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(54) Title: CYCLIC PEPTIDES TARGETING α4β7 INTEGRIN

(57) Abstract: There is described herein antagonists of α4β7 integrin, and more particularly to cyclic peptide antagonists. Accordingly, there is described herein a compound of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are various substituents; stereocentres 1*, 2* and 3* are each independently selected from R and S; n is 1, 2, 3, or 4 and where n is 2-4, Z is an amino terminus of an amino acid; -C=0- adjacent L is the carboxy terminus of an amino acid; and L along with Z and -C=0- is a peptide.

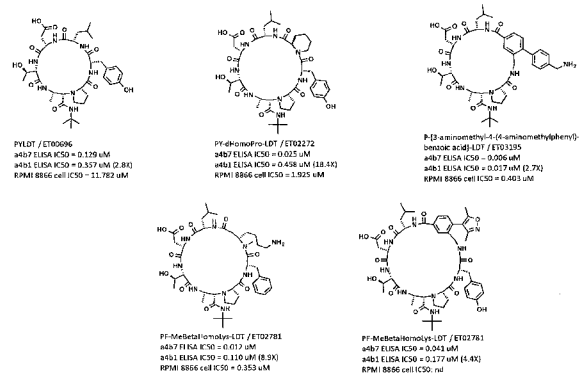
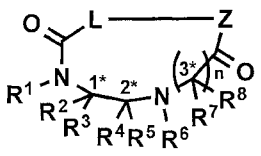


Figure 1



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CYCLIC PEPTIDES TARGETING α4β7 INTEGRIN

RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application No. 62/254003 filed on November 11, 2015, incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to antagonists of α4β7 integrin, and more particularly to cyclic peptide antagonists.

BACKGROUND OF THE INVENTION

Integrins are transmembrane receptors that are the bridges for cell-cell and cell-extracellular matrix (ECM) interactions. When triggered, integrins trigger chemical pathways to the interior (signal transduction), such as the chemical composition and mechanical status of the ECM.

Integrins are obligate heterodimers, having two different chains: the α (alpha) and β (beta) subunits.

The α4β7 integrin is expressed on lymphocytes and is responsible for T-cell homing into gut-associated lymphoid tissues through its binding to mucosal addressin cell adhesion molecule (MAdCAM), which is present on high endothelial venules of mucosal lymphoid organs.

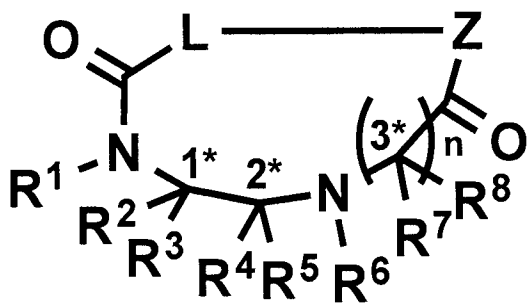
Inhibitors of specific integrin-ligand interactions have been shown effective as anti-inflammatory agents for the treatment of various autoimmune diseases. For example, monoclonal antibodies displaying high binding affinity for α4β7 have displayed therapeutic benefits for gastrointestinal auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis.

There is a need to develop improved α4β7 antagonists to prevent or treat inflammatory conidtions and/or autoimmune diseases.

Certain methods of making cyclic peptides (nacellins) are described in Applicant's PCT Publication No. WO 2010/105363.

SUMMARY OF THE INVENTION

In an aspect, there is provided, a compound of formula (I):



(I)

wherein

R^1 is H; lower alkyl; aryl; heteroaryl; alkenyl; or heterocycle; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

R^2 and R^3 are each independently an amino acid chain of a proteinogenic or a non-proteinogenic alpha-amino acid,

provided that R^2 and R^3 may be covalently linked to each other to form a ring;

R^4 and R^5 are each independently H; lower alkyl; aryl; heteroaryl; alkenyl; heterocycle; acids of the formula –C(O)OH; esters of the formula –C(O)OR* wherein R* is selected from alkyl and aryl; amides of the formula –C(O)NR**R***, wherein R** and R*** are independently selected from H, alkyl and aryl; -CH_2C(O)R, wherein R is selected from –OH, lower alkyl, aryl, -loweralkyl-aryl, or –NRaRb, where Ra and Rb are independently

selected from H, lower alkyl, aryl or –loweralkyl-aryl; or -C(O)Rc, wherein Rc is selected from lower alkyl, aryl or –lower alkyl-aryl; or –lower alkyl-ORd, wherein Rd is a suitable protecting group or OH group; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

provided that R^2 or R^3 can be covalently linked to R^1 to form a cyclic secondary amine, and /or to R^4 or R^5 to form a ring, R^4 and R^5 may also be covalently linked to each other to form a ring;

R^6 is H, lower alkyl, benzyl, alkenyl, lower alkyloxy; aryl; heteroaryl; heterocycle; –C(O)R****, wherein R**** is independently selected from alkyl, aryl, heteroaryl, amino, aminoalkyl, aminoaryl, aminoheteroaryl, alkoxy, aryloxy, heteroaryloxy; $-CH_2C(O)R$; or -C(O)Rc; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents,

or along with R^7 or R^8, a cyclic side chain of a proteinogenic or a non-proteinogenic amino acid having, the N-terminus thereof being the N-R^6, wherein the proteinogenic or a non-proteinogenic amino acid can be substituted with a suitable substituent;

R^7 and R^8 are independently selected from the amino acid side chains of a proteinogenic or a non-proteinogenic alpha-amino acid having the N-terminus thereof being the N-R^6, or may form a cyclic side chain with R^6;

stereocentres 1*, 2* and 3* are each independently selected from R and S;

n is 1, 2, 3, or 4 and where n is 2-4, each R^7 and each R^8 are independent of each other; and

wherein Z is an amino terminus of an amino acid; -C=O- adjacent L is the carboxy terminus of an amino acid; and L along with Z and –C=O- is a peptide having the following formula:

$$X^y – X^z – X^1 – X^2 – X^3$$

wherein X^y and X^z are each independently a proteinogenic or non-proteinogenic amino acid;

X^1 is Leucine or tert-butyl-Ala;

X^2 is Asp; and

X^3 is any amino acid listed under column X^3 of Table 1B.

In an aspect, there is provided, a pharmaceutical composition comprising a compound described herein along with the pharmaceutically acceptable carrier. The pharmaceutical composition may be formulated for any one of oral delivery, topical delivery and parenteral delivery.

In an aspect, there is provided, a method of treating inflammation or an autoimmune disease in a patient, comprising administering to the patient a therapeutically effective amount of the compound described herein. Preferably the inflammation or an autoimmune disease is gastrointestinal.

In an aspect, there is provided, a method for treating a condition in a patient associated with a biological function of an α4β7 integrin, the method comprising administering to the patient a therapeutically effective amount of the compound described herein.

In an aspect, there is provided, a method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound described herein, wherein the disease or condition is a local or systemic infection of a virus or retrovirus.

In an aspect, there is provided, a method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound described herein, wherein the hepatitis A, B or C, hepatic encephalopathy, non-alcoholic steatohepatitis, cirrhosis, variceal bleeding, hemochromatosis, Wilson disease, tyrosinemia, alpha-1-antitrypsin deficiency, glycogen storage disease, hepatocellular carcinoma, liver cancer, primary biliary cholangitis, primary sclerosing

cholangitis, primary biliary sclerosis, biliary tract disease, autoimmune hepatitis, or graft-versus-host disease.

BRIEF DESCRIPTION OF FIGURES AND TABLES

These and other features of the preferred embodiments of the invention will become more apparent in the following detailed description in which reference is made to the appended drawings and tables wherein:

Figure 1 shows representative compounds of the present application, namely from the following classes, 18-membered ring, 21-membered ring, 21-membered ring (non-canonical, i.e. having a delta amino acid), 22-membered ring, and 24-membered ring.

Figure 2 shows a representative 18-membered ring compound along with variations made at certain positions with corresponding α4β7 integrin ELISA IC50 binding values associated with those variations.

Figure 3 shows a representative 21-membered ring compound along with variations made at certain positions with corresponding α4β7 integrin ELISA IC50 binding values associated with those variations.

Figure 4 shows a representative 21-membered ring (non-canonical, i.e. having a delta amino acid) compound along with variations made at certain positions with corresponding α4β7 integrin ELISA IC50 binding values associated with those variations.

Figure 5 shows a representative 22-membered ring compound along with variations made at certain positions with corresponding α4β7 integrin ELISA IC50 binding values associated with those variations.

Figure 6 shows results of T lymphocyte trafficking studies (from peripheral blood to mesenteric lymph nodes) following single doses of various compounds.

Figure 7 shows the pharmacokinetic profile for a test article (ET1792) via one and two oral doses in naïve mice.

Figure 8 shows the pharmacokinetic profile for a test article (ET1792) after a single oral dose.

Figure 9 shows the exposure of ET2451 in the liver of naïve mice that have received the test compound as a single oral or intravenous dose.

Figure 10 shows the disease activity index score for the various treatment groups at day 5 and day 8 following the initiation of dextran sulfate sodium treatment in mice.

Figure 11 shows data from ex vivo assessments of the colon taken from mice exposed to DSS and treated with various test compounds.

Figure 12 shows further detail on the colon injury following DSS exposure and test nacellin treatment in mice.

Figure 13 shows the outcome of FACS analyses of T lymphocyte content in peripheral lymph nodes, mesenteric lymph nodes and peripheral blood taken from mice exposed to DSS irritant and treated for three days with various test nacellins or control.

Table 1 shows compounds exhibiting α4β7 integrin affinity, selectivity and/or activity; and specifically with respect to these compounds: (A) the structure of the linker portion; (B) the structure of the peptide portion; and (C) the affinity, selectivity and activity values.

To aid reading of the table, the following is noted:

Table 1A:

If R2 is H and R3 is CH3, the carbon atom bearing R2 and R3 has S-configuration.

If R2 is CH3 and R3 is H, the carbon atom bearing R2 and R3 has R-configuration.

If R2 is H and R3 is CH2-S-Ph, the carbon atom bearing R2 and R3 has S-configuration.

If R4 is H and R5 is C(O)-NH-tert-Butyl, the carbon atom bearing R4 and R5 has S-configuration.

If R4 is C(O)-NH-tert-Butyl and R5 is H, the carbon atom bearing R4 and R5 has R-configuration.

If R1 and R2 are both Pro-, the R1 and R2 substituents are covalently bound and form the pyrrolidine ring of Pro.

Table 1B

If R6 and R7 are both Pro, the R6 and R7 substituents are covalently bound and form the pyrrolidine ring of Pro.

If R6 and R8 are both dPro, the R6 and R8 substituents are covalently bound and form the pyrrolidine ring of dPro.

If R6 and R7 are both [(4S)-fluoro-Pro], the R6 and R7 substituents are covalently bound and form the pyrrolidine ring of [(4S)-fluoro-Pro].

If R7 is Nva and R8 is H, the carbon atom bearing R7 and R8 has S-configuration.

If R6 and R7 are both Hyp, the R6 and R7 substituents are covalently bound and form the pyrrolidine ring of Hyp.

If no entry exists under column Xz, the residue is absent.

Table 1C

If no entry exists under any of the columns, no data was collected.

Table 2 shows compounds exhibiting less α4β7 integrin affinity, selectivity and/or activity; and specifically with respect to these compounds: (A) the structure of the linker portion; (B) the structure of the peptide portion; and (C) the affinity, selectivity and activity values.

To aid reading of the table, the following is noted:

Table 2A

If R2 is H and R3 is CH3, the carbon atom bearing R2 and R3 has S-configuration.

If R2 is CH3 and R3 is H, the carbon atom bearing R2 and R3 has R-configuration.

If R4 is H and R5 is C(O)-NH-tert-Butyl, the carbon atom bearing R4 and R5 has S-configuration.

If R4 is C(O)-NH-tert-Butyl and R5 is H, the carbon atom bearing R4 and R5 has R-configuration.

If R1 and R2 are both Pro-, the R1 and R2 substituents are covalently bound and form the pyrrolidine ring of Pro.

Table 2B

If R6 and R7 are both Pro, the R6 and R7 substituents are covalently bound and form the pyrrolidine ring of Pro.

If R6 and R8 are both dPro, the R6 and R8 substituents are covalently bound and form the pyrrolidine ring of dPro.

If no entry exists under column Xz, the residue is absent.

Table 2C

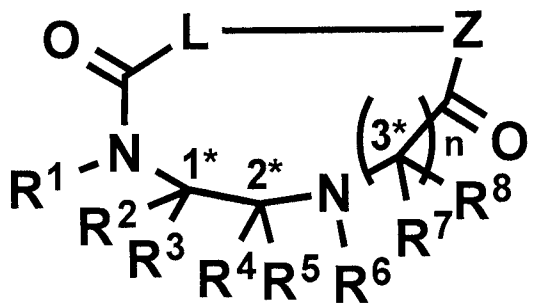
If no entry exists under any of the columns, no data was collected.

Table S1 is a correspondence table linking the compounds described herein with the synthesis protocols outlined in the methods and materials.

DETAILED DESCRIPTION

In the following description, numerous specific details are set forth to provide a thorough understanding of the invention. However, it is understood that the invention may be practiced without these specific details.

In an aspect, there is provided, a compound of formula (I):



(I)

wherein

R^1 is H; lower alkyl; aryl; heteroaryl; alkenyl; or heterocycle; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

R^2 and R^3 are each independently an amino acid chain of a proteinogenic or a non-proteinogenic alpha-amino acid,

provided that R^2 and R^3 may be covalently linked to each other to form a ring;

R^4 and R^5 are each independently H; lower alkyl; aryl; heteroaryl; alkenyl; heterocycle; acids of the formula –C(O)OH; esters of the formula –C(O)OR* wherein R* is selected from alkyl and aryl; amides of the formula –C(O)NR**R***, wherein R** and R*** are independently selected from H, alkyl and aryl; $-CH_2C(O)R$, wherein R is selected from –OH, lower alkyl, aryl, -loweralkyl-aryl, or –NRaRb, where Ra and Rb are independently selected from H, lower alkyl, aryl or –loweralkyl-aryl; or -C(O)Rc, wherein Rc is selected from lower alkyl, aryl or –lower alkyl-aryl; or –lower alkyl-ORd, wherein Rd is a suitable protecting group or OH group; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

provided that R^2 or R^3 can be covalently linked to R^1 to form a cyclic secondary amine, and /or to R^4 or R^5 to form a ring, R^4 and R^5 may also be covalently linked to each other to form a ring;

R^6 is H, lower alkyl, benzyl, alkenyl, lower alkyloxy; aryl; heteroaryl; heterocycle; –C(O)R****, wherein R**** is independently selected from alkyl, aryl, heteroaryl, amino,

aminoalkyl, aminoaryl, aminoheteroaryl, alkoxy, aryloxy, heteroaryloxy; -$CH_2C(O)R$; or -C(O)Rc; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents,

or along with R^7 or R^8, a cyclic side chain of a proteinogenic or a non-proteinogenic amino acid having, the N-terminus thereof being the N-R^6, wherein the proteinogenic or a non-proteinogenic amino acid can be substituted with a suitable substituent;

R^7 and R^8 are independently selected from the amino acid side chains of a proteinogenic or a non-proteinogenic alpha-amino acid having the N-terminus thereof being the N-R^6, or may form a cyclic side chain with R^6;

stereocentres 1*, 2* and 3* are each independently selected from R and S;

n is 1, 2, 3, or 4 and where n is 2-4, each R^7 and each R^8 are independent of each other; and

wherein Z is an amino terminus of an amino acid; -C=O- adjacent L is the carboxy terminus of an amino acid; and L along with Z and –C=O- is a peptide having the following formula:

$$X^y – X^z – X^1 – X^2 – X^3$$

wherein X^y and X^z are each independently a proteinogenic or non-proteinogenic amino acid;

X^1 is Leucine or tert-butyl-Ala;

X^2 is Asp; and

X^3 is any amino acid listed under column X^3 of Table 1B.

The compounds shown in Tables 1A, 1B and 1C exhibit antagonistic activity against α4β7 integrin and having selectivity over α4β1 integrin. A person skilled in the art would expect

that substituents R^1-R^8 and amino acids X^y, X^z, X^1, X^2, and X^3 outlined in -Tables 1A and 1B with respect to different compounds could be combined in any manner and would likely result in a compound that would exhibit α4β7 integrin activity and selectivity.

As used herein, the term "amino acid" refers to molecules containing an amine group, a carboxylic acid group and a side chain that varies. Amino acid is meant to include not only the twenty amino acids commonly found in proteins but also non-standard amino acids and unnatural amino acid derivatives known to those of skill in the art, and therefore includes, but is not limited to, alpha, beta and gamma amino acids. Peptides are polymers of at least two amino acids and may include standard, non-standard, and unnatural amino acids. A peptide is a polymer of two or more amino acids.

The following abbreviations are used herein:

Abbreviation	Description
1,2-cis-ACHC	cis-2-aminocyclohexanecarboxylic acid
1,2-trans-ACHC	trans-2-aminocyclohexanecarboxylic acid
1Nal	1-napthylalanine
2Abz	anthranilic acid, 2-aminobenzoic acid
2Igl	2-indanylglycine
2Nal	2-napthylalanine
Abu	2-aminobutyric acid
Aic	aminoindan-2-carboxylic acid
alloIle	allo-sioleucine, (2S,3R)-2-amino-3-methylpentanoic acid
alloThr	allo-threonine, (2S,3S)-2-amino-3-hydroxybutyric acid
alphaMePhe	α-methyl-phenylalanine, (S)-(−)-2-amino-2-methyl-3-phenylpropionic acid
Asp(ethyl ester)	aspartic acid β-ethyl ester
Atc	2-aminotetraline-2-carboxylic acid
Aze	azetidine-2-carboxylic acid
BHT	butylated hydroxytoluene
Bip	biphenylalanine
C10	sebacic acid
C12	dodecanedioic
C7	pimelic acid
C8	suberic acid
C9	azelaic acid
Cha	β-cyclohexyl alanine, (S)-2-amino-3-cyclohexylpropionic acid
Chg	cyclohexyl glycine

cis-dhyp	cis-D-4-Hydroxyproline, (2R,4R)-4-Hydroxypyrrolidine-2-carboxylic acid
cycloLeu	cyclo leucine, 1-Aminocyclopentane-1-carboxylic acid
cyclopropylAla	β-cyclopropyl alanine, (S)-2-amino-3-cyclopropyl-propionic acid
d2Igl	2-indanyl-D-glycine
Dap(Cbz)	Nβ-Z-2,3-diaminopropionic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
dHyp	trans-D-4-hydroxyproline, (2R,4S)-4-hydroxypyrrolidine-2-carboxylic acid
DIAD	diisopropyl azodicarboxylate
DIG	diglycolic acid
DIPEA	N,N-diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
dMeArg	N-methyl-D-arginine
dMebetaHomoLys	N-methyl-D-β-homoLys
dMeLys	N-methyl-D-Lysine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dNle	D-norleucine
dOrn	D-ornithine
dOrn(dimethyl)	Nδ-dimethyl-D-ornithine
dPip	D-pipecolic acid, D-homoPro
dSer(OBn)	O-benzyl-D-serine
dTic	(3R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
dTiq	D-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid
dTyr(OAllyl)	O-allyl-D-tyrosine
dTyr(OBn)	O-benzyl-D-tyrosine
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
Fmoc	9-fluorenylmethoxycarbonyl
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCTU	2-(6-chloro-1H-benzotriazole-1-yl)- 1,1,3,3-tetramethylaminium hexafluorophosphate
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
His(Bn)	Nτ-benzyl-histidine
HomocycloLeu	homocyclo leucine, 1-Aminocyclohexanecarboxylic acid
Hyp	trans-4-hydroxyproline, (2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid
Hyp(OBn)	O-benzyl-trans-4-hydroxyproline
MeAsp	N-methyl aspartic acid
MebetaHomoLys	N-methyl β-homoLysine
MebetaHomoLys(Me)2	Nα-methyl-Nε-dimethyl-β-homoLysine
MeLeu	N-methyl leucine

MeMet	N-methyl methionine
MePhe	N-methyl phenylalanine
metaY(Opr)	metaTyrosine
MeThr	N-methyl threonine
MeTyr	N-methyl tyrosine
NMP	N-methylpyrrolidone
Nosyl chloride	2-nitrobenzenesulfonyl chloride
Nva	norvaline
Orn(acetamide)	Nδ-acetamide-ornithine
Orn(benzamide)	Nδ-benzamide-ornithine
Orn(ethylcarbamate)	Nδ-ethylcarbamate-ornithine
Orn(methanesulfonamide)	Nδ-methanesulfonamide-ornithine
Orn(pentyl amide)	Nδ-pentyl amide-ornithine
PDA	1,4-phenyldiacetic acid
Pen	penicillamine, β,β-dimethyl-cysteine
Pip	pipecolic acid, homoPro
Sar	sarcosine, N-methyl glycine
tertbutylAla	β-tert-butyl alanine, neopentylglycine
TFA	trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	tetrahydrofuran
Thr(OBn)	O-benzyl-threonine
Thr(OEt)	O-ethyl-threonine
Thr(OMe)	O-methyl-threonine
Tic	(3S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TIS	triisopropylsilane
Tyr(2-methoxy diaryl ether)	O-2-methoxy-phenyl-tyrosine
Tyr(2-tolyl diaryl ether)	O-2-methyl-phenyl-tyrosine
Tyr(3,4-difluoro diaryl ether)	O-3,4-difluoro-phenyl-tyrosine
Tyr(3,4-dimethyl diaryl ether)	O-3,4-dimethyl-phenyl-tyrosine
Tyr(3-CO2Me diaryl ether)	O-3-methylester-phenyl-tyrosine
Tyr(3-fluoro diaryl ether)	O-3-fluoro-phenyl-tyrosine
Tyr(3-methoxy diaryl ether)	O-3-methoxy-phenyl-tyrosine
Tyr(3-methyl diaryl ether)	O-3-methyl-phenyl-tyrosine
Tyr(4-CF3 diaryl ether)	O-4-trifluoromethyl-phenyl-tyrosine
Tyr(4-CO2H diaryl ether)	O-4-carboxylate-phenyl-tyrosine
Tyr(4-CO2Me diaryl ether)	O-4-methylester-phenyl-tyrosine
Tyr(4-fluoro diaryl ether)	O-4-fluoro-phenyl-tyrosine

Tyr(4-methoxy diaryl ether)	O-4-methoxy-phenyl-tyrosine
Tyr(OAllyl)	O-allyl-tyrosine
Tyr(OPh)	O-phenyl-tyrosine
vinyl-Br-Leu	2-amino-4-bromo-4-pentenoic acid

The term "suitable substituent" as used in the context of the present invention is meant to include independently H; hydroxyl; cyano; alkyl, such as lower alkyl, such as methyl, ethyl, propyl, n-butyl, t-butyl, hexyl and the like; alkoxy, such as lower alkoxy such as methoxy, ethoxy, and the like; aryloxy, such as phenoxy and the like; vinyl; alkenyl, such as hexenyl and the like; alkynyl; formyl; haloalkyl, such as lower haloalkyl which includes CF_3, CCl_3 and the like; halide; aryl, such as phenyl and napthyl; heteroaryl, such as thienyl and furanyl and the like; amide such as $C(O)NR_aR_b$, where R_a and R_b are independently selected from lower alkyl, aryl or benzyl, and the like; acyl, such as $C(O)\text{-}C_6H_5$, and the like; ester such as $\text{-}C(O)OCH_3$ the like; ethers and thioethers, such as O-Bn and the like; thioalkoxy; phosphino; and $-NR_aR_b$, where R_a and R_b are independently selected from lower alkyl, aryl or benzyl, and the like. It is to be understood that a suitable substituent as used in the context of the present invention is meant to denote a substituent that does not interfere with the formation of the desired product by the processes of the present invention.

As used in the context of the present invention, the term "lower alkyl" as used herein either alone or in combination with another substituent means acyclic, straight or branched chain alkyl substituent containing from one to six carbons and includes for example, methyl, ethyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, and the like. A similar use of the term is to be understood for "lower alkoxy", "lower thioalkyl", "lower alkenyl" and the like in respect of the number of carbon atoms. For example, "lower alkoxy" as used herein includes methoxy, ethoxy, *t*-butoxy.

The term "alkyl" encompasses lower alkyl, and also includes alkyl groups having more than six carbon atoms, such as, for example, acyclic, straight or branched chain alkyl substituents having seven to ten carbon atoms.

The term "aryl" as used herein, either alone or in combination with another substituent, means an aromatic monocyclic system or an aromatic polycyclic system. For example, the term "aryl" includes a phenyl or a napthyl ring, and may also include larger aromatic polycyclic systems, such as fluorescent (eg. anthracene) or radioactive labels and their derivatives.

The term "heteroaryl" as used herein, either alone or in combination with another substituent means a 5, 6, or 7-membered unsaturated heterocycle containing from one to 4 heteroatoms selected from nitrogen, oxygen, and sulphur and which form an aromatic system. The term "heteroaryl" also includes a polycyclic aromatic system comprising a 5, 6, or 7-membered unsaturated heterocycle containing from one to 4 heteroatoms selected from nitrogen, oxygen, and sulphur.

The term "cycloalkyl" as used herein, either alone or in combination with another substituent, means a cycloalkyl substituent that includes for example, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloalkyl-alkyl-" as used herein means an alkyl radical to which a cycloalkyl radical is directly linked; and includes, but is not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. A similar use of the "alkyl" or "lower alkyl" terms is to be understood for aryl-alkyl-, aryl-loweralkyl- (eg. benzyl), -lower alkyl-alkenyl (eg. allyl), heteroaryl-alkyl-, and the like as used herein. For example, the term "aryl-alkyl-" means an alkyl radical, to which an aryl is bonded. Examples of aryl-alkyl- include, but are not limited to, benzyl (phenylmethyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl.

As used herein, the term "heterocycle", either alone or in combination with another radical, means a monovalent radical derived by removal of a hydrogen from a three- to seven-membered saturated or unsaturated (including aromatic) cyclic compound containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of such heterocycles include, but are not limited to, aziridine, epoxide, azetidine, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, hydantoin, diazepine, imidazole, isoxazole, thiazole, tetrazole, piperidine, piperazine, homopiperidine,

homopiperazine, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide or pyrimidine, and the like.

The term "alkenyl", as used herein, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight chain radical containing two or more carbon atoms, at least two of which are bonded to each other by a double bond. Examples of such radicals include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl.

The term "alkynyl", as used herein is intended to mean an unsaturated, acyclic straight chain radical containing two or more carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of such radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl.

The term "alkoxy" as used herein, either alone or in combination with another radical, means the radical -O-(C_{1-n})alkyl wherein alkyl is as defined above containing 1 or more carbon atoms, and includes for example methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. Where n is 1 to 6, the term "lower alkoxy" applies, as noted above, whereas the term "alkoxy" encompasses "lower alkoxy" as well as alkoxy groups where n is greater than 6 (for example, n = 7 to 10). The term "aryloxy" as used herein alone or in combination with another radical means –O-aryl, wherein aryl is defined as noted above.

A protecting group or protective group is a substituent introduced into a molecule to obtain chemoselectivity in a subsequent chemical reaction. Many protecting groups are known in the art and a skilled person would understand the kinds of protecting groups that would be incorporated and could be used in connection with the methods described herein. In "protecting group based peptide synthesis", typically solid phase peptide synthesis, the desired peptide is prepared by the step-wise addition of amino acid moieties to a building peptide chain. The two most widely used protocols, in solid-phase synthesis, employ tert-butyloxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc) as amino protecting groups. Amino protecting groups generally protect an amino group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used amino protecting groups are disclosed in Greene, T. W. et al., Protective

Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons (1999). Amino protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxyacetyl, .alpha.-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; alkoxy- or aryloxy-carbonyl groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, .alpha.-,.alpha.-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Amine protecting groups also include cyclic amino protecting groups such as phthaloyl and dithiosuccinimidyl, which incorporate the amino nitrogen into a heterocycle. Typically, amino protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, Alloc, Teoc, benzyl, Fmoc, Boc and Cbz. It is well within the skill of the ordinary artisan to select and use the appropriate amino protecting group for the synthetic task at hand.

In some embodiments, R^1 is H.

In some embodiments, R^2 or R^3 is covalently linked to R^1 to form proline having NR^1 as the N-terminus.

In some embodiments, R^2 and R^3 are not both H.

In some embodiments, R^2 and R^3 are each independently selected from the group consisting of amino acid chains of a proteinogenic or a non-proteinogenic alpha-amino acids.

In some embodiments, R^2 and R^3 are H and CH_3 respectively or vice versa.

In some embodiments, R^2 or R^3 is -CH2-S-R^s, wherein R^s is selected from lower alkyl; lower amino alkyl; aryl; heteroaryl; alkenyl; or heterocycle; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents; preferably R^s is phenyl or phenyl substituted with lower alkyl, halogen; or lower amino alkyl.

In some embodiments, R^4 and R^5 are not both H.

In some embodiments, R** and R*** are not both H.

In some embodiments, R^4 and R^5 are each independently H, or C(O)-NHR^t, wherein R^t is H or a lower alkyl. Preferably, R^t is tert-butyl or H.

In some embodiments, R^6 is H.

In some embodiments, R^6 and either R^8 or R^9 form a ring resulting in a proline residue having N-R^6 as its N-terminus.

In some embodiments, n is 1.

In some embodiments, Z along with L and –C=O is any one of SEQ ID NOs. 1-380.

In some embodiments, X^1 is Leu.

In some embodiments, X^2 is Asp.

In some embodiments, X^3 is Thr.

In some embodiments, X^3 is Val.

In some embodiments, X^3 is Ile.

In some embodiments, X^y and X^z are each independently a proteinogenic or non-proteinogenic alpha-amino acid.

In some embodiments, X^z is a proteinogenic or non-proteinogenic beta-amino acid.

In some embodiments, X^z is betaHomoLys or MethylbetaHomoLys.

In some embodiments, X^y and X^z are each a primary amino acid.

In some embodiments, X^y and X^z are each any amino acid listed under column X^y and column X^z respectively of Table 1B.

In various embodiments, the compound is any one of compounds 1-397.

In certain embodiments, there is provided pharmaceutically acceptable salts of the compounds described herein. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible, which are suitable for treatment of diseases without undue toxicity, irritation, and allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by treatment of an amino group with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2- naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Also, amino groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric,

and organic acids such as oxalic, maleic, succinic, and citric. In certain embodiments, any of the peptide compounds described herein are salt forms, e.g., acetate salts.

In an aspect, there is provided, a pharmaceutical composition comprising a compound described herein along with the pharmaceutically acceptable carrier. The pharmaceutical composition may be formulated for any one of oral delivery, topical delivery and parenteral delivery.

As used herein, "pharmaceutically acceptable carrier" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the pharmacological agent.

In an aspect, there is provided, a method of treating inflammation or an autoimmune disease in a patient, comprising administering to the patient a therapeutically effective amount of the compound described herein. Preferably the inflammation or an autoimmune disease is gastrointestinal.

In an aspect, there is provided, a method for treating a condition in a patient associated with a biological function of an α4β7 integrin, the method comprising administering to the patient a therapeutically effective amount of the compound described herein.

In some embodiments, the condition or disease is Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease, Celiac disease (nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis, radiotherapy, chemotherapy, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic

bronchitis, chronic sinusitis, asthma, primary sclerosing cholangitis, human immunodeficiency virus (HIV) infection in the GI tract, eosinophilic asthma, eosinophilic esophagitis, gastritis, colitis, microscopic colitis, graft versus host disease, colitis associated with radio- or chemo-therapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, chronic granulomatous disease, glycogen storage disease type 1b, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Wiskott-Aldrich Syndrome, or pouchitis resulting after proctocolectomy and ileoanal anastomosis and various forms of gastrointestinal cancer, osteoporosis, arthritis, multiple sclerosis, chronic pain, weight gain, and depression. In another embodiment, the condition is pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma or graft versus host disease.

In preferable embodiments, is an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease.

In an aspect, there is provided, a method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound described herein, wherein the disease or condition is a local or systemic infection of a virus or retrovirus.

In some embodiments, the a virus or retrovirus is echovirus 1 and 8, echovirus 9/Barty Strain, human papilloma viruses, hantaviruses, rotaviruses, adenoviruses, foot and mouth disease virus, coxsackievirus A9, human parechovirus 1 or human immunodeficiency virus type 1.

In an aspect, there is provided, a method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound described herein, wherein the hepatitis A, B or C, hepatic encephalopathy, non-alcoholic steatohepatitis, cirrhosis, variceal bleeding, hemochromatosis, Wilson disease, tyrosinemia, alpha-1-antitrypsin deficiency, glycogen storage disease, hepatocellular carcinoma, liver cancer, primary biliary cholangitis, primary sclerosing cholangitis, primary biliary sclerosis, biliary tract disease, autoimmune hepatitis, or graft-versus-host disease.

In some embodiments, the compound inhibits binding of α4β7 integrin to MAdCAM. Preferably, the compound selectively inhibits binding of α4β7 integrin to MAdCAM.

In any embodiment, the patient is preferably a human.

As used herein, the terms "disease", "disorder", and "condition" may be used interchangeably.

As used herein, "inhibition," "treatment," "treating," and "ameliorating" are used interchangeably and refer to, e.g., stasis of symptoms, prolongation of survival, partial or full amelioration of symptoms, and partial or full eradication of a condition, disease or disorder in a subject, e.g., a mammal.

As used herein, "prevent" or "prevention" includes (i) preventing or inhibiting the disease, injury, or condition from occurring in a subject, e.g.., a mammal, in particular, when such subject is predisposed to the condition but has not yet been diagnosed as having it; or (ii) reducing the likelihood that the disease, injury, or condition will occur in the subject.

As used herein, "therapeutically effective amount" refers to an amount effective, at dosages and for a particular period of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the pharmacological agent may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the pharmacological agent to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the pharmacological agent are outweighed by the therapeutically beneficial effects.

In some embodiments, the compound is administered by a form of administration selected from the group consisting of oral, intravenous, peritoneal, intradermal, subcutaneous, intramuscular, intrathecal, inhalation, vaporization, nebulization, sublingual, buccal, parenteral, rectal, vaginal, and topical.

In some embodiments, the compound is administered as an initial does followed by one or more subsequent doses and the minimum interval between any two doses is a period of less than 1 day, and wherein each of the doses comprises an effective amount of the compound.

In some embodiments, the effective amount of the compound is the amount sufficient to achieve at least one of the following selected from the group consisting of: a) about 50% or greater saturation of MAdCAM binding sites on α4β7 integrin molecules; b) about 50% or greater inhibition of α4β7 integrin expression on the cell surface; and c) about 50% or greater saturation of MAdCAM binding sites on α4β7 molecules and about 50% or greater inhibition of α4β7 integrin expression on the cell surface, wherein i) the saturation is maintained for a period consistent with a dosing frequency of no more than twice daily; ii) the inhibition is maintained for a period consistent with a dosing frequency of no more than twice daily; or iii) the saturation and the inhibition are each maintained for a period consistent with a dosing frequency of no more than twice daily.

In some embodiments, the compound is administered at an interval selected from the group consisting of around the clock, hourly, every four hours, once daily, twice daily, three times daily, four times daily, every other day, weekly, bi-weekly, and monthly.

The advantages of the present invention are further illustrated by the following examples. The examples and their particular details set forth herein are presented for illustration only and should not be construed as a limitation on the claims of the present invention.

EXAMPLES

Methods and Materials

Synthesis

Methods applicable for making the cyclic peptides described herein can be found generally in Applicant's PCT Publication No. WO 2010/105363 and in an application filed on the same day herewith titled "Fragment Synthesis of Cyclic Peptides" (Attorney Docket No. 55813832-6PCT) and claiming common priority to U.S. Provisional Application No. 62/254003 filed on November 11, 2015.

More specifically, the below protocols were used to synthesize each of the compounds as indicated in Table S1.

Protocol A: General nacellin synthesis

1. Preparation of resin: Fmoc amino acid (1.1 eq. with respect to resin) was dissolved in CH_2Cl_2 (10 mL/g of resin). If the amino acid did not dissolve completely, DMF was added slowly dropwise until a homogeneous mixture persisted upon stirring/sonication. The 2-chlorotrityl resin was allowed to swell in CH_2Cl_2 (5 mL/g of resin) for 15 minutes. The CH_2Cl_2 was then drained and the Fmoc amino acid solution was added to the vessel containing the 2-Cl Trt resin. DIPEA was added (2 eq. with respect to the amino acid) and the vessel was agitated for five minutes. Another 2 eq. of DIPEA was then added and the vessel was left to agitate for an additional 60 minutes. The resin was then treated with methanol (1 mL/g of resin) to endcap any remaining reactive 2-Cl Trt groups. The solution was mixed for 15 minutes, drained and then rinsed with CH_2Cl_2 (x3), DMF (x3), CH_2Cl_2 (x2), and MeOH (x3). The resin was then dried under vacuum and weighed to determine the estimated loading of Fmoc amino acid.

2. Preparation of linear peptide sequence via manual or automated synthesis: Fully protected resin-bound peptides were synthesized via standard Fmoc solid-phase peptide chemistry manually or using an automated peptide synthesizer. All *N*-Fmoc amino acids were employed.

a. Fmoc deprotection: the resin was treated with 20% piperidine in NMP twice, for 5 and 10 minutes respectively, with consecutive DMF and NMP washes after each addition.

b. Fmoc amino acid coupling: the resin was treated with 3 eq. of Fmoc amino acid, 3 eq. of HATU and 6 eq. of DIPEA in NMP for 60 minutes. For difficult couplings, a second treatment with 3 eq. of Fmoc amino acid, 3 eq. of HATU and 6 eq. of DIPEA in NMP for 40 minutes was employed.

3. General cleavage with retention of protecting groups: Once the desired linear sequence was synthesized, the resin was treated with either 1.) 1:3, HFIP:CH_2Cl_2 or 2.) 5% TFA in CH_2Cl_2, twice for 30 minutes each, to afford cleavage from the solid support. The solvent was then removed, followed by trituration twice with chilled *tert*-butyl methyl ether (or diethyl ether/hexanes) to give the desired product. The purity was then analyzed by reverse-phase LCMS.

Protocol B: Preparation of N-alkylated Fmoc amino acid building blocks

1. Resin prep: see protocol A, step 1

2. Fmoc deprotection: see protocol A, step 2a

3. Nosyl protection: The deprotected resin was stirred in CH_2Cl_2 (5 mL/mmol of resin) and DIPEA (6.5 eq.). A solution of Nosyl chloride (4.0 eq.) was added slowly, dropwise, over 30 minutes, to avoid a rapid exothermic reaction. After the addition was complete, stirring was continued at room temperature for three hours. The resulting nosyl-protected resin was filtered and washed with CH_2Cl_2, MeOH, CH_2Cl_2, and THF.

4. N-Methylation: To a suspension of resin in THF (10 mL/mmol of resin) was added a solution of triphenylphosphine (5 eq.) in THF (2 M) and MeOH (10 eq.). The stirring suspension was cooled in an ice bath. A solution of DIAD (5 eq.) in THF (1 M) was added dropwise, via addition funnel. After addition was complete the bath was removed and the reaction was stirred at room temperature for an additional 90 minutes. The resin was filtered, washed with THF (x4), CH_2Cl_2 (x3), and THF (x2).

5. Nosyl-deprotection: To a suspension of resin in NMP (10 mL/mmol of resin) was added 2-mercaptoethanol (10.1 eq.) and DBU (5.0 eq.). The solution became a dark green colour. After five minutes, the resin was filtered, washed with DMF until washes ran colourless. This procedure was repeated a second time, and the resin was then washed a final time with CH_2Cl_2.

6. Fmoc protection: To a suspension of resin in CH_2Cl_2 (7 mL/mmol of resin) was added a solution of Fmoc-Cl (4 eq.) in CH_2Cl_2 (7 mL), and DIPEA (6.1 eq.). The suspension was stirred at room temperature for four hours then filtered and washed with CH_2Cl_2 (x2), MeOH (x2), CH_2Cl_2 (x2), and Et_2O (x2).

7. Cleavage from resin: see protocol A, step 3

Protocol C: Reductive amination

1. Fmoc Weinreb amide formation: a mixture of Fmoc amino acid (1 mmol), *N,O*-dimethylhydroxylamine·HCl (1.2 eq.), and HCTU (1.2 eq.) in CH_2Cl_2 (6.5 mL), was cooled

to 0 °C. DIPEA (3 eq.) was then slowly added to the stirring mixture. The cooling bath was removed and the reaction was stirred at room temperature for 16 h. A 10% solution of HCl (4 mL) was added resulting in the formation of a precipitate, which was removed through filtration. The filtrate was washed with 10% HCl (3 x 4 mL) and brine (2 x 4 mL). The organic phase was then dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude Fmoc Weinreb amide, which was used in the next reaction without purification.

2. Fmoc amino aldehyde formation: lithium aluminum hydride powder (3 eq.) was placed in a dry flask. THF (Sigma-Aldrich, 250 ppm of BHT, ACS reagent > 99.0 %, 6.5 mL) was added, and the resulting slurry was cooled to -78 °C, with stirring. To the slurry was added a solution of the Fmoc Weinreb amide in THF (10 mL). The reaction vessel was transferred to an ice/water bath, and maintained at 0 °C for 1 h. To the reaction at 0 °C, was added dropwise acetone (1.5 mL), then H_2O (0.25 mL) and then the reaction was left to stir for an additional hour at room temperature. The mixture was filtered through Celite, washed with EtOAc (10 mL) and MeOH (10 mL), and the filtrate was concentrated. The crude material was dissolved in $CHCl_3$ (6.5 mL) and washed with brine (2 x 3 mL) and the organic phase was then dried over Na_2SO_4, filtered and concentrated to give the Fmoc amino aldehyde.

3. Reductive amination on-resin: the linear peptide on-resin was placed in a solid-phase peptide synthesis reaction vessel and diluted with DMF (22 mL/g of resin). The Fmoc aldehyde (4.0 eq.) was added and the reaction was left to shake overnight. The solution was then drained and the resin was washed with CH_2Cl_2 (x3) and DMF (x3). The resin was then diluted with a mixture of MeOH/CH_2Cl_2 (22 mL/g of resin, 1:3 ratio) and $NaBH_4$ (7 eq.) was subsequently added. The mixture was left to shake for four hours, then the solution was drained and the resin was washed with CH_2Cl_2 (x3) and DMF (x3).

Protocol D: Fragment-based macrocyclization

In a two-dram vial, 0.1 mmol of the linear peptide and DEPBT (1.5 eq.) were dissolved in 5 mL of freshly distilled THF (0.02 M). DIPEA (3 eq.) was then added and the reaction mixture was left to stir overnight at room temperature (16 h). Tetraalkylammonium carbonate resin (6 eq.) was then added to the reaction mixture and stirring was continued

for an additional 24 h. The reaction was then filtered through a solid-phase extraction vessel and rinsed with CH_2Cl_2 (2 mL). The filtrate and washes were combined and the solvent was removed under reduced pressure.

Protocol E: Aziridine aldehyde-based macrocyclization

The linear peptide was dissolved in TFE (if solubility problems were encountered, a 50:50 mixture of TFE:CH_2Cl_2 was used for the cyclization). Then 0.6 eq. of (*S*)-aziridine-2-carboxaldehyde dimer (prepared as per literature protocol: *J. Am. Chem. Soc.* **2006**, *128* (46), 14772–14773 and *Nat. Protoc.* **2010**, *5* (11), 1813–1822) as a TFE stock solution (0.2 M) was added, giving a final reaction mixture concentration of 0.1 M. *tert*-Butyl isocyanide (1.2 eq.) was then added and the reaction mixture was stirred for four hours. Progress was analyzed along the way via LC-MS.

Protocol F: Nucleophilic ring-opening of acyl aziridine, post macrocyclization

a.) Thioacetic acid/thiobenzoic acid: thio acid (4 eq.) was added to the crude reaction mixture. Reaction progress was monitored by LC-MS, and was generally complete after 1-2 hours.

Or alternatively, *b.) Thiophenol:* thiophenol (4 eq.) and DIPEA (4 eq.) were added to the crude cyclization mixture. Reaction progress was monitored by LC-MS, and was generally complete after 1-2 hours. Solvent was removed under reduced pressure and dried under vacuum. Crude material was either triturated with Et_2O/hexanes or TBME, or alternatively, diluted with H_2O, frozen and lyophilized.

Protocol G: General Suzuki coupling, post macrocyclization

An iodo-Phe-containing macrocycle (0.1 mmol), Na_2CO_3 (2 eq.), substituted boronic acid (1.1 eq.) and 4 mL of water:acetonitrile (1:1 ratio) were combined in a microwave vial. The mixture was degassed via N_2 flow for 10 minutes. While under N_2, silicon based Pd-catalyst (Siliacat-DPP Pd heterogenous catalyst, 0.05 eq.) was added. The reaction vial was sealed and placed in the microwave for 10 minutes at 150 °C. Reaction progress was monitored by LCMS. Once complete, the reaction was filtered through a Celite plug and the solvent was removed under reduced pressure.

Protocol H: General Ulmann coupling, post macrocyclization

Under inert atmosphere, the peptide macrocycle (0.018 mmol) was placed in a 2-dram vial containing 2 mL of dry CH_2Cl_2. $Cu(OAc)_2$ (1 eq.), benzene boronic acid (2 eq.) and 4 Å (oven-dried) molecular sieves were then added to the vial followed by DIPEA (4 eq.). The contents of the vial were stirred at room temperature overnight. The reaction progress was assessed by LCMS. Once the reaction was deemed complete, the mixture was filtered through a Celite plug and the solvent was removed under reduced pressure.

Protocol I: General global deprotection and cleavage

Deprotection of the side chain protecting groups was achieved by dissolving the peptides in 2 mL of a cleavage cocktail consisting of TFA:H_2O:TIS (95:2.5:2.5) for two hours. Subsequently, the cleavage mixture was evaporated under reduced pressure and the peptides were precipitated twice from chilled diethyl ether/hexanes (or *tert*-butyl methyl ether).

Protocol J: General cleavage of reductively-labile protecting groups

a.) Pd/C and formic acid debenzylation: the benzyl protected macrocycle (0.35 mmol) was dissolved in MeOH (8 mL) with 10% formic acid, 50% wt. Pd/C (1 mg) and heated to 55 °C. Once the reaction was deemed complete, the mixture was filtered through a Celite plug, washed with MeOH and the solvent was removed under reduced pressure.

Or alternatively, *b.) Raney Ni desulfurization/debenzylation:* Raney Ni slurry (1-2 mL) was added directly to the cyclization reaction mixture and stirred vigorously overnight. The vial was then centrifuged and the liquid was transferred using a pipette to a tared vial. MeOH was added to the vial containing Raney Ni. The vial was then sonicated, vortexed, and centrifuged. Again, the liquid was transferred to a tared vial. This process was repeated with EtOAc and then a final time with MeOH. The combined washes were then removed under reduced pressure and the residue dried under vacuum.

Protocol K: Amidation of side chain, post macrocyclization

Macrocycle (0.021 mmol) was dissolved in 1 mL of CH_3CN. K_2CO_3 (5 eq.) and acid chloride (2 eq.) were then added and the reaction mixture was left to stir at room temperature overnight. Reaction progress was checked by LC-MS in the morning. Upon completion, the solvent was removed by reduced pressure.

Protocol L: Fluorescent dye attachment

The macrocycle (4 µmol) was dissolved in DMSO (200 µL). DIPEA (5 eq.) was then added. In a separate vial, 5 mg of fluorescent dye as the NHS ester was dissolved in 200 µL of DMSO. The macrocycle solution was then added to the solution of the fluorescent label. The reaction mixture was stirred overnight. Reaction progress was checked by LC-MS in the morning and then the solvent was removed by lyophilization.

Protocol M: Purification methods

All macrocycles were purified using reverse-phase flash column chromatography using a 30 g Redi*Sep* C18 Gold Column. The gradient consisted of eluents A (0.1% formic acid in double distilled water) and B (0.1% formic acid in HPLC-grade acetonitrile) at a flow rate of 35 mL/min.

Integrin α4β7 – MAdCAM-1 ELISA competition assay

Definitions and acronyms

BSA: Bovine serum albumin

DMSO : Dimethyl sulfoxide

HRP : Horseradish peroxydase

PBS : Phosphate buffered saline

TMB : 3,3',5,5'-tetramethylbenzidine

Required products

Product	Company	Catalog #
Recombinant human integrin α4β7	R&D Systems	5397-A3-050
Recombinant human MAdCAM-1 Fc Chimera	R&D Systems	6056-MC-050
Goat anti-human IgG Fc specific (HRP)	Abcam	Ab97225
$NaHCO_3$	BDH	ACS 804
Na_2CO_3	BDH	ACS 777
Tris-Cl	Fisher	BP 153-1
NaCl	EMD	7710
$MnCl_2 \cdot 4\ H_2O$	Sigma	M-3634
BSA	Omni Pur	2930
H_2SO_4	Fisher	A300-212
KCl	BDH	ACS 645
Na_2HPO_4	Sigma	S-0876
KH_2PO_4	Sigma	P3786
DMSO	SAFC	RES2166D-A101X
TMB (SureBlue Reserve)	KPL	53-00-00
Tween 20	Sigma	D7949
96-well flat bottomed plates Microlon 200 (med binding)	Greiner	655001
96-well round bottomed plates	Costar	3797

Specific material

Equipment	Feature
Plate washer	HydroSpeed Tecan
Plate reader	Infinite 1000 Tecan
Humidified chamber	
Plate shaker	85 rpm

Solutions

Carbonate buffer pH 9,6 (50 mM), Tris-Cl (1 M), Blocking buffer (50 mM Tris, 150 mM NaCl, 1 mM $MnCl_2$, 1 % BSA, 0,05% Tween), Assay buffer (50 mM Tris, 150 mM NaCl, 1 mM $MnCl_2$, 0,1 % BSA, 0,05% Tween), Wash buffer (50 mM Tris, 100 mM NaCl, 1 mM $MnCl_2$, 0,05% Tween), H_2SO_4 1M, PBS, Dilution solution (400 µL DMSO in 40 mL of Assay buffer)

Protocol

1.1 Preparation of α4β7.

1.1.1 Add 500 µL of PBS to the vial. Do not vortex and leave it on ice for 15 minutes. Mix by inversion before use. Keep at 4°C for up to 1 month.

