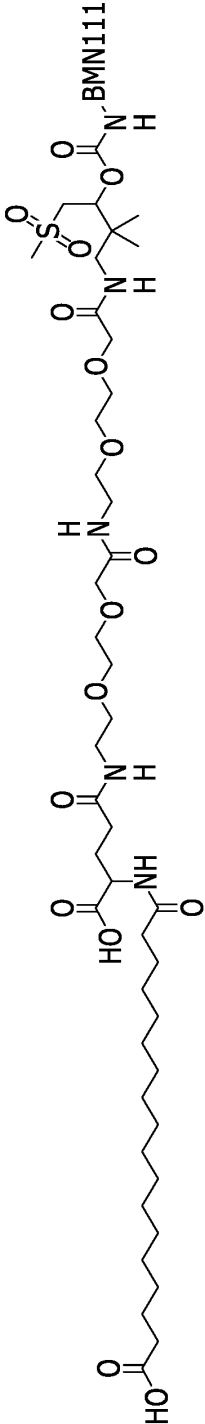


CNP conjugate with lipid moiety, glutamic acid, spacer, and electronic linker



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

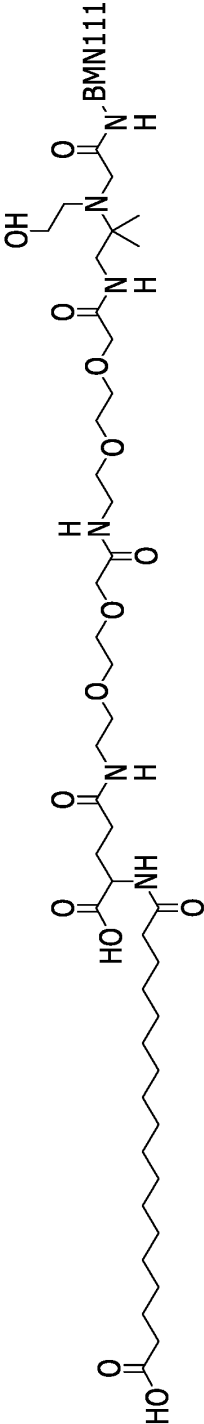


Figure 1

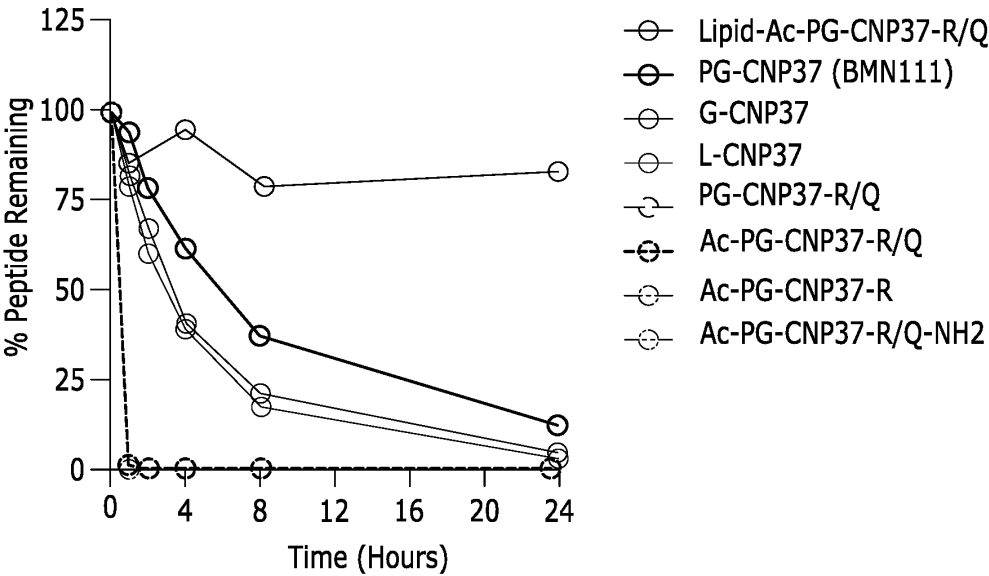


Figure 2A

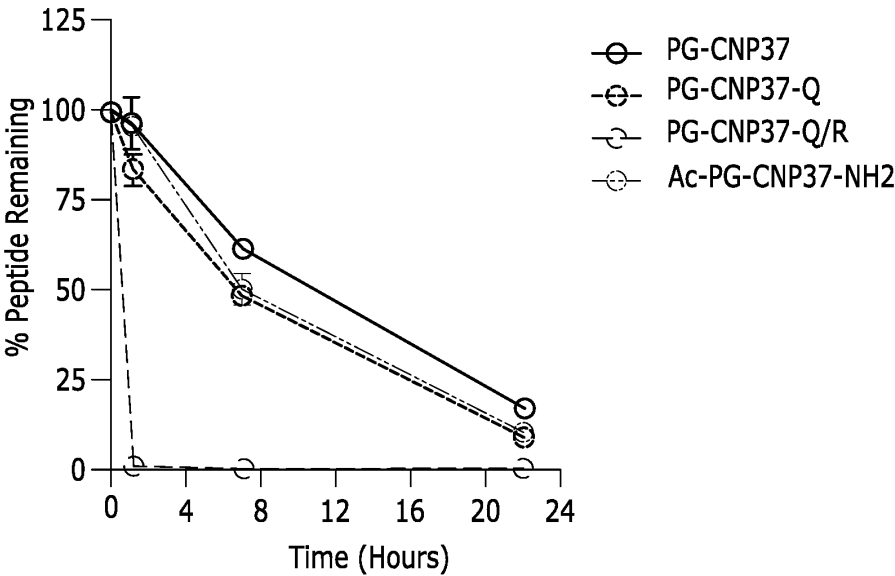


Figure 2B

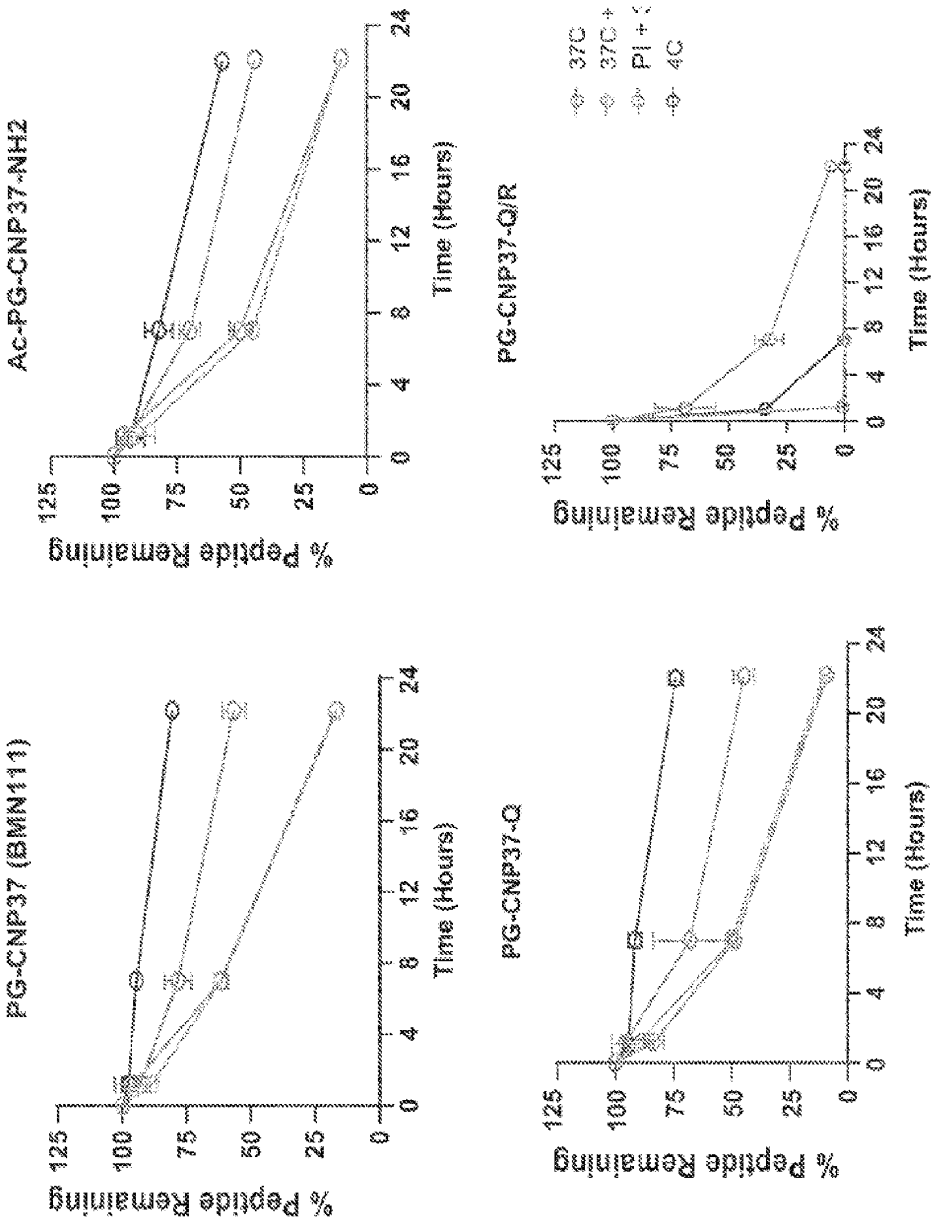
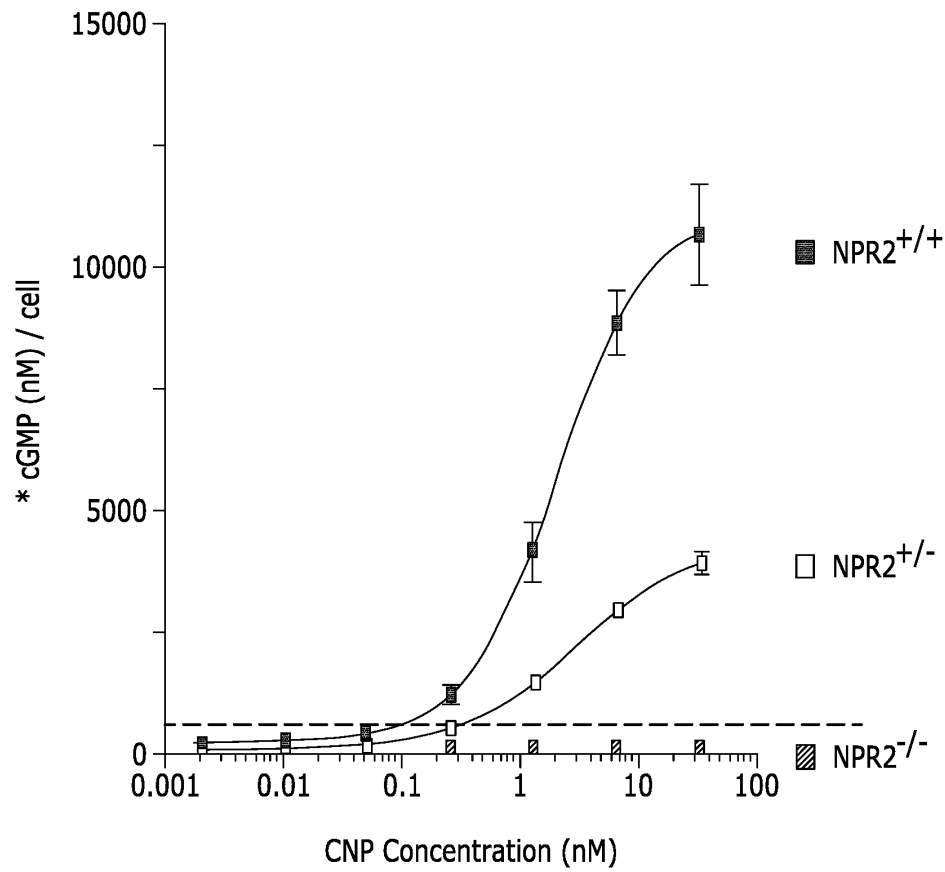


Figure 3



cGMP EC₅₀ = 96nM

Figure 4

NPR2 Clone, nucleotide sequence

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

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCCG
GGGGCACGGMCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTGGG
CCTGGCCACGGGTGGGTCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCACTG
CCCGTGGACCTGCGGTTTGTACGCTCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCAC
CACTGCGCGCTGTGGATCTCMGCTGTACCATGACCCCGACCTTCTGTTGGGCCCTGGTTGT
GTGTACCCTGCTGCCTCTGTGGCTCGCTTTCCTCGCACTGGCACCTTCCCCTCCTGACTG
CGGGTGCAGTGGCCTCTGGCTTTCAGCTMGMTGAGCATTATCGTACCCTGGTTCGCACT
GGCCCCTCTGCGCCCMGCTGGGTGAGTTCGTAGTGACATTACACGGGCACTTCMTTGGAC
TGCTCGGGCTGCTTTCGTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTCACC
ATCGAGGGGGTGTTCGAGGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACCAGGTGTATA
CCCGAGAGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

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

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCC
GGGGGCACGGMCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTG
GGCCTGGCCACGGGTGGGTCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCA
CTGCCCGTGGACCTGCGGTTTGTACGCTCCGMCTAGACGGCGCCTGCTCTGAGTACCTGG
CACTGCGCGCTGTGGATCTCMGCTGTACCATGACCCCGACCTTCTGTTGGGCCCTGGT
TGTGTGTACCCTGCTGCCTCTGTGGCTCGCTTTCCTCGCACTGGCACCTTCCCCTCCTGA
CTGCGGGTGCAGTGGCCTCTGGCTTTCAGCTMGMTGAGCATTATCGTACCCTGGTTCGC
ACTGGCCCCTCTGCGCCCMGCTGGGTGAGTTCGTAGTGACATTACACGGGCACTTCMTT
GACTGCTCGGGCTGCTTTCGTGTATCTGGATGCTCGCACAGATGACCGGCCCCACTACTTC
ACCATCGAGGGGGTGTTCGAGGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACCAGGTGT
ATACCGAGAGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

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

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTCC
GGGGGCACGGMCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCTG
GGCCTGGCCACGGGTGGGTCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCA
CTGCCCGTGGACCTGCGGTTTGTACGCTCCGMCTAGACGGCGCCTGCTCTGAGTACCTG
GCACCACTGCGCGCTGTGGATCTCMGCTGTACCATGACCCCGACCTTCTGTTGGGCCCTG
GTTGTGTGTACCCTGCTGCCTCTGTGGCTCGCTTTCCTCGCACTGGCACCTTCCCCTCCT
GACTGCGGGTGCAGTGGCCTCTGGCTTTCAGCTMGMTGAGCATTATCGTACCCTGGTTC
GCACTGGCCCCTCTGCGCCCMGCTGGGTGAGTTCGTAGTGACATTACACGGGCACTTCAC
AATTGGAAGTGTGCTCGGGCTGCTTTCGTGTATCTGGATGCTCGCACAGATGACCGGCCCCAC
TACTTCACCATCGAGGGGGTGTTCGAGGCCCTGCAGGGCAGCMCCTCAGTGTGCMCACC
AGGTGTATACCGAGAGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGG
GCGCA

