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Review

Indole-Based Macrocyclization by Metal-Catalyzed Approaches

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Abstract: This review is dedicated to the different varieties of macrocycles synthesis bearing indole units in their architecture by metal-catalyzed strategies. The progress of the new macrocyclization approaches is persisted be a keen area of research. Macrocycles contain a wide variety of molecules, and among those, heteroaryl motifs are valuable constituents that provide an attractive feature to macrocyclic systems. Indole represents one of the privileged pharmacophores against a variety of targets with various biological applications. Among the nitrogen-based heterocycles, indole plays a prominent role in organic synthesis, medicinal chemistry, pharmaceuticals, natural products synthesis, agrochemicals, dye and fragrances, and drug design. These scaffolds are widely distributed in several bioactive natural products and synthetic macrocycles constructed against a specific biochemical target and the most common constituents of naturally occurring molecules. Due to its immense importance, the progress of novel approaches for the synthesis of indole-based scaffolds has increased steadily. The majority of the macrocycles synthesis proceeds through the macrolactamization and macrolactonization, as well as the C–C bond macrocyclization process described by metal-catalyzed ring-closing metathesis (RCM) and coupling reactions. Among macrocyclizations, metal-catalyzed approaches are considered one of the most powerful tools for synthetic chemists in the design of a variety of macrocycles. This review aims to give a comprehensive insight into the synthesis of varieties of macrocycles bearing indole scaffold catalyzed by various transition metals that emerged in the literature over the last two decades. We hope that this review will persuade synthetic chemists to search for novel strategies for the C–C bond macrocyclization by metal-catalyzed protocols.

Keywords: macrocyclization; heterocycles; coupling reactions; transition-metal catalysis; indole-based macrocycles

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1. Introduction

Macrocycles are versatile motifs that have met considerable attention from synthetic chemists over the last several decades, specifically those who are involved with natural product synthesis. The curiosity aroused in the synthesis of macrocyclic compounds has been raised steadily due to their enormous impact on bioactive natural products, chemical biology, polymers, drug design and development, bioorganic chemistry, supramolecular chemistry, pharmaceutics, and medicinal chemistry [1–5]. Macrocycles are chemical entities that have a cyclic structure consisting of 12-membered or more atoms with bigger rings. These are very important common privileged scaffolds for drug design and increasing interest in their study continuously. Because of their broad range of biological activities, such as anti-microbial, anti-inflammatory, antileishmanial, anti-cancer and anti-trypanosomatidial properties, these macrocyclic systems are considered an attractive target in pharmaceutical development, as well as in drug discovery [6–11]. Some of the macrocycles containing hetero atoms are served as hosts in supramolecular chemistry

and act as selective complexing agents and catalysts [12,13]. The structural topography of macrocycles provides outstanding molecular recognition, as well as useful molecular carriers for delivering drug molecules and therapeutic biomolecules. Macrocyclic scaffolds bearing hetero atoms are worthwhile compounds with a broad spectrum of medicinal and pharmacological activities [14]. Some of the macrocyclic motifs are considered probes or drugs to aim protein–protein interactions, will impart higher metabolic activity, and can improve selectivity and enhance the binding affinity [15,16]. Basically, these are broadly found in nature and the structure of these macrocycles which performs a degree of conformational pre-organization due to restricted rotation. The macrocyclic ring system possesses a unique structural feature and conformational flexibility, which offers to be selective and highly effective when basic functional groups interact with biological targets [17]. Most of the macrocycles exhibit enhanced lipophilicity and promising drug-like properties, such as better cell membrane permeability, oral bioavailability, well metabolic stability, and good solubility, along with appropriate pharmacokinetic and pharmacodynamic properties [18]. Some of the structures of biologically active natural macrocycles (**1**–**8**) are displayed in Figure 1.

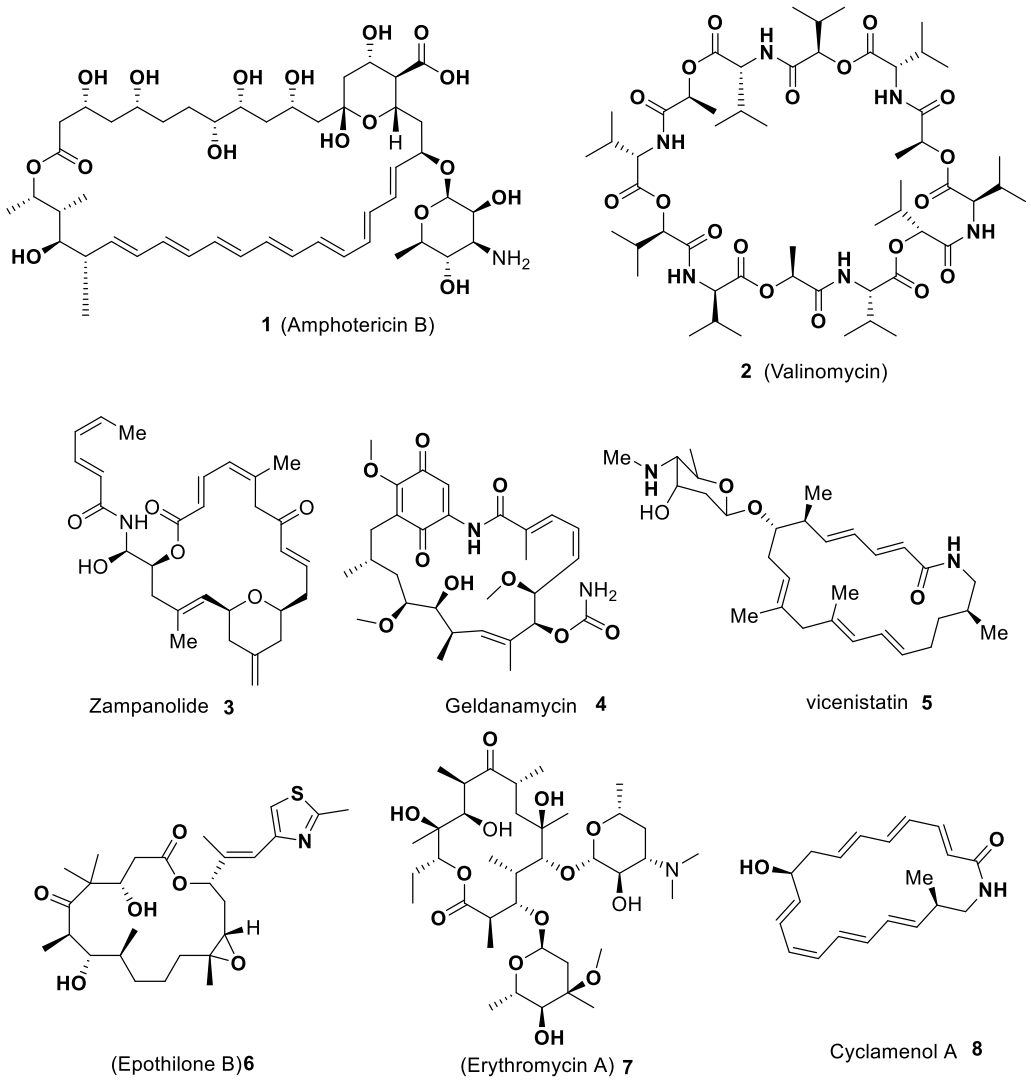


Figure 1. Selected examples of bio-active natural macrocycles (**1**–**8**).

In Figure 1, we described those biological activities, such as Amphotericin B **1** (antifungal medication) has been used for the treatment of invasive fungal infections and leishmaniasis. Valinomycin **2** is an effective natural antibiotic and is employed as an agent

to induce apoptosis. It can selectively transport alkali metal ions through biological and synthetic membranes. Zampanolide **3** is a microtubule-stabilizing polyketide owning effective cytotoxicity towards various cancer cell lines. Geldanamycin **4** is a macrocyclic polyketide synthesized by a Type I polyketide synthase. It is a 1,4-benzoquinone ansamycin antitumor antibiotic which inhibits the Hsp90 and induces the degradation of proteins that are mutated or overexpressed in cancer cells. Vicenistatin **5** is a strong polyketide antitumor antibiotic and shows in vitro cytotoxicity toward human promyelocytic leukemia HL-60 and human colon cancer COLO205 cells. Epithilone B **6** has been confirmed to be potent in vivo anticancer activity and inhibits microtubule functions. It prevents cancer cells from dividing by interfering with the tubulin. Erythromycin A **7** is a macrolide that is studied to be an effective and one of the safest antibiotics and broadly utilized in clinical medicine against infections caused by Gram-positive bacteria and pulmonary infections. Cyclamenol A **8** (an anti-inflammatory agent) is one of the macrocyclic polyene lactam natural products that inhibit leukocyte adhesion to endothelial cells [14–19].

Natural products having macrocyclic skeletons possess numerous pharmacological properties, and biochemical functions have led to their drug development. These macrocyclic scaffolds are conformationally pre-organized and offer distinct functionality and stereochemical complexity in their architecture, which results in better affinity and good selectivity for protein targets [20]. There are vast benefits of macrocycles, especially when compared with their linear counterparts. The design and development of drug-like macrocycles is always a fascinating area of research in medicinal chemistry and has received immense interest from organic chemists over recent years [6]. The macrocyclization strategy is promising for the design of drugs, as well as it reduces the entropic loss allied with the ligand by adaptation of a favorable conformation, which may lead to improved potency and selectivity. Some of the well-known macrocyclic drugs, such as Rezafungin (for the treatment of candidemia and invasive candidiasis), Lorlatinib (anti-cancer drug), Pacritinib (for the treatment of myelofibrosis), Selepressin (vasodilatory hypotension), Rifaximin (antibiotic), Ciclosporin (immunosuppressant), Tacrolimus (immunosuppressive), Everolimus (antineoplastic chemotherapy drug) are currently being used as drugs in the market [21].

Because of its promising biological activities, nitrogen-bearing heterocycles have always been considered as a desirable target for the synthetic community. Over the past several decades, *N*-based heterocycles have drawn much attention from synthetic chemists and chemical biologists because of their special ability to bind a variety of receptors, and they are embedded in numerous natural products and medicinally relevant substances [22,23]. Among a variety of heterocyclic scaffolds, indole is a unique core referred to as a privileged pharmacophore present in the multiple biologically active scaffolds. Some of the indole units are found in natural and synthetic macrocycles with prominent biological functions, and it is a key synthon in the numerous clinically important drugs for the cure of cancer, circulatory disease, Alzheimer's disease, and neuro disorders [24]. Additionally, indole is one of the most nitrogen heterocycles, particularly in medicinal and pharmaceutics. Macrocycles bearing indole moiety occur in many natural alkaloids and unnatural products [25]. Because of its binding ability, some of the C_2-symmetric indole scaffolds are known to exhibit inhibitory activities against Gram-positive bacteria *Bacillus subtilis* and *Micrococcus luteus*. Indole-based C_2-symmetric new chemical entities (NCEs) are expected to show a distinct role in medicinal chemistry. Based on its potential biological activities and pharmacological applications, intense study and much effort have been dedicated to the design and synthesis of a variety of indole-based analogs [26]. The structure of some important biologically active indole-based macrocycles is shown in Figure 2 [27–30].

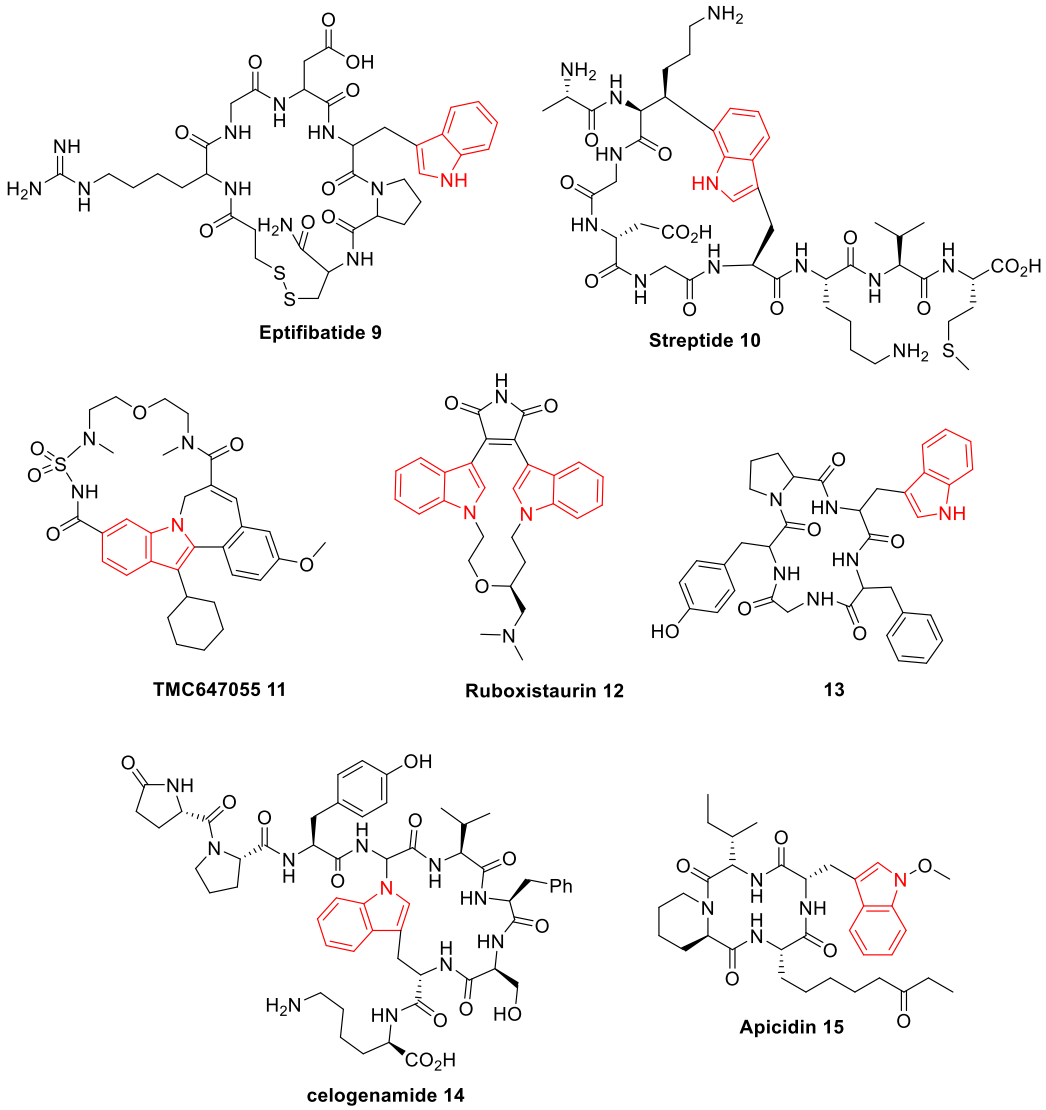


Figure 2. Representative examples of bio-active indole-based macrocycles (**9**–**15**).

