

FIG. 39C

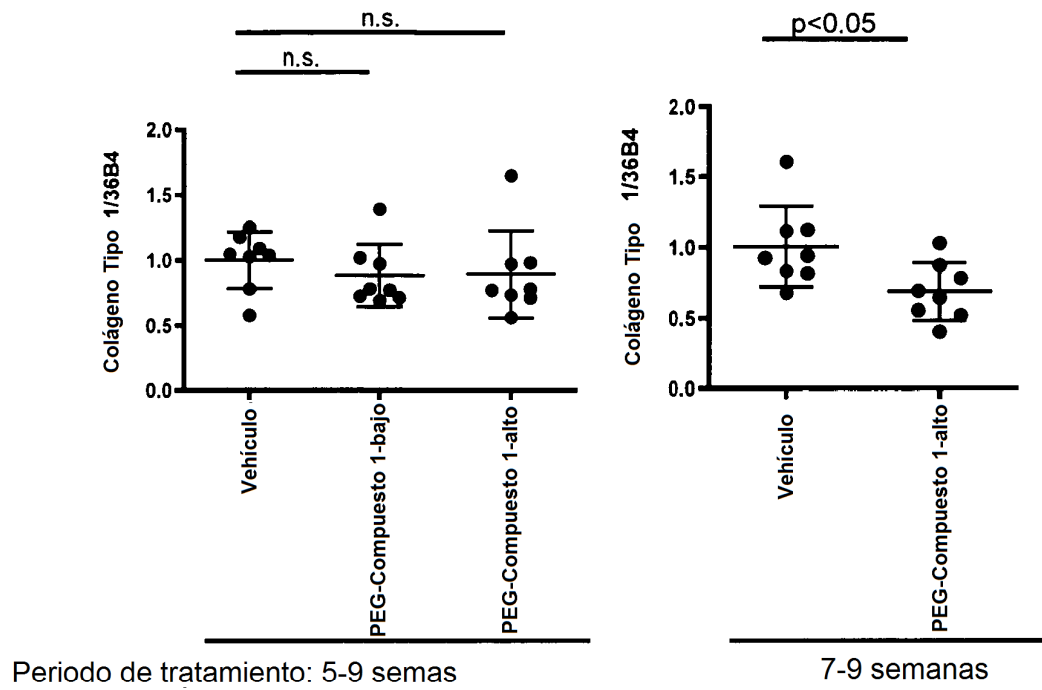


FIG. 39D

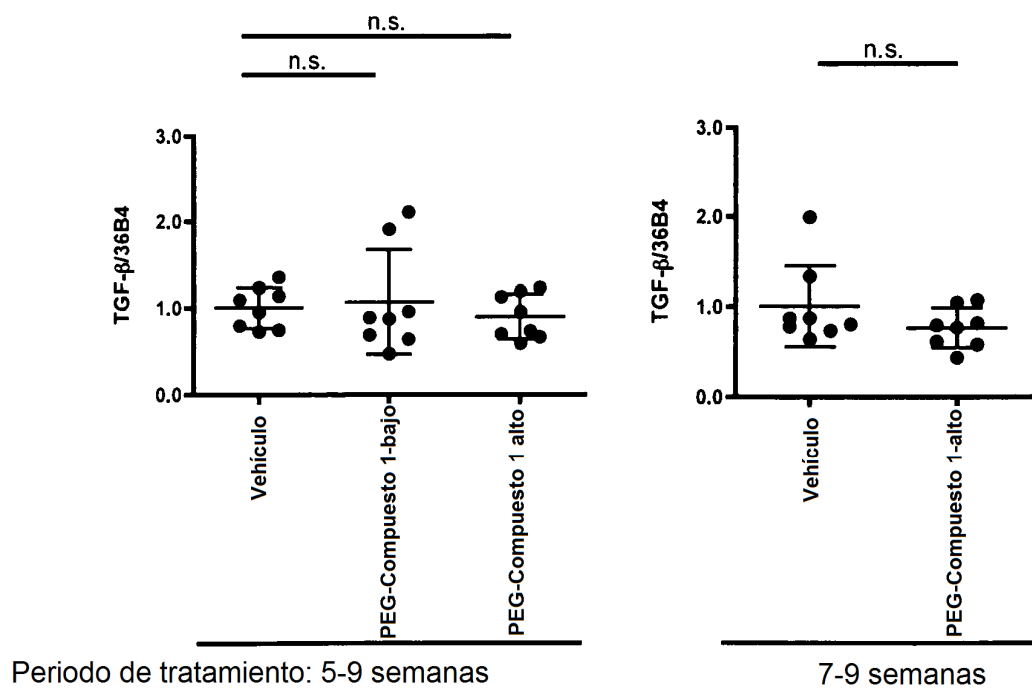


FIG. 40A.

Nombre del Compuesto	SEQ ID NO:	Arreglo de fusión	Péptido de Conexión	SEQ ID NO:
Compuesto 101	401	PKE(2)-L1-FGF21(Cmp. 2)	GS	354
Compuesto 102	402	PKE(2)-L2-FGF21(Cmp. 2)	GGGS	355
Compuesto 103	403	PKE(2)-L3-FGF21(Cmp. 2)	EEEEEEEEED	356
Compuesto 104	404	PKE(2)-L4-FGF21(Cmp. 2)	PSPEPTPEP	357
Compuesto 105	405	PKE(2)-L5-FGF21(Cmp. 2)	GSHHHHHHHGS	358
Compuesto 106	406	PKE(2)-L6-FGF21(Cmp. 2)	GGGSGGGSGGGGS	359
Compuesto 107	407	PKE(2)-L7-FGF21(Cmp. 2)	GGGSGGGSGGGGS	360
Compuesto 108	408	PKE(2)-L8-FGF21(Cmp. 2)	GSGSGSGSGSGSGS	361
Compound 109	409	PKE(2)-L9-FGF21(Cmp. 2)	PSTPTSPSTPTSPS	362
Compuesto 110	410	PKE(2)-L10-FGF21(Cmp. 2)	RGEEKKKEKEEERETKP	363
Compuesto 111	411	PKE(2)-L11-FGF21(Cmp. 2)	GGGSGGGSGGGSGGGGS	364
Compuesto 112	412	PKE(2)-L12-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	365
Compound 113	413	PKE(2)-L13-FGF21(Cmp. 2)	PSTPTSPSTPTSPSPSTPTSPSTPTSPS	366
Compuesto 114	414	PKE(2)-L14-FGF21(Cmp. 2)	PSPEP	367
Compuesto 115	415	PKE(2)-L15-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEP	368
Compuesto 116	416	PKE(2)-L16-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	369
Compuesto 117	417	PKE(2)-L17-FGF21(Cmp. 2)	PTPEPPSPPTPEPPSP	370
Compuesto 118	418	PKE(2)-L18-FGF21(Cmp. 2)	PSPEPGGSGPTPEP	371
Compuesto 119	419	PKE(2)-L19-FGF21(Cmp. 2)	PSPEEEEEEDPTPEP	372
Compuesto 120	420	PKE(2)-L20-FGF21(Cmp. 2)	PSPEPTPEEEEEEDPSPEPTPEP	373
Compuesto 121	421	PKE(2)-L21-FGF21(Cmp. 2)	PTPEPPSPPTPEEEEEEDPSPEPTPEPPSP	374
Compuesto 122	422	PKE(2)-L22-FGF21(Cmp. 2)	PTPEPPSPPTPEPGGSGSPPTPEPPSP	375
Compuesto 123	423	PKE(2)-L23-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	376

FIG. 40B.