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

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCGTCCTC
CGGGGGCACGGMCTGACGCTGGCGGTGGTGCTGCCAGMCACAACCTGAGCTATGCCT
GGCCTGGCCACGGGTGG

Figure 5

GTCCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGGCACTGCCCCTGGACCTGCG
 GTTGTGCTAGCTCCGMCTAGACGGCGCCTGCTCTGAGTACCTGGCACCCTGCGCGCTGT
 GGATCTCAAGCTGTACCATGACCCCGACCTTCTGTTGGGCCCTGGTTGTGTGTACCCTGC
 TGCCTCTGTGGCTCGCTTTCCTCGCACTGGCACCTTCCCCTCCTGACTGCGGGTGCAGT
 GGCCTCTGGCTTTCAGCTMGMTGAGCATTATCGTACCCTGGTTCGCACTGGCCCCCTCTG
 CGCCCMGCTGGGTGAGTTCGTAGTGACATTACACGGGCACTTCMTTGGACTGCTCGGGC
 TGCTTTGCTGTATCTGGATGCTCGCACAGATGACCGGCCCACTACTTCACCATCGAGGG
 GGTGTTTGAGGCCCTGCAGGGCAGCAACCTCAGTGTGCAACACCAGGTGTATACCCGAG
 AGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCMCGGGCGCA

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

ATGGCACTGCCATCCCTGCTACTGGTGGTGGCAGCCCTGGCAGGTGGGGTGCCTCCTC
 CGGGGGCACGGMCTGACGCTGGCGGTGGTGTGCCAGMCACAACCTGAGCTATGCCT
 GGGCCTGGCCACGGGTGGTCTGCTGTGGCACTGGCTGTGGAGGCGCTGGGCCGGG
 CACTGCCCCTGGACCTGCGGTTTGTAGCTCCGMCTAGACGGCGCCTGCTCTGAGTACC
 TGGCACCGGGGTGTTTGAGGCCCTGCAGGGCAGCMCTCAGTGTGCAACACCAGGTGT
 ATACCCGAGAGCCAGGTGGCCCTGAGCMGCCACCCACTTCATCAGAGCCAACGGGCGCA

NPR2 Clone, predicted protein product sequence

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

MALPSLLLVMMLAGGVRPPGARNLTAWLPEHNLSYAWAWPRVGPVALAVEALGRALPV
 DLRVSSSEL
 DGACSEYLAPLRAVDLKLHYDPDLLLGPVCVPMVSARFASHWHLPLLTAGAVASGFMKNE
 HYRTLVRTG
 PSAPKLGEFVVTLHGHNWTARMLLYLDARTDDRPHYFTIEGVFEALQGSNLSVQHGVYTR
 EPGGPEQAT
 HFIRANGRIVYICGPLEMLHEILLQAQRENLTNGDYVFFYLDVFGESLRAGPTRATGRPQQD
 NRTQEQAQAL
 REAFQTVLVITYREPPNPEYQEFQNRLLIRAREDFGVELAPSLMNLIAAGCFYDGILLYAQVLNE
 TIQEGGTRED
 GLRIVEKMQGRRYHGVTLVVMMDKNNDRETDFVLWAMGDLESQDFQPMHYSGAEKQIW
 WTGRPIPW VKGAPLDNPPCAFDDDPSCDKTPLSTLAIVALGTGITFIM FGVSSFLI FRK
 LMLEKELASMLWRIRWEELQF
 GNSDRYHKGAGSRLTSLRGSSYGSMLTAHGKYQIFANTGHFKGNWAIKHVNKKRIELTR
 QVLFELKHMRD

Figure 5 (Continued)

VQFNHLTRFIGACIDPPNICIVTEYCPRGSLQDILENDSINLDWMFRYSLINDLVKGMAFLHN
SISSHGSLKSS
NCWDSRFVLKITDYGLASFRSTAEPDDSHALYAKKLWTAPELLSGNPLPTTGMQKADVYSF
AIIHQEIALRSG
PFYLEGDLSPKEIVQKVRNGQRPYFRPSIDRTQLNEELVLLMERCWAQDPTERPDFGQIKG
FIRRFNKEGGT
SILDNLLLMEQYANNLEKLVEERTQAYLEEKRAEALLYQILPHSVAEQKRGQVQAEAFD
SVTIYFSDIVGF TALSAESTPMQWTLNDLYTCFDAIIDNFDVYKVETIG DAYMWSG LPGR
NGQRHAPE
IARMALALLDAVSSFRIRHRPHDQLRLRIGVHTGPVCAGVVGLKMPRYCLFGDTVNTASRME
SNGQALKIHVSSTTKDALDELGC FQLELRGDVEMKGKGMRTYWLLGERKGPPGGL*

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

MALPSLLLVMLAGGVPPGARNLTAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVD
LRFVSSEL
DGACSEYLAPLRAVDLKLYHDPDLLLPGPCVYPMSVARFASHWHLPLLTAGAVASGFMKNE
HYRTLVRTGPSAPKLGEFVVTLHGHNWTARMMLLYLDARTDDRPHYFTIEGVFEALQGSNLS
VQHQQYTREPGEQAT

HFIRANGRIVYICGPLEMLHEILLQAQRENLTNGDYVFFYLDVFGESLRAGPTRATGRPWQD
NRTQEQAAQAL
REAFQTVLVITYREPPNPEYQEFQNRLLIRAREDFGVELAPSLMNLIAAGCFYDGILLYAQVLNE
TIQEGGTRED
GLRIVEKMQGRRYHGVTGLVMDKNNDRETDFVLWAMGDLESGDFQPMHYSGAEKQIW
WTGRPIPW VKGAPPLDNPPCAFDLDDPSCDKTPLSTLAIVALGTGITFIM FGVSSFLI FRK
LMLEKELASMLWRIRWEELQF
GNSDRYHKGAGSRLTSLRGSSYGSMTAHGKYQIFANTGHFKGNWAIKHVNKKRIELTR
QVLFELKHMED
VQFNHLTRFIGACIDPPNICIVTEYCPRGSLQDILENDSINLDWMFRYSLINDLVKGMAFLH
NSISSHGSLKSS
NCWDSRFVLKITDYGLASFRSTAEPDDSHALYAKKLWTAPELLSGNPLPTTGMQKADVYSF
AIIHQEIALRSG
PFYLEGDLSPKEIVQKVRNGQRPYFRPSIDRTQLNEELVLLMERCWAQDPTERPDFGQIKG
FIRRFNKEGGT
SILDNLLLMEQYANNLEKLVEERTQAYLEEKRAEALLYQILPHSVAEQKRGQVQAEAFD
SVTIYFSDIV
GF TALSAESTPMQWTLNDLYTCFDAIIDNFDVYKVETIG DAYMWSG LPGRNGQRHAPE
IARMALALLDAVS
SFRIRHRPHDQLRLRIGVHTGPVCAGVVGLKMPRYCLFGDTVNTASRMESNGQALKIHVS
TTKDDELGC FQLELRGDVEMKGKGMRTYWLLGERKGPPGGL*

Figure 5 (Continued)

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

MALPSLLLVVMLAGGVRPPGARNLT LAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPV
DLRFVSSEL
DGACSEYLAPLRAVDLKLYHDPDLLLGP GCVYPMSVARFASHWHLPLLTAGAVASGFMKNE
HYRTLVRTGPSAPKLG EFVVT LHGHFTIGLLGLLCCIWM LAQMTGPTTSPSRGCLRPCRMT
SVCNTRCIPESQVALSKPPTS SEPTGALCISMRWRCFMRSCFRPRGRT*

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

MALPSLLLVVMLAGGVRPPGARNLT LAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVD
LRFVSSELDGACSEYLAPLRAVDLKLYHDPDLLLGP GCVYPMSVARFASHWHLPLLTAGAVA
SGFMKNEHYRTLVRTGPSAPKLGEFVVT LHGHFNWTARMLLYLDARTDDRPHYFTIRGGV*

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

MALPSLLLVVMLAGGVRPPGARNLT LAWLPEHNLSYAWAWPRVGPAVALAVEALGRALPVD
LRFVSSELDGACSEYLAPGCLRPCRMTSVCNTRCIPESQVALSKPPTSSEPTGALCISAARW
RCFMRSCFRPRG RT*

Figure 5 (Continued)

Figure 6

Genetic Variants Found in NPR2 Genes

NPR2 Mutations			
G21R	P301S	QS00X	R74SQ
A48S	R318Q	HS0BD	R819C
A59T	R358W	G541S	T861I
V102A	E359A	A549T	V883M
R110G	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

Genetic variance found in the 5 Core genes

[illegible]

Figure 7 cont'd

[illegible]

Genetic variants found in the 5 Core genes

[illegible]

Figure 7 cont'd

[illegible]

Figure 7 cont'd

concrete variables found in the 5 Categories

[illegible]

Figure 7 cont'd

[illegible]