The macrocyclization efficiency totally varies on the size and structure, as well as the structural pre-organization of the linear substrates. Mostly, the assembly of macrocycles is considered as an exciting task and a crucial step for synthetic chemists. Because of its interesting biological activity, as well as the intractable synthetic complexity of naturally occurring macrocycles, several research groups have diverted their significant efforts to explore highly effective and easiest synthetic methods for the design of macrocycles. From the literature search, a number of reports have been available for the synthesis of different varieties of macrocycles from several macrocyclization strategies [31]. These include the olefin metathesis reactions (RCM) [32], coupling reactions catalyzed by transition metals [33], macrolactonization [34], Cu (I) mediated click chemistry [35], macrolactamization [36], thiol-ene photochemical strategy [37], S_N2 & S_N2Ar reactions [38], cross-couplings by palladium metal [39], Horner–Emmons olefination [40], Pd (0)-mediated Larock indole annulation [41], intramolecular radical macrocyclization by light source [42], Ugi reaction [43], and IMDAR (intramolecular Diels–Alder reaction) strategies [44].

There are two well-known metal-catalyzed macrocyclizations for the design and synthesis of biologically relevant scaffolds, such as the olefin metathesis (RCM) catalyzed by ruthenium and CuAAC (copper-catalyzed alkyne–azide cycloaddition) which are extensively reviewed in recently [45,46]. In this review, we are mainly focusing on the synthesis of a variety of macrocycles bearing indole motifs involving intramolecular C–C and C–H

bond cyclization reactions by a metal-catalyzed approach. We hope that this review will offer an effective source for medicinal chemists, particularly those who are involved in total synthesis as well as fascinated by macromolecule research. Finally, we anticipate that this review will stimulate additional interest in developing new strategies for indole macrocycles by synthetic chemists from diverse areas from both industry and academic points of view.

2. Metal Catalyzed Strategies toward the Indole Macrocycles

Advanced catalysts, also called precious metal catalysts, are prepared from gold, silver, platinum, ruthenium, palladium, and rhodium, which speed up chemical reactions without altering themselves. These metal-based catalysts are broadly utilized nowadays in pharmaceutical, refining industries, and various chemical manufacturing units. Additionally, these metal catalysts show many advantages, such as their catalytic activity is high, which can accelerate chemical reactions more effectively. As well as displays better selective performance, good thermal stability, higher surface area, porosity, chemical inertness, sustainability, versatility, and longevity. The usage of metal-free catalysts has been increasing in recent years to develop industrial benefits with respect to more economical, eco-friendly, and environmental and safety considerations. Most metal-free catalysts are based on many forms of carbon sources. The catalyst with Ru center is most popular both in industrial and academic because of its properly stable tolerance to moisture and air, as well as a higher affinity toward olefin instead of other groups. Over the past several decades, synthetic chemists demonstrated various metal-catalyzed approaches toward the synthesis of a variety of heteroaryl-based macrocycles [47]. These strategies provide powerful synthetic protocols with diverse applications, particularly in pharmaceuticals, natural product synthesis, and drug development [48]. In comparison with the standard protocols, these approaches do not require pre-functionalization of substrates which affects on minimization of waste and atom economy. Additionally, these developed synthetic strategies can often be easily applied in the synthesis of other macrocyclic scaffolds. In metal-catalyzed approaches, cross-coupling and RCM reactions are deliberated as one of the most valuable protocols for the easiest formation of C–C bonds [47–49]. Here in, we outlined various metal-catalyzed strategies that can be used to make C–C bonds and ring closures to construct small drug-like molecules and complex architectures via multistep domino sequences.

2.1. Ruthenium (Ru) Catalyzed Macrocyclizations: Ring-Closing Metathesis [RCM]

To design and synthesis of different varieties of macrocyclic indole scaffolds have received considerable interest from medicinal chemists because of their frequent existence in naturally occurring molecules, pharmaceuticals, and bioactive compounds. In the last few decades, several new methods have been developed for the synthesis of varieties of indole frameworks; among those protocols, olefin metathesis (RCM) is considered one of the most effective approaches [50]. The ring-closure process is always a trivial task with yields based on the size and geometry of the bridging linker. The RCM is an effective and appropriate protocol for C–C bond formation and an appropriate approach for the synthesis of complex frameworks. The RCM protocol has been used to produce medium to large carbocycles, heterocycles and various complex macrocycles starting with suitable olefinic precursors [51]. Various strategies by transition-metal catalysts have opened the door for the efficient construction of C–C bonds in a variety of complex targets and macrocyclic systems [52]. The ruthenium-based catalysts were utilized in the various protocols, and they display a functional group tolerance with maximum level (Figure 3). The term metathesis was obtained from the Greek word “meta” & “thesis” (change and position), which mean the replacement of double bonds between two olefin moieties. The ring-closing metathesis (RCM) has received considerable attention as compared to other metathetic protocols, such as enyne metathesis (EM) and cross-enyne metathesis (CEM). The mechanism was suggested by Chauvin for the RCM reaction. It proceeds through metallo-cyclobutene

generation and ring-opening to produce cyclic olefin with ethylene formation [53]. In this review, we deliberate the progress of RCM toward the synthesis of simple and intricate cage-like macrocyclic indole derivatives.

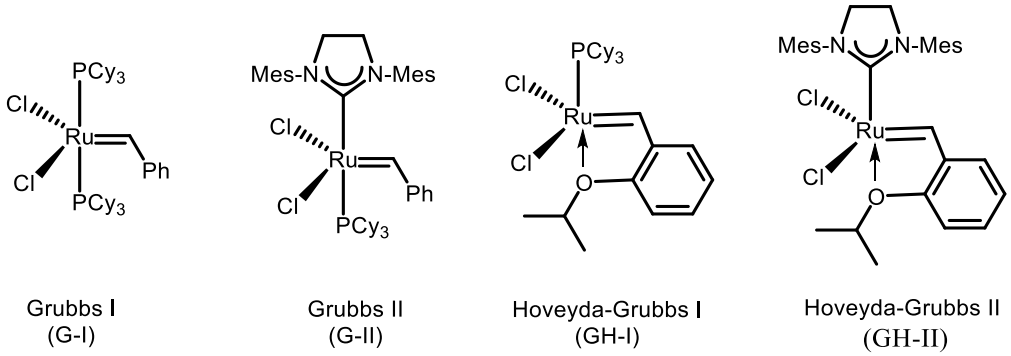
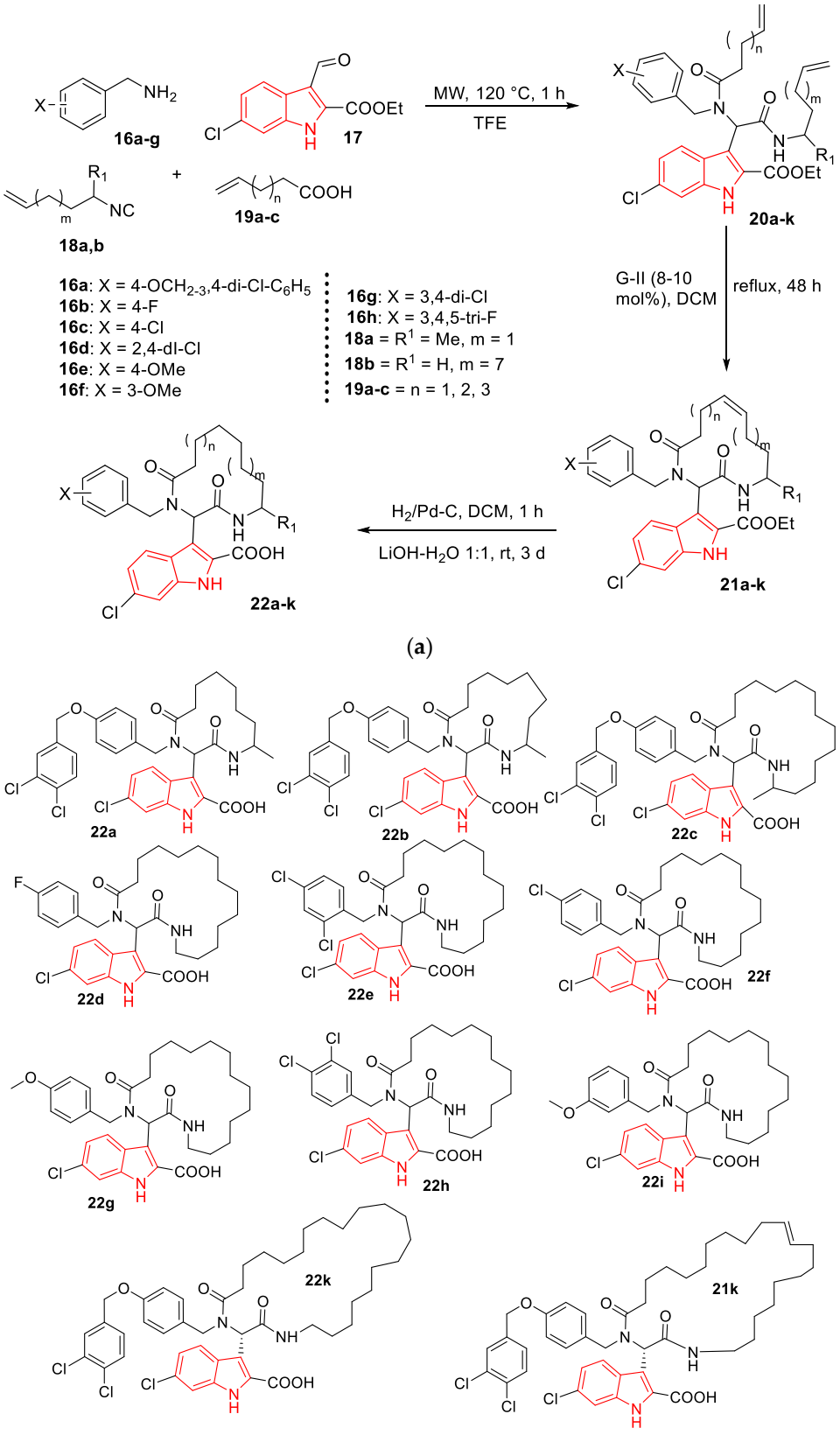


Figure 3. Ruthenium-based catalysts for metathesis reactions.

Domling and co-workers reported a series of various new macrocyclic p53-MDM2 inhibitors **22a**–**k** through the Ugi four-component approach and RCM as key steps (Scheme 1a,b) [54]. These indole-based macrocycles were alternatively to stapled peptides, which are targets for huge hydrophobic surface area produced by Tyr67, Gln72, His73, Val93, and Lys94, yielding the derivatives with affinity to MDM2 in the nanomolar range. For this, they proceeded with the Ugi reaction with an equimolar mixture of the substituted benzylamine **16**, aldehyde **17**, isocyanide **18**, and acid **19** in trifluoroethanol (TFE) was irradiated at 120 °C for 1 h under MWI conditions to generate the compounds **20a**–**k** (Scheme 1a,b). Later, the RCM of diolefin deviates from the usage of the G-II catalyst to afford compounds **21** as a mixture of isomers (E and Z). Since the existence of the double bond provides two isomeric systems and notably reduces the macrocyclic flexibility, further hydrogenation of these unsaturated scaffolds with Pd/C to deliver the saturated compounds **22a**–**k**. Next, ester hydrolysis delivers the acids **22a**–**k** for biological screening (Scheme 1a,b).

Muthusamy et al. reported [55] symmetrical pentacyclic thiazaindole macrocyclic derivatives **26a**–**d** were derived from 2-oxindole **23** via RCM as the key approach (Figure 4). For macrocyclization, they used Grubbs' second-generation catalyst, as well as Lewis acid as an additive. In this regard, they performed cyclization with symmetrical diolefins **25a**–**d** under different conditions with the usage of G-II catalyst with an additive to produce the corresponding macrocyclic thiazaindoles **26a**–**d** with varying sizes of ring ranging between 13–17 membered generated as a mixture of *Z*/*E* isomers (Figure 4).

In 2012, McGowan et al. reported a series of macrocyclic indoles as HCV NS5B polymerase inhibitors [56]. In this regard, the macrocyclic indoles synthesis **34a**–**d** (Scheme 2) started with the 2-bromoindole derivative in five steps via RCM. Bromo derivative **27** was subjected to the 3-furanboronic acid under Suzuki–Miyaura cross-coupling, followed by alkylation of **28** with bromomethylacetate with NaH to generate the acetate **29**. Regioselective ester cleavage of **29** followed by amino-acid coupling with the different alkenylamines using HATU in DMF deliver the amides **31a, b**. Basic hydrolysis of the second ester group and subsequent coupling of the alkenes **32a**–**c** using standard amino acid coupling conditions in DMF provided dialkenes **33a**–**d** in good yields. Finally, RCM of dialkenes using Hoveyda–Grubbs catalyst (5 mol %) afforded indole-based macrocycles **34a**–**d** (Figure 5).



Scheme 1. (**a**) Synthetic route to indole macrocycles **21a–k** via RCM as a key step. (**b**) Library of various indole macrocycles via U-4CR/RCM Strategy.

