Review

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Multicomponent Reactions in the Last 30 Years: How are we Today?

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In this review, the works carried out in Brazil with multicomponent reactions over a period of 30 years were mapped through search in the literature (PubMed, Scopus, and Web of Science). A significant increase in papers with multicomponent reactions in Brazil was identified. In total, 243 articles with 6,672 citations (average of 27.46 citations *per* article) were found. Biginelli, Ugi, Mannich, Passerini and Hantzsch are the most employed reactions, and the articles were classified in medicinal chemistry, catalyst, mechanism, green chemistry, asymmetric synthesis and fluorescent. A bibliometric analysis with the 243 articles was performed, including the number of publications, citations, predominant journals, Brazilian universities with the highest number of publications on the subject, and international collaborations.

Keywords: multicomponent reactions, organic synthesis, medicinal chemistry, green chemistry, catalyst

1. Introduction

A medicinal chemistry project that aims to discover new drugs requires a tremendous effort from scientists involved in all stages of the process, since medicinal chemistry is characterized as interdisciplinary. Despite the great scientific and technological advances achieved today, the discovery of new therapeutic agents can still take more than a decade, with many obstacles to be overcome, mainly related to the pre-clinical phase of research.[1,2] Chemical strategies to shorten and accelerate this research time have been developed over time, such as the emergence of Combinatorial Chemistry in the 80s (CombiChem).[3] Thirty years ago, reactions were carried out and compounds were built one by one, libraries were slowly built and tests were carried out only at the end of synthesizing all the planned compounds. There was no concern about speeding up the generation of libraries of bioactive compounds (hits). Developed in the 1990s, CombiChem is a technique for discovering hits that deals with the rapid and simultaneous synthesis of different compounds ready for testing, thanks to computerized and automated processes.[4–7] In CombiChem, syntheses must employ as few steps as possible and provide compounds with high degree of purity or that can be easily purified. Therefore, multicomponent reactions (MCRs) were easily aggregated at that time, and the first articles were written with Ugi and Biginelli reactions.[8–12]

MCRs are reactions carried out involving at least three different reagents, in just one-step (one pot), in a single reaction flask, in which all atoms, or most of them, of the reactants are part of the product. In these reactions, two reactants react to form a more reactive intermediate, which in turn will react with the next reactant, and so on; until the last step, which is irreversible, leading to the product, and producing cascade reactions. Therefore, more than one reaction mechanism may be involved, which explains

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the existence of several publications about mechanism on a given MCR, as it will be described in this text. In most cases this type of synthesis is simple to perform, the mixing of reagents does not generate secondary products and the yields are rather quantitative. Through MCRs, a vast array of products can be potentially generated and synthesized by exploring the multiple possibilities of reagent combinations in a single experimental procedure.[13] It is very useful for synthesizing the final product, and also for obtaining an intermediate product in a convergent or linear synthesis, and can lead to the construction of libraries of compounds of all sizes and of great chemical and structural diversity. It can be used to synthesize both structurally simple and complex compounds, with varied applicability.

MCRs are currently widely used in organic synthesis, distributed in several areas such as Catalysis,[14] Nanomaterials,[15] Liquid Crystals,[16] Green Chemistry,[17] and Medicinal Chemistry.[18] Today there is a range of reviews and even books dealing with MCRs due to their wide application in these different areas of Chemistry. In the fields of medicinal chemistry and organic synthesis, it is not different; several researchers have adopted MCR as a tool and created texts on the subject easily available in scientific databases accessible on the internet, for instance. MCRs have been known for over 180 years and the majority of them are identified by the names of the corresponding researchers. The most popular ones are known as Strecker synthesis, Mannich reaction, Biginelli reaction, Hantzsch reaction, Passerini, and Ugi condensation. In Figure 1, we have two examples of structures of Biginelli and Ugi adducts described, highlighting the components (multiple reagents) condensed into a single reaction product.

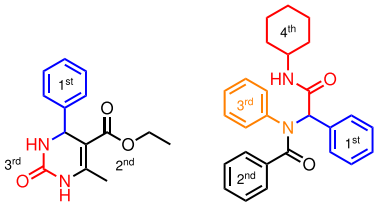


Figure 1. Structures of Biginelli (dihydropyrimidinone) and Ugi (α-aminoacyl amide) adducts obtained from MCRs with three and four components, respectively.

The success attributed to MCRs is derived from the many apparent advantages of this methodology over other convergent or linear synthetic processes. The advantages are related to the efficiency of the process, in terms of atomic economy, time, and energy, and reduced generation of waste. In this sense, MCRs align with many principles of Green Chemistry.[19,20]

Due to the importance and great usefulness of MCRs in both academy and industry, we decided to map the work carried out in Brazil involving this synthetic strategy, by a search carried out in the literature over a period of 30 years. Knowing the most used reactions, the catalysis methods or associated equipment, the synthesized compounds and their applications seemed very interesting to us as they enable better design for those who work or want to work with MCR, both in synthesis and medicinal chemistry. Our goals are to dive into the work carried out with MCR rather than make an intensive review, with reaction mechanisms or experimental details, but to investigate the adherence of Brazilian researchers to this synthetic tool over the last 30 years. The idea is not just to verify that Brazilian research work with MCR in their projects, but rather to observe what the data show us. To this end, we will start with a brief history of MCRs (so the reader can compare with related scientific findings of the time), followed by the international data on MCR and their connection with medicinal chemistry, as well as data from publications by Brazilians on MCR. In order to accomplish these objectives, we conducted the search using scientific repositories and databases such as Web of Science, PubMed and Scopus.

Our perspective is to publicize the work of Brazilian researchers, map the areas of activity and detect the degree of adherence to this olden but modern way of carrying out organic synthesis. With this work, we also hope to further popularize MCR and Brazilian groups that adopt MCR in their laboratories, perhaps attract young synthetic chemists, since the Journal of the Brazilian Chemical Society (JBCS) has a broad readership. The importance of such reactions for medicinal chemistry is evident and this was the reason why we presented this review.

2. Brief History

The first MCRs published in the literature were three-component, and date back to the first half of the 19th and early 20th centuries. The timeline in Figure 2 shows the first reported MCRs. From this, we can see that the first report of a tri-component appeared in 1838 by Laurent and Gerhardt[21] in France. These two chemists worked with essential oils, mainly curcumin, and in their experiments, they observed that in the presence of ammonia, compound **A** precipitated. This essential oil contained benzaldehyde and hydrocyanic acid and, in the presence of ammonia, formed these crystals.

Some years later, in 1850, in an attempt to prepare lactic acid from a mixture of ammonia, acetaldehyde and hydrogen cyanide, Strecker[22] obtained a compound different from the one initially desired, an α-aminonitrile compound.

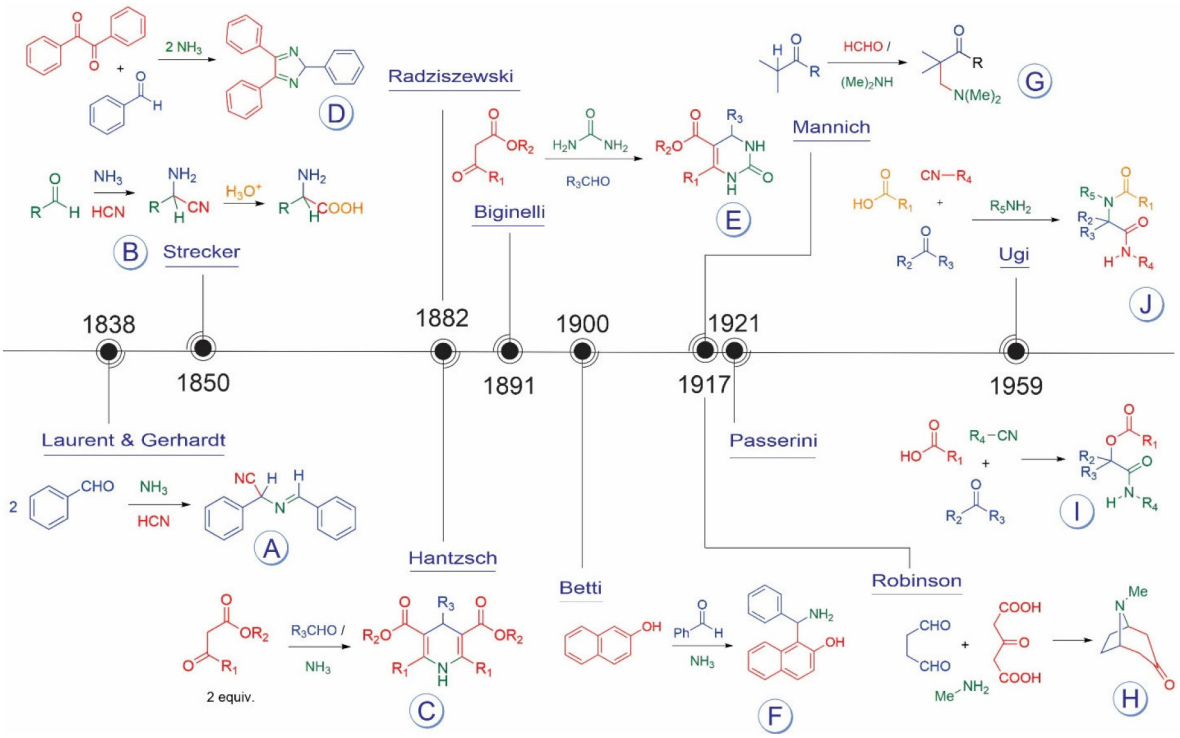


Figure 2. The first MCRs published in the scientific literature.

Strecker published his first findings "…combined an acetaldehyde-ammonium solution with hydrocyanic acid in the same flask for 12 hours, producing a brown mass at the end. The reaction were repeated but immediately vaporizing the aqueous solution of acetaldehyde-ammonium and HCN in a water bath; leaving a thick, brown syrup, which after a few hours produced crystals in a brown mass. This reaction crude was dissolved in boiling water and, when cooled, formed crystals, thin, colorless and very shiny needles…". It was in this way that Strecker could synthesize useful and structurally different amino acids, by the simplest and fastest method ever carried out. This opened the way for other chemists to use this reaction and the emergence and establishment of the synthesis of several amino acids, including on an industrial scale.

Three decades later, the first heterocycles were obtained with the works of Hantzsch[23] and Radzisewski[24] in 1882 and Biginelli[25] in 1891 (Figure 2). Dr Arthur Hantzsch[23] reported the synthesis of pyridine derivatives (compound **C**): "...condensation between acetoacetic ether and ammonium aldehyde can easily occur....". In the same year, Radzisewski[24] published the synthesis of imidazole **D** by mixing benzyl, benzaldehyde and two equivalent of ammonia. Biginelli[25] first published an acyclic product of the reaction between ethyl acetoacetate, benzaldehyde and urea. However, with further studies he corrected his findings, publishing the reaction product as a pyrimidine derivative **E**.[25]

A few years later, in 1900, Mario Betti[26] published the synthesis of 1-(α-aminobenzyl)-2-naphthol **F** from a three-component reaction between β-naphthol, benzaldehyde and ammonia. This reaction is known today as Betti reaction.[27] Continuing this tour through the past, at the beginning of the 20th century (Figure 2), professor of pharmaceutical chemistry Carl Mannich published his findings involving the synthesis of α-methylamine **F**.[28-30] From this work, this reaction became known as the Mannich reaction, which is an α-aminomethylation reaction that occurs between ammonia or primary or secondary amines, aldehyde and compounds with active methylene. It is interesting to note that it was in a publication by Mannich and Krösche[29] in 1912 that the term "component" was used for the first time: "*…Es ist mithin gleichgültig, in welcher Reihenfolge die Komponenten : Antipyrin, Formaldehyd, Ammoniak and Salzsaure aufeinander einwirken, immer entsteht dasselbc schwer losliche salzsaure Salz…*". Such reaction today is one of the most used in organic synthesis to produce β-amino carbonyl compounds.[30] In this same year, Robert Robinson published the synthesis of tropinone **H**, a tropane alkaloid. Until Robinson's work this compound was obtained by oxidation of torponine, a natural metabolite.[31]

In a recent work, Alexander Dömling[32] makes an excellent analysis of the Passerini and Ugi reactions and their connection with the Schiff reaction. In this manuscript, when briefly addressing the history of these two reactions, the author highlights that Passerini,

together with Mario Betti and Pietro Biginelli, were Schiff's students in his Laboratory at the Florence University. Hugo Schiff is known for the condensation reaction between amines and aldehydes or ketones to form imines, known as Schiff base. Dömling[33] highlights the interesting fact that imines are intermediates in the MCRs discovered by these three chemists, with both Betti and Biginelli making their discoveries in Schiff's laboratory. Passerini,[34] years later, published a tri-component reaction between cyanides, aldehydes or ketones and carboxylic acid to form amide bonds, enabling the synthesis of peptides. Almost thirty years later, Ivair Ugi[35] added another reagent: an amine. Ugi, bringing together aldehyde, CN-derivatives, amine and carboxylic acid, produced α-aminoacyl amide derivatives **J**, which enables the synthesis of peptidomimetics, for example. With this we had the first tetra-component reaction ever carried out, greatly increasing the possibility of generating chemical and structural diversity. The Passerini and Ugi reactions are known as isocianide-based multicomponent reactions (IMCR).

3. Methodology

Three types of literature searches were carried out. Only original articles and reviews were included in the search, and the scope was limited to the title, abstract, and author keywords. The period evaluated was from 1993 to 2023. Firstly, PubMed, Scopus, and Web of Science databases were searched using the following keywords: "multicomponent reaction", "organic chemistry", "organic synthesis" and "medicinal chemistry", using the boolean operator "AND". In a second analysis, the keyword "medicinal chemistry" was removed. A third search was performed with the same databases and using the keywords: Strecker AND Reaction, Hantzsch AND Reaction, Biginelli AND Reaction, Mannich AND Reaction, Passerini AND Reaction, and Ugi AND Reaction. The country filter "Brazil" was added to each of the six searches performed for each name reaction.

For data analysis, the files were exported in BibTeX format and submitted to the Rayyan web server[36] to eliminate duplicates. Subsequently, the file was exported to the Publish or Perish software[37] for document organization. The bibliometric analysis was performed using Bibliometrix,[38] employing the BibTeX file. For analysis and presentation of the results, GraphPad Prism 9.0 for Windows[39] was used. A more detailed bibliometric analysis was specifically performed for the search focused on Brazilian research.

4. Results and Discussion

4.1. Global overview

First, we plotted the use of MCR around the world, covering a little more than 30 years (1989-2023), and this resulted in Figure 3. This figure shows the distribution of publications with MCR over this period where the enormous growth of MCRs in the last thirty years is evident. This growth can be analyzed from different points of view. It is observed that until the year 2000, very little was found and after this date there was an increase of publications. On the other hand, in the period from 1997 to 2010, the number of papers presented good growth, if compared to the previous period. This increase may have been slow, but it was irreversible and there may be many causes for this increase. Nevertheless, perhaps one of them is the possibility of using MCR to quickly discover new hits with useful therapeutic activity. If we imagine that the period 1994-2010 was the "golden" age of CombiChem publications (after this time there was a decrease in publications on CombiChem in the literature), we clearly see the increase of MCR publications in this period. In this sense, it is possible that a just one-step quickly generating library with great chemical and structural diversity has made MCR very attractive in medicinal chemistry and CombiChem at the time.[8] Moreover, we cannot fail to mention the importance of the Biginelli reaction that forms dihydropyrimidinone (DHPM) in this growth of MCR. We can find scarce publications in 1989-1999 about synthesis of DHPM by Biginelli reaction.[9,11,40–42] However, the discovery in 1999 that monastrol,[43] a DHPM, as the first Eg5 kinesin inhibitor, leading to a new mechanism of antitumor action, also contributed to the growth observed since the 2000s. After 2010, the increase was even greater as the popularity of MCR as synthesis strategy spread to areas other than medicinal chemistry and organic synthesis. Still, the possibility of applying the principles of Green Chemistry is another factor that should not be disregarded as significant to explain the fast growth of MCR.

