CHEMISTRY OF BIPYRAZOLES: SYNTHESIS AND APPLICATIONS

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Chemistry of Bipyrazoles: Synthesis and Applications

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CONTENTS

PREFACE

Pyrazole is one of the most valuable nitrogen-based heterocycles and is incorporated in the constitution of a wide range of pharmaceuticals and agrochemicals. Direct connection of two pyrazole units produces six different bipyrazole skeletons that can be classified as i) *N*-*N* bond connected 1,1`-bipyrazoles; ii) *C*-*N* bond connected 1,3`- and 1,4`-bipyrazoles and iii) *C*-*C* bond connected 3,3`-, 3,4`- and 4,4`-bipyrazoles.

This book presents the recent achievements in the synthetic platforms toward the directly connected bipyrazole systems and their applications in academic, industrial, and material science fields. The construction of the targeted bipyrazole heterocycles was carried out *via* a wide-range of synthetic routes that grasp the attention of graduate and postgraduate chemists and pharmacists and material science researchers to make more efforts in this area to reach high impact findings for their applications in our life.

Most of the reported bipyrazoles are highly bioactive heterocycles demonstrating a broad array of significant inhibitory activities against several human diseases and agricultural pesticides and herbicides. They also have considerable applications in the material science area *via* involvement in the construction of metal-organic frameworks (MOFs) with distinguished industrial applications.

This book is presented in five chapters describing the synthesis of six connected bipyrazole systems and their brilliant and vibrant applications. As a result, we expect that the provided book chapters will be of pronounced support and a valuable source for the scientific community for developing new bipyrazole-based fascinating candidates towards optimization of their pharmacological benefits in the treatment of diseases as well as building up new MOFs for daily life applications that serve the humanity and industry.

We hope that the researchers and readers will find new ideas based on the provided work. Finally, we are very thankful to the Bentham Science Publishers for giving us the chance to publish this book.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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CHAPTER 1

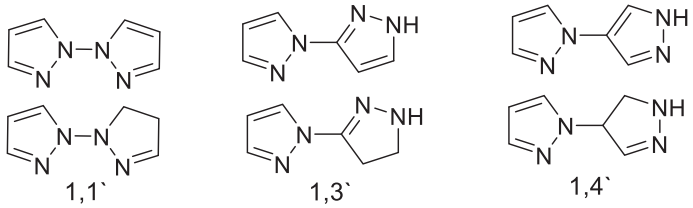
Chemistry of *N,N*- and *C,N*-Linked Bipyrazole Derivatives

Abstract: The synthetic routes to three differently connected bipyrazole systems, namely; 1,1`-, 1,3`- and 1,4`-bipyrazoles were reported. The main synthetic platforms were cyclocondensation reactions. Many of the reported bipyrazole derivatives had potent applications in material science as well as in pharmaceutical fields.

Keywords: 1,1`-bipyrazoles, 1,3`-bipyrazoles, 1,4`-bipyrazoles, Cross-coupling, Cyclocondensation, Nitrilimines.

1. INTRODUCTION

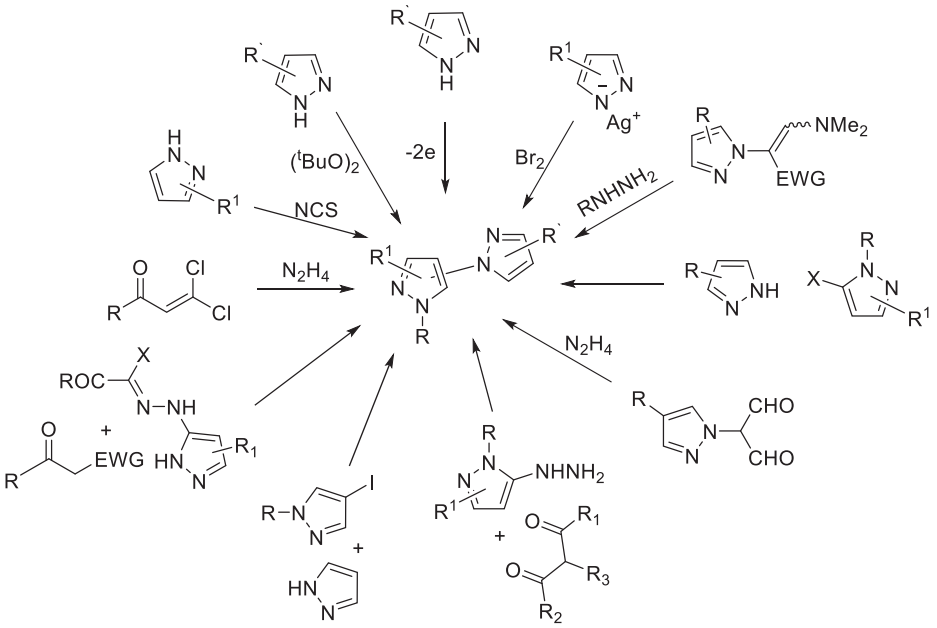
Bipyrazoles are nitrogen heterocycles that are consisted of two pyrazole moieties connected directly by a covalent sigma bond without any space linker. In this chapter, the considered connections are either *N,N*- or *C,N*-connection types. The *N,N*-linked bipyrazoles are named as 1,1`-bipyrazoles, and those *C,N*-bonded compounds are named as either 1,3`-bipyrazoles or 1,4`-bipyrazoles as shown in Scheme (**1**).



Scheme (1). The directly connected *N,N*- and *C,N*- bipyrazole systems.

The fulfilling pathways are: 1) reactions of tetracarbonyl or dihydroxydicarbonyl building units with hydrazines, 2) reaction of pyrazoles having a difunctional-side arm with hydrazines, 3) reaction of pyrazolyl-hydrazines with difunctional compounds (*e.g*. dicarbonyl, hydroxycarbonyl, ketonitrile or dinitrile substrates), and 4) metal catalyzed C-C cross coupling reactions of pyrazoles *via* C-H activation (Scheme **2**).

