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Importance and synthesis of benzannulated medium-sized and macrocyclic rings (BMRs)

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Cyclic molecular frameworks, especially the benzannulated medium-sized and macrocyclic ring (BMR) systems, constitute an integral component of a large number of biologically significant natural or synthetic molecules. Many of these BMR compounds are either approved as drugs or have reached the late developmental stages in clinical trials. Such cyclic systems have been shown to possess great potential, especially in the discovery of new anticancer leads. Efforts from synthetic chemists have led to the development of elegant new strategies for the construction of BMR scaffolds of medicinal importance. This review intends to highlight the importance of benzannulated medium-sized and macrocyclic rings (BMRs) and the strategies developed over the years for their synthesis.

1. Introduction

Cyclic molecular frameworks occupy a unique segment of chemical space. Cyclic scaffolds, particularly medium-sized and macrocyclic rings, are useful for organizing the overall presentation of functional groups to biological targets.[1] The conformational constraint provided by cyclic scaffolds can afford enhanced binding affinity compared to corresponding linear structures.[2] Conformational restriction has also been correlated with improved bioavailability[3] and, in some cases, enhanced cell permeability.[4,5] Thus, cyclic scaffolds enable molecules to achieve a high degree of structural pre-organization such that key functional groups can interact across extended binding sites in proteins without a major entropic loss in binding. These cyclic systems can therefore be highly potent as well as selective. In the past decade, their chemical diversity has expanded significantly, supported by advances in bioinformatics and synthetic methodology. As a consequence, this structural type has now been successfully tested on most biological target classes.

Medium-sized (7- to 11-membered) rings constitute an important class of cyclic frameworks. Medium-ring carbo- and hetero-cycles are quite significant in organic chemistry as they form the structural core of a large number of biologically active natural products[6] and medicinally important synthetic compounds that address diverse and challenging biological targets.[7] Marine organisms have produced various non-terpenoid acetogenenins containing halogenated medium-ring ethers. These natural metabolites contain a number of different ring sizes such as (+)-laurencin (**1**), (−)-isolaurallene (**2**), (+)-prelaureatin (**3**), (+)-obtusenyne (**4**), (+)-laurallene (**5**), and (+)-brasilenyne (**6**), as shown in Fig. 1a.[8] The importance of medium-ring compounds can also be seen from their existence in many of the bioactive natural products shown in Fig. 1a such as (−)-ovatolide (**7**),[9] cephalosporolide G (**8**),[10] octalactins A (**9**) and B (**10**),[11] fulvine (**11**),[12] crispatine (**12**),[13] monocrotaline (**13**),[14] and dicrotaline (**14**).[14] Although there are synthetic challenges associated with the synthesis of medium-sized rings, efforts from synthetic chemists have led to the generation of unnatural medium ring compounds **15–18** (Fig. 1a).[15] However, despite their occurrence in many important natural products, medium-sized rings are absent among the current top 200 brand name and top 200 generic drugs, perhaps due to the limited methods for their synthesis. While synthetic approaches to 5- and 6-membered rings are common *via* cyclization and cycloaddition reactions, strategies to form medium-sized rings are often inhibited due to entropic factors and transannular interactions, which can pose unique challenges for the synthesis of such molecular frameworks.[16]

Macrocycles, on the other hand, have been defined as ring systems consisting of 12 or more atoms[7] and constitute the skeletal framework of a diverse range of bioactive natural products such as (−)-pyrenophorin (**19**), (−)-griseoviridin (**20**), (+)-aspicilin (**21**), fluvicin B1 (**22**), (+)-migrastatin (**23**), (−)-dactylolide (**24**), zampanolide (**25**), epothilones A–F (**26–31**), and synthetic molecules **32–34**, as shown in Fig. 1b. Many natural products possess a macrocyclic core, suggesting that an evolutionary advantage may be associated with the production of secondary metabolites based upon these scaffolds.[17,18] Macrocyclic compounds are attractive targets when searching for novel structures with biological activity due to the fact that naturally occurring macrocycles often display diverse and interesting biological activities such as antibiotic, anticancer, antifungal, and immunosuppressive activities as seen for

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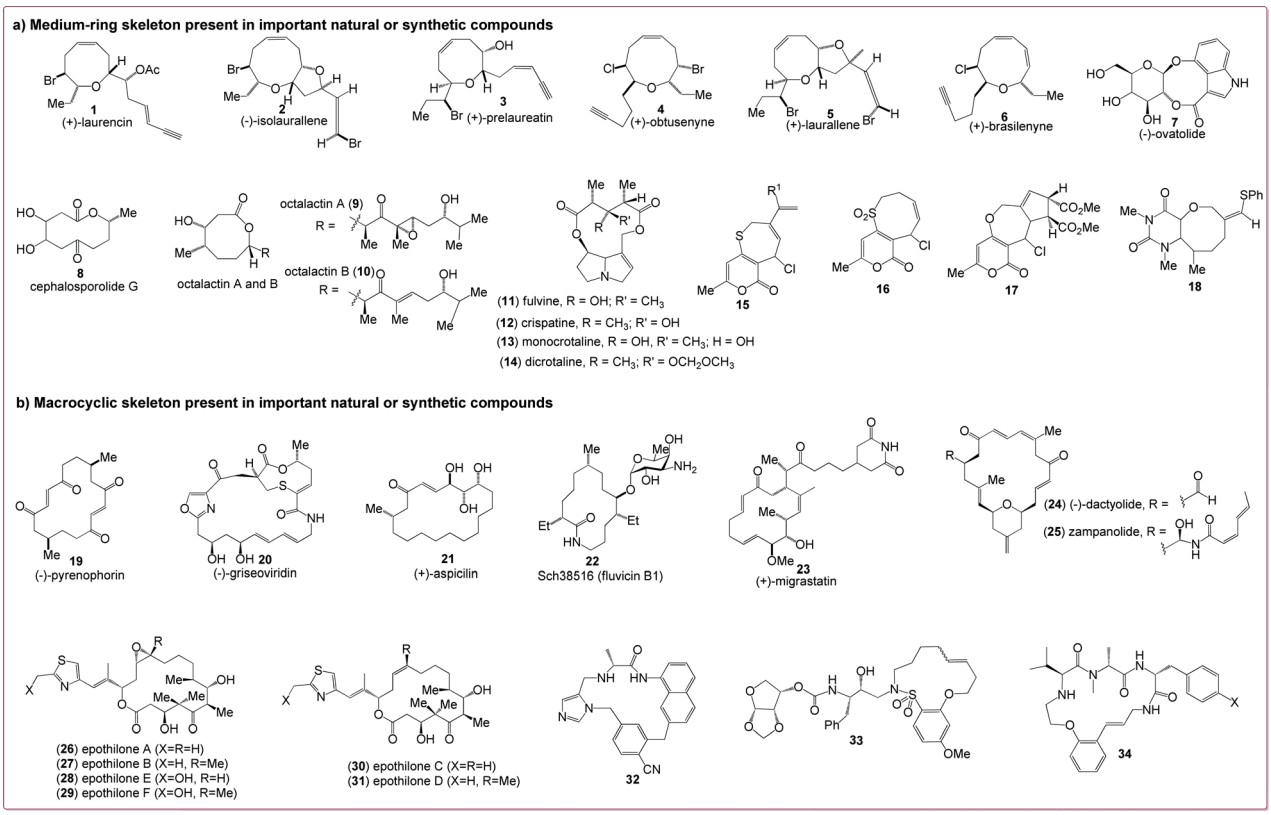


Fig. 1 Abundance of medium-sized and macrocyclic ring skeleton in bioactive natural and synthetic molecules.

erythromycin,[19] epothilone B[20] amphotericin B,[21] and rapamycin,[22] respectively. Macrocyclic drug candidates have originated either from natural sources or synthetic macrocycles. Exploitation of natural product macrocycles has yielded several drugs that are either approved for clinical use or have reached late-stage clinical development, such as the mTOR inhibitor Torisel® (temsirolimus),[23,24] the microtubulin stabilizer Ixempra® (ixabepilone),[25,26] the Hsp90 inhibitor 17-allylaminogeldanamycin,[27] vancomycin,[28] and cyclosporine.[29] The medicinal chemistry of macrocyclic natural products usually involved direct use as therapeutic agents or the functionalization of the natural product scaffold by semisynthesis. This parallels

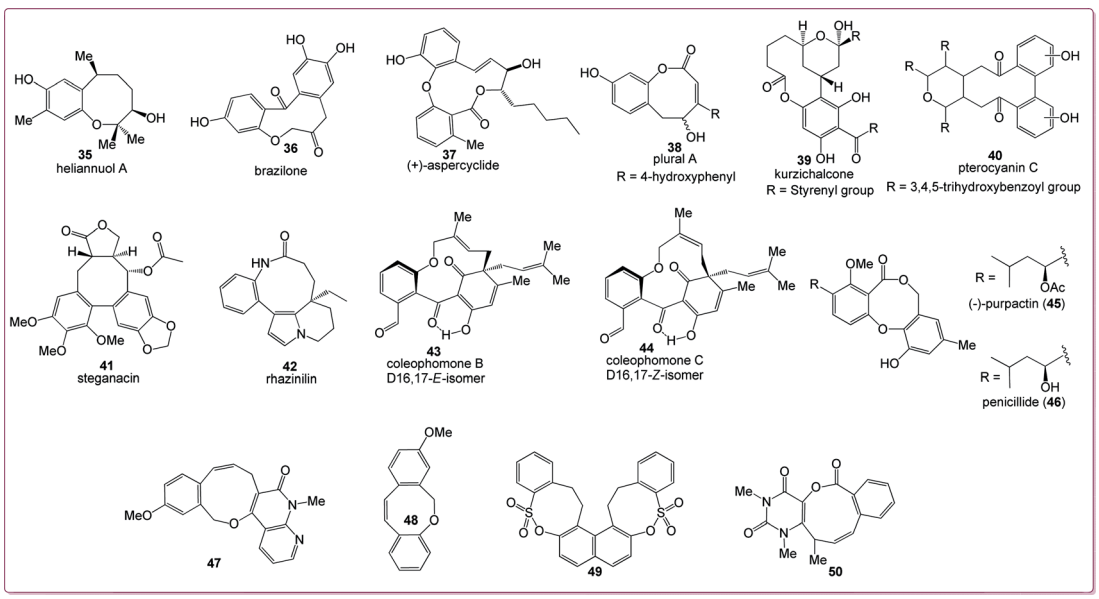


Fig. 2 Benzannulated medium-sized rings in biologically significant natural products and synthetic molecules.

significant advances in the total synthesis of macrocyclic natural products during the past two decades.[30,31] Thus, the potential for macrocycles as drugs is evident from the above facts.

Macrocycles inherently possess a lower number of rotatable bonds and hence, are conformationally more restricted than their acyclic analogues, which can potentially impart greater target binding and selectivity with improved oral bioavailability.[3] Topologically, macrocycles have the unique ability to span large surface areas, which makes them especially suited for targets displaying shallow surfaces, which can prove to be quite challenging for acyclic small molecules. Thus, macrocyclic compounds have long been clinically useful and attention is now being focused on the wider use of macrocyclic scaffolds in medicinal chemistry in the search for new drugs for increasingly challenging targets.

2. Benzannulated medium-sized and macrocyclic rings (BMRs)

The medium-sized and macrocyclic ring scaffolds annulated to an aromatic system are termed benzannulated medium-sized rings and benzannulated macrocycles, respectively. Furthermore, 1,3- or 1,4-linkages with benzene rings have been named in this review as bridged benzannulated medium-sized or macrocyclic rings (*e.g.* cyclophanes). The abbreviation BMR has been used for all such cyclic systems in this review. BMRs are of particular interest owing to their presence in an innumerable number of bioactive natural molecules and pharmacologically important synthetic molecules.

2.1. Biological significance of benzannulated medium-sized rings

Benzannulated medium-sized rings are of great interest due to their presence in a number of biologically significant natural molecules, which include aryl ethers such as heliannuol A (**35**, allelopathic activity)[32] and brazilone (**36**, anticoagulant),[33] diaryl ethers such as aspercyclide A (**37**, IgE receptor inhibitor, prevention of allergic rhinitis or asthma),[34] aryl esters such as plural A (**38**, Chinese traditional medicine component)[35] and kurzichalcone (**39**, anticancer)[36] and biaryls such as pterocayanin C (**40**, anticancer, antiviral),[37] steganacin (**41**, antileukemic)[38] and rhazinilin (**42**, anticancer),[39] as shown in Fig. 2. Benzannulated medium-rings also constitute the core of coleophomones B (**43**) and C (**44**) (which show anti-fungal and serine protease enzyme inhibition activities),[40] purpactin A (**45**, acyl-CoA-cholesterol acyl transferase inhibitor),[41] and penicillide (**46**, antagonist of the peptide hormone oxytocin and inhibitor of cholesterol ester transfer protein).[42,43] Many synthetically produced benzannulated medium-ring compounds (**47–50**) have also appeared in the literature (listed in Fig. 2). The presence of the medium-ring skeleton in bioactive natural products clearly indicates that the benzannulated medium-ring framework is a biologically significant system.