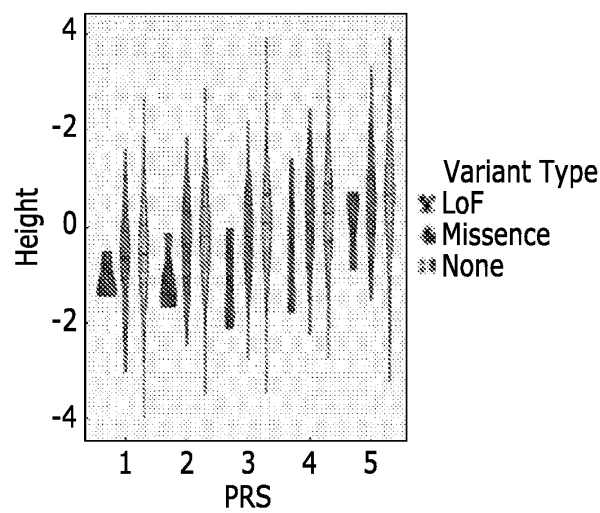


Figure 8A

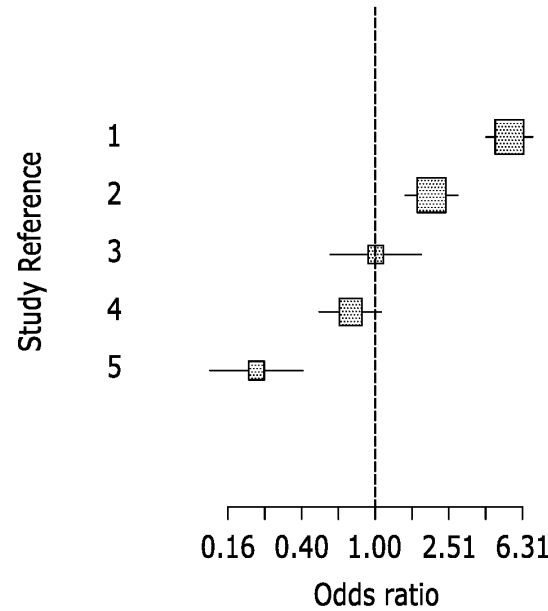


Figure 8B

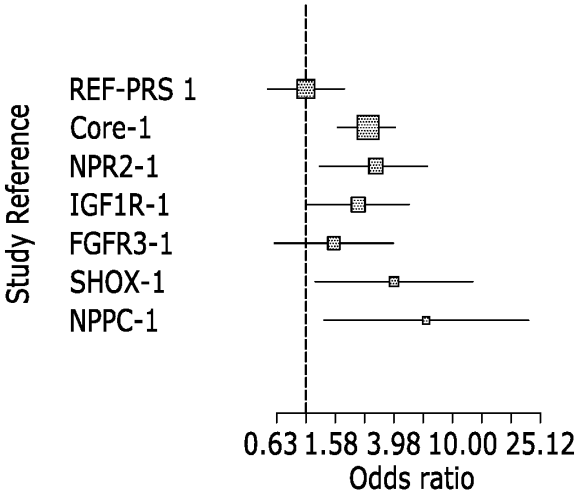


Figure 8C

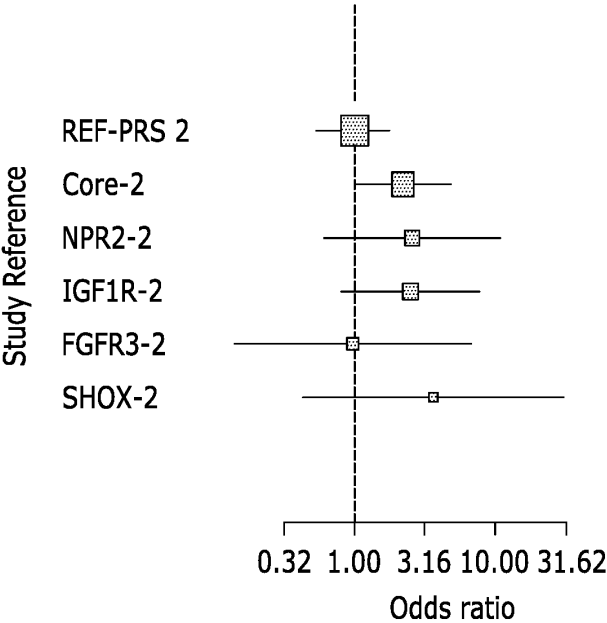


Figure 8D

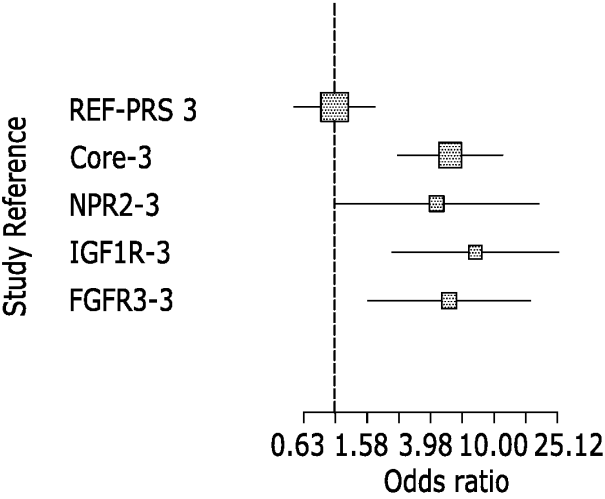


Figure 8E

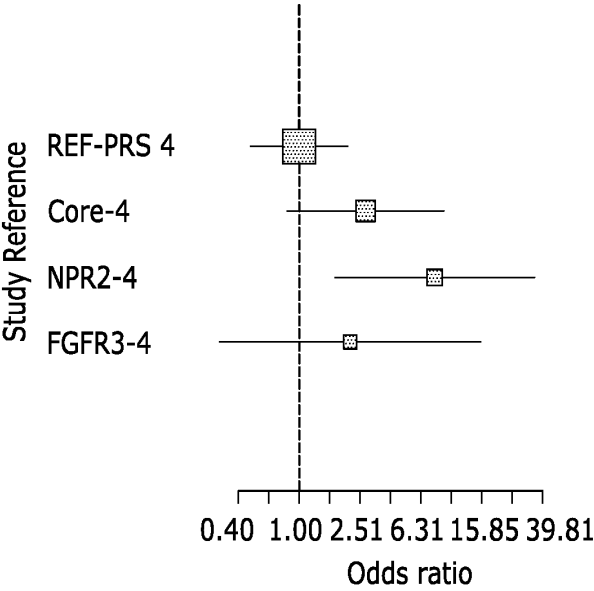


Figure 8F

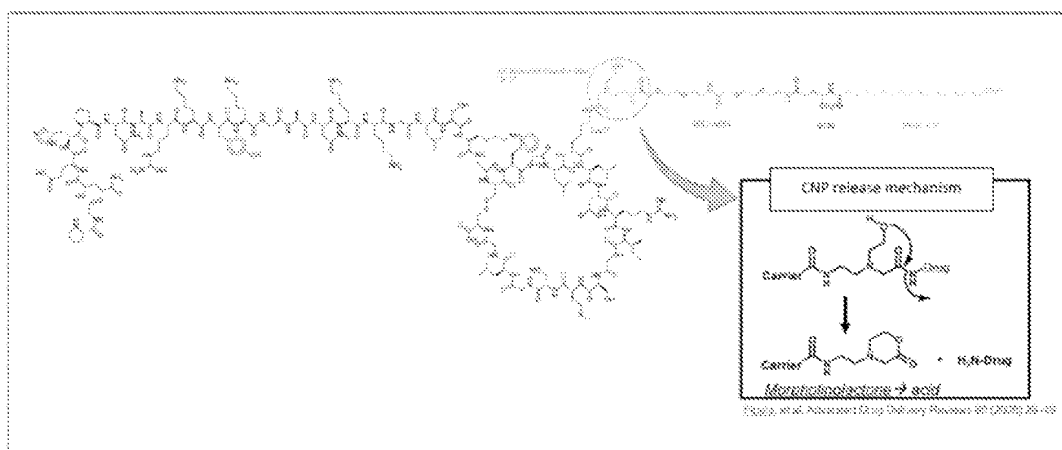
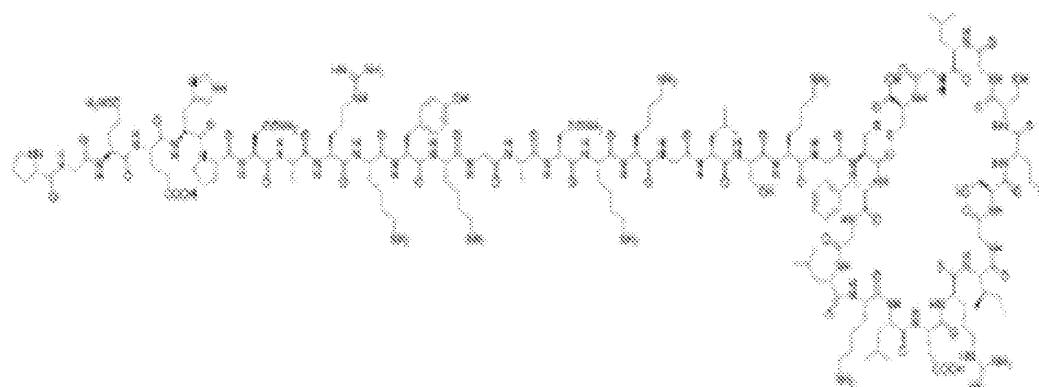
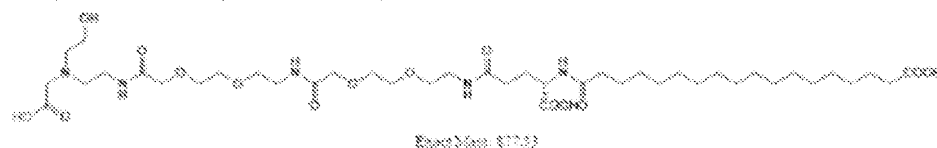


Figure 9



-B: Lipid + Linker (stable form)



-C: BICIN linker



Figure 10

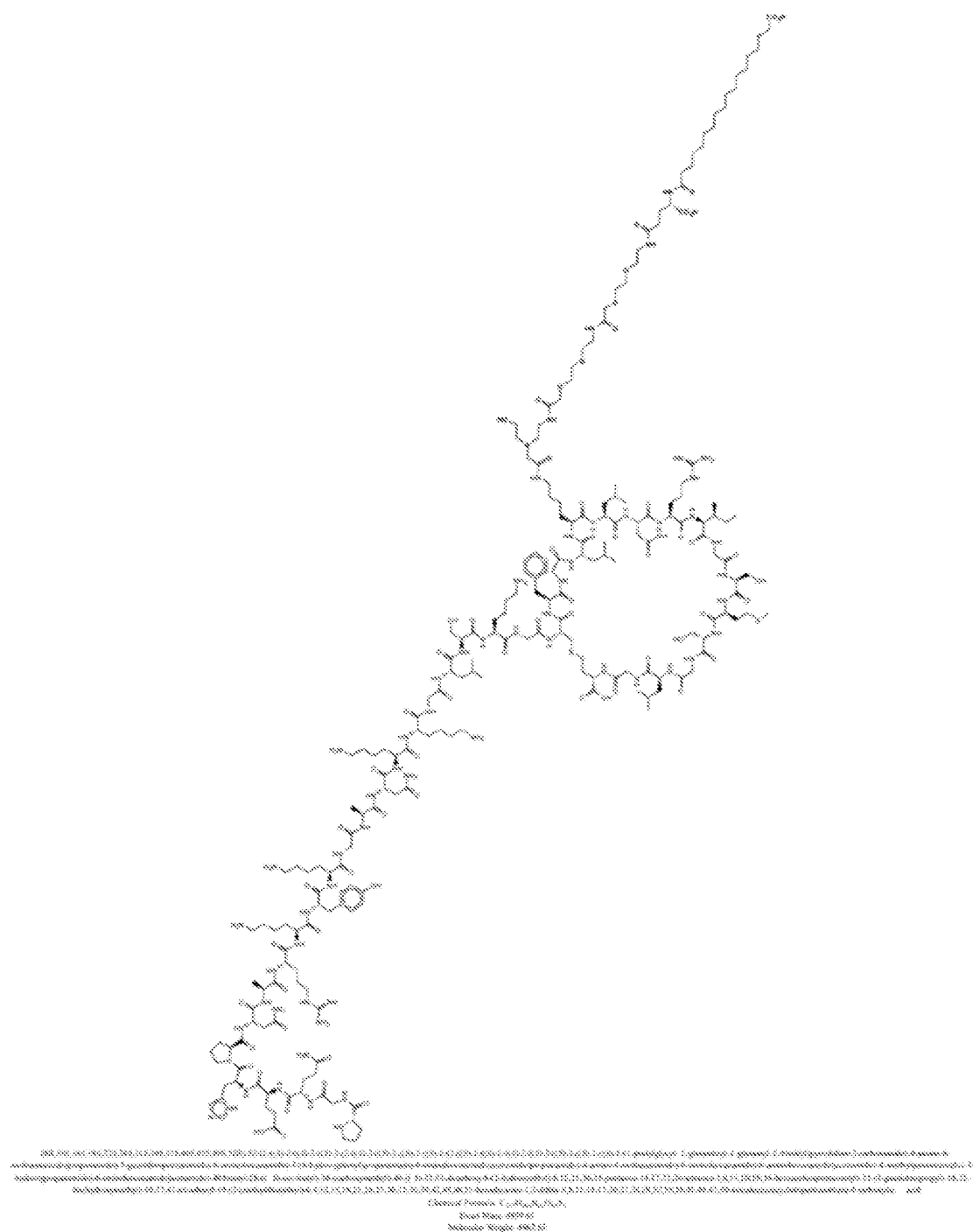


FIGURE 11

Figure 12

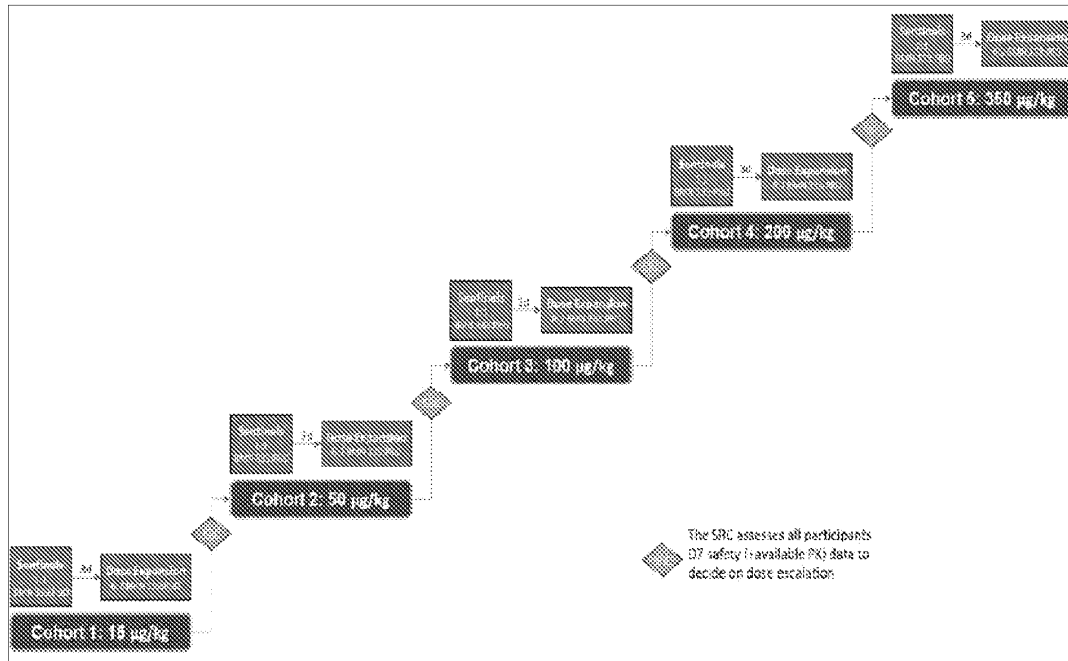
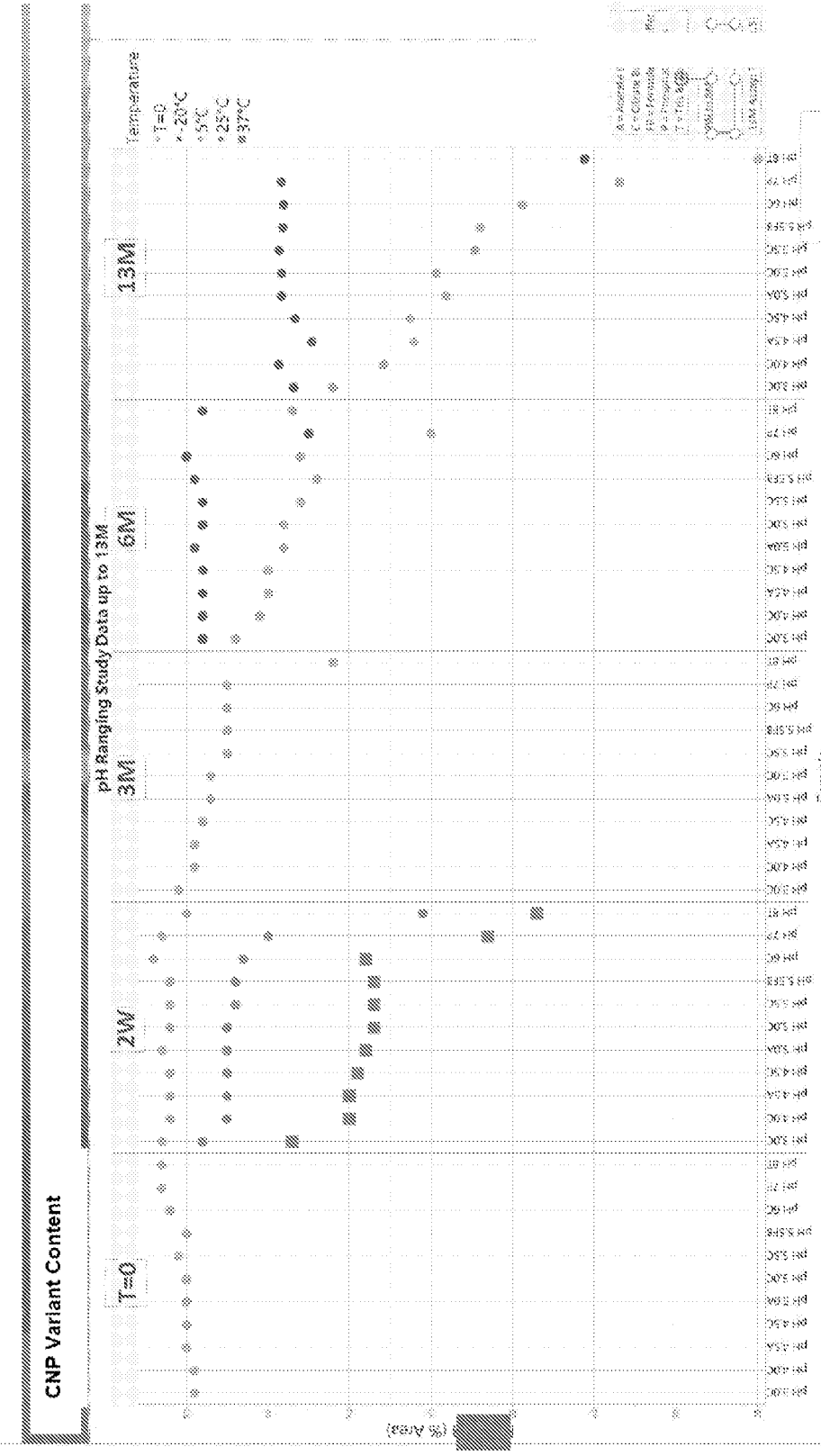