Nombre del Compuesto	SEQ ID NO:	Arreglo de Fusión	Péptido de Conexión	SEQ ID NO:
Compuesto 124	424	HuSA(C34A)-L201-FGF21(Cmp. 2)	GS	354
Compuesto 125	425	HuSA(C34A)-L202-FGF21(Cmp. 2)	GGGGS	355
Compuesto 126	426	HuSA(C34A)-L203-FGF21(Cmp. 2)	GETGS	377
Compuesto 127	427	HuSA(C34A)-L204-FGF21(Cmp. 2)	GGGSGGGGS	378
Compuesto 128	428	HuSA(C34A)-L205-FGF21(Cmp. 2)	GETSSGEGT	379
Compuesto 129	429	HuSA(C34A)-L206-FGF21(Cmp. 2)	GGGSGGGSGGGGS	359
Compuesto 130	430	HuSA(C34A)-L207-FGF21(Cmp. 2)	GETGSGEGTGSTGS	380
Compuesto 131	431	HuSA(C34A)-L208-FGF21(Cmp. 2)	GGGSGGGSGGGSGGGGS	381
Compuesto 132	432	HuSA(C34A)-L209-FGF21(Cmp. 2)	GETGSGEGTGSTGAGES	382
Compuesto 133	434	HuSA(C34A, des Leu-585)-L211-FGF21(Cmp. 2)	GGGSGGGSGGGSGGGGS	359
Compuesto 134	435	HuSA(C34A, des Leu-585)-L207-FGF21(Cmp. 2)	GETGSGEGTGSTGS	380
Compuesto 135	436	HuSA(C34A, des Leu-585)-L211-FGF21(Cmp. 1)	GGGSGGGSGGGSGGGGS	359
Compuesto 136	437	HuSA(C34A, des Leu-585)-L207-FGF21(Cmp. 1)	GETGSGEGTGSTGS	380
Compuesto 137	440	FGF21(Cmp. 2)-L205-HuSA(C34A)	GETSSGEGT	379
Compuesto 138	441	FGF21(Cmp. 2)-L209-HuSA(C34A)	GETGSGEGTGSTGAGES	382
Compuesto 139	442	FGF21(Cmp. 2)-L210-HuSA(C34A)	GETGSGEGTGSTGAGESGTGSGEGGS	383
Compuesto 140	443	FGF21(Cmp. 1)-L209-HuSA(C34A)	GETGSGEGTGSTGAGES	382
Compuesto 141	446	FGF21(Cmp. 2)-L209-HuSA(C34A)-G4Sx3-FGF21(Cmp. 2)	GETGSGEGTGSTGAGES	382
Compuesto 142	447	FGF21(Cmp. 1)-L209-HuSA(C34A)-G4Sx3-FGF21(Cmp. 1)	GETGSGEGTGSTGAGES	382
Compuesto 143	448	FGF21(Cmp. 2)-L209-HuSA(C34A, des Leu-585)-G4Sx3-FGF21(Cmp. 2)	GETGSGEGTGSTGAGES	382
Compuesto 144	449	FGF21(Cmp. 1)-L209-HuSA(C34A, des Leu-585)-G4Sx3-FGF21(Cmp. 1)	GETGSGEGTGSTGAGES	382
Compuesto 145	450	FGF21(Cmp. 2)-L210-HuSA(C34A)-G4Sx3-FGF21(Cmp. 2)	GETGSGEGTGSTGAGESGTGSGEGGS	383
Compuesto 146	451	FGF21(Cmp. 1)-L210-HuSA(C34A)-G4Sx3-FGF21(Cmp. 1)	GETGSGEGTGSTGAGESGTGSGEGGS	383

FIG. 40C

Nombre del Compuesto	SEQ ID NO:	Arreglo de Fusión	Péptido de Conexión	SEQ ID NO:
Compuesto 147	452	PKE(1)-L1-FGF21(Cmp. 2)	GS	354
Compuesto 148	453	PKE(1)-L2-FGF21(Cmp. 2)	GGGS	355
Compuesto 149	454	PKE(1)-L3-FGF21(Cmp. 2)	EEEEEEEEED	356
Compuesto 150	455	PKE(1)-L4-FGF21(Cmp. 2)	PSPEPTPEP	357
Compuesto 151	456	PKE(1)-L5-FGF21(Cmp. 2)	GSHHHHHHHHGS	358
Compuesto 152	457	PKE(1)-L6-FGF21(Cmp. 2)	GGGSGGGSGGGGS	359
Compuesto 153	458	PKE(1)-L7-FGF21(Cmp. 2)	GGGSGGGSGGGGS	360
Compuesto 154	459	PKE(1)-L8-FGF21(Cmp. 2)	GGSGSGSGSGSGGS	361
Compuesto 155	460	PKE(1)-L9-FGF21(Cmp. 2)	PSTPTPSPTPTPS	362
Compuesto 156	461	PKE(1)-L10-FGF21(Cmp. 2)	RGGEKKKKEKEEQEERETKP	363
Compuesto 157	462	PKE(1)-L11-FGF21(Cmp. 2)	GGGSGGGSGGGSGGGGS	364
Compuesto 158	463	PKE(1)-L12-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	365
Compuesto 159	464	PKE(1)-L13-FGF21(Cmp. 2)	PSTPTPSPTPTPSPTPTPSPTPTPS	366
Compuesto 160	465	PKE(1)-L14-FGF21(Cmp. 2)	PSPEP	367
Compuesto 161	466	PKE(1)-L15-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEP	368
Compuesto 162	467	PKE(1)-L16-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	369
Compuesto 163	468	PKE(1)-L17-FGF21(Cmp. 2)	PTPEPPSPPTPEPPSP	370
Compuesto 164	469	PKE(1)-L18-FGF21(Cmp. 2)	PSPEPGGGSPTPEP	371
Compuesto 165	470	PKE(1)-L19-FGF21(Cmp. 2)	PSPEPEEEDPTPEP	372
Compuesto 166	471	PKE(1)-L20-FGF21(Cmp. 2)	PSPEPTPEPEEEDPSPEPTPEP	373
Compuesto 167	472	PKE(1)-L21-FGF21(Cmp. 2)	PTPEPPSPPTPEPEEEDPSPEPTPEPPSP	374
Compuesto 168	473	PKE(1)-L22-FGF21(Cmp. 2)	PTPEPPSPPTPEPGGSGSPPTPEPPSP	375
Compuesto 169	474	PKE(1)-L23-FGF21(Cmp. 2)	PSPEPTPEPPSPPTPEPPSPPTPEP	376

FIG. 40D

Nombre del Compuesto	SEQ ID NO:	Arreglo de Fusión	Péptido de Conexión	SEQ ID NO:
Compuesto 170	475	Fc(hlgG1a_191)-L7-FGF21(Cmp. 2)	GGGGSGGSGGGGS	360
Compuesto 171	476	Fc(hlgG1a_191)-L250-FGF21(Cmp. 2)	GGGGSGGSGGSGGSGGSGGSGGGS	350
Compuesto 172	477	Fc(hlgG1a_191)-L12-FGF21(Cmp. 2)	PSPEPTPEPPSPPEPTPEPPSPPEPTPEP	365
Compuesto 173	478	Fc(hlgG1a_191)-L251-FGF21(Cmp. 2)	PSPEPTPEPPSPPEP	351
Compuesto 174	479	Fc(hlgG1a_191)-L5-FGF21(Cmp. 2)	GSHHHHHHHHGS	358
Compuesto 175	480	Fc(hlgG1a_191)-L252-FGF21(Cmp. 2)	ELQLEESAAEAQEGELE	352
Compuesto 176	481	Fc(hlgG1a_190)-L253-FGF21(Cmp. 2)	SSGGSGGSGGSGGSGGSGGS	353
Compuesto 177	482	Fc(hlgG1a_191)-L6-FGF21(Cmp. 2)	GGGGSGGSGGSGGSGGS	359
Compuesto 178	483	Fc(hlgG1a_189)-L6-FGF21(Cmp. 2)	GGGGSGGSGGSGGSGGS	359
Compuesto 179	484	Fc(hlgG1a_191)-L7-FGF21-1aa(Cmp. 2)	GGGGSGGSGGSGGSGGS	360
Compuesto 180	485	Fc(hlgG1a_191)-L7-FGF21-3aa(Cmp. 2)	GGGGSGGSGGSGGSGGS	360
Compuesto 181	486	Fc(hlgG1f_1.1_186)-L7-FGF21(Cmp. 2)	GGGGSGGSGGSGGSGGS	360
Compuesto 182	487	Fc(hlgG1a_191b)-L7-FGF21(Cmp. 2)	GGGGSGGSGGSGGSGGS	360

