CHEMICAL REVIEWS

Review

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Chemistry and Biology Of Multicomponent Reactions

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1. INTRODUCTION: MCR SPACE, SHAPE AND DIVERSITY

Multicomponent reactions (MCRs) are one-pot reactions employing more than two starting materials, for example, 3, 4, ..., 7, where most of the atoms of the starting materials are incorporated in the final product.[1] Several descriptive tags are regularly attached to MCRs (Figure 1): they are atom economic, for example, the majority if not all of the atoms of the starting materials are incorporated in the product; they are efficient, for example, they efficiently yield the product since the product is formed in one-step instead of multiple sequential steps; they are convergent, for example, several starting materials combine in one reaction to form the product; they exhibit a very high bond-forming-index (BFI), for example, several non-hydrogen atom bonds are formed in one synthetic transformation.[2] Therefore MCRs are often a useful alternative to sequential multistep synthesis.

Many basic MCRs are name reactions, for example, Ugi,[3] Passerini,[4] van Leusen,[5] Strecker,[6] Hantzsch,[7] Biginelli,[8] or one of their many variations. For example, in the Ugi reaction the primary scaffold is mostly dictated by the type of acid component (and to a less degree by the amine component), for example, carboxylic acid, carbonic acid, thiocarboxylic acids,[9] HN_3, H_2O, H_2S, HNCO, HNCS, and phenol, which is one of the few recent innovations regarding primary scaffold diversity in Ugi reactions,[10] leading to α-acylaminocarboxamides, carbamates, α-acylaminothiocarbonamides, tetrazoles, α-aminoamides, α-aminothioamides, hydantoines, thiohydantoines and α-aminoarylamides.[11] Additionally, since MCRs are often highly compatible with a range of unprotected orthogonal functional groups, on a second level, the scaffold diversity of MCR can be greatly enhanced by the introduction of orthogonal functional groups into the primary MCR product and reacting them in subsequent transformations, e.g. ring forming reaction. This two layered strategy has been extremely fruitful in the past leading to a great manifold of scaffolds now routinely used in combinatorial and medicinal chemistry for drug discovery purposes (Figure 2).[12]

Thus the initial MCR derived product can be considered as a synthetic hub to a vast diversity of novel cyclic or acyclic scaffolds by employing different secondary transformations. Typically, only 1−3 synthetic steps are needed to synthesize libraries of drug-like advanced compounds. A versatile example

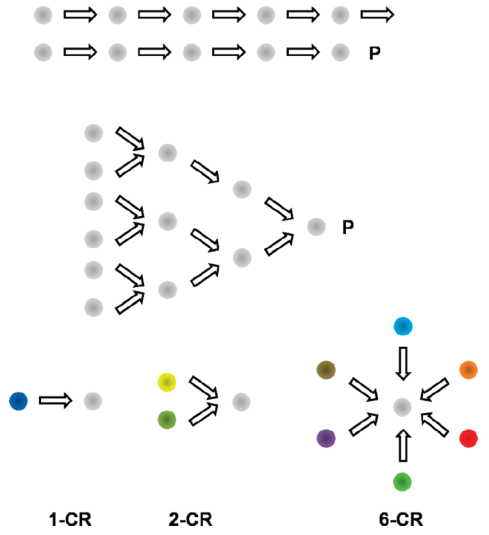

Figure 1. Top: Multistep syntheses can be divergent (sequential) or convergent. Bottom: In analogy MCR reactions are convergent and one or two component reactions are divergent.

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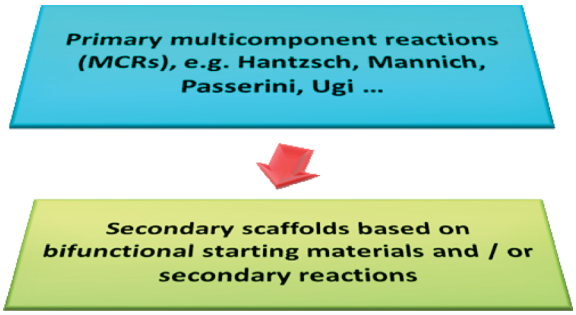


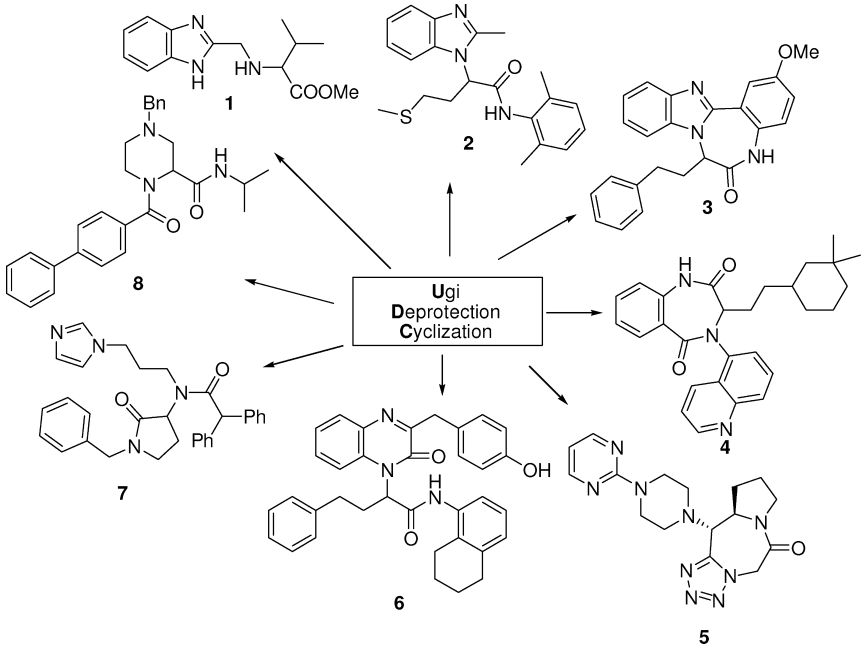
Figure 2. Immense scaffold diversity based on MCR is derived from primary (often "classical") MCRs and secondary reactions made possible by the great functional group compatibility of MCRs. Reprinted with permission from ref 12b. Copyright 2009 American Chemical Society.

of this strategy are the UDC-procedures (**U**gi-**D**eprotection-**C**ylization) leading to a great scaffold diversity, e.g. benzimidazoles (**1**, **2**, **3**), benzodiazepinedione (**4**), tetrazolo-diazepinone (**5**), quinoxalinones (**6**), γ-lactames (**7**), and piperazines (**8**) (Scheme 1).[13]

The rapid and easy access to biologically relevant compounds by MCRs and the scaffold diversity of MCRs has been recognized by the synthetic community in industry and academia as a preferred method to design and discover biologically active compounds. MCR chemistry has been reviewed multiple times in the past in journals and books, however focusing mostly on diverse synthetic and structural aspects.[12a,13n,14] The biological activities of MCR derived molecules has been review in the past.[12a,13j,14t,15] However there has never been an extensive summary of the biological properties and potential of MCR derived molecules in one review.[15] The biological chemistry of MCRs however is very rich and provides great opportunities for drug hunters and researchers interested in small molecular weight compounds with biological activity. Therefore we want to fill a gap writing this dedicated review on MCR's chemistry and biology. Because of the overwhelming number of published examples of compounds with bioactivity and synthesized by MCR chemistry, however this contribution intends to give an overview based on a personal selection of recent and significant examples rather than a comprehensive review.

Chemical space is the ensemble of all possible molecules, which is believed to contain at least 10^{60} organic molecules below 500 Da of possible interest for drug discovery.[16] This number is mindboggling and impossible to even enumerate or screen. In addition the majority of the compounds, likely, would be very difficult to synthesize or even unstable. An interesting, because it is synthetically largely amenable, chemical subspace is the MCR chemical space. In the following we therefore define the MCR chemical space as the ensemble of possible molecules which can be synthesized by the multitude of MCR chemistry. This practical definition of chemical space has the advantage of synthetic feasibility, which is important to test the computationally driven hypothesis (e.g., similarity, pharmacophore, docking searches). Ultimately, the success of small molecule drug discovery projects depends on the sector of chemical space chosen for discovery, optimization, and development. Current design efforts are therefore directed toward target class specific compound libraries.[17] The 3-dimensional shape of ligands in addition to electrostatic complementarity between receptor and ligand is one of the most crucial descriptors of bioactive compounds as it determines its interaction with its targets.[18] This has been recently taken into account by designing topography-biased compound libraries using MCR chemistry (Figure 3).[19] Indeed, it can be shown that the 3D-shape space of MCR scaffolds differ considerably from other scaffold spaces. Some of these MCR libraries are more diffuse represented in the property space than others and conventional backbones, which can be understood based on their different shape and their higher substituent density. The high density of atoms of MCR-based compounds seems to play an important role in their propensity

Scheme 1. UDC Strategy Allows for the Great Scaffold Diversification of an Initial Ugi Reaction by Using Orthogonal Protected Bifunctional Starting Materials



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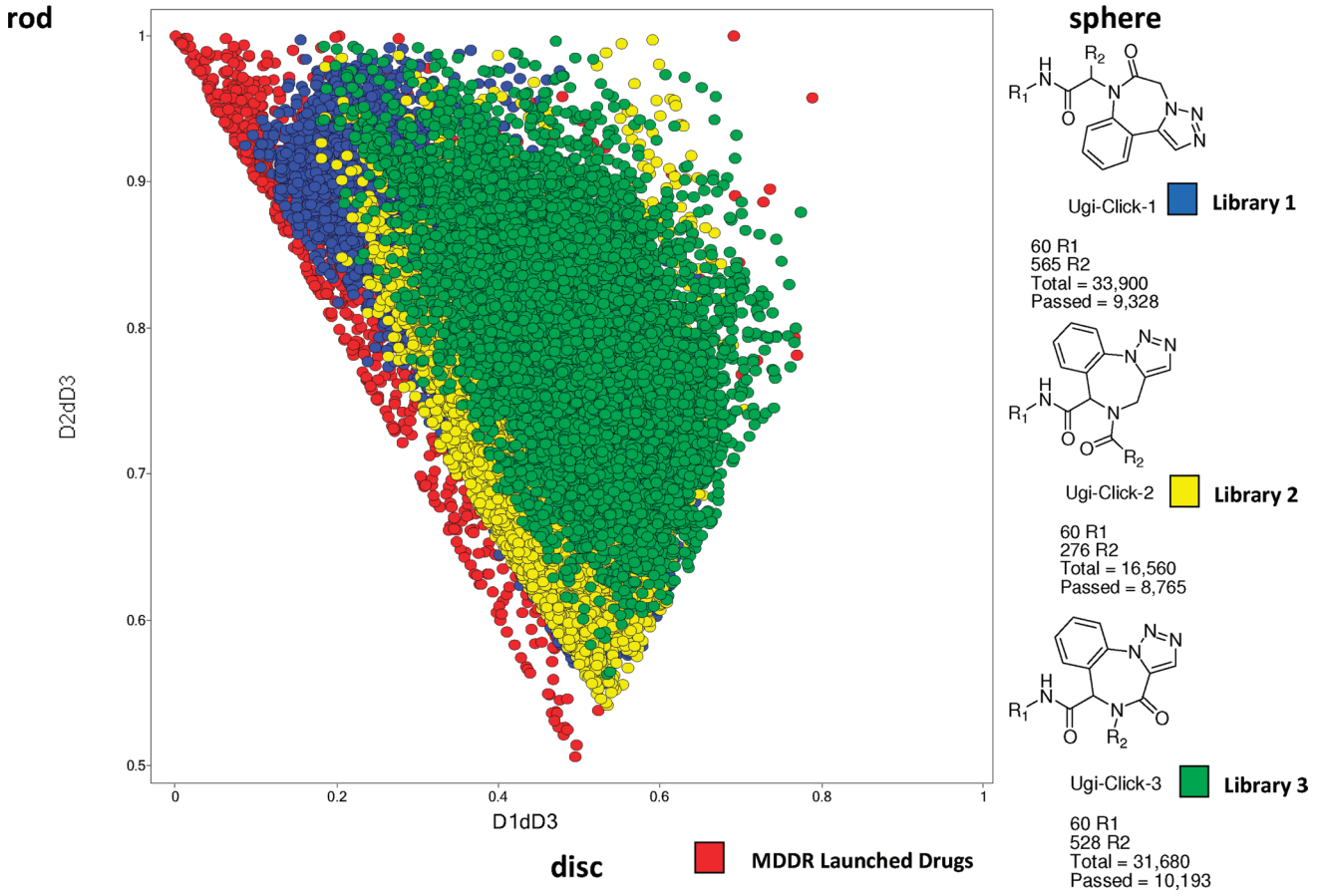

Figure 3. Distributions of MoI-derived shapes for rule-of-five compliant libraries deriving from the corresponding color-coded scaffolds (Reprinted with permission from Dr. Akritopoulou-Zanze, Abbott Laboratories). Normalized principal moments of inertia were plotted in two dimensions resulting in a triangular scatter plot, which facilitates the comparison of different compound sets of varying shape (details on the method can be found in ref 19).

for specific target classes where traditional non-MCR compounds seem to have lower screening hit rates, e.g. protein−protein interactions (PPIs). With this in mind strong emphasis is put on examples with structural and mechanistic information.

Chemical transformations toward rare scaffold types annotated with unusual physicochemical properties are amenable by MCR in a straightforward, short manner. For example, recently, the construction of libraries of bicyclic lactam with bridgehead amide nitrogen (**9** and **10**) has been reported by the synthesis sequential Ugi/RCM/Heck.[20] X-ray diffraction studies revealed that the bicyclic products contain varying degrees of pyramidalization of the bridgehead nitrogen atom (Figure 4). Such compounds cannot be easily accessed by other chemical methods and certainly not in such a high number and diversity.

Another uniquely shaped scaffold, 3-azabicyclo[4.2.0]octan-4-one derivative (**15**), can be synthesized by combining the Ugi multicomponent reaction with [2 + 2] enone-olefin photochemical transformations (Figure 5). During this transformation up to five stereocenters are formed; however in most cases only two diastereomers are observed.[21] This scaffold displays a very stiff tricyclic ring system with only minor degrees of rotation. The number of rotatable bonds is a very important parameter in compound optimization as it has major influence on orally bioavailability of drugs and on binding affinity.

A third example is the recently described assembly of polycyclic indole alkaloid-type libraries (**19**) by the combination Ugi/Pictet−Spengler reaction (Figure 6).[22] Notable, in this scaffold is the ease of formation of a quaternary carbon stemming from the cyclic oxo carboxylic acid input.

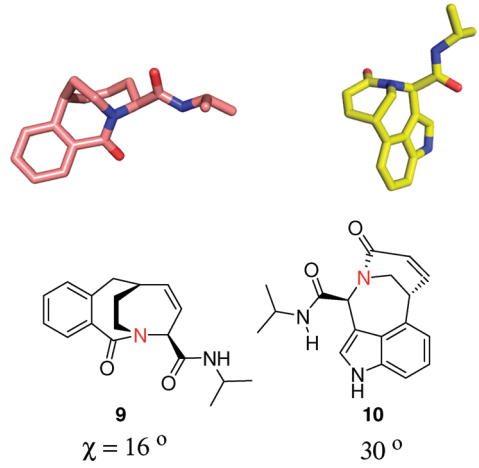

Figure 4. Two examples (**9** and **10**) of the 3D structure of unusual pyramidalized nitrogen in bicyclic bridgeheaded amides accessible by a 3-step sequence Ugi/RCM/Heck. The pyramidalization χ of planar formamide is 0° and 60° for a fully pyramidalized sp^3 atom and is calculated from the X-ray structures.

A tricyclic scaffold with unusual shape provided by MCRs is the biomimetic transformation of 2-deoxyribose, aryl amine and

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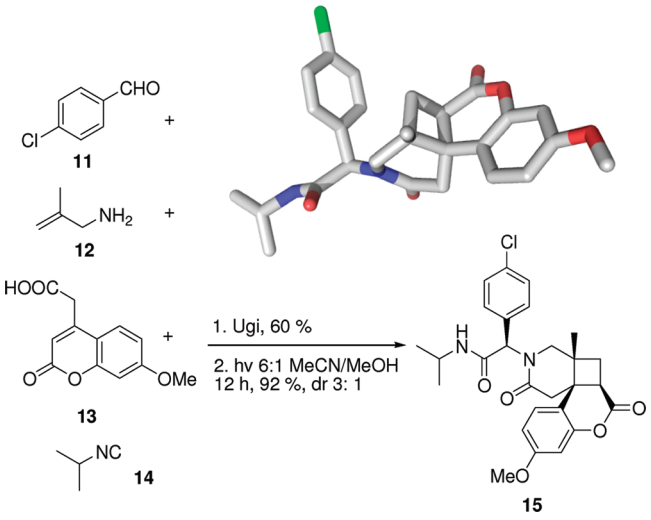

Figure 5. Ugi MCR involving orthogonal coumarine **13** and allyl moieties **12** followed by a [2 + 2] photocyclization leads to unusual densely functionalized scaffolds and libraries thereof.

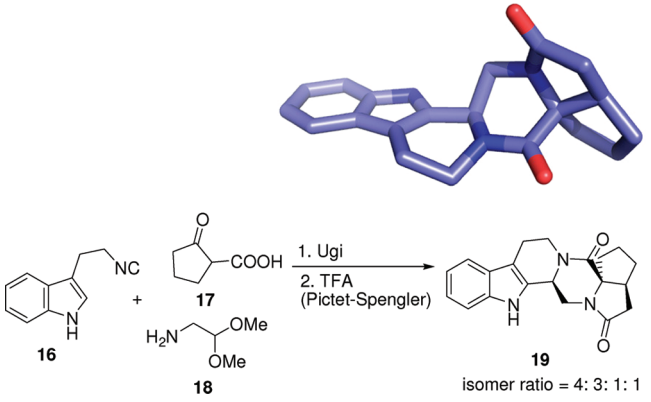

Figure 6. Complex indole natural-product-like polycyclic compounds **19** made in two steps from simple commercial starting materials, involving a U-4CR and a subsequent Pictet–Spengler cyclization (CCDC ID 749252).

acetyl acetone under $InCl_3$ catalysis, stereospecifically leading to aminols (**23**, Figure 7).[23] The reaction typically leads to 1:1

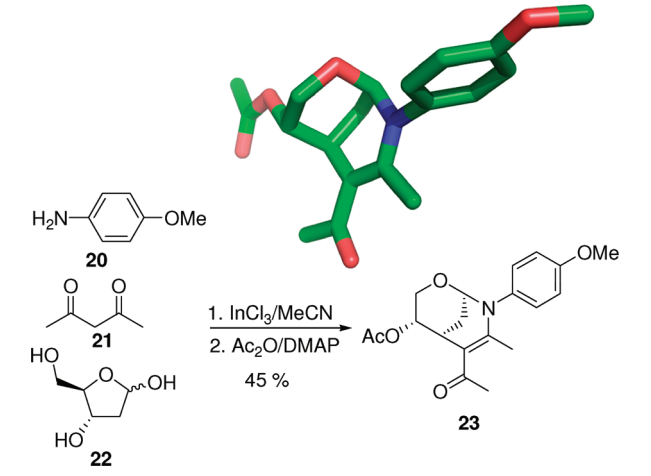

Figure 7. Unusual bicyclic aminol scaffold **23** and 3D structure as determined by X-ray structure analysis (CCDC ID 675996).

mixtures of two diastereomers and shows considerable scope in the nature of the substitutents of the aniline component (**20**).

A fragment of repetitive occurrence in investigational drugs is the cyclopropyl group. In addition the cyclopropyl group widely occurs in natural products with often interesting biological activities. Through the synthesis of cyclopropylisocyanides (**26**) from isocyanoacetic acid esters libraries of cyclopropyl containing compounds (**28**) can be easily generated under very mild conditions (Figure 8).[24]

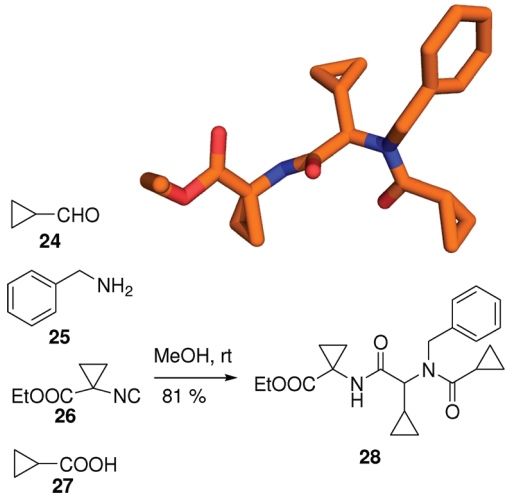

Figure 8. Compounds **28** with three cyclopropene groups can be easily assembled using a mild and convergent U-MCR (CCDC ID 604792).

Spirocompounds are considered privileged structures and often show interesting biological activity. They are frequently occurring fragments in drugs and natural products. Spiroheterocycle synthesis can be accomplished using different classes of MCRs. A popular access to stiff spirocycles with indole fragments starts from isatin (**29**) and cyanoacetic ethyl ester (**30**) and different classes of bisnucleophiles, such as **31**. For example, tetracyclic heterospiro compound **32** can be isolated in 72% yield.[25] Additionally, very elegant enantioselective approaches toward spirooxindoles with p53-mdm2 anticancer activity using distinct organocascade reactions have been recently published.[26]

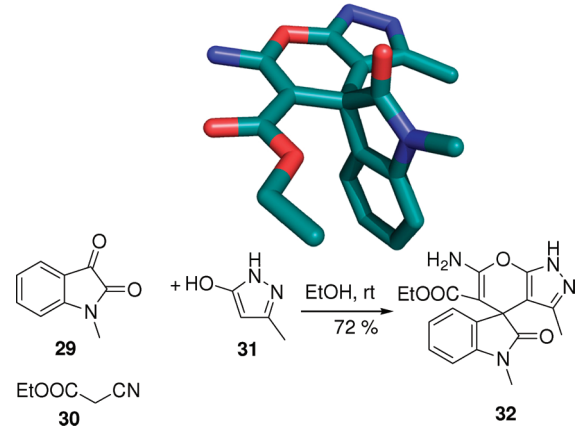

Figure 9. Spiroheterocycles of great diversity, for example, **32** can be accessed by different MCRs (CCDC ID 643526).

Natural-product-like macrocycles have been generated in an efficient sequence involving MCR and different ring closure

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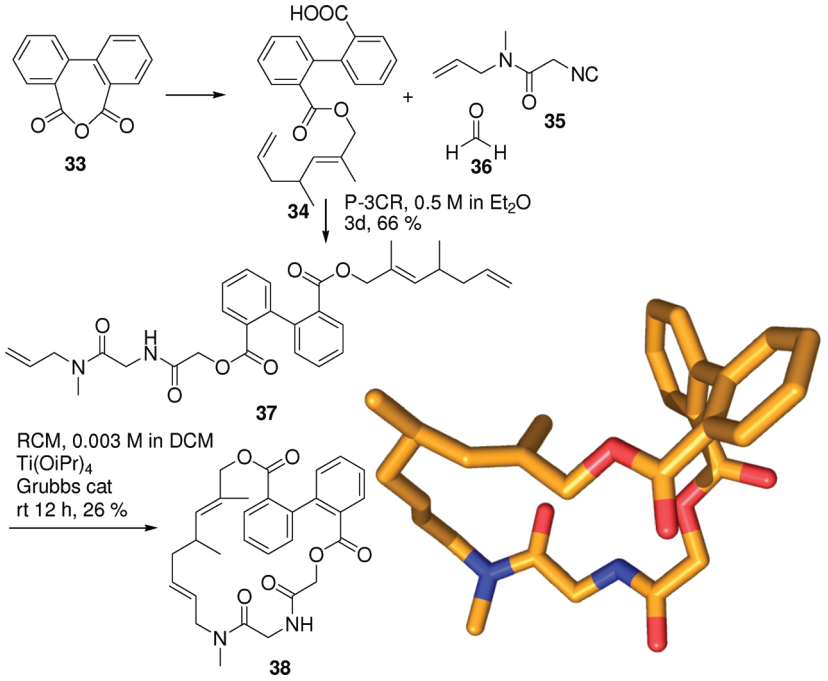

Figure 10. Macrocyclic compounds **38** featuring natural-product-like properties can be assembled by an efficient and short three-step sequence involving a Passerini-3CR (CCDC ID 200226).

techniques.[27] The 22-membered ring compound **38**, for example can be made in three steps from commercially available starting materials using a Passerini-3CR (intermediate **37**) followed by a RCM (Figure 10). It contains several attributes reminiscent to natural products: the different stereo elements, atropisomerism generated by the biphenyl axis, a double bond, a tertiary amide, an ester moiety and a stereogenic carbon. The macrocycle features reduced flexibility due to an intramolecular hydrogen bond. Similar to many natural macrocycles the molecule displays a hydrophobic and a hydrophilic face. In fact synthetic macrocycles are a highly underexploited structural class for drug discovery.[28]

An extended bicyclic "flat-land" chemotype **42** can be exemplified in great diversity by employing a three component reaction of 5- and 6-membered (hetero-) aromatic amidines (**39**), aldehydes (**40**), and isocyanides (**41**), an MCR discovered at the same time by three different groups (Figure 11).[29] Clearly, such heterocycles have potential as GPCR and kinase directed agents and several examples will be discussed later on. This very popular MCR has been recently extensively reviewed.[30]

The 3D shape, the special arrangement of the H-bond donor and acceptor moieties, the charge distribution of the lead compound and its binding into the target pocket are of great importance for the primary compound-target interaction. It also forms the basis of a drug discovery process called scaffold hopping.[32] During scaffold hopping an existing biological active scaffold is transformed into a chemically unrelated scaffold with similar biological activity and similar binding features to its biological target. Scaffold hopping is an essential process in order to improve binding, selectivity and ADMET properties but also to create new intellectual property (IP) and to overall improve the chances to successfully maneuver projects through development toward the market. In this context it is important to be aware of the diversity of scaffolds offered by a certain type of chemistry. Thus in Figure 12 fifteen different piperazines are depicted which can be reportedly accessed by IMCR.[33] Optimal leverage of the chemical space offered by MCR chemistry by drug design requires

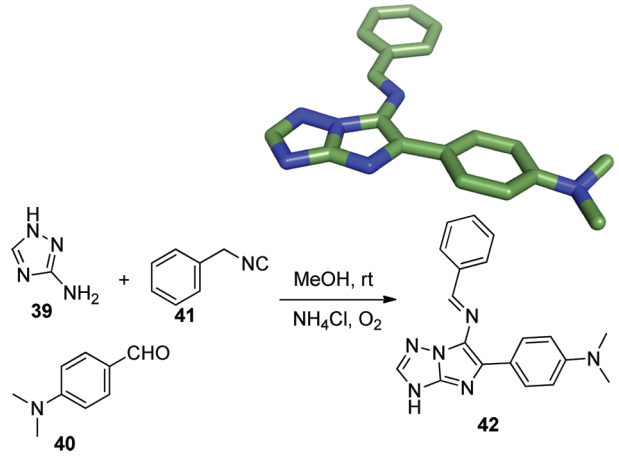

Figure 11. Flat heteroaromatic bicyclic chemotype (**42**) by the Groebke–Bienaymé–Blackburne–MCR (GBB-MCR) (CCDC ID 614188).[31]

the knowledge of the 2D parameters of the different scaffold as well as their 3D pharmacophore. 2D descriptors for example are the connectivity, the quality and quantity of H-bond donors and acceptors, whereas 3D descriptors are the 3D structure, shape, the 3D H-bond donor and acceptor distribution and directionality.

Currently, the majority of bioactive compounds based on MCR chemistry belong to only a few scaffold classes. The reason for this is the rapid pace by which the MCR field is moving. Consequently, many new scaffolds have only been recently discovered; therefore the general knowledge about their chemistry and biology is yet poor. Thus, there are 36 piperazine scaffolds described to be accessible only using isocyanide-based MCR chemistry.[33] The majority of these backbones have not been exploited in drug discovery yet. In fact the majority of bioactive molecule reported in this review is based only on a small number of MCRs. These major MCRs are summarized in Table 1.

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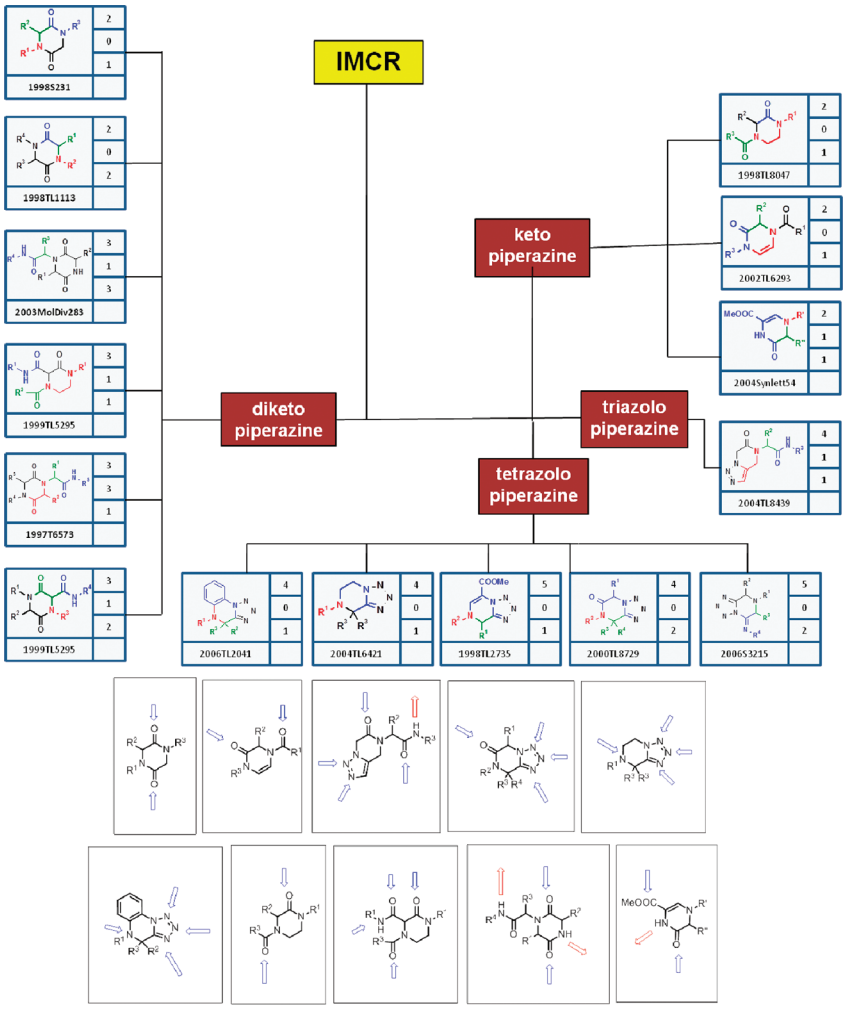

Figure 12. Sector of the piperazine scaffold space offered by IMCR.[33] Above the relationship of 15 different piperazine scaffolds based on different heterocyclic systems and hydrogen-bond donor−acceptor features. Below several piperazine scaffolds are shown with their imminent 2D hydrogen bond donor−acceptor propensity (blue and red arrows, H-bond acceptors and donors, respectively).

2. MCRS BY TARGET CLASS

Currently, the number of drug targets is surprisingly low compared to the number of human genes and posttranslational modifications thereof as revealed by the human genome project and work based upon. Thus it has been reviewed that current target counts are of the order of hundreds, whereas estimations of the number of potential drug targets are an order of magnitude higher. Specifically the number of targets for current drugs on the market is only 218.[36] Estimates of the total number of targets suitable for drug discovery have been published often referred to as the druggable genome and are between 3000 and 5000 depending on the metric.[37] Whatever the hypothetical number of targets is, the fundamental question arising is how to connect the chemical space with the biological space to efficiently generate bioactive compounds. In the following, we will discuss biological activity of compounds based on MCRs categorized by the different drug targets classes and aim to elaborate the connectivity of chemical and biological space.

