Design and synthesis of non-peptide integrin inhibitors

Pro Gradu Thesis

Jyväskylä University
Department of Chemistry
Section of Organic Chemistry

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Abstract

In the literature section journal articles involving the design and synthesis of nonpeptide inhibitors are presented. The articles were located by using the Internet and downloaded or retrieved from the libraries of Jyväskylä University and Oulu University.

The experimental section shows the attempted syntheses for a potential nonpeptide inhibitor for the integrin $\alpha_{II}\beta_1$. Professor Kari Rissanen designed 12 possible target molecules which were tested on a computer model of integrin $\alpha_{II}\beta_1$ by Bio-Tie Therapies. 10 molecules showed at least some binding potential due to their suitable size, flexibility and three branches with negative charges.

Due to the limited time available only syntheses of molecule **669** and modified versions of molecules **673** and **677** were attempted.

It was attempted to test the reduction reaction on the small molecule **680** with a cyano group and an ester bond in order to see whether the ester bond would tolerate the conditions without breaking. The synthesis of *p*-ethyl ester benzyl amine **682'** was unsuccesfully attempted.

The synthesis of target molecule **669** failed.

Target molecule **673**:
The synthesis of 4-cyano benzyl bromide **685** was succesful but the synthesis of diketone **688** failed.

Target molecule **677**:
The synthesis of diol **690** was succesful but the synthesis of molecule **691**, modified version of molecule **677**, failed.

Foreword

The articles studied were located in the Internet using the SciFinder Scholar program and downloaded or retrieved from the libraries of Jyväskylä University and Oulu University.

The experimental section was carried out in the fall of 2001 at Jyväskylä University in co-operation with Bio-Tie Therapies

The counselor and supervisor for the thesis was professor Kari Rissanen (Department of Chemistry, Section of Organic Chemistry at Jyväskylä University).

Contents

Abbreviations

Ada	Adamant-1-yl
AIBN	α,α'-azo-*iso*-butyronitrile
Arg	arginine
Asp	aspartate
Bn, Bzl	benzyl
Cbz	carbobenzoxy group
DMAP	dimethylaminopropylamine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
d	duplet
Fmoc	N[(9H-fluoren-9-ylmethoxy)carbonyl]oxysuccinimide
Gly	glycine
GP	glycoprotein
m	multiplet
MS	mass spectrum
NBS	N-bromosukkinimide
NMR	nuclear magnetic resonance
PPA	polyphosphoric acid
ppm	parts per million
Pth	phthalimide
RLE	rabbit liver esterase
s	singlet
t	triplet
TAB	*tert*-butylamine borane
TCP	trityl chloride polystyrol
TFA	trifluoro acetic acid
THF	tetrahydrofuran
Tr	triphenylmethyl
Z	Cbz, carbobenzoxy group

1 Preface

For the literature section of the thesis scientific journals were investigated to find synthesis routes for non-peptide integrin inhibitors. The inhibitors were then divided into several subsidiary groups according to their chemical structure. Since many molecules could have been listed under two or more groups, there is some overlapping. Most of the research conserning non-peptide integrin inhibitors is focused on the RGD (Arg-Gly-Asp) sequence which is recognized by the platelet fibrinogen receptor $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) and the vitronectin receptor $\alpha_V\beta_3$.[5]

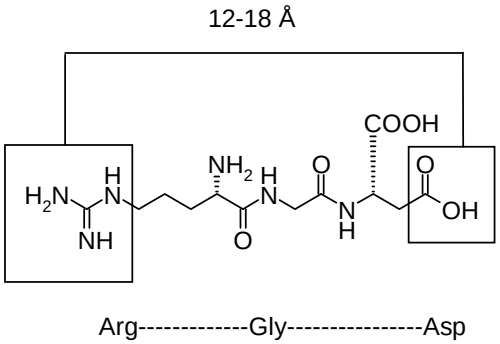


Figure 1.[1] RGD sequence.

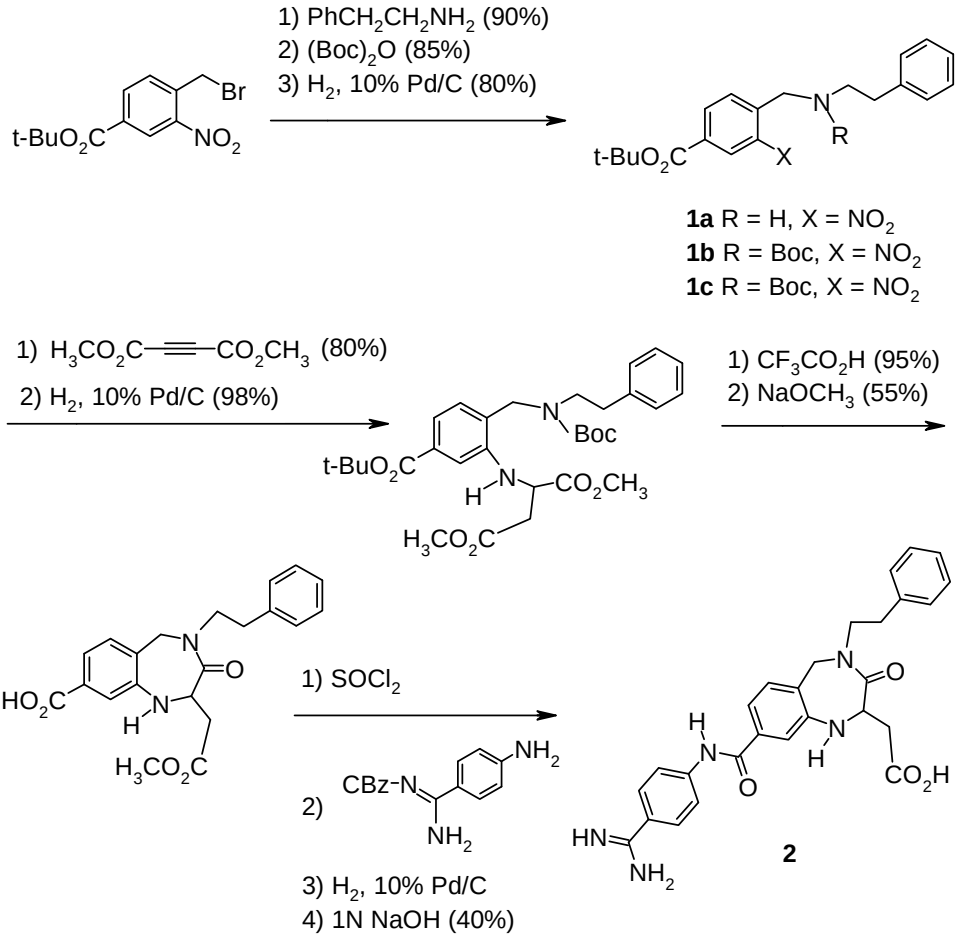
The RDG sequence plays a key part in aggregation of platelets causing vaso-occulsive disorders such as unstable angina, myocardial infarction, transient ischemic attacks, stroke and thrombosis ($\alpha_{IIb}\beta_3$).[32,36] Also, it's involved in osteoclast-mediated bone resorption - $\alpha_V\beta_3$ is present in osteoclasts but not bone forming osteoblasts.[39] Cyclic peptides with RGD are potent inhibitors, which has led to the search for non-peptido-mimetic inhibitors.[34] There are significant structural differences between RGD-containing cyclic peptides which makes it very difficult to design a single molecular pharmacophore for fibrinogen or vitronectin receptor binding.[4]

The less studied $\alpha_{IV}\beta_1$, VLA-4 (very late antigen 4) found in stimulated monocytes and lymphnotes binds to cytokine-activated endothelial cells and to finbronectin causing diseases such as asthma and multiple sclerosis.[43]

2 Benzodiazepine and benzazepine compounds

2.1 Compounds containing a benzamidine or *p*-cyanophenyl unit

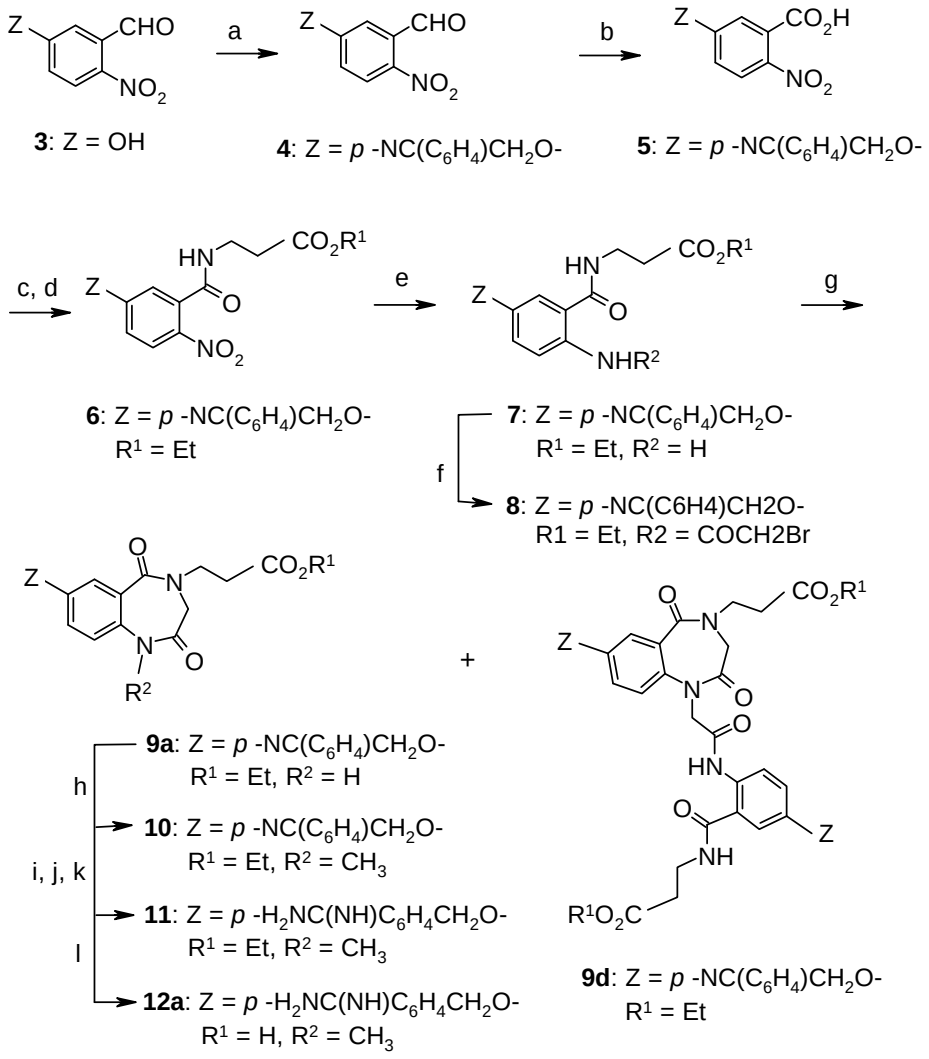
Ku *et al.* have designed a high-affinity, potent, non-peptide GPIIb/IIIa antagonist **2** based on the stucture of a constrained RGD-containing cyclic peptide.[2]



Scheme 1. The synthesis of molecule **2**.[2]

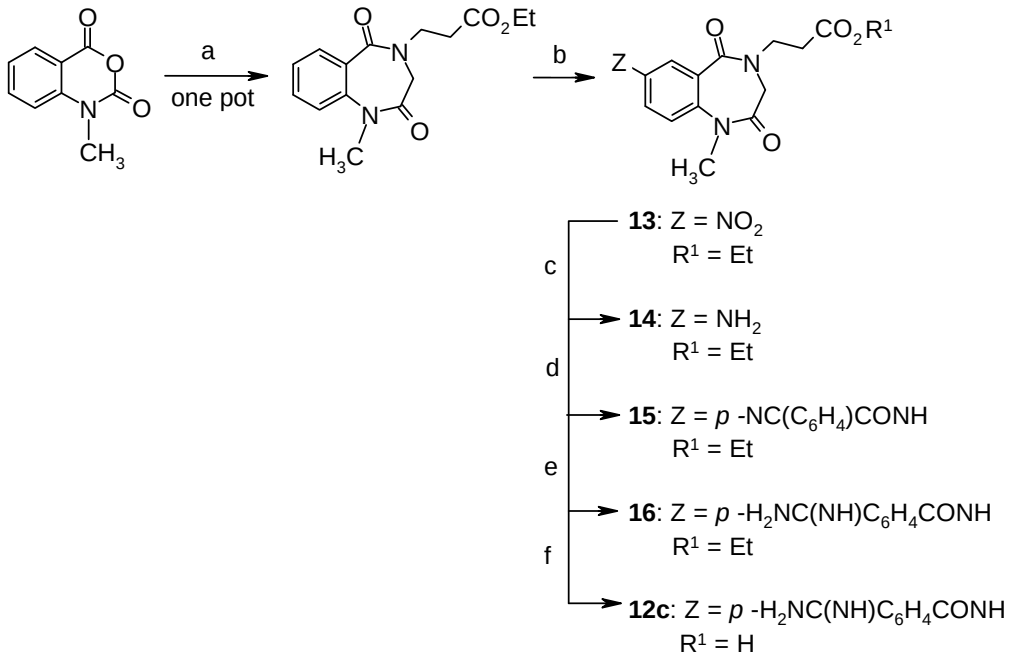
Ku *et al.* found that the 1,4-benzodiazepine nucleus helps mimic the C-7 turn around Asp and the extended Gly residue thus providing conformational rigidity.

Robarge *et al*. have synthesized several potent tricyclic GPIIbIIIa antagonists.[3] According to retrosynthetic analysis the required precursors for the benzyloxy, ethynyl and amide series of tricyclic GPIIb/IIIa antagonists were secondary amines **9a-c**, Schemes 3, 4 and 16.



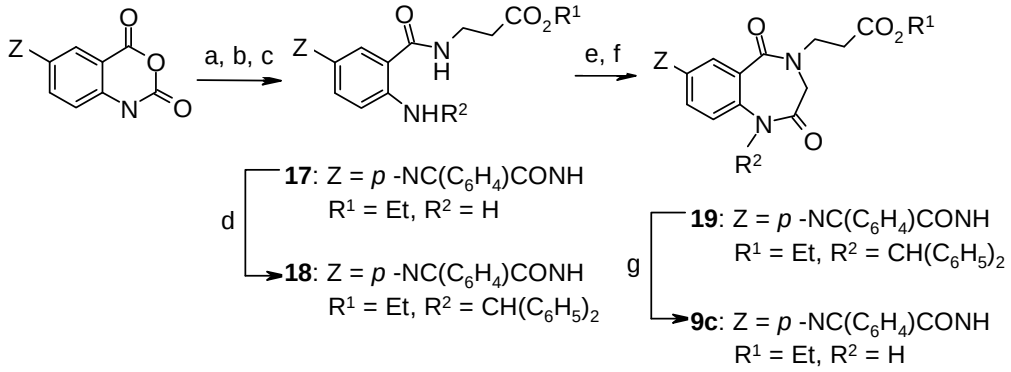
(a) K_2CO_3, DMF, *p*-$NC(C_6H_4)CH_2Br$, 104%; (b) $KMnO_4$, Bu_4NBr, H_2O, C_5H_5N, 45% (ratio of **5**/*p*-$NC(C_6H_4)CO_2H$, ca. 5/1); (c) $(COCl)_2$, C_6H_6, DMF, 65°C; (d) $ClH_3NCH_2CH_2CO_2Et$, $NaHCO_3$, THF/H_2O (1/2), 94%; (e) $SnCl_2$, H_2O, EtOAc/EtOH; (f) $BrCOCH_2Br$, H_2O/CH_2Cl_2, triturate w/ EtOH to purify (or recrystallize from EtOH), 50-70%; (g) powdered K_2CO_3/DMF (0.018-0.026 M), 50°C, 2-3 h, 53-77%; (h) MeI, Cs_2CO_3, DMF, rt, 75%; (i) pyridine/Et_3N(1/1), H_2S, 50°C, 4 h; (j) CH_2Cl_2/MeI (5/1), sealed tube, 50°C, 1 h; (k) NH_4OAc (xs), MeOH, 50°C, 12 h, RP HPLC, 64% (overall from **10**); (l) THF/NaOH (aq. 4.2 equiv.), RP HPLC, 75%.

Scheme 2. Synthesis of benzodiazepinediones.[3]



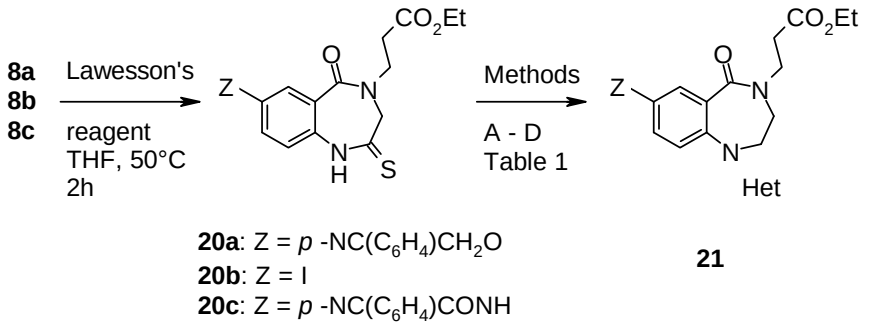
(a) Cl $H_3NCH_2CH_2CO_2Et$, CH_2Cl_2, Et_2N, 40°C; CH_2Cl_2, KPhos pH 7.0, $BrCH_2COBr$, 5-25°C; CH_2Cl_2, DBU, rt, 93% from *N*-methyl isatoic anhydride; (b) HNO_3, 0-25°C, $NaHCO_3$/EtOAc, 73%; (c) CH_3CN, Et_3N, Pd-C. HCO_2H, 5-25°C, then reflux, 98%; (d) CH_2Cl_2, Et_3N, *p* -$CN(C_4H_4)COCl$, 0-25°C, 73%; (e) pyridine/ Et_3N (1.4/1), H_2S, 70%, 24 h; CH_2Cl_2, MeI (xs), reflux; NH_4OAc (xs), EtOH, 50°C, 24 h, 24% (three steps); (f) THF 50% aq. NaOH (xs), 57%.

Scheme 3. Synthesis of benzodiazepinedione **12c**.[3]



(a) H_2, 5% Pd-C, DMA; (b) *p*-$NC(C_6H_4)COCl$, NEt_3, DMAP; (c) Cl $H_3NCH_2CH_2CO_2Et$, NEt_3, DMAP; 56% overall for the three steps; (d) 2,6-lutidine, $ClCH_2CH_2Cl$, Ph_2CHBr, 60°C, 3 h, 86%; (e) $BrCH_2COBr$, CH_2Cl_2/H_2O; (f) Cs_2CO_3, DMF, 93% overall for the two steps; HF, anisole, $H_3CCH_2SCH_3$, -196-0°C, 56%

Scheme 4. Synthesis of benzodiazepinedione **9c**.[3]



20a: Z = *p* -NC(C_6H_4)CH_2O
20b: Z = I
20c: Z = *p* -NC(C_6H_4)CONH

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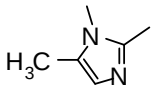
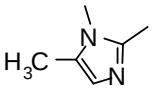
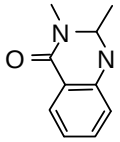
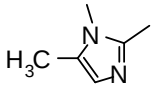
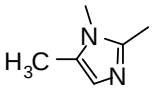
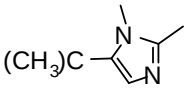
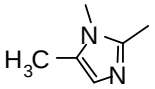
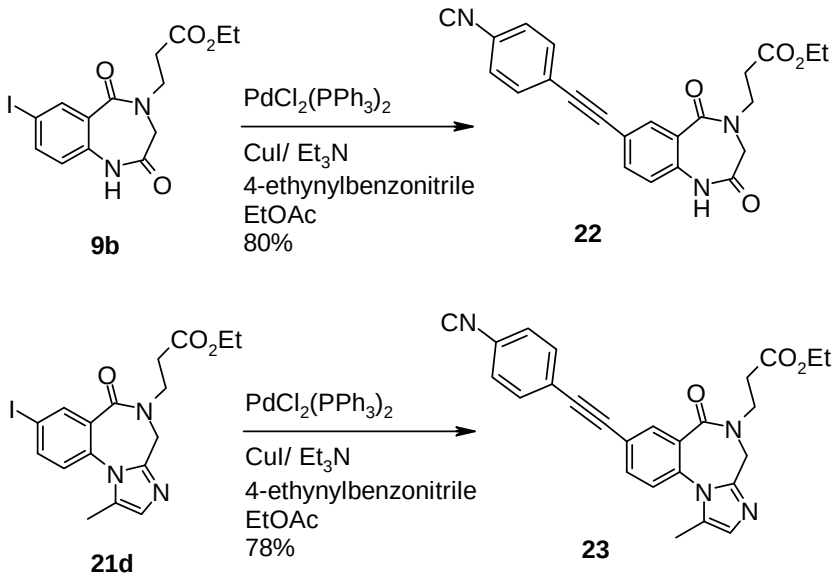
(A) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH; ii. propargyl amine, C_5H_5N(HCl), $PhCH_3$, reflux, 5 h; (B) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH,; ii. $H_3CCONHNH_2$ or $(H_3C)_3CONHNH_2$, C_5H_5N(HCl), $C_6H_5CH_3$, reflux, 5 h; (C) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH; ii. methyl anthranilate, C_5H_5N(HCl), $C_6H_5CH_3$, reflux, 6 h; (D) i. MeI, CH_3CN (anhyd.), sealed tube, charge w/ MeI at t = 6,7, and 8 h after reflux. Reflux for 8.5 h; ii. propargyl amine, , C_5H_5N(HCl), $C_6H_5CH_3$, reflux, 6 h.

Scheme 5. Synthesis of thioamides **20a-c** and tricyclic intermediates **21a-g**.[3]

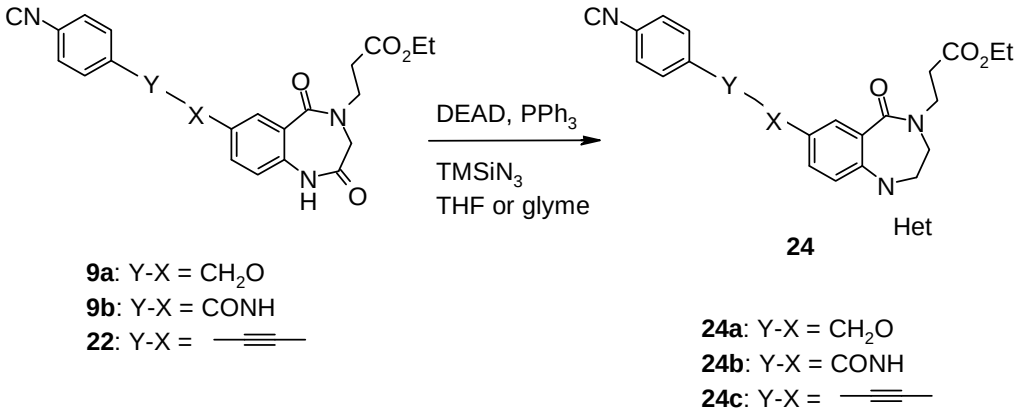
Table 1. Synthesis of thioamides **20a-c** (Scheme 5) and tricyclic intermediates **21a-g**.[3]

Thioamide	Method	Product	Z	Het	Yield
20a	A	**21a**	*p*-NC[C(6)H(4)]CH(2)O		22 %
20a	B	**21b**	*p*-NC[C(6)H(4)]CH(2)O		63 %
20a	C	**21c**	*p*-NC[C(6)H(4)]CH(2)O		33 %
20b	A	**21d**	I		66 %
20b	B	**21e**	I		91 %
20b	B	**21f**	I		81 %
20c	D	**21g**	*p*-NC[C(6)H(4)]CH(2)O		23 %

(A) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH; ii. propargyl amine, $C_5H_5N(HCl)$, $PhCH_3$, reflux, 5 h; (B) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH,; ii. $H_3CCONHNH_2$ or $(H_3C)_3CONHNH_2$, $C_5H_5N(HCl)$, $C_6H_5CH_3$, reflux, 5 h; (C) i. MeI, H_2O, Bu_4NHSO_4 (cat.), NaOH; ii. methyl anthranilate, $C_5H_5N(HCl)$, $C_6H_5CH_3$, reflux, 6 h; (D) i. MeI, CH_3CN (anhyd.), sealed tube, charge w/ MeI at t = 6,7, and 8 h after reflux. Reflux for 8.5 h; ii. propargyl amine, , $C_5H_5N(HCl)$, $C_6H_5CH_3$, reflux, 6 h.



Scheme 6. Synthesis of benzonitriles **22** and **23**.[3]



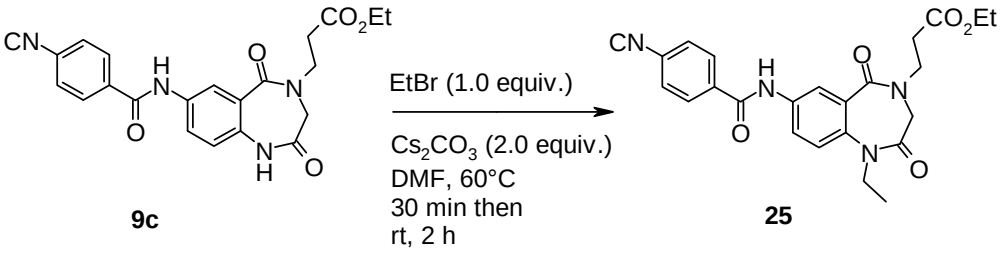
Scheme 7. Synthesis of tricyclic tetrazoles **24a-c**.[3]

Table 2. Synthesis of tricyclic tetrazoles **24a-c**.[3]

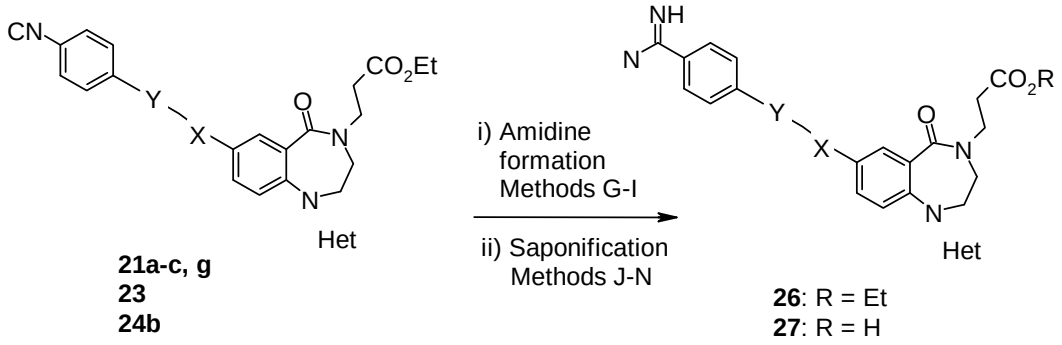
Reactant	Method	Product	Y - X	Het	Yield
8a	E	**24a**	CH(2)O		72 %
8c	F	**24b**	CONH		52 %
22	G	**24c**			68 %

(E) i. DEAD (1.0 equiv.), $TMSiN_3$ (1.0 equiv.), THF (anhyd.), rt, 24 h; ii. charge rx. with additional 1.0 equiv. of reagents, rt, 48 h; (F) DEAD (2.0 equiv.), $TMSiN_3$ (2.0 equiv.), glyme (anhyd.), rt, 16 h.

It was found that the linker at C-7 can be modified to an ether with retention of anti-aggregatory potency, and to an amide for increased potency in comparison with the ethynyl linker.



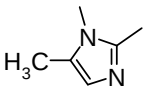
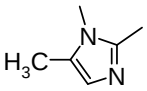
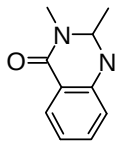
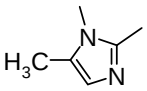
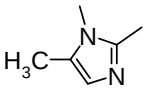
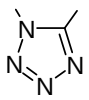
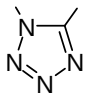
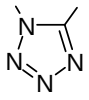
Scheme 8. Selective alkylation of **9c**.[3]



(G) i. H_2S, Et_3N or Et_2NH/C_5H_5N (1/1), rt, 2 h; ii. MeI, CH_2Cl_2, 50°C, 30 min; iii. NH_4OAc, EtOH or MeOH, 50°C, 30 min; (H) i. H_2S, Et_3N/ C_5H_5N (1/1), 50°C, 90 min; ii. MeI, CH_3CN (anhyd.) sealed tube, 85°C, 1h; iii. NH_4OAc, EtOH, rt, 18 h; (I) i. H_2S, Et_3N/C_5H_5N (1/1), 50°C, 90 min; ii. MeI, N-Me pyrrolidinone (anhyd.), rt, 24 h;iii. NH_4OAc (anhyd.), EtOH, 18 h; (J) NaOH (aq.), EtOH or MeOH, rt; (K) $LiOH/H_2O_2$, THF/H_2O, rt; (L) 50% TFA/H_2O, 60°C, 3h; (M) NaOH, $THF/MeOH/H_2O$ (3/2/1), rt, 18 h; (N) LiOH, THF/H_2O, (3/1), rt, 40 h.

Scheme 9. Conversion of tricyclic benzonitriles **21a-c**, **24g**, **23** and **24b** into amidino acids **26c-i**.[3]

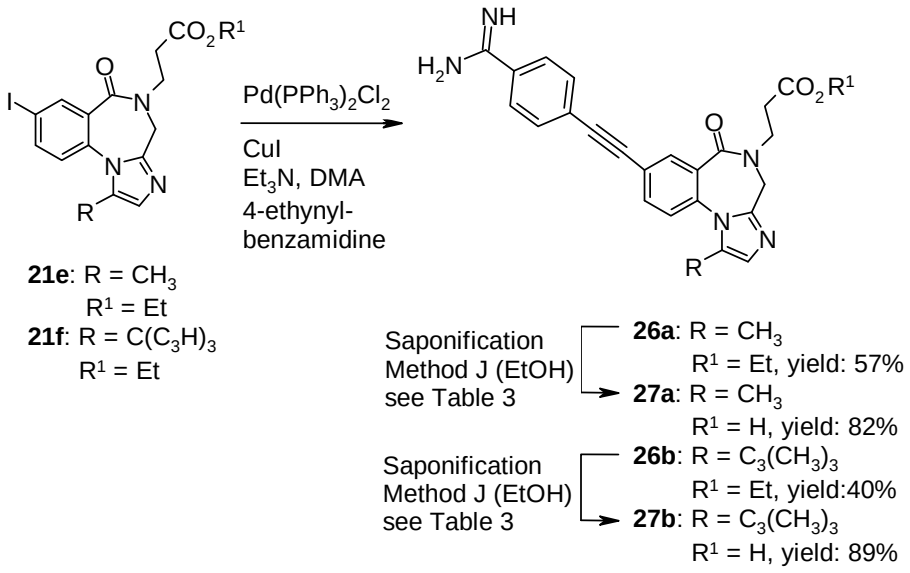
Table 3. Conversion of tricyclic benzonitriles **21a-c**, **24g**, **23** and **24b** into amidino acids **26c-i**.[3]

NCAr	Y-X	Het	Method*	Prod.	Yield	Method**	Prod.	Yield
21a	CH(2)O		G	**26c**	nd	J (MeOH)	**27c**	5% overall from **21a**
21b	CH(2)O		G	**26d**	26 %	J (EtOH)	**27d**	10% overall from **24b**
21c	CH(2)O		G	**26e**	71 %	K,L	**27e**	10% and 39%, 46%
21g	CONH		H	**26f**	24 %	M	**27f**	24 %
23			G	**26g**	16 %	J (MeOH)	**27g**	85 %
24a	CH(2)O		G	**26h**	66 %	J (MeOH)	**27h**	83
24b	CONH		I	**26i**	18 %	N	**27i**	65 %
24c			G	**26j**	34 %	J (MeOH)	**27j**	95 %

*(G) i. H_2S, Et_3N or Et_2NH/C_5H_5N (1/1), rt, 2 h; ii. MeI, CH_2Cl_2, 50°C, 30 min; iii. NH_4OAc, EtOH or MeOH, 50°C, 30 min; (H) i. H_2S, Et_3N/ C_5H_5N (1/1), 50°C, 90 min; ii. MeI, CH_3CN (anhyd.) sealed tube, 85°C, 1h; iii. NH_4OAc, EtOH, rt, 18 h; (I) i. H_2S, Et_3N/C_5H_5N (1/1), 50°C, 90 min; ii. MeI, N-Me pyrrolidinone (anhyd.), rt, 24 h;iii. NH_4OAc (anhyd.), EtOH, 18 h.

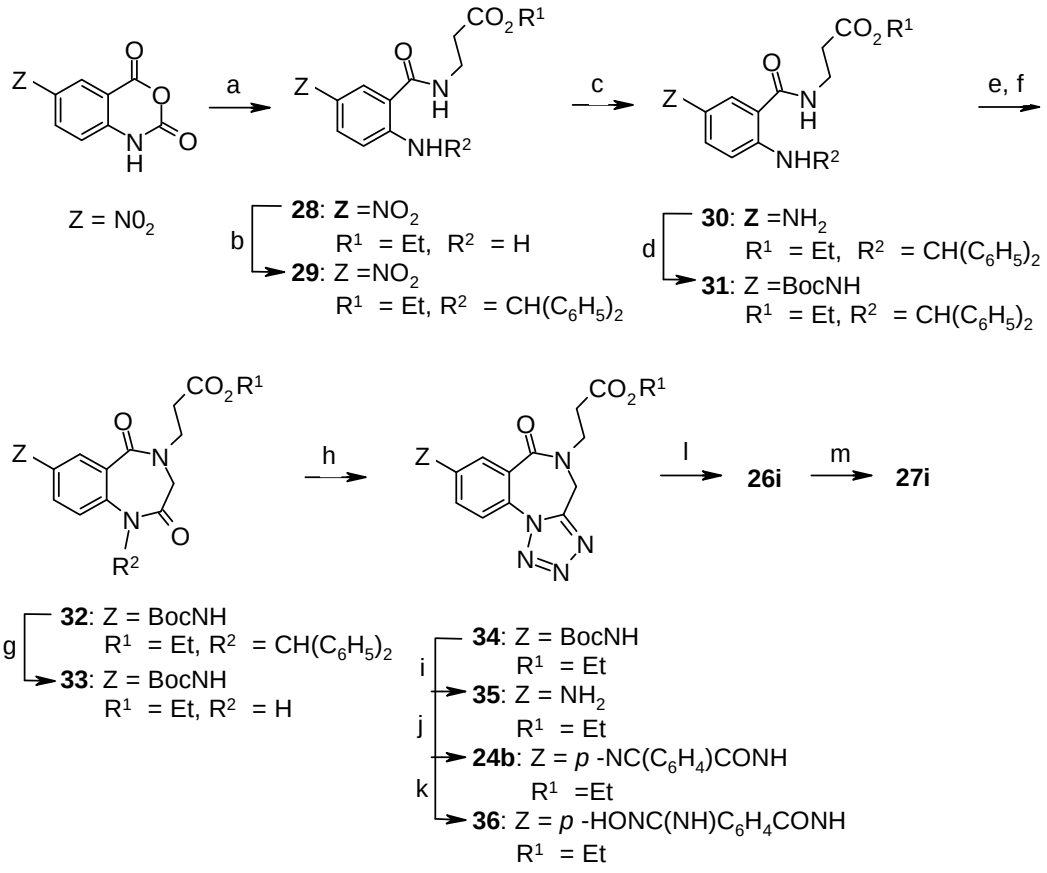
**(J) NaOH (aq.), EtOH or MeOH, rt; (K) $LiOH/H_2O_2$, THF/H_2O, rt; (L) 50% TFA/H_2O, 60°C, 3h; (M) NaOH, $THF/MeOH/H_2O$ (3/2/1), rt, 18 h; (N) LiOH, THF/H_2O, (3/1), rt, 40 h.

Robarge *et al.* found that a tricyclic scaffold may be optimal for steric reasons since the tetracyclic quinazoline **27e** exhibited a dramatic decrease (100-fold) in activity.[3]



Scheme 10. Synthesis of triazole tricyclic compounds **27a** and **27b**.[3]

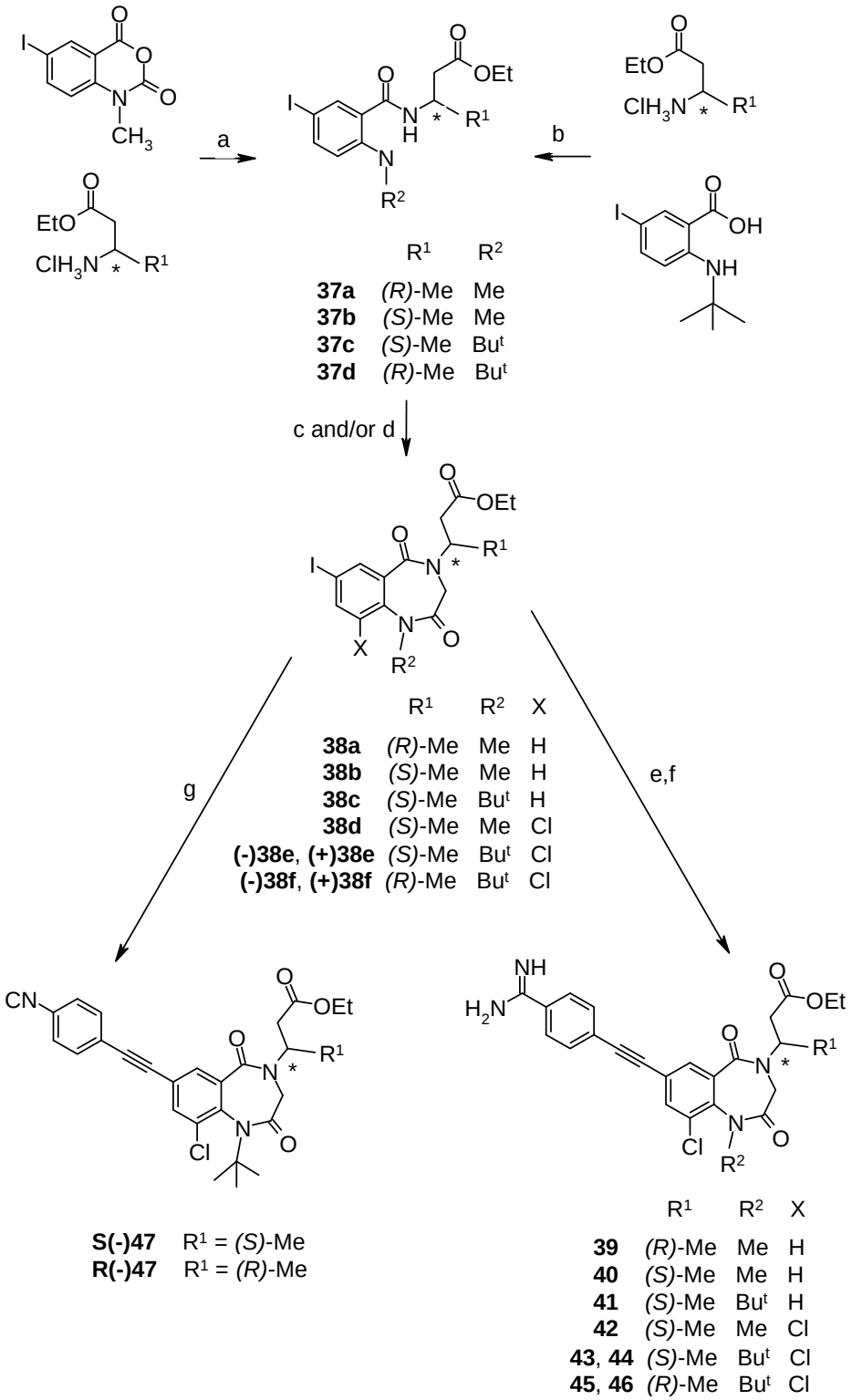
The most potent antagonist of the series was tricyclic **27i** with an amide linker at C^7 and a tetrazole heterocycle. Tricyclic antagonists **27a**, **27b**, **27d** and **27f-j** exhibited a retention of potency (i.e. less than a twofold decrease) relative to the comparative bicyclic progenitor.[3] **27c** was the exception exhibiting a fourfold loss in potency relative to **12a**.



(a) Cl $NCH_2CH_2CO_2Et$, NEt_3, DMAP, CH_2Cl_2, rt, 39%; (b) 2,6-lutidine, K_2CO_3, $ClCH_2CH_2Cl$, Ph_2CHBr, 83°C, 91%; (c) NEt_3, HCO_2H, 5% Pd-C (4% by wt), rt, 81%; (d) BOC-ON=$(CH_3)COCO_2N$=$C(C_6H_5)CN$, DMAP, THF, reflux, 90%; (e) $BrCH_2COBr$, KPhos/ CH_2Cl_2, rt, 71%; (f) DBU, CH_2Cl_2, rt, 71% from **30**; (g) $Pd(OH)_2$, HOAc, 40 psi. 60°C, 77%; (h) PPh_3, DEAD, $TMSiN_3$, rt, 57%; (i) TFA, CH_2Cl_2, $NaHCO_3$, 81%; (j) *p* -$CN(C_6H_4)COCl$, $NaHCO_3$, THF, 50°C, 70%: (k) $H_2NOH(HCl)$, NaOEt, 60°C, 79%; (l) Ac_2O, HOAc, 5% Pd-C (6% by wt), H_2, 1 atm, rt, 55%; (m) LiOH, THF/H_2O (3/1), rt, 65%.

Scheme 11. Improved synthesis of tricyclic tetrazole **27i**.[3]

Blackburn *et al.* have designed and synthesized a benzodiazepinedione group of GPIIb/IIIa antagonists derived from the RGD-containing cyclic peptide G4120.[4] They studied the effect of chiral substitution at C-11 by comparing compounds **39** and **40** in the protein-protein assay (ELISA) and physiologically relevant (PRP) platelet aggregation assay. They found **40** to be 10-fold more potent than its enantiomer **39**.[4] The absolute configuration of **40** is in contrast to the stereochemical preference for peptidal and other non-peptidal GPIIb/IIIa antagonists.[4]



	R1	R2
37a	*(R)*-Me	Me
37b	*(S)*-Me	Me
37c	*(S)*-Me	Bu^t
37d	*(R)*-Me	Bu^t

	R1	R2	X
38a	*(R)*-Me	Me	H
38b	*(S)*-Me	Me	H
38c	*(S)*-Me	Bu^t	H
38d	*(S)*-Me	Me	Cl
(-)38e, **(+)38e**	*(S)*-Me	Bu^t	Cl
(-)38f, **(+)38f**	*(R)*-Me	Bu^t	Cl

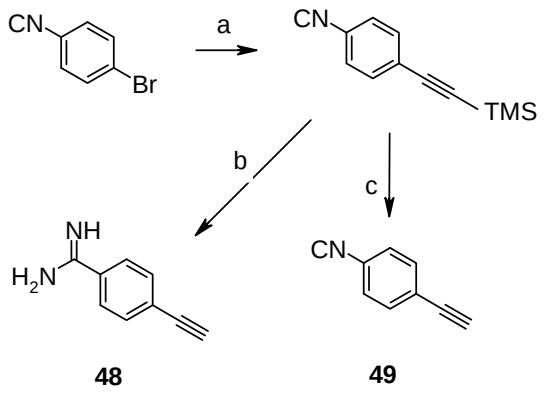
S(-)47 R1 = *(S)*-Me
R(-)47 R1 = *(R)*-Me

	R1	R2	X
39	*(R)*-Me	Me	H
40	*(S)*-Me	Me	H
41	*(S)*-Me	Bu^t	H
42	*(S)*-Me	Me	Cl
43, **44**	*(S)*-Me	Bu^t	Cl
45, **46**	*(R)*-Me	Bu^t	Cl

(a) DMF or CH_2Cl_2, Et_3N, DMAP; (b) EDC, HOBT, Et_3N,; (c) Cl_2, AcOH; (d) i. $BrCH_2COBr$, ii. Cs_2CO_3, DMF or DBU, CH_2Cl_2 or $C_6H_5CH_3$; (e) Pd(II), Cu(I), Et_3N, **48**, DMF; (f) LiOH; (g) Pd(II), Cu(II), Et_3N, **49**, EtOAc.

Scheme 12. Synthesis of benzodiazepinediones **39-46**, **S(-)47** and **R(-)47**.[4]

Compound **43** was found to be a conformationally rigid and potent GPIIb/IIIa antagonist.



(a) Pd(II), Cu(I), Et_3N, trimethylsilylacetylene, EtOAc; (b) i. H_2S, pyridine, ii. MeI, iii. NH_4OAc, EtOH; (c) K_2CO_3, MeOH.

Scheme 13. Synthesis of 4-ethynylbenzamidine **48** and 4-ethynylbenzonitrile **49**.[4]

Keenan *et al.* have synthesized potent and selective $\alpha_V\beta_3$ antagonists.[5] Compounds **50** and **51** (Fig. 2), **56** and **57** (Fig.4) and **58**-**63** (Fig.5) were synthesized by coupling of the appropriate amine to the 1,4-benzodiazepine-7-carboxylic acid as seen in Scheme 18. Keenan *et al.* gathered evidence that the lengh required for optimal binding to $\alpha_V\beta_3$ is shorter than for $\alpha_{IIb}\beta_3$.[5]

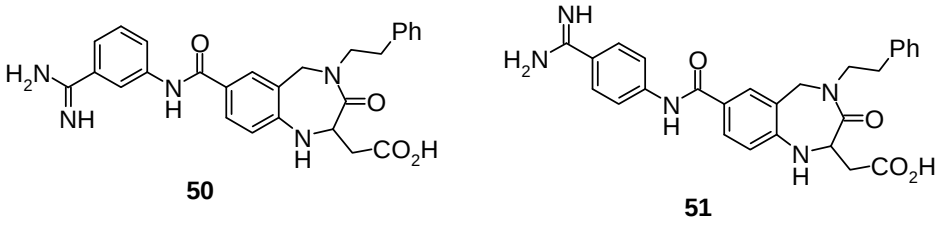
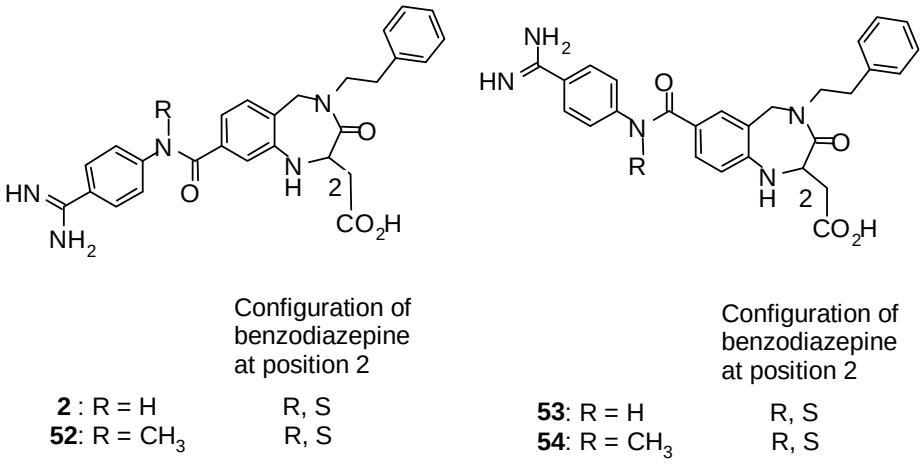


Figure 2. Benzamidine-containing $\alpha_V\beta_3$ antagonists.[5]

Having a shorter distance between the carboxyl terminus and the amidine terminus, *m*-benzamidine **50** showed greater affinity for $\alpha_V\beta_3$ than for $\alpha_{IIb}\beta_3$, and *p*-benzamidine **51** was found to be a potent $\alpha_{IIb}\beta_3$ antagonist.[5]

Samanen *et al.* have investigated and synthesized potent, selective 3-oxo-1,4-benzodiazepine GPIIb/IIIa integrin antagonists.[6]

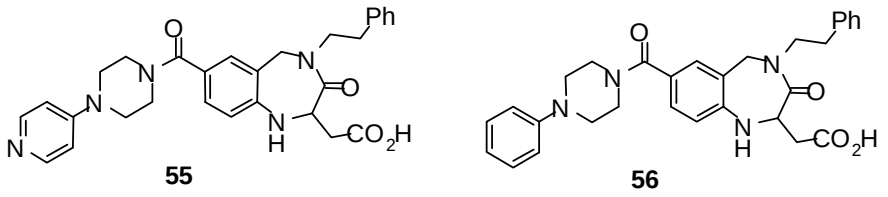


2 : R = H R, S
52: R = CH_3 R, S

53: R = H R, S
54: R = CH_3 R, S

Figure 3. 3-oxo-1,4-benzodiazepine GPIIb/IIIa antagonists.[6]

2.2 Compounds containing a piperazine unit



55 **56**

Figure 4. Piperazine-containing $\alpha_V\beta_3$ antagonists.[5]

Keenan *et al.* discovered that the pyridyl nitrogen in **55** was responsible for the much greater affinity for $\alpha_{IIb}\beta_3$ compared to that of **56**.[5] The affinities of the two compounds for $\alpha_V\beta_3$ were comparable, caused by the central anilino nitrogen.[5]

2.3 Compounds containing a benzimidazole unit

Keenan *et al.* have synthesized a highly potent and selective $\alpha_V\beta_3$ antagonist **62**.[5]

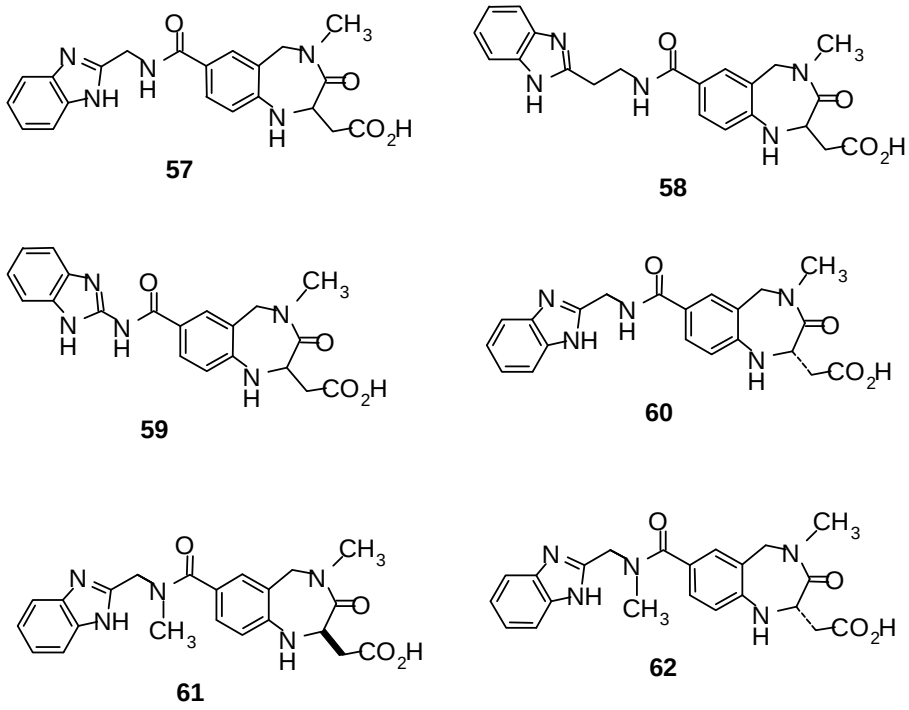
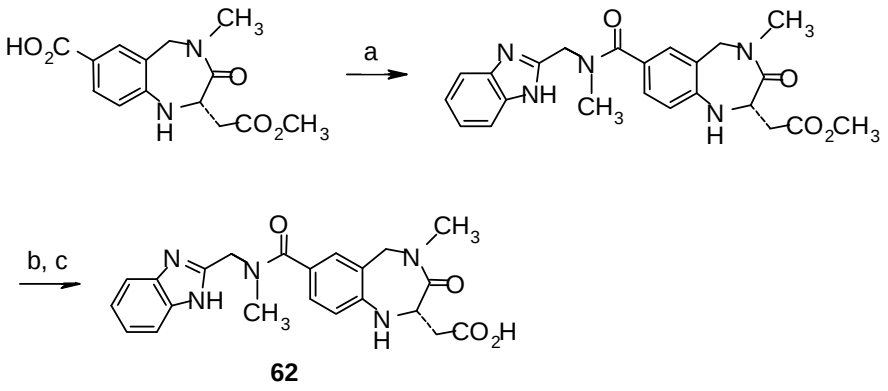


Figure 5. Benzimidazole-containing $\alpha_V\beta_3$ antagonists.[5]

Keenan *et al.* found **57** to be a potent and selective $\alpha_V\beta_3$ antagonist partly due to its optimal length.[5] They also found the (*S*)-enantiomer **60**, identical to the natural configuration of Asp, to be almost entirely responsible for the affinity thus providing further evidence of the 1,4-benzodiazepine acting as a Gly-Asp mimic.[5] In their previous work Keenan *et al.* had discovered increased affinity due to amide N-methylation. Based on this information they synthesized **62**, a highly potent and selective $\alpha_V\beta_3$ antagonist.[5]

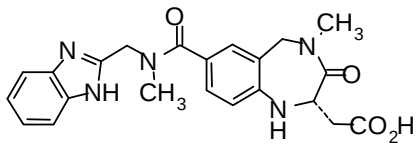


62

(a) 2-(methylaminomethyl)benzimidazole • TFA, DCC, $(i\text{-}Pr)_2NEt$, DMF (100%); (b) 2 N NaOH, MeOH; (c) HCl to pH 6.0 (71%).

Scheme 14. Synthesis of $\alpha_V\beta_3$ antagonist **62**.[5]

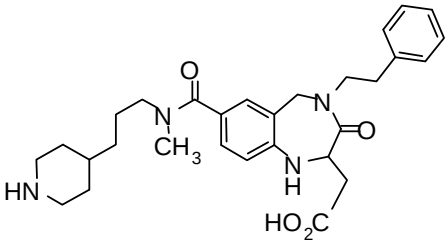
Miller *et al.* have synthesized a series of highly potent, orally active small molecule $\alpha_V\beta_3$ antagonists (Fig. 6, 8 and) based on a 2-benzazepine Gly-Asp. [7]



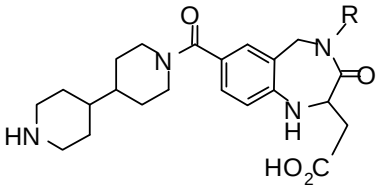
63

Figure 6. A potent $\alpha_V\beta_3$ antagonist.[7]

2.4 Compounds containing a piperidine unit



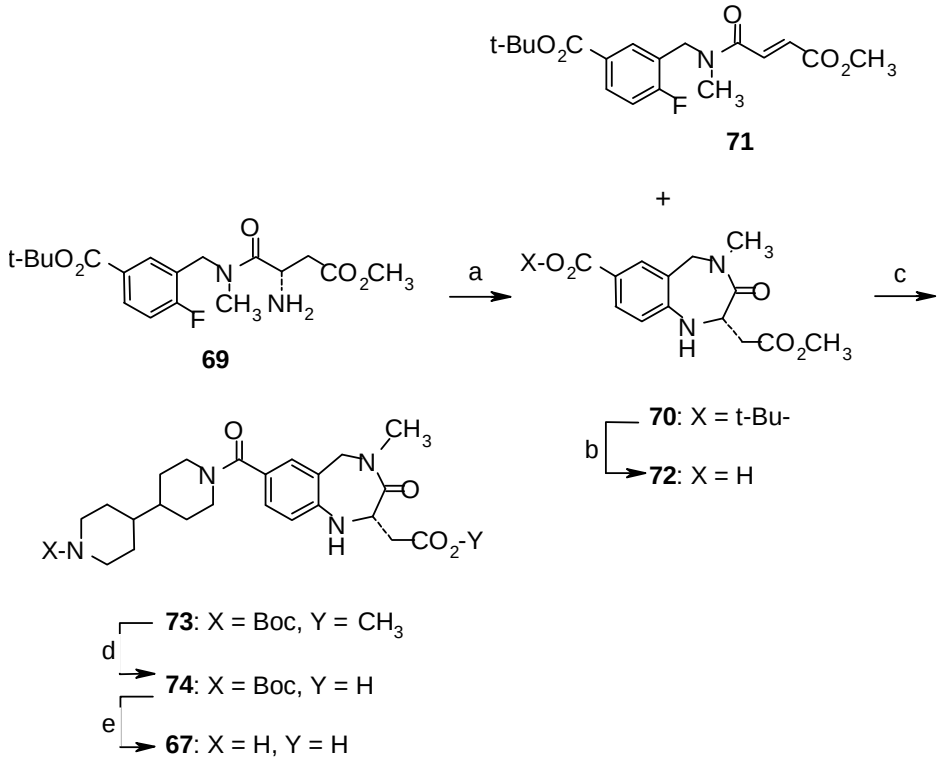
	Configuration of benzodiazepine at position 2
64	R, S



	R	Configuration of benzodiazepine at position 2
65	CH_2CH_2Ph	R, S
66	CH_3	R, S
67	CH_3	S
68	CH_3	R

Figure 7. 3-oxo-1,4-benzodiazepine GPIIb/IIIa antagonists by Samanen *et al.*[6]

Compound **64** was found to have high affinity for GPIIb/IIIa and high potency in the platelet aggregation assay. Also **65** is a potent GPIIb/IIIa antagonist.[6] Compound **67** is a potent, orally active antiaggregatory agent. Its *R*-enantiomer **68** has considerably lower affinity.



(a) 0.1 M **69** in anhydrous DMSO, 125°C (47% of **70**, 28% of **71**); (b) 1:1 TFA/CH_2Cl_2, anisole (95%); (c) 1-Boc-4,4'-bipiperidine, EDC, (*i*-Pr)$_2$NEt, DMF (94%); 2.0 N NaOH (2 equiv.), 1:1 MeOH/THF, then AcOH (81%); (e) 4 M HCl in dioxane, $CHCl_3$, then neutralization of excess reagent with ca. 1.0 N KOH in EtOH to give **67**-HCl (75%) and precipitation from aqueous solution at pH 6.8 (83%).

Scheme 15. Homochiral synthesis of 3-oxo-1,4-benzodiazepine **67**.[6]

2.5 Compounds containing a pyridine unit

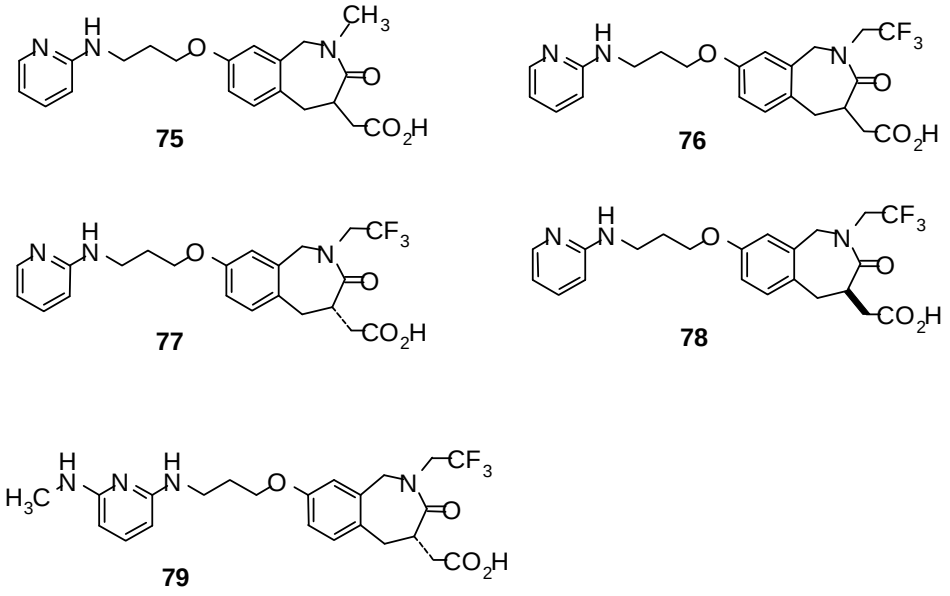
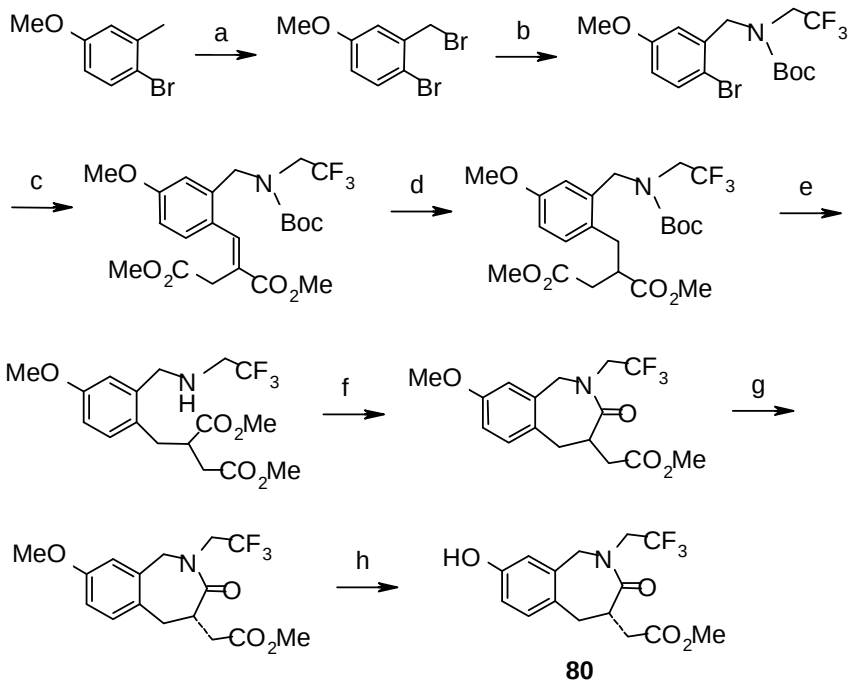


Figure 8. $\alpha_V\beta_3$ antagonists synthesized by Miller *et al.*[7]

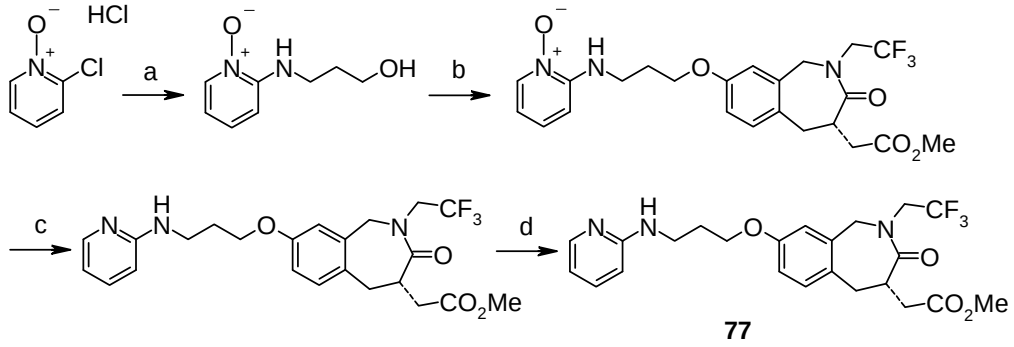
The *S*-enantiomer of **76**, compound **77** has greater affinity for $\alpha_V\beta_3$ than the *R*-enantiomer **78**. Miller *et al.* also discovered compounds **77** and **79** to have great affinity for $\alpha_V\beta_5$, and minimal affinity for both $\alpha_{IIb}\beta_3$ and $\alpha_V\beta_1$.[7]

Miller *et al.* found proof that *in vitro* biological activity and oral bioavailability of benzazepine-based antagonists may be improved by increasing lipophilicity by appropiate manipulation of the 2-position substitute.[7]



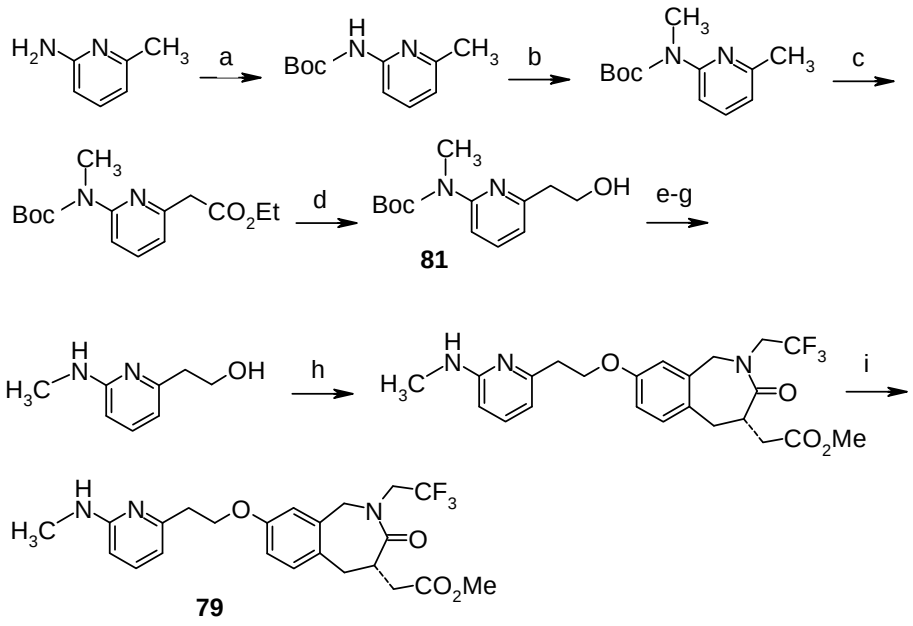
(a) NBS, $(BzO)_2$, *hv*, CH_2Cl_2 (81%); (b) $NaN(Boc)CH_2CF_3$, DMF (77%); (c) dimethyl itaconate, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$NEt, CH_3CH_2CN, reflux (92%); (d) H_2, Pd/C, EtOAc (90%); (e) TFA, anisole, CH_2Cl_2 (86%); (f) (*n*-Pr)$_3$N, TFA, xylenes, reflux (81%); (G) chiral HPLC (46%, 99+% ee); (h) BBr_3, CH_2Cl_2 (99%).

Scheme 16. The synthesis of starting material **80**.[7]



(a) 3-Amino-1-propanol, $NaHCO_3$, *tert*-amyl alcohol, reflux (96%); (b) **80**, Ph_3P, DIAD, THF (75%); (c) cyclohexene, 10% Pd/C, *i*- PrOH, reflux (76%); (d) 1.0 N NaOH, dioxane, then 1.0 N HCl (86%).

Scheme 17. The synthesis of highly potent $\alpha_V\beta_3$ antagonist **77**.[7]

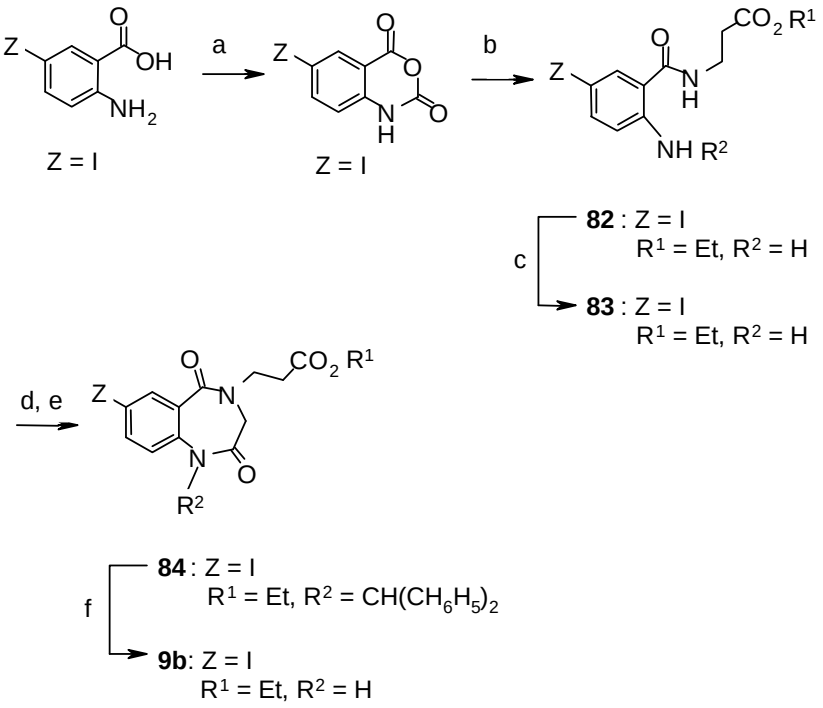


(a) $(Boc)_2O$, neat, 50°C (99%); (b) NaH, CH_3I, DMF (87%); (c) LDA, $(EtO)_2C{=}O$, THF, 0°C (100%); (d) $LiBH_4$, THF, reflux (100%); (e) 4 N HCl/dioxane, anisole, then aq. NaOH; (f) HCO_2H, EtOAc; (g) aq. NH_4OH (52% from **81**); (h) **80**, Ph_3P, DIAD, THF (91%); (i) 1.0 N NaOH, MeOH, then acetic acid (82%).

Scheme 18. The synthesis of highly potent $\alpha_V\beta_3$ antagonist **79**.[7]

2.6 Other benzodiazepine compounds

As reported in 2.1, **9b** is one of the required precursors for the benzyloxy, ethynyl and amide series of tricyclic GPIIb/IIIa antagonists portrayed by Robarge *et al*.[3]



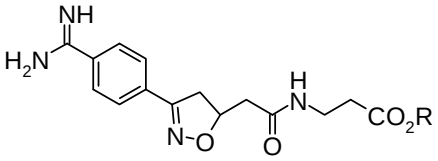
(a) K_2CO_3/H_2O, 0°C, $COCl_2$, 84%; (b) $ClH_3NCH_2CH_2CO_2Et$, DMF, Et_3N, DMAP (cat.), 90%; (c) Ph_2CHCl, 2,6-lutidine, DMF, 50°C, 56%; (d) $BrCH_2COBr$, CH_2Cl_2/H_2O, rt; (e) NaH, DMF, 48°C from **83**; (f) HF (g), anisole, $H_3CCH_2SCH_3$, -196°C, 80% or TFA/Et_3SiH (3/1), reflux, 16 H, 40%.