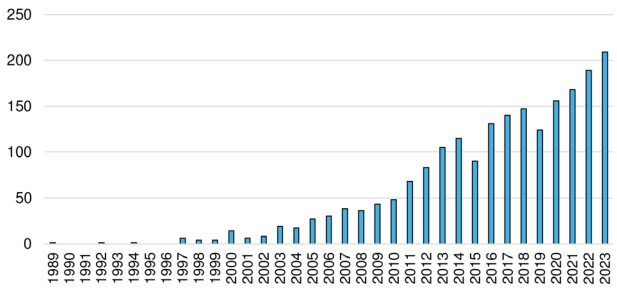


Figure 3. Distribution of publications with MCR around the world over the 30-year period.

4.2. Brazil overview

In this section, data extracted by the third search are shown, using the following keywords: Strecker AND Reaction, Hantzsch AND Reaction, Biginelli AND Reaction, Mannich AND Reaction, Passerini AND Reaction, and Ugi AND Reaction, with duplicates excluded. Afterwards, a visual inspection was carried out to exclude publications outside the topic of this research, and in the end, 243 articles by Brazilian authors remained. Table 1 shows the results of the search aimed at Brazilian publications with the changes of keywords.

Table 1. Brazilian publications with specific MCR name reactions

Database	Keywords[a]	Number of publications
PubMed/Scopus/ Web of Science	Reaction AND Biginelli	96
	Reaction AND Hantzsch	43
	Reaction AND Mannich	100
	Reaction AND Passerini	19
	Reaction AND Strecker	11
	Reaction AND Ugi	53
Total		243

[a]Search by filter Brazil.

4.3. Analysis of the scientific production

The analysis of scientific production on MCRs in Brazil is disclosed in Figure 4. The scientific output of Brazilian authors about MCRs experienced an expressive growth from the early 2000s, reaching 243 articles by the end of the observation period, as illustrated in Figure 4a. The collective impact of the 243 articles is reflected in a total of 6,672 citations, averaging 27.46 citations *per* article. The distribution of citations presented an asymmetric pattern, with 25 articles receiving zero citations, 10 articles cited once, 9 articles cited twice, and 11 articles cited three times. Conversely, one article reached 439 citations, providing unique insights into the synthesis of DHPMs using a recyclable indium(III) bromide catalyst.[44] Additionally, 11 articles fell within the citation range of 100 to 200, as depicted in Figure 4b, visually representing the distribution of citations. These numbers emphasize the scientific contributions made by Brazilian authors in the field of MCRs, highlighting diverse publication trends and a noteworthy impact on the scholarly landscape.

The most significant contributors to this field were the JBCS (17 articles), the Journal of Organic Chemistry (15 articles), and New Journal of Chemistry (13 articles), as indicated in Figure 4c. Figure 4d depicts the journals with the highest citation counts in the 243 analyzed publications, with the Journal of Organic Chemistry, Tetrahedron Letters and Angewandte Chemie emerging as the most frequently cited. Initial publications on MCRs surfaced in the 2000s, primarily in the JBCS, the Journal of Organic Chemistry, Tetrahedron, and Tetrahedron Letters. Notably, a shift occurred in the publication patterns of Brazilian authors towards Royal Society of Chemistry (RSC) Advances, New Journal of Chemistry, European Journal of Organic Chemistry, and ChemistrySelect in the late 2000s and early 2010s, possibly linked to the emergence and visibility gain of these journals (Figure 4e).

Regarding the institutions, UFRGS (Universidade Federal do Rio Grande do Sul) and UnB (Universidade de Brasília) presented the highest number of publications, with 77 and 68 articles, respectively. The top 10 most productive Brazilian universities are represented in Figure 4f. All these publications also resulted in important scientific collaborations involving Brazil and other countries, as may be observed in the map described in Figure 4g. Cuba, Germany, the United Kingdom, Chile, and Spain were the countries with the highest number of mutual publications with Brazilian authors.

The temporal evolution of word frequency in the publication titles was extracted using bibliometrix package[38] and subjected to manual analysis with the aim of identifying trends. Given the extensive pool of words within article titles, a manual selection process was undertaken to identify and categorize the most significant terms, subsequently visualized in graphs. According to our analysis, the Biginelli reaction emerged as the most extensively investigated, followed by Ugi and Mannich reactions. On the other hand, Passerini and Hantzch reactions appeared with lower frequency in article titles (Figure 5a). In terms of publication objectives, Figure 5b illustrates that mechanistic investigations and the development of catalysts were the predominant research focus, followed by the asymmetric synthesis and exploration of fluorescent properties, particularly in more recent years. Figure 5c elucidates the evolving research trends, revealing a growing interest in the investigation of biological properties of molecules obtained through MCRs, with particular emphasis on anticancer and antioxidant activities. A depth analysis of article titles revealed a prevalent presence of terms associated with green chemistry, as depicted in Figure 5d.

Our search led us to a panoramic view of Brazilian researchers and their interests in the application of MCRs in their laboratories. The cumulative representation of these terms exhibited a notable growth particularly post the 2010s, as illustrated in the accompanying graph (Figure 3).

In order to further explore the results, together with

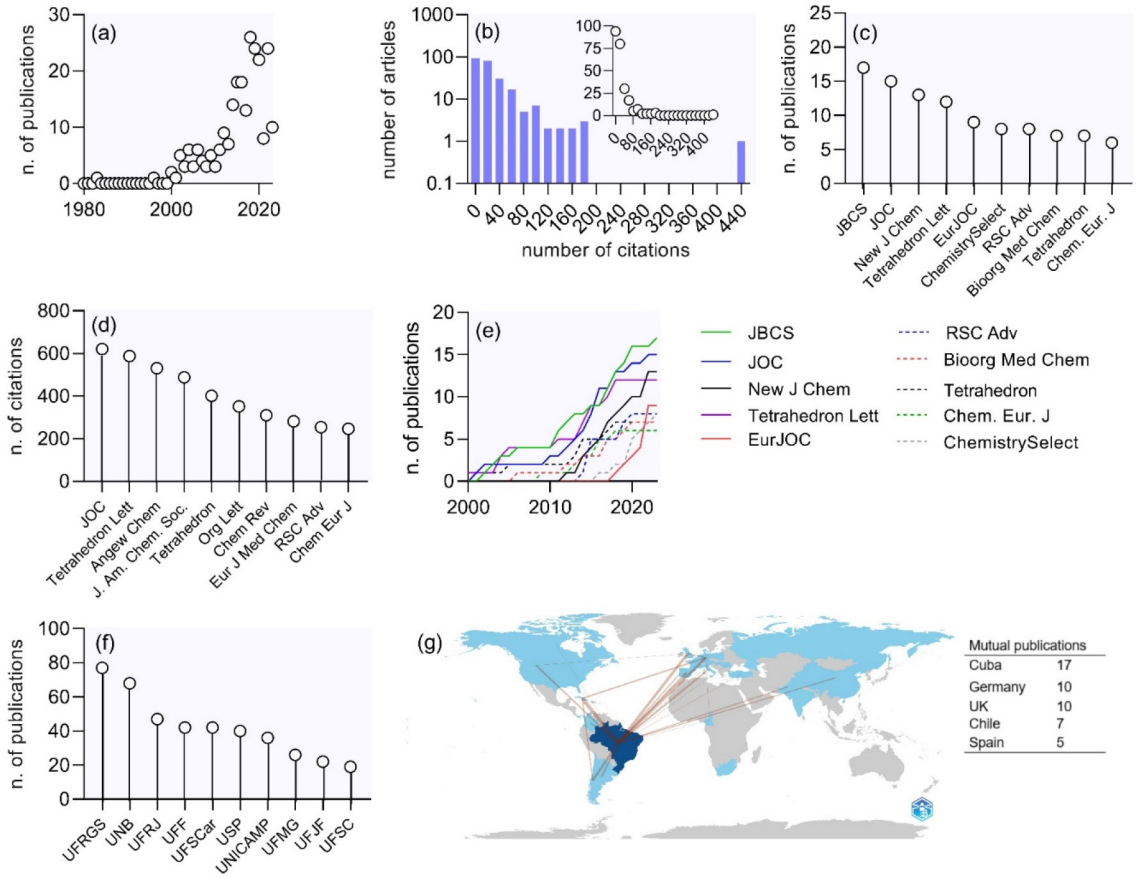


Figure 4. Analysis of Scientific Production on MCRs in Brazil. (a) The increase in the number of publications is illustrated; (b) the distribution of citations for these articles is depicted using a logarithmic scale with the upper part of the figure presenting the same analysis without the use of a logarithmic scale; (c) the ten main journals where Brazilian authors publish on MCRs are highlighted; (d) the ten most cited journals are presented, with (e) a temporal distribution of the publications; (f) the top 10 universities with the most expressive production in MCRs are shown; (g) Brazil's international partners in MCR research.

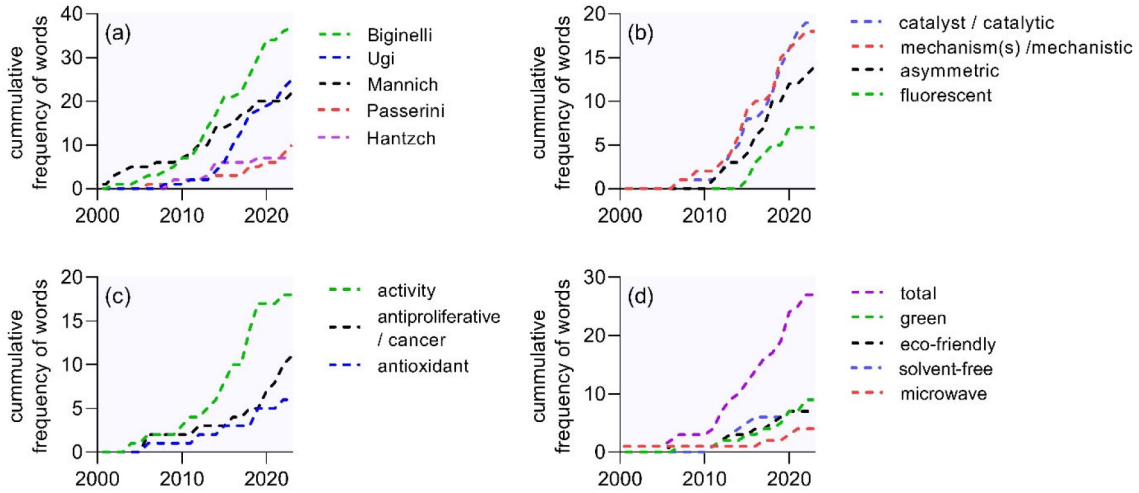


Figure 5. Word frequency over time found in the titles of articles about MCRs published by Brazilian authors. The data are grouped into (a) type of reaction; (b) aim of publication; (c) biological investigation and (d) green chemistry aspects.

the extracted data, we delved deeper and looked in more detail at the publications and grouped them into five areas: medicinal chemistry, development of catalysts, green chemistry approaches, organic synthesis and mechanism studies. The investigations in these areas by Brazilian authors are topics covered in the next sections of this article. We also considered review articles, and these will be considered elsewhere.

4.4. Medicinal chemistry investigations

Our literature survey regarding the usage of MCRs in medicinal chemistry studies developed or associated with Brazilian researchers and institutions led to a total of 28 papers in the period analyzed, which can be further appreciated by the reaction sub-sections and are summarized in Table 2. Four MCRs were contemplated in the survey: (*i*) Ugi reactions: represented by Ugi four center three component reaction (Ugi-4C-3CR), Ugi four component reaction (Ugi-4CR) and Ugi five center four component reaction (Ugi-5C-4CR); (*ii*) Passerini reaction; (*iii*) Biginelli reactions and (*iv*) Hantzsch reactions. The most reported MCR was Biginelli reaction, which was used in 15 papers, followed by Hantzsch (7 papers), Ugi (5 papers) and Passerini (2 papers).

A synthesis reported by Silva *et al.*[50] used Passerini followed by Ugi-4CR to produce epoxy-

Table 2. Summary of the reported MCRs in medicinal chemistry area according to our literature survey

Synthesized compound	Number of compounds	Reaction	Biological activities method	Best result	Reference
Ugi and Passerini reaction					
4-Aminoquinoline γ- and δ-lactam	16	Ugi-4C-3CR	enzymatic; cell: *P. falciparum* *T. brucei*	compound **1**: enzyme: IC_{50} = 17.62 μM *P. falciparum*: IC_{50} = 0.096 μM; compound **2**: *T. brucei:* ED_{50} = 1.44 μM	45
Bestatin's derivative	24	Ugi-4CR and Ugi-5C-4CR	enzymatic; cell: *P. falciparum*	compound **4**: enzyme: K_i = 0.4 μM IC_{50} in cells: P*f*3D7 = 18 μM P*f*FcB1 = 16 μM	46
Isomannide derivative	10	Ugi-4CR	enzymatic	compound **5**: IC_{50} = 4.0 μM (competitive inhibitor) compound **6**: IC_{50} = 12.6 μM	47
Peptoid	13	Ugi-4CR	cell: *L. amazonensis* promastigotes	compound **7**: IC_{50} = 2.80 μM compound **8**: IC_{50} = 2.61 μM compound **9**: IC_{50} = 7.90 μM	48
Epoxy-α-acyloxycarboxamide	17	Passerini	enzymatic	compound **10**: IC_{50} = 1.33 μM	49
Epoxy-α-acyloxycarboxamide	5	Passerini + Ugi-4CR	enzymatic	compound **11**: K_i = 5.45 μM compound **12**: K_i = 9.57 μM	50
Biginelli reaction					
DHPM	8	Biginelli	*in vitro* antioxidant capacity	compounds **13**, **14** and **15**: best results	51
DHPM	26	Biginelli	*in vitro* antioxidant capacity; cell: cytotoxicity in seven cancer cell lines	compounds **16**-**19**: best antioxidant capacity; compound **20** all cancer cells: GI_{50} < 32.64 μM	52
DHPM	14	Biginelli	cell: cytotoxicity in seven cancer cell lines	compound **21**: IC_{50} = 5.93-20.60 μM	53
DHPM	14	Biginelli	cell: cytotoxicity in C6	compounds **22**-**25**: highest activities	54
*N*1-Aryl-substituted DHPM	22	Biginelli	cell: cytotoxicity in C6 and U138; *in vivo* toxicity: *C. elegans*	compounds **26** and **27**: IC_{50} = 54.7-142.7 μM; *C. elegans*: LC_{50} = 29.80-32.90 μM	55
*N*1-Aryl-substituted DHPM	1	Biginelli	cell: cytotoxicity in T24 *in vivo* toxicity: *C. elegans*	compound **28**: IC_{50} = 10.73 μM; *C. elegans*: decrease of multivulvas number; *C. elegans*: LC_{50} > 600 μM	18
DHPM	10	batch continuous flow Biginelli	cell: cytotoxicity in three cancer cell lines	compounds **29-31**: induced death > 50% in 72 h treatment	56

Table 2. Summary of the reported MCRs in medicinal chemistry area according to our literature survey (cont.)