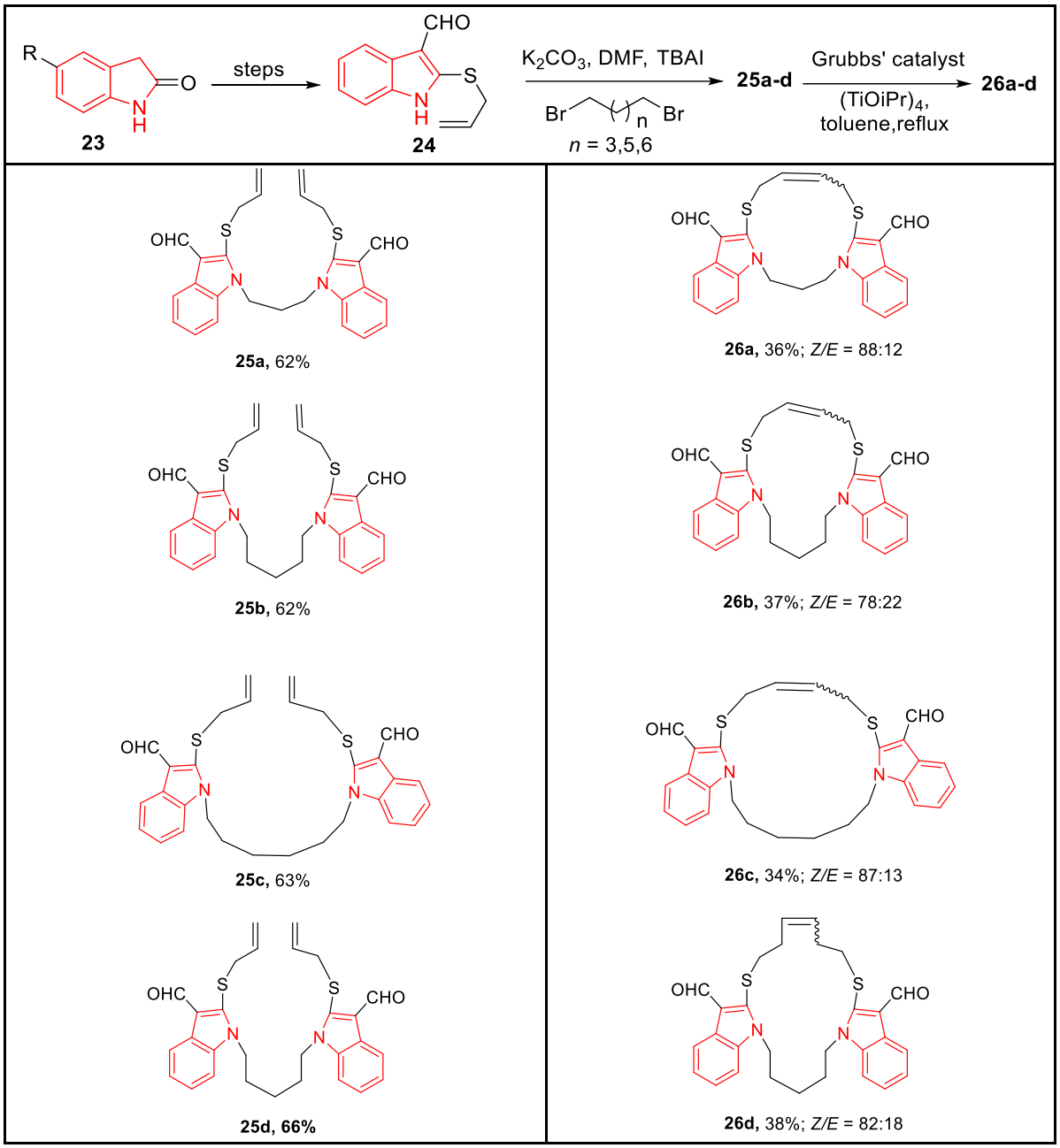
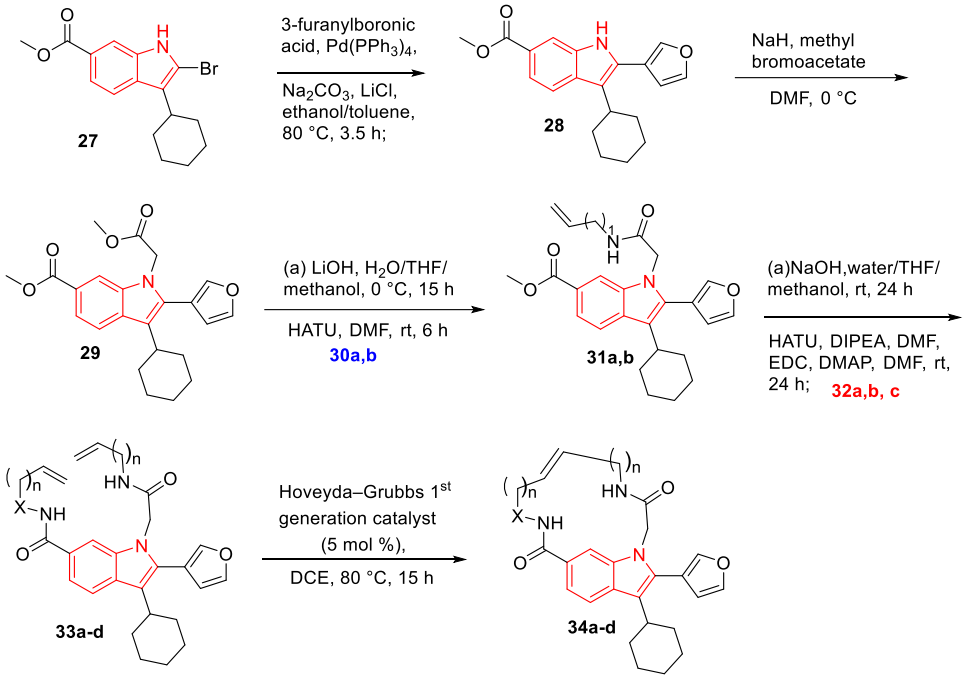


Figure 4. Synthetic approach to different pentacyclic macrocyclic thiazaindoles via RCM.



Scheme 2. Synthesis of macrocyclic indoles **34a**–**d**.

The Pyne group synthesized several indole-based macrocyclic peptoids **43a**–**c** as a potential antibacterial scaffold realized via a ruthenium-catalyzed RCM as a key step [57]. In this regard, they started with the commercially available indole acids **35a**–**c** with base and allyl bromide in excess amounts producing the mixture of both the allyl esters **36a**–**c** and the diallylated products **37a**–**c** (Scheme 3). Further, saponification with LiOH gave the acid derivatives **38a**–**c**. Next, the coupling of these acids **38a**–**c** with the dipeptide, such as L-allylGlyOMe-D-Lys 15 via EDCI coupling, generate the different dienes **39a**–**c**. Finally, RCM of dienes **39a**–**c** with G-I catalyst produces the ring-closing frameworks, such as macrocyclic indoles **40a**–**c** having a distinct mixture of both E/Z forms. Further, **40a**–**c** was treated with HCl, gave the cyclic peptoids as their hydrochloride salts **41a**–**c,** which, on TFA treatment, followed by reaction with triflylguanidine delivered the corresponding guanidine derivatives **42a**–**c**. Finally, deprotection with TFA yielded the cyclic peptoids **43a**–**c** for biological screening.

Burke and co-workers reported [58] indole-based macrocyclic tetrapeptide mimetic **51** based on olefin metathesis protocol (RCM) (Scheme 4). Macrocycle **51** exhibits unique in vitro Grb2 SH2 domain-binding affinity (*K*d = 93 pM) in extracellular assays while exerting blockade of Grb2 association with cognate intracellular proteins in entire cell assays at lower concentrations. The construction of macrocycle **51** was achieved with the key precursor **45** obtained in 5 steps from 3-(5-methylindolyl) propanoic acid **44**. The coupling of **45** proceeded with *N*-Boc Asn-OH with diisopropylcarbodiimide (DIPCDI) in the presence of 1-hydroxybenzotriazole (HOBt), and subsequent deprotection of Boc by 2 N HCl produces the free amine **46**. Later on, amine on coupling with *N*-Fmoc 1-aminocyclohexanecarboxylic acid (*N*-Fmoc Ac_6c) followed by piperidine-mediated N-deprotection gave **47,** which on ester coupling by **48** with the aid of HOAt and EDCI.HCl gave the dialkene **49** with satisfactory yields. Finally, the RCM of compound **49** with the Grubbs catalyst delivered the protected macrocycle **50** as a transform which, on TFA treatment, gave the sodium salt **51**.

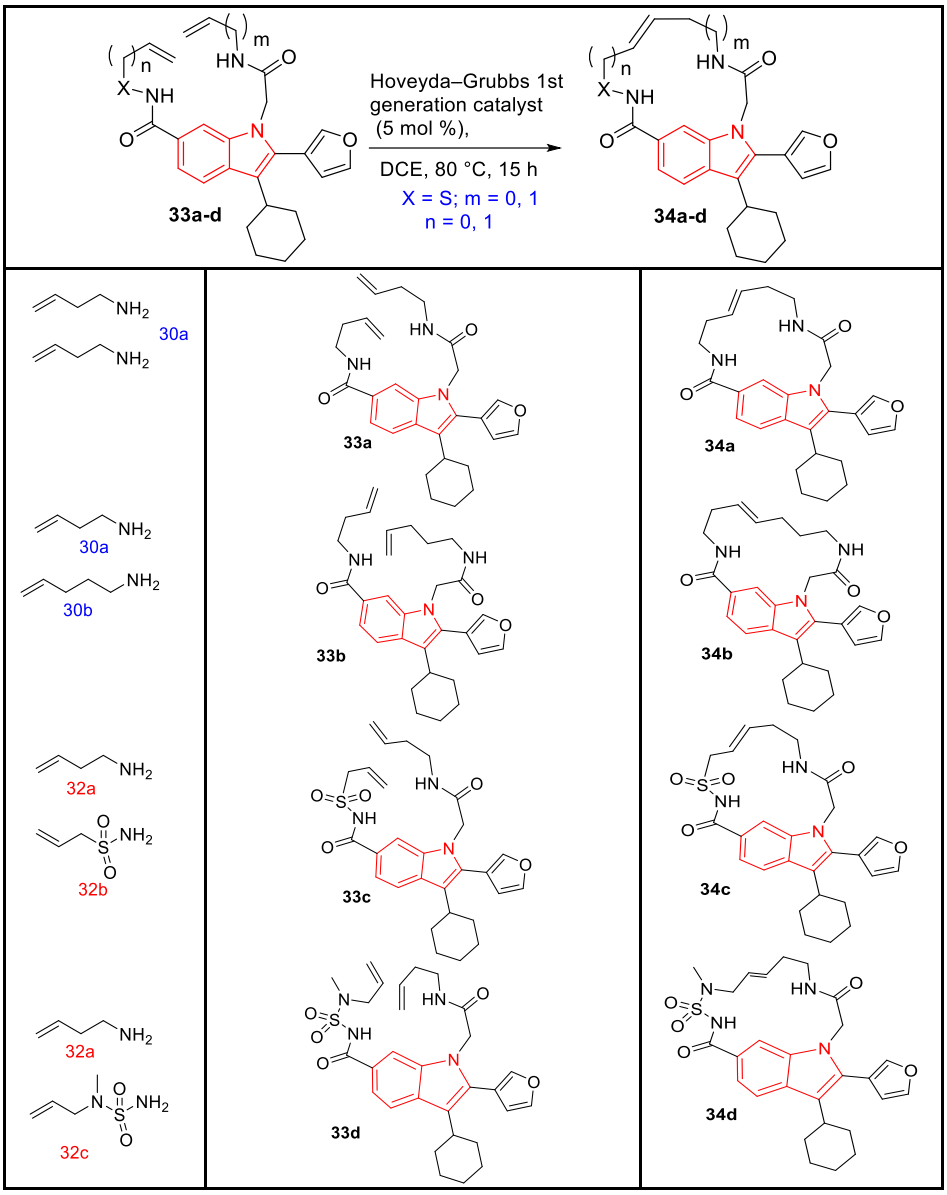
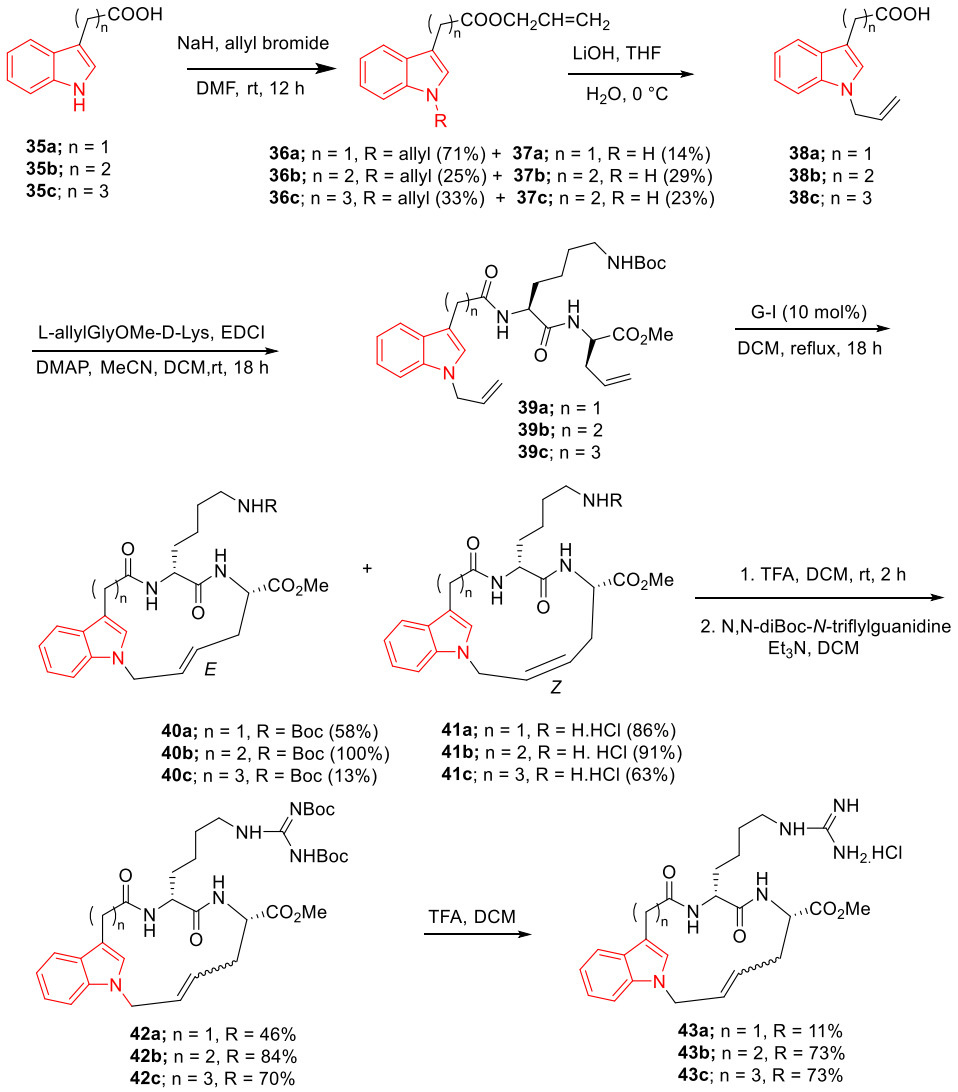
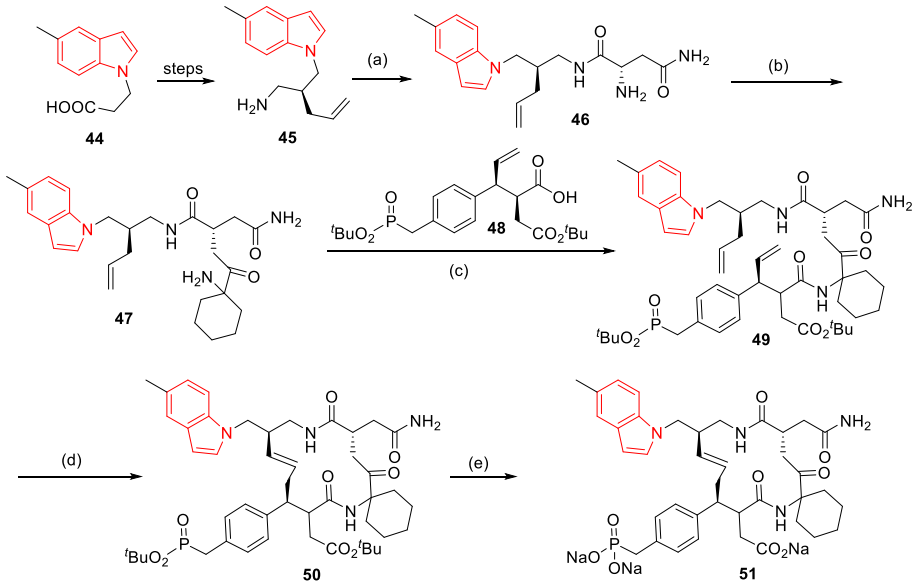


Figure 5. Synthesis of macrocyclic indoles.



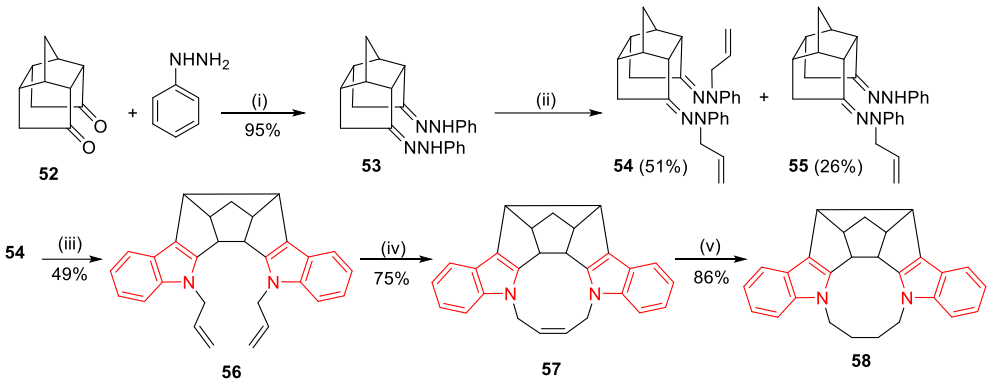
Scheme 3. Synthesis of macrocyclic indole peptoids **43a–c**.