Scheme 19. Synthesis of benzodiazepinedione **9b**.[3]

3 Isoxazoline and oxazolidinone compounds

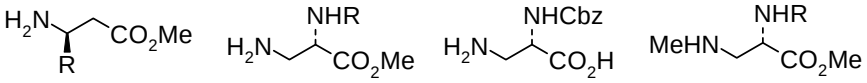
3.1 Isoxazoline and oxazolidinone compounds containing a benzamidine unit

Xue *et al.*.have designed a series of potent GPIIb/IIIa antagonists based on XR299 (**85a**). They studied the effect on activity of lipophilic *α*- and *β*-substitution of the carboxylate moiety.[8]



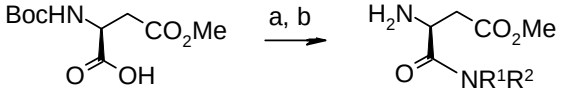
85a: R = H
85b: R = Et

Figure 9. A selective GPIIb/IIIA antagonist.[8]



86 **87** **88** **89a**: R =Cbz
89b: R = CO_2*n*-Bu

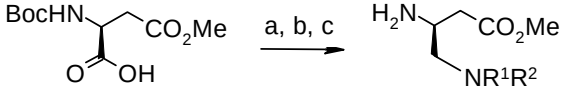
Figure 10. Starting material for the synthesis of substituted *β*-alanines.[8]



90

(a) NHR^1R^2, Et_3N, TBTU, EtOAc; (b) 4 M HCl-dioxane.

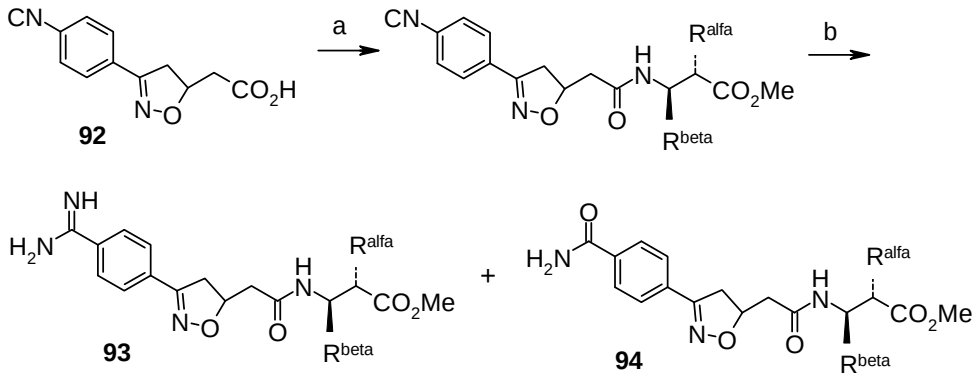
Scheme 20. Preparation of aspartic acid *β*-amides.[8]



91

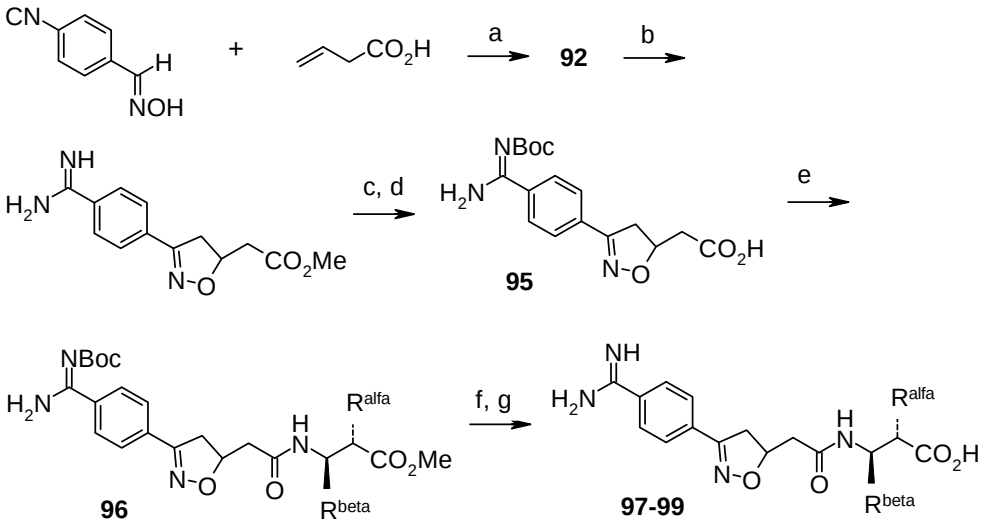
(a) NHR^1R^2, Et_3N, TBTU, EtOAc; (b) BH_3-THF; (c) 4 M HCl-dioxane.

Scheme 21. Synthesis of *β*-(aminomethyl)-*β*-alanines.[8]



(a) **86**, **87**, **90**, or **91**, TBTU, DMF, Et_3N; (b) HCl(anhyd), MeOH, 0 °C, then NH_3, MeOH, 0 °C.

Scheme 22. Early method for synthesis of isoxazolinylacetamides.[8]

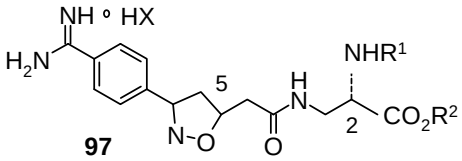


(a) Clorox, THF; (b) HCl(anhyd), MeOH, 0 °C, then NH_3, MeOH, 0 °C; (c) Boc_2O, Et_3N, DMF; (d) LiOH, MeOH-H_2O; (e) **86**, **87**, **90**, or **91**, TBTU, DMF, Et_3N, DMF; (f) TFA, CH_2Cl_2; (g) ester hydrolysis: saponification using lithium hydroxide in aqueous methanol, acidic hydrolysis using aqueous 6 M HCl in dioxane or 40% conc. HCl/formic acid, or esterase hydrolysis using rabbit liver esterase.

Scheme 23. Convergent method for preparation of isoxazolinylacetamides.[8]

Xue *et al.* found that lipophilic substituents placed *α* (**97a-z**, Table 4) or *β* (**98a-g**,Table 5 and **99a-m**, Table 6) to the carboxylate moiety resulted in increased potency in most cases.[8]

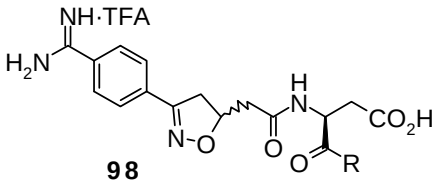
Table 4. Diaminopropionates **97**.[8]



97

Compd	R^1	R^2	Stereochemistry 5	2	HX
97a	H	H	(*R*, *S*)	(*S*)	TFA
97b	$CO(CH_2)_2Ph$	H	(*R*, *S*)	(*S*)	TFA
97c	CO-2-napthyl	H	(*R*, *S*)	(*S*)	TFA
97d	CO-C_6H_4-4-Et	H	(*R*, *S*)	(*R*)	TFA
97e	CO-C_6H_4-4-Ph	H	(*R*, *S*)	(*S*)	TFA
97f	CONHPh	CH_3	(*R*, *S*)	(*S*)	TFA
97g	$CONHCH_2Ph$	H	(*R*, *S*)	(*S*)	TFA
97h	$SO_2(CH_2)_2CH_3$	H	(*R*, *S*)	(*S*)	TFA
97i	CO_2CH_3	H	(*R*, *S*)	(*S*)	TFA
97j	$CO_2CH(CH_3)_2$	H	(*R*, *S*)	(*S*)	TFA
97k	$CO_2(CH_2)_5CH_3$	H	(*R*, *S*)	(*S*)	TFA
97l	CO_2CH_2Ph	H	(*R*, *S*)	(*S*)	TFA
97m	$CO_2(CH_2)_2Ph$	H	(*R*, *S*)	(*S*)	TFA
97n	$CO_2CH_2CH(CH_3)_2$	H	(*R*, *S*)	(*S*)	TFA
97o	$CO_2(CH_2)_2CH=CH_2$	H	(*R*)	(*S*)	TFA
97p	$CO_2(CH_2)_2$c-C_5H_9	H	(*R*, *S*)	(*S*)	TFA
97q	$CO_2(CH_2)_2$c-C_3H_5	H	(*R*, *S*)	(*S*)	TFA
97r	$CO_2(CH_2)_2CF_3$	H	(*R*, *S*)	(*S*)	TFA
97s	CO_2CH_2-C_6H_4-4-Br	H	(*R*, *S*)	(*S*)	TFA
97t	CO_2CH_2-C_6H_4-2-Cl	H	(*R*, *S*)	(*S*)	TFA
97u	$CO_2(CH_2)_3CH_3$	H	(*R*, *S*)	(*S*)	TFA
97v	$CO_2(CH_2)_3CH_3$	CH_3	(*R*)	(*S*)	HCl
97w	$CO_2(CH_2)_3CH_3$	H	(*R*)	(*S*)	TFA
97x	$CO_2(CH_2)_3CH_3$	H	(*R*, *S*)	(*R*)	HCl
97y	$CO_2(CH_2)_3CH_3$	H	(*R*, *S*)	(*S*)	HCl
97z	$CO_2(CH_2)_3CH_3$	H	(*R*)	(*R*)	HCl

Table 5. Aspartic acid β-amides **98**.[8]



98

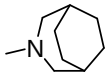
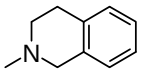
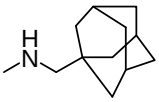
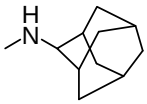
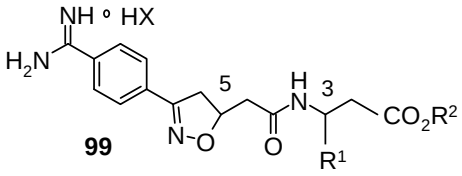
Compd	R	Compd	R
98a	-NH$(CH_2)_2$Ph	**98e**	
98b		**98f**	
98c		**98g**	-N(Bn)*n*-Bu
98d			

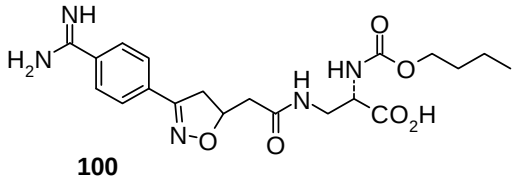
Table 6. β-Substituted β-alanines **99**.[8]



99

			Stereochemistry		
Compd	R^1	R^2	5	3	HX
99a	*gem*-dimethyl	H	(*R, S*)		TFA
99b	CH_2CH_2-2-Py	H	(*R, S*)	(*R*)	TFA
99c	CH_2CH_2-3-Py	H	(*R, S*)	(*R*)	TFA
99d	CH_2CH_2-4-Py	H	(*R, S*)	(*R*)	TFA
99e	CH_2Ph	H	(*R, S*)	(*R*)	TFA
99f	CH_2Ph	H	(*R, S*)	(*S*)	HCl
99g	3-Py	H	(*R*)	(*R*)	TFA
99h	CH_2CO_2H	H	(*R, S*)		TFA
99i	Et	H	(*R*)	(*R*)	TFA
99j*	$CH_2CH(CH_3)_2$	CH_3	(*R*) or (*S*)	(*R*)	TFA
99k	$CH_2N(CH_2)_4$	CH_3	(*R, S*)	(*S*)	TFA
99l*	$CH_2N(CH_3)_2$	CH_3	(*R*) or (*S*)	(*S*)	TFA
99m*	$CH_2N(CH_3)_2$	CH_3	(*S*) or (*R*)	(*S*)	TFA

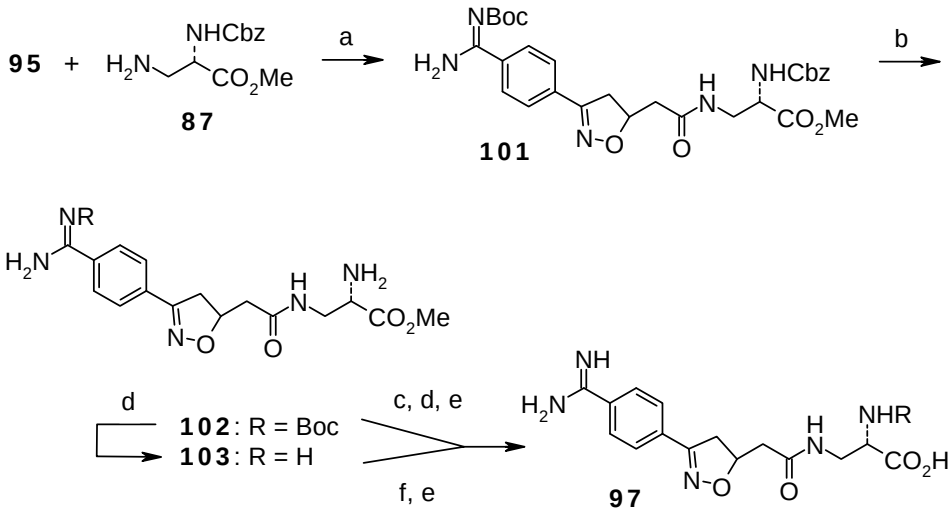
* Stereochemistry at the 5-position indicates a single, but unassigned, stereoisomer.



100

Figure 11. A potent GPIIb/IIIa antagonist.[8]

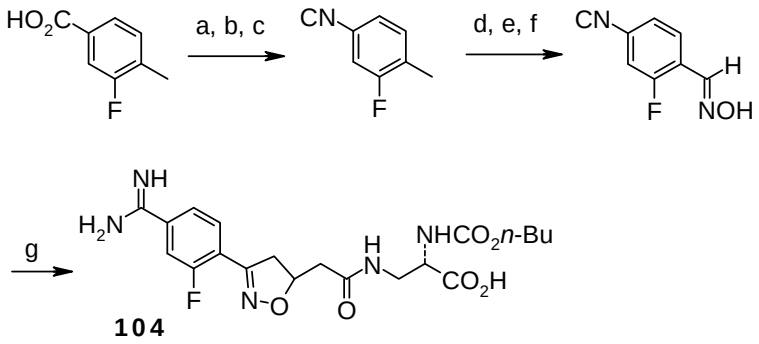
Compound **100** was prepared in a fashion similar to that depicted in Scheme 20.



(a) TBTU, Et_3N, DMF; (b) 1,4-cyclohexadiene, 10% Pd/C, MeOH; (c) RSO_2Cl, etc., Et_3N, CH_2Cl; (d) TFA, CH_2Cl; (e) LiOH, THF(aq); (f) RSO_2Cl, RCOCl, etc., $NaHCO_3$, MeCN(aq).

Scheme 24. Selective functionalization of the α-amino group.[8]

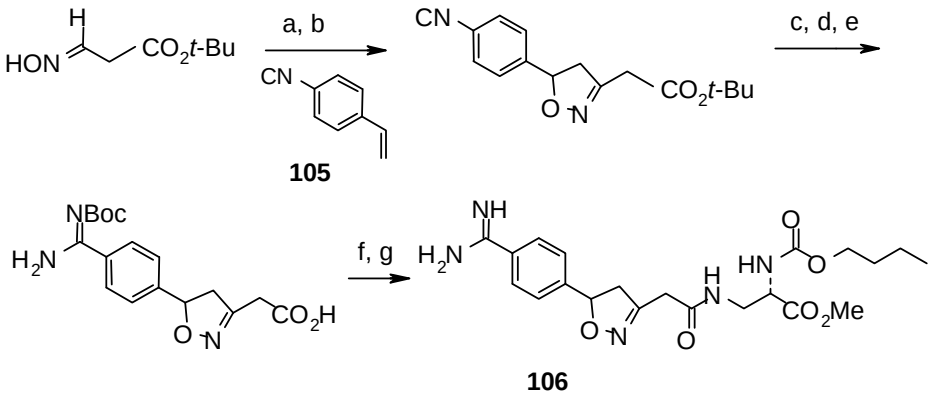
Xue *et al.* expected to increase potency by fluoro-substitution but **104** showed almost a 2-fold decrease in *in vitro* potency when compared to **97u**.[8]



(a) $SOCl_2$, Δ; (b) NH_3(aq); (c) $ClCOCCl_3$, Et_3N, CH_2Cl_2; (d) NBS, CCl_4; (e) $Me_3NO•2H_2O$, DMSO, CH_2Cl_2; (f) $NH_2OH•HCl$, K_2CO_3, MeOH(aq), Δ; (g) route analogous to that depicted in Scheme 20.

Scheme 25. Synthesis of fluoro-substituted benzamidine **104**.

Reverse-orientation isoxazoline **106** proved to have almost complete lack of antiplatelet activity.[8]

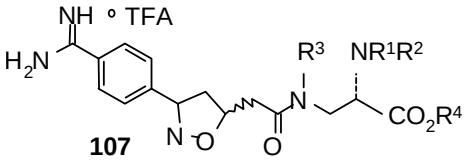


(a) Cl_2, CH_2Cl_2, -40 °C; (b) **105**, Na_2CO_3, THF(aq); (c) HCl(anhyd), MeOH, 0 °C, then NH_3, MeOH, 0 °C; (d) Boc_2O, Et_3N, dioxane; (e) LiOH, THF-H_2O; (f) **87u**, TBTU, Et_3N, EtOAc; (g) TFA, CH_2Cl_2.

Scheme 26. Synthesis of reverse-orientation isoxazoline **106**.[8]

Compared to the secondary amides **97l** and **97u** the *N*-methylated compounds **107a-b** showed reduced potency. The carbamate *N*-methylation (**107c**) resulted in further loss of potency.[8]

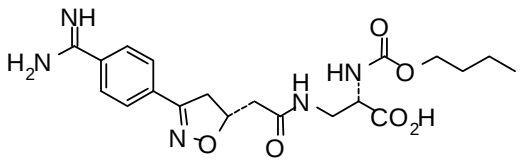
Table 7. *N*-methylated diaminopropionates **107**.[8]



107

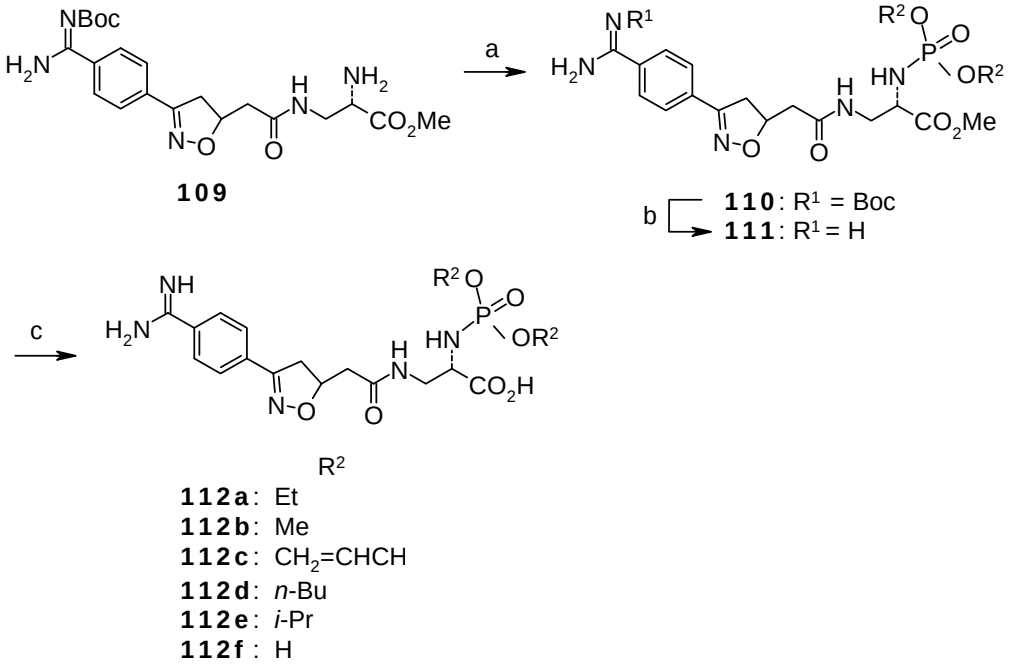
Compd	R^1	R^2	R^3	R^4
107a	CO_2CH_2Ph	H	CH_3	CH_3
107b	$CO_2(CH_2)_3CH_3$	H	CH_3	H
107c	CO_2CH_2Ph	CH_3	CH_3	H

Wityak *et al.* designed phosphoramidate-containing high affinity GPIIb/IIIa antagonists **112a-f** based on antagonists **85a** and **108**.[9]



108

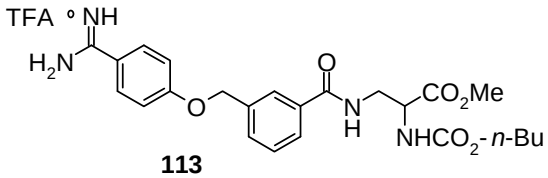
Figure 12. Isoxazolinylacetamide GPIIb/IIIa antagonist XV459, **108**.[9]



(a) $P(OR^2)_3$, I_2, CH_2Cl_2, then **109**; (b) TFA, CH_2Cl_2; (c) RLE, HEPES, pH 7.0.

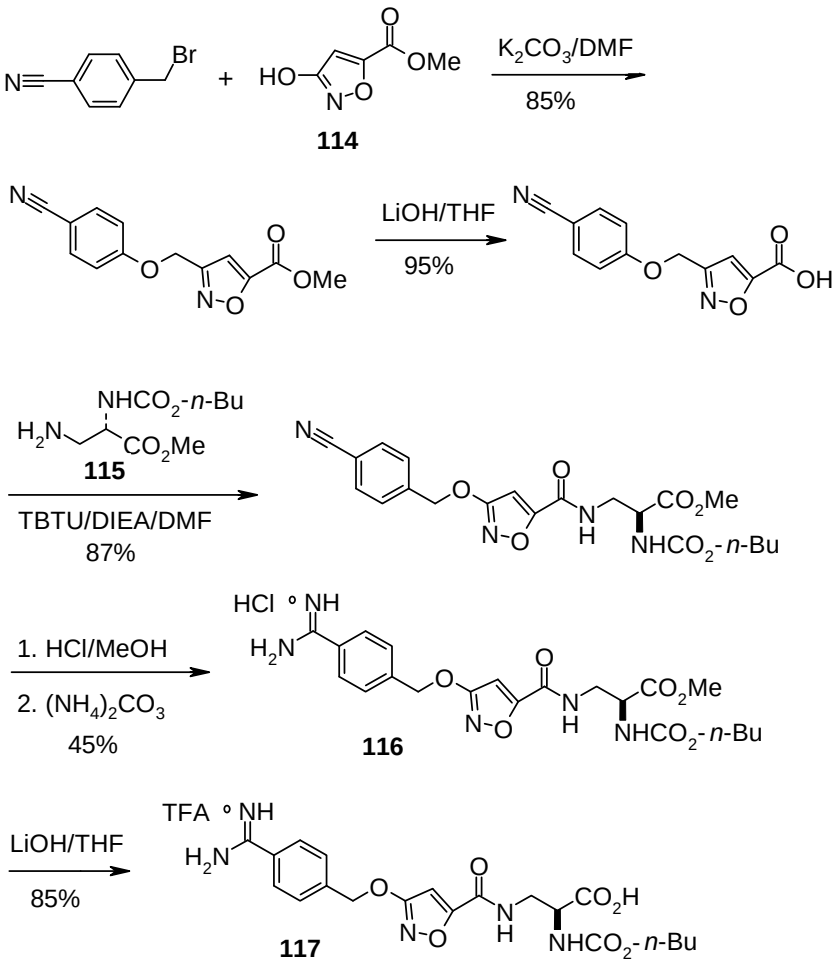
Scheme 27. Synthesis of phosphoramidates **112a-f**.[9]

Xue *et al.* have designed an active GPIIb/IIIa antagonist XU065, **116**, based on a potent *in vitro* GPIIb/IIIa antagonist XU057, **113**.[10] Compound **113** showed poor *in vivo* potency in dogs, but the replacement of the phenyl ring with an isoxazole ring to yield **116** resulted in significant improvement in *in vivo* potency.[10] When administered to dogs, the inactive **116** is hydrolyzed to the corresponding carboxylic acid **117**, an active platelet aggregation inhibitor.[10]



113

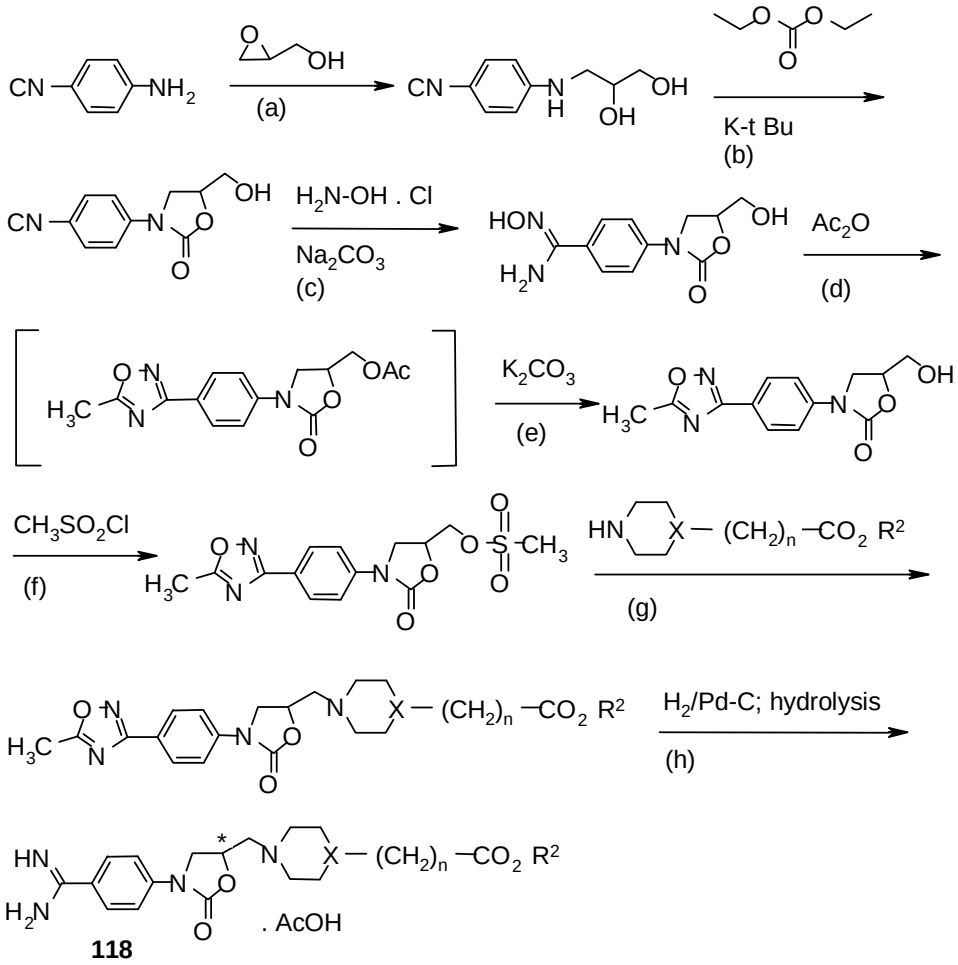
Figure 13. A potent *in vitro* GPIIb/IIIa antagonist XU057.[10]



114 **115** **116** **117**

Scheme 28. Synthesis of XU065, **116**, and the corresponding acid **117**.[10]

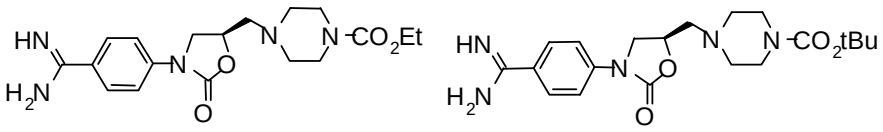
Gante *et al.* have synthesized a series of GPIIb/IIIa antagonists based on the oxazolidinonemethyl scaffold.[11]



118

(a) 2:1 (molar ratio), MeOH, 20 h refl., 70%; (b) 1:6:0.05, 2 h 100°C, 85%; (c) 1:3:4, MeOH, 6 h refl., 80%; (d) Ac_2O as solvent, 4 h 120°C, evaporated; (e) 1:1.2, MeOH, 6 h refl., 80% total; (f) 1:1.25, pyridine, 0.5 h 5°C, 12 h rt, 94%; (g) 1:2, acetonitrile, 16 h refl., 70-90%; (h) a) EtOH/acetic acid (2:1) b) add. of H_2O, rt, 80-90%.

Scheme 29. Synthesis of oxazolidinone compounds **118**.[11]



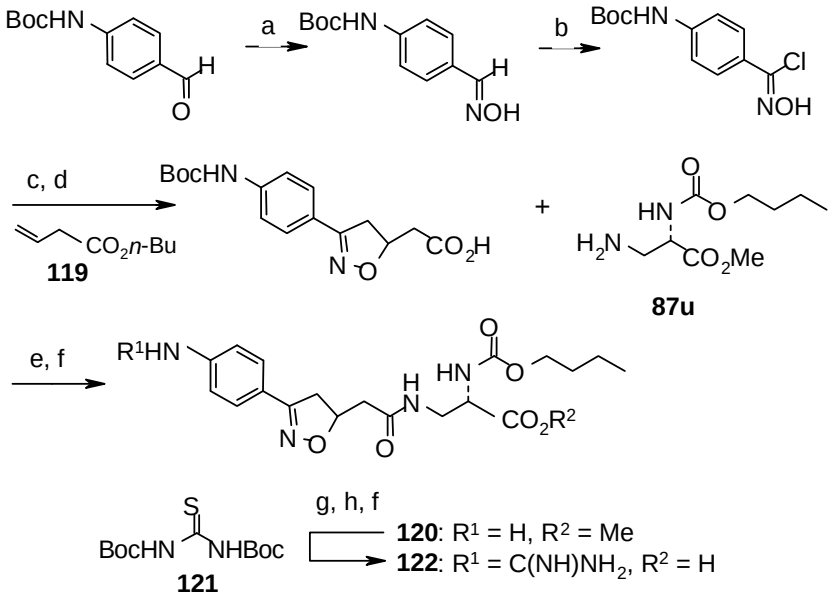
118a **118b**

Figure 14. Oxazolidinone compounds **118a-b**.

Compounds **118a-b** showed negligible activity in the guinea pig.[11]

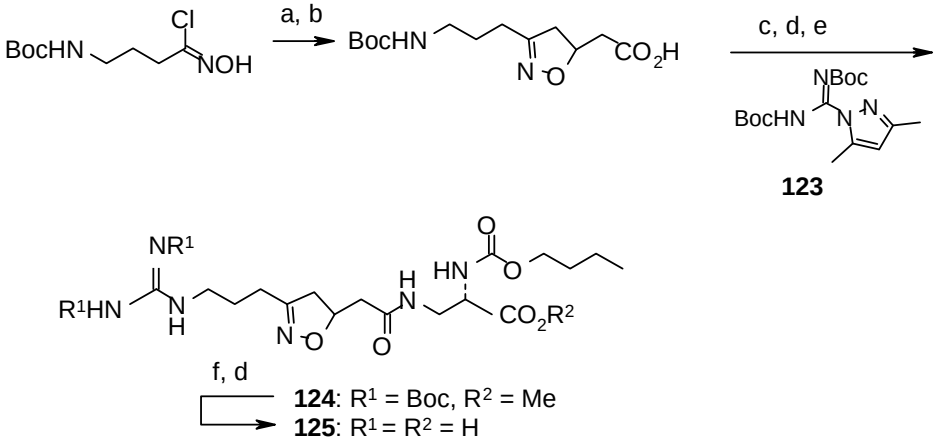
3.2 Other isoxazoline and oxazolidinone compounds

Xue *et al.* found that the absence of the benzamidine moiety in **125** resulted in significant loss of potency when compared to **97u** but the phenyl derivative **122** retained much of the *in vitro* potency of **97u**.[8] This is believed to be caused by the beneficial hydrophobic shielding effect of the aryl group on the amidino group.[8]



(a) NH_2OH•HCl, Na_2CO_3, EOH; (b) NCS, DMF; (c) Na_2CO_3, **119**, THF(aq); (d) LiOH, THF(aq), then HOAc; (e) **87u**, TBTU, Et_3N, EtOAc; (f) TFA, CH_2Cl_2; (g) **121**, Et_3N, $HgCl_2$, DMF; (h) LiOH, THF(aq).

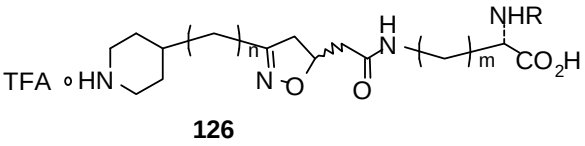
Scheme 30. Synthesis of *N*-formamidinoaniline **122**.[8]



(a) Na_2CO_3, **118**, THF(aq); (b) LiOH, THF(aq); (c) **87u**, TBTU, Et_3N, EtOAc; (d) TFA, CH_2Cl_2; (e) **123**, Et_3N, CH_2Cl_2; (f) LiOH, THF(aq).

Scheme 31. Preparation of alkylguanidine **125**.[8]

Table 8. Piperidines **126**.[8]

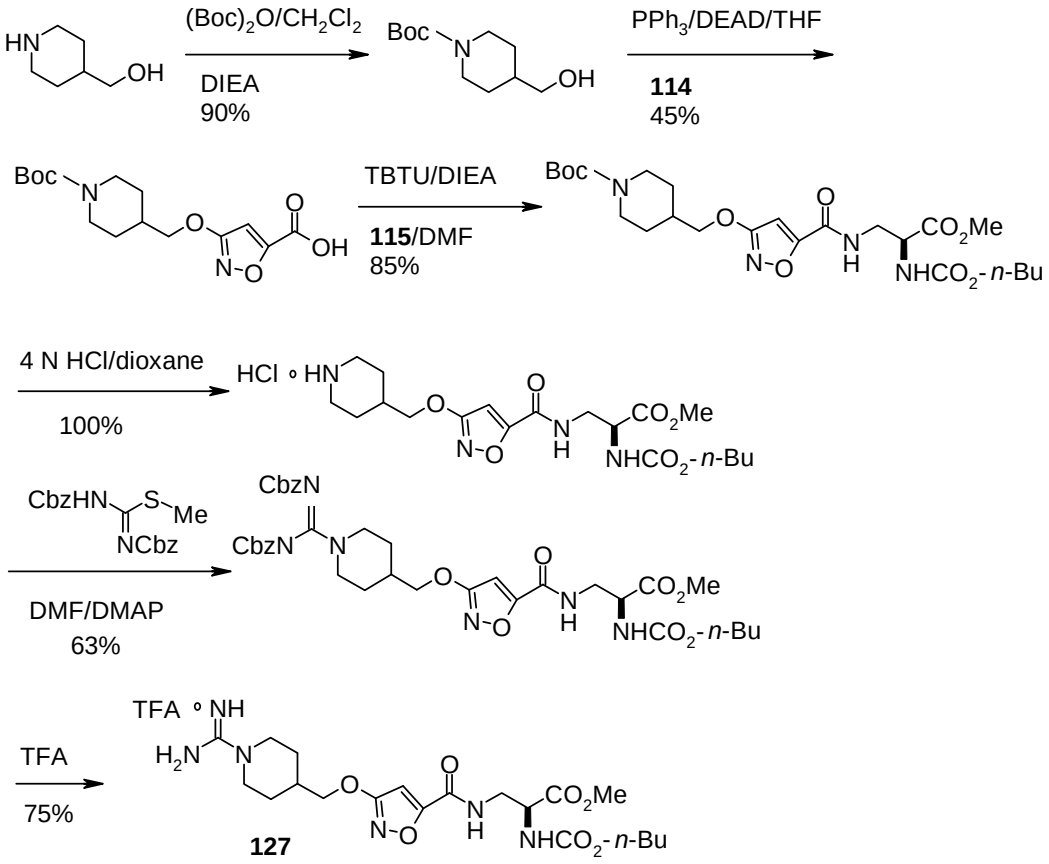


126

Compd	R	n	m
126a	$CO_2(CH_2)_3CH_3$	0	1
126b	$CO_2(CH_2)_3CH_3$	1	1
126c	$CO_2(CH_2)_3CH_3$	1	2
126d	$CO_2(CH_2)_3CH_3$	2	1
126e	$SO_2(CH_2)_3CH_3$	2	1
126f	CO_2CH_2Ph	2	1
126g	$CO_2(CH_2)_3CH_3$	3	1

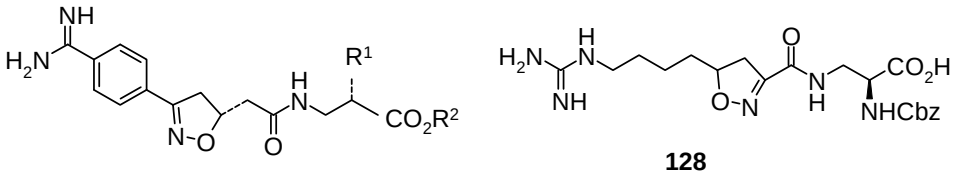
Piperidines **126a-g** were prepared in a fashion similar to that depicted in Scheme 23.

Xue *et al.* found that the replacement of the 4-amidinophenyl group of **127** with the *N*-amidinopiperidin-4-yl group in **128** resulted in a fourfold loss in the platelet aggregation inhibitory activity.[10]



Scheme 32. Synthesis of *N*-amidinopiperidine **127**.[10]

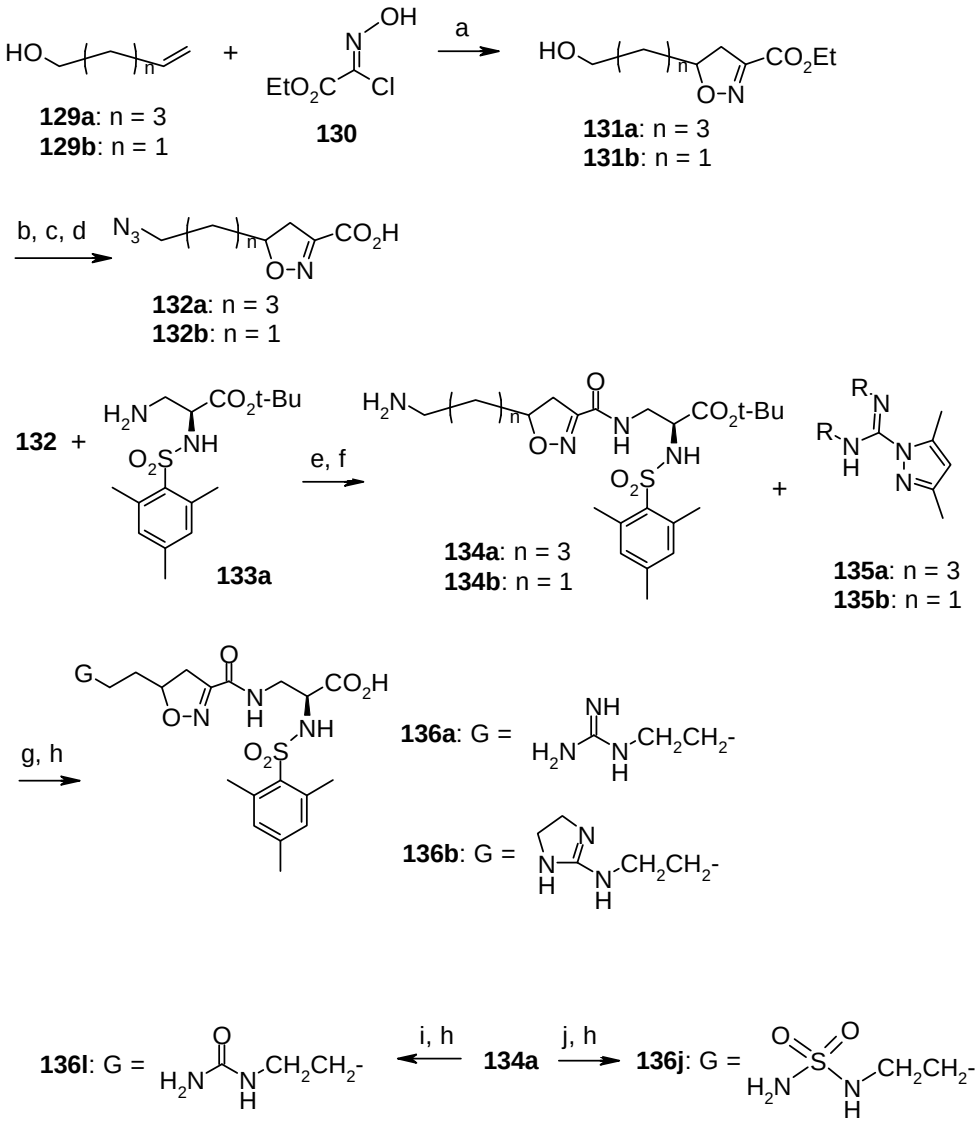
Pitts *et al.*studied the effects of structural changes in the guanidine mimetic and the substituent *α* to the carboxylate in order to find a highly selective integrin $\alpha_V\beta_3$ antagonist.[12]



85c: R^1 = $NHCO_2$*n*-Bu, R^2 = Me

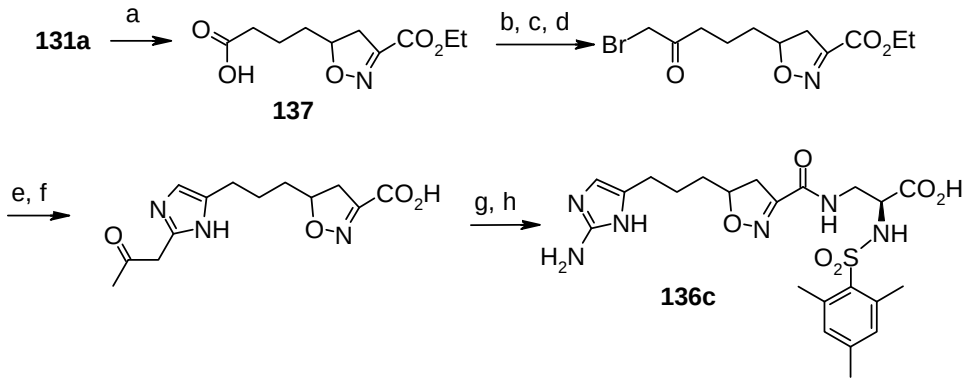
128

Figure 15. Lead compounds for a selective $\alpha_V\beta_3$ antagonist.[12]



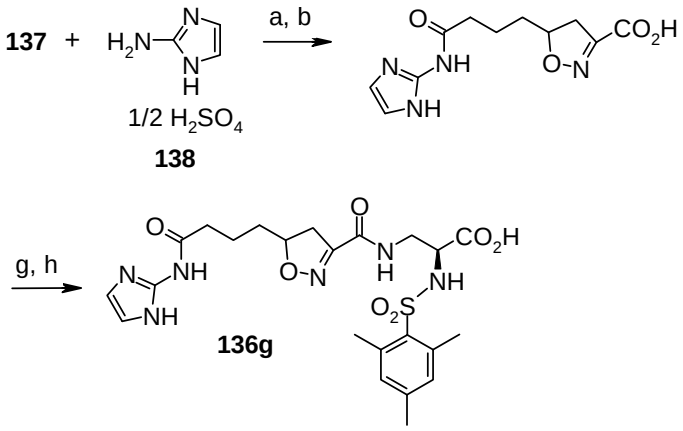
(a) $NaHCO_3$(aq), THF, 0°C-rt; (b) *p*-TsCl, pyridine; (c) NaN_3, DMF; (d) NaOH, H^+; (e) BOP, **133a**, Hunig's base; (f) Ph_3P, dioxane, NH_4OH(aq); (g) **135**, 80°C, dioxane; (h) TFA; (i) TMSNCO; (j) $ClSO_2NCO$, *t*-BuOH.

Scheme 33. Synthesis of the guanidine mimetics **136a, 136b, 136i** and **136j**.[12]



(a) Jones reagent; (b) oxalyl chloride, cat. DMF; (c) diazomethane; (d) HBr(g); acetylguanidine; (f) NaOH, HCl; (g) BOP, **133a**, *N*-methylmorpholine; (h) H_2SO_4, 60°C.

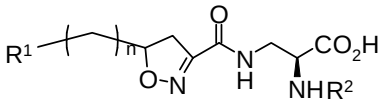
Scheme 34. Synthesis of imidazole **136c**.[12]



(a) **138**, BOP, Hunig's base, 70°C; (b) LiOH, dioxane(aq), H^+; (c) BOP, **133a**, *N*-methylmorpholine; (d) TFA.

Scheme 35. Synthesis of the acylaminoimidazole **136g**.[12]

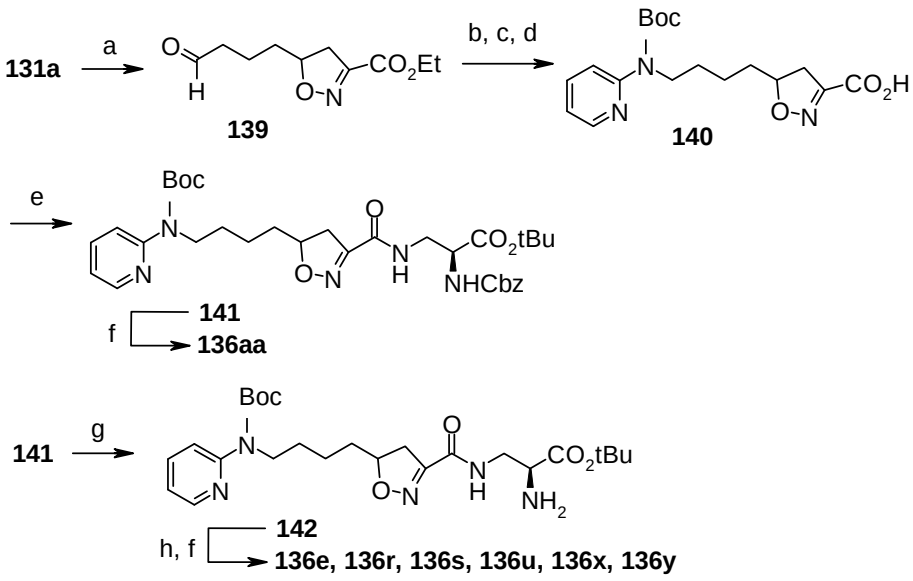
Table 9. Isoxazolines **136**.[12]



136

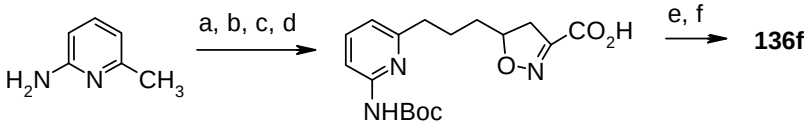
Compd	R^1	R^2	n
136d	imidazol-2-ylNH	2,4,6-$(CH_3)_3C_6H_2SO_2$	4
136e	pyridin-2-ylNH	2,4,6-$(CH_3)_3C_6H_2SO_2$	4
136f	2-aminopyridin-6-yl	2,4,6-$(CH_3)_3C_6H_2SO_2$	3
136h	imidazol-2-ylNHCONH	2,4,6-$(CH_3)_3C_6H_2SO_2$	2
136k	isoquinolin-1-ylNH	2,4,6-$(CH_3)_3C_6H_2SO_2$	4
136l	isoquinolin-3-ylNH	2,4,6-$(CH_3)_3C_6H_2SO_2$	4
136m	imidazol-2-ylNH	2,6-$(Cl)_2C_6H_3SO_2$	4
136n	imidazol-2-ylNH	2-Cl-6-$(CH_3)C_6H_3SO_2$	4
136o	imidazol-2-ylNH	2,6-$(Cl)_2$-4-$(Ph)C_6H_2SO_2$	4
136p	imidazol-2-ylNH	2,6-$(CH_3)_2$-4-$(Ph)C_6H_2SO_2$	4
136q	imidazol-2-ylNH	$C_6H_5SO_2$	4
136r	pyridin-2-ylNH	2,6-$(CH_3)_2$-4-$(Ph)C_6H_2SO_2$	4
136s	pyridin-2-ylNH	$C_6H_5SO_2$	4
136t	imidazol-2-ylNH	1-$C_{10}H_7SO_2$	4
136u	pyridin-2-ylNH	1-$C_{10}H_7SO_2$	4
136v	imidazol-2-ylNH	3,5-$(CH_3)_2$isoxazol-4-ylSO_2	4
136w	imidazol-2-ylNH	4-$(Ph)C_6H_4SO_2$	4
136x	pyridin-2-ylNH	4-$(Ph)C_6H_4SO_2$	4
136y	pyridin-2-ylNH	4-(*i*-Pr)$C_6H_4SO_2$	4
136z	imidazol-2-ylNH	H	4
136aa	pyridin-2-ylNH	$(C_6H_5CH_2O)CO$	4
136bb	imidazol-2-ylNH	2,4,6-$(CH_3)_3C_6H_2SO_2$	2
136cc	imidazol-2-ylNH	**136s** isomer 1	4
136dd	imidazol-2-ylNH	**136s** isomer 2	4
136ee	imidazol-2-ylNH	(R)-2,4,6-$(CH_3)_3C_6H_2SO_2$	4

Compounds **136g** and **136h** demonstrated high potency and selectivity towards integrin $\alpha_V\beta_3$.[12] Pitts *et al.* found that the *α*-substituent was required for potent activity and that 2,6-substituted arylsulfonamides were optimal.[12]



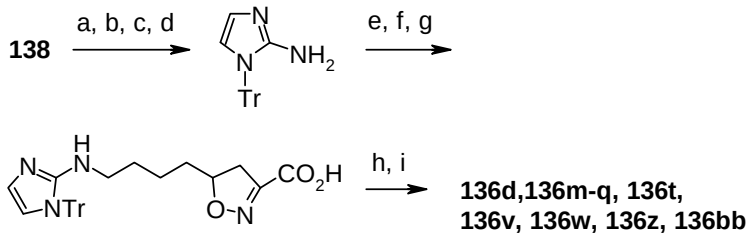
(a) Oxalyl chloride, DMSO, Et_3N, -70°C; (b) sodium triacetoxyborohydride, 2-aminopyridine; (c) Boc_2O, pyridine, cat. DMAP; (d) LiOH, dil H^+; (e) BOP, *tert*-butyl N^2-benzyloxycarbonul-2(*S*)-2,3-diaminopropionate **133b**, *N*-methylmorpholine; (f) TFA; (g) H_2, 40 psi, $Pd/BaSO_4$; (h) arylsulfonyl chloride, pyridine.

Scheme 36. Synthesis of 2-aminopyridines **136aa, 136e, 136r, 136s, 136u, 136x** and **136y**.[12]



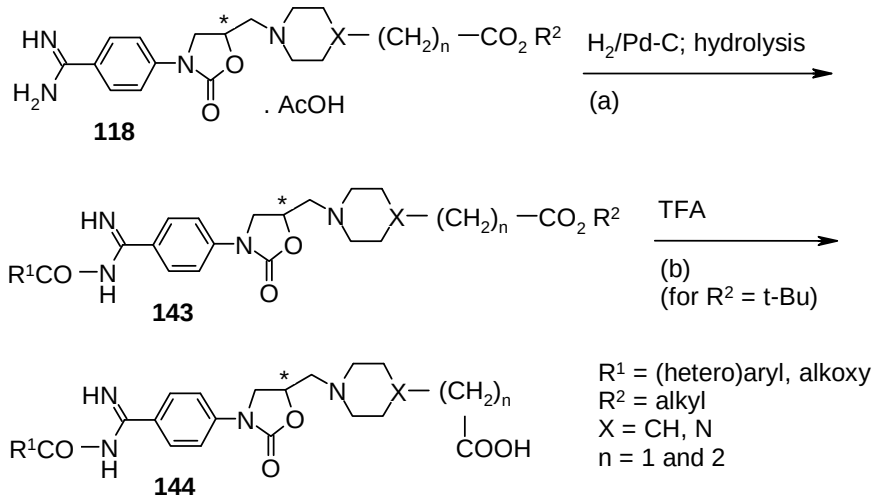
(a) Boc_2O, 40°C; (b) LDA, -78°C, then 4-bromobutene; (c) **130**, $NaHCO_3$, THF(aq), 0°C-rt; (d) NaOH, dil H^+; (e) BOP, **133a**, *N*-methylmorpoline; TFA.

Scheme 37. Synthesis of the 2-aminopyridin-6-yl **136f**.[12]



(a) $NaOCH_3$, -78°C-rt; (b) phthalic anhydride, melt; (c) triphenylmethyl chloride, pyridine; (d) N_2H_4, EtOH, reflux; (e) **139**, toluene, reflux; (f) sodium triacetoxyborohydride; (g) LiOH, H^+; (h) TBTU, **133**, *N*-methylmorpholine; (i) TFA, reflux.

Scheme 38. Synthesis of 2-aminoimidazoles **136d, 136m-q, 136t, 136v, 136w** and **136bb**.[12]



(a) 1:1.2:2.2, CH_2Cl_2/H_20, 1 h 5-8°C, 75-80%.; (b) TFA as solvent, 2 h rt, 90-95%.

Scheme 39. Synthesis of oxazolidinone compounds **143** and **144**.[11]

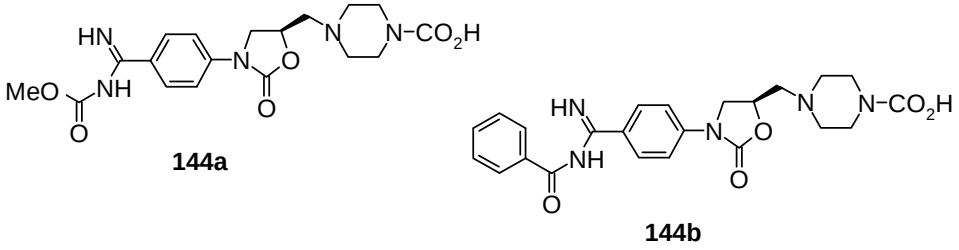
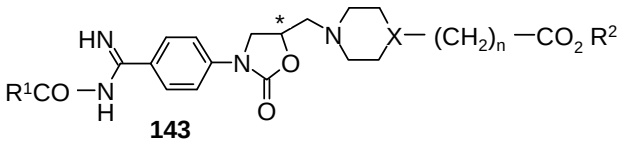


Figure 16. Oxazolidinone compounds **144a-b**.

Compounds **144a-b** showed negligible activity in the guinea pig whereas compounds **143d, 143n, 143o** and **143v** (Table 10) showed high activity.[11]

Table 10. Oxazolidinone compounds **143a-v**.[11]



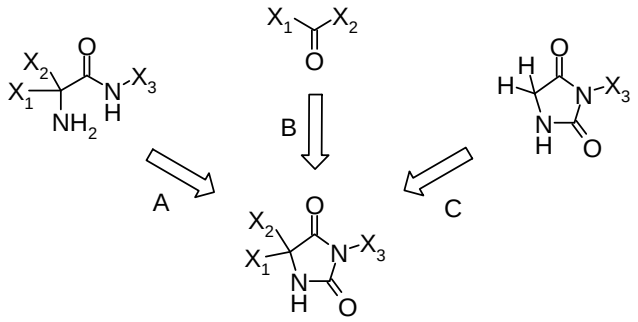
143

Compd.	R^1	R^2	X	n	config.
143a	phenyl	Et	CH	0	(RS)
143b	phenyl	Et	CH	1	(RS)
143c	phenyl	Et	CH(OH)	1	(RS)
143d	phenyl	Et	N	1	(R)
143e	phenyl	Et	N	1	(S)
143f	phenyl	Et	N	2	(R)
143g	phenyl	Et	N	2	(S)
143h	phenyl	tBu	N	1	(R)
143i	phenyl	tBu	N	2	(RS)
143j	4-MeO- phenyl	Et	N	1	(R)
143k	3-CF_3-phenyl	Et	N	1	(R)
143l	3-pyridyl	Et	N	1	(RS)
143m	2-furyl	Et	N	1	(RS)
143n	MeO	Me	N	1	(R)
143o	MeO	Et	N	1	(R)
143p	MeO	Et	N	1	(RS)
143q	MeO	Et	N	2	(RS)
143r	MeO	tBu	N	1	(RS)
143s	EtO	Et	N	1	(R)
143t	BnO	Et	N	1	(R)
143u	iPr	Et	N	1	(R)
143v	phenoxy	Et	N	1	(RS)

4 Hydantoin compounds

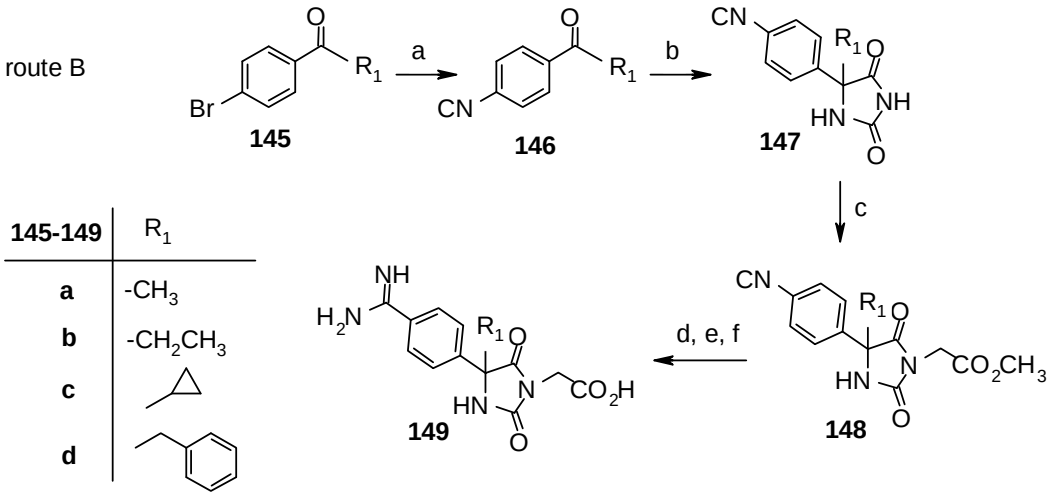
4.1 Compounds containing a benzamidine unit

Stilz *et al.* synthesized a series of active GP IIb/IIIa antaganonists based on the hydantoin scaffold.[13]



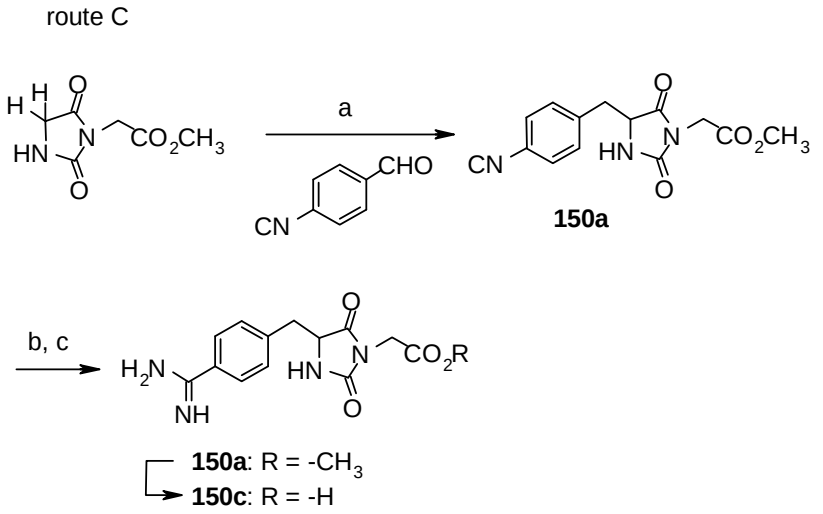
Scheme 40. Preparation of the hydantoin scaffold.[13]

Amino acids (route A), ketones/aldehydes (route B) and unsubstituted hydantoins (route C) were used as precursors for the hydantoin scaffold (Scheme 37).[13]



(a) CuCN, DMF, reflux; (b) KCN, $(NH_4)_2CO_3$; (c) Cl-$CH_2CO_2CH_3$, KI, $NaOCH_3$; (d) HCl, ethanol; (e) NH_3, isopropanol; (f) HCl, reflux.

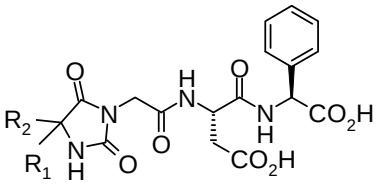
Scheme 41. Synthesis of compound **149**.[13]

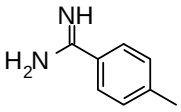
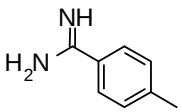
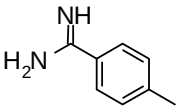
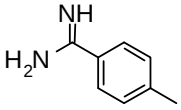
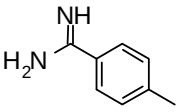
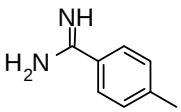
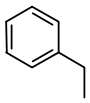
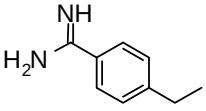


(a) CuCN, DMF, reflux; (b) KCN, $(NH_4)_2CO_3$; (c) Cl-$CH_2CO_2CH_3$, KI, $NaOCH_3$; (d) HCl, ethanol; (e) NH_3, isopropanol; (f)HCl, reflux.

Scheme 42. Synthesis of compound **150c**.[13]

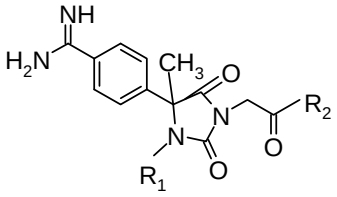
Table 11. Arginine replaced GP IIb/IIIa inhibitors.[13]

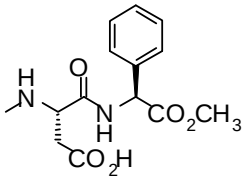
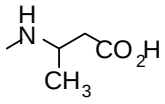
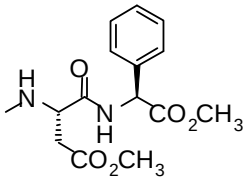
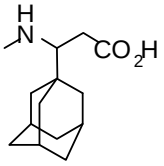
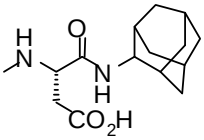
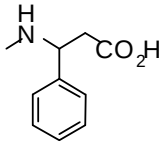
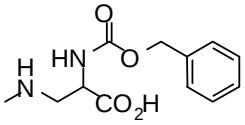
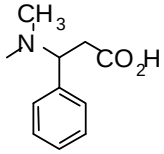
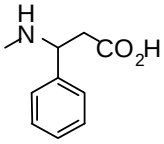


Comp	R_1	R_2	Comp	R_1	R_2
151		CH_3	**155**		CH_3CH_2
152'		CH_3	**156**		
153'	CH_3		**157**		
154		H			

The suitability of benzamidine for substituting arginine is suggested by the 36-fold greater activity of compound **153** compared to the parent compound **179** (Scheme 44).[13]

Table 12. C-terminal variation of GP IIb/IIIa inhibitors.[13]



Comp	R_1	R_2	Comp	R_1	R_2
158	H		**163**	H	
159	H		**164**	H	
160	H		**165**	CH_3CH_2	
161	H		**166**	H	
162	H				

Compounds **158, 160, 161** and **162** showed good fibrinogen receptor binding activity.[13]

The ethyl ester prodrug **171** (Figure 18) is an orally active antithrombotic agent.[13]

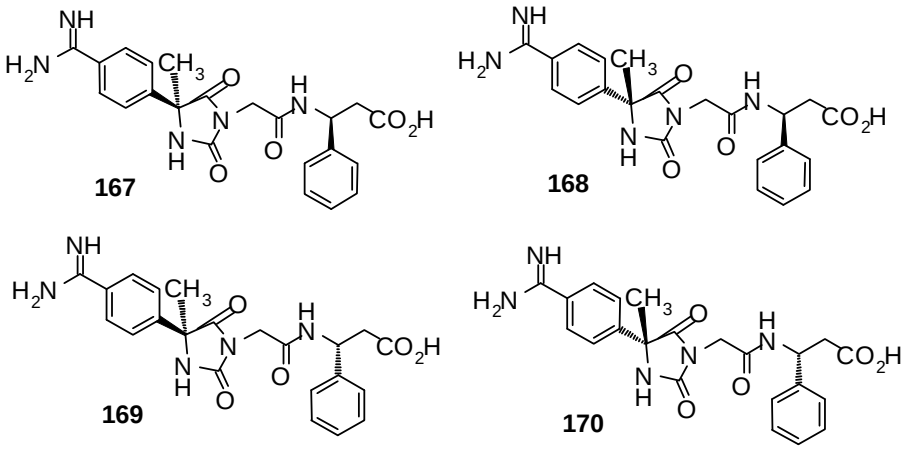


Figure 17. Stereoisomeres of **162**.[13]

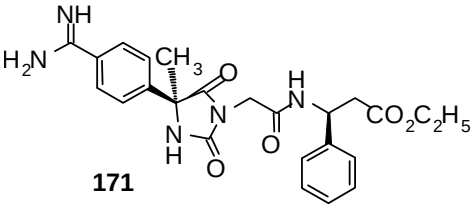
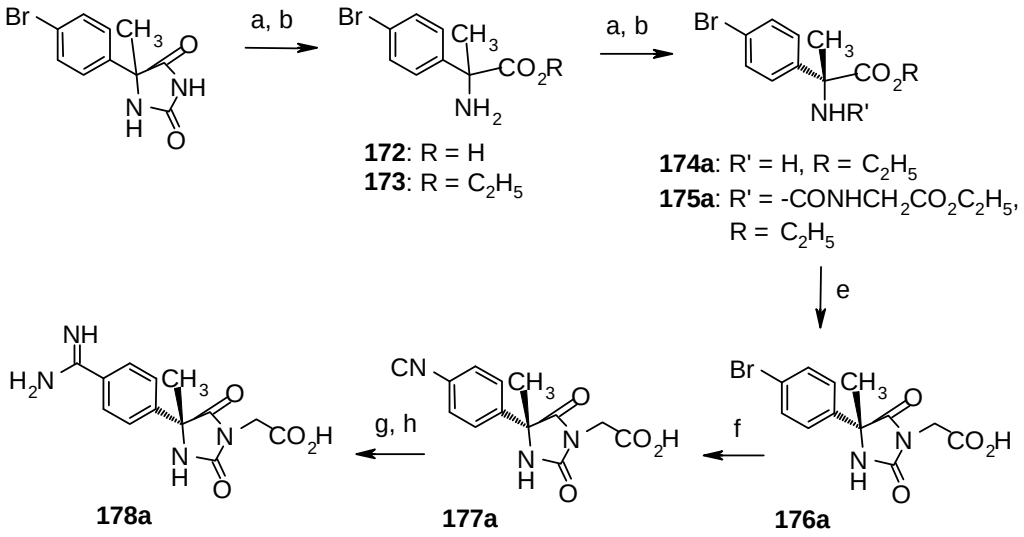


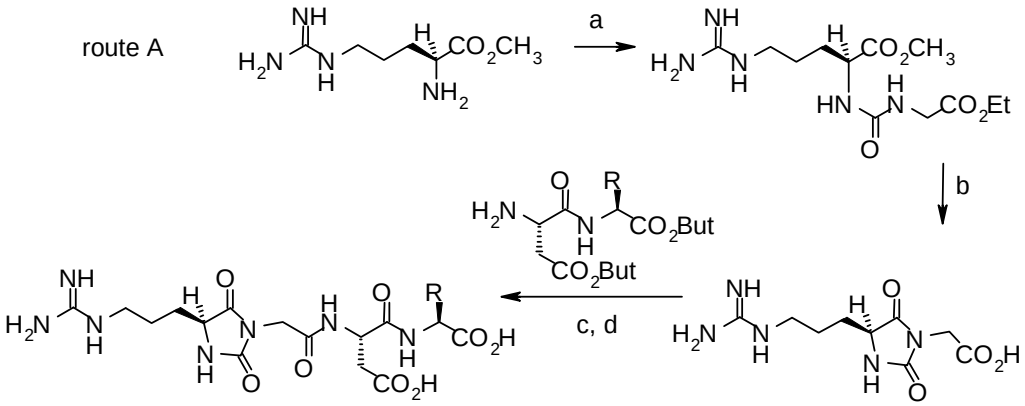
Figure 18. Maleic acid salt **171**.[13]



(a) NaOH, 145°C, 10 bar; (b) HCl, ethanol; (c) *R*-mandelic acid, isopropanol, diisopropyl ether; (d) ethoxycarbonylmethyl isocyanate, DMF, *N*-ethylmorpholine; (e) 6 N HCl; (f) CuCN, DMF; (g) HCl, ethanol; (h) NH_3, ethanol.

Scheme 43. Synthesis of compound **178a**.[13]

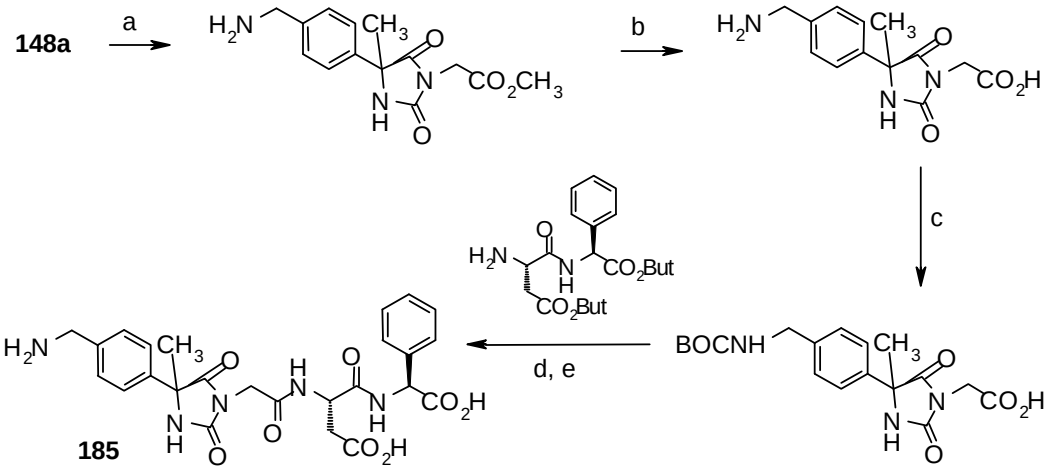
4.2 Other hydantoin compounds



(a) Ethoxycarbonylmethyl isocyanate, *N*-ethylmorpholine, DMF, reflux; (c) DCC, HOBt, DMF; (d) TFA.