Kamal M. Dawood and Ashraf A. Abbas



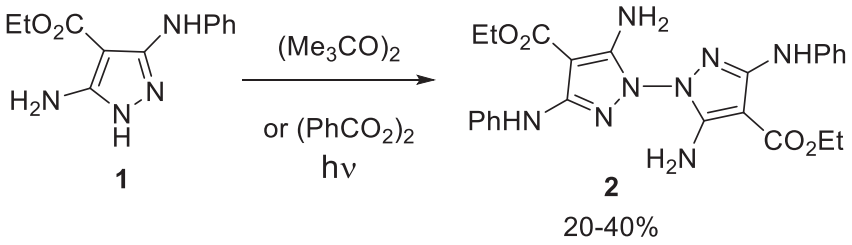
Scheme (2). The possible synthetic routes to *N,N*- and *C,N*-bipyrazoles.

Pyrazoles are one of the most abundant nitrogen heterocyclic compounds that have huge pharmaceutical and agro-chemical industrial applications [1 - 6]. Bipyrazoles are also a very interesting bioactive class of heterocycles that had pronounced biological activities. Particularly, 1,3`-bipyrazole derivatives had potent inhibitory activities against various diseases. For example, they exhibited cytotoxic [7], antimicrobial [8], anti-inflammatory [9] and antidiabetic activities [10] as well as herbicidal activities with excellent weed-controlling effects [11 - 13], potential agricultural pesticides [14, 15]. On the other hand, several 1,4`-bipyrazole derivatives were reported to have pronounced cytotoxicity activities [16] and for the treatment of Parkinson's disease [17]. The 1,4`-bipyrazole derivatives were employed as efficient ligands in the palladium-catalyzed C-N and C-O cross-coupling reactions of aryl halides with urea and with primary alcohols derivatives [18 - 22].

2. SYNTHESIS OF BIPYRAZOLE SYSTEMS

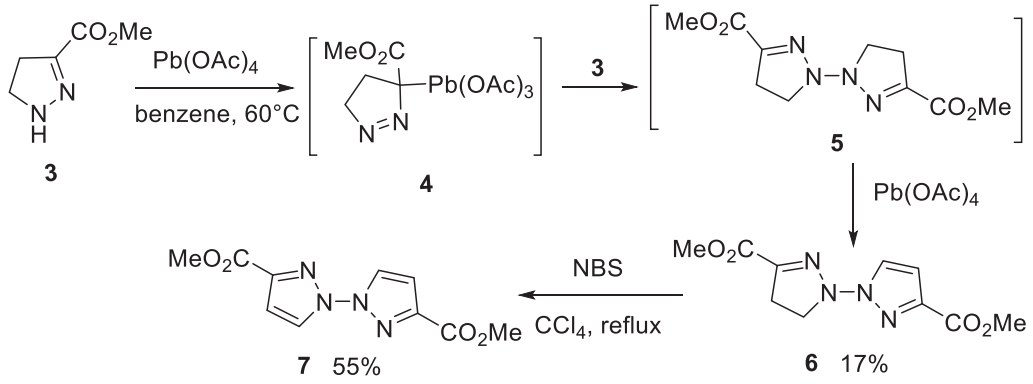
2.1. Synthesis of 1,1`-Bipyrazoles

Formation of the 1,1'-bipyrazole derivative **2** was performed by photolysis of ethyl 5-amino-3-(phenylamino)pyrazole-4-carboxylate **1** with *tert*-butyl peroxide or with dibenzoyl peroxide under mild reaction conditions. The reaction took place *via* radical dimerization of the pyrazole **1** (Scheme **3**) [23].



Scheme (3). Synthesis of 1,1`-bipyrazole **2**.

The dihydro-1,1'-bipyrazole derivative **6** was obtained from the reaction of 3-methoxycarbonyl-2-pyrazoline **3** with lead tetraacetate in benzene at 60°C. The reaction proceeded *via* the pyrazoline intermediate **4** which underwent further attack on **3** to give **6** in 17% yield. The ^{13}C NMR of compound **6** showed five peaks δ 52.3, 109.1 129.4 142.3 161.3 ppm due to OCH_3, pyrazole-carbons (C-4, C-5 and C-3) and C=O, respectively. The oxidation of **6** with *N*-bromosuccinimide (NBS) in refluxing carbon tetrachloride in the presence of a few drops of dry pyridine resulted in the formation of the symmetrical 1,1`-bipyrazole **7** in 55% yield (Scheme **4**) [24].



Scheme (4). Synthesis of 1,1`-bipyrazole **7**.

2.2. Synthesis of 1,3`-bipyrazoles

The 1,3-bipyrazole derivative derivatives **10** were synthesized, in good yields, from the reaction of the hydrazino-pyrazole derivative **8** with various symmetrical and unsymmetrical 1,3-dicarbonyl compounds **9** in the presence of 5% HCl (Scheme **5**) [7]. The ^{1}H NMR spectrum of compound **10** (R_1=R_2= Me, R_3= H) displayed five singlet peaks at δ 2.16, 2.61, 3.32, 3.67 (due to four CH_3 protons) and 6.11 due to CH-proton and its ^{13}C NMR exhibited nine peaks at δ 11.0

CHAPTER 2

Chemistry of 3,3`-Bipyrazole Derivatives

Abstract: Synthesis of 3,3`-bipyrazole systems was achieved *via* interesting synthetic methodologies such as 1,3-dipolar cycloaddition reactions, cyclocondensation reactions and metal catalysed C-H activation reactions. Construction of the structurally related 3,3`-bipyrazolines or 3-(pyrazol-3-yl)pyrazolines is described.

Keywords: 3,3`-bipyrazoles, 3,3`-bipyrazolines, Cyclocondensation, Cyclo addition, Cross-coupling, Nitrilimines.

