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INDUSTRIAL APPLICATIONS OF MULTIPLE BOND-FORMING TRANSFORMATIONS (MBFTs)

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15.1 INTRODUCTION

Multiple bond-forming transformations (MBFTs) involving multicomponent reactions (MCRs) can be defined as processes in which three or more reactants introduced simultaneously are combined through covalent bonds to form a single product, regardless of the mechanisms and protocols involved [1].

Many basic MCRs are name reactions, for example, Ugi [2], Passerini [3], van Leusen [4], Strecker [5], Hantzsch [6], Biginelli [7], or one of their many variations. Several descriptive tags are regularly attached to MCRs because they are atom economical, 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 are combined
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.

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 react them in subsequent transformations, for example, ring-forming
reactions. 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 [8].

A versatile example of this strategy are the Ugi–deprotection–cyclization
procedures (UDC) leading to a great scaffold diversity, for example, benzimidaza-
zoles, benzodiazepinedione, tetrazolodiazepinone, quinoxalinones, γ-lactames, and
piperazines [9]. Similarly, MBFTs require the involvement of substrates exhibiting
multiple potential reaction sites and the selective control of their reactivity in
each individual bond-forming event. Some classes of densely functionalized small
molecules have been shown to be particularly suited for use in these transformations,
and in this context 1,2- and 1,3-dicarbonyl compounds are exceptional synthetic
platforms [10]. The rapid and easy access to biologically relevant compounds by
MCRs and their scaffold diversity have been recognized by the synthetic community
in industry and academia as a preferred method to design and discover biologically
active compounds. Although the list of MCR applications towards the synthesis
of marketed drugs or drugs under development is much longer, we will focus and
discuss in the following sections eight recent examples.

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15.2.1 Xylocaine

The reaction of isocyanides, oxo components, and primary or secondary amines
yields α-amino carbonamides, as disclosed by Ugi in 1959. The reaction has been
employed by Ugi early to synthesize the local anesthetic Xylocaine (Scheme 15.1)
[11]. It clearly shows the genius of Ivar Ugi who recognized the important
applications of MCR chemistry several decades before the area of combinatorial
chemistry was born. Xylocaine alters depolarization in neurons by blocking the
fast voltage-gated sodium (Na\(^+\)) channels in the cell membrane. While there are
many synthetic approaches toward Xylocaine, such as the one in Scheme 15.1, Ugi’s
approach is among the shortest and without doubt the most convergent and diverse
ones. For example, many newer derivatives of the same class of anesthetics can
be synthesized by the same route by simple variation of the three starting material
classes, namely amine, oxo and isocyanide components (Scheme 15.2).
Industrial Synthesis of Xylocaine

\[
\text{NH}_2 \quad \text{ClCH}_2\text{COCl} \quad \xrightarrow{} \quad \text{HN} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{NHEt}_2 \quad \xrightarrow{} \quad \text{Xylocaine}
\]

Ugi 3CR Synthesis of Xylocaine

\[
\text{1} + \text{2} + \text{3} \quad \xrightarrow{} \quad \text{Xylocaine}
\]

**Scheme 15.1** Synthesis of Xylocaine.

**Scheme 15.2** Derivatives of Xylocaine.

### 15.2.2 Almorexant

Almorexant is a first-in-class orexin receptor antagonist that was undergoing Phase III clinical trials for insomnia until 2011. The tetrahydroisoquinoline derivative was originally discovered from a series of Ugi/Pictet–Spengler reaction products. Originally developed by Actelion, from 2007 Almorexant was being reported as a potential
blockbuster drug, as its novel mechanism of action (orexin receptor antagonism) was thought to produce better quality sleep and fewer side effects than the traditional benzodiazepine and $z$-drugs that dominate the multibillion dollar insomnia medication market [12] (Figure 15.1).

The discovery synthesis of Almorexant starts with an Ugi three-component reaction (Ugi-3CR) between benzaldehyde (4), 2-(3,4-dimethoxyphenyl)ethanamine (5), and methyl isocyanide (6) affording product 7, which in a post-Pictet–Spengler reaction with 3-(4-(trifluoromethyl)phenyl)propanal (8) in the presence of strongly acidic conditions gives the end product Almorexant (9). Clearly, the synthesis is not stereoselective and yields four different stereoisomers, of which only one is biologically highly active (Scheme 15.3).

