UNIVERSITY OF TROMSØ UIT

FACULTY OF SCIENCE AND TECHNOLOGY
DEPARTMENT OF CHEMISTRY

Design, Synthesis and Biological Activity of Small α-Aminoboron Containing Peptidomimetics

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A dissertation for the degree of
Philosophiae Doctor

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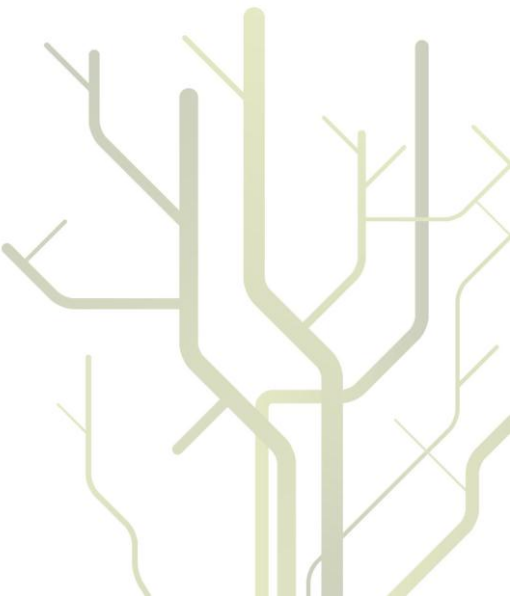

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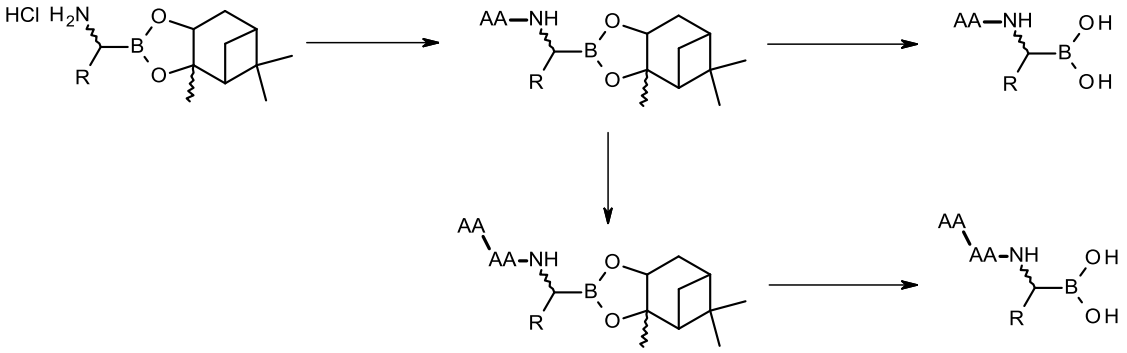
ABSTRACT

Antimicrobial peptides (AMPs) are a special group of small amphipathic peptides (which hold both hydrophilic and hydrophobic regions) composed of different amino acids and produced by all living organisms as a part of innate immunity. With the increasing microbial resistance to traditional antibiotics the need for unconventional therapeutic has become crucial.

This thesis deals with the design and synthesis of a library of α-aminoboronic di- and tri- peptides and investigation of their biological activity against different bacteria strains, fungi and kinases in order to discover compounds that can further be developed into drugs.

Preliminary results have provided a broad spectrum of data regarding structure-activity relationship of synthesized peptides and several new potential therapeutics have been discovered.



LIST OF PAPERS

Paper I

Ultrasound promoted dimerization of benzylic halides. *Olga V. Gozhina, Ivar K. Thomassen and Tore Lejon* , Synthetic Communications (accepted)

Paper II

Boron containing peptidomimetics – a novel class of selective anti-tubercular drugs. *Alexey S. Gorovoy, Olga V. Gozhina, John Sigurd Svendsen, Anna A. Domorad, George V. Tetz, Victor V. Tetz and Tore Lejon,* Chemical Biology & Drug Design (accepted)

Paper III

(3a*S*,4*S*,6*S*,7a*R*)-hexahydro-3a,5,5-trimethyl-2-phenyl-4,6-methano-1,3,2-benzodioxaborole. *Tore Lejon, Olga V. Gozhina and Victor N. Khrustalev,* Acta Crystallographica Section E, **2012**, E68, o3103.

Paper IV

Synthesis and anti-tubercular activity of β-substituted and α,β-disubstituted β-aminoboronates and boronic acids. *Alexey S. Gorovoy, Olga V. Gozhina, John Sigurd Svendsen, George V. Tetz, Anna A. Domorad, Victor V. Tetz and Tore Lejon* (submitted)

Paper V

Synthesis and antimicrobial activity of α-aminoboronic containing peptidomimetics. *Olga V. Gozhina, John Sigurd Svendsen and Tore Lejon* (manuscript)

ABBREVIATIONS

α	alpha
β	beta
boc	*tert*-butyloxycarbonyl
^{13}C	carbon spectra (NMR)
calcd	calculated (MS)
C. albicans	*Candida albicans*
DCM	dichloromethane
E. coli	*Escherichia coli*
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
Et_2O	diethyl ether
^{1}H	proton spectra (NMR)
H^+	proton (hydrogen ion)
HCl	hydrogen chloride
HOBt	1-hydroxybenzotriazole
IR	infrared
MIC	minimum inhibitory concentration observed
HRMS	high-resolution mass spectrometry
M^+	molecular ion peak (MS)
M. tuberculosis	*Mycobacterium tuberculosis*
NMR	nuclear magnetic resonance
P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*
S. pyogenes	*Streptococcus pyogenes*
THF	tetrahydrofuran

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1. INTRODUCTION

Since almost every substance on Earth contains carbon, organic chemistry is all around us. Many fundamental bases of biotechnology, biochemistry, and medicine are constructed on organic substances and their important role in life processes, for example, enzymes, vitamins, proteins, and carbohydrates make humans existence possible. Organic chemistry is a large branch of chemistry that deals with the structure, properties, and reaction ability of compounds that contain carbon (hydrocarbons). Carbon is a very special element due to its location in the periodic table, since it is sited in the middle of the second row carbon is able to form stable organic compounds by sharing its electrons with other elements (with formation of persistent covalent bonds).

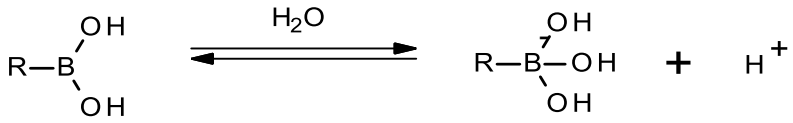
From this point of view it was very exciting to investigate a chemistry of elements lying next to carbon in the periodic table, for example, chemistry of boron, which has not been developed yet as it deserves to be, though the first boron-containing organic compounds have been synthesized a long time ago.

1.1. General background

Boronic acids are well known from literature since 19th century, evaluating over the years into a broadly studied field of chemistry. The usefulness of boronic acid compounds as pharmaceuticals is connected to their unique electronic and chemical properties since boron occupies a special place in the periodic table. Boron is in the same period as carbon, but has one less electron. So it has many similarities with carbon in structural details, which makes it useful in the world of carbon in organic chemistry.

One important property of boronic acids is that they are organic Lewis acid because of they possess a vacant *p*-orbital. By coordinating basic molecules, the resulting tetrahedral intermediate gets a configuration similar to carbon.

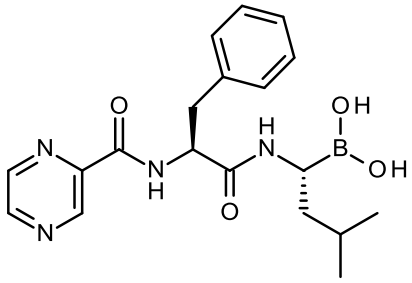
So boronic acids can easily convert from neutral and trigonal planar sp^2 boron to anionic tetrahedral sp^3 boron (as shown in Scheme 1.1) under physiological conditions.



Scheme 1.1 Equillibrium between trigonal planar sp^2 boron and tetrahedral sp^3 boron.

The simple procedure of synthesis and the stability of the group leads to use in a wide range of significant synthetic reactions as Suzuki–Miyaura coupling,[1-3] asymmetric synthesis of amino acids,[4] carboxylic acid activation[5,6] and hydroboration.[7] However, the use of boronic acids in medicinal chemistry has mostly been overlooked due to the opinion inside the medicinal chemistry community that boron is toxic.[8-10]

This opinion probably comes from the fact that boric acid ($B(OH)_3$) is a component of ant poisons. Another basis for the toxicity problem must have arisen from the toxicity of Velcade®[11-13] the only boron-based therapeutic on the market which is broadly recommended by oncologists. Velcade® is approved for the treatment of multiple myeloma and works as inhibitor of the proteasome. Recent research has shown that the toxicity of Velcade® is due to its mechanism of action and not because boron is present in the molecule.[14]



Velcade

Figure 1.1 The structure of Velcade® (bortezomib).

Nuclear properties of the boron atom can also be useful in medicine, for example, Boron Neutron Capture Therapy (BNCT) for the treatment of cancer represents an important role of boron in chemistry. This application is based on the unique property of boron-10, which is able to emit α-particles by undergoing irradiation with neutron. Since α-particles are very unstable they do not travel for a long distance (only a few millimeters), so they are good choice for localized radiation therapy.[15,16]

Boron is also included in a number of natural products isolated from bacteria, such as the antibiotic boromycin[17] (Figure 1.2) and tartrolon B (Figure 1.3).[18]

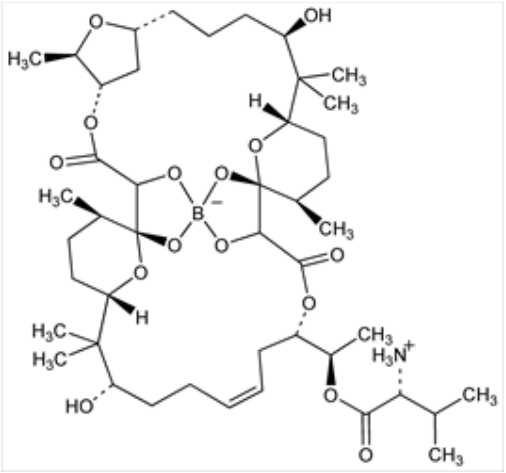


Figure 1.2 The structure of boromycin (copied from medicinescomplete.com).

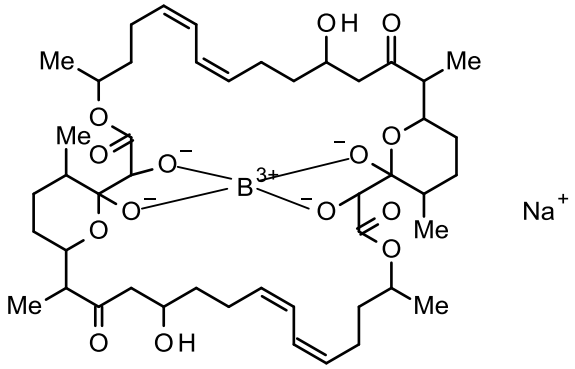


Figure 1.3 The structure of tartrolon B.

These natural products illustrate that boron is tolerated in biological systems and can be used as antimicrobial agent without negative consequences for human health as will be discussed in the following chapter.

1.2. Antimicrobial Peptides

The treatment of bacterial contagions with different antibiotics is one of the important processes of modern medicine, but a major limitation in antibiotic development is the difficulty of finding new structures with the same biological properties as traditional antibiotics, but showing a lower level of toxicity for the patient and a higher standard of action against bacterial pathogens. It is a significant challenge for chemists to create antibiotics with novel structures and/or mode of action.

Antimicrobial peptides (AMPs) are small proteins with wide range antimicrobial activity against bacteria and viruses. These peptides are often positively charged and have both a hydrophilic and hydrophobic sides that help the molecule to be soluble either in aqueous or organic environments. Antimicrobial peptides (AMPs) kill target cells through different mechanisms.

In our laboratories synthesis and antimicrobial application of various peptides has been broadly investigated by Prof. Svendsen.[19-21]

As discussed above, the utility of boronic acid compounds as therapeutics is generally based on their easy conversion between the trigonal sp^2 and tetrahedral sp^3 forms, which make them perfect transition state analogs in hydrolytic processes.

1.2.1. Boron-containing Anti-microbial Peptides: Discovery and Development

The antimicrobial properties of simple arylboronic acid derivatives were investigated in the 1930s for the first time.[22] The activity of arylboronic acids in plants has been examined, and some of them were found to promote root growth.[23] Several boronic acids and their

derivatives were determined to be good at sterilizing house flies.[24] Also, boronic acids and esters demonstrate antifungal activity.[25,26]

A large class of antibiotics is represented by β-lactam antibiotics, which includes penicillin derivatives, monobactams, cephalosphorins (cephems), and carbapenems, so this class of antibiotics is the most commonly prescribed treatments, and the following discussion concerns β-lactam antibiotics due to their significance in medicine.

The increase of bacteria's resistance to β-lactam antibiotics has been established as imminent danger to human health in the twenty-first century. The common mechanism of resistance to cephalosporins and penicillins is the production of β-lactamase enzymes by bacteria. The bacterial β-lactamases initiate the destruction of β-lactam antibiotics through an efficient hydrolysis of the lactam bond, which lead to antibiotic resistance to the β-lactam family of antibiotics.

Two strategies have been developed to combat this resistance:

1.) The synthesis of new β-lactam antibiotics which can resist enzymatic hydrolysis and deactivation.

2.) Development of β-lactamase inhibitors in accordance with already established arsenal of antibiotics.

In the second case, boronic acid is acting as a transition state inhibitor. The boron atom is well known to behave as an electrophile that imitates the carbonyl group of the β-lactam. The boron forms a tetrahedral sp^3 geometry with the catalytic serine, imitating the transition state of the complex enzyme-adduct, and blocking access to the active site of the β-lactam ring of a drug molecule.[8]

Cephalothin is the antibiotic against AmpC type β-lactamases (AmpC type β-lactamases usually obtained from cephalosporin-resistant Gram-negative bacteria). Shoichet's group illustrated that the closer the structure of boronic acid is like the natural substrate, better the effectiveness (Structures are outlined on Figure 1.4).[27,28]

More the structure imitates the β-lactam of cephalothin, the larger the inhibition. With boronic acid **1** inhibition is the weakest. Addition of a phenyl ring **2** provides a 10 times increase in potency. The introduction of a *meta*-carboxyl group into a phenyl ring gives improvement of the activity for AmpC type β-lactamase to provide the most effective inhibitor, boronic acid **3**. Boronic acid **4** was also synthesized as the most potent inhibitor of the produced group, but it seems to the same level of activity with compound **3**.

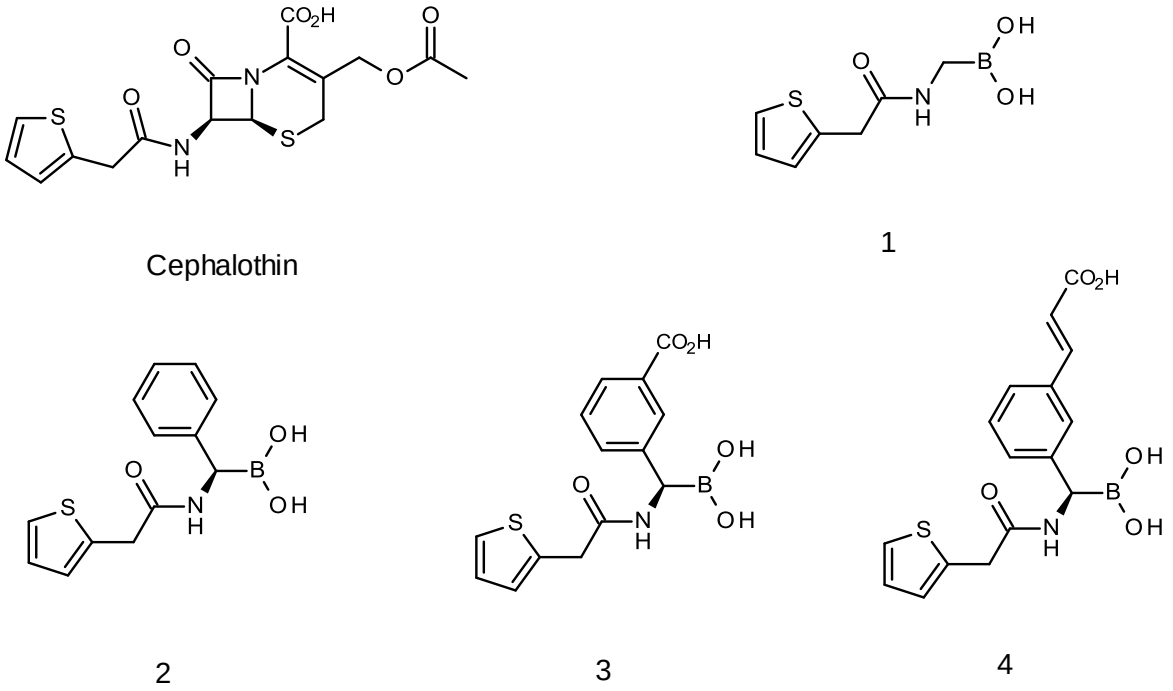


Figure 1.4 The structures of cephalothin and mimicking boronic acids.

Boronic acids β-lactamase inhibitors are transition-state analogues (Figure 1.5) which means that the β-lactam recognition part is displaced with a boronic acid.[29-31] This allows to create a tetrahedral sp^3 adduct by interaction of a covalent bond with the active site of a serine residue. The replacement makes these boron containing inhibitors innovative enough to avoid many of the resistance mechanisms.[27]

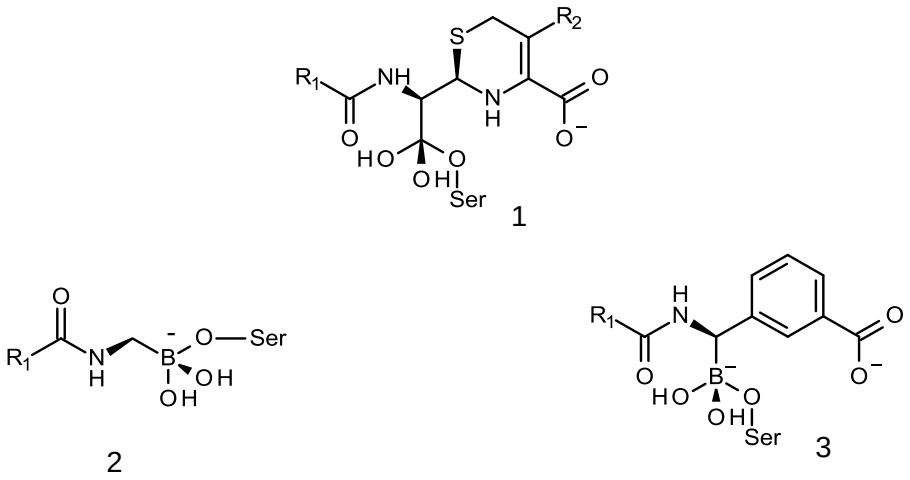


Figure 1.5 The structures of intermediate of a cephalosporin in a serine *β*-lactamase **1** and its transition state boron containing analogues - glycylboronic acid **2** and *m*-carboxyphenyl-glycylboronic acid **3**.

In 1978, Kiener and Waley discovered that *meta*-aminophenylboronic acid and phenylboronic acid poorly inhibit *β*-lactamase from *Bacillus cereus*.[32] Later it was found that aromatic boronic acids (Figure 1.6) behave as weak inhibitors of *β*-lactamases from *P. aeruginosa* and *E. coli*.[33]

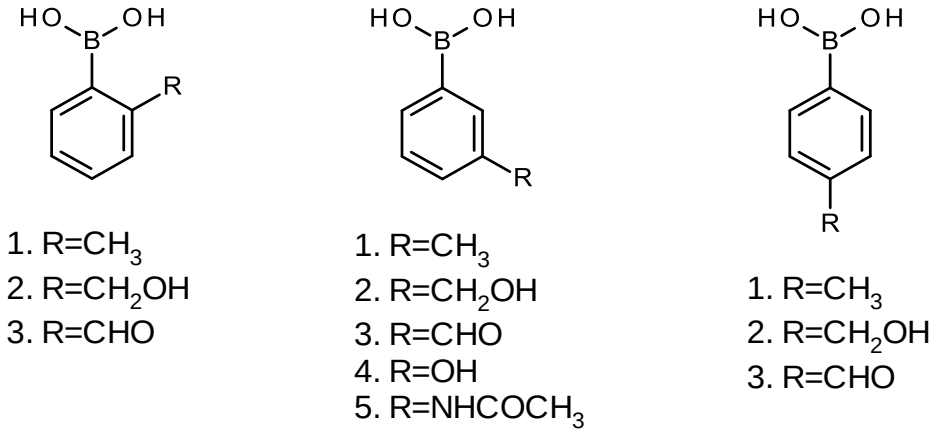


Figure 1.6 The structures of *ortho*-, *meta*- and *para*- substituted boronic acids as inhibitors of *P. aeruginosa* and *E. coli*.

So it is quite obvious that boronic acids have more possibilities to be used in medicine due to their therapeutic potential in many areas of chemistry.

1.2.2. Tuberculosis. Boron-containing Antimycobacterial Agents

Tuberculosis (TB) is the leading cause of death in the world among bacterial infectious diseases. The disease affects about 1.7 billion people which is equal to one-third of the entire world population. TB is caused by a bacterium called *Mycobacterium tuberculosis*, that usually attacks the lungs, but also it can attack any part of the body such as the spine, kidney, and brain. If it is not treated correctly and in proper time, TB can be fatal.

The treatment of tuberculosis has always been complicated due to formation of new multi-resistant strains.

The standard antibiotic combination for the TB treatment is a mixture of isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), and rifampicin (RIF) (Figure 1.7).

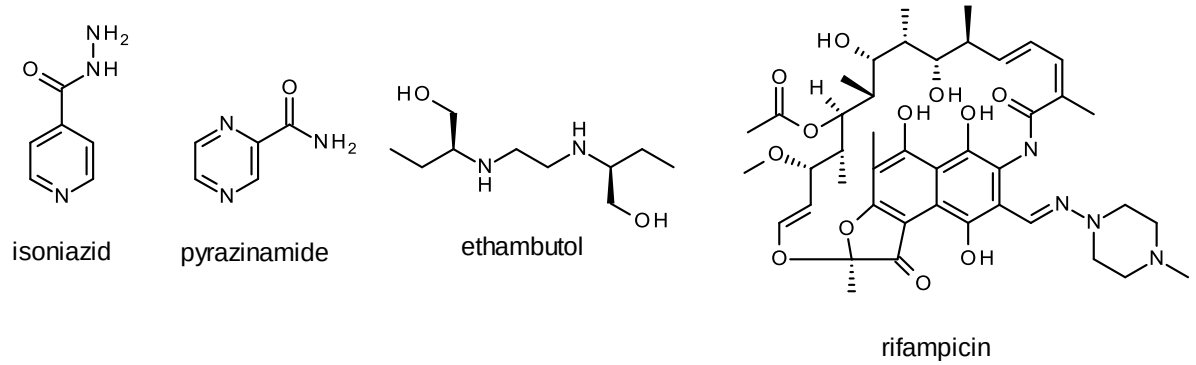


Figure 1.7 The structures of isoniazid, rifampin, pyrazinamide, and ethambutol.

Boron-containing compounds are not commonly known as inhibitors of *Mycobacterium tuberculosis*, but it has been reported about several classes of such compounds possess satisfactory inhibitor activity.

The use of borole derivatives, including benzoxaboroles, benzazaboroles and benzthiaboroles, as therapeutics for the treatment of different diseases caused by bacteria or viruses including *Mycobacterium tuberculosis* have been described.[34]

Compounds having the peptide-likely general structure **1** (Figure 1.8) have been successfully used as treatment of TB.[35]

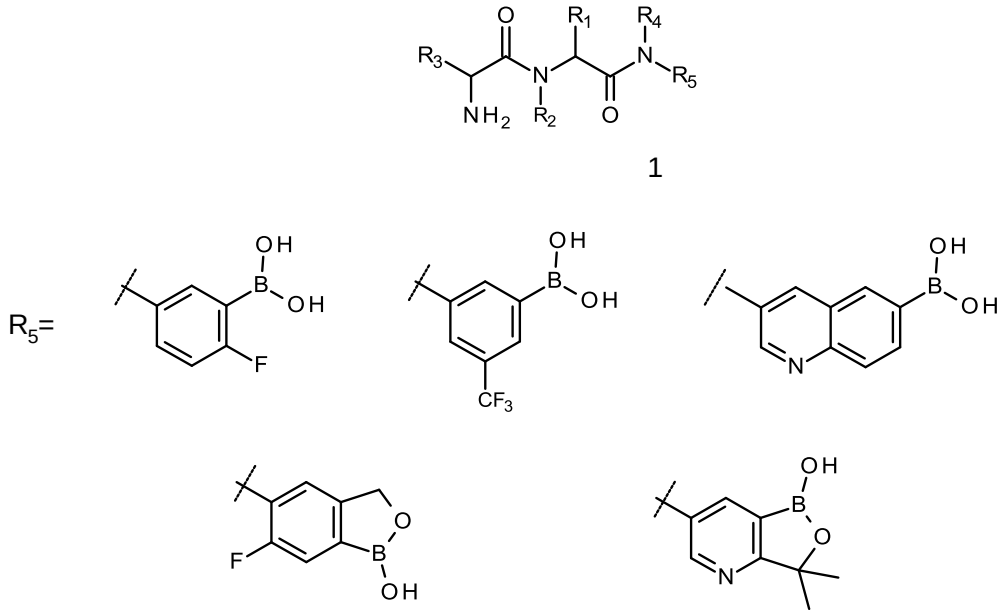
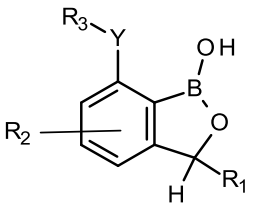
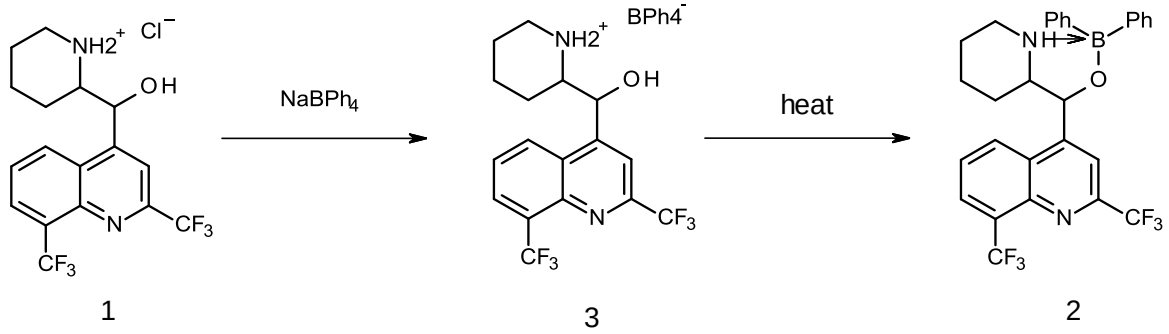


Figure 1.8 The structures of active boron-containing compounds against *Mycobacterium tuberculosis.*

Other inventions provide a compounds having a following general structure to be active against *Mycobacterium tuberculosis*.[36,37]

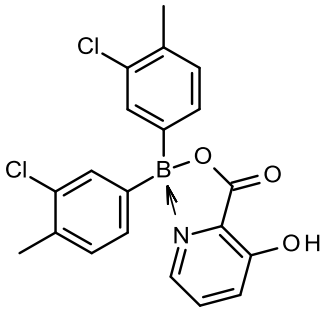


In 2010 the anti-tubercular activity of oxazolidine derivatives of mefloquine, formed by reaction of mefloquine with arene aldehydes has been described.[38] Following on from this study, an oxazaborolidine derivative of mefloquine, namely diphenyl[(*R**,*S**)-(2,8-bis(trifluoromethyl)quinolin-4-yl)]piperidin-2-yl-methanolato- O,N]boron **2** was synthesized by thermolysis of erythro-(±)-mefloquinium tetraphenylborate, **3**, as shown in Scheme 1.2. Both compounds display antitubercular activities as indicated by the minimum inhibitory concentrations (MIC) of 50 and 12.5 μg/ml, respectively, in vitro assays against M. tuberculosis H37Rv ATTC 27294.[39]



Scheme 1.2 Formation of **2** and **3**.

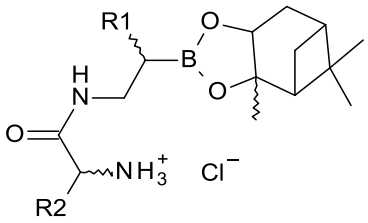
Similar structure have been shown to have a broad spectrum antibacterial activity including *Mycobacterium tuberculosis* ATCC 25177.[40]

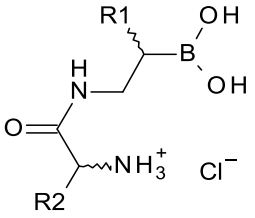


Huilin Li determined the inhibition mechanism of the dipeptidyl boronate N-(4-morpholine)carbonylb-(1-naphthyl)-L-alanine-L-leucine boronic acid (MLN-273). The

boron-containing peptide structure improves perspectives for designing *Mycobacterium tuberculosis* specific proteasomal inhibitors which could be a novel approach to chemotherapy of tuberculosis.[41]

Recently it has been demonstrated in our laboratory that β-aminoboronic peptides (general scaffold is outlined below) turn out to be active against *Mycobacterium tuberculosis* in concentrations as low as 5 μg/mL.[42,43]





These results seem to be very promising and therefore it has been decided to continue this investigation by synthesis of α-aminoboronic peptides and test them as potential antimycobacterial agents.

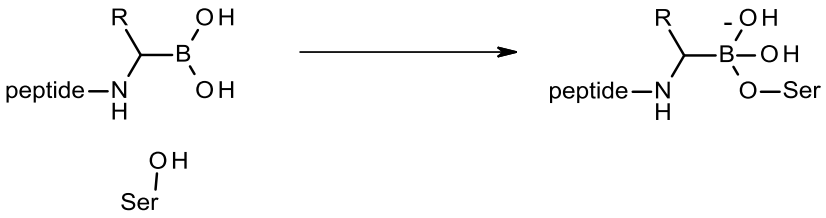
1.3. Boron-Containing Enzyme Inhibitors: Structure and Activity

In recent years the application of boronic acids as therapeutics was broadened into the wide area of protein inhibition. In medicinal chemistry, the use of boronic acids as enzyme inhibitors reflects the value of boron as a carbon analog in the binding process.

Boronic acids represent a large class of enzyme inhibitors[44,45] and have been used for the development of inhibitors of peptidases/proteases,[46-48] kinases,[49-51] proteasomes,[52-54] arginase,[55] as well as transpeptidases.[56]

Most results have been reported in the field of serine proteases.[57,58] Several simple aryl or alkyl boronic acids were recognized as serine protease inhibitors already in the 1970s.[59-62] Since then, a large amount of various boronic acid compounds with appropriate peptide sequences have been produced to be used as more potent and selective inhibitors.[63-65]

When boron containing enzyme inhibitor is examined as a drug, its specificity is very important to avoid some undesirable effects. For example, improved specificity of potent boron containing peptide analogues was achieved by the development of the α-aminoalkylboronic acid analogues of ordinary α-amino acids. The most common mechanism of inhibition is the formation of a tetracoordinate boronate complex by coordination of the hydroxyl nucleophile of the active serine part, imitating the tetrahedral intermediate for amidolysis as outlined in Scheme 1.3.[66,67]



Scheme 1.3 The proposed mechanism of binding of peptide boronic acid by the serine protease hydroxyl group.

Other inhibition mechanisms have been identified, for example, the formation of covalent adducts with histidine residues in the active site.[68-70] When it was compared with aldehyde-based inhibitors of hydrolytic enzymes, the easy transformation of boronic acids to their sp^3 form makes them better transition state analogues.[71]

Protein kinases form a large family of enzymes that catalyze the transfer of the terminal phosphoryl group of ATP (Adenosine-5'-triphosphate) to their specific protein substrates.

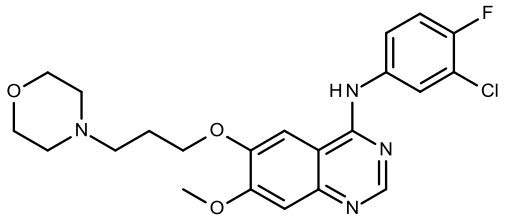
It has been demonstrated that protein phosphorylation controls many aspects of cellular function such as metabolism, division, movement, survival and death. So any disorder of normal phosphorylation can change cell function and cause disease.[72]

Kinases are broadly investigated due to their significant role in signal transduction and diseases.[73,74] Small-molecule kinase inhibitors are the subject of increasing interest, both as

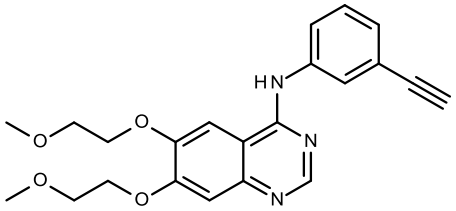
experimental tools for understanding the physiological roles of these enzymes and as potential therapeutics. Therefore, the attention of chemists over the past decades has been devoted to the synthesis, identification, and development of such compounds. Actually, 20-30% of pharmaceutical discovery programs are focused on kinases.[75,76]

The main problem of many kinase inhibitors is lack of specificity.[73] This might be explained by the common fold and similar ATP-binding site that many kinases share.[77]

Nakamura reported the prolonged inhibitory activity of a boron-conjugated 4-anilinoquinazoline toward the EGFR (epidermal growth factor receptor) tyrosine kinase.[49,78] This investigation was based on Fry and co-workers report concerning 4-anilinoquinazoline (PD 153035) as a specific inhibitor toward EGFR tyrosine kinase.[79] Since their discovery, various 4-anilinoquinazoline derivatives have been synthesized, and ZD-1839 (Iressa™),[80] and OSI-774 (Tarceva™)[81,82] have been developed as inhibitors of EGFR kinase and approved for non-small-cell lung cancer (NSCLC) therapy.



Iressa



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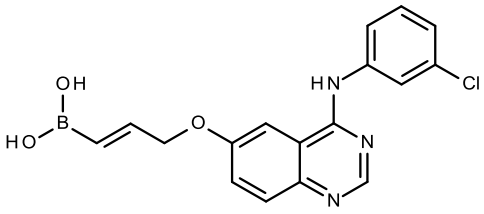
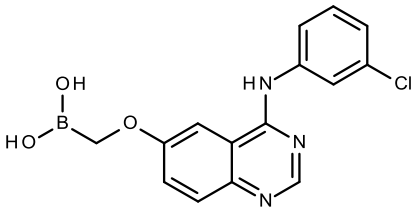




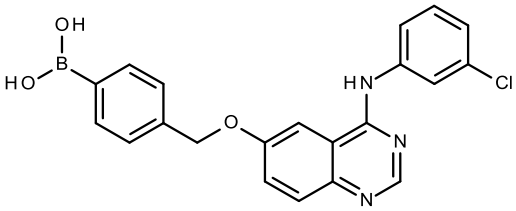


Figure 1.9 The structures of ZD-1839 (Iressa™), OSI-774 (Tarceva™), and their boron-containing analogues.

Several groups have reported the synthesis of N-*boc*-5-sulfonamidoindolil-2-boronic acid for the preparation of novel KDR (kinase insert domain receptor) kinase inhibitors.[83,84]

Protein kinases have preferences for substrates, which are detected by the so-called recognition motif. This sequence represents specific amino acids neighboring the phosphorylation component and it is significant in substrate recognition by the protein kinase. Peptides that mimic this part possess the potential to be substrate competitive inhibitors.

Fewer peptide substrate-competitive inhibitors of kinase than ATP-competitive ligands have been reported. The peptide inhibitors are, however, ideal for combinatorial chemical strategies. A library of small-peptide inhibitors of protein kinase have been created.[85]

Macrocyclic tetrapeptide mimetics possess activity as inhibitor of tyrosine kinases which is an attractive target for therapeutic intervention in many types of cancer (Figure 1.10).[86]

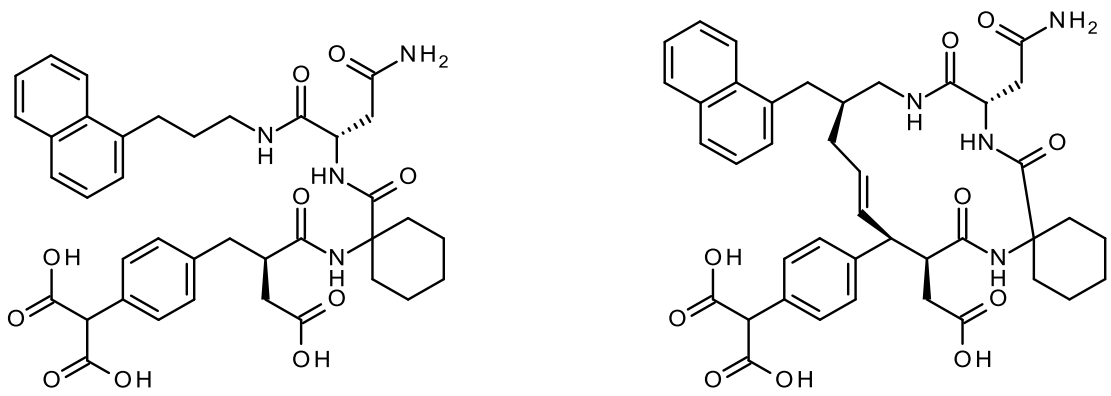


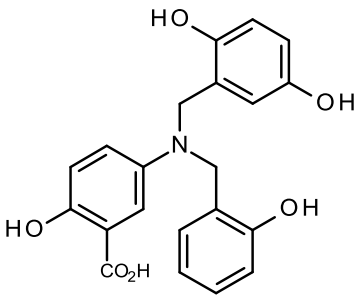
Figure 1.10 The structures potent non-phosphorus containing peptide mimetic that exhibits significant antiproliferative (cell grow inhibition) effects against breast cancer.

The progress in the development of a strong substrate-mimetic inhibitor of serine/threonine protein kinase has been reported.[87] Synthetic short peptides derived from the PKI (protein kinase inhibitors) sequence (5-22 residues) are effective inhibitors of protein kinase as well.[88,89] So peptides or small compounds that mimic the interaction of HM (hydrophobic motif) with so-called 'PIF pocket' (substrate-docking site of kinase) may function as activators of PDK1(phosphoinositide-dependent protein kinase).[90]

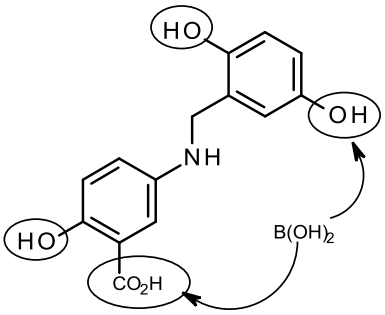
Small tyrosine kinase inhibitor peptide mimetics that binds to the auto-phosphorylation site of tyrosine kinases has been developed, which is another approach to the development of a novel endogenous (developing from within) antiviral pathway. [91]

Some researchers are focused in their investigations of boronic acid-based inhibitors of different tyrosin kinases on the active pharmacophore 1 of lavendustin A.

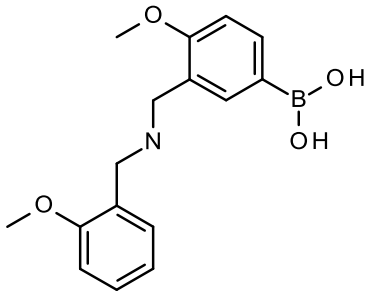
Lavendustin A is the EGFR (epidermal growth factor receptor) protein tyrosine kinase (PTK) inhibitor obtained from a butyl acetate extraction of a *Streptomyces grisolovendus* culture filtrate.[92] The active pharmacophore **2** is a secondary amine containing three phenolic hydroxyl group and a carboxyl group. It was considered to react with EGFR-PTK by employment of hydrogen bonds formed by these functional groups. Inhibition properties were supposed to become better by replacing those hydroxyl and carboxyl groups with boronic acid groups. A series of aminoboronic acids has been synthesized based on the structure of lavendustin **1** pharmacophore **2** (Figure 1.11).[93-97] Their inhibitory activity against the protein tyrosine kinases and several protein kinases was investigated.



1. Lavendustin A



2. active pharmacophore



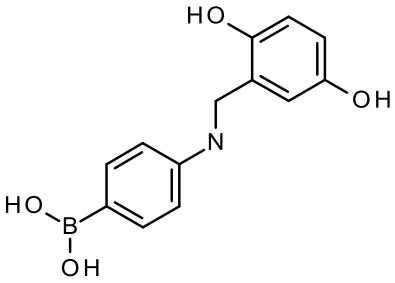


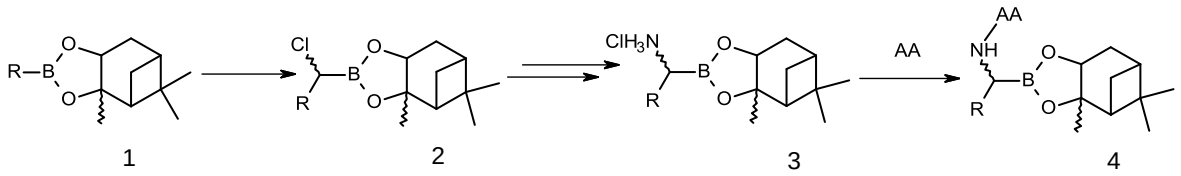
Figure 1.11 Introduction of a boronic acid group into the active pharmacophore of lavendustin A.

Some inhibition activity detected in a series of aminoboronic acids as well. 4-Methoxy-3-((2 methoxyphenylamino)methyl)-phenylboronic acid inhibited EGFR tyrosin kinase, whereas 4-(2,5-dihydroxybenzy-l-amino) phenylboronic acid displayed inhibitory activity of protein kinase. The selective inhibition of enzymes quite often is considered to be due to the substitution of some of the hydroxy groups or carboxyl group of an inhibitor for a boronic acid group.

1.4. Essential chemical background

In this study range of α-aminoboronic peptides have been synthesized and tested on different bacteria strains and their enzyme inhibition properties have been established. The synthetic process includes two major steps: the synthesis of α-aminoboronic acid derivatives

3 (Chapter 3.1) and coupling of them with different L-amino acids (AA) (Chapter 3.2) as shown in Scheme 1.4.



Scheme 1.4 The general route of synthesis of α-aminoboronic peptides.

A general synthetic route to chiral α-aminoboronic acid derivatives **3** by stereoselective homologation of pinanediol boronic esters **1** has been established by Matteson.[71,98] This allowed the synthesis of many potent boronic acid based enzyme inhibitors. Some after several modifications of this general route have been developed and used for the synthesis of different kinds of enzyme inhibitors.[99-101]

This methodology has been successfully applied for the synthesis of a various natural products such as (2*S*, 3*R*, 1'*R*) - stegobinone, (-) - microcarpalide, Velcade® (the first successfully developed boron containing pharmaceutical used in the treatment of multiple myeloma).[102-107]

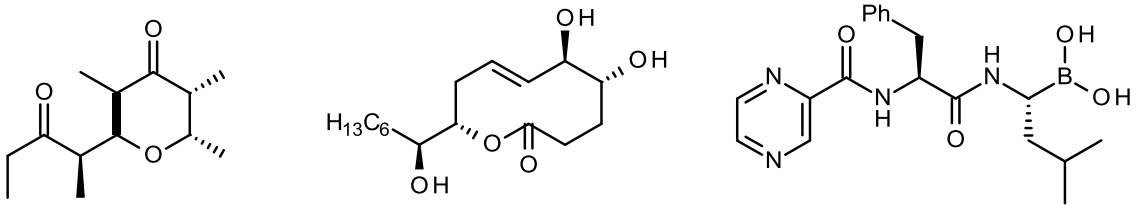


Figure 1.12 The structures of (2*S*, 3*R*, 1'*R*) - stegobinone, (-) - microcarpalide, Velcade®.

Peptide coupling has been performed applying the solution phase methodology yielding desired α-aminoboronic peptides **4**.

1.5. References

1. Miyaura, N., K. Yamada, and A. Suzuki, *A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides.* Tetrahedron Letters, 1979. **20**(36): pp. 3437-3440.
2. Thakur, A., K. Zhang, and J. Louie, *Suzuki-Miyaura coupling of heteroaryl boronic acids and vinyl chlorides.* Chemical Communications, 2012. **48**(2): pp. 203-205.
3. Oberli, M.A. and S.L. Buchwald, *A General Method for Suzuki–Miyaura Coupling Reactions Using Lithium Triisopropyl Borates.* Organic Letters, 2012. **14**(17): pp. 4606-4609.
4. Petasis, N.A. and I.A. Zavialov, *A New and Practical Synthesis of α-Amino Acids from Alkenyl Boronic Acids.* Journal of the American Chemical Society, 1997. **119**(2): pp. 445-446.
5. Latta, R., G. Springsteen, and B. Wang, *ChemInform Abstract: Development and Synthesis of an Arylboronic Acid Based Solid-Phase Amidation Catalyst.* ChemInform, 2001. **32**(51): pp. 1611-1613.
6. Yang, W., et al., *Catechol pendant polystyrene for solid-phase synthesis.* Tetrahedron Letters, 2002. **43**(36): pp. 6339-6342.
7. Brown, H.C. and B.C.S. Rao, *A New Technique for the Conversion of Olefins into Organoboranes and Related Alcohols.* Journal of the American Chemical Society, 1956. **78**(21): pp. 5694-5695.
8. Hall, D. G., *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*. Wiley-VCH, Weinheim, 2005.
9. Matterson, D. S., *Stereodirected Synthesis with Organoboranes.* Springer, Berlin, 1995.
10. Brown, H. C., *Organic Synthesis via Boranes*, Wiley, New York, 1975.
11. Gallwitz, B., *Sitagliptin: profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes (update)* Drugs Today, 2007. **43**(11): pp.801–814.

12. Menashe, J., *Managing and avoiding bortezomib toxicity.* Community Oncology, 2007. **4**(8): pp. 480-484.
13. Wu, K., et al., *Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice.* Haematologica, 2005. **90**(7): pp. 996-997.
14. Adams, J., *Protein homeostasis in cancer.* ACS ProSpectives: the discovery and selection of successful drug candidates. Boston, MA , USA, 29 April –2 May 2007.
15. Soloway, A.H., et al., *The Chemistry of Neutron Capture Therapy.* Chemical Reviews, 1998. **98**(4): pp. 1515-1562.
16. Spielvogel, B.F., A. Sood, B. R. Shaw and I. H. Hall, *From boron analogues of amino acids to boronated DNA: potential new pharmaceuticals and neutron capture agents.* Pure Appl. Chem., 1991. **63**(3): pp. 415-418.
17. Kohno, J., et al., *Boromycin, an Anti-HIV Antibiotic.* Bioscience, Biotechnology, and Biochemistry, 1996. **60**(6): pp. 1036-1037.
18. Moore, B.S. and C. Hertweck, *Biosynthesis and attachment of novel bacterial polyketide synthase starter units.* Natural Product Reports, 2002. **19**(1): pp. 70-99.
19. Stensen, W., Leeson, F.A., Rekdal, O., Svendsen, J.S., *Antimicrobial peptides.* PCT Int. Appl. (2010), WO 2010038041.
20. Stensen, W., Haug, B.E., Rekdal, O., Svendsen, J.S., *Preparation of tripeptide amides as antimicrobial agents.* PCT Int. Appl. (2009), WO 2009081152.
21. Haug, B. E., Stensen, W., Kalaaji, M., Rekdal, O., Svendsen, J.S., *Synthetic Antimicrobial Peptidomimetics with Therapeutic Potential.* Journal of Medicinal Chemistry, 2008. **51**(14): pp. 4306-4314.
22. Bean, F.R. and J.R. Johnson, *Derivatives of Phenylboric Acid, Their Preparation and Action upon Bacteria. II. Hydroxyphenylboric Acids1.* Journal of the American Chemical Society, 1932. **54**(11): pp. 4415-4425.

23. Torssell, K., J. H. McLendon, G. F. Somers, *Chemistry of Arylboric Acids. VIII. The Relationship between Physico-chemical Properties and Activity in Plants.* Acta Scand. Chem., 1958. 12: pp. 1373–1385.

24. Settepani, J. A., J. B. Stokes and A. B. Borkovek, *Control and management of insect populations by chemosterilants.* J. Med. Chem. 1970. 13: pp. 128 –131.

25. Vogels, C.M., et al., *ChemInform Abstract: Synthesis and Antifungal Properties of Benzylamines Containing Boronate Esters.* ChemInform, 2002. **33**(2): pp. 1115-1123.

26. Irving, A.M., et al., *Synthesis and antifungal and antibacterial bioactivity of cyclic diamines containing boronate esters.* New Journal of Chemistry, 2003. **27**(10): pp. 1419-1424.

27. Caselli, E., et al., *Energetic, structural, and antimicrobial analyses of β-lactam side chain recognition by β-lactamases.* Chemistry & Biology, 2001. **8**(1): pp. 17-31.

28. Morandi, F., et al., *Nanomolar Inhibitors of AmpC β-Lactamase.* Journal of the American Chemical Society, 2002. **125**(3): pp. 685-695.

29. Crompton, I. E., Cuthbert, B. K., Lowe, G., Waley, S. G., *Beta-lactamase inhibitors. The inhibition of serine beta-lactamases by specific boronic acids.* The Biochemical journal, 1988. **251**(2): pp. 453-459.

30. Chen, C.C.H., et al., *Structure of a Phosphonate-inhibited β-Lactamase: An Analog of the Tetrahedral Transition State/Intermediate of β-Lactam Hydrolysis.* Journal of Molecular Biology, 1993. **234**(1): pp. 165-178.

31. Strynadka, N.C.J., et al., *Structure-based design of a potent transition state analogue for TEM-1 β-lactamase.* Nat Struct Mol Biol, 1996. **3**(8): pp. 688-695.

32. Kiener, P.A. and S.G. Waley, *Reversible inhibitors of penicillinases.* Biochem. J., 1978. **169**(1): pp. 197-204.

33. Beesley, T., et al., *The inhibition of class C β-lactamases by boronic acids.* Biochem. J., 1983. **209**(1): pp. 229-230.

34. Lee, V., Plattner, J. J., Benkovic, S. J., Baker, S. J., Maples, K. R., et al. *Preparation of hydrolytically-resistant borole derivatives as antibacterial and antiviral therapeutics.* PCT Int. Appl. (2005), WO 2005013892.
35. Glinka, T., Higuchi, R., Hecker, S., Eastman, B., Rodny, O., *Boron-containing polybasic bacterial efflux pump inhibitors and therapeutics uses thereof.* PCT Int. Appl. (2012), WO 2012109164.
36. Hernandez, V. S., Ding, C., Plattner, J. J., et al., *Boron-containing small molecules.* PCT Int. Appl. (2012), WO 2012033858.
37. Baker, S. J., Sanders, V., Akama, T., Bellinger-Kawahara, C., Freund, Y., Maples, K. R., Plattner, J. J., et al., *Boron-containing small molecules as anti-inflammatory agents.*, PCT Int. Appl. (2007), WO 2007095638.
38. Goncalves, R.S.B., et al., *ChemInform Abstract: Synthesis and Antitubercular Activity of New Mefloquine-Oxazolidine Derivatives.* ChemInform, 2011. **42**(14): pp. 6095-6100.
39. Wardell, J.L., et al., *Mefloquine derivatives: Crystal structures and anti-tubercular activities of diphenyl[((R*,S*)-2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl-methanolato-O,N]boron and (±)-erythro-mefloquinium tetraphenylborate solvates.* Journal of Molecular Structure, 2011. **990**(1–3): pp. 67-74.
40. Weimin, M., Kohut, L., Khan, J., and M.R.K., *A Novel Synthetic Boronic Acid Ester with A Broad Spectrum of Antibacterial Activity,* Alley American Academy of Dermatology, 64th Annual Meeting. March 3 - 7, 2006, San Francisco, CA.
41. Hu, G., et al., *Structure of the Mycobacterium tuberculosis proteasome and mechanism of inhibition by a peptidyl boronate.* Molecular Microbiology, 2006. **59**(5): pp. 1417-1428.
42. Gorovoy, A.S., Gozhina, O.V., Svendsen, J.S., Domorad, A.A., Tetz, G.V., Tetz V.V. and Lejon, T., *Boron containing peptidomimetics – a novel class of selective anti-tubercular drugs.* Chemical Biology & Drug Design (accepted)

43. Gorovoy, A.S., Gozhina, O.V., Svendsen, J.S., and Lejon, T., Patent GB 1200338.0 Filing date 9 January 2012
44. Dembitsky, V.M., et al., *Natural occurrence of boron-containing compounds in plants, algae and microorganisms.* Plant Science, 2002. **163**(5): pp. 931-942.
45. Baker, S.J., et al., *Therapeutic potential of boron-containing compounds.* Future Medicinal Chemistry, 2009. **1**(7): pp. 1275-1288.
46. Venkatraman, S., et al., *Potent inhibitors of HCV-NS3 protease derived from boronic acids.* Bioorganic & Medicinal Chemistry Letters, 2009. **19**(1): pp. 180-183.
47. LeBeau, A.M., et al., *Potent and Selective Peptidyl Boronic Acid Inhibitors of the Serine Protease Prostate-Specific Antigen.* Chemistry & Biology, 2008. **15**(7): pp. 665-674.
48. Albers, H., et al., *Discovery and optimization of boronic acid based inhibitors of autotaxin.* Journal of Medicinal Chemistry, 2010. **53**(13): pp. 4958-67.
49. Nakamura, H., et al., *Selective inhibition of EGFR and VEGFR2 tyrosine kinases controlled by a boronic acid substituent on 4-anilinoquinazolines.* Med.Chem.Comm, 2010. **1**(4): pp. 282-286.
50. Morgillo, F., et al., *Antitumor activity of bortezomib in human cancer cells with acquired resistance to anti-epidermal growth factor receptor tyrosine kinase inhibitors.* Lung Cancer, 2011. **71**(3): pp. 283-290.
51. Li, Q.-F., et al., *Bortezomib and sphingosine kinase inhibitor interact synergistically to induces apoptosis in BCR/ABl+ cells sensitive and resistant to STI571 through down-regulation Mcl-1.* Biochemical and Biophysical Research Communications, 2011. **405**(1): pp. 31-36.
52. Groll, M., et al., *Crystal Structure of the Boronic Acid-Based Proteasome Inhibitor Bortezomib in Complex with the Yeast 20S Proteasome.* Structure, 2006. **14**(3): pp. 451-456.

53. Labutti, J., et al., *Oxidative Deboronation of the Peptide Boronic Acid Proteasome Inhibitor Bortezomib: Contributions from Reactive Oxygen Species in This Novel Cytochrome P450 Reaction.* Chemical Research in Toxicology, 2006. **19**(4): pp. 539-546.
54. Milo, L.J., et al., *Chemical and Biological Evaluation of Dipeptidyl Boronic Acid Proteasome Inhibitors for Use in Prodrugs and Pro-Soft Drugs Targeting Solid Tumors.* Journal of Medicinal Chemistry, 2011. **54**(13): pp. 4365-4377.
55. Cama, E., et al., *Inhibitor Coordination Interactions in the Binuclear Manganese Cluster of Arginase.* Biochemistry, 2004. **43**(28): pp. 8987-8999.
56. Zervosen, A., et al., *Synthesis and evaluation of boronic acids as inhibitors of Penicillin Binding Proteins of classes A, B and C.* Bioorganic & Medicinal Chemistry, 2012. **20**(12): pp. 3915-3924.
57. Matteson, D.S., *α-Amido boronic acids: A synthetic challenge and their properties as serine protease inhibitors.* Medicinal Research Reviews, 2008. **28**(2): pp. 233-246.
58. Yang, W., X. Gao, and B. Wang, *Boronic acid compounds as potential pharmaceutical agents.* Medicinal Research Reviews, 2003. **23**(3): pp. 346-368.
59. Lienhard, G.E. and K.A. Koehler, *2-Phenylethaneboronic acid, a possible transition-state analog for chymotrypsin.* Biochemistry, 1971. **10**(13): pp. 2477-2483.
60. Rawn, J.D. and G.E. Lienhard, *Binding of boronic acids to chymotrypsin.* Biochemistry, 1974. **13**(15): pp. 3124-3130.
61. Bauer, C.-A. and G. Pettersson, *Effect of Boric Acid on the Catalytic Activity of Streptomyces griseus Protease 3.* European Journal of Biochemistry, 1974. **45**(2): pp. 473-477.
62. Matthews, D.A., et al., *X-ray crystallographic study of boronic acid adducts with subtilisin BPN' (Novo). A model for the catalytic transition state.* Journal of Biological Chemistry, 1975. **250**(18): pp. 7120-7126.

63. Jun, H. and O.D.A. Jun'ichi, *Aminophosphonic and Aminoboronic Acids as Key Elements of a Transition State Analogue Inhibitor of Enzymes.* Bioscience, Biotechnology, and Biochemistry, 1997. **61**(2): pp. 211-218.
64. Dicko, A., Bui-Van, T., Baboulene, M., Dousset, B., *γ-Amino-boronic acids mediated passive transport of glycopyranosides through a liquid organic membrane.* Main Group Metal Chem. 2001. **24**(1): pp. 15-20.
65. Knott, K., et al., *N-Terminal peptidic boronic acids selectively inhibit human ClpXP.* Organic & Biomolecular Chemistry, 2010. **8**(15): pp. 3451-3456.
66. Kettner, C.A. and A.B. Shenvi, *Inhibition of the serine proteases leukocyte elastase, pancreatic elastase, cathepsin G, and chymotrypsin by peptide boronic acids.* Journal of Biological Chemistry, 1984. **259**(24): pp. 15106-15114.
67. Smoum, R., et al., *Boron Containing Compounds as Protease Inhibitors.* Chemical Reviews, 2012. **112**(7): pp. 4156-4220.
68. Tsilikounas, E., C.A. Kettner, and W.W. Bachovchin, *Boron-11 NMR spectroscopy of peptide boronic acid inhibitor complexes of α-lytic protease. Direct evidence for tetrahedral boron in both boron-histidine and boron-serine adduct complexes.* Biochemistry, 1993. **32**(47): pp. 12651-12655.
69. Stoll, V.S., et al., *Differences in Binding Modes of Enantiomers of 1-Acetamido Boronic Acid Based Protease Inhibitors: Crystal Structures of γ-Chymotrypsin and Subtilisin Carlsberg Complexes.* Biochemistry, 1998. **37**(2): pp. 451-462.
70. Bone, R., et al., *Serine protease mechanism: structure of an inhibitory complex of α-lytic protease and a tightly bound peptide boronic acid.* Biochemistry, 1987. **26**(24): pp. 7609-7614.
71. Matteson, D.S., K.M. Sadhu, and G.E. Lienhard, *R-1-Acetamido-2-phenylethaneboronic acid. A specific transition-state analog for chymotrypsin.* Journal of the American Chemical Society, 1981. **103**(17): pp. 5241-5242.

72. Cohen, P., *Protein kinases - the major drug targets of the twenty-first century?* Nat Rev Drug Discov, 2002. **1**(4): pp. 309-315.
73. Davies, S., et al., *Specificity and mechanism of action of some commonly used protein kinase inhibitors.* The Biochemical Journal, 2000. **351**(Pt 1): pp. 95-105.
74. Feldman, R.A., T. Hanafusa, and H. Hanafusa, *Characterization of protein kinase activity associated with the transforming gene product of Fujinami sarcoma virus.* Cell, 1980. **22**(3): pp. 757-765.
75. Bishop, A.C., et al., *A chemical switch for inhibitor-sensitive alleles of any protein kinase.* Nature, 2000. **407**(6802): pp. 395-401.
76. Gray, N.S., et al., *Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors.* Science, 1998. **281**(5376): pp. 533-538.
77. Hanks, S.K., A.M. Quinn, and T. Hunter, *The Protein Kinase Family: Conserved Features and Deduced Phylogeny of the Catalytic Domains.* Science, 1988. **241**(4861): pp. 42-52.
78. Ban, H.S., et al., *Discovery of boron-conjugated 4-anilinoquinazoline as a prolonged inhibitor of EGFR tyrosine kinase.* Organic & Biomolecular Chemistry, 2009. **7**(21): pp. 4415-4427.
79. Fry, D.W., et al., *A Specific Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase.* Science, 1994. **265**(5175): pp. 1093-1095.
80. Wakeling, A.E., et al., *ZD1839 (Iressa).* Cancer Research, 2002. **62**(20): p. 5749-5754.
81. Moyer, J.D., et al., *Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase.* Cancer Research, 1997. **57**(21): pp. 4838-4848.
82. Shepherd, F.A., et al., *Erlotinib in Previously Treated Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2005. **353**(2): pp. 123-132.
83. Fraley, M.E., et al., *Optimization of the indolyl quinolinone class of KDR (VEGFR-2) kinase inhibitors: effects of 5-amido- and 5-sulphonamido-indolyl groups on*

pharmacokinetics and hERG binding. Bioorganic & Medicinal Chemistry Letters, 2004. **14**(2): pp. 351-355.

84. Payack, J.F., et al., *A Concise Synthesis of a Novel Antiangiogenic Tyrosine Kinase Inhibitor.* The Journal of Organic Chemistry, 2004. **70**(1): pp. 175-178.
85. Laudet, B., et al., *Structure-based design of small peptide inhibitors of protein kinase CK2 subunit interaction.* Biochem J, 2007. **408**(3): pp. 363-373.
86. Phan, J., et al., *Crystal Structures of a High-affinity Macrocyclic Peptide Mimetic in Complex with the Grb2 SH2 Domain.* Journal of Molecular Biology, 2005. **353**(1): pp. 104-115.
87. Kayser, K.J., et al., *Modifications of the GSK3β substrate sequence to produce substrate-mimetic inhibitors of Akt as potential anti-cancer therapeutics.* Bioorganic & Medicinal Chemistry Letters, 2007. **17**(7): pp. 2068-2073.
88. Cheng, H.C., et al., *A potent synthetic peptide inhibitor of the cAMP-dependent protein kinase.* Journal of Biological Chemistry, 1986. **261**(3): pp. 989-992.
89. Glass, D.B., et al., *Differential and common recognition of the catalytic sites of the cGMP-dependent and cAMP-dependent protein kinases by inhibitory peptides derived from the heat-stable inhibitor protein.* Journal of Biological Chemistry, 1986. **261**(26): pp. 12166-12171.
90. Engel, M., et al., *Allosteric activation of the protein kinase PDK1 with low molecular weight compounds.* EMBO J, 2006. **25**(23): pp. 5469-5480.
91. Ahmed, C.M., et al., *SOCS-1 Mimetics Protect Mice against Lethal Poxvirus Infection: Identification of a Novel Endogenous Antiviral System.* Journal of Virology, 2009. **83**(3): pp. 1402-1415.
92. Onoda, T., et al., *Isolation of a Novel Tyrosine Kinase Inhibitor, Lavendustin A, from Streptomyces griseolavendus.* Journal of Natural Products, 1989. **52**(6): pp. 1252-1257.

93. Chen, H., et al., *Synthesis and structure-activity studies of a series of [(hydroxybenzyl)amino]salicylates as inhibitors of EGF receptor-associated tyrosine kinase activity.* Journal of Medicinal Chemistry, 1993. **36**(25): pp. 4094-4098.
94. Chen, H., et al., *Structure-Activity Relationships in a Series of 5-[(2,5-Dihydroxybenzyl)amino]salicylate Inhibitors of EGF-Receptor-Associated Tyrosine Kinase: Importance of Additional Hydrophobic Aromatic Interactions.* Journal of Medicinal Chemistry, 1994. **37**(6): pp. 845-859.
95. Nussbaumer, P., et al., *Novel Antiproliferative Agents Derived from Lavendustin A.* Journal of Medicinal Chemistry, 1994. **37**(24): pp. 4079-4084.
96. Mu, F., et al., *Synthesis and Investigation of Conformationally Restricted Analogues of Lavendustin A as Cytotoxic Inhibitors of Tubulin Polymerization.* Journal of Medicinal Chemistry, 2002. **45**(21): pp. 4774-4785.
97. Lepple-Wienhues, A., et al., *Tyrosine Kinases Open Lymphocyte Chloride Channels.* Cellular Physiology and Biochemistry, 2000. **10**(5-6): pp. 307-312.
98. Matteson, D.S. and R. Ray, *Directed chiral synthesis with pinanediol boronic esters.* Journal of the American Chemical Society, 1980. **102**(25): pp. 7590-7591.
99. Matteson, D.S. and D. Majumdar, *Homologation of boronic esters to .alpha.-chloro boronic esters.* Organometallics, 1983. **2**(11): pp. 1529-1535.
100. Matteson, D.S., P.K. Jesthi, and K.M. Sadhu, *Synthesis and properties of pinanediol α-amido boronic esters.* Organometallics, 1984. **3**(8): pp. 1284-1288.
101. Kinder, D.H. and J.A. Katzenellenbogen, *Acylamido boronic acids and difluoroborane analogs of amino acids: potent inhibitors of chymotrypsin and elastase.* Journal of Medicinal Chemistry, 1985. **28**(12): pp. 1917-1925.
102. Hiscox, W.C. and D.S. Matteson, *Asymmetric synthesis of the Japanese beetle pheromone via boronic esters.* Journal of Organometallic Chemistry, 2000. **614–615**(0): pp. 314-317.

103. Matteson, D.S., H.-W. Man, and O.C. Ho, *Asymmetric Synthesis of Stegobinone via Boronic Ester Chemistry.* Journal of the American Chemical Society, 1996. **118**(19): pp. 4560-4566.

104. Matteson, D.S. and M.L. Peterson, *Synthesis of L-(+)-ribose via (S)-pinanediol (αS)-α-bromoboronic esters.* The Journal of Organic Chemistry, 1987. **52**(23): pp. 5116-5121.

105. Davoli, P., et al., *Total synthesis of (-)-microcarpalide, a novel microfilament disrupting metabolite.* Organic & Biomolecular Chemistry, 2004. **2**(1): pp. 38-47.

106. Davoli, P., et al., *Enantioselective total synthesis of (–)-microcarpalide.* Tetrahedron, 2005. **61**(18): pp. 4427-4436.

107. Adams, J., et al., *Potent and selective inhibitors of the proteasome: Dipeptidyl boronic acids.* Bioorganic & Medicinal Chemistry Letters, 1998. **8**(4): pp. 333-338.

2. AIMS OF THE THESIS

The main goal of the project was to develop a library of drug-like α-aminoboronic peptide mimetics and test for antimicrobial activity. An additional aim was to establish the structure-activity relation of the produced peptides in order to optimize design of novel peptide mimetics.

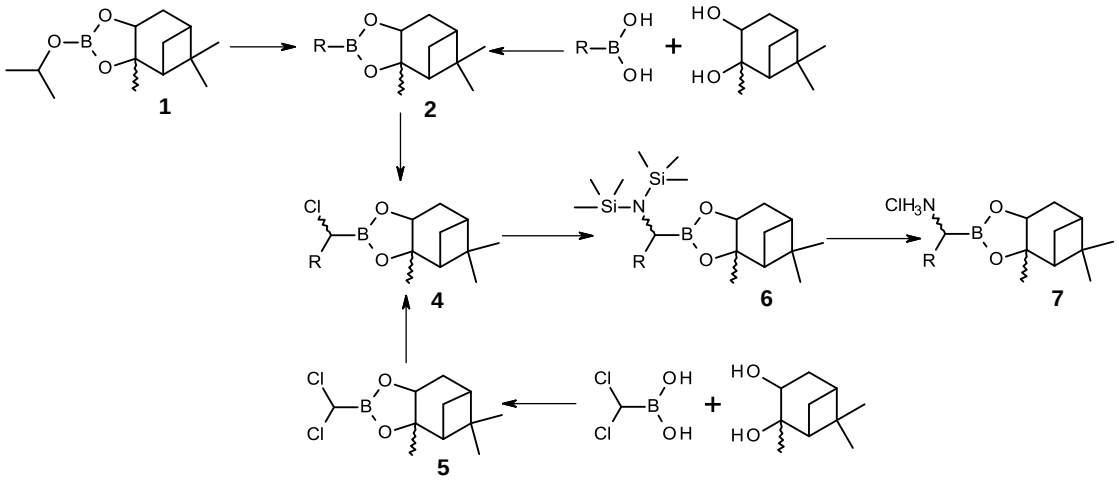
To achieve these main goals the specific aims have been formulated as:

- To develop an efficient synthetic route to α-aminoboronates and α-aminoboronic peptides.
- To test the synthesized compounds on different bacterial strains and investigate kinase inhibition.
- To investigate structure-activity relationship based on the obtained results.

3. RESULTS AND DISCUSSION

3.1. Synthesis of Starting Materials

α-Aminoboronic esters **7** used for peptide synthesis in this investigation were prepared as shown in Scheme 3.1 employing the general strategy developed by Matteson. Matteson homologation of the pinanediol esters **2** yields the α-chloroboronic esters **4**, following treatment of which with hexamethyldisilazane gives the corresponding silylated aminoboronic esters **6** by turn successfully convert into desired hydrochloric salts **7**.



Scheme 3.1 The general route of preparation of α-aminoboronic esters.

3.1.1. Synthesis of Pinanediol

Boronic acids are best handled as ester derivatives, in which both of the hydroxyl groups are protected with diols.[1] Chiral diol protective groups are also needed in order to prevent formation of racemic mixtures of products in Matteson homologation reaction.[2-5] A large number of chiral auxiliary diols have been reported.[1,6-8]

The most common protective diols are pinanediol,[2,5,9] DICHED ((*R*, *R*[1], 2-Dicyclohexyl–1,2–ethandiol)[10,11] and DIPED ((*S*, *S*)–Diisopropylethandiol)[12] (Figure 3.1).

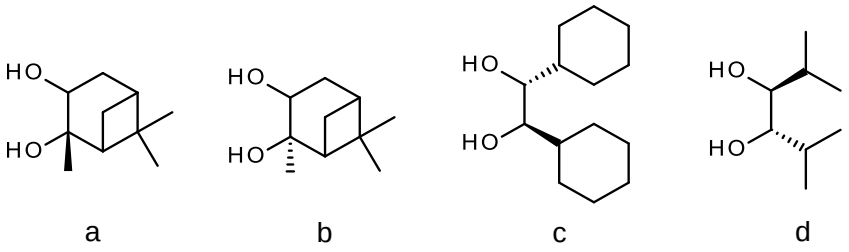


Figure 3.1 The structures of the common chiral auxiliaries: **a**. (1*S*,2*S*,3*R*,5*S*)-(+)-2, 3-Pinanediol, **b**. (1*R*,2*R*,3*S*,5*R*)-(-)-2,3-Pinanediol, **c**. *(R,R)*-(-)-1,2-Dicyclohexyl-1,2-ethanediol, **d**. (*S*, *S*)–Diisopropylethandiol.

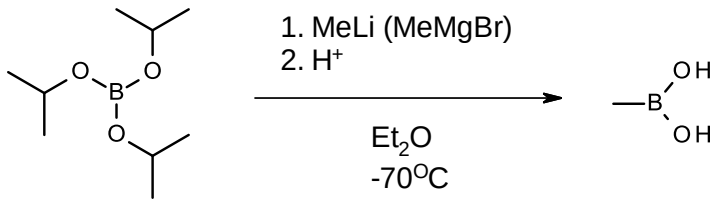
Pinanediol has been chosen for our research as the most easily and cheaply commercially obtainable diol and because it may be prepared in the laboratory from low-cost, technical grade α-pinene.[13,14]

The preparation of both (+)- and (-)-pinanediols followed a well-established procedure[15] by osmium tetraoxide promoted oxidation of (+)– and (-)-α-pinenes respectively.

