CHAPTER VI

Synthesis of some pharmaceutically important heterocyclic scaffolds and further functionalization via C-C coupling reactions

VI.A. Introduction

Heterocyclic compounds form an important class of organic chemistry possessing both biological and industrial application.[1] Particularly five- and six-membered heterocyclic compounds containing –N, –O and –S heterocycles have drawn huge attention of the pharmaceutical industry due to their enormous therapeutic value,[2] and utilization in drug discovery processes as well.[3] Benzimidazole (Figure VI.A.1) is one such important class of compounds which attract much attention of synthetic chemists due to their therapeutic applications such as in antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics.[4] They have also found applicaton in dyes,[5] chemosensing,[6] fluorescence,[7] corrosion science,[8] and as ligands for complexation with transition metals.[9] Recently electron transfer properties of benzimidazole functionalized Ru complexes have been explored in highly efficient dye sensitive solar cells (DSSC).[10] Because of such versatile applications a milder, safer, sustainable and environment friendly efficient synthetic route towards functionalized benzimidazoles has remained the target of many organic chemists.

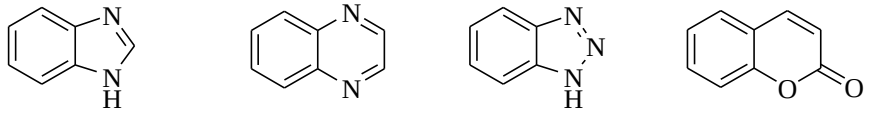


Figure VI.A.1. Core structure of some biologically active heterocyclic compounds

Another important class of nitrogen-containing heterocyclic compounds which are the core constituents of many pharmacologically active agents are quinoxalines (Figure VI.A.1).[11] The quinoxaline ring is present in various biologically active compounds possessing antibiotic, anti-inflammatory, antimicrobial,[12] antidiabetic,[13] and antiviral activity against retroviruses including HIV.[14] In addition, quinoxaline derivatives are also associated with a wide spectrum of biological effects including anticancer,[15] antifungal, and antidepressant activities.[16,17] However, most of the traditional synthetic routes towards quinoxalines suffer from a variety of drawbacks like pollution, high cost, poor chemical yields etc. Thus there has been a need for an environmentally benign strategy to synthesize such a useful pharmacophore.

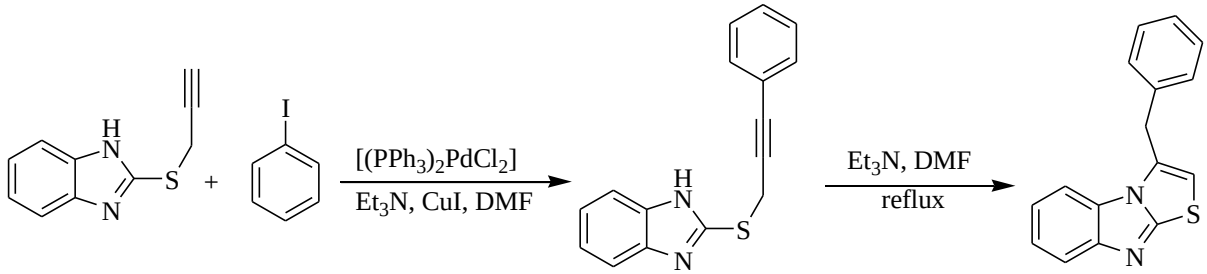
Benzotriazole (Figure VI.A.1) is another pharmaceutically leading heterocyclic scaffold. Variety of biological activities like anti-inflammatory,[18] anti-nociceptive,[19] anticonvulsant,[20] antimicrobial,[21] protein kinase inhibiting,[22] and immunosuppressive activities,[23] sought the importance of this moiety. Besides benzotriazoles are drawing enormous attention as

synthetic auxiliary and catalyst in coupling reactions since they are inexpensive, non-toxic, highly stable in the reaction condition and easily removed after completion.[24,25]

Coumarin (Figure VI.A.1) is another useful naturally occurring or synthesized heterocyclic compound called bezopyrones. Coumarin derivatives have diverse applications such as pharmaceutical agents,[26] solution dynamic probes,[27] fluorescent metal ion sensors,[28] laser dyes,[29] and organic sensitizers in high-efficiency dye-sensitized solar cells,[30] as well as coumarins have recently gained increasing importance due to their potential in pharmaceutical, agrochemical and fragrance industries. Coumarin derivatives are also widely applied in food and cosmetic industry.[31] Therefore the synthesis and biological activities of coumarin derivatives occupy an important position in heterocyclic chemistry as well as in medicinal chemistry.