Kotha and co-workers demonstrated methods for the assembly of bisindole macrocycles via Fischer indolization (FI) and olefin metathesis [59]. For this, compound **52** (tetracyclic dione) was exposed to phenyl hydrazine and L-(+)-TA: DMU (30:70) deliver the hydrazone intermediate **53** followed by allylation with base and allyl bromide to generate the mono and diallylated hydrazone **55** & **54**. Later, diallyl derivative **54** proceeded for FI with the same ratio of L-(+)-TA:DMU gave the macrocyclic bis-indole **56** with a 49% of yield. Finally, the diindole **56** on RCM (G-II catalyst) to afford the ring-closure product **57** (75%) and further treatment with hydrogen and Pd/C (10 mol %) delivered the macrocyclic diindole **58** (Scheme 5).



Scheme 4. Synthetic approach toward indole-based macrocyclic tetrapeptide mimetic **51**.

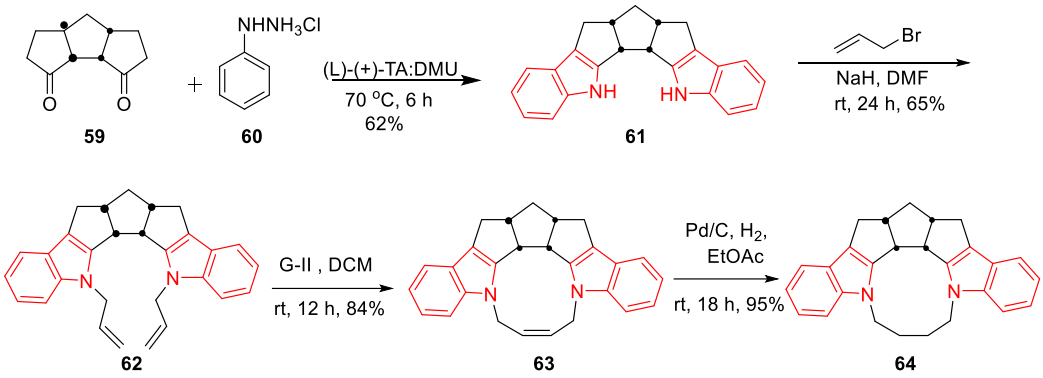
Reagents and conditions: (a) (i) Boc-Asn-OH, DIPCDI, HOBt, DMF, rt, 12 h; (ii) HCl(aq) (2 N), ACN, rt, 12 h; (b) (i) Fmoc-1-amino-cyclohexenecarboxylic acid, EDCI-HCl, HOBt, DMF, rt, 12 h; (ii) piperidine, ACN, rt, 2 h; (c) **48**, EDCI.HCl, HOAt, DMF, 50 °C, 24 h; (d) Grubbs catalyst, DCM, reflux, 48 h; (e) (i) TFA-$HS(CH_2)_2SH$-H_2O, rt, 1 h; (ii) aq. $NaHCO_3$.



Scheme 5. Synthetic route to macrocyclic bisindole **57** by FI sequence and RCM.

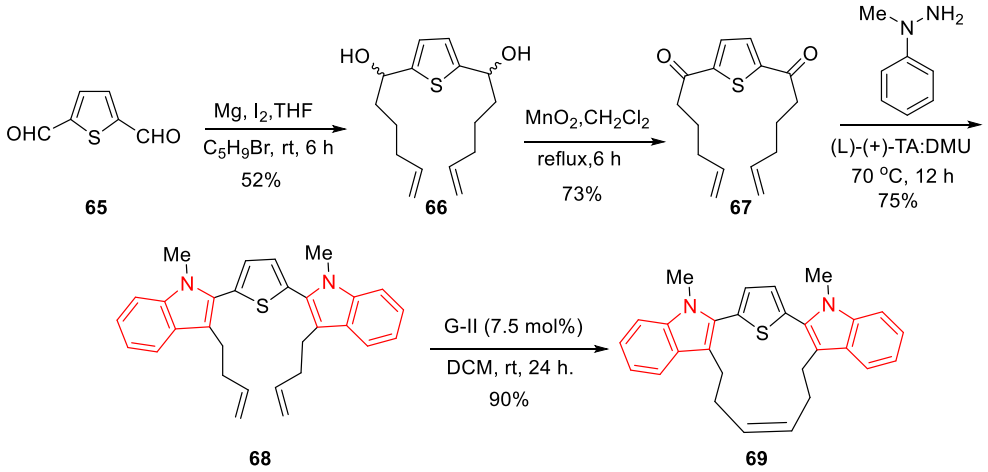
Reagents and conditions: (i) phenylhydrazine, L-(+)-TA:DMU, 12 h, 80 °C, 95%; (ii) NaH, allyl bromide, DMF, rt, 2 h, (iii) L-(+)-TA:DMU, 12 h, 80 °C; (iv) G-II, DCM, rt, 24 h; (v) Anhydrous EtOAc, 10% Pd/C, H_2, rt, 24 h.

A simple strategy by Kotha's group [60] for the dione conversion **59** to the indoles macrocycles **63** and **64** by a greener approach by FI sequence with TA: DMU had been depicted in Scheme 6. In this view, the indole scaffold **61** was treated for *N*-allylation followed by RCM to produce the indole-based macrocycle **63**, which on hydrogenation by Pd/C, delivered the aza-macrocycle derivative **64** (Scheme 6).



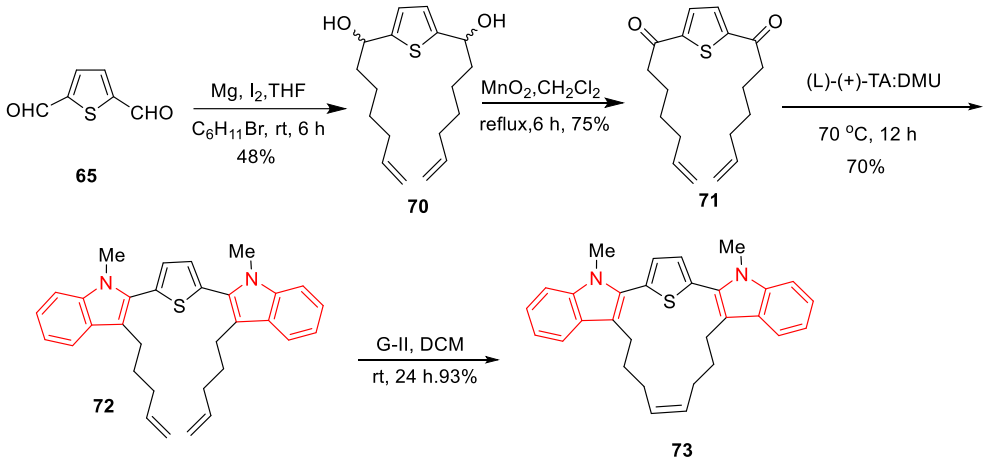
Scheme 6. Synthetic route to macrocyclic bisindole **64** realized on RCM sequence.

Kotha et al. reported thiophene-based indole macrocycles via RCM sequence [61]. In this regard, the Grignard addition to thiophene-2,5-dicarbaldehyde **65** with the aid of hexenyl Grignard yielded the diol **66,** which on MnO_2 oxidation gave the dione **67** followed by Fisher indolization with 1-methyl-1-phenylhydrazine gave the bis-indole product **68** which on olefin metathesis protocol with the G-II catalyst gave the macrocyclic indole **69** (Scheme 7).



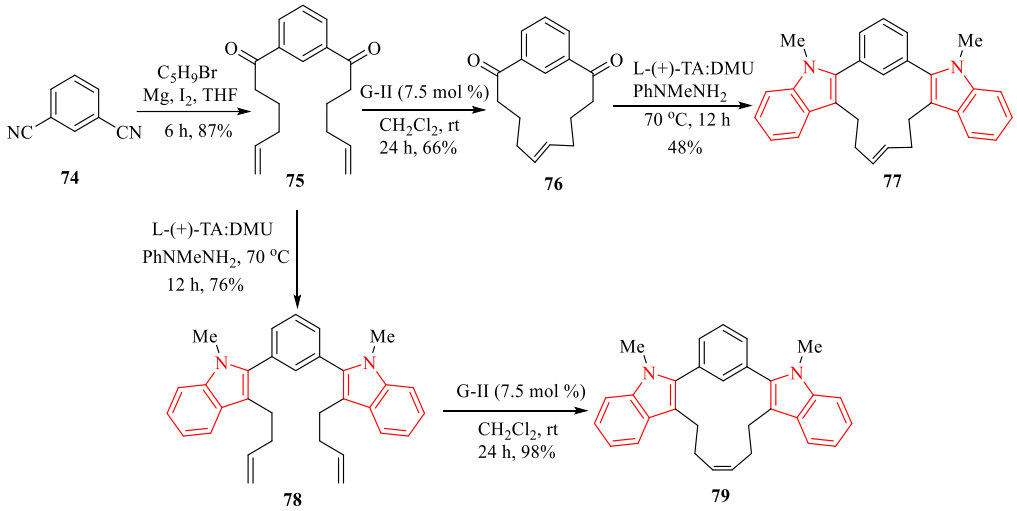
Scheme 7. Thiophene-based indole macrocycle **69** by RCM.

They also reported the other derivative by variation in the Grignard reagent; in this regard, thiophene-2,5-dicarbaldehyde **65** was treated with 5-hexenylmagnesium bromide to yield diol **70**. Later, compound **70** on MnO_2 oxidation delivers the dione **71,** followed by Fisher indolization (FI) with 1-methyl-1-phenylhydrazine to give **72** bearing indole frameworks. Afterward, the indole framework **72** on exposure with Grubbs second generation catalyst (G-II) produces the indole-based macrocycle **73** [61] (Scheme 8).



Scheme 8. Thiophene derived indole macrocycle **73** by RCM.

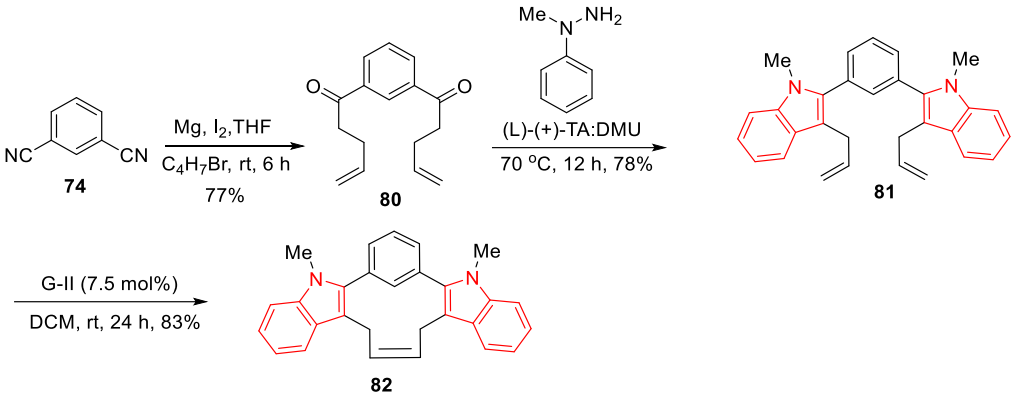
These types of macrocyclic scaffolds might be valuable for supramolecular chemistry due to their heterocyclic-based cage architectures. Kotha group also reported other varieties of macrocyclic bis-indole with variations in the stereochemistry with respect to double bond configuration generated during the metathesis sequence, mainly depending on the synthetic sequence used in the approach [62]. FI followed by RCM gave the cis derivative; in other cases, RCM followed by FI sequence delivers the trans derivative. In this regard, the dialkene **75** was subjected to metathesis to deliver the cyclized dione **76** to hold the double bond with transform. Further, the trans olefin **76** proceeded to Fisher indolization (FI) with 1-methyl-1-phenylhydrazine with TA: DMU gave the macrocyclic indole derivative **77** containing trans alkene. The dialkene derivative **78** on ring-closing metathesis by metathesis (G-II) catalyst gave the indole macrocycle **79** [62] (Scheme 9). It is exciting to observe that the stereochemistry of the double bond present in cyclophane **79** is in the *cis* form, proved by XRD studies.



Scheme 9. Synthesis of different indole-based macrocycles **77** & **79** with trans/cis configurations.

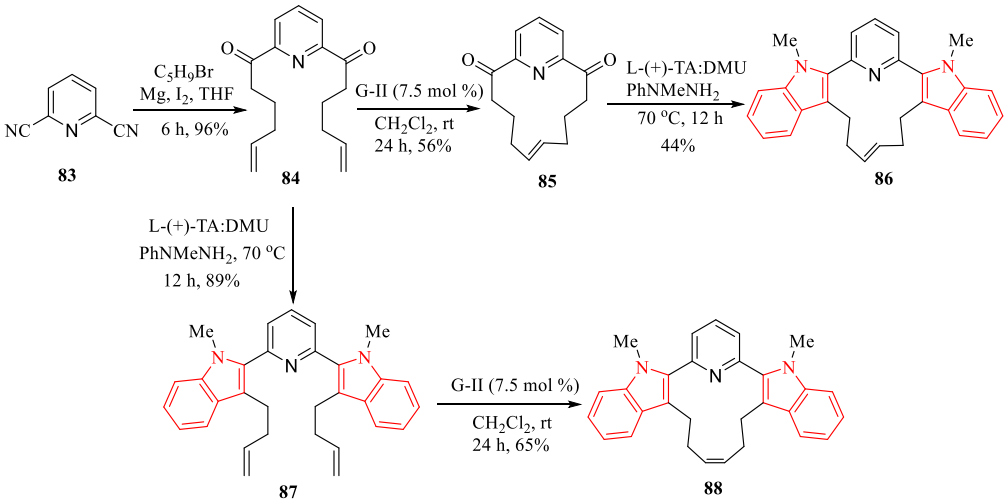
Similarly, isophthalonitrile **74** was reacted with the butenyl Grignard to deliver the dione **80**. Next, the alkenyl dione **80** underwent FI sequence with 1-methyl-1-phenylhydrazine with the aid of (L)-(+)-TA; DMU to produce the di-indole system **81** followed by metathesis sequence with G-II catalyst deliver the ring-closing product **82** with *cis* configuration (Scheme 10). The difficulty of the cyclization (RCM) with dione **80** might be due to the strain involved during the macrocycle formation step, and alkene chains may not be positioned in the appropriate configuration to make the cyclization process. However, in

the case of **82**, the ailment is completely different. The crowed indole frames attached to the side chains control the orientation of the alkene chains to ease the ring closure [62].