2.1. Proteases

Of the >500 known human proteases, >10% are under investigation as drug targets in pharmaceutical industry.[38] Additionally, many parasite, bacterial and viral proteases represent important targets for drug discovery.[39] Proteases cleave biological material into smaller fragments for metabolic, anabolic, or signaling purposes. They are involved in all fundamental biological and in many pathogenic processes. Clearly, based on the number of different protease inhibitors in therapeutic use, proteases are druggable, that is small molecular weight inhibitors with suitable pharmacological properties can be developed. An archetypical, highly efficacious and successful class of drugs in this area is the β-lactam antibiotics. The design of protease inhibitors relays often on the powerful idea of transition state mimics. The fundamental idea is to design non cleavable molecular fragments resembling the transition state of the enzyme mechanism and otherwise mimicking the shape and pharmacophore of the central part of the substrate. In another successful approach, the active side amino acids or other functional moieties, for example, metals, are captured by the inhibitor in a covalent or noncovalent manner. These moieties are often called "warheads" since they provide initial inhibitory and mechanism-based activity, whereas potency and selectivity to related targets can be achieved by targeting specific substrate pockets in the proteases. Thus protease inhibitors often contain α-ketoamide, (nor)statine or hydroxamic acid moieties. MCRs are very useful for the rapid assembly of diverse protease-type

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Table 1. Majority of Bioactive Compounds Reported Here Belong to a Relatively Small Number of MCRs

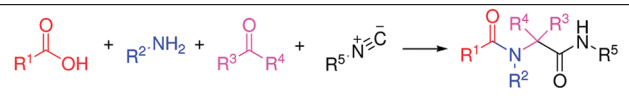
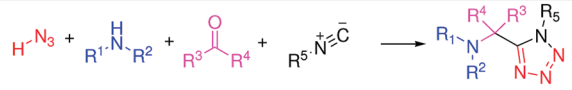
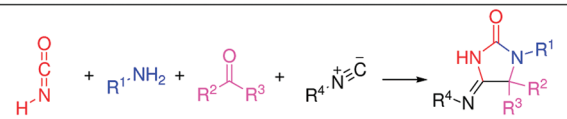
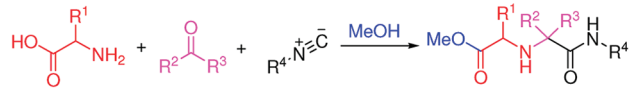
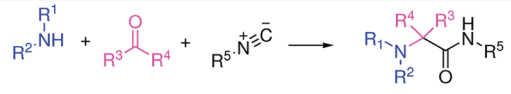
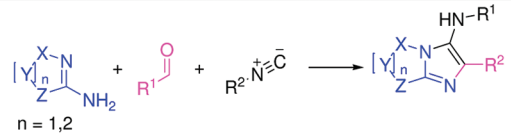
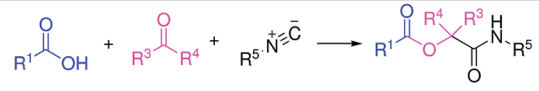
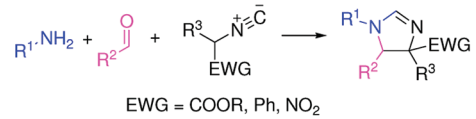
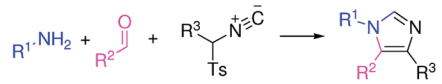
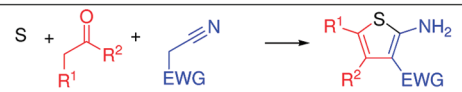
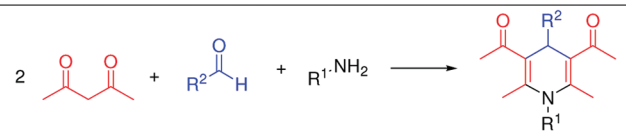
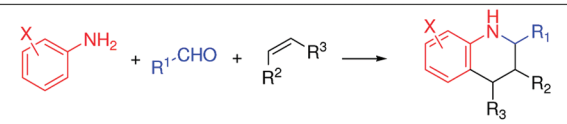
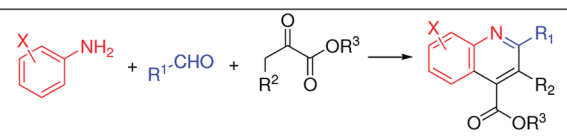
	Ugi-4CR
	Ugi-4CR tetrazole
	Ugi-4CR hydantoine
	Ugi-5C-4CR
	Ugi-3CR
	Groebke-Bienaymé-Blackburn-3CR
	Passerini-3CR
	Orru-3CR
	Van Leusen-3CR
	Gewald-3CR
	Hantzsch-3CR
	Povarov-3CR[34]
	Doebner-3CR[35]

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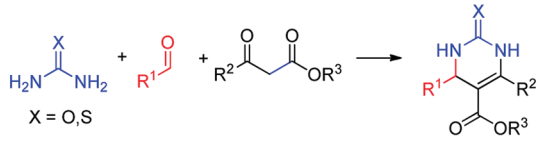
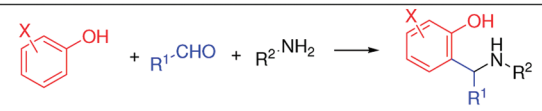
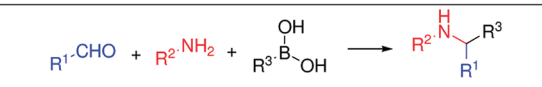
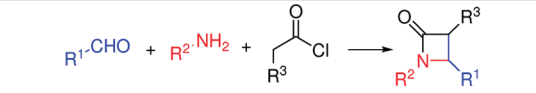
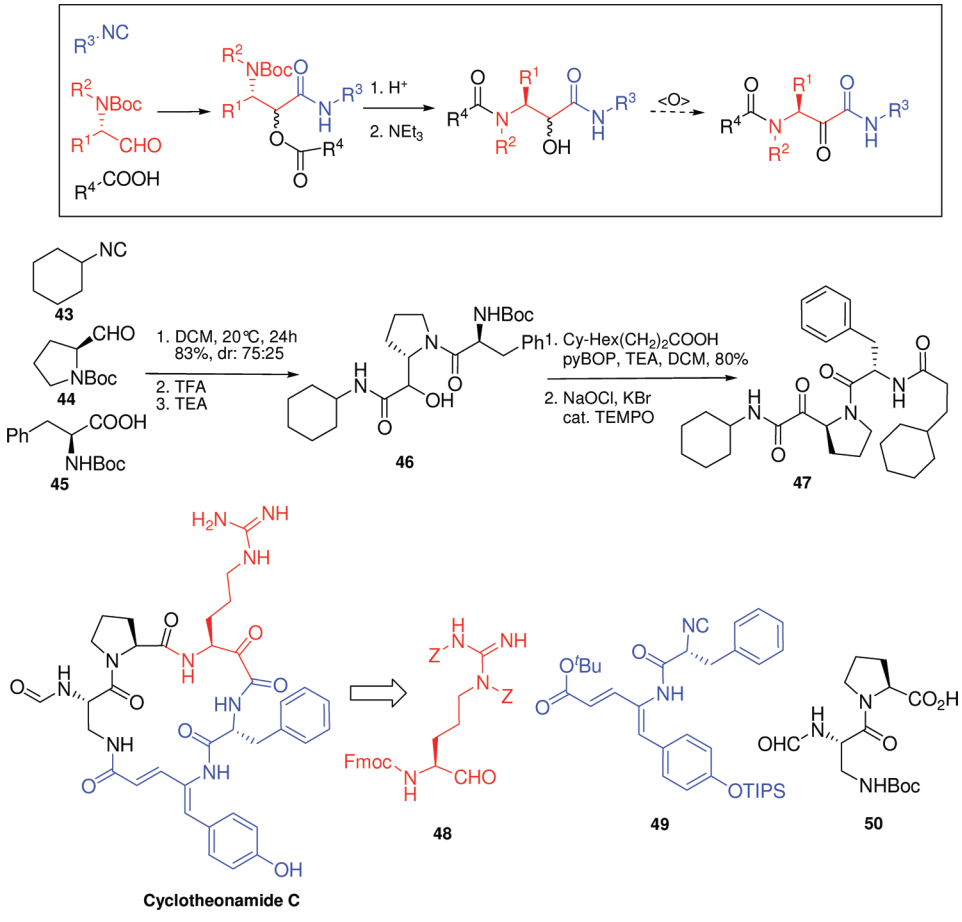
Table 1. continued

	Biginelli-3CR
	Betti-3CR
	Petasis-3CR
	Staudinger-3CR

compound libraries. Already in the 1960s, Hagedorn and Eholzer prepared α-hydroxy acid amides and Ugi prepared α-hydroxy tetrazoles by developing special Passerini conditions thus providing the foundation for such powerful protease inhibitor synthesis strategies.[40]

The most efficient way to access complex, structurally advanced and "screening-ready" α-keto-amide and hydroxymethyl-amide based protease inhibitors scaffolds is the so-called Passerini-reaction-amine-deprotection-acyl-migration strategy (PADAM), which was independently described by two groups (Scheme 2).[41]

Scheme 2. Top: The Generalized Scheme As an Archetypical Example to Illustrate the Synthetic Power of MCR Chemistry. Middle: In a Sequence of Only 2−3 Steps, Molecular Diversity of High Relevance for Protease Inhibitors (47) is Assembled. Bottom: The Complex Natural Product Thrombin Inhibitor Cyclotheonamide C Has Been Synthesized Using This Strategy As a Key Transformation in an Unprecedented Efficient and Convergent Approach.



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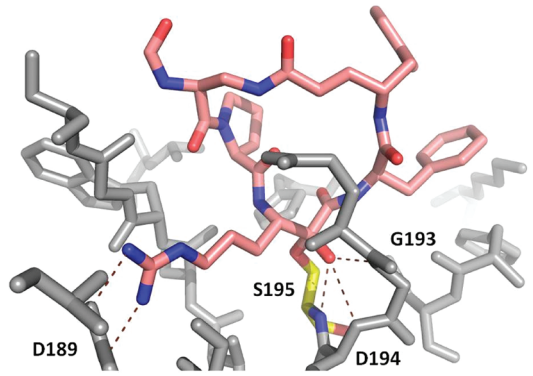
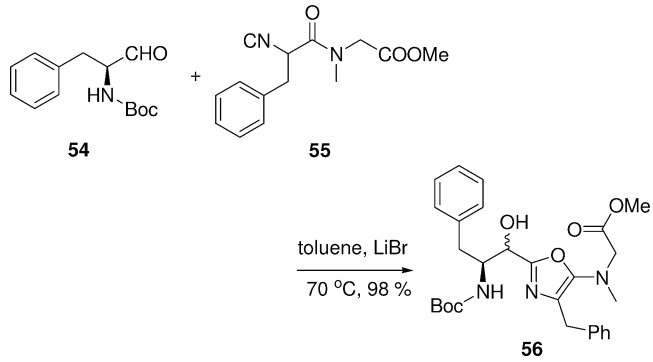


Figure 13. Cyclotheonamide C in complex with human thrombin (PDB ID 1TYN). Thrombin receptor is shown as gray sticks (several amino acids have been omitted for clarity). Highlighted in pink cyclotheoamide C and in yellow the active side Ser195 forming a covalent hemi acetale bond with the α-ketoamide moiety of cyclotheonamide C. Additionally, the structure is stabilized by a hydrogen bond network of the hydroxyl group of the hemi acetale and backbone amide Gly[193], Asp[194], and Ser[195], the so-called oxy anion hole.

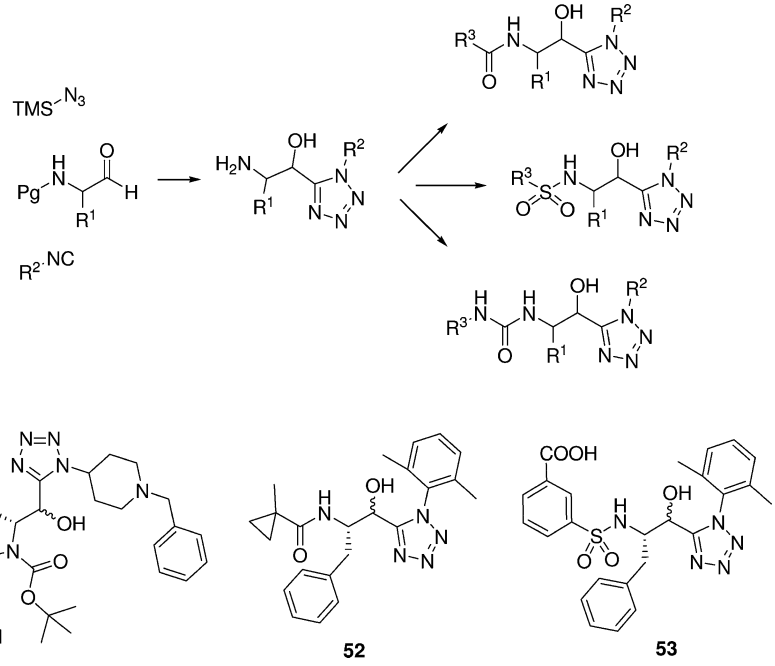
This elegant 2−3 step sequence involves an initial Passerini reaction of a (chiral) *N*-protected amino acid derived aldehyde. Upon deprotection of the P-3CR intermediate an O ⇒ N transacylation occurs yielding a hydroxymethyl-amide, which eventually can be oxidized to the keto-amide. For example, compound **47** comprising a prolyl endopeptidase inhibitor can be assembled in only 3 steps from commercially available starting materials isocyanide **43**, aldehyde **44**, and carboxylic acid **45**, using the PADAM strategy.[42] Classical sequential synthesis of compound **47** likely requires many more synthetic steps. Similarly impressively the complex thrombin inhibitor natural product cyclotheonamide C (IC_{50} = 2.9−200 nM), isolated from the marine sponges *Theonella swinhoei* and *Theonella ircinia*, has been assembled with hitherto unreported elegance using PADAM.[43] Cyclotheonamide C has been cocrystallized with thrombin representing a model compound for the understanding of the molecular interaction in the complex and the requirements for compounds to effectively inhibit the serine protease (Figure 13).[44] The α-ketoamide fragment derived from the aldehyde component during the P-3CR is covalently attached to the active site Ser195. Respective PADAM sequences of thrombin inhibitors have been performed on a kilogram scale to obtain material for (pre)clinical development.[43b]

Protease inhibitor-type compound libraries have been designed based on the initial discovery by Ugi of the access to hydroxymethyl tetrazoles using a variant of the Passerini reaction: a 3-step short sequence performed with α-amino aldehydes, followed by deprotection and N-functionalization (Scheme 3).[45] This reaction sequence has been elaborated for the automated synthesis of ten thousands of compounds, for example, yielding compounds **51**, **52**, and **53**. Cleary, these constitute Asp-protease biased libraries comprising norstatine type motifs. Significantly, recently, several enantio- and

Scheme 4. Heterocyclic Norstatine 56 Accessible by an intramolecular Passerini Variation of Isocyanoacetamides 55 and α-Amino Acid Derived Aldehydes 54



Scheme 3. 2-Hydroxy-3-amino-ethyltetrazoles (51−53) as Targeted Asp-Protease Library Accessible in High Number and Diversity by the 3-Step Sequence Passerini Reaction, Deprotection, and Acylation



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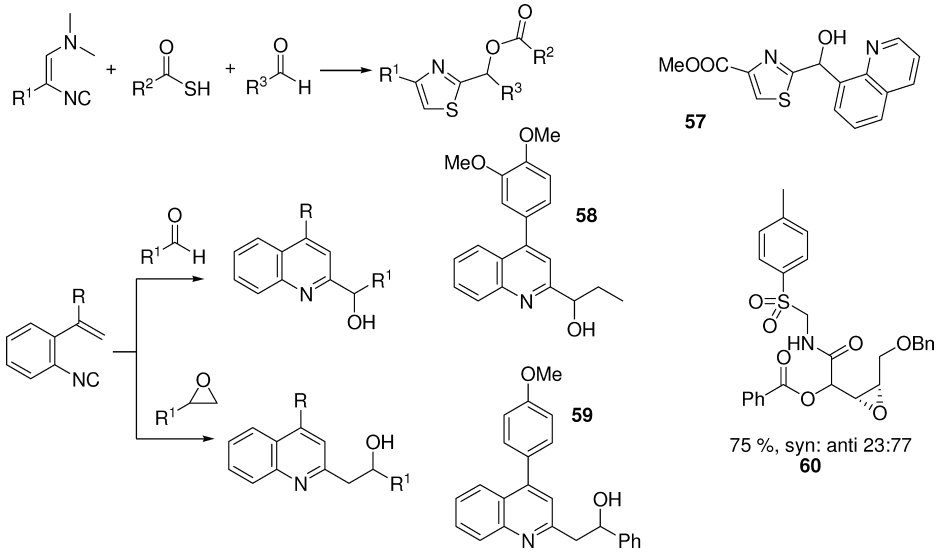
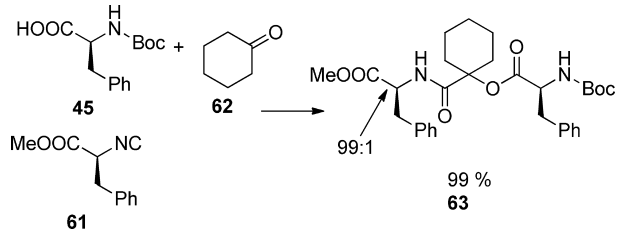
Scheme 5. Various Heterocyclic Motifs Combined with a Secondary Alcohol Amenable by Different (Intramolecular) Isocyanide Chemistry Variations and a Potentially Protease-Reactive Passerini Product



Scheme 6. Ugi and Passerini Reaction Can Be Performed under Retention of Stereochemistry Using Chiral α-Amino Acid Derived Isocyanides



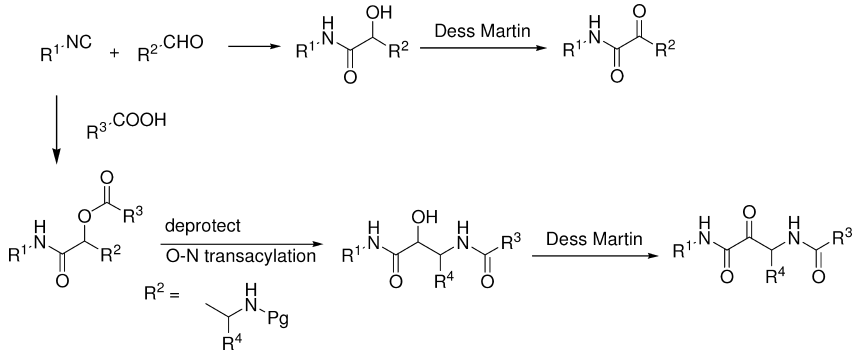
diastereoselective approaches toward this important class of biological active compounds have been described, the most efficient one using catalytic amounts of a chiral Al-salen complex.[46]

A two component Passerini type yields products containing oxazole norstatine-type motifs (**56**, Scheme 4) in typically very good chemical yield.[47] Clearly, this backbone has considerable potential for the design and synthesis of enzyme inhibitors. In addition the oxazole ring hides the otherwise ubiquitary isocyanide secondary amide, thus reducing the number of H-bond donors and acceptors. Recently, a catalytic, highly enantioselective variation of this MCR has been described using a heterobimetallic $Ga(OiPr)_3/Yb(OTf)_3$/chiral Schiff base complex.[48]

Other heterocyclic protease inhibitor backbones (**57**−**59**) with proteases inhibitory potential, having reduced isocyanide-dependent amide character and being amenable by isocyanide chemistry in just 1−2 steps are shown in Scheme 5.[49] All these examples have a reduced number of amide bonds as compared to the parent Ugi or Passerini backbone by replacing the amide group by a heterocyclic motif. Clearly, such bioisosteric replacements can potentially greatly enhance the pharmacodynamic and pharmacokinetic properties of their nonheterocyclic isocyanide chemistry parents. Clearly, the secondary hydroxyl function also has potential as protease inhibitor needle.[50] Compound **60** is an example of a potentially protease-reactive Passerini product with an epoxide moiety.[49d]

The influence of the α-amino acid *N*-protecting groups on the degree of racemization during P-3CR and U-4CR was only recently investigated. Their influence turns out to be crucial and is also not constant when the amino acid is changed. After optimization, the Passerini reaction product **63** was obtained with 99% yield and >98% *de* from cyclohexanone **62** as the carbonyl component (Scheme 6).[51] Similar results can be obtained with the Ugi reaction involving chiral α-amino acid derived isocyanides if specific precautions are taken.[52] Despite recent innovations, in fact, reliable syntheses of chiral

Scheme 7. Use of Passerini Reactions to Convergently Synthesize the α-Ketoamide Fragment, Which Is Essential in Many Classes of Serine Protease Inhibitors



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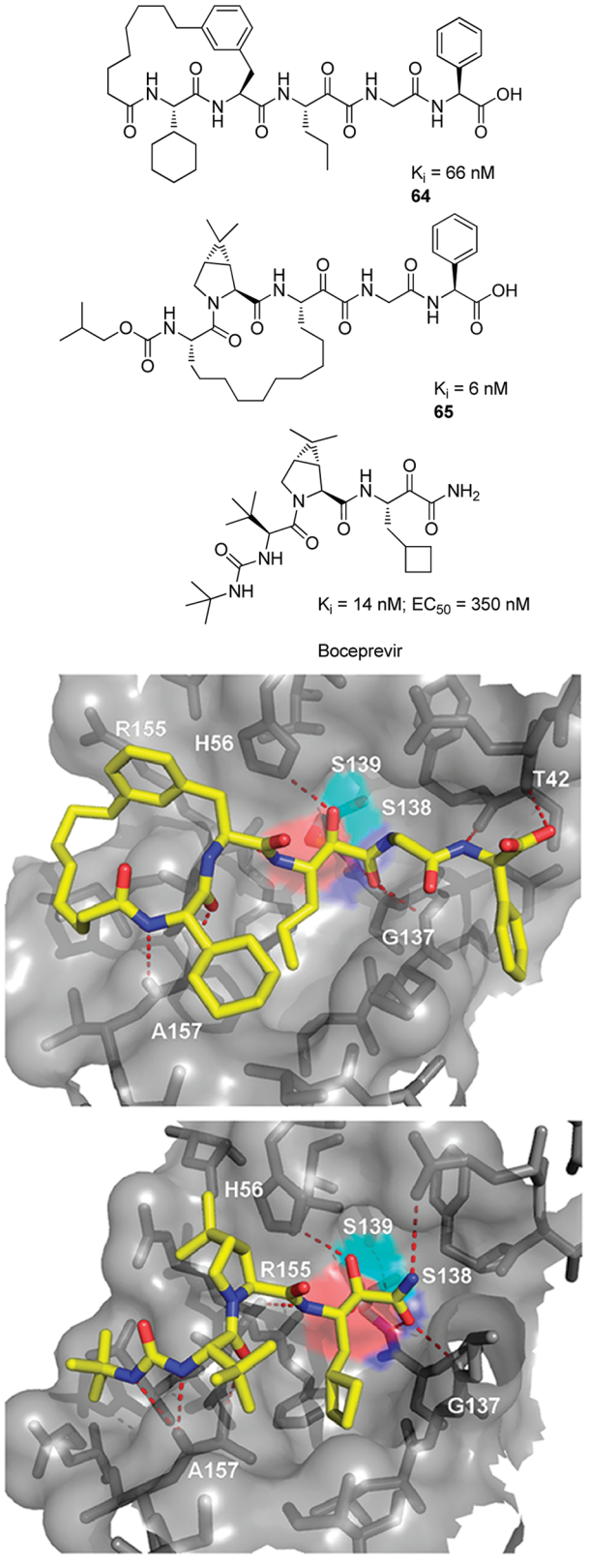

Figure 14. Atomic details of a macrocyclic (**64**, top) and linear (Boceprevir, bottom) α-ketoamide HCV NS3 protease inhibitors (PDB IDs 2A4Q and 2OC8). The active side Ser is marked by a cyan surface, the inhibitor by yellow sticks, and the binding surface of the protease is shown as gray surface and sticks.

isocyanoacetates have been invented by Ugi and can be accomplished by careful selection of dehydration conditions.[53] Also it is well-known that dipeptide derived or longer isocyanides are configurationally stable.[54] Additionally, orthoesters have been recently introduced as new racemisation free protecting groups for α-amino acid derived isocyanides. These materials have the additional advantage of being solid and odor less.[55]

2.1.1. Serine/Threonine Proteases. The catalytic mechanism of serine proteases is comparatively well established.[56] Serine proteases display a key nucleophilic serine in the active site responsible for cleaving the substrate. Other features characterizing serine proteases include the *oxy anion hole*, a site nearby the active site serving to stabilize the negatively charged transition state during the nucleophilic attack of the serine onto the cleavable bond. Human and infectious organism derived serine proteases are major targets for pharmaceutical interventions.[57] As an example, the NS3 protease has been recognized as an essential target to develop treatments for hepatitis C, on which several compounds are currently undergoing advanced clinical trials. Hepatitis C virus is a major worldwide health problem leading to chronic infections in ∼200 million people in addition to the fact that a major fraction of population is a silent carrier of the virus.

However, HCV NS3 protease inhibitor discovery is very challenging since it requires rather large fragments of the natural substrate making the inhibitor molecules quite large, with many chiral centers and thus difficult to synthesize. An often reoccurring key element in many HCV NS3 protease inhibitors, the α-ketoamide structure can be synthesized using the classical Passerini reaction or the PADAM strategy (Scheme 7). During the discovery of α-ketoamide HCV NS3 protease inhibitors, for example this reaction was instrumental in order to optimize the C-terminal part of the inhibitors residing near the active site.[58] Cyclic and acyclic HCV NS3 protease have been described and synthesized using key Passerini transformations.[59] The exocyclic α-ketoamide unit in compound **64**, for example, and similar compounds has been synthesized using a P-3CR followed by oxidation of the secondary hydroxyl group.

Numerous cocrystal structures between α-ketoamide inhibitors and the HCV NS3 protease have been recently solved and show key molecular interactions with the different functional moieties (Figure 14). The macrocyclic HCV inhibitors **64** and **65** feature 17-membered rings encircling Ala156 in a "donut-shaped" conformation thus providing many hydrogen bonds and additional van der Waals contacts.[60] The *n*-propyl side chain of **64** fits very well into the S1 pocket. The side chain is introduced via the aldehyde component in the P-3CR. Boceprevir is the first-in-class recently approved HCV NS3 inhibitors which showed excellent clinical trial results.[61] It is a linear and primary α-ketoamide with oral bioavailability (Figure 14). The keto moiety forms a reversible covalent adduct with the active site Ser139. An extended network of hydrogen bonds of the peptidic backbone to the HCV NS3 protease is formed. Additionally, strong hydrogen bond interactions are made by the oxy-anion hole amino acids Ser138 and Gly137. By forming a covalent adduct, the enzyme mechanism is inhibited.

Factor-Xa (FXa) is an important blood coagulation medicinal chemistry target. Noncovalent FXa inhibitors based on the phenylglycine backbone have been disclosed (Scheme 8).[62] The Ugi chemistry represented an intriguing approach to this scaffold and offered the potential advantage of enabling to draw upon the commercial availability of a wide variety of aryl aldehydes as the requisite starting materials. It has been noted

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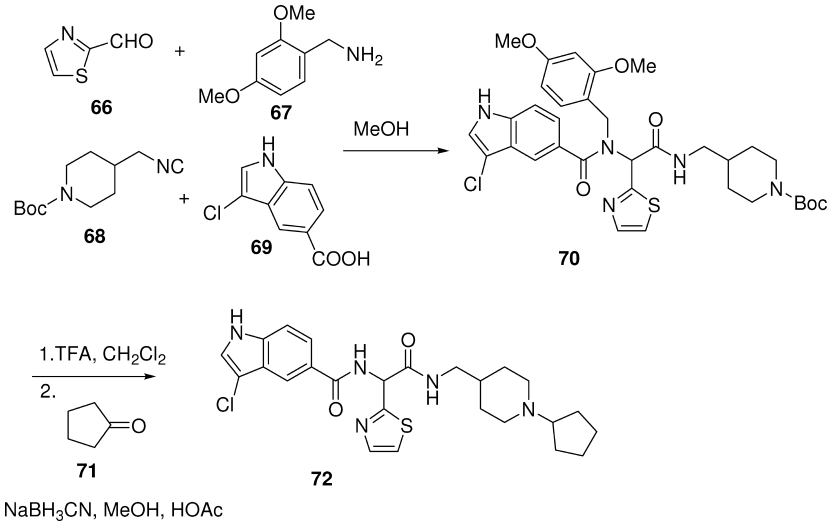
Scheme 8. Convergent FXa Inhibitor (72) Synthesis by U-4CR



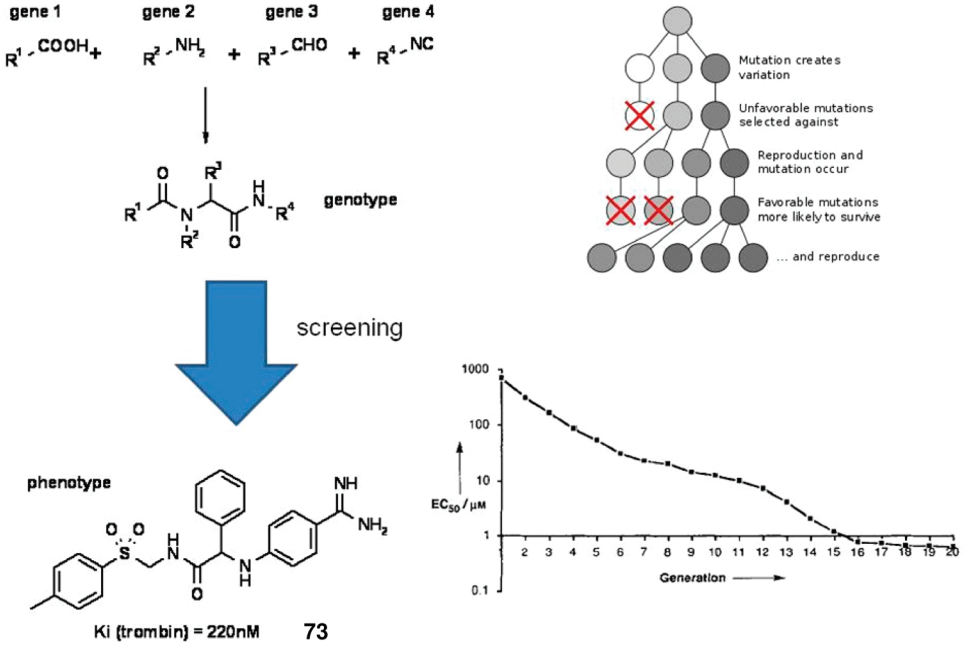
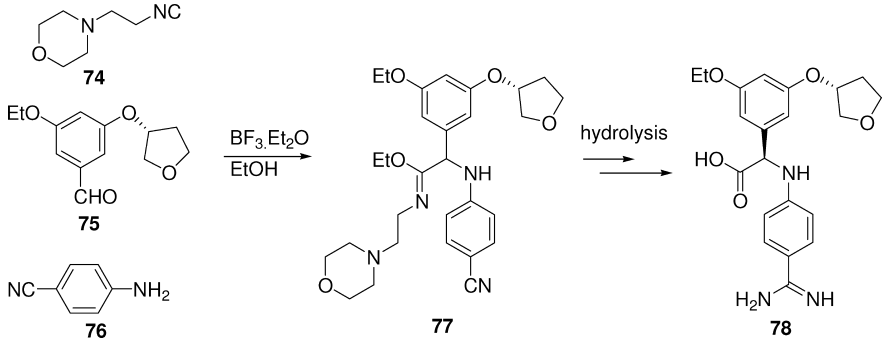


Figure 15. U-4CR and U-3CR based generation of potent and selective thrombin inhibitors (73) using genetic algorithm techniques. In the graph, the evolution of active compounds (EC_{50}) over the number of generations is shown.

Scheme 9. Synthesis of an Oral Bioavailable, Highly Potent, and Selective FVIIa Inhibitors 78 Involves a U-3CR Variation



that despite the moderate yield (not optimized 24%) of the U-4CR to form racemic compound **70**, the Ugi route was found to be superior to alternate approaches involving the synthesis of 2-thiazolyl glycine for multigram preparation of compound **72**. Additionally, it has to be noted that recently, the very mild cleavable chiral 4-methoxy-1-ethylamino group has been

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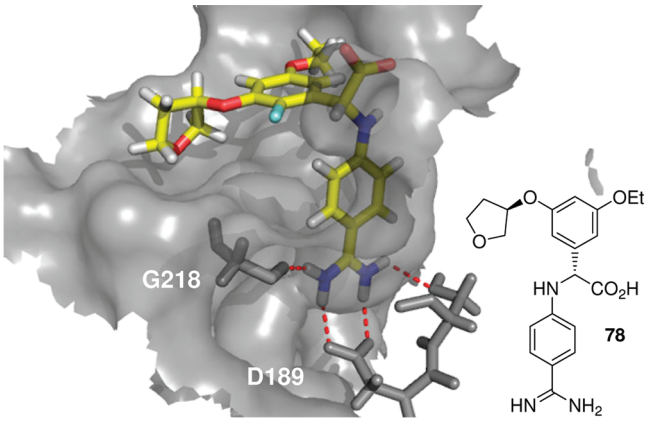
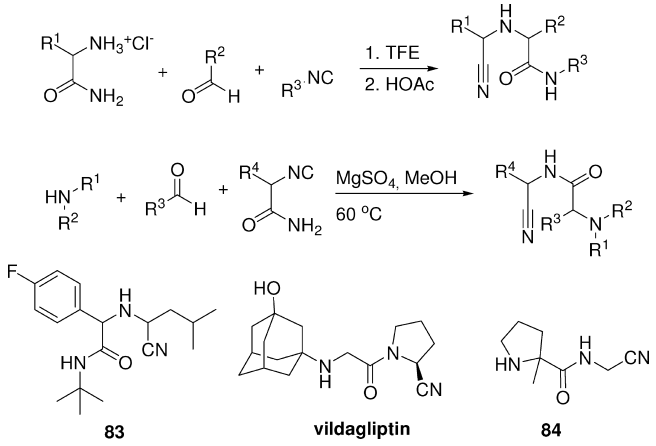


Figure 16. *N*-Aroyl phenylglycine derivative **78** cocrystallized with FVIIa (PDB ID 2BZ6).

introduced in Ugi chemistry as a chiral auxiliary.[63] This method makes the synthesis of even very racemisation-prone chiral *N*-acylaminoamides possible.[63]

An interesting approach to screen the immensely large chemical space of MCR chemistry, however physically synthesize only a small fraction of possible compounds, is the genetic algorithm (GA).[64] GA is an optimization method that uses techniques inspired by evolutionary biology such as inheritance, fitness, mutation, selection, and crossover (also called recombination). GAs are advantageously applied in complex systems whenever exact solutions cannot be generated, for example, drug discovery. In one application of GAs potent thrombin inhibitors (220 nM) have been found within a chemical space of 320 000 U-3CR and U-4CR products based on 10 isocyanides, 40 aldehydes, 10 amines, and 40 carboxylic acids. The starting material classes represent the different gene classes. Twenty starting compounds based on the theoretical MCR space have been generated randomly in a first generation. These are screened for their inhibitory activity against thrombin (fitness function). The best compounds are computationally stored and are also allowed to undergo recombination and mutation, thus ensuring survival of the most active structures and "breading" of even more active structures in the next generation. After only 16 generations of evolution, the average effective inhibitory activity of the 20 best products at each generation was submicromolar. In generation 18, after physically synthesizing only 400 products out of a theoretic space of 320 000 compounds the highly active compound **73** was found (Figure 15). This approach is highly significant as it can systematically and effectively search very large chemical spaces provided by MCR chemistry while having to synthesize

Scheme 11. Marketed DPP-IV Inhibitor Vildagliptin and Two Complementary MCR Approaches toward the Pharmacophore α-Amino Nitrile

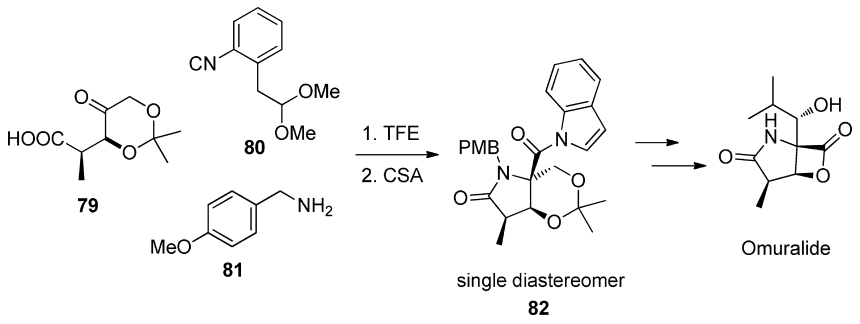


only a small number of compounds. It does not require structural insight into the target nor does it require target knowledge at all (e.g., using a phenotypic assay).