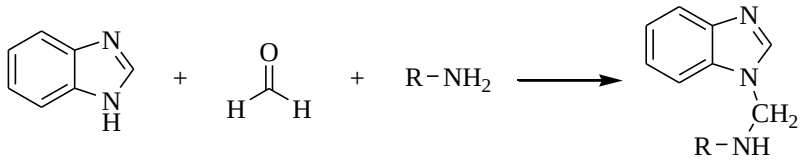
VI.B. Background and objectives

Heravi et al. offered a strategy to the synthesis of substituted 3-benzylthiazolo[3,2-*a*]benzimidazoles from 2-mercaptopropargyl benzimidazole and various iodobenzenes catalyzed by Pd-Cu via Sonogashira coupling.[32]



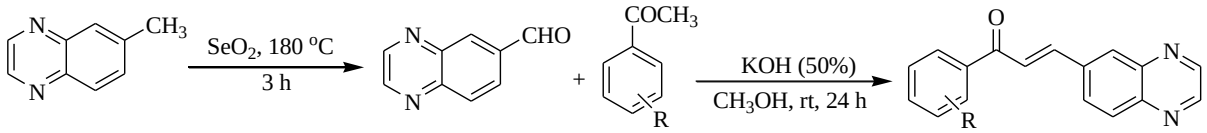
Scheme VI.B.1. Pd-Cu-catalyzed synthesis of substituted 3-benzylthiazolo[3,2-*a*]benzimidazoles

Recently *N*-substituted benzimidazole derivatives having anti-HIV and anti-viral activities have been prepared by Selvam et al. via mannich reaction between formaldehyde, benzimidazole and active hydrogen compounds like sulphanilamide, sulphadimidine, phthalimide, benzamide and few more.[33]



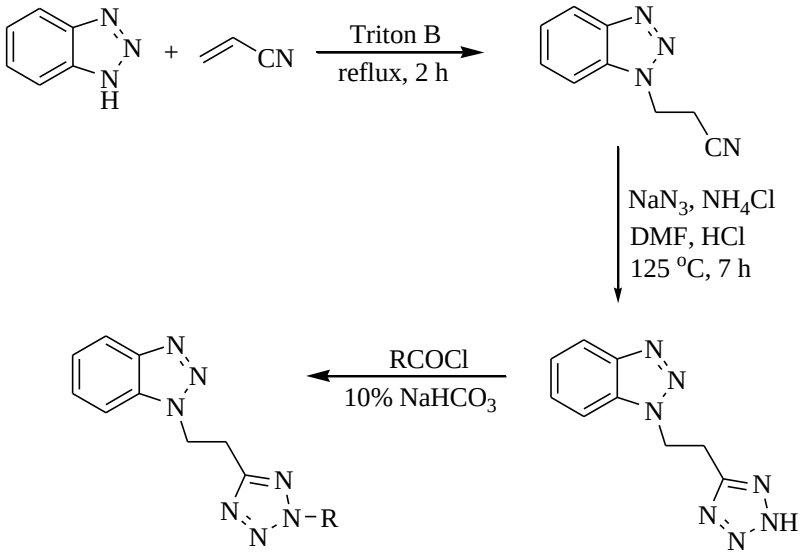
Scheme VI.B.2. *N*-substituted benzimidazole derivatives via mannich reaction

Very recently Winter and Gozzi et al. synthesized quinoxaline substituted chalcones as a potential inhibitor of breast cancer resistance protein ABCG2 from quinoxaline-6-cabaldehyde and corresponding acetophenones via aldol condensation.[34]



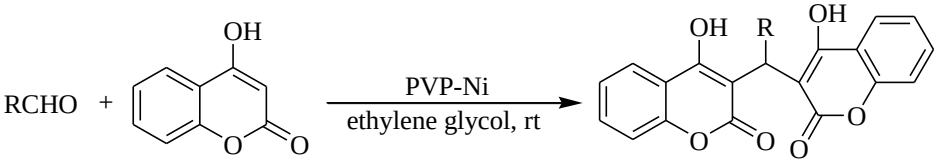
Scheme VI.B.3. Synthesis of quinoxaline substituted chalcones via aldol condensation