2.2. Biological significance of benzannulated macrocycles

Benzannulated macrocycles are of considerable interest in drug discovery in light of their therapeutic value. They are appealing for drug discovery as they provide diverse functionality in a conformationally pre-organized ring structure, often resulting in high affinity and selectivity for protein targets. The majority of current macrocyclic drugs are derived from natural sources, and several synthetic macrocycles are now in pre-clinical and clinical development.

2.2.1. Naturally occurring benzannulated macrocycles. Benzannulated macrocyclic motifs are commonly found in natural products and thus provide privileged scaffolds for medicinal chemistry programs in modern drug discovery (Fig. 3).[7,17] The naturally occurring bridged benzannulated macrocycles **51** (K-13) and **52** (OF4949-IV) are anti-HIV agents[44] while **53** is a 90 nM inhibitor of HSP90.[45] Note that the compounds **54–57** have shown potent antitumor activities.[46] Benzannulated macrocycles **59–62** were found to be potent and selective inhibitors of mammalian V-ATPase. Indeed, these naturally occurring V-ATPase inhibitors are expected to be promising molecules for the treatment of diseases such as

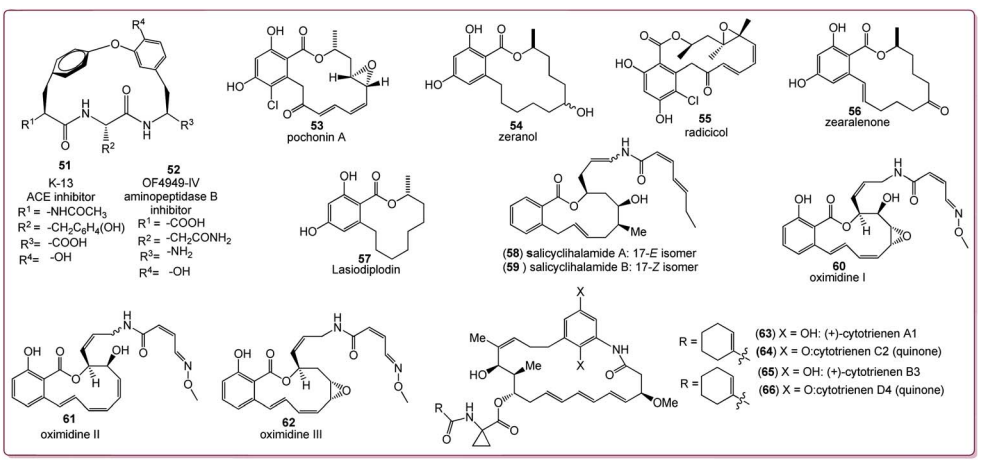


Fig. 3 Benzannulated macrocyclic ring skeleton present in bioactive natural products.

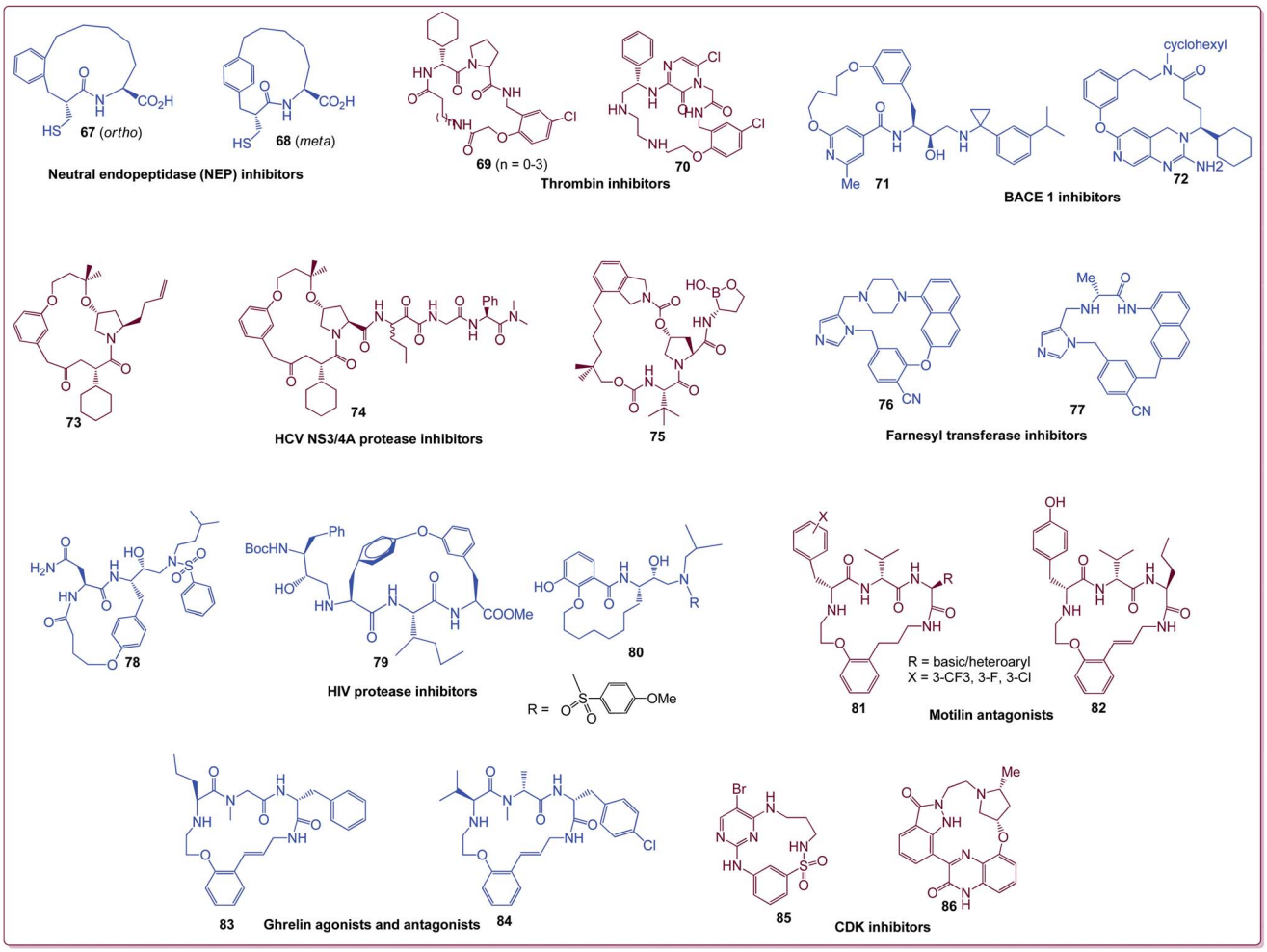


Fig. 4 Biologically important synthetic benzannulated macrocycles.

cancer and osteoporosis.[47] Compounds **63–66** are a group of naturally occurring bridged benzannulated macrocycles.

2.2.2. Synthetic benzannulated macrocycles. The biological significance of unnatural benzannulated macrocycles can be seen from the fact that such cyclic systems have been used successfully on most pharmaceutical target classes, which include (1) enzyme inhibitors, (2) agonists and antagonists of G protein-coupled receptors (GPCRs), (3) disruptors of protein–protein interactions and (4) DNA quadruplex stabilizers. The following examples will shed light on the usefulness of synthetic benzannulated macrocycles in drug discovery (Fig. 4).

(a) Neutral endopeptidase (NEP) inhibition. Ksander *et al.* reported that *ortho*- and *meta*-substituted benzannulated macrocycles **67** and **68** (bridged benzannulated) displayed potent neutral endopeptidase (NEP) inhibition (IC_{50} of **67** = 3 nM and that of **68** = 8 nM) with a high selectivity for angiotensin-converting enzyme (ACE, IC_{50} of **67** = 8 nM and that of **68** = 4 nM).[48,49]

(b) Thrombin inhibitors. Benzannulated macrocycles **69** (K_i 0.4–2.9 nM) and **70** (K_i = 0.09 nM) are potent and selective thrombin inhibitors.

(c) BACE-1 inhibitors. The bridged benzannulated macrocycles **71** and **72** are highly potent BACE-1 inhibitors with IC_{50} values of 70 nM (cell) and 7 nM (cell), respectively.[50,51]

(d) Hepatitis C virus (HCV) NS3 protease inhibitors. Bridged benzannulated macrocyclic scaffolds **73** (K_i = 530 and IC_{50} = 400 nM) and **74** (K_i = 6 nM and IC_{50} = 130 nM) are potent hepatitis C virus (HCV) NS3 protease inhibitors with nanomolar activities. Finally, Li *et al.* recently reported novel NS3 inhibitor **75** with submicromolar cellular inhibition of the NS3 protease (K_i = 43 nM and IC_{50} = 780 nM).[52]

(e) Farnesyl transferase inhibitors (FTase). The inhibition of FTase has been pursued as an approach to treat cancer, leading to several clinical candidates. The scaffolds **76** and **77** possess excellent FTase inhibitory activities (IC_{50} = 0.1 and 1.3 nM respectively).[53,54]

(f) HIV protease inhibition. The bridged benzannulated macrocyclic compounds **78** and **79** and the benzannulated macrocycle **80** displayed nanomolar potency towards HIV protease inhibition with K_i values of 0.6, 15 and 0.7 nM, respectively.[55]

(g) Motilin antagonists. Benzannulated macrocyclic motilin antagonist **81** was identified from an HTS campaign, and it

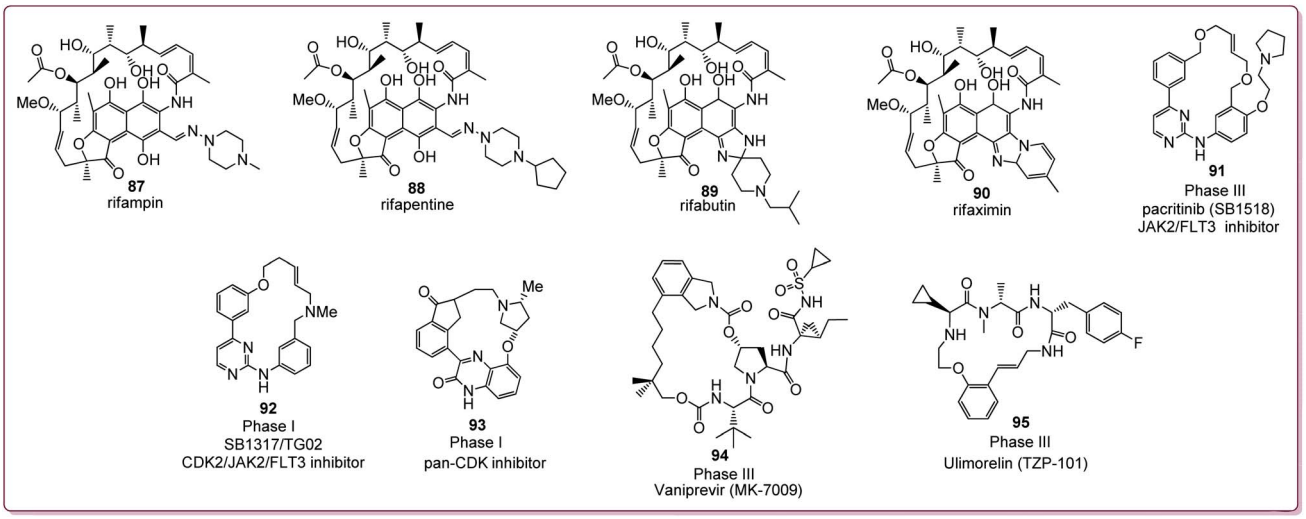


Fig. 5 Benzannulated macrocyclic rings as drugs and clinical candidates.

possesses a high potency (IC_{50} = 137 nM). Lead optimization studies led to multiple analogues with low nanomolar potency, including analogue **82** (IC_{50} = 1–20 nM).[56]

(h) Ghrelin agonists. Hoveyda *et al.* identified the benzannulated macrocycle **83** as a ghrelin agonist possessing an EC_{50} of 68 nM, a high level of potency.[57] The analogue **84** has been found to be more active with an EC_{50} value of 14 nM.[58]

