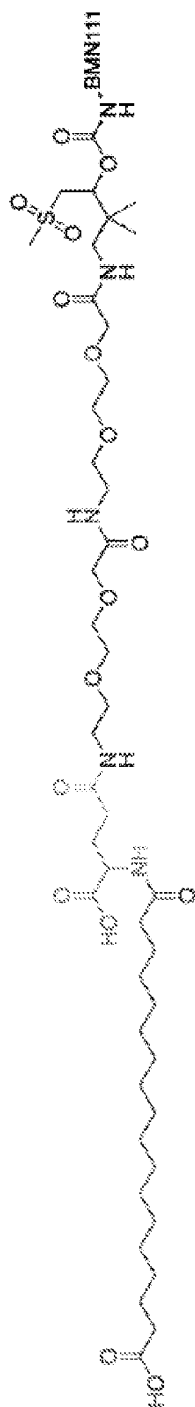


Figure 1

CNP conjugate with lipid moiety, glutamic acid, spacer, and electronic linker



CNP conjugate with lipid moiety, glutamic acid, spacer, and peptoid linker

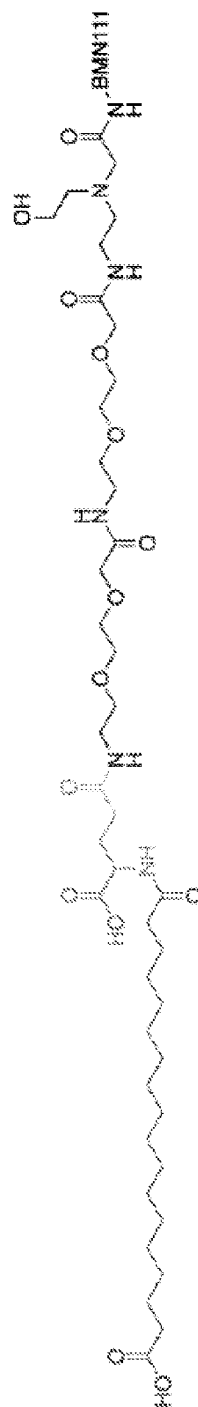


Figure 2A

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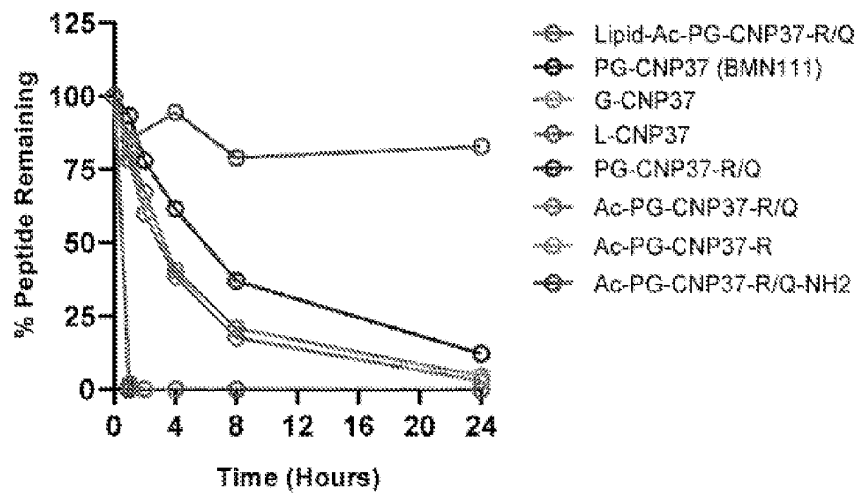
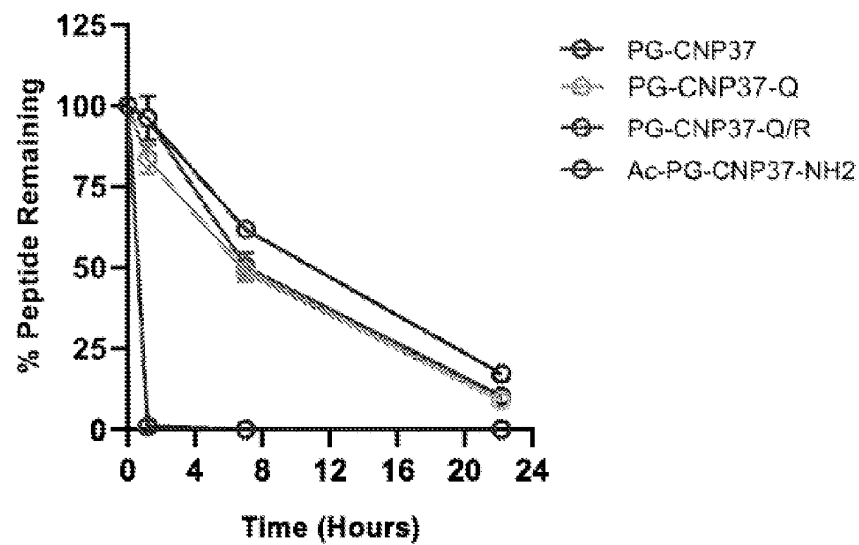


Figure 2B



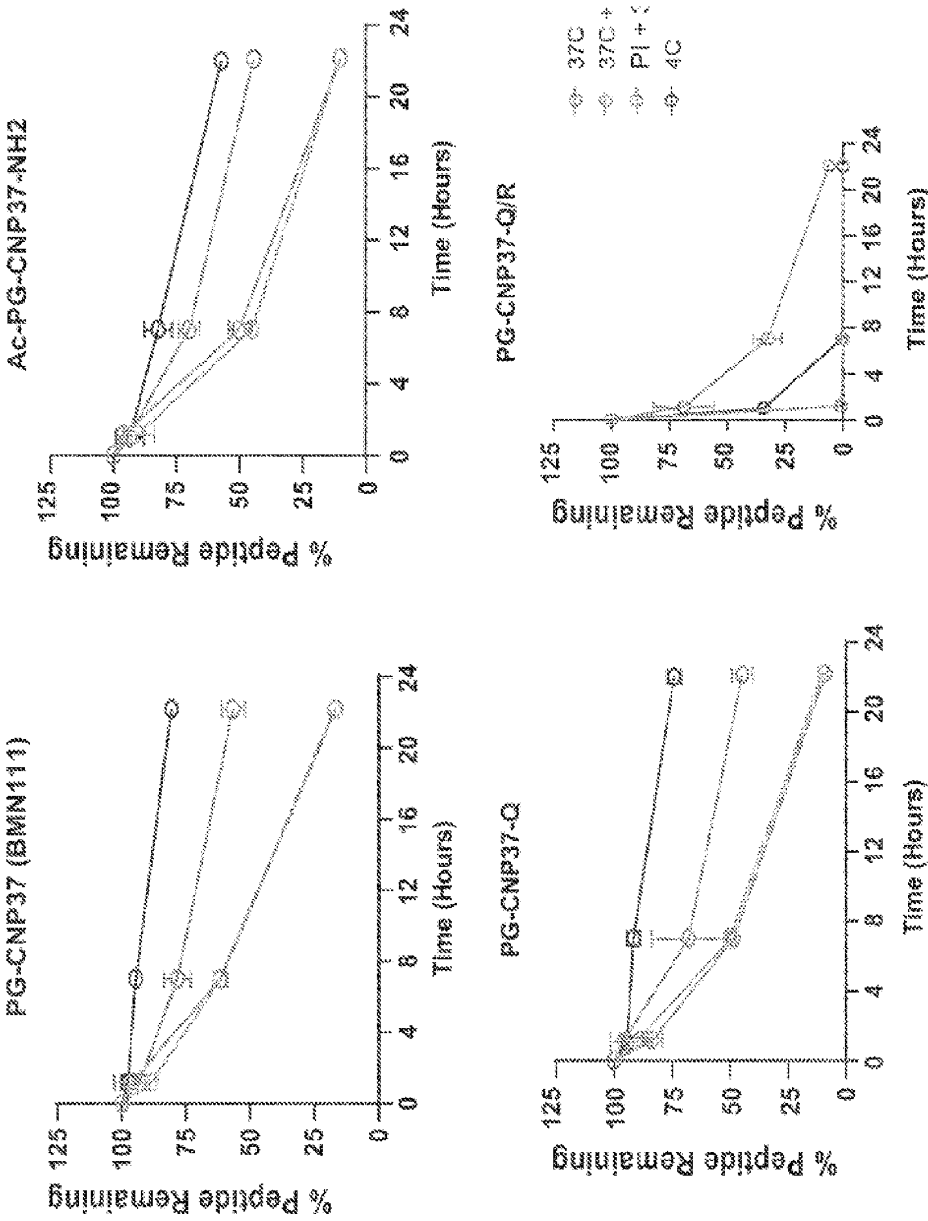


Figure 3

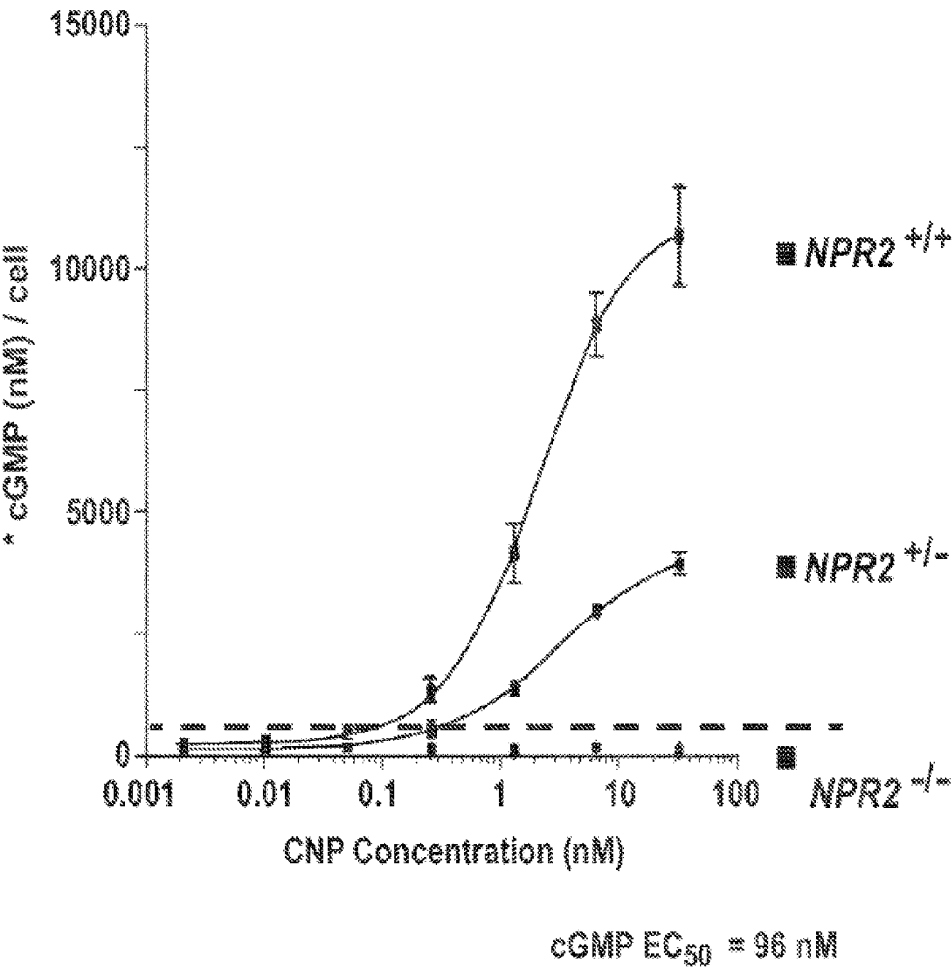


Figure 4

NPR2 Clone, nucleotide sequence

Clone 47, Allele I (SEQ ID NO: 57):

