

# On the industrial applications of MCRs: molecular diversity in drug discovery and generic drug synthesis

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**Abstract** During the last decades, multicomponent chemistry has gained much attention in pharmaceutical research, especially in the context of lead finding and optimization. Here, in particular, the main advantages of multicomponent reactions (MCRs) like ease of automation and high diversity generation were utilized. In consequence of these beneficial properties, a plethora of new MCRs combined with appropriate classical reaction sequences have been published, the accessible chemical space was extended steadily. In the meantime, the desired high diversity became a challenge itself, because by now the systematic use of this huge and unmanageable space for drug discovery was limited by the lack of suitable computational tools. Therefore, this article provides an insight for the rational use of this enormous chemical space in drug discovery and generic drug synthesis. In this context, a short overview of the applied cheminformatics, necessary for the virtual screening of the biggest available chemical space, is given. Furthermore, some examples for recently developed multicomponent sequences are presented.

**Keywords** Chemical space · Drug discovery · Generic drug synthesis · Heterocycles · MCR · Multicomponent reactions · Virtual screening

## Abbreviations

MDM2 Murine double minute 2  
TOTO Topological torsion  
SAR Structure–activity relationship

## MCRs as a powerful tool for creation of chemical diversity and synthesis rationalization

Synthetic sequences that enable the automated parallel synthesis of polysubstituted heterocycles have attracted considerable attention in recent years [1,2]. Robust synthesis of “lead-like” compounds permits the fast preparation of compound libraries suitable for lead discovery [3,4]. Therefore, easily automated multicomponent reactions (MCRs) are powerful tools for high-throughput approaches [5,6].

The highly diverse chemical space amenable is a major characteristic of MCRs and is in constant expansion [7]. One of the strategies used to diversify the product range of well-known MCRs consists in involving bi-functional or suitable starting materials for subsequent post-condensation reactions [8–13]. For example, the UDC-(Ugi/De-boc/Cyclize) pathway developed by Hulme and co-workers allows the production of a large range of biologically relevant heterocycles [14–17]. Another strategy for the generation of new products is to combine different MCRs in a sequential way [18,19] or in a one-pot procedure [20].

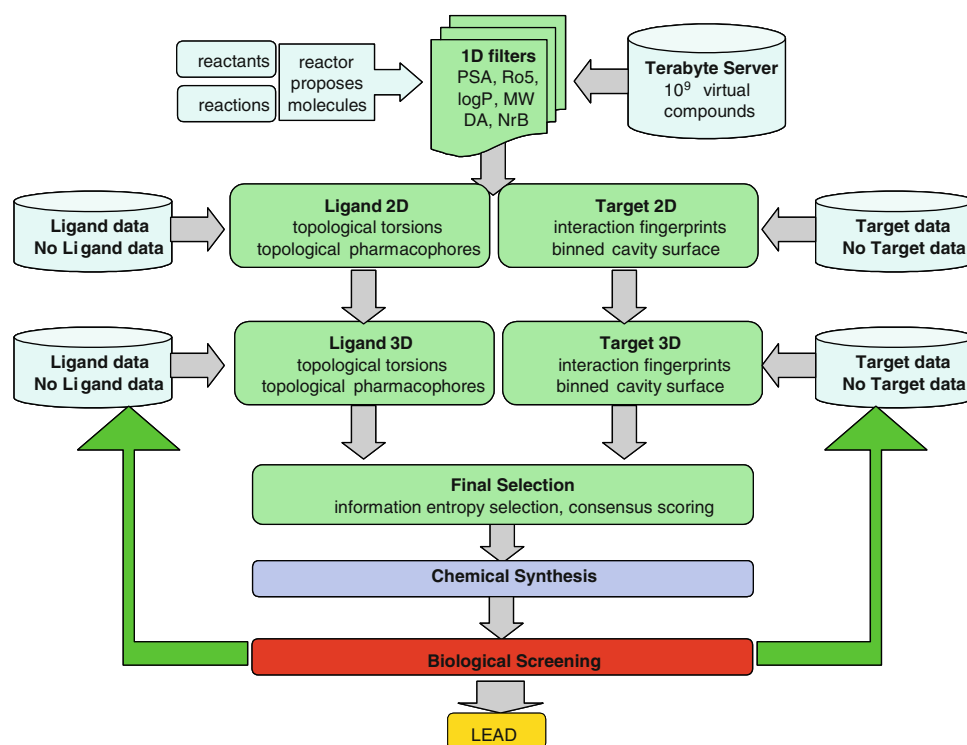
Not only are MCRs a powerful tool for the creation of chemical diversity and new chemical entities in drug discovery, they also represent an excellent methodology for synthesis rationalization [21,22], e.g., in the production of natural products [23].