(i) CDK inhibitors. Deregulation of kinase signaling pathways can be useful in the treatment of cancer. The benzannulated macrocyclic compounds **85** and **86** are highly potent antiproliferative agents. Compound **85** showed IC_{50} values of 20 nM (CDK1), 140 nM (CDK2), 40 nM (VEGFR-R2), and 200 nM (MCF7), while **86** showed IC_{50} values of 1 nM (CDK1), 3.4 nM (CDK2), 6.4 nM (CDK4), and 12 nM (CDK6).[59,60]

3. Benzannulated macrocyclic rings as drugs and clinical candidates

Macrocycles, particularly benzannulated macrocycles, have broad applications in drug discovery and development. Numerous benzannulated macrocyclic compounds present exceptional therapeutic potential and unrivalled biological activities[17,59] and many of these molecules have been developed into approved drugs (Fig. 5).[17,18] The benzannulated macrocyclic rifamycin drug family includes rifampin (**87**), rifapentine (**88**), rifabutin (**89**) and rifaximin (**90**), which constitute a notable class of antibiotic drugs.[61]

Moreover, a number of benzannulated or bridged benzannulated macrocycles have entered clinical development (Fig. 5) such as the dual JAK2/FLT3 inhibitor pacritinib (**91**), now in advanced Phase III trials,[62,63] and the CDK2/JAK2/FLT3 inhibitor **92** (SB1317) in Phase I trials.[64] The pan-CDK inhibitor **93** is another example of a synthetic benzannulated macrocyclic ring, proposed as a development candidate[65] (Fig. 5). The efforts from synthetic chemists delivered a clinical candidate, vaniprevir (**94**, MK-7009). It possessed outstanding *in vitro* (IC_{50} = 50 pM) and excellent *in cellulo* potency (IC_{50} = 3–20 nM), combined with advantageous selectivity compared to several other HCV NS3/4A inhibitors.[66] Ulimorelin (**95**, TZP-101) is another example of a benzannulated macrocycle, which demonstrated efficacy in Phase II clinical studies when administered intravenously for the treatment of postoperative ileus and acute gastroparesis.[67] Note that ulimorelin has finally entered Phase III clinical trials.

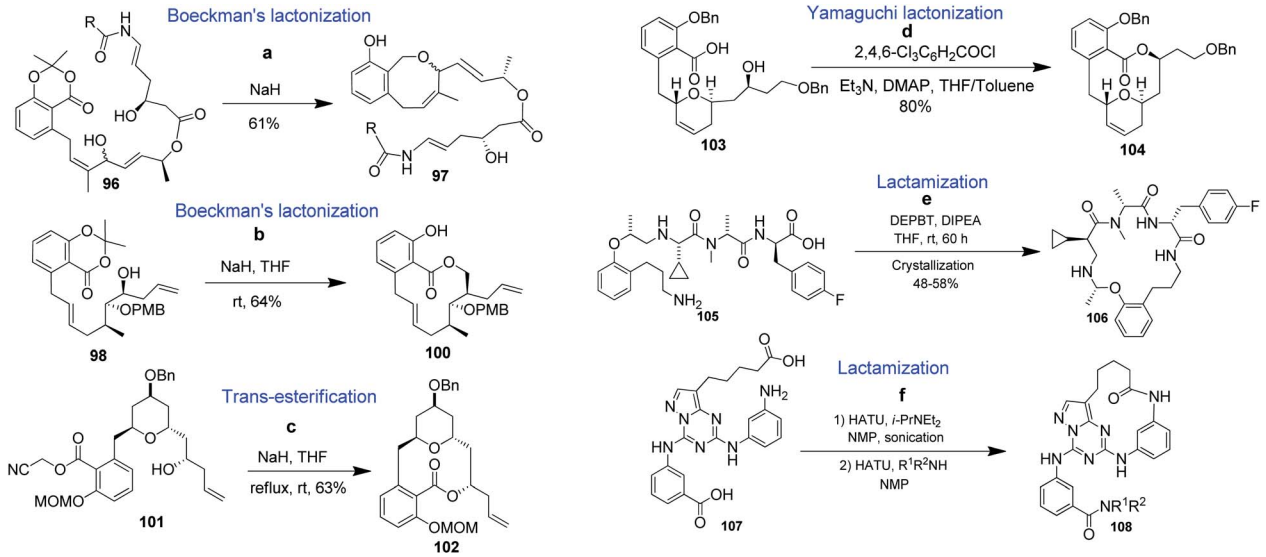
4. General strategies for the synthesis of benzannulated medium-sized and macrocyclic rings (BMRs)

One of the challenges associated with the exploration of the medium-ring or macrocyclic framework for drug discovery is the difficulty in synthesizing such structures. Fascinated by their intriguing biological activity and inspired by the intractable synthetic complexity of naturally occurring medium-sized or macrocyclic rings, much effort has been devoted to explore highly efficient and superior synthetic methods for the preparation of medium-sized rings or macrocycles.[68–71] Among the cyclization methodologies, lactonization, lactamization, transition metal catalyzed coupling reactions, ring-closing metathesis, and click chemistry represent the most efficient and commonly used synthetic approaches for the construction of BMR frameworks.

4.1. Lactonization and lactamization

Lactones constitute a major part of synthetic or naturally occurring BMRs, which mediate diverse biological activities.[72] For their synthesis, many reports regarding efficient cyclizations have been published. In general, the most frequently used and attractive cyclic approaches still involve the direct lactonization of acids and alcohols using various activation schemes.[73]

Porco *et al.* reported the synthesis of 8-membered benzolactone (**97**) from **96** in a Boeckman-type lactonization (Scheme 1a).[74] A methodology related to Boeckman's lactonization has



Scheme 1 Lactonization and lactamization strategies for the synthesis of benzannulated medium-sized and macrocyclic rings.

also been used in the synthesis of salicylihalamide **100** (Scheme 1b).[75] Panek *et al.* used a cyanomethyl ester previously described in intermolecular transesterifications[76] in the synthesis of apicularen (**102**, Scheme 1c).[77] S. S. Palimkar *et al.* reported the synthesis of the pyran-based macrocyclic benzolactone (−)-apicularen (**104**) from compound **103**, where the key cyclization step was a Yamaguchi coupling (Scheme 1).[78]

Among the many methods for synthesizing lactams, the most common and efficient approach is lactamization. Lactamization of **105** followed by purification by crystallization provided **106** in very good overall yield (Scheme 1e).[79] Nie *et al.* reported the formation of bridged benzannulated macrocycle **108** *via* a lactamization strategy in the presence of two carboxylic acids (**107**), using a one-pot, two-step diamide synthesis (Scheme 1f).[80]

4.2. Transition metal catalyzed coupling reactions

Over the past few decades, transition metal catalyzed cross coupling reactions have become a prominent tool for creating new C–C, C–O or C–N bonds.[81] Among transition metals, the most versatile metal is palladium, which has huge applications in the syntheses of BMR scaffolds as depicted in Scheme 2.

Zhu and coworkers reported the total synthesis of bridged benzannulated macrocycle **110** by applying microwave-assisted intramolecular Suzuki–Miyaura cross coupling as a key step for macrocyclization (Scheme 2a).[82] An intramolecular Suzuki–Miyaura reaction of tripeptidomimetic **111** yielded the strained bridged benzannulated 14-membered macrocycle **112** (Scheme 2b).[83] Saito and coworkers applied the Sonogashira reaction to prepare benzannulated macrocycles by treatment with catalytic $Pd(CH_3CN)_2Cl_2$, ligand XPhos, and Cs_2CO_3 in dioxane. The terminal alkyne **114** was added dropwise to the diluted aryl iodide **113** for 5 h to obtain the final product **115** in 13% yield (Scheme 2c).[84] The Sonogashira reaction has also been successfully utilized for a series of bridged benzannulated macrocyclic peptide mimetics as illustrated in Scheme 2d for the synthesis of tripeptidomimetic **117**.[85]

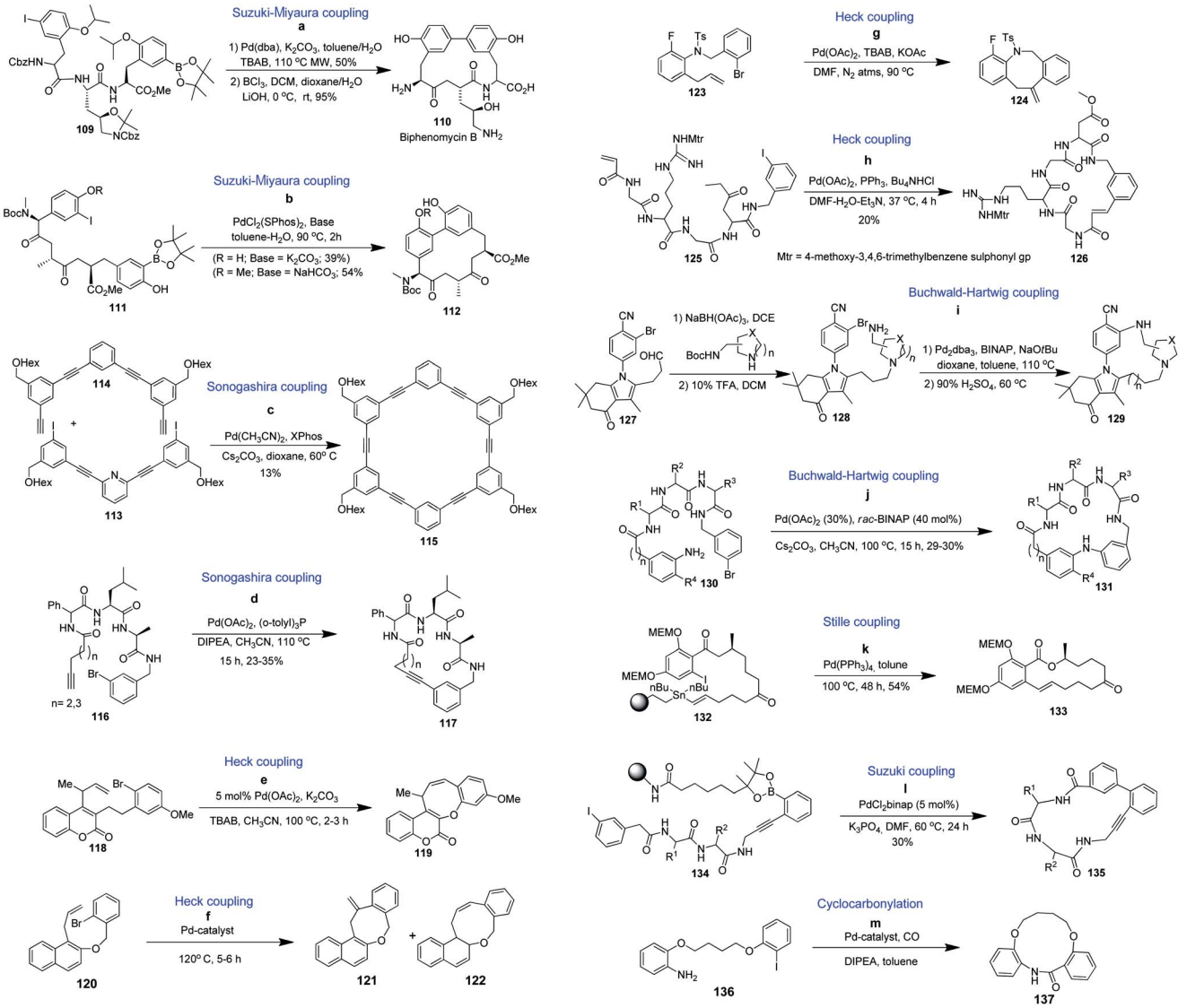
Intramolecular Heck coupling has also found an application in the synthesis of a large number of biologically significant macrocycles, but there is only one report of it being utilized for the synthesis of benzannulated ring ethers. The Heck reaction to synthesize **118** was carried out using 5 mol% $Pd(OAc)_2$ as catalyst, K_2CO_3 as base, and TBAB as an additive in CH_3CN at 80 °C for 2 hours, and the benzannulated medium-ring compound **119** was obtained in 70% yield (Scheme 2e).[86]

K. C. Majumdar *et al.* reported an efficient and high yielding method for the synthesis of benzannulated 8- and 9-membered ring ethers (**121** and **122**) *via* a palladium-catalyzed intramolecular Heck reaction (Scheme 2f).[87]

When the intramolecular Heck reaction was performed with the substrate **123** applying the concept of Jeffrey's two-phase protocol in the presence of $Pd(OAc)_2$, KOAc and TBAB in dry DMF under a nitrogen atmosphere for 6 h, the benzannulated eight-membered *exo*-Heck product **124** was obtained in 72–79% yield (Scheme 2g).[88] Heck methodology was also employed in the solid phase construction of cyclic RGD peptidomimetic **126** (Scheme 2h).[89]

Zapf and coworkers designed and synthesized the amino-based bridged benzannulated macrocyclic structure **129** *via* the Buchwald–Hartwig reaction (Scheme 2i).[90] Balraju and Iqbal also employed the Buchwald–Hartwig C–N coupling reaction for macrocyclization in the construction of bridged benzannulated macrocycle **131** constrained with a diphenylamine linker (Scheme 2j).[91]

Stille coupling provided the key step in a cyclization release solid phase synthesis strategy directed toward macrocyclic natural product **133** (Scheme 2k).[92] Li and Burgess reported solid phase linker **134** specifically for enabling a simultaneous Suzuki coupling, macrocyclization, and resin release process giving an alternative method for the construction of benzannulated macrocycles of the type **135** (Scheme 2l).[93] Shui-Ming Lu



Scheme 2 Synthesis of benzannulated medium-sized and macrocyclic rings *via* Pd-catalyzed coupling reactions.