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCCGGGGGCACG
GMCCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTGGGCCTGGCCACGGGTGG
GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGCACTGCCCGTGGACCTGCGGTTTGTACG
TCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCCTGCGCGCTGTGGATCTCMGCTGTACCAT
GACCCCGACCTTCTGTTGGGCCCTGGTTGTGTACCCTGCTGCCTCTGTGGCTCGCTTTGCCCTGCACTG
GCACCTTCCCTCCTGACTGCGGGTGCACTGGCCTCTGGCTTTGCAGCTMGMTGAGCATTATCGTACC
CTGGTTGCACTGGCCCTCTGCGCCCMGCTGGGTGAGTTGCTAGTGACATTACACGGGCACCTTCMTT
GGACTGCTCGGGCTGCTTTGCTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTCACCATCGA
GGGGGTGTTTGAAGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACCAGGTGTATACCCGAGAGCCAG
GTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

Clone 35, Allele I (SEQ ID NO: 58):

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCCGGGGGCACG
GMCCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTGGGCCTGGCCACGGGTGG
GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGCACTGCCCGTGGACCTGCGGTTTGTACG
TCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCCTGCGCGCTGTGGATCTCMGCTGTACCAT
GACCCCGACCTTCTGTTGGGCCCTGGTTGTGTACCCTGCTGCCTCTGTGGCTCGCTTTGCCCTGCACTG
GCACCTTCCCTCCTGACTGCGGGTGCACTGGCCTCTGGCTTTGCAGCTMGMTGAGCATTATCGTACC
CTGGTTGCACTGGCCCTCTGCGCCCMGCTGGGTGAGTTGCTAGTGACATTACACGGGCACCTTCMTT
GGACTGCTCGGGCTGCTTTGCTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTCACCATCGA
GGGGGTGTTTGAAGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACCAGGTGTATACCCGAGAGCCAG
GTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

Clone 35, Allele 2 (SEQ ID NO: 59):

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCCGGGGGCACG
GMCCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTGGGCCTGGCCACGGGTGG
GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGCACTGCCCGTGGACCTGCGGTTTGTACG
TCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCCTGCGCGCTGTGGATCTCMGCTGTACCAT
GACCCCGACCTTCTGTTGGGCCCTGGTTGTGTACCCTGCTGCCTCTGTGGCTCGCTTTGCCCTGCACTG
GCACCTTCCCTCCTGACTGCGGGTGCACTGGCCTCTGGCTTTGCAGCTMGMTGAGCATTATCGTACC
CTGGTTGCACTGGCCCTCTGCGCCCMGCTGGGTGAGTTGCTAGTGACATTACACGGGCACCTTCACA
ATTGGAAGTCTCGGGCTGCTTTGCTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTCACCAT
CGAGGGGGTGTGTTGAAGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACCAGGTGTATACCCGAGAGC
CAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

Clone 47, Allele I (SEQ ID NO: 60)

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCCGGGGGCACG
GMCCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTGGGCCTGGCCACGGGTGG

Figure 5 (cont'd)

GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCACTGCCCCTGGACCTGCGGTTTGTACAGC
TCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCCTGCGCGCTGTGGATCTCAAGCTGTACCAT
GACCCCGACCTTCTGTTGGGCCCTGGTTGTGTGTACCCTGTGCCTCTGTGGCTCGCTTTGCCTCGCACTG
GCACCTTCCCCTCCTGACTGCGGGTGCAGTGGCCTCTGGCTTTGCAGCTMGMTGAGCATTATCGTACC
CTGGTTCGCACTGGCCCCCTGCGCCCCMGCTGGGTGAGTTCGTAGTGACATTACACGGGCACTTCMTT
GGACTGCTCGGGCTGCTTTGCTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTCACCATC G
AGGGGGTGTGTTGAGGCCCTGCAGGGCAGCAACCTCAGTGTGCAACACCAGGTGTATACCCGAGAGCCA
GGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

Clone 47, Allele 2(SEQ ID NO: 61):

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCCTCCTCCGGGGGCACG
GMCCTGACGCTGGCGGTGGTGTGCCAGMCACAACCTGAGCTATGCCTGGGCCTGGCCACGGGTGG
GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCACTGCCCCTGGACCTGCGGTTTGTACAGC
TCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCAGGGGTGTTGAGGCCCTGCAGGGCAGCMC
CTCAGTGTGCAACACCAGGTGTATACCCGAGAGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGA
GCCAACGGGGCGCA

NPR2 Clone, predicted protein product sequence

Clone 47, Allele 1(SEQ ID NO: 62):

MALPSLLLVMLAGGVRPPGARNLTAWLPEHNLSYAWAWPRVGPVALAVEALGRALPVDLRFVS
SEL
DGACSEYLAPLRAVDLKLHYDPDLLLPGPCVYPMSVARFASHWHLPLLTAGAVASGFMKNEHYRTL
VRTG
PSAPKLGEFVVTLHGHNWTARMMLLYLDARTDDRPYFTIEGVFEALQGSNLSVQHQQVYTREPGGP
EQAT
HFIRANGRIVYICGPLEMLHEILLQAQRENLTNGDYVFFYLDVFGESLRAGPTRATGRPWQDNRTQEQAQA
L
REAFQTVLVITYREPPNPEYQEFQNRLLIRAREDFGVELAPSLMNLIAAGCFYDGILLYAQVLNETIQEGGTRE
D
GLRIVEKMQGRRYHGVTLGVVMDKNNRETDFVLWAMGDLESQDFQPMHYSGAEKQIWWTGRPI
PW VKGAPPLDNPPCAFDLDDPSCDKTPLSTLAIVALGTGITFIM FGVSSFLI FRKLM
LEKELASMLWRIRWEELQF
GNSDRYHKGAGSRLTSLRGSSYGSLMTAHGKYQIFANTGHFKGNWAIKHVNKKRIELTRQVLFELKHMR
D

Figure 5 continued

VQFNHLTRFIGACIDPPNICIVTEYCPRGSLQDILENDSINLDWMFRYSLINDLVKGMAFLHNSIISSHGSLKS
S
NCWDSRFVLKITDYGLASFRSTAEPDDSHALYAKKLWTAPELLSGNPLPTTGMQKADVYSFAILQEIALRS
G
PFYLEGLDLSPEIVQKVRNGQRPYFRPSIDRTLNEELVLLMERCWAQDPTERPDFGQIKGFIRRFNKEG
GT
SILDNLLLRMEQYANNLEKLVEERTQAYLEEKRAEALLYQILPHSVAEQKRGETVQAEAFDSVTIYFSDIV
GF TALSAESTPMQWTLLNDLYTCFDAIIDNFDVYKVETIG DAYMWSG LPGRNGQRHAPE
IARMALALLDAVSSFRIRHRPHDQLRLRIGVHTGPVCAGVVGKMPRYCLFGDTVNTASRMESNGQALKI
HVSSTTKDALDELGC FQLELRGDVEMKGKGMRTYWLLGERKGPPGLL*

Clone 35, Allele I (SEQ ID NO: 63):

MALPSLLLVMLAGGVRPPGARNLTLAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVDLRFVS
SEL
DGACSEYLAPLRAVDLKLHYDPDLLGPGCVYPMSVARFASHWHLPLLTAGAVASGFMKNEHYRTLVRTG
PSAPKLGEFVTLHGHNWTARMMLLYLDARTDDRPHYFTIEGVFEALQGSNLSVQHQVYTREPGGPEQAT

HFIRANGRIVYICGPLEMLHEILLQAQRENLTNGDYVFFYLDVFGESLRAGPTRATGRPWQDNRTQEQAQA
L
REAFQTVLVITYREPPNPEYQEFQNRLLIRAREDFGVELAPSLMNLIAAGCFYDGILLYAQVLNETIQEGGTRE
D
GLRIVEKMQGRRYHGVGTGLVVMCKNNRETDFVLWAMGDLESQDFQPMHYSGAEKQIWWTGRPI
PW VKGAPPLDNPPCAFDLDDPSCDKTPLSTLAIVALGTGITFIM FGVSSFLI FRKLM
LEKELASMLWRIRWEELQF
GNSDRYHKGAGSRLTSLRGSSYGSLMTAHGKYQIFANTGHFKGNWAIKHVNKKRIELTRQVLFELKHMR
D
VQFNHLTRFIGACIDPPNICIVTEYCPRGSLQDILENDSINLDWMFRYSLINDLVKGMAFLHNSIISSHGSLKS
S
NCWDSRFVLKITDYGLASFRSTAEPDDSHALYAKKLWTAPELLSGNPLPTTGMQKADVYSFAILQEIALRS
G
PFYLEGLDLSPEIVQKVRNGQRPYFRPSIDRTLNEELVLLMERCWAQDPTERPDFGQIKGFIRRFNKEG
GT
SILDNLLLRMEQYANNLEKLVEERTQAYLEEKRAEALLYQILPHSVAEQKRGETVQAEAFDSVTIYFSDIV
GF TALSAESTPMQWTLLNDLYTCFDAIIDNFDVYKVETIG DAYMWSG LPGRNGQRHAPE
IARMALALLDAVS
SFRIRHRPHDQLRLRIGVHTGPVCAGVVGKMPRYCLFGDTVNTASRMESNGQALKIHVSSTTKDALDEL
GC FQLELRGDVEMKGKGMRTYWLLGERKGPPGLL*

Figure 5 continued

Clone 35, Allele 2 (SEQ ID NO: 64):

MALPSLLLVMMLAGGVRPPGARNLTAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVDLRFVS
SEL
DGACSEYLAPLRAVDLKLYHDPDLLGPGCVYPMSVARFASHWHLPLLTAGAVASGFMKNEHYRTLVRTG
PSAPKLG EFVVTLHGHFTIGLLGLLCCIWM LAQMTGPTTSPSRGCLRPCRMTSVCNTRCI
PESQVALSKPPTS SEPTGALCISMRWRCFMRSCFRPRGRT*

Clone 47, Allele 1 (SEQ ID NO: 65):

MALPSLLLVMMLAGGVRPPGARNLTAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVDLRFVSSEL
DGACSEYLAPLRAVDLKLYHDPDLLGPGCVYPMSVARFASHWHLPLLTAGAVASGFMKNEHYRTLVRTG
PSAPKLGEFVVTLHGHFNWTARMLLYLDARTDDRPHYFTIRGGV*

Clone 47, Allele 2 (SEQ ID NO: 66):

MALPSLLLVMMLAGGVRPPGARNLTAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVDLRFVSSEL
DGACSEYLAPGCLRPCRMTSVCNTRCIPESQVALSKPPTSSEPTGALCISAARWRCFMRSCFRPRG RT*