Figure 14



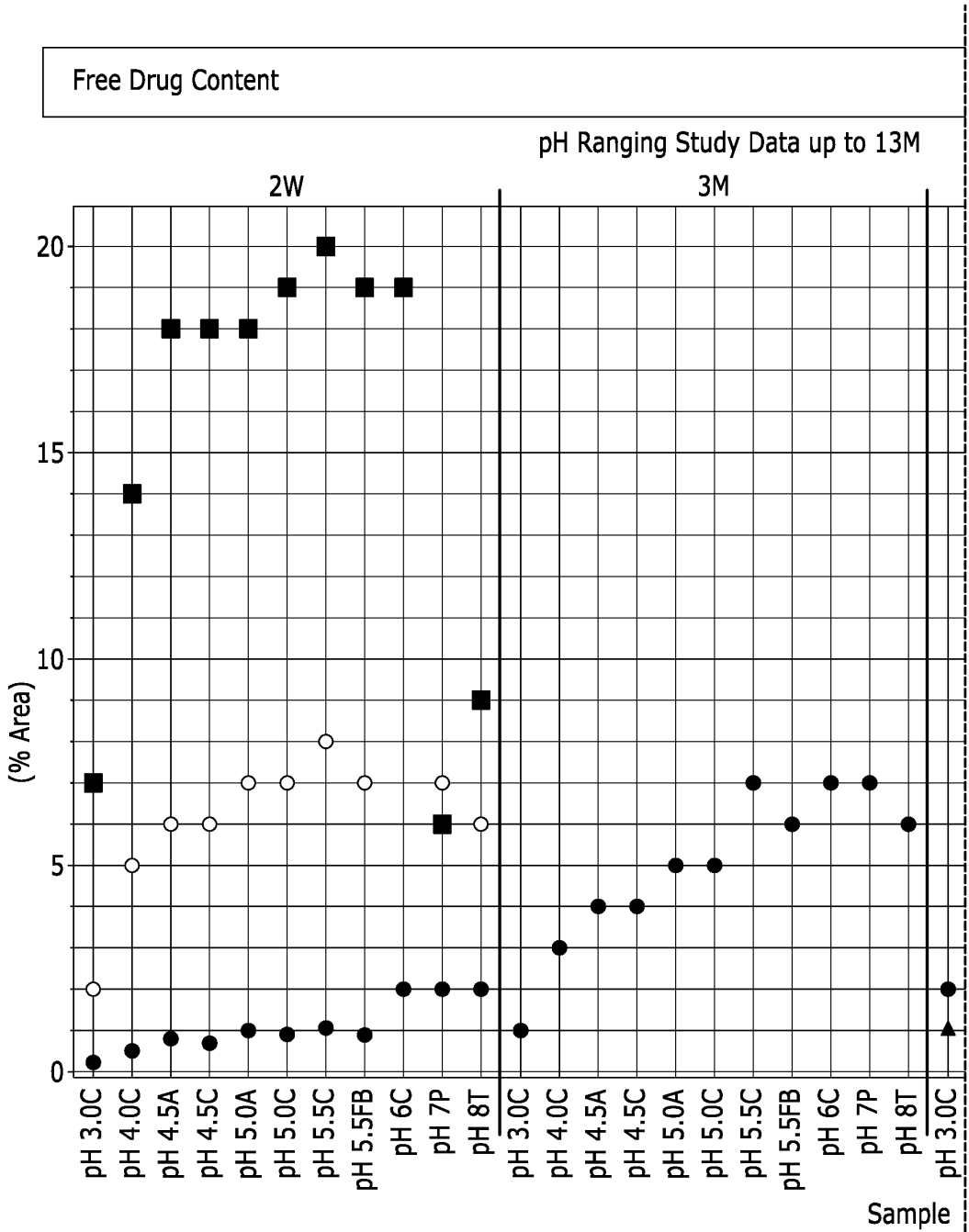


Figure 15

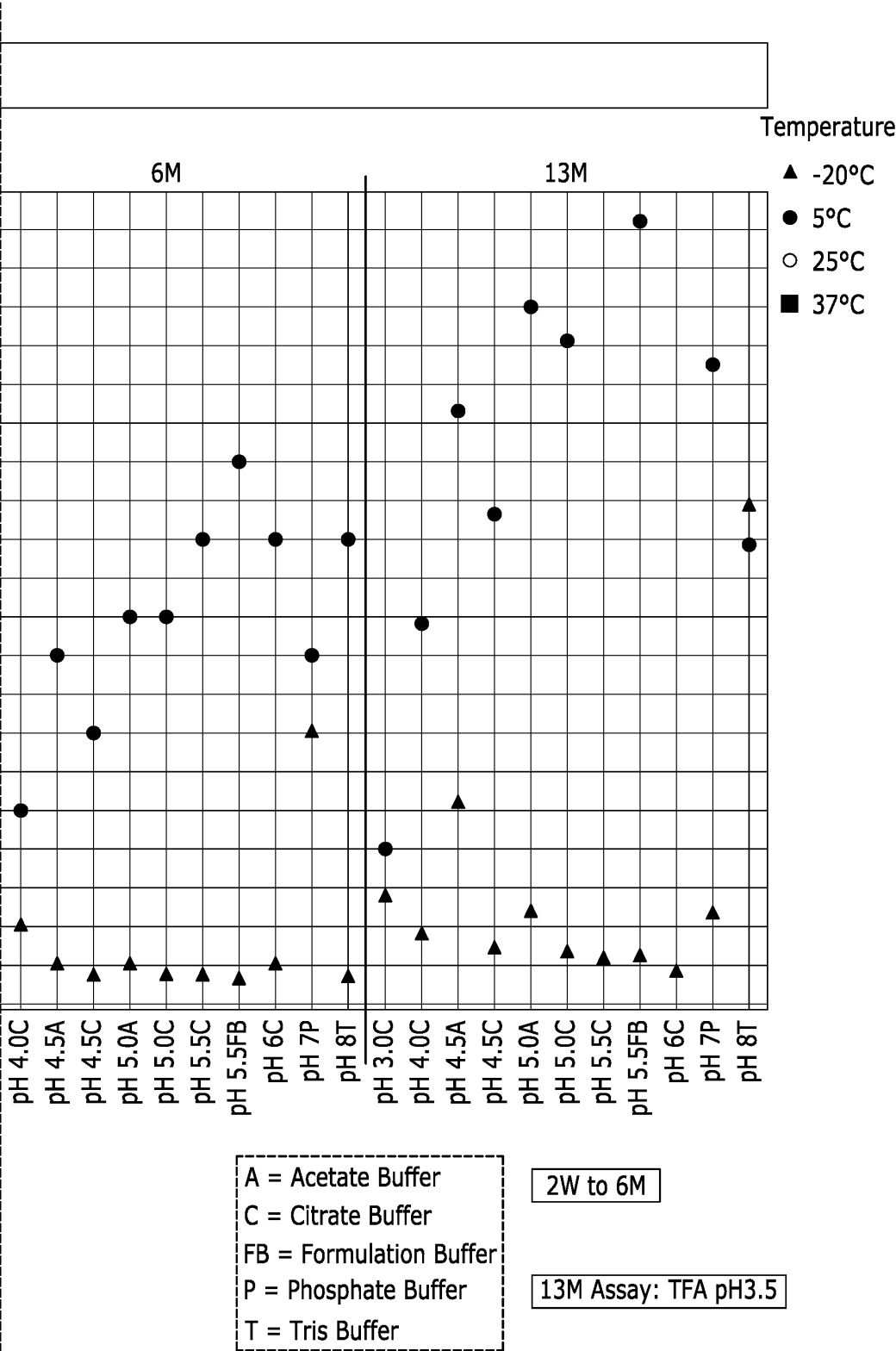


Figure 15 (Continued)

SUBSTITUTE SHEET (RULE 26)

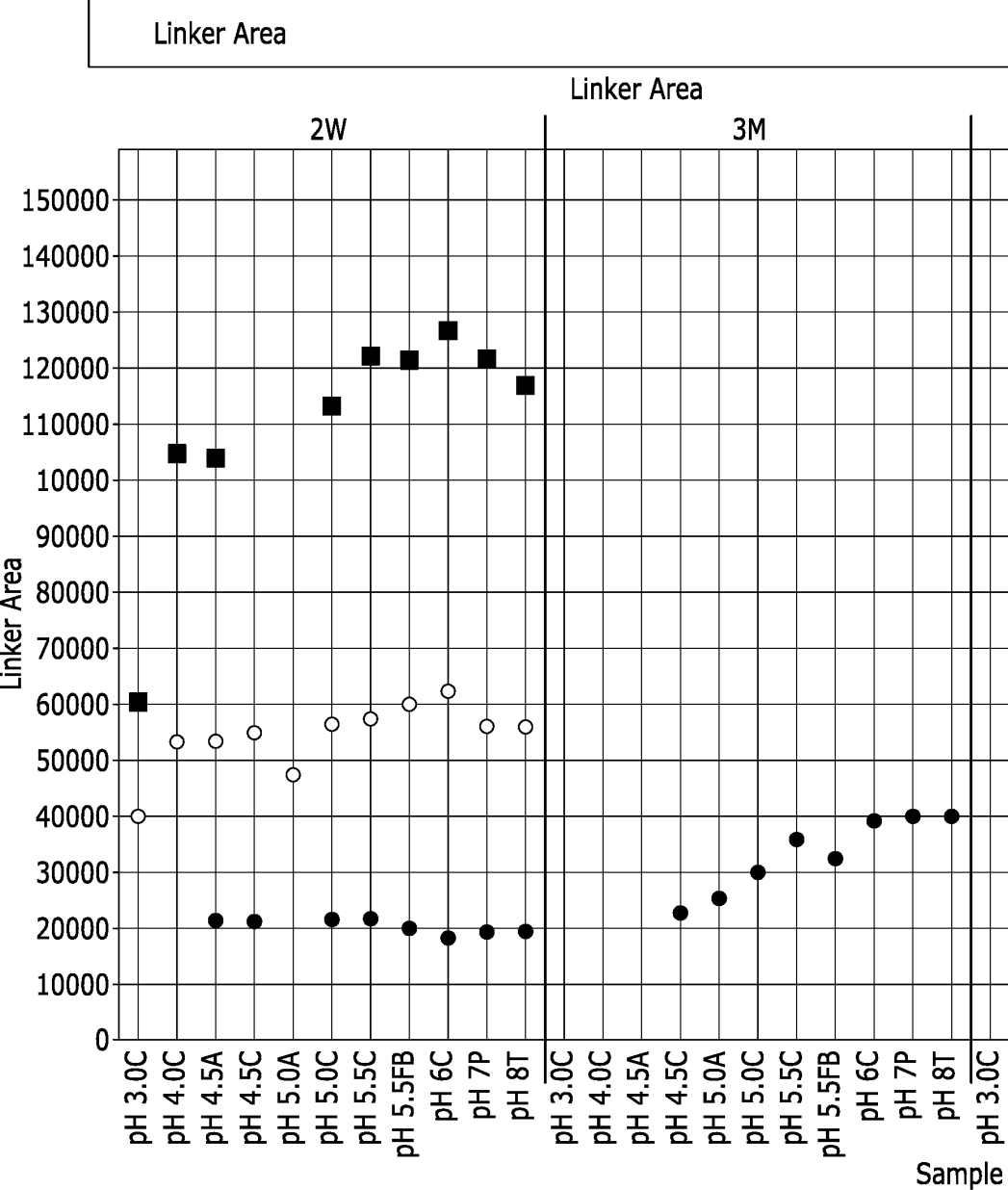


Figure 16

SUBSTITUTE SHEET (RULE 26)

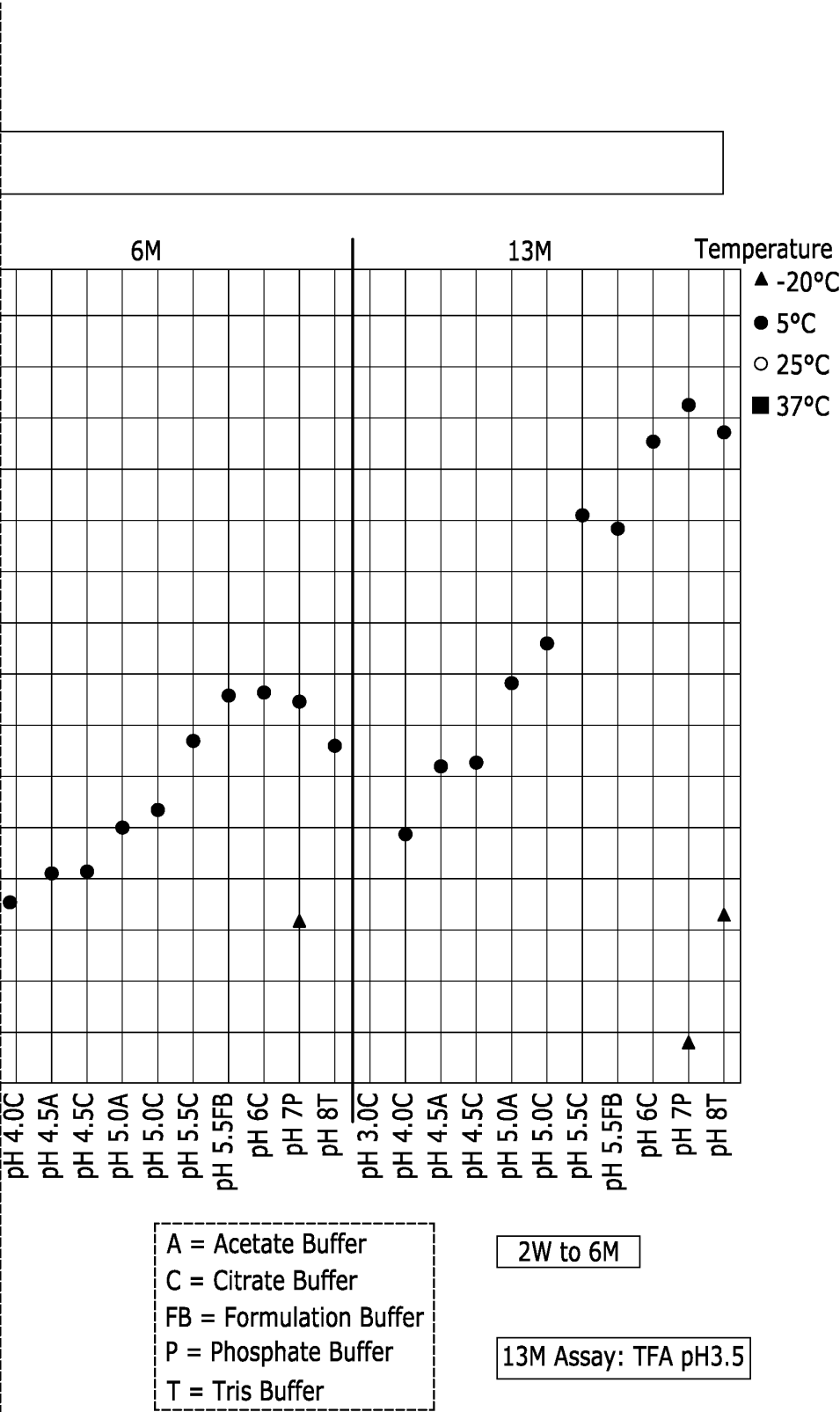


Figure 16 (Continued)

