ABSTRACT

The thesis entitled **"SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SUGAR-BORONATE ESTERS"** has been divided into five chapters.

CHAPTER I

INTRODUCTION

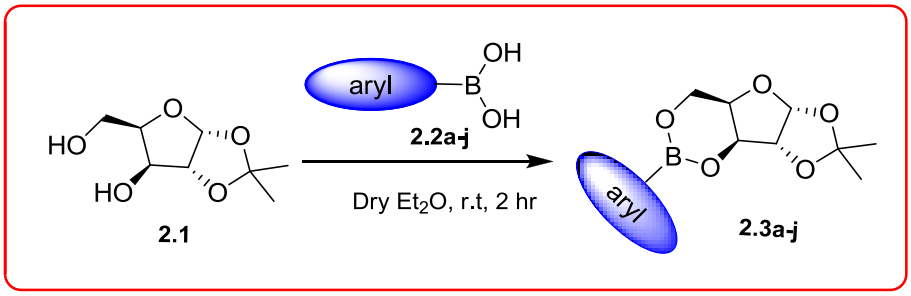
Chapter I introduces the brief overview of medicinal applications of boronic acids and related compounds. A brief description on boronate esters has been included. Significance of carbohydrates in biological processes and carbohydrates derived medicinal compounds has been discussed. In addition, biological significance of boron-carbohydrate interactions is also described.

CHAPTER II

ARYL BORONATE ESTERS OF 1,2-*O*-ISOPROPYLIDENE-α-D-XYLOFURANOSE: SYNTHESIS AND ANTIMICROBIAL ACTIVITY

In this chapter the efficient synthesis, characterization and antimicrobial activity of aryl boronate esters of 1,2-*O*-isopropylidene-α-D-xylofuranose have been reported. The synthetic route for the aryl boronate esters is described in **Scheme 2.1**. Reaction of 1,2-*O*-isopropylidene-α-D-xylofuranose (**2.1**) derived from D-xylose with aryl boronic acids (**2.2a-j**) in dry Et_2O at room temperature for 2 hours

provides corresponding 1,2-*O*-isopropylidene-α-D-xylofuranose-3,5-aryl boronate esters (**2.3a-j**) in good to excellent yields.



Scheme 2.1

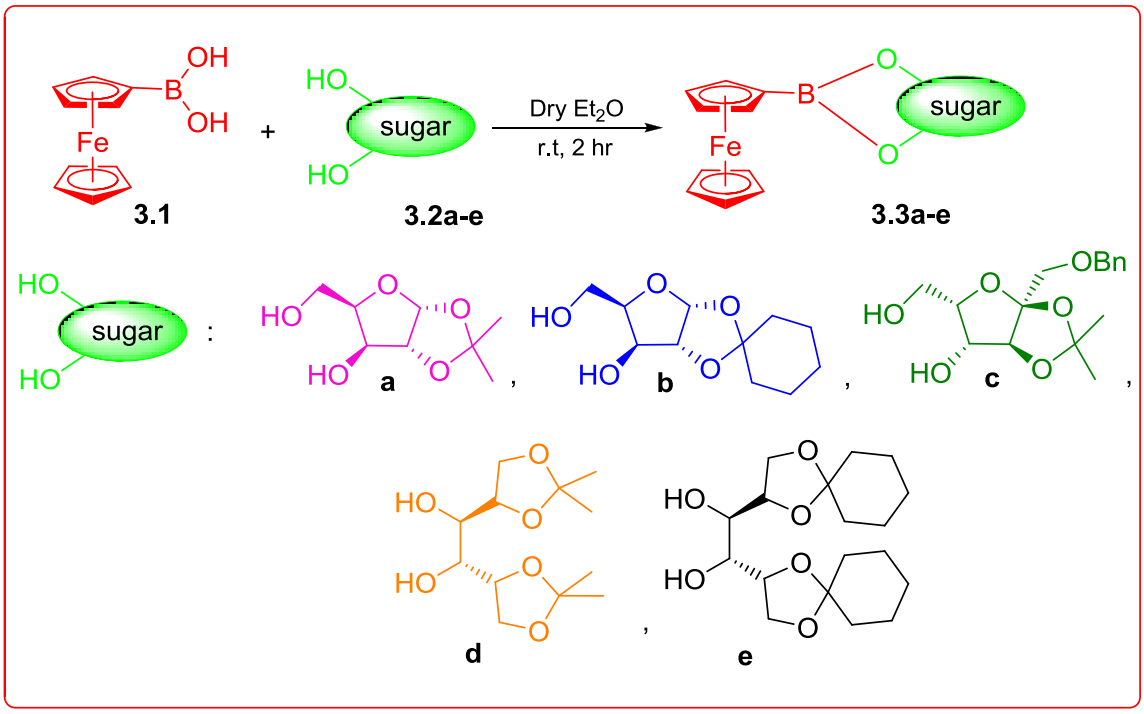
All the aryl boronate esters were well characterized by ^{1}H, ^{13}C and ^{11}B-NMR, FT-IR, elemental analysis and EI-MS. Further, the molecular structure of compound **2.3a** was characterized by single crystal X-ray diffraction studies. All the aryl boronate esters were evaluated for antimicrobial activity and exhibited moderate to good activity against most of the tested bacterial and fungal strains. Among all the boronate esters, **2.3g** and **2.3h** displayed better antibacterial and antifungal activities against all the tested microorganisms.

