Review

Insights on the Synthesis of N-Heterocycles Containing Macrocycles and Their Complexion and Biological Properties

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Abstract: Macrocyclic chemistry has been extensively developed over the past several decades. In fact, the architecture of new macrocyclic models has undergone exponential growth to offer molecules with specific properties. In this context, an attempt is made in this study to provide an overview of some synthetic methods allowing the elaboration of N-heterocycles containing macrocycles (imidazole, triazole, tetrazole, and pyrazole), as well as their applications in the complexation of metal cations or as pharmacological agents.

Keywords: azole; biological activity; coordination properties; macrocycle

1. Introduction

The design and synthesis of new macrocyclic architectures as large receptor compounds have received considerable attention in recent years owing to their encapsulating properties toward several guests [1]. This makes them highly important in multiple potential applications in molecular recognition, transport, biological models, or selective catalysis [1–3]. The importance of macrocyclic chemistry is also associated with a large number of natural complex macrocycles, including chlorophyll, haemoglobin, and vitamin B12, in which the receptors are porphyrin rings, and guests are magnesium, iron, or cobalt ions, respectively. In addition, nonactin and valinomycin are another class of natural oxygen macrocycles known as natural antibiotics that are obtained from Streptomyces species [4,5]. In 1967, Pedersen et al. [6] described the crown ethers as the first macrocycles exhibiting selective complexation properties toward the alkali and alkaline earth metal cations. This pioneer finding was followed by the elaboration of cryptands and spherands of Lehn and Cram, respectively [7,8] who were awarded the Nobel Prize in 1987 [9]. Thereafter, the design and synthesis variability of such macrocyclic systems exponentially increased by varying the cavity size and nature, and the number of the donor atoms as well as the attached lateral arms through changing the ratio and substituents of starting materials [10]. Such structural and electronic modifications have been extended to the introduction of N-heterocycle rings such pyrazole, imidazole, or pyrazine into the motif cycle to increase the number of sp2-hybridised N-donor atoms [11] and, consequently, to improve the ability of the corresponding macrocycles to complex both hard and soft cations such as alkali and transition metal cations of different oxidation states [12]. In this context, several studies in the literature have provided reviews that summarise the synthesis of some N-heterocyclic macrocycles. In 2008, McGinley and Fleming [13] reviewed some studies on the macrocycles containing tetrazole functional groups. Recently, Yang et al. highlighted recent advances in the synthesis and structure of N-heterocyclic carbazenes based on macrocycles and their applications [14]. As a continuation to these pioneering studies, the focus of the present review is to give the reader deep insights into the synthesis of some kind of macrocyclic molecules reported in recent decades, as well as some pertinent details related to their complexation and biological properties.

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2. Synthesis of Imidazolic Macrocycles

In 2003, Wagner-Wysiecka et al. [15] reported the synthesis of two imidazole-based macrocyclic chromogenic derivatives 1 and 2 by coupling imidazole with the bis-diazonium salts (Figure 1) under basic medium (pH = 11–12) and high dilution conditions, respectively. These compounds were obtained in medium yields (42% and 30% for 1 and 2). This study revealed that these imidazole-based macrocycle ligands coordinate preferentially alkali and alkaline earth cations and the ion-selective membrane electrodes doped with such imidazole derivatives are sodium-selective electrodes.

![Figure 1](image1.png)

Figure 1. Final step of the synthesis of macrocycles 1 and 2 (Reprinted with permission from ref. [15]. Copyright 2003 Elsevier).

A few years later (2010), Nshimyumukiza et al. [16] described a new family of compounds based on the 5-aryl-1H-imidazole motif (Figure 2), for which the chemical synthesis involves a three-step sequence: aromatic nucleophilic substitution (SNAr), Suzuki coupling, and ring-closing metathesis (RCM) reaction [17]. This method allowed the preparation of a variety of novel macrocyclic substrates 3–7 in good overall yields. Biological evaluation of synthesised imidazole-containing macrocycles revealed that they display good binding activity toward the A3 adenosine (h) receptor, dopamine D1 (h) receptor, chloride channel (GABA-gated), and choline transporter (h) CHT1.

![Figure 2](image2.png)

Figure 2. Structures of macrocycles reported by Nshimyumukiza et al. [16] (Reprinted with permission from ref. [16]. Copyright 2010 Elsevier).

Van Den Berge et al. also used principally the same method to elaborate other 5-aryl-1H-imidazole-containing macrocycles 8–10 by varying the size cavity (Figure 3) [18]. They found that the cyclisation step yield increased with an increase in the chain length. Biological evaluation of the two optically pure enantiomers of one of these molecules enabled them to investigate the influence of chirality on biological activities.
with a suitable dibromide (Figure 5). They found that all the obtained sulphonophanes exhibit good antibacterial and antifungal activity against five bacterial strains and the human pathogenic fungus Candida albicans.

Hymel et al. [19] reported the synthesis of tripeptide ligands with decreased molecular weight 11–14 (Figure 4). This was conducted by C-terminal macrocyclisation, employing N(π),N(τ)-bis-alkylated residues as ring junctions and showing improved target selectivity for the polo-box domain of polo-like kinase 1 (Plk1 PBD) versus the PBDs of Plk2 and Plk3.