FIG. 41

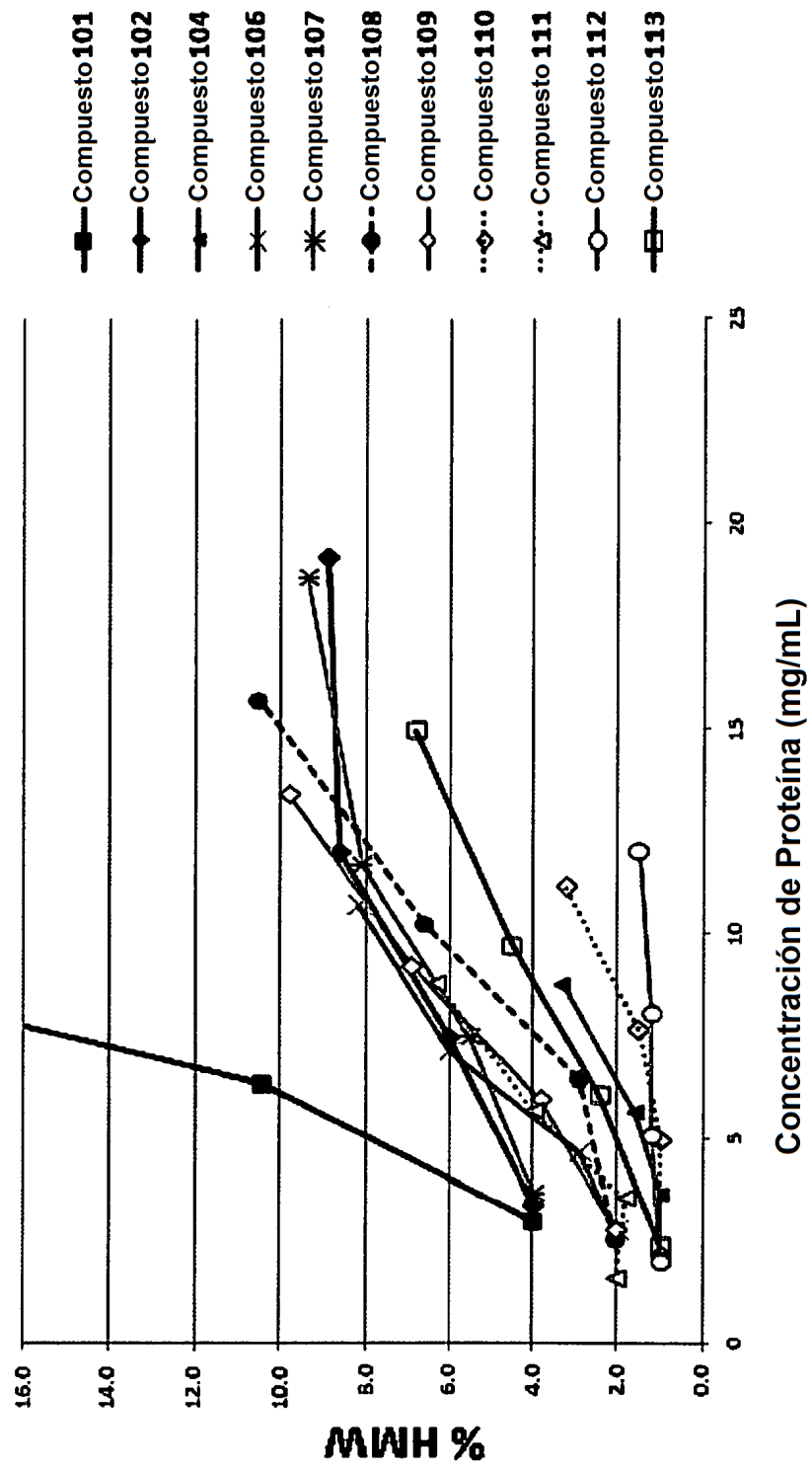


FIG. 42A

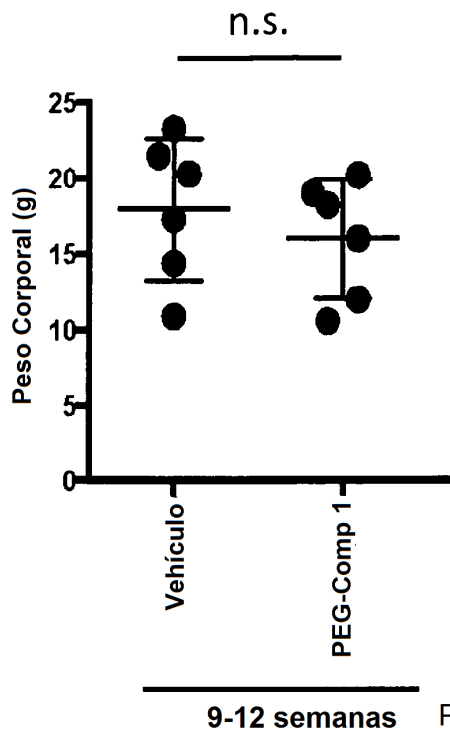


FIG. 42B

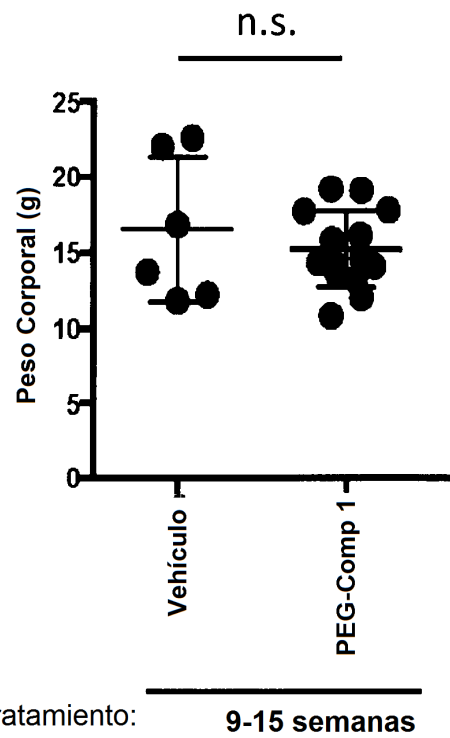


FIG. 43A

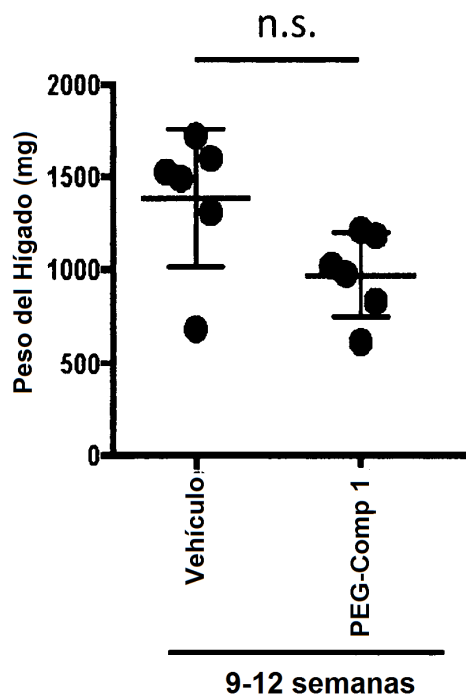


FIG. 43B

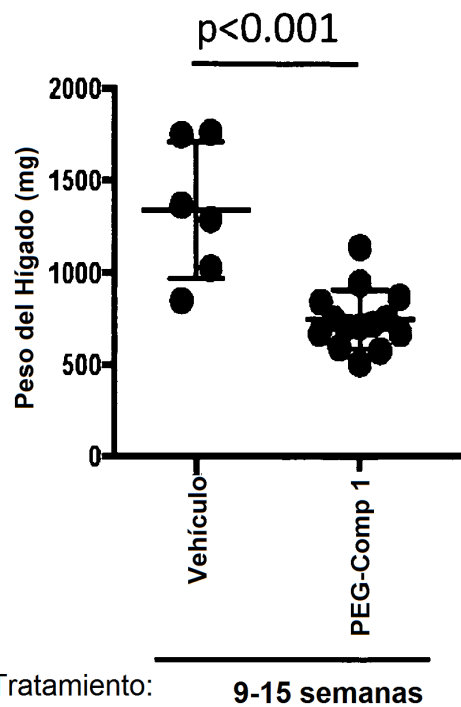


FIG. 44A

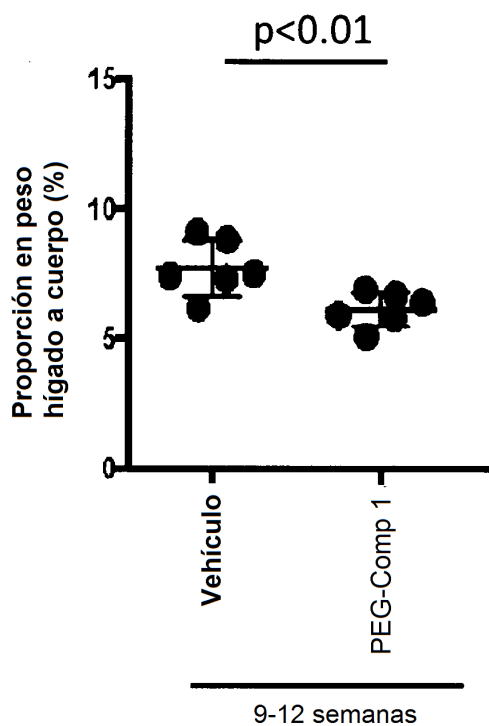


FIG. 44B

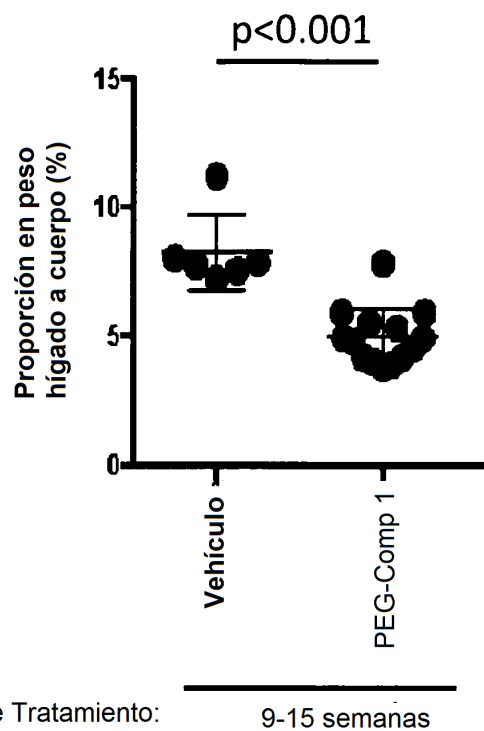


