Pergamon

Tetrahedron 57 (2001) 7073–7105

TETRAHEDRON

Tetrahedron report number 579

Arginine mimetics

Lucija Peterlin-Mašič and Danijel Kikelj*

Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday

Received 4 August 2000

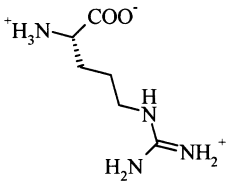
Contents

1. Introduction

Peptidomimetics have found wide application as bioavailable, biostable and potent mimetics of naturally occurring biologically active peptides.[1] L-Arginine (**1**) is a guanidino group-containing basic amino acid which is positively charged at neutral pH and is involved in many important physiological and pathophysiological processes. Many enzymes display a preference for the arginine residue that is found in many natural substrates and in synthetic inhibitors of many trypsin-like serine proteases,[2] e.g. thrombin,[3] Factor Xa[4] and trypsin,[2] and in integrin receptor antagonists,[5] used to treat many blood-coagulation disorders. Nitric oxide (NO), which is produced by oxidation of L-arginine (**1**) in an NADPH- and O_2-dependent process catalyzed by isoforms of nitric oxide synthase (NOS), exhibits diverse roles in both normal and pathological physiologies and has been postulated to be a contributor to the etiology of various diseases including septic shock, inflammatory arthritis and neurodegenerative diseases. Development of NOS inhibitors as well as analogues and mimetics of the natural substrate, L-arginine, is desirable for potential therapeutic use and for a better understanding of their conformation when bound in the arginine binding site.[6]

* Corresponding author. Tel.: +386-1-4769-561; fax: +386-1-425-80-31; e-mail: danijel.kikeljd@ffa-server.ffa.uni-lj.si

PII: S0040-4020(01)00507-5



1

The guanidino residue of arginine in many substrates, inhibitors and antagonists forms strong ionic interactions with the carboxylate of an aspartic acid moiety, which provides specificity for the basic amino acid residue in the active site. A highly basic guanidino moiety incorporated in enzyme inhibitors or receptor antagonists is, however, often associated with low selectivity and poor bioavailability after peroral application. A significant effort has therefore been focused on the design and preparation of arginine mimetics that can confer selective inhibition for specific trypsin-like serine proteases and NOS inhibitors, as well as integrin receptor antagonists, and which possess reduced basicity for enhanced oral bioavailability. This review describes arginine mimetics designed and synthesized to mimic the function of the arginine moiety in numerous peptidomimetic compounds, with the aim of obtaining better activity, selectivity and oral bioavailability. The classification is according to structural type. The review covers arginine mimetics with basic guanidine and amidine moieties, conformationally constrained mimetics, and mono- and bicyclic heterocyclic arginine mimetics with reduced basicity. Within each group, the compounds are further classified into α-amino acid arginine mimetics and arginine side-chain mimetics lacking the carboxyl or the amino group.

2. Arginine mimetics with guanidino and modified guanidino moieties

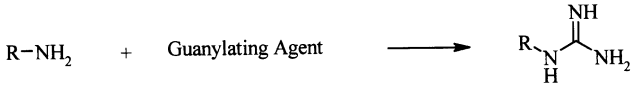
The highly basic nature and nucleophilic character of the guanidino moiety in arginine normally necessitates suitable protection for this group before subsequent chemical manipulation. Protection of the guanidine function with a single benzyloxycarbonyl (Cbz) group does not prevent the formation of piperidones (δ-lactams), which are the most important byproducts in the reactions of activated arginine derivatives. If the *t*-butyloxycarbonyl (Boc) group is introduced instead of the Cbz group, to protect the arginine side chain, a very useful arginine derivative (N^{α}-Cbz-N^{ω}-Boc-Arg) is obtained, which allows selective removal of the N^{α}-protecting group. The possibility of lactam formation is not, however, excluded. On the other hand, two acyl protecting groups on the guanidino moiety show more promise.[7] Di-benzyloxycarbonyl- and di-*t*-butyloxycarbonyl guanidines, when used to block two nitrogens in the guanidino group, provide the desired blocking of cyclization. Verdini et al. reported the synthesis of N^{α}-Cbz- and N^{α}-Fmoc-N^{ω},$N^{\omega\prime}$,-di(Boc)-protected arginine derivatives [**5**; R=$(CH_2)_3$CH(COOH)NH-Cbz, $(CH_2)_3$CH-(COOH)NH-Fmoc], useful for solid- and solution-phase peptide synthesis, starting from *N*,*N*-di-(*t*-butoxycarbonyl)-*S*-methylisothiourea **3** and N^{α}-protected ornithine.[8]

The difficulties associated with the use of conventionally protected arginine derivatives in peptide synthesis can be circumvented by incorporating into the peptide chain the appropriate ornithine- or suitable amine-containing precursors ('ornithine⇒arginine' strategy) in the earlier stages of the peptide synthesis. At a later stage of the synthesis, the amino groups are deprotected and guanylated.[7,9]

2.1. α-Amino acid arginine mimetics

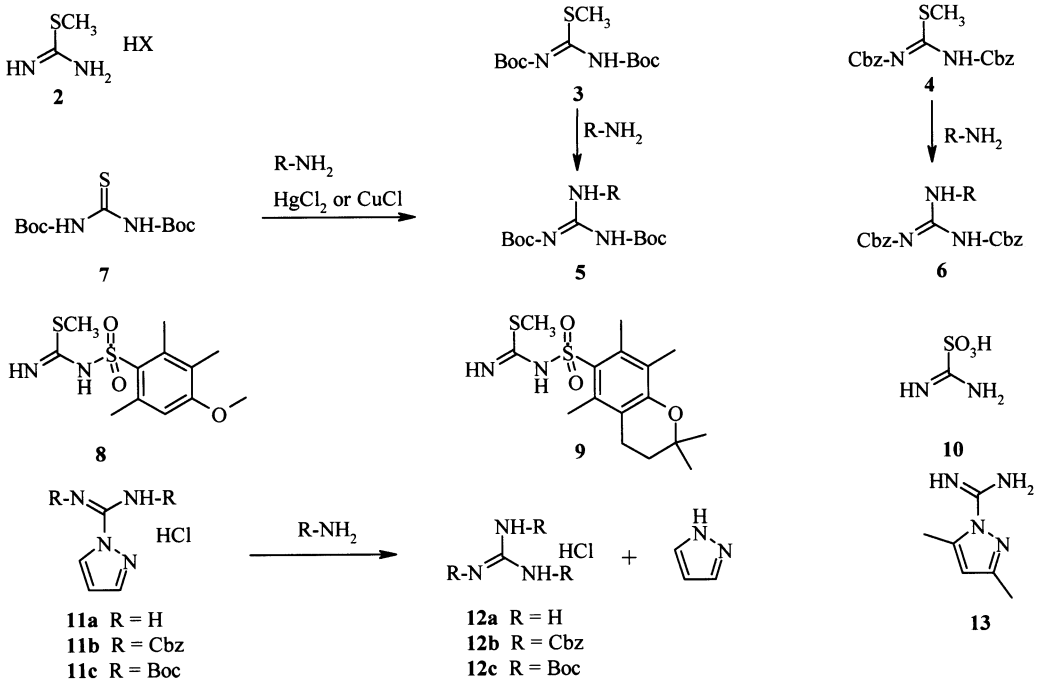
2.1.1. Arginine mimetics with aliphatic side chains

2.1.1.1. Guanylating reagents. The potential medicinal chemistry application of guanidino group-containing compounds relies on effective synthetic methods for preparing guanidines, which are focused on the development of different guanylating reagents, described by Yamamoto and Kojima.[10] Classically, guanidines have been prepared by reaction of an amine with various guanylating agents. The most frequently used guanylating reagents for preparing various protected and unprotected guanidine moieties in arginine and arginine mimetics are described in this section.



The *S*-alkylisothiourea derivatives, e.g. *S*-methylisothiouronium salts **2**,[11,12] are widely employed reagents for efficient preparation of protected and unprotected guanidine moieties from amines. They are prepared by methylation of thiourea with methyl iodide or dimethyl sulfate.[13] This is one of the most useful methods for preparing a variety of guanidino group-containing arginine mimetics, generally in good to excellent yields. The byproduct of this reaction, a noxious, foul-smelling gas, methyl mercaptan, has a threshold of detection by humans of about 1 ppb. *N*,*N*-Di-(*t*-butoxycarbonyl)-*S*-methylisothiourea **3**[8,14] and *N*,*N*-di-(benzyloxycarbonyl)-*S*-methylisothiourea **4**,[14a,15] which are soluble in organic solvents, are versatile guanylating reagents for the preparation of di-*t*-butoxycarbonyl- and di-benzyloxycarbonyl-protected guanidine moieties **5** and **6**. The reaction of *N*,*N*-di-(*t*-butoxycarbonyl)thiourea **7**[16] with amines in the presence of mercury(II) chloride provides an efficient method for the synthesis of di-Boc-protected guanidine derivative **5**, especially from amino compounds which are highly deactivated, either sterically or electronically. The reactivity of **7** may be increased by the use of a mercury or copper salt via complex formation with the thiourea sulfur atom.[17] The di-Cbz protecting group, however, is not always compatible with functional group manipulations. The 2,3,4-trimethyl-4-methoxybenzenesulfonyl (Mtr-) and 2,2,5,7,8-pentamethylchroman-6-sulfonyl- (Pmc-)[18] protected *S*-methylisothioureas **8** and **9**[19] are reagents for the direct conversion of amines to Mtr- and Pmc-monoprotected guanylated amino acids. These protecting groups can be cleaved off by trifluoroacetic acid and are stable to most organometallics, bases and hydrolytic conditions.

The widely used reagent aminoiminomethanesulfonic acid (**10**) efficiently converts primary amines to the corresponding monosubstituted guanidine derivatives under mild basic



Scheme 1.

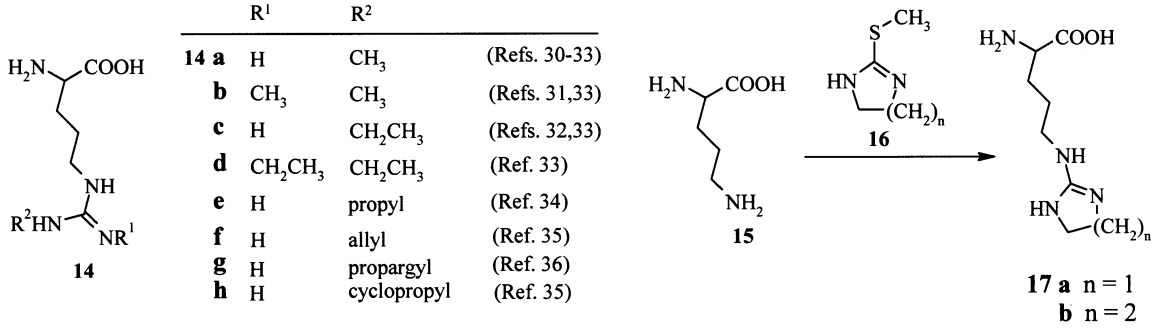
conditions at room temperature. This crystalline reagent is readily prepared by the peracetic acid oxidation of formamidinesulfinic acid.[20]

1*H*-Pyrazole-1-carboxamidine hydrochloride (1-guanylpyrazole hydrochloride) (**11a**)[21] possesses the stability, reactivity and solubility properties desirable for a versatile reagent applicable to efficient guanylation, especially of sterically unhindered primary and secondary aliphatic amines under mild conditions, and was also found to be suitable in solid-phase peptide synthesis. Bis-urethane (Cbz, Boc) derivatives of 1-guanylpyrazole **11b**[22] and **11c**[22,23] were found to be more reactive than **11a** for amine guanylation and can serve as valuable synthetic tools where the guanylation of relatively unreactive amines under mild conditions, together with suitable protection of the guanidine moiety, is required during the preparative procedure. Monosubstituted guanidinium salts are also obtained by the reaction of amines with 3,5-dimethyl-1-guanylpyrazole nitrate **13**,[24] which is produced by the reaction of acetylacetone with aminoguanidine nitrate (Scheme 1).

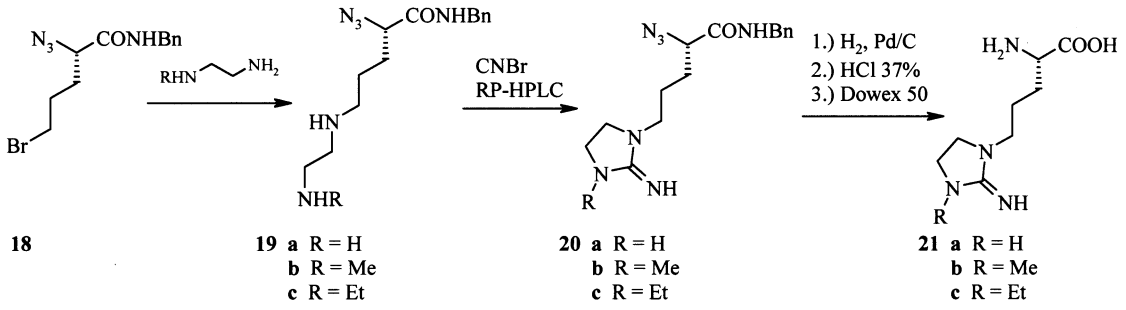
Other reagents for preparing alkyl- and arylguanidines from amines include acylated thioureas,[25] *O*-methylisourea hydrogen sulfate,[26] carbodiimides,[27] cyanamides,[28] isocyanide dichlorides,[27a] chloroformamidines[29] and *S*,*S*-dimethyl-*N*-sulfonyliminodithiocarbonimidates.[10]

2.1.1.2. Acyclic and cyclic *N*-alkylarginines. Acyclic (**14a**–**h**)[30–36] and cyclic alkylarginines (**17a**,**b**)[33] are prepared by the 'ornithine⇒arginine' strategy. Treatment of alkyl-[37] and cycloalkylthioureas[33] with methyl iodide provides the corresponding *S*-alkylisothiouronium iodides, e.g. **16**, which are used as reagents for the conversion of ornithine (**15**) to the alkyl- (**14a**–**h**) and cycloalkyl-substituted arginines **17a**,**b** (Scheme 2).

Ethylene-bridged N^{δ}-to-N^{ω} analogues of L-arginine (**21a**–**c**)[38] have been prepared starting from (2*S*)-2-azido-5-bromovaleric acid, which is synthesized using Evans chiral auxiliary to stereoselectively introduce the α-azido group into the appropriate ω-bromo acid.[39] After protection of the carboxylic group as a benzyl amide **18**, which is necessary due to possible six-membered lactam formation,



Scheme 2.



Scheme 3.

18 is treated with excess ethylenediamine or *N*-ethylethylenediamine to afford **19a** and **19c**, which, after immediate treatment with cyanogen bromide, provide cyclized products **20a** and **20c**. Reduction of the azido group and acid-catalyzed cleavage of the amide bond gives the cyclic arginine derivatives **21a** and **21c** in 61 and 49% overall yields from the corresponding bromovaleric acid (Scheme 3). Reaction of *N*-methylethylenediamine with **18** results in significantly lower yields, due to the formation of a mixture of both methylated isomers. The measured pK_a of the ethylene-bridged arginine analogues **21a–c** is approximately 11.[38]

2.1.1.3. Electrophilic arginines. The carboxylic group of arginine in many trypsin-like serine protease inhibitors may be replaced by various electrophilic moieties to obtain aldehydes **22a**, boronic acid analogues **22b**,[40] phosphonates **22c**,[41] fluoroalkyl ketones **22d**,[42] dicarbonyl compounds **22e**,[43] heteroaryl ketones **22f**,[44] and chloromethyl ketones **22g**[45] (Fig. 1). These electrophilic arginines bind to Ser^{195} of the catalytic triad in trypsine-like serine proteases, e.g. thrombin, thereby mimicking the transition state of amide bond hydrolysis and contributing considerably to the binding affinity.

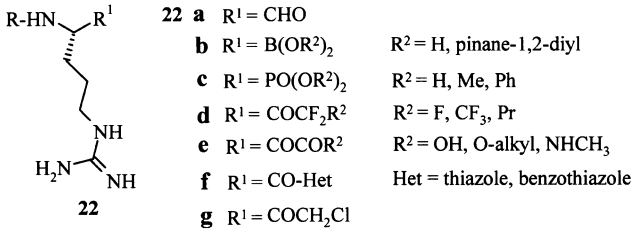
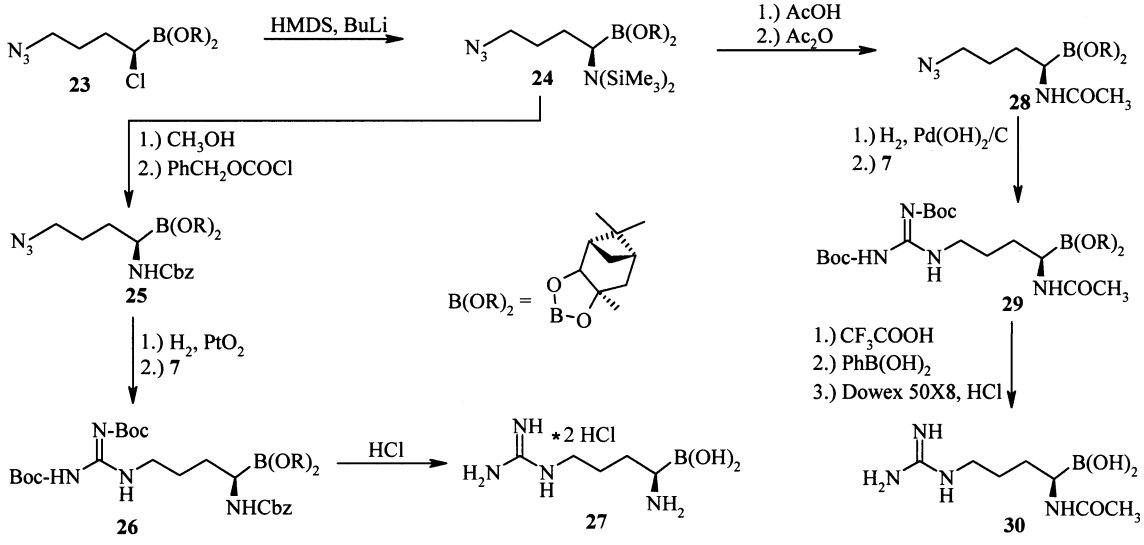


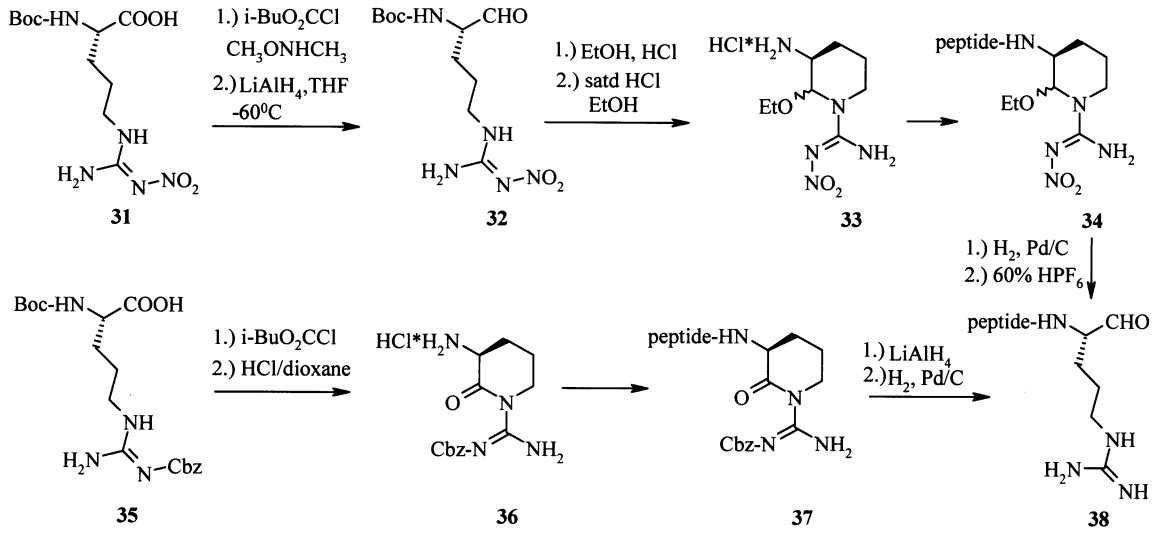
Figure 1. Electrophilic arginines.

(*R*)-Boroarginine dihydrochloride **27** and its N^{α}-acetyl derivative **30** were prepared as substrates and inhibitors of nitric oxide synthase (NOS).[46] The general synthetic sequence is based on the asymmetric synthetic methodology developed by Matteson and coworkers.[47] The amino function α to the boronate group is introduced by displacement of chloride in the α-chloroboronic ester **23** using lithium hexamethyldisilazane (HMDS) to obtain **24** followed by desilylation and Cbz protection. Selective reduction of the azido function over PtO_2 in 60% yield and subsequent guanylation using *N*,*N*-di-(*t*-butoxycarbonyl)-*S*-methylisothiourea (**7**) in the presence of mercury(II) chloride provides **26**. Deprotection of **26** produces (*R*)-boroarginine as its dihydrochloride salt **27** (Scheme 4).

The acetamido derivative **28** is obtained by cleavage of the trimethylsilyl protecting group of the amine **24** using acetic acid and acetic anhydride. Using the route described for the



Scheme 4.



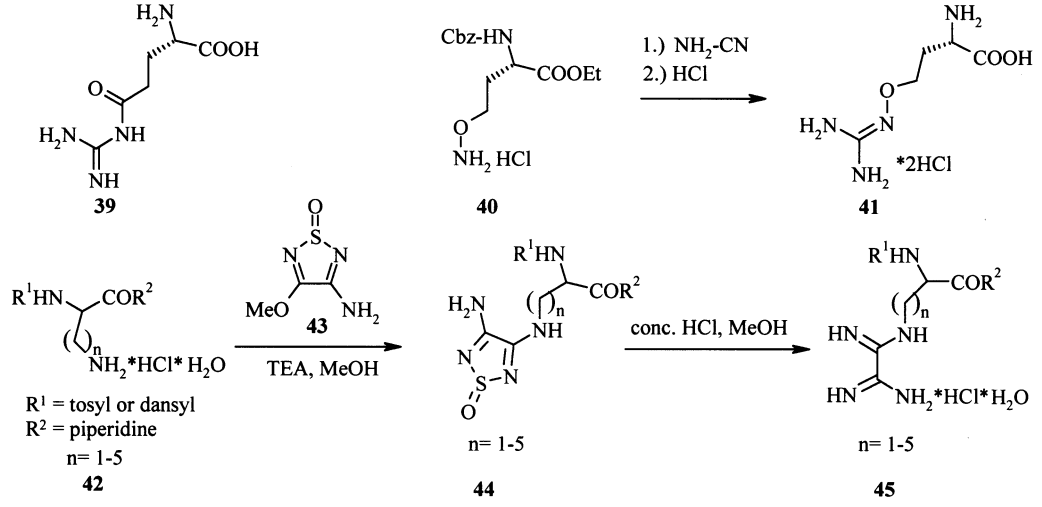
Scheme 5.

preparation of **26** from **25**, **29** is obtained in 60% yield from **28**. Removal of the Boc groups of **29** followed by cleavage of the pinanediol protecting group, using phenylboronic acid in a two-phase ether/water system, affords boroarginine **30**. (*R*)-1-amino-4-guanidino-butylboronic acid (**27**) is unstable in aqueous solution when kept at room temperature for long periods (>6 h), in contrast to the acetyl derivative **30**, which is much more stable.[46]

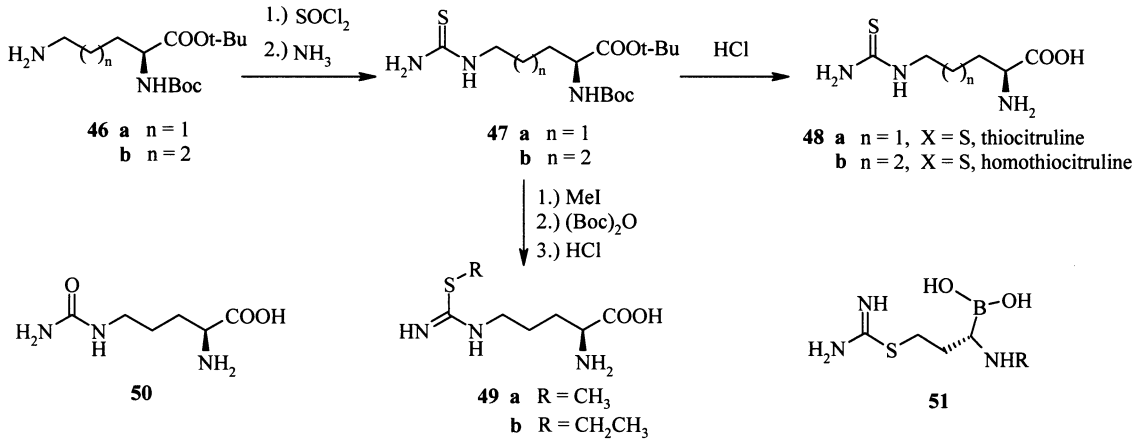
N^g-Nitro-L-arginyl ethyl aminal hydrochloride **33** is a protected arginine aldehyde synthon and a key intermediate for the synthesis of peptidyl arginals **38**. Peptidyl arginals (arginine aldehydes) inhibit Factor VIIa, Factor Xa and thrombin, which are all trypsin-like serine proteases involved in the coagulation cascade.[48] The final aldehyde structure **38** is generated by simple hydrolysis of the peptide aminal moiety in **34** with HPF_6 or aqueous HCl.[49] Conversion of Boc-N^g-nitro-L-arginine **31** into the Weinreb amide in 88% yield, reduction with lithium aluminum hydride to the aldehyde **32**, and aminal formation by treatment with ethanol in the presence of a catalytic amount of HCl at room temperature, produces aminal **33** in 81% yield as a 2:1–6:1 (*SS*/*RR*) mixture of diastereomers. Cleavage of the Boc protecting group produces amino-aminal **33** as a 12:1 mixture of diastereomers (Scheme 5). The observed change in the ratio of diastereomers during deprotection is most likely a consequence of their thermodynamic stabilities.[49]

The second method for the synthesis of the peptidyl arginals **38** utilises the late stage hydride reduction of an N^g-Cbz-arginine lactam (**37**) as reported by Schuman et al.[50] The key lactam intermediate **36** is readily prepared from Boc-Arg(Cbz)OH (**35**). Coupling of the *N*-deprotected lactam **36** with suitably protected peptides gives the peptide lactams **37**, which can be reduced by lithium aluminum hydride, followed by careful hydrogenolytic removal of protecting groups, to afford the peptide arginals **38**.[51]

2.1.1.4. Arginine mimetics with modified aliphatic side chains. 5-Keto-L-arginine (**39**) is prepared by the reaction of L-glutamic acid 5-methyl ester with guanidine (Scheme 6). It is a potential conformationally restricted analogue of



Scheme 6.