Rajakumar et al. [20] reported the synthesis of some novel imidazole-based dicationic sulphonophanes 15–22 incorporating various spacer units by capping a precyclophane with a suitable dibromide (Figure 5). They found that all the obtained sulphonophanes exhibit good antibacterial and antifungal activity against five bacterial strains Bacillus subtilis, Staphylococcus aureus, Vibrio cholera, Escherichia coli, Proteus vulgaris, and the human pathogenic fungus Candida albicans.

Mehrparvar et al. [21] reported the synthesis and structural investigation of a platform consisting of two imidazole amino acids, which are connected through two azobenzene units 23 and 24 (Figure 6). This platform can be switched by light from the elongated trans, trans-isomer 23 to the compact cis, cis isomer 24, and back.

Mageed et al. [22] described the synthesis of new cyclophanes 25–28 (Figure 7) containing two imidazole-2-thione moieties linked by two xylylene groups by the reaction of imidazolium-linked cyclophanes with sulphur in the presence of K₂CO₃ and using methanol as solvent. Structures of the new cyclophanes were confirmed and investigated by NMR spectroscopy, as well as by X-ray diffraction studies.

Recently, Thapa and Kilyanek [23] communicated the synthesis of a new macrocycle 29 consisting of a 20-membered ring containing two imidazolium salt functionalities in five steps. The last one is the condensation of a mixture containing N-benzylbis(3-imidazolyl) amine and N-benzylbis(3-bromopropyl)amine in high dilution to prevent possible oligomerisation side reactions, and the macrocycle was obtained in 60% yield. The reaction of this macrocyclic salt with silver oxide afforded bis-macrocyclic silver (I) complexes (Figure 8).

Weiss et al. [24] synthesised a new family of macrocyclic imidazolylboranes, by reacting 1-trimethylsilylimidazoles and haloboranes XB(R₁)₂ through the boron/silicon exchange using 2-bromoimidazole 30–33 (Figure 9). The resulting macrocycles had the zwitterionic
character and contain imidazolyl rings linked through their nitrogen atoms by BH\textsubscript{2}. They also employed a new synthetic strategy to prepare these macrocyclic imidazolylboranes, including the preparation and cyclisation of bis(imidazolyl)boronium chlorides.

![Structures of macrocycles 15–22](image)

Figure 5. Structures of macrocycles 15–22 (Reprinted with permission from ref. [20]. Copyright 2011 Elsevier).

Mehrparvar et al. [21] reported the synthesis and structural investigation of a platform consisting of two imidazole amino acids, which are connected through two azobenzene units 23 and 24 (Figure 6). This platform can be switched by light from the elongated trans, trans-isomer 23 to the compact cis, cis-isomer 24, and back.

![Structures of conformational macrocycles 23 and 24](image)

Figure 6. Structures of conformational macrocycles 23 and 24 (Reprinted with permission from ref. [21]. Copyright 2018 John Wiley and Sons).

Mageed et al. [22] described the synthesis of new cyclophanes 25–28 (Figure 7) containing two imidazole-2-thione moieties linked by two xylylene groups by the reaction of imidazolium-linked cyclophanes with sulphur in the presence of K\textsubscript{2}CO\textsubscript{3} and using methanol as solvent. Structures of the new cyclophanes were confirmed and investigated by NMR spectroscopy, as well as by X-ray diffraction studies.
Iwanek et al. [25] presented a very simple and efficient synthesis of tetrameric boron-imidazole macrocycles 34 and 35 involving the reaction of imidazole or 2-methylimidazole and triethylborane (Figure 10). The synthesis of these macrocycles was performed in two steps. First, an equimolar amount of triethylborane in tetrahydrofuran was added to imidazole or 2-methylimidazole, followed by refluxing for about 1 h. Next, the tetrahydrofuran was evaporated, mesitylene was added, and the mixture was refluxed at mesitylene boiling temperature for several hours.
Figure 10. Tetrameric boron–imidazole macrocycles 34 and 35 (Reprinted with permission from ref. [26]. Copyright 2012 Elsevier).

Sargent et al. [26] described the synthesis, spectroscopic properties, and computational analysis of an imidazole-based analogue of porphycene—namely, ‘imidacene’ 37. The reductive coupling of a diformyl-substituted 2,2′-biimidazole using low-valent titanium gives the intermediate macrocycle 36. This step was followed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Figure 11). This macrocycle was found to undergo rapid decomposition, even in the absence of light and air. Through high-level theoretical calculations, they explained this instability by the presence of a delocalised 18 π-electron pathway in both imidacene and porphycene that provides less aromatic stabilisation energy.

Figure 11. Synthetic route of macrocycle 37 (Reprinted with permission from ref. [26]. Copyright 2003 John Wiley and Sons).