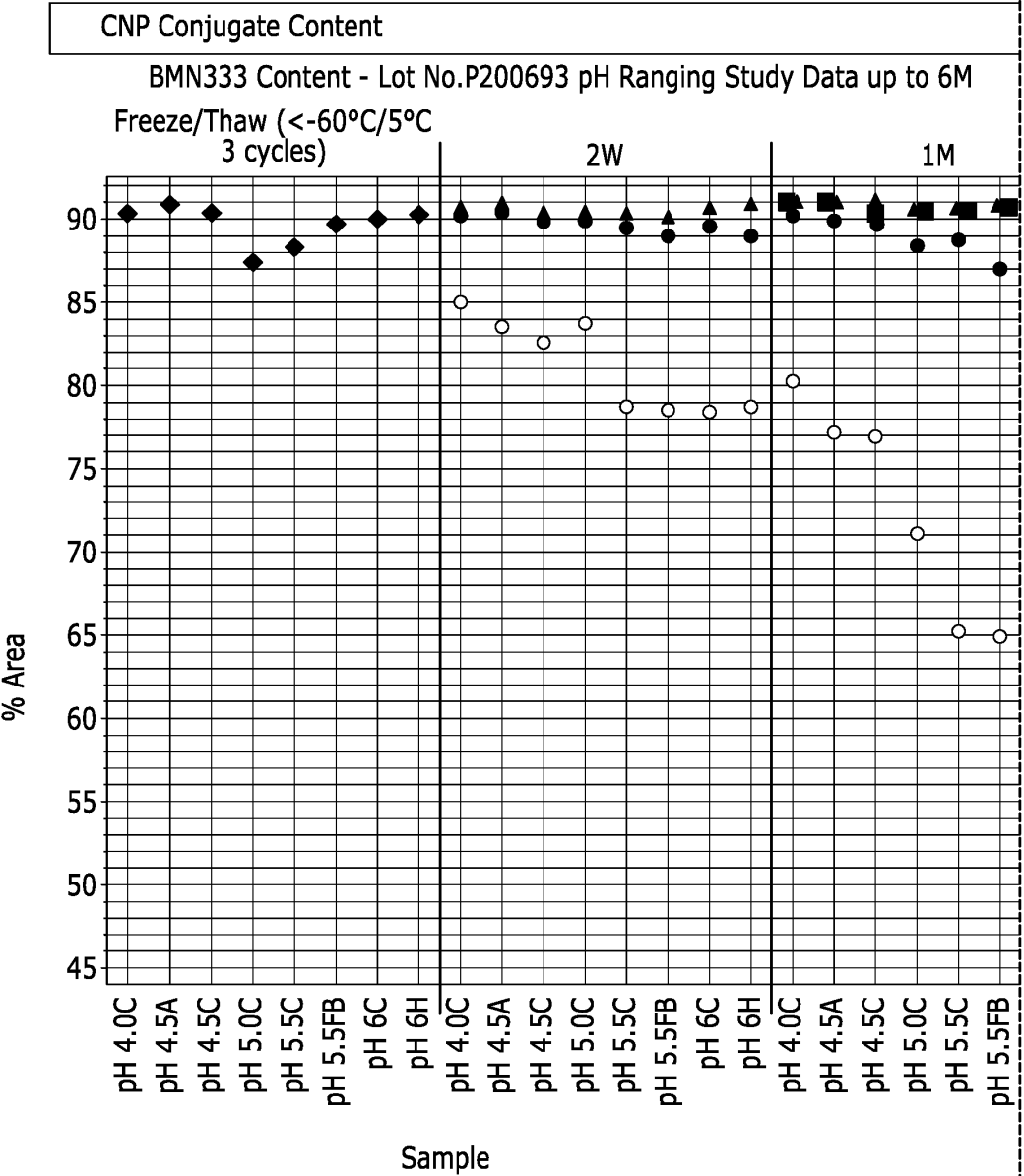


Figure 17

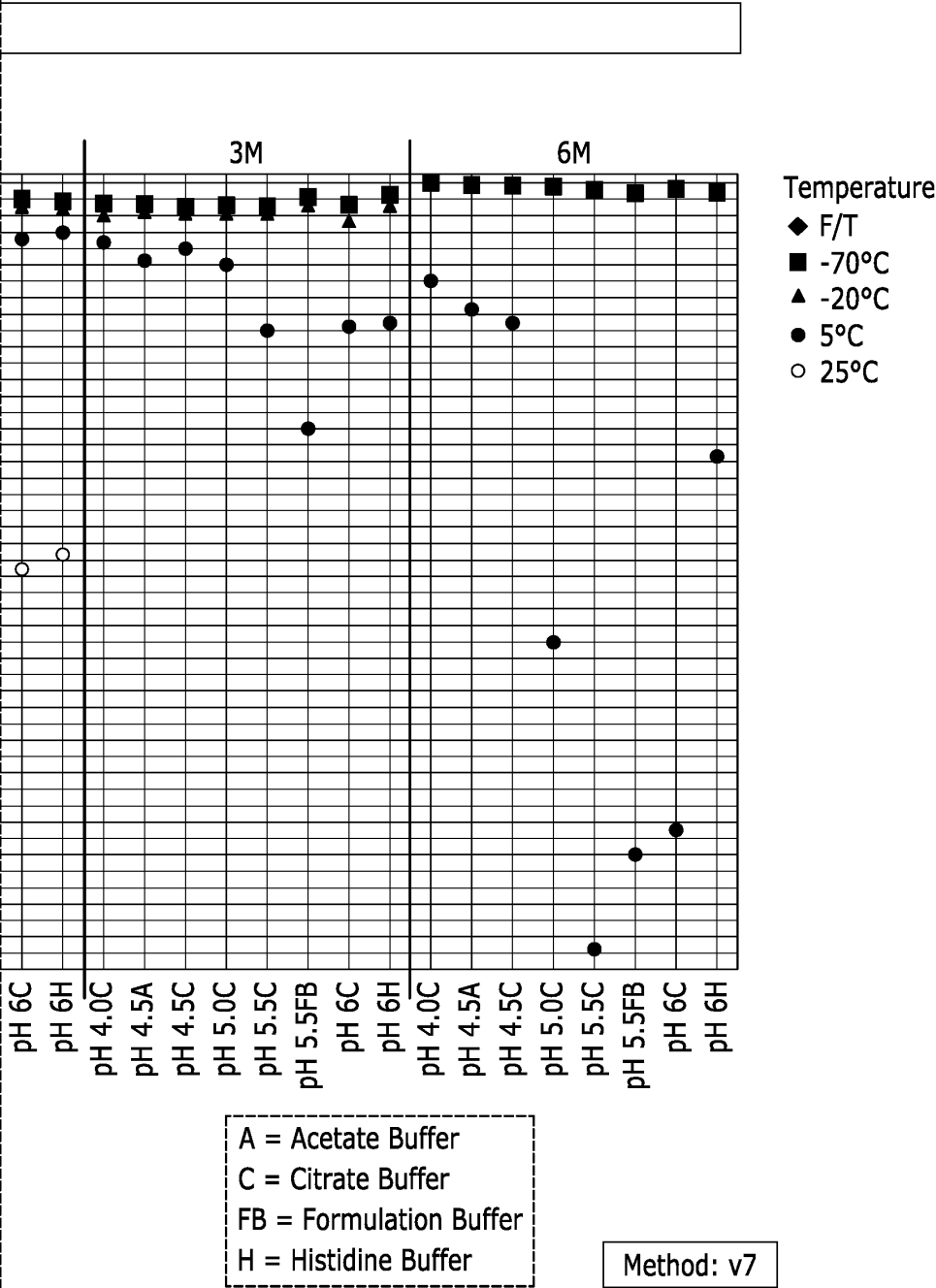


Figure 17 (Continued)