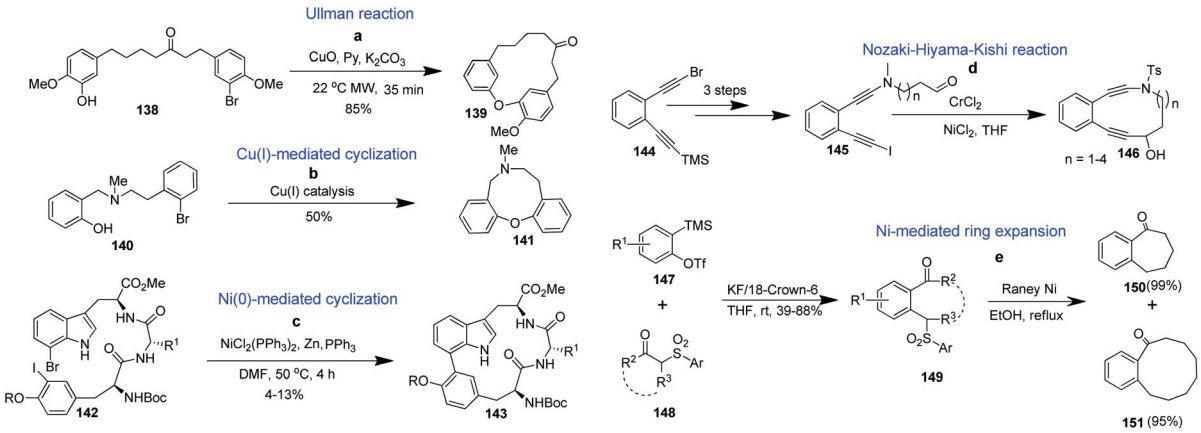
et al. reported an intramolecular cyclocarbonylation method with palladium-complexed dendrimers on silica gel as catalysts for the synthesis of 12 to 18-membered benzannulated macrocyclic ethers like **137** from iodoamine **136**, as depicted in Scheme 2m.[94] This process can tolerate a wide variety of functional groups, including halide, ether, ketone, and ester.

Apart from Pd, other transition metals, like Ni, Cu, and Cr, have also found applications in the synthesis of benzannulated cyclic systems. Thus, microwave-assisted cyclization by different strategies provides an efficient route to synthesize diverse medium-sized heterocycles[95] and macrocycles.[96] Recently, Sun's group reported a microwave-assisted intramolecular Ullmann reaction to yield bridged benzannulated macrocyclic diaryl ether analogues (**139**) from **138** (Scheme 3a).[97] P. Mestichelli *et al.* reported the synthesis of compounds such as **141** in the presence of catalytic quantities of Cu(I). Readily accessible acyclic precursors like **140** can undergo an intramolecular C–O bond-forming reaction (Scheme 3b).[98]

Nickel-mediated cyclization of **142** provided the target molecule **143** (Scheme 3c).[99] Poloukhtine *et al.* reported that Nozaki–Hiyama–Kishi conditions gave benzannulated medium-sized rings or macrocycles of the type **146** (Scheme 3d).[100] Zhang *et al.* reported that by ring expansion and desulfonylation reactions, medium- and large-sized benzannulated rings of the type **150** and **151** were obtained in excellent yields (Scheme 3e).[101]

4.3. Biomimetic and oxidative ring expansions

Owing to the limitations of conventional cyclization-based approaches to medium-ring synthesis, these structures remain severely underrepresented in current probe and drug discovery efforts. R. A. Bauer *et al.* established an alternative biomimetic ring expansion approach to the diversity-oriented synthesis of medium-ring libraries. As depicted in Scheme 4, the oxidative



Scheme 3 Synthesis of benzannulated medium-sized and macrocyclic rings *via* Cu(II), Ni(II) and Cr(II) catalyzed reactions.

de-aromatization of bicyclic phenols (**152**) affords polycyclic cyclohexadienones (**153**) that undergo efficient ring expanding re-aromatization to form benzannulated medium-ring scaffolds (**154**), as depicted in Scheme 4a.[102] The ring expansion reaction can be induced using three complementary reagents that avoid competing dienone-phenol rearrangements and is driven by re-aromatization of a phenol ring adjacent to the scissile bond. This method was also successfully applied to bicyclic phenols (**155**) to afford polycyclic cyclohexadienones (**156**) that undergo efficient ring expansion to form benzolactones of the type **157** (Scheme 4b). Cheminformatic analysis of the resulting first-generation library confirms that these molecules occupy chemical space overlapping with medium-ring natural products and distinct from that of synthetic drugs and drug-like libraries.

F. Kopp *et al.* have developed a concise, modular oxidative ring expansion approach for the synthesis of macrolactones involving oxidative cleavage of a bridging double bond in polycyclic enol ethers (**158**). These substrates undergo ring expansion to afford highly functionalized medium-ring and macrocyclic benzolactones of the type **159** (Scheme 4c).[103]

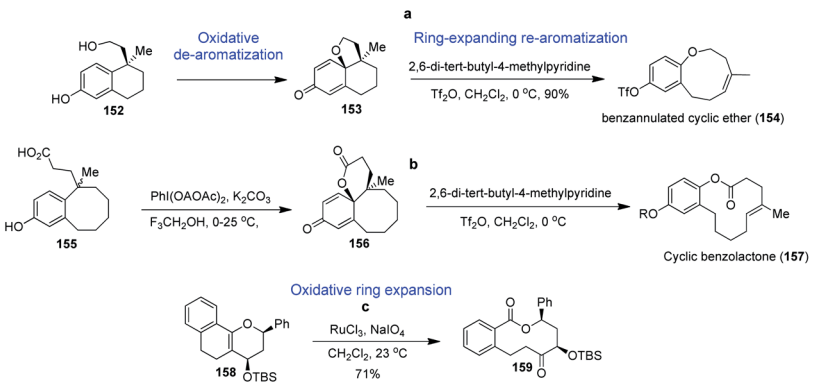
4.4. Nucleophilic substitutions

S_N2 and S_NAr reactions have found application in the synthesis of benzannulated macrocycles as exemplified in the synthesis of bridged benzannulated macrocycle **161** depicted in Scheme 5a.[58] S_NAr methodology was utilized as a key step in the solid phase synthesis of benzannulated macrocyclic thio-ether-based dipeptidomimetic **164** designed as a mimic of the β-turn structure of neurotrophin growth factors (Scheme 5b).[104]

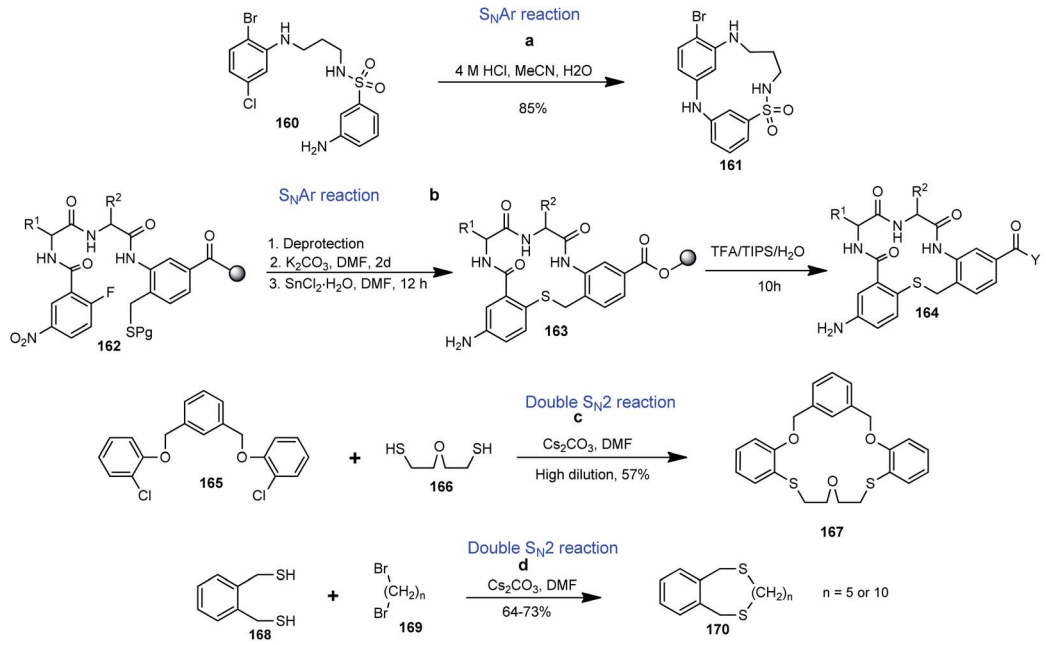
Eun-Ju Kang *et al.* reported the formation of benzannulated macrocyclic thio-ethers by the S_N2 reaction of dichloride (**165**) and 2-mercaptoethyl ether (**166**), leading to the formation of macrocyclic thio-ether **167** (Scheme 5c).[105] Buter *et al.* also reported the synthesis of benzannulated macrocyclic thio-ether **170** *via* the S_N2 reaction of a cesium thiolate (generated *in situ* from dithiol **168** and Cs_2CO_3 in DMF) with dibromide (**169**) (Scheme 5d).[106]

4.5. Ring-closing metathesis (RCM)

The construction of medium-sized rings and macrocycles by ring-closing metathesis (RCM) is often used as the key step in the synthesis of natural products containing large rings. This reaction is attractive because of its high functional group compatibility and the possibility for further transformations. The determination of suitable reaction conditions is critical for the success of the synthesis. There are numerous examples of benzannulated medium-sized or macrocyclic rings synthesized by RCM.



Scheme 4 Synthesis of benzannulated rings *via* biomimetic and oxidative ring expansions.



Scheme 5 Synthesis of benzannulated medium-sized and macrocyclic rings *via* S_NAr and S_N2 reactions.

R. Mamouni *et al.* reported that bis-allyl ether derivative **171** directly led to the corresponding benzannulated medium-ring compound **172** in good to excellent yield under RCM conditions (Scheme 6a).[107] S. K. Chattopadhyay *et al.* reported that when a dichloromethane solution of **173** and commercially available Grubbs' catalyst I was stirred at room temperature under nitrogen atmosphere, the reaction proceeded smoothly to afford the bis-benzoxepine **174** in 90% yield (Scheme 6b).[108] Fürstner *et al.* developed an RCM-based approach to synthesize benzannulated macrocyclic intermediate **176** which was then converted to (*R*)-(+)-lasiodiplodin (Scheme 6c).[109] Evano *et al.* reported the synthesis of bridged benzannulated macrocycle **178** with excellent selectivity and yield (Scheme 6d).[110] The highly strained benzannulated medium ring of coleophomones B and C (**180** and **181**) was constructed using an impressive olefin metathesis reaction to build the bond between C-16 and C-17 (Scheme 6e).[111]

Beck *et al.* reported a combination of Ugi and Passerini type MCR with RCM and described the potential applicability of this sequence for generating many diverse benzannulated macrocycles.[112] The approach for a representative compound is outlined in Scheme 6f, wherein 22-membered benzannulated macrocycle **185** was produced after a tandem sequence beginning from acid **182**, isocyanide **183** and paraformaldehyde.