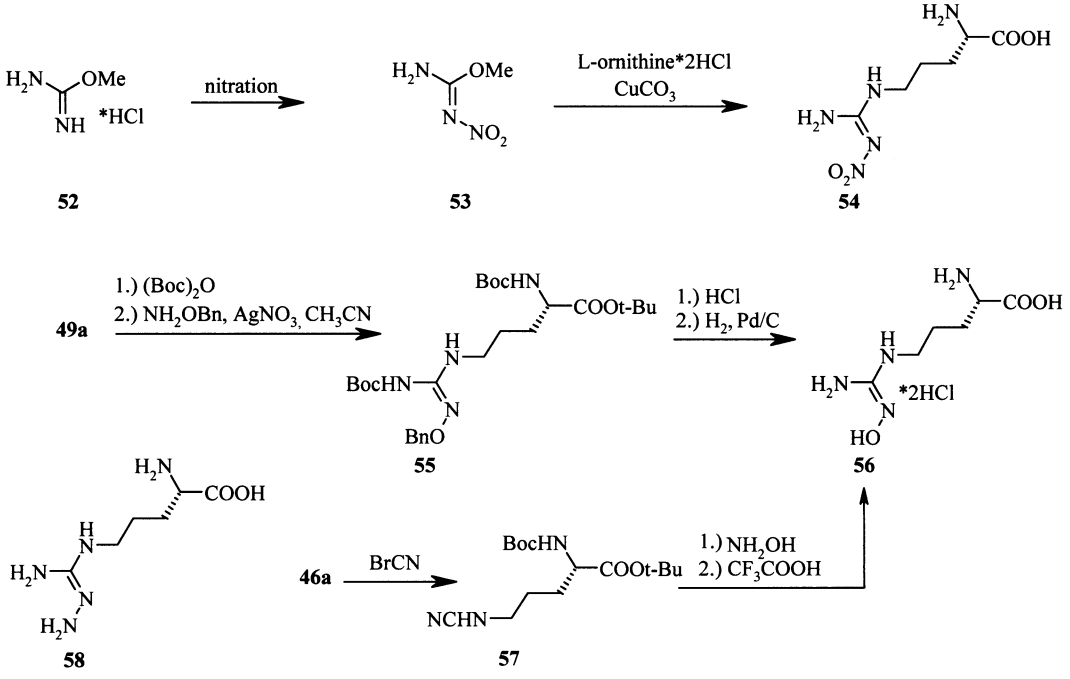


Scheme 7.

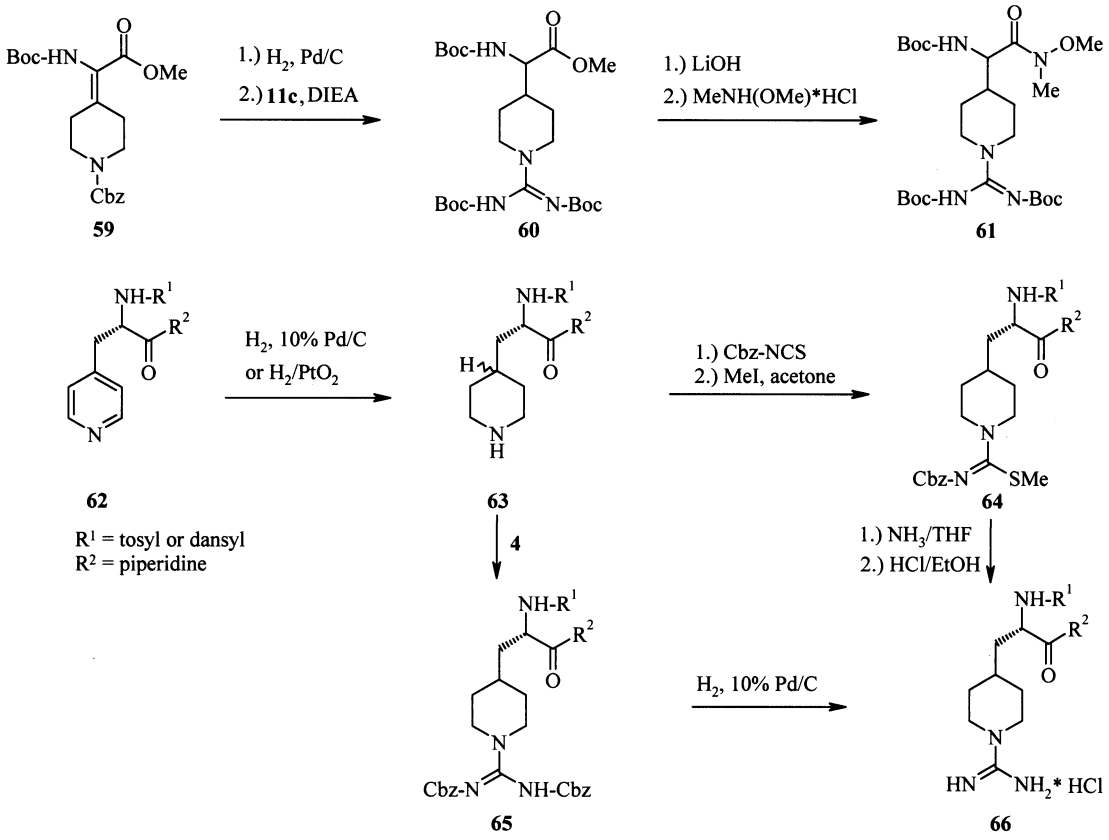
arginine because of intramolecular hydrogen bonding interactions of the carbonyl moiety with the α-amino group. In addition to its possible cyclic structure, the carbonyl group strongly decreases the pK_a of the guanidine moiety. The less basic acylguanidine moiety has a pK_a of 7.6 and is an isosteric replacement for the guanidine group in many thrombin inhibitors.[52,53] L-Canavanine dihydrochloride (**41**) has been synthesized from **40** in 80% yield by the cyanamide method, in contrast to the isothiourea or isourea methods that give much lower yields of **41**.[54] L-Canavanin, with an oxyguanidine moiety, has a guanidino pK_a of 7 and has been incorporated into potent thrombin inhibitors.[55] Bisamidines or bisguanidines **45** are prepared by the reaction of the appropriate amine **42** with 3-amino-4-methoxy-1,2,5-thiadiazole *S*-oxide (**43**) in refluxing methanol to form thiadiazole *S*-oxide intermediates **44**. Hydrolysis under acidic conditions furnishes the bisamidines **45** as their HCl salts.[56,57]

2.1.1.5. Mimetics with a modified guanidine moiety. L-Citrulline (**50**)[58,59] is a natural product of the NOS catalyzed NADPH- and O_2-dependent conversion of L-arginine (**1**). The reaction of N^{α}-(*t*-butyloxycarbonyl)-ornithine *t*-butyl ester (**46a**) or its homologue **46b** with thiophosgene, followed by reaction with ammonia in methanolic solution and subsequent deprotection, provides thiocitrulline (**48a**) and homothiocitrulline (**48b**) (Scheme 7). Alkylation of the thiourea compound **47a** provides *S*-methyl-L-thiocitrulline (**49a**) and *S*-ethyl-L-thiocitrulline (**49b**). Citrulline analogues **48a**,**b** and **49a**,**b** are potent NOS inhibitors.[58,59] An isothiourea function containing the arginine mimetic **51** has been introduced into potent boroarginine thrombin inhibitors.[60]

(L-)-Nitroarginine (**54**) is either commercially available or can be prepared by the isourea method, nitration of *O*-methylisourea hydrochloride (**52**) affording the nitro-isourea compound **53**, which is reacted with ornithine



Scheme 8.



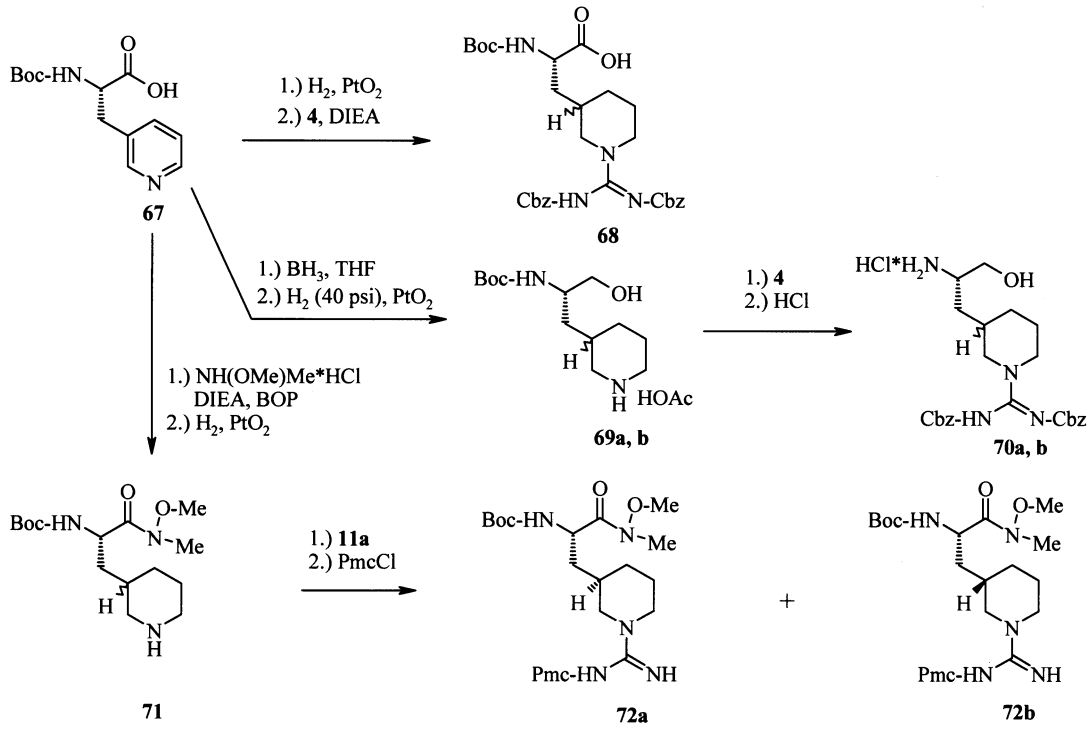
Scheme 9.

dihydrochloride in the presence of copper carbonate to give the (L-)-nitroarginine (**54**)[61] (Scheme 9).

The synthesis of (L-)-N^{ω}-hydroxyarginine dihydrochloride (**56**), the putative biosynthetic precursor of nitric oxide,[6] is also outlined in Scheme 8. The isothiourea compound **49a** is first *N*-Boc protected in 69% yield. Replacement of the methylthio moiety of **49a** with *O*-benzylhydroxylamine in the presence of $AgNO_3$ at 0°C affords **55** in 90% yield. Hydrogenolysis of the benzyl group in 89% yield, and subsequent removal of the Boc groups and hydrolysis of the *t*-butyl ester with 4 M hydrochloric acid, provides hydroxyarginine **56** as a dihydrochloride salt.[62] An alternative method for the preparation of hydroxyarginine **56** involves the reaction of cyanamide **57**, prepared from protected ornithine **46a** with cyanogen bromide, with hydroxylamine, followed by deprotection.[63] (L-)-N^{ω}-aminoarginine (**58**) is prepared by the reaction of the suitably protected isothiourea derivative **49a** with hydrazine and subsequent deprotection.[64]

2.1.2. Conformationally constrained guanidine-containing arginine mimetics. The application of peptidomimetic inhibitors that contain the conformationally constrained arginine side-chain moiety is currently an area of active investigation. Incorporation of conformationally constrained arginine and arginine side-chain mimetics into the peptidomimetic enzyme inhibitors can contribute a favourable entropic component to binding in the enzyme active site and can improve the selectivity for a target relative to compounds with a highly flexible arginine side chain.

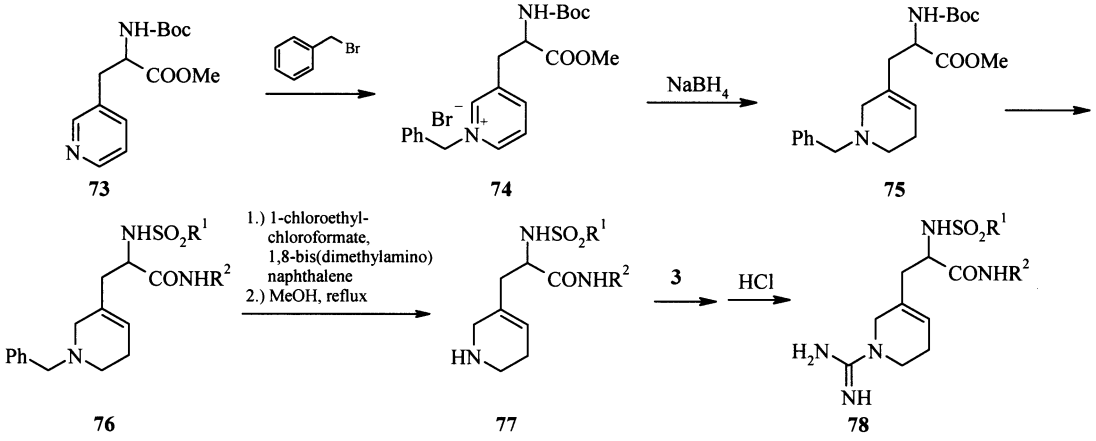
2.1.2.1. *N*-Amidinopiperidines and *N*-amidinopyrrolidines. 4-Amidinopiperidine derivatives **61** and **66**, which are constituents of potent and selective thrombin inhibitors, have been obtained according to Scheme 9. The α,β-didehydro-α-amino acid derivative **59** is prepared by Wittig–Horner reaction of *N*-(*t*-butoxycarbonyl)-phosphono glycine trimethyl ester with *N*-(benzyloxycarbonyl)-4-piperidone in the presence of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU). Hydrogenation of **59** affords a piperidine derivative, which is guanylated with reagent **11c** in the presence of diisopropylethylamine (DIEA) to yield di-Boc protected amidinopiperidine derivative **60** in 82% yield. This compound (**60**) can be readily transformed, for example, to the corresponding Weinreb amide **61**, which can be converted to various electrophilic carbonyl derivatives by reduction to the aldehyde or reaction with various lithiated heterocycles. Likewise, the Weinreb amides may be reduced to aldehydes and subsequently oxidized to the corresponding carboxylates which are suitable for solid- or solution-phase synthetic techniques.[65] The racemic *N*-amidinopiperidine derivative **66** is synthesized by catalytic hydrogenation of **62**, followed by direct guanylation with *N*,*N*-di-(benzyloxycarbonyl)-*S*-methylisothiourea (**4**) to the di-protected 4-guanylpiperidine **65** and subsequent hydrogenation. Alternatively, stepwise guanylation, employing addition of *N*-(benzyloxycarbonyl)isothiocyanate to **63**, activation of the resulting thiourea with methyl iodide to give **64**, subsequent treatment with ammonia and hydrolysis, leads to the free guanidines which can be converted to their hydrochloride salts **66**.[56]



Scheme 10.

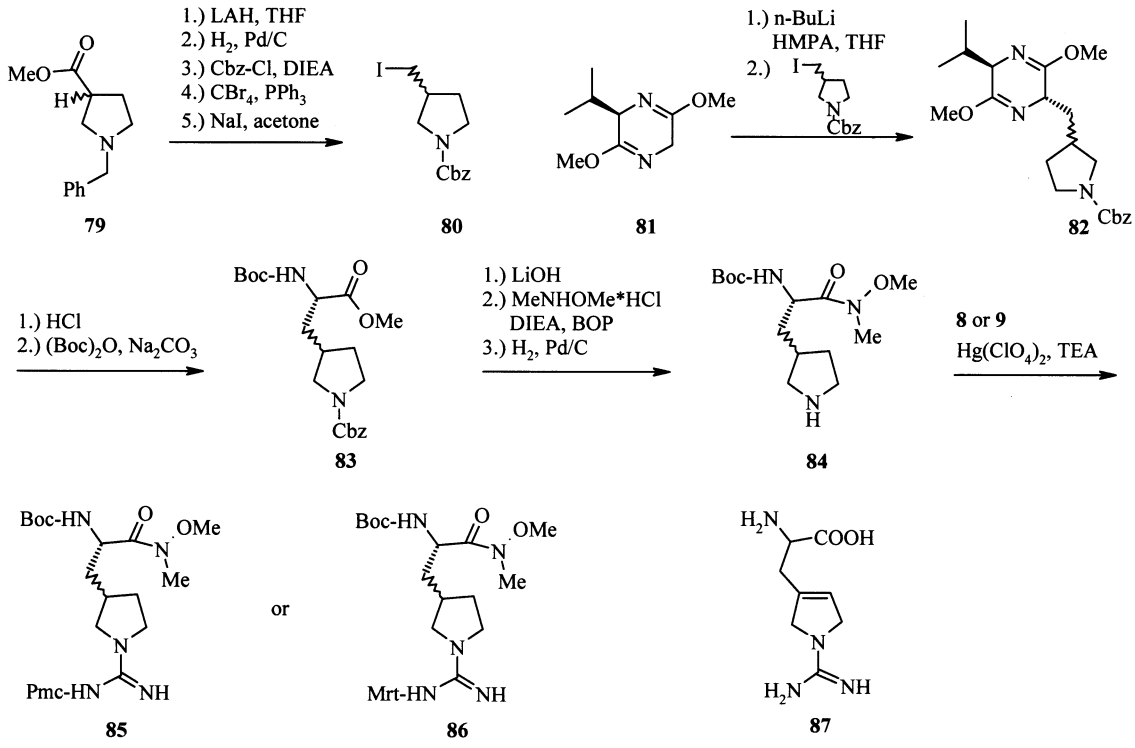
The protected 1-amidinopiperidin-3-ylalanine arginine mimetic **68**, designed for incorporation into Factor Xa inhibitors, is prepared starting from the commercially available *N*-α-Boc-D-pyridylalanine (**67**) in two steps (Scheme 10). Hydrogenation followed by guanylation using *N*,*N*-di-(benzyloxycarbonyl)-*S*-methylisothiourea (**4**) provides the diprotected 1-amidinopiperidine **68**.[66] Reduction of **67** with borane yielding *N*-α-Boc-L-3-pyridinylalaninol, followed by catalytic hydrogenation, generates alaninols **69a**,**b** quantitatively as an equimolar mixture of diastereomers. Guanylation of the resulting piperidine ring nitrogen atom with **4** produces the corresponding di-protected alaninols **70a,b**, which are constituents of thrombin inhibitors.[67,68] The reaction of *N*-α-Boc-D-pyridylalanine **67** with *N*,*O*-dimethylamine hydrochloride, benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) and DIEA in *N*,*N*-dimethylformamide gives the Weinreb amide in 85% yield which, upon reduction using PtO_2 in acetic acid, gives **71**. Guanylation of **71** with 1*H*-pyrazole-1-carboxamidine hydrochloride (**11a**) and subsequent protection with 2,2,5,7,8-pentamethylchroman-6-sulfonyl chloride in the presence of sodium hydroxide in acetone at 0°C, affords the separable diastereomers **72a** and **72b** in a 1.8:1 ratio.[69,70]

The preparation of 1-amidino-1,2,5,6-tetrahydro-3-pyridylalanine derivatives **78** is depicted in Scheme 11. Benzylation of the 3-pyridinylalanine derivative **73**, providing the *N*-benzylpyridinium salt **74**, followed by partial reduction using sodium borohydride in ethanol, leads to compound **75**. The derivatised compound **76** is debenzylated using 1-chloroethyl chloroformate in the presence of 1,8-bis-



R^1, R^2 = remaining part of the molecule of the thrombin inhibitor

Scheme 11.

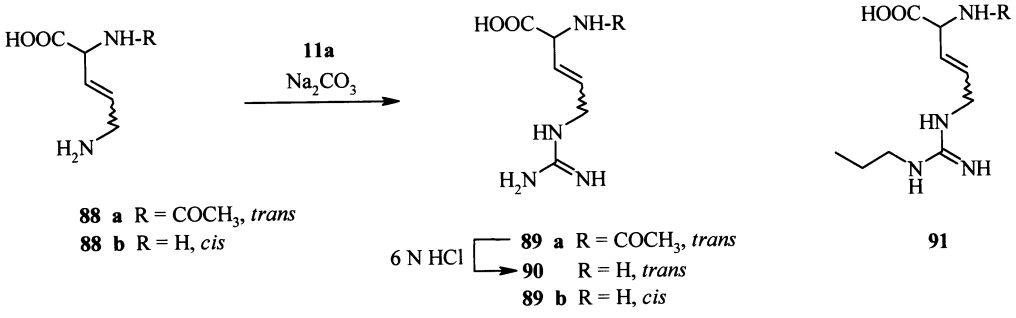


Scheme 12.