Rajasekaran and Rajagopal synthesized 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[*d*][1,2,3]triazoles,[23] from condensation of 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzotriazole with appropriate acid chlorides for the development of new compounds with potential anti-nociceptive[19] and anti-inflammatory activity.[18]



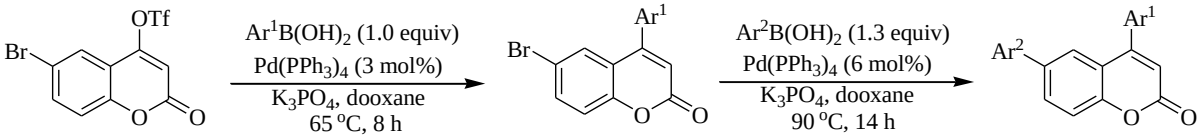
Scheme VI.B.4. Triton B-mediated synthesis of 1-[2-(1*H*-tetrazol-5-yl)ethyl]-1*H*-benzo[*d*][1,2,3]triazoles

Khurana and Vij performed another Knoevenagel condensation reaction between aldehydes and 4-hydroxycoumarin in ethylene glycol followed by rapid Michael addition using polyvinyl pyrrolidone (PVP)-stabilized nickel nanoparticles for the synthesis of bis-coumarins at room temperature.[35]



Scheme VI.B.5. Knoevenagel condensation reaction for the synthesis of bis-coumarins

Arylated coumarins (neoflavones) have been conveniently synthesized via Suzuki–Miyaura reactions of 4-trifluoromethylsulfonyloxy-6-bromocoumarin by Langer et al.[36]



Scheme VI.B.6. Arylated coumarins synthesized via Suzuki–Miyaura reactions

Functionalization can induce different biological and pharmacological activities in these important scaffolds. Some of them are represented in Figure VI.B.2.