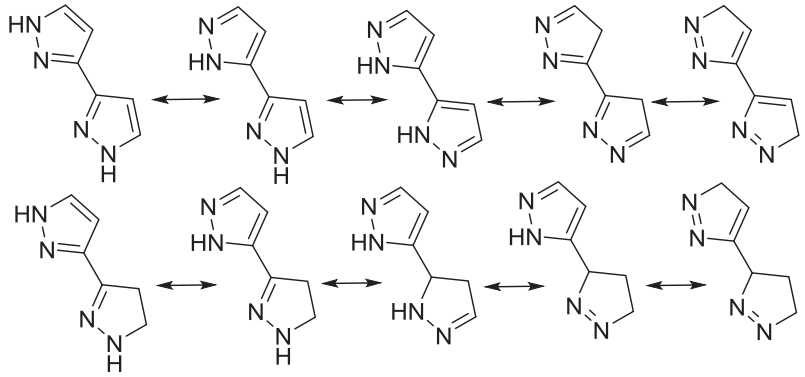
1. INTRODUCTION

3,3`-Bipyrazoles, 3,3`-bipyrazolines and 3-(pyrazol-3-yl)pyrazolines are all structurally related C-C directly connected two pyrazole units by sigma bond between 3,3`-positions without any spacer. There are several tautomeric structural formulae that can be drawn for such 3,3`-bipyrazole derivatives, as depicted in Scheme (**1**). The synthetic pathways for the 3,3`-bipyrazole structures are briefly summarized in Scheme (**2**). Such routes are: 1) reactions of tetracarbonyl or dihydroxydicarbonyl building units with hydrazines, 2) reaction of pyrazoles having a difunctional-side arm at position 3 with hydrazines, 3) reaction of 3-pyrazolylhydrazines with difunctional compounds, 4) 1,3-dipolar cycloaddition of pyrazolyl-nitrilimines with olefins or acetylenes, and 5) 1,3-dipolar cycloaddition of bis-nitrilimines with two equivalents of olefins or acetylenes.

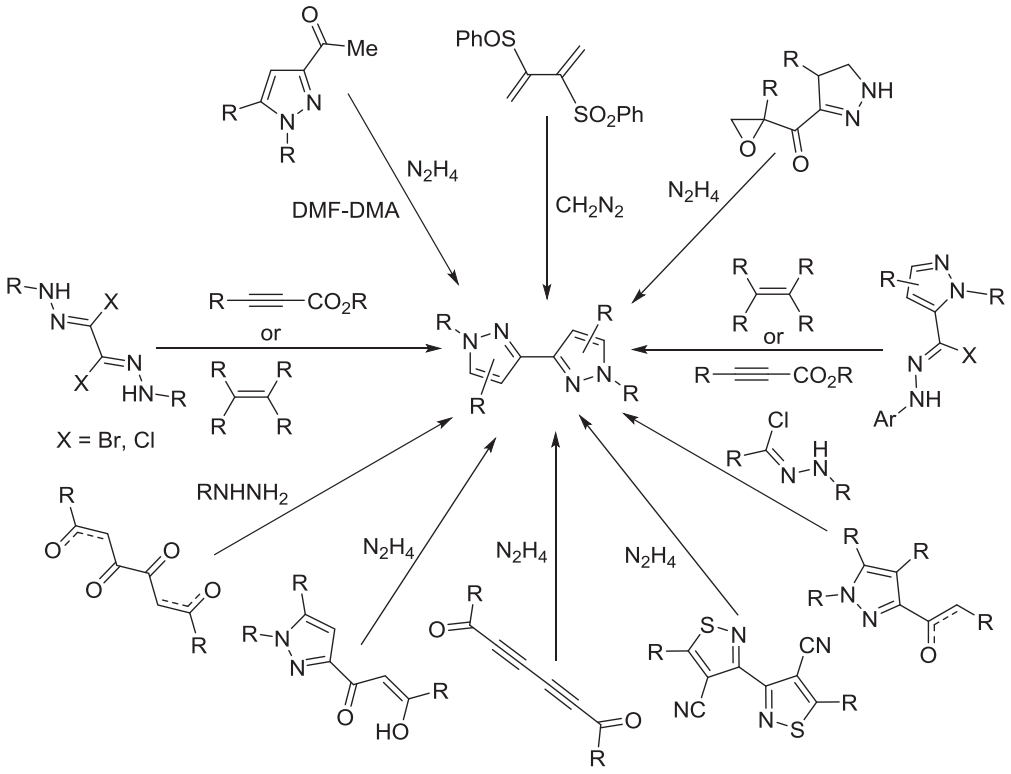
The 3,3`-bipyrazole derivatives had several academic and industrial applications. They formed complexes with copper(I/II) that were efficiently used for oxidation of catechol to o-quinine with the atmospheric dioxygen [1]. Their ruthenium(II) complexes showed good catalytic activity and transfer of hydrogen in catalyzed hydrogenation reactions [2, 3], and their palladium(II)-complexes were reported as good precatalysts for Suzuki-Miyaura C-C cross-coupling reactions in aqueous media [4]. They have involved in the synthesis of poly(3,3′-bipyrazole) derivatives with high thermal stability and electrochemical activity [5]. Nitration of 3,3-bipyrazole gave several polynitro-3,3`-bipyrazole derivatives that were found to be metal-free primary explosives with high energetic properties and excellent thermal stability [6 - 8]. .

Kamal M. Dawood and Ashraf A. Abbas

The 3,3'-bipyrazole derivatives also had solvatochromic behaviour [9] The platinum and osmium complexes of 3,3`-bipyrazoles were also useful as emitting materials for organic light-emitting diode (OLED) [10 - 12]. 3,3`-Bipyrazole derivatives were also reported to have high antitumor inhibitory activity [13].



Scheme (1). The possible tautomeric forms of 3.3`-bipyrazoles.

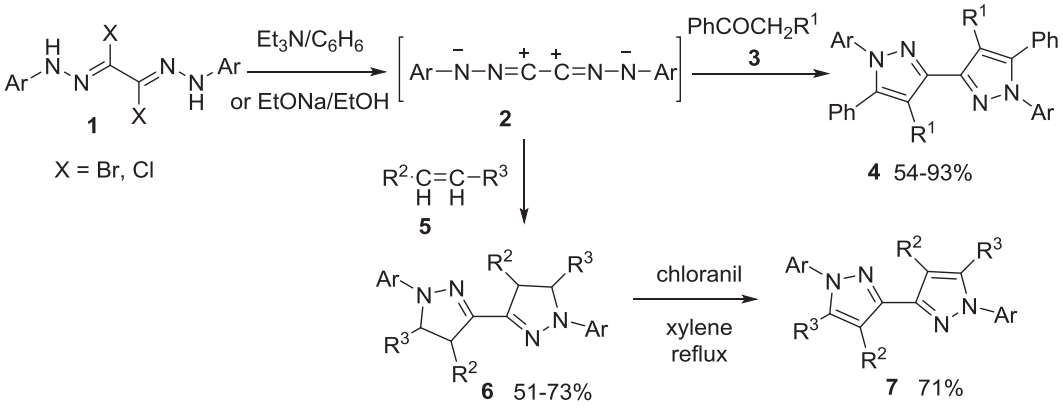


Scheme (2). The possible synthetic routes to 3,3`-bipyrazoles.