3.1.2. Synthesis of Methylboronic Acid

Boronic acids are frequently used as synthetic intermediates in various processes, for example, they play an important role in the preparation of α-aminoboronic esters as was shown in the Scheme 3.1, so quite a few successful methods for their synthesis have been developed.

One of the first and most common routes of preparing alkylboronic acids involves the reaction of an organometallic intermediate (e.g. lithium or magnesium) with a borate ester at low temperature as shown in Scheme 3.2.



Scheme 3.2 The synthesis of methylboronic acid.

Free boronic acid is obtained following a standard aqueous workup to hydrolyze the unstable boronic ester. Methylboronic acid can also be synthesized by treating trimethylboroxine (methylboric anhydride) with water.[16,17]

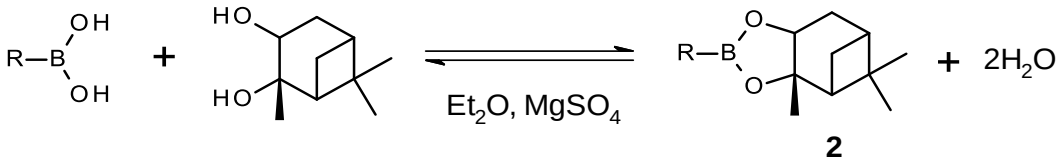
Brown and Cole reported that the interaction of several types of organolithium intermediates with tri*iso*-propyl borate was very effective for the synthesis of boronic acids.[18,19] Trimethyl borate can also be used for this kind of transformation.[20] To help minimize the possible formation of borinic acids and boranes by multiple displacements the reaction procedure includes the dropwise addition of the organolithium to a solution of tri*iso*-propyl borate in diethyl ether cooled to –78 °C.

Two boronic acids have been used for this investigation: phenylboronic acid (which is commercially available) and methylboronic acid synthesized[21] by way of treatment of tri*iso*-propyl borate with methyl lithium at –78 °C as was outlined in Scheme 3.2.

3.1.3. Synthesis of Substituted Boronates

As was mentioned before for convenience in separation, purification and characterization, boronic acids are often best used as their ester derivatives, in which the two hydroxyl groups are protected. Boronic esters are characterized by a satisfactory stability, allowing chromatographic purification of the intermediates and removal of the ester group at the end of the synthetic route (if the acid is needed).

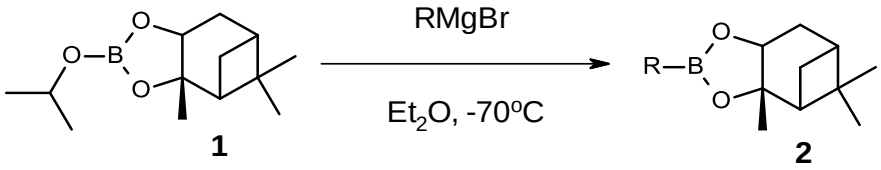
The synthesis of boronic esters **2** from boronic acids and diols is straightforward.[22] The process is an equilibrium as shown in Scheme 3.3, and the course of the reaction is promoted when the boronate product is insoluble in the reaction solvent. Alternatively, ester formation can be driven with the use of a dehydrating agent (e.g., magnesium sulfate) or by azeotropic distillation of the water.



Scheme 3.3 The synthesis of boronic ester from boronic acid and (+)-pinanediol.

Phenyl and methylboronic esters (derived from both (-)- and (+)-pinanediol) were formed from equimolar amounts of the corresponding boronic acid and pinanediol in the presence of magnesium sulfate.[3,8,23,24]

Another synthetic route to various boronic esters **2** was performed by slow addition of Grignard reagent to a solution of *iso*-propoxyboronate **1** in dry ether at low temperature as shown in Scheme 3.4.[25-27,28]



Scheme 3.4 The synthesis of boronic ester from (+)-*iso*-propoxyboronate.

Iso-propoxyboronate **1** by turn was synthesized by refluxing of a mixture of pinanediol and tri*iso*-propoxyborate in anhydrous toluene.[29]

All synthesized compounds are outlined in the Table 3.1. The yields of the boronates are satisfactory with the exception of the 1-naphthyl substituent. In this case home-made Grignard reagent[30] has been used and this caused an unexpected homocoupling reaction with the formation a new carbon-carbon covalent bond. This will be discussed in the following chapter.

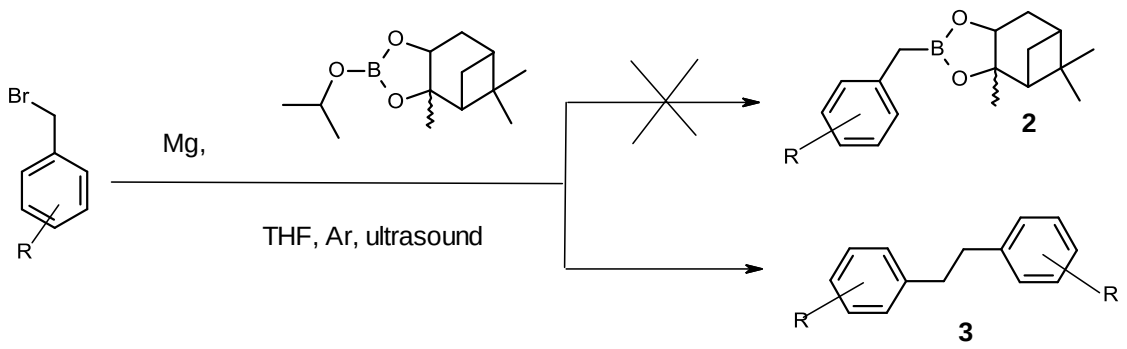
Table 3.1 Synthesized pinanediol boronic esters.

	Compound	Yield, %
2.1	(-)-Pinanediol Methylboronate	98
2.2	(+)-Pinanediol Methylboronate	98
2.3	(-)-Pinanediol *Iso*-propylboronate	75
2.4	(+)-Pinanediol *Iso*-propylboronate	65
2.5	(-)-Pinanediol Phenylboronate	99
2.6	(+)-Pinanediol Phenylboronate	97
2.7	(-)-Pinanediol 4-Fluoro-Phenylboronate	99
2.8	(-)-Pinanediol Benzylboronate	64
2.9	(+)-Pinanediol Benzylboronate	95
2.10	(-)-Pinanediol Phenethylboronate	66
2.11	(+)-Pinanediol Phenethylboronate	88
2.12	(-)-Pinanediol 1-Naphthylmethylboronate	75*

* As a mixture with 1-methylnaphthalene and the coupling product (see next chapter)

3.1.4. Homocoupling reaction promoted by ultrasound

During attempts to synthesize benzylboronates when home-made benzylic Grignard reagents were used unexpected results arose. It was discovered that a homocoupling reaction with formation of a new carbon-carbon bond had occurred yielding a biaryl product **3** instead of aryl boronate **2** as shown in Scheme 3.5.



Scheme 3.5 The formation of coupling product **3** instead of aryl boronate **2.**

The reaction of homocoupling of benzyl halides is well-described in the literature and the biaryl products can be very useful, for example, numerous compounds containing the biaryl component have been used as important intermediates for the synthesis of pharmaceuticals[31] and polymers.[32] Many different methods have already been evolved to reach the efficient way of synthesis of biaryl compounds, among them photolysis of benzyl halides using a variety of experimental techniques,[33,34] flash vacuum pyrolisys over magnesium,[35] electrochemical coupling in lithium perchlorate solution using magnesium electrodes.[36] Other methods include Single Electron Transfer (SET) in the reaction of lithium thiolates with trityl halides, which has been studied in detail.[37] SET is also involved in the chemoselective reductions of vicinal dihalides with magnesium in methanol.[38] The most convenient method for the preparation of biphenyl compounds is the transition-metal-catalyzed direct coupling of corresponding halides. Various nickel,[39-41] palladium,[42-44] cobalt,[45] zinc,[46,47] iron[48-50] and ruthenium[51] catalyst precursors have been reported to support the homocoupling of aryl halides under relatively mild reaction conditions.

Several aryl halides have been investigated in this research and it was found that only primary and secondary benzylic halides react. Aliphatic and aromatic benzyl halides do not undergo of homocoupling reaction in these conditions.

At the beginning it was believed that *iso*-propoxyboronate **1** is a catalyst of this process. However when the reaction was carried out without *iso*-propoxyboronate **1** it was discovered that the homocoupling was promoted by ultrasound which seems to be the easiest

and cheapest reaction condition in comparison with previously described. Ultrasonic promotion of homocoupling could easily be applied in industry.

In all experiments the only by-product detected after work-up was the result of protonation of the initially formed Grignard reagent.

Reactivity seems to be influenced by both steric and electronic factors as yields were lower when the aromatic moiety was substituted with strongly electron withdrawing groups and triphenyl methylbromide did not react at all. (Table 3.2)[52] It has been observed that solvent plays an important role in this interaction as well. Using dry diethyl ether some amount (about 30-50%) of the desired product could be obtained, while carrying the reaction in THF provides only biaryl coupling product.

Table 3.2 Isolated yields from the reaction of homocoupling.

Starting Material	Yield, %
α-Bromomethyl naphtalene	40
9-Bromofluorene	91
Bromo-diphenylmethane	75
α -Bromotoluene	23
4-Bromo- α -bromotoluene	12[a]
4-Methyl- α -bromotoluene	48
2-Methyl- α -bromotoluene	61
2-Bromo- α -bromotoluene	13[a]
3-Bromo- α -bromotoluene	19[a]
3-Methyl- α -bromotoluene	31
3-Trifluoromethyl- α -bromotoluene	28
4-Trifluoromethyl- α -bromotoluene	4[a]
2-Trifluoromethyl- α -bromotoluene	No reaction
α -Chloromethyl naphthalene and 9-Bromofluorene (1:1)	82 [b]

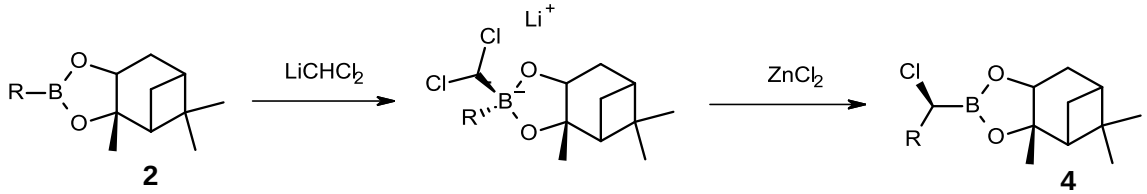
[a] Isolated by preparative TLC

[b] All three possible products were formed

3.1.5. Synthesis of Cl-Containing Intermediates via Matteson Homologation or Nucleophilic Substitution

The synthesis of boron-containing enantiomerically pure compounds has always been a challenge for organic chemists until the early 1980s when Matteson reported a convenient route to chiral boronic esters, the so-called Matteson homologation reaction.[3,8,53,54]

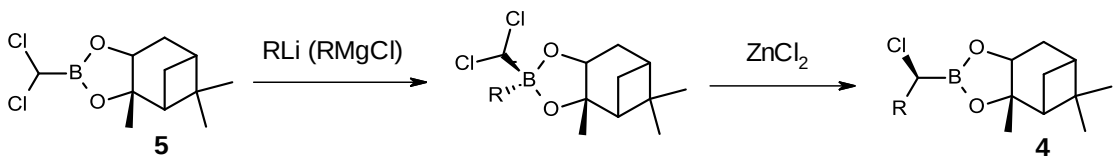
The Matteson homologation involves the reaction of freshly prepared (dichloromethyl)lithium with the boronic ester of chiral diols **2** followed by zinc chloride-promoted rearrangement of the transition $LiCHCl_2$-borate complex yielding a (α-chloroalkyl)boronic ester **4** with a high diastereomeric purity[55] as shown in Scheme 3.6.



Scheme 3.6 The mechanism of Matteson homologation reaction using (+)-pinanediol as chiral auxiliaries.

In this reaction asymmetry can be introduced using an enantiopure chiral diol, e.g. pinanediol,[56-59] 1,2-dicyclohexyl-1,2-ethandiol (DICHED),[60-63] 2,3-butanediol[7,64,65] and cedranediol.[66]

Another route to (α-chloroalkyl)boronic esters **4** is an addition of alkyl lithium or Grignard reagent to a dichloromethaneboronic ester[67] **5** as shown in Scheme 3.7, but this method provides lower level of stereocontrol.[68]



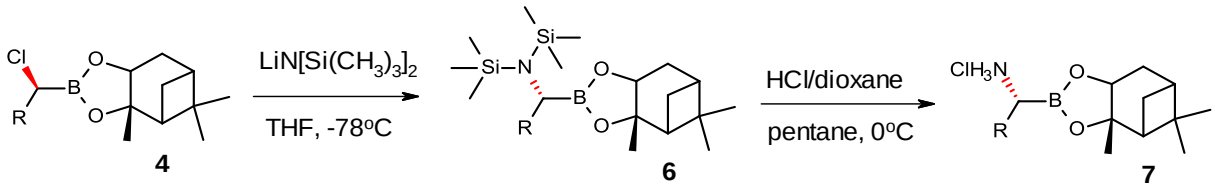
Scheme 3.7 Nucleophilic substitution leading to enantiomerically enriched (α-chloroalkyl)boronic esters **4.**

In the work described in this thesis the synthesis of (α-chloroalkyl)boronic esters **4** was based on both of these methods. At the very beginning it had been decided to use dichloromethaneboronic ester **5** as starting material due to its synthetic availability (it is easily synthesized by stirring dichloromethaneboronic acid with the corresponding pinanediol)[67], but lower yields (compared to Matteson homologation) have been observed. In an attempt to increase the yield and diastereomeric purity, the Matteson homologation was employed for the synthesis of (α-chloroalkyl)boronic esters **4**.

Most of the products were obtained as mixtures with starting materials and forwarded to the next step without purification. All the (α-chloroalkyl)boronic esters **4** were detected and found to be accordance with already published spectroscopic data.[4,5,23,28,54,69,70]

3.1.6. Synthesis of α-Aminoboronic Esters

The last step to α-aminoboronic esters **7** includes the displacement of chloride by a lithium bis(trimethylsilyl)amide group with a reversal of the configuration of a chiral carbon, followed by acidolysis of the intermediate compound **6** yielding α-aminoboronic ester **7** as a hydrochloride salt as outlined in Scheme 3.8.



Scheme 3.8 Synthesis of α-aminoboronic ester **7.**

The nucleophilic substitution reaction involved treating of α-chloroboronic ester **4** with one equivalent of lithium bis(trimethylsilyl)amide in anhydrous THF at -78°C.[71-73] It is important to use anhydrous solvent to obtain high yields of the desired product. Intermediate bis-silane protected amino boronic esters **6** were not isolated due to their complicated

purification and were forwarded to the next step as crude oils (the crude mixture usually contained unhomologated boronic ester **2** and bis-silane protected amino boronic ester **6**).

The reaction of desilylation involved the treatment of silylated compound **6** with anhydrous HCl or trifluoroacetic acid in pentane at 0°C to give the resulting α-aminoboronic ester **7** as a stable hydrochloride salt[67,69,74] or trifluoroacetate salt.[71]

Free α-aminoboronic esters **7** are unstable as a result of the migration of boron from carbon to nitrogen and the generation the corresponding amines as shown in Scheme 3.9.[75]

Rearrangement of this type was observed in the case of 1-naphthylethyl substituent at the chiral carbon. The silylated 1-naphthylethyl compound was isolated as colorless crystals in good yield and X-ray data was obtained (Figure 3.2), but in the course of the desilylation process under acidic conditions this compound proved to be unstable and migration of boron from carbon to nitrogen took place.

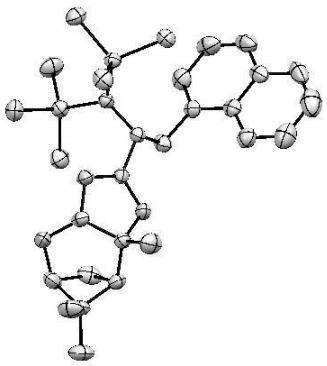
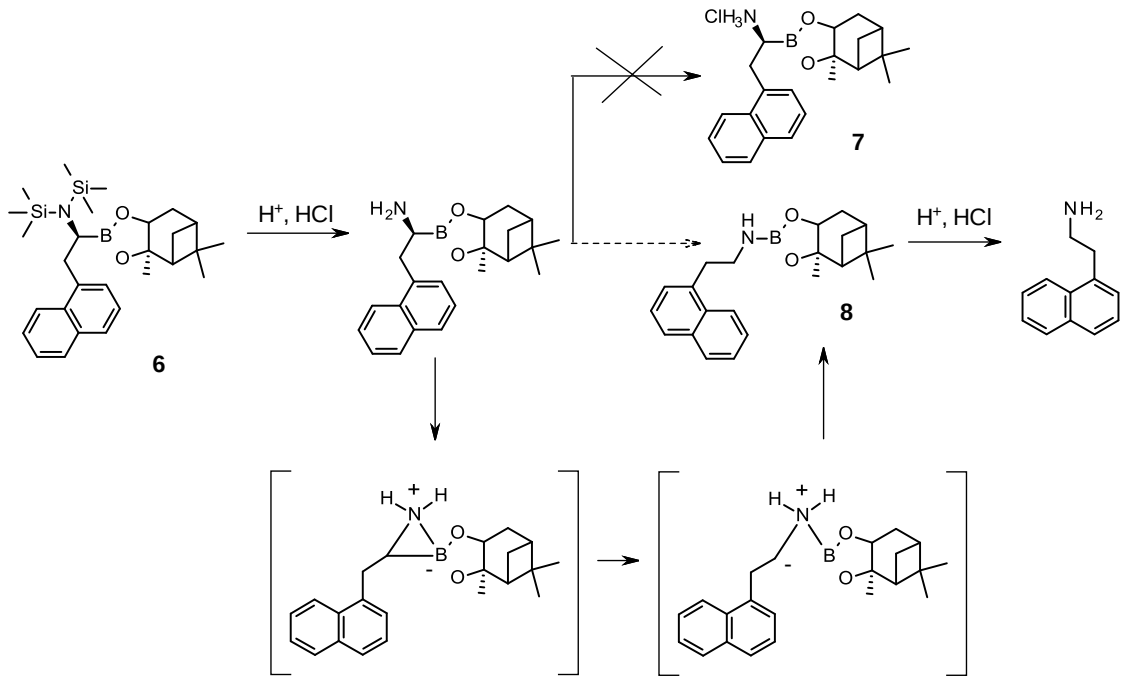


Figure 3.2 The X-ray structure of (-)-pinanediol (1*R*)-[1-bis(trimethylsilyl)amide-2-(1-naphthyl)ethyl]boronate.

In attempts to produce its hydrochloric salt **7** 1-naphthaleneethanamine was unexpectedly obtained with 99% yield. It appears that after desilylation by hydrochloric acid

the rearrangement of free amine occurs faster than the salt formation with help of hydrochloric acid due to steric hindrance.

The mechanism of the destructive rearrangement includes intramolecular nucleophilic attack by the free amino group on boron followed by ring opening and proton migration to form **8** as shown in Scheme 3.9.[25,76] Then the cleavage of nitrogen-boron bond occurs in the presence of protons (e.g. protic solvents, acidic conditions).



Scheme 3.9 The mechanism of the desilylation reaction of (-)-pinanediol (1*R*)-[1-bis(trimethylsilyl)amide-2-(1-naphthyl)ethyl]boronate.

It was suggested that the pinanediol moiety of the molecule could be protonated by hydrochloric acid giving the following structure, but it has not been paid a valuable attention to this.

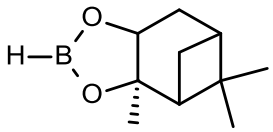


Figure 3.3 The possible structure of pinanediol moiety after acidic cleavage the (-)-pinanediol (1*R*)-[1-bis(trimethylsilyl)amide-2-(1-naphthyl)ethyl]boronate.

All synthesized α-aminoboronic esters **7** are summarized in the Table 3.3. Low yields of some of the products can be explained by their high solubility in dioxane (hydrochloric acid solution in dioxane has been used) or by the purity of the starting materials as well. All the yields were calculated keeping in the mind the impure character of the starting materials and in accordance with conversion degree by proton NMR.

Table 3.3 Isolated yields of α-aminoboronic esters **7.**

	Compound	Yield, %
7.1	(-)-Pinanediol (1*R*)-(1-Aminoethyl)boronate Hydrochloride	43
7.2	(+)-Pinanediol (1*S*)-(1-Aminoethyl)boronate Hydrochloride	22
7.3	(-)-Pinanediol (1*R*)-(1-Amino-2-methylpropyl)boronate Hydrochloride	59
7.4	(+)-Pinanediol (1*S*)-(1-Amino-2-methylpropyl)boronate Hydrochloride	64
7.5	(-)-Pinanediol (1*R*)-(1-Aminobenzyl)boronate Hydrochloride	63
7.6	(+)-Pinanediol (1*S*)-(1-Aminobenzyl)boronate Hydrochloride	49
7.7	(-)-Pinanediol (1*R*)-[1-Amino-(4-fluorophenyl)methyl]boronate Hydrochloride	52
7.8	(-)-Pinanediol (1*R*)-(1-Amino-2-phenylethyl)boronate Hydrochloride	60
7.9	(+)-Pinanediol (1*S*)-(1-Amino-2-phenylethyl)boronate	54

	Hydrochloride	
7.10	(-)-Pinanediol (1*R*)-(1-Amino-3-phenylpropyl)boronate Hydrochloride	18
7.11	(+)-Pinanediol (1*S*)-(1-Amino-3-phenylpropyl)boronate Hydrochloride	47

3.1.7. Experimental Part

THF was freshly distilled from sodium benzophenone ketyl. *n*-Butyllithium 2.7 M in heptane, $ZnCl_2$ 1 M in diethyl ether and all Grignard reagents (with the exception of 1-naphthylmethyl substituted) were purchased from Sigma-Aldrich Co. NMR spectra were recorded on a Varian Mercury 400 plus (399.65/100.54 MHz). ^{13}C NMR spectra were obtained with broadband proton decoupling. Signals from carbons α-to boron were not detected. IR spectra were recorded on a Varian 7000e FT-IR spectrometer. Optical rotation was measured on an AA-10R polarimeter (Optical activity Ltd.). Mass spectra were measured on a Thermo electron LTQ Orbitrap XL + Electrospray ion source (ION-MAX). Samples were dissolved in pure methanol and infused by syringe pump at a flow rate of 5μl/min. No molecular ion was detected for compounds containing boronic acid due to anhydride (boroxine) formation in the ion source.

The positions of characteristic vibration frequencies synthesized compounds are shown in the following table:

Group	Frequency in cm^{-1}
B-C	1100-1185
C-F	1100-1250
B-O	1310-1350
C=O	1670-1820
C-H	2850-3000
N-H	3300-3500

Preparation of (-)-Pinanediol.

In a 1L three-necked, round-bottom flask, fitted with a mechanical stirrer, reflux condenser, and heating mantle were placed (-)-α-pinene (34.3 g, 0.25 mol), N-methylmorpholine N-oxide (62.1 mL. of 50% in water, 1.2 equiv), water (22.5 mL), acetone (250 mL), pyridine (0.25 mL), and osmium tetroxide (0.25 g, 0.98 mmol).

The mixture was heated to reflux while stirring rapidly. After 2-3 days at reflux, the reaction mixture became homogeneous and all of the starting material appeared to be consumed (monitored by mixture color – supposed to become greenish). After cooling in an ice bath, sodium metabisulfite (10 g), magnesol* (5 g), and sodium sulfate (20 g) were added. The mixture was warmed to room temperature while stirring vigorously for 2h and filtered through a pad of Celite. After concentration of the filtrate on a rotary evaporator to remove the acetone, the residue was partitioned between diethyl ether (500 mL) and water (300 mL).

After separation the organic layer was washed with saturated sodium thiosulfate, 2N hydrochloric acid, water, saturated sodium hydrogen carbonate, and brine. The solution was dried over magnesium sulfate and concentrated to brown oil (30.59 g, 71% yield) (pure product according H^1 NMR).

* magnesol was prepared as a mixture of SiO_2/MgO in 2:1 ratio.

^{1}H NMR (400 MHz, Chloroform-d) δ 3.98 (dd, *J* = 9.3, 5.1 Hz, 1H), 2.88 – 2.50 (s,broad, 2H), 2.45 (dddd, *J* = 13.6, 9.3, 3.6, 2.4 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.00 (t, *J* = 5.8 Hz, 1H), 1.91 (tt, *J* = 6.0, 3.0 Hz, 1H), 1.62 (ddd, *J* = 14.0, 5.2, 2.5 Hz, 1H), 1.35 (d, *J* = 10.3 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 0.93 (s, 3H).
$[\alpha]^{23}{}_D$ = -8.84 (c 0.356, toluene)

Preparation of (+)-Pinanediol.

(+)-Pinanediol has been prepared according to exactly the same procedure. (39.62 g, 92% yield)

^{1}H NMR (400 MHz, Chloroform-d) δ 3.99 (dd, *J* = 9.3, 5.1 Hz, 1H), 2.90 – 2.57 (s, broad, 2H), 2.45 (dddd, *J* = 13.6, 9.3, 3.6, 2.4 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.00 (t, *J* = 5.8 Hz, 1H), 1.92 (tt, *J* = 6.0, 3.0 Hz, 1H), 1.62 (ddd, *J* = 14.0, 5.2, 2.5 Hz, 1H), 1.34 (d, *J* = 10.4 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 0.93 (s, 3H).

Preparation of Methylboronic Acid.[21]

Tri*iso*-propyl borate (22.7 mL, 0.1 mol) was added to diethyl ether (60 mL). This was cooled in a dry ice/acetone bath and methyl lithium 1.6 M (66.5 mL, 0.1 mol) was added drop wise. When the addition was complete, the cooling bath was removed and the reaction was allowed to warm to room temperature over three hours.

With vigorous stirring, water (20 mL) was added slowly. The resulting mixture was stirred for 30 minutes. The water layer was separated and the organic layer was extracted once with water (25 mL). The combined water layer was evaporated *in vacuo* at 50°C.

The resulting white solid residue was stirred with diethyl ether (300 mL) and concentrated hydrochloric acid was added slowly until the pH of the aqueous layer stayed at 2.0. The aqueous layer was saturated with sodium chloride (about 25 g) and this two-phase mixture was stirred overnight. Then the ether layer was separated. The aqueous layer was extracted with three portions of ether (150 mL). The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo* at 50°C. The resulting granular solid was treated with pentane (150 mL) and stirred for 30 minutes. After filtration the solid was washed with a little pentane and dried at room temperature to give the title compound (4.6 g, 73% yield).

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 0.20 (s, 3H). (in accordance with literature data)

Preparation of (-)-Pinanediol Methylboronate 2.1.

To the solution of methylboronic acid (0.9 g, 0.015 mol) in diethyl ether (40 mL) was added (-)-pinanediol (2.56 g, 0.015 mol) and of anhydrous magnesium sulfate (0.5g). The mixture was stirred for 3 hours at room temperature. Then magnesium sulfate was filtered off and the solution evaporated in rotovap to give the resulting product (2.86 g, 98% yield) as colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 4.25 (d, J = 8.7 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.27 – 2.17 (m, 1H), 2.03 (t, J = 5.5 Hz, 1H), 1.97 – 1.80 (m, 2H), 1.39 (s, 3H), 1.28 (s, 3H), 1.12 (d, J = 10.9 Hz, 1H), 0.83 (s, 3H), 0.28 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 84.92, 50.84, 39.06, 37.64, 35.00, 28.20, 26.62, 25.98, 23.52.

$[\alpha]^{23}_{D}$ = -45.02° (c 0.422, toluene)

Preparation of (+)-Pinanediol Methylboronate 2.2.

Similarly, methylboronic acid (8.23 g, 0.137 mol) and (+)-pinanediol (23.35 g, 0.137 mol) in diethyl ether (200 mL) and anhydrous magnesium sulfate (3 g) were transformed into (+)-pinanediol methylboronate (26.09 g, 98% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 4.24 (dd, *J* = 8.7, 1.8 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.25 – 2.15 (m, 1H), 2.02 (t, *J* = 5.6 Hz, 1H), 1.95 – 1.78 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 1.11 (d, *J* = 10.9 Hz, 1H), 0.83 (s, 3H), 0.27 (s, 3H).

Preparation of (-)-Pinanediol Phenylboronate 2.5.

To a solution of phenylboronic acid (7.16 g, 0.059 mol) in diethyl ether (150 mL) was added (-)-pinanediol (10 g, 0.059 mol) and anhydrous magnesium sulfate (2 g). The mixture was stirred for 3 hours at room temperature. Then magnesium sulfate was filtered out and the solution evaporated *in vacuo* to give the resulting product (15.13 g, 99% yield) as colorless oil.

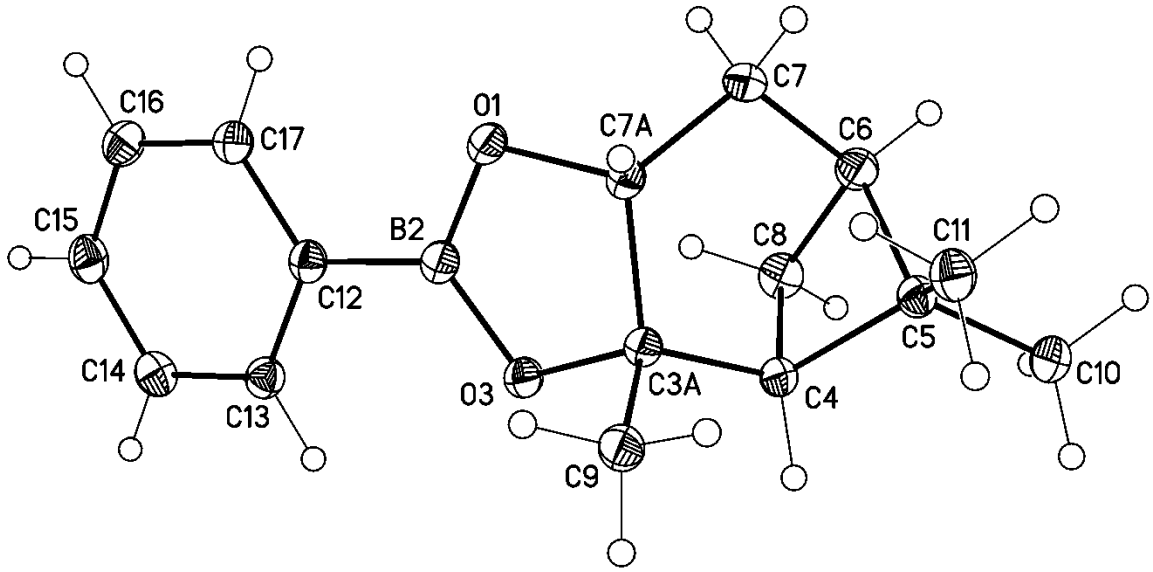
^{1}H NMR (400 MHz, Chloroform-d) δ 7.82 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.56 – 7.34 (m, 3H), 4.46 (dd, *J* = 8.8, 1.9 Hz, 1H), 2.48 – 2.35 (m, 1H), 2.28 – 2.20 (m, 1H), 2.18 – 2.10 (m, 1H), 2.04 – 1.87 (m, 2H), 1.48 (s, 3H), 1.31 (s, 3H), 1.23 (d, *J* = 10.9 Hz, 1H), 0.89 (s, 3H).
$[\alpha]^{23}_{D}$ = -4.2 (c 0.1188, DCM)

Preparation of (+)-Pinanediol Phenylboronate 2.6.

Similarly, phenylboronic acid (7.16 g, 0.059 mol) and (+)-pinanediol (10 g, 0.059 mol) in diethyl ether (150 mL) and anhydrous magnesium sulfate (2 g) were transformed into (+)-pinanediol phenylboronate (14.57 g, 97% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.25 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.63 – 7.35 (m, 3H), 4.46 (dd, *J* = 8.8, 1.9 Hz, 1H), 2.41 (ddd, *J* = 8.6, 8.0, 5.6 Hz, 1H), 2.23 (ddd, *J* = 10.8, 6.1, 2.3 Hz, 1H), 2.15 (d, *J* = 5.9 Hz, 1H), 1.96 (ddd, *J* = 12.2, 5.5, 3.0 Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 1.23 (d, *J* = 10.8 Hz, 1H), 0.90 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 135.62, 134.76, 132.68, 131.15, 127.97, 127.72, 86.22, 78.24, 51.42, 39.54, 38.19, 35.57, 28.71, 27.10, 26.49, 24.04.

The product was crystallized from hexane and X-ray structure was obtained.[77]



X-Ray Crystal Data of (+)-Pinanediol Phenylboronate 2.6.

Empirical formula $C_{16}H_{21}BO_2$, Formula weight 256.14, Temperature 100(2) K, Wavelength 0.71073 Å, Crystal system Orthorhombic, Space group $P2_12_12_1$, Unit cell dimensions a = 8.4974(3) Å = 90°, b = 11.8566(4) Å = 90°, c = 13.9580(4) Å = 90°, Volume 1406.27(8) Å3, Z=4, Density (calculated) 1.210 Mg/m^3, Absorption coefficient 0.076 mm^{-1}, F(000) 552, Crystal size 0.25 x 0.22 x 0.18 mm^3, Theta range for data collection 2.25 to 29.99°, Index ranges -11<=h<=11, -16<=k<=16, -19<=l<=19, Reflections collected 18494, Independent reflections 4095 [R(int) = 0.0322], Completeness to theta = 29.99° 100.0 %, Absorption correction Semi-empirical from equivalents, Max. and min. Transmission 0.986 and 0.981, Refinement method Full-matrix least-squares on F2, Data / restraints / parameters 4095 / 0 / 175, Goodness-of-fit on F2 1.001, Final R indices [for 3876 rflns with I>2σ(I)] R1 = 0.0349, wR2 = 0.0880 R indices (all data) R1 = 0.0375, wR2 = 0.0898, Largest diff. peak and hole 0.245 and -0.259 e.Å^{-3}.

Preparation of (-)-Pinanediol *Iso*-propoxyboronate 1.1.

To a solution of (-)-pinanediol (8 g, 0.047 mol) in anhydrous toluene (70 mL) tri*iso*-propyl borate (10.6 g, 13 mL, 0.056 mol, 1.2 equiv) was added. The reaction mixture was refluxed for 2 hours and then cooled to room temperature. After concentration of the mixture the residue was distilled *in vacuo* (80° C/ 0.8 mbar) to give boronate (10.1 g, 90% yield) as colorless liquid.

^{1}H NMR (400 MHz, Chloroform-d) δ 4.39 – 4.27 (m, 1H), 4.23 (dd, *J* = 8.6, 1.4 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.25 – 2.15 (m, 1H), 2.01 (t, *J* = 5.5 Hz, 1H), 1.94 – 1.77 (m, 2H), 1.37 (s, 3H), 1.26 (s, 3H), 1.19 (d, *J* = 6.2 Hz, 6H), 1.10 (d, *J* = 6.1 Hz, 1H), 0.80 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 84.10, 67.43, 51.57, 39.45, 38.26, 35.78, 28.54, 27.06, 26.34, 24.34, 24.26, 23.94.

Preparation of (+)-Pinanediol *Iso*-propoxyboronate 1.2.

Similarly, reflux of the mixture of (+)-pinanediol (20.69 g, 0.12 mol) and tri*iso*-propyl borate (27.4g, 33.3 mL, 0.145 mol, 1.2 equiv) in anhydrous toluene (250 mL) give the resulting (+)-pinanediol *iso*-propoxyboronate (29.29 g, 99% yield) as pale yellow liquid.

^{1}H NMR (400 MHz, Chloroform-d) δ 4.41 – 4.28 (m, 1H), 4.24 (dd, *J* = 8.7, 1.5 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.22 (ddd, *J* = 10.9, 6.2, 3.2 Hz, 1H), 2.03 (dt, *J* = 11.0, 5.5 Hz, 1H), 1.87 (dq, *J* = 5.1, 3.2 Hz, 2H), 1.37 (s, 3H), 1.26 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 6H), 1.12 (d, *J* = 6.1 Hz, 1H), 0.81 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 84.10, 67.42, 51.59, 39.46, 38.27, 35.79, 28.55, 27.07, 26.35, 24.35, 24.32, 24.27, 23.95.

Preparation of (-)-Pinanediol *Iso*-propylboronate 2.3.

To the solution of (-)-pinanediol *iso*-propyloxy boronate (10 g, 0.042 mol) in the anhydrous diethyl ether (150 mL) *iso*-propylmagnesium chloride 2M (31.5 mL, 0.063 mol, 1.5 equiv) was added drop wise at -70° C. The reaction mixture was stirred at this temperature for 2 hours, then warmed to room temperature and stirred overnight.

To this HCl/dioxane 4M (11.55 mL, 0.0462 mol, 1.1 equiv) was added at -10° C. The mixture was stirred for 1.5 hour, and then filtered through a pad of Celite and evaporated under reduced pressure to yield (7.01 g, 75% yield) of colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 4.23 (dd, *J* = 8.8, 2.0 Hz, 1H), 2.32 (ddt, *J* = 14.0, 8.7, 2.5 Hz, 1H), 2.19 (dtd, *J* = 10.8, 6.2, 2.3 Hz, 1H), 2.03 (t, *J* = 5.6 Hz, 1H), 1.92 – 1.75 (m, 2H), 1.36 (s, 3H), 1.27 (s, 3H), 1.08 (d, *J* = 10.9 Hz, 2H), 0.99 (d, *J* = 7.0 Hz, 6H), 0.83 (s, 3H).

Preparation of (+)-Pinanediol *Iso*-propylboronate 2.4.

Similarly, treatment of the solution of (+)-pinanediol *iso*-propyloxy boronate (20 g, 0.084 mol) in anhydrous diethyl ether (200 mL) by *iso*-propylmagnesium chloride 2M (46.2

mL, 0.092 mol, 1.1 equiv) by following addition of HCl/dioxane 4M (23 mL, 0.092 mol, 1.1 equiv) and *vacuo* distillation (1.7^{-2} mbar, 44-50°C) lead to the resulting (+)-pinanediol *iso*-propylboronate (12.15 g, 65% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 4.23 (dd, J = 8.7, 1.9 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.26 – 2.13 (m, 1H), 2.03 (t, J = 5.6 Hz, 1H), 1.94 – 1.76 (m, 2H), 1.36 (s, 3H), 1.27 (s, 3H), 1.09 (t, J = 9.1 Hz, 2H), 0.99 (d, J = 6.7 Hz, 6H), 0.83 (s, 3H).

Preparation of (-)-Pinanediol 4-Fluoro-Phenylboronate 2.7.

To a solution of (-)-pinanediol *iso*-propyloxy boronate (6 g, 0.025 mol) in anhydrous diethyl ether (130 mL) 4-fluorophenylmagnesium chloride 1M (27.7 mL, 0.027 mol, 1.08 equiv) was added drop wise at -70° C. The reaction mixture was stirred at this temperature for 2 hours, then allowed to warm to room temperature and stirred overnight.

To this HCl/dioxane 4M (6.75 mL, 0.027 mol, 1.1 equiv) was added at -10° C. The mixture was stirred for 1.5 hour, and then filtered through a pad of Celite and evaporated under reduced pressure to yield (7.27 g, 99% yield) of colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.81 (t, J = 7.2 Hz, 2H), 7.06 (t, J = 8.9 Hz, 2H), 4.45 (d, J = 8.6 Hz, 1H), 2.51 – 2.34 (m, 1H), 2.32 – 2.20 (m, 1H), 2.15 (t, J = 5.4 Hz, 1H), 1.97 (d, J = 15.5 Hz, 2H), 1.48 (s, 3H), 1.31 (s, 3H), 1.20 (d, J = 10.9 Hz, 1H), 0.89 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 166.28 , 163.79 , 136.99 (d, J = 8.4 Hz), 114.86 (d, J = 20.2 Hz), 86.35 , 78.32 , 51.41 , 39.51 , 38.19 , 35.53 , 28.68 , 27.08 , 26.47 , 24.02.
IR: ν 2918, 1359, 1089 cm^{-1}
$[\alpha]^{23}_D$ = -10.5 (*c* 1.8, hexane)
HRMS: calcd for $C_{16}H_{20}BFO_2$ 274.14, found 274.10

Preparation of (-)-Pinanediol Benzylboronate 2.8.

To a solution of (-)-pinanediol *iso*-propyloxy boronate (16.42 g, 0.069 mol) in anhydrous diethyl ether (180 mL) benzylmagnesium bromide 2M (34.5 mL, 0.069 mol) was added drop wise at -70° C. The reaction mixture was stirred at this temperature for 2 hours, then allowed to warm to room temperature and stirred overnight.

To this HCl/dioxane 4M (19 mL, 0.076 mol, 1.1 equiv) was added at -10° C. The mixture was stirred for 1.5 hour, and then filtered through a pad of Celite and evaporated

under reduced pressure to yield 21.3g (>100%) of light brown oil. It was distilled *in vacuo* (1.5^{-2} mbar, 94-100°C) to yield (11.91 g, 64% yield) of colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.07 (m, 5H), 4.29 (dd, *J* = 8.8, 1.9 Hz, 1H), 2.37 (s, 2H), 2.34 – 1.79(m, 5H), 1.38 (s, 3H), 1.29 (s, 3 H), 1.07 (d, *J* = 10.9 Hz, 1H), 0.84 (s, 3H).

Preparation of (+)-Pinanediol Benzylboronate 2.9.

Similarly, treatment of the solution of (+)-pinanediol *iso*-propyloxy boronate (19.55 g, 0.082 mol) in anhydrous tetrahydrofuran (200 mL) by benzylmagnesium chloride 2M (41 mL, 0.082 mol) by following addition of HCl/dioxane 4M (26 mL, 0.090 mol, 1.1 equiv) lead to the resulting (+)-pinanediol benzylboronate (21.16 g, 95% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.10 (m, 5H), 4.29 (dd, *J* = 8.7, 1.9 Hz, 1H), 2.36 (s, 2H), 2.35 – 1.76 (m, 5H), 1.38 (s, 3H), 1.29 (s, 3H), 1.05 (d, *J* = 10.9 Hz, 1H), 0.83 (s, 3H).

Preparation of (-)-Pinanediol Phenethylboronate 2.10.

The treatment of the solution of (-)-pinanediol *iso*-propyloxy boronate (14.84 g, 0.062 mol, 1 equiv) in anhydrous ether (150 mL) by phenethylmagnesium bromide 1M (69 mL, 0.069 mol, 1.1 equiv) by following addition of HCl/dioxane 4M (17.2 mL, 0.069 mol, 1.1 equiv) lead to the resulting (-)-pinanediol phenethylboronate (11.67 g, 66% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.18 (m, 5H), 4.27 (dt, *J* = 8.8, 2.5 Hz, 1H), 2.76 (t, *J* = 9.5 Hz 2H), 2.40 – 2.14 (m, 2H), 2.04 (td, *J* = 5.6, 2.4 Hz, 1H), 1.91 (dddd, *J* = 12.7, 9.8, 7.2, 2.6 Hz, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 1.21(t, *J* = 9.5 Hz, 2H), 1.01 (d, *J* = 11.0 Hz, 1H), 0.84 (s, 3H).

Preparation of (+)-Pinanediol Phenethylboronate 2.11.[28]

To the solution of (+)-pinanediol *iso*-propyloxy boronate (13.85 g, 0.058 mol, 1 equiv) in anhydrous tetrahydrofuran (150 mL) phenethylmagnesium bromide 1M (64 mL, 0.064 mol, 1.1 equiv) was added drop wise at -70° C. The reaction mixture was stirred at this temperature for 2 hours, then allowed to warm to room temperature and stirred overnight.

To this HCl/dioxane 4M (16 mL, 0.064 mol, 1.1 equiv) was added at -10° C. The mixture was stirred for 1.5 hour, and then filtered through a pad of Celite and evaporated under reduced pressure to yield pale yellow oil (14.46 g, 88 % yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.14 (m, 5H), 4.26 (dt, *J* = 8.8, 2.5 Hz, 1H), 2.75 (t, *J* = 9.5 Hz 2H), 2.39 – 2.13 (m, 2H), 2.04 (td, *J* = 5.6, 2.4 Hz, 1H), 1.89 (dddd, *J* = 12.7, 9.8, 7.2, 2.6 Hz, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 1.20 (t, *J* = 9.5 Hz, 2H), 1.01 (d, *J* = 11.0 Hz, 1H), 0.84 (s, 3H).

Preparation of (-)-Pinanediol 1-Naphthylmethylboronate 2.12.

The Grignard reagent was made according to a standard procedure[30] from magnesium (0.27 g, 0.011 mol), iodine (catalytic amount) in anhydrous diethyl ether (20 mL) and 1-(chloromethyl)naphthalene (2.0 g, 0.011 mol) in diethyl ether (15 mL) at reflux under argon and the reaction mixture was sonicated for 4-5 hours. Then the mixture was allowed to achieve room temperature and added drop wise to a solution of (-)-pinanediol *iso*-propyloxy boronate (1.7 g, 0.0073 mol, 0.66 equiv) in anhydrous diethyl ether (10 mL) at -70° C. The reaction mixture was stirred at this temperature for 2 hours, then allowed to warm to room temperature and stirred overnight.

To this HCl/dioxane 4M (3 mL, 0.012 mol, 1.1 equiv) was added at -10° C. The mixture was stirred for 1.5 hour, and then filtered through a pad of Celite and evaporated under reduced pressure to yield (2.73 g, 75% yield) of crude product (a mixture with coupling product. see next chapter.). Analytical sample was purified by PTLC (preparative thin layer chromatography) with 5% ethyl acetate in pentane elution to afford (-)-pinanediol 1-naphthylmethylboronate.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.07 (ddd, J = 7.8, 1.6, 0.6 Hz, 1H), 7.85 (dd, J = 7.5, 2.1 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.55 – 7.36 (m, 4H), 4.27 (dd, J = 8.7, 2.0 Hz, 1H), 2.78 (s, 2H), 2.34 – 2.22 (m, 1H), 2.21 – 2.10 (m, 1H), 2.07 – 2.01 (m, 1H), 1.90 – 1.71 (m, 2H), 1.38 (s, 3H), 1.27 (s, 3H), 1.09 (d, J = 10.9 Hz, 1H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 135.91 , 134.05 , 132.60 , 128.80 , 126.61 , 126.03, 125.64, 124.76 , 86.16 , 78.22 , 51.48 , 39.69 , 38.38 , 35.67 , 28.88 , 27.29 , 26.70 , 24.23 .

$[\alpha]^{23}_D$ = -13.84 (c 0.61, DCM)

General Procedure for Preparation of Bibenzyl-derivatives 3 from Benzyl Halides.

A three-necked flask equipped with an argon inlet, a condenser and a dropping funnel was charged with magnesium turnings (60 mmol) and 1-2 crystals of iodine. A small amount of tetrahydrofuran was added to cover the magnesium, and a solution of halide (100 mmol) in tetrahydrofuran (50mL) was added drop wise. The reaction was performed in an ultrasound bath, keeping the temperature of the mixture below 30° by the occasional addition of ice.

After the addition was complete, the reaction mixture was sonicated for 3 hours before it was quenched with 5% aqueous hydrochloric acid (50 mL). After separation, the water phase was extracted with diethyl ether (3 x 20 mL). The organic phases were then combined and dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Column chromatography was performed on silica using pentane to elute any impurities and 5% ethyl acetate in pentane to elute the product. All spectroscopic data was in accordance with earlier published data.[39,41,50,78]

Preparation of dichloromethylboronic acid.[67,79]

To a solution of methylene dichloride (3 mL, 0.048 mol, 1 equiv) in anhydrous tetrahydrofuran (60 mL) under argon *n*-butyl lithium 2.5M (17.6 mL, 0.044 mol, 0.92 equiv) was added drop wise at -100°. After 0.5 hour trimethylborate (5.36 mL, 0.048 mol, 1 equiv) was added slowly. The reaction mixture was stirred over 1 hour and then hydrolyzed with 5N HCI (7 mL). The solution was allowed to reach room temperature, the organic layer was separated and the aqueous layer extracted twice with ether (30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated to give a white solid (6.56 g, >100%) of crude product.

^{1}H NMR (400 MHz, Chloroform-d) δ 5.32 (s, 3H).

Preparation of (-)-Pinanediol dichloromethylboronate 5.[79]

The crude white solid (5.7 g, 0.044 mol, 1.05 equiv) obtained above was dissolved in anhydrous tetrahydrofuran (60 mL) and (-)-pinanediol (7.14 g, 0.042 mol, 1 equiv) was added.

The reaction mixture was stirring at room temperature overnight over magnesium sulfate, then inorganic was filtered off and solvent was distilled out *in vacuo* giving the desired product as colorless oil (11.71 g, 99% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 5.39 (s, 1H), 4.46 (dd, *J* = 8.7, 1.9 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.27 (dq, *J* = 8.9, 3.6, 2.9 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.93 (ddd, *J* = 11.6, 4.2, 2.8 Hz, 2H), 1.45 (s, 3H), 1.29 (s, 3H), 1.20 (d, *J* = 11.2 Hz, 1H), 0.84 (s, 3H).

Preparation of (-)-Pinanediol (1*R*)-(1-Chlorobenzyl)boronate 4.5.

Phenylmagnesium chloride 2M (25 mL, 0.05 mol, 1.2 equiv) was added drop wise at -78°C to a solution of (-)-pinanediol dichloromethyl boronate **5** (l1 g, 0.042 mol, 1 equiv) in anhydrous diethyl ether (200 mL). After 15 min $ZnCl_2$ 1M (21 mL, 0.021 mol, 0.5 equiv) was added slowly at this temperature. Then the reaction mixture was allowed to warm and stirred over 2 hours at room temperature. The inorganic precipitate was filtered off and the solvents were removed *in vacuo.* The residue was dissolved in pentane, washed with water and dried over magnesium sulfate. Removal of the solvent gives a product (10.26 g, 90% conversion, 81% crude yield) which has been forwarded to next step without purification.

Characteristic singlet ClCHB in the proton NMR at 4.35 ppm.

Preparation of (-)-Pinanediol (1*R*)-(1-Chloro-2-methylpropyl)boronate 4.3.

Synthesis performed as described above using *iso*-propylmagnesium chloride yielding the desire product with 40% crude yield (94% conversion)

Characteristic doublet ClCHB in the proton NMR at 3.45 ppm, *J* = 7.1 Hz.

General Procedure of Matteson Homologation.[5]

A magnetically stirred solution of anhydrous dichloromethane (7.6 mL, 0.118 mol, 2 equiv) in anhydrous tetrahydrofuran (130 mL) cooled in liquid nitrogen/ethanol bath to -100°C was treated with *n*-buthyl lithium 2.7M (28.4 mL, 0.077 mol, 1.3 equiv) over a period a 50 min (under argon). After 20 min to the resulting mixture a solution of pinanediol alkylboronate **2** (15.13 g, 0.059 mol, 1 equiv) in anhydrous tetrahydrofuran (20 mL) was

added drop wise. The mixture was stirred over 30 min at this temperature. Then $ZnCl_2$ 1M (89 mL, 0.089 mol, 1.5 equiv) was added slowly. Cold bath was removed and the reaction was allowed to warm to room temperature and was stirred during 3 hours. Then pentane (200 mL) was added and the mixture was washed with pre-cooled saturated ammonium chloride solution. The organic layer was concentrated under reduced pressure, diluted again with pentane (200 mL) and washed with pre-cooled saturated ammonium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure yielding pale yellow (or colorless) oil (50-100% conversion by NMR) of the desired compound.

Most of the products were obtained as mixtures with starting material **2** and used on next step without purification. They have been identified based on characteristic signals of ClCHB proton in comparison with earlier published data.[5,23,28,53,69,70]

(-)-Pinanediol (1*R*)-(1-Chloroethyl)boronate 4.1.

75% crude yield, 50% conversion. Characteristic quartet ClCHB in the proton NMR at 3.57 ppm, J = 7.5 Hz.

(+)-Pinanediol (1*S*)-(1-Chloroethyl)boronate 4.2.

87% crude yield, 60% conversion. Characteristic quartet ClCHB in the proton NMR at 3.56 ppm, J = 7.5 Hz.

(+)-Pinanediol (1*S*)-(1-Chloro-2-methylpropyl)boronate 4.4.

87% crude yield, 70% conversion. Characteristic doublet ClCHB in the proton NMR at 3.31 ppm, J = 6.6 Hz.

(+)-Pinanediol (1*S*)-(1-Chlorobenzyl)boronate 4.6.

77% crude yield, 60% conversion. Characteristic singlet ClCHB in the proton NMR at 4.39 ppm.

(-)-Pinanediol (1*R*)-[1-Chloro-(4-fluorophenyl)methyl]boronate 4.7.

96% crude yield, 80% conversion. Characteristic singlet ClCHB in the proton NMR at 4.52 ppm.

(-)-Pinanediol (1*R*)-(1-Chloro-2-phenylethyl)boronate 4.8.

79% yield, 100% conversion. Characteristic triplet ClCHB in the proton NMR at 3.66 ppm, *J* = 8.0 Hz.

(+)-Pinanediol (1*S*)-(1-Chloro-2-phenylethyl)boronate 4.9.

80% yield, 100% conversion. Characteristic triplet ClCHB in the proton NMR at 3.67 ppm, *J* = 8.0 Hz.

(-)-Pinanediol (1*R*)-(1-Chloro-3-phenylpropyl)boronate 4.10.

79% crude yield, 50% conversion. Characteristic triplet ClCHB in the proton NMR at 4.00 ppm, *J* = 7.0 Hz.

(+)-Pinanediol (1*S*)-(1-Chloro-3-phenylpropyl)boronate 4.11.

69% crude yield, 70% conversion. Characteristic triplet ClCHB in the proton NMR at 4.08 ppm, *J* = 7.0 Hz.

(-)-Pinanediol (1*R*)-[1-Chloro-2-(1-naphthyl)ethyl]boronate 4.12.

99% crude yield, 80% conversion. Characteristic triplet ClCHB in the proton NMR at 3.85 ppm, *J* = 8.2 Hz.

General Procedure of Prepararion of α-Aminoboronic Esters 7.

To the solution of α-chloroboronic ester **4** (0.022 mol, 1 equiv) in anhydrous tetrahydrofuran (40 mL) lithium bis(trimethylsilyl)amide 1M (0.022 mol, 1 equiv) was added slowly at -78°. The mixture was allowed to warm and stirred over 3 hours at room temperature. The solvent was removed *in vacuo* and pentane (100 mL) was added to the residue. The inorganic precipitate was filtered off through a pad of Celite, and filtrate was evaporated under reduced pressure to give colorless (pale yellow) oil. To the solution of this bis-silyl intermediate **6** in pentane (60 mL) HCl/dioxane 4M (0.066 mol, 3 equiv) was added slowly at 0°C. The reaction was allowed to warm to room temperature and stirred overnight. Solid was filtered, washed with pentane and dried in the air atmosphere to give a white powder of pure product with yields about 40-95%.

(-)-Pinanediol (1*R*)-(1-Aminoethyl)boronate Hydrochloride 7.1.

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.47 (dd, J = 8.8, 1.8 Hz, 1H), 2.95 (q, J = 7.7 Hz, 1H), 2.42 (dd, J = 14.4, 8.8 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.07 (t, J = 5.4 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.44 (s, 3H), 1.35 (d, J = 7.7 Hz, 3H), 1.32 (s, 3H), 1.15 (d, J = 11.0 Hz, 1H), 0.87 (s, 3H).
^{13}C NMR (101 MHz, Methanol-d_4) δ 86.24, 77.59, 49.80, 38.06, 36.63, 33.37, 26.13, 24.76, 24.54, 21.59, 12.24.
$[\alpha]^{23}_{D}$ = + 10.2 (c 0.74, CH3OH)
Yield: 43%

(+)-Pinanediol (1*S*)-(1-Aminoethyl)boronate Hydrochloride 7.2.

^{1}H NMR (400 MHz, Deuterium oxide-d_2) δ 4.43 (d, J = 7.3 Hz, 1H), 3.04 – 2.90 (m, 1H), 2.40 – 2.24 (m, 1H), 2.18 (dd, J = 9.9, 5.2 Hz, 1H), 1.98 (t, J = 5.4 Hz, 1H), 1.85 (s, 1H), 1.72 (d, J = 14.9 Hz, 1H), 1.33 (s, 3H), 1.25 (d, J = 7.8 Hz, 3H), 1.18 (s, 3H), 0.94 (d, J = 11.1 Hz, 1H), 0.73 (s, 3H).
^{13}C NMR (101 MHz, Deuterium oxide-d_2) δ 88.43, 78.70, 50.59, 38.98, 37.70, 34.44, 27.43, 26.19, 25.73, 23.04, 13.68.
IR: ν 3138, 3046, 1405, 1238 cm^{-1}
$[\alpha]^{23}_{D}$ = + 8.3 (c 0.12, CH3OH)
HRMS: calcd for $C_{12}H_{23}O_2NB$ 224.1837, found 224.1816
Yield: 22%

(-)-Pinanediol (1*R*)-(1-Amino-2-methylpropyl)boronate Hydrochloride 7.3.

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.49 (dd, J = 8.8, 2.0 Hz, 1H), 2.78 (d, J = 5.2 Hz, 1H), 2.44 (ddt, J = 14.1, 8.8, 2.4 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.12 – 2.04 (m, 2H), 1.95 (td, J = 5.7, 2.8 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.45 (s, 3H), 1.33 (s, 3H), 1.20 (d, J = 11.0 Hz, 1H), 1.08 (t, J = 6.5 Hz, 6H), 0.89 (s, 3H).
^{13}C NMR (101 MHz, Methanol-d_4) δ 87.32, 77.99, 66.83, 51.09, 38.35, 29.08, 28.86, 27.29, 24.12, 20.44, 19.64.
IR: ν 2959, 2868, 1390, 1109 cm^{-1}
$[\alpha]^{23}_{D}$ = -16.3 (*c* 0.15, CH_3OH)
Yield: 59%

(+)-Pinanediol (1*S*)-(1-Amino-2-methylpropyl)boronate Hydrochloride 7.4.

^{1}H NMR (400 MHz, Dimethyl sulfoxide-d_6) δ 4.37 (d, J = 7.4 Hz, 1H), 2.37 - 1.99 (m, 3H), 1.92 (dd, J = 12.5, 7.0 Hz, 1H), 1.81 - 1.68 (m, 3H), 1.31 (s, 3H), 1.19 (s, 3H), 1.15 (d, J = 10.8 Hz, 1H), 0.88 (dd, J = 16.1, 6.7 Hz, 6H), 0.74 (s, 3H).
^{13}C NMR (101 MHz, Dimethyl sulfoxide-d_6) δ 87.10, 77.78, 66.75, 51.04, 38.23, 35.17, 28.75, 27.26, 26.56, 24.11, 20.62, 20.41, 19.64.

IR: ν 3397, 2960, 1402, 1121 cm^{-1}

$[\alpha]^{23}_D$ = + 15.6 (*c* 0.16, CH_3OH)

HRMS: calcd for $C_{14}H_{27}O_2NB$ 252.2146, found 252.2129

Yield: 64%

(-)-Pinanediol (1*R*)-(1-Aminobenzyl)boronate Hydrochloride 7.5.

^1H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.32 (m, 5H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.08 (s, 1H), 2.51 – 2.34 (m, 1H), 2.21 – 2.06 (m, 1H), 2.02 (t, *J* = 5.4 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.45 (s, 3H), 1.29 (s, 3H), 1.03 – 0.92 (m, 1H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Dimethyl sulfoxide-d_6) δ 136.15 , 129.15 , 128.49 , 125.40 , 87.41 , 78.22 , 51.15 , 41.76 , 38.32 , 35.16 , 28.54 , 27.24 , 26.10 , 24.04.

IR: ν 3382, 2969, 1406, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -19 (*c* 0.97, CH_3OH)

HRMS: calcd for $C_{17}H_{25}O_2NB$ 286.1945, found 286.1973

Yield: 63%

(+)-Pinanediol (1*S*)-(1-Aminobenzyl)boronate Hydrochloride 7.6.

^1H NMR (400 MHz, Dimethyl sulfoxide-d_6) δ 8.57 (s, broad, 3H), 7.53 – 7.29 (m, 5H), 4.49 – 4.38 (m, 1H), 3.99 (s,1H), 2.38 – 2.19 (m, 1H), 1.99 (dd, *J* = 9.8, 5.1 Hz, 1H), 1.92 (t, *J* = 5.5 Hz, 1H), 1.86 – 1.67 (m, 2H), 1.34 (s, 3H), 1.21 (s, 3H), 0.89 (d, *J* = 10.8 Hz, 1H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, Dimethyl sulfoxide-d_6) δ 136.10, 129.06, 128.50, 128.18, 87.28, 78.12, 51.11, 39.06, 38.25, 35.08, 28.51, 27.15, 26.02, 23.98.

IR: ν 3145, 2969, 1394, 1121 cm^{-1}

$[\alpha]^{23}_D$ = + 21.7 (*c* 1.80, CH_3OH)

HRMS: calcd for $C_{17}H_{25}O_2NB$ 286.1945, found 286.1973

Yield: 49%

(-)-Pinanediol (1*R*)-[1-Amino-(4-fluorophenyl)methyl]boronate Hydrochloride 7.7.

^1H NMR (400 MHz, Methanol-d_4) δ 7.56 – 7.42 (m, 2H), 7.16 (t, *J* = 8.1 Hz, 2H), 4.50 (d, *J* = 8.4 Hz, 1H), 4.13 (s, 1H), 2.40 - 1.91 (m, 5H), 1.45 (s, 3H), 1.27 (s, 3H), 0.97 (d, *J* = 11.1 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 130.27 (d, *J* = 8.5 Hz), 115.61 (d, *J* = 22.0 Hz), 87.77, 78.99, 51.08, 39.21, 37.91, 34.66, 27.43, 26.04, 25.87, 22.92.

IR: ν 3148, 2926, 1396, 1224, 1121 cm^{-1}

$[\alpha]^{23}_D$ = - 12.0 (*c* 2.04, CH_3OH)

HRMS: calcd for $C_{17}H_{24}O_2NBF$ 304.1863, found 304.1879

Yield: 52%

(-)-Pinanediol (1*R*)-(1-Amino-2-phenylethyl)boronate Hydrochloride 7.8.

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 – 7.26 (m, 5H), 4.48 (dd, *J* = 8.9, 1.9 Hz, 1H), 3.22 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.14 – 2.96 (m, 2H), 2.51 – 2.37 (m, 1H), 2.25 (dtd, *J* = 12.9, 6.1, 2.6 Hz, 1H), 2.04 (t, *J* = 5.5 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H), 1.09 (d, *J* = 11.1 Hz, 1H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Dimethyl sulfoxide-d$_6$) δ 137.46, 129.58, 128.88, 127.21, 87.18, 77.98, 50.99, 39.18, 38.22, 35.56, 34.94, 28.55, 27.23, 26.20, 24.02.

IR: ν 2912, 1405, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -1.8 (*c* 0.28, CH$_3$OH)

HRMS: calcd for $C_{18}H_{27}O_2NB$ 300.2144, found 300.2129

Yield: 60%

(+)-Pinanediol (1*S*)-(1-Amino-2-phenylethyl)boronate Hydrochloride 7.9.

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.42 – 7.18 (m, 5H), 4.46 (dd, *J* = 8.9, 1.9 Hz, 1H), 3.22 (t, *J* = 7.2 Hz, 1H), 3.04 (ddd, *J* = 22.4, 14.2, 7.3 Hz, 2H), 2.52 – 2.33 (m, 1H), 2.23 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.03 (t, *J* = 5.4 Hz, 1H), 1.90 (dd, *J* = 12.5, 10.2 Hz, 2H), 1.40 (s, 3H), 1.29 (s, 3H), 1.09 (d, *J* = 11.0 Hz, 1H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 136.36, 128.88, 128.58, 127.02, 87.64, 78.85, 50.98, 39.29, 37.84, 35.03, 34.52, 27.38, 26.00, 25.85, 22.84.

IR: ν 2917, 1410, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = - 7.7 (*c* 0.13, CH$_3$OH)

HRMS: calcd for $C_{18}H_{27}O_2NB$ 300.2144, found 300.2129

Yield: 54%

(-)-Pinanediol (1*R*)-(1-Amino-3-phenylpropyl)boronate Hydrochloride 7.10.

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.35 – 7.19 (m, 5H), 4.58 – 4.43 (m, 1H), 2.90 (t, *J* = 7.4 Hz, 1H), 2.77 (ttd, *J* = 13.6, 9.4, 8.7, 5.4 Hz, 2H), 2.44 - 2.33 (m, 2H), 2.17 - 1.90 (m, 5H), 1.47 (s, 3H), 1.33 (s, 3H), 1.20 (d, *J* = 11.0 Hz, 1H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 140.56 , 128.20 , 128.00 , 125.93 , 87.62 , 78.75 , 51.06 , 46.94 , 39.36 , 37.88 , 34.63 , 32.10 , 31.47 , 27.44 , 25.98 , 22.86 .

IR: ν 3028, 2917, 1401, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = - 5.0 (*c* 0.4, CH$_3$OH)

HRMS: calcd for $C_{19}H_{29}O_2NB$ 314.2273, found 314.2292

Yield: 18%

(+)-Pinanediol (1*S*)-(1-Amino-3-phenylpropyl)boronate Hydrochloride 7.11.

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.33 – 7.17 (m, 5H), 4.56 – 4.45 (m, 1H), 2.91 (t, *J* = 7.3 Hz, 1H), 2.85 – 2.69 (m, 2H), 2.52 –2.32 (m, 2H), 2.11 (t, *J* = 5.5 Hz, 1H), 2.03 (qd, *J* = 13.6, 11.9, 6.5 Hz, 2H), 1.98 – 1.90 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H), 1.21 (d, *J* = 11.0 Hz, 1H), 0.90 (s, 3H).
^{13}C NMR (101 MHz, Methanol-d_4) δ 140.58 , 128.12 , 125.95 , 87.61 , 78.75 , 51.06 , 46.97 , 39.37 , 37.89 , 34.64 , 32.13 , 31.47 , 27.47 , 26.00 , 22.90 .
IR: ν 3047, 2912, 1406, 1122 cm^{-1}
$[\alpha]^{23}_{D}$ = +28.81 (*c* 0.59, CH_3OH)
HRMS: calcd for $C_{19}H_{29}O_2NB$ 314.2273, found 314.2287
Yield: 47%

(-)-Pinanediol (1*R*)-[1-bis(trimethylsilyl)amide-2-(1-naphthyl)ethyl]boronate 6.12.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.10 (d, *J* = 8.5, 1H), 7.84 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.69 (d, *J* = 7.7, 1H), 7.55 – 7.41 (m, 2H), 7.39 – 7.31 (m, 2H), 4.32 (d, *J* = 8.8 Hz, 1H), 3.73 (dt, *J* = 13.6, 4.0 Hz, 1H), 3.10 – 2.83 (m, 2H), 2.46 – 2.25 (m, 1H), 2.15 (ddt, *J* = 11.1, 6.1, 2.7 Hz, 1H), 2.03 (td, *J* = 5.5, 2.2 Hz, 1H), 1.94 – 1.78 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.04 (d, *J* = 10.9 Hz, 1H), 0.85 (s, 3H), -0.02 (s, broad, 18H).
^{13}C NMR (101 MHz, Chloroform-d) δ 138.05 , 134.27 , 132.52 , 128.96 , 127.79 , 126.69, 125.73 , 125.30 , 124.38 , 86.08 , 78.54 , 51.61 , 39.72 , 38.67 , 38.39 , 35.68 , 28.66 , 27.30 , 26.60 , 24.25 , 3.03.
IR: ν 2952, 1245, 1150, 928, 776 cm^{-1}
$[\alpha]^{23}_{D}$ = +52.42 (*c* 1.75, DCM)
HRMS: calcd for $C_{28}H_{45}O_2NBSi_2$ 494.3058, found 494.3076
Yield: 86%

3.1.8. References

1. Hall D.G., *Boronic Acids. Preparation, Application in organic synthesis and Medicine;* WILEY-VCH, Weinheim, 2005.
2. Matteson, D.S., *Boronic Esters in Stereodirected Synthesis.* Tetrahedron, 1989. **45**(7): pp. 1859-1885.
3. Matteson, D.S. and R. Ray, *Directed chiral synthesis with pinanediol boronic esters.* Journal of the American Chemical Society, 1980. **102**(25): pp. 7590-7591.
4. Matteson, D.S., P.K. Jesthi, and K.M. Sadhu, *Synthesis and properties of pinanediol α-amido boronic esters.* Organometallics, 1984. **3**(8): pp. 1284-1288.

5. Matteson, D.S., K.M. Sadhu, and M.L. Peterson, *99% Chirally selective synthesis via pinanediol boronic esters: insect pheromones, diols, and an amino alcohol.* Journal of the American Chemical Society, 1986. **108**(4): pp. 810-819.
6. Brown, H.C., et al., *Addition compounds of alkali metal hydrides. 28. Preparation of potassium dialkoxymonoalkylborohydrides from cyclic boronic esters. A new class of reducing agents.* The Journal of Organic Chemistry, 1986. **51**(3): pp. 337-342.
7. Rangaishenvi, M.V., B. Singaram, and H.C. Brown, *Chiral synthesis via organoboranes. 30. Facile synthesis, by the Matteson asymmetric homologation procedure, of α-methyl boronic acids not available from asymmetric hydroboration and their conversion into the corresponding aldehydes, ketones, carboxylic acids, and amines of high enantiomeric purity.* The Journal of Organic Chemistry, 1991. **56**(10): pp. 3286-3294.
8. Matteson, D.S., et al., *Directed chiral synthesis by way of α-chloro boronic esters.* Organometallics, 1983. **2**(11): pp. 1536-1543.
9. Matteson, D.S., *α-Halo boronic esters: intermediates for stereodirected synthesis.* Chemical Reviews, 1989. **89**(7): pp. 1535-1551.
10. Matteson, D.S., D. Maliakal, and L. Fabry-Asztalos, *Synthesis of a (β-acetamido-α-acetoxyethyl)boronic ester via azido boronic esters.* Journal of Organometallic Chemistry, 2008. **693**(13): pp. 2258-2262.
11. Hiscox, W.C. and D.S. Matteson, *An Efficient Preparation of (R*,R*)-1,2-Dicyclohexylethane-1,2-diol, a Superior Chiral Director for Synthesis with Boronic Esters.* The Journal of Organic Chemistry, 1996. **61**(23): pp. 8315-8316.
12. Matteson, D.S. and A.A. Kandil, *(S, S)-diisopropylethanediol ("DIPED"): A new chiral director for the α-chloro boronic ester synthesis.* Tetrahedron Letters, 1986. **27**(33): pp. 3831-3834.
13. Jacobsen, E.N., et al., *Asymmetric dihydroxylation via ligand-accelerated catalysis.* Journal of the American Chemical Society, 1988. **110**(6): pp. 1968-1970.