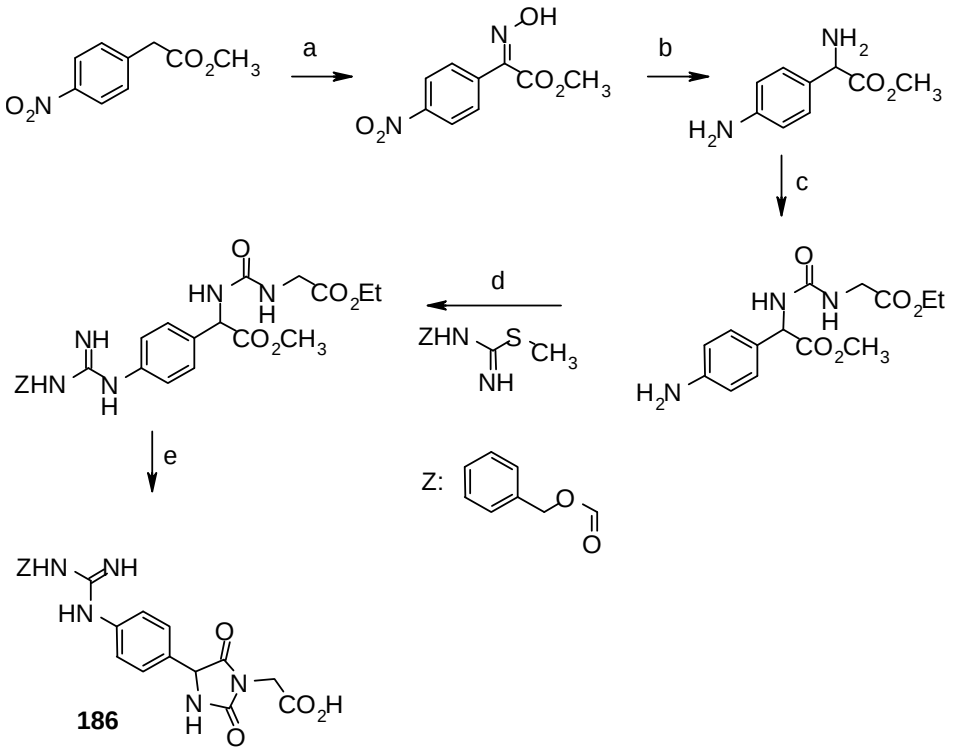
Scheme 44. Synthesis of compounds **179-184**.[13]

Compounds **181, 182 and 184** exhibited greater potency than **179, 180** and **183** showing that aliphatic or aromatic residues are favorable compared to the carboxy terminal serine.[13]



(a) Ethanol, acetic acid, 10% Pd/C, 2h, 3 bar; (b) conc. HCl, 100°C, 6 h; (c) dioxane, H_2O, di-*tert*-butyl dicarbonate; (d) DCC, HOBt, DMF; (e) TFA, methanol, Pd/C, rt, 2h.

Scheme 45. Synthesis of compound **185**.[13]



(a) Isoamylnitrite, methanol, $NaOCH_3$; (b) HCl, methanol, DMF, 10% Pd/C, H_2; (c) ethoxycarbonyl-methyl isocyanate, *N*-ethylmorpholine, DMF, -20°C; (d) 1-benzyloxycarbonyl-2-methyl-isothiourea, CH_3CO_2H, methanol; (e) HCl, CH_3CO_2H, 80°C.

Scheme 46. Synthesis of compound **186**.[13]

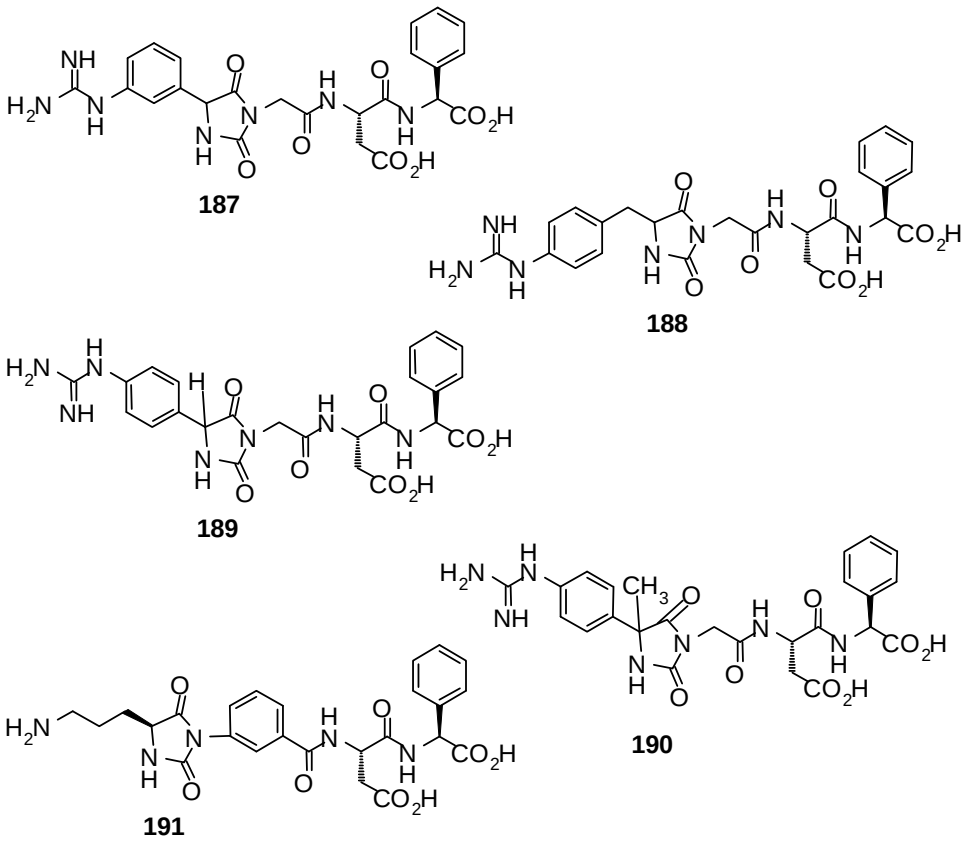
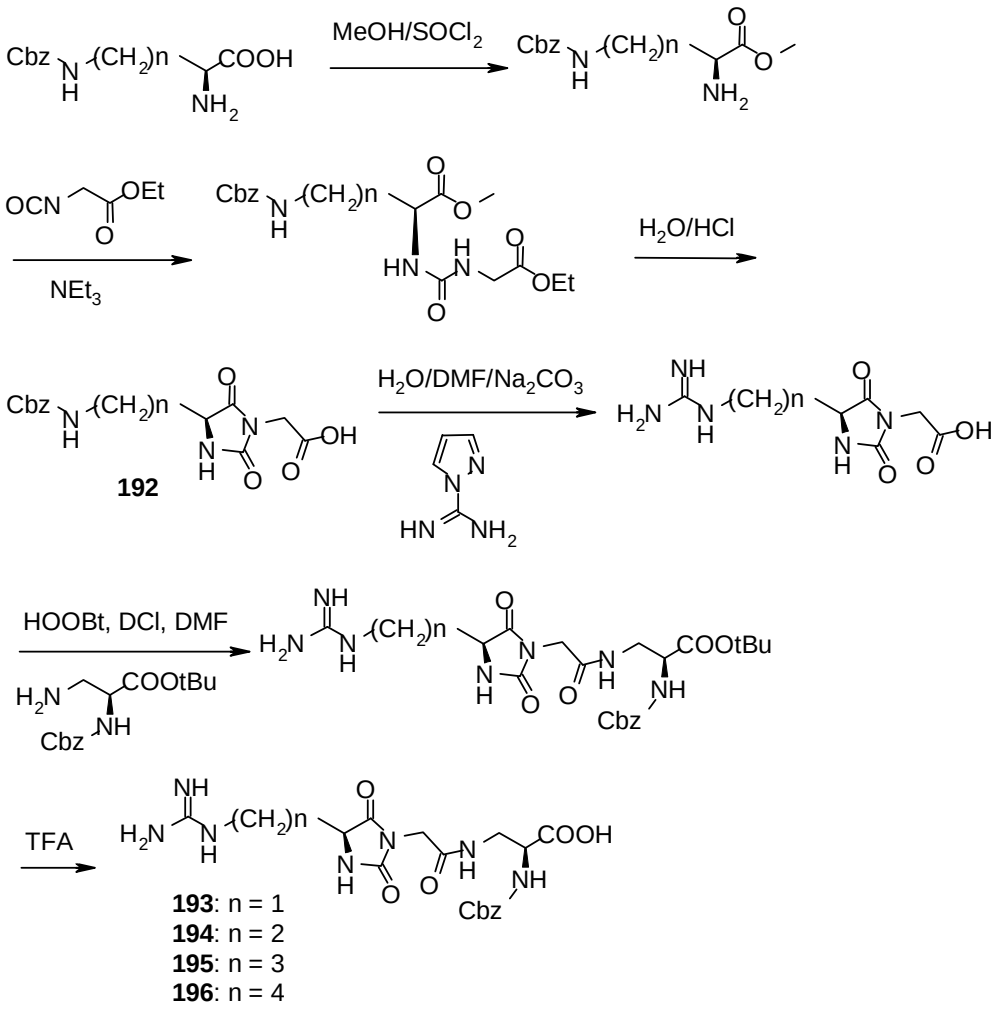


Figure 19. Arginine replaced GP IIb/IIIa inhibitors **187-191**.[13]

Compounds **185, 189** and **190** showed much greater potency compared to compounds **187** and **188** which suggests that *p*-substitution of the rigid phenyl ring is favored over *m*-substitution and a more flexible phenylmethylene.[13]

Peyman *et al.* have designed a series of $\alpha_V\beta_3$ antagonists containing a hydantoin scaffold.[14]

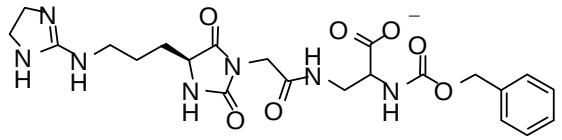


Scheme 47. Synthesis of integrin antagonists **193-196**.[14]

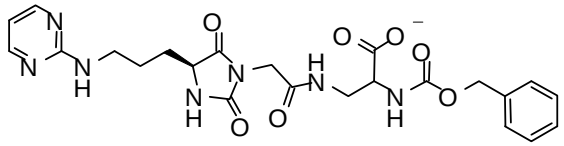
Compound **197** (Figure 20) is synthesized by treatment of **192** with 2-methylthio-2-imidazoline, and **198** (Figure 20) by reaction of **192** with 2-bromopyrimidine, followed in each case by the last two steps from Scheme 47.

Peyman *et al.* found compound **193** to have the optimal distance (12 bonds) between the C-terminal carboxyl group and the N-terminal guanidino group for an $\alpha_V\beta_3$ antagonist whereas for $\alpha_{IIb}\beta_3$ compound **194** with its 13 bonds showed higher affinity.[14] They also found cyclic guanidines to be preferred over non-cyclic guanidines as arginine mimetics for both $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ selectivity. When comparing the effect of the lipophilic side

chain Peyman *et al.* found compound **193** to clearly have the most favorable one (Cbz), compound **195** having the least favorable lipophilic side chain.[14]

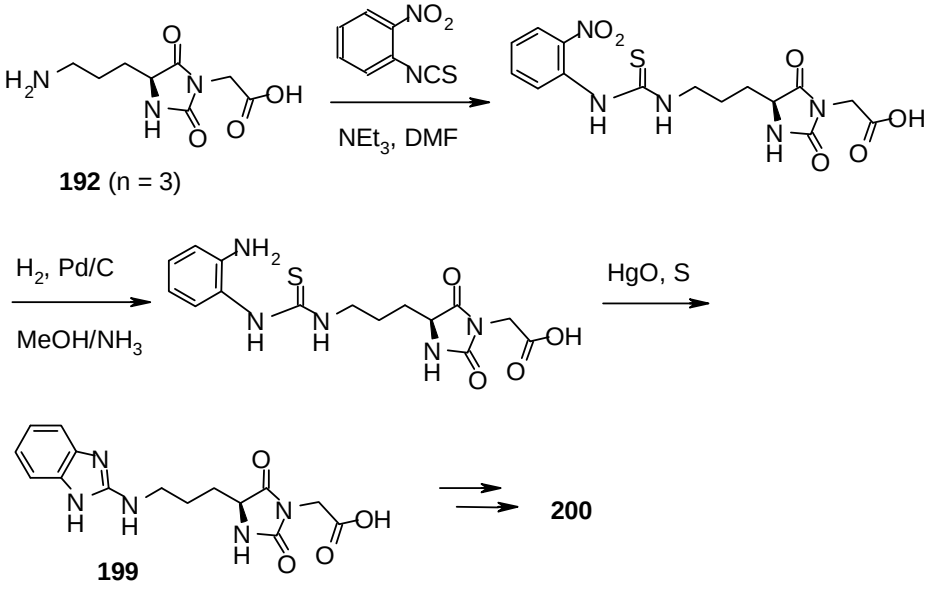


197



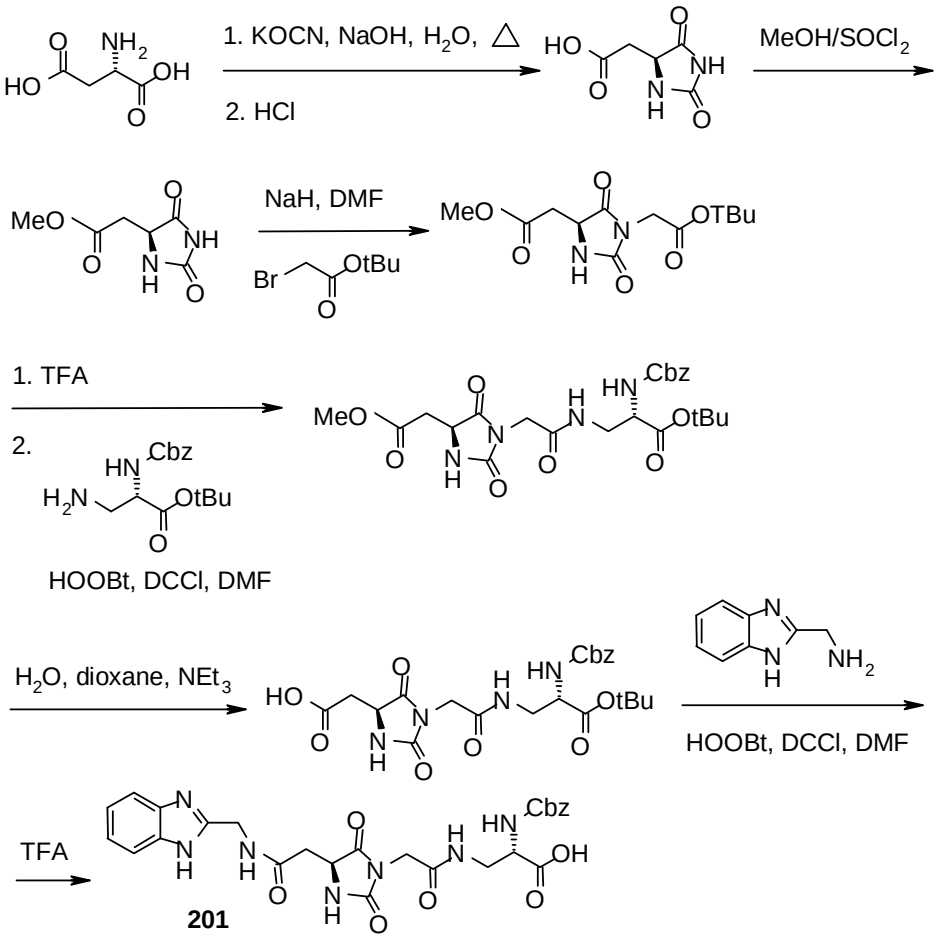
198

Figure 20. Integrin antagonists **197** and **198**.



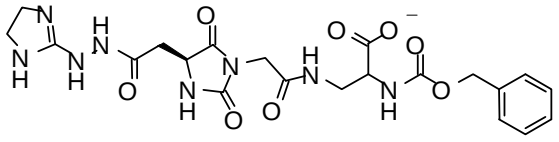
Compound **199** is reacted further as in Scheme 36 to yield antagonist **200**.

Scheme 48. Synthesis of benzimidazole containing integrin antagonist **200**.[14]



Scheme 49. Synthesis of benzimidazole containing integrin antagonist **201**.[14]

Compound **202** (Figure 21) was prepared in a similar way to that depicted in Scheme 46 using (4,5-dihydro-imidazol-2-yl)-hydrazine instead of 2-aminomethyl-benz-imidazole.[14]



202

Figure 21. Integrin antagonist **202**.

Compounds **203-207** (Figure 22) were prepared by catalytic hydrogenation of **193** to remove the Cbz group and coupling of the appropriate side chain to the free amino function.[14]

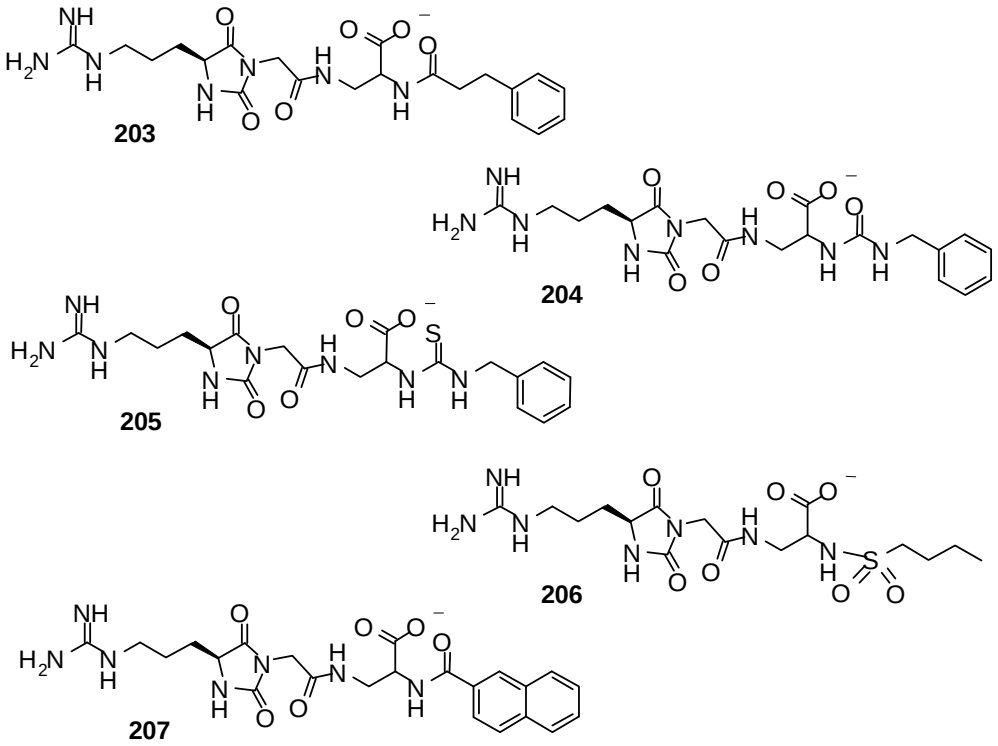
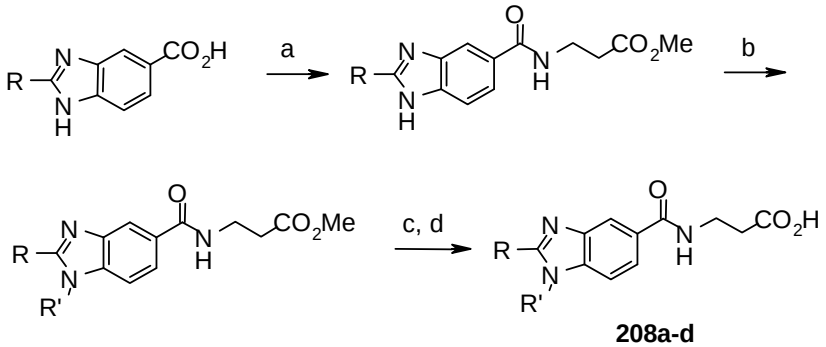


Figure 22. Integrin antagonists **203-207**.

5 Benzimidazole, benzoxazole and imidazopyridine compounds

5.1 Benzimidazole, benzoxazole and imidazopyridine compounds containing a benzamidine or *p*-cyanophenyl unit

Xue *et al.* have designed a series of potent GP IIb/IIIa antagonists having a benzamidine as the basic moiety and an α-carbamate or sulfonamide substituted β-alanine as the acidic moiety.[15]



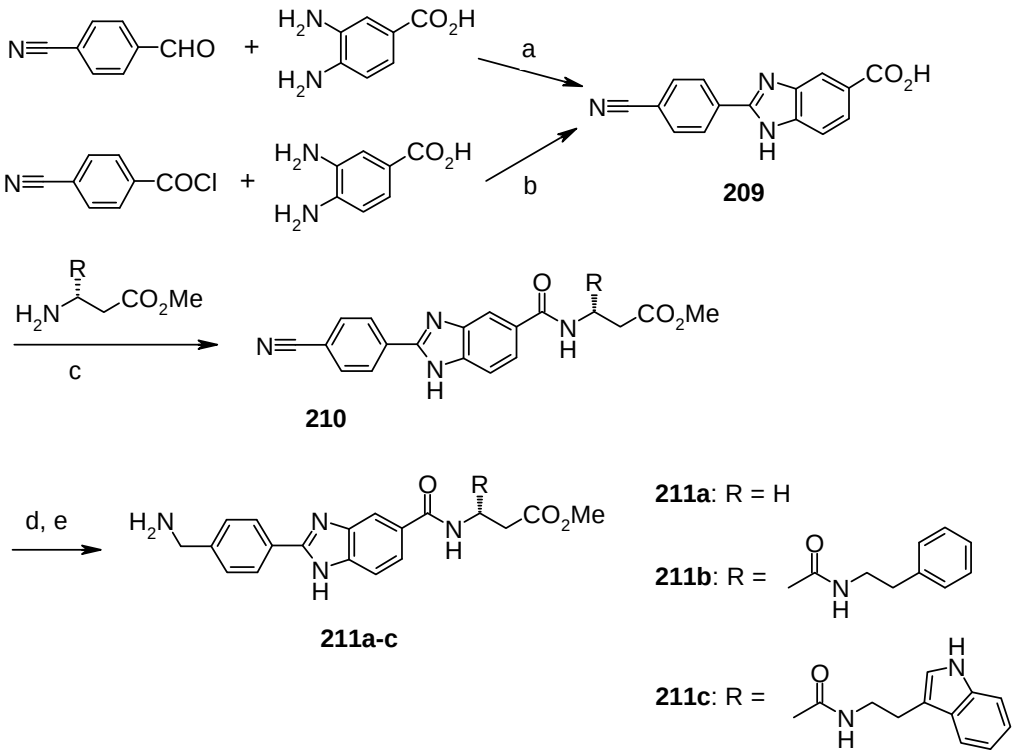
208a-d

208a: R = H, R' = 4-aminomethyl)benzyl
208b: R = H, R' = 4-amidinobenzyl
208c: R = CH_3, R' = 4-amidinobenzyl
208d: R = H, R' = 4-piperidinepropyl

(a) β-AlaOMe, TBTU, DIEA, DMF, 80-90%; (b) 4-cyanobenzyl bromide or N-Cbz-4-piperidinepropyl bromide, NaH, DMF, 40-60%; (c) H_2, Pd/C, DMF, 80-90% (**208a** and **208d**) or (1) HCl, MeOH, (2) NH_3, MeOH, 40-60% (**208b** and **208c**); (d) NaOh, MeOH, 80-90%.

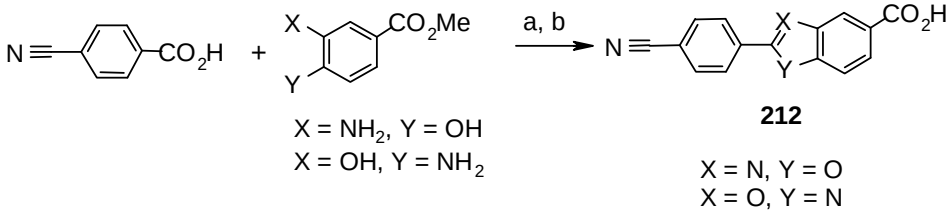
Scheme 50. Synthesis of compounds **208a-d**.[15]

Compound **208a** was found to be the least active of the four compounds in the inhibition of platelet aggregation showing that a benzamidine or a 4-piperidinepropyl group is preferred over a 4-aminomethylbenzyl group.



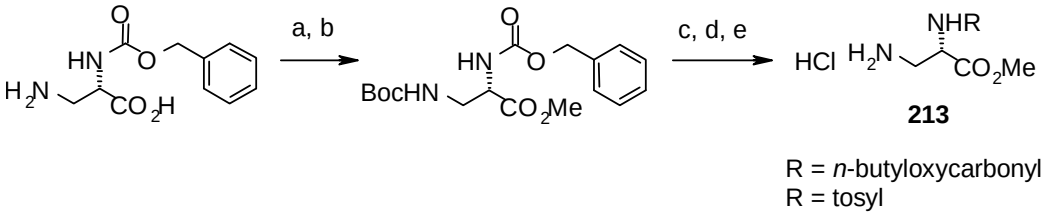
(a) (1) DMF, molecular sieves (2) CH_3CO_2H, reflux, 25%; (b) CH_3CO_2H, reflux, 30%; (c) TBTU, DIEA, DMF, 70-90%; (D) H_2, Pd/C, DMF, HCl, 80-90%; (e) NaOH, MeOH, 80-90%.

Scheme 51. Synthesis of compounds **210** and **211a-c**.[15]



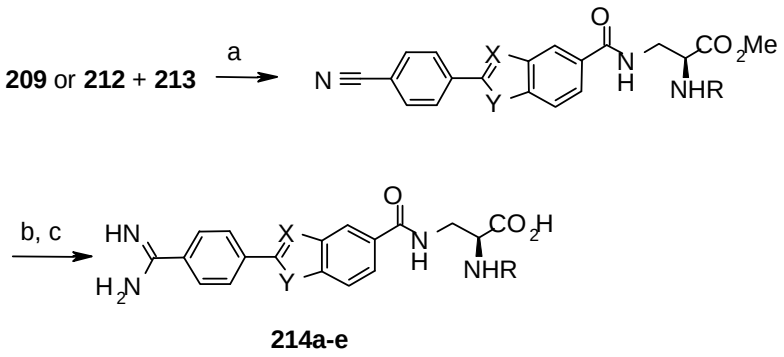
(a) Boric acid, xylene, reflux, 30-40%; (b) NaOH, MeOH, 80-90%.

Scheme 52. Synthesis of compounds **212**.[15]



(a) MeOH, 4 N HCl/dioxane, 90%; (b) $(Boc)_2O$, DIEA, $CHCl_3$, 85%; (C) H_2, Pd/C, MeOH, 100%; (d) *n*-butyl chloroformate or *p*-toluenesulfonyl chloride, DIEA, $CHCl_3$, 60-80%; (e) 4 N HCl/dioxane, 100%.

Scheme 53. Synthesis of compounds **213**.[15]



(a) TBTU, DIEA, DMF, 80-85%; (b) (1) HCl, MeOH (2) NH_3, MeOH, 40-60%; (c) NaOH, MeOH, 80-90%.

Scheme 54. Synthesis of compounds **214a-e**.[15]

Compounds **214a-e** were found to be very potent GP IIb/IIIa inhibitors, **214a** being the least active.

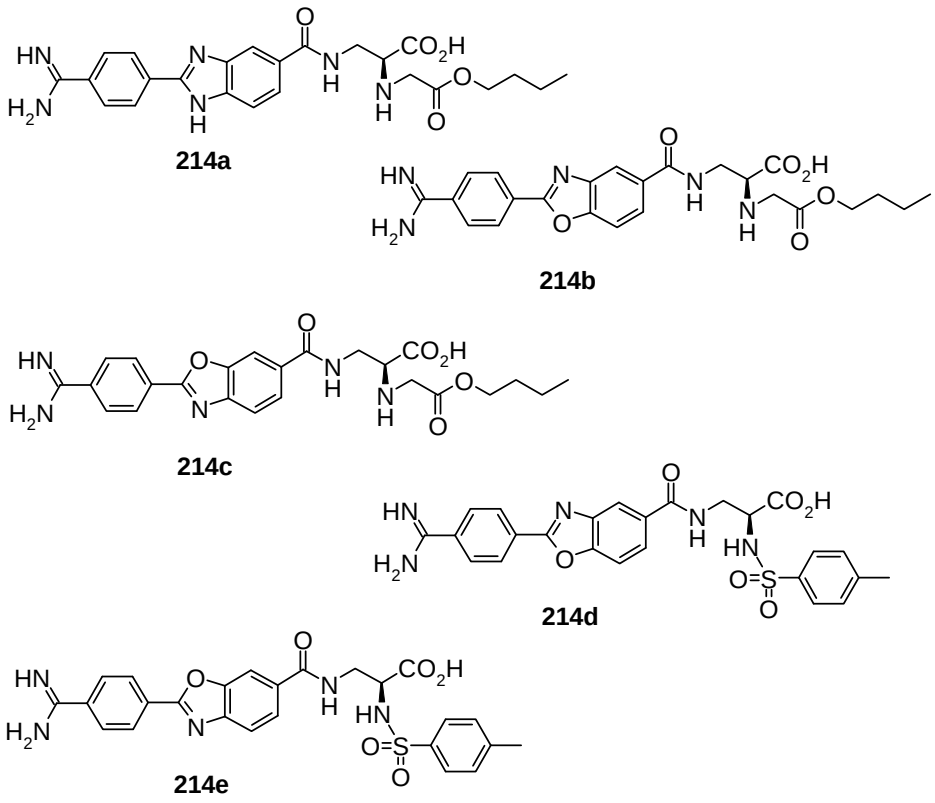
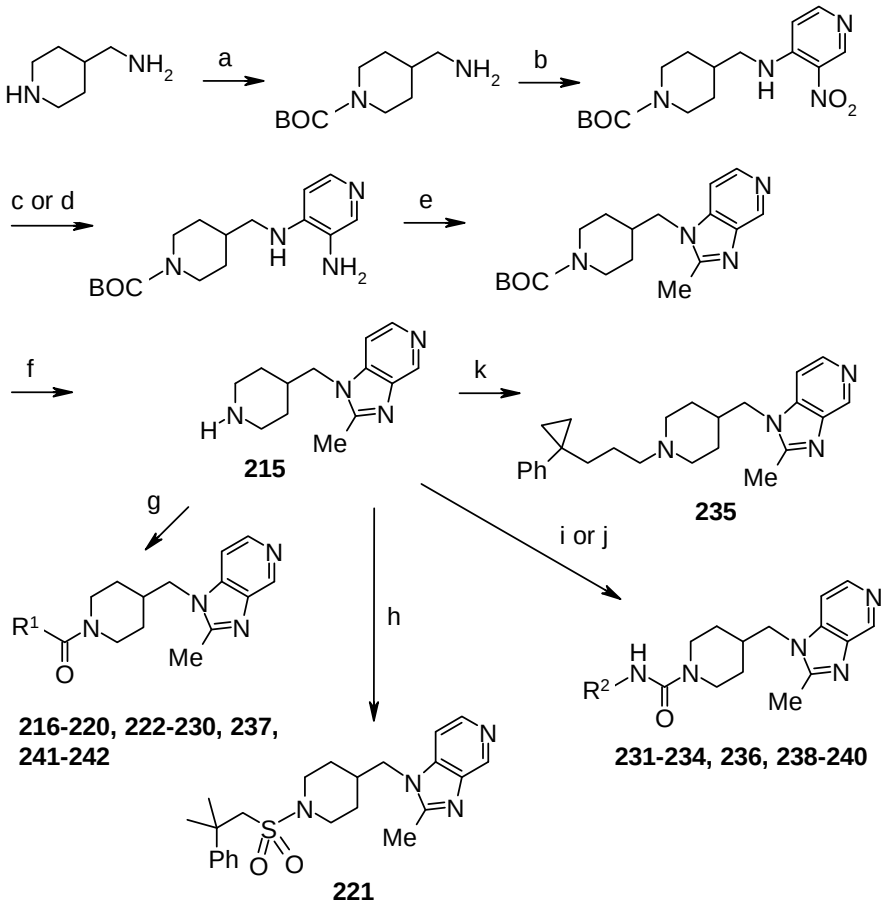


Figure 23. Benzimidazole/benzoxazole analogs **214a-e**.

5.2 Other benzimidazole, benzoxazole and imidazopyridine compounds

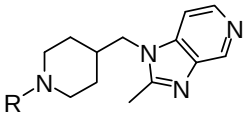
Carceller *et al.* have designed a series of 1-[(1-acyl-4piperidyl)methyl]-1*H*-2-methylimidazo[4,5-*c*]pyridine derivatives as potent, orally active platelet-activating factor (PAF) antagonists.[16]

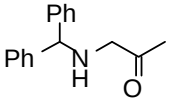
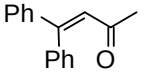
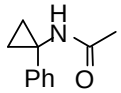
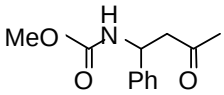
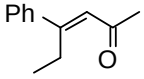
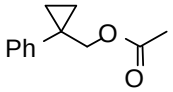
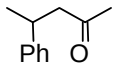
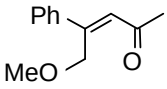
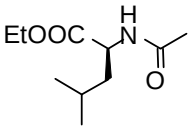
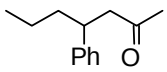
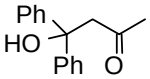
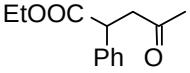
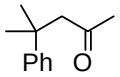
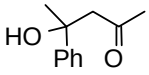
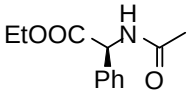
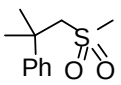
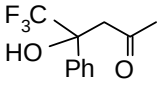
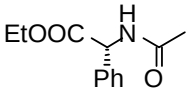
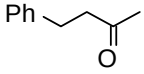
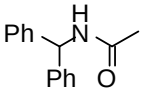
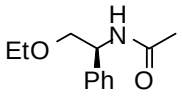
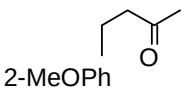
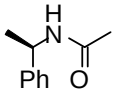
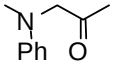
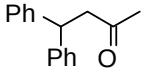
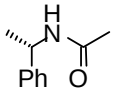
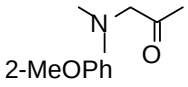


(a) BOC_2O, $CHCl_3$, room temperature, 18 h; (b) 4-chloro-3-nitropyridine, Et_3N, CH_3Cl, reflux for 18 h, 64% (two steps); (c) H_2, 10% Pd/C, MeOH, 18 h; (d) $Na_2S_2O_4$, pyridine/H_2O, room temperature, 18 h; (e) ethyl acetimidate hydrochloride, EtOH, reflux, 18 h, 62% (two steps); (f) 6.5 N HCl_g/dioxane, MeOH, room temperature, 18 h, 78%; (g) R^1COOH, DCC, HOBT, DMF, room temperature, 18 h; (h) $Ph(CH_3)_2CCH_2SO_2Cl$, Et_3N, $CHCl_3$, room temperature, 18 h; (i) R^2COOH, $(PhO)_3$, Et_3N, benzene, 90 °C, 2 h and then **215** was added, 90 °C, 18 h; (j) $R^2NHCOOPh$, pyr, 130 °C, 18 h; (k) $Ph(C_3H_4)CH_2OCOOPh$, pyr, 130 °C, 18 h.

Scheme 55. Synthesis of imidazopyridines **216-242**.[16]

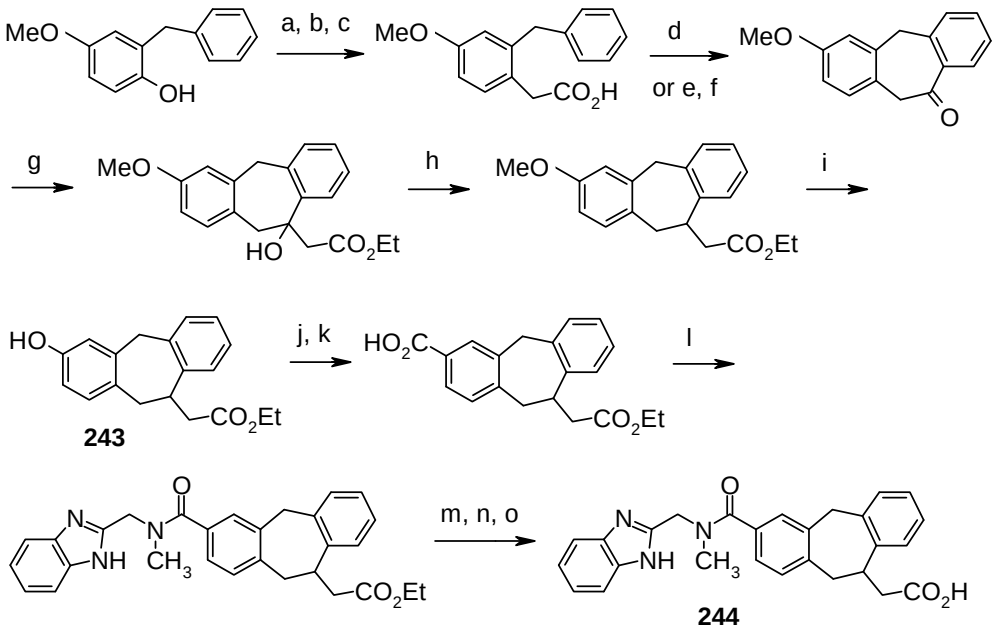
Table 13. Imidazopyridines **216**-**242**.[16]



Comp	R	Comp	R	Comp	R
216		**225**		**234**	
217		**226**		**235**	
218		**227**		**236**	
219		**228**		**237**	
220		**229**		**238**	
221		**230**		**239**	
222		**231**		**240**	
223		**232**		**241**	
224		**233**		**242**	

According to Carceller *et al.* having three coordination centers is beneficial to this type of PAF antagonist: an sp^2 nitrogen at a given distance from and orientation to an amide or other isosteric groups, and another coordination center such as a cyano group close to the sp^2 nitrogen. Carceller *et al.* also found that branched substitution of the acyl moiety and a methoxy group at the 2-position of the aromatic ring increased activity. Compound **224** was found to be the most potent PAF antagonist.[16]

Miller *et al.* have synthesized potent vitronectin receptor antagonists.[17]



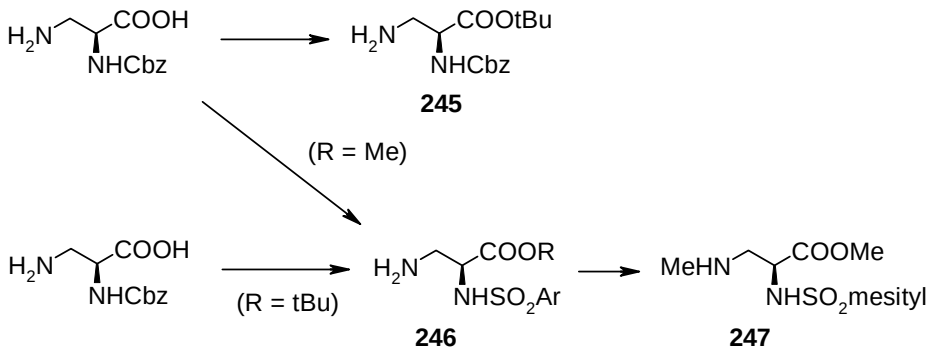
(a) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C to RT (96%); (b) (allyl)$SnBu_3$, LiCl, $(Ph_3P)_2PdCl_2$, DMF, 95 °C (99%); (c) $RuCl_3$, H_5IO_6, CH_3CN, H_2O, 0 °C to RT (74%); (d) PPA, 100-110 °C (48%); (e) $(COCl)_2$, benzene, reflux; (f) $AlCl_3$, CH_2Cl_2, 0 °C to RT (71%) for two steps); (g) EtOAc/LiHMDS, THF, -78 °C (73%); (h) H_2, 10% Pd/C, conc HCl, AcOH (91%); (i) EtSH, $AlCl_3$, CH_2Cl_2, 0 °C to RT (95%); (j) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C to RT (92%); (k) CO, $Pd(OAc)_2$, KOAc, dppf, DMSO, 70 °C (95%); (l) 2-(methylamino)methylbenzimidazole dihydrochloride, EDC, HOBt · H_2O, (*i*-Pr)$_2$NEt, DMF (95%); (m) 1.0 N LiOH, THF, H_2O, 40°C; (n) 1.0 N HCl, H_2O; (o) 5% $NaHCO_3$, MeOH (45% for three steps).

Scheme 56. Synthesis of compound **244**.[17]

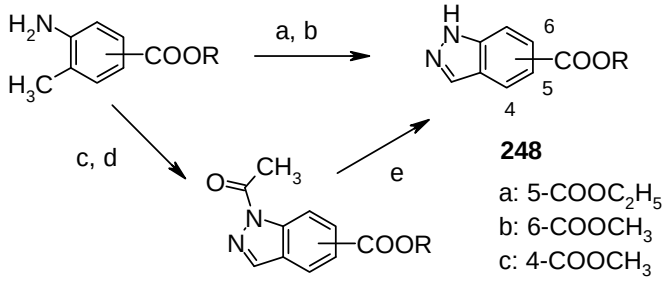
Compound **244** has good affinity for $\alpha_V\beta_3$ and poor affinity for $\alpha_{IIb}\beta_3$. Significant improvement of activity was achieved with the similar ether-linked compound **647** (Scheme 133, chapter 11).[17]

6 Indazole compounds

Batt *et al.* have synthesized a series of indazole-containing $\alpha_V\beta_3$ integrin antagonists.[18]

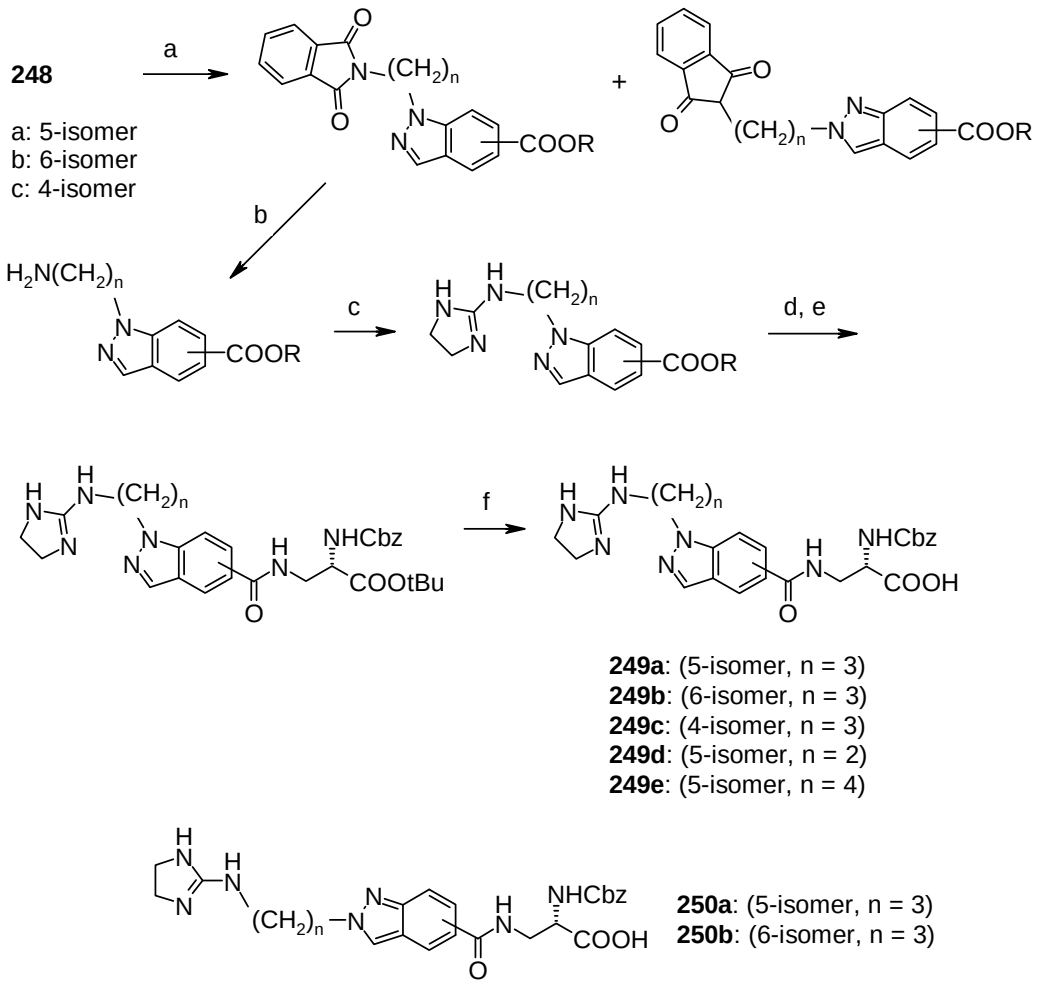


Scheme 53. Preparation of diaminopropionate derivatives.[18]



(a) HCl, NH_4BF_4, $NaNO_2$, 0 °C; (b) KOAc, $CHCl_3$; (c) Ac_2O, KOAc, $CHCl_3$; (d) nAmONO, 18-crown-6, $CHCl_3$, Δ; (e) HCl, H_2O, EtOH.

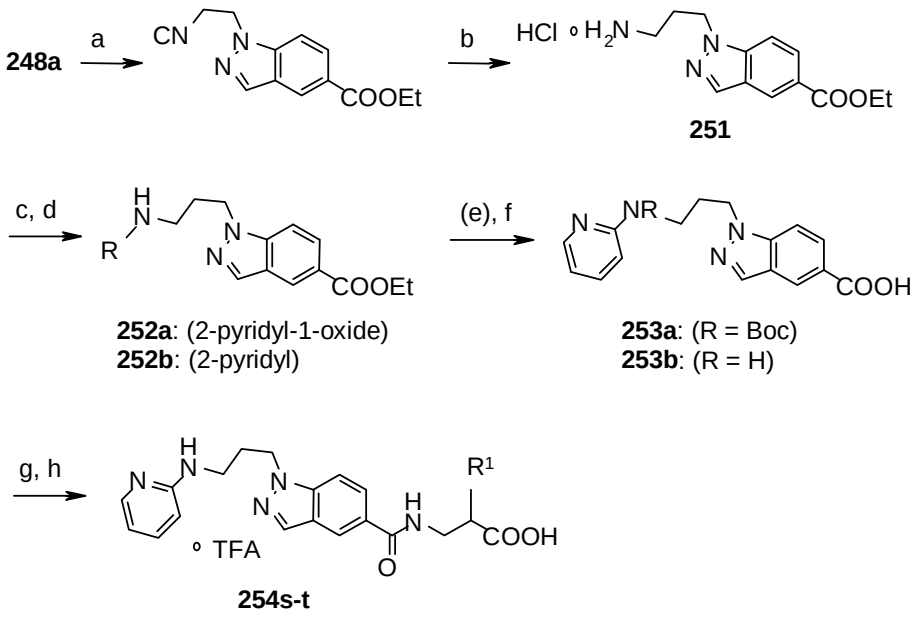
Scheme 57. Preparation of indazolecarboxylate esters.[18]



(a) $KN(TMS)_2$, $PhthN(CH_2)_nBr$, THF, Δ; (b) H_2NNH_2, EtOH; (c) 2-MeS-4,5-dihydroimidazole·HI, pyridine, Δ; (d) NaOH, H_2O, EtOH, Δ, HCl, H_2O; (e) **245**, DCC, HOBT, DMF; (f) CF_3COOH, CH_2Cl_2.

Scheme 58. Initial synthetic approach by Batt *et al*.[18]

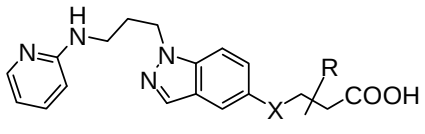
Batt *et al.* used **249a** as the lead compound due to its good binding to integrin $\alpha_V\beta_3$.[18]



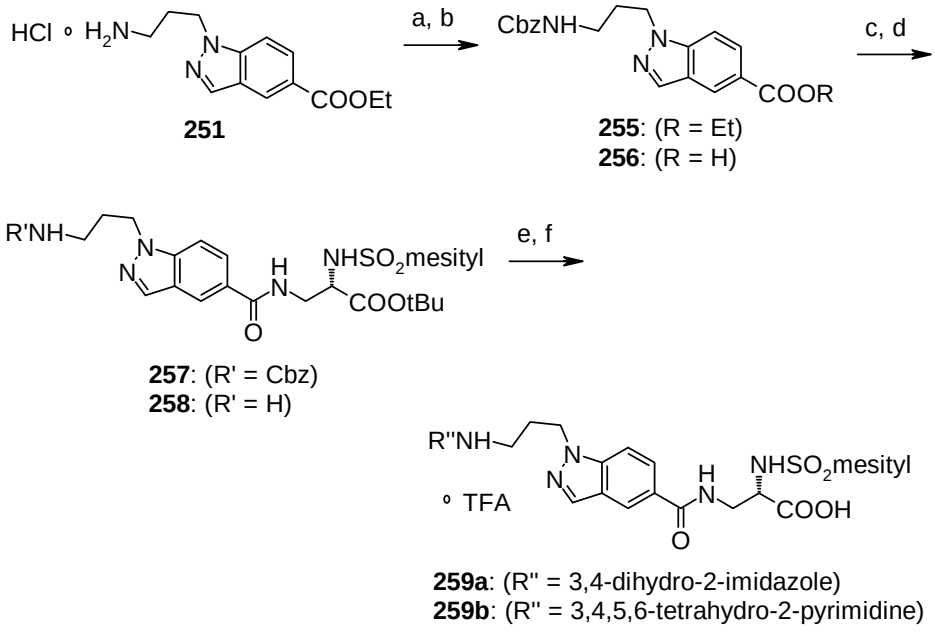
(a) CH_2=CHCN, $NaN(TMS)_2$ (cat.), EtOH, Δ; (b) H_2, Pd/C, $CHCl_3$, EtOH; (c) 2-chloropyridine 1-oxide, $NaHCO_3$, nBuOH, 100 °C; (d) H_2, Pd/C, $CHCl_3$; or $HCOONH_4$, Pd/C, EtOH, Δ; (e) Boc_2O, DMAP, CH_2Cl_2; (f) NaOH, H_2O, EtOH, then H_3O^+; (g) **245**, **246**, or related amine, DCC, HOBT, DMF; (h) CF_3COOH, CH_2Cl_2; optionally followed by NaOH in H_2O for methyl esters.

Scheme 59. Preparation of aminopropyl intermediate **251** and aminopyridine derivatives.[18]

Table 14. Compounds **254a-k, m, n** and **p-t**.[18]

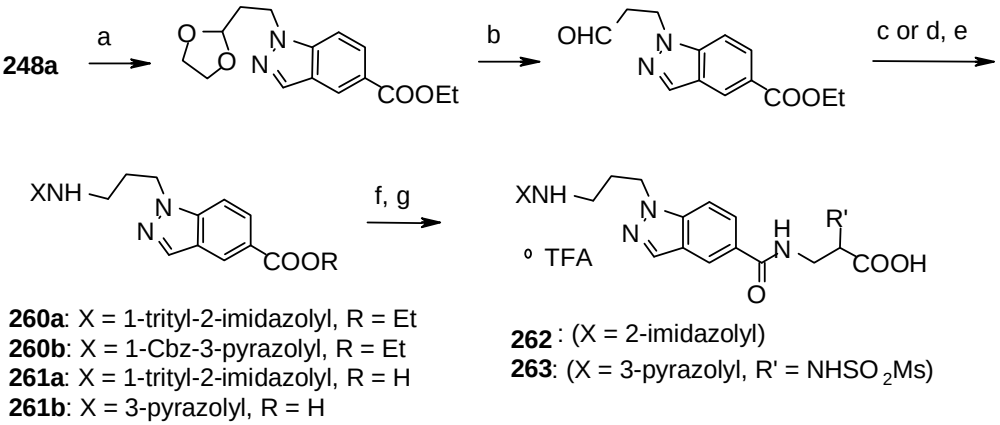


Compd	X	R
254a	-CONH-	α-(S)-$NHSO_2$mesityl
254b	-CON(Me)-	α-(S)-$NHSO_2$mesityl
254c	-CONH-	H
254d	-CONH-	α-(S)-$NHSO_2CH_2Ph$
254e	-CONH-	β-(S)-$CONH(CH_2)_2Ph$
254f	-CONH-	β-(S)-CONHmesityl
254g	-CONH-	α-(S)-NHCOOiBu
254h	-CONH-	α-(S)-NHCONHPh
254i	-CONH-	α-(S)-$NHCONHCH_2Ph$
254j	-CONH-	α-(S)-$NHCO(CH_2)_2Ph$
254k	-CONH-	α-(S)-$NHCOCH_2$iBu
254m	-CONH-	α-(S)-$NHSO_2Ph$
254n	-CONH-	α-(S)-$NHSO_2$nBu
254p	-CONH-	α-(S)-$NHSO_2CH_2Ph$
254q	-CONH-	α-(S)-$NHSO_2NH$iBu
254r	-CONH-	α-(S)-$NHSO_2NHCH_2Ph$
254s	-CONH-	α-(S)-$NHSO_2NHPh$
254t	-CONH-	α-(S)-$NHSO_2NH$mesityl



(a) $BzOOCCl$, Et_3N, CH_2Cl_2; (b) $LiOH$, H_2O, THF; (c) **246**, DCC, HOBT, DMF; (d) $Pd(OH)_2$, 1,4-cyclohexadiene, MeOH, Δ; (e) **259a**: (1) **258**, 2-methylthio-4,5-dihydroimidazole hydroiodide, pyridine, Δ, (2) TFA, CH_2Cl_2. **259b**: (1) **258**, 2-methylthio-3,4,5,6-tetrahydropyrimidine, pyridine, Δ, (2) TFA, CH_2Cl_2; (f) CF_3COOH, CH_2Cl.

Scheme 60. Variation of the basic group late in the synthesis.[18]



(a) $NaN(TMS)_2$, 2-(2-bromoethyl)-1,3-dioxolane, THF, Δ; (b) HOAc, H_2O, Δ; (c) (for **262**:) 1-trityl-2-amino-imidazole, toluene, Δ (-H_2O), $NaBH(OAc)_3$; (d) (for **263**:) 1-Cbz-3-aminopyrazole, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (e) NaOH, H_2O, EtOH, Δ; (f) **245**, **246**, or related amine, DCC, HOBT, DMF; (g) see text.

Scheme 61. Basic group introduction by reductive amination.[18]

Step g in Scheme 61 is as follows (compounds **262** are prepared from **261a**, compound **263** from **260b**):

For **262a** [from **246** (R = *tert*-butyl, Ar = mesityl)]: (1) MeOH, HOAc, Δ, (2) CH_2Cl_2, TFA.

Compounds **262b-g, 262p** and **262r-t** are prepared using the procedure for preparing **262a**:

For **262b**: from **246** (R = *tert*-butyl, Ar = mesityl),

262c: from **245**,

262d: from **246** (R = *tert*-butyl, Ar = mesityl),

262e: from *N*-mesitylenesulfonylethylenediamine trifluoroacetate,

262f: from *β*-alanine *tert*-butyl ester,

262g: from **246** (R = *tert*-butyl, Ar = phenyl),

262p: from **246** (R = methyl, Ar = 4-biphenyl),

262r: from **246** (R = methyl, Ar = 2,6-dichlorophenyl),

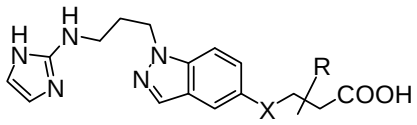
262s: from **246** (R = methyl, Ar = 2,6-dimethylphenyl),

262t: from **246** (R = *tert*-butyl, Ar = 4-phenyl-2,6-dimethylphenyl).

For **262u** [from **246** (R = methyl, Ar = 1-naphthyl)]: (1) EtOH, NaOH, Δ, then HCl (2) TFA, Δ.

263 [from **246** (R = *tert*-butyl, Ar = 2,4,6-trimethylphenyl)]: CH_2Cl_2, TFA.

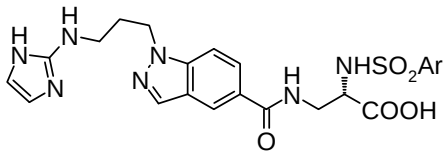
Table 15. Compounds **262a** and **c-f**.[18]



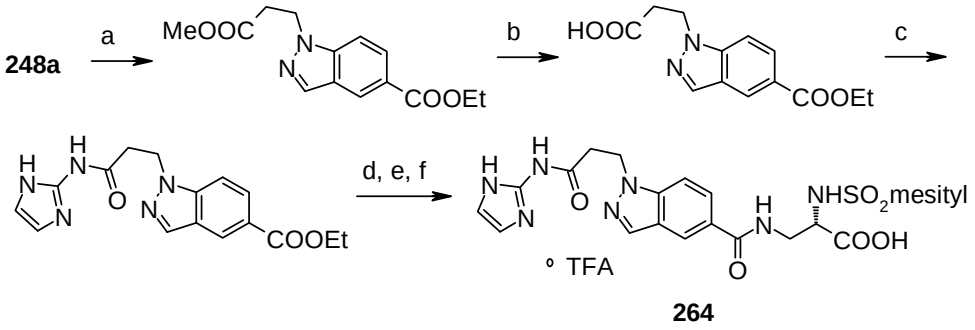
Compd	X	R
262a	-CONH-	α-(S)-$NHSO_2$mesityl
262c	-CONH-	α-(S)-$NHCO_2CH_2Ph$
262d	-CONH-	α-(R)-$NHSO_2$mesityl
262e	-CONH-	$NHSO_2$ mesityl
262f	-CONH-	H

Compound **262a** exhibited good affinity for $\alpha_V\beta_3$ with nine-fold selectivity over GPIIbIIIa.[18]

Table 16. Compounds **262g-k, m, n** and **p-v**.[18]

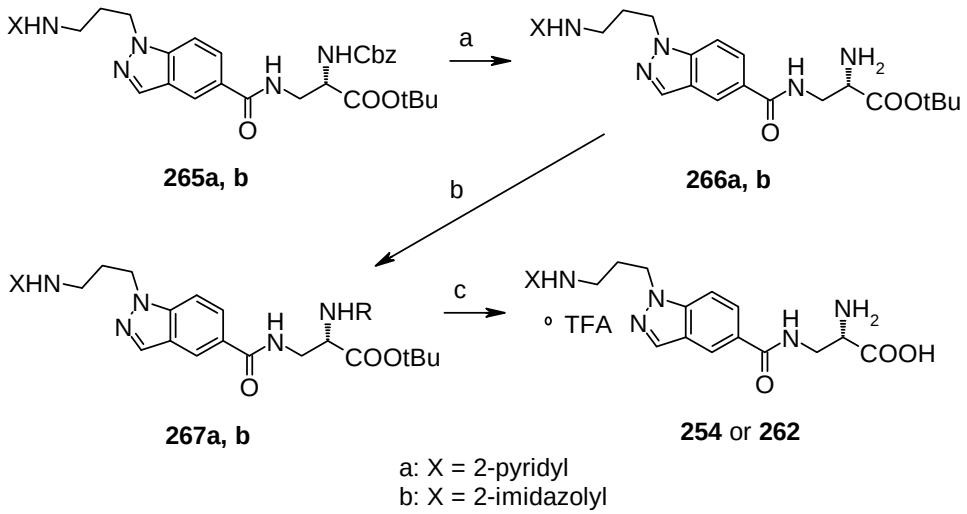


Compd	Ar	Compd	Ar
262g	Ph	**262p**	4-Ph-Ph
262h	4-Me-Ph	**262q**	3,4-Cl_2-Ph
262i	4-Cl-Ph	**262r**	2,6-Cl_2-Ph
262j	4-MeO-Ph	**262s**	2,6-Me_2-Ph
262k	4-CF_3-Ph	**262t**	2,6-Me_2-4-Ph-Ph
262m	4-AcNH-Ph	**262u**	1-naphtyl
262n	4-t-butyl-Ph	**262v**	2-naphtyl



(a) Methyl acrylate, tBuOH, KOtBu, THF, Δ; (b) LiOH, H_2O, THF; (c) 2-aminoimidazole sulfate, iPr_2NEt, BOP, DMF, 70 °C; (d) LiOH, H_2O, THF; (e) **246** (R = tBu, Ar = mesityl), DCC, HOBT, DMF; (f) CF_2COOH, CH_2Cl_2.

Scheme 62. Imidazole amide preparation.[18]



(a) H_2, Pd/C, EtOH; (b) see text; (c) TFA, CF_3COOH, CH_2Cl_2.

Scheme 63. Variation of α-substituent late in the synthesis.[18]

Step b in Scheme 63 is as follows (compounds **254** are prepared from **266a**, compounds **262** from **266b**):

For **254g**: pyridine, 4-(dimethylamino)pyridine, DMF, isobutyl chloroformate,

254a: pyridine, 4-(dimethylamino)pyridine, DMF, mesitylenesulfonyl chloride,

254h: iPr_2NEt, CH_2Cl_2, phenyl isocyanate,

254i: iPr_2NEt, CH_2Cl_2, benzyl isocyanate,

254j: hydrocinnamic acid, DCC, HOBT, THF,

254k: 4-methylvaleric acid, DCC, HOBT, THF.

The following compounds are prepared using the procedure for preparing **254g**:

254m: from benzenesulfonyl chloride,

254n: from 1-butanesulfonyl chloride,

254p: from phenylmethanesulfonyl chloride,

254q: from 2-methylpropanesulfamyl chloride,

254r: from phenylmethanesulfamyl chloride,

254s: from benzenesulfamyl chloride,

254t: from mesitylenesulfamyl chloride.

The following compounds are prepared from **266b** using the procedure for preparing **262h**:

262h: pyridine, 4-(dimethylamino)pyridine, DMF, *p*-toluenesulfonyl chloride,

262i: from 4-chlorobenzenesufonyl chloride,

262j: from 4-methoxybenzenesulfonyl chloride,

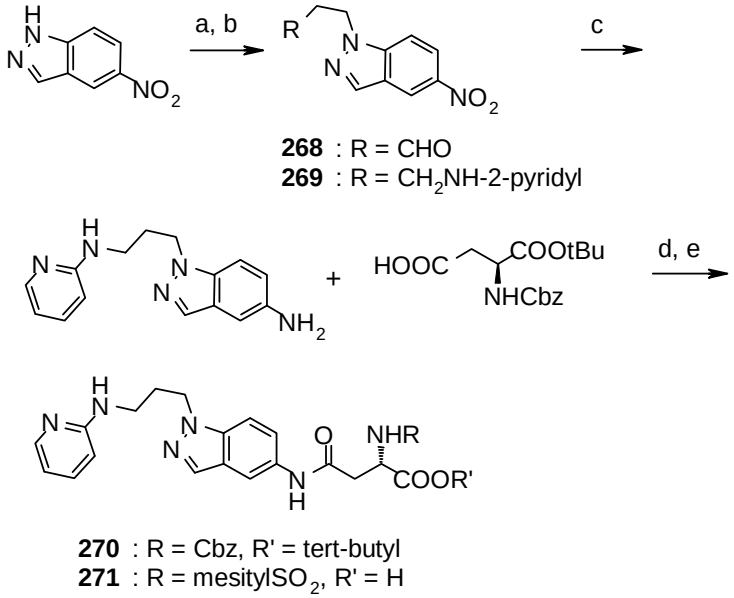
262k: from 4-trifluoromethylbenzenesulfonyl chloride,

262m: from 4-acetamidobenzenesulfonyl chloride,

262n: from 4-*tert*-butylbenzenesulfonyl chloride,

262q: from 3,4-dichlorobenzenesulfonyl chloride,

262v: from 2-naphtalenesulfonyl chloride.



(a) See Scheme 57; (b) Fe, HOAc, 90 °C; (c) DCC, HOBT, DMF; (d) see Scheme 59.

Scheme 64. Preparation of retro-amide **271**.[18]

Basic groups 2-aminopyridine and 2-amino-imidazole increased the potency of the indazole series compared to 2-aminoimidazoline. Batt *et al.* found aryl sulfonamides to be the most potent exosite-binding groups with mesitylenesulfonamide analogue **262a** demonstrating excellent potency and nine-fold selectivity with respect to GPIIbIIIa.

7 Azatide and azacarba-peptide compounds

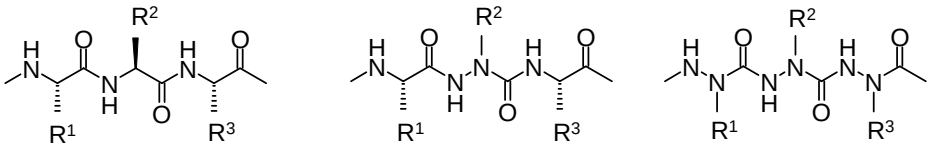


Figure 24. Comparison of a peptide, azapeptide and azatide. [18]

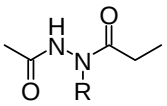
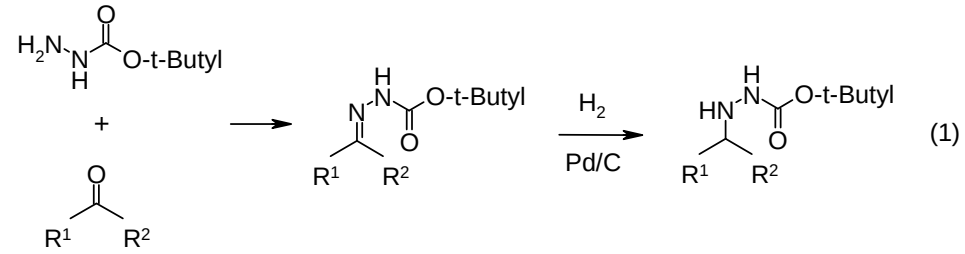
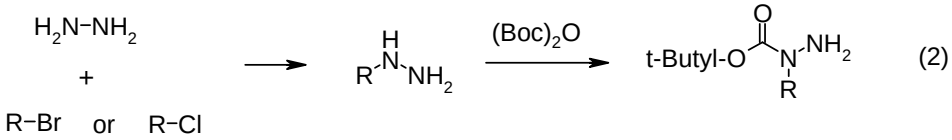


Figure 25. Azacarba-peptide.[20]

Han and Janda have developed an efficient method for the solution and liquid phase syntheses of an azatide oligomer consisting of monomeric α-aza-amino acids.[19]



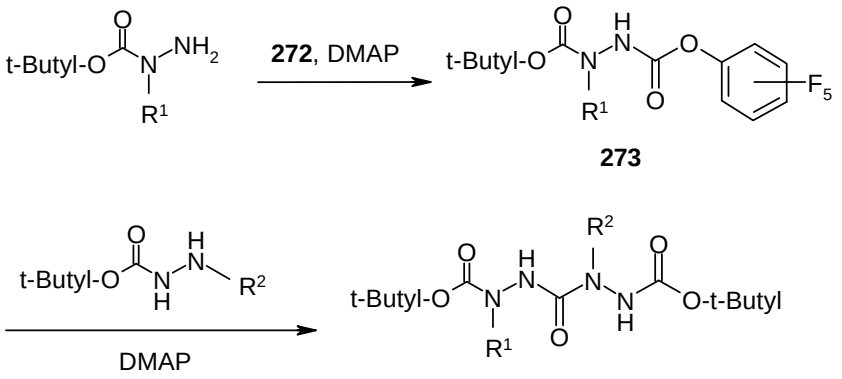


Scheme 65. Preparation of Boc-protected alkylhydrazine monomers.[19]

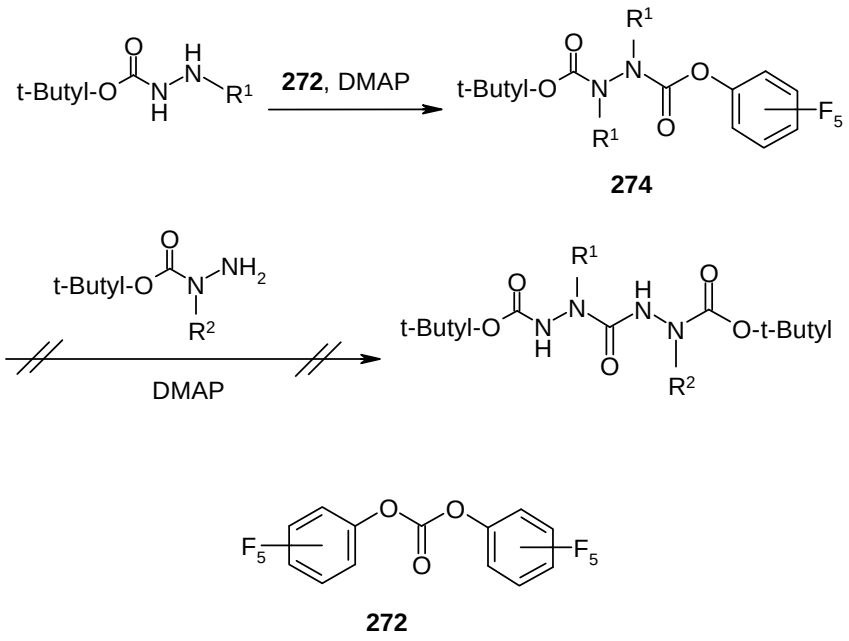
Reagents *p*-nitrophenyl chloroformate, carbonyldi-imidazole, bis(2,4-dinitrophenyl) carbonate, and trichloromethyl chloroformate were found to be unsuccessful in coupling two aza-amino acids together. Bis(pentafluorophenyl) carbonate **272** (Scheme 66) was chosen for the following reasons: the powerful electron-withdrawing ability of the

pentafluorophenol group, the minimizing of steric problems by the fluoro substituents, easy preparation and the easy-to-handle crystalline form.

