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

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Altaf Hussain,[ab] S. K. Yousuf,[b] Debaraj Mukherjee*[ab]

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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 reached the late developmental stages in clinical trials. Such cyclic systems have been shown to possess great potential especially towards the discovery of new anticancer leads. Efforts from synthetic chemists have led to the development of new elegant 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 strategies available for their synthesis developed over the years.

Introduction

Cyclic molecular frameworks occupy a unique segment of chemical space. Cyclic scaffolds particularly the 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, the cyclic scaffolds enable a molecule 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 on binding. These cyclic systems can therefore be highly potent as well as selective. In the past decade, their chemical diversity 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 heterocycles are quite significant in organic chemistry as these are the structural core of a large number of biologically active natural products[6] and medicinally important synthetic compounds to address diverse and challenging biological targets.[7] Marine organisms have produced various nonterpenoid 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**), (+)-brasilenyne (**6**) as shown in figure 1a.[8] Importance of medium-ring compounds can also be seen from their existence in many bioactive natural products shown in figure 1a such as (-)-ovatolide (**7**),[9] cephalosporolides G (**8**),[10] octalactins A (**9**) and B (**10**),[11] fulvine (**11**),[12] crispatine (**12**)[13] monocrotaline (**13**)[14], dicrotaline (**14**).[14] Although there are synthetic challenges associated with the synthesis of medium rings, efforts from synthetic chemists have led to the generation of unnatural medium ring compounds **15-18** (figure 1a).[15] However, despite their occurrence in many important natural products, medium 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 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 a 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**), (+)-aspicin (**21**), fluvicin B1 (**22**), (+)-migrastatin (**23**), (-)-dictyolide (**24**), zampanolide (**25**), epothilones A-F (**26-31**), and synthetic molecules **32-34** as shown in figure 1b. Many natural products have 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

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-allylamino-geldanamycin,[27] vancomycin,[28] cyclosporine[29] etc. The medicinal chemistry of macrocyclic natural products usually involved direct use as a therapeutic agent or functionalization of the natural product scaffold by semisynthesis. It parallels 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.

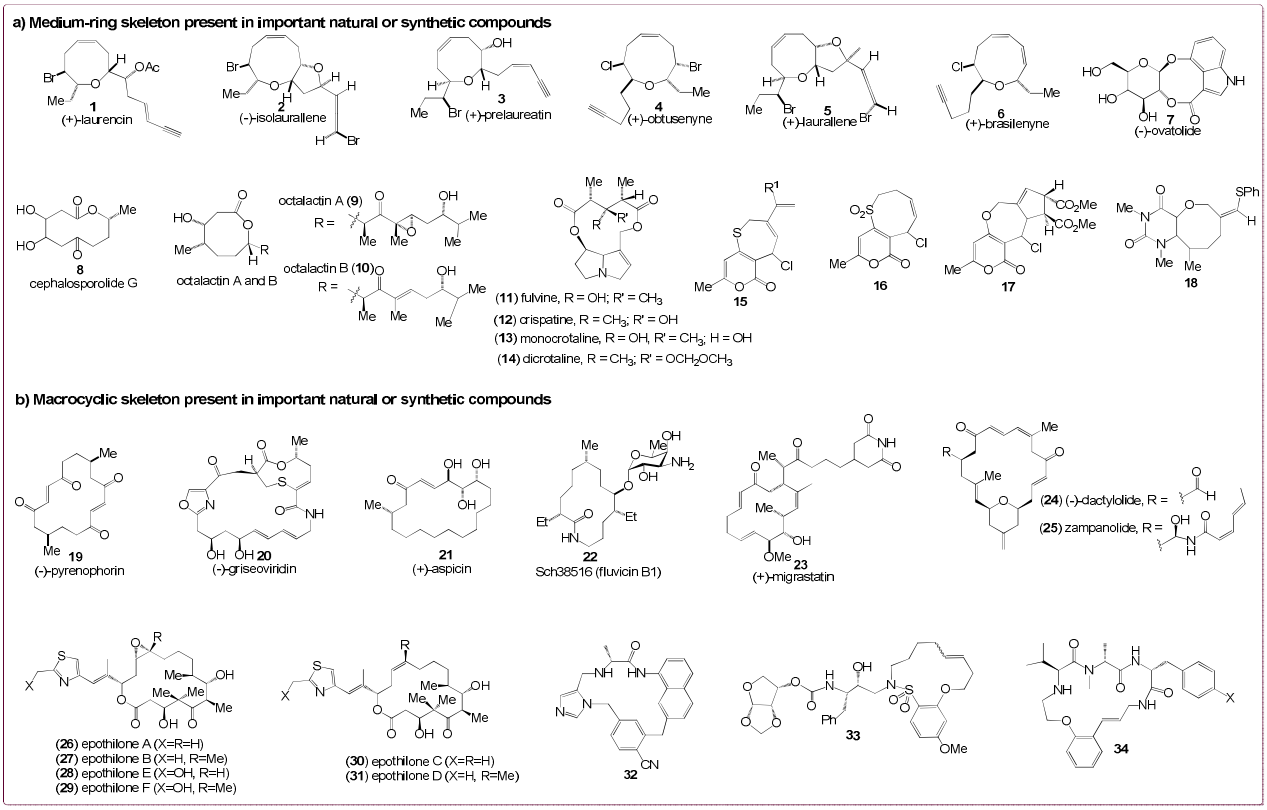


Figure 1. Abundance of medium-sized and macrocyclic ring skeleton in bioactive natural and synthetic molecules.

Macrocycles inherently possess a lower number of rotatable bonds and hence, are conformationally more restricted than their acyclic analogues, which potentially can impart higher 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, the 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.

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

The medium-sized and macrocyclic ring scaffolds annulated to an aromatic system are termed as benzannulated medium rings or benzannulated macrocycles respectively.. Further, 1,3- or 1,4-linkage with benzene ring has been termed 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 innumerable number of bioactive natural and pharmacoclogically important synthetic molecules.

2.1. Biological significance of benzannulated medium rings

Benzannulated medium-sized rings are of great interest due their presence in a number of biologically significant natural molecules which include aryl ethers such as the 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 figure 2. Benzannulated medium-rings also constitute the core of coleophomones B (**43**) and C (**44**) showing anti-fungal and

serine protease enzyme inhibition activities),[40] purpactin A (**45**, acyl-CoA-colesterol acyl transferase inhibitor),[41] penicillide (**46**, antagonists of the peptide hormone oxytocin and inhibitors of cholesterol ester transfer protein).[42,43] Many synthetically produced benzannulated medium-ring compounds (**47**-**50**) have also appeared in literature (enlisted in figure 2). The presence of medium-ring skeleton in bioactive natural products clearly indicates the benzannulated medium-ring framework is a biologically significant system.

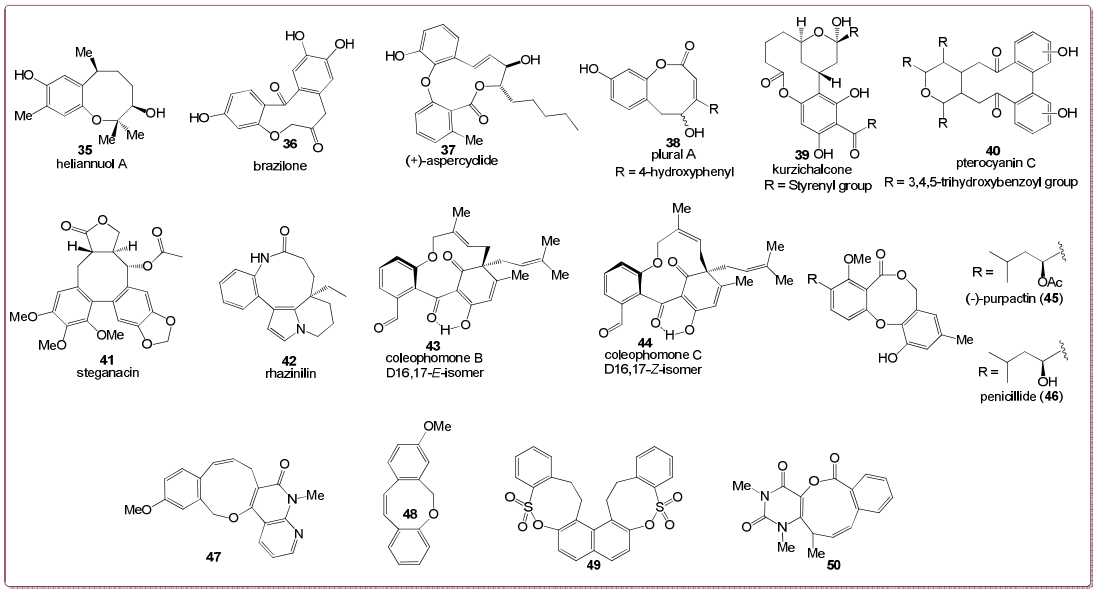


Figure 2. Benzannulated medium-rings in biologically significant natural products and synthetic molecules.

2.2.0. Biological significance of benzannulated macrocycles

Benzannulated macrocycles are of extreme 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 (figure 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] 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 cancer and osteoporosis.[47] The compounds **63**-**66** are a group of naturally occurring bridged benzannulated macrocycles.

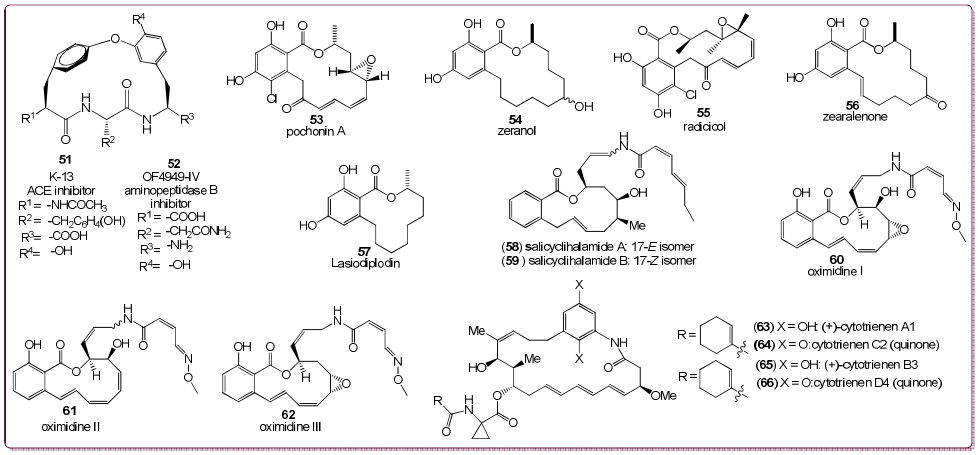


Figure 3. Benzannulated macrocyclic ring skeleton present in bioactive natural products.

