureas gave molecular weights up to 242500 g/mol with excellent yields of up to 95%. This set of polythioureas displayed distinct activities such as the detection of mercury pollution with high sensitivity and selectivity and the ability to efficiently clean Hg^{2+} to obtain clean drinking water.



Scheme 29. a-b. Polymerisation of sulfur, diamines, and diisocyanides to form polythioureas.

Polymers with aggregation-induced emission (AIE) have properties with advantages such as structural diversity, multifunctionalities, efficient solid-state fluorescence, and good processability, as shown in Scheme 30 [49]. The 3CR of diynes (**a**), dialdehydes (**b**), and secondary amines (**c**) at 140 °C using indium trichloride as catalyst and *o*-xylene as a solvent gave rise to polymers (**33**) with AIE in Scheme 30a. Scheme 30b shows the successful 3CR polycoupling of diynes (**a**), aldehydes (**b**), and primary amines (**c**) using copper

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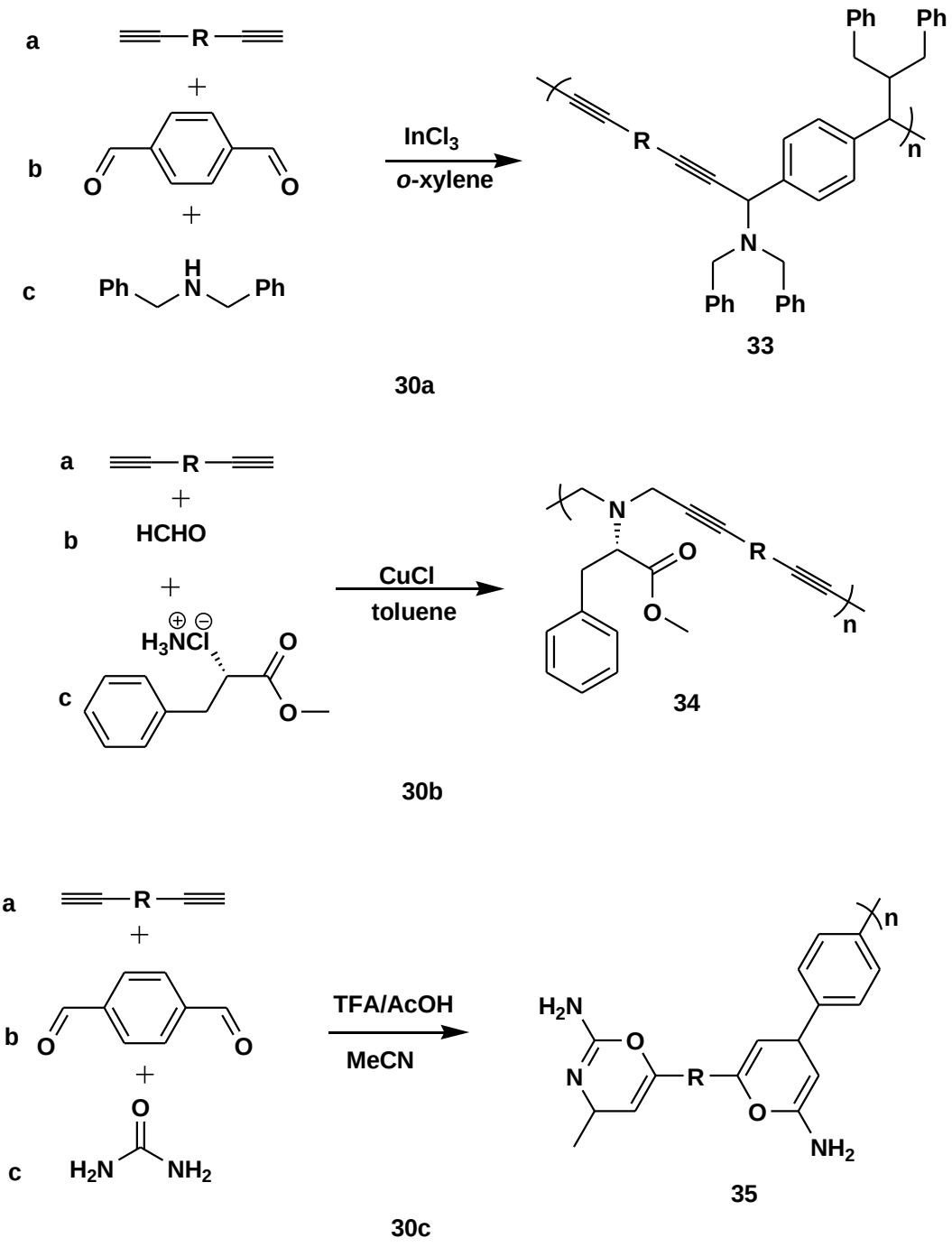
chloride as a catalyst and toluene as solvent at 100 °C to afford polymers (**34**). The metal-free 3CR polycoupling of diynes (**a**), aldehydes (**b**), and urea (**c**) to produce polymers (**35**) with AIE was achieved at 90 °C using acetonitrile as a solvent in Scheme 30c.



Scheme 30. a-c. Polymers with aggregation-induced emission (AIE).

The reaction of isocyanides (**a**), amines (**b**), and elemental selenium (**c**) *via* 3CR to form selenoureas polymers (**36**) using dichloromethane as a solvent at room temperature was reported by Tuten and co-workers [50] as shown in Scheme 31. The reaction proceeds through the isocyanide reacting with selenium powder to form isoselenocyanates, and this process is 100% atom economy. Isoselenocyanates are formed in situ from elemental selenium and isocyanides, leading to the reaction with amines that gives rise to selenourea polymers.

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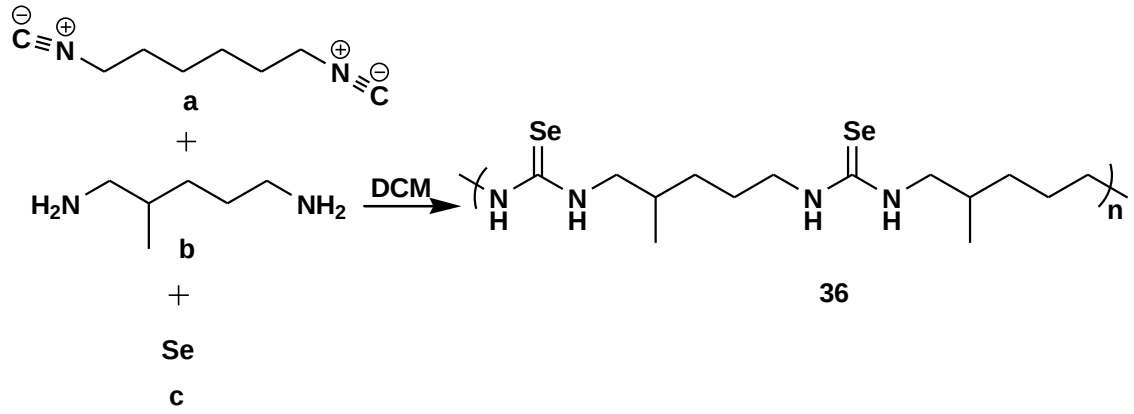
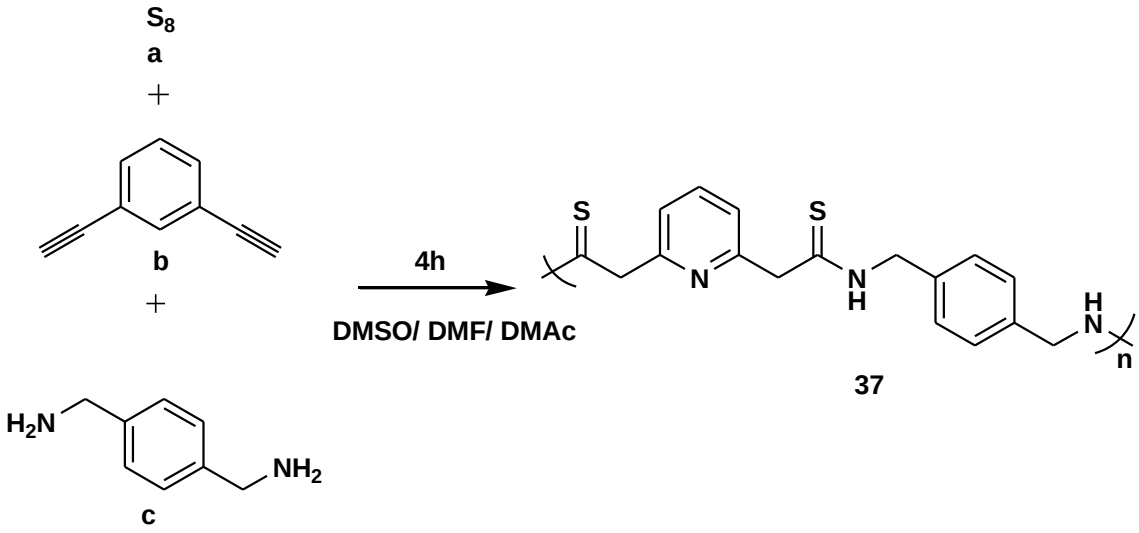


Scheme 31. 3CR of diisocyanide, diamine and selenium to form polymers.

The polythioamides (**37**) were achieved by Zang and co-workers [51] from room temperature to 40 °C under catalyst-free conditions by treating sulfur (**a**), aromatic alkyne (**b**), and diamines (**c**) using polar aprotic solvents such as DMSO, DMF, and DMAc, as shown in Scheme 32. The well-defined structures of polythioamides were achieved with good to high yields and high molecular weights up to 95100 g/mol. The functional polythioamides (**37**) exhibit interesting photo-physical and photo-chemical properties.



Scheme 32. Polymerisation of sulfur, alkynes and diamines to afford polythioamides.

The reaction of bis(*N*-sulfonyl aziridine)s (**a**), tosyl isocyanate (**b**), and diols (**c**) using organocatalyst and THF as solvent at 60 °C gave rise to poly(sulfonamide urethane)s (**38**) in good to excellent yield, as shown in Scheme 33 [52].

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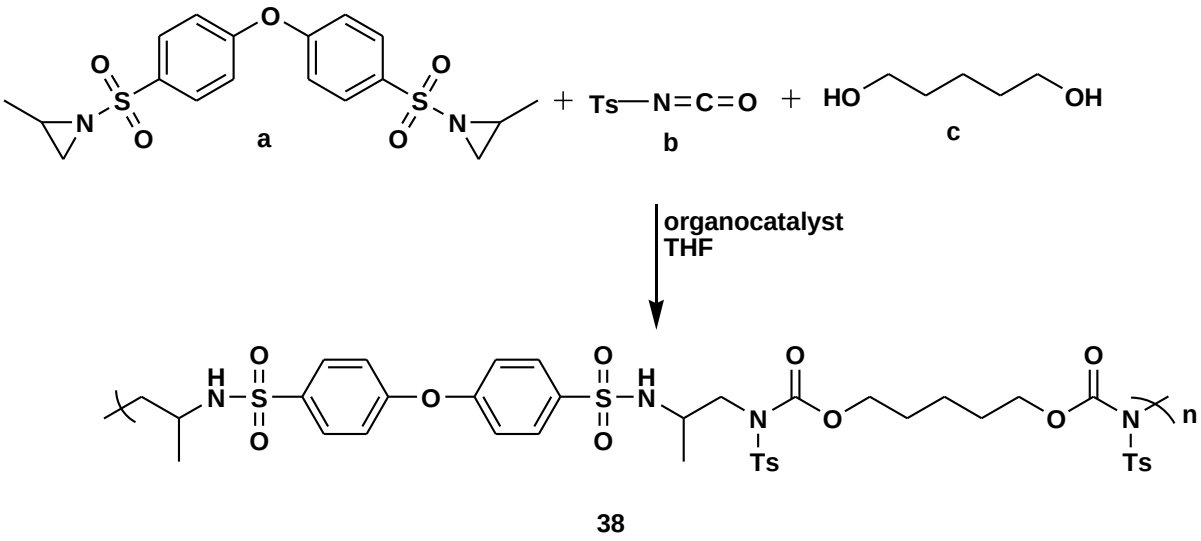
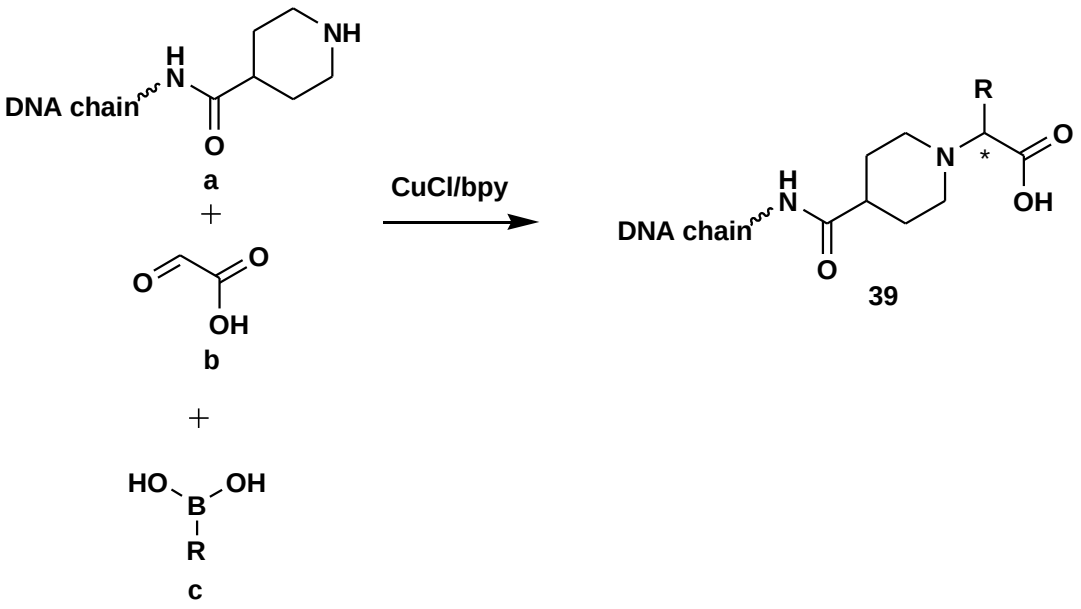


Scheme 33. Synthesis of poly(sulfonamide urethane).

2.4. Solid-phase synthesis

Solution-phase synthesis has historically been the dominant method as a foundation for the synthesis and discovery of heterocyclic bioactive scaffolds. The emergence of solid-phase synthesis (SPS) paved the way for the development of bioactive heterocyclic compounds and distinct structural diversity. MCRs contributed towards the process of creating solid-phase protocols that could speed up the discovery of new drugs and active heterocyclic compounds. As an ongoing research field, there are a lot of incoming methods and reports in the literature on solid-phase synthesis *via* MCRs.