## Rational use of MCRs in the drug discovery process: virtual space and in silico screening

MCRs open up a huge space of possible compounds that was typically represented in analogy to the cosmological universe [6]. Currently, one of the major challenges is to use this highly diverse and formidable space of MCR-products in a

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**Fig. 1** Workflow in silico screening, hit generation, iterative “hit to lead” optimization



rational way for the drug discovery process [24]. Suitable computational tools are needed to deal with this huge space of compounds. By using a virtual 2D-reactor program [25], we are able to generate all possible MCR-products from more than 400 different MCRs reported in the literature employing commercially available starting materials. In a second step, frequent hitters or compounds containing reactive or toxic groups are excluded. As a result, we have access to a unique and innovative 2D-virtual library containing more than one billion of drug-like molecules. Powerful chemoinformatic tools are then necessary to navigate this space and make it searchable. Choosing the right set of descriptors is crucial for this task and it was shown that topological torsions, topological pharmacophores and 2D fingerprints are most suitable for very large database searches where both key parameters, computing time and validity of generated hits, stay within reasonable frames [26]. By running through a succession of application specific 1D filters, 2D topological filters and 3D docking, suitable structures can be extracted from the virtual space. Computational work can start either from known ligands, target information such as X-ray crystallography and homology models, or a combination of both. The most promising candidates from the 2D selection are then refined by conventional molecular modelling and finally selected for real synthesis in the laboratory. Finally, the synthesized compounds are tested in a suitable panel of initial enzymatic and cellular assays. The results build a base for further iterative optimization cycles (Fig. 1).

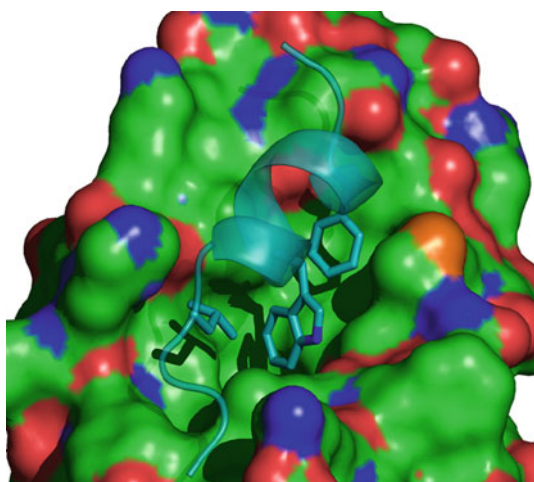
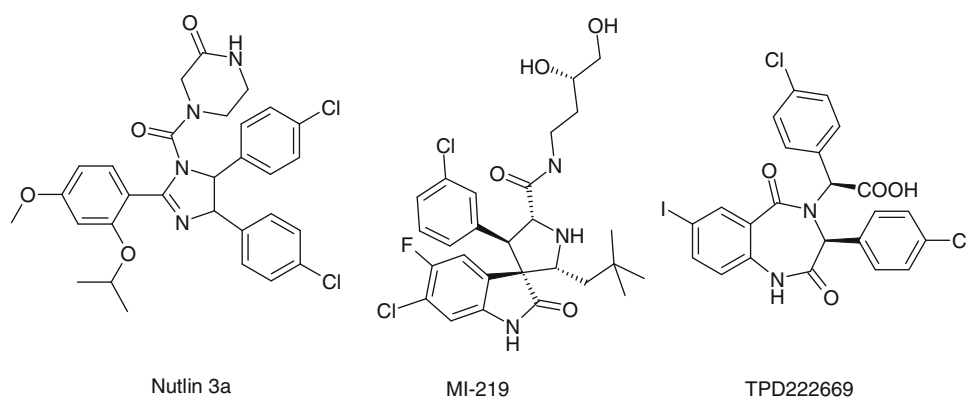
Using this strategy, we were able to identify new chemical scaffolds for inhibition of the p53–MDM2 protein–protein

interaction [27]. The functional loss of human tumour suppressor protein p53 occurs through mutation or overexpression of its cellular antagonist MDM2. Several studies have shown that the disruption of the MDM2–p53 complex can activate the p53 pathway and inhibit tumour growth [28–31]. Thus, disruption of the MDM2–p53 interaction is a novel therapeutic strategy for cancer cells that still are endowed with wild-type p53 [32,33], and a variety of small-molecule drug-like compounds have been reported by several pharmaceutical companies that bind at the p53-binding site of MDM2 (Fig. 2) [34]. Usually, the discovery of small molecule inhibitors of protein–protein interactions is complicated by the large interaction sites between the two proteins. In the case of the p53–MDM2 interaction, the contact site is relatively small (800 Å<sup>2</sup>) and only three essential amino acids of p53 (Phe<sup>19</sup>, Trp<sup>23</sup> and Leu<sup>26</sup>) are crucially involved in the interaction with MDM2 so that small molecules like Nutlin-3 are suitable to bind at the p53-domain of MDM2 [35] (Fig. 3).

The knowledge of structurally diverse ligands (represented in Fig. 2) provides a good basis for ligand-based scaffold-hopping compound selection and design. Screening for structurally similar compounds with alternative scaffolds was performed by using a modified topological torsion (TOTO) substructure descriptor which has the form:

$$M \text{ ACHPi ACHPj ACHPk ACHPl}$$

for which i, j, k, and l are consecutively bonded atoms, M is the multiplicity of a given unique TOTO found in the compound, A is the atom number, C is the charge, H is the number

**Fig. 2** Published inhibitors of the p53–MDM2 interaction**Fig. 3** p53 binding at MDM2 (binding triad)

of attached hydrogen atoms, and P is the number of p electrons on the respective atom.