Lefort and coworkers reported on two new efficient catalytic systems for the enantioselective synthesis of the intermediate 10 needed for the synthesis of Almorexant (Scheme 15.4) [13]. The first one relies on an asymmetric hydrogenation of 11 using an iridium complex with a ferrocene-based ligand, while the second one relies on an asymmetric transfer hydrogenation of 11 using a ruthenium catalyst with a diamine ligand. Both catalysts were studied further, and appeared to be suitable for large-scale manufacturing (Scheme 15.5). Had Almorexant not been stopped from Phase III clinical trials in 2011, a final choice would have been guided mainly by the cost of materials for the two routes, considering the availability of the production units and the delivery time of the raw materials.
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Scheme 15.4  Almorexant and its key intermediate.

Scheme 15.5  Asymmetric hydrogenation of 11 with Ir/TaniaPhos and asymmetric transfer hydrogenation with Noyori catalyst toward 10.

Interestingly, TaniaPhos catalysts used in the asymmetric hydrogenations can be synthesized from the (R)-Ugi amine 15 in two steps [14]. The (R)-Ugi amine can be synthesized via a Mannich reaction between ferrocene 12, dimethyl amine (13), and acetaldehyde (14) (Scheme 15.6) [15].

15.2.3  (−)-Oseltamivir (Tamiflu®)

New infectious diseases appear regularly in different parts of the globe, most recently swine flu, creating new global health threats. The appearance of new
Scheme 15.6 Synthesis of (R)-Ugi amine.

multiple-drug-resistant seasonal flu and infectious and deadly influenza pandemics in regular intervals of 20–40 years is of great concern. Current weaponry to fight influenza can only build on a handful of chemotherapeutic options besides immunization. While immunization is suitable to control seasonal flu, it is not believed to work with new flu pandemics. The anti-influenza neuraminidase inhibitor (−)-Oseltamivir is one of the few remaining chemotherapy options, and has been recently synthesized by the Hayashi group by a remarkably short and high-yielding asymmetric synthesis (Scheme 15.7) [16]. The synthesis consists of a one-pot MCR
involving the Michael reaction of α-alkoxyaldehyde (16) and cis-nitroalkene 17, catalyzed by (S)-diphenylprolinol silyl ether (18), proceeded in the presence of HCO₂H in chlorobenzene to afford the Michael product 19 in good yield with excellent diastereo and enantioselectivity. Ethyl acryl derivative 20 and Cs₂CO₃ were added to the same pot, generating the desired product 21 and two different intermediates that were later converted into 21 by the addition of EtOH. In the next step, the Michael reaction of toluenethiol (22), followed by epimerization at the α-position of the nitro group, afforded the thiol Michael adduct 23a with the desired stereochemical configuration. By addition of Zn and TMSCl to the same vessel, reduction of the nitro group gave the amine 23b, from which a retro-Michael reaction of the thiol group proceeded by treatment with a base to afford Oseltamivir (Tamiflu) in a single pot and without the need to exchange or evaporate solvents. The gram-scale synthesis was demonstrated in 28% total yield to afford 1.02 g of product from nitroalkene 17 (1.5 g) in a one-pot procedure (Scheme 15.7).

15.2.4 Telaprevir (Incivek®)

Hepatitis C is a viral infectious disease affecting more than 200 million people worldwide and is currently treated by a combination of PEGylated interferon and ribavirin. However, a significant number of patients do not respond to this therapy because of adverse effects or viral rebound due to resistant strains. Recently, the hepatitis C virus (HCV) NS3 protease has emerged as a clinically validated target for the treatment of hepatitis C infection. Two peptidic HCV NS3 protease inhibitors, Telaprevir and Boceprevir (Figure 15.2), have recently been approved for the treatment of HCV infection. The reported technical synthesis of Telaprevir involves a lengthy, highly linear strategy relying on standard peptide chemistry and involving more than 20 steps [17]. For example, the central bicyclic proline derivative is synthesized in racemic form via a nine-step sequence. The desired enantiomer is obtained only after chiral HPLC separation. Optimization of the synthesis of Telaprevir could significantly lower the cost of goods, thereby making this promising drug available to a large proportion of the world population in future.