Other new (tetrakis)imidazolium macrocyclic receptor system 38 was synthesised by Wong et al. [27]. This product was obtained using stepwise alkylation reactions of bis(imidazolium) precursor compound (Figure 12). They used the 1H NMR titration to study the binding properties of the resulting macrocycle toward halogen and benzoate anions in competitive conditions using acetonitrile–water (9:1) as solvent. Unfortunately, it was not possible for them to determine the stability constant values.

Figure 12. Synthesis of tetra-imidazolic macrocycle salt 38 (Reprinted with permission from ref. [27]. Copyright 2005 Royal Society of Chemistry).

3. Synthesis of Tetrazolic Macrocycles

Yu et al. [28] presented the synthesis of a series of novel macrocyclic structures 39–43 incorporating one tetrazole ring by reacting dibromoalkanes with a tetrazole derivative in
the presence of alkali metal bases (Figure 13). Through a systematic study, they provided evidence of the effect of the radius alkali cation on the yield of the synthesised macrocycles. They suggested that these macrocyclic tetrazoles should offer a new class of photoactivatable tetrazole reagents for the bioorthogonal tetrazole–alkene cycloaddition reaction in living systems.

Abdelraheem et al. [29] revealed the synthesis of another family of monotetrazole-containing macrocycles 44–47, in two steps through accessible starting materials (Figure 14). The first step comprises a chemoselective amidation of amino acid-derived isocyanocarboxylic acid esters with unprotected symmetrical diamines to afford diverse α-isocyanoo-ω-amines. In the second step, the α-isocyanoo-ω-amines undergo an Ugi tetrazole reaction to close the macrocycle. This strategy allowed these authors short access to 11–19-membered macrocycles in which substituents could be independently varied at three different positions.

![Synthesis of monomeric macrocycles 39–43](image)

**Figure 13.** Synthesis of monomeric macrocycles 39–43 (Reprinted with permission from ref. [28]. Copyright 2010 John Wiley and Sons).

**Figure 14.** Monomeric macrocycles 44–47.
Voitekhovich et al. [30] described the synthesis of two new 15-membered macrocycles 48, 49 with tetrazol-2,5-diyl moieties units linked by 3-oxapentane-1,5-diyl and 2,5-dimethylhexane-2,5-diyl bridges (Figure 15). Their synthesis involved condensation of 1,5-bis(tetrazol-5-yl)-3-oxapentane or 1,5-bis(1-methyltetrazol-5-yl)-3-oxapentane with 2,5-dimethylhexane-2,5-diol in 65% aqueous perchloric acid. Structures of these obtained macrocyclic compounds were confirmed by single-crystal X-ray analysis.

The macrocycle 48 reacts with copper(II) chloride or copper(II) tetrafluoroborate hexahydrate to give complexes [Cu3Cl6(80%)](H2O)2(BF4)2(H2O) [31]. According to single-crystal X-ray analysis, both complexes were found to be coordination polymers (Figure 16).

Figure 15. Elaboration of macrocycles 48 and 49 (Reprinted with permission from ref. [30]. Copyright 2012 Elsevier).

Figure 16. Copper complexes based on tetrazolic macrocycle 48 (Reprinted with permission from ref. [31]. Copyright 2017 American Chemical Society).

In 2007, Bond et al. described the syntheses of tetra-tetrazole macrocycles, containing two bis-tetrazole units 50–65 linked by a variety of alkyl chain lengths from 4–8 carbons by reacting one equivalent of 1, n-bis(tetrazol-5-yl)benzene and one equivalent of 1,2-, 1,3- or 1,4-[bis(2-(n-bromoalkyl)-tetrazol-5-yl)]benzene in dimethylformamide under nitrogen atmosphere and in the presence of potassium carbonate (Figure 17) [32]. The crystal structures of three of these derivatives were also reported. It was found that the macrocycle conformation is influenced by the length of the alkyl chain linker, the relative orientation of the tetrazole rings on the benzene ring, and by intermolecular interactions.
with an odd number of carbon atoms (Tetra-tetrazole macrocycle (n = 7) contains an unexpected ‘host–guest’ interaction through the binding of a chloroform solvent molecule. The resulting deviation of the macrocycle from planarity results from a combination of the ‘host–guest’ interaction and strong intermolecular interactions between adjacent tetrazole and phenylene rings.

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\begin{align*}
\text{Figure 17. Structures of tetra-tetrazolic macrocycles 50–65} & \quad (\text{Reprinted with permission from ref. [32]. Copyright 2007 Elsevier).} \\
\end{align*}
\]

Two years later, they revealed the syntheses of other tetra-tetrazole macrocycles 66–69, containing two 1,3-bis(tetrazole)benzene units linked by a variety of n-alkyl chain lengths with an odd number of carbon atoms (n = 3, 5, 7, or 9 carbon atoms) (Figure 18) [33]. Tetra-tetrazole macrocycle (n = 7) contains an unexpected ‘host–guest’ interaction through the binding of a chloroform solvent molecule. The resulting deviation of the macrocycle from planarity results from a combination of the ‘host–guest’ interaction and strong intermolecular interactions between adjacent tetrazole and phenylene rings.

\[
\begin{align*}
\text{Figure 18. Tetrazolic macrocycles 66–69} & \quad (\text{Reprinted with permission from ref. [33]. Copyright 2009 Elsevier).} \\
\end{align*}
\]

The same group also substituted the phenyl by the pyridine ring to develop two new series of tetra-tetrazole macrocycles containing two 2,6-bis(tetrazole)pyridine units, linked by a variety of n-alkyl chain lengths 70–73 (Figure 19) [34]. The crystal structure of one of such tetra-tetrazole macrocycles was also structurally characterised and revealed a bowl-shaped conformation.