Our descriptor differs from other recent implementations [36] by the use of M and that the number of possible atom types is not limited by predefined conventions. This atom pair descriptor method [37] delivers structurally similar compounds, but neglects the concept of core scaffolds that are implicitly or explicitly encoded in many other typical 2D similarity search methods.

Nutlin-3 was then used as a probe to extract similar compounds from our database. Whereas conventional similarity screening implemented in chemical databases yields, as expected, imidazoline-type compounds as most similar, our TOTO-based 2D similarity screening delivered 278 similar compounds of various scaffolds. Using the program LIGSITE<sup>csc</sup> [38], the p53-binding site of MDM2 was extracted from the X-ray crystal structure.

After generating a library of conformers, molecules from the 2D selection step were further evaluated for their 3D shape fit with the p53-binding pocket. Finally, the computational search yielded virtual hits especially from two novel MCR-

accessible scaffold classes for potential p53–MDM2 interaction inhibition: isoquinoline-1-ones **1** and pyrrolinones **2**.

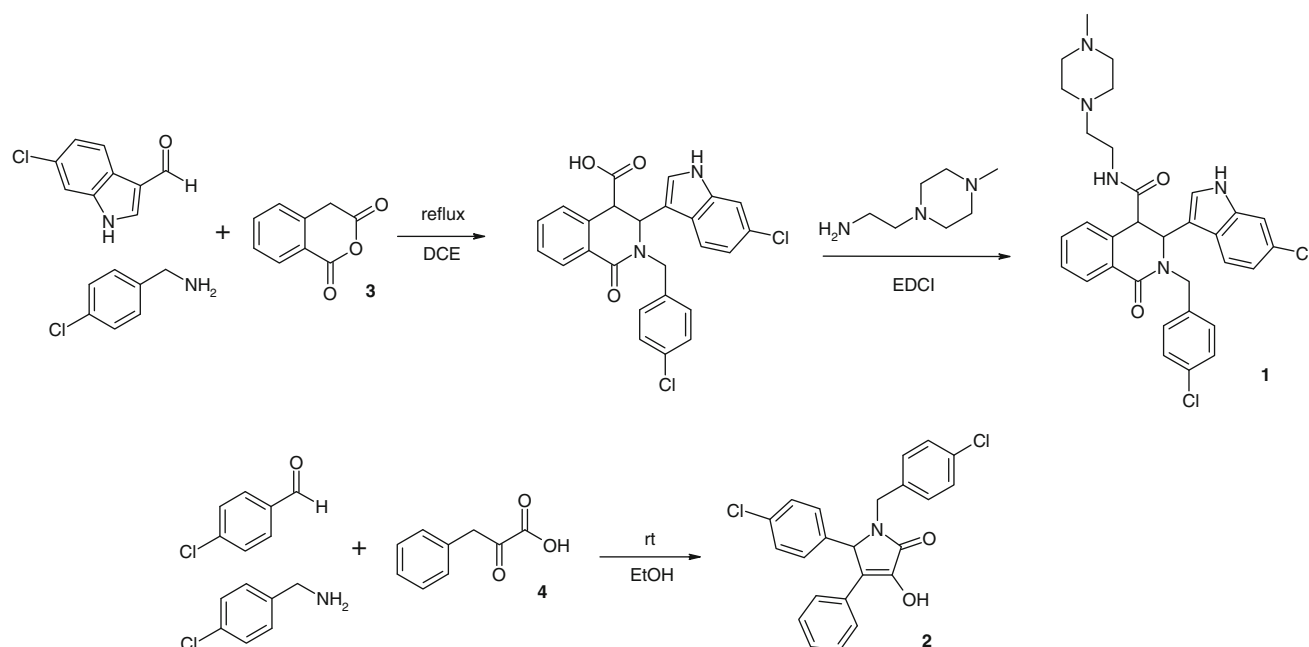
Isoquinolinones **1** were synthesized by one-pot condensation of a Schiff base with homophthalic anhydride **3** [39] followed by amide formation and pyrrolinones **2** obtained by a one-pot Doebner condensation of a Schiff base with alpha-keto acids **4** [40] (Scheme 1).

In total about 80 compounds belonging to these two scaffold classes have been synthesized by our research group in the course of a SAR-study and “hit to lead” optimization. The binding of the PXN compounds to MDM2 was measured with different biophysical methods such as Biacore, isothermal calorimetry as well as NMR, using <sup>15</sup>N labelled MDM2. All methods show consistent results, a 1:1 binding stoichiometry, no unfolding of MDM2 [27]. Especially, <sup>15</sup>N-labelled MDM2 protein binding studies showed that PXN compounds bind reversibly to MDM2 at the same site utilized by Nutlin-3 (Fig. 4).