14. Erdik, E. and D.S. Matteson, *Kinetics of osmium tetraoxide catalyzed trimethylamine N-oxide oxidations of cyclohexene and α-pinene to diols.* The Journal of Organic Chemistry, 1989. **54**(11): pp. 2742-2748.
15. Wityak, J., et al., *Synthesis of Thrombin Inhibitor DuP 714.* The Journal of Organic Chemistry, 1995. **60**(12): pp. 3717-3722.
16. Burg, A.B., *Methylboric Acid and its Anhydride; The Methylboron Fluorides.* Journal of the American Chemical Society, 1940. **62**(8): pp. 2228-2234.
17. Snyder, H.R., J.A. Kuck, and J.R. Johnson, *Organoboron Compounds, and the Study of Reaction Mechanisms. Primary Aliphatic Boronic Acids1.* Journal of the American Chemical Society, 1938. **60**(1): pp. 105-111.
18. Brown, H.C. and T.E. Cole, *Organoboranes. 31. A simple preparation of boronic esters from organolithium reagents and selected trialkoxyboranes.* Organometallics, 1983. **2**(10): pp. 1316-1319.
19. Brown, H.C. and T.E. Cole, *Organoboranes. 39. Convenient procedures for the preparation of methylboronic acid and trimethylboroxin.* Organometallics, 1985. **4**(5): pp. 816-821.
20. Wong, K.-T., et al., *Efficient and Convenient Nonaqueous Workup Procedure for the Preparation of Arylboronic Esters.* The Journal of Organic Chemistry, 2002. **67**(3): pp. 1041-1044.
21. Mueller, Richard H., *Preparation of boronic acid derivatives.* Patent U.S. (1991), US 5039795.
22. Morandi, S., et al., *Enantiomeric excess of 1,2-diols by formation of cyclic boronates: an improved method.* Tetrahedron: Asymmetry, 2005. **16**(17): pp. 2918-2926.
23. Martichonok, V. and J.B. Jones, *Probing the Specificity of the Serine Proteases Subtilisin Carlsberg and α-Chymotrypsin with Enantiomeric 1-Acetamido Boronic Acids. An Unexpected Reversal of the Normal "l"-Stereoselectivity Preference.* Journal of the American Chemical Society, 1996. **118**(5): pp. 950-958.

24. Brown, H.C., B.T. Cho, and W.S. Park, *Addition compounds of alkali metal hydrides. 31. Preparation and properties of chiral dialkoxy monoalkylborohydrides. A new class of asymmetric reducing agents.* The Journal of Organic Chemistry, 1987. **52**(18): pp. 4020-4024.
25. Dembitsky, V.M. and M. Srebnik, *Synthesis and biological activity of α-aminoboronic acids, amine-carboxyboranes and their derivatives.* Tetrahedron, 2003. **59**(5): pp. 579-593.
26. Hansen, K.K., et al., *Synthesis and Evaluation of Macrocyclic Transition State Analogue Inhibitors for α-Chymotrypsin.* The Journal of Organic Chemistry, 2003. **68**(22): pp. 8465-8470.
27. Hawkins, V.F., M.C. Wilkinson, and M. Whiting, *Mild and Selective Synthesis of an Aryl Boronic Ester by Equilibration of Mixtures of Boronic and Borinic Acid Derivatives.* Organic Process Research & Development, 2008. **12**(6): pp. 1265-1268.
28. Wienand, A., et al., *Design, synthesis and biological evaluation of selective boron-containing thrombin inhibitors.* Bioorganic & Medicinal Chemistry, 1999. **7**(7): pp. 1295-1307.
29. Simov, B.P., et al., *Chiral Carbanions, Part 4: Borylation of (Trimethylsilyl)methyl N,N-Dialkylcarbamates - Diastereoselectivity and Structural Studies.* Synthesis, 2004. **2004**(EFirst): pp. 2704-2710.
30. Schlosser M., *Organometallics in Synthesis. A Manual*. JOHN WILEY&SONS, LTD, The Atrium, Southern Gate, Chichester, West Sussex, England, 2002.
31. Hassan, J., et al., *Catalytic alternative of the Ullmann reaction.* Tetrahedron, 1998. **54**(45): pp. 13793-13804.
32. Taylor, P.N., et al., *Insulated Molecular Wires: Synthesis of Conjugated Polyrotaxanes by Suzuki Coupling in Water.* Angewandte Chemie International Edition, 2000. **39**(19): pp. 3456-3460.

33. Slocum, G.H. and G.B. Schuster, *Photochemistry of naphthylmethyl halides. Direct and sensitized paths to homolytic and heterolytic carbon-halogen bond cleavage.* The Journal of Organic Chemistry, 1984. **49**(12): pp. 2177-2185.
34. Arnold, B., et al., *Homolytic versus heterolytic cleavage for the photochemistry of 1-naphthylmethyl derivatives.* Canadian Journal of Chemistry, 1985. **63**(11): pp. 3140-3146.
35. Aitken, A.R.,et al., *Flash vacuum pyrolysis over magnesium. Part 1. Pyrolysis of benzylic, other aryl/alkyl and aliphatic halides.* J. Chem. Soc., Perkin Trans., 2002. **1**: pp. 402-415.
36. Kweon, D., et al., *Organic electrochemical synthesis utilizing Mg electrodes (1). Facile reductive coupling reactions of aromatic halides.* Bull. Korean Chem. Soc., 2003. **24**(8): pp.1049-1050.
37. Ashby, E.C., et al., *Single electron transfer in reactions of alkyl halides with lithium thiolates.* The Journal of Organic Chemistry, 1985. **50**(25): pp. 5184-5193.
38. Khurana, J.M., A.G. neé Puri, and R.K. Bankhwal, *Chemoselective Reduction of Vicinal-Dihalides with Mg-MeOH via SET.* Synthetic Communications, 1997. **27**(10): pp. 1801-1809.
39. Inaba, S., H. Matsumoto, and R.D. Rieke, *Highly reactive metallic nickel: reductive homocoupling reagent for benzylic mono- and polyhalides.* The Journal of Organic Chemistry, 1984. **49**(12): pp. 2093-2098.
40. Barhdadi, R., et al., *Room-temperature ionic liquids as new solvents for organic electrosynthesis. The first examples of direct or nickel-catalysed electroreductive coupling involving organic halides.* Chemical Communications, 2003(12): pp. 1434-1435.
41. Chen, T., et al., *Homocoupling of benzyl halides catalyzed by POCOP–nickel pincer complexes.* Tetrahedron, 2012. **68**(31): pp. 6152-6157.

42. Wakui, H., et al., *Palladium-Catalyzed Reaction of 2-Hydroxy-2-methylpropiophenone with Aryl Bromides: A Unique Multiple Arylation via Successive C–C and C–H Bond Cleavages.* Journal of the American Chemical Society, 2004. **126**(28): pp. 8658-8659.
43. Chang, Y.M., et al., *Homocoupling of Aryl Iodides and Bromides Using a Palladium/Indium Bimetallic System.* Synthetic Communications, 2005. **35**(13): pp. 1851-1857.
44. Punna, S., D.D. Díaz, and M.G. Finn, *Palladium-Catalyzed Homocoupling of Arylboronic Acids and Esters Using Fluoride in Aqueous Solvents.* Synlett, 2004. **2004** (EFirst): pp. 2351-2354.
45. Chen, S.-Y., et al., *Cobalt-catalyzed homo-coupling of aryl and alkenyl bromide using atmospheric oxygen as oxidant.* Tetrahedron Letters, 2009. **50**(49): p. 6795-6797.
46. Sá, A.C.P.F.d., et al., *Reductive coupling reaction of benzyl, allyl and alkyl halides in aqueous medium promoted by zinc.* Journal of the Brazilian Chemical Society, 2003. **14**: pp. 429-434.
47. Hu, Y.-L., et al., *Facile and Efficient Reductive Homocoupling of Benzyl and Aryl Halides Catalyzed by Ionic Liquid in the Presence of Metallic Zinc and Copper.* Catalysis Letters, 2011. **141**(3): pp. 467-473.
48. Khurana, J.M., S. Chauhan, and G.C. Maikap, *Facile reductive coupling of benzylic halides with ferrous oxalate dihydrate.* Organic & Biomolecular Chemistry, 2003. **1**(10): pp. 1737-1740.
49. Li, Y.-Z., et al., *Cross Dehydrogenative Arylation (CDA) of a Benzylic C□H Bond with Arenes by Iron Catalysis.* Angewandte Chemie International Edition, 2009. **48**(21): pp. 3817-3820.
50. Liu, J. and B. Li, *Facile Synthesis of Bibenzyl by Reductive Homocoupling of Benzyl Halides in Aqueous Media.* Synthetic Communications, 2007. **37**(19): pp. 3273-3278.

51. Li, Y. and T. Izumi, *Ruthenium-Catalyzed Coupling Reaction of Benzylic Halides.* Synthetic Communications, 2003. **33**(20): pp. 3583-3588.
52. Gozhina, O.V., Thomassen, I.K., and Lejon. T., *Ultrasound promoted dimerization of benzylic halides.* Synthetic Communications (accepted)
53. Matteson, D.S. and D. Majumdar, *α-Chloro boronic esters from homologation of boronic esters.* Journal of the American Chemical Society, 1980. 102(25): pp. 7588-7590.
54. Matteson, D.S. and D. Majumdar, *Homologation of boronic esters to α-chloro boronic esters.* Organometallics, 1983. **2**(11): pp. 1529-1535.
55. Brown, H. C. and P. V. Ramachandran, *Recent advances in the boron route to asymmetric synthesis.* Pure Appl. Chem., 1994. **66**(2): pp. 201-212.
56. Ramachandran, P.V. and M.P. Jennings, *Asymmetric hydroboration and Matteson homologation for the preparation of fluorinated α-phenethanols.* Journal of Fluorine Chemistry, 2007. **128**(7): pp. 827-831.
57. Matteson, D.S., K.M. Sadhu, and G.E. Lienhard, *R-1-Acetamido-2-phenylethaneboronic acid. A specific transition-state analog for chymotrypsin.* Journal of the American Chemical Society, 1981. **103**(17): pp. 5241-5242.
58. Matteson, D.S., et al., *[(1R)-1-acetamido-3-(methylthio)propyl]boronic acid and the x-ray structure of its ethylene glycol ester.* Organometallics, 1989. **8**(3): pp. 726-729.
59. Matteson, D.S. and E. Erdik, *Epimerization of α-chloroboronic esters by lithium and zinc chlorides.* Organometallics, 1983. **2**(9): pp. 1083-1088.
60. Mantri, P., D.E. Duffy, and C.A. Kettner, *New Asymmetric Synthesis of α-Aminoboronic Acids Containing Functionalized Side Chains.* The Journal of Organic Chemistry, 1996. **61**(16): pp. 5690-5692.
61. Matteson, D.S. and H.-W. Man, *Hydrolysis of Substituted 1,3,2-Dioxaborolanes and an Asymmetric Synthesis of a Differentially Protected syn,syn-3-Methyl-2,4-hexanediol.* The Journal of Organic Chemistry, 1996. **61**(17): pp. 6047-6051.

62. Singh, R.P. and D.S. Matteson, *Asymmetric Homologation of Boronic Esters Bearing Azido and Silyloxy Substituents.* The Journal of Organic Chemistry, 2000. **65**(20): pp. 6650-6653.

63. Matteson, D.S., *New asymmetric syntheses with boronic esters and fluoroboranes.* Pure Appl. Chem., 2003. 75(9): pp. 1249-1253.

64. Soundararajan, R., G. Li, and H.C. Brown, *Homologation of representative boronic esters using in situ generated (halomethyl)lithiums: A comparative study.* Tetrahedron Letters, 1994. **35**(48): pp. 8957-8960.

65. Sadhu, K.M., et al., *(R,R)-2,3-Butanediol as chiral directing group in the synthesis of (S)-α-chloro boronic esters.* Organometallics, 1984. **3**(5): pp. 804-806.

66. Song, Y., et al., *Asymmetric Homologation of Cedranediol Boronic Esters and X-Ray Structure of Cedranediol 1-Chloro-1- Phenylmetylboronate.* Synthetic Communications, 1999. **29**(3): pp. 415-422.

67. Elgendy, S., et al., *Facile routes to 1-halo-1-alkyl boronic esters as precursors for novel thrombin inhibitors.* Tetrahedron, 1994. **50**(12): pp. 3803-3812.

68. Thomas, S.P., et al., *Homologation and alkylation of boronic esters and boranes by 1,2-metallate rearrangement of boron ate complexes.* The Chemical Record, 2009. **9**(1): pp. 24-39.

69. Priestley, E. Scott, *Preparation of peptide inhibitors of hepatitis C virus NS3 protein.* U.S. Pat. Appl. Publ. (2002), US 20020177725.

70. Cook, Nigel Scott, et al., *Preparation of peptide boronic acid derivatives having protease inhibiting activity.* PCT Int. Appl. (1994), WO 9420526.

71. Shenvi, A.B., Kettner, C. A., *α-Aminoboronic acid peptides.* U.S. (1985), US 4499082.

72. Tsai, D.J.S. and D.S. Matteson, *Pinanediol [α-(trimethylsilyl)allyl]boronate and related boronic esters.* Organometallics, 1983. **2**(2): pp. 236-241.

73. Thomson, J.M., et al., *Probing Active Site Chemistry in SHV β-Lactamase Variants at Ambler Position 244.* Journal of Biological Chemistry, 2006. **281**(36): pp. 26734-26744.

74. Kettner, C.A., Jagannathan, S., Forsyth, T.P., *Preparation of α-aminoboronate esters by sequential alkylation of (arylthio)methylboronate ester, cleavage of arylthio group and halogenation by metal halide and amination.* U.S. (2003), US 6586615.

75. Amiri, P., et al., *Benzamidomethaneboronic acid: Synthesis and inhibition of chymotrypsin.* Archives of Biochemistry and Biophysics, 1984. **234**(2): pp. 531-536.

76. Dembitsky, V.M. and M. Srebnik, *Chemistry of α-Aminoboronic Acids and their Derivatives*, in *Amino Acids, Peptides and Proteins in Organic Chemistry*2009, Wiley-VCH Verlag GmbH & Co. KGaA. pp. 145-187.

77. Lejon, T., Gozhina, O.V., and Khrustalev, V.N., *(3aS,4S,6S,7aR)-hexahydro-3a,5,5-trimethyl-2-phenyl-4,6-methano-1,3,2-benzodioxaborole.* Acta Crystallographica Section E Online, **2012**, E68, o3103.

78. Sridevi, V.S., W.K. Leong, and Y. Zhu, *Catalytic Reductive Coupling of 9-Bromofluorene.* Organometallics, 2005. **25**(1): pp. 283-288.

79. Rathke, M.W., E. Chao, and G. Wu, *The preparation and reactions of esters of dichloromethaneboronic acid.* Journal of Organometallic Chemistry, 1976. **122**(2): pp. 145-149.

3.2. Peptide Coupling

3.2.1. Peptide Synthesis

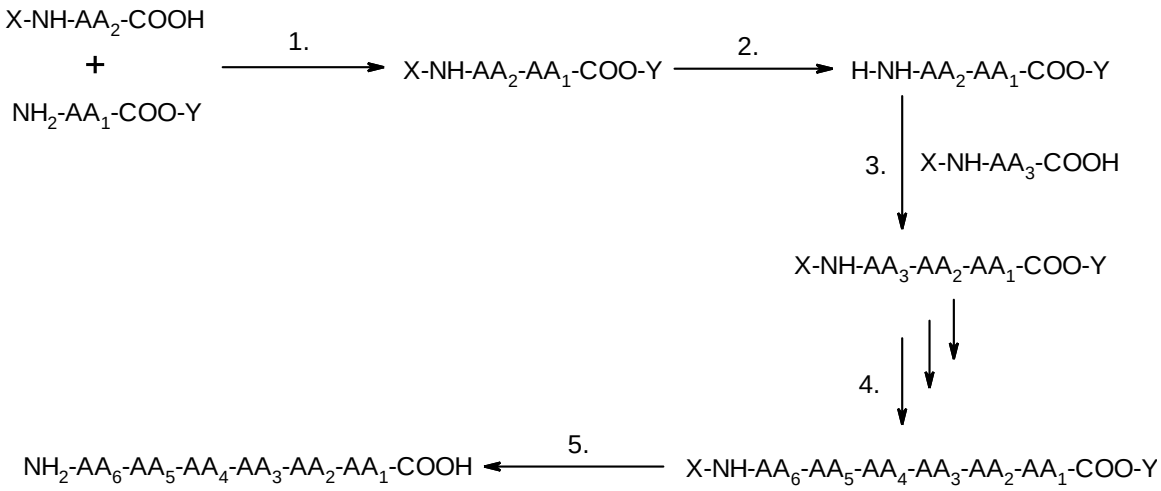
Peptides are present in every living organism, and appear as hormones, enzymes and antibiotics. They form a major component of muscle, skin and hair. Consequently, chemists have been very interested in synthesizing them in the laboratory conditions.

Peptide bond formation is the reaction which drives the polymerization of amino acids into peptides and, consequently, proteins. Peptides are small being composed of a few amino acids. In this thesis only small peptides have been investigated (containing only two or three amino acids). Peptide bond is usually formed by the condensation of the carboxyl group of one amino acid with the amino group of the second with following elimination of water. This process can be continued by joining of other amino acids and yield an amino acid chain.[1] A peptide chain usually has a carboxylate group at one end (called the C-terminus) and an amino group at another end (called the N-terminus).

In modern peptide synthesis methodologies, two protocols are often used – one is based on synthesis in solution and the other includes synthesis on a solid support (solid phase).

General Outline of Solution Phase Peptide Synthesis

Solution phase peptide synthesis is a classical route of peptide synthesis. It is based on a coupling the N-terminus of the growing peptide chain with the carboxyl group of the incoming amino acid (generally the same principles are employed in solid phase peptide synthesis) as shown in Scheme 3.10.



Scheme 3.10 The route of solution phase peptide synthesis.

As outlined in Scheme 3.10, the formation of a peptide bond in solution needs the interaction between one acid protected at its N-terminus and the other at its C-terminus. Then the protected dipeptide is isolated and N-protecting group is cleaved. So in order to obtain the desired peptide protecting groups and coupling reagent have to be selected carefully.

Suitable protective groups (X and Y) have to be selected, and then protected amino acids react with each other (1) with a new amide bond formation giving a protected dipeptide, followed by selective cleavage of N - protecting group (2). The processes of coupling and deprotection may be repeated with a chain growing until the resulting peptide is obtained (3, 4, 5).[2]

The process of linking of individual amino acids can be performed through employment of various coupling reagents such as EDC, CDI, HBTU, HATU, TSTU, DCC, DIC et al.[3-5]

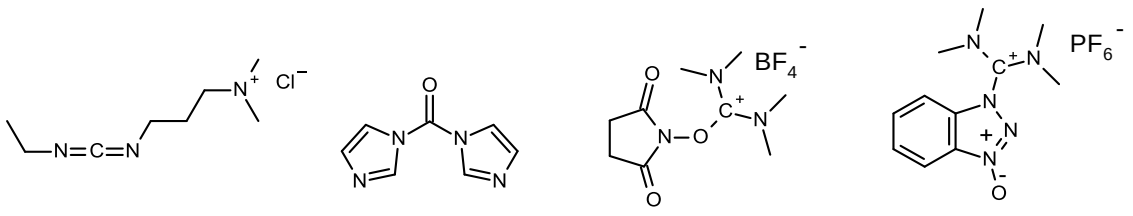


Figure 3.4 Structures of some of the most common coupling reagents.

Protecting Groups

Special groups have been developed in order to be attached to amino acid functional groups (carboxyl and amino groups) and block, or protect, the functional group from side reactions. These protecting groups can be separated into two major classes: N-terminal protecting groups and C-terminal protecting groups.

The C-terminus is most frequently protected by an alkyl or aryl ester as well as insoluble polymeric support may be considered to be the C-terminus protector in the solid phase peptide synthesis.[2]

As long as boronic acids have two hydroxyl groups different diols are used for protection.

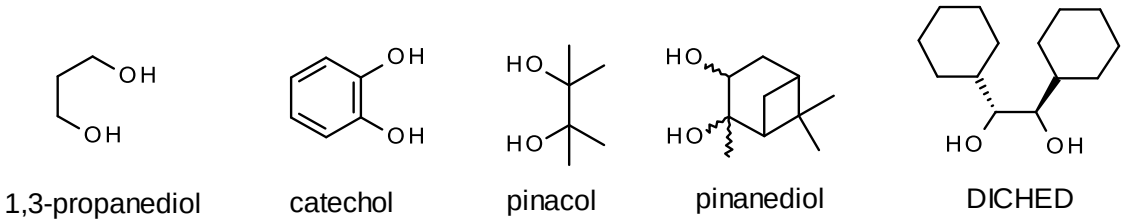
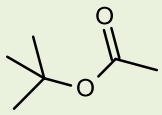
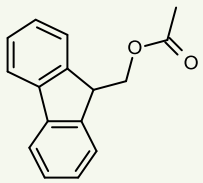
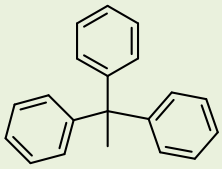
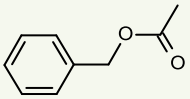
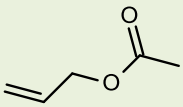


Figure 3.5 Structures of the most common C - terminal (B - terminal) protecting groups.

There are number of N-terminal protecting groups.[6] The most common examples are summarized in the Table 3.4.

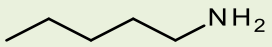
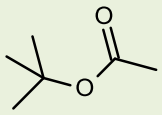
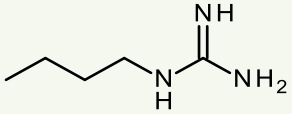
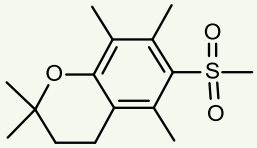
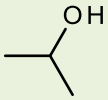
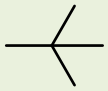
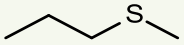
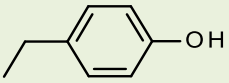
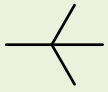
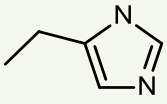
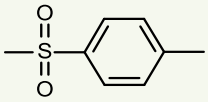
Table 3.4 The most common N-terminal protecting groups and their removal conditions.

Name and Structure	Removal conditions
tert-butyloxycarbonyl(Boc) 	a) 4M HCl in dioxane b) 1.25M HCl in methanol c) 30-50% TFA-DCM
9-fluorenylmethyloxycarbonyl (Fmoc) 	a) Morpholine in organic solvent b) NH_3 10 hours c) Piperidine (piperazine) in organic solvents
triphenylmethyl(Tri) 	a) 1% TFA-DCM b) 0.2% TFA, 1% H_2O-DCM
benzyloxycarbonyl (Z) 	a) H_2 cat. b) BBr_3 c) TFA at high temperature
allyloxycarbonyl (Alloc) 	a) $Pd(PPh)_3$, cat b) $NH_3{\cdot}BH_3$ in organic solvents

Some amino acids contain a third functional group that required a protection as well, *e.g.* the ε-amino group of lysine, the guanidine group of arginine or β-mercapto group of cysteine. There are numerous side-chain protecting groups which have to be chosen

depending on peptide coupling reaction conditions, deprotection methods. The common examples of the side chain protecting groups are summarized in the following table.

Table 3.5 Some common side chains protecting groups of the selected amino acids.

Amino acid	Side chain	Protection
lysine (lys)		*tert*-butyloxycarbonyl(Boc) 
arginine (arg)		2,2,5,7,8-pentamethyl-chroman-6-sulphonyl (Pmc) 
threonine (thr)		*tert*-butyl (*t*-Bu) 
methionine (met)		oxidation to S=O (sometimes)
tyrosine (tyr)		*tert*-butyl (*t*-Bu) 
histidine (his)		*p*-toluenesulfonyl (Tos) 

In the peptide coupling process various different protecting groups are often used. It is essential that they are chosen in order to permit the selective deprotection of some protecting

groups without any affect on other protecting groups. Therefore protecting schemes are developed to match protecting groups in one molecule in order to avoid unwanted deprotection.

Another important development in the area of peptide coupling reactions was the discovery of racemization suppressants, these contributing to considerable improvements in optical purity. However, undesired racemization can occur at the C-terminal amino acid residue in the course of a coupling reaction.

Fortunately, these side processes can be minimized, even eliminated completely, by adding an appropriate racemization suppressing agent such as 1-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HOSu) and this minimizes the loss of the optical integrity at the chiral center.[5]

HOBt HOSu

Figure 3.6 Structures of 1-hydroxybenzotriazole (HOBt) and N-hydroxysuccinimide (HOSu).

General Outline of Solid Phase Peptide Synthesis (SPPS)

Another approach to peptide coupling is solid phase synthesis which is mostly applied in preparation of long-chain peptides due to the simple separation of the growing peptide from reaction mixture and various by-products.

The innovatory principle behind solid phase peptide synthesis (SPPS) as presented by Merrifield[7] is that if the peptide is attached to an insoluble polymer support all soluble pollutions can be removed from the peptide-solid support matrix by filtration and washed away at the end of each coupling step. After the desired peptide has been obtained, it can be released from the polymeric support.

The solid support is a synthetic polymer containing reactive groups such as –OH, which are constructed so that they can react rapidly with the carboxyl group (or boronic acid group) of N-protected amino acid attaching it to polymer.[8] The amino protecting group can be removed and second N-protected amino acid can be reacted with this amino acid. These steps are repeated until the desired peptide is yielded. In order to finish the whole process, different reagents are used to break the bond between the C-terminal amino acid and the polymer support.[9] Some examples of solid supports for boronic acids are given below (Figure 3.7).

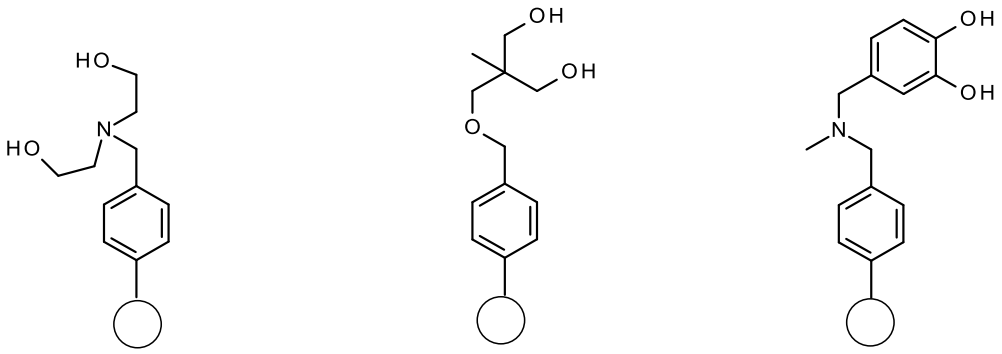


Figure 3.7 Structures of solid supports for boronic acid immobilization.

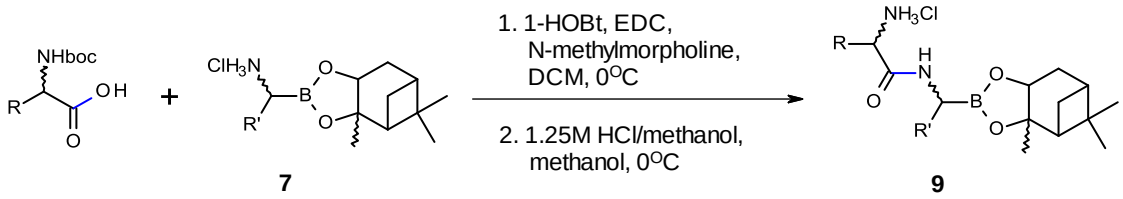
It was decided to activate C-terminal (B-terminal in our case) of the incoming amino acid using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) that reacts with the boronic acid group to form a highly reactive intermediate by turn rapidly displaced by nucleophilic attack from the deprotected (with help of N-methylmorpholine) amino group on the N-terminus to form the new peptide bond. EDC forms extremely reactive intermediate therefore racemization of the chiral carbon of amino acid can take place, so reagent (1-hydroxybenzotriazole (HOBt)) that reacts with the intermediate forming a less-reactive HOBt ester intermediate that decreases the risk of racemization was added.

As was outlined above HOBt, EDC and Boc-protective group were chosen to perform the peptide coupling in this investigation due to their commercial availability, simple work-up and deprotection in the reaction sequence.

Peptide coupling with L-amino acids was performed in DCM at 0°C giving resulting boc-protected peptides with high yield.[10] Column chromatography was sometimes nedeed to purify the products.

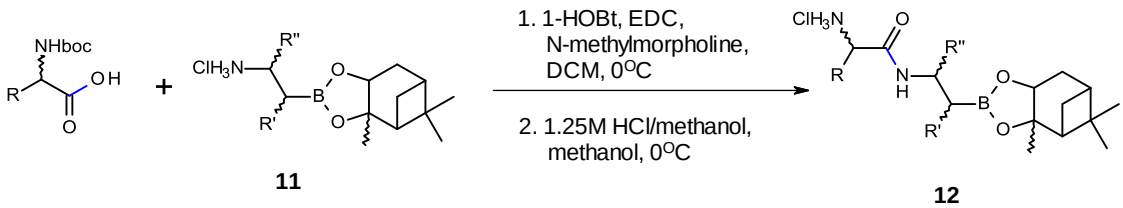
Then the protected peptide was treated with 1.25M HCl/methanol with stirring at 0°C followed by solvent evaporation to give pure hydrochloride salt of the amine **9** as a white powder as outlined in Scheme 3.11.

The processes of coupling and boc-deprotection were repeated until desired tripeptide **10** was obtained.



Scheme 3.11 The general scheme for solution phase α-aminoboronic peptide synthesis.

Coupling reactions of some β-aminoboronic pinanediol esters **11** with the ordinary L-amino acids have also been performed using the same procedure (Scheme 3.12), as a part of a larger project connected with synthesis and antimicrobial studies of dipeptides containing β-aminoboronic acids.[11]

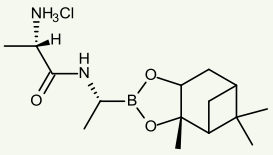
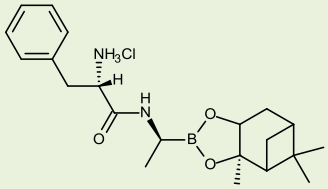
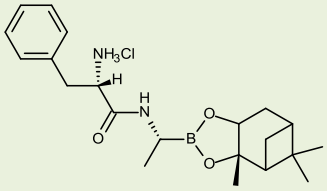


Scheme 3.12 The general scheme for a solution phase β-aminoboronic peptide synthesis.

The following library of peptides was created employing the substituents of different types in order to cover as large a field of structures as possible, *e.g.* aliphatic, branched aliphatic, aromatic, substituted aromatic, heterocyclic.

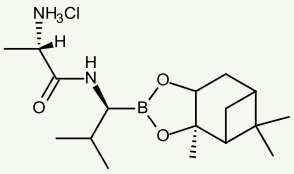
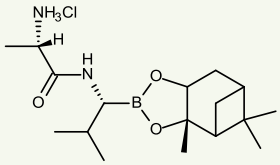
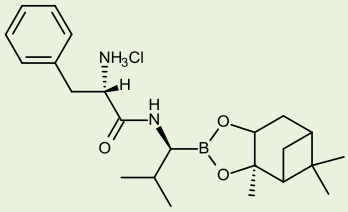
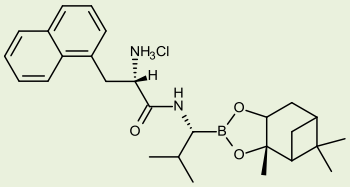
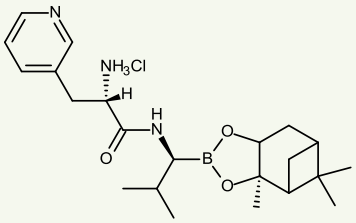
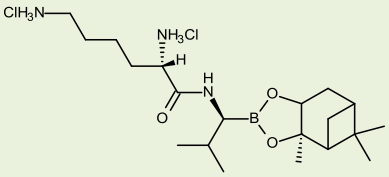
All the structures and yields of synthesized peptides are summarized in the following tables. For convenience in the interpretation of the results the closest fit structures are placed next to each other. Some of the yields are low, but due to time constraints optimization of the reaction conditions/work up has not been performed.

Table 3.6 Synthesized methyl α-aminoboronic dipeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
		 9.1	80
 9.2	38*	 9.3	93

*Compound **9.2** was obtained with low yield because it was prepared at the very beginning of the study.

Table 3.7 Synthesized *iso*-propyl α-aminoboronic dipeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 9.4	99	 9.5	94
 9.6	99	 9.7	71
 9.8	39*		
 9.9	48*		

*Compound **9.9** was obtained with low yield because it was prepared at the very beginning of the study and the yield of the compound **9.8** was low (optimization has not been performed).

Table 3.8 Synthesized phenyl α-aminoboronic dipeptides as pinanediol esters.

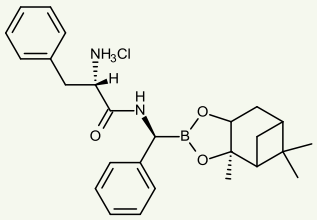
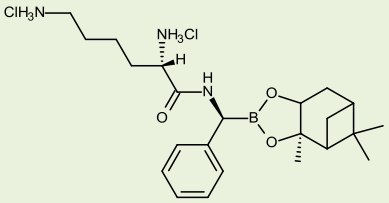
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 9.10	99		
 9.11	83		

Table 3.9 Synthesized 4-F-phenyl α-aminoboronic dipeptides as pinanediol esters.

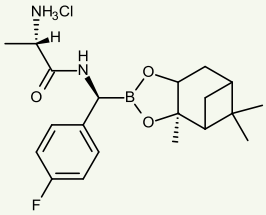
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 9.12	98		

Table 3.10 Synthesized benzyl α-aminoboronic dipeptides as pinanediol esters.

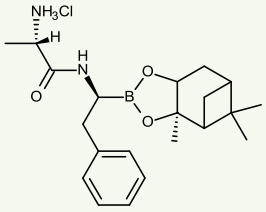
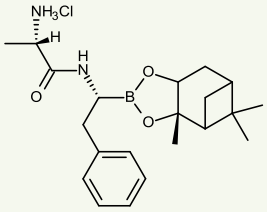
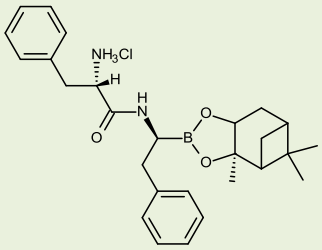
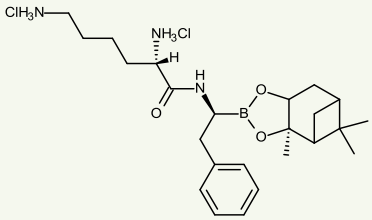
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 9.13	99	 9.14	92
 9.15	91		
 9.16	77		

Table 3.11 Synthesized phenethyl α-aminoboronic dipeptides as pinanediol esters.

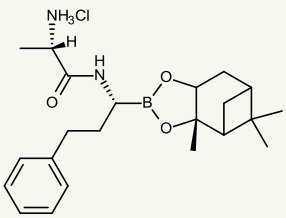
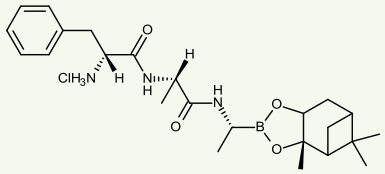
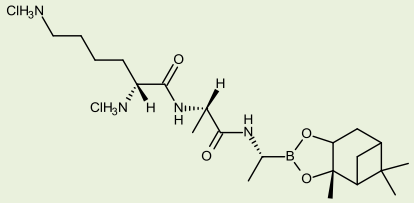
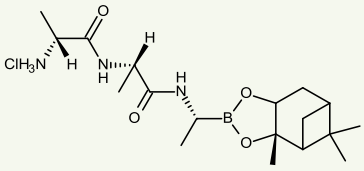
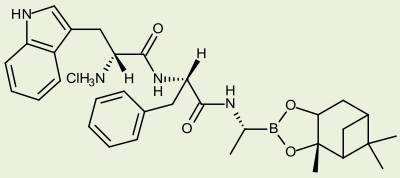
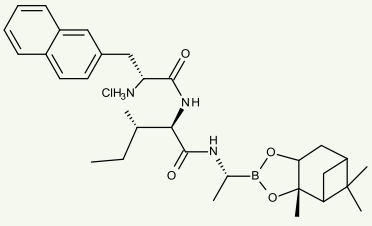
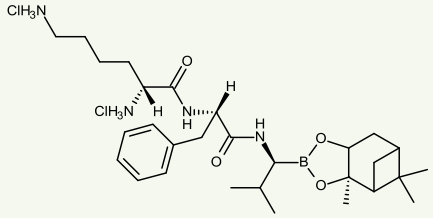
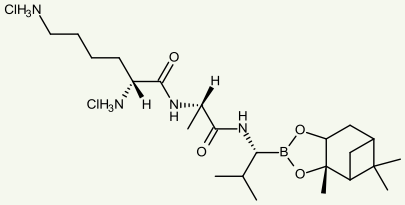
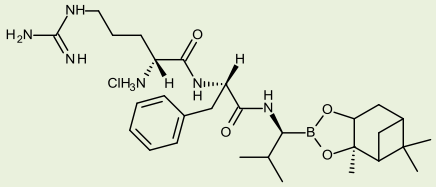
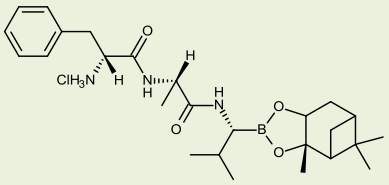
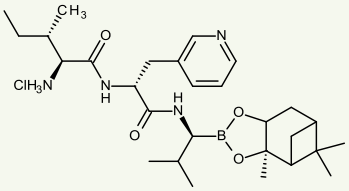
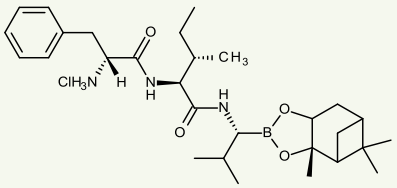
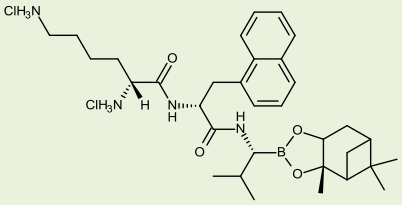
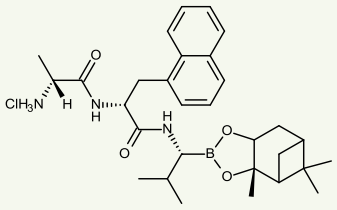
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
		 9.17	85

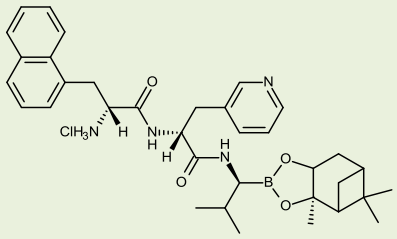
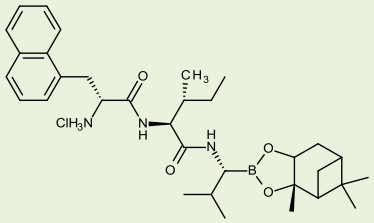
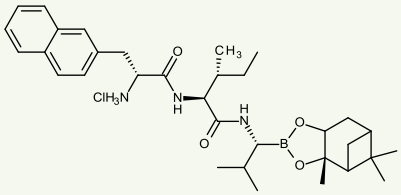
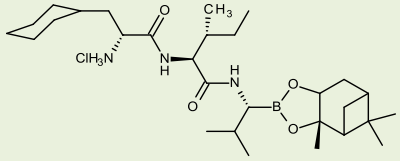
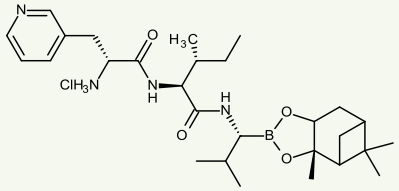
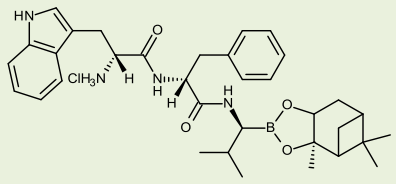
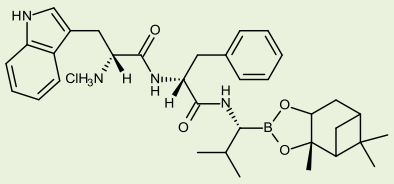
Table 3.12 Synthesized methyl α-aminoboronic tripeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
		 10.1 (196)	88
		 10.2 (197)	71
		 10.3 (199)	68
		 10.4 (316)	63
		 10.5 (395)	38*

*Compound **10.5** was obtained with low yield.

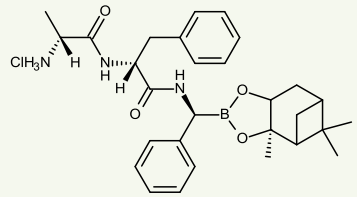
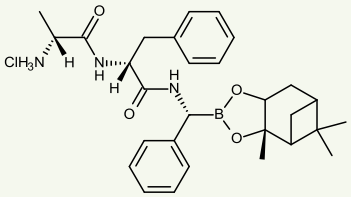
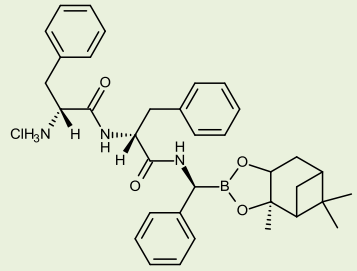
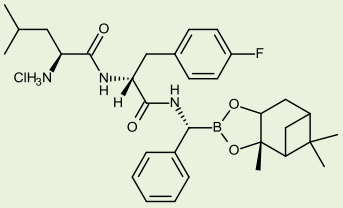
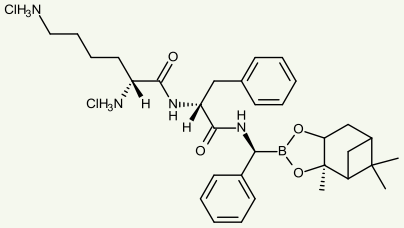
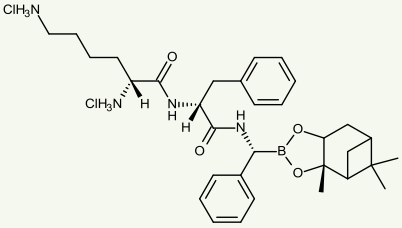
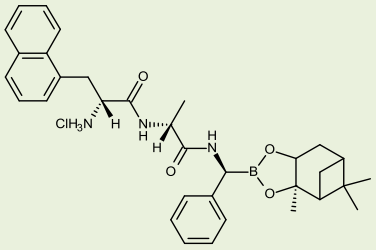
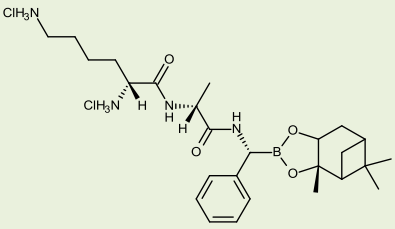
Table 3.13 Synthesized *iso*-propyl α-aminoboronic tripeptides as pinanediol esters.

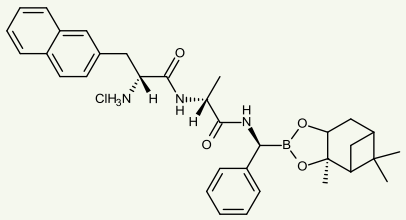
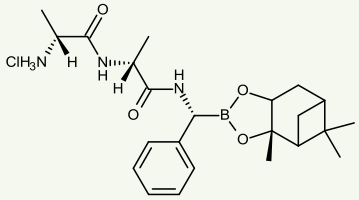
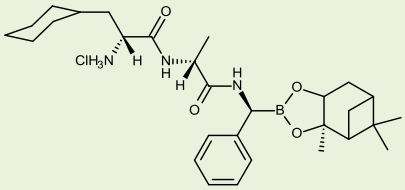
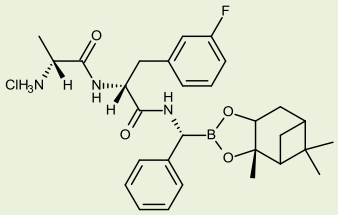
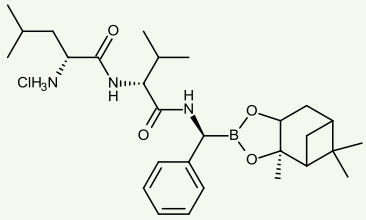
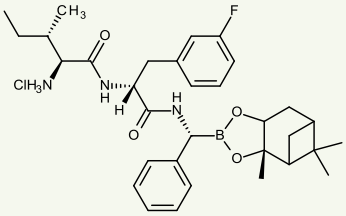
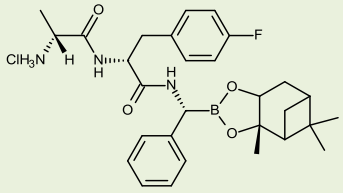
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 10.6	95	 10.7	91
 10.8	29*	 10.9	99
 10.10	47*	 10.11	95
		 10.12	72
		 10.13	77

 10.14	63	 10.15	99
		 10.16	98
		 10.17	85
		 10.18	92
 10.19	67	 10.20	67

*Compound **10.10** was obtained with low yield so as it depends on a purification mistake; the yield of compound **10.8** depends on the nature of incoming arginine amino acid, which is always challenge to work with.

Table 3.14 Synthesized phenyl α-aminoboronic tripeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 10.21	90	 10.22	66
 10.23	85	 10.24	90
 10.25	97	 10.26	93
 10.27	88	 10.28	89

	88		94
10.29		10.30	
	96		58*
10.31		10.32	
	74		75
10.33		10.34	
			50*
		10.35	

*The yields of the compounds **10.32** and **10.35** are low probably due to difficulties in the linking process of the incoming alanine amino acid and fluoro-substituted phenylalanine.

Table 3.15 Synthesized 4-F-phenyl α-aminoboronic tripeptide as pinanediol ester.

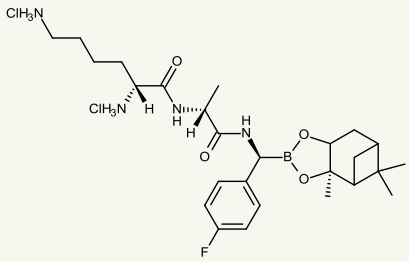
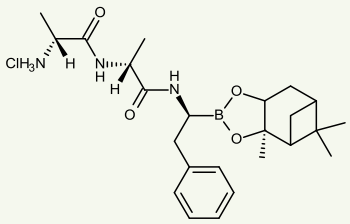
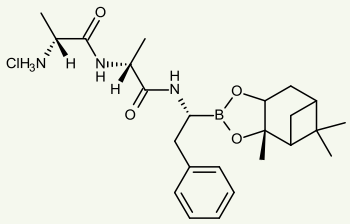
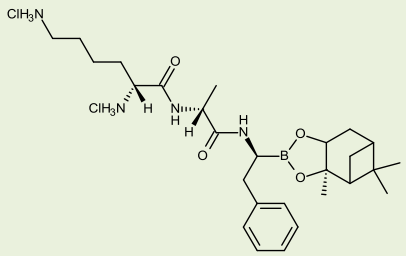
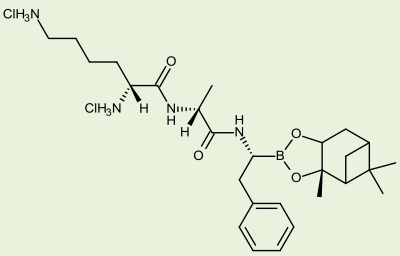
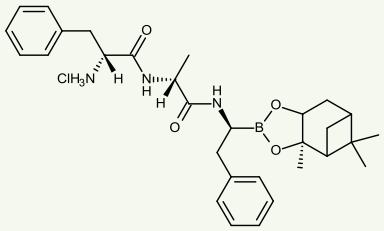
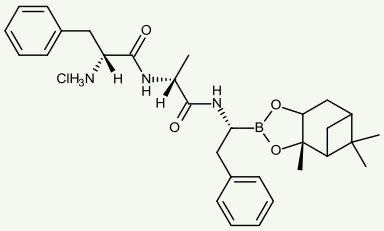
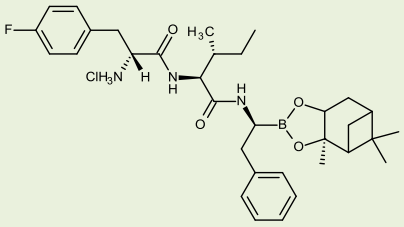
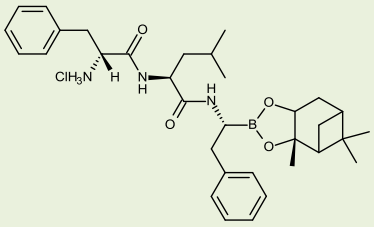
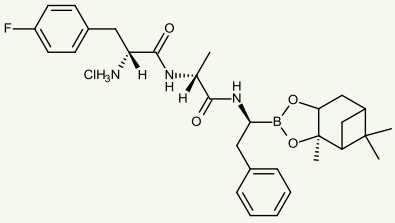
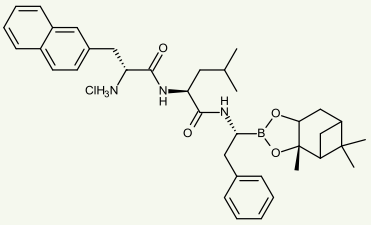
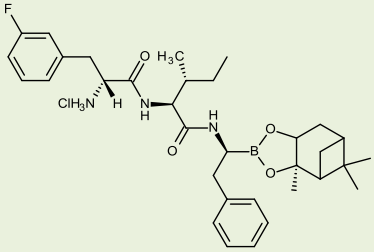
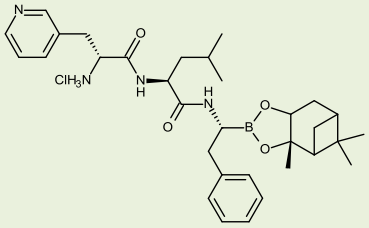
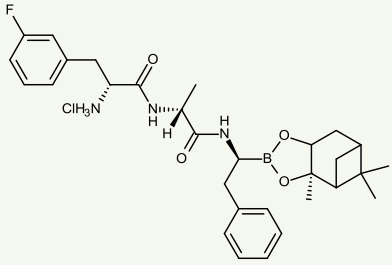
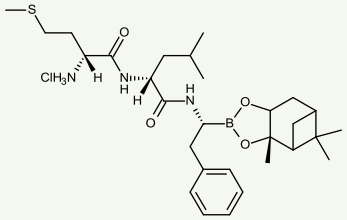
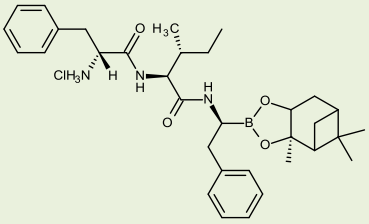
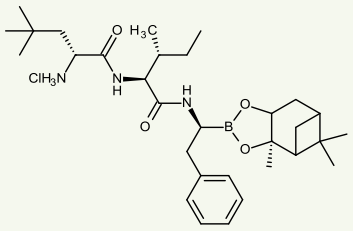
(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 10.36	99		

Table 3.16 Synthesized benzyl α-aminoboronic tripeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 10.37	85	 10.38	99
 10.39	56	 10.40	99
	67		96

10.41		10.42	
	63		99
10.43		10.44	
	68		91
10.45		10.46	
	43*		69
10.47		10.48	
	60		90
10.49		10.50	
	41*		

10.51



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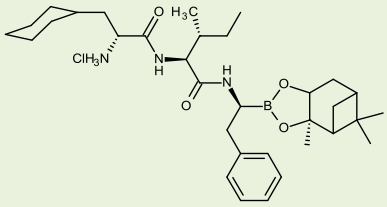
10.52



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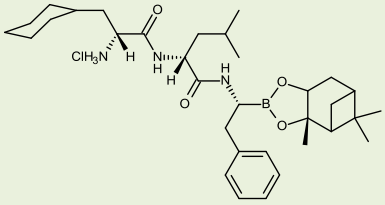
10.53



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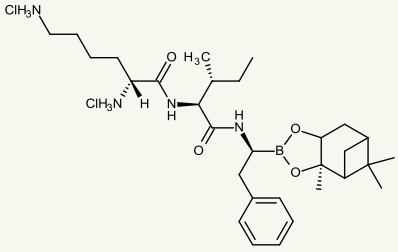
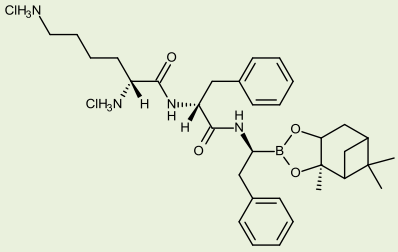
10.54



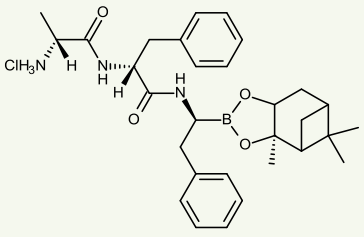
53

10.55



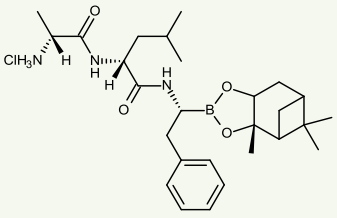
94

10.56



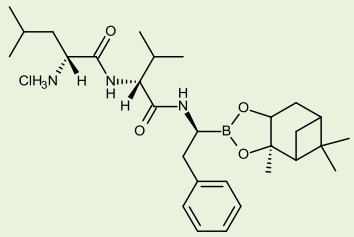
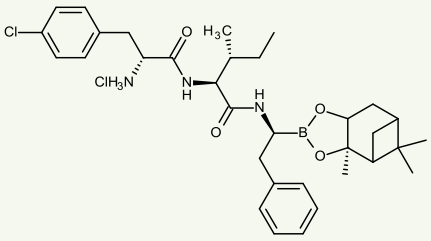
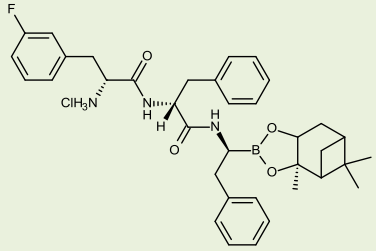
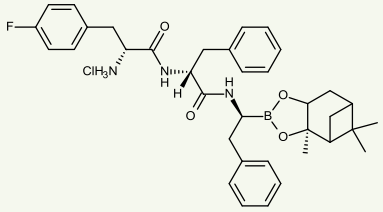
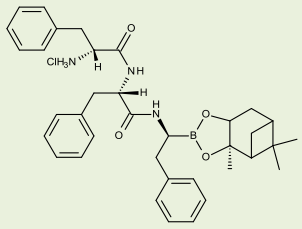
86

10.57



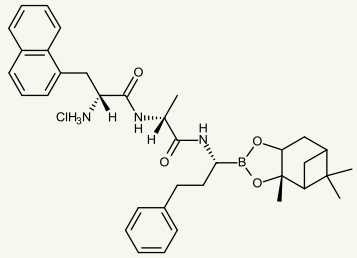
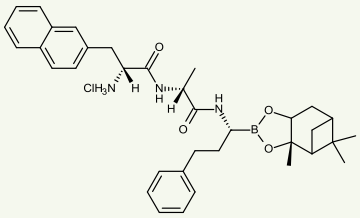
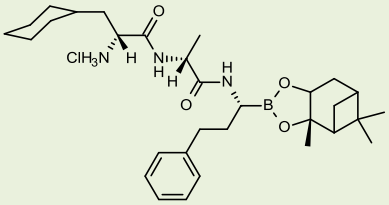
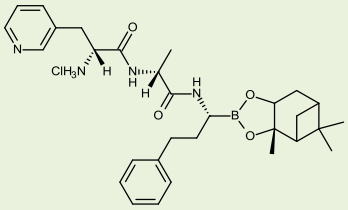
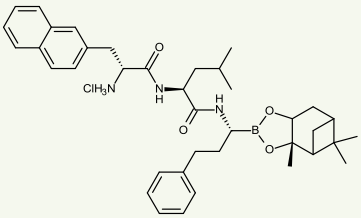
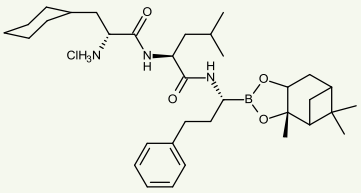
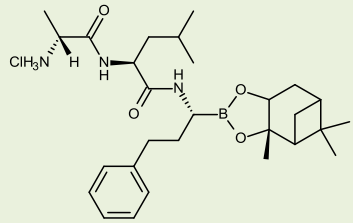
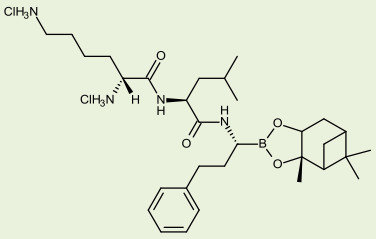
92

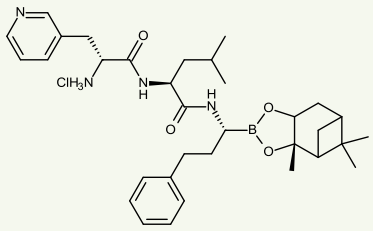
10.58

 10.59	80
 10.60	47*
 10.61	82
 10.62	39*
 10.63	89

*The yields of the compounds **10.47, 10.60** and **10.62** are low probably due to difficulties in the linking process of the incoming halo-substituted amino acid with boron-containing dipeptide. Compounds **10.51** and **10.53** were obtained with relatively low yields possibly due to purifications mistake or structural peculiarities of the amino acids.

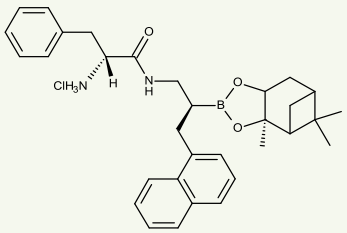
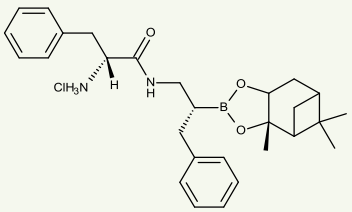
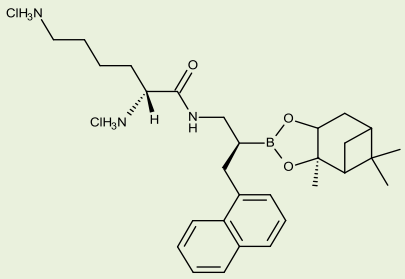
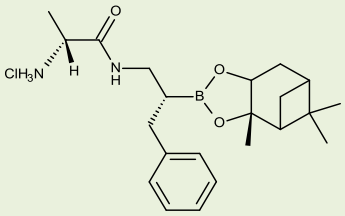
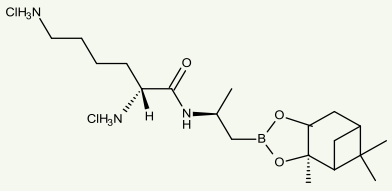
Table 3.17 Synthesized phenethyl α-aminoboronic tripeptides as pinanediol esters.

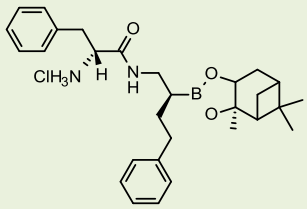
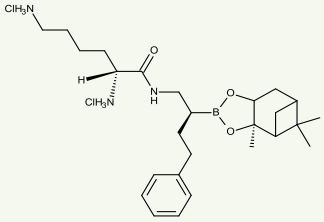
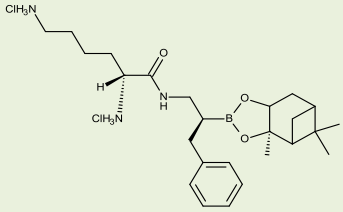
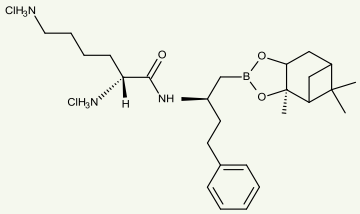
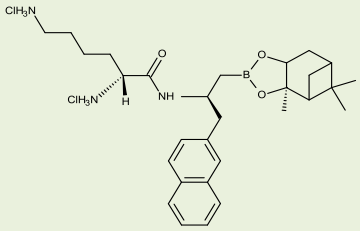
(+)-ester			
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 10.64	88	 10.65	79
 10.66	99	 10.67	45*
 10.68	77	 10.69	72
	86		92

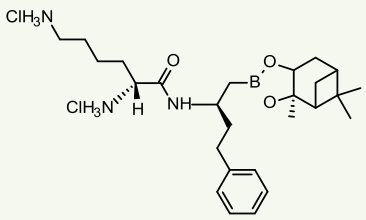
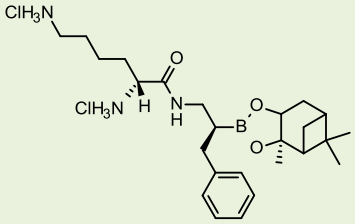
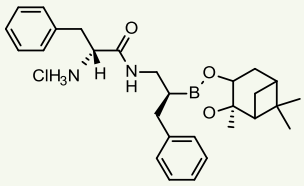
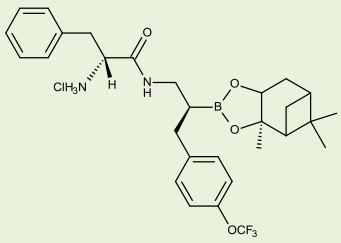
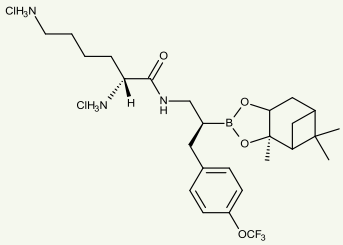
10.70		10.71	
			76
		10.72	

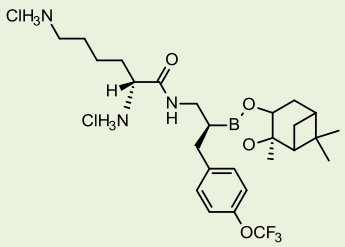
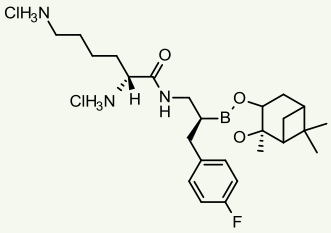
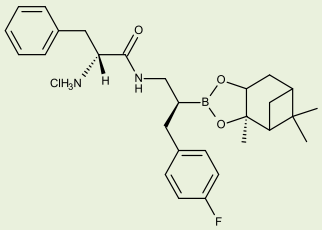
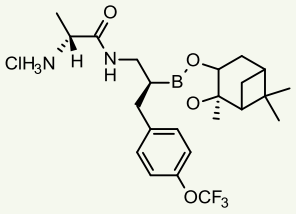
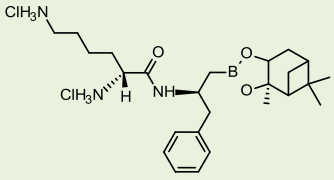
*Compound **10.67** was obtained with relatively low yield due to purification mistake or structural peculiarities of the incoming amino acid.

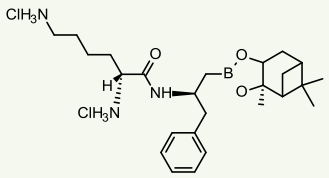
Table 3.18 Synthesized β-aminoboronic dipeptides as pinanediol esters.

(-)-ester		(+)-ester	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
	47*		80
12.1		12.2	
	92		99
12.3		12.4	
	96		
12.5			

 12.6	57
 12.7 D-Lysine	99
 12.8 D-Lysine	57
 12.9	99
 12.10	27*

 12.11	42*
 12.12	91
 12.13	71
 12.14	67
 12.15	76

 12.16 D-Lysine	59
 12.17	99
 12.18	96
 12.19	75
 12.20	95



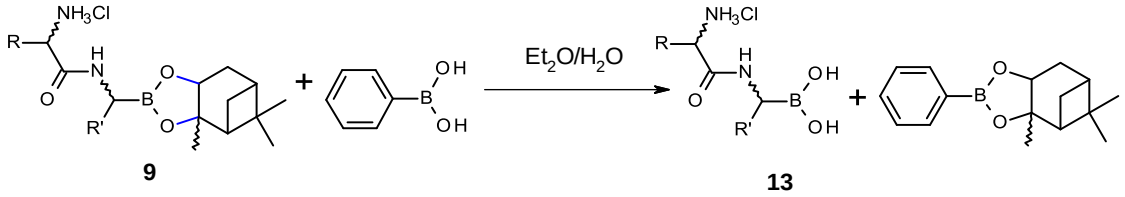
12.21 D-Lysine

*Compounds **12.1**, **12.10** and **12.11** were obtained with relatively low yields due to steric hindrance in the molecule of β-aminoboronic pinanediol ester.

3.2.2. Synthesis of Free Boronic Acid Peptides. Deprotection of Pinanediol

Several general methods for the ester deprotection are known, but they often performed ether in harsh acidic or oxidizing conditions.[12,13] Cleavage of these esters can be performed by methods involving deprotection with boron trichloride[14-16] or acidic hydrolysis[17,18] as well.

One of the gentler methods for the deprotection of pinanediol is transesterification in the presence of polystyrene-boronic acid[19] as well as with excess of phenylboronic acid as shown for α-aminoboronic ester dipeptide in Scheme 3.13.[10,20,21]



Scheme 3.13 The reaction of pinanediol cleavage by transesterification with an excess of phenylboronic acid.

This reaction is most effective under phase-transfer conditions where the resulting boron-containing peptide is water soluble and easily can be separated from excess organic-soluble phenylboronic acid.

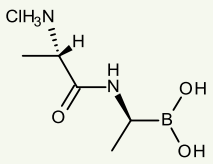
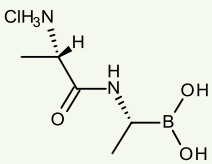
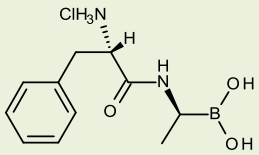
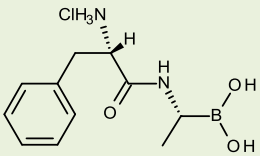
At the beginning of this investigation the attempt was made to deprotect pinanediol by refluxing of an ester in 3 N HCl over 1 hour, but low yields and partial destruction of a

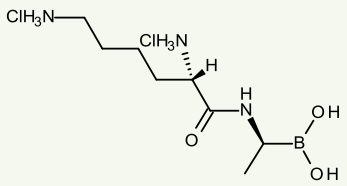
peptide bond have been observed. Most of the products had to be purified by column chromathography which was complicated due to very similar R_f values of a product and by-products (chain-fragments). So afterwards it has been decided to use phenylboronic acid as a reagent for the conversion of pinanediol esters **9**, **10**, **12** to the corresponding free boronic acids **13**, **14** and **15**.

The products were obtained as white (pale yellow) solids very soluble in water with 85-99% of purity which was enough to perform necessary testing. The starting amino acids were the only impurity in the final peptides. Some of the yields are relatively low, but it does not have any significance in this investigation since the procedure is not going to be expanded to the industrial scale.

All the structures and the yields of synthesized di- and tri- peptides are summarized in the following tables. For the convenience in the interpretation of the results the closest fit structures were placed next to each other. Some of the yields are low, but due to time constraints optimization of the reaction conditions/work up has not been performed.

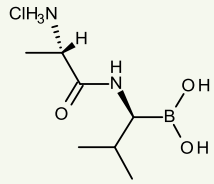
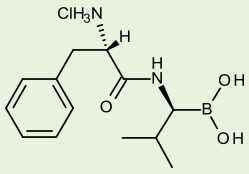
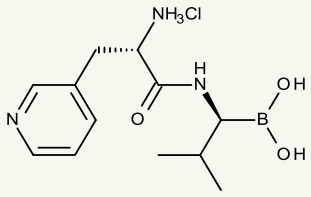
Table 3.19 Synthesized methyl α-aminoboronic dipeptides as boronic acids.

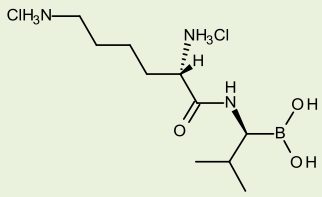
(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
	50[a*]		65[a]
13.1		13.2	
	80[a]		87[a]
13.3		13.4	

 13.5	75[a]		

a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.
*Compound **13.1** was obtained with relatively low yield because it was prepared at the very beginning of the study.

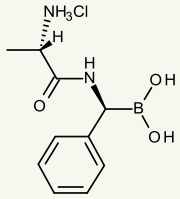
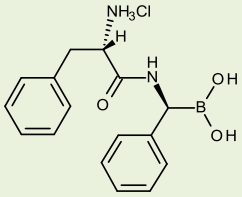
Table 3.20 Synthesized *iso*-propyl α-aminoboronic dipeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 13.6	43[a]*		
 13.7	72[a]		
 13.8	99[b]		

	49[a*]		
13.9			

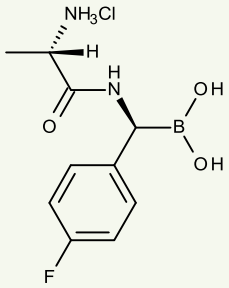
a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.
*Compounds **13.6** and **13.9** were obtained with relatively low yield because they were prepared at the very beginning of the study.

Table 3.21 Synthesized phenyl α-aminoboronic dipeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
	73[a]		
13.10			
	44[a*]		
13.11			

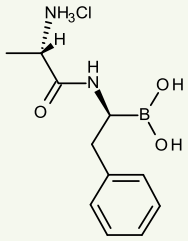
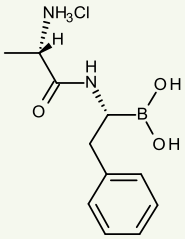
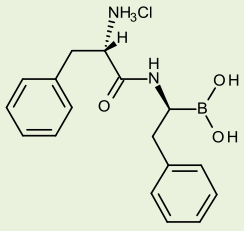
a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.
*Compound **13.11** was obtained with relatively low yield because it was prepared at the very beginning of the study.

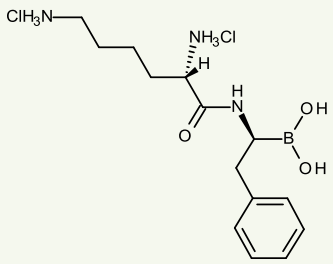
Table 3.22 Synthesized 4-F-phenyl α-aminoboronic dipeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 13.12	85[b]		

b. The compound was prepared by transesterification by phenylboronic acid.

Table 3.23 Synthesized benzyl α-aminoboronic dipeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 13.13	54[a]	 13.14	92[b]
 13.15	35[a*]		

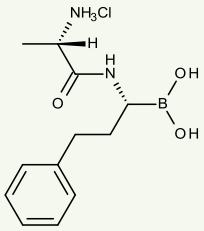


33[a*]

13.16

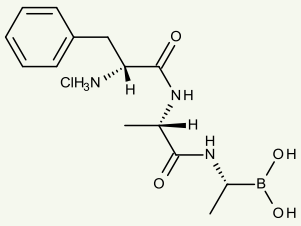
a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.
*Compounds **13.15** and **13.16** were obtained with relatively low yields due to the acidic hydrolysis and difficulties in the chromatography process after it.