2. SYNTHESIS OF 3,3`-BIPYRAZOLE SYSTEMS

2.1. From 1,3-Dipolar Cycloaddition Reactions

When the *bis*-arylnitrilimines **2** (generated *in situ* from the treatment of *bis*-hydrazonyl halides **1** with triethylamine in dry benzene) was treated with the active methylene compounds **3**, they resulted in the formation of the 3,3'-bipyrazole derivatives **4** in high yields. Similarly, the *bis*-arylnitrilimines **2** underwent 1,3-dipolar cycloaddition reactions with the activated olefins **5** to give the 3,3'-bi(2-pyrazolines) **6.** Oxidation of compound **6** (R^2 = Ph, R^3 = COPh, Ar = Ph) with chloranil afforded the corresponding 3,3'-bipyrazole derivative **7** in 71% yield (Scheme **3**) [14].



Scheme (3). Synthesis of 3,3`-bipyrazole **4** and **7**.

Regioselective synthesis of polysubstituted 3,3'-bi-1*H*-pyrazole derivatives **10** was carried out *via* 1,3-dipolar cycloaddition reaction of the *bis*-arylnitrilimines **2** with the cinnamonitriles **8** to yield the cycloadducts 5,5'-dicyano-4,4',5,5'-tetrahydro-3,3'-bi-1*H*-pyrazoles **9** in 40-75% yields. Aromatization of compounds **9** *via* thermal elimination of hydrogen cyanide under the basic reaction conditions afforded the 3,3'-bi-1*H*-pyrazole derivatives **10** in good yields (Scheme **4**) [15].

CHAPTER 3

Chemistry of 3,4`-Bipyrazoles

Abstract: All the possible synthetic routes to the 3,4`-bipyrazole systems were thoroughly reported. Such synthetic platforms include: cyclocondensation and 1,3-dipolar cycloaddition reactions. Many of the reported 3,4`-bipyrazoles have potent applications in the field of pharmaceutical and material science.

Keywords: 1,3-dipolar cycloaddition, 3,4`-bipyrazoles, 3,4`-bipyrazolines, Cross-coupling, Cyclocondensation, Pyrazolylhydrazones.

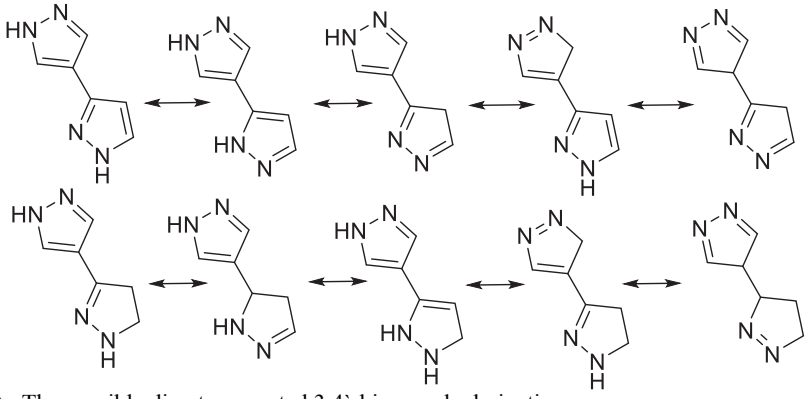
1. INTRODUCTION

Various 3,4`-bipyrazoles ring skeletons were reported in the literature. They are composed of either two aromatic pyrazole units or 4-pyrazolyl attached with pyrazoline at C-3 or 4-pyrazolinyl attached to pyrazole at C-3. As a result, there will be the aromatic 3,4`-bipyrazole skeleton or partially aromatic pyrazolylpyrazoline skeleton. The two pyrazole unites are connected directly with a sigma bond between the two units. A number of tautomeric forms can be constructed, as shown in Scheme (**1**). Synthesis of such 3,4`-bipyrazole skeletons was achieved *via* several synthetic routes as outlined in Scheme (**2**). Such synthetic routes include: 1) cyclocondensation of an activated 4-pyrazole ring having chalcones or 1,3-dicarbonyl functions with hydrazines; 2) 1,3-dipolar cycloaddition of pyrazolylhydrazones with activated olefins or acetylenes; 3) 1,3-dipolar cycloaddition of nitrilimines with bis-olefines with nitrilimines or diazo-alkanes; and 4) C-C cross coupling reactions of pyrazolylboronic acids with halopyrazoles or pyrazoles themselves *via* C-H activation using palladium catalysts.