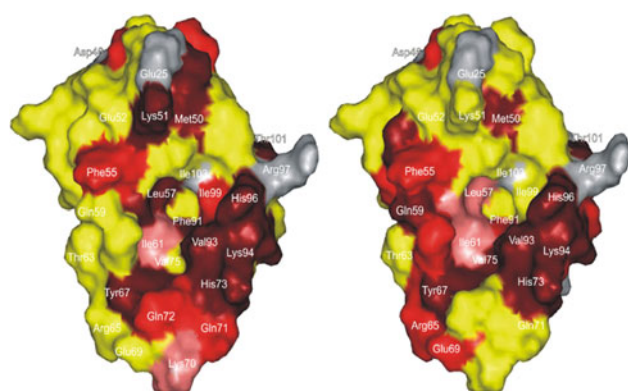
Furthermore, it was shown that the discovered inhibitors were able to induce apoptosis and the expression of p53-related genes, but only the isoquinolin-1-one-based inhibitors stabilised p53 [27]. In conclusion, our in silico compound-selection process permitted the detection of selective inhibitors of the p53–MDM2 protein–protein interaction from a virtual MCR-based chemical space.

#### Diversity-oriented syntheses of polysubstituted heterocycles by the combination of MCRs with intramolecular post-condensation reactions

To enlarge the molecular diversity of our virtual space of MCR-products, during the last years we developed new combinations of the Ugi reaction with post-condensation reactions, giving access to new polysubstituted and biologically relevant heterocycles. We particularly focused on combinations of the Ugi reaction with metal-catalyzed (Pd, Cu) intramolecular cyclization reactions and nucleophilic aromatic substitutions (S<sub>N</sub>Ar).



**Scheme 1** New inhibitors of the p53–MDM2 interaction synthesized by MCRs



**Fig. 4** PNX523 (*left*) and Nutlin-3 (*right*) effects on the surface of MDM2 observed by NMR titration. (*Red*: NMR chemical shifts >0.15 ppm or peak is missing after addition of the compound; *pink*: shifts between 0.1 and 0.15 ppm; *yellow*: shifts <0.1 or no shift). Picture taken from [27]

#### Ugi-4CR-metal-catalyzed post-condensation

In the course of our own research on new post-condensation modifications, we first reported new combinations of the Ugi-four component reaction with palladium catalyzed post-condensation such as the Heck reaction [41–45] or the Buchwald-Hartwig N-arylation reaction [46–49].

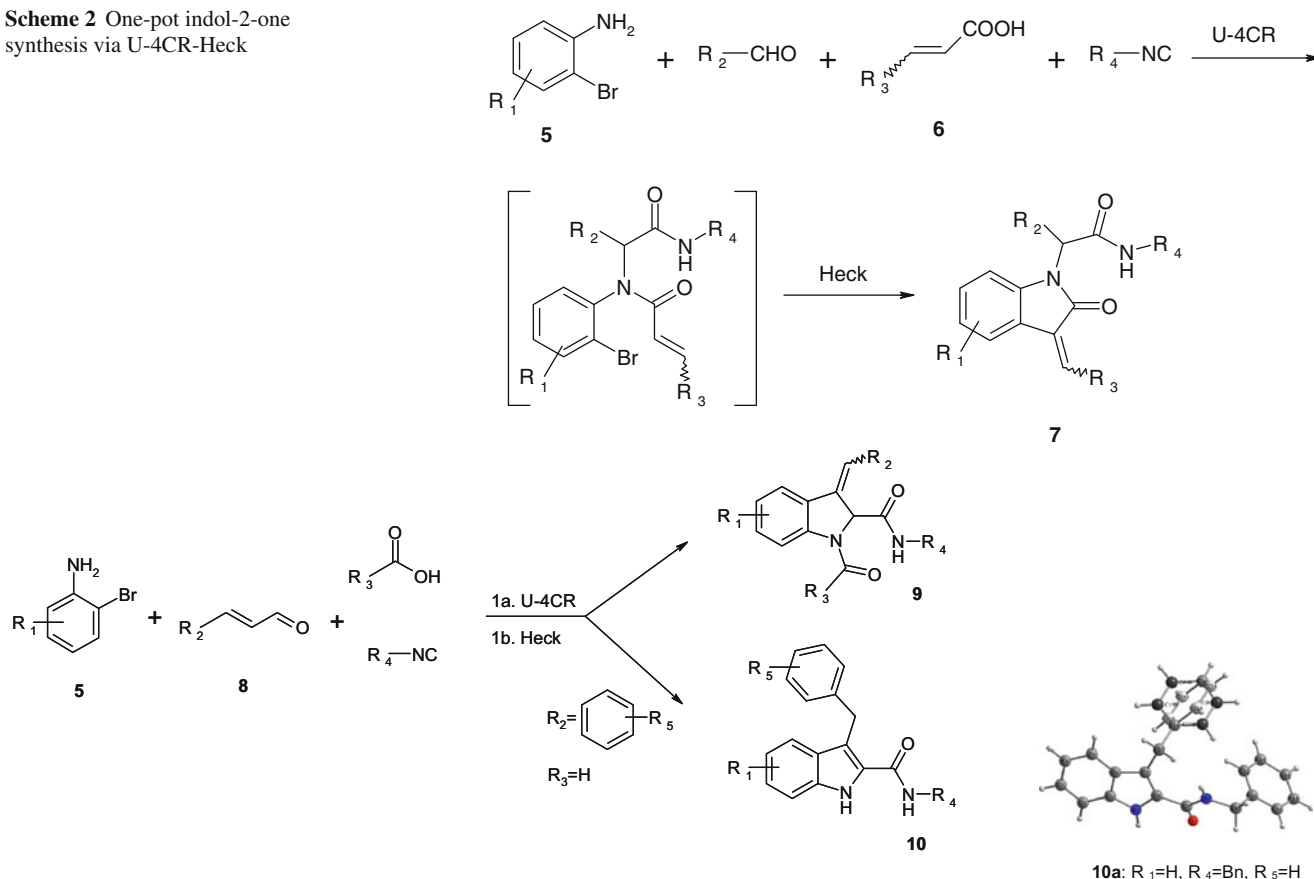
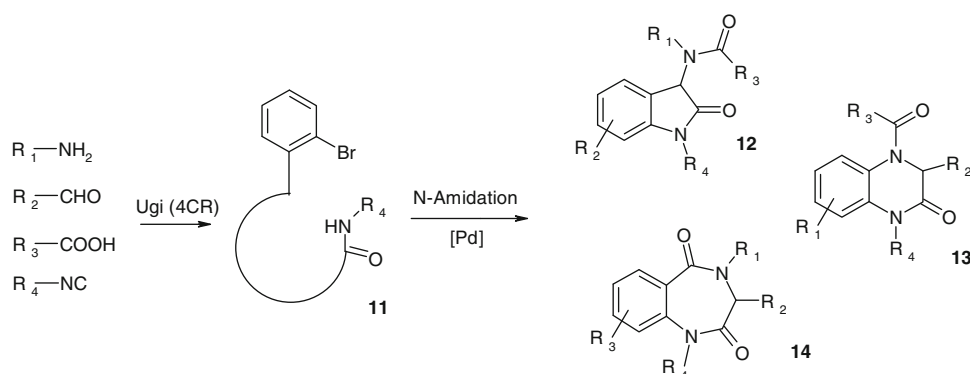
First we enlarged the product scope of the Ugi-Heck reaction (U-4CR-Heck) initially developed by Gracias et al. [50] and Xiang et al. [9]. Using the advantages of multicomponent and classical sequential chemistry, it is very convenient