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 inhibitions, (2) agonists and antagonists of G protein-coupled receptors (GPCRs), (3) disruption of protein-protein interactions and (4) DNA quadruplex stabilization. The following examples will put light on the usefulness of synthetic benzannulated macrocycles in the drug discovery program (figure 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).[52,53]

b) Thrombin inhibitors: Benzannulated macrocycles **69** (Ki 0.4-2.9 nM) and **70** (Ki = 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} value of 70 nM (cell) and 7 nM (cell) respectively.[54,55]

d) Hepatitis C virus (HCV) NS3 protease inhibitors: Bridged benzannulated macrocyclic scaffolds **73** (Ki = 530 and IC_{50} 400 nM) and **74** (Ki = 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 inhibitors **75** with submicromolar cellular inhibition of the NS3 protease (Ki 43 nM and IC_{50} 780 nM).[56]

e) Farnesyl transferase inhibitors (FTase): The inhibition of FTase has been pursued as an approach to fight cancer, leading to several clinical candidates. The scaffolds **76** and **77** possessed excellent FTase inhibitory activities (0.1 and 1.3 nM respectively).[57,58]

f) HIV protease inhibition: The bridged benzannulated macrocyclic compounds **78**, **79** and benzannulated macrocycle **80** displayed nanomolar potency towards HIV protease inhibition with Ki values of 0.6, 15 and 0.7 nM respectively.[59]

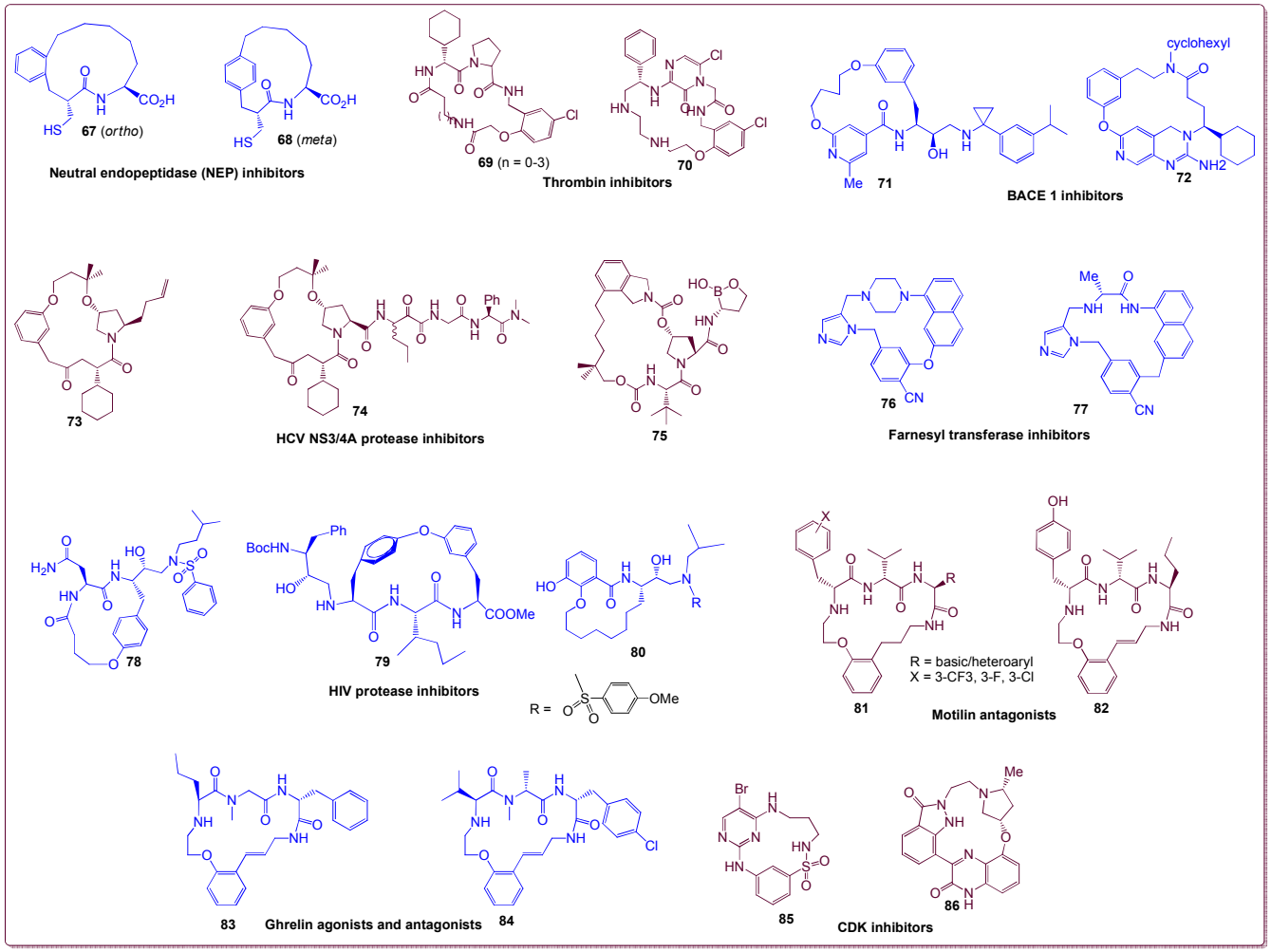


Figure 4. Biologically important synthetic benzannulated macrocycles.

g) Motilin antagonists: From HTS campaign, benzannulated macrocyclic motilin antagonist **81** was identified, possessing a high potency (IC_{50} = 137 nM). Lead optimization studies led to multiple analogues with low nanomolar potency, including analogues (**82**, IC_{50} = 1-20 nM).[60]

h) Ghrelin agonists: Hoveyda et al. identified the benzannulated macrocycle **83** as a ghrelin agonist possessing EC_{50} = 68 nM, a high level of potency.[61] The analogue **84** has been found to be more active with EC_{50} value of 14 nM.[62]

i) CDK inhibitors: Deregulation of kinase signaling pathways can lead to the treatment of cancer. The benzannulated macrocyclic compounds **85** and **86** are highly potent antiproliferative agents. The compound **85** showed the IC_{50} values of 20 nM (CDK1), 140 nM (CDK2), 40 nM (VEGFR-R2), 200 nM (MCF7) while **86** showed the IC_{50} values of 1 nM (CDK1), 3.4 nM (CDK2), 6.4 nM (CDK4), 12 nM (CDK6).[58,59]

3.0. 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.[17,63] and many of these molecules have been developed into approved drugs (figure 5).[17,18] The benzannulated macrocyclic drug rifamycin family include rifampin (**87**) rifapentine (**88**), rifabutin (**89**) and rifaximin (**90**) which constitute a notable class of antibiotic drugs.[65]

Moreover, a number of benzannulated or bridged benzannulated macrocycles have entered clinical development (figure 5), such as the dual JAK2/FLT3 inhibitor pacritinib (**91**), now in advanced Phase III trials[66,67] the CDK2/JAK2/FLT3 inhibitor (**92**, SB1317) in Phase I trial.[68] The pan-CDK inhibitor (**93**) is a another example of synthetic benzannulated macrocyclic ring proposed as a development candidate[69] (figure 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.[70] Ulimorelin (**95**, TZP-101) is another example of benzannulated macrocycle which demonstrated efficacy in phase 2 clinical studies when administered intravenously for the treatment of postoperative ileus and acute gastroparesis.[71] Ulimorelin finally entered phase 3 clinical trials.

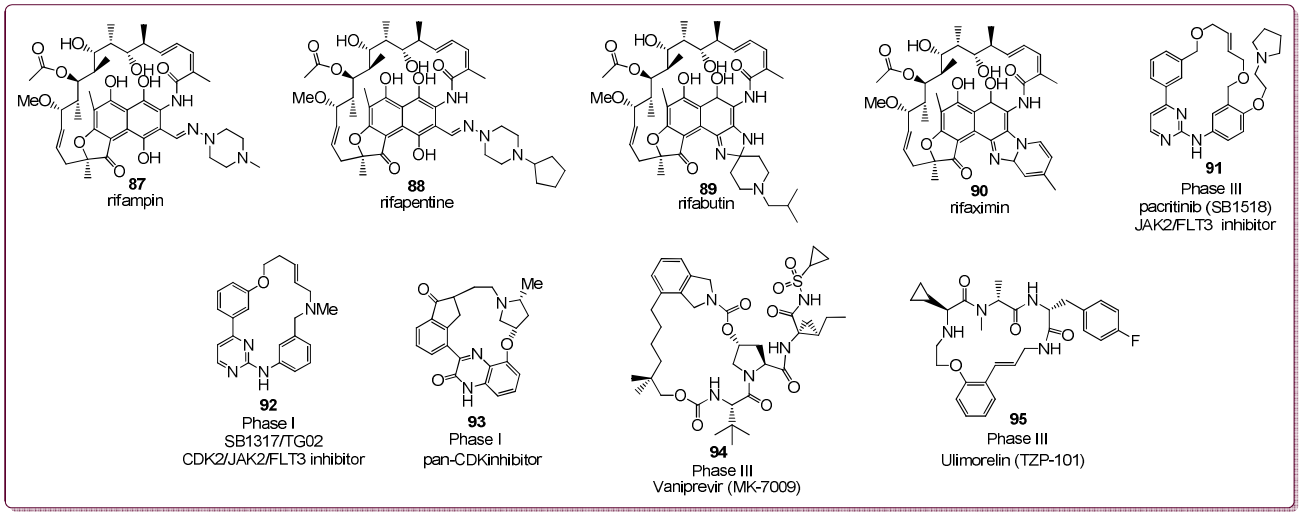


Figure 5. Benzannulated macrocyclic rings as drugs and clinical candidates.

4.0 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 intriguing biological activity and inspired by intractable synthetic complexity of naturally occurring medium-ring or macrocycles, much effort has been devoted to explore highly efficient and superior synthetic methods for the preparation of medium-ring or macrocycles.[72-75]Among the cyclization methodologies, lactonization, lactamization, transition metal catalyzed coupling reaction, ring-closing metathesis, and click chemistry represent the most efficient and commonly used synthetic approaches for construction of BMR frameworks.