Factor VIIa (FVIIa), another key intervention point of the blood coagulation cascade has been extensively targeted with MCR chemistry. A potential advantage of targeting FVIIa over FXa is that specific inhibition of the TF/FVIIa complex results in an antithrombotic effect without enhancing bleeding propensity, a possible side effect of coagulation inhibitors.[65] Synthesis of the *N*-aroyl phenylglycine derivatives **78** involves a BF_3-catalyzed addition of the diaroyl Schiff base in ethanol onto a suitable isocyanide (benzyl or morpholinoethyl **74**) (Scheme 9). The intermediate ethyloxyimidine **77** has to be extensively hydrolyzed and the isocyanide only contributes the carbon resulting in the carboxylic carbonyl.[66]

An advanced compound **78** had good potency and selectivity, was oral active as a double prodrug in the guinea pig, and showed a dose-dependent antithrombotic effect in an established model of arterial thrombosis without prolonging bleeding time. This compound has also be crystallized with its target (Figure 16).[67] The amidine group forms a strong charge charge complex with the Asp189 at the bottom of the S1 pocket. The aniline NH forms a hydrogen bond to Ser195 and the carboxylate of the amino acid another favorable charge charge interaction to Lys192. Selectivity to the related thrombin pocket can be accomplished by the introduction of the *m*-ethoxy group, which cannot be accommodated easily in thrombin.

Scheme 10. Synthesis of Proteasome Inhibitor and Natural Product Omuralide by an Elegant Short Sequence Involving an Intermolecular and Highly Stereoselective U-4CR Using a New Cleavable Isocyanide



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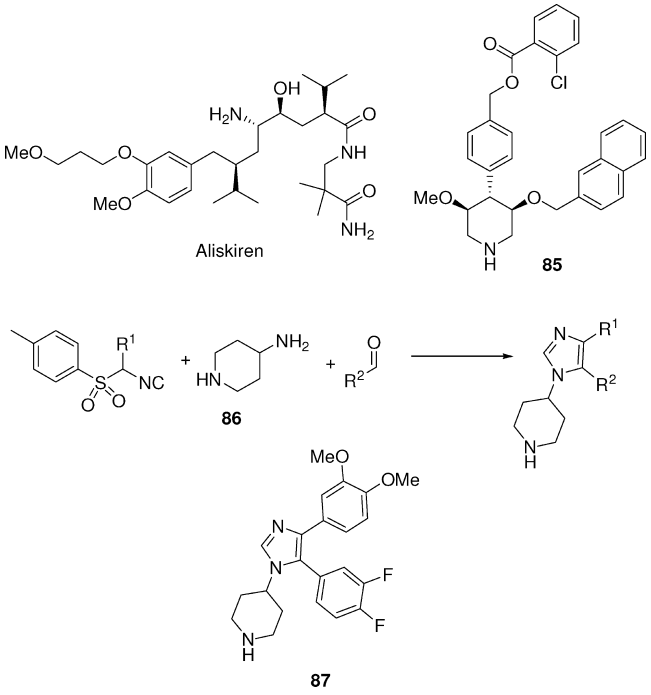
Scheme 12. Approved Renin Inhibitor Aliskiren, an Early Piperazine Inhibitor (85) and General One-Pot Synthesis of 1,4,5-Trisubstituted Imidazole Using Van Leusen's 3CR of TOSMICs, Aldehydes, and Unprotected 4-Aminopiperazine (86)



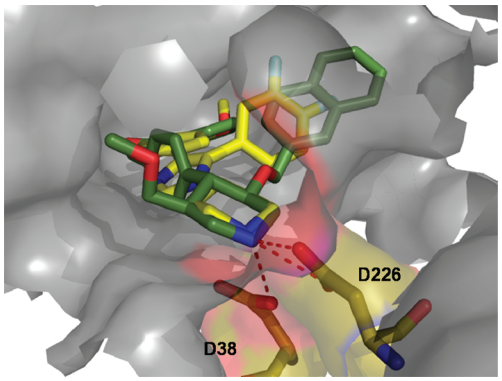


Figure 17. Inhibitor **85** (green sticks) (PDB ID 1PR8) and a docked piperazine imidazole inhibitor **87** (yellow sticks) bound into a very deep cleft in renin. The piperazine-N is sandwiched between the two active side Asp38 and Asp226 (pink sticks) and replacing the active water.

The human cytomegalovirus (HCMV) protease catalyzes the maturational process of the herpes virus assembly protein and plays a key role during the manufacture of the viral capsid. It is an attractive target for potential antiherpes-virus agents with novel structures and new mechanisms. A chemical library containing 32 compounds with different substitutions on the U-4CR skeleton and incorporating an α-ketoamide moiety was prepared by the oxidation of a precursor α-hydroxylamide library, which was constructed from the four types of building blocks: 4 carboxylic acids, 2 amines, 2 aldehydes, and 2 hydroxyl group-containing isocyanides based on a U-4CR following liquid phase strategies.[68]

The natural product and proteasome inhibitor omuralide has been synthesized in a stereo controlled manner using a

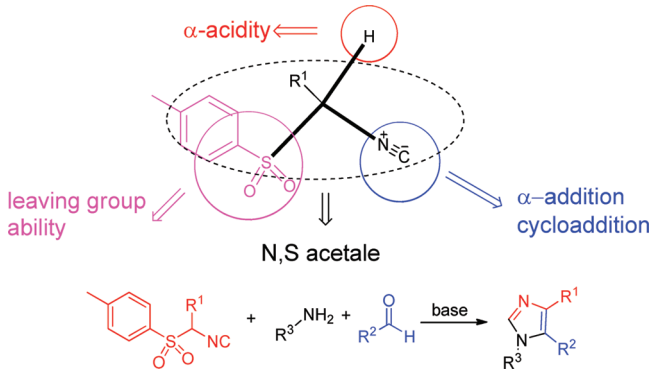


Figure 18. TOSMIC is a densely functionalized reagent, which accounts for its versatility in different reaction pathways.

intramolecular U-4CR of the ketocarboxylic acid **79** as a key step (Scheme 10).[69] Herein a novel convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**80**) was used, which was introduced independently by two groups.[70] The *p*-methoxybenzylamine **81** is used as an ammonia surrogate. The indole acyl of the intermediate **82** resulting from the convertible isocyanide can be cleaved under very mild conditions.

Dipeptidyl peptidase IV (DPP-IV) is a serine protease that degrades the incretin hormone glucagon-like peptide 1 (GLP-1), a peptide required for the glucose-dependent regulation of insulin. Inhibition of DPP-IV is a very successful therapeutic principle: Vildagliptin (Scheme 11), FDA approved for diabetes type-2 treatment, increases the level of active GLP-1, resulting in improved glucose tolerance. The common pharmacophore of many current DPP-IV inhibitors is an α-amino nitrile. On the basis of the crystal structures of chemically related pyrrolidine nitriles with DPP-IV, it is believed that the α-amino nitrile forms a reversible covalent imidate ester adduct with the active site serine (Ser610).[71] Interestingly, α-amino nitriles are accessible in two different ways using Ugi-type MCRs. First, the reaction of amino acid derived α-amino amides with oxocomponents and isocyanides, surprisingly yield α-aminoacyl nitriles (compound **83**).[72] Second, the reaction of amino acid derived α-amidoisocyanides also yields α-aminonitriles (compound **84**).[73] Both reactions are clearly complementary since they represent different scaffolds and populate different areas of the chemical space of α-amino nitriles. Additionally, different starting materials are utilized in both reactions.

2.1.2. Aspartyl Proteases. Aspartyl proteases, disproportionally underrepresented in the proteasome as compared to serine proteases, are a very important and successful class of targets.[74] In fact more drugs against Asp proteases are approved than for all other protease classes together. For e.g. renin is a major target for cardiovascular diseases. The renin-angiotensine-aldosterone system (RAAS) has a key role in the regulation of blood pressure and has yielded already three important drug classes, the aldosterone receptor antagonists, the AT_1 receptor blocker and the ACE inhibitors.[75] Renin inhibitors are expected to partly replace the therapeutic importance of the ACE inhibitors. Currently, the one renin inhibitor approved is aliskiren, a secondary hydroxyl transition state mimic. Notably, aliskiren is a rather complex molecule incorporating 4 stereocenter and has to be synthesized by a lengthy 20 step synthesis.[76] Most of the currently described renin inhibitors incorporate similar hydroxyl needles. A decade

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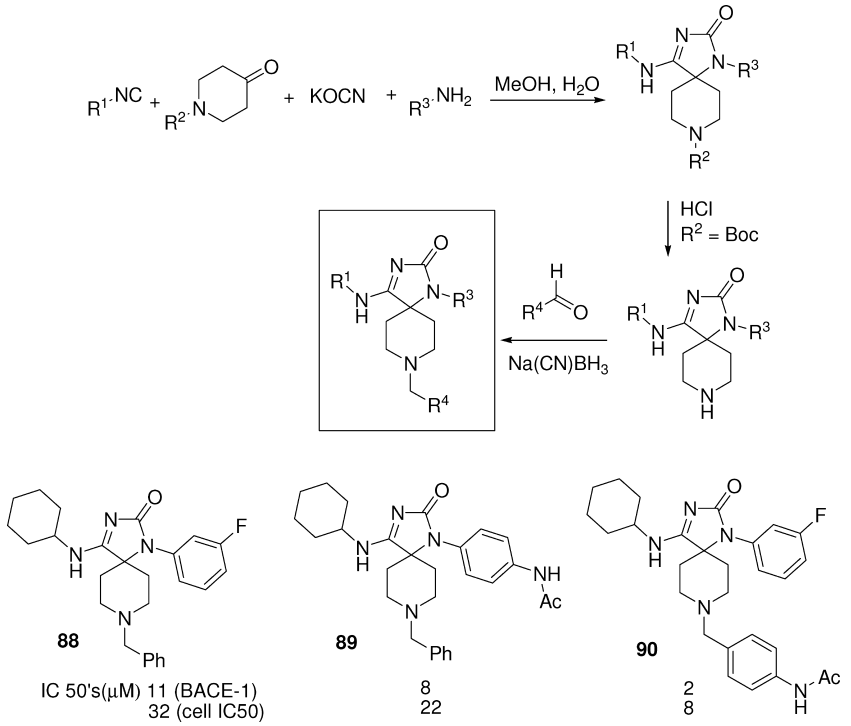
Scheme 13. Synthesis of Spiropiperidine-hydantoine-4-imides (88−90) by Ugi-MCR and Representative BACE Inhibitors with Their Bioactivity



ago, however, 3,4,5-trisubstituted piperazines (**85**) have been described as renin inhibitors. It was shown by X-ray structure analysis that this class of compounds induce a major rearrangement in the active site.[77] Recently, a piperazine-imidazole class of Asp protease inhibitors, for example, compound **87** was described which is convergently amenable by van Leusen's MCR from substituted TOSMICs, aldehydes and 4-aminopiperidine (**86**) under protecting group free conditions (Scheme 12).[78]

The binding mode of aliskiren and the piperazine inhibitors (**85** and **87**) is quite different. Aliskiren acts as a classical substrate mimic.[79] The X-ray structure of a piperazine inhibitor together with a modeled representative piperazine-imidazole **87** is shown in Figure 17.

The chemistry of tosylmethyisocyanide (TOSMIC) and derivatives was started by the Dutch chemist van Leusen.[80] TOSMICs display a high functional group density. Thus TOSMIC chemistry is determined by three distinct properties: the isocyanide reactivity, the strong α-acidity of the adjacent methylene group embedded between the two electron-withdrawing sulfone and isocyanide group (*N*,*S*-acetal) and the leaving group ability of the sulfone group (Figure 18). As a result TOSMIC chemistry is very versatile and is now widely used for the synthesis of many different heterocyclic systems. An outstandingly useful MCR is the vL-3CR which can lead to 1,4,5-trisubstituted, 4,5-, 1,4-, and 1,5-disubstituted or 1-, 4-, and 5-monosubstituted imidazoles. The mechanism involves Schiff base formation, addition of the isocyanide carbanion to the imine and subsequent ring closure and sulfinic acid elimination. This reaction likely can be considered as the most versatile to substituted imidazoles. Additionally, because of the availability of many α-substituted TOSMICs the accessible imidazole chemical space is very large.[80a,81] The imidazole scaffold is incorporated in quite a number of drugs.

Cerebral deposition of amyloid β-peptide (Abeta) is an early and critical feature of Alzheimer's disease. Abeta generation in the brain depends on proteolytic cleavage of the amyloid precursor protein (APP) by two proteases: β-secretase (BACE) and γ-secretase. These proteases are prime therapeutic targets.[82] β-Secretase belongs to the small class of human aspartyl proteases. Recent inhibitors are mostly of complex, peptide-like structure enriched in asymmetric carbons and in amide bonds, build around a warhead statine motif.[83] Additionally, development of β-secretase inhibitors is challenging since the target protein is compartmented in the brain; thus inhibitors must penetrate the blood-brain-barrier (BBB). Recently, hydantoine based inhibitors (**88−90**) have been described which can be synthesized in a 3-step sequence involving a one-pot MCR using a variation of the classical Ugi MCR.[84] In this reaction, a primary amine a piperidine-4-one, and isocyanide and potassium cyanate react to yield iminohydantoine (Scheme 13).

An X-ray structure analysis of a cocrystal of the small molecular weight inhibitor **90** and BACE-1 revealed a novel mode of binding whereby the inhibitor interacts with the catalytic aspartates via bridging water molecules (Figure 19). Libraries of spirocyclic heterocycles have been prepared in a one-pot fashion using a variation of the Ugi MCR. Noteworthy is the ease of formation of the quaternary carbon center at room temperature, which is a general consequence of using ketones in the Ugi reaction. The design and synthesis of spirocycles is a challenging task because it involves the creation of a quaternary center, which itself is considered to be one of the most difficult tasks among synthetic transformations. Iminohydantoins in principle can exist in different tautomeric forms, however, analysis of the hydrogen bonding pattern in the cocrystal structure of **90** favors one tautomer.

Although the initially described compounds are not highly potent they show several noteworthy features. The best

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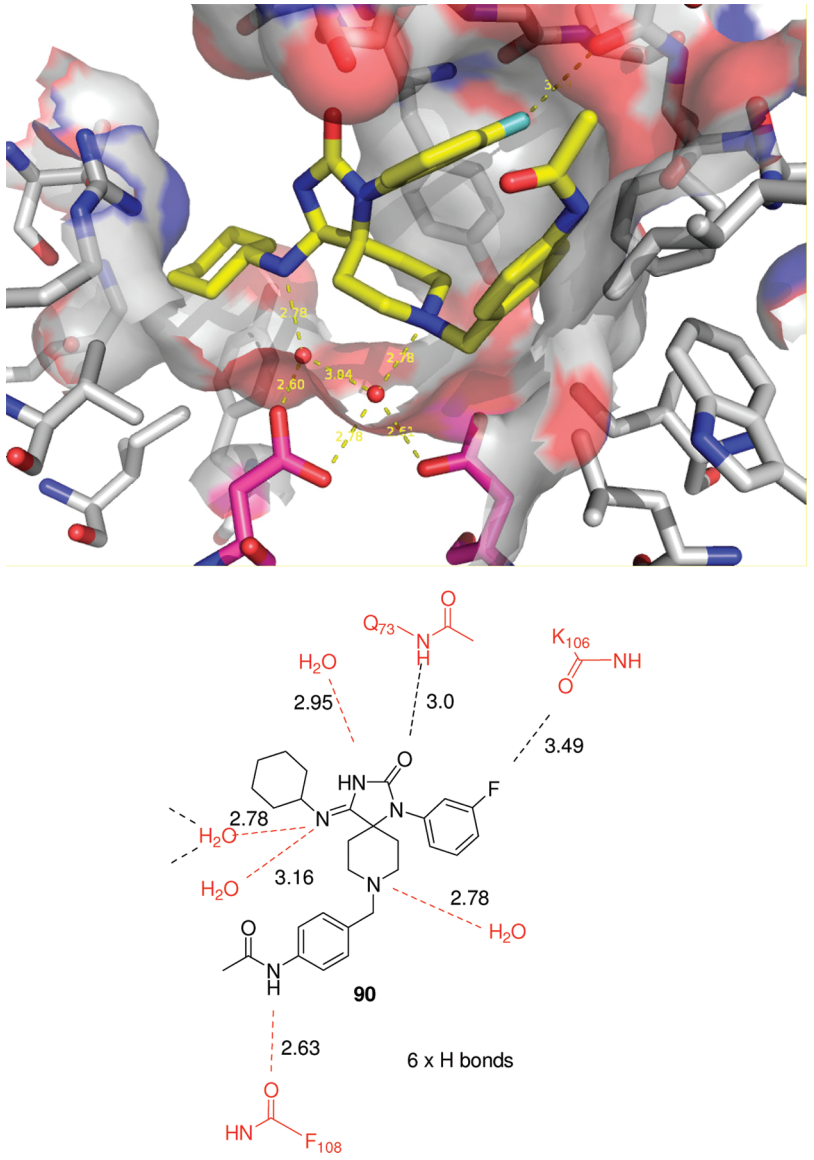


Figure 19. New MCR derived scaffold showing promising BACE-1 activity. Top: Synthesis of the general scaffold involving a key Ugi-4CR and representative inhibitors (**90**) with enzyme and cellular activity. Bottom: Binding mode of compound **90** (PDB ID 3E3W) and schematic representation of the major short contacts to the BACE-1 receptor and to water molecules. There is no direct contact of the ligand to the two catalytic asp; it is, however, mediated by two crystal water molecules. Also noteworthy is a short contact between the fluorine of the ligand and a backbone carbonyl-O with the aromatic plane almost perpendicular to the amide group (α(CF−OC) = 177°). The distance of 3.49 Å, however, is more than the sum of the atom radii (r(F) 1.47 Å + r(O) 1.52 Å = 2.99 Å). The two central Asp residues are marked pink.

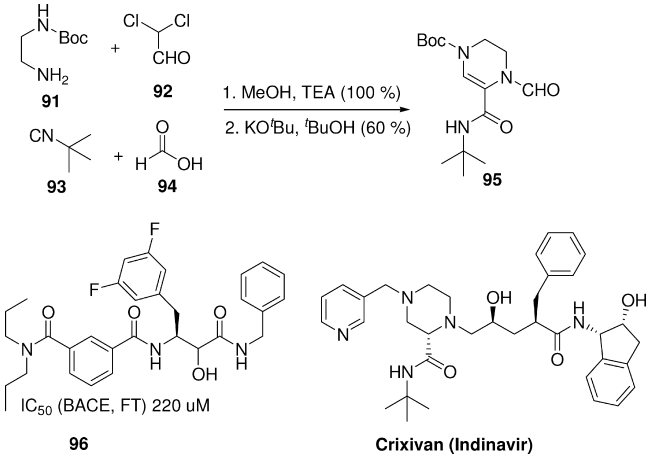
compound **90** shows an in vitro enzyme based IC_{50} of 2 μM and the activity in cell based assays only worsened by a factor of 4. Additionally, the compound shows useful plasma and brain concentrations and is no phospho-glyco-protein (PGP) efflux pump substrate.

A different Passerini-MCR involving strategy toward BACE inhibitors has been reported providing weak inhibitors (**96**) which might form a starting point for further optimization (Scheme 14).[85] These examples clearly show how challenging it is to target the flat and spatially extensive BACE active site with useful activity and at the same time accomplish oral bioavailability and entrance through the BBB.

The third Asp protease of high pharmaceutical interest is the HIV protease. Of the currently available HIV medications 7 drugs are HIV protease inhibitors. Similar to the above-mentioned HCV NS3 protease inhibitors the described inhibitors are quite large and have a peptide-like appearance (e.g., **96** and indinavir). Often they have to be synthesized by sequential up to 20 step synthesis. Therefore it is worthwhile to consider alternative synthesis approaches involving MCRs. E.g. the key intermediate piperazine of indinavir can be advantageously and stereoselectively synthesized using a key and quantitative U-4CR followed by an enantioselective hydrogenation (Scheme 14).[86] The introduction of the MCR into the total synthesis can lead to a considerable shorter synthesis and eventually reduced cost-of-goods.

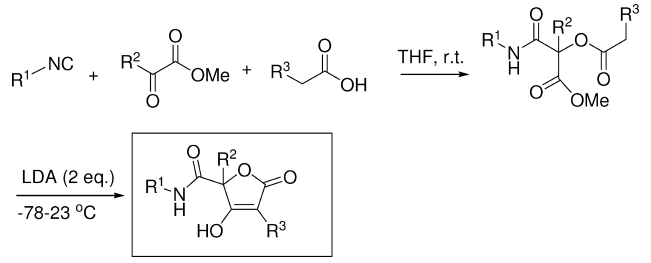
Another research group asked the question if HIV protease inhibitors can also be de novo designed using convergent MCR chemistry.[87] The design of a 2-step reaction sequence involving a Passerini reaction with α-oxocarboxylicacid esters and a subsequent Dieckmann ring closure indeed leads to low micromolar hits resulting also in an unprecedented MCR

Scheme 14. Introduction of MCR Chemistry into the Total Synthesis of Complex Pharma Products Can Potentially Lead to a Considerable Shortage of Steps and Thus to Lower Cost-of-Goods As Exemplified Here with the HIV Protease Inhibitor Crixivan (Indinavir)



scaffold: tetronic acid (Scheme 15). A cocrystal structure of a molecule **97** with HIV protease underscores the validity of this synthesis design concept (Figure 20). This de novo MCR

Scheme 15. Sequence P-3CR–Dieckmann Condensation Leads into a Tetronic Acids Backbone with HIV Protease Inhibitor Activity



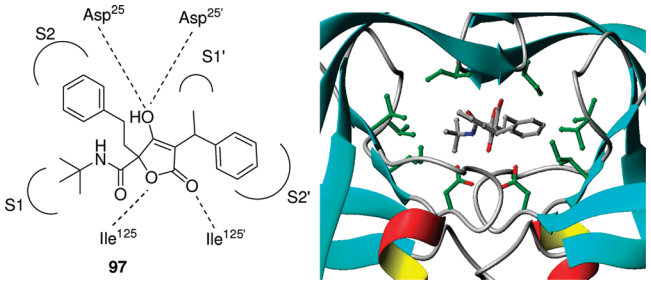


Figure 20. Cocrystal of a tetronic acid MCR-derivative (**97**) bound into HIV protease. The enol group is sandwiched between the two active site aspartates.

approach seems to be quite promising and the initial hits can be potentially further optimized for potency and selectivity.

2.1.3. Metallo Proteases. The recent FDA approval of the histone deacetylase (HDAC) inhibitor SAHA as an anticancer drug for the treatment of the manifestations of cutaneous T-cell lymphoma spurred the search for novel, improved, and more selective compounds not only for cancer therapy but also for application for the treatment of human brain disorders, such as Rubinstein–Taybi syndrome, Rett syndrome, Friedreich's ataxia, Huntington's disease, and multiple sclerosis.[88] Popular mechanism based warheads found in metallo protease inhibitors are hydroxamic acids and thiols which form complexes with the active side metal (usually Zn) and thus stop the catalytic cycle. The challenge with these strongly metal complexating functional groups is to introduce selectivity and thus to potentially reduce side effects. Recently, *o*-phenylendiamine monoamides were discovered as a novel warhead for metallo proteases (Scheme 16).[89] Thus compound **98** was synthesized by a U-3CR and showed good activity and selectivity. A complementary approach using the U-4CR and subsequent hydroxylamination also yields active hydroxamic acids (**99**) of unprecedented variability.[90]

2.1.4. Cysteine Proteases. Cysteine protease inhibitors typically depend on potent warhead moieties, which are often covalently and (ir)reversibly reacting with the nucleophilic active site cysteine, for example, epoxides, nitriles, α-ketoamides, α-ketoheterocycles, halo-ketones, diazo-ketones, peptidyl aldehydes, or epoxy-succinyl derivatives.[91] Several of these warheads have been already discussed to be accessible in great diversity and numbers by Passerini- and Ugi-type MCRs. Remaining challenges for the clinical development of cysteine protease inhibitors include, that is, metabolic, for example, protease and chemical stability, selectivity of the highly reactive warhead units, solubility and cellular penetrability.

Calpains are calcium-activated neutral proteases belonging to the papain superfamily of cysteine proteases; several of these calpains have implications in diseases such as Alzheimer, brain and cardiac ischemia, spinal cord injury, muscular dystrophy, and cataract. Recently, compounds have been described targeted the orphan X-chromosome-linked inherited Duchenne muscular dystrophy (DMD). The compounds are prepared by PADAM and exhibit impressive enzyme and muscle cellular activity (Scheme 17).[92] The nonpolar lipophilic residue, lipoyl of compound **100** is believed to provide muscle cell targeting properties to selectively shuttle compound into disease tissue.[93] Selected inhibitors of this series have been tested as well in a mouse model and showed significantly improved relevant histopathological parameters demonstrating their potential as a treatment for this devastating disease.

The pathways of apoptosis involve a cascade of initiator and effector caspases. Caspase-3 is known to be the main executioner of apoptosis through cleavage of protein substrates that leads to irreversible cell death.[94] 4-Aryl-4*H*-chromene (**104**), for example, is a multicomponent condensation product of malonodinitrile (**101**), benzaldehyde (**103**), and 8-hydroxyindole (**102**) effectively inhibiting caspases and comprising a nonpeptide backbone.[95]

Among non-IMCRs, those of cyanoacetic acid derivatives are extremely versatile regarding the multiplicity of scaffolds (Scheme 18). (For a recent comprehensive review, see ref 96.) Often these MCRs involve primary Knoevenagel-type condensations of the cyanoacetic acid derivative with an aldehyde or ketone, followed by a Michael attack of a nucleophile and a subsequent ring closure via a second nucleophile through attack of the nitrile. A disadvantage of those MCRs is the current low variability of the cyanoacetic acid input. A recent combinatorial access to cyanoacetamides, however, is enhancing the value by greatly expanding the large MCR scaffold space of cyanoacetic acid derivatives.[97] A well-known MCR of this class is the Gewald-3CR (G-3CR), which has recently gained ground by the usage of cyanoacetamides.[98]

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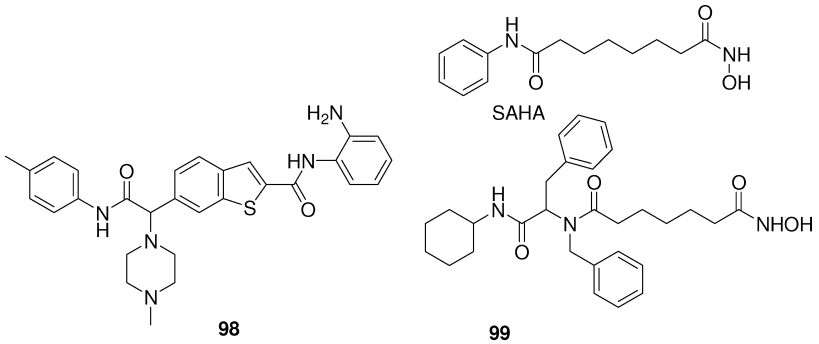
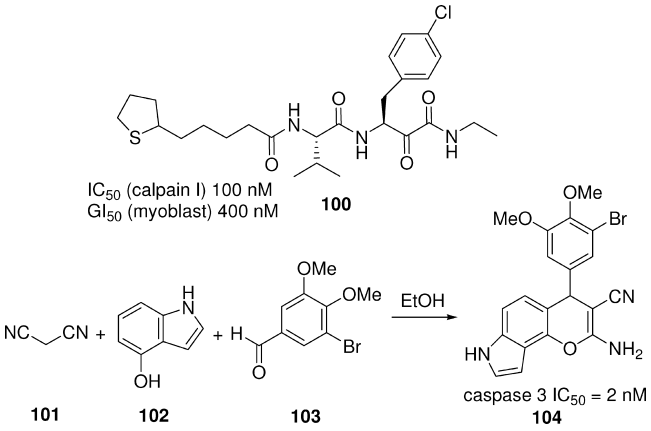
Scheme 16. Top: Recently Approved Metalloproteinase Inhibitor SAHA; Bottom: U-3CR Product with a Novel Type of Metal Binding War Head, Monoacyl-*o*-phenylendiamine (98) and Hydroxamic Acids (99)



Scheme 17. Selected Reported Cysteine Protease Inhibitors



2.2. Kinases

Kinases have emerged over the last two decades as one of the most prolific therapeutic targets with many drugs under clinical evaluation or in clinical practice.[99] They are a large class of enzymes dephosphorylating hydroxyl containing amino acids in target proteins. According to their substrate specificity, one broadly distinguishes Ser/Thr from (receptor) Tyr kinases. They are involved in many different pathophysiological processes and are among the most popular contemporary target classes in pharmaceutical industry. Most kinase inhibitors currently under development are ATP mimics. They display an often heterocyclic aromatic flat topology mimicking the adenosine heterocycles of ATP and an adjacent hydrogen donor−acceptor moiety mimicking the amidine substructure of ATP. Many opportunities exist to employ MCR chemistry in the kinase field. A p38 kinase inhibitor SB220025 was recently clinically evaluated in phase III for rheumatoid arthritis. The synthesis of SB220025 involves a vL-3CR and the corresponding α-4-fluorophenyl substituted tosylmethylisocyanide (**105**) has been produced in 500 kg batches.[100] A cocrystal of SB220025 and the p38 kinase has been published and can serve to understand the crucial features of kinase inhibitors and their connection to this MCR scaffold (Figure 21).[101]

Substituted 2-aminofuranes could be active as kinase inhibitors as they show the hallmarks: they are flat aromatic heterocycles and they incorporate an adjacent hydrogen donor−acceptor moiety which is suited to undergo a hydrogen bond network with the hinge region of the active site of kinases (Figure 22).[102] Recently, a multitude of new MCR approaches have been published resulting in this scaffold.