Figure 6

Genetic Variants Found in NPR2 Genes

NPR2 Mutations			
G21R	P301S	QS00X	R74SQ
A48S	R318Q	HS0BD	R819C
A59T	R358W	G541S	T8611
V102A	E359A	A549T	V883M
R11OG	1364fs	R562Q	T907M
A164G	E389O	R601H	G917R
1226V	E415K	R601S	R921Q
Y250X	K480N	E609K	R957C
R263H	A488P	S721R	L1009V
T297M	1494S	E727Q	

Figure 7 cont'd

[illegible]

Figure 7 cont'd
Genetic variants found in the 5 Core genes

Constant variables found in the 5 Core questions

[illegible]

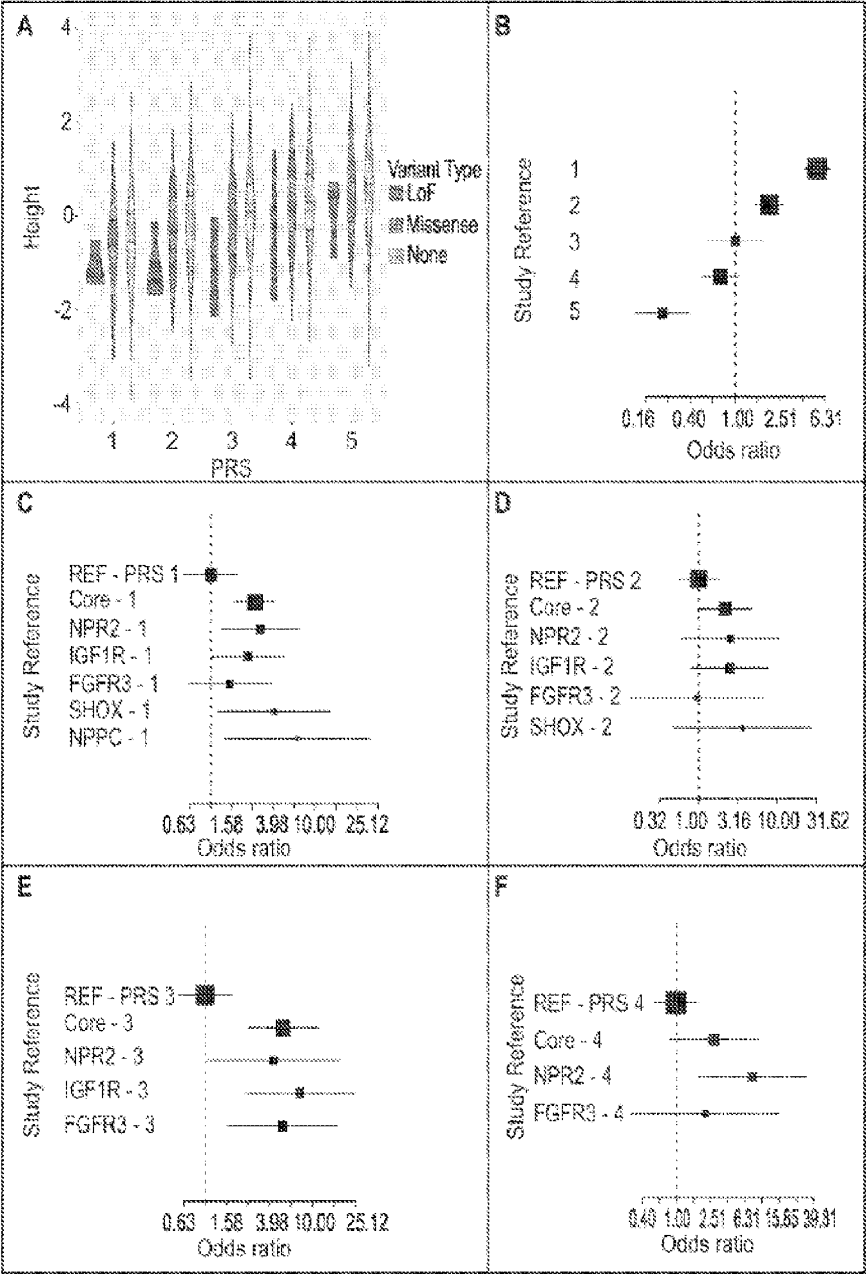
Figure 7 cont'd

Concomitant variables found in the 5 categories

[illegible]

Figure 7 cont'd

[illegible]



Figures 8A - 8F

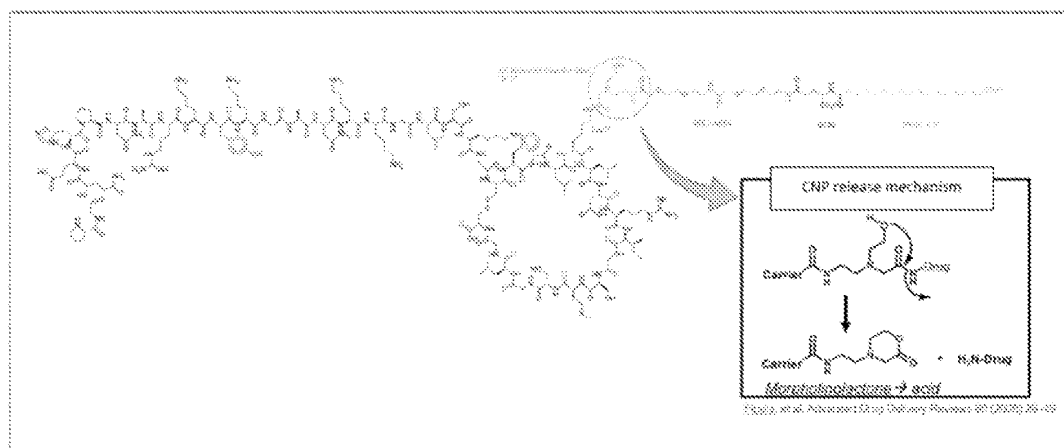
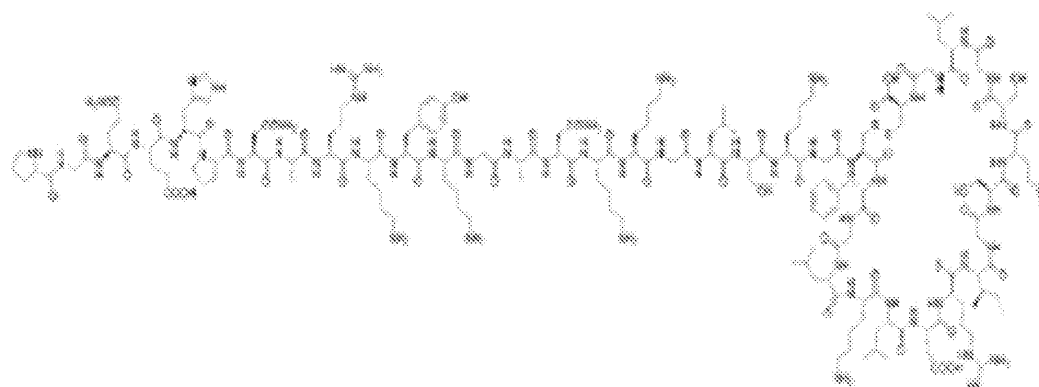
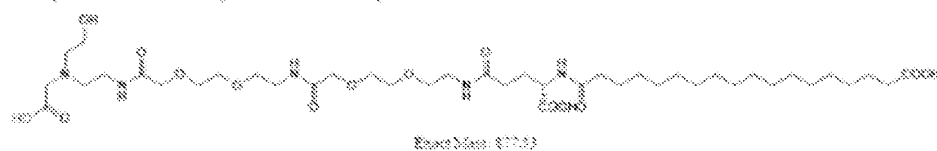


Figure 9



-B: Lipid + Linker (stable form)