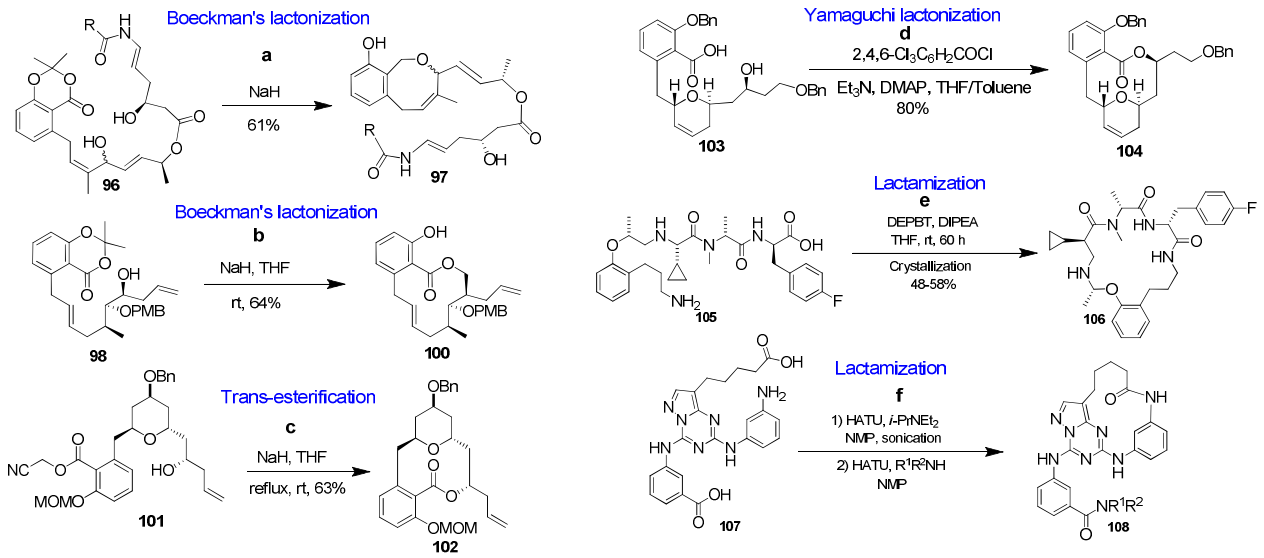
4.1. Lactonization and Lactamization

Lactones constitute a major part of synthetic or naturally occurring BMRs, which mediate diverse biological activities.[76] For their synthesis, many reports regarding efficient cyclizations have been published. In general, the most frequently used and attractive cyclic approaches still come to

the direct lactonization of acids and alcohols using various activation schemes.[77]

Porco et al. reported the synthesis of 8-membered benzolactone (**97**) from **96** in a Boeckman type lactonization (scheme 1a).[78] A methodology related to Boeckman's lactonization has also been used in the synthesis of salicylihalamide **100** (scheme 1b).[79] Panek et al. used a cyanomethyl ester previously described in intermolecular transesterifications[80] in the synthesis of apicularen (**102**, scheme 1c).[81] S. S. Palimkar et al. reported the synthesis of pyran based macrocyclic benzolactone (-)-apicularen (**104**) from compound **103** where the key cyclization step was Yamaguchi coupling (scheme 1).[82]

Among many methods for synthesizing lactams, the most common and efficient approach is lactamization. Lactamization of **105** followed by purification by crystallization to provide **106** in very good overall yield (scheme 1e).[83] Nie et al. reported the formation of bridged benzannulated macrocycle **108** via lactamization strategy in the presence of two carboxylic acids (**107**), allowing a one-pot, two-step diamide formation conditions (scheme 1f).[84]



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

4.2. Transition metal catalyzed coupling reactions

Over the past decades, transition metal catalyzed cross coupling reactions have become a striking tool for creating new C-C, C-O or C-N bonds.[85] Among transition metals, the most versatile metal is palladium which has huge application 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).[86] Intramolecular Suzuki-Miyaura reaction of tripeptidomimetic **111** yielded the strained bridged benzannulated 14-membered macrocycle **112** (scheme 2b).[87] Saito and coworkers applied the Sonogashira reaction to prepare benzannulated macrocycles by the treatment of catalyst $Pd(CH_3CN)_2Cl_2$, 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 get the final product **115** in 13% yield (scheme 2c).[88] 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 tripeptidomimetics **117**.[89]

Intramolecular Heck coupling have also found its application in the synthesis of a large number of biologically significant macrocycles but there is only one report where it is utilized for the synthesis of benzannulated ring ethers. Heck reaction of **118** was carried out using 5 mol% of $Pd(OAc)_2$ as catalyst, K_2CO_3 as base, TBAB as additive in CH_3CN at 80 °C for 2 hours, the benzannulated medium-ring compound **119** was obtained in 70% yields (scheme 2e).[90]

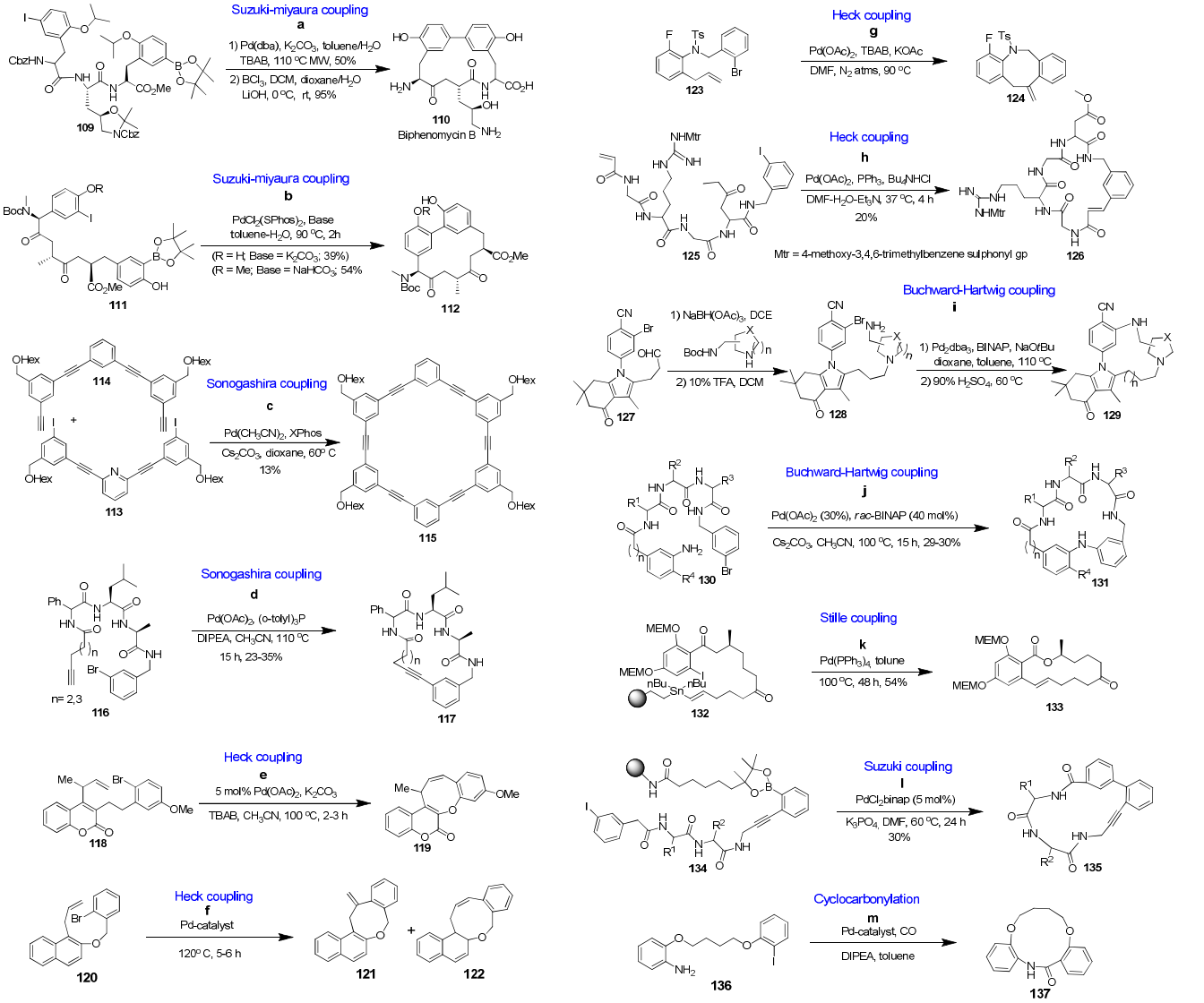
K. C. Majumdar et al. reported an efficient and high yielding method for the synthesis of benzannulated 8- and 9-membered ring ethers (**121** and **122**) via palladium-catalyzed intramolecular Heck reaction (scheme 2f).[91]

When the intramolecular Heck reaction was conducted 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% yields (scheme 2g).[92] Heck methodology was also employed in the solid phase construction of cyclic RGD peptidomimetics **126** (scheme 2h).[93]

Zapf and coworkers designed and synthesized the amino-based bridged benzannulated macrocyclic structure **129** via the Buchwald-Hartwig reaction (scheme 2i).[94] Balraju and Iqbal also employed the Buchwald-Hartwig C-N coupling reaction for macrocyclization in the construction of a bridged

benzannulated macrocycle **131** constrained with a diphenylamine linker (scheme 2j).[95]

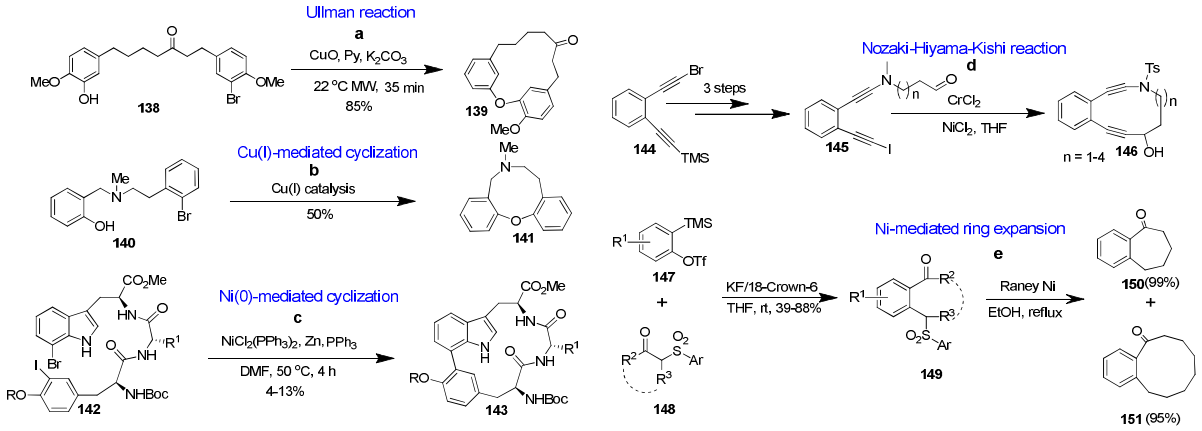
Stille coupling provided the key step in a cyclization release solid phase synthesis strategy directed toward macrocyclic natural product **133** (scheme 2k).[96] Li and Burgess reported solid phase linker **134** specifically for enabling a simultaneous Suzuki coupling, macrocyclization, and resin release process giving an alternative method for the construction of benzannulated macrocycles of the type **135** (scheme 2l).[97] Shui-Ming Lu 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).[98] This process can tolerate a wide variety of functional groups, including halide, ether, ketone, and ester.