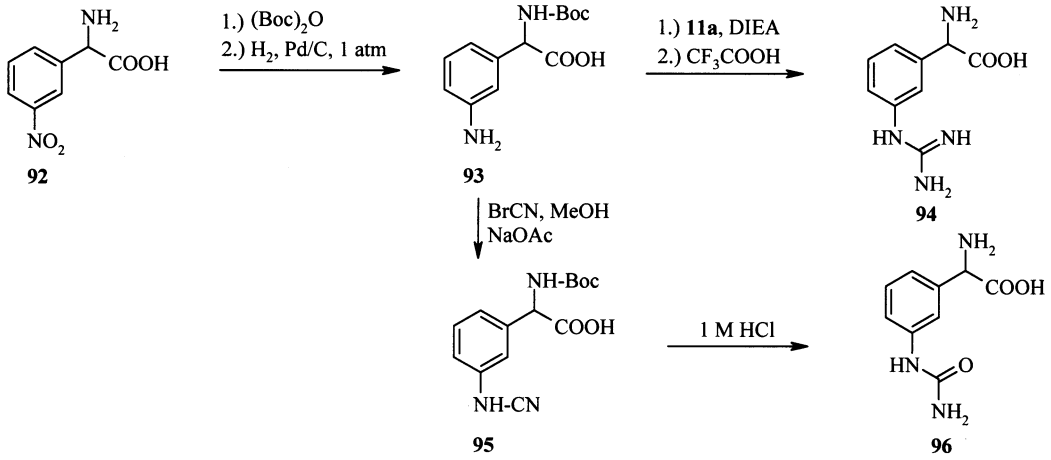
(dimethylamino)naphthalene and, following decarboxylation of the intermediate carbamate on heating with an alcohol under reflux, yields **77**. In the following step, guanylation using *N*,*N*-di(*t*-butoxycarbonyl)-*S*-methylisothiourea (**3**)[8,14] and final deprotection of the Boc protecting groups affords the amidinotetrahydropyridylalanine derivative **78**, which is a constituent of potent antithrombotics.[71]

The key step in the preparation of N^{α}-Boc-protected Weinreb amide **84** and its guanylated derivatives **85** and **86** is the synthesis of the side chain in position 3 of pyrrolidine **79**, which is prepared by 1,3-dipolar cycloaddition reaction of methyl acrylate and azomethine ylide, derived from condensation of *N*-benzylglycine and formaldehyde and subsequent decarboxylation[72] (Scheme 12). The classical chiral auxiliary **81** of Schöllkopf et al.[73] is alkylated with the iodide **80**, which is prepared in five steps from compound **79**. The alkylation reaction was optimized using hexamethylphosphoramide (HMPA) as a cosolvent to provide the desired product **82** in 66% yield. Bis-lactim ether derivative **82** is hydrolyzed to a mixture of D-valine methyl ester and Cbz-protected 3-pyrrolidinylalanine methyl ester. The crude methyl ester is N^{α}-Boc protected and the target compound **83** is readily separated from D-valine methyl ester by flash chromatography. Hydrolysis of the methyl ester **83** and reaction of the resulting carboxylate with *N*,*O*-dimethylhydroxylamine hydrochloride gives the Weinreb amide which, after cleavage of the Cbz group, affords **84**. Guanylation using Mtr- and Pmc-protected *S*-methylisothioureas **8** and **9**[19] forms both the Mtr- and Pmc-protected amino acid derivatives **85** and **86**. These constrained arginine mimetics are coupled to a variety of template structures (e.g. D-Phe-Pro-OH) to obtain thrombin inhibitors.[74] The synthesis of the amidinopyrrolinylalanine derivative **87**, which is incorporated as an arginine mimetic into potent thrombin inhibitors, is described in the patent literature.[75]

2.1.2.2. Arginine mimetics with unsaturated side chains. The conformationally restricted arginine analogue, (*E*)-3,4-didehydro-D,L-arginine (**90**), is prepared by classical guanylation of (*E*)-2-acetamido-5-amino-3-pentenoic acid (**88a**) with 1*H*-pyrazole-1-carboxamidine hydrochloride (**11a**), followed by deprotection of the



Scheme 13.



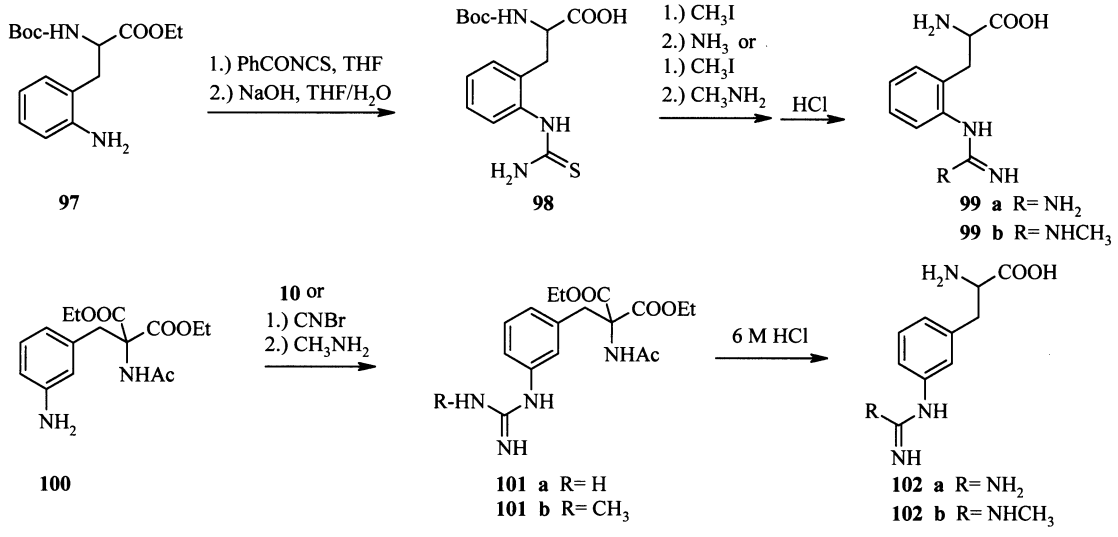
Scheme 14.

N-acetyl group of compound **89a** (Scheme 13). (*Z*)-3,4-Didehydro-D,L-arginine **89b** is obtained from (*Z*)-3,4-didehydro-ornithine **88b** employing the same guanylation reaction. Guanylation of **88a** with 1*H*-pyrazole-*N*-propyl-1-carboxamidine in aqueous Na_2CO_3 provides (*E*)-*N*-propyl-3,4-didehydro-D,L-arginine (**91**). These conformationally restricted arginine analogues are synthesised as substrates or inhibitors of isozymes of NOS.[76]

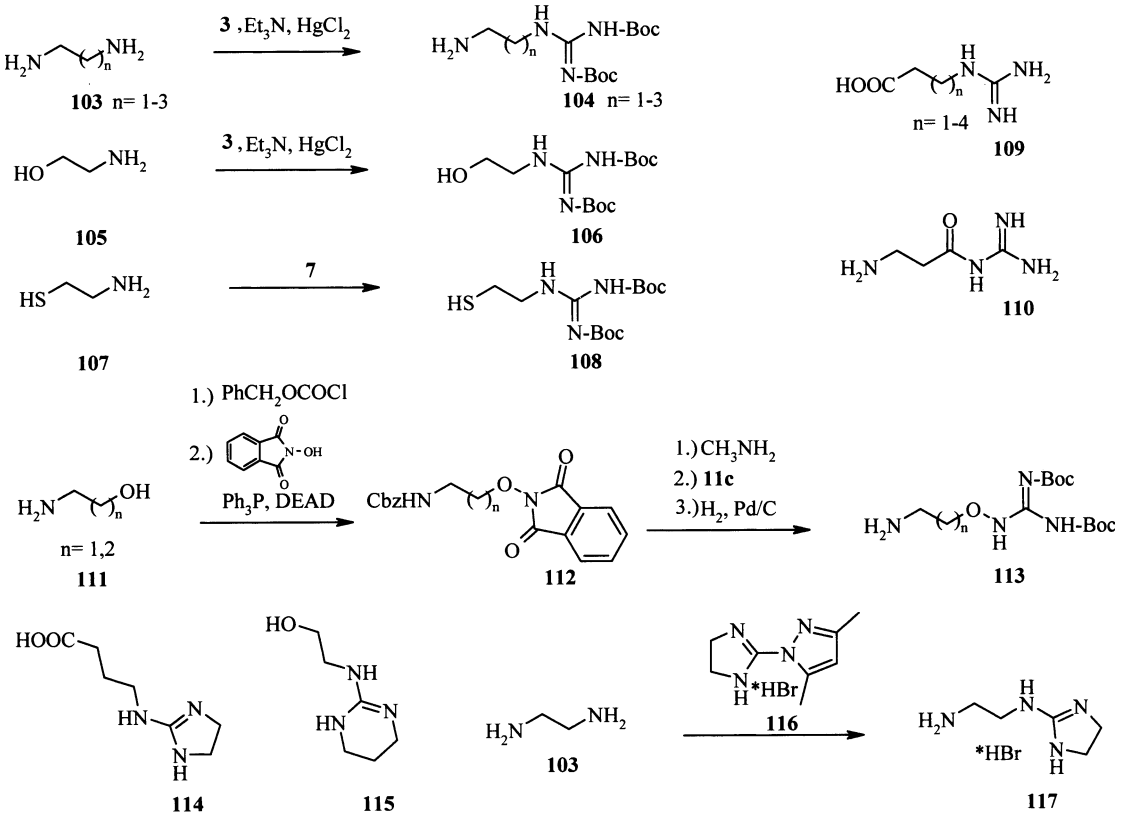
Conformationally restricted arginine mimetics **94** and **96** incorporating a benzene ring in the arginine backbone are presented in Scheme 14. *m*-Guanidino-D,L-phenylglycine (**94**) is synthesised from 3-nitrophenylglycine (**92**) by *N*-Boc protection followed by catalytic hydrogenation of the nitro group to give compound **93**. Guanylation of **93** with **11a** and subsequent *N*-Boc deprotection affords **94**. 3-Ureido-D,L-phenylglycine (**96**), a potential oxidation product of **94**, is obtained by conversion of compound **93** to the cyanamide derivative **95** followed by simultaneous hydrolysis and deprotection.[76]

For the synthesis of the arginine mimetics, **99a** and **99b**, the amino ester **97** is reacted with benzoyl isothiocyanate in THF at 0°C and, on warming overnight to room temperature, gives the corresponding *N*-benzoylisothiourea. Removal of the benzoyl group with concomitant saponification of the ester moiety gives the thiourea **98** in 86% yield (Scheme 15). Sulfur alkylation of **98**, treatment with excess methanolic ammonia in a sealed reaction vessel at 80°C, and *N*-Boc deprotection provides the guanidino compound **99a**. In a similar process, *S*-alkyl group displacement of the above isothiourea with ethanolic methylamine leads to nonseparable mixture of N^G-monomethyl- and N^G,$N^{G'}$-dimethylguanidines. Removal of the Boc protecting group and final reverse phase HPLC purification gives the desired guanidino compound **99b**.[77]

Isomeric mimetics **102a** and **102b** are prepared from the acetamidomalonate derivative **100**, which is obtained by alkylation of 3-nitrobenzyl bromide with diethyl acetamidomalonate followed by hydrogenation of the nitro group. Compound **100** is guanylated by aminoiminosulfonic acid (**10**),[20] further deprotected and then decarboxylated with refluxing 6 M aqueous hydrochloric acid to the target guanidino compound **102a**. Alternatively, *N*-methylguanidine **101b** is obtained efficiently in 88% yield by conversion of **100** to its cyanamide derivative and subsequent addition of methylamine. Exposure of **101b** to refluxing aqueous hydrochloric acid gives *N*-methyl-substituted guanidine **102b**.[77]



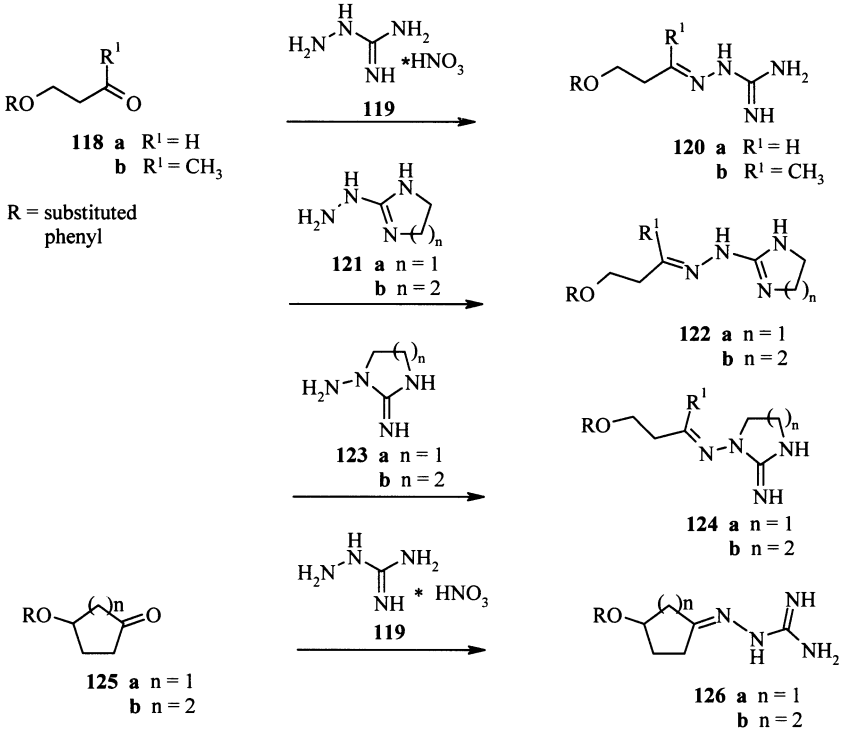
Scheme 15.



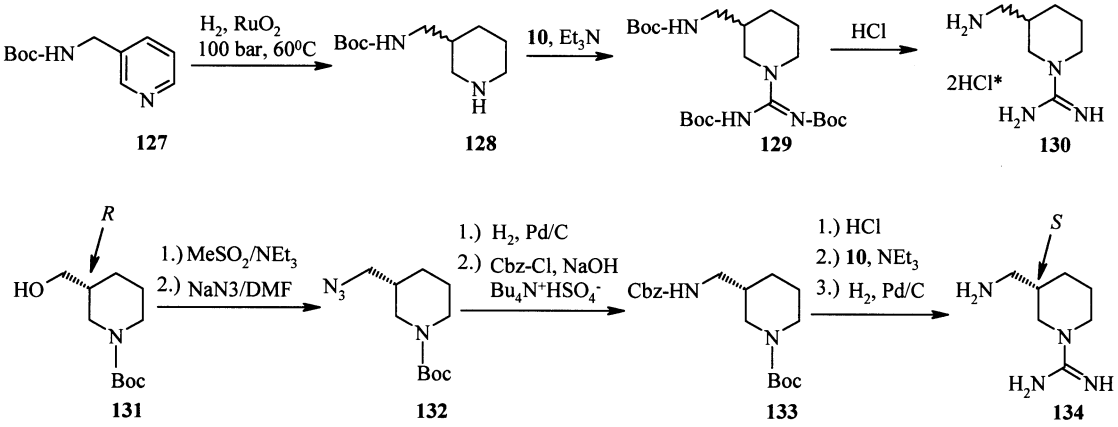
Scheme 16.

2.2. Arginine side-chain mimetics

Arginine side-chain mimetics **104**,[78,79] **106**[79] and **108**,[79] lacking the C-terminus of the arginine residue with a fully protected guanidine moiety, are prepared by the 'ornithine ⇒arginine' method from the readily available starting amines **103**, **105** and **107**, using appropriate guanylating reagents (Scheme 16). These mimetics have been incorporated



Scheme 17.

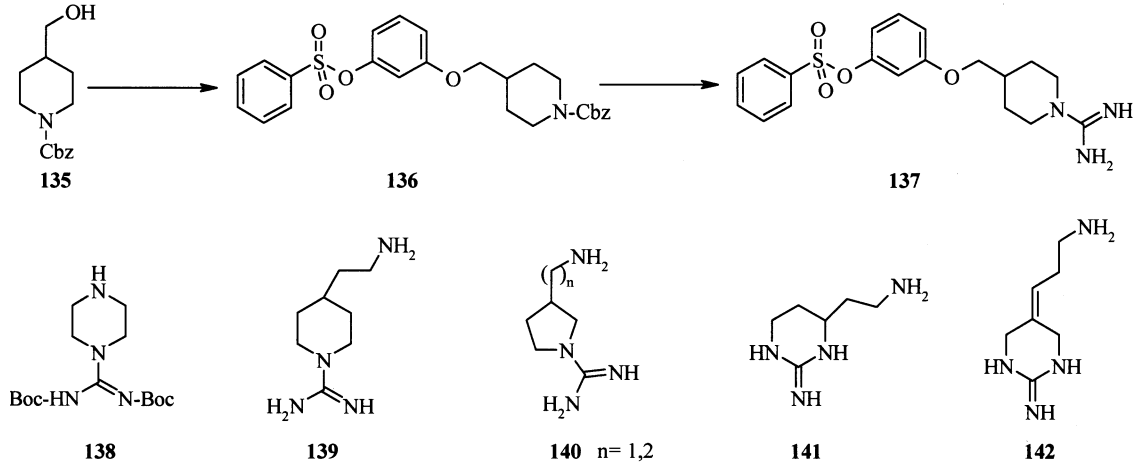


Scheme 18.

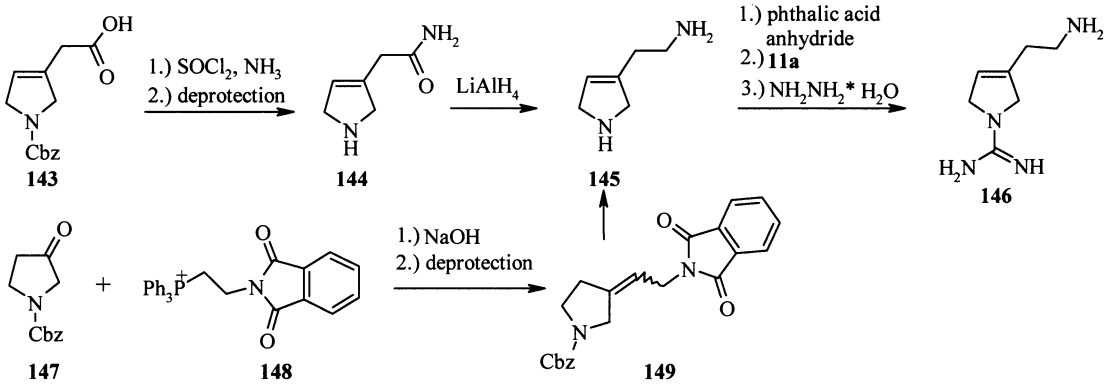
into many nonpeptidic integrin antagonists.[79] Arginine side-chain mimetics **109** with a carboxyl residue are prepared by guanylation of the appropriate ω-amino carboxylic acids with *S*-methylisothiouronium salts **2**.[80] Compound **110**, with a less basic acylguanidino group, can be prepared analogously to 5-keto-L-arginine (**39**) and has been incorporated as the P1 residue into potent thrombin inhibitors.[53] For the synthesis of arginine side-chain mimetics **113**, amino alcohols **111** are first protected with a Cbz protecting group and then coupled to *N*-hydroxyphthalimide using a Mitsunobu coupling procedure to yield **112**.[80] After removing the phthalimido protecting group, using methylamine or hydrazine hydrate, the resulting alkoxyamines are guanylated with di-Boc protected 1-guanylpyrazole **11c**. Cleavage of the protecting groups affords canavanine analogues **113** without a C-terminus.[81] The isothiourea method described for the synthesis of cyclic alkylarginines **17a** and **17b**[33] is also used for preparing cyclic arginine side-chain mimetics **114** and **115** from commercially available amines.[79] 2-(3,5-Dimethyl-1-pyrazolyl)-4,5-dihydroimidazole hydrobromide (**116**)[82] is used as a reagent for the synthesis of cyclic guanidine **117** from diamine **103**.[79]

Preparation of the amidinohydrazone compounds **120**, **122**, **124** and **126** comprises the condensation of aldehydes **118a** (R^1=H) or ketones **118b** (R^1=CH_3) and **125a**,**b** with hydrazine derivatives, i.e. aminoguanidine nitrate **119**, 2-hydrazinoimidazoline **121a**, 2-hydrazinotetrahydropyrimidine **121b** and heterocyclic amines **123a**,**b**[83] (Scheme 17). Amidinohydrazones have been used as less basic isosteres for the guanidine moiety in many potential thrombin inhibitors[84] and integrin receptor antagonists.[85]

The preparation of the conformationally constrained arginine side-chain mimetics *RS*-, *R*- and *S*-3-(aminomethyl)-piperidine-1-carboxamidine is depicted in Scheme 18. Conversion of *N*-Boc protected 3-picolylamine **127** into the racemic arginine side-chain mimetic **130** involves hydrogenation of the pyridine ring, guanylation of the ring nitrogen of **128** by aminoiminomethanesulfonic acid (**10**),[20] and final cleavage of the Boc protecting groups of **129**. Enantiomerically pure arginine side-chain mimetic **134** is obtained from protected *R*-3-(hydroxymethyl)piperidine **131**.[86] The hydroxy group of **131** is transformed via azide **132** to the Cbz protected amine **133**. Cleavage of the Boc protecting group, guanylation by **10**, and final deprotection of the primary amine by catalytic hydrogenation yields enantiomerically pure **134**. The *R*-enantiomer of **134** is prepared in the same way, starting with the *S*-alcohol. These arginine side-chain mimetics have been incorporated via an aliphatic amino group into potent and selective thrombin inhibitors.[87]



Scheme 19.



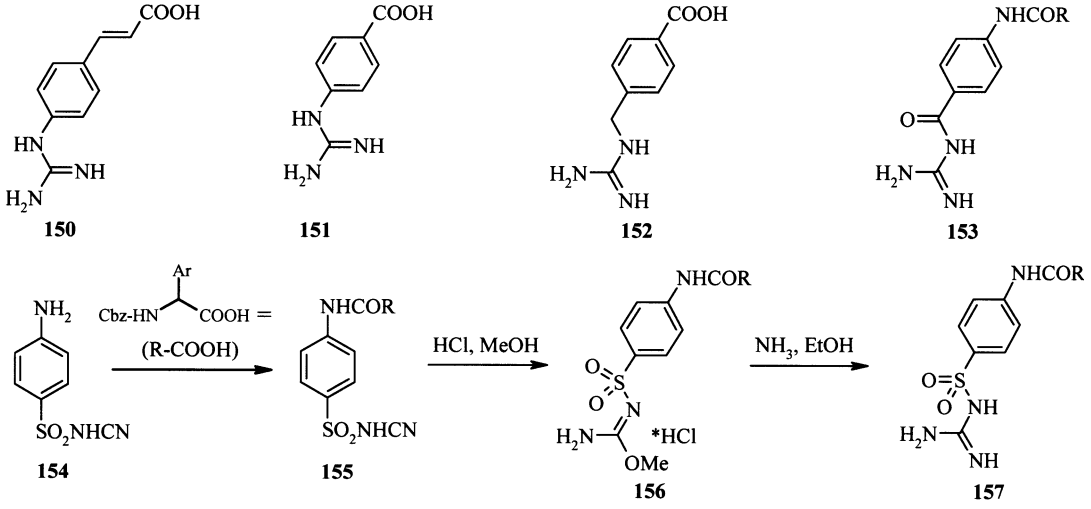
Scheme 20.