to synthesize various acrylic products by the Ugi reaction and to initiate a subsequent ring closing by a classical intramolecular Heck-reaction. First by involving 2-bromoanilines **5** and acrylic carboxylic acids **6** in the Ugi reaction, we developed a novel one-pot solution phase procedure for the preparation of highly substituted indol-2-ones **7** [51] (Scheme 2).

In the same way, new N-heterocycles were amenable by involving 2-bromoanilines **5** and acrylic aldehydes **8**. For instance, this U-4CR-Heck reaction yielded generally dihydroindoles **9** or substituted 1H-indoles **10** by involving cinamaldehydes and formic acid in our one-pot procedure (Scheme 3). Under the last conditions, the resulting formic group was partially cleaved. Successive isomerisation led to the pharmacologically relevant 1H-indoles **10** with moderate to good yields [52].

The area of palladium chemistry is diverse and a plethora of other post-condensation modifications can be envisaged. Thus, we also reported a new strategy for the preparation of polysubstituted indol-2-ones **12**, quinoxalin-2-ones **13** and benzodiazepine-2,5-diones **14** based on the combination of the Ugi four-component reaction and a palladium-assisted intramolecular N-aryl amidation [53] (Scheme 4).

The final ring-closing reaction was performed by a classical intramolecular N-aryl amidation of the Ugi product's secondary amide **11** catalyzed by palladium and an appropriate ligand system under basic conditions. This reaction was extensively investigated and optimized by Buchwald and co-workers who developed numerous specific ligands and palladium-based catalytic systems. For a rapid proof of concept,

**Scheme 2** One-pot indol-2-one synthesis via U-4CR-Heck**Scheme 3** One-pot syntheses of highly diverse indole scaffolds by the Ugi/Heck reaction**Scheme 4** Indol-2-ones, quinoxalin-2-ones and benzodiazepin-2,5-diones via Ugi(4CR)-Pd assisted N-aryl amidation strategy

we used  $\text{Pd}_2(\text{dba})_3$  and tri-*o*-tolylphosphine in combination with a carbonate base in a two-step solution phase procedure leading to the desired N-heterocyclic scaffolds with moderate to good yields. Later, new ligands were used which improved the overall yields of this synthetic strategy [54].