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

Apart from Pd, other transition metals like Ni, Cu, Cr etc. have also found application in the synthesis of benzannulated cyclic systems. In this regard, microwave-assisted cyclization by different strategies provides an efficient route to synthesize diverse medium-sized heterocycles[99] and macrocycles.[100] Recently, Sun's group reported microwave-assisted intramolecular Ullmann reaction to yield bridged benzannulated macrocyclic diaryl ether analogues (**139**) from **138** (scheme 3a).[101] 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** undergo an intramolecular C-O bond-forming reaction (scheme 3b).[102]

Nickel-mediated cyclization of **142** provided the target molecule **143** (scheme 3c).[103] Poulukhtine et al. reported that Nozaki-Hiyama-Kishi conditions gave the benzannulated medium-ring or macrocycles of the type **146** (scheme 3d).[104] Zhang et al. reported that by ring expansions and desulfonylations, medium- and large-sized benzannulated rings of the type **150** and **151** were obtained in excellent yields (scheme 3e).[105]

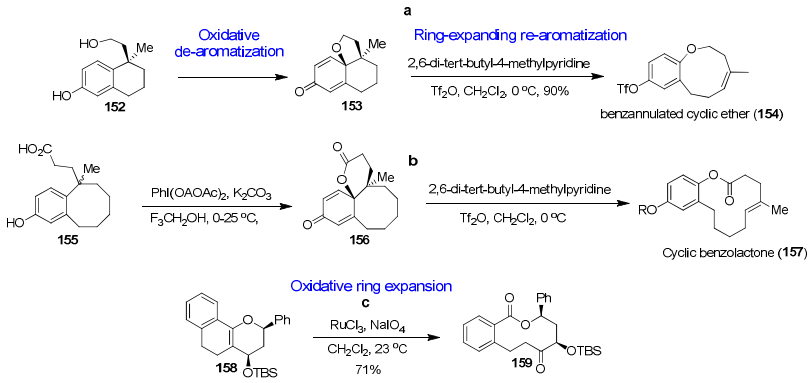


Scheme 3. Synthesis of benzannulated medium-sized and macrocyclic rings via Cu(II), Ni(II) and Cr(II) catalyzed reactions.

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. have established an alternative biomimetic ring expansion approach to the diversity-oriented synthesis of medium-ring libraries. As depicted in scheme 4, the oxidative de-aromatization of bicyclic phenols (**152**) afford polycyclic cyclohexadienones (**153**) that undergo efficient ring expanding re-aromatization to form benzannulated medium-ring scaffolds (**154**) as depicted in scheme 4a.[106] 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).[107]

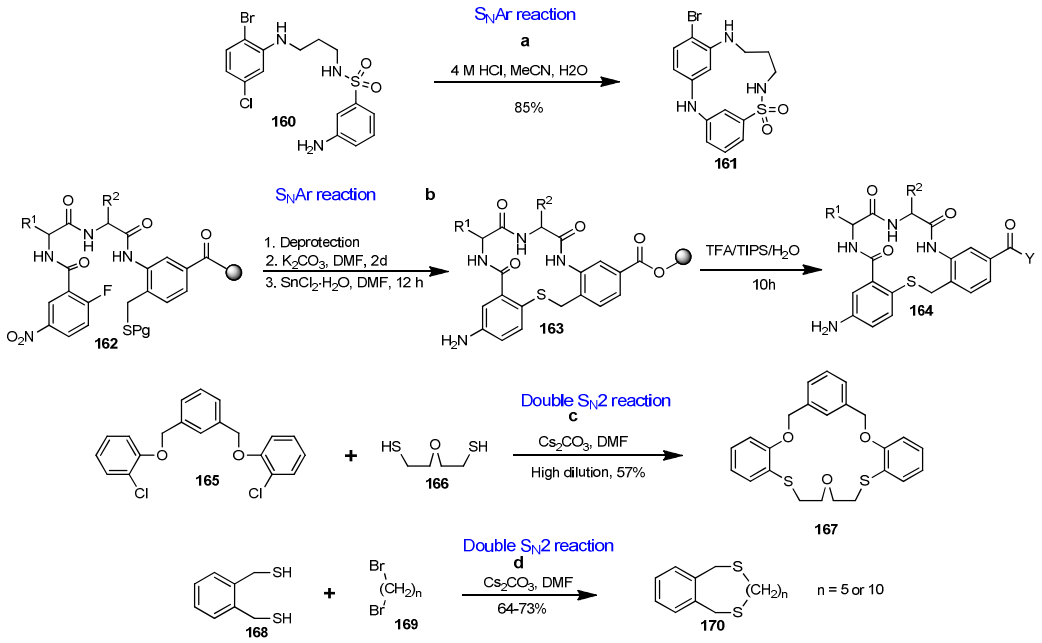


Scheme 4. Synthesis of benzannulated rings through biomimetic and oxidative ring expansions.

4.4. Nuclephilic substitutions

S_N2 and S_NAr reactions has found application in the synthesis of benzannulated macrocycles as exemplified in the synthesis of bridged benzannulated macrocycle **161** depicted in scheme 5a.[62] S_NAr methodology was utilized as a key step in the solid phase synthesis of benzannulated macrocyclic thio-ether based dipeptidomimetic **164** designed as mimic of the *β*-turn structure of neurotrophin growth factors (scheme 5b).[108]

Eun-Ju Kang et al. reported he formation of benzannulated macrocyclic thio-ethers by S_N2 reaction of dichloride (**165**) and 2-mercaptoethyl ether (**166**) leading to the formation of macrocyclic thio-ether **167** (scheme 5c).[109] Buter et al. also reported the synthesis of benzannulated macrocyclic thio-ethers **170** via S_N2 reaction of cesium thiolates (generated *in situ* from dithiol (**168**) and Cs_2CO_3 in DMF) with dibromide (**169**) (scheme 5d).[110]



Scheme 5. Synthesis of benzannulated medium-sized and macrocyclic rings through S_NAr and S_N2 reaction..

4.5. Ring-closing metathesis (RCM)

The construction of medium-ring 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 finding of suitable reaction conditions is critical for the success of the synthesis. There numerous examples of benzannulated medium-rings or macrocyclic rings synthesized by RCM.

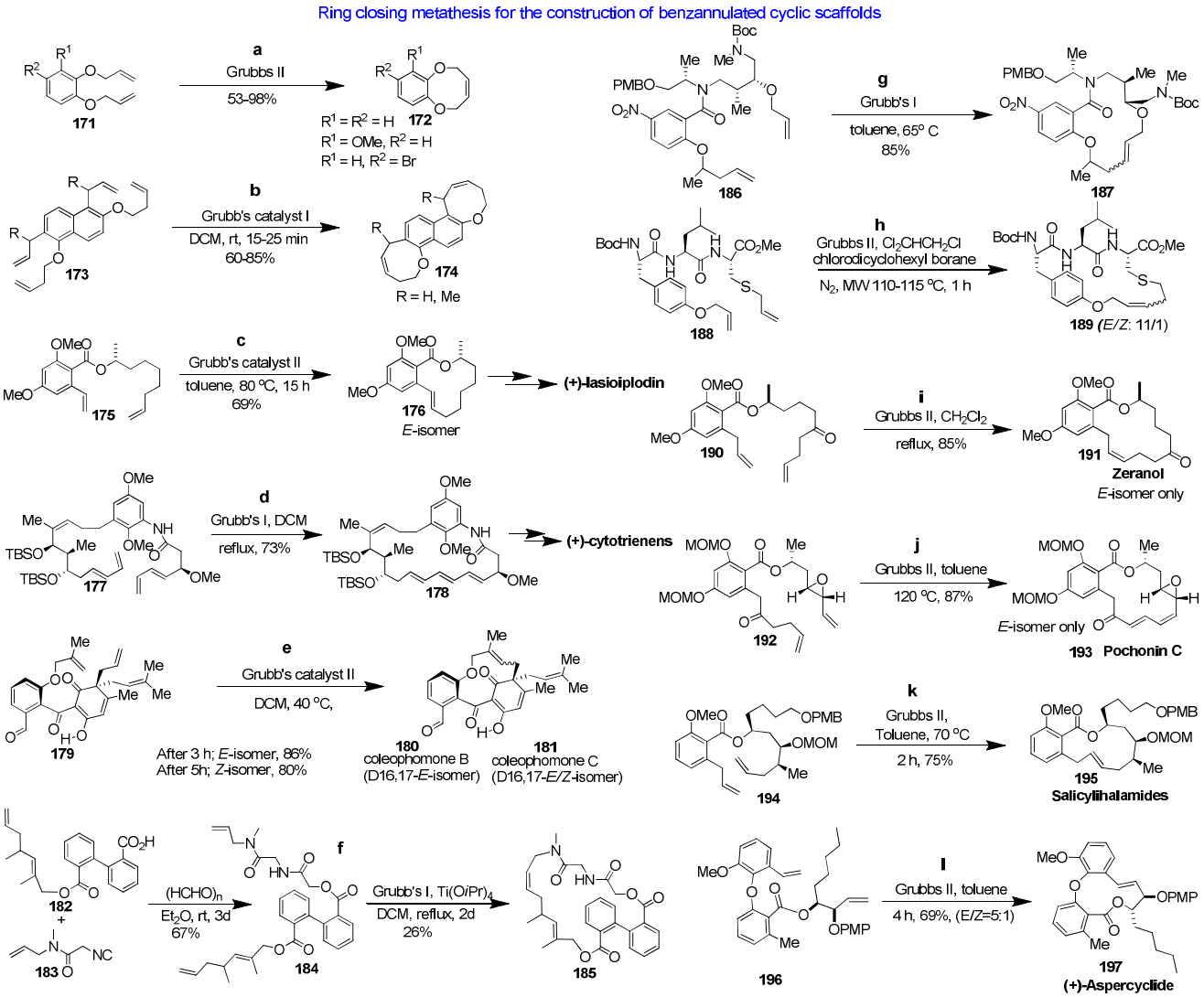
R. Mamouni et al. reported that bis-allyl ether derivatives **171** directly led to the corresponding benzannulated medium rings **172** in good to excellent yield under RCM conditions (scheme 6a).[111] S. K. Chattopadhyay et al. reported that when a dichloromethane solution of **173** and commercially available Grubbs' catalyst 1 was stirred at room temperature under nitrogen atmosphere the reaction proceeded smoothly to give the bis-benzoxepine **174** in 90% yield (scheme 6b).[112] Fürstner et al. developed an RCM-based approach to synthesize benzannulated macrocyclic intermediate **176** which was then converted to (R)-(+)-lasiodiplodin (scheme 6c).[113] Evano et al. reported the synthesis of bridged benzannulated macrocycle **178** with excellent selectivity and yield (scheme 6d).[114] The highly strained benzannulated medium ring of coleophomones B and C (**180** and **181**) was constructed by using an impressive olefin metathesis reaction to build the bond between C-16 and C-17 (scheme 6e).[115]