CHAPTER III

FERROCENYL BORONATE ESTERS OF CARBOHYDRATES: SYNTHESIS AND ANTIBACTERIAL ACTIVITY

The third chapter deals with the synthesis, characterization and antibacterial activities of ferrocenyl boronate esters of carbohydrates. The synthetic route for the ferrocenyl boronate esters is outlined in **Scheme**

3.1. Reaction of ferroceneboronic acid (**3.1**) with protected sugar diols (**3.2a-e**) derived from D-xylose, L-sorbose, and D-mannitol in dry Et_2O at room temperature for 2 hours provides corresponding ferrocenyl boronate esters (**3.3a-e**) in good yields. The preparation of the respective protected sugar diols was done based on the reported literature procedure.



Scheme 3.1

All the ferrocenyl boronate esters **3.3a**-**e** are air- and moisture-stable, orange/yellow microcrystalline solids. Their purity and identity were unambiguously established with the help of elemental analysis, FT-IR, multinuclear NMR (^{1}H, ^{13}C and ^{11}B) and UV/visible spectroscopy. Further, the electrochemical behavior of the esters was studied by cyclic

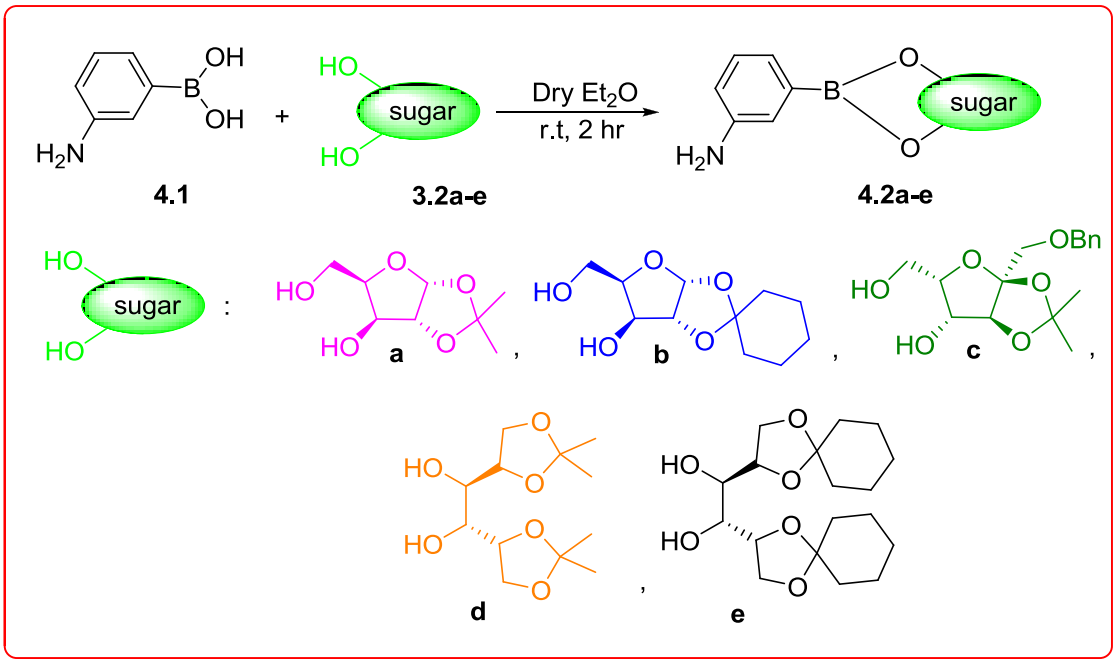
voltammetry (CV). Additionally, the molecular structures of the two compounds, **3.3a** and **3.3c** were solved by single crystal X-ray diffraction analysis. *In vitro* antibacterial activity of the carbohydrate-based ferrocenyl boronate esters **3.3a**-**e** was screened against three representative Gram-positive and Gram-negative bacteria. Some of them showed moderate to good activity against tested bacterial strains. In particular, ferrocenyl boronate ester containing sorbofuranose derivative **3.3c** exhibited good activity against all the screened microorganisms. It exhibits excellent inhibitory activity against *E. coli* with MIC 4.68 µg/mL. These results clearly indicate the importance of sugar scaffolds in the design of ferrocene–boron–carbohydrate hybrids.