1. Starting from 1-R^1-hydrazine carboxylic acid, 1,1-dimethylethyl ester:



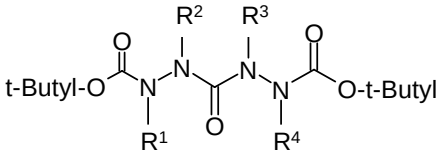
2. Starting from 2-R^1-hydrazine carboxylic acid, 1,1-dimethylethyl ester:



Scheme 66. Routes for solution phase diazatide synthesis.[19]

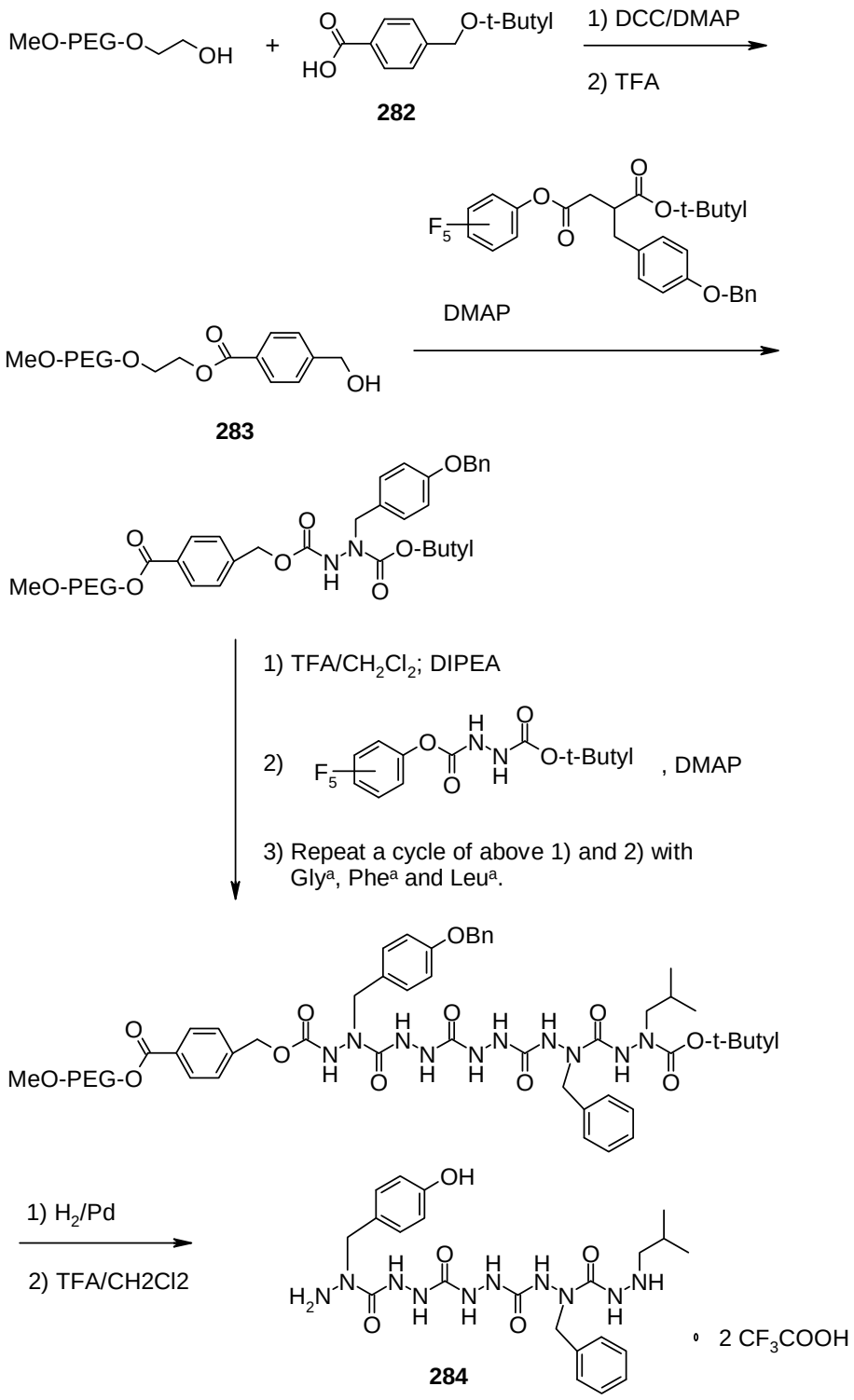
Coupling procedure 1 in Scheme 66 proved successful in producing a good yield of diazatides with few side reactions. Coupling procedure 2 was not successful.

Table 17. Preparation of diazatides starting from 1-R'-hydrazinecarboxylic acid, 1,1-dimethylethyl ester. [19]



Compd	R^1	R^2	R^3	R^4	yield (%)
275	H	H	H	H	92
276	methyl	H	H	methyl	91
277	H	methyl	H	methyl	90
278	H	methyl	H	benzyl	85
279	H	methyl	H	isobutyl	84
280	H	isobutyl	H	isobutyl	82
281	H	isopropyl	H	isopropyl	84

Han and Janda also used polymer-supported liquid phase synthesis to prepare a small well-defined α-azatide with poly(ethylene glycol) monomethyl ether (MeO-PEG) functioning as a terminal-protecting group for the product (Scheme 67). Methyl *p*-(hydroxymethyl)benzoate was *O*-protected as the *tert*-butyl ether by treatment with iso-butylene and acid.[19] The methyl ester was then hydrolyzed by lithium oxide providing **282** (Scheme 67).



Scheme 67. MeO-PEG supported Leu-enkephalin azatide synthesis.[19]

Sulyok *et al.* have synthesized a low molecular weight RGD mimetic library, including highly active and selective nonpeptide $\alpha_v\beta_3$ integrin antagonists based on lead

compound **285** (Figure 26).[19] Compound **285** has good affinity and selectivity toward the $\alpha_v\beta_3$ integrin receptor (IC_{50}: 150 nM), but Sulyok *et al.* aimed at preparing a compound with greater lipophilicity in order to enhance the medical prospects of the product in comparison to compound **285**.

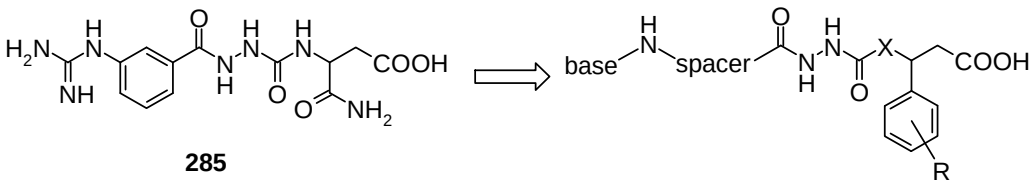


Figure 26. Aza-RGD mimetics with various aromatic α-amino acids (X = NH) or glutaric acids (X = CH_2) and different guanidine mimetics derived from compound **285**.[20]

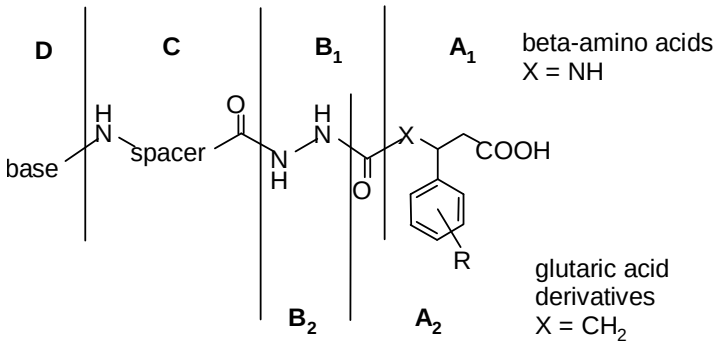
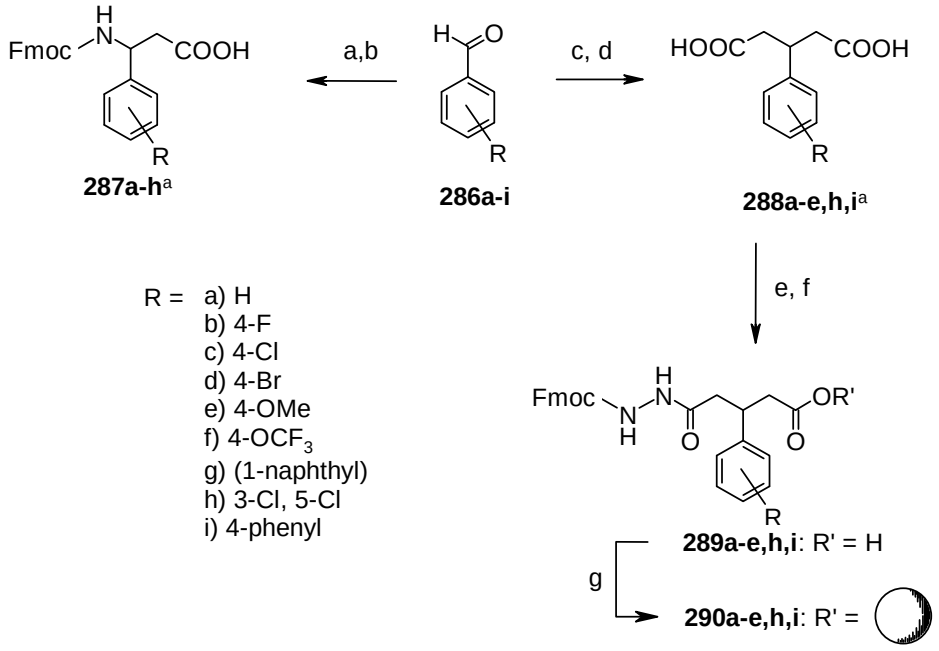


Figure 27. Retrosynthetic analysis of the RGD mimetic library obtaining four different building blocks: carboxylic acid A_1 (α -amino acids) and A_2 (glutaric acids), B_1 (aza-glycine) and B_2 (hydrazine), spacer C, and basic building block D.[20]

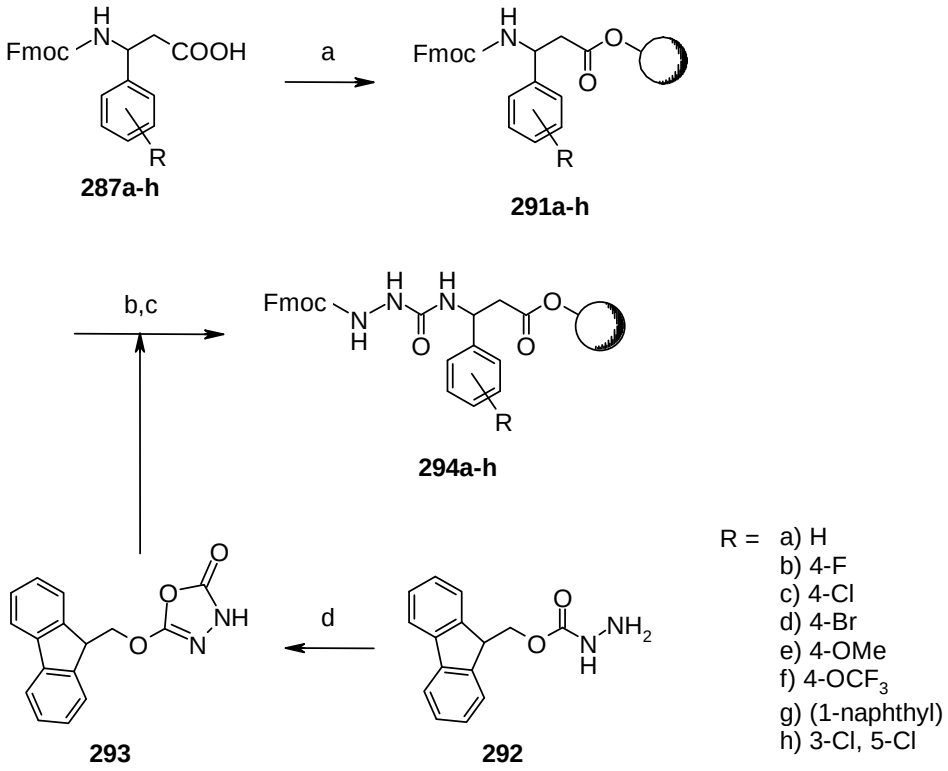
An aromatic (3-aminobenzoic acid) and an aliphatic (5-aminopentanoic acid) spacer were used as building block C. Guanidine was used as building block D and so were the more lipophilic methylamidine and 2-aminopyridine. Guanidine and methylamidine were used in connection with an aromatic spacer, and aminopyridine with an aliphatic spacer.[20]



Reagents: (a) NH_4OAc, malonic acid, EtOH (74-88%); (b) Fmoc-Cl, $NaHCO_3$, dioxane (76-98%); (c) ethyl acetoacetate, piperidine (cat.) (42-85%); (d) 20 M KOH, 85°C (68-99%); (e) acetic anhydride (62-89%); (f) *N*-Fmoc-hydrazine, THF (100%); (g) TCP resin, DIEA, CH_2Cl_2.

[a] Compounds **287d, 287g** and **288a** were purchased from commercially available sources.

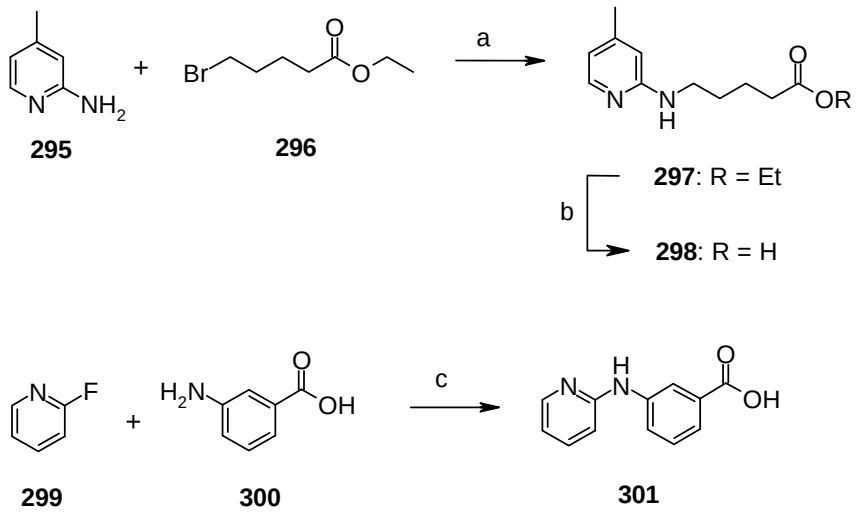
Scheme 68.[20] Synthesis of building blocks A_2.



Reagents: (a) TCP resin, DIEA, CH_2Cl_2; (b) 20% piperidine/DMF; (c) 5-(9*H*-fluoren-9-ylmethoxy)-1,3,4-oxadiazol-2(3*H*)-one (**293**); (d) phosgene (1.9 M solution in toluene), sat. $NaHCO_3$, CH_2Cl_2 (85%).

Scheme 69.[20] Synthesis of the resin-bound Fmoc-protected aza-Gly-*β*-amino acid derivatives **294a-h** (building blocks A_1B_1).

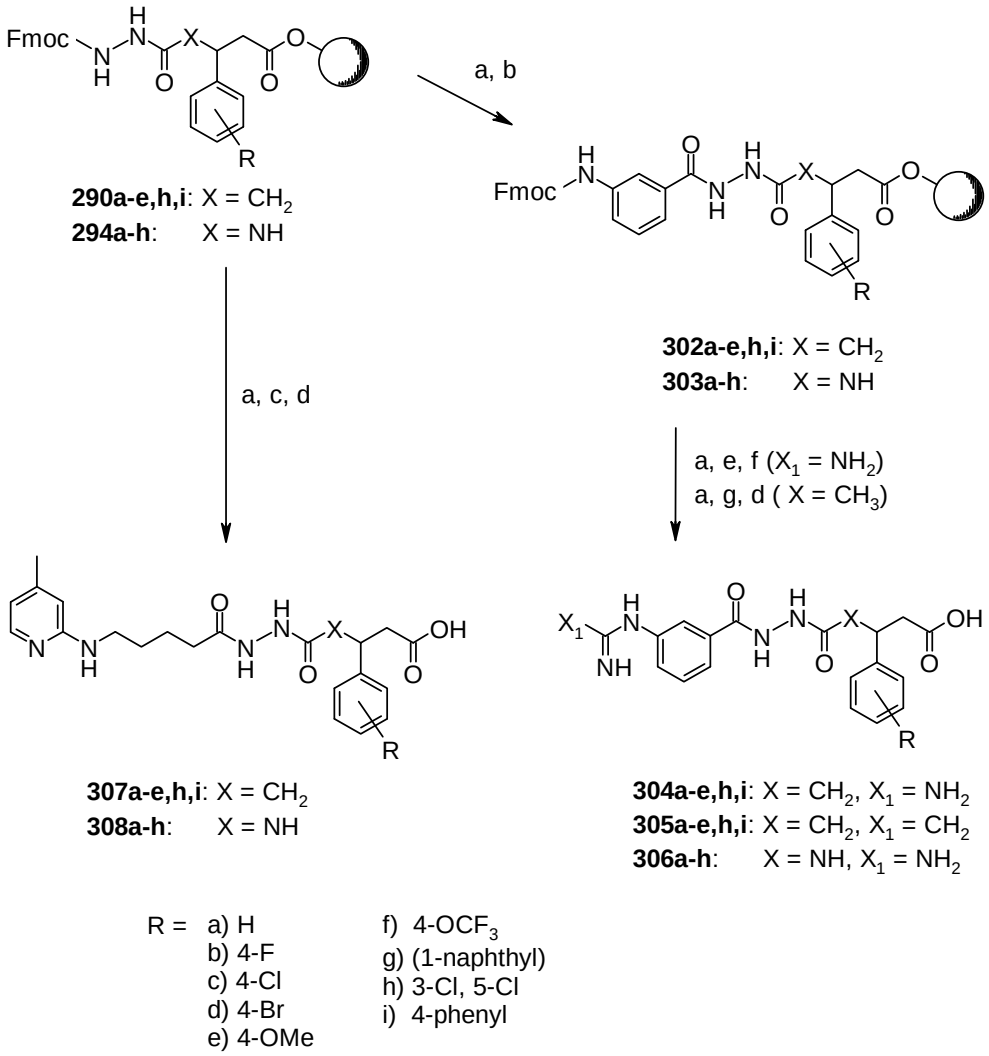
Next is the coupling of building blocks C and D. 2-Aminopyridine was linked to the spacer molecule C in solution (Scheme 70), whereas guanidine or amidine are coupled on solid support.[20]



Reagents: (a) 100°C (23%); (b) 1 N NaOH (64%); (c) NaH, DMF, 80°C (10%).

Scheme 70.[20] Synthesis of building blocks CD **298** [5-(4-methylpyridine-2-yl)aminopentanoic acid] and **301**.

After removing the Fmoc-protection from aza-compounds **290a-e,h,i** (X = CH_2) and **294a-h** (X = NH) with piperidine, building blocks C and CD were coupled under standard solid-phase coupling conditions (Scheme 71).[20]



Reagents: (a) 20% piperidine/DMF; (b) 3-(*N*-Fmoc-amino)benzoic acid, HATU, collidine, DMF; (c) 5-(4-methylpyridine-2-yl)aminopentanoic acid (**298**), HATU, collidine, DMF; (d) AcOH/TFE/CH_2Cl_2 (1:1:3); (E) *N,N'*-bis-Boc-1-guanolpyrazole, $CHCl_3$, 50°C; (f) 95% TFA/ 5% TIPS; (g) *S*-2-naphthyl-methyl thioacetimidate hydrobromide, DIEA, NMP.

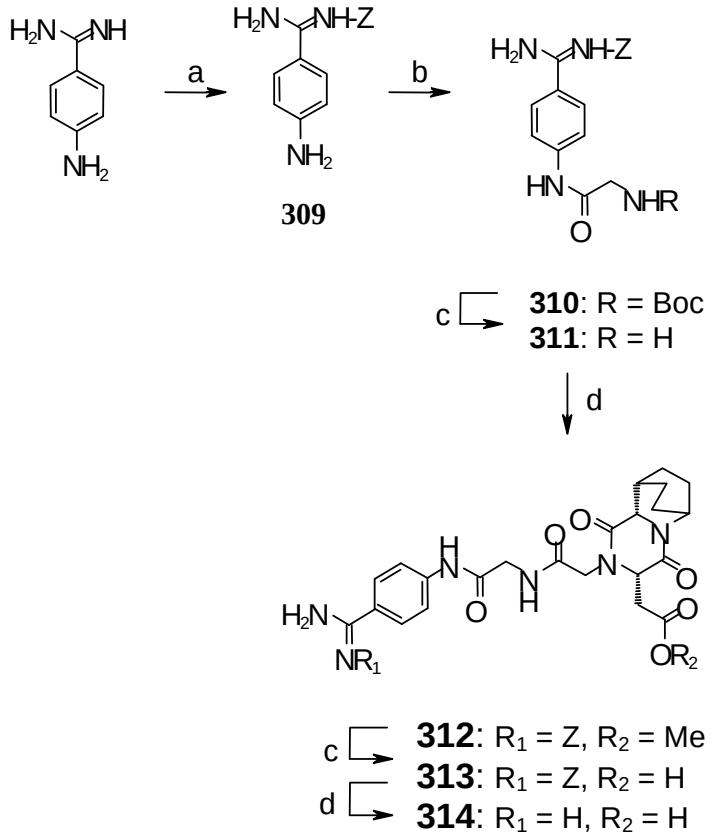
Scheme 71.[20] Synthesis of aza-RGD mimetics.

All compounds synthesized by Sulyok *et al.* show little or no activities to $\alpha_{IIb}\beta_3$ (IC_{50} > 10,000 nM) with many showing good affinity to $\alpha_v\beta_3$, hence constructing a library of highly active and selective RGD mimetics.[20]

8 Benzamidine compounds

8.1 Benzamidine compounds containing a piperazine unit

Pons *et al.* have synthesized a 2,5-diketopiperazine peptidomimetic (**314**, Scheme 69) which shows selective platelet-aggregation activity. Compound **314** shows selectivity towards inhibiting the binding of fibrinogen to its receptor GPIIb/IIIa.This selectivity may be caused by the benzamidine group and the rigidity brought on by the diketo-piperazine group. [20]

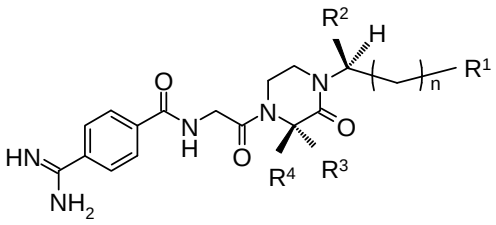


(a) ZCl, NaOH, THF, H_2O (50%); (b) $(Boc\ Gly)_2O$, DMAP, dichloromethane (42%); (c) TFA, dichloro-methane (74%); (d) DCC, DMAP, dichloromethane (31%); (e) NaOH, dioxane, H_2o (73%); (f) $H_2/Pd(OH)_2/C$, EtOH (49%).

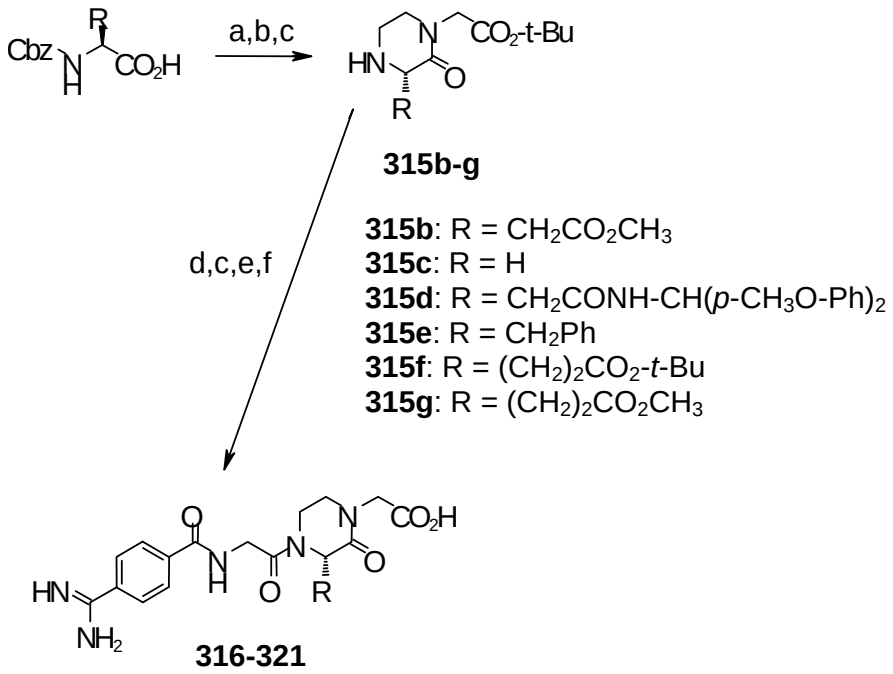
Scheme 72.[21] Synthesis of compound **314**.

Sugihara *et al.* have synthesized several benzamidine compounds containing a 2-oxpiperazine unit, one of which is a potent and orally active GPIIb/IIIa antagonist (**316**, Table 18). See also compounds **415d** and **415h** in 9.1,Table 23.[21]

Table 18. The substituents of compounds **316-326**.[22]

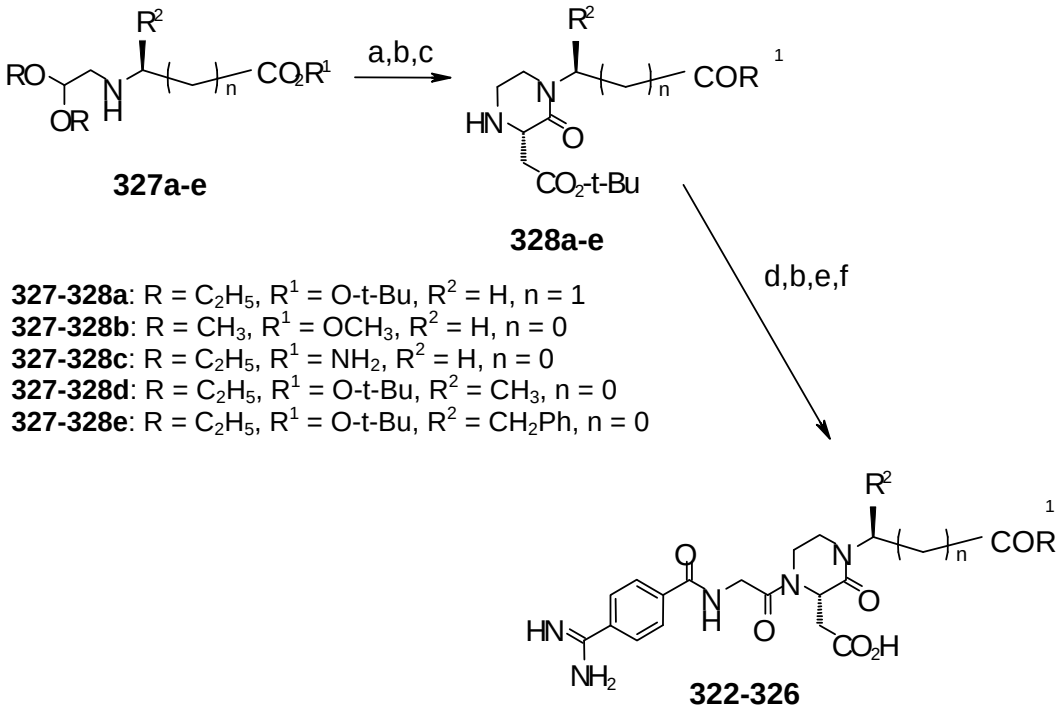


Compound	R^1	R_2	R^3	R^4	n
316	CO_2H	H	$CH_2CO_2CH_3$	H	0
(*R*)-316	CO_2H	H	H	$CH_2CO_2CH_3$	0
317	CO_2H	H	H	H	0
318	CO_2H	H	CH_2CONH_2	H	0
319	CO_2H	H	CH_2Ph	H	0
320	CO_2H	H	$CH_2CH_2CO_2H$	H	0
321	CO_2H	H	$(CH_2)_2CO_2CH_3$	H	0
322	CO_2H	H	CH_2COH_2	H	1
323	CO_2CH_3	H	CH_2COH_2	H	0
324	$CONH_2$	H	CH_2COH_2	H	0
325	CO_2H	CH_3	CH_2COH_2	H	0
326	CO_2H	CH_2Ph	CH_2COH_2	H	0



(a) *tert*-butyl *N*-(2,2-dimethoxyethyl)glycine, EDC; (b) *p*-TsOH in toluene; (c) H_2, Pd/C in MeOH; (d) *N*-Cbz-Gly-OH, EDC; (e) 4-aminobenzoyl chloride, $NaHCO_3$ in dioxane/H_2O; (f) TFA.

Scheme 73.[22] Synthesis of compounds **316-321**.



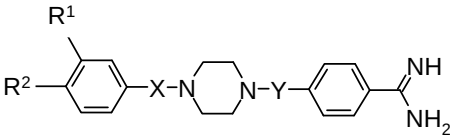
327-328a: R = C_2H_5, R^1 = O-t-Bu, R^2 = H, n = 1
327-328b: R = CH_3, R^1 = OCH_3, R^2 = H, n = 0
327-328c: R = C_2H_5, R^1 = NH_2, R^2 = H, n = 0
327-328d: R = C_2H_5, R^1 = O-t-Bu, R^2 = CH_3, n = 0
327-328e: R = C_2H_5, R^1 = O-t-Bu, R^2 = CH_2Ph, n = 0

(a) *N*-Cbz-Asp(*O*-*t*-Bu)-OH, EDC; (b) *p*-TsOH in toluene; (c) H_2, Pd/C in MeOH; (d) *N*-Cbz-Gly-OH, EDC; (e) 4-amidinobenzoyl chloride, $NaHCO_3$ in dioxane/H_2O; (f) TFA.

Scheme 74.[22] Synthesis of compounds **322-326**.

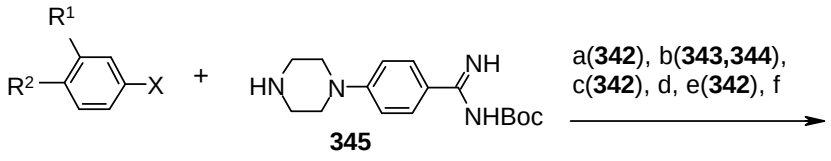
J.H. van Maarseveen *et al.* have synthesized an orally active GPIIb/IIIa antagonist based on a *N,N'*-bisphenylpiperazine scaffold (**338**, Table 19) along with other phenyl-piperazine compounds.[22]

Table 19. The substituents of compounds **329**-**341**.[23]



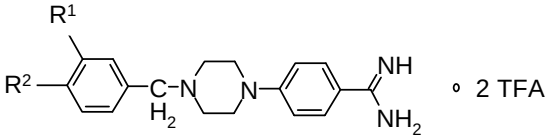
Compound	R^1	R_2	X	Y
329	HO_2C-CH_2-O-	H	-CH_2-	-
330	HO_2C-CH_2-	H	-CH_2-	-
331	H	HO_2C-CH_2-	-CH_2-	-
332	HO_2C-CH_2-O-	H	-	-CH_2-
333	HO_2C-CH_2-	H	-	-CH_2-
334	H	HO_2C-CH_2-	-	-CH_2-
335	HO_2C-CH_2-O-	H	-	-
336	HO_2C-CH_2-	H	-	-
337	H	HO_2C-CH_2-	-	-
338	H	HO_2C-CH_2-O-	-	-
339	H	HO_2C-CH_2-CH_2-	-	-
340	H	HO_2C-$C(CH_3)_2$-O-	-	-
341	H	HO_2C-$(CH_2)_3$-O-	-	-

Compound **339** showed ten times less potency than **338** caused by the substitution of the carboxymethyleneneoxy group by a carboxyethyl group, and substitution by the carboxyisopropylideneoxy group in **340** caused a 1000-fold decrease in activity.[23]

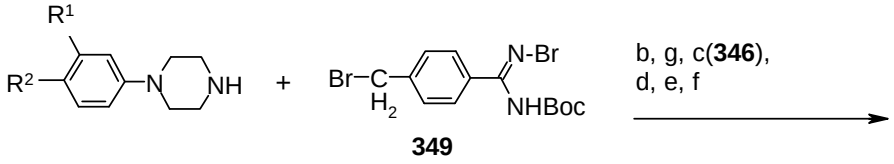


345

342: R^1 =HO-, R^2 = H, X = CHO
343: R^1 =HO_2C-CH_2-, R^2 = H, X = -CH_2Br
344: R^1 =H, R^2 = HO_2C-CH_2-, X = -CH_2Br

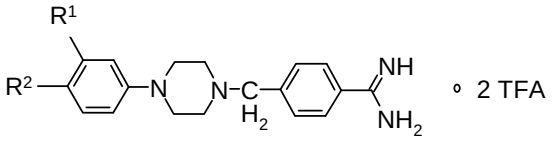


329-331

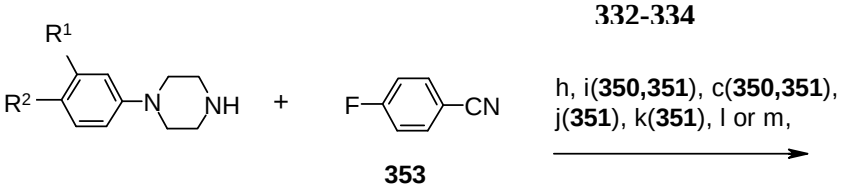


349

346: R^1 =HO-, R^2 = H
347: R^1 =MeO_2C-CH_2-, R^2 = H
348: R^1 =H, R^2 = EtO_2C-CH_2-

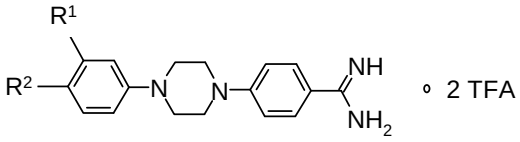


332-334



353

350: R^1 =MeO, R^2 = H
347, **348**
351: R^1 =H, R^2 = MeO
352: R^1 =H, R^2 = $tBuO_2C$-CH_2-CH_2-



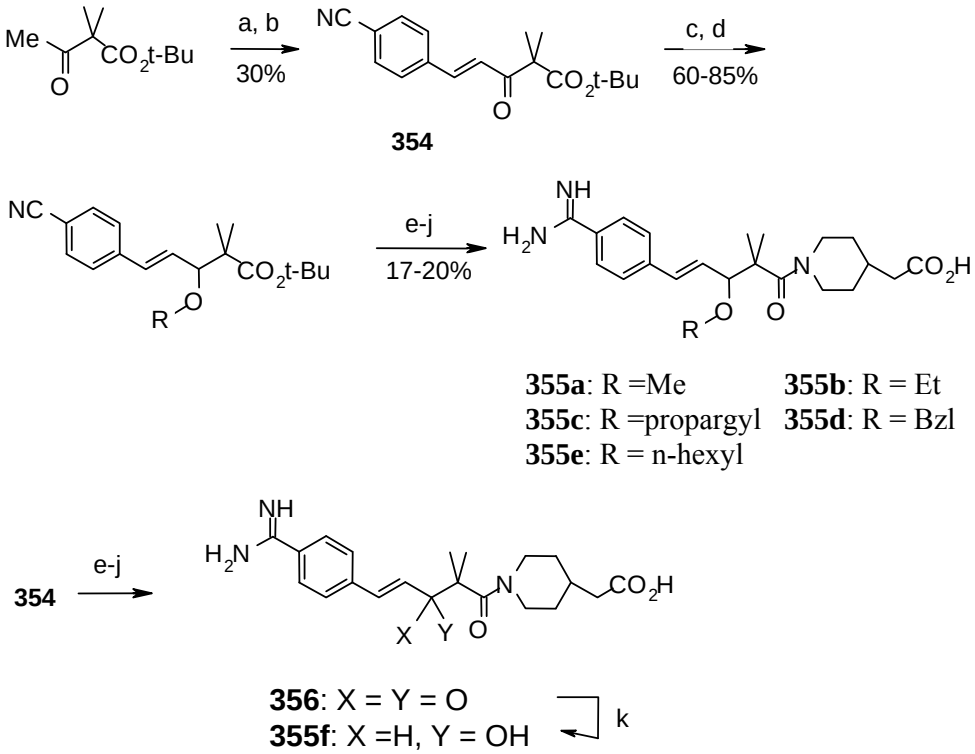
335-341

(a) $Ti(OiPr)_4$, $NaCNBH_3$; (b) Et_3N, DMF; (c) Cl-CH_2-CO_2Me, K_2CO_3, KI, DMF; (d) TFA/CH_2Cl_2=1/1; (e) HOAc/H_2O=1/4, reflux; (f) RP-18 preparative HPLC (MeCN/H_2O/0.1% TFA); (g) 5% $Na_2S_2O_3$, reflux; (h) K_2CO_3, NMP, reflux; (i) BBr_3, CH_2Cl_2, -75ºC; (j) Br-$(CH_3)_2$C-CO_2tBu, K_2CO_3, DMF; (k) Br-$(CH_2)_3$-CO_2tBu, KI, K_2CO_3, DMF; (l) *I*: H_2S, Et_3N, pyridine. *ii*: MeI, acetone, reflux. *iii*: NH_4Oac, MeOH, reflux; (m) *i*: NH_2OH•HCl, KotBu, MeOH. *Ii*: H_2Pd/(C), HOAc.

Scheme 75.[23] Synthesis of compounds **329-341**.

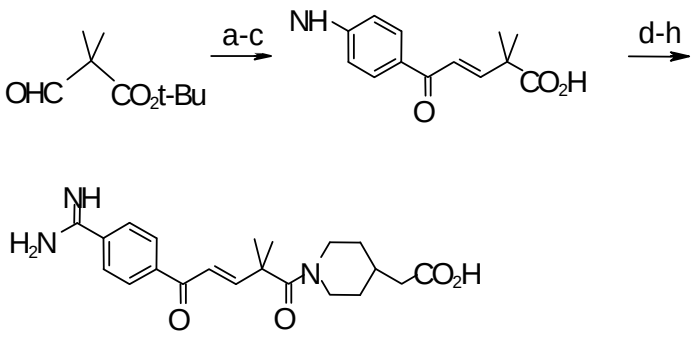
8.2 Benzamidine compounds containing a piperidine unit

Asari *et al*. synthesised a series of new GPIIb/IIIa inhibitors, NSL-95315 (**355a-f**, Scheme 76) and NSL-95317 (**357**, Scheme 77) with an (E)-double bond or an enone group adjacent to a benzamidine moiety. They found that molecules **355a** and **357** showed inhibitory activity for collagen-induced human platelet aggregation.[23]



(a) LDA, THF, 4-cyanobenzaldehyde; (b) MsCl, Py; (c) $NaBH_4$, MeOH, $CeCl_3$; (d) NaH, THF, alkyl iodide; (e) TFA; (f) methyl piperidine-4-acetate, CH_2Cl_2, BOP reagent; (g) H_2S, Py, TEA; (h) MeI, acetone, reflux; (i) CH_3COONH_4, MeOH, reflux; (j) aq. NaOH, MeOH; (k) $NaBH_4$, MeOH.

Scheme 76. The synthesis of inhibitor **355**. [24]

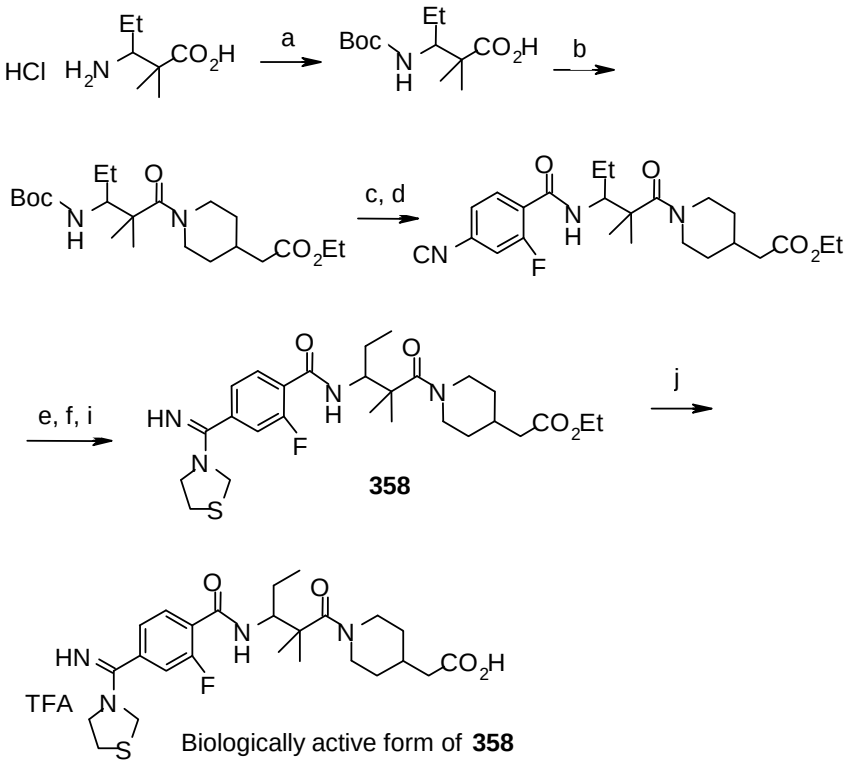


357

(a) 4-cyanoacetophenone, LDA, THF, -78°C, 1h; (b) MsCl, Py; (c) TFA; (d) methyl piperidine-4-acetate, CH_2Cl_2, BOP reagent, DIEA; (g) H_2S, Py, TEA; (h) MeI, acetone; (i) CH_3COONH_4, MeOH; (j) aq. NaOH, MeOH.

Scheme 77. The synthesis of inhibitor **357**.[24]

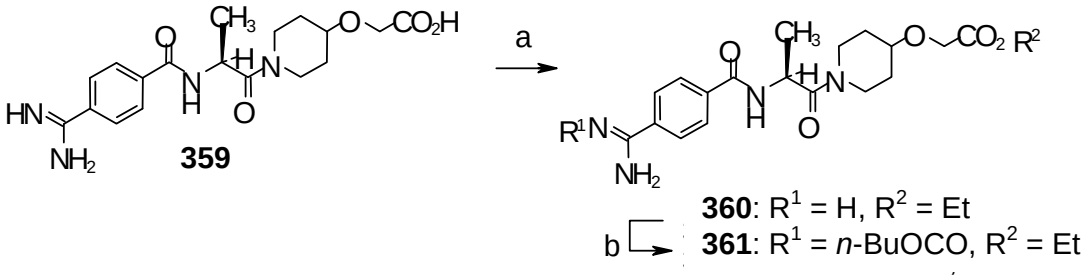
Hayashi *et al.* have synthesized a highly potent fibrinogen receptor inhibitor NSL-96184 (**358**, Scheme 78).[24] The compound shows inhibition of collagen-induced platelet aggregation in human PRP.



(a) $(Boc)_2O$, 10% Na_2CO_3, dioxane; (b) benzyl, methyl, or ethyl piperidine- 4-acetate, HATU, DIEA, CH_2Cl_2; (c) TFA, anisole, 0°C; (d) 2-halo-4-cyanobenzoic acid, WSCD*HCl, HOBt, DMF; (e) H_2S, Et_3N, pyridine; (f) MeI, acetone, reflux; (g) CH_3COONH_4, MEOH, reflux; (h) $Pd(OH)_2$, 90% aqueous MeOH containing 2% AcOH; or LiOH, 80% aqueous MeOH; (i) amine, MeOH, reflux; (j) LiOH, 80% aqueous MeOH.

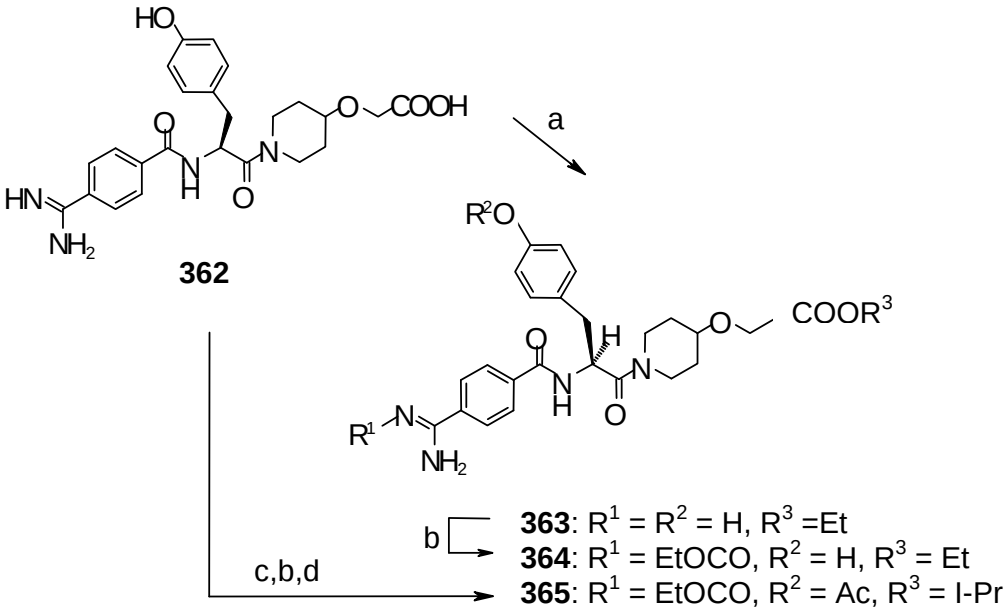
Scheme 78. The synthesis of compound **358**.[25]

Weller *et al.* have synthesized series of orally active prodrugs derived from potent and selective GPIIb/IIIa antagonists **359** (Scheme 79) and **362** (Scheme 80).[25]



(a) EtOH, H_2SO_4; (b) *n*-BuOCOCl, NaOH, CH_2Cl_2.

Scheme 79. Preparation of prodrug derivatives of **359**.[26]



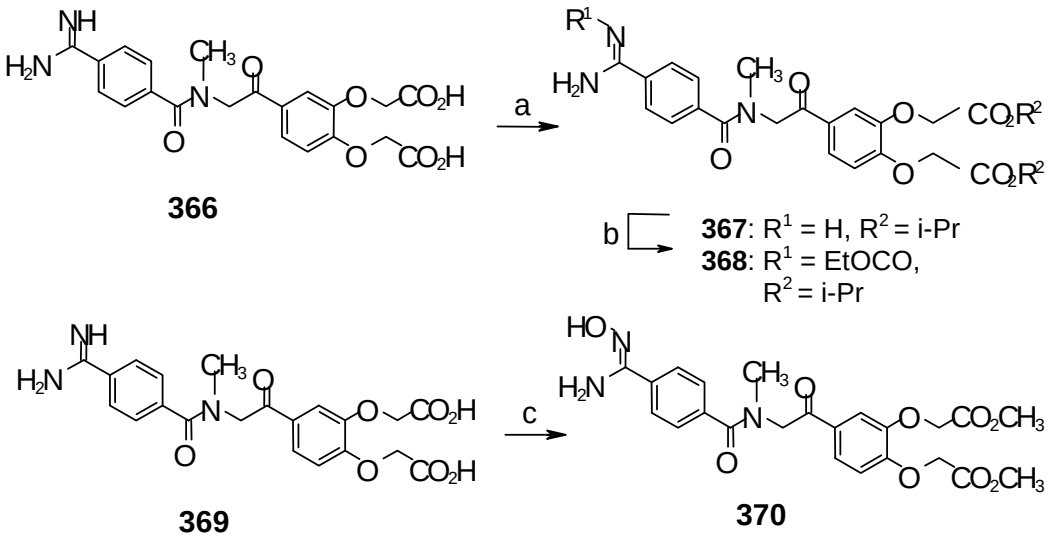
(a) EtOH, H_2SO_4; (b) EtOCOCl, NaOH, CH_2Cl_2; (c) 2-propanol, H_2SO_4; (d) Ac_2O, K_2CO_3.

Scheme 80. Preparation of prodrug derivatives of **362**.[26]

8.3 Other benzamidine compounds

See also 3.1, 4.1 and 5.1.

Weller *et al.* have synthesized orally active prodrug derivatives of a potent GPIIb/IIIa antagonist **366** (Scheme 81) of which **370** is most potent.[26]



(a) 2-propanol, H_2SO_4; (b) EtOCOCl, NaOH, CH_2Cl_2; (c) NH_2OH•HCl, Na, MeOH.

Scheme 81. Preparation of prodrug derivatives of **366**.[26]

Kottirsch *et al.* have synthesized several highly potent and orally active GPIIb/IIIa antagonists based on a weak GPIIb/IIIa antagonist, ornithine sulfonamide **371** (Fig. 28), the most potent antagonist being **379** (Table 20).[26]

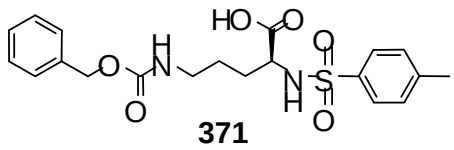


Figure 28. [26] A weak GPIIb/IIIa antagonist.

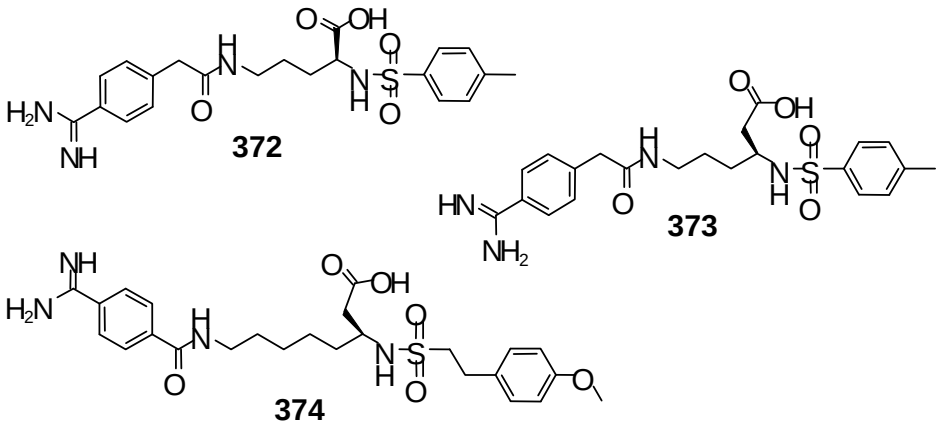
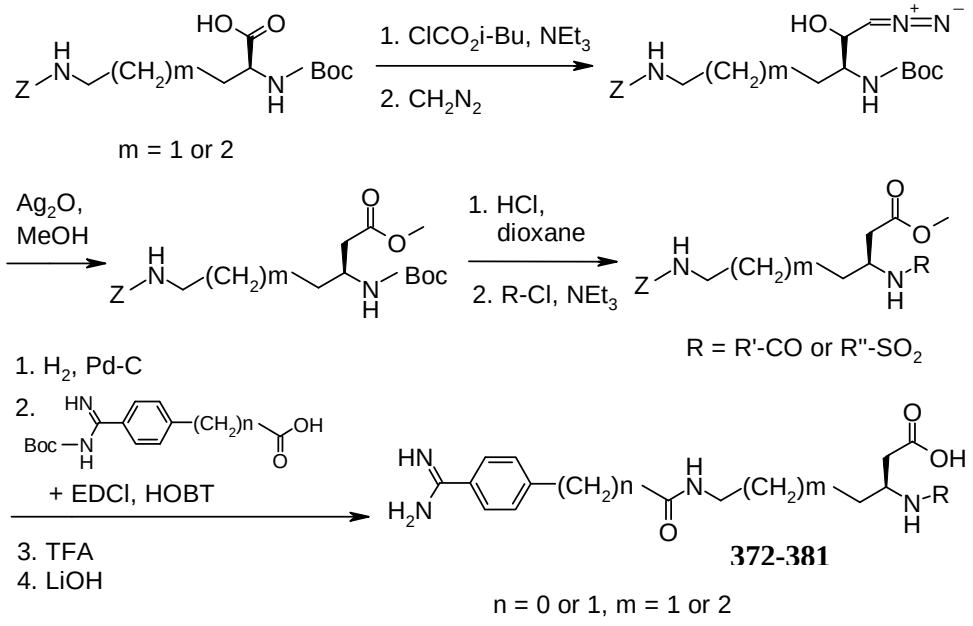


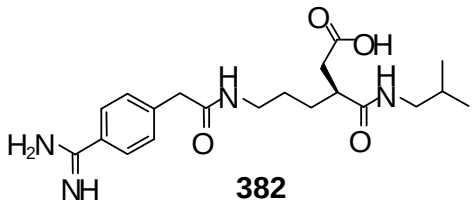
Figure 29. GPIIb/IIIa antagonists.

The synthesis of compounds **372-374** is described in Scheme 79. Compound **372** is only a weak GPIIb/IIIa antagonist, but a drastic increase in activity was obtained by adding a methylene group to the side chain to yield **373**.[26] Compound **374** is also a potent GPIIb/IIIa antagonist.



Scheme 82. Preparation of beta-amino acid GPIIb/IIIa antagonists.[26]

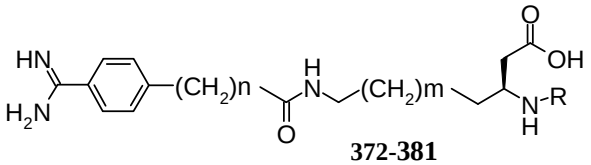
Compound **382** was synthesized from 4-azido-pentanoic acid by enentioselective α-alkylation with tert-butyl bromo-acetate to give a Gly-Asp ethylene isostere which was converted to **382** using standard reaction conditions.



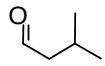
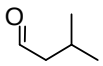
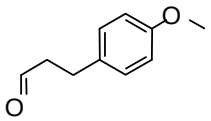
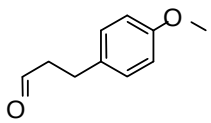
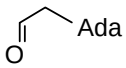
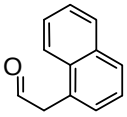
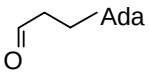
382

Figure 30.[27] A weak GPIIb/IIIa antagonist.

Table 20. Beta-amino acid-type GPIIb/IIIa antagonists.[27]



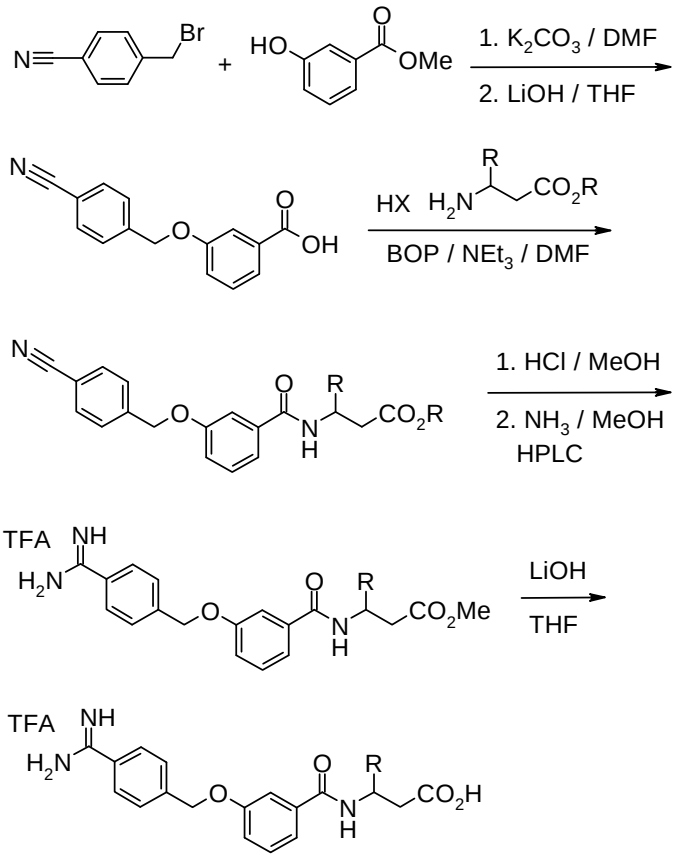
372-381

No.	m, n	R	no.	m, n	R
375	1, 1		**379**	2, 0	
376	1, 1		**380**	2, 0	
377	1, 1		**381**	2, 0	
378	1,1				

When comparing **382** and **375** Kottirsch *et al.* found that the inverted amide bond in **375** increases activity in the platelet aggregation and fibrinogen binding assay 7-9-fold. They also found the *S*-enantiomer of **379** to be greatly more active an antagonist than the *R*-enantiomer.[27]

Xue *et al.* have investigated RGD mimetics with a 3-substituted benzoic acid core and a benzamidine moiety, and a series of *β*- and *α*-substituted *β*-alanine derivatives as aspartic acid surrogates. *β*-Substitution of *β*-alanine with a methyl group was found to increase activity whereas a trifluoromethyl group decreased it.[27]

The replacement of *β*-alanine with N^2-substituted L-2,3-diaminopropionic acid derivatives caused a dramatic increase in activity.



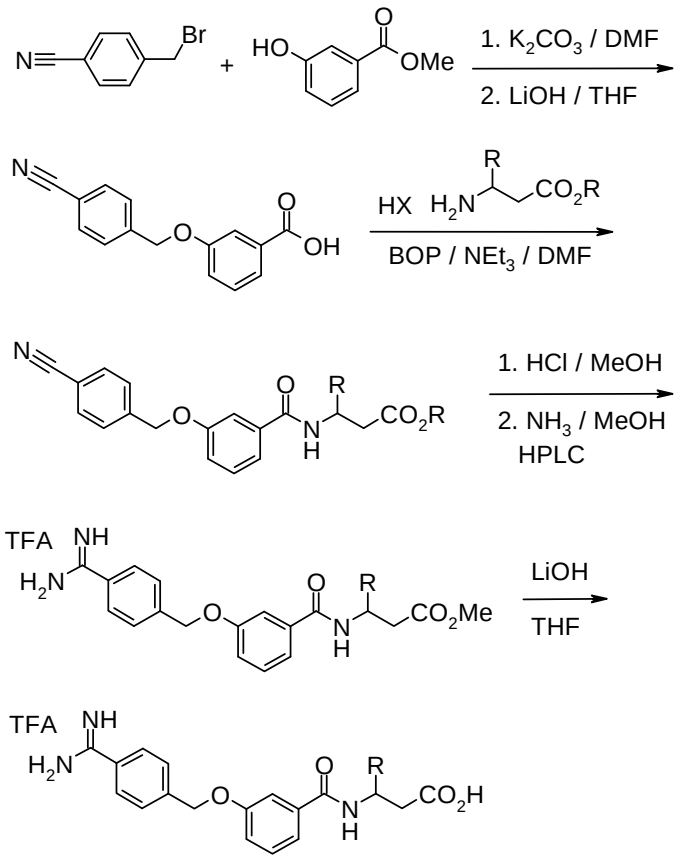
383a-b

383a: R = H

383b: R = CH_3

Scheme 83.[28] The synthesis of a *β*-alanine compound and its *β*-methyl derivative.

The *β*-methyl *β*-alanine compound yielded an improved inhibition of ADP-induced platelet aggregation in human PRP compared to the unsubstituted *β*-alanine compound.



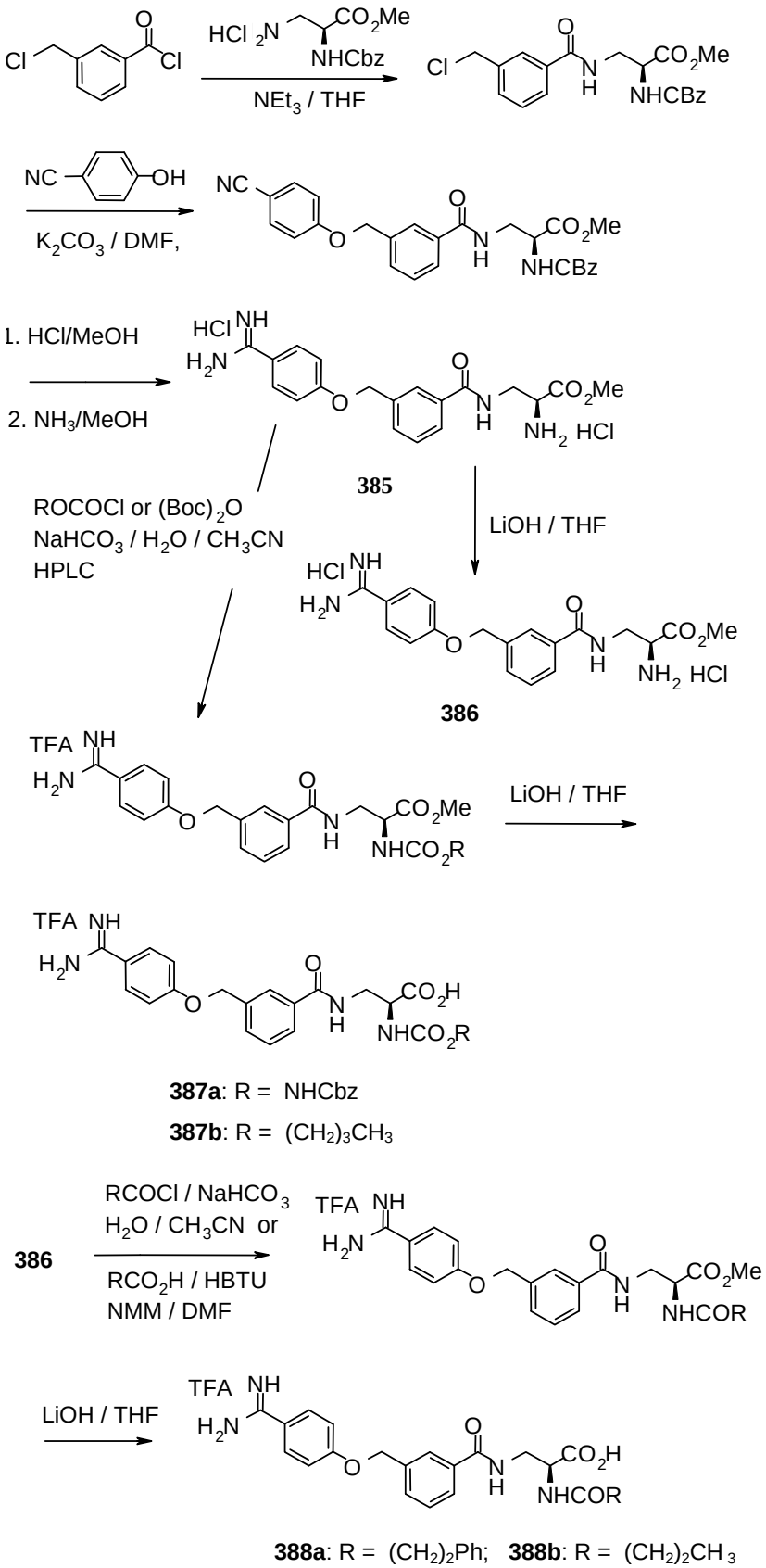
384a-b

384a: R = CH_3

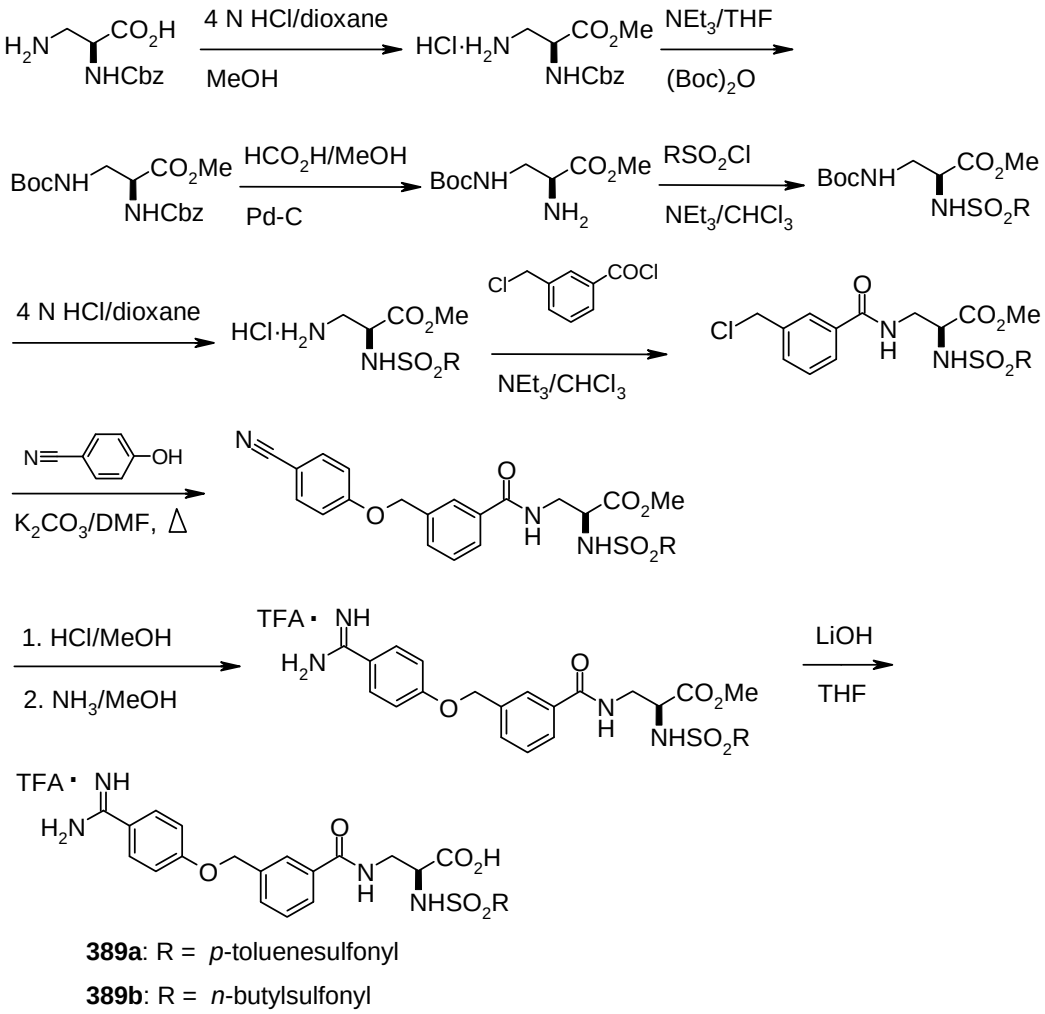
384b: R = CF_3

Scheme 84.[28] The synthesis of a *β*-methyl *β*-alanine compound and its trifluoromethyl derivative.

The *β*-trifluoromethyl derivative **384b** was found to have considerably lower inhibitory activity than the *β*-methyl compound **384a**. N^2-substituted L-2,3-diaminopropionic acid derivatives (Scheme 85) afforded up to 100-fold enhancement in potency over the *β*-alanine.



Scheme 85.[28] The synthesis of compounds containing diaminopropionic acid derivatives.

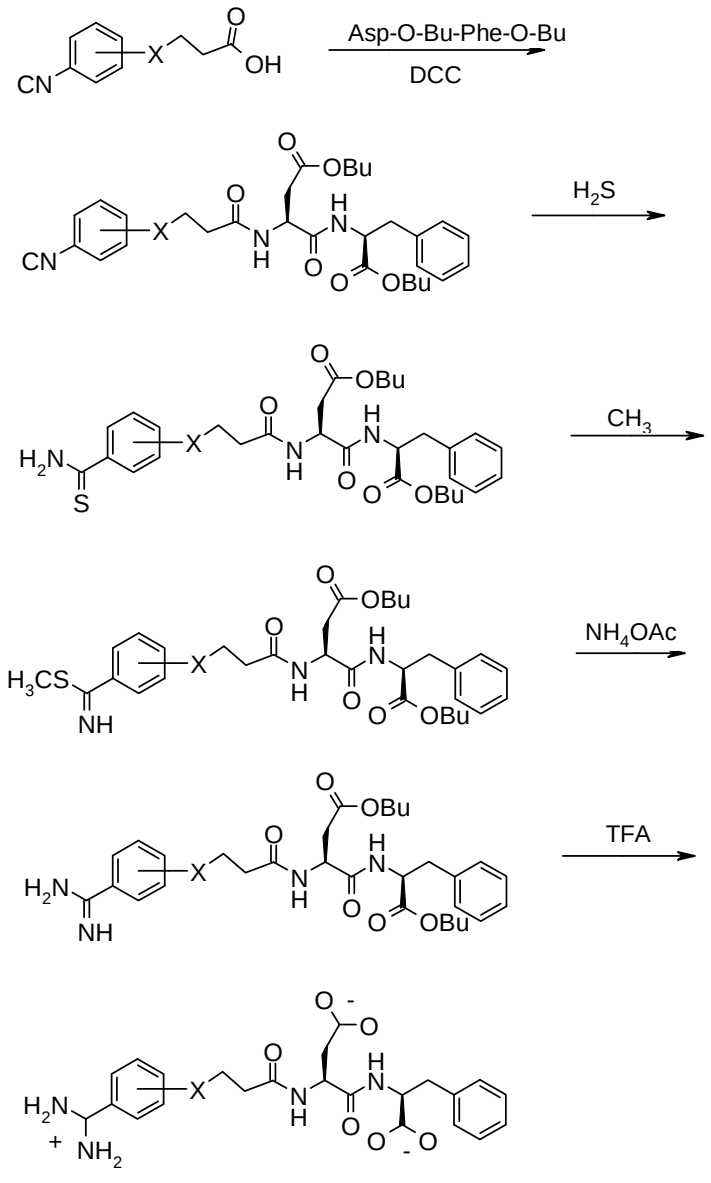


Scheme 86.[27] The synthesis of GPIIb/IIIa antagonists **389a-b**.

Preparation of **389a-b** was first attempted similar to the synthesis shown in Scheme 85 using compound **385** as starting material, but this route failed. Both **389a** and **389b** are potent GPIIb/IIIa antagonists, **389a** being slightly more active.[27]

The study of α-substituents (sulfonamide, carbamate and amide) showed no apparent preference with respect to *in vitro* potency.[27]

Zablocki, Miyano *et al.* prepared a series of benzamide derivatives and measured their inhibition of collagen-induced platelet aggregation in canine PRP. The group found there is a 1000-fold increase in inhibitory potency over the natural RGDF ligand when the Arg-Gly of the RGDF sequence of the peptidomimetic has been replaced with 5-(4-amidinophenyl)pentanoyl mimetic. Benzamide was chosen since it has the charge localized on two nitrogens, as opposed to three in guanidine, allowing for more favorable electrostatic interactions with a negatively charged receptor site. Also, the reinforced ionic interaction provides a favorable alignement of dipole moments.[29]



Scheme 87. The general synthetic sequence for *m*- and *p*-amidinophenyl derivatives.[29]

Table 21.[29] Target compound: Substituents of *p*-amidinophenyl based RGDF mimetics.