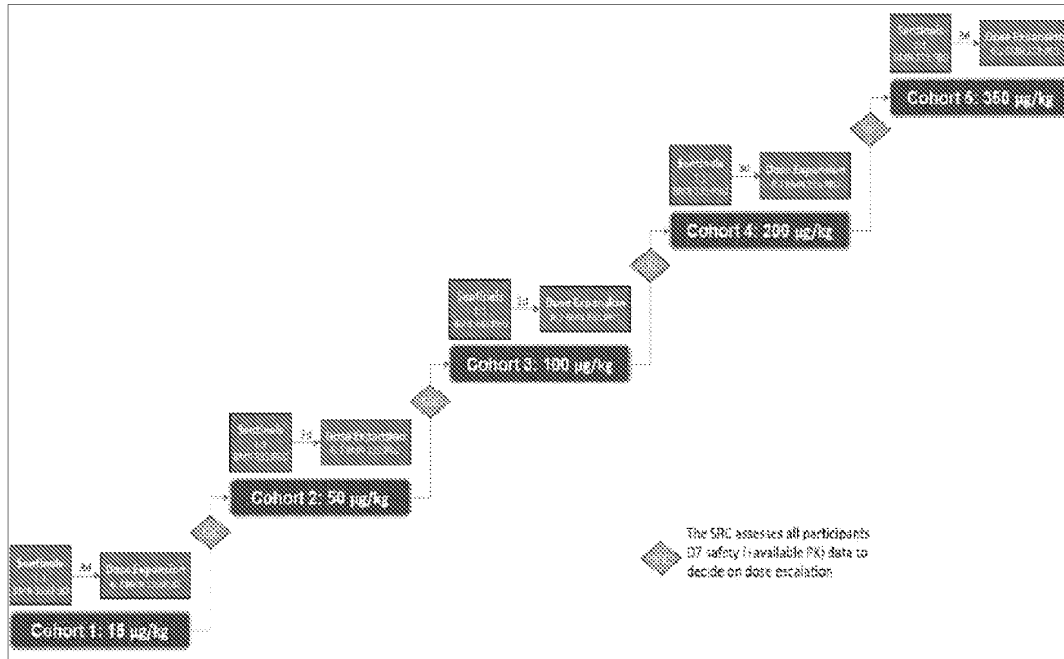


-C: BICIN linker



Figure 10

Figure 12



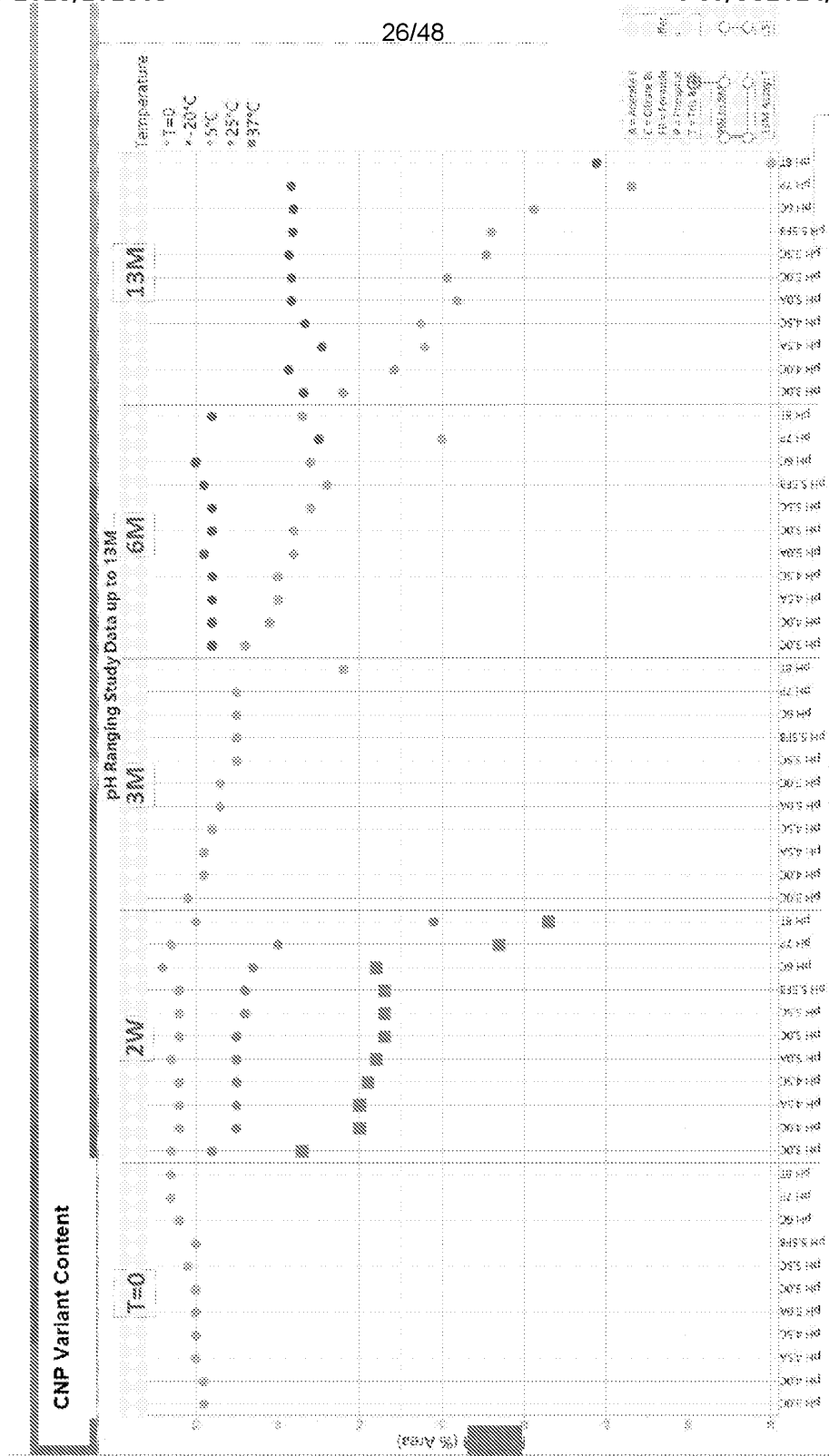


Figure 14

Figure 15

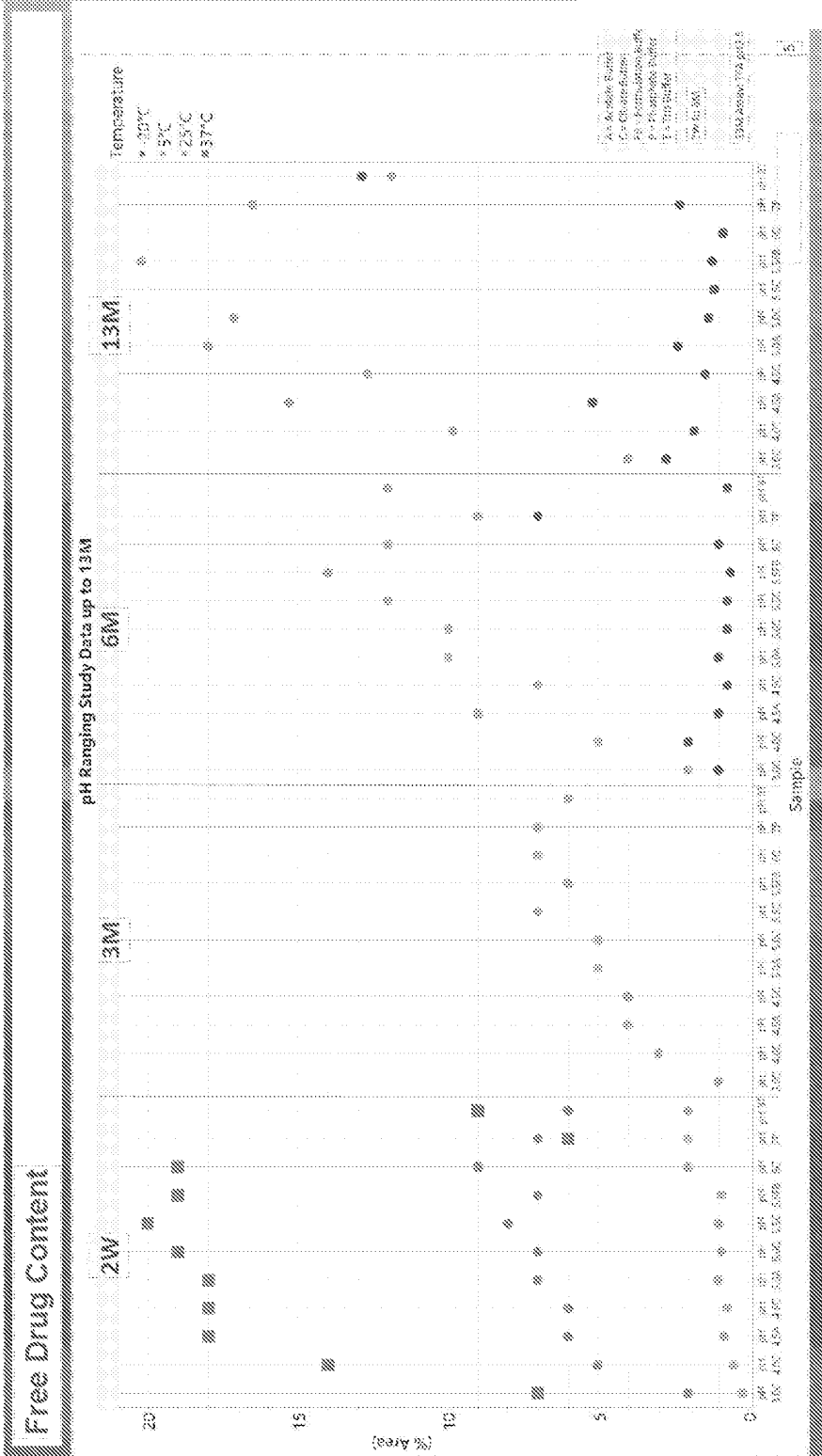


Figure 16

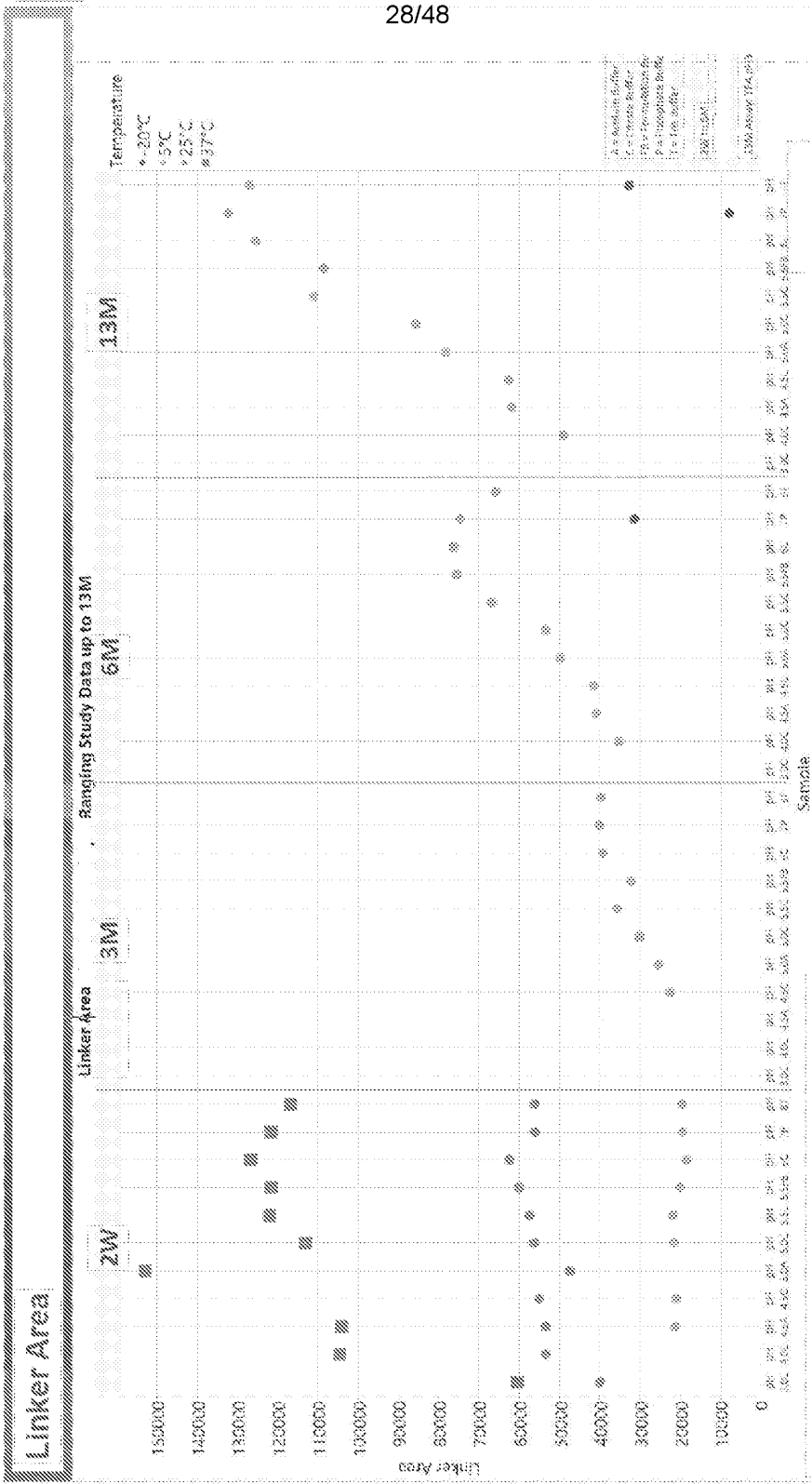


Figure 17

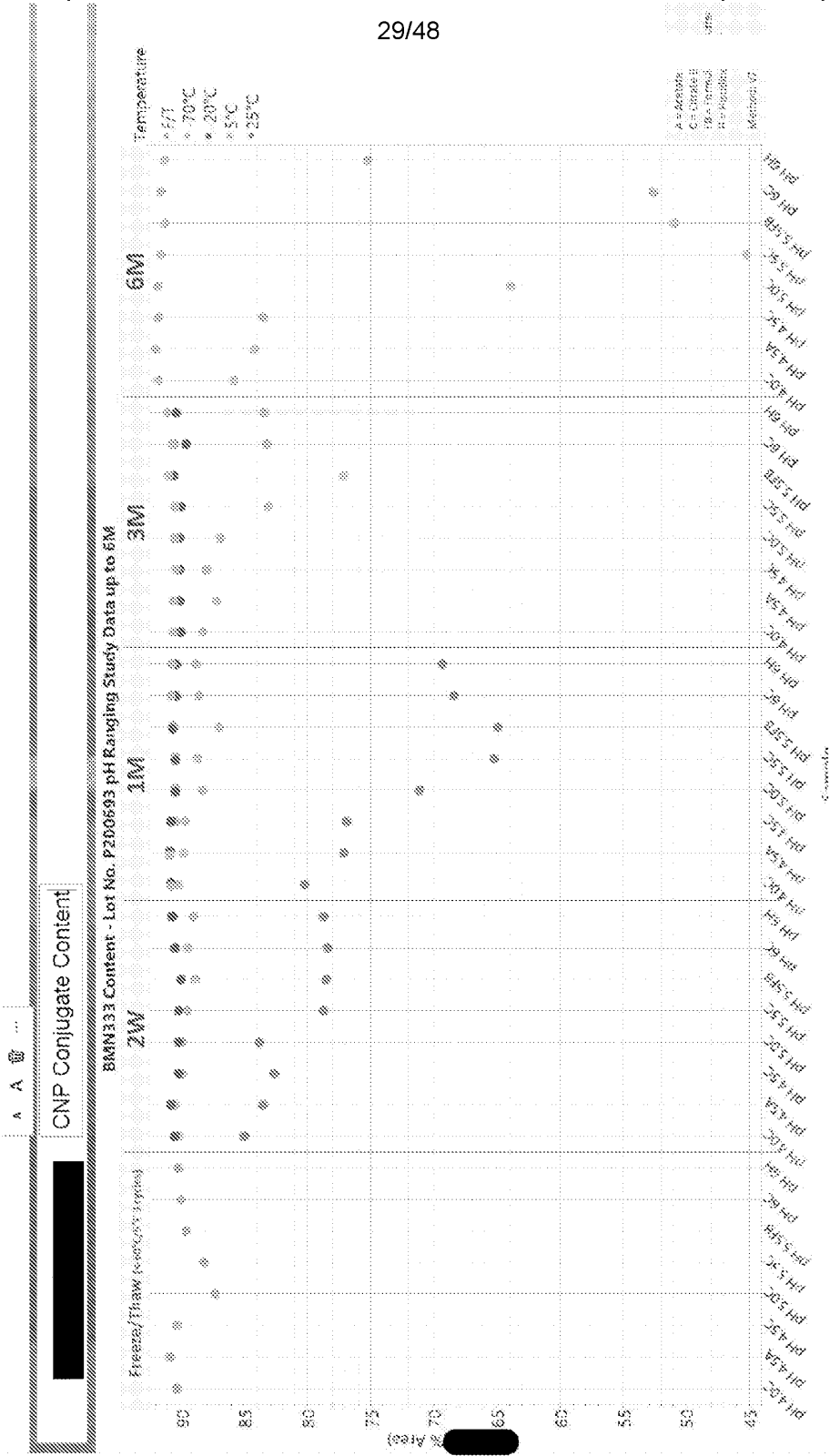


Figure 18

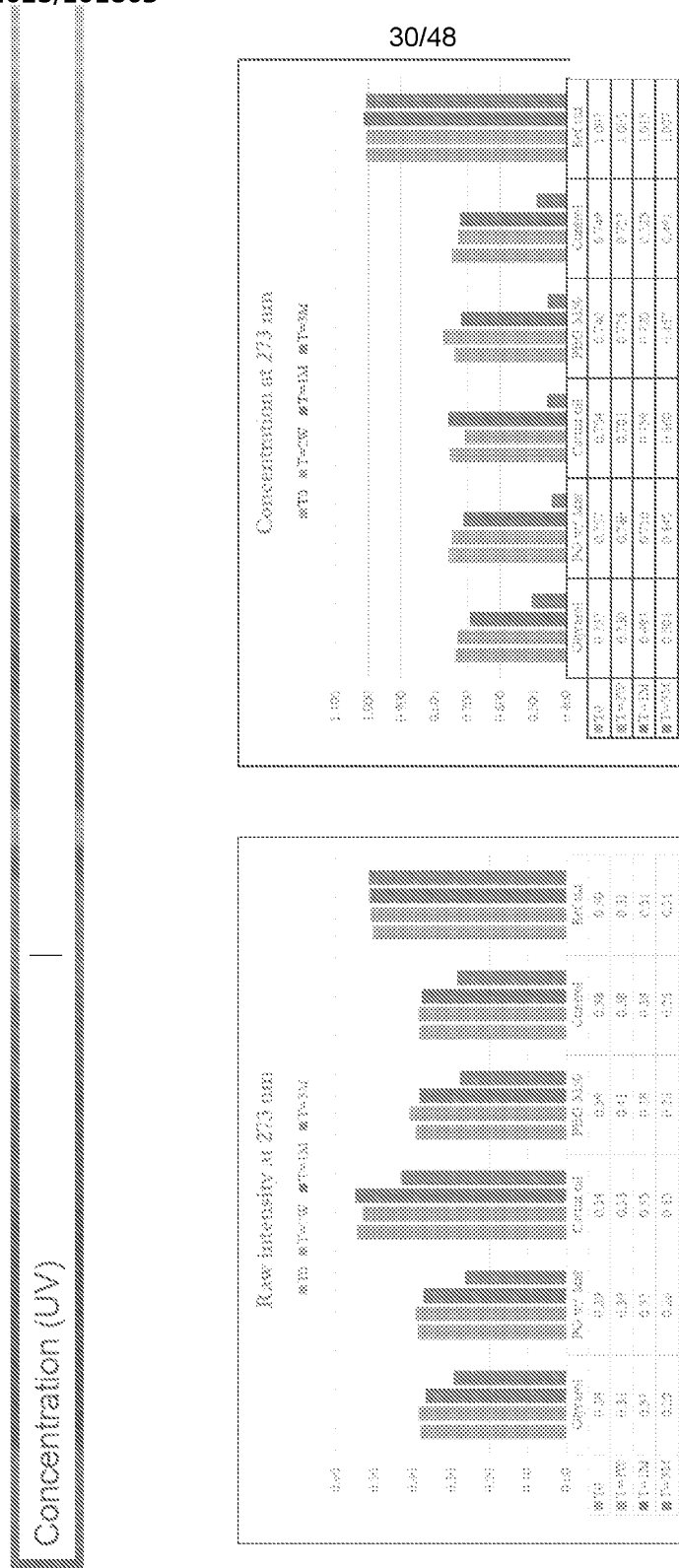


Figure 20

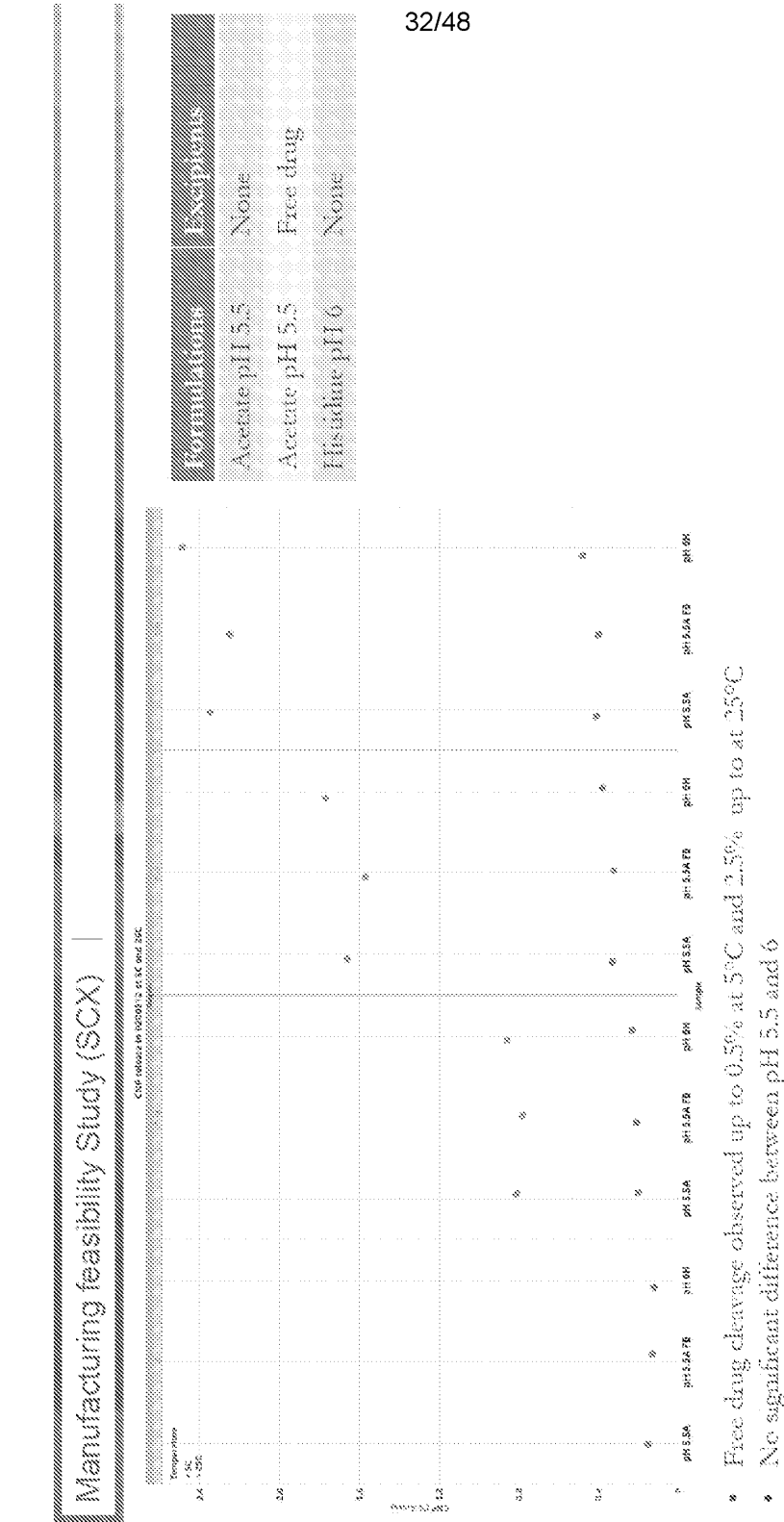


Figure 22

clinical trial

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RP %Area

Buffer	Test Article	Timepoint	CNP	Linker	Predrug	Σ Other	RRT=0.23	RRT=0.24
10mM pH5.5C FB	TA1	T=0	0.6	ND	89	10.4	ND	ND
10mM pH6.0H FB	TA2	T=0	0.6	ND	90	9.6	ND	ND
10mM pH5.5H FB	TA3	T=0	0.6	ND	90	9.8	ND	ND
10mM pH5.2H FB	TA4	T=0	0.6	ND	90	9.5	ND	ND