For further expansion in molecular diversity, we finally combined the Ugi-4CR with a copper-catalyzed cyclization yielding substituted benzoxazoles **15** and benzothiazoles **16** [55] (Scheme 5). The post-condensation is based on a C-X cross-coupling of the *ortho*-halophenylamide originating from the isocyanide and is believed to proceed via an oxidative insertion/reductive elimination pathway manifold

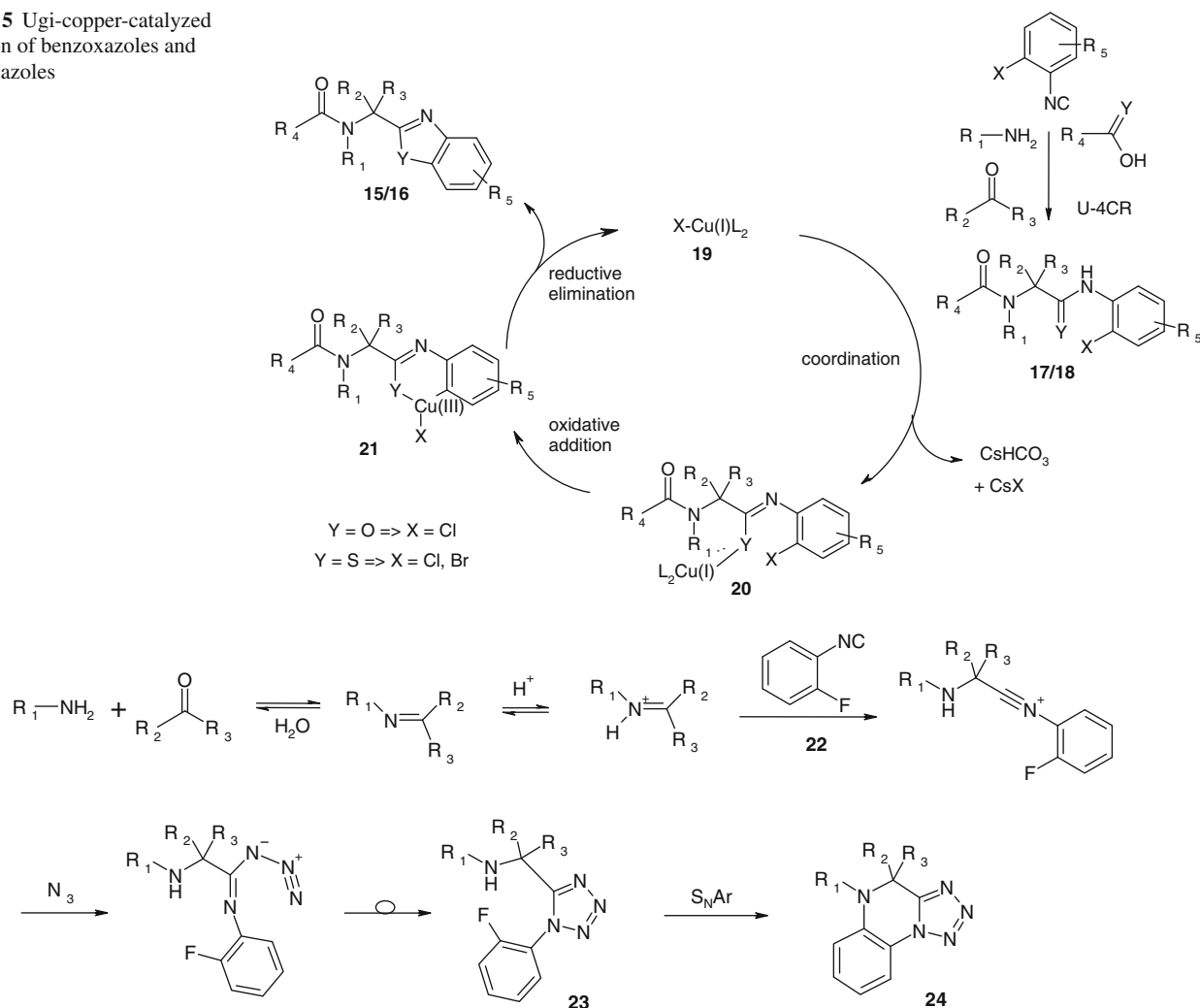
in analogy with other Cu- and Pd-catalyzed C-X bond formations [56–68]. Herein the first step of the post-condensation reaction involves the coordination of the amide group **17/18** with catalyst **19** to give intermediate **20**, then followed by an oxidative insertion to **21** and finally a reductive elimination to release the product **15/16** with simultaneous regeneration of catalyst **19**.

#### Ugi-4CR- $\text{S}_{\text{N}}\text{Ar}$

Diverse scaffolds are amenable by combining the Ugi reaction with various nucleophilic aromatic substitutions.



**Scheme 5** Ugi-copper-catalyzed formation of benzoxazoles and benzothiazoles



**Scheme 6** Two-step synthesis of 4,5-dihydro-1,5-a quinoxalines

The initial input in this field was given by Hulme and co-workers who reported the synthesis of small libraries of indazolinones, benzazepines and benzoxazepines [69,70] through an Ugi-  $S_NAr$  synthetic strategy. Inspired by this work, we developed a new and versatile two-step solution-phase synthesis of fused tetrazolo[1,5-a]quinoxalines **24** [71] (Scheme 6). The first step of this synthesis consists in a classical Ugi-tetrazole reaction yielding bis-substituted tetrazoles **23** [72,73].