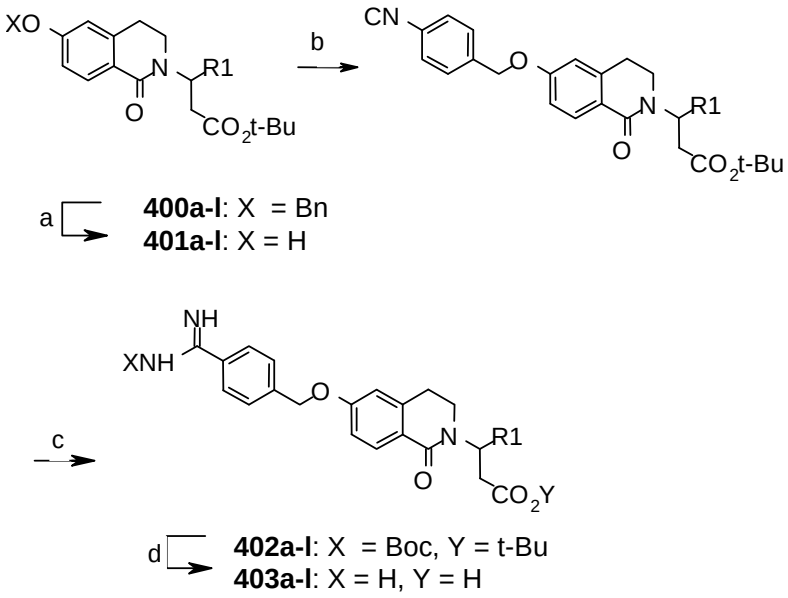
Compound	X
390	CH_2
391	CH_2 CH_2
392	CH_2 CH_2 CH_2
393	CH_2CO
394	CH_2CHOH
395	t-CHCH
396	CC

Table 22.[29] Target compound: Substituents of *m*-amidinophenyl based RGDF mimetics.

Compound	X
397	CH_2 CH_2
398	CH_2 CH_2 CH_2
399	c-$CHCH_2CH_2$

Molecule **391** was found to be a very potent inhibitor of ADP-induced platelet aggregation in canine PRP. The *m*-amidine derivatives were found to be dramatically less potent than the *p*-amidino series. [29]

Fisher, Gunn *et al.* have synthesized a series of disubstituted 3,4-dihydroisoquinolines that contain an ether-linked benzamidine at C_6 and a β-substituted aspartate mimic at C_2.[30]



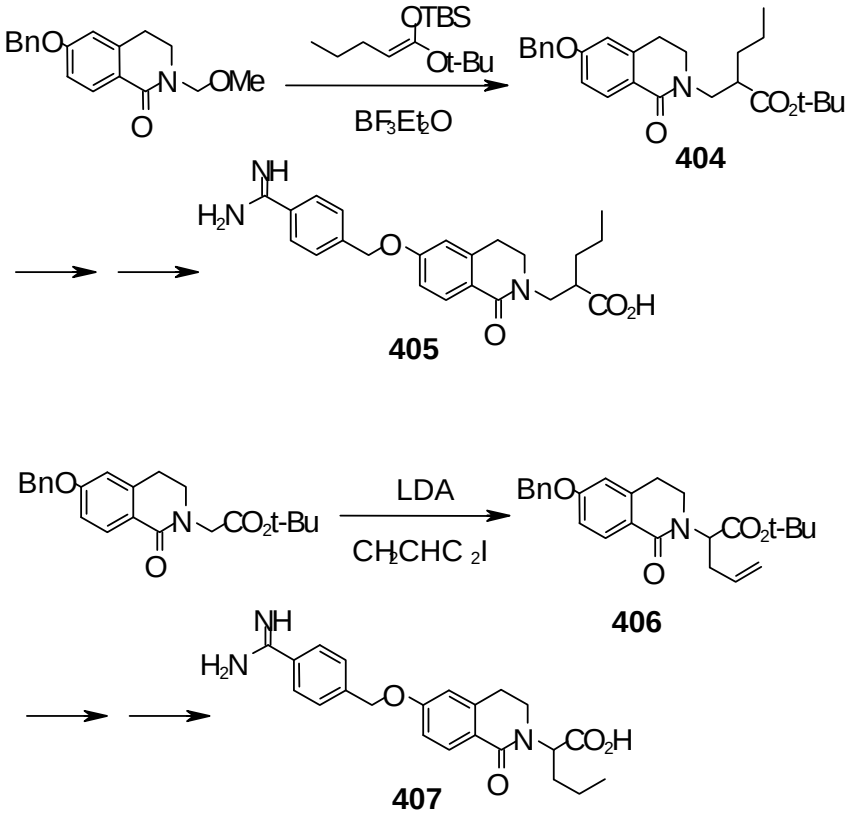
(a) H_2 Pd/C; (b) *p*-cyanobenzyl bromide-K_2CO_3;
(c) H_2S-MeI-NH_4OAc-Boc_2O; (d) TFA

Scheme 88. The synthesis of *β*-substituted isoquinolene propionates.[30]

Table 23.[30] The substituents of compounds **400-403**.

Compound **400-403**	R
a	H
b	CH_2 CH_3
c	$(CH_2)_2CH_3$
d	$(CH_2)_3CH_3$
e	$(CH_2)_4CH_3$
f	$(CH_2)_5CH_3$
g	$(CH_2)_3OCH_2CH_3$
h	$(CH_2)_3OCH_3$
i	$CH_2O(CH_2)_2OCH_3$
j	Ph
k	*p*-$C_6H_4CO_2CH_3$
l	*p*-$C_6H_4OCH_3$

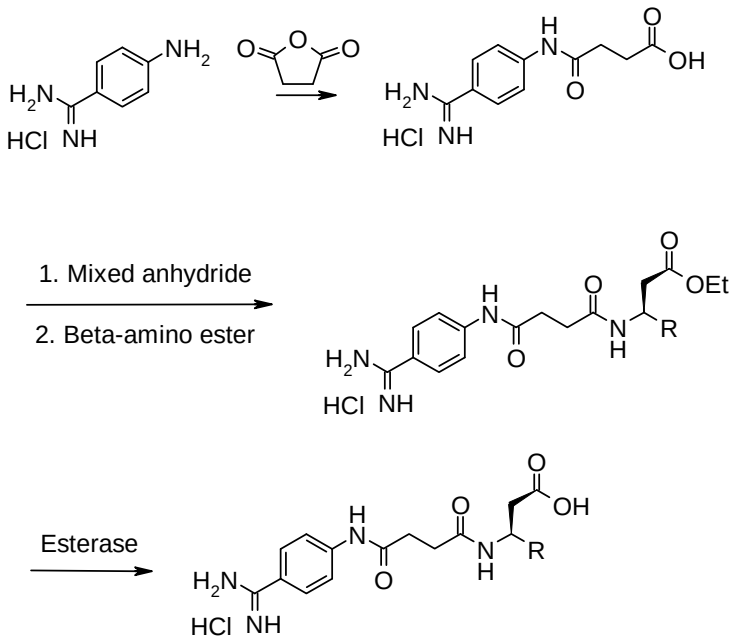
Amidino analogues were also prepared by way of an α-substituted isoquinoline propionate and an α-substituted isoquinoline acetate (Scheme 89). The desired molecules **405** and **407** were obtained from the intermediates **404** and **406** by using the same procedure as for compounds **403** (Scheme 88).



Scheme 89. The synthesis of two α-substituted isoquinoline analogues.[30]

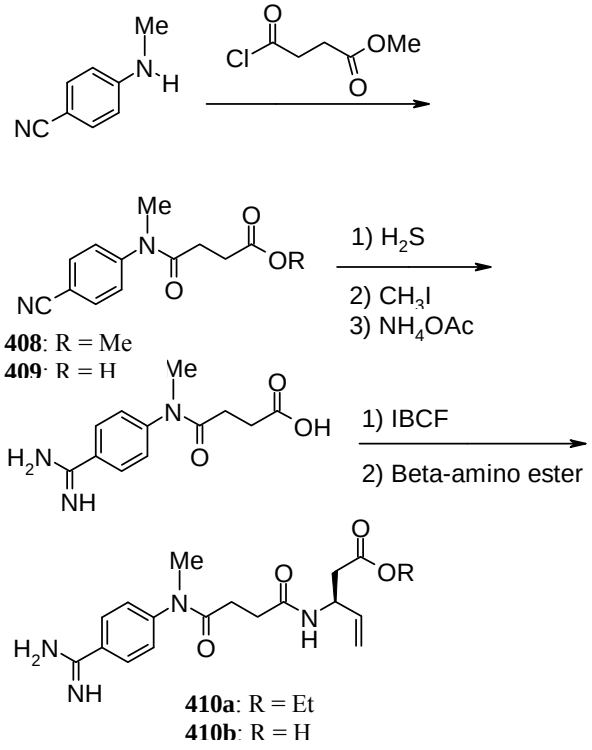
It was found that compared to the non-substituted isoquinoline propionate the alkyl substituents afforded a 10-fold increase in intrinsic activity and aryl substituents yielded a 40-fold improvement in inhibiting ADP induced platelet aggregation in human PRP.[30]

Zablocki, Rico *et al.* have prepared a series of compounds with an (aminobenzamidino)-succinyl (ABAS) Arg-Gly surrogate (Scheme 90).[31] Both ester prodrug and acid forms of the compounds were prepared.

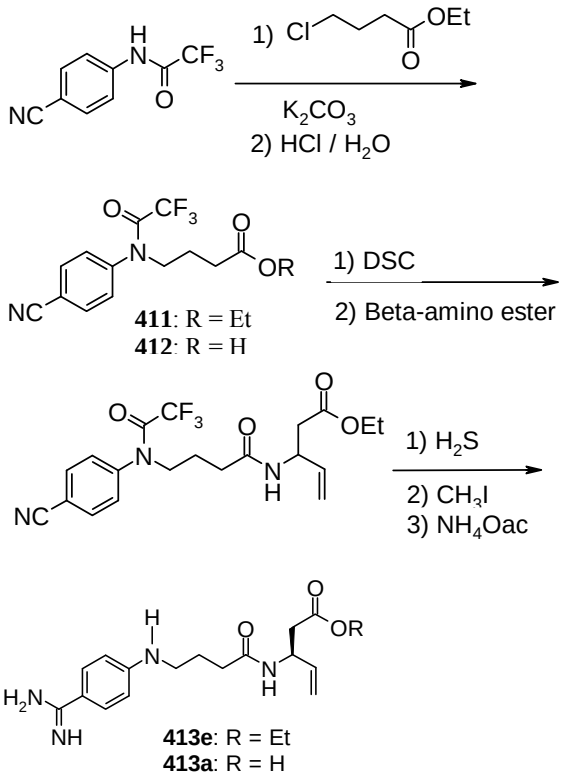


Scheme 90. The general synthetic sequence for the ABAS series.[31]

Several derivatives were prepared in which the amide bond adjacent to the benzamidine was modified or replaced (Scheme 91). Also, an ester/acid pair of aniline derivatives was prepared (Scheme 92).



Scheme 91.[31] The synthesis of methylamino derivatives **410a-b**.



Scheme 92.[31] The synthesis of an ester/acid pair of aniline derivatives.

The most potent inhibitor of collagen-induced platelet aggregation in canine PRP was found to be an ABAS series molecule **414**:

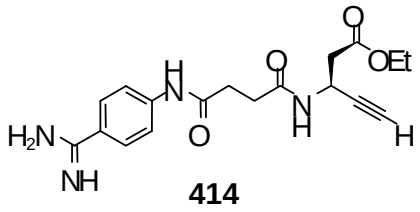


Figure 31.[31] A potent inhibitor of platelet aggregation.

9 Other piperazine compounds

9.1 2-oxopiperazine compounds

Sugihara *et al.* have designed and synthesized two possible GPIIb/IIIa antagonists **415a** and **416** based on the RGDF sequence, with (*S*)-1-(carboxymethyl)- and (*S*)-1-phenyl-ethyl-2-oxopiperazine-3-acetic acids as the Aso-Phe mimic and a {*trans*-[4-(guanidino-methyl)cyclohexyl]carbonyl}glycyl group as an Arg-Gly mimic. Compound **415a** was used as the lead compound due to its significant antiaggregatory activity and binding affinity, whereas compound **416** showed no activity.[22]

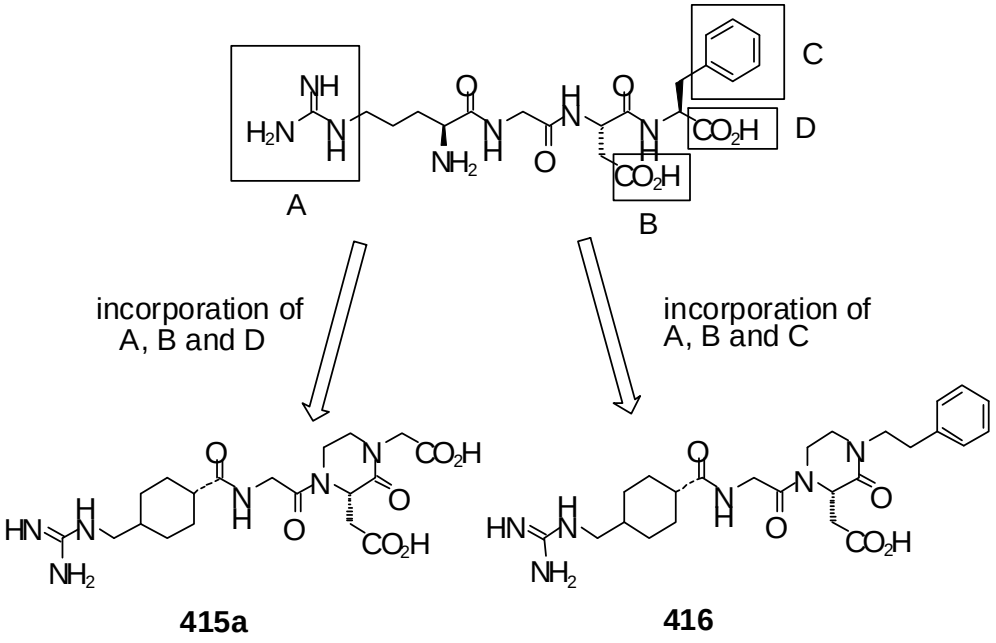
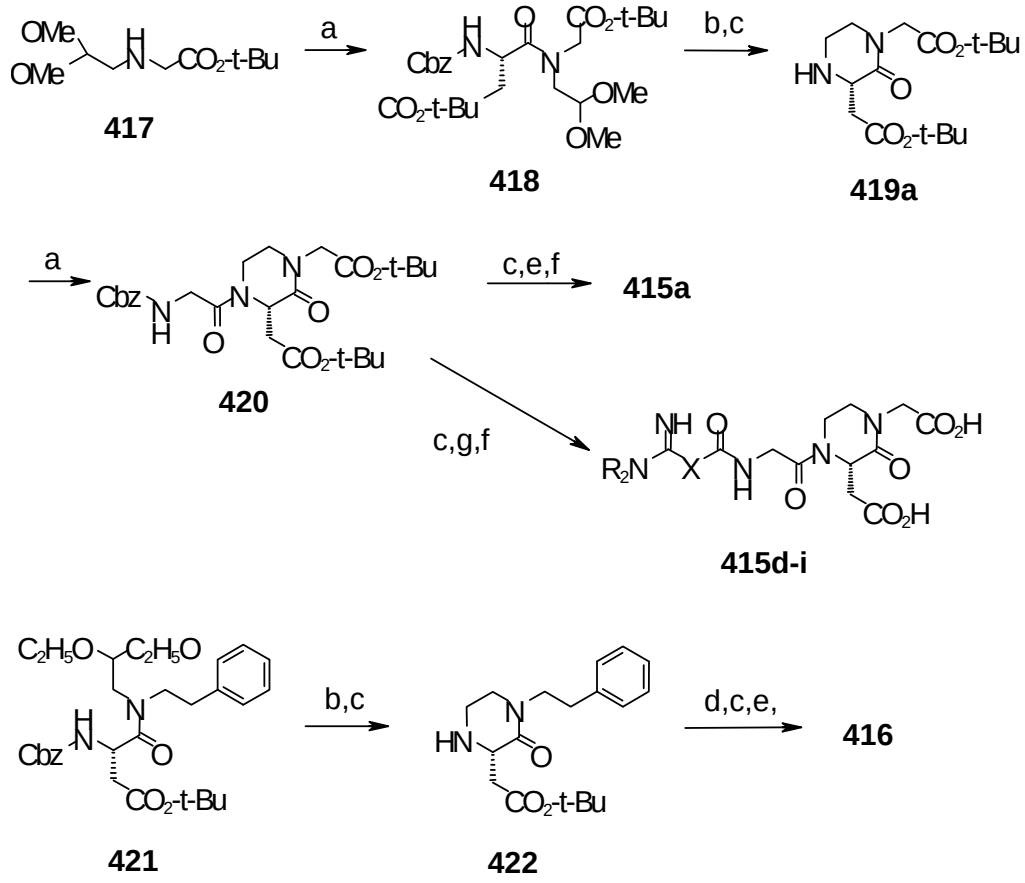


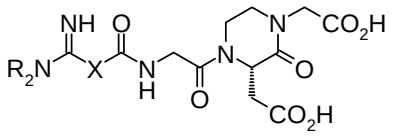
Figure 33. Two hypothetical candidates **415a** and **416**, incorporating the function of the RGDF peptide into a 2-oxopiperazine scaffold as a peptide mimic.[22]

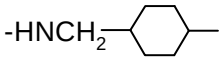
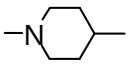
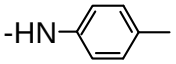
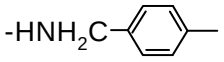
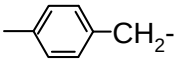
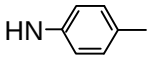


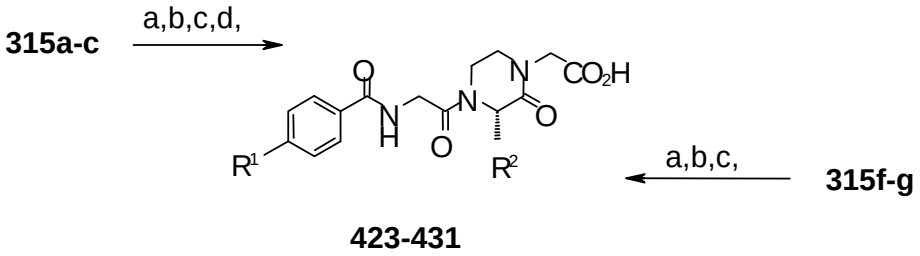
(a) *N*-Cbz-Asp(*O*-*t*-Bu)-OH, EDC; (b) *p*-TsOH in toluene; (c) H_2, Pd/C in MeOH; (d) *N*-Cbz-Gly-OH, EDC; (e) *trans*-(guanidinomethyl)cyclohexanecarboxylic acid, HOSu, DCC in DMF; (f) TFA; (g) $R_2N(HN=)C\text{-}X\text{-}CO_2H$, HOSu, DCC.

Scheme 93.Synthesis of compounds **415a-i** and 416.[22]

Table 24.[22] The substituents of compounds **415a-i**.



Compound **415**	X	R
a		H
b	-NH$(CH_2)_4$-	H
c		H
d		H
e		H
f		H
g		H
h		H
i		CH_3

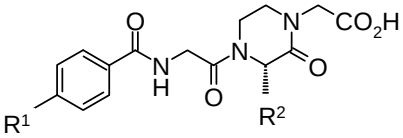


423-431

(a) *N*-Cbz-Gly-OH, EDC; (b) H_2, Pd/C in MeOH; (c) (*N*-Cbz-aminoalkyl)benzoic acid, DEPC, Et_3N in DMF; (d) TFA.[22]

Scheme 94.[22] The synthesis of compounds **423-431**.

Table 25.[22] The substituents of compounds **423-431**.



Compound	R^1	R_2
423	H_2NCH_2	CH_2CO_2H
424	$H_2N(CH_2)_2$	CH_2CO_2H
425	$H_2N(CH_2)_3$	CH_2CO_2H
426	$H_2N(CH_2)_2$	H
427	$H_2N(CH_2)_2$	CH_2CO_2H
428	$H_2N(CH_2)_2$	$(CH_2)_2CO_2H$
429	$H_2N(CH_2)_2$	$(CH_2)_2CO_2CH_3$
430	$(CH_3)_2N(CH_2)_2$	$(CH_2)_2CO_2H$
431	$(CH_3)_2N(CH_2)_2$	$(CH_2)_2CO_2CH_3$

Compound **427** showed significant activity on a guinea pig platelet aggregation assay, but the activity was lost 1 h after iv-administration to guinea pigs.

9.2 2,5-Diketopiperazine compounds

Pons *et al.* have synthesized a series of RGD mimetic molecules with the highly constrained bifunctional diketopiperazine **435** as a scaffold in search for potential $\alpha_{IIb}\beta_3$ or $\alpha_{IIb}\beta_3$ antagonists. 2,5-Diketopiperazines were chosen as the subject since they express stability to proteolysis, rigidity and are easily synthesized.[21]

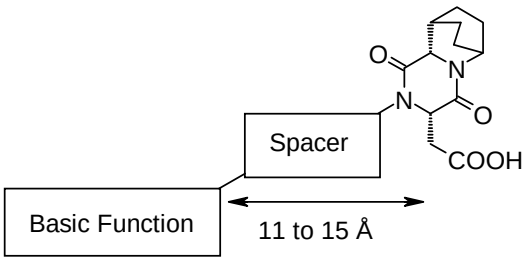
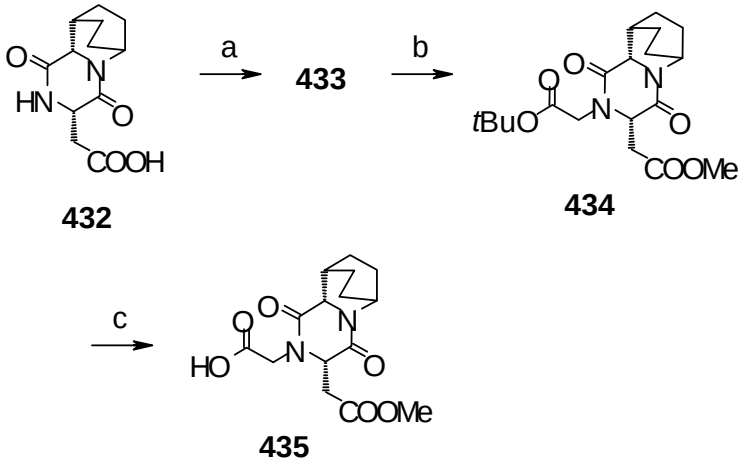


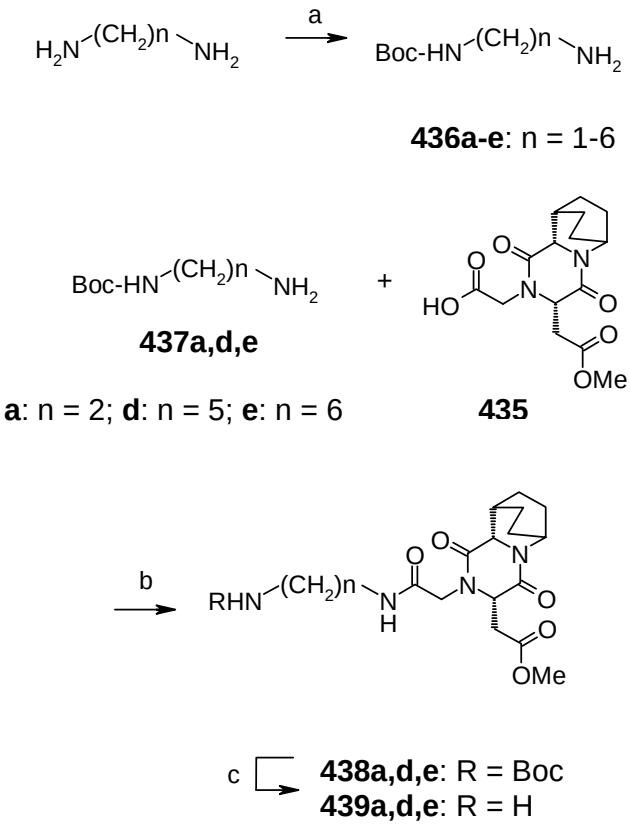
Figure 34. General scheme of derivatives studied.[21]



432 **434** **435**

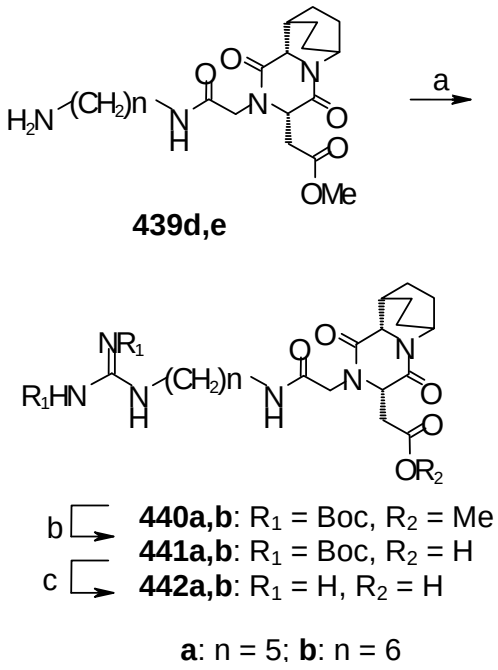
(a) $SOCL_2$, MeOH, 25°C (quantitative yield); (b) NaH, $BrCH_2COOtBu$, THF, 25°C (75%); (c) TFA, 25°C (quantitative yield).

Scheme 95. *N*-Alkylation of the diketopiperazine.[21]



(a) Boc_2O, $CHCl_3$ (95%); (b) DCC, DMAP, dichloromethane (**438a** 90%, **438d** 70%, **438e** 63%); (c) TFA, dichloromethane (quantitative yields).

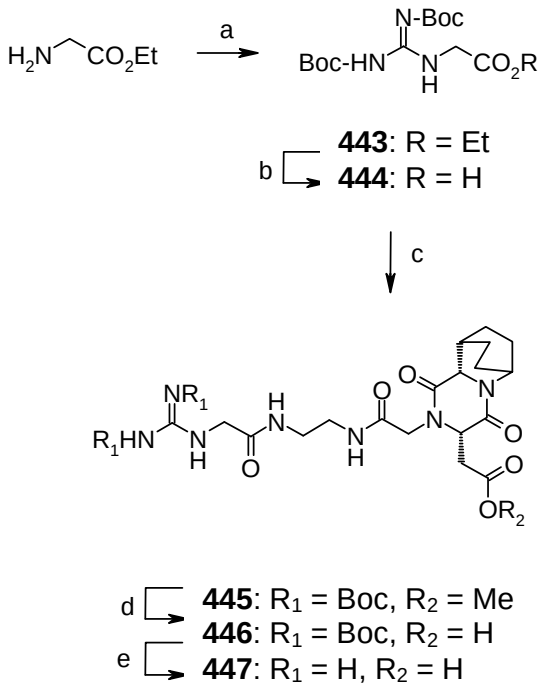
Scheme 96. Synthesis of compounds **439a,d,e**.[21]



(a) Boc-NH-C(=S)-NH-Boc, $HgCl_2$, NEt_2, DMF (**440a** 76%, **440b** 88%); (b) NaOH (2N), H_2O, dioxane (**441a** quantitative yield, **441b** 85%); (c) TFA, dichloromethane (**442a** 63%, **442b** 56%).

Scheme 97. Introduction of the guanidine function.[21]

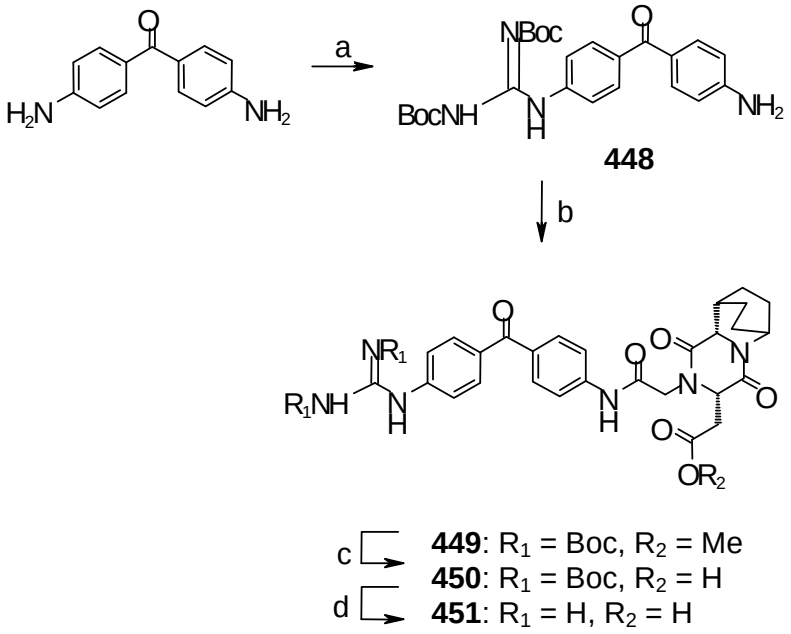
Compounds **442a** and **b** showed no inhibitory activity on the fibrinogen or the fibronectin.[21]



(a) Boc-NH-C(=S)-NH-Boc, $HgCl_2$, NEt_2, DMF (72%); (b) NaOH (2N), H_2O, dioxane (83%); (c) **439a**, DCC, DMAP, dichloromethane (80%); (d) NaOH (2N), H_2O, dioxane (75%); (e) TFA, dichloromethane (78%).

Scheme 98.[21] Synthesis of compound **447**.

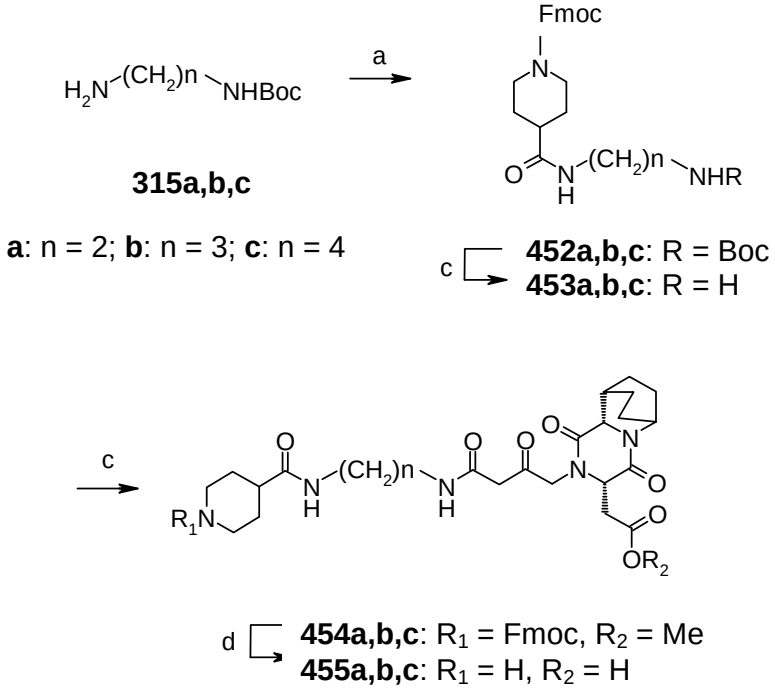
Compound **447** showed no inhibitory activity on the fibrinogen or the fibronectin.[21]



(a) Boc-NH-C(=S)-NH-Boc, $HgCl_2$, pyridine, DMF (64%); (b) **435**, DCC, DMAP, dichloromethane (44%); (c) NaOH (2 N), H_2O, dioxane (quantitive yield); (d) TFA, dichloromethane (76%).

Scheme 99. Synthesis of compound **451**.[21]

Compound **451** showed no inhibitory activity on the fibrinogen or the fibronectin.[21]



Scheme 100. Synthesis of compounds **455a-**c.[21]

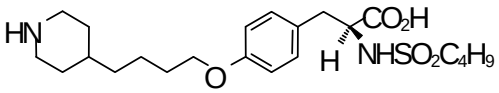
Compounds **455a-c** showed no no inhibitory activity on the fibrinogen or the fibronectin.[21]

See also Scheme 75 (8.1) and compound **511h** (Table 30 in 10.1).

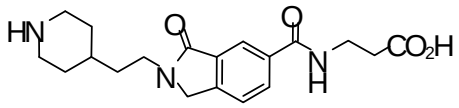
10 Other piperidine compounds

10.1 Piperidine compounds containing a sulfonamide group

Egbertson, Hartman *et al.* have synthesized a series of alkyl or aryl sulfonamide GPIIb/IIIa antagonists which show high activity for activated and unactivated platelet receptors. It appears the sulfonamide group such as that in **456** interacts with a binding site region cyclic inhibitors can't reach. Compound **456** shows excellent *in vivo* efficacy but its activity after oral administration is short-term. Analog **457** was chosen as the lead compound due to its favorable central constraint and active platelet inhibition in dogs. The aim was a more to find a more potent antagonist with a smaller required dosage. [28]

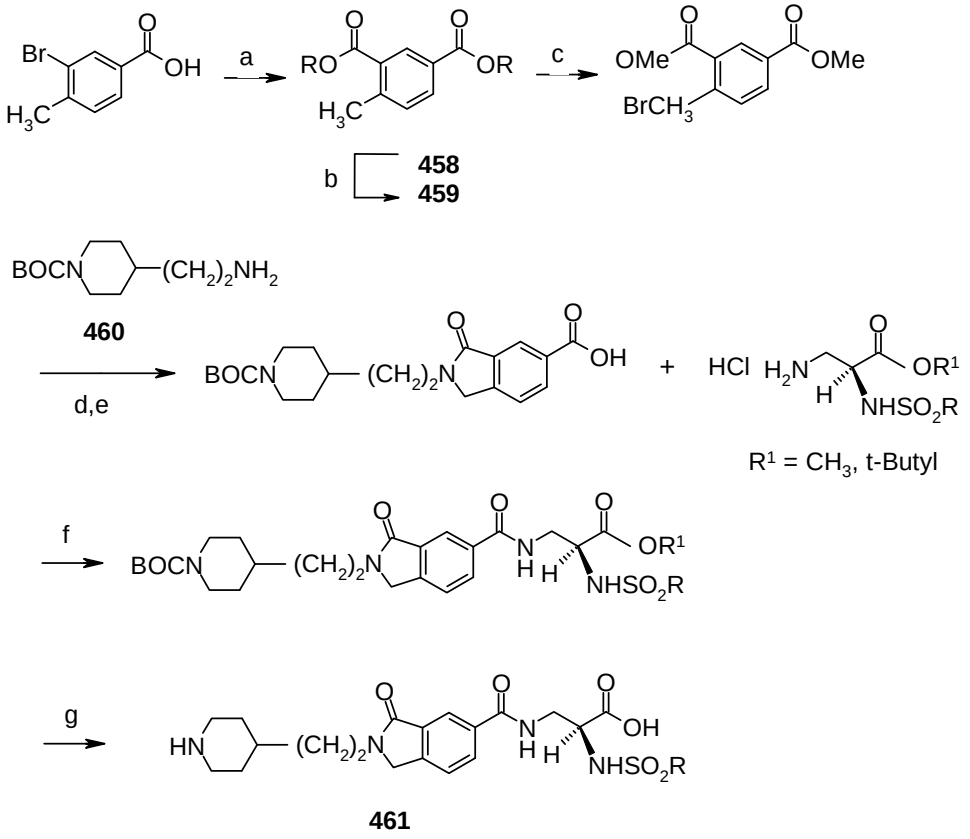


456 (L-700,462; MK-383, AGGRASTAT™



457 (L-709,780)

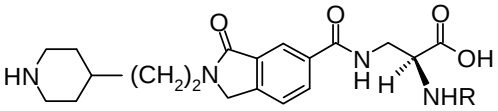
Figure 35. Small molecule fbrinogen receptor antagonists.[32]



(a) 1.1 equiv. CH_3MgBr / 0˚C, then 2 equiv. *n*-BuLi / -65˚C, solid CO_2, (85%); (b) CH_3OH / HCl, (95%); (c) 1 equiv. NBS, 5 mol-% dibenzoyl peroxyl, CCl_4, reflux (80%); (d) **460**, C_6H_6, 1 equiv. TEA, reflux, (80%); (e) 5 equiv. LiOH / 1:1:1 MeOH / THF / H_2O, quant; (f) BOP / DMF / N-methyl morpholine (50-80%); (g) 6 N HCl / dioxane or HCl / EtOAc (90%).

Scheme 101. Preparation of α-sulfonylamido isoindolinones.[32]

Table 26. Sulfonamide derivatives of lead compound **456**.[32]

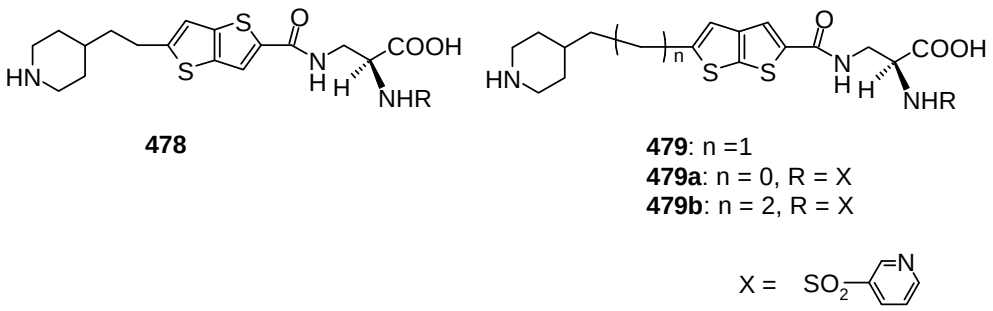


Compound	R
462	SO_2CH_3
463	$SO_2(CH_2)_3CH_3$
464	$SO_2(CH_2)_3CH_3$
465	$SO_2CH_2CH(CH_3)_2$
466	$SO_2(CH_2)_4CH_3$
467	$SO_2(CH_2)_2OCH_2CH_3$
468	$CO(CH_2)_4CH_3$
469	$CONH(CH_2)_3CH_3$
470	$CONHCH_2C_6H_5$
471	$SO_2NH(CH_2)_3CH_3$
472	$SO_2C_6H_5$
473	$SO_2$2-thienyl
474	$SO_2$3-pyridyl
475	$SO_2CH_2C_6H_5$
476	$SO_2$4-$(CO_2H)C_6H_4$
477	$SO_2$2-$(CO_2H)C_6H_4$

In general, the aryl sulfonamides **472-477** showed more potential than the alkyl sulfonamides.[32]

Compounds **463-477** demonstrated ten to thirty-fold improvements in potency over **457** with compound **474** showing both very good *in vivo* potency and 20-fold improvement in oral activity compared to compound **457**.[32]

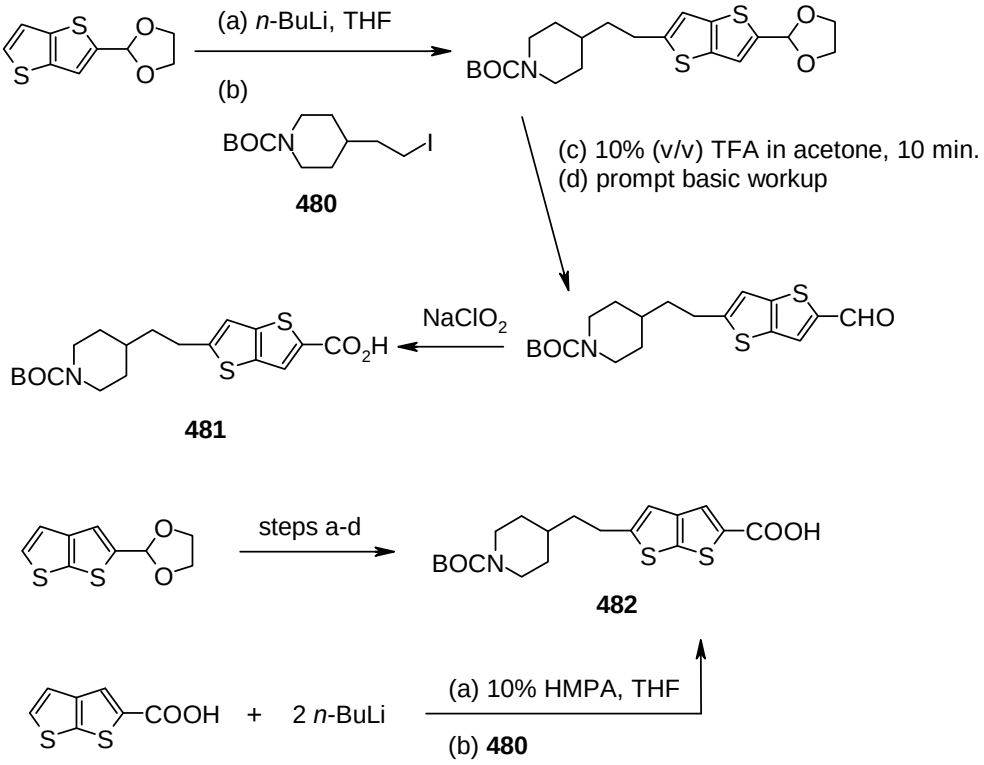
Prugh *et al.* designed and synthesized two series of potent GPIIb/IIIa inhibitors derived from compounds **478** and **479** by using compound **456** as a lead compound. Compound **487** shows excellent oral activity in the dog.[29]



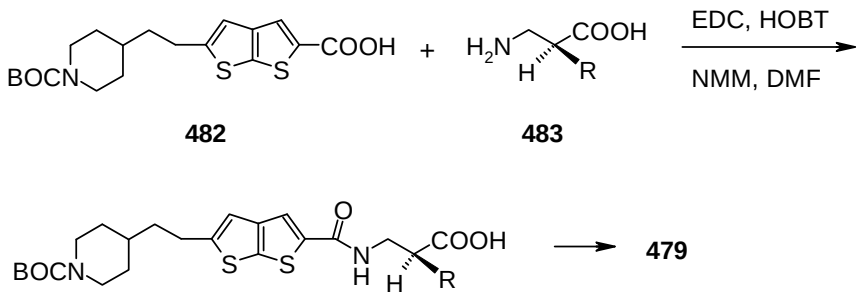
478

479: n =1
479a: n = 0, R = X
479b: n = 2, R = X

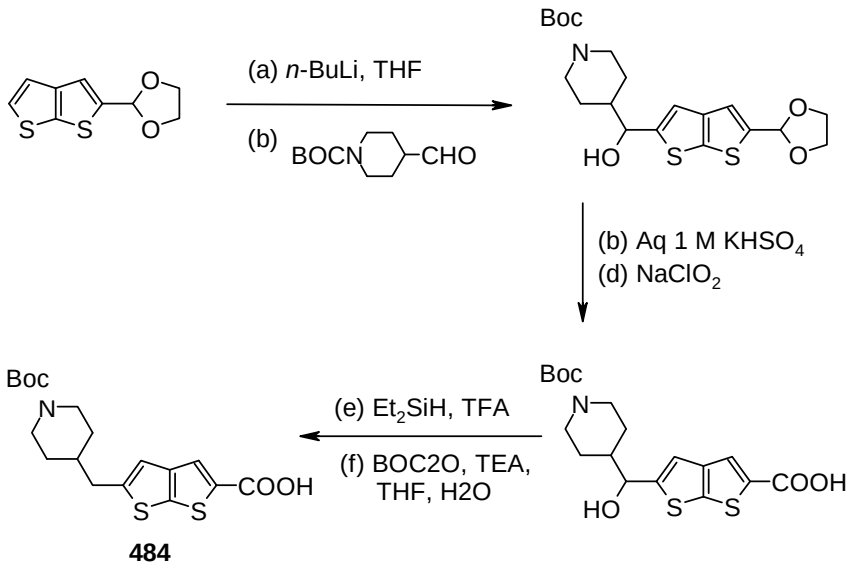
Figure 36.Compounds **478** and **479**.[33]



Scheme 102.[33] Synthesis of intermediates **481** and **482**.



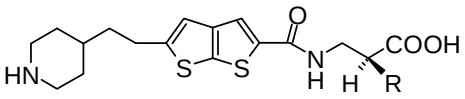
Scheme 103.[33] Synthesis of compound **479**.



Scheme 104.[33] Synthesis of intermediate **484**.

Compound **479a** was synthesized by coupling intermediate **484** with compound **483** followed by deblocking.[33]

Table 27. α-Substituted thienol(2,3-*b*)thiophene analogs of **479**[33]



479

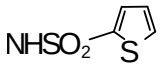
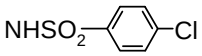
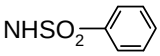
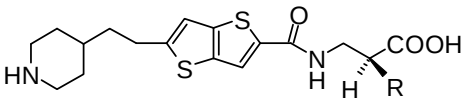
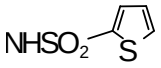
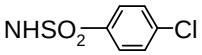
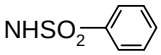
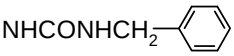
Compound	R
485	
486	
487	
488	$NHSO_2C_4H_9$
489	H
490	

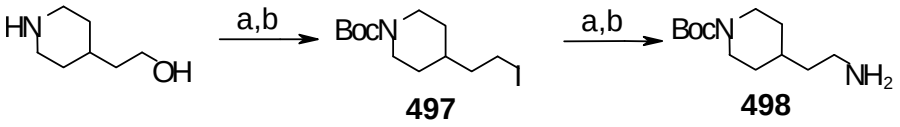
Table 28. α-Substituted thienol(3,2-*b*)thiophene analogs of **478**.[33]



478

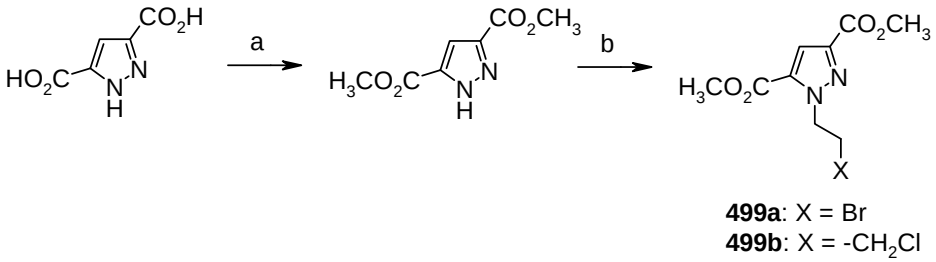
Compound	R
491	
492	
493	
494	$NHSO_2C_4H_9$
495	H
496	

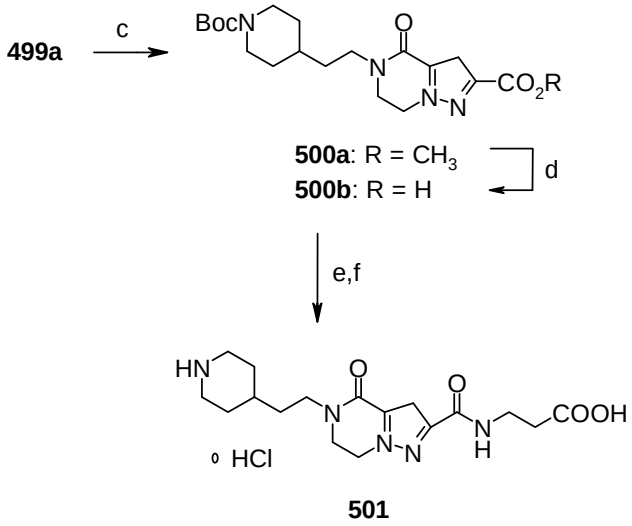
Askew, Bednar *et al.* have synthesized several analogues of compound **501,** including a potent and selective GPIIb/IIIa inhibitor **508** (L-738,167).[30]



(a) Boc_2O, CH_2Cl_2; (b) I_2, Ph_3P, imidazole, toluene; (c) NaN_3, DMSO; (d) H_2, Pd/C, MeOH.

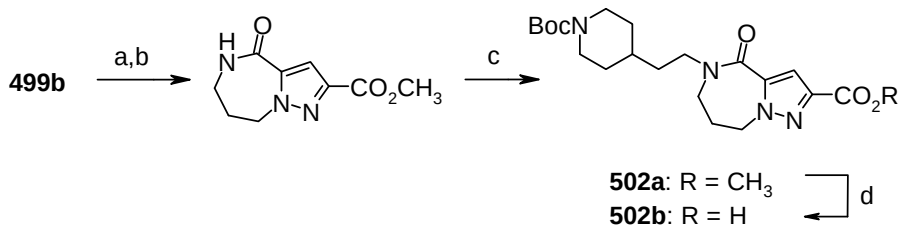
Scheme 105.[34] Synthesis of intermediate **498**.





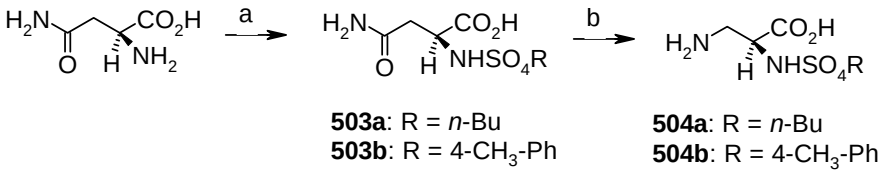
(a) HCl, MeOH; (b) $Br(CH_2)_2Br$ or $Br(CH_2)_3Cl$, CH_3CN, K_2CO_3: (c) **498**, CH_3CN, Et_3N; (d) LiOH, THF/H_2O; (e) *β*-alanine *t*-Bu ester • HCl, EDC, Et_3N, CH_2Cl_2; (f) HCl, EtOAc.

Scheme 106.[34] Synthesis of pyrazolopiperazinone analog **501**.



(a) NaN_3, DMSO; (b) H_2, Pd/C, MeOH; (c) NaOH, **497**, DMF; (d) LiOH, THF/H_2O.

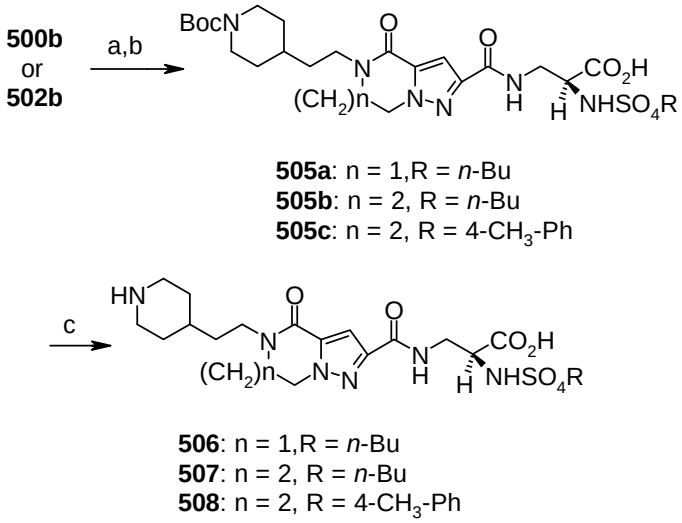
Scheme 107.[34] Synthesis of compound **502b**.



(a) RSO_2Cl, NaOH, dioxane/H_2O; (b) Br_2, NaOH,H_2O.

Scheme 108.[34] Synthesis of α-sulfonamido-β-alanines **504a-b**.

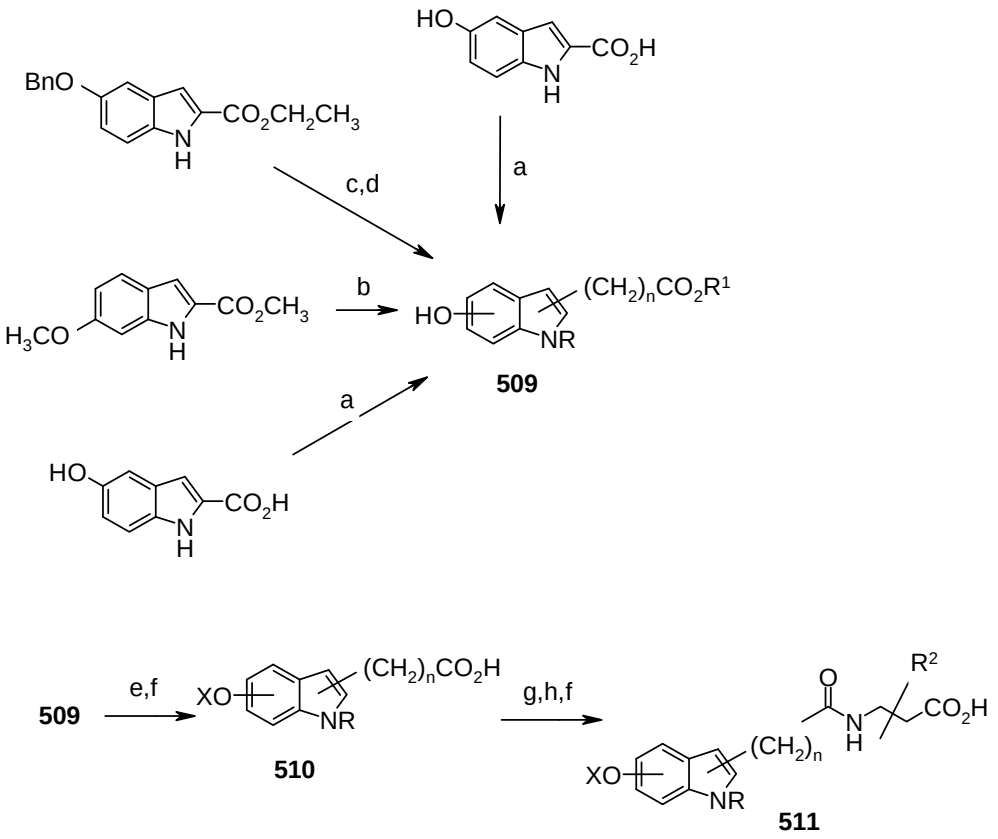
During the synthesis of described in Scheme 109, the coupling of **504a** and **b** with **500b** and **502b** was done without carboxylate protection using the mixed anhydride method in order to avoid racemization.[34]



(a) *i*-BuOCOCl, *N*-methylmorpholine, THF; (b) **504a** or **504b**, THF/H_2O; (c) HCl, EtOAc.

Scheme 109.[34] Synthesis of compound **508**.

Brashear *et al.* have synthesized a series of potent GPIIb/IIIa inhibitors including **511a** which demonstrates great oral activity in the rhesus monkey.[31]

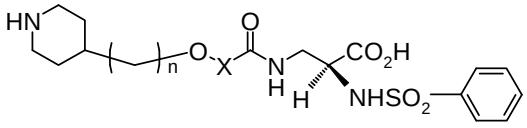


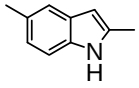
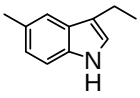
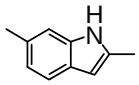
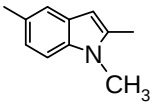
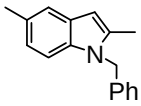
(a) CH_2N_2 EtOAc; (b) BBr_3, THF; (c) NaH, MeI or BnBr; (d) H_2, 10% Pd/C, EtOH; (e) X-OH, DEAD, PPh_3 in THF or X-Cl, Cs_2CO_3, DMF; (f) 1 N NaOH, THF/MeOH; (g)) β-alanine ester, BOP, NM, CH_3N; (h) HCl (gas), EtOAc.

Scheme 110.[35] Synthesis of compound **511**.

Boc-protection of the *N*-terminus was applied in the syntheses of compounds **511a, 511b, 511h** and **511j**.[35]

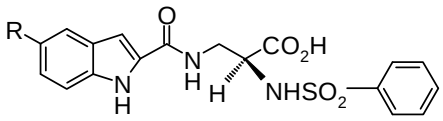
Table 29.[35] Analogues **a-g** of compound **511**.

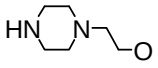
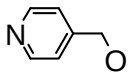
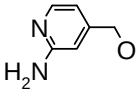
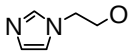
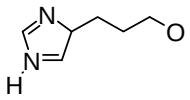


Compound	n	R
511a	1	
511b	2	
511c	1	
511d	1	
511e	1	
511f	2	
511g	1	

The greater potency of compounds **511a** and **511b** shows that the 2-position on the indole ring is the preferred position of the acid terminus. The difference in potency between a one-carbon linker and a two-carbon linker was found not significant.[35]

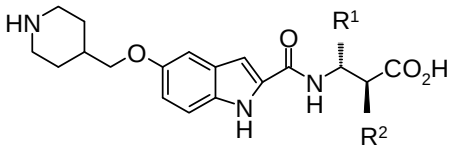
Table 30.[35] Analogues **h-l** of compound **511**.

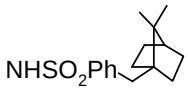
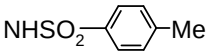
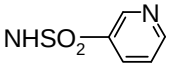


Compound	R
511h	
511i	
511j	
511k	
511l	

The more basic compounds **511h** (as well as **511a** and **511b**) showed more potency than the less basic compounds **511i-l**.[35]

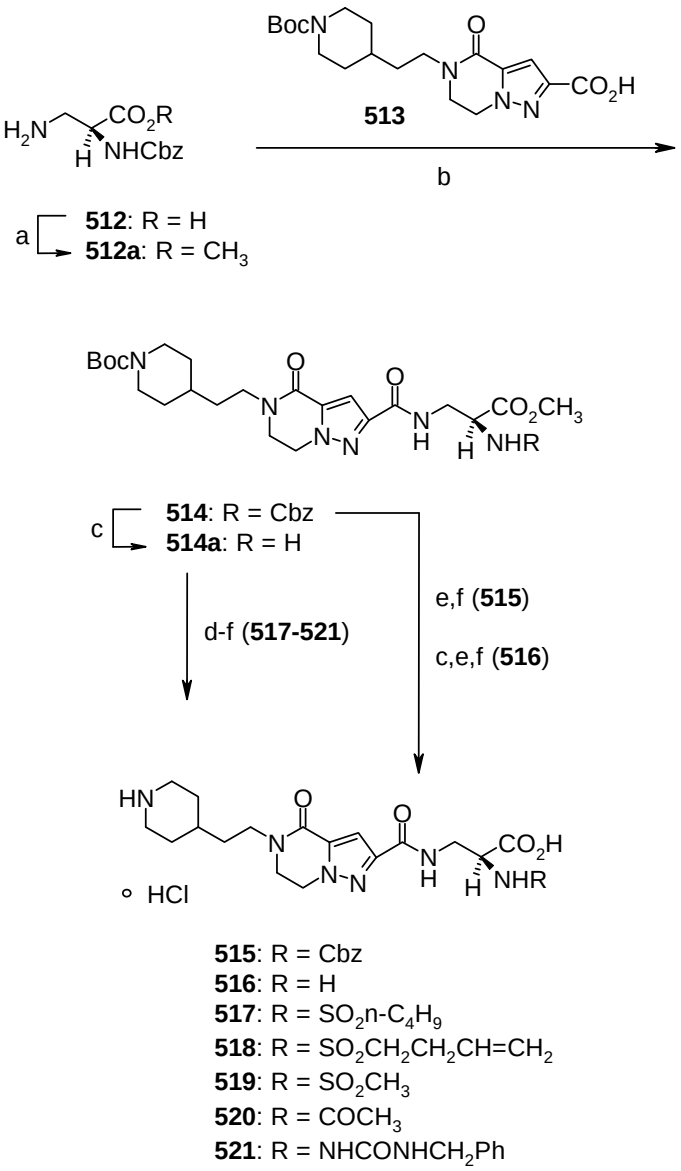
Table 31.[35] Analogues **m-q** of compound **511**.



Compound	R^1	R^2
511m	H	H
511n	(*R,S*)-pyrid-3-yl	H
511o	H	
511p	H	
511q	H	

Compounds **511p** and **511q** showed excellent affinity in platelet aggregation but could not sustain it for long as opposed to **511a**.[35]

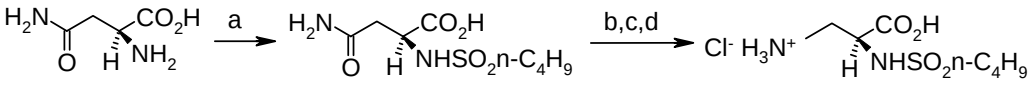
Askew, McIntyre *et al.* have synthesized a series of pyrazolopiperazinone fibrinogen receptor antagonists including an orally active and selective GPIIb/IIIa inhibitor, compound **517** (L-734,115).[32]



(a) HCl, MeOH, (100%); (b) **512a**, EDC,HOBt, DMF, (95%); (c) H_2, 10% Pd/C, EtOH, (100%); (d) RSO_2Cl, RCOCl, or RNCO, CH_2Cl_2, Et_3N, (65-100%); (e) LiOH, THF, H_2O, (100%); (f) HCl, EtOAc, 0˚C, (85-98%).

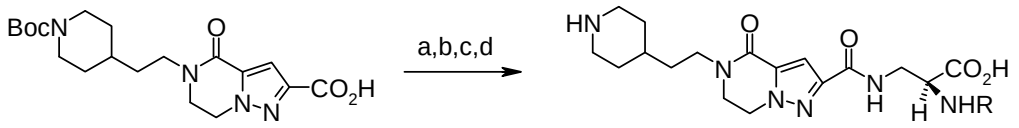
Scheme 108.[36] Synthesis of compounds **515-521**.

A high yield of compounds **515-521** was obtained by the synthesis described in Scheme 108. However, because of the 10-15% racemization during the ester hydrolysis an alternate route was developed (Schemes 109-110).[36]



(a) *n*-$BuSO_2Cl$, 50% aquaeous dioxane, (65%); (b) Br_2, NaOH; (c) Boc_2O, THF, (85%); (d) HCl, EtOAc, (98%).

Scheme109.[36] Synthesis of compound **522**.



(a) *i*-BuCOCl, N-methylmorpholine, THF, 0˚C, (98%); (b) **522**, THF/H_2O, 0˚C, (83%); (c) HCl, EtOAc, 0˚C, (100%); (d) ion exchange chromatography, Dowex 50XB-200, (85%).

Scheme110.[36] Non-racemizing synthesis of compound **517**.

Liverton *et al.* have synthesized a series of 3,6-substituted quinazolinedione and quinazolinone fibrinogen receptor antagonists with good *in vitro* activity. The activity after i.v.infusion in dogs was however short-term. [33]

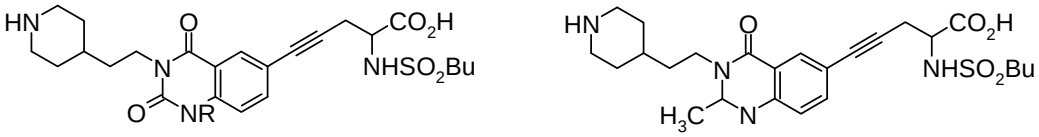
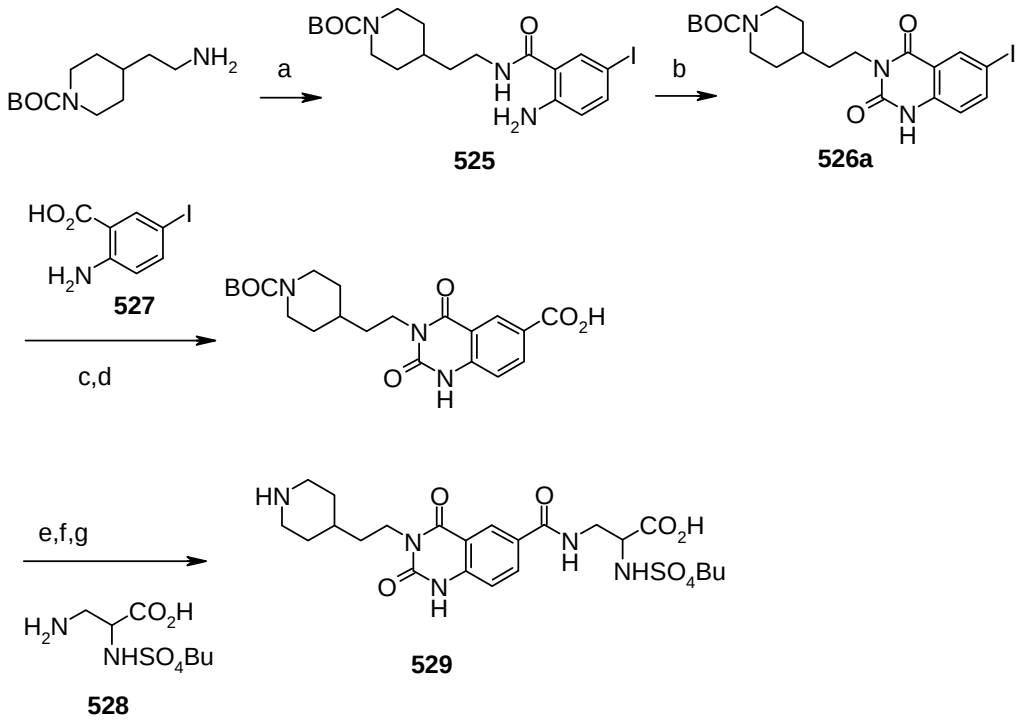


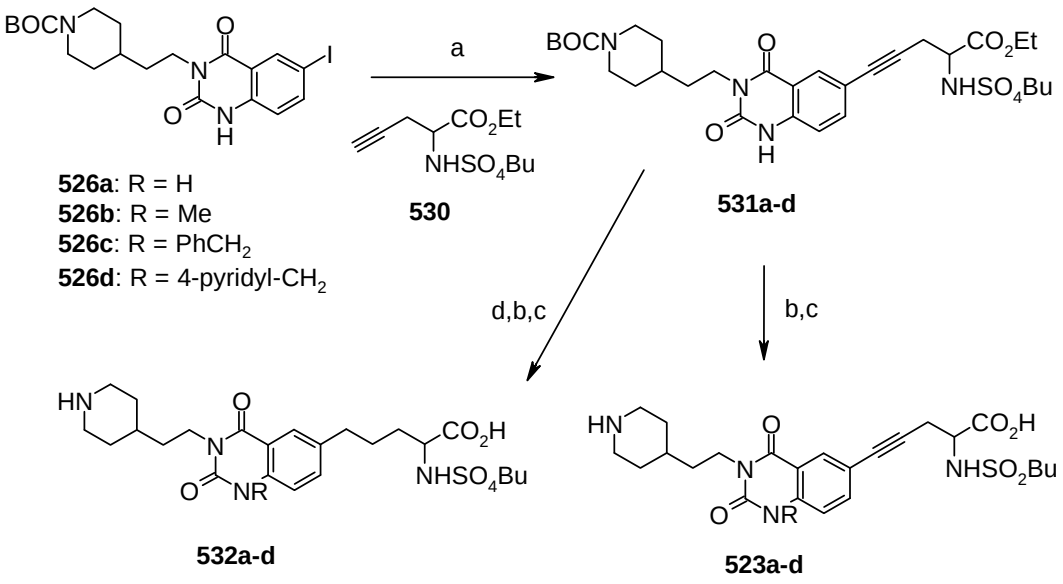
Figure 37.[37] Target compounds **523a-d** and **524**.



(a)EDC, HOBt, Net_3, DMF, rt, 56%; (b) carbonyldiimidazole, THF, 60˚C, 3 h, 70%; (c) $Pd(PPh_3)_4$, CO (balloon), toluene, slow addition of Bu_3Sn, 50˚C; (d) H_2O_2, $NaClO_2$, phosphate buffer pH 4.3, rt; (e) **528**, EDC, HOBt, Net_3, DMF, rt; (f) LiOH, THF, H_2O; (g) HCl, EtOAc, 0˚C.

Scheme 111.[37] Synthesis of compound **529**.

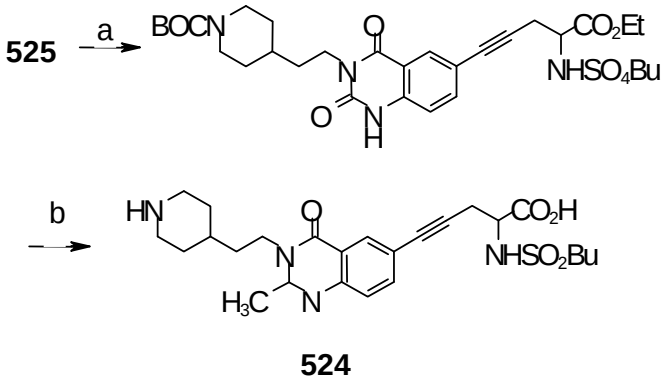
Compound **529** shows potency toward platelet aggregation inhibition but the substitution of C-terminal amide linkage with an acetylene gives compound **523a** 17-fold increase in activity.[37]



(a) **530**, $Pd(PPh_3)_4$, CuI, $HNEt_2$, 40˚C; (b) LiOH, THF, H_2O; (c) HCl, EtOAc, 0˚C; (d) H_2, 50psi, Pd/C, EtOAc.

Scheme 112.[37] Synthesis of compounds **523a-d** and **532a-d**.

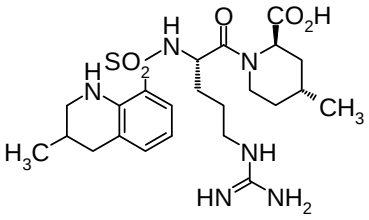
The reduction of the acetylene as in compounds **532a-d** resulted only in slight decrease in activity as did the N1-substitutions (compounds **523b-d** and **532b-d**).[37]



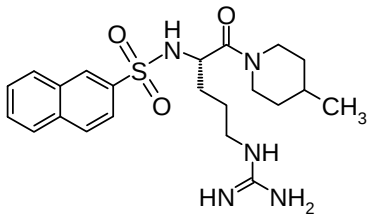
(a) $(EtO)_3CH$, 160˚C, 3 h, 93%; (b) steps a,b,c from Scheme 110.

Scheme 113.[37]Synthesis of compound **524**.

Misra *et al.* have synthesized a group of human α-thrombin inhibitors based on the potent and selective thrombin inhibitor Argatroban (compound **533**)[34]



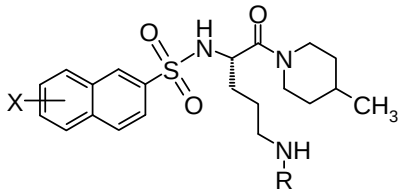
533 (Argatropan)



534

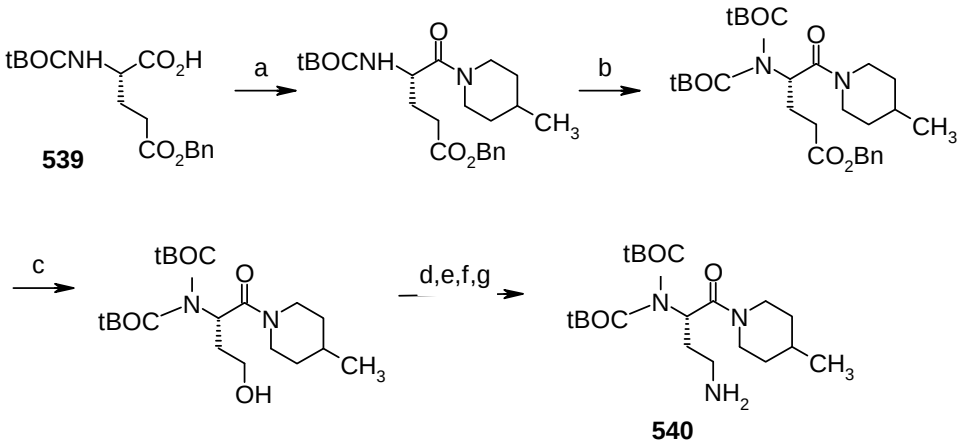
Figure 38.[38] Thrombin inhibitor **533** and its structurally simplified analog **534**.