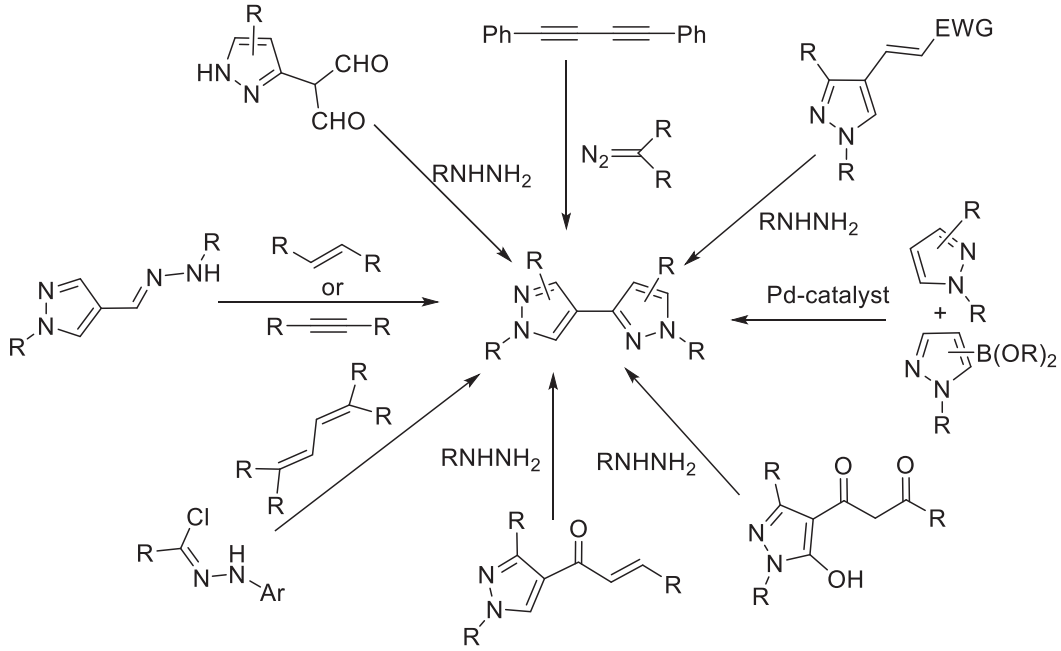
The fully aromatic 3,4`-bipyrazoles and their partially aromatic ones (pyrazolylpyrazolines) are potent inhibitory active heterocycles with significant biological potentialities. The 3,4`-bipyrazole derivatives were also considered to have anticancer [1 - 5], antimicrobial [6 - 12], anti-inflammatory [13 - 19], antioxidant [20], antitubercular [21 - 23] and antimalarial activities [24]. They

Kamal M. Dawood and Ashraf A. Abbas

were found to be effective enzyme inhibitors against carbonic anhydrase inhibitory activity [25], human Tropomyosin-related kinase A (TrkA) [26 - 30], and Janus kinase (JAK1/JAK2) [31]. 3,4`-Bipyrazole-based metal coordination complexes were reported to display remarkable pharmaceuticals applications. For example, gold(III) and iridium(II) complexes of 3,4`-bipyrazoles were useful as anticancer agents [4, 5]. In addition, the palladium(II) and platinum(II) complexes of 3,4`-bipyrazoles were found to have excellent antibacterial and antifungal activities [6, 32].



Scheme (1). The possible direct connected 3,4`-bipyrazole derivatives

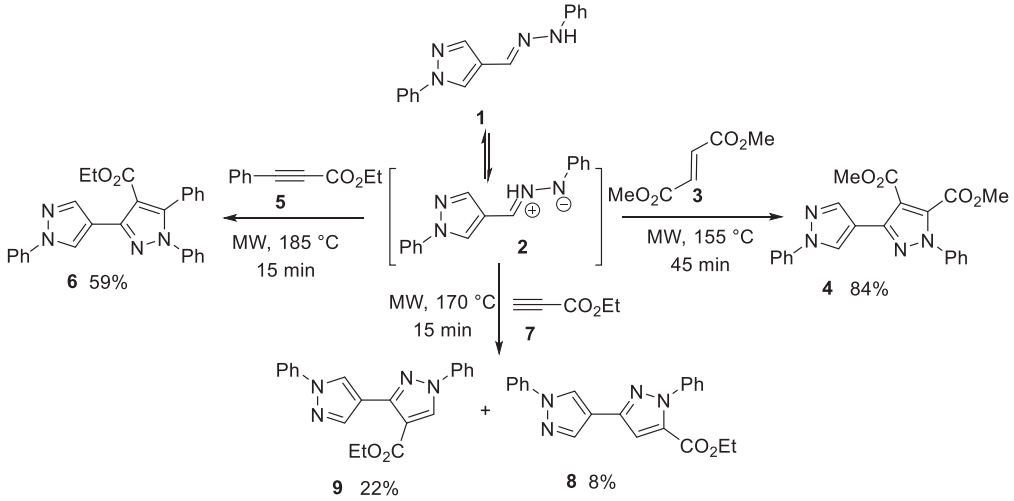


Scheme (2). The possible synthetic routes to 3,4`-bipyrazoles systems

2. SYNTHESIS OF 3,4`-BIPYRAZOLE DERIVATIVES

2.1. From 1,3-dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition of 4-pyrazolylformylhydrazone **1** with some activated dipolarophiles such as dimethyl fumarate **3** and ethyl 3-phenylpropiolate **5** under solvent-free conditions using microwave irradiation technique resulted in the construction of the corresponding 3,4`-bipyrazoles **4** and **6**, respectively. Similar reaction of the hydrazone **1** with ethyl propiolate **7** under microwave heating at 170 °C afforded a mixture of the 3,4`-bipyrazole derivatives **8** and **9** (Scheme **3**). The ^{1}H NMR analysis of structure **9** presented the following data: δ 5 1.37 (t, J = 7.1 Hz, 3H, CH_3), 4.33 (q, J = 7.1 Hz, 2H, CH_2), 7.35 (s, 1H, H-5'), 7.28-7.48 (m, 8H, ArH`s) 7.64 (d, J = 8.6 Hz, 2H, *o*-H 1-Ph), 8.17 (s, 1H, H-3), 8.40 (s, 1H, H-5). Mechanistically, the regioselective cycloaddition process proceeded *via* the addition of the dipolarophiles **3** and **5** to the dipolar intermediate **2** followed by aromatization *via* air oxidation [33, 34]. Carrying out the 1,3-dipolar cycloaddition of the pyrazolylhydrazone **1** with dimethyl fumarate (**3**) under classical thermal heating at same temperature and reaction time on an oil bath led to the formation of the bipyrazole **4** in only 17% yield. The obtained result confirmed the advantage of microwave radiation in organic synthesis compared with classical heating.



Scheme (3). Synthesis of the 3,4`-bipyrazoles **4, 6, 8** and **9**.