CHAPTER IV

SUGAR-BORONATE ESTER TETHERED PYRIDYL-IMINE PALLADIUM(II) COMPLEXES: SYNTHESIS AND ANTICANCER ACTIVITY

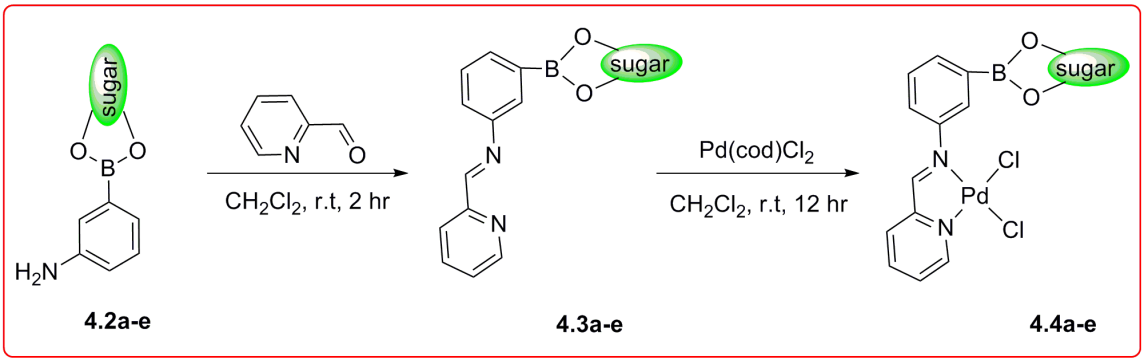
This chapter describes synthesis, characterization and *in vitro* anticancer studies of palladium(II) pyridyl-imine Schiff base complexes containing boronate esters of sugars. The synthetic protocol for the sugar-boronate ester containing pyridyl-imine palladium(II) complexes is depicted in **Scheme 4.1** and **4.2**. To investigate the efficiency of sugar-boronate ester scaffold tethered pyridyl-imine palladium(II) complexes towards anticancer activity, aminophenyl boronate esters of

carbohydrates were first synthesized, as the key precursors for the preparation of palladium complexes. As shown in **Scheme 4.1**, 3′-aminophenyl boronate esters (**4.2a**-**e**) were synthesized by the reaction of 3-aminophenyl boronic acid (**4.1**) with protected sugar diols (**3.2a**-**e**) derived from D-xylose, L-sorbose and D-mannitol, respectively in dry Et_2O at room temperature for 2 hours.



Scheme 4.1

The palladium complexes **4.4a**-**e** were prepared in good yields by one-pot reaction of $Pd(cod)Cl_2$ (1 equivalent) with pyridyl-imine ligands **4.3a**-**e** [generated in situ by the condensation of 3′-aminophenyl boronate esters **4.2a**-**e** (1 equivalent) with 2-pyridinecarboxaldehyde (1 equivalent)] in dichloromethane at room temperature as shown in **Scheme 4.2**.



Scheme 4.2

All the palladium(II) complexes **4.4a-e** are air- and moisture-stable orange/yellow microcrystalline solids. Their purity and identity were unambiguously established with the help of analytical techniques and spectroscopy. Additionally, to gain further insight into the coordination chemistry of these palladium complexes, the structure of compound **4.4a** was established by single-crystal X-ray diffraction analysis.