Final concentration is 100 µg/mL

1.1 Preparation of MadCam-Fc.

1.1.1 Add 500 µL of Assay buffer to the vial. Do not vortex and leave it on ice for 15 minutes. Mix by inversion before use. Keep at 4°C for up to 1 month.

Final concentration is 100 µg/mL

1.2 Absorption of α4β7 onto the plate.

1.2.1 Dilute α4β7 at a concentration of 1 µg/mL in fresh carbonate buffer.

1.2.2 Using a 12-chanel pipette, distribute 100 µL per well.

1.2.3 Incubate the plate 16-18 hours at 4°C in a humidified chamber.

1.3 Blocking step

1.3.1 Pour the content of the plate over the sink followed by gently dabbing the plate upside down on a blotting paper.

1.3.2 Add 250 µL of blocking buffer per well.

1.3.3 Incubate at 23-25°C for 1 hour.

1.3.4 Wash the plate using the plate washer: method "MadCam"

1.4 Preparation of compound dilutions

1.4.1 During the blocking step, prepare serial dilutions of the test compounds

- Add 100 µL of dilution solution in wells of rows #1 to #11 in a dilution plate
- Add 198 µL of assay buffer in wells of row #12
- Add 2 µL of test compounds in the appropriate well in row #12
- Using a multichannel pipette, mix thoroughly the content of the wells in row #12
- Do serial dilutions, starting with row #12 to #1 by transferring 100 µL well to well. Mix thoroughly between each transfer.

1.4.2 Immediately after the wash step (7.3.4), transfer 50 µL of the compounds from the dilution plate to the test plate.

1.4.3 Add 100 µL of assay buffer in well A1 and A2 (Blank).

1.4.4 Add 50 µL of dilution solution in well A3 to A12 (Maximal binding).

1.5 Addition of MadCam-Fc

1.5.1 Dilute the MadCam-Fc at 1µg/mL in Assay buffer

1.5.2 Add 50 µL to each well of the test plate (except wells A1 and A2)

1.5.3 Incubate at 23-25°C for 2 hours under agitation (85 rpm).

1.5.4 Wash the plate using the plate washer: method "MadCam"

1.6 Addition of anti-human IgG (Fc specific)-HRP

1.6.1 Dilute the anti-human IgG Fc specific-HRP (1:2000) in Assay buffer

1.6.2 Add 100 µL of diluted anti-human IgG in each well.

1.6.3 Incubate at 23-25°C for 1 hour under agitation (85 rpm).

1.6.4 Wash the plate using the plate washer: method "MadCam"

1.7 Revelation

1.7.1 Add 100 µL of TMB.

1.7.2 Stop the reaction after 2 minute-incubation by adding 50 µL H_2SO_4 1M

1.7.3 Read the $OD_{450\ nm}$ with the plate reader.

Integrin α4β1 – VCAM-1 ELISA competition assay

Definitions and acronyms

BSA: Bovine serum albumin

DMSO : Dimethyl sulfoxide

HRP : Horseradish peroxydase

PBS : Phosphate buffered saline

TMB : 3,3',5,5'-tetramethylbenzidine

Required products

Product	Company	Catalog #
Recombinant human integrin α4β1	R&D Systems	5668-A4-050
Recombinant human VCAM-1 Fc Chimera	R&D Systems	862-VC-100
Goat anti-human IgG Fc specific (HRP)	Abcam	Ab97225
$NaHCO_3$	BDH	ACS 804
Na_2CO_3	BDH	ACS 777
Tris-Cl	Fisher	BP 153-1
NaCl	EMD	7710
$MnCl_2 \cdot 4\ H_2O$	Sigma	M-3634
BSA	Omni Pur	2930
H_2SO_4	Fisher	A300-212
KCl	BDH	ACS 645
Na_2HPO_4	Sigma	S-0876
KH_2PO_4	Sigma	P3786
DMSO	SAFC	RES2166D-A101X
TMB (Slow)	Thermo Fisher	34024
Tween 20	Sigma	D7949
96-well flat bottomed plates Microlon 200 (med binding)	Greiner	655001

96-well round bottomed plates	Costar	3797

Specific material

Equipment	Feature
Plate washer	HydroSpeed Tecan
Plate reader	Infinite 1000 Tecan
Humidified chamber	
Plate shaker	85 rpm

Solutions

Carbonate buffer pH 9,6 (50 mM), Tris-Cl (1 M), Blocking buffer (50 mM Tris, 150 mM NaCl, 1 mM $MnCl_2$, 1 % BSA, 0,05% Tween), Assay buffer (50 mM Tris, 150 mM NaCl, 1 mM $MnCl_2$, 0,1 % BSA, 0,05% Tween), Wash buffer (50 mM Tris, 100 mM NaCl, 1 mM $MnCl_2$, 0,05% Tween), H_2SO_4 1M, PBS, Dilution solution (400 µL DMSO in 40 mL of Assay buffer)

Protocol

1.8 Preparation of α4β1.

1.8.1 Add 500 µL of PBS to the vial. Do not vortex and leave it on ice for 15 minutes. Mix by inversion before use. Keep at 4°C for up to 1 month.

Final concentration is 100 µg/mL

1.9 Preparation of VCam-Fc.

1.9.1 Add 500 µL of Assay buffer to the vial. Do not vortex and leave it on ice for 15 minutes. Mix by inversion before use. Keep at 4°C for up to 1 month.

Final concentration is 200 µg/mL

1.10 Absorption of α4β1 onto the plate.

1.10.1 Dilute α4β1 at a concentration of 0.5 µg/mL in fresh carbonate buffer.

1.10.2 Using a 12-chanel pipette, distribute 100 µL per well.

1.10.3 Incubate the plate 16-18 hours at 4°C in a humidified chamber.

1.11 Blocking step

1.11.1 Pour the content of the plate over the sink followed by gently dabbing the plate upside down on a blotting paper.

1.11.2 Add 250 µL of blocking buffer per well.

1.11.3 Incubate at 23-25°C for 1 hour.

1.11.4 Wash the plate using the plate washer: method "MadCam"

1.12 Preparation of compound dilutions

1.12.1 During the blocking step, prepare serial dilutions of the test compounds

- Add 100 µL of dilution solution in wells of rows #1 to #11 in a dilution plate
- Add 198 µL of assay buffer in wells of row #12
- Add 2 µL of test compounds in the appropriate well in row #12
- Using a multichannel pipette, mix thoroughly the content of the wells in row #12

- Do serial dilutions, starting with row #12 to #1 by transferring 100 µL well to well. Mix thoroughly between each transfer.

1.12.2 Immediately after the wash step (7.3.4), transfer 50 µL of the compounds from the dilution plate to the test plate.

1.12.3 Add 100 µL of assay buffer in well A1 and A2 (Blank).

1.12.4 Add 50 µL of dilution solution in well A3 to A12 (Maximal binding).

1.13 Addition of VCam-Fc

1.13.1 Dilute the VCam-Fc at 1µg/mL in Assay buffer

1.13.2 Add 50 µL to each well of the test plate (except wells A1 and A2)

1.13.3 Incubate at 23-25°C for 2 hours under agitation (85 rpm).

1.13.4 Wash the plate using the plate washer: method "MadCam"

1.14 Addition of anti-human IgG (Fc specific)-HRP

1.14.1 Dilute the anti-human IgG Fc specific-HRP (1:2000) in Assay buffer

1.14.2 Add 100 µL of diluted anti-human IgG in each well.

1.14.3 Incubate at 23-25°C for 1 hour under agitation (85 rpm).

1.14.4 Wash the plate using the plate washer: method "MadCam"

1.15 Revelation

1.15.1 Add 100 µL of TMB (slow TMB).

1.15.2 Stop the reaction after 30 minute-incubation by adding 50 µL H_2SO_4 1M

1.15.3 Read the $OD_{450\ nm}$ with the plate reader.

RPMI8866 cell adhesion competition assay

Material:

1) Recombinant human MAdCAM-1 Fc Chimera, R&D Systems, 6056-MC-050
2) RPMI 8866 cells (grown in RPMI 1640 media supplemented with 10% FBS and 1% Pen/Step)
3) RPMI 1640 media, Wisent, 350-000-CL

Protocol:

1) Coat Maxisorp plate (Nunc 442404) with 100ul (0.25ug/ml in coating buffer) Madcam overnight at 4°C.
2) Wash 2X (300ul) with wash buffer using an e1200 Biohit 8-channel pipette with aspirate speed set to 4 and dispense speed set to 1.
3) Block with 250ul blocking buffer for 1hr at RT with the same pipette settings as above.
4) Collect 10M RPMI 8866 cells/plate in 50ml tube. Top off with PBS and spin 5min at 250 rpm.
5) Resuspend cells to 10M/ml in PBS containing 5uM Calcein.
6) Incubate cells at 37 °C in the dark for 30 min.
7) Top off cells with PBS and spin.
8) Resuspend cells to 2M/ml in neat RPMI 1640 media.
9) Prepare compounds in binding buffer (prepare 100ul per replicate).
10) Empty blocking buffer and wash plate 1X with 300ul PBS (pipette settings as in step 2).

11) Transfer 50ul of compound/control and 50ul of cells to each well and incubate in the dark for 45min.

12) Read plate on Biotek Neo using FITC 96 bottom read for pre-wash readings.

13) Add 150ul PBS (pipette settings as in step 2).

14) Invert plate and blot on paper towel.

15) Gently add 200ul PBS (pipette settings as in step 2), invert plate and blot on paper towel.

16) Add 100ul PBS using e300 Biohit 8-channel pipette with aspirate speed set to 4 and dispense speed set to 1.

17) Read plate on Biotek Neo using FITC 96 bottom read for pre-wash readings.

Buffers

Coating buffer (50mM carbonate)

Dissolve 420mg sodium bicarbonate in 100ml water (Soln 1). Dissolve 270mb sodium carbonate in 50ml water (Soln 2). Add Soln 2 to Soln 1 to a pH of 9.6

Wash buffer

0.05% Tween 20 in PBS

Blocking buffer

1% Nonfat Dry Milk in PBS

Binding buffer

1.5 mM $CaCl_2$

0.5 mM $MnCl_2$

50 mM Tris-HCl, pH to 7.5 with HCl

Plasma protein binding determination

An equilibrium dialysis (HTDialysis) method was used employing 50% plasma collected from CD-1 mice or Sprague-Dawley rats and incubated with K2EDTA. Test articles were assessed at 1 microM concentration in three replicates. Incubation time as 5 hours and plasma and buffer standards were assessed using LC/MS/MS. Percentage recovery was calculated as $(C_{buffer} + C_{plasma})/[average]C_{initial}$, $[average]C_{initial}$ being measured in triplicate from the test samples prior to dialysis. Percentage of compound unbound was calculated as C_{buffer}/C_{plasma}.

Aqueous solubility assay

Aqueous solubility was determined by using 1, 0.5 or 0.2 mM (maximum) of test compound in phosphate buffered saline with pH of 7.4. Solutions were incubated for four hours at room temperature and stirred at 600 rpm and run in triplicate. Centrifugation was performed for 15 minutes at 6000 rpm and solution concentration was determined using HPLC-UV (photodiode array detector acquiring between 220 nm, and 300 nm wavelengths).

Cytochrome P450 inhibition assay

Human liver microsomes (at 0.25 mg/ml, except for CYP1A2, where a concentration of 0.5 mg/ml was employed) were used to assess the IC_{50} (in duplicate; concentration range of 0.25 nM to 15 microM) for test compounds on the activity four isoforms of cytochrome P450 ("CYP"): CYP2D6, CYP3A4, CYP2C9 and CYP1A2. The following substrates were employed: dextromethorphan (15 microM, CYP2D6), testosterone (50 microM, CYP3A4), diclofenac (10 microM, CYP2C9) and phenacetin (100 microM, CYP1A2). Control inhibitors were quinidine (0.03 nM to 1.5 microM, CYP2D6), ketoconazole (0.08 nM to 5 microM, CYP3A4), miconazole (0.25 nM to 15 microM, CYP2C9) and alpha-naphoflavone (0.03 nM to 1.5 microM, CYP1A2). Incubation time was 10-20 minutes and metabolites assessed were dextrorphan (CYP2D6), 6-beta-OH-testosterone (CYP3A4), 4'-OH-diclofenac (CYP2C9) and acetaminophen (CYP1A2). Internal standards were labetalol (CYP2D6), loratidine (CYP3A4), carbamazepine (CYP2C9) and metoprolol (CYP1A2). Analyses were performed using standard LC/MS/MS protocols.

In vivo T lymphocyte trafficking analyses

Animal care committee. The animal care facility employed is accredited by the Canadian Council on Animal Care (CCAC). This study was approved by a certified Animal Care Committee and complied with CACC standards and regulations governing the use of animals for research.

Animals. Female C57Bl/6 mice (Charles River, St-Constant, Qc), weighting 16-19g at delivery were used for this study. Following arrival in the animal facility, all animals were subjected to a general health evaluation. An acclimation period of 7-14 days was allowed before the beginning of the study.

Housing environment. The animals were housed under standardized environmental conditions. The mice were housed in auto-ventilated cages, 2-3 per cage. Each cage was equipped with a manual water distribution system. A standard certified commercial rodent diet was provided *ad libitum*. Tap water was provided *ad libitum* at all times. It is considered that there are no known contaminants in the diet and water that would interfere with the objectives of the study. Each cage was identified for the corresponding group, indicating the treatment and the identity of the animals housed in the cage. Mice from different treatment groups were not mixed.

The animal room was maintained at a controlled temperature of 21.5 ± 1°C and a relative humidity of 40 ± 10%. A controlled lighting system assured 12 hours light, 12 hours dark per day to the animals. Adequate ventilation of 8-10 air changes per hour was maintained.

Administration of DSS. Dextran sulfate sodium (DSS) was administered to C57Bl/6 mice through addition to their drinking water at 2-3%. Mice accessed the DSS-treated water ad libitum over a 5-day period. Body weight and disease activity index ("DAI") were measured on Day 5 in order to distribute DSS-treated animals in two uniform groups prior to dosing. Specific symptoms associated with colitis were scored based on the severity of each particular symptoms: 1- blood in stool (negative hemoccult, positive hemoccult, blood traces in stool visible, rectal bleeding); 2- stool consistency (normal, soft but still formed, very soft, diarrhea); 3- posture and fur (normal; ruffled fur; ruffled fur combined to slight hunched posture and slight dehydration; ruffled fur combined to hunched posture,

dehydration and altered walking; moribund (euthanasia is mandatory before the animal reach this point). The overall DAI score was the sum of the three parameters (maximum score of 9). DAI assessment was performed on Day 5 only (prior to dosing).

Oral dosing of the test article and vehicle. On day 6, the test articles were administered in the morning, as a single slow bolus (over approximately 5 seconds) via oral route, according to the procedure of administration of solution by gavage: the animal was firmly restrained. A bulb-tipped gastric gavage needle of 22G was passed through the side of the mouth and was advanced towards the oesophagus. The test articles and the vehicle were dosed orally at 10 mL/kg. Dosing volume was individually adjusted according to the body weight of each animal to reach the target dose.

Intravenous dosing of the test article and the vehicle. On day 6, the test article, DATK32 antibody, and the vehicle were administered in the morning, as a single slow bolus injection (over approximately 5 seconds) via the tail vein, according to the procedure of administration of solution by intravenous administration: the animal was restrained and its tail was warmed prior to dosing. A needle of 30G was used to inject the test article, or the vehicle, through the median tail vein at a dosing volume of 5 mL/kg. Dosing volume was individually adjusted according to the body weight of each animal to reach the target dose of DATK32 control antibody.

Collection of samples. On Day 6, five hours after test article or vehicle dosing, the animals were euthanized by cardiac puncture under general anesthesia, according to the "Guide to the Care and Use of Experimental Animals" published by the CCAC. Blood was transferred in a Sarstedt tube containing EDTA. Mesenteric and peripheral (inguinal, auxiliary and brachial) lymph nodes were collected and transferred on ice to corresponding tubes containing cold PBS. Nodes were kept on ice until tissue preparation.

Cell population labeling. Blood was withdrawn by cardiac puncture and collected on EDTA-coated tubes. Mensenteric lymph nodes (MLN) and peripheral lymph nodes (PLN) were also collected. Mononuclear cells from the tissues were isolated using density gradient (Lympholyte) and they were stained with fluorescent antibodies. The cells (5 x 104) were first incubated 15 minutes with BD mouse FcBlock (Fcγ III/II Receptor) followed

by a 30-minute incubation with specific antibodies. After washes, cells were fixed using BD Fix Solution.

Specific antibodies used:

Antibodies	Company	Catalog #
CD3 FITC	BD Biosciences	555274
CD4 APC	BD Biosciences	553051
CD11a PE	BD Biosciences	553121
CD45 PE	BD Biosciences	553081
α4β7 PE	eBiosciences	12-5887
CD34 PE	BD Biosciences	551387

Percentage of different subpopulations of T lymphocytes were then analyzed using FACS-Calibur cytometer.

In vivo pharmacokinetic assessments in rodents

Oral bioavailability of test compounds was conducted by assessing plasma exposure of following one or two oral doses in mice and, in some cases, comparing said plasma exposure with that following a single intravenous dose of the same compound.

More detail on experimental design follows:

Group ID	Test article ID	Route	No. & sex of animals	Dosing Frequency	Dose (mg/kg)	Concen-tration (mg/mL)	Volume (mL/kg)	Sample Collection
1		*p.o.*	18 M	once	40	4	10	Terminal blood (3 mice/time-point)
2		*p.o.*	18 M	twice*	40	4	10	

*Dosing will occur 8 hours apart.

In all cases, formulation of test compound was 30% Labrasol in PBS (v/v) for oral dosing and 25% PEG-400 in PBS (v/v) for intravenous dosing.

Collection of peripheral blood proceeded as follows:

Group ID	Blood collection time (h)	Volume/animal/time-point
1 &2*	0.0833, 0.5, 1, 2, 3 & 5	~0.6 mL

*For Group 2, sample collection will be conducted following the second dose.

In some cases, collections proceeded up to 24 hours. Also note that in a few studies, liver and colon were also collected from mice concomitantly with peripheral blood and on a terminal (and serial) basis.

Other study details include:

Animals: Male CD-1 mice (20 - 25 g) from Charles River Labs were acclimatized for a minimum of 5 days prior to dosing. Body weights were recorded on the day of dosing.

Food restriction: Animals dosed p.o. were deprived of food overnight and fed ~2 h following dosing.

Clinical observations: Animals were observed at the time of dosing and each sample collection. Any abnormalities were documented.

Dosing: The formulation containing the test compound were administered p.o. by gavage with disposable feeding needles.

Sample collection: Terminal blood and tissue samples were collected under O2/CO2 anesthesia by cardiac puncture. The colon samples (a 0.5 cm section, 2.5 cm distal to the cecum) will be excised, rinsed with ice cold PBS, blotted and weighed (as applicable). The livers will be blotted and weighed. Plasma, liver and colon samples will be stored frozen at -80 degrees centigrade until bioanalysis.

Sample processing/storage: All blood samples were transferred into K2EDTA tubes on wet ice and centrifuged within 5 min (3200 x g for 5 min at 4oC) to obtain plasma. Samples were stored frozen at–80°C until bioanalysis.

Sample retention: Plasma samples were analyzed and any remaining samples were stored frozen at–80°C until the study is completed. Remaining sample were discarded.

Bioanalytical method qualification and sample analysis:

Matrix: mouse plasma

Instrumentation: AB Sciex API 4000 Q-TRAP MS/MS system equipped with an Agilent LC system with a binary pump, a solvent degasser, a thermostatted column compartment, a CTC autosampler and a divert valve installed between the column and mass spectrometer inlet.

Method qualification:

The determination of the quantification dynamic range using non-zero calibration standards (STDs) in singlet. The STDs will consist of a blank matrix sample (without IS), a zero sample (with IS), and at least 6 non-zero STDs covering the expected range and including the lower level of quantitation (LLOQ).

Three injections of a system suitability sample (neat solution containing the analytes and IS) bracketing the batch.

Method acceptance criteria:

At least 75% of non-zero STDs must be included in the calibration curve with all back-calculated concentrations within ±20% deviation from nominal concentrations (±25% for the lower level of quantification, LLOQ).

The correlation coefficient (r) of the calibration curve must be greater than or equal to 0.99.

The area ratio variation between the pre-and post-run injections of the system suitability samples is within±25%.

Samples which are >1-fold the highest calibration standard, will be diluted and re-assayed along with a corresponding dilution quality control standard.

Sample analysis batch:

Three injections of a system suitability sample bracketing the batch

The STDs in ascending order bracketing the study samples and dosing solutions

1. The study samples

2. The dosing solutions diluted as 3 independent dilutions into blank matrix (mouse plasma)

8-day efficacy study in DSS model (therapeutic) with ET02451-01 (Compound No. 340) and ET02452-01 (Compound No. 341)

Study design

Cohort	N	UC	Treatment	Dose	Volume
1	5	DSS	vehicle	0 mg/kg	5 mL/kg (p.o.)
2	5	DSS	ET02451-01	40 mg/kg	5 mL/kg (p.o.)
3	5	DSS	ET02452-01	40 mg/kg	5 mL/kg (p.o.)
4	5	DSS	ET02452-01	65 mg/kg	5 mL/kg (i.p.)
5	5	DSS	DATK32	15 mg/kg	6 mL/kg (i.p.)

Description of tested compounds

Name: Vehicle Labrasol/PBS

Volume: 8.0 mL

Solution: Labrasol (30 %)/PBS (70 %)

Storage: 4 °C

Name: ET02451 (Compound No. 340)

Volume: 3.7 mL

Solution: 8 mg/mL in Labrasol (30 %)/PBS (70 %)

Storage: 4 °C

Name: ET02452 (Compound No. 341)

Volume: 3.45 mL

Solution: 8 mg/mL in Labrasol (30 %)/PBS (70 %)

Storage: 4 °C

Name: ET02452 (Compound No. 341)

Volume: 3.40 mL

Solution: 13 mg/mL in PEG400 (40 %)/PBS (60 %)

Storage: 4 °C

Name: DATK32 Antibody (eBiosciences # 14-5887-85, lot# 4282190)

Volume: 5 mL

Solution: 0.5 mg/mL concentrated to 2.5 mg/mL following concentration step

Storage: 4 °C

Name: Vehicle PEG/PBS

Volume: 8.0 mL

Solution: PEG400 (40 %)/PBS (60 %)

Storage: 4 °C

Animal care committee. The animal care facility employed is accredited by the Canadian Council on Animal Care (CCAC). This study was approved by a certified Animal Care Committee and complied with CACC standards and regulations governing the use of animals for research.

Animals. Female C57Bl/6 mice (Charles River, St-Constant, Qc), weighting 16-19g at delivery were used for this study. Following arrival in the animal facility, all animals were subjected to a general health evaluation. An acclimation period of 7-14 days was allowed before the beginning of the study.

Housing environment. The animals were housed under standardized environmental conditions. The mice were housed in auto-ventilated cages, 2-3 per cage. Each cage was equipped with a manual water distribution system. A standard certified commercial rodent diet was provided *ad libitum*. Tap water was provided *ad libitum* at all times. It is considered that there are no known contaminants in the diet and water that would interfere with the objectives of the study. Each cage was identified for the corresponding group, indicating the treatment and the identity of the animals housed in the cage. Mice from different treatment groups were not mixed.

The animal room was maintained at a controlled temperature of 21.5 ± 1°C and a relative humidity of 40 ± 10%. A controlled lighting system assured 12 hours light, 12 hours dark per day to the animals. Adequate ventilation of 8-10 air changes per hour was maintained.

Oral dosing of the test article and the vehicle. From Day 5 to Day 8, nacellins and the vehicle were administered as a single slow bolus (over approximately 5 seconds) via oral route (p.o.), according to the procedure of administration of solution by gavage: the animal was firmly restrained. A bulb-tipped gastric gavage needle of 22G was passed through the side of the mouth and was advanced towards the oesophagus. The test articles and the vehicle were dosed orally at 5 mL/kg. Dosing volume was individually adjusted according to the body weight of each animal to reach the target dose of ET02451and ET02452 (40 mg/kg).

Intraperitoneal dosing of the test articles and the vehicle. On day 5, DATK32 antibody was administered in only on Day 5, as a single slow bolus (over approximately 5 seconds) via the i.p. route. ET02452 prepared in PEG400 (40 %)/PBS (60%) and the i.p. vehicle (PEG400 (40%)/PBS (60%)) were administered from Day 5 to Day 8. Intraperitoneal administration was performed accordingly to the following procedure: the mouse was restrained manually and held with the head and body tilted downward. The tip of the needle (27 G) was inserted through the skin and just past the abdominal wall. A short pull back of the plunger of the syringe was done prior to administration of the solution to make sure that the syringe was not inserted in any abdominal organ (fluid would be pulled back into the syringe in this case). Dosing volume was individually adjusted according to the body weight of each animal to reach the target dose of DATK32 antibody (15 mg/kg) and of ET02452 (65 mg/kg).

Inflammation Score. Once the mouse was euthanized, the colon was collected and its length was measured. Lesion length was also measured. Colon inflammation was scored based on severity of oedema and ulceration.

Disease Activity Index (DAI) assessment. Body weight and DAI were measured on Day 5 in order to distribute DSS-treated animals in two uniform groups prior dosing. Specific symptoms associated to UC were scored based on the severity of each particular symptoms: 1- blood in stool (negative hemoccult, positive hemoccult, blood traces in stool visible, rectal bleeding); 2- stool consistency (normal, soft but still formed, very soft, diarrhea); 3- posture and fur (normal; ruffled fur; ruffled fur combined to slight hunched posture and slight dehydration; ruffled fur combined to hunched posture, dehydration and altered walking; moribund (euthanasia is mandatory before the animal reach this point). The overall DAI score was the sum of the three parameters (maximum score 9). Body weight measurement and DAI assessment were performed also on Day 8 to evaluate the effect of the treatments.

Collection of samples. On Day 8, five hours after ET02451-01, ET02452-01 and vehicle dosing, the animals were euthanized by cardiac puncture under general anesthesia, according to the "Guide to the Care and Use of Experimental Animals" published by the CCAC. Blood was transferred in a Sarstedt tube containing EDTA. Mesenteric and peripheral (inguinal, auxiliary and brachial) lymph nodes were collected and transferred on ice in corresponding tubes containing cold PBS. Nodes were kept on ice until tissue preparation.

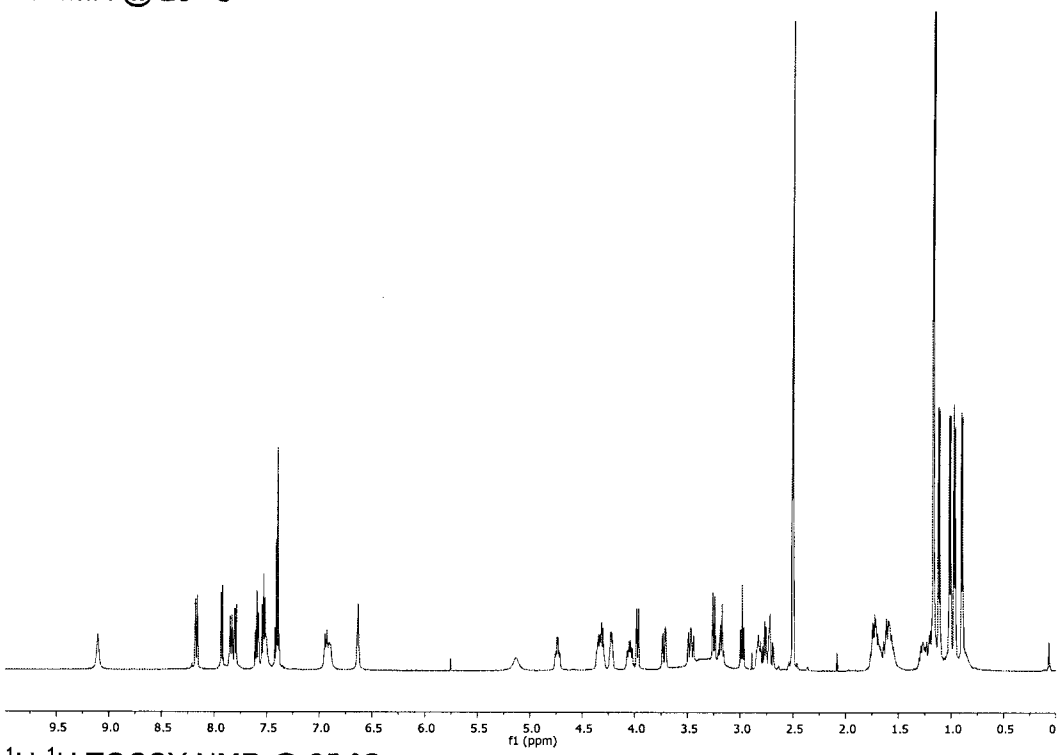
Cell population labeling. Blood was withdrawn by cardiac puncture and collected on EDTA-coated tubes. Mensenteric lymph nodes (MLN) and peripheral lymph nodes (PLN) were also collected. Mononuclear cells from the tissues will be isolated using density gradient (Lympholyte) and they were stained with fluorescent antibodies. The cells (5 x 104) were first incubated 15 minutes with BD mouse FcBlock (Fcγ III/II Receptor) followed by a 30-minute incubation with specific antibodies. After washes, cells were fixed using BD Fix Solution. Percentage of different subpopulations of T lymphocytes were then analysed using FACSCalibur cytometer. Antibodies employed were the same as listed for the single-dose PD studies above.

Results and Discussion

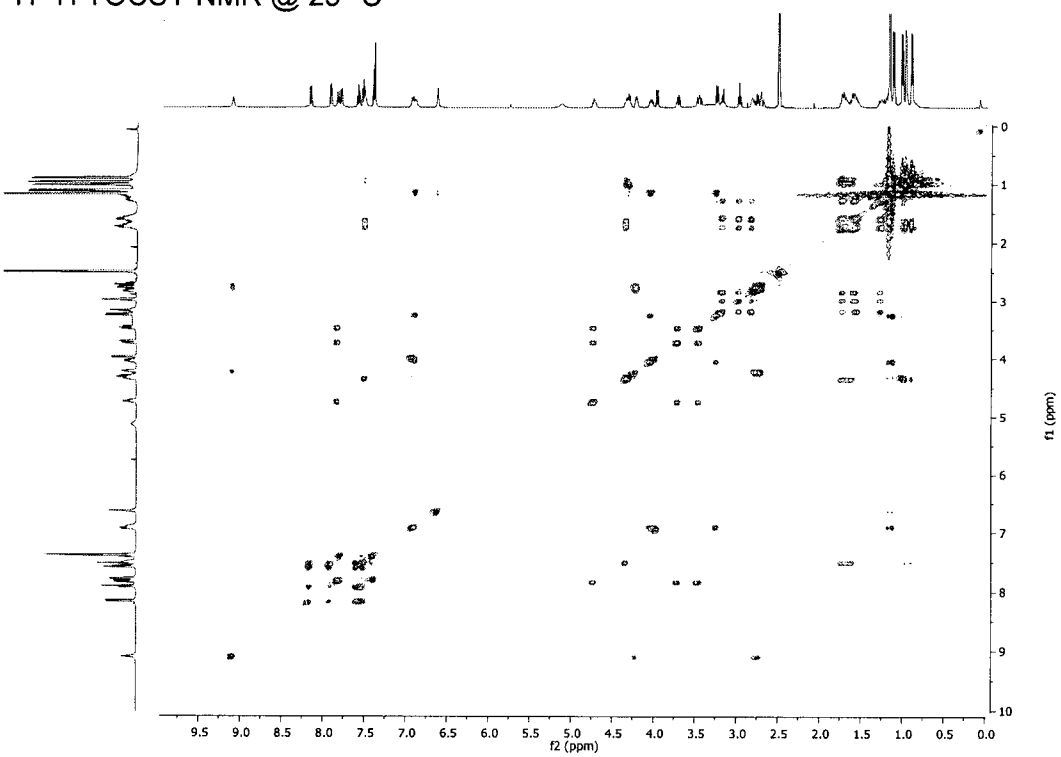
Compounds were synthesized in accordance with the above-noted methods. A selection of compounds were characterized using NMR (not all data shown). A subset of NMR data is provided below for select compounds.