FIG. 45A

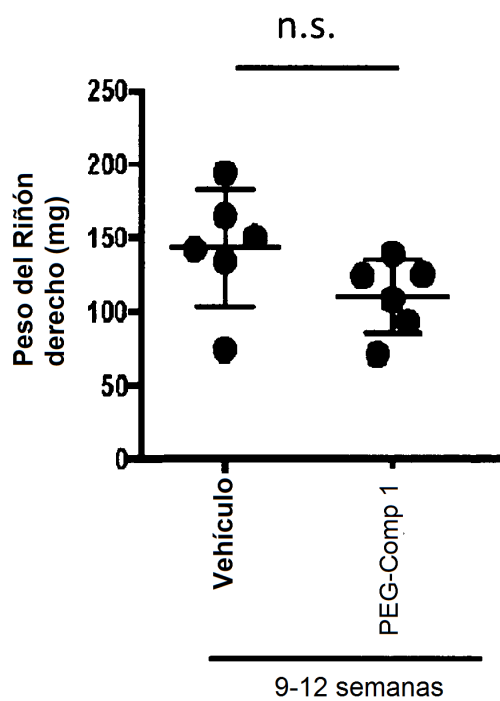


FIG. 45B

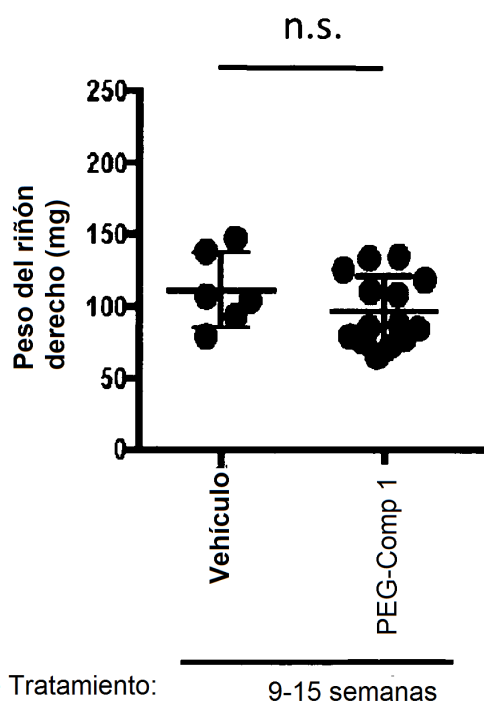


FIG. 46A

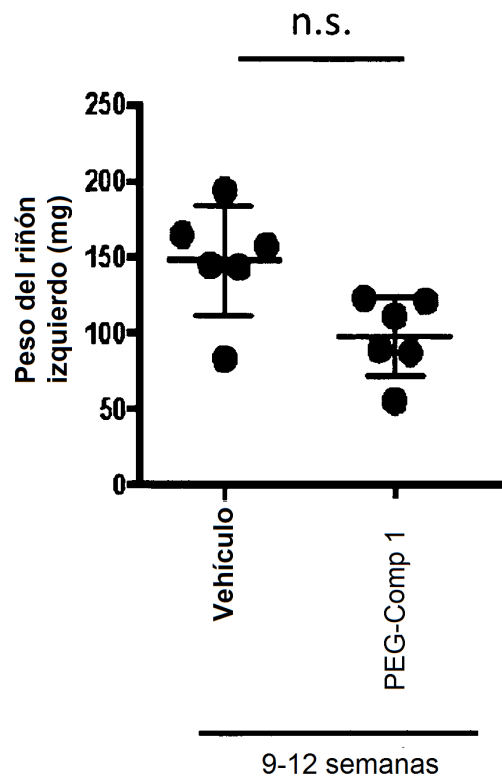


FIG. 46B

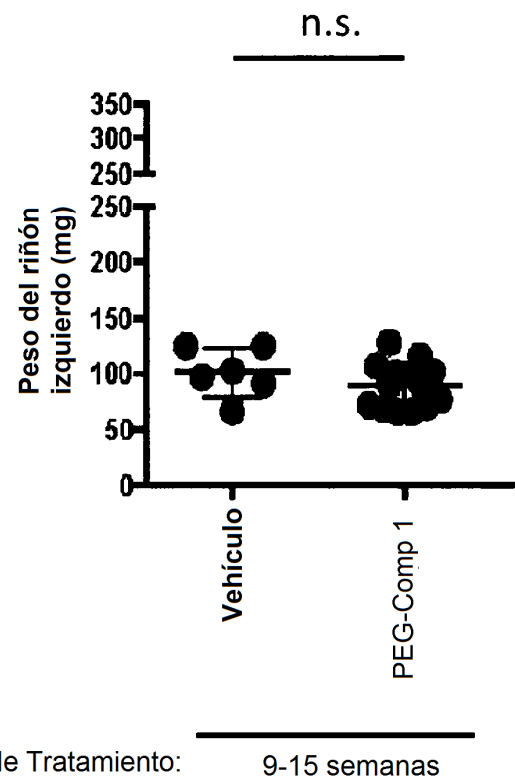


FIG. 47A

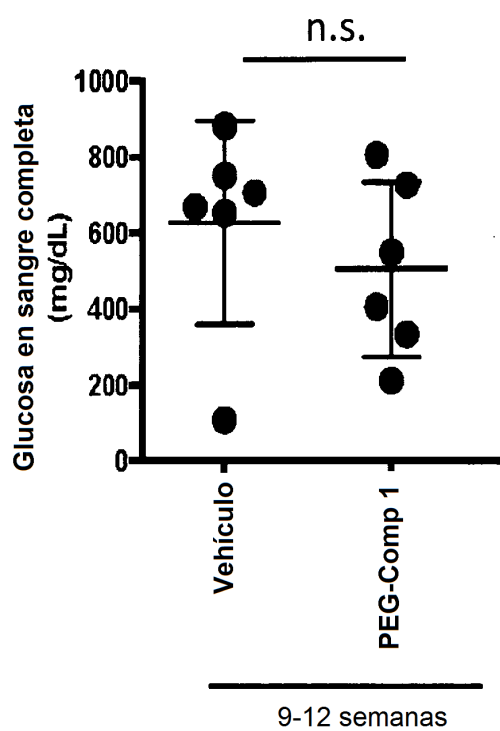


FIG. 47B

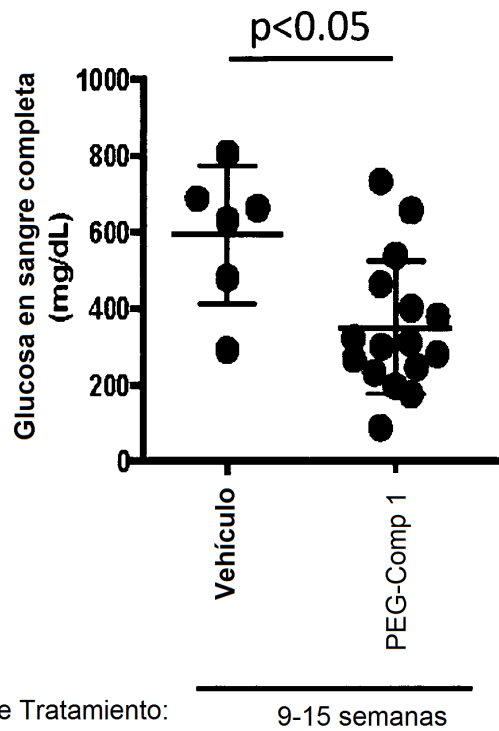


FIG. 48A

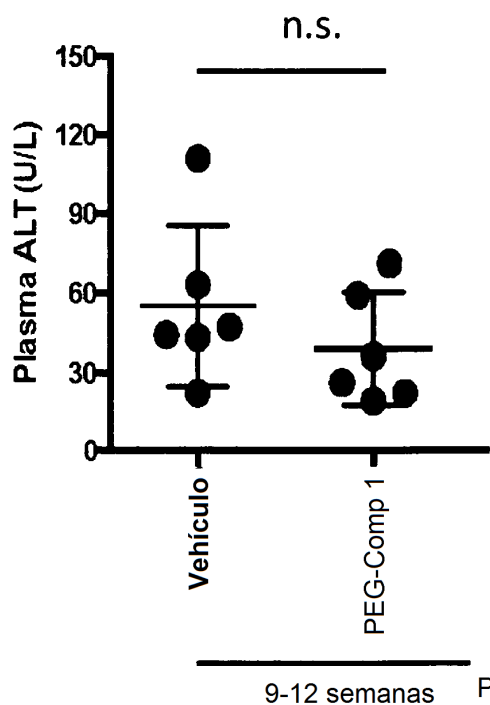