This versatile MCR chemistry is based on the acetylene isocyanide adduct first described in a seminal paper by Winterfeld.[103] This reactive intermediate can be described as a zwitterionic or carbine-type mesomeric form and is the starting point of a rich MCR chemistry resulting in a diversity of scaffolds (Scheme 19). E.g. the reaction of isocyanides with acetylendicarboxylic acid methyl esters (**107**, DMAD) and suitable acids yields highly substituted 2-aminofuranes (**108**).[104] Acidic components described are *N*,*N*-dimethylbarbituric acid,[105] 3,6-dihydroxypyridazine,[106] (iso)nicotinic acid,[107] 4-hydroxycoumarins,[108] vicinal tricarbonyl systems,[109] 2-pyridinecarboxaldehyde,[110] isatin,[111] 4-arylurazoles,[112] phenols,[113] 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one,[114] 3-methylcyclopentane-1,2,4-trione, yielding 4*H*-pyrano[3,2-*d*]pyrimidine (**109**),[115] 3-amino-5,8-dioxo-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazines (**118**),[106] 2,3-dihydro-1,3-dioxo-1*H*,5*H*-pyrazolo-[1,2-*a*][1,2,4]triazoles (**119**),[112] 5*H*-imidazo[2,1-*b*][1,3]-oxazine derivatives (**106**),[114] annulated 2-amino-4*H*-pyrans (**123**),[108] 4H-chromene derivatives (**121**), respectively.[113] A facile and direct synthetic entry to 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylic acid derivatives (**117**) based on the reaction of DMAD, α-amino acids with isocyanides or carbodiimide (DCC) as condensation agents under neutral conditions was reported.[116] In an extension of these synthetic ideas, it was described recently, that isocyanide, aldehyde, dimedone, and ammonium acetate react in a 4-CR fashion to highly substituted 1*H*-indole-4(5*H*)-ones.[117] DMAD can also be reacted with benzoic acid derivatives and isocyanides in the presence of triphenylphosphine to yield highly substituted 2-aminofuranes.[118] The same scaffold is available by the reaction of benzoylchloride, DMAD and isocyanide.[119] However, whereas electron-withdrawing groups in para position of the benzoylchloride yield 2-aminofuranes, others result in 2,5-dihydro-1*H*-pyrroles.[119] Aliphatic α-acidic carboxylic acids under the same conditions react with DMAD and isocyanides to form 2,5-diaminofurans.[120] Similarly, *N*-(2-pyridyl)amides, isocyanides, and DMAD undergo cyclization to 4*H*-pyrido[1,2-*a*]-pyrimidines, which after N-deprotection can yield kinase inhibitory signature.[121] These DMAD incorporating MCRs are very interesting regarding their structural diversity and taking into account that the two ester functionalities can be further regioselectively functionalized, for example, by amidation thus also providing a large chemical space. Another additional benefit of these reactions is that they often are

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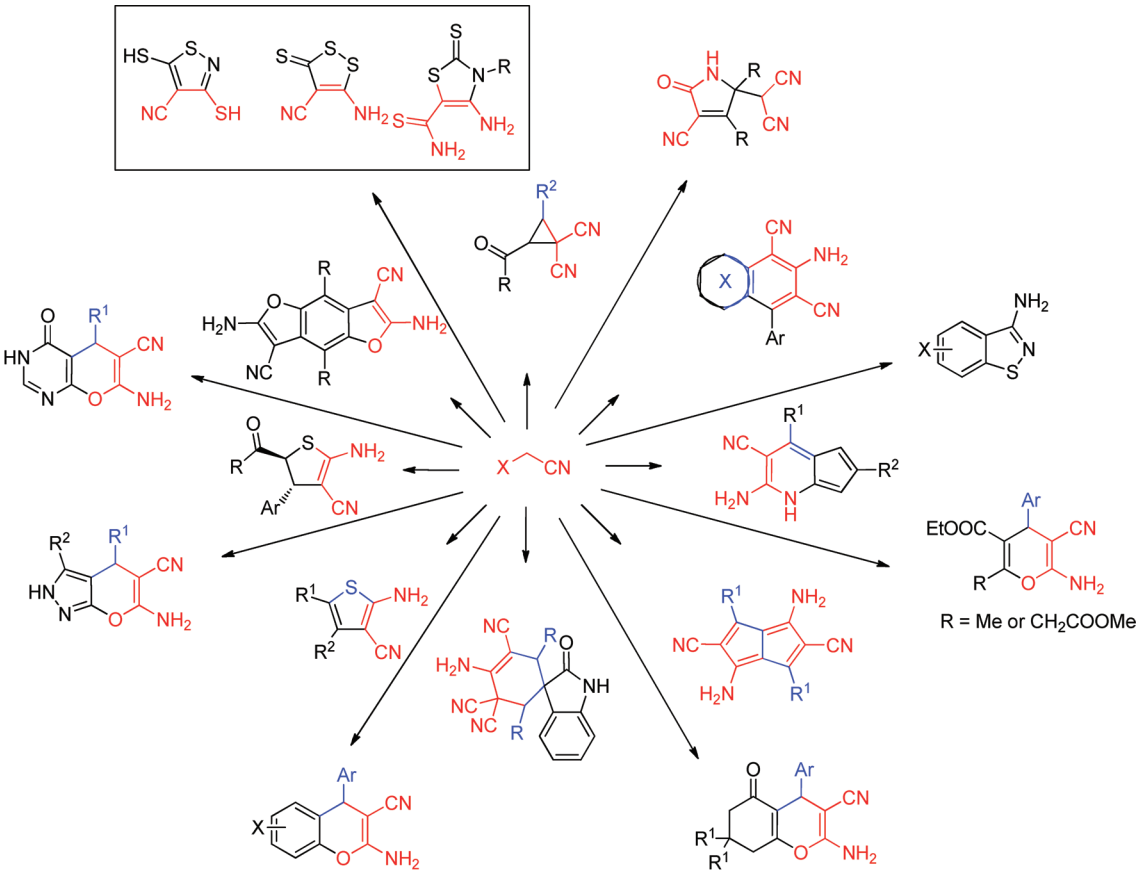
Scheme 18. MCR Scaffold Diversity of Malonodinitrile Derivatives



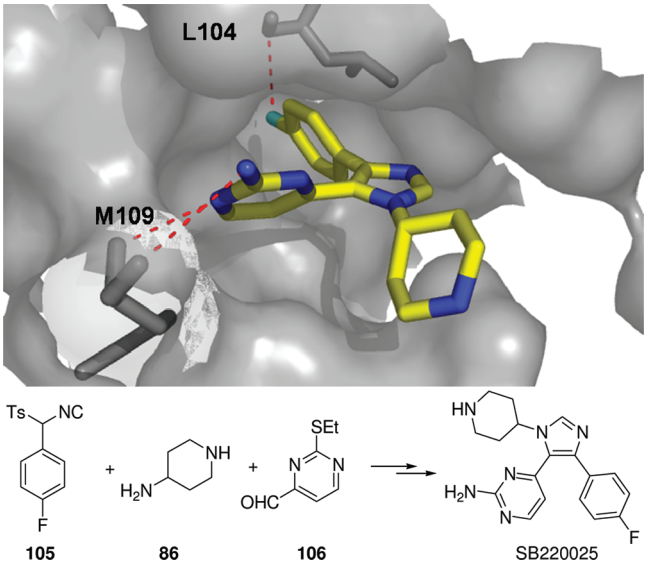


Figure 21. vL-3CR compound SB220025 is a potent p38 inhibitor. Top: Binding of SB220025 into p38 active site (PDB ID 1BL7). The 2-amino portion forms hydrogen bonds, the kinase hinge region and the fluorine of the ligand is involved in a short contact to the backbone carbonyl-C (3.1 Å). Bottom: Reaction scheme of the vL-3CR.

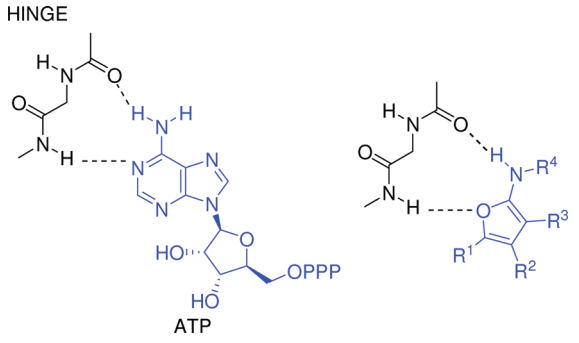


Figure 22. MCR-derived 2-aminofuranes are potential kinase scaffolds displaying kinase inhibitor specific pharmacophores: they are flat heteroaromatic and display a vicinal H-bond donor/acceptor moiety (shown in comparison to the ATP bond to the hinge region of kinases).

performed under very mild conditions and the products are easily purified.

Eph (erythropeitin-producing hepatoma) tyrosine kinase cell surface receptors are the largest tyrosine kinase family with therapeutic implications in e.g. cancer and nerve regeneration.[122] Active site EphB4 inhibitors were discovered by a virtual docking/fragmentation approach of a large 730 000 collection among them high ranking G-3CR compound **124** (Scheme 20).[123]

The Gewald 3-CR (G-3CR) of cyanoacetic acid derivatives, methylene active carbonyls and elemental sulfur is a popular MCR often used in drug discovery yielding 2-amino-3-carbonyl thiophenes (e.g., **126**−**136**) (Scheme 21).[124] These reactions are quite versatile and can lead to a large number of substituted thiophenes otherwise difficult to access. The interest in Gewald products also steams from the fact that the thiophene moiety is bioisosteric to benzene. Thus Gewald products can also be considered as bioisosteric to anthranilic acid derivatives. As

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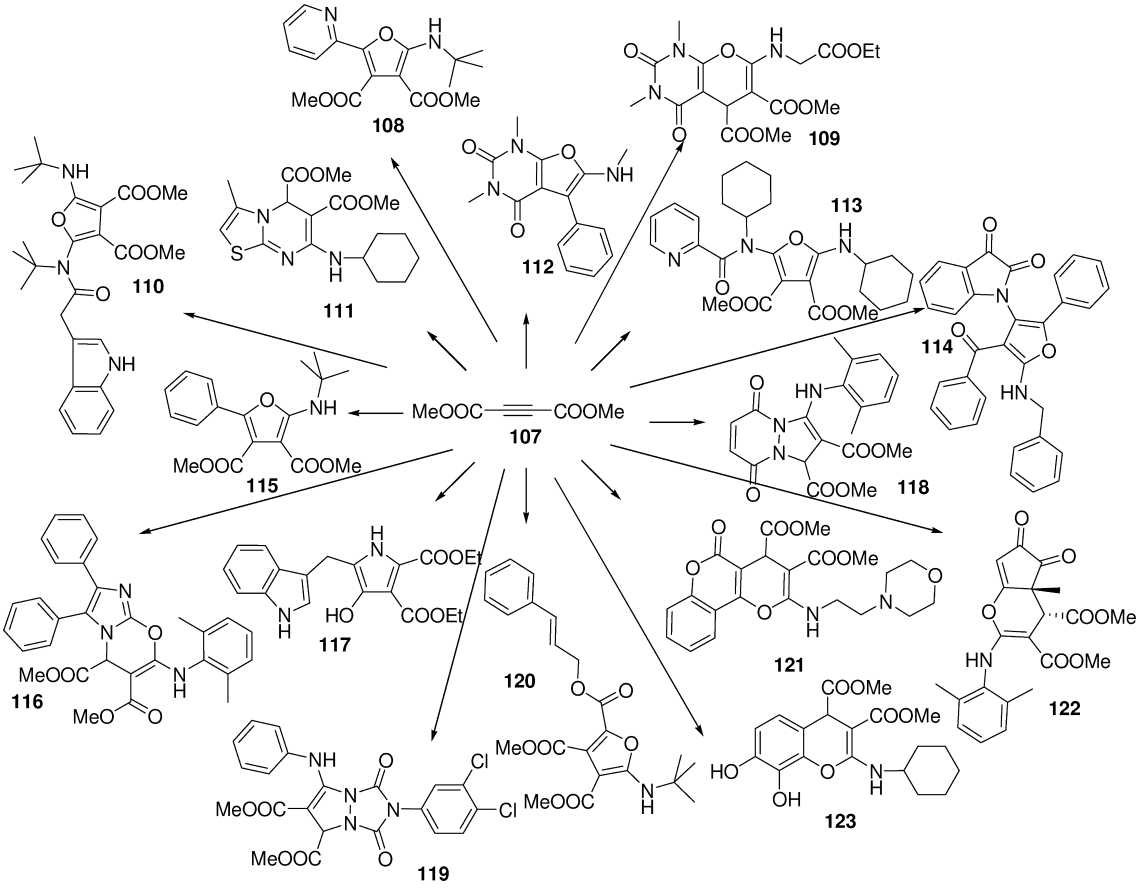
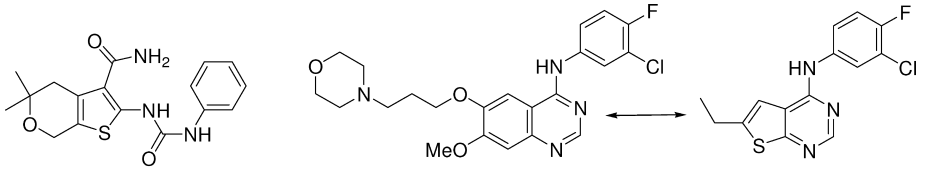
Scheme 19. MCR Chemistry of Acetylenedicarboxylicacid Diesters (DMAD) Leads to Multiple Scaffolds (108−123) with Hydrogen Donor−Acceptor Fragments Thus Potentially Providing a Kinase Inhibitor Pharmacophore



Scheme 20. Kinase Inhibitors by Gewald MCR



opposed to the difficulty in accessing substituted anthranilic acids, however, Gewald thiophenes are available in great numbers. Additionally, Gewald products can be easily transformed into further scaffolds by secondary transformations (Scheme 21).[125] Thus, condensation of Gewald products with formamide opens a versatile synthetic avenue to thiopheno-2-aminopyrimidine type kinase inhibitors (**125**, **126**) (Scheme 20). Compound **126** is a moderate potent KDR inhibitor (IC_{50} = 4.6 μM), while derivatives display low nM activity, significant oral efficacy and favorable pharmacokinetic profiles.[126]

Applying the isostery concept thienopyrimidine based derivatives **125** of the marketed anticancer drug gefitinib have been synthesized based on G-3CR (Scheme 21).[127]

Five- and 6-membered (hetero)aromatic amidines react with aldehydes and isocyanides to form bicyclic imidazo[*1,2-x*]-heterocycles derivatives (GBB-3CR).[29,30] *o*-Formyl benzoic acid esters (**138**) input together with *tert*-butylisocyanide (**93**) leads in a straightforward manner into polycyclic heteroaromatic ring systems (Figure 23) displaying in addition a vicinal H-bond donor/acceptor fragment.[129] These compounds clearly incorporate the kinase pharmacophore. A library of compounds (**139-144**) has been profiled against a panel of diverse kinases and potent and selective inhibitors have been discovered (Figure 23). Potent compounds with differential selectivity have been obtained, which can be further optimized using secondary transformations addressing different binding regions in the active site of kinases.

Rho-associated kinase isoform 1 (ROCK1a) is an enzyme involved in diverse cellular signaling functions such as smooth muscle contraction, cytoskeleton rearrangement, cell migration, and proliferation.[131] This compound is accessible by a 3-CR of acetoacetamide (**145**), benzamidine (**146**), and pyridinecarbaldehyde (**147**). The compound **148** has been cocrystallized with Rho kinase.

An elegant synthesis of the highly active marine natural product meridianin isolated from the ascidian *Aplidium*

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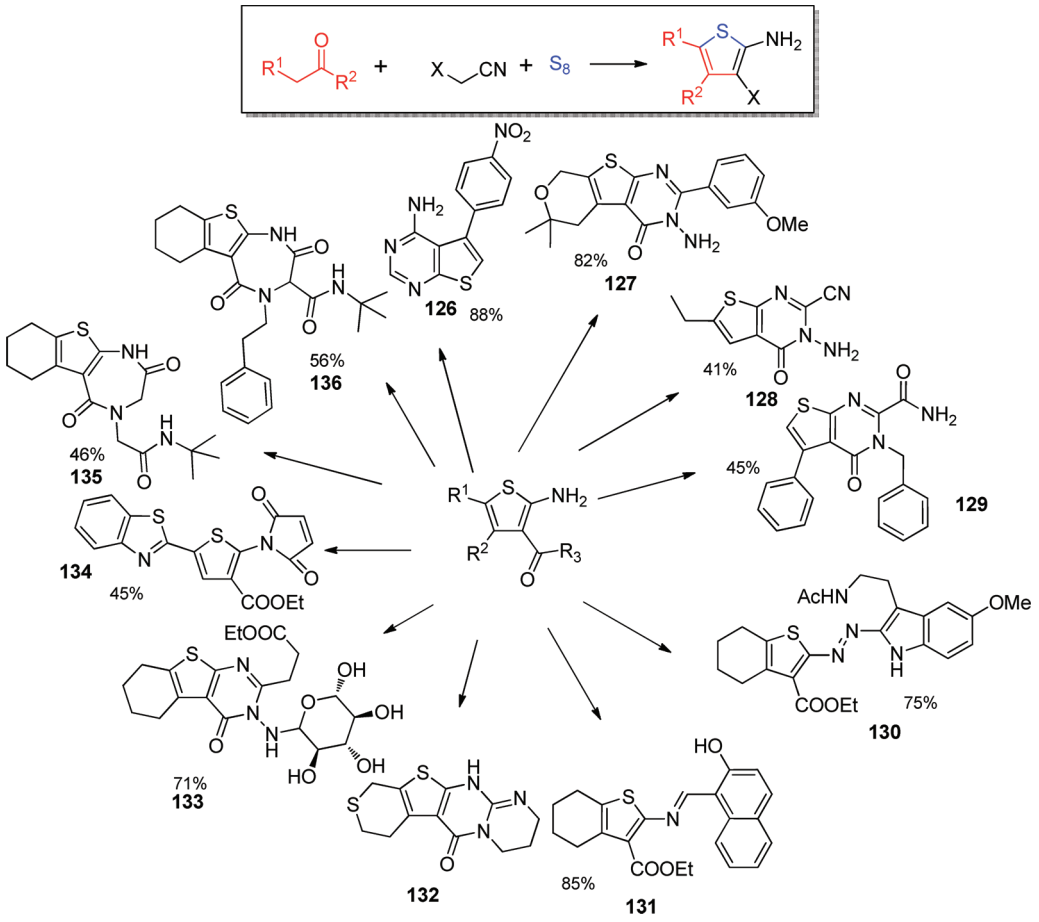
Scheme 21. Diversity of Products Based on Secondary Reaction of the Initial G-3CR[126a,128]



meridianum was reported using a four-component pyrimidine synthesis.[132] The 2,4,6-trisubstituted pyrimidines are synthesized based upon an elegant consecutive carbonylative coupling−cyclocondensation sequence (Figure 24). Several derivatives are highly active multi kinase inhibitors. Cocrystal structure of several derivatives and SAR have been reported.[133]

2.3. Phosphatases and Phosphate Mimics

Whereas kinases have been extremely successful as drug targets leading to many clinical and preclinical drugs, phosphatases are rather difficult to target by small molecules while retaining an acceptable pharmacokinetics/pharmacodynamics (PKPD) profile. Glucose-6-phosphate translocase (G6PT), part of the G6 Pase system is a promising diabetes type-II target.[134] By using the above-described GA strategy new, potent and selective G6PT inhibitors (**153** and **154**) have been discovered in iterative rounds of evolutionary optimization (Figure 25).[135] Different scaffold spaces based on vL-3CR and reductive amination/acylation chemistries were investigated. Within the performed evolutionary cycles of synthesis, analytics, screening, and library design, promising lead structures were found. In a second step the best compounds from the first phase served as structural prototypes for a similarity-triggered genetic algorithm to select molecules for focused compound libraries around these lead structures. Maintaining the reaction scheme, a refinement of the used building blocks was achieved and compounds with high activity were identified. Finally, the preferred substituents were transferred into a new chemical backbone, using the advantage of one-step MCR chemistry while maintaining the biological activity. In the shown cases, the genetic algorithm has proven its capability as a library design tool to select diverse compounds from a given large chemical space based either on measured biological activities or on chemical similarity.

The Hantzsch dihydropyridine synthesis is a classical MCR discovered by Arthur Hantzsch in 1881.[7] It is the four component reaction between ammonia or a primary amine, a benzaldehyde derivative and two equivalents of a 1,3-dioxo derivative (H-4CR). The proposed mechanism involves a Knoevenagel condensation of one oxo component and an enamine formation of the other oxo component followed by a Michael-type addition and subsequent ring formation under dehydration conditions. Many improvements using different catalysts have been described, including Montmorillonite K10 clay, sulfonic acid on silica gel, ultrasound on silica gel absorbed starting materials or different solvent systems, for example, water or ionic liquids. The H-4CR has led to potent glycogen phosphorylase b inhibitors (**155**, Figure 25).[136] The dihydropyridine-5,6-dicarboxylate groups mimic the phosphate group of ligands that bind to the allosteric site and contact three arginine residues (Arg309, 310, and 193). Several water molecules play a crucial role in mediating a strong hydrogen bond network.

Synthesis of compound libraries based on the tandem aza [4 + 2] cycloaddition/allylboration multicomponent reaction between 1-aza-4-boronobutadienes (**156**), maleimides (**157**), and aldehydes (**158**) have been described (**161**, Scheme 23). They involve and use multiple strategies, including liquid phase

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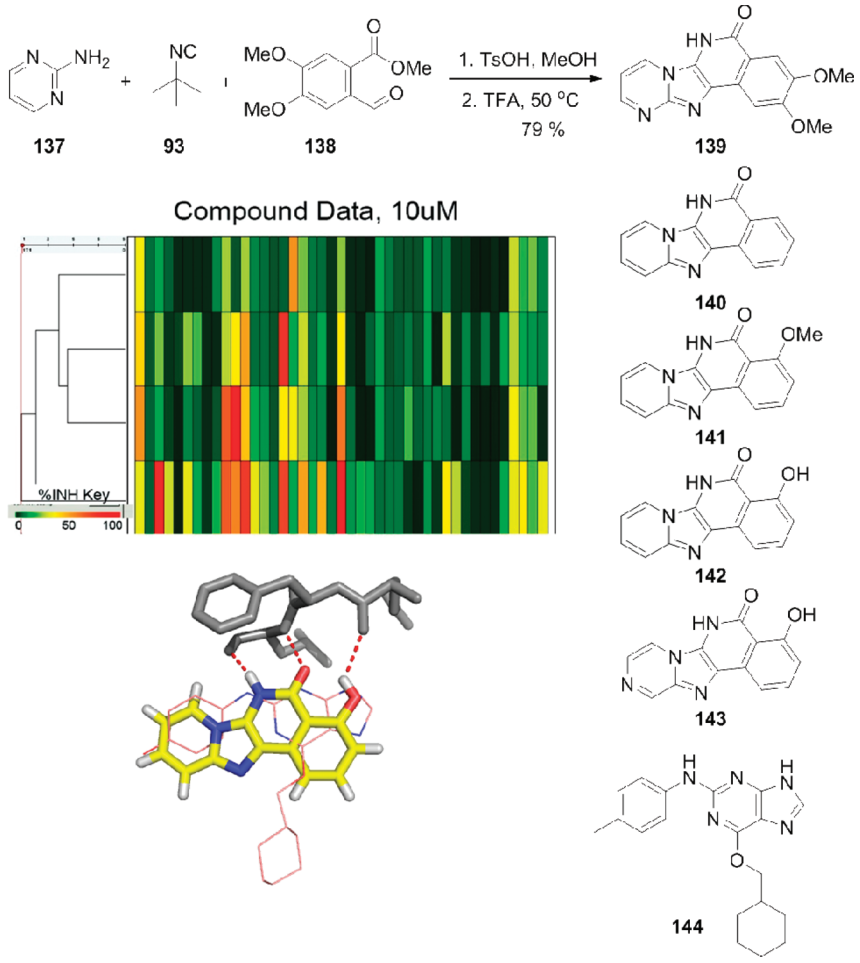
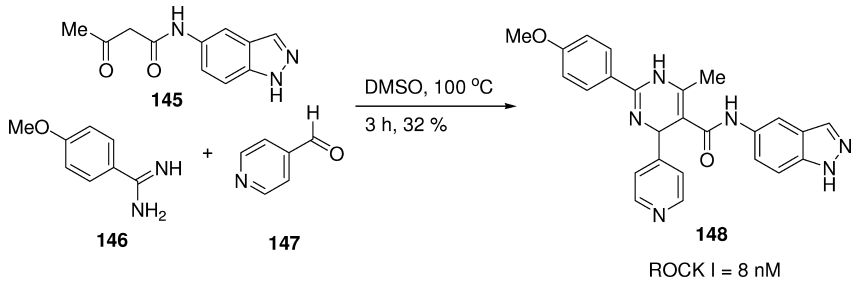


Figure 23. MCR kinase inhibitors. Top: 2-Step synthesis of kinase inhibitors (**139**) using the GBB-3CR. Middle: Selectivity profile of some representative compounds (**140**–**143**) against a panel of kinases. Bottom: Docking of compound **142** (yellow sticks) into the active site of CDK2 together with the cocrystallized anilino-purine compound **144** (pink lines) (PDB ID 1OI9).[130] Compound **142** forms a strong hydrogen bond network with the hinge region of CDK2 (red dotted lines), a prerequisite for a potent kinase inhibitor.

Scheme 22. Synthesis of the Potent Rho Kinase Inhibitors 148 by a 3-CR



synthesis with resin capture and two solid phase variants.[137] The compounds were screened against several phosphatases, including PTP1B, MPTPA, MPTPB, VEPTP, and PP1 and the dual-specificity phosphatases Cdc25A and VHR and two examples (**162**–**163**) showed activity.

2.4. Other Enzymes

Dihydroorotate dehydrogenase (DHODH) is a key enzyme of the de novo pyrimidine biosynthesis, converting dihydroorotate to orotate. DHODH inhibitors are believed to have implications for the control of inflammatory processes but have been also investigated for other indications, for example, cancer and malaria.

A DHODH inhibitor, brequinar has been synthesized by the Doebner-3CR of α-ketoacid (**165**), substituted benzaldehyde (**166**) and substituted aniline (**164**) and has undergone multiple clinical trials for cancer and immunosuppression.[138] A cocrystal structure has been published.[139] The inhibitor is situated in a long hydrophobic channel and makes an important charge charge interaction with the Arg136 (Figure 26).

Cyclooxygenase (COX) is an enzyme responsible for the synthesis of prostanoids and represents a major inflammation and pain target. The group of nonsteroidal anti-inflammatory drugs, such as the well-known aspirin and ibuprofen are COX inhibitors. Recently, imidazo[1,2-*a*]pyridine derivatives were designed as novel COX-2 inhibitors, 10-fold more potent than

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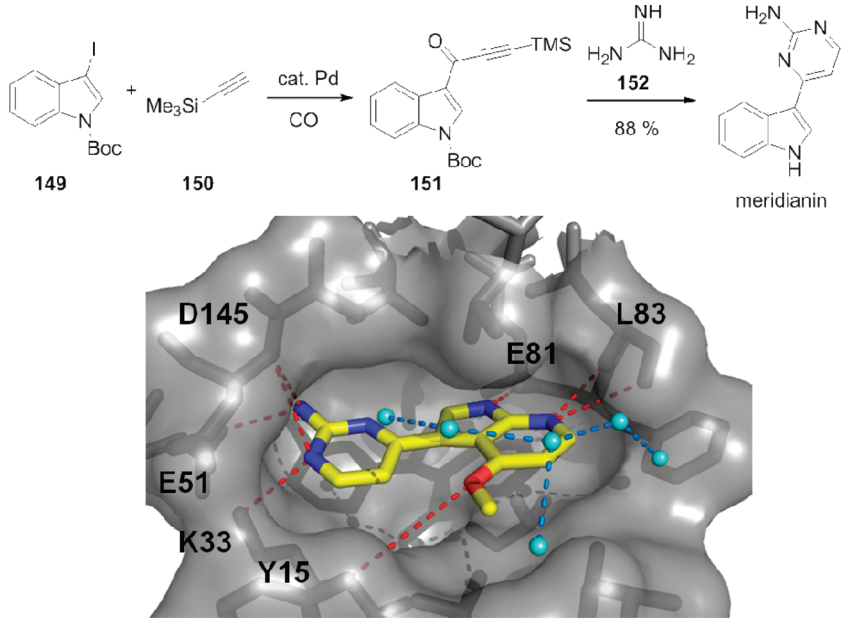

Figure 24. Kinase inhibitory natural product meridianin in a short and efficient MCR synthesis and its natural origin, an *Aplidium sp.* sponge. Bottom: The cocrystal structure of the 7-aza meridianin in complex with CDK2 (PDB ID 3BHT). Shown with red dotted lines is the extensive H-bond network of the natural products with the hinge region and other amino acid side chains of the receptor. A tight water network on top of meridianin is shown as turquoise balls and blue dotted lines.

celecoxib as an analgesic and an anti-inflammatory agent in several disease relevant animal models (Figure 27).[140] Docking studies were used to rationalize the results. The compound **170** is orally bioavailable. Compound **170** is a product of the GBB-3CR variation of the Ugi reaction and can be synthesized in one step from the isocyanide (**167**), benzaldehyde (**169**), and 2-aminopyridine (**168**) in 60% yield. Interestingly, the same class of compounds was also found by an unrelated approach. A ligand based virtual screening cascade of a commercially available library involving 2D similarity, shape and 3D pharmacophore similarity served to find new and potent 5-lipoxygenase inhibitors (Figure 27).[141] Several of the high ranking hits are MCR reaction products, including G-3CR (**173**) and GBB-3CR (**172**). Clearly, such an approach is suited to economically screen large MCR libraries and to produce different hits based on different MCR scaffolds *sic* "scaffold-hopping".

3′,5′-Nucleotide phosphodiesterase enzymes (PDE) play dominant therapeutic roles in depression, emetic response and inflammation showing a distinct subtype specificity. A tetrahydrobenzothiophene bisamide (**174**) was recently discovered as a potent and modestly PDE4B-over 4D-selective inhibitor and has emerged from an HTS based on docking models.[142] The compound has been synthesized using a three step procedure involving a key Gewald-3CR. Co-crystal structure of PDE4 with Gewald compounds (**174**) revealed that the compounds are rather rigid in forming an intramolecular hydrogen bridge between the 2-amide and the 3-carboxy group (Figure 28). This is in agreement with numerous small molecule X-ray structures of the Gewald scaffold.[125a] Additionally, the cocrystal structure of **174** with the receptor was surprising since a considerable induced fit was observed; this is in contrast to dozens of previous apo and cocrystal structures. These results can be helpful in designing subtype specific PDE inhibitors.

2.5. G-Protein Coupled Receptors

GPCR ligands derived from MCR chemistry are particular popular as indicated by the wealth of patent applications, compounds in development and on the market. In fact GPCRs are the single largest drug target class, representing 25−50% of marketed drugs.[143] GPCR drug discovery in the past was dominated by HTS, however the recent structure elucidation of several novel GPCRs in addition to rhodopsin provides the foundation to complementary techniques, for example, homology modeling and structure-based design.[144] The orexin receptor was discovered during an effort to deorphanize brain related GPCRs. Orexins, also called hypocretins, are a pair of highly excitatory neuropeptide hormones that are produced by a very small population of cells in the lateral and posterior hypothalamus and they send projections throughout the brain. The orexin system is involved into a range of basic physiological states, including wakefulness and food intake and is therefore an important new target area for drug discovery.[145] Almorexant is a first-in-class orexin receptor antagonist, currently undergoing phase III clinical development for insomnia.[146] The tetrahydroisoquinoline derivative was originally discovered from a series of Ugi/Pictet−Spengler reaction products (Scheme 24).[147]

Preterm labor is the major reason for neonatal morbidity and occurs in 10% of all birth worldwide. Currently, antagonistic derivatives of the neurohypophyseal nonapeptide hormone oxytocin are used to control preterm labors, however they are associated with the typical disadvantages of peptide drugs, such as lacking oral bioavailability, short half live time and potential immunogenicity. The diketopiperazine scaffold (**175**) has been discovered in a HTS campaign and developed to the first clinical class of small molecular weight oxytocin antagonists (Figure 29). The optimized derivative GSK221149A is undergoing advanced clinical trials to study safety, tolerability and metabolism.[148] GSK221149A is a very potent (K_i = 650 pM) and selective oxytocin antagonist and has been shown to

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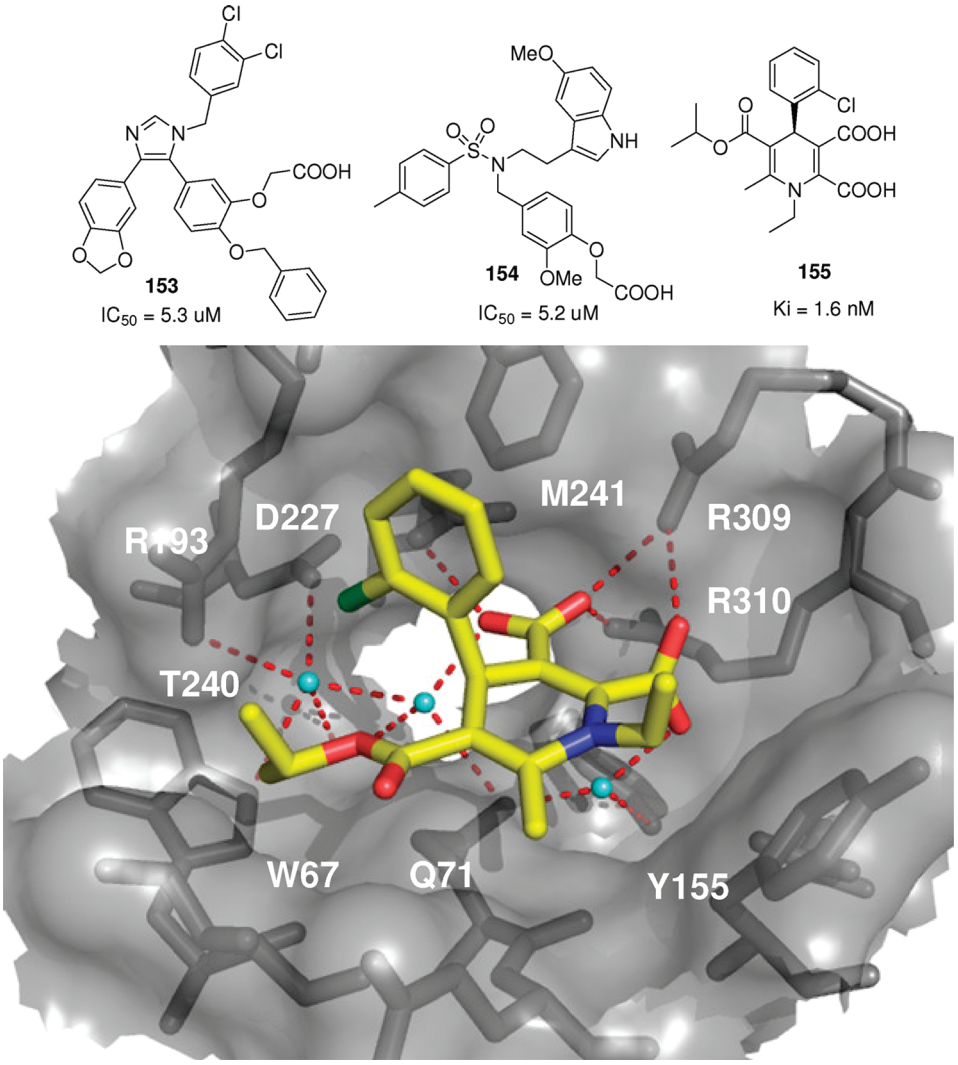
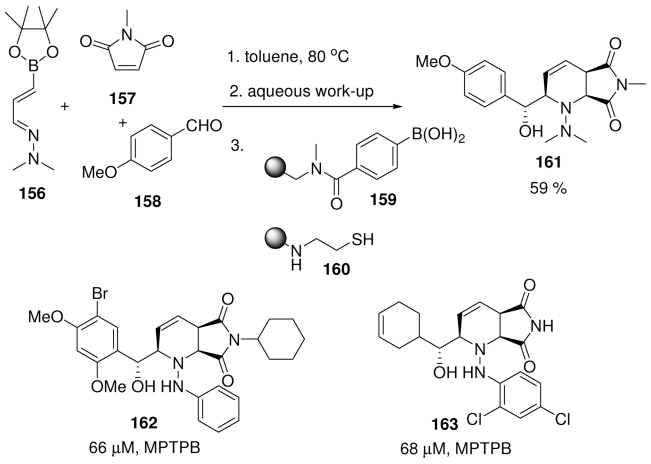


Figure 25. Top: Structure of different MCR derived phosphatase inhibitors. Bottom: Glycogen phosphatase (PDB ID 2AMV) in complex with a Hantzsch MCR derived dihydropyrimidine **155**. Note the typical boat conformation of the central heterocycle.