10mM pH4.0A FB	TA5	T=0	0.4	ND	90	9.7	ND	ND
10mM pH3.0C FB	TA6	T=0	0.3	ND	90	9.6	ND	ND
10mM pH5.5C FB	TA1	Pre-dosing	0.4	ND	89	10.3	ND	ND
10mM pH6.0H FB	TA2	Pre-dosing	0.4	ND	89	10.3	ND	ND
10mM pH5.5H FB	TA3	Pre-dosing (	0.5	ND	90	9.9	ND	0.3
10mM pH5.2H FB	TA4	Pre-dosing	0.5	ND	90	9.7	ND	0.2
10mM pH4.0A FB	TA5	Pre-dosing (	0.4	ND	91	8.9	ND	ND
10mM pH3.0C FB	TA6	Pre-dosing (	0.3	ND	91	9.2	ND	ND
10mM pH5.5C FB	TA1	Post-dosing	0.4	ND	89	10.8	ND	0.2
10mM pH6.0H FB	TA2	Post-dosing	0.5	ND	99	10.6	ND	0.2
10mM pH5.5H FB	TA3	Post-dosing	0.5	ND	99	10.3	ND	0.2
10mM pH5.2H FB	TA4	Post-dosing	0.5	ND	89	10.2	0.1	0.2
10mM pH4.0A FB	TA5	Post-dosing	0.3	ND	90	9.5	0.1	0.2
10mM pH3.0C FB	TA6	Post-dosing	0.3	ND	90	9.5	0.1	0.2