Synthesized compound	Number of compounds	Reaction	Biological activities method	Best result	Reference
DHPM-fatty acid hybrid (substitution site: C5)	18	Biginelli	cell: cytotoxicity in C6 in 24 h treatment	compound **32** reduced cell viability: 50%	57
DHPM-fatty acid hybrid (substitution site: C6)	6	Biginelli	cell: cytotoxicity in C6 in 48 h treatment	compound **33**: IC_{50} = 5.11 μM; compound **34**: C6: IC_{50} = 5.11 μM	58
DHPM-benzazol hybrid	6	Biginelli	cell: cytotoxicity in three cancer cell lines	compounds **35** and **36**: IC_{50} < 40 μM; compound **37**: IC_{50} = 10.7-158.7 μM	59
DHPM-cinnamic acids hybrid	6	Biginelli	cell: cytotoxicity in two prostate cancer cell lines	compound **38**: IC_{50} = 11.5-51.7 μM; compounds **39** and **40**: best activity against prostate cancer cell lines	60
DHPM	37	ionic liquid catalyzed Biginelli	cell: cytotoxicity	the compounds displayed promising cytotoxic profile	61
DHPM	26	ionic liquid catalyzed Biginelli	enzymatic	compound **41**: K_i = 0.96 μM; compound **42**: K_i = 0.57 μM	62
DHPM and pyrrolopyrimidinones hybrid	30	Biginelli	cell: chloroquine resistant *P. falciparum*; cytotoxicity; *in vivo*: *P. berghei* parasitemia reduction in rats	compound **43**: IC_{50} = 2.98 μM; compound **44**: IC_{50} = 1.76 μM; compound **45**: IC_{50} = 3.12 μM; compounds **43**-**45**: reduce parasitemia in 33-60% (rats)	63
DHPM-quinone hybrid	19	Biginelli	cell: chloroquine resistant *P. falciparum*	compound **46**: IC_{50} = 1.15 μM compound **47**: IC_{50} = 1.5 μM	64
Hantzsch reaction					
1,4-DHP	14	Hantzsch	*in vitro* antioxidant capacity cell: cytotoxicity in seven cancer cell lines	compound **48**: SC_{50} = 30.4-217.5 μM compound **49**: SC_{50} = 31.5-181.8 μM	65
1,4-DHP and one 1,3-oxazin-6-one	8	Hantzsch	cell: cytotoxicity in nine cancer cell lines	compound **51**: IC_{50} = 4.63 μM compound **52**: IC_{50} = 4.10 μM	66
PHQ-fatty acids hybrid	15	Hantzsch-4C	cell: cytotoxicity in C6	compound **53**: reduced viability in 40%	67
Symmetrical and unsymmetrical 1,4-DHP	42	Hantzsch	*in vitro* antioxidant capacity	compounds **54**-**56**: best activities	68
PHQ-fatty acids hybrid	18	Hantzsch-4C	*in vitro* antioxidant capacity	compound **57**: EC_{50} = 2.11-4.69 μM	69
Hydroquinoline-1,4-DHPs hybrid	10	microwave assisted modified Hantzsch	photochemistry *in vitro*: BSA binding	photochemistry: absorption maxima region ca. 350 nm BSA binding: strong interaction	70,71
1,4-DHP	5	Hantzsch	photosystem II fluorescence bioassay	best compounds: **60** and **61** (reduced fluorescence parameters)	72

4C, 5C: four or five center; 3, 4 or 5CR: three, four or five component reactions; IC_{50}: half-maximal inhibitory concentration; EC_{50}: half maximal effective concentration; K_i: inhibitory constant; DHPM: dihydropyrimidinone; GI_{50}: half-maximal cell growth inhibition; C6: rat glioma cell line; U138: human glioblastoma cell line; T24: human urothelial bladder cancer cell line; LC_{50}: half-maximal lethal concentration; DHP: dihydropyridines; SC_{50}: half-maximal scavenging concentration; PHQ: polyhydroquinoline; BSA: bovine serum albumin; ED_{50}: effective dose in half of population.

α-acyloxycarboxamides derivatives, for this reason, a total of 29 reports is depicted on Figure 6a. Regarding the number of compounds, the same profile was achieved, on which the Biginelli adducts were the most synthesized scaffold, with 243 compounds, followed by Hantzsch adducts (113), Ugi (68) and Passerini (17 exclusive Passerini compounds and 5 Passerini + Ugi resultant compounds, totaling 22 compounds) (Figure 6b).

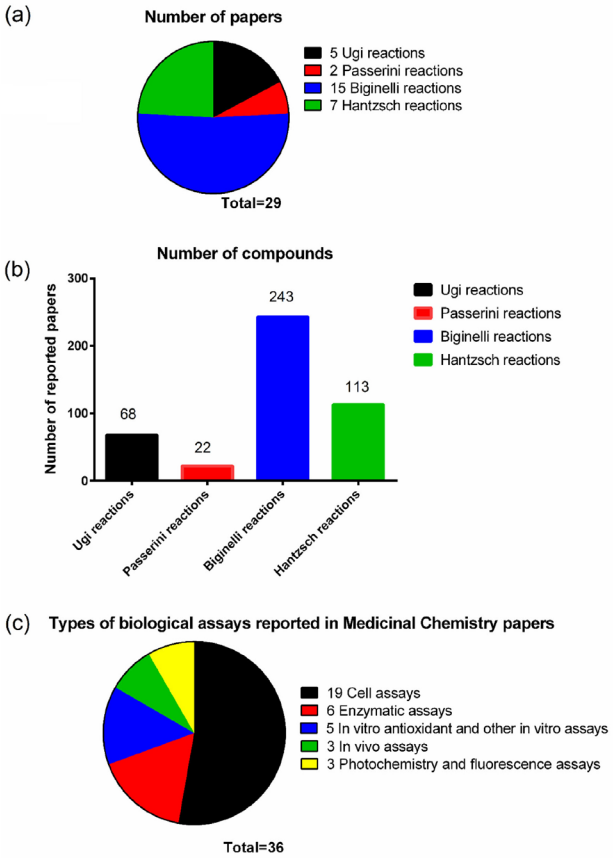


Figure 6. Literature survey results on the usage of MCR in medicinal chemistry in Brazil. (a) Number of papers regarding the most used MCRs; (b) number of the reported compounds synthesized using MCR; (c) number of assays reported in MCR papers regarding the respective type of biological experiment.

In medicinal chemistry, not only the synthesis novelty, efficiency and eco-friendly reactions are pursued, but the importance also relies on the biological activities. The biological and related assays were assembled into five distinct groups, as follows: (*i*) cell assays; (*ii*) enzymatic assays; (*iii*) *in vitro* antioxidant and other *in vitro* assays (such as: serum protein binding assay); (*iv*) *in vivo* assays and (*v*) photochemistry and fluorescence assays (Figure 6c). As we may notice, nineteen papers reported the use of cell assays to verify cytotoxicity towards cancer cell lines (16 papers) and protozoa (a total of five papers mentioned antiprotozoal activity assays, in which *Plasmodium falciparum* (*P. falciparum*) was described in four studies, *L. amazonensis* was reported in one paper and *T. brucei* was described in one study together with *P. falciparum*). Regarding the six papers that used enzymatic assays: (*i*) two of them used *P. falciparum* recombinant targets (falcipain 2 and M1 alanyl-aminopeptidase); (*ii*) two papers reported the screening in human cathepsin isoforms (L, V and K); (*iii*) one mentioned targeting the human kallikrein isoforms and (*iv*) one disclosed the assay in *Canavalia ensiformis* urease. Four papers reported the *in vitro* antioxidant capacity of the synthesized compounds by the following methods (the numbers in parenthesis indicate the quantity of studies in which the method was performed): DPPH (2,2-diphenyl-1-picrylhydrazyl) (3), ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (2), FRAP (ferric reducing ability of plasma) (2), TBARS (thiobarbituric acid reactive substances) (2), DCFH-DA (dichloro-dihydro-fluorescein diacetate) (2) and NBT (nitro blue tetrazolium) (1). Three studies used *in vivo* assays to evaluate either pharmacological outcomes (e.g., parasitemia reduction and decrease in the number of a characteristic phenotype) or toxicological (LD_{50}, mean lethal concentration). These results evidence the importance of two remarked research areas in Brazil: neglected diseases and cancer. Moreover, two papers reported the usage of photochemistry analysis to verify the fluorescence profile of the compounds, which may lead to dual-function molecules (theragnostic compounds), whereas one paper described the usage of fluorescence assay to verify the potential inhibition of a target.

4.4.1 Ugi and Passerini reactions

The compounds reported as the most active, whose synthesis procedure was accomplished with Ugi and Passerini reactions are depicted in Figure 7 and ordered in subgroups A-E for reader's convenience. The major findings of each study are presented in the section.

A paper conducted by Musonda *et al.*[45] described the synthesis of a series of sixteen 4-aminoquinoline containing γ- and δ-lactams scaffold (Figure 7, A). The lactams rings were produced through Ugi four-center three-component reaction (Ugi-4C-3CR). The reaction was accomplished through parallel synthesis using previously synthesized diamines containing the quinoline group, levulinic, or 4-acetylbutiric acid and *tert*-butylisocyanide or cyclohexylisocyanide. The yields ranged from 60 to 77%. The compounds were screened against chloroquine-resistant W2 strain of *P. falciparum*. It was highlighted that, generally, compounds containing δ-lactam ring were more potent than those with γ-lactam. Regarding the number of carbons in the methylene linker of diamine's moiety, it was

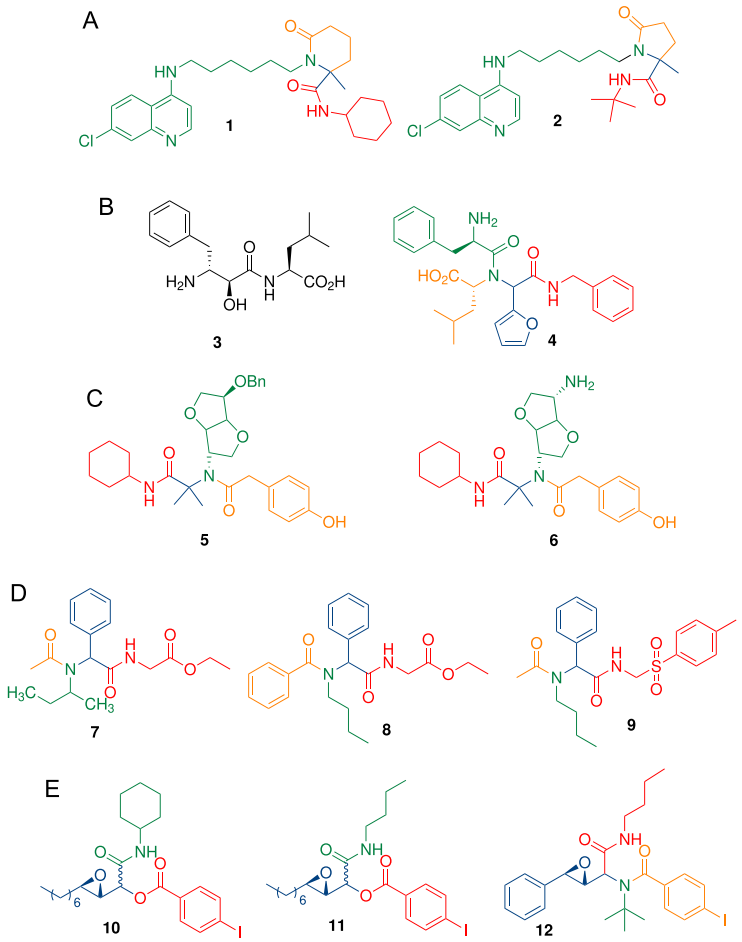


Figure 7. The most active compounds synthesized using Ugi and/or Passerini reactions.

shown that a 6-carbon spacer was more efficient than others. Considering the subpart derived from isocyanide, the *tert*-butyl group in δ-lactams led to more potent compounds, whereas the cyclohexyl counterpart was better associated to the γ-lactam. The best compound of the series (**1**) displayed a half-maximal inhibitory concentration (IC_{50}) value of 0.096 μM (chloroquine = 0.24 μM), which was also capable to inhibit recombinant falcipain-2 enzyme (IC_{50} = 17.62 μM). Furthermore, the compounds were also tested against *T. brucei* S427 strain, in which compound **2** inhibited the growth with an ED_{50} (half maximal effective concentration) of 1.44 μM.

González-Bacerio *et al.*[46] reported the synthesis and the antimalarial activity of twenty-four derivatives of bestatin (Figure 7, B). Bestatin (**3**) is a natural product from *Streptomyces olivoretticuli*, which acts as a transition-state inhibitor of several aminopeptidases including the *P. falciparum* M1 alanyl-aminopeptidase (PfA-M1). There is coordination between the catalytic zinc of PfA-M1 and the α-hydroxyamide moiety of **3**, as well as several hydrophobic interactions between bulky substituents (benzyl and isobutyl) and the S1 and S1' pockets of the enzyme. The authors highlighted a combinatorial multicomponent approach previously designed to identify inhibitors for a similar enzyme from *Escherichia coli*. The approach used two Ugi MCRs: (*i*) Ugi four-component reaction (Ugi-4CR) and (*ii*) Ugi five-center four-component reaction (Ugi-5C-4CR). Eleven *N*-alkylated branched peptides were obtained using Ugi-4CR, which employed Boc-protected phenylalanine and leucine methyl ester with several aldehydes and isocyanides, while the other thirteen peptidomimetics were produced using Ugi-5C-4CR. According to the authors, all the MCR and deprotection sequence showed good to excellent yields. The best compound (**4**) inhibited both the recombinant PfA-M1 and the *in vitro* growth of *P. falciparum*. The compound displayed inhibition values as following: (a) K_i (inhibitory constant) value of 0.4 ± 0.1 μM toward recombinant plasmodium falciparum falcipain (rPfA-M1), (*ii*) IC_{50} value of 18 ± 7 μM toward chloroquine-sensitive strain (3D7) and (*iii*) IC_{50} value of 16 ± 5 μM toward chloroquine-resistant strain (FcB1).

Barros *et al.*[47] proposed a series of 10 isomannide derivatives synthesized by Ugi-4CR (Figure 7, C). The

reaction used three modified isomannides (two amine derivatives and one bis-isocyanide) as either amine or cyanide component of the reaction in combination with benzoic acids and different *para*-substituted phenylacetic acids. The authors evaluated the inhibitory activity of the compounds against human kallikreins (KLK1, 2, 3, 5, 6 and 7). It was found that five compounds displayed activity against KLK1 and KLK7, where compounds **5** and **6** were the most active against KLK1 with IC_{50} values equal to 4.0 ± 0.1 μM and 12.6 ± 0.2 μM, respectively. The mechanism of inhibition of compound **5** was investigated through Lineweaver-Burk plot, which indicated competitive inhibition. A SAR (structure activity relationship) analysis indicated that molecular flexibility and an electron-donor group in the *para*-substituted phenylacetic acid enhance the activity. An *in silico* investigation was accomplished using molecular docking followed by molecular dynamics (MD) simulation in order to evaluate the enzyme changes in the presence of the inhibitor. The MD simulation highlighted the changing in the conformation of compound **5** inside the active site, indicating high flexibility and the existence of important interactions with the binding pockets.[47]

Previdi *et al.*[48] used microwave-assisted synthesis of thirteen functionalized peptoids through Ugi-4CR and screened the compounds against promastigote forms of *Leishmania amazonensis* (Figure 7, D). The reaction provided the resultant peptoids with yield of 55 to 80%. The biological evaluation of the compounds against *L. amazonensis* promastigotes after 48 h of incubation indicated that the best of the series was **7**-**9** with IC_{50} values of 2.80 ± 0.38, 2.61 ± 0.42 and 7.90 ± 0.42 μM, respectively. According to the authors,[48] the antileishmanial activity was higher for benzamides than for acetamides, whereas the presence of an *N-sec*-butylacetamido group further improved the activity compared to *N*-butylacetamido group.