Compound No. 9

^{1}H NMR @ 25 °C



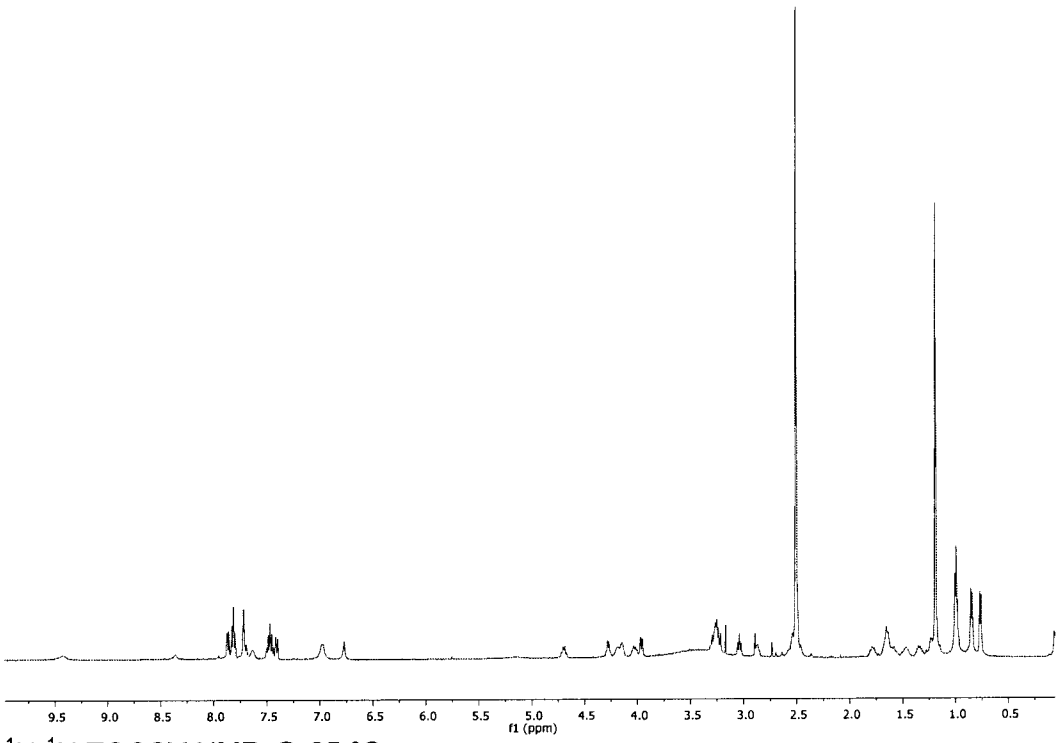
^{1}H-^{1}H TOCSY NMR @ 25 °C



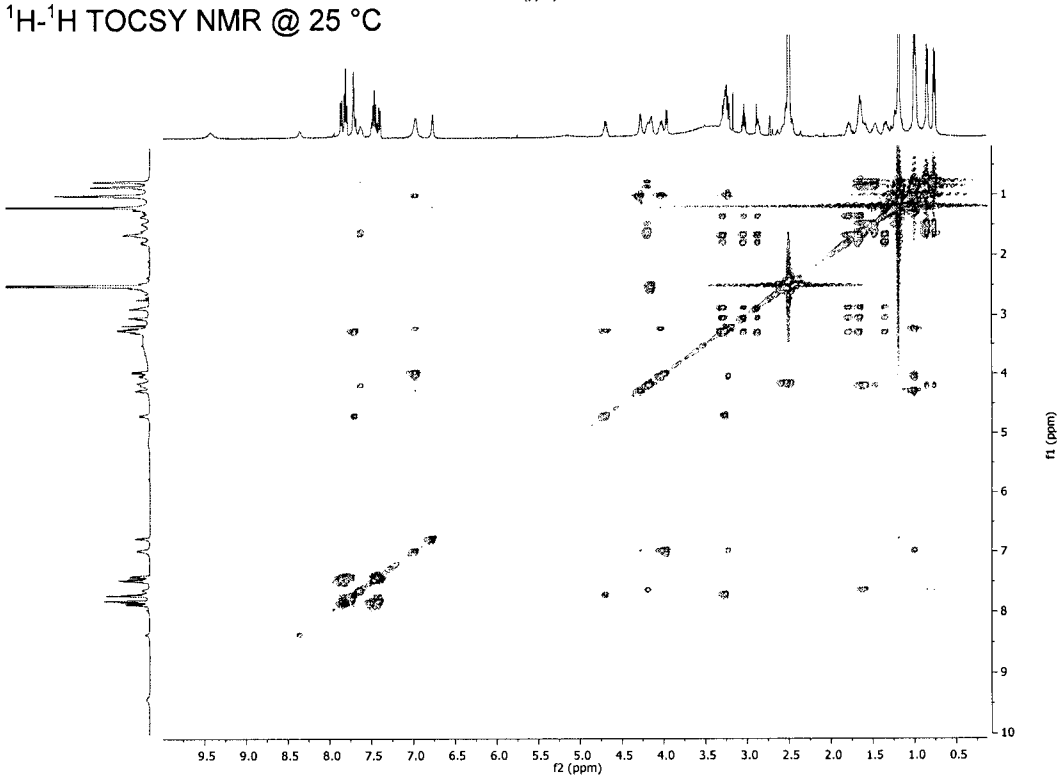
5

Compound No. 10

^{1}H NMR @ 25 °C



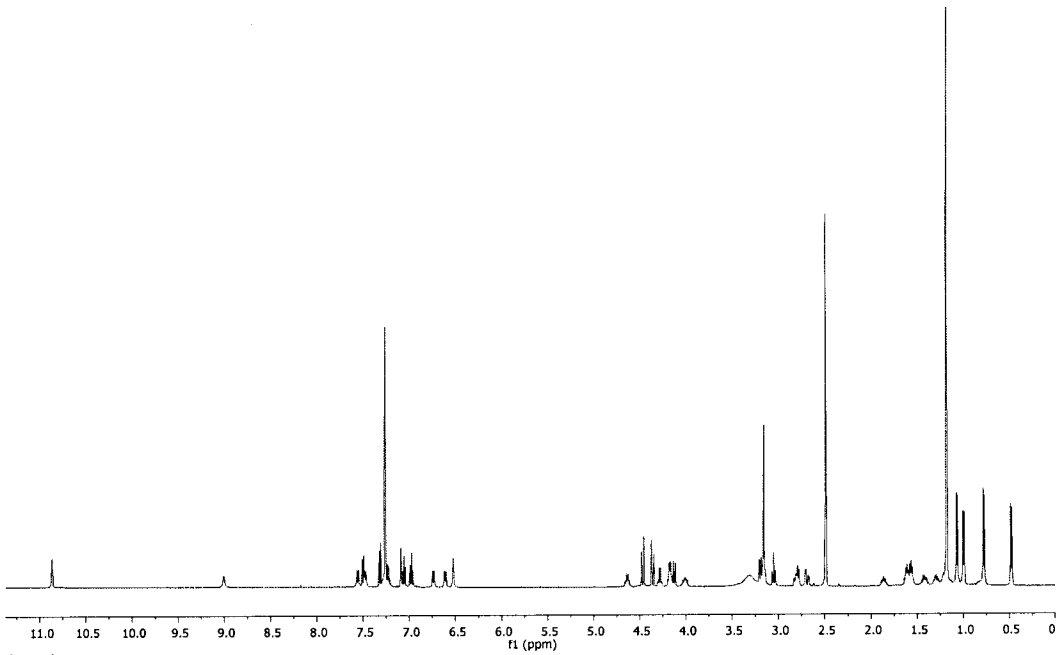
^{1}H-^{1}H TOCSY NMR @ 25 °C



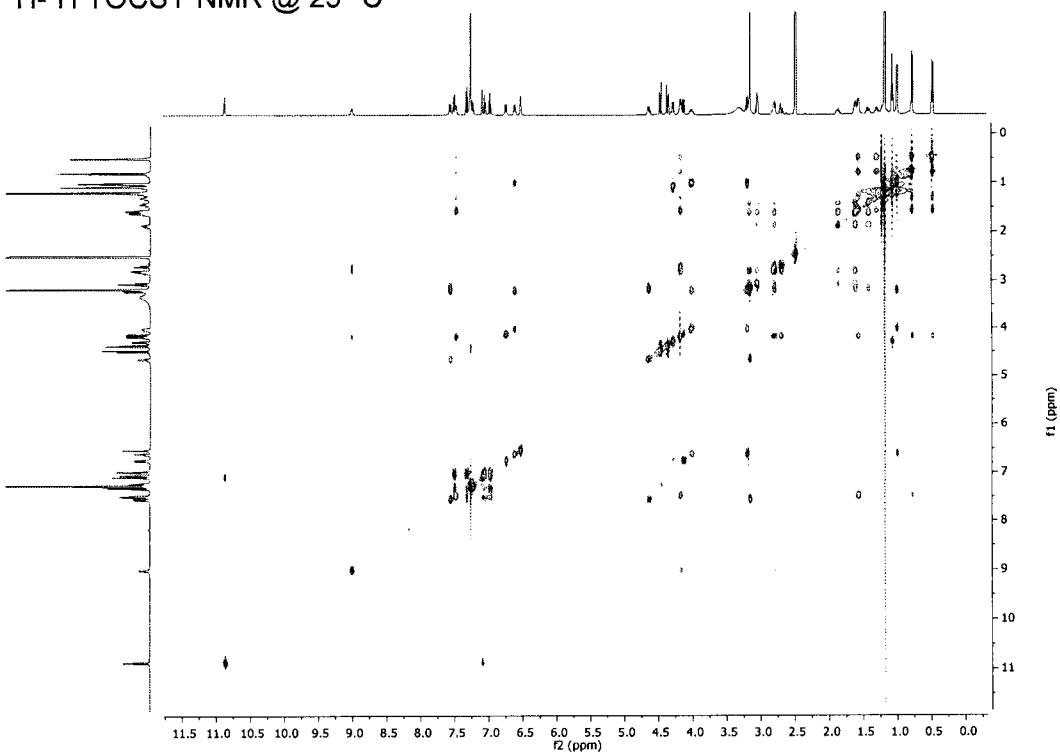
5

Compound No. 11

^{1}H NMR @ 25 °C

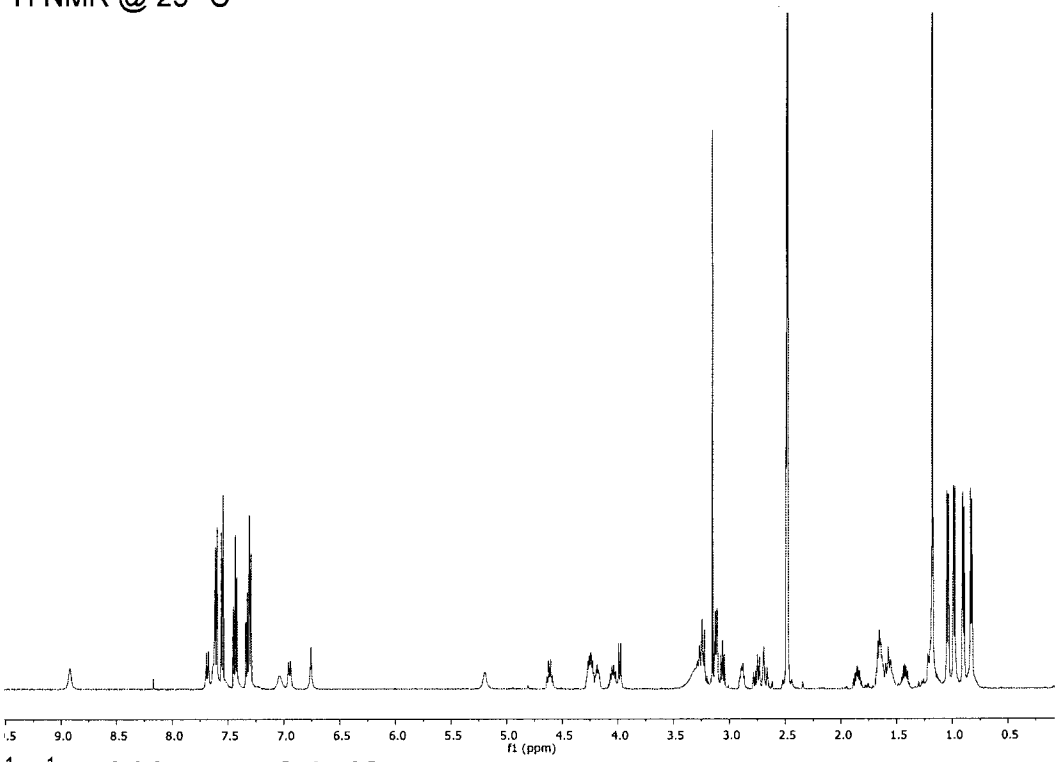


^{1}H-^{1}H TOCSY NMR @ 25 °C

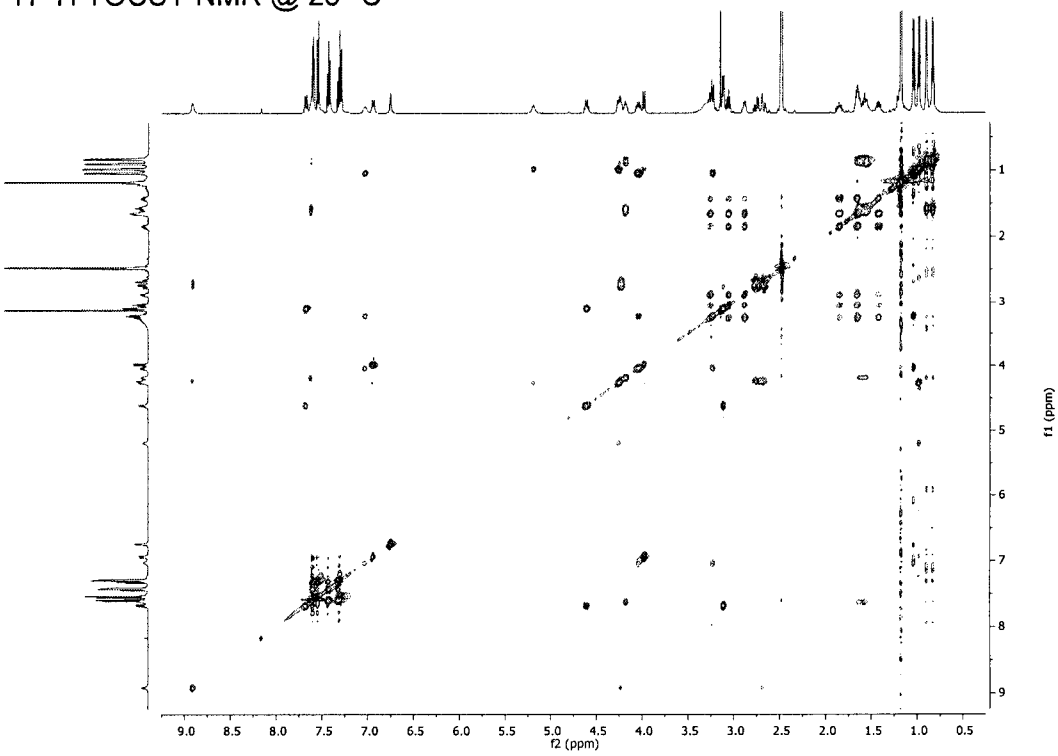


Compound No. 12

^{1}H NMR @ 25 °C



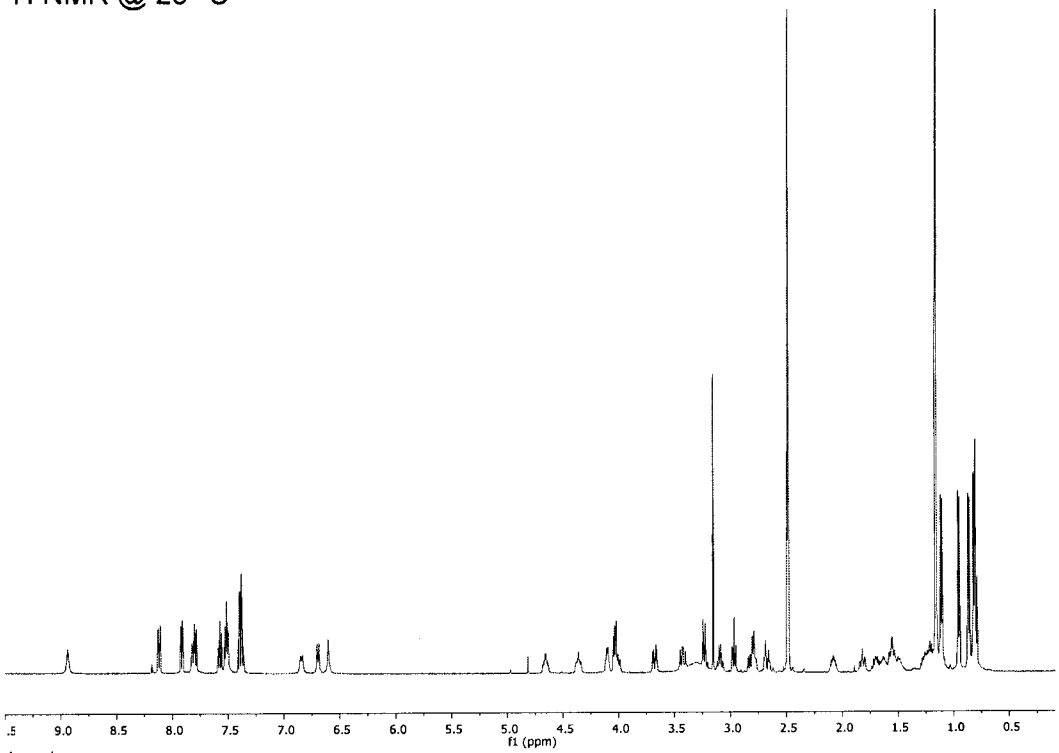
^{1}H-^{1}H TOCSY NMR @ 25 °C



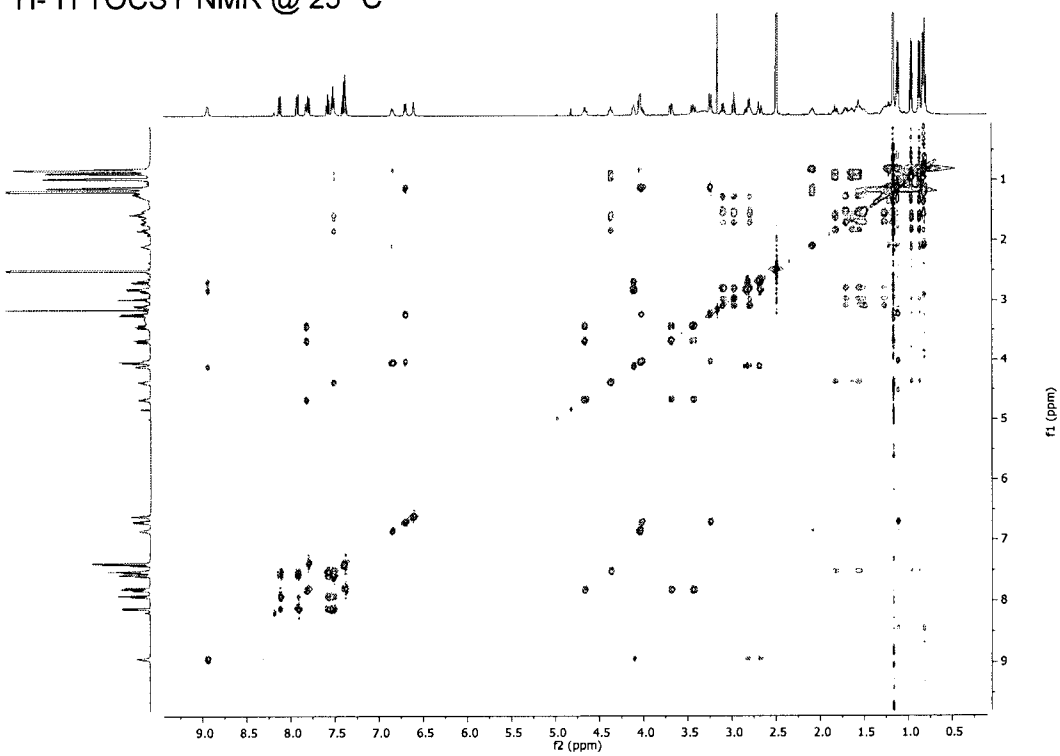
5

Compound No. 14

^{1}H NMR @ 25 °C



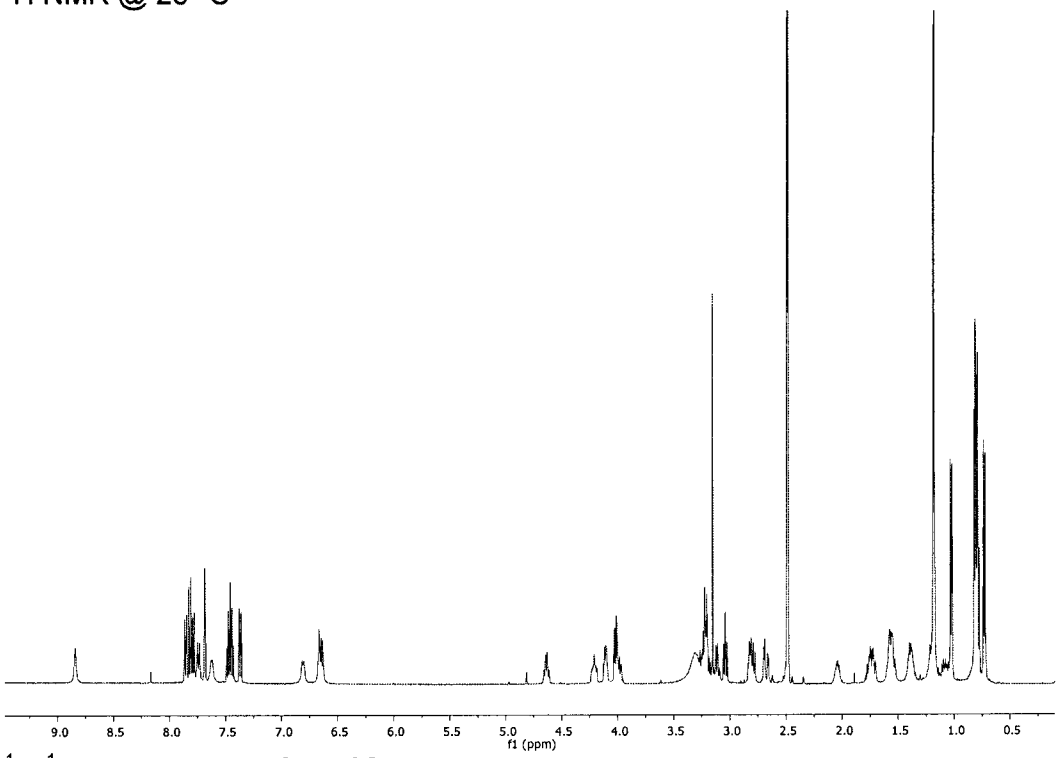
^{1}H-^{1}H TOCSY NMR @ 25 °C



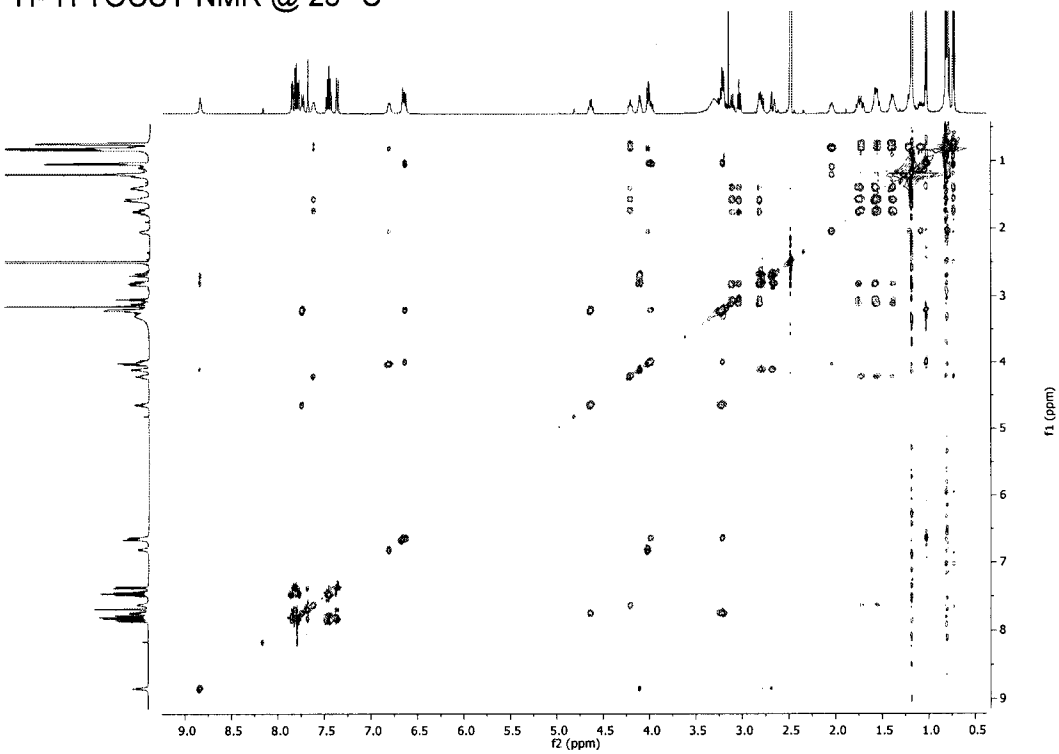
5

Compound No. 15

^{1}H NMR @ 25 °C



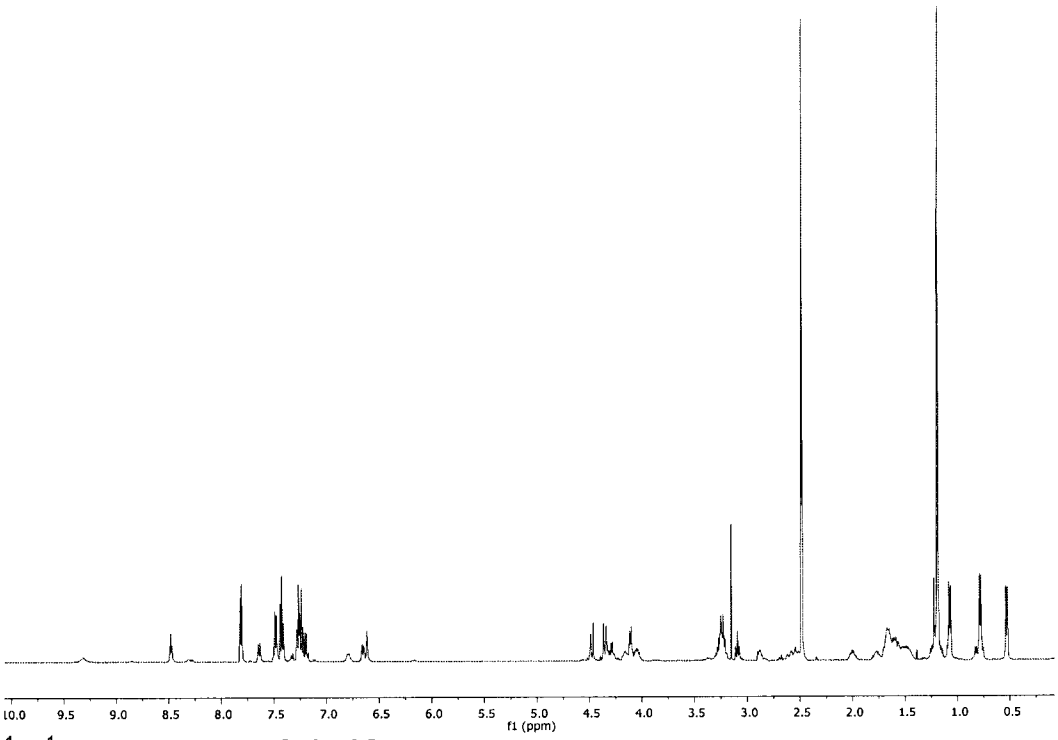
^{1}H-^{1}H TOCSY NMR @ 25 °C



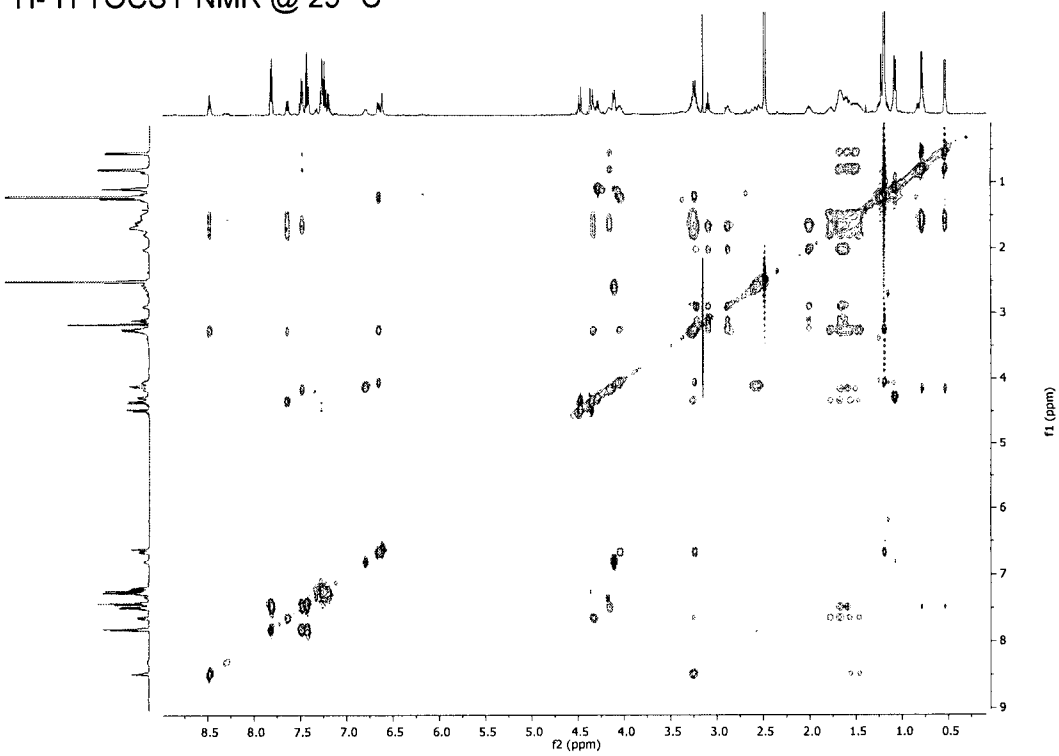
5

Compound No. 34

^{1}H NMR @ 25 °C



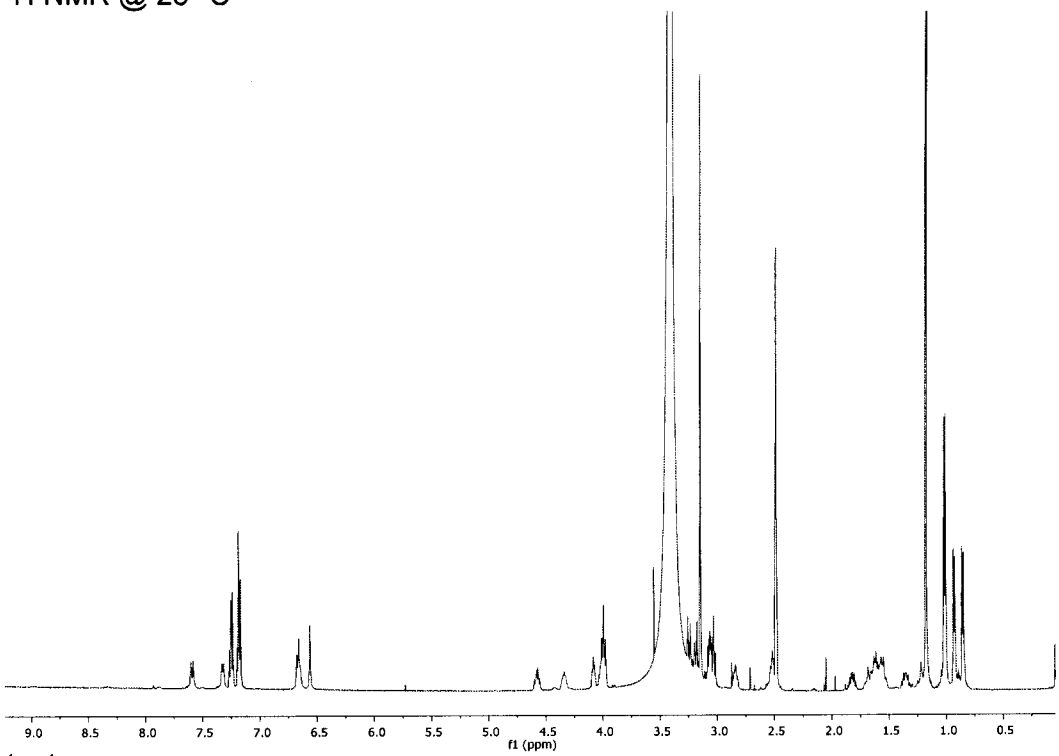
^{1}H-^{1}H TOCSY NMR @ 25 °C



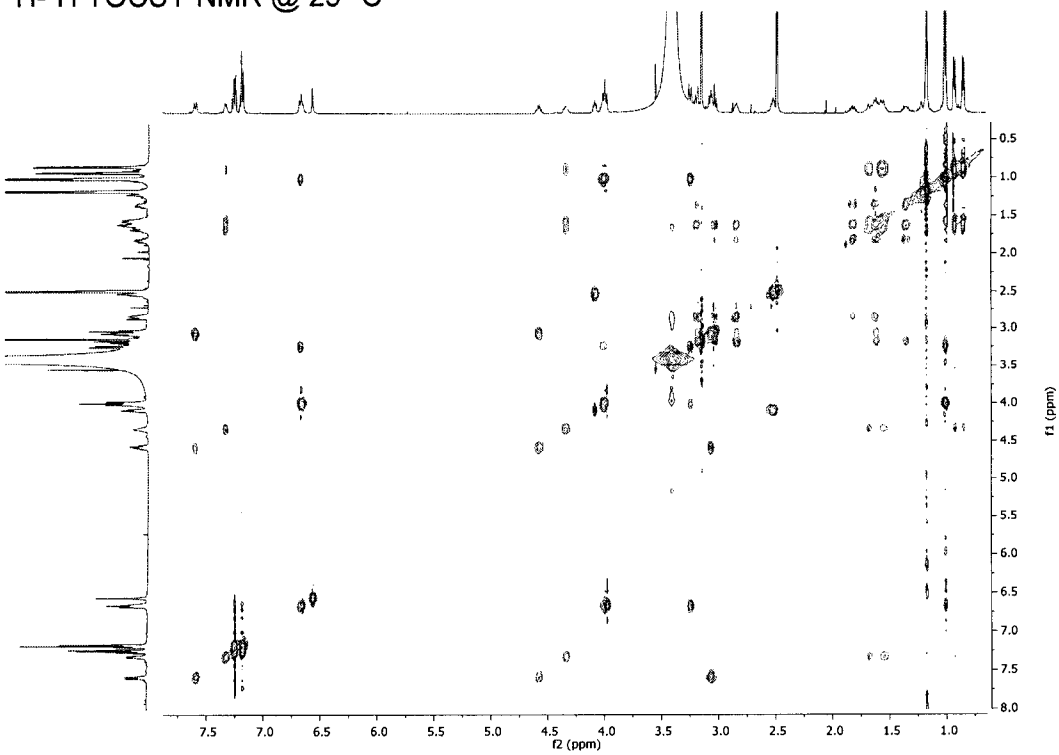
5

Compound No. 40

^{1}H NMR @ 25 °C



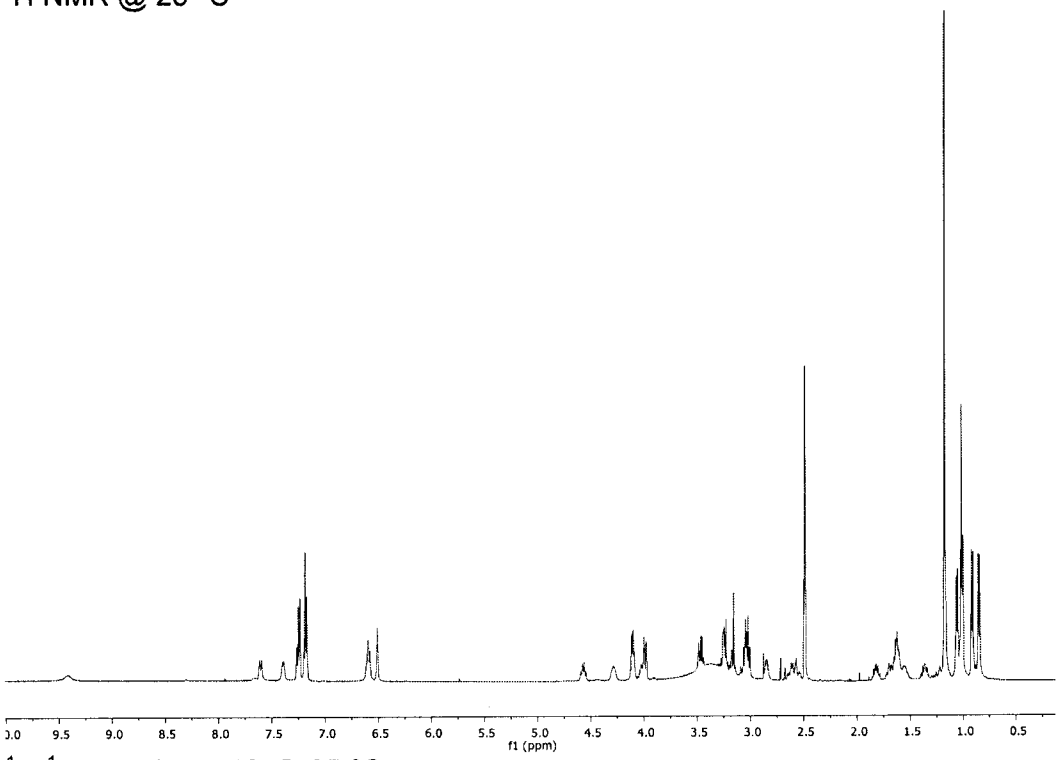
^{1}H-^{1}H TOCSY NMR @ 25 °C



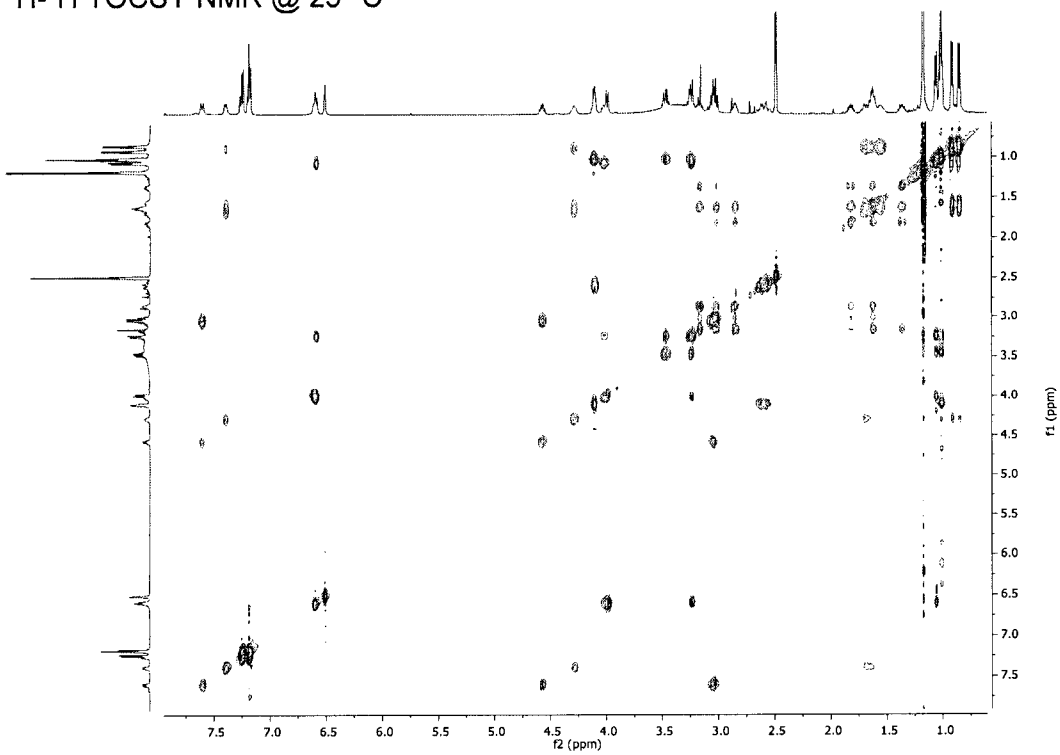
5

Compound No. 41

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



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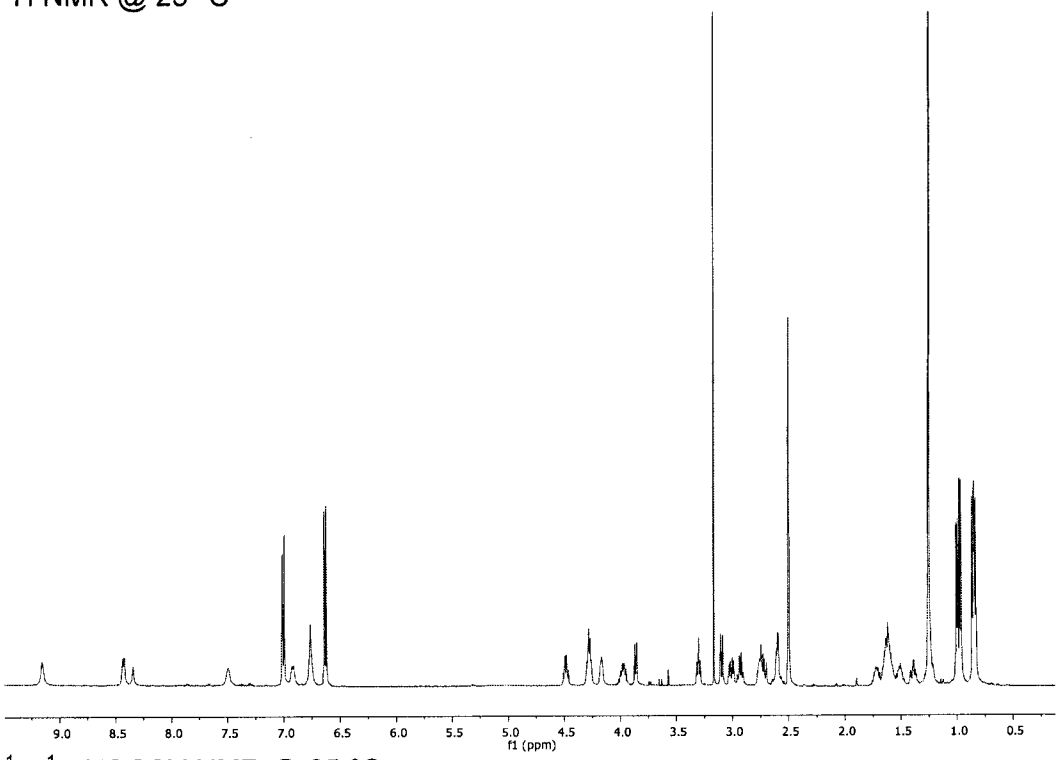
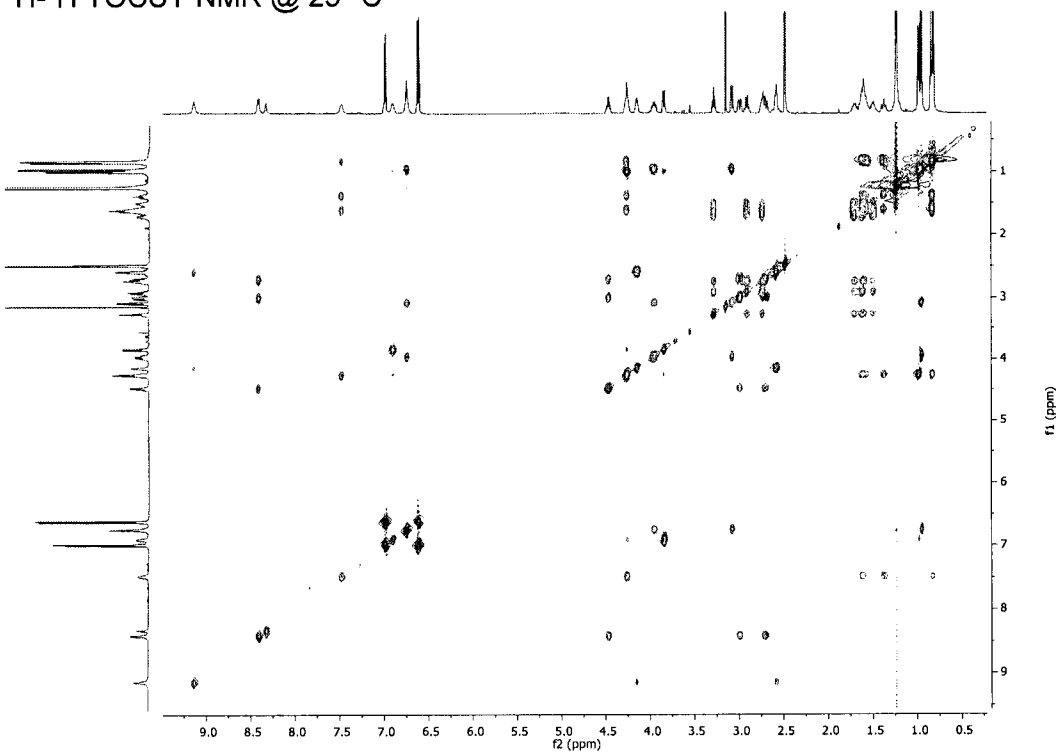
Compound No. 42

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



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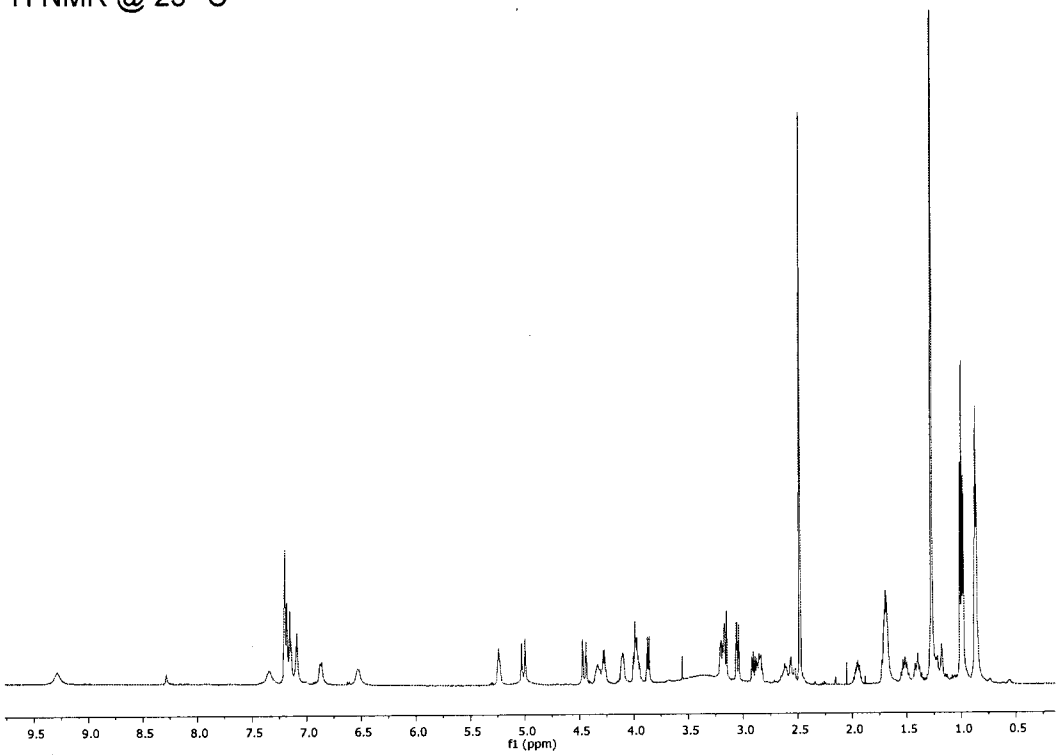
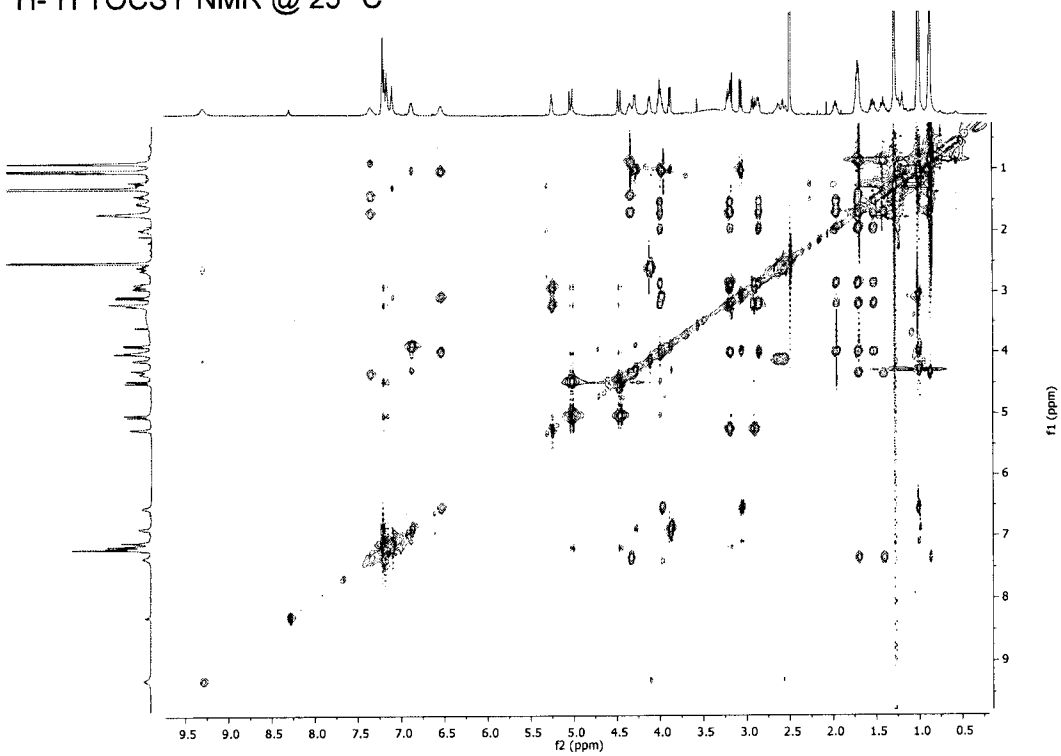
Compound No. 43

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



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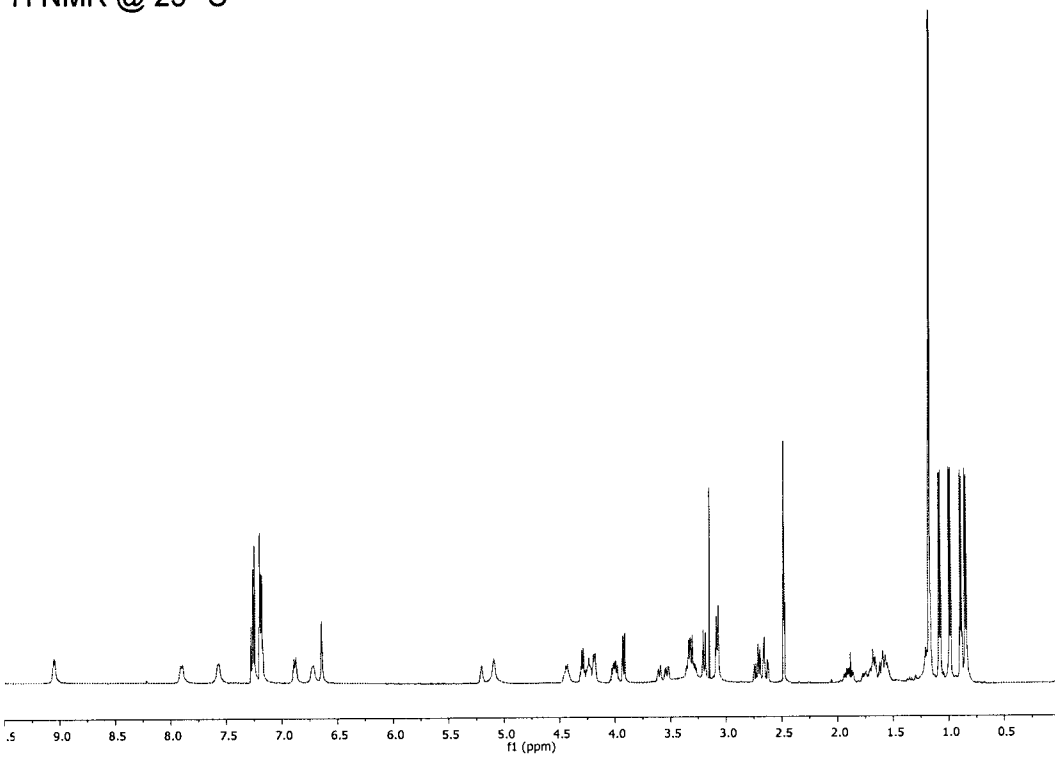
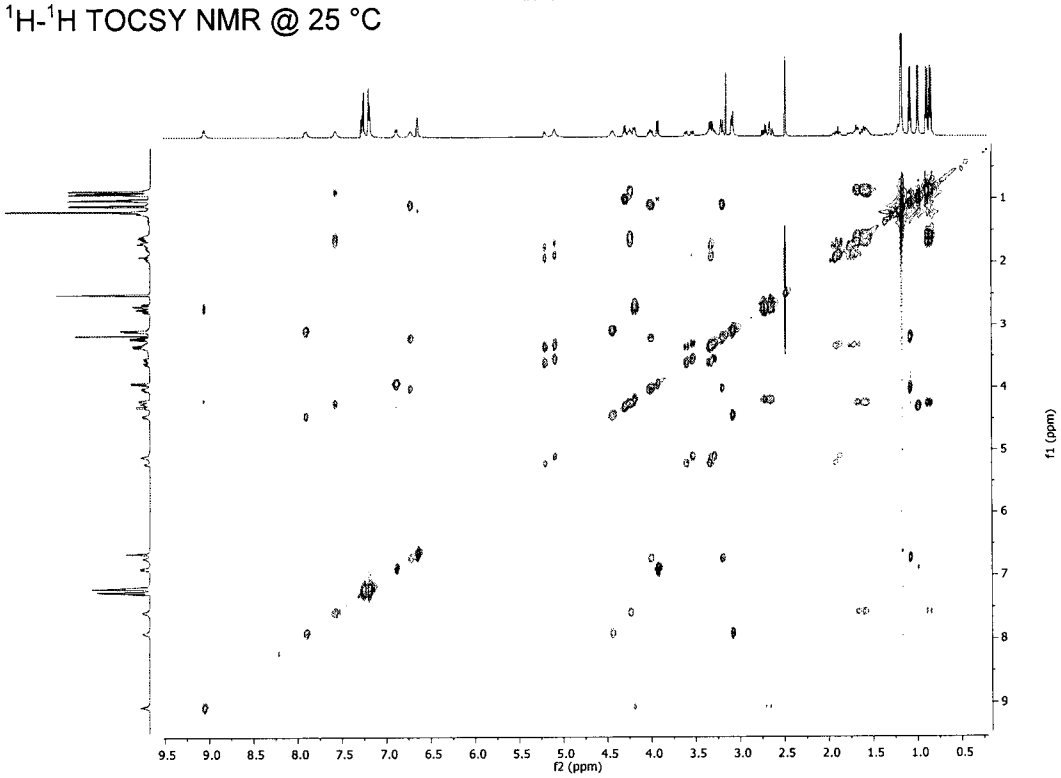
Compound No. 45

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



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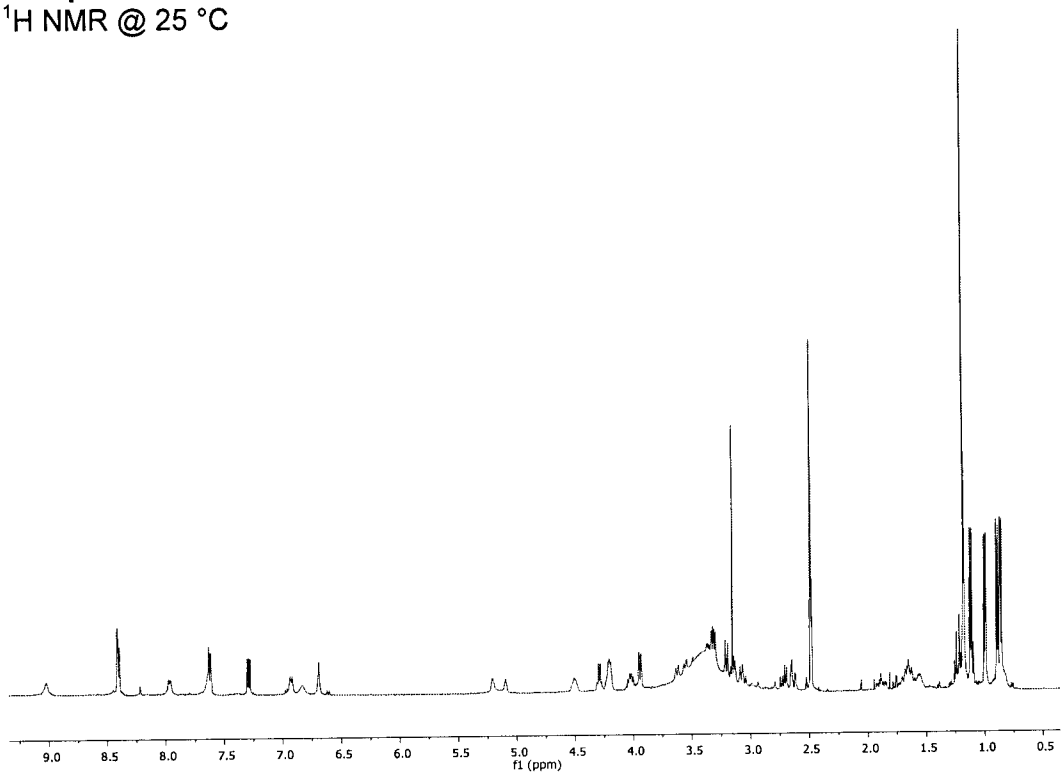
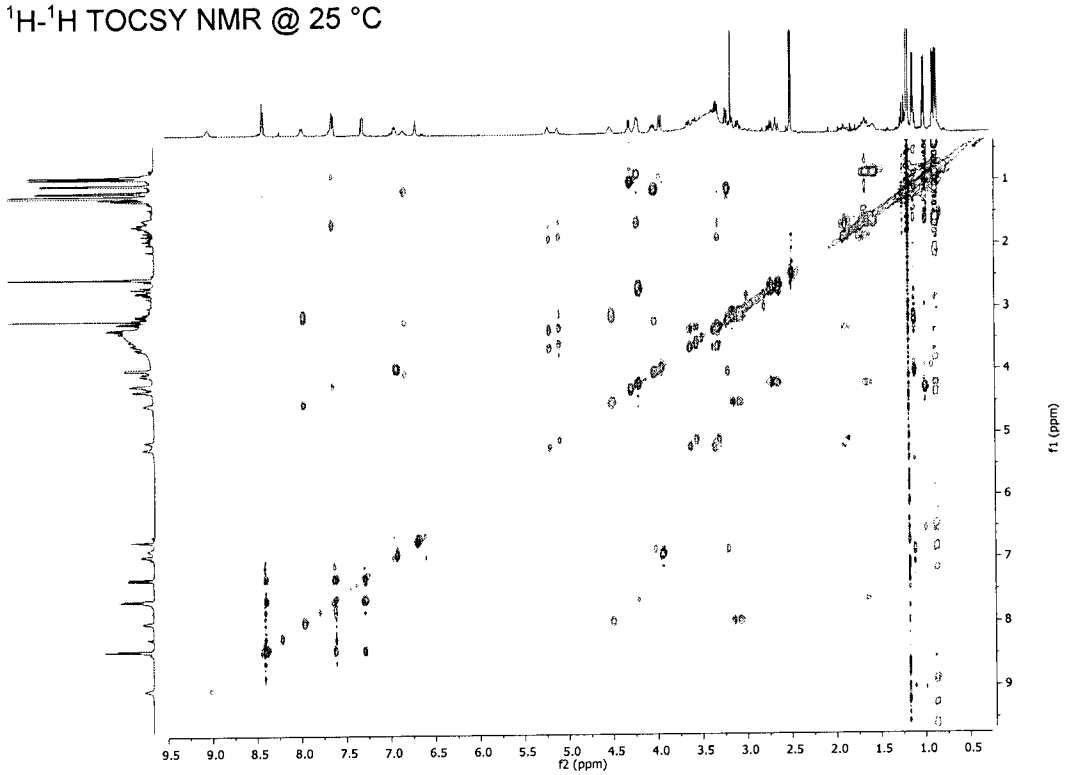
Compound No. 47