The preparation of the non-amide-based thrombin inhibitor **137** includes Mitsunobu coupling between alcohol **135** and the corresponding phenol to obtain the piperidine derivative **136** (Scheme 19). After deprotection, the compound **136** is guanylated using aminoiminomethanesulfonic acid (**10**)[20] to provide the amidinopiperidine-based inhibitor **137**.[88,89] Conversion of piperazine to the di-Boc protected piperazine-1-carboxamidine **138** involves classical guanylation using *S*-methylisothiouronium salts **2**. This building block has been incorporated by nucleophilic aromatic substitution and subsequent deprotection into potent nonpeptide integrin antagonists.[79] Arginine side-chain mimetics **139** and **140** are prepared similarly and have, along with the cyclic guanidines, **141** and **142**, been employed as arginine mimetics in anticoagulants.[90] Arginine side-chain mimetic **142** has also been incorporated into compounds with thrombin and trypsin inhibitory action.[91]

Preparation of arginine mimetic **146** with an *N*-amidinopyrroline functionality includes amidation of **143** followed by deprotection to afford compound **144**, reduction of the amide group with lithium aluminum hydride to give **145**, protection of its primary amino group with phthalic acid anhydride, guanylation of the secondary amine and subsequent cleavage of the phthalimido group by hydrazine hydrate (Scheme 20). Intermediate **145** can also be prepared by rearrangement of the exocyclic double bond in compound **149**, which is prepared by a Wittig reaction of ketone **147** with the triphenylphosphonium salt **148**. The arginine side-chain mimetic **146** is a versatile intermediate for the synthesis of serine protease inhibitors.[75]

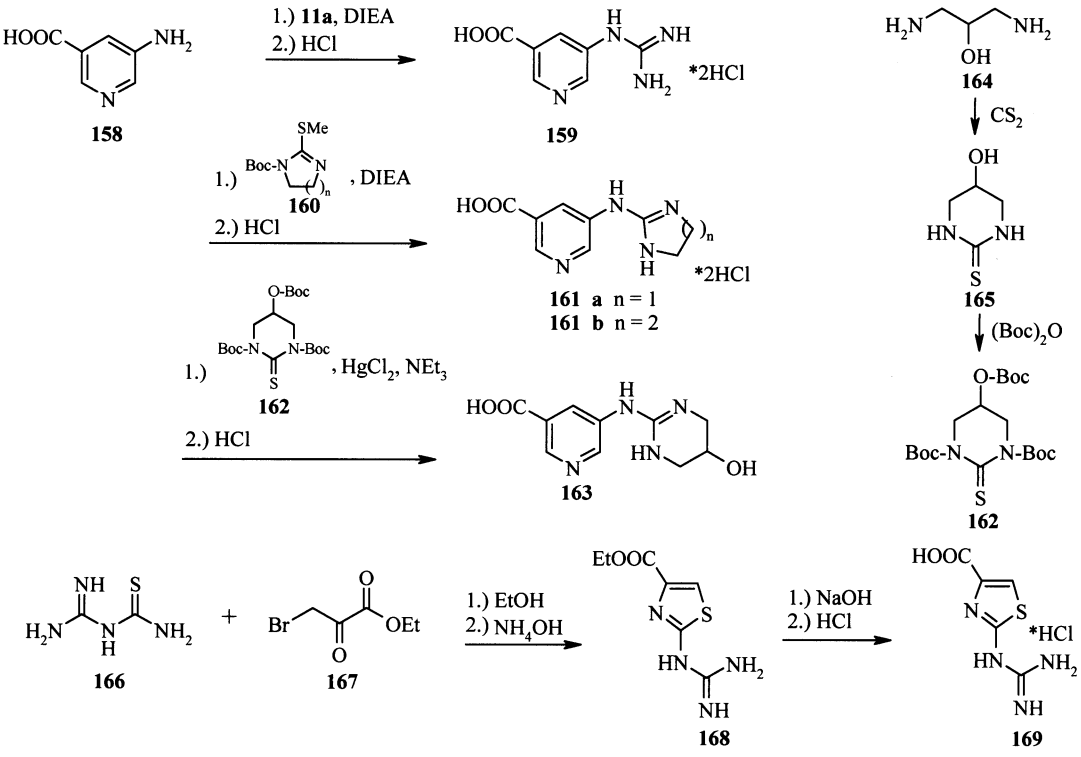
Arginine replacement in RGD (Arg-Gly-Asp) mimetics, 4-guanidinocinnamic acid (**150**), is obtained via guanylation of the corresponding 4-aminocinnamic acid.[92] Arginine side-chain mimetics **151** and **152** are synthesized analogously by guanylation of the respective amino- and aminomethyl-substituted benzoic acids.[93] Guanylation of acylated *p*-aminobenzoic acid with mono-Boc protected guanidine and final deprotection leads to the thrombin inhibitors **153** comprising the *N*-benzoylguanidino moiety[53] (Scheme 21).

The sulfonylguanidino moiety of **157** is obtained by Pinner reaction (anhydrous HCl in methanol) of the corresponding sulfonylcyanamide **155**, which is obtained by acylation of **154**,[94] to afford the *N*-sulfonyl-*O*-methylisourea **156**, which, on reaction with alcoholic ammonia, leads to the sulfonylguanidine **157** (Scheme 21). The sulfonylguanidines reported by Supuran et al. have pK_a values for the guanidine



R = remaining part of the molecule of the thrombin inhibitor

Scheme 21.



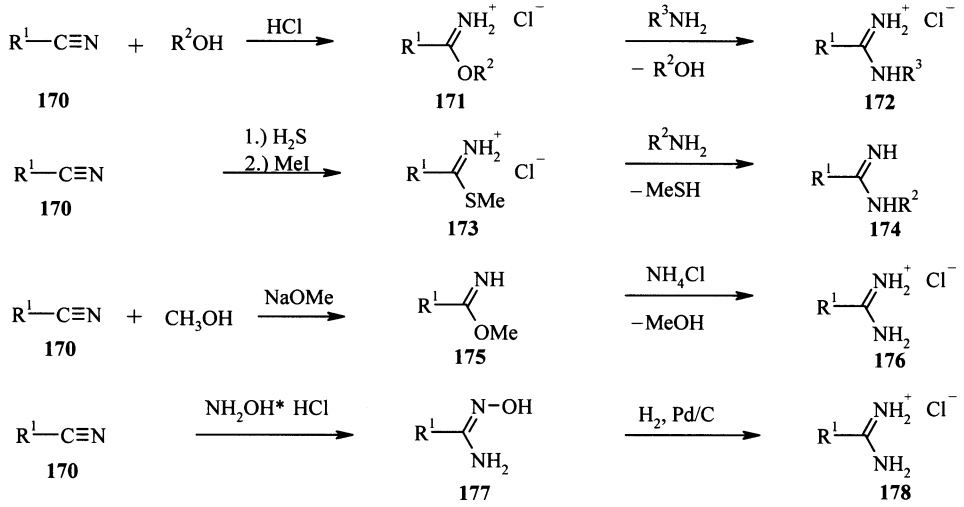
Scheme 22.

moiety of 7.9–8.4, these being about 10^4 times less basic than guanidines and amidines. These molecules also possess a weakly acidic character, with another ionization step at a pK_a value of 6.2–7.3 (depending on substitution), due to loss of the $-SO_2NH$-proton. These features are important for obtaining bioavailable serine protease (e.g. thrombin) inhibitors with improved water solubility, due to facilitated salt formation at the relatively acidic $-SO_2NH-$ group.[95]

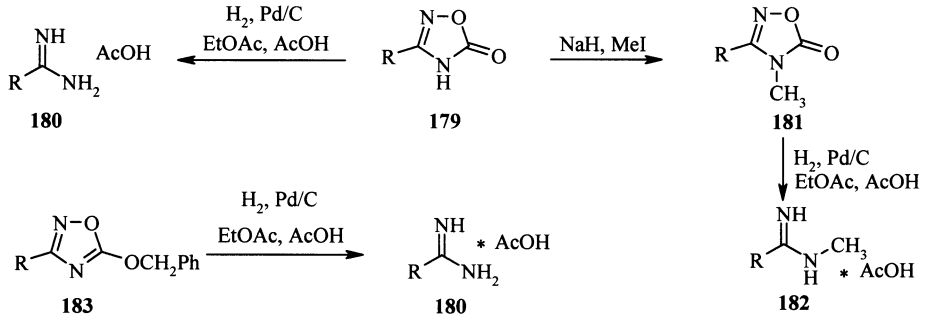
Arginine side-chain mimetics **159**, **161a**,**b** and **163**, which are derivatives of pyridine-3-carboxylic acid containing a guanidino or cyclized guanidino moiety, are obtained from 5-aminonicotinic acid (**158**) using 1*H*-pyrazole-1-carboxamidine hydrochloride (**11a**), cycloalkyl-S-methylisothiourea **160** or the cyclothiourea derivative **162** as guanylating agents. The cyclothiourea reagent **162** is prepared from 1,3-diamino-2-propanol (**164**) by cyclization with CS_2 to obtain **165** and subsequent Boc protection according to Scheme 22. 2-Guanidinothiazole-4-carboxylic acid (**169**) is obtained by condensation of amidinothiourea (**166**) and ethyl 3-bromo-2-oxopropanoate (**167**) to give **168**, followed by ester hydrolysis and salt formation to provide **169**. These arginine mimetics have been incorporated into integrin receptor antagonists.[96]

3. Amidine-based arginine mimetics

Amidines, the nitrogen analogues of carboxylic acids, are



Scheme 23.



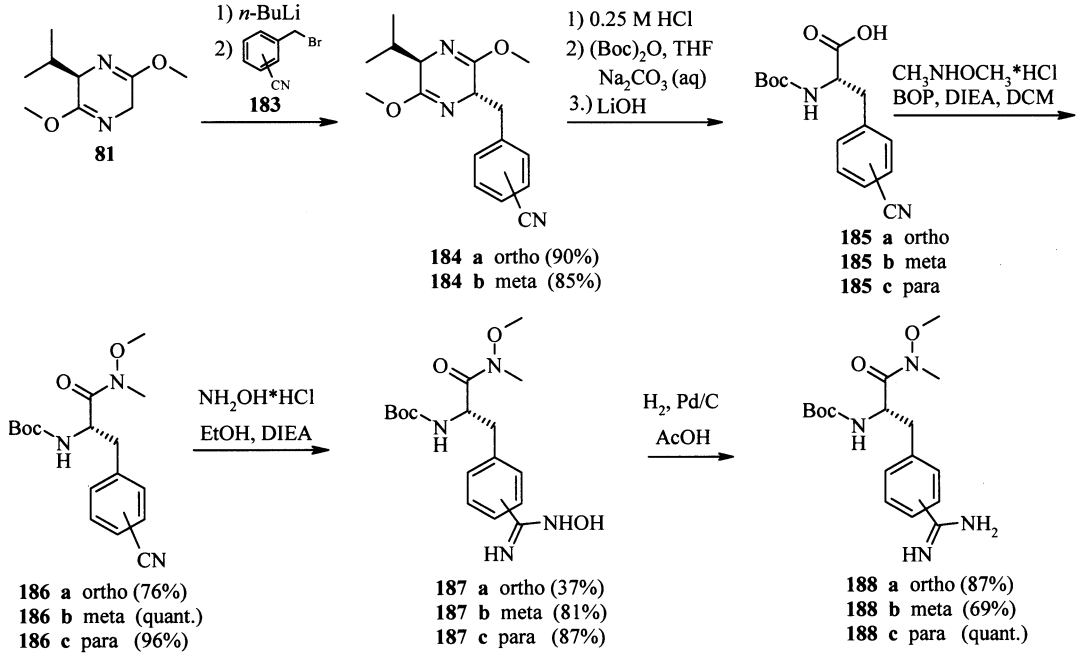
Scheme 24.

structural parts of numerous compounds of biological interest. A number of synthetic inhibitors of serine proteases, NOS and integrin antagonists possess an amidino moiety as a replacement for the guanidino group that confers specificity for a receptor or for the active site of an enzyme. Similar to guanidines, amidines are strongly basic as a result of a resonance-stabilized symmetrical amidinium ion, formed by protonation of the imino nitrogen atom.[97]

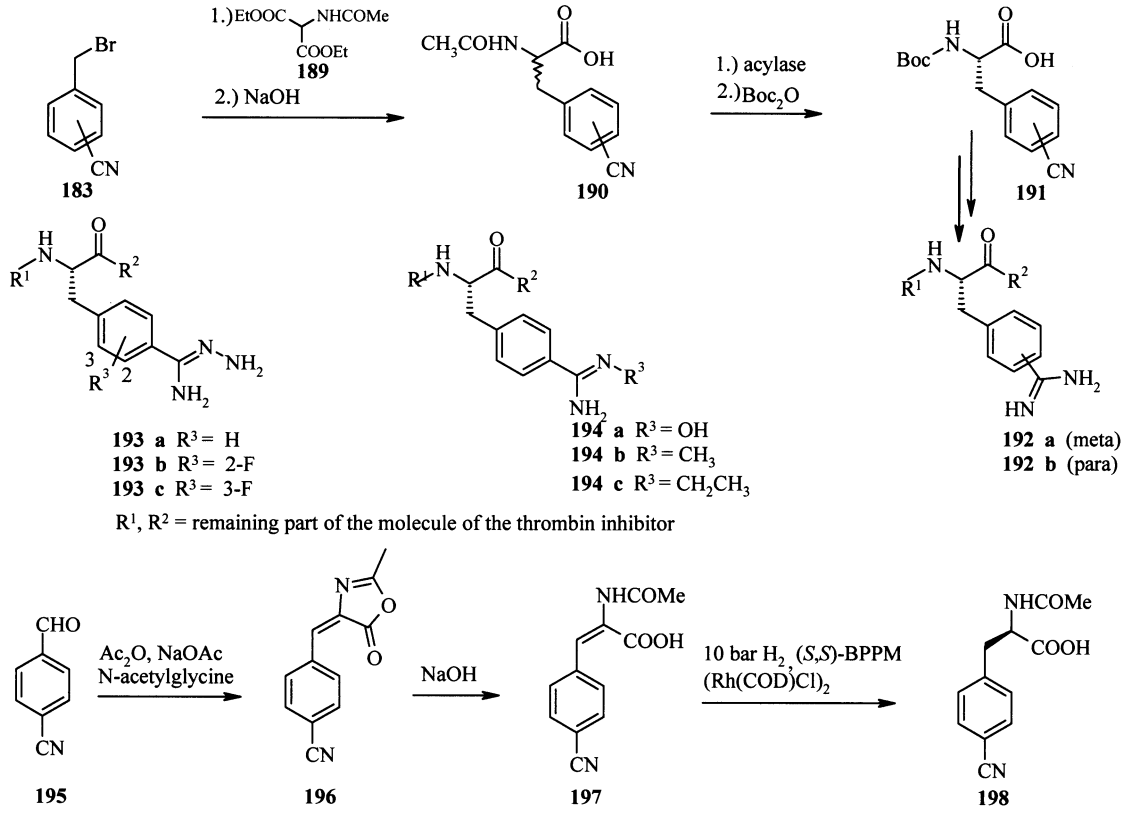
The highly basic nature of the amidine moiety normally necessitates that suitable protection for this group is achieved before subsequent chemical manipulation. The benzamidine moiety, which imitates the guanidinoalkyl side chain of arginine, is usually prepared by incorporation of a benzonitrile moiety into a suitable precursor in the earlier stages of the synthetic procedure. At a later stage of the synthesis or at the end of the procedure, the nitrile group is transformed into the amidino moiety by known methodologies (Scheme 23).

The syntheses of amidines from nitriles, amides, thioamides, lactams and miscellaneous other precursors (e.g. from orthoesters, heterocyclic compounds or isocyanides) have been reviewed by Boyd.[98] Among these methods, one of the most versatile means of preparing benzamidine arginine mimetics is the transformation of a nitrile moiety into an amidino group. The most useful methods for the transformation of nitrile-containing precursors into amidine-based arginine mimetics are depicted in Scheme 23.

The widely used classical Pinner synthesis, by addition of dry HCl gas to a mixture of a nitrile **170** and an alcohol in the absence of water, leads to the imino ester hydrochloride **171**. These imino esters can be converted to a variety of amidines **172** by treatment with different amines.[98,99] A modified Pinner synthesis includes the addition of hydrogen sulfide to the nitrile **170** in the presence of triethylamine to obtain a thioamide, which, on conversion to the thioimidate hydrochloride **173**, further reacts with amines to give amidines **174**.[98] Imino esters **175** can be prepared by base-catalysed addition of alcohol (methanol) to the nitriles **170** and further transformed by subsequent reaction with ammonium chloride into the amidine hydrochlorides **176**.[98,100] Amidines **178** can also be prepared efficiently by catalytic hydrogenation of amidoximes **177**, which are obtained by



Scheme 25.



Scheme 26.

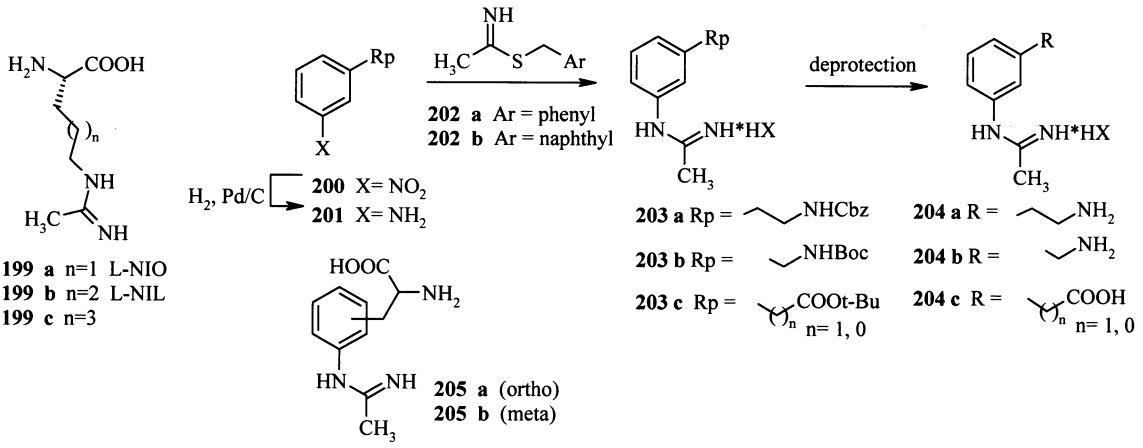
treatment of nitriles **170** with hydroxylamine hydrochloride in the presence of triethylamine.[101]

1,2,4-Oxadiazolin-5-ones **179** and 5-benzyloxy-1,2,4-oxadiazoles **183** are useful precursors to, and protected forms of, the amidine moiety. The compounds **179** are readily prepared from amidoximes by condensation with ethyl chloroformate or, alternatively, via ultrasound-mediated cycloaddition of nitrile oxides to trichloroacetonitrile, to give trichloromethyl oxadiazole and subsequent hydrolysis. Both compounds, upon hydrogenation under mild conditions at atmospheric pressure in the presence of 10% palladium on carbon and at least one equivalent of acetic acid, liberate the parent amidines **180** as their acetate salts. In addition, 1,2,4-oxadiazolin-5-ones **179** are base stable and the acidic nature of the heterocycle (pK_a of 5.1–6.6, depending upon substitution)[102] should permit, upon alkylation, access upon hydrogenation of **181** to the *N*-alkylated amidines **182**[103] (Scheme 24). This principle was applied to the synthesis of [5,5]-*trans*-fused indane lactone thrombin inhibitors.[104,105]

3.1. α-Amino acid arginine mimetics with amidino groups

3.1.1. Amidinophenylalanines. Isomers of amidinophenylalanine, in which the benzamidine moiety mimics the guanidinoalkyl side chain of arginine, are important structural elements for constructing thrombin inhibitors, such as N^{α}-[(2-naphthylsulfonyl)glycyl]-4-amidinophenylalanylpiperidine (NAPAP)[106] and its derivatives. The N^{α}-Boc protected (*S*)-2- and (*S*)-3-cyanophenylalanines **185a**,**b** can be prepared using a minor variation of the Schöllkopf methodology[73] as depicted in Scheme 25. The Schöllkopf *bis*-lactim ether **81** derived from Val-Gly is reacted with *n*-butyllithium and subsequent alkylation of the resulting lithium salt with either 2- or 3-cyanobenzyl bromide **183** gives the *trans*-disubstituted derivatives **184a** and **184b**. The *bis*-lactim ether derivatives are hydrolyzed into a mixture of 2- or 3-cyanophenylalanine methyl ester and D-valine methyl ester. The crude methyl esters are N^{α}-Boc protected and the target compounds are readily separated from *N*-Boc-D-valine methyl ester by flash chromatography in 46 and 58% yield, respectively. Hydrolysis of the methyl esters gives the carboxylates **185a** and **185b**. Addition of the carboxylates **185a**,**b** and commercially available **185c** to *N*,*O*-dimethylhydroxylamine hydrochloride gives the Weinreb amides **186a**–**c**, which are converted to their respective amidinophenylalanines **188a**–**c** using catalytic hydrogenation[101] of the intermediary amidoximes **187a**–**c**.[107]

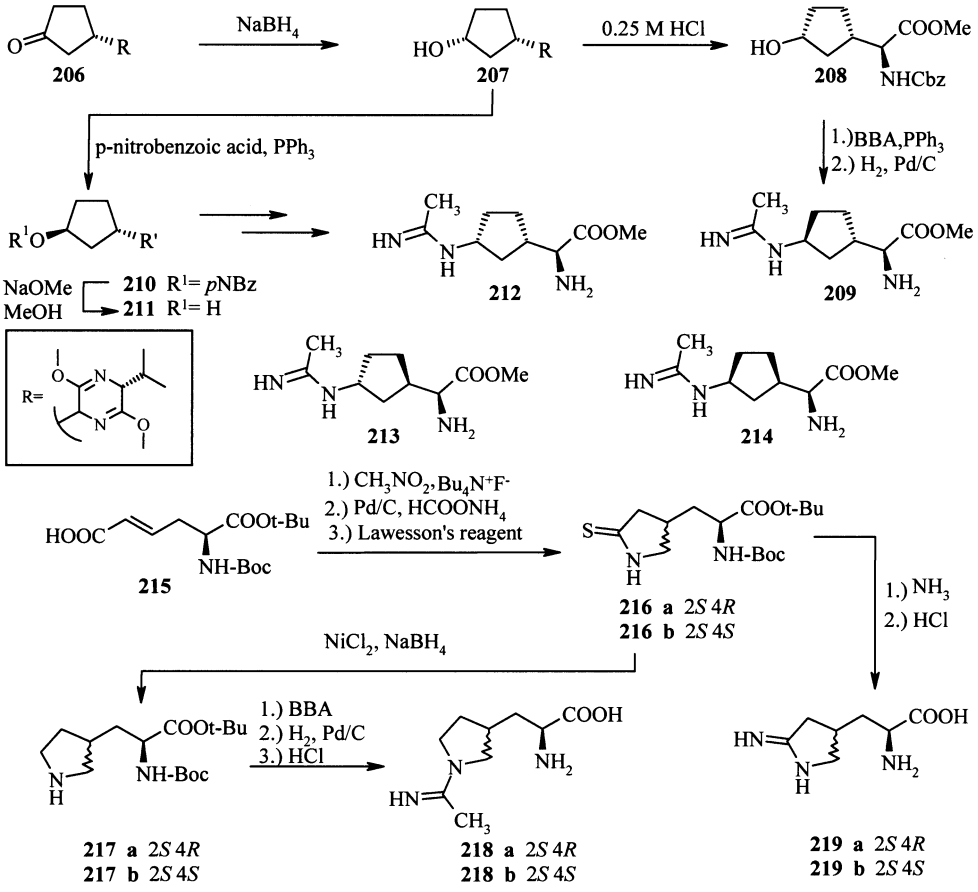
The (*S*)-configuration in the α-amino acid moiety of amidinophenylalanine can also be controlled by kinetic enantioselective deacylation of racemic **190**, catalyzed by kidney acylase[108] at pH 7. The racemic intermediates **190** are prepared by condensation of diethyl acetamidomalonate (**189**) with α-bromotoluonitriles **183**, followed by subsequent saponification and decarboxylation. By this method compounds **192a** and **192b** are obtained from **191** using the modified Pinner reaction or the imidate route for transforming a nitrile into an amidine moiety.[109,110] The same procedure is used for preparing benzamidrazones **193a**–**c** with a fluoro-substituted phenyl ring, using hydrazine as an



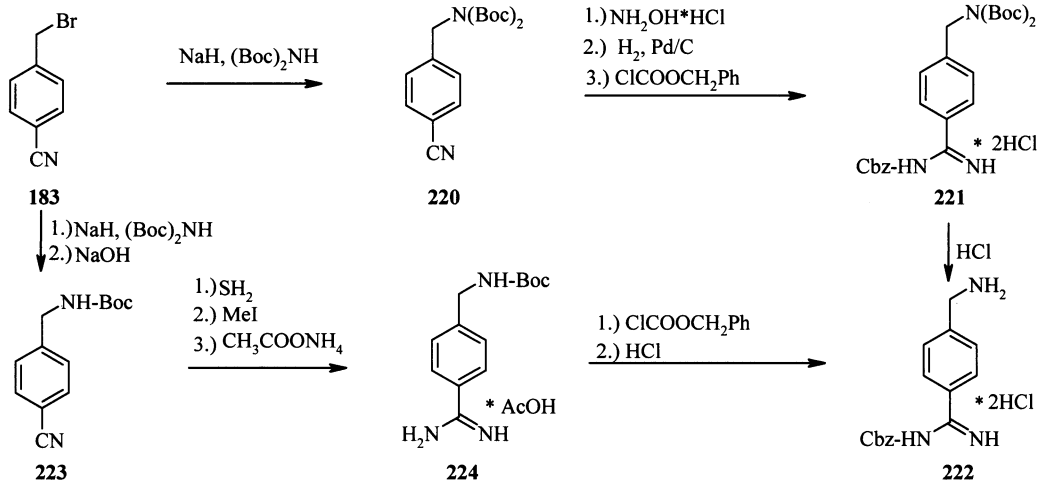
Scheme 27.

amine reagent in the modified Pinner reaction.[111] The fluorine hydrophobic and electron-withdrawing effects often provide drug candidates with improved pharmacokinetic properties without affecting their intrinsic activity, due to the similar steric demands of fluorine and hydrogen.[112] Incorporation of hydroxylamine hydrochloride, methylamine and ethylamine as the amine components in the modified Pinner synthesis provides benzamidoximes **194a** and *N*-alkyl-benzamidines **194b,c**[113] (Scheme 26).