Potowski and co-workers achieved substituted α-aryl glycines (**39**) in a 3CR of amines (**a**), boronic acids (**b**), and glyoxalic acid (**c**) at room temperature using DMF as a solvent,as shown in Scheme 34 [53]. As a result, the Petasis 3CR procedure is very appealing for the manufacture of DNA-encoded small molecule screening libraries. It was discovered that the copper (I)/bipyridine reagent system in dry organic solvents promotes the Petasis reaction.



Scheme 34. The substituted α-aryl glycines from 3CR.

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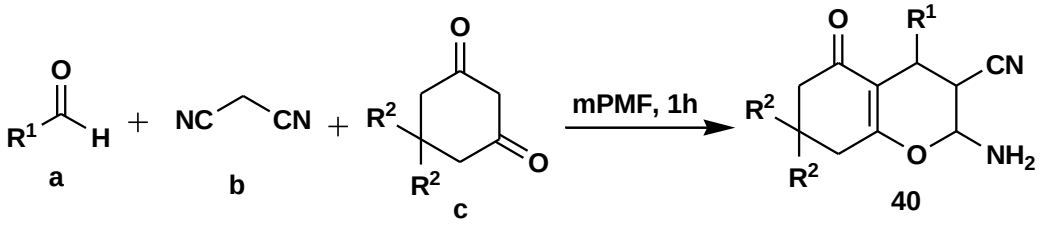
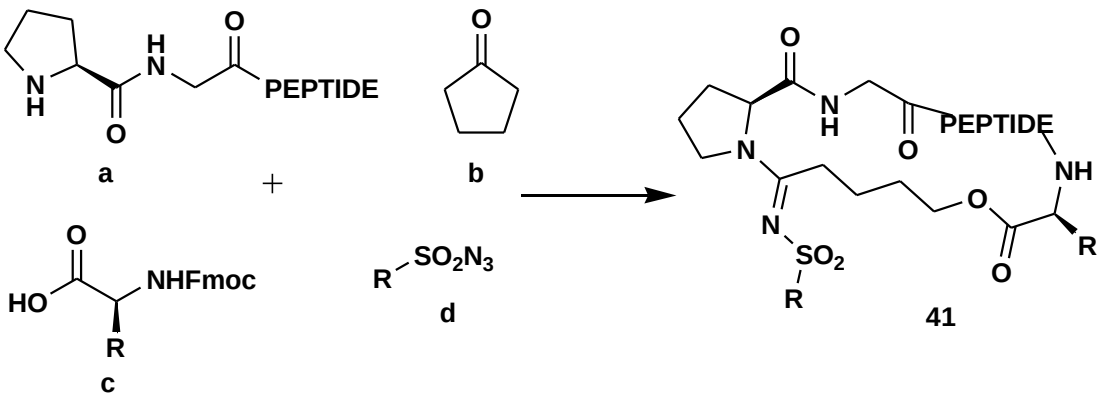
The synthesis of 2-amino-4*H*-benzo[*b*]pyrans (**40**) was achieved from a 3CR of 4-chlorobenzaldehyde (**a**), malononitrile (**b**), and 5,5-dimethyl-1,3-cyclohexadione (dimedone) (**c**) using mesoporous poly-melamine-formaldehyde (mPMF) as a heterogeneous catalyst for one hour at room temperature, as shown in Scheme 35 [54]. The reaction conditions also adhered to green chemistry principles after using the planetary ball milling process at room temperature with no solvents. This method also presents good outcomes such as a short reaction time, broad substrate scope, no sequential reactions, good yields, and the employment of a safe mPMF catalyst that can be recovered for reuse. The outcome of this study demonstrated that porous organic polymers consisting of Lewis base sites with acceptor-donner hydrogen bonding functional groups and high porosity are significant and accelerate the formation of MCR in solid-phase reactions.



Scheme 35. Synthesis of 2-amino-4*H*-benzo[*b*]pyrans from one-pot multicomponent reaction in solid-phase reactions.

Bucci and co-workers reported 4CR of metal-free 1,3-dipolar cycloaddition of cyclopentanone-proline enamines (**a**), pentanone (**b**), carboxylic acid (**c**) and sulfonylazides (**d**) for the synthesis of amidino depsipeptide (**41**), as shown in Scheme 36 [55]. The on-resin multicomponent reaction proceeds by the formation of a primary cycloadduct followed by ring opening and molecular rearrangement to allow a linear sulfonyl amidine functionalised containing a peptide chain and a diazoalkane. The resultant diazo function reacts with the carboxylic group from the *N*-Fmoc-protected amino acids to form an amidino depsipeptide with a C4 aliphatic chain. This method provides stable peptide-bond bioisosteres.



Scheme 36. Solid phase MCR for the synthesis of depsipeptides.

Mendez and co-workers reported a solid phase on resin multicomponent reaction of the amine (**a**), carbonyl (**b**), and isocyanide (**c**) to obtain tetrazole-peptidomimetics (**42**), as shown in Scheme 37 [56]. The on-resin reaction of paraformaldehyde consisted of imine formation and transimination of the resin-bound amino acid using the piperidinium ion, followed by the addition of the isocyanide component and $TMSN_3$, and shaking for 72 hours.

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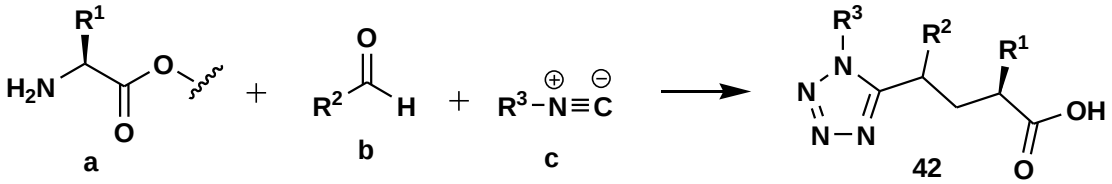
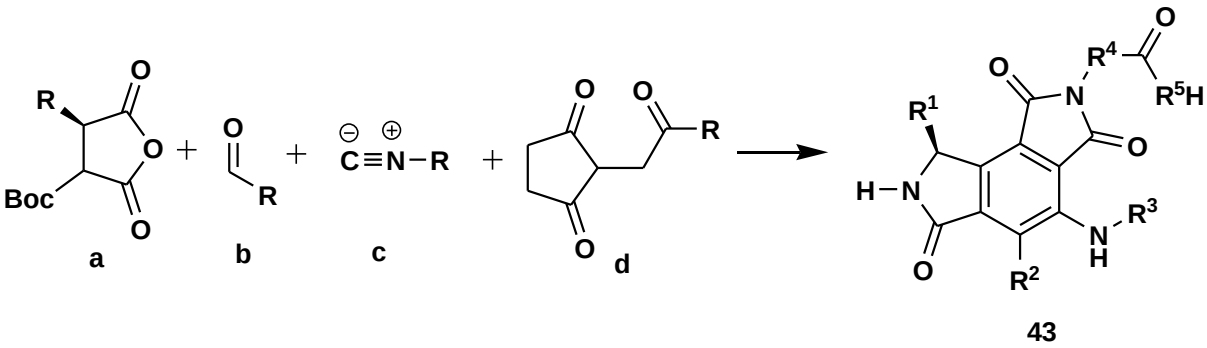


Scheme 37. Solid-phase synthesis of tetrazole-peptidomimetics by on-resin Ugi-azide-4CR.

The solid phase multicomponent reaction of chiral β-keto lactam (**a**) with an aldehyde (**b**), an isocyanide (**c**), and a dienophile (**d**) gave rise to 3-substituted soindolinone (**43**) derivatives, as demonstrated in Scheme 38 [57]. Further optimisation was done using the microwave irradiation as the source of energy to achieve good to excellent yields.

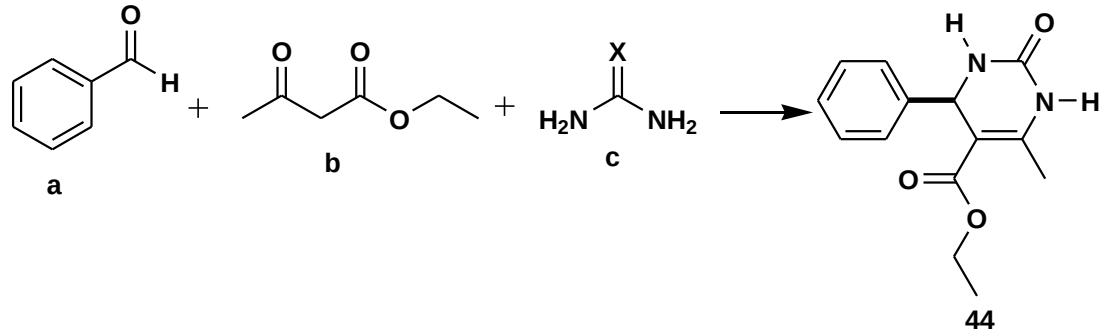


Scheme 38. Solid-phase synthesis of 3-substituted soindolinone derivatives.

2.5. Asymmetric catalysis

The synthesis of useful desired products, enantiopure natural scaffolds, and bioactive compounds *via* asymmetric multicomponent reactions remains one of the most reliable and applied methods of reaction. This method presents beneficial advantages such as reduction of sequential steps during synthesis, atom economy, and recyclable catalysts. The development of new asymmetric MCRs is triggered by the existence of organocatalysis. Nonetheless, there are still a lot of accomplishments to be made, and several reactions that were reported still don't exhibit good chiral induction control. To overcome issues like poor enantioselectivities, new catalytic techniques and insights are needed for intervention.

The multicomponent reaction of an aldehyde (**a**), 1,3-dicarbonyl compound (**b**), and urea/thiourea (**c**) using counteranion directed catalysis (ACDC) and ionic liquid effect (ILE) at 30 °C for 72 hours gave rise to an enantioselective Biginelli reaction, as shown in Scheme 39 [58].



Scheme 39. Enantioselective multicomponent reaction.

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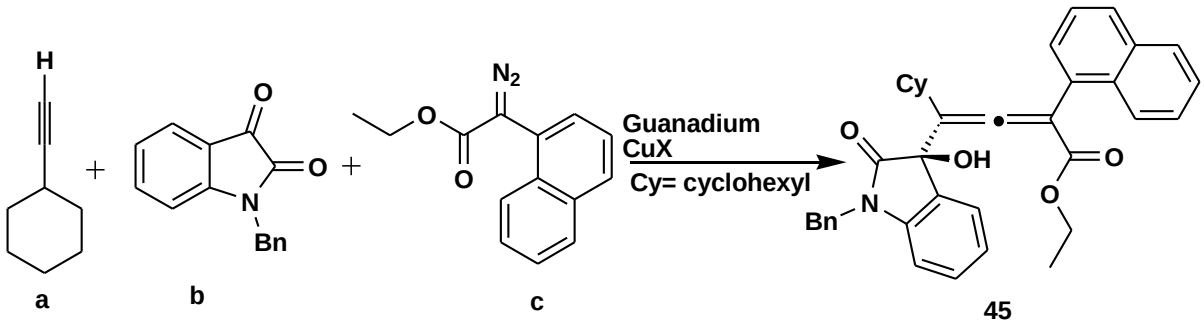
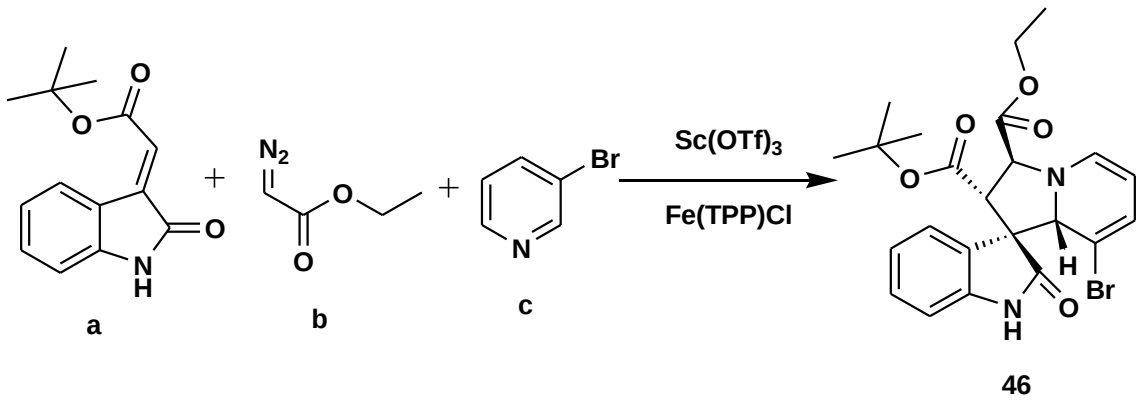
Tang and colleagues [59] reported the synthesis of tetrasubstituted allenes (**45**) by using a catalytic asymmetric 3CR of terminal alkynes (**a**) and isatins (**b**) in the presence of α-diazoesters. The axially chiral tetrasubstituted allenoates containing a stereogenic core resulted from this one-pot synthesis, as demonstrated in Scheme 40. The reaction was promoted by the chiral guanidinium salt (10 mol%) and CuCl as catalyst, with chloroform as an additive.



Scheme 40. Enantioselective multicomponent reaction.

Zhang and co-workers reported a highly enantioselective method for the synthesis of tetrahydroindolizines (**46**) from the reaction of alkenyloxindole (**a**) with diazoacetate (**b**) in the presence of pyrimidine (**c**) [60]. The 3CR were performed using an achiral iron (tetraporphyriinato) chloride with chiral *N,N'*-dioxide-scandium (III) complex catalysts to obtain tetrahydroindolizines in good to excellent yields, as shown in Scheme 41. The reactions were carried out at mild temperatures of 30 °C, with dichloromethane or methyl acetate serving as solvents.



Scheme 41. High enantioselective method for the synthesis of tetrahydroindolizines.

The 3CR of indoles (**a**) with 2,3-dihydropyran (**b**) and methylene malonates (**c**) gave rise to optically active tetracyclic indolines (**47a-b**) bearing four continuous stereocenters (Scheme 42) [61]. The reactions were carried out using a copper (II) catalyst and bis-oxazoline (BOX) at 50 °C with toluene and fluorobenzene as a solvent. Due to the one-pot asymmetric multicomponent reaction's efficiency, a variety of tetracyclic indoline derivatives with superior diastereo- and enantioselectivities were produced in high yields, as reported by Khang and co-workers.