Figure 15.2 HCV NS3 protease inhibitors.
Recently Orru and coworkers composed a highly efficient and stereoselective synthesis of Telaprevir (Incivek) based on biocatalysts and MCRs [18]. The synthesis comprises only 11 steps in total compared to 24 in the originally reported procedure.

A retrosynthetic analysis of 24 using an MCR sequence is presented in Scheme 15.8. The required starting materials for the key Ugi-type 3CR were the carboxylic acid 25, cyclic imine 26, and isocyanide 28. The acid 25 could be accessed by standard peptide chemistry, while imine 26 was generated in situ from the commercially available 27 by catalytic oxidation with the enzyme MAO-N (monoamine oxidase N) from Aspergillus niger. The isocyanide 28 was accessed via a Passerini three-component reaction (P-3CR) of 29, 30, and acetic acid.

Coupling of pyrazinecarboxylic acid (33) and 1-cyclohexylglycine methyl ester (34) with a subsequent saponification afforded 35 in excellent yield (Scheme 15.9). Subsequent coupling with 1-tert-leucine methyl ester 36 and saponification furnished the required optically pure acid 37. The Orru group was able to significantly increase both the atom and step economy as well as the overall yield (74% vs 11% over four steps) of acid 37 compared to the already known synthesis routes.

The construction of the isocyanide fragment 28 was done in three steps in which a Passerini three-component reaction (P-3CR) played a key role. Commercial (S)-2-amino-1-pentanol (32) was transformed to formamide 33 by N-formylation. Following the work of Ngouansavanh and Zhu [19], the group was able to combine
both the oxidation of alcohol 33 and a P-3CR, which gave access to 34 in a one-pot process. Both the alcohol oxidation and the Passerini reaction were performed in CH₂Cl₂, with the acetic acid, a by-product in the Dess–Martin oxidation, used as the carboxylic acid input in the P-3CR. Thus, one-pot Dess–Martin oxidation/Passerini reaction of 38 furnished 39 in 60% yield. Dehydration then afforded the required isocyanide 28 in very good yield (87%). No racemization of the C3 stereocenter was observed. This crucial fragment was thus accessible in only three steps from commercial starting materials (Scheme 15.10).

The last step towards the three-component Ugi-type coupling envisaged in the retrosynthesis is described below. The, commercial amine 27 was oxidized to imine 26 (94% ee) by MAO-N, as previously described [20], which was then combined with 25 and 28 give the advanced intermediate 40. Finally, cleavage of the acetate followed by Dess–Martin oxidation gave Telaprevir (24) as a 83:13:4 mixture of diastereomers, with one minor diastereomer derived from the incomplete stereoinduction of the Ugi-type 3CR and the other from the minor enantiomer of imine 26. Flash chromatography allowed straightforward separation of the diastereomers to afford pure Telaprevir (24) in 80% yield over the last two steps (Scheme 15.11).

### 15.2.5 Ezetimibe (Zetia®)

Another recently approved compound is the cholesterol absorption inhibitor Ezetimibe (Zetia®) (Figure 15.3) discovered and initially produced by Schering-Plough, with a linear synthesis of seven steps [21–23]. The commercial process toward the synthesis of Ezetimibe (Zetia) starts with a CBS reduction (5% catalyst load) of ketone 41, affording chiral alcohol 42 in 95% yield. Judicious choice of the trimethylsilyl protecting group allowed clean in situ protection of both the benzylic and phenolic
hydroxyl groups with TMS-Cl. Alcohol 42 was treated with 2 equiv of TMS-Cl, followed by titanium enolate formation (TiCl$_4$), and then addition of phenolic imine. Excess TMS-Cl present in the reaction reacted with the C4-phenol to afford crystalline 43. Cyclization mediated by BSA and TBAF proceeded smoothly, but 2 equiv of TBAF were required to get complete deprotection of the benzylic and phenolic hydroxyl groups. Minor modifications of this process have been used to produce Ezetimibe (Zetia) on a commercial scale (Scheme 15.12) [24, 25].