Jendrala et al. used asymmetric hydrogenation of *N*-acetyl-α,β-didehydroamino acid **197** catalysed by rhodium(I)-(2*S*,4*S*)-1-*t*-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine (BPPM)[114] for the large-scale preparation of (*R*)-4-cyanophenylalanine **198** with 96% ee. The azlactone **196** is prepared from commercial *p*-cyanobenzaldehyde (**195**) according to the conventional method with *N*-acetylglycine in acetic anhydride.[115] Hydrolysis in hot aqueous NaOH solution provides *N*-acetyl-α,β-didehydro-*p*-cyanophenylalanine (**197**). Finally, transformation of the **198** cyano group into an amidino functionality is achieved by hydrogenolysis of the intermediary amidoxime group (Scheme 26).[116]



Scheme 28.

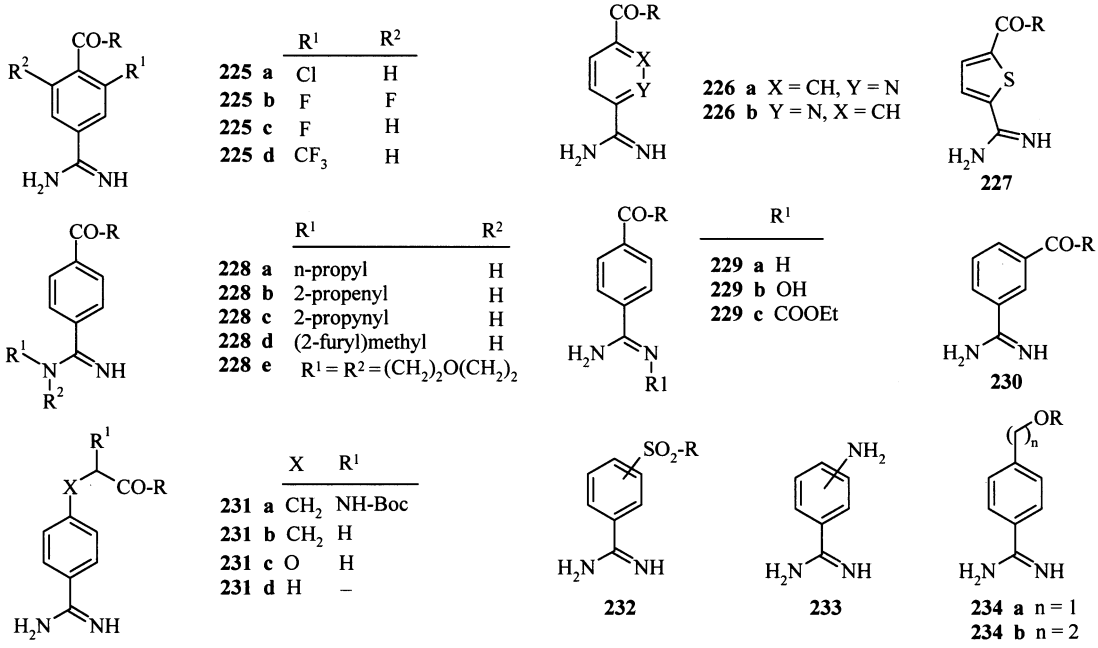


Scheme 29.

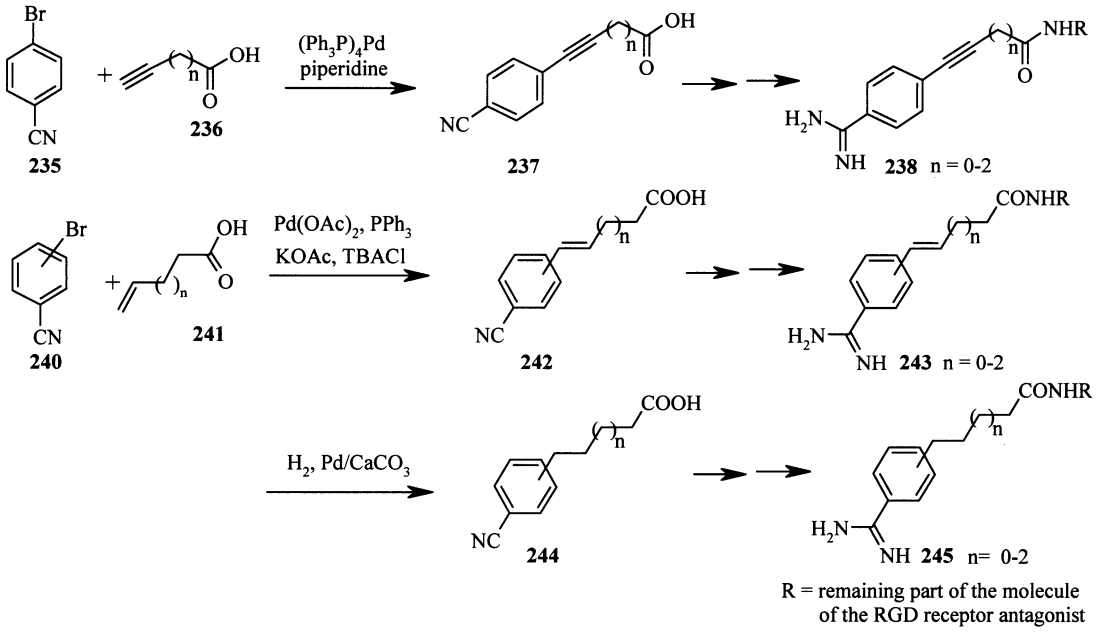
3.1.2. *N*-Phenyl- and *N*-alkyl-substituted acetamidines. *N*-Phenylacetamidines **204a–c**, which are conformationally restricted analogues of the arginine-based NOS inhibitors L-NIO **199a**, L-NIL **199b** and **199c**, are prepared as illustrated in Scheme 27. The key transformation in this sequence involves the use of *S*-benzyl- (**202a**), or preferably the odourless *S*-naphthylmethyl-thioimidate (**202b**),[117] to convert the substituted anilines **201** via protected intermediates **203a–c** to *N*-phenylacetamidines **204a–c**.[118]

Successful conversion of amine **144** (see Scheme 20) to acetamidine **205a** is performed using S-benzyl-thioimidate hydrobromide **202a**, which is sufficiently reactive to preclude intramolecular cyclisation of **144** to the corresponding lactam under various reaction conditions. Treatment of amine **144** with **202a** in ethanol at 0°C yields the hydrobromide salt of Boc protected acetamidine in 30% yield along with the undesired cyclised compound, which is also isolated in 30% yield. Removal of the Boc protecting group and ester hydrolysis gives amidine **205a** in 32% yield. An alternative synthetic strategy is employed for the preparation of acetamidine analogue **205b**. The acetamidine intermediate is synthesized from compound **147** (see Scheme 20) and *O*-ethyl acetimidate in a very sluggish, low-yielding process. Deprotection and ester hydrolysis affords the final amidine compound **205b**.[91]

Rigid analogues of (L-)-*N*-iminoethylornithine **199a** are prepared starting from the known (3*S*)-substituted cyclopentanone **206**.[119] Reduction of the carbonyl group with sodium borohydride leads predominantly to (1*R*,3*S*)-cyclopentanol **207**. Cleavage of the pyrazine ring using Schöllkopf conditions and subsequent protection affords **208**. Amidination with *N*,*N*′-bis(benzyloxycarbonyl)acetamidine (BBA)[120]



Scheme 30.



Scheme 31.

under Mitsunobu conditions gives, after hydrolysis of the Cbz groups, (2*S*,3*S*,5*S*)-acetamidine **209**. Starting from **207**, two successive Mitsunobu reactions, first with *p*-nitrobenzoic acid (*p*NBzOH), then with BBA, gives (2*S*,3*S*,5*R*)-isomer **212** after hydrogenolysis of the Cbz groups. (2*S*,3*R*,5*R*)-Isomer **213** and (2*S*,3*R*,5*S*)-isomer **214** are obtained analogously starting from (3*R*)-substituted cyclopentanone. Rigid analogues **218a**,**b** and **219a**,**b** of (L-)-*N*-iminoethylornithine are obtained from protected amino acid **215**, which is converted in three steps to the thiolactones **216a**,**b**. Ammonolysis and subsequent cleavage of the protective groups affords amino acids **219a**,**b**. Desulfurization of the thiolactams **216a**,**b** by nickel chloride and sodium borohydride yields cyclic compounds **217a**,**b**. Amidine formation using BBA, sequential hydrogenolysis and acid treatment results in the target molecules **218a**,**b**[121] (Scheme 28).

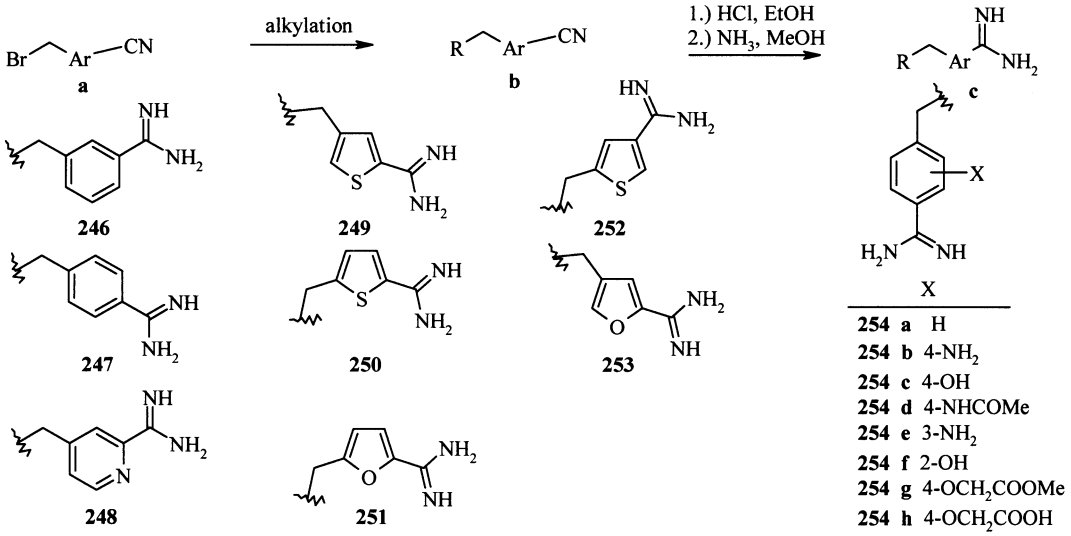
3.2. Benzamidines and heteroarylbenzamidines as arginine side-chain mimetics

The industrial preparation of protected 4-aminomethylbenzamidine **222**, which is the key intermediate for the synthesis of the potent thrombin inhibitor melagatran, relies on the transformation of the cyano group of **220** into the amidinium functionality of **221** by hydrogenolysis of the corresponding amidoxime. Compound **222** is conveniently prepared as depicted in Scheme 29 on a kilogram scale with 43% total yield. Starting from **183**, compound **222** can also be prepared via **224**, which is prepared from **223** by a modified Pinner synthesis. The overall yield for this pathway is 46%, but transformation of the intermediary thioimidate liberates methyl mercaptan, a highly toxic gas, the generation of which is not recommended from an industrial point of view.[122]

Benzamidines **225a**–**d**, that contain halo groups *meta* to the amidine moiety, as well as heteroaryl amidines **226a**,**b** and **227** illustrated in Scheme 30, are obtained from the corresponding cyanoaryl-(heteroaryl)carboxylic acids, which are commercially available or prepared according to the literature.[123] The nitrile moiety in these molecules is transformed into an amidine using a modified thio-Pinner sequence (Scheme 23). These arginine isosteres have found use in the preparation of RGD mimetics.[123]

N-Alkylated benzamidines **228a**–**e** are obtained using the same method from 4-cyanobenzoic acid. Cyano compounds are converted by classical Pinner reaction (Scheme 23) to the imidates, which are treated with appropriate amines to afford a series of *N*-alkylated amidines.[124] Treatment of an imidate with hydroxylamine affords amidoxime **229b**. The amidoxime group can serve as a prodrug functionality for the amidino group. Application of this principle led to orally active fibrinogen receptor antagonists.[125] Ethoxycarbonylation of the amidino group affords acylated benzamidine **229c**.[125] Benzamidine **230** is obtained analogously as benzaimidines **228a**–**e** from 3-cyanobenzoic acid.

For the synthesis of RGD mimetics **231a**–**d** and **232**, *N*-Boc-4-cyanophenylalanine, 4-cyanohydrocinnamic acid, 4-cyanophenoxyacetic acid, 4-cyanophenylacetic acid, 3-cyanobenzoic acid and 4-cyanobenzenesulfonic acid are incorporated into the RGD mimetic chain, whereupon a known modified Pinner reaction (Scheme 23) is used for the conversion of the cyano group into the amidino functionality.[126] 3- and 4-Aminobenzonitrile are precursors for 3- and 4-aminobenzamidines **233**, which are used in the synthesis of non-peptide RGD mimics.[124] Similarly, ether-linked benzamidinequinolones **234a**,**b**, RGD receptor antagonists, are prepared by alkylation of the corresponding quinolinols with 4-cyanobenzyl bromide or Mitsunobu coupling of 4-cyanophenylalkanols with the appropriate heteroaryl alcohol. The cyano group is finally converted to the amidine moiety using the thioimidate method (Scheme 23).[127]



Scheme 32.

The benzonitrile carboxylic acids **237**, **242** and **244** can be prepared according to Scheme 31. The halobenzonitriles **235** or **240** are coupled to an alkynoic- (**236**) or alkenoic- (**241**) carboxylic acid using a palladium(0)-based coupling reaction. The conditions for the palladium coupling reaction differ for the alkynoic and alkenoic acid coupling components. For the alkynoic acids, tetrakis(triphenylphosphine)-palladium(0) is employed as the catalyst and piperidine as the solvent whereas for the alkenoic acids, the extremely mild phase-transfer conditions of Jeffery and Larock (a tetrabutylammonium salt, palladium(II) acetate, potassium acetate and dimethyl formamide) are used. Compounds with an alkyl moiety **245** are obtained via selective catalytic reduction of the double bond. The benzonitriles **237**, **242** and **244** are converted to mimetics of RGD peptides **238**, **243** and **245**, by derivatisation of the carboxylic group and final conversion of the cyano to the amidino moiety by the thioimidate method, in near quantitative yields.[128,129]

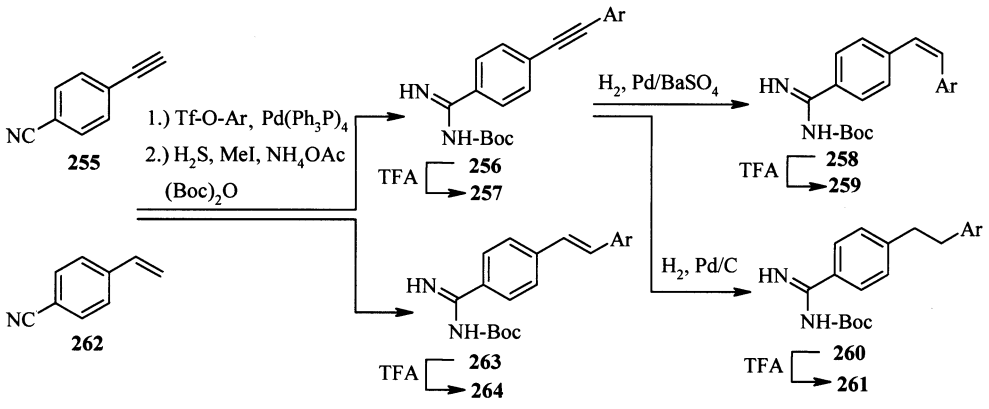
Aryl- and heteroarylamidines **246**–**253**[130] and **254a**–**h**[131,132] (Scheme 32) are prepared from their respective halomethyl-aryl- or halomethylheteroarylnitriles **a**, which are incorporated into different nucleophilic peptidomimetic chains to obtain nitriles **b**. The cyano group of **b** is transformed into the amidino functionality of **c** via imidate formation under Pinner conditions, followed by ammonolysis or by an alternative method via a thioimidate intermediate.[130–132]

Benzamidines **257**, **259**, and **261**, containing side chains with different grades of unsaturation, are prepared by palladium catalyzed coupling of (4-cyanophenyl)acetylene **255**[133] with the corresponding aryl triflate. Similarly, reaction of an aryl triflate with 4-cyanostyrene **262** using the method of Heck[134] affords after Boc-deprotection of **263**, the *trans*-olefin **264**. The nitrile moiety is transformed into a Boc-protected amidine of **256** by the classical thioimidate method.[127] Selective hydrogenation of **257** with palladium on barium sulfate yields, after deprotection of **258**, the *cis*-olefin **259**, while hydrogenation using palladium on carbon as a catalyst affords, after deprotection of **260**, the alkane **261** (Scheme 33).[127]

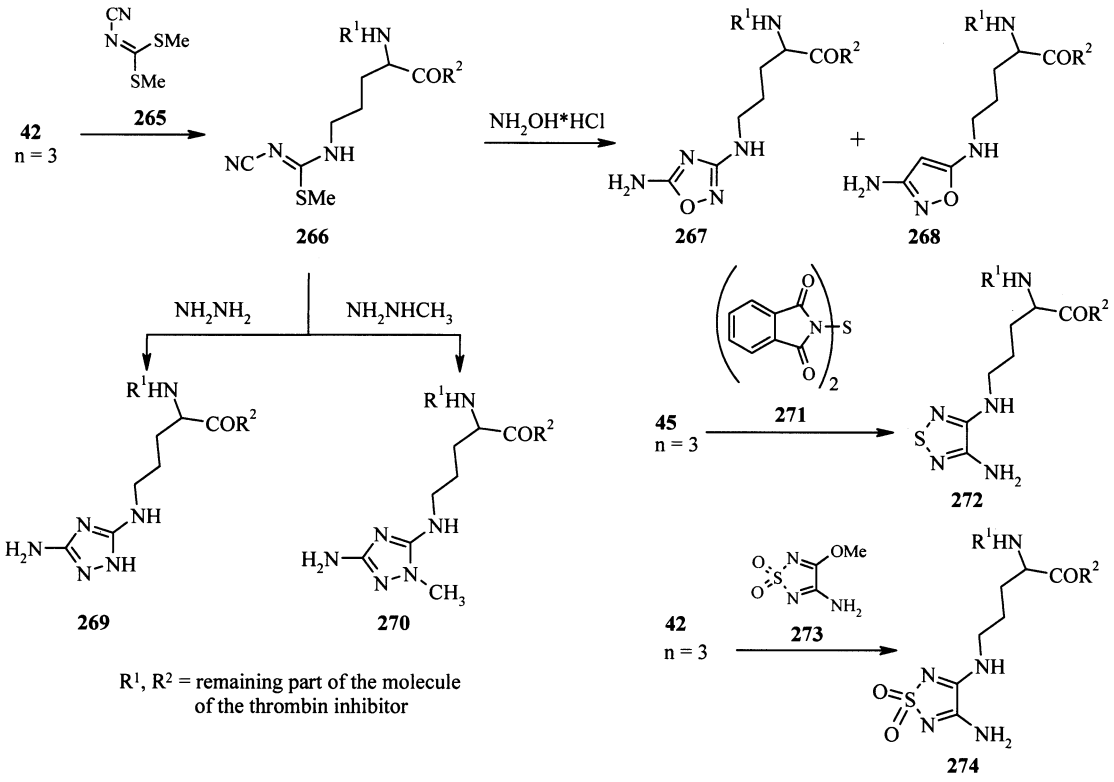
4. Heteroaromatic mimetics of arginine

4.1. α-Amino acid heteroaromatic arginine mimetics

The presence of highly basic functionalities such as guanidine



Scheme 33.

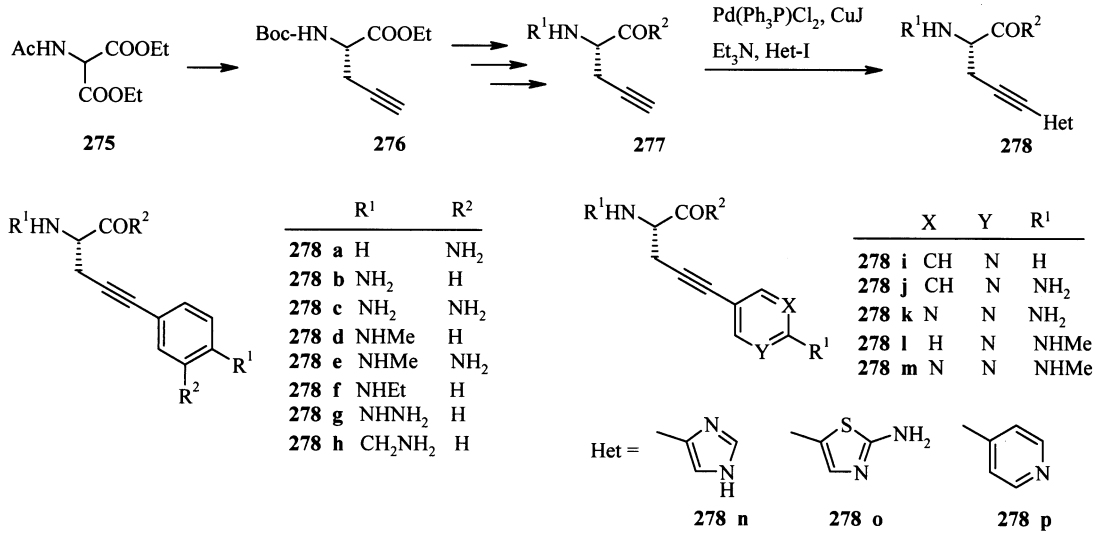


Scheme 34.

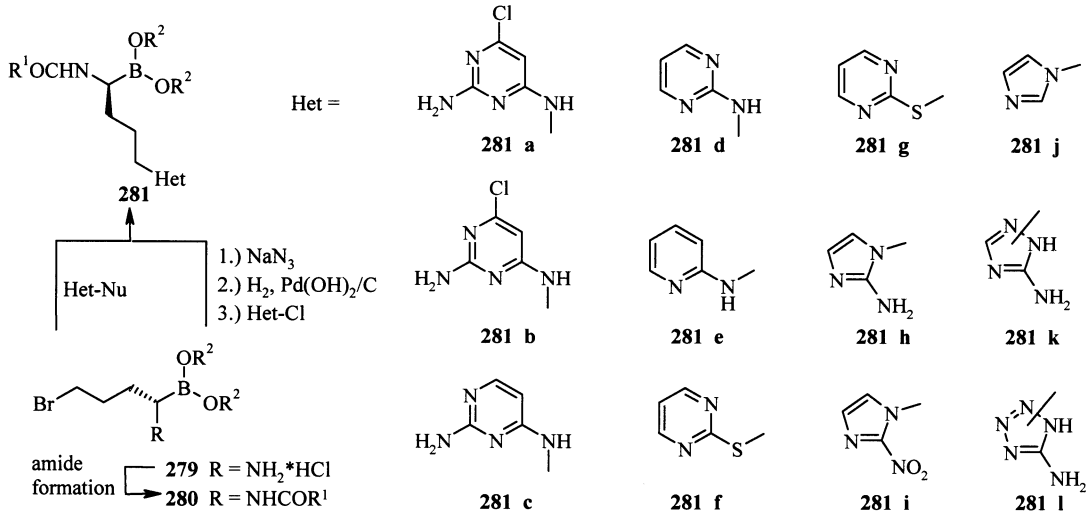
and amidine is often associated with poor oral bioavailability of peptidomimetic drugs. Replacement of the highly basic guanidine and amidine groups with moderately basic heteroaryl and amino-heteroaryl moieties therefore constitutes a general approach towards selective and orally bioavailable trypsin-like serine protease inhibitors and fibrinogen receptor antagonists.[3,5]

Protected lysine derivatives **42** (see Scheme 6) are transformed into heterocyclic nuclei **267–270** with reduced basicity as bioisosteric replacements of the arginine moiety in thrombin inhibitors.[56] Reaction of **42** with dimethyl *N*-cyanodithioiminocarbonate (**265**) affords *N*-cyano-*S*-methylisothiourea **266**, which is transformed with hydrazines and hydroxylamine into the triazoles **269** and **270** and a mixture of regioisomeric oxazoles **267** and **268**. Reaction of bis-amidine **45** (see Scheme 6) with *N*,*N*-thiobisphthalimide (**271**) affords thiadiazole mimetic **272**. Treatment of the amine **42** with 3-amino-4-methoxy-1,2,5-thiadiazole-*S*,*S*-dioxide (**273**)[57] in refluxing methanol gives the thiadiazole-*S*,*S*-dioxide compound **274** in good yield[56] (Scheme 34).