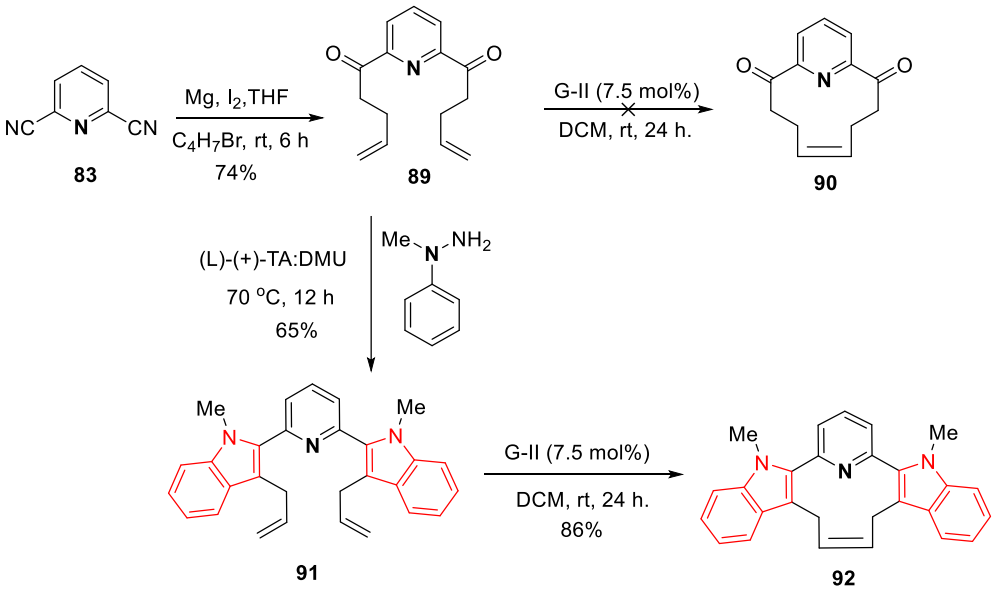
Scheme 10. Synthesis of indole-based macrocycle **82** by RCM.

Further extension of the strategy, Kotha et al. reported heteroaryl-based macrocycles via RCM. In this regard, 2,6-pyridinedicarbonitrile **83** was treated with pentenylGrignard to yield the di-olefin **84** and metathesis of **84** with the aid of the Grubbs second generation catalyst to give the RCM derivative **85** (Scheme 11) with *trans* orientation. The macrocycle **85** proceeded to FI to yield the bis-indole macrocycle **86** (Scheme 11). Further alkenyl dione **84** on treatment with 1-methyl-1-phenylhydrazine with TA: DMU gave the alkenyl bis-indole derivative **87**, which was exposed to metathesis catalyst (G-II) to give the ring-closure product **88** (Scheme 11), and the double bond present here is in the cis form [62].



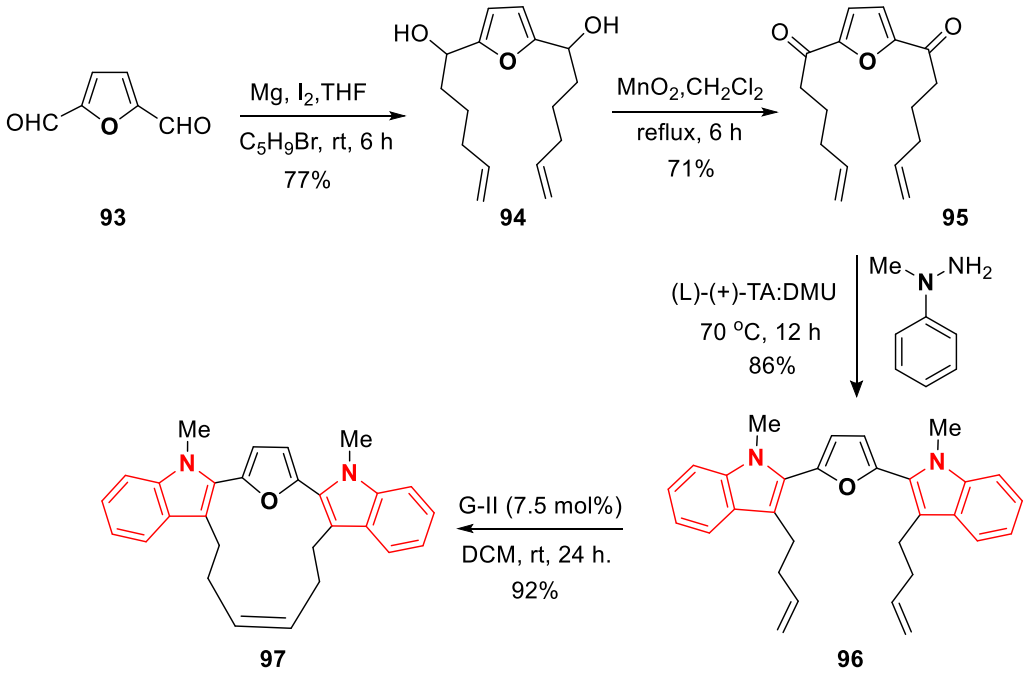
Scheme 11. Synthesis of heteroaryl indole-based macrocycle **86** & **88** with trans/cis configurations.

Additionally, 2,6-pyridinedicarbonitrile **83** was subjected to 4-bromo-1-butene to generate the dione **89** and followed by RCM protocol. However, the anticipated cyclization by RCM did not happen. In this context, compound **89** was exposed to FI sequence with 1-methyl-1-phenylhydrazine with TA: DMU as a deep eutectic media yield the indole derivative dialkene **91**, and then metathesis sequence with the Grubbs catalyst (G-II) to produce the RCM product **92** [62] (Scheme 12).



Scheme 12. Synthesis of heteroaryl indole-based macrocycle **92** by RCM.

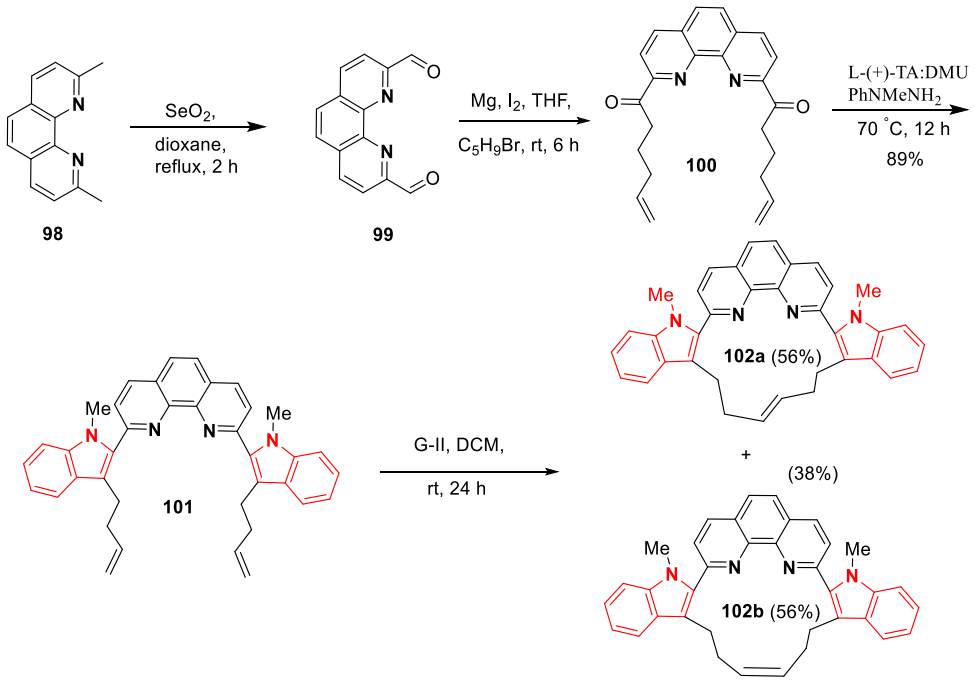
Later on, the expansion of these results with modifying to other variety of heterocycles, 2,5-furandicarboxaldehyde **93** on treatment with 4-pentenyl magnesium bromide gave the diol **94,** and alkenyl diol **94** on MnO_2 oxidation generated the dione **95** further on FI sequence with 1-methyl-1-phenylhydrazine to produce the dialkene indole system **96**. Further, RCM of **96** with G-II catalyst delivers the indole-based macrocycle **97** [62] (Scheme 13).



Scheme 13. Synthesis of macrocyclic scaffold **97**.

Kotha et al. reported [63] another variety of phenanthroline-derived macrocyclic bis-indole demonstrated by FI and RCM by readily accessible 2,9-dimethyl-1,10-phenanthroline **98**. The oxidation of **98** with SeO_2 delivers the 1,10-phenanthroline-2,9-dicarbaldehyde, which in addition to Grignard reagent and subsequent auto-oxidation, delivered the compound **100** bearing dione unit, which on further FI sequence delivered the required compound **101**. Further, cyclization is realized by RCM protocol to generate phenanthroline-

based macrocycles bearing indole scaffolds **102a** and **102b** (Scheme 14). The ease of isomers is due to the large macrocycle cavity, and it can accommodate cis and trans-forms.



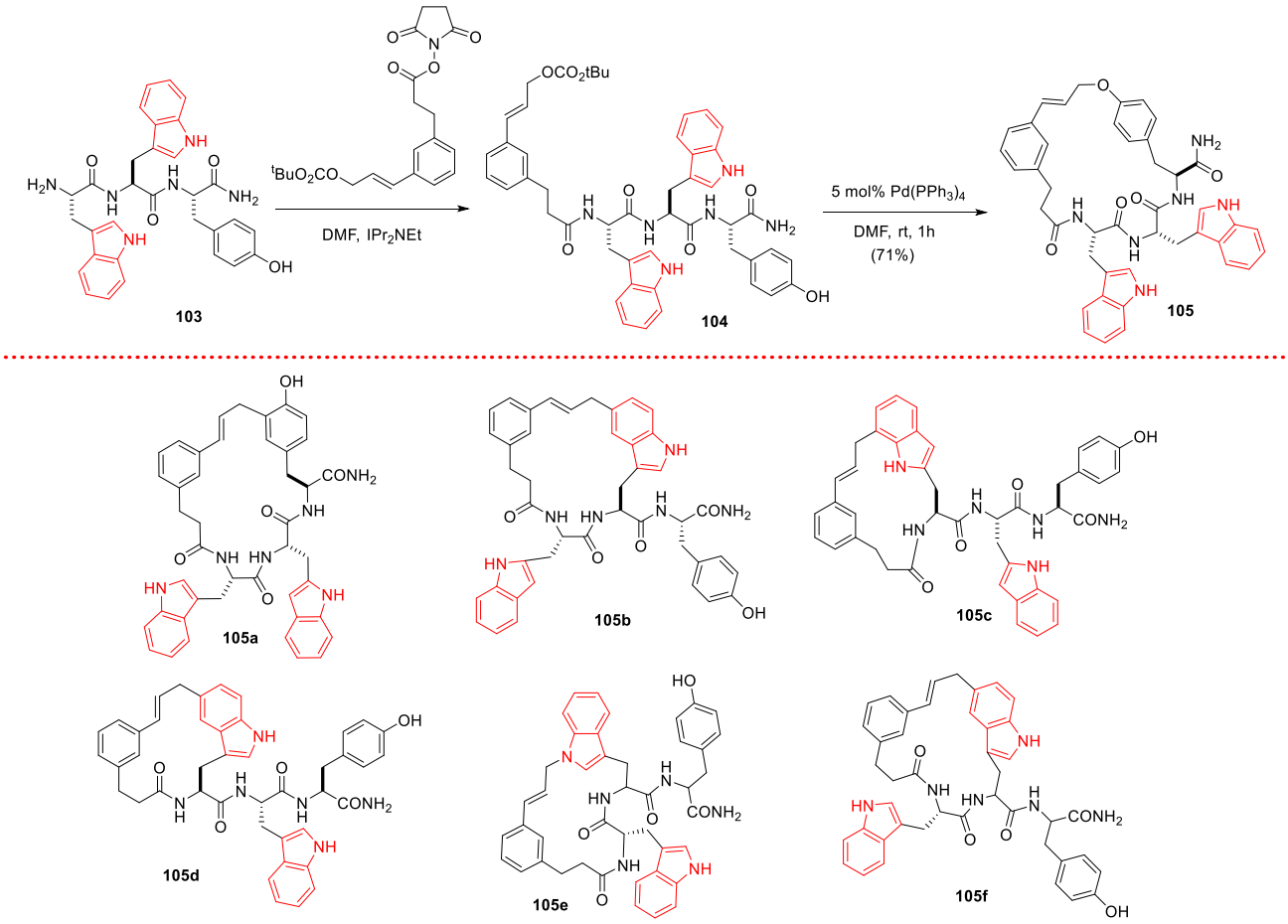
Scheme 14. Synthesis of phenanthroline-based indole macrocyclic derivative **101** & **102**.

2.2. Palladium (Pd) Catalyzed Indole-Based Macrocyclizations

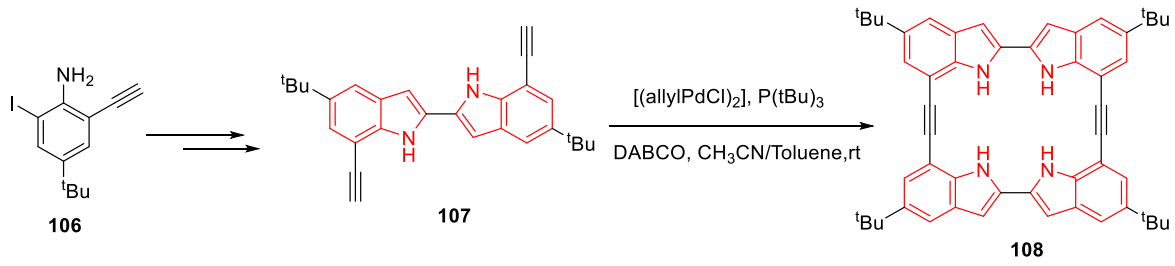
From the past few years, palladium-catalyzed approaches have become much more popular and broadly explored in the construction of complex architectures from simple linear precursors without any usage of protecting groups and create new bonds by coupling of C–H/C–H or C–H/N–H based bonds. For the better improvement of mild and selective reactions for the conversion of C–H bonds into C–C and C–O/N/S bonds is a trivial task in synthetic chemistry. These approaches are tolerant to diverse functionalities and become the most significant tools in the functionalization of various complicated scaffolds and planning to construct several kinds of molecules with respect to atom- and the step-economical way [47–49].

Peptides are well known for their application in various biological process, but due to their poor bioavailable properties and limited stability in vivo, it has been substituted by peptidomimetics. Moreover, macrocyclic peptidomimetics possess great valuable properties as compared to their linear precursors. In 2013 Patrick G. Harran and their co-workers gave given a new strategy [64] for the synthesis of a library of indole-based peptidomimetics macrocycles **105a–f** catalyzed by palladium (Scheme 15).

In biological and chemical processes, anions play a significant role in various aspects. So, selectively distinguishing and quantifying is essential. In 2005, Kyu-Sung Jeong and co-workers synthesized [65] indole-based macrocycle **108** (Scheme 16) from dialkyne derivative **107** via palladium-catalyzed strategy for the receptor of anions (I^-, Br^-, CN^-, NO_3^-, HSO_4^-, N_3^-, Cl^-, $H_2PO_4^-$, ACO^- and F^-). The macrocycle will facilitate the binding with anion by H-bond (N-H). The selective binding properties were studied by the different chemical shifts of the N-H proton of the macrocycle in ^1H NMR.