Beck et al. reported a combination of the Ugi and Passerini type MCR with RCM and described the potential applicability of this sequence for generating libraries of diverse benzannulated macrocycles.[116] The approach for a representative compound is outlined in scheme 6f, wherein 22-membered benzannulated macrocycle **185** was produced after the tandem sequence beginning from acid **182**, isocyanide **183** and paraformaldehyde.

Dandapani et al. have demonstrated the use of RCM for the generation of a skeletally diverse library of benzannulated macrocyclic ethers of the type **187** by diversity-oriented synthesis approach (scheme 6g).[117]

Abell et al. demonstrated ring closing metathesis approach in the synthesis of S-containing bridged benzannulated macrocycle **189** (*E/Z* ratio: 11:1) from scaffold **188** under MW irradiation combined with Lewis acid conditions (scheme 6h).[118]

Ring-closing metathesis (RCM) has been extensively used for the synthesis of resorcylic acid lactones (RALs).[119] There are numerous parameters that influence metathesis reactions, and so there are no general conditions that can be given that will guarantee the success of the process.[120] Fürstner et al. developed an RCM-based approach to zeranol (**191**) using Grubbs second generation catalyst under reflux conditions and synthesized selectively *E*-isomer in 85% yield as depicted in scheme 6i.[121] 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.[122] C. Herb et al. cyclized the ester **194** to produc the macrocyclic benzolactone core structure of salicylihalamides (**195**) through ring closing metathesis (scheme 6k).[123] A. Fürstner and C. Müller reported the total synthesis of (+)-aspercyclide,[124] in which the key step was a kinetically controlled RCM reaction of cyclization precursor **196** to form medium-ring benzolactone core of (+)-aspercyclide (**197**) as depicted in scheme 6l.



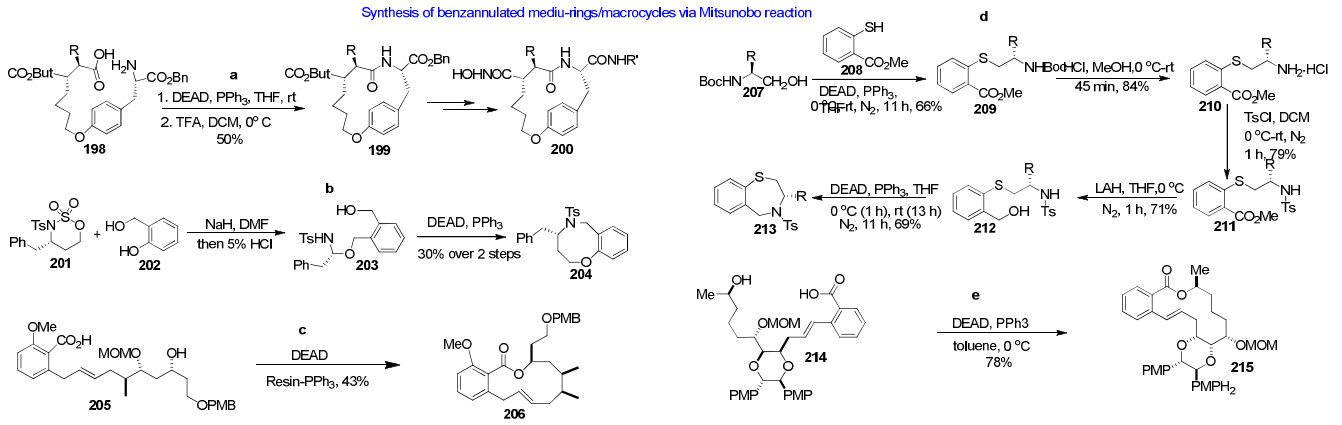
Scheme 6. Application of Ring closing metathesis in the construction of medium- and large-sized benzannulated rings.

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)[125] 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** led to the formation of scaffold **204** in 30% overall yield as shown in scheme 7b.[126] Another variant of Mitsunobu reaction was reported to affect the closure of a 13-membered lactone in the presence of supported triphenyphosphine in a low yield (10%) but was recently more successful in the formal synthesis of salicylihalamides (**206**, scheme 7c).[123,127]

The intramolecular Mitsunobu cyclization between the sulphonamide and benzylic hydroxyl in **212** (derived from amino acid **207** through a series of reaction 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.[128]

Macrocyclization of cyclization precursor **214** under Mitsunobu conditions (DEAD, PPh_3, toluene, 0 °C) gave rise to benzolactone **215** in 78% yields (scheme 7e). Most likely, conformational constraints on the backbone, imposed by the dioxane ring, facilitated the formation of the macrocycle.[129]



Scheme 7. Synthesis of benzannulated medium-rings and macrocycles via Mitsunobo reaction.

4.7. 0. Other cyclization methods

4.7.1. Cycloaddition reactions

Cycloaddition reactions have been extensively utilized for the synthesis of cyclic compounds but it is not well exploited for the construction of benzannulated cyclic frameworks. The only report by Llorente et al .They investigated the formation of benzannulated macrocycles from *α,ω*-diynes (**216**) in cobalt-mediated co-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).[130]

4.7. 2. Prins cyclization

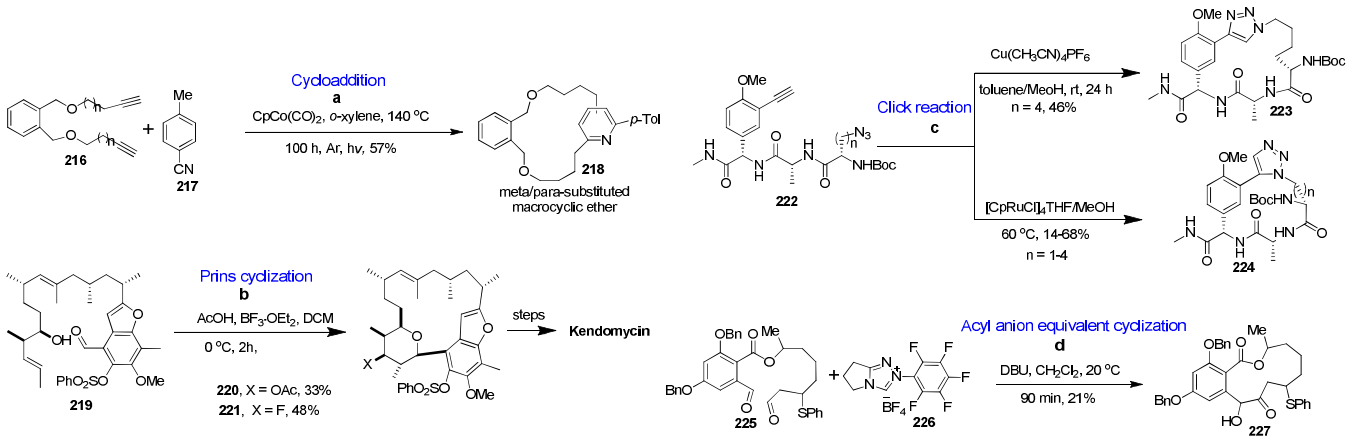
Bahnck et al. reported an intramolecular Prins cyclization that assembles the benzannulated macrocyclic rings in good yields. The Prins macrocycle formation is aided by the conformational preference of precursor **219**. The work demonstrates the potential of the Prins cyclization to form benzannulated macrocyclic rings (**220** and **221)** as depicted in scheme 8b.[131]

4.7.3. Click reaction

Liskamp and co-workers applied click reaction 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).[132]

4.7.4. Acyl anion equivalent macrocyclization

Recently, Miller's group has reported a novel acyl anion equivalent 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% yields (scheme 8d.[133]



Scheme 8. Synthesis of benzannulated cyclic compounds via cycloaddition, Prins cyclization, click reaction and Acyl nnion equivalent macrocyclization strategies.

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

The carbohydrates along with their derivatives particularly 1,2;5,6-di-*O*-isopropylidene-a-D-glucofuranoside, unsaturated sugars (glycals), peracetylated sugars etc. 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. Further, they have a very unique arrangement of functional groups and hence their usefulness as chiral pool in organic synthesis. Moreover, the carbohydrates can act as template on which complex medium-sized or macrocyclic ring scaffolds could be constructed. Following are the literature reports on the synthesis of biologically useful BMR frameworks from carbohydrates.