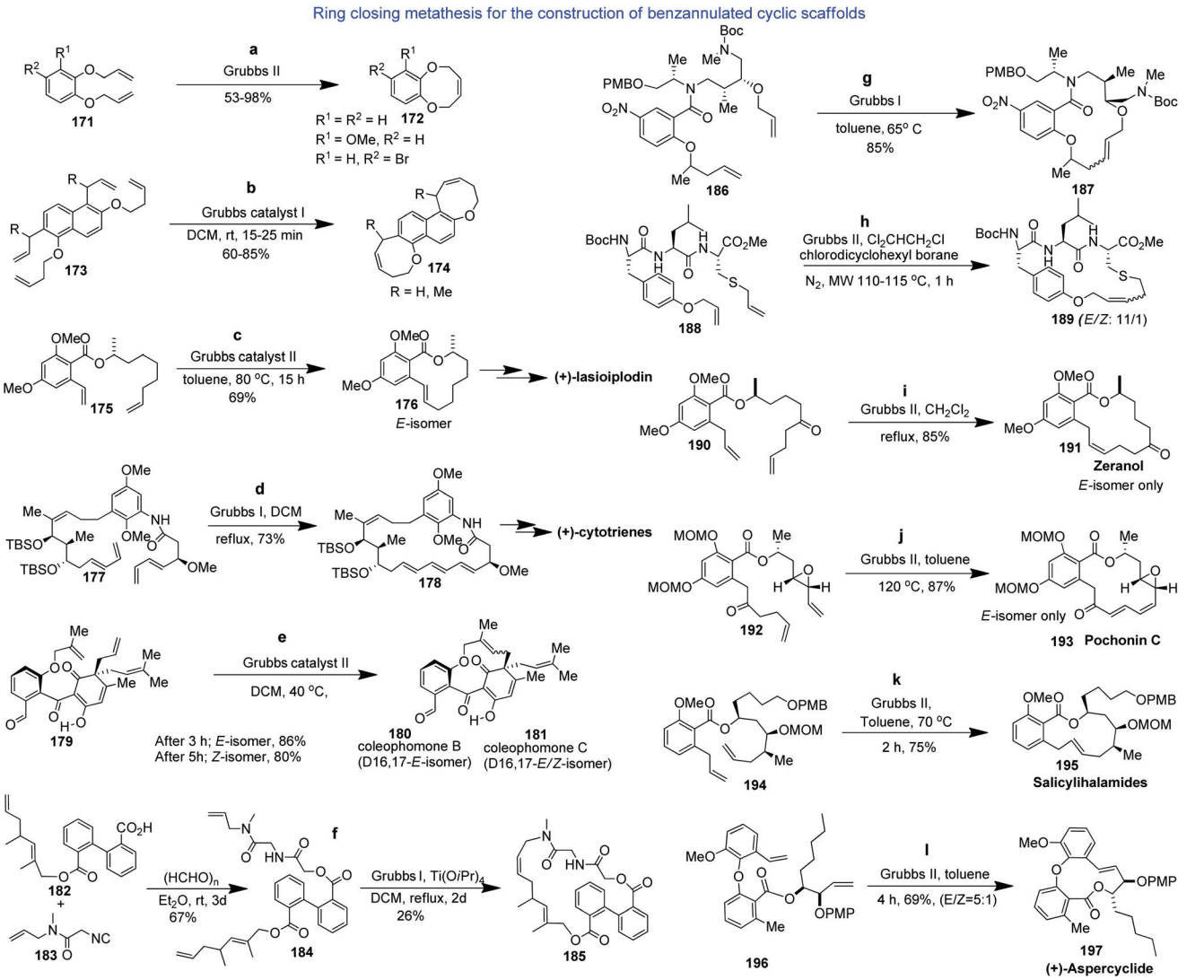
Dandapani *et al.* demonstrated the use of RCM for the generation of skeletally diverse benzannulated macrocyclic ethers such as **187** by a diversity-oriented synthesis approach (Scheme 6g).[113]

Abell *et al.* demonstrated the ring closing metathesis approach in the synthesis of S-containing bridged benzannulated macrocycle **189** (*E*/*Z* ratio: 11 : 1) from scaffold **188** using MW irradiation combined with Lewis acid conditions (Scheme 6h).[114]

Ring-closing metathesis (RCM) has been extensively used for the synthesis of resorcylic acid lactones (RALs).[115] There are numerous parameters that influence metathesis reactions; therefore, there are no general conditions that can be given that will guarantee the success of the process.[116] Fürstner *et al.* developed an RCM-based approach to zeranol (**191**) using Grubbs' second generation catalyst under reflux conditions and selectively synthesized the *E*-isomer in 85% yield as depicted in Scheme 6i.[117] S. Barluenga *et al.* reported the synthesis of pochocin C *via* polyene RCM. They treated the diene **192** at 120 °C leading exclusively to macrocyclic benzolactone **193** in 10 minutes, as shown in Scheme 6j.[118] C. Herb *et al.* cyclized the ester **194** to produce the macrocyclic benzolactone core structure of salicylihalamide (**195**) through ring closing metathesis (Scheme 6k).[119] A. Fürstner and C. Müller reported the total synthesis of (+)-aspercyclide,[120] in which the key step was a kinetically controlled RCM reaction of cyclization precursor **196** to form the medium-ring benzolactone core of (+)-aspercyclide (**197**), as depicted in Scheme 6l.

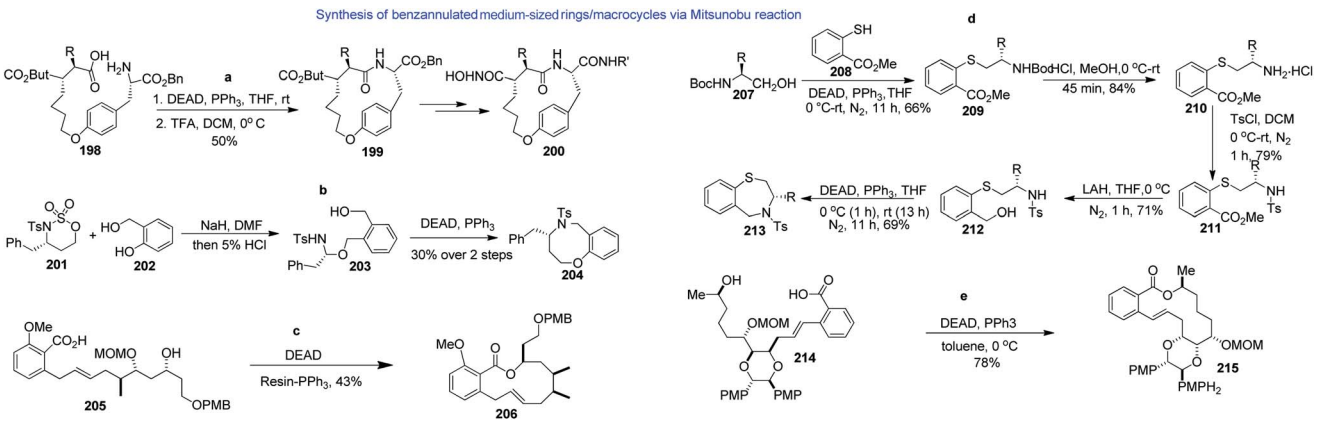
4.6. Mitsunobu reaction

The Mitsunobu reaction and its variants are among the most useful reactions in synthetic chemistry. Not surprisingly, therefore, this mild and versatile chemistry has also found some utility for the construction of BMR scaffolds. For example, the bridged benzannulated macrocycle **200** was synthesized starting from amino acid **198** (Scheme 7a)[121] while the benzannulated medium-ring ether (**48**) was prepared *via* nucleophilic cleavage of enantiomerically pure 1,2-cyclic sulfamidate **201** with phenol derivative **202**, followed by Mitsunobu reaction of **203**, which led to the formation of scaffold **204** in 30% overall

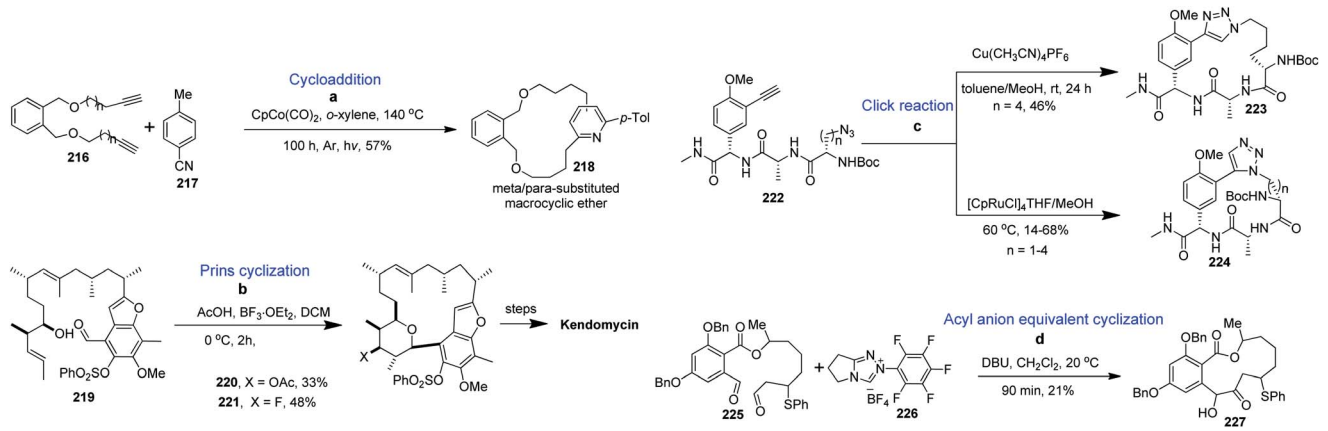


Scheme 6 Application of ring closing metathesis in the construction of medium- and large-sized benzannulated rings.

yield, as shown in Scheme 7b.[122] Another variant of the Mitsunobu reaction was reported to affect the closure of a 13-membered lactone in the presence of supported triphenylphosphine in low yield (10%) but was recently more successful in the formal synthesis of salicylihalamides (**206**, Scheme 7c).[119,123]



Scheme 7 Synthesis of benzannulated medium-sized rings and macrocycles *via* Mitsunobu reaction.



Scheme 8 Synthesis of benzannulated cyclic compounds *via* cycloaddition, Prins cyclization, click chemistry and acyl anion equivalent macrocyclization strategies.

The intramolecular Mitsunobu cyclization between the sulphonamide and benzylic hydroxyl in **212** (derived from amino acid **207** through a series of reactions, as depicted in Scheme 7d) furnished enantiomerically pure benzannulated medium-ring thio-ethers of the type **213** in 69% yield, as depicted in Scheme 7d.[124]

Macrocyclization of cyclization precursor **214** under Mitsunobu conditions (DEAD, PPh_3, toluene, 0 °C) gave rise to benzolactone **215** in 78% yield (Scheme 7e). Most likely, conformational constraints on the backbone, imposed by the dioxane ring, facilitated the formation of the macrocycle.[125]

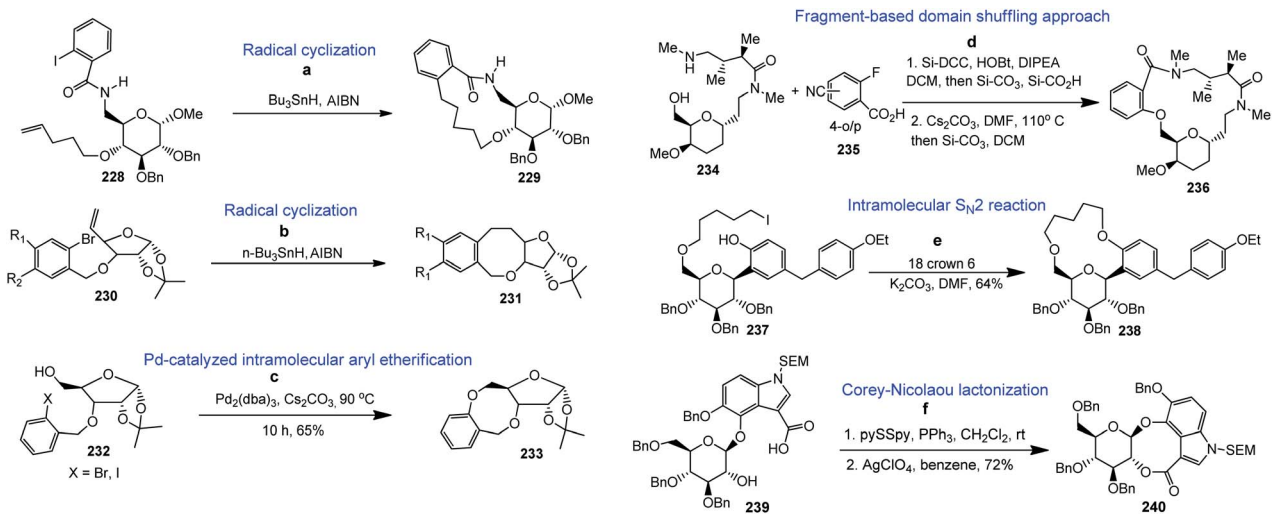
4.7. Other cyclization methods

4.7.1. Cycloaddition reactions. Cycloaddition reactions have been extensively utilized for the synthesis of cyclic compounds, but this chemistry is not well exploited for the construction of benzannulated cyclic frameworks. The only report by Llorente *et al.* involves the formation of benzannulated macrocycles from α,ω-diynes (**216**) in cobalt-mediated cyclotrimerization reactions. α,ω-Diynes underwent metal-mediated [2 + 2 + 2] cycloadditions with nitriles (**217**) in the presence of $CpCo(CO)_2$ to yield benzannulated macrocyclic ethers such as **218** (Scheme 8a).[126]