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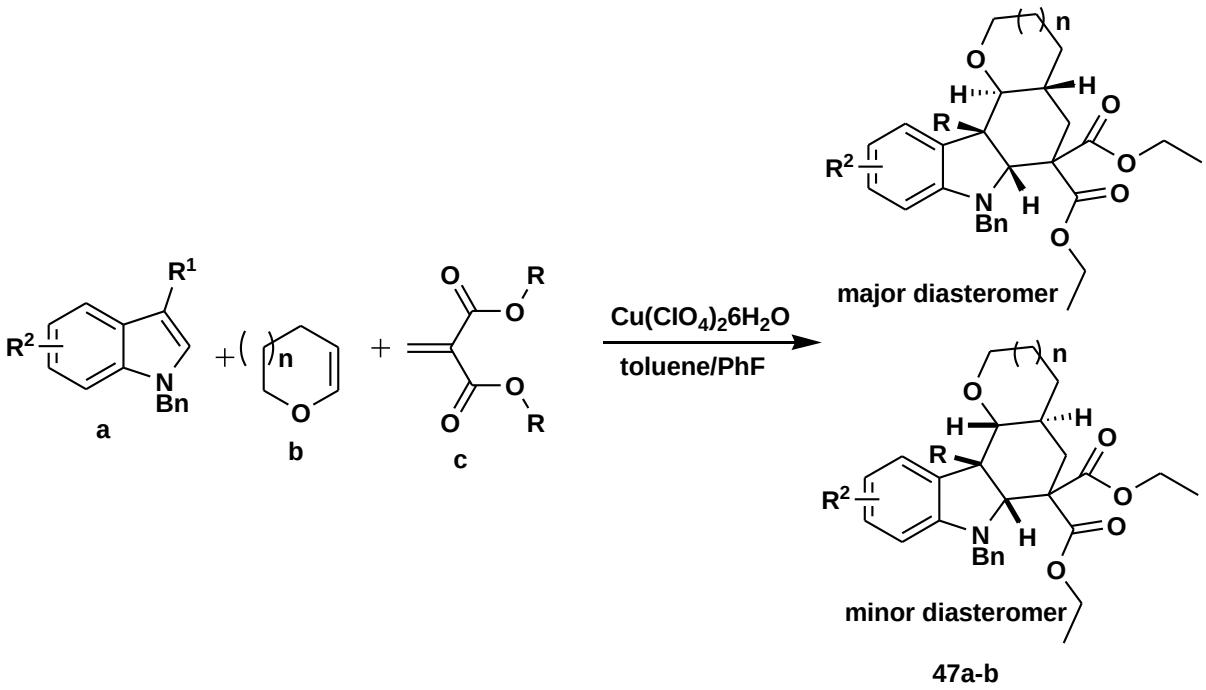
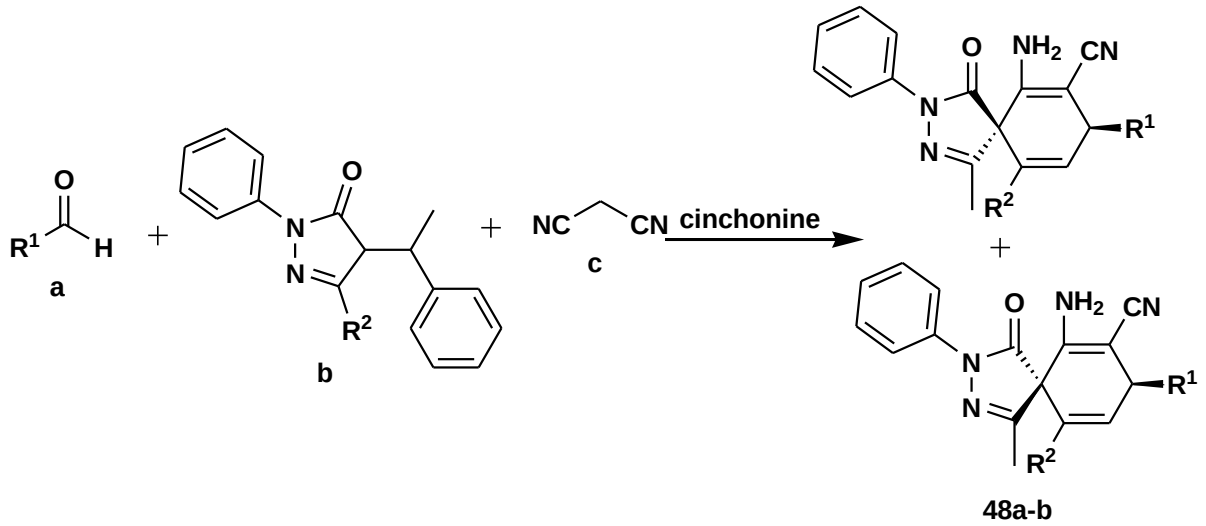


Scheme 42. The synthesis of optically active tetracyclic indolines.

Ji and co-workers [62] reported the asymmetric catalytic reaction of benzaldehyde (**a**) with α-arylidene pyrazolinones (**b**) and malononitrile (**c**) at -10 °C using dichloromethane as a solvent and chiral cinchonine as catalyst to produce spiropyrazolones (**48a –b**) (Scheme 43). This method produced spiropyrazolones (**48a –b**) in good to high yields with better refined enantioselectivities and good diastereoselectivities. When different solvents were tested, it was discovered that dichloromethane, toluene, chloroform, and dichloromethane gave better yields and great diastereoselectivity of product formation, however, it was observed that there is little effect on the enantioselectivity. Solvents such as acetonitrile and tetrahydrofuran were found to be unsuitable for this kind of reaction. The best temperature suitable for the reactions was found to be -10 °C.



Scheme 44. The asymmetric catalytic synthesis of spiropyrazolones.

The 3CR of benzothiazole (**a**) with isocyanide derivative (**b**), and dimethyl 2-benzylidenemalonate (**c**) using $Mg(OTf)_2$/L-$RaPr_2$ as a catalysts with $(CH_2Cl)_2$ as a solvent at 35

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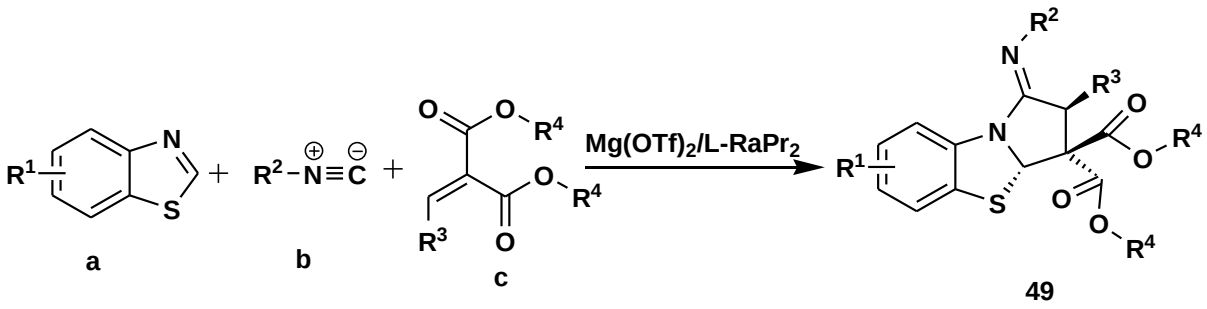
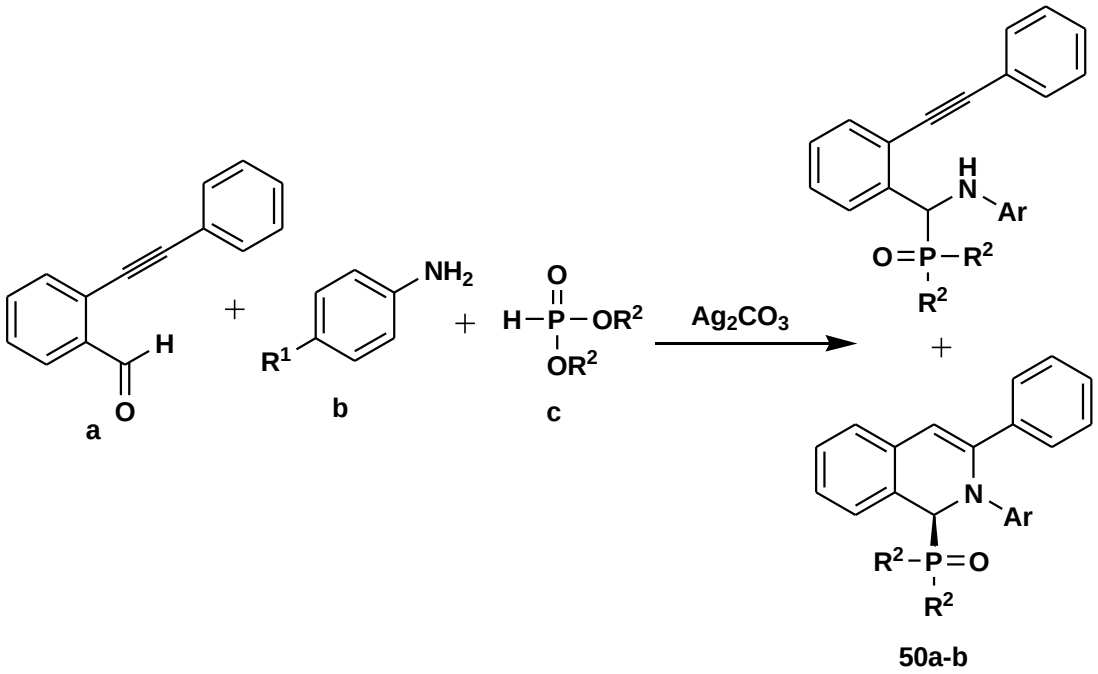
°C gave rise to hydrothiazole derivatives (**49**) as reported by Xiong and co-workers [63] (Scheme 45). The developed chiral hydrothiazole derivatives achieved high enantioselectivity and good yields up to 98%.



Scheme 45. The asymmetric synthesis of hydrothiazole derivatives.

The efficient enantioselective multicomponent reaction of 2-alkynylbenzaldehydes (**a**) with amines (**b**), and dimethylphosphonate (**c**) in the presence of chiral silver spirocyclic phosphate acid catalyst (SPA) gave rise to chiral phosphonylated 1,2-dihydroisoquinoline derivatives cyclic (**50a-b**) (Scheme 46) [64]. The chiral phosphonylated 1,2-dihydroisoquinoline derivatives were achieved in high yields up to 99% with great enantioselectivities up to 94% enantiomeric excess (ee).



Scheme 46. The asymmetric synthesis of hydrothiazole derivatives.

The catalyst-free multicomponent reaction of aliphatic diamines (**a**) with diethyl chlorothiophosphate (**b**), and diphenyl phosphoryl chloride (**c**) gave rise to symmetric (**51**) and asymmetric (**52**) bisphosphoramidates and bisphosphoramidothioates (**53**) as reported by Zamudio-Medina and co-workers [65] (Scheme 47). The reactions provided a good yield of the desired products at low temperatures (0 °C) in the presence of trimethylamine base and dichloromethane as a solvent.

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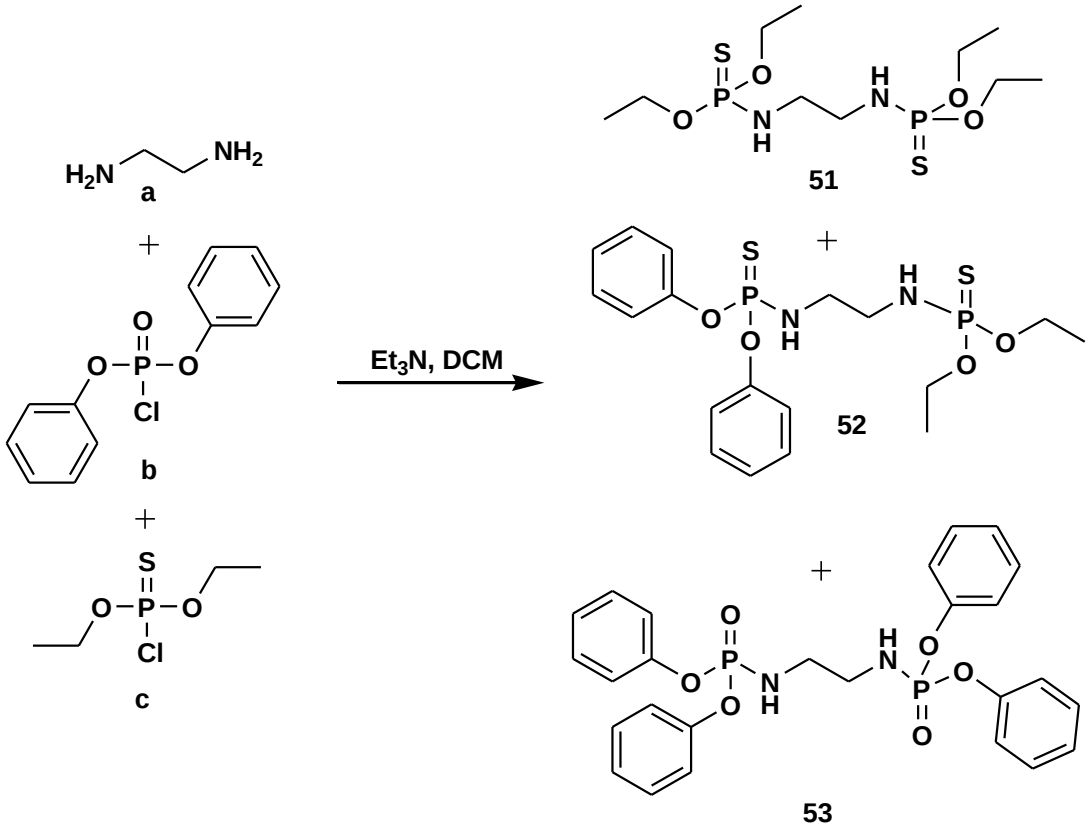

Scheme 46. The single-step synthesis of symmetric and (novel) asymmetric bisphosphoramidate and bisphosphoramidothioate derivatives.

2.6. C-H functionalisation

The carbon-hydrogen bond is the most prevalent bond in organic compounds, however, the formation of these bonds is relatively challenging. The synthesis and formation of this bond are more efficient and atom-economical. Practically, the initial replacement of a hydrogen with a reactive functional group occurs using different approaches to permit the process of C-H functionalisation. The C-H functionalisation chemistry in MCRs covers the synthesis, preparation, and modification of useful scaffolds in organic chemistry.

Borpartra and co-workers [66] reported the synthesis of pyrimido[4,5-*d*]-pyrimidines (**54**) from a 3CR of 6-aminouracils (**a**), aldehydes (**b**) and secondary amines (**c**) in ethanol as a solvent at room temperature using acetic acid as a catalyst, as shown in Scheme 47. The process begins with the initial reaction of 6-Aminouracil (**a**) and aldehyde (**b**), followed by the amine attack. The formation of the final product occurs *via* intramolecular *α*-C-H functionalisation. It was discovered that when using (20 mol%) of acetic acid in ethanol, the percentage yields were high at room temperature, however, when the reaction was heated under reflux the percentage yields dropped. Their investigation further revealed that other solvents such as water, acetonitrile, dimethylformamide, and toluene were used to improve the percentage yield at room temperature.