The 4-pyrazolylformylhydrazones **1** underwent similar 1,3-dipolar cycloaddition with β-nitrostyrenes **10** under solvent-free microwave irradiation condition (at 130°C for 10 min) to give a mixture of the 3,4'-bipyrazole derivatives **11** and **12** (Scheme **4**) [33, 35].

CHAPTER 4

Chemistry of 4,4`-Bipyrazoles

Abstract: Synthesis of a huge number of 4,4`-bipyrazole derivatives was achieved employing various synthetic platforms. This chapter outlines all possible routes (such as cyclocondensation, 1,3-dipolar cycloaddition and dimerization reactions) towards the construction of the 4,4`-bipyrazole heterocycles.

Keywords: 1,3-dipolar cycloaddition, 4,4`-bipyrazoles, Cross-coupling, Cyclocondensation, Hydrazonoyl halides.

1. INTRODUCTION

The 4,4`-bipyrazole ring skeletons can have the possible tautomeric forms that are constructed in Fig. (**1**). Synthesis of 4,4`-bipyrazoles was achieved through a number of synthetic routes as outlined in Fig. (**2**). The reported synthetic routes are as follows: 1) cyclocondensation of the activated 4-pyrazole ring having dicarbonyl functions with hydrazines; 2) cyclocondensation of tetraketones or bis-enals with hydrazines; 3) 1,3-dipolar cycloaddition of nitrilimines or diazomethane with bis-olefines, and 4) dimerization of pyrazole ring *via* electrolysis or homocoupling reactions using palladium catalysts.

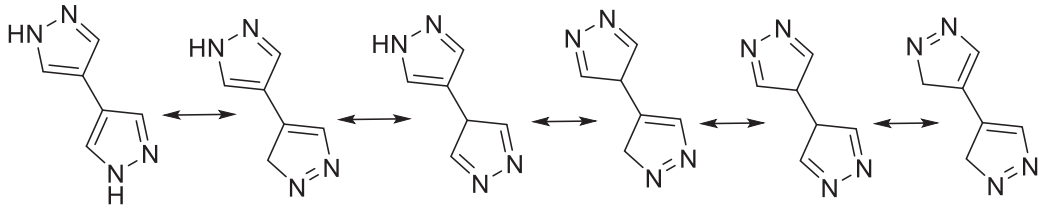


Fig. (1). The possible tautomeric forms of 4,4`-bipyrazole systems.

Kamal M. Dawood and Ashraf A. Abbas

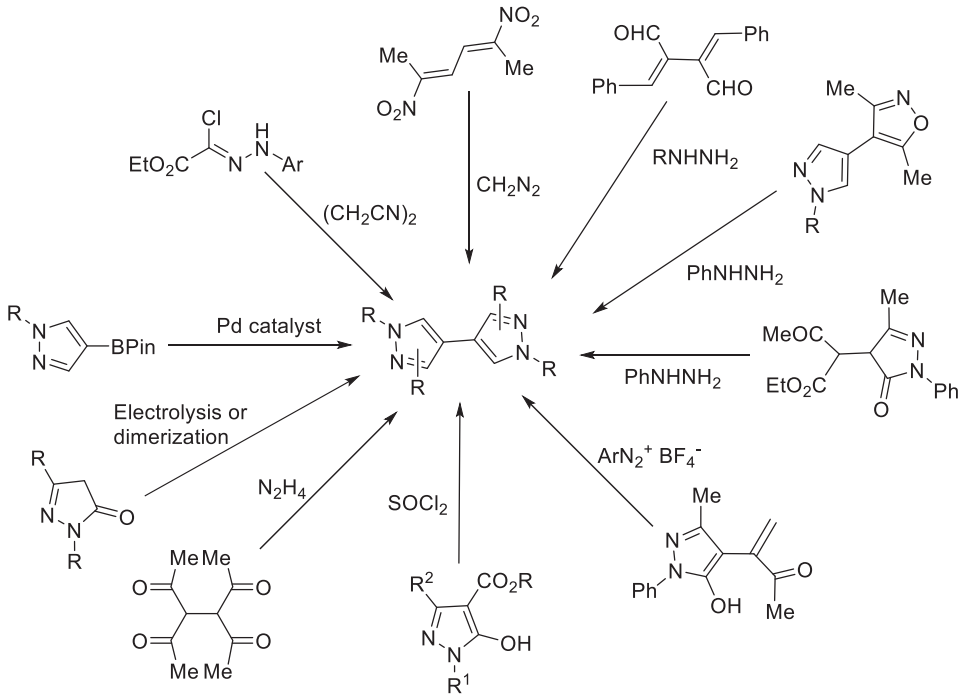


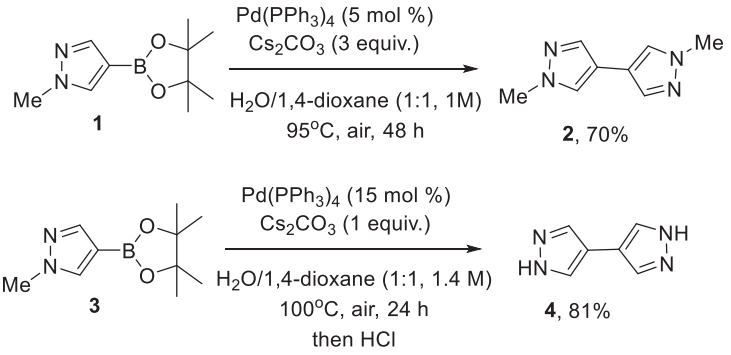
Fig. (2). The possible synthetic routes to 4,4`-bipyrazole systems.

4,4`-Bipyrazole derivatives were found to possess high biological potency and industrial applications. Some 4,4`-bipyrazole derivatives had a selective Janus kinase-1 (JAK1) inhibitory activity [1, 2]. Some 5,5'-dihydroxy-4,4'-bipyrazole derivatives were found to be useful for treatment of cerebral ischemia, heart diseases, gastrointestinal diseases, cancer, aging and inflammation, where they are effective in capturing the active oxygen and free radicals that are responsible for adult diseases [3 - 5]. Palladium(II) and platinum(II) complexes of 4,4′-bipyrazole were reported as potential anticancer agents [6], and the 4,4'-bipyrazol--Gadolonium(III) complexes were effective Paramagnetic Contrast Agent for clinical Magnetic Resonance Imaging (MRI) [7]. The nitrated 4,4`-bipyrazoles were classified as energetic and explosive materials [8, 9]. 4,4'-Bipyrazole systems were incorporated in the construction of several metal-organic frameworks (MOF). The MOF had promising diverse applications in drug delivery, gas separations, sensing, electrical conductivity, energy storage. and participated in forming porous coordination polymers with potential uses as solid sorbents, ion exchangers and heterogeneous catalysts [10 - 23].