Placebo 34

Figure 23

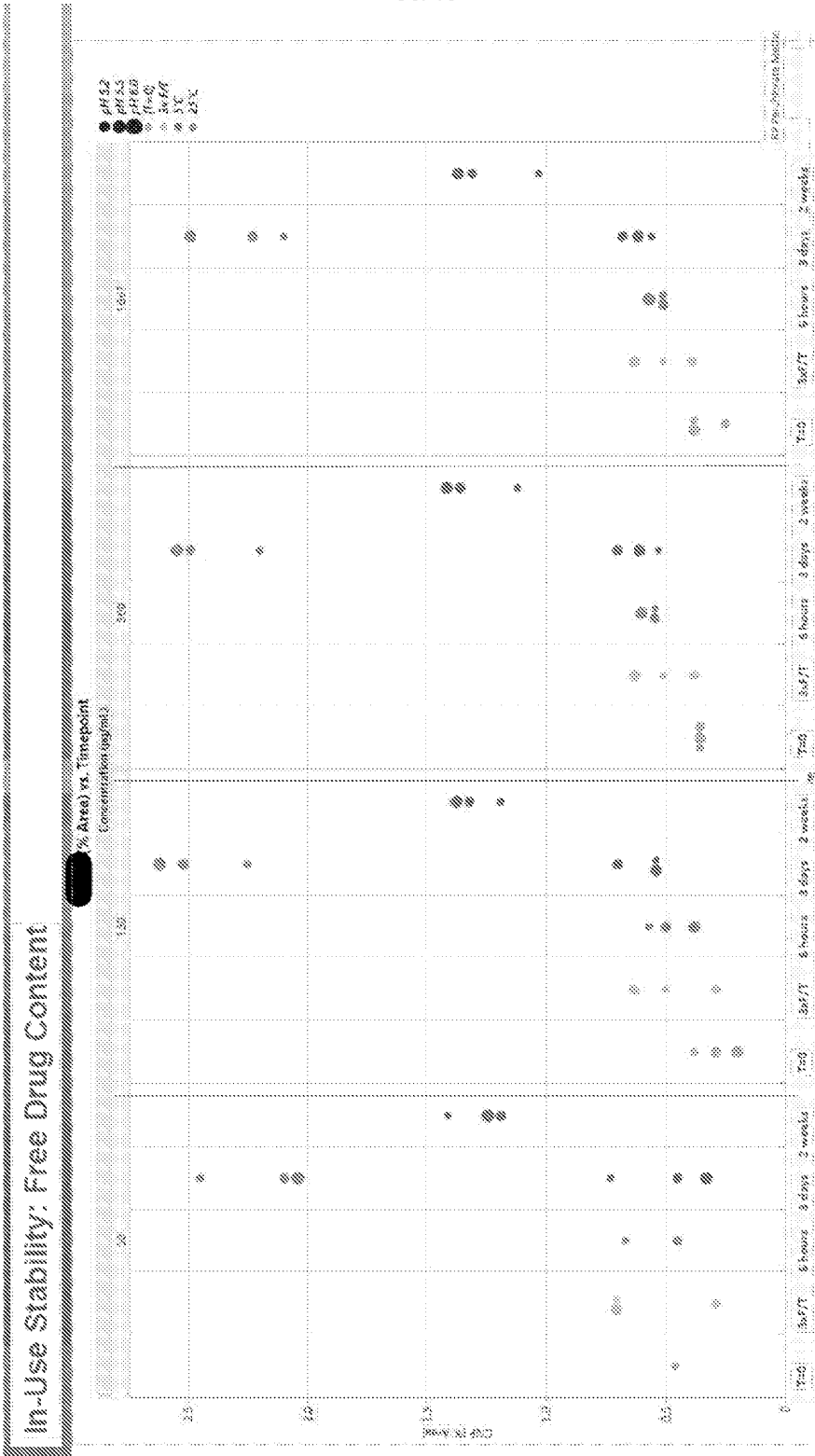


Figure 24

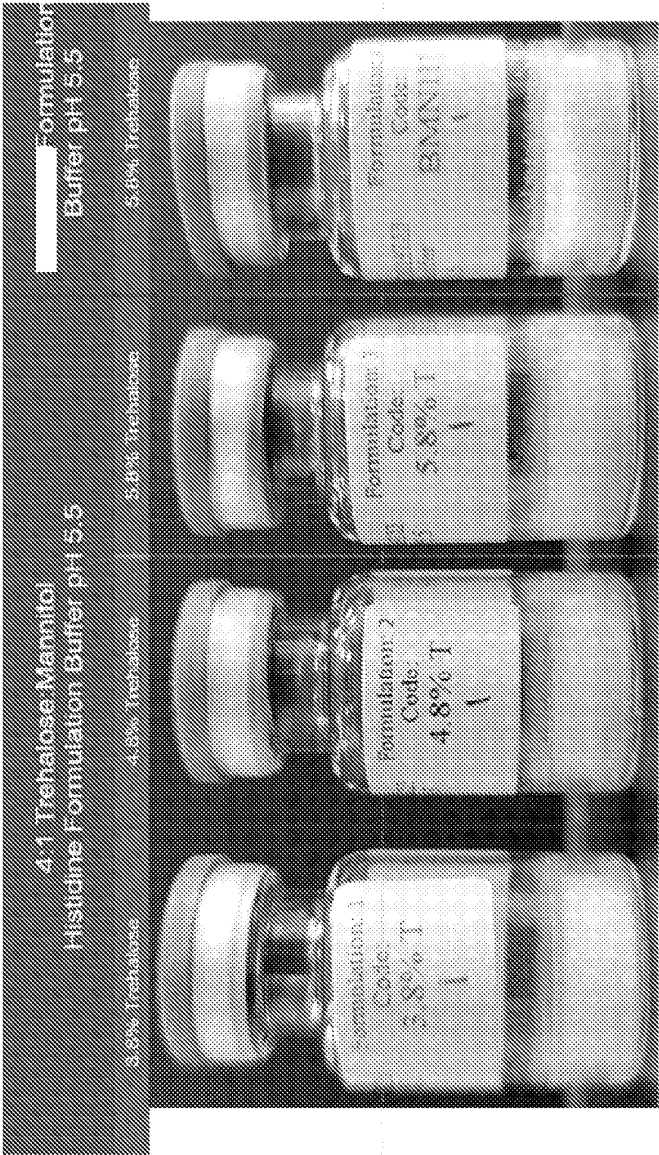


Figure 25A

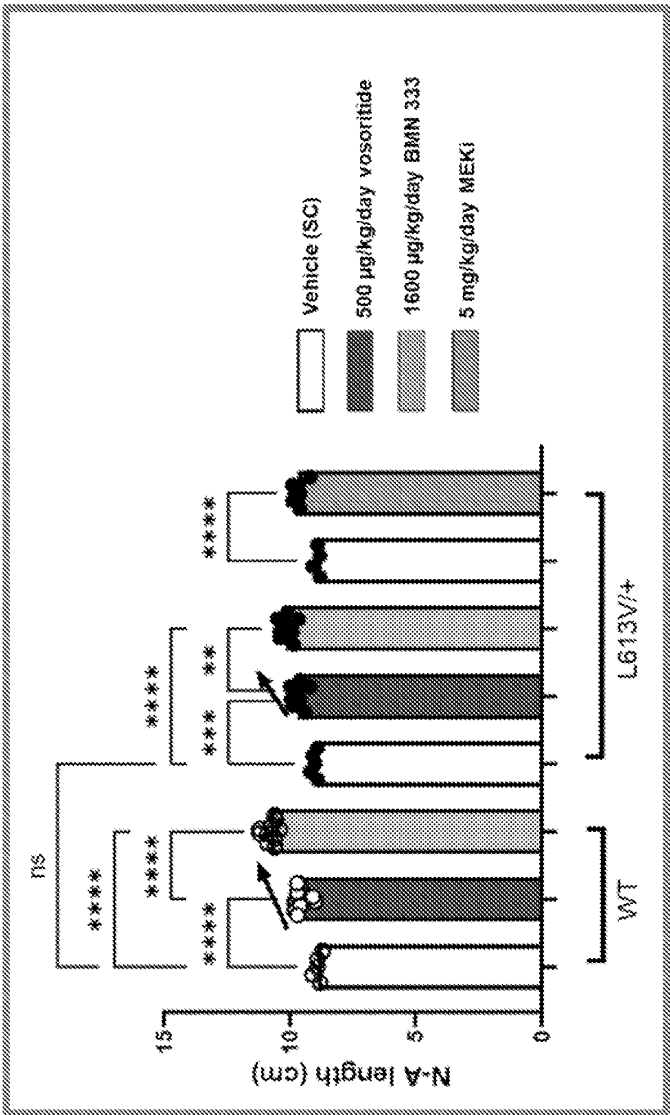


Figure 25B

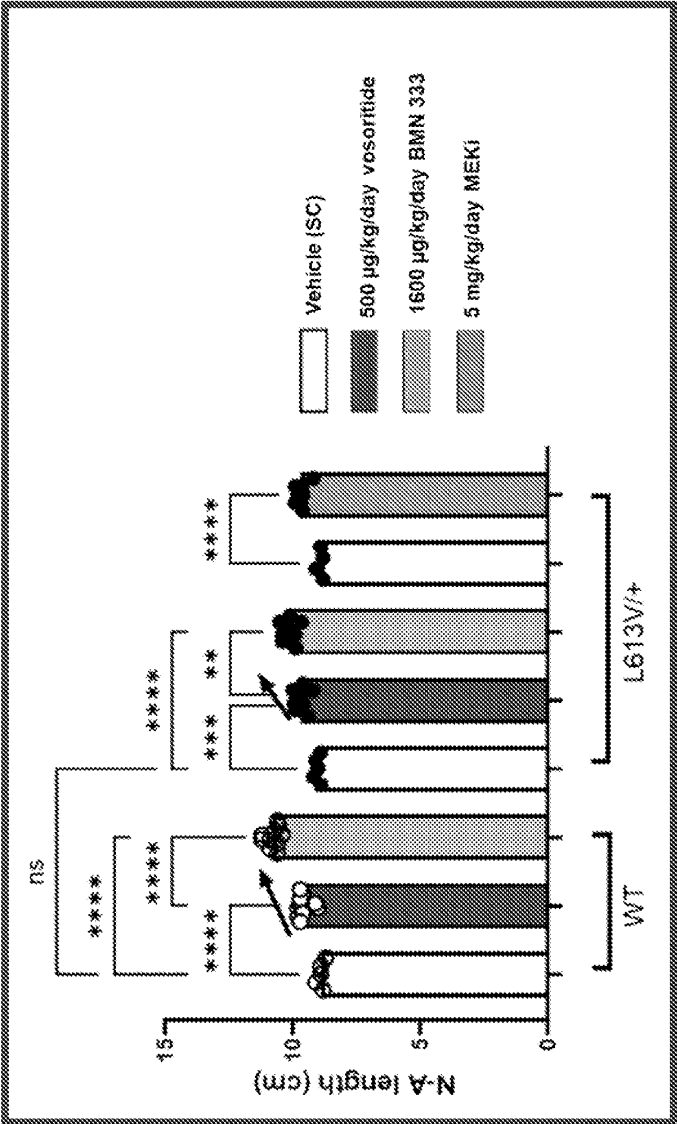
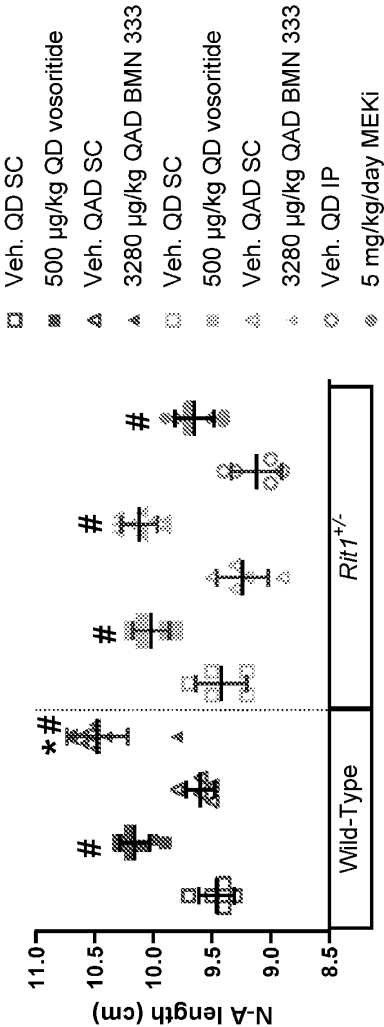


Figure 26



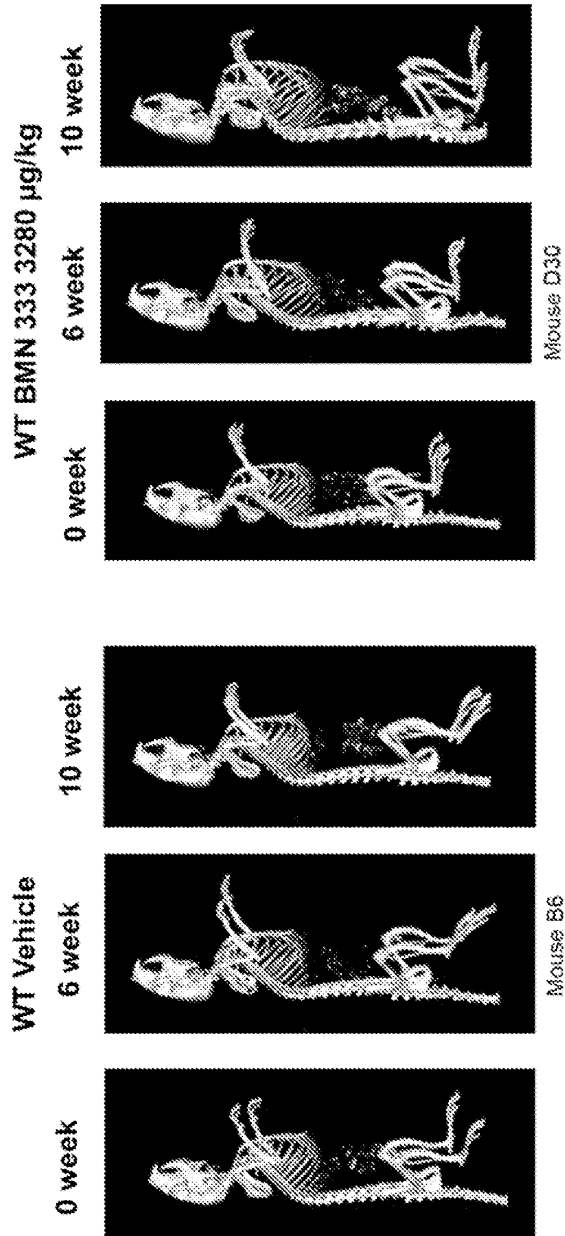


Figure 27