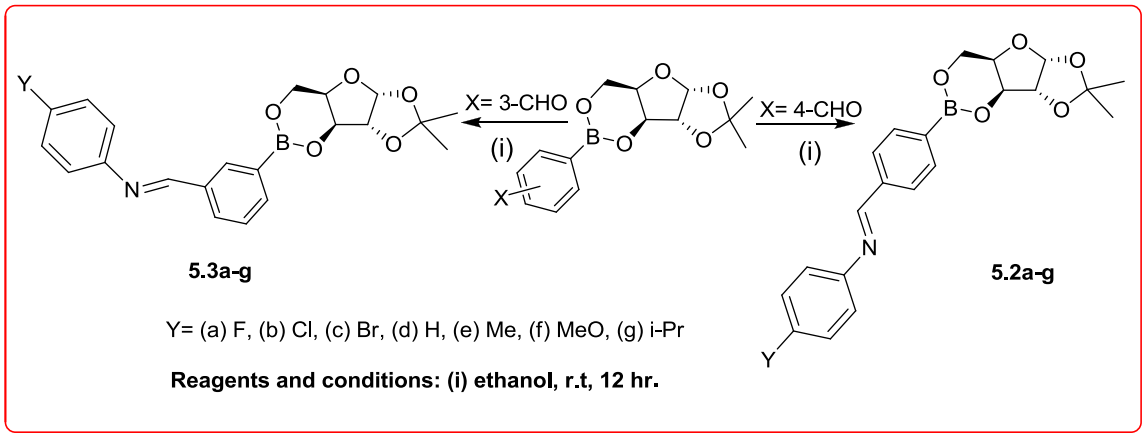
The preliminary cytotoxic profile of the synthesized sugar boronate ester scaffold tethered pyridyl-imine palladium(II) complexes **4.4a-e** was evaluated against two human cancer cell lines, including colon (HT-29) and breast (MDA-MB-231) cancer cells and normal non-tumorigenic human embryonic kidney (HEK-293T) cells by employing the MTT assay. Gratifyingly, all of the palladium complexes **4.4a-e** displayed good to moderate cytotoxicity against both the cancer cells with IC_{50} values ranging from 4.27 to 34.76 μM, suggesting a general role of boronate ester of the carbohydrate moiety in cancer cells growth inhibition.

To study the binding affinity and the mode of binding between DNA and the palladium(II) complexes **4.4a-e**, which have significant effect against the tested cancer cell lines, a series of biophysical studies were carried out, including UV/visible, CD and viscosity measurements. These results indicate the partial intercalation of complexes **4.4a-e** with CT-DNA, which may substantiate the biological activities offered by them in the tested cancer cell lines.

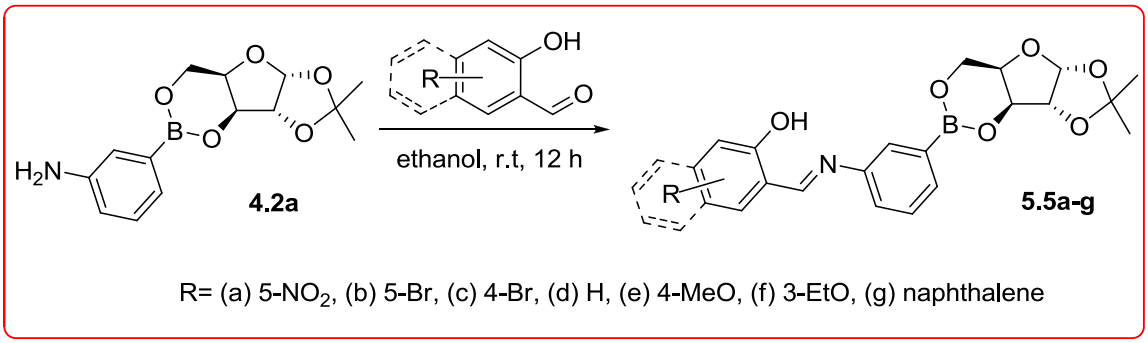
CHAPTER V

SCHIFF BASE TETHERED BORONATE ESTERS OF 1,2-*O*-ISOPROPYLIDENE-α-D-XYLOFURANOSE: SYNTHESIS AND ANTIMICROBIAL ACTIVITY

This chapter describes the synthesis, characterization and antimicrobial activity of Schiff base tethered boronate ester of 1,2-*O*-isopropylidene-α-D-xylofuranose. A series of twenty one imines containing boronate ester of 1,2-*O*-isopropylidene-α-D-xylofuranose **5.2a-g**, **5.3a-g** and **5.5a-g** were synthesised as shown in **Scheme 5.1** and **Scheme 5.2**, respectively.



Scheme 5.1



Scheme 5.2

All the imines were isolated in good to excellent yields without column chromatography. Their purity and identity were unambiguously established with the help of elemental analysis, multinuclear NMR (^{1}H, ^{13}C and ^{11}B) and FT-IR spectroscopy. Additionally, the molecular structures of the two compounds, **5.2c** and **5.3e** were characterized by single crystal X-ray diffraction studies.

All the synthesized compounds were evaluated for *in vitro* antimicrobial activity against various Gram-positive and gram-negative bacterial and fungal strains. The *in vitro* antibacterial and antifungal

evaluation showed that most of the synthesized sugar-boronate ester conjugated Schiff bases exhibited moderate to good antimicrobial activities. In particular, compound **5.5a** exhibited potent activity against all the tested bacterial and fungal microorganisms comparable or even better than standard drugs.