Scheme 23. MCR Library Synthesis of Phosphatase Inhibitors Involving Hetero-Diels–Alder of Unsaturated Schiff Bases and Allylboration



inhibit oxytocin-induced uterine contractions in the anaesthetized rat. Interestingly, the compound (MW 495 Da) is a >20 fold more potent receptor antagonist than the current clinically used peptide derivative Atosiban (MW 994 Da). Moreover GSK221149A displays a far superior selectivity profile over the peptide drug with respect to the related vasopressin receptors (>1400-fold).[149] In addition, GSK221149A is orally bioavailable, in contrast to the peptide derivative.

Because of the convergent and efficient nature of the MCR chemistry detailed SAR has been performed.[151] To rapidly establish SAR and the optimal stereochemistry all 8 stereoisomers of this Ugi DKP backbone had to be synthesized. In a landmark paper all 8 different stereoisomers have been synthesized using different strategies, however all involving Ugi chemistry (Scheme 25 and 26).[152] E.g. reaction of the chiral *N*- and *C*-protected amino acid derivatives (**177**), respectively with *tert*-butylisocyanide (**93**) and benzaldehyde (**176**) yields the Ugi product **179**. *N*-deprotection and cyclization under basic conditions yields the two stereosisomers **180** (*RRR*) and **181** (*RRS*) differing in the benzaldehyde derived stereocenter (Scheme 25). The two diastereomers can be conveniently separated using silica chromatography.

The *RRR* stereoisomer **180** can be prepared alternatively using an initial U-5C-4CR employing unprotected L-Leu HCl salt, benzaldehyde (**176**) and *tert*-butylisocyanide (**93**), yielding

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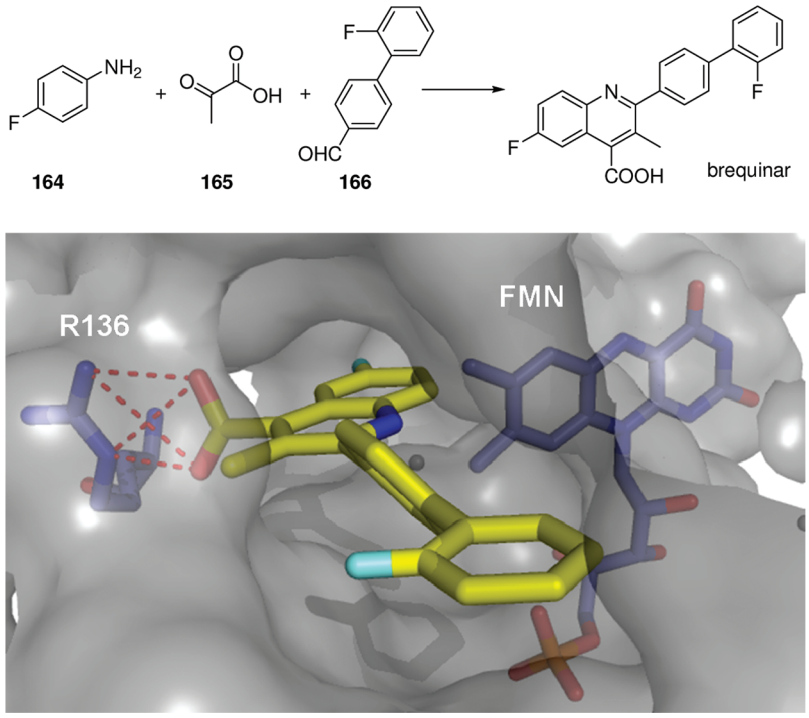

Figure 26. Top: DHODH inhibitor brequinar synthesized by Doebner-3CR. Bottom: Doebner-MCR product is located in a deep and hydrophobic protein binding site (PDB ID 1UUO). The key interaction is the salt bridge between the carboxylic acid and the guanidine unite of Arg136. Noteworthy the tight interaction of the two fluorine atoms located at the isoquinoline and the external biphenyl ring with the hydrophobic protein environment.

the iminodicarboxylic acid mono amide derivative **182** in very good yields and diastereoselectivity (Scheme 26). Saponification, acylation (**183**), N-deprotection and subsequent cyclization yields the expected stereoisomer on a multi mg scale. The other stereoiosmers were synthesized using similar strategies and enantiomerically pure amino acids as starting materials. Attempts to simplify the DKPs, for example, by removing the Ugi side chain and providing "classical" DKPs did lead to inactive compounds. Clearly, such highly substituted DKPs are not readily available by other synthetic strategies involving 2-CRs.[33,153]

Corticotropin releasing factor (CRF) is a 41-amino acid peptide hormone involved in stress response. It exerts its activity through binding to the GPCR receptor CRF1-r. Antagonists are under investigation for generalized anxiety disorder and for the potential treatment of alcoholism. A novel series of CRF1 antagonists was discovered by using a computational library design strategy and differing much from previous CRF antagonist pharmacophores.[154] The *N*-phenylphenylglycine amides, such as **184**, were synthesized in a two-step process involving a boronic acid Mannich (Petasis) MCR followed by amidation (Scheme 27).[155] These compounds were synthesized as racemic mixtures and separated rapidly using chiral supercritical CO_2 fluid chromatography (SFC). Generally, only one enantiomer showed activity. Additionally, preliminary pharmacokinetic studies showed encouraging results. An alternative pathway to this compound class consists of the U-3CR. Based on the different availabilities of the starting materials of the two approaches different chemical spaces can be investigated. Recently, a major improvement of the U-3CR has been reported using phenylphosphinic acid in toluene under refluxing conditions.[156]

The 3-CR product of two equivalents of 5,5-dimethylcyclohexane-1,3-dione (**191**) and salicylaldehyde (**192**) yielding a xanthene derivative (**193**) has been shown to potently antagonize NPY, a 36 amino acid peptide with potent, centrally mediated orexigenic (stimulates food intake) effects (Figure 30). The lead compound **193** is a selective and orally active neuropeptide Y5 receptor antagonist and has an advantageous PKPD profile, including penetration of the blood-brain barrier. Thus compound **193** and its derivatives will serve as valuable tools to study biology of NPY receptor in cell-based systems as well as in vivo.[157]

α-Amino acid derived isocyano esters, but interestingly not the amides, react with aldehydes or ketones and primary amines to yield stereospecifically the corresponding *syn*-imidazoline as a major product. This Orru-3CR is useful because three independent starting materials which are all available abundantly allow the access to a very large chemical space.[159] The reaction has been recently used to discover *m*-opioid receptor selective inhibitors (**194**, Scheme 28).[160]

Melanin-concentrating hormone (MCH) is orexigenic and thus represents an important pharmaceutical target. Chiral dihydropyrimidone inhibitor (SNAP-7941) currently undergoes preclinical evaluation as an anorectic, antidepressant and anxiolytic agent. The compound can be produced by the Biginelli-MCR and recently two enantioselective routes toward its synthesis have been published, both employing again MCRs (Scheme 29).[161] The first route uses an asymmetric Mannich reaction of ethyl acetoacetate **195** and imine **196** in the presence of cinchona alkaloid catalyst **197**. The second route employs an asymmetric Biginelli reaction catalyzed by chiral binapthol derived phosphoric acid **203**. Thus Biginelli intermediate **204** can be formed in 96% yield in an *er* of 95:5. The heterocycle was purified by recrystallization to

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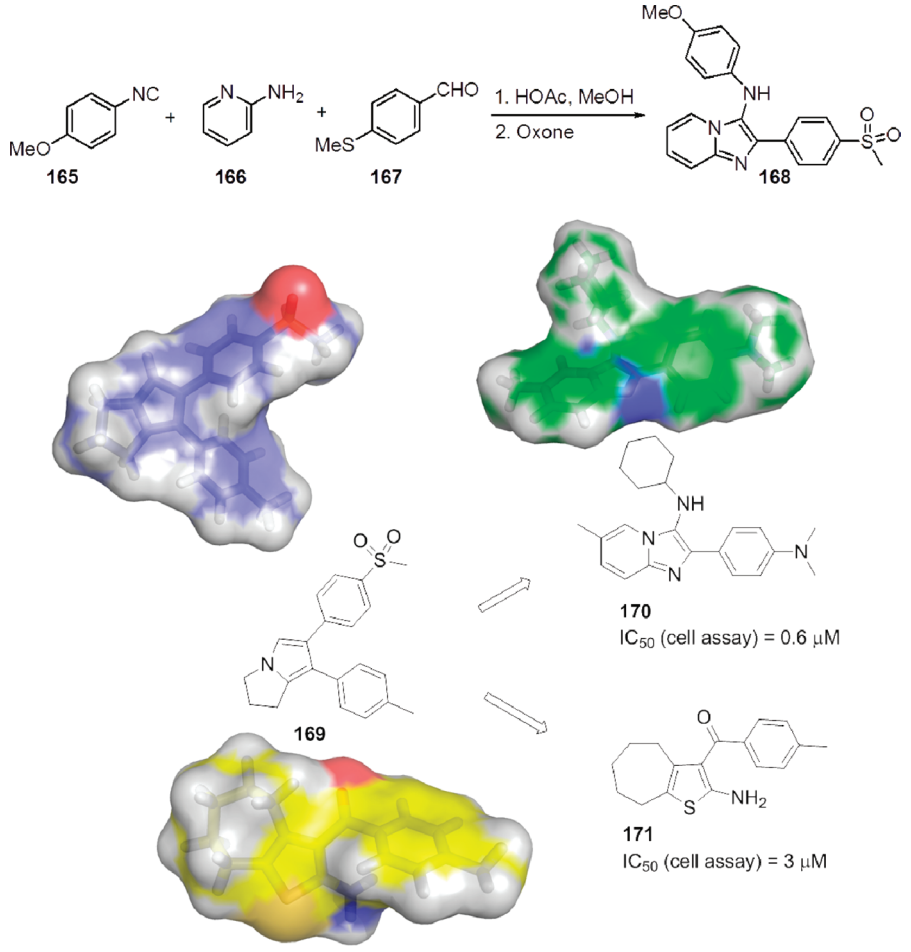

Figure 27. Scaffold hopping via virtual screening towards discovery of inhibitors. Top: Novel COX2 inhibitor synthesized by GBB-3CR. Bottom: Compound **171** served as a template to screen a 1323 compound library using a screening cascade. Amongst the hits several scaffolds based on MCR were discovered. The most potent hit, compound **172**, showed nanomolar activity in a cell-based assay.

provide DHPM enantiomerically pure. The asymmetric Mannich reaction catalyzed by cinchona alkaloids and the asymmetric Biginelli reaction catalyzed by chiral phosphoric acids were equally effective at producing the desired heterocycle.

The complement system is comprised of a cascade of interrelated proteases that are activated in response to immunoglobins binding to a foreign antigen. Activation of the complement systems leads to a stepwise hierarchy of proteolytic cleavage events ultimately leading to the release of bioactive fragments (C3a, C4a, and C5a) known as anaphylatoxins. C5a is recognized as a potent mediator of inflammation by recruiting inflammatory cells to the site of infection or injury. Novel C5a receptor antagonists **208** based on U-4CR have been disclosed and found useful as a tool for the rapid identification of antagonists with low in vitro clearance.[162] A large number of compounds with 'lead-like' potency were prepared but these had poor metabolic stability. Thus rapid MCR chemistry helped to identify weaknesses of a lead series and consequently it was not progressed into lead optimization (Figure 31).

A recently characterized G-protein coupled receptor, GRP40 is believed to represent a selective target for type 2 diabetes. GPR40 is preferentially expressed in the pancreas with elevated levels reported in the islets and also in the pancreatic β-cell lines. A HTS screening identified MCR products **206** of homophtalicacid anhydride and primary amines and aldehydes (Figure 31).[163] Few rounds of optimization revealed a candidate with GPR40 activity and satisfactory PK parameters.

The endocannabinoid system (ECS), and specifically the cannabinoid type 1 (CB1) receptor, plays a pivotal role in energy homeostasis and is a major obesity target. Recent clinical trials however revealed that several CB1 receptor inverse agonists/antagonists were associated with major side effects. In order to potentially overcome these side effects compounds are synthesized to have an improved profile. Thus bioisosteric replacement of the hydrazide functionality with a suitably substituted imidazole using van Leusen's MCR was recently proposed (**208**).[164] Equally potent compounds could be achieved showing an excellent overlap of the different pharmacophore elements and being orally bioactive (Figure 31).

Gonadotropin-releasing hormone (Gn-RH) is secreted from the hypothalamus and its action on the pituitary gland then leads to the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Their involvement in the biology of reproduction made them key targets for drug discovery. The bulky hydrophobic amino acid residue in position 6 appears to be very important for the high potency of the analogues. An efficient method for the synthesis of some Gn-RH analogues based on Ugi reaction has been developed (Scheme 30).[165] Four-component reaction of *N*- and *C*-terminus peptides, aromatic aldehydes and isocyanides affords novel Gn-RH analogues derived from triptorelin and gonadorelin. Mild

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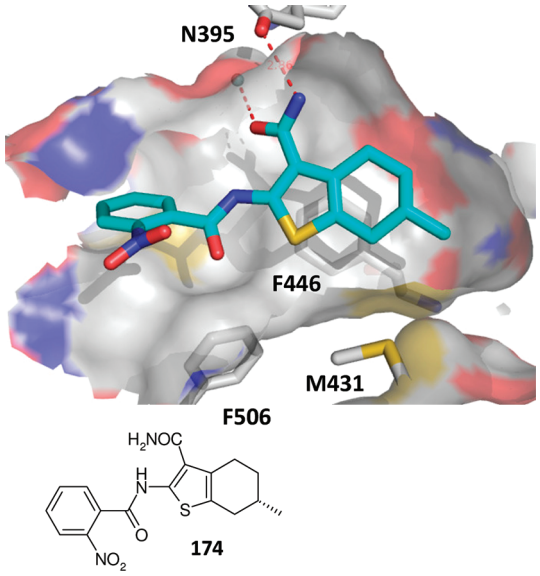
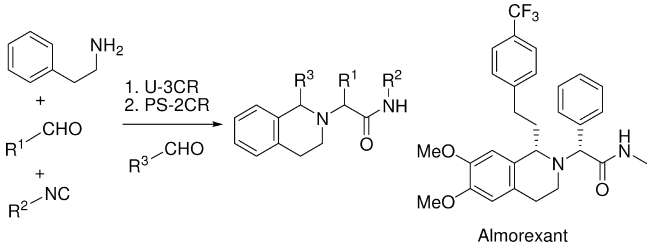


Figure 28. Gewald-3CR product **174** (turquoise sticks) as subtype specific 3′,5′-nucleotide phosphodiesterase enzyme inhibitor bound to PDE4B (PDB ID 3HMV). The inhibitor pocket is shown in a cutoff view. Several amino acid side chains are removed for clarity. The primary amide of the inhibitor makes a hydrogen bonding contact to Asn395 and an adjacent water molecule. A $\pi-\pi$ interaction can be observed between the thiophene ring and Phe446. Additionally there are hydrophobic contacts to Phe506 and Met431.

Scheme 24. Structure of Almorexant, a First in Class Orexin I Antagonists Currently in Advanced Clinical Trials for Sleeping Disorders



ligation of two peptide fragments is one of the earliest applications of the Ugi MCR in biological chemistry and has been recently named the Ugi-ligation.[166] Potential advantages of such modified peptides could be their enhanced protease stability, the easy tunability of hydrophobicity/hydrophilicity properties via the other components and their different biological activity. Moreover, one can imagine that certain bioactive conformation of otherwise flexible peptides could be frozen.

2.6. Ion Channels/Transporter

Channels are the gates of charged and uncharged small molecules between the inside and the extracellular world of cells. They play an eminent role in the transduction of information. Malfunctional channels on the other hand play an outstanding role in many diseases.[167] With a lot of recent information available on structures of channels a rational approach to channel drug discovery is now feasible besides HTS.[167b,168] Specifically, chloride channels are involved in a wide range of biological functions and thus are an important class of drug targets.[169] Interestingly, however, chloride channels are relatively under-explored as a target class for drug discovery as elucidation of their physiological roles has lagged behind that of many other channels. They are involved for example in epithelial fluid secretion, cell-volume regulation, neuroexcitation, smooth-muscle contraction and acidification of intracellular organelles. Diseases associated with chloride channels are cystic fibrosis, macular degeneration, myotonia, kidney stones, renal salt wasting, secretory diarrheas, polycystic kidney disease, osteoporosis and hypertension and hyperekplexia, just to name a few.

Thus, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel cause cystic fibrosis. α-Acylaminocarboxamides **209** has been identified by high-throughput screening and can be accessed synthetically by a classical Ugi 4-CR (Scheme 31).[170] This phenylglycine derivative can correct defective gating in a number of CF-causing CFTR mutants. Thus compound **210** could display a lead structure for the development of a drug for cystic fibrosis.

Calcium-activated chloride channels (CaCCs) are widely expressed in mammalian tissues, including intestinal epithelia, where they facilitate fluid secretion. Potent, selective CaCC inhibitors have not been available. Recent small molecule screening to identify inhibitors of human intestinal CaCC(s), using a halide influx assay, identified several classes of CaCC inhibitors.[171] The most potent inhibitors identified were of the Gewald scaffold, for example, 3-acyl-2-aminothiophene **210** (Scheme 31). SAR studies based on several derivatives were performed and yielded insight into optimal potent compounds. Interestingly, cylohexanone derived compounds are active whereas cyclopentanone derived Gewald heterocyles with one carbon less were inactive. Small-molecule CaCC inhibitors may be useful in pharmacological dissection of CaCC functions and in reducing intestinal fluid losses in CaCC-mediated secretory diarrheas.[171]

The Hantzsch reaction has attracted a lot of interest due to a block buster drug based on this scaffold: nifedipine (**211** in Scheme 32).[172] This drug comprises antihypertensive properties, targets heart specific Ca^{2+} channels and represented a major breakthrough in the treatment of heart diseases.

Diydropyridines can be easily oxidized to the corresponding pyridine derivatives, for example, using ammonium nitrate/Montmorillonite K10 Clay during the H-4CR.[173] Alternatively, the Hantzsch products can be separated and oxidized to, for example, **212** with all kinds of oxidizers, for example, DDQ.[174] The unsymmetrical Hantzsch reaction using two different β-keto-esters has been optimized for a plant-scale manufacture of the potassium-channel opener ZD0947(**213** in Scheme 32).[175] The Hantzsch MCR is also satisfactory working with C-glycosylated reagents as displayed in 2,4-dihydropyridine **215** (Figure 32).[176]

The reaction of isocyanides, oxo components, and primary or secondary amines yields α-amino carbonamides, as disclosed by Ugi in 1959.[177] The reaction has been employed by Ugi to synthesize the local anesthetic Xylocaine (**215**) and many derivatives thereof (Scheme 33). Xylocaine alters depolarization in neurons, by blocking the fast voltage gated sodium (Na^+) channels in the cell membrane.

Philanthotoxin-433 (PhTX-433), a low molecular weight natural polyamine toxin that originally isolated from the venom of wasp, showed potential noncompetitive inhibitory effects on various types of ionotropic receptors in the central nervous system such as ionotropic glutamate receptors (iGluRs) and nicotinic acetylcholine receptors (nAChRs) in mammalians and in insects. Polyamines have been recently deemed to be "universal templates" in drug discovery.[178] Libraries of PhTX-433

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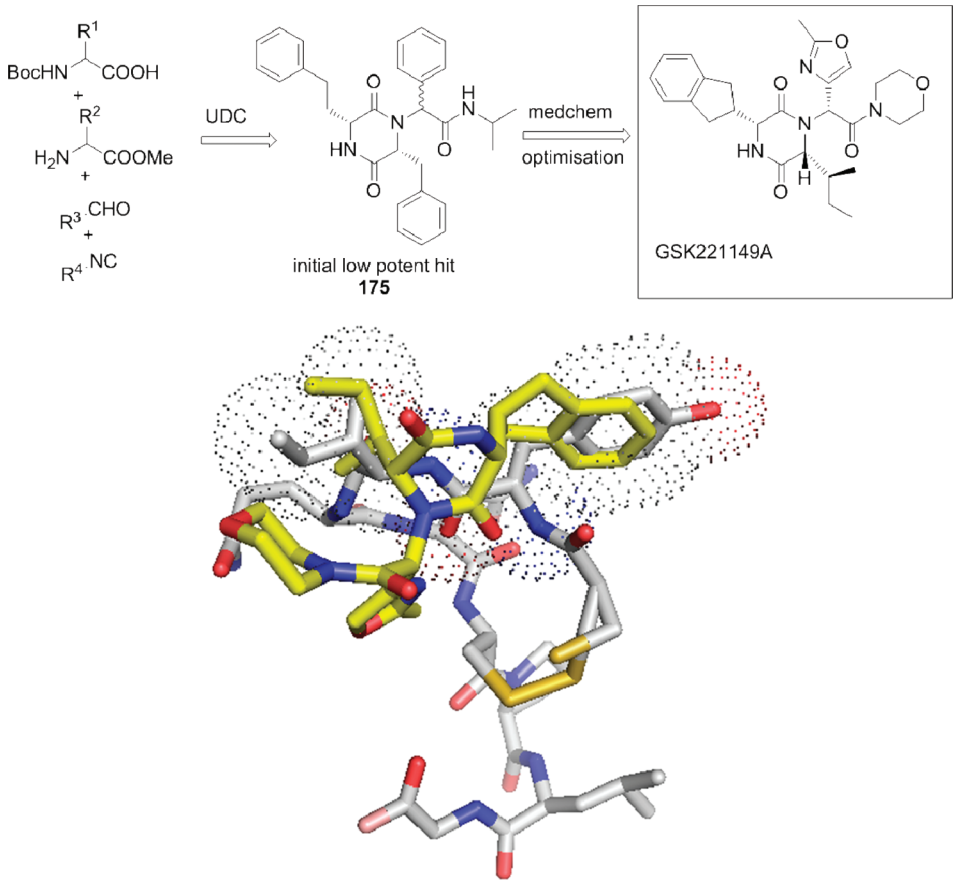
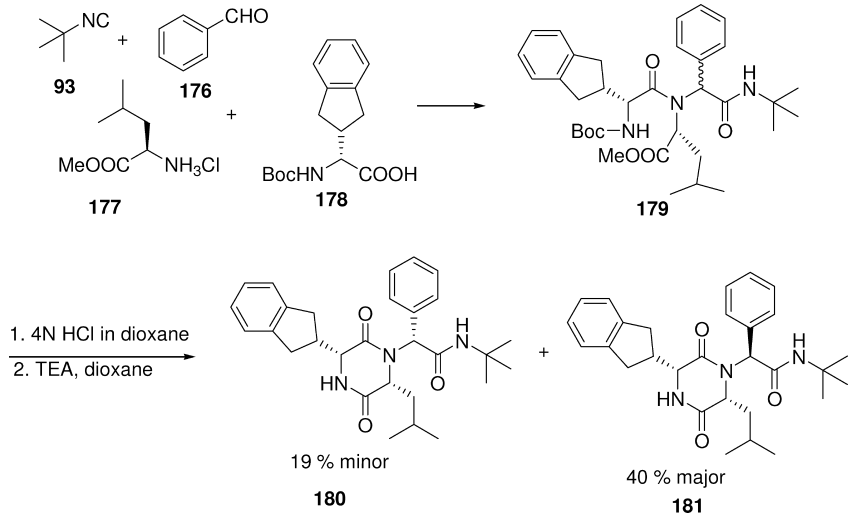


Figure 29. Top: Retrosynthesis of the oxytocin antagonist (compound **175** and GSK221149A). Bottom: X-ray structure of oxytocin (gray sticks, PDB ID 1XY2) and an energy minimized model of GSK221149A (yellow sticks).[150] It is hypothesized that the Indane part of GSK221149A mimics Tyr2 and the Ile fragment Ile3 of oxytocin. The oxazole fragment imparts a conformational look and the morpholine water solubility, respectively.

Scheme 25. Synthesis of the (*RRR*)-180 and (*RRS*)-181 Stereoisomers of Oxytocin Antagonist Derivatives



analogs were synthesized using Ugi's MCR (Scheme 34).[179] It is well-known that Ugi reactions often are faster and higher yielding if performed under high concentration. Here the MCR was performed under solventless conditions and 20 reactions were analyzed with no solvent or using the standard solvent methanol. In average 10% higher yields have been obtained under solventless conditions and the reaction time could be reduced to less than 1 h. A typical example is compound **216** (Scheme 34). Additionally, recently a concise synthesis of polyamines using Ugi MCR and subsequent exhaustive reduction was described giving now easy access to this "universal template", for example, **217**.[180]

Compound **220** was found to be a selective T-type Ca-channel blocker equipotent to the marketed compound milbefradil.[181] This morpholin-2-one-5-carboxamide and derivatives were prepared by using the one-pot Ugi MCR of

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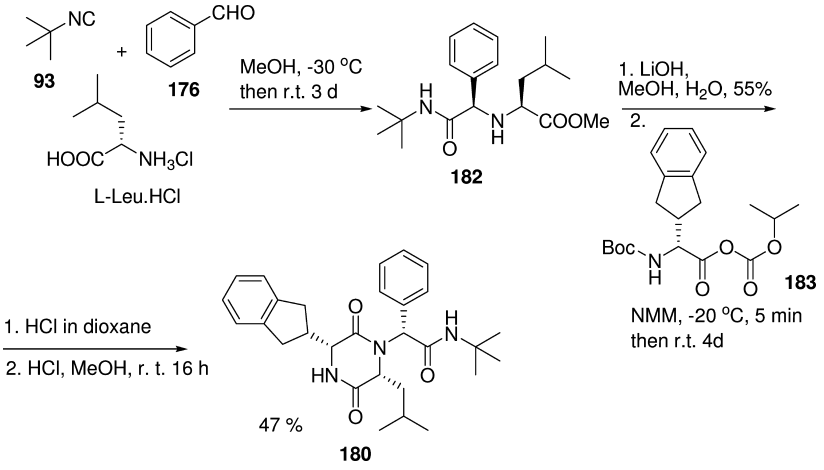
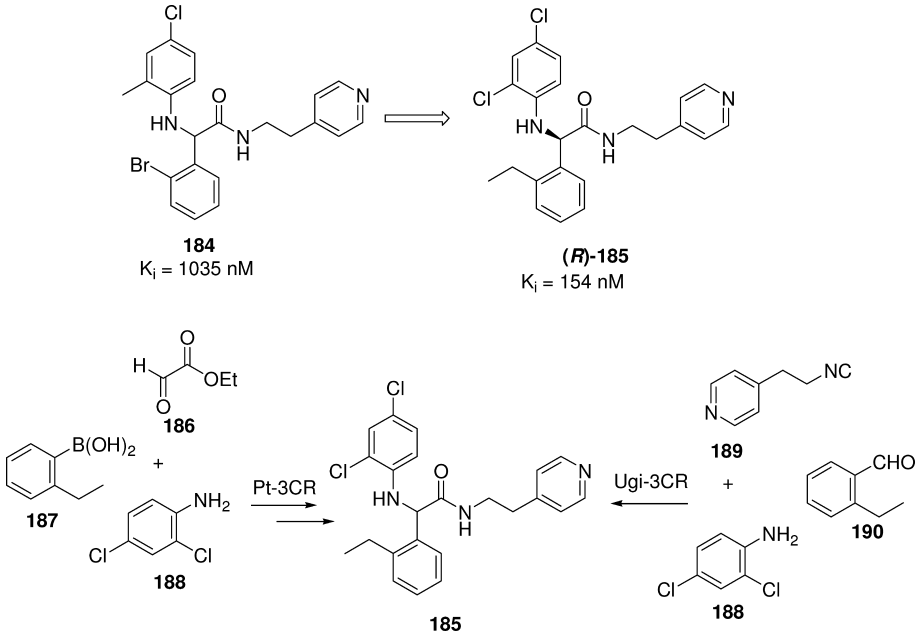
Scheme 26. Alternative MCR Synthesis of the *RRR* and *SSS* Stereoisomers of Oxytocin Antagonist Derivatives



Scheme 27. CRF Receptor Antagonist (*R*)-185 Optimization by Petasis or U-3CR



glycolaldehyde (**219**), an isocyanide (**41**), and an α-amino acid (**218**). The use of the non-nucleophilic polar trifluoroethanol as a solvent is essential to suppress intermolecular reactions. The voltage-dependent Ca^{2+} channels (VDCC) are the primary route for translating electrical signals into biochemical events underlying key processes such as enzyme activity, neurotransmitter release, neuronal excitability, neurite outgrowth, and gene transcription.

Atrial fibrillation (AF) and flutter are the very common cardiac arrhythmias encountered in clinical practice. The ultrarapid delayed rectifier potassium current plays a significant role in the repolarization of the atrial action potential and selective inhibition of this current in human atrial myocytes prolongs action potential duration. Prolongation of the action potential is believed to prolong the atrial effective refractory period; therefore inhibition of the respective potassium channel Kv1.5 would produce an appropriate antiarrhythmic effect. Dihydropyrazolopyrimidine is a potent and selective inhibitor of the potassium channel Kv1.5 (Scheme 34).[182] The Biginelli-3CR of benzaldehyde, 3-aminopyrazole and β-ketoester and two more subsequent reactions yielded dihydropyrazolopyrimidines, for example, **221** with an IC_{50} for Kv1.5 block of 30 nM without significant block of other cardiac ion channels. The orally bioavailable compound **221** undergoes development for AF.[183]

The discovery of the first class of subtype-selective inhibitors of the human excitatory amino acid transporter subtype 1 (EAAT1) is reported. An SAR of 25 analogues was presented that addresses the influence of substitutions at the 4- and 7-positions of the parental skeleton 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. The most potent analogue **222** (Scheme 34) displays high nanomolar inhibitory activity at EAAT1 and a >400-fold selectivity over EAAT2 and EAAT3, making it a highly valuable pharmacological tool. Corresponding chromene derivatives can be conveniently accessed by a 3-CR of malonodinitrile (**101**), 4-methoxybenzaldehyde (**158**), and 5-(naphthalen-1-yl)cyclohexane-1,3-dione (Scheme 34).[184]

The P2 × 7 receptor is a ligand-gated ion-channel and expressed on different lineages of cells, including macrophages,

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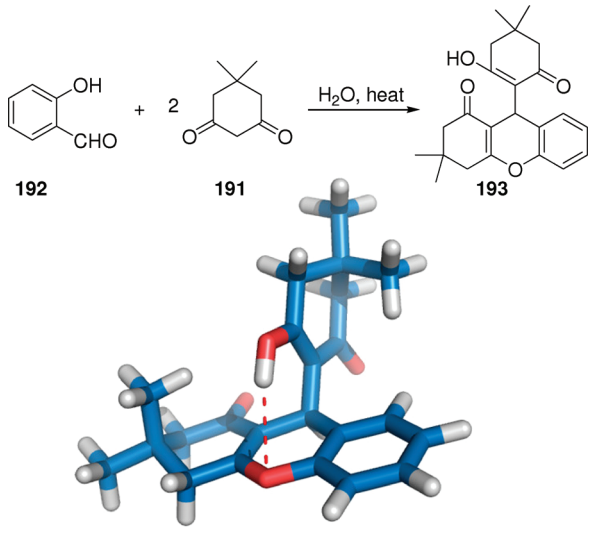
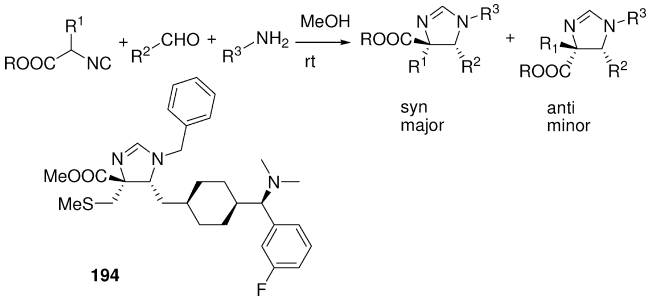


Figure 30. Potent NPY antagonist **193** made by an old[158] and experimentally simple MCR.