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\begin{align*}
\text{Figure 19. Structures of tetra-tetrazolic macrocycles 70–73} & \quad (\text{Reprinted with permission from ref. [34]. Copyright 2011 Elsevier).} \\
\end{align*}
\]
4. Synthesis of 1,2,4 Triazolic Macrocycles

In 2007, Elwahy et al. [36] conveyed an elegant route for the synthesis of a series of novel macrocyclic Schiff bases containing two triazole rings 74−80 in good yields (Figure 20). They were obtained by heating bis-amines with the corresponding bis-aldehydes in refluxing acetic acid under high dilution conditions. Attempts to synthesise macrocyclic Schiff bases containing pyridine and two triazole rings were also described.

![Figure 19. Tetrazolic macrocycle bearing pyridine moiety 70–73 (Reprinted with permission from ref. [34]. Copyright 2011 Elsevier).](image)

Teng et al. [35] studied theoretically complexes resulting from a tetra-tetrazolic macrocycle with some organic contaminants using density functional theory (DFT). They found that this tetra-tetrazole shows good binding affinity towards these molecules, and the stabilities of the formed complexes are affected by the number and effectiveness of the hydrogen bonds.

Foroughifar et al. [38] prepared two new aza-crown macrocycles 81 and 82, bearing two 1,2,4 triazolic rings by reacting of 1,2-, 1,3-, and 1,4-bis(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)alkanes with bisaldehydes in acetic acid under reflux. They were obtained in...
70-76% yield. The reaction of these aza-crown macrocycles with iodomethane and benzyl chloride gave exclusively the target lariat macrocycles 83–86, also in good yields (Figure 21).

They also reported a simple and efficient method for the preparation of azathia crown macrocycles 87–92 containing two triazole subunits [39]. First, a series of new 1,2/1,3-bis[o-(N-methylidenamino-5-aryl-3-thiol-4H-1,2,4-triazole-4-yl)phenoxy]alkane derivatives were prepared by condensation of 4-amino-5-(aryloxy)-4H-1,2,4-triazole-3-thiols or 2-amino-5-mercaptotriazole with bis-aldehydes. Then, the reaction of the obtained compounds with dibromoalkanes allowed obtaining the desired macrocycles (Figure 22). This method does not require high dilution techniques and provides the expected azathia macrocycles in good yields, ranging from 55% to 68%.

Figure 21. Alkylation of triazolic macrocycles 81 and 82 (Reprinted with permission from ref. [38]. Copyright 2009 © Georg Thieme Verlag KG).

Avaji et al. [40] conveyed the synthesis of a series of tetra-triazolic macrocycles by condensing an equimolar ethanol mixture of 2,6-diformyl-4-methylphenol and bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkanes, and in the presence of a few drops of concentrated HCl. The macrocycles were obtained in good yields (60–65%). Due to the fact that they were found insoluble in common organic solvents, the corresponding La(III) and Th(IV) complexes were synthesised by template condensation of 2,6-diformyl-4-methylphenol,
bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkanes and La(NO₃)₃ 6H₂O/Th(NO₃)₄ 5H₂O in 2:2:1 molar ratio in ethanol. The antimicrobial activities of macrocycles and their metal complexes were evaluated. Some compounds showed promising results.

Patil et al. [41] used procedures described by Avaji et al. [40] to elaborate four 1,2,4 tetra-triazolic macrocycles through a [2+2] cyclisation of Ortho-phthalaldehyde and bis-(4-amino-5-mercapto-1,2,4-triazole-3-yl)alkanes, as well as their corresponding Co²⁺, Ni²⁺ and Cu²⁺ complexes. The biological results demonstrated that all the Schiff bases possess antimicrobial activity, and their metal(II) complexes showed more promising activities than the Schiff bases. The interaction of copper(II) complexes with DNA was investigated by utilising gel electrophoresis. It was found that all copper(II) complexes cleave DNA efficiently.

Kumar et al. [42] presented the synthesis of a new 1,2,4 triazolic macrocycle entitled S,S′-[benzene-1,3-diylbis(4H-1,2,4-triazole-5,3-diyl)]bis[[5-benzene-1,3-diyl-4H-1,2,4-triazol-3-yl)sulfanyl]ethanethioate) 93 (Figure 23) from isophthalic dihydrazide through a multistep reaction sequence. The desired compound and all intermediates were obtained in good yields (58–68%). Their antibacterial potency was evaluated against four different bacterial strains and was found comparable with that of the standard drug ciprofloxacin. The synthesised compounds were further studied for their possible in vitro antioxidant effects by DPPH scavenging, total antioxidant capacity, total reductive capacity, and H₂O₂ scavenging activity. It also possessed a good antioxidant activity when compared with the standards.