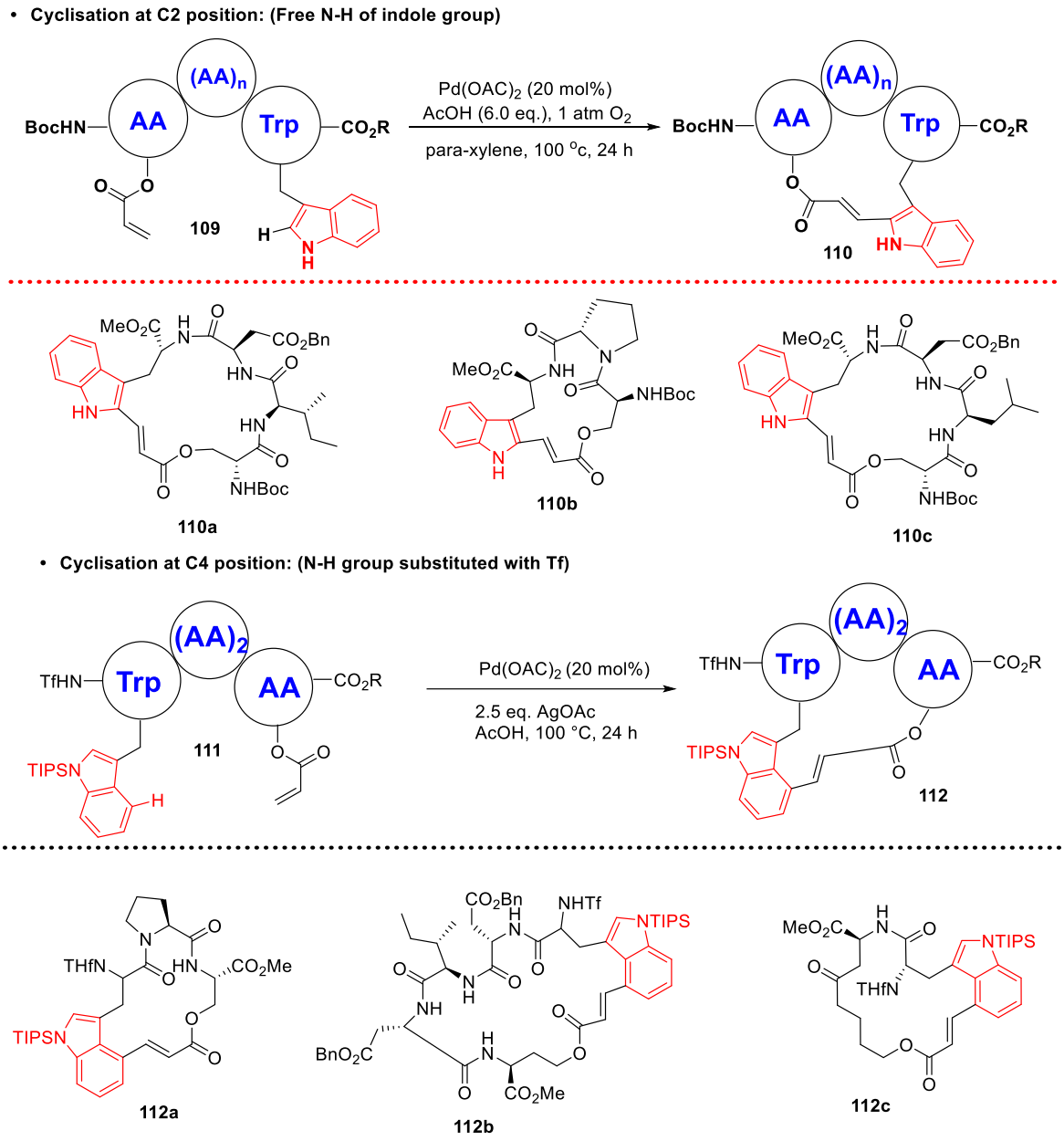


Scheme 15. Indole-based Macrocyclic peptidomimetics via palladium-catalyzed approach.



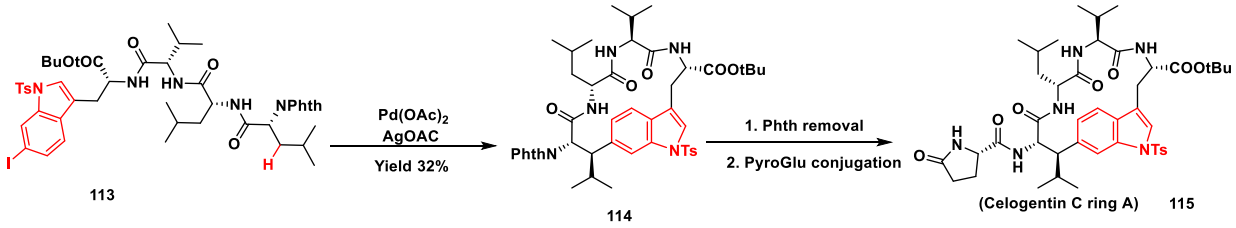
Scheme 16. Indole-based macrocyclic scaffolds for anion receptors by palladium-catalyzed approach.

In 2020, Huan Wang et al. designed a novel synthetic methodology [66] for the synthesis of indole-based macrocycles by a C-H activation process catalyzed by palladium. The novelty of the synthetic strategy is to use the peptide backbone of the peptide as an endogenous directing group which provides novel Trp-alkene crosslinks (Scheme 17). The cross-links/cyclization happened between the C2 position of the indole group. At the same time, when the nitrogen atom of the indole group was substituted with trifluorosulfonamide (Tf), it directed the cyclization at the C4 position of the tryptophan ring [66].



Scheme 17. Synthesis of indole-based macrocycles **112a–c** catalyzed by palladium via C-H activation.

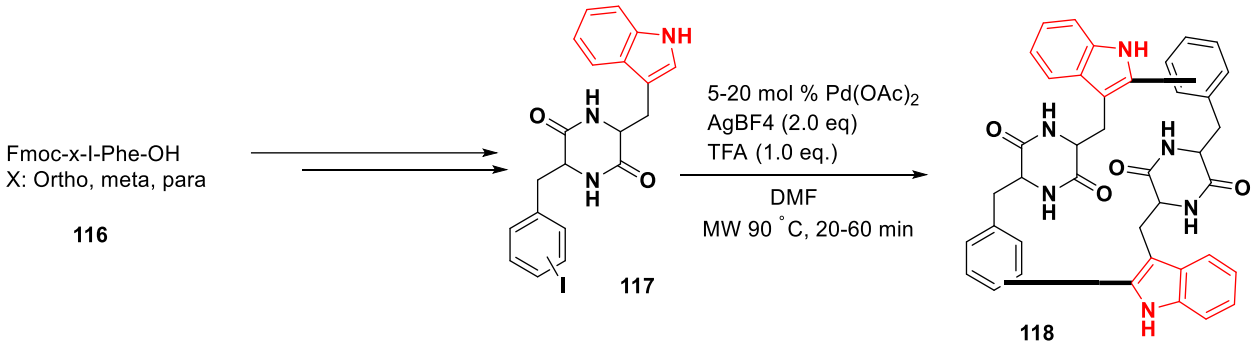
In 2017, Wang et al. established a novel strategy for the synthesis of a library of amine-based macrocycles from linear amine-based molecules [67]. The synthetic strategy was also validated for the synthesis of natural existing indole-based macromolecules, for example, Celogentin C. Furthermore, they compared the bioactive properties between macrocycle frames with respective linear frameworks, which reveals that macrocycles are more bioactive as compared to linear frameworks (Scheme 18). The synthesis of macrocycles starts from existing modified peptides [68].



Scheme 18. Synthesis of natural existing Cβ-Ar linked macrocycle, Celogentin C ring A.

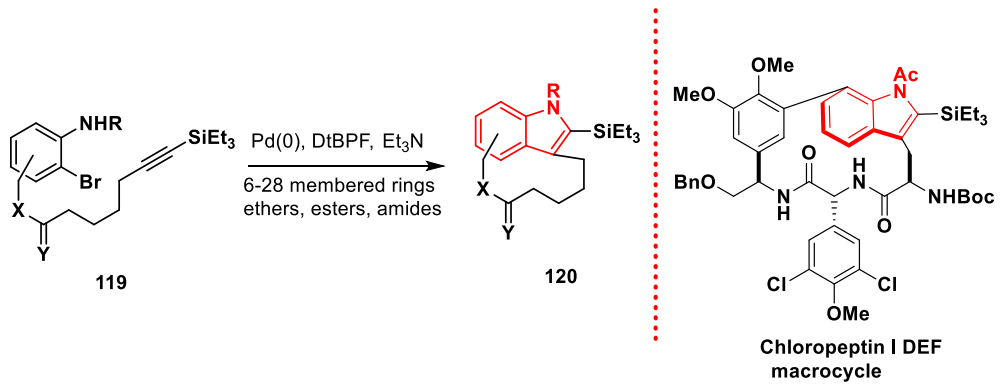
The macrocyclization reactions were carried out by well-known C–C coupling in the presence of a palladium catalyst. The coupling reaction happened between the β-carbon of the amino acids (e.g., Ala, Val) and the phenyl ring of phe/Trp.

Peptides are the foremost biomacromolecules; their metabolic stability makes them away from various biomedical applications. On the other hand, cyclo pepties are more stable and have high bioactive properties. In 2016 Lavilla et al. gave given one scheme for the palladium-catalyzed synthesis of monomeric (intramolecular C–C coupling) and dimeric (intermolecular C–C coupling) cyclopeptide (Scheme 19) [69].



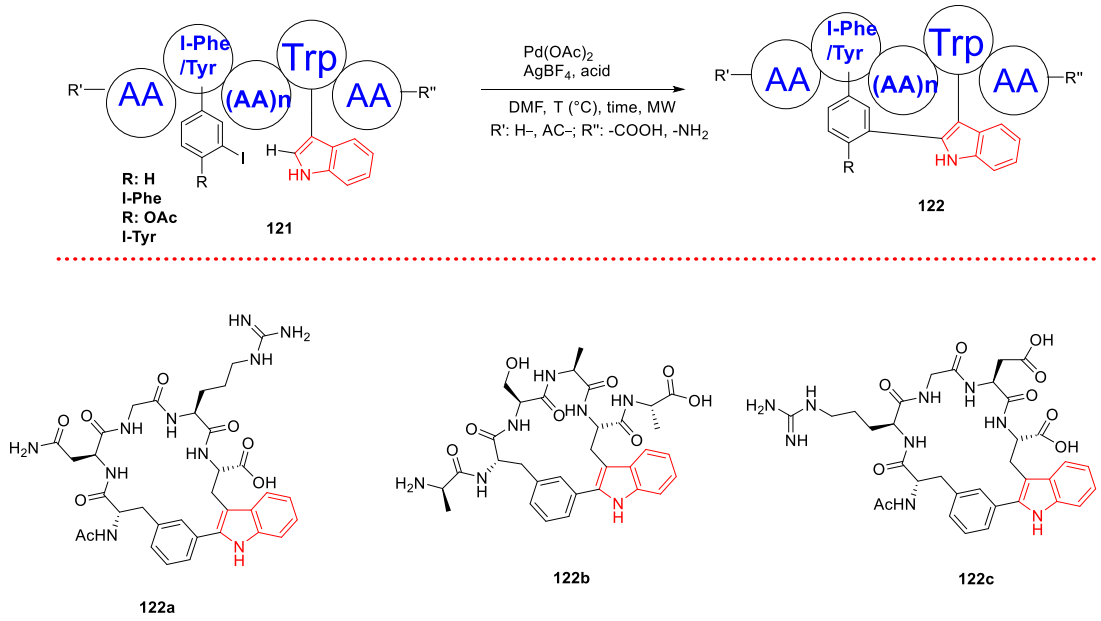
Scheme 19. Synthesis of natural existing Cβ-Ar linked macrocycle, Celogentin C ring A.

In 2013, Boger et al. reported a palladium-catalyzed indole-based macrocycle for the synthesis of natural (chloropeptin I versus II DEF ring) and unnatural isomeric macrocycle from triethyl silylated alkyne (Scheme 20) [41].



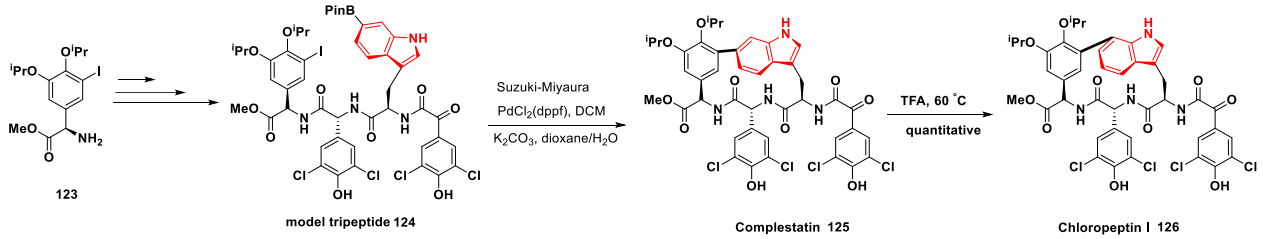
Scheme 20. Synthesis of indole-based macrocyclic fragment **120** useful for Chloropeptin I DEF.

In 2015, Rodolfo Lavilla and coworkers reported a novel strategy for the synthesis of new peptide architecture via C-H activation, clipping between tryptophan-phenylalanine/tyrosine residues (Scheme 21). The C-H activation reaction was carried out by a palladium catalyst. Furthermore, the biomedical application of synthesized macrocyclic peptides corresponding to liner peptides was also studied [70].



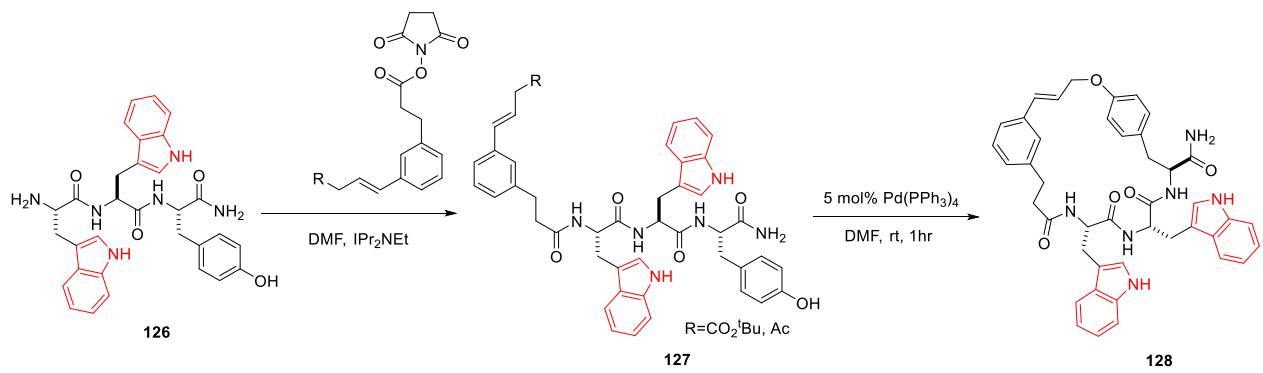
Scheme 21. Synthesis of indole-based macrocyclic peptides.