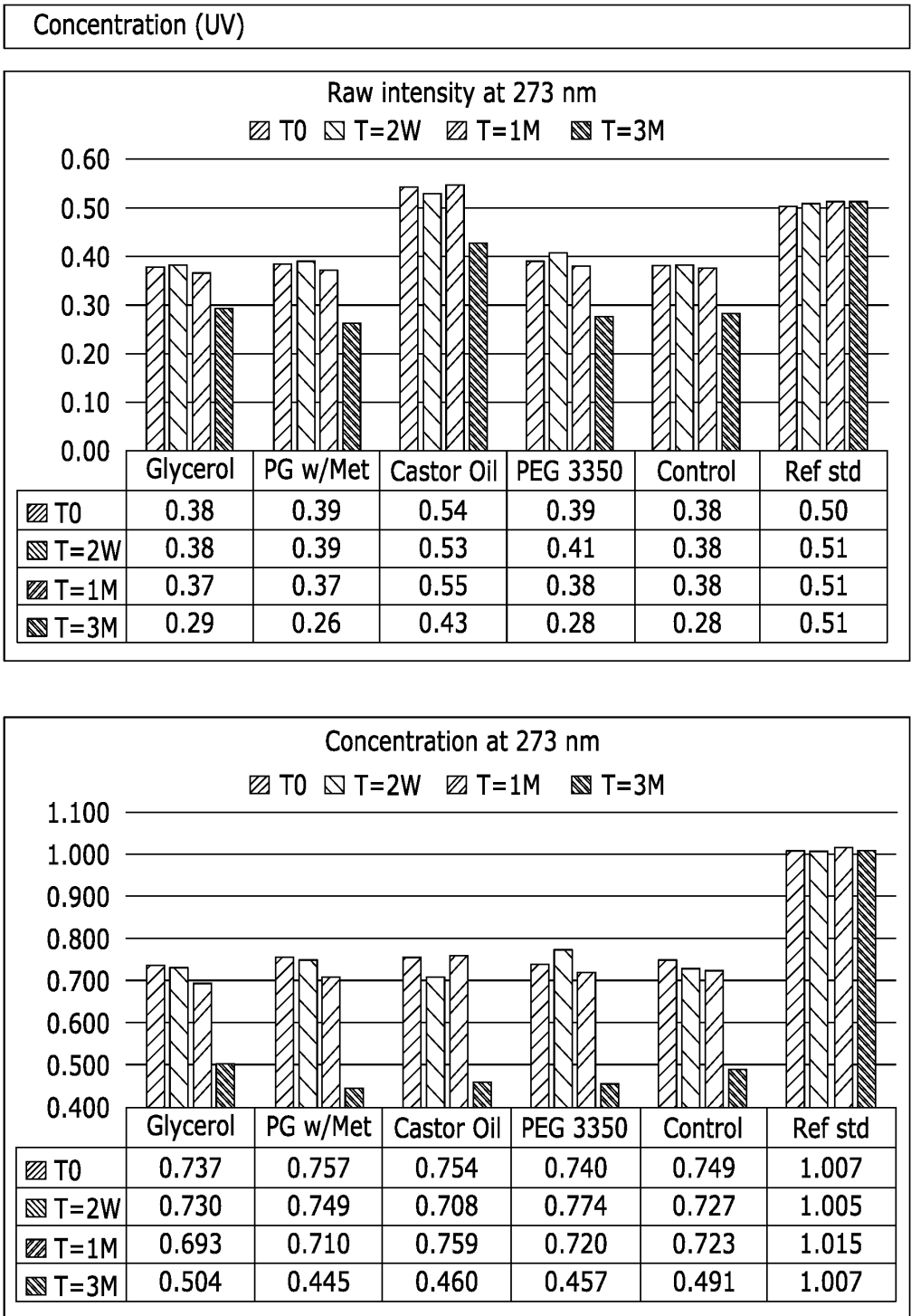


Figure 18

Figure 19

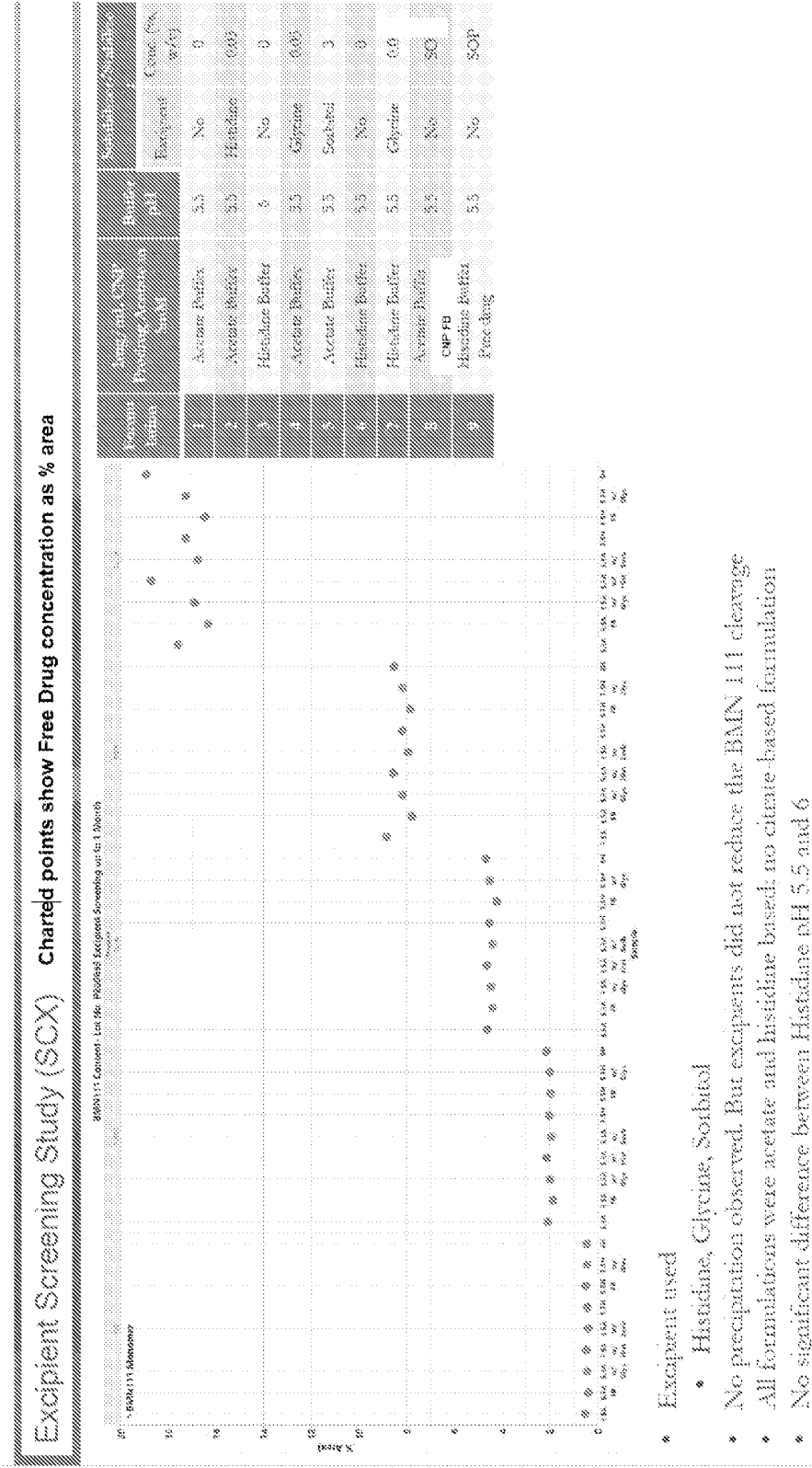


Figure 20

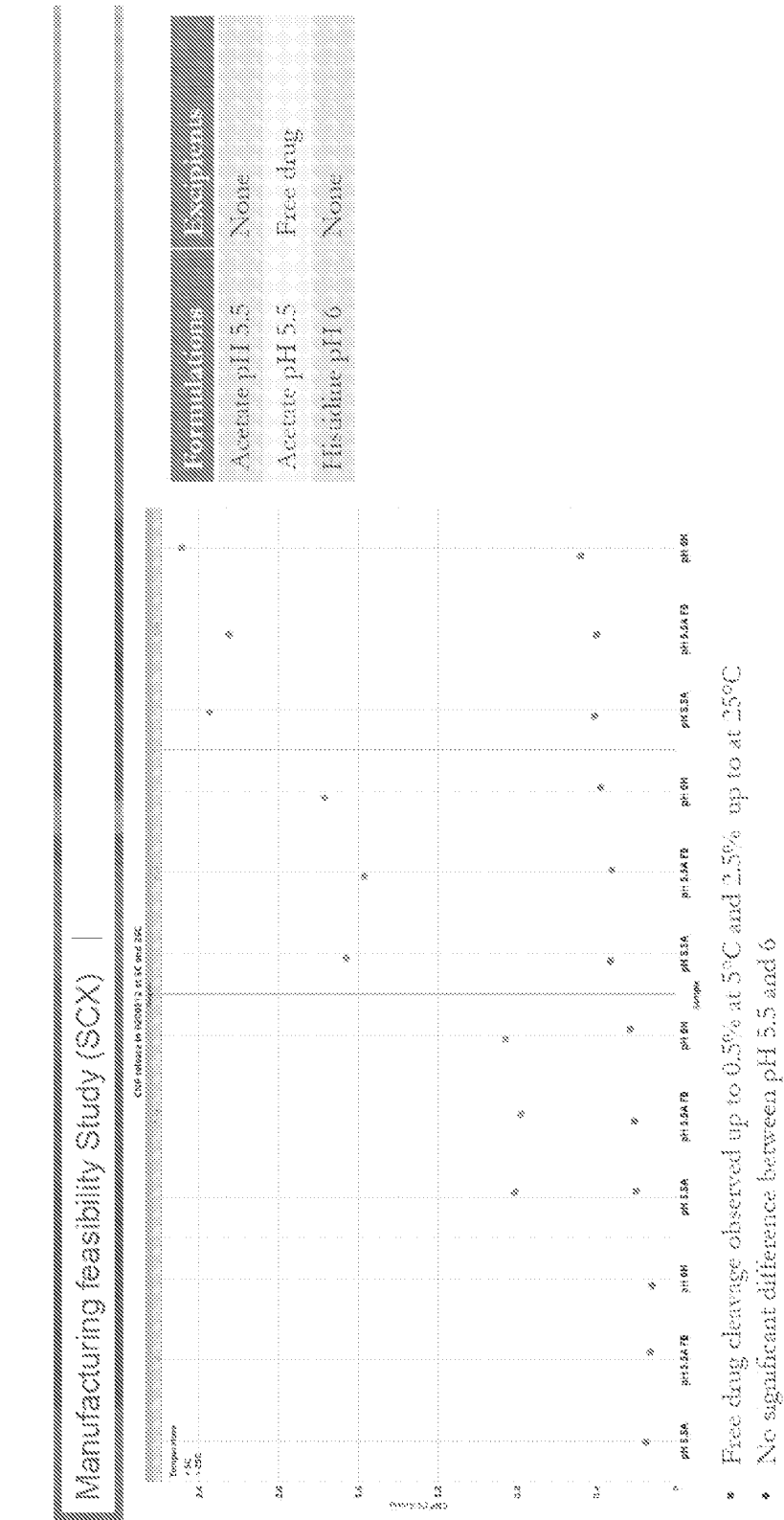


Figure 21

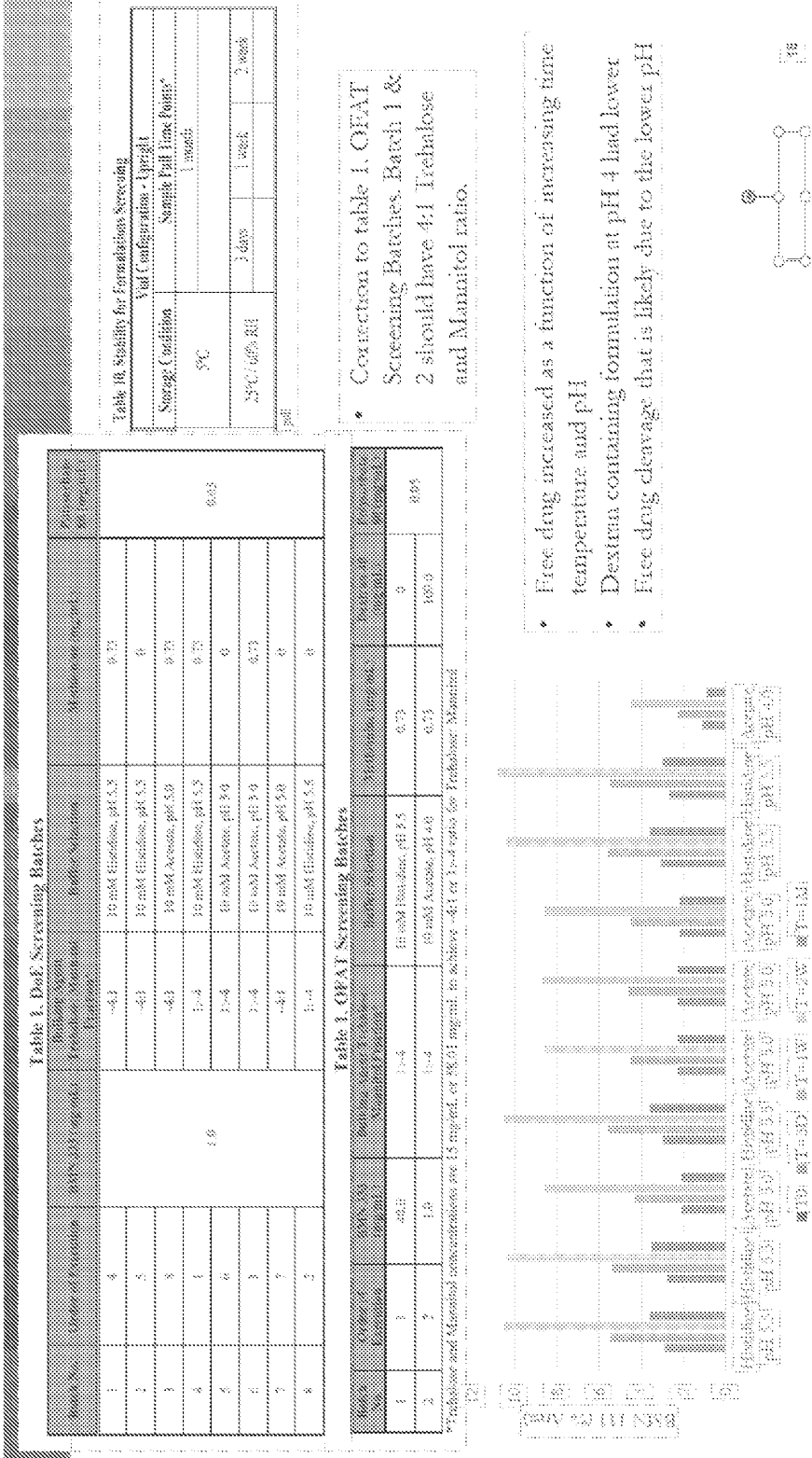


Figure 22



Buffer	Test Article	Timepoint	CNP	Label	Prodng	Σ Other	RR1=0.23	RR1=0.24
5mM pH5.5C FB	TA1	T=0	0.6	ND	89	10.1	ND	ND
	TA2	T=0	0.6	ND	90	9.6	ND	ND
	TA3	T=0	0.6	ND	90	9.8	ND	ND
	TA4	T=0	0.6	ND	90	9.5	ND	ND
	TA5	T=0	0.4	ND	90	9.7	ND	ND
	TA6	T=0	0.5	ND	90	9.6	ND	ND
5mM pH5.5C FB	TA1	Pre-dosing	0.4	ND	89	10.3	ND	ND
	TA2	Pre-dosing	0.4	ND	89	10.3	ND	ND
	TA3	Pre-dosing (	0.5	ND	90	9.9	ND	0.3
	TA4	Pre-dosing	0.5	ND	90	9.7	ND	0.2
	TA5	Pre-dosing (	0.4	ND	91	8.9	ND	ND
	TA6	Pre-dosing (	0.5	ND	91	9.2	ND	ND
10mM pH5.5C FB	TA1	Post-dosing	0.4	ND	89	10.8	ND	0.2
	TA2	Post-dosing	0.5	ND	89	10.6	ND	0.2
	TA3	Post-dosing	0.5	ND	89	10.3	ND	0.2
	TA4	Post-dosing	0.5	ND	89	10.2	0.1	0.2
	TA5	Post-dosing	0.5	ND	90	9.5	0.1	0.2
	TA6	Post-dosing	0.5	ND	90	9.5	0.1	0.2

chlorella k12

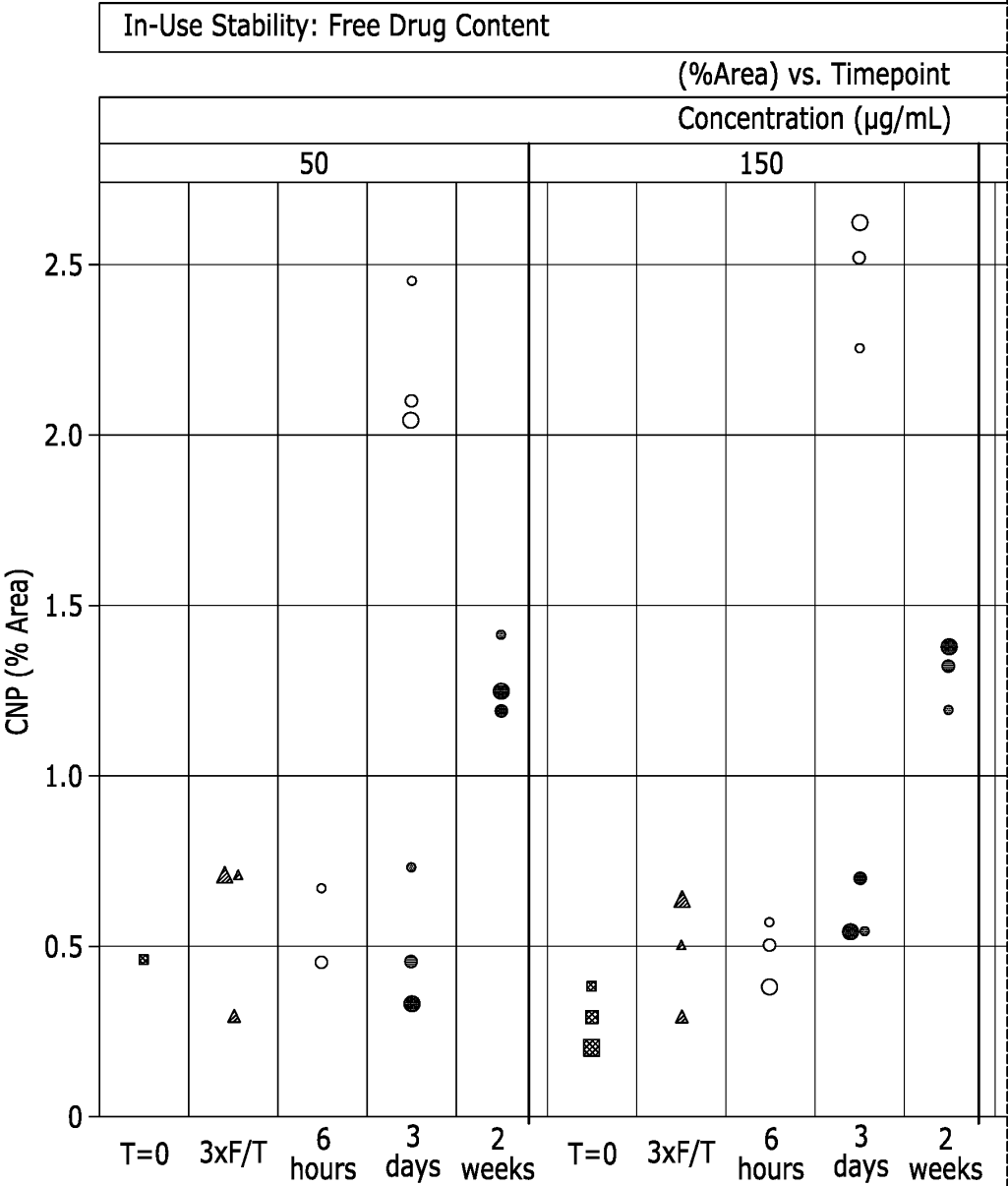


Figure 23

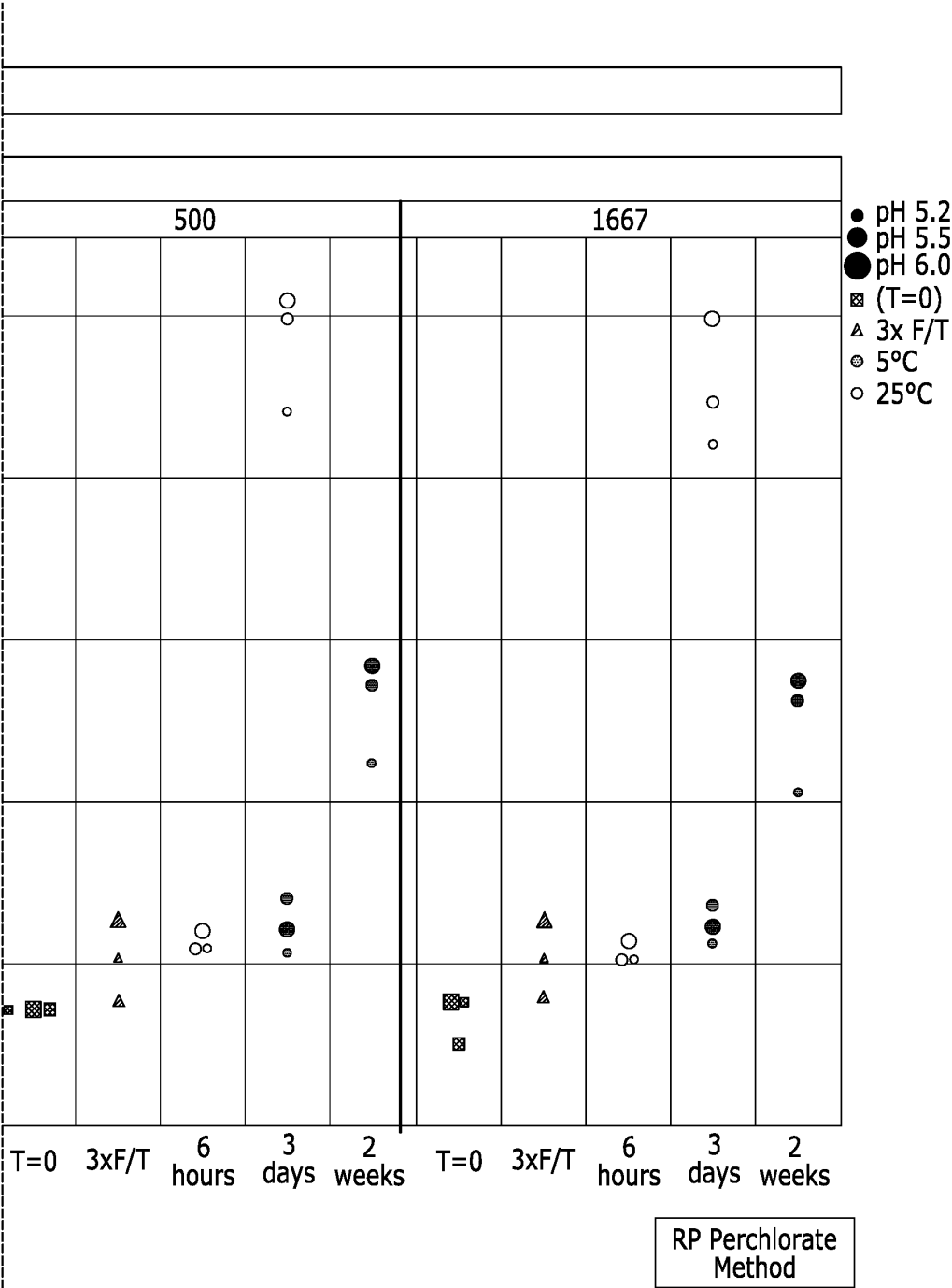


Figure 23 (Continued)