Scheme 28. Orru-3CR and a Biologically Active *m*-Opioid Receptor Antagonist (194) Thereof



microglia, mast cells and T- and B-lymphocytes. Activation of the P2 × 7 receptor has been implicated in giant cell formation, regulation of cell proliferation, release of proinflammatory cytokines to name a few. Recent preclinical in vivo studies suggest implications of P2 × 7 receptor for inflammatory, neuropathic and visceral pain treatments.[185] Several scaffold classes have been disclosed as modulators of P2x7 receptor, piperidinone, pyrrole and isoindole carboxamide derivatives (Scheme 35).[186] Corresponding compound classes, for example, **225** can be convergently synthesized by isocyanide-based MCRs using bifunctional and reactive oxocarboxylic acids **223**.[187]

Alantrypinone is an insecticidal alkaloid that acts as a selective antagonist for housefly (vs rat) GABA receptors, and is considered to be a lead compound for the development of safer insecticides. The natural product and a library of derivatives thereof have been elegantly synthesized using a key one-pot MCR under microwave conditions and a subsequent hetero-Diels–Alder reaction (Scheme 36).[188] The first step constitutes a condensation between anthranilic acid **226** and Boc-protected alanine in the presence of triphenyl-phosphite. Then the glycine methylester was added and treated under microwave conditions to yield the dihydro-quinazoline. Upon treatment with Borontrifluoride etherate and final oxidation the quinazoline (**227**) can be isolated. A Diels–Alder reaction with the isatine derived in situ formed dienophile 228 finally yields alantrypinone. Detailed SAR based on substituted anthranilic acids (**226**), indones (**228**), and different amino acids is described.

2.7. Protein–Protein Interactions

Protein–protein interactions (PPIs) are a rather complex group of pharmaceutical targets being systematically studied only in recent years. Often PPIs are mediated by large interfaces, do not show deep and spatially confined binding isles ("hot spots"), and thus, are difficult to target by small molecules. In fact it has been reported over and over that PPI modulator identification is challenging with today's HTS libraries.[189] On the other hand PPIs sometimes are suitable for small molecule binding especially in the presence of deep and rather small binding grooves. Thus, PPIs targetable by small molecules have been classified by the dimensions and electrostatics of their interfaces.[190]

CCR5 is a chemokine receptor that is highjacked by the HIV to enter the cell and with the recent approval of maraviroc it consists a validated and new target to fight AIDS. Taking up the privileged structure idea pharma company scientists synthesized spirodiketopiperazines **231** using Ugi reactions (Scheme 37).[191] Among all synthetic pathways to (di)(keto)piperazines IMCRs certainly are the most versatile ones.[33,153] Several hundred spiroketopiperazines have been synthesized using solid- and liquid-phase techniques. Very potent, however poorly water-soluble compounds have been discovered. Interestingly, a metabolite was found to be even more active and also more water-soluble. An exemplary synthesis is shown in Scheme 37. Also to mention is the use of the commercial morpholinoethylisocyanide as a cleavable isocyanide.[190] An advanced compound, aplaviroc is undergoing clinical trials.

The PPI between the transcription factor p53 and its negative regulator protein mdm2 has been reported to play an important role in the chemo and radiation resistance of cancers.[192] The interaction has been described in molecular detail and the dimension and character of the binding site indicate a suitable small molecule target.[193] One of the first potent antagonists of this interaction described is the imidazolidine class of nutlins.[194] Numerous biological studies indicate their potential usefulness in cancer therapy.[195] In additions to the nutlins, several other small molecular weight compounds amenable by MCR chemistry have been recently described. The first classes of compounds discovered by a high throughput screening exercise are highly substituted benzodiazepindiones (**238**).[196] The compound class is generally accessible by a Ugi-4CR of anthranilic acids, cyclohexenyl isocyanides (**237**) as a representative of the convertible isocyanides, aldehydes and primary amines.[197] Cyclisation via a Münchnone intermediate results in the target class. Due to the general, efficient and versatile access in excess of 20.000 derivatives have been produced and screened. Detailed SAR has been published and a high resolution X-ray structure of a representative benzodiazepinone in the mdm2 binding site has been reported (Figure 33).

The scaffold of 4-carboxy tetrahydroquinolines **243** has been reported as mdm2 binder as shown by detailed 2D-NMR studies.[198] In addition, the ability to dissociate the preformed p53/mdm2 complex was reported by a new NMR experiment called antagonist induced dissociation assay (AIDA).[199] E.g. compound **243** antagonizes the complex with a K_D of 1 μM. The compound class was discovered by a computational chemistry approach using a ligand based scaffold-hopping compound selection. The same approach yielded **245** as a novel

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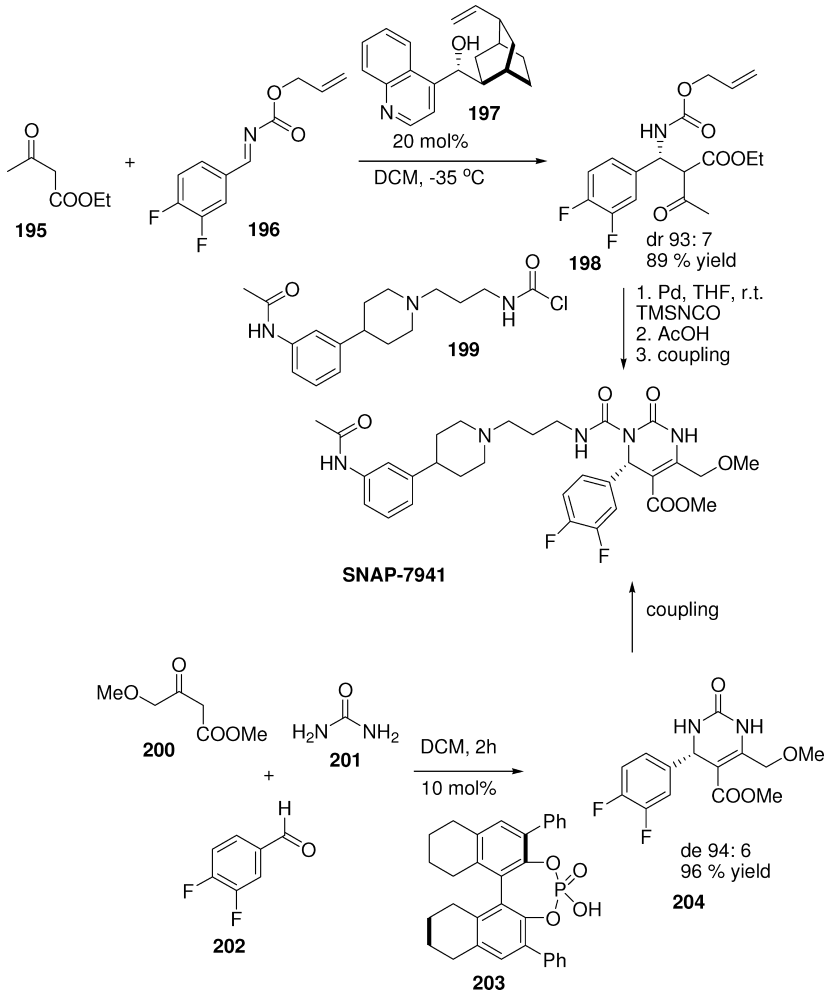
Scheme 29. Two Scale-Up Asymmetric Routes toward a Preclinical MCH Inhibitor SNAP-7941



p53/mdm2 antagonist. Both classes can be efficiently synthesized by appropriate MCRs. The first tetrahydroisoquinoline derivative **243** is the product of 3-CR of homophtalicacid anhydride (**239**) an appropriate aldehyde (**240**) and primary amine (**241**), following the amidation of free carboxylic acid and amine (**242**); whereas the second pyrrolidone-derivative **245** can be accessed by a variation of the Döbner MCR (Scheme 38). Both classes of compounds show mechanism-based activities in cellular assays.

A novel drug discovery technique based on the tight interplay of computational and MCR chemistry, docking, and high content screening yielded 10 unprecedented scaffolds predicted to bind into the p53 binding site of mdm2 and have been subsequently shown to bind as predicted by HSQC NMR experiments and cocrystal structure analysis.[200] The key steps of the approach are as follows: The interface of a particular PPI is analyzed and certain amino acid side chains are classified as anchor residues according to their high burriedness. The assumption is that the more a side chain is buried in the receptor the higher its energetic contribution. Next the anchor side chain is imposed on many different MCR scaffolds and virtual libraries are generated, in a way that all compounds contain the anchor residue. Next the virtual library is docked into the PPI interface in a way that the anchor of the compounds is overlapping with the corresponding amino acid side chain using the freeware ANCHOR.QUERY (http://anchorquery.ccbb.pitt.edu/). From the corresponding docking lists compounds are chosen for synthesis and screening based on shape complementarity, electrostatic interactions and practical aspects such as ease of synthesis based on available starting materials. Although this approach resembles a fragment-based approach, however it overcomes one of its current limitations, the fragment optimization, by combining the fragment with a very large and efficiently accessible chemical space: MCR (Figure 34).[201]

Several predicted compound classes (**246**−**254**) showed potent cellular activity and could be optimized from initial μM to nM affinity due to the convergent MCR chemistry approach (Scheme 39).[200] The binding mode of a van Leusen indoloimidazole into the p53 binding site in mdm2 is shown in Figure 35 and 36 as revealed by X-ray structure analysis and as predicted by the above approach.[202] This approach makes advantageous use of MCR chemistry since several backbones are predicted at the same time and could be optimized in parallel thus reducing the effect of attrition of a particular scaffold due to inferior properties. Additionally, the scaffolds are intrinsically optimization friendly since they are based on MCR chemistry. This parallel drug discovery approach seems to have high predictive power. Significantly, this approach can be an alternative to current drug discovery techniques in this area namely high throughput screening (HTS). A freely accessible web server was build up performing this analysis

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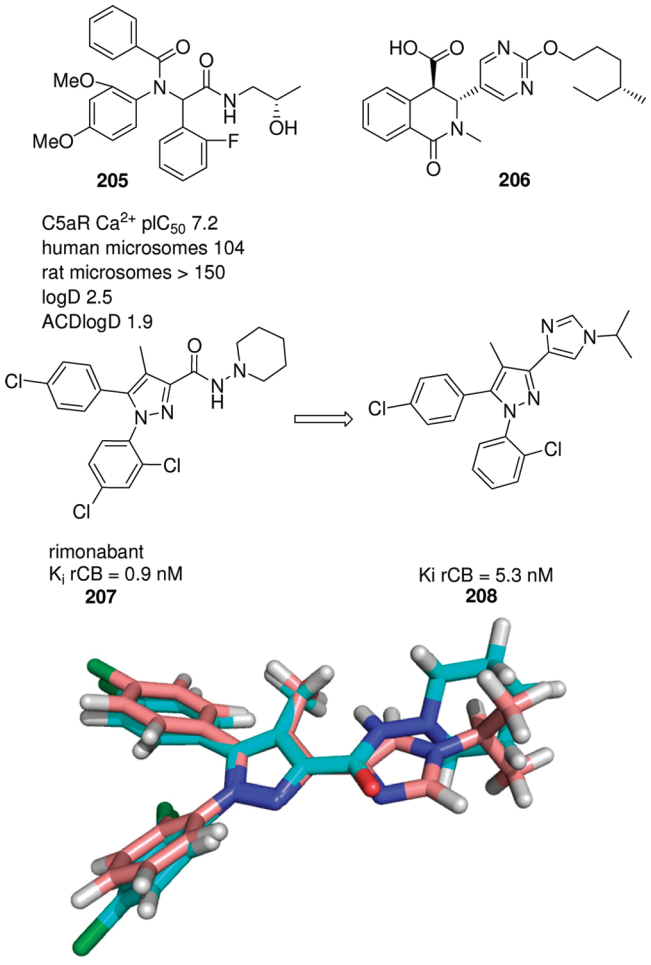
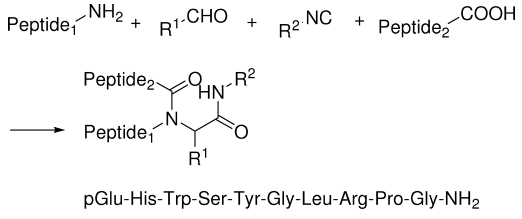
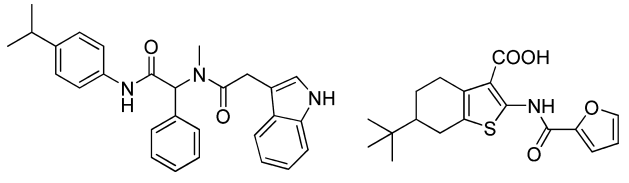


Figure 31. Various GPCR MCR-receptor binders. Bottom: Overlap of the CB1 receptor antagonist rimonabant with an imidazole isostere **208** synthesized by vL-3CR.

Scheme 30. Ugi-Ligation of Gn-RH Analogues



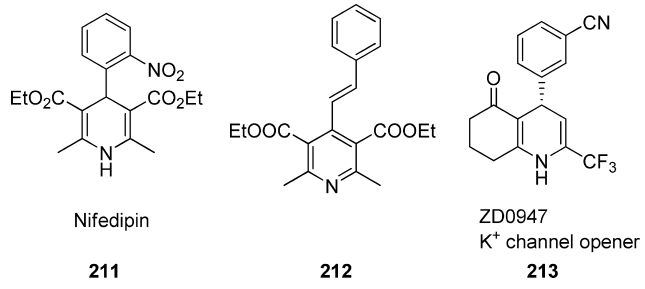
Scheme 31. Examples of Chloride Channel Interacting MCR Products



for any given protein protein interactions (http://anchorquery.ccbb.pitt.edu/).

Most of the scaffolds resulting from this approach are drug like and straightforward to optimize since they are MCR

Scheme 32. Channel Blockers Derived from the Classical Hantzsch-4CR



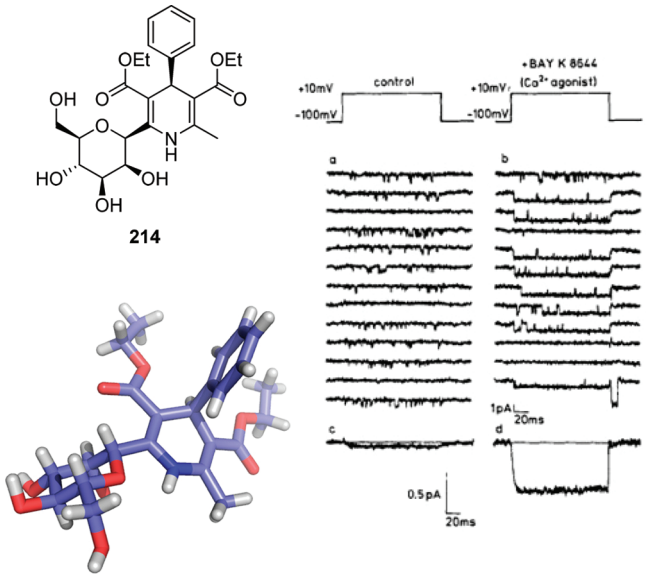
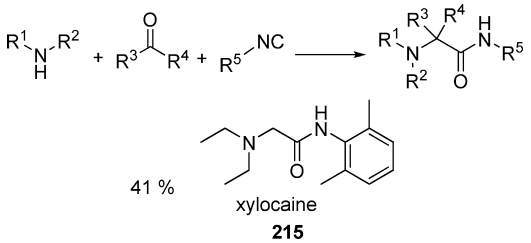


Figure 32. Left: Structure and X-ray structure of glycosylated dihydropyridine **214** in its typical bioactive boat conformation (CCDC ID 182892). Right: Patch-clamp recording for individual Ca^{2+} channels in the absence (left) and in the presence (right) of a dihydropyridine calcium antagonist.

Scheme 33. U-3CR Scheme and the Structure of Xylocaine, Which Can Be Advantageously Synthesized by It



derived. As an example the imidazoline scaffold derived from the Orru-3CR with initial double digit μM K_i could be optimized to 1 μM compounds with high water solubility.[203] One of the discovered scaffolds, imidazolindoles, has been previous described as anticancer active and some derivatives show high affinity to mdm2.[204] E.g. compound **253** has a K_i = 400 nM and could be cocrystallized with mdm2 (Figure 35).[202]

The improved amide **254** has a K_i = 4 nM to mdm2 and, interestingly also shows low uM affinity to mdm4. The first X-ray cocrystal structure of a small molecule binding to mdm4 could be subsequently solved (Figure 36).[202] Clearly, the indole moiety of the indoloimidazoles overlaps with the p53-Trp23

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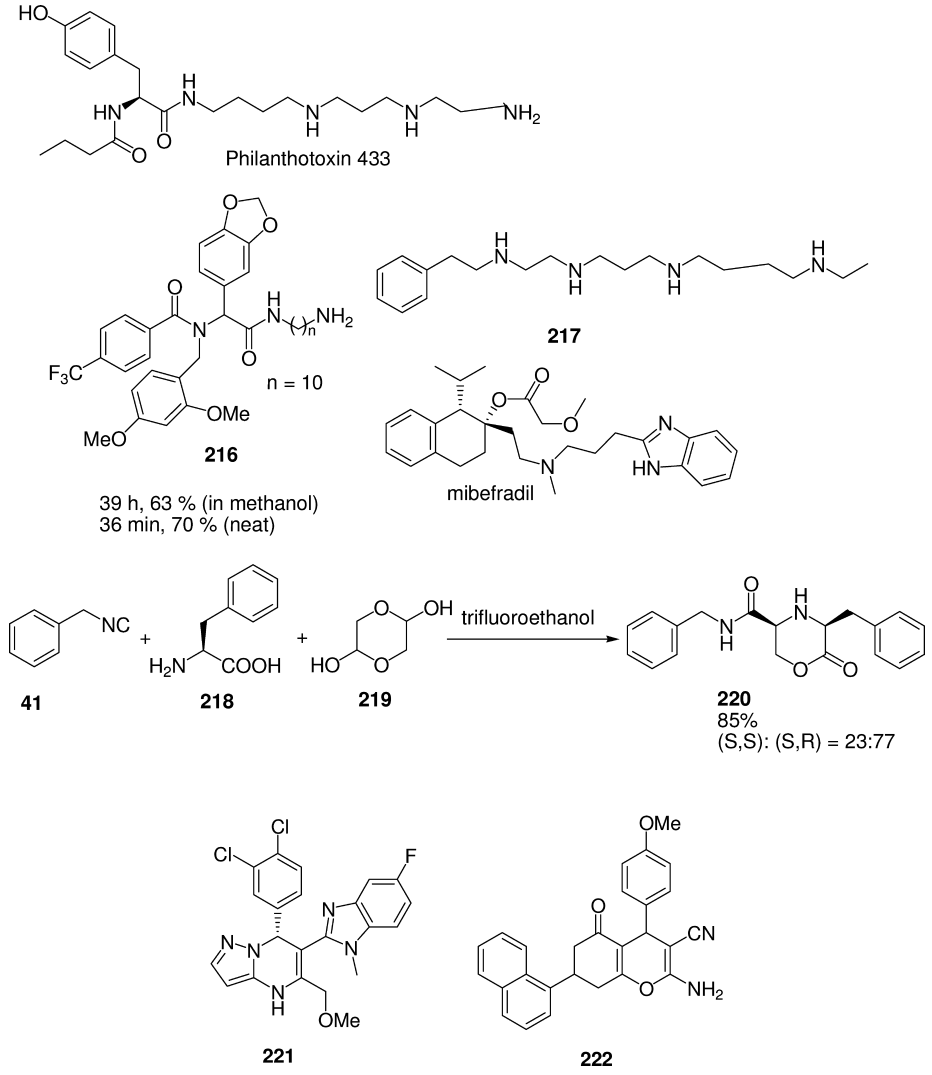
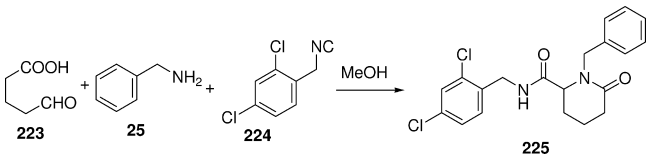
Scheme 34. Different MCR Derived Channel Modulators and the Natural Product Philanthotoxin-433



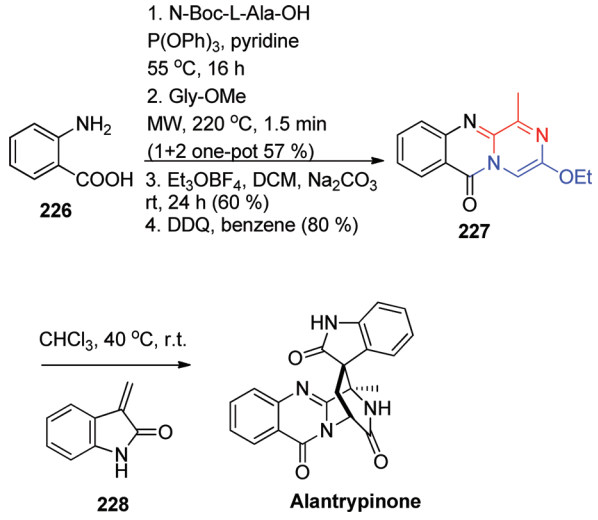
Scheme 35. Intramolecular Ugi-MCR Leading into Activators of $P2X_7$ Receptor (225)



almost perfectly in both structures which nicely validate the above-described process. The phenyl group points into the Phe19 and the *p*-chlorobenzyl group into the Leu26 pockets, respectively.

Inhibitors of apoptosis proteins (IAP) are an eight-membered family, defined by the presence of a baculovirus IAP repeat (BIR) protein domain, and they are key regulators of apoptosis.[205] XIAP is unique among IAP proteins, because of its ability to inhibit and directly bind to activated caspases. Through its BIR2 domain with its N-terminal linker, XIAP binds to the active site of effectors caspase-3 or -7 and prevents substrate binding and induces subsequently apoptosis.[206] Using the known tetrapeptide AlaValProIle, specifically, the N-terminal Ala-Val anchor several new scaffolds (**255**–**259**) based on MCR chemistry have been discovered using the above-described anchor based drug discovery approach (Scheme 40).[207]

Scheme 36. Natural Product Alantrypinone MCR Synthesis: In 227 the Ala and Gly Fragments Are Shown in Red and Blue, Respectively.



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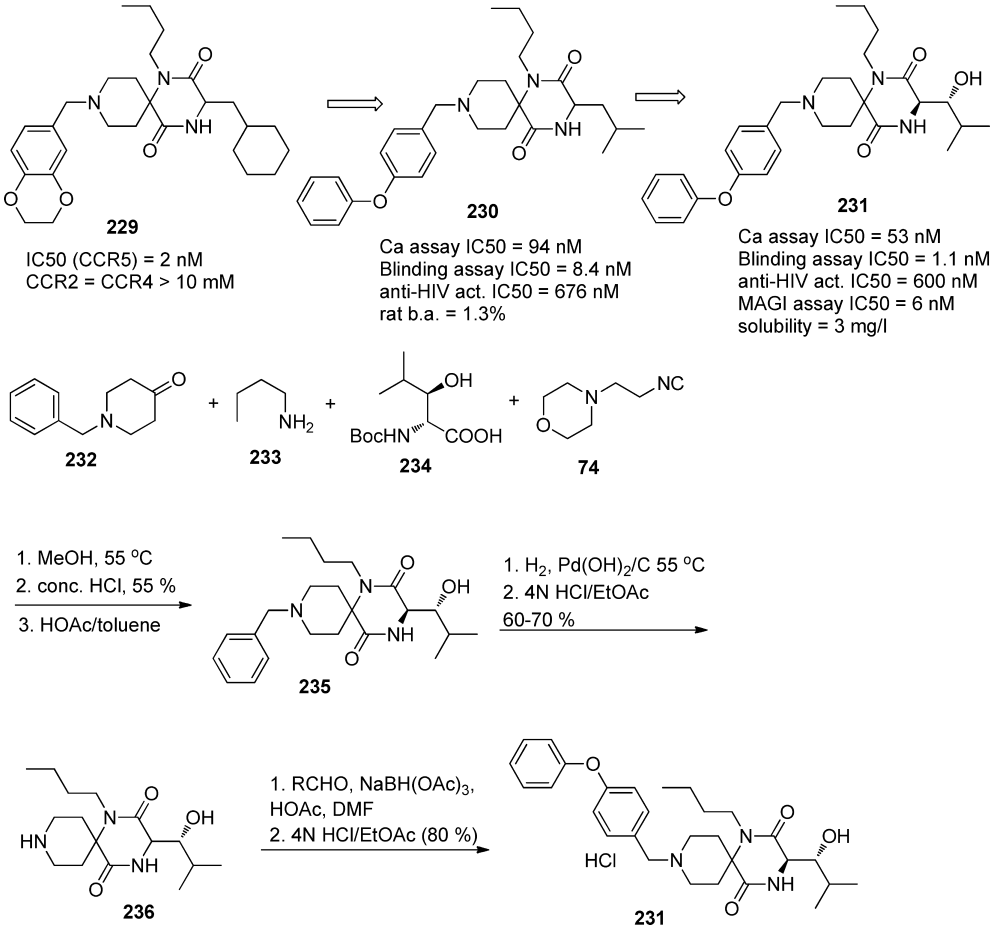
Scheme 37. Potent Protein−Protein Interaction Antagonists 231 of the Entrance of HIV into Cells Have Been Assembled Using Ugi-4CR



Clinical development of the antagonist of antiapoptotic Bcl family proteins by ABT-737 is a success story of the new fragment-based drug discovery approach.[208] Simplified derivatives (**260**) have been synthesized using a very fast and convergent access: U-4CR, followed by S_nAr substitution, thereby introducing an isosteric replacement of the central *N*-acylsulfonamide for an *α*-acylaminocarboxamides (Ugi backbone) (Scheme 41).[209]

Heat shock proteins (Hsps) are a family of highly conserved molecular chaperones responsible for the folding of nascent protein chains, for the refolding of misfolded proteins, and for the degradation of polypeptide substrates that are unable to achieve their native conformations. They have recently become important molecular targets for cancer, malaria, and stroke. Several Hsp90 inhibitors undergo clinical trials for cancer. The first small molecular weight compounds targeting the less known Hsp70 brother are products of two MCRs, the Ugi and Biginelli reaction.[210] The active compounds alter the ATP hydrolytic rate, an event that is catalyzed by the N-terminal, ATPase domain in Hsp70s. The binding and hydrolysis of ATP and the release of ADP are linked to the binding and entrapment of polypeptide substrates in the C-terminal half of Hsp70. Some of these agents also inhibit the proliferation of transformed cell lines and the growth of the malaria parasite, which like, cancer cells, requires high levels of diverse Hsp70s for its survival.[211] Additionally, the in silico design of compounds interacting with the Hsp70 peptide recognition site has been reported.[212] These compounds were designed to mimic the trileucine motif of Hsp70 peptides, specifically based on the anchor residue Leu and with built-in water solubility. They have been synthesized by a U-4CR (Scheme 42).

The discovery of a new MCR subsequently also leads to a new class of protein protein interaction antagonists. Thus, the three-component synthesis of diversely substituted and fused amino-pyrrolo-heterocycles by the condensation of activated methylene compounds, aldehydes and isonitriles was recently reported (Scheme 43). This efficient 3CR leads to a diversity of heterocycles in a one-pot fashion and is useful for the synthesis of tens of thousands of discrete compounds.[213] By a high throughput screening approach, 3-alkyl-2-phenethylindolizine-1-carbonitriles (**268**) were found to be potent inhibitors of the protein−protein interaction between vascular endothelial growth factor (VEGF) and neuropilin-1, a process which is believed to be involved in the invasion of tumor cells into human prostate.

The RGD (arginine-glycine-aspartic acid) loop contains peptides that are the molecular attachment points of many cellular and extracellular matrices. Along with the integrins, their receptors constitute a major system for cell adhesion,[214] which is crucial in many pathological processes, such as tumor metastasis, angiogenesis, osteoporosis, and thrombosis. Drug-like RGD mimetic development is challenging due to the receptor imposed zwitterionic requirements for the ligands. Two groups independently reported RGD mimics using Ugi MCRs (**269**−**270**, Scheme 44).[215] Although the molecules display rather large molecular weight and abundant peptide character, these works nicely shows the advantages of MCR

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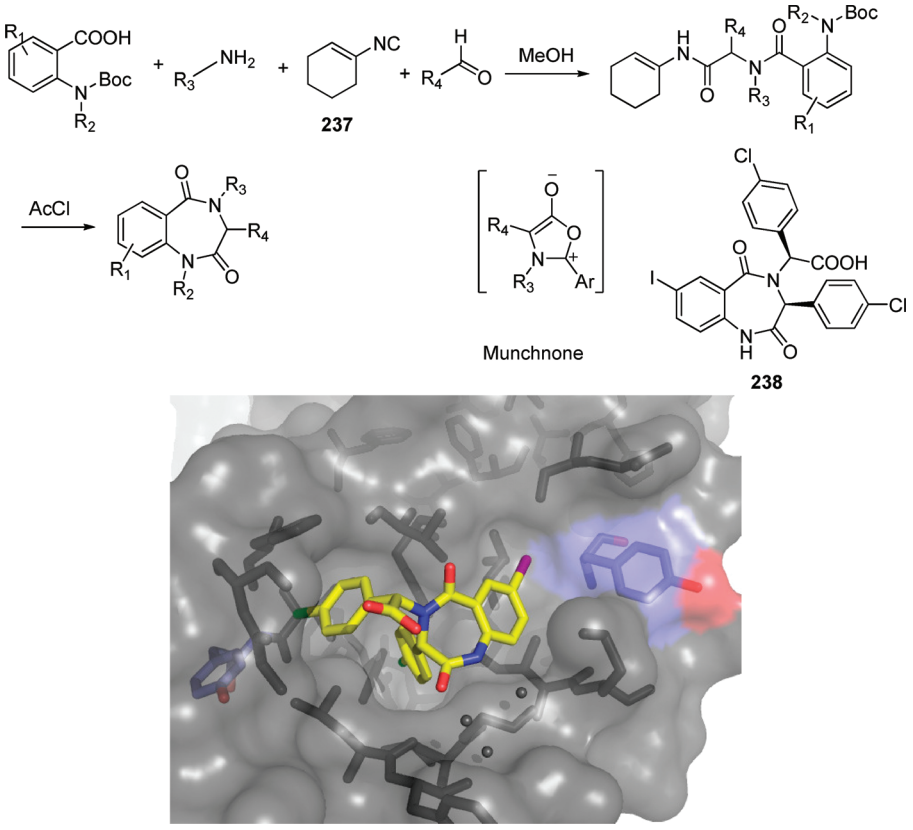
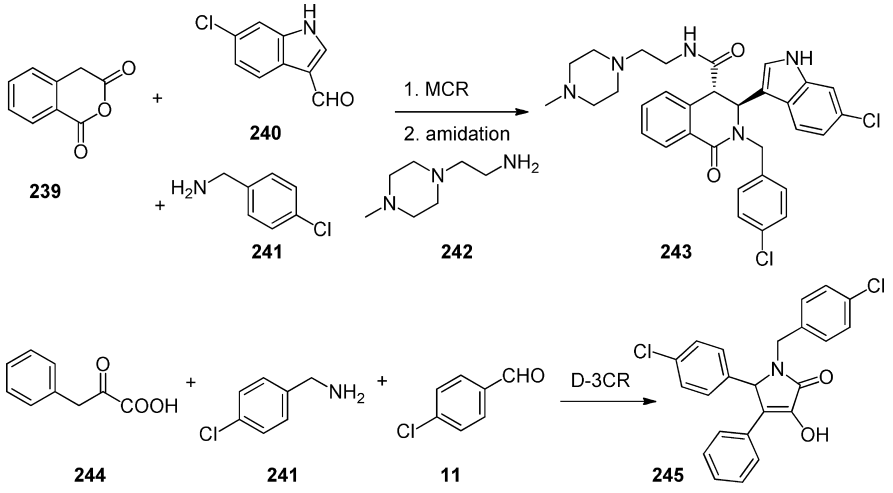


Figure 33. Synthesis and cocrystal structure of potent small molecular weight p53-mdm2 antagonists **238**. The synthesis involves a U-4CR of N-protected anthranilic acid, a primary amine, and aldehyde and the convertible isocyanide cyclohexenylisocyanide, followed by acid deprotection and cyclization via a Münchone intermediate. A highly affine benzodiazepindione derivative **238** bound to mdm2 is shown below (PDB ID 1T4F). The 4-chlorophenyl glycine, the 4-chlorophenyl, and the 7-iodophenyl moieties occupy the Leu26, Trp23,and Phe19 binding pockets in mdm2, respectively.