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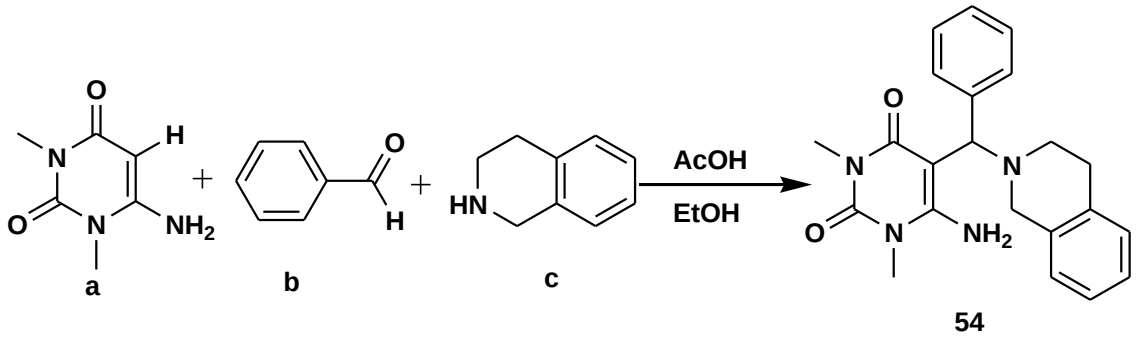
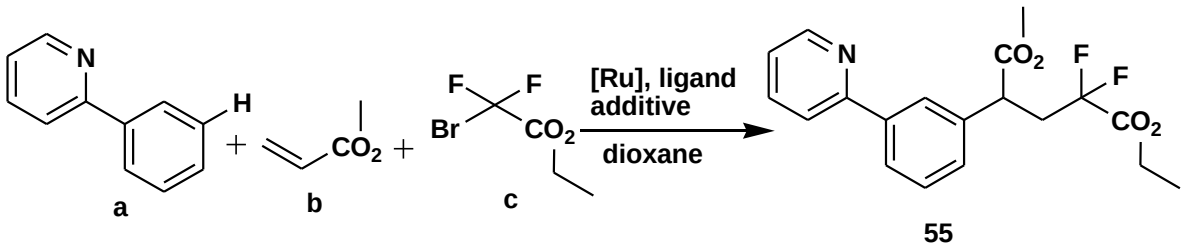


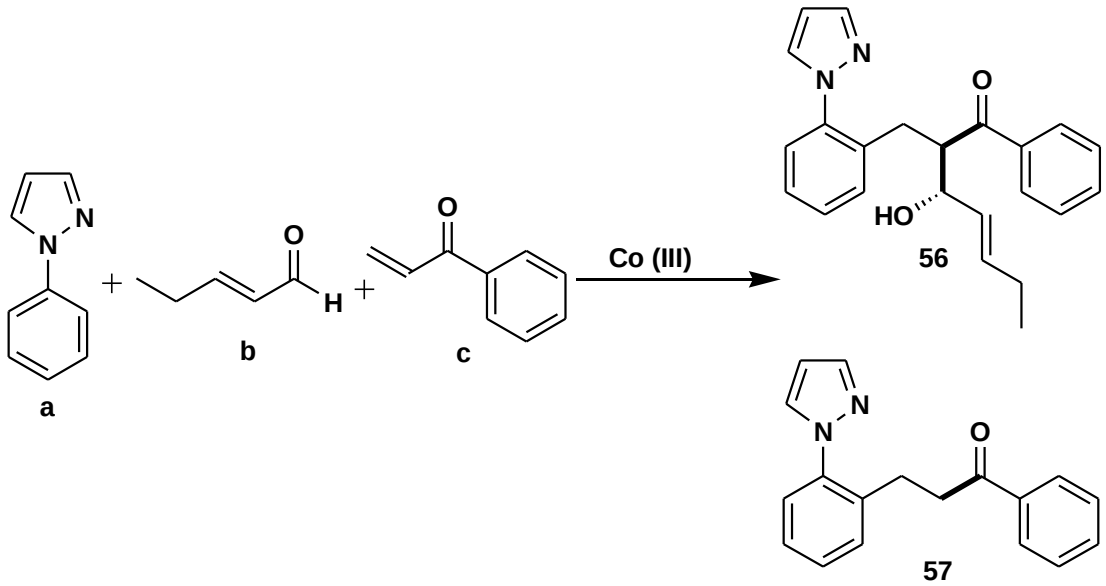
Scheme 47. The 3CR C-H functionalisation towards synthesis of pyrimido[4,5-*d*]-pyrimidines.

The 3CR of 2-phenylpyridine (**a**), methyl acrylate (**b**), and ethyl bromodifluoroacetate (**c**) using 1,4 dioxane as a solvent at 60 °C under catalytic conditions of ruthenium (II) biscarboxylate with electron-deficient ligand P(4-$C_6H_4CF_3$)$_3$ gave better percentage yield up to 65% for the alkylation of alkenes, as shown in Scheme 48 [67].



Scheme 48. The 3CR C-H functionalisation using ruthenium as a catalyst.

A 3CR of *N*-phenyl pyrazole (**a**), crotonaldehyde (**b**), and phenyl vinyl ketone (**c**) gave rise to (2R, 3S, E)-2-(2-(*1H*-pyrazol-1-yl)benzyl)-3-hydroxy-1-phenylhex-4-en-1-one (**56**) and 3-(2-(*1H*-pyrazol-1-yl)phenyl)-1-phenylpropan-1-one (**57**) using a Co(III) complex containing a chiral cyclopentadienyl ligand, as shown in Scheme 49 [68]. The diastereoselective and enantioselective C-H functionalisation reactions gave good percentage yields under Co(III) as a catalyst, however, when rhodium was used, the reaction never materialise. Additionally, when other solvents such as dioxane or Me-THF employed, the reactions were not efficient.



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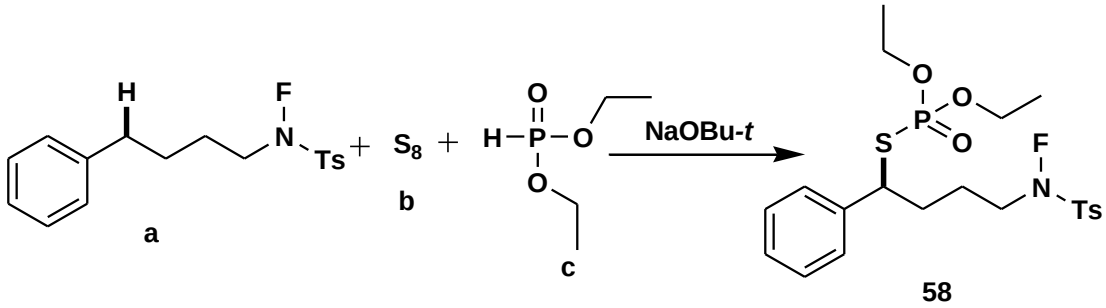
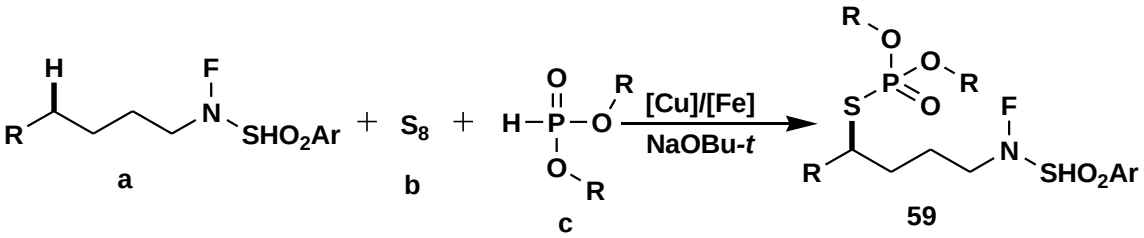
Scheme 49. The diastereoselective and enantioselective C-H functionalisation reaction.

Shi and co-workers [69] reported the multicomponent reaction of primary and secondary C(sp3)-H of *N*-fluoro-substituted amides (**a**) in the presence of elemental sulfur (**b**), and P(O)H compounds (**c**) to afford phosphorothiolation products (**58 and 59**), as shown in both Scheme 50 and 51 . In Scheme 50, when the reaction was performed using 10 mol% $Cu(OTf)_2$, at 40 °C for a period of 24 hours in the presence of 10 mol% bipy, and 2.0 equiv of NaO*t*Bu under argon using $PhCF_3$ as a solvent, the conversion resulted in a 15% yield. This was improved when dichloromethane was used as a solvent. Another finding was that when (CuX_2) was employed instead of $Cu(OTf)_2$, the reaction conversion improved to 45% yield (X is $CF_3COCHCOCH_3$).



Scheme 50. Multicomponent phosphorothiolation.

The investigation was further done to check the effect of substituents by employing substrates with electron-donating and electron-withdrawing groups on the aromatic ring, which resulted in a good improvement in percentage yield. In addition, the scope was increased by exploring P(O)-H compounds such as $HP(O)(OnBu)_2$ and $HP(O)(OiPr)_2$, resulting in good yields.



Scheme 51. Exploring the multicomponent phosphorothiolation.

The highly diastereoselective C-H functionalisation multicomponent reaction of pyrrolidine (**a**), 4-hydroxycoumarin (**b**), and benzaldehyde (**c**) gave rise to 4-hydroxy-6-methyl-2-pyroneo[2,3-*b*]pyrrole derivatives (**60**), as demonstrated in Scheme 52 [70].

When the reaction was performed at 120 °C using toluene as a solvent, the percentage yield conversion was better as compared to high temperatures of 140-150 °C. In addition, it was discovered that using low boiling-points solvents doesn't improve yields. In order to improve the yields, Mandal and co-workers used Bronsted acids as additives.

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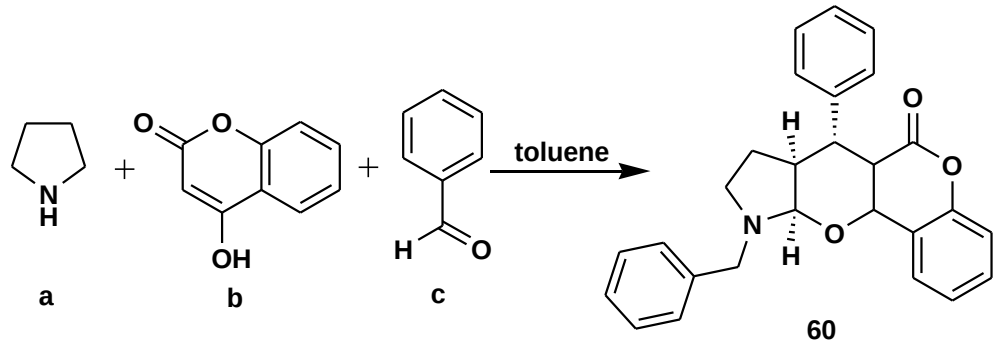
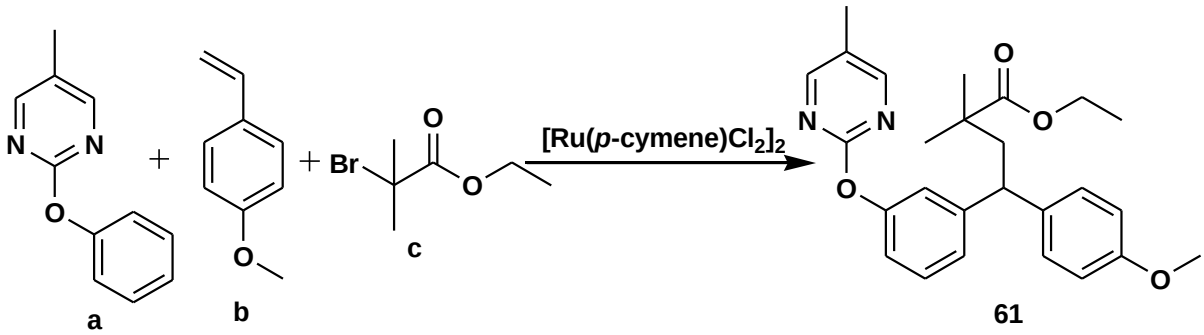


Scheme 52. Metal-free C-H functionalisation multicomponent reaction.

Luan and co-workers [71] reported the C-H functionalisation multicomponent reaction of phenol derivatives (**a**) in the presence of olefin (**b**) and alkyl bromides (**c**) using ruthenium as a catalyst with sodium carbonate, sodium acetate, and P(4-$ClC_6H_4)_3$ under argon conditions at 120 °C for 12 hours to afford functionalised phenols (**61**), as shown in Scheme 53. The substrate scope was successfully tested for all three components, including phenols (**a**), olefins (**b**), and alkyl bromides (**c**). The scope expansion on the phenol component revealed that the aromatic substrates, including electron-donating and electron-withdrawing groups resulted in good reactivity with percentage yield range of 15 – 71%. When the olefin substrate scope was investigated, substantially more products were obtained compared to the phenol substrate scope in a percentage yields range 22 – 76%. The third component alkyl bromides substrate, as anticipated, presented good reactivity and only produced eight examples of desired compounds with a percentage yield 50–81%, except for the *tert*-butyl bromide group, which was difficult to obtain.



Scheme 53. The C-H functionalisation of phenol derivatives,.

Pillitteri and co-workers [72] reported the use of polyoxometalate tetrabutylammonium decatungstate (TBADT) with sodium hydrogen sulphate in a C-H functionalisation multicomponent reaction of anilines (**a**) with aldehydes (**b**) and a radical source (**c**) in acetonitrile for 24 hours, as shown in Scheme 54. In order to investigate different conditions, acidic additives were tested and found to improve percent yield, whereas other additives, such as molecular sieves, could not improve reactivity. The scope of the components was successfully explored for the radical source, giving twelve examples of desired products (**62**) with a percentage yield ranging from 20–82%, whereas aldehydes were reported to give twelve examples with a percent yield in the range of 20–85%. The anilines were reported to give the highest yield of 97% with only five examples of desired products.