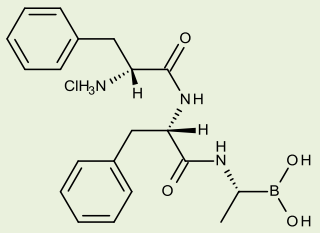
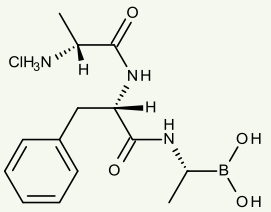
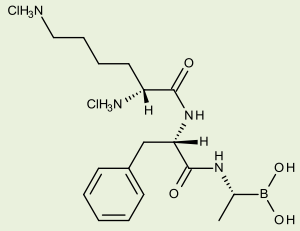
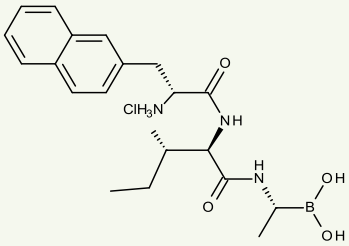
Table 3.24 Synthesized phenethyl α-aminoboronic dipeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
		 13.17	99[b]

b. The compound was prepared by transesterification by phenylboronic acid.

Table 3.25 Synthesized methyl α-aminoboronic tripeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
		 14.1	75[a]

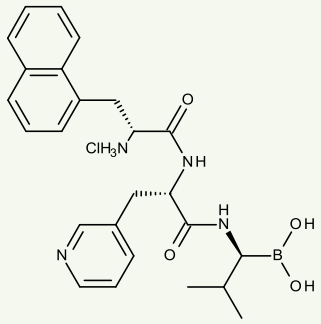
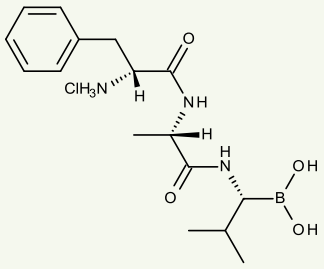
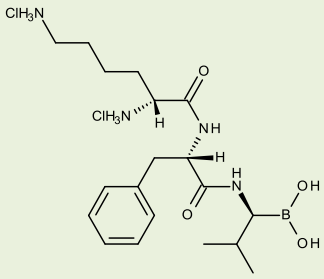
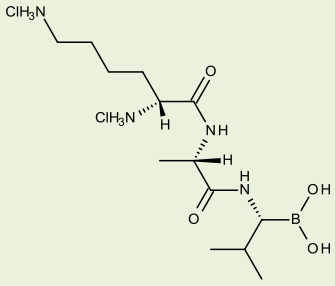
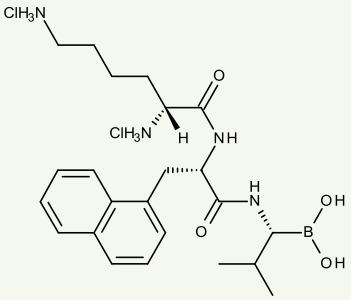
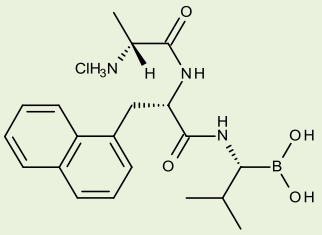
	 14.2	56[a]
	 14.3	17[a]*
	 14.4	24[a]*
	 14.5	78[b]

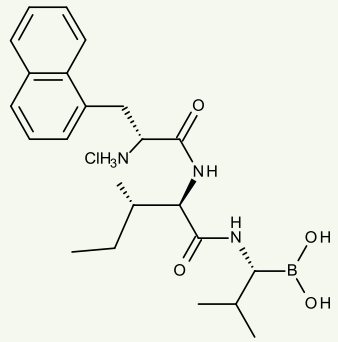
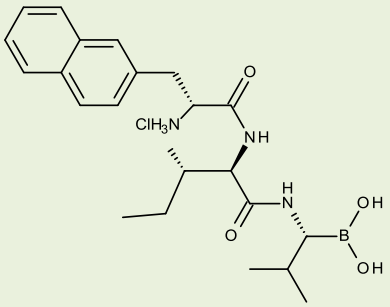
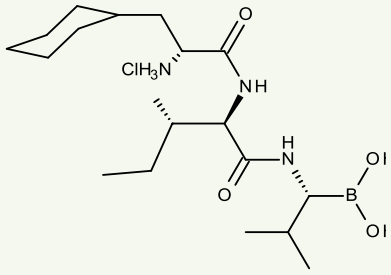
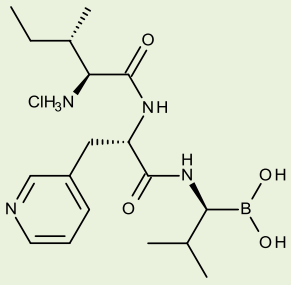
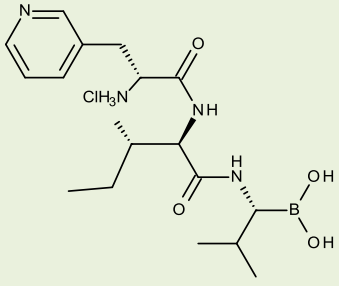
a. compound was prepared by acidic hydrolysis.

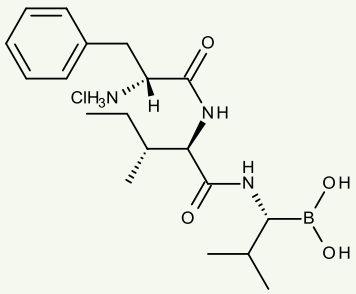
b. compound was prepared by transesterification by phenylboronic acid.

*Compounds **14.3** and **14.4** were obtained with relatively low yields due to the acidic hydrolysis and difficulties in the chromatography process after it.

Table 3.26 Synthesized *iso*-propyl α-aminoboronic tripeptides as boronic acids.

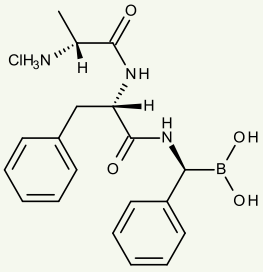
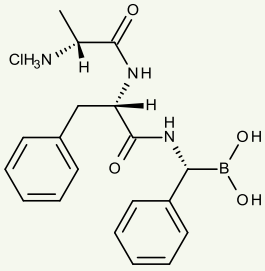
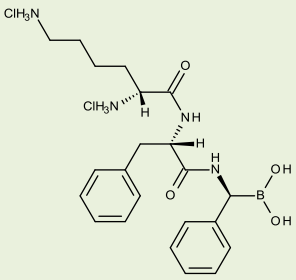
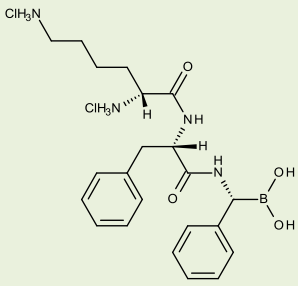
(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 14.6	91[b]	 14.7	53[a]
 14.8	87[a]	 14.9	96[a]
		 14.10	99[b]
			98[b]

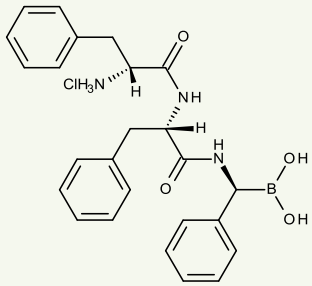
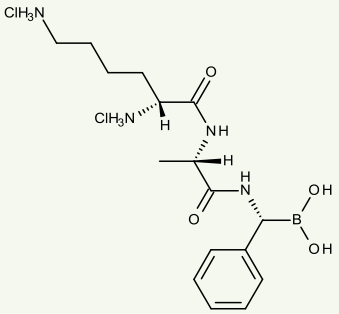
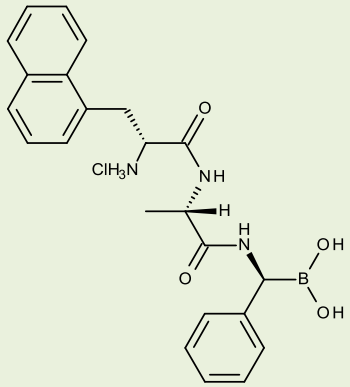
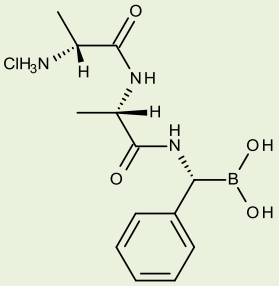
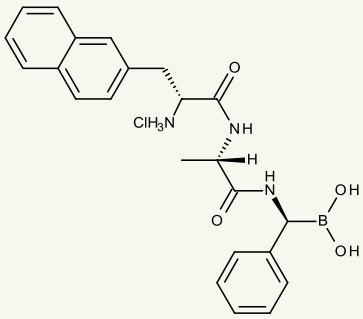
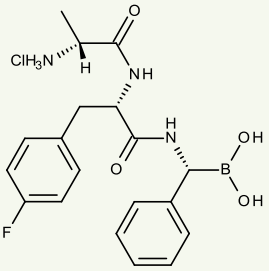
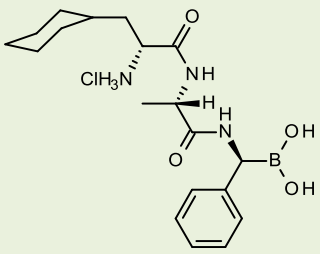
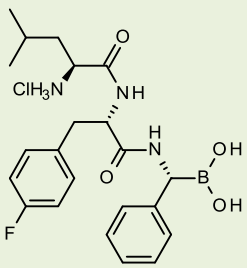
14.11		
		55[b]
14.12		
		76[b]
14.13		
		81[b]
14.14		
		99[b]
80[b]		

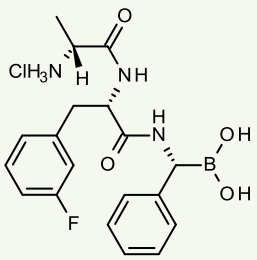
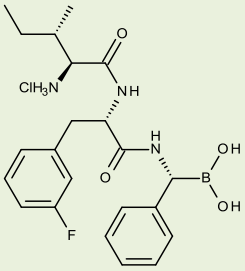
14.15		14.16	
			99[b]
		14.17	

a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.

Table 3.27 Synthesized phenyl α-aminoboronic tripeptides as boronic acids.

(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
	88[a]		57[a]
14.18		14.19	
	21[a]*		44[a]*
14.20		14.21	

	47[a]*		62[a]
14.22		14.23	
	78[b]		91[a]
14.24		14.25	
	98[b]		99[b]
14.26		14.27	
	99[b]		81[b]
14.28		14.29	

		 14.30	99[b]
		 14.31	93[b]

a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.
*Compounds **14.20**, **14.21** and **14.22** were obtained with relatively low yields due to the acidic hydrolysis and difficulties in the chromatography process after it.

Table 3.28 Synthesized 4-F-phenyl α-aminoboronic tripeptides as boronic acids.

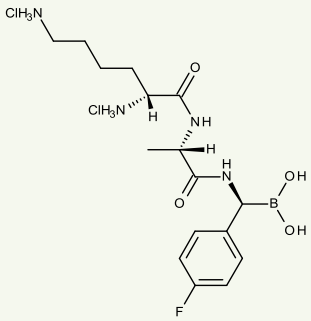
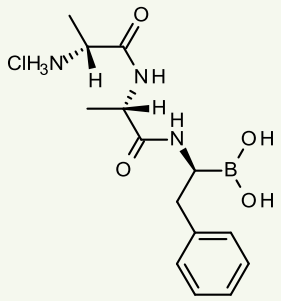
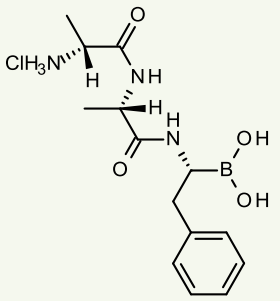
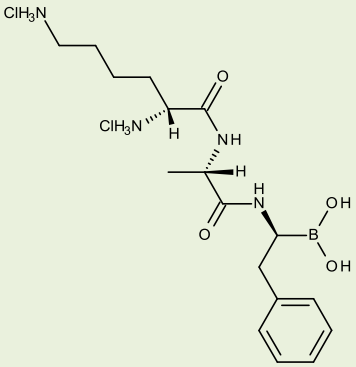
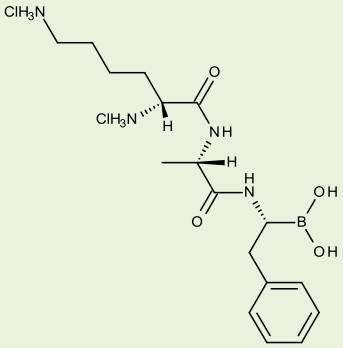
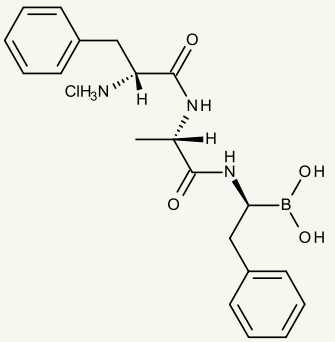
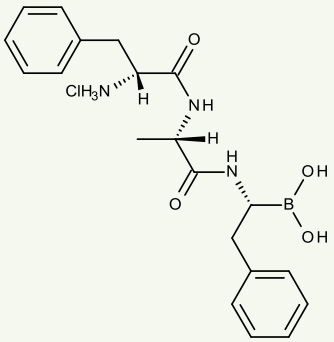
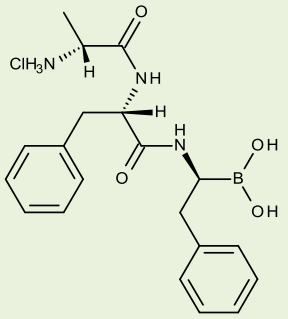
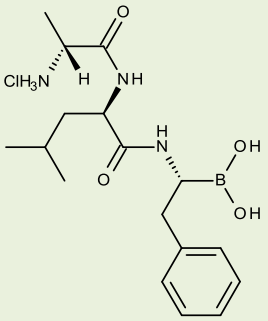
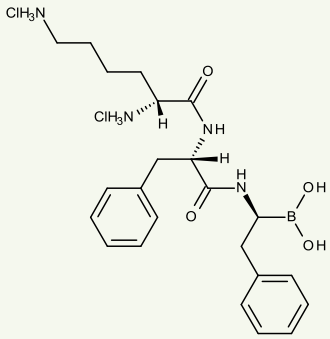
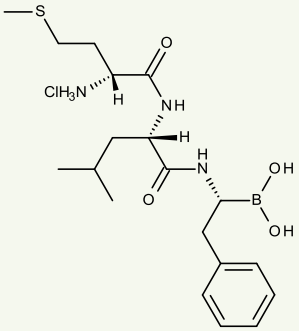
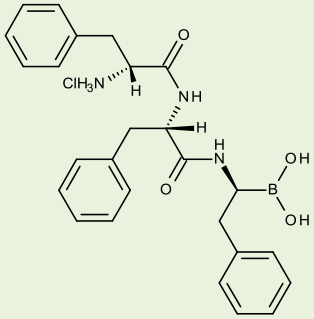
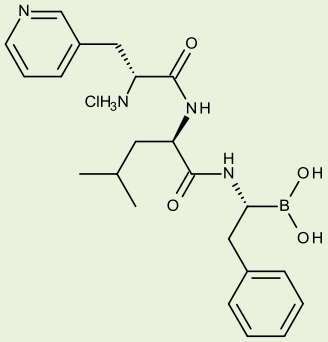
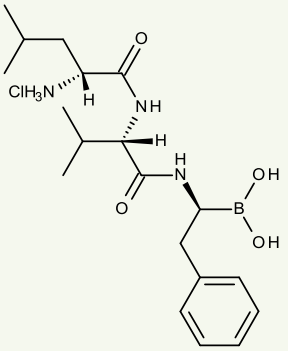
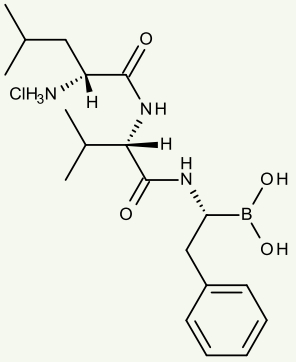
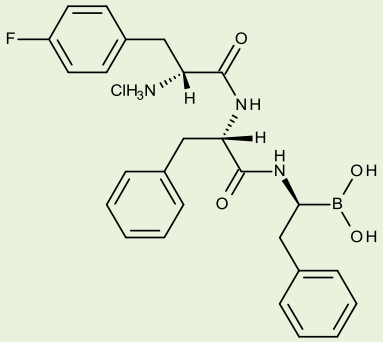
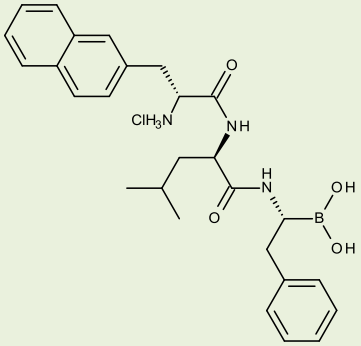
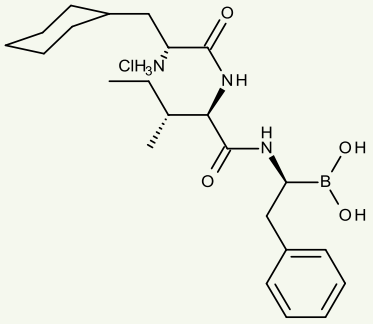
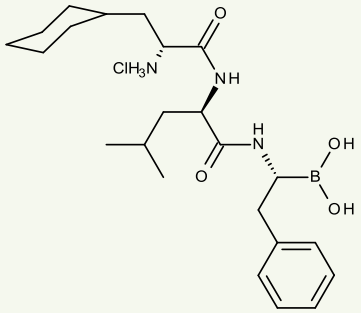
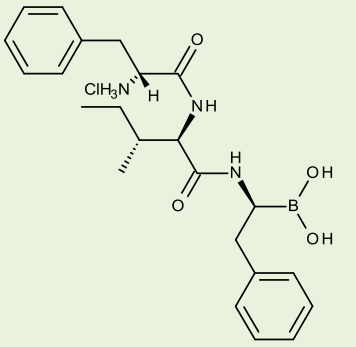
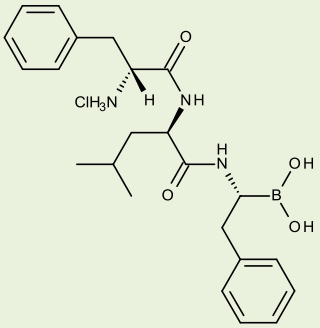
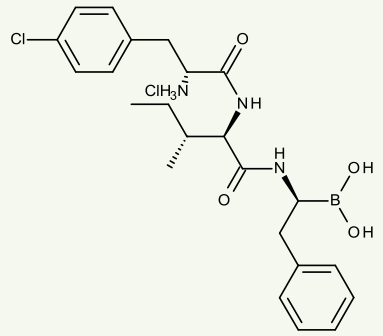
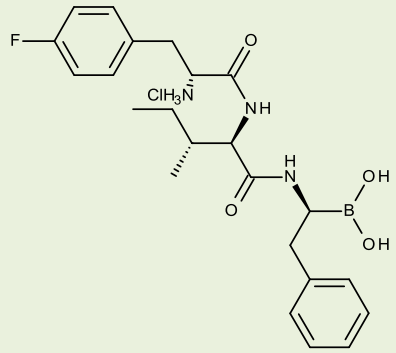
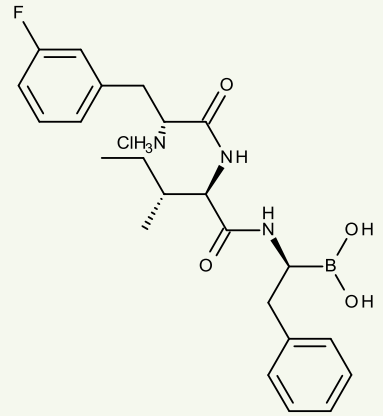
(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 14.32	54[a]		

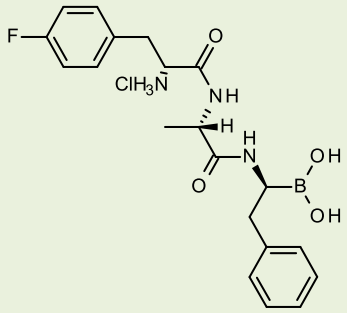
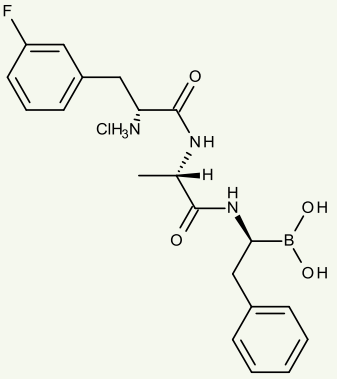
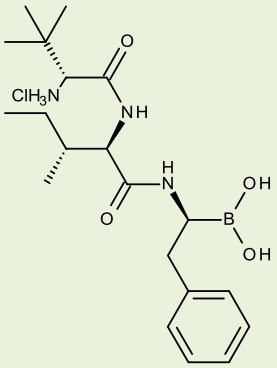
Table 3.29 Synthesized benzyl α-aminoboronic tripeptides as boronic acids.

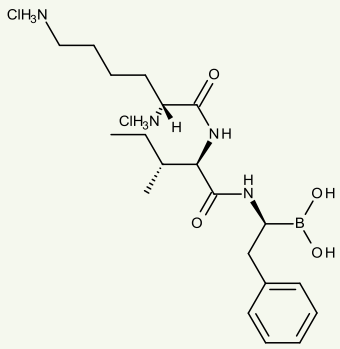
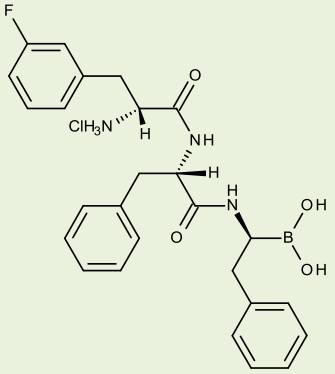
(-)-acid		(+)-acid	
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 14.33	99[a]	 14.34	99[b]
 14.35	99[a]	 14.36	99[b]
 14.37	80[a]	 14.38	77[b]

	65[a]		99[b]
14.39		14.40	
	57[a]		58[b]
14.41		14.42	
	68[a]		99[b]
14.43		14.44	
	83[b]		87[b]

14.45		14.46	
	99[b]		91[b]
14.47		14.48	
	85[b]		99[b]
14.49		14.50	
	99[b]		99[b]
14.51		14.52	

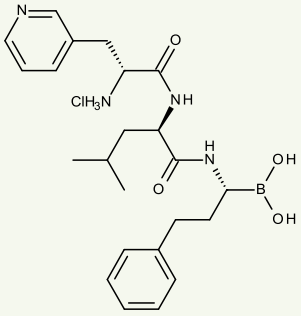
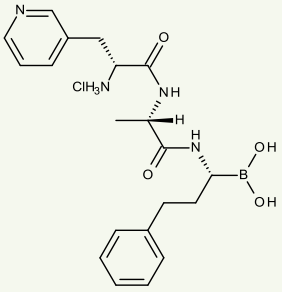
 14.53	69[b]
 14.54	99[b]
 14.55	87[b]

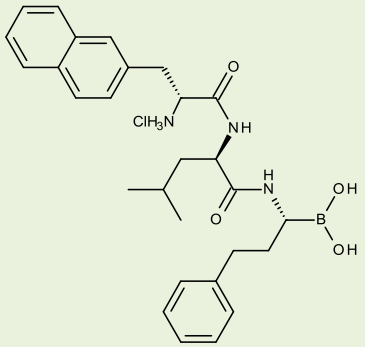
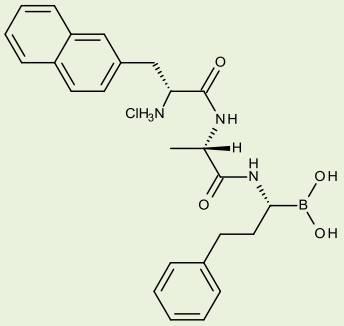
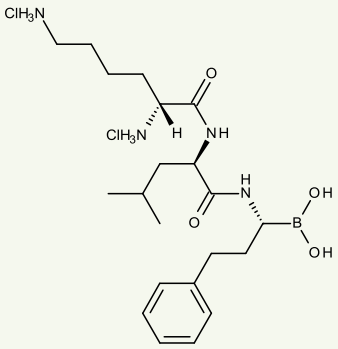
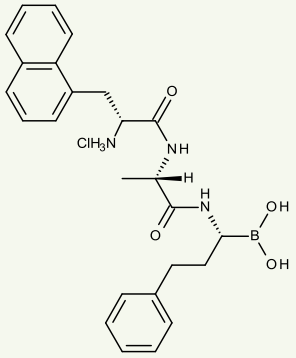
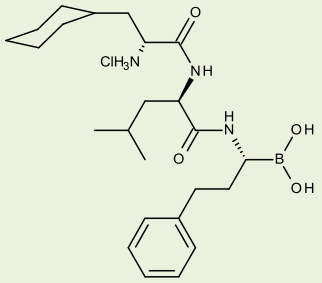
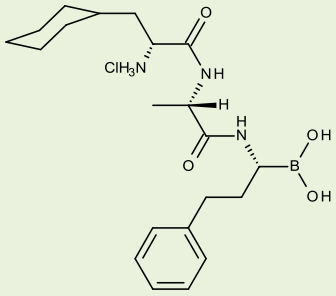
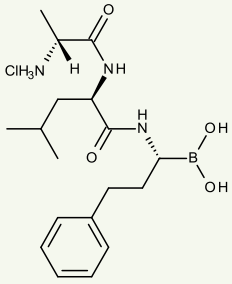
 14.56	90[b]
 14.57	85[b]
 14.58	99[b]

 14.59	99[b]
 14.60	88[b]

a. compound was prepared by acidic hydrolysis.
b. compound was prepared by transesterification by phenylboronic acid.

Table 3.30 Synthesized phenethyl α-aminoboronic tripeptides as boronic acids.

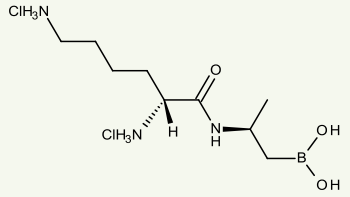
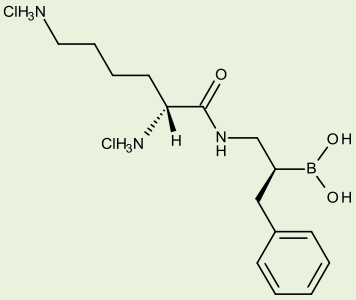
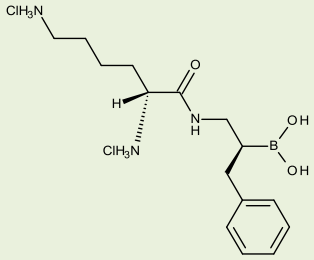
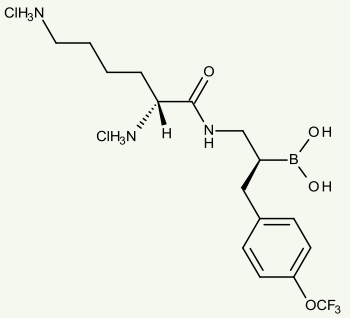
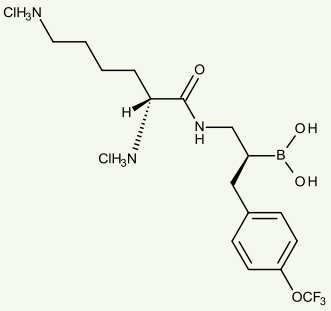
(+)-acid			
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 14.61	99[b]	 14.62	83[b]

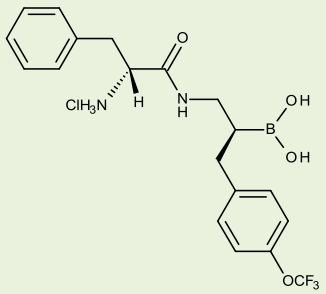
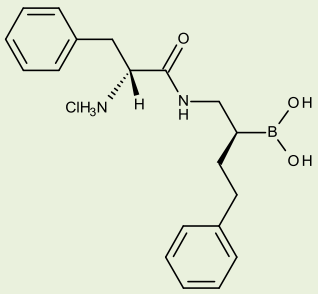
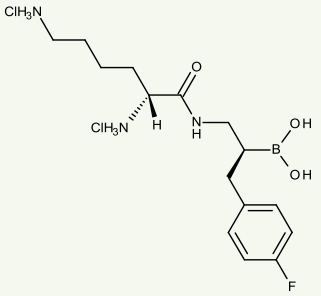
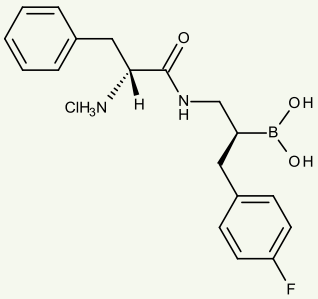
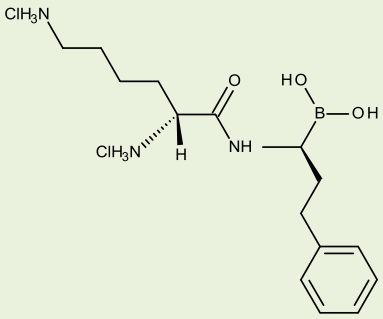
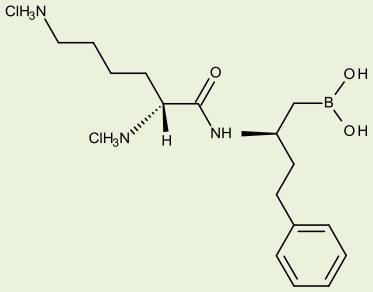
 14.63	58[b]	 14.64	18[b*]
 14.65	91[b]	 14.66	99[b]
 14.67	56[b]	 14.68	86[b]
 14.69	99[b]		

a. compound was prepared by acidic hydrolysis.

b. compound was prepared by transesterification by phenylboronic acid.
*Compound **14.64** was obtained with relatively low yield possibly due to mistakes in the work-up process.

Table 3.31 Synthesized β-aminoboronic dipeptides as boronic acids.

(-)-acid			
Compound structure	**Yield, %**	**Compound structure**	**Yield, %**
 15.1	61[a]		
 15.2	52[a]	 15.3 D-Lysine	91[a]
 15.4	41[b]*	 15.5 D-Lysine	84[b]

	31[a*]		70[a]
15.6		15.7	
	84[b]		82[b]
15.8		15.9	
	74[a]		99[a]
15.10		15.11	

a. compound was prepared by acidic hydrolysis.

b. compound was prepared by transesterification by phenylboronic acid.

*Compound **15.4** was obtained with relatively low yield possibly due to mistakes in the work-up process. Compound **15.6** was obtained with relatively low yield due to the acidic hydrolysis and difficulties in the chromatography process after it.

3.2.3. Experimental part

Protected amino acids HOBt and EDC were purchased from Sigma-Aldrich Co., Chem-Impex International Inc. and Shanghai Mocell Biotech Co.,Ltd. and used as received.

NMR spectra were recorded on a Varian Mercury 400 plus (399.65/100.54 MHz). ^{13}C NMR spectra were obtained with broadband proton decoupling. Signals from carbons α-to boron were not detected. IR spectra were recorded on a Varian 7000e FT-IR spectrometer. Optical rotation was measured on an AA-10R polarimeter (Optical activity Ltd.). Mass spectra were measured on a Thermo electron LTQ Orbitrap XL + Electrospray ion source (ION-MAX). Samples were dissolved in pure methanol and infused by syringe pump at a flow rate of 5µl/min. No molecular ion was detected for compounds containing boronic acid due to anhydride (boroxine) formation in the ion source.

The positions of characteristic vibration frequencies synthesized compounds are shown in the following table:

Group	Frequency in cm^{-1}
B-C	1100-1185
C-F	1100-1250
B-O	1310-1350
C=O	1670-1820
C-H	2850-3000
N-H	3300-3500

General procedure for peptide coupling. [10]

To a solution of boc-protected amino acid (0.0012 mol, 1equiv) in dichloromethane (30 mL) was added 1-hydroxybenzotriazole (HOBt) (0.16 g, 0.0012 mol, 1 equiv) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (0.3 g, 0.0016 mol, 1.3 equiv) at 0°C. The reaction mixture was stirred over 30 min. and α – (or β-) aminoboronic ester **7** (or **11**) (0.0012 mol, 1 equiv) was added, followed by N-methylmorpholine (0.26 mL,

0.0024 mol, 2 equiv), and the mixture was allowed to warm slowly to room temperature overnight. The solution was washed with water, 1 M potassium bisulfate, and sodium carbonate solution. The organic layer was filtered through a pad of silica gel, continuing elution with ethyl acetate. Evaporation of the filtrate yielded the protected dipeptides in 80-99% yield.

General procedure for amine deprotection. [10]

The protected peptide (0.0012 mol) was treated with a 1.25 M solution hydrochloric acid in methanol (25 mL). The solution was stirred over 3 hours at 0°C. Then the solvent was evaporated *in vacuo* giving hydrochloride as white powder with 99% yield.

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a- tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]propanamide 9.1

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.38 – 4.29 (m, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.08 (q, *J* = 7.4 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.21 (ddd, *J* = 10.5, 6.2, 3.1 Hz, 1H), 2.00 (t, *J* = 5.5 Hz, 1H), 1.87 (ddd, *J* = 16.4, 9.9, 2.4 Hz, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.21 (d, *J* = 7.5 Hz, 3H), 1.15 (d, *J* = 7.3 Hz, 1H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.03, 85.43, 77.53, 51.47, 39.53, 37.85, 35.19, 27.66, 26.18, 25.78, 22.99, 16.18, 14.92.

IR: ν 3376, 2916, 1666, 1383, 1121cm^{-1}

$[\alpha]^{23}_{D}$ = -3.8 (*c* 3.44, CH_3OH)

HRMS: calcd for $C_{15}H_{28}O_3N_2B$ 295.2076, found 295.2187

Yield: 80%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-3-phenyl-propanamide 9.2

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.40 – 7.25 (m, 5H), 4.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.01 (t, *J* = 7.3 Hz, 1H), 3.09 (ddd, *J* = 43.6, 13.8, 7.4 Hz, 2H), 2.97 (q, *J* = 7.3 Hz, 1H), 2.38 (ddt, *J* = 13.9, 8.7, 2.4 Hz, 1H), 2.21 (dtd, *J* = 12.0, 6.1, 2.2 Hz, 1H), 2.01 (t, *J* = 5.6 Hz, 1H), 1.91 – 1.78 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 1.26 (d, *J* = 12.7 Hz, 1H), 1.10 (d, *J* = 7.5 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.95, 134.48, 129.42, 127.61, 104.99, 85.69, 77.70, 53.82, 51.68, 39.73, 38.09, 37.67, 35.47, 27.93, 26.36, 26.03, 23.19, 15.12.

IR: ν 3392, 2922, 1668, 1377, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +31.9 (*c* 0.20, CH_3OH)

HRMS: calcd for $C_{21}H_{32}O_3N_2B$ 371.3041, found 371.2502

Yield: 38%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-3-phenyl-propanamide 9.3

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.41 – 7.24 (m, 5H), 4.33 (dd, *J* = 8.8, 1.9 Hz, 1H), 4.06 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.13 (ddd, *J* = 10.7, 10.2, 4.8 Hz, 2H), 2.98 (q, *J* = 7.4 Hz, 1H), 2.47 – 2.32 (m, 1H), 2.28 – 2.16 (m, 1H), 2.01 (t, *J* = 5.5 Hz, 1H), 1.87 (ddd, *J* = 16.5, 9.8, 2.4 Hz, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.24 (d, *J* = 7.4 Hz, 1H), 1.09 (d, *J* = 7.5 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.39, 134.02, 129.34, 129.15, 128.60, 127.37, 85.55, 77.57, 53.53, 51.49, 39.53, 37.86, 37.12, 35.17, 27.65, 26.17, 25.82, 22.98, 14.92.

IR: ν 3219, 2917, 1667, 1377, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +34.7 (*c* 0.88, CH$_3$OH)

HRMS: calcd for $C_{21}H_{32}O_3N_2B$ 371.3041, found 371.2503

Yield: 93%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-2-methyl-propanamide 9.4

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 3.95 (q, *J* = 7.0 Hz, 1H), 2.99 (dd, *J* = 8.3, 6.5 Hz, 1H), 2.44 – 2.29 (m, 1H), 2.27 – 2.15 (m, 1H), 2.04 – 1.77 (m, 4H), 1.49 (d, *J* = 7.0 Hz, 3H), 1.41 – 1.35 (m, 4H), 1.30 (s, 3H), 1.06 – 0.94 (m, 6H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.34, 83.93, 76.06, 50.03, 38.18, 36.53, 36.50, 33.85, 28.28, 26.40, 24.57, 21.66, 18.06, 17.66, 15.54.

IR: ν 3215, 2954, 1667, 1374, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -7.3 (*c* 0.27, CH$_3$OH)

HRMS: calcd for $C_{17}H_{32}O_3N_2B$ 323.2, found 323.1

Yield: 99%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]propanamide 9.5

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.34 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 2.99 (d, *J* = 6.3 Hz, 1H), 2.38 (ddt, *J* = 14.0, 9.0, 2.4 Hz, 1H), 2.21 (ddt, *J* = 8.1, 5.9, 3.1 Hz, 1H), 2.00 (t, *J* = 5.6 Hz, 1H), 1.98 – 1.80 (m, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.40 (s, 3H), 1.29 (d, *J* = 8.2 Hz, 4H), 0.99 (dd, *J* = 6.8, 4.6 Hz, 6H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.18 , 85.49 , 77.59 , 51.33 , 39.52 , 37.86 , 35.11 , 29.54, 27.74 , 26.11 , 25.89 , 22.99 , 19.36 , 19.07 , 16.53 .

IR: ν 3363, 2916, 1663, 1367, 1121 cm^{-1}

$[\alpha]^{23}_{D}$ = -15.8 (*c* 2.00, CH$_3$OH)

HRMS: calcd for $C_{17}H_{32}O_3N_2B$ 323.2610, found 323.2502

Yield: 94%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-3-phenyl-propanamide 9.6

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.40 – 7.23 (m, 5H), 4.34 (d, *J* = 7.3 Hz, 1H), 4.13 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.24 – 3.00 (m, 2H), 2.98 (t, *J* = 6.3 Hz, 1H), 2.46 – 2.31 (m, 1H), 2.28 – 2.15 (m, 1H), 2.02 (t, *J* = 5.7 Hz, 1H), 1.94 – 1.76 (m, 3H), 1.41 (s, 3H), 1.31 (s, 4H), 1.03 – 0.76 (m, 9H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 169.71, 132.99, 127.87, 127.79, 125.94, 84.23, 76.15, 52.29, 49.93, 38.12, 36.49, 36.24, 33.74, 28.20, 26.47, 24.75, 24.56, 21.63, 17.94, 17.69.

IR: ν 3285, 2930, 1673, 1387, 1139 cm^{-1}

$[\alpha]^{23}_{D}$ = +66.2 (*c* 0.39, CH_3OH)

HRMS: calcd for $C_{23}H_{37}O_3N_2B$ 400.3, found 399.1

Yield: 99%

(2*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-2-methyl-3-(1-naphthyl)propanamide 9.7

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.21 (d, *J* = 8.7 Hz, 1H), 7.93 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.86 (dd, *J* = 7.4, 2.3 Hz, 1H), 7.63 (ddt, *J* = 8.4, 5.0, 1.5 Hz, 1H), 7.55 (ddd, *J* = 9.5, 5.9, 1.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 4.32 – 4.23 (m, 2H), 3.66 – 3.52 (m, 2H), 2.80 – 2.60 (m, 1H), 2.45 – 2.28 (m, 1H), 2.24 – 2.10 (m, 1H), 1.99 (t, *J* = 5.4 Hz, 1H), 1.89 (dt, *J* = 5.4, 2.8 Hz, 1H), 1.84 – 1.66 (m, 2H), 1.40 (s, 3H), 1.30 (d, *J* = 2.6 Hz, 4H), 0.90 – 0.81 (m, 6H), 0.68 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.74 , 134.20 , 131.72 , 129.94 , 128.66 , 128.32 , 126.45, 125.66 , 125.32 , 122.97 , 85.37 , 77.37 , 52.68 , 51.42, 39.57 , 37.86 , 35.10 , 34.20 , 29.29 , 27.82 , 26.16 , 25.93 , 23.04 , 19.30 , 19.24 .

IR: ν 3211, 2918, 1666, 1367, 1121 cm^{-1}

$[\alpha]^{23}_{D}$ = +102.17 (*c* 0.46, CH_3OH)

HRMS: calcd for $C_{27}H_{38}O_3N_2B$ 449.4165, found 449.2970

Yield: 71%

(2*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-2-methyl-3-(3-pyridyl)propanamide 9.8

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.96 (d, *J* = 6.9 Hz, 1H), 8.88 (s, 1H), 8.70 (d, *J* = 7.8 Hz, 1H), 8.14 (t, *J* = 7.0 Hz, 1H), 4.39 (t, *J* = 7.8 Hz, 2H), 3.47 (d, *J* = 7.0 Hz, 1H), 2.86 (d, *J* = 6.0 Hz, 1H), 2.50 – 2.33 (m, 1H), 2.21 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.04 (d, *J* = 5.6 Hz, 1H), 1.97 – 1.78 (m, 4H), 1.42 (s, 3H), 1.30 (d, *J* = 10.3 Hz, 4H), 0.95 – 0.86 (m, 9H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 167.14 , 148.37 , 142.29 , 140.60 , 135.51 , 127.39 , 85.97 , 77.69 , 52.60 , 51.24 , 39.45 , 37.90 , 35.05 , 33.93 , 29.68 , 27.80 , 26.14 , 25.91 , 23.03 , 19.40 , 19.15.

IR: ν 3220, 2929, 1673, 1374, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +51.85 (*c* 0.54, CH_3OH)

HRMS: calcd for $C_{22}H_{35}O_3N_3B$ 449.3455, found 400.2766

Yield: 39%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]heptanamide 9.9

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.32 (dd, *J* = 8.8, 1.9 Hz, 1H), 3.91 (t, *J* = 6.6 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.80 (d, *J* = 6.6 Hz, 1H), 2.46 – 2.29 (m, 1H), 2.26 – 2.14 (m, 1H), 1.91 (dddd, *J* = 17.4, 14.0, 11.0, 5.2 Hz, 6H), 1.70 (dd, *J* = 15.5, 7.8 Hz, 2H), 1.57 – 1.46 (m, 2H), 1.39 (s, 4H), 1.29 (s, 3H), 1.04 – 0.96 (t, 6H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 171.12, 85.07, 77.38, 51.99, 51.74, 39.84, 39.16, 38.08, 35.58, 31.65, 29.66, 28.20, 26.93, 26.41, 26.15, 23.30, 21.75, 19.84, 19.49.

IR: ν 3383, 2921, 1665, 1368, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +28.2 (*c* 0.49, CH_3OH)

HRMS: calcd for $C_{20}H_{39}O_3N_3B$ 380.3557, found 380.3077

Yield: 48%

N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-3-phenyl-propanamide 9.10

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 – 7.13 (m, 10H), 4.29 (t, *J* = 7.4 Hz, 1H), 4.13 (s, 1H), 3.18 (ddd, *J* = 29.6, 13.7, 7.4 Hz, 2H), 2.29 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.17 – 2.02 (m, 1H), 1.98 (t, *J* = 5.5 Hz, 1H), 1.80 (s, 1H), 1.66 (d, *J* = 14.2 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.15 (d, *J* = 10.7 Hz, 1H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 169.62, 139.05, 133.82, 129.26, 129.20, 129.17, 128.68, 128.15, 128.00, 127.44, 126.72, 126.22, 85.57, 77.55, 53.19, 51.53, 39.41, 37.86, 37.15, 35.13, 27.66, 26.16, 25.71, 23.00.

IR: ν 3029, 2918, 1674, 1496, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +47.0 (*c* 0.5, CH_3OH)

HRMS: calcd for $C_{26}H_{34}O_3N_2B$ 433.3739, found 433.2657

Yield: 99%

N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]heptanamide 9.11

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.07 – 6.83 (m, 5H), 3.94 (d, *J* = 8.8 Hz, 1H), 3.85 (d, *J* = 7.2 Hz, 2H), 2.71 – 2.50 (m, 2H), 1.93 (d, *J* = 7.8 Hz, 1H), 1.85 – 1.70 (m, 1H), 1.62 (dd, *J* = 13.7, 8.1 Hz, 3H), 1.50 – 1.27 (m, 4H), 1.13 (t, *J* = 16.4 Hz, 3H), 1.03 (s, 3H), 0.98 – 0.81 (m, 4H), 0.51 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.73, 139.74, 128.25, 126.91, 126.44, 85.63, 77.67, 66.98, 51.85, 39.71, 39.14, 38.11, 35.46, 30.87, 28.01, 26.79, 26.49, 26.03, 23.32, 21.62.

IR: ν 3385, 2915, 1668, 1338, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +38.72 (*c* 0.75, CH$_3$OH)

HRMS: calcd for $C_{23}H_{38}O_3N_3B$ 415.3801, found 414.2922

Yield: 83%

N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-(4-fluorophenyl)methyl]-2-methyl-propanamide 9.12

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33 – 7.24 (m, 2H), 7.11 – 6.98 (m, 2H), 4.28 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.24 – 4.10 (m, 2H), 2.29 (ddd, *J* = 13.9, 8.8, 2.3 Hz, 1H), 2.10 (ddd, *J* = 10.7, 6.2, 2.0 Hz, 1H), 1.97 (t, *J* = 5.5 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.70 – 1.59 (m, 1H), 1.53 (d, *J* = 7.0 Hz, 3H),1.36 (s, 3H), 1.27 (s, 3H), 1.16 (d, *J* = 10.7 Hz, 1H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 160.50, 135.50, 128.36 (d, *J* = 8.1 Hz), 114.56 (d, *J* = 21.4 Hz), 104.99, 85.42, 77.48, 51.59, 39.45, 37.84, 35.20, 27.62, 26.14, 25.73, 22.97, 16.01.

IR: ν 2917, 1643, 1339, 1222, 1121 cm^{-1}

$[\alpha]^{23}_{D}$ = +33.7 (*c* 0.92, CH$_3$OH)

HRMS: calcd for $C_{20}H_{29}O_3N_2BF$ 375.2679, found 375.2250

Yield: 98%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]propanamide 9.13

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.12 (m, 5H), 4.33 (d, *J* = 8.4 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.47 – 3.36 (m, 1H), 2.91 (ddd, *J* = 23.2, 13.9, 7.8 Hz, 2H), 2.43 – 2.24 (m, 1H), 2.20 – 2.03 (m, 1H), 1.96 (t, *J* = 5.0 Hz, 1H), 1.82 (d, *J* = 14.7 Hz, 2H), 1.38 (d, *J* = 10.2 Hz, 6H), 1.28 (s, 3H), 1.13 (d, *J* = 10.8 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.01 , 139.40 , 128.85 , 127.96 , 125.96 , 85.86 , 77.77 , 51.30 , 39.45 , 37.82 , 36.36 , 34.95 , 27.66 , 26.12 , 25.71 , 22.96 , 16.30.

IR: ν 3334, 2920, 1661, 1377, 1120 cm^{-1}

$[\alpha]^{23}_{D}$ = +49.3 (*c* 2.16, CH$_3$OH)

HRMS: calcd for $C_{21}H_{32}O_3N_2B$ 371.3041, found 371.2500

Yield: 99%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]propanamide 9.14

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.28-7.08 (m, 5H), 4.32 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.90 (q, *J* = 7.0 Hz, 1H), 3.33 – 3.21 (m, 1H), 2.89 (qd, *J* = 13.9, 7.8 Hz, 2H), 2.46 – 2.27 (m, 1H), 2.20 – 2.04 (m, 1H), 1.96 (t, *J* = 5.4 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.15 (d, *J* = 10.9 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.23, 139.36, 128.81, 128.00, 125.99, 85.65, 77.66, 51.38, 39.48, 37.82, 36.18, 34.96, 27.64, 26.13, 25.67, 22.97, 16.35.

IR: ν 3215, 2914, 1669, 1376, 1121 cm^{-1}

$[\alpha]^{23}_{D}$ = -49.4 (*c* 1.8, CH$_3$OH)

HRMS: calcd for $C_{21}H_{32}O_3N_2B$ 371.3041, found 371.2500

Yield: 92%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-3-phenyl-propanamide 9.15

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.41 – 7.10 (m, 10H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.06 (dd, *J* = 12.3, 5.6 Hz, 1H), 3.38 (t, *J* = 7.3 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.98 – 2.76 (m, 3H), 2.48 – 1.97 (m, 3H), 1.82 (d, *J* = 14.6 Hz, 2H), 1.38 (s, 3H), 1.29 (s, 3H), 1.12 (d, *J* = 10.8 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.60, 139.24, 134.02, 129.20, 129.13, 128.82, 128.68, 128.01, 127.43, 126.01, 85.87, 77.76, 53.56, 51.30, 39.44, 37.82, 37.28, 36.38, 34.93, 27.69, 26.13, 25.70, 22.97.

IR: ν 3397, 2917, 1664, 1376, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +62.5 (*c* 0.12, CH$_3$OH)

HRMS: calcd for $C_{27}H_{36}O_3N_2B$ 447.4006, found 447.2813

Yield: 91%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]heptanamide 9.16

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33 – 7.16 (m, 5H), 4.36 (d, *J* = 7.5 Hz, 1H), 3.85 (t, *J* = 6.2 Hz, 1H), 3.41 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.07 – 2.79 (m, 4H), 2.46 – 2.31 (m, 1H), 2.21 – 2.07 (m, 1H), 1.98 (t, *J* = 5.3 Hz, 1H), 1.89 – 1.71 (m, 4H), 1.69 – 1.57 (m, 2H), 1.39 (s, 3H), 1.35 – 1.25 (m, 5H), 1.18 (d, *J* = 10.6 Hz, 1H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.83, 139.52, 128.79, 128.00, 125.96, 85.91, 77.78, 51.97, 51.33, 39.45, 38.85, 37.83, 36.23, 34.96, 30.67, 27.70, 26.64, 26.11, 25.71, 22.95, 21.08.

IR: ν 2920, 1669, 1375, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +53.8 (*c* 2.10, CH$_3$OH)

HRMS: calcd for $C_{24}H_{39}O_3N_3B$ 428.3988, found 428.3079

Yield: 91%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]propanamide 9.17

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.29 – 7.11 (m, 5H), 4.33 (dd, *J* = 8.8, 1.9 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.05 (dd, *J* = 8.2, 6.3 Hz, 1H), 2.69 (dddd, *J* = 23.0, 15.6, 8.3, 5.1 Hz, 2H), 2.45 – 2.31 (m, 1H), 2.21 (qd, *J* = 6.4, 3.3 Hz, 1H), 2.00 (t, *J* = 5.5 Hz, 1H), 1.94 – 1.81 (m, 4H), 1.52 (d, *J* = 7.1 Hz, 3H), 1.40 (s, 3H), 1.33 (d, *J* = 10.8 Hz, 1H), 1.30 (s, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.41 , 141.71 , 128.04, 128.01 , 125.52 , 85.49 , 77.52 , 51.42 , 47.94 , 39.54 , 37.86 , 35.21 , 33.06 , 32.69 , 27.72 , 26.16 , 25.89 , 23.02 , 16.34 .

IR: ν 3214, 2924, 1669, 1376, 1121 cm^{-1}

$[\alpha]^{23}_D$ = -13.63 (*c* 0.44, CH_3OH)

HRMS: calcd for $C_{22}H_{34}O_3N_2B$ 385.3308, found 385.2657

Yield: 85%

(2*S*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-2-(3-phenylpropanoylamino)propanamide 10.1

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.39-7.17 (m, 5H), 4.58 (q, *J* = 7.1 Hz, 1H), 4.20 – 4.10 (m, 1H), 3.25 – 3.16 (m, 1H), 3.10 – 2.94 (m, 2H), 2.75 (q, *J* = 7.2 Hz, 1H), 2.33 (ddd, *J* = 13.8, 8.5, 2.9 Hz, 1H), 2.14 (ddt, *J* = 10.7, 6.9, 3.5 Hz, 1H), 1.95 (t, *J* = 5.5 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.34 (s, 3H), 1.26 (d, *J* = 5.9 Hz, 4H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.70 , 168.24 , 134.18 , 129.12 , 128.77 , 127.49 , 83.16 , 76.09 , 54.14 , 52.12 , 46.95 , 39.87 , 37.77 , 37.10 , 36.22 , 33.89 , 28.27 , 26.32 , 23.09 , 17.02 , 16.10 .

IR: ν 3211, 2927, 1653, 1375, 1090 cm^{-1}

$[\alpha]^{23}_D$ = -20.8 (*c* 0.48, CH_3OH)

HRMS: calcd for $C_{24}H_{37}O_4N_3B$ 442.3823, found 442.2863

Yield: 88%

N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.2

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.57 (q, *J* = 7.1 Hz, 1H), 4.19 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.95 (q, *J* = 6.2 Hz, 1H), 2.98 (q, *J* = 7.3 Hz, 3H), 2.36 (ddt, *J* = 13.9, 8.8, 2.5 Hz, 1H), 2.16 (ddt, *J* = 8.2, 6.0, 3.1 Hz, 1H), 1.98 – 1.87 (m, 4H), 1.73 (ddd, *J* = 14.9, 6.8, 2.9 Hz, 3H), 1.54 (q, *J* = 8.0

Hz, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.38 (d, *J* = 7.1 Hz, 4H), 1.30 (s, 3H), 1.16 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.34 , 168.40 , 83.24 , 76.11 , 52.50 , 52.09 , 46.95 , 46.13 , 39.88 , 38.84 , 37.79 , 36.21 , 30.53 , 28.35 , 26.74 , 26.06 , 23.12 , 21.44 , 16.10 , 14.99 .

IR: ν 3198, 2926, 1660, 1375, 1140 cm^{-1}

$[\alpha]^{23}_D$ = -30.4 (*c* 0.28, CH_3OH)

HRMS: calcd for $C_{21}H_{40}O_4N_4B$ 423.3806, found 423.3137

Yield: 71%

(2*S*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-2-(propanoylamino)propanamide 10.3

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.55 (q, *J* = 7.1 Hz, 1H), 4.16 (dd, *J* = 5.9, 2.8 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 2.71 (q, *J* = 7.1 Hz, 1H), 2.33 (dd, *J* = 12.6, 10.0 Hz, 1H), 2.13 (dd, *J* = 10.3, 6.1 Hz, 1H), 1.94 (t, *J* = 5.5 Hz, 1H), 1.90 – 1.72 (m, 2H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 1H), 1.13 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.83, 169.43, 82.96, 75.97, 52.15, 48.64, 45.91, 39.91, 37.76, 36.28, 28.26, 26.36, 26.06, 23.13, 16.24, 16.10, 15.04.

IR: ν 2982, 2927, 1665, 1375, 1123 cm^{-1}

$[\alpha]^{23}_D$ = -56.3 (*c* 0.16, CH_3OH)

HRMS: calcd for $C_{18}H_{33}O_4N_3B$ 366.2859, found 366.2559

Yield: 68%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-3-phenyl-6-(1H-indole)–4-oxo-hexanamide 10.4

The product is not well recognizable by NMR due to bad shimming, but MS data shows a molecular ion of the correct compound.

IR: ν 3229, 2928, 1652, 1376, 1095 cm^{-1}

$[\alpha]^{23}_D$ = +4 (*c* 1, CH_3OH)

HRMS: calcd for $C_{32}H_{42}O_4N_4B$ 557.5150, found 557.3294

Yield: 63%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]ethyl]-5-methyl-2-[(1R)-1-methylpropyl]-6-(2-naphthyl)-4-oxo-hexanamide 10.5

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.88 (ddd, *J* = 19.2, 14.3, 9.9 Hz, 4H), 7.56 – 7.46 (m, 3H), 4.45 – 4.37 (m, 1H), 4.33 (q, *J* = 7.2, 6.1 Hz, 1H), 4.23 – 4.14 (m, 1H), 3.47 (ddd, *J* = 50.1, 14.4, 5.0 Hz, 1H), 3.28 – 3.01 (m, 1H), 2.73 (t, *J* = 7.4 Hz, 1H), 2.38 – 2.25 (m, 1H), 2.20 – 2.10 (m,

1H), 1.93 (td, *J* = 9.6, 7.8, 5.3 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.64 (dtt, *J* = 16.5, 8.4, 3.7 Hz, 2H), 1.33 (s, 3H), 1.25 (s, 4H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 171.11 , 168.53 , 133.66 , 132.97 , 131.45 , 128.71 , 128.28, 127.51 , 125.92 , 83.17 , 76.15 , 53.88 , 52.10 , 39.87 , 37.65 , 36.93 , 36.24 , 33.76 , 28.32 , 26.32 , 24.71 , 23.07 , 15.21 , 14.33 , 13.22 , 9.90.

IR: ν 3208, 2930, 1652, 1373, 1123 cm^{-1}

$[\alpha]^{23}_D$ = -20.83 (*c* 0.72, CH_3OH)

HRMS: calcd for $C_{31}H_{45}O_4N_3B$ 534.5214, found 534.3498

Yield: 38%

N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]amino]-1-benzyl-2-oxo-ethyl]heptanamide 10.6

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.36 – 7.16 (m, 5H), 4.23 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.92 (t, *J* = 6.4 Hz, 1H), 3.19 – 3.01 (m, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.45 (d, *J* = 6.8 Hz, 1H), 2.37 (ddt, *J* = 13.6, 8.8, 2.4 Hz, 1H), 2.15 (td, *J* = 6.7, 3.5 Hz, 1H), 1.98 (t, *J* = 5.5 Hz, 1H), 1.89 (pd, *J* = 6.6, 6.0, 2.5 Hz, 3H), 1.85 – 1.75 (m, 2H), 1.71 (td, *J* = 8.8, 4.3 Hz, 2H), 1.54 – 1.43 (m, 3H), 1.42 (s, 3H), 1.29 (s, 3H), 0.97 – 0.85 (m, 9H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.49, 168.43, 136.06, 128.98, 128.28, 126.70, 83.12, 76.36, 52.45, 51.97, 39.91, 38.88, 37.81, 37.02, 35.97, 30.59, 29.27, 28.43, 26.71, 26.37, 26.06, 25.85, 23.26, 21.21, 19.74, 19.08.

IR: ν 3284, 2924, 1643, 1368, 1122 cm^{-1}

HRMS: calcd for $C_{29}H_{48}O_4N_4B$ 527.5304, found 527.3763

Yield: 95%

N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.7

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.60 (q, *J* = 7.1 Hz, 1H), 4.23 (d, *J* = 6.9 Hz, 1H), 3.95 (d, *J* = 6.1 Hz, 1H), 3.01 – 2.92 (m, 2H), 2.61 (d, *J* = 6.6 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.23 – 2.07 (m, 1H), 2.03 – 1.78 (m, 6H), 1.77 – 1.65 (m, 2H), 1.54 (dt, *J* = 15.3, 7.7 Hz, 2H), 1.46 (d, *J* = 1.1 Hz, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.21 (d, *J* = 12.4 Hz, 1H), 0.99 (dd, *J* = 11.0, 6.7 Hz, 6H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.11 , 168.32 , 83.36 , 76.42 , 52.53 , 51.87 , 46.63 , 39.86 , 38.87 , 37.83 , 35.86 , 30.68 , 29.17 , 28.45 , 26.60 , 26.30 , 25.98 , 23.19 , 21.49 , 19.80 , 19.13 , 16.64 .

IR: ν 3334, 2928, 1676, 1367, 1120 cm^{-1}

$[\alpha]^{23}_D$ = -44.8 (*c* 1.64, CH_3OH)

HRMS: calcd for $C_{23}H_{44}O_4N_4B$ 451.4339, found 451.3450

Yield: 91%

N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]amino]-1-benzyl-2-oxo-ethyl]-7-amino-7-imino-heptanamide 10.8

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.36 – 7.20 (m, 5H), 4.23 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.90 (t, *J* = 6.2 Hz, 1H), 3.23 (t, *J* = 6.6 Hz, 2H), 3.08 (ddd, *J* = 52.8, 13.9, 7.6 Hz, 2H), 2.47 (d, *J* = 6.9 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.21 – 2.12 (m, 1H), 2.00 (t, *J* = 5.5 Hz, 1H), 1.86 (dddt, *J* = 27.5, 13.4, 10.7, 7.3 Hz, 6H), 1.67 (dt, *J* = 15.5, 8.1 Hz, 2H), 1.44 (d, *J* = 8.9 Hz, 4H), 1.30 (s, 3H), 0.93 (dd, *J* = 13.9, 6.7 Hz, 6H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.45 , 168.61 , 157.23 , 135.99 , 128.92 , 128.28 , 126.72, 83.27 , 76.47 , 52.33 , 51.92 , 40.52 , 39.88 , 37.80 , 37.13 , 35.94 , 29.16 , 28.37 , 26.29 , 26.07 , 23.55 , 23.20 , 19.77 , 19.08 .

IR: ν 3327, 2928, 1652, 1369, 1121 cm^{-1}

$[\alpha]^{23}_D$ = +24.5 (*c* 0.45, CH_3OH)

HRMS: calcd for $C_{29}H_{48}O_4N_6B$ 555.5438, found 555.3825

Yield: 29%

(2*S*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-2-(3-phenylpropanoylamino)propanamide 10.9

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.26 (m, 5H), 4.62 (q, *J* = 7.0 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.40 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.97 (dd, *J* = 14.4, 9.7 Hz, 1H), 2.56 (d, *J* = 6.7 Hz, 1H), 2.41 – 2.26 (m, 1H), 2.12 (dd, *J* = 10.1, 5.9 Hz, 1H), 1.94 (t, *J* = 5.4 Hz, 1H), 1.91 – 1.76 (m, 3H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.20 (d, *J* = 15.8 Hz, 1H), 1.00 (dd, *J* = 11.5, 6.7 Hz, 6H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.41, 168.20, 134.22, 129.20, 128.83, 127.51, 83.19, 76.30, 54.16, 51.91, 46.58, 39.87, 37.82, 37.38, 35.94, 33.48, 29.20, 28.45, 26.38, 26.01, 23.25, 19.87, 19.22, 16.74.

IR: ν 3219, 2927, 1672, 1370, 1120 cm^{-1}

$[\alpha]^{23}_D$ = -35.7 (*c* 1.12, CH_3OH)

HRMS: calcd for $C_{26}H_{41}O_4N_3B$ 470.4357, found 470.3185

Yield: 99%

(2*S*,3*R*)-N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-2,3-dimethyl-pentanamide 10.10

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (s, 1H), 8.82 (d, *J* = 5.8 Hz, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 5.8 Hz, 1H), 4.27 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.83 (d, *J* = 5.3 Hz, 1H), 3.43 – 3.32 (m, 2H), 2.58 (d, *J* = 6.5 Hz, 1H), 2.36 (ddt, *J* = 13.7, 8.7, 2.4 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.01 (t, *J* = 5.5 Hz, 1H), 1.97 – 1.77 (m, 5H), 1.65 – 1.50 (m, 1H), 1.39 (d, *J* = 9.7 Hz, 4H), 1.31 (s, 3H), 1.23 (dtd, *J* = 13.5, 7.1, 2.7 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.01 – 0.87 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 171.56 , 167.96 , 147.92 , 141.79 , 139.90 , 137.52 , 127.21, 84.37 , 76.94 , 57.37 , 51.66 , 39.70 , 37.83 , 36.69 , 35.52 , 34.29 , 29.36 , 28.07 , 26.22 , 25.93 , 24.04 , 23.09 , 19.55 , 19.00 , 13.72 , 10.44 .

IR: ν 3268, 2931, 1652, 1373, 1121 cm^{-1}

$[\alpha]^{23}_{D}$ = +46.29 (*c* 0.54, CH_3OH)

HRMS: calcd for $C_{28}H_{46}O_4N_4B$ 513.5037, found 513.3607

Yield: 47%

(2*R*,5*S*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-6-phenyl-hexanamide 10.11

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 – 7.26 (m, 5H), 4.47 (d, *J* = 8.0 Hz, 1H), 4.22 (ddd, *J* = 14.0, 7.8, 3.0 Hz, 2H), 3.42 – 2.86 (m, 2H), 2.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 2.32 (ddt, *J* = 14.3, 9.0, 2.3 Hz, 1H), 2.13 (dtd, *J* = 10.3, 5.9, 2.3 Hz, 1H), 1.96 – 1.79 (m, 5H), 1.65 (ddd, *J* = 13.7, 7.5, 3.5 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.05 – 0.92 (m, 14H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.98 , 168.40 , 134.03 , 129.15 , 128.83 , 127.52 , 83.03 , 76.24 , 55.09 , 54.01 , 51.94 , 39.88 , 37.78 , 37.43 , 36.64 , 35.90 , 29.17 , 28.46 , 26.28 , 25.96 , 24.70 , 23.16 , 20.01 , 19.57 , 14.43 , 9.82 .

IR: ν 3031, 2928, 1674, 1368, 1122cm^{-1}

$[\alpha]^{23}_{D}$ = -34.29 (*c* 0.35, CH_3OH)

HRMS: calcd for $C_{29}H_{47}O_4N_3B$ 512.5157, found 512.3654

Yield: 95%

(2*S*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-(1-naphthylmethyl)-4-oxo-decanamide 10.12

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.90 (dd, *J* = 8.1, 3.0 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.3, 4.6 Hz, 1H), 7.54 – 7.38 (m, 3H), 4.26 (d, *J* = 8.4

Hz, 1H), 3.97 (t, *J* = 6.5 Hz, 1H), 3.76 – 3.47 (m, 2H), 2.97 (dt, *J* = 15.4, 7.6 Hz, 3H), 2.39 (d, *J* = 8.0 Hz, 1H), 2.15 (dd, *J* = 10.1, 5.2 Hz, 1H), 1.91 (ddt, *J* = 28.5, 22.5, 9.9 Hz, 4H), 1.80 – 1.63 (m, 3H), 1.62 – 1.44 (m, 4H), 1.42 (s, 3H), 1.29 (s, 3H), 0.90 (d, *J* = 5.3 Hz, 4H), 0.65 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.26 , 168.47 , 134.09 , 131.66 , 131.51 , 128.60 , 127.82, 126.19 , 125.64 , 122.96 , 83.30 , 76.30 , 52.53 , 51.93 , 51.48 , 39.92 , 38.90 , 37.84 , 35.85 , 34.59 , 30.75 , 28.97 , 28.59 , 26.70 , 25.97 , 23.21 , 21.46 , 19.86 , 19.66 , 19.38 .

IR: ν 3188, 2923, 1674, 1368, 1121 cm^{-1}

$[\alpha]^{23}_D$ = +57.89 (*c* 0.19, CH$_3$OH)

HRMS: calcd for $C_{33}H_{50}O_4N_4B$ 577.5894, found 577.3920

Yield: 72%

(2*S*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-(1-naphthylmethyl)-4-oxo-hexanamide 10.13

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.17 (dd, *J* = 8.7, 3.2 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.1 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.43 (dt, *J* = 14.5, 7.3 Hz, 2H), 4.26 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.95 (t, *J* = 7.1 Hz, 1H), 3.61 – 3.50 (m, 2H), 2.32 (d, *J* = 8.2 Hz, 1H), 2.22 – 2.07 (m, 1H), 1.96 (t, *J* = 5.4 Hz, 1H), 1.86 (td, *J* = 13.6, 12.7, 6.2 Hz, 2H), 1.74 – 1.60 (m, 1H), 1.56-1.38 (m, 5H), 1.41 (s, 3H), 1.29 (s, 3H), 0.90 (s, 3H), 0.81 (d, *J* = 6.6 Hz, 1H), 0.62 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.54 , 169.35 , 134.10 , 131.57 , 128.59 , 127.83 , 126.14, 125.45 , 125.24 , 122.95 , 83.02 , 76.25 , 51.98 , 51.25 , 48.63 , 39.93 , 37.80 , 35.89 , 34.67 , 28.48 , 26.31 , 25.94 , 23.20 , 19.86 , 19.38 , 16.29 .

IR: ν 3197, 2925, 1673, 1373, 1120 cm^{-1}

$[\alpha]^{23}_D$ = +31.25 (*c* 0.16, CH$_3$OH)

HRMS: calcd for $C_{30}H_{43}O_4N_3B$ 520.4947, found 520.3341

Yield: 77%

(2*S*)-N-[(1*R*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]amino]-2-oxo-1-(3-pyridylmethyl)ethyl]-2-methyl-3-(1-naphthyl)propanamide 10.14

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.84 (s, 1H), 8.80 (d, *J* = 5.7 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.08 (t, *J* = 6.9 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 4.33 (t, *J* = 7.6 Hz, 1H), 4.28 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.40 (m, 2H), 2.64 (d, *J* = 6.4 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.14 (d, *J* = 13.2 Hz, 1H), 1.96 (t, *J* = 5.6 Hz, 1H), 1.92 – 1.76 (m, 4H), 1.33 (d, *J* = 29.2 Hz, 4H), 1.20 (s, 3H), 0.94 (d, *J* = 6.7 Hz, 6H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 171.25 , 168.47 , 147.94 , 141.81 , 139.81 , 137.52 , 134.23, 131.72 , 129.82 , 128.74 , 128.50 , 128.12 , 127.15 , 126.51 , 125.74 , 125.33 , 123.01 , 84.55 , 77.01 , 53.18 , 51.95 , 51.56 , 47.19 , 46.98 , 39.61 , 37.79 , 35.46 , 34.31 , 29.50 , 28.10 , 26.06 , 23.07 , 19.51 , 19.18 .

IR: ν 3182, 2930, 1673, 1373, 1121 cm^{-1}

$[\alpha]^{23}_D$ = +50 (*c* 0.46, CH$_3$OH)

HRMS: calcd for $C_{35}H_{46}O_4N_4B$ 597.5792, found 597.3607

Yield: 63%

(2*S*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-[(1*R*)-1-methylpropyl]-6-(1-naphthyl)-4-oxo-hexanamide 10.15

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.64 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.50 (q, *J* = 4.2 Hz, 2H), 4.49 (d, *J* = 8.1 Hz, 1H), 4.39 (dd, *J* = 10.6, 4.6 Hz, 1H), 4.21 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.91 – 3.32 (m, 2H), 2.52 (d, *J* = 7.5 Hz, 1H), 2.37 – 2.24 (m, 1H), 2.17 – 2.07 (m, 1H), 2.02 – 1.77 (m, 5H), 1.69 (ddd, *J* = 14.0, 7.6, 3.6 Hz, 1H), 1.48 (dd, *J* = 9.1, 6.7 Hz, 1H), 1.34 (s, 4H), 1.23 (s, 3H), 1.08 – 0.95 (m, 12H), 0.81 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.90 , 168.63 , 134.32 , 131.78 , 129.77 , 128.67 , 128.07, 126.46 , 125.78 , 125.30 , 123.01 , 83.05 , 76.23 , 55.32 , 53.09 , 51.92 , 39.87 , 37.76 , 36.50 , 35.91 , 34.69 , 29.17 , 28.56 , 26.24 , 25.96 , 24.83 , 23.12 , 20.03 , 19.61 , 14.42 , 9.85.