Scheme 38. MCR Compounds 243 and 245 Antagonizing p53-mdm2



chemistry in providing fast, efficient and convergent access to biologically relevant screening compounds.

Heteroaryldihydropyrimidines have been reported to inhibit Hepatitis B virus replication by drug-induced depletion of nucleocapsids although the exact mechanism-of-action is unknown.[216] Compound **271**, for example possess potent in vitro and in vivo antiviral activity. Such compounds have been synthesized by multicomponent condensation of a suitable amidine, benzaldehyde and acetoacetate by a Biginelli variation.

It is intriguing to note that numerous molecules amenable by MCR chemistry have been described in the past to antagonize PPIs. MCR-derived molecules represent a significant fraction of currently described PPI (ant)agonists and support the notion that MCR space is especially suitable for PPIs. A hypothesis why MCR reaction products are more suitable to (ant)agonize than "traditional" compounds libraries relates to their general higher atom density. Protein protein interfaces contain mostly a very dense array of interactions, including van der Waals,

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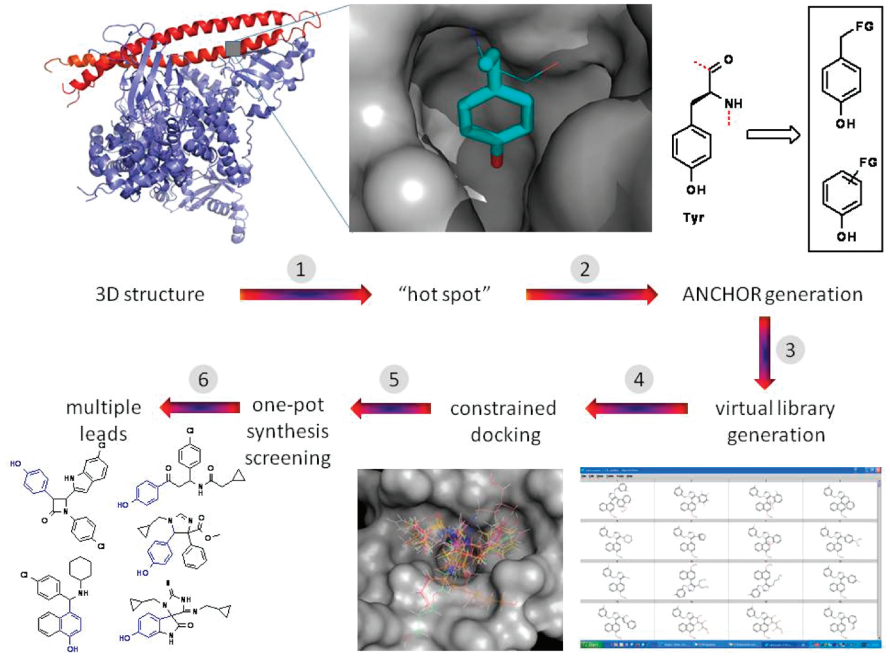
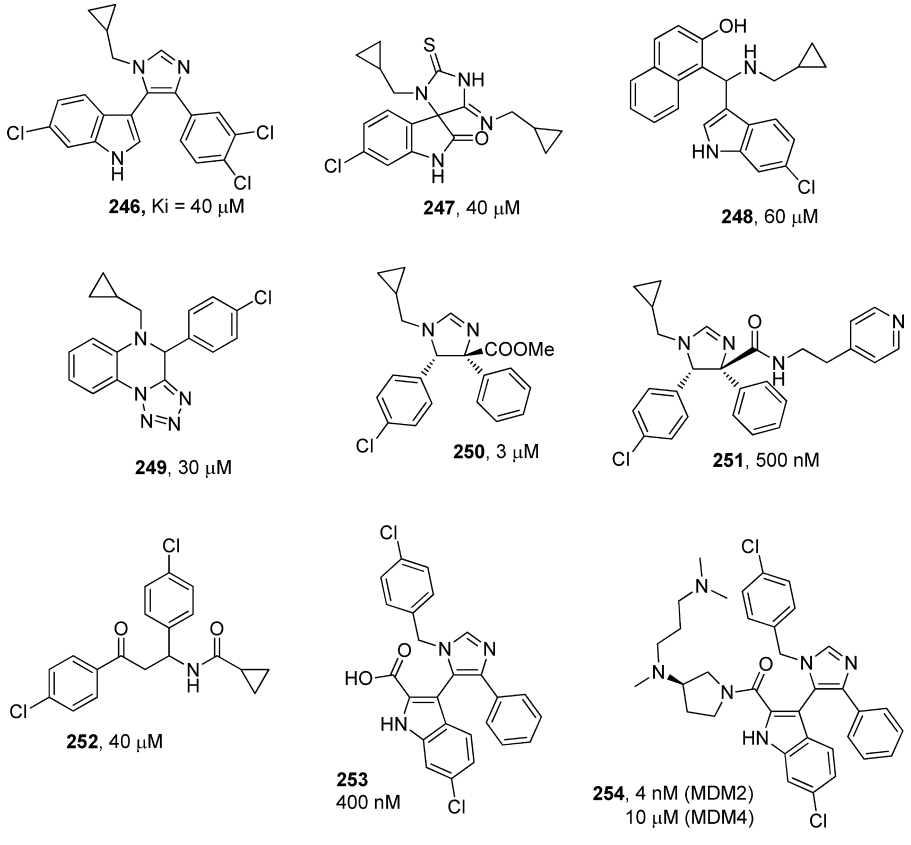


Figure 34. Schematic process of discovery of PPI antagonists, based on structural information, hot spot anchors, and rapid MCR chemistry.

Scheme 39. P53-mdm2 Antagonists (246−254) Accessible by MCR and Predicted by a New Approach, ANCHOR-QUERY



hydrogen bonds and charge charge interactions. A typical small drug-like molecule only allows for rather few interactions to a target structure due to the very much reduced amount of atoms, functional groups and substituents per volume around a given scaffold. MCR scaffolds, however, are known to be much more densely functionalized than other scaffolds. In fact MCR scaffolds have been often described as peptide-mimetics with the advantage, however of much reduced secondary amide bonds and thus more drug likeness.

2.8. Miscellaneous

The proportion of engineered antibodies approved for diagnostics and human therapy has increased significantly

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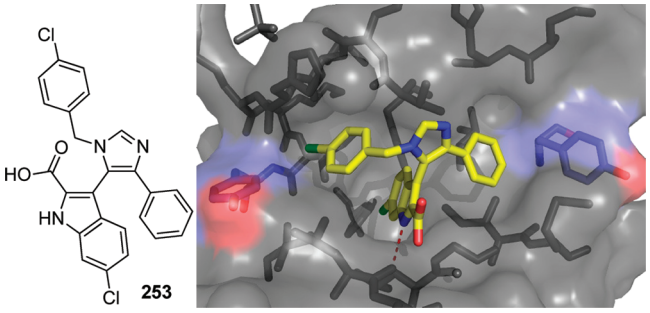


Figure 35. Interaction of vL-indoloimidazole **254** with the p53 binding islet of the mdm2 receptor (PDB ID 3LBK). The anchor residue chloro-indole occupies the Trp23 binding site, whereas the 4-chlorobenzyl mimics the Leu26 and the phenyl moiety the Phe19 site. Notably, the indole forms a nice hydrogen bridge to Leu54 backbone carbonyl of the mdm2 receptor similar to the $Trp23^{p53}$ mdm2 interaction.

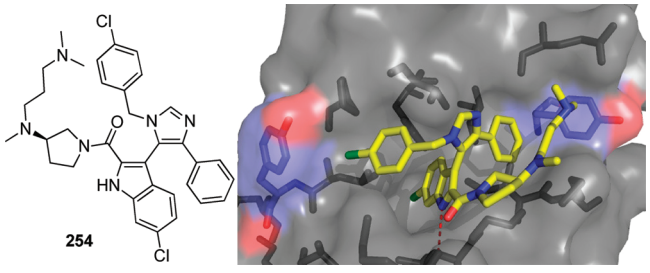
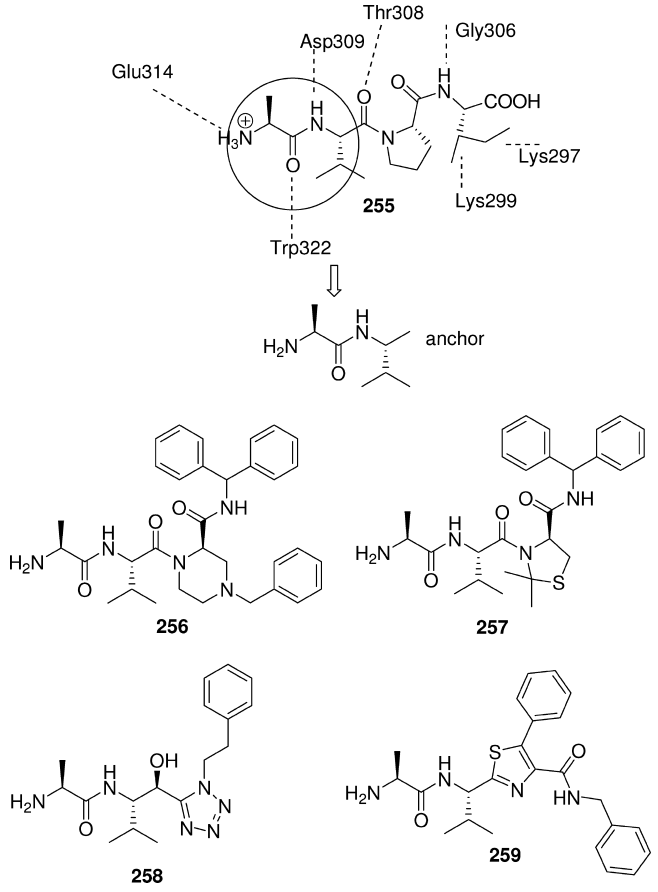


Figure 36. Interaction of vL-indoloimidazole **254** with the p53 binding site of the mdm4 receptor (PDB ID 3LBJ). The anchor residue chloro-indole occupies the Trp23 binding site, whereas the 4-chlorobenzyl mimics the Leu26 and the phenyl moiety the Phe19 site. Notable, the indole forms a nice hydrogen bridge to Leu54 backbone carbonyl of the mdm2 receptor similar to the $Trp23^{p53}$ mdm2 interaction.

during the past decade. At present, 17 human therapeutic monoclonal antibodies (mAbs) are on the market; additionally multiple other mAbs are currently undergoing final clinical trials and they are representing nearly a quarter of all biologics undergoing trials.[217] To date, six Fab molecules have been also approved by the FDA for human use. These monovalent immunoglobulin fragments provide therapeutic alternatives to their parental relatives, by retaining their antigenic specificity, while being produced more economically. Such Fabs have to be large scale produced and purified using affinity chromatography. A novel use of the U-4CR to generate a solid-phase library suitable for the purification of immunoglobulins and their fragments by affinity chromatography has been reported.[218] An optimized candidate for production purposes was obtained and also docked into a human Fab fragment to rationalize the binding interaction (Figure 37). The Ugi scaffold offers an alternative route to the well-defined triazine chemistry for generating synthetic ligands. The final ligand **272** clearly suggests the potential of the Ugi scaffold in the development of potent ligands. Because of its synthetic nature, compound **272** is expected to be inexpensive to produce.

The farnesoid X receptor (FXR), is a nuclear hormone receptor with activity similar to that seen in other steroid receptors such as estrogen or progesterone. FXR is expressed at high levels in the liver and intestine. FXR modulators are believed to be useful for the treatment of increased lipid and cholesterol levels. A recently disclosed FXR modulator is composed of a highly substituted benzimidazole **276** which can

Scheme 40. Top: Pharmacophore of XIAP Antagonists. The N-Terminus Is Very Important in Forming a Tight Charge Charge Interaction with Glu314. In Addition to the Tight Network of Hydrogen Bonds Addressing the Hydrophobic Pockets, the Central Heterocycle with cis-Geometry Is of Importance for Inhibitor Design. Bottom: Several MCR Scaffolds with Micromolar XIAP Activity and Accessible by a Rather Short Synthesis Sequence



be accessed by UDC (Scheme 45).[220] Compound **276**, for example shows an affinity for FXR of 13 nM.

MCR have been frequently described for the synthesis of bioactive compounds to treat neglected tropical diseases (NTDs). Drug discovery for NTD is not a high priority for pharma companies due to the financially unattractive market and the prohibiting high costs of development.[221] This application seems to be perfectly suited for MCRs since the costs of the early discovery chemistry and the cost-of-goods (COG) of the drug production are potentially very low. Praziquantel, for example, is a member of the 12 drugs comprising the WHO list of essential medicines.[222] It is used to treat the parasitical disease schistosomiasis also called bilharziose. Schistosomiasis is one of the largest burden of mankind affecting more than 200 million people worldwide.[223] Importantly, there is evidence for a strong correlation between schistosomiasis and HIV infection in Africa. Thus, the urinary form of schistosomiasis, which affects up to 50% of women in parts of Africa, damages the lining of the vagina, the first defensive barrier against HIV. An affordable $0.32 (US) solution per treatment for preventing HIV/AIDS has thus been recently proposed based on the highly effective and low-cost antischistosomal drug praziquantel (PZQ).[224] The

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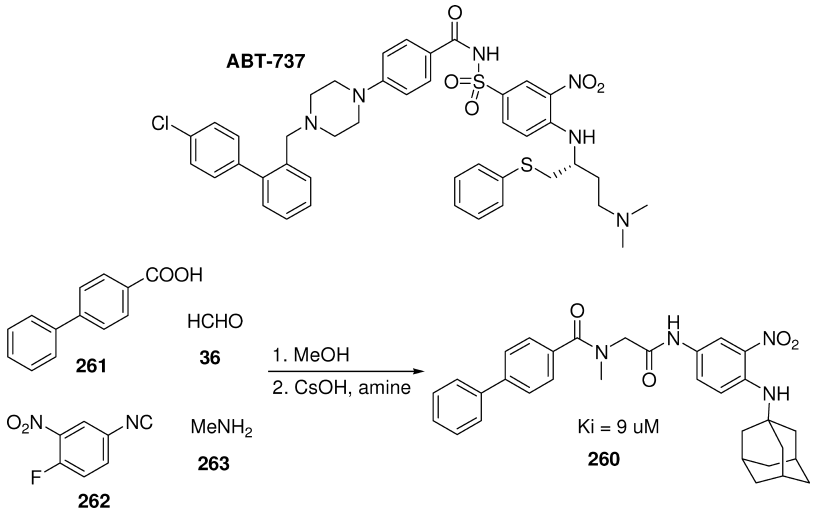
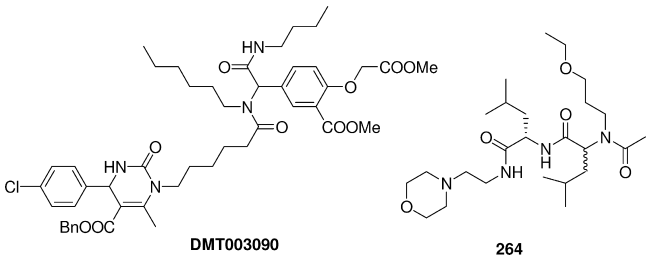
Scheme 41. Antagonists of Antiapoptotic Bcl2



Scheme 42. HSP-70 Inhibitors by MCR



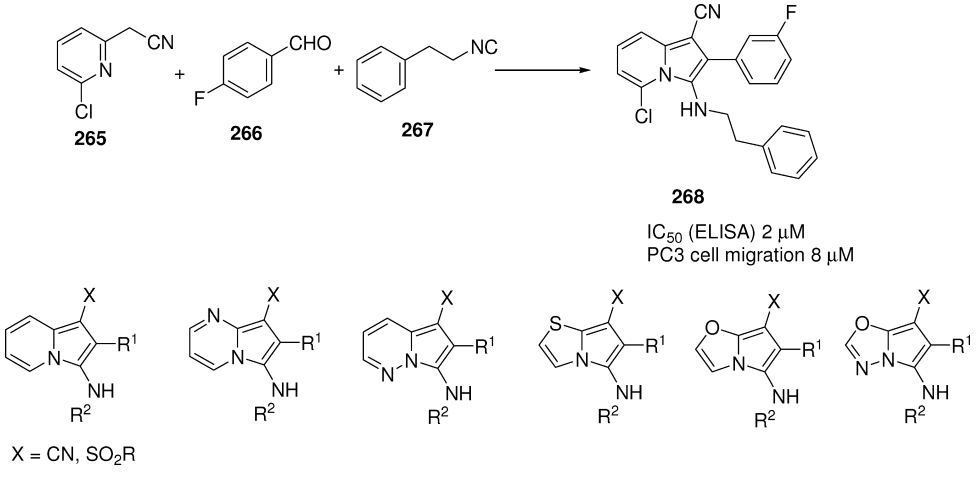
tetrahydroisoquinoline derivative PZQ is the major drug to treat this disease due to its advantageous properties, including efficiency, safety and low cost-of-goods to potentially reach a very large number of infected patients.[225] Current technical syntheses involve sequential 5−7 step sequences. Recently, a considerably shorter and scalable synthesis including an Ugi and subsequent Pictet−Spengler approach has been described, which has the potential to further reduce the COG of this life saving essential drug.[226] COG is a key factor for the development of drugs neglected tropical diseases. Moreover this approach allows for the synthesis of many analogs based on the central MCR chemistry to overcome potentially upcoming occurrence of resistance.[227]

MCR reactions have been described several times to discover novel agents to treat malaria.[228] For example, 4-aminoquinoline 2-imidazolines have been recently described to be active against the malaria parasites against two strains of *Plasmodium falciparum* and *Trypanosoma brucei*.[228] Compound **280** was the most active across all parasites with ED_{50} = 3.3 nM against a chloroquine sensitive strain, ED_{50} = 33 nM against a chloroquine-resistant strain and ED_{50} = 70 nM against *T. brucei* and can be synthesized by the Orru-3-CR.

Aryloxy cyclohexyl imidazoles (**281**), which can be beneficially synthesized by a key α-aminoalkylation of cyclohexanone, 2 equivalents of formaldehyde and pyrrolidine, and subsequent transformations have been described as a novel class of antileishmanial agents (Scheme 47).[229] These compounds are superior than the existing drugs, sodium stibogluconate and pentamidine in respect to IC_{50} and SI values. Promising compounds were tested further in vivo. Among all, compound **281** exhibited significant in vivo inhibition of 79%, thus providing new structural lead for leishmaniasis.

Novel nucleoside analogues, for example, compound **282** based on the approved antiviral drug Cidofovir have been synthesized as potential antiviral and antileishmanial agents via different variations of the Ugi MCR. Several synthetic products showed antileishmanial activity in the 10^{-5} M range.[230]

Scheme 43. New MCR Lead to a New Class of VEGF Receptor Antagonists



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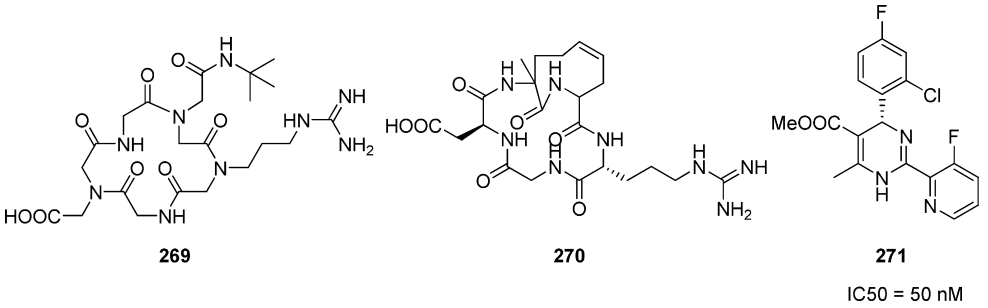
Scheme 44. Peptide-like RGD Mimetics 269 and 270 and a Viral Capsid Assembly Inhibitor 271 by MCRs



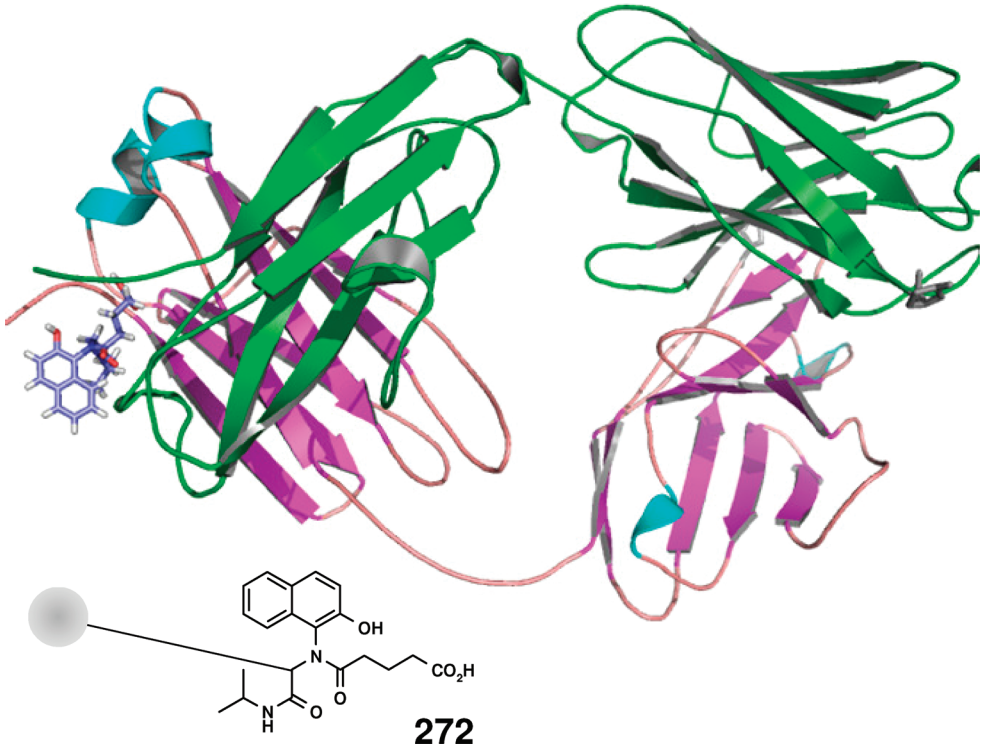
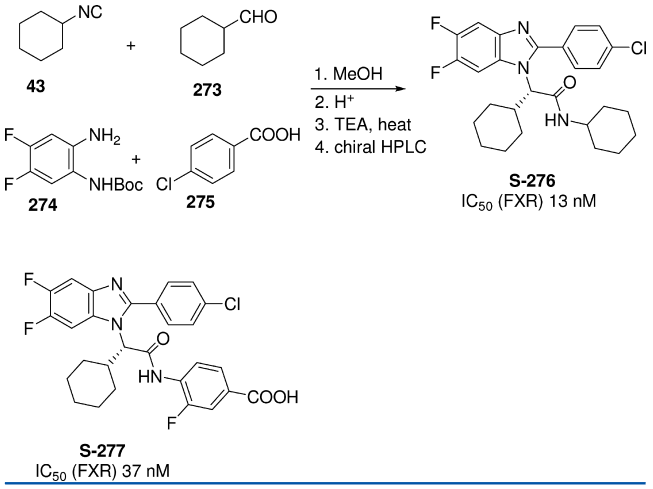


Figure 37. Sepharose solid-support-bond Ugi products (**272**) for the affinity purification of therapeutic Fab fragments. Docking of the best Ugi ligand (blue sticks) into human Fab fragment (PDB ID 1AQK).[219]

Scheme 45. FXR Nuclear Hormone Receptor Modulator by UDC



Glutamine synthetase is required by *M. tuberculosis* for nitrogen metabolism and mycobacterial cell-wall biosynthesis and has emerged as a potential target for antibiotics against TB. Functionalized 3-amino-imidazo[1,2-a]pyridines – products of the GBB-3CR have been discovered as a novel class of drug-like *Mycobacterium tuberculosis* glutamine synthetase inhibitors with impressive activity. Compound **283**, for example, is much more active than the so far known inhibitors L-methionine-SR-sulfoximine and phosphinothricin.[231]

New infectious diseases appear regularly in diverse parts of the globe, most recently swine flu, creating new global health threats. The upcoming of new multiple drug resistance and highly infectious and deadly influenza is of great concern. Current weaponry to fight influenza can only build on a handful of chemotherapeutic options besides immunization. The anti-influenza neuraminidase inhibitor (−)-oseltamivir is one of them and has been synthesized by a remarkably short and high-yielding asymmetric synthesis taking advantage of a one-pot MCR involving an asymmetric Michael addition of aldehyde **284** to nitro compound **286** subsequent second Michael addition/intramolecular Horner–Wardsworth–Emmons reaction with vinylphosphonate **285**.[232] Subsequent treatment with *p*-toluenethiol **287** afforded the heavily functionalized

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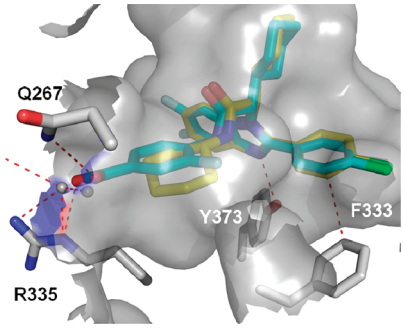
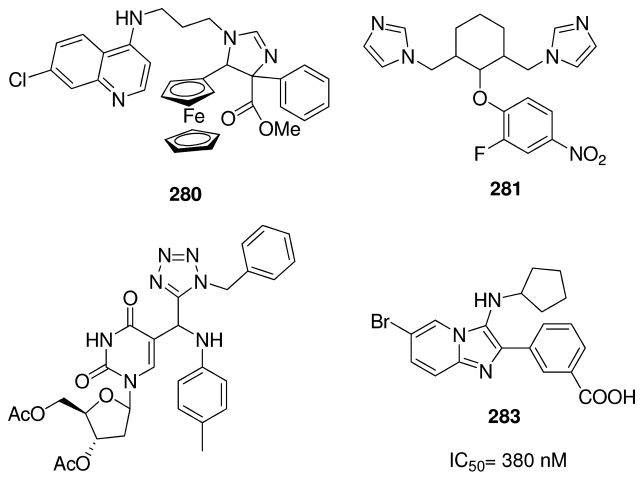


Figure 38. Alignment of the cocrystal structures of **S-276** (yellow sticks) and optimized **S-278** (marine sticks) to hFXR (PDB ID 3OKI, 3OMM). The FXR binding site of 3OKI is shown as gray surface and selected amino acids as sticks. The inhibitors are encapsulated almost fully into the receptor. The highly conserved Tyr373 is making a hydrogen bridge to the scaffold benzimidazole-3N and is key to the efficient ligand binding (red dotted line). π-Stacking can be seen between Phe333 and the carboxylic acid derived p-chlorophenol. Ser336 (not shown for clarity) is engaged into hydrogen binding to the amide-NH resulting from the isocyano component. Additionally, in the hydrophilicity-optimized structure **277** a *p*-carboxyphenyl moiety at the mouth of the binding site mimics two tight waters (gray balls), forming an extensive hydrogen bond network with Arg335 and Gln267. The *o*-fluoro substituent of the isocyanide derived phenyl of **277** is accommodated in a hydrophobic bulb formed by the two Met332 and 294 (not shown for clarity) forming short hydrophobic contacts.

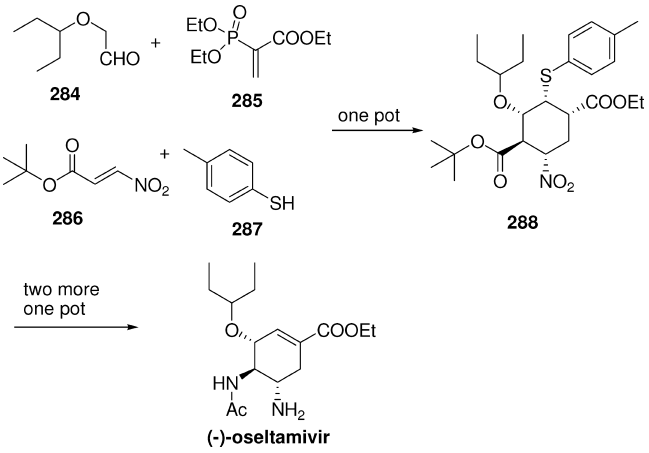
ethylcyclohexanecarboxylate **288** in good yield (70%) in a single-pot operation (Scheme 48). This work represents a landmark of efficiency in organic synthesis: In only nine reactions, a total of three separate one-pot operations, and one purification by column chromatography the drug is stereoselectively amenable in overall excellent yields (from nitroalkene 57%). All the reagents are inexpensive, and the synthesis compares very favorably with the current technical synthesis.[233]

Of considerable interest is the anticancer activity described for BG-3CR products binding to the emerging cancer target kinesin motor spindle protein. A potent inhibitor, monastrol, which was synthesized from ethyl 3-oxobutanoate (**195**), thiourea (**289**), and 3-hydroxybenzaldehydehas (**290**), has been first discovered by a phenotypical cell-based screening (Figure 39).[234] Several high resolution X-ray structures have been reported and the role of the BG-scaffold in their binding can be studied.[235] Another cocrystallized MCR derived molecule with atomic resolution is the Gewald thiophene **291**.[236] Recent evidence supports a mechanism by which monastrol and similar compound weaken the interaction of the motor kinesin Eg5 and the microtubule by an allosteric mechanism.[235,237] Both molecules bind into a deep hydrophobic allosteric pocket, however establishing different molecular interactions.

Scheme 47. MCR Compounds for NTDs

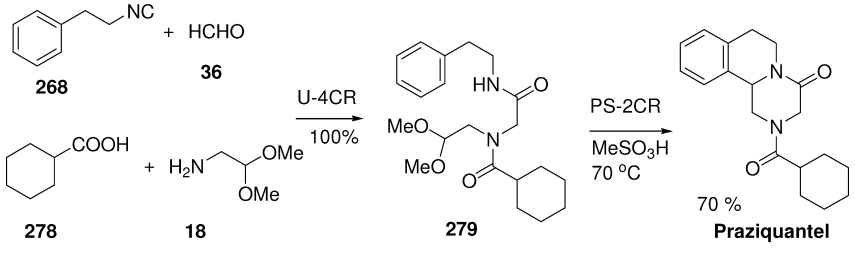


Scheme 48. Enantioselective and Short Oseltamivir Synthesis



Crystal structure of the motor protein KSP in complex with monastrol (Figure 39 above: yellow sticks, PDB ID: 1Q0B) and the Gewald thiophene (Figure 39 below; PDB ID: 2UYM). The thiourea and 3-hydroxy benzaldehyde portion of the Biginelli backbone is buried deeply in an induced-fit binding site some 12 Å apart from the ATP binding site. The phenolic hydroxyl group forms a hydrogen bond to the backbone carbonyl of Glu118 and to Arg119. The thiourea sulfur undergoes extensive van der Waals contacts to aliphatic amino acids. Note the planar structure of the Biginelli backbone and the orthogonal exit of the phenol

Scheme 46. Schistosomiasis Drug PZQ Can Be Convergently Assembled Using a Key U-4CR and PS-2CR



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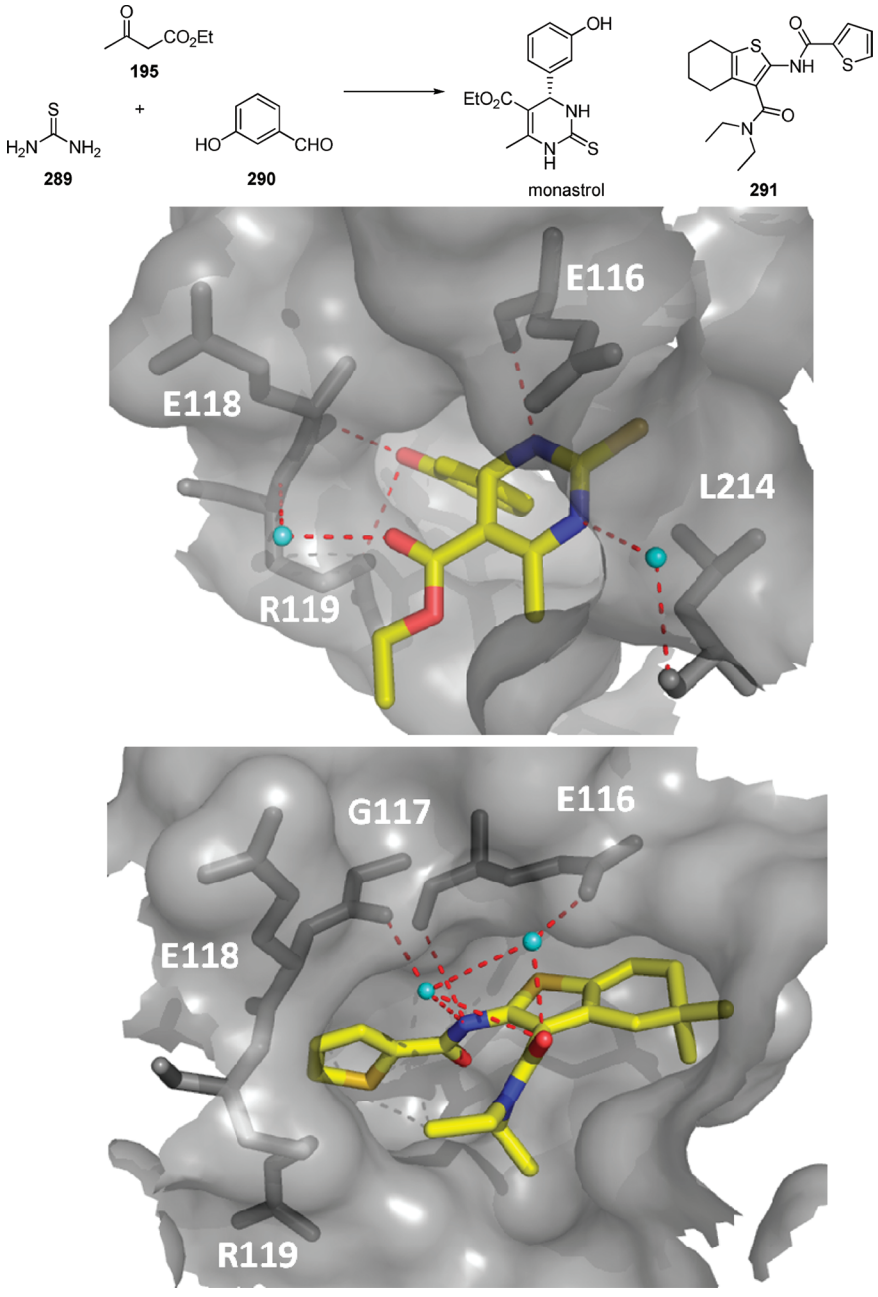

Figure 39. Synthesis of Biginelli product monastrol and a Gewald thiophene **291**.

substituent. The Gewald backbone, does not make any direct hydrogen bond contacts to the protein, however they are mediated by two water molecules (aquamarine ball). The carbonyl component and the cyanoacetamide component side chain of the Gewald product form strong van der Waals interactions with excellent shape complementarity to the binding pocket. In both X-ray structures tightly bound water play a prominent role.