4:1 Trehalose:Mannitol Histidine Formulation Buffer pH 5.5			Formulation Buffer pH 5.5
3.8% Trehalose	4.8% Trehalose	5.8% Trehalose	5.8% Trehalose
			

Figure 24

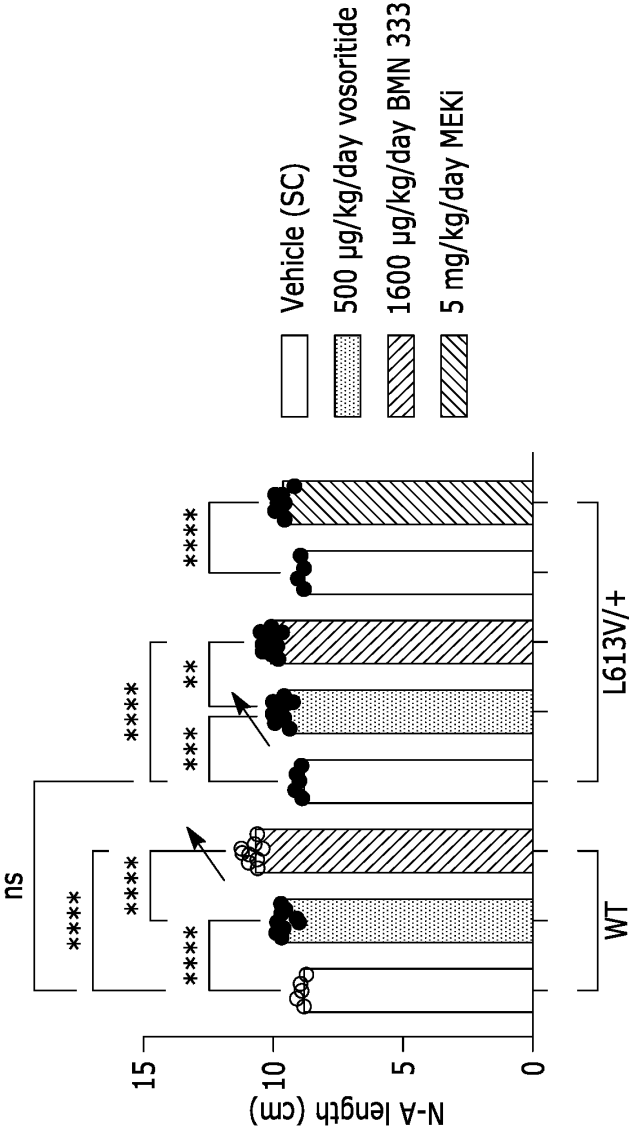


Figure 25A

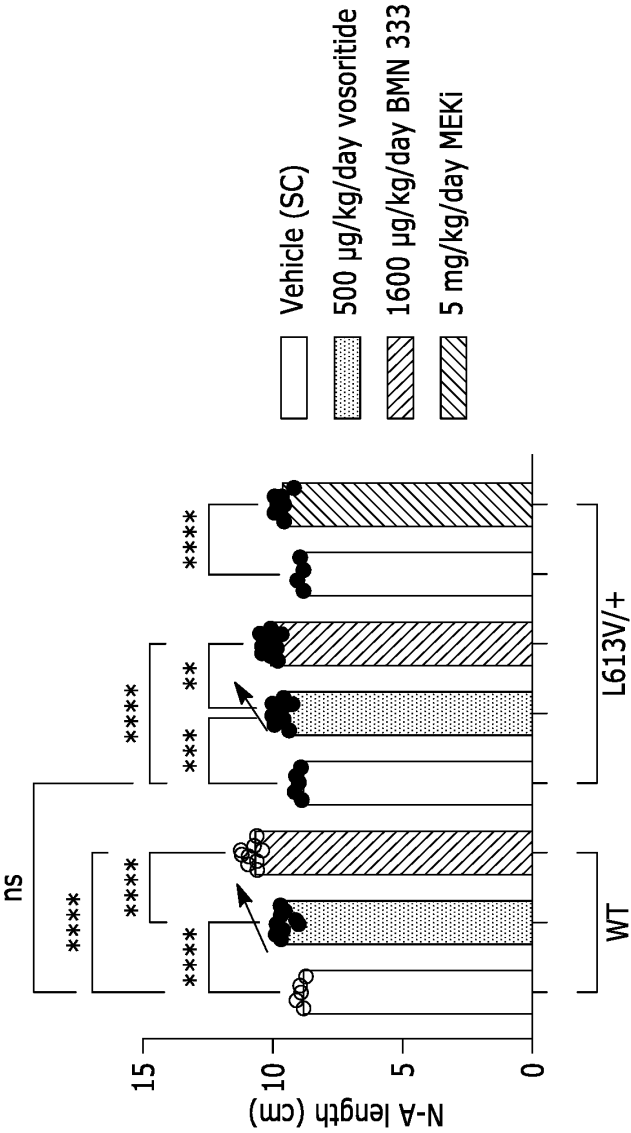


Figure 25B

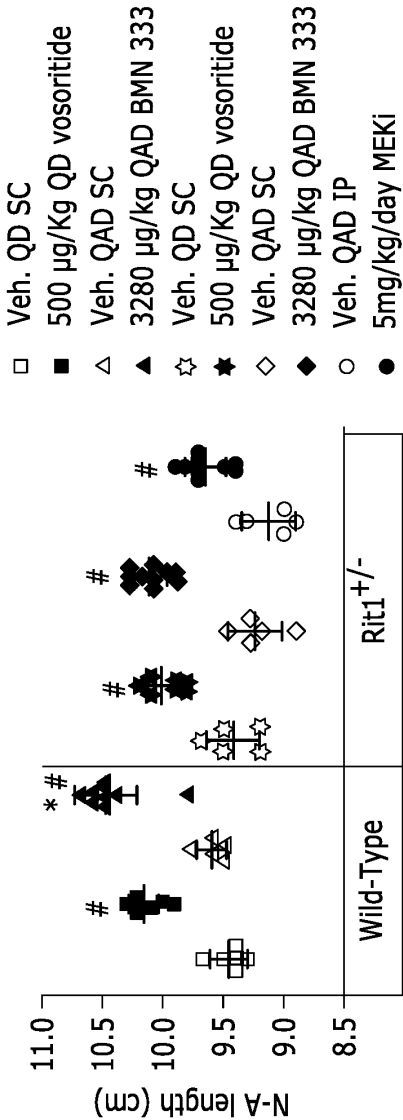


Figure 26

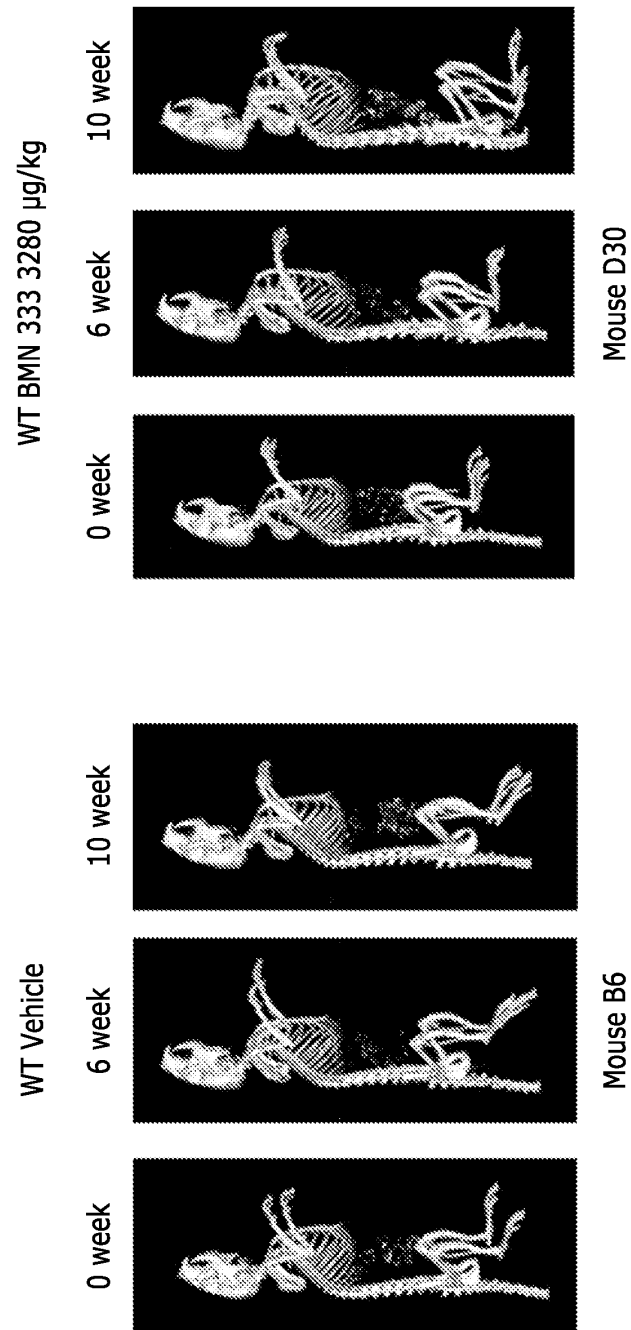


Figure 28 - Plasma Pharmacokinetics of CNP Prodrug and Released Vosoritide in Mice Following a Single SC Dose

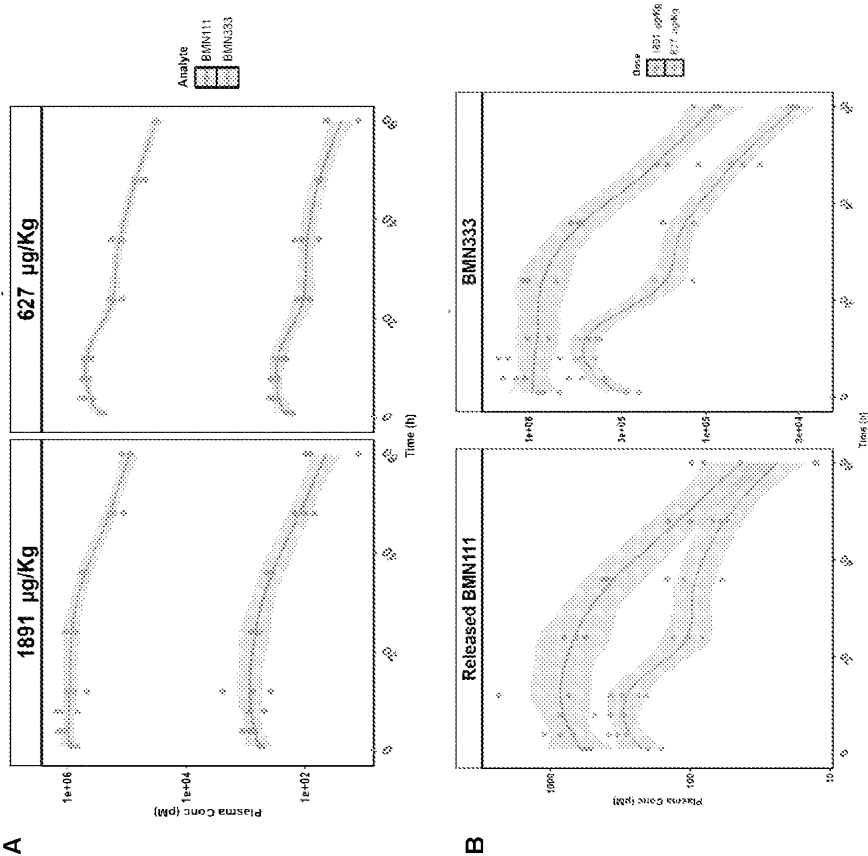
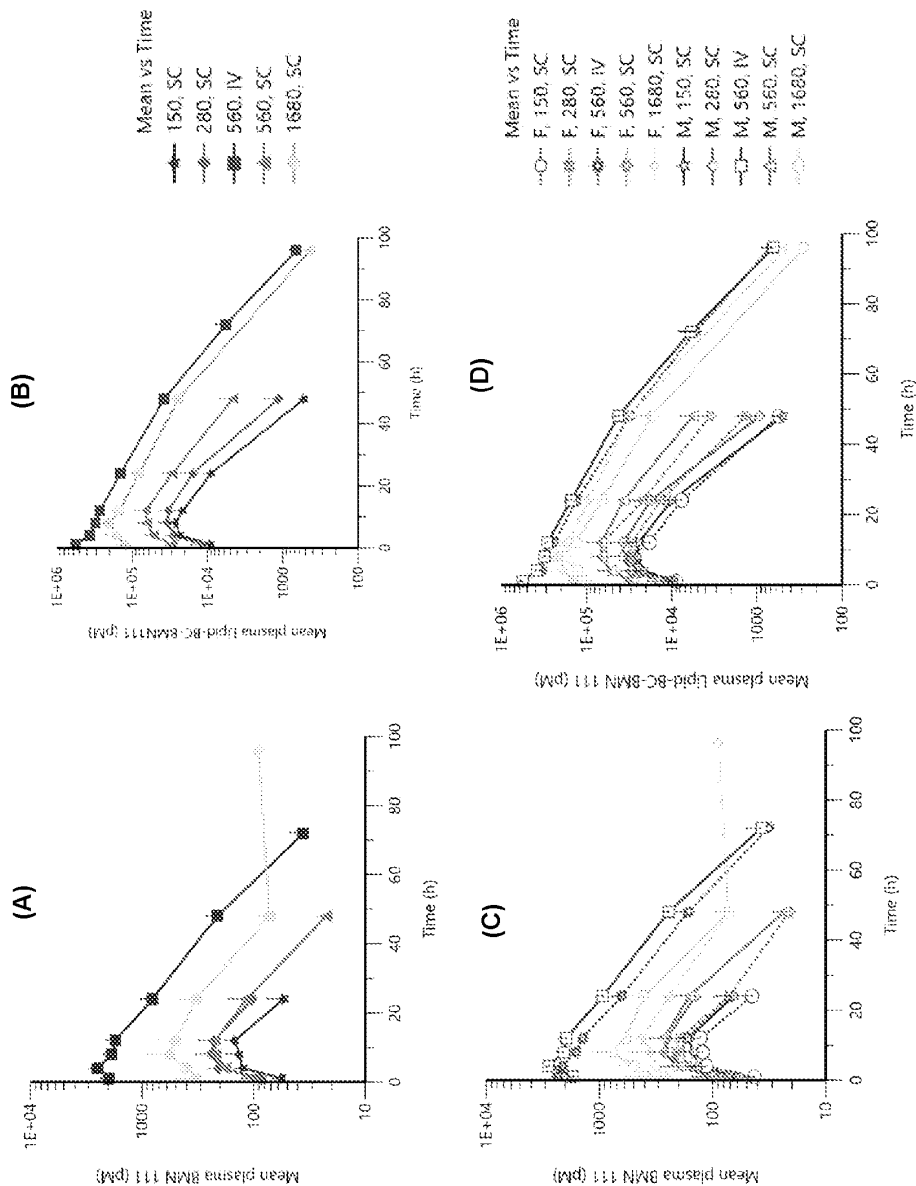