![Structure of tetra-triazolic macrocycle 93](image)

**Figure 23.** Structure of tetra-triazolic macrocycle 93 (Reprinted with permission from ref. [42]. Copyright 2012 John Wiley and Sons).

Chu Zheng et al. [43] sought to synthesise a new macrocyclic ligand with four 1,2,4 triazole subunits by reacting bis(5-amino-1H-1,2,4-triazole) and dichloromethane without metal ions but did not succeed. Nevertheless, they were able to elaborate on the corresponding metal complexes (Fe²⁺, Co²⁺, and Ni²⁺) in methanol as solvent. The fluorescence quenching spectra and UV–Vis spectra were used to study the interaction of complexes with bovine serum albumin (BSA).

5. Synthesis of 1,2,3 Triazolic Macrocycles

Kelly et al. [44] reported the synthesis of some mono 1,2,3 triazolic macrocycles through a regioselective intramolecular Huisgen cycloaddition, carried out on various azido alkyn substrates. Using catalyst control, a common intermediate was converted to two structurally unique macrocycles with either a 1,5- or a 1,4-triazole resulting in an n (94) or n + 1 (95) ring size by using Ru and Cu as a catalyst, respectively (Figure 24).
The structure of these macrocycles was confirmed by NMR spectroscopy and high-resolution mass spectrometry (HRMS). They found that the obtained macrocycles could act as inhibitors of norovirus 3CL protease.

Bogdan et al. [45] generated a series of triazolic macrocycles 96–101 (Figure 25), with drug-like functionality and properties by simple and efficient copper-catalysed azide–acetylene cycloaddition reaction. These macrocycles were obtained in a 5 min reaction without resorting to the high-dilution conditions typical of macrocyclisation reactions, as well as in up to 90% yield.

The same team reported a new macrocyclisation strategy to synthesise 5-iodo-1,2,3-triazole-containing macrocycles 102–104 (Figure 26) [46]. The macrocycles were generated using a simple and efficient copper-catalysed cycloaddition in flow and under environmentally friendly conditions. This methodology also permits the facile, regioselective synthesis of 1,4,5 trisubstituted-1,2,3-triazole-containing macrocycles using palladium-catalysed cross-coupling reactions.

**Figure 24.** Effect of the catalyst nature on cyclisation (Reprinted with permission from ref. [44]. Copyright 2009 American Chemical Society).

**Figure 25.** Structures of monotriazolic macrocycles 96–101 (Reprinted with permission from ref. [45]. Copyright 2010 John Wiley and Sons).

**Figure 26.** Structures of tetra-triazolic macrocycles 102–104 (Reprinted with permission from ref. [46]. Copyright 2011 American Chemical Society).
Sessler et al. [47] also utilised the copper(I)-catalysed cycloaddition to synthesise cell-permeable 1,2,3 triazole-based macrocycles 105–116 with peptidyl backbone (Figure 27). The structure of these macrocycles was confirmed by NMR spectroscopy and high-resolution mass spectrometry (HRMS). They found that the obtained macrocycles could act as inhibitors of norovirus 3CL protease.

In their paper published in 2009, Sandra Binauld et al. [49] reported a subsequent CuAAC intramolecular cyclisation, performed under pseudo-high-dilution conditions, providing a series of novel macrocycles 120–123 with different ring sizes (Figure 29). This pathway was shown to be a facile, high-yielding process and can be accurately controlled.

Hernández-Vázquez et al. [48] presented a multicomponent and rapid protocol for the synthesis of structurally diverse bis(aryl ether) macrocycles bearing one triazolic ring. This method allowed the synthesis of a family of 27 analogues with 20–117, 21–118, and 22–119 membered rings (Figure 28). Some of the compounds displayed interesting cytotoxicity against cancer (PC-3) and breast (MCF-7) cell lines, especially those bearing an aliphatic or a trifluoromethyl substituent on the N-phenyl moiety (R2) (IC50 < 13 μM).

In their paper published in 2009, Sandra Binauld et al. [49] reported a subsequent CuAAC intramolecular cyclisation, performed under pseudo-high-dilution conditions, providing a series of novel macrocycles 120–123 with different ring sizes (Figure 29). This pathway was shown to be a facile, high-yielding process and can be accurately controlled.
Caricato et al. [50] described the synthesis of bi-1,2,3 triazolic macrocycle 124 (Figure 30) through CuAAC ‘click’ reactions in the cyclisation step using toluene as solvent. Their methodology consists of fixing 1,2,3-triazole moieties within the macrocyclic backbone, which are able to directionally coordinate anions through CH⋯X–hydrogen bonds.

Anandhan et al. [51] reported the synthesis of two triazole-based macrocyclic amides through click chemistry. They showed good anti-inflammatory activity even at low concentrations (50 µg/mL) when compared with that of the reference drug prednisolone.