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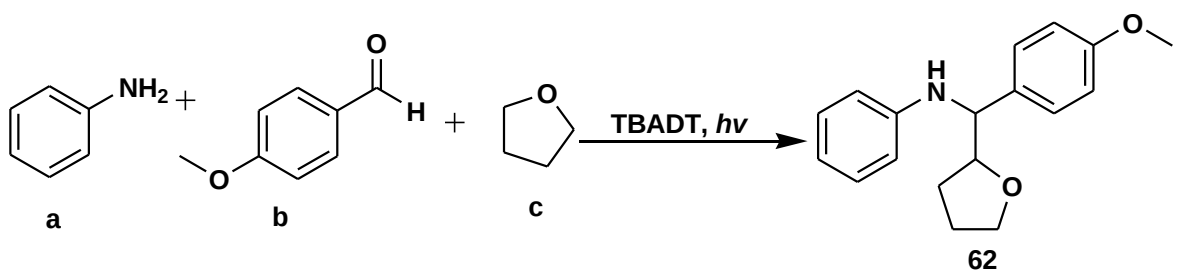
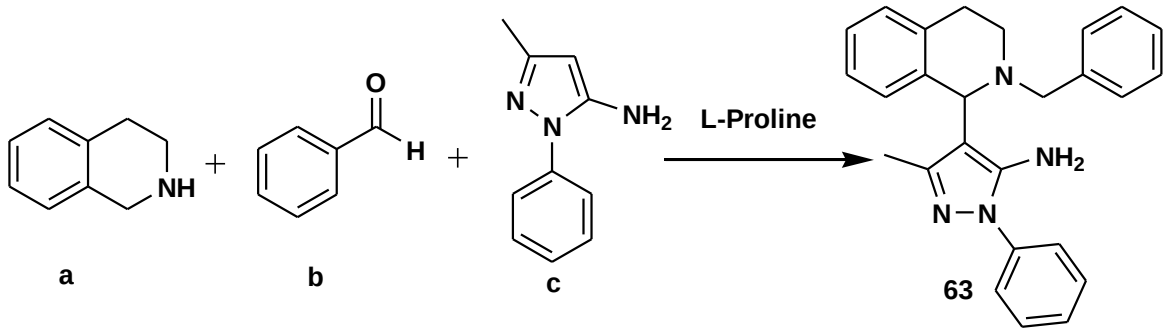


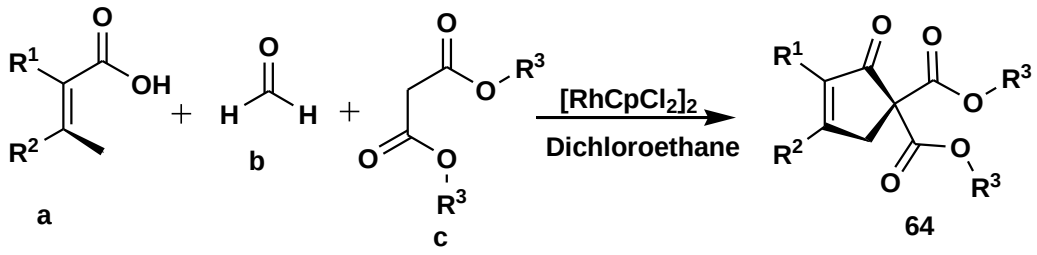
Scheme 54. The C-H functionalisation multicomponent reaction of a radical source.

The C-H functionalisation multicomponent reaction of tetrahydroisoquinolines (**a**) in the presence of aldehyde (**b**) and aminopyrazoles/indoles (**c**) using L-proline as a promoter was reported by Rahman and co-workers, as shown in Scheme 55 [73]. As reported when benzoic acid, acetic acids or Lewis acids were employed as promoters the reactivity was poor and resulted in lower percentage yields of the desired products (**63**). When L-proline was used as a catalyst at 120 °C under neat conditions even better results were achieved. The solvents effects were also tested by using dimethylformamide, acetonitrile, toluene, ethanol, and dimethyl sulfoxide; however, the outcome showed that solvent-free condition were the best for obtaining the products. It was also discovered that when the temperature was optimised there was no improvement in yields, whereas decreasing time resulted in yield decreases. The substrate scope was investigated by employing various aldehydes containing electron-withdrawing and electron donating groups.



Scheme 55. The C-H functionalisation multicomponent reaction of tetrahydroisoquinolines.

The C-H activation multicomponent reaction of acrylic acids (**a**), formaldehyde (**b**), and malonates (**c**) using rhodium as a catalyst and dichloromethane as a solvent at 130 °C for 3 hours was reported by Yu and co-workers, as shown in Scheme 56 [74]. It was reported that the reaction is triggered by the C-H activation of carboxyl-directed rhodium-catalysed vinylic, followed by formaldehyde and malonate to afford the desired cyclopentenone products (**64**).



Scheme 56. Synthesis of cyclopentenones using C-H functionalisation multicomponent reaction.

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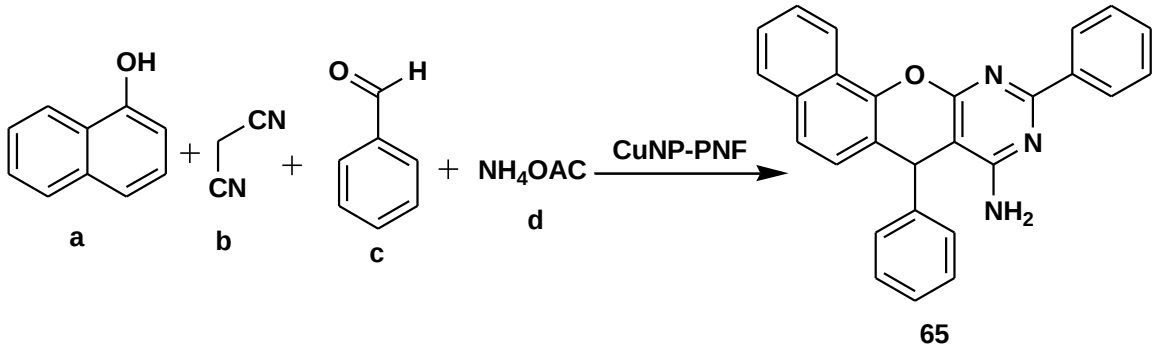
2.7. Peptide synthesis

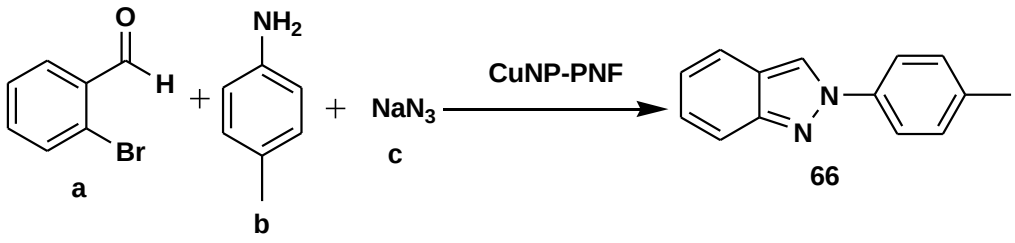
Peptides are often classified as amino acid chains with up to 50 residues that are flexible (have minimal secondary structure). Peptides are the building blocks of proteins, and contain fewer amino acids than a protein consists of. Peptides and proteins are known to be the most flexible and programmable polymers. They provide the solution to the basic biological operating principles and, in theory, permit the design of materials and structures with functions that are comparable to or even superior to those of the living world. There have been several developments in the synthesis of peptides *via* multicomponent reactions.

Taherinia and co-workers reported the multicomponent reaction of α-naphthol (**a**) with malononitrile (**b**) and benzaldehyde (**c**) in the presence of ammonium acetate (**d**) using CuNP-PNF as a catalyst at 130 °C to afford chromeno [2,3-*d*] pyrimidin-8-amine (**65**), as shown in Scheme 57 [75].



Scheme 57. Multicomponent synthesis of chromeno [2,3-*d*] pyrimidin-8-amine.

Moreover, the same author mentioned above, further reported the multicomponent reaction of 2-bromobenzaldehydes (**a**), *p*-toluidine (**b**) and NaN_3 (**c**), in the presence of CuNP-PNF as a catalyst using solvents such as water, toluene, DMSO, or polyethylene glycol (PEG) to afford 2*H*-indazole (**66**) at 130 °C (Scheme 58).



Scheme 58. Synthesis of indazole.

Martzel and colleagues [76] reported the multicomponent Knoevenagel-aza-Michael-cyclocondensation reaction of meldrum (**a**) with aldehydes (**b**), and acids of hydroxamic acid (**c**)-derived from naturally occurring α-amino acids to afford isoxazolidin-5-ones (**67**) possessing an *N*-protected α-amino acid, as demonstrated in Scheme 59. The reaction produced the isoxazolidin-5-ones (**67**) with good to high diastereoselectivities using a quinidine derived $(DHQD)_2PHAL$ catalyst in dichloromethane and toluene as solvents at 30 °C for 5 hours. Prolonging the reactions up to 24 hours allows the scope increment and overcomes the limitation of these reactions by producing up to a 99% yield of isoxazolidinone diastereoisomers, which were even possible to separate.

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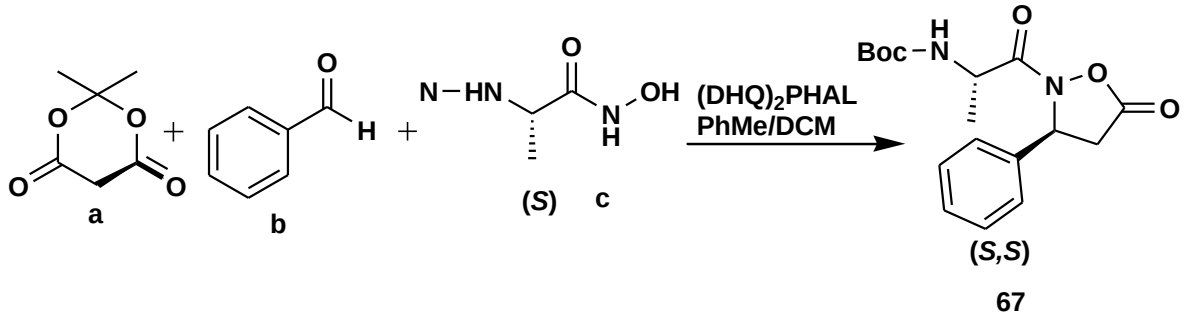
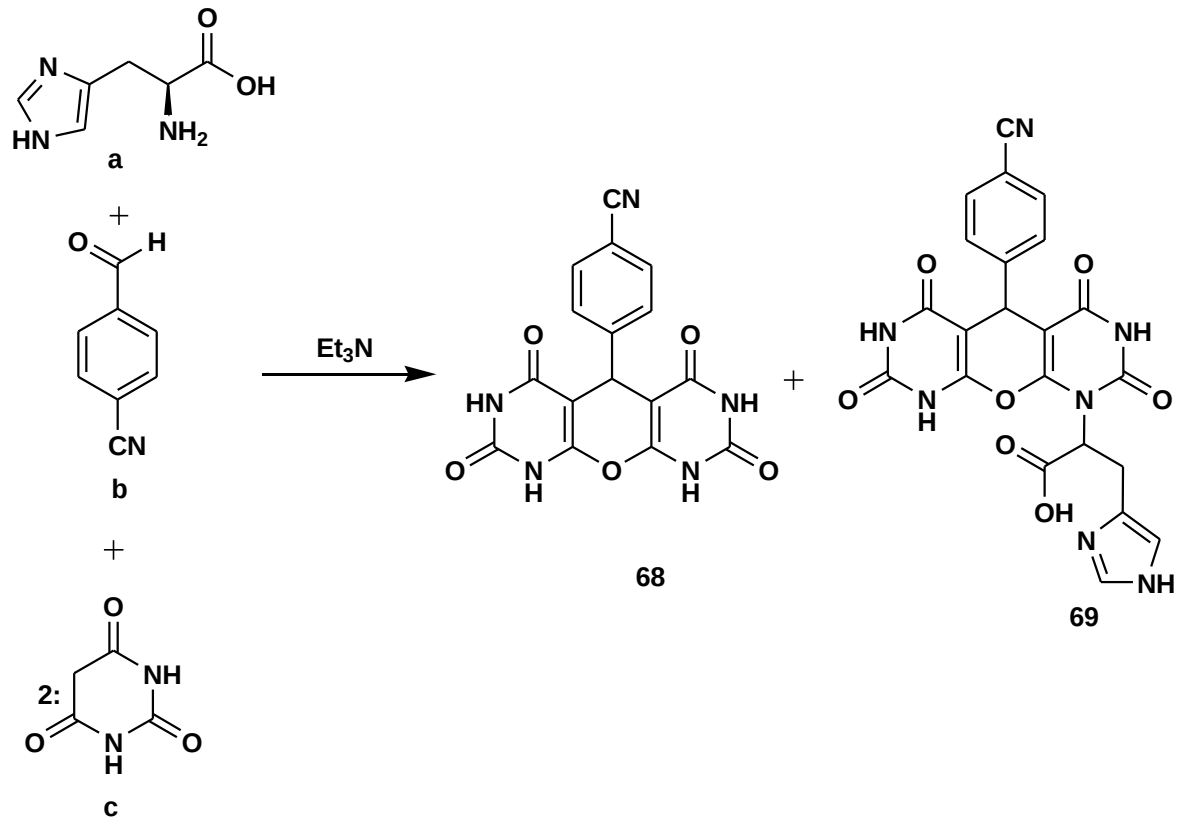


Scheme 59. Multicomponent reaction for the synthesis of isoxazolidin-5-ones.

Nourisefat and colleagues [77] described the reaction of l-histidine (**a**), 4-cyanobenzaldehyde (**b**), and barbituric acid (**c**) in the presence of triethylamine (Et_3N) as a catalyst using ethanol as a solvent under reflux conditions to produce structurally complex molecules (**68-69**), as shown in Scheme 60. This Hantzsch multicomponent reaction consists of amino acids and peptides, of which the scope was widen by the introduction of other substrates such as pyrimidine, xanthene, and acridine. The reactions were investigated at various temperatures, and it was discovered that 80 °C was conducive and suitable for this reactions. Different solvents such as dichloromethane, water, and toluene were tested; however, ethanol was found to be a better suitable solvent. With water as the solvent, an impressive yield was produced, although the isolated yield was said to be lower than that of ethanol.



Scheme 60. Hantzsch multicomponent reaction of l-histidine, 4-cyanobenzaldehyde and barbituric acid.