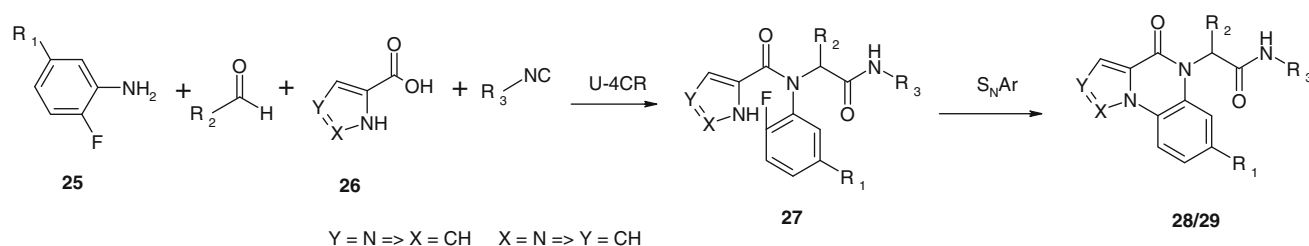
We introduced 2-fluorophenylisocyanide **22** as a new bifunctional starting material in this multicomponent synthesis. In the presence of a base and at higher temperature, the final cyclization takes place by nucleophilic aromatic substitution reaction in which the hydrogen-bearing nitrogen NH of the secondary amine moiety acts as the nucleophile, fluorine as the leaving group [74].

Similarly, we investigated a novel two-step synthesis procedure for the preparation of highly substituted 4-oxo-4H-imidazo[1,5-a]quinoxalines **28** and 4-oxo-4H-pyrazol-

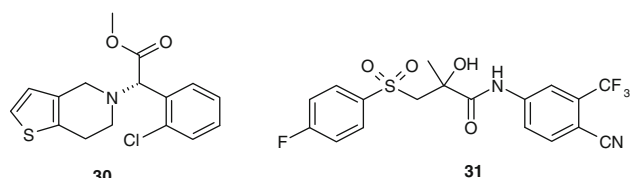
o[1,5-a]quinoxalines **29** [75]. The use of 2-fluoroanilines **25** and heterocyclic carboxylic acids **26** as bifunctional starting materials enables the subsequent nucleophilic aromatic substitution reaction (Scheme 7). We used two different carboxylic acids, 1H-imidazole-4-carboxylic acid and 1H-pyrazole-3-carboxylic acid leading to the two different tricyclic scaffolds **28/29**. The subsequent  $S_NAr$  cyclisation requires a suitable base to enhance the nucleophilicity of the heterocyclic nitrogen N1 by deprotonation and capture of the hydrogen fluoride released during the reaction. Cesium or potassium carbonates as base in combination with microwave irradiation at a reaction temperature of 150 °C in DMF are the ideal cyclization conditions in this case.

#### MCRs for generic drug synthesis

Interestingly, it is also possible to detect in our chemical space already marketed therapeutic compounds. This opens



**Scheme 7** Synthesis of 4-oxo-4H-imidazo[1,5-a]quinoxalines and 4-oxo-4H-pyrazolo[1,5-a]quinoxalines



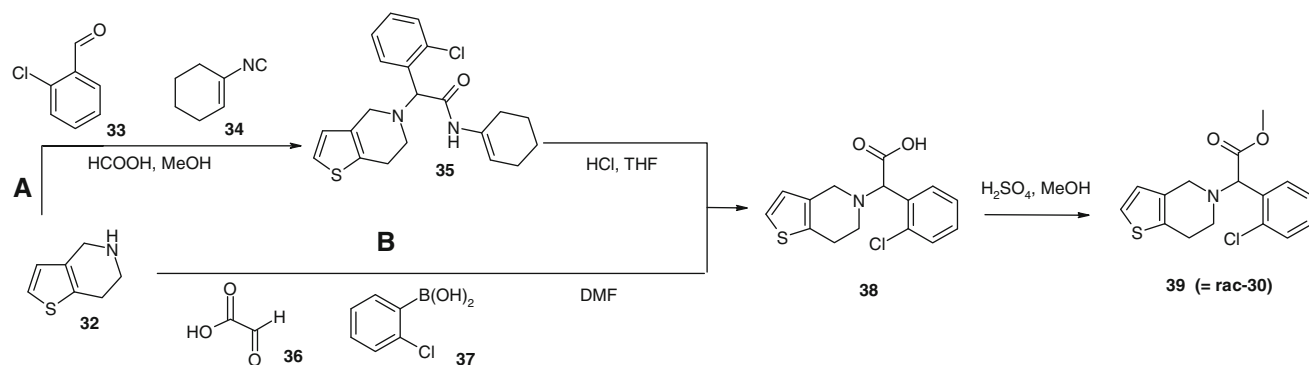
**Fig. 5** Structures of (*S*)-clopidogrel and bicalutamide

up the MCR-based synthesis of generic drug as possible new application of MCRs in the pharmaceutical industry. For illustration, we have reported alternative, MCR-based synthetic approaches for the well-known marketed drugs, (*S*)-clopidogrel (Plavix®) **30** and bicalutamide **31** [76] (Fig. 5).