IR: ν 3184, 2930, 1673, 1369, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -22.22 (*c* 0.18, CH$_3$OH)

HRMS: calcd for $C_{33}H_{49}O_4N_3B$ 562.5747, found 562.3811

Yield: 99%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-[(1*R*)-1-methylpropyl]-6-(2-naphthyl)-4-oxo-hexanamide 10.16

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.95 – 7.79 (m, 4H), 7.49 (ddd, *J* = 8.3, 6.0, 1.9 Hz, 3H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.34 (dd, *J* = 9.9, 3.9 Hz, 1H), 4.22 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.62 – 3.05 (m, 2H), 2.52 (dd, *J* = 7.4, 1.5 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.13 (ddd, *J* = 9.4, 6.8, 4.8 Hz, 1H), 1.97 – 1.80 (m, 5H), 1.67 (ddd, *J* = 13.9, 7.6, 3.5 Hz, 1H), 1.48 (d, *J* = 10.4 Hz, 1H), 1.35 (s, 3H), 1.32 – 1.26 (m, 1H), 1.24 (s, 3H), 1.08 – 0.92 (m, 12H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.86 , 168.40 , 133.66 , 132.97 , 128.70 , 128.25 , 127.37, 126.51 , 126.07 , 125.85 , 83.10 , 76.30 , 55.18 , 53.91 , 51.93 , 39.87 , 37.70 , 36.68 , 35.89 , 29.19 , 28.47 , 26.25 , 25.97 , 24.70 , 23.13 , 19.99 , 19.55 , 14.44 , 9.83 .

IR: ν 3185, 2926, 1668, 1368, 1121 cm^{-1}

$[\alpha]^{23}_D$ = -50 (*c* 0.28, CH$_3$OH)

HRMS: calcd for $C_{33}H_{49}O_4N_3B$ 562.5747, found 562.3811

Yield: 98%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-6-cyclohexyl-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-hexanamide 10.17

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.44 – 4.38 (m, 1H), 4.21 (dd, *J* = 8.9, 2.2 Hz, 1H), 4.00 (dd, *J* = 10.1, 4.5 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.39 – 2.29 (m, 1H), 2.18 – 2.08 (m, 1H), 1.96 (t, *J* = 5.5 Hz, 1H), 1.84 (tt, *J* = 13.7, 2.7 Hz, 6H), 1.79 – 1.60 (m, 7H), 1.51 – 1.44 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.12-0.93 (m, 17H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.98 , 169.51 , 82.94 , 76.19 , 54.99 , 51.99 , 50.54 , 39.93 , 39.14 , 37.80 , 36.49 , 35.95 , 33.62 , 33.06 , 31.49 , 29.15 , 28.74 , 26.31 , 25.86 , 25.40 , 24.74 , 23.20 , 20.03 , 19.59 , 14.39 , 9.76 .

IR: ν 2924, 1663, 1369, 1122cm^{-1}

$[\alpha]^{23}_D$ = -50 (*c* 0.2, CH$_3$OH)

HRMS: calcd for $C_{29}H_{53}O_4N_3B$ 518.5634, found 518.4124

Yield: 85%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-methyl-propyl]-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-6-(3-pyridyl)hexanamide 10.18

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.89 (d, *J* = 5.9 Hz, 2H), 8.69 (dd, *J* = 23.0, 7.9 Hz, 1H), 8.15 (dd, *J* = 8.1, 5.8 Hz, 1H), 4.52 (dd, *J* = 7.3, 4.8 Hz, 1H), 4.42 (d, *J* = 8.0 Hz, 1H), 4.24 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.67 – 3.35 (m, 2H), 2.61 (d, *J* = 7.3 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.15 (td, *J* = 6.9, 6.5, 3.5 Hz, 1H), 1.97 – 1.77 (m, 5H), 1.65 (tdd, *J* = 11.4, 7.3, 3.8 Hz, 2H), 1.40 (d, *J* = 16.1 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.06 – 0.92 (m, 12H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.86 , 167.08 , 148.49 , 142.11 , 140.67 , 135.09 , 127.52, 83.45 , 76.40 , 55.58 , 52.76 , 51.91 , 39.84 , 37.82 , 36.47 , 35.81 , 33.60 , 29.14 , 28.38, 26.26 , 25.98 , 24.67 , 23.14 , 20.02 , 19.49 , 14.39 , 9.78 .

IR: ν 3178, 2931, 1686, 1375, 1122cm^{-1}

$[\alpha]^{23}_D$ = -11.11 (*c* 0.63, CH$_3$OH)

HRMS: calcd for $C_{28}H_{46}O_4N_4B$ 513.5037, found 513.3607

Yield: 92%

N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]2-methyl-propyl]-3-phenyl-6-(1*H*-indole)–4-oxo-hexanamide 10.19

The product is not well recognizable by NMR due to bad shimming, but MS data shows a molecular ion of the correct compound.

IR: ν 3221, 2927, 1674, 1368, 1120 cm^{-1}

$[\alpha]^{23}_D$ = -20 (*c* 1.1, CH_3OH)

HRMS: calcd for $C_{34}H_{46}O_4N_4B$ 585.5684, found 585.3607

Yield: 67%

N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]2-methyl-propyl]-3-phenyl-6-(1*H*-indole)–4-oxo-hexanamide 10.20

The product is not well recognizable by NMR due to bad shimming, but MS data shows a molecular ion of the correct compound.

IR: ν 3219, 2928, 1674, 1372, 1120 cm^{-1}

$[\alpha]^{23}_D$ = -0.5 (*c* 2, CH_3OH)

HRMS: calcd for $C_{34}H_{46}O_4N_4B$ 585.5684, found 585.3607

Yield: 67%

(2*S*)-N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-3-phenyl-2-(propanoylamino)propanamide 10.21

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.38 – 7.07 (m, 10H), 4.09 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.94 (dt, *J* = 13.9, 6.9 Hz, 1H), 3.74 (s, 1H), 3.17 (ddd, *J* = 22.1, 13.8, 7.7 Hz, 2H), 2.23 – 2.04 (m, 2H), 1.96 (t, *J* = 5.5 Hz, 1H), 1.75 (s, 1H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.48 (s, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 0.92 (d, *J* = 12.0 Hz, 1H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.74, 169.83, 140.62, 135.68, 128.92, 128.38, 127.65, 126.88, 125.63, 125.24, 82.97, 76.06, 52.26, 52.00, 48.22, 39.92, 37.77, 36.52, 36.20, 28.25, 26.38, 26.30, 23.14, 16.09.

IR: ν 3202, 2923, 1674, 1386, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +51.8 (*c* 2.2, CH_3OH)

HRMS: calcd for $C_{29}H_{39}O_4N_3B$ 504.4521, found 504.3028

Yield: 90%

(2*R*)-N-[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-3-phenyl-2-(propanoylamino)propanamide 10.22

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (dt, *J* = 14.0, 7.5 Hz, 5H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.14 – 7.04 (m, 1H), 6.84 (d, *J* = 7.3 Hz, 2H), 4.94 (t, *J* = 7.5 Hz, 1H), 4.10 (d, *J* = 8.4 Hz, 1H), 4.02 (d, *J* = 6.5 Hz, 1H), 3.83 (s, 1H), 3.27 (d, *J* = 7.6 Hz, 2H), 2.22 – 2.07 (m, 2H), 1.95 (t, *J* =

4.5 Hz, 1H), 1.75 (s, 1H), 1.63 – 1.59 (m, 1H), 1.54 (d, *J* = 6.4 Hz, 3H), 1.47 (d, *J* = 9.9 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 177.75, 169. 83, 140.48, 135.68, 129.26, 129.09, 128.62, 127.71, 126.98, 125.51, 125.25, 82.92, 75.94, 51.97, 48.67, 48.17, 47.96, 47.74, 47.53, 47.32, 39.92, 37.81, 36.65, 33.54, 28.42, 26.53, 23.31, 16.53.

IR: ν 3204, 2923, 1678, 1453, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -39.7 (*c* 1.32, CH_3OH)

HRMS: calcd for $C_{29}H_{39}O_4N_3B$ 504.4521, found 504.3028

Yield: 66%

(2*S*)-N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-3-phenyl-2-(3-phenylpropanoylamino)propanamide 10.23

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 – 7.10 (m, 15H), 4.16 (dd, *J* = 9.4, 4.6 Hz, 1H), 4.11 (d, *J* = 6.4 Hz, 1H), 3.76 (s, 1H), 3.39 (dd, *J* = 14.6, 4.5 Hz, 1H), 3.19 (ddd, *J* = 21.8, 13.6, 7.6 Hz, 2H), 3.02 (dd, *J* = 14.6, 9.4 Hz, 2H), 2.23 – 2.13 (m, 1H), 2.07 (s, 1H), 1.95 (t, *J* = 5.6 Hz, 1H), 1.75 (s, 1H), 1.47 (dd, *J* = 11.5, 7.3 Hz, 2H), 1.32 (s, 3H), 1.25 (s, 3H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.72, 168.59, 140.56, 135.62, 134.13, 129.15, 128.93, 128.90, 128.42, 128.10, 127.64, 127.51, 126.90, 125.80, 125.30, 83.19, 76.17, 54.05, 52.24, 39.86, 37.75, 37.14, 36.79, 28.25, 26.34, 23.11.

IR: ν 3369, 2924, 1674, 1373, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +33.9 (*c* 3.80, CH_3OH)

HRMS: calcd for $C_{35}H_{43}O_4N_3B$ 580.5486, found 580.3341

Yield: 85%

(2*S*)-N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-[(4-fluorophenyl)methyl]-2-oxo-ethyl]-2,4-dimethyl-pentanamide 10.24

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.15 – 7.05 (m, 5H), 6.83 (d, *J* = 7.6 Hz, 2H), 4.11 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.81 (s, 1H), 3.23 (d, *J* = 8.1 Hz, 2H), 2.24 – 2.04 (m, 2H), 1.94 (t, *J* = 5.6 Hz, 1H), 1.80 – 1.64 (m, 4H), 1.48 – 1.38 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H), 0.99 (q, *J* = 4.8 Hz, 7H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.44 , 169.44 , 131.02 , 127.57 , 125.61 , 125.25 , 115.31, 115.09 , 83.00 , 76.09 , 52.26 , 51.96 , 51.26 , 40.37 , 39.89 , 37.77 , 36.13 , 35.80 , 28.47, 26.31 , 23.91 , 23.15 , 22.07 , 20.27 .

IR: ν 3204, 2872, 1653, 1372, 1224, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -23.33 (*c* 0.6, CH_3OH)

HRMS: calcd for $C_{32}H_{44}O_4N_3BF$ 564.5226, found 564.3403

Yield: 90%

N-[(1*S*)-2-[[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-benzyl-2-oxo-ethyl]heptanamide 10.25

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.42 – 7.10 (m, 10H), 4.90 (t, *J* = 7.6 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.01 (t, *J* = 5.7 Hz, 1H), 3.76 (s, 1H), 3.26 – 3.12 (m, 2H), 2.86 – 2.73 (m, 2H), 2.26 – 2.13 (m, 1H), 1.96 (dt, *J* = 13.5, 5.9 Hz, 3H), 1.80 (s, 1H), 1.65 (dd, *J* = 15.2, 7.6 Hz, 2H), 1.54 – 1.40 (m, 4H), 1.38 (s, 3H), 1.27 (s, 3H), 1.10 (d, *J* = 24.4 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.82, 168.84, 140.84, 135.57, 129.01, 128.92, 128.44, 128.12, 127.89, 126.93, 125.37, 125.21, 82.98, 76.01, 52.37, 52.29, 52.06, 39.97, 38.85, 37.80, 36.46, 36.27, 30.43, 28.44, 26.71, 26.43, 23.25, 20.89.

IR: ν 3367, 2924, 1674, 1372, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +44.5 (*c* 5.1, CH$_3$OH)

HRMS: calcd for $C_{32}H_{46}O_4N_4B$ 561.5468, found 561.3607

Yield: 97%

N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-benzyl-2-oxo-ethyl]heptanamide 10.26

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.43 – 7.30 (m, 5H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 2H), 4.12 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.94 (t, *J* = 6.4 Hz, 1H), 3.82 (s, 1H), 3.29 – 3.21 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.15 (ddd, *J* = 23.9, 12.2, 7.2 Hz, 2H), 1.95 (q, *J* = 6.4, 5.8 Hz, 2H), 1.91 – 1.82 (m, 1H), 1.76 (dq, *J* = 5.7, 2.9 Hz, 1H), 1.69 (p, *J* = 7.7 Hz, 2H), 1.54 – 1.40 (m, 4H), 1.31 (s, 3H), 1.26 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.49 , 168.69 , 140.27 , 129.16 , 128.59 , 127.64 , 126.94, 125.67 , 125.29 , 83.11 , 76.05 , 52.48 , 52.21 , 51.97 , 47.17 , 46.96 , 39.88 , 38.85 , 37.80 , 36.57 , 36.13 , 30.72 , 28.43 , 26.70 , 23.16 , 21.49 .

IR: ν 3372, 2922, 1678, 1367, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -22.4 (*c* 1.16, CH$_3$OH)

HRMS: calcd for $C_{32}H_{46}O_4N_4B$ 561.5468, found 561.3607

Yield: 93%

(2*R*)-N-[(1*S*)-2-[[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-methyl-2-oxo-ethyl]-2-methyl-3-(1-naphthyl)propanamide 10.27

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.91 (d, *J* = 7.0 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.30 (dq, *J* = 14.8, 7.7 Hz, 5H), 7.25 –

7.14 (m, 2H), 4.73 (q, *J* = 7.0 Hz, 1H), 4.36 (dd, *J* = 8.7, 5.9 Hz, 1H), 4.33 (s, 1H), 4.10 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.90 – 3.44 (m, 2H), 2.22 – 2.01 (m, 2H), 1.93 (t, *J* = 5.5 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.54 – 1.49 (m, 3H), 1.47 (d, *J* = 3.0 Hz, 1H), 1.37 (d, *J* = 7.1 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 178.41 , 168.68 , 140.78 , 134.22 , 131.73 , 130.06 , 128.61, 128.25 , 127.75 , 127.06 , 126.86 , 126.49 , 125.90 , 125.27 , 123.01 , 82.99 , 76.11 , 53.32 , 52.29 , 47.20 , 39.89 , 37.74 , 36.20 , 34.26 , 28.24 , 26.33 , 23.14 , 16.94 , 15.68 .

IR: ν 3214, 2942, 1663, 1374, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +123.64 (*c* 0.55, CH_3OH)

HRMS: calcd for $C_{33}H_{41}O_4N_3B$ 554.5111, found 554.3185

Yield: 86%

N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.28

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.34 – 7.03 (m, 5H), 4.66 (dd, *J* = 14.4, 7.3 Hz, 1H), 4.07 (dd, *J* = 11.9, 6.5 Hz, 2H), 3.86 (s, 1H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.15 – 1.99 (m, 2H), 1.99 – 1.81 (m, 4H), 1.71 – 1.61 (m, 3H), 1.58 (d, *J* = 7.2 Hz, 3H), 1.48 – 1.38 (m, 2H), 1.23 (s, 3H), 1.16 (s, 4H), 0.73 (s, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 178.77, 169.80, 140.41, 128.36, 127.08, 126.04, 125.73, 83.52, 75.82, 52.71, 51.80, 46.78, 39.56, 38.81, 37.61, 35.73, 30.42, 29.65, 28.45, 26.78, 26.25, 23.53, 21.36, 16.27.

IR: ν 2921, 1678, 1371, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -65.0 (*c* 1.20, CH_3OH)

HRMS: calcd for $C_{26}H_{42}O_4N_4B$ 485.4504, found 485.3294

Yield: 89%

(2*R*)-N-[(1*S*)-2-[[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-methyl-2-oxo-ethyl]-2-methyl-3-(2-naphthyl)propanamide 10.29

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 – 7.78 (m, 4H), 7.50 (ddd, *J* = 17.4, 8.0, 2.7 Hz, 3H), 7.32 – 7.14 (m, 5H), 4.76 (q, *J* = 7.2 Hz, 1H), 4.32 (dd, *J* = 9.2, 4.8 Hz, 1H), 4.28 (d, *J* = 2.1 Hz, 1H), 4.09 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.63 – 3.16 (m, 2H), 2.22 – 2.02 (m, 2H), 1.98 – 1.87 (m, 1H), 1.73 (dq, *J* = 6.0, 2.8 Hz, 1H), 1.55 (d, *J* = 7.2 Hz, 3H), 1.52 – 1.43 (m, 1H), 1.41 (d, *J* = 7.2 Hz, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 172.76 , 168.54 , 140.81 , 133.62 , 132.92 , 131.61 , 128.77, 128.51 , 128.21 , 127.69 , 127.55 , 127.07 , 126.18 , 125.28 , 83.01 , 76.11 , 53.99 , 52.29, 46.09 , 42.55 , 39.89 , 37.74 , 37.33 , 36.19 , 28.22 , 26.32 , 23.12 , 15.89 .

IR: ν 3216, 2921, 1663, 1370, 1122cm^{-1}

$[\alpha]^{23}_D$ = +37.1 (*c* 0.62, CH_3OH)

HRMS: calcd for $C_{33}H_{41}O_4N_3B$ 554.5111, found 554.3185

Yield: 88%

(2*R*)-N-[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-2-(propanoylamino)propanamide 10.30

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.27 (t, *J* = 7.6 Hz, 2H), 7.21 – 7.03 (m, 3H), 4.76 – 4.59 (m, 1H), 4.07 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 1H), 2.22 – 2.04 (m, 2H), 1.93 (t, *J* = 5.6 Hz, 1H), 1.74 (td, *J* = 5.6, 2.8 Hz, 1H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.49 – 1.40 (m, 1H), 1.26 (d, *J* = 3.1 Hz, 6H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 178.97 , 169.77 , 140.81 , 127.74 , 125.51 , 125.31 , 82.82, 75.92 , 52.26 , 48.64, 47.18 , 46.97 , 46.02 , 39.87 , 37.76 , 36.17 , 28.25 , 26.32, 23.16 , 16.21.

IR: ν 3271, 2934, 1685, 1386, 1121cm^{-1}

$[\alpha]^{23}_D$ = -97.3 (*c* 1.48, CH_3OH)

HRMS: calcd for $C_{23}H_{35}O_4N_3B$ 428.3557, found 428.2715

Yield: 94%

(2*R*)-N-[(1*S*)-2-[[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-methyl-2-oxo-ethyl]-3-cyclohexyl-2-methyl-propanamide 10.31

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 – 7.08 (m, 5H), 4.72 (q, *J* = 7.5 Hz, 1H), 4.39 (s, 1H), 4.07 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.98 (dt, *J* = 13.1, 6.6 Hz, 1H), 2.21 – 2.05 (m, 2H), 1.94 (t, *J* = 5.6 Hz, 1H), 1.91 – 1.65 (m, 13H), 1.52 (d, *J* = 7.1 Hz, 3H), 1.47 – 1.39 (m, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.92 , 169.59 , 140.86 , 128.12 , 127.66 , 125.71 , 82.86 , 76.01 , 52.30 , 50.61 , 45.91 , 39.92 , 38.88 , 37.73 , 36.20 , 33.49 , 33.07 , 31.68 , 28.32 , 26.33 , 26.08 , 25.38 , 23.11 , 15.70 .

IR: ν 3212, 2921, 1659, 1374, 1122cm^{-1}

$[\alpha]^{23}_D$ = +87.27 (*c* 0.55, CH_3OH)

HRMS: calcd for $C_{29}H_{45}O_4N_3B$ 510.4998, found 510.3498

Yield: 96%

N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-[(3-fluorophenyl)methyl]-2-oxo-ethyl]-2-methyl-propanamide 10.32

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.18 (tt, *J* = 15.8, 9.2 Hz, 7H), 6.90 (d, *J* = 7.6 Hz, 2H), 4.11 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.94 (q, *J* = 7.7 Hz, 1H), 3.82 (s, 1H), 3.23 (dt, *J* = 13.9, 7.8 Hz, 2H), 2.22 – 2.05 (m, 2H), 1.94 (t, *J* = 5.6 Hz, 1H), 1.74 (s, 1H), 1.50 (d, *J* = 7.1 Hz, 4H), 1.45 – 1.37 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.34 , 169.67 , 162.98 (d, *J* = 244.8 Hz), 140.30, 138.52, 130.25 (d, *J* = 8.5 Hz), 127.66, 125.67, 115.92 (d, *J* = 21.7 Hz), 113.69 (d, *J* = 21.1 Hz), 83.11 , 76.15 , 52.22 , 51.74 , 39.86 , 37.76 , 36.30 , 36.04 , 28.23 , 26.28 , 23.13 , 16.38.

IR: ν 3062, 2929, 1616, 1253, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -56.67 (*c* 0.3, CH$_3$OH)

HRMS: calcd for $C_{29}H_{38}O_4N_3BF$ 522.4426, found 522.2934

Yield: 58%

(2*S*)-N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]-2-isopropyl-7-methyl-2-(pentanoylamino)propanamide 10.33

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.20 (m, 5H), 4.42 (d, *J* = 7.8 Hz, 1H), 4.37 (d, *J* = 1.8 Hz, 1H), 4.05 (dd, *J* = 8.9, 2.6 Hz, 2H), 2.20 (q, *J* = 7.1 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.94 (t, *J* = 5.5 Hz, 1H), 1.77 (dq, *J* = 16.7, 8.6, 7.1 Hz, 5H), 1.29 (s, 3H), 1.25 (s, 3H), 1.09 (dd, *J* = 15.3, 6.8 Hz, 6H), 1.02 (dt, *J* = 6.9, 4.1 Hz, 7H), 0.81 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.75 , 169.93 , 140.78 , 128.12 , 125.26 , 116.84 , 82.77 , 75.92 , 56.07 , 52.26 , 51.35 , 40.28 , 39.93 , 37.70 , 36.22 , 29.94 , 28.27 , 26.35 , 23.90 , 23.16 , 22.04 , 20.86 , 20.51 , 18.29 , 17.79.

IR: ν 3064, 2936, 1653, 1373, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = +40.14 (*c* 1.42, CH$_3$OH)

HRMS: calcd for $C_{28}H_{45}O_4N_3B$ 498.4890, found 498.3509

Yield: 74%

(2*R*,3*R*)-N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-[(3-fluorophenyl)methyl]-2-oxo-ethyl]-2,3-dimethyl-pentanamide 10.34

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.25 – 7.02 (m, 7H), 6.87 (d, *J* = 7.5 Hz, 2H), 4.11 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.82 (s, 1H), 3.75 (d, *J* = 5.4 Hz, 1H), 3.26 (d, *J* = 7.9 Hz, 2H), 2.22 – 2.12 (m, 1H), 2.08 (dd, *J* = 10.6, 5.9 Hz, 1H), 1.93 (t, *J* = 5.6 Hz, 3H), 1.76 – 1.68 (m, 1H), 1.57 (ddt, *J* = 15.2, 10.6, 5.3 Hz, 2H), 1.45 – 1.36 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), (t, *J* = 7.4 Hz, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.92 , 168.05 , 163.01 (d, *J* = 244.9 Hz), 140.25 , 130.34, 128.05 , 127.60 , 125.86 , 125.31 , 115.99 (d, *J* = 22.0 Hz), 113.70 (d, *J* = 21.1 Hz), 116.10 , 115.88 , 113.81 , 113.60 , 83.22 , 76.20 , 57.42 , 52.21 , 51.92 , 39.84 ,37.78 , 36.72 , 36.01 , 28.31 , 26.36 , 26.18 , 23.97 , 23.14 , 13.96 , 10.33.

IR: ν 3199, 2929, 1673, 1387, 1144 cm^{-1}

$[\alpha]^{23}_D$ = -28 (*c* 0.5, CH$_3$OH)

HRMS: calcd for $C_{32}H_{44}O_4N_3BF$ 564.5226, found 564.3403

Yield: 75%

N-[(1*R*)-2-[[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-phenyl-methyl]amino]-1-[(4-fluorophenyl)methyl]-2-oxo-ethyl]-2-methyl-propanamide 10.35

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.38 (dt, *J* = 8.5, 4.7 Hz, 2H), 7.17 – 7.05 (m, 5H), 6.83 (d, *J* = 7.6 Hz, 2H), 4.11 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.93 (q, *J* = 7.1 Hz, 1H), 3.80 (s, 1H), 3.21 (p, *J* = 5.4 Hz, 2H), 2.14 (ddd, *J* = 23.6, 11.7, 7.5 Hz, 2H), 1.94 (t, *J* = 5.6 Hz, 1H), 1.75 (d, *J* = 5.5 Hz, 1H), 1.54 – 1.46 (m, 4H), 1.45 – 1.36 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.69 , 169.60 , 132.26 , 131.75, 131.60, 131.00 , 130.94, 128.04, 127.57 , 125.58 , 125.28, 83.03 , 75.12 , 52.24 , 44.99 , 39.88 , 37.76 , 36.08 , 35.88 , 28.25 , 26.34 , 26.22 , 23.11 , 16.26.

IR: ν 3205, 2929, 1674, 1386, 1223, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -100 (*c* 0.1, CH$_3$OH)

HRMS: calcd for $C_{29}H_{38}O_4N_3BF$ 522.4426, found 522.2934

Yield: 50%

N-[(1*S*)-2-[[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-(4-fluorophenyl)methyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.36

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.23 – 7.15 (m, 2H), 7.03 (t, *J* = 8.8 Hz, 2H), 4.69 (t, *J* = 7.3 Hz, 1H), 4.07 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.03 (t, *J* = 6.1 Hz, 1H), 3.82 (s, 1H), 2.96 – 2.85 (m, 2H), 2.25 – 2.10 (m, 2H), 2.06 – 1.86 (m, 3H), 1.82 – 1.62 (m, 4H), 1.55 (t, *J* = 6.6 Hz, 4H), 1.43 – 1.36 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 178.56, 168.73, 136.89, 127.13 (d, *J* = 8.0 Hz), 114.38 (d, *J* = 21.6 Hz), 82.95, 76.11, 52.38, 52.29, 46.08, 39.93, 38.85, 37.75, 36.31, 30.38, 28.34, 26.71, 26.37, 23.20, 21.06, 15.63.

IR: ν 3359, 2923, 1675, 1370, 1221, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +38.7 (*c* 1.28, CH$_3$OH)

HRMS: calcd for $C_{26}H_{41}O_4N_4BF$ 503.4408, found 503.3199

Yield: 99%

(2*S*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-(propanoylamino)propanamide 10.37

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.22 (d, *J* = 32.7 Hz, 5H), 4.56 (t, *J* = 6.9 Hz, 1H), 4.17 (d, *J* = 8.0 Hz, 1H), 4.02 (t, *J* = 13.6 Hz, 1H), 2.96 (dd, *J* = 9.0, 6.2 Hz, 1H), 2.80 (ddd, *J* = 23.2, 13.9, 7.7 Hz, 2H), 2.41 – 2.22 (m, 1H), 1.99 (d, *J* = 4.0 Hz, 1H), 1.90 (t, *J* = 5.1 Hz, 1H), 1.77 (d, *J* = 13.9 Hz, 2H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.19 (d, *J* = 10.3 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.82, 169.46, 140.06, 128.77, 128.03, 125.79, 83.24, 76.26, 51.99, 48.72, 46.08, 39.86, 37.72, 37.06, 35.87, 28.27, 26.40, 25.88, 23.21, 16.24, 16.18.

IR: ν 3277, 2924, 1634, 1375, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +57.4 (*c* 0.68, CH_3OH)

HRMS: calcd for $C_{24}H_{37}O_4N_3B$ 564.3823, found 442.2872

Yield: 85%

(2*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-(propanoylamino)propanamide 10.38

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33 – 7.11 (m, 5H), 4.55 (q, *J* = 7.2 Hz, 1H), 4.18 (d, *J* = 7.5 Hz, 1H), 3.94 (q, *J* = 7.0 Hz, 1H), 2.97 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.78 (ddd, *J* = 23.5, 14.1, 7.8 Hz, 2H), 2.43 – 2.21 (m, 1H), 2.01 (dd, *J* = 10.1, 5.8 Hz, 1H), 1.91 (t, *J* = 5.4 Hz, 1H), 1.77 (d, *J* = 14.7 Hz, 2H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.21 (d, *J* = 10.2 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.33, 169.34, 140.03, 128.68, 128.04, 125.81, 83.13, 76.16, 52.01, 48.56, 45.88, 39.84, 37.71, 37.10, 35.90, 28.30, 26.31, 25.83, 23.12, 16.31.

IR: ν 3207, 2913, 1681, 1375, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -60.5 (*c* 1.2, CH_3OH)

HRMS: calcd for $C_{24}H_{37}O_4N_3B$ 564.3823, found 442.2872

Yield: 99%

N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.39

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.36 – 7.13 (m, 5H), 4.55 (q, *J* = 6.9 Hz, 1H), 4.19 (d, *J* = 7.5 Hz, 1H), 4.00 (d, *J* = 6.1 Hz, 1H), 3.06 – 2.93 (m, 3H), 2.80 (ddd, *J* = 23.3, 13.9, 7.7 Hz, 2H), 2.40 – 2.23 (m, 1H), 2.09 – 1.86 (m, 4H), 1.77 (t, *J* = 11.2 Hz, 4H), 1.65 – 1.50 (m, 2H), 1.40 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.16 (d, *J* = 10.4 Hz, 1H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.54, 168.44, 140.02, 128.80, 128.02, 125.81, 83.44, 76.39, 52.50, 51.94, 46.33, 39.82, 38.94, 37.72, 37.16, 35.83, 30.47, 28.31, 26.66, 26.37, 25.91, 23.23, 21.30, 16.19.

IR: ν 3375, 2921, 1673, 1374, 1123 cm^{-1}

$[\alpha]^{23}_D$ = +63.2 (*c* 0.68, CH_3OH)

HRMS: calcd for $C_{27}H_{44}O_4N_4B$ 499.4770, found 499.3450

Yield: 56%

N-[(1*R*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-methyl-2-oxo-ethyl]heptanamide 10.40

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33 – 7.16 (m, 5H), 4.63 – 4.48 (m, 1H), 4.18 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.95 (dt, *J* = 13.2, 6.6 Hz, 1H), 2.98 (ddd, *J* = 22.2, 12.1, 6.9 Hz, 3H), 2.92 – 2.69 (m, 2H), 2.38 – 2.22 (m, 1H), 2.00 (dd, *J* = 10.8, 6.0 Hz, 1H), 1.92 (dt, *J* = 11.1, 5.9 Hz, 2H), 1.88 – 1.82 (m, 1H), 1.80 – 1.76 (m, 1H), 1.73 – 1.69 (m, 2H), 1.63 – 1.49 (m, 3H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.15 (d, *J* = 10.4 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.89 , 168.45 , 139.90 , 128.66, 128.08, 125.85 , 83.37 , 76.25 , 52.51 , 51.94 , 46.16 , 39.82 , 38.90, 37.73 , 36.99 , 35.83 , 30.66 , 28.43 , 26.60 , 26.32 , 25.82 , 23.16 , 21.58 , 16.35 .

IR: ν 3199, 2925, 1676, 1374, 1123 cm^{-1}

$[\alpha]^{23}_D$ = -45.6 (*c* 2.04, CH_3OH)

HRMS: calcd for $C_{27}H_{44}O_4N_4B$ 499.4770, found 499.3450

Yield: 99%

(2*S*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-(3-phenylpropanoylamino)propanamide 10.41

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.45 – 7.13 (m, 10H), 4.57 (q, *J* = 6.9 Hz, 1H), 4.28 – 4.11 (m, 2H), 3.40 – 3.31 (m, 1H), 3.05 (dd, *J* = 14.3, 8.7 Hz, 1H), 2.97 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.82 (ddd, *J* = 23.1, 13.9, 7.7 Hz, 2H), 2.41 – 2.15 (m, 1H), 1.97 (dd, *J* = 9.8, 6.0 Hz, 1H), 1.90 (t, *J* = 5.4 Hz, 1H), 1.83 – 1.73 (m, 2H), 1.40 (d, *J* = 7.1 Hz, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.18 (d, *J* = 3.1 Hz, 1H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.45, 168.16, 140.04, 134.21, 129.31, 128.82, 128.03, 127.48, 125.81, 83.41, 76.35, 54.10, 51.97, 46.27, 39.82, 37.71, 37.09, 35.80, 33.46, 28.26, 26.37, 25.85, 23.19, 16.28.

IR: ν 3383, 2919, 1671, 1373, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +80.5 (*c* 0.64, CH_3OH)

HRMS: calcd for $C_{30}H_{41}O_4N_3B$ 518.4788, found 518.3185

Yield: 67%

(2*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-(3-phenylpropanoylamino)propanamide 10.42

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.43 – 7.11 (m, 10H), 4.57 (q, *J* = 7.2 Hz, 1H), 4.25 – 4.06 (m, 2H), 3.32 (dd, *J* = 8.2, 3.0 Hz, 1H), 2.88 (dddd, *J* = 63.7, 23.5, 11.7, 7.8 Hz, 4H), 2.42 – 2.18 (m, 1H), 2.14 – 1.95 (m, 1H), 1.89 (t, *J* = 5.4 Hz, 1H), 1.81 – 1.69 (m, 2H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.30 (s, 3H), 1.22 (d, *J* = 9.1 Hz, 4H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.00, 168.31, 140.02, 134.17, 129.07, 128.85, 128.75, 128.08, 127.53, 125.85, 83.37, 76.27, 54.10, 51.96, 46.19, 39.80, 37.72, 37.42, 37.06, 35.85, 28.31, 26.30, 25.84, 23.12, 16.30.

IR: ν 3194, 2914, 1678, 1375, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -48.8 (*c* 1.6, CH_3OH)

HRMS: calcd for $C_{30}H_{41}O_4N_3B$ 518.4788, found 518.3185

Yield: 96%

(2*S*,3*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-[[(2*S*)-3-(4-fluorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanamide 10.43

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.43 – 7.36 (m, 2H), 7.34 – 7.24 (m, 5H), 7.23 – 7.12 (m, 2H), 4.39 (d, *J* = 8.1 Hz, 1H), 4.27 – 4.13 (m, 2H), 3.12 – 2.68 (m, 4H), 2.30 (ddd, *J* = 12.1, 7.0, 2.3 Hz, 1H), 1.99 (dt, *J* = 12.3, 3.9 Hz, 1H), 1.94 – 1.83 (m, 2H), 1.80 (dq, *J* = 14.6, 5.7, 4.3 Hz, 2H), 1.63 (ddd, *J* = 13.5, 7.3, 3.4 Hz, 1H), 1.35 (s, 3H), 1.23 (d, *J* = 11.6 Hz, 4H), 0.98 – 0.86 (m, 8H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.06 , 168.22 , 162.46 (d, *J* = 244.8 Hz), 140.09 , 131.23 (d, *J* = 8.2 Hz), 128.73 , 128.11 , 128.00 , 125.77 , 115.53 (d, *J* = 21.9 Hz), 83.21 , 76.25 , 54.79 , 53.90 , 52.02 , 39.85 , 37.68 , 37.24 , 36.34 , 35.89 , 28.30 , 26.33 , 25.85 , 24.60 , 23.14 , 13.97 , 9.77 .

IR: ν 3271, 2928, 1637, 1373, 1224, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +52 (*c* 0.5, CH_3OH)

HRMS: calcd for $C_{33}H_{46}O_4N_3BF$ 578.5493, found 578.3560

Yield: 63%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-isobutyl-5-methyl-4-oxo-6-phenyl-hexanamide 10.44

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.42 – 7.16 (m, 10H), 4.61 (dd, *J* = 9.3, 5.6 Hz, 1H), 4.23 – 4.11 (m, 2H), 3.07 – 2.66 (m, 4H), 2.36 – 2.22 (m, 1H), 2.07 – 1.96 (m, 1H), 1.89 (t, *J* = 5.5 Hz, 1H), 1.83 – 1.66 (m, 5H), 1.65 – 1.53 (m, 1H), 1.29 (s, 3H), 1.24 (d, *J* = 7.6 Hz, 4H), 0.97 (dd, *J* = 17.0, 6.2 Hz, 6H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.75 , 168.48 , 140.02 , 134.07 , 129.14 , 128.87 , 128.71, 128.07 , 127.56 , 125.85 , 83.25 , 76.23 , 54.05 , 51.99 , 48.69 , 40.19 , 39.81 , 37.70 , 37.51 , 37.13 , 35.91 , 28.35 , 26.29 , 25.87 , 24.35 , 23.09 , 21.66 , 20.52 .

IR: ν 3202, 2928, 1683, 1369, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -63.64 (*c* 0.55, CH_3OH)

HRMS: calcd for $C_{33}H_{47}O_4N_3B$ 560.5588, found 560.3654

Yield: 99%

(2*R*)-N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-methyl-2-oxo-ethyl]-3-(4-fluorophenyl)-2-methyl-propanamide 10.45

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.37 (ddd, *J* = 10.8, 6.5, 3.8 Hz, 2H), 7.30 – 7.24 (m, 5H), 7.17 – 7.11 (m, 2H), 4.62 – 4.51 (m, 1H), 4.20 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.17 – 4.07 (m, 1H), 3.10 – 2.70 (m, 5H), 2.36 – 2.23 (m, 1H), 2.00 (ddt, *J* = 10.4, 6.1, 3.0 Hz, 1H), 1.91 (t, *J* = 5.5 Hz, 1H), 1.86 – 1.72 (m, 2H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.21 (d, *J* = 10.4 Hz, 1H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.27 , 167.91 , 162.46 (d, *J* = 245.3 Hz), 140.05 , 131.19 (d, *J* = 8.1 Hz), 129.99 (d, *J* = 3.0 Hz), 128.76 , 127.99 , 125.77 , 115.50 (d, *J* = 21.9 Hz)125.77 , 115.61 , 115.39 , 83.45 , 76.39 , 53.98 , 51.97 , 39.81 , 37.70 , 37.14 , 36.24 , 35.80 , 28.19 , 26.28 , 25.83 , 23.10 , 16.24 .

IR: ν 3220, 2927, 1653, 1375, 1224, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +55 (*c* 0.4, CH_3OH)

HRMS: calcd for $C_{30}H_{40}O_4N_3BF$ 536.4693, found 536.3090

Yield: 68%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-isobutyl-5-methyl-6-(2-naphthyl)-4-oxo-hexanamide 10.46

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.96 – 7.86 (m, 3H), 7.81 (s, 1H), 7.54 – 7.45 (m, 3H), 7.32 – 7.14 (m, 5H), 4.62 (dd, *J* = 9.3, 5.5 Hz, 1H), 4.29 (dd, *J* = 10.1, 4.0 Hz, 1H), 4.19 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.57 – 3.07 (m, 2H), 3.07 – 2.98 (m, 1H), 2.96 – 2.68 (m, 2H), 2.35 – 2.22 (m, 1H), 2.10 – 1.93 (m, 1H), 1.88 (q, *J* = 5.5 Hz, 1H), 1.76 (tdd, *J* = 15.3, 7.6, 4.4 Hz, 4H), 1.62 (dt, *J* =

10.8, 5.7 Hz, 1H), 1.31 (s, 3H), 1.25 (d, *J* = 10.3 Hz, 1H), 1.22 (s, 3H), 0.98 (dd, *J* = 16.7, 6.1 Hz, 6H), 0.81 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.75 , 168.51 , 140.02 , 133.66 , 132.97 , 131.50 , 128.73, 128.21 , 128.12 , 127.41 , 127.36 , 126.49 , 126.11 , 125.86 , 83.30 , 76.27 , 53.92 , 51.98, 48.81 , 40.20 , 39.81 , 37.70 , 37.15 , 35.91 , 28.36 , 26.27 , 25.88 , 24.36 , 23.08 , 21.68 , 20.53 .

IR: ν 3029, 2912, 1683, 1386, 1123cm^{-1}

$[\alpha]^{23}_D$ = -70.51 (*c* 0.78, CH$_3$OH)

HRMS: calcd for $C_{37}H_{49}O_4N_3B$ 610.6178, found 610.3811

Yield: 91%

(2*S*,3*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-[[(2*S*)-3-(3-fluorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanamide 10.47

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 (td, *J* = 8.0, 5.9 Hz, 1H), 7.31 – 7.24 (m, 5H), 7.20 – 7.02 (m, 3H), 4.40 (d, *J* = 8.1 Hz, 1H), 4.26 – 4.13 (m, 2H), 3.12 – 2.67 (m, 4H), 2.38 – 2.22 (m, 1H), 2.04 – 1.95 (m, 1H), 1.89 (dt, *J* = 11.9, 6.6 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.62 (ddd, *J* = 13.7, 7.4, 3.5 Hz, 1H), 1.34 (s, 3H), 1.22 (d, *J* = 13.3 Hz, 4H), 0.98 – 0.86 (m, 8H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.02 , 168.21 , 163.09 (d, *J* = 245.5 Hz), 140.08 , 136.85 (d, *J* = 7.4 Hz), 130.68 (d, *J* = 8.5 Hz), 128.71 , 127.99 , 115.97 (d, *J* = 22.1 Hz), 114.35 (d, *J* = 21.3 Hz) , 125.76 , 125.16 (d, *J* = 3.0 Hz), 83.24 , 76.28 , 54.79 , 53.79 , 52.00 , 39.83 , 37.68 , 37.15 , 36.84 , 36.48 , 35.86 , 28.27 , 26.29 , 25.85 , 24.57 , 23.11 , 13.97 , 9.77 .

IR: ν 3271, 2930, 1638, 1385, 1254, 1146 cm^{-1}

$[\alpha]^{23}_D$ = +46 (*c* 1, CH$_3$OH)

HRMS: calcd for $C_{33}H_{46}O_4N_3BF$ 578.5493, found 578.3560

Yield: 43%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-isobutyl-5-methyl-4-oxo-6-(3-pyridyl)hexanamide 10.48

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.88 (dd, *J* = 11.2, 5.4 Hz, 2H), 8.63 (d, *J* = 8.2 Hz, 1H), 8.14 (dd, *J* = 8.0, 5.5 Hz, 1H), 7.28 (d, *J* = 4.3 Hz, 4H), 7.17 (h, *J* = 4.1 Hz, 1H), 4.59 (dt, *J* = 9.4, 5.3 Hz, 1H), 4.46 (dd, *J* = 7.2, 5.0 Hz, 1H), 4.26 – 4.19 (m, 1H), 3.66 – 3.32 (m, 2H), 3.10 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.95 – 2.72 (m, 2H), 2.29 (ddt, *J* = 11.9, 8.8, 3.5 Hz, 1H), 2.01 (dd, *J* = 11.2, 5.9 Hz, 1H), 1.91 (t, *J* = 5.3 Hz, 1H), 1.75 (ddt, *J* = 16.8, 9.2, 3.7 Hz, 4H), 1.66 – 1.50 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.17 (d, *J* = 10.4 Hz, 1H), 1.02 – 0.92 (m, 6H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.16 , 167.13 , 148.52 , 142.10 , 140.77 , 139.86 , 135.07, 128.77 , 128.09 , 127.62 , 125.90 , 83.62 , 76.37 , 52.71 , 51.94 , 49.15 , 40.03 , 39.77 , 37.73 , 37.02 , 35.78 , 33.58 , 28.32 , 26.29 , 25.83 , 24.30 , 23.12 , 21.63 , 20.68 .

IR: ν 3368, 2932, 1684, 1369, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -53.13 (*c* 0.64, CH$_3$OH)

HRMS: calcd for $C_{32}H_{46}O_4N_4B$ 561.5448, found 561.3607

Yield: 69%

(2*R*)-N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-methyl-2-oxo-ethyl]-3-(3-fluorophenyl)-2-methyl-propanamide 10.49

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.42 (tt, *J* = 8.0, 5.1 Hz, 2H), 7.31 – 7.24 (m, 5H), 7.21 – 7.15 (m, 2H), 4.56 (q, *J* = 7.1 Hz, 1H), 4.20 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.14 (dt, *J* = 9.1, 4.7 Hz, 1H), 3.13 – 2.70 (m, 5H), 2.36 – 2.23 (m, 1H), 2.04 – 1.94 (m, 1H), 1.90 (t, *J* = 5.5 Hz, 1H), 1.78 (dq, *J* = 9.4, 3.0 Hz, 2H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 10.5 Hz, 1H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.23 , 167.91 , 163.09 (d, *J* = 245.6 Hz), 140.06 , 136.89 (d, *J* = 7.3 Hz), 128.76 , 127.99 , 125.78 , 115.94 (d, *J* = 21.8 Hz), 114.35 (d, *J* = 21.2 Hz) , 83.51 , 76.43 , 53.87 , 51.95 , 40.58 , 39.79 , 37.70 , 37.06 , 36.82 , 35.77 , 28.17 , 26.26 , 25.84 , 23.08 , 16.24 .

IR: ν 3243, 2930, 1655, 1375, 1254, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +80 (*c* 0.4, CH$_3$OH)

HRMS: calcd for $C_{30}H_{40}O_4N_3BF$ 536.4693, found 536.3090

Yield: 60%

(2*R*)-N-[(*R*)-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-7-methyl-2-(1-methyl)sulfanylpropanyl(pentanoylamino)propanamide 10.50

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.16 (m, 5H), 4.58 (dd, *J* = 9.2, 5.9 Hz, 1H), 4.18 (dt, *J* = 8.5, 2.8 Hz, 1H), 4.06 – 3.97 (m, 1H), 3.01 – 2.83 (m, 2H), 2.61 (ddt, *J* = 12.6, 6.0, 2.2 Hz, 2H), 2.36 – 2.25 (m, 1H), 2.23 – 2.14 (m, 1H), 2.13 (s, 3H), 2.11 – 1.96 (m, 2H), 1.92 (dd, *J* = 6.7, 4.3 Hz, 1H), 1.83 – 1.64 (m, 4H), 1.61 – 1.51 (m, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.21 (d, *J* = 10.5 Hz, 1H), 0.97 (dd, *J* = 14.0, 6.2 Hz, 6H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.75 , 168.40 , 140.02 , 128.74 , 128.23 , 125.84 , 83.19 , 76.21 , 52.15 , 52.01 , 48.68 , 40.18 , 39.87 , 37.72, 37.16 , 35.96 , 30.99 , 28.72, 28.55, 26.34 , 25.89 , 24.31 , 23.16 , 21.63 , 20.60 , 13.81.

IR: ν 3200, 2925, 1675, 1369, 1123 cm^{-1}

$[\alpha]^{23}_D$ = -60 (*c* 0.8, CH_3OH)

HRMS: calcd for $C_{29}H_{47}O_4N_3BS$ 544.5812, found 544.3375

Yield: 90%

(2*S*,3*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-3-methyl-2-[[(2*S*)-2-methyl-3-phenyl-propanoyl]amino]pentanamide 10.51

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 – 7.14 (m, 10H), 4.41 (d, *J* = 8.1 Hz, 1H), 4.25 (dd, *J* = 8.9, 4.9 Hz, 1H), 4.22 – 4.15 (m, 1H), 3.40 – 2.99 (m, 2H), 2.98 – 2.68 (m, 4H), 2.29 (ddd, *J* = 14.2, 7.8, 3.1 Hz, 1H), 1.99 (dt, *J* = 12.0, 4.0 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.83 – 1.73 (m, 2H), 1.61 (ddp, *J* = 15.1, 7.6, 4.1 Hz, 1H), 1.35 (s, 3H), 1.22 (d, *J* = 10.4 Hz, 4H), 0.96 – 0.86 (m, 6H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.15 , 168.43 , 140.09 , 134.13 , 129.23 , 128.85 , 128.56, 128.06 , 127.49 , 125.78 , 83.19 , 76.25 , 54.75 , 53.97 , 52.02 , 39.85 , 37.68 , 37.19 , 36.80 , 36.46 , 35.88 , 28.30 , 26.32 , 25.86 , 24.59 , 23.14 , 13.99 , 9.80 .

IR: ν 3275, 2931, 1652, 1375, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +40 (*c* 0.5, CH_3OH)

HRMS: calcd for $C_{33}H_{47}O_4N_3B$ 560.5588, found 560.3661

Yield: 41%

(2*S*)-N-[(1*R*,2*R*)-1-[[(1*S*)-1-[(3aR)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]carbamoyl]-2-methyl-butyl]-2,3,3-trimethyl-butanamide 10.52

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.32 – 7.13 (m, 5H), 4.35 (d, *J* = 8.3 Hz, 1H), 4.15 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.69 (s, 1H), 2.97 – 2.60 (m, 4H), 2.29 (ddd, *J* = 13.8, 8.1, 2.5 Hz, 1H), 2.08 – 1.96 (m, 1H), 1.91 (t, *J* = 5.5 Hz, 1H), 1.88 – 1.74 (m, 3H), 1.62 (ddd, *J* = 13.7, 7.4, 3.4 Hz, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.21 (d, *J* = 10.5 Hz, 1H), 1.14 (s, 9H), 0.93 – 0.90 (m, 6H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.79 , 167.45 , 140.17 , 128.74 , 128.04 , 125.75 , 83.22 , 76.25 , 61.04 , 54.78 , 52.00 , 39.85 , 37.66 , 37.13 , 36.33 , 35.87 , 33.15 , 28.21 , 26.32 , 25.86 , 25.62 , 25.30 , 24.52 , 23.13 , 13.90 , 9.82 .

IR: ν 3213, 2932, 1652, 1375, 1123 cm^{-1}

$[\alpha]^{23}_D$ = +47.5 (*c* 0.4, CH_3OH)

HRMS: calcd for $C_{30}H_{49}O_4N_3B$ 526.5424, found 526.3811

Yield: 57%

(2*R*,3*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-[[(2*S*)-3-cyclohexyl-2-methyl-propanoyl]amino]-3-methyl-pentanamide 10.53

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.31 – 7.15 (m, 5H), 4.36 (d, *J* = 8.8 Hz, 1H), 4.17 (d, *J* = 8.5 Hz, 1H), 4.01 (dd, *J* = 8.9, 5.8 Hz, 1H), 2.95 – 2.64 (m, 4H), 2.36 – 2.19 (m, 1H), 2.11 – 1.96 (m, 1H), 1.94 – 1.89 (m, 1H), 1.88 – 1.58 (m, 11H), 1.43 (dd, *J* = 27.4, 13.5 Hz, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.23 – 1.18 (m, 2H), 1.03 (tdd, *J* = 12.9, 7.9, 4.3 Hz, 2H), 0.95 – 0.90 (m, 6H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.12 , 169.55 , 140.15 , 128.69 , 128.04 , 125.74 , 83.11 , 76.16 , 54.66 , 52.02 , 50.72 , 39.87 , 39.04 , 37.69 , 37.18 , 36.58 , 36.26 , 35.90 , 33.41 , 32.01 , 28.32 , 26.34 , 26.10 , 25.47 , 24.59 , 23.14 , 13.95 , 9.76 .

IR: ν 3292, 2924, 1637, 1366, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +64 (*c* 0.5, CH_3OH)

HRMS: calcd for $C_{33}H_{53}O_4N_3B$ 566.6065, found 566.4124

Yield: 37%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-6-cyclohexyl-2-isobutyl-5-methyl-4-oxo-hexanamide 10.54

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.34 – 7.14 (m, 5H), 4.57 (dd, *J* = 9.4, 5.7 Hz, 1H), 4.17 (dd, *J* = 8.7, 2.1 Hz, 1H), 3.95 (dd, *J* = 10.2, 4.3 Hz, 1H), 2.95 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.90 – 2.64 (m, 2H), 2.30 (ddd, *J* = 14.7, 6.3, 3.5 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.90 (q, *J* = 4.7, 4.2 Hz, 1H), 1.82 – 1.38 (m, 14H), 1.33 (s, 3H), 1.26 (s, 3H), 1.21 (dd, *J* = 11.7, 7.2 Hz, 2H), 1.02 – 0.88 (m, 9H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.02 , 169.58 , 140.04 , 128.67 , 128.09 , 125.82 , 83.03 , 76.11 , 52.05 , 50.47 , 40.14 , 39.89 , 39.11 , 37.71 , 37.18 , 36.01 , 33.72 , 33.07 , 31.36 , 28.66 , 26.34 , 26.06 , 25.37 , 24.31 , 23.16 , 21.66 , 20.53 .

IR: ν 3202, 2924, 1673, 1369, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -27.45 (*c* 0.78, CH_3OH)

HRMS: calcd for $C_{33}H_{53}O_4N_3B$ 566.6065, found 566.4126

Yield: 77%

(2*S*)-N-[(1*R*,2*R*)-1-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]carbamoyl]-2-methyl-butyl]-2-methyl-heptanamide 10.55

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.16 (m, 5H), 4.36 (d, *J* = 8.5 Hz, 1H), 4.20 – 4.16 (m, 1H), 4.05 (td, *J* = 6.3, 3.0 Hz, 2H), 3.04 – 2.98 (m, 3H), 2.92 – 2.62 (m, 2H), 2.37 – 2.25 (m,

1H), 1.93 (dt, *J* = 11.0, 6.2 Hz, 4H), 1.76 (tdd, *J* = 9.8, 5.4, 2.9 Hz, 5H), 1.58 – 1.49 (m, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.20 (d, *J* = 10.4 Hz, 1H), 0.93 (d, *J* = 6.9 Hz, 6H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.34 , 168.74 , 140.09 , 128.71 , 128.07 , 125.79 , 83.15 , 76.21 , 54.77 , 52.44 , 52.02 , 39.88 , 38.96 , 37.70 , 37.36 , 36.05 , 30.67 , 28.34 , 26.77 , 26.35 , 25.94 , 24.63 , 23.22 , 21.31 , 9.69 .

IR: ν 3027, 2930, 1652, 1386, 1123 cm^{-1}

$[\alpha]^{23}_D$ = +64.29 (*c* 0.6, CH_3OH)

HRMS: calcd for $C_{30}H_{50}O_4N_4B$ 541.5571, found 541.3920

Yield: 53%

N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-benzyl-2-oxo-ethyl]heptanamide 10.56

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.38 – 7.15 (m, 10H), 4.76 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.26 – 4.16 (m, 1H), 3.90 (t, *J* = 6.2 Hz, 1H), 3.09 (dd, *J* = 13.9, 6.5 Hz, 1H), 3.03 – 2.80 (m, 5H), 2.71 – 2.60 (m, 1H), 2.40 – 2.25 (m, 1H), 2.10 – 2.00 (m, 1H), 1.98 – 1.84 (m, 3H), 1.85 – 1.66 (m, 4H), 1.52 (dd, *J* = 15.3, 7.8 Hz, 2H), 1.39 (s, 3H), 1.28 (s, 3H), 1.20 – 1.16 (m, 1H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 174.98, 168.55, 139.93, 135.92, 128.92, 128.70, 128.26, 128.02, 126.72, 125.83, 83.47, 76.39, 52.43, 52.10, 51.91, 39.81, 38.90, 37.73, 37.18, 36.91, 35.86, 33.37, 30.58, 28.33, 26.77, 26.30, 25.91, 23.18, 21.23.

IR: ν 3213, 2921, 1673, 1373, 1123 cm^{-1}

$[\alpha]^{23}_D$ = +60.9 (*c* 1.61, CH_3OH)

HRMS: calcd for $C_{33}H_{48}O_4N_4B$ 575.5735, found 575.3763

Yield: 94%

(2*S*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-3-phenyl-2-(propanoylamino)propanamide 10.57

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.37 – 7.14 (m, 10H), 4.78 (d, *J* = 6.5 Hz, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 3.87 (dt, *J* = 13.5, 6.8 Hz, 1H), 3.10 (dd, *J* = 13.8, 6.4 Hz, 1H), 3.00 – 2.79 (m, 3H), 2.69 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.43 – 2.21 (m, 1H), 2.00 (d, *J* = 6.5 Hz, 1H), 1.94 (t, *J* = 5.4 Hz, 1H), 1.80 (d, *J* = 11.5 Hz, 2H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.24 – 1.18 (m, 1H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.22, 169.53, 139.95, 135.96, 128.89, 128.67, 128.24, 128.09, 128.01, 126.71, 125.79, 83.32, 76.28, 51.95, 51.85, 48.61, 39.83, 37.73, 36.97, 35.85, 33.37, 28.27, 26.31, 25.87, 23.14, 16.21.

IR: ν 3209, 2922, 1656, 1374, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +58.5 (*c* 1.18, CH_3OH)

HRMS: calcd for $C_{30}H_{41}O_4N_3B$ 518.4788, found 518.3185

Yield: 86%

(2*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-isobutyl-5-methyl-4-oxo-hexanamide 10.58

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.14 (m, 5H), 4.57 (dd, *J* = 9.3, 5.7 Hz, 1H), 4.18 (dd, *J* = 8.8, 2.1 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 1H), 2.95 (dd, *J* = 9.4, 6.0 Hz, 1H), 2.90 – 2.62 (m, 2H), 2.30 (ddd, *J* = 11.5, 7.7, 2.1 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.91 (t, *J* = 5.5 Hz, 1H), 1.73 (ddt, *J* = 29.1, 15.2, 5.5 Hz, 4H), 1.63 – 1.51 (m, 1H), 1.49 (d, *J* = 7.1 Hz, 3H), 1.32 (s, 3H), 1.26 (s, 3H), 1.21 (d, *J* = 10.3 Hz, 1H), 0.96 (dd, *J* = 15.8, 6.2 Hz, 6H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.11 , 169.61 , 140.03 , 128.70 , 128.06 , 125.82 , 83.01 , 76.09 , 52.05 , 48.53 , 40.10 , 39.87 , 37.71 , 37.19 , 35.97 , 28.38 , 26.36 , 25.86 , 24.33 , 23.17 , 21.65 , 20.53 , 16.44 .

IR: ν 3200, 2928, 1675, 1370, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -72.88 (*c* 0.59, CH_3OH)

HRMS: calcd for $C_{27}H_{43}O_4N_3B$ 484.4624, found 484.3341

Yield: 92%

(2*S*)-N-[(*S*)-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-isopropyl-7-methyl-2-(pentanoylamino)propanamide 10.59

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33 – 7.13 (m, 5H), 4.30 (d, *J* = 7.9 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 1H), 2.96 – 2.64 (m, 3H), 2.28 (ddd, *J* = 11.4, 8.4, 4.1 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.99 (dd, *J* = 9.4, 5.4 Hz, 1H), 1.90 (t, *J* = 5.5 Hz, 1H), 1.83 – 1.67 (m, 5H), 1.33 (s, 3H), 1.25 (s, 3H), 1.18 – 1.13 (m, 1H), 1.07 – 0.92 (m, 12H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.18 , 169.63 , 140.07 , 128.68 , 128.02 , 125.79 , 83.08 , 76.15 , 55.93 , 51.98 , 51.37, 40.29 , 39.85 , 37.67 , 37.05 , 35.86 , 30.24 , 28.29 , 26.33 , 25.85 , 23.92 , 23.14 , 21.96 , 20.70 , 17.81 , 17.51 .

IR: ν 3062, 2929, 1635, 1373, 1123 cm^{-1}

$[\alpha]^{23}_D$ = +47.54 (*c* 1.22, CH_3OH)

HRMS: calcd for $C_{29}H_{47}O_4N_3B$ 512.5157, found 512.3665

Yield: 80%

(2*S*,3*R*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-2-[[(2*S*)-3-(4-chlorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanamide 10.60

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.13 (m, 5H), 4.37 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.20 (ddd, *J* = 10.8, 8.3, 3.4 Hz, 2H), 3.13 – 2.66 (m,

4H), 2.41 – 2.18 (m, 1H), 1.97 (dd, *J* = 10.2, 5.8 Hz, 1H), 1.88 (dt, *J* = 15.8, 6.8 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.68 – 1.56 (m, 1H), 1.34 (s, 3H), 1.25 – 1.17 (m, 4H), 0.91 (dd, *J* = 8.9, 6.7 Hz, 7H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.99 , 168.10 , 140.07 , 133.39 , 132.74 , 130.97 , 128.79, 128.05 , 125.76 , 83.23 , 76.26 , 54.80 , 53.71 , 52.02 , 39.85 , 37.68 , 37.25 , 36.39 , 35.89 , 28.30 , 26.32 , 25.84 , 24.60 , 23.13 , 13.96 , 9.74 .

IR: ν 2963, 2929, 1652, 1375, 1122cm^{-1}

$[\alpha]^{23}_D$ = +38.9 (*c* 0.9, CH_3OH)

HRMS: calcd for $C_{33}H_{46}O_4N_3BCl$ 595.0041, found 594.3264

Yield: 47%

(2*R*)-N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-benzyl-2-oxo-ethyl]-3-(3-fluorophenyl)-2-methyl-propanamide 10.61

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 – 7.10 (m, 14H), 4.79 (dd, *J* = 8.3, 6.7 Hz, 1H), 4.21 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.13 (dd, *J* = 8.8, 4.9 Hz, 1H), 3.29 – 2.93 (m, 5H), 2.92 – 2.59 (m, 2H), 2.39 – 2.22 (m, 1H), 1.99 (td, *J* = 6.4, 3.0 Hz, 1H), 1.93 (t, *J* = 5.5 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.37 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 10.4 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.53 , 168.04 , 163.07 (d, *J* = 245.5 Hz), 139.89 , 138.93, 136.67 , 135.95 , 128.94 , 128.73 , 128.37 , 128.09 , 115.97 (d, *J* = 21.8 Hz), 114.35 (d, *J* = 21.0 Hz) , 83.66 , 76.48 , 55.12 , 53.77 , 52.26 , 51.89 , 40.61 , 39.77 , 37.81 , 35.71 , 34.99 , 28.23 , 26.28 , 25.83 , 23.11 .

IR: ν 3215, 2924, 1653, 1374, 1254, 1146 cm^{-1}

$[\alpha]^{23}_D$ = +74.26 (*c* 1.01, CH_3OH)

HRMS: calcd for $C_{36}H_{44}O_4N_3BF$ 612.5657, found 612.3403

Yield: 82%

(2*R*)-N-[(1*S*)-2-[[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]amino]-1-benzyl-2-oxo-ethyl]-3-(4-fluorophenyl)-2-methyl-propanamide 10.62

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.09 (m, 14H), 4.77 (t, *J* = 7.5 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.09 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.29 – 2.93 (m, 5H), 2.92 – 2.68 (m, 2H), 2.31 (t, *J* = 11.3 Hz, 1H), 1.99 (dd, *J* = 10.8, 5.9 Hz, 1H), 1.92 (t, *J* = 5.5 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.37 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 10.3 Hz, 1H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 174.55 , 168.01 , 162.47 (d, *J* = 245.0 Hz), 139.89 , 135.95, 131.23 , 131.14 , 128.82 (d, *J* = 19.4 Hz), 128.12 (d, *J* = 28.8 Hz), 126.71 , 125.79 , 115.52 (d, *J* =

21.9 Hz), 83.62 , 76.46 , 71.83, 53.90 , 52.20 , 51.91 , 39.78 , 37.72 , 37.12 , 36.22 , 35.74 , 28.24 , 26.28 , 25.83 , 23.11 .

IR: ν 3060, 2922, 1653, 1374, 1224, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +62 (*c* 0.5, CH_3OH)

HRMS: calcd for $C_{36}H_{44}O_4N_3BF$ 612.5657, found 612.3403

Yield: 39%

(2*S*)-N-[(1*S*)-1-[(3a*R*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-2-phenyl-ethyl]-3-phenyl-2-(3-phenylpropanoylamino)propanamide 10.63

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.47 – 7.12 (m, 15H), 4.78 (t, *J* = 8.9 Hz, 1H), 4.21 (d, *J* = 8.0 Hz, 1H), 4.10 (dd, *J* = 8.9, 4.7 Hz, 1H), 3.16 – 2.93 (m, 5H), 2.79 (ddd, *J* = 23.3, 14.0, 7.8 Hz, 2H), 2.40 – 2.19 (m, 1H), 1.98 (dd, *J* = 10.0, 6.4 Hz, 1H), 1.92 (t, *J* = 5.4 Hz, 1H), 1.89 - 1.76 (m, 2H), 1.37 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 10.3 Hz, 1H), 0.84 (s, 3H).

13C NMR (101 MHz, Methanol-d_4) δ 174.65, 168.25, 139.91, 135.97, 134.05, 129.21, 128.93, 128.86, 128.27, 128.11, 128.00, 127.52, 126.71, 125.80, 83.60, 76.46, 54.00, 52.18, 51.91, 39.79, 37.72, 37.16, 37.01, 35.75, 28.25, 26.29, 25.84, 23.12.

IR: ν 3271, 2927, 1653, 1374, 1022 cm^{-1}

$[\alpha]^{23}_D$ = +46.3 (c 6.80, CH_3OH)

HRMS: calcd for $C_{36}H_{45}O_4N_3B$ 594.5753, found 594.3498

Yield: 89%

(2*R*)-N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]amino]-1-methyl-2-oxo-ethyl]-2-methyl-3-(1-naphthyl)propanamide 10.64

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.26 (dd, *J* = 8.4, 6.1 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.56 (tt, *J* = 8.1, 6.6, 2.6 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.31 – 7.15 (m, 5H), 4.65 – 4.53 (m, 1H), 4.37 – 4.26 (m, 1H), 4.23 – 4.15 (m, 1H), 3.92 – 3.33 (m, 2H), 2.80 – 2.65 (m, 3H), 2.41 – 2.28 (m, 1H), 2.13 (d, *J* = 10.2 Hz, 1H), 1.94 (t, *J* = 5.4 Hz, 1H), 1.91 – 1.85 (m, 1H), 1.80 (td, *J* = 18.2, 15.9, 10.1 Hz, 3H), 1.48 (d, *J* = 2.9 Hz, 3H), 1.34 (s, 4H), 1.24 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.64 , 168.36 , 142.09 , 134.30 , 131.71 , 129.88 , 128.69 , 128.00 , 126.49 , 125.79 , 125.65 , 122.93 , 83.28, 76.17 , 53.18 , 52.02 , 46.46 , 39.86 , 37.80 , 36.18 , 34.60 , 33.40 , 33.13 , 28.40 , 26.29 , 26.11 , 23.12 , 16.16 .

IR: ν 3207, 2919, 1670, 1374, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -17.46 (*c* 0.63, CH_3OH)

HRMS: calcd for $C_{35}H_{45}O_4N_3B$ 582.5645, found 582.3498

Yield: 88%

(2*R*)-N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]amino]-1-methyl-2-oxo-ethyl]-2-methyl-3-(2-naphthyl)propanamide 10.65

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 – 7.79 (m, 5H), 7.52 – 7.46 (m, 3H), 7.30 – 7.21 (m, 4H), 4.63 (p, *J* = 7.6, 7.2 Hz, 1H), 4.27 (dt, *J* = 7.0, 3.6 Hz, 1H), 4.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.58 – 3.50 (m, 1H), 3.20 – 3.08 (m, 1H), 2.72 (ddt, *J* = 11.5, 6.5, 3.6 Hz, 3H), 2.40 – 2.29 (m, 1H), 2.21 – 2.09 (m, 1H), 1.96 (t, *J* = 5.4 Hz, 1H), 1.83 (ddt, *J* = 8.1, 5.9, 3.2 Hz, 2H), 1.74 (dq, *J* = 15.0, 7.6 Hz, 2H), 1.50 (d, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.26 (s, 4H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.66 , 168.26 , 142.06 , 133.64 , 132.95 , 131.54 , 128.71, 128.30 , 128.04 , 128.01 , 127.96 , 127.37 , 126.49 , 126.12 , 125.86 , 125.42 , 83.30 , 76.20 , 53.97 , 52.02 , 46.95 , 46.33 , 39.87 , 37.80 , 37.57 , 36.16 , 33.38 , 33.14 , 28.36 , 26.19 , 23.11 , 16.29 .

IR: ν 3211, 2928, 1650, 1374, 1123cm^{-1}

$[\alpha]^{23}_{D}$ = -72.73 (*c* 0.11, CH_3OH)

HRMS: calcd for $C_{35}H_{45}O_4N_3B$ 582.5645, found 582.3498

Yield: 79%

(2*R*)-N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]amino]-1-methyl-2-oxo-ethyl]-3-cyclohexyl-2-methyl-propanamide 10.66

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.27 – 7.10 (m, 5H), 4.59 (q, *J* = 7.1 Hz, 1H), 4.19 (dt, *J* = 8.6, 2.3 Hz, 1H), 4.01 – 3.90 (m, 1H), 2.75 – 2.64 (m, 3H), 2.35 (ddt, *J* = 11.2, 8.9, 2.4 Hz, 1H), 2.14 (ddd, *J* = 9.7, 6.9, 4.7 Hz, 1H), 1.96 (td, *J* = 5.7, 2.0 Hz, 1H), 1.86 (ddt, *J* = 10.3, 5.2, 2.7 Hz, 4H), 1.81 – 1.61 (m, 10H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 3H), 1.28 (s, 4H), 1.05 – 0.91 (m, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.02 , 169.33 , 142.07 , 128.03 , 127.99 , 125.40 , 83.09 , 76.05 , 52.07 , 50.54 , 46.09 , 39.95 , 39.08 , 37.81 , 36.27 , 33.48 , 33.30 , 31.59 , 28.62 , 26.36 , 26.23 , 25.38 , 23.19 , 16.27 .

IR: ν 3210, 2923, 1667, 1374, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -57.69 (*c* 0.26, CH_3OH)

HRMS: calcd for $C_{31}H_{49}O_4N_3B$ 538.5532, found 538.3811

Yield: 99%

(2*R*)-N-[(1*S*)-2-[[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]amino]-1-methyl-2-oxo-ethyl]-2-methyl-3-(3-pyridyl)propanamide 10.67

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.89 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.66 (d, *J* = 7.9 Hz, 1H), 8.12 (q, *J* = 7.3 Hz, 1H), 7.25 (dt, *J* = 14.8, 7.5 Hz, 5H), 4.59 (q, *J* = 7.3 Hz, 1H), 4.41 (t, *J* = 6.1 Hz, 1H), 4.25 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.67 – 3.35 (m, 2H), 2.81 (q, *J* = 6.0, 4.6 Hz, 1H), 2.72 (ddq, *J* = 14.6, 10.8, 7.9, 6.6 Hz, 2H), 2.37 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.17 (dt, *J* = 11.1, 6.1 Hz, 1H), 1.98 (t, *J* = 5.5 Hz, 1H), 1.88 (tdt, *J* = 19.4, 10.1, 5.0 Hz, 3H), 1.80 (d, *J* = 4.1 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 4H), 1.43 (d, *J* = 6.8 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.12 , 166.89 , 148.52 , 142.23 , 141.96 , 140.69 , 135.10, 128.07 , 128.03 , 127.99 , 127.53 , 125.47 , 83.74 , 76.40 , 52.67 , 51.95 , 47.17 , 46.96 , 39.81 , 37.83 , 36.03 , 33.52 , 33.31 , 33.01 , 28.31 , 26.18 , 23.11 , 16.26 .

IR: ν 3365, 2927, 1684, 1375, 1123 cm^{-1}

$[\alpha]^{23}_{D}$ = -38.04 (*c* 0.92, CH_3OH)

HRMS: calcd for $C_{30}H_{42}O_4N_4B$ 533.4935, found 533.3294

Yield: 45%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]-2-isobutyl-5-methyl-6-(2-naphthyl)-4-oxo-hexanamide 10.68

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 – 7.80 (m, 4H), 7.49 (qd, *J* = 6.8, 5.8, 3.8 Hz, 3H), 7.29 – 7.13 (m, 5H), 4.66 (dd, *J* = 9.1, 5.6 Hz, 1H), 4.33 (dd, *J* = 9.8, 4.2 Hz, 1H), 4.21 (dd, *J* = 8.8, 2.1 Hz, 1H), 3.63 – 3.09 (m,2H), 2.73 (qd, *J* = 6.6, 2.7 Hz, 3H), 2.33 (dq, *J* = 11.4, 5.4, 3.6 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.93 (q, *J* = 4.7, 4.1 Hz, 1H), 1.86 – 1.62 (m, 7H), 1.52 – 1.45 (m, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 1.00 (dd, *J* = 15.9, 6.1 Hz, 6H), 0.83 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.48 , 168.47 , 142.06 , 133.64 , 132.96 , 131.47 , 128.71, 128.26 , 128.02 , 127.39 , 126.56 , 126.08 , 125.84 , 125.43 , 83.20 , 76.15 , 53.90 , 52.04, 48.97 , 40.14 , 39.88 , 37.78 , 37.58 , 36.20 , 33.47 , 33.26 , 28.43 , 26.22 , 24.36 , 23.13 , 21.69 , 20.62 .