Corrêa and co-workers[49,50] reported the use of Passerini MCR for the synthesis of epoxy-α-acyloxycarboxamides in two papers (Figure 7, E). The first paper[49] reported the synthesis of seventeen compounds with yields ranging from 12 to 98%. The compounds were screened against human recombinant cathepsins L, V and K (CatL, CatV and CatK). The best compound (**10**) inhibited CatL through a tight binding uncompetitive mode with K_i value of 1.33 μM. In the other article a combining approach was accomplished which the synthesis of epoxypeptidomimetics through a green asymmetric process that combined Passerini MCR to build asymmetric epoxides and Ugi-4CR. The process led to the synthesis of five compounds with yield ranging from 22 to 67%. The newly synthesized compounds and four previously prepared epoxypeptidomimetics were screened against CatK and CatL. According to the authors, "all the compounds had satisfactory inhibition (> 70%)" at 25 μM. Two compounds (**11** and **12**) were selected for the evaluation of the mechanism of inhibition. Both compounds showed mixed inhibition mode in CatK with K_i values of 5.45 and 9.57 μM, respectively. The molecular docking predicted that both compounds would not bind to the orthosteric site of CatK with a putative uncompetitive inhibition mode, corroborating with the experimental results.[50]

4.4.2. Biginelli reactions

The most active compounds obtained using Biginelli reaction are illustrated in Figure 8 and sorted in subgroups A-M for sake of clarity. The major findings of each study are presented in the section. Stefani and Gatti[73] described the synthesis of a series of eight DHPMs using ultrasound irradiation (Figure 8, A). The synthesis was performed using different β-ketoesters, aromatic aldehydes (benzylaldehyde or 3-nitro-benzaldehyde), urea and ammonium chloride (NH_4Cl) in methanol. The reaction products displayed yields ranging from 65 to 90%. The compounds had their antioxidant capacity investigated using TBARS and DCFH-DA assays to evaluate lipid peroxidation and reactive oxygen species (ROS)'s scavenging capacity. According to the authors, compounds **13** and **14** displayed the best activity in TBARS assay, inhibiting the lipid peroxidation induced by Fe + EDTA (ethylenediaminetetraacetic acid), while compounds **13** and **15** were the most potent in reducing ROS levels.

Another study[52] reported the synthesis of a series of 26 Biginelli adducts including monastrol and some previously reported compounds through Biginelli reaction, employing different aldehydes, ethyl acetoacetate, urea or thiourea and *p*-sulfonic acid calix[4] arene as catalyst, with yields ranging from 31 to 92% (Figure 8, B). The authors evaluated the scavenging capacity of reactive nitrogen/oxygen species (RNS and ROS), as well as the antiproliferative activity of the compounds. According to the authors, compounds **16**-**19** showed the best antioxidant capacities of RNS/ROS scavengers. Regarding the antiproliferative activity, the compound that showed the best inhibition profile was compound **20** with half-maximal cell growth inhibition (GI_{50}) values lower than 10 μg mL^{-1} (32.64 μM, manually converted).

A paper by Russowsky *et al.*[53] described the synthesis of a series of fourteen DHPMs, employing Biginelli reaction, using: urea or thiourea, aldehyde, ethyl acetoacetate and $SbCl_3$ as catalyst in different organic solvents (CH_3CN or tetrahydrofuran (THF)) (Figure 8, C). The reactions resulted in 65 to 97% of yield. The compounds were evaluated

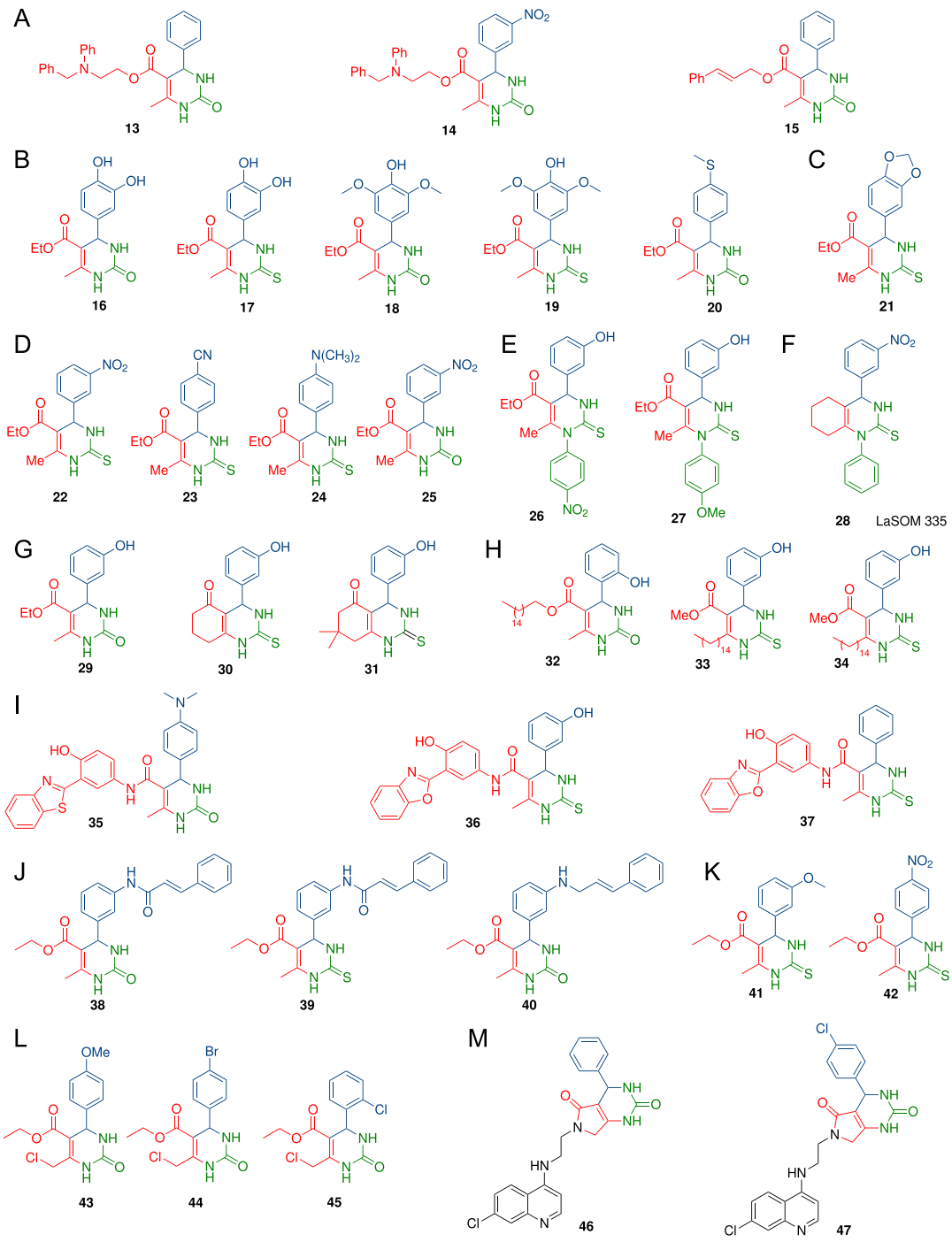


Figure 8. The most active compounds synthesized using Biginelli reaction.

against seven human cancer cell lines. The most potent of the series was the compound **21**, considering the following cell lines and respective IC_{50} values in μg mL^{-1} (the data was manually converted to μM for convenience): UACC.62, melanoma cell line (6.0 μg mL^{-1}, 18.73 μM); 786-0, kidney cancer cell line (2.0 μg mL^{-1}, 6.24 μM); HT-29, colon cancer cell line (2.5 μg mL^{-1}, 7.80 μM); MCF-7, breast cancer (1.9 μg mL^{-1}, 5.93 μM) and OVCAR03, ovarian cancer (6.6 μg mL^{-1}, 20.60 μM).

Canto *et al.*[54] described the synthesis of DHPMs library containing 14 compounds through Biginelli reaction, using: (*i*) different substituted aromatic aldehydes, (*ii*) ethyl acetoacetate, (*iii*) urea or thiourea, (*iv*) triethylorthoformate (TEOF) as dehydrating agent and (*v*) a Brønsted acid (citric or oxalic acid) as catalyst (Figure 8, D). The authors identified that the best combinations were the use of two equivalent of TEOF as dehydrating agent and either 10 mol% of citric or oxalic acid as catalyst for a

period varying from 1 to 2 h at 100 °C, with yields from 66 to 97%. The synthesized compounds were evaluated according to their cytotoxicity against rat glioma (C6) and human glioblastoma (U138-MG) cell lines. Four compounds (**22**-**25**) were described as showing the highest observed cytotoxic effect on the tested cell lines. Notwithstanding, compound **25** was considered the most effective of them all.

As extension of this work, two others were developed to investigate new modifications in the DHPM scaffold. The first[55] was synthesized a focused library of *N*-1-biphenyl DHPMs by a three-step convergent reaction: (*i*) N-1 substitution at the thiourea moiety, (*ii*) amide hydrolysis and (*iii*) Biginelli reaction (Figure 8, E). A total of 22 compounds presented yields ranging from 40 to 82%. The authors used a molecular docking protocol in Eg5 kinesin, the molecular target of monastrol, in order to select the compounds for screening. The virtual screening highlighted two compounds as the best potential inhibitors of the series. Compounds **26** and **27** were selected for the antitumor activity evaluation against U138 and C6 glioma cell lines with IC_{50} values as follows: (*i*) U138: 114.1 and 142.7 μM and (*ii*) C6: 54.7 and 57.1 μM, for **26** and **27**, respectively. Moreover, the authors reported that both compounds displayed similar results to monastrol in the cell cycle analysis and in immunocytochemistry, revealing that they can inhibit Eg5 kinesin. The *in vivo* toxicity of the compounds was assessed using *Caenorhabditis elegans* (*C. elegans*) model, in which the compounds displayed safe profiles (**26**, LC_{50} (half-maximal lethal concentration) = 32.90 mM and **27**, LC_{50} = 29.80 mM).

The second paper was conducted by Kagami and co-workers,[74] which reported the antitumor activity against bladder cancer cells of compound **28**, named as LaSOM® 335 (Figure 8, F), previously synthesized by the group. The authors described a high activity of the compound on human urothelial bladder cancer cell line (T24) with IC_{50} value equal to 10.73 ± 0.53 μM. In addition, the authors evaluated the antitumor effect in the *C. elegans* alternative model (MT4244 strain) and the *in vivo* toxicity (N2 and MT4244). The MT4244 strain contains a mutation in *let-60* gene, which is homologue to Ras in humans, leading to gain-of-function responsible for the multivulval phenotype. LaSOM® 335 was able to decrease the number of multivulva in the worms, which suggest the *let-60* downregulation. The authors hypothesized that the compound would interfere with the epidermal growth factor receptor (EGFR)-Ras pathway, acting either between EGFR and Ras or after the mitogen-activated protein kinase kinase (MEK) enzyme. Regarding the toxicity in both strains, the compound was considered safe, with reduction of the worms' survival only when exposed to 600 μM. Also, the compound was capable of reducing the CD73 (cluster of differentiation 73) expression at 10 μM.

One paper[56] was found to report the synthesis of ten compounds using Biginelli reaction under batch and continuous flow conditions, employing coordination polymers with yields ranging from 80 to 99% (Figure 8, G). Nine of the synthesized compounds were screened for antiproliferative activity against three human cancer cell lines (MCF-7, A549 and Caco-2) and were also evaluated against healthy fibroblasts. Regarding the cytotoxic effect on healthy fibroblasts, none of the compounds produced more than 40% of cell death after 72 h in the tested concentration of 1.00 mM. The cytotoxicity evaluation in the cancer cell lines pointed out that the compounds oxomonastrol (**29**), enastron (**30**) and dimethylenastron (**31**) induced death in more than 50% of the cells against the three cell lines in the concentrations ranging from 100 μM to 1 mM for 72 h of treatment.

Two studies[57,58] narrated the synthesis of hybrids DHPM-fatty acids. Treptow *et al.*[57] synthesized a series of eighteen C5-substituted hybrids with yields ranging from 70 to 92% (Figure 8, H). The Biginelli reaction employed different aromatic aldehydes, urea or thiourea and previously transesterified β-ketoesters containing the fatty acid chain. The reaction used catalytic amount of $InCl_3$ in acetonitrile. The compounds had their biological activity evaluated against C6 rat glioma cell line in a 24 h treatment and the cytotoxicity was assessed in an organotypic hippocampal model. According to the authors, compound **32** was the most potent, reducing cell viability by circa of 50% at 10 μM. The cytotoxicity evaluation showed that the hybrid DHPM-fatty acid did not cause neural cell damage in the concentration of 200 μM.

In the second study, de Oliveira *et al.*[58] produced a series of six C6-substituted hybrid DHPM-fatty acids employing 3-hydroxybenzaldehyde, urea or thiourea and transesterified β-ketoesters using sulfamic acid as catalyst (Figure 8, H). The reaction yields ranged from 74 to 85%. The compounds were screened in C6 rat glioma cell line in a 48 h treatment and compared to monastrol and compound **32**. Compounds **33** and **34** displayed the best inhibition profile, with IC_{50} values of 5.11 and 6.85 μM, respectively, whereas monastrol displayed values equal to 87.83 μM, and the C5 substituted hybrid **32** a value of 16.68 μM. The authors concluded that the substitution at C6 influenced the biological activity, whereas the size of the fatty acid chain did not show interference.

A paper[59] described the synthesis of six DHPM hybrids containing benzazol moieties (Figure 8, I). The compounds were designed to possess fluorescence

and were also evaluated against three cancer cell lines. The Biginelli reaction was performed using previously synthesized benzazolic β-ketoamides, different aromatic aldehydes, urea or thiourea with formic acid as catalyst under refluxing THF for 24 h. The reactions yielded from 50 to 70%. The compounds showed absorption maxima in ultraviolet (UV-A) region with dual emission behavior related to normal (ca. 400 nm) and tautomeric (higher than 510 nm) species. Regarding the cytotoxic activity profile in cancer cell lines, the most potent compounds were **35** and **36**, which achieved IC_{50} values lower than 40 μM in all cancer cell lines (MCF-7, Caco-2 and PC3) and in healthy prostate cells (PNT2). Compound **37** was the most selective; it was able to inhibit prostate cancer cell lines (PC3) with IC_{50} of 10.7 μM compared to 158.7 μM in PNT2.

Barbosa *et al*.[60] synthesized six dihydropyrimidinone-cinnamic acid hybrids and investigated their antiproliferative activity and cell-death mechanism (Figure 8, J). The DHPM was synthesized using Biginelli reaction, which employed 3-nitrobenzaldehyde, ethyl acetoacetate and urea under acid conditions. The nitro intermediate was then reduced to amine using $SnCl_2.2H_2O$, which were hybridized with cinnamic acids (*trans*-cinnamic, *trans*-caffeic and *trans*-ferulic acids) through amide coupling using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) as coupling agent, obtaining three compounds. The achieved yields ranged from 42 to 97%. The hybrids were screened against two prostate cancer cell lines (LNCaP and PC-3) and a normal prostate cell line (RWPE-1) and compound **38** showed the best activity values with IC_{50} of 11.5 ± 5.9 and 15.7 ± 1.8 μM for LNCaP and PC-3 prostate cancer cell lines, respectively, while the cytotoxicity value for the RWPE-1 was 51.7 ± 5 μM. These results led to further development of compound **38** through bioisosterism and molecular simplification strategies. Therefore, three compounds were obtained with hybrids **39** and **40**, showing the best activity results against the prostate cancer cell lines. The antiproliferative effect toward PC-3 cells for the three compounds did not induce cell death neither cell cycle arrest. Furthermore, the authors showed that compound **40** was capable of inhibit the autophagic flux.