4.9.1. Radical cyclization

Radical reactions have extensively been utilized for the construction of medium-sized to large ring macrocycles. Faraco et al. reported the tributyltin 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 7a).[134] 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 7b).[135]

4.9.2. 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 7c).[136]

4.9.3. Fragment-based domain shuffling approach

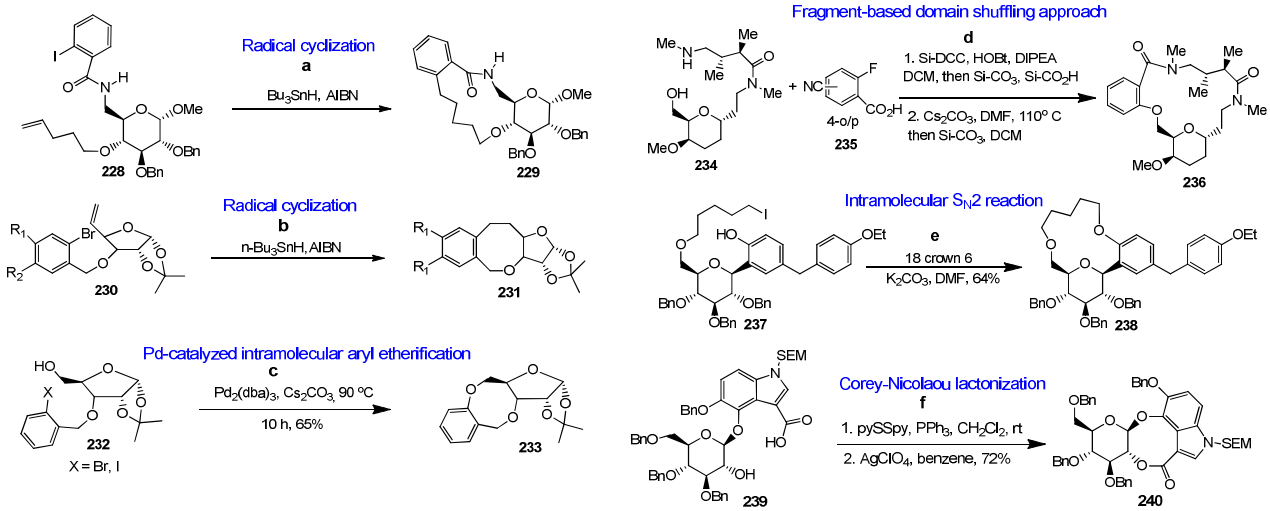
Eamon Comer et al. reported a fragment-based domain shuffling approach for the synthesis of a library of pyran-containing benzannulated macrocyclic ethers such as **236** using **234** and **235** as starting materials (scheme 7d).[137] A key feature of the design strategy was to use a synthetic route with three fragments that can be readily interchanged or "shuffled" to produce subtly different variants with distinct molecular shapes.

4.9.4. Intramolecular S_N2 reaction

Intramolecular S_N2 reactions are well utilized for cyclizations for example, Kim et al. synthesized carbohydrate based benzannulated macrocyclic ethers such as **238** (potential antidiabetic agents), with the ring-closure carried out using an S_N2 reaction on the substrate **237** (scheme 7e).[138]

4.9.5. 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 7f). [9,139]

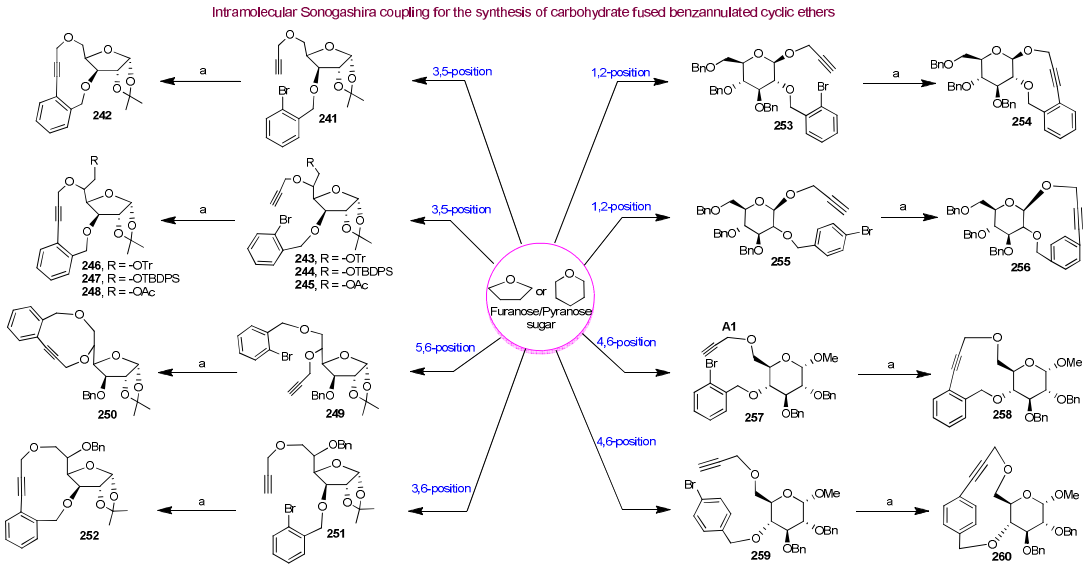


Scheme 7. Synthesis of medium- and large-sized rings using carbohydrates chiral template.

4.9.6. Intramolecular Sonogashira and Heck cyclizations

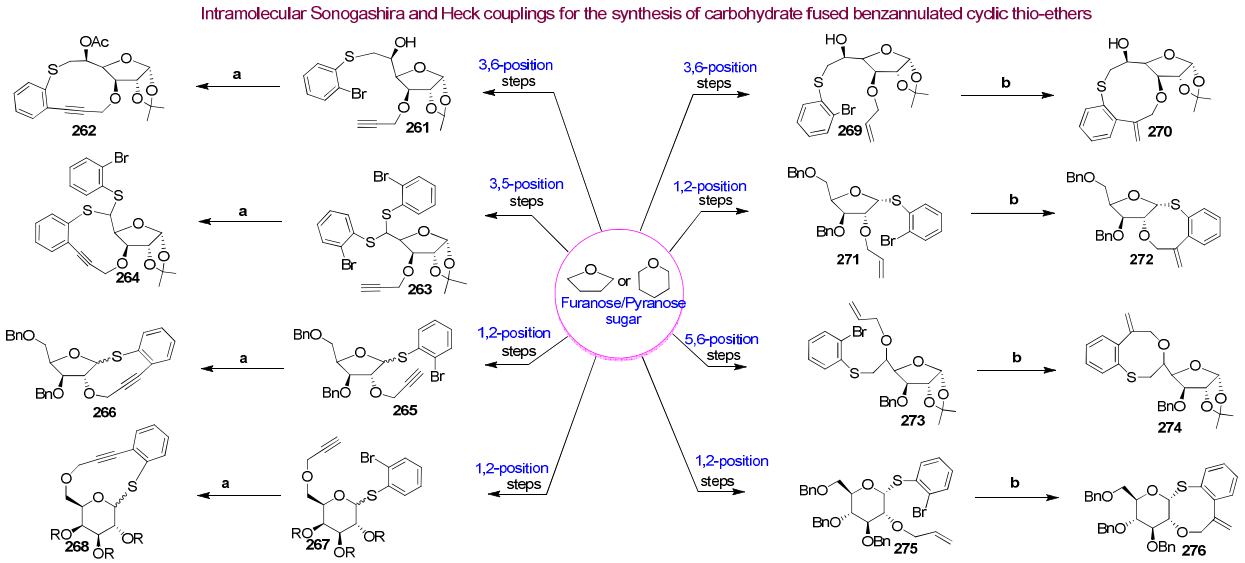
Our group successfully used the carbohydrates as chiral template for the construction of chiral benzannulated medium-sized or macrocyclic ring (BMR) ethers (shown in scheme 8), thio-ethers (shown in scheme 9) and benzolactones (shown in scheme 10) using a newly developed heterogeneous Pd-catalyst through C-C coupling reactions. The building blocks containing the requisite moieties (aryl halide and terminal alkyne groups for

Sonogashira coupling) required 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 8).[140]

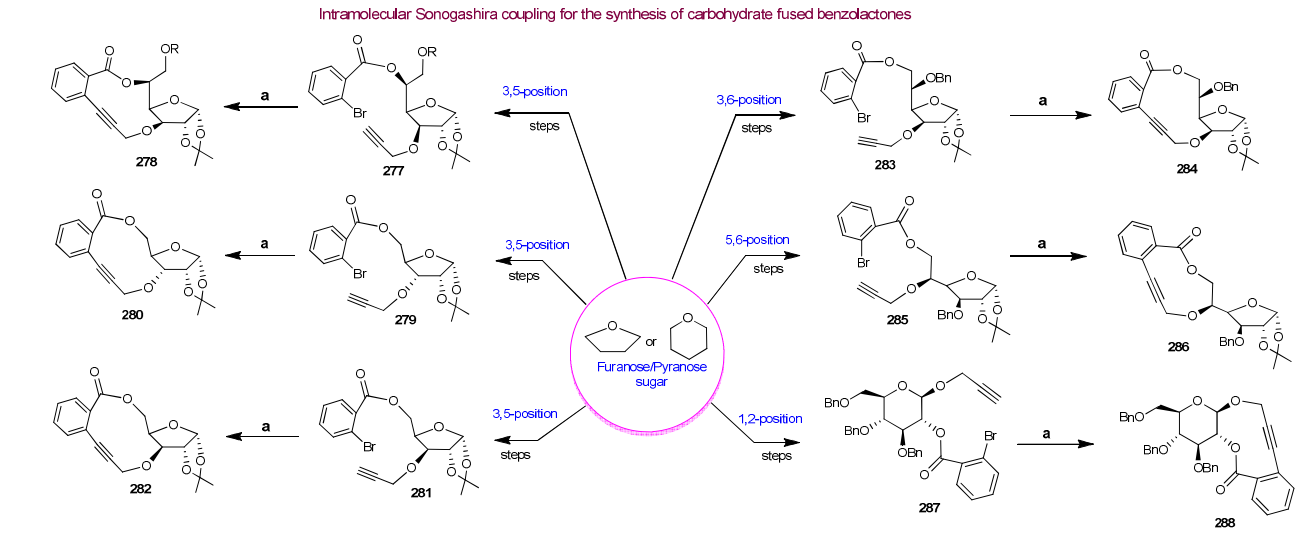


Scheme 8. Synthesis of benzannulated medium-ring or macrocyclic ethers fused with carbohydrates via Pd-catalyzed C-C coupling reaction. *Regents & conditions:* (a) Heterogeneous Pd-catalyst(100 wt %), CuI (5 mol%), THF, rt, 20h, 81-90 % yields

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 template. All the building blocks containing the required moieties (aryl halide and alkene or alkyne) were then cyclised through Sonogashira and Heck coupling reactions to produce the BMR thio-ethers fused with carbohydrates (scheme 9).[141]



Scheme 9. Synthesis of benzannulated medium-ring and macrocyclic thio-ethers fused with carbohydrates via Pd-catalyzed C-C coupling reactions. *Reagents & conditions*: (a) Heterogeneous Pd-catalyst (100 wt%), CuI (5 mol%), THF, rt, 20 h, 81-90% yields; (b) $Pd(OAc)_2$(10 wt%), Cs_2CO_3 (2.75 equiv.), TBAB (1equiv.), DMF , 100°C, 57-59%.