Alternatively, the multicomponent Staudinger-3CR can also be used to access Ezetimibe (Zetia) [26]. In fact, the first synthesis of Ezetimibe was based on

Scheme 15.12  Schering–Plough commercial process to Ezetimibe (Zetia®).
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![Chemical structures and reaction schemes]

**Scheme 15.13** Staudinger-3CR process to Ezetimibe (Zetia®).

A Staudinger-type reaction. Treatment of acyl chloride 44 with imine 45 in the presence of a base afforded the trans-β-lactam 46 containing adequate substitution at the nitrogen and C4 carbon atoms (Scheme 15.13). Pure enantiomers were isolated by means of chiral chromatography. Ester hydrolysis, formation of the corresponding acyl chloride, and subsequent Negishi-type coupling gave ketone 47, which was reduced with a borane–methyl sulfide complex, affording a mixture of diastereoisomers which were again separated by chiral chromatography. Final debenzylolation led to the desired product Ezetimibe (Zetia®).

### 15.2.6 Crixivan (Indinavir®)

The HIV-1 protease (HIV PR) is known to play a critical role in the reproduction of human immunodeficiency virus, the causative agent for AIDS. Site-directed mutagenesis of this virally encoded protease results in the production of noninfectious virions. Therefore, HIV-1 protease has been considered as one of the most attractive targets for AIDS chemotherapy. Much effort has been concentrated on the development of effective inhibitors of HIV PR, and a number of inhibitors featuring various structural motifs have been reported [27].
Of the currently available HIV medications, seven 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. Often, they have to be synthesized in sequence with up to 20 synthesis steps. Therefore, it is worthwhile considering alternative synthetic approaches involving MCRs. For example, the key intermediate piperazine 49 of Crixivan (Indinavir) produced by Merck was advantageously and stereoselectively synthesized using a key and quantitative U-4CR followed by an enantioselective hydrogenation [28].

A key step in the assembly of the HIV protease inhibitor Crixivan (Indinavir) is the coupling of the enantiomerically pure epoxide 48 with the enantiomerically pure piperazine 49 to afford the backbone of the drug (Scheme 15.14).

The synthesis of the epoxide 48 is described in Scheme 15.15 in three steps, starting with a diastereoselective allylation of the lithium (Z)-enolate of 50 followed by a diastereoselective conversion of 51 to iodohydrin 52 via NIS-mediated cyclic iodoimidate formation and hydrolysis. Finally a base-mediated conversion of 52 to the epoxide 48 was accomplished, with all three steps giving excellent yields [29].

In contrast, the second main building block for the synthesis of the drug, namely piperazine 49, was not that easily prepared because of the large number of steps (five) needed to get access to the hydrogenation intermediate 53. So, although the chiral hydrogenation occurs in high yield and high enantiomeric excess using the Rh-BINAP catalyst (Scheme 15.16), the synthesis of 49 was abandoned and a new methodology involving a Ugi-4CR was introduced.

Piperazine 49 was ingeniously assembled from readily available starting materials such as N-Boc-ethylenediamine (54), dichloroacetaldehyde (55), tert-butyl isocyanide (56), and formic acid. The resulting Ugi adduct 57 could be isolated; however,
the desired vinylchloride 58 was obtained more conveniently in essentially quantitative overall yield by the Et₃N-induced HCl elimination from 57. Interestingly, 58 exists as a single diastereomer, which is the Z-isomer (Scheme 15.17) [28].

The subsequent cyclization of 58 and 59 proved difficult. The most promising results were obtained with alkoxide bases such as LiOtBu, NaOtBu, and KOtBu, with KOtBu being the best choice. An acceptable yield (60%) in the cyclization was realized by careful control of the amount of base, concentration, and solvent of the reaction. With a short synthesis of the tetrahydropyrazine 59 in hand, Merck also examined the chiral hydrogenation of this substrate (Scheme 15.18). Tetrahydropyrazine 59 differed from the frequently examined N-acyl dehydroamino acid hydrogenation substrates not only by the position of the double bond in the ring between two nitrogen atoms but also by the scarcely preceded use of the formyl group for the protection of N-1. A screen of various Rh- and Ru-based catalysts under a standard set of conditions (3.5 atm H₂, 18 h, MeOH, 2 mol% catalyst) was undertaken. The best activity and enantioselectivity was obtained using the Rh-BINAP catalyst,
and complete conversion of 59 to 60 could be achieved at 100 atm H₂ pressure at 40 °C in MeOH with 7 mol% catalyst giving the product with 97% ee.