IR: ν 3201, 2926, 1673, 1369, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = -48.57 (*c* 0.7, CH_3OH)

HRMS: calcd for $C_{38}H_{51}O_4N_3B$ 624.6445, found 624.3990

Yield: 77%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]-6-cyclohexyl-2-isobutyl-5-methyl-4-oxo-hexanamide 10.69

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.29 – 7.11 (m, 5H), 4.61 (dd, *J* = 9.2, 5.7 Hz, 1H), 4.19 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.96 (dd, *J* = 10.1, 4.3 Hz, 1H), 2.67 (dtd, *J* = 13.9, 11.1, 10.3, 6.5 Hz, 3H), 2.35 (ddt, *J* = 13.6, 8.6, 2.3 Hz, 1H), 2.14 (ddd, *J* = 12.7, 6.5, 4.5 Hz, 1H), 1.95 (t, *J* = 5.6

Hz, 1H), 1.85 (ddt, *J* = 13.0, 6.5, 3.1 Hz, 4H), 1.82 – 1.51 (m, 12H), 1.47 (d, *J* = 10.2 Hz, 1H), 1.37 (s, 3H), 1.28 (s, 4H), 0.98 (dd, *J* = 13.3, 6.0 Hz, 9H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.64 , 169.54 , 142.04 , 128.02 , 127.98 , 125.41 , 83.02 , 76.04 , 52.08 , 50.51 , 48.70 , 47.87 , 40.00 , 39.94 , 39.10 , 37.79 , 36.29 , 33.62 , 33.55 , 33.28 , 33.06 , 31.46 , 28.66 , 26.35 , 26.22 , 25.94 , 25.38 , 24.32 , 23.17 , 21.65 , 20.60 .

IR: ν 3209, 2924, 1669, 1369, 1122 cm^{-1}

$[\alpha]^{23}_D$ = -46.97 (*c* 0.66, CH$_3$OH)

HRMS: calcd for $C_{34}H_{55}O_4N_3B$ 580.6332, found 580.4300

Yield: 72%

(2*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]-2-isobutyl-5-methyl-4-oxo-hexanamide 10.70

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.29 – 7.10 (m, 5H), 4.61 (dd, *J* = 9.2, 5.5 Hz, 1H), 4.24 – 4.14 (m, 1H), 4.01 (q, *J* = 6.8 Hz, 1H), 2.70 (ddd, *J* = 9.6, 6.5, 3.3 Hz, 2H), 2.64 (t, *J* = 7.1 Hz, 1H), 2.34 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.12 (dd, *J* = 10.5, 5.6 Hz, 1H), 1.94 (t, *J* = 5.5 Hz, 1H), 1.79 (dddd, *J* = 37.9, 20.3, 8.7, 4.2 Hz, 6H), 1.65 – 1.56 (m, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.46 (d, *J* = 10.3 Hz, 1H), 1.35 (s, 3H), 1.27 (s, 3H), 0.97 (dd, *J* = 15.0, 6.0 Hz, 6H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.93 , 169.66 , 142.05 , 128.00 , 127.96 , 125.42 , 82.94, 75.95 , 52.08 , 48.65 , 40.01 , 39.97 , 37.79 , 36.28 , 33.47 , 33.27 , 28.44 , 26.40 , 26.12 , 24.35 , 23.22 , 21.70 , 20.62 , 16.47 .

IR: ν 3321, 2932, 1673, 1373, 1118 cm^{-1}

$[\alpha]^{23}_D$ = -89.58 (*c* 0.48, CH$_3$OH)

HRMS: calcd for $C_{28}H_{45}O_4N_3B$ 498.4890, found 498.3513

Yield: 86%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]-2-isobutyl-5-methyl-4-oxo-decanamide 10.71

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.30 – 7.12 (m, 5H), 4.65 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.21 (dd, *J* = 8.7, 2.2 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 2.96 (dt, *J* = 15.1, 7.6 Hz, 2H), 2.75 – 2.66 (m, 3H), 2.37 (ddt, *J* = 13.7, 8.7, 2.4 Hz, 1H), 2.15 (ddd, *J* = 8.8, 6.8, 4.8 Hz, 1H), 1.96 (td, *J* = 7.6, 6.5, 3.4 Hz, 1H), 1.92 – 1.42 (m, 14H), 1.38 (s, 3H), 1.29 (s, 3H), 0.99 (dd, *J* = 14.6, 6.0 Hz, 6H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.36 , 168.63 , 141.99 , 128.05 , 127.98 , 125.45 , 83.19 , 76.07 , 52.46 , 52.05 , 48.82 , 40.01 , 39.97 , 38.86 , 37.82 , 36.22 , 33.42 , 33.18 , 30.72 , 28.53 , 26.63 , 26.34 , 26.12 , 24.29 , 23.18 , 21.77 , 20.72 .

IR: ν 3363, 2928, 1683, 1386, 1123 cm^{-1}

$[\alpha]^{23}_D$ = -83.85 (*c* 1.3, CH_3OH)

HRMS: calcd for $C_{31}H_{53}O_4N_4B$ 555.5917, found 555.4095

Yield: 92%

(2*R*,5*R*)-N-[(1*R*)-1-[(3a*S*)-4-ethyl-3a,5,5-trimethyl-4,6,7,7a-tetrahydrobenzo[d][1,3,2]dioxaborol-2-yl]-3-phenyl-propyl]-2-isobutyl-5-methyl-4-oxo-6-(3-pyridyl)hexanamide 10.72

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (s, 1H), 8.85 (d, *J* = 5.8 Hz, 1H), 8.65 (d, *J* = 8.1 Hz, 1H), 8.12 (dd, *J* = 8.1, 5.7 Hz, 1H), 7.30 – 7.14 (m, 5H), 4.63 (dd, *J* = 8.9, 6.0 Hz, 1H), 4.48 (t, *J* = 6.0 Hz, 1H), 4.24 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.53 (ddd, *J* = 100.7, 14.8, 6.1 Hz, 2H), 2.85 – 2.66 (m, 3H), 2.37 (ddd, *J* = 11.4, 8.8, 4.6 Hz, 1H), 2.23 – 2.11 (m, 1H), 1.97 (t, *J* = 5.5 Hz, 1H), 1.93 – 1.58 (m, 7H), 1.47 (d, *J* = 10.8 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H), 1.00 (dd, *J* = 17.0, 6.2 Hz, 6H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.98 , 167.11 , 148.51 , 142.04 , 141.96 , 140.73 , 135.04, 128.07 , 128.01 , 127.58 , 125.48 , 83.53 , 76.27 , 52.66 , 52.02 , 49.29 , 40.02 , 39.93 , 37.82 , 36.11 , 33.53 , 33.38 , 33.11 , 28.36 , 26.30 , 26.11 , 24.31 , 23.13 , 21.62 , 20.70 .

IR: ν 3185, 2928, 1684, 1369, 1122cm^{-1}

$[\alpha]^{23}_D$ = -51.72 (*c* 0.29, CH_3OH)

HRMS: calcd for $C_{33}H_{48}O_4N_4B$ 575.5735, found 575.3784

Yield: 76%

a) Synthesis of free boronic acids by acidic hydrolisys.[18]

A protected peptide (0.003 mol) was refluxed for 1 hour in 3N hydrochloric acid (15mL). The resulting mixture was extracted with dichloromethane (4×10 mL). The aqueous layer was concentrated under reduced pressure to give white solid of the title compound.

In some cases the product was purified by column chromatography eluting with methanol in dichloromethane (3-20%).

b) Synthesis of free boronic acids by transesterification.[21]

To a solution of protected peptide (0.19 g, 0.00033 mol, 1 equiv) in the mixture of diethyl ether - water (20:20 ml) was added phenylboronic acid (0.2 g, 0.0016 mol, 5 equiv). The resulting mixture was rapidly stirred overnight and then layers were allowed to separate.

The aqueous phase was washed with diethyl ether (3×15mL) and concentrated *in vacuo* at 40°C giving white (pale yellow) solid.

[(1*S*)-1-(propanoylamino)ethyl]boronic acid 13.1

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.05 (q, *J* = 7.3 Hz, 1H), 3.02 (q, *J* = 7.4 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 1H), 1.15 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 16.49 , 15.37 , 13.79 .

IR: ν 3339, 2931, 1635, 1377, 1113 cm^{-1}

$[\alpha]^{23}_{D}$ = +13.29 (*c* 0.83, CH_3OH)

Yield: 50% [a]

[(1*R*)-1-(propanoylamino)ethyl]boronic acid 13.2

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.00 (q, *J* = 7.0 Hz, 1H), 3.09 (q, *J* = 7.4 Hz, 1H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR and $[\alpha]^{23}_{D}$ data was impossible to obtain due to very low concentration of the compound.

IR: ν 3237, 2928, 1658, 1380, 1115 cm^{-1}

Yield: 65% [a]

[(1*S*)-1-(3-phenylpropanoylamino)ethyl]boronic acid 13.3

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 - 7.24 (m, 5H), 4.22 (t, *J* = 7.6 Hz, 1H), 3.18 (d, *J* = 7.3 Hz, 2H), 2.98 (q, *J* = 7.3 Hz, 1H), 1.04 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 170.00 , 134.33 , 129.44 , 128.91 , 127.68 , 53.44 , 37.34 , 14.85 .

IR: ν 2872, 1653, 1397, 1136 cm^{-1}

$[\alpha]^{23}_{D}$ = +29.0 (*c* 0.86, CH_3OH)

Yield: 80% [a]

[(1*R*)-1-(3-phenylpropanoylamino)ethyl]boronic acid 13.4

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.39 (ddd, *J* = 31.2, 19.1, 6.9 Hz, 5H), 4.24 (t, *J* = 7.5 Hz, 1H), 3.26 – 3.18 (m, 2H), 2.85 (q, *J* = 7.3 Hz, 1H), 1.03 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 169.04, 133.58, 129.40, 129.09, 127.94, 53.40, 36.67, 14.79.

IR: ν 3259, 2970, 1658, 1366, 1080 cm^{-1}

$[\alpha]^{23}_{D}$ = +13.5 (*c* 0.52, CH_3OH)

Yield: 87% [a]

[(1*S*)-1-(heptanoylamino)ethyl]boronic acid 13.5

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.03 (t, *J* = 6.2 Hz, 1H), 3.05 (q, *J* = 7.5 Hz, 1H), 3.11 - 2.93 (m, 2H), 2.00 – 1.91 (m, 2H), 1.82 – 1.69 (m, 2H), 1.53 - 1.41 (m, 2H), 1.17 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 170.49 , 52.48 , 39.21 , 30.80 , 26.77 , 22.10 , 15.06 .

IR: ν 3367, 2933, 1606, 1399, 1138 cm^{-1}

$[\alpha]^{23}_{D}$ = +18.66 (*c* 1.61, CH_3OH)

Yield: 75% [a]

[(1*S*)-2-methyl-1-(propanoylamino)propyl]boronic acid 13.6

^{1}H NMR (400 MHz, Methanol-d_4) δ 4.10 (d, *J* = 7.0 Hz, 1H), 1.84 (q, *J* = 7.0 Hz, 1H), 1.51 (dd, *J* = 7.1, 4.2 Hz, 6H), 0.88 (d, *J* = 6.7 Hz, 4H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 171.33 , 48.74 , 28.58 , 19.84 , 16.83 , 15.34.

IR: 3349, 2961, 1654, 1387, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = +6.1 (*c* 1.46, CH_3OH)

Yield: 43% [a]

[(1*S*)-2-methyl-1-(3-phenylpropanoylamino)propyl]boronic acid 13.7

^{1}H NMR (400 MHz Methanol-d_4) δ 7.27-7.44 (m, 5H), 4.27 (dt, *J* = 11.8, 6.1 Hz, 1H), 3.26 – 3.04 (m, 2H), 1.84 – 1.70 (m, 1H), 1.13 – 0.99 (m, 1H), 0.94 – 0.72 (m, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 170.00, 134.40, 129.46, 128.92, 127.68, 53.94, 37.53, 36.09, 29.11, 19.66.

$[\alpha]^{23}_{D}$ = +25.0 (*c* 2.24, CH_3OH)

Yield 72% [a]

[(1*S*)-2-methyl-1-[[(2*S*)-2-methyl-3-(3-pyridyl)propanoyl]amino]propyl]boronic acid 13.8

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.95 (s, 1H), 8.88 (d, *J* = 5.5 Hz, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.15 (t, *J* = 6.7 Hz, 1H), 4.48 (q, *J* = 10.3, 8.5 Hz, 1H), 3.59 – 3.34 (m, 2H), 3.09 – 2.88 (m, 1H), 1.83 (dt, *J* = 13.9, 6.9 Hz, 1H), 0.84 (dq, *J* = 16.3, 11.0, 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 167.53 , 148.15 , 142.21 , 140.69 , 135.64 , 127.49 , 52.94 , 52.40 , 33.95 , 29.02 , 19.53 .

IR: ν 3233, 2959, 1663, 1388, 1120 cm^{-1}

$[\alpha]^{23}_{D}$ = +28.75 (*c* 0.8, CH_3OH)

Yield: 99 % [b]

[(1*S*)-1-(heptanoylamino)-2-methyl-propyl]boronic acid 13.9

^{1}H NMR (400 MHz, Methanol-d_4) δ 3.94 (t, *J* = 6.6 Hz, 1H), 3.06 (d, *J* = 6.7 Hz, 1H), 2.99 – 2.91 (m, 2H), 1.87 (ddd, *J* = 20.2, 13.0, 6.4 Hz, 3H), 1.78 – 1.69 (m, 2H), 1.59 – 1.45 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 168.87, 53.02, 39.11, 31.08, 28.38, 26.86, 21.86, 19.38.

IR: ν 3391, 2926, 1657, 1375, 1122 cm^{-1}

$[\alpha]^{23}_D$ = +19.5 (*c* 0.46, CH_3OH)

Yield: 49% [a]

[(*S*)-(2-methylpropanoylamino)-phenyl-methyl]boronic acid 13.10

^1H NMR (400 MHz, Methanol-d_4) δ 7.52 – 7.32 (m, 5H), 4.04 (t, *J* = 7.2 Hz, 2H), 1.60 – 1.52 (d, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 171.16 , 129.24 , 128.70 , 128.26 , 126.73 , 48.58 , 15.18 .

IR: ν 3373, 2917, 1647, 1376, 1121 cm^{-1}

$[\alpha]^{23}_D$ = +3.6 (*c* 1.38, CH_3OH)

Yield 73% [a]

[(*S*)-[[(2*S*)-2-methyl-3-phenyl-propanoyl]amino]-phenyl-methyl]boronic acid 13.11

^1H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.51 – 7.19 (m, 10H), 4.21 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.78 (s, 1H), 3.20 (ddd, *J* = 58.9, 14.5, 7.7 Hz, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 172.12, 134.26, 129.50, 129.31, 128.93, 128.06, 54.66, 35.84.

IR: ν 3363, 2902, 1733, 1483, 1209 cm^{-1}

$[\alpha]^{23}_D$ = -6.34 (*c* 0.79, CH_3OH)

Yield: 44% [a]

[(1*R*)-1-(4-fluorophenyl)-3-oxo-pentyl]boronic acid 13.12

^1H NMR (400 MHz, Methanol-d_4) δ 7.34 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 4.40 (s, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 169.52 , 162.11 (d, *J* = 244.0 Hz), 134.13 (d, *J* = 3.5 Hz), 129.24 (d, *J* = 8.1 Hz), 114.82 (d, *J* = 21.9 Hz) , 42.06 , 16.33 .

IR: ν 3209, 2933, 1667, 1509, 1222, 1114 cm^{-1}

$[\alpha]^{23}_D$ = +12.75 (*c* 1.02, CH_3OH)

Yield: 85% [b]

[(1*S*)-2-phenyl-1-(propanoylamino)ethyl]boronic acid 13.13

^1H NMR (400 MHz, Deuterium Oxide-d_2) δ 6.86 – 6.63 (m, 5H), 3.52 (q, *J* = 6.9 Hz, 1H), 2.53 – 2.41 (m, 2H), 2.37 (t, *J* = 8.7 Hz, 1H), 1.03 – 0.88 (m, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 172.02 , 136.28 , 128.64 , 128.13 , 126.95 , 48.21 , 34.34 , 14.78.

IR: ν 2982, 1740, 1381, 1113 cm^{-1}

$[\alpha]^{23}_D$ = +21.3 (*c* 0.96, CH_3OH)

Yield: 54% [a]

[(1*R*)-2-phenyl-1-(propanoylamino)ethyl]boronic acid 13.14

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.33-7.17 (m, 5H), 4.05 (t, 1H), 3.25 (q, *J* = 7.7, 6.9 Hz, 1H), 2.96 – 2.76 (m, 2H), 1.50 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 170.77 , 139.51 , 128.74 , 128.08 , 125.96 , 54.67 , 29.45 , 16.47 .

IR: ν 3220, 2926, 1659, 1379, 1114 cm^{-1}

$[\alpha]^{23}_{D}$ = -42.3 (*c* 1.2, CH_3OH)

Yield: 92% [b]

[(1*S*)-2-phenyl-1-(3-phenylpropanoylamino)ethyl]boronic acid 13.15

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.38 – 7.11 (m, 10H), 4.17 (t, *J* = 7.3 Hz, 1H), 3.06 (dt, *J* = 34.0, 9.0 Hz, 4H), 2.80 (t, *J* = 10.2 Hz, 1H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.32 , 134.05 , 131.71 , 129.18 , 128.72 , 128.05 , 127.44, 126.97 , 125.99 , 37.19 , 36.46 , 35.40 .

IR: ν 3207, 2926, 1603, 1343, 1122 cm^{-1}

$[\alpha]^{23}_{D}$ = +43.3 (*c* 0.60, CH_3OH)

Yield: 35% [a]

[(1*S*)-1-(heptanoylamino)-2-phenyl-ethyl]boronic acid 13.16

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.38 – 7.17 (m, 5H), 3.96 (s, 1H), 3.46 (d, *J* = 8.1 Hz, 1H), 2.99 – 2.71 (m, 4H), 1.87 – 1.73 (m, 2H), 1.72-1.67 (m, 2H), 1.33 (t, *J* = 13.8 Hz, 2H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 169.43 , 139.40 , 128.90 , 128.06 , 126.00 , 51.75 , 38.86 , 36.45 , 30.70 , 26.59 , 21.40 .

IR: ν 3211, 2927, 1662, 1388, 1137 cm^{-1}

$[\alpha]^{23}_{D}$ = +30.2 (*c* 0.63, CH_3OH)

Yield: 33% [a]

[(1*R*)-3-phenyl-1-(propanoylamino)propyl]boronic acid 13.17

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.18-7.34 (m, 5H), 4.11- 4.03 (m, 1H), 2.98-3.11 (m, 1H), 2.65 (ddq, *J* = 19.9, 13.4, 6.9 Hz, 2H), 1.85 (tq, *J* = 15.8, 7.4 Hz, 2H), 1.55 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 169.57 , 141.87 , 141.39 , 128.17 , 125.51 , 38.80 , 33.12 , 30.74 , 16.40.

IR: ν 3346, 2936, 1653, 1380, 1114 cm^{-1}

$[\alpha]^{23}_{D}$ = -12.82 (*c* 1.17, CH_3OH)

Yield: 99% [b]

[(1*R*)-1-[[(2*S*)-2-(3-phenylpropanoylamino)propanoyl]amino]ethyl]boronic acid 14.1

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 – 7.29 (m, 5H), 4.58 (q, *J* = 7.2 Hz, 1H), 4.12 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.31 – 2.96 (m, 2H), 2.75 (q, *J* = 7.2 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.89 , 168.53 , 134.19 , 129.12 , 128.78 , 127.50 , 54.18, 44.53 , 37.20 , 16.07 , 14.56.

IR: ν 3232, 2928, 1675, 1384, 1149 cm^{-1}

Yield: 75% [a]

[(1*R*)-1-[[(2*R*)-3-phenyl-2-(3-phenylpropanoylamino)propanoyl]amino]ethyl]boronic acid 14.2

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.23 (m, 10H), 4.76 (t, *J* = 7.8 Hz, 1H), 4.12 (d, *J* = 7.7 Hz, 1H), 3.26 (d, *J* = 4.3 Hz, 1H), 3.14 (d, *J* = 7.6 Hz, 2H), 2.96 (dd, *J* = 14.5, 8.3 Hz, 1H), 2.67 (q, *J* = 7.0 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.03, 168.59, 135.45, 134.11 , 129.10, 129.04, 128.77 , 128.37 , 127.49 , 126.92 , 54.11 , 51.62 , 47.20 , 37.14, 14.49 .

IR: ν 3209, 2927, 1643, 1393, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = -5.0 (*c* 0.40, CH_3OH)

Yield: 56% [a]

[(1*R*)-1-[[(2*R*)-2-(2-methylpropanoylamino)-3-phenyl-propanoyl]amino]ethyl]boronic acid 14.3

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.32-7.25 (m, 5H), 4.73 (t, *J* = 7.8 Hz, 1H), 3.91 (d, *J* = 8.1 Hz, 1H), 3.12 (dd, *J* = 7.9, 3.3 Hz, 2H), 2.64 (d, *J* = 7.3 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.32, 169.62, 135.49, 129.00, 128.34 , 126.90, 51.53, 48.58, 36.78, 16.18, 14.49.

IR: ν 3204, 2929, 1622, 1375, 1118 cm^{-1}

$[\alpha]^{23}_{D}$ = -62.5 (*c* 0.06, CH_3OH)

Yield: 17% [a]

[(1*R*)-1-[[(2*S*)-2-(heptanoylamino)-3-phenyl-propanoyl]amino]ethyl]boronic acid 14.4

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.34-7.28 (m, 5H), 4.68 (t, *J* = 8.2 Hz, 1H), 3.99 (t, *J* = 6.3 Hz, 1H), 3.11 (tdd, *J* = 13.2, 9.0, 5.5 Hz, 2H), 2.95 (dd, *J* = 15.7, 8.0 Hz, 2H), 2.64 (q, *J* = 7.3 Hz, 1H), 1.93 – 1.77 (m, 2H), 1.72 – 1.55 (m, 2H), 1.42 – 1.29 (m, 2H), 0.86 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.39, 168.77, 135.45, 129.08, 128.36, 126.93, 52.50, 51.87, 38.95, 36.71, 30.73, 26.73, 21.30, 14.55.

IR: ν 3190, 2927, 1675, 1366, 1222 cm^{-1}

$[\alpha]^{23}_{D}$ = -6.3 (*c* 0.16, CH_3OH)

Yield: 24% [a]

[(1*R*)-1-[[(2*S*)-2-[(1*R*)-1-methylpropyl]-6-(2-naphthyl)-4-oxo-hexanoyl]amino]ethyl]boronic acid 14.5

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.95 – 7.80 (m, 4H), 7.54 – 7.47 (m, 3H), 4.46 (d, *J* = 7.9 Hz, 1H), 4.37 (dt, *J* = 11.0, 5.8 Hz, 2H), 3.52 (dd, *J* = 14.2, 4.8 Hz, 1H), 3.18 (dd, *J* = 14.4, 8.9 Hz, 1H), 2.03 – 1.88 (m, 1H), 1.65 (ddt, *J* = 14.4, 7.1, 3.5 Hz, 1H), 1.36 – 1.24 (m, 1H), 1.11 (d, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 171.14 , 168.51 , 133.62 , 132.92 , 131.47 , 128.71 , 127.52, 126.70 , 125.91 , 58.12 , 54.25 , 36.92 , 33.77 , 24.76 , 14.69 , 13.35 , 9.93 .

IR: ν 3210, 2932, 1641, 1383, 1151 cm^{-1}

$[\alpha]^{23}_{D}$ = -40.43 (*c* 0.47, CH$_3$OH)

Yield: 78% [b]

[(1*S*)-2-methyl-1-[[(2*R*)-2-[[(2*S*)-2-methyl-3-(1-naphthyl)propanoyl]amino]-3-(3-pyridyl)propanoyl]amino]propyl]boronic acid 14.6

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.91 (s, 1H), 8.80 (d, *J* = 5.5 Hz, 1H), 8.63 (d, *J* = 7.9 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 5.8 Hz, 2H), 4.35 (d, *J* = 8.3 Hz, 1H), 3.81 – 3.43 (m, 2H), 3.38 (d, *J* = 11.0 Hz, 2H), 2.41 (d, *J* = 8.7 Hz, 1H), 1.80 (q, *J* = 7.6, 7.1 Hz, 1H), 0.90 (tt, *J* = 18.5, 8.8 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 173.16 , 168.61 , 147.86 , 141.85 , 140.00 , 137.17 , 134.16, 131.70 , 129.81 , 128.71 , 128.50 , 128.11 , 127.17 , 126.52 , 125.76 , 125.26 , 123.00 , 53.22 , 50.81 , 34.19 , 28.74 , 28.16 , 19.78.

IR: ν 3234, 2957, 1652, 1395, 1120 cm^{-1}

$[\alpha]^{23}_{D}$ = +35.71 (*c* 0.7, CH$_3$OH)

Yield: 91% [b]

[(1*R*)-2-methyl-1-[[(2*S*)-2-(3-phenylpropanoylamino)propanoyl]amino]propyl]boronic acid 14.7

^{1}H NMR (400 MHz, Deuterium Oxide-d$_2$) δ 7.47 – 7.20 (m, 5H), 4.49 (q, *J* = 7.1 Hz, 1H), 4.24 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.16 (ddd, *J* = 22.1, 14.2, 7.3 Hz, 2H), 2.47 – 2.30 (m, 1H), 1.85 – 1.64 (m, 1H), 1.37 (dd, *J* = 7.0, 4.1 Hz, 3H) 1.01 – 0.75 (m, 6H).

^{13}C NMR (101 MHz, Deuterium Oxide-d$_2$) δ 176.25, 168.82, 133.42, 129.41, 129.11, 127.96, 54.07, 46.82, 36.64, 28.21, 19.95, 19.79, 16.49.

IR: ν 3347, 2957, 1678, 1386, 1139 cm^{-1}

$[\alpha]^{23}_{D}$ = -46.3 (*c* 0.40, CH$_3$OH)

Yield: 53% [a]

[(1*S*)-1-[[(2*S*)-2-(heptanoylamino)-3-phenyl-propanoyl]amino]-2-methyl-propyl]boronic acid 14.8

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.39 – 7.19 (m, 5H), 3.96-3.91 (m, 1H), 3.15 (q, *J* = 7.8 Hz, 2H), 2.97 (s, 3H), 2.27 (d, *J* = 8.0 Hz, 1H), 1.97 – 1.84 (m, 2H), 1.81 – 1.64 (m, 3H), 1.51 (s, 2H), 0.90 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.90 , 168.74 , 135.69 , 129.12 , 128.40 , 126.95 , 52.66 , 47.81 , 39.19 , 36.89 , 30.79 , 28.50 , 26.76 , 21.49 , 20.00 , 19.73 .

IR: ν 3353, 2957, 1675, 1388, 1141 cm^{-1}

$[\alpha]^{23}_{D}$ = +31.91 (*c* 1.50, CH$_3$OH)

Yield: 87% [a]

[(1*R*)-1-[[(2*S*)-2-(heptanoylamino)propanoyl]amino]-2-methyl-propyl]boronic acid 14.9

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.65 (q, *J* = 7.2 Hz, 1H), 4.01 (t, *J* = 6.3 Hz, 1H), 3.00 (t, *J* = 7.5 Hz, 2H), 2.43 (d, *J* = 8.4 Hz, 1H), 1.95 (tt, *J* = 13.8, 5.8 Hz, 2H), 1.79 (ddd, *J* = 16.0, 13.3, 7.0 Hz, 3H), 1.60 (q, *J* = 7.5 Hz, 2H), 1.53 (d, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 11.1, 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Deuterium Oxide-d$_2$) δ 176.89, 169.46, 52.58, 46.71, 38.98, 30.21, 28.17, 26.23, 20.93, 19.91, 19.84, 16.29.

IR: ν 3363, 2937, 1677, 1367, 1170 cm^{-1}

$[\alpha]^{23}_{D}$ = -39.8 (*c* 0.88, CH$_3$OH)

Yield: 96% [a]

[(1*R*)-2-methyl-1-[[(2*S*,5*R*)-5-methyl-2-(1-naphthylmethyl)-4-oxo-decanoyl]amino]propyl]boronic acid 14.10

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.47 – 7.38 (m, 2H), 4.04 (d, *J* = 6.4 Hz, 1H), 3.80 – 3.47 (m, 2H), 2.99 (q, *J* = 7.7 Hz, 3H), 2.18 (s, 1H), 1.96 (dt, *J* = 11.0, 6.2 Hz, 2H), 1.76 (dd, *J* = 11.2, 6.3 Hz, 2H), 1.63 – 1.42 (m, 3H), 0.81 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 171.98 , 168.75 , 134.08 , 131.64 , 128.61 , 127.89 , 126.27, 125.56 , 125.21 , 123.00 , 52.53 , 38.95 , 34.32 , 30.73 , 26.70 , 21.41 , 19.70 .

IR: ν 3193, 2954, 1673, 1367, 1164 cm^{-1}

$[\alpha]^{23}_{D}$ = + 37.18 (*c* 0.78, CH$_3$OH)

Yield: 99% [b]

[(1*R*)-2-methyl-1-[[(2*S*)-5-methyl-2-(1-naphthylmethyl)-4-oxo-hexanoyl]amino]propyl]boronic acid 14.11

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.52 (q, *J* = 7.3, 6.0 Hz, 1H), 7.46 – 7.36 (m, 2H),

4.03 (t, *J* = 7.0 Hz, 1H), 3.73 – 3.47 (m, 2H), 2.19 (d, *J* = 7.6 Hz, 1H), 1.53 (dd, *J* = 13.6, 6.9 Hz, 5H), 0.81 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.50 , 169.66 , 134.09 , 131.63 , 131.15 , 128.60 , 127.87, 126.26 , 125.54 , 125.18 , 122.98 , 48.76 , 34.48 , 28.32 , 19.99 , 19.55 , 16.24.

IR: ν 3196, 2956, 1670, 1384, 1117 cm^{-1}

$[\alpha]^{23}_D$ = + 25 (*c* 0.52, CH_3OH)

Yield: 98% [b]

[(1*R*)-2-methyl-1-[[(2*R*,5*R*)-5-methyl-2-[(1*R*)-1-methylpropyl]-6-(1-naphthyl)-4-oxo-hexanoyl]amino]propyl]boronic acid 14.12

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.28 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.57 – 7.44 (m, 3H), 4.53 (d, *J* = 7.8 Hz, 1H), 4.42 (t, *J* = 7.4 Hz, 1H), 3.83 – 3.43 (m, 2H), 2.33 (s, 1H), 2.01 – 1.86 (m, 1H), 1.86 – 1.71 (m, 1H), 1.66 (ddd, *J* = 14.2, 7.6, 3.8 Hz, 1H), 1.36 – 1.16 (m, 1H), 0.97 (ddd, *J* = 12.1, 8.5, 5.8 Hz, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.97 , 168.71 , 134.22 , 131.81 , 129.84 , 128.71 , 128.50, 128.18 , 126.50 , 125.74 , 125.27 , 123.04 , 54.43 , 53.12 , 36.61 , 34.31 , 28.53 , 24.92 , 20.09 , 14.11 , 9.92 .

IR: ν 3048, 2933, 1669, 1369, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -2.77 (*c* 0.72, CH_3OH)

Yield: 55% [b]

[(1*R*)-2-methyl-1-[[(2*R*,5*R*)-5-methyl-2-[(1*R*)-1-methylpropyl]-6-(2-naphthyl)-4-oxo-hexanoyl]amino]propyl]boronic acid 14.13

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.87 (ddd, *J* = 11.6, 7.4, 3.5 Hz, 4H), 7.50 (ddd, *J* = 9.3, 7.0, 4.4 Hz, 3H), 4.56 (d, *J* = 7.9 Hz, 1H), 4.41 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.61 – 3.07 (m, 2H), 2.29 (s, 1H), 1.94 (d, *J* = 13.7 Hz, 1H), 1.79 (ddd, *J* = 13.0, 6.6, 2.5 Hz, 1H), 1.67 (ddd, *J* = 13.7, 7.3, 3.5 Hz, 1H), 1.38 – 1.25 (m, 1H), 1.04 – 0.92 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.12 , 168.54 , 133.63 , 132.94 , 131.51 , 128.45 ,127.41, 126.73 , 126.05 , 125.82 , 54.30 , 53.94 , 37.34 , 36.68 , 28.54 , 24.83 , 20.03 , 14.20 , 9.89 .

IR: ν 3053, 2962, 1669, 1369, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -33.89 (*c* 0.59, CH_3OH)

Yield: 76% [b]

[(1*R*)-1-[[(2*R*,5*R*)-6-cyclohexyl-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-hexanoyl]amino]-2-methyl-propyl]boronic acid 14.14

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.47 (d, *J* = 7.8 Hz, 1H), 4.05 (dd, *J* = 9.0, 5.8 Hz, 1H), 2.32 (d, *J* = 9.2 Hz, 1H), 2.01 – 1.87 (m, 1H), 1.87 – 1.58 (m, 10H), 1.47 (dd, *J* = 10.7, 5.8 Hz, 1H), 1.41 – 1.17 (m, 5H), 1.04 – 0.90 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.25 , 169.69 , 50.60 , 39.07 , 37.80 , 36.35 , 33.07 , 32.04 , 28.55 , 25.95 , 25.72 , 25.46 , 24.89 , 20.06 , 14.21 , 9.85 .

IR: ν 3357, 2926, 1653, 1368, 1117 cm^{-1}

$[\alpha]^{23}_D$ = -32.20 (*c* 0.59, CH$_3$OH)

Yield: 81% [b]

[(1*S*)-1-[[(2*S*)-2-[[(2*S*,3*R*)-2,3-dimethylpentanoyl]amino]-3-(3-pyridyl)propanoyl]amino]-2-methyl-propyl]boronic acid 14.15

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.95 (s, 1H), 8.83 (d, *J* = 5.4 Hz, 1H), 8.69 (d, *J* = 7.8 Hz, 1H), 8.12 (t, *J* = 6.7 Hz, 1H), 5.14-5.09 (m, 1H), 3.84 (d, *J* = 5.0 Hz, 1H), 3.54 – 3.32 (m, 2H), 2.45 (d, *J* = 8.1 Hz, 1H), 1.96 (h, *J* = 4.6 Hz, 1H), 1.81 (h, *J* = 6.9 Hz, 1H), 1.57 (ddp, *J* = 14.4, 7.2, 3.8, 3.2 Hz, 1H), 1.32 – 1.14 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.94 (dt, *J* = 19.0, 6.9 Hz, 9H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 173.45 , 168.14 , 147.85 , 141.86 , 140.05 , 127.26 , 57.35,50.52 , 36.63 , 33.97 , 28.69 , 24.02 , 19.76 , 19.52 , 13.66 , 10.38 .

IR: ν 3365, 2934, 1646, 1371, 1118 cm^{-1}

$[\alpha]^{23}_D$ = +46.88 (*c* 0.32, CH$_3$OH)

Yield: 80% [b]

[(1*R*)-2-methyl-1-[[(2*R*,5*R*)-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-6-(3-pyridyl)hexanoyl]amino]propyl]boronic acid 14.16

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.94 (dd, *J* = 20.1, 9.8 Hz, 2H), 8.77 (d, *J* = 8.0 Hz, 1H), 8.16 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.53 (d, *J* = 7.9 Hz, 2H), 3.54 (ddd, *J* = 58.4, 14.5, 6.8 Hz, 2H), 2.42 (d, *J* = 8.8 Hz, 1H), 1.92 (q, *J* = 7.8 Hz, 1H), 1.86 – 1.73 (m, 1H), 1.64 (ddt, *J* = 14.7, 7.4, 3.8 Hz, 1H), 1.39 – 1.23 (m, 1H), 1.06 – 0.90 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.91 , 167.55 , 148.34 , 142.31 , 140.57 , 135.31 , 127.52, 52.93 , 45.65 , 36.50 , 33.67 , 28.71 , 24.83 , 20.11 , 14.27 , 9.95 .

IR: ν 3360, 2962, 1683, 1386, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -4.88 (*c* 1.23, CH$_3$OH)

Yield: 99% [b]

[(1*R*)-2-methyl-1-[[(2*R*,5*S*)-5-methyl-2-[(1*R*)-1-methylpropyl]-4-oxo-6-phenyl-hexanoyl]amino]propyl]boronic acid 14.17

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 – 7.29 (m, 5H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.30 (q, *J* = 7.6, 6.7 Hz, 1H), 3.44 – 2.94 (m, 2H), 2.35 (s, 1H), 1.94 (p, *J* = 6.4, 5.3 Hz, 1H), 1.81 (p, *J* = 7.2 Hz, 1H), 1.66 (ddd, *J* = 14.0, 7.5, 3.6 Hz, 1H), 1.34 – 1.26 (m, 1H), 1.12-0.91 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.07 , 168.53 , 134.03 , 129.29 , 128.92 , 127.50 , 54.02 , 37.79 , 37.08 , 36.61 , 24.83 , 20.06 , 14.26 , 9.91 .

IR: ν 3379, 2931, 1668, 1368, 1117 cm^{-1}

$[\alpha]^{23}_D$ = -70 (*c* 1, CH_3OH)

Yield: 99% [b]

[(*S*)-[[(2*S*)-2-(2-methylpropanoylamino)-3-phenyl-propanoyl]amino]-phenyl-methyl]boronic acid 14.18

^1H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.10 (m, 10H), 4.04 (q, *J* = 6.9 Hz, 1H), 3.74 (s, 1H), 3.26 (d, *J* = 7.8 Hz, 2H), 1.54 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.33, 170.00, 135.45, 129.05, 128.97, 128.43, 128.22, 128.09, 127.75, 127.10, 126.37, 125.58, 48.72, 36.45, 16.35, 16.23.

IR: ν 3187, 2934, 1668, 1384, 1116 cm^{-1}

$[\alpha]^{23}_D$ = +54.9 (*c* 1.62, CH_3OH)

Yield: 88% [a]

[(*R*)-phenyl-[[(2*R*)-3-phenyl-2-(propanoylamino)propanoyl]amino]methyl]boronic acid 14.19

^1H NMR (400 MHz, Methanol-d_4) δ 7.35 (m, 5H), 7.12 (dp, *J* = 14.1, 7.0, 6.3 Hz, 3H), 6.72 (d, *J* = 7.3 Hz, 2H), 3.94 (q, *J* = 7.0 Hz, 1H), 3.73 (s, 1H), 3.26 (dd, *J* = 8.2, 2.5 Hz, 2H), 1.50 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 180.70, 177.10, 140.33, 135.31, 129.12, 128.61 , 127.59, 127.11, 125.54 , 125.13, 51.37, 36.51, 35.62, 16.22.

IR: ν 3345, 2924, 1677, 1395, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -21.2 (*c* 0.52, CH_3OH)

Yield: 57% [a]

[(*S*)-[[(2*S*)-2-(heptanoylamino)-3-phenyl-propanoyl]amino]-phenyl-methyl]boronic acid 14.20

^1H NMR (400 MHz, Methanol-d_4) δ 7.39 – 7.09 (m, 10H), 4.01 (d, *J* = 5.9 Hz, 1H), 3.70 (s, 1H), 3.26 (d, *J* = 7.9 Hz, 2H), 2.92 (dd, *J* = 23.6, 5.9 Hz, 2H), 1.92 (d, *J* = 12.9 Hz, 2H), 1.71 (dd, *J* = 13.9, 7.0 Hz, 2H), 1.59 – 1.43 (m, 2H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.14, 168.98, 129.02, 128.92, 128.42, 128.21, 127.74, 127.05, 126.48, 125.53, 52.44, 38.89, 37.36, 36.43, 30.66, 26.68, 21.26.

IR: ν 3385, 2923, 1669, 1390, 1169 cm^{-1}

$[\alpha]^{23}_D$ = +67.6 (*c* 1.05, CH_3OH)

Yield: 21% [a]

[(*R*)-[[(2*R*)-2-(heptanoylamino)-3-phenyl-propanoyl]amino]-phenyl-methyl]boronic acid 14.21

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.32 – 6.94 (m, 8H), 6.36 (d, *J* = 7.3 Hz, 2H), 4.78 (dd, *J* = 9.4, 7.3 Hz, 1H), 3.86 (t, *J* = 6.5 Hz, 1H), 3.64 (s, 1H), 3.08 (ddd, *J* = 23.1, 13.6, 8.4 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 1.71 (dd, *J* = 13.6, 6.7 Hz, 2H), 1.55 – 1.38 (m, 2H), 1.21 (dd, *J* = 15.8, 8.0 Hz, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 175.88, 169.65, 139.92, 134.82, 129.27, 129.12, 128.48, 127.67, 125.84, 124.80, 52.57, 51.95, 38.86, 36.05, 30.24, 26.21, 20.94.

IR: ν 3352, 2930, 1679, 1382, 1179 cm^{-1}

$[\alpha]^{23}_{D}$ = -7.1 (*c* 0.28, CH_3OH)

Yield: 44% [a]

[(*S*)-phenyl-[[(2*S*)-3-phenyl-2-(3-phenylpropanoylamino)propanoyl]amino]methyl]boronic acid 14.22

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.40 – 7.05 (m, 15H), 4.95 (t, *J* = 7.6 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.71 (s, 1H), 3.24 (d, *J* = 7.8 Hz, 2H), 3.03 (dd, *J* = 14.7, 9.1 Hz, 2H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 168.62, 168.04, 140.48, 136.84, 135.30, 134.05, 129.02, 128.94, 128.22, 127.77, 127.52, 127.05, 126.47, 125.29, 54.10, 37.60, 37.01, 36.91.

IR: ν 3358, 2925, 1667, 1364, 1179 cm^{-1}

$[\alpha]^{23}_{D}$ = +57.4 (*c* 1.01, CH_3OH)

Yield: 47% [a]

[(*R*)-[[(2*R*)-2-(heptanoylamino)propanoyl]amino]-phenyl-methyl]boronic acid 14.23

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.24 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 4.56 (t, *J* = 5.7 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 1H), 3.76 (s, 1H), 2.72 (t, *J* = 7.5 Hz, 2H), 1.82 (dd, *J* = 14.9, 7.8 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.46 (d, *J* = 7.3 Hz, 3H), 1.35 – 1.25 (m, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 178.34, 169.74, 140.53, 128.64, 126.09, 125.24, 52.61, 46.64, 38.88, 30.23, 26.29, 20.89, 16.13.

IR: ν 3219, 2941, 1678, 1386, 1018 cm^{-1}

$[\alpha]^{23}_{D}$ = -48.6 (*c* 0.76, CH_3OH)

Yield: 62% [a]

[(*S*)-[[(2*S*)-2-[[(2*R*)-2-methyl-3-(1-naphthyl)propanoyl]amino]propanoyl]amino]-phenyl-methyl]boronic acid 14.24

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.75 (m, 3H), 7.69 – 7.41 (m, 4H), 7.35 – 7.13 (m, 5H), 4.73 (q, *J* = 7.2 Hz, 1H), 4.36 (q, *J* = 7.7 Hz, 1H), 4.31 (s, 1H), 3.89 – 3.45 (m, 2H), 1.53 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 172.53 , 168.69 , 140.67 , 138.32 , 134.16 , 131.72 , 130.07, 128.94 , 127.76 , 126.96 , 126.73 , 125.90 , 125.28 , 123.07 , 53.36 , 46.07 , 34.13 , 16.96 .

IR: ν 3197, 2928, 1665, 1379, 1165 cm^{-1}

$[\alpha]^{23}_D$ = +92.55 (*c* 0.94, CH_3OH)

Yield: 78% [b]

[(*R*)-phenyl-[[(2*S*)-2-(propanoylamino)propanoyl]amino]methyl]boronic acid 14.25

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.13 (t, *J* = 7.6 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 2H), 4.49-4.47 (q, 1H), 3.99 – 3.88 (q, 1H), 3.70 (s, 1H), 1.42 – 1.28 (m, 6H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 178.98 , 170.89 , 139.89 , 128.75 , 128.46 , 125.15, 48.81 , 46.36 , 16.29 , 15.90.

IR: ν 3189, 2986, 1677, 1385, 1169 cm^{-1}

$[\alpha]^{23}_D$ = -69.7 (*c* 1.14, CH_3OH)

Yield: 91% [a]

[(*S*)-[[(2*S*)-2-[[(2*R*)-2-methyl-3-(2-naphthyl)propanoyl]amino]propanoyl]amino]-phenyl-methyl]boronic acid 14.26

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (ddt, *J* = 19.6, 10.4, 4.5 Hz, 4H), 7.55 – 7.44 (m, 3H), 7.37 – 7.12 (m, 5H), 4.77 (q, *J* = 7.2 Hz, 1H), 4.34 (ddd, *J* = 14.3, 8.4, 5.3 Hz, 1H), 4.25 (s, 1H), 3.60 – 3.16 (m, 2H), 1.57 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 179.06 , 168.59 , 140.73 , 133.60 , 132.88 , 131.61 , 128.89, 128.13 , 127.82 , 127.06 , 126.17 , 125.25 , 54.02 , 42.54 , 37.22 , 16.10 .

IR: ν 3212, 2931, 1663, 1371, 1157 cm^{-1}

$[\alpha]^{23}_D$ = +65.06 (*c* 0.83, CH_3OH)

Yield: 98% [b]

[(*R*)-[[(2*R*)-3-(4-fluorophenyl)-2-(2-methylpropanoylamino)propanoyl]amino]-phenyl-methyl]boronic acid 14.27

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.40 (dd, *J* = 8.4, 5.3 Hz, 2H), 7.19 – 7.06 (m, 5H), 6.75 (d, *J* = 7.4 Hz, 2H), 4.95 (t, *J* = 8.3 Hz, 1H), 3.98 (q, *J* = 7.0 Hz, 1H), 3.76 (s, 1H), 3.25 (dd, *J* = 8.2, 3.7 Hz, 2H), 1.51 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.98 , 170.02 , 162.26 (d, *J* = 244.4 Hz), 140.39 , 131.05 (d, *J* = 8.1 Hz), 127.56 , 127.10 , 125.19 , 115.23 (d, *J* = 21.6 Hz), 51.48 , 48.70 , 35.70 , 16.35.

IR: ν 3391, 2924, 1653, 1223, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -32.76 (*c* 0.58, CH_3OH)

Yield: 99% [b]

[(*S*)-[[(2*S*)-2-[[(2*R*)-3-cyclohexyl-2-methyl-propanoyl]amino]propanoyl]amino]-phenyl-methyl]boronic acid 14.28

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.36 – 7.10 (m, 5H), 4.76 (q, *J* = 6.6 Hz, 1H), 4.38 (s, 1H), 3.98 (ddd, *J* = 17.2, 8.7, 5.8 Hz, 2H), 1.88 – 1.62 (m, 10H), 1.56 (d, *J* = 7.0 Hz, 3H), 1.07 – 0.92 (m, 2H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 178.99 , 169.67 ,140.82 , 128.13 , 127.63 , 125.53 , 50.83 , 45.77 , 42.62 , 38.88 , 33.29 , 32.04 , 25.94 , 25.70 , 25.43 , 15.91.

IR: ν 3206, 2924, 1657, 1383, 1159 cm^{-1}

$[\alpha]^{23}_{D}$ = +101.72 (*c* 0.58, CH$_3$OH)

Yield: 99% [b]

[(*R*)-[[(2*R*)-2-[[(2*S*)-2,4-dimethylpentanoyl]amino]-3-(4-fluorophenyl)propanoyl]amino]-phenyl-methyl]boronic acid 14.29

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.40 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.18 – 7.05 (m, 5H), 6.73 (d, *J* = 7.4 Hz, 2H), 4.96 (t, *J* = 7.7 Hz, 1H), 3.96 (d, *J* = 7.6 Hz, 1H), 3.75 (s, 1H), 3.25 (dt, *J* = 13.7, 7.7 Hz, 1H), 1.80 – 1.62 (m, 4H), 1.00 (d, *J* = 5.0 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.94 , 169.55 , 162.26 (d, *J* = 244.6 Hz), 140.31 , 131.09 (d, *J* = 8.0 Hz), 128.34 , 127.54 , 125.57 , 115.25 (d, *J* = 21.5 Hz), 51.58 , 42.58 , 40.30 , 35.63 , 23.92 , 21.82 , 20.85.

IR: ν 3390, 2931, 1652, 1390, 1223, 1159 cm^{-1}

$[\alpha]^{23}_{D}$ = -38.59 (*c* 0.57, CH$_3$OH)

Yield: 81% [b]

[(*R*)-[[(2*R*)-3-(3-fluorophenyl)-2-(2-methylpropanoylamino)propanoyl]amino]-phenyl-methyl]boronic acid 14.30

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.05 (m, 7H), 6.80 (d, *J* = 7.5 Hz, 2H), 4.96 (t, *J* = 8.2 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 1H), 3.77 (s, 1H), 3.31 – 3.24 (m, 2H), 1.52 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.02 , 169.81 , 163.01 (d, *J* = 245.4 Hz), 140.34 , 132.67, 128.00 , 127.64 , 125.58 , 125.34 , 115.97 (d, *J* = 21.9 Hz), 51.29 , 45.88 , 36.09 , 16.22.

IR: ν 3369, 2931, 1653, 1386, 1251, 1143 cm^{-1}

$[\alpha]^{23}_{D}$ = -43.86 (*c* 0.57, CH$_3$OH)

Yield: 99% [b]

[(*R*)-[[(2*R*)-2-[[(2*R*,3*R*)-2,3-dimethylpentanoyl]amino]-3-(3-fluorophenyl)propanoyl]amino]-phenyl-methyl]boronic acid 14.31

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.25 – 7.06 (m, 7H), 6.76 (d, *J* = 7.4 Hz, 2H), 5.00 (td, *J* = 8.1, 5.2 Hz, 1H), 3.80 (d, *J* = 5.4 Hz, 1H), 3.76 (s, 1H), 3.26 (d, *J* = 13.8 Hz, 1H), 1.95 (dtd, *J* =

10.8, 6.9, 3.9 Hz, 1H), 1.57 (dtd, *J* = 14.7, 7.3, 3.4 Hz, 1H), 1.20 (ddt, *J* = 13.7, 9.6, 6.9 Hz, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 175.19 , 168.18 , 140.22 , 130.37 (d, *J* = 8.1 Hz), 129.15 , 128.04 , 127.06 , 125.05 , 116.03 (d, *J* = 21.9 Hz), 113.76 , 57.44 , 51.20, 36.61 , 36.17 , 24.08 , 13.89 , 10.31 .

IR: ν 3200, 2934, 1653, 1392, 1251, 1144 cm^{-1}

$[\alpha]^{23}_D$ = -29.31 (*c* 0.58, CH_3OH)

Yield: 93% [b]

[(*S*)-(4-fluorophenyl)-[[(2*S*)-2-(heptanoylamino)propanoyl]amino]methyl]boronic acid 14.32

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.07 – 6.88 (m, 4H), 4.58 (d, *J* = 7.3 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.74 (s, 1H), 2.82 (dd, *J* = 13.8, 6.7 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.60 – 1.48 (m, 2H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.29 (dd, *J* = 15.9, 7.6 Hz, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 178.01 , 169.61 , 160.96 (d, *J* = 240.8 Hz), 136.03 , 126.85 , 115.19 (d, *J* = 21.4 Hz), 52.70 , 46.34 , 39.00 , 30.23 , 26.24 , 20.91 , 15.91 .

IR: ν 2916, 1682, 1363, 1221, 1160 cm^{-1}

$[\alpha]^{23}_D$ = +91.3 (*c* 0.52, CH_3OH)

Yield: 54% [a]

[(1*S*)-2-phenyl-1-[[(2*S*)-2-(propanoylamino)propanoyl]amino]ethyl]boronic acid 14.33

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.39 – 7.22 (m, 5H), 4.43 (q, *J* = 7.2 Hz, 1H), 3.05 (dq, *J* = 12.8, 7.2, 6.4 Hz, 2H), 2.92 – 2.59 (m, 2H), 1.47 (d, *J* = 7.1 Hz, 3H), 1.31 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 172.41 , 170.49 , 139.83 , 128.96 , 127.36 , 126.40, 48.81 , 35.93 , 34.76 , 16.28 , 15.15 .

IR: ν 2986, 1680, 1395, 1115 cm^{-1}

$[\alpha]^{23}_D$ = +45.8 (*c* 0.48, CH_3OH)

Yield: 99% [a]

[(1*R*)-2-phenyl-1-[[(2*R*)-2-(propanoylamino)propanoyl]amino]ethyl]boronic acid 14.34

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.34 – 7.15 (m, 5H), 4.56 (q, *J* = 7.2 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 2.97 (t, *J* = 7.6 Hz, 1H), 2.92 – 2.56 (m, 2H), 1.52 (d, *J* = 7.2 Hz, 3H), 1.45 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.65, 169.70 , 140.31 , 128.59 , 128.12 , 125.79, 36.54 , 16.27.

IR: ν 3196, 2936, 1670, 1360, 1118 cm^{-1}

$[\alpha]^{23}_D$ = -87.26 (*c* 1.57, CH_3OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*S*)-2-(heptanoylamino)propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.35

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.41 – 7.18 (m, 5H), 4.43 (q, *J* = 7.1 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.04 (dd, *J* = 9.9, 5.8 Hz, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.76 (ddd, *J* = 24.1, 13.9, 7.9 Hz, 2H), 1.87 (dd, *J* = 15.8, 7.1 Hz, 2H), 1.74 – 1.58 (m, 2H), 1.50 – 1.34 (m, 2H), 1.29 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 176.05, 169.39, 139.79, 129.04, 128.88, 128.60, 126.41, 52.62, 47.05, 38.98, 35.94, 30.19, 26.23, 20.92, 16.16.

IR: ν 3372, 2938, 1678, 1381, 1167 cm^{-1}

$[\alpha]^{23}_{D}$ = +79.8 (*c* 0.52, CH_3OH)

Yield: 99% [a]

[(1*R*)-1-[[(2*R*)-2-(heptanoylamino)propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.36

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.28-7.17 (m, 5H), 4.50 (q, *J* = 7.1 Hz, 1H), 3.94 (t, *J* = 6.3 Hz, 1H), 2.94 (q, *J* = 7.2, 6.7 Hz, 3H), 2.70 (ddd, *J* = 95.4, 13.9, 7.5 Hz, 2H), 1.88 (dt, *J* = 11.1, 6.3 Hz, 2H), 1.70 (p, *J* = 7.6 Hz, 2H), 1.53 (q, *J* = 7.9 Hz, 2H), 1.41 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.75, 168.69 , 140.29 , 128.56 , 128.08 , 125.74 , 52.45, 45.94 , 38.99 , 36.53 , 30.62 , 26.70 , 21.23 , 16.31 .

IR: ν 3384, 2935, 1674, 1381, 1170 cm^{-1}

$[\alpha]^{23}_{D}$ = -52.9 (*c* 4.12, CH_3OH)

Yield: 99% [b]

[(1*S*)-2-phenyl-1-[[(2*S*)-2-(3-phenylpropanoylamino)propanoyl]amino]ethyl]boronic acid 14.37

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.45-7.21 (m, 10H), 4.41 (q, *J* = 7.1 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.12 (tt, *J* = 21.6, 7.0 Hz, 2H), 3.04 – 2.95 (m, 1H), 2.74 (ddd, *J* = 24.1, 14.0, 7.9 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 175.63, 168.83, 139.76, 133.54, 129.44, 129.09, 129.06, 128.95, 127.99, 126.48, 54.14, 47.23, 36.64, 36.01, 16.47.

IR: ν 3367, 2935, 1679, 1378, 1157 cm^{-1}

$[\alpha]^{23}_{D}$ = +75.0 (*c* 0.64, CH_3OH)

Yield: 80% [a]

[(1*R*)-2-phenyl-1-[[(2*R*)-2-(3-phenylpropanoylamino)propanoyl]amino]ethyl]boronic acid 14.38

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 – 7.14 (m, 10H), 4.58 (q, *J* = 7.1 Hz, 1H), 4.22 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.35 – 3.29 (m, 1H), 3.02 (dd, *J* = 14.4, 8.7 Hz, 2H), 2.78 (ddd, *J* = 98.1, 14.0, 7.5 Hz, 2H), 1.47 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d4) δ 177.45 , 168.49 , 140.28 , 134.15 , 129.26 , 128.73, 128.15, 127.50 , 125.84 , 54.16, 46.28, 37.12 , 36.53 , 16.37.

IR: ν 3201, 2929, 1673, 1361, 1158 cm^{-1}

$[\alpha]^{23}_{D}$ = -72.81 (*c* 2.28, CH_3OH)

Yield: 77% [b]

[(1*S*)-2-phenyl-1-[[(2*S*)-3-phenyl-2-(propanoylamino)propanoyl]amino]ethyl]boronic acid

14.39

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.38 – 7.11 (m, 10H), 4.63 (t, *J* = 7.6 Hz, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 3.00 (dt, *J* = 17.8, 7.7 Hz, 3H), 2.82 (dd, *J* = 13.8, 5.8 Hz, 1H), 2.69 – 2.56 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 173.47, 170.44, 139.62, 135.74, 129.26, 129.12, 128.82, 128.63, 127.32, 126.46, 53.16, 48.80, 36.70, 35.75, 16.41.

IR: ν 3215, 2931, 1652, 1388, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = +100.0 (*c* 1.30, CH_3OH)

Yield: 65% [a]

[(1*R*)-1-[[(2*R*)-2-isobutyl-5-methyl-4-oxo-hexanoyl]amino]-2-phenyl-ethyl]boronic acid

14.40

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35 – 7.15 (m, 5H), 4.59 (dd, *J* = 9.2, 5.3 Hz, 1H), 4.03 (q, *J* = 6.8 Hz, 1H), 2.96 (t, *J* = 7.4 Hz, 1H), 2.75 (ddd, *J* = 111.1, 13.8, 7.3 Hz, 2H), 1.73 (td, *J* = 9.9, 5.5 Hz, 2H), 1.58 (dq, *J* = 10.7, 5.7 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 3H), 0.96 (dd, *J* = 15.6, 6.0 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.62 , 169.91 , 140.31 , 128.59 , 128.13 , 125.81 , 39.96 , 36.60 , 24.37 , 21.70 , 20.54 , 16.38 .

IR: ν 3341, 2958, 1669, 1368, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = -108.08 (*c* 0.99, CH_3OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*S*)-2-(heptanoylamino)-3-phenyl-propanoyl]amino]-2-phenyl-ethyl]boronic acid

14.41

^{1}H NMR (400 MHz, Deuterium Oxide-d_2) δ 7.41 – 7.17 (m, 10H), 4.68 (t, *J* = 7.8 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.10 – 2.96 (m, 5H), 2.77 (ddd, *J* = 23.3, 13.9, 7.8 Hz, 2H), 1.97 – 1.84 (m, 2H), 1.71 (td, *J* = 15.2, 7.8 Hz, 2H), 1.42 (dd, *J* = 15.6, 7.8 Hz, 2H).

^{13}C NMR (101 MHz, Deuterium Oxide-d_2) δ 173.21, 169.36, 139.43, 135.61, 129.07, 128.79, 128.62, 127.38, 126.48, 53.41, 52.64, 38.96, 36.64, 35.58, 30.29, 26.27, 20.93.

IR: ν 3199, 2930, 1647, 1393, 1080 cm^{-1}

$[\alpha]^{23}_{D}$ = +69.8 (*c* 2.25, CH_3OH)

Yield: 57% [a]

[(1*R*)-1-[[(2*S*)-4-methyl-2-(4-methylsulfanylbutanoylamino)pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.42

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.35 – 7.15 (m, 5H), 4.64 – 4.52 (m, 1H), 4.07 (d, *J* = 7.6 Hz, 1H), 3.02 – 2.84 (m, 2H), 2.66 – 2.56 (m, 3H), 2.13 (dd, *J* = 7.3, 3.2 Hz, 5H), 1.79 – 1.67 (m, 2H), 1.56 (td, *J* = 11.3, 10.1, 5.9 Hz, 1H), 1.01 – 0.86 (m, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 172.74 , 168.61 , 140.38 , 128.85 , 128.08 , 125.76 , 52.18 , 40.08 , 36.61 , 31.00 , 28.58 , 24.43 , 21.73 , 20.58 , 13.85 .

IR: ν 3369, 2928, 1663, 1369, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = -72.44 (*c* 0.98, CH$_3$OH)

Yield: 58% [b]

[(1*S*)-2-phenyl-1-[[(2*S*)-3-phenyl-2-(3-phenylpropanoylamino)propanoyl]amino]ethyl]boronic acid 14.43

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 – 7.12 (m, 15H), 4.16 (dd, *J* = 8.2, 4.8 Hz, 1H), 3.18 – 2.98 (m, 4H), 2.93 – 2.80 (m, 2H), 2.62 (dd, *J* = 15.2, 10.9 Hz, 1H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.53, 168.28, 140.32, 135.68, 133.94, 129.25, 128.94, 128.80, 128.56, 128.28, 128.06, 127.52, 126.83, 125.73, 53.95, 51.60, 48.47, 37.01, 36.58.

IR: ν 3211, 2935, 1674, 1372, 1024 cm^{-1}

$[\alpha]^{23}_{D}$ = +71.4 (*c* 1.96, CH$_3$OH)

Yield: 68% [a]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-4-oxo-6-(3-pyridyl)hexanoyl]amino]-2-phenyl-ethyl]boronic acid 14.44

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.90 (d, *J* = 10.6 Hz, 2H), 8.75 (d, *J* = 7.7 Hz, 1H), 8.15 (t, *J* = 6.6 Hz, 1H), 7.35 – 7.11 (m, 5H), 4.59 (dd, *J* = 9.2, 5.4 Hz, 1H), 4.45 (d, *J* = 6.4 Hz, 1H), 3.52 (ddd, *J* = 50.9, 14.2, 6.3 Hz, 2H), 3.06 (dd, *J* = 9.3, 5.9 Hz, 1H), 2.97 – 2.61 (m, 2H), 1.84 – 1.67 (m, 2H), 1.55 (dq, *J* = 9.3, 5.2, 3.8 Hz, 1H), 0.97 (dd, *J* = 15.2, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.97 , 167.45 , 148.43 , 142.29 , 140.61 , 140.22 , 135.26, 128.74 , 128.13 , 127.54 , 125.84 , 52.90 , 40.07 , 36.51 , 33.60 , 24.32 , 21.72 , 20.56 .

IR: ν 3356, 2956, 1681, 1368, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = -57.27 (*c* 1.1, CH$_3$OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*S*)-2-isopropyl-7-methyl-4-oxo-octanoyl]amino]-2-phenyl-ethyl]boronic acid 14.45

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.35-7.19 (m, 5H), 4.37 (d, *J* = 8.3 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 1H), 2.96 – 2.82 (m, 2H), 2.59 (d, *J* = 11.5 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.73 (dt, *J* = 16.4, 8.8 Hz, 3H), 1.13 – 0.85 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.25 , 169.74 , 140.37 , 128.51 , 128.11 , 125.78 , 51.49 , 47.10 , 40.33 , 36.54 , 30.11 , 23.97 , 21.92 , 21.02 , 18.02 , 17.74.

IR: ν 3027, 2931, 1649, 1370, 1171 cm^{-1}

$[\alpha]^{23}_{D}$ = +82.24 (*c* 1.52, CH$_3$OH)

Yield: 83% [b]

[(1*R*)-1-[[(2*S*)-3-methyl-2-(4-methylpentanoylamino)butanoyl]amino]-2-phenyl-ethyl]boronic acid 14.46

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.37 – 7.17 (m, 5H), 4.34 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.03 (d, *J* = 8.6 Hz, 1H), 3.17 (t, *J* = 7.8 Hz, 1H), 2.98 (dd, *J* = 9.3, 6.2 Hz, 2H), 2.67 – 2.55 (m, 1H), 1.71 (dq, *J* = 14.2, 6.5 Hz, 3H), 1.10 – 0.96 (m, 12H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.75 , 169.75 , 140.34 , 128.88 , 126.88 , 125.83 , 51.31 , 40.35 , 36.75 , 33.13 , 30.33 , 23.90 , 21.90 , 20.67 , 18.05 , 17.81 .

IR: ν 3027, 2935, 1669, 1373, 1178 cm^{-1}

$[\alpha]^{23}_{D}$ = -68.67 (*c* 0.83, CH$_3$OH)

Yield: 87% [b]

[(1*S*)-1-[[(2*S*)-2-[[(2*R*)-3-(4-fluorophenyl)-2-methyl-propanoyl]amino]-3-phenyl-propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.47

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.40 – 7.06 (m, 14H), 4.13 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.30 – 2.98 (m, 5H), 2.97 – 2.78 (m, 2H), 2.63 (dt, *J* = 13.9, 9.0 Hz, 1H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.016 , 168.11 , 162.48 (d, *J* = 244.9 Hz), 140.26 , 135.68 , 131.20 (d, *J* = 8.0 Hz) , 128.92 , 128.55 , 128.29 , 128.05 , 126.84 , 125.74 , 115.48 (d, *J* = 21.6 Hz) , 53.91 , 44.95 , 37.10 , 36.60 , 36.13 .

IR: ν 3061, 2922, 1645, 1371, 1224, 1113 cm^{-1}

$[\alpha]^{23}_{D}$ = +77.42 (*c* 0.62, CH$_3$OH)

Yield: 99% [b]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-6-(2-naphthyl)-4-oxo-hexanoyl]amino]-2-phenyl-ethyl]boronic acid 14.48

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.94 – 7.81 (m, 4H), 7.55 – 7.46 (m, 3H), 7.34 – 7.13 (m, 5H), 4.64 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.34 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.59 – 3.10 (m, 2H), 3.01 – 2.83 (m, 2H), 2.63 (dd, *J* = 13.7, 9.1 Hz, 1H), 1.75 (h, *J* = 5.5, 4.8 Hz, 2H), 1.62 (dd, *J* = 10.2, 5.1 Hz, 1H), 0.97 (dd, *J* = 15.0, 5.8 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.25 , 168.57 , 140.34 , 133.64 , 132.94 , 131.56 , 128.64, 128.31 , 128.15 , 127.47 , 127.36 , 126.71 , 126.07 , 125.84 , 53.99 , 40.18 , 37.38 , 36.60, 24.36 , 21.69 , 20.66 .

IR: ν 3325, 2958, 1669, 1368, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -67(*c* 1, CH_3OH)

Yield: 91% [b]

[(1*S*)-1-[[(2*R*,3*R*)-2-[[(2*S*)-3-cyclohexyl-2-methyl-propanoyl]amino]-3-methyl-pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.49

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.32 – 7.15 (m, 5H), 4.42 (d, *J* = 8.7 Hz, 1H), 4.01 (dt, *J* = 10.1, 5.0 Hz, 1H), 2.89 (q, *J* = 7.2, 5.5 Hz, 2H), 2.65 – 2.50 (m, 1H), 1.84 – 1.60 (m, 10H), 1.35 (ddd, *J* = 15.8, 8.2, 3.2 Hz, 2H), 1.22 (qd, *J* = 13.0, 5.8 Hz, 2H), 0.92 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.19 , 169.64 , 140.44 , 128.45 , 128.08 , 125.73 , 50.69 , 39.01 , 36.63 , 35.99 , 33.38 , 31.98 , 26.03 , 25.46 , 24.62 , 14.00 , 9.56 .

IR: ν 3027, 2924, 1645, 1385, 1116 cm^{-1}

$[\alpha]^{23}_D$ = +85.11 (*c* 0.47, CH_3OH)

Yield: 85% [b]

[(1*R*)-1-[[(2*R*,5*R*)-6-cyclohexyl-2-isobutyl-5-methyl-4-oxo-hexanoyl]amino]-2-phenyl-ethyl]boronic acid 14.50

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.35 – 7.16 (m, 5H), 4.59 (t, *J* = 7.1 Hz, 1H), 3.97 (dd, *J* = 8.9, 5.3 Hz, 1H), 2.99 – 2.83 (m, 2H), 2.60 (dd, *J* = 13.9, 9.4 Hz, 1H), 1.88 – 1.63 (m, 10H), 1.35 (q, *J* = 12.6 Hz, 2H), 1.22 (t, *J* = 12.0 Hz, 1H), 0.98 (dt, *J* = 12.8, 6.1 Hz, 9H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 177.48 , 169.67 , 140.43 , 128.55 , 128.12 , 125.77 , 50.62 , 40.07 ,39.03 , 36.63 , 33.29 , 32.96 , 31.94 , 25.96 , 25.72 , 25.43 , 24.33 , 21.67 , 20.65 .

IR: ν 3027, 2924, 1667, 1386, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -77.33 (*c* 0.75, CH_3OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*R*,3*R*)-3-methyl-2-[[(2*S*)-2-methyl-3-phenyl-propanoyl]amino]pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.51

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.44 – 7.15 (m, 10H), 4.45 (d, *J* = 7.3 Hz, 1H), 4.30 (dt, *J* = 13.4, 6.6 Hz, 1H), 3.35 (dd, *J* = 14.5, 4.7 Hz, 1H), 3.06 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.72 – 2.57 (m, 1H), 1.93 (q, *J* = 7.7 Hz, 1H), 1.63 (d, *J* = 9.6 Hz, 1H), 1.26 (dt, *J* = 14.5, 7.5 Hz, 1H), 0.94 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.96 , 168.49 , 140.38 , 134.00 , 129.30 , 128.91 , 128.66, 128.12 , 127.53 , 125.78 , 53.95 , 37.05 , 36.67 , 36.31 , 24.71 , 14.10 , 9.72 .

IR: ν 3028, 2933, 1668, 1361, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = +113.82 (*c* 0.94, CH_3OH)

Yield: 99% [b]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-4-oxo-6-phenyl-hexanoyl]amino]-2-phenyl-ethyl]boronic acid 14.52

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 – 7.15 (m, 10H), 4.63 (t, *J* = 7.3 Hz, 1H), 4.22 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.40 – 2.86 (m, 4H), 2.64 (dd, *J* = 13.9, 9.6 Hz, 1H), 1.75 (ddd, *J* = 13.8, 9.9, 5.2 Hz, 2H), 1.62 (dt, *J* = 11.0, 5.6 Hz, 1H), 0.98 (dd, *J* = 16.3, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.28 , 168.54 , 140.39 , 134.06 , 129.20 , 128.79 , 128.61, 128.13 , 127.52 , 125.80 , 54.05 , 40.15 , 37.16 , 36.63 , 24.36 , 21.68 , 20.61 .

IR: ν 3029, 2957, 1673, 1386, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = -83.33 (*c* 0.78, CH_3OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*R*,3*R*)-2-[[(2*S*)-3-(4-chlorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.53

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.14 (m, 5H), 4.43 (d, *J* = 8.5 Hz, 1H), 4.24 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.11 – 2.85 (m, 4H), 2.63 (td, *J* = 11.5, 5.1 Hz, 1H), 1.88 (d, *J* = 11.7 Hz, 1H), 1.63 (s, 1H), 1.26 – 1.16 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.11 , 168.17 , 140.34 , 133.41 , 132.71 , 131.02 , 128.85, 128.66 , 128.11 , 125.77 , 53.74 , 36.69 , 36.28 , 24.68 , 14.07 , 9.67 .