Table 32.[38] The substituents of arylsulfonamides **535a-b, 536a-b, 537** and **538**.



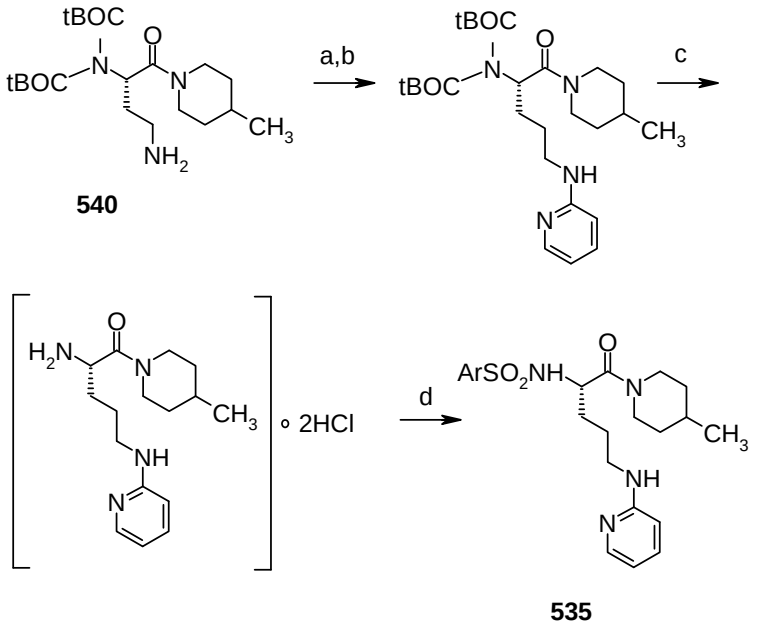
Compound	R	X
535a		H
535b		5-OCH_3
536a		H
536b		5-OCH_3
537		H
538		H

The decreasing basicity of the compounds (**535a-b**>**536a-b**>**537**>**538**) also translated into decreasing potency, making compounds **535a** and **535b** the most potent human α-thrombin inhibitors of the group.[38]



(a) 4-Methylpiperidine/EDAC/HOBt/NMM/DMF, 0 to 25˚C, 100%; (b) $(tBoc)_2O$ (10 eq)/4-pyrrolidino-pyridine/CH_3CN, 85˚C, 72%; (c) $LiCl/NaBH_4/EtOH$, 25˚C, 72%; (d) $MsCl/Et_3N/CH_3Cl_2$, -20˚C, 97%; (e) NaI (5eq)/acetone, 25˚C, 93%; (f) NaN_3/DMF, 25˚C, 100%; (g) 10% Pd-C/H_2(1atm)/CH_3OH, 100%.

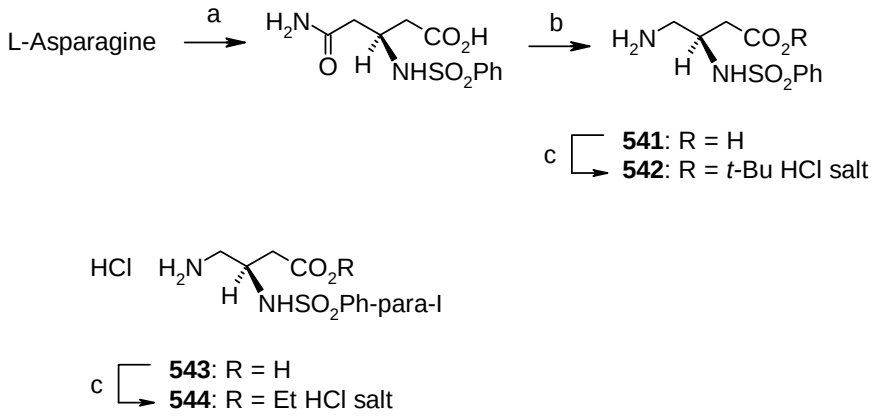
Scheme 114.[38] Synthesis of intermediate **540**.



(a) 2-Chloropyridine-N-oxide • $HCl/NaHCO_3$/1-butanol, 100˚C, 47%; (b)) 10% Pd-C/HCO_2NH_4/EtOH, reflux, 60%; (c) HCl/dioxane, 25˚C, 100%; (d) $ArSO_2Cl/Et_3N$ (4 eq)/CH_2Cl_2, 0˚C, 75-95%.

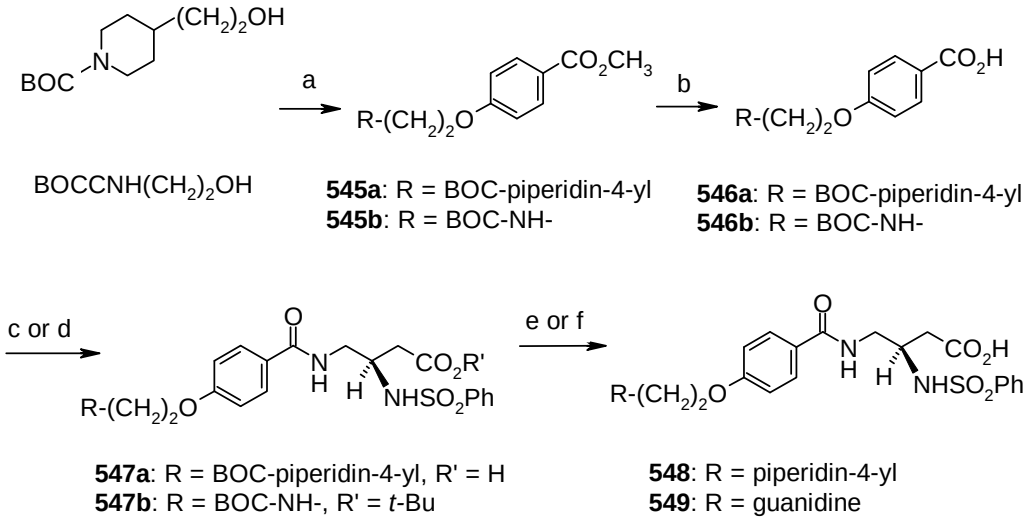
Scheme 115.[38] Synthesis of compound **535**.

Duggan, Duong *et al.* have synthesized a series of potent vitronectin receptor $\alpha_V\beta_3$ antagonists based on the potent fibrinogen receptor $\alpha_V\beta_3$ antagonist **548**.[35]



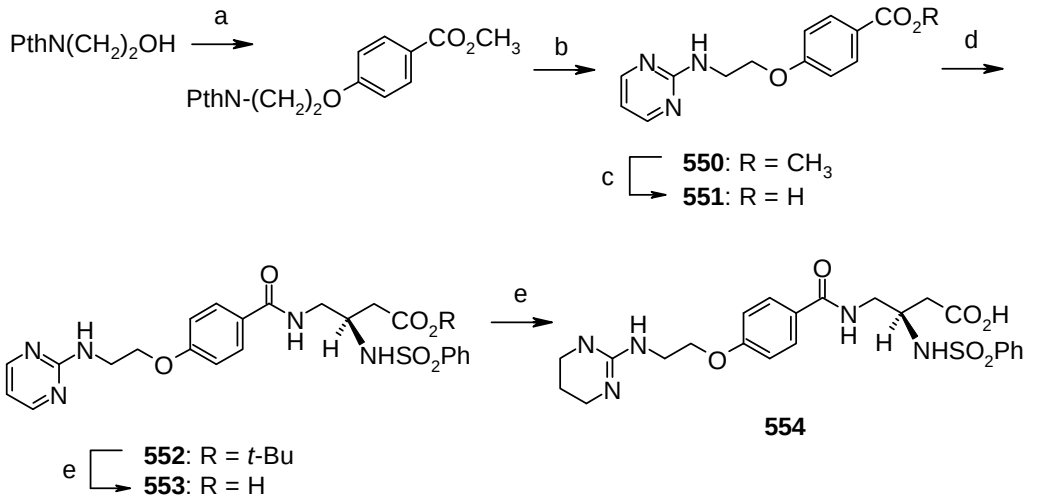
(a) NaOH, H_2O, phenylsulfonyl chloride; (b) NaOH, dioxane, Br_2; (c) isobutylene, H_2SO_4 then 1 N HCl ether; (d) ethanol/HCl.

Scheme 116.Preparation of 3-amino-2(*S*)-arylsulfonylaminopropionic acids and esters.[39]



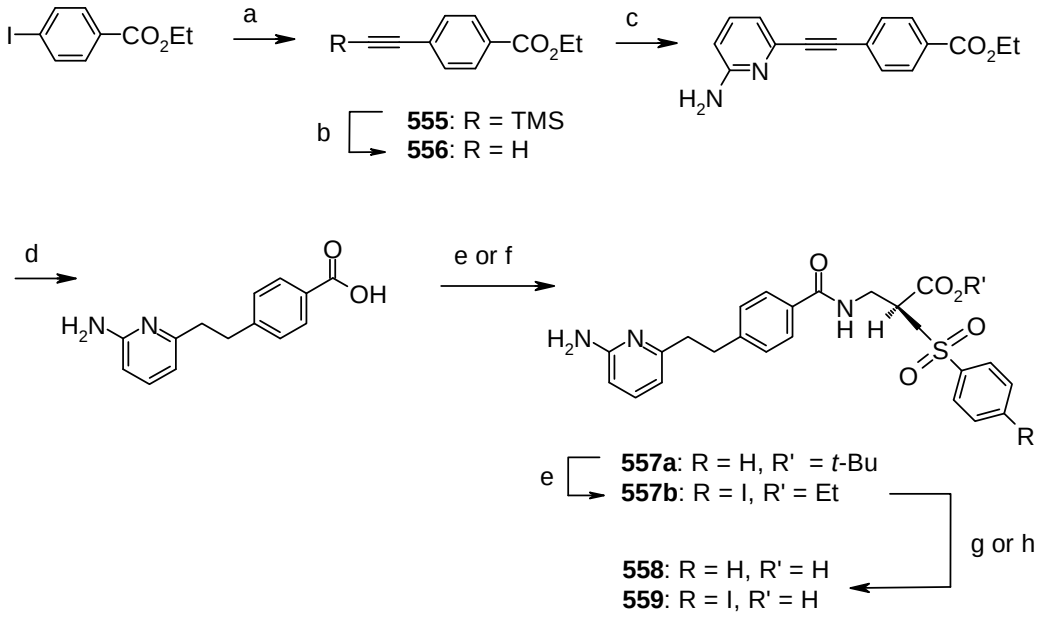
(a) THF, Ph_3P, diethyl diazodicarboxylate, methyl 4-hydroxybenzoate; (b) NaOH; (c) BOP reagent, DMF, 4.methylmorpholine, **541**; (d) BOP reagent, CH_3CN, 4-methylmorpholine, **542**; (e) TFA, CH_2Cl_2 then aq DMF, Net(*i*-Pr)$_2$, 3,5-dimethylpyrazole-1-carboxamidine nitrate.

Scheme 117. Preparation of compounds **548** and **549**.[39]



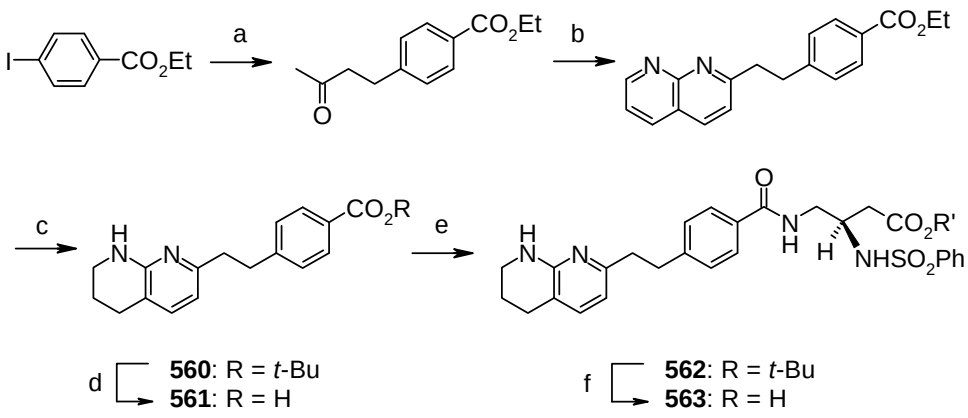
(a) THF, PhP_3, diethyl diazodicarboxylate, methyl 4-hydroxybenzoate; (b) hydrazine, MeOH, then DMF, Net(*i*-Pr)$_2$, 2-bromopyrimidine, 80 ºC; (c) NaOH, MeOH, 60 ºC; (d) EDC, HOBT, 4-methylmorpholine, **542**; (e) TFA, CH_2Cl_2; (f) 10% Pd/C, H_2, HOAc/HCl.

Scheme 118. Preparation of compound **554**.[39]



(a) TMSC=CH, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_3CN, 100 ºC; (b) K_2CO_3, EtOH; (c) 2-amino-6-bromo-pyridine, Net_3, $(Ph_3P)_2PdCl_2$, CH_3CN; (d) 10% Pd/C, then 6 N HCl; (e) EDC, HOBT, DMF, 4-methylmorpholine, **542**; (f) EDC, HOBT, DMF, 4-methylmorpholine, **544**,; (g) TFA, CH_2Cl_2; (h) 6 N HCl.

Scheme 119. Preparation of compounds **558** and **559**. [39]



(a) 3-buten-2-ol, $Pd(OAc)_2$, Net_3, CH_3CN, 100 ºC; (b) 2-amino-3-formylpyridine, EtOH, L-proline, reflux; (c) 10% Pd/C, EtOH, H_2; (d) 6 N HCl; (e) BOP reagent, CH_3CN, 4-methylmorpholine, **542**; (F) 6 N HCl.

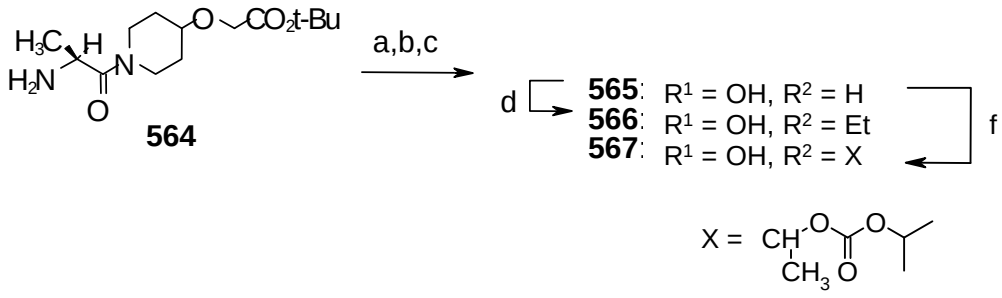
Scheme 120. Preparation of compound **563**.[39]

The 5,6,7,8-tetrahydro[1,8]napthyridine moiety forms a lipophilic, moderately basic N-terminus which helps give $\alpha_V\beta_3$ antagonists excellent potency and selectivity thus making compound **563** a potent inhibitor of bone resorption *in vitro* and *in vivo*.[39]

10.2 Remaining other piperidine compounds

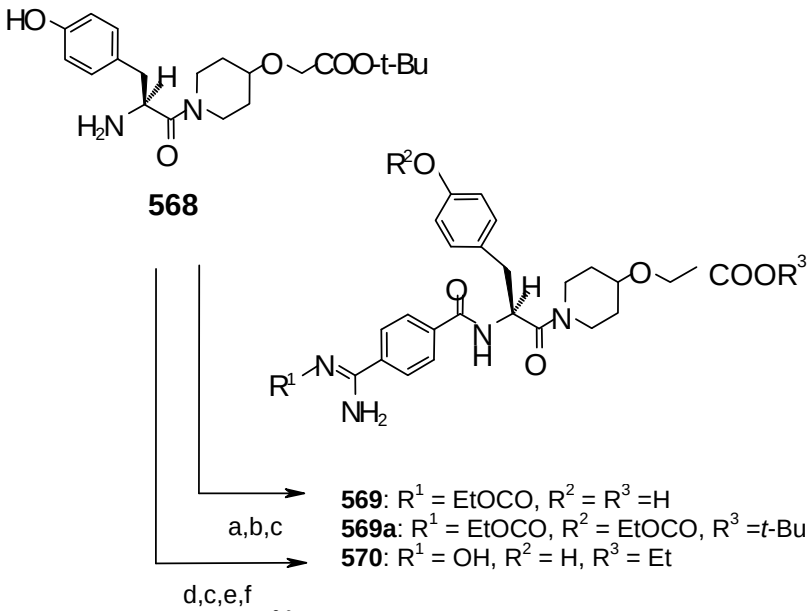
See also Scheme 80 (8.2) and compound **415c** (Table 24 in 9.1).

Weller *et al.* have synthesized an orally active prodrug **447** derived from a potent and selective GPIIb/IIIa antagonist **358** (Scheme 76 in 8.2). With the oral bioavailability improved 20-fold it was shown that an amidoxime group can serve as a prodrug functionality for an amidino group.[26]



(a) EtOH, H_2SO_4; (b) *n*-BuOCOCl, NaOH, CH_2Cl_2; (c) 4-NCC_6H_4COCl, $NaHCO_3$, CH_2Cl_2; (d) NH_2OH • HCl, Na, CH_3OH; (e) HCOOH; (f) 1-iodoethyl isopropyl carbonate, dicyclohexylamine, DMF.

Scheme 121.[26] Preparation of prodrugs **565-567**.

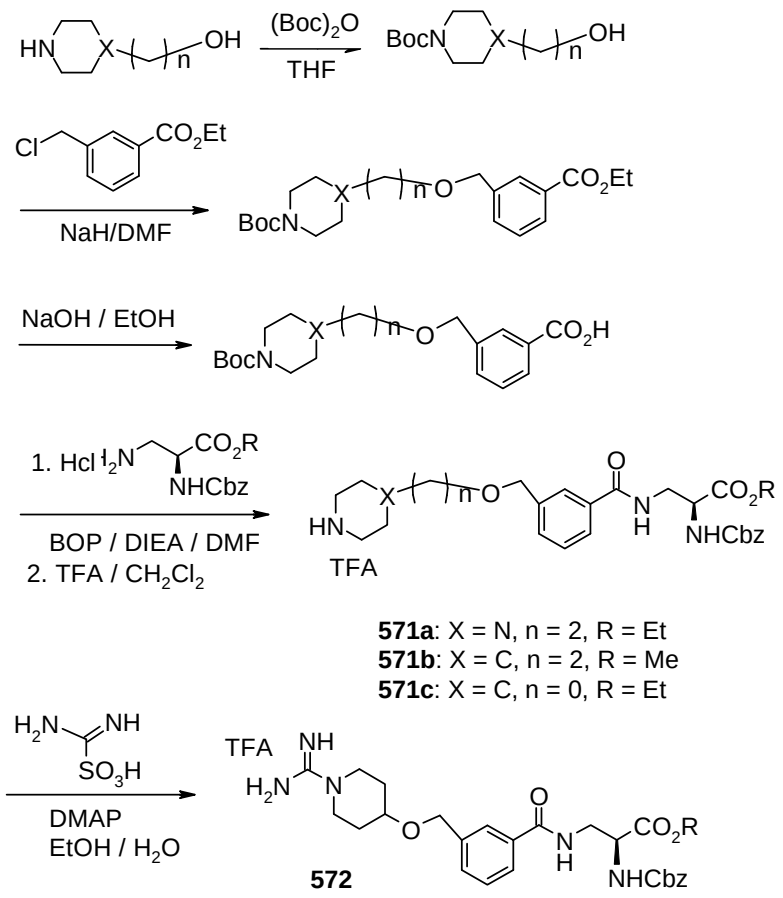


(a) 4-$NH_2C(NH)C_6H_4COCl$, pyridine; (b) EtOCOCl, NaOH, CH_2Cl_2; (c) HCOOH; (d) 4-NCC_6H_4COCl, $NaHCO_3$, CH_2Cl_2; (e) NH_2OH•HCl, Na, MeOH; (f) EtOH, H_2SO_4.

Scheme 122. Preparation of compounds **569, 569a** and **570**. [26]

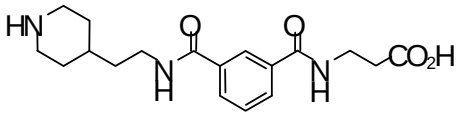
Compound **568** was derived from compound **362** (Scheme 80 (8.2) by coupling of *N*-Z-Tyr-OH with *tert*-butyl (4-piperidinyloxy)acetate followed by catalytic hydrogenation.[26]

Xue *et al.* have synthesized potent GPIIb/IIIa antagonists (see also 8.3) including **572**. The *N*-amidinopiperidin-4-yl group proved to yield a higher potency than the smaller piperaxine or piperidine groups of **571a-c**.[28]



Scheme 123.[28] Synthesis of compounds **571a-c** and **572**.

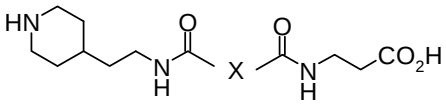
Egbertson, Naylor *et al.* have synthesized a group of m-phthalic acid analogs based on the fibrinogen receptor antagonist **573,** and subsequently a potent, selective and orally active fibrinogen receptor antagonist, compound **579**.[36]

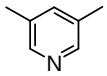
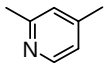
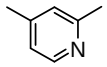
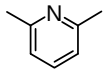


573

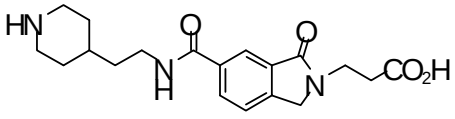
Figure 39.[40] Lead compound **573**.

Table 33. Pyridine analogs of compound **573**.[40]

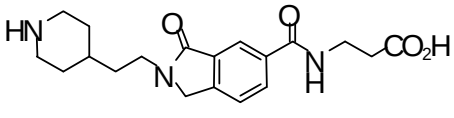


Compound	X
574	
575	
576	
577	

Compounds **574-576** show relatively similar potency to each other, whereas compound **577** demonstrated a potency 100-fold smaller. It was calculated that the position of the pyridine nitrogen causes the molecule to favor a rotational isomere in which dipole moments are opposed in stead of aligned, making compound **577** less potent than the other analogs.This lead to the design of the constrained isoindolinone compounds **578** and **579** in which the carbonyl groups are in the same plane as the phenyl ring.[40]

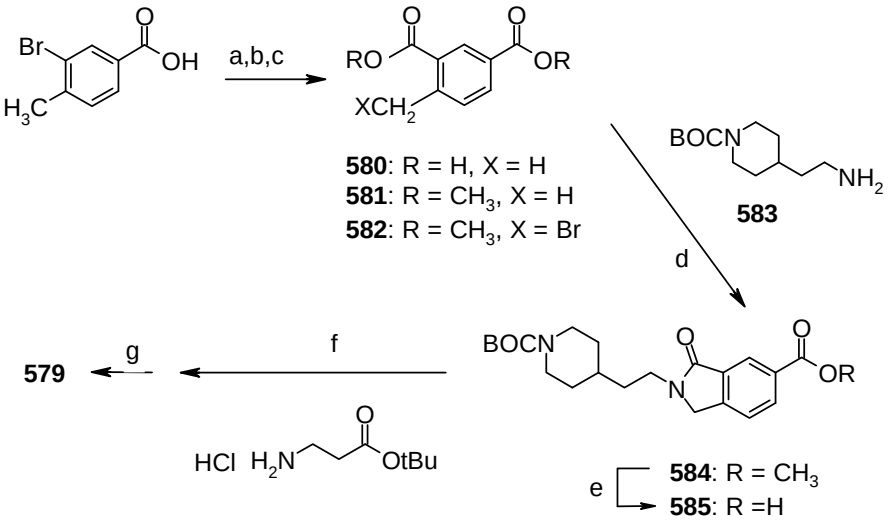


578



579

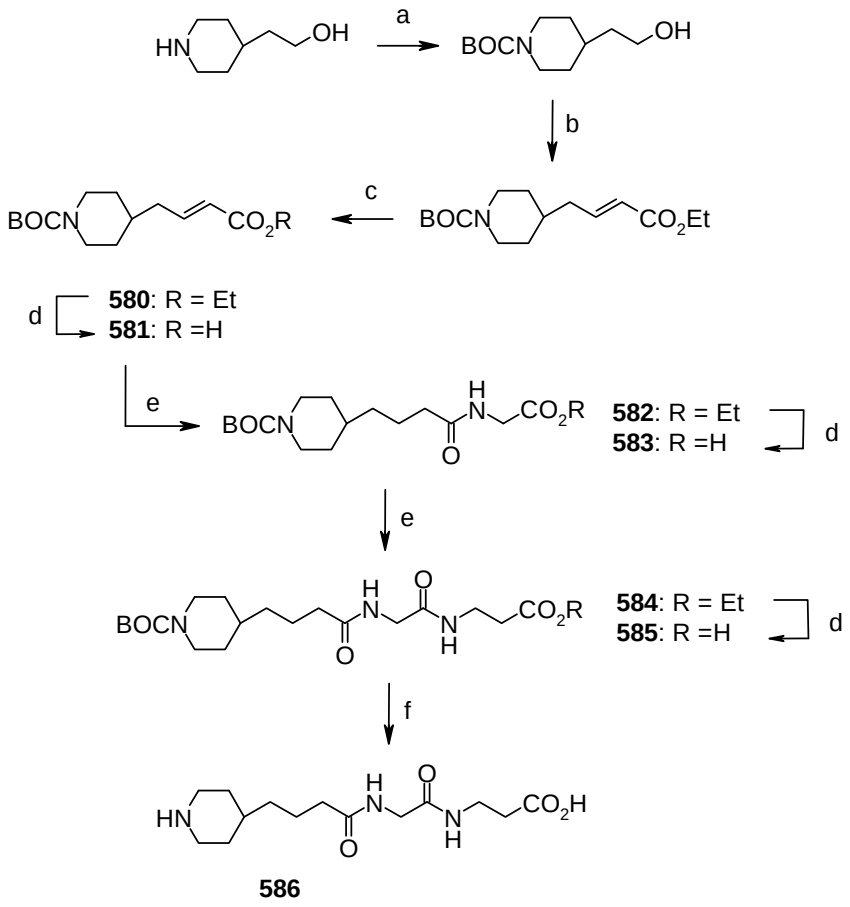
Figure 40. Constrained amide fibrinogen receptor antagonists.[40]



(a) 1.1 eq CH_3MgBr/0 ºC, then 2 eq *n*BuLi/-65 ºC, solid CO_2, 85%; (b) CH_3OH/HCl, 95%; (c) NBS, CCl_4, 80%; (d) **583**,C_6H_6, reflux, 80%; (e) LiOH/MeOH, THF, H_2O, quant.; (f) N-methylmorpholine, BOP reagent, CH_3CN, 80%; (g) HCl(gas)/EtOAc, 95%.

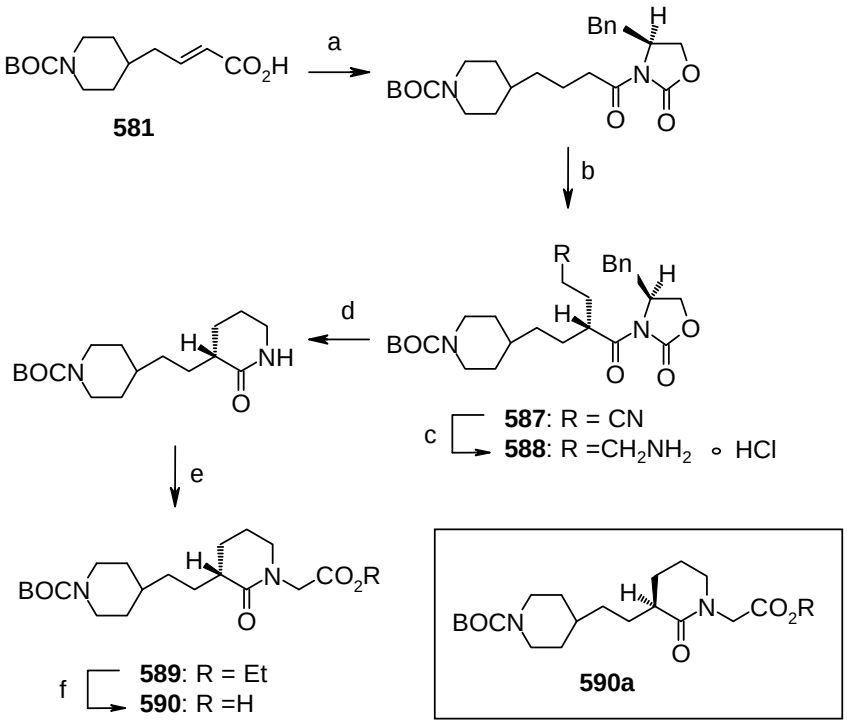
Scheme 124. Preparation of compound **579**.[40]

Duggan, Naylor-Olsen *et al.* have synthesized a potent and orally active fibrinogen receptor antagonist, compound **594** (L-734,217).[37]



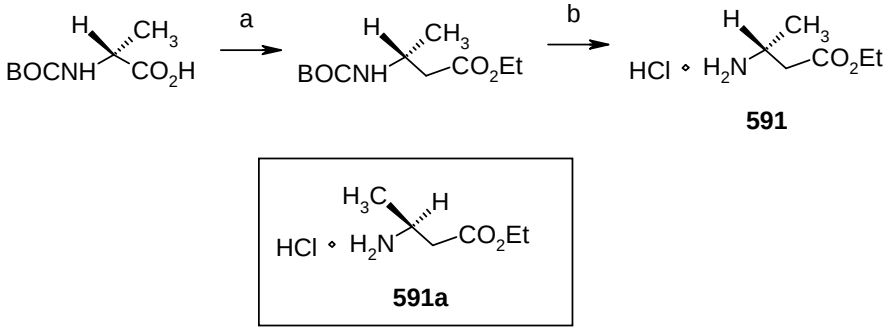
(a) Boc_2O, DMF; (b) Swern oxidation, then (carbethoxymethylene)triphenylphosphorane; (c) 10% Pd/c, H_2, EtOAC; (d) 1 N NaOH, ethanol; (e) EDC, HOBT, Net_3, DMF; (f) TFA/CH_2Cl_2.

Scheme 125.[41] Synthesis of compound **586**.



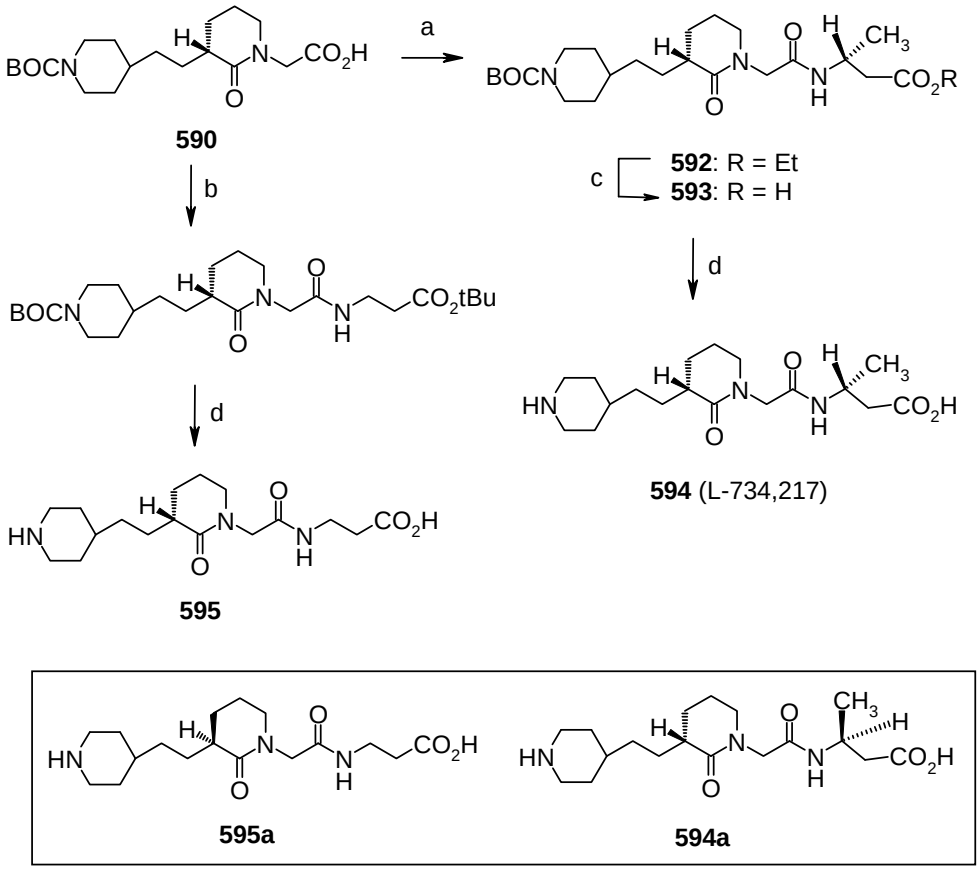
(a) Pivaloyl chloride, THF, Net_3, (*S*)-4-benzyl-2-oxazolidinone; (b) Ti(O-*I*-Pr)Cl_3, *I*-Pr_2EtN, CH_2Cl_2, acrylonitrile; (c) PtO_2, H_2, $CH_3OH/CHCl_3$; (d) $NaHCO_3$; CH_3CN; (e) NaHMDS, THF, ethyl bromoacetate; (f) 1 N NaOH, CH_3OH.

Scheme 126.[41] Synthesis of intermediate **590**.



(a) Isobutyl chlorofoormate, EtOAc, NMM, diazomethane, then silver benzoate, Net_3, MeOH; (b) EtOAc, HCl.

Scheme 127.[41] Synthesis of compound **590**.

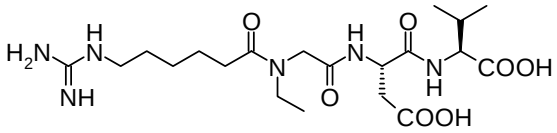


(a) EDC, HOBT, Net_3, DMF, **591** or **591a**; (b) EDC, HOBT, Net_3, DMF, *β*-alanine *tert*-butyl ester; (c)1 N NaOH, CH_3OH; (d) TFA/CH_2Cl_2.

Scheme 128.[41] Synthesis of compounds **594** and **595**.

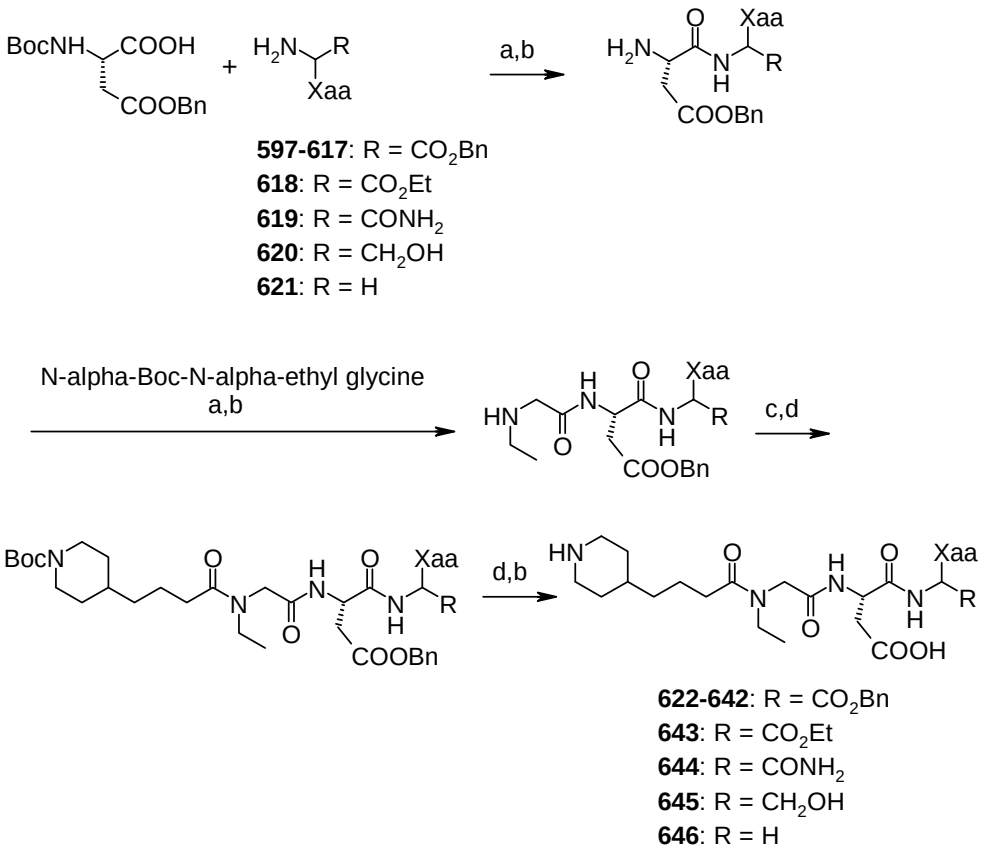
Compound **594** shows 2-3-fold more potency at *in vitro* platelet aggregation than compound **595**, but diastereomer **594a** 10-fold less than compound **595**.[41]

Klein *et al.* have synthesized a series of compounds with excellent *in vitro* potency for inhibiting platelet aggregation, excellent selectivity, a high oral activity and extended duration of action, based on lead compound **596**, the most potent being compound **628**.[38]



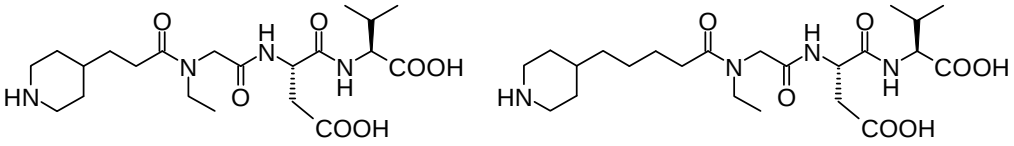
596

Figure 41.[42] Lead compound **596**.



(a) Isopropyl chloroformate, *N*-methylpiperidine, CH_2Cl_2, rt, 16 h, 80-90%; (b) 1:3 TFA/ CH_2Cl_2, 0 ºC, 2 h, then saturated $NaHCO_3$, 100%; (c) 6-guanidinohexanoic acid (for **622**), *N*-α-Boc-3-(4-piperidinyl)-propionic acid (for **623**), *N*-α-Boc-4-(4-piperidinyl)propionic acid (for **624** and **626-646**), *N*-α-Boc-5-(4-piperidinyl)propionic acid (for **625**); (d) BOP-Cl, Net_3, CH_2Cl_2, 0 ºC, 14 h, 70-80%; (e) H_2, 25 wt-% 10 % Pd/C, 9:1 MeOH/AcOH, 55 psi, 24 h, 95%.

Scheme 129. Synthesis of compounds **622-646**.[42]

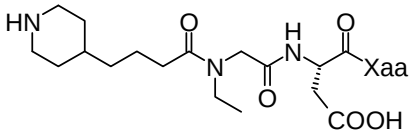


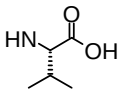
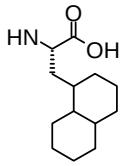
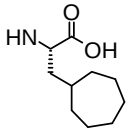
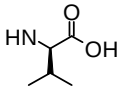
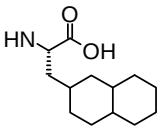
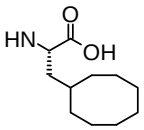
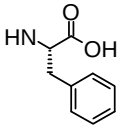
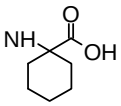
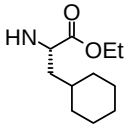
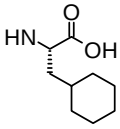
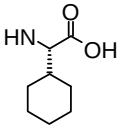
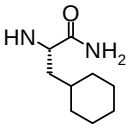
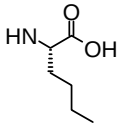
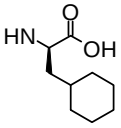
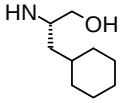
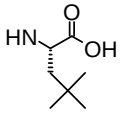
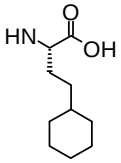
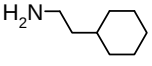
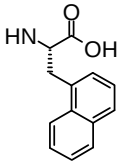
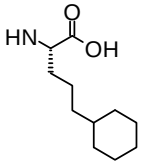
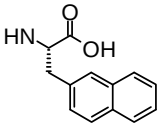
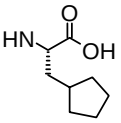
623 **625**

Figure 42.[42] Compounds **623** and **625**.

Compounds **623** and **625** show considerable less potency than compound **624** implying the optimal chain length to be three carbons. Klein *et al.* also conclude that both the replacement of guanidine by piperidine and alkylation of the glycine nitrogen are needed to improve the oral activity of the parent peptide, as demonstrated in compound **624**.[42]

Table 34.[42] The substituents of compounds **624** and **626-646**.



Compd	Xaa	Compd	Xaa	Compd	Xaa
624		**633**		**641**	
626		**634**		**6342**	
627		**635**		**643**	
628		**636**		**644**	
629		**637**		**645**	
630		**638**		**646**	
631		**639**			
632		**640**			

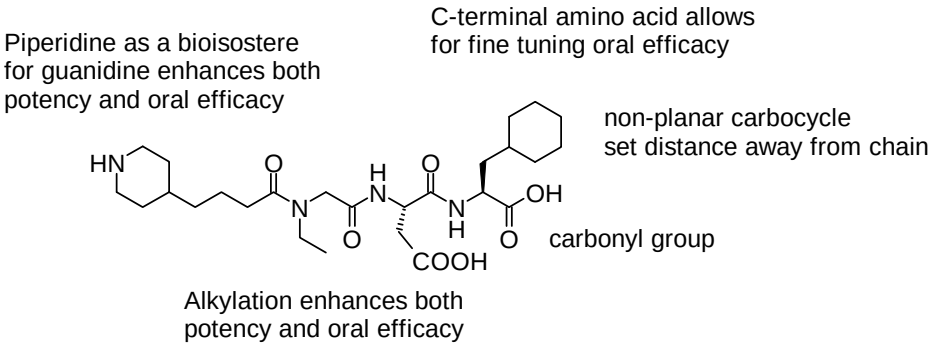
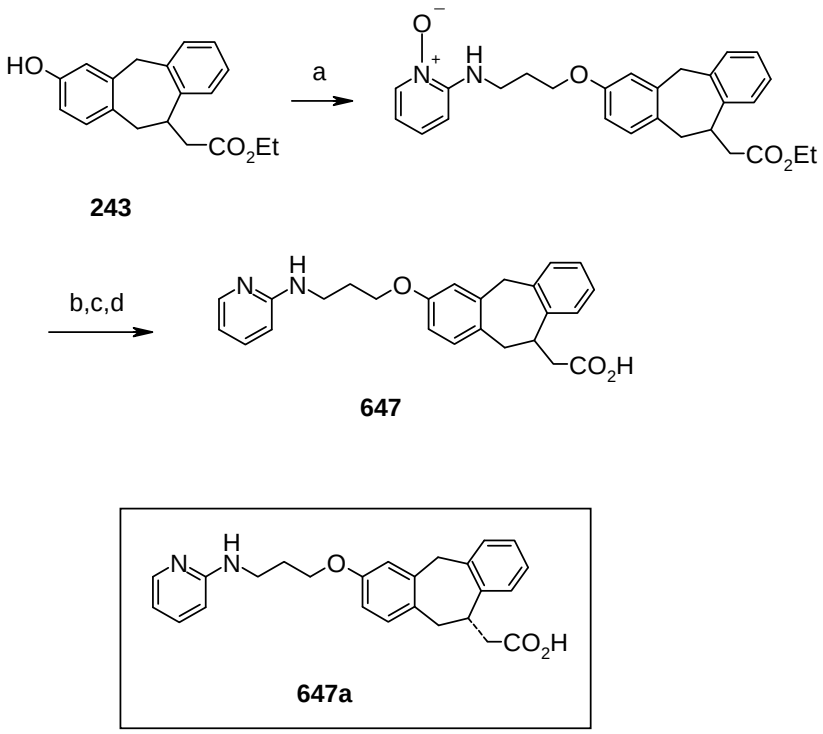


Figure 42. Structure-oral activity relationships for peptide-based fibrinogen receptor antagonists.[42]

11 Other pyridine compounds

See also Schemes 36 and 37 (3.2), Table 14 (6), compound **511i** in Table 32 (10.1) and compounds **535a-b** in Table 32 (10.1).

Miller *et al.* have synthesized a selective $\alpha_V\beta_3$ antagonist, compound **647**. The (*S*)-enantiomer **647a** proved to be over 100-fold more active than the (*R*)-enantiomer.[17]



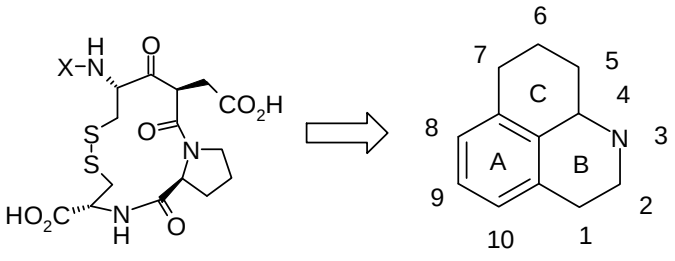
(a) 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, DEAD, Ph_3P, DMF (75%); (b) cyclohexene, 10% Pd/C, *i*-PrOH, reflux (63%); (c) 1.0 N NaOH, EtOH, 50 ºC; (d) 1.0 N HCl, H_2O (79% for two steps).

Scheme 130. Synthesis of compound **647**. [17]

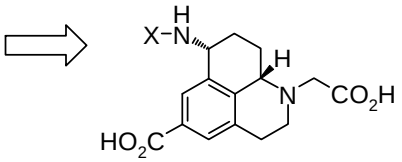
12 Tricyclic compounds

See also Schemes 10 and 11 (2.1).

Ho *et al*. have synthesized two tricyclic tetrahydrobenzo[ij]quinolines, weakly active integrin $\alpha_{Iv}\beta_1$ antagonists (compounds **663** and **665**) based on the LDV sequence on the CS-1 fragment of the integrin. The syntheses were done using a Bischler-Napieraski reaction and Friedel-Crafts cyclization via an epoxide.[39]

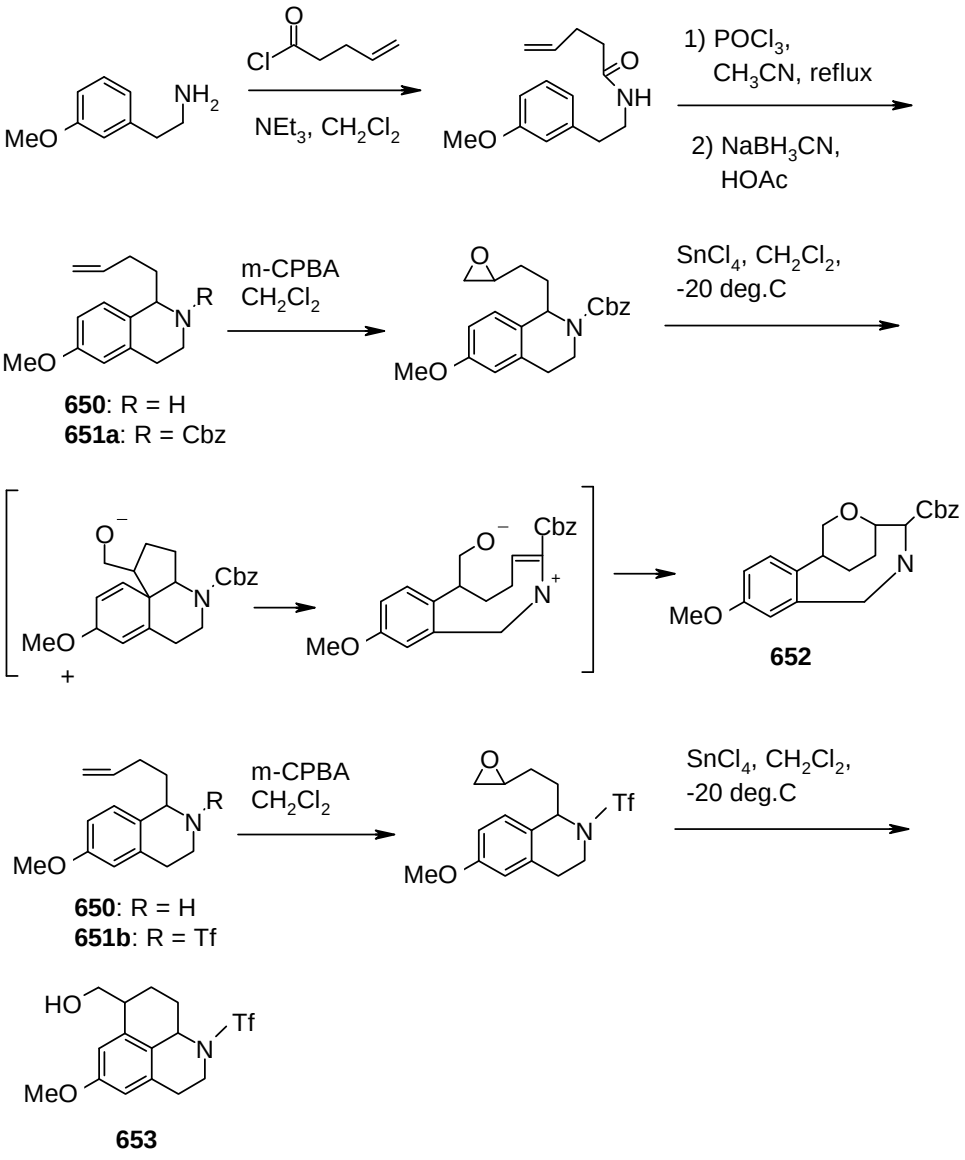


648

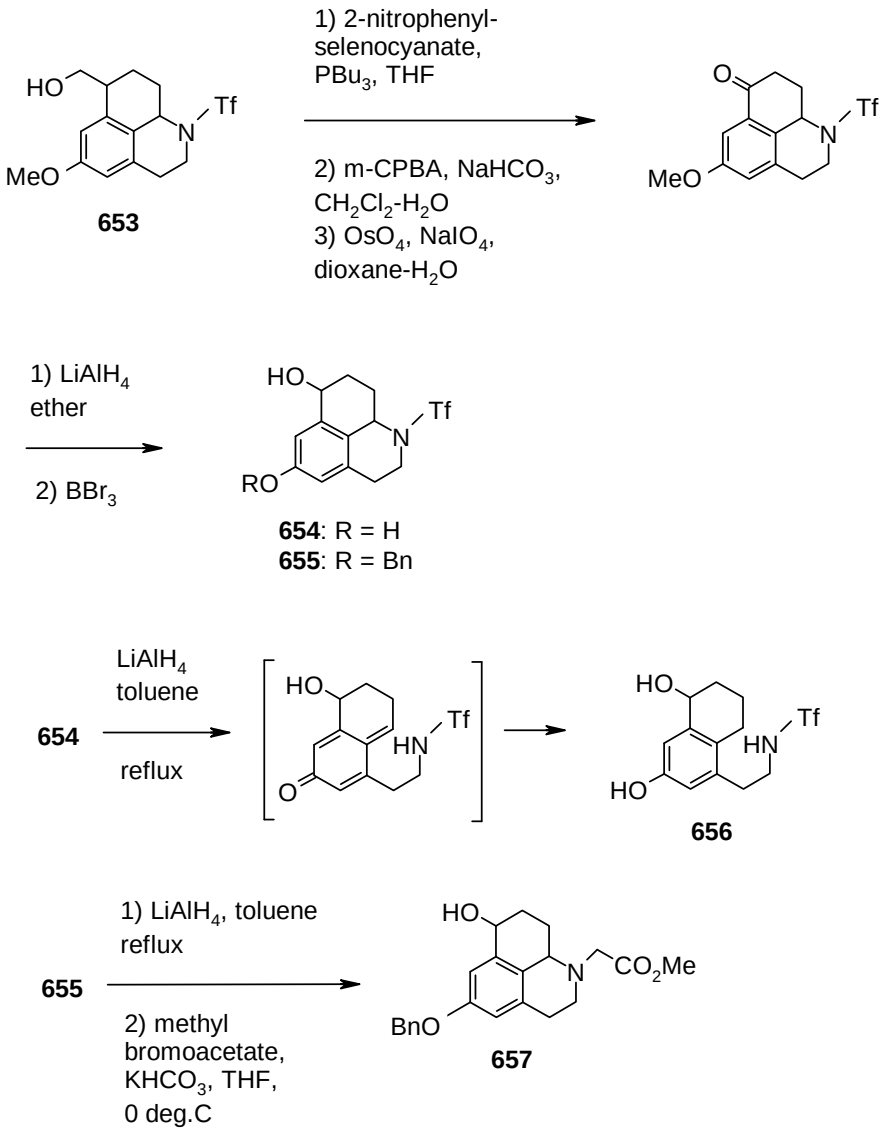


649

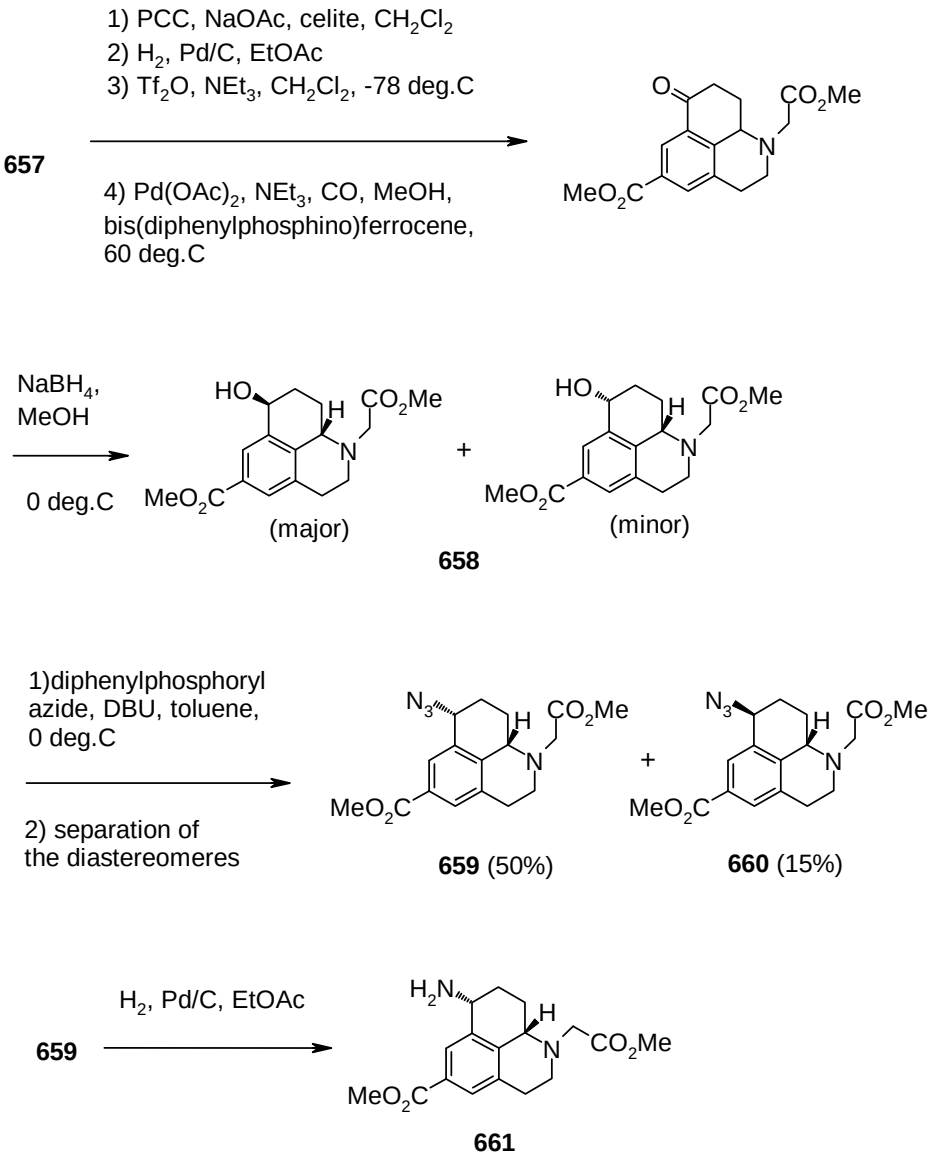
Scheme 131.[43] Lead compound **648** and tricyclic VLA-4 antagonist **649**.



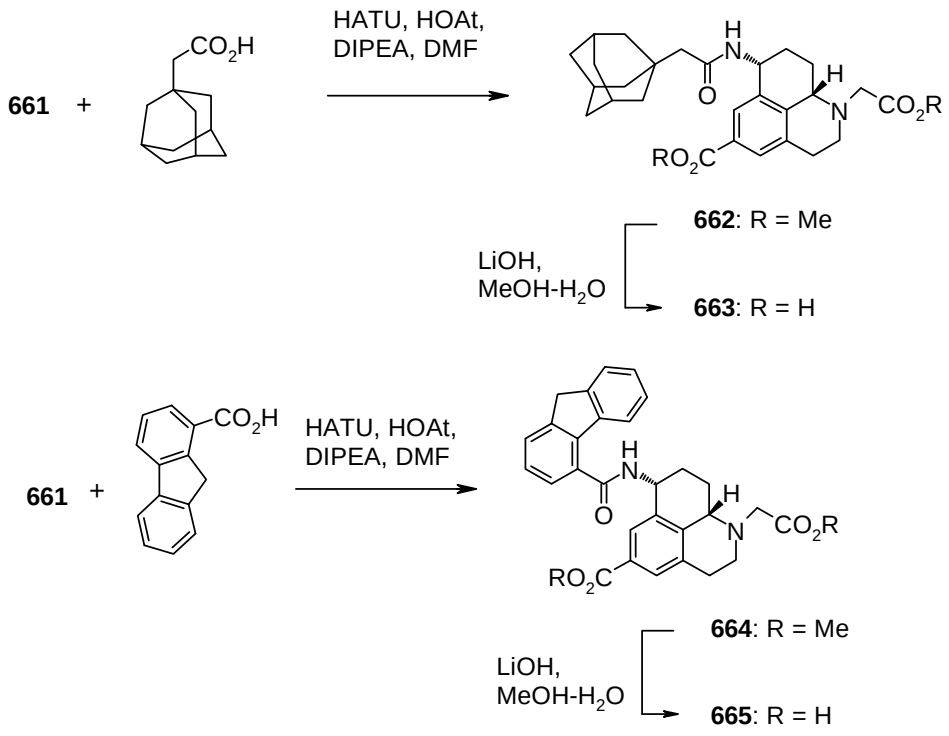
Scheme 132.[43] Synthesis of intermediate **653**.



Scheme 133.[43] Synthesis of compound **657**.



Scheme 134.[43] Synthesis of compound **661**.



Scheme 135.[43] Synthesis of compounds **663** and **665**.

13 Summary

Most of the research conserning non-peptide integrin inhibitors is focused on the RGD (Arg-Gly-Asp) sequence which is recognized by the platelet fibrinogen receptor $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) and the vitronectin receptor $\alpha_V\beta_3$.[5]

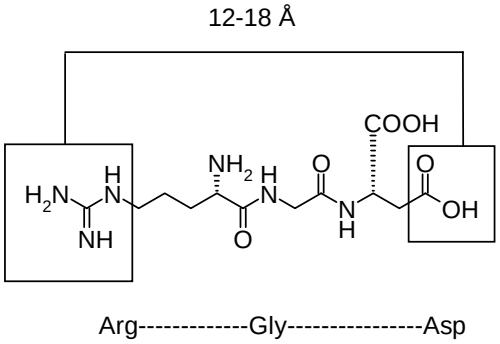


Figure 1.[1] RGD sequence.

The RDG sequence plays a key part in aggregation of platelets causing vaso-occulsive disorders such as unstable angina, myocardial infarction, transient ischemic attacks, stroke and thrombosis ($\alpha_{IIb}\beta_3$).[32,36] Also, it's involved in osteoclast-mediated bone resorption - $\alpha_V\beta_3$ is present in osteoclasts but not bone forming osteoblasts.[39]

The less studied $\alpha_{IV}\beta_1$, VLA-4 (very late antigen 4) found in stimulated monocytes and lymphnotes binds to cytokine-activated endothelial cells and to fibronectin causing diseases such as asthma and multiple sclerosis.[43]

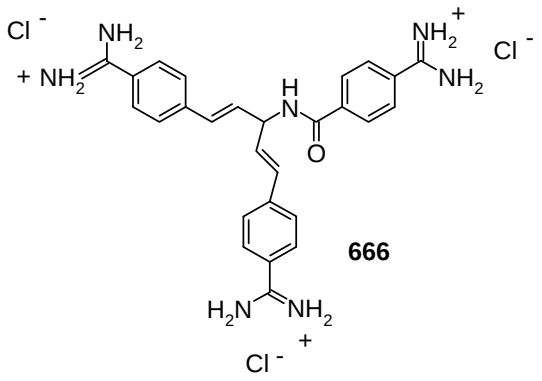
When evaluating the potency of non-peptide GPIIb/IIIa inhibitors tricyclic form seems to be favoured over tetracyclic form.[3]

Lipophilic substituents at α or β to the carboxylate moiety often result in increased potency.[8,20] Aliphatic or aromatic residues are favorable compared to carboxy terminal serine.[13] Benzamide and piperidine groups are highly beneficial N-terminal substituents, with benzamide having the positive charge localized on two nitrogens allowing for favorable electrostatic interactions with a negatively charged receptor site.[29]

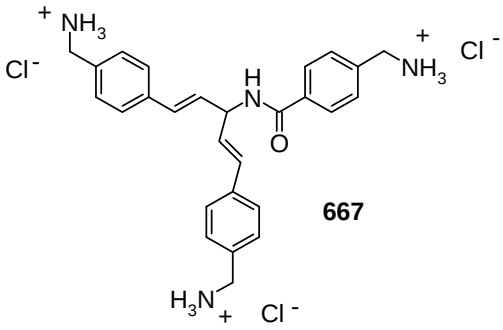
EXPERIMENTAL SECTION

14 Preface

The aim of the experimental work was to synthesize a potential nonpeptide inhibitor for the integrin $\alpha_{II}\beta_1$. Twelve target molecules (fig. 43, molecules **666-677**) were designed by professor Kari Rissanen based on the information gathered by Bio-Tie Therapies.



666



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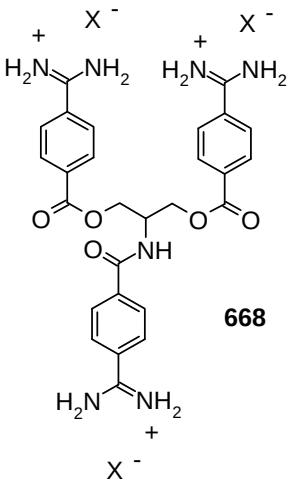

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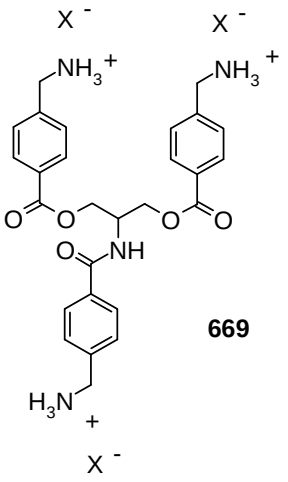
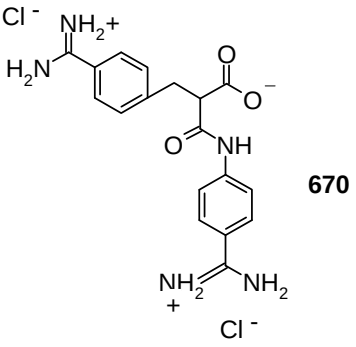


669



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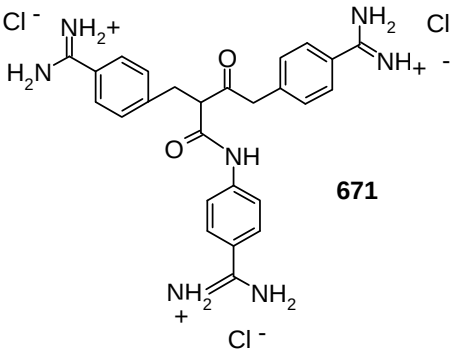

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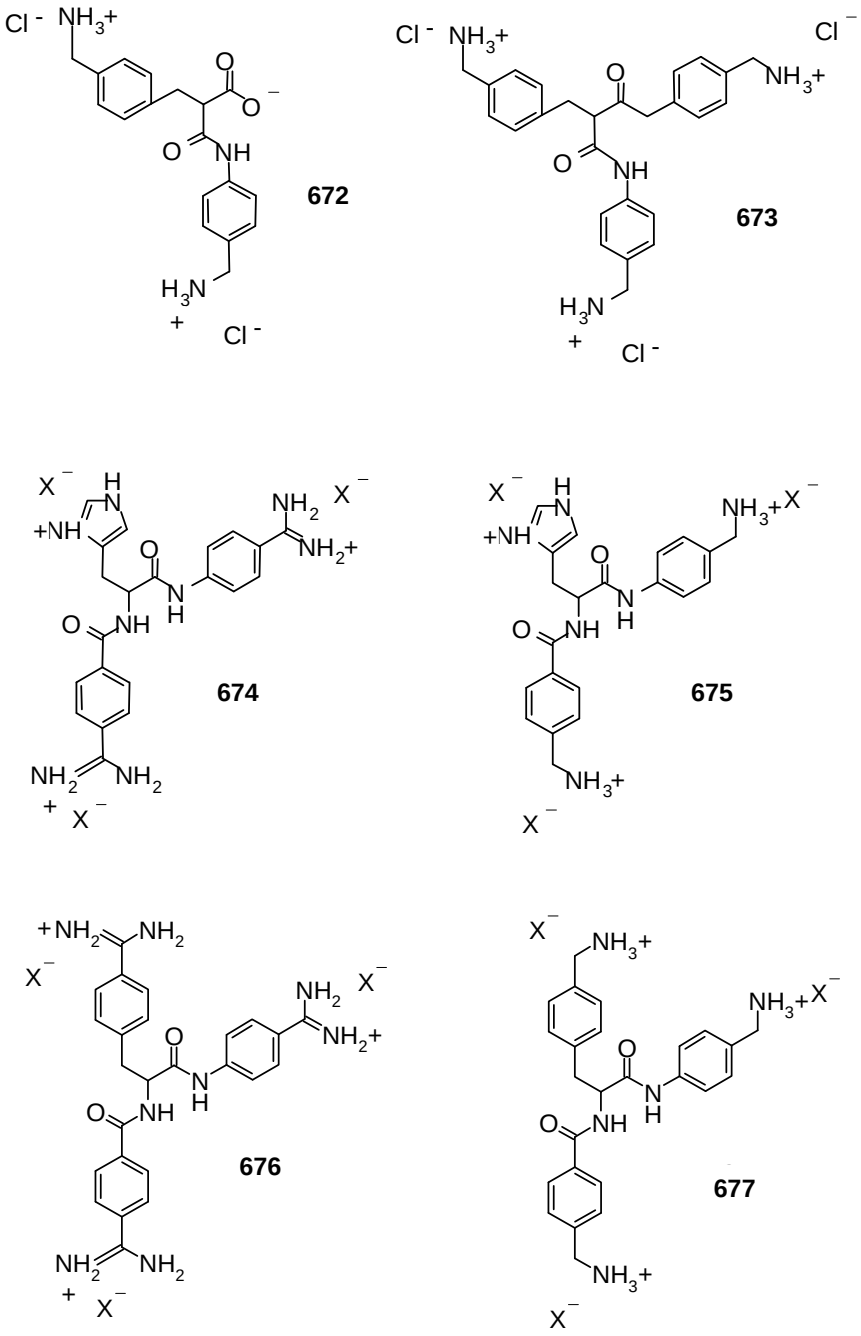


Figure 43. The target molecules.

Molecules **666-669. 671, 673, 676** and **677** showed binding potential on a computer model of the integrin $\alpha_{II}\beta_1$ due to their suitable size, flexibility and three branches with negative charges. Molecules **674** and **675** showed some binding potential.

15 The plan for synthesis

The plan was to try to synthesize as many of the target molecules as possible by constructing a neutral molecule of smaller molecules and then reducing it. Due to the limited time the syntheses of only molecule **669** and modified versions of molecules **673** and **677** were attempted.

First, the reduction reaction was to be tested on the small molecule **680** with a cyano group and an ester bond in order to see whether the ester bond would tolerate the conditions without breaking.

16 The syntheses

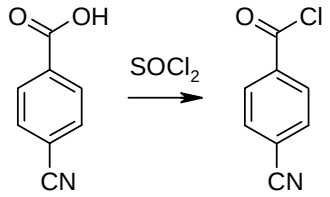
16.1 The synthesis of target molecule 669

16.1.1 4-Cyanobenzoyl ethyl ester 680

The synthesis was done by following the synthesis route for ethylvinyl acetate[40].

16.1.1.1 4-Cyanobenzoyl chloride 679

Since the 4-cyanobenzoyl chloride needed as a starting material was in an opened container an ^{1}H NMR spectrum was obtained. According to the spectrum some of the chloride had turned into its acid form. It was estimated that the acid / acid chloride ratio in the starting material was 1:1.

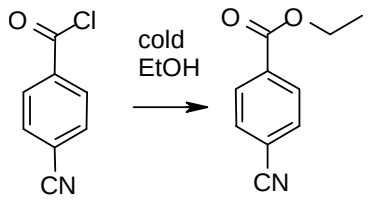


678 **679**

Scheme 136. The synthesis of 4-cyanobenzoyl chloride **679**.

A two-necked flask is equipped with a reflux condenser and a gas trap. Approximately 20 mL $SOCl_2$ is heated gently in the flask on a water bath with stirring and 1.29 g (8.28 mmol) acid **678** / acid chloride **679** mixture is added during 30 minutes. The mixture is heated gently for 30 minutes. The liquid is removed by a rotatory evaporator. The yield is 1.45 g (8.74 mmol).