2. SYNTHESIS OF 4,4`-BIPYRAZOLE DERIVATIVES

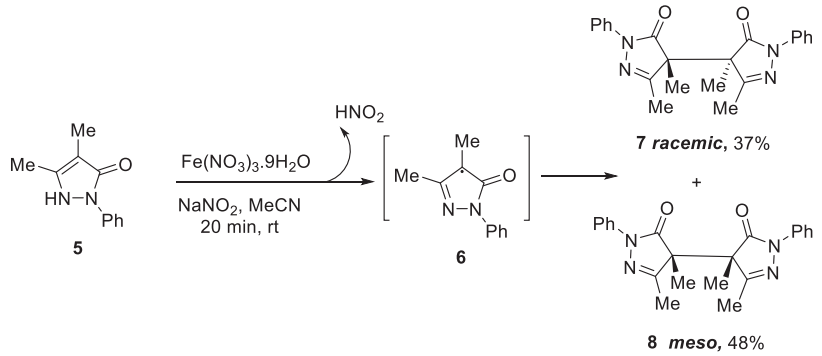
2.1. From Dimerization of Pyrazoles

Homocoupling of the pyrazolylboronic esters **1** and **3** catalyzed by $Pd(PPh_3)_4$ (5 mol%), in water solvent using Cs_2CO_3 as a base in the open air, led to the production of the symmetric 4,4'-bipyrazoles **2** and **4** in good yields, respectively (Scheme **1**) [11].



Scheme (1). Synthesis of the 3,4'-bipyrazole derivatives **2** and **4**.

Treatment of the pyrazolin-5-one **5** with $Fe(ClO_4)_3$ at ambient temperature led to its oxidative dimerization and formation of a diastereomeric mixture of 4,4'-bipyrazole-3,3'-diones **7** (*racemic,* 32% yield) and **8** (*meso,* 44% yield). The ^{1}H NMR spectral data of the *racemic* product **7** in $CDCl_3$ were as following: δ 1.60 (s, 6H, 2Me), 2.19 (s, 6H, 2Me), 7.18 (t, *J* = 7.3 Hz, 2H, ArH`s), 7.45–7.31 (m, 4H, ArH`s), 7.85 (d, *J* = 7.9 Hz, 4H, ArH`s); however the $^1$H NMR spectrum of the *meso*-compound **8** showed the following data: δ 1.73 (s, 6H, 2Me), 1.93 (s, 6H, 2Me), 7.22 (t, *J* = 7.3 Hz, 2H, ArH`s), 7.49–7.34 (m, 4H, ArH`s), 7.89 (d, *J* = 8.2 Hz, 4H, ArH`s). The reaction was supposed to took place *via* the pyrazolyl radical intermediate **6** as shown in Scheme (**2**) [24].



Scheme (2). Synthesis of 4,4`-bipyrazoles diastereomers **7** and **8**.

CHAPTER 5

Applications of Bipyrazole Derivatives

Abstract: Numerous bipyrazole-based metal-organic frameworks (MOF) were synthesized *via* mixing a number of bipyrazole ligands with several transition-metal cations, and the obtained MOF represented interesting applications in the field of material science and pharmaceuticals due to their high degree of crystallinity and internal porosity. There are photo-luminescence, sensing, gas separations, electrical conductivity, and energy storage, among those interesting applications.

Keywords: Bipyrazoles, Energetic organic materials, Gas separation, MOF, Nitropyrazoles, OLED.

1. INTRODUCTION

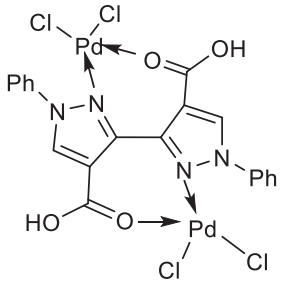
Recently, bipyrazole-based *metal coordination compounds* displayed interesting applications in pharmaceuticals and in material science. For example, gold(III) and ruthenium(II) complexes of bipyrazoles were proved to be anticancer agents [1, 2], and copper(I) complexes had excellent antibacterial activity [3], whereas gold(III), platinum(II), osmium(II) and copper(I) complexes were involved in the fabrication of luminescence Organic Light-Emitting Diodes (OLED) and laser materials [4 - 7]. Bipyrazole ligands coordinate up to four different metal centers to give three-dimensional structures known as metal–organic frameworks (MOFs). Such MOFs had promising wide applications in drug delivery, sensing, gas separations, electrical conductivity, and energy storage due to their high degree of crystallinity and internal porosity [8, 9]. Bipyrazoles (especially Bippyphos) played an important role as ligands for palladium-catalyzed cross-coupling reactions of aryl halides [10 - 13].

2. APPLICATIONS OF BIPYRAZOLE DERIVATIVES

2.1. Bipyrazoles as Ligands

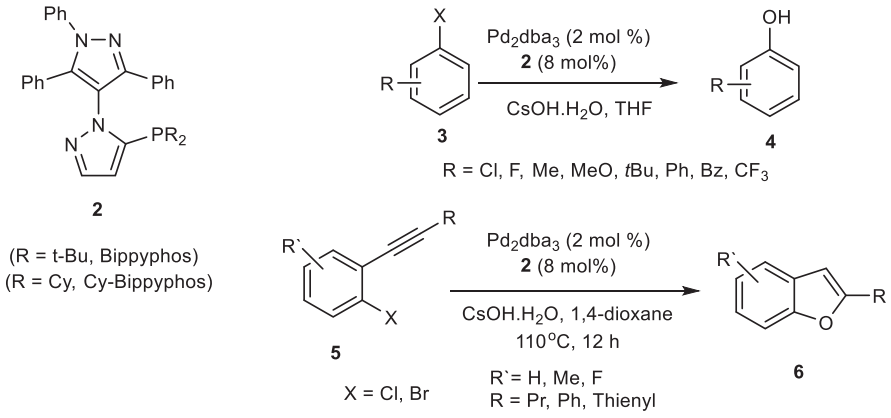
The 3,3`-bipyrazole-based Pd(II)-complex **1** was synthesized and reported as an efficient precatalyst for Suzuki-Miyaura C-C cross-coupling reactions of aryl halides with arylboronic acids in aqueous media [14].