IR: ν 3028, 2935, 1669, 1361, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = +83.33 (*c* 0.48, CH_3OH)

Yield: 69% [b]

[(1*S*)-1-[[(2*R*,3*R*)-2-[[(2*S*)-3-(4-fluorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.54

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.33 – 7.15 (m, 5H), 7.11 (t, *J* = 8.6 Hz, 2H), 4.43 (d, *J* = 8.3 Hz, 1H), 4.26 (dd, *J* = 8.3, 4.9 Hz, 1H), 3.05 (dt, *J* = 14.4, 7.3 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.75 – 2.53 (m, 1H), 1.91 (s, 1H), 1.62 (d, *J* = 10.9 Hz, 1H), 1.24 (dt, *J* = 15.0, 7.4 Hz, 1H), 1.01 – 0.83 (m, 7H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.15 , 168.29 , 162.45 (d, *J* = 244.9 Hz), 140.37 , 131.25 (d, *J* = 8.0 Hz), 129.92 , 128.58 , 128.09 , 125.75 , 115.47 (d, *J* = 21.7 Hz), 163.67 , 53.91 , 36.70 , 36.28 , 36.16 , 24.67 , 14.05 , 9.64 .

IR: ν 3028, 2933, 1668, 1386, 1225, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = +60.82 (*c* 0.97, CH_3OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*R*,3*R*)-2-[[(2*S*)-3-(3-fluorophenyl)-2-methyl-propanoyl]amino]-3-methyl-pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.55

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.46 – 6.98 (m, 9H), 4.45 (d, *J* = 7.2 Hz, 1H), 4.29 (s, 1H), 3.37 (d, *J* = 13.7 Hz, 1H), 3.05 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.99 – 2.85 (m, 2H), 2.65 (dd, *J* = 13.9, 9.0 Hz, 1H), 1.91 (s, 1H), 1.64 (s, 1H), 1.25 (s, 1H), 1.02 – 0.81 (m, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.04 , 168.27 , 163.04 (d, *J* = 245.5 Hz), 140.38 , 136.71 (d, *J* = 7.3 Hz), 130.66 (d, *J* = 8.1 Hz), 128.61 , 128.11 , 125.77 , 116.12 (d, *J* = 21.8 Hz), 53.81 , 36.93 , 36.77 , 36.39 , 24.71 , 14.13 , 9.77 .

IR: ν 3028, 2934, 1645, 1359, 1254, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = +68.92 (*c* 0.74, CH_3OH)

Yield: 87% [b]

[(1*S*)-1-[[(2*S*)-2-[[(2*R*)-3-(4-fluorophenyl)-2-methyl-propanoyl]amino]propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.56

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.39 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.31 – 7.23 (m, 5H), 7.11 (t, *J* = 8.7 Hz, 2H), 4.64 – 4.52 (m, 1H), 4.19 (dd, *J* = 8.1, 5.3 Hz, 1H), 3.36 – 2.99 (m, 2H), 3.01 – 2.61 (m, 3H), 1.43 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 172.75 , 168.09 , 162.44 (d, *J* = 244.7 Hz), 140.36 , 131.27 (d, *J* = 8.1 Hz), 128.65 , 128.08 , 125.75 , 115.43 (d, *J* = 21.6 Hz) , 53.99 , 36.66 , 36.17 , 35.01 , 16.30 .

IR: ν 3218, 2934, 1650, 1378, 1224, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = +74.75 (*c* 0.99, CH_3OH)

Yield: 90% [b]

[(1*S*)-1-[[(2*S*)-2-[[(2*R*)-3-(4-fluorophenyl)-2-methyl-propanoyl]amino]propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.57

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.40 (q, *J* = 7.3 Hz, 2H), 7.35-7.26 (m, 5H), 7.22 – 7.12 (m, 2H), 4.58 (q, *J* = 6.5 Hz, 1H), 4.21 (t, *J* = 6.8 Hz, 1H), 3.40 – 3.01 (m, 2H), 3.00 – 2.59 (m, 3H), 1.43 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 168.05 , 164.24 , 161.80 , 140.38 , 138.98 , 136.84 , 130.62, 128.61 , 128.12 , 126.01 , 125.77 , 125.30 , 116.23 , 116.01 , 114.46 , 114.25 , 53.91 , 49.29 , 48.22 , 47.10 , 40.64 , 36.65 , 35.05 , 17.16 , 16.44 .

IR: ν 3058, 3026, 1652, 1372, 1254, 1146 cm^{-1}

$[\alpha]^{23}_{D}$ = +87.10 (*c* 0.93, CH_3OH)

Yield: 85% [b]

[(1*S*)-1-[[(2*R*,3*R*)-3-methyl-2-[[(2*S*)-2,3,3-trimethylbutanoyl]amino]pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.58

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.34 – 7.15 (m, 5H), 4.43 (d, *J* = 8.9 Hz, 1H), 3.69 (s, 1H), 2.98 – 2.47 (m, 3H), 1.90 (t, *J* = 8.4 Hz, 1H), 1.73 – 1.61 (m, 1H), 1.22 (dd, *J* = 14.2, 8.0 Hz, 1H), 1.14 (s, 9H), 0.91 (tt, *J* = 8.9, 5.3 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.74 , 167.67 , 140.47 , 128.55 , 128.10 , 125.75 , 61.00 , 36.83 ,

35.77 , 33.12 , 25.65 , 24.58 , 13.98 , 9.61 .

IR: ν 3027, 2935, 1645, 1376, 1116 cm^{-1}

$[\alpha]^{23}_{D}$ = +78.31 (*c* 0.83, CH$_3$OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*R*,3*R*)-3-methyl-2-[[(2*S*)-2-methylheptanoyl]amino]pentanoyl]amino]-2-phenyl-ethyl]boronic acid 14.59

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.36 – 7.16 (m, 5H), 4.49 – 4.36 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 1H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.93 – 2.85 (m, 2H), 2.66 – 2.45 (m, 1H), 1.94 (h, *J* = 8.0, 7.3 Hz, 4H), 1.82 – 1.71 (m, 2H), 1.55 (p, *J* = 8.9, 8.1 Hz, 2H), 1.26 (dt, *J* = 14.4, 7.5 Hz, 1H), 0.93 (d, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 176.31 , 168.91 , 140.31 , 128.50 , 128.11 , 125.78 , 52.41 , 38.93 , 36.75 , 35.79 , 30.79 , 26.71 , 24.64 , 21.38 , 14.04 , 9.57 .

IR: ν 3197, 2933, 1644, 1385, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = +112.12 (*c* 0.66, CH$_3$OH)

Yield: 99% [b]

[(1*S*)-1-[[(2*S*)-2-[[(2*R*)-3-(3-fluorophenyl)-2-methyl-propanoyl]amino]-3-phenyl-propanoyl]amino]-2-phenyl-ethyl]boronic acid 14.60

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.37 – 7.03 (m, 14H), 4.17 (dq, *J* = 11.9, 6.1, 5.4 Hz, 1H), 3.46 – 2.86 (m, 7H), 2.72 – 2.58 (m, 1H).

^{13}C NMR (101 MHz, Methanol-d$_4$) δ 175.45 , 168.14 , 163.03 (d, *J* = 245.4 Hz), 136.70 , 129.01, 128.62 , 128.33 , 128.09 , 126.87 , 126.54 , 125.78 , 125.29 , 116.10 (d, *J* = 21.6 Hz), 114.38 (d, *J* = 21.2 Hz), 53.82 , 40.66 , 37.14 , 36.68 , 35.01 .

IR: ν 3029, 2930, 1650, 1360, 1254, 1115 cm^{-1}

$[\alpha]^{23}_{D}$ = +41.26 (*c* 1.43, CH$_3$OH)

Yield: 88% [b]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-4-oxo-6-(3-pyridyl)hexanoyl]amino]-3-phenyl-propyl]boronic acid 14.61

^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.96 – 8.85 (m, 2H), 8.74 (d, *J* = 7.9 Hz, 1H), 8.13 (t, *J* = 6.8 Hz, 1H), 7.29 – 7.11 (m, 5H), 4.66 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.45 (t, *J* = 6.5 Hz, 1H), 3.55

(ddd, *J* = 63.8, 14.4, 6.5 Hz, 2H), 2.72 (ddd, *J* = 15.9, 12.0, 6.9 Hz, 3H), 1.80 (ddt, *J* = 30.1, 16.6, 6.7 Hz, 4H), 1.63 (dt, *J* = 10.9, 5.7 Hz, 1H), 0.99 (dd, *J* = 14.3, 6.0 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.95 , 167.43 , 148.37 , 142.30 , 142.09 , 140.58 , 135.24, 128.03 , 127.99 , 127.51 , 125.44 , 52.89 , 40.00 , 33.55 , 32.60 , 24.33 , 21.69 , 20.60 .

IR: ν 3025, 2931, 1684, 1369, 1116cm^{-1}

$[\alpha]^{23}_D$ = -35 (*c* 0.8, CH_3OH)

Yield: 99% [b]

[(1*R*)-1-[[(2*S*)-2-[[(2*R*)-2-methyl-3-(3-pyridyl)propanoyl]amino]propanoyl]amino]-3-phenyl-propyl]boronic acid 14.62

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.91 (s, 1H), 8.86 (d, *J* = 5.4 Hz, 1H), 8.73 (d, *J* = 7.7 Hz, 1H), 8.12 (t, *J* = 6.7 Hz, 1H), 7.30 – 7.11 (m, 5H), 4.61 (q, *J* = 7.1 Hz, 1H), 4.40 (t, *J* = 6.4 Hz, 1H), 3.54 (ddd, *J* = 48.1, 14.4, 6.4 Hz, 2H), 2.81 – 2.59 (m, 3H), 1.90 – 1.68 (m, 2H), 1.49 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.22 , 167.17 , 148.46 , 142.34 , 142.11 , 140.59 , 135.22, 128.02 , 127.48 , 125.42 , 52.84, 46.37 , 33.47 , 32.54 , 16.34 .

IR: ν 3223, 2916, 1682, 1366, 1154 cm^{-1}

$[\alpha]^{23}_D$ = -33.33 (*c* 0.45, CH_3OH)

Yield: 83% [b]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-6-(2-naphthyl)-4-oxo-hexanoyl]amino]-3-phenyl-propyl]boronic acid 14.63

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.81 (m, 4H), 7.49 (td, *J* = 7.7, 3.0 Hz, 3H), 7.30 – 7.13 (m, 5H), 4.69 (td, *J* = 8.9, 8.4, 3.9 Hz, 1H), 4.33 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.60 – 3.13 (m, 2H), 2.75 – 2.58 (m, 3H), 1.93 – 1.62 (m, 5H), 0.99 (dd, *J* = 15.2, 5.9 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 176.92 , 168.53 , 142.15 , 133.62 , 132.94 , 131.47 , 128.62, 128.31 , 128.07 , 128.01 , 127.38 , 126.63 , 126.07 , 125.85 , 125.41 , 53.97 , 44.46 , 40.14 , 37.31 , 33.50 , 32.55 , 24.37 , 21.62 , 20.67 .

IR: ν 3362, 2928, 2869, 1669, 1368, 1115 cm^{-1}

$[\alpha]^{23}_D$ = -59.38 (*c* 0.64, CH_3OH)

Yield: 58% [b]

[(1*R*)-1-[[(2*S*)-2-[[(2*R*)-2-methyl-3-(2-naphthyl)propanoyl]amino]propanoyl]amino]-3-phenyl-propyl]boronic acid 14.64

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.81 (m, 4H), 7.54 – 7.44 (m, 3H), 7.30 – 7.13 (m, 5H), 4.68 – 4.58 (m, 1H), 4.29 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.52 (dd, *J* = 14.2, 5.5 Hz, 1H), 3.20 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.72 – 2.60 (m, 3H), 1.88 – 1.64 (m, 2H), 1.50 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.29 , 168.33 , 142.16 , 133.61 , 132.93 , 131.53 , 128.60, 128.27 , 128.16 , 127.39 , 127.33 , 126.68 , 126.07 , 125.84 , 125.45 , 54.00 , 46.00 , 37.28 , 33.42 , 32.46 , 16.30 .

IR: ν 3367, 2927, 1669, 1372, 1116 cm^{-1}

$[\alpha]^{23}_D$ = -23.33 (*c* 0.30, CH_3OH)

Yield: 18% [b]

[(1*R*)-1-[[(2*R*,5*R*)-2-isobutyl-5-methyl-4-oxo-decanoyl]amino]-3-phenyl-propyl]boronic acid 14.65

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.31 – 7.11 (m, 5H), 4.65 (dd, *J* = 9.1, 5.3 Hz, 1H), 4.04 (d, *J* = 6.3 Hz, 1H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.68 (dtt, *J* = 19.7, 13.9, 7.6 Hz, 3H), 1.95 (h, *J* = 7.0 Hz, 2H), 1.77 (dq, *J* = 30.6, 6.9 Hz, 6H), 1.60 (ddd, *J* = 27.6, 14.2, 7.8 Hz, 3H), 1.00 (dd, *J* = 15.0, 5.8 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.55 , 168.98 , 142.08 , 128.09 , 127.99 , 125.45 , 52.45 , 45.21 , 39.85 , 38.94 , 33.50 , 32.64 , 30.73 , 26.69 , 24.39 , 21.76 , 21.33 , 20.57.

IR: ν 3026, 2937, 1683, 1368, 1151 cm^{-1}

$[\alpha]^{23}_D$ = -88.24 (*c* 1.36, CH_3OH)

Yield: 91% [b]

[(1*R*)-1-[[(2*S*)-2-[[(2*R*)-2-methyl-3-(1-naphthyl)propanoyl]amino]propanoyl]amino]-3-phenyl-propyl]boronic acid 14.66

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.62 (dd, *J* = 8.3, 6.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.29 – 7.10 (m, 5H), 4.59 (q, *J* = 7.0 Hz, 1H), 4.38 – 4.29 (m, 1H), 3.66 (ddd, *J* = 127.7, 14.4, 7.5 Hz, 2H), 2.77 – 2.54 (m, 3H), 1.89 – 1.68 (m, 2H), 1.46 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.40 , 168.49 , 142.15 , 134.21 , 131.73 , 129.93 , 128.72, 128.49 , 128.33 , 126.53 , 125.76 , 125.36 , 123.06 , 53.26 , 47.04 , 34.25 , 33.44 , 32.40 , 16.15 .

IR: ν 3051, 2932, 1653, 1372, 1114 cm^{-1}

$[\alpha]^{23}_D$ = -3.33 (*c* 1.2, CH_3OH)

Yield: 99% [b]

[(1*R*)-1-[[(2*R*,5*R*)-6-cyclohexyl-2-isobutyl-5-methyl-4-oxo-hexanoyl]amino]-3-phenyl-propyl]boronic acid 14.67

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.29 – 7.11 (m, 5H), 4.65 (dd, *J* = 9.1, 5.6 Hz, 1H), 4.00 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.75 – 2.57 (m, 3H), 1.87 – 1.59 (m, 15H), 1.54 – 1.40 (m, 1H), 1.37 – 1.26 (m, 1H), 1.21 (tt, *J* = 12.3, 3.9 Hz, 1H), 1.00 (dd, *J* = 13.3, 6.2 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 177.26 , 169.66 , 142.14 , 128.05 , 127.93 , 125.38 , 50.64, 39.95 , 39.01 , 33.53 , 33.23 , 32.95 , 32.65 , 31.99 , 25.94 , 25.70 , 25.44 , 24.36 , 21.68 , 20.65 .
IR: ν 3360, 2924, 1668, 1368, 1115 cm^{-1}
$[\alpha]^{23}_D$ = -61.29 (*c* 0.62, CH_3OH)
Yield: 56% [b]

[(1*R*)-1-[[(2*S*)-2-[[(2*R*)-3-cyclohexyl-2-methyl-propanoyl]amino]propanoyl]amino]-3-phenyl-propyl]boronic acid 14.68

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.30 – 7.12 (m, 5H), 4.63 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.00 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.67 (dddd, *J* = 22.4, 15.6, 7.3, 4.7 Hz, 3H), 1.87 – 1.61 (m, 11H), 1.51 (d, *J* = 5.8 Hz, 3H), 1.41 – 1.25 (m, 2H), 0.99 (ddq, *J* = 16.7, 8.6, 4.3 Hz, 2H).
^{13}C NMR (101 MHz, Methanol-d_4) δ 177.81 , 169.48 , 142.14 , 128.01 , 127.94 , 125.45 , 50.66 , 46.04 , 38.91 , 33.48 , 33.04 , 32.62 , 32.20 , 30.98 , 25.96 , 25.83 , 25.47 , 16.23.
IR: ν 3026, 2924, 1652, 1362, 1115 cm^{-1}
$[\alpha]^{23}_D$ = -42.45 (*c* 1.39, CH_3OH)
Yield: 86% [b]

[(1*R*)-1-[[(2*R*)-2-isobutyl-5-methyl-4-oxo-hexanoyl]amino]-3-phenyl-propyl]boronic acid 14.69

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.20 (ddd, *J* = 25.4, 16.4, 7.2 Hz, 5H), 4.65 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.00 (t, *J* = 7.0 Hz, 1H), 2.65 (tt, *J* = 13.6, 6.6 Hz, 3H), 1.74 (dddd, *J* = 48.1, 26.2, 12.2, 6.4 Hz, 5H), 1.53 (d, *J* = 6.5 Hz, 3H), 0.99 (dd, *J* = 15.6, 5.8 Hz, 6H).
^{13}C NMR (101 MHz, Methanol-d_4) δ 177.43 , 169.81 , 142.10 , 128.03 , 127.94 , 125.39 , 48.65 , 39.88 , 33.49 , 32.62 , 24.41 , 21.66 , 20.53 , 16.28 .
IR: ν 3197, 2933, 1683, 1369, 1114 cm^{-1}
$[\alpha]^{23}_D$ = -87.18 (*c* 0.39, CH_3OH)
Yield: 99% [b]

3.2.4. References

1. Montalbetti, C.A.G.N. and V. Falque, *Amide bond formation and peptide coupling.* Tetrahedron, 2005. **61**(46): pp. 10827-10852.
2. *Amino acids, peptides and proteins in organic chemistry Vol. 2. Modified amino acids, organocatalysis and enzymes* 2009, Weinheim: Wiley-VCH-Verl.
3. Han, S.-Y. and Y.-A. Kim, *Recent development of peptide coupling reagents in organic synthesis.* Tetrahedron, 2004. **60**(11): pp. 2447-2467.

4. Li, P. and J.C. Xu, *Highly Efficient Synthesis of Sterically Hindered Peptides Containing N-Methylated Amino Acid Residues using a Novel 1H-Benzimidazolium Salt.* Tetrahedron, 2000. **56**(51): pp. 9949-9955.
5. El-Faham, A. and F. Albericio, *Peptide Coupling Reagents, More than a Letter Soup.* Chemical Reviews, 2011. **111**(11): pp. 6557-6602.
6. Isidro-Llobet, A., M. Álvarez, and F. Albericio, *Amino Acid-Protecting Groups.* Chemical Reviews, 2009. **109**(6): pp. 2455-2504.
7. Merrifield, R.B., *Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide.* Journal of the American Chemical Society, 1963. **85**(14): pp. 2149-2154.
8. Coin, I., M. Beyermann, and M. Bienert, *Solid-phase peptide synthesis: from standard procedures to the synthesis of difficult sequences.* Nat. Protocols, 2007. **2**(12): pp. 3247-3256.
9. Fields, G.B., *Introduction to Peptide Synthesis*, in *Current Protocols in Immunology* 2001, John Wiley & Sons, Inc.
10. Snow, R.J., et al., *Studies on Proline Boronic Acid Dipeptide Inhibitors of Dipeptidyl Peptidase IV: Identification of a Cyclic Species Containing a B-N Bond.* Journal of the American Chemical Society, 1994. **116**(24): pp. 10860-10869.
11. Gorovoy, A.S., Gozhina, O.V., Svendsen, J.S., Domorad, A.A., Tetz, G.V., Tetz, V.V., and Lejon, T., *Boron containing peptidomimetics – a novel class of selective anti-tubercular drugs.* Chemical Biology & Drug Design (accepted)
12. Inglis, S.R., et al., *Observations on the Deprotection of Pinanediol and Pinacol Boronate Esters via Fluorinated Intermediates.* The Journal of Organic Chemistry, 2009. **75**(2): pp. 468-471.
13. Rangaishenvi, M.V., B. Singaram, and H.C. Brown, *Chiral synthesis via organoboranes. 30. Facile synthesis, by the Matteson asymmetric homologation procedure, of .alpha.-methyl boronic acids not available from asymmetric hydroboration and their conversion into the corresponding aldehydes, ketones,*

carboxylic acids, and amines of high enantiomeric purity. The Journal of Organic Chemistry, 1991. **56**(10): pp. 3286-3294.

14. Matteson, D.S., P.K. Jesthi, and K.M. Sadhu, *Synthesis and properties of pinanediol α-amido boronic esters.* Organometallics, 1984. **3**(8): pp. 1284-1288.
15. Kinder, D.H. and J.A. Katzenellenbogen, *Acylamido boronic acids and difluoroborane analogs of amino acids: potent inhibitors of chymotrypsin and elastase.* Journal of Medicinal Chemistry, 1985. **28**(12): pp. 1917-1925.
16. Malan, C. and C. Morin, *A Concise Preparation of 4-Borono-l-phenylalanine (l-BPA) from l-Phenylalanine.* The Journal of Organic Chemistry, 1998. **63**(22): p. 8019-8020.
17. Morandi, S., et al., *Structure-based optimization of cephalothin-analogue boronic acids as β-lactamase inhibitors.* Bioorganic & Medicinal Chemistry, 2008. **16**(3): pp. 1195-1205.
18. Morandi, F., et al., *Nanomolar Inhibitors of AmpC β-Lactamase.* Journal of the American Chemical Society, 2003. **125**(3): pp. 685-695.
19. Pennington, T.E., C. Kardiman, and C.A. Hutton, *Deprotection of pinacolyl boronate esters by transesterification with polystyrene–boronic acid.* Tetrahedron Letters, 2004. **45**(35): pp. 6657-6660.
20. Coutts, S.J., et al., *Two efficient methods for the cleavage of pinanediol boronate esters yielding the free boronic acids.* Tetrahedron Letters, 1994. **35**(29): pp. 5109-5112.
21. Wityak, J., et al., *Synthesis of Thrombin Inhibitor DuP 714.* The Journal of Organic Chemistry, 1995. **60**(12): pp. 3717-3722.

3.3. Biological Activity

Due the to success of the results of antimicrobial tests of β-aminoboronic peptides (antitubercular activity at a level of MIC 5 mg/L has been detected) the library of synthesized α-aminoboronic di- and tri- peptides has been tested against the same bacterial strains *i.e. Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyogenes* (ATCC 19615), *Mycobacterium tuberculosis* (H37Rv) and fungi *Candida albicans* (ATCC 90028). Quite high levels of antimicrobial activity of some α-aminoboronic peptides have been established as will be discussed below.

In addition the inhibitory properties of a peptide possessing antitubercular activity have been investigated in the enzyme-catalyzed conversion of chorismate to prephenate (the process is related to screening for new antitubercular drugs) and the cytotoxicity of the peptide has been determined as well.

The kinase inhibitory activity of some peptides has also been examined. This was of interest, because the human organism includes more than 500 different protein kinase genes, which composes about 2% of all human genes, so evaluation of inhibitory activity of α-aminoboronic antimicrobial peptides was significant due to selectivity reasons.

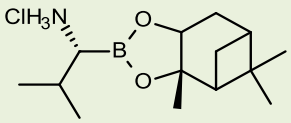
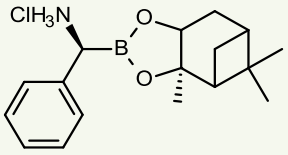
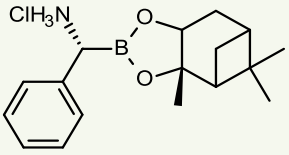
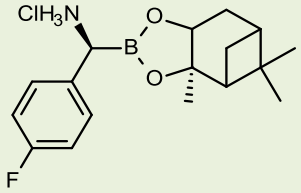
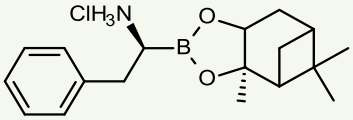
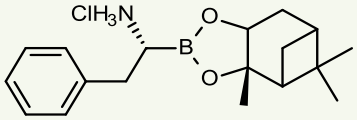
All the data are being discussed in the following sub-chapters.

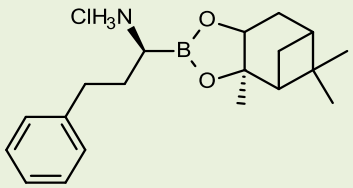
3.3.1. Antibacterial Activity

As it was outlined above the library of previously synthesized α-aminoboronic di- and tri- peptides has been tested against different bacterial strains and fungi including *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyogenes* (ATCC 19615), *Candida albicans* (ATCC 90028), and *Mycobacterium tuberculosis* (H37Rv). The tests have been performed at the **Department of Microbiology, Virology and Immunology of St. Petersburg State Pavlov Medical University** by chemists of **Victor V. Tetz** laboratory.

First of all antimicrobial and antifungal activities of some α-aminoboronates **7** (starting materials for peptide coupling) have been investigated as a background study of the biological properties of boron containing bioisosteres of amino acids. All the data are summarized in the following table and only positive results has been displayed (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

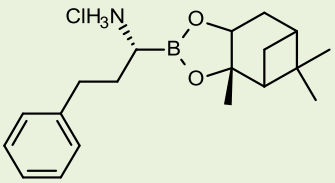
Table 3.32 Antimicrobial activity of α-aminoboronates **7**.

(-)-ester	(+)-ester
	 7.4 M. tuberculosis 500/500 P. aeruginosa ≈500/-
 7.5 S. aureus 500/≈500 M. tuberculosis 500/500	 7.6 M. tuberculosis 500/500
 7.7 -/-	
 7.8 M. tuberculosis ≈500/-	 7.9 -/-



7.10

M. tuberculosis 500/≈500



7.11

-/-

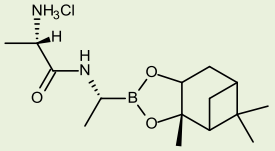
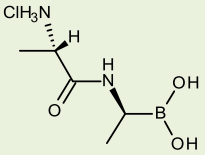
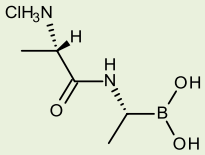
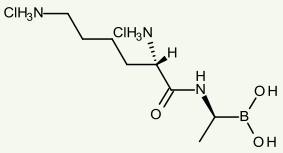
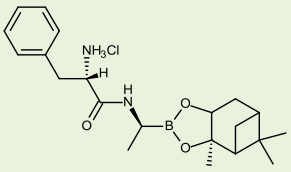
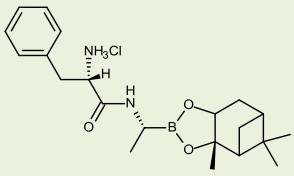
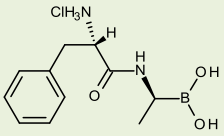
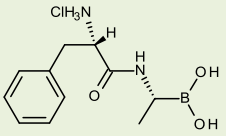
Some antibacterial activity of α-aminoboronates **7** has been observed, but these compounds do not appear to be very effective antimicrobial agents, so it was believed that α-aminoboron containing peptides will provide a higher value of antimicrobial activity.

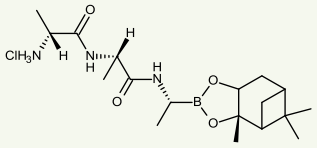
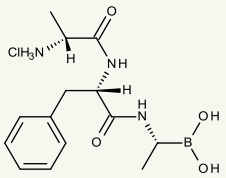
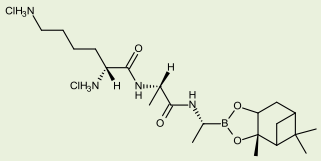
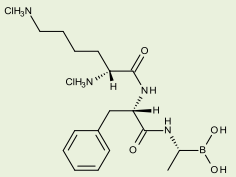
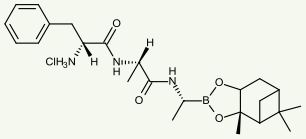
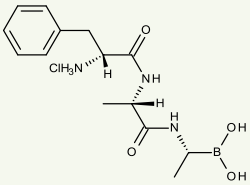
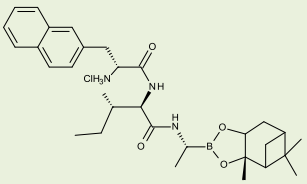
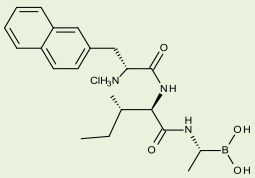
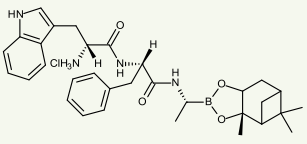
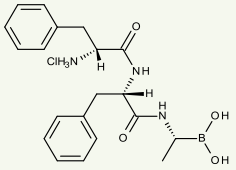
The creation of a new library was started with methyl α-aminoboronic esters **7.1** and **7.2** as the simplest representatives of α-aminoboronates by coupling them with one or two ordinary L-amino acids yielding di- or tri- peptides, respectively.

For convenience in interpretation of the results α-aminoboronic peptides with either pinanediol moiety or free boronic acid part were combined in one table. Each table represents peptides holding the same substituent at the α-aminoboronate moiety. The structures were displayed in the tables depending on their similarity to each other and only positive activity has been displayed. The structures of the compounds active at MIC 5 mg/L (marked by red color) will be summarized in one table and discussed extensively after all the tables.

The sign ≈ before the concentration value (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L) means that a result is uncertain due to different data from three repetitions.

Table 3.33 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing a methyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

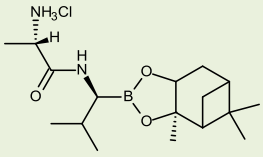
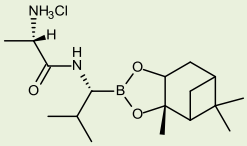
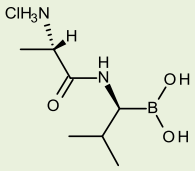
(-)-ester	(+)-ester	(-)-acid	(+)-acid
			
	9.1 -/-	13.1 S. aureus 500/500 E. coli ≈500/500 E. faecalis 500/- M. tuberculosis 50/50	13.2 -/-
			
		13.5 S. aureus 50/50 E. coli 500/500 E. faecalis 500/500	
			
9.2 M. tuberculosis ≈50/-	9.3 S. aureus ≈500/- E. coli ≈500/- C. albicans ≈500/- M. tuberculosis ≈500/500	13.3 S. aureus 500/≈500 M. tuberculosis 50/50	13.4 -/-

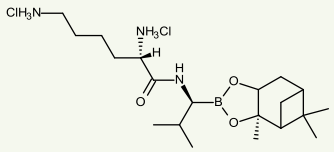
 10.3 -/-	 14.3 C. albicans 500/500
 10.2 -/-	 14.4 M. tuberculosis 500/≈500
 10.1 -/-	 14.1 -/-
 10.5 S. aureus 500/500 S. pyogenes 500/500 C. albicans ≈500/500 M. tuberculosis -/500	 14.5 S. pyogenes ≈500/500 M. tuberculosis ≈500/500
 10.4 S. aureus 500/500 S. pyogenes ≈50/≈500 M. tuberculosis ≈500/≈500	 14.2 S. pyogenes 500/- C. albicans 500/500 M. tuberculosis

500/500

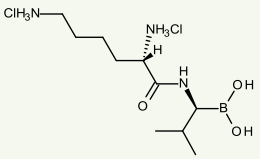
The small library of the peptides holding a methyl substituent at α-aminoboronate moiety possesses antimicrobial and antifungal activity at quite high valuess (MIC 500 and 50 mg/L) therefore they do not have any potential to be developed as antimicrobial and antifungal agents at least in this investigation. Based on data shown above one can not draw any conclusions about structure-activity relations (though a lot of possible amino acid, as well as boronate/boronic acid combinations have been tested) therefore it was decided to enlarge the substituent at α-aminoboronate moiety, for example, using the branched aliphatic *iso*-propyl group. Despite the fact that antimicrobial activity of the synthesized peptides is low, it was surprising to discover that boron-containing dipeptides possess antibacterial activity at high concentration values whereas their ordinary analogues are not active and the peptide chain must be increased at least by one unit to obtain a tripeptide as it had been shown by the Prof. Svendsen group.[1-4]

Table 3.34 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing an *iso*-propyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

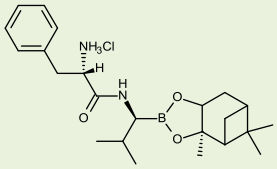
(-)-ester	(+)-ester	(-)-acid	(+)-acid
			
9.4 M. tuberculosis ≈500/-	9.5 S. aureus ≈50/- C. albicans 500/500 M. tuberculosis ≈500/-	13.6 M. tuberculosis 500/≈500	



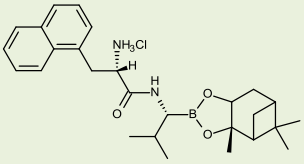
9.9
M. tuberculosis
≈500/≈500



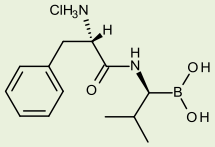
13.9
-/-



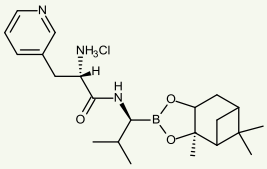
9.6
M. tuberculosis
500/≈500



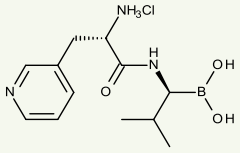
9.7
S. aureus ≈500/500
C. albicans -/≈500
M. tuberculosis -/500



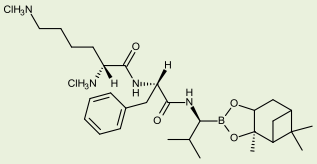
13.7
M. tuberculosis
500/-



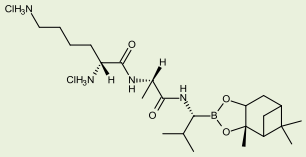
9.8
S. aureus 500/500
S. pyogenes -/≈500
P. aeruginosa-/≈5
M. tuberculosis ≈500/-



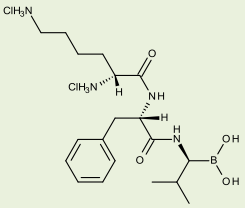
13.8
S. pyogenes ≈500/-
M. tuberculosis
≈500/-



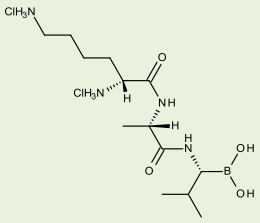
10.6
C. albicans ≈500/≈500
M. tuberculosis ≈50/≈50



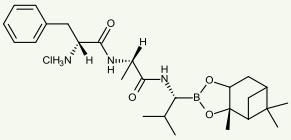
10.7
C. albicans 500/500
M. tuberculosis
500/500



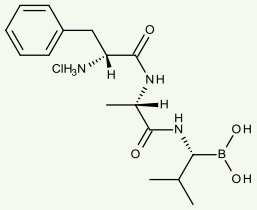
14.8
-/-



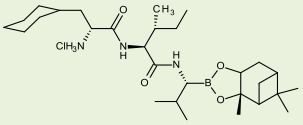
14.9
C. albicans 50/50
M. tuberculosis
500/-



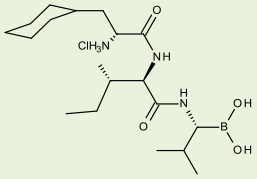
10.9
S. aureus 500/-
C. albicans 500/500
M. tuberculosis
500/500



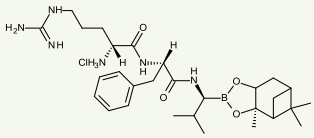
14.7
S. pyogenes 500/-
C. albicans 50/500
M. tuberculosis
500/500



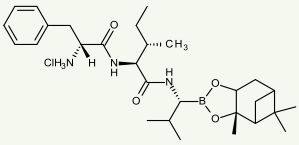
10.17
S. aureus ≈500/500
S. pyogenes -/500
C. albicans -/500
M. tuberculosis
500/500



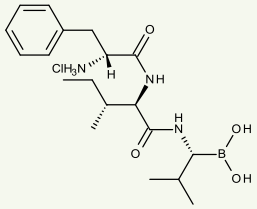
14.14
S. aureus ≈50/500
E. coli ≈500/-
S. pyogenes
≈500/≈500
C. albicans -/500
M. tuberculosis
500/500



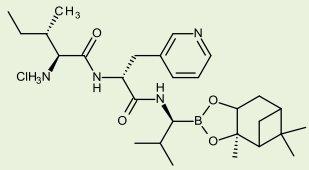
10.8
C. albicans ≈500/-
M. tuberculosis 500/500



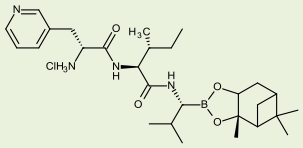
10.11
S. aureus ≈500/500
S. pyogenes -/500
M. tuberculosis
500/500



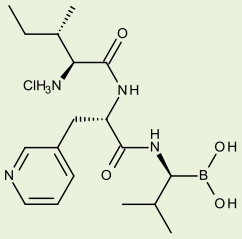
14.17
E. coli ≈500/-
C. albicans 500/-
M. tuberculosis
500/500



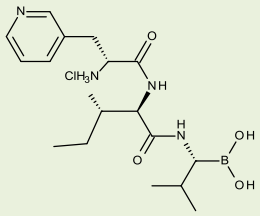
10.10
S. aureus ≈500/-
C. albicans ≈500/500
P. aeruginosa ≈500/-
M. tuberculosis
≈500/500



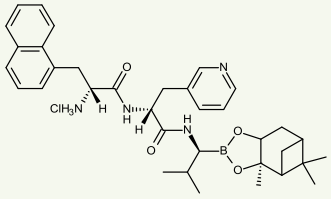
10.18
C. albicans ≈500/-
M. tuberculosis
500/500



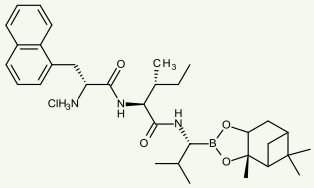
14.15
-/-



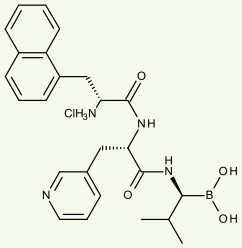
14.16
M. tuberculosis
500/500



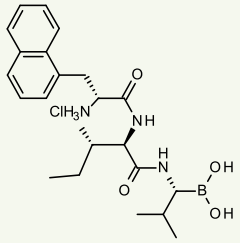
10.14
S. aureus -/500
S. pyogenes -/500
C. albicans 500/500
M. tuberculosis
≈500/≈500



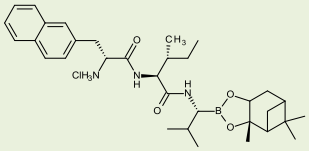
10.15
S. aureus ≈500/500
M. tuberculosis
≈50/50



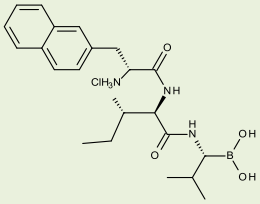
14.6
M. tuberculosis
≈500/-



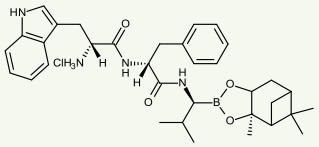
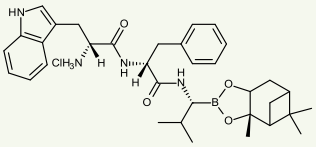
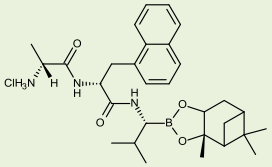
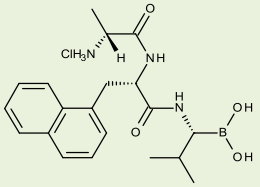
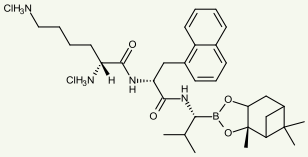
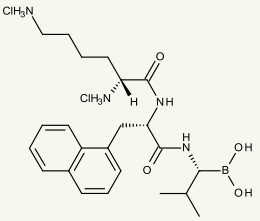
14.12
S. aureus 500/500
M. tuberculosis
50/500



10.16
S. aureus ≈50/500
S. pyogenes -/≈500
C. albicans ≈500/500
M. tuberculosis
500/50



14.13
S. aureus 500/≈500
E. coli ≈500/-
S. pyogenes 500/500
C. albicans 500/-
M. tuberculosis
500/500

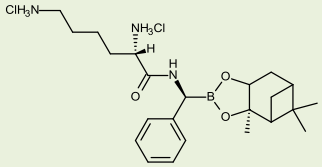
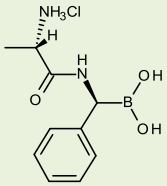
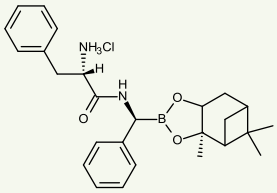
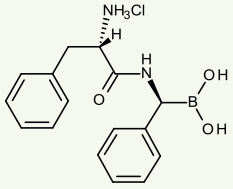
 10.19 S. aureus 500/500 S. pyogenes ≈500/500 C. albicans 500/≈50 M. tuberculosis -/≈500	 10.20 S. aureus 500/500 S. pyogenes ≈500/500 M. tuberculosis ≈500/≈500	
	 10.13 S. aureus 500/500 E. coli 500/500 S. pyogenes 500/500 C. albicans 500/500 P. aeruginosa ≈500/- M. tuberculosis -/500	 14.11 P. aeruginosa ≈500/- M. tuberculosis ≈500/500
	 10.12 E. coli -/≈500 S. pyogenes 500/- C. albicans 500/- P. aeruginosa ≈500/- M. tuberculosis 500/500	 14.10 S. aureus 500/500 P. aeruginosa ≈500/- M. tuberculosis 500/500

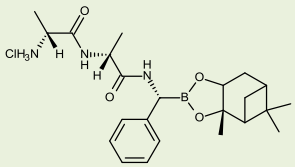
Most of the peptides containing an *iso*-propyl substituent at the α-aminoboronate moiety possess antimicrobial and antifungal activity at quite high concentration values (MIC 500 and 50 mg/L) therefore they have a very poor potential as antimicrobial and antifungal agents. Compound **9.8** is active against *Pseudomonas aeruginosa* at the level of MIC 5 mg/L, but the test results have shown a lack of activity at MIC 500 and 50 mg/L, so it seems to be

active only if diluted well. This is a known effect called Inverse Dose-Response which is represented by increasing of biological activity of a compound with falling concentration, but before further investigation this data must be verified.

So it might be concluded that small aliphatic substituents at α-aminoboronate moiety (both straight and branched) do not promote an increase in activity and more bulky substituents are needed to be introduced into the molecule.

Table 3.35 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing a phenyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

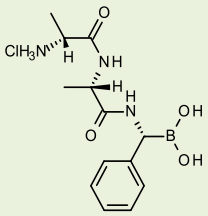
(-)-ester	(+)-ester	(-)-acid	(+)-acid
 9.11 M. tuberculosis ≈5/500		 13.10 M. tuberculosis ≈500/500	
 9.10 S. aureus 500/- S. pyogenes 500/- M. tuberculosis ≈500/500		 13.11 M. tuberculosis 500/-	



10.30

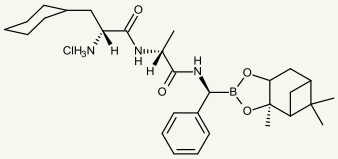
M. tuberculosis

500/≈500



14.25

-/-

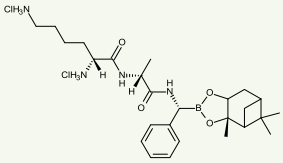


10.31

S. aureus 500/500

C. albicans -/≈500

M. tuberculosis 500/-



10.28

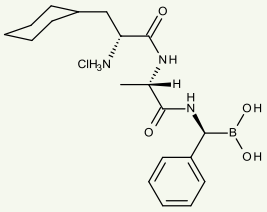
C. albicans

≈500/500

M. tuberculosis

≈500/500

S. aureus ≈500/-

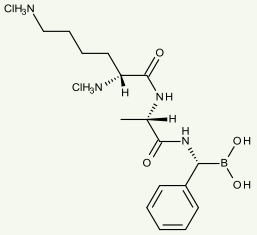


14.28

C. albicans -/≈5

M. tuberculosis

500/-



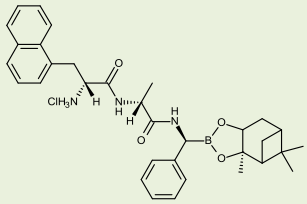
14.23

S. aureus ≈500/-

C. albicans ≈500/-

M. tuberculosis

≈50/≈50



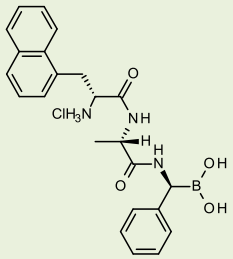
10.27

S. pyogenes 500/500

C. albicans ≈500/≈500

M. tuberculosis

≈500/500

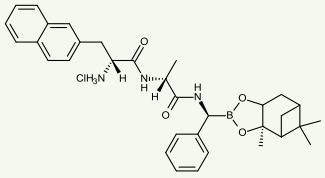


14.24

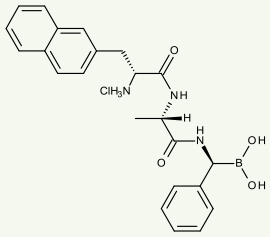
S. aureus 500/500

M. tuberculosis

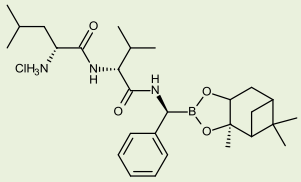
≈500/500



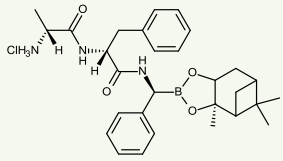
10.29
S. aureus 500/500
E. coli 500/≈500
S. pyogenes 500/500
C. albicans ≈500/≈5
M. tuberculosis ≈500/50



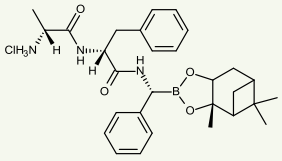
14.26
S. aureus ≈500/-
E. coli 500/500
S. pyogenes 500/500
M. tuberculosis
≈500/500



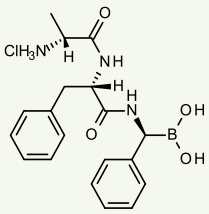
10.33
S. aureus -/500
S. pyogenes -/≈500
C. albicans -/500
M. tuberculosis -/≈500



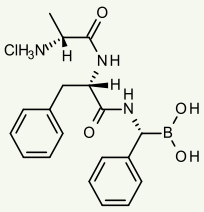
10.21
S. aureus 500/≈500
E. coli 500/500
S. pyogenes 500/500
P. aeruginosa 500/-
M. tuberculosis 500/500



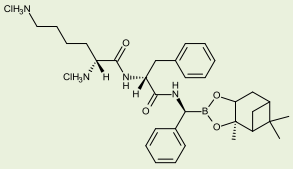
10.22
M. tuberculosis
≈50/500



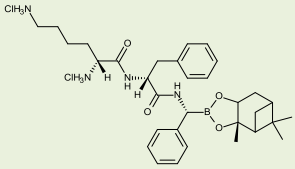
14.18
S. aureus 500/500
E. coli 500/-
S. pyogenes 500/500
P. aeruginosa 500/-
M. tuberculosis
500/500



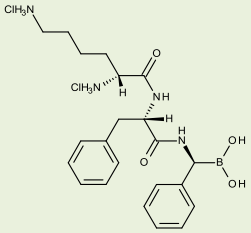
14.19
S. aureus -/5
C. albicans ≈500/≈5
M. tuberculosis
500/500



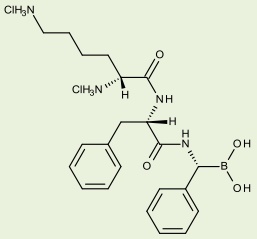
10.25
S. aureus 500/500
E. coli 500/500
S. pyogenes 500/500
P. aeruginosa 500/500
M. tuberculosis 500/500



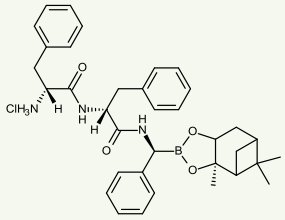
10.26
S. aureus 500/-
E. coli 500/-
S. pyogenes 500/-
C. albicans 500/500
P. aeruginosa ≈500/-
M. tuberculosis
≈50/500



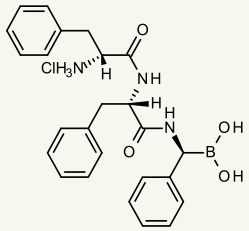
14.20
S. aureus 500/500
E. coli 500/500
S. pyogenes 500/500
C. albicans ≈500/-
P. aeruginosa
500/≈500
M. tuberculosis
500/500



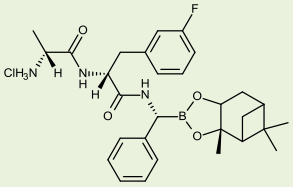
14.21
C. albicans 500/-
M. tuberculosis
500/500



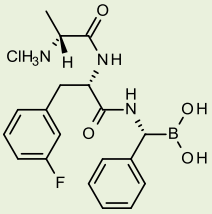
10.23
S. aureus -/500
S. pyogenes -/500
C. albicans ≈500/-



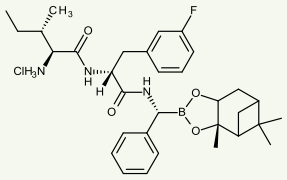
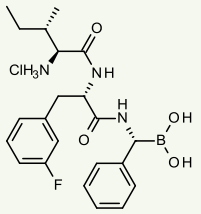
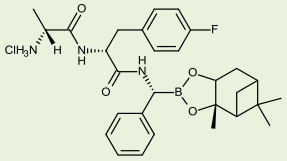
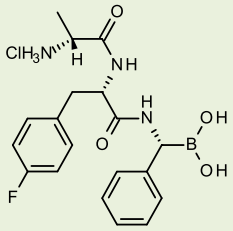
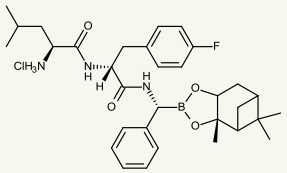
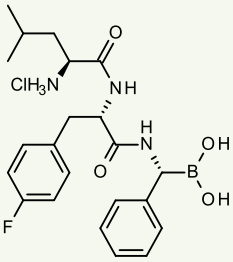
14.22
C. albicans ≈500/-



10.32
M. tuberculosis
500/500



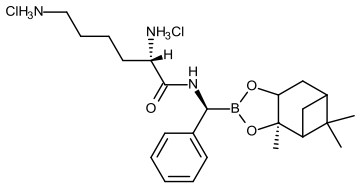
14.30
M. tuberculosis
50/50

 10.34 S. aureus 500/500 M. tuberculosis 500/500	 14.31 M. tuberculosis ≈50/500
 10.35 S. aureus ≈500/- C. albicans 500/- M. tuberculosis 500/500	 14.27 M. tuberculosis ≈500/≈500
 10.24 S. aureus 500/500 M. tuberculosis ≈50/500	 14.29 S. aureus ≈500/- M. tuberculosis 500/500

Most of the peptides containing a phenyl substituent at the α-aminoboronate moiety possess antimicrobial and antifungal activity at quite high values (MIC 500 and 50 mg/L) therefore they have a low potential to be developed as antimicrobial and antifungal agents, but switching an aliphatic substituent at α-aminoboronate moiety by aromatic ring was beneficial since four compounds active at MIC 5 mg/L have been obtained.

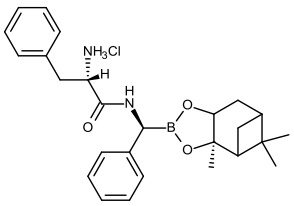
Compound **9.11** is selectively active against *Mycobacterium tuberculosis* at the level of MIC 5 mg/L, but the result is uncertain so the compound can be taken into account as a potential antimicrobial worth further investigation. This compound seems to be more active than its β-analogue,[7] but switching cationic group to bulky one provides decreasing anti TB activity of α-compound and does not affect antimycobacterial properties of β-peptide.

α-peptide



9.11

M. tuberculosis ≈5/500



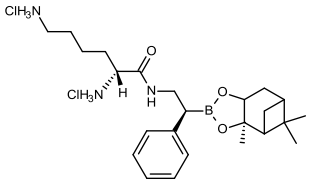
9.10

S. aureus 500/-

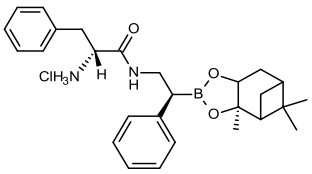
S. pyogenes 500/-

M. tuberculosis ≈500/500

β-peptide



M.tuberculosis 500/500



M.tuberculosis 500/500

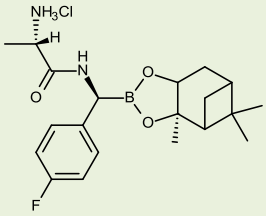
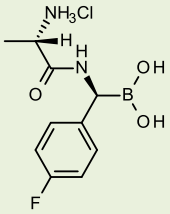
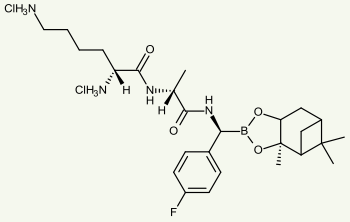
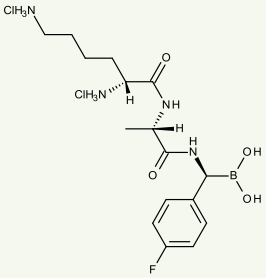
(only anti TB activity has been reported in the paper)

Compound **14.19** is active against *Staphylococcus aureus* at MIC 5 mg/L, and therefore has potential to be developed as antimicrobial atreatment. Compounds **10.29, 14.19** and **14.28** are active against *Candida albicans* at MIC 5 mg/L, but in all cases the results are uncertain so they need to be investigated more widely as potential antifungal agents.

It is well-known that the introduction of a fluorine atom into a molecule is an advantage for its lipophilicity (an important tool for a molecule to be active *in vivo*) and also it can assist in interaction between the binding sites of enzymes and the compound, so it was

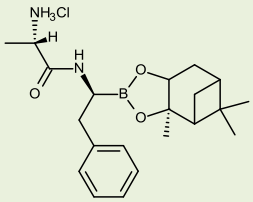
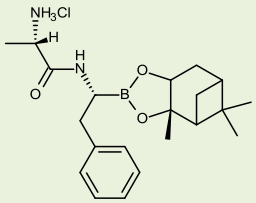
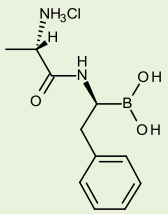
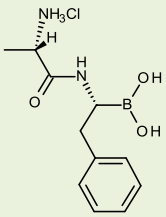
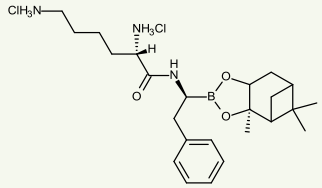
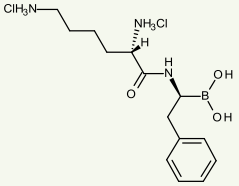
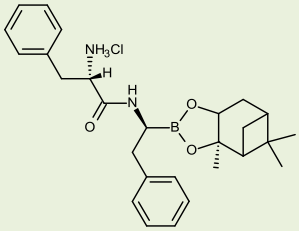
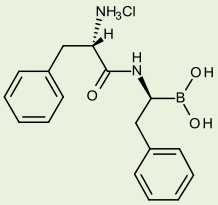
believed that incorporation of a fluorinated phenyl ring on the α-aminoboronate moiety would increase the antimicrobial activity.

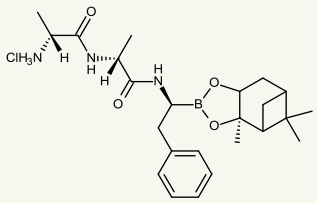
Table 3.36 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing a 4-F-phenyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

(-)-ester	(+)-ester	(-)-acid	(+)-acid
			
9.12 C. albicans ≈500/≈500 M. tuberculosis 500/500		13.12 M. tuberculosis ≈500/≈500	
			
10.36 M. tuberculosis 500/500		14.32 M. tuberculosis ≈50/≈50	

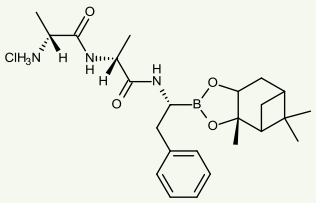
The introduction of a fluorine atom into a phenyl ring of α-aminoboronate moiety did not bring any improvements in antimicrobial and antifungal activities of α-aminoboronic peptides. They are still active at quite high concentration values (MIC 500 and 50 mg/L) therefore do not have large potential to be developed as antimicrobial and antifungal agents. After this unsuccessful attempt of introduction of a heteroatom into α-aminoboronate moiety another direction of its development has been chosen namely usage homologous series of a phenyl, *i.e.* benzyl, phenethyl.

Table 3.37 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing a benzyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

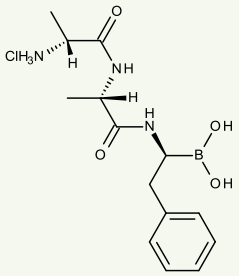
(-)-ester	(+)-ester	(-)-acid	(+)-acid
			
9.13 S. aureus ≈50/- M. tuberculosis 500/500	9.14 -/-	13.13 S. aureus 5/5 E. coli ≈500/- S. pyogenes 5/5	13.14 S. aureus -/500 M. tuberculosis 500/500
			
9.16 S. aureus -/≈5 S. pyogenes ≈500/- P. aeruginosa ≈500/- M. tuberculosis 500/-		13.16 S. pyogenes ≈500/- M. tuberculosis -/500	
			
9.15 E. coli 500/- C. albicans 500/≈500 M. tuberculosis ≈50/500		13.15 S. pyogenes ≈500/- M. tuberculosis 500/≈500	



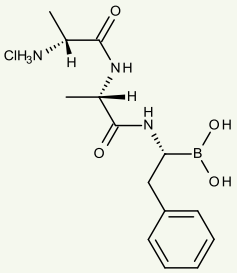
10.37
S. aureus 500/500
S. pyogenes 500/500



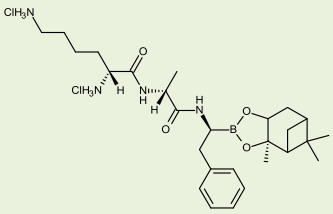
10.38
S. aureus -/≈500
P. aeruginosa 500/-
M. tuberculosis 500/500



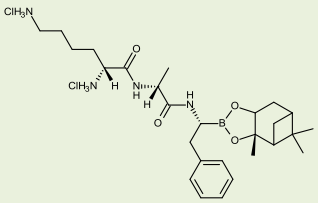
14.33
-/-



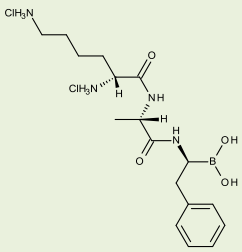
14.34
C. albicans ≈500/≈500



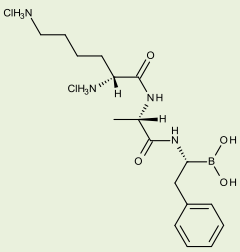
10.39
S. aureus ≈50/-
M. tuberculosis 500/500



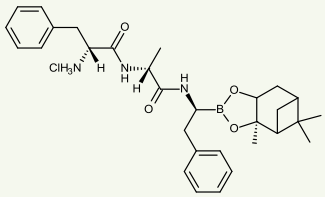
10.40
S. pyogenes ≈5/500
P. aeruginosa ≈500/-
C. albicans 500/500



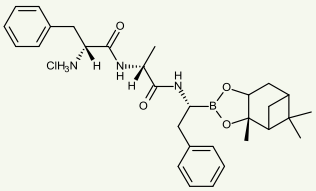
14.35
-/-



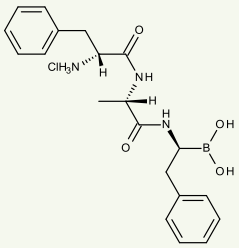
14.36
S. pyogenes 500/-
C. albicans 500/≈500



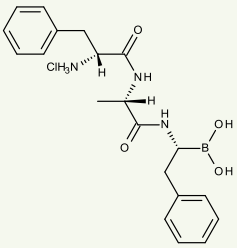
10.41
S. aureus 500/500
S. pyogenes 500/500
C. albicans 500/500
M. tuberculosis 500/500



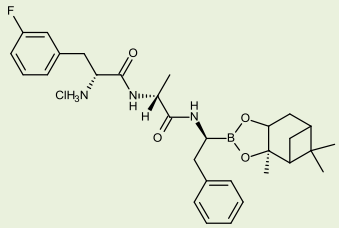
10.42
S. aureus 500/500
S. pyogenes 500/500
P. aeruginosa 500/-
C. albicans 500/500
M. tuberculosis 500/500



14.37
M. tuberculosis ≈5/≈5



14.38
C. albicans 500/500
M. tuberculosis 500/-

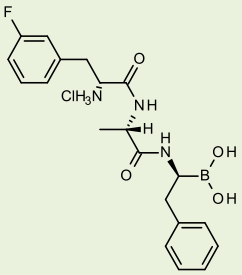


10.49

S. aureus 500/500

C. albicans ≈50/≈50

M. tuberculosis ≈50/≈50

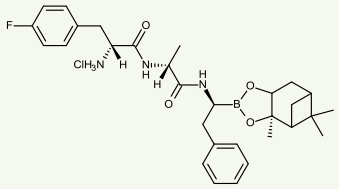


14.57

S. aureus ≈5/-

C. albicans 500/-

M. tuberculosis ≈50/500

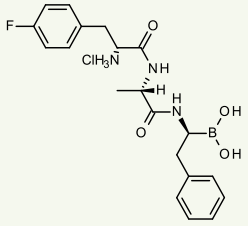


10.45

S. aureus 500/500

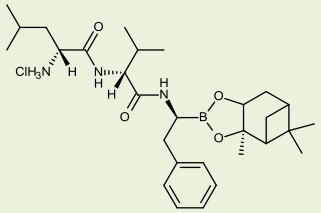
C. albicans ≈5/500

M. tuberculosis 500/≈50



14.56

M. tuberculosis 500/500



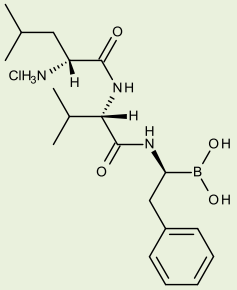
10.59

S. aureus 500/500

S. pyogenes 500/500

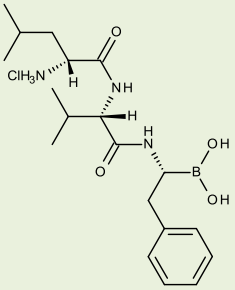
C. albicans 500/500

M. tuberculosis -/≈500



14.45

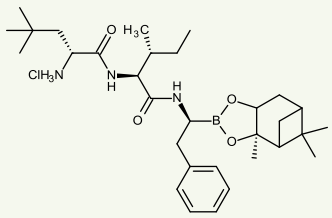
S. pyogenes 500/-



14.46

C. albicans -/50

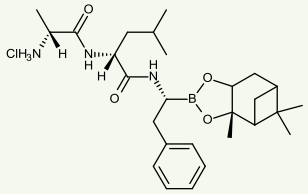
M. tuberculosis ≈500/≈500



10.52

C. albicans ≈500/≈500

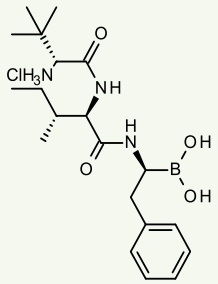
M. tuberculosis 500/500



10.58

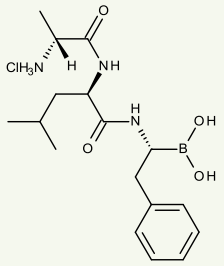
S. aureus 500/500

C. albicans 500/500



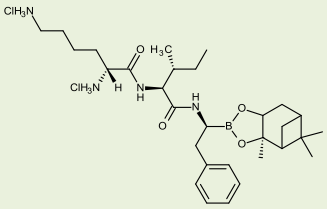
14.58

M. tuberculosis ≈500/≈500



14.40

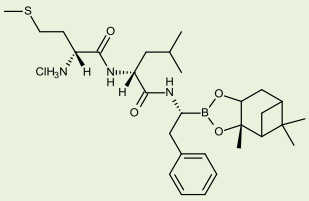
M. tuberculosis ≈500/50



10.55

C. albicans 500/500

M. tuberculosis ≈50/500

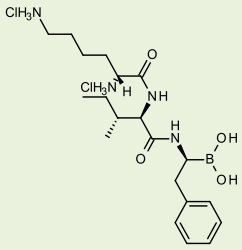


10.50

C. albicans -/≈50

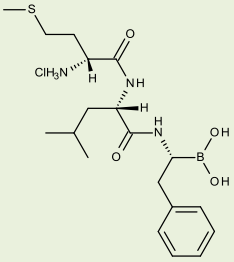
P. aeruginosa 500/-

M. tuberculosis 500/500



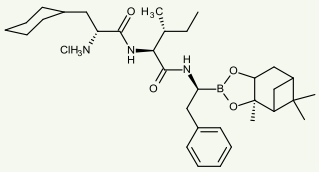
14.59

C. albicans ≈500/-



14.42

C. albicans ≈500/≈500

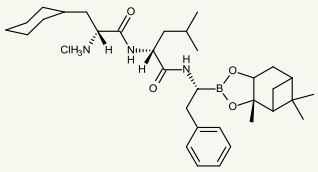


10.53

S. aureus 500/500

C. albicans ≈500/-

M. tuberculosis 50/50



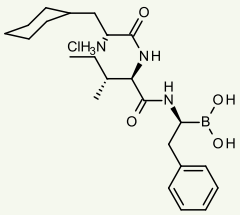
10.54

S. aureus 500/500

S. pyogenes 500/500

C. albicans -/500

M. tuberculosis ≈50/50

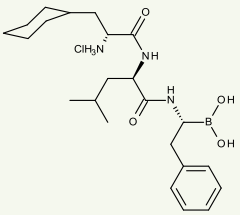


14.49

S. aureus 500/500

C. albicans -/≈500

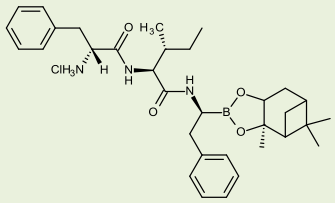
M. tuberculosis 500/500



14.50

C. albicans ≈500/50

M. tuberculosis ≈50/50

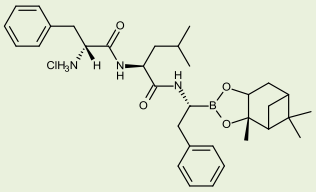


10.51

S. aureus 500/500

C. albicans 500/500

M. tuberculosis 500/500



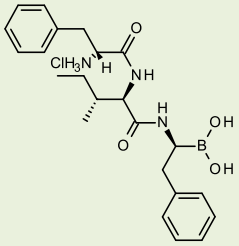
10.44

S. aureus 500/500

S. pyogenes -/≈500

C. albicans ≈500/500

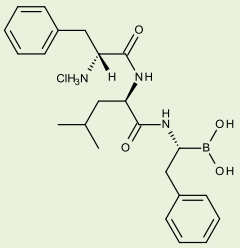
M. tuberculosis ≈500/500



14.51

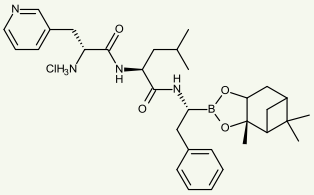
S. aureus 500/≈500

M. tuberculosis 500/500



14.52

M. tuberculosis ≈500/50



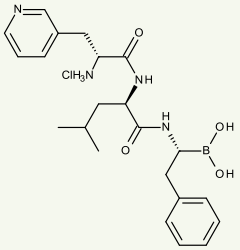
10.48

S. aureus 500/500

S. pyogenes 500/500

C. albicans ≈500/≈50

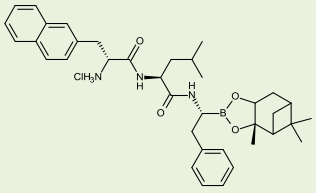
M. tuberculosis 500/500



14.44

C. albicans ≈500/≈500

M. tuberculosis ≈500/500



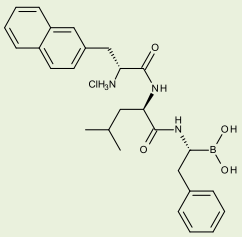
10.46

S. aureus ≈500/500

S. pyogenes ≈500/500

C. albicans -/≈50

M. tuberculosis -/50



14.48

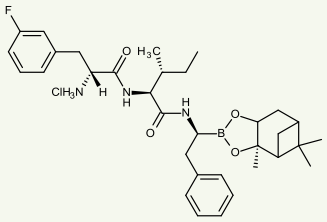
S. aureus 500/500

S. pyogenes 500/500

E. coli 500/500

C. albicans ≈500/≈500

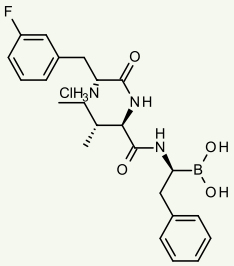
M. tuberculosis -/500



10.47

S. aureus 500/500

M. tuberculosis 50/50

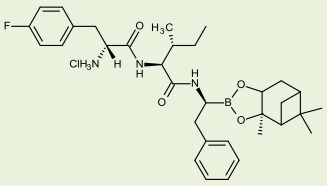


14.55

S. aureus 500/500

M. tuberculosis

≈50/≈50

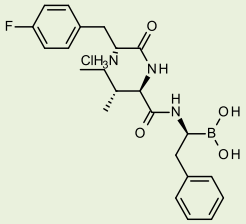


10.43

S. aureus 500/500

C. albicans 500/500

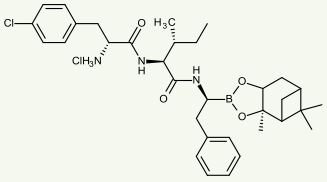
M. tuberculosis 50/≈50



14.54

M. tuberculosis

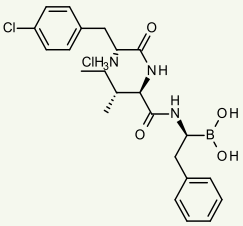
500/500



10.60

C. albicans ≈500/500

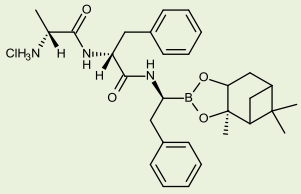
M. tuberculosis ≈50/≈50



14.53

M. tuberculosis

-/≈500



10.57

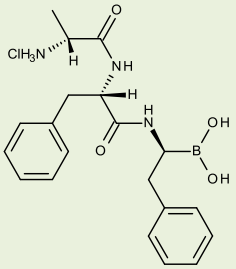
S. aureus -/≈500

E. coli ≈500/≈500

S. pyogenes 500/500

C. albicans 500/500

M. tuberculosis 500/500

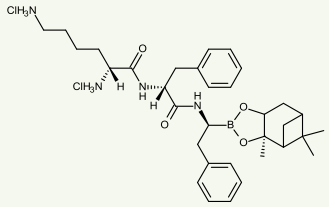
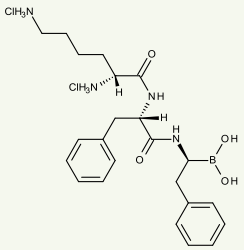
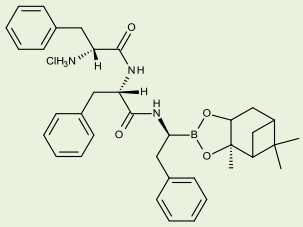
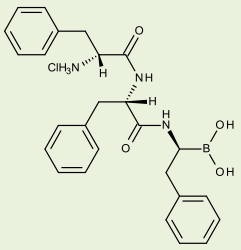
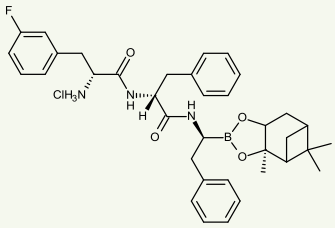
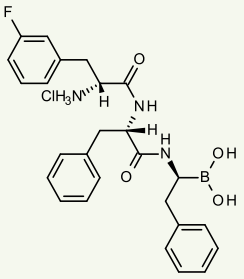


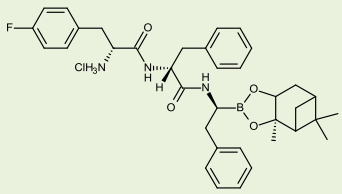
14.39

P. aeruginosa

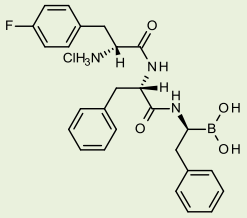
≈50/-

M. tuberculosis

	500/500
 10.56 S. aureus 500/500 S. pyogenes 500/500 E. coli 500/500 P. aeruginosa 500/- C. albicans 500/≈500 M. tuberculosis 500/500	 14.41 C. albicans ≈500/≈500 M. tuberculosis 500/500
 10.63 S. aureus -/≈50 S. pyogenes -/500 C. albicans ≈500/500 M. tuberculosis 500/≈500	 14.43 S. pyogenes 500/≈500 C. albicans ≈500/≈500 M. tuberculosis 50/500
 10.61 S. aureus -/≈500 C. albicans 500/500 M. tuberculosis 500/500	 14.60 S. aureus -/≈500 M. tuberculosis 500/≈500



10.62
P. aeruginosa ≈500/-
M. tuberculosis 500/500



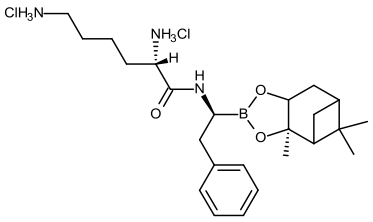
14.47
S. aureus 500/≈500
M. tuberculosis
500/≈500

Increasing the carbon chain of α-aminoboronate moiety by one CH_2 group (benzyl substituent) made it possible to obtain six new compounds active at MIC 5 mg/L though the majority are still active at quite high values (MIC 500 and 50 mg/L). Introduction of a fluorine atom into the molecule using fluorinated incoming amino acids has not led to any increase in activity. The antimicrobial activity of compounds **10.45** and **14.57** is determined by the amino acid sequence – alanine between two bulky groups, rather than the presence of fluorine (that will be discussed after the last table summarizing all the peptides active at MIC 5 mg/L).