The Ugi-four component reaction of cyclohexyl isocyanide (**a**), aniline derivatives (**b**), and 2-methoxy quinoline-3-carbaldehyde derivatives (**c**) in the presence of lipoic acid (**d**) gave rise to a series of quinoline-based peptides (**70**), as shown in Scheme 61 [78]. The

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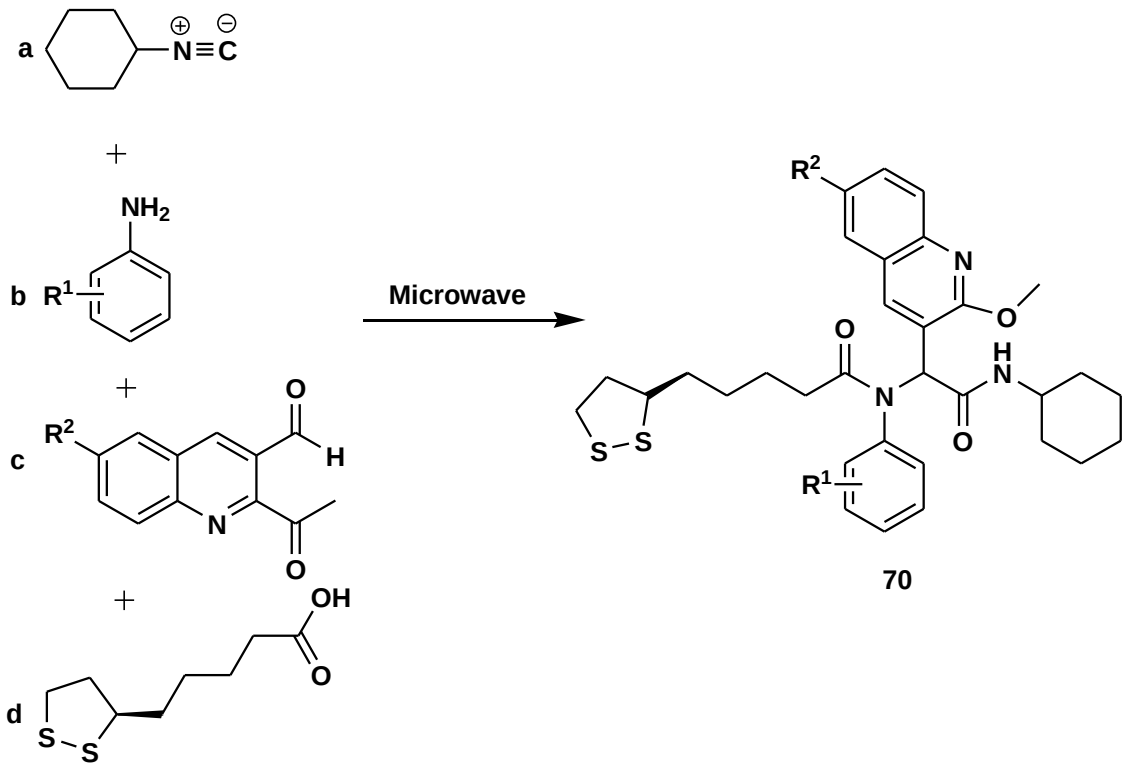
reactions were performed under microwave irradiation to obtain excellent yields with high purity of quinolone products using methanol as a solvent at 110 °C for 15 min. Other solvents that were investigated involved water, ethanol, acetonitrile, and dichloromethane, which gave relatively average yields, whereas methanol gave rise to a 90% yield of the desired product.



Scheme 61. The Ugi-four component reaction for the synthesis of quinolines.

De la Torre and co-workers [79] used an adopted method from Margio and co-workers [80] and Tiecco and co-workers [81] by treating *N*-(phenylseleno)phthalimide (**a**) in the presence of propanal (**b**) using Jørgensen's catalyst and *p*-nitrobenzoic acid (additive) at 1-20 °C for 24 hours in toluene to obtain benzylamine (**c**), as shown in Scheme 62. The prepared benzylamine (**c**) was used in a Ugi-4 component reaction with aniline (**d**), *tert*-butyl isocyanide (**e**), and acetic acid (**f**) in the presence of sodium sulphate (Na_2SO_4) as a drying agent to achieve the selenium-based peptoids (**71**) conjugates in moderate to good yields.

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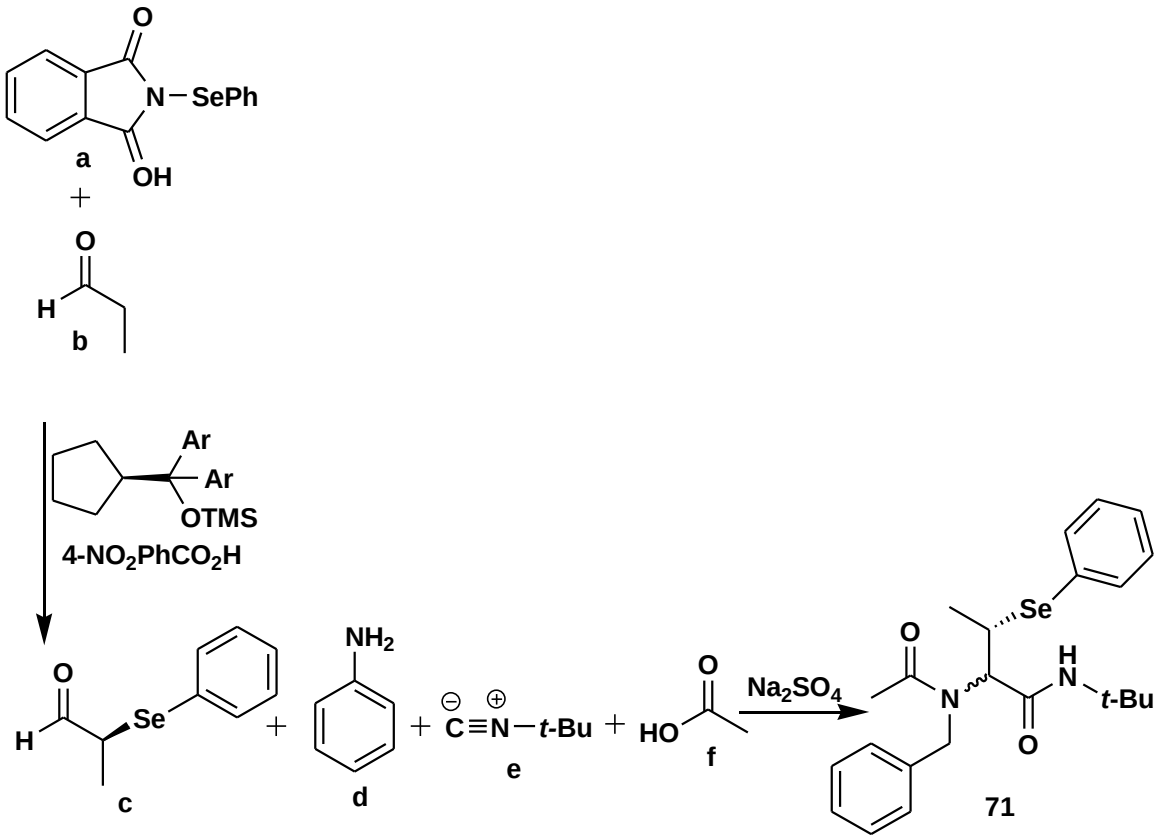
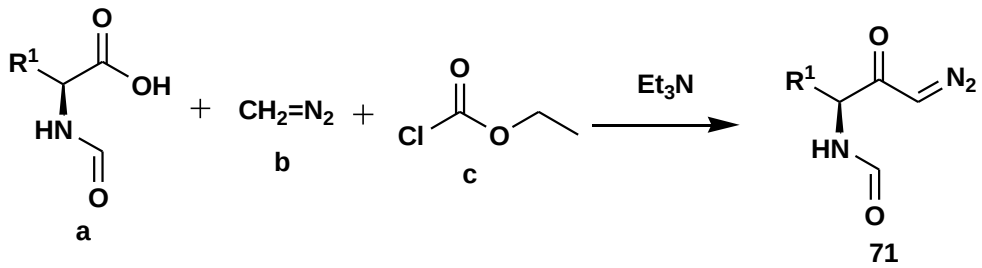


Scheme 62. Ugi-4 component reaction for the synthesis of peptoids and peptides.

Zarezin and co-workers reported the multicomponent synthesis of peptides (**72**) and depsipeptides (**73**) containing a *β*-amino acid fragment in good yields, as demonstrated in Schemes 63 and 64 [82]. The reaction of *N*-formyl amino acid (**a**), *N*-methylmorpholine (**b**), and ethyl chloroformate (**c**) in THF as a solvent at -20 °C for 5h in the presence of triethylamine afforded (*S*)-*N*-(4-Diazo-3-oxobutan-2-yl)formamide (**72**) derivatives, as shown in Scheme 63.



Scheme 63. Multicomponent synthesis of diazoketones.

When an amine (**a**), an isocyanide (**b**), carboxylic acid (**c**), and an aldehyde (**d**) were set for a reaction in dry methanol for 12 hours at room temperature, (3*S*)-Methyl 3-(2-(N-benzylbenzamido)-3-methylbutanamido)- 4-phenylbutanoate (**73**) derivatives were afforded, as displayed in Scheme 64.

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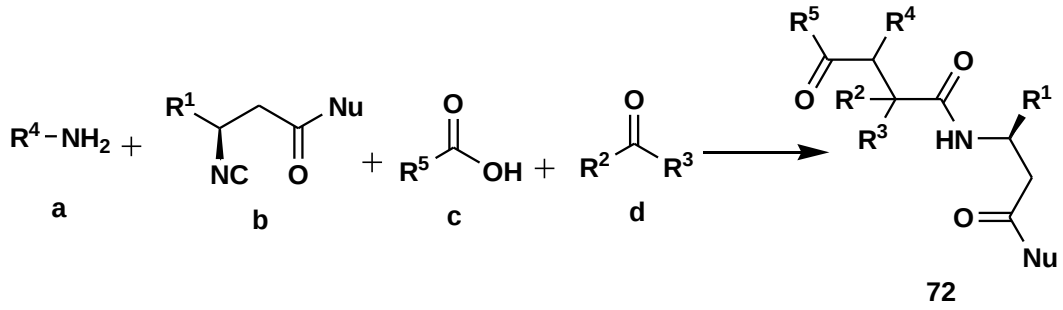
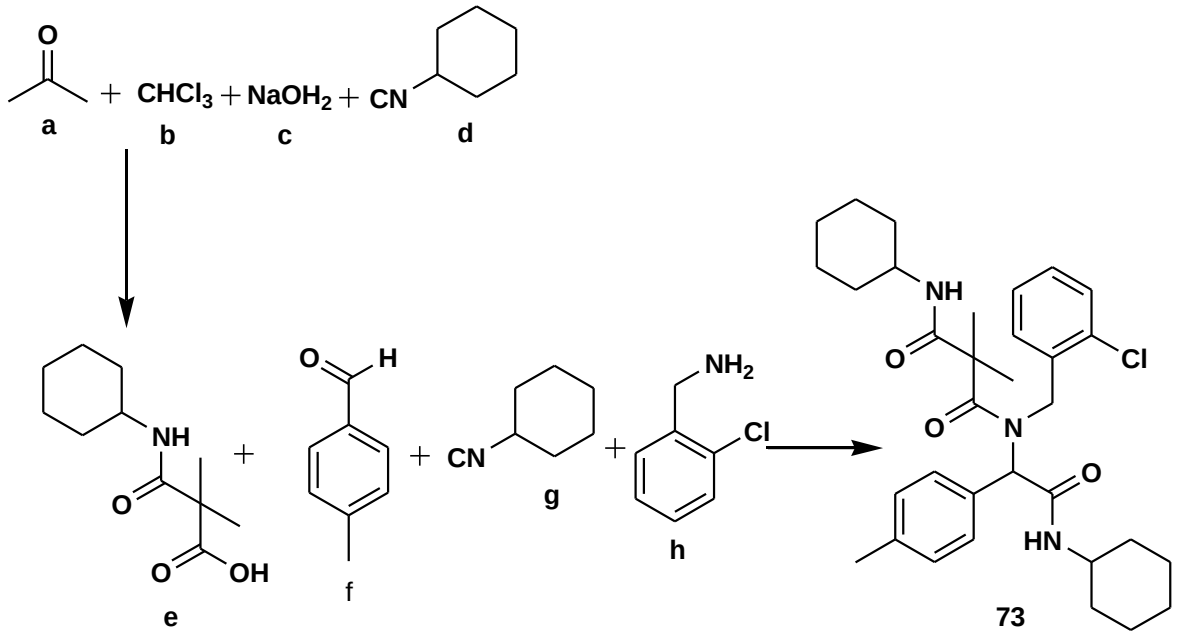


Scheme 64. Ugi-4 multicomponent for synthesis of peptides.

Farhid and co-workers reported the synthesis of pseudo-peptides (**73**) *via* isocyanide-based consecutive Bargellini/Ugi multicomponent reactions [83]. The reaction of acetone (**a**), chloroform (**b**), sodium hydroxide (**c**), and isocyanides (**d**) *via* Bargellini reaction gave rise to 3-carboxamido-isobutyric acids (**e**), this was then followed by the Ugi multicomponent strategy using 3-carboxamido-isobutyric acids (**e**) with aldehyde (**f**), isocyanides (**g**) and an amides to produce pseudo-peptides (**73**) containing three amide bonds, as demonstrated in Scheme 65.



Scheme 65. Synthesis of pseudo-peptides.

3. Conclusions

MCRs have been used for more than a century; yet it is still unclear who made the first discovery and first publication of an MCR, however, the Strecker multicomponent reaction [84] (S-3CR) was described in 1850, followed by the Hantzsch [85] dihydropyridine (DHP) synthesis reported in 1882. To date, MCRs are considered an advantageous approach because of their ability to rapidly generate molecular diversity and structural complexity of interest for different applications [86,87].

The involvement of MCRs in the synthesis of bioactive scaffolds in medicinal chemistry and drug discovery paved the way for the discovery and preparation of drugs such as lidocaine (xylocaine) [88], mandipropamid [89],nifedipine (procardia) [90], ezetimibe (zetia) [91], and prostaglandin B1 [92].

MCRs approach is considered an alternative route that adheres to green chemistry standards practiced in laboratories. MCRs offer a great chance for green chemical production methods to realise safe environments and pleasant practices in laboratories. The use of green solvents, working at mild temperatures, utilising biocatalysts, and engaging in catalyst-free reactions are some of the most well-known suggested practices and circumstances for a green chemical process.

The development of polymer science and innovative materials has been greatly accelerated by multicomponent polymerisation (MCP). These polymeric materials have distinctive mechanical, chemical, optical, thermal, fluorescence sensing, and optoelectronic features that improve their various practical chemical applications. In addition MCRs are used in solid-phase synthesis (SPS) and peptide synthesis for the development of bioactive heterocyclic compounds with distinct structural diversity.

On the other hand, multicomponent asymmetric reactions produce useful desired products, such as enantiopure natural scaffolds and bioactive compounds with benefits such as atom economy and recyclable catalysts. Whereas C-H functionalisation in MCRs can be done in different approaches, however, the formation of a C-H bond is relatively challenging in useful organic compounds. The synthesis and formation of this bonds is more efficient and atom-economical during the preparation and modification of scaffolds in organic chemistry. MCRs remains a better alternative route for organic synthesis todate as demonstrated in this review and in the future.