Scheme 10. Synthesis of medium-ring or macrocyclic benzolactones fused with carbohydrates via Pd-catalyzed C-C coupling reactions. *Regents & conditions* (a) Heterogeneous Pd-catalyst (100 wt%), CuI (5 mol%), THF, rt, 20h, 81-90% yields.

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 the carbohydrate as chiral template under similar conditions coupling as shown in scheme 10.[142] 1-2, 3-5, 3-6 and 5-6 positions of sugar were utilized for the construction of the medium-ring or macrocyclic skeleton. The requisite furanose/pyranose scaffolds were synthesized utilising conventional protection-deprotection strategies like benzylation, tritylation, detritylation, EDC coupling, propargylation etc.

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 of the BMR compounds are either 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) but the methods for the construction of benzannulated medium-rings (7-11 membered) need to be further explored. Further, 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

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[a]*Acedemy of Scientific and Innovative Research (AcSIR), New Delhi, India. Fax: +91-191-2569111; Tel: +91-191-2569000; E-mail: dmukherjee@iiim.ac.in*
[b]*Indian Institute of Integrative Medicine (CSIR-IIIM), Canal Road, Jammu (J&K), India. Fax: +91-191-2569111; Tel: +91-191-2569000; E-mail: dmukherjee@iiim.ac.in*

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, M. N. James, *Biochemistry,* 1998, **37**, 16839-16845.
3. Veber, D.F. S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward, 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, T. Kodadek, *Chem. Biol.* 2007, **14**, 671-677.
6. (a) T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds*, Vol. 2; Academic Press: New York and London, 1972; (b) D. J. Faulkner, *Nat. Prod. Rep*. 1984, **1**, 251-280.
7. J. Mallinson, I. Collins, *Future Med. Chem.,* 2012, **4**, 1409-1438.
8. S. E. Denmark, S. M. Yang, *J. AM. CHEM. SOC.* 2004, **126**, 12432-12440.
9. A. Delgado, J. Clardy, *J. Org. Chem.* 1993, **58**, 2862-2866, and references cited therein.
10. A. Farooq, J. Gordon, J. R. Hanson, J. A. Takahashi, *Phytochemistry,* 1995, **38**, 557.
11. D. M. Tapiolas, M. Roman, W. Fenical, T. J. Stout, J. Clardy, *J. Am. Chem. Soc*. 1991, **113**, 4682-4683.
12. C. C. J. Culvenor, L. W. Smith, *Aust. J. Chem.* 1963, **16**, 239-245.
13. O. P. Suri, C. K. Atal, *Current Sci.* 1967, **36**, 614-615.
14. R. Adams, B. L. Van Duuren, *J. Am. Chem. Soc.* 1953, **75**, 2377-2379.
15. K. C. Majumdar, *RSC Advances*, 2011, **1**, 1152-1170.
16. G. Illuminati, and L. Mandolini, *Acc. Chem. Res.* 1981, **14**, 95-102.
17. E. M. Driggers, S. P. Hale, Lee J, N. K. Terrett *Nat. Rev. Drug Discov.* 2008, **7**, 608-624.
18. L. A. Wessjohann, E. Ruijter, D. Garcia-Rivera, W. Brandt, *Mol. Divers.* 2005, **9**, 171-186.
19. (a) S. Pal, *Tetrahedron*, 2006, **62**, 3171-3200; (b) L. Katz, 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, S. B. Horwitz, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 757-759.

21. K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc.* 1987, **109**, 2821-2822.
22. K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, 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, R. Sridhara R. Pazdur. 2010, *Oncologist,* **15**, 428-435.
24. E. Raymond, J. Alexandre, S. Faivre K. Vera, E. Materman, J. Boni, C. Leister, J. Korth-Bradley, A. Hanauske, J. P. Armand, *J. Clin. Oncol.* 2004, **22**, 2336-2347.
25. A. Conlin, M. Fornier, C. Hudis, S. Kar, P. Kirkpatrick , *Nat. Rev. Drug Discov.* 2007, **6**, 953-954.
26. S. Goodin, *Am. J. Health Syst. Pharm.* 2008, **65**, S10-S15.
27. E. Mcdonald, P. Workman, 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, G. M. Eliopoulos, *J. Clin Microbiol.* 2004, **42**, 2398-402.
29. D. A. Cantrell, K. A. Smith, *Science.* 1984, **224** 1312-1316.
30. A. Gradillas, Perez-Castells, J. *Angew. Chem. Int. Ed.* 2006, **45,** 6086-6101.
31. A. Parenty, X. Moreau, Campagne, *J. M. Chem. Rev.* 2006, **106**, 911-939.
32. F.A. Macías, R.M. Varela, A. Torres, J.M.G. Molinillo, and F.R. Fronczek, *Tetrahedr. Lett.* 1993, **34**, 1999-2002.
33. T. Shimokawa, J. Kinjo, J. Yamahara, M. Yamasaki, and T. Nohara, *Chem. Pharm. Bull. (Tokyo),* 1985, **33**, 3545-3547.
34. S. B. Singh, H. Jayasuriya, D. L. Zink, J. D. Polishook, A. W. Dombrowski, H. Zweerink, *Tetrahedr. Lett.* 2004, **45**, 7605-7608.
35. Y. Shirataki, Y. Tagaya, I. Yokoe, and M. Komatsu, *Chem. Pharm. Bull. (Tokyo),* 1987, **35**, 1637-1640.
36. X. Fu, T. Sévenet, F. Remy, M. Païs, A. Hamid, A. Hadi, 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, 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, *Tetrahedr. Lett.* 1972, **13**, 909-912.
40. H. Urata, A. Kinoshita, K. S. Misono, F. M. Bumpus, A. Husain, *J. Biol. Chem.* 1990, **265**, 22348-22357.
41. H. Tomoda, H. Nishida, R. Masuma, J. Cao, S. Okuda, S. Omura, *J. Antibiot.* 1991, **44**, 136-143.
42. G. M. Salituro, D. J. Pettibone, B.V. Clineschmidt, J. M. Williamson, D. L. Zink, *Bioorg. Med. Chem. Lett.* 1993, **3**, 337-340.
43. D. Brückner, F. T. V. Hafner, Li, C. Schmeck, J. Telser, A. Vakalopoulos, G. Wirtz, *Bioorg. Med. Chem. Lett.* 2005, **15**, 3611-3614.
44. (a) H. Kase, M. Kaneko, K. Yamada, *J. Antibiot.* 1987, *40*, 450-454; (b) S. Sano, K. Ikai, K. Katayama, K. Takesako, 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, N. Kindler, *Tetrahedron,* 1999, **55,** 8215-8230.
47. (a) S. S. Palimkar, J. Uenishi, H. Ii, *J. Org. Chem.* 2012*,* **77***,* 388-399; (b) M. Huss, O. Vitavska, A. Albertmelcher, S. Boeckelmann, C. Nardmann, K. Tabke, F. Tiburcy, H. Wieczorek, *Eur. J. Cell Biol.* 2011, **90**, 688-695.
48. D. Krahn, C. Ottmann, M. Kaiser, *Curr. Med. Chem.* 2011, **18**, 5052-5060.
49. W. Erb, J. Zhu, *Nat. Prod. Rep.* 2013, **30**, 161-174.
50. L.A. Wessjohann, E. Ruijter, D. Garcia-RiveraBrandt, *Mol. Divers.* 2005, **9**, 171-186.
51. B.F. Ruan, H.L. Zhu, *Curr. Med. Chem.* 2012, **19**, 2652-2664.
52. G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, C. McMartin, R. Bohacek, *J. Med. Chem.* 1997, **40**, 506-514.
53. G. M. Ksander, R. de Jesus, A. Yuan, R. D. Ghai, A. Trapani, C. R. McMartin, Bohacek, *J. Med. Chem.* 2011, **54**, 1961-2004.
54. 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, U. Neumann, *Bioorg. Med. Chem. Lett*. 2010, **20**, 603-607.
55. 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, E. W. Baxter, *Bioorg. Med. Chem. Lett*. 2010, **20**, 3158-3160.
56. 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. W. Pennicott, Zou, J. Wright, *Bioorg. Med. Chem. Lett.* 2010, **20**, 5695-5700.
57. 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, T. M. Williams, *J. Am. Chem. Soc.* 2001, **123**, 2107-2108.
58. 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, T. M. Williams, *Bioorg. Med. Chem. Lett.* 2004, **14**, 639-643.
59. 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, H. G. Selnick, *Bioorg. Med. Chem. Lett.* 2003, **13**, 2781-2784.
60. E. Marsault, K. Benakli, S. Beaubien, C. Saint-Louis, R. Deziel, G. Fraser, *Bioorg. Med. Chem. Lett.* 2007, **17**, 4187-4190.
61. E. Marsault, M. L. Peterson, *J. Med. Chem.* 2011, **54**, 1961-2004.
62. G. L. Fraser, H. R. Hoveyda, *PCT Intl Appl*. WO 06/046977, 2005.
63. U. Lucking, G. Siemeister, M. Schafer, H. Briem, M. Kruger, P. Lienau, R. Jautelat, *ChemMedChem,* 2007, **2**, 63-77.
64. N. Kawanishi, T. Sugimoto, J. Shibata, K. Nakamura, K. Masutani, M. Ikuta, H. Hirai, *Bioorg. Med. Chem. Lett.* 2006, **16**, 5122-5126.
65. X. Yu, D. Sun, *Molecules,* 2013, **18**, 6230-6268.
66. 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, J. W. Wood, *Leukemia,*2011, **25**, 1751-1759.
67. R. S. Komrojki, M. Wadleigh, J. F. Seymour, presented at: *53rd ASH Annual Meeting and Exposition*. San Diego Convention Center, San Diego, CA, USA, 10-13 December 2011.
68. A. D. William, A. C. H. Lee, K. C. Goh, *J. Med. Chem.* 2012,**55**, 169-196.
69. H. Hirai, I. Takahashi-Suziki, T. Shimomura, K. Fukasawa, T. Machida, T. Takaki, M. Kobayashi, T. Eguchi, *Investigational New Drugs,* 2011, **29**, 534-543.
70. 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, J. P. Vacca, *Antimicrob. Agents Chemother*. 2010, **54**, 305-311.
71. K. C. Lasseter, L. Shaughnessy, D. Cummings, J. C. Pezzullo, W. Wargin, R. Gagnon, J. Oliva, G. Kosutic, *J. Clin. Pharmacol*. 2008, **48**, 193-202.
72. J.C. Collins, K. James, *Med. Chem. Commun.* 2012, **3,** 1489-1495.
73. D.C. Harrowven, S.L. Kostiuk, *Nat. Prod. Rep.* 2012, **29,** 223-242.
74. N. K. Terrett, *Drug Discov. Today Technol*. 2010, **7**, e97-e104.
75. L. Wessjohann, E. Ruijter, In *Natural Product Synthesis I*; Springer Berlin Heidelberg: Berlin, Germany, **2005**; Volume 243, pp. 137-184.
76. A. E. Horton, O.S. May, M.R.J. Elsegood, M.C. Kimber, *Synlett* 2011, **22**, 797-800.
77. A. Parenty, X. Moreau, G. Niel, J.M. Campagne, *Chem. Rev.* 2013, **113**, PR1-PR40.
78. R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman, J. A. Porco Jr, *J. Am. Chem. Soc.* 2003, **125**, 7889-7901.