The use of ionic liquids as catalysts in Biginelli reaction and the compounds that had their pharmacological activity investigated were reported by two different groups. The first paper conducted by Ramos *et al*.[61] reported the obtention of a series of thirty-seven DHPM derivatives and had their cytotoxicity evaluated against MCF-7 cell line. The authors developed the production of the catalysts, which were used in Biginelli together with distinct aromatic aldehydes, urea or thiourea and 1,3-dicarbonyl compounds with yields ranging from 42 to 99%. According to the authors, the compounds were promising regarding the cytotoxicity profile in breast cancer cell line MCF-7 and were also considered virtually non-toxic in healthy fibroblasts cells. The second paper was reported by Braga *et al*.,[62] which synthesized twenty-six Biginelli adducts employing an ionic liquid-assisted protocol (Figure 8, K). The authors prepared and used 1-butyl-3-(4-sulfobutyl)-1*H*-imidazol-3-ium chloride as Brønsted acid catalyst. The synthesis protocol was conducted under microwave irradiation and used aldehyde, ethyl acetoacetate and urea or thiourea as reagents with yields ranging from 4 up to 92%. The authors evaluated the compounds' capacity to inhibit *Canavalia ensiformis* (jack bean) urease. Two compounds (**41** and **42**) were found to inhibit the enzyme competitively with K_i values of 0.96 ± 0.01 and 0.57 ± 0.16 mM, respectively. The authors[62] reported that the dihydropyrimidinthiones showed better results than the urea analogs, which was consistent with the results observed in the literature.

Two papers were conducted and reported by Rogerio *et al*.[63,64] regarding the synthesis of DHPMs using hybrid proposals and assessing the antiplasmodial activity. In the first paper, the authors proposed the synthesis of pyrimidinones and pyrrolopyrimidinones (Figure 8, L). The DHPMs were obtained via Biginelli reaction employing aromatic aldehydes, urea, ethyl 4-chloroacetate and HCl as catalyst. The resultant intermediates were used as reagents for a subsequent substitution/cyclization step, using phenylethylamine or benzylamine to produce the pyrrolopyrimidinones. A total of thirty compounds, nine of which were novel, were synthesized using the protocol, with yields ranging from 10 to 84.4%. The authors investigated biological activity using the chloroquine resistant W2 strain of *P. falciparum* and the cytotoxicity in buffalo green monkey (BGM) cells. Three compounds displayed the best profiles regarding activity and safety: **43**-**45**, with IC_{50} values of 2.98 ± 0.2, 1.76 ± 0.27, 3.12 ± 0.06 μM, correspondingly. These compounds were evaluated in an i*n vivo* model of parasitemia reduction in mice infected with *P. berghei*. The compounds were able to reduce the parasitemia in 33-60% at day eight, post-inoculation.[63] In the second paper,[64] the DHPM moiety was combined to a quinoline nucleus using a similar protocol (Figure 8, M). Nineteen compounds were obtained with yields ranging from 6 to 54.3%. The authors screened the compounds against W2 strain of *P. falciparum* and cytotoxicity in BGM cells. Two compounds (**46** and **47**) showed the best inhibition profile with IC_{50} values of 1.15 ± 0.1 and 1.5 ± 0.8 μM and the best selectivity indexes (SI) with values of > 869.5 and > 666.6, respectively.

4.4.3. Hantzsch reactions

The bioactive Hantzsch adducts produced are reported in Figure 9 and organized in subgroups A-D for sake of clarity. The major findings of each study are presented in the section.

The synthesis of fourteen 1,4-dihydropyridines (1,4-DHPs) using eco-friendly catalysts (citric or lactic acid) was performed by Pacheco *et al.*[65] The compounds had their reactive species' scavenging capacity evaluated through DPPH and NBT assays for RNS/ROS, respectively. Compounds **48** and **49** were the best 1,4-DHPs found in DPPH scavenging assay (Figure 9, A). The adducts were tested at a concentration of 160 μM and scavenged 85 and 94% of the radical, respectively. The mean scavenge concentration (SC_{50}) were determined and corresponded to 30.4 and 31.5 μM, whereas resveratrol displayed SC_{50} equal to 34.5 μM. The authors highlighted that a hydroxyl group at *para* position and oxygenated groups (hydroxyl or methoxyl) at *meta* position in the aromatic ring contributed to the scavenging activity of both compounds. In a similar manner, compounds **48** and **49** were also the best in the NBT assay, in which they showed SC_{50} values of 217.5 and 181.8 μM, respectively; however, they were less potent than resveratrol, which achieved SC_{50} of 98 μM. Moreover, the fourteen 1,4-DHPs were also screened against nine different cancer cell lines and compared to doxorubicin. According to the authors, compound **50** displayed the broadest spectrum of action, affecting 7 cell lines at concentrations lower than 15 μg mL^{-1}.

Sandjo *et al.*[66] reported the synthesis of seven 1,4-DHPs and one unexpected 1,3-oxazin-6-one, employing the classical Hantzsch reaction (Figure 9, B). The compounds were synthesized using different arylaldehydes, β-ketoesters (ethyl acetoacetate or ethyl benzoylacetate) and ammonium acetate. The reaction was catalyzed by $BiCl_3$ in THF under reflux. The yields ranged from 10 to

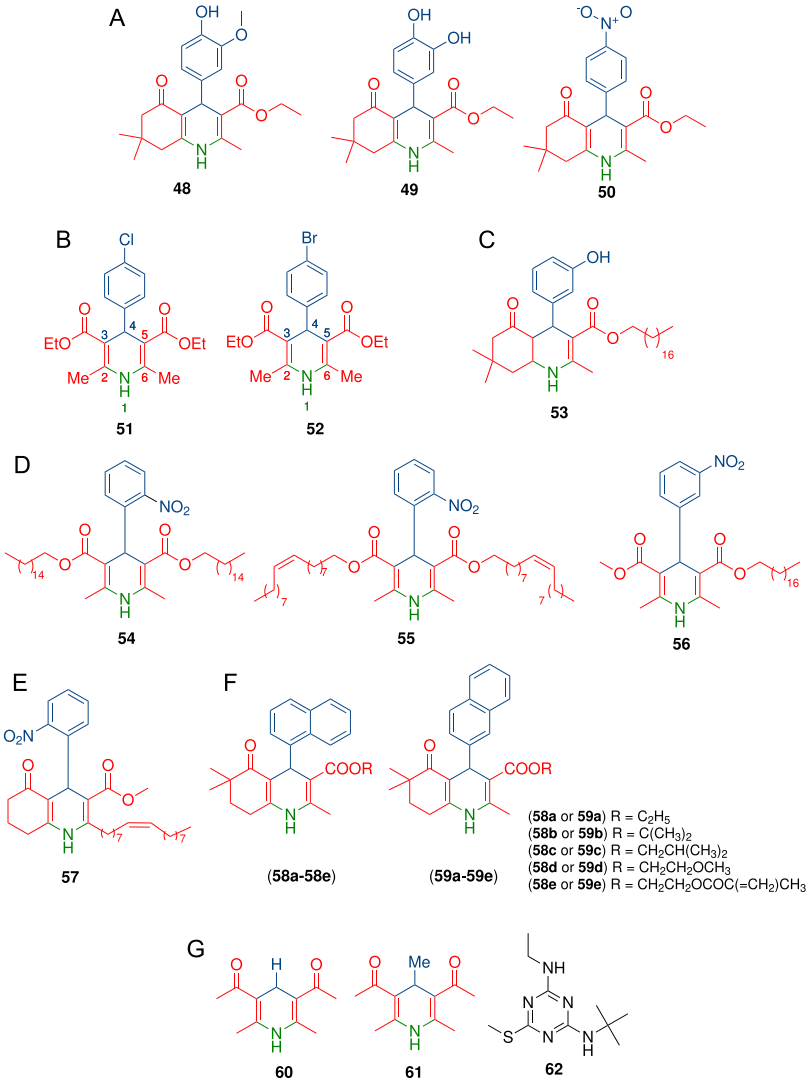


Figure 9. The most active compounds synthesized using Hantzsch reaction.

92%. The compounds were screened against nine cancer cell lines, in which compounds **51** and **52** displayed the best activities on leukemia cell lines, with IC_{50} values of 4.63 and 4.10 μM, respectively. The authors observed that the presence of a methyl group at C2 or C6 position of the heterocyclic scaffold in halogenated DHPs led to more cytotoxic compounds than those with phenyl at the same position.

Cabrera *et al*.[67,68] reported two papers using Hantzsch reactions in order to produce polyhydroquinolines (PHQs) and dihydropyridines (DHPs). The synthesis of fifteen 3-substituted PHQ-fatty acid hybrids was accomplished through Hantzsch four-component (Hantzsch-4C) reaction, using: (*i*) three fatty β-ketoesters (palmitic, stearic and oleic esters), (*ii*) five distinct aromatic aldehydes, (*iii*) dimedone and (*iv*) ammonium acetate, using sulfamic acid or indium chloride as catalysts. The use of sulfamic acid as catalyst resulted in yields ranging from 68 to 81%, whereas the use of indium chloride ranged from 62 to 75%. Moreover, the authors evaluated the antiproliferative activity of the palmitic and stearic derivatives against rat glioma (C6) cell lines. Compound **53** (Figure 9, C) was reported as the most active, which reduced the cell viability by 40% at 5 μM. In the other paper, the authors proposed the synthesis of DHPs, which was performed using: (*i*) ten different aldehydes, (*ii*) ammonium acetate and (*iii*) fatty β-ketoesters using sulfamic acid as catalyst. The authors also reported the unsymmetrical synthesis using methyl acetoacetate or the stearic β-ketoester, in order to reduce the lipophilicity of the compounds. A total of thirty-three symmetrical and ten unsymmetrical hybrids were synthesized with yields ranging from 47 to 92% and from 43 to 78%, for symmetrical and unsymmetrical reactions, respectively. The compounds were evaluated regarding their antioxidant capacity, considering the following assays: ABTS radical scavenging, DPPH radical scavenging and FRAP. The authors highlighted that most of the compounds derived from palmitic and oleic acid showed good antioxidant capacity. Furthermore, the compounds containing a nitro group at the benzaldehyde moiety, to known **54**-**56**, showed the best antioxidant potential in ABTS, DPPH and FRAP assays, respectively (Figure 9, D).

A similar contribution was reported by Brinkenhoff *et al*.,[69] which employed Hantzsch-4C reaction to synthesize eighteen PHQs containing long-chain fatty chains (oleic, stearic and palmitic acids) at position 2 and 3 of the PHQ core, with yields ranging from 69 to 88% (Figure 9, E).[69] The authors evaluated the antioxidant activities of the produced compounds through ABTS, DPPH and FRAP assays. The results pointed out that derivatives containing 2-nitrobenzaldehyde and either palmitic (C16:0) or oleic (C18:1) chains showed better antioxidant activity. Furthermore, compound **57** containing the oleic chain displayed the highest antioxidant activity as follows: (*i*) ABTS assay, EC_{50} = 3.80 μM (2.95-4.47); (*ii*) DPPH assay, EC_{50} = 2.11 μM (1.47-3.51); (*iii*) FRAP assay, EC_{50} = 4.69 μM (3.69-5.10). These results were comparable to two reference compounds, BHT (butylated hydroxytoluene) and vitamin E. Finally, the researchers highlighted that the nitro group in the *ortho* position of the aromatic moiety associated to the fatty chain linked to the Hantzsch scaffold led to better antioxidant activity, which was in consonance to what was observed for the fatty DHPs described in the literature.

An article[70] reported theoretical studies, photophysics investigation, and binding investigations in bovine serum albumin (BSA) of a series of ten 1,4-dihydropyridine-based hexahydroquinoline-3-carboxylates (**58a**-**58e**; **59a**-**59e**) (Figure 9, F). The reaction was performed using 4,4-dimethyl-1,3-cyclohexanedione, different alkyl acetoacetate, 1- or 2-naphtaldehyde and excess of ammonium acetate. The authors reported that the compounds showed absorption maxima in the UV region (ca. 350 nm), fluorescence emission in the violet-blue regions (406-445 nm) and the substituents did not affect the photophysics behavior. Furthermore, the compounds showed a strong interaction with BSA, observed by a decrease in the protein's fluorescent emission when the compounds were added. The docking simulations highlighted the preferable interaction site close to tryptophan (Trp213), which would be responsible for the fluorescence quenching effects.

One group[72] reported the synthesis of five 1,4-DHPs and evaluated their inhibitory activity towards photosystem II (PSII) using a fluorescence bioassay to develop new herbicides (Figure 9, G). The four-component Hantzsch reaction was performed using different aldehydes, pentane-2,4-dione, ammonium acetate and L-proline as catalyst, whereas one compound was obtained without catalyst under refluxing water. The reaction yielded 21 to 81%. Regarding the PSII inhibition, according to the authors, the best results were obtained by compounds **60** and **61** which decreased fluorescence parameters indicating the inhibition of the electron transport chain of PSII. The authors observed that compounds with smaller substituents (hydrogen and methyl) had better activities than compounds with aromatic substituents. In addition, molecular docking studies were developed on the protein D1 of PSII (D1-PSII) of the cyanobacteria *Thermosynechoccus vestitus* BP-1 complexed with terbutryn (**62**), which showed important hydrogen bonding interactions with histidine 215 (His215), serine 264 (Ser264) and phenylalanine 265 (Phe265).

4.5. Organic synthesis approaches

The potential for generating chemical diversity through MCRs reactions may be highlighted using the Ugi reaction for synthesizing a wide variety of peptide derivatives. Peptomers were obtained through a simple route using the Ugi reaction. The synthesis involved the reaction among carboxylic acids or protected amino acids, primary amines, isocyanides, and aldehydes in methanol at room temperature.[75]

An increase in structural complexity may be reached using two consecutive MCRs. The synthesis of cyclic peptoids was performed employing consecutive Ugi reactions.[76] The synthesis of acylhydrazino-peptomers was achieved through the hydrazino-Ugi four-component reaction, followed by hydrolysis and subsequent hydrazino-Ugi reaction.[77] In another approach, two sequential Ugi reactions using trimethylsilyl azide, separated by a hydrazinolysis step, were used for the synthesis of acylhydrazines bearing 1,5-disubstituted tetrazoles.[78]

In addition to the use of consecutive Ugi reactions, an increase in chemical diversity may be achieved by combining Ugi and Passerini reactions, an approach used for the synthesis of cyclic pentadepsipeptoids.[79] *N*-Glucosyl, *N*-methyl, and *N*-acid substitute peptides were obtained from the combination of Ugi and Passerini reactions.[80]

Another important advanced aspect linked with the Ugi reaction was the synthesis of molecules using amines or isonitriles,[81] or carboxylic acids as bifunctional reagents.[82] The use of a dicarboxylic acid in the Passerini reaction produced an α-acyloxy-amide adduct, which, when subjected to decarbonylation/decarboxylation, produced α-hydroxy amides.[83] These strategies enable the obtention of high level of molecular complexity in only one step. The wide substrate scope for the starting materials for Ugi and Passerini reactions goes beyond the use of bifunctional reagents, so that [C60]-fullerene functionalized with a carboxylic acid was used in these reactions.[84]

Polymers are another class of molecules achieved by Ugi reactions. Some authors[85,86] investigated the synthesis of fluorescent microspheres of poly(ethylene glycol)-poly(lactic acid)-fluorescein polymers. In addition, MCRs were used for chemical diversity generation using natural products as building blocks. Mannich reaction among lawsone (a naphthoquinone), an aromatic aldehyde, and an aromatic or aliphatic amine was described.[87] Hybrid DHPMs-perillyl alcohol with a 1,2,3-triazoyl as a linker were obtained by the click chemistry reaction between propargyl DHPMs and azides obtained from perillyl alcohol.[88]