16.1.1.2 4-Cyanobenzoyl ethyl ester 680



679 **680**

Scheme 137. The synthesis of 4-cyanobenzoyl ethyl ester **680**.

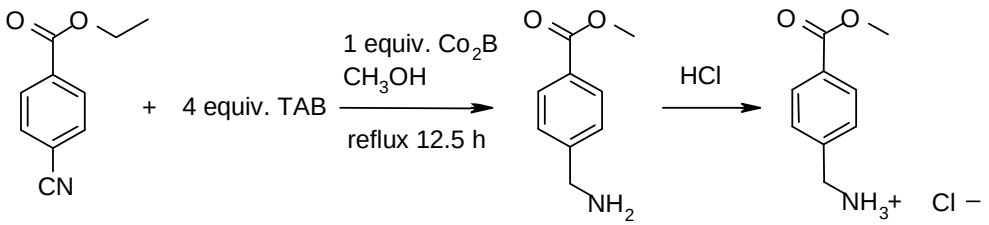
Approximately 30 mL abs. ethanol is cooled on ice. All of the acid chloride **679** from 3.1.1.1 is added slowly with stirring. The ice bath is removed and the mixture is allowed to stand for 1 h. The liquid is removed by a rotatory evaporator. The yield is 1.37 g (7.8 mmol).

^{1}H NMR (AC-d6): δ = 8.19-8.17 (m, 2H), 7.95-7.92 (m, 2H), 4.42-4.38 (m, 2H), 2.78 (s, 1H), 1.41-1.37 (m, 3H) ppm.

^{13}C NMR (AC-d6): δ = 206.30, 206.15, 205.99, 165.56, 135.40, 133.45, 130.92, 118.72, 117.16, 62.40, 30.47, 30.38, 30.32, 30.27, 30.17, 30.07, 29.92, 29.77, 29.61, 29.46, 14.55 ppm.

16.1.2 *p*-Ethyl ester benzyl amine 682'

16.1.2.1 *p*-Methyl ester benzyl amine 681'



680 **681'** **681**

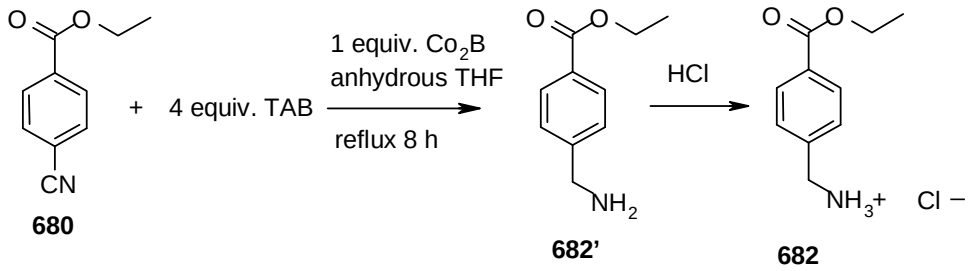
Scheme 138. The synthesis of *p*-methyl ester benzyl amine[41] **681'** and its chloride salt **681**.

Approximately 50 mL methanol, 0.37 g (2.89 mmol) Co_2B, 1.00 g (11.52 mmol) TAB and 0.50 g (2.85 mmol) 4-cyanobenzoyl ethyl ester **680** are refluxed with stirring for 12.5 h. The liquid is removed by a rotatory evaporator. The amine **681'** is extracted with approximately 50mL $CHCl_3$ and the solid removed by filtering.

The amine is extracted from the chloroform as an ammonium salt **681** by using 2 M HCl. The acidic solution is made basic with 2 M NaOH and the amine removed by filtering. The yield is 0.01 g. A mixture of products is obtained possibly due to intermolecular bonding.

The basic solution from 3.1.2.1 is condensed to 30 mL and made acidic with HCl in order to transform the possibly present **681'** into an ammonium chloride. The solution is evaporated with a rotatory evaporator. No desired product is present.

16.1.2.2 *p*-Ethyl ester benzyl amine 682' in anhydrous THF



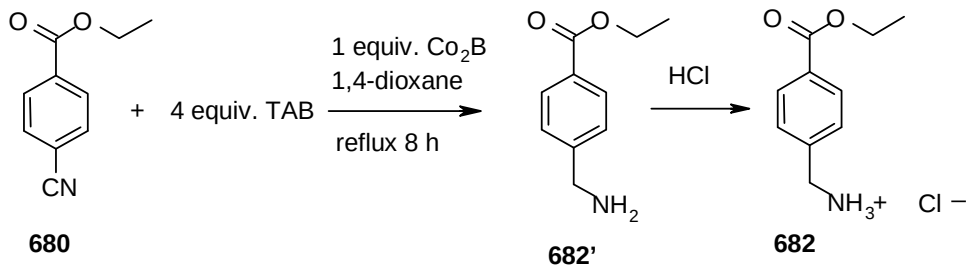
Scheme 139. The synthesis of *p*-ethyl ester benzyl amine **682'** in anhydrous THF and its chloride salt **682**.

0.29 g (2.28 mmol) Co_2B, 0.69 g (8.00 mmol) TAB and 0.38 g (2.20 mmol) ester **680** are ground to a powder and added to a flask containing 40 mL anhydrous THF. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator. The product is extracted with 40 mL $CHCl_3$ and the solid removed by filtering.

Extraction with HCl: 3 mL of 2 M HCl is diluted with water to 35 mL which is then used to extract the $CHCl_3$ solution. The solution is evaporated with a rotatory evaporator.

The yield is 1.33 g. No desired product is detected.

16.1.2.3 *p*-Ethyl ester benzyl amine 682' in 1,4-dioxane



680 **682'** **682**

Scheme 140. The synthesis of *p*-ethyl ester benzyl amine **682'** in 1,4-dioxane and its chloride salt **682**.

0.29 g (2.28 mmol) Co_2B, 0.70 g (7.99 mmol) TAB and 0.39 g (2.20 mmol) ester **680** are ground to a powder and added to a flask containing 40 mL 1,4-dioxane. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator. The product is extracted with 40 mL $CHCl_3$ and the solid removed by filtering.

Extraction with HCl: 3 mL of 2 M HCl is diluted with water to 35 mL which is then used to extract the $CHCl_3$ solution. The solution is evaporated with a rotatory evaporator.

The yield is 1.24 g.

The removal of *tert*-butyl ammonium chloride from the solid is attempted by dissolving the possible desired product **682** in $CHCl_3$:

The solid is added to 40 mL $CHCl_3$. The solution is stirred and let stand for a while. The remaining solid is removed by filtering and the cloudy $CHCl_3$ solution evaporated with a rotatory evaporator. The result is a fine white powder.

The yield is 0.08 g. No desired product detected.

16.1.2.4 *p*-Ethyl ester benzyl amine 682' in anhydrous THF

The attempted synthesis route is the same as in 16.1.2.2 (scheme 139).

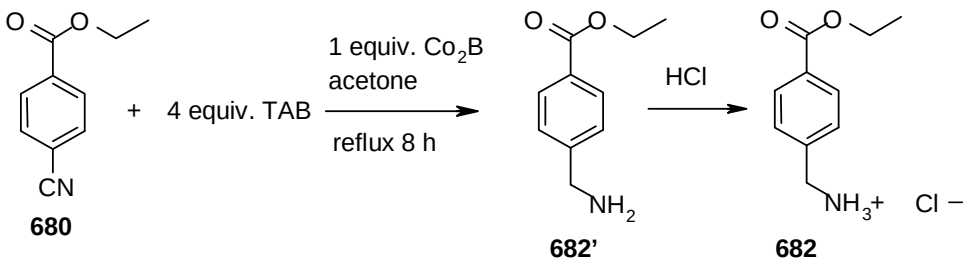
0.64 g (5.00 mmol) Co_2B, 1.74 g (20.00 mmol) TAB and 0.88 g (5.00 mmol) ester **680** are ground to a powder and added to a flask containing 80 mL anhydrous THF. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator. The product is extracted with 90 mL $CHCl_3$ and the solid removed by filtering.

Extraction with 2 M HCl. The solution is made slightly basic (pH 8) with 2 M NaOH. Some white solid is formed.

The solution is concentrated to one half using a rotatory evaporator and filtered with suction. All of the solid remains in the pores of the filter and the change in mass isn't registered by the scale.

50 mL $CHCl_3$ is added to the filtrate for possible extraction. After filtering the solution is evaporated with a rotatory evaporator. No solid remains in the flask.

16.1.2.5 *p*-Ethyl ester benzyl amine 682' in acetone



680 **682'** **682**

Scheme 141. The synthesis of *p*-ethyl ester benzyl amine **682'** in acetone and its chloride salt **682**.

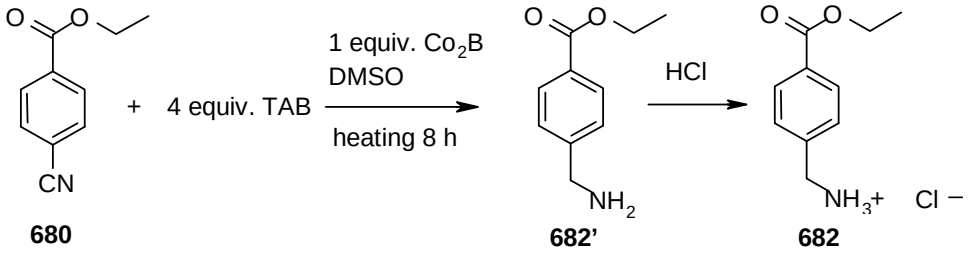
0.64 g (5.00 mmol) Co_2B, 1.74 g (20.02 mmol) TAB and 0.88 g (5.00 mmol) ester **680** are ground to a powder and added to a flask containing 80 mL acetone. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator. A black syrup-like residue remains.

Extraction with 90 mL $CHCl_3$ (the residue is dissolved), the solid is removed by filtering with suction (very slow). The solution is golden brown.

Extraction with 70 mL 2 M HCl. The $CHCl_3$-layer is coffee-colored, the HCl-layer golden brown.

The experiment is discontinued due to the fact that the formation of the desired product is highly unlikely.

16.1.2.6 *p*-Ethyl ester benzyl amine 682' in DMSO



680 **682'** **682**

Scheme 142. The synthesis of *p*-ethyl ester benzyl amine **682'** in DMSO and its chloride salt **682**.

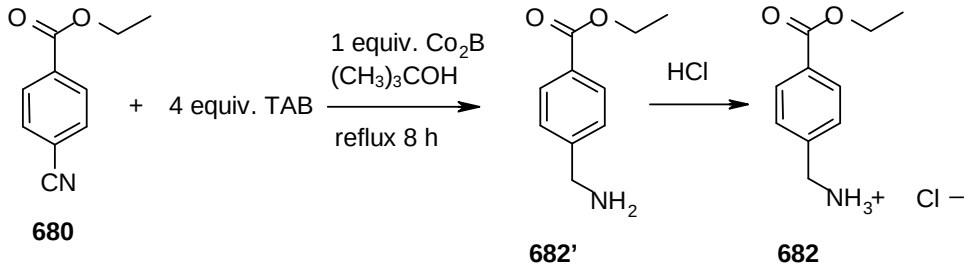
0.64 g (5.00 mmol) Co_2B, 1.74 g (20.01 mmol) TAB and 0.88 g (5.01 mmol) ester **680** are ground to a powder and added to a flask containing 80 mL DMSO. The mixture is heated (95ºC) in an oil bath with stirring for eight hours. The DMSO is removed by vacume distillation. The residue is a black and white powder.

Extraction with 90 mL $CHCl_3$ (most of the residue isn't dissolved), the solid is removed by filtering. The solution is turquoise.

Extraction with 2 M HCl. The $CHCl_3$-layer turns yellowish and cloudy, the HCl-layer is pink.

The HCl solution is made slightly basic (pH 8) with 2M NaOH. The purple solid is removed by filtering. The yield is 0.19g. The presence of the desired product is highly unlikely.

16.1.2.7 *p*-Ethyl ester benzyl amine 682' in *tert*-butanol



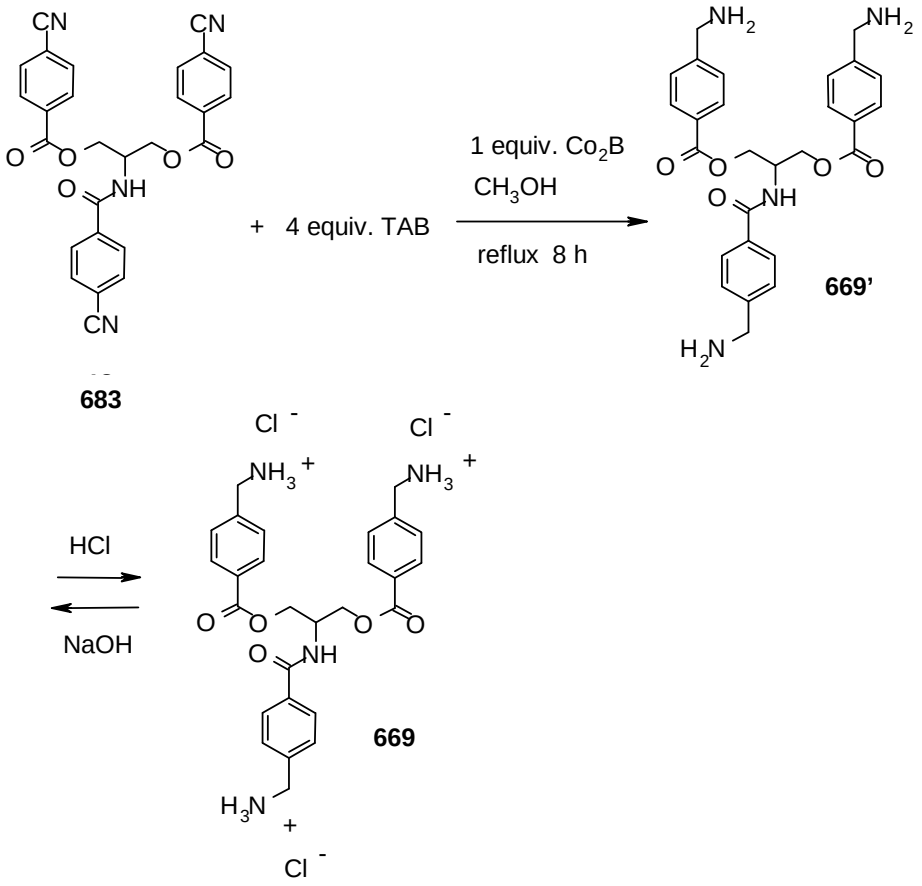
Scheme 143. The synthesis of *p*-ethyl ester benzyl amine **682'** in *tert*-butanol and its chloride salt **682**.

0.37 g (2.86 mmol) Co_2B, 1.00 g (11.46 mmol) TAB and 0.51 g (2.91 mmol) ester **680** are ground to a powder and added to a flask containing 50 mL *tert*-butanol. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator.

Extraction with 50 mL $CHCl_3$.The solid is removed by filtering with suction after ½ h. Extraction with 2 M HCl. The $CHCl_3$-layer is cloudy, the HCl-layer clear.

The HCl solution is made slightly basic (pH 8) with 2M NaOH. A small amount of white solid is formed. The solution is allowed to evaporate overnight to a half. The solid is removed by filtering. The presence of the desired product is highly unlikely.

16.1.3 Target molecule 669 in methanol



Scheme 144. The attempted synthesis of triamine **669'** in methanol and its chloride salt, target molecule **669**.

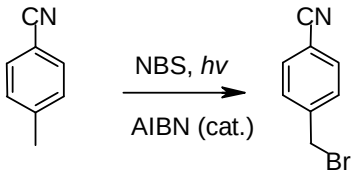
0.43 mmol (0.06 g) Co_2B, 1.68 mmol (0.15 g) TAB and 0.43 mmol (0.20 g) diester **683** are ground to a powder and added to a flask containing 20 mL CH_3OH. The mixture is refluxed in an oil bath with stirring for eight hours. The solution is evaporated with a rotatory evaporator.

Extraction with 20 mL $CHCl_3$.The solid is removed by filtering with suction after ½ h. Extraction with 6 mL 2 M HCl. Both the $CHCl_3$-layer and the HCl-layer are cloudy.

The HCl solution is made slightly basic (pH 8) with 2 M NaOH. The solution is allowed to evaporate overnight to a half. The solid is removed by filtering with suction. The presence of the desired product is highly unlikely.

16.2 The synthesis of a modified version 688 of target molecule 673

16.2.1 4-Cyano benzyl bromide 685



684 **685**

Scheme 145. The synthesis of 4-cyano benzyl bromide **685** in NBS.[42]

a) 20 mL CCl_4, 1.01 g (8.61 mmol) *p*-tolunitrile **684** and 1.52 g (8.54 mmol) NBS in a two-necked flask are brought to a gentle reflux in an oil bath with stirring. The oil bath is removed and a 100 W light bulb aimed at the solution. Some AIBN is added quickly and the apparatus covered in tin foil. The refluxing stops. After three hours the white solution turns bright orange. The reaction is stopped after 4.5 h total. The solution has turned white. The solution is immediately filtered with suction and evaporated with a rotatory evaporator. The yield is 1.39 g.

^{1}H NMR ($CDCl_3$): δ = 8.00-7.96 (d, 1H), 7.85-7.80 (d,1H), 7.67 (s, 1H), 7.63-7.59 (d, 2H), 7.55 (s, 1H), 7.50-7.47 (d,2H), 7.27-7.25 (t, 1H), 6.62 (s, 1H), 4.48 (s, 2H), 2.42 (s,1H), 1.72 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$): δ = 146.07, 143.62, 142.78, 132.83, 132.51, 131.98, 129.81, 129.77, 129.65, 127.34, 118.27, 117.77, 113.49, 112.15, 109.27, 77.51, 77.21, 77.00, 76.49, 68.12, 38.66, 31.41, 25.09, 21.76 ppm.

b) The experiment is repeated using 40 mL CCl_4, 3.00 g (25.62 mmol) *p*-tolunitrile and 5.01 g (28.17 mmol) NBS. The reaction is stopped after 3.5 h. The solution is immediately filtered with suction and evaporated with a rotatory evaporator.

40 mL $CHCl_3$ is added to dissolve the solid. The solution is washed with water, saturated $NaHCO_3$ and water, then evaporated with a rotatory evaporator. The yield is 4.97 g.

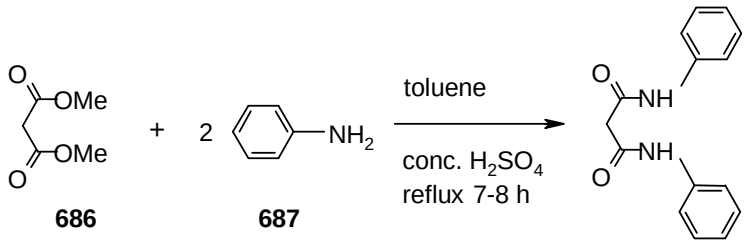
^{1}H NMR ($CDCl_3$): δ = 7.98 (s, 1H), 7.65-7.62 (d, 2H), 7.55 (s, 1H), 7.55-7.48 (d, 2H), 7.28-7.25 (t, 1H), 6.63 (s, 1H), 2.41 (s, 1H), 1.72 (s, 1H), 1.54 (s, 1H) ppm.

The solids obtained from the two experiments are combined and dissolved in 50 mL $CHCl_3$. The solution is dried with Na_2SO_4 and evaporated with a rotatory evaporator.
50 mL toluene is added to the flask which is heated to dissolve all of the solid. The solution is allowed to cool. No crystallization perceptible.

Half of the toluene is removed by distillation, still no crystallization perceptible. The solution is refridgerated overnight and the powdery white solid removed by filtering with suction. The yield is 2.26 g (11.53 mmol).

^{1}H NMR ($CDCl_3$): δ = 7.68 (s, 1H), 7.65-7.62 (d, 2H, 7.51-7.48 (d, 2H), 4.47 (s, 2H) ppm.

16.2.2 Malonyl dianilide 688



686 **687** **688**

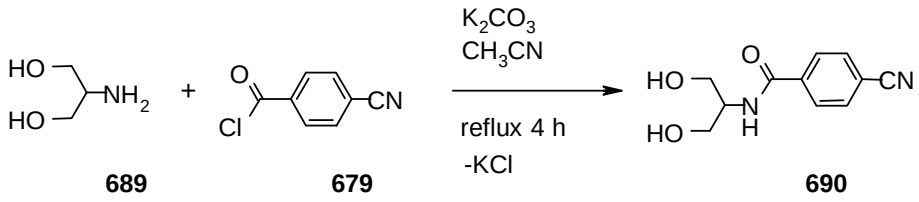
Scheme 146. The synthesis of malonyl dianilide **688** in toluene.

A mixture of 50 mL dry toluene, 1.56 g (11.81 mmol) dimethyl malonate **686**, 2.42 g (25.99 mmol) anilin **687**and 3 drops H_2SO_4 in a flask is heated to 90ºC for 8 h. White solid is formed almost instantly.

The cooled mixture is filtered with suction. The yield is 0.46 g. The solid won't dissolve in H_2O, EtOH, MetOH, DMSO or acetone and only slightly in $CHCl_3$.
The filtrate is washed with water and dried with Na_2SO_4. The toluene is removed by distillation. A dark brown viscous liquid with some solid remains in the flask. The yield is 2.26 g. No desired product detected.

16.3 The synthesis of a modified version 691 of target molecule 677

16.3.1 *N*-(*p*-cyanobenzoyl)-2-amino-propan-1,3-diol 690



689 **679** **690**

Scheme 147. The synthesis of **690** in CH_3CN.

16.3.1.1 Serinol 689, K_2CO_3 and 4-cyanobenzoyl chloride 679 1:1:1

A mixture of 30 mL acetonitrile CH_3CN, 0.49 g (5.33 mmol) serinol **689** and 0.74 g (5.35 mmol) K_2CO_3 in a flask is heated with stirring in an oil bath. 0.86 g (5.35 mmol) 4-cyanobenzoyl chloride **679** in 20 mL acetonitrile is added slowly with a dropping funnel. The mixture is brought to a reflux for four hours.

The yellow solution is filtered and the filtrate evaporated with a rotatory evaporator. The yield is 1.12g (a syrup-like residue). No desired product detected.

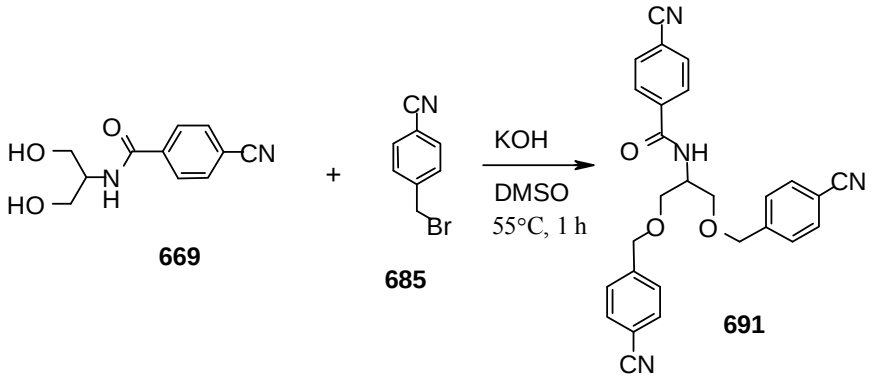
16.3.1.2 Serinol 689, K_2CO_3 and 4-cyanobenzoyl chloride 679 1:3:1, no heating

A mixture of 20 mL acetonitrile CH_3CN, 0.33 g (3.63 mmol) serinol **689** and 1.50g (10.87 mmol) K_2CO_3 in a flask is heated in an oil bath. 0.60 g (3.63 mmol) 4-cyanobenzoyl chloride **679** in 30 mL acetonitrile is added slowly with a dropping funnel. The mixture is stirred for 6½ h.

The white solution is filtered and the filtrate evaporated with a rotatory evaporator. The yield is 0.74 g (3.36 mmol, yellowish solid).
^{1}H NMR (CD_3OD): δ = 8.01-7.97 (d, 2H), 7.85-7.81 (d, 2H), 4.19-4.15 (m, 1H), 3.75-3.72 (d, 4H), 3.32-3.29 (m, 2H) ppm.

16.3.2 *N* -[2-(1,3-*p*-cyanobenzyloxy)]-*p*-cyanobenzoyl amine 691

The synthesis was attempted by way of alkylation of alcohols with an alkyl halide[43].



Scheme 148. The synthesis of **691** in DMSO.

16.3.2.1 Diol 690, 4-cyanobenzyl bromide 685 and KOH 1:2:4 in acetone

0.32 g (5.65 mmol) ground KOH and 3 mL acetone are stirred in a flask. KOH is partly dissolved. 0.30 g (1.36 mmol) diol **690** and 0.53 g (2.72 mmol) 4-cyanobenzyl bromide **685** are added. The mixture is stirred at 55ºC in a water bath for one hour, turning from yellow to brown. The acetone is removed with a rotatory evaporator.

50 mL water is added to the brown viscous residue. After stirring for ½ h the brown residue is partly dissolved. Extraction with 60 mL CH_2Cl_2, the residue is completely dissolved. The solution is washed with water, dried with Na_2SO_4 and evaporated with a rotatory evaporator. The yield is 0.51 g (a very viscous yellow liquid). No desired product detected.

16.3.2.2 Diol 690, 4-cyanobenzyl bromide 685 and KOH 1:4:8 in DMSO

0.61 g (10.90 mmol) ground KOH and 3 mL DMSO are stirred in a flask. 0.30 g (1.36 mmol) diol **690** and 1.07 g (5.45 mmol) 4-cyanobenzyl bromide **685** are added. The mixture is stirred at 55ºC in a water bath for one hour, turning from yellow to brown, then poured into 30 mL water. A gum-like residue remains on the magnet, the mixture turns yellow.

Extraction with 90 mL CH_2Cl_2. The solution is washed with water, dried with Na_2SO_4 and evaporated with a rotatory evaporator, leaving a yellow residue. The yield is 0.14 g. No desired product detected.

17 Summary

The aim was to synthesize a potential inhibitor for the integrin $\alpha_{II}\beta_1$. Twelve target molecules were designed. The plan was to try to synthesize as many of the target molecules as possible by constructing a neutral molecule of smaller molecules and then reducing it. Due to the limited time the syntheses of only molecule **669** and modified versions of molecules **673** and **677** were attempted.

The starting molecule 4-cyanobenzoyl ethyl ester **680** was synthesized successfully.

It was attempted to reduce the cyano group of the small molecule **680** (4-cyanobenzoyl ethyl ester) in order to see whether the ester bond would tolerate the conditions without breaking. The synthesis of *p*-ethyl ester benzyl amine **682'** was unsuccesfully attempted in anhydrous THF, 1,4-dioxane, acetone, DMSO and *tert*-butanol. A suitable solvent wasn't found and only mixtures of unwanted products were obtained. Due to the diminishing time left, syntheses of target molecules were started.

The synthesis of target molecule **669** failed due to the breaking up of the starting molecule **683**.

The synthesis of 4-cyano benzyl bromide **685**, a "building block" for a modified version **688** of target molecule **673**, was succesful but the synthesis of the other "building block", malonyl dianilide **688**, failed due to unwanted bonding.

The synthesis of diol **690**, a "building block" for a modified version **691** of target molecule **677**, was succesful after increasing the relative amount of K_2CO_3 and conducting the synthesis without heating. However, the synthesis of molecule **691** alternately in acetone and DMSO failed due to unwanted bonding.

Reagents and equipment

Table 34: The reagents used in the syntheses.

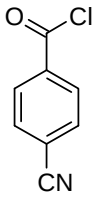
Reagent	Supplier	Purity
$SOCl_2$	Riedel-de Haën	≥ 98%
EtOH	Primalco	99.5%
4-cyanobenzoic acid	Aldrich	appr. 50% (orig. 98%)
Co_2B	K. Nättilä	
TAB	Aldrich	97%
CH_3OH	Riedel-de Haën	99.8%
$CHCl_3$	Riedel-de Haën	99.0-99.4%
HCl		2M
NaOH		2M
Na_2SO_4	Merck	≥ 99%
HCl	Riedel-de Haën	≥ 37%
THF		
1,4-dioxane		
$CHCl_3$	Riedel-de Haën	99.8%
acetone	Riedel-de Haën	p.a.
DMSO	Rathburn Chemicals LTD	HPLC grade
$(CH_3)_3COH$	Merck	p.a.
p-tolunitrile	Aldrich	98%
CCl_4	Merck	≥ 99.8%
NBS	Riedel-de Haën	98%
AIBN	Merck	
toluene		
dimethyl malonate	Aldrich	98%
anilin	Merck	p.a.
2-amino-1,3-propandiol (serinol)	Aldrich	98%
K_2CO_3		
CH_3CN	Mallinckrodt	HPLC grade

The equipment used for analyzing the products of the syntheses:

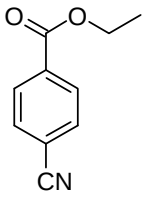
NMR spectrometers: Bruker Avance DPX 250 and Bruker Avance DRX 500.

MS spectrometer: VG AutoSpec HRMS spectrometer.

Synthesized molecules



679



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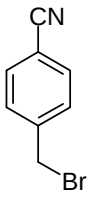
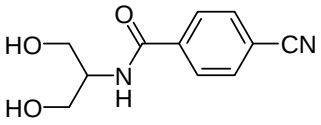


685



690

References

1. Harada, T.; Katada, J.; Tachiki, A.; Asari, T.; Iijima, K.; Uno, I.; Ojima, I.; Hayashi, Y. *Bioorg. Med. Chem.* **1997**, *7*, 209-212.

2. Ku, T. W.; Ali, F. E.; Barton, L. S.; Bean, J. W.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, L.; Eggleston, D. S.; Gleason, J. G.; Huffman, W. F.; Hwang, S. M.; Jakas, D. R.; Karash, C. B.; Keenen, R. M.; Kopple, K. D.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Peishoff, C. E.; Samanen, J. M.; Uzinskas, I.; Venslavsky, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8861-8862.

3. Robarge, K. D.; Dina, M. S.; Somers, T. C.; Lee, A.; Rawson, T. E.;Olivero, A. G.; Tischler, M. H.; Webb, II, R. R.; Weese, K. J.; Aliagas, I.; Blackburn, B. K. *Bioorg. Med. Chem.* **1998**, *6*, 2345-2381.

4. Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717-729.

5. Keenan, R. M.; Miller, W. H.; 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.

6. Samanen, J. M.; Ali, F. E.; Barton, L. S.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, W.; Chen, L.; Erhard, K.; Feuerstein, G.; Heys, R.; Hwang, S.-M.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Kwon, C.; Lee, C.-P.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M.; Peishoff, C. E.; Rhodes, G.; Ross, S.; Shu, A.; Simpson, R.; Takata, D.; Yellin, T. O.; Uszinskas, I.; Venslavsky, J. W.; Yuan, C.-K.; Huffman, W. F. *J. Med. Chem.* **1996**, *39*, 4867-4870.

7. Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P.J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J.W.; Yuan, C. C.-K.; Haltiwanger, R. C.; Gawen, M.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22-26.

8. Xue, C.-B.; Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Batt, D. G.; Cain, G. A.; Sworin, M.; Rockwell, A. L.; Roderick, J. J.; Wang, S.; Orwat, M. J.; Frietze, W. E.; Bostrom, L. L.; Liu, J.; Higley, A.; Rankin, F. W.; Tobin, A. E.; Emmett, G.; Lalka, G. K.; Sze, J. Y.; Di Meo, S. V.; Mousa, S. A.; Thoolen, M. J.; Racanelli, A. L.; Hausner, E. A.; Reilly, T. M.; DeGrado, W. F.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 2064-2084.

9. Wityak, J.; Tobin, A. E.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 123-126.

10. Xue, C.-B.; Roderick, J.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499-3504.

11. Gante, J.; Juraszyk, H.; Raddatz, P.; Wurziger, H.; Bernotat-Danielowski, S.; Melzer, G.; Rippmann, F. *Bioorg. Med. Chem.* **1996**, *6*, 2425-2430.

12. Pitts, W. J.; Wityak, J.; Smallheer, J. M.; Tobin, A. E.; Jetter, J. W.; Buynitsky, J. S.; Harlow, P. P.; Solomon, K. A.; Corjay, M. H.; Mousa, S. A.; Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 27-40.

13. Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klinger, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158-1176.

14. Peyman, A.; Wehner, V.; Knolle, J.; Stilz, H. U.; Breipohl, G.; Scheunumann, K.-H.; Carniato, D.; Ruxer, J.-M.; Gourvest, J.-F.; Gadek, T. R.; Bodary, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 179-182.

15. Xue, C.-B.; Rafalski, M.; Roderick, J.; Eyermann, C. J.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 339-344.

16. Carceller, E.; Merlos, M.; Giral, M.; Balsa, D.; García-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 487-493.

17. 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.

18. Batt, D. G.; Petraitis, J. J.; Houghton, G. C.; Modi, D. P.; Cain, G. A.; Corjay, M. H.; Mousa, S. A.; Bouchard, P. J.; Forsythe, M. S.; Harlow, P. P.; Barbera, F. A.; Spitz, S. M.;Wexler, R. R.; Jadhav, P. K. *J. Med. Chem.* **2000**, *43*, 41-58.

18. Han, H.; Janda K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539-2544.

19. Sulyok, G. A. G.; Gibson, C.; Goodman, S.L.; Hölzemann, G.; Wiesner, M.; Kessler, H. *J. Med. Chem.* **2001**, *44*, 1938-1950.

20. Pons, J.-F.; Fauchére, J.-L.; Lamaty, F.; Molla, A.; Lazaro, R. *Eur. J. Org. Chem.* **1998**, 853-859.

21. Sugihara, H.; Fukushi, H.; Miyawaki, T.; Imai, Y.; Terashita, Z:; Kawamura, M.; Fujisawa, Y.; Kita, S. *J. Med. Chem.* **1998**, *41*, 489-502.

22. van Maarseveen, J. H.; den Hartog, J. A. J.; Reinders, J.-H.; Brakkee, J.; Schön, U.; Kehrbach, W.; Kruse, C. G. *Bioorg. Med. Chem.* **1998**, *8*, 1531-1536.

23. Asari, T.; Ishikawa, S.; Sasaki, T.; Katada, J.; Hayashi, Y.; Harada, T.; Yano, M.; Yasuda, E.; Uno, I.; Ojima, I. *Bioorg. Med. Chem.* **1997**, *16*, 2099-2104. *Bioorg. Med. Chem.* **1997**, *19*, 2537-2542.

24. Hayashi,Y.; Katada, J.; Harada, T.; Tachiki, A.; Iijima, K.; Takiguchi, Y.; Muramatsu, M.; Miyazaki, H.; Asari, T.; Okazaki, T.; Sato, Y.; Yasuda, E.; Yano, M.; Uno, I.; Ojima, I. *J. Med. Chem.* **1998**, *41*, 2345-2360.

25. Weller, T.; Alig, L.; Beresini, M.; Blackburn, B.; Bunting, S.; Hadváry, P.; Hürzeler Müller, M.; 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.

26. Kottirsch, G.; Zerwes, H.-G.; Cook, N. S.; Tapparelli, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 727-732.

27. Xue, C.-B.; Roderick, J.; Jackson, S.; Rafalski, M.; Roockwell, A.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem.* **1997**, *5*, 693-705.

29. Zablocki, J. A.; Miyano, M.; Garland, R. B.; Pireh, D.; Schretzman, L.; Rao, S. N.; Lindmark, R.J.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J.G.; Feigen, L. P. *J. Med. Chem.* **1993**, *36*, 1811-1819.

30. Fisher, M. J.;Gunn, B. P.; Harms, C. S.; Kline, A.D., Mullaney, J. T., Scarborough, R. M.; Skelton, M. A.; Um, S. L.; Utterback; Jakubowski, J. A. *Bioorg. Med. Chem. Lett.* **1993**, *7*, 2537-2542.

31 . Zablocki, J. A.; Rico, J. G.; Garland, R. B.; Rogers, T. E.; Williams, K.; Schretzman, L. A.; Rao, S. A.; Bovy, P. R.; Tjoeng, F. S.; Lindmark, R. J.; Toth, M. V.; Zupec, M. E.; McMacmins, D. E.; Adams, S. P.; Miyano, M.; Markos, C. S.; Milton, M. N.; Paulson, S.; Herin, M.; Jacqmin, P.; Nicholson, N. S.; Panzer-Knodle, S. G.; Haas, N. F.; Page, J. D.; Szalony, J. A.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem.* **1995**, *38*, 2378-2394.

28. Egbertson, M. S.; Hartman, G. D.; Gould, R. J.; Bednar, B.; Bednar, R. A.; Cook, J. J.; Gaul, S. L.; Holahan, M. A.; Libby, L. A.; Lynch Jr., J. J.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Vassallo, L. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2519-2524.

29. Prugh, J. D.; Gould, R. J.; Lynch, R. J.; Zhang, G.; Cook, J. J.; Holahan, M. A.; Stranieri, M. T.; Sitko, G. R.; Gaul, S. L.; Bednar, R. A.; Bednar, B.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 865-870.

30. Askew, B. C.; Bedmar, R. A.; Bedmar, B.; Claremon, D. A.; Cook, J. J.; McIntyre, C. J.; Hunt, C. A.; Gould, R. J.; Lynch, R. J.; Lynch Jr., J. J.; Gaul, S. L.; Stranieri, M. T.; Sitko, G. R.; Holahan, M. A.; Glass, J. D.; Hamill, T.; Gorham, L. M.; Prueksaritanont, T.; Baldwin, J. J.; Hartman, G. D. *J. Med. Chem.* **1997**, *40*, 1779-1788.

31. Brashear, K. M.; Cook, J. J.; Bednar, B.; Bednar, R. A.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Hartman, G. D.; Hutchinson, J. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2793-2798.

32. Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Baldwin, J. J.; Anderson, P. S.; Gould, R.J.; Lynch, R. J.; Chang, C. C.-T.; Cook, J. J.; Lynch, J. J.; Holahan, M. A.; Sitko, G. R.; Stranieri, M. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1531-1536.

33. Liverton, N. J.; Armstrong, D. J.; Claremon, D. A.; Remy, D. C.; Baldwin, J. J.; Lynch, R. J.; Zhang, G.; Gould, R. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 483-486.

34. Misra, R. N.; Kelly, Y. F.; Brown, B. R.; Roberts, D. G. M.; Chong, S.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2165-2170.

35. Duggan, M. E.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Perkins, J. J.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. a.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736-3745.

36. Egbertson, M. S.; Naylor, A. M.; Hartman, G. D.; Cook, J. J.; Gould, R. J.; Holahan, M. A.; Lynch Jr., J. J.; Lynch, R. J.; Stranieri, M. T.; Vassallo, L. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1835-1840.

37. Duggan, M. E.; Naylor-Olsen, A. M.; Perkins, J. J.; Anderson, P. S.; Chang, C. T.-C.; Cook, J. J.; Gould, R. J.; Ihle, N. C.; Hartman, G. D.; Lynch, J. J.; Lynch, R. J.; Manno, P. D.; Schaffer, L. W.; Smith, R. L. *J. Med. Chem.* **1995**, *38*, 3332-3341.

38. Klein, S. I.; Molino, B. F.; Czekaj, M.; Gardner, C. J.; Chu, V.; Brown, K.; Sabatino, R. D.; Bostwick, J. S.; Kasiewski, C.; Bentley, R.; Windish, V.; Perrone, M.; Dunwiddie, C. T.; Leadley, R. J. *J. Med. Chem.* **1998**, *41*, 2492-2502.

39. Ho, W.-B.; Broka, C. *J. Org. Chem.* **2000**, *65*, 6743-6748.

40. Vogel. *Vogel's Textbook of Organic Chemistry*. 4th edition.

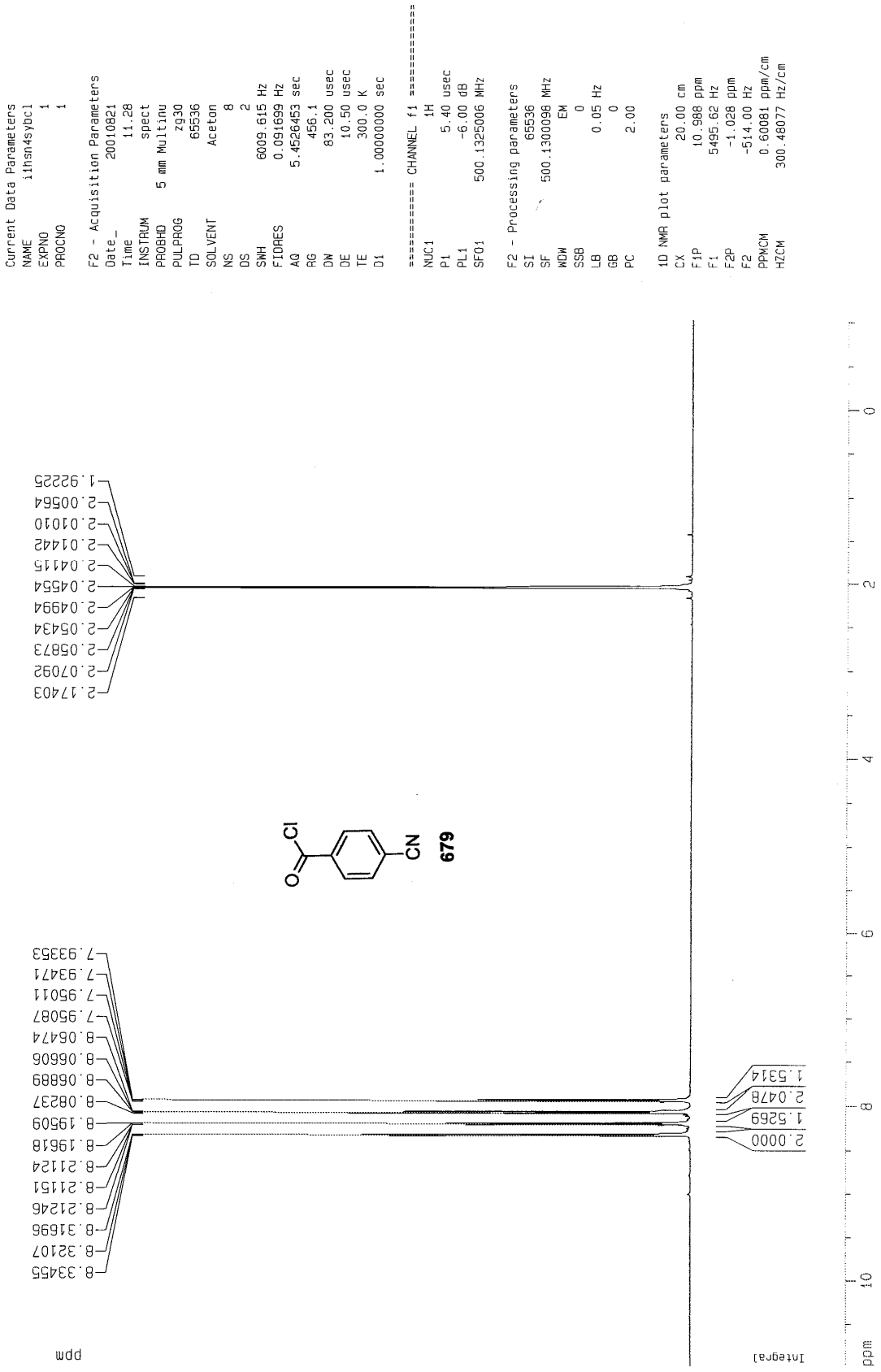
41. Heinzman, S.W.; Ganem, B.J. *Am. Chem. Soc.,* **1982**, *104*, 6801-6802.

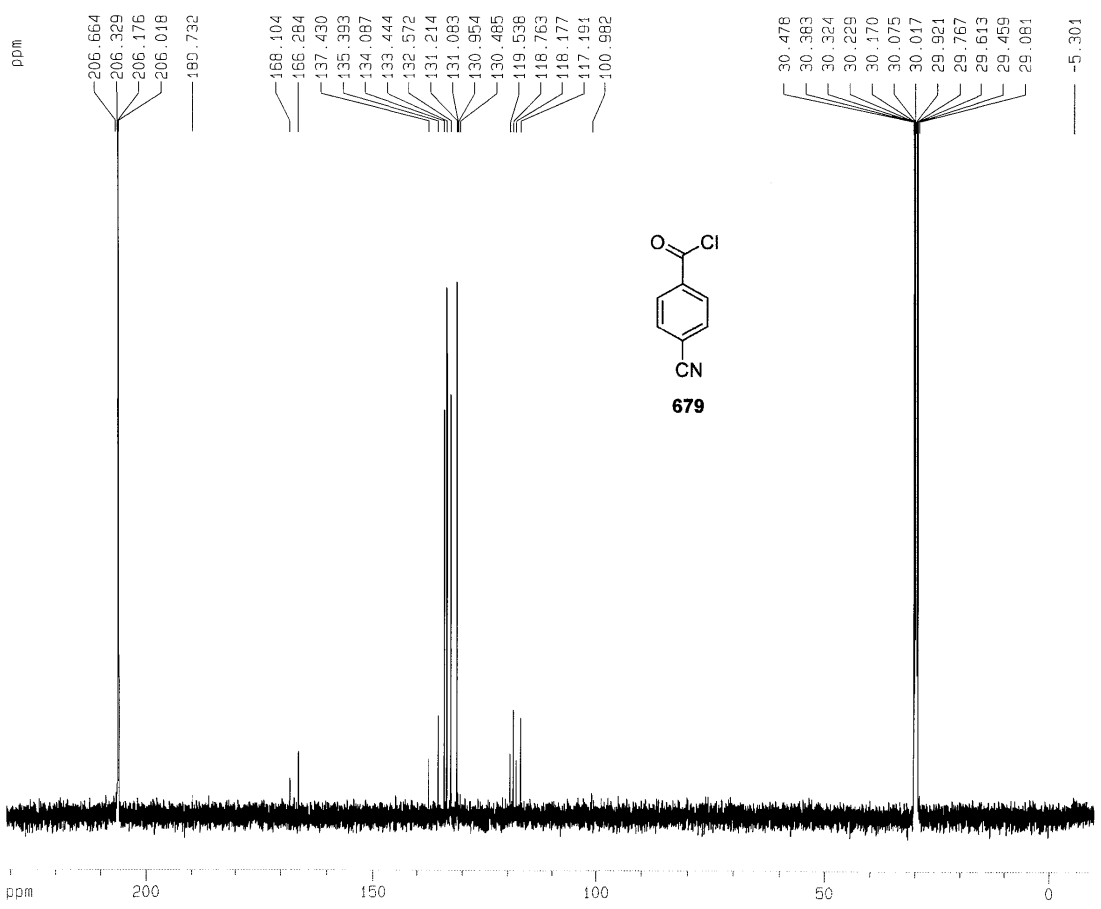
42. Lahtinen, T. *Π-prismandit. niiden synteesit ja kompleksoituminen.* Licentiate thesis, Jyväskylä University, Department of Chemistry, **1998**, 48-49.

43. Johnstone, R.A.W.; Rose, M.E. *A rapid,simple,and mild procedure for alkylation of phenols, alcohols, amids and acids.*Tetrahedron, **1979**, *35*, 2169-2173.

Appendices

APPENDIX 1: ^{1}H NMR and ^{13}C spectra for **679**.





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PROCNO	1

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PULPROG	zgpg30
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SOLVENT	Aceton
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SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0813940 sec
RG	1149.4
DW	16.500 usec
DE	10.50 usec
TE	300.0 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec

========== CHANNEL f1 ========

NUC1	13C
P1	12.60 usec
PL1	-2.00 dB
SFO1	125.7715723 MHz

========== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	14.00 dB
PL12	19.00 dB
PL13	120.00 dB
SFO2	500.1330008 MHz

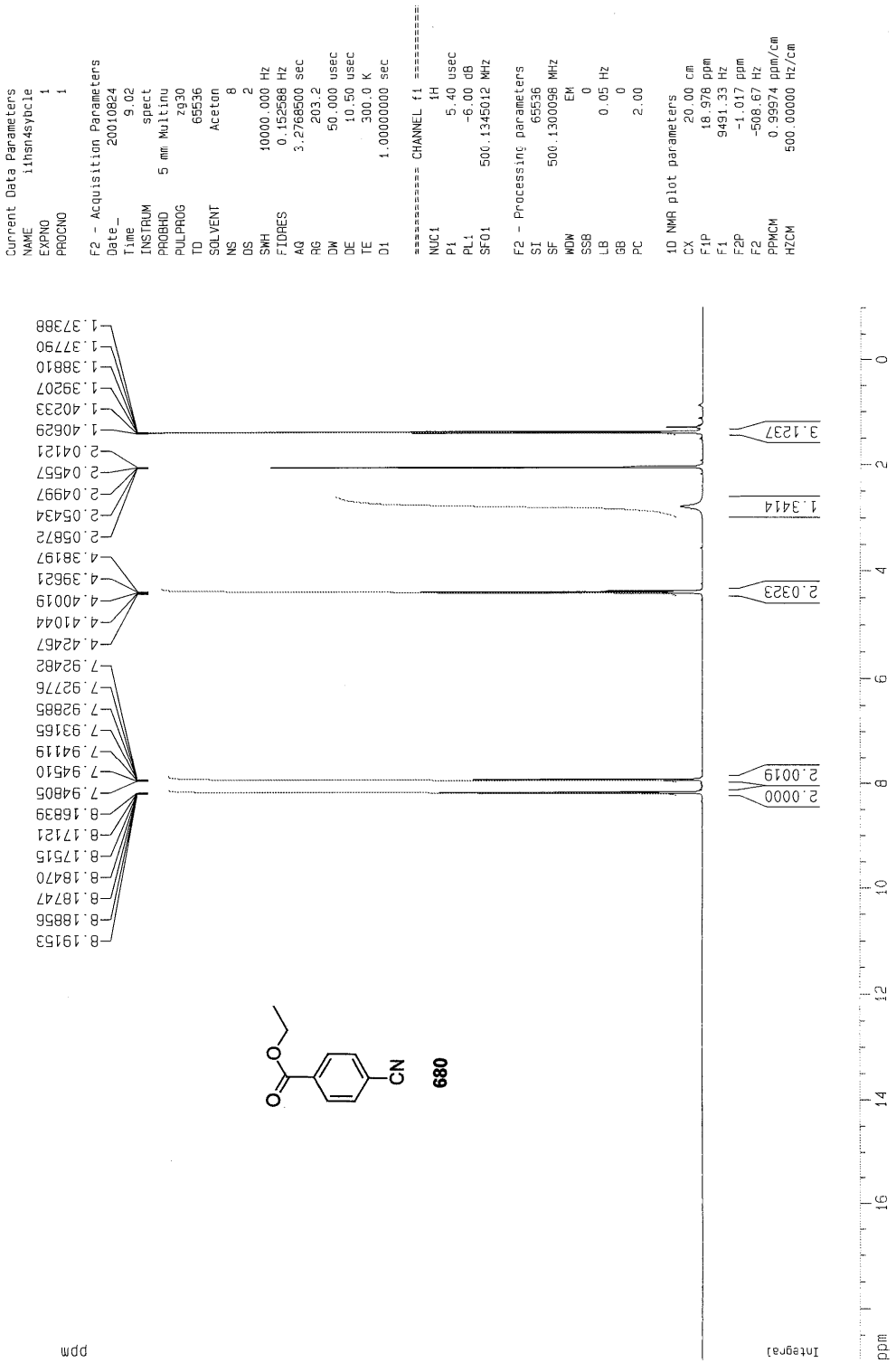
F2 - Processing parameters

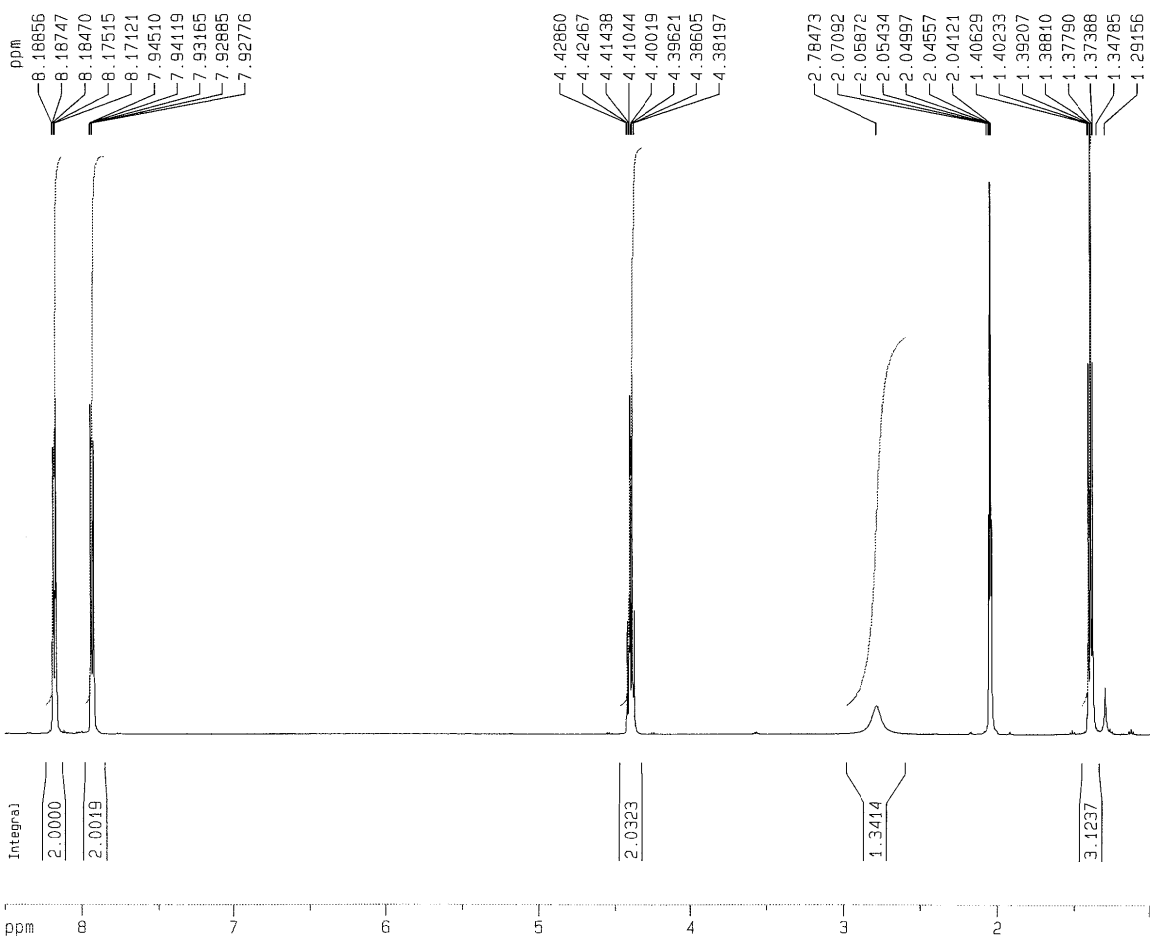
SI	65536
SF	125.7576621 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	231.093 ppm
F1	29061.74 Hz
F2P	-9.870 ppm
F2	-1241.29 Hz
PPMCM	12.04818 ppm/cm
HZCM	1515.15149 Hz/cm

APPENDIX 2: ^{1}H NMR and ^{13}C spectra for **680**.



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EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
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INSTRUM            spect
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PULPROG             zg30
TD                 65536
SOLVENT           Aceton
NS                     8
DS                     2
SWH            10000.000 Hz
FIDRES             0.152588 Hz
AQ             3.2768500 sec
RG                 203.2
DW                50.000 usec
DE                10.50 usec
TE                300.0 K
D1             1.00000000 sec

============ CHANNEL f1 =============
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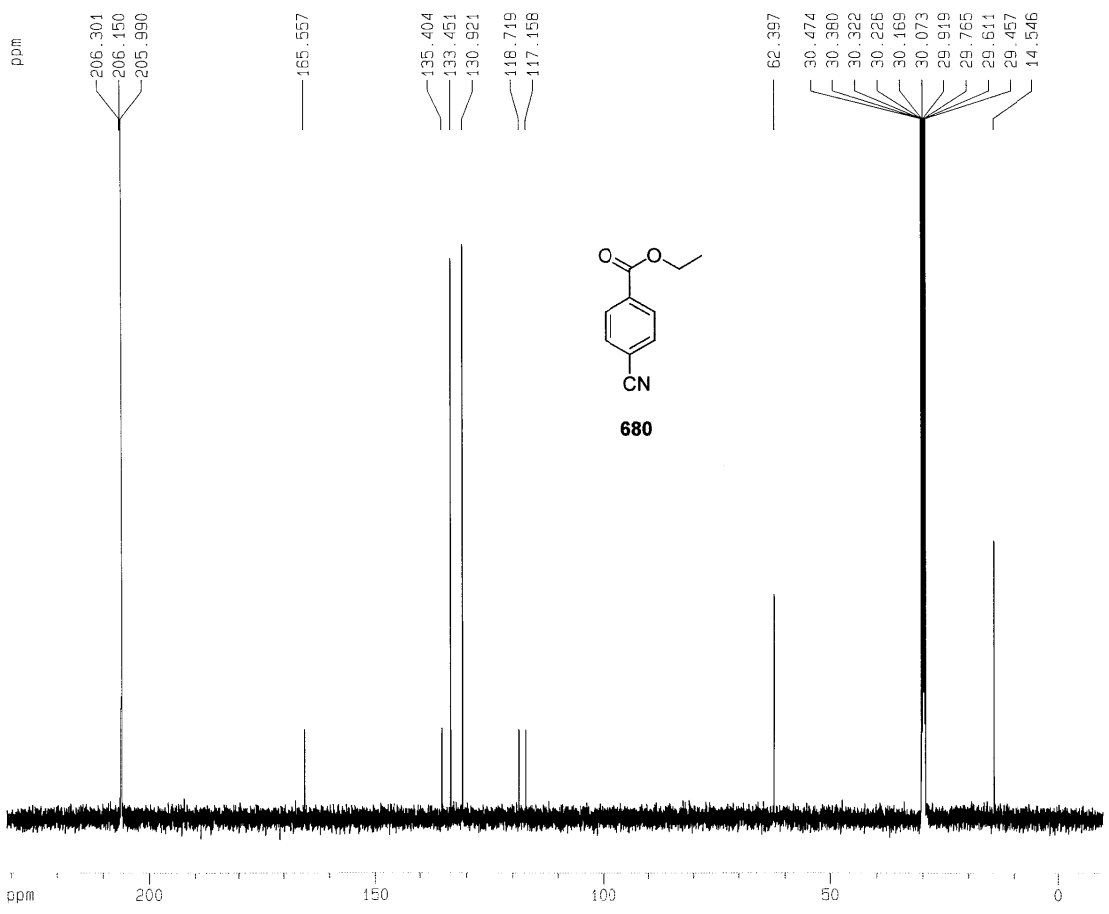
P1                  5.40 usec
PL1                -6.00 dB
SFO1         500.1345012 MHz

F2 - Processing parameters
SI                 65536
SF           500.1300098 MHz
WDW                   EM
SSB                    0
LB                  0.05 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 20.00 cm
F1P                8.500 ppm
F1               4251.10 Hz
F2P                1.000 ppm
F2                500.13 Hz
PPMCM           0.37500 ppm/cm
HZCM          187.54875 Hz/cm
```




```
Current Data Parameters
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EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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Time                9.12
INSTRUM            spect
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TD                 65536
SOLVENT          Aceton
NS                   2290
DS                      2
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813940 sec
RG               1149.4
DW                16.500 usec
DE                10.50 usec
TE                300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec

============ CHANNEL f1 =============
NUC1                13C
P1                12.60 usec
PL1               -2.00 dB
SFO1         125.7715723 MHz

============ CHANNEL f2 =============
CPDPRG2         waltz16
NUC2                1H
PCPD2            100.00 usec
PL2               14.00 dB
PL12              19.00 dB
PL13              120.00 dB
SFO2         500.1330008 MHz

F2 - Processing parameters
SI                 65536
SF           125.7576630 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.00