First, we developed a racemic synthesis of the antiplatelet agent **30** [77,78], the world's second highest selling pharmaceutical in 2007 [79] (Scheme 8). The active pharmaceutical ingredient can be regarded as an ester of a non-natural  $\alpha$ -amino acid and is, therefore, accessible by different synthetic routes based on MCR-chemistry. A three-component Ugi reaction with a convertible isocyanide (Method A) and a Petasis reaction (Method B) with suitable starting materials were improved to synthesize the carboxylic acid **38** precursor of racemic (*R,S*)-clopidogrel **39** (Scheme 8). The Ugi reaction (U-3CR) [80,81] involves the commercially available 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine **32**, 2-chlorobenzaldehyde **33** and 1-isocyano-cyclohexene **34** as acid-labile cleavable isocyanide [82].

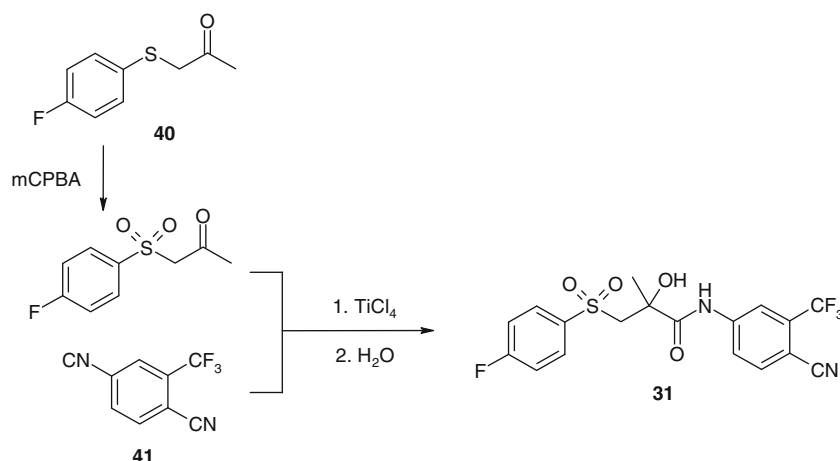
Subsequent cleavage of the isocyanide moiety with aqueous hydrochloric acid allowed fast and complete conversion of **35** to the desired carboxylic acid **38**. An alternative one-step synthetic route to the precursor **38** was carried out by using the Petasis reaction discovered by Petasis and Akritopoulou [83]. This reaction can be regarded as a boronic acid Mannich reaction. In a further optimization protocol, its practical use for the synthesis of non-natural  $\alpha$ -amino acids from alkenyl boronic acids and glyoxylic acid has been reported [84]. Thus, we employed compound **32**, glyoxylic acid **36** and 2-chloro-phenylboronic acid **37** in a Petasis three-component reaction (Petasis-3CR) leading to the formation of carboxylic acid **38**. After obtention of the precursor **38** by these two different methods, a final esterification step yielded the desired racemic clopidogrel **39** with high conversion, high purity and acceptable to good overall yields of, respectively, 44% (Method B) and 73% (Method A).

As a second illustration of the potential use of MCRs in the field of generic drug production, we presented a short, efficient two-step synthesis of the non-steroidal antiandrogen bicalutamide **31** (Casodex®), which is the leading antiandrogen used for the treatment of prostate cancer [85,86]. The key step is a Passerini reaction (P-3CR) assisted by titanium tetrachloride (Scheme 9). The Passerini reaction is a classical MCR already discovered in the 1920s [87]. It has been shown that in the  $\text{TiCl}_4$ -assisted Passerini reaction the isocyanide forms an adduct with  $\text{TiCl}_4$  [88]. The adduct then reacts with the carbonyl compound and upon hydrolysis of the reaction mixture an  $\alpha$ -hydroxyamide is formed. For our objective, the



**Scheme 8** Synthesis of (*R,S*)-clopidogrel via U-3CR with Armstrong isocyanide (Method A) or Petasis-3CR (Method B) followed by esterification

**Scheme 9** Synthesis of (*R,S*)-bicalutamide **31** via  $\text{TiCl}_4$ -assisted Passerini reaction



$\text{TiCl}_4$ -assisted Passerini reaction is a very attractive method as it directly leads to the  $\alpha$ -hydroxyamide moiety of bicalutamide without necessity for an additional ester cleavage step.

Our MCR synthesis produced racemic bicalutamide **31** from commercially available starting materials **40**, **41** in a two-step process with a very satisfying overall yield of 66%.

Further scale-up experiments and studies about the cost of building blocks could determine if these reactions are suitable for industrial application, including price reduction of the marketed products. However, we demonstrated that MCRs are also a powerful tool for the rationalization of marketed drugs synthesis.

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