In 2007, Zhu et al. synthesized highly atropdiastereoselective DEFG rings of two natural existing indole-based macrocycles, i.e., complestatin and chloropeptin I, by the Suzuki–Miyaura reaction. The First Suzuki coupling reaction, catalyzed by the palladium and 16-membered DEFG ring of complestatin, ring **125,** was prepared from compound **123** via Chloropeptin **124**. Complestatin **126** was formed by acidic treatment of Chloropeptin I **125** with excellent stereospecific yield (Scheme 22) [71].



Scheme 22. Synthesis of indole-based macrocyclic fragment useful for Complestatin.

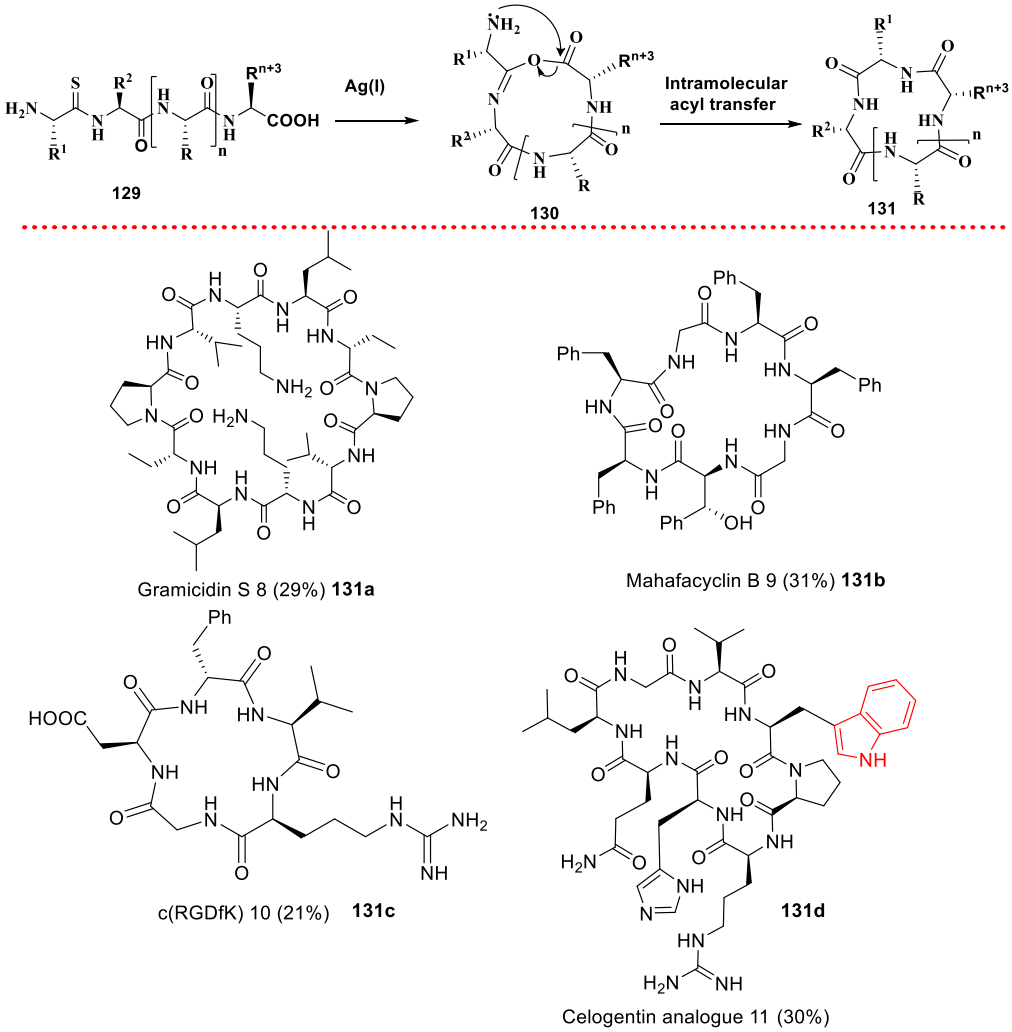
In 2013, Harran et al. developed a novel palladium catalyst-based synthetic methodology for the synthesis of macrocyclic peptides **128** from native unprotected precursor **126** (Scheme 23). The mechanism of the synthesis was followed by the addition of Boc-protected compound 127 with the Pd $(PPh_3)_4$ [72].



Scheme 23. Synthesis of indole-based macrocycle via templated-based cyclizations.

2.3. Silver (Ag) Catalyzed Indole-Based Macrocyclizations

Macrocyclic peptides are considered an interesting molecular framework for drug development. Because of their structural stiffness, high affinity for the target proteins, stability to proteases, and potential membrane permeability, and stability to proteases, cyclic peptides offer good therapeutic potential. Epimerization and cyclodimerization result in the slow downing of peptide macrocyclization. In 2019, Hutton et al. reported [73] a synthetic strategy to overcome these by using silver (Ag(I)) promoted macrocyclization of peptides **131a–d** containing an N-terminal thioamide prepared from peptide precursors **129** via intramolecular acyl transfer of **130**. Head-to-tail macrocyclization was carried out by situating the thioamide functional group at the N-terminal of the peptide chain (Scheme 24).

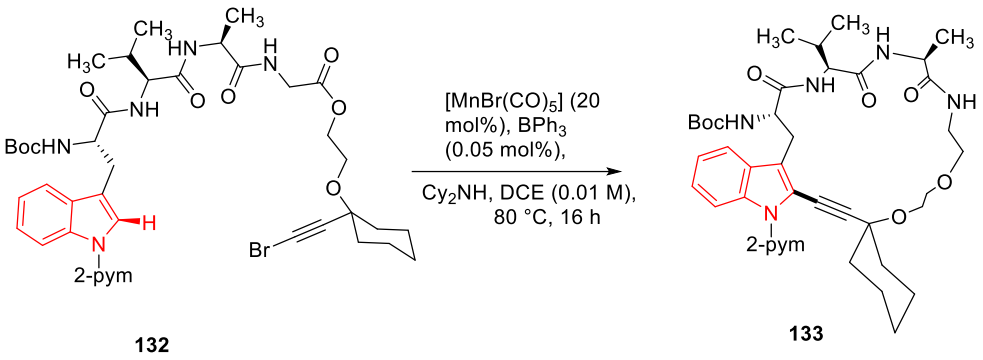


Scheme 24. Macrocyclization of peptide thioamides by Ag(I) and other examples of cyclic peptides synthesized.

First, the C-terminal of amino acid will react with the thiamide functional group in the presence of a silver catalyst, which enables the N-terminal to come closer to C-terminal **130**. The amino group at the N-terminal undergoes nucleophilic attack on the carbonyl group and thereby generating an amide bond through 1,4 acyl transfer. This acyl transfer is facilitated by the extrusion of Ag_2S. In this procedure Ag(I) has two functions; one is to template the cyclization by putting the N-terminal and C-terminal close together and thereby helping in the head-to-tail macrocyclization. Secondly, Ag(I) chemoselectively facilitates the thioamide nucleophilic attack by the carboxylate. The reaction was completed within one 1 h and resulted in a good yield.

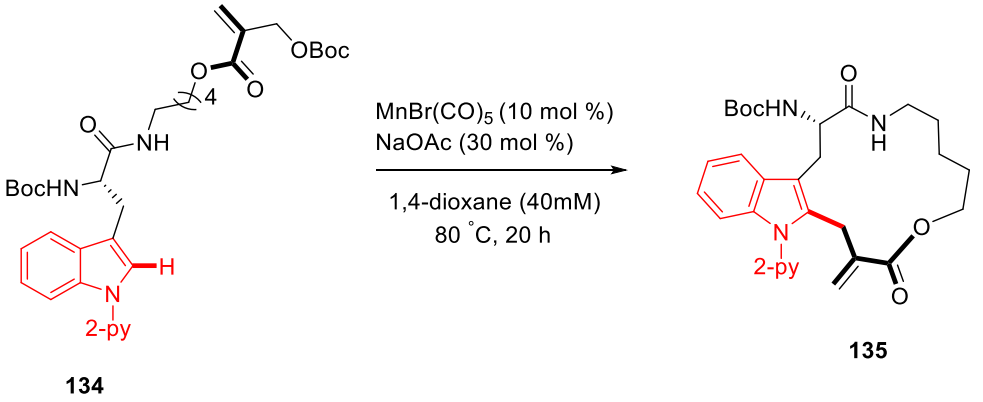
2.4. Manganese (Mn) Catalyzed Indole-Based Macrocyclizations

Ackermann et al. successfully synthesized cyclic peptides containing indole motif **133** via a manganese-catalyzed C-H alkylation starting from acyclic peptide **132**. Macrocyclization was carried out in highly diluted conditions [74]. An example of the manganese-catalyzed variant of C-H activation is shown in Scheme 25.



Scheme 25. Manganese-catalyzed C-H alkynylation for cyclic peptide **133** bearing indole scaffold.

Macrocyclization was carried out through the intramolecular C2 alkynylation of indole. It was discovered that dicyclohexylamine and DCE were the best base and solvent for this reaction. The loading of the Mn(I) catalyst is reduced by the addition of Lewis-acidic triphenyl borane. An unbiased amino acid derivative **134** undergoes C-H alkynylation to yield a 15-membered indole macrocycle **135,** as shown in Scheme 26 [75].



Scheme 26. Synthesis of indole-based macrocycle **135** by C-H alkynylation.

2.5. Copper (Cu) Catalyzed Indole Based Macrocyclizations

Indole plays a role as a significant class of heterocyclic ring systems that have been extensively explored for its broad range of applications in pathophysiological conditions, for example, cancer, microbial cancer, viral infections, inflammation, depression, migraine, emesis, hypertension, etc. [76]. Miranda et al. developed a new method to practically synthesize novel tryptamine-based macrocycles **138a–l** by from Boc-protected indole derivative by combining two reactions, such as Ugi four-component reaction (Ugi 4 CR) and copper catalyze click cycloaddition (CuAAC) as shown in Figure 6 [77].

An aldehyde, an amine, a carboxylic acid, and an isocyanide are taken as starting materials in the Ugi reaction for the construction of the peptoid backbone. These starting materials can be chosen according to our desired peptoid motif. The macrocyclization process is performed through a Copper-catalyzed click reaction resulting in the formation of 1,4 substituted triazole. Combining Ugi 4 CR and click reaction produces a macrocyclic scaffold with a peptoid moiety, a 1,3-substituted indole nucleus, and a triazole ring. An example of such a tryptamine-based macrocycle is given in Scheme 27. This reaction

is microwave-assisted, and copper bromide and DBU were used as catalysts. 110 °C temperature and toluene as a solvent gave satisfactory yield.

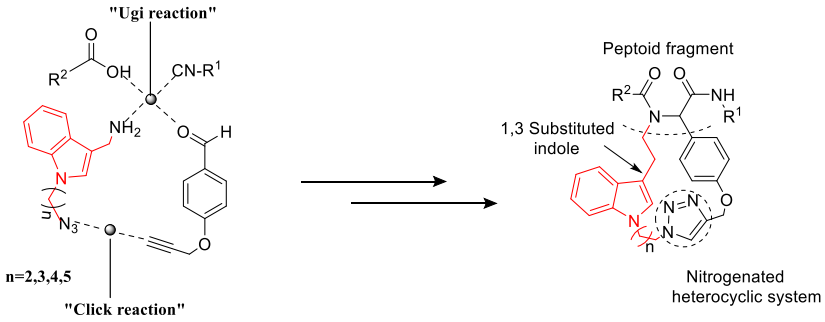
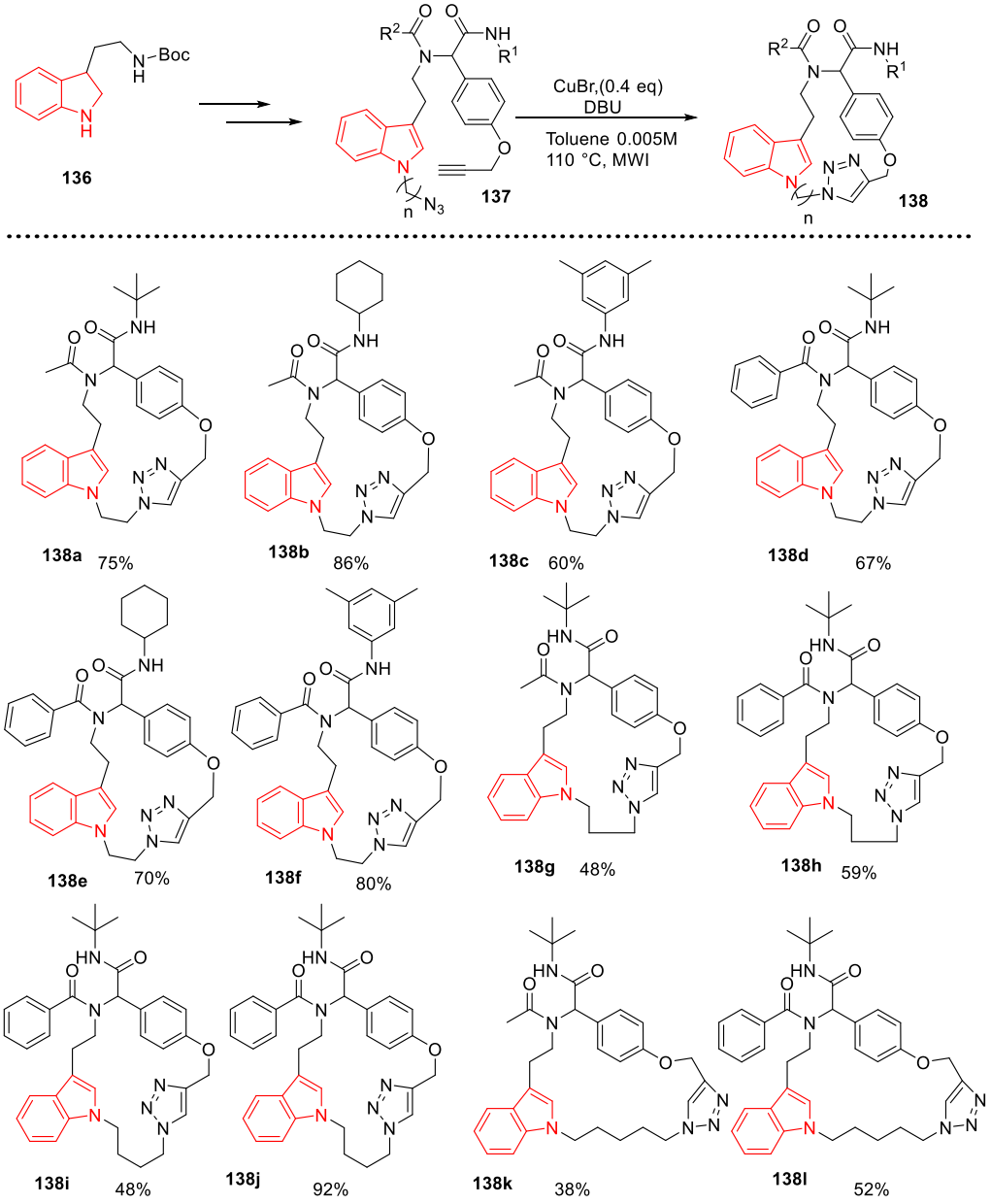