Author Contributions: Conceptualization R.L.M, E.M.C; investigation R.L.M, E.M.C; writing—original draft R.L.M; writing—review and editing T.J.R, E.M.C R.L.M; project administration R.L.M, funding acquisition R.L.M, T.J.R. All authors have read and agreed to the published version of the manuscript. R.L.M., T.J.R and E.M.C.

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References

1. Rocha, R.O.; Rodrigues, M.O.; Neto, B.A.D. Review on the Ugi Multicomponent Reaction Mechanism and the Use of Fluorescent Derivatives as Functional Chromophores. *ACS Omega*, **2020**, *5*, 972-979.
2. Zhong. Y. Arylformylacetonitriles in Multicomponent Reactions Leading to Heterocycles. Eur. *J. Org. Chem.* **2022**, e202201038, 1-11.
3 Yazdani., H.; Hooshmand, S.E.; Stenzel M.H. Fusion of Cellulose and Multicomponent Reactions: Benign by Design. *ACS Sustainable Chem. Eng*. **2022**, 10, 4359-4373.
4. Mohlala, R.L.; Coyanis, E.M.; Fish, M.Q; Fernandes, M.A.; Bode, M.L. Synthesis of 6-Membered-Ring Fused Thiazine-Dicarboxylates and Thiazole-Pyrimidines via One-Pot Three-Component Reactions. *Molecules*, **2021**;26, 5493.
5. Tang, X.; Zhu, S.; Ma,Y.; Wen, R.; Cen, L.; Gong, P.; Wang, J. A Simple and Efficient Synthesis of Highly Substituted Indeno[1,2-b]pyrrole and Acenaphtho[1,2-b]pyrrole Derivatives by Tandem Three-Component Reactions. Molecules, 2018, 23, 3031.
6. Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed*., **2000**, *39*, 3168-3210.
7. Wu, L.; Liu, Y.; Li, Y. Synthesis of Spirooxindole-O-Naphthoquinone-Tetrazolo[1,5-a]Pyrimidine Hybrids as Potential Anticancer Agents. *Molecules*, **2018**, 23, 1-9, doi:10.3390/molecules23092330.
8. Paprocki, D.; Madej, A.; Koszelewski, D.; Brodzka, A.; Ostaszewski, R. Multicomponent Reactions Accelerated by Aqueous Micelles. *Front. Chem*., **2018**, 6, 502. doi: 10.3389/fchem.2018.00502. [CrossRef].
9. Yang, X.; Wu, L. Synthesis of Novel 1,4-Naphthoquinones Possessing Indole Scaffolds Using In(OTf)3 in Solvent-Free Conditions. *Molecules*, **2018**, 23, 1-8, doi:10.3390/molecules23081954.

10. Shahedi, M.; Habibi, Z.; Yousefi, M.; Braskd, J.; Mohammadi, M. Improvement of biodiesel production from palm oil by co-immobilization of Thermomyces lanuginosa lipase and Candida antarctica lipase B: Optimization using response surface methodology. *Int. J. Biol. Macromol.*, **2021**, 170, 490-502.
11. Paprocki, D.; Madej, A.; Koszelewski, D.; Brodzka, A.; Ostaszewski, R. Multicomponent Reactions Accelerated by Aqueous Micelles. *Front. Chem*., **2018**, 6, 502. doi: 10.3389/fchem.2018.00502. [CrossRef]
12. Tang, X.; Zhu, S.; Ma, Y.; Wen, R.; Cen, L.; Gong, P.; Wang, J. A Simple and Efficient Synthesis of Highly Substituted Indeno[1,2-*b*]pyrrole and Acenaphtho[1,2-b]pyrrole Derivatives by Tandem Three-Component Reactions. *Molecules*, **2018**, 23, 1-10; doi:10.3390/molecules23113031.
13. Blakemore, D.C.; Castro, L.; Churcher, I.; Rees, D.C.; Thomas, A.W.; Wilson, D.M.; Wood, A. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem*. **2018**, 10, 383-394.
14. Gioiello, A.; Piccinno, A.; Lozza, A.M.; Cerra, B. The Medicinal Chemistry in the Era of Machines and Automation: Recent Advances in Continuous Flow Technology. *J. Med. Chem*. **2020**, 63, 6624-6647.
15. Milovi´c, E.; Jankovi´c, N.; Petronijevi´c, J.; Joksimovi´c, N.; Kosani´c, M.; Stanojkovic´, T., Matic´, I.; Grozdanic´, N.; Klisuric´, O.; Stefanovic, S. Synthesis, Characterization, and Biological Evaluation of Tetrahydropyrimidines: Dual-Activity and Mechanism of Action *Pharmaceutics*, **2022**, 14, 2254, 1-12.
16. Chavan, K.A.; Shukla, M.; Chauhan, A.N.S.; Maji, S.; Mali, G.; Bhattacharyya, S.; Erande, R.D. Effective Synthesis and Biological Evaluation of Natural and Designed Bis(indolyl)methanes via Taurine-Catalyzed Green Approach. ACS Omega, **2022**, 7, 10438-10446.
17. Mali, G.; Shaikh, B.A.; Garg, S.; Kumar, A.; Bhattacharyya, S.; Erande, R.D.; Chate, A.V. Design, Synthesis, and Biological Evaluation of Densely Substituted Dihydropyrano[2,3-c]pyrazoles *via* a Taurine-Catalyzed Green Multicomponent Approach. *ACS Omega*, **2021**, 6, 30734-30742.
18. Popovics-Toth, N.; Turpanova, M.; Nemeth, K.; Hackler, L.; Puskas, L.G.; Balint, E. Synthesis of arylphosphinoyl-functionalized dihydroisoquinolines by Reissert-type reaction and their biological evaluation. *Tetrahedron*, 111, **2022**, 132720.
19. Venkatesh, R.; Shankar, G.; Narayanan, A.C.; Modi, G.; Sabiah, S.; Kandasamy, J. Multicomponent Synthesis of S-Benzyl Dithiocarbamates from para-Quinone Methides and Their Biological Evaluation for the Treatment of Alzheimer's Disease. *J. Org. Chem*. **2022**, 87, 6730-6741.
20. Butera, R.; Ważyńska, M.; Magiera-Mularz, K.; Plewka, J.; Musielak, B.; Surmiak, E.; Sala, D.; Kitel, R.; De Bruyn, M.; Nijman, H.W.; Elsinga, P.H.; Holak, T.A.; Dömling, A. Design, Synthesis, and Biological Evaluation of Imidazopyridines as PD-1/PD-L1 Antagonists. *ACS Med. Chem. Lett*. **2021**, 12, 768-773.
21. Vahedi, M.M.; Asghari, S.; Tajbakhsh, M.; Mohseni, M.; Khalilpour. A. One-pot three-component synthesis of novel pyrano[3,2-e]pyrazolo[1,5-a]pyrimidines and investigation of their biological. *Journal of Molecular Structure,* 1284, **2023**, 135446.
22. Yang, Z.-J.; Gong, Q.-T.; Wang, Y.; Yu, Y.; Liu, Y.-H.; Wang, N.; Yu, X.-Q. Biocatalytic tandem multicomponent reactions for one-pot synthesis of 2-Amino-4H-Pyran library and in vitro biological. *Molecular Catalysis*, 491, **2020**, 110983.
23. Martinez-Amezaga, M.; Giordano, R.A.; Gori, D.N.P.; Squizatto, C.P.; Giolito, M.V.; Scharovsky, O.G.; Rozados, V.R.; Rico, M.J.; Mata, E.G.; Delpiccolo, C.M.L. Synthesis of propargylamines: Via the A3 multicomponent reaction and their biological evaluation as potential anticancer agents. *Org. Biomol. Chem*., **2020**, 18, 2475-2486.
24. Ayoup, M.S.; Wahby, Y.; Abdel-Hamid, H.; Ramadan, E.S.; Teleb, M.; Abu-Serie, M.M.; Noby, A. Design, synthesis and biological evaluation of novel α-acyloxy carboxamides via Passerini reaction as caspase 3/7 activators. *European Journal of Medicinal Chemistry*, 168, **2019**, 340-356.
25. Pradeep, M.A.; Kumar, N.R.; Swaroop, D.K.; Reddy, N.S.; Sirisha, K.; Kumar, C.G.; Babu, N.J.; Ganapathi, T.; Narsaiah, B. Design and Synthesis of Novel Pyrimidine/Hexahydroquinazoline-Fused Pyrazolo[3,4-b]Pyridine Derivatives, Their Biological Evaluation and Docking Studies. *ChemistrySelect*. **2019**, 4, 138-144.
26. Vasava, M.S.; Bhoi, M.N.; Rathwa, S.K.; Shetty, S.S.; Patel, R.D.; Rajani, D.P.; Rajani, S.D.; Patel, A.; Pandya, H.A.; Patel, H.D. Novel 1,4-dihydropyrano[2,3-c]pyrazole derivatives: Synthesis, characterization, biological evaluation and in silico study. *Journal of Molecular Structure*, **2019**, 1181, 383-402.
27. Bhagat, S.; Supriy, M.; Pathak, S.; Sriram, D.; Chakraborti, A.K. α-Sulfonamidophosphonates as new anti-mycobacterial chemotypes: Design, development of synthetic methodology, and biological evaluation. *Bioorganic Chemistry*. **2019**, 82, 246-252.
28. Karypidou, K.; Ribone, S.R.; Quevedo, M.A.; Persoons, L.; Pannecouque, C.; Dehaena, W. Synthesis, biological evaluation and molecular modeling of a novel series of fused 1,2,3-triazoles as potential anti-coronavirus agents. *Bioorganic & Medicinal Chemistry Letters*, **2018**, 28, 3472-3476.
29. Chate, A.V.; Dongre, R.M.; Khaire, M.K.; Bondle, G.M.; Sangshetti, J.N.; Damale, M. β-CD-catalyzed multicomponent domino reaction: synthesis, characterization, in silico molecular docking and biological evaluation of pyrano[2,3-*d*]-pyrimidinone derivatives. *Res Chem Intermed*, **2018**, 44, 6119-6136.
30. Anastas, P.T.; Warner, J.C. Green Chemistry: Theory and Practice, *Oxford University Press*, **1998**.
31. Asfaw, N.; Chebude, Y.; Ejigu, A.; Hurisso, B.B., Licence, P.; Smith, R.L.; Tang, S.LY.; Poliakoff, M. The 13 Principles of Green Chemistry and Engineering for a Greener Africa.
Green Chem., **2011**, *13*, 1059-1060.
32. Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.*, **2010**, *39*, 301-312.
33. Xu, J.; Yang, H.; He, L.; Huang, L.; Shen, J., Li; W.; Zhang, P. Synthesis of (E)-Quinoxalinone Oximes through a Multicomponent Reaction under Mild Conditions. *Org. Lett*. **2021**, 23, 195-201.

34 Wu, Y.; Chen, J-Y.; Ning, J.; Jiang, X.; Deng, J.; Deng, Y.; Xu, X.; He, W-M. Electrochemical multicomponent synthesis of 4-selanylpyrazoles under catalyst- And chemical-oxidant-free conditions. *Green Chem*., **2021**, 23, 3950-3954.

35 . Qu, C.; Liu, R.; Wang, Z.; Lv, Y.; Yue, H.; Wei, W. Visible-light-driven multicomponent reactions to access S-alkyl phosphorothioates using elemental sulfur as the sulfur source. *Green Chem*., **2022**, 24, 4915-4920.

36. Das, S.; Paul, S.; Mitra, B.; Pariyar, G.C.; Ghosh P. PEG-200: A versatile green solvent assisted catalyst-free one-pot three-component synthesis of functionalised N-amino-3-cyano-2-pyridone. *Results in Chemistry*, 5, **2023**, 100871.

37. Khaligh N.G.; Mihankhah T. Green and Solid-Phase Synthesis of New Dihydro-[1,2,4]Triazolo[1,5-a]Pyrimidine Scaffolds by Using Poly-Melamine-Formaldehyde as a Nitrogen-Rich Porous Organocatalyst. *POLYCYCLIC AROMATIC COMPOUNDS*, **2022**, 42, 942-950.

38. Li, K.; Lv, Y.; Lu, Z.; Yun, X.; Yan S. An environmentally benign multi-component reaction: Highly regioselective synthesis of functionalized 2-(diarylphosphoryl)-1,2-dihydro-pyridine derivatives. *Green Synthesis and Catalysis* 3, **2022**, 59-68.

39. Paul, S.; Das, S.; Mitra, B.; Pariyar, G.C.; Ghosh, P. β-Cyclodextrin: a green supramolecular catalyst assisted eco-friendly one-pot three-component synthesis of biologically active substituted. *RSC Adv*., **2023**, 13, 5457-5466.

40. Kerru, N.; Maddila, S.; Jonnalagadda, S.B. A Facile and Catalyst-Free Microwave-Promoted Multicomponent Reaction for the Synthesis of Functionalised 1,4-Dihydropyridines With Superb Selectivity and Yields. *Front. Chem.* **2021**, 9, 638832.

41 . Ma, X.; Zhang, X, Awad.; J.M.; Xie, G.; Qiu, W.; Zhang, W. One-pot synthesis of tetrahydro-pyrrolobenzodiazepines and tetrahydro-pyrrolobenzodiazepinones through sequential 1,3-dipolar cycloaddition/: N-alkylation (N-acylation)/Staudinger/aza-Wittig reactions *Green Chem*., **2019**, 21, 4489-4494.

42. El-Lateef, H. M. A.; Abdelhamid, A.A.; Khalaf, M.M.; Gouda, M.; Elkanzi, N. A. A.;
El-Shamy, H., Ali, A.M. Green Synthesis of Novel Pyridines *via* One-Pot Multicomponent Reaction and Their Anti-Inflammatory Evaluation. *ACS Omega*, **2023**, 8, 11326-11334.

43. Tian, T.; Hu, R.; Tang, B. Z. Room Temperature One-Step Conversion from Elemental Sulfur to Functional Polythioureas through Catalyst-Free Multicomponent Polymerizations. *J. Am. Chem. Soc*. **2018**, 140, 6156-6163. [CrossRef].

44 . Velencoso, M. M.; Battig, A.; Markwart, J. C.; Schartel, B.; Wurm, F. R. Molekulare Brandbekämpfung – wie moderne Phosphorchemie zur Lösung der Flammschutzaufgabe beitragen kann. *Angew. Chem.,Int. Ed*. **2018**, 57, 10450-10467.