FIG. 48B

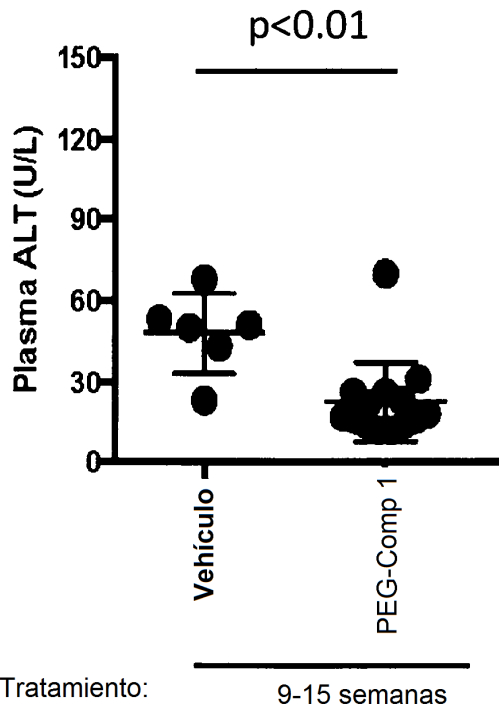


FIG. 49A

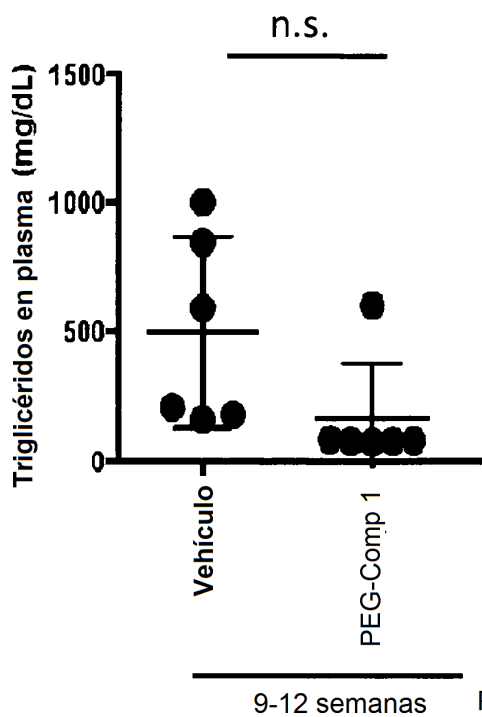


FIG. 49B

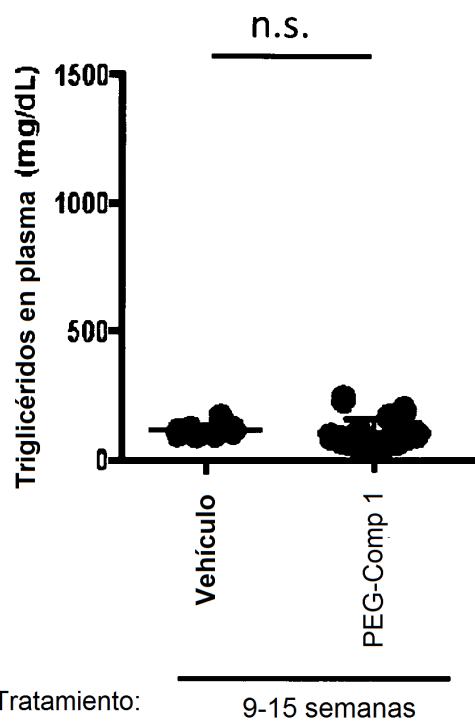


FIG. 50A

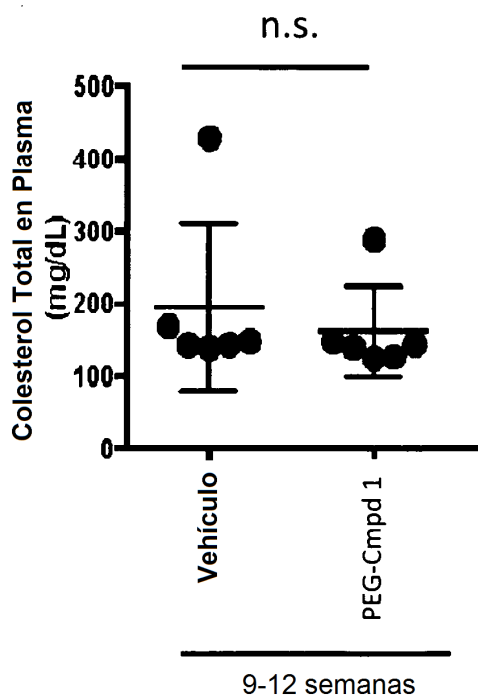


FIG. 50B

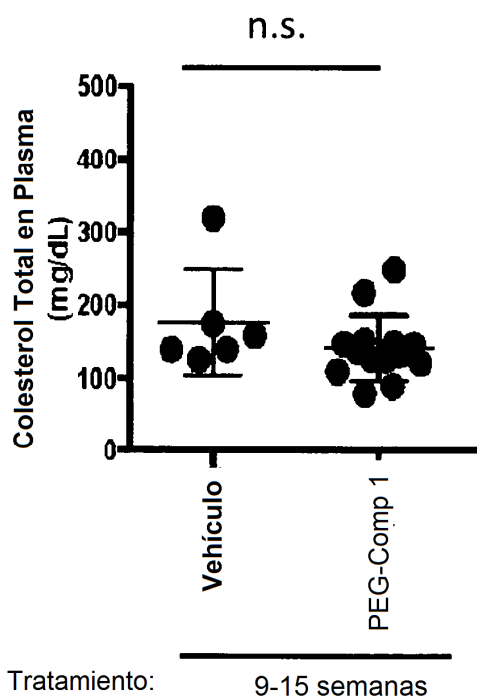


FIG. 51A

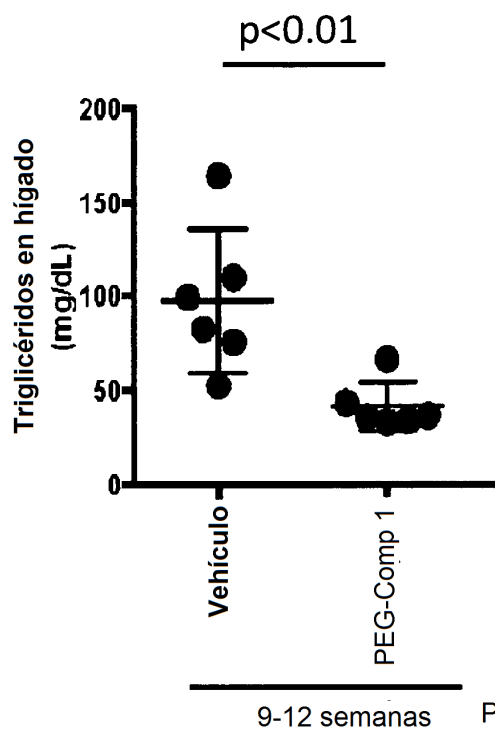


FIG. 51B

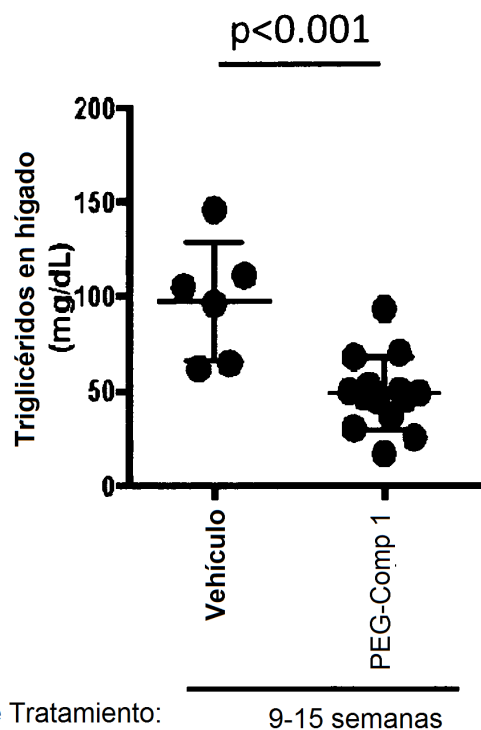