The synthesis of aryl- and heteroaryl-substituted propargylglycine derivatives **278a–p**, constituents of potent thrombin



Scheme 35.

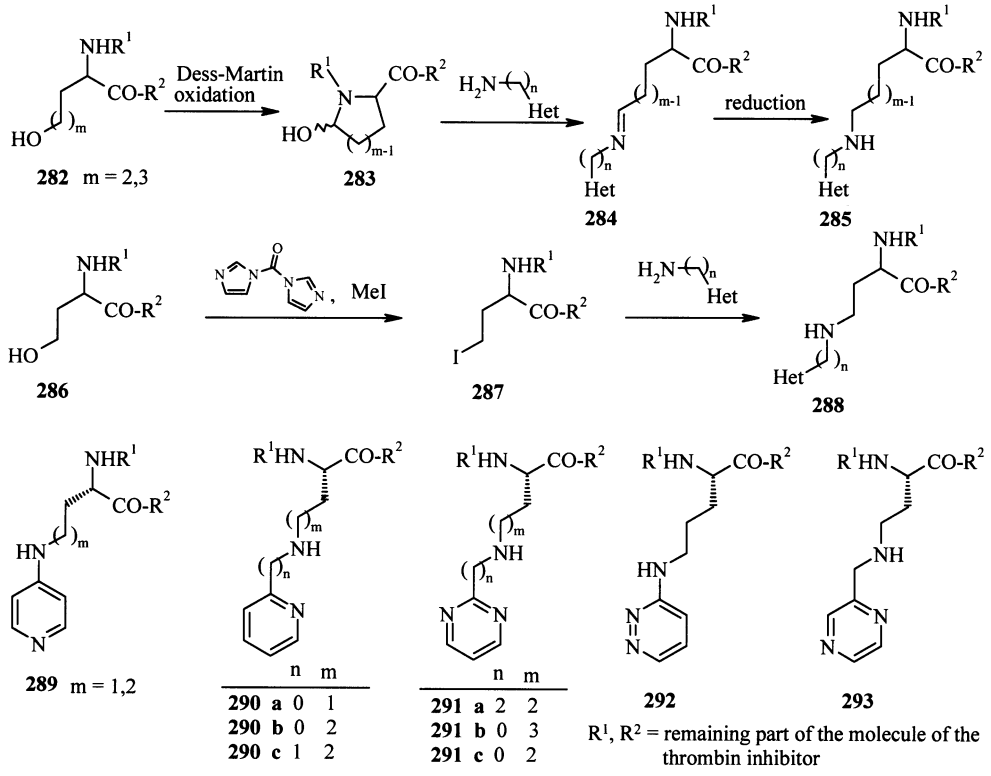


Scheme 36.

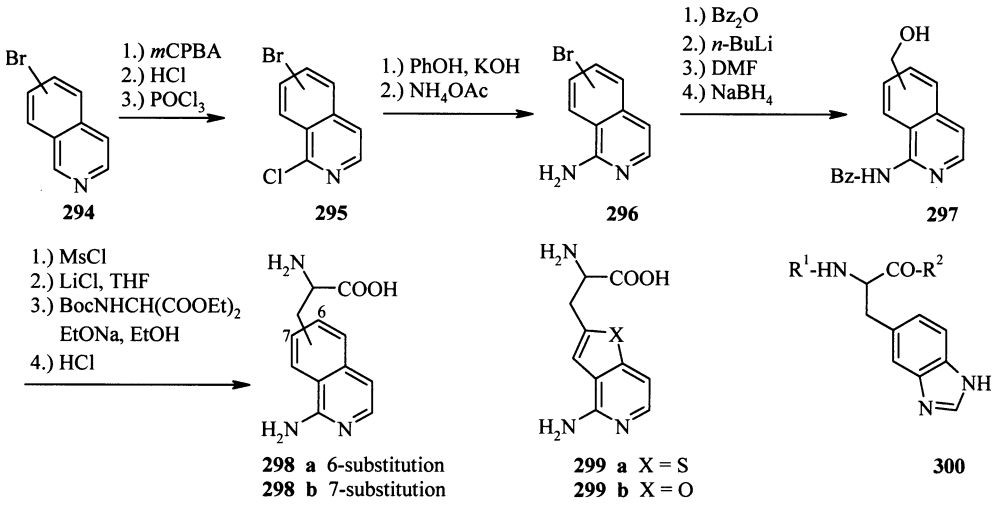
inhibitors with neutral and mildly basic heterocyclic moieties,[135] is outlined in Scheme 35. The requisite optically active amino acid template, (*S*)-*N*-Boc-propargylglycine (**276**), is prepared in four steps starting from diethyl acetylaminomalonate (**275**) and propargyl bromide.[136] The palladium catalysed coupling[137] of propargylglycine derivatives **277** with a variety of aryl and heteroaryl halides[135] at room temperature gives compounds of general structure **278** in good yield.

The guanidine moiety in the boroarginine side chain of thrombin inhibitors has been replaced with various five- and six-membered heterocycles **281a–l** ranging in ring size and basicity (Scheme 36). All the guanidino group replacements are prepared from α-aminoboronic acid **279**. Alkylation of its derivative **280** with appropriate functionalised heterocyles (Het-Nu) leads to the compounds **281f–l**. Alternatively, compounds **281a–e** are prepared via the boroornithine intermediate obtained by azide formation from **280** and subsequent catalytic hydrogenation, followed by chlorine displacement of halo-heterocycles.[138]

Dess–Martin oxidation of alcohols **282** followed by cyclization affords predominantly aminal **283** (Scheme 37). Formation of imine **284** by treatment of **283** with the appropriate heterocyclic amine and subsequent reduction of **284**



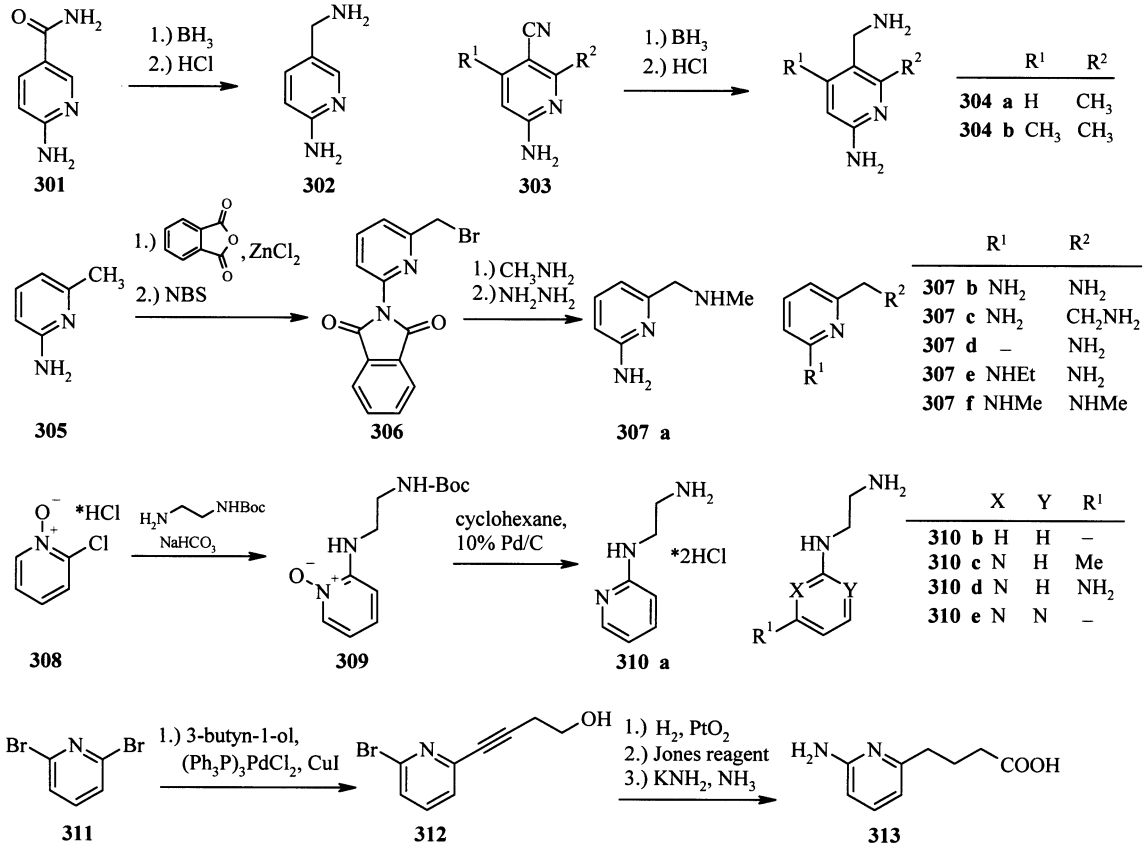
Scheme 37.



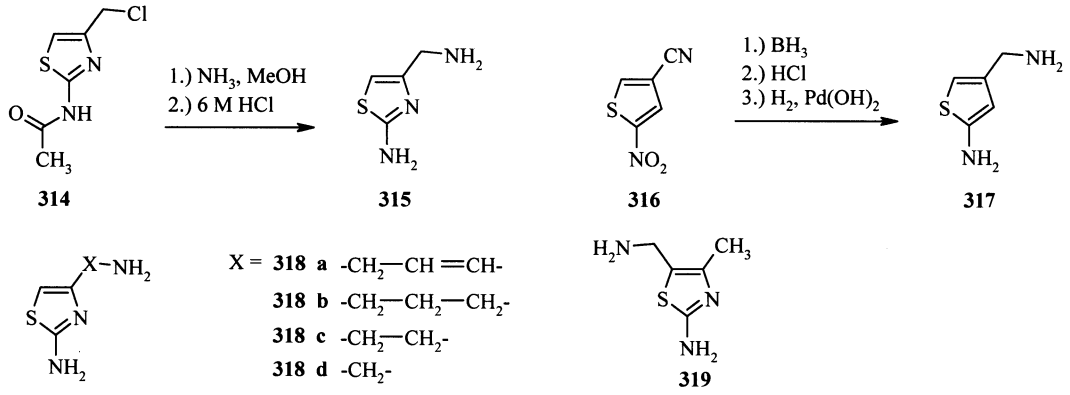
Scheme 38.

with lithium borohydride produces heteroaryl compounds **285**. Compounds **288** can be prepared from the alcohol **286** by forming the iodide **287** and subsequent reaction with various heterocyclic amines. An alternative procedure involves conversion of **286** to the amino analogue of **287** and treatment of this amine intermediate with halogenated heteroaryls. These heteroaromatic amines **289**–**293** are useful intermediates for the preparation of potent thrombin inhibitors.[139]

The [6- and 7-(1-aminoisoquinolinyl)] alanines **298a**[140] and **298b**[141] (pK_a=7.5) are prepared starting from 6- or 7-bromoisoquinoline (**294**), as depicted in Scheme 38. The successful introduction of the amino functionality at position 1 of bromoisoquinolines **296** includes *N*-oxidation of **294** followed by introduction of chlorine at position 1 to give **295**. Substitution of chlorine by phenoxide and, finally, introduction of the amino functionality gives 1-amino-isoquinoline **296**. The α-amino acid residue is introduced by the long classical route, which includes first protection of the amino group, *trans*-metallation using an excess of *n*-butyllithium, and quenching with *N*,*N*-dimethylformamide



Scheme 39.



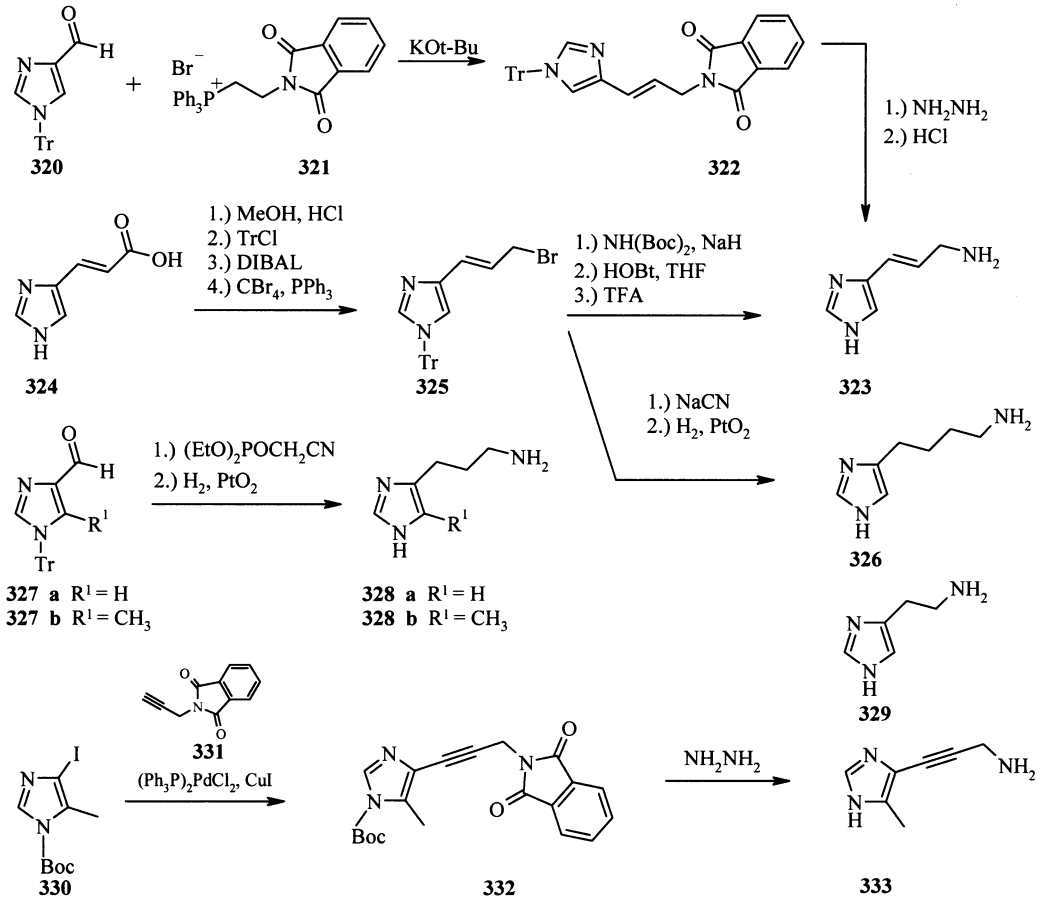
Scheme 40.

to yield aldehyde, which is reduced to the alcohol **297**. Transformation of the alcohol **297** into the corresponding chloride, substitution of the chloride by a protected aminomalonate, followed by hydrolysis and decarboxylation, affords racemic amino acid compounds **298a** and **298b**.[140,141]

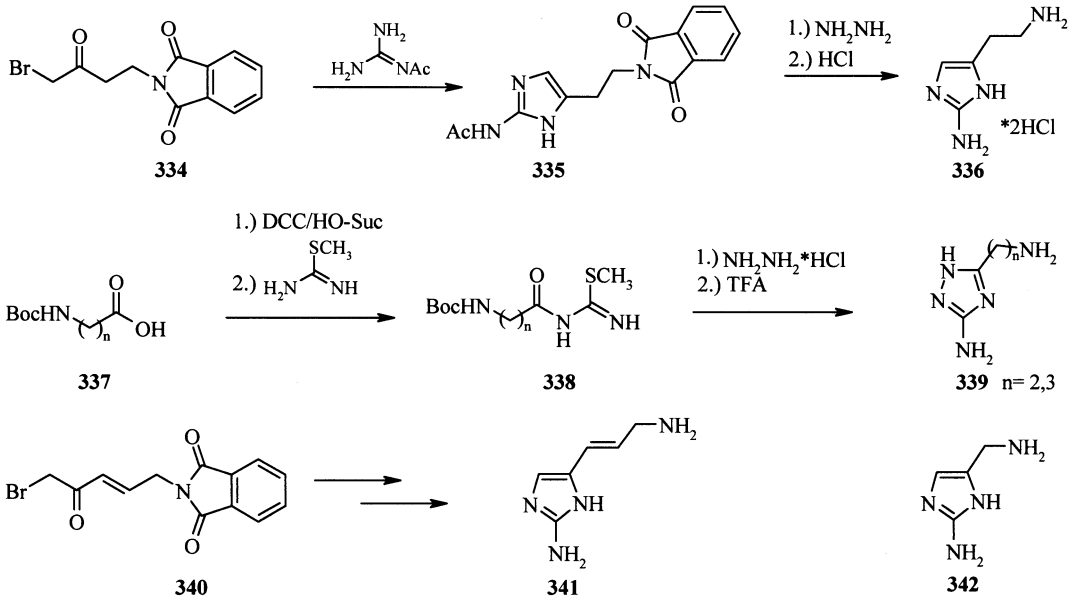
A similar procedure is used to prepare an aminothienopyridine-(**299a**) and an aminofuropyrimidine-alanine derivative **299b**, the difference being that formylation of position 2 of protected heterocycle is achieved by treatment with strong base and subsequent addition of *N*,*N*-dimethylformamide.[141,142] The benzimidazole side chain of **300**, a constituent of potential thrombin inhibitors, is prepared in one step by catalytic reduction of the corresponding *o*-aminonitrophenylalanine precursor using palladium on charcoal in formic acid or by acylation of the corresponding *o*-diaminophenylalanine derivative.[143]

4.2. Heteroaromatic arginine side-chain mimetics

Recently, there has been intensive progress in the design and synthesis of less basic heterocyclic arginine side-chain mimetics which incorporate two nitrogens in essentially



Scheme 41.



Scheme 42.

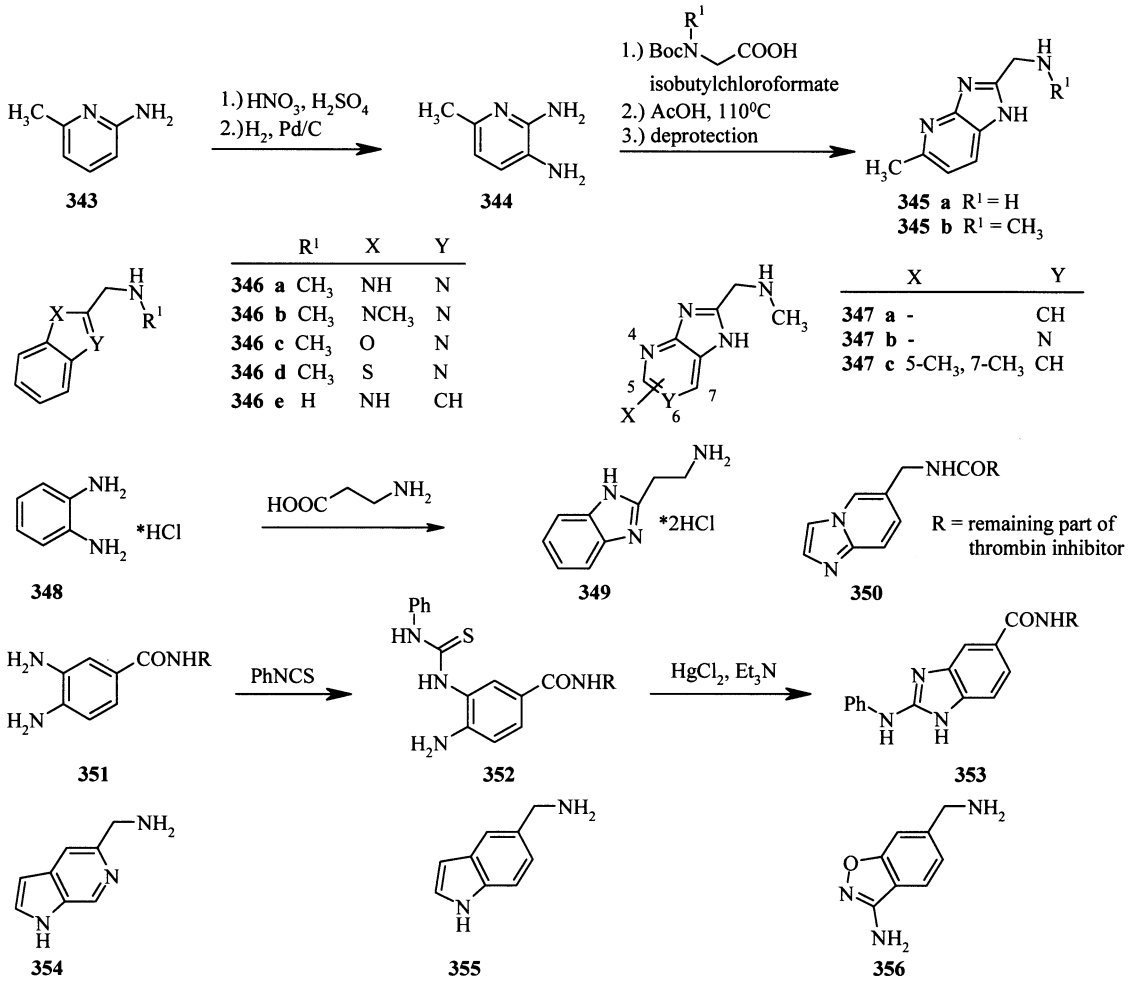
the same spatial relationship as an amidine or guanidine function. These arginine side-chain mimics include imidazoles, aminoimidazoles, aminopyrimidines, aminoquinolines, aminoisoquinolines, benzimidazoles, imidazopyrimidines and aminothiazoles.