MCRs are a good choice for the synthesis of hybrid molecules so that one of the building blocks may be functionalized with functional groups suitable for use in the MCRs. The use of benzoxazoles bearing aldehydes was used in the Biginelli reaction, yielding fluorescent compounds.[89] In another investigation, aldehydes with benzothiazoles and benzoxazoles were used for the synthesis of fluorescent DHPMs.[90] Furthermore, hybrid coumarins-DHPMs with a coumarin scaffold at the C-6 position were obtained using active methylene hydrogen compounds linked to a coumarin.[91] Triazole obtained by cycloaddition between C-4 propargyl-DHPMs and azides was used for the synthesis of hybrid DHPMs-triazoles.[92] Asymmetrical Hantzsch reaction using derivative fatty acids as building blocks led to the obtention of hybrid fatty acid dihydropyridines.[93] Ugi reaction using a coumarin functionalized with a carboxylic acid produced fluorescent molecules.[94]

The use of alternative building blocks is an important strategy for chemical diversity generation using MCRs. Regarding the Biginelli reaction, the majority of investigations use non-substituted ureas or thioureas, and some investigations involved the synthesis of N-1 substituted DHPMs, using *N*-substituted thioureas.[95] As the majority of DHPMs are also synthesized using 1,3-dicarbonyl compounds as active methylene hydrogen, an investigation obtained DHMPs using simple and cyclic ketones instead of 1,3-dicarbonyl. Together with this modification, the same investigation used *N*-substituted thioureas, obtaining a library of biphenyl DHMPs with a high level of structural diversity. The efforts involving the synthesis of *N*1-aryl-substituted DHPMs led to the discovery of the C–N axial chirality for the first time in this class of heterocycles. The substituent attached to the ortho position of the aromatic ring at N1 position produced a steric hindrance able to avoid the free C–N rotation, generating a chirality axi.[96]

In addition to the last applications, MCRs make it possible to explore unconventional routes, revealing novel chemical possibilities. This condition may be exemplified by the synthesis of β-aryl-γ-nitroesters using an MCR among Meldrum's acid, aromatic aldehydes, alcohols, and nitromethane.[97] MCRs adducts are also suitable for post MCR modifications, increasing structural diversity and leading to new scaffolds. In this context, the synthesis of 2,5-diketopiperazines by intramolecular cyclization of *N*-alkylated Ugi adducts can be highlighted.[98]

MCRs reactions usually assemble the principles of green chemistry with a good level of simplicity, making it suitable for exploring didactical aspects. Recently, the Biginelli reaction was applied in a practical class aiming

to demonstrate concepts linked with parallel chemistry and the use of microwaves.[99] In addition to the Biginelli reaction, the Mannich reaction was also explored for didactical purposes.[100]

This brief analysis showed the potential to be explored behind the MCRs, involving the use of bifunctional starting materials, the use of alternative building blocks, consecutive MCRs, the application in the synthesis of natural-product-like scaffolds, polymers, and hybrid compounds and with didactical purposes. All these approaches contributed to making the scope of applications of MCRs wider and producing structural diversity.

4.6. Catalyst development

With a growing technological and pharmacological focus on compounds derived from MCRs, there is considerable interest in enhancing the efficiency and accessibility of their synthesis. The efforts in the development of new catalysts with applications in MCRs, specifically focusing on the Biginelli, Hantzch, Ugi, and Passerini reactions, are documented in Table 3.

Among these, the Biginelli reaction has garnered significant attention, emerging as the most extensively investigated reaction in terms of catalyst development. A notable number of 20 publications have concentrated their efforts on developing catalysts for the Biginelli reaction, presenting a diverse array of synthetic methodologies tailored for the efficient synthesis of DHPMs. Some advances involved the use of Lewis acids,[44,101] zeolites with ionic liquids,[102] Lewis acids with ionic liquids,[103] magnetically active catalysts that make their recovery easy,[104] organometallic complexes,[105] and catalysts obtained from industrial wastes.[106] These approaches enabled the synthesis of a wide diversity of oxo and thio DHPMs, employing aromatic and aliphatic aldehydes, as well as those bearing ferrocenyl groups.[107]

Regarding the Hantzsch reaction, though a minor number of publications focused on catalyst development, these advances allowed for the generation of chemical diversity by obtaining symmetrical and non-symmetrical 1,4-dihydropyridines,[108-111] hybrid sugars-dihydropyridines,[112] and oxidized derivatives (2-arylpyridines).[113]

Other investigations focused on catalyst applications in new multicomponent strategies, such as the synthesis of 1,2,3-triazoles through MCRs involving benzyl halide, sodium azide, and alkynes,[113] as well as the multicomponent synthesis of triarylimidazoles,[101] Mannich,[108] and Passerini adducts.[114] All these advances are summarized in Table 3. This concerted effort towards catalyst innovation underscores the pivotal role of these reactions in the pursuit of advanced synthetic strategies and therapeutic discoveries.

4.7. MCRs mechanism overview

The study of reaction mechanisms is a fascinating and provocative area of chemical science that challenges scientists in their understanding and logical construction of how chemical phenomena occur. In organic chemistry, the challenge of establishing the mechanisms of organic reactions is enormous, considering the diversity and complexity of the organic substances involved. In this regard, substances are grouped according to the electronic characteristics of the functional group present in the structure. Thus, from the 1940s onwards, the products of organic reactions have been studied, and their formation mechanisms were tentatively elucidated based on kinetic, spectroscopic, isotopic, stereochemical evidence, and others.[126] With the emergence of computational tools since the late 1960s, new theoretical evidence was added to experimental data to aid in the study of mechanisms of organic reactions. Thus, classical mechanisms for organic reactions gradually emerged over time, all grounded in experimental and theoretical evidence, and currently constitute the framework of our knowledge of organic reaction mechanisms. These include mechanisms for nucleophilic and electrophilic substitution reactions, electrophilic and nucleophilic additions, reactions of carbonyl compounds, pericyclic reactions, and so on.[127]

The success of the investigative area of the aforementioned reaction mechanisms lies in the fact that they occur with a relatively simpler reaction kinetics involving few steps, with one of them defined as the rate-determining step. Intermediates are detected either directly or indirectly, and additional isotopic and stereochemical evidence further reinforces the proposed mechanistic explanation.

From the investigative standpoint of the reaction mechanism of MCRs, the challenge is enormous when considering that there are dozens of theoretical synthetic pathways to obtain the desired product.[128] In solution, unlike classical reactions, it is not rational to establish a single reaction alternative for the rate-determining step, since, theoretically, we can have different combinations of multiple reagents used in MCRs. Additionally, the fact that by-products can also be formed adds to the complexity, and the proposed mechanism should, to some extent, provide an explanatory alternative for the formation of sub-products. Thus, the kinetic approach used to elucidate mechanisms in other reactions is rarely employed in MCR studies.

Table 3. Development of new catalysts applied to MCRs with involvement of Brazilian research groups

Condition	Representative molecules	Reference
Biginelli reaction		
$InBr_3$, ethanol, reflux, 7 h	oxo and thio DHPMs	44
$InBr_3$ and $InCl_3$, ethanol, reflux	oxo and thio DHPMs with ferrocenyl at 4 and 5 positions	107
$InBr_3$, THF, reflux	oxo and thio trichloromethylated tetrahydropyrimidinones	115
$SnCl_2.2H_2O$, ethanol and acetonitrile reflux	oxo and thio DHPMs with aromatic aldehydes	116
$In(OTf)_3$, acetonitrile, reflux	oxo and thio DHPMs with aromatic aldehydes	117
Cu/silica xerogel composite, etanol, acetonitrile, THF and toluene	oxo DHPMs with aromatic aldehydes	118
Tetrabutylammonium bromide or ammonium bromide, solvent free 100 ºC	oxo and thio DHPMs with aromatic aldehydes	119
p-Sulfonic acid calixarenes organocatalyst, ethanol, reflux	oxo and thio DHPMs with aliphatic and aromatic aldehydes	52
β-Cyclodextrin, free-solvent, 100 ºC	oxo and thio DHPMs with aliphatic and aromatic aldehydes	120
Mono or dicarboxylic acids, ethanol, reflux	oxo and thio DHPMs with aromatic aldehydes	121
Metal-containing ionic liquids or zeolite β and $H_3PW_{12}O_{40}$ supported on zeolite β	oxo and thio DHPMs with several aldehydes and hydrogen methylene active compounds	102
Niobium nanocatalyst (Fe_3O_4@Nb_2O), ethanol, 80 ºC	oxo and thio DHPMs with aromatic and aliphatic aldehydes	104
$FeCl_3$ and $CuCl_2$; HCl and CF_3COOH	protocols applied to the monastrol synthesis	122
N-alkylated sulfamic acid, methanol, reflux	oxo and thio DHPMs, with aromatic aldehydes and a long alkyl chain at C5 position	14
Preyssler heteropoly acid in silica matrix, solvent-free, 80 ºC	oxo DHPMs using aldehydes derivates from furfuraldehyde	123
Silica functionalized with *p*-sulfonic acid calix[4]arene, microwave, 90 ºC	oxo DHPMs using aromatic and aliphatic aldehydes	124
$NbCl_5$ in a liquid ionic, 100 ºC	the Biginelli reaction is performed utilizing benzaldehyde, ethyl acetoacetate and urea	103
[Cu(isonicotinate ion)$_2$(H_2O)$_4$] complex and Cu(isonicotinate ion)$_2$, solvent-free	oxo DHPMs using aromatic aldehydes	105
Chemically and/or thermally treated Nb_2O_5, solvent-free	oxo and thio DHPMs with aromatic aldehydes	125
Hantzsch reaction		
Proline derivative organocatalysts, methanol, room temperature	1,4-dihydropyridines functionalized with sugars	111
In–SiO_2–composite, solvent-free, 100 ºC	symmetrical and non-symmetrical 1,4-dihydropyridines	109
Ionic liquid bearing an anionic heteropoly acid derivative, 90 ºC	symmetrical 1,4-dihydropyridines	108
p-Sulfonic acid calix[6]arene, solvent-free conditions, 25 ºC, under air atmosphere	Hantzsch-like reaction was used for the synthesis of 2-arylpyridines	112
Zeolite Y, ethanol, 50 ºC, microwave	symmetrical 1,4-dihydropyridines	110
Others MCRs		
Ionic liquid bearing an anionic heteropoly acid derivative, 30 ºC	β-amino carbonyl compounds from Mannich reaction with structural variations in the three reagents	108
Organocatalyst (diarylprolinolsilylethers), ethanol/water	Passerini adducts bearing epoxides	114
Nine Lewis acids. Better results with $CeCl_3.7H_2O$ and $SnCl_2.2H_2O$, ethanol, reflux	triarylimidazoles	101
Cu/SiO_2 composite, water, 70 ºC	MCR 1,2,3-triazoles synthesis from benzyl halide, sodium azide and alkines	113

DPHM: dihydropyrimidinone; THF: tetrahydrofuran; MCR: multicomponent reaction.

The use of disruptive techniques for the mechanistic elucidation of complex reactions involving more than three reagents and multiple alternative pathways for the formation of intermediates and products, such as in MCRs, is presented and discussed in various articles in the literature.[129] The many aspects surrounding the study of MCR mechanisms were exemplarily discussed by Neto and co-workers[130] in the seminal article published in 2021.

The most common techniques used to evaluate MCRs mechanisms are control experiments, nuclear magnetic

resonance (NMR) studies, and mass spectrometry (MS). Theoretical density functional theory (DFT) studies are sometimes employed to aid in elucidating reactive intermediates and in diastereoselective[96] and enantioselective[131,132] reactions. In this section, we will present some aspects of the mechanisms of MCRs for the reactions of Biginelli, Hantzsch, Passerini, and Ugi.

4.7.1. Biginelli's mechanism

The MCR of Biginelli is a chemical transformation that produces a highly substituted DHPM cycloadduct (Scheme 1) from an aldehyde (generally aromatic), a 1,3-dicarbonyl compound, and a nitrogen-containing urea (or thiourea), mediated by acid catalysts (Lowry-Brønsted or Lewis).[91,99,100,133] Considering the multiple alternative synthesis pathways of DHPMs in solution resulting from the intrinsic reactivity of the carbonyl compounds and the amine present in the reaction medium, three mechanisms are postulated to describe the formation of DHPMs. The formation mechanisms of the iminium, enamine, and Knoevenagel intermediates are the real possibilities presented in the Biginelli reaction, as in solution, these intermediates must be considered in elucidating the mechanism of this MCR.[42]

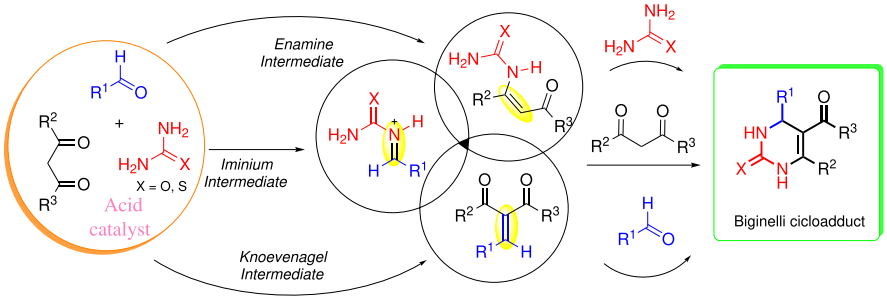
Scheme 1 succinctly describes the formation of Biginelli cycloadducts through the potential intermediates mentioned above. In a generic manner, without considering the pre-equilibrium steps that occur in solution with the acid catalysts in the reaction medium, two steps can be proposed. The first step leads to the formation of reactive intermediates iminium, enamine, and Knoevenagel, and the second step involves the collapse of these intermediates through the condensation reaction with the third component available in the reaction medium. This description gives us an idea of the tremendous effort exerted by researchers in the search for evidence that favors a specific mechanism over others and which tools to use to monitor the consumption of reagents and/or intermediates and the formation of the Biginelli product. Although some traditional catalyst-free MCRs rely solely on the inherent reactivity of the reagents,[134,135] efforts have intensified to develop novel and versatile MCRs that often require a catalyst.[122,136,137]

In the face of the diversity of elementary reactions and stages of MCRs, and the complexity of elucidating their respective mechanisms, electrospray ionization (ESI) mass spectrometry (MS) and tandem mass spectrometry (MS/MS) technique stand out and prove to be extremely useful for monitoring reactive species formed in solution and analyzing them in the gas phase.[138]

In 2005, in a pioneering work by Guo *et al.*,[139] the mechanism of a three-component Pd-catalyzed reaction involving organic halides, 2-(2,3-allenyl)malonates, and imines was elucidated using the high-resolution ESI-MS/MS technique. The characterization of cationic key intermediates and the establishment of the catalytic cycle were achieved. This study demonstrated how key intermediates could be properly analyzed and characterized through MSn experiments.

For the Biginelli reaction, Eberlin and co-workers[140] demonstrated in 2009 how the ESI(+)-MS(/MS) tool, combined with DFT calculations, was useful in elucidating the mechanistic preference of the Biginelli reaction. Under acid-catalyzed conditions, employing MCRs with an equimolar mixture of benzaldehyde, urea, and ethyl acetoacetate mediated by formic acid as the catalyst (0.1%), the authors were able to demonstrate that the preferred mechanistic pathway for the reaction was through the iminium pathway, as evidenced by the detection of the cationic iminium ion at *m/z* 149 (Figure 10). These mechanistic insights were crucial for clarifying the proposed mechanism of the Biginelli reaction, as depicted in Scheme 2. The experimental data allowed the authors to discard the enamine and Knoevenagel mechanisms, pointing to the iminium ion mechanism as the likely path in solution for forming the Biginelli adduct.