1D NMR plot parameters
CX                20.00 cm
F1P              231.086 ppm
F1             29060.82 Hz
F2P               -9.878 ppm
F2             -1242.21 Hz
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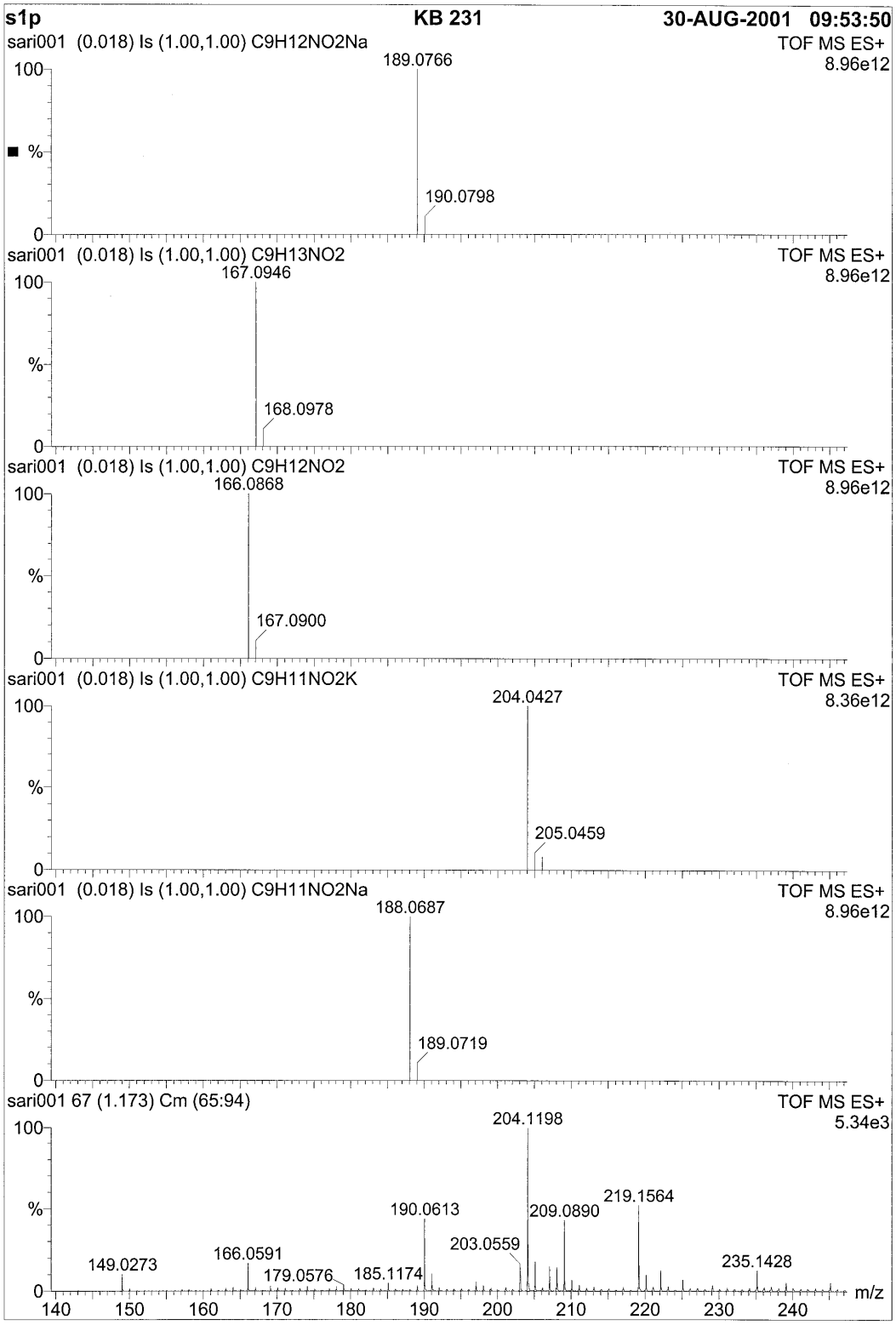
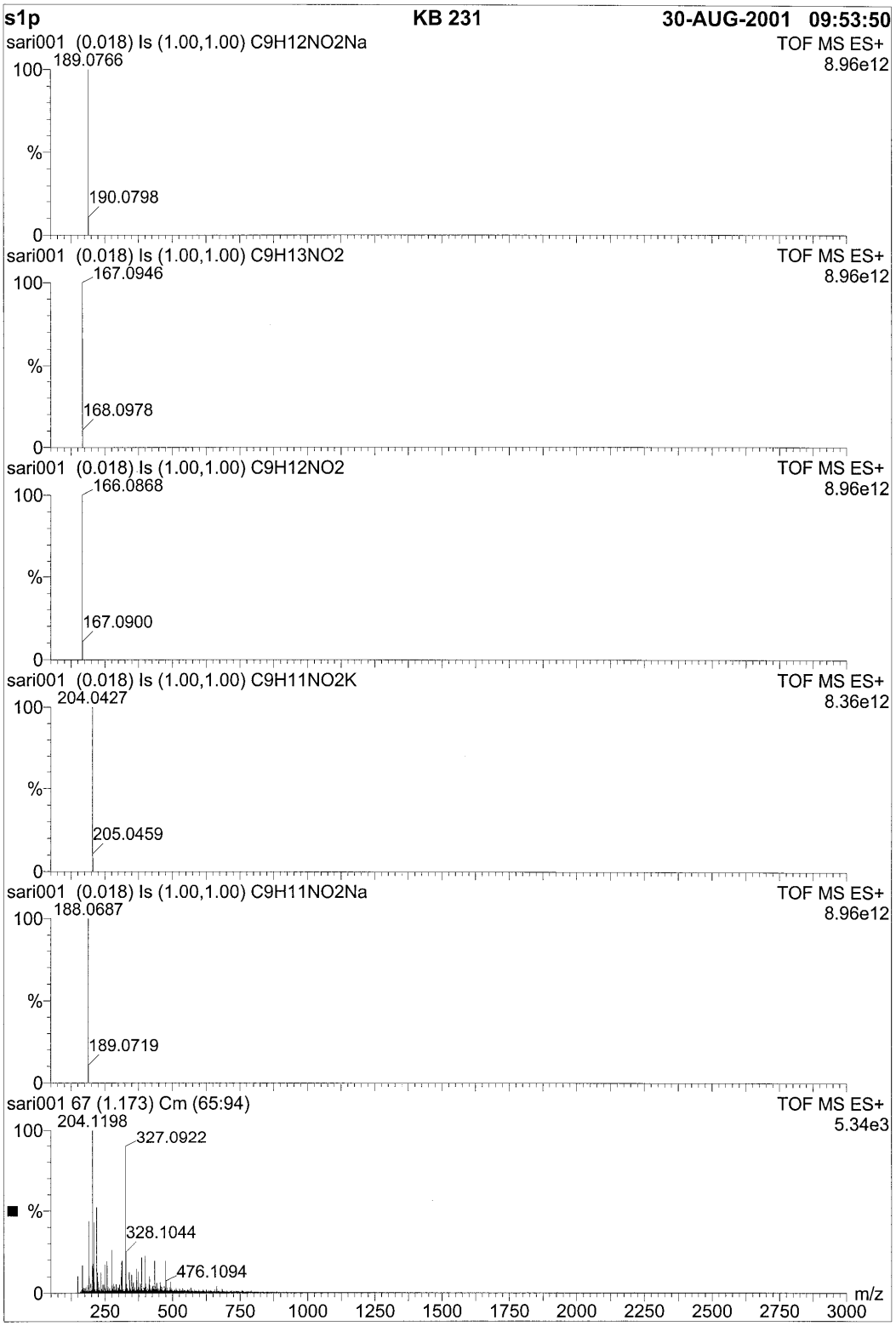
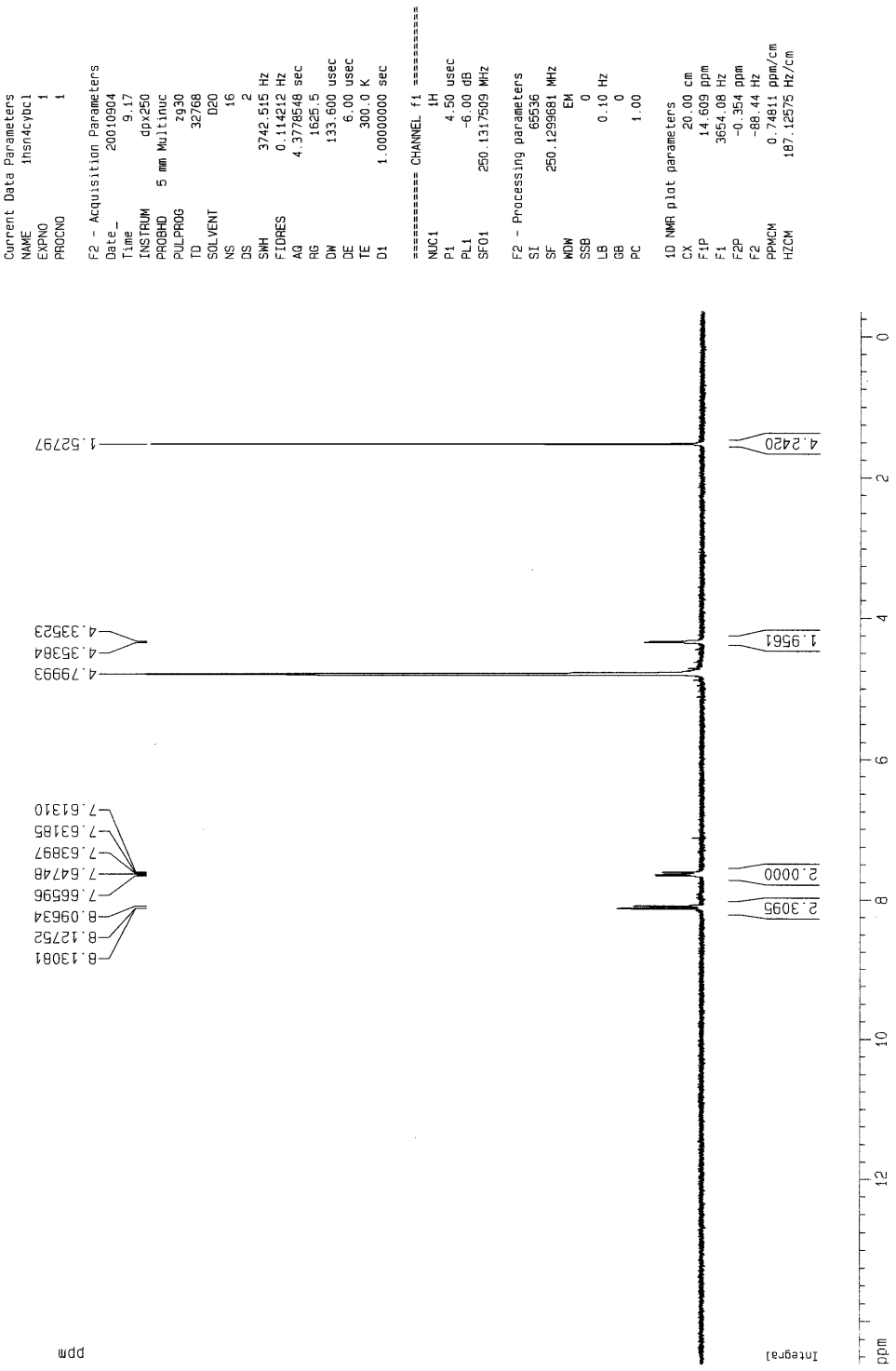
HZCM         1515.15149 Hz/cm
```

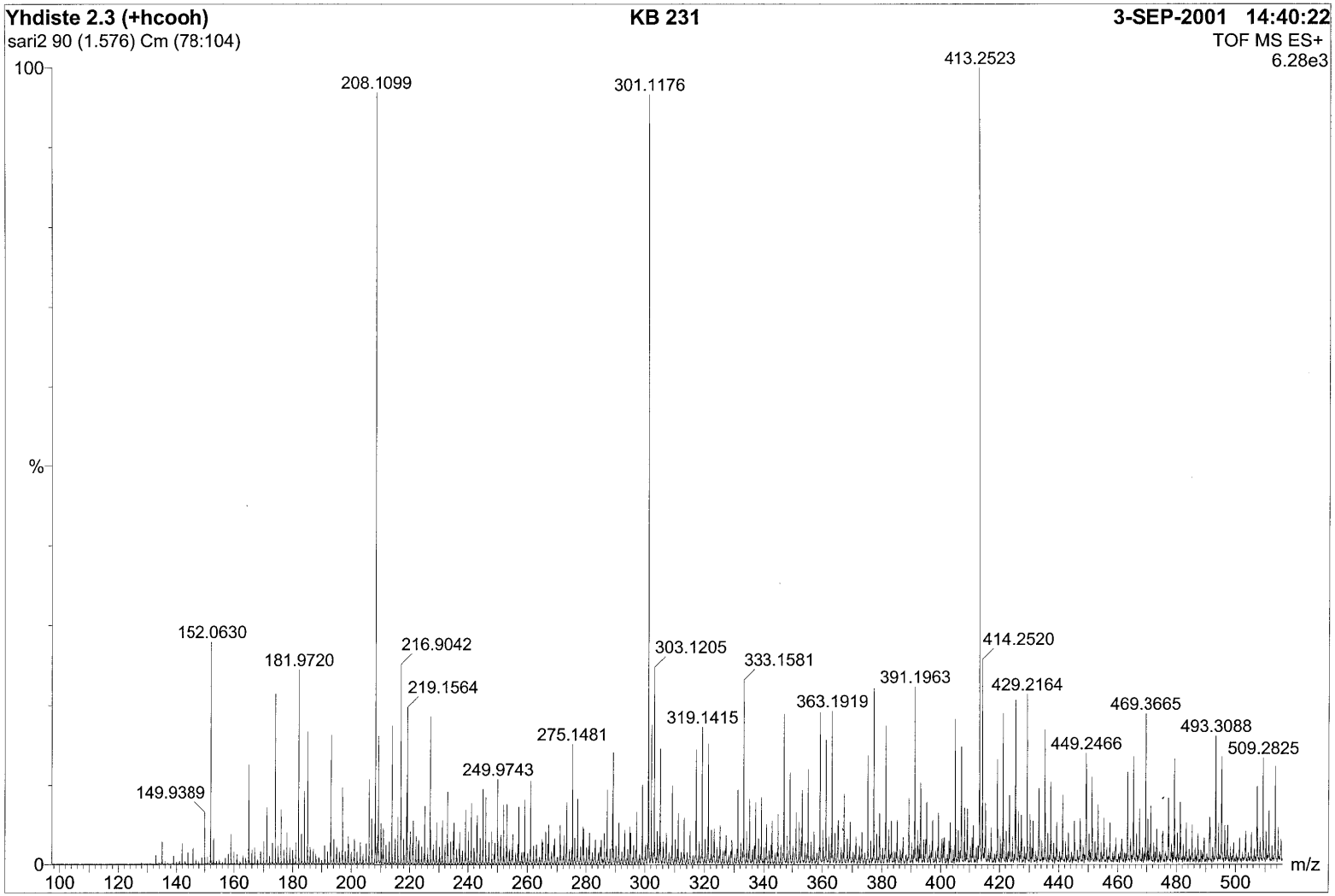
APPENDIX 3: MS spectra for attempted synthesis of **681'**.




s1p
KB 231
30-AUG-2001 09:53:50
sari001 (0.018) Is (1.00,1.00) C9H12NO2Na
TOF MS ES+
8.96e12
189.0766
190.0798
sari001 (0.018) Is (1.00,1.00) C9H13NO2
TOF MS ES+
8.96e12
167.0946
168.0978
sari001 (0.018) Is (1.00,1.00) C9H12NO2
TOF MS ES+
8.96e12
166.0868
167.0900
sari001 (0.018) Is (1.00,1.00) C9H11NO2K
TOF MS ES+
8.36e12
204.0427
205.0459
sari001 (0.018) Is (1.00,1.00) C9H11NO2Na
TOF MS ES+
8.96e12
188.0687
189.0719
sari001 67 (1.173) Cm (65:94)
TOF MS ES+
5.34e3
204.1198
327.0922
328.1044
476.1094
100
%
0
m/z
250
500
750
1000
1250
1500
1750
2000
2250
2500
2750
3000

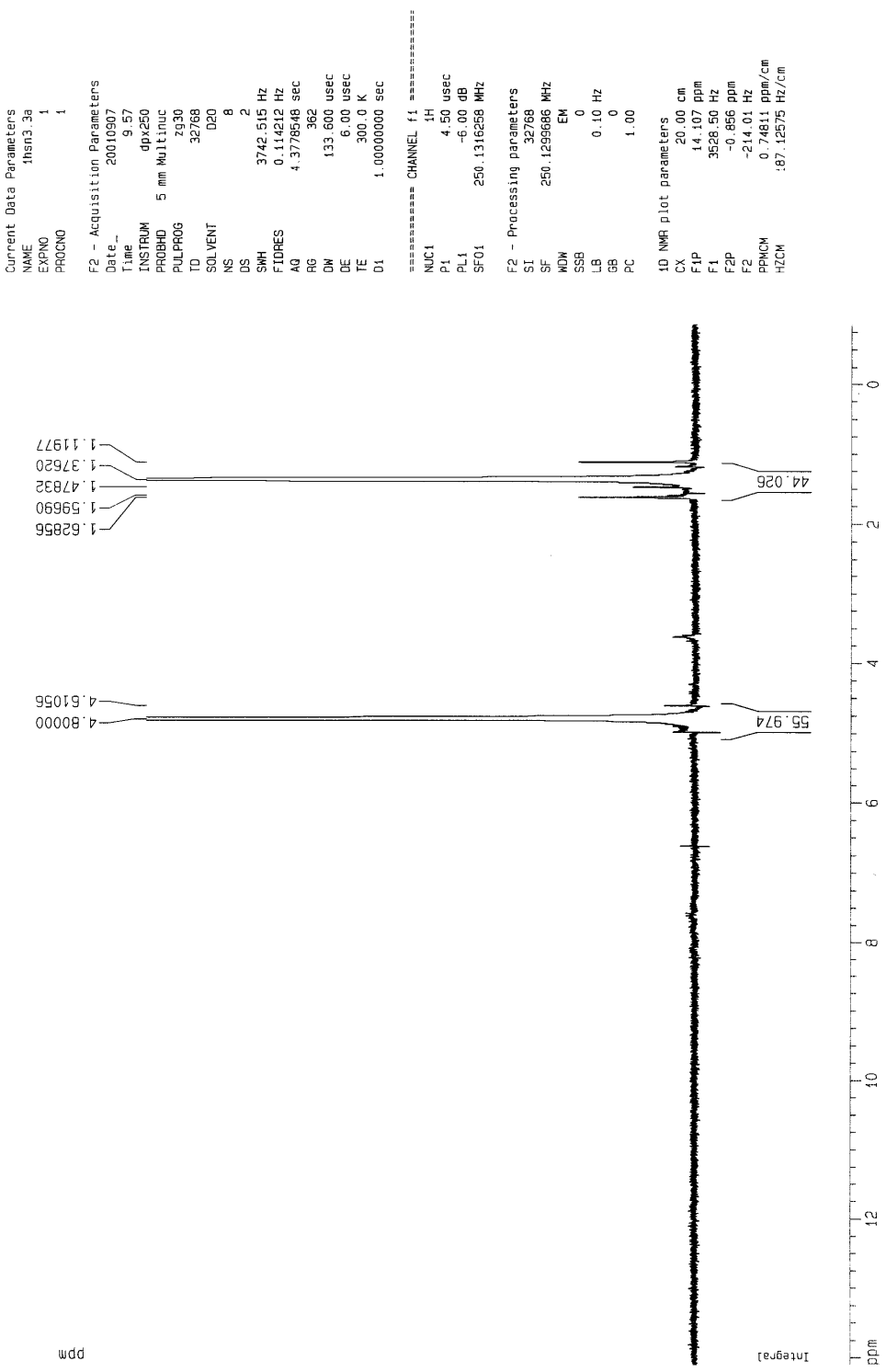
APPENDIX 4: ^{1}H NMR and MS spectra for attempted synthesis of **681.**



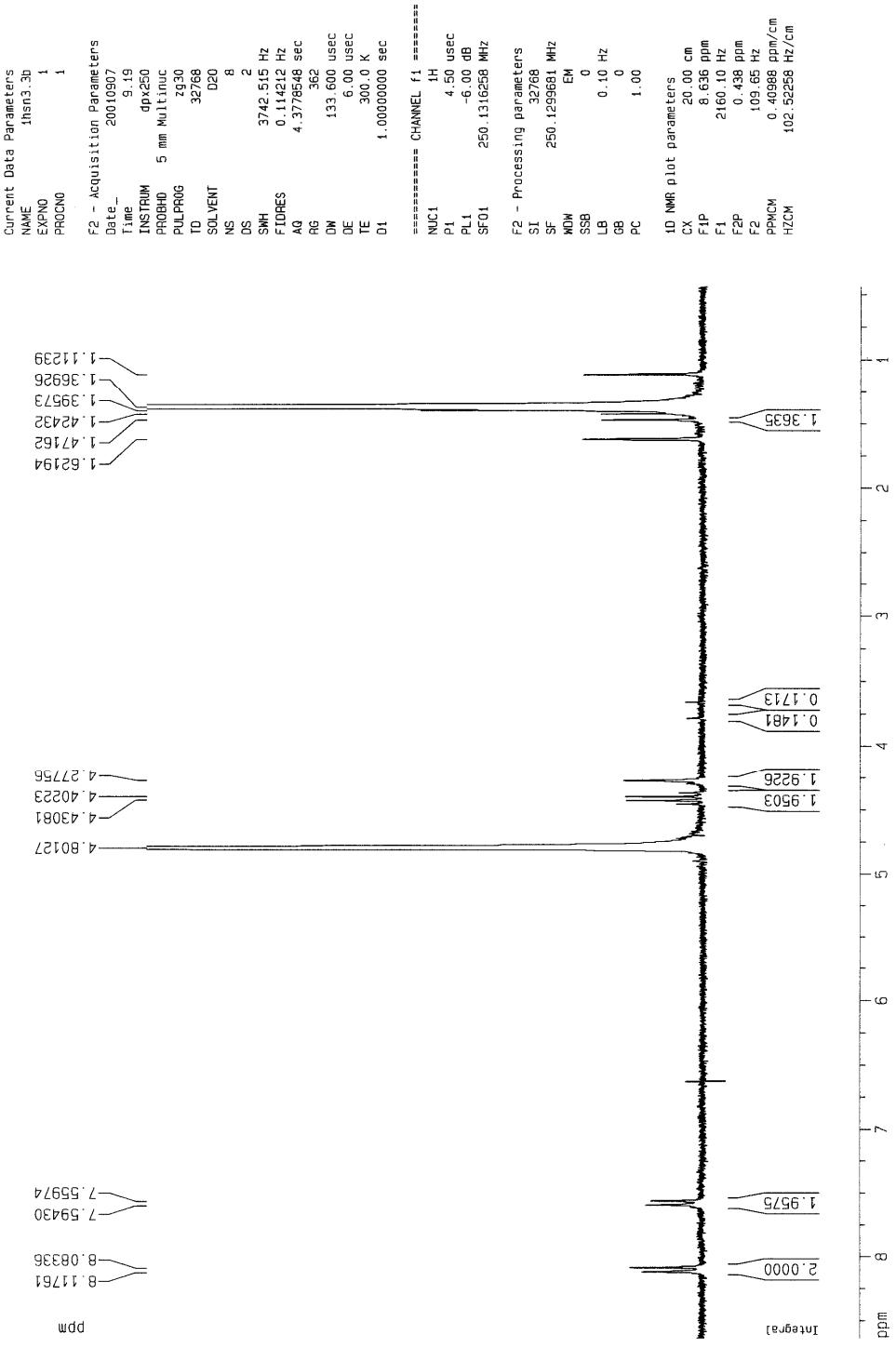

Yhdiste 2.3 (+hcooh)
KB 231
3-SEP-2001 14:40:22
sari2 90 (1.576) Cm (78:104)
TOF MS ES+
6.28e3
100
%
0
208.1099
301.1176
413.2523
152.0630
181.9720
216.9042
219.1564
303.1205
333.1581
391.1963
414.2520
429.2164
363.1919
319.1415
469.3665
493.3088
509.2825
449.2466
275.1481
249.9743
149.9389
100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500
m/z

APPENDIX 5: ^{1}H NMR spectra for attempted synthesis of **682**.

a)



b)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PROCNO 1
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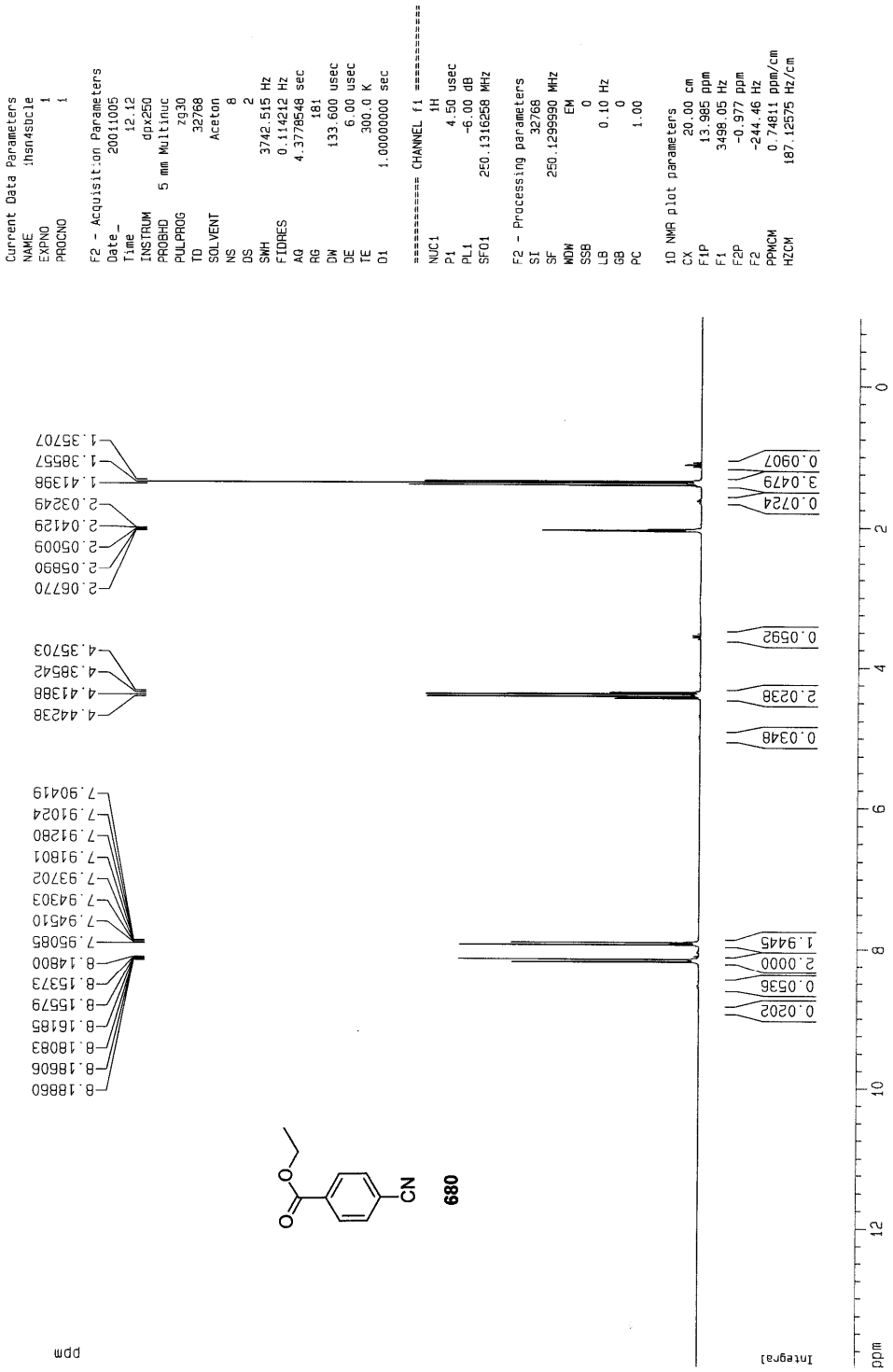
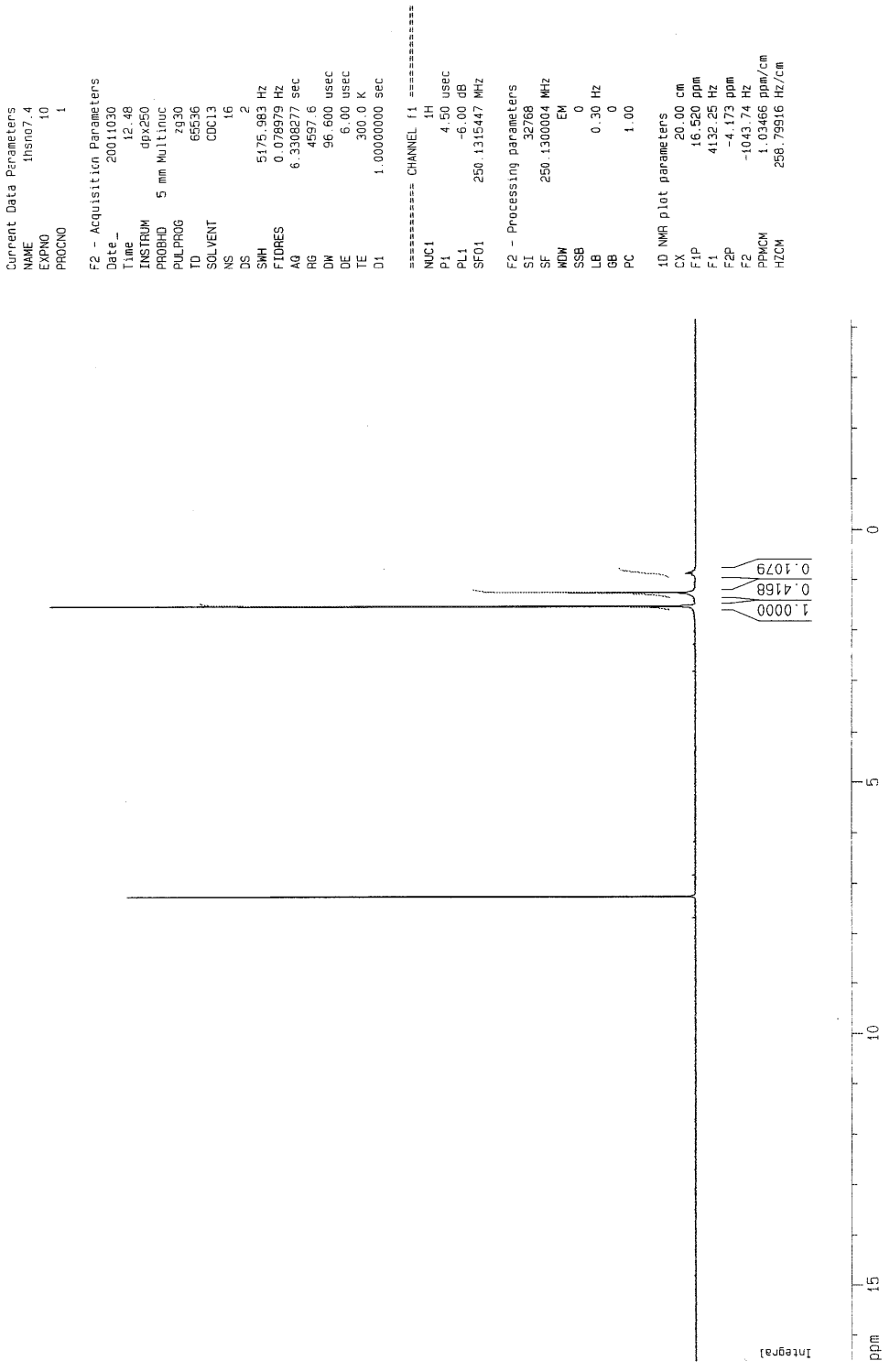
INSTRUM dpx250
PROBHD 5 mm Multinuc
PULPROG zg30
TD 32768
SOLVENT D20
NS 8
DS 2
SWH 3742.515 Hz
FIDRES 0.114212 Hz
AQ 4.3778548 sec
RG 362
DW 133.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
========== CHANNEL f1 ========
NUC1 1H
P1 4.50 usec
PL1 -6.00 dB
SFO1 250.1316258 MHz
F2 - Processing parameters
SI 32768
SF 250.1299681 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 8.636 ppm
F1 2160.10 Hz
F2P 0.438 ppm
F2 109.65 Hz
PPMCM 0.40988 ppm/cm
HZCM 102.52258 Hz/cm
1.12239
1.36926
1.39573
1.42432
1.47162
1.62194
4.27756
4.40223
4.43081
4.80127
7.55974
7.59430
8.08336
8.11761
1.3635
0.1481
0.1713
1.9226
1.9503
1.9575
2.0000
ppm
Integral

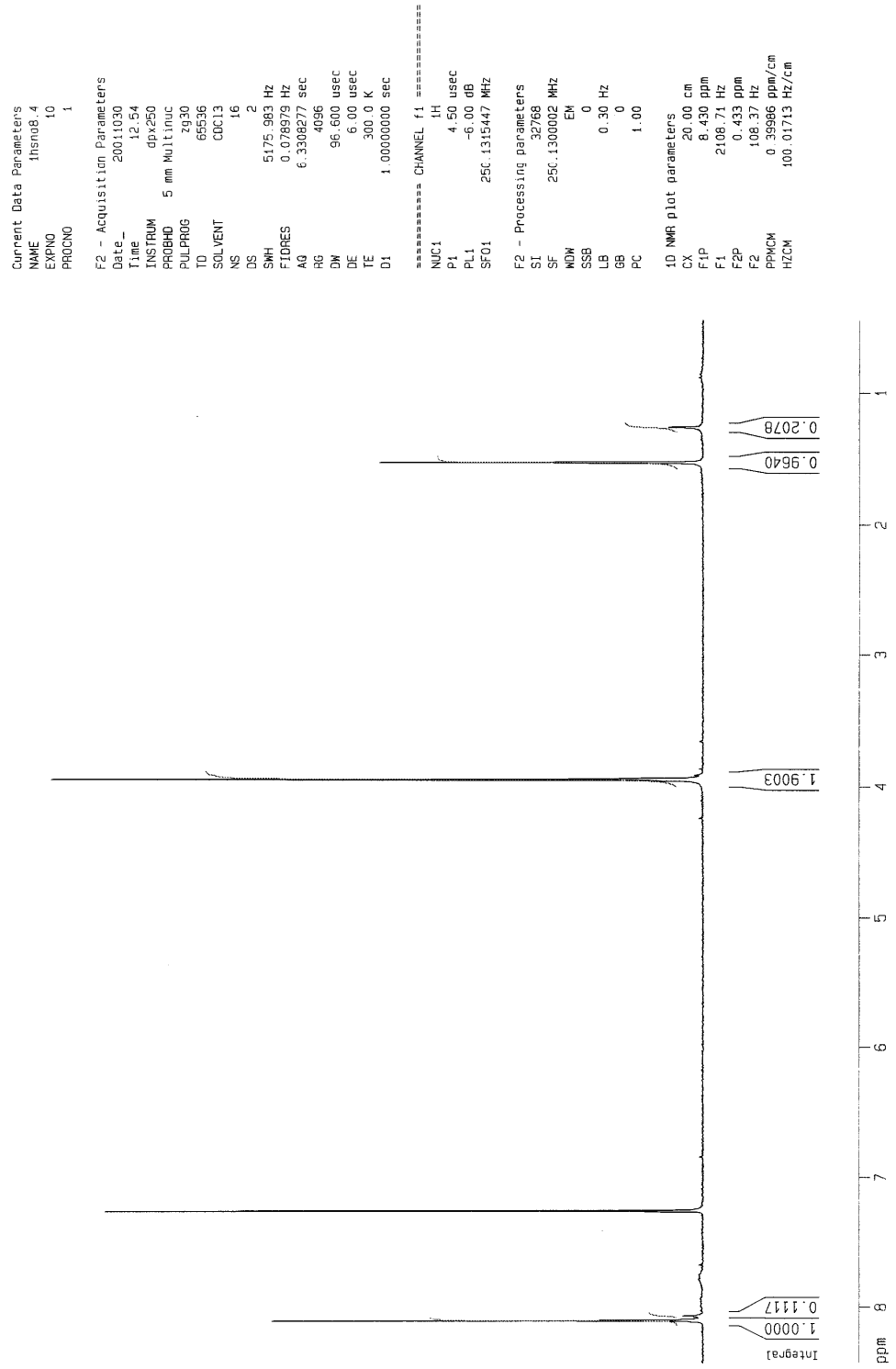
APPENDIX 6: ^{1}H NMR spectrum for **680**.



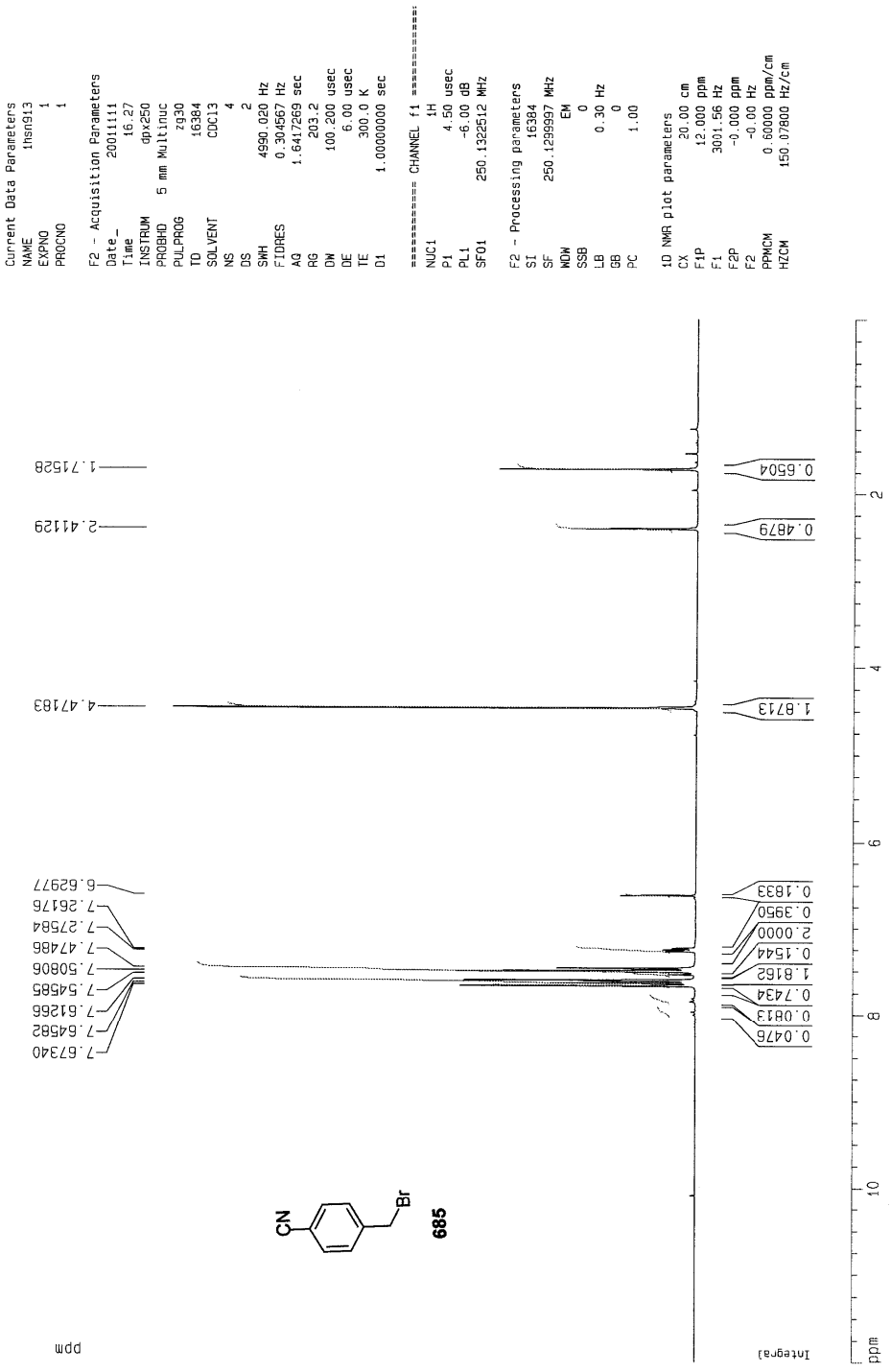
APPENDIX 7: ^{1}H NMR spectrum for attempted synthesis of **682'**.

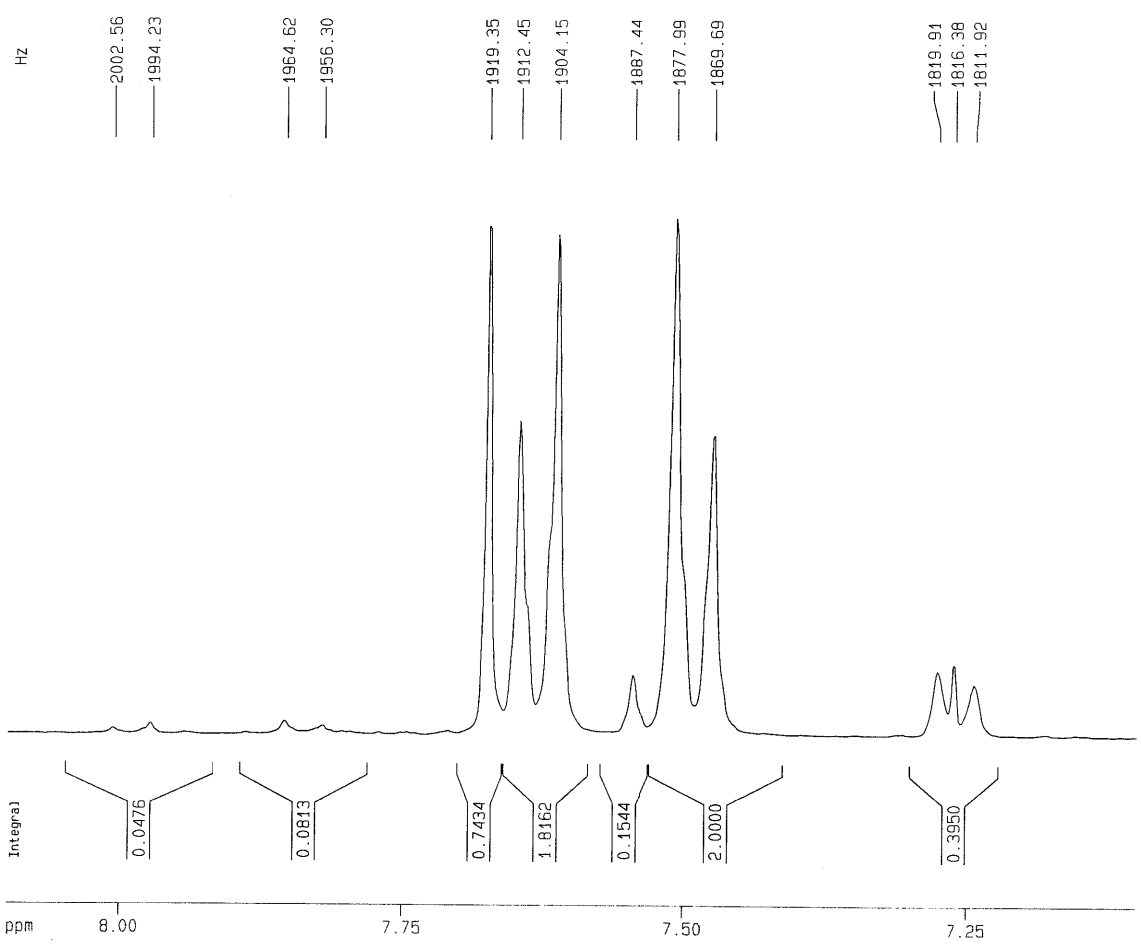


APPENDIX 8: ^{1}H NMR spectrum for attempted synthesis of **669'**.



APPENDIX 9: ^{1}H NMR and ^{13}C spectra for **685** a).






```
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PROCNO                     1

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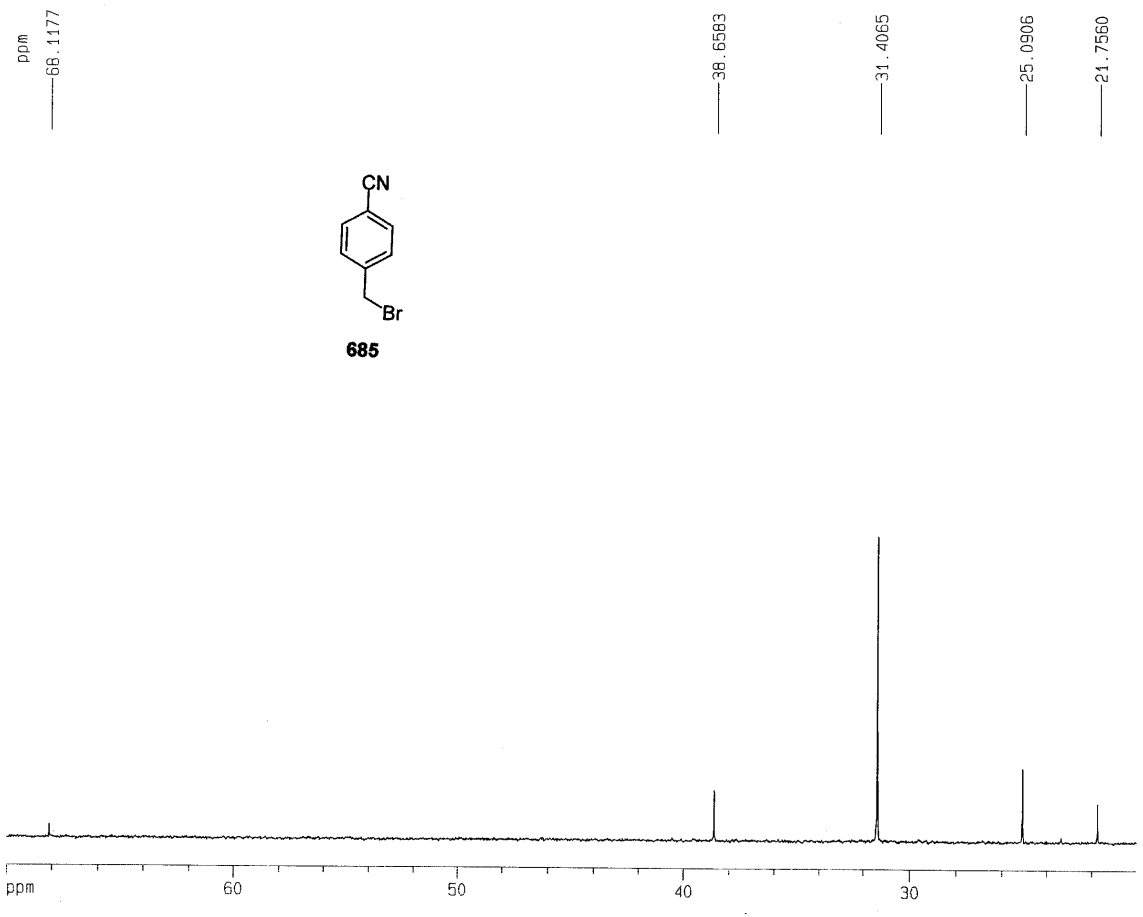
PULPROG                zg30
TD                     16384
SOLVENT                CDCl3
NS                         4
DS                         2
SWH                4990.020 Hz
FIDRES             0.304567 Hz
AQ                 1.6417269 sec
RG                     203.2
DW                   100.200 usec
DE                     6.00 usec
TE                     300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 =============
NUC1                       1H
P1                      4.50 usec
PL1                    -6.00 dB
SFO1             250.1322512 MHz

F2 - Processing parameters
SI                         16384
SF               250.1299997 MHz
WDW                        EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                    8.100 ppm
F1                   2026.05 Hz
F2P                    7.100 ppm
F2                   1775.92 Hz
PPMCM                0.05000 ppm/cm
HZCM                12.50651 Hz/cm
```




```
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PROCNO                      1

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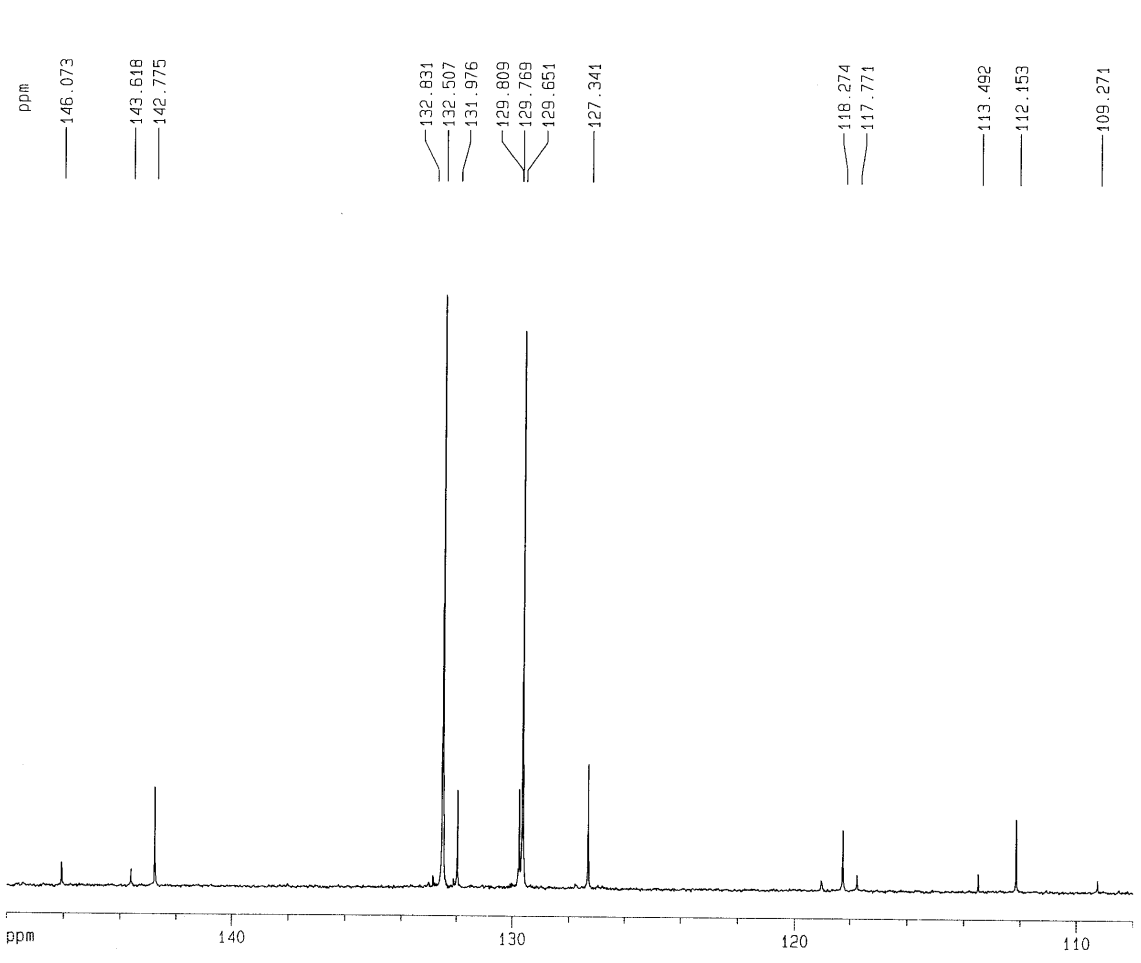
TD                      32768
SOLVENT                 CDCl3
NS                      20311
DS                          2
SWH                15723.271 Hz
FIDRES              0.479836 Hz
AQ                  1.0420724 sec
RG                     5792.6
DW                     31.800 usec
DE                      6.00 usec
TE                     300.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
D12                0.00002000 sec

============ CHANNEL f1 =============
NUC1                      13C
P1                      12.10 usec
PL1                     -6.00 dB
SFO1               62.9027614 MHz

============ CHANNEL f2 =============
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                     -6.00 dB
PL12                    20.00 dB
PL13                    20.00 dB
SFO2              250.1310005 MHz

F2 - Processing parameters
SI                      32768
SF                 62.8952420 MHz
WDW                        EM
SSB                         0
LB                      1.00 Hz
GB                          0
PC                      1.00

1D NMR plot parameters
CX                      20.00 cm
F1P                     70.000 ppm
F1                    4402.67 Hz
F2P                     20.000 ppm
F2                    1257.90 Hz
PPMCM                 2.50000 ppm/cm
HZCM                157.23810 Hz/cm
```



Current Data Parameters

NAME	13csn913
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	16.35
INSTRUM	dpx250
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	20311
DS	2
SWH	15723.271 Hz
FIDRES	0.479836 Hz
AQ	1.0420724 sec
RG	5792.6
DW	31.800 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	12.10 usec
PL1	-6.00 dB
SFO1	62.9027614 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	20.00 dB
PL13	20.00 dB
SFO2	250.1310005 MHz

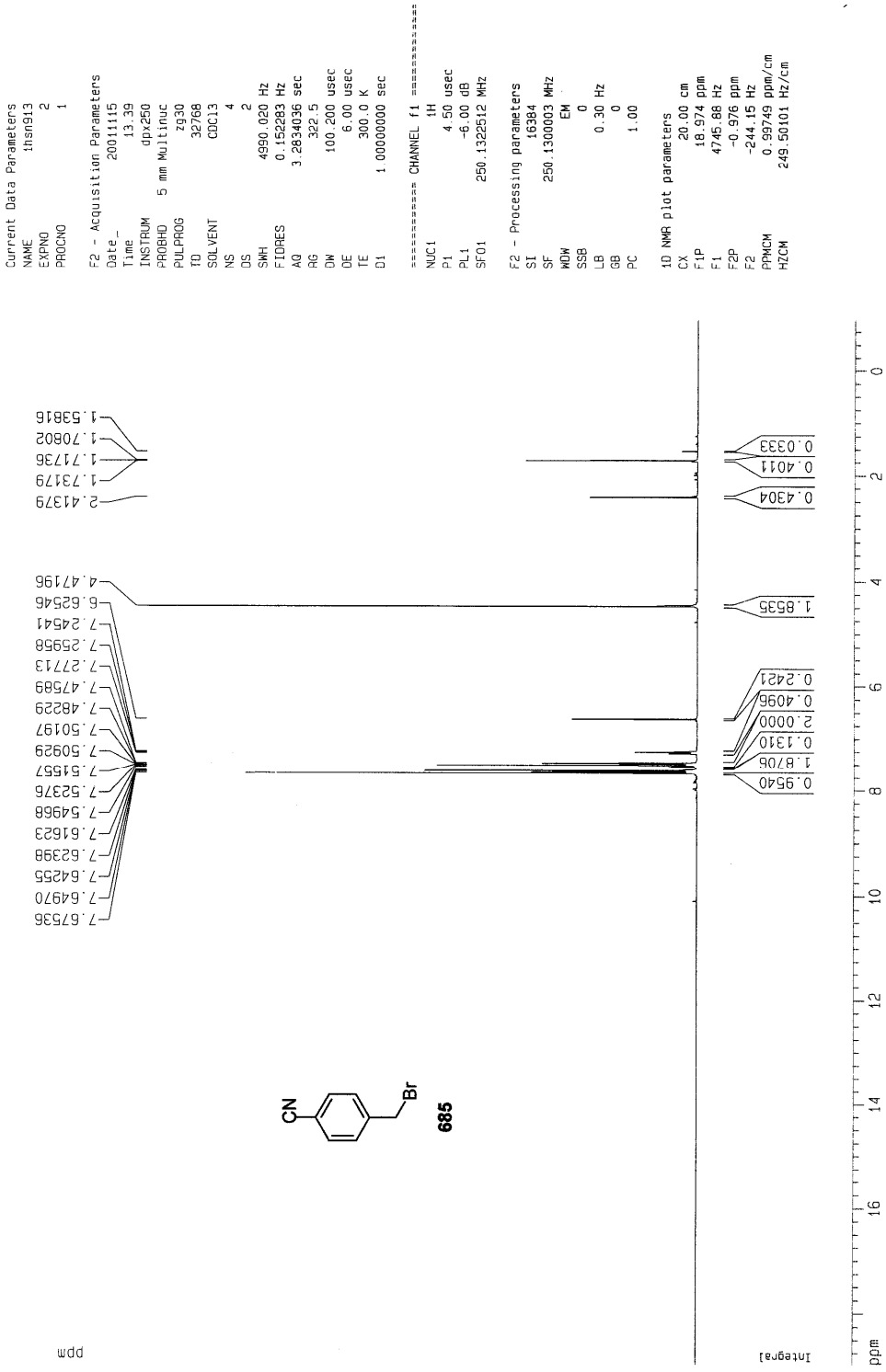
F2 - Processing parameters

SI	32768
SF	62.8952420 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00

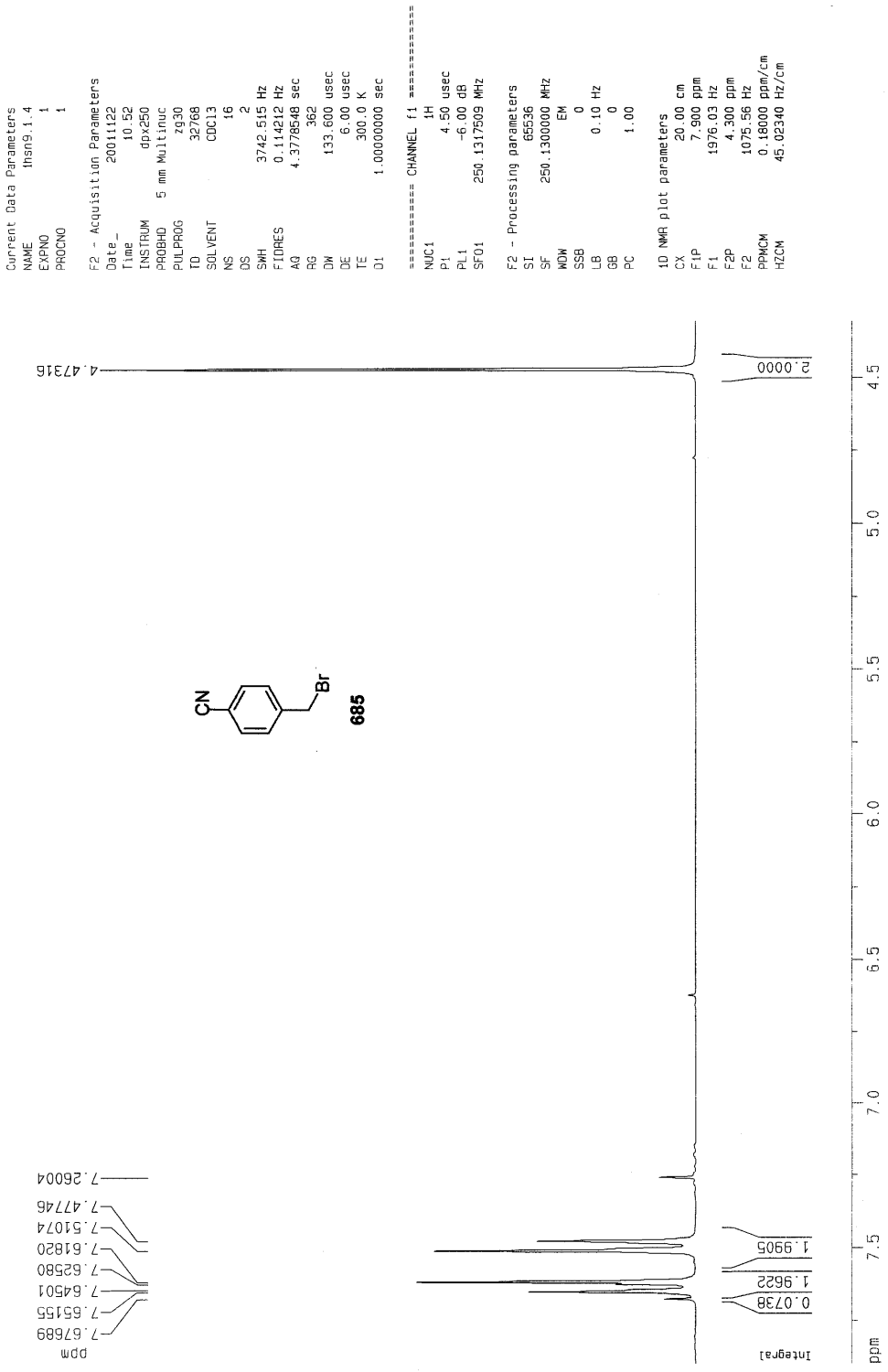
1D NMR plot parameters

CX	20.00 cm
F1P	148.000 ppm
F1	9308.50 Hz
F2P	108.000 ppm
F2	6792.69 Hz
PPMCM	2.00000 ppm/cm
HZCM	125.79048 Hz/cm

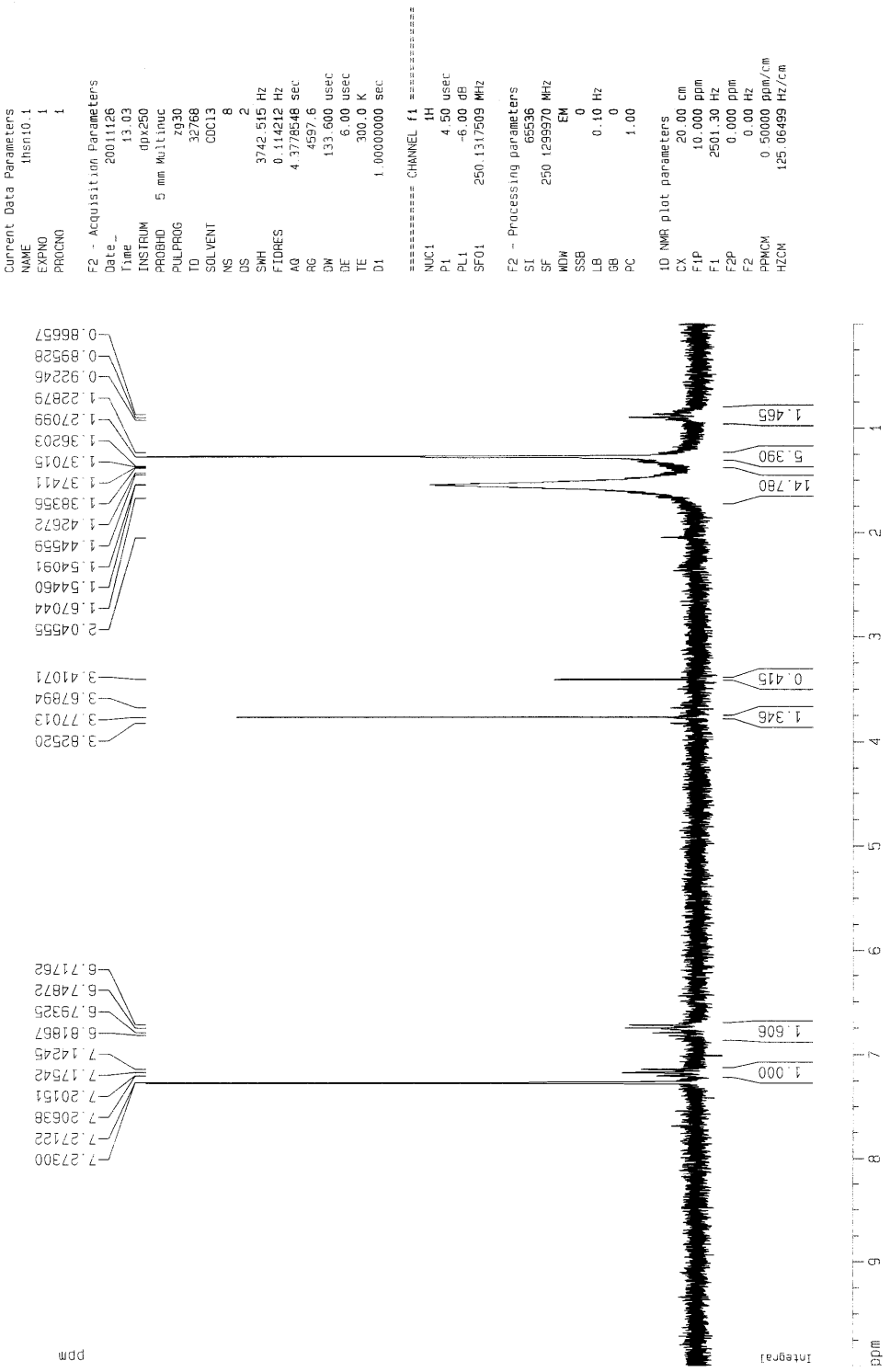
APPENDIX 10: ^{1}H NMR spectrum for **685** b).



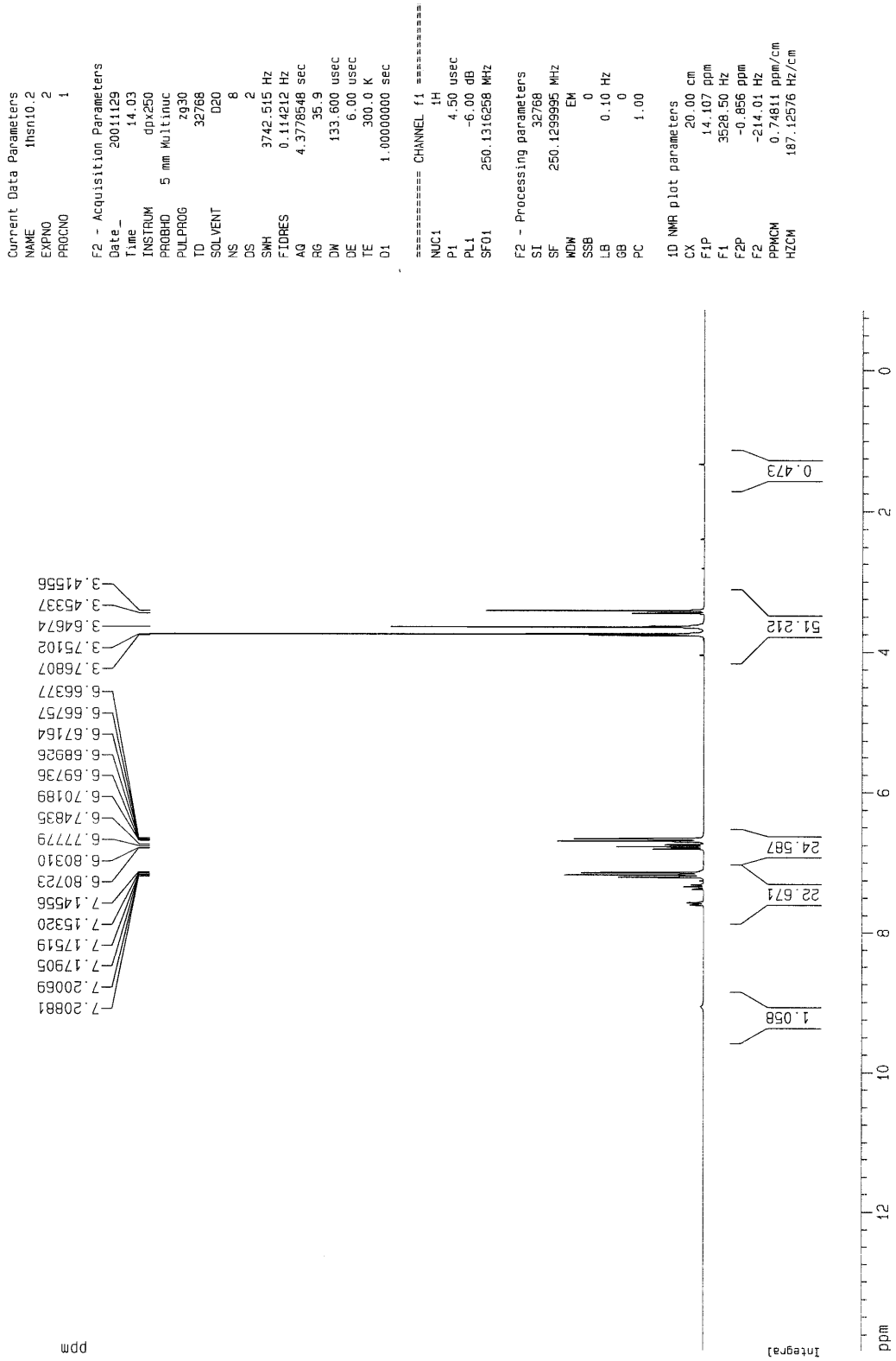
APPENDIX 11: ^{1}H NMR spectrum for **685** (combined).



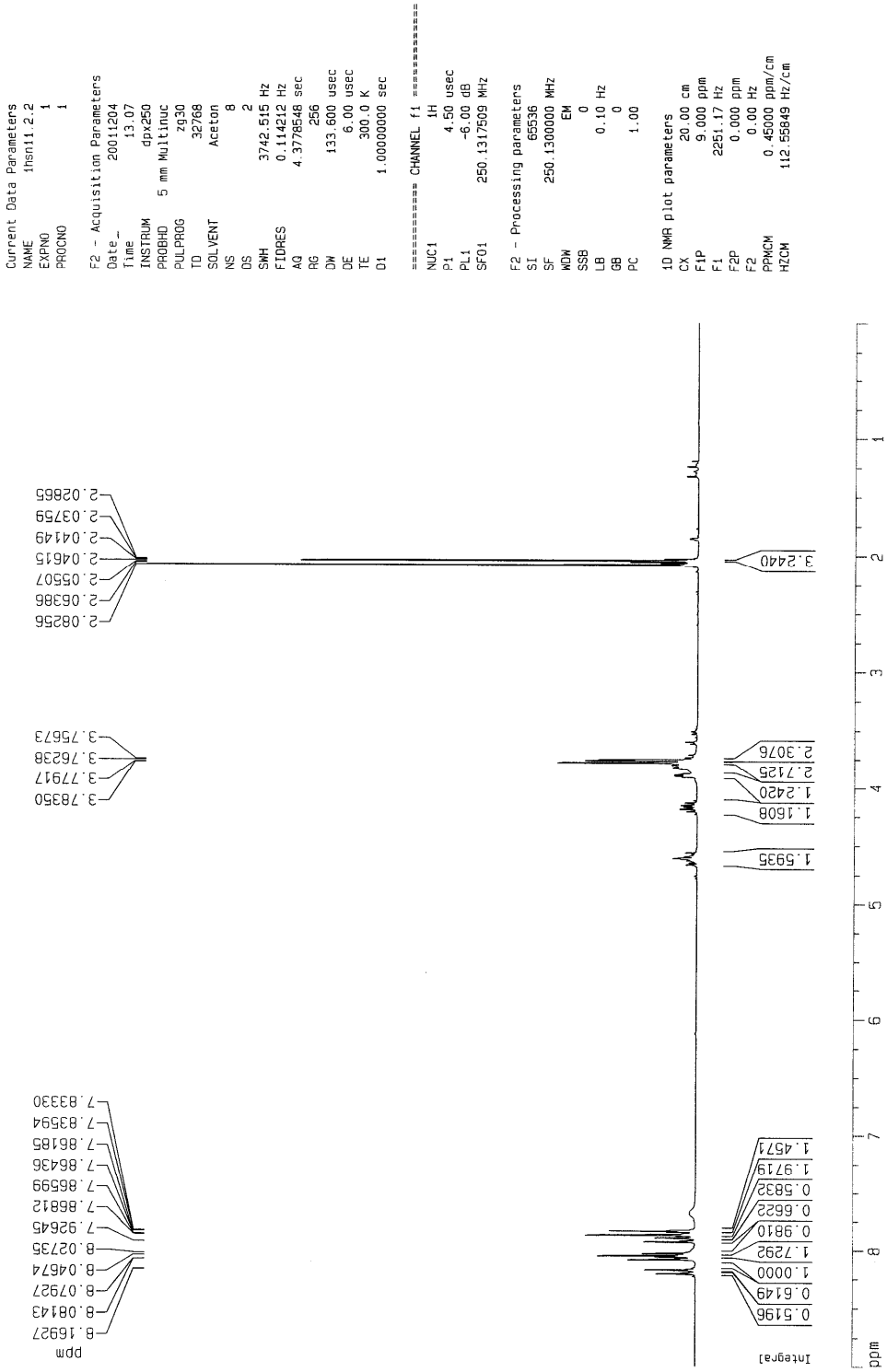
APPENDIX 12: ^{1}H NMR spectrum for attempted synthesis of **688**.



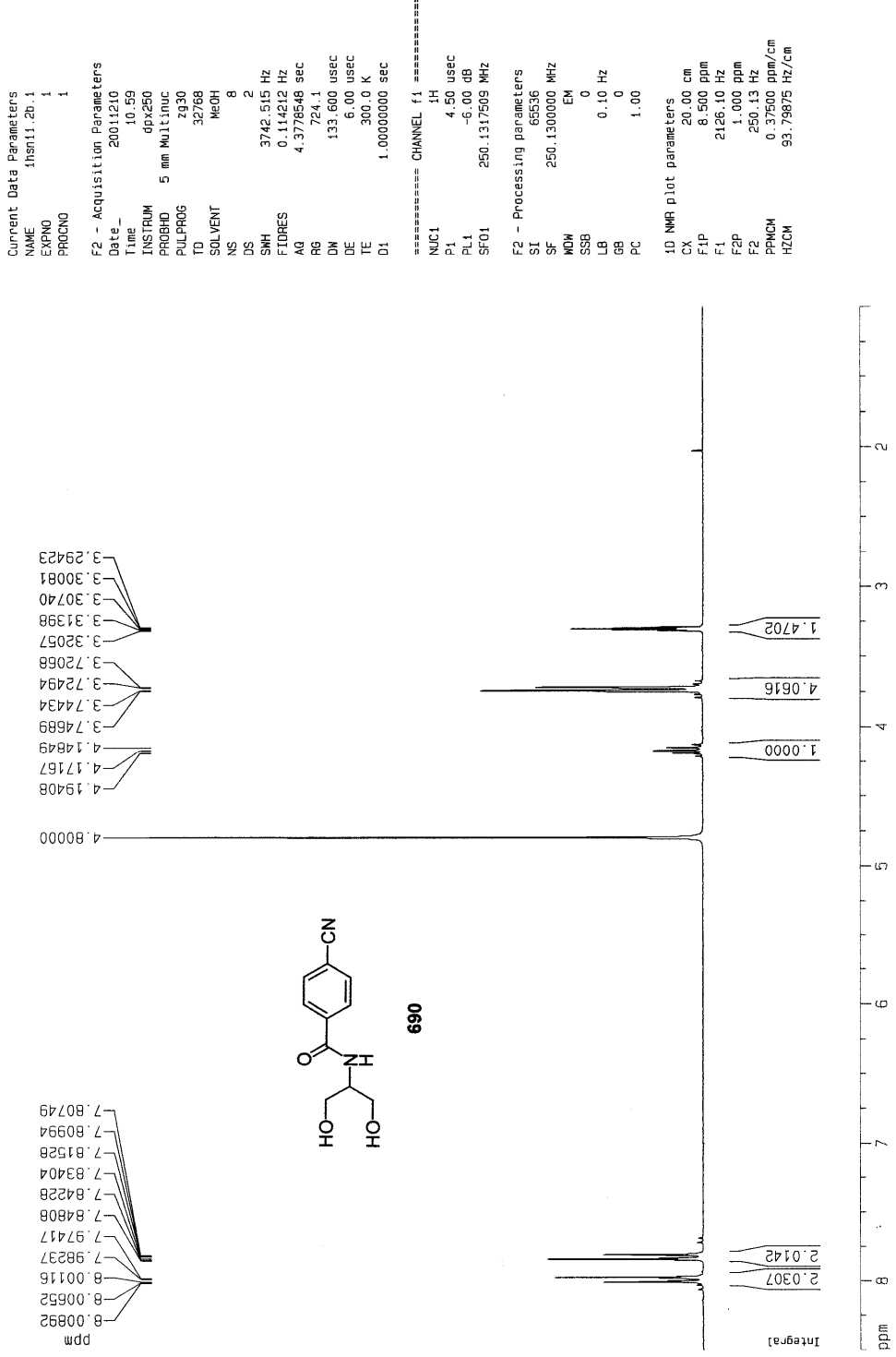
APPENDIX 13: ^{1}H NMR spectrum for attempted synthesis of **688** (filtrate).



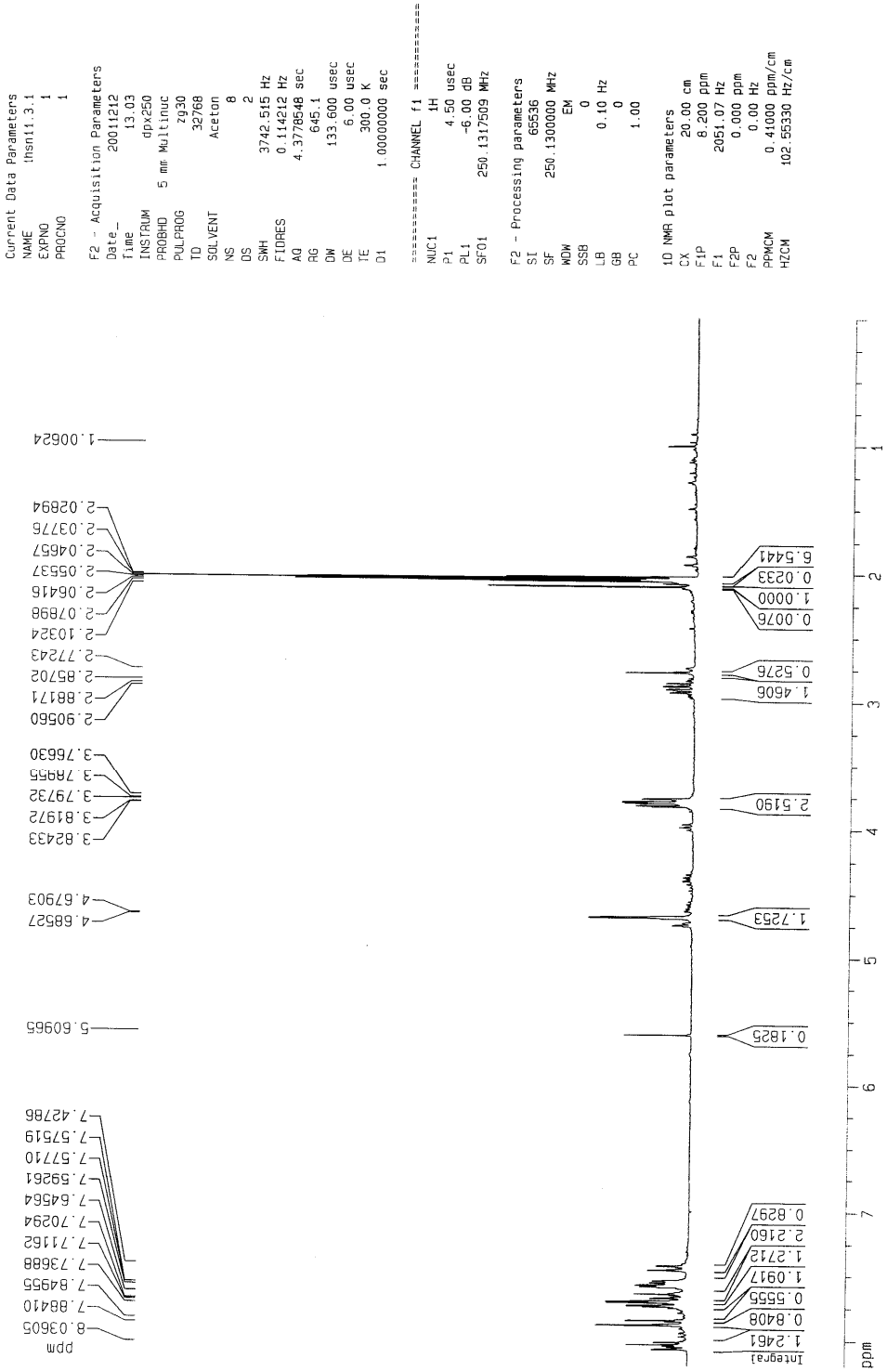
APPENDIX 14: ^{1}H NMR spectrum for attempted synthesis of **690** (16.2.3.1).



APPENDIX 15: ^{1}H NMR spectrum for **690** (16.2.3.2).



APPENDIX 16: ^{1}H NMR spectrum for attempted synthesis of **691** (16.2.4.1).



APPENDIX 17: ^{1}H NMR spectrum for attempted synthesis of **691** (16.2.4.2).