FIG. 52A

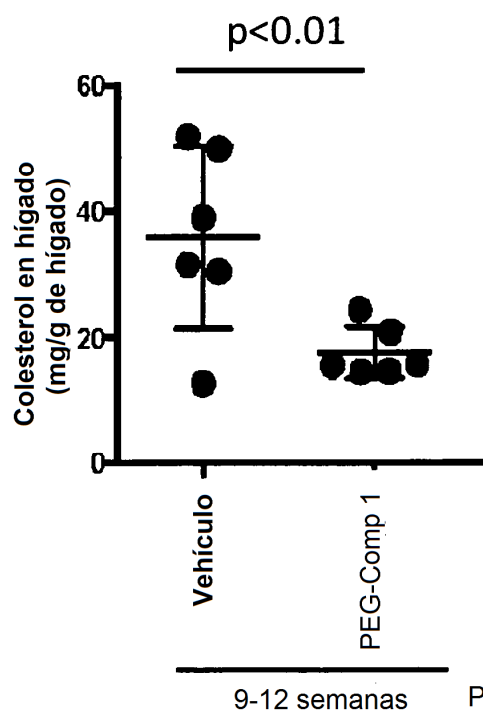
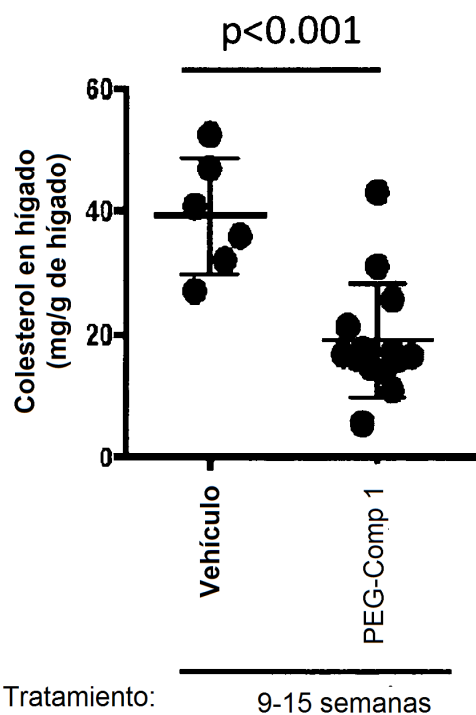


FIG. 52B



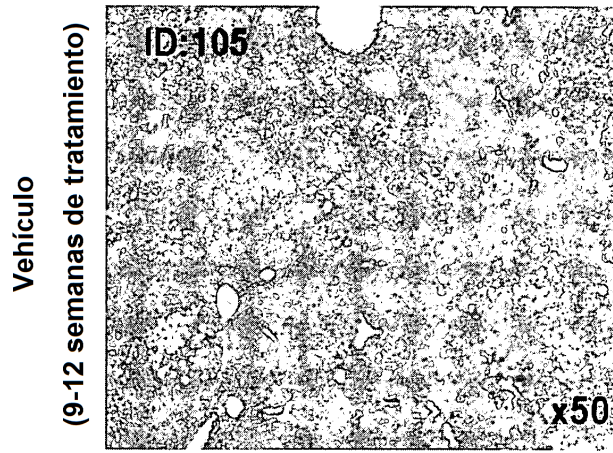


FIG. 53A

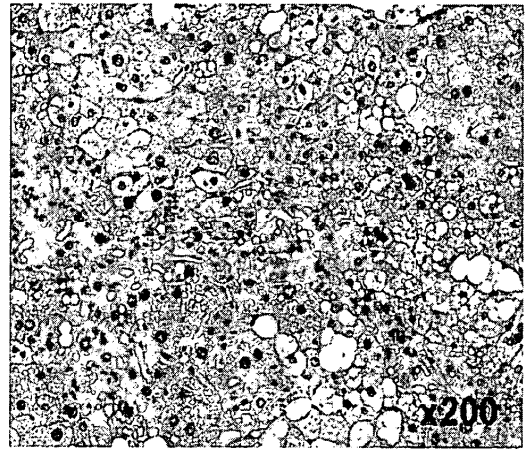


FIG. 53B

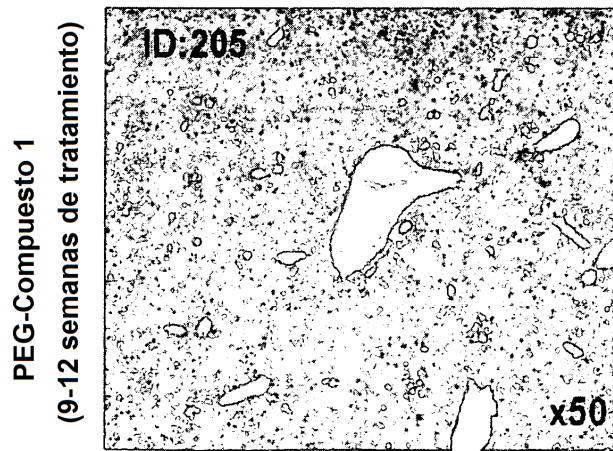


FIG. 53C

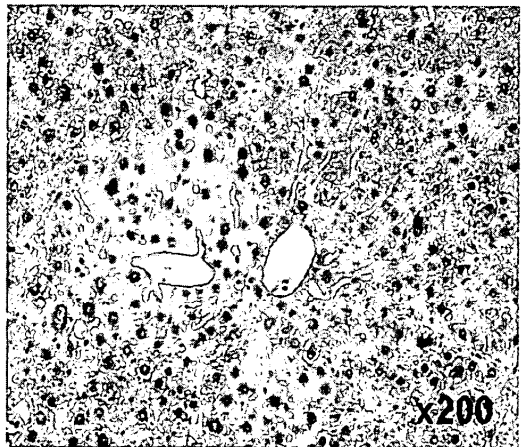


FIG. 53D

Vehículo
(9-15 semanas de tratamiento)