Li et al. [52] described the synthesis of two novel ferrocene-containing macrocyclic triazoles 125 and 126 using a ‘click’ reaction (Figure 31). The anions binding abilities of these macrocycles were evaluated, and results revealed that these receptors have exclusive electrochemical sensing of H$_2$PO$_4^-$.

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**Figure 29.** Structures of bitriazolic macrocycles 120–123 with different size cavities (Reprinted with permission from ref. [49]. Copyright 2009 John Wiley and Sons).

**Figure 30.** Structures of bitriazolic macrocycles 124 (Reprinted with permission from ref. [50]. Copyright 2012 Elsevier).
Hradilová et al. [53] developed a new approach for the preparation of macrocycles containing two, three, and four 1,2,3-triazole motifs 127–129 from simple compounds such as 2-azidobenzoic acid, propargyl bromide, and propargyl anthranilate (Figure 32). The macrocyclic precursor was constructed by a series of steps which include cycloaddition of an azide with an alkyne, alkylation of a carboxylic acid with propargyl bromide, and formation of an azide from an amino group.

White et al. [54] conveyed the synthesis of two tetra-1,2,3 triazole macrocycles 130 and 131 in good yields using the copper(I)-catalysed cycloaddition of bis-triazole azides and bis-alkynes (Figure 33). One of them was alkylated to give a cyclic tetra-triazolium receptor, which complexed anions strongly in competitive DMSO–water mixtures. In 1:1 DMSO–water, the tetracationic receptor exhibited a preference for the larger halides, bromide, and iodide.
Khan et al. [55] presented the elaboration of a novel fluorescent bis-calix[4]arene macrocycle 132 bearing four 1,2,3 triazole rings and incorporating metal-binding pockets (Figure 34). The structures of this macrocycle and its precursors were checked via NMR and MS, as well as X-ray crystallography. Macrocycle 132 displayed selective fluorescence quenching after interacting with Cu$^{2+}$ in the presence competing metal cations including Mg$^{2+}$, Ca$^{2+}$, Ba$^{2+}$, Ag$^{+}$, Zn$^{2+}$, Ti$^{4+}$, Cd$^{2+}$, Hg$^{2+}$, Pb$^{2+}$, In$^{3+}$, La$^{3+}$, Cr$^{3+}$, Ni$^{2+}$, Sb$^{3+}$, V$^{5+}$, Fe$^{3+}$, Co$^{2+}$, Sn$^{2+}$, Sn$^{2+}$, and Tl$^{+}$. The Cu$^{2+}$ limit of detection was found to be 40 Nm, much lower than its threshold level (~20 µM) in drinking water permitted by the US Environmental Protection Agency (EPA). Furthermore, drinking water samples from Karachi University (Pakistan), spiked with Cu$^{2+}$, were analysed with the sensing system, and the results showed an excellent agreement with the fluorescence quenching phenomenon of the macrocycle examined in deionised water. Importantly, it could be used to detect Cu$^{2+}$ in living cells.

Figure 33. Triazolic macrocycles 130 and 131 with good anion-complexing properties (Reprinted with permission from ref. [54]. Copyright 2012 Royal Society of Chemistry).

Figure 34. Structure of macrocycle 132 as selective sensor towards Cu$^{2+}$ (Reprinted with permission from ref. [55]. Copyright 2016 Elsevier).

6. Synthesis of Pyrazolic Macrocycles

Belda et al. [56] reported the synthesis of a novel cyclophane 133 consisting of a 1H-pyrazole moiety linked through methylene groups to a 1,5,9,13-tetraazadecane chain (Figure 35). According to Belda et al., this is one of the first reported syntheses of a [1+1] condensation 1H-pyrazole azamacroyclic ligand. This macrocycle was obtained by a macrocyclisation reaction of the tosylated polyamine with either 1H-3,5-bis(chloromethyl)pyrazole in CH$_3$CN using K$_2$CO$_3$ as a base. The crystal structures of the corresponding copper II com-
plexes show that Cu$^{2+}$ coordination leads to the formation of 2:2 Cu$^{2+}$:L dinuclear dimeric complexes in which the 1H-pyrazole units lose a proton behaving as bis(monodentate) bridging ligands.

![Diagram](image1)

**Figure 35.** The structure of 1H-pyrazole cyclophane 133 (Reprinted with permission from ref. [56]. Copyright 2013 American Chemical Society).

Ashok et al. [57] conveyed an efficient approach to the synthesis of fused pyrazole-annulated macrocycles. This was performed by Vilsmeier–Haack reaction of substituted o-hydroxyacetophenones with phenylhydrazine, followed by reduction of the resulting pyrazolyl aldehydes yielded the corresponding alcohols. These precursors upon alkylation with dibromoalkanes gave the target library. the final macrocycles were screened for their antimicrobial activity. This investigation revealed that most of the tested compounds displayed some inhibitory effects on the growth of the tested Gram-positive and Gram-negative bacterial strains, while a low inhibitory activity against the tested fungal strains was observed.