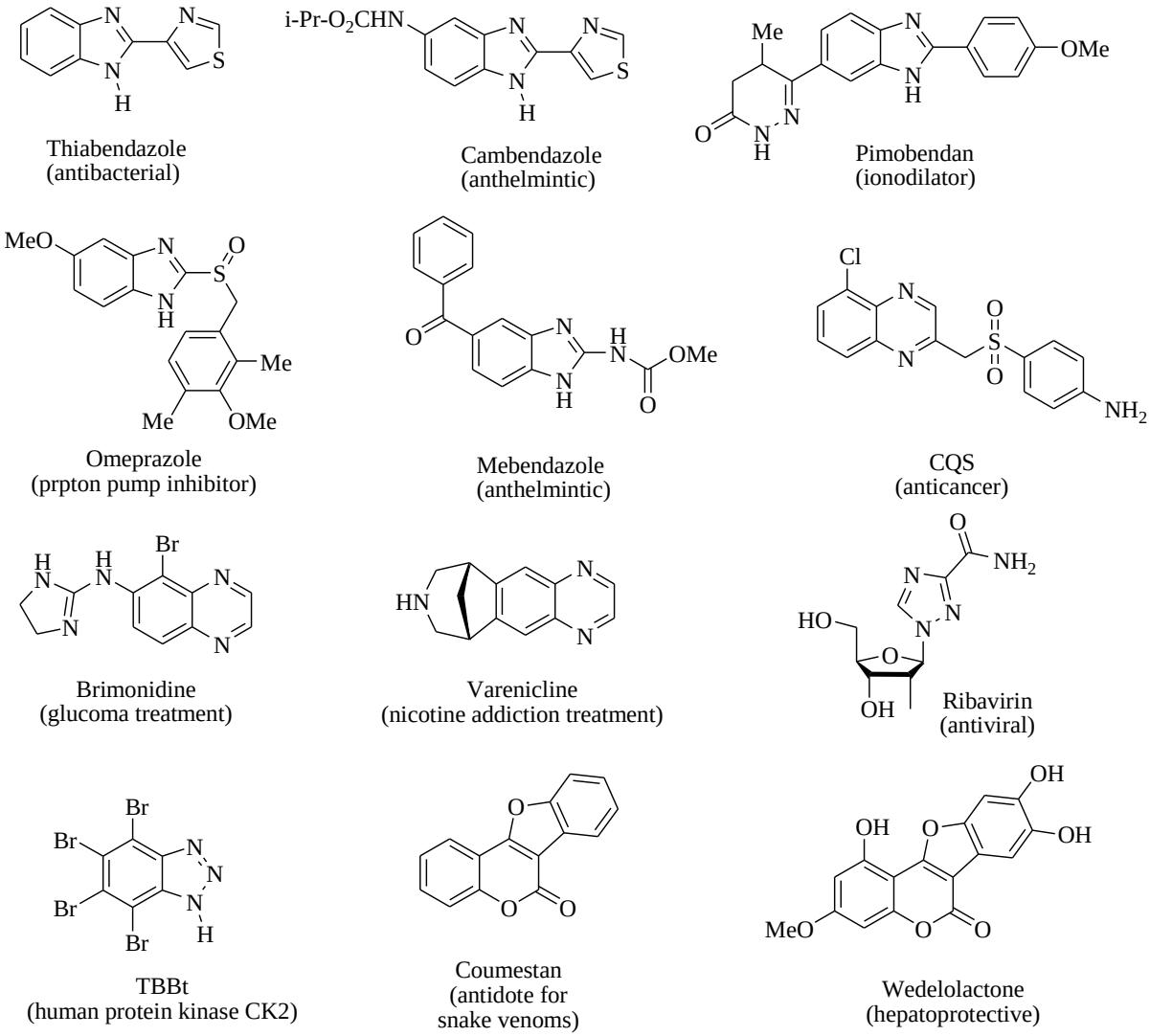


Figure VI.B.2. Different functionalized scaffolds with their activity

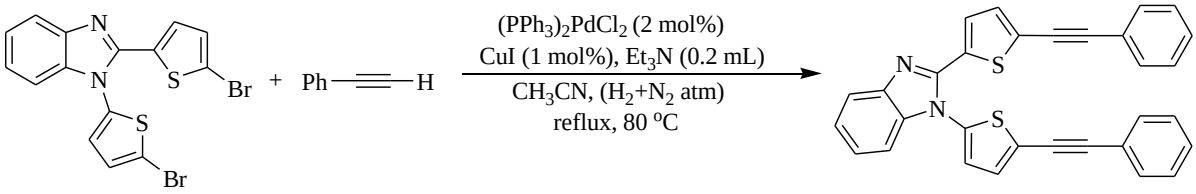
As for example benzimidazole derivatives like thiabendazole, cambendazole, pimobendan, Omeprazole, Mebendazole possess antibacterial, anthelmintic, ionodilator, proton pump inhitors and anthelmintic activities respectively; quinoxaline derivatives like chloroquinaxoline sulphonamide (CQS), brimonidine and varenicline show anticancer, glaucoma treatment and nicotine addition treatment respectively; 4,5,6,7-tetrabromo-1H-

1,2,3-benzotriazole (TBBt) and riavirin derivatives of benzotriazole are found in human protein kinase CK2 and in the treatment of antiviral activities respectively. Again coumarin derivatives coumestan and wedelolactone are used as antidote for snake venoms and potential hepatoprotective activity to inhibit the HCV NS5B polymerase which is critical for hepatitis C virus replication respectively.[37,38] Hence our main objective here is to functionalize these moieties and explore their biological activities.

However, this chapter describes some preliminary studies of exploratory nature and will be investigated in details in future studies. The preliminary results are presented below.

VI.C. Results and discussion

Earlier in this lab 1,2-bis(4-bromocyclopenta-1,3-dienyl)-1H-benzo[d]imidazole (**1**) was prepared from the condensation of o-phenylenediamine with 5-bromo-thiophene-2-carboxaldehyde catalyzed by iron(III)sulphate-silica.[39] We first attempted to funtionalize **1** by phenyl acetylene (**2**) via sonogashira coupling. Initially, in a flask a mixture of **1** (1 mmol), **2** (2.2 mmol), TEA (0.2 mL), CuI (1 mol%) and catalyst $Pd(PPh_3)_4$ (2 mol%) was taken in DMF solvent. Continuing with this mixture at room temperature, no conversion occurred even after 4 hrs. Again with increasing the temperature of the reaction mixture to 70-80 ^oC, no change was observed. To our delight, when we performed the same reaction using $(PPh_3)_2PdCl_2$ as a catalyst and CH_3CN as solvent, we obtained the desired product in 85% yield under N_2 atmosphere in refluxing condition.