Compound **14.37** is selectively active against *Mycobacterium tuberculosis* in a concentration of MIC 5 mg/L, but further investigations are needed in order to determine if the inverse dose-response relationship observed is an actual effect. Compounds **14.57, 9.16** and **13.13** are active against *Staphylococcus aureus* at a level of MIC 5 mg/L, so they possess a potential to be developed as antimicrobial treatment. Compounds **13.13** and **10.40** appear to be active against *Streptococcus pyogenes* as well (MIC 5 mg/L). Compound **10.45** is active against *Candida albicans* at a level of MIC 5 mg/L, but the result is uncertain so the peptide is needed to be investigated more widely as a potential antifungal.

Comparison some α-dipeptides with their β-analogues[7] revealed that the α-compounds are generally less active then the β-analogues, but the compound **9.16** is 100 times more active against *Staphylococcus aureus* than its β-analogue.

α-peptide



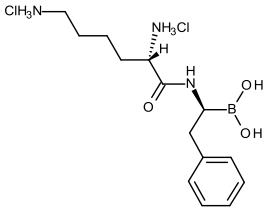
9.16

S. aureus -/≈5

S. pyogenes ≈500/-

P. aeruginosa ≈500/-

M. tuberculosis 500/-

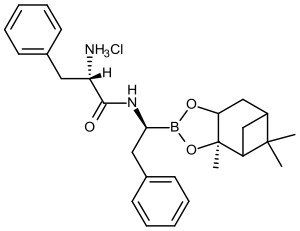


13.16

S. pyogenes ≈500/-

M. tuberculosis

-/500



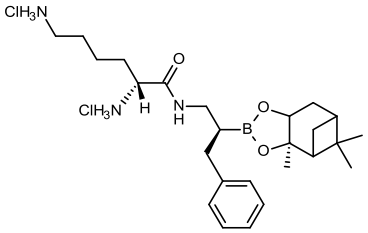
9.15

E. coli 500/-

C. albicans 500/≈500

M. tuberculosis ≈50/500

β-peptide

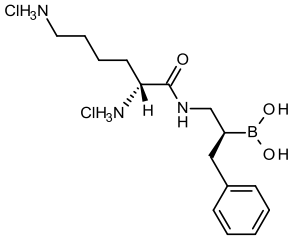


S.aureus 500/500

S.pyogenes 500/500

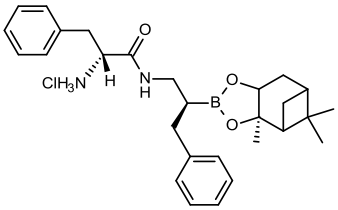
P.aeruginosa 500/500

M.tuberculosis 5/5



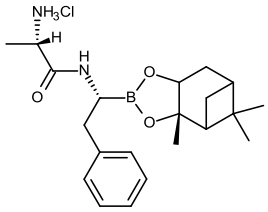
M. tuberculosis 5/5

(only anti TB activity has been reported in the paper)



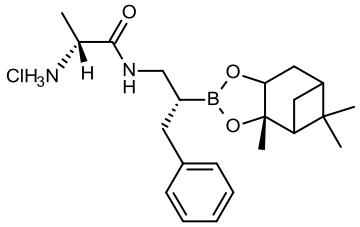
M. tuberculosis 5/50

(only anti TB activity has been reported in the paper)



9.14

-/-

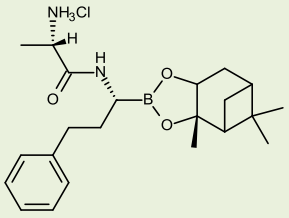
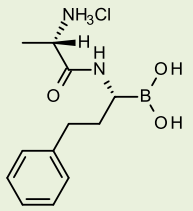


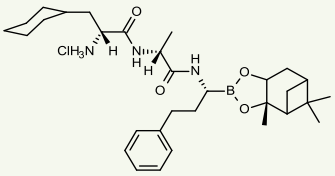
M. tuberculosis 50/500

(only anti TB activity has been reported in the paper)

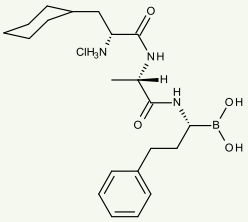
After the positive results obtained by increasing the size of the substituent at α-aminoboronate moiety (phenyl – benzyl) it was decided to continue these efforts by the introduction of one more –CH_2- group into the homologous series.

Table 3.38 Antimicrobial and antifungal activities of α-aminoboronic di- and tri- peptides containing a phenethyl substituent at α-aminoboronate moiety (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

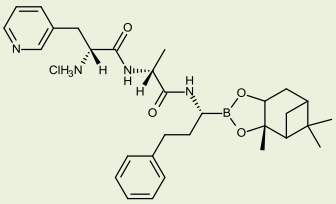
(-)-ester	(+)-ester	(-)-acid	(+)-acid
	 9.17 C. albicans ≈500/- M. tuberculosis 500/500		 13.17 C. albicans -/≈500 M. tuberculosis 500/≈500



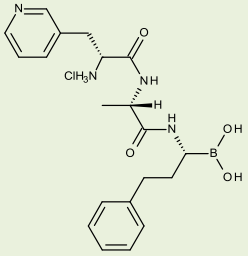
10.66
S. aureus ≈500/500
S. pyogenes ≈500/500
C. albicans -/≈50
M. tuberculosis ≈50/500



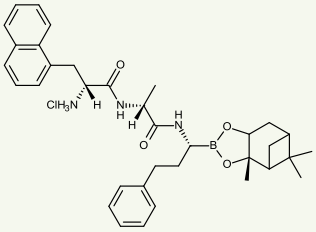
14.68
C. albicans ≈500/-
M. tuberculosis
500/500



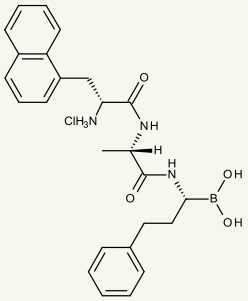
10.67
S. aureus 500/500
S. pyogenes 500/-
E. coli -/≈5
P. aeruginosa 500/-
C. albicans 500/≈50
M. tuberculosis
≈500/≈500



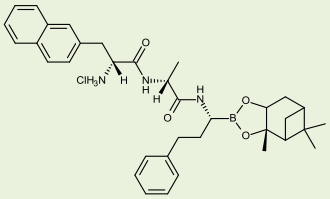
14.62
C. albicans 500/500



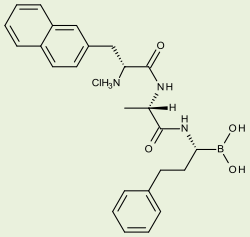
10.64
S. aureus ≈500/500
M. tuberculosis 500/500



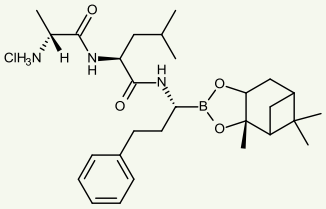
14.66
S. aureus 500/500
S. pyogenes 500/-
E. coli ≈50/-
C. albicans ≈500/-
M. tuberculosis
≈500/-



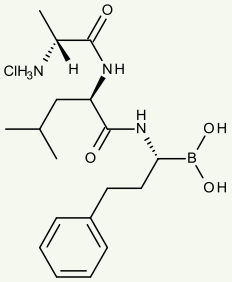
10.65
S. aureus -/500
S. pyogenes -/500
C. albicans -/500
M. tuberculosis ≈50/≈50



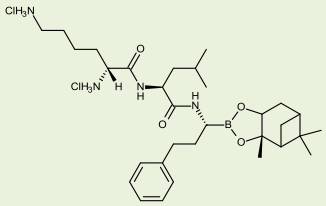
14.64
S. aureus ≈500/500
S. pyogenes ≈500/-
E. coli ≈500/-
P. aeruginosa ≈500/-
C. albicans ≈500/500
M. tuberculosis 500/500



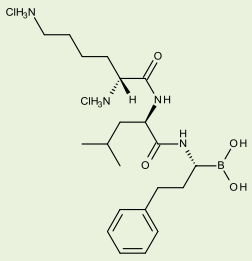
10.70
S. aureus 500/500
S. pyogenes ≈500/-
E. coli ≈500/-
C. albicans ≈500/500
M. tuberculosis 500/500



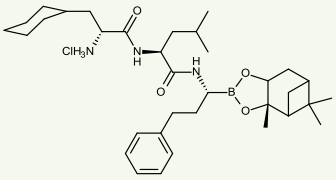
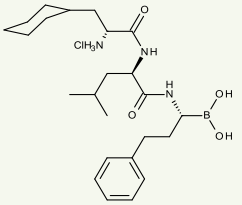
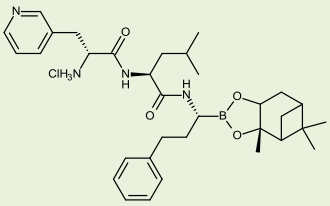
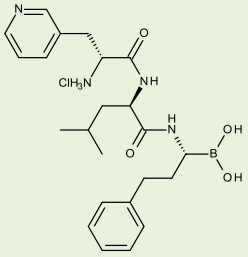
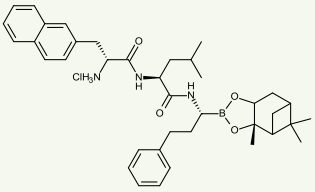
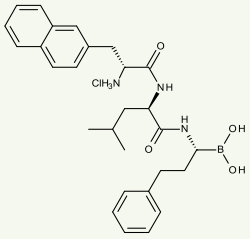
14.69
M. tuberculosis 500/500



10.71
S. aureus 500/500
S. pyogenes 500/500
E. coli 500/500
P. aeruginosa 500/500
C. albicans 500/500
M. tuberculosis 500/500



14.65
M. tuberculosis 500/500

	 10.69 S. aureus ≈50/50 S. pyogenes -/500 C. albicans -/≈500 M. tuberculosis ≈50/50	 14.67 S. aureus ≈500/500 S. pyogenes ≈500/500 E. coli ≈500/- C. albicans ≈500/500 M. tuberculosis ≈500/500
	 10.72 S. pyogenes ≈500/500 C. albicans ≈500/- M. tuberculosis 500/50	 14.61 M. tuberculosis 500/500
	 10.68 S. aureus ≈50/50 C. albicans -/≈500 M. tuberculosis ≈500/500	 14.63 C. albicans ≈500/- M. tuberculosis ≈50/50

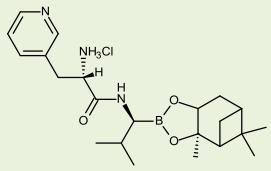
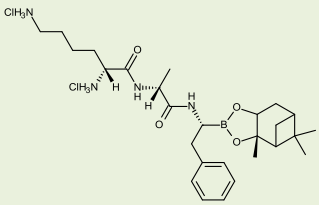
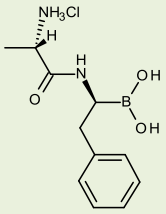
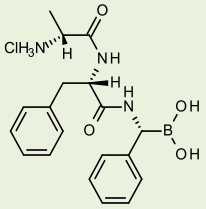
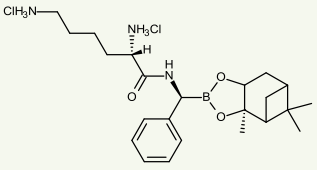
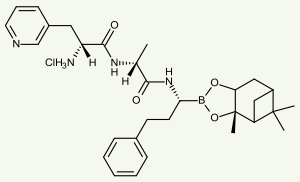
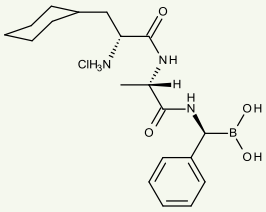
Increasing the carbon chain of α-aminoboronate moiety by two CH_2 groups (phenethyl substituent) did not lead to any improvements of the activity values. The majority of the library of peptides containing a phenethyl substituent at α-aminoboronate moiety

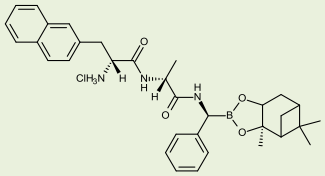
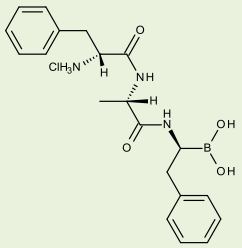
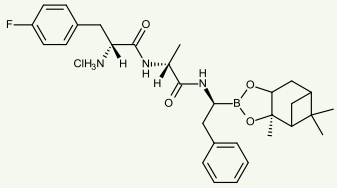
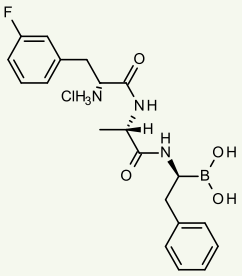
possesses antimicrobial and antifungal activity at quite high values (MIC 500 and 50 mg/L) therefore they have very poor potential to be developed as antimicrobial and antifungal agents.

Only the compound **10.67** has an activity against *Escherichia coli* at MIC 5 mg/L, but it seems to be uncertain and needed further investigation.

All the α-aminoboronic peptides active at MIC 5 mg/L are summarized in the following table.

Table 3.39 α-Aminoboronic peptides possessing antimicrobial and antifungal activities at MIC 5 mg/L (liquid/solid media).

(-)-ester	(+)-ester	(-)-acid	(+)-acid
 9.8 S. aureus 500/500 S. pyogenes -/≈500 P. aeruginosa-/≈5 M. tuberculosis ≈500/-	 10.40 S. pyogenes ≈5/500 P. aeruginosa ≈500/- C. albicans 500/500	 13.13 S. aureus 5/5 E. coli ≈500/- S. pyogenes 5/5	 14.19 S. aureus -/5 C. albicans ≈500/≈5 M. tuberculosis 500/500
 9.11 M. tuberculosis ≈5/500	 10.67 S. aureus 500/500 S. pyogenes 500/- E. coli -/≈5 P. aeruginosa 500/- C. albicans 500/≈50 M. tuberculosis	 14.28 C. albicans -/≈5 M. tuberculosis 500/-	

≈500/≈500	
 10.29 S. aureus 500/500 E. coli 500/≈500 S. pyogenes 500/500 C. albicans ≈500/≈5 M. tuberculosis ≈500/50	 14.37 M. tuberculosis ≈5/≈5
 10.45 S. aureus 500/500 C. albicans ≈5/500 M. tuberculosis 500/≈50	 14.57 S. aureus ≈5/- C. albicans 500/- M. tuberculosis ≈50/500

Conclusively, most active peptides (at 5 mg/L) displayed above are derived from (-)-pinanediol boronates (columns 1 and 3), the opposite configuration of α-chiral carbon lacks antimicrobial and antifungal activity.

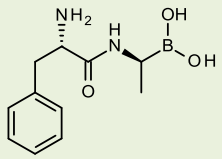
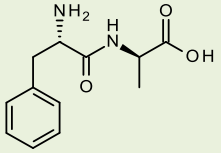
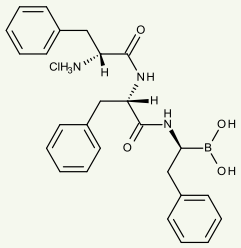
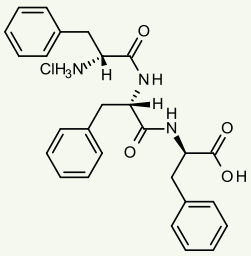
It seems that a phenyl ring must be present in the molecule since all the peptides contain it on the α-aminoboronate moiety (with an exception of compound **9.8**) as well as L-amino acids contain a phenyl ring (heteroaromatic ring **9.8, 10.67** or substituted phenyl ring **10.45, 14.57**) that does not contradict previously described data for ordinary analogues.[1,3]

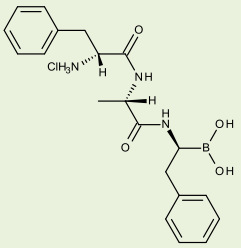
All the active dipeptides (**9.11, 9.8** and **13.13**) are consist of a phenyl ring and an aliphatic moiety, therefore for the future screening all the possible variations of these have to be examined.

L-Alanine is present in all the structures of the tripeptides as a second amino acid (bonded to α-aminoboronate moiety) with the exception of **14.19** where L-alanine is a third one. Generally, most of the tripeptides hold L-alanine between two phenyl containing components, so further investigation has to be conducted in this area of structures.

There was only one question left in the investigation of antimicrobial and antifungal activities of boron containing peptides – what is the role of boron atom in the molecule? It was found by the comparison of biological activity of α-aminoboronic peptides with their amino acid analogues.

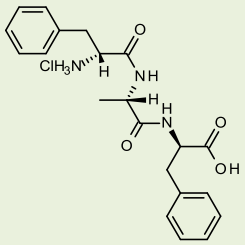
Table 3.40 Antimicrobial and antifungal activities of α-aminoboronic peptides in comparison with their amino acid analogues (concentration of compound tested – 500 mg/L, 50 mg/L, 5 mg/L; liquid/solid media).

Boron-containing peptide	Amino acid analogue*
 13.3 S. aureus 500/≈500 M. tuberculosis 50/50	 -/-
 14.43 S. pyogenes 500/≈500 C. albicans ≈500/≈500 M. tuberculosis 50/500	 C. albicans ≈500/- P. aeruginosa ≈500/-



14.37

M. tuberculosis ≈5/≈5



C. albicans 500/500

M. tuberculosis 500/500

*Amino acid peptides have been purchased from Shanghai Mocell Biotech Co.,Ltd. and used as received.

These results revealed that the antimicrobial (especially antimycobacterial) activity of α-aminoboronic peptides is highly dependent on the nature of acid residue, more specifically, by the type of atom directly bonded to the α-chiral carbon.

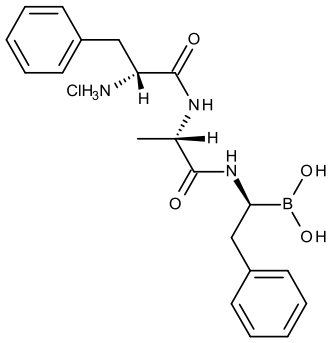
Generally, the antimycobacterial activity of boron containing compounds is higher, for example, compound **14.37** is very selectively active against TB at MIC 5 mg/L whereas its ordinary analogue possesses antitubercular activity at MIC 500 mg/L with falling of selectivity, therefore boron containing peptides should be prioritized compare to ordinary ones in anti TB drug development area.

3.3.2. Enzyme-Catalyzed Conversion of Chorismate to Prephenate

During this study other scientists were interested in our peptides in order to investigate them in other fields of chemistry, for example, in conversion of chorismate to prephenate which is the key step in the biosynthetic route leading to phenylalanine and tyrosine in bacteria and other organisms. This conversion is catalyzed by a special enzyme called chorismate mutase, which has been found only in bacteria, fungi and higher plants, and is absent in mammals. This makes chorismate mutase a promising target for the creation of new herbicides and anti-bacterial/anti-fungal products. Furthermore, some of the structural peculiarities of chorismate mutase allow developing of unique inhibitors targeted to specific microorganisms, for example, *Mycobacterium tuberculosis.*

Since some of the α-aminoboronic peptides possess antitubercular activity it was decided to investigate binding to and stabilization of the secreted chorismate mutase by one of them. This was performed applying the Thermofluor assay (Fluorescence Thermal Shift Assay or Temperature dependent Fluorescence) that is a fast and easy method which provides a fluorescence measurement of thermally-induced protein melting. The temperature when protein melts is a measure of protein stability.

The following α-aminoboronic peptide showing antitubercular activity at 5 mg/L was tested:



The experiment has been carried out by **Steffi Munack** a PhD-student from the Department of Chemistry, University in Oslo.

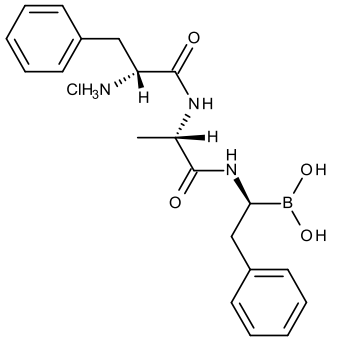
The compound have not turned out to be very active in this conversion, so it might be concluded that the secreted chorismate mutase is not the best target for α-aminoboronic peptides.

3.3.3. Cytotoxicity Investigation

Cytotoxicity is a compound's ability of being poisonous to cells. Therefore it is a subject of a broad pharmaceutical study in the area of cancer research. Compound with a low toxicity level to a healthy cells and poisoning cancer cells is a major goal of medicinal chemists.

In the case of this investigation however it was important to discover a low level of cytotoxicity of synthesized peptides so as they are potential antitubercular drugs.

The cytotoxicity of α-aminoboronic peptide showing antitubercular activity at 5 mg/L (the same compound as in the previous sub-chapter) has been measured by **Cyprotex Discovery Ltd.**



No significant respond was observed at any of the cell health parameters measured, for the concentration range tested (Assay summary and cell health parameters have mostly been copied from Cyprotex report and placed in Experimental Part).

So the tested α-aminoboronic peptide does not possess any toxic properties that can be considered positive for this particular study since the compound is a potential antitubercular agent.

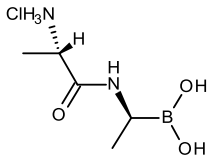
3.3.4. Protein Kinase Inhibitor Activity

As was discussed in Introduction small boron containing molecules/peptides are very promising targets as kinase inhibitors, therefore knowledge of kinase inhibition activity of α-aminoboronic peptides was very important to us because many kinases have been found to be deeply involved in the processes leading to tumour cell growth. Therefore if α-aminoboronic peptides have appeared to be successful kinase inhibitors, a new project connected with anticancer drug development could have been initiated, otherwise α-aminoboronic peptides can be classified as antimicrobial agents does not affecting any kinases.

The kinase inhibitory activity of fifteen α-aminoboronic peptides (at conc. 100 μM) has been investigated by **International Centre for Kinase Profiling**. All the data are

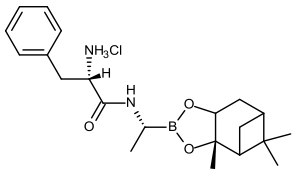
summarized in two tables and can be found in Experimental Part, as well as abbreviation expansion of the list of kinases that have been investigated.

Short summary of kinase activity of tested peptides is placed below.



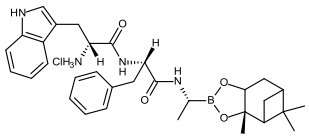
13.1
S. aureus 500/500
E. coli ≈500/500
E. faecalis 500/-
M. tuberculosis 50/50

Compound **13.1** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. IKKe (158%), ERK2 (152%).



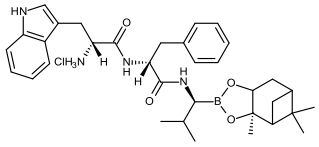
9.3
S. aureus ≈500/-
E. coli ≈500/-
C. albicans ≈500/-
M. tuberculosis ≈500/500

Compound **9.3** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases e.g. ERK2 (151%), IKKe (139%), p38g MAPK (133%), MNK1 (133%) and BTK (146%).



10.4
S. aureus 500/500
S. pyogenes ≈50/≈500
M. tuberculosis ≈500/≈500

Compound **10.4** selectively inhibits MAPKAP-K3 (40%) and CAMK1 (47%) kinases, but also works as a promoter of several kinases ERK2 (140%), p38g MAPK (161%) etc.

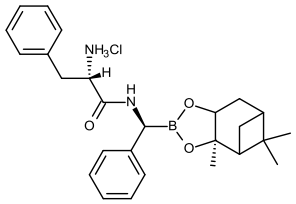


10.19

Compound **10.19** turned to be one of the best kinase inhibitor out of the all set of peptides. It successfully inihibits the following targets: PKBb (28%), SGK1 (30%), S6K1 (39%), MAPKAP-K3 (38%), CAMK1 (29%), SmMLCK (23%), CHK2 (48%), DYRK1A (39%), NEK6

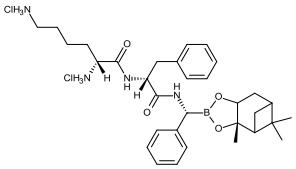
S. aureus 500/500
S. pyogenes ≈500/500
C. albicans 500/≈50
M. tuberculosis -/≈500

(45%), CLK2 (42%), EF2K (48%), SYK (36%), BTK (26%), TrkA (47%), VEG-FR (48%), but on the other hand it promotes very well e.g. ERK2 (129%), p38g MAPK (147%), Src (165%), ZAP70 (150%) and EPH-B1(140%).



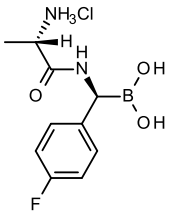
9.10
S. aureus 500/-
S. pyogenes 500/-
M. tuberculosis ≈500/500

Compound **9.10** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (142%), p38g MAPK (150%), Src (131%), ZAP70 (121%).



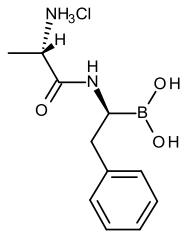
10.26
S. aureus 500/-
E. coli 500/-
S. pyogenes 500/-
C. albicans 500/500
P. aeruginosa ≈500/-
M. tuberculosis ≈50/500

Compound **10.26** selectively inhibits S6K1 (43%) and EF2K (49%) kinases, but also works as a promoter of several kinases e.g. ERK2 (156%), p38g MAPK (150%), Src (128%).



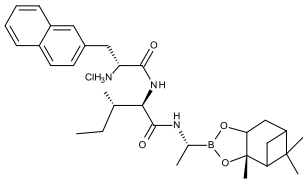
13.12
M. tuberculosis ≈500/≈500

Compound **13.12** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (143%), p38g MAPK (151%).



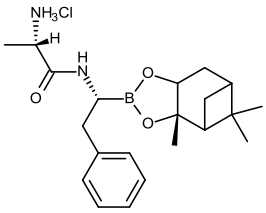
13.13
S. aureus 5/5
E. coli ≈500/-
S. pyogenes 5/5

Compound **13.13** selectively inhibits CK2 (32%) kinase, but also works as a promoter of several kinases e.g. ERK2 (161%), p38g MAPK (133%).
Therefore this compound can be investigated furher as antimicrobial, but its kinase inhibitor/promoter properties must be taken on account.



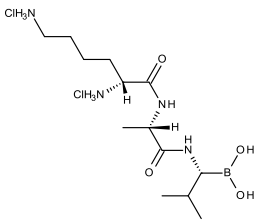
10.5
S. aureus 500/500
S. pyogenes 500/500
C. albicans ≈500/500
M. tuberculosis -/500

Compound **10.5** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (147%), p38g MAPK (136%), PHK (134%), IKKe (147%), Src (124%)



9.14
-/-

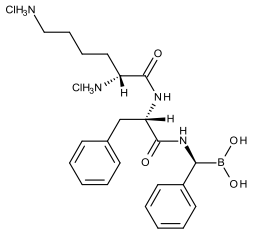
Compound **9.14** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (150%), p38g MAPK (140%), Src (136%).



14.9
C. albicans 50/50

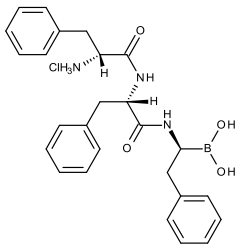
Compound **14.9** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (143%), p38g MAPK (147%), BTK (130%).

M. tuberculosis 500/-



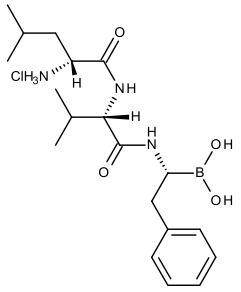
Compound **14.20** selectively inhibits S6K1 (49%), CAMK1 (12%) and EF2K (38%) kinases, but also works as a promoter of several kinases e.g. ERK2 (134%), p38g MAPK (164%), MNK1(133%) and Src (143%).

14.20
S. aureus 500/500
E. coli 500/500
S. pyogenes 500/500
C. albicans ≈500/-
P. aeruginosa 500/≈500
M. tuberculosis 500/500



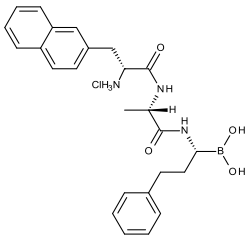
Compound **14.43** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (153%), p38g MAPK (141%).

14.43
S. pyogenes 500/≈500
C. albicans ≈500/≈500
M. tuberculosis 50/500



Compound **14.46** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (145%), p38g MAPK (155%), Src (122%), BTK (136%), VEG-FR (126%).

14.46
C. albicans -/50
M. tuberculosis ≈500/≈500



14.64
S. aureus ≈500/500
S. pyogenes ≈500/-
E. coli ≈500/-
P. aeruginosa ≈500/-
C. albicans ≈500/500
M. tuberculosis 500/500

Compound **14.64** does not possess any significant activity as kinase inhibitor, but is able to promote some of kinases, e.g. ERK2 (154%), p38g MAPK (180%), Src (135%).

Conclusively, α-aminoboronic peptides can be utilized either as inhibitors or promoters of different kinase types. Kinases ERK2, p38g MAPK, PKCa, MNK1 and Src are succesfully promoted by all tested compounds up to 180% of inhibition, that may be useful in gene therapy.*

All the tested peptides promote different types of kinase in a varying degree, so future screening for the new kinase promoters should be carried out in the direction of increasing of selectivity.

Several kinase inhibitors have arisen in this investigation, thus compound **10.19** inhibit the greatest amount of targets (15 different kinases out of 139 tested), and so it can be considered as potential kinase inhibitor, but the lack of selectivity must be kept in the mind. The most successful kinase inhibitor (the lowest % of inhibition) is compound **14.20** which inhibits S6K1 (49%), CAMK1 (12%) and EF2K (38%) kinases. It also possess high level of selectivity since it targets only 3 kinase types out of 139 tested. Compound **13.13** is the most selective kinase inhibitor that target only one kinase type CK2 with quite low level of inhibition (32%).

Therefore, the further screening for new kinase inhibitors among α-aminoboronic peptides should be carried out based on structures of peptides listed above. The structures of

new potential kinase inhibitors definitely should contain a phenyl ring or condensed heteroaromatic rings (tryptophan in the structures of peptides **10.19** and **10.4**), whereas condensed aromatic rings (naphthyl substituent in the compounds **10.5** and **14.64**) do not provide any inhibitor activity of the structure. Most of the kinase inhibitors derived from (-)-α-aminoboronates and represented as free boronic acids and pinanediol esters as well.

*Gene therapy treats various gene disorders by substituting defective genes by normal ones. The main challenge of the therapy is gene introduction efficiency that might be achieved by improving the kinase promoter.[5,6]

3.3.5. Experimental Part

Antibacterial Activity Investigation

Materials and methods (this part of the chapter has been copied from our collaborators report)

Bacterial strains: *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *Streptococcus pyogenes* (ATCC 19615), *Candida ablicans* (ATCC 90028), and *Mycobacterium tuberculosis* (H37RW).

Medium and culture conditions: The liquid media used for bacterial growth were Luria-Bertani (Becton Dickinson, Sparks, MD) and Mueller-Hinton (bio-Merieux, Paris, France) broths, medium Saburo for Candida and N1 for mycobacteria. The strains were grown at 37°C, and liquid cultures were incubated without shaking. Before use in the biofilm experiments, the cells were harvested and washed twice with 0.15M isotonic phosphate buffer (pH 7.2), and the cell suspensions were standardized to an optical density at 520 nm of 0.8.

Cultivation in the presence of compound tested - 24 h at 37°C.

Concentration of compound tested – 500 mg/L; 50 mg/L; 5 mg/L.

CFU (Colony forming units) assay. Total number of CFU was determined by the serial dilution method in tubes – 2 times and plates (1 time) and plating on the appropriate solid media.

Results of these 3 repeats (middle value) were summarized in the tables in corresponding sub-chapter.

Enzyme-Catalyzed Conversion of Chorismate to Prephenate

The investigated compound was subjected to a thermal shift assay, determining the shift of the melting points Tm of the secreted chorismate mutase (*MtCM) and the internal chorismate mutase (MtCM) of *Mycobacterium tuberculosis.* The final protein concentration

in the assay is 0.5 mg/ml (*MtCM = 27 µM, MtCM = 49.6 µM). The peptide was dissolved in DMSO to a concentration of 200 mM and used in the assay at a final concentration of 8 mM. SYPRO® Orange (sigma Aldrich) was used as fluorescent dye for the readout. The experiments were performed on a LightCycler® 480 real time PCR machine from Roche in a volume of 25 µl in 384 well plates heating up the plate from 20 to 95°C. The melting curve determinations were undertaken in triplicates. Furthermore, interactions of the compound with the dye or the protein alone were investigated in order to rule out false positives or negatives. For *MtCM the transition state analogue (TSA) of the reaction could be used as reference compound.

Reaction conditions:

*MtCM: 0.5 mg/ml C-terminally His-tagged *MtCM, Sypro Orange 1:1000, 100 mM Potassium Phosphate buffer pH 7.5, 150 mM NaCl, 8 mM compound.

MtCM: 0.5 mg/ml MtCM, Sypro Orange 1:1000, 100 mM bicine buffer pH 9.0, 150 mM NaCl, 8 mM compound.

Results *MtCM:

The tested compound shows a slight shift in the melting temperature Tm (Δ Tm = + 3.1 K), which is not considered as a hit at these high concentrations of 8 mM in the assay setup (cf. TSA, final concentration in sample: 0.6 mM, Δ Tm = 9.3 K).

Results MtCM:

The compound seems to slightly destabilize the protein, leading to negative shifts in Tm. This could be interesting in case the compound would not address the active site of the protein, but have other allosteric binding sites. Unfortunately, those negative shifts are mostly inconclusive. From experience, compounds giving those results in thermal shift assays are not active.

Enzyme assay

*MtCM stop assay

Initial rate of the enzyme-catalyzed conversion of chorismate to prephenate was determined. Reaction was carried out in a volume of 500 µl in 50 mM Potassium phosphate buffer, pH 7.5, 100 µM chorismate, 3 nM *MtCM and stabilization additives. The peptide was dissolved in DMSO to 12 mM, added to the assay solutions (120 µM final concentration in the assay) and incubated at 30 °C in a Eppendorf thermomixer comfort at 550 rpm. The reaction was stopped after 3.5, 6.5 and 10 min, respectively, by addition of 50 µl 5 M HCl and incubation was continued at 30 °C in order to convert prephenate to phenylpyruvic acid. Thereafter, 50 µl 10 M NaOH were added to deprotonate the acid to phenylpyruvate. With that method, the formation of prephenate could be recorded by absorption measurements at 320 nm. Blank absorbance from samples at 0 min incubation was prepared for subtraction from the absorbance measured for the enzyme activity determination. The initial rate was determined from the slope of the resulting graph (A320nm against time) and this was always corrected for the spontaneous background reaction at 30 °C. The resulting initial rate, vinit. [s-1], was compared to the reaction without compound present and the reaction performed in presence of the transition state analogue of the enzymatic reaction, the best inhibitor known to date for *MtCM (final concentration in assay: 11.1 µM, Ki = 3.7 µM [1], vinit. = 4.07 ± 0.27 s-1, 31 ± 1.2 % residual activity). The result shows that the tested compound has no inhibitory effect against *MtCM, the slight enhanced residual activity that occurs in some cases might be due to systematic errors. **(The experimental part has been copied from Steffi Munack report).**

Cytotoxicity Investigation

Cytotoxicity Screening Panel CYP0590-R1A has been used. Multiparametric approach using High Content Screening (HCS) was employed as well.

Assay Summary	
Incubation time	72h
Concentrations (µM)	0.04, 0.1, 0.4, 1.0, 4.0, 10, 40, 100

Replicates per concentration	3
Cell line	HepG2

Several cell health parameters have been measured:

Cell count: a decreasing number of cells indicate toxicity due to necrosis (loosing of membrane integrity), apoptosis (the process of programmed cell death) or reduction in cellular proliferation.

Nuclear area: An increase of nuclear size can indicate necrosis and decrease can indicate apoptosis.

DNA structure: An increase in DNA structure can indicate DNA fragmentation and chromosomal instability.

Cell membrane permeability: An increase in cell membrane permeability is a general indicator of cell death.

Mitochondrial mass: A decrease in mitochondrial mass indicates loss of total mitochondria and an increase implies mitochondrial swelling or an adaptive response to cellular energy demands.

Mitochondrial membrane potential: A decrease indicates a loss of mitochondrial membrane potential and mitochondrial toxicity, increase in mitochondrial membrane potential indicates an adaptive response to cellular energy demands.

Cytochrome c release: An increase in cytochrome c release is one of the hallmarks of the apoptosis signaling cascade.

Protein Kinase Inhibitor Activity

All the results are placed in two tables. There are two columns below each compound number, first (indicated by bold font) represents % of inhibitory activity and a second column is a standard deviation of assay duplicates (not very valuable data for a preliminary

discussion). Values below 50% (marked by red color) stand for relatively successful kinase inhibition, whereas compounds with value higher 100% (marked by dark blue color) might be considered as kinase promoters.

Table 3.41 Kinase inhibitory activitiy of α-aminoboronic peptides. (part 1)

Plate Barcode	13.1		9.3		10.4		10.19		9.10		10.26		13.12		13.13	
MKK1	114	43	89	5	82	11	75	9	86	6	80	2	87	5	89	12
MKK2	103	8	92	2	90	16	86	7	88	1	98	10	104	13	108	5
MKK6	81	5	87	2	75	5	97	11	87	3	84	10	87	8	84	8
ERK1	83	0	83	3	82	10	90	9	82	13	75	5	87	4	76	5
ERK2	152	11	151	3	140	3	129	2	142	2	156	4	143	16	161	21
ERK5	98	7	100	6	92	12	90	4	87	8	80	4	82	10	94	16
JNK1	93	2	100	7	95	4	94	6	94	2	83	4	99	4	88	2
JNK2	96	6	107	6	92	6	99	5	102	10	92	1	102	1	107	2
JNK3	79	2	85	10	88	17	104	10	82	13	91	6	84	12	92	7
p38a MAPK	92	0	97	10	79	5	74	0	90	1	89	6	94	2	104	5
p38b MAPK	113	38	104	5	91	8	73	8	89	4	83	1	102	8	88	4
p38g MAPK	118	3	133	32	161	18	147	19	150	5	150	3	151	10	133	26
p38d MAPK	96	1	108	6	108	4	113	20	115	17	109	6	123	20	112	8
ERK8	78	15	99	22	84	8	85	5	90	2	94	21	96	4	116	18
RSK1	92	9	91	7	89	2	77	2	90	12	87	2	78	3	81	7
RSK2	107	6	105	16	58	8	51	1	59	8	64	5	79	7	84	17
PDK1	86	10	91	0	95	8	96	2	100	1	96	1	102	2	95	0
PKBa	98	8	104	5	81	5	70	8	100	3	97	11	105	3	101	4
PKBb	118	10	114	7	56	7	28	6	96	1	90	8	116	13	129	5
SGK1	96	1	94	5	60	4	30	14	78	3	72	11	88	5	94	12
S6K1	78	7	97	3	61	6	39	1	80	14	43	4	83	12	92	2
PKA	85	5	91	7	87	8	80	4	93	7	85	3	91	4	93	13
ROCK 2	93	3	91	1	91	2	85	6	96	7	89	2	90	3	101	16

PRK2	101	7	103	14	105	13	80	5	101	7	95	7	94	3	96	13
PKCa	105	8	102	18	104	12	114	13	107	19	107	18	97	24	92	7
PKCγ	91	4	98	5	73	11	65	8	100	2	105	9	94	3	93	6
PKCz	88	26	112	3	108	4	111	14	109	12	104	14	113	6	108	11
PKD1	81	6	77	1	77	7	70	3	84	3	92	4	107	3	100	1
STK33	103	1	109	6	97	9	104	2	102	5	100	1	95	5	89	4
MSK1	96	0	108	9	63	1	51	1	66	3	54	0	99	5	96	6
MNK1	101	5	133	9	125	14	104	10	107	8	105	3	114	10	119	5
MNK2	110	15	107	23	100	18	100	15	84	11	101	14	87	4	95	19
MAPKAP-K2	100	11	103	3	96	8	103	0	96	0	89	3	102	2	94	4
MAPKAP-K3	75	6	87	0	40	3	38	2	61	9	72	1	76	3	87	4
PRAK	90	5	89	6	104	3	76	5	86	2	84	4	88	2	97	10
CAMKKb	94	1	101	4	73	4	64	1	80	5	75	6	98	2	94	6
CAMK1	104	4	106	3	47	2	29	15	62	2	64	0	103	0	107	1
SmMLCK	76	1	95	3	58	7	23	3	58	12	57	10	89	8	84	8
PHK	122	4	126	14	120	9	109	1	107	1	108	9	106	7	111	7
DAPK1	91	3	86	8	69	2	61	8	81	8	85	0	87	13	94	8
CHK1	96	2	99	5	81	5	82	0	84	0	78	7	100	1	96	8
CHK2	80	10	105	5	84	3	48	8	85	1	79	4	91	3	87	4
GSK3b	72	6	94	6	75	5	70	2	68	6	67	6	99	5	75	10
CDK2-Cyclin A	84	6	91	4	90	1	86	4	77	4	89	1	96	0	96	2
CDK9-Cyclin T1	72	1	98	8	67	2	87	21	81	2	74	15	89	8	84	14
PLK1	80	23	113	9	104	19	79	9	76	12	80	9	92	8	92	0
Aurora A	97	16	108	19	106	9	110	5	112	13	120	4	123	11	117	10
Aurora B	115	10	109	9	87	0	104	22	106	11	122	4	107	5	121	22
TLK1	96	16	92	28	98	19	98	4	97	6	105	12	88	11	96	12
LKB1	106	2	102	4	86	2	97	11	90	8	91	6	90	1	92	4
AMPK	94	6	97	4	82	4	102	13	91	8	116	24	90	1	104	8
AMPK (hum)	96	10	104	4	119	2	99	2	101	7	99	2	92	10	104	2
MARK1	96	7	85	3	95	8	81	4	77	2	91	6	81	10	90	1

MARK2	93	1	86	1	78	1	82	0	79	3	91	3	96	3	86	12
MARK3	84	5	85	16	75	7	77	10	81	4	90	8	86	4	81	8
MARK4	100	14	104	8	81	13	78	43	90	9	98	11	112	10	108	6
BRSK1	94	13	88	5	79	6	67	9	84	5	80	0	90	0	93	2
BRSK2	91	16	98	14	73	2	72	4	70	2	75	5	91	2	104	13
MELK	100	14	110	6	115	9	93	8	94	4	91	0	88	4	99	7
NUAK1	104	16	107	2	118	4	115	11	113	3	107	3	100	9	103	3
SIK2	86	2	94	3	77	5	75	7	75	9	76	2	93	4	101	1
SIK3	107	1	103	13	101	10	102	2	115	4	105	15	126	6	120	19
TSSK1	52	8	91	25	78	8	76	1	74	8	82	4	86	12	82	16
CK1γ2	97	4	109	16	85	12	100	15	89	6	87	0	96	11	102	6
CK1δ	100	11	98	1	91	21	95	9	93	1	96	7	98	4	99	1
CK2	104	13	96	19	99	3	87	4	101	3	96	5	105	5	32	5
TTBK1	86	8	96	3	94	9	83	8	104	8	92	7	99	2	94	17
TTBK2	119	20	105	0	99	15	93	9	94	7	93	3	103	17	91	1
DYRK1A	92	2	90	6	58	5	39	13	68	7	76	10	88	4	97	1
DYRK2	92	3	97	6	93	21	84	7	85	9	93	3	97	12	100	10
DYRK3	86	1	95	8	87	8	83	15	104	6	99	1	110	9	99	9
NEK2a	91	1	98	2	105	12	104	2	92	7	86	9	87	7	93	2
NEK6	102	11	105	15	77	25	45	27	80	28	79	1	93	5	106	25
IKKb	87	2	82	1	77	2	51	6	85	4	87	7	90	6	106	3
IKKe	158	9	139	22	114	9	94	21	120	5	115	2	92	18	101	7
TBK1	85	2	97	4	112	19	96	10	88	5	96	8	97	1	94	1
PIM1	105	6	94	3	73	7	53	2	70	2	85	10	96	8	98	13
PIM2	95	4	102	13	77	1	81	11	91	5	94	8	98	6	98	4
PIM3	89	1	97	2	74	5	50	3	70	0	68	6	87	1	94	9
SRPK1	96	15	81	6	78	1	73	2	83	2	77	3	79	6	95	5
EF2K	87	5	94	4	62	20	42	7	61	2	49	4	76	4	90	17
EIF2AK3	95	1	95	2	80	7	87	2	93	17	103	2	96	13	93	3
HIPK1	81	12	88	4	84	4	86	4	80	5	72	8	78	5	85	4
HIPK2	91	1	88	16	87	8	76	2	82	8	81	1	89	2	81	14
HIPK3	75	2	94	4	75	10	72	1	75	7	74	0	84	4	86	10
CLK2	113	1	98	7	74	8	48	4	83	7	100	4	95	3	104	7
PAK2	90	23	89	19	78	12	111	26	86	17	93	26	86	10	94	28
PAK4	67	4	98	23	92	29	113	22	96	13	112	17	89	25	86	1

PAK5	78	6	82	9	75	11	109	4	82	9	75	7	88	3	85	8
PAK6	101	2	99	10	98	9	89	10	103	5	91	8	104	1	104	2
MST2	101	10	118	31	93	11	93	1	95	10	88	15	111	24	110	12
MST3	100	3	105	8	97	10	83	1	85	5	92	1	98	8	99	6
MST4	103	3	111	9	107	16	95	2	106	6	104	10	95	4	99	7
GCK	87	6	86	7	86	9	91	3	89	2	91	4	99	9	85	10
MAP4K3	95	15	97	14	87	13	83	11	85	3	87	1	93	1	90	2
MAP4K5	101	7	105	6	97	0	101	17	99	3	98	0	109	6	103	6
MINK1	98	13	106	12	98	10	67	42	96	12	99	9	100	14	107	15
MEKK1	103	4	101	2	87	2	90	16	95	0	93	1	95	5	93	8
MLK1	102	2	96	4	95	2	88	7	77	0	90	1	99	1	97	4
MLK3	94	4	96	15	88	11	84	6	87	11	91	7	96	8	101	10
TESK1	101	9	109	11	104	12	102	14	99	14	109	12	104	11	105	7
TAO1	99	6	98	3	85	9	96	1	94	2	100	1	90	5	87	2
ASK1	98	3	107	0	98	7	99	7	98	7	109	7	111	0	113	7
TAK1	91	8	107	10	86	14	74	7	94	21	84	20	95	23	97	7
IRAK1	103	13	109	5	106	8	103	4	99	3	96	4	108	4	97	10
IRAK4	110	30	111	32	92	14	103	28	106	32	107	37	98	5	108	17
RIPK2	78	0	85	4	79	2	78	0	86	3	85	5	92	1	102	3
OSR1	120	8	109	3	111	2	116	1	102	3	106	13	114	3	113	5
TTK	83	5	90	2	76	4	67	1	83	11	88	2	92	16	103	13
MPSK1	88	9	92	13	84	3	74	2	85	4	81	1	72	2	77	1
WNK1	84	9	109	42	101	17	109	12	98	14	95	8	95	12	105	16
ULK1	98	8	98	2	93	3	95	6	96	5	95	10	94	7	103	5
ULK2	106	5	98	9	101	1	106	5	103	1	104	11	98	2	94	4
TGFBR1	107	2	108	16	98	5	98	17	76	20	94	1	90	28	96	3
Src	113	0	124	7	132	6	165	8	131	15	128	11	112	9	115	9
Lck	94	17	101	22	114	5	106	17	92	9	72	7	93	3	81	11
CSK	104	8	100	1	95	11	103	4	91	1	101	12	94	8	97	6
YES1	105	3	98	8	94	12	92	5	88	3	86	17	93	16	103	10
ABL	81	5	86	1	74	4	66	0	93	1	89	7	96	8	100	9
BTK	132	5	146	7	83	5	36	16	76	1	93	12	112	1	121	10
JAK2	91	10	89	15	96	25	104	5	98	20	106	23	96	8	95	8
SYK	107	10	113	3	75	8	26	1	75	7	66	8	101	16	118	10
ZAP70	99	11	127	13	116	17	150	17	121	38	97	11	112	17	102	0

TIE2	100	8	105	15	77	4	53	5	72	0	56	12	86	8	91	7
BRK	74	10	71	8	76	6	69	1	67	0	71	10	77	17	75	3
EPH-A2	109	5	117	5	78	6	72	1	86	4	87	9	106	7	112	16
EPH-A4	98	6	104	28	92	2	91	3	95	3	97	5	102	12	102	11
EPH-B1	99	16	95	12	110	13	140	2	96	7	106	13	102	7	89	3
EPH-B2	122	5	127	2	103	10	85	6	104	6	106	22	103	26	103	4
EPH-B3	104	1	112	9	84	12	57	11	77	6	84	1	116	9	93	3
EPH-B4	118	5	121	9	109	9	130	3	108	6	106	6	110	11	108	1
FGF-R1	103	2	94	2	64	9	58	3	72	1	58	8	90	8	99	6
HER4	88	15	99	6	92	6	71	15	103	12	98	2	112	3	107	6
IGF-1R	92	17	99	13	86	18	83	7	113	16	94	10	94	5	107	20
IR	89	25	100	5	85	22	92	12	89	15	97	12	102	9	97	7
IRR	95	1	94	5	91	8	91	5	89	3	96	6	92	5	101	2
TrkA	97	13	81	2	60	7	47	6	50	9	58	6	70	0	95	20
DDR2	85	7	88	3	91	4	95	6	95	5	101	2	91	7	97	3
VEG-FR	83	6	102	2	102	4	48	2	81	14	76	24	94	16	90	11
PDGFRA	94	15	111	3	97	13	103	5	94	9	101	11	110	3	96	6

Table 3.41 Kinase inhibitory activitiy of α-aminoboronic peptides. (part 2)

Plate Barcode	10.5		9.14		14.9		14.20		14.43		14.46		14.64	
MKK1	90	1	90	4	112	30	74	5	82	11	82	4	86	9
MKK2	89	4	118	4	102	1	88	18	95	3	91	4	87	8
MKK6	93	8	91	6	95	5	109	15	90	4	93	6	100	3
ERK1	104	13	90	10	93	6	89	3	99	0	104	10	102	2
ERK2	147	13	150	6	143	0	134	15	153	14	145	6	154	3
ERK5	111	3	96	1	110	7	100	1	102	1	99	5	93	9
JNK1	99	5	96	2	93	10	109	9	98	3	99	8	92	1
JNK2	112	18	120	1	121	21	111	7	111	7	123	8	102	5
JNK3	101	7	109	3	95	7	100	2	103	23	96	3	109	25
p38a MAPK	95	4	99	17	96	1	102	6	103	10	107	4	105	8
p38b MAPK	107	1	108	16	97	7	100	1	101	0	101	13	97	11

p38g MAPK	136	14	140	2	147	12	164	7	141	12	155	3	180	15
p38d MAPK	109	17	106	3	108	1	114	2	114	7	110	14	133	3
ERK8	82	29	96	1	98	10	105	14	98	3	93	4	102	9
RSK1	91	3	92	5	95	6	85	12	83	7	95	10	93	10
RSK2	101	22	101	5	101	2	94	14	72	10	99	4	76	16
PDK1	107	3	111	5	101	2	115	2	109	0	108	2	102	5
PKBa	104	9	94	3	96	0	91	7	97	3	100	12	105	1
PKBb	115	2	122	5	108	5	57	6	99	27	102	2	99	3
SGK1	69	4	99	7	102	0	58	8	85	3	84	5	92	11
S6K1	77	6	93	6	93	3	49	9	125	44	90	2	81	1
PKA	91	2	88	4	98	2	105	12	93	1	94	0	95	3
ROCK 2	114	8	104	1	100	1	112	10	108	3	107	5	102	5
PRK2	104	1	119	4	111	5	92	22	94	5	108	1	110	25
PKCa	118	1	100	3	104	6	104	3	111	1	106	12	102	2
PKCγ	106	1	118	10	102	4	119	6	115	2	105	3	103	4
PKCz	91	23	110	11	113	14	99	10	106	22	117	15	101	22
PKD1	85	1	89	0	85	2	121	14	95	2	106	3	110	5
STK33	103	3	93	1	108	10	98	11	91	1	93	2	88	1
MSK1	65	4	95	4	106	7	62	9	88	4	112	21	82	6
MNK1	121	7	118	7	123	10	133	4	118	11	121	5	125	5
MNK2	114	13	114	10	120	3	111	7	114	17	109	8	116	1
MAPKAP-K2	106	6	98	12	110	5	73	11	112	0	103	15	111	7
MAPKAP-K3	72	6	96	2	88	1	83	6	71	8	83	6	67	9
PRAK	97	7	99	3	91	5	112	14	95	3	113	5	107	7
CAMKKb	85	7	95	3	91	0	91	0	92	6	95	2	92	1
CAMK1	73	3	103	14	108	1	12	4	96	4	101	10	79	1
SmMLCK	72	9	83	1	84	2	66	2	90	3	100	2	85	3
PHK	134	14	121	10	112	2	114	7	111	18	94	6	112	0
DAPK1	101	3	85	10	75	4	82	2	77	1	90	2	77	6
CHK1	98	11	102	1	94	3	90	7	98	1	97	5	96	7
CHK2	92	14	97	4	100	16	84	7	90	3	100	0	99	0

GSK3b	82	3	95	4	106	8	96	18	72	9	96	1	94	20
CDK2-Cyclin A	104	3	97	3	85	3	88	11	101	0	101	1	94	7
CDK9-Cyclin T1	82	5	90	3	99	1	105	5	97	8	99	5	90	1
PLK1	96	26	120	12	97	14	89	3	93	7	94	7	88	3
Aurora A	89	1	93	12	97	13	106	23	111	14	106	0	109	4
Aurora B	101	0	105	12	120	11	106	3	100	12	109	9	113	11
TLK1	95	21	97	14	102	6	96	2	98	3	103	11	111	12
LKB1	116	5	116	2	105	1	108	2	100	6	96	5	97	2
AMPK	93	3	89	2	87	7	85	11	98	1	90	4	75	8
AMPK (hum)	122	5	103	2	100	9	94	4	107	21	87	3	74	7
MARK1	87	1	91	5	90	4	94	11	75	5	95	13	81	6
MARK2	93	3	83	4	86	1	89	1	87	15	98	3	83	1
MARK3	97	4	81	1	88	1	90	12	81	6	92	2	77	5
MARK4	102	16	92	1	101	4	103	11	88	11	100	0	92	12
BRSK1	91	4	93	2	86	3	90	2	86	7	91	5	88	4
BRSK2	78	1	103	4	102	9	109	6	73	2	107	4	77	7
MELK	102	1	109	16	100	0	101	11	97	10	98	5	84	8
NUAK1	91	10	112	0	106	1	104	1	101	28	112	2	94	3
SIK2	90	2	95	3	89	2	90	4	83	10	84	7	95	9
SIK3	93	4	101	8	100	27	121	12	86	3	109	16	104	16
TSSK1	57	2	74	4	114	13	97	0	91	4	90	5	77	0
CK1γ2	111	4	117	16	92	6	88	1	104	20	96	17	90	12
CK1δ	118	15	107	1	107	11	101	11	96	7	112	6	104	3
CK2	118	13	99	20	115	2	113	4	117	1	97	8	103	5
TTBK1	103	1	80	1	100	6	88	14	95	10	98	9	96	1
TTBK2	101	6	97	11	100	16	92	2	100	1	93	0	93	0
DYRK1A	91	3	89	1	108	12	102	9	91	13	98	5	93	0
DYRK2	95	3	99	5	98	4	104	14	95	11	97	14	98	1
DYRK3	93	0	102	12	104	12	106	2	104	11	120	7	117	4
NEK2a	91	2	93	9	91	15	100	0	94	1	96	15	84	7
NEK6	80	8	102	19	106	20	90	7	93	16	104	11	96	25
IKKb	84	7	82	9	95	1	84	8	81	7	107	27	104	4

IKKe	147	66	120	16	110	4	123	13	107	2	103	8	98	0
TBK1	90	9	102	1	105	5	105	9	88	3	108	7	107	7
PIM1	96	7	89	1	90	5	81	2	82	1	97	9	90	10
PIM2	85	4	89	3	94	4	93	3	98	10	101	2	92	2
PIM3	114	2	106	10	96	0	97	6	100	4	100	0	105	1
SRPK1	111	3	85	8	86	1	94	1	88	1	93	2	99	2
EF2K	93	15	98	11	95	2	38	15	87	11	86	3	76	4
EIF2AK3	110	4	82	9	106	12	86	8	99	5	105	6	89	4
HIPK1	97	5	97	4	94	9	93	8	98	5	96	6	91	12
HIPK2	95	8	97	1	89	6	89	11	95	1	92	8	91	6
HIPK3	94	0	101	9	93	6	94	5	102	12	98	6	91	5
CLK2	97	8	97	4	97	11	84	8	73	2	92	4	87	14
PAK2	84	18	100	14	96	10	87	6	102	7	93	2	84	8
PAK4	75	3	105	7	98	15	108	31	76	26	92	8	68	8
PAK5	84	1	97	1	98	1	88	7	85	8	96	13	69	9
PAK6	103	9	117	12	115	22	97	3	95	4	103	10	97	7
MST2	113	13	93	6	94	8	92	4	96	7	94	5	89	10
MST3	98	8	86	2	89	2	90	3	100	10	96	6	96	7
MST4	102	7	104	21	93	6	77	9	97	1	101	5	90	14
GCK	92	1	90	4	94	2	92	4	105	3	88	3	96	8
MAP4K3	100	10	93	15	97	14	93	4	100	14	102	13	94	6
MAP4K5	101	5	93	3	93	1	90	5	92	1	96	1	105	9
MINK1	104	2	93	2	95	3	81	2	106	6	111	2	114	12
MEKK1	114	4	93	4	100	5	99	7	98	15	90	6	106	7
MLK1	98	0	107	7	98	2	91	3	95	12	95	11	92	5
MLK3	105	1	91	1	93	2	82	4	98	14	92	1	94	4
TESK1	98	8	100	2	102	4	113	2	100	3	99	1	116	2
TAO1	101	8	96	2	99	12	89	1	92	4	97	8	79	7
ASK1	100	5	103	2	100	7	96	1	96	8	107	2	103	11
TAK1	88	1	93	1	104	7	71	10	89	4	109	20	97	6
IRAK1	117	6	109	4	99	2	98	1	89	2	98	6	107	9
IRAK4	114	19	107	16	101	8	99	19	101	30	96	12	99	6
RIPK2	92	7	88	1	89	2	89	10	98	3	94	3	103	4
OSR1	94	7	104	14	94	1	89	7	95	15	107	18	102	12
TTK	92	1	88	1	91	4	87	9	91	7	97	9	83	1

MPSK1	92	15	85	2	87	7	83	3	75	4	79	0	83	0
WNK1	82	10	89	19	110	31	92	12	103	21	101	8	106	10
ULK1	110	2	109	12	100	7	100	2	105	3	110	15	112	9
ULK2	89	1	91	2	101	2	98	0	86	6	96	6	108	11
TGFBR1	108	17	98	13	103	5	108	2	108	1	100	11	112	1
Src	124	10	136	11	103	1	143	12	102	9	122	7	135	6
Lck	104	5	108	16	102	12	111	6	88	8	107	2	99	9
CSK	100	5	101	1	103	15	98	9	102	1	108	12	96	24
YES1	115	14	96	11	87	13	94	2	99	5	53	58	113	3
ABL	86	6	89	5	89	8	99	0	95	3	97	2	98	1
BTK	105	4	118	11	130	7	107	2	102	9	136	8	114	3
JAK2	100	29	91	3	101	13	108	11	101	9	99	3	107	4
SYK	84	13	111	16	111	15	97	11	94	12	111	9	96	7
ZAP70	102	15	106	22	109	9	108	5	99	10	106	5	97	11
TIE2	92	0	93	4	81	2	80	5	80	3	80	7	88	11
BRK	75	3	78	7	81	2	77	2	76	7	72	9	92	13
EPH-A2	77	1	103	17	106	12	101	5	94	1	100	10	99	19
EPH-A4	107	5	101	5	107	6	100	3	96	9	101	11	109	8
EPH-B1	123	9	108	9	98	15	105	9	117	14	121	5	103	7
EPH-B2	104	0	104	3	90	1	120	7	105	12	104	8	97	4
EPH-B3	97	15	100	11	93	10	83	13	92	7	99	13	101	13
EPH-B4	106	10	98	14	104	15	107	4	106	4	107	5	100	3
FGF-R1	97	16	97	3	75	17	68	10	75	15	91	3	80	12
HER4	106	3	82	2	91	7	102	3	92	6	110	4	106	4
IGF-1R	88	12	87	16	86	3	72	2	97	1	97	1	90	1
IR	101	21	107	14	92	19	97	13	98	11	109	11	108	13
IRR	91	2	98	1	87	3	92	8	96	4	98	8	101	2
TrkA	81	4	82	12	81	10	89	1	73	3	70	3	73	7
DDR2	106	10	98	8	97	1	94	8	99	8	96	3	102	3
VEG-FR	102	3	91	24	80	2	96	9	106	17	126	22	98	6
PDGFRA	96	7	97	0	113	11	102	7	110	1	110	2	109	5

Kinases abbreviation expansion*

ABL	Abelson murine leukemia viral oncogene homolog
AMPK	AMP-activated protein kinase
ASK	Apoptosis signal regulating kinase
BRK	Breast tumour kinase
BRSK	Brain-specific kinase
BTK	Bruton agammaglobulinemia tyrosine kinase
CaMK	calmodulin-dependent kinase
CaMKK	CaMK kinase
CDK	cyclin dependent kinase
CHK	checkpoint kinase
CK	casein kinase
CLK	CDC-like Kinase
CSK	C-terminal Src kinase
DAPK	Death-Associated Protein Kinase
DDR	Discoidin domain receptor tyrosine kinase
DYRK	dual-specificity tyrosine-phosphorylated and regulated kinase
eIF	eukaryotic translation initiation factor
EF2K	elongation-factor-2-kinase
EPH	ephrin
ERK	extracellular-signal-regulated kinase
FGF-R	fibroblast-growth-factor receptor
GCK	germinal centre kinase
GSK	glycogen synthase kinase
HER4	V-erb a erythroblastic leukemia viral oncogene homolog 1
HIPK	homeodomain-interacting protein kinase
IGF	insulin-like growth factor
IKK	inhibitory κB kinase
IR	insulin receptor
IRAK	Interleukin-1 Receptor-Associated Kinase
IRR	insulin related receptor
JAK	Janus Kinase
JNK	c-Jun N-terminal kinase
Lck	lymphocyte cell-specific protein tyrosine kinase
LKB1,	Ser/Thr Kinase 11
MO25,	Ser/Thr Kinase 11
STRAD	Ser/Thr Kinase 11
MAP4K	mitogen-activated protein kinase kinase kinase kinase

MAPKAP-K	MAPK-activated protein kinase
MARK	microtubule-affinity-regulating kinase
MEKK	mitogen-activated protein kinase kinase kinase
MELK	maternal embryonic leucine-zipper kinase
MINK	misshapen-like kinase
MLCK	smooth-muscle myosin light-chain kinase
MLK	mixed lineage kinase
MNK	MAPK-integrating protein kinase
MSK	mitogen- and stress-activated protein kinase
MPSK	Myristoylated and Palmitoylated serine/threonine protein Kinase
MST	mammalian homologue Ste20-like kinase
NEK	NIMA (never in mitosis in Aspergillus nidulans)-related kinase
NUAK	SnF1-like Kinase
OSR	Oxidative Stress Responsive
PAK	p21-activated protein kinase
PHK	phosphorylase kinase
PDGFR	platelet-derived growth factor receptor
PDK	3-phosphoinositide-dependent protein kinase
PIM	provirus integration site for Moloney murine leukaemia virus
PKA	cAMP-dependent protein kinase
PKB	protein kinase B (also called Akt)
PKC	protein kinase C
PKD	protein kinase D
PLK	polo-like kinase
PRAK	p38-regulated activated kinase
PRK	protein kinase C-related kinase
RIPK	receptor interacting protein kinase
ROCK	Rho-dependent protein kinase
RSK	p90 ribosomal S6 kinase
S6K	S6 kinase
SGK	serum- and glucocorticoid-induced kinase
Src	sarcoma kinase
SRPK	serine-arginine protein kinase
STK	Serine / Threonine Kinase
SIK	salt inducible protein kinase
SYK	spleen tyrosine kinase
TAK	Transforming growth factor beta activated kinase
TAB	TAK1 binding subunit
TAO	thousand and one amino acid protein kinase

TBK	TANK-binding kinase
TESK	testis-specific kinase
TGFBR	transforming growth factor, beta receptor
TIE	Tunica Internal Endothelial cell kinase
TLK	tousled-like kinase
TrkA	Neurotrophic tyrosine kinase, receptor, type 1
TSSK	testis-specific serine kinase
TTBK	tau tubulin kinase
TTK	Phosphotyrosine picked threonine kinase
ULK	unc-51-like kinase
VEGFR	vascular endothelial growth factor receptor
WNK	With No Lysine deficient protein kinase
YES	Yamaguchi sarcoma viral oncogene homologue
ZAP	zeta chain (TCR) associated protein kinase

**All the expansions have been taken from International Centre for Kinase Profiling web-page.*

3.3.6. References

1. Stensen, W., Haug, B. E., Rekdal, O., Svendsen, J.S., *Preparation of tripeptide amides as antimicrobial agents.* PCT Int. Appl. (2009), WO 2009081152.
2. Strøm, M. B., Haug, B. E., Skar, M. L., Stensen, W., Stiberg, T., Svendsen, J.S., *The Pharmacophore of Short Cationic Antibacterial Peptides.* Journal of Medicinal Chemistry, 2003, **46**(9): pp. 1567-1570.
3. Svenson, J., Karstad,R., Flaten, G.E., Brandsdal,B.-O., Brandl,M., Svendsen, J.S., *Altered Activity and Physicochemical Properties of Short Cationic Antimicrobial Peptides by Incorporation of Arginine Analogues.* Molecular Pharmaceutics, 2009, **6**(3): pp. 996–1005.
4. Svenson, J., Brandsdal,B.-O., Stensen, W., Svendsen, J.S., *Albumin Binding of Short Cationic Antimicrobial Micropeptides and Its Influence on the in Vitro Bactericidal Effect.* Journal of Medicinal Chemistry, 2007, **50**(14): pp. 3334-3339.
5. Verma, I.M., Weitzman, M.D., *Gene therapy: Twenty-First Century Medicine.* Annual Review of Biochemistry, 2005, 74: pp. 711-738.

6. Verma, I.M. and Somia, N., *Gene therapy - promises, problems and prospects.* Nature, 1997, 389: pp. 239-242.
7. Gorovoy, A.S., Gozhina, O.V., Svendsen, J.S., Domorad, A.A., Tetz, G.V., Tetz V.V. and Tore Lejon, *Boron containing peptidomimetics – a novel class of selective anti-tubercular drugs.* Chemical Biology & Drug Design (accepted)

4. Conclusions

The synthesis and biological activity evaluation of diversity of α-aminoboronic peptides which were not broadly studied as promising antimicrobial agents have been discussed in this thesis.

A big library of α-aminoboronic peptides (175 compounds) was synthesized from α-aminoboronates and a diversity of L-amino acids adopting a highly efficient standard solution phase coupling procedure for our needs. α-Aminoboronates, by turn, were derived from alkyl(aryl)-boronates employing Matteson homologation reaction (that allowed creating a new chiral center) following by introduction of an amino group into the molecule.

Antimicrobial and antifungal activities of the synthesized α-aminoboronic peptide library have been established as well as kinase inhibitor properties of some peptides. The test results revealed several compounds with high biological activity that can be evaluated as potential antimicrobial, antifungal and kinase inhibitors or promoters.

The synthesized library enables understanding and predicting what groups, peptide sequence and optical configuration of the α-chiral carbon (next to boron) are important to achieve a higher level of biological activity, which allows to propose structure-activity relationships.

Developing of the library of α-aminoboronic peptides is worth to be continued, keeping in the mind significant parameters for improving biological activity.

Paper I

Paper II

Paper III

Paper IV

Paper V

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