79. G. A. Holloway, H. M. Hugel, M. A. Rizzacasa, *J. Org. Chem.* 2003, **68**, 2200-2204.
80. R. Shen, C. T. Lin, J. A. Porco Jr, *J. Am. Chem. Soc.* 2002, **124**, 5650-5651.
81. Q. Su, J. S. Panek, *J. Am. Chem. Soc.* 2004, **126**, 2425-2430.
82. S. S. Palimkar, J. Uenishi, H. Ii, *J. Org. Chem.* 2012, **77**, 388-399.
83. E. Marsault, L. Ouelet, C. Saint-Louis, S. Beaubien, K. Benakli, H. R. Hoveyda, M. L. Peterson, S. Bhat, *U.S. Pat. Appl.* 2009/0198050, 2008.
84. Z. Nie, C. Perretta, P. Erickson, S. Margosiak, J. Lu, A. Averill, R. Almassy, S. Chu, *Bioorg. Med. Chem. Lett.* 2008, **18**, 619-623.
85. W. Zhang, J.S. Moore, *Angew. Chem. Int. Ed.* 2006, **45**, 4416-4439.
86. R. Lépine, J. Zhu, *Org. Lett.* 2005, **7**, 2981-2984.
87. J. N. L. Dufour, J. Zhu, *Chem. Eur. J.* 2010, **16**, 10523-10534.
88. R. Yamasaki, A. Shigeto, S. Saito, *J. Org. Chem.* 2011, **76**, 10299-10305.
89. V. Balraju, D. S. Reddy, M. Periasamy, J. Iqbal, J. *Org. Chem.* 2005, **70**, 9626-9628.
90. K. C. Majumdar, B. Chattopadhyay, K. Ray, *Tetrahedron Lett.* 2007, *48*, 7633-7636.
91. (a) K. C. Majumdar and B. Chattopadhyay, *Synthesis*, 2009, 2385; (b) K. C. Majumdar and B. Chattopadhyay, *Synlett,* 2008, 0979-0982.
92. K. C. Majumdar, B. Chattopadhyay and S. Samanta, *Tetrahedr. Lett.,* 2009, **50**, 3178-3181.
93. K. Akaji, K. Teruya, M. Akaji, S. Aimoto, *Tetrahedron*, 2001, **57**, 2293-2303.
94. C.W. Zapf, J.D. Bloom, J. L. McBean, R.G. Dushin, J.M. Golas, H. Liu, J. Lucas, F.Boschelli, E. Vogan, J.I. Levin, *Bioorg. Med. Chem. Lett.* 2011, **21**, 3627-3631.
95. V. Balraju, J. Iqbal, *J. Org. Chem*. 2006, **71**, 8954-8956.
96. K. C. Nicolaou, N. Winssinger, J. Pastor, F. Murphy, *Angew. Chem., Int. Ed.* 1998, **37**, 2537-2547.
97. W. Li, K. Burgess, *Tetrahedron Lett.* 1999, **40**, 6527-6530.
98. S. M. Lu, H. Alper, *Chem. Eur. J.* 2007, **13**, 5908-5916.
99. A. Sharma, P. Appukkuttan, E. van der Eycken, *Chem. Commun.* 2012, **48**, 1623-1637.
100. Q. Su, A.B. Beeler, E. Lobkovsky, J.A. Porco, J. S. Panek, *Org. Lett.* 2003, **5**, 2149-2152.
101. L. Shen, C.J. Simmons, D. Sun, *Tetrahedr. Lett.* 2012, **53**, 4173-4178.
102. P. Mestichelli, M. J. Scott, W. R. J. D. Galloway, J. Selwyn, J. S. Parker, D. R. Spring, *org. Lett.* 2013, **15**, 5448-5451.
103. A. Berthelot, S. Piguel, G. Le Dour, J. Vidal, *J. Org. Chem.* 2003, **68**, 9835-9838.
104. A. Poloukhtine, V. Rassadin, A. Kuzmin, V. V. Popik, *J. Org. Chem.* 2010, **75**, 5953-5962.
105. T. Zhang, X. Huang, J. Xue, S. Sun, *Tetrahedr. Lett.* 2009, **50**, 1290-1294.
106. R. A. Bauer, T. A. Wenderski. D. S. Tan, *Nat. Chem. Biol.* 2013, **9**, 21-30.
107. F. Kopp, C. F. Stratton, L. B. Akella, D. S. Tan, *Nature Chem. Biol.* 2012, **8**, 358-365.
108. M. C. Zaccaro , H. B. Lee, M. Pattarawarapan, Z. Xia, A. Caron, P. J. L. Heureux, Y. Bengio, K.Burgess, H. U. Saragovi, *Chem. Biol.* 2005, *12*, 1015-1028.
109. E. J. Kang, S .Y. Lee, H. Lee, S. S. Lee, *Inorg. Chem.* 2010, **49**, 7510-7520.
110. J. Buter, R. M. Kellogg, *J. Org. Chem.* 1981, **46**, 4481-4485.
111. R. Mamouni, M. Soukri, S. Lazar, M. Akssira, G. Guillaumet, *Tetrahedr. Lett.* 2004, **45**, 2631-2633.
112. S. K. Chattopadhyay, T. Biswas and S. Maity, *Synlett*, 2006, 2211.
113. A. Fürstner, G. Seidel, N. Kindler, *Tetrahedron,* 1999, **55**, 8215-8230.
114. G. Evano, J. V. Schaus, J. S. Panek, *Org. Lett.* 2004, **6**, 525-528.
115. K. C. Nicolaou, T. Montagnon, G. Vassilikogiannkabis, C. J. N. Mathison, *J. Am. Chem. Soc.* 2005, **127**, 8872-8888.
116. B. Beck, G. Larbig, B. Mejat, M. Magnin-Lachaux, A. Picard, E. Herdtweck, A. Domling, *Org. Lett.* 2003, **5**, 1047-1050.
117. S. Dandapani, L. A. Marcaurelle, *Nat. Chem. Biol.* 2010, **6**, 861-863.
118. A. D. Abell, N.A. Alexander, S.G. Aitken, H. Chen, J. M. Coxon, M.A. Jones , S.B. Mc Nabb, A. Muscroft-Taylor, *J. Org. Chem.* 2009, **74**, 4354-4356.
119. J. Pérez-Castells, A. Gradillas, *Angew. Chem. Int. Ed*. 2006, **45**, 6086-6101.
120. S. Y. Hong, M.W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* 2004, **126**, 7414-7415.
121. A. Fürstner, G. Seidel, N. Kindler, *Tetrahedron.* 1999, **55**, 821-8230.
122. S. Barluenga, P. L.Spez, E. Moulin, N. Winssinger, *Angew. Chem.* 2004, **116**, 3549-3552; *Angew. Chem. Int. Ed.* 2004, **43**, 3467 - 3470.
123. C. Herb, A. Bayer, M. E. Maier, *Chem. Eur. J.* 2004, **10**, 5649-5660.
124. A. Fürstner, C. Müller, *Chem. Commun.* 2005, 5583-5585.
125. K. C. Swamy, N. N. Kumar ; E. Balaraman, K. V. Kumar, *Chem. Rev*. 2009, **109**, 2551-2651.
126. J. Rujirawanich, T. Gallagher, *Org. Lett.* 2009, **11**, 5494-5496.
127. C. Herb, M. E. Maier, *J. Org. Chem.* 2003, **68**, 8129-8135.
128. J. K. Mishra, G. Panda, *J. Comb. Chem.* 2007, **9**, 321-338.
129. A. Delgado, J. Clardy, *J. Org. Chem.* 1993, **58**, 2862, and references cited therein.
130. L. V. R. Boñaga, H. C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo, B. E. Maryanoff, *J. Am. Chem. Soc.* 2005, **127**, 3473-3485.
131. B. Kevin Bahnck , S. D. Rychnovsky, *J. Am. Chem. Soc.* 2008, **130**, 13177-13181.
132. J. Zhang, J. Kemmink, D.T.S. Rijkers, R. M. J. Liskamp, *Org. Lett.* 2011, **13**, 3438-3441.
133. S. M. Mennen, S. J. Miller, *J. Org. Chem*. 2007, **72**, 5260-5269.
134. 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 , M. A. F. Prado, *J. Braz. Chem. Soc.* 2009, **20**, 1504-1514.
135. (a) P. Chattopadhyay, M. Mukherjee, S. Ghosh, *Chem. Commun*. 1997, 2139-2140; (b) A. Neogi, T. P. Majhi, N. Ghoshal, P. Chattopadhyay, *Tetrahedron*, 2005, **61**, 9368-9374.
136. A. Neogi, T. P. Majhi, B. Achari, P. Chattopadhyay, *Eur. J. Org. Chem.* 2008, 330-336.
137. E. Comer, H. Liu, A. Joliton, A. Clabaut, C. Johnson, L. B. Akella, L. A. Marcaurelle, *PNAS,* 2011,**108**, 6751-6756.
138. M. J. Kim, S. H. Lee, S. O. Park, H. Kang, J .S. Lee , K. N. Lee , M. E. Jung, J. Kim, J. Lee, *Bioorg. Med. Chem.* 2011, **19**, 5468-5479.
139. E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* 1974, **96**, 5614.
140. A. Hussain, S. K. Yousuf, D.Kumar, L. Mallikharjuna, S.Maity, B. Singh, D. Mukherjee, *Adv. Synth.Catal.* 2012, **354**, 1933-1940.
141. A. Hussain, S. K. Yousuf, D. Kumar, L. Mallikharjuna, B. Singh, D. Mukherjee, *Tetrahedron*, 2013, **69**, 5517-5524.
142. A. Hussain, L. Mallikharjuna, D. K. Sharma, A. K. Tripathi, B. Singh, D. Mukherjee, *RSC Adv.* 2013, **3**, 19899-19904.