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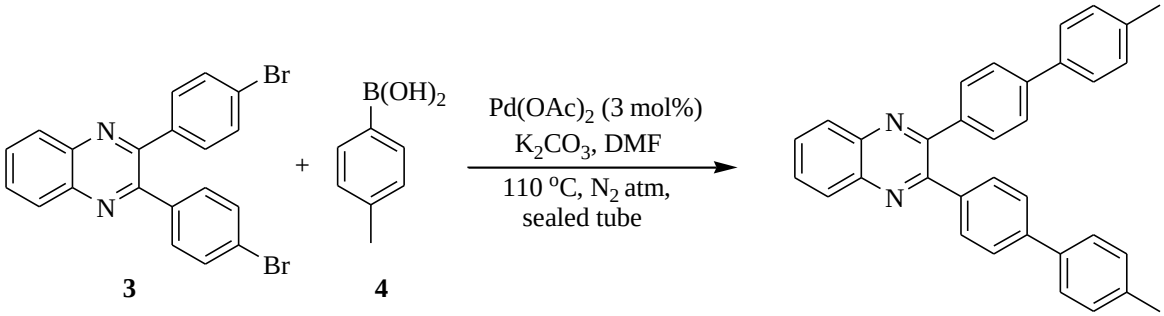
Scheme VI.C.7. $(PPh_3)_2PdCl_2$-catalyzed Sonogashira coupling on benzimidazole

Again for the preparation of functionalized quinoxalines, we used 2,3-bis(4-bromophenyl)quinoxaline (**3**).[40] Initially, to carry out Suzuki coupling reaction we chose **3** and phenylboronic acid (**4**).



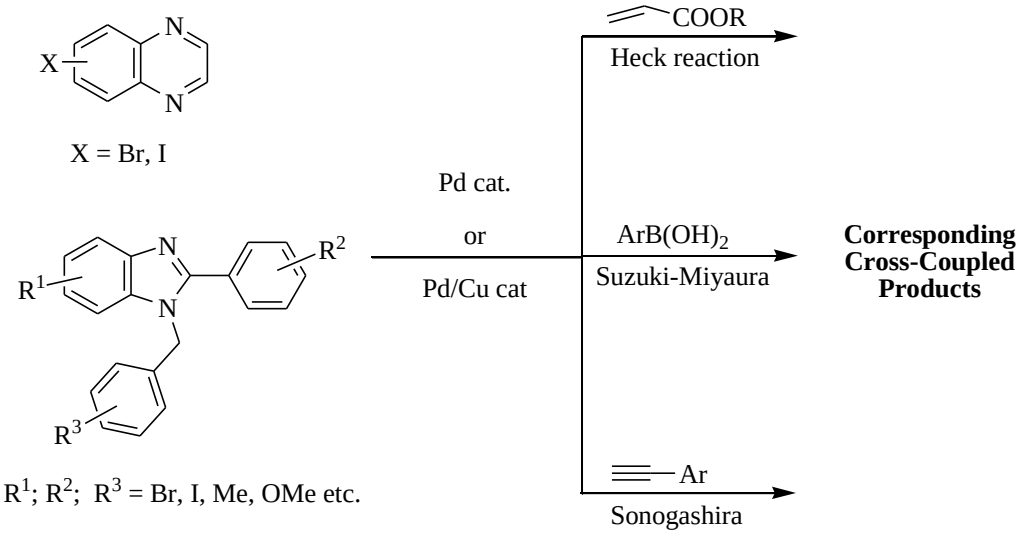
Scheme VI.C.8. Suzuki coupling reaction on quinoxalines catalyzed by $Pd(OAc)_2$

When catalyzed by $Pd(OAc)_2$ using K_2CO_3 in DMF at 110 ^oC, no desired product was obtained. But with the same catalyst when the reaction was performed under N_2 atmosphere, above 95% yield of the desired product was obtained.

VI.D. Future plan of work

Our future plan for the proposed syntheses are summarised as follows:

We would like to introduce some inorganic oxides or clay materials (may be doped with metal) to carry out the solid-phase syntheses of the heterocycles. Some new derivatives of quinoxalines are to be prepared. Again we would like to prepare 1,2-dihalosubstituted benzimidazoles to perform Heck, Suzuki-Miyaura or Sonogashira coupling reactions using polymer-soaked Pd or Pd/Cu catalysts, as outlined briefly in scheme VI.D.9.