Javier Pitarch et al. [58] described the synthesis of a new macrocycle 134 obtained by dipodal [2+2] condensation of the polyamine 3-(naphthalen-2-ylmethyl)pentane-1,5-diamine with 1H-pyrazole-3,5-dicarbaldehyde, followed by a reduction using NaBH$_4$ (Figure 36). This macrocycle presented five measurable protonation steps in the 2.0–11.0 pH range. Through fluorescence emission studies, they found that the Zn$^{2+}$ coordination promotes a boat-like shape conformation that approaches both fluorophores and facilitates the formation of an excimer which reaches its highest emission for a 1:1 (Zn$^{2+}$:159) molar ratio.

![Diagram](image2)

**Figure 36.** Synthetic pathway of bipyrazolic macrocycle 134 (Reprinted with permission from ref. [58]. Copyright 2010 Royal Society of Chemistry).
Reviriego et al. [59] used an improved synthetic method to synthesise 26-membered diaza tetraester crowns (135, 136) and 39-membered triaza hexaester crowns (137, 138) containing two and three pyrazolic moieties, respectively (Figure 37). This was performed by reacting the cyclic stannoxanes obtained from RN-diethanolamine (R = Me, Bu) and dibutyltin oxide 1H-pyrazole-3,5-dicarbonyl dichloride. The new structures were confirmed by their analytical and spectroscopic data. Both diaza tetraester crowns 135 and 136, containing two 1H-pyrazole units, self-assembled into dimeric species through the formation of four hydrogen bonds involving the two NH pyrazole groups and the two tertiary amine groups of both crowns, as proved by X-ray crystallography and NMR analysis.

![Figure 37. Macrocycles 135-138 containing two and three pyrazolic moieties (Reprinted with permission from ref. [59]. Copyright 2011 American Chemical Society).](image)

Ali et al. [60] reported a simple synthetic method for the preparation of four new phosphorus macrocycles 139–142 (Figure 38) in which the pyrazole rings are appended to a phosphorus atom. The methodology was based on the cyclocondensation reaction of bis(4-formylpyrazolyl) phosphine oxides with nitrogen nucleophiles that contain active terminal amino groups. A preliminary antimicrobial evaluation of the tested compounds showed that they had low-to-moderate activities, compared with the reference drugs.

![Figure 38. Phosphorus bipyrazolic macrocycles 139–142 (Reprinted with permission from ref. [60]. Copyright 2013 TÜBİTAK).](image)

Sanchez-Moreno et al. [61] elaborated pyrazole-containing macrobicyclic polyamine 143 and three pyrazole-containing monocyclic polyamines 144–146 (Figure 39). Bicyclic macrocyclic...
They found that the ability of this macrocycle to extra selectively K
pyrazolyl) alkane (143) via the condensation of 1\,n bis(3-pyridyl-2-ylethylamino)-5'-methyl-l'-pyrazole-3,5-dicarbaldehyde with tris(2-aminoethyl)amine and Bis(2-aminoethyl)amine, respectively, followed by further reaction steps. The in vitro and in vivo anti-
Trypanosoma cruzi activity was studied. The compounds were more active against the parasite and less toxic against Vero cells than the reference drug benznidazole; in addition, 144 and 145 were especially effective, whereas cryptand 144 was the most active, particularly in the chronic phase.

| Structure | Chemical Formula |
|-----------|------------------|
| 143       | (65%)            |
| 144       | R1 = Me; R2 = H  | (70%)            |
| 145       | R1 = Bn; R2 = H  | (83%)            |
| 146       | R1 = H; R2 = (CH2)2Me | (53%)            |

Figure 39. Structure of macrocycles 143–146 (Reprinted with permission from ref. [61]. Copyright 2012 American Chemical Society).

These compounds were also assayed on Leishmania infantum and Leishmania braziliensis species [62]. There were found more active and less toxic than glucantime. Both infection rates and ultrastructural alterations confirmed that 143 and 145 were highly leishmanicidal and induced extensive parasite cell damage. Modifications in the excretion products of parasites treated with 143–145 were also consistent with substantial cytoplasm alterations. Compound 145 was highlighted as a potent inhibitor of Fe-SOD in both species, whereas its effect on human CuZn-SOD was poor.

In 1997, Bol et al. [63] established the synthesis of two new tetrapyrazolic macrocycles with two pyridyl lateral arms by condensation of 1\,n bis(3'-chloromethyl-5'-methyl-l'-pyrazolyl) alkane (n = 2 or 3) with the 1\,n bis(3-pyridyl-5'-methyl-l'-pyrazolyl) alkane (n = 2 or 3) in tetrahydrofuran and acetonitrile, respectively. These two macrocycles formed stable copper I, copper II and Zinc II complexes.

Malek et al. [64] reported the synthesis of another family of new symmetrical tetrapyrazolic macrocycles 147–149, also bearing two lateral arms. They were obtained through a [2+2] cyclocondensation of a primary amine with the 1\,n bis(3'-chloromethyl-5'-methyl-l'-pyrazolyl) alkane (n = 1, 3) in acetonitrile using the high dilution condition (Figure 40). In the case of n = 3, they also observed the formation of the macrocycle resulting from [1+1] cyclisation due to the flexibility of the chlorinated derivative.