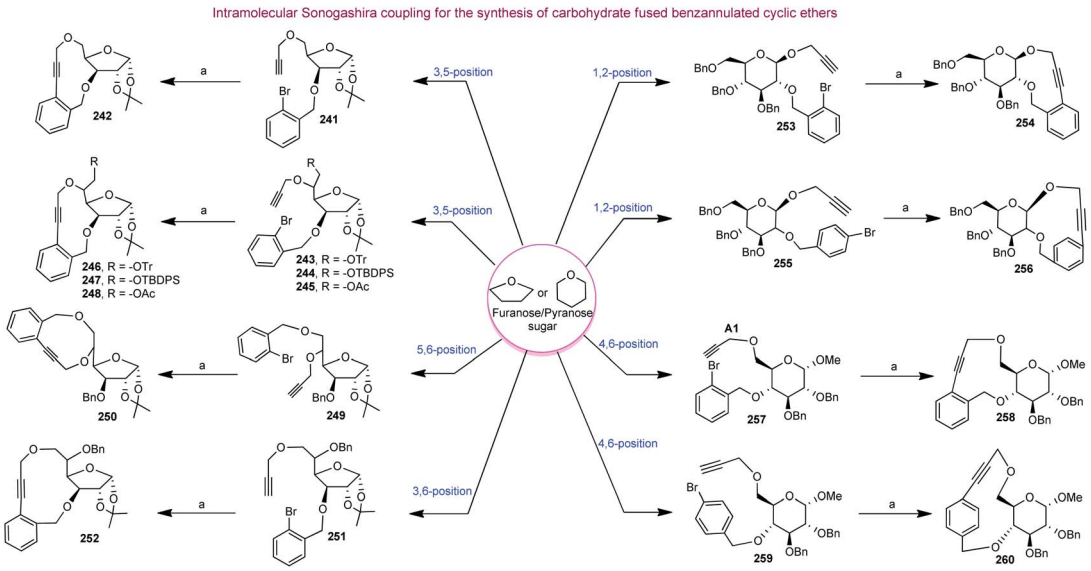
4.7.2. Prins cyclization. Bahnck *et al.* reported an intramolecular Prins cyclization that assembles the benzannulated macrocyclic rings in good yield. The Prins macrocycle formation is aided by the conformational preference of precursor **219**. The work of Bahnck *et al.* demonstrates the potential of the Prins cyclization to form benzannulated macrocyclic rings (**220** and **221**), as depicted in Scheme 8b.[127]

4.7.3. Click chemistry. Liskamp and co-workers applied click chemistry to furnish the regioselective synthesis of vancomycin mimics with 1,4- and 1,5-disubstituted triazole-containing bridged benzannulated macrocyclic tripeptides (**223** and **224**) by employing $Cu(CH_3CN)_4PF_6$ and $[Cp^*RuCl]_4$ catalysts (Scheme 8c).[128]

4.7.4. Acyl anion equivalent macrocyclization. Recently, Miller's group reported a novel acyl anion equivalent



Scheme 9 Synthesis of medium- and large-sized rings using carbohydrates as a chiral template.



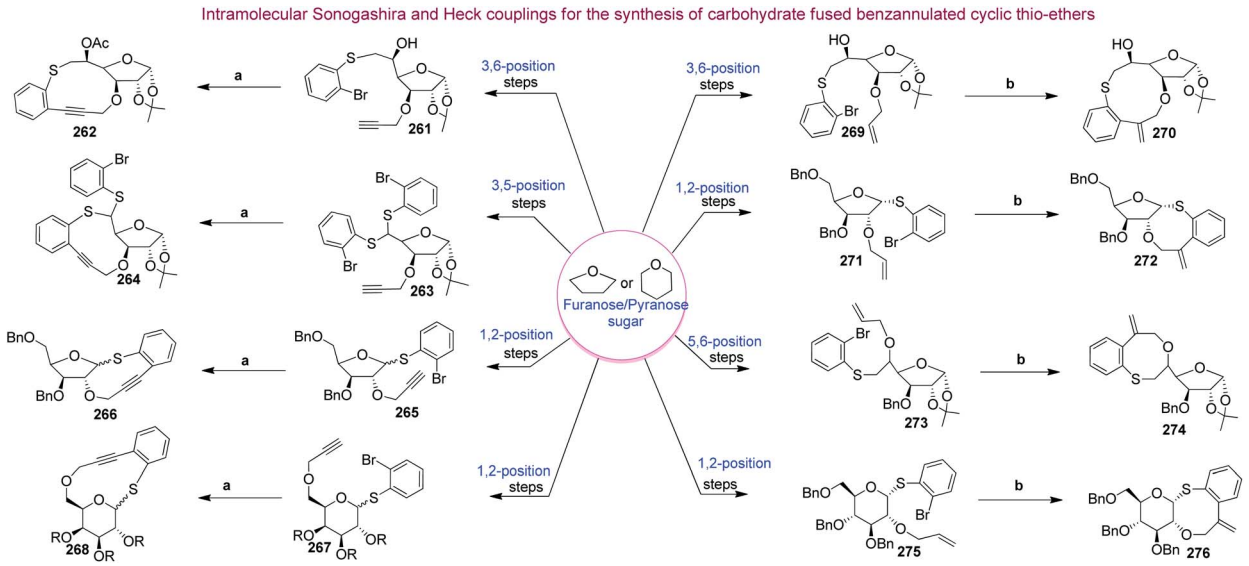
Scheme 10 Synthesis of benzannulated medium-ring or macrocyclic ethers fused with carbohydrates *via* Pd-catalyzed C–C coupling reactions. Regents and conditions: (a) heterogeneous Pd catalyst (100 wt%), CuI (5 mol%), THF, rt, 20 h, 81–90% yield.

macrocyclization based on proposed biosynthetic pathways in their work toward *trans*-resorcylide. In this method, the dialdehyde **225** was reacted with DBU and a carbene precursor **226** to produce lactone **227** in 21% yield (Scheme 8d).[129]

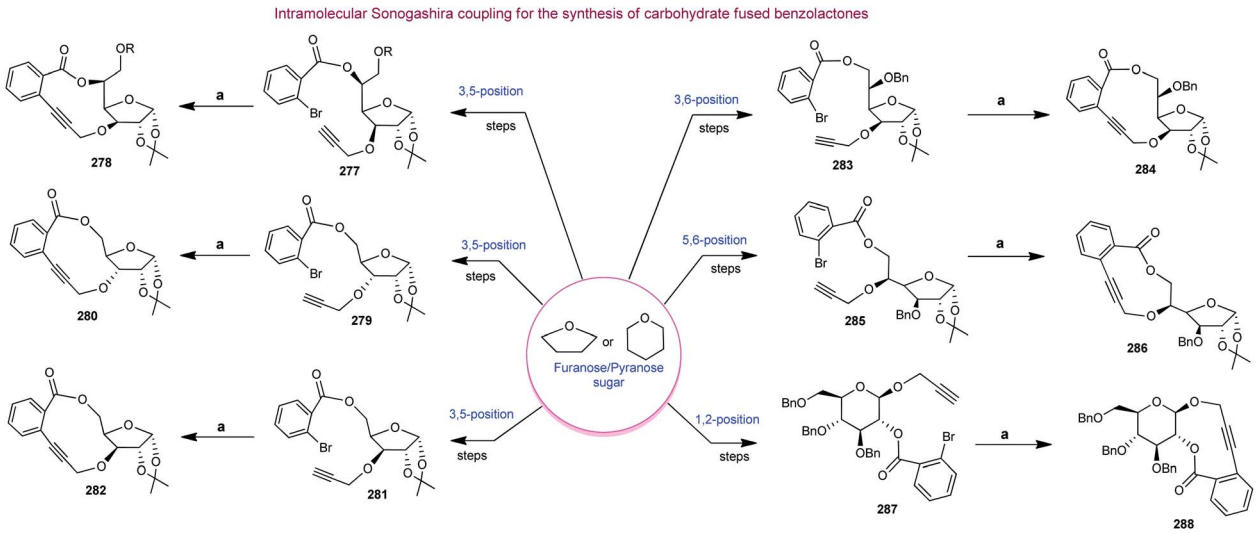
4.8. Synthesis of medium-ring and macrocyclic scaffolds from carbohydrates

Carbohydrates along with their derivatives, particularly 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranoside, unsaturated sugars (glycals), peracetylated sugars, have long been recognised as extremely useful starting materials in organic synthesis. Among the various chiral pool molecules existing in nature, carbohydrates occupy an exceptional space since they are easily accessible in nature, cheap and enantiomerically pure. Furthermore, they have a very unique arrangement of functional groups, and hence they are useful as a chiral pool in organic synthesis. Moreover, carbohydrates can act as templates on which complex medium-sized or macrocyclic ring scaffolds can be constructed. Following are the literature reports on the synthesis of biologically useful BMR frameworks from carbohydrates.

4.8.1. Radical cyclization. Radical reactions have been extensively utilized for the construction of medium-sized to large ring macrocycles. Faraco *et al.* reported the tributyltin



Scheme 11 Synthesis of benzannulated medium-ring and macrocyclic thio-ethers fused with carbohydrates *via* Pd-catalyzed C–C coupling reactions. Reagents and conditions: (a) heterogeneous Pd catalyst (100 wt%), CuI (5 mol%), THF, rt, 20 h, 81–90% yield; (b) $Pd(OAc)_2$ (10 wt%), Cs_2CO_3 (2.75 equiv.), TBAB (1 equiv.), DMF, 100 °C, 57–59%.



Scheme 12 Synthesis of medium-ring or macrocyclic benzolactones fused with carbohydrates *via* Pd-catalyzed C–C coupling reactions. Regents and conditions: (a) heterogeneous Pd catalyst (100 wt%), CuI (5 mol%), THF, rt, 20 h, 81–90% yield.

hydride (Bu_3SnH) mediated radical cyclization of unsaturated iodides such as **228**, which furnished benzannulated macrocyclic ethers of the type **229** with 11-, 12- and 20-membered rings by regioselective *endo* aryl radical carbocyclization (Scheme 9a).[130] Partha *et al.* reported a regioselective aryl radical cyclization of the 5,6-deoxy-D-xylo-5-enofuranosides (**230**) with tributyltin hydride (Bu_3SnH) giving the chiral benzannulated medium-ring ethers fused with carbohydrates such as **231** as depicted in Scheme 9b.[131]

4.8.2. Pd-catalyzed intramolecular aryl etherification. A. Neogi *et al.* reported Pd-catalyzed intramolecular aryl etherification using bulky binaphthylphosphane or bis(diphenylphosphanyl)ferrocene ligands for the synthesis of benzannulated medium ring ether **233** (Scheme 9c).[132]

4.8.3. Fragment-based domain shuffling approach. Eamon Comer *et al.* reported a fragment-based domain shuffling approach for the synthesis of a library of pyran-containing benzannulated macrocyclic ethers such as **236** using **234** and **235** as starting materials (Scheme 9d).[133] A key feature of the design strategy was to use a synthetic route with three fragments that can be readily interchanged or "shuffled" to produce subtly different variants with distinct molecular shapes.