Figure 28 - Plasma Pharmacokinetics of CNP Prodrug and Released Vosoritide in Mice Following a Single SC Dose

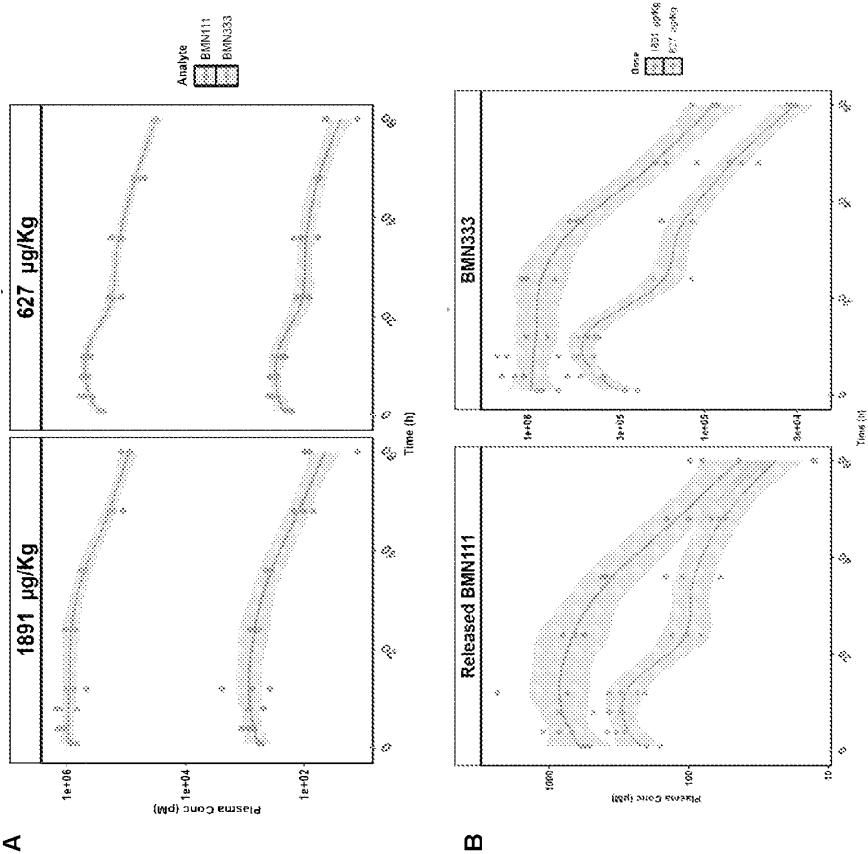
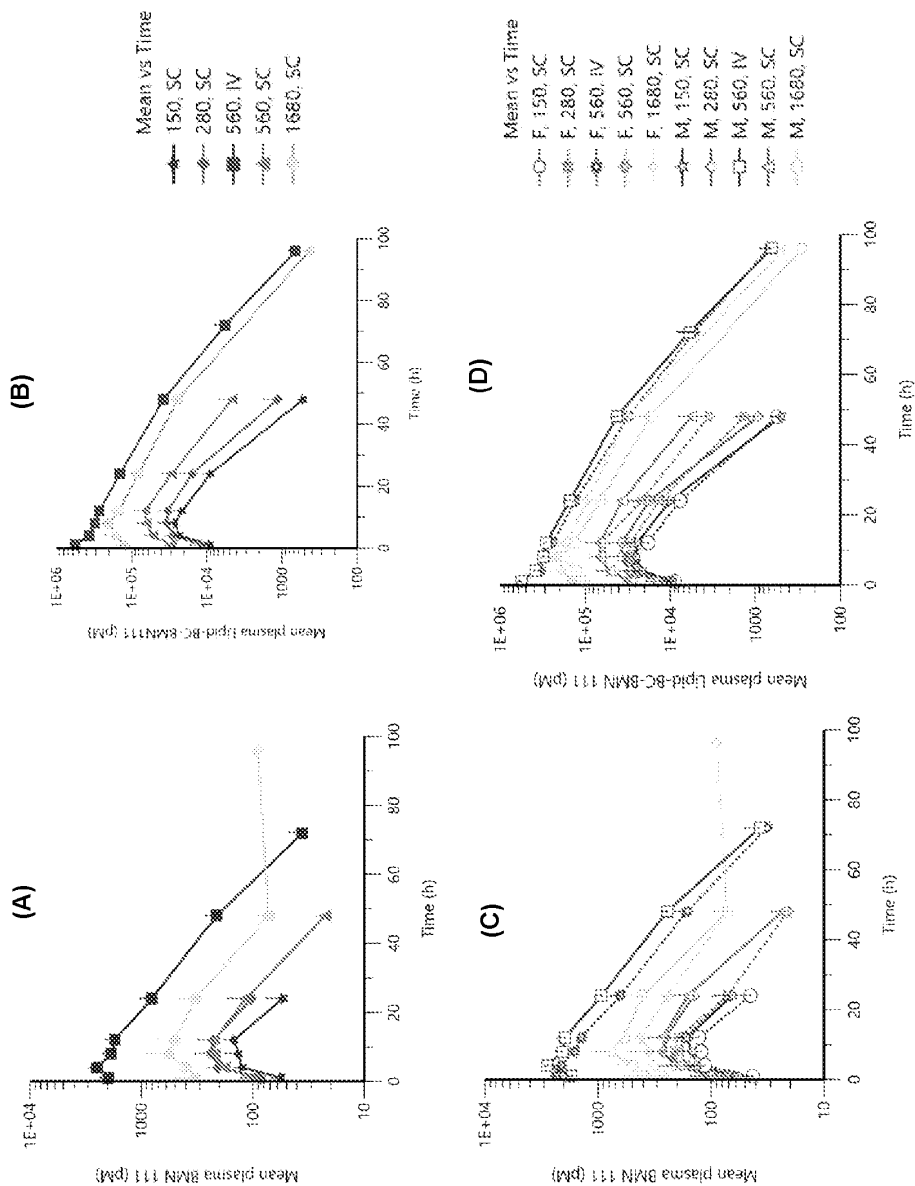


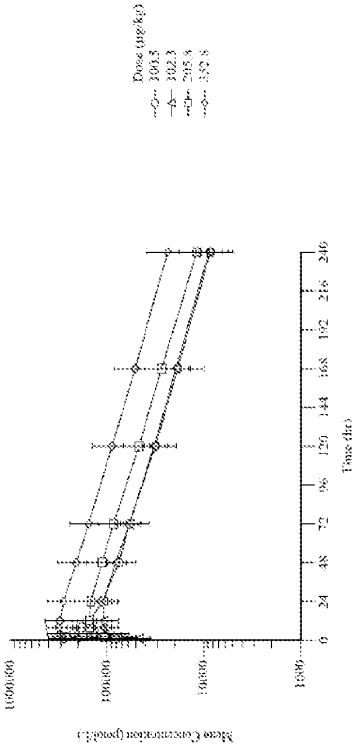
Figure 29 - Mean (±SD) Plasma Vosoritide and CNP Prodrug Concentration-Time Profiles after a Single Dose of CNP Prodrug