^{1}H NMR @ 25 °C



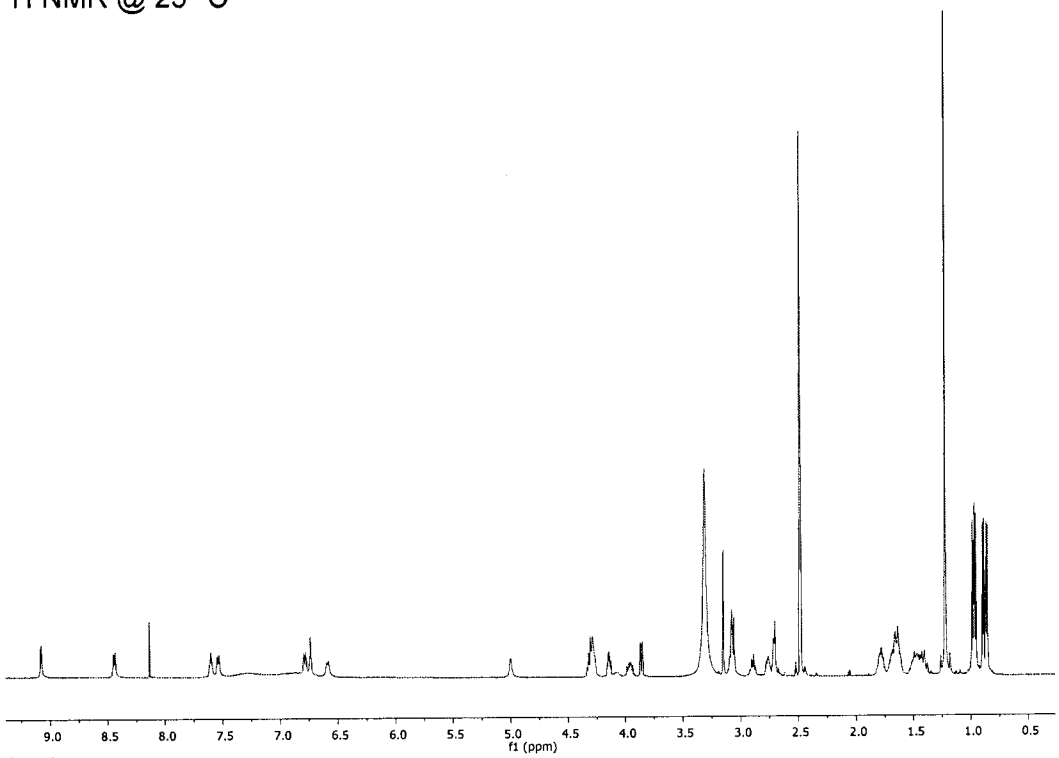
^{1}H-^{1}H TOCSY NMR @ 25 °C



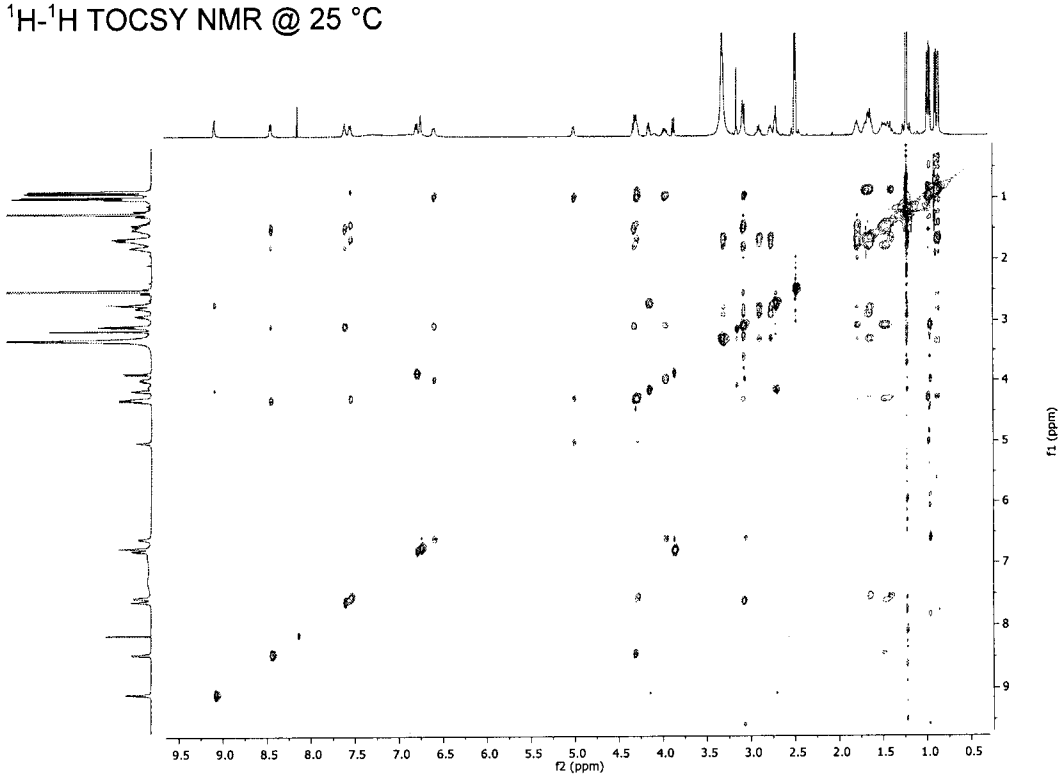
5

Compound No. 50

^{1}H NMR @ 25 °C



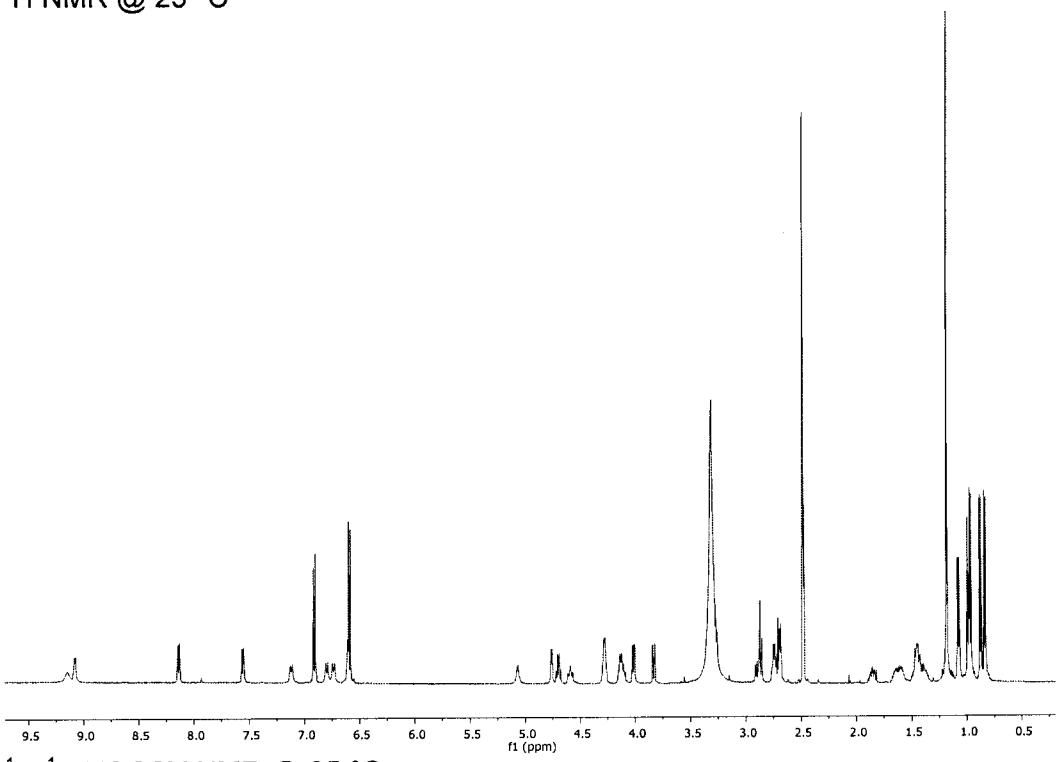
^{1}H-^{1}H TOCSY NMR @ 25 °C



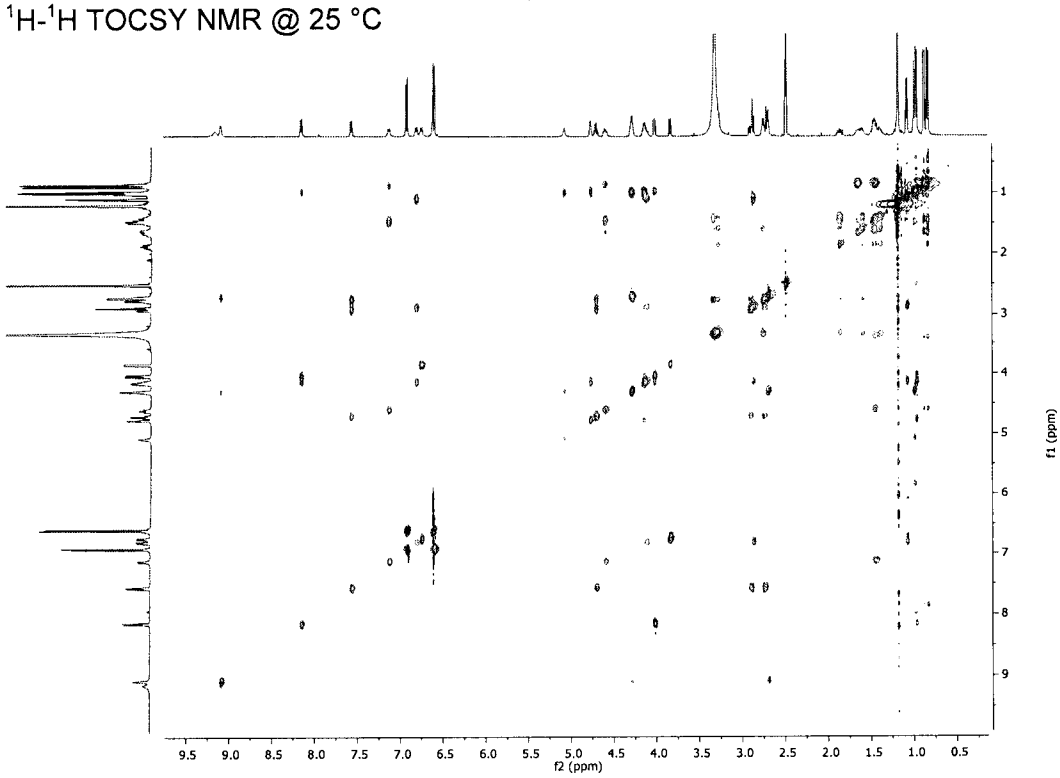
5

Compound No. 100

^{1}H NMR @ 25 °C



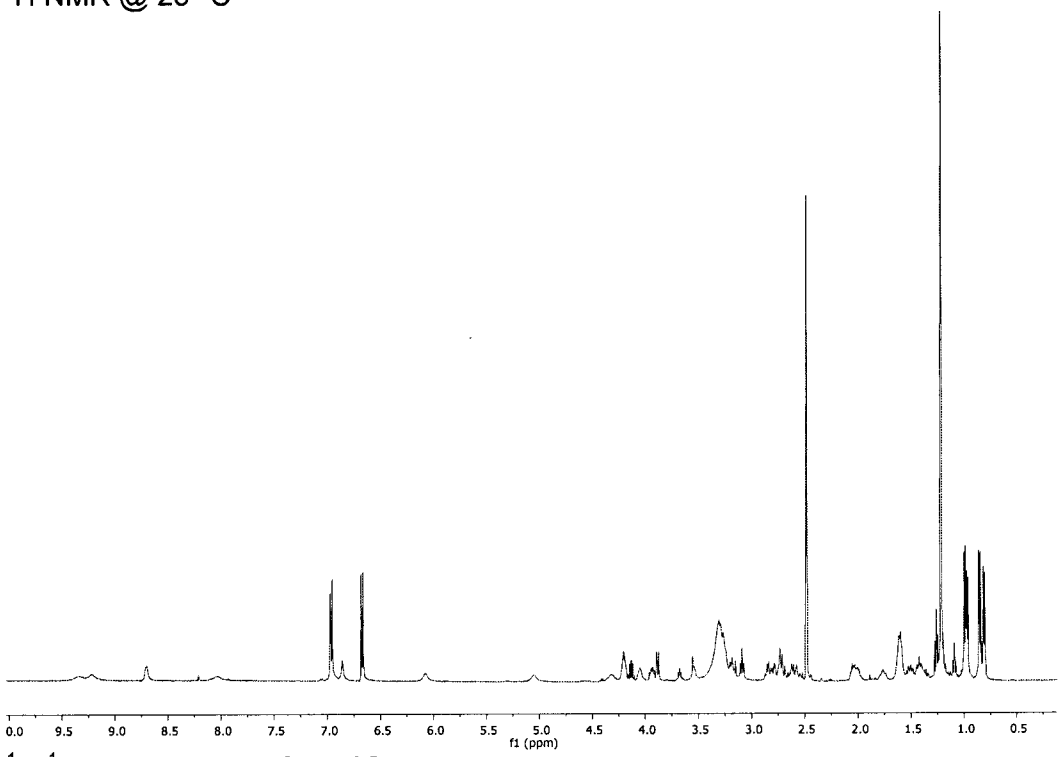
^{1}H-^{1}H TOCSY NMR @ 25 °C



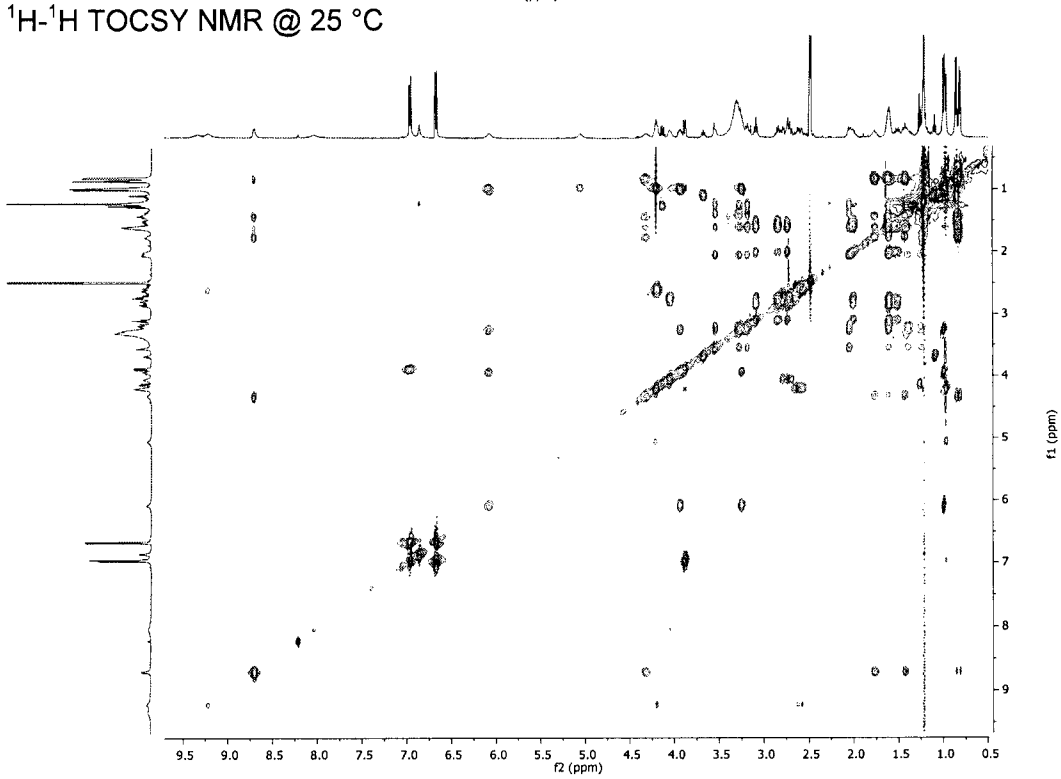
5

Compound No. 101

^{1}H NMR @ 25 °C



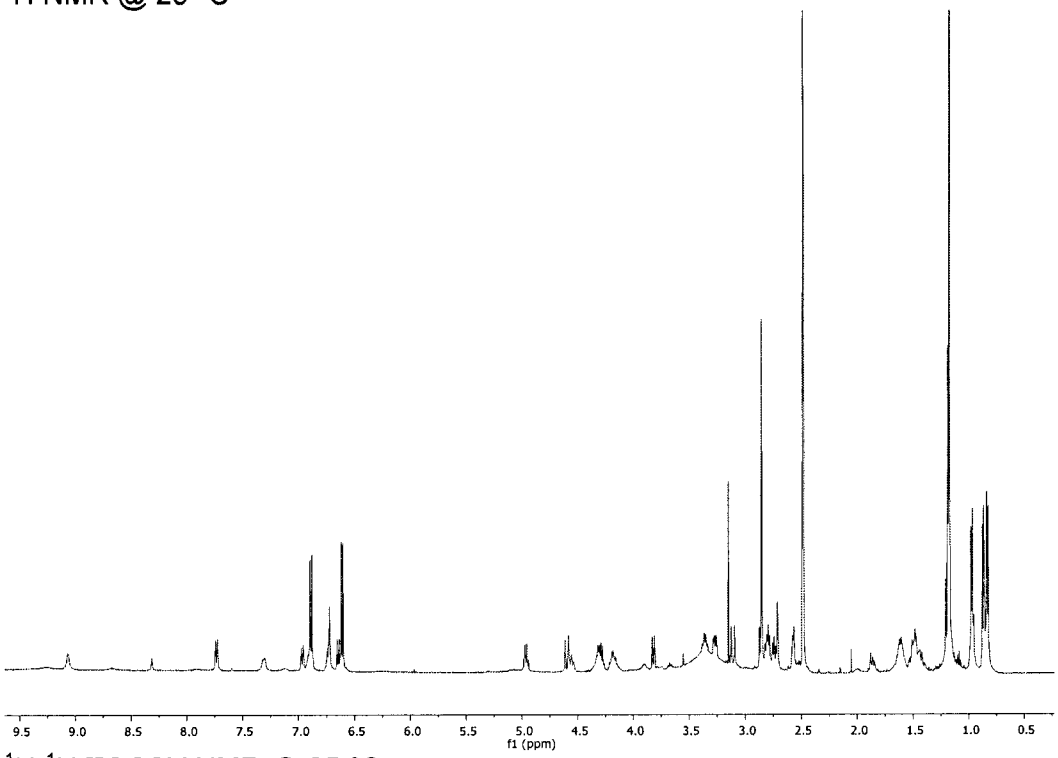
^{1}H-^{1}H TOCSY NMR @ 25 °C



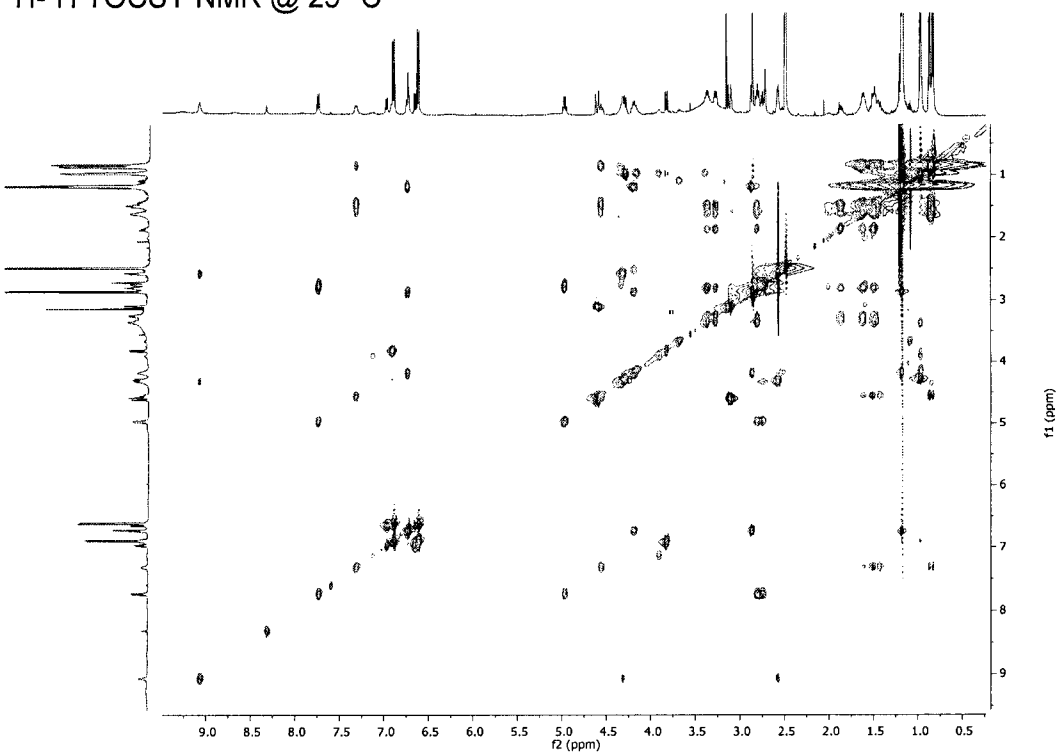
5

Compound No. 103

^{1}H NMR @ 25 °C



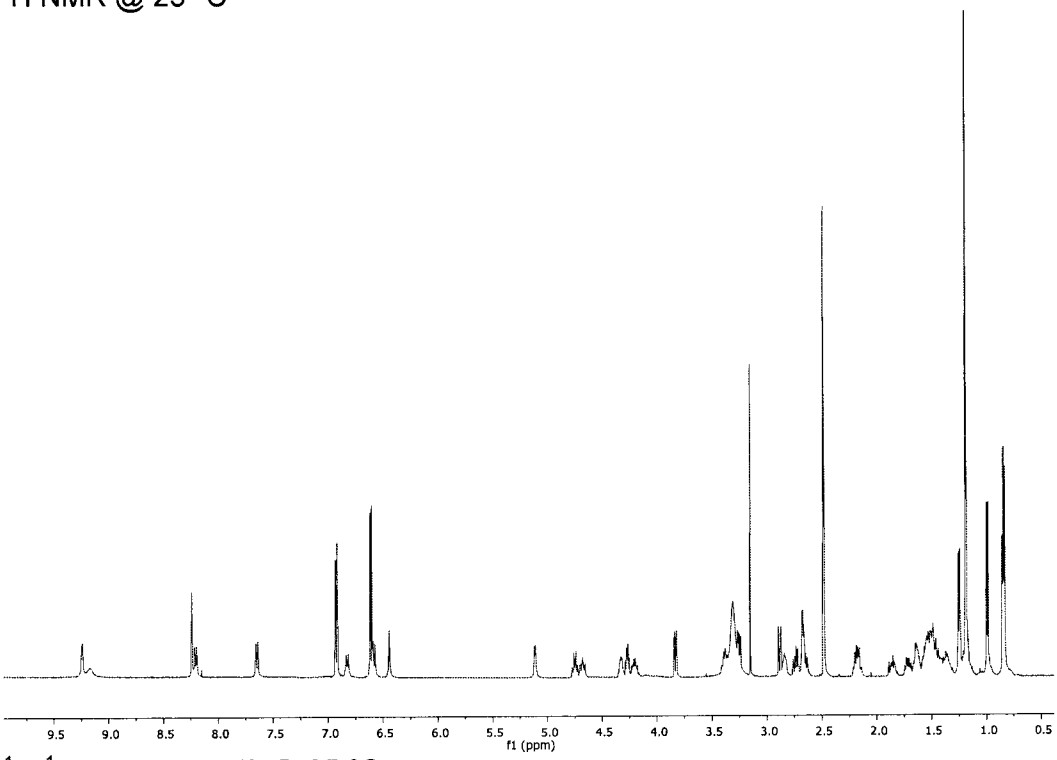
^{1}H-^{1}H TOCSY NMR @ 25 °C



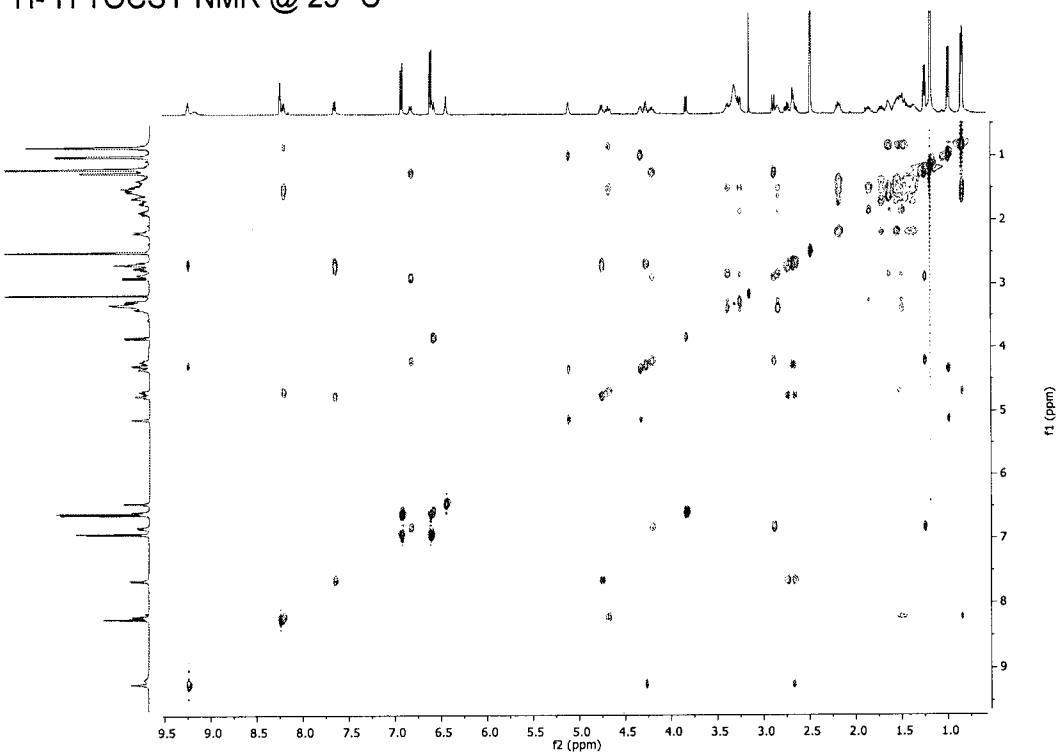
5

Compound No. 104

^{1}H NMR @ 25 °C



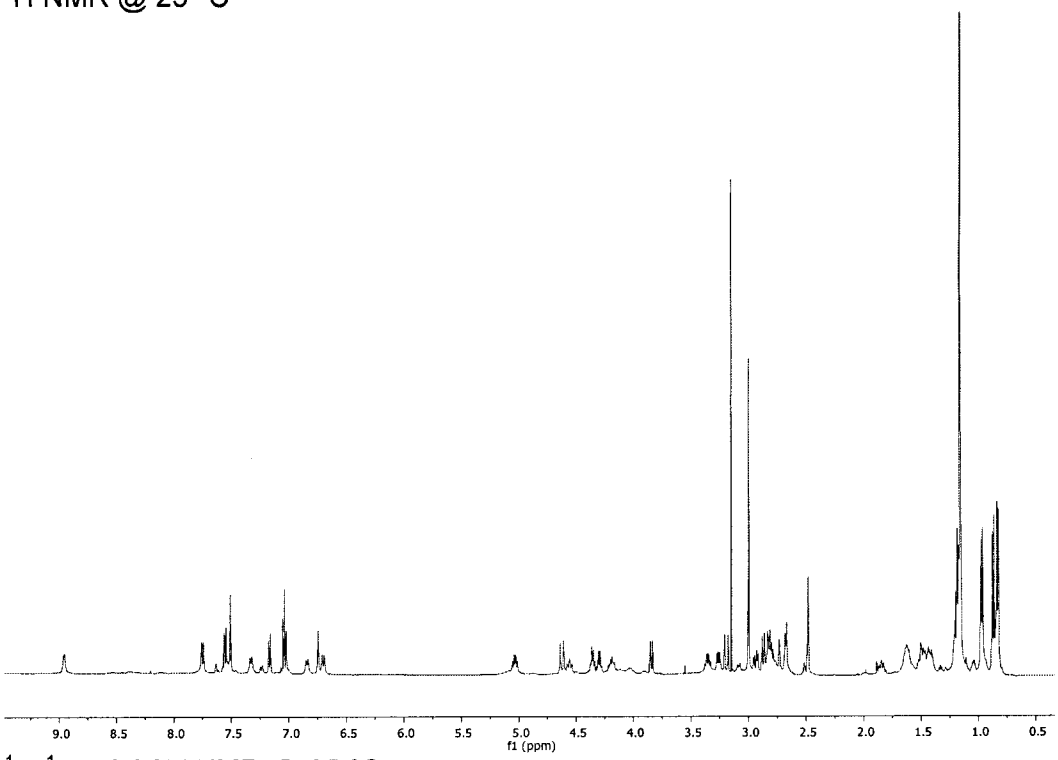
^{1}H-^{1}H TOCSY NMR @ 25 °C



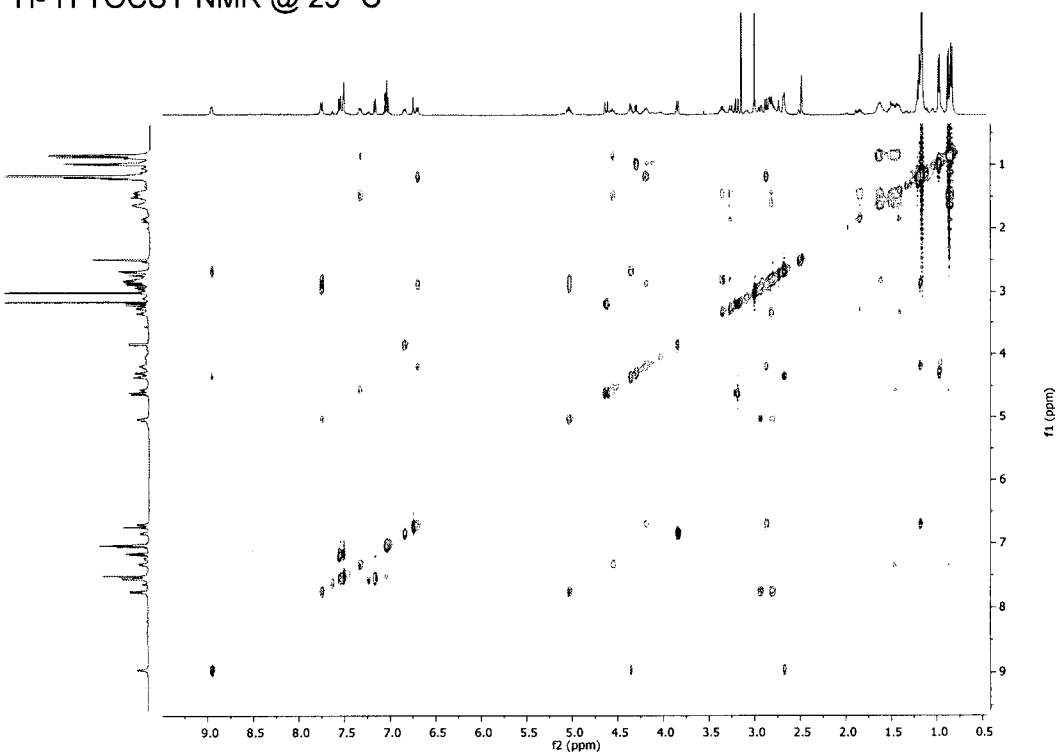
5

Compound No. 106

^{1}H NMR @ 25 °C



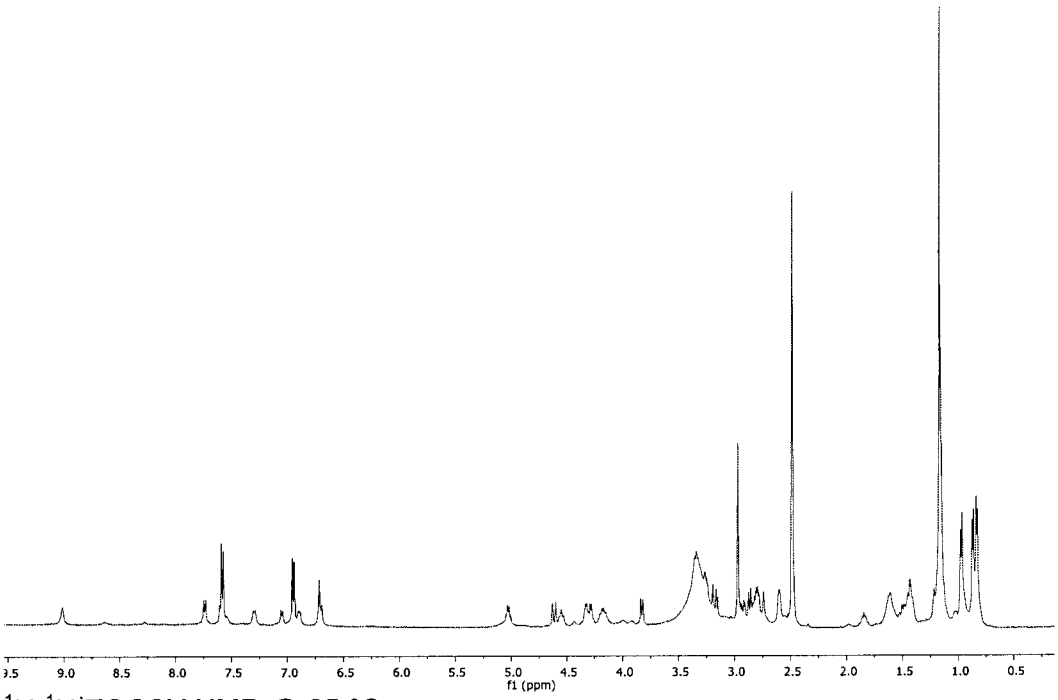
^{1}H-^{1}H TOCSY NMR @ 25 °C



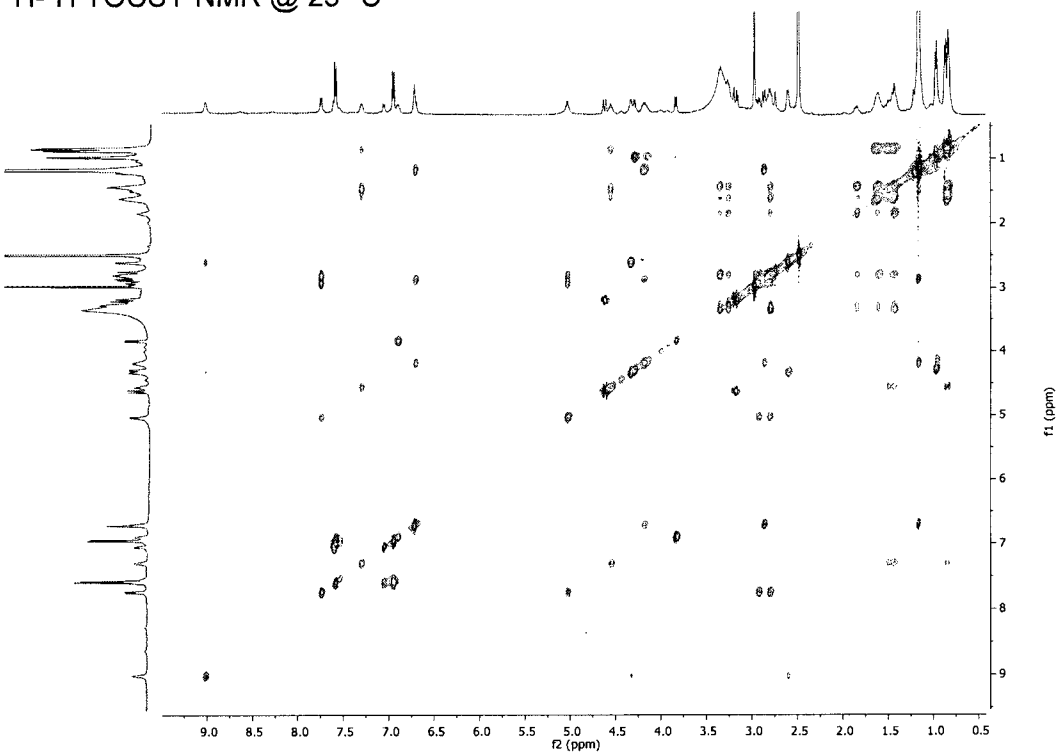
5

Compound No. 107

^{1}H NMR @ 25 °C



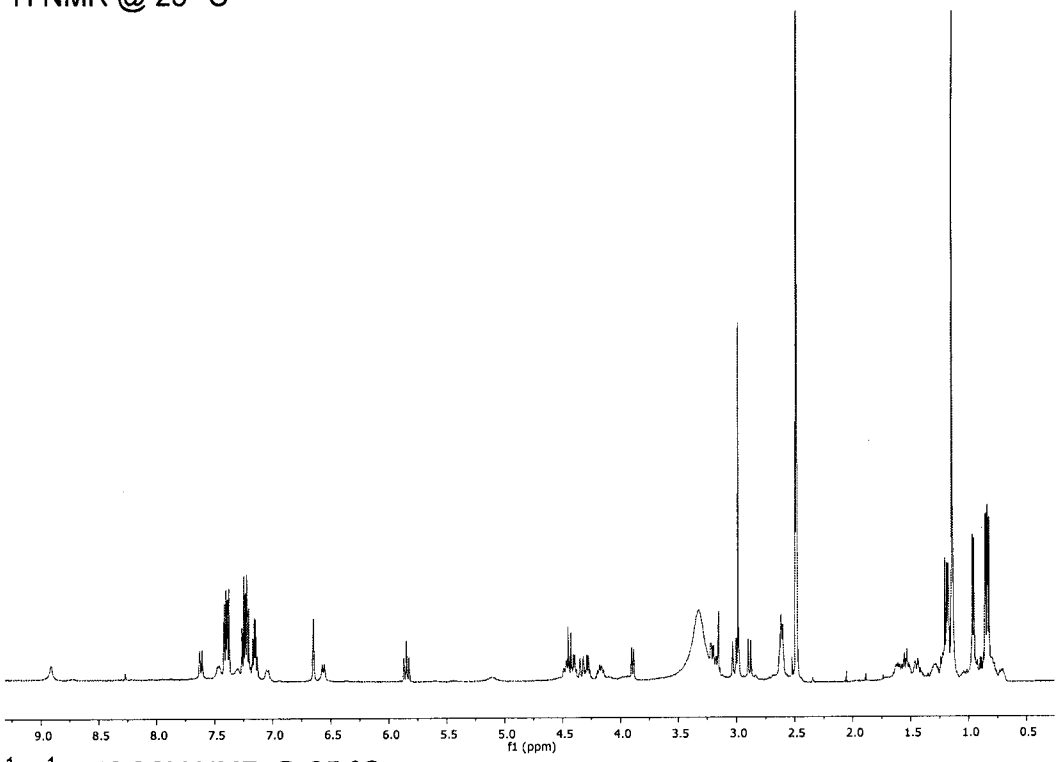
^{1}H-^{1}H TOCSY NMR @ 25 °C



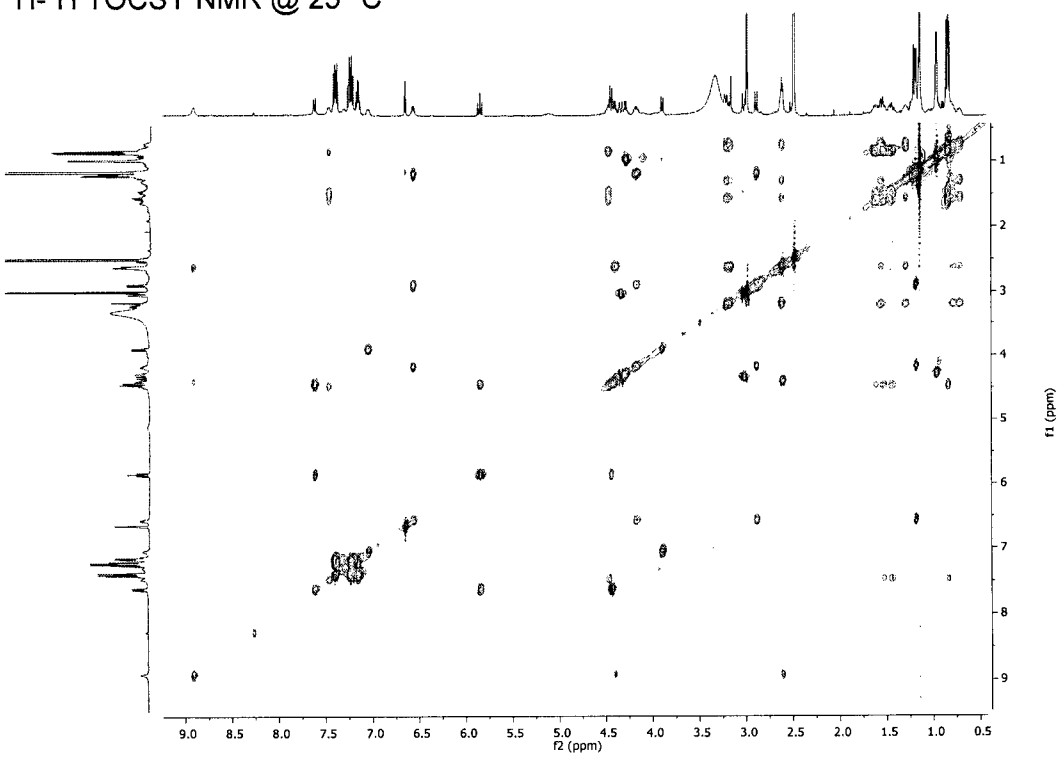
5

Compound No. 108

^{1}H NMR @ 25 °C



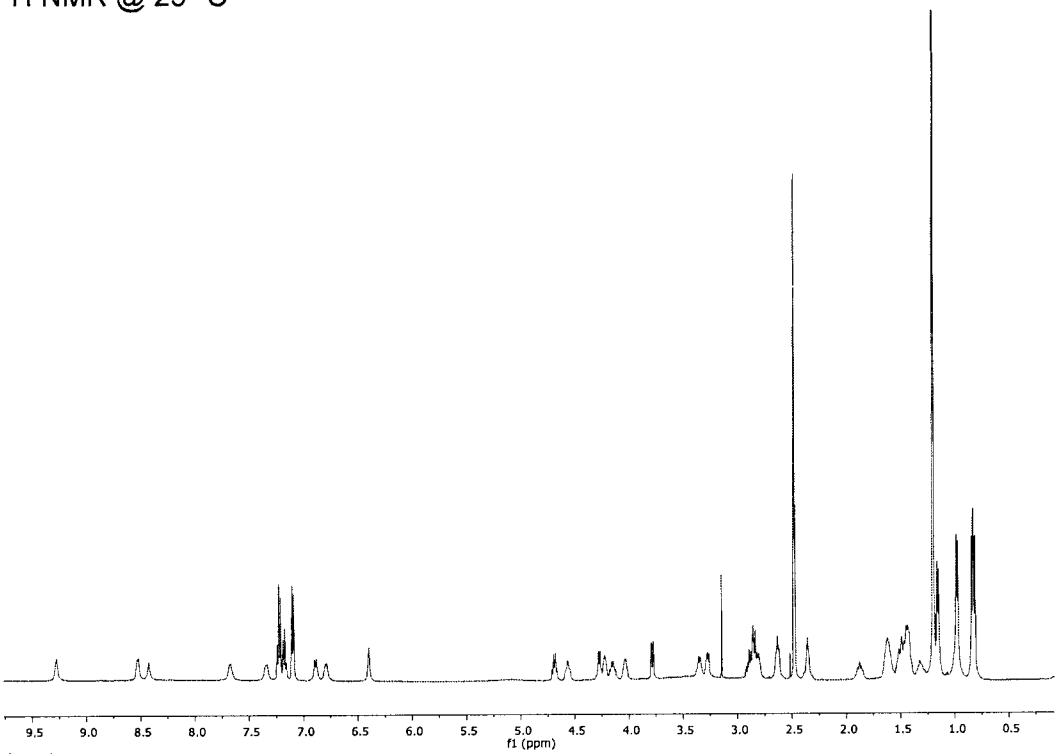
^{1}H-^{1}H TOCSY NMR @ 25 °C



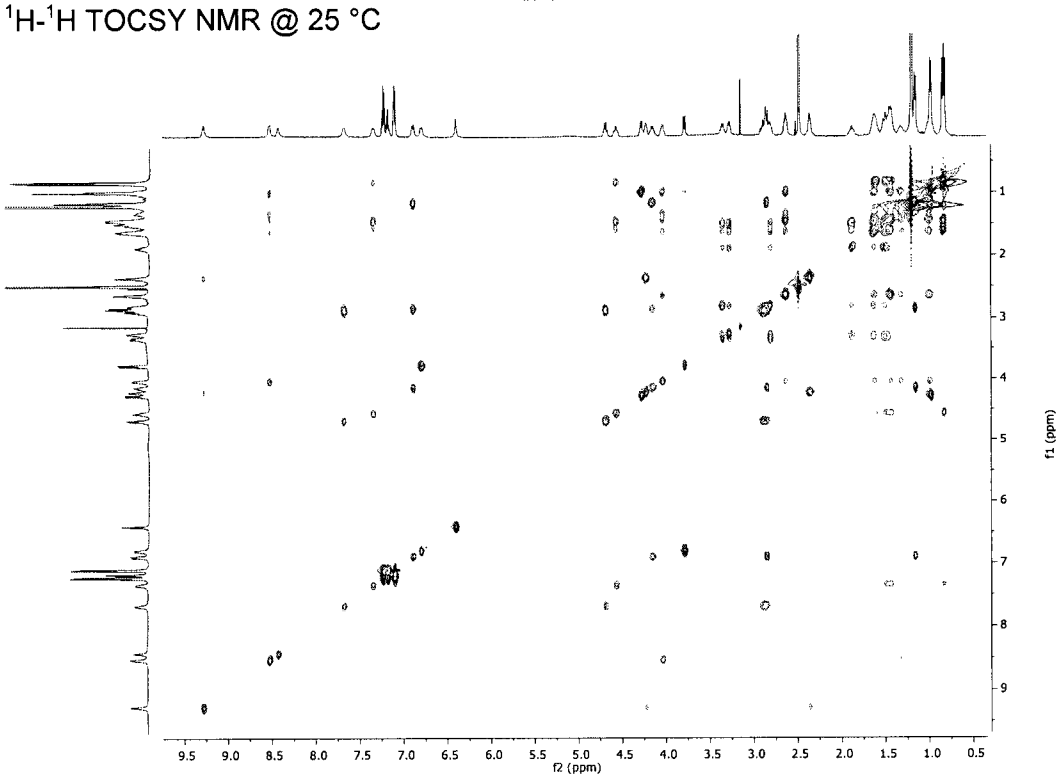
5

Compound No. 109

^{1}H NMR @ 25 °C



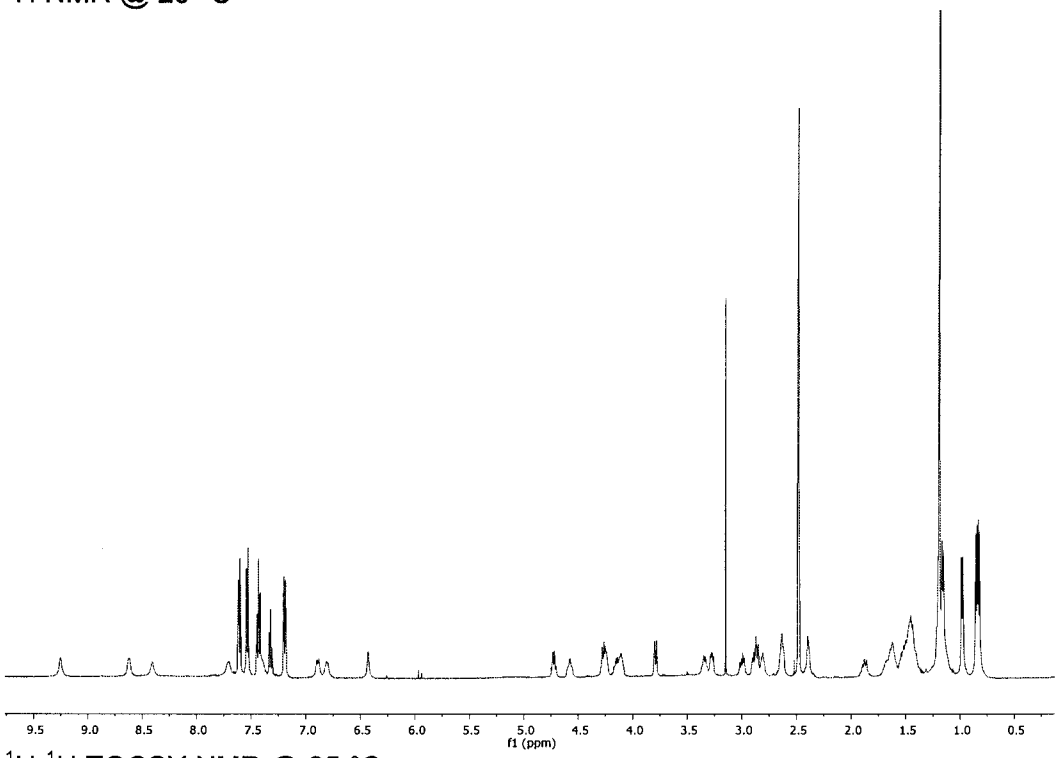
^{1}H-^{1}H TOCSY NMR @ 25 °C



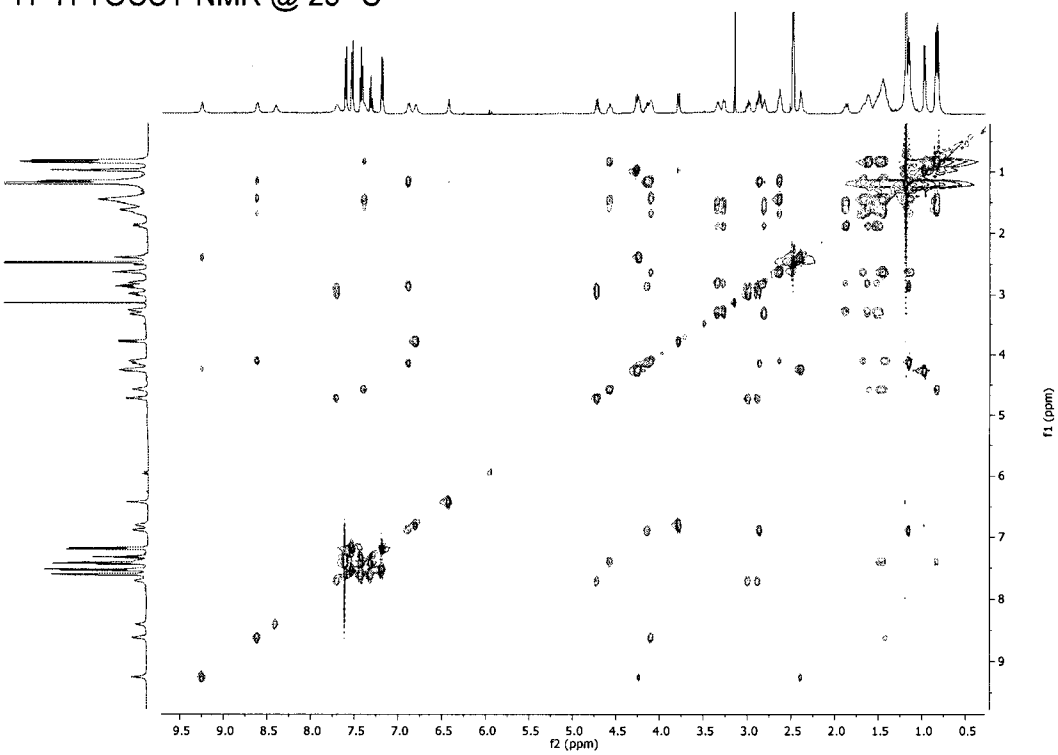
5

Compound No. 110

^{1}H NMR @ 25 °C



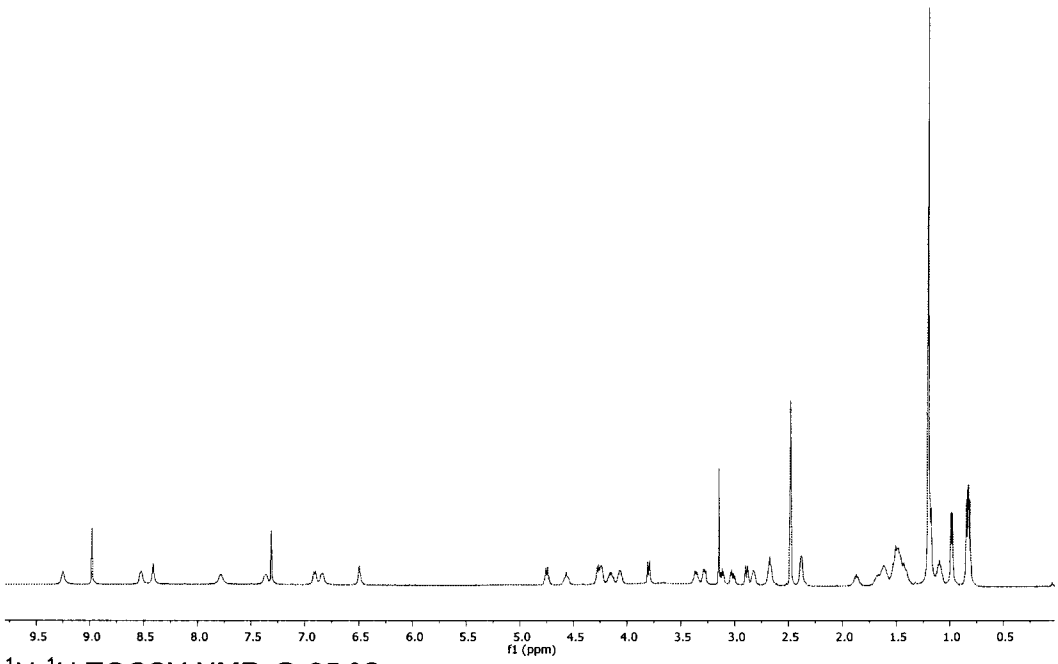
^{1}H-^{1}H TOCSY NMR @ 25 °C



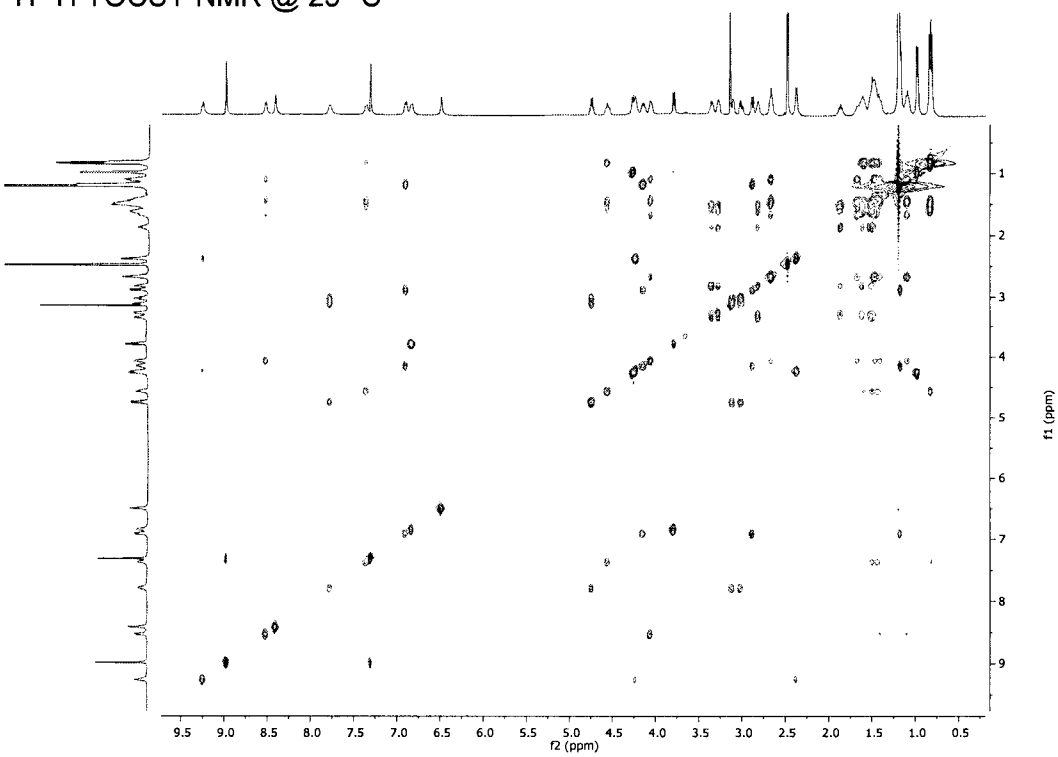
5

Compound No. 111

^{1}H NMR @ 25 °C



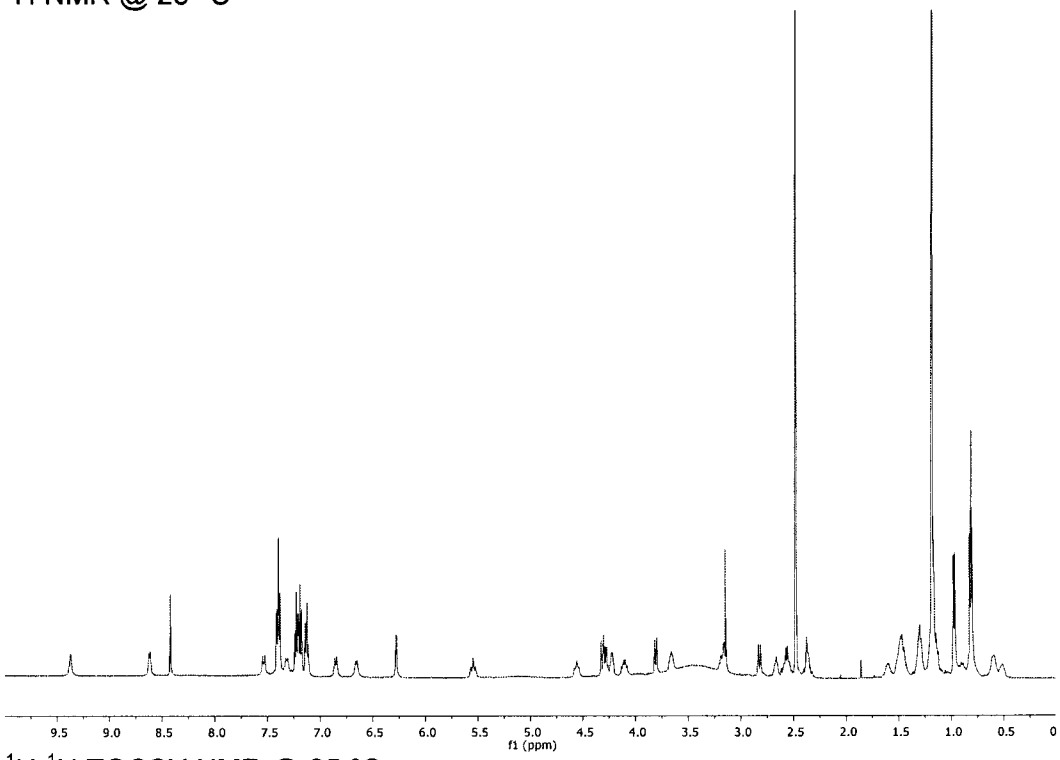
^{1}H-^{1}H TOCSY NMR @ 25 °C



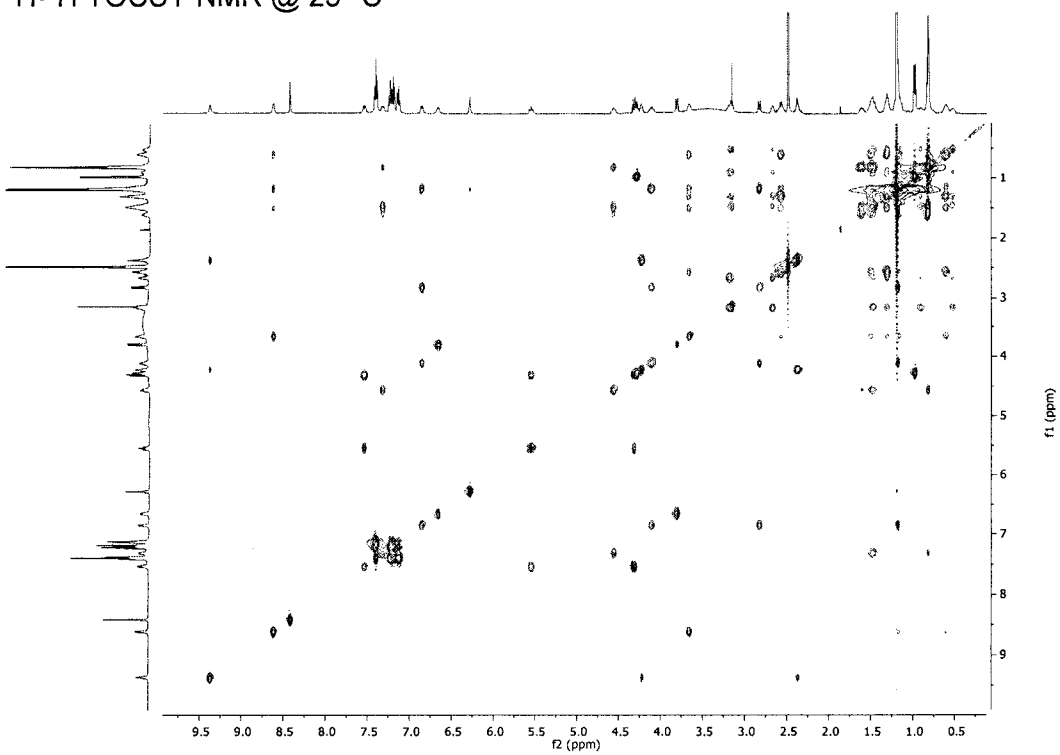
5

Compound No. 112

^{1}H NMR @ 25 °C



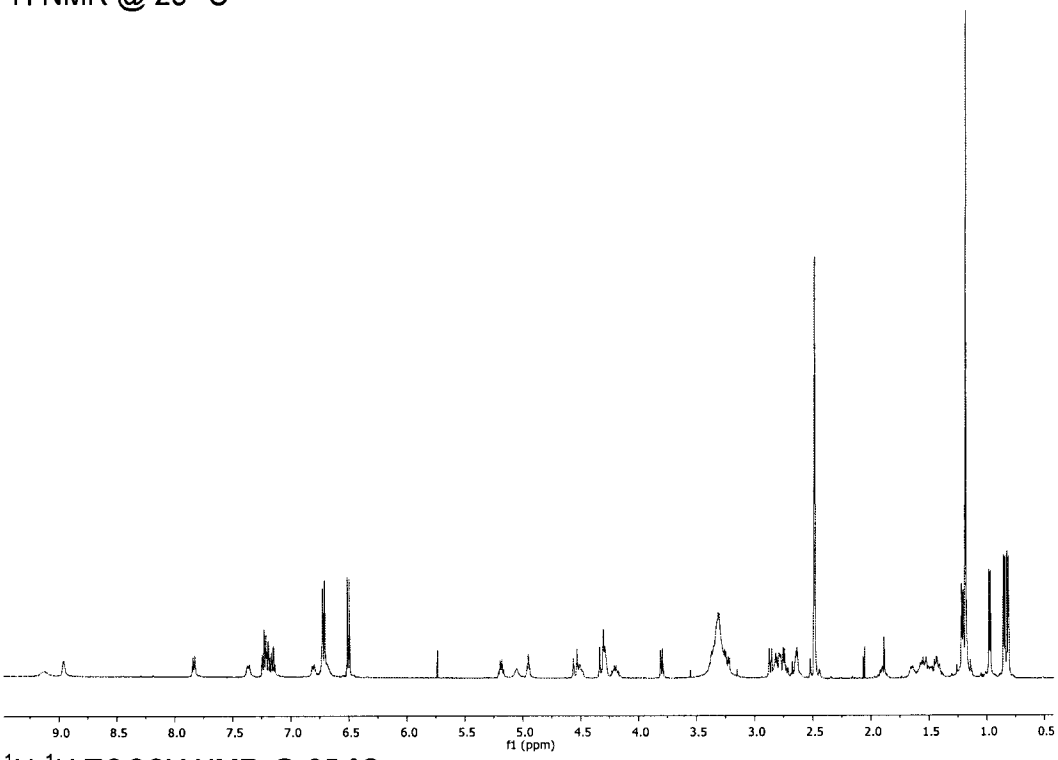