4.8.4. Intramolecular S_N2 reaction. Intramolecular S_N2 reactions have been extensively utilized for cyclizations. For example, Kim *et al.* synthesized carbohydrate based benzannulated macrocyclic ethers such as **238** (potential antidiabetic agents), where the ring closure was carried out using an S_N2 reaction on the substrate **237** (Scheme 9e).[134]

4.8.5. Corey–Nicolaou lactonization. A total synthesis of (−)-ovatolide was developed by Delgado and Clardy. They used the Corey–Nicolaou protocol in the lactonization step, and the eight-membered benzolactone (**240**) was obtained in 72% yield after treatment of scaffold **239** with 2,2′-dipyridyl disulfide (pySSpy) and PPh_3 (Scheme 9f).[9,135]

4.8.6. Intramolecular Sonogashira and Heck cyclizations. Our group successfully used carbohydrates as chiral templates for the construction of chiral benzannulated medium-sized or macrocyclic ring (BMR) ethers (shown in Scheme 10), thio-ethers (shown in Scheme 11) and benzolactones (shown in Scheme 12) using a newly developed heterogeneous Pd catalyst through C–C coupling reactions. The building blocks containing the requisite moieties (aryl halide and terminal alkyne groups for Sonogashira coupling) were prepared from simple, commercially available, cheap sugar derivatives such as 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranoside, D-glucal and α-D-methyl glucoside by strategic installation of functional groups using the same reaction conditions, but by adjusting the chronology of the reaction steps. All the building blocks were cyclized *via* heterogeneous Pd-catalyzed Sonogashira reaction to generate the targeted BMR ethers fused with furanose or pyranose sugars (Scheme 10).[136]

Our next target was to synthesize a series of BMR thio-ethers. In general, the synthesis of different building blocks involves acetonide deprotection, alkylation/arylation, epoxidation, epoxide opening, sugar aldehyde generation and glycosylation reactions. It is noteworthy that using glycosylation reactions, we managed to create both *cis*- and *trans*-stereochemistry, which enables us to generate *cis*/*trans* fused benzannulated medium-ring thio-ethers on carbohydrate chiral templates. All the building blocks containing the required moieties (aryl halide and alkene or alkyne) were then cyclised *via* Sonogashira and Heck coupling reactions to produce the BMR thio-ethers fused with carbohydrates (Scheme 11).[137]

Finally, our group reported the synthesis of 10-, 11- and 12-membered chiral benzolactones fused to furanose/pyranose sugars in good to excellent yields using carbohydrates as chiral templates under similar coupling conditions, as shown in Scheme 12.[138] The 1-2, 3-5, 3-6 and 5-6 positions of the sugars were utilized for the construction of the medium-ring or macrocyclic skeletons. The requisite furanose/pyranose scaffolds were synthesized utilising conventional protection–deprotection strategies like benzylation, tritylation, detritylation, EDC coupling, and propargylation.

5. Conclusions

Benzannulated medium-ring and macrocyclic ring (BMR) scaffolds have been found to be of immense potential in contemporary medicinal chemistry and drug discovery programs due to their unique structural properties. Many BMR compounds have either been approved as drugs or reached the late developmental stages in clinical trials. Although efforts from synthetic and medicinal chemists have led to the development of a large number of new elegant synthetic strategies for the construction of highly potent benzannulated macrocyclic rings (12-membered or above), methods for the construction of benzannulated medium-sized rings (7–11 membered) need to be further explored. Furthermore, it has been shown that carbohydrates could be an excellent starting point for the construction of chiral BMRs due to their inherent chirality and the presence of different types of hydroxyl groups.

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Notes and references

1 T. P. Majhi, B. Achari and P. Chattopadhyay, *Heterocycles*, 2007, **71**, 1011–1052.
2 A. R. Khan, J. C. Parrish, M. E. Fraser, W. W. Smith, P. A. Bartlett and M. N. James, *Biochemistry*, 1998, **37**, 16839–16845.
3 D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615–2623.
4 T. Rezai, B. Yu, G. L. Millhauser, M. P. Jacobson and R. S. Lokey, *J. Am. Chem. Soc.*, 2006, **128**, 2510–2511.
5 Y. U. Kwon and T. Kodadek, *Chem. Biol.*, 2007, **14**, 671–677.
6 (*a*) T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds*, Academic Press, New York and London, 1972, vol. 2; (*b*) D. J. Faulkner, *Nat. Prod. Rep.*, 1984, **1**, 251–280.
7 J. Mallinson and I. Collins, *Future Med. Chem.*, 2012, **4**, 1409–1438.
8 S. E. Denmark and S. M. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 12432–12440.
9 A. Delgado and J. Clardy, *J. Org. Chem.*, 1993, **58**, 2862–2866, and references cited therein.
10 A. Farooq, J. Gordon, J. R. Hanson and J. A. Takahashi, *Phytochemistry*, 1995, **38**, 557.
11 D. M. Tapiolas, M. Roman, W. Fenical, T. J. Stout and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 4682–4683.
12 C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, 1963, **16**, 239–245.
13 O. P. Suri and C. K. Atal, *Curr. Sci.*, 1967, **36**, 614–615.
14 R. Adams and B. L. Van Duuren, *J. Am. Chem. Soc.*, 1953, **75**, 2377–2379.
15 K. C. Majumdar, *RSC Adv.*, 2011, **1**, 1152–1170.
16 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95–102.
17 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608–624.
18 L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera and W. Brandt, *Mol. Diversity*, 2005, **9**, 171–186.
19 (*a*) S. Pal, *Tetrahedron*, 2006, **62**, 3171–3200; (*b*) L. Katz and G. W. Ashley, *Chem. Rev.*, 2005, **105**, 499–527.
20 D. S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T. C. Chou, L. He and S. B. Horwitz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 757–759.
21 K. C. Nicolaou, R. A. Daines, T. K. Chakraborty and Y. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 2821–2822.
22 K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa and P. Bertinato, *J. Am. Chem. Soc.*, 1993, **115**, 4419–4420.
23 V. E. Kwitkowski, T. M. Prowell, A. Ibrahim, A. T. Farrell, R. Justice, S. S. Mitchell and R. S. R. Pazdur, *Oncologist*, 2010, **15**, 428–435.
24 E. Raymond, J. Alexandre, S. Faivre, K. Vera, E. Materman, J. Boni, C. Leister, J. Korth-Bradley, A. Hanauske and J. P. Armand, *J. Clin. Oncol.*, 2004, **22**, 2336–2347.
25 A. Conlin, M. Fornier, C. Hudis, S. Kar and P. Kirkpatrick, *Nat. Rev. Drug Discovery*, 2007, **6**, 953–954.
26 S. Goodin, *Am. J. Health-Syst. Pharm.*, 2008, **65**, S10–S15.
27 E. Mcdonald, P. Workman and K. Jones, *Curr. Top. Med. Chem.*, 2006, **6**, 1091–1107.
28 G. Sakoulas, P. A. Moise-Broder, J. Schentag, A. Forrest, R. C. Moellering Jr and G. M. Eliopoulos, *J. Clin. Microbiol.*, 2004, **42**, 2398–2402.
29 D. A. Cantrell and K. A. Smith, *Science*, 1984, **224**, 1312–1316.
30 A. Gradillas and J. Perez-Castells, *Angew. Chem., Int. Ed.*, 2006, **45**, 6086–6101.
31 A. Parenty, X. Moreau and J. M. Campagne, *Chem. Rev.*, 2006, **106**, 911–939.
32 F. A. Macías, R. M. Varela, A. Torres, J. M. G. Molinillo and F. R. Fronczek, *Tetrahedron Lett.*, 1993, **34**, 1999–2002.
33 T. Shimokawa, J. Kinjo, J. Yamahara, M. Yamasaki and T. Nohara, *Chem. Pharm. Bull.*, 1985, **33**, 3545–3547.
34 S. B. Singh, H. Jayasuriya, D. L. Zink, J. D. Polishook, A. W. Dombrowski and H. Zweerink, *Tetrahedron Lett.*, 2004, **45**, 7605–7608.
35 Y. Shirataki, Y. Tagaya, I. Yokoe and M. Komatsu, *Chem. Pharm. Bull.*, 1987, **35**, 1637–1640.
36 X. Fu, T. Sévenet, F. Remy, M. Païs, A. Hamid, A. Hadi and L. M. Zeng, *J. Nat. Prod.*, 1993, **56**, 1153–1163.
37 S. Quideau and K. S. Feldman, Ellagitannin chemistry, *Chem. Rev.*, 1996, **96**, 475–504.
38 S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo and R. F. Bryan, *J. Am. Chem. Soc.*, 1973, **95**, 1335–1336.
39 D. J. Abraham, R. D. Rosenstein, R. L. Lyon and H. H. S. Fong, *Tetrahedron Lett.*, 1972, **13**, 909–912.

40 H. Urata, A. Kinoshita, K. S. Misono, F. M. Bumpus and A. Husain, *J. Biol. Chem.*, 1990, **265**, 22348–22357.
41 H. Tomoda, H. Nishida, R. Masuma, J. Cao, S. Okuda and S. Omura, *J. Antibiot.*, 1991, **44**, 136–143.
42 G. M. Salituro, D. J. Pettibone, B. V. Clineschmidt, J. M. Williamson and D. L. Zink, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 337–340.
43 D. Brückner, F. T. Hafner, V. Li, C. Schmeck, J. Telser, A. Vakalopoulos and G. Wirtz, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3611–3614.
44 (*a*) H. Kase, M. Kaneko and K. Yamada, *J. Antibiot.*, 1987, **40**, 450–454; (*b*) S. Sano, K. Ikai, K. Katayama, K. Takesako and T. Nakamura, *J. Antibiot.*, 1986, **39**, 1685–1696.
45 E. Moulin, S. Barluenga and N. Winssinger, *Org. Lett.*, 2005, **7**, 5637–5639.
46 (*a*) A. S. Khartulyari, M. Kapur and M. E. Maier, *Org. Lett.*, 2006, **8**, 5833–5836; (*b*) A. Fiirstner, G. Seklel and N. Kindler, *Tetrahedron*, 1999, **55**, 8215–8230.
47 (*a*) S. S. Palimkar, J. Uenishi and H. Ii, *J. Org. Chem.*, 2012, **77**, 388–399; (*b*) M. Huss, O. Vitavska, A. Albertmelcher, S. Boeckelmann, C. Nardmann, K. Tabke, F. Tiburcy and H. Wieczorek, *Eur. J. Cell Biol.*, 2011, **90**, 688–695.
48 G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, C. McMartin and R. Bohacek, *J. Med. Chem.*, 1997, **40**, 506–514.
49 G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, A. Trapani, C. McMartin and R. Bohacek, *J. Med. Chem.*, 2011, **54**, 1961–2004.
50 A. Lerchner, R. Machauer, C. Betschart, S. Veenstra, H. Rueeger, C. McCarthy, M. Tintelnot-Blomley, A. L. Jaton, S. Rabe, S. Desrayaud, A. Enz, M. Staufenbiel, P. Paganetti, J. M. Rondeau and U. Neumann, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 603–607.
51 Y. Huang, E. D. Strobel, C. Y. Ho, C. H. Reynolds, K. A. Conway, J. A. Piesvaux, D. E. Brenneman, G. J. Yohrling, H. M. Arnold, D. Rosenthal, R. S. Alexander, B. A. Tounge, M. Mercken, M. Vandermeeren, M. H. Parker, A. B. Reitz and E. W. Baxter, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3158–3160.
52 X. Li, Y. K. Zhang, Y. Liu, C. Z. Ding, Y. Zhou, Q. Li, J. J. Plattner, S. J. Baker, S. Zhang, W. M. Kazmierski, L. L. Wright, G. K. Smith, R. M. Grimes, R. M. Crosby, K. L. Creech, L. H. Carballo, M. J. Slater, R. L. Jarvest, P. Thommes, J. A. Hubbard, M. A. Convery, P. M. Nassau, W. McDowell, T. J. Skarzynski, X. Qian, D. Fan, L. Liao, Z. J. Ni, L. E. Pennicott, W. Zou and J. Wright, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5695–5700.
53 C. J. Dinsmore, M. J. Bogusky, J. C. Culberson, J. M. Bergman, C. F. Homnick, C. B. Zartman, S. D. Mosser, M. D. Schaber, R. G. Robinson, K. S. Koblan, H. E. Huber, S. L. Graham, G. D. Hartman, J. R. Huff and T. M. Williams, *J. Am. Chem. Soc.*, 2001, **123**, 2107–2108.
54 C. J. Dinsmore, C. B. Zartman, J. M. Bergman, M. T. Abrams, C. A. Buser, J. C. Culberson, J. P. Davide, M. Ellis-Hutchings, C. Fernandes, S. L. Graham, G. D. Hartman, H. E. Huber, R. B. Lobell, S. D. Mosser, R. G. Robinson and T. M. Williams, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 639–643.
55 P. G. Nantermet, J. C. Barrow, C. L. Newton, J. M. Pellicore, M. Young, S. D. Lewis, B. J. Lucas, J. A. Krueger, D. R. McMasters, Y. Yan, L. C. Kuo, J. P. Vacca and H. G. Selnick, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2781–2784.
56 E. Marsault, K. Benakli, S. Beaubien, C. Saint-Louis, R. Deziel and G. Fraser, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4187–4190.
57 E. Marsault and M. L. Peterson, *J. Med. Chem.*, 2011, **54**, 1961–2004.
58 G. L. Fraser and H. R. Hoveyda, PCT Intl Appl. WO 06/046977, 2005.
59 U. Lucking, G. Siemeister, M. Schafer, H. Briem, M. Kruger, P. Lienau and R. Jautelat, *ChemMedChem*, 2007, **2**, 63–77.
60 N. Kawanishi, T. Sugimoto, J. Shibata, K. Nakamura, K. Masutani, M. Ikuta and H. Hirai, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5122–5126.
61 X. Yu and D. Sun, *Molecules*, 2013, **18**, 6230–6268.
62 S. Hart, K. C. Goh, V. Novotny-Diermayr, C. Y. Hu, H. Hentze, Y. C. Tan, B. Madan, C. Amalini, Y. K. Loh, L. C. Ong, A. D. William, A. Lee, A. Poulsen, R. Jayaraman, K. H. Ong, K. Ethirajulu, B. W. Dymock and J. W. Wood, *Leukemia*, 2011, **25**, 1751–1759.
63 R. S. Komrojki, M. Wadleigh and J. F. Seymour, *presented at: 53rd ASH Annual Meeting and Exposition*, San Diego Convention Center, San Diego, CA, USA, pp. 10–13, December 2011.
64 A. D. William, A. C. H. Lee and K. C. Goh, *J. Med. Chem.*, 2012, **55**, 169–196.
65 H. Hirai, I. Takahashi-Suziki, T. Shimomura, K. Fukasawa, T. Machida, T. Takaki, M. Kobayashi and T. Eguchi, *Invest. New Drugs*, 2011, **29**, 534–543.
66 N. J. Liverton, S. S. Carroll, J. Dimuzio, C. Fandozzi, D. J. Graham, D. Hazuda, M. K. Holloway, S. W. Ludmerer, J. A. McCauley, C. J. McIntyre, D. B. Olsen, M. T. Rudd, M. Stahlhut and J. P. Vacca, *Antimicrob. Agents Chemother.*, 2010, **54**, 305–311.
67 K. C. Lasseter, L. Shaughnessy, D. Cummings, J. C. Pezzullo, W. Wargin, R. Gagnon, J. Oliva and G. Kosutic, *J. Clin. Pharmacol.*, 2008, **48**, 193–202.
68 J. C. Collins and K. James, *Med. Chem. Commun.*, 2012, **3**, 1489–1495.
69 D. C. Harrowven and S. L. Kostiuk, *Nat. Prod. Rep.*, 2012, **29**, 223–242.
70 N. K. Terrett, *Drug Discovery Today: Technol.*, 2010, **7**, e97–e104.
71 L. Wessjohann and E. Ruijter, in *Natural Product Synthesis I*, Springer Berlin Heidelberg, Berlin, Germany, 2005, vol. 243, pp. 137–184.
72 A. E. Horton, O. S. May, M. R. J. Elsegood and M. C. Kimber, *Synlett*, 2011, **22**, 797–800.
73 A. Parenty, X. Moreau, G. Niel and J. M. Campagne, *Chem. Rev.*, 2013, **113**, PR1–PR40.
74 R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman and J. A. Porco Jr, *J. Am. Chem. Soc.*, 2003, **125**, 7889–7901.