Different aminopyridyl moieties, which have been incorporated into bioavailable thrombin inhibitors and nonpeptide vitronectin receptor antagonists, are depicted in Scheme 39. Aminopyridyl synthons **301**–**304** of these peptidomimetics[144–146] are prepared by rapid and quantitative reduction of the amide or nitrile group of 6-aminonicotinamide (**301**), and 2,4-dimethyl- and 2-methyl-3-cyano-6-aminopyridine (**302**) using a seven-fold excess of diborane at room temperature.[147] The method for the preparation of 2-amino-6-(aminomethyl)pyridine arginine side-chain mimetics **307a**–**f** includes the phthalimide protection of 2-amino-6-picoline (**305**), bromination of the methyl group, displacement of the bromine in **306** with an appropriate amine, and final hydrazinolysis of the phthalimide protecting group.[148] Reaction of 2-chloropyridine *N*-oxide hydrochloride (**308**) with *N*-Boc-ethylenediamine, reduction of *N*-oxide **309** by transfer hydrogenation and deprotection of the Boc-group leads to the 2-[(aminoethyl)amino] pyridine arginine side-chain mimetic **310a** in good yield. Compounds **310b**–**f** are prepared analogously.[148] Palladium catalysed coupling of 2,6-dibromopyridine (**311**) with 3-butyn-1-ol leads to the monodisplacement product **312** in 51% yield. Reduction of the alkyne **312**, Jones oxidation to the carboxylic acid and displacement of bromine affords aminopyridine compound **313** with a carboxylic group in the aliphatic side chain.[148]

Chlorine displacement of 2-acetamido-4-(chloromethyl)-1,3-thiazole (**314**) with ammonia in methanol and subsequent acid hydrolysis of the acetyl group provides 2-amino-4-(aminomethyl)-1,3-thiazole (**315**) in 88% yield[149] (Scheme 40). Nitrile reduction of the commercially available 2-nitro-4-cyanothiophene (**316**) by diborane and catalytic reduction of the nitro group leads to 2-amino-4-(aminomethyl)thiophene (**317**).[143] Recent patent literature describes the preparation of aminoalkyl-substituted aminothiazole synthons **318a**–**d** and **319**, which have been incorporated into potent thrombin inhibitors.[149]

Moderately basic imidazole moieties with different chain lengths have been successfully used as isosteric replacements for guanidino and amidino groups in many potent thrombin inhibitors and fibrinogen receptor antagonists. Compounds containing a three- or four-carbon tether are prepared from urocanic acid (**324**), which is transformed in four steps to the allylic bromide derivative **325**. Displacement of the bromide in **325** with the sodium salt of $NH(Boc)_2$, followed by deprotection, leads to the conformationally constrained arginine side-chain mimetic **323**[149–151] (Scheme 41). Alternatively, compound **323** can be prepared by reaction of *N*-trityl-imidazole-4-carbaldehyde (**320**) with the phosphonium salt **321** to obtain the intermediate **322**, followed by cleavage of both protecting groups.[152] Cyanation of bromide **325** and subsequent exhaustive hydrogenation affords the four-carbon-tethered compound **326**.[149–151] Horner-Emmons olefination of aldehydes **327a**,**b** followed by hydrogenation produced imidazole derivatives **328a** and **328b**.[149–151] Compound **329** containing the two-carbon-tether is prepared from histamine.[149–151] Bis(triphenylphosphine)palladium(II) chloride- and copper iodide-mediated coupling of *N*-propargylphthalimide **331** with compound **330**, which is prepared by iodination of 4-methylimidazole under basic conditions followed by Boc protection of the imidazole nitrogen atom, leads to the intermediate **332**. After deprotection with hydrazine, the imidazole propargylamine **333** is obtained.[149]

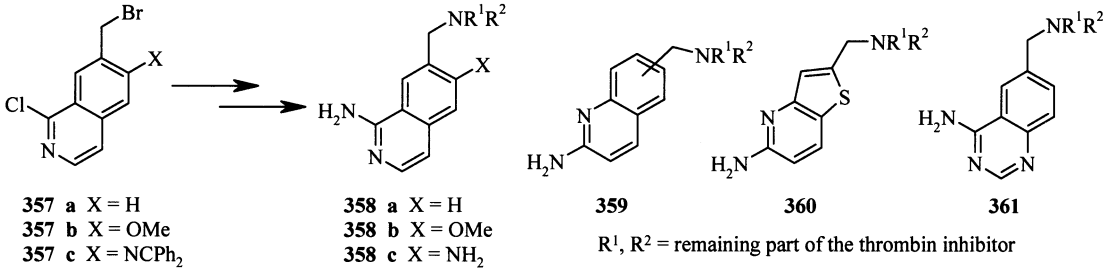
Cyclization of 1-bromo-4-phthalimido-2-butanone (**334**) and *N*-acetylguanidine, followed by simultaneous removal of the *N*-phthaloyl protecting group along with the *N*-acetyl group of **335** using hydrazine, affords 2-aminohistamine (**336**) in 23% overall yield (Scheme 42). The same method



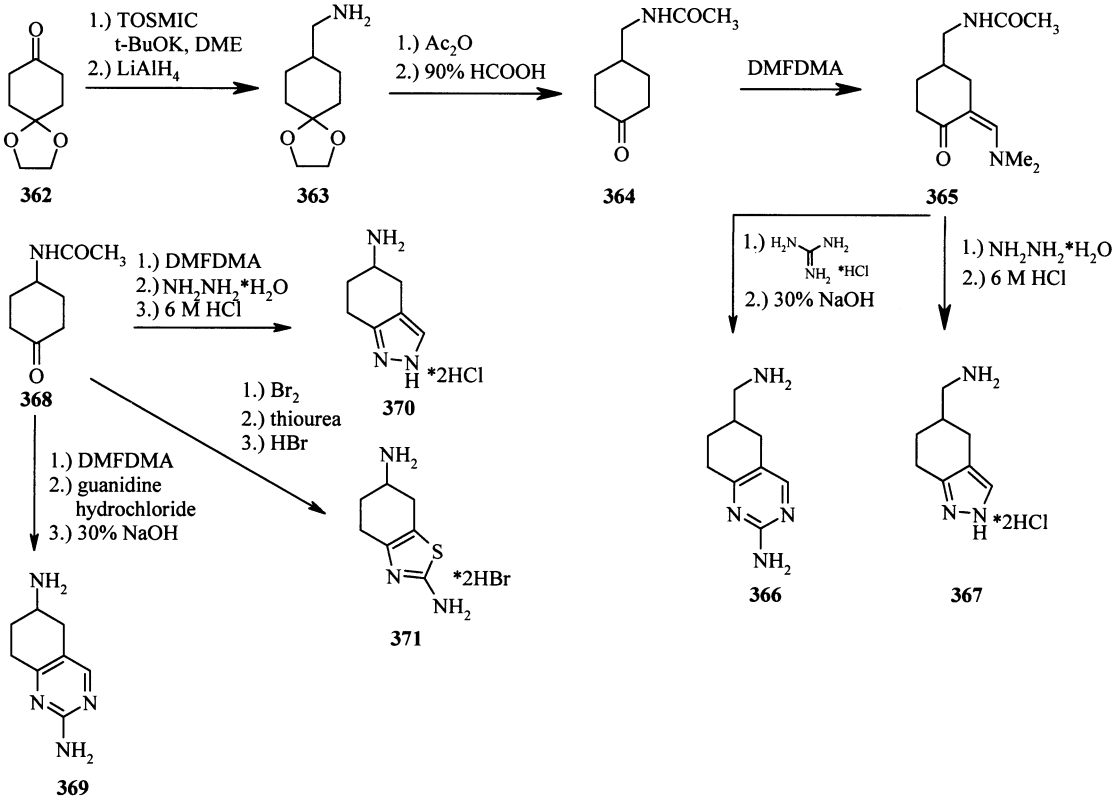
Scheme 43.

is used for the preparation of amino-imidazole compound **341** from α-bromoketone **340**.[153] The critical step in the synthesis of aminotriazole compounds **339** is the *S*-methyl thiourea derivatization of the appropriate protected carboxylic acid **337**. Cyclization of **338** with hydrazine and deprotection leads to the compounds **339** with pK_a values of between 7 and 8.[53] Aminoimidazole compound **342** is also used as an isosteric replacement for the guanidine side chain of arginine in thrombin inhibitors.[148]

The preparation of benzimidazole and imidazopyridine derivatives as arginine mimetics in vitronectin receptor antagonists is depicted in Scheme 43.[154–157] The benzimidazole and imidazopyridine compounds **345a**,**b**,[154–157] **346a**–**e**[156] and **347a**–**c**[154] are prepared from appropriately substituted 1,2-diaminoheterocycles such as **344**, which is prepared by nitration and subsequent reduction from **343**, or 1,2-phenylenenediamine, with Boc-glycine or Boc-sarcosine, by appropriate modification of the general procedure for preparing substituted benzimidazoles.[158] Scheme 43 depicts a representative synthesis of 2-aminomethyl-5-methyl-1(*H*)-imidazo[4,5-*b*]pyridine (**345a**).[154] The reaction of *o*-phenylenediamine hydrochloride (**348**) with β-alanine leads to the benzimidazole derivative **349**.[154] For the preparation of the imidazopyridine compound **350**, which is used as a heterocyclic arginine mimetic in thrombin inhibitors,[159,160] 2-aminopyridine is reacted with bromoacetaldehyde in the presence of a base.



Scheme 44.



Scheme 45.

Reaction of *o*-phenylenediamines **351** with phenylisothiocyanate affords thiourea **352** in 69% yield. Treatment of **352** with mercury(II) chloride and triethylamine at ambient temperature gives 2-aminobenzimidazoles **353**, which have been used as heterocyclic arginine side-chain mimetics.[77] Recently, two industrial research groups have reported nonbasic or weakly basic bicyclic heterocyclic arginine mimetics **354**,[161] **356**[162] and **355**,[163] which are intermediates for potent and selective thrombin inhibitors.

Conformational restriction of the benzamidine group (pK_a=11.6) by a hydrocarbon bridge leads to less basic aminoisoquinoline derivatives with a pK_a of 7.6. Aminoisoquinolines **358a–c** are prepared from intermediate 7-bromomethylisoquinolines **357a–c**.[164–166] The closely related 2-aminoquinolines **359**, 5-aminothieno[3,2-*b*]pyridines **360** and 4-aminoquinazolines **361** listed in Scheme 44 have also been used as arginine mimetics in potent Factor Xa inhibitors.[164–166]

The preparation of arginine side-chain mimetics **366**, **367** and **369–371** containing a five- or six-membered *N*-heterocyclic ring, optionally substituted by an amino group, thus mimicking the guanidino moiety of arginine, and a saturated cyclohexane ring with an amino or aminomethyl group mimicking the arginine trimethylene side chain, is outlined in Scheme 45. The synthesis of arginine mimetics **366** and **367** includes the preparation of the key intermediate enamino ketone **365**, which is obtained from commercially available 1,4-cyclohexanedione monoethylene ketal (**362**) by sequential procedure of reductive cyanation, reduction of the nitrile with lithium aluminium hydride, acetilation of **363**, deprotection and condensation of **364** with DMFDMA. The reaction of the enamino ketone **365** with guanidine hydrochloride or hydrazine hydrate, followed by hydrolysis, affords the heterocyclic compounds **366** and **367**.[167] Arginine mimetics **369**,[168] **370**[169] and **371**[170] are prepared analogously from the key intermediate **368**[168] by cyclocondensation with guanidine, hydrazine and thiourea, respectively. These heterocyclic arginine side-chain mimetics have been used to construct thrombin inhibitors.[171]

Acknowledgements

The authors thank Professor Roger Pain for critical reading of the manuscript.

References

1. (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720. (b) Goodman, M.; Ro, S. Burger's medicinal chemistry and drug discovery. In *Peptidomimetics for Drug Design*; Wolff, M. E., Ed.; Wiley: New York, 1995, pp 803–861.
2. (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341. (b) Böhm, H. J.; Klebe, G.; Kubinyi, H. *Wirkstoffdesign*, Spektrum Akademischer Verlag GmbH: Heilderberg, 1996, pp 469–485. (c) Ripka, W. C.; Vlasuk, G. P. *Ann. Rep. Med. Chem.* **1997**, *32*, 71–89.
3. (a) Tucker, T. J.; Isaacs, R. C. A. In *The development of novel noncovalent thrombin inhibitors*, Abell, A., Ed.; *Advances in Amino Acid Mimetics and Peptidomimetics*; 1999; Vol. 2, pp 53–87. (b) Rewinkel, J. B. M.; Adang, A. E. P. *Curr. Pharm.*

Design **1999**, *5*, 1043–1075. (c) Wiley, M. R.; Fisher, M. J. *Exp. Opin. Ther. Pat.* **1997**, *7*, 1265–1282. (d) Kimball, S. D. *Curr. Pharm. Design* **1995**, *1*, 441–468. (e) Menear, K. *Curr. Med. Chem.* **1998**, *5*, 457–468. (f) Sanderson, P. E. J.; Naylor-Olsen, A. M. *Curr. Med. Chem.* **1998**, *5*, 289–304.

4. (a) Hauptmann, J.; Stürzebecher, J. *Thromb. Res.* **1999**, *93*, 203–241. (b) Ripka, W.; Brunck, T.; Stanssens, P.; La Roche, Y.; Lauwereyes, M.; Lambeir, A. M.; Lasters, I.; De Maeyer, M.; Vlasuk, G.; Levy, O.; Miller, T.; Webb, T.; Tamura, S.; Pearson, D. *Eur. J. Med. Chem.* **1995**, *30*, 87–100.
5. (a) Zablocki, J.; Rao, S. N.; Baron, D. A.; Flynn, D. L.; Nicholson, N. S.; Feigen, L. P. *Curr. Pharm. Design* **1995**, *1*, 533–558. (b) Eldred, C. D.; Judkins, B. D. *Progr. Med. Chem.* **1999**, *36*, 29–91. (c) Hoekstra, W. J.; Poulter, B. L. *Curr. Med. Chem.* **1998**, *5*, 195–204.
6. (a) Marletta, M. A. *J. Med. Chem.* **1994**, *37*, 1901–1905. (b) Macdonald, J. E. *Ann. Rep. Med. Chem.* **1996**, *31*, 221–230.
7. Bodansky, M. *Principles of Peptide Synthesis*; Springer: New York, 1984; Vol. 192, pp 137–141.
8. Verdini, A. S.; Lucietto, P.; Fossati, G.; Giordani, C. *Tetrahedron Lett.* **1992**, *33*, 6541–6542.
9. (a) Barany, G.; Merrifield, R. B. *The Peptides*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1980; Vol. 2, pp 169–175. (b) Rzeszotarska, B.; Masiukiewicz, E. *Org. Prep. Proc. Int.* **1988**, *20*, 427–464.
10. Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 485–526, Chapter 10.
11. Rasmussen, C. R.; Villani Jr., F. J.; Reynolds, B. E.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Powell, E. T.; Molinari, A. J. *Synthesis* **1988**, 456–459.
12. Shotr, J. H.; Biermacher, U.; Dunnigan, D. A.; Leth, T. D. *J. Org. Chem.* **1963**, *6*, 275–277.
13. (a) King, H.; Tonkin, S. M. *J. Chem. Soc.* **1946**, 1063–1069. (b) McKay, A. F.; Hatton, W. G.; Braun, R. O. *J. Am. Chem. Soc.* **1956**, *78*, 6144–6147. (c) Jen, T.; Van Hoeven, H.; Groves, W.; McLean, R. A.; Love, B. *J. Med. Chem.* **1975**, *18*, 90–99.
14. (a) Bergeron, R. J.; McMains, J. S. *J. Org. Chem.* **1987**, *52*, 1700–1703. (b) Monache, G. D.; Botta, B.; Monache, F. D.; Espinal, R.; De Bonnevaux, S. C.; De Luca, C.; Botta, M.; Corelli, F.; Carmignani, M. *J. Med. Chem.* **1993**, *36*, 2956–2963.
15. (a) Nowak, K.; Kania, L. *Rozc. Chem.* **1969**, *43*, 1953–1960. (b) Lal, B.; Gangopadhyay, A. K. *Tetrahedron Lett.* **1996**, *37*, 2287–2290.
16. Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Synth. Commun.* **1993**, *23*, 1443–1445.
17. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677–7680.
18. (a) Ramage, R.; Green, J. *Tetrahedron Lett.* **1987**, *28*, 2287–2290. (b) Fujino, M.; Wakimasu, M.; Kitada, C. *Chem. Pharm. Bull.* **1981**, *29*, 2825–2831.
19. Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711–8714.
20. (a) Kim, K.; Lin, Y.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183–3186. (b) Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882–1884. (c) Miller, A. E.; Bischoff, J. J. *Synthesis* **1986**, 777–779. (d) Miller, A. E.; Bischoff, J. J. *Adv. Exp. Med. Biol.* **1986**, *197*, 925–929.
21. (a) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 249–2502. (b) Bredereck, H.; Effenberger, F.; Hajek, M. *Chem. Ber.* **1965**, *98*, 3178–3183.
22. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389–3392.
23. Drake, B.; Patek, M.; Lebi, M. *Synthesis* **1994**, 579–582.
24. (a) Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M. *Can. J. Chem.* **1958**, *36*, 1541–1549. (b) Fotsch, C. H.; Wong, C. H. *Tetrahedron Lett.* **1994**, *35*, 3481–3484.
25. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933–5936.
26. Granier, C.; Pedroso, E. M.; van Rietschoten, J. *Eur. J. Biochem.* **1978**, *82*, 293–299.
27. (a) Rasmussen, C. R. US 4,414,211, 1983 (b) Mikolajczyk, M. M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233–284.
28. Davis, T. L. *Org. Synth.* **1927**, *7*, 46–48.
29. Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278–2295.
30. (a) Corbin, J. L.; Reporter, M. *Anal. Biochem.* **1974**, *57*, 310–312. (b) Feldman, P. L.; Griffith, O. W.; Hong, H.; Stuehr, D. J. *J. Med. Chem.* **1993**, *36*, 491–496. (c) Ferrario, F.; Levi, S.; Sala, A.; Trupiano, F. *Synth. Commun.* **1991**, *21*, 191–196.
31. Patthy, A.; Bajusz, S.; Patthy, L. *Acta Biochem., Biophys. Acad. Sci. Hung.* **1997**, *12*, 191–196.
32. Cho, Y. B.; Furst, G.; Paik, W. K. *Anal. Biochem.* **1974**, *139*, 377–382.
33. Kennedy, K. J.; Simandan, T. L.; Dix, T. A. *Synth. Commun.* **1998**, *28*, 741–746.
34. Zhang, H. Q.; Fast, W.; Marletta, M. A.; Martasek, P.; Silverman, R. B. *J. Med. Chem.* **1997**, *40*, 3869–3870.
35. Olken, N. M.; Marletta, M. A. *J. Med. Chem.* **1992**, *35*, 1137–1144.
36. Fast, W.; Huff, E.; Silverman, R. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1449–1454.
37. Rasmussen, C. R.; Villani, F. J.; Weaner, L. E.; Reynolds, B. E.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Powell, E. T.; Milinari, A. J. *Synthesis* **1986**, 456–459.
38. Lundquist, J. T.; Orwig, K. S.; Dix, T. A. *J. Org. Chem.* **1999**, *64*, 9265–9267.
39. Lundquist, J. T.; Dix, T. A. *Tetrahedron Lett.* **1997**, *39*, 775–778.
40. (a) De Nanteuil, G.; Gloanec, P.; Lila, C.; Portevin, B.; Boudon, A.; Rupin, A.; Verbeuren, T. J. *Bioorg. Med. Chem. Lett.* **1995**, *3*, 1019–1024. (b) Lebarbier, C.; Carreaux, F.; Carboni, B. *Synthesis* **1996**, 1371–1374. (c) Fevig, J. M.; Abelman, M. M.; Brittelli, D. R.; Kettner, C. A.; Knabb, R. M.; Weber, P. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 295–300.
41. (a) Cheng, L.; Goodwin, C. A.; Scully, M. F.; Kakkar, V. V.; Claeson, G. *Tetrahedron Lett.* **1991**, *32*, 7333–7336. (b) Wang, C. L. J.; Taylor, T. L.; Mical, A. J.; Spitz, S.; Reilly, T. M. *Tetrahedron Lett.* **1992**, *33*, 7667–7670.
42. Neises, B.; Broersma, R. J.; Tarnus, C.; Piriou, F.; Remy, J. M.; Lintz, C.; Heminger, E. F.; Kutcher, L. W. *Bioorg. Med. Chem. Lett.* **1995**, *3*, 1049–1061.
43. (a) Hakansson, K.; Tulinsky, A.; Abelman, M. M.; Miller, T. A.; Vlasuk, G. P.; Bergum, P. W.; Lim-Wilby, M. S. L.; Brunck, T. K. *Bioorg. Med. Chem.* **1995**, *3*, 1009–1017. (b) Abelman, M. M.; Pearson, D. A.; Vlasuk, G. P.; Webb, T. R. WO Patent Appl. 9,421,673, 1994.

44. (a) Costanzo, M. J.; Maryanoff, B. E.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H. C.; Andrade-Gordon, P.; Kauffman, J. A.; Lewis, J. M.; Krishnan, R.; Tulinsky, A. *J. Med. Chem.* **1996**, *39*, 3039–3043. (b) Tamura, S. Y.; Shamblin, B. M.; Brunck, T. K.; Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1359–1364. (c) Akiyama, Y.; Tsutsumi, S.; Hatsushiba, E.; Ohuchi, S.; Okonogi, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 533–538.
45. Klein, S. I.; Dener, J. M.; Molino, B. F.; Gardner, C. J.; Alisa, R. D.; Dunwiddie, C. T.; Kasiewski, C.; Leadley, R. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2225–2230.
46. Lebarbier, C.; Carreaux, F.; Carboni, B.; Boucher, J. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2573–2576.
47. Matteson, D. S. *Stereodirected Synthesis with Organoboranes*. Springer: Berlin, 1995, pp 196.
48. (a) Bajusz, S.; Szell, E.; Bagdy, G.; Barabas, E.; Horvath, G.; Dioszegi, M.; Fittler, Z.; Szabo, G.; Juhazs, A.; Tomori, E.; Szilagyi, G. *J. Med. Chem.* **1990**, *33*, 1729–1735. (b) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2573–2578. (c) Semple, J. E.; Minami, N. K.; Tamura, S. Y.; Brunck, T. K.; Nutt, R. F.; Ripka, W. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2421–2426.
49. Tamura, S. Y.; Semple, J. E.; Ardecky, R. J.; Leon, P.; Carpenter, S. H.; Ge, Y.; Shamblin, B. M.; Weinhouse, M. I.; Ripka, W. C.; Nutt, R. F. *Tetrahedron Lett.* **1996**, *37*, 4109–4112.
50. Schuman, R. T.; Rothenberger, R. B.; Campbell, C. S.; Smith, G. F.; Gifford-Moore, D. S.; Paschal, J. W.; Gesellschen, P. D. *J. Med. Chem.* **1995**, *38*, 4446–4453.
51. (a) Marlowe, C. K.; Sinha, U.; Gunn, A. C.; Scarborough, R. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 13–16. (b) Balasubramanian, N.; St. Laurent, D. R.; Federici, M. E.; Meanwell, N. A.; Wright, J. J.; Schumacher, W. A.; Seiler, S. M. *J. Med. Chem.* **1993**, *36*, 300–303.
52. Grootenhuis, P. D. J.; De Man, A. P. A.; Adang, A. E. P. WO Patent Appl. 9,730,073, 1997.
53. Adang, A. E. P.; Lucas, H.; de Man, P. A.; Engh, R. A.; Grootenhuis, D. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3603–3608.
54. Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 499.
55. Siedem, C. WO Patent Appl. 9,926,926, 1999.
56. St. Laurent, D. R.; Balasubramanian, N.; Han, W. T.; Trehan, A.; Federici, M. E.; Meanwell, N. A.; Wright, J. J.; Seiler, S. M. *Bioorg. Med. Chem.* **1995**, *3*, 1145–1156.
57. (a) Crenshaw, R. R.; Algieri, A. A. US 4,588,826, 1986 (b) Balasubramanian, N.; Han, W. T. US 5,328,932, 1994.
58. (a) Narayanan, K.; Griffith, O. W. *J. Med. Chem.* **1994**, *37*, 885–887. (b) Shearer, B. G.; Lee, S.; Oplinger, J. A.; Frick, L. W.; Garvey, E. P.; Furfine, E. S. *J. Med. Chem.* **1997**, *40*, 1901–1905.
59. Furfine, E. S.; Harmon, M. F.; Paith, J. E.; Knowles, R. G.; Salter, M.; Kiff, R. J.; Duffy, C.; Hazelwood, R.; Oplinger, J. A.; Garvey, E. P. *J. Biol. Chem.* **1994**, *269*, 26677–26683.
60. De Nanteuil, G.; Lila, C.; Gloanec, P.; Laubie, M.; Verbeuren, T.; Simonet, S.; Rupin, A. EP Patent Appl. 6,887,88, 1995.
61. (a) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 497, Chapter 10. (b) Furfine, E. S.; Harmon, M. F.; Paith, J. E.; Garvey, E. P. *Biochemistry* **1993**, *32*, 8512–8517.
62. Feldman, P. L. *Tetrahedron Lett.* **1991**, *32*, 875–878.
63. Wallace, G. C.; Fukuto, J. M. *J. Med. Chem.* **1991**, *34*, 1748–1750.
64. (a) Gross, S. S.; Stuehr, D. J.; Aisaka, K.; Saffe, E. A.; Levi, R.; Griffith, O. W. *Biochem. Biophys. Res. Commun.* **1990**, *270*, 96–203. (b) Yamamoto, Y.; Kojima, S. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 498, Chapter 10.
65. Plummer, J. S.; Berryman, K. A.; Cai, C.; Cody, W. L.; DiMaio, J.; Doherty, A. M.; Edmunds, J. J.; He, J. X.; Holland, D. R.; Levesque, S.; Kent, D. R.; Narasimhan, L. S.; Rubin, J. R.; Rapundalo, S. T.; Siddiqui, M. A.; Susser, A. J.; St.-Denis, Y.; Winocour, P. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3409–3414.
66. Tamura, S. Y.; Levy, O. E.; Uong, T. H.; Reiner, J. E.; Goldman, E. A.; Ho, J. Z.; Cohen, C. R.; Bergum, P. W.; Nutt, R. F.; Brunck, T. K.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 745–749.
67. Levy, O. E.; Semple, J. E.; Lim, M. L.; Reiner, J.; Rote, W. E.; Dempsey, E.; Richard, B. M.; Zhang, E.; Tulinsky, A.; Ripka, W. C.; Nutt, R. F. *J. Med. Chem.* **1996**, *39*, 4527–4530.
68. Levy, O. E.; Tamura, S. Y.; Nutt, R. F.; Ripka, W. C. US 5,883,107, 1999.
69. Plummer, J. S.; Berryman, K. A.; Cai, C.; Cody, W. L.; DiMaio, J.; Doherty, A. M.; Eaton, S.; Edmunds, J. J.; Holland, D. R.; Lafleur, D.; Levesque, S.; Narasimhan, L. S.; Rubin, J. R.; Rapundalo, S. T.; Siddiqui, M. A.; Susser, A.; St-Denis, Y.; Winocour, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 835–840.
70. Cody, W. L.; Cai, C.; Doherty, A. M.; Edmunds, J. J.; He, J. X.; Narasimhan, L. S.; Plummer, J. S.; Rapundalo, S. T.; Rubin, J. R.; Van Huis, C. A.; St-Denis, Y.; Winocour, P. D.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2497–2502.
71. Danilewicz, J. C. WO Patent Appl. 9,633,993, 1996.
72. Joucla, M.; Mortier, J. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1566–1567.
73. (a) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798–799. (b) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091.
74. Kent, D. R.; Cody, W. L.; Doherty, A. M. In *Peptides; Frontiers of Peptide Science*, Tam, J. P., Kaumaya, P. T. P., Eds.; Proceedings of the 15th American Peptide Symposium, Kluwer Academic: Dordrecht, 1997; pp 688–689.
75. Engh, R.; Konetschnyrapp, S.; Krell, H.; Martin, U.; Tsaklakidis, C. WO Patent Appl. 9,721,725, 1997.
76. Lee, Y.; Marletta, M. A.; Martasek, P.; Roman, L. J.; Masters, B. S. S.; Silverman, R. B. *Bioorg. Med. Chem.* **1999**, *7*, 1097–1104.
77. Shearer, B. G.; Lee, S.; Franzmann, K. W.; White, H. A. R.; Sanders, D. C. J.; Kiff, R. J.; Garvey, E. P.; Furfine, E. S. *Bioorg. Med. Chem.* **1997**, *7*, 1763–1768.
78. Wagner, J.; Kallen, J.; Ehrhardt, C.; Evenou, J. P.; Wagner, D. *J. Med. Chem.* **1998**, *41*, 3664–3674.
79. Nicolaou, K. C.; Trujillo, J. I.; Jandeleit, B.; Chibale, K.; Rosenfeld, M.; Diefenbach, B.; Cheresh, D. A.; Goodman, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1185–1208.
80. Mitsunobu, O. *Synthesis* **1981**, 1–28.
81. Siedem, C. WO Patent Appl. 9,926,926, 1999.