Subsequent studies conducted by Neto and co-workers[141] on acid-catalyzed MCRs involving Brønsted-Lowry and Lewis acids, metal cations, and ionic liquids unequivocally indicate that the preferential operating mechanism was through the iminium ion for different Biginelli adducts



Scheme 1. Preparation of Biginelli cycloadduct by three possible reactive intermediates.

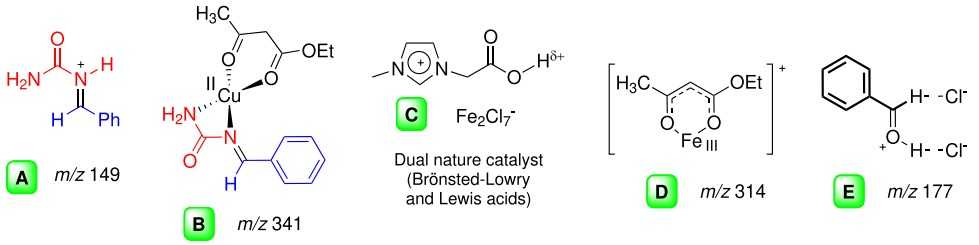
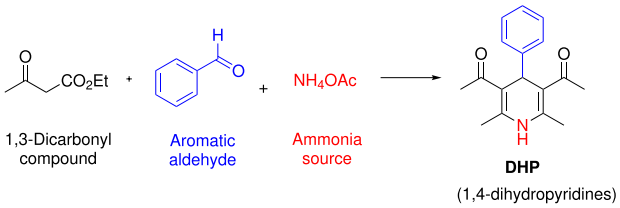


Figure 10. Species detected by ESI-MS/MS in Biginelli reactions catalyzed by Brønsted-Lowry and Lewis acids.



Scheme 2. The classical Hantzsch reaction by three components and the formation of cycloadduct 1,4-dihydropyridines (DHP).

synthesized. Figure 10 describes some cationic fragments that were crucial for elucidating the mechanisms of MCRs by recording the respective ions based on their *m/z* ratios. Figure 10 shows the iminium ion **A** with an *m/z* ratio of 149 detected in Eberlin's work, while the metal intermediate **B** is the metal complex determined with *m/z* 341. The complexation of metal ions in solution is stabilized by the 1,3-dicarbonyl reagent, and the formation of the iminium ion is assisted by the coordinating action of the Cu^{II} ion, facilitating water elimination in the catalytic cycle.

In this direction, the effect of ionic liquids, such as **C**, in homogeneous and heterogeneous MCRs was also investigated, corroborating spectroscopic evidence that points to the iminium ion mechanism as dominant in the Biginelli reaction.[102,142,143] Ionic reactive species **D** and **E** in the catalytic cycle with *m/z* ratios of 314 and 177 were detected as carriers of the 1,3-dicarbonyl compound and activators of the electrophilic reagent benzaldehyde, respectively.[135,144]

Another elegant solution to unravel the mechanism of MCRs was applied by Eberlin and co-workers[145] and Neto and co-workers,[61] using the strategy of tagging charged species and employing them in MCRs while monitoring their performance over time.[146] This interesting strategy resolves some mechanistic elucidation challenges using high-resolution ESI-MS/MS, as neutral intermediates are invisible to the technique. This means that these intermediates are not observed and cannot be detected or characterized in ESI-MS/MS. Thus, the use of charge-tagged reagents with permanent charges positioned away from the reactive center promotes ionization (transfer of species from solution to the gas phase), allowing their detection in MS. This multicomponent synthesis strategy eliminates the need for acid-base catalysts and enables the acquisition of kinetic data closer to the Biginelli reaction under neutral conditions. Figure 11 depicts some examples of reagents labelled with negative and positive charges used for MS investigations of reaction mechanisms according to the cited reference in this review.

4.7.2. Hantzsch's mechanism

The Hantzsch reaction is one of the oldest reactions involving one equivalent of amine, two equivalents of 1,3-dicarbonyl ester, and one equivalent of (aromatic) aldehyde to produce the cyclodiene 1,4-dihydropyridines (Scheme 2). Depending on reaction conditions and reagents, side products, low yields, and irreproducibility can complicate the mechanistic elucidation of this three-component reaction, whose mechanism is quite complex due to the numerous possibilities that the reagents must generate the desired product: DHP.

Mechanistic studies of the Hantzsch reaction are a laborious and complex task, considering that multiple reaction steps can be theoretically proposed. Previous studies utilizing ESI-MS/MS spectroscopy have shown that, in solution, at least 5 mechanisms are plausible, with key evidence obtained from ^{15}N and ^{13}C NMR analyses conducted by Katritzky *et al.*[147] In these solution studies, the authors demonstrated that the rate-limiting step of the reaction was the Michael addition of chalcone to enamine, which, after cyclization and dehydration, produces the corresponding DHP.

An overall description of the mechanisms of the Hantzsch reaction is presented in Scheme 3, with the details of the steps described in the cited references.

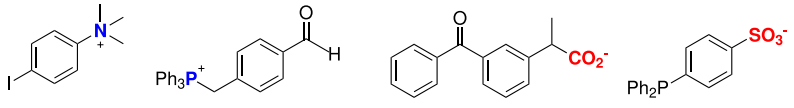


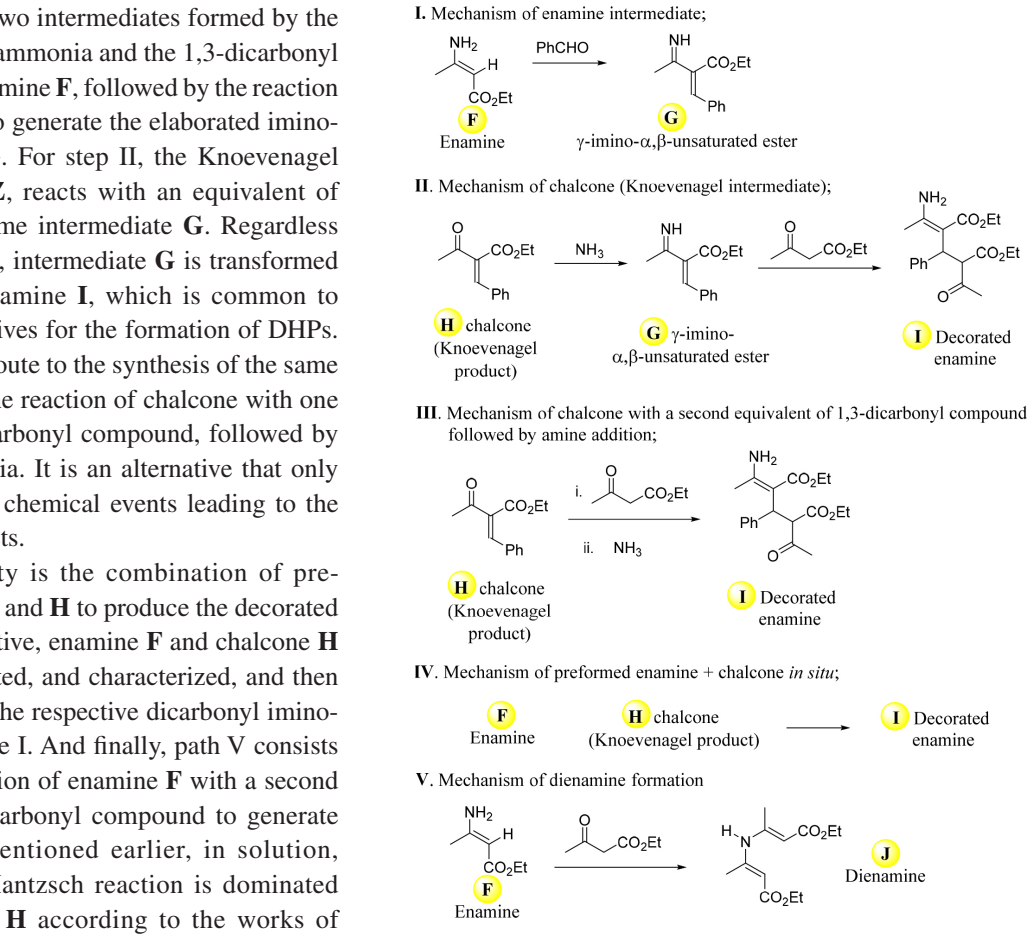
Figure 11. Representative examples of charge-tagged reagents (cationic in blue and anionic in red) derivatives used for MS investigations for MCRs.

Steps I and II start from two intermediates formed by the condensation reaction of ammonia and the 1,3-dicarbonyl compound to produce enamine **F**, followed by the reaction with aromatic aldehyde to generate the elaborated imino-α,β-unsaturated esters **G**. For step II, the Knoevenagel intermediate, chalcone **Z**, reacts with an equivalent of ammonia to form the same intermediate **G**. Regardless of the chosen path I or II, intermediate **G** is transformed into a new decorated enamine **I**, which is common to both mechanistic alternatives for the formation of DHPs. Path III is an alternative route to the synthesis of the same intermediate **I**, through the reaction of chalcone with one equivalent of the 1,3-dicarbonyl compound, followed by the reaction with ammonia. It is an alternative that only changes the order of the chemical events leading to the formation of DHP products.

The fourth possibility is the combination of pre-formed reactive species **F** and **H** to produce the decorated enamine **I**. In this alternative, enamine **F** and chalcone **H** can be synthesized, isolated, and characterized, and then used in the formation of the respective dicarbonyl imino-γ-unsaturated intermediate I. And finally, path V consists of the condensation reaction of enamine **F** with a second equivalent of the 1,3-dicarbonyl compound to generate the dienamine **J**. As mentioned earlier, in solution, the mechanism of the Hantzsch reaction is dominated by intermediates **F** and **H** according to the works of Rodrigues *et al.*[130] and Katritzky *et al.*[147]

Electrospray ionization mass spectrometry (ESI-MS) is a valuable tool that provides us with the opportunity to capture valuable intermediates from the solution for elucidating the mechanisms of complex and multi-step reactions such as MCRs. Even in situations where the intermediates are neutral, the use of molecular tagging becomes a crucial accessory for understanding the mechanisms of MCRs.[144,148]

For the Hantzsch reaction, mass spectrometry data indicated that the dominant species were those recorded with protonated ions at *m/z* 130 and 218, corresponding to the protonated species **F** + H$^+$ and **K** + H$^+$, respectively (Figure 12). The data obtained from NMR in solution, combined with ESI-MS data, guide the choice of the mechanism that better describes the Hantzsch reaction. Among the five alternatives presented as probable rate-limiting steps, alternatives II, III, and IV converge to the same intermediate **I** + H$^+$ recorded as an ion at *m/z* 348, which describes the decorated enamine **I** in its protonated form. The decorated enamine **I** is common to the theoretically proposed paths II, III, and IV, and the DHP product is thus obtained from this characterized intermediate, detected both in NMR solution and in the gas phase via ESI-MS/MS.



Scheme 3. Possible mechanism paths for Hantzsch reaction.

4.7.3. Passerini and Ugi's mechanisms

The Passerini reaction is a chemical reaction involving

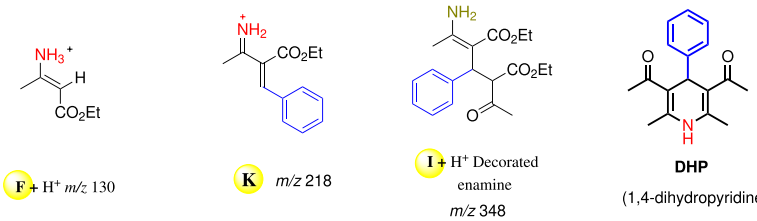


Figure 12. Species recorded in ESI-MS/MS experiments with labeling and non-labeling of reagents for the multicomponent Hantzsch mechanism for the synthesis of DHPs.

an isocyanide, an aldehyde (or ketone), and a carboxylic acid to form an α-acyloxy amide derivative, while the Ugi reaction involves an aldehyde, an amine, an isocyanide, and a carboxylic acid to afford an α-acetoamide carboxamide derivative, an IMCR. Scheme 4 generically describes the formation of Passerini and Ugi adducts through the methodology of MCRs.

Both reactions share some similarities due to the presence of the reagent aldehydes, alkyl isocyanides, and carboxylic acids. The activation step for both reactions involves the aldehyde, but in a distinct manner. The mechanism of these reactions is well-described in the literature,[33] and new information and evidence are available from the study of ESI-MS/MS with tagged-reagents and DFT calculations.

The complexation effect with the consequent approximation of the three reagents in the Passerini reaction is tentatively described in Figure 13, which incorporates some experimental evidence, such as the accelerated reaction rate in aprotic polar solvents,[149,150] and the selectivity results were evidenced by the results obtained by Frey *et al.*[151] The hydrogen transfer during the isocyanide insertion may not be synchronous (pseudopericyclic) as presented in Figure 13.[151] However, the compaction in the transition state is guided by electrostatic interactions of hydrogen bonds and the isocyanide reagent strongly suggests that this model could be formed during the reaction, despite the lack of experimental data due to the rapid collapse of intermediates leading to the α-acyloxy amide derivative product (Scheme 4).

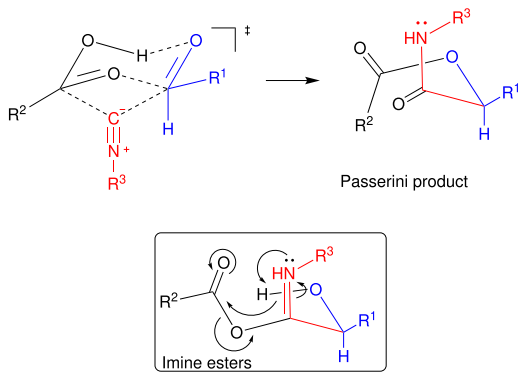


Figure 13. Transition state outlined by complexation in Passerini IMCRs rendering the Passerini product and the electron delocalization model depicted on non-detectable intermediate imine ester using curved arrows.

In the Ugi reaction, the mechanism of this IMCR begins with the formation of the reactive imine (or iminium) intermediate, followed by a three-component reaction with the other reagents present.[152] In the final step, the Mumm rearrangement of the advanced intermediate occurs to produce the α-acetoamide carboxamide derivatives.

The Ugi reaction is preferably conducted in protic polar solvents, although it can also be carried out in aprotic polar solvents. Figure 14 presents the proposed structures involved in the mechanism of the Ugi reaction, highlighting the competitive cationic species iminium ion and cationic intermediate **L**, and the three-component cluster responsible for the formation of the Ugi product.

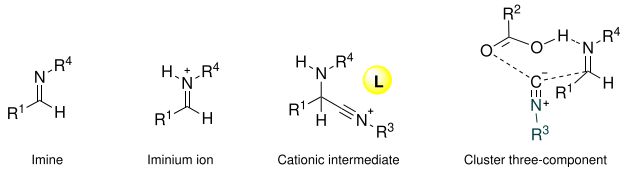


Figure 14. Description of reactive intermediates participating in the Ugi IMCRs under neutral and acidic conditions.

The presence of the cationic intermediate **L** (nitrilium ion) in Ugi reactions was elegantly demonstrated by Neto *et al.*[153,154] through the detection of an ion with *m/z* corresponding to the cationic species **L** tagged with the basic precursor in the form of an amine, as shown in Figure 15 for Ugi IMCRs. Under these conditions, the slow step in the IMCRs mechanism was the formation of intermediate **L**, with the detection of the corresponding cationic ion **L**.