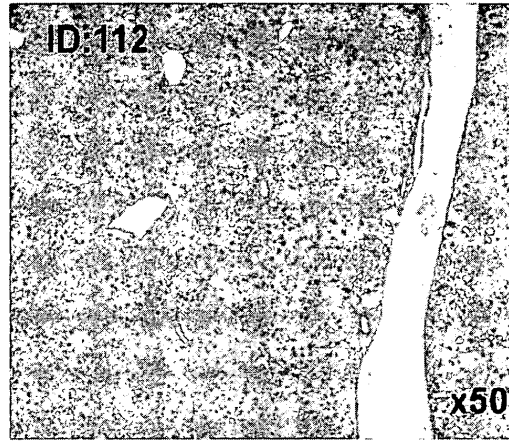


FIG. 53E

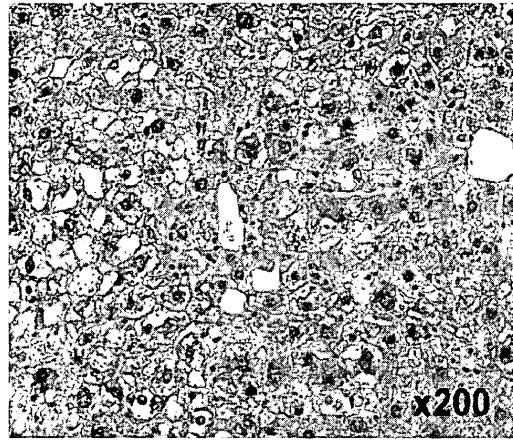


FIG. 53F

PEG-Compuesto 1
(9-15 semanas de tratamiento)



FIG. 53G

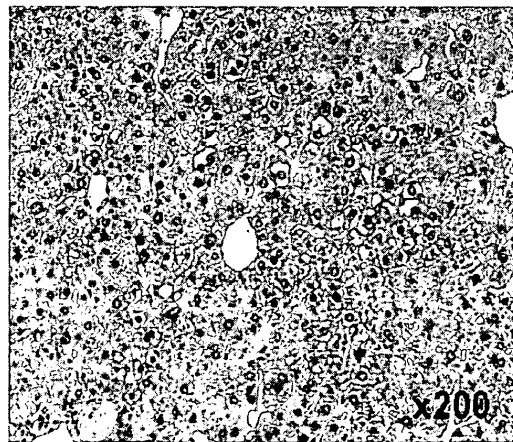


FIG. 53H

FIG. 54A

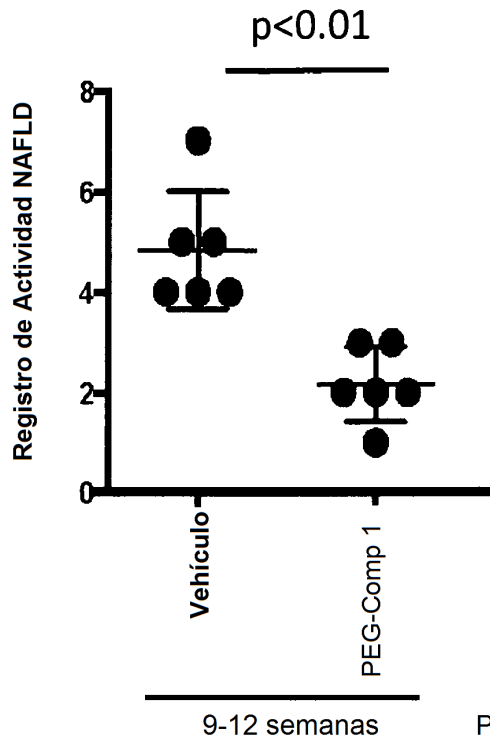
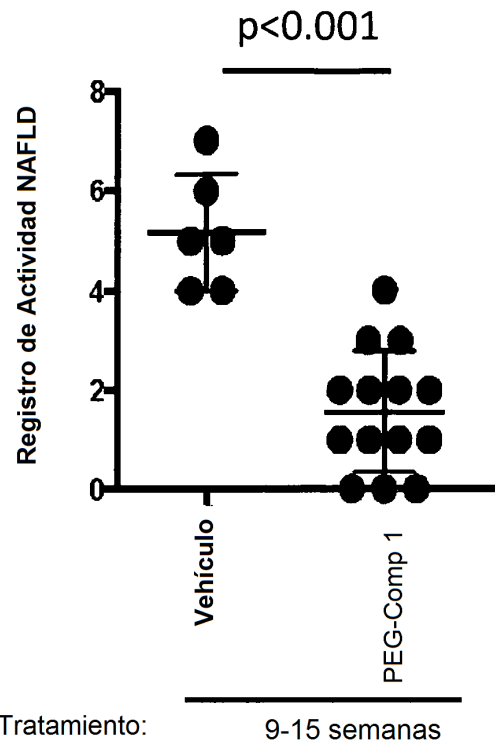


FIG. 54B



Periodo de Tratamiento:

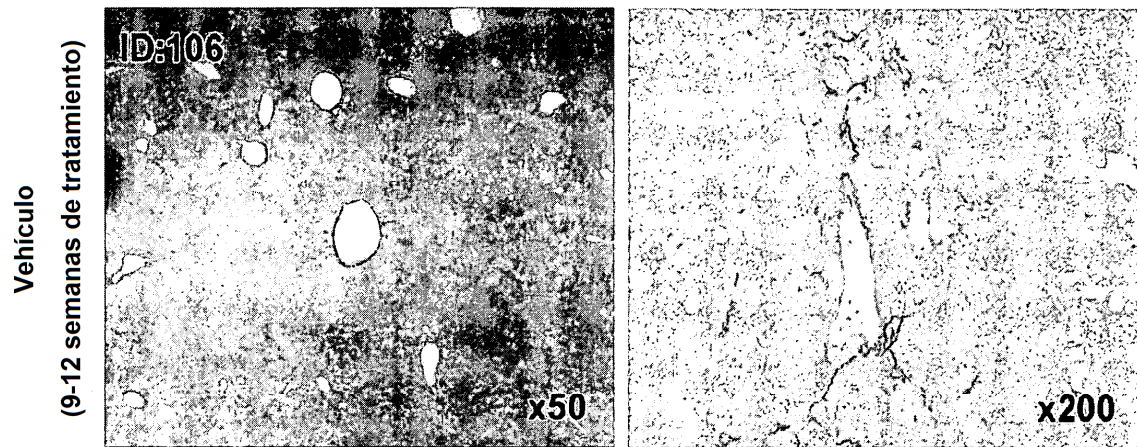


FIG. 55A

FIG. 55B

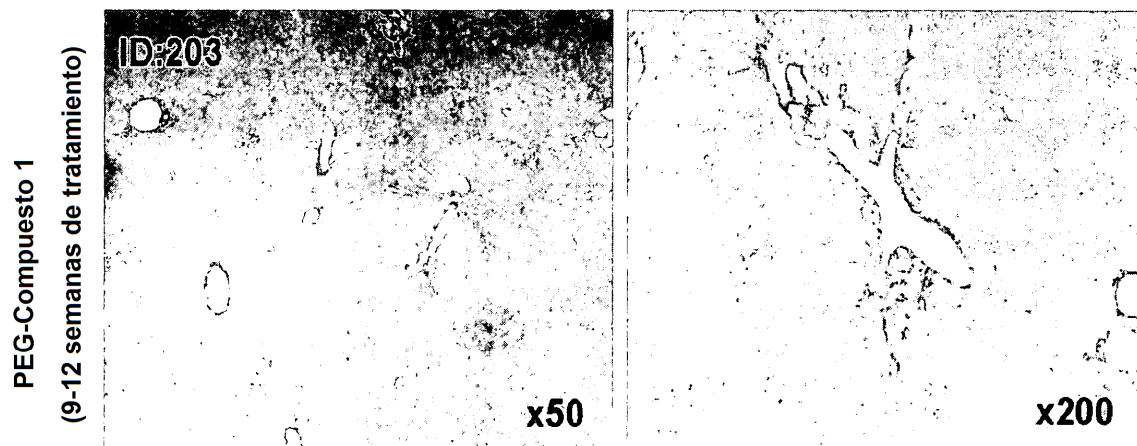


FIG. 55C

FIG. 55D

Vehículo
(9-15 semanas de tratamiento)