The macrocycle with isopropyl lateral arms can also be obtained by a 2 + 2 reaction of a tripodal ligand and dibromomethane using phase transfer catalysis (PTC) in high-dilution conditions. Nevertheless, the yield of the desired macrocycle remained practically unchangeable. These tetrapyrazolic macrocycles were found to be able to complex and transport across a solid membrane selectively the K+ cation.

Cherfi et al. [65] also conveyed the synthesis of another macrocycle with two long flexible lateral arms bearing a donor group using the same method reported by Malek et al. [64]. They found that the ability of this macrocycle to extra selectively K+ is improved with the increasing the lateral arm length.
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Figure 40. Tetrapyrazolic macrocycles 147–149 with functionalised lateral arms.

As a continuation of these studies, Harit et al. [66,67] synthesised a new generation of bi-functionalised tetrapyrazolic macrocycles 150–152 by reaction of 1,4-bis(3′-chloromethyl-5′-methyl-1′-pyrazolyl) butane with primary amines with the aim to increase the cavity size of these compounds (Figure 41). Indeed, the resulting compound was found to be complex and also transport selectively the Cs\(^+\) cation.

![Diagram of macrocycle 150-152](image)

**Figure 41.** Other tetrapyrazolic macrocycles 150–152 with two sidearms.

They also elaborated a new generation of this kind of macrocycles using the same method and changing the bis-chlorinated derivative (n = 1) by its brominated homologue to improve the cyclisation reaction yield. However, no particular change was obtained [68]. Besides their ability to complex selectively K\(^+\), they possessed some antibacterial activity (32 μg/mL) against both Gram-positive and Gram-negative bacteria. Other homologues of macrocycles reported by Bol et al. [63] were also synthesised. They also showed an affinity to complex K\(^+\) cation and some antibacterial activity [69].

Radi et al. [70,71] used the same strategy performed by Malek et al. [64] to synthesise two tetrapyrazolic macrocycles 153 and 154 with different cavity sizes and bear one lateral arm (Figure 42). This was performed by [1+1] cyclisation of a chlorinated derivative with 3 aminopropan-1-ol to obtain the macrocycle 154, and the 1,2 dibromoethane with a tetrapod ligand to obtain the macrocycle 153. These macrocycles were also found to have a complexing affinity towards both alkali and heavy metal cations.

![Diagram of macrocycles 153-154](image)

**Figure 42.** Tetrapyrazolic macrocycles 153–154 with functionalised lateral arms.

As a continuation of the studies of Tarrago [72], Harit et al. [73] elaborated a new macrocycle 155 with an aromatic lateral arm bearing a hydroxyl group (Figure 43). The synthesis was achieved via two pathways and led to two different yields. The study of the complexing properties of this macrocycle towards the alkali metal ions (Li\(^+\), Na\(^+\), K\(^+\), Cs\(^+\)) showed remarkable extraction and transport [74] selectivities for the lithium cation in competitive conditions.
The reaction conditions considerably affect the size and conformation, granting access to a new range of macrocyclic architectures. It was revealed that the synthesis of macrocyclic molecules is a promising area that continues to grow year by year, giving the opportunity to design new active agents with excellent biological and complexing properties.

Recently, Dahmani et al. [75] reported two new organotin (IV) bipyrazole-dicarboxylate macrocyclic complexes 156 and 157 (Figure 44) by condensing of one equivalent of the bipyrazole-dicarboxylic acids 1,1′-(propane-1,3-diyl)bis(5-methyl-1H-pyrazole-3-carboxylic acid) or 1,1′-(2-hydroxypropane-1,3-diyl)bis(5-methyl-1H-pyrazole-3-carboxylic acid) with two equivalents of oxide di-(n-butyl)tin. These macrocycles possess an interesting fungicidal activity against the pathogenic strain *Fusarium oxysporum f. sp. albedinis*.

![Figure 42](image-url)  
**Figure 42.** Tetrapyrazolic macrocycles 153 and 154 with one lateral arm (Reprinted with permission from ref. [71] Copyright 2006 Elsevier; Reprinted with permission from ref. [71] Copyright 2004 Elsevier).

![Figure 43](image-url)  
**Figure 43.** Tetrapyrazolic macrocycles 155 with one aromatic lateral arm.

![Figure 44](image-url)  
**Figure 44.** Organotin (IV) bipyrazole-dicarboxylate macrocyclic complexes 156 and 157.

### 7. Conclusions

In summary, the aim of this review was to give readers an overview of some methods for the synthesis of several N-heterocyclic five-membered ring structures (Imidazole, triazole, tetrazole, or pyrazole) containing macrocycles, as well as their applications in different fields such as pharmacology, biology, and complexation of alkali or transition metal cations. The reaction conditions considerably affect the size and conformation, granting access to a new range of macrocyclic architectures. It was revealed that the synthesis of macrocyclic...
molecules is a promising area that continues to grow year by year, giving the opportunity to design new active agents with excellent biological and complexing properties.

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