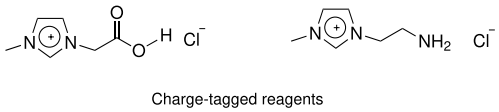
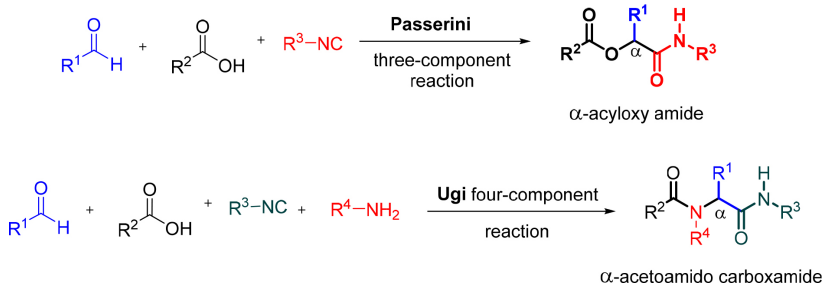


Figure 15. Imidazolium-tagged reagents in acid (MAI.Cl) and amine form.

The final step of the Ugi IMCRs is the Mumm rearrangement, as presented in Scheme 5. The formation



Scheme 4. Preparation of IMCRs by three-component Passerini and four-component Ugi protocols.

of the three-component cluster leads to the generation of a mixed anhydride, which rapidly collapses via Mumm rearrangement to produce the Ugi IMCRs product.

The mechanism described in Scheme 5 is a summarized, non-catalyzed version for the formation of the Ugi product. Under this condition, the mechanism starts from the pre-formed imine, which is activated by the presence of the acidic component in the medium. This polar complex, in which the reagents self-organize to form the three-component cluster (Scheme 5), produces the imidate intermediate, followed by the Mumm rearrangement to yield α-acetoamido carboxamide derivatives.

The polar clusters help us understand the effect that aprotic polar solvents DCM (CH_2Cl_2) and protic solvents (MeOH) have on the reaction concerning conversion and selectivity. The mechanism of Ugi IMCRs under acidic conditions considers the participation of reactive cationic intermediates described in Figure 16, iminium and nitrilium ions (**L**). However, more detailed versions of the mechanism under these circumstances have been studied using polar protic solvents such as MeOH, EtOH, and aprotic solvents such as DCM.[149]

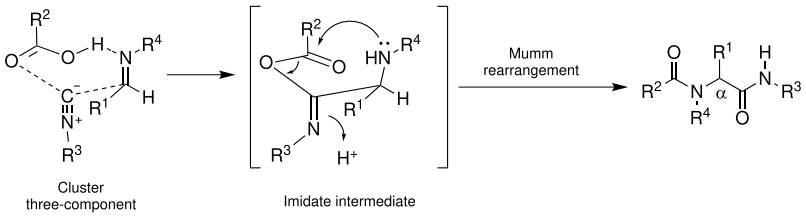
In addition to the mechanistic complexity of this reaction that yields α-acetoamido carboxamide derivatives, another product competes with the formation of the Ugi product when 2 equivalents of amine, 1 equivalent of aldehyde, and 1 equivalent of isocyanide are used in the absence of carboxylic acid (pseudofourcomponent protocol). Under this condition, α-amino amidines (**M**) were obtained from the reaction using 2 equivalents of amine.[155] The solvent-dependent Ugi reaction is a very important topic that affects the reactivity and selectivity in these IMCRs.

In the study reported by Amarante and co-workers,[149] alternative mechanisms for the formation of the Ugi product were proposed through collected data from ESI-MS/MS, isotopic labeling experiments, and DFT calculations. The selectivity of the reaction, namely the ratio of the Ugi product to the alternative pseudo-four-component product α-amino amidines (**M**), was also evaluated. In this regard, a solvent-dependent Ugi mechanism was established by the detection of ions with *m/z* 297 and 300, corresponding to ions **O** and **P** obtained in CH_3OH and CD_3OD, respectively.

The detection of these ions opens up a new possibility for an alternative mechanism in which the solvent acts as a nucleophilic catalyst favoring the formation of the tetrahedral intermediate N. The collapse of this intermediate **N** leads to the formation of the imidate intermediate (Scheme 5). The increased selectivity in favor of the α-acetoamido carboxamide derivative and disfavoring the formation of α-amino amidines (**M**) is thus governed by the protic nature of the solvent and the non-nucleophilic catalyst (camphorsulfonic acid, CSA) used in these mechanistic studies of Ugi IMCRs.[156-158]

5. MCR and Green Chemistry

We found papers where there is an evident concern, and this was apparent in the titles of the papers, with the use of greener synthetic routes, for example, in the presence or absence of catalysts, nature of catalyst, solvent, temperature, shorter reaction times, ease of product purification, among other methods. The use of equipment and techniques such as microwave irradiation, flow chemistry, mechanochemistry and ultrasound were used for synthesis of different compounds. Table 4 displays all references found related to green chemistry and MCR. In total, 38 articles were analyzed and seventeen are related to Biginelli, to Hantzsch, six to Passerini, and four to Ugi. Eleven of them have reactions performed under microwave irradiations and five



Scheme 5. Mumm rearrangement by collapse of intermediate originated from cluster three-component.

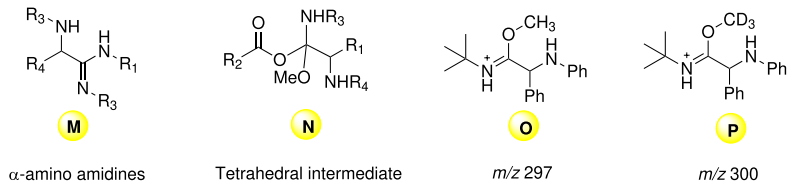


Figure 16. Imidazolium-tagged reagents in acid (MAI.Cl) and amine form.

performed by flow chemistry, while two papers are related to ultrasound and mecanochemistry (entries 3 and 35, respectively). The majority of papers preconizes the use of green solvents like ethanol:water mixture, ionic liquids, polyethylene glycol 400 (PEG 400), H_2O, propylene carbonate, dimethylcarbonate (DMC), diethylcarbonate (DEC), ethanol and ethyl lactate. Seven authors select the reaction without solvent (entries 1, 6, 10, 13, 19, 37 and 27). The use of friendly promoters or catalysts was also found, such as the use of weak and biodegradable acids like citric, oxalic, tartaric and lactic, the use of I_2 as a catalyst, the use of a mixture of Al_2O_3-$HClO_4$ in ethanol,

Table 4. Publications using equipment or/and green reactions conditions

entry	Reaction	Equipment	Reaction conditions	Reference
1	Biginelli	microwave[a]	solvent free	73
2	Passerini	–	ionic liquids or PEG 400 as greener reaction media	159
3	Biginelli	ultrasound	–	51
4	Hantzsch	–	H_2O solvent[b]	160
5	Ugi	microwave	–	161
6	Passerini	microwave	solvent free	162
7	Biginelli	–	TEOF, associated with citric acid or oxalic acid, solvent free	54
8	Biginelli	–	citric acid or tartaric acid as promoter	163
9	Passerini	–	organocatalyst (diarylprolinolsilylethers) /ethanol:water	114
10	Hantzch	–	In-SiO_2 composite catalyst/solvent-free	109
11	Biginelli	–	ionic liquids	141
12	Hantzsch	–	citric or lactic acid as catalysts	65
13	Biginelli	–	solvent free	120
14	Biginelli	–	ionic liquid	102
15	Hantzsch	microflow chemistry	–	164
16	Ugi	flow chemistry	–	165
17	Biginelli	microwave	H_2O solvent	166
18	Biginelli	flow chemistry	coordination polymers	56
19	Hantzsch	–	solvent free	167
20	Bucherer-Bergs reaction	microwave	–	168
21	Biginelli	–	propylene carbonate as solvent/I_2 as catalyst	169
22	Hantzsch	microwave	–	170
23	Ugi	flow chemistry	–	171
24	Passerini	microwave	DMC and DEC as solvent	172
25	Ugi	microwave	–	173
26	Biginelli	–	ionic liquid	131
27	Passerini	flow chemistry	–	174
28	Hantzsch	microwave	USY-zeolite catalyst	175
29	Biginelli	–	calix[4]arene as catalyst	124
30	Biginelli	–	ionic liquids	62
31	Biginelli	–	ionic liquids	142
32	Passerini	–	solvent mixture (ethanol:water)	176
33	Biginelli	–	alumina/perchloric acid (Al_2O_3-$HClO_4$)/ethanol	177
34	Biginelli	–	solvent ethyl lactate	178
35	Biginelli	mecanochemistry	solvent free	179
36	GBB	microwave	reusable homogeneous Brønsted acidic catalyst	17,180
37	Hantzsch	microwave	USY-zeolite catalyst	110
38	Biginelli	microwave[a]/ parallel synthesis	solvent free/TEOF as promoter	99

[a]Domestic multi-mode microwave oven; [b]two-step. PEG400: polyethylene glycol 400; TEOF: triethylorthoformate; DMC: dimethylcarbonate; DEC: diethylcarbonate; USY-zeolite: USY/Ultrastable Y zeolite.

In-SiO_2 composite, USY-zeolite (USY; ultrastable Y zeolite), calix[4]arene as catalysts and triethyl ortoformate (TEOF) as promoter of Biginelli reaction (entry 7). It is worth mentioning two works[181,182] found dealing with two MCRs different from the five that we selected in this work. We are talking about three-component Bucherer-Bergs and Groebke-Blackburn-Bienaymé (GBB) reactions. The first of them (Bucherer-Bergs) was carried out under microwave irradiation to generate a hydantoin library, published by Corrêa and co-workers[168] (entry 20). The Bucherer-Bergs reaction was patented in 1929 by Berg and later published by Bucherer, where he achieved better results by changing the temperature and pressure of the reaction. It is a three-component reaction between ketones, $(NH_4)_2CO_3$ and KCN to form hydantoins. In the second case, GBB reaction was used by Longo Jr. and co-workers[180] (entry 36) to synthesize libraries of imidazo[1,2-*a*]pyridines,imidazo[2,1-*b*]thiazoles and 1-(butyl-4-sulfonic)-3-methylimidazolium salts bearing different anions under microwave irradiation and with a reusable homogeneous Brønsted acidic catalyst. GBB reaction was carried out using aromatic amidines in reaction with aldehydes and nitrile derivatives.[183]

6. Review Articles

In our search, we found fifteen review articles dealing with the subject at hand published over a 30-year period. Table 5 reveals the publications found and quickly takes the reader to the main information before reading the references in detail. We observed that from the first review in 2006 by Andrade and co-workers[162] (entry 1), there was a significant growth. We can see that the majority are reviews on MCR (seven articles) dealing with synthesis and biological activity (entries 6, 9 and 14), green approaches (entries 2 and 13), asymmetric synthesis (entry 11) and recent advances (entry 3). The other reviews are about some MCR such as the Biginelli Reaction with four articles: two about chemistry and pharmacological activities (entries 4, 8 and 12) and another about green approaches (entry 5). With one article, we find the general aspects of the Mannich Reaction (entry 7), investigations on mechanism and the use of fluorescent compounds and another about developments of asymmetric synthesis in Strecker, Mannich, Passerini and Ugi reactions (entry 15).

7. Conclusions

With this work, we had the opportunity to simultaneously deepen and expand our knowledge about MCR. With the methods selected for a search in the MCR literature and publications by Brazilian researchers over the last 30 years, it was possible to draw a general overview of these works. It was possible to detect a significant increase in papers with MCR. In total we found 243 articles and these had 6,672 citations, with an average of 27.46 citations *per* article. It was possible to detect that Brazilians preferably work with Biginelli, Ugi, Mannich, Passerini and Hantzsch, but other MCRs are also emerging such as Bucherer-Bergs and GBB. We also note that the majority of articles can be classified into the following areas of interest: Medicinal Chemistry; Catalyst; Mechanism; Green Chemistry; Asymmetric

Table 5. The fifteen review articles published over a 30-year period

entry	MCR or kind of reaction	Subject	Reference
1	Passerini	eco-friendly approach	162
2	MCR	green approach	184
3	MCR	general aspects 2008 and 2011	185
4	Biginelli	pharmacological properties	186
5	Biginelli	solvent-free and catalyst-free reaction	135
6	MCR	synthesis of biologically active molecules	187
7	Mannich	general aspects	188
8	Biginelli	chemistry and biology	189
9	MCR	synthesis of bioactive compounds	190
10	Ugi	mechanism and the use of fluorescent derivatives	152
11	MCR	catalytic enantioselective	191
12	Biginelli	chemical diversity generation of bioactive derivatives.	192
13	MCR	sustainable and reusable catalyst	193
14	MCR	total synthesis of biologically active molecules	194
15	Strecker, Mannich, Passerini and Ugi	synthetic developments of asymmetric	195

MCR: multicomponent reaction.

Synthesis and Fluorescent. The survey concerning the usage of MCR in medicinal chemistry studies performed by Brazilian researchers and institutions in the last thirty years highlighted that the Biginelli reaction was the most reported and used reaction, which led to the development of 243 compounds, followed by Hantzsch adducts, with 113. Regarding the biological evaluation assays employed in Brazil, we may point out that Brazilian studies were more focused on two main themes: (*i*) the discovery of new potent anticancer compounds and (*ii*) the design of original and effective candidates for neglected tropical diseases. Few studies reported the complete investigation of mechanism of action in both enzymatic and *in vitro* cell models. Moreover, most of the toxicity evaluation was accomplished in *in vitro* cell models with three studies reporting the use of *in vivo* models of which only two studies use alternative *in vivo* models such as *C. elegans*. An overview of the four MCRs was presented, emphasizing the mechanistic discussion and the challenges these MCRs pose in elucidating the mechanism. As highlighted by the literature, traditional tools for mechanistic investigation are not sufficient for the complete definition of MCR mechanisms, and tandem mass ESI-MS/MS spectroscopy offers a new perspective, especially with the labeling strategy of the reagents participating in these complex and intriguing mechanisms.

Acknowledgments

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Author Contributions

Henrique B. de Lima was responsible for data curation, formal analysis, investigation, methodology, validation, visualization, writing (original draft review and editing); Gustavo M. das Neves for conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing (original draft, review and editing); Itamar Luís Gonçalves for conceptualization, data curation, formal analysis, investigation, validation, visualization, writing (original draft, review and editing); Aloir Merlo for conceptualization, formal analysis, investigation, project administration, supervision, validation, visualization, writing (original draft, review and editing); Vera Eifler-Lima for conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization writing (original draft, review and editing), researcher leader.

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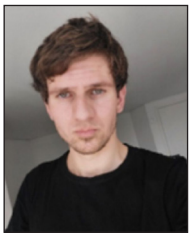
Gustavo M. das Neves *is Bachelor in Biomedicine from UFCSPA in 2009 and in Pharmacy from UFRGS in 2015. He completed his master's and PhD in Pharmaceutical Sciences at UFRGS in 2022. He has experience in Medicinal Chemistry with emphasis on computer-aided drug design and drug repositioning using molecular modelling techniques and virtual screening, such as: molecular docking, derivation of pharmacophoric patterns and QSAR. Currently he is a post-doctoral researcher at Medicinal Organic Synthesis Laboratory (LaSOM) supervised by Professor Vera Lucia Eifler-Lima.*



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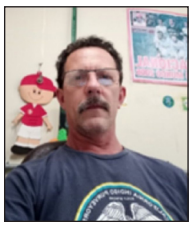
Aloir A. Merlo *is a full professor at Institute of Chemistry, UFRGS, Brazil. He graduated at UFSC in 1993 (Professor Gallardo) and obtained post-doctorate in 2012*



at Hull University (Professor Kelly). Teaching activities started very early (1983) and, since 1995, he has been working at the Chemistry Institute. He has been honored with Teaching Awards nine times. Prof Merlo is the author or coauthor of over 70 scientific papers, reviews, books and book chapters. His current research is focused on liquid crystals (LCs) with special emphasis on synthesis of isoxazoline and isoxazole, which has been extensively studied since 2005.

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