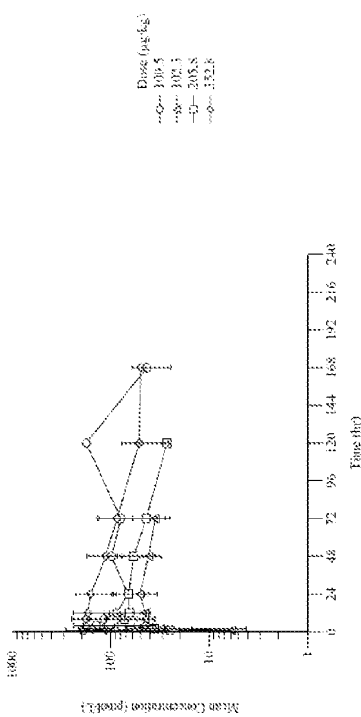
BMN 111; vosoritide; Lipid-BC-BMN 111, CNP Prodrug.
Mean plasma vosoritide (A,C) and CNP Prodrug (B,D) concentrations for each group of animals combined (A,B) and by sex (C,D); error bars represent the standard deviations from the mean concentrations

Figure 30 - Mean ($\pm$ SD) Concentration vs. Time Curves for CNP Prodrug and Vosoritide in NHP Plasma Following IV or SC Administration of CNP Prodrug

(A) CNP Prodrug



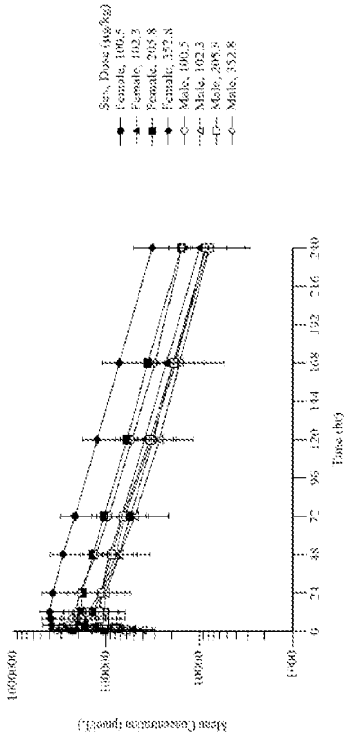
(B) Vosoritide



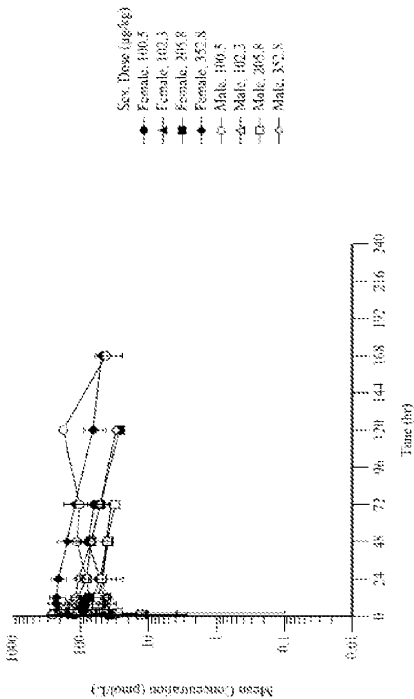
Mean plasma CNP Prodrug (A) and vosoritide (B) concentrations for each group of animals as combined; error bars represent the standard deviations from the mean concentrations.

Figure 31 Mean (± SD) Concentration vs. Time Curves for CNP Prodrug and Vosoritide in Male and Female NHP Plasma Following IV or SC Administration of CNP Prodrug

(A) CNP Prodrug

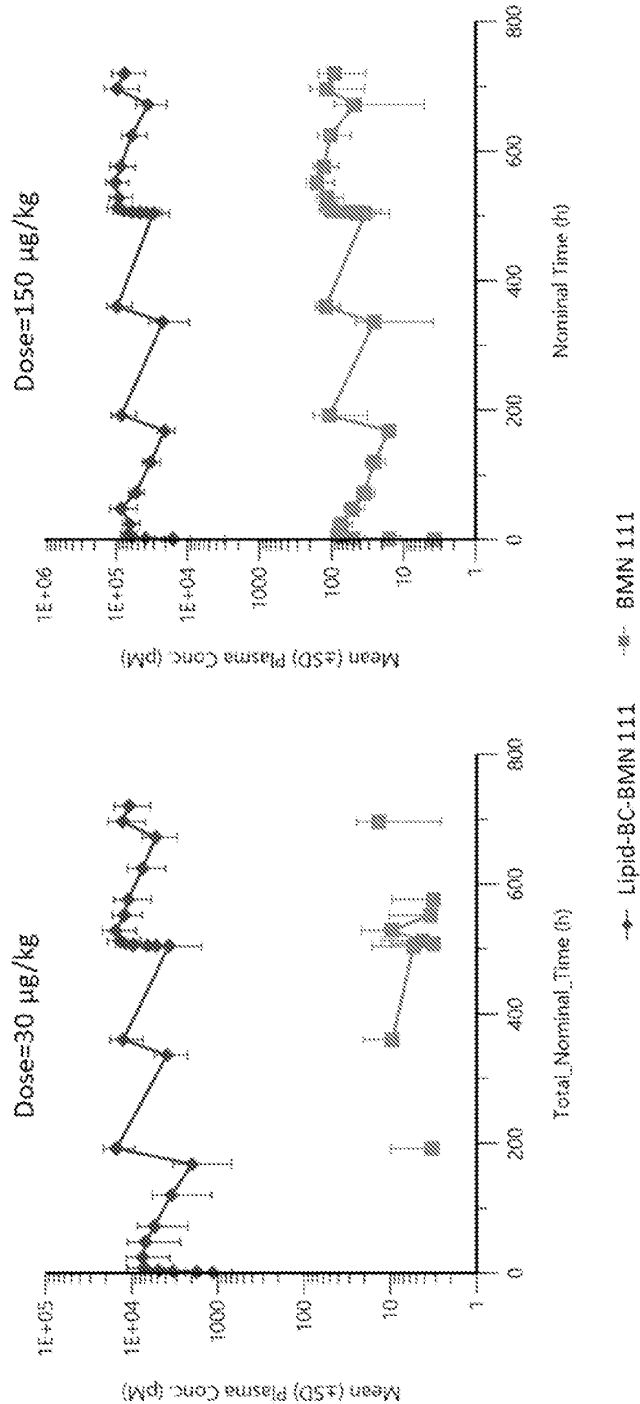


(B) Vosoritide



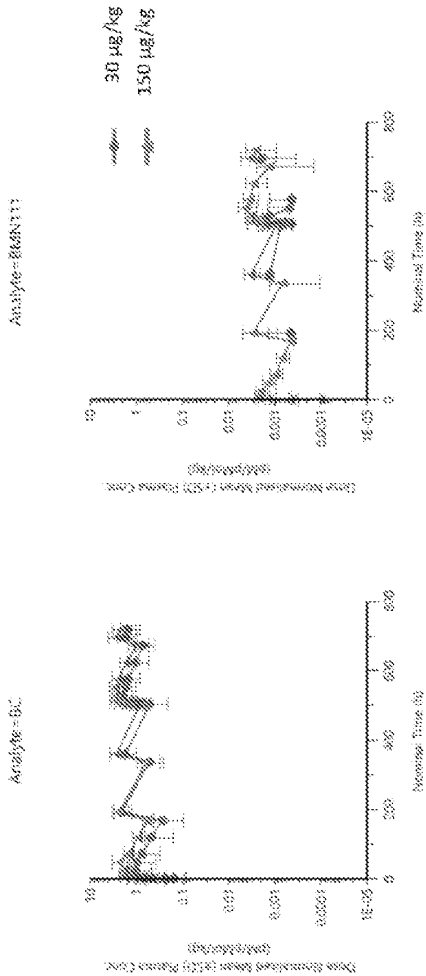
Mean plasma CNP Prodrug (A) and vosoritide (B) concentrations for each group of male and female NHPs; error bars represent the standard deviations from the mean concentrations.

Figure 32A Mean ($\pm$ SD) Plasma Vosoritide and CNP Prodrug Concentration-Time and dose normalized mean Plasma Vosoritide and CNP Prodrug Concentration-Time profile



Mean plasma vosoritide and CNP Prodrug (A) and dose normalized mean plasma (B) concentrations for each group of animals; error bars represent the standard deviations from the mean concentrations.

Figure 32B Mean (±SD) Plasma Vosoritide and CNP Prodrug Concentration-Time and dose normalized mean Plasma Vosoritide and CNP Prodrug Concentration-Time profile



Mean plasma vosoritide and CNP Prodrug (A) and dose normalized mean plasma a vosoritide and CNP Prodrug (B) concentrations for each group of animals; error bars represent the standard deviations from the mean concentrations.

Figure 33 – Mean (±SD) Plasma Vosoritide and CNP Prodrug Concentration-Time Comparing Day 1 vs Day 22

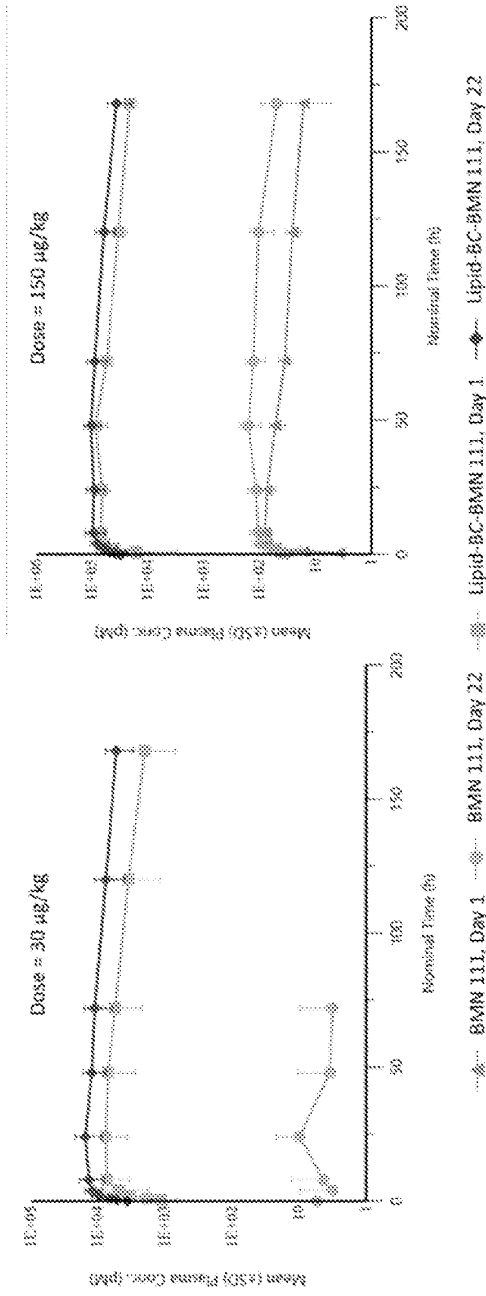


FIGURE 34