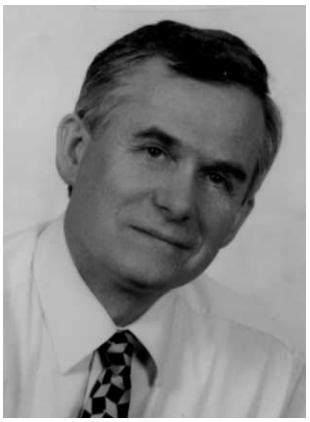
82. 2-(3,5-Dimethylpyrazolyl)-4,5-dihydroimidazole hydrobromide is available from Maybridge Chemical Co. Ltd.
83. Illig, C., WO Patent Appl. 9,736,580, 1997.
84. Soll, R. M.; Lu, T.; Tomczuk, B.; Illig, C. R.; Fedde, C.; Eisennagel, S.; Bone, R.; Murphy, L.; Spurlino, J.; Salemme, F. R. *Bioorg. Med. Chem.* **2000**, *10*, 1–4.
85. Wen-Fu Ku, T. WO Patent Appl. 9,626,190, 1996.
86. (a) Wirz, B.; Walther, W. *Tetrahedron: Asymmetry* **1992**, *3*, 1049–1054. (b) Wirz, B.; Walther, W. *Tetrahedron: Asymmetry* **1992**, *3*, 1087–1088.
87. Hilpert, K.; Ackermann, J.; Banner, D. W.; Gast, A.; Gubernator, K.; Hadvary, P.; Labler, L.; Müller, K.; Schmid, G.; Tschopp, T. B.; van de Waterbeemd, H. *J. Med. Chem.* **1994**, *37*, 3889–3901.
88. Lu, T.; Illig, C. R.; Tomczuk, B.; Soll, R. M.; Subasinghe, N. L.; Bone, R. F. WO Patent Appl. 9,711,693, 1997.
89. Lu, T.; Soll, R. M.; Illig, C. R.; Bone, R.; Murphy, L.; Spurlino, J.; Salemme, F. R.; Tomczuk, B. E. *Bioorg. Med. Chem.* **2000**, *10*, 79–82.
90. Antonsson, K. T.; Bylund, R.; Gustafsson, N. D.; Nilsson, N. U. I. WO Patent Appl. 9,429,336, 1994.
91. Konetschny-Rapp, S.; Krell, H. W.; Martin, U.; WO Patent Appl. 9,611,941, 1996.
92. Klein, S. I.; Czekaj, M.; Molino, B. F.; Chu, V. *Bioorg. Med. Chem.* **1997**, *7*, 1773–1778.
93. Hayashi, Y.; Harada, T.; Katada, J.; Tachiki, A.; Iijima, K.; Asari, T.; Uno, I.; Ojima, I. In *Peptides; Frontiers of Peptide Science*, Tam, J. P., Kaumaya, P. T. P., Eds.; *Proceedings of the 15th American Peptide Symposium*; Kluwer Academic: Dordrecht, 1997; pp 216–217.
94. (a) Winnek, P. S.; Anderson, G. W.; Marson, H. W.; Faith, E.; Roblin, R. O. *J. Am. Chem. Soc.* **1942**, *64*, 1682–1685. (b) Supuran, C. T.; Scozzafava, A.; Briganti, F. *J. Enzyme Inhib.* **1999**, *14*, 289–306.
95. Supuran, C. T.; Scozzafava, A.; Briganti, F.; Clare, B. W. *J. Med. Chem.* **2000**, *43*, 1793–1806.
96. Chandrakumar, N. S.; Desai, B. N.; Devadas, B.; Huff, R.; Khanna, I. K.; Rao, S. N.; Rico, J. G.; Rogers, T. E.; Ruminski, P. G.; Russell, M. A.; Yu, Y.; Gasiecki, A. F.; Malecha, J. W.; Miyashiro, J. M. WO Patent Appl. 9,952,896, 1999.
97. Oszczapowicz, J. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 623–688.
98. Boyd, G. V. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, pp 339–366.
99. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992, p 892.
100. For a review of imino esters, see: Neilson, D. G. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, Chapter 9, pp 425–483.
101. Stüber, W.; Koschinsky, R.; Reers, M.; Hoffmann, D.; Czech, J.; Dickneite, G. *Pept. Res.* **1995**, *8*, 78–85.
102. Katritzky, A. R.; Wallis, B.; Brownlee, R. T. C.; Topsom, R. D. *Tetrahedron* **1965**, *21*, 1681–1692.
103. Bolton, R. E.; Coote, S. J.; Finch, H.; Lowdon, A.; Pegg, N.; Vinader, M. V. *Tetrahedron Lett.* **1995**, *36*, 4471–4474.
104. Pass, M.; Bolton, R. E.; Coote, S. J.; Finch, H.; Hindley, S.; Lowdon, A.; McDonald, E.; McLaren, J.; Owen, M.; Pegg, N. A.; Mooney, C. J.; Tang, C. M.; Parry, S.; Patel, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 431–436.
105. Flinch, H.; Pegg, N. A.; McLaren, J.; Lowdon, A.; Bolton, R.; Coote, S. J.; Dyer, U.; Montana, J. G.; Ower, M. R.; Dowle, M.; Buckley, D.; Ross, B. C.; Campbell, C.; Dix, C.; Mooney, C.; Tang, C. M.; Patel, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2955–2960.
106. (a) Brandstetter, H.; Turh, D.; Hoeffken, W.; Grosse, D.; Stürzebecher, J.; Martin, P. D.; Edwards, B. F. P.; Bode, W. *J. Mol. Biol.* **1992**, *226*, 1085–1099. (b) Turk, D.; Stürzebecher, J.; Bode, W. *FEBS Lett.* **1991**, *287*, 133–138.
107. Kent, D. R.; Cody, W. L.; Doherty, A. M. *J. Pept. Res.* **1998**, *52*, 201–207.
108. Acylase can be purchased from Sigma (A 3010).
109. Kim, S.; Hwang, S. Y.; Kim, Y. K.; Yun, M.; Oh, Y. S. *Bioorg. Med. Chem. Lett.* **1997**, *10*, 769–774.
110. Stürzebecher, J.; Prasa, D.; Hauptmann, J.; Vieweg, H.; Wikström, P. *J. Med. Chem.* **1997**, *40*, 3091–3099.
111. Lee, K.; Jung, W. H.; Hwang, S. Y.; Lee, S. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2483–2486.
112. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197.
113. Lee, K.; Hwang, S. Y.; Hong, S.; Hong, C. Y.; Lee, C. S.; Shin, Y.; Kim, S.; Yun, M.; Yoo, Y. J.; Kang, M.; Oh, Y. S. *Bioorg. Med. Chem.* **1998**, *6*, 869–876.
114. Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954–2960.
115. Tripathy, P. K.; Mukerjee, A. K. *Synthesis* **1984**, 418–422.
116. Jendralla, H.; Seuring, B.; Herchen, J.; Kulitzscher, B.; Wunner, J.; Stuber, W.; Koschinsky, R. *Tetrahedron* **1995**, *51*, 12047–12058.
117. Shearer, B. G.; Oplinger, J. A.; Lee, S. *Tetrahedron Lett.* **1997**, *38*, 179–182.
118. Collins, J. L.; Shearer, B. G.; Oplinger, J. A.; Lee, S.; Garvey, P.; Salter, M.; Duffy, C.; Burnette, T. C.; Furfine, E. S. *J. Med. Chem.* **1998**, *41*, 2858–2871.
119. Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *100*, 1238–1239.
120. Eustache, J.; Grob, A. *Tetrahedron Lett.* **1995**, *36*, 2045–2046.
121. Eustache, J.; Grob, A.; Lam, C.; Sellier, O.; Schulz, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2961–2966.
122. Lila, C.; Gloanec, P.; Cadet, L.; Herve, Y.; Fournier, J.; Leborgne, F.; Verbeuren, T.; De Nanteuil, G. *Synth. Commun.* **1998**, *28*, 4419–4429.
123. Fisher, M. J.; Giese, U.; Harms, C. S.; Kinnick, M. D.; Lindstorm, T. D.; McCowan, J. R.; Mest, H. J.; Morin, J. r.; J, M.; Mullaney, J. T.; Paal, M.; Rapp, A.; Rühter, G.; Ruterbories, K. J.; Sall, D. J.; Scarborough, T. S.; Schotten, T.; Stenzel, W.; Towner, R. D.; Um, S. L.; Utterback, B. G.; Wyss, V. L.; Jakubowski, J. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 385–389.
124. Okumura, K.; Shimazaki, T.; Aoki, Y.; Yamashita, H. *J. Med. Chem.* **1998**, *41*, 4036–4052.
125. Weller, T.; Alig, L.; Beresini, M.; Blackburn, B.; Bunting, S.; Hadvary, P.; Müller, M. H.; Knopp, D.; Levet-Trafit, B.; Lipari, M. T.; Modi, N. B.; Müller, M.; Refino, C. J.; Schmitt, M.; Schönholzer, P.; Weiss, S.; Steiner, B. *J. Med. Chem.* **1996**, *39*, 3139–3147.
126. Alig, L.; Edenhofer, A.; Hadvay, P.; Hürzeler, M.; Knopp, D.; Müller, M.; Steiner, B.; Trzeciak, A.; Weller, T. *J. Med. Chem.* **1992**, *35*, 4393–4407.
127. Fisher, M. J.; Gunn, B.; Harms, C. S.; Kline, A. D.; Mullaney, T.; Nunes, A.; Scarborough, R. M.; Arfsten,

A. E.; Skelton, A.; Um, S. L.; Utterback, B. G.; Jakubowski, J. A. *J. Med. Chem.* **1997**, *40*, 2085–2101.
128. Zablocki, J. A.; Miyano, M.; Garland, R. B.; Pireh, D.; Schretzman, L.; Rao, S. N.; Lindmark, R. J.; Penzer-Knodle, S. G.; Nicholson, N. S.; Taite, B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1993**, *36*, 1811–1819.
129. Zablocki, J. A.; Tjoeng, F. S.; Bovy, P. R.; Miyano, M.; Garland, R. B.; Williams, K.; Schretzman, L.; Zupec, M. E.; Rico, J. G.; Lindmark, R. J.; Toth, M. V.; McMackins, D. E.; Adams, S. P.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. *Bioorg. Med. Chem. Lett.* **1995**, *3*, 539–551.
130. Ewing, W. R.; Becker, M. R.; Manetta, V. E.; Davis, R. S.; Pauls, H. W.; Mason, H.; Choi-Sledeski, Y. M.; Green, D.; Cha, D.; Spada, A. P.; Cheney, D. L.; Mason, J. S.; Maignan, S.; Guilloteau, J. P.; Brown, K.; Collusi, D.; Bentley, I.; Bostwick, J.; Kasiewski, C. J.; Morgan, S. R.; Leadley, R. J.; Dunwiddie, C. T.; Perrone, M. H.; Chu, V. *J. Med. Chem.* **1999**, *42*, 3557–3571.
131. Choi-Sledeski, Y. M.; McGarry, D. G.; Green, D.; Mason, H. J.; Becker, M. R.; Davis, R. S.; Ewing, W. R.; Dankulich, W. P.; Manetta, V. E.; Morris, R. L.; Spada, A. P.; Cheney, D. L.; Brown, K. D.; Collusi, D. J.; Chu, V.; Heran, C. L.; Morgan, S. R.; Bentley, R. G.; Leadley, R. J.; Maignan, S.; Guilloteau, J. P.; Dunwiddie, C. T.; Pauls, H. W. *J. Med. Chem.* **1999**, *42*, 3572–3587.
132. Becker, M. R.; Ewing, W. R.; Davis, R. S.; Pauls, H. W.; Ly, C.; Li, A.; Mason, H. J.; Choi-Sledeski, Y. M.; Spada, A. P.; Chu, V.; Brown, K. D.; Colussi, D. J.; Leadly, R. J.; Bentley, R.; Bostwick, J.; Kasiewski, C.; Morgan, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2753–2758.
133. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–631.
134. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.
135. Lee, K.; Kwang, S. Y.; Park, C. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1013–1018.
136. Crisp, G. T.; Robertson, T. A. *Tetrahedron* **1992**, *48*, 3239–3250.
137. Crisp, G. T.; Robertson, T. A. *Tetrahedron Lett.* **1992**, *48*, 3239–3250.
138. Dominguez, C. D.; Carini, D. J.; Weber, P. C.; Knabb, R. M.; Alexander, R. S.; Kettner, C. A.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1996**, *7*, 79–84.
139. Misra, R. N. US 5,371,091, 1994.
140. Rewinkel, J. B. M.; Lucas, H.; van Galen, P. J. M.; Noach, A. B. J.; van Dinthler, T. G.; Rood, A. M. M.; Jenneboer, A. J. S. M.; van Boeckel, C. A. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 685–690.
141. Rewinkel, J. B. M.; Lucas, H.; Smit, M. J.; Noach, A. B. J.; van Dinthler, T. G.; Rood, A. M. M.; Jenneboer, A. J. S. M.; van Boeckel, C. A. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2837–2842.
142. Van Boeckel, C. A. A.; van Galen, P. J. M.; Rewinkel, J. B. M. WO Patent Appl. 9,847,876, 1998.
143. Biberach, A. H. ; Laupheim, R. S.; Psiorz, M.; am Rhein, I., Warthausen, K. B.; Biberach, T. M.; Mittelbiberach, R. Z. US 5,391,556, 1995.
144. Feng, D. M.; Gardell, S. J.; Lewis, S. D.; Bock, M. G.; Chen, Z.; Freidinger, R. M.; Naylor-Olsen, A. M.; Ramjit, H. G.; Woltmann, R.; Baskin, E. P.; Lynch, J. J.; Lucas, R.; Shafer, J. A.; Dancheck, K. B.; Chen, I. W.; Mao, S. S.; Kruger, J. A.; Hare, T. R.; Mulichak, A. M.; Vacca, J. P. *J. Med. Chem.* **1997**, *40*, 3726–3733.
145. Sanderson, P. E.; Lyle, T. A.; Cutrona, K. J.; Dyer, D. L.; Dorsey, B. D.; McDonough, C. M.; Naylor-Olsen, A. M.; Chen, I. W.; Chen, Z.; Cook, J. J.; Cooper, C. M.; Gardell, S. J.; Hare, T. R.; Krueger, J. A.; Lewis, S. D.; Lin, J. H.; Lucas, Jr., B. J.; Lyle, E. A.; Lynch, Jr., J. J. *J. Med. Chem.* **1998**, *41*, 4466–4474.
146. Coburn, C. A.; Rush, D. M.; Williams, P. D.; Homnick, C.; Lyle, E. A.; Lewis, S. D.; Lucas, Jr., J. B.; Di Muzio-Mower, J. M.; Juliano, M.; Krueger, J. A.; Vastag, K.; Chen, I. W.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1069–1072.
147. Brown, H. C.; Heim, P. *J. Org. Chem.* **1983**, *38*, 912–916.
148. Keenan, R. M.; Miller, W. H.; Barton, L. S.; Bondinell, W. E.; Cousins, R. D.; Eppley, D. F.; Hwang, S. M.; Kwon, C.; Lago, M. A.; Nguyen, T. T.; Smith, B. R.; Uzinskas, I. N.; Yuan, C. C. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1801–1806.
149. Isaacs, R. C. A.; Naylor-Olsen, A. M.; Dorsey, B. D.; Newton, C. L. WO Patent Appl. 9,842,342, 1998.
150. Wiley, M. R.; Weir, L. C.; Briggs, S. L.; Chirgadze, N. Y.; Clawson, D.; Gifford-Moore, D. S.; Schacht, A. L.; Smith, G. F.; Vasudevan, V.; Zornes, L. L.; Klimkowski, V. J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2767–2772.
151. Klimkowski, V. J.; Wiley, M. R. US 5,811,402, 1998.
152. Sellier, C.; Buschauer, A.; Elz, S.; Schunack, W. *Liebigs Ann. Chem.* **1992**, 317–323.
153. Little, T. L.; Eebber, S. E. *J. Org. Chem.* **1994**, *59*, 7299–7305.
154. Keenan, R. M.; Lago, A. M.; Miller, W. H.; Ali, F. E.; Cousins, R. D.; Hall, L. B.; Hwang, S. M.; Jakas, D. R.; Kwon, C.; Louden, C.; Nguyen, T. T.; Ohlstein, E. H.; Rieman, D. J.; Ross, S. T.; Samanen, J. M.; Smith, B. R.; Stadel, J.; Takata, D. T.; Vickery, L.; Yuan, C. C. K.; Yue, T. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3171–3176.
155. Miller, W. H.; Bondinell, W. E.; Cousins, R. D.; Erhard, K. F.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Newlander, K. A.; Ross, S. T.; Haltiwanger, R. C.; Bradbeer, J.; Drake, F. H.; Gowen, M.; Hoffman, S. J.; Hwang, S. M.; James, I. E.; Lark, M. W.; Lechowska, B.; Rieman, D. J.; Stroup, G. B.; Vasko-Moser, J. A.; Zembryki, D. L.; Azzarano, L. M.; Adams, P. C.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1807–1812.
156. Keenan, R. M.; Miller, W.; Lago, A. M.; Ali, F. E.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Hwang, S. M.; Jakas, D. R.; Ku, T. W.; Kwon, C.; Nguyen, T. T.; Reader, V. A.; Rieman, D. J.; Ross, S. T.; Takata, D. T.; Uzinskas, I. N.; Yuan, C. C. K.; Smith, B. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3165–3170.
157. Keenan, R. M.; Miller, W.; Kwon, C.; Ali, F. E.; Callahan, J. F.; Calvo, R. R.; Hwang, S. M.; Kopple, K. D.; Peishoff, C. E.; Samanen, J. M.; Wong, A. S.; Yuan, C. K.; Huffman, W. F. *J. Med. Chem.* **1997**, *40*, 2289–2292.
158. Nestor, Jr., J. J.; Horner, B. L.; Ho, T. L.; Jones, G. H.; McRae, G. I.; Vickery, B. H. *J. Med. Chem.* **1984**, *27*, 320–325.
159. Sanderson, P. E.; Naylor-Olsen, A. M. WO Patent Appl. 9,961,442, 1999.
160. Starrett, Jr., J. E.; Montzka, T. A.; Crosswell, A. R.; Cavanagh, R. L. *J. Med. Chem.* **1989**, *32*, 2204–2210.
161. Sanderson, P. E.; Lyle, T. A.; Dorsey, B. D.; Stanton, M. G.; Staas, D.; Coburn, C.; Naylor-Olsen, A. D.; Morrissette,

M. M.; Selnick, H. G.; Nanterment, P. G.; Williams, P. D.; Stauffer, K. J.; Burgey, C.; Isaacs, R. WO Patent Appl. 0,026,211, 2000.
162. Sanderson, P. E.; Lyle, T. A.; Dorsey, B. D.; Stanton, M. G.; Naylor-Olsen, A. D. WO Patent Appl. 0,026,210, 2000.
163. Blagg, J.; Brown, A. D.; Gautier, E. C. L.; Smith, J. D.; McElroy, A. B. EP Patent Appl. 0,997,474, 2000.
164. Choi-Sledeski, Y. M.; Becker, M. R.; Green, D. M.; Davis, R.; Ewing, W. R.; Mason, H. J.; Ly, C.; Spada, A.; Liang, G.; Cheney, D.; Barton, J.; Chu, V.; Brown, K.; Colussi, D.; Bentley, R.; Leadley, R.; Dunwiddie, C.; Pauls, H. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2539–2544.
165. Gong, Y.; Becker, M.; Choi-Sledeski, Y. M.; Davis, R. S.; Salvino, J. M.; Chu, V.; Brown, K. D.; Pauls, H. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1033–1036.
166. Choi-Sledeski, Y. M.; Pauls, H. W.; Barton, J. N.; Ewing, W. R.; Green, D. M.; Becker, M. R. WO Patent Appl. 9,825,611, 1998.
167. Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron Lett.* **2000**, *41*, 5589–5592.
168. Marinko, P.; Obreza, A.; Peterlin-Mašič, L.; Krbavčič, A.; Kikelj, D. *J. Heterocycl. Chem.* **2000**, *37*, 405–409.
169. Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481–491.
170. Schneider, C. S.; Mierau, J. *J. Med. Chem.* **1987**, *30*, 494–498.
171. Kikelj, D.; Peterlin-Mašič, L.; Marinko, P.; Breznik, M.; Stegnar, M.; Trampuš-Bakija, A.; Fortuna, M. Slovene Patent Appl. P-200000111, 2000.

Biographical sketch

Lucija Peterlin-Mašič was born in 1974 in Ljubljana, Slovenia. In 1998 she received her BSc degree in pharmacy from the University of Ljubljana. She is currently working on her PhD thesis under the mentorship of Professor Danijel Kikelj (University of Ljubljana) in the field of design and synthesis of new thrombin inhibitors as potential antithrombotics. Her research interests include medicinal chemistry, combinatorial chemistry, peptidomimetics, peptide and heterocyclic synthesis and molecular modelling.



Danijel Kikelj received his Diploma in pharmacy in 1978 and a Master of Science Degree in 1983 from the University of Ljubljana, Slovenia. He received his PhD in 1988 from the University of Heidelberg (Germany) under the direction of Professor R. Neidlein in the field of heterocyclic chemistry. After returning to the Faculty of Pharmacy, University of Ljubljana he took the position of an Assistant Professor of pharmaceutical chemistry in 1990. He was promoted to Associate Professor in 1995 and to Full Professor of pharmaceutical chemistry in 2000. From 1991 till 1992 he was a Professor of pharmaceutical chemistry at the Faculty of Pharmacy of the Heidelberg University. His current research interests focus on the design and synthesis of peptidomimetics, stereoselective synthesis and heterocyclic chemistry.