^{1}H-^{1}H TOCSY NMR @ 25 °C



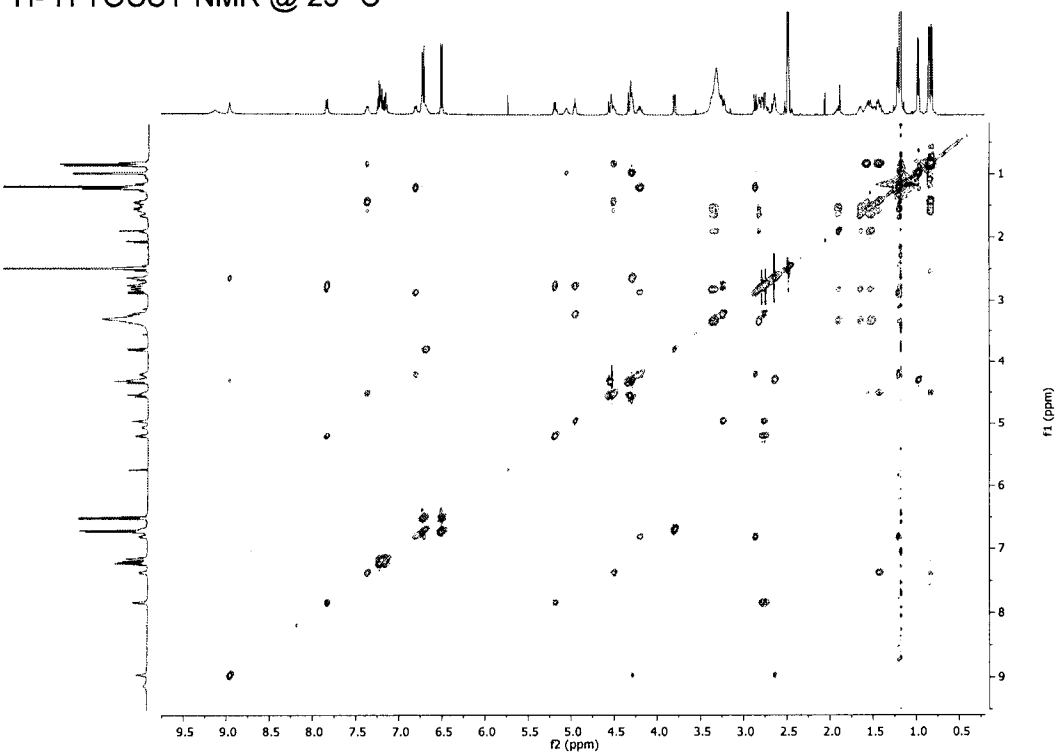
5

Compound No. 123

^{1}H NMR @ 25 °C

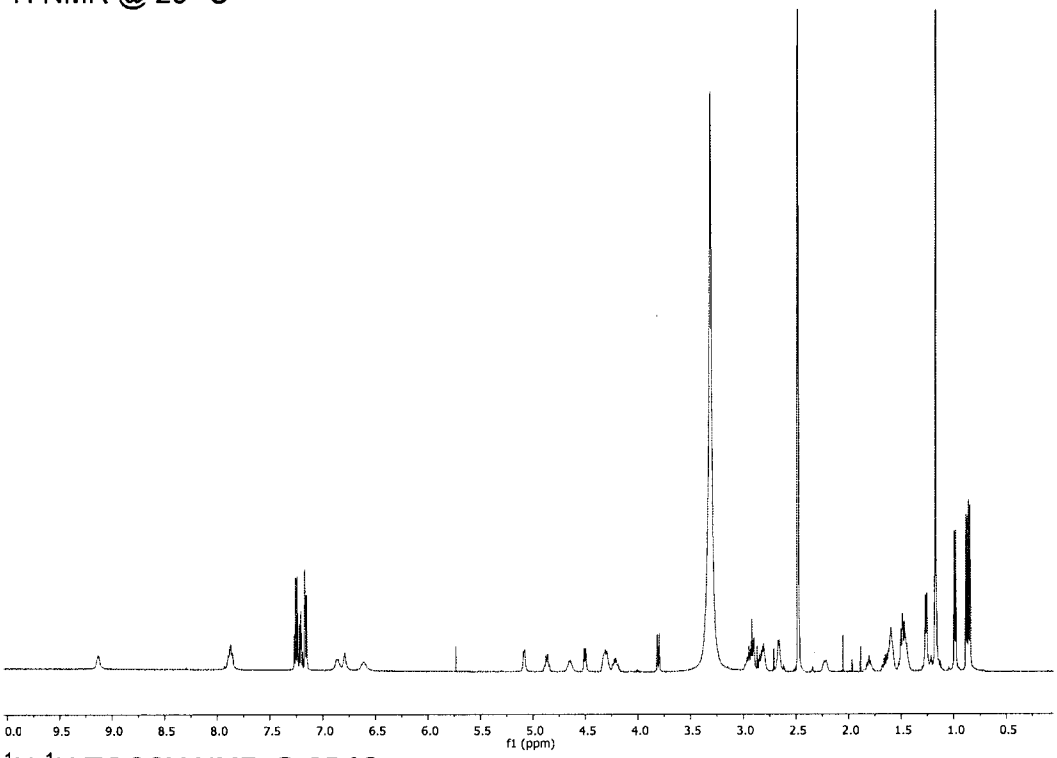


^{1}H-^{1}H TOCSY NMR @ 25 °C

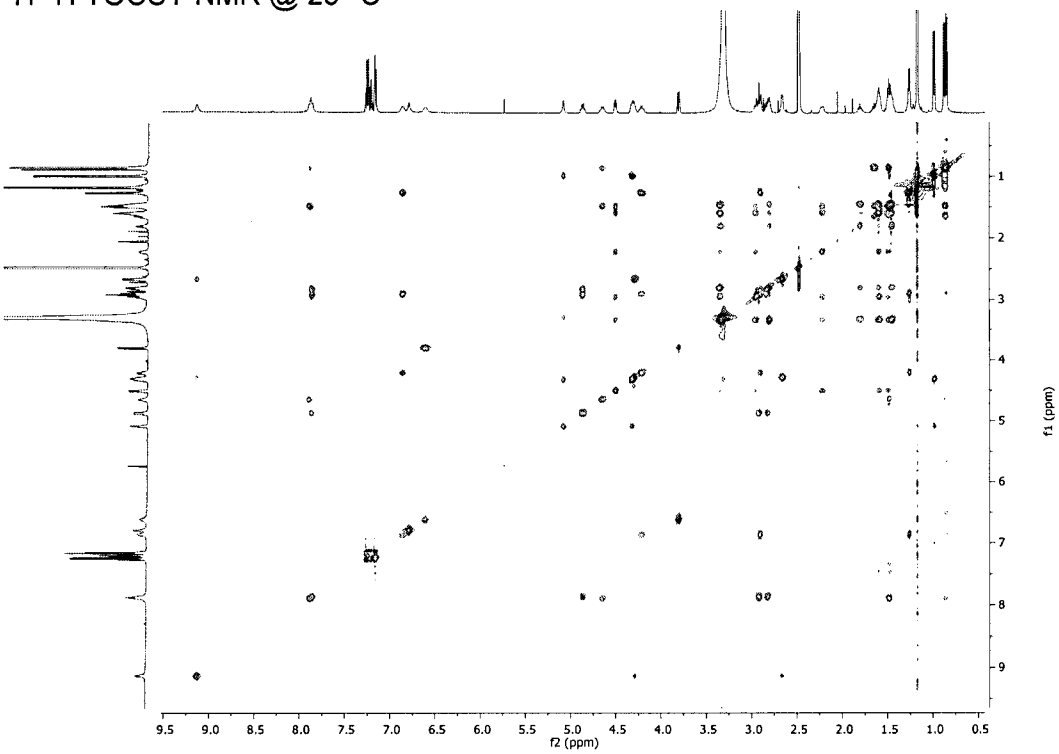


Compound No. 126

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



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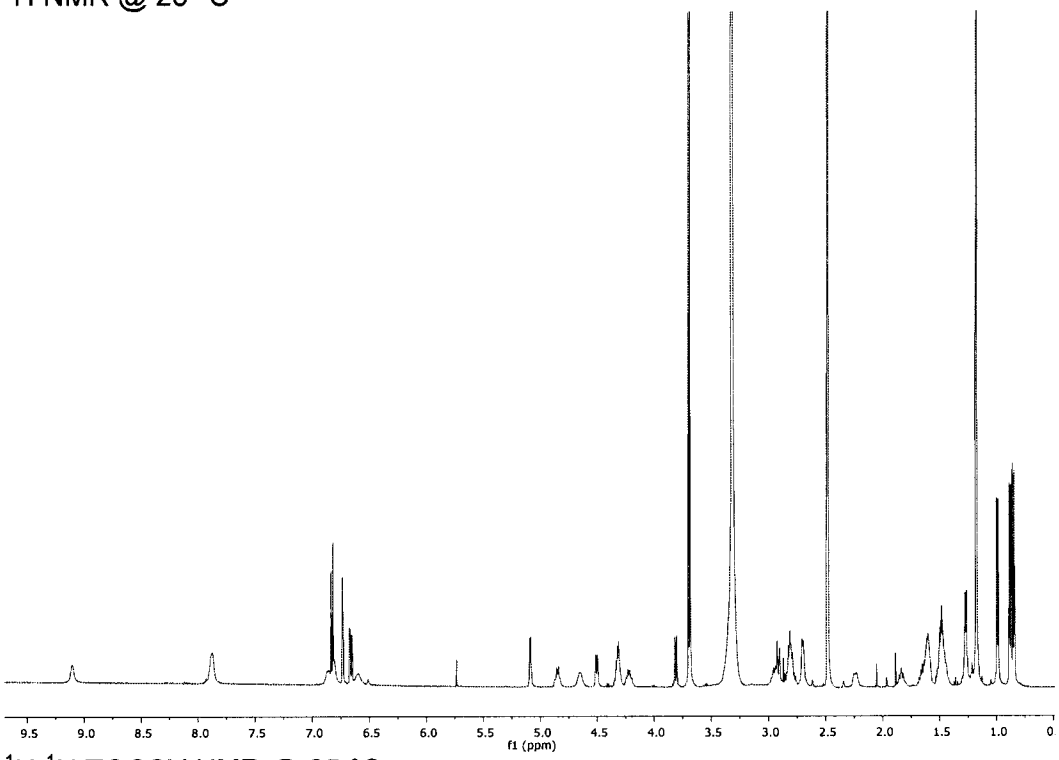
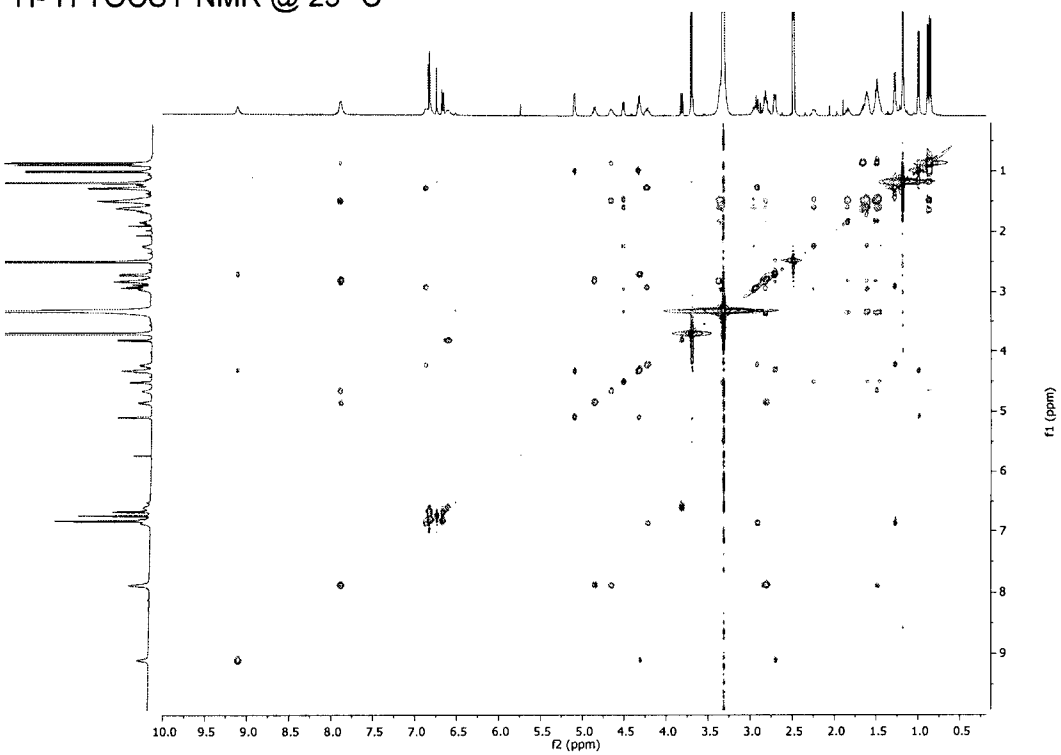
Compound No. 127

^{1}H NMR @ 25 °C



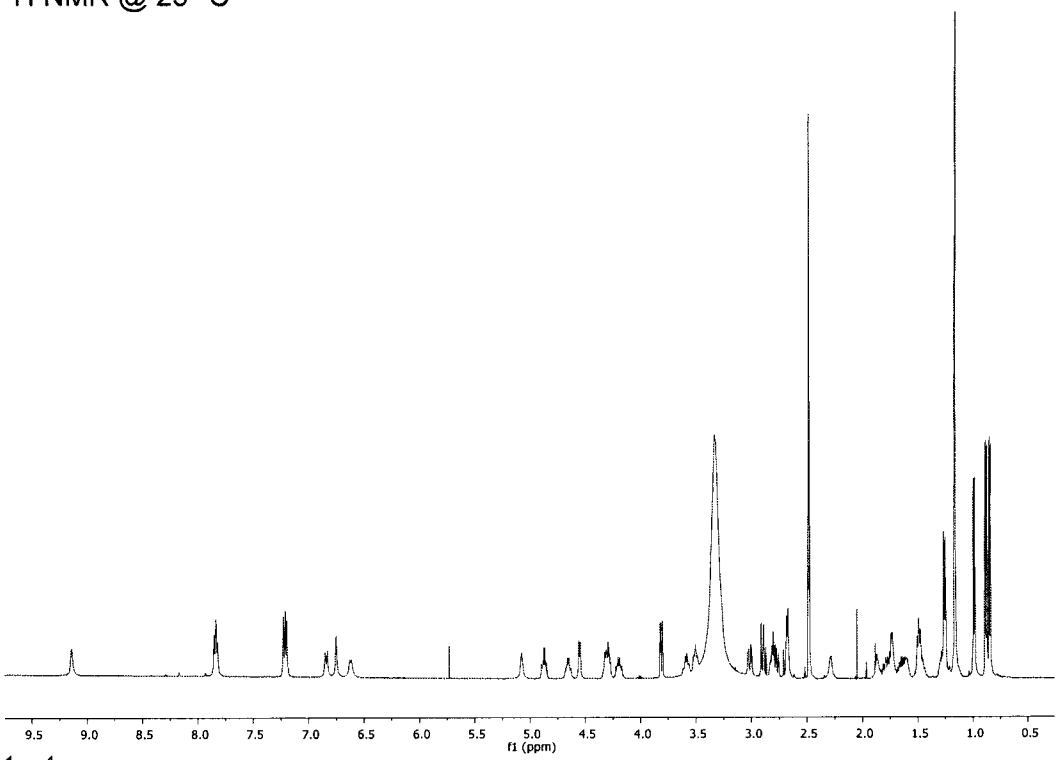
^{1}H-^{1}H TOCSY NMR @ 25 °C



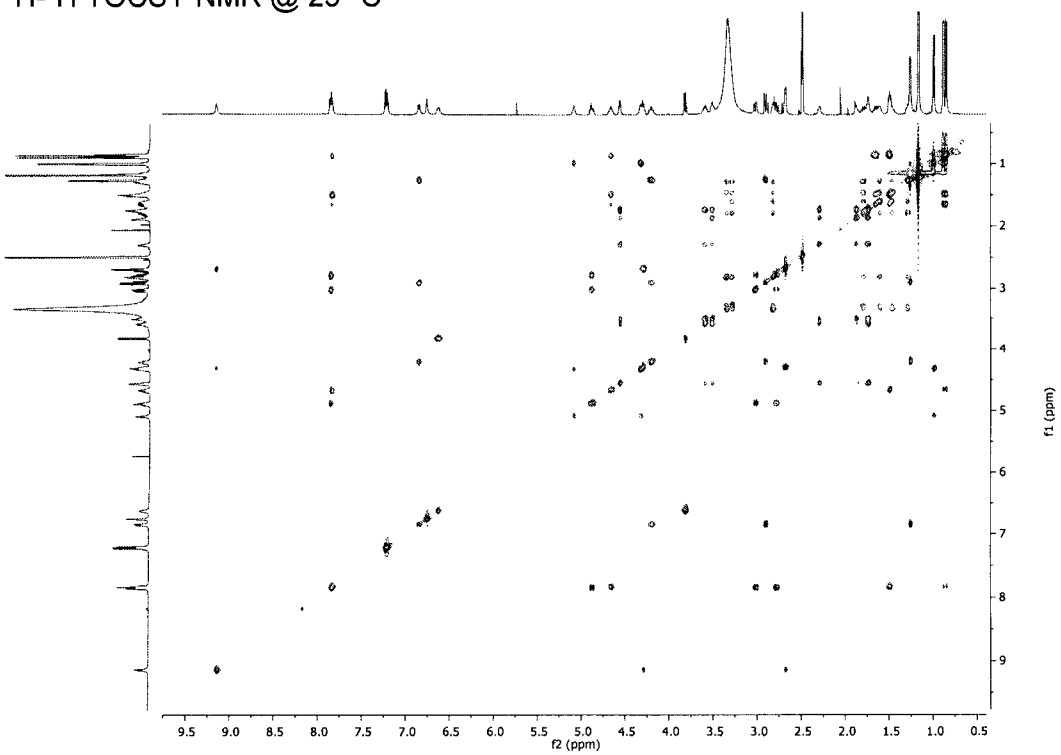
5

Compound No. 128

^{1}H NMR @ 25 °C



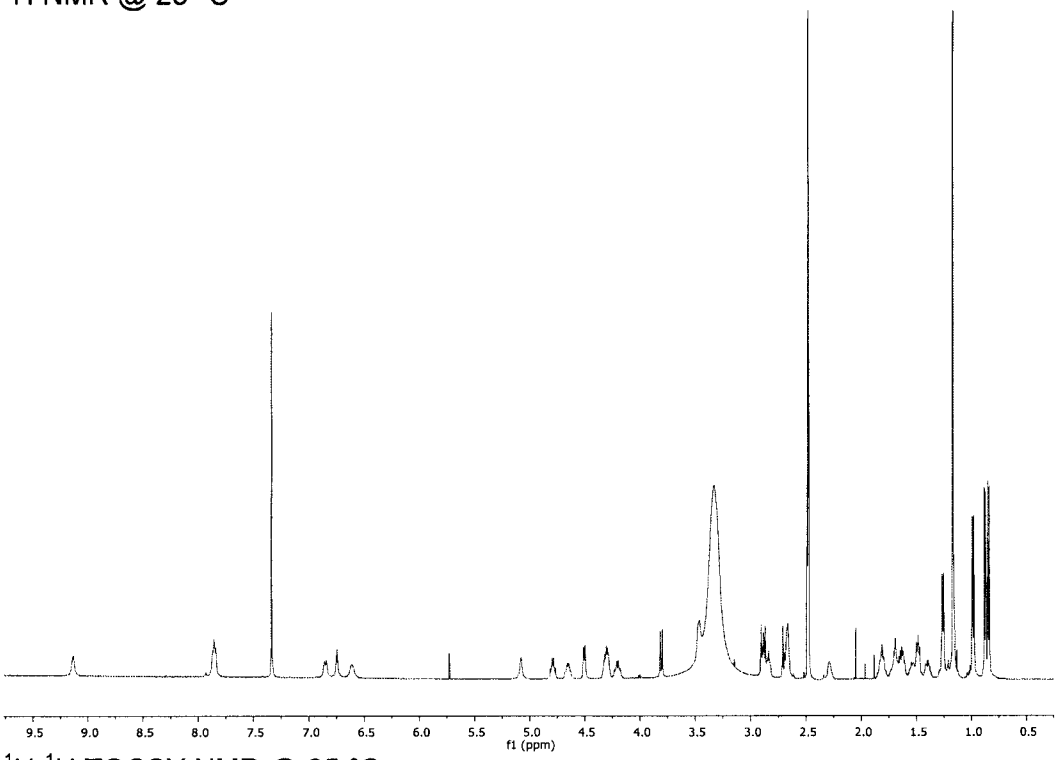
^{1}H-^{1}H TOCSY NMR @ 25 °C



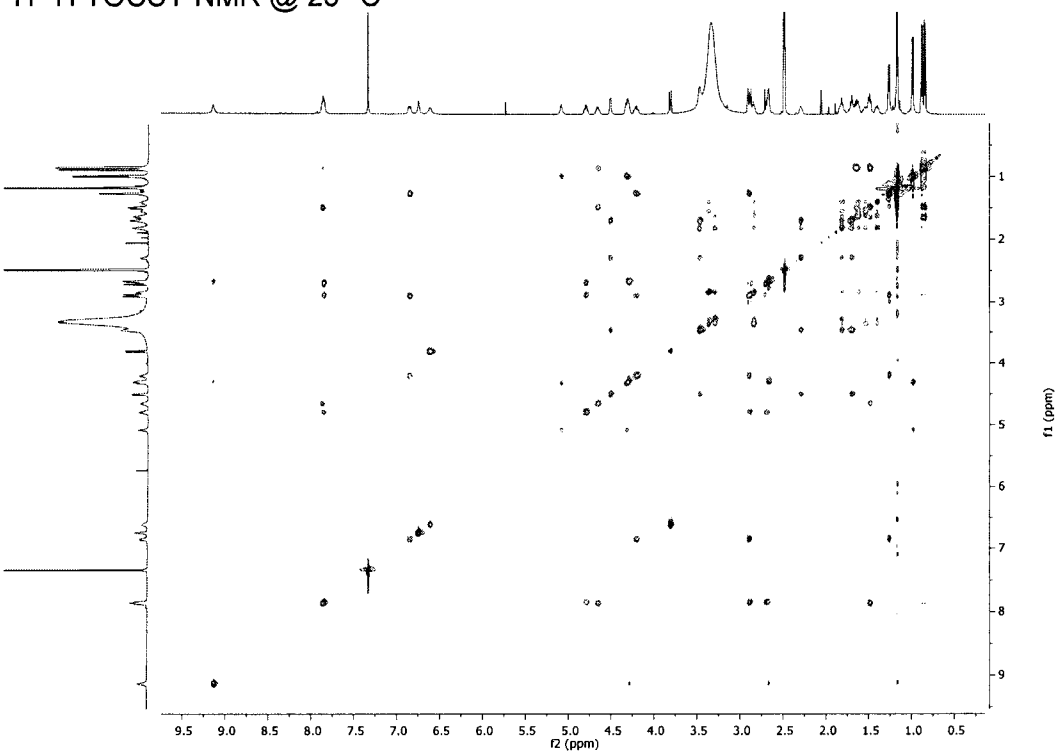
5

Compound No. 129

^{1}H NMR @ 25 °C



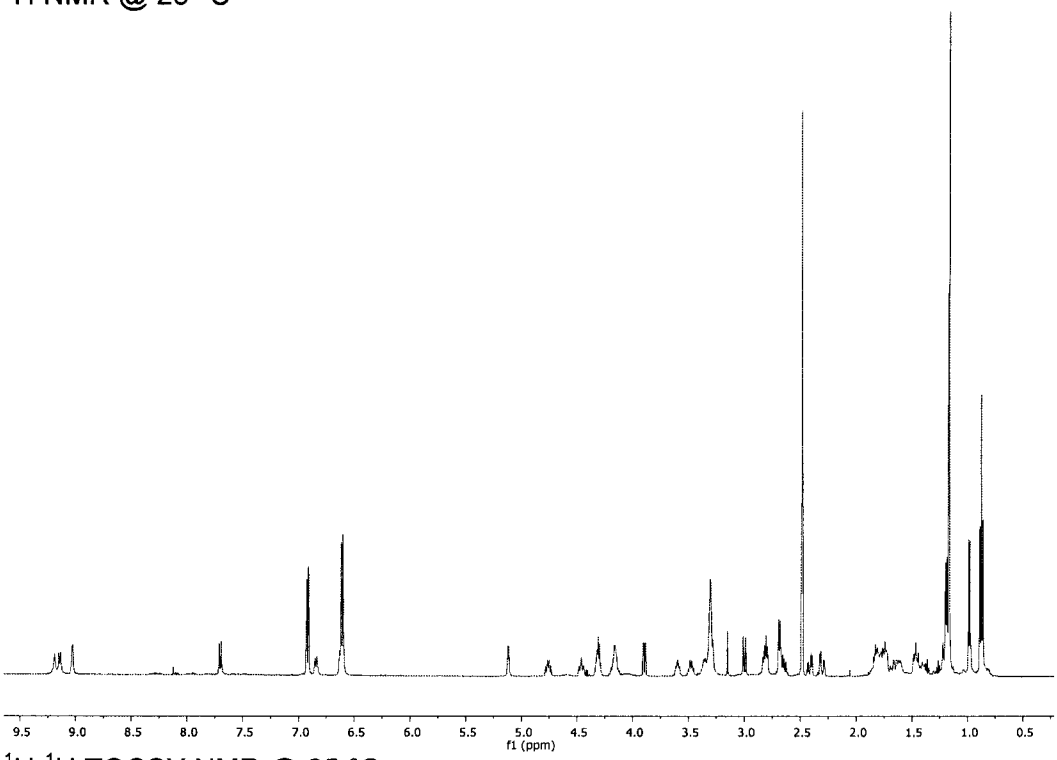
^{1}H-^{1}H TOCSY NMR @ 25 °C



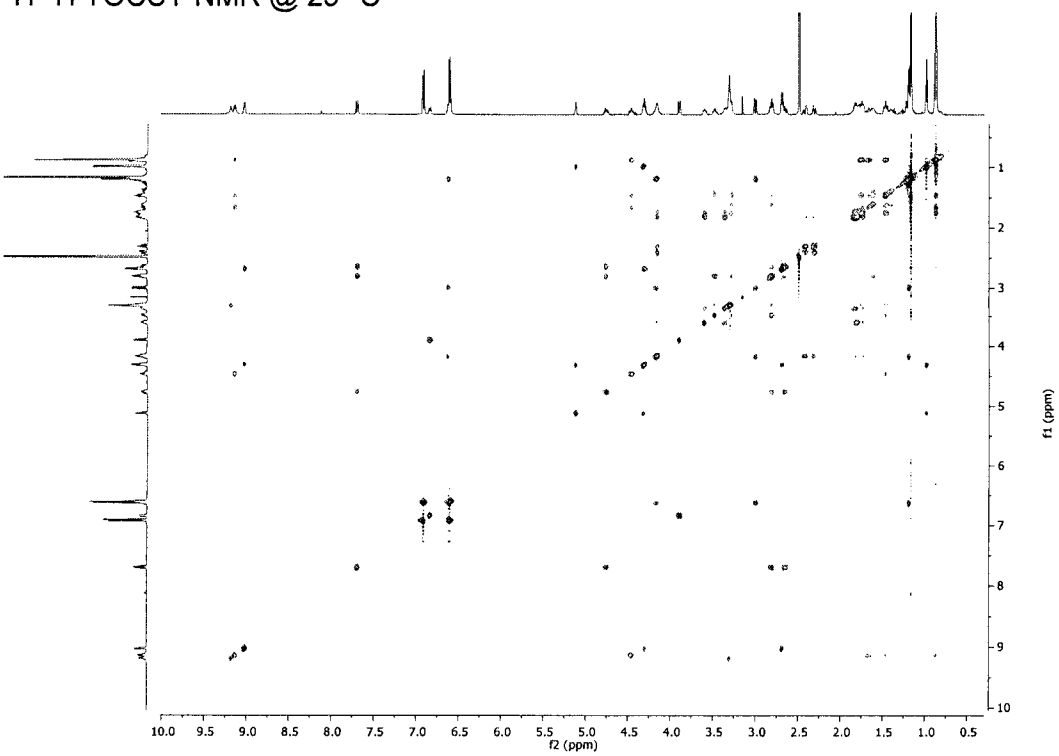
5

Compound No. 229

^{1}H NMR @ 25 °C

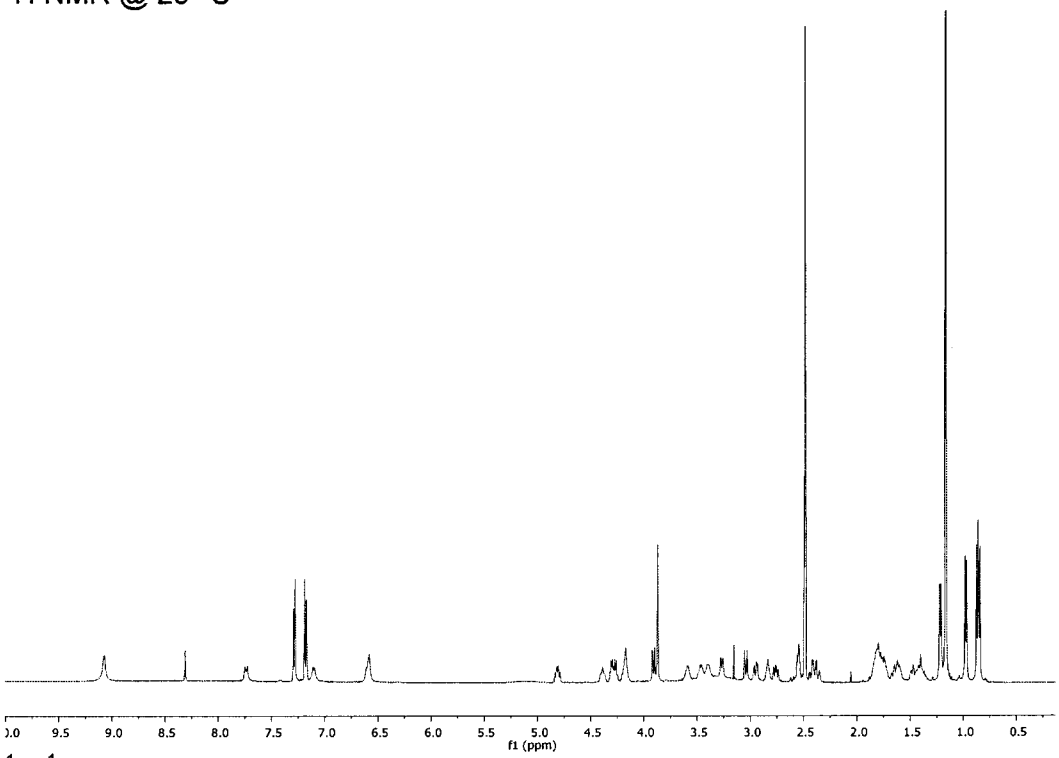


^{1}H-^{1}H TOCSY NMR @ 25 °C

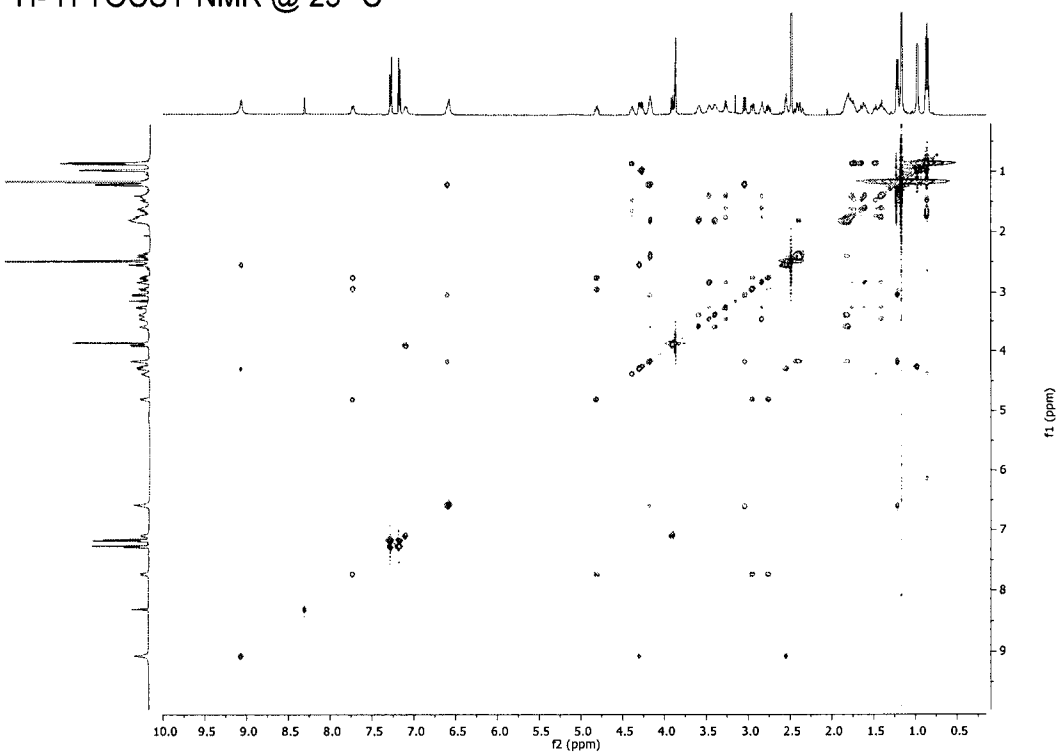


Compound No. 230

^{1}H NMR @ 25 °C

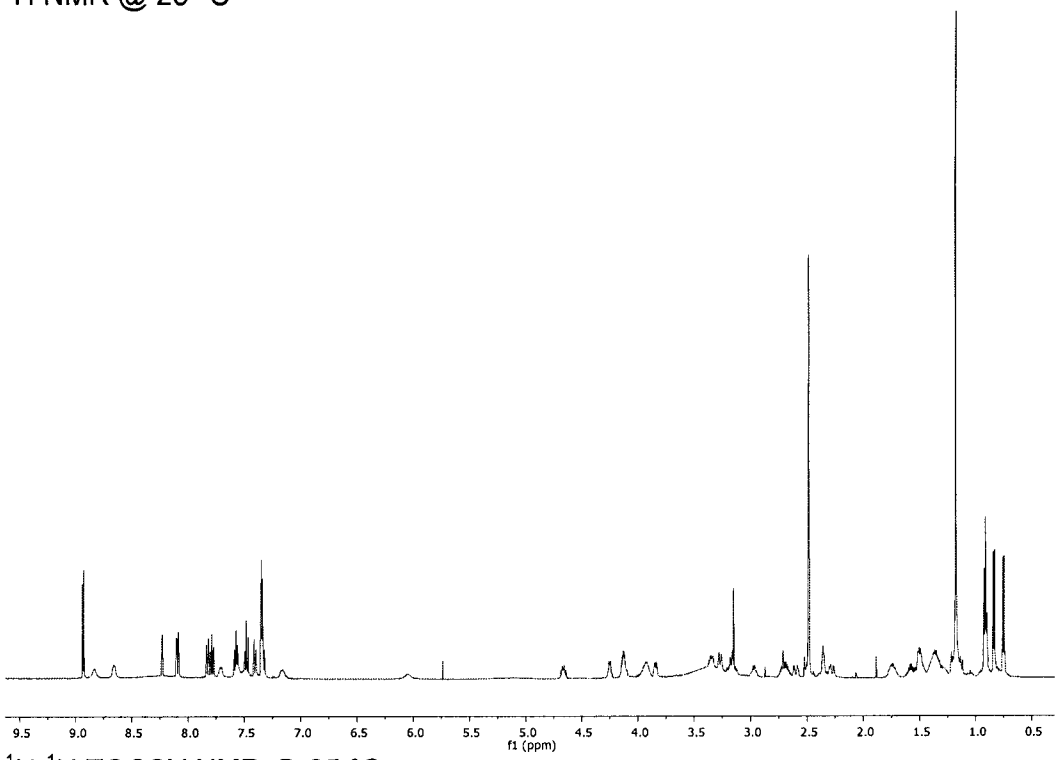


^{1}H-^{1}H TOCSY NMR @ 25 °C

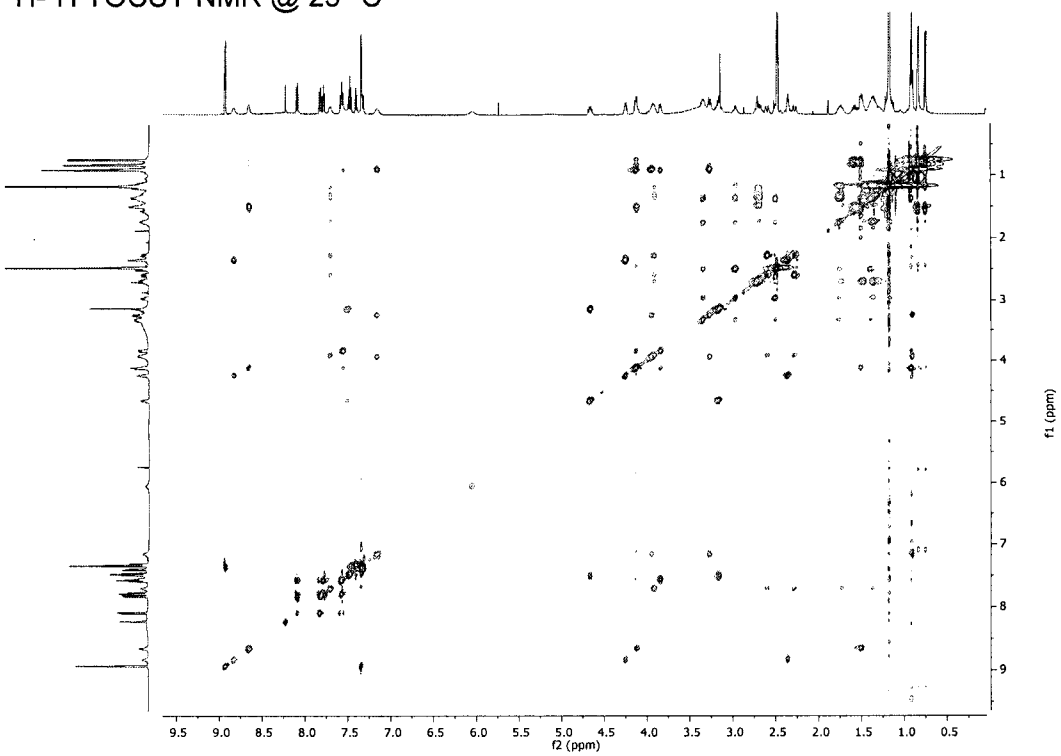


Compound No. 266

^{1}H NMR @ 25 °C



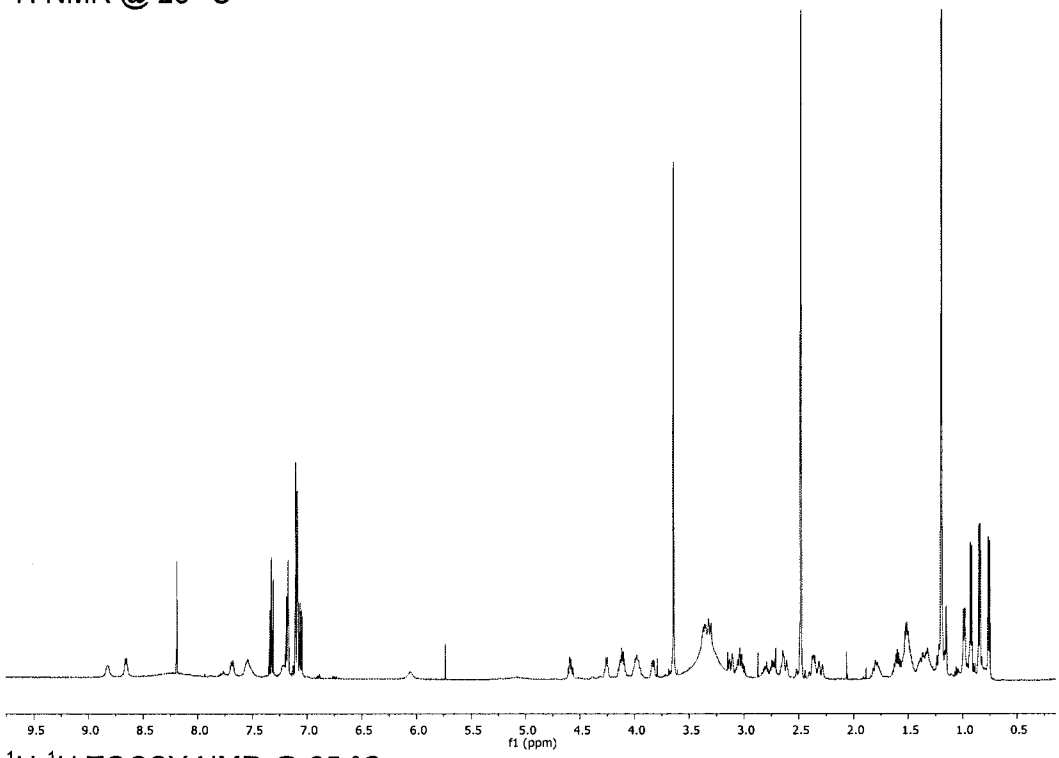
^{1}H-^{1}H TOCSY NMR @ 25 °C



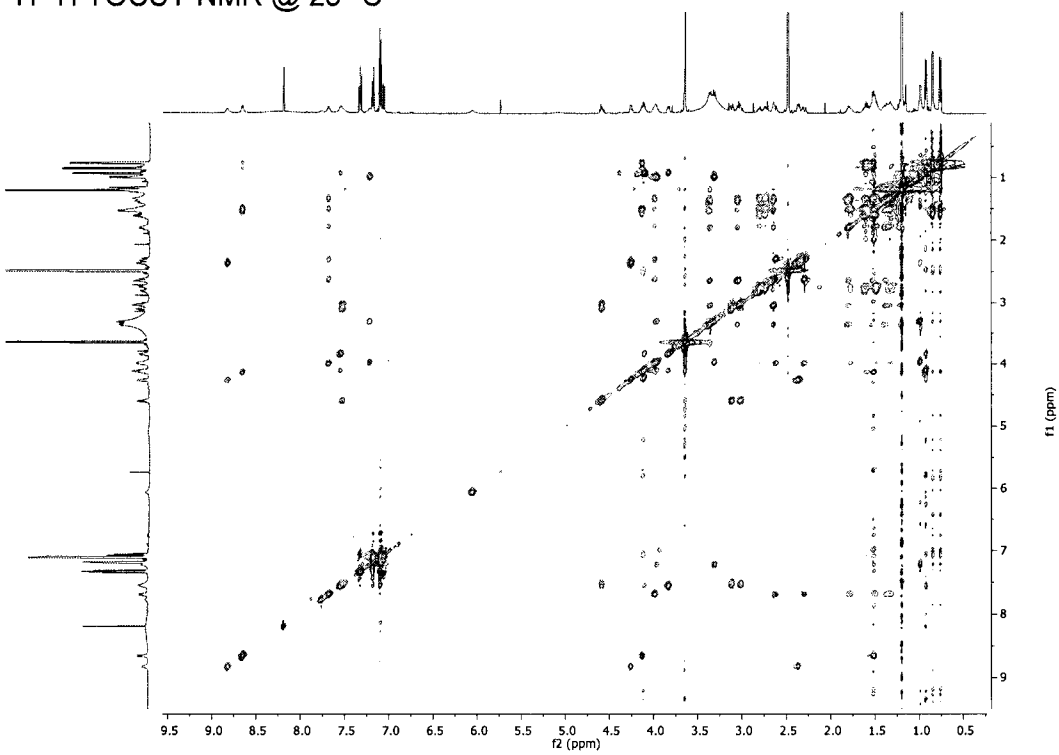
5

Compound No. 269

^{1}H NMR @ 25 °C



^{1}H-^{1}H TOCSY NMR @ 25 °C



5

Plasma protein binding determination

The sequestration of nacellins by plasma proteins was relatively low. In rat plasma, free fraction (% unbound) ranged from an 9.5% to 76.9% (mean of 42.6%), whereas in mouse plasma, free fraction ranged from 15.7% to 79.9% (mean of 47.8%). Plasma protein binding for the small molecule positive control, propranolol, was in the normal range of ~21% (free fraction) in mouse plasma and ~15% (free fraction) in rat plasma. The compounds assessed include:

ET01792 (Compound No. 5)

ET00762 (an analog of Compound No. 5, in which the phenylalanine residue has been replaced by a tryptophan residue)

ET01813 (Compound No. 12)

ET01827 (Compound No. 15)

List of compounds	% unbound (C_{buffer}/C_{plasma}) Mouse plasma						% recovery	Control buffer/Buffer at 0.1 uM	
	1	2	3	Average	sd	%RSD		Recovery	Cdonor/Creceiver
ET01792	64.8	52.9	67.9	**61.9**	7.9	13%	130%	108%	80%
ET00762	80.6	74.4	75.7	**76.9**	3.3	4%	150%	99%	79%
ET01813	24.7	22.2	18.8	**21.9**	3.0	14%	113%	128%	94%
ET01827	10.0	9.3	9.3	**9.5**	0.4	4%	103%	70%	86%
Propranolol	22.8	20.1	20.1	21.0	1.6	7%	93%		

List of compounds	% unbound (C_{buffer}/C_{plasma}) Rat plasma						% recovery
	1	2	3	Average	sd	%RSD	
ET01792	82.9	77.3	79.5	**79.9**	2.8	4%	97%
ET00762	83.3	76.1	70.2	**76.5**	6.6	9%	94%
ET01813	15.8	20.1	21.7	**19.2**	3.1	16%	89%
ET01827	16.2	17.4	13.6	**15.7**	1.9	12%	143%
Propranolol	14.6	14.7	14.7	**14.7**	0.1	0%	79%

Aqueous solubility assay

As shown in the table below, the aqueous solubility of integrin alpha-4-beta-7-inhibiting nacellins was relatively high, with a mean solubility of 715 microM. The range of solubilities measured in triplicate for 15 distinct compounds was 183 microM to greater

than 1000 microM. Note that the maximum concentration evaluated was different for different test articles based on the presumed aqueous solubility. The compounds assessed include:

UM0131995-05 (Compound No. 4)

UM0132366-01 (Compound No. 87)

UM0132368-01 (Compound No. 88)

UM0132369-01 (Compound No. 89)

UM0132370-01 (Compound No. 52)

UM0132371-01 (Compound No. 90)

UM0132374-01 (Compound No. 65)

UM0132375-02 (Compound No. 42)

UM0132376-01 (Compound No. 92)

UM0132377-01 (an analog of Compound No. 92, in which the lysine residue has been replaced by an ornithine residue)

UM0134839-01 (an analog of Compound No. 455, in which the phenylalanine and betaHomoLys residues have been replaced by a tyrosine residue)

UM0134690-01 (Compound No. 358)

UM0134830-01 (an analog of Compound No. 159, in which the tyrosine and alanine residues have been exchanged with respect to position within the sequence)

UM0134677-01 (Compound No. 158)

UM0134700-01 (Compound No. 62)

List of compounds	Maximal solubility evaluated (μM)	Determined concentration (μM)			Mean	SD	RSD (%)
		Rep 1	Rep 2	Rep 3			
UM0131995-05	1000	883.9	897.3	914.7	898.6	15.4	1.7
UM0132366-01	500	474.2	477.4	451.9	467.8	13.9	3.0
UM0132368-01	1000	926.3	917.9	934.8	926.3	8.4	0.9
UM0132369-01	1000	874.4	885.9	887.3	882.5	7.1	0.8
UM0132370-01	200	187.0	182.4	180.2	183.2	3.5	1.9
UM0132371-01	1000	786.7	837.3	879.6	834.5	46.6	5.6
UM0132374-01	200	179.4	184.0	185.9	183.1	3.3	1.8
UM0132375-02	1000	966.6	960.0	936.8	954.5	15.6	1.6
UM0132376-01	1000	990.7	958.6	939.5	962.9	25.9	2.7
UM0132377-01	200	225.7	218.9	211.2	218.6	7.3	3.3
UM0134839-01	1000	1038.0	1000.1	1004.0	1014.0	20.8	2.1
UM0134690-01	1000	957.3	950.5	920.8	942.9	19.4	2.1
UM0134830-01	1000	1012.0	1016.4	971.7	1000.0	24.7	2.5
UM0134677-01	200	225.4	230.6	217.8	224.6	6.4	2.9
UM0134700-01	1000	1044.8	988.2	950.6	994.5	47.4	4.8

Cytochrome P450 inhibition assay

The inhibitory activity of various nacellins against four isoforms of cytochrome P450 was assessed using human liver microsomes. The four isoforms evaluated were: CYP2D5, CYP3A4, CYP2C9, and CYP1A2. As shown below, for the seven nacellins evaluated in this experiment, 85% of the results of the assays showed an IC_{50} > 15 microM (above the limit of detection). However, IC_{50}s of <10 microM, and in one case, <1 microM, were recorded for a few compounds. These compounds were subjected to a structural analysis so as to understand the functional groups contributing to this mild CYP450-inhibiting activity. The compounds assessed include:

ET01792 (Compound No. 5)

ET00762-02 (an analog of Compound No. 5, in which the phenylalanine residue has been replaced by a tryptophan residue)

ET01813 (Compound No. 12)

ET00328-01 (an analog of Compound No. 4, in which the tyrosine, leucine, aspartic acid and threonine residues have been replaced by threonine, methyl leucine, valine and phenylalanine residues)

ET01827 (Compound No. 15)

ET01842-01 (Compound No. 413)

List of compounds	IC50 (mM)			
	CYP2D6	CYP3A4	CYP2C9	CYP1A2
ET01792-01	>15	> 15	>15	>15
ET00762-02	>15	>15	>15	>15
ET01813-01	>15	>15	>15	>15
ET00328-01	>15	9.7	>15	>15
ET01827-01	>15	>15	>15	>15
ET01838-01	11	3.7	>15	>15
ET01842-01	>15	0.89*	>15	>15
Quinidine	0.17	---	---	---
Ketoconazole	---	0.023	---	---
Miconazole	---	---	0.32	---
α-naphthoflavone	---	---	---	0.05

In vivo T lymphocyte trafficking analyses

The ability of several integrin alpha-4-beta-7-inhibiting nacellins to attenuate the trafficking of integrin alpha-4-beta-7-expressing T lymphocytes was demonstrated in *in vivo* pharmacodynamics studies in DSS-treated mice. As shown in Figure 6, this study was conducted in mice exposed for 5 days to dextran sulfate in their drinking water. On day 6, single doses of test articles were administered and, 5-6 hours later, peripheral blood, mesenteric lymph nodes and other tissues were collected and assessed.

As shown, the murine anti-alpha-4-beta-7 monoclonal antibody (DATK32; 25 mg/kg) substantially reduces homing of integrin a4b7+ T lymphocytes to the mesenteric lymph nodes ("MLN"), but did not affect the counts of CD11a+ T lymphocytes in the peripheral blood. As for the nacellins, at 100 mg/kg, the high oral bioavailability nacellin, ET1792 (Compound No. 5), but not the low oral bioavailability nacellin, ET2154 (Compound No. 105), evoked a significant reduction of homing to the MLN following oral dosing. When the dose of ET2154 was increased to 200 mg/kg, it evoked a significant and robust attenuation of homing to the MLN. These results demonstrate the importance of oral bioavailability (and the concomitant systemic exposure) to attenuate trafficking of T lymphocytes via an integrin alpha-4-beta-7 – MAdCAM facilitated extravasation event from high endothelial venules in gut-associated lymphoid tissues. Under no circumstances did test nacellins produce a significant change in the content of CD11a+ T cells in peripheral blood (similarly, no changes in the CD34 and CD45 T lymphocyte content in peripheral blood was recorded for any nacellin; data not shown).

In vivo pharmacokinetic assessments in rodents

We assessed the pharmacokinetic profile of several integrin alpha-4-beta-7-inhibiting nacellins following oral doses, and in some cases, intravenous doses for naïve mice.

As shown in the Figure 7 below, one and two oral doses of ET1792 (Compound No. 5) at 48 mg/kg to naïve mice produced significant absorption and systemic exposure. The exposure (AUC-0-tlast) following the first dose was 1,475 h*ng/ml, whereas following the second dose, the exposure was 2,188 h*ng/ml. The maximum plasma concentration recorded after the first dose was nearly 1,600 ng/ml.

Referring to Figure 8, in a second study of orally administered ET1792 (at 40 mg/kg), a similar profile was recorded, with an exposure (AUC0-tlast) of 589 h*ng/ml. The biphasic absorption and delayed Tmax is likely indicative of an initial transcellular perfusion of enterocytes followed by a more prolonged transcellular perfusion.

In a subsequent study of ET1813 (Compound No. 12), single doses were administered via oral gavage (40 mg/kg) and intravenous injection (5 mg/kg). The absorption of this compound was less than that of ET1792, with a calculated oral bioavailability of ~1%, despite a significant terminal half-life of nearly 2 hours.

PK parameter summary for *i.v.* dosing.

Parameter	Parameter estimate for each animal				
	R01	R02	R03[a]	Mean (n=2)	SD
C_0 (ng/mL)	6330	7590	*9980*	6960	n/a
Apparent $t_{1/2}$ (h)	1.45	2.79	*0.225*	2.12	n/a
$AUC_{0\text{-}inf}$ (h*ng/mL)	741	711	*1290*	726	n/a
CL_s (mL/h/kg)	6740	7030	*3880*	6885	n/a
$MRT_{0\text{-}inf}$ (h)	0.253	0.136	*0.166*	0.195	n/a
V_{ss} (mL/kg)	1700	957	*645*	1329	n/a

PK parameter summary for *p.o.* dosing

Parameter	Parameter estimate for each animal				
	R04	R05	R06	Mean	SD
t_{max} (h)	0.0833	0.0833	0.0833	0.0833	0.000
C_{max} (ng/mL)	387	28.0	22.9	146	209
Apparent $t_{1/2}$ (h)	4.47	0.638	0.466	1.86	2.26
$AUC_{0\text{-}inf}$ (h*ng/mL)	166	3.77	3.74	57.8	93.7
$MRT_{0\text{-}inf}$ (h)	1.48	0.449	0.409	0.779	0.607
F (%)	2.86	0.0649	0.0644	0.996	1.61

Another set of pharmacokinetic studies were performed on ET2451 (Compound No. 340) in naïve mice. In this study, compound exposure in plasma, colon and liver were measured following both single oral doses (40 mg/kg) and single intravenous doses (5 mg/kg). As illustrated in the Figure 9 and in the tables below, ET2451 was found to have an oral bioavailability of approximately 11% in plasma, and closer to 100% in colon. Also noteworthy is the difference in elimination half-life: in plasma the half-life was found to be ~30 minutes following oral dosing, whereas the half-life in colon was greater than 21 hours. We also assessed bioavailability in the liver (figure below), which was similar to that measured in the plasma (~8%) but half-life was significantly longer at ~8 hours following oral dosing. It is clear from this study and others that the main route of elimination of ET2451 and other nacellins is through hepatobiliary clearance.

Summary of Plasma PK Parameters for ET02451

Parameter	Unit	Estimate	
		i.v.	*p.o.*
C_0	ng/mL	1408	n/a
t_{max}	h	0.083	0.0833
C_{max}	ng/mL	1326	4638
Apparent $t_{1/2}$	h	2.00	0.537
$AUC_{0\text{-tlast}}$	h*ng/mL	778	686
$AUC_{0\text{-inf}}$	h*ng/mL	778	690
CL	mL/kg/h	6426	n/a
$MRT_{0\text{-inf}}$	h	0.698	0.689
V_{ss}	mL/kg	4487	n/a
F	%	100	11.0

n/a denotes not applicable.

Summary of Colon PK Parameters for ET02451

Parameter	Unit	Estimate	
		i.v.	*p.o.*
t_{max}	h	2.00	2.00
C_{max}	ng/mL	8210	49115
Apparent $t_{1/2}$	h	3.40	21.5
$AUC_{0\text{-tlast}}$	h*ng/mL	17109	130746
$AUC_{0\text{-inf}}$	h*ng/mL	17140	145327
$MRT_{0\text{-inf}}$	h	3.43	4.59
AUC Ratio (Colon/Plasma)		22.0	211

Summary of Liver PK Parameters for ET02451

Parameter	Unit	Estimate	
		i.v.	*p.o.*
t_{max}	h	0.0833	2.00
C_{max}	ng/mL	16613	4792
Apparent $t_{1/2}$	h	9.60	7.94
$AUC_{0\text{-tlast}}$	h*ng/mL	8289	6024
$AUC_{0\text{-inf}}$	h*ng/mL	8460	6054
$MRT_{0\text{-inf}}$	h	2.00	2.11
AUC Ratio (Liver/Plasma)		10.9	8.78

C_0	concentration extropolated to time zero following an i.v. dose
t_{max}	time at which maximum concentration is observed
C_{max}	maximum observed concentration
Apparent $t_{1/2}$	apparent terminal half-life
$AUC_{0\text{-tlast}}$	area under the concentration vs time curve from time 0 to the time of the last measurable concentration
$AUC_{0\text{-inf}}$	area under the concentration vs time curve from time 0 to infinity
CL	systemic clearance
$MRT_{0\text{-tlast}}$	mean residence time from time zero to the time of the last measurable concentration
V_{ss}	steady-state volume of distribution
F	oral bioavailability = (Dose^{iv}*AUC^{po})/(Dose^{po}*AUC^{iv})*100

8-day efficacy study in DSS model (therapeutic)

We assessed the efficacy of two distinct nacellins in the DSS experimental model of ulcerative colitis: ET2451 (Compound No. 340) and ET2452 (Compound No. 341). As shown above, ET2451 demonstrates significant absorption from the gut and systemic exposure following oral dosing, whereas ET2452 is a low oral bioavailability entity. Both test compounds were administered b.i.d. to mice over the course of three days - following an initial 5-days exposure to DSS (2-3%) in their drinking water. The efficacy and

pharmacodynamics effect of the nacellins was compared to the mouse anti-integrin alpha-4-beta-7 mAb, DATK32. ET2452 was administered both orally and, to another group, via i.p. injection. The objective of this experimental design was to demonstrate that, although it may not be efficacious when administered orally, it produced substantial efficacy with i.p. dosing.

Disease activity index ("DAI") score was assessed individually based on the severity of three specific symptoms: blood in stool, stool consistency and general health assessment (posture, fur and dehydration), on Day 5 and 8. As shown in Figure 10, DAI score increased significantly from Day 5 to Day 8 in DSS+vehicle control group. Oral administration of ET02451-01 and i.p. administration of DATK32 led to a reduction of 15 % and 19 % respectively, but only the ET02451-01-evoked effect proved statistically significant. Oral administration of ET02452-01 did not have any beneficial effect on DAI. In contrast, intraperitoneal ET02452-01 treatment led to a significant reduction of DAI score on Day 8, by 46 %, in comparison to DSS+vehicle control group ($p < 0.05$). In fact, ET02452-01 i.p. treatment prevented the increased severity of UC symptoms observed in the control vehicle-treated group, from day 5 to day 8.

Ulcerative colitis is associated with inflammatory changes of the intestinal tract with reduction of the length of the mice colon (raw data in Annex IV). DSS+vehicle control group showed a mean colon length of 4.3 ± 0.3 cm and a lesion length of 1.7 ± 0.3 cm corresponding to a lesion/colon length of 40% (Figure 11). Treatments did not have any effect on colon length (Figure 11). However, ET02451-01 significantly reduced the lesion length of this group ($p < 0.05$), leading to a significant improvement of the lesion/colon length ratio, by reaching a value of lesion/colon length of 12% ($p< 0.05$). Oral and i.p. administration of ET02452-01 led to a reduction of lesion length by 53 % and 20 % respectively, in comparison to the control vehicle treated-group, but these reductions were not statistically significant (Figure 11B). Beside, DATK32, administered on Day 5 by i.p. route, led to a reduction, not statistically significant, of 45% in comparison to the control vehicle treated-group.

Whether treatments would have been compared in separate experiments, a Student t-test would have been used for statistical comparison of each test article treated-group with the control vehicle treated-group. In that case, by a separated Student t-test, a statistical

significant effect by oral ET02452-01 and i.p. DATK32 would have been obtained on lesion length and lesion/colon length.

The final score of colon inflammation was calculated by multiplying macroscopic score x lesion/colon length ratio for each mouse. Referring to Figure 12, the measurement of this parameter shows a significant reduction of lesion inflammation by the oral administration of ET02451-01 (by 77 %) and ET02452-01 (by 76 %) in comparison to the control vehicle-treated group. Intraperitoneal administration of ET02452-01 and DATK32 led to a reduction of 39 % and 53 % respectively, but this effect was not statistically significant.

Cell populations

There are no statistical differences between the percentage of CD3+CD4+CD11a+ T cell populations in vehicle mice and compound-treated ones in the three tissues tested (see Figure 13). In all tissues, the population of CD34+ cells is the same in vehicle- and –nacellin-treated mice. However, a significant increase ($p<0.01$) of CD34+ cells is observed in the mice receiving the anti- α4β7 antibody (DATK32). For the CD3+CD4+α4β7+ cell population, no difference was observed in blood neither in peripheral lymph nodes. However, a significant decrease of this population was observed in mesenteric lymph nodes in mice receiving ET02452 (Compound No. 341) i.p. or ET02451 (Compound No. 340) p.o. Intraperitoneal administration of DATK32 also significantly decreased the percentage of CD3+CD4+α4β7+ T lymphocytes.

It is of note that over 600 macrocycles were made that exhibited less activity than those summarized in Tables 1A, 1B and 1C. A selection of the macrocycles with less or little activity are summarized in Tables 2A, 2B and 2C.

Although preferred embodiments of the invention have been described herein, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims. All documents disclosed herein, including those in the following reference list, are incorporated by reference.

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
1	H	H	CH2-S-Ph	H	C(O)-NH-*tert*-Butyl
2	H	H	CH2-S-Ph	H	C(O)-NH-*tert*-Butyl
3	H	H	CH2-S-Ph	H	C(O)-NH-*tert*-Butyl
4	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
5	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
6	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
7	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
8	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
9	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
10	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
11	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
12	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
13	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
14	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
15	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
16	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
17	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
18	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
19	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
20	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
21	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
22	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
23	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
24	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
25	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
26	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
27	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
28	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
29	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
30	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
31	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
32	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
33	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
34	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
35	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
36	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
37	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
38	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
39	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
40	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
41	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
42	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
43	H	CH_3	H	H	C(O)-NH-*tert*-Butyl
44	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
45	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
46	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
47	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
48	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
49	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
50	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
51	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
52	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
53	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
54	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
55	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
56	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
57	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
58	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
59	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
60	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
61	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
62	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
63	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
64	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
65	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
66	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
67	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
68	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
69	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
70	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
71	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
72	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
73	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
74	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
75	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
76	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
77	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
78	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
79	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
80	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
81	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
82	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
83	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
84	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
85	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
86	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
87	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
88	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
89	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
90	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
91	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
92	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
93	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
94	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
95	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
96	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
97	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
98	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
99	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
100	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
101	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
102	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
103	H	CH_3	H	H	C(O)-NH-*tert*-Butyl
104	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
105	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
106	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
107	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
108	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
109	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
110	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
111	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
112	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
113	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
114	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
115	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
116	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
117	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
118	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
119	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
120	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
121	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
122	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
123	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
124	H	CH_3	H	H	C(O)-NH-*tert*-Butyl
125	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
126	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
127	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
128	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
129	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
130	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
131	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
132	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
133	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
134	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
135	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
136	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
137	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
138	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
139	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
140	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
141	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
142	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
143	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
144	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
145	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
146	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
147	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
148	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
149	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
150	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
151	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
152	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
153	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
154	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
155	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
156	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
157	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
158	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
159	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
160	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
161	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
162	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
163	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
164	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
165	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
166	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
167	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
168	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
169	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
170	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
171	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
172	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
173	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
174	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
175	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
176	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
177	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
178	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
179	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
180	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
181	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
182	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
183	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
184	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
185	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
186	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
187	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
188	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
189	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
190	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
191	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
192	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
193	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
194	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
195	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
196	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
197	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
198	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
199	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
200	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
201	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
202	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
203	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
204	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
205	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
206	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
207	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
208	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
209	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
210	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
211	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
212	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
213	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
214	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
215	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
216	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
217	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
218	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
219	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
220	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
221	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
222	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
223	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
224	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
225	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
226	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
227	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
228	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
229	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
230	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
231	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
232	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
233	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
234	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
235	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
236	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
237	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
238	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
239	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
240	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
241	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
242	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
243	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
244	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
245	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
246	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
247	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
248	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
249	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
250	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
251	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
252	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
253	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
254	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
255	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
256	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
257	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
258	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
259	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
260	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
261	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
262	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
263	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
264	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
265	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
266	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
267	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
268	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
269	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
270	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
271	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
272	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
273	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
274	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
275	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
276	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
277	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
278	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
279	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
280	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
281	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
282	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
283	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
284	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
285	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
286	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
287	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
288	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
289	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
290	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
291	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
292	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
293	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
294	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
295	PRO-	PRO-	H	H	C(O)-NH-*tert*-Butyl
296	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
297	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
298	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
299	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
300	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
301	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
302	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
303	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
304	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
305	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
306	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
307	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
308	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
309	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
310	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
311	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
312	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
313	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
314	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
315	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
316	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
317	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
318	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
319	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
320	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
321	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
322	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
323	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
324	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
325	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
326	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
327	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
328	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
329	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
330	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
331	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
332	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
333	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
334	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
335	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
336	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
337	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
338	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
339	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
340	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
341	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
342	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
343	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
344	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
345	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
346	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
347	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
348	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
349	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
350	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
351	H	H	CH_3	C(O)-NH-*tert*-Butyl	H
352	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
353	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
354	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
355	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
356	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
357	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
358	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
359	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
360	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
361	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
362	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
363	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
364	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
365	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
366	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
367	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
368	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
369	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
370	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
371	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
372	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
373	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
374	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
375	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
376	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
377	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
378	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
379	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
380	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
381	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
382	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
383	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
384	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
385	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
386	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
387	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
388	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
389	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
390	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1A

Compound No.	R^1	R^2	R^3	R^4	R^5
391	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
392	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
393	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
394	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
395	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
396	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
397	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^1	X^2	X^3
1	1	PRO	PRO	H	Y	L	D	V
2	2	PRO	PRO	H	H	L	D	V
3	3	PRO	PRO	H	Y	L	D	T
4	3	PRO	PRO	H	Y	L	D	T
5	4	PRO	PRO	H	F	L	D	T
6	5	PRO	PRO	H	HomoPhe	L	D	T
7	6	PRO	PRO	H	Cha	L	D	T
8	7	PRO	PRO	H	W	L	D	I
9	8	PRO	PRO	H	1Nal	L	D	T
10	9	PRO	PRO	H	2Nal	L	D	T
11	10	PRO	PRO	H	W	L	D	Thr(OBn)
12	11	PRO	PRO	H	Bip	L	D	T
13	12	PRO	PRO	H	Tyr(OPh)	L	D	T
14	13	PRO	PRO	H	1Nal	L	D	I
15	14	PRO	PRO	H	2Nal	L	D	I
16	15	PRO	PRO	H	2Nal	L	D	Thr(OBn)
17	16	[(4S)-fluoro-Pro]	[(4S)-fluoro-Pro]	H	W	L	D	T
18	17	PRO	PRO	H	Bip	L	D	Thr(OBn)
19	18	PRO	PRO	H	Tyr(2-tolyl diaryl ether)	L	D	T
20	19	PRO	PRO	H	Tyr(4-CF3 diaryl ether)	L	D	T
21	20	PRO	PRO	H	Tyr(4-methoxy diaryl ether)	L	D	T
22	21	PRO	PRO	H	Tyr(4-fluoro diaryl ether)	L	D	T
23	22	PRO	PRO	H	Tyr(2-methoxy diaryl ether)	L	D	T
24	23	PRO	PRO	H	Tyr(3-methoxy diaryl ether)	L	D	T
25	24	PRO	PRO	H	Tyr(3-fluoro diaryl ether)	L	D	T
26	25	PRO	PRO	H	Tyr(3,4-difluoro diaryl ether)	L	D	T
27	26	PRO	PRO	H	Tyr(3-methyl diaryl ether)	L	D	T
28	27	PRO	PRO	H	Tyr(3,4-dimethyl diaryl ether)	L	D	T
29	28	PRO	PRO	H	Tyr(4-CO2Me diaryl ether)	L	D	T
30	29	PRO	PRO	H	Tyr(3-CO2Me diaryl ether)	L	D	T
31	30	PRO	PRO	H	Tyr(4-CO2H diaryl ether)	L	D	T
32	31	HYP	HYP	H	F	L	D	T
33	32	PRO	PRO	H	metaY(Opr)	L	D	T
34	33	PRO	PRO	H	Orn(benzamide)	L	D	Thr(OBn)
35	34	PRO	PRO	H	Orn(acetamide)	L	D	Thr(OBn)
36	35	PRO	PRO	H	Orn(methanesulfonamide)	L	D	Thr(OBn)
37	36	PRO	PRO	H	Orn(ethylcarbamate)	L	D	Thr(OBn)
38	37	PRO	PRO	H	Orn(pentyl amide)	L	D	Thr(OBn)
39	38	PRO	PRO	H	R	L	D	T
40	39	PRO	PRO	H	F	L	D	Thr(OMe)

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^1	X^2	X^3
41	40	PRO	PRO	H	F	L	D	Thr(OEt)
42	41	PRO	PRO	H	dTyr	L	D	T
43	42	PRO	PRO	H	dTic	L	D	T
44	43	HYP	HYP	H	[3-(3'-pyridyl)-Ala]	L	D	T
45	44	[(4R)-fluoro-Pro]	[(4R)-fluoro-Pro]	H	F	L	D	T
46	45	[(4R)-fluoro-Pro]	[(4R)-fluoro-Pro]	H	Bip	L	D	T
47	46	[(4R)-fluoro-Pro]	[(4R)-fluoro-Pro]	H	[3-(3'-pyridyl)-Ala]	L	D	T
48	47	[(4R)-fluoro-Pro]	[(4R)-fluoro-Pro]	H	Y	L	D	T
49	48	[(4S)-fluoro-Pro]	[(4S)-fluoro-Pro]	H	Y	L	D	T
50	49	PRO	PRO	H	dArg	L	D	T
51	50	PRO	PRO	H	dPip	L	D	T
52	51	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	L	D	T
53	52	PRO	PRO	H	Y	L	D	I
54	53	PRO	PRO	H	(4-aza-Phe)	L	D	T
55	54	PRO	PRO	H	Y	L	D	Pen
56	55	PRO	PRO	H	(vinyl-Br-Leu)	L	D	T
57	56	PRO	PRO	H	Hyp(OBn)	L	D	T
58	56	PRO	PRO	H	Hyp(OBn)	L	D	T
59	57	PRO	PRO	H	Dap(Cbz)	L	D	T
60	58	PRO	PRO	H	His(Bn)	L	D	T
61	59	PRO	PRO	H	(4-amino-Phe)	L	D	T
62	60	PRO	PRO	H	(4-aza-dPhe)	L	D	T
63	61	PRO	PRO	H	Hyp	L	D	T
64	62	PRO	PRO	H	dTrp	L	D	T
65	63	PRO	PRO	H	M	L	D	T
66	64	PRO	PRO	H	dMet	L	D	T
67	65	PRO	PRO	H	(4-guanidino-Phe)	L	D	T
68	66	PRO	PRO	H	(3-aza-Phe)	L	D	T
69	42	PRO	PRO	H	dTic	L	D	T
70	67	PRO	PRO	H	(3-aza-dPhe)	L	D	T
71	68	PRO	PRO	H	Nva	L	D	T
72	69	PRO	PRO	H	dNle	L	D	T
73	70	PRO	PRO	H	dLys	L	D	T
74	71	PRO	PRO	H	dPro	L	D	T
75	72	PRO	PRO	H	dOrn	L	D	T
76	73	PRO	PRO	H	(3-benzothienyl-Ala)	L	D	T
77	74	PRO	PRO	H	dTyr(OAllyl)	L	D	T
78	75	PRO	PRO	H	dSer(OBn)	L	D	T
79	76	PRO	PRO	H	[3-(4-thiazolyl)-dAla]	L	D	T
80	77	PRO	PRO	H	(3-benzothienyl-dAla)	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^Z	X^1	X^2	X^3
81	78	PRO	PRO	H	[3-(2-thienyl)-dAla		L	D	T
82	79	PRO	PRO	H	(4-aminomethyl-Phe)		L	D	T
83	80	PRO	PRO	H	dOrn(dimethyl)		L	D	T
84	81	PRO	PRO	H	(4-amino-dPhe)		L	D	T
85	82	PRO	PRO	H	(4-aminomethyl-dPhe)		L	D	T
86	83	PRO	PRO	H	dTyr(OBn)		L	D	T
87	84	PRO	PRO	H	P		L	D	T
88	85	PRO	PRO	H	cycloLeu		L	D	T
89	86	PRO	PRO	H	Aic		L	D	T
90	87	PRO	PRO	H	Tyr(OAllyl)		L	D	T
91	88	PRO	PRO	H	Chg		L	D	T
92	89	PRO	PRO	H	K		L	D	T
93	90	PRO	PRO	H	(2-aza-dPhe)		L	D	T
94	91	PRO	PRO	H	(2-aza-Phe)		L	D	T
95	92	PRO	PRO	H	[2-(2-pyridyl)-4-thiazolyl-Ala]		L	D	T
96	93	PRO	PRO	H	[2-(3-pyridyl)-4-thiazolyl-Ala]		L	D	T
97	94	PRO	PRO	H	[2-(4-pyridyl)-4-thiazolyl-Ala]		L	D	T
98	95	PRO	PRO	H	dTiq		L	D	T
99	96	PRO	PRO	H	[1-(S)-isoindoline-carboxylic acid]		L	D	T
100	97	PRO	PRO	H	Y	dThr	L	D	T
101	98	PRO	PRO	H	Y	P	L	D	T
102	99	PRO	PRO	H	Y	dPro	L	D	T
103	100	PRO	PRO	H	Y	Sar	L	D	T
104	101	PRO	PRO	H	Y	cycloLeu	L	D	T
105	100	PRO	PRO	H	Y	Sar	L	D	T
106	102	PRO	PRO	H	(3-iodo-Phe)	Sar	L	D	T
107	103	PRO	PRO	H	(4-iodo-Phe)	Sar	L	D	T
108	104	PRO	PRO	H	(3,3-diphenyl-Ala)	Sar	L	D	T
109	105	PRO	PRO	H	F	dLys	L	D	T
110	106	PRO	PRO	H	Bip	dLys	L	D	T
111	107	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dLys	L	D	T
112	108	PRO	PRO	H	(3,3-diphenyl-Ala)	dLys	L	D	T
113	109	PRO	PRO	H	Y	dLys	L	D	I
114	110	PRO	PRO	H	Y	dArg	L	D	T
115	111	PRO	PRO	H	Y	dSer	L	D	T
116	112	PRO	PRO	H	Bip	Sar	L	D	T
117	113	PRO	PRO	H	1Nal	Sar	L	D	T
118	114	PRO	PRO	H	Y	Pip	L	D	T
119	115	PRO	PRO	H	(2-iodo-Phe)	Sar	L	D	T
120	116	PRO	PRO	H	1Nal	dLys	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^z	X^1	X^2	X^3
121	117	PRO	PRO	H	Y	dLys	L	D	MeThr
122	118	PRO	PRO	H	F	Sar	L	D	T
123	119	PRO	PRO	H	Y	dTic	L	D	T
124	99	PRO	PRO	H	Y	dPro	L	D	T
125	120	PRO	PRO	H	Y	dPip	L	D	T
126	121	PRO	PRO	H	F	dPro	L	D	T
127	122	PRO	PRO	H	(3,4-dimethoxy-Phe)	dPro	L	D	T
128	123	PRO	PRO	H	(3,4,5-trifluoro-Phe)	dPro	L	D	T
129	124	PRO	PRO	H	(3,5-dibromo-Tyr)	dPro	L	D	T
130	125	PRO	PRO	H	F	dPip	L	D	T
131	126	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dPip	L	D	T
132	127	PRO	PRO	H	(4-aminomethyl-Phe)	dPip	L	D	T
133	128	PRO	PRO	H	[2-iodo-Phe]	dPip	L	D	T
134	129	PRO	PRO	H	(2-phenyl-Phe)	dPip	L	D	T
135	130	PRO	PRO	H	[2-(2-methoxy-phenyl)-Phe]	dPip	L	D	T
136	131	PRO	PRO	H	[2-(3-methoxy-phenyl)-Phe]	dPip	L	D	T
137	132	PRO	PRO	H	[2-(4-methoxy-phenyl)-Phe]	dPip	L	D	T
138	133	PRO	PRO	H	Bip	dPip	L	D	T
139	134	PRO	PRO	H	Y	Hyp	L	D	T
140	135	PRO	PRO	H	Y	dHyp	L	D	T
141	136	PRO	PRO	H	Y	(cis-dHyp)	L	D	T
142	137	dPRO	H	dPRO	dTyr	dPip	L	D	T
143	138	PRO	PRO	H	1Nal	dPip	L	D	T
144	139	PRO	PRO	H	2Nal	dPip	L	D	T
145	140	PRO	PRO	H	(4-aminomethyl-Phe)	dTic	L	D	T
146	141	PRO	PRO	H	(3-aminomethyl-Phe)	dTic	L	D	T
147	142	PRO	PRO	H	(3-aminomethyl-dPhe)	dTic	L	D	T
148	143	PRO	PRO	H	MeTyr	dPip	L	D	T
149	144	PRO	PRO	H	Y	dPip	L	D	alloThr
150	145	PRO	PRO	H	Y	dPip	tertbutylAla	D	T
151	146	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dHyp	L	D	T
152	147	PRO	PRO	H	(4-aminomethyl-Phe)	dHyp	L	D	T
153	148	PRO	PRO	H	Y	dPip	L	D	I
154	149	PRO	PRO	H	Y	dMeLys	L	D	I
155	150	PRO	PRO	H	Y	dNle	L	D	T
156	151	PRO	PRO	H	F	dHyp	L	D	T
157	152	PRO	PRO	H	Y	dMeArg	L	D	T
158	153	PRO	PRO	H	Y	G	L	D	T
159	154	PRO	PRO	H	Y	A	L	D	T
160	155	PRO	PRO	H	Y	dAla	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^z	X^1	X^2	X^3
161	156	PRO	PRO	H	M	G	L	D	T
162	157	PRO	PRO	H	Tyr(OAllyl)	Sar	L	D	T
163	158	PRO	PRO	H	Tyr(OAllyl)	G	L	D	T
164	159	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	Sar	L	D	T
165	160	PRO	PRO	H	(4-aminomethyl-Phe)	G	L	D	T
166	161	PRO	PRO	H	Tyr(OAllyl)	dVal	L	D	T
167	162	PRO	PRO	H	Tyr(OAllyl)	dSer	L	D	T
168	163	PRO	PRO	H	Tyr(OAllyl)	dAla	L	D	T
169	164	PRO	PRO	H	Tyr(OAllyl)	P	L	D	T
170	165	PRO	PRO	H	Tyr(OAllyl)	dPro	L	D	T
171	166	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dVal	L	D	T
172	167	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dSer	L	D	T
173	168	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dAla	L	D	T
174	169	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	P	L	D	T
175	170	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dPro	L	D	T
176	171	PRO	PRO	H	(4-aminomethyl-Phe)	P	L	D	T
177	172	PRO	PRO	H	(4-aminomethyl-Phe)	dPro	L	D	T
178	173	PRO	PRO	H	cycloLeu	P	L	D	T
179	174	PRO	PRO	H	[2-(2-pyridyl)-4-thiazolyl-Ala]	Sar	L	D	T
180	175	PRO	PRO	H	[2-(2-pyridyl)-4-thiazolyl-Ala]	dPro	L	D	T
181	176	PRO	PRO	H	[2-(3-pyridyl)-4-thiazolyl-Ala]	Sar	L	D	T
182	177	PRO	PRO	H	[2-(3-pyridyl)-4-thiazolyl-Ala]	dPro	L	D	T
183	178	PRO	PRO	H	[2-(4-pyridyl)-4-thiazolyl-Ala]	dPro	L	D	T
184	179	PRO	PRO	H	[3-(2-aminobenzyl-4-thiazolyl)-Ala]	Sar	L	D	T
185	180	PRO	PRO	H	[2-(amino-benzyl)-4-thiazolyl-Ala]	dPro	L	D	T
186	181	PRO	PRO	H	dTyr	dPip	L	D	I
187	182	PRO	PRO	H	(2-aminomethyl-Phe)	Aze	L	D	T
188	183	PRO	PRO	H	Y	dPip	L	D	Abu
189	184	PRO	PRO	H	(3-aminomethyl-Phe)	dTic	L	D	Abu
190	185	PRO	PRO	H	(2,4-dichloro-Phe)	dPip	L	D	T
191	186	PRO	PRO	H	(3-phenyl-dPhe)	dPip	L	D	T
192	187	PRO	PRO	H	[3-(5-quinolinyl)-dPhe]	dPip	L	D	T
193	188	PRO	PRO	H	Y	betaHomoLys	L	D	T
194	189	PRO	PRO	H	Y	betaHomoPro	L	D	T
195	190	PRO	PRO	H	Y	betaHomoLys	L	D	T
196	191	PRO	PRO	H	Y	2Abz	L	D	T
197	192	PRO	PRO	H	F	betaHomoLys	L	D	T
198	193	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys	L	D	T
199	194	PRO	PRO	H	(4-aminomethyl-Phe)	betaHomoLys	L	D	T
200	195	PRO	PRO	H	Y	betaHomoLys	L	D	Thr(OBn)