45. Wang, T.; Zhang, N.; Bai, W.; Bao, Y. Synthesis of Stable Thiazole-Linked Covalent Organic Frameworks via a Multicomponent Reaction. One-Step Multicomponent Polymerizations for the Synthesis of Multifunctional AIE Polymers *Polym. Chem*. **2020**, 11, 3095-3114.

46. Su, X.; Han, T.; Niu N.; Li, H.; Wang, D.; Tang B.Z. Facile Multicomponent Polymerizations toward Multifunctional Heterochain Polymers with α,β-Unsaturated Amidines. *Macromolecules*, **2021**, 54, 9906-9918.

47 . Xu, L.; Zhou, T.; Liao, M., Hu; R., Tang, Z.B. Multicomponent Polymerizations of Alkynes, Sulfonyl Azides, and 2-Hydroxybenzonitrile/2-Aminobenzonitrile toward Multifunctional Iminocoumarin/Quinoline-Containing Poly(N-sulfonylimine)s. *ACS Macro Lett*. **2019**, 8, 2, 101-106.

48. Tian, T.; Hu,R.; Tang, B.Z. Room Temperature One-Step Conversion from Elemental Sulfur to Functional Polythioureas through Catalyst-Free Multicomponent Polymerizations. *J. Am. Chem. Soc*. **2018**, 140, 6156-6163. [CrossRef]

49. Su, X.; Gao, O.; Wang, D.; Han, T.; Tang B.Z. One-Step Multicomponent Polymerizations for the Synthesis of Multifunctional AIE Polymers. *Macromol. Rapid Commun*. **2021**, 42, 2000471.

50. Tuten, B.T.; Bloesser, F.R.; Marshall, D.L.; Michalek, L.; Schmitt, C.W.; Blanksby, S.J.; Barner-Kowollik, C. Polyselenoureas *via* Multicomponent Polymerizations Using Elemental Selenium as Monomer. *ACS Macro Lett*. **2018**, 7, 898-903.

51. Zhang, L.; Hu, Y.; Hu R.; Tang, B.Z. Room temperature synthesis of polythioamides from multicomponent polymerization of sulfur, pyridine-activated alkyne, and amines. *Chem. Commun*., **2022**, 58, 1994.

52. Chen, Q.; Ye J.; Zhu, L.; Luo J.; Cao, X.; Zhang, Z. Organocatalytic multicomponent polymerization of bis(aziridine)s, diols, and tosyl isocyanate toward poly(sulfonamide urethane)s. *European Polymer Journal*, 180, **2022**, 111585.

53. Potowski, M.; Esken, R.; Brunschweiger, A. Translation of the copper/bipyridine-promoted Petasis reaction to solid phase-coupled DNA for encoded library synthesis. *Bioorganic & Medicinal Chemistry*, 28, **2020**, 115441.

54. Zaharani, L.; Khaligh, N, G.; Mihankhah, T.; ·Johan, M.R. Application of nitrogen-rich porous organic polymer for the solid-phase synthesis of 2-amino-4H-benzo[*b*]pyran scaffolds using ball milling process. *Molecular Diversity*, **2021**, 25:323-332.

55. Bucci, R.; Dapiaggi, F.; Macut, H.; Pieraccini, S.; Sironi, M.; Gelmi, M.L.; Erba, E.; Pellegrino, S. On-resin multicomponent 1,3-dipolar cycloaddition of cyclopentanone–proline enamines and sulfonylazides as an efficient tool for the synthesis of amidino depsipeptide mimics. *Amino Acids*, **2020**, 52, 15-24.

56 . Mendez,Y.; Armas, G.D.; Perez, I.; Rojas, T.; Valdes-Tresanco, E.V.; Izquierdo,M.; del Rivero, M.A.; Alvarez-Ginarte Y.M.; Valiente,P.A.; Soto,C.; de Leon L.; Vasco,A.V.; Scott, W.L.; Westermann, B.; Gonzalez-Bacerio, G.; Rivera, D.G. Discovery of potent and selective inhibitors of the Escherichia coli M1-aminopeptidase via multicomponent solid-phase synthesis of tetrazole-peptidomimetics. *European Journal of Medicinal Chemistry* 163, **2019**, 481-499.

57. Massarano, T.; Mazir, A.; Lavi, R.; Byk, G. Solid-Phase Multicomponent Synthesis of 3-Substituted Isoindolinones Generates New Cell-Penetrating Probes as Drug Carriers. *ChemMedChem*, **2020**, 15, 833-838.

58. Alvim, H.G.O.; Pinheiro, D.L.J.; Carvalho-Silva, V.H.; Fioramonte, M.; Gozzo, F. C.; da Silva, W.A.; Amarante, G.W.; Neto, B.A.D. Combined Role of the Asymmetric Counteranion-Directed Catalysis (ACDC) and Ionic Liquid Effect for the Enantioselective Biginelli Multicomponent Reaction. *J. Org. Chem*. **2018**, 83, 12143-12153.

59. Tang, Y.; Xu, J.; Yang, J.; Lin, L.; Feng, X.; Liu1, X. Asymmetric Three-Component Reaction for the Synthesis of Tetrasubstituted Allenoates via Allenoate-Copper Intermediates. *Chem*, **2018**, 4, 1658-1672.
60. Zhang, D.; Lin, L.; Yang, J.; Liu, X.; Feng, X. Asymmetric Synthesis of Tetrahydroindolizines by Bimetallic Relay Catalyzed Cycloaddition of Pyridinium Ylides. *Angew. Chem. Int. Ed*. **2018**, 57, 12323-12327.
61. Kuang, X-K.; Zhu, J.; Zhou, L.; Wang, L.; Wang, S.R.; Tang, Y. Synergetic Tandem Enantiomeric Enrichment in Catalytic Asymmetric Multi-Component Reactions (AMCRs): Highly Enantioselective Construction of Tetracyclic Indolines with Four. *ACS Catal.* **2018**, 8, 4991-4995.
62. Ji, Y-L.; Li, H-P.; Ai, Y-Y.; Li, G.; He, X-H.; Huang, W.; Huang, R-Z.; Han, B. Enantio- A nd diastereoselective synthesis of spiropyrazolones: Via an organocatalytic [1 + 2 + 3] multicomponent reaction. *Org. Biomol. Chem*., **2019**, 17, 9217-9225.
63. Xiong, Q.; Li, G.; Dong, S.; Liu, X.; Feng, X. Enantioselective Synthesis of Hydrothiazole Derivatives via an Isocyanide-Based Multicomponent Reaction. *Org. Lett*. **2019**, 21, 877-8775
64. Zou, L.; Huang, J.; Liao, N.; Liu, Y.; Guo, O.; Peng, Y. Catalytic asymmetric three-component reaction of 2-alkynylbenzaldehydes, amines, and dimethylphosphonate. *Org. Lett*. **2020**, 22, 693-6937.
65. Zamudio-Medina, A.; Pérez-Hernández, N.; Castrejón-Flores, J.L.; Romero-García, S.; Prado-García, H.; Bañuelos-Hernández, A.; Franco-Pérez M. Obtaining symmetric and asymmetric bisphosphoramidates and bisphosphoramidothioates by a single step multicomponent reaction. *Phosphorus, Sulfur and Silicon and the Related Elements*, **2021**, 196, 634-642.
66. Borpatra, P.J.; Rastogi G.K.; Saikia B-S.; Deb, M.L.; Baruah, P.K. Multi-Component Reaction of 6-Aminouracils, Aldehydes and Secondary Amines: Conversion of the Products into Pyrimido[4,5-*d*]pyrimidines through C-H Amination/Cyclization. *ChemistrySelect*, **2019**, 4, 3381-3386.
67 Wang, X.-G.; Li Y.; Liu, H.-C.; Zhang, B.-S.; Gou, X.-Y.; Wang, Q.; Ma, J.-W.; Liang,.Y.-M. Three-Component Ruthenium-Catalyzed Direct Meta-Selective C-H Activation of Arenes: A New Approach to the Alkylarylation of Alkenes. *J. Am. Chem. Soc*. **2019**, 141, 13914-13922
68. Herraiz, A.G.; Cramer, N. Cobalt(III)-Catalyzed Diastereo- and Enantioselective Three-Component C–H Functionalization. *ACS Catal*. **2021**, 11, 11938-11944.
69. Shi, S.; Zhang, P.; Luo C.; Zhuo, S.; Zhang, Y.; Tang, G.; Zhao, Y. Copper-Catalyzed Remote C(sp3)-H Phosphorothiolation of Sulfonamides and Carboxamides in a Multicomponent Reaction. *Org. Lett*. **2020**, 22, 1760-1764.
70. Mandal, S.; Dwari, S.; Jana, C.K. Metal Free C-H Functionalization Enabled Diastereoselective Multicomponent Reaction of N-Heterocycles to Fused Heteropolycycles. *J. Org. Chem*. **2018**, 83, 8874-8887.
71. Luan, Y-Y.; Gou, X-Y.; Shi, W-Y.; Liu, H-C.; Chen, X.; Liang, Y.M. Three-Component Ruthenium-Catalyzed meta-C-H Alkylation of Phenol Derivatives. *Org. Lett*. **2022**, 24, 1136-1140.
72. Pillitteri, S.; Ranjan, P.; Voskressensky, L.G.; Van der Eycken, E.V., Sharma, U.K. Alkylation of in situ generated imines via photoactivation of strong aliphatic C-H bonds. *Molecular Catalysis*, 514, **2021**, 111841.
73. Rahman, I.; Deka, B.; Thakuri, R.; Mohit, L.; Deb, M.L.; Baruah, P.K. L-Proline-catalyzed regioselective C1 arylation of tetrahydroisoquinolines through a multicomponent reaction under solvent-free conditions. *Org. Biomol. Chem*., **2020**,18, 6514.
74. Yu, S.; Hong, C.; Liu, Z.; Zhang, Y. Synthesis of Cyclopentenones through Rhodium-Catalyzed C-H Annulation of Acrylic Acids with Formaldehyde and Malonates. *Org. Lett*. **2021**, 23, 5054-5059.
75. Taherinia, Z.; Ghorbani-Choghamarani, A.; Hajjami, M. Decorated Peptide Nanofibers with Cu Nanoparticles: An Efficient Catalyst for the Multicomponent Synthesis of Chromeno [2, 3-d] pyrimidin-8-amines, Quinazolines and 2H- Indazoles. *ChemistrySelec*t, **2019**, 4, 2753-2760.
76. Martzel, T.; Annibaletto, J.; Millet, P.; Pair, E.; Sanselme, M.; Oudeyer, S.; Levacher, V.; Briere, J-F. Organocatalytic Multicomponent Synthesis of α/β-Dipeptide Derivatives. *Chem. Eur. J*. **2020**, 26, 8541-8545.
77. Nourisefat, M.; Panahi, F.; Khalafi-Nezhad, A. Amino acids and peptides as reactants in multicomponent reactions: modification of peptides with heterocycle backbones through combinatorial chemistry. *Molecular Diversity*, **2019**, 23, 317-331.
78. Thangaraj, M.; Gengana, R.M.; Ranjan, B.; Muthusamy, R. Synthesis, molecular docking, antimicrobial, antioxidant and toxicity assessment of quinoline peptides. *Journal of Photochemistry & Photobiology, B: Biology*. **2018**, 178, 287-295.
79. De la Torre A.F.; Ali A.; Galetto F.Z.; Braga A.L.; Delgado J.A.C.; Paixão M.W. One-pot organocatalytic/multicomponent approach for the preparation of novel enantioenriched non-natural selenium-based peptoids and peptide–peptoid conjugates. *Molecular Diversity*, **2020**, 24, 1-10.
80Marigo, M.; Wabnitz, T.C.; Fielenbach, D.; Jørgensen, K.A. Enantioselective Organocatalyzed α Sulfenylation of Aldehydes. *Angew Chem Int Ed*, **2005**, 44:794-797.
81. Tiecco, M.; Carlone, A.; Sternativo, S.; Marini, F.; Bartoli, G.; Melchiorre, P. Organocatalytic asymmetric α-selenenylation of aldehydes. *Angew Chem Int Ed*, **2007**, 46, 6882-6885.
82. Zarezin, D.P.; Shmatova, O.I.; Nenajdenko, V,G. Chiral β3-isocyanopropionates for multicomponent synthesis of peptides and depsipeptides containing a β-amino acid fragment. *Org. Biomol. Chem*., **2018**, 16, 5987-5998.
83. Farhid, H., Nazeri, M.T., Shaabani, A., Armaghan, M., Janiak, C. Isocyanide-based consecutive Bargellini/Ugi reactions: an efficient method for the synthesis of pseudo-peptides containing three amide bonds. *Amino Acids*, **2021**, 53, 1-10.
84. Strecker D., Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper. Annalen der Chemie und Pharmacie,. *Ann. Chem. Pharm*. **1850,** *75*, 27-45.
85. Hantzsch, A. Ueber die synthese pyridinartiger verbindungen aus acetessigäther und aldehydammoniak. *Liebigs Ann. Chem.*, **1882**, *215*, 1-82.

 doi:10.20944/preprints202306.0345.v1

86. Mohlala, R.L.; Coyanis, E.M.; Fernandes, M.A.; Bode, M.L. Catalyst-free synthesis of novel 1,5-benzodiazepines and 3,4-dihydroquinoxalines using isocyanide-based one-pot, three- and four-component reactions. *RSC Adv* **2021**;11, 24466-24473.
87. Mohlala, R.L.; Coyanis, E.M.; Fernandes, M.A.; Bode, M.L. Synthesis of highly functionalised 5-membered ring fused pyrimidine derivatives using an isocyanide-based one-pot, three component reaction. *Tetrahedron Lett*, **2020**;61,151796.
88. Ugi, I.; Steinbrückner C. *Chem. Ber.*, **1961**, *94*, 734-742.
89. Lamberth, C, Jeanguenat, A, Cederbaum, F, De Mesmaeker, A, Zeller, M,. Kempf H.-J., Zeun R, *Bioorg. Med. Chem*., **2008**, *16*, 1531-1545.
90. Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem. Int. Ed. Engl*, **1981**, *20*, 762-769.
91. Rosenblum, S.B.; Huynh. T.; Afonso, A.; Davis, H.R.; Yumibe, N.; Clader, J.W.; Burnett, D.A. Discovery of 1-(4-Fluorophenyl)-(3R)-[3-(4-fluorophenyl)-(3S)- hydroxypropyl]-(4S)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A Designed, Potent, Orally Active Inhibitor of Cholesterol Absorption. *J. Med. Chem*., **1998**, *41*, 973-980.
92. Vazquez-Romero, A.; Cardenas, L.; Blasi, E.; Verdaguer, X.; Riera, A. Synthesis of Prostaglandin and Phytoprostane B1 *Via* Regioselective Intermolecular Pauson−Khand Reactions. *Org. Lett*., **2009**, *11*, 3104-3107.