In the last step of the synthesis the formyl group in 60 had to be removed without the racemization of the newly formed chiral center. Since the N-1 protecting group is derived from the acid used in the Ugi condensation, the use of a carbamate protecting group, such as Cbz, was precluded. The scientists envisioned that only easily deprotected amides, such as formamide, might allow the required mild deprotection. Indeed, treatment of 60 with dilute aqueous NaOH cleanly removed the formyl group, but with concomitant racemization: the enantiomeric excess of 49 was reduced to 80% from the 99% of the starting material even when the deprotection was performed at 0 °C. Remarkably, heating 60 with 35% aqueous hydrazine led to a clean deprotection to give 49 in 91% yield while leaving the enantiomeric purity essentially unchanged at 98% (Scheme 15.18).

15.2.7 Oxytocine Antagonists: Retosiban and Epelsiban

Preterm labor is the major reason for neonatal morbidity and occurs in 10% of all births worldwide. Currently, antagonistic derivatives of the neurohypophyseal nonapeptide hormone oxytocin are used to control preterm labors, but they are associated with the typical disadvantages of peptide drugs, such as lacking oral bioavailability, short half-life times, and potential immunogenicity. The diketopiperazine scaffold 61 has been discovered in an High Throughput Screening (HTS) campaign, which, after further medicinal chemistry optimization, developed into the first clinical class of small molecular weight oxytocin antagonists Epelsiban and Retosiban. The latter is also the first oxytocin antagonist drug developed for the treatment of premature ejaculation in men (Scheme 15.19) [30, 31].

Because of the convergent and efficient nature of the MCR chemistry, detailed structure–activity relationship (SAR) of the scaffold substituents could be performed,

Scheme 15.19  Oxytocin antagonists Epelsiban and Retosiban.
giving rapid access to all eight stereoisomers of this Ugi Diketopiperazine (DKP) backbone in a landmark paper involving Ugi chemistry [32] (Scheme 15.20).

For example, reaction of the chiral N- and C-protected amino acid derivatives \(62\) and \(63\), respectively, with tert-butyl isocyanide \(64\) and benzaldehyde \(65\) yields the Ugi product \(66\). N-deprotection and cyclization under basic conditions yields the two stereoisomers \(67\) (\(R,R,R\)) and \(68\) (\(R,R,S\)), differing in the benzaldehyde-derived stereocenter. The two diastereomers can be conveniently separated using silica chromatography (Scheme 15.21).

The \((R,R,R)\) stereoisomer \((67)\) can be prepared alternatively using an initial U-5C-4CR employing unprotected \(L\)-Leu HCl salt \((69)\), benzaldehyde \((65)\), and tert-butyl isocyanide \((64)\), yielding the iminodicarboxylic acid mono amide derivative \(70\) in very good yields and diastereoselectivity. Saponification, acylation, N-deprotection, and subsequent cyclization yielded the expected stereoisomer \(67\) on a multi-milligram scale. The other stereoisomers were synthesized using similar strategies and enantiomerically pure amino acids as starting materials. It is important to note that two different variations of the Ugi chemistry have been employed in this exercise, namely the U-5C-4CR and the Ugi-4CR (Scheme 15.22). Interestingly, both the discovery synthesis and the later technical syntheses of the two clinical compounds were performed by Ugi chemistry.