Kamal M. Dawood and Ashraf A. Abbas



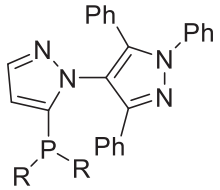
1

5-(Di-*tert*-butylphosphino)-1′,3′,5′-triphenyl-1′*H*-[1,4′]bipyrazole (Bippyphos) (**2**) was reported as an efficient co-catalyst in the palladium-catalyzed hydroxylation of several (hetero)aryl halides **3** under mild conditions as well as in the synthesis of substituted benzofurans and related heteroaromatic derivatives [11] (Scheme **1**).



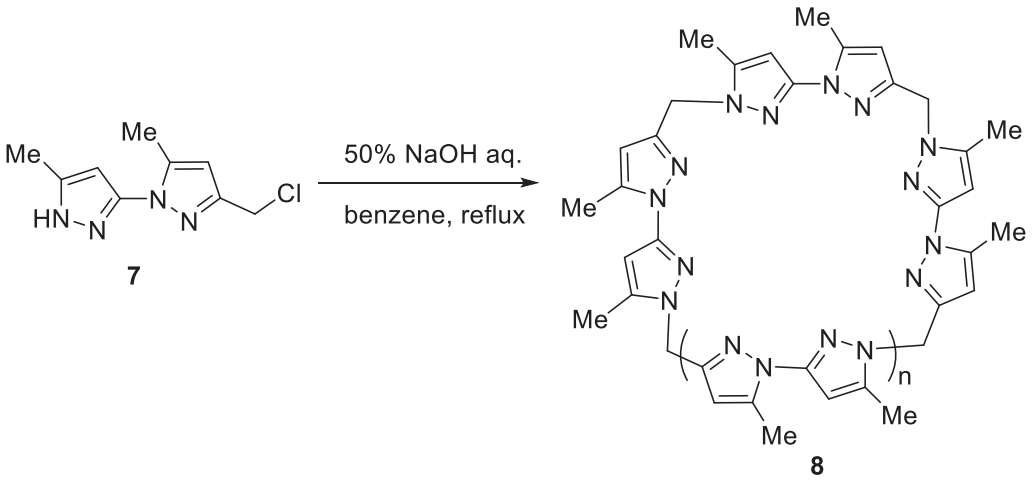
Scheme (1). Synthesis of hydroxyl compounds **4** and substituted benzofurans **6**.

The bipyrazole derivatives (bippyphos) **2** were applied as efficient ligands in the palladium-catalyzed C-O and C-N cross-coupling reactions of aryl halides with primary alcohols and with urea derivatives, respectively [12, 13, 15 - 17].



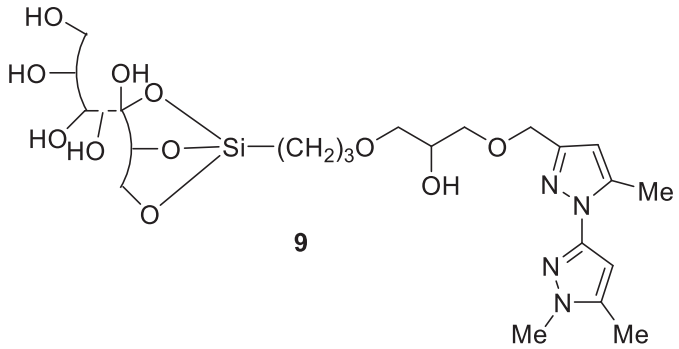
2 R = *t*-Bu, 1-adamantyl

Polycondensation of 5,5′-dimethyl-3-chloromethyl-1,3′-bipyrazole **7** was achieved in refluxing benzene in the presence of 50% NaOH solution and led to the formation of the polypyrazolic macrocycle **8** in 75% yield (Scheme **2**). The polypyrazolic macrocycles showed excellent complexing properties as ligands with the alkali metal cations [18].



Scheme (2). Synthesis of the polypyrazolic macrocycle **8**.

The immobilized bipyrazole **9** on the surface of epoxy-silica presented good thermal stability based on the thermogravimetric analysis, and it had good binding and adsorption abilities for Hg^{2+}, Cd^{2+}, Pb^{2+}, Zn^{2+}, K^{+}, Na^{+} and Li^{+} cations [19].



2.2. Bipyrazoles in Synthesis of Polybipyrazoles

Dehalogenative polycondensation of 3,3′-dichloro-5,5′-bipyrazoles **10** using a mixture of $Ni(cod)_2$ and 2,2′-bipyridine in DMF at 60°C resulted in the formation of poly(5,5′-bipyrazole-3,3′-diyl) derivatives **11** (Scheme **3**). The obtained polymers were characterized by their high thermal stability and electrochemical

SUBJECT INDEX

A

B

C

D

E

F

N

O

P

R

S

T

U

V

W

Z

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Ashraf A. Abbas

Ashraf A. Abbas has been a Professor of organic chemistry at Cairo University since 2009. He obtained his Ph.D. in 1997. He was awarded a DAAD fellowship at Fakultat fur Chemie, Universitat of Konstanz (Germany), in 1996, to finalize his Ph.D. and a UNESCO fellowship at TIT, Japan, 2001. He was awarded the prize of Dr. M. Abdel Salam (2001) for young scientists, the Cairo University encouragement award in 2004, the TWAS prize for young scientists in 2004, which was provided by ICTP-Strada, Trieste, Italy, and the State Award in Chemistry, 2005. He published many papers in the field of macrocycles and bis-heterocycles.