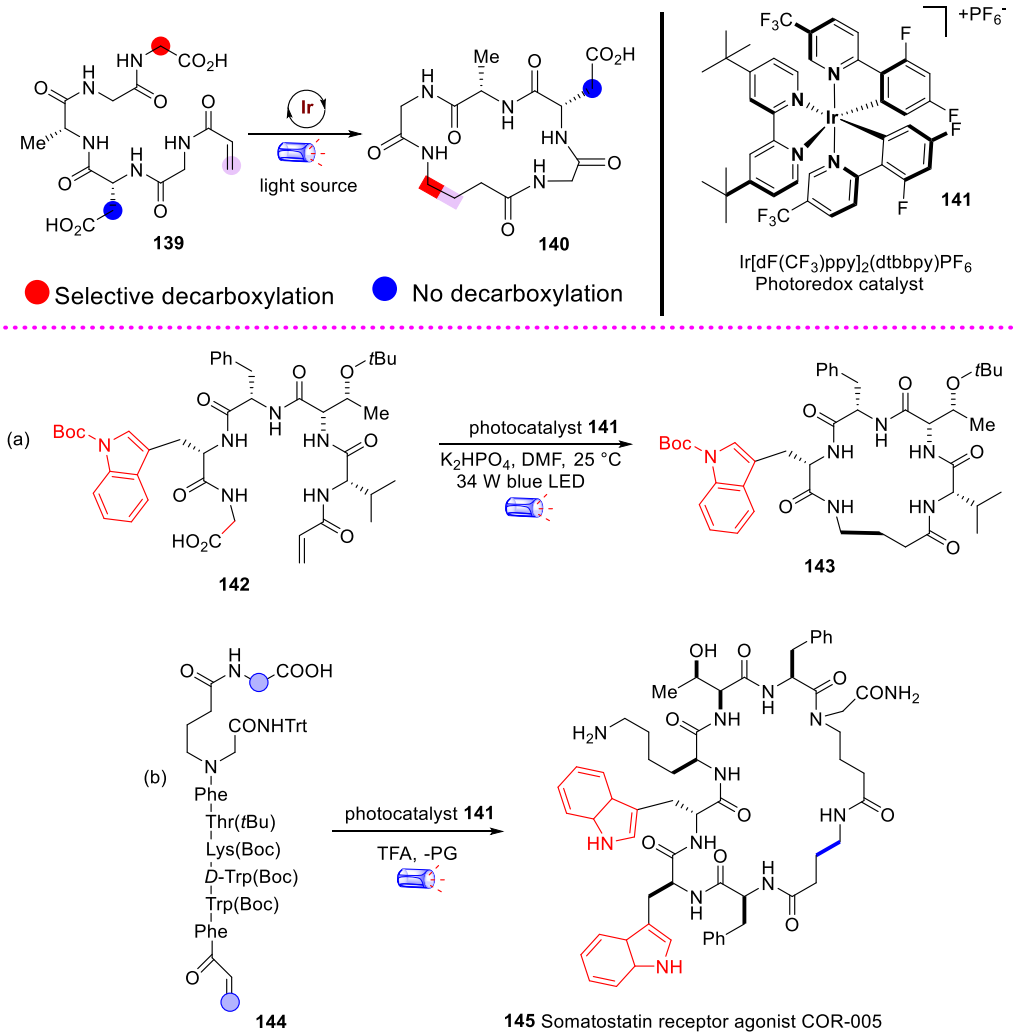
Figure 6. Synthesis strategy toward indole macrocycles via Ugi reaction and click reaction containing a 1,3 substituted indole, a peptoids moiety, and a triazole ring and a peptoid moiety.



Scheme 27. Synthesis of indole macrocycles via Ugi reaction and Cu-catalyzed click cycloaddition.

2.6. Iridium (Ir) Catalyzed Indole-Based Macrocyclizations

Recently, a wide spectrum of experts in academic and pharmaceutical contexts have paid considerable interest to cyclic peptides. The preparation of molecules that fall under the structural class of cyclic peptides can be difficult using conventional synthetic techniques. In 2017, MacMillan et al. reported [78] a photo redox-enabled decarboxylative macrocyclization of peptides that contains N-terminal Michael acceptors by utilizing an iridium-based photocatalyst (Scheme 28). The C-terminal carboxylate group selectively undergoes SET oxidation to generate a carboxyl radical, followed by decarboxylation producing α-amino radical. Subsequent intramolecular attack of this nucleophilic α-amino radical on the pendant Michael acceptor finally resulted in traceless macrocyclization (Scheme 28).

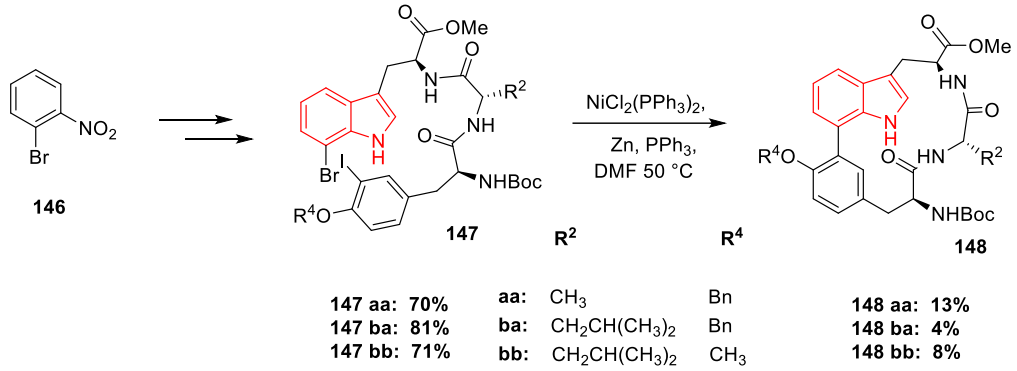


Scheme 28. Iridium-catalyzed approach to indole-based macrocyclic peptides.

2.7. Nickel (Ni) Catalyzed Indole-Based Macrocyclizations

The enzyme peptidase of the proteasome 20S, a multicatalytic protease that is essential to numerous intracellular processes, was reported to be particularly strong, reversible, and non-covalently inhibited by TMC-95A [79]. So, its inhibition offers a favorable target for drug development. In 2003, Vidal and co-workers developed a synthetic strategy for three constrained macrocyclic peptide **148aa**, **148ba**, and **148bb** analogs that can act as powerful proteasome inhibitors (Scheme 29) from **147** (obtained from 146 in multiple steps) via Ni-catalyzed macrocyclization. The important step in the synthesis is the Ni (0)-assisted macrocyclization of tripeptides that contains halogenated aromatic side groups that can

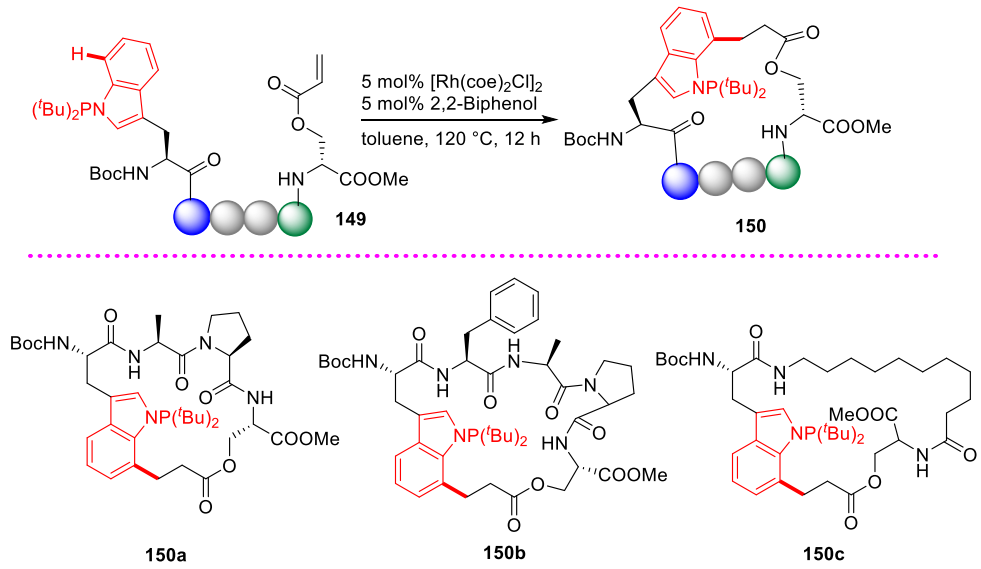
facilitate the generation of the biaryl junction [80]. A low yield is observed during the macrocyclization, probably due to the constrained nature of the macrocycle imparted by the sp^2 carbon located at the C-6 position [81].



Scheme 29. Nickel-catalyzed approach to indole-based macrocyclic peptides.

2.8. Rhodium (Rh) Catalyzed Indole-Based Macrocyclizations

A step-efficient method for peptide functionalization is transition metal-catalyzed C-H activation [82]. In 2022, Huan Wang and co-workers reported a technique for late-stage peptide ligation and macrocyclization that involves the C7 alkylation of tryptophan residues at the C7 position under the influence of rhodium (Scheme 30). This process makes use of an N-Pt Bu2 directing group and accepts a range of peptide and alkene substrates and peptides. This study is the first to demonstrate deconjugative isomerization-based site-selective peptide C-H alkylation using internal olefins (Figure 7). Additionally, this approach gives users access to peptide macrocycles with distinctive Trp(C7)-alkyl crosslinks and significant cytotoxicity for cancer cells [83].



Scheme 30. Rhodium-catalyzed approach to indole-based macrocyclic peptides **150a–c**.

Maleimide is widely used in numerous industries, particularly in the production of peptide medicines and antibody-drug conjugates [84]. However, biomolecules need to have active reaction centers like cysteine, thiol, or other linkers in order to conjugate the maleimide moiety with them [85]. The creation of a technique for directly decorating maleimide on biomolecules, particularly peptides devoid of cysteine, is crucial. In 2020, Liu et al. demonstrated a method to synthetically decorate peptides with maleimide by C-H alkylating tryptophan and tryptophan-containing peptides **152a**,**b** from linear chain **151** containing maleimide by the action of rhodium (III) based catalyst (Scheme 31). The

approach is quite tolerant of both protective and functional groups. Moreover, methods to utilize intramolecular and inter-molecular C-H activation to generate a tryptophan-based macrocycle were explored [86].

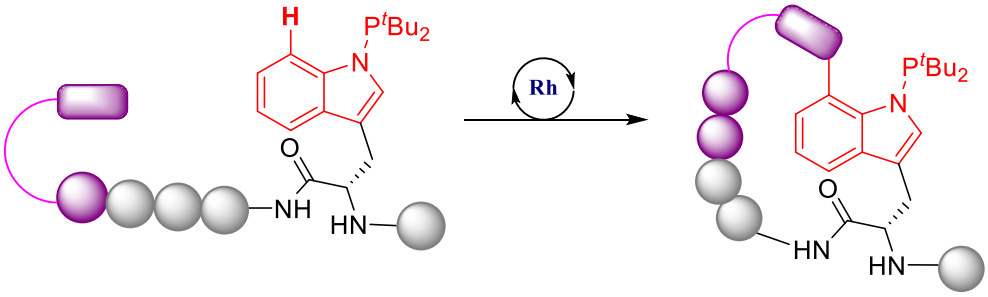
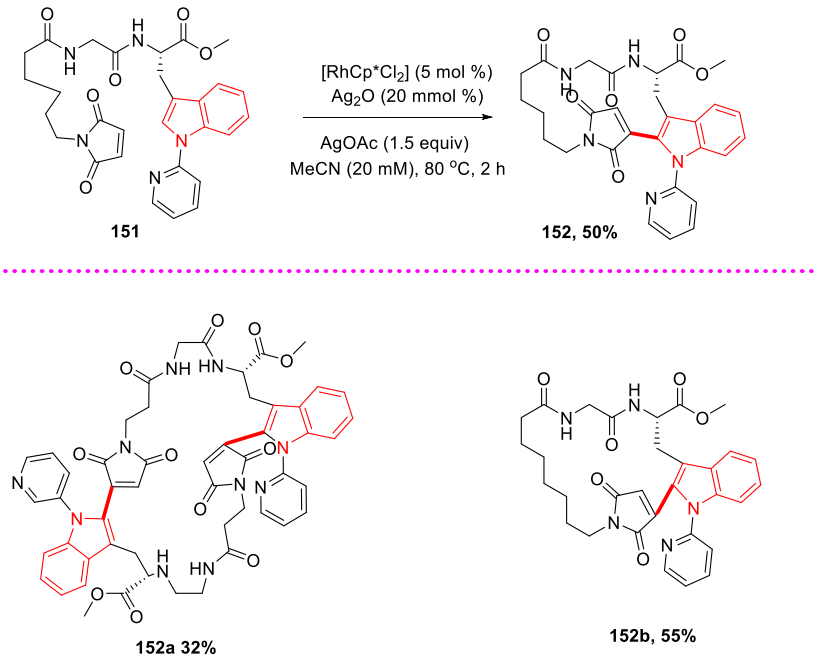


Figure 7. Rhodium-mediated indole-based macrocyclization.



Scheme 31. Rhodium-catalyzed approach to indole-based macrocyclic peptides.

3. Conclusions

In conclusion, the described metal-catalyzed approaches are allowed for the synthesis of various heteroaryl macrocycles bearing indole units with high structural diversity and complexity. There has been rising interest in recent years in the progress of macrocyclic frameworks containing heteroaryl systems due to their valuable applications in numerous fields of research. Moreover, derivatives of the indole scaffold are extensively dispersed in a number of biologically relevant molecules and play a prominent role as key synthons for the synthesis of medicinally important small molecule drugs, synthesis of natural products, and pharmaceuticals. Thus, novel approaches to attain indole-based macrocycles remain urgent in synthetic organic chemistry. Macrocyclic indole frameworks have emerged as well as attractive synthetic targets because of their unique structures, facile functionalization, and diverse application in various fields. The development of novel indole-based architectures has always been an interesting aspect for researchers in various fields of sciences, especially medicinal, pharmaceutical, supramolecular, and macrocyclic research areas. The common synthetic strategies employed for these scaffolds are systematically summarized, as well as application of some of the biologically relevant indole macrocyclic systems are highlighted. In this review, we are mainly focusing on the synthesis of different kinds of macrocycle

synthesis bearing indole motif involving intramolecular C–C and C–H bond cyclization reactions catalyzed by different metals. These frameworks signify a fascinating class of molecules that has grown immense interest, mainly in drug discovery and pharmaceutics in recent years. It is also anticipated that novel macrocyclization approaches, as well as well-known protocols, such as RCM, click chemistry (CuAAc), and biosynthesis, will expand and give a direction to the applicability of macrocyclic systems as therapeutics and to related applications. Still, there are some challenges and barriers to synthetic chemists that persist in finding and amplifying cell permeable and bioavailable macrocyclic frameworks. We hope that this review will provide insight to medicinal chemists, specifically those who are involved in total synthesis, as well as those fascinated by macromolecule research and drug discovery. Finally, we anticipate that this review will stimulate much interest in developing new strategies for indole-based macrocyclic scaffolds by synthetic chemists from diverse areas from both industry and academic points of view.

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