**General Procedure for the Preparation of Compounds 67 and 68 by Sollis et al. [32]**

To a solution of \((R)\)-leucine methyl ester hydrochloride \((63)\) (600 mg) in methanol \((8 \text{ mL})\) was added triethylamine \((0.46 \text{ mL})\) and benzaldehyde \((65)\) \((0.22 \text{ mL})\). The mixture was stirred for 2.5 h before \((2R)\)-\(((t\text{-butoxy carbonyl})amino)2,3-dihydro-1H-inden-2-yl\)ethanoic acid \((62)\) \((962 \text{ mg})\) and \(t\text{-butylisonitrile} \((65)\) \((0.56 \text{ mL})\) were sequentially added. After stirring the mixture for 18 h, the solvent was removed *in vacuo*, and the residue was dissolved in dichloromethane \((4 \text{ mL})\) and trifluoroacetic acid \((10 \text{ mL})\) and stirred for 3 h at ambient temperature. After
this time, the solvent was removed in vacuo. The residue was treated with triethylamine in dioxane (2% solution, 20 mL) and was left to stir overnight. After this time, the dioxane was removed in vacuo, and the residue was dissolved in dichloromethane. The solution was washed with 0.1 M hydrochloric acid solution, and the organic phase was separated using a hydrophobic frit and evaporated in vacuo. This crude material was purified by flash chromatography eluting with ethyl acetate/cyclohexane (50–100% ethyl acetate) to give the less polar diastereomer \((2R)-N-(t\text{-}butyl)-2-[(3R,6R)-3-(2,3\text{-}dihydro-1\text{-}H\text{-}inden-2\text{-}yl)-6\text{-}isobutyl-2,5\text{-}dioxopiperazin-1\text{-}y1]-2\text{-}phenylethanolide (67)\) as a white solid (120 mg, 19%).

This also gave the more polar diastereomer 68 as a white solid (622 mg, 40%).
15.2.8 Praziquantel (Biltricide®)

Neglected tropical diseases (NTDs) such as schistosomiasis, ascariasis, trichuriasis, hookworm infection, and onchocerciasis are a group of infectious conditions that mainly afflict the world’s poorest people, leading to chronic or long-term illness, impaired childhood development, disfigurement, and decreased productive capacity. They are thus the primary reason for the poverty of the majority of people in developing countries. Three drugs are currently being used to fight the most devastating and common NTDs, with Praziquantel (PZQ or Biltricide) (76) being the most effective to treat schistosomiasis [33]. While the other two drugs are fully donated by the producing pharmaceutical companies to treat the suffering population, unfortunately, Praziquantel is currently not donated in sufficient quantities. So the need for a cheap and environmental friendly route to it synthesis has interested the scientific and industrial community for a long time. In the next paragraphs, we discuss some examples of these efforts and ultimately present and discuss an MCR approach that provides be the fastest and easiest access to Praziquantel while competitive by cost-of-good measures (Figure 15.4).

The classical Merck synthesis first proposed in 1977 is still widely used to produce Praziquantel (Biltricide) on a large scale [34]. It consists of a five-step sequential synthesis using inexpensive and readily available starting materials. The first step is a Reissert reaction of isoquinoline 71 with potassium cyanide and benzyl chloride to give 72 in 95% yield. The resulting product 72 is catalytically hydrogenated under pressure to yield 73. Further acylation with chloroacetyl chloride (74) yields 75. Base-catalyzed ring closure and final hydrogenation of the benzoyl group yields PZQ-(76) [35]. The first step of this sequence (71 to 72) is can be environmentally unfriendly because of the use of highly toxic cyanide that is used in great excess along with large quantities of toxic aqueous waste. In fact, deadly accidents have been reported repeatedly in China (Scheme 15.23).

In early 1983, the Korean company Shin Poong pursued a low-cost strategy to produce PZQ-(76) in bulk and to circumvent extensive patent protection, and thus became by 1993 the largest global producer of PZQ-(76). Their strategy involves treatment of chloroacetyl chloride (74) with phenylethylamine (77) to give (78), which then undergoes an amino alkylation reaction with amino acetaldehyde

![Figure 15.4 Praziquantel (PZQ or Biltricide®).](image-url)
dimethyl acetal to produce 79. Cyclization to 80 was achieved by treatment with concentrated sulfuric acid. Compound 80 was then converted by acylation with cyclohexane carbonyl chloride to PZQ-(76) (Scheme 15.24) [36].