Scheme VI.D.9. Functionalization on benzimidazoles and quinoxalines

In this lab we have recently developed a new novel synthetic route towards the synyhesis of imidazo[1,2-a]pyridine and further one-pot synthesis of 3-sulfenylimidazo[1,2-a]pyridine catalyzed by green carbocatalyst GO (as described in Chapter II). Various derivatives containing –Br, –I, –Cl substituents have been prepared for further functionalization. The

halogen-bearing heterocycles would be functionalized by using metal-catalyzed cross-coupling reactions.

VI.E. Experimental section:

VI.E.1. General information

General informations of experimental section are given in Chapter II under II.E.1. General information (Page–47).

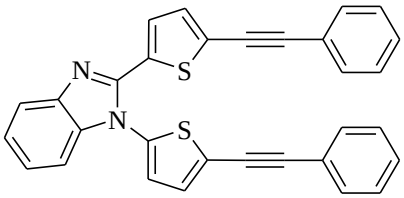
VI.E.2. Procedure for preparation of benzimidazole derivatives in scheme VI.7

A mixture of **1** (1 mmol), **2** (2.2 mmol), TEA (0.2 mL), CuI (1 mol%) and catalyst $(PPh_3)_2PdCl_2$ (2 mol%) was taken in CH_3CN solvent under both H_2 and N_2 atmosphere in a flask and reflux at 80 ^oC for 8 hours. The mixture was then cooled, diluted with water (5 mL) and extracted with diethyl ether (3x10 mL). The combined ethereal extracts were dried (anhy. Na_2SO_4) and concentrated to afford the product which was separated by column chromatography over silica gel and elution with pet ether-ethyl acetate mixture afforded the desired product in 85% yield.

VI.E.3. Procedure for preparation of quinoxaline derivatives in scheme VI.8

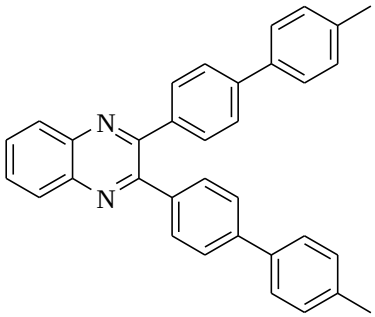
A mixture of **3** (1 mmol), **4** (2.2 mmol), K_2CO_3 (2 eq.) and catalyst $Pd(OAc)_2$ (3 mol%) was taken in DMF solvent under N_2 atmosphere in a sealed tube at 110 ^oC for 10 hours. The mixture was then cooled, diluted with water (5 mL) and extracted with diethyl ether (3x10 mL). The combined ethereal extracts were dried (anhy. Na_2SO_4) and concentrated to afford the product which was separated by column chromatography over silica gel and elution with pet ether-ethyl acetate mixture afforded the desired product in 95% yield.

VI.E.4. Spectral data



2-(5-(2-phenylethynyl)thiophen-2-yl)-1-((5-(2-phenylethynyl)thiophen-2-yl)methyl)-1*H*-benzo[*d*]imidazole, Obtained as light yellow solid, m.p. 196-199 ^oC (decomposition), ^1H NMR (300 MHz, $CDCl_3$), δ: 5.93 (s, 2H), 6.87 (d, J = 6.9 Hz, 1H), 7.05-7.10 (m, 1H), 7.24-

7.38 (m, 13H), 7.43-7.60 (m, 2H), 7.68-7.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 44.1, 81.9, 95.5, 109.8, 112.3, 120.1, 122.3, 123.4, 123.8, 125.5, 125.9, 126.8, 128.1, 128.38, 128.4, 128.6, 128.9, 130.0, 130.9, 131.4, 131.5, 132.0, 132.3, 132.5, 135.7, 139.9, 142.8, 146.6.



2,3-bis(4-methylbiphenyl)quinoxaline, Pale yellow solid, m.p. 204-206 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.42 (s, 6H), 7.17-7.25 (m, 2H), 7.31-7.36 (m, 2H), 7.42-7.44 (m, 4H), 7.62-7.65 (m, 8H), 7.80 (s, 2H), 8.24 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 21.6, 127.2, 127.8, 128.4, 128.7, 129.3, 130.2, 137.6, 138.5, 140.3, 141.1, 141.8, 153.1.

VI.F. References

References for chapter VI are given in Bibliography section (page 149–151).