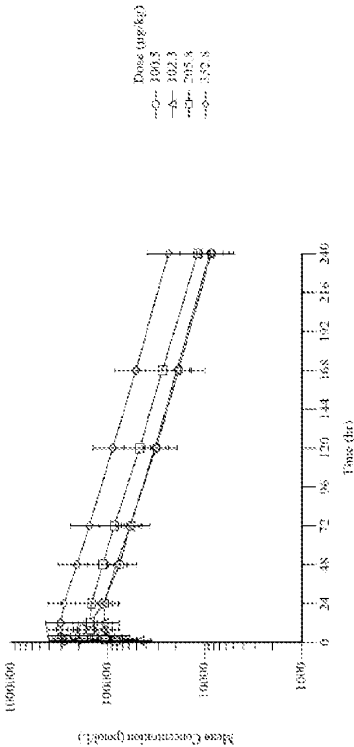
Figure 29 - Mean (±SD) Plasma Vosoritide and CNP Prodrug Concentration-Time Profiles after a Single Dose of CNP Prodrug



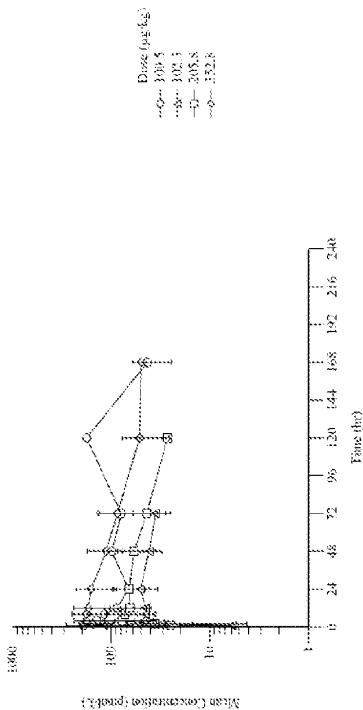
BMN 111; vosoritide; Lipid-BC-BMN 111, CNP Prodrug.
Mean plasma vosoritide (A,C) and CNP Prodrug (B,D) concentrations for each group of animals combined (A,B) and by sex (C,D); error bars represent the standard deviations from the mean concentrations

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



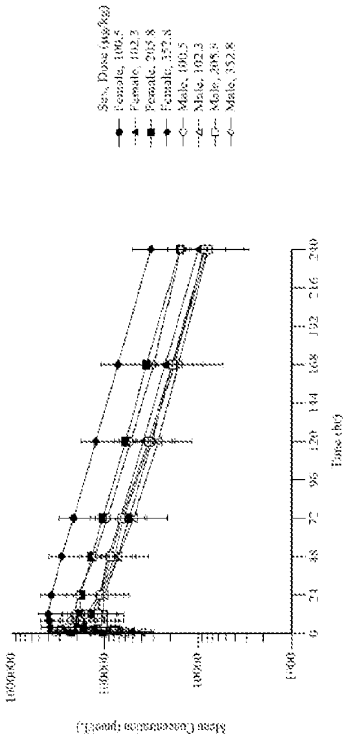
(B) Vosoritide



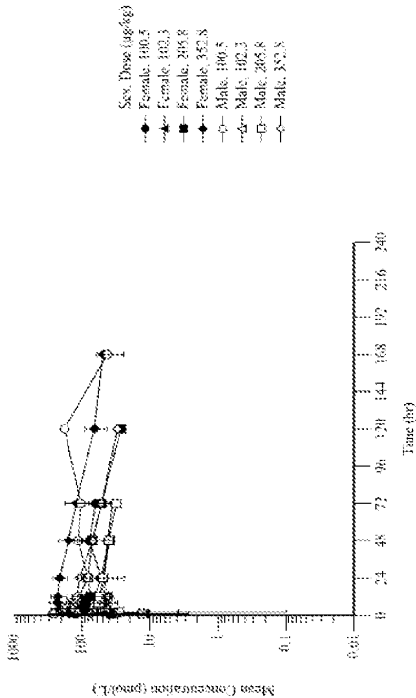
Mean plasma CNP Prodrug (A) and vosoritide (B) concentrations for each group of animals as combined; error bars represent the standard deviations from the mean concentrations.

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

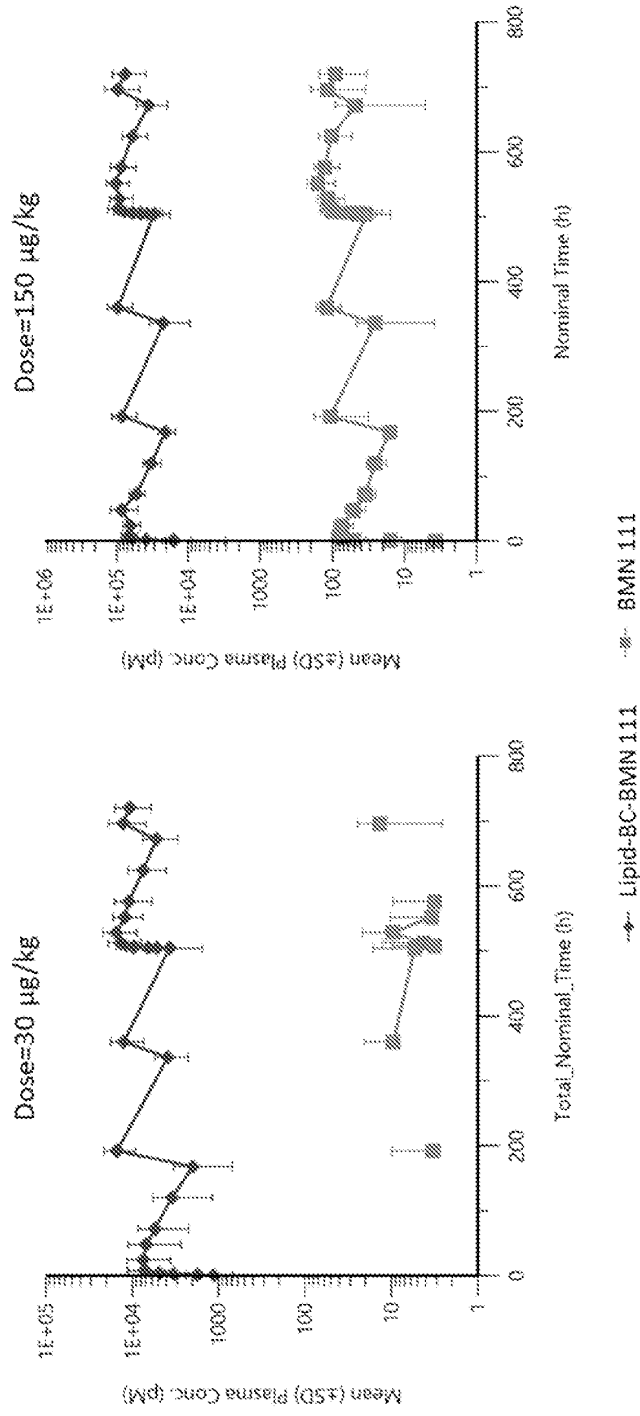


(B) Vosoritide



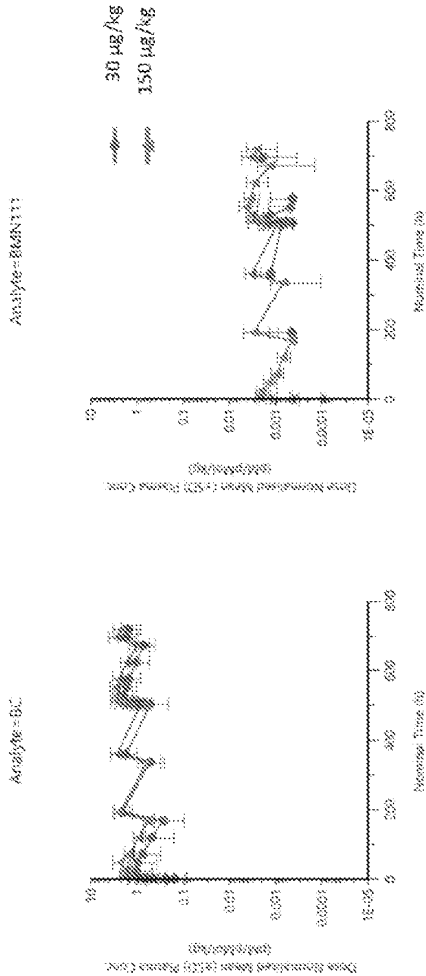
Mean plasma CNP Prodrug (A) and vosoritide (B) concentrations for each group of male and female NHPs; error bars represent the standard deviations from the mean concentrations.

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



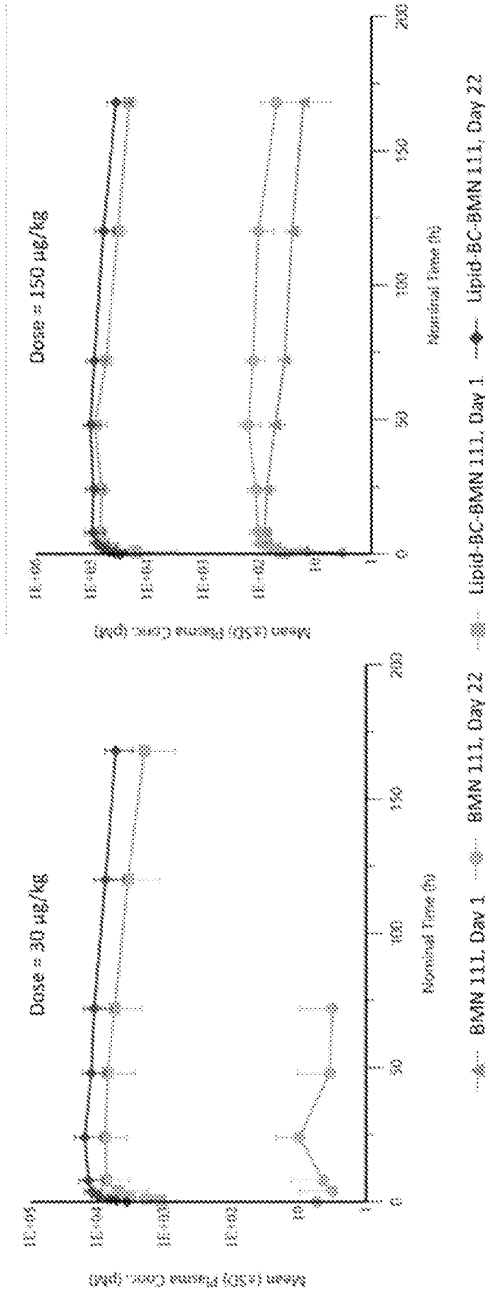
Mean plasma vosoritide and CNP Prodrug (A) and dose normalized mean plasma (B) concentrations for each group of animals; error bars represent the standard deviations from the mean concentrations.

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 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 Vorosotide and CNP Prodrug Concentration-Time Comparing Day 1 vs Day 22



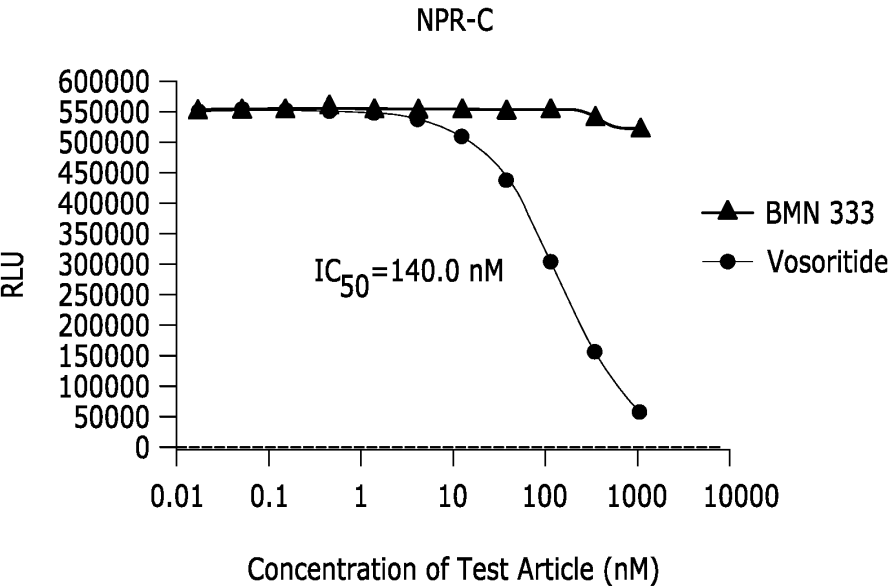
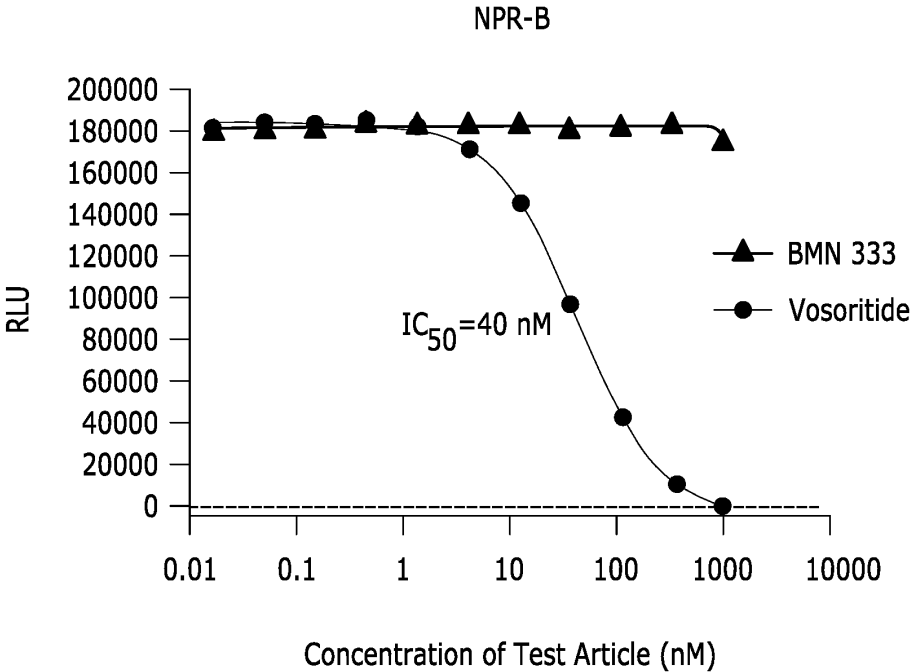


Figure 34