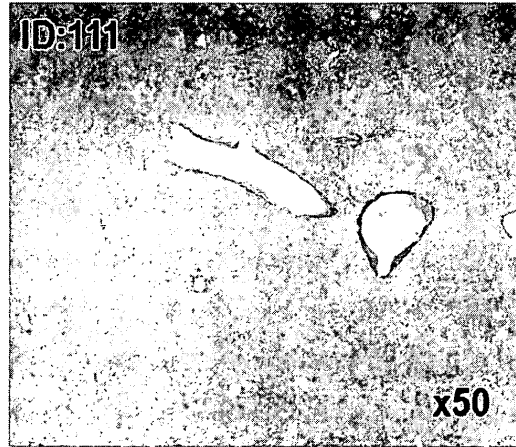


FIG. 55E

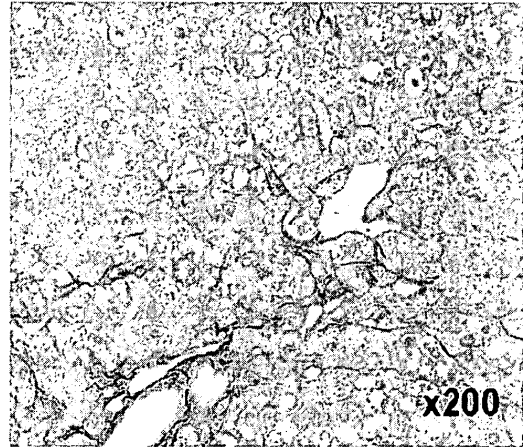


FIG. 55F

PEG-Compuesto 1
(9-15 semanas de tratamiento)

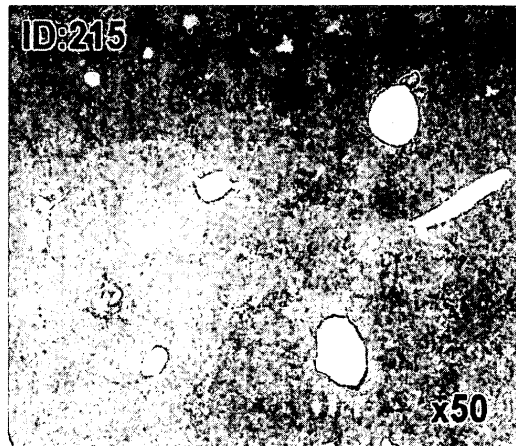


FIG. 55G

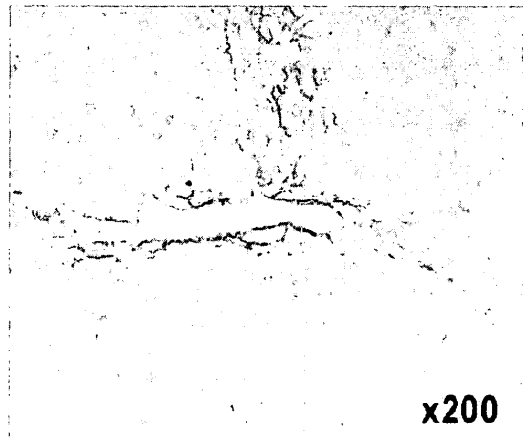


FIG. 55H

FIG. 56A

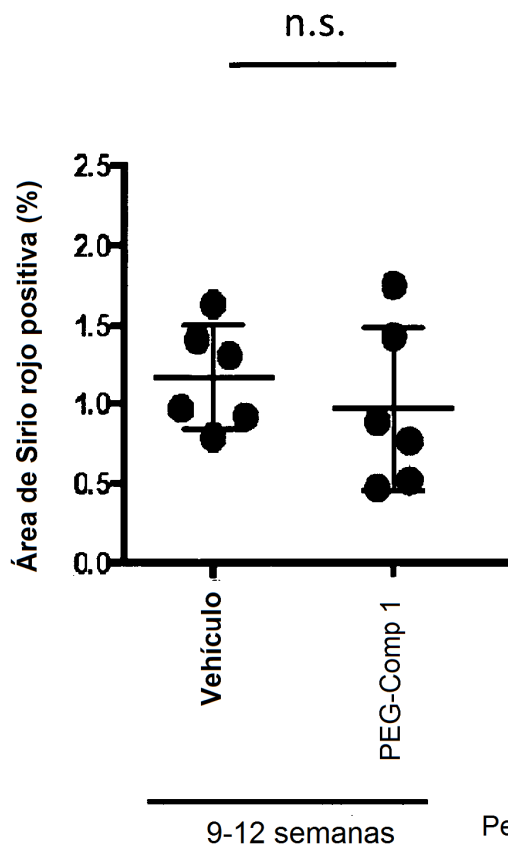
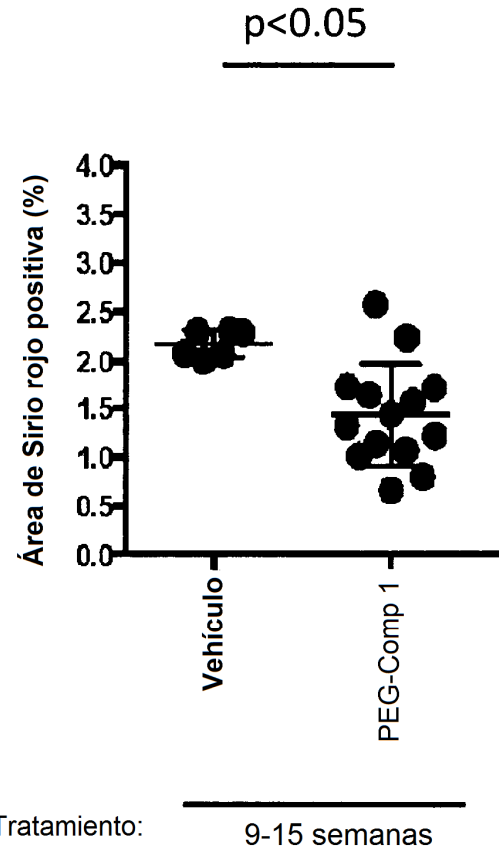


FIG. 56B



Periodo de Tratamiento:

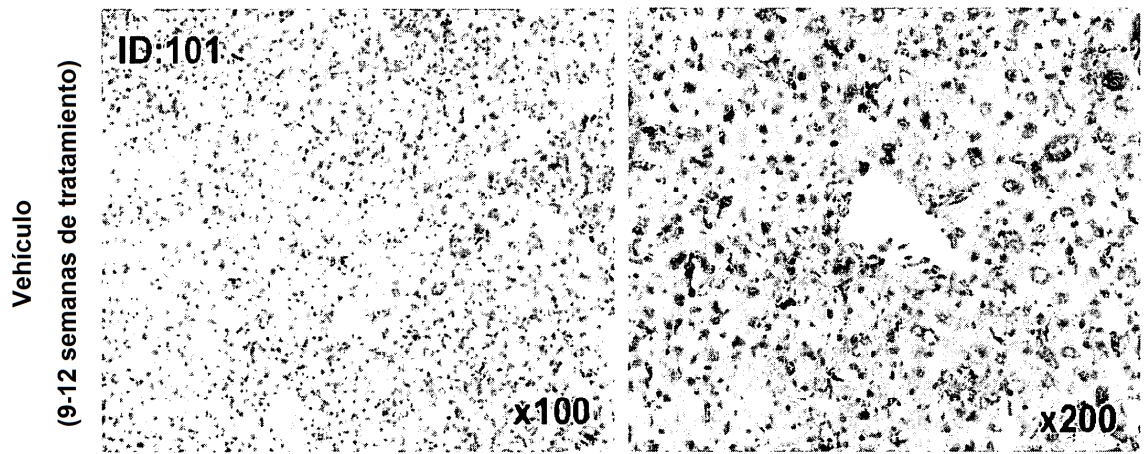


FIG. 57A

FIG. 57B