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^1	X^1	X^2	X^3
201	196	PRO	PRO	H	MeTyr	dbetaHomoLys	L	D	T
202	197	PRO	PRO	H	1Nal	betaHomoLys	L	D	T
203	198	PRO	PRO	H	2Nal	betaHomoLys	L	D	T
204	199	PRO	PRO	H	Bip	betaHomoLys	L	D	T
205	200	PRO	PRO	H	(2-iodo-Phe)	betaHomoLys	L	D	T
206	201	PRO	PRO	H	[2-(2,5-dimethyl-isoxazole)-Phe]	betaHomoLys	L	D	T
207	202	PRO	PRO	H	(2-phenyl-Phe)	betaHomoLys	L	D	T
208	202	PRO	PRO	H	(2-phenyl-Phe)	betaHomoLys	L	D	T
209	203	PRO	PRO	H	[(2-piperazinyl-2-Phenyl)-Phe]	betaHomoLys	L	D	T
210	204	PRO	PRO	H	Cha	betaHomoLys	L	D	T
211	205	PRO	PRO	H	W	betaHomoLys	L	D	T
212	206	PRO	PRO	H	dTrp	betaHomoLys	L	D	T
213	207	PRO	PRO	H	(3-aminomethyl-Phe)	betaHomoLys	L	D	T
214	208	PRO	PRO	H	(4-aminomethyl-dPhe)	betaHomoLys	L	D	T
215	209	PRO	PRO	H	(4-aminomethyl-Phe)	betaHomoLys	L	D	I
216	210	PRO	PRO	H	Y	dbetaHomoLys	L	D	I
217	211	PRO	PRO	H	dArg	betaHomoLys	L	D	T
218	212	PRO	PRO	H	(4-aminomethyl-Phe)-reduced	betaHomoLys	L	D	T
219	213	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dbetaHomoLys	L	D	I
220	214	PRO	PRO	H	F	dbetaHomoLys	L	D	I
221	215	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	MebetaHomoLys	L	D	T
222	216	PRO	PRO	H	(4-aminomethyl-Phe)	MebetaHomoLys	L	D	T
223	217	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys	L	D	I
224	218	PRO	PRO	H	Tic	betaHomoLys	L	D	T
225	219	PRO	PRO	H	dTic	betaHomoLys	L	D	T
226	220	PRO	PRO	H	dTic	dbetaHomoLys	L	D	T
227	221	PRO	PRO	H	Y	betaHomoIle	L	D	T
228	222	PRO	PRO	H	(4-aminomethyl-Phe)	betaHomoPro	L	D	T
229	223	PRO	PRO	H	Y	dbetaHomoPro	L	D	T
230	224	PRO	PRO	H	(4-aminomethyl-Phe)	dbetaHomoPro	L	D	T
231	225	PRO	PRO	H	R	betaHomoLys	L	D	T
232	226	PRO	PRO	H	F	MebetaHomoLys	L	D	T
233	227	PRO	PRO	H	Phe-reduced	betaHomoLys	L	D	T
234	228	PRO	PRO	H	(3-aminomethyl-dPhe)	betaHomoLys	L	D	T
235	229	PRO	PRO	H	-[3-(1-piperazinyl)phenyl]-Phe]-betaHomol	betaHomoLys	L	D	T
236	230	PRO	PRO	H	[3-(4-thiazolyl)-dAla]	betaHomoLys	L	D	T
237	231	PRO	PRO	H	(2-bromo-Phe)	betaHomoLys	L	D	T
238	232	PRO	PRO	H	(2-chloro-Phe)	betaHomoLys	L	D	T
239	233	PRO	PRO	H	(2-fluoro-Phe)	betaHomoLys	L	D	T
240	234	PRO	PRO	H	(2-CF3-Phe)	betaHomoLys	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^Z	X^1	X^2	X^3
241	235	PRO	PRO	H	(2,4-dichloro-Phe)	betaHomoLys	L	D	T
242	236	PRO	PRO	H	(2-aminomethyl-Phe)	betaHomoLys	L	D	T
243	237	PRO	PRO	H	[2-(4-quinolinyl)-Phe]	betaHomoLys	L	D	T
244	238	PRO	PRO	H	[2-(5-quinolinyl)-Phe]	betaHomoLys	L	D	T
245	239	PRO	PRO	H	[2-(3-quinolinyl)-Phe]	betaHomoLys	L	D	T
246	240	PRO	PRO	H	dhomoPhe	betaHomoLys	L	D	T
247	241	PRO	PRO	H	(2-iodo-dPhe)	betaHomoLys	L	D	T
248	242	PRO	PRO	H	(2-phenyl-dPhe)	betaHomoLys	L	D	T
249	243	PRO	PRO	H	[(2-piperazinyl-2-Phenyl)-dPhe]	betaHomoLys	L	D	T
250	244	PRO	PRO	H	Y	betaHomoLys	L	D	I
251	245	PRO	PRO	H	Y	betaHomoLys	L	D	V
252	246	PRO	PRO	H	dTyr	betaHomoLys	L	D	I
253	247	PRO	PRO	H	(4-aminomethyl-dPhe)	betaHomoLys	L	D	I
254	248	PRO	PRO	H	(4-aminomethyl-Phe)	betaHomoLys	L	D	V
255	249	PRO	PRO	H	(3-iodo-Phe)	betaHomoLys	L	D	T
256	250	PRO	PRO	H	(3-phenyl-Phe)	betaHomoLys	L	D	T
257	251	PRO	PRO	H	[3-(2-methoxy-phenyl)-Phe]	betaHomoLys	L	D	T
258	252	PRO	PRO	H	[3-(2,6-dimethoxy-phenyl)-Phe]	betaHomoLys	L	D	T
259	253	PRO	PRO	H	[3-(2-trifluoromethoxy-phenyl)-Phe]	betaHomoLys	L	D	T
260	254	PRO	PRO	H	(4-iodo-Phe)	betaHomoLys	L	D	T
261	255	PRO	PRO	H	[4-(2-methoxy-phenyl)-Phe]	betaHomoLys	L	D	T
262	256	PRO	PRO	H	[4-(2-trifluoromethoxy-phenyl)-Phe]	betaHomoLys	L	D	T
263	257	PRO	PRO	H	alphaMePhe	betaHomoLys	L	D	T
264	258	PRO	PRO	H	MePhe	betaHomoLys	L	D	T
265	259	PRO	PRO	H	[3-(2,6-dimethyl-phenyl)-Phe]	betaHomoLys	L	D	T
266	260	PRO	PRO	H	[3-(quinolin-4-yl)-Phe]	betaHomoLys	L	D	T
267	261	PRO	PRO	H	[3-(3,4-difluoro-phenyl)-Phe]	betaHomoLys	L	D	T
268	262	PRO	PRO	H	[4-(2,6-dimethyl-phenyl)-Phe]	betaHomoLys	L	D	T
269	263	PRO	PRO	H	[4-(2-chloro-6-methoxy-phenyl)-Phe]	betaHomoLys	L	D	T
270	264	PRO	PRO	H	[3-(4-thiazolyl)-Ala]-reduced	betaHomoLys	L	D	T
271	265	PRO	PRO	H	[2-[4-(1-piperazinyl)phenyl]-Phe]	betaHomoLys	L	D	T
272	266	PRO	PRO	H	[2-(2,6-dimethylphenyl)-Phe]	betaHomoLys	L	D	T
273	267	PRO	PRO	H	[2-(benzothiazol-5-yl)-Phe]	betaHomoLys	L	D	T
274	268	PRO	PRO	H	HomoPhe	betaHomoLys	L	D	T
275	269	PRO	PRO	H	(piperidine-4-amino-4-carboxylic acid)	betaHomoLys	L	D	T
276	270	PRO	PRO	H	[2-(2,5-dimethyl-isoxazole)-dPhe]	betaHomoLys	L	D	T
277	271	PRO	PRO	H	dTyr	betaHomoLys	L	D	V
278	272	PRO	PRO	H	(4-aminomethyl-dPhe)	betaHomoLys	L	D	T
279	273	PRO	PRO	H	[2-(2-chloro-6-methoxyphenyl)-Phe]	betaHomoLys	L	D	T
280	274	PRO	PRO	H	2Igl	betaHomoLys	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^Z	X^1	X^2	X^3
281	275	PRO	PRO	H	d2Igl	betaHomoLys	L	D	T
282	276	PRO	PRO	H	Atc	betaHomoLys	L	D	T
283	277	PRO	PRO	H	Y	betaHomoLys	L	D	alloIle
284	278	PRO	PRO	H	dTyr	betaHomoLys	L	D	alloIle
285	279	PRO	PRO	H	(4-aminomethyl-Phe)	betaHomoLys	L	D	alloIle
286	280	PRO	PRO	H	[2-[2,5-Bis(trifluoromethyl)phenyl]-Phe]	betaHomoLys	L	D	T
287	281	PRO	PRO	H	[2-[2,5-Bis(trifluoromethyl)phenyl]-Phe]	betaHomoLys	L	D	T
288	282	PRO	PRO	H	Aic	betaHomoLys	L	D	T
289	283	PRO	PRO	H	P	betaHomoLys	L	D	T
290	284	PRO	PRO	H	dPro	betaHomoLys	L	D	T
291	285	PRO	PRO	H	Pip	betaHomoLys	L	D	T
292	286	PRO	PRO	H	[2-(3-Pyridyl)-Phe]	betaHomoLys	L	D	T
293	287	PRO	PRO	H	[2-(4-Pyridyl)-Phe]	betaHomoLys	L	D	T
294	288	PRO	PRO	H	[2-(3-bromo-2-Pyridyl)-Phe]	betaHomoLys	L	D	T
295	289	PRO	PRO	H	Y	dbetaHomoLys	L	D	T
296	290	PRO	PRO	H	(N-benzyl-Gly)	betaHomoLys	L	D	T
297	291	PRO	PRO	H	[2-(2-bromo-3-Pyridyl)-Phe]	betaHomoLys	L	D	T
298	292	PRO	PRO	H	[3-(2-chloro-6-methoxy-phenyl)-Phe]	betaHomoLys	L	D	T
299	293	PRO	PRO	H	[3-(benzothiazol-5-yl)-Phe]	betaHomoLys	L	D	T
300	294	PRO	PRO	H	(2-aminomethyl-Phe)	MebetaHomoLys	L	D	T
301	295	PRO	PRO	H	(2-aminomethyl-dPhe)	MebetaHomoLys	L	D	T
302	296	PRO	PRO	H	[3-(4-thiazolyl)-dAla]	MebetaHomoLys	L	D	T
303	297	PRO	PRO	H	[2-(2-trifluoromethoxy-phenyl)-dPhe]	MebetaHomoLys	L	D	T
304	298	PRO	PRO	H	Tic	MebetaHomoLys	L	D	T
305	299	PRO	PRO	H	dTic	MebetaHomoLys	L	D	T
306	300	PRO	PRO	H	[2-(5-quinolinyl)-dPhe]	betaHomoLys	L	D	alloThr
307	301	PRO	PRO	H	Y	betaHomoLys	L	D	alloThr
308	302	PRO	PRO	H	Y	MebetaHomoLys	L	D	T
309	303	PRO	PRO	H	MeTyr	MebetaHomoLys	L	D	alloThr
310	304	PRO	PRO	H	MeTyr	MebetaHomoLys	L	D	T
311	305	PRO	PRO	H	MePhe	MebetaHomoLys	L	D	T
312	306	PRO	PRO	H	(2-fluoro-Phe)	MebetaHomoLys	L	D	T
313	307	PRO	PRO	H	(2-fluoro-MePhe)	MebetaHomoLys	L	D	T
314	308	PRO	PRO	H	(2,4-dichloro-Phe)	MebetaHomoLys	L	D	T
315	309	PRO	PRO	H	(2,4-dichloro-MePhe)	MebetaHomoLys	L	D	T
316	310	PRO	PRO	H	(2-aminomethyl-MePhe)	MebetaHomoLys	L	D	T
317	311	PRO	PRO	H	[3-(2,6-dimethoxy-phenyl)-dPhe]	betaHomoLys	L	D	T
318	312	PRO	PRO	H	[3-(4-Quinolinyl)-dPhe]	betaHomoLys	L	D	T
319	313	PRO	PRO	H	betaHomoLys	Aze	L	D	T
320	314	PRO	PRO	H	(3-phenyl-dPhe)	betaHomoLys	L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^4	X^1	X^2	X^3
321	315	PRO	PRO	H	[3-(2-trifluoromethoxy-phenyl)-dPhe]	betaHomoLys	L	D	T
322	316	PRO	PRO	H	[3-(2-methoxy-phenyl)-dPhe]	betaHomoLys	L	D	T
323	317	PRO	PRO	H	[2-(5-quinolinyl)-MePhe]	MebetaHomoLys	L	D	T
324	318	PRO	PRO	H	F	betaHomoNle	L	D	T
325	319	PRO	PRO	H	F	MebetaHomoLys(Me)2	L	D	T
326	320	PRO	PRO	H	MePhe	MebetaHomoLys(Me)2	L	D	T
327	321	PRO	PRO	H	M	MebetaHomoLys	L	D	T
328	322	PRO	PRO	H	Igl	MebetaHomoLys	L	D	T
329	323	PRO	PRO	H	HomoPhe	MebetaHomoLys	L	D	T
330	324	PRO	PRO	H	Hyp(OBn)	MebetaHomoLys	L	D	T
331	325	PRO	PRO	H	(1,2-cis-ACHC)	MebetaHomoLys	L	D	T
332	326	PRO	PRO	H	MeMet	MebetaHomoLys	L	D	T
333	327	PRO	PRO	H	betaHomoLys	betaHomoLys	L	D	T
334	328	PRO	PRO	H	BetaHomoPhe	MebetaHomoLys	L	D	T
335	329	PRO	PRO	H	betahomoMet	MebetaHomoLys	L	D	T
336	330	PRO	PRO	H	Y	-aminomethyl-4-bromo-benzoic aci	L	D	T
337	331	PRO	PRO	H	Y	inomethyl-4-(4-aza-phenyl)-benzoi	L	D	T
338	332	PRO	PRO	H	Y	ıethyl-4-(2,5-dimethyl-isoxazole)-be	L	D	T
339	333	PRO	PRO	H	Y	ıethyl-4-(3-aminomethyl-phenyl)-be	L	D	T
340	334	PRO	PRO	H	omethyl-4-[4-(1-piperazinyl)-phenyl]-benzoic acid]		L	D	T
341	335	PRO	PRO	H	-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
342	336	PRO	PRO	H	(3-aminomethyl-4-bromo-benzoic acid)		L	D	T
343	337	PRO	PRO	H	ıomethyl-4-(2,5-dimethyl-isoxazole)-benzoic acid]		L	D	T
344	338	dPRO	H	dPRO	[3-aminomethyl-4-(4-pyridyl)-benzoic acid]		L	D	T
345	339	PRO	PRO	H	inomethyl-(4-methylpyrazole-3-yl)-benzoic acid]		L	D	T
346	340	PRO	PRO	H	-aminomethyl-4-(3-quinolinyl)-benzoic acid]		L	D	T
347	341	PRO	PRO	H	-aminomethyl-4-(5-quinolinyl)-benzoic acid]		L	D	T
348	342	PRO	PRO	H	ıomethyl-4-[2-(1-piperazinyl)phenyl]-benzoic acid]		L	D	T
349	343	PRO	PRO	H	ıomethyl-4-[3-(1-piperazinyl)phenyl]-benzoic acid]		L	D	T
350	344	PRO	PRO	H	hyl-4-[2-(3-(piperidin-4-ylmethoxy)phenyl]-benzoic acid]		L	D	T
351	345	PRO	PRO	H	[3-aminomethyl-4-(4-pyridyl)-benzoic acid]		L	D	Thr(OBn)
352	346	PRO	PRO	H	[3-aminomethyl-4-(4-pyridyl)-benzoic acid]		L	D	alloThr
353	347	PRO	PRO	H	-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
354	348	PRO	PRO	H	ıomethyl-4-[4-(1-piperazinyl)phenyl]-benzoic acid]		tertbutylAla	D	T
355	349	PRO	PRO	H	-aminomethyl-4-(4-quinolinyl)]-benzoic acid		L	D	T
356	334	PRO	PRO	H	ethyl-4-[4-(1-piperazinyl-4-FITC)phenyl]-benzoic acid]		L	D	T
357	350	PRO	PRO	H	(N-benzyl-3-aminomethyl-benzoic acid)		L	D	T
358	351	PRO	PRO	H	(3-aminomethyl-benzoic acid		L	D	T
359	352	PRO	PRO	H	(3-aminomethyl-5-bromo-benzoic acid)		L	D	T
360	353	PRO	PRO	H	(3-aminomethyl-6-bromo-benzoic acid)		L	D	T

TABLE 1B

Compound No.	Seq. ID. No.	R^5	R^7	R^8	X^Y	X^t	X^1	X^2	X^3
361	336	PRO	PRO	H	(3-aminomethyl-4-bromo-benzoic acid)		L	D	T
362	354	PRO	PRO	H	-aminomethyl-5-(4-aza-phenyl)-benzoic acid]		L	D	T
363	355	PRO	PRO	H	-aminomethyl-4-(3-thiophenyl)-benzoic acid]		L	D	T
364	356	PRO	PRO	H	ıyl-4-(4-N,N-dimethyl-carboxamide-phenyl)-benzoic acid]		L	D	T
365	357	PRO	PRO	H	-aminomethyl-4-(4-aza-phenyl)-benzoic acid]		L	D	T
366	358	PRO	PRO	H	-aminomethyl-4-(3-aza-phenyl)-benzoic acid]		L	D	T
367	359	PRO	PRO	H	ninomethyl-4-(4-hydroxy-phenyl)-benzoic acid]		L	D	T
368	360	PRO	PRO	H	omethyl-4-[5-(2,4-dimethyl)thiazole]-benzoic acid]		L	D	T
369	361	PRO	PRO	H	nomethyl-4-(3-N,N-dimethylaniline)-benzoic acid]		L	D	T
370	362	PRO	PRO	H	ıminomethyl-4-(2-fluoro-pyridyl)-benzoic acid]		L	D	T
371	363	PRO	PRO	H	-aminomethyl-4-(5-pyrimidinyl)-benzoic acid]		L	D	T
372	364	PRO	PRO	H	nethyl-4-(3-N,N-dimethyl-diaryl ether)-benzoic acid]		L	D	T
373	365	PRO	PRO	H	-aminomethyl-4-(3-CF3-phenyl)-benzoic acid]		L	D	T
374	366	PRO	PRO	H	nomethyl-4-(2,5-dimethoxy-phenyl)-benzoic acid]		L	D	T
375	367	PRO	PRO	H	methyl-4-[(2,3,4-tri-methoxy)-phenyl]-benzoic acid]		L	D	T
376	368	PRO	PRO	H	ninomethyl-4-(4-carboxy)-phenyl)-benzoic acid]		L	D	T
377	369	PRO	PRO	H	3-aminomethyl-4-(piperonyl)-benzoic acid]		L	D	T
378	370	PRO	PRO	H	(3-aminomethyl-4-piperidinyl-benzoic acid)		L	D	T
379	371	PRO	PRO	H	3-aminomethyl-4-morpholinyl-benzoic acid)		L	D	T
380	372	PRO	PRO	H	-aminomethyl-4-(N,N-dimethyl)-benzoic acid]		L	D	T
381	373	PRO	PRO	H	nomethyl-4-(2-aminomethylphenyl)-benzoic acid]		L	D	T
382	374	PRO	PRO	H	nomethyl-4-(3-aminomethylphenyl)-benzoic acid]		L	D	T
383	375	PRO	PRO	H	nomethyl-4-(4-aminomethylphenyl)-benzoic acid]		L	D	T
384	376	PRO	PRO	H	-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	Abu
385	377	H	Nva	H	-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
386	334	PRO	PRO	H	-4-[4-(1-piperazinyl-4-AlexaFluor 647)phenyl]-benzoic acid]		L	D	T
387	378	PRO	PRO	H	(N-methyl-3-aminomethyl-benzoic acid)		L	D	T
388	379	PRO	PRO	H	thyl-3-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
389	380	PRO	PRO	H	[2-(5-quinolinyl)-Phe]-reduced	betaHomoLys	L	D	T
390	334	PRO	PRO	H	omethyl-4-[4-(1-piperazinyl)-phenyl]-benzoic acid]		L	D	T
391	334	PRO	PRO	H	omethyl-4-[4-(1-piperazinyl)-phenyl]-benzoic acid]		L	D	T
392	334	PRO	PRO	H	omethyl-4-[4-(1-piperazinyl)-phenyl]-benzoic acid]		L	D	T
393	31	HYP	HYP	H	F		L	D	T
394	31	HYP	HYP	H	F		L	D	T
395	31	HYP	HYP	H	F		L	D	T
396	31	HYP	HYP	H	F		L	D	T
397	31	HYP	HYP	H	F		L	D	T

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
1	0.164	0.162	0.988	
2	0.109	0.185	1.697	
3	0.192	0.475	2.474	25.000
4	0.129	0.357	2.8	11.782
5	0.087	0.062	0.7	7.916
6	0.103	0.200	1.9	
7	0.117	0.190	1.6	23.000
8	0.103	0.096	0.9	
9	0.061	0.106	1.7	
10	0.052	0.070	1.3	
11	0.051	0.094	1.8	3.602
12	0.063	0.113	1.8	8.885
13	0.097	0.171	1.8	19.520
14	0.026	0.025	1.0	2.664
15	0.040	0.026	0.7	3.071
16	0.086	0.053	0.6	1.624
17	0.173			26.923
18	0.120			
19	0.114			15.044
20	0.146			8.716
21	0.092			9.466
22	0.100			11.556
23	0.176	0.458	2.6	18.880
24	0.087	0.192	2.2	7.632
25	0.096	0.209	2.2	12.431
26	0.088	0.236	2.7	14.070
27	0.067	0.161	2.4	10.478
28	0.117	0.264	2.3	12.562
29	0.073	0.167	2.3	8.133

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
30	0.058	0.162	2.8	9.277
31	0.057	0.215	3.7	7.950
32	0.100	0.311	3.1	11.161
33	0.090	0.324	3.6	13.059
34	0.043	0.083	1.9	1.153
35	0.039	0.096	2.5	1.230
36	0.112	0.215	1.9	2.392
37	0.036	0.063	1.8	0.856
38	0.065	0.120	1.9	1.899
39	0.152	0.595	3.9	7.576
40	0.063	0.119	1.9	
41	0.042	0.106	2.5	
42	0.079	0.232	2.9	
43	0.026	0.072	2.8	
44	0.083	0.188	2.3	
45	0.074	0.238	3.2	
46	0.106	0.258	2.4	
47	0.061	0.135	2.2	6.777
48	0.094	0.332	3.5	20.686
49	0.137	0.326	2.4	17.374
50	0.023	0.290	12.6	3.709
51	0.031	0.102	3.3	
52	0.075	0.367	4.9	14.719
53	0.182			21.956
54	0.190			23.916
55	0.113	0.119	1.1	
56	0.058	0.200	3.5	4.203
57	0.059	0.148	2.5	
58	0.156	0.445	2.9	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
59	0.197	0.610	3.1	
60	0.066	0.214	3.3	6.554
61	0.063	0.223	3.6	
62	0.027	0.115	4.3	2.548
63	0.107	0.251	2.3	
64	0.046	0.268	5.8	5.367
65	0.005	0.095	18.1	1.033
66	0.093	0.326	3.5	6.348
67	0.075	0.341	4.5	5.093
68	0.067	0.280	4.2	4.158
69	0.022	0.060	2.7	2.646
70	0.035	0.099	2.9	1.163
71	0.184	0.816	4.4	
72	0.151	0.409	2.7	7.284
73	0.144	1.247	8.6	17.304
74	0.100	0.763	7.6	15.503
75	0.171	1.209	7.1	13.166
76	0.114	0.466	4.1	6.267
77	0.036	0.185	5.1	5.633
78	0.069	0.272	3.9	6.479
79	0.110	0.552	5.0	13.217
80	0.053	0.556	10.6	3.599
81	0.054	0.241	4.5	5.405
82	0.073	0.213	2.9	5.716
83	0.179	1.226	6.9	32.316
84	0.035	0.218	6.2	6.143
85	0.052	0.206	3.9	4.229
86	0.050	0.167	3.3	4.074
87	0.019	0.269	14.1	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
88	0.011	0.166	14.9	
89	0.016	0.232	14.4	
90	0.009	0.317	35.0	
91	0.126	1.824	14.5	
92	0.053	1.063	19.9	
93	0.078	0.311	4.0	6.009
94	0.080	0.250	3.1	9.484
95	0.125	0.303	2.4	
96	0.138	0.321	2.3	
97	0.124	0.311	2.5	
98	0.021	0.058	2.7	
99	0.057	0.154	2.7	
100	0.132	0.453	3.4	4.446
101	0.129	0.609	4.7	16.092
102	0.021	0.136	6.6	1.464
103	0.108	1.631	15.1	
104	0.120	0.506	4.2	
105	0.110	1.734	15.8	9.731
106	0.059	1.109	18.7	
107	0.150	2.390	16.0	
108	0.077	0.814	10.5	13.867
109	0.133	3.312	24.9	15.287
110	0.185	3.923	21.3	21.753
111	0.100	3.923	39.3	12.926
112	0.138	3.008	21.7	17.420
113	0.052	0.709	13.7	7.634
114	0.083	1.889	22.8	6.866
115	0.125	1.121	9.0	15.436
116	0.166	1.385	8.4	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
117	0.158	1.381	8.7	
118	0.112	0.132	1.2	14.202
119	0.079	1.688	21.5	14.057
120	0.157	3.000	19.1	
121	0.192	2.187	11.4	
122	0.090	1.666	18.6	16.615
123	0.007	0.019	2.5	1.138
124	0.013	0.104	8.3	1.172
125	0.025	0.458	18.4	1.925
126	0.024	0.135	5.6	1.232
127	0.025	0.196	7.8	
128	0.026	0.296	11.4	
129	0.065	0.636	9.7	
130	0.022	0.125	5.6	1.327
131	0.026	0.080	3.1	
132	0.029	0.309	10.8	3.626
133	0.015	0.080	5.3	
134	0.023	0.178	7.6	
135	0.024	0.119	4.9	
136	0.032	0.209	6.6	
137	0.033	0.254	7.8	
138	0.024	0.118	5.0	
139	0.100	0.073	0.7	
140	0.053	0.512	9.6	
141	0.019	0.036	2.0	
142	0.164	0.084	0.5	
143	0.033	0.068	2.1	
144	0.043	0.027	0.6	6.083
145	0.023	0.045	2.0	3.268

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
146	0.016	0.012	0.7	0.672
147	0.052	0.039	0.8	
148	0.086	0.105	1.2	
149	0.046	0.546	12.0	12.600
150	0.054	0.447	8.2	
151	0.053	0.218	4.1	
152	0.102	1.347	13.2	
153	0.006	0.017	2.8	0.125
154	0.117	2.664	22.8	
155	0.054	1.085	20.3	
156	0.019	0.258	13.3	1.412
157	0.067	3.707	55.3	
158	0.110	1.537	14.0	15.746
159	0.053	0.467	8.9	41.275
160	0.141	1.349	9.5	8.794
161	0.135	2.035	15.1	6.662
162	0.107	1.875	17.5	16.696
163	0.126	1.389	11.0	22.489
164	0.127	3.288	25.8	30.192
165	0.128	2.918	22.8	30.337
166	0.179	1.382	7.7	
167	0.147	1.997	13.6	
168	0.077	1.051	13.6	17.847
169	0.176	0.488	2.8	
170	0.013	0.104	8.0	1.033
171	0.128	0.658	5.1	14.357
172	0.096	1.030	10.7	9.922
173	0.054	0.719	13.4	12.042
174	0.160	0.619	3.9	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
175	0.018	0.130	7.2	0.986
176	0.189	1.202	6.3	
177	0.019	0.463	24.0	2.853
178	0.027	0.113	4.1	2.710
179	0.174	2.656	15.2	
180	0.013	0.068	5.1	0.841
181	0.180	2.272	12.6	
182	0.017	0.083	5.0	1.128
183	0.014	0.105	7.5	1.070
184	0.099	0.953	9.6	
185	0.018	0.095	5.4	0.662
186	0.062	0.027	0.4	
187	0.083	0.404	4.9	
188	0.027	0.189	7.0	7.308
189	0.018	0.019	1.0	2.251
190	0.021	0.145	7.0	2.470
191	0.083	4.020	48.4	
192	0.118	6.823	57.8	37.800
193	0.092	0.303	3.3	5.621
194	0.038	0.207	5.4	4.617
195	0.049	1.917	38.9	7.931
196	0.158	0.275	1.7	
197	0.044	1.327	30.2	7.441
198	0.041	1.223	29.9	5.089
199	0.069	3.138	45.2	19.350
200	0.134	0.352	2.6	
201	0.061	0.695	11.4	
202	0.086	0.680	8.0	
203	0.055	0.534	9.8	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
204	0.063	0.429	6.8	
205	0.047	1.517	32.2	2.231
206	0.046	2.890	63.0	27.621
207	0.025	0.460	18.5	
208	0.019	0.522	28.1	4.679
209	0.035	1.977	56.9	16.508
210	0.072	1.148	16.0	
211	0.060	2.511	42.2	8.101
212	0.068	2.190	32.1	
213	0.055	2.247	41.2	10.605
214	0.069	4.222	60.8	72.055
215	0.033	0.413	12.4	
216	0.123	2.509	20.4	
217	0.034	1.088	31.8	
218	0.190	3.135	16.5	
219	0.147	3.253	22.1	
220	0.096	1.740	18.2	
221	0.015	0.165	11.1	0.248
222	0.013	0.212	16.1	0.325
223	0.015	0.122	8.2	0.549
224	0.055	2.978	53.9	10.962
225	0.099	4.523	45.6	18.130
226	0.094	10.797	115.0	4.076
227	0.034	0.047	1.4	1.491
228	0.034	0.503	14.7	
229	0.058	0.075	1.3	
230	0.120	0.131	1.1	
231	0.031	0.993	32.0	
232	0.012	0.110	8.9	0.353

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
233	0.094	3.861	41.0	19.372
234	0.099	3.203	32.3	
235	0.025	1.553	62.6	4.614
236	0.060	6.203	104.2	7.320
237	0.020	0.870	43.9	5.131
238	0.025	1.049	42.3	8.425
239	0.020	0.641	32.3	4.407
240	0.027	0.905	33.2	12.040
241	0.031	3.207	103.4	6.006
242	0.067	5.307	79.0	8.335
243	0.026	0.767	29.4	2.007
244	0.016	0.753	46.7	0.719
245	0.024	0.414	17.5	3.067
246	0.120	17.702	147.1	
247	0.035	4.614	132.8	15.134
248	0.045	3.088	69.2	16.371
249	0.045	4.233	94.8	23.107
250	0.017	0.150	8.7	0.401
251	0.024	0.349	14.8	1.386
252	0.032	0.390	12.1	2.408
253	0.069	1.087	15.6	
254	0.055	1.803	33.0	
255	0.043	3.024	69.7	
256	0.072	3.246	45.1	9.562
257	0.058	1.604	27.5	
258	0.056	1.584	28.4	
259	0.058	5.995	102.8	4.279
260	0.165	9.562	58.1	
261	0.096	23.155	241.0	16.926

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
262	0.080	3.740	47.0	
263	0.102	2.345	23.1	
264	0.117	5.560	47.5	
265	0.039	1.818	46.2	
266	0.037	1.206	33.0	11.641
267	0.044	1.936	44.1	20.440
268	0.076	1.868	24.6	
269	0.056	1.764	31.6	
270	0.160	17.562	109.8	18.900
271	0.033	1.151	34.6	
272	0.041	2.383	58.1	
273	0.012	0.303	24.6	1.730
274	0.026	0.454	17.5	7.938
275	0.101	0.779	7.7	
276	0.134	14.235	106.2	
277	0.052	0.357	6.9	
278	0.104	1.062	10.2	
279	0.100	5.847	58.2	
280	0.010	0.400	39.7	2.150
281	0.144	3.161	21.9	
282	0.119	0.626	5.2	
283	0.128	1.495	11.7	
284	0.046	0.228	5.0	
285	0.089	0.553	6.2	
286	0.064	5.236	81.9	
287	0.084	3.553	42.1	
288	0.136	1.664	12.2	
289	0.038	0.349	9.3	1.242
290	0.067	1.894	28.4	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
291	0.035	0.777	22.4	8.742
292	0.030	0.374	12.4	
293	0.019	0.198	10.6	4.008
294	0.045	0.937	20.7	
295	0.094	20.950	222.7	18.900
296	0.155	14.698	94.8	
297	0.037	0.786	21.3	
298	0.076	4.349	57.2	
299	0.002	0.090	41.5	0.556
300	0.022	0.225	10.4	0.672
301	0.018	0.846	47.6	1.020
302	0.012	0.598	51.6	1.764
303	0.020	0.497	24.8	1.662
304	0.015	0.293	19.0	0.191
305	0.008	0.221	26.6	3.533
306	0.104	2.763	26.5	
307	0.091	4.343	47.8	
308	0.039	0.480	12.3	1.982
309	0.008	0.023	3.0	0.126
310	0.017	0.300	17.6	0.434
311	0.007	0.198	27.6	0.158
312	0.011	0.145	13.4	0.273
313	0.011	0.206	19.2	0.210
314	0.011	0.138	12.8	0.305
315	0.013	0.312	24.9	0.431
316	0.022	0.349	16.2	0.690
317	0.047	0.685	14.5	9.408
318	0.091	1.513	16.6	
319	0.065	0.309	4.8	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
320	0.163	0.127	0.8	
321	0.101	7.368	72.7	
322	0.093	4.166	44.7	
323	0.025	0.297	11.8	1.056
324	0.110	1.058	9.6	11.844
325	0.020	0.170	8.6	0.714
326	0.017	0.476	28.4	0.280
327	0.010	0.128	13.2	0.308
328	0.010	0.234	24.1	0.368
329	0.005	0.050	10.6	0.326
330	0.005	0.179	32.9	0.185
331	0.016	0.093	6.0	0.399
332	0.010	0.120	12.5	0.140
333	0.046	0.757	16.5	12.922
334				5.061
335				4.956
336	0.162	0.917	5.6	
337	0.061	0.177	2.9	
338	0.041	0.177	4.4	
339	0.051	0.299	5.8	
340	0.019	0.048	2.5	0.263
341	0.012	0.026	2.1	0.306
342	0.041	0.139	3.4	
343	0.018	0.029	1.6	0.269
344	0.052	0.107	2.1	
345	0.039	0.052	1.3	
346	0.028	0.011	0.4	0.580
347	0.023	0.030	1.3	
348	0.027	0.041	1.5	

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
349	0.023	0.043	1.9	0.479
350	0.027	0.055	2.0	
351	0.160	0.184	1.2	
352	0.024	0.005	0.2	0.070
353	0.031	0.103	3.3	
354	0.050	0.175	3.5	
355	0.048	0.069	1.4	
356	0.017	0.027	1.6	
357	0.102	0.406	4.0	
358	0.127	1.108	8.7	34.923
359	0.053	0.450	8.5	7.880
360	0.125	0.779	6.2	18.937
361	0.049	0.288	5.9	2.843
362	0.043	0.238	5.6	
363	0.022	0.105	4.8	1.571
364	0.018	0.074	4.0	0.602
365	0.017	0.064	3.7	0.638
366	0.023	0.059	2.6	0.384
367	0.018	0.053	3.0	0.535
368	0.010	0.024	2.4	0.342
369	0.024	0.069	2.9	0.974
370	0.015	0.047	3.1	0.661
371	0.016	0.055	3.4	0.482
372	0.024	0.104	4.3	2.133
373	0.018	0.074	4.1	0.879
374	0.018	0.081	4.5	1.246
375	0.015	0.067	4.5	1.164
376	0.019	0.078	4.1	1.135
377	0.013	0.045	3.6	0.839

TABLE 1C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
378	0.042	0.182	4.3	
379	0.033	0.161	4.9	
380	0.041	0.217	5.3	
381	0.010	0.010	1.1	0.323
382	0.012	0.025	2.0	
383	0.006	0.017	2.7	0.403
384	0.020	0.049	2.5	2.260
385	0.039	0.023	0.6	1.548
386	0.044	0.034	0.8	2.604
387	0.063	6.133	96.7	16.142
388	0.009	0.102	12.0	0.336
389	0.042	0.234	5.535	6.664
390	0.010	0.017	1.749	0.019
391	0.011	0.025	2.138	0.022
392	0.011	0.062	5.427	0.056
393	0.035	0.109	3.137	0.635
394	0.039	0.133	3.429	0.860
395	0.042	0.126	2.998	1.521
396	0.044	0.063	1.424	1.953
397	0.079	0.158	1.987	2.061

TABLE 2A

Compound No.	R^1	R^2	R^3	R^4	R^5
5	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
398	H	H	H	H	H
399	H	H	CH_3	H	C(O)-NH2
4	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
400	H	H	H	C(O)-NH-*tert*-Butyl	H
401	H	H	H	H	C(O)-NH-*tert*-Butyl
402	H	H	CH_3	H	H
403	H	H	CH_3	C(O)-NH-*tert*-Butyl	H
404	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
405	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
406	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
407	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
408	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
409	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
410	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
411	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
412	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
413	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
414	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
415	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
416	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
417	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
418	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
419	H	CH_3	H	C(O)-NH-*tert*-Butyl	H

TABLE 2A

Compound No.	R^1	R^2	R^3	R^4	R^5
420	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
125	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
421	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
422	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
423	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
424	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
425	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
426	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
427	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
428	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
429	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
430	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
431	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
432	PRO-	PRO-	H	H	C(O)-NH-*tert*-Butyl
341	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
433	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
434	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
435	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
436	PRO-	PRO-	H	C(O)-NH-*tert*-Butyl	H
437	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
232	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
438	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
439	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
440	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
441	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
442	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
443	H	H	CH_3	C(O)-NH-*tert*-Butyl	H

TABLE 2A

Compound No.	R^1	R^2	R^3	R^4	R^5
444	H	CH_3	H	C(O)-NH-*tert*-Butyl	H
445	PRO-	PRO-	H	C(O)-NH-*tert*-Butyl	H
446	PRO-	PRO-	H	H	C(O)-NH-*tert*-Butyl
447	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
448	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
449	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
450	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
270	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
451	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
452	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
453	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
454	H	H	CH_3	H	C(O)-NH-*tert*-Butyl
455	H	H	CH_3	H	C(O)-NH-*tert*-Butyl

TABLE 2B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^z	X^1	X^2	X^3
5	4	PRO	PRO	H	F		L	D	T
398	4	PRO	PRO	H	F		L	D	T
399	4	PRO	PRO	H	F		L	D	T
4	3	PRO	PRO	H	Y		L	D	T
400	3	PRO	PRO	H	Y		L	D	T
401	3	PRO	PRO	H	Y		L	D	T
402	3	PRO	PRO	H	Y		L	D	T
403	3	PRO	PRO	H	Y		L	D	T
404	3	PRO	PRO	H	Y		L	D	T
405	381	PRO	PRO	H	L		D	T	Y
406	382	PRO	PRO	H	D		L	D	T
407	383	PRO	PRO	H	1-(R)-isoindoline-carboxylic acid		L	D	T
408	384	PRO	PRO	H	betaHomoLys		L	D	T
409	385	PRO	PRO	H	Y		cyclopropylAla	D	T
410	386	PRO	PRO	H	Y		betaHomoLeu	D	T
411	387	PRO	PRO	H	Y		W	D	T
412	388	PRO	PRO	H	Y		L	betaHomoAsp	T
413	389	PRO	PRO	H	2Nal		L	HomoSer	I
414	390	PRO	PRO	H	2Nal		L	Asp(ethyl ester)	I
415	391	PRO	PRO	H	Y		L	D	H
416	392	PRO	PRO	H	Y		L	D	(2-aza-Phe)
417	393	PRO	PRO	H	Y		L	D	betaHomoThr
418	394	dPro	H	dPro	dTyr		dLeu	dAsp	dThr
419	395	dPro	H	dPro	dThr		dAsp	dLeu	dTyr
420	396	PRO	PRO	H	dThr		dAsp	dLeu	dTyr
125	120	PRO	PRO	H	Y	dPip	L	D	T
421	397	dPro	H	dPro	Y	dPip	L	D	T
422	398	PRO	PRO	H	dTic	G	L	D	T
423	399	PRO	PRO	H	dAla	Y	L	D	T
424	400	PRO	PRO	H	(2-aminomethyl-phenylacetic acid)		L	D	T
425	401	PRO	PRO	H	Y	dMet	L	D	T
426	402	PRO	PRO	H	Y	dTiq	L	D	T
427	403	PRO	PRO	H	Y	dPip	MeLeu	D	T

TABLE 2B

Compound No.	Seq. ID. No.	R^6	R^7	R^8	X^Y	X^Z	X^1	X^2	X^3
428	404	PRO	PRO	H	Y	Sar	HomocycloLeu	D	T
429	405	PRO	PRO	H	Y	dLys	L	D	dThr
430	406	PRO	PRO	H	Y	dPip	L	D	betaHomoIle
431	407	PRO	PRO	H	Y	L	D	T	dAla
432	120	PRO	PRO	H	Y	dPip	L	D	T
341	335	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
433	408	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic acid]		MeLeu	D	T
434	409	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	MeAsp	T
435	410	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	MeThr
436	335	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic acid]		L	D	T
437	411	PRO	PRO	H	i-aminomethyl-4-(4-quinolinyl)-benzoic aci	K	L	D	T
232	226	PRO	PRO	H	F	MebetaHomoLys	L	D	T
438	412	PRO	PRO	H	[4-(2,6-dimethoxy-phenyl)-Phe]	betaHomoLys	L	D	T
439	413	PRO	PRO	H	Y	1,2-trans-ACHC	L	D	T
440	414	PRO	PRO	H	Y	betaAla	L	D	T
441	415	PRO	PRO	H	Y	(2-aminobenzoic acid)	L	D	T
442	416	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	dMebetaHomoLys	L	D	T
443	190	PRO	PRO	H	Y	betaHomoLys	L	D	T
444	417	dPro	H	dPro	Y	betaHomoLys	L	D	T
445	190	PRO	PRO	H	Y	betaHomoLys	L	D	T
446	190	PRO	PRO	H	Y	betaHomoLys	L	D	T
447	418	PRO	PRO	H	L	D	T	F	betaHomoLys
448	419	PRO	PRO	H	Y	L	G	D	T
449	420	PRO	PRO	H	L	D	T	A	P
450	421	PRO	PRO	H	Y	L	D	T	A
270	264	PRO	PRO	H	[3-(4-thiazolyl)-Ala]-reduced	betaHomoLys	L	D	T
451	422	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys-reduced	L	D	T
452	423	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys	Leu-reduced	D	T
453	424	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys	L	Asp-reduced	T
454	425	PRO	PRO	H	[3-(4-thiazolyl)-Ala]	betaHomoLys	L	D	Thr-reduced
455	426	PRO	PRO	H	F	betaHomoLys-reduced	L	D	T

TABLE 2C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
5	0.087	0.062	0.7	7.916
398	39.605	38.211		
399				47
4	0.129	0.357	2.8	11.782
400	7.348	4.904		
401	1.27	3.843		
402	6.45	2.842		
403	6.45	2.842		
404	6.45	2.842		
405	40.313			
406	3.832			
407	3.664	3.727		
408	3.22	19.216		
409	3.025			
410	3.817			
411	40			
412	7.633			
413	27.726			26.923
414	50			26.923
415	45.263			
416	56.579	49.128		
417	6.515			
418	15.5	28.42		

TABLE 2C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
419	15.5	28.42		
420	3.116	3		
125	0.025	0.458	18.4	1.925
421	0.462	0.726		
422	1.273	2.122		
423	10			
424	1.0			
425	1.575	3.717		
426	3.665	3.727		
427	1.04	1.2		
428	3.665	1.012		
429	3.116	3.00		
430	2.933	8.69		
431	10			
432	4.33	2.905		
341	0.012	0.026	2.1	0.306
433	7.904	37.5		
434	3.746	29.919		
435	0.231	0.342		
436	4.82	13.377		
437	5.305	7.302		
232	0.012	0.110	8.9	0.353
438	0.941	21.709		
439	1.579	1.902		
440	1.833	9.679		
441	0.994	4.095		

TABLE 2C

Compound No.	a4b7 ELISA IC_{50} (mM)	a4b1 ELISA IC_{50} (mM)	Selectivity ELISA	RPMI 8866 cell IC_{50} (mM)
442	2.281	4.701		
443	7.442	28.424		
444	7.566	28.424		
445	10.492	1.123		
446	10.541	26.869		
447	8.109	8.859		
448	50			
449	6.494	4.658		
450	0.400	2.007		
270	0.160	17.562	109.8	18.900
451	41.17	86.84		
452	2.009	110		
453	2.251	36.125		
454	8.274	43.01		
455	20.512	96.78		

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
1		A,E,Fb,I,M
2		A,E,Fb,I,M
3		A,E,Fb,I,M
4		A,E,Fa,Jb,I,M
5		A,E,Fa,Jb,I,M
6		A,E,Fa,Jb,I,M
7		A,E,Fa,Jb,I,M
8		A,E,Fa,Jb,I,M
9	780.4	A,E,Fa,Jb,I,M
10	780.4	A,E,Fa,Jb,I,M
11	859.4	A,E,Fa,Jb,I,M
12	806.4	A,E,Fa,Jb,I,M
13		A,E,Fa,Jb,H,I,M
14	792.4	A,E,Fa,Jb,I,M
15	792.4	A,E,Fa,Jb,I,M
16		A,E,Fa,Jb,I,M
17		A,E,Fa,Jb,I,M
18		A,E,Fa,Jb,I,M
19		A,E,Fa,Jb,H,I,M
20		A,E,Fa,Jb,H,I,M
21		A,E,Fa,Jb,H,I,M
22		A,E,Fa,Jb,H,I,M
23		A,E,Fa,Jb,H,I,M
24		A,E,Fa,Jb,H,I,M
25		A,E,Fa,Jb,H,I,M
26		A,E,Fa,Jb,H,I,M
27	836.4	A,E,Fa,Jb,H,I,M
28		A,E,Fa,Jb,H,I,M
29	880.4	A,E,Fa,Jb,H,I,M
30	880.4	A,E,Fa,Jb,H,I,M
31	866.4	A,E,Fa,Jb,H,I,M
32		A,E,Fa,Jb,I,M
33		A,E,Fa,Jb,H,I,M
34	891.4	A,E,Fa,Jb,K,I,M
35	829.4	A,E,Fa,Jb,K,I,M
36		A,E,Fa,Jb,K,I,M
37	859.4	A,E,Fa,Jb,K,I,M
38	871.4	A,E,Fa,Jb,K,I,M
39		A,E,Fa,Jb,I,M
40	744.4	A,E,Fa,Jb,I,M
41	758.4	A,E,Fa,Jb,I,M
42	746.4	A,D,I,M
43	742.4	A,D,I,M
44		A,E,Fa,Jb,I,M
45	748.4	A,E,Fa,Jb,I,M
46		A,E,Fa,Jb,I,M
47	749.3	A,E,Fa,Jb,I,M
48		A,E,Fa,Jb,I,M
49		A,E,Fa,Jb,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
50	739.4	A,D,I,M
51		A,D,I,M
52		A,D,I,M
53		A,D,I,M
54		A,D,I,M
55		A,D,I,M
56		A,D,I,M
57		A,D,I,M
58		A,D,I,M
59		A,D,I,M
60		A,D,I,M
61		A,D,I,M
62		A,D,I,M
63		A,D,I,M
64		A,D,I,M
65		A,D,I,M
66		A,D,I,M
67		A,D,I,M
68		A,D,I,M
69		A,D,I,M
70		A,D,I,M
71		A,D,I,M
72		A,D,I,M
73		A,D,I,M
74		A,D,I,M
75		A,D,I,M
76		A,D,I,M
77		A,D,I,M
78		A,D,I,M
79		A,D,I,M
80		A,D,I,M
81		A,D,I,M
82		A,D,I,M
83		A,D,I,M
84		A,D,I,M
85		A,D,I,M
86		A,D,I,M
87		A,D,I,M
88		A,D,I,M
89		A,D,I,M
90		A,D,I,M
91		A,D,I,M
92		A,D,I,M
93		A,D,I,M
94		A,D,I,M
95		A,D,G,I,M
96		A,D,G,I,M
97		A,D,G,I,M
98		A,D,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
99		A,D,I,M
100	847.4	A,D,I,M
101	843.6	A,D,I,M
102	843.6	A,D,I,M
103	817.4	A,D,I,M
104	857.4	A,D,I,M
105	817.4	A,D,I,M
106	927.2	A,D,I,M
107	927.2	A,D,I,M
108	877.4	A,D,I,M
109	858.4	A,D,I,M
110	934.4	A,D,I,M
111	865.4	A,D,I,M
112	934.4	A,D,I,M
113	886.4	A,D,I,M
114	902.4	A,D,I,M
115	833.4	A,D,I,M
116	877.4	A,D,I,M
117	851.4	A,D,I,M
118	857.4	A,D,I,M
119	927.2	A,D,I,M
120	908.4	A,D,I,M
121	888.4	A,D,I,M
122	801.4	A,D,I,M
123	905.4	A,D,I,M
124	843.4	A,D,I,M
125	857.4	A,D,I,M
126	827.4	A,D,I,M
127	887.4	A,D,I,M
128	881.4	A,D,I,M
129	1001.2	A,D,I,M
130		A,D,I,M
131		A,D,I,M
132		A,D,I,M
133		A,D,I,M
134		A,D,G,I,M
135		A,D,G,I,M
136		A,D,G,I,M
137		A,D,G,I,M
138		A,D,I,M
139		A,D,I,M
140		A,D,I,M
141		A,D,I,M
142		A,D,I,M
143	891.1	A,D,I,M
144	891.1	A,D,I,M
145	918.1	A,D,I,M
146	918.1	A,D,I,M
147	918.1	A,D,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
148	871.1	A,D,I,M
149	857.1	A,D,I,M
150	871.1	A,D,I,M
151	850.0	A,D,I,M
152	872.1	A,D,I,M
153	869.2	A,D,I,M
154	900.2	A,D,I,M
155	859.4	A,D,I,M
156	843.4	A,D,I,M
157	916.2	A,D,I,M
158		A,D,I,M
159		A,D,I,M
160		A,D,I,M
161		A,D,I,M
162		A,D,I,M
163		A,D,I,M
164		A,D,I,M
165		A,D,I,M
166		A,D,I,M
167		A,D,I,M
168		A,D,I,M
169		A,D,I,M
170		A,D,I,M
171		A,D,I,M
172		A,D,I,M
173		A,D,I,M
174		A,D,I,M
175		A,D,I,M
176		A,D,I,M
177		A,D,I,M
178		A,D,I,M
179		A,D,G,I,M
180		A,D,G,I,M
181		A,D,G,I,M
182		A,D,G,I,M
183		A,D,G,I,M
184		A,D,G,I,M
185		A,D,G,I,M
186	869.3	A,D,I,M
187	842.4	A,D,I,M
188	842.1	A,D,I,M
189	902.1	A,D,I,M
190	909.1	A,D,I,M
191	948.4	A,D,G,I,M
192	968.4	A,D,G,I,M
193	861.4	A,D,I,M
194	857.4	A,D,I,M
195	888.4	A,D,I,M
196	702.4	A,D,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
197		A,D,I,M
198		A,D,I,M
199		A,D,I,M
200		A,D,I,M
201		A,D,I,M
202		A,D,I,M
203		A,D,I,M
204		A,D,I,M
205		A,D,I,M
206	967.2	A,D,G,I,M
207	948.2	A,D,G,I,M
208	948.2	A,D,G,I,M
209		A,D,G,I,M
210		A,D,I,M
211		A,D,I,M
212		A,D,I,M
213		A,D,I,M
214		A,D,I,M
215		A,D,I,M
216	900.4	A,D,I,M
217		A,D,I,M
218		A,C,D,I,M
219		A,D,I,M
220		A,D,I,M
221	893.1	A,B,D,I,M
222	915.2	A,B,D,I,M
223	891.1	A,D,I,M
224		A,D,I,M
225		A,D,I,M
226		A,D,I,M
227		A,D,I,M
228		A,D,I,M
229	857.4	A,D,I,M
230	870.4	A,D,I,M
231		A,D,I,M
232	886.2	A,B,D,I,M
233		A,C,D,I,M
234		A,D,I,M
235		A,D,G,I,M
236		A,D,I,M
237	952.0	A,D,I,M
238		A,D,I,M
239	890.2	A,D,I,M
240		A,D,I,M
241		A,D,I,M
242		A,D,I,M
243		A,D,G,I,M
244	999.3	A,D,G,I,M
245		A,D,G,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
246		A,D,I,M
247		A,D,I,M
248		A,D,G,I,M
249		A,D,G,I,M
250	900.2	A,D,I,M
251	886.1	A,D,I,M
252		A,D,I,M
253		A,D,I,M
254		A,D,I,M
255	998.4	A,D,I,M
256	948.6	A,D,G,I,M
257	978.6	A,D,G,I,M
258	1008.6	A,D,G,I,M
259	1032.6	A,D,G,I,M
260	998.4	A,D,I,M
261	978.4	A,D,G,I,M
262	1032.4	A,D,G,I,M
263	886.6	A,D,I,M
264	886.6	A,D,I,M
265	976.6	A,D,G,I,M
266	1000.6	A,D,G,I,M
267	984.5	A,D,G,I,M
268	976.6	A,D,G,I,M
269	1012.6	A,D,G,I,M
270		A,C,D,I,M
271		A,D,G,I,M
272		A,D,G,I,M
273	1005.3	A,D,G,I,M
274		A,D,I,M
275		A,D,I,M
276		A,D,G,I,M
277		A,D,I,M
278		A,D,I,M
279		A,D,I,M
280	898.1	A,D,I,M
281		A,D,I,M
282		A,D,I,M
283		A,D,I,M
284		A,D,I,M
285		A,D,I,M
286		A,D,G,I,M
287		A,D,G,I,M
288		A,D,I,M
289		A,D,I,M
290		A,D,I,M
291		A,D,I,M
292		A,D,G,I,M
293	949.2	A,D,G,I,M
294		A,D,G,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
295		A,D,I,M
296		A,D,I,M
297		A,D,G,I,M
298	1012.6	A,D,G,I,M
299	1005.4	A,D,G,I,M
300	915.2	A,B,D,I,M
301	915.2	A,B,D,I,M
302	893.2	A,B,D,I,M
303	1047.3	A,B,D,I,M
304	898.2	A,B,D,I,M
305	898.2	A,B,D,I,M
306		A,D,G,I,M
307		A,D,I,M
308		A,B,D,I,M
309	916.2	A,B,D,I,M
310	916.2	A,B,D,I,M
311	900.2	A,B,D,I,M
312	904.2	A,B,D,I,M
313	918.2	A,B,D,I,M
314	954.1	A,B,D,I,M
315	968.1	A,B,D,I,M
316	929.2	A,B,D,I,M
317		A,D,G,I,M
318	999.4	A,D,G,I,M
319	808.6	A,D,I,M
320	917.4	A,D,G,I,M
321	1032.4	A,D,G,I,M
322	978.5	A,D,G,I,M
323		A,B,D,G,I,M
324		A,D,I,M
325	914.3	A,B,D,I,M
326	928.2	A,B,D,I,M
327	870.2	A,B,D,I,M
328	912.2	A,B,D,I,M
329	900.4	A,B,D,I,M
330	942.5	A,B,D,I,M
331	852.5	A,B,D,I,M
332	884.6	A,B,D,I,M
333	867.2	A,D,I,M
334	900.4	A,B,D,I,M
335	884.5	A,B,D,I,M
336		A,D,I,M
337		A,D,G,I,M
338		A,D,G,I,M
339		A,D,G,I,M
340		A,D,G,I,M
341		A,D,G,I,M
342		A,D,I,M
343		A,D,G,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
344		A,D,G,I,M
345		A,D,G,I,M
346		A,D,G,I,M
347		A,D,G,I,M
348		A,D,G,I,M
349		A,D,G,I,M
350		A,D,G,I,M
351		A,D,G,I,M
352		A,D,G,I,M
353		A,D,G,I,M
354		A,D,G,I,M
355		A,D,G,I,M
356		A,D,G,I,M,L,M
357		A,D,I,M
358		A,D,I,M
359		A,D,I,M
360		A,D,I,M
361		A,D,I,M
362		A,D,G,I,M
363		A,D,G,I,M
364		A,D,G,I,M
365		A,D,G,I,M
366		A,D,G,I,M
367		A,D,G,I,M
368		A,D,G,I,M
369		A,D,G,I,M
370		A,D,G,I,M
371		A,D,G,I,M
372		A,D,G,I,M
373		A,D,G,I,M
374		A,D,G,I,M
375		A,D,G,I,M
376		A,D,G,I,M
377		A,D,G,I,M
378		A,D,G,I,M
379		A,D,G,I,M
380		A,D,G,I,M
381		A,D,G,I,M
382		A,D,G,I,M
383		A,D,G,I,M
384		A,D,G,I,M
385		A,D,G,I,M
386		A,D,G,I,M
387		A,B,D,I,M
388		A,B,D,G,I,M
389	985.2	A,C,D,G,I,M
398		A,D,I,M
399		A,D,I,M
400		A,D,I,M

Table S1

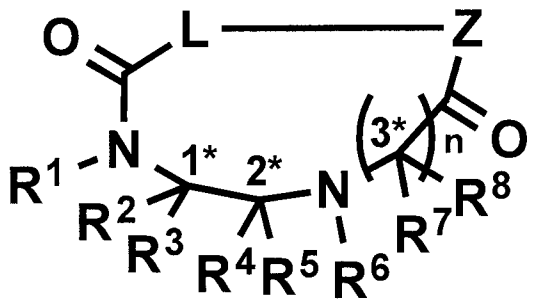
Compound No.	LC-MS (m/z)	Experimental Protocol
401		A,D,I,M
402		A,D,I,M
403		A,D,I,M
404		A,D,I,M
405		A,E,Fa,Jb,I,M
406		A,E,Fa,Jb,I,M
407		A,D,I,M
408		A,D,I,M
409		A,D,I,M
410		A,D,I,M
411		A,E,Fa,Jb,I,M
412		A,D,I,M
413		A,E,Fa,Jb,I,M
414		A,E,Fa,Jb,I,M
415		A,D,I,M
416		A,D,I,M
417		A,D,I,M
418		A,D,I,M
419		A,D,I,M
420		A,D,I,M
421		A,D,I,M
422		A,D,I,M
423		A,D,I,M
424		A,D,I,M
425		A,D,I,M
426		A,D,I,M
427		A,D,I,M
428		A,D,I,M
429		A,D,I,M
430		A,D,I,M
431		A,D,I,M
432		A,D,I,M
433		A,D,G,I,M
434		A,D,G,I,M
435		A,D,G,I,M
436		A,D,G,I,M
437		A,D,G,I,M
438		A,D,G,I,M
439		A,D,I,M
440		A,D,I,M
441		A,D,I,M
442		A,B,D,I,M
443		A,D,I,M
444		A,D,I,M
445		A,D,I,M
446		A,D,I,M
447		A,D,I,M
448		A,D,I,M
449		A,D,I,M

Table S1

Compound No.	LC-MS (m/z)	Experimental Protocol
450		A,D,I,M
451		A,C,D,I,M
452		A,C,D,I,M
453		A,C,D,I,M
454		A,C,D,I,M
455		A,C,D,I,M

CLAIMS:

1. A compound of formula (I):



(I)

wherein

R^1 is H; lower alkyl; aryl; heteroaryl; alkenyl; or heterocycle; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

R^2 and R^3 are each independently an amino acid chain of a proteinogenic or a non-proteinogenic alpha-amino acid,

provided that R^2 and R^3 may be covalently linked to each other to form a ring;

R^4 and R^5 are each independently H; lower alkyl; aryl; heteroaryl; alkenyl; heterocycle; acids of the formula –C(O)OH; esters of the formula –C(O)OR* wherein R* is selected from alkyl and aryl; amides of the formula –C(O)NR**R***, wherein R** and R*** are independently selected from H, alkyl and aryl; -CH_2C(O)R, wherein R is selected from –OH, lower alkyl, aryl, -loweralkyl-aryl, or –NRaRb, where Ra and Rb are independently selected from H, lower alkyl, aryl or –loweralkyl-aryl; or -C(O)Rc, wherein Rc is selected from lower alkyl, aryl or –lower alkyl-aryl; or –lower alkyl-ORd, wherein Rd is a suitable protecting group or OH group; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents;

provided that R^2 or R^3 can be covalently linked to R^1 to form a cyclic secondary amine, and /or to R^4 or R^5 to form a ring, R^4 and R^5 may also be covalently linked to each other to form a ring;

R^6 is H, lower alkyl, benzyl, alkenyl, lower alkyloxy; aryl; heteroaryl; heterocycle; –C(O)R****, wherein R**** is independently selected from alkyl, aryl, heteroaryl, amino, aminoalkyl, aminoaryl, aminoheteroaryl, alkoxy, aryloxy, heteroaryloxy; $-CH_2C(O)R$; or -C(O)Rc; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents,

or along with R^7 or R^8, a cyclic side chain of a proteinogenic or a non-proteinogenic amino acid having, the N-terminus thereof being the N-R^6, wherein the proteinogenic or a non-proteinogenic amino acid can be substituted with a suitable substituent;

R^7 and R^8 are independently selected from the amino acid side chains of a proteinogenic or a non-proteinogenic alpha-amino acid having the N-terminus thereof being the N-R^6, or may form a cyclic side chain with R^6;

stereocentres 1*, 2* and 3* are each independently selected from R and S;

n is 1, 2, 3, or 4 and where n is 2-4, each R^7 and each R^8 are independent of each other; and

wherein Z is an amino terminus of an amino acid; -C=O- adjacent L is the carboxy terminus of an amino acid; and L along with Z and –C=O- is a peptide having the following formula:

$$X^y – X^z – X^1 – X^2 – X^3$$

wherein X^y and X^z are each independently a proteinogenic or non-proteinogenic amino acid;

X^1 is Leucine or tert-butyl-Ala;

X^2 is Asp; and

X^3 is any amino acid listed under column X^3 of Table 1B.