Currently, one other company also produces PZQ-(76) at production scale using a method similar to that of Shin Poong. In their process, phenylethylamine (77) is treated with glycyl chloride hydrochloride (81) to produce 82. This then undergoes an amino alkylation reaction with 2-chloro-1,1-dimethoxyethane to produce 83, which is then cyclized via polytungstic acid in dichloromethane. Compound 80 is then converted by acylation with cyclohexane carbonyl chloride to PZQ-(76) (Scheme 15.25) [37].

The latest and most convergent addition to the manifold PZQ-(76) syntheses was described by Cao and Dömling (Scheme 15.26) [38]. This efficient synthesis employs, as a key step, an Ugi four-component reaction (U-4CR) between the readily available cheap starting materials phenylethyl isocyanide (84), formaldehyde (86), amino acetaldehyde dimethyl acetal (85), and cyclohexane carboxylic acid (87). The Ugi reaction gives the advanced intermediate 88 in quantitative yield under mild conditions. Compound 88 can be converted into PZQ-(76) by a Pictet–Spengler reaction under strongly acidic conditions. Overall, this short two-step process affords PZQ-(76) from inexpensive and readily available starting materials in 70% yield.
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NH₂Cl

O

NH₃Cl

NaHCO₃, CH₂Cl₂

0 °C to 15 °C

HN

O

EtOH, rt

Cl

OMe

Na₂CO₃

HN

O

OMe

CH₂Cl₂, rt

H₃PW₁₂O₄₀

Scheme 15.25 The Yixing Xinyu Chemical factory process to PZQ-(76).

Scheme 15.26 Ugi MCR PZQ-(76) synthesis by Dömling.

General Procedure for the Preparation of Compound 76 by Dömling [38]

SYNTHESIS OF 88 (UGI REACTION) To a mixture of paraformaldehyde (86) (3.33 g, 0.11 mol), 2,2-dimethoxyethylamine (85) (11.67 g, 0.11 mol), and cyclohexyl carboxylic acid (87) (14.22 g, 0.11 mol) in methanol (110 mL), (2-isocyanoethyl)benzene (84) (15.0 g, 0.11 mol) was added dropwise at 8 °C. After stirring at room temperature for 48 h, the mixture was concentrated. The residue was dissolved in diethyl ether (150 mL) and washed with water (100 mL) and brine (100 mL), and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration. After concentration, a pale yellowish oil was obtained, which upon standing crystallized to yield 88 (40.9 g, 98%).

SYNTHESIS OF PRAZIQUANTEL (76) (PICTET–SPENGLER REACTION) N-(2,2-Dimethoxyethyl)-N-(2-oxo-2-(2 phenethylamino)ethyl)cyclohexanecarboxamide (70) (30.0 g, 79.8 mmol) was added portion-wise to methanesulfonic acid (104.0 mL, 1.6 mol) at 8 °C. After heating at 70 °C for 6 h, the reaction mixture was poured into an ice–water mixture and adjusted to pH 8 with an aqueous solution of NaOH (20%). The solution was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with brine (100 mL), dried, and concentrated to afford 75 (19.0 g, 76%) as a yellowish solid. The residue was recrystallized from ethyl acetate/hexane (1:1) to afford 76 (16.2 g, 65%) as a white solid.
15.3 SUMMARY AND OUTLOOK

Different large-scale technical syntheses of six marked drugs along with two drugs that are currently in clinical trials were presented in this chapter. We tried to describe the power and efficiency of MCRs through detailed schemes on how this approach toward the synthesis of a drug or even an intermediate is always more attractive, useful and intellectually stimulating. Each section gave a short introduction on the original/commercial synthetic approach with which that drug is produced. Clearly, each MCR in the synthesis of drugs has its domain of application. Sometimes, MCR might be specifically useful in the discovery chemistry for the fast and time-saving evaluation of the SAR of a compound class. However, the discovery route might not be pursued during the Good manufacturing practice (GMP) upscaling of large quantities for clinical trials. Instead, another chemistry route might be used, for example, because of issues of stereochemistry. In other cases, however, modified MCR chemistries also used in the preclinical discovery routes might be suitable for upscaling of the production. Clearly, the growing number of compounds on the market and under development, discovered and synthesized by MCR technologies, manifests their growing importance for the scientific and industrial community.

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