A product (**295**) of the Povarov-3CR from benzaldehyde (**176**), aniline (**292**), and electron-rich olefin (**293**) were found to be a kinesin-5 inhibitor (Figure 40).[238] The compound showed promising potency in an in vivo xenograft model of colo 205 cells and is currently undergoing early investigation in clinical cancer trials.

Coenzyme A is a ubiquitous cofactor in many different enzymes. Many of these are involved in pathogenic processes. Malonyl-CoA transferase (FabD), for example is an essential enzyme involved in the assembly of fatty acids. Because of the considerable difference of the human enzyme form, the bacterial one FabD consists an antibacterial target.[239] An approach to inhibit FabD could be for example by modified CoA derivatives. Recently, glutathione, and homoglutathione derivatives (**296** and **297**) were synthesized by the Ugi four-component reaction using various benzylthio aldehydes and ketones as carbonyl building blocks (Scheme 49).[240]

FTY720 is a clinically investigated immunosuppressive, and it also shows very promising clinical results in multiple sclerosis treatment. This fungal natural product myriocin-derived agent seems to work on lymphocyte trafficking by antagonizing the sphingosine-1-phosphate after being phosphorylated by sphingosine kinase. A short two-step synthesis using the Petasis reaction (Pt-3CR, a boronic acid Mannich reaction variation) of dihydroxyacetone **298**, benzylamine **25**, and vinylboronic acid **299** was reported (Scheme 50).[241]

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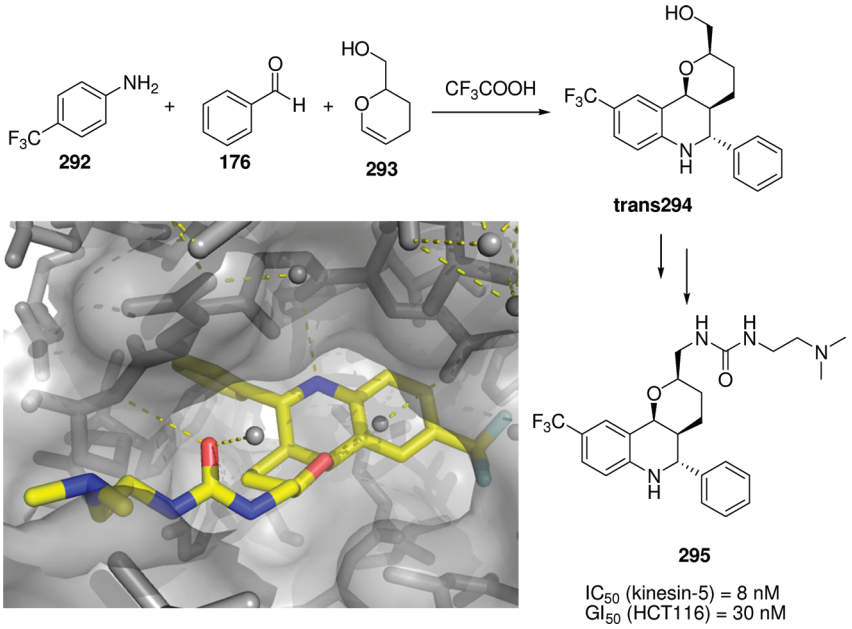
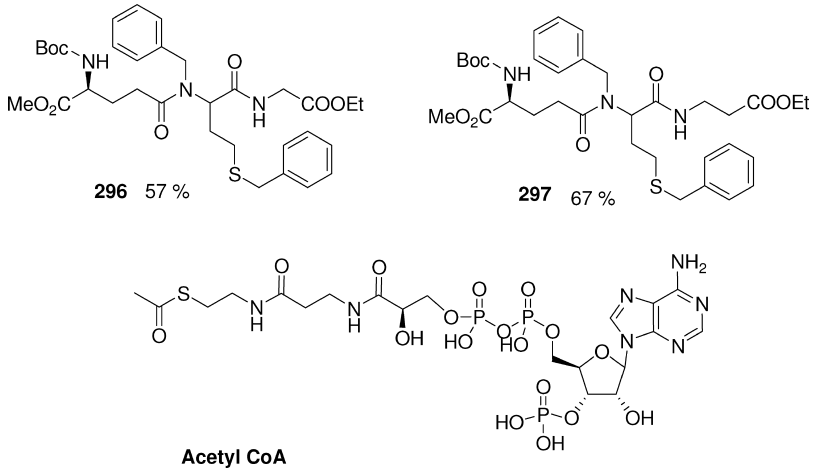
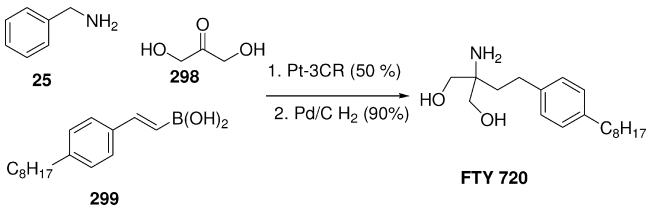


Figure 40. Cocrystal structure of **295** with kinesin-5. The dilemma of target-required hydrophobicity and inherent bad water solubility, poor PK properties, and metabolic instability was solved by adding the solubilizing dimethylaminoethylamine urea moiety onto the water space exiting tetrahydropyrane ring. The tetrahydroquinoline NH is involved into a hydrogen bond to backbone carbonyl Glu116 as is the urea carbonyl forming a hydrogen bond to a water molecule and backbone carbonyl Arg119.

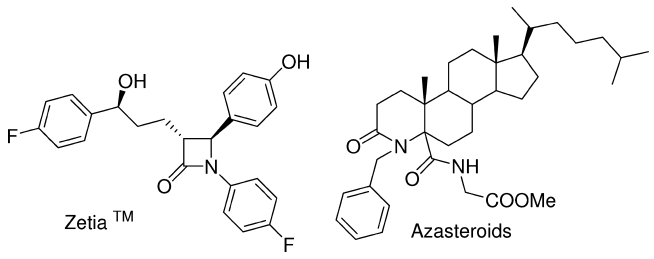
Scheme 49. (Homo) Glutathione Derivatives by U-4CR and the Structure of Acetyl CoA



Scheme 50. Immunosuppressive and Anti-MS Drug FTY720 Synthesized by Petasis-3CR



Scheme 51. Staudinger-3CR Product Zetia and a Bioactive Aza-Steroid



Another recently approved compound the cholesterol absorption inhibitor Zetia (ezetimibe) is produced by a Staudinger-3CR (Scheme 51).[242] During the Staudinger reaction a methylene active acylchloride (ketene precursor) reacts with a Schiff base formed by aldehyde and amine, likely in a stepwise cycloaddition process.[243] Although the reaction cannot be performed by the simultaneous addition of all starting materials at once, a convenient one pot protocol exists.[244]

Steroids are ubiquitous often highly potent hormones involved in most aspects of health and disease. Historically, steroids have played an extraordinary role in the collection of

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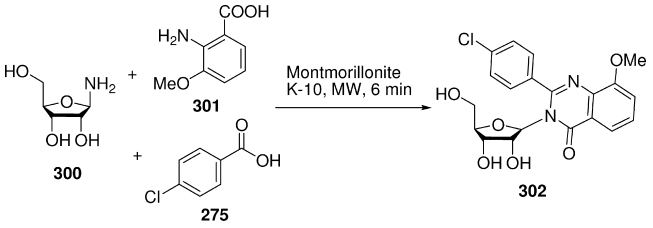
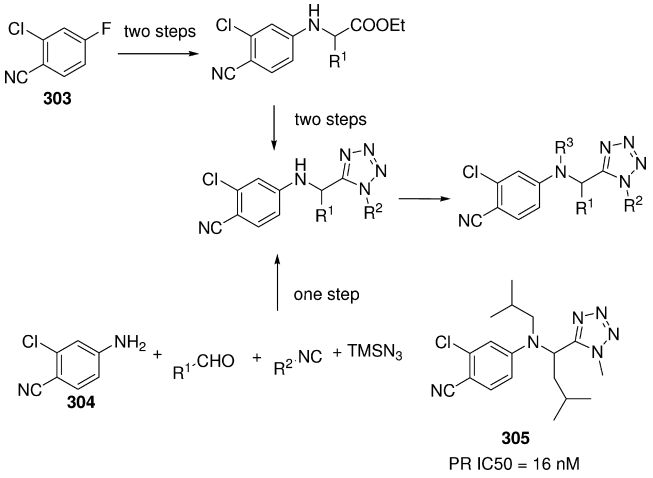
Scheme 52. Antiviral Quinazolinone N-Nucleoside (302)



Scheme 53. Classical Synthesis of a Progesterone Receptor Agonist and a Corresponding MCR Synthesis



drug and still many steroids are used in different therapeutic areas. Azasteroids can be easily synthesized in high diversity and numbers using MCR (Scheme 51).[245]

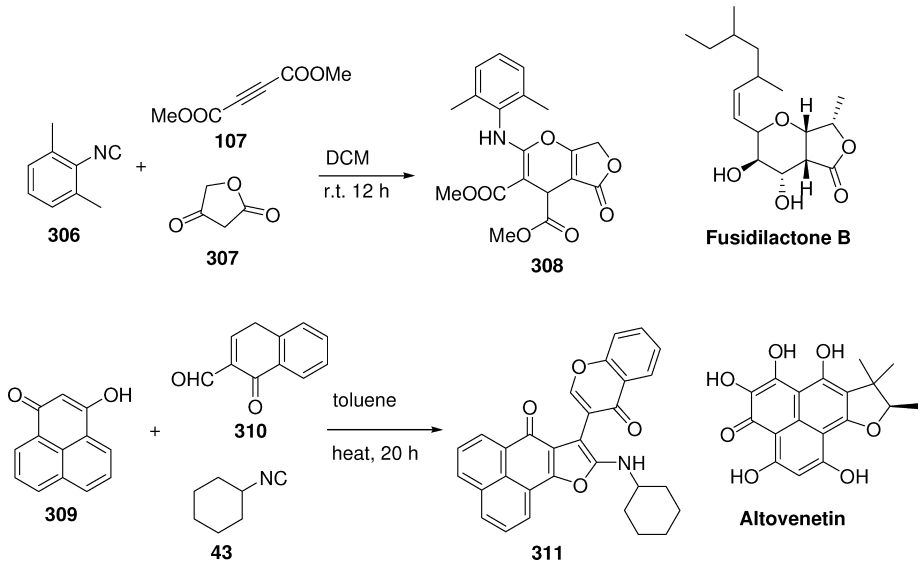
Potentially antiviral 4-(3*H*)-quinazolinone *N*-nucleosides (**302**) have been elegantly assembled by the MCR of anthranilic acid, ribosylamine and a substituted/unsubstituted benzoic acid in a one-pot reaction under MW irradiation and solvent-free conditions (Scheme 52).[246]

The progesterone receptor (PR), is an intracellular steroid nuclear receptor that specifically binds progesterone. α-Amino-tetrazoles amenable by U-4CR have been recently disclosed as potent and selective partial agonists and have potential as a new treatment for endometriosis.[247] Compound **305**, for example, optimized for potency, selectivity and P450 inhibition, has excellent oral half-life time and is suitable for in vivo pharmacology studies (Scheme 53).

A 3-CR of an isocyanide, a dialkyl acetylenedicarboxylate, and tetronic acid in dichloromethane at room temperature afforded 4*H*-furo[3,4-b]pyran derivatives (**308**).[248] These compounds are structurally closely related with some natural products, for example, TAN-2483B and fusidilactones with several reported biological activities, including strong c-src kinase inhibitory action, in vivo bone protection and a broad spectrum of activity against cultured tumor cell lines, including adriamycin-resistant HL-60 cells. A related MCR of alkyl isocyanides various aldehydes and 3-hydroxy-1*H*-phenalene-1-one yields 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-one (**311**) derivatives, which are reminiscent to the furophenalenone scaffold of many natural products, such as atrovenetin with multiple described biological activities (Scheme 54).[249] Combinatorial applications were described and scope and limitations were reported.

Discovery and development of plant protecting and other agrochemical materials also seems to be an important application of MCR chemistry, since the COG of the active ingredient is a key parameter in this area. A successful case of the application of MCR for the generation of valuable bioactive compounds is the recent market approval of mandipropamide a plant protecting agent discovered and made by isocyanide based MCRs including Passerini and Ugi reactions.[250] Noteworthy, in this elegant synthetic scheme is the one-pot isocyanide formation/$TiCl_4$-mediated Passerini reaction from the formamide precursor **312** without isolation of the isocyanide. The intermediate Passerini product **313** is then alkylated by propargylbromide to yield the marketed product (Figure 41). The compound is highly active against a variety of economically important plant pathogens leading to crop destruction of potato, tomato late, and grape. Thus, the effective concentration to kill 80% of the pathogen *Phytophthora infestans* (grape downy mildew) is only 100 μg/l (EC_{80}).

Scheme 54. MCRs Leading into Natural-Product-like Furopyrans



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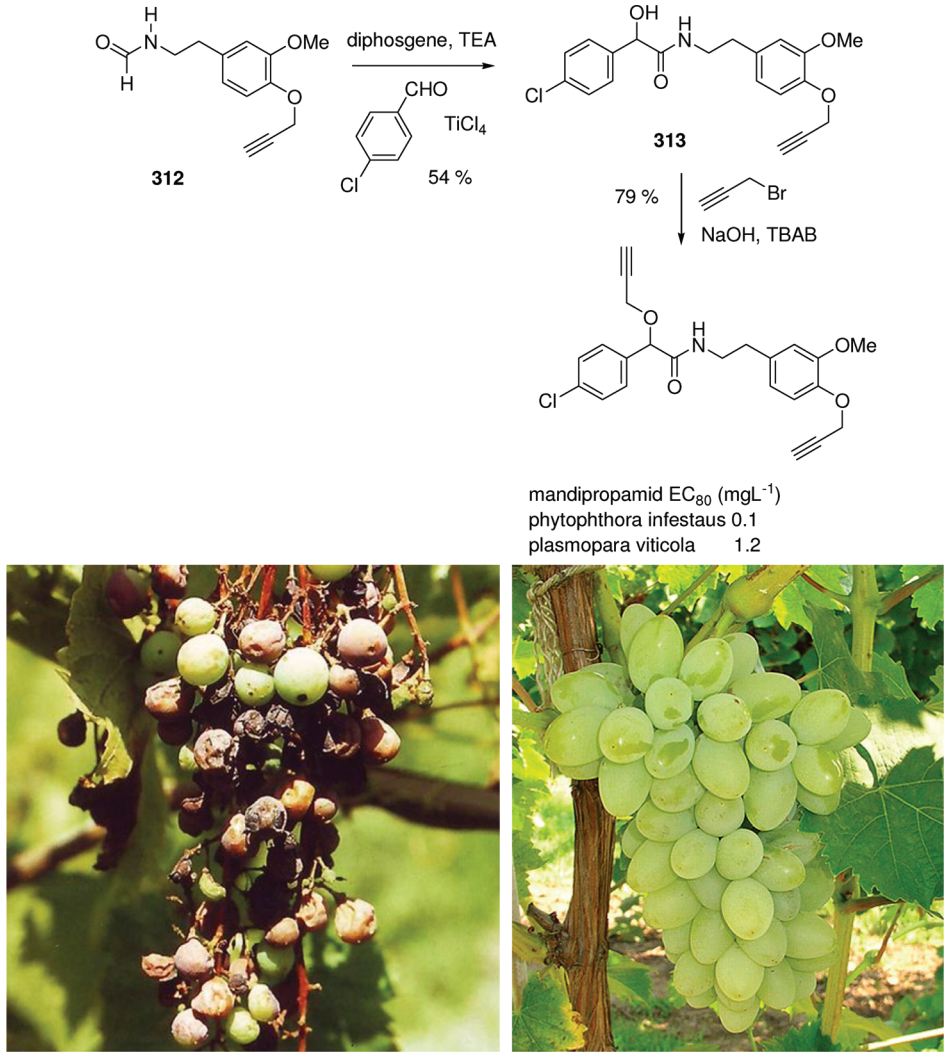
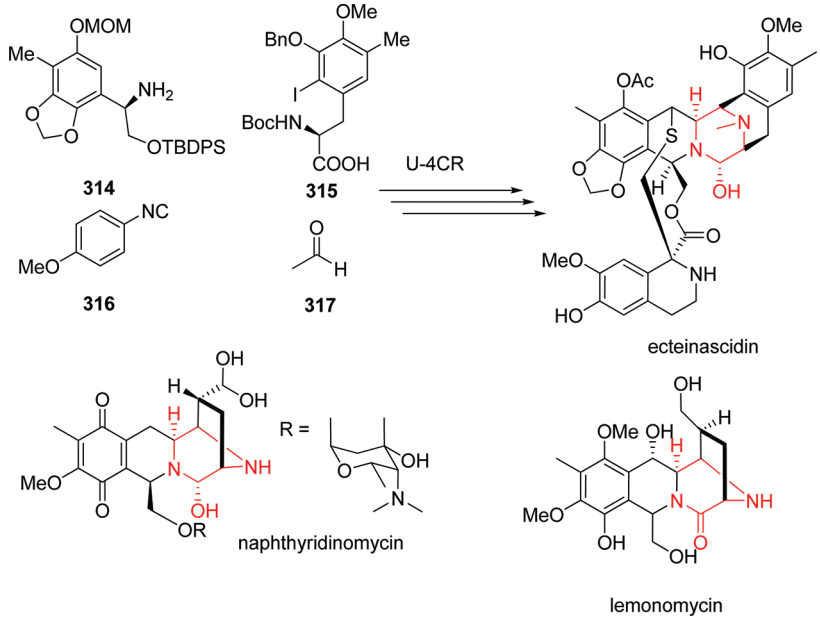


Figure 41. Marketed mandipropamide as an agrochemical application of MCRs. It is used to protect wine grapes from fungal infections. Bottom: Infected and healthy grapes (*Phytophthora infestans*).

Scheme 55. Napthyridinomycin, Lemonomycin, and Ecteinascidin's Piperazine Moiety All Have Been Assembled Using One-Pot U-4CR



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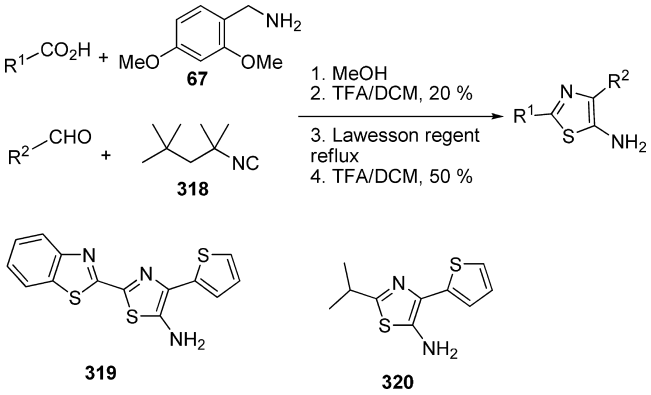
Another agrochemical application of MCR is the short synthesis of novel avermectin derivatives as insecticital agents through the diastereoselective Ugi reaction to an phenylsulfinimide intermediate.[251] Fipronil is a new fluorinated pyrazole with high insecticide activity and derivatives thereof have been synthesized by the Mannich reaction of hydrazones coupled with a [4 + 1] cycloaddition with isocyanides.[252]

Key diketopiperazine moieties in the DNA targeting anticancer natural products naphthyridinomycin, lemonomycin and the clinical liposarcoma compound ecteinascidin have been assembled using Ugi-MCRs as key steps (Scheme 55).[253]

The recent discovery of 2,4-diphenylthiazolyl-5-amides **319** and **320** as antiprion agents lead to a straightforward and general access toward this scaffold class involving a short sequence of U-4CR involving ammonia equivalent and the acid cleavable Walborsky reagent **318**, followed by acid amine deprotection and thiazole formation and finally acidic amide deprotection.[254] The substituents introduced at the 2- and 4-positions are derived from simple and widely variable building blocks, carboxylic acids and aldehydes respectively. Though yields are modest, the route offers access to a large number of diverse new compounds, based around this pharmaceutically relevant substructure, which would otherwise be considerably more difficult to prepare by alternative routes.

Scheme 56. Versatile Assembly of 5-Aminothiazoles (319 and 320) Based on the U-4CR Leading to Antiprion-Active Compounds

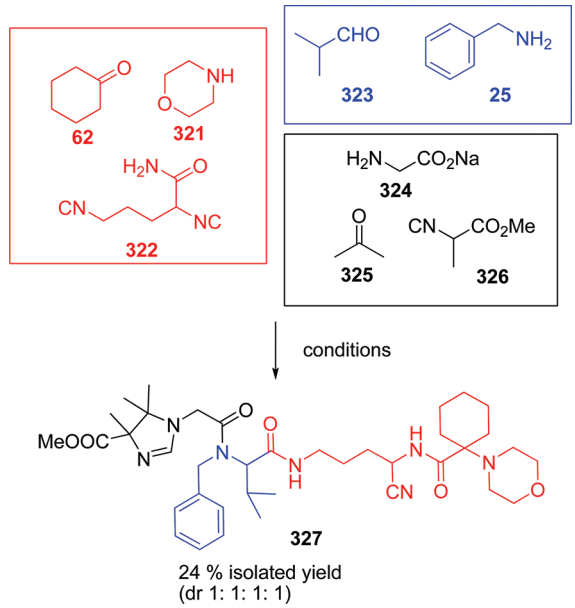


4. SUMMARY AND OUTLOOK

MCRs are a useful class of reactions for the never-ending hunt for biologically active compounds and complementarily add into the large arsenal of tool boxes available to the modern chemist. How do MCR derived molecules differ from the others? One distinguishing feature is the densely functionalization of MCR derived molecules. Because several ligands are introduced around a common scaffold, typically the ligand density as well as the number of functional groups can be very high. On the basis of the densely functionalized scaffolds and their often nonflat, sometimes spirocyclic nature the 3D shape of MCR derived molecules is different from the rest. An ever-increasing body of data suggests that in fact MCR derived molecules might be more suitable for certain drug discovery areas than other type of molecules. Thus, the high number of MCR derived molecules in the area of protein protein interactions is striking. An advantage of MCR chemistry is the very large chemical space, probably the largest available chemical space for discovery and medicinal chemistry purposes. This also poses very high demands for the right choice of the discovery strategy, for example, high throughput screening or structure-based design. Clear financial and technical limits are given for the screenable library size in traditional HTS.[225] A promising and complementary strategy which leverages the strength of MCR chemistry is the use computation screening and e.g. genetic algorithms.

Twenty years ago MCR chemistry was broadly unrecognized and only considered of use for the synthesis of specific classes of compounds. Only recently its broad applicability and values were recognized by the synthetic community, including the short and highly efficient synthetic access to a plethora of scaffold with very large numbers of compounds per scaffold. Access to many different types of pharmacophores exemplified in different MCRs backbones turned out to be of particular value for the discovery of bioactive compounds. Additionally, many MCR can be performed in an enantioselective manner. Often MCR chemistry suites well the discovery phase and later on the production of the candidate use different chemistry. In other cases, however, MCR chemistry can be advantageously used during discovery chemistry as well as in the production phases. Different large scale technical productions of advanced compounds have been described using MCR. The growing number of compounds on the market and in clinical evaluation discovered and synthesized by MCR technologies manifests their growing importance. Whereas in the past we witnessed only few examples of MCRs in natural product total synthesis, the efficiency and convergence of these reactions will certainly become of great value in future natural product synthesis. A final aspect of MCR chemistry should not be kept secret: MCR chemistry is intellectually stimulating and can be very aesthetic (Scheme 57).[255] MCR chemistry and biology certainly has a bright future!

Scheme 57. Who Can Solve the Jigsaw? One-Pot 8-CR to Compound 327 Based on Three Sequential MCRs with an 85% Yield Per Bond Formation



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Author Contributions

K.W. and W.W. contributed equally to this manuscript.

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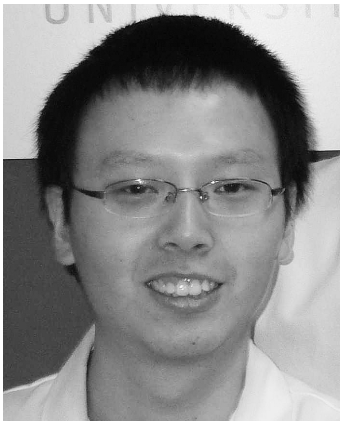
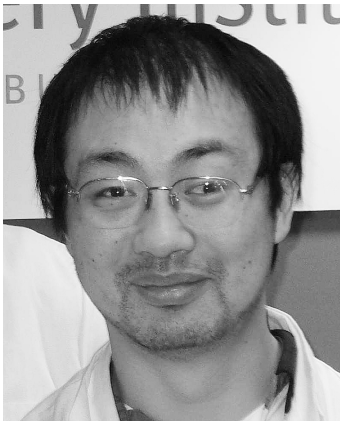
Biographies

Alexander Dömling (born 1964) studied Chemistry & Biology at the Technical University Munich (TUM). He performed his PhD under the surveillance of the late Ivar Ugi working on the "Seven Component Reaction". As a Feodor Lynen Fellow of the Alexander von Humboldt foundation he performed his postdoc in the laboratory of the Nobel laureate Barry Sharpless working on novel multicomponent reactions (MCRs) of hydrazines, epoxides, and carboxylic acid derivatives. In 1996, he started the biotech company Morphochem and served as vice president chemistry and board member until 2004. During this time several drug candidates have been discovered at Morphochem and are currently in late preclinical or clinical trials. In 2003, he performed the Habilitation at the TUM and received the "Lehrerlaubniss in Chemie". Since 2004 he is faculty member at the TUM. In 2006, he accepted an professor position in the School of Pharmacy (Drug Discovery Institute) at the University of Pittsburgh with secondary appointments in the department of chemistry and computational and systems biology. Recently he accepted a position as chair for drug design at the University of Groningen, The Netherlands. His research interest are centred around MCRs, including new MCR, stereoselective MCRs, chemoinformatic of MCRs and its applications to medicinal and combinatorial chemistry. Specifically, he is interested in the rational design protein protein interactions (ant)agonists, protease inhibitors and drugs for neglected tropical diseases (NTD). His therapeutic interests include cancer, NTD, COPD, diabetes, and infectious diseases. He is offering his expertise in MCR chemistry to pharma and agro companies and to Universities by performing in-house short courses.



Wei Wang was born in Hubei, China in 1980. He obtained his B.S. in chemistry from Wuhan University in 2000. He completed his Ph. D. thesis under guidance of Prof. Yuanyin Chen and Prof. Shuling Gong in Wuhan University in 2005. He moved to the U.S.A. and took a researcher position to study the carbene and super base catalyst under Prof Yong Gao, at Southern Illinois University after one year as synthetic chemist at a pharmaceutical company in Shanghai. In 2008, he joined the Dömling laboratory at the University of Pittsburgh. Recently he accepted a position as associate professor in school of pharmaceutical sciences in Wuhan University, China. His synthetic research currently targets the p53-HDM2/HDMX system and combinational and parallel synthesis methodologies based on multi-component reactions.



Kan Wang was born in Anhui, China in 1975. He obtained his B.S. in Applied Chemistry from University of Science and Technology of China in 1997. He went to Shanghai Institute of Organic Chemistry and obtained M.S. in 2000 under Prof. Jianxun Wen focused in liquid crystal material. In 2001 he went to University of Pittsburgh and obtained his Ph.D. in organic chemistry in 2007 under Prof. Scott G. Nelson focused in organometallic and organo catalysis methodology and synthesis. Currently he is working with Prof. Alexander Doemling on the design and synthesis of new drugs and combinatorial chemistry research. He has produced >20 peer reviewed papers.

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ABBREVIATIONS

Abeta	amyloid β-peptide
AIDA	antagonist induced dissociation assay
AF	atrial fibrillation
APP	amyloid precursor protein
BACE	β-secretase
BBB	blood-brain-barrier
Bcl	B-cell lymphoma
BG-3CR	Biginelli three component reaction
BIR	baculovirus IAP repeat protein domain
CaCCs	Calcium-activated chloride channels
CB1	cannabinoid type 1 receptor
Cdc25A	cell division cycle 25 homologue A
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator chloride channel
CoA	coenzyme A
COG	cost-of-goods
COX	cyclooxygenase
CRF	corticotropin releasing factor
DCC	dicyclohexylcarbodiimide

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHODH	dihydroorotate dehydrogenase
DMAD	acetylenedicarboxylicacid diester
DMAD	dimethylaminopyridine
DMD	Duchenne muscular dystrophy
DKP	diketopiperazine
DPP-IV	dipeptidyl peptidase IV
ECS	endocannabinoid system
EAAT1	excitatory amino acid transporter subtype 1
EphB4	ephrin type-B receptor 4
Fab	fragment antibody
FabD	malonyl-CoA transferase
FDA	food and drug administration
FSH	follicle-stimulating hormone
FVIIa	blood coagulation factor VIIa
FXa	blood coagulation factor-Xa
FXR	farnesoid X receptor
G-3CR	Gewald three component reaction
GA	genetic algorithm
GABA	γ-amino butyric acid
GBB-MCR	Gröbcke-Blackburne-Bienaymé-MCR
Gn-RH	gonadotropin-releasing hormone
GLP-1	incretin hormone glucagon-like peptide 1
GPCR	G-protein coupled receptor
G6PT	glucose-6-phosphate translocase
IAP	inhibitor of apoptosis proteins
H-4CR	Hantzsch four component reaction
HDAC	histone deacylase enzyme
HIV	human immunosuppressive virus
HL-60	human promyelocytic leukemia cells
Hsp	heat shock protein
HSQC	heteronuclear single quantum coherence
HTS	high throughput screening
iGluR	ionotropic glutamate receptors
IMCR	isocyanide-based multicomponent reaction
LH	luteinizing hormone
mAb	monoclonal antibody
MCR	multicomponent reaction
MDM2	mouse double minute 2, negative regulator of p53
MDM4	mouse double minute 4, negative regulator of p53
MCH	melanin-concentrating hormone
MoI	Program suite to calculate shapes of molecules: Pipeline Pilot, SciTegic, Inc. 10188 Telesis Court, Suite 100, San Diego, CA 92121, USA, http://www.scitegic.com/products_services/pipeline_pilot.htm.
MPTPA/B	*Mycobacterium tuberculosis* protein tyrosine phosphates A and B
MW	micro wave
nAChRs	nicotinic acetylcholine receptors
NPY	neuropeptide Y
NTDs	neglected tropical diseases
PADAM	Passerini-reaction-Amine-Deprotection-Acyl-Migration
PDE	3′,5′-nucleotide phosphodiesterase
P-3CR	Passerini three component reaction
P53	transcription factor
PGHS-2	prostaglandin H synthase-2
PGP	phosphor-glyco-protein
PhTX-433	philanthotoxins-433
PKPD	pharmacokinetic pharmacodynamic
PPI	protein protein interaction
PR	progesterone receptor
Pt-3CR	Petasis three component reaction
PTP1B	tyrosine-protein phosphatase nonreceptor type 1
PS	Pictet−Spengler reaction
PZQ	praziquantel
RCM	ring closing metathesis
RAS	renin-angiotensine-aldosterone system
RGD	arginine-glycine-aspartic acid motif
Ro5	rule of five
ROCK1a	Rho-associated kinase isoform 1
SAHA	suberoylanilide hydroxamic acid, Vorinostat
SAR	structure activity relationship
SFC	super critical carbondioxide fluid chromatography
TF	tissue factor
U-4CR	Ugi four component reaction
U-5C-4CR	Ugi five center four component reaction
UDC	Ugi-deprotection-cyclization
VDCC	voltage-dependent Ca2+ channels
VEGF	vascular endothelial growth factor
vL-3CR	van Leusen three component reaction
XIAP	x-linked inhibitor of apoptosis protein

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