2. The compound of claim 1, wherein R^1 is H.

3. The compound of claim 1, wherein R^2 or R^3 is covalently linked to R^1 to form proline having NR^1 as the N-terminus.

4. The compound of any one of claims 1-3, wherein R^2 and R^3 are not both H.

5. The compound of claim 1 or 2, wherein R^2 and R^3 are each independently selected from the group consisting of amino acid chains of a proteinogenic or a non-proteinogenic alpha-amino acids.

6. The compound of claim 1 or 2, wherein R^2 and R^3 are H and CH_3 respectively or vice versa.

7. The compound of claim 1 or 2, wherein R^2 or R^3 is -CH2-S-R^s, wherein R^s is selected from lower alkyl; lower amino alkyl; aryl; heteroaryl; alkenyl; or heterocycle; all of which are optionally substituted at one or more substitutable positions with one or more suitable substituents; preferably R^s is phenyl or phenyl substituted with lower alkyl, halogen; or lower amino alkyl.

8. The compound of any one of claims 1-4, wherein R^4 and R^5 are not both H.

9. The compound of any one of claims 1-4, wherein R** and R*** are not both H.

10. The compound of any one of claims 1-4, wherein R^4 and R^5 are each independently H, or C(O)-NHR^t, wherein R^t is H or a lower alkyl.

11. The compound of claim 10, wherein R^t is tert-butyl.

12. The compound of claim 10 wherein R^t is H.

13. The compound of any one of claims 1-12, wherein R^6 is H.

14. The compound of any one of claims 1-12, wherein R^6 and either R^8 or R^9 form a ring resulting in a proline residue having N-R^6 as its N-terminus.

15. The compound of any one of claims 1-14, wherein n is 1.

16. The compound of any one of claims 1-15, wherein Z along with L and –C=O is any one of SEQ ID NOs. 1-380.

17. The compound of any one of claims 1-16, wherein X^1 is Leu.

18. The compound of any one of claims 1-16, wherein X^2 is Asp.

19. The compound of any one of claims 1-16, wherein X^3 is Thr.

20. The compound of any one of claims 1-16, wherein X^3 is Val.

21. The compound of any one of claims 1-16, wherein X^3 is Ile.

22. The compound of any one of claims 1-21, wherein X^y and X^z are each independently a proteinogenic or non-proteinogenic alpha-amino acid.

23. The compound of any one of claims 1-21, wherein X^z is a proteinogenic or non-proteinogenic beta-amino acid.

24. The compound of any one of claims 1-21, wherein X^z is betaHomoLys or MethylbetaHomoLys.

25. The compound of any one of claims 1-21, wherein X^y and X^z are each a primary amino acid.

26. The compound of any one of claims 1-21, wherein X^y and X^z are each any amino acid listed under column X^y and column X^z respectively of Table 1B.

27. The compound of claim 1, being any one of compounds 1-397.

28. A pharmaceutical composition comprising the compound of any one of claims 1-27 along with the pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, formulated for oral delivery.

30. The pharmaceutical composition of claim 28, formulated for topical delivery.

31. The pharmaceutical composition of claim 28, formulated for parenteral delivery.

32. A method of treating inflammation or an autoimmune disease in a patient, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27.

33. The method of claim 32, wherein the inflammation or an autoimmune disease is gastrointestinal.

34. A method for treating a condition in a patient associated with a biological function of an α4β7 integrin, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27.

35. The method of any one of claims 32 and 34, wherein the condition or disease is Inflammatory Bowel Disease (IBD), ulcerative colitis, Crohn's disease, Celiac disease (nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis, radiotherapy, chemotherapy, pouchitis resulting after proctocolectomy and ileoanal anastomosis, gastrointestinal cancer, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, primary sclerosing cholangitis, human immunodeficiency virus (HIV) infection in the GI tract, eosinophilic asthma, eosinophilic esophagitis, gastritis, colitis, microscopic colitis, graft versus host disease, colitis associated with radio- or chemo-therapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, chronic granulomatous disease, glycogen storage disease type 1b, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Wiskott-Aldrich Syndrome, or pouchitis resulting after proctocolectomy and ileoanal anastomosis and various forms of gastrointestinal cancer, osteoporosis, arthritis, multiple sclerosis, chronic pain, weight gain, and depression. In another embodiment, the condition is pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma or graft versus host disease.

36. The method of claim 35, wherein the condition is an inflammatory bowel disease.

37. The method of claim 36, wherein the inflammatory bowel disease is ulcerative colitis.

38. The method of claim 36, wherein the inflammatory bowel disease is Crohn's disease.

39. A method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27, wherein the disease or condition is a local or systemic infection of a virus or retrovirus.

40. The method of claim 39, wherein the a virus or retrovirus is echovirus 1 and 8, echovirus 9/Barty Strain, human papilloma viruses, hantaviruses, rotaviruses, adenoviruses, foot and mouth disease virus, coxsackievirus A9, human parechovirus 1 or human immunodeficiency virus type 1.

41. A method for treating a disease or condition in a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-27, wherein the hepatitis A, B or C, hepatic encephalopathy, non-alcoholic steatohepatitis, cirrhosis, variceal bleeding, hemochromatosis, Wilson disease, tyrosinemia, alpha-1-antitrypsin deficiency, glycogen storage disease, hepatocellular carcinoma, liver cancer, primary biliary cholangitis, primary sclerosing cholangitis, primary biliary sclerosis, biliary tract disease, autoimmune hepatitis, or graft-versus-host disease.

42. The method of any one of claims 31-41, wherein the compound inhibits binding of α4β7 integrin to MAdCAM.

43. The method of claim 42, wherein the compound selectively inhibits binding of α4β7 integrin to MAdCAM.

44. The method of any one of claims 31-43, wherein the patient is a human.

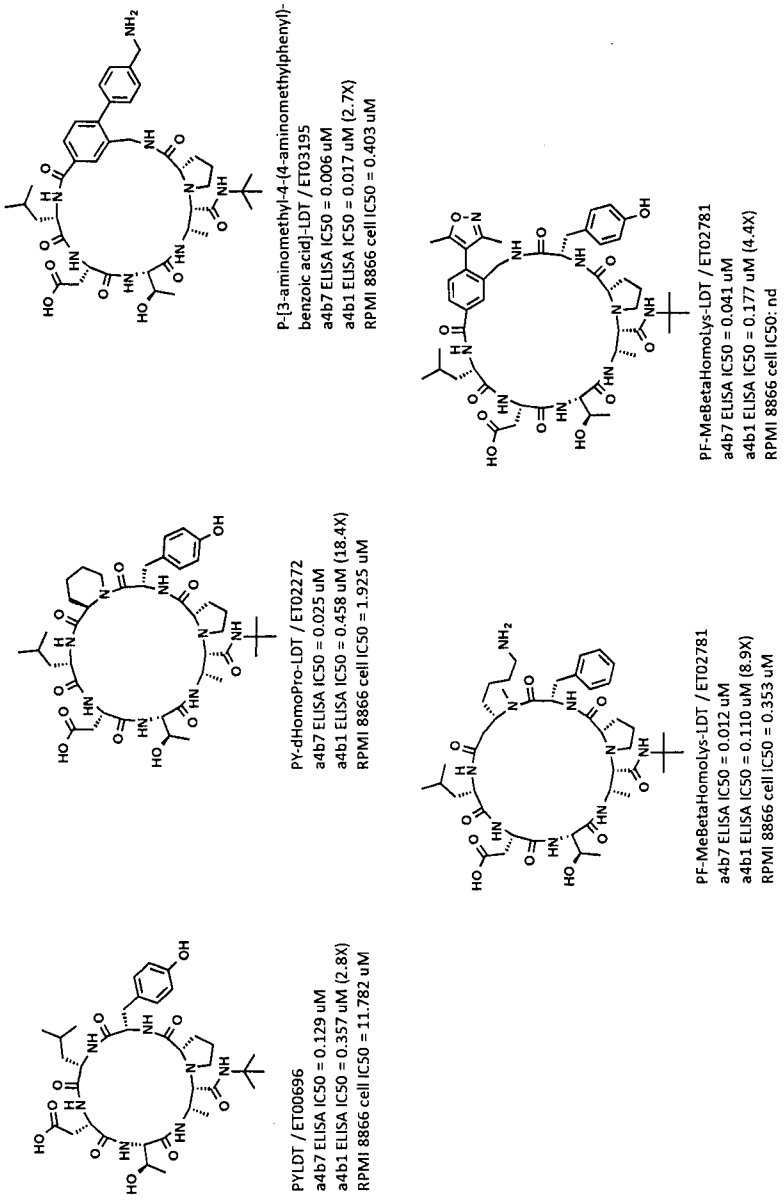

P-[3-aminomethyl-4-(4-aminomethylphenyl)-benzoic acid]-LDT / ET03195
a4b7 ELISA IC50 = 0.006 uM
a4b1 ELISA IC50 = 0.017 uM (2.7X)
RPMI 8866 cell IC50 = 0.403 uM
PF-MeBetaHomolys-LDT / ET02781
a4b7 ELISA IC50 = 0.041 uM
a4b1 ELISA IC50 = 0.177 uM (4.4X)
RPMI 8866 cell IC50: nd
PY-dHomoPro-LDT / ET02272
a4b7 ELISA IC50 = 0.025 uM
a4b1 ELISA IC50 = 0.458 uM (18.4X)
RPMI 8866 cell IC50 = 1.925 uM
PF-MeBetaHomolys-LDT / ET02781
a4b7 ELISA IC50 = 0.012 uM
a4b1 ELISA IC50 = 0.110 uM (8.9X)
RPMI 8866 cell IC50 = 0.353 uM
PYLDT / ET00696
a4b7 ELISA IC50 = 0.129 uM
a4b1 ELISA IC50 = 0.357 uM (2.8X)
RPMI 8866 cell IC50 = 11.782 uM

Figure 1

Leu	a4b7 IC50 (uM)
Cha	0.375
vinyl-Br-Leu	0.609
Nle	0.785
HomoLeu	1.703
cyclopropylAla	3.025
CF3-(d/l)Leu	3.358
Nle	3.668
(d/l)Leu	3.615
Cha	3.896
Phe	30.00
Trp	40.00

Asp	a4b7 IC50 (uM)
Asp(alcohol)	27.726
Asp(OBn)	40
Asp(OEt)	50 (27 cell)

Thr	a4b7 IC50 (uM)
Ile	0.026
Thr(OBn)	0.036
Thr(OEt)	0.042
Thr(OMe)	0.063
Pen	0.113
Val	0.109
dCys-Me ether	0.262
cyclohexylGly	0.389
allo-Ile	0.475
Cys	1.00
Cys(Acm)	1.00
thio-dPro	1.00
*t*Bu-Gly	1.088
Asn	4.00
Gln	15
His	45.3
2-aza-dPhe	56.6

PYLDT / ET00696

a4b7 ELISA IC50 = 0.129 uM

a4b1 ELISA IC50 = 0.357 uM (2.8X)

RPMI 8866 cell IC50 = 11.782 uM

"Tyr"	a4b7 IC50 (uM)
Met	0.005
Tyr(O-allyl)	0.009
CycloLeu	0.011
Aic	0.016
Pro	0.019
dTiq	0.021
dTic	0.022
dArg	0.023
1Nal	0.026
4-aza-dPhe	0.03
dHomoPro	0.03
3-aza-dPhe	0.04
4-amino-dPhe	0.035
Orn(ethylCarb)	0.04
dTyr(O-allyl)	0.036
Orn(Ac)	0.039
2Nal	0.04
Phe	0.042
dTrp	0.046
dTyr(O-Bn)	0.05
Trp	0.051
4-aminoMe-dPhe	0.052
benzthiophenhyl-dAla	0.053
Lys	0.053
2-thiophen-yl-dAla	0.054
L-Disc	0.057
Tyr(4-CO2H diaryl ether)	0.057
Met-sulfoxide	0.243
P-Cit-LDT	0.825
Dab	0.873
Gly	0.963
Ser(OBn)	0.995
Tic	1.05
Asn	1.078
Glu	1.496
Asp	3.832
D-Disc	3.664
Asp-acyl-methanesulfonamide	6.935

Figure 2

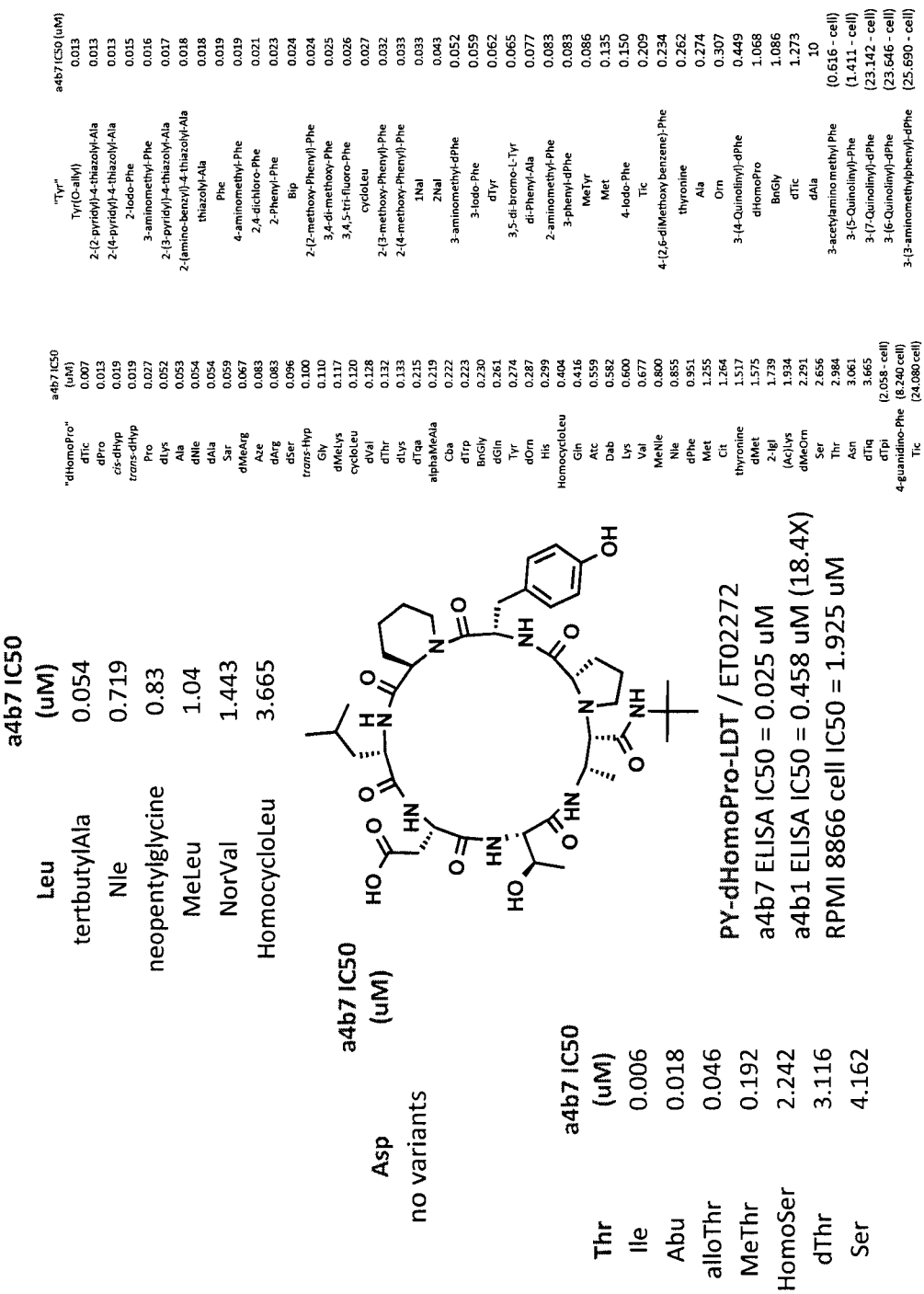

Leu
a4b7 IC50 (uM)
tertbutylAla 0.054
Nle 0.719
neopentylglycine 0.83
MeLeu 1.04
NorVal 1.443
HomocycloLeu 3.665
Asp
no variants
a4b7 IC50 (uM)
Thr 0.006
Ile 0.018
Abu 0.046
alloThr 0.192
MeThr 2.242
HomoSer 3.116
dThr 4.162
Ser
a4b7 IC50 (uM)
"dHomoPro" 0.007
dTic 0.013
dPro 0.019
cis-dHyp 0.019
trans-dHyp 0.027
Pro 0.052
dLys 0.053
Ala 0.054
dNle 0.054
dAla 0.059
Sar 0.067
dMeArg 0.083
Aze 0.083
dArg 0.096
dSer 0.100
trans-Hyp 0.110
Gly 0.117
dMeLys 0.120
cycloLeu 0.128
dVal 0.132
dThr 0.133
dLys 0.215
dTqa 0.219
alphaMeAla 0.222
Cba 0.223
dTrp 0.230
BnGly 0.261
dGln 0.274
Tyr 0.287
dOrn 0.299
His 0.404
HomocycloLeu 0.416
Gln 0.559
Atc 0.582
Dab 0.600
Lys 0.677
Val 0.800
MeNle 0.855
Nle 0.951
dPhe 1.255
Met 1.264
Cit 1.517
thyronine 1.575
dMet 1.739
2-Igl 1.934
(Ac)Lys 2.291
dMeOrn 2.656
Ser 2.984
Thr 3.061
Asn 3.665
dTiq (2.058 - cell)
dTpi (8.240 cell)
4-guanidino-Phe (24.080 cell)
Tic
"Tyr" a4b7 IC50 (uM)
Tyr(O-allyl) 0.013
2-(2-pyridyl)-4-thiazolyl-Ala 0.013
2-(4-pyridyl)-4-thiazolyl-Ala 0.013
2-Iodo-Phe 0.015
3-aminomethyl-Phe 0.016
2-(3-pyridyl)-4-thiazolyl-Ala 0.017
2-(amino-benzyl)-4-thiazolyl-Ala 0.018
thiazolyl-Ala 0.018
Phe 0.019
4-aminomethyl-Phe 0.019
2,4-dichloro-Phe 0.021
2-Phenyl-Phe 0.023
Bip 0.024
2-(2-methoxy-Phenyl)-Phe 0.024
3,4-di-methoxy-Phe 0.025
3,4,5-tri-fluoro-Phe 0.026
cycloLeu 0.027
2-(3-methoxy-Phenyl)-Phe 0.032
2-(4-methoxy-Phenyl)-Phe 0.033
1Nal 0.033
2Nal 0.043
3-aminomethyl-dPhe 0.052
3-Iodo-Phe 0.059
dTyr 0.062
3,5-di-bromo-L-Tyr 0.065
di-Phenyl-Ala 0.077
2-aminomethyl-Phe 0.083
3-phenyl-dPhe 0.083
MeTyr 0.086
Met 0.135
4-Iodo-Phe 0.150
Tic 0.209
4-(2,6-diMethoxy benzene)-Phe 0.234
thyronine 0.262
Ala 0.274
Orn 0.307
3-(4-Quinolinyl)-dPhe 0.449
dHomoPro 1.068
BnGly 1.086
dTic 1.273
dAla 10
3-acetylamino methyl Phe (0.616 - cell)
3-(5-Quinolinyl)-Phe (1.411 - cell)
3-(7-Quinolinyl)-dPhe (23.142 - cell)
3-(6-Quinolinyl)-dPhe (23.646 - cell)
3-(3-aminomethylphenyl)-dPhe (25.690 - cell)
PY-dHomoPro-LDT / ET02272
a4b7 ELISA IC50 = 0.025 uM
a4b1 ELISA IC50 = 0.458 uM (18.4X)
RPMI 8866 cell IC50 = 1.925 uM

Figure 3

a4b7 IC50 (uM)
Leu
tertbutylAla 0.048
3-aminomethyl benzoic acid 7.630
MeLeu 7.904
a4b7 IC50 (uM)
Asp
MeAsp 3.746
Asp(ethyl ester) (8.277 - cell)
3-aminomethyl-4-(4-aminomethylphenyl) -benzoic acid
a4b7 IC50 (uM)
Thr
Abu 0.020
Thr(O-Bn) 0.024
alloThr 0.031
MeThr 0.231
a4b7 IC50 (uM)
~ 50 variants
0.009 – 10.0 uM IC50s
P-[3-aminomethyl-4-(4-aminomethylphenyl)-benzoic acid]-LDT / ET03195
a4b7 ELISA IC50 = 0.006 uM
a4b1 ELISA IC50 = 0.017 uM (2.7X)
RPMI 8866 cell IC50 = 0.403 uM

Figure 4

Asp
Asp-reduced amide
Glu
a4b7 IC50 (uM)
2.251
(47.25 - cell)
Leu
Leu-reduced amide
neopentylGly
Phe
a4b7 IC50 (uM)
2.009
(1.310 cell)
(47.25 - cell)
Thr
Ile
alloThr
Val
Thr(OBn)
alloIle
betaHomoIsoLeu
a4b7 IC50 (uM)
0.015
0.017
0.024
0.043
0.046
2.933
Phe
MeBetaHomoLys
betaHomoLys
MebetaHomoLys(Me)2
BetaHomoIsoLeu
betaHomoPro
dBetaHomoPro
dbetaHomoLys
Aze
betaHomoThr
betaHomoNle
dBetaHomoPro
anthranilic acid
PF-Nip-LDT
cis-2-aminocyclohexanecarboxylic acid
betahomoAla
(1S,2R)-2-aminocyclohexane carboxylic acid
betaAla
trans-2-aminocyclohexanecarboxylic acid
PY-propionimide-LDT
dBetaHomoPhe
dLys
(1R,2R)-2-aminocyclohexanecarboxylic acid
3-aminomethyl-phenylacetic acid
dMebetaHomoLys
MebetahomoLys(Ac)
a4b7 IC50 (uM)
0.002
0.017
0.034
0.034
0.058
0.061
0.065
0.092
0.110
0.120
0.158
0.215
0.276
0.278
0.297
0.300
0.412
0.576
0.829
1.135
1.579
1.973
2.281
(0.784 - cell)
PF-MeBetaHomoLys-LDT / ET02781
a4b7 ELISA IC50 = 0.012 uM
a4b1 ELISA IC50 = 0.110 uM (8.9X)
RPMI 8866 cell IC50 = 0.353 uM

Figure 5

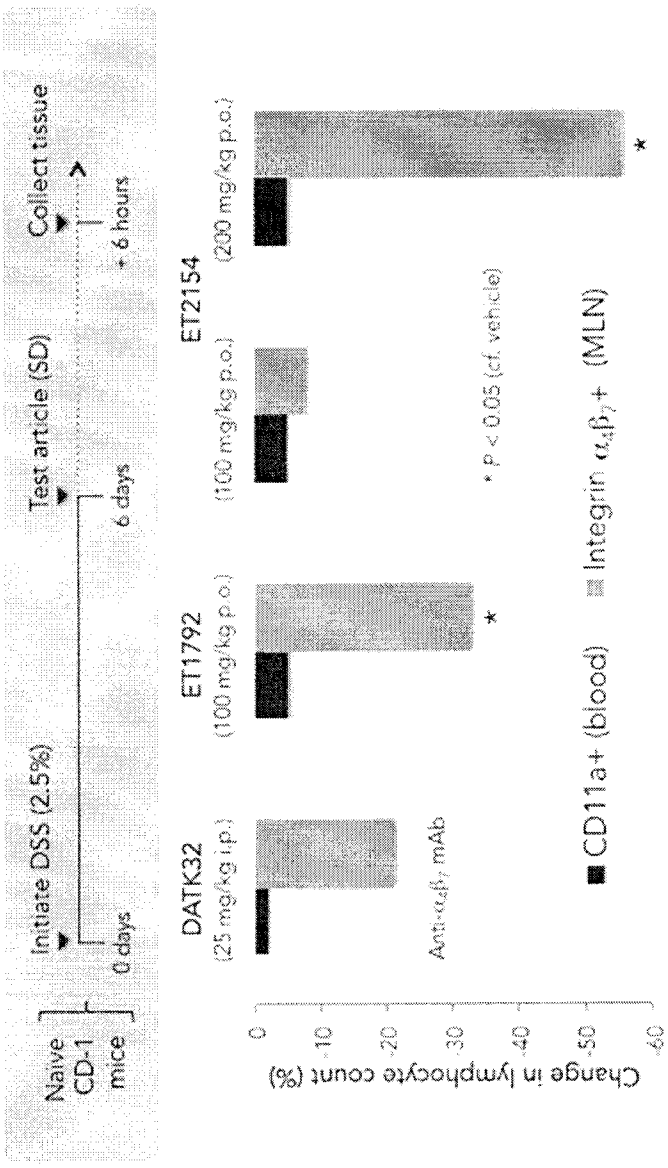
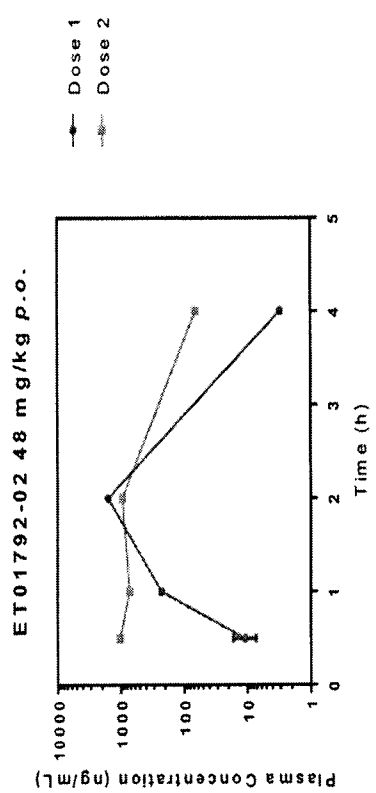

Naive CD-1 mice
Initiate DSS (2.5%)
0 days
Test article (SD)
6 days
Collect tissue
+ 6 hours
DATK32
(25 mg/kg i.p.)
ET1792
(100 mg/kg p.o.)
ET2154
(100 mg/kg p.o.)
(200 mg/kg p.o.)
Anti-α4β7 mAb
* p < 0.05 (cf. vehicle)
CD11a+ (blood)
Integrin α4β7+ (MLN)
Change in lymphocyte count (%)
0
10
20
30
40
50
60

Figure 6



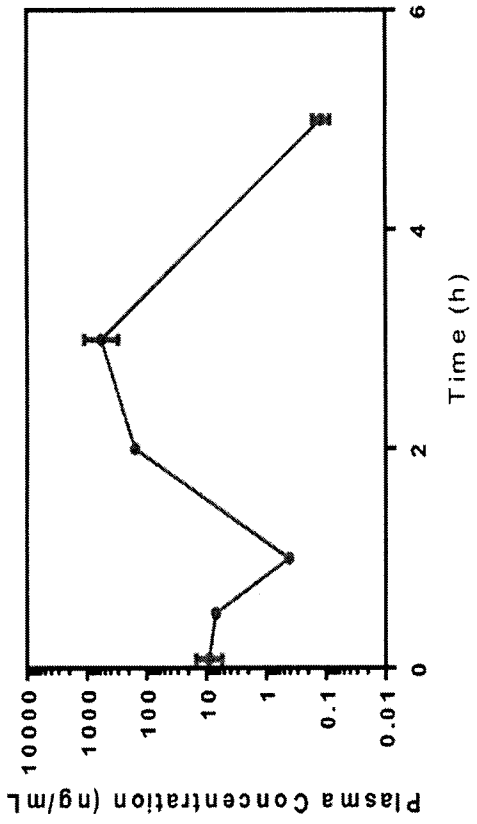
Summary of PK Parameters for ET01792-02

Parameter	Unit	Estimate	
		First dase	Second dose
t_{max}	h	2.00	0.500
C_{max}	ng/mL	1587	1026
Apparent $t_{1/2}$	h	nc	nc
$AUC_{0\text{-}tlast}$	h*ng/mL	1475	2188
$AUC_{0\text{-}inf}$	h*ng/mL	nc	nc
$MRT_{0\text{-}tlast}$	h	1.99	1.59

nc denotes not calculable as a clear terminal elimination phase was not observed.

t_{max} time at which maximum concentration is observed
C_{max} maximum observed concentration
Apparent $t_{1/2}$ apparent terminal half-life
$AUC_{0\text{-}tlast}$ area under the concentration *vs* time curve from time 0 to the time of the la
$AUC_{0\text{-}inf}$ area under the concentration *vs* time curve from time 0 to infinity
$MRT_{0\text{-}tlast}$ mean residence time from time zero to the time of the last measurable conc

Figure 7



Summary of PK Parameters for ET01792-03

Parameter	Unit	Estimate
t_{max}	h	3.00
C_{max}	ng/mL	581
Apparent $t_{1/2}$	h	nc
$AUC_{0\text{-tlast}}$	h*ng/mL	589
$AUC_{0\text{-inf}}$	h*ng/mL	nc
$MRT_{0\text{-tlast}}$	h	2.77

Figure 8

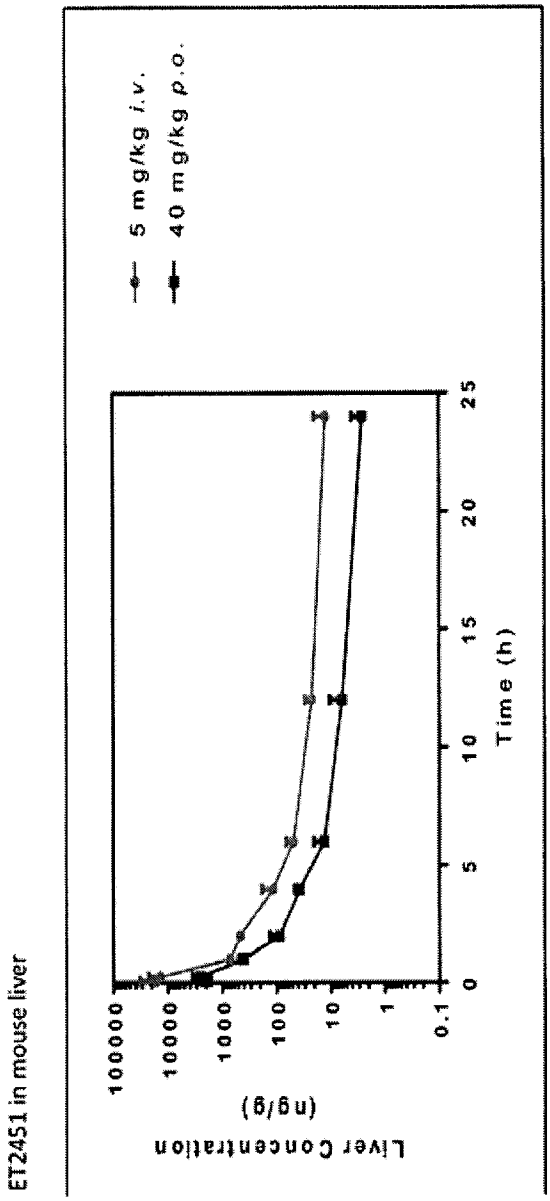

ET2451 in mouse liver
Liver Concentration (ng/g)
100000
10000
1000
100
10
1
0.1
0
5
10
15
20
25
Time (h)
5 mg/kg i.v.
40 mg/kg p.o.

Figure 9

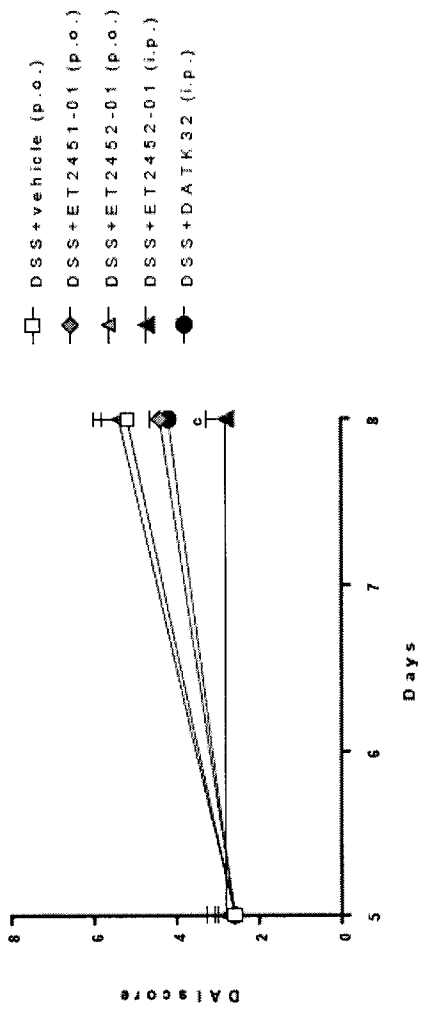
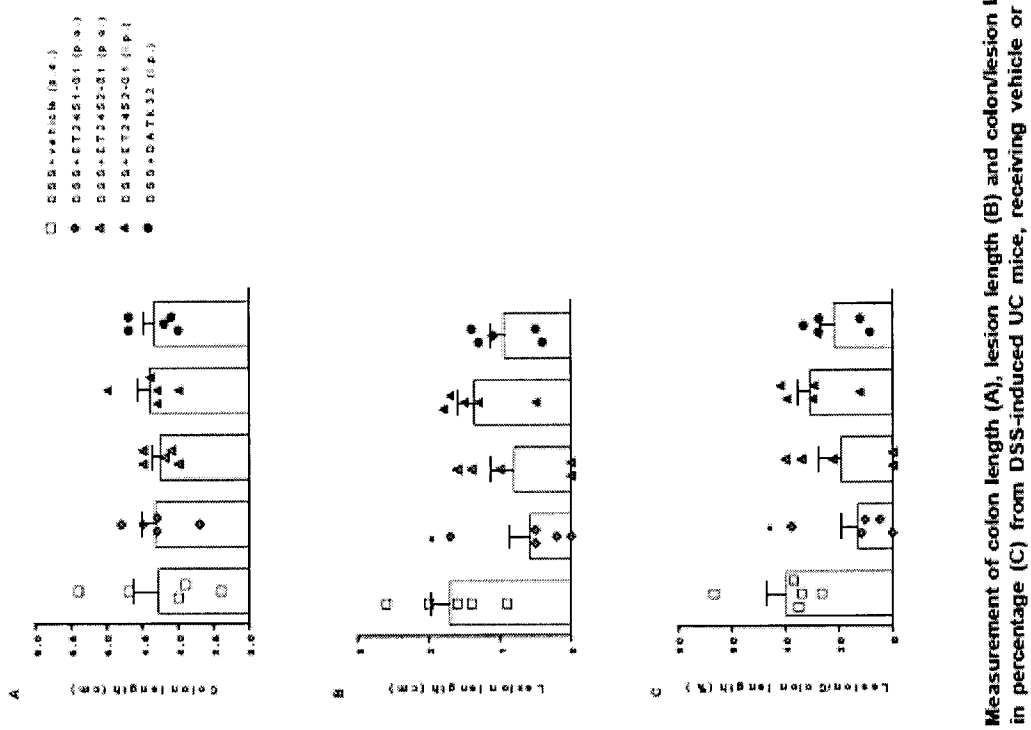
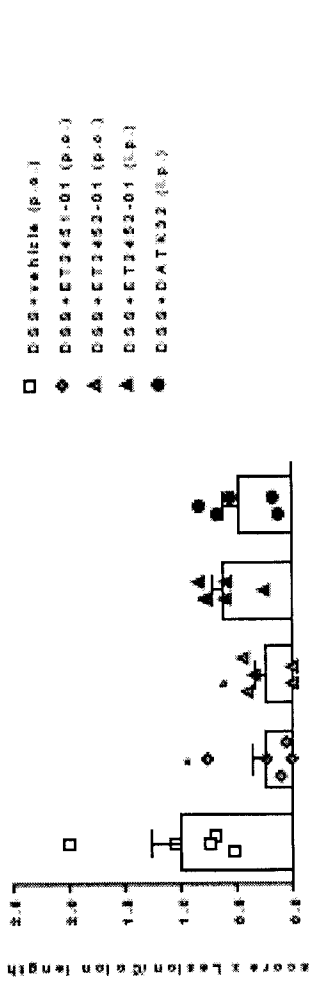

DSS+vehicle (p.o.)
DSS+ET2451-01 (p.o.)
DSS+ET2452-01 (p.o.)
DSS+ET2452-01 (i.p.)
DSS+DATK32 (i.p.)
DAI score
Days
0
2
4
6
8
5
6
7
8
c

Figure 10



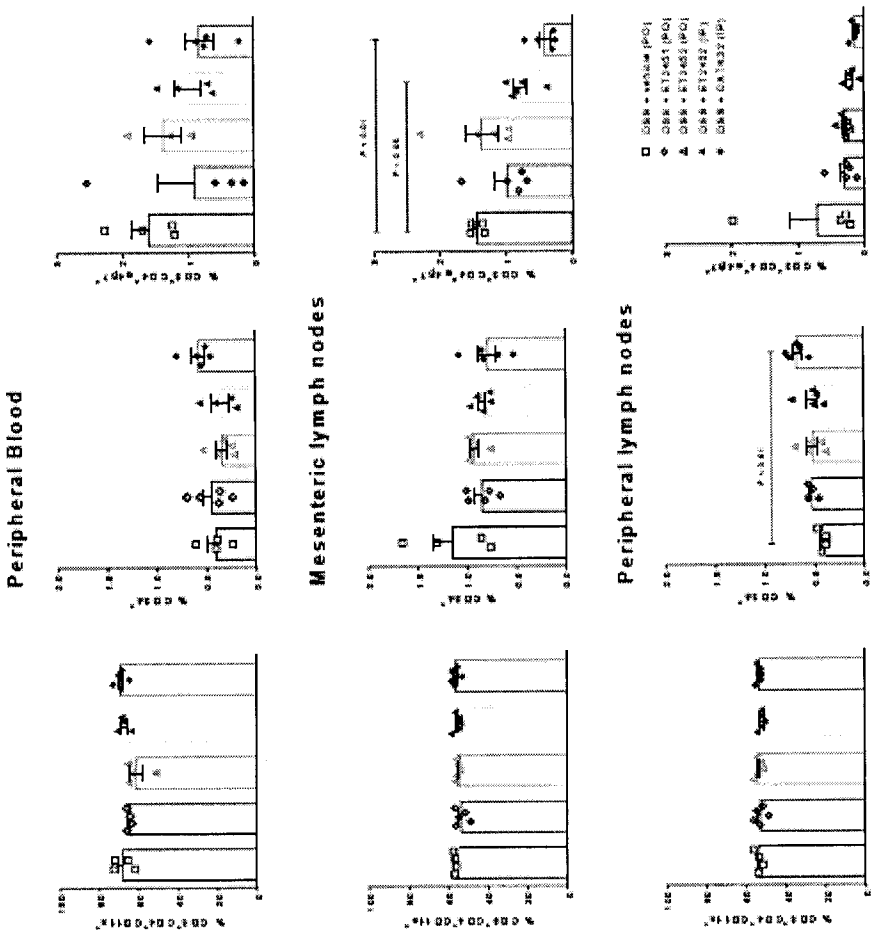
Measurement of colon length (A), lesion length (B) and colon/lesion length ratio in percentage (C) from DSS-induced UC mice, receiving vehicle or treatments either by oral or i.p. route.

Figure 11



Macroscopic inflammation score x colon/lesion length ratio calculated for the different groups of DSS-induced UC mice, receiving vehicle or treatments either by oral or i.p. route.

Figure 12



Percentage of different cell populations in peripheral blood, mesenteric lymph nodes or peripheral lymph nodes in DSS-induced UC mice receiving vehicle, nacellins or anti-α4β7 (DATK32)

Figure 13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2016/000274

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07K 7/06*** (2006.01) , ***A61K 38/08*** (2006.01) , ***A61P 1/00*** (2006.01) , ***A61P 29/00*** (2006.01) , ***A61P 37/06*** (2006.01) , ***C07K 14/705*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K 7/06 (2006.01) , ***A61K 38/08*** (2006.01) , ***A61P 1/00*** (2006.01) , ***A61P 29/00*** (2006.01) , ***A61P 37/06*** (2006.01) , ***C07K 14/705*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Electronic databases: Questel Orbit, Google Patents, Canadian Patent Database, Pubmed-NCBI, and STN.
Search Terms: cyclic peptide, alph 4 beta 7, antagonist, inhibitor, and MAdCAM.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/0193465 A1 (BHANDARI et al.) 10 July 2014 (10-07-2014)	1-44

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report 19 December 2016 (19-12-2016)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Joel Karwatsky (819) 576-2121

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2016/000274

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claim Nos.: 32-44
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 32-44 are directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under PCT Rule 39.1(iv). However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claims 1-27.

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2016/000274

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2014193465A1	10 July 2014 (10-07-2014)	US2014193465A1	10 July 2014 (10-07-2014)
		AU2013329135A1	30 April 2015 (30-04-2015)
		AU2014248321A1	29 October 2015 (29-10-2015)
		CA2888479A1	17 April 2014 (17-04-2014)
		CA2908593A1	09 October 2014 (09-10-2014)
		CN105102470A	25 November 2015 (25-11-2015)
		CN105339383A	17 February 2016 (17-02-2016)
		EP2906584A1	19 August 2015 (19-08-2015)
		EP2906584A4	15 June 2016 (15-06-2016)
		EP2981544A1	10 February 2016 (10-02-2016)
		EP2981544A4	07 December 2016 (07-12-2016)
		HK1213583A1	08 July 2016 (08-07-2016)
		IN3039DEN2015A	02 October 2015 (02-10-2015)
		JP2015533833A	26 November 2015 (26-11-2015)
		JP2016518351A	23 June 2016 (23-06-2016)
		KR20150084808A	22 July 2015 (22-07-2015)
		KR20160011625A	01 February 2016 (01-02-2016)
		SG11201502812WA	28 May 2015 (28-05-2015)
		SG11201508178UA	27 November 2015 (27-11-2015)
		US2014193465A1	10 July 2014 (10-07-2014)
		US9273093B2	01 March 2016 (01-03-2016)
		US2014294901A1	02 October 2014 (02-10-2014)
		WO2014165448A1	09 October 2014 (09-10-2014)
		WO2014059213A1	17 April 2014 (17-04-2014)