75 G. A. Holloway, H. M. Hugel and M. A. Rizzacasa, *J. Org. Chem.*, 2003, **68**, 2200–2204.
76 R. Shen, C. T. Lin and J. A. Porco Jr, *J. Am. Chem. Soc.*, 2002, **124**, 5650–5651.
77 Q. Su and J. S. Panek, *J. Am. Chem. Soc.*, 2004, **126**, 2425–2430.
78 S. S. Palimkar, J. Uenishi and H. Ii, *J. Org. Chem.*, 2012, **77**, 388–399.
79 E. Marsault, L. Ouelet, C. Saint-Louis, S. Beaubien, K. Benakli, H. R. Hoveyda, M. L. Peterson and S. Bhat, *U.S. Pat.*, Appl. 2009/0198050, 2008.
80 Z. Nie, C. Perretta, P. Erickson, S. Margosiak, J. Lu, A. Averill, R. Almassy and S. Chu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 619–623.
81 W. Zhang and J. S. Moore, *Angew. Chem., Int. Ed.*, 2006, **45**, 4416–4439.
82 R. Lépine and J. Zhu, *Org. Lett.*, 2005, **7**, 2981–2984.
83 J. N. L. Dufour and J. Zhu, *Chem.–Eur. J.*, 2010, **16**, 10523–10534.
84 R. Yamasaki, A. Shigeto and S. Saito, *J. Org. Chem.*, 2011, **76**, 10299–10305.
85 V. Balraju, D. S. Reddy, M. Periasamy and J. Iqbal, *J. Org. Chem.*, 2005, **70**, 9626–9628.
86 K. C. Majumdar, B. Chattopadhyay and K. Ray, *Tetrahedron Lett.*, 2007, **48**, 7633–7636.
87 (*a*) K. C. Majumdar and B. Chattopadhyay, *Synthesis*, 2009, 2385; (*b*) K. C. Majumdar and B. Chattopadhyay, *Synlett*, 2008, 0979–0982.
88 K. C. Majumdar, B. Chattopadhyay and S. Samanta, *Tetrahedron Lett.*, 2009, **50**, 3178–3181.
89 K. Akaji, K. Teruya, M. Akaji and S. Aimoto, *Tetrahedron*, 2001, **57**, 2293–2303.
90 C. W. Zapf, J. D. Bloom, J. L. McBean, R. G. Dushin, J. M. Golas, H. Liu, J. Lucas, F. Boschelli, E. Vogan and J. I. Levin, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3627–3631.
91 V. Balraju and J. Iqbal, *J. Org. Chem.*, 2006, **71**, 8954–8956.
92 K. C. Nicolaou, N. Winssinger, J. Pastor and F. Murphy, *Angew. Chem., Int. Ed.*, 1998, **37**, 2537–2547.
93 W. Li and K. Burgess, *Tetrahedron Lett.*, 1999, **40**, 6527–6530.
94 S. M. Lu and H. Alper, *Chem.–Eur. J.*, 2007, **13**, 5908–5916.
95 A. Sharma, P. Appukkuttan and E. van der Eycken, *Chem. Commun.*, 2012, **48**, 1623–1637.
96 Q. Su, A. B. Beeler, E. Lobkovsky, J. A. Porco and J. S. Panek, *Org. Lett.*, 2003, **5**, 2149–2152.
97 L. Shen, C. J. Simmons and D. Sun, *Tetrahedron Lett.*, 2012, **53**, 4173–4178.
98 P. Mestichelli, M. J. Scott, W. R. J. D. Galloway, J. Selwyn, J. S. Parker and D. R. Spring, *Org. Lett.*, 2013, **15**, 5448–5451.
99 A. Berthelot, S. Piguel, G. Le Dour and J. Vidal, *J. Org. Chem.*, 2003, **68**, 9835–9838.
100 A. Poloukhtine, V. Rassadin, A. Kuzmin and V. V. Popik, *J. Org. Chem.*, 2010, **75**, 5953–5962.
101 T. Zhang, X. Huang, J. Xue and S. Sun, *Tetrahedron Lett.*, 2009, **50**, 1290–1294.
102 R. A. Bauer, T. A. Wenderski and D. S. Tan, *Nat. Chem. Biol.*, 2013, **9**, 21–30.
103 F. Kopp, C. F. Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, 2012, **8**, 358–365.
104 M. C. Zaccaro, H. B. Lee, M. Pattarawarapan, Z. Xia, A. Caron, P. J. L. Heureux, Y. Bengio, K. Burgess and H. U. Saragovi, *Chem. Biol.*, 2005, **12**, 1015–1028.
105 E. J. Kang, S. Y. Lee, H. Lee and S. S. Lee, *Inorg. Chem.*, 2010, **49**, 7510–7520.
106 J. Buter and R. M. Kellogg, *J. Org. Chem.*, 1981, **46**, 4481–4485.
107 R. Mamouni, M. Soukri, S. Lazar, M. Akssira and G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 2631–2633.
108 S. K. Chattopadhyay, T. Biswas and S. Maity, *Synlett*, 2006, 2211.
109 A. Fürstner, G. Seidel and N. Kindler, *Tetrahedron*, 1999, **55**, 8215–8230.
110 G. Evano, J. V. Schaus and J. S. Panek, *Org. Lett.*, 2004, **6**, 525–528.
111 K. C. Nicolaou, T. Montagnon, G. Vassilikogiannkabis and C. J. N. Mathison, *J. Am. Chem. Soc.*, 2005, **127**, 8872–8888.
112 B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck and A. Domling, *Org. Lett.*, 2003, **5**, 1047–1050.
113 S. Dandapani and L. A. Marcaurelle, *Nat. Chem. Biol.*, 2010, **6**, 861–863.
114 A. D. Abell, N. A. Alexander, S. G. Aitken, H. Chen, J. M. Coxon, M. A. Jones, S. B. Mc Nabb and A. Muscroft-Taylor, *J. Org. Chem.*, 2009, **74**, 4354–4356.
115 J. Pérez-Castells and A. Gradillas, *Angew. Chem., Int. Ed.*, 2006, **45**, 6086–6101.
116 S. Y. Hong, M. W. Day and R. H. Grubbs, *J. Am. Chem. Soc.*, 2004, **126**, 7414–7415.
117 A. Fürstner, G. Seidel and N. Kindler, *Tetrahedron*, 1999, **55**, 821–8230.
118 S. Barluenga, P. L. Spez, E. Moulin and N. Winssinger, *Angew. Chem.*, 2004, **116**, 3549–3552; *Angew. Chem., Int. Ed.*, 2004, **43**, 3467–3470.
119 C. Herb, A. Bayer and M. E. Maier, *Chem.–Eur. J.*, 2004, **10**, 5649–5660.
120 A. Fürstner and C. Müller, *Chem. Commun.*, 2005, 5583–5585.
121 K. C. Swamy, N. N. Kumar, E. Balaraman and K. V. Kumar, *Chem. Rev.*, 2009, **109**, 2551–2651.
122 J. Rujirawanich and T. Gallagher, *Org. Lett.*, 2009, **11**, 5494–5496.
123 C. Herb and M. E. Maier, *J. Org. Chem.*, 2003, **68**, 8129–8135.
124 J. K. Mishra and G. Panda, *J. Comb. Chem.*, 2007, **9**, 321–338.
125 A. Delgado and J. Clardy, *J. Org. Chem.*, 1993, **58**, 2862, and references cited therein.
126 L. V. R. Boñaga, H. C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo and B. E. Maryanoff, *J. Am. Chem. Soc.*, 2005, **127**, 3473–3485.
127 B. Kevin Bahnck and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 2008, **130**, 13177–13181.
128 J. Zhang, J. Kemmink, D. T. S. Rijkers and R. M. J. Liskamp, *Org. Lett.*, 2011, **13**, 3438–3441.
129 S. M. Mennen and S. J. Miller, *J. Org. Chem.*, 2007, **72**, 5260–5269.

130 R. F. P. Faraco, G. C. B. de Oliveira, G. D. Pinto, A. P. C. Rocha, R. J. Alves, R. B. Alves, P. V. Abdelnur, M. N. Eberlin and M. A. F. Prado, *J. Braz. Chem. Soc.*, 2009, **20**, 1504–1514.
131 (*a*) P. Chattopadhyay, M. Mukherjee and S. Ghosh, *Chem. Commun.*, 1997, 2139–2140; (*b*) A. Neogi, T. P. Majhi, N. Ghoshal and P. Chattopadhyay, *Tetrahedron*, 2005, **61**, 9368–9374.
132 A. Neogi, T. P. Majhi, B. Achari and P. Chattopadhyay, *Eur. J. Org. Chem.*, 2008, 330–336.
133 E. Comer, H. Liu, A. Joliton, A. Clabaut, C. Johnson, L. B. Akella and L. A. Marcaurelle, *PNAS*, 2011, **108**, 6751–6756.
134 M. J. Kim, S. H. Lee, S. O. Park, H. Kang, J. S. Lee, K. N. Lee, M. E. Jung, J. Kim and J. Lee, *Bioorg. Med. Chem.*, 2011, **19**, 5468–5479.
135 E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614.
136 A. Hussain, S. K. Yousuf, D. Kumar, L. Mallikharjuna, S. Maity, B. Singh and D. Mukherjee, *Adv. Synth. Catal.*, 2012, **354**, 1933–1940.
137 A. Hussain, S. K. Yousuf, D. Kumar, L. Mallikharjuna, B. Singh and D. Mukherjee, *Tetrahedron*, 2013, **69**, 5517–5524.
138 A. Hussain, L. Mallikharjuna, D. K. Sharma, A. K. Tripathi, B. Singh and D. Mukherjee, *RSC Adv.*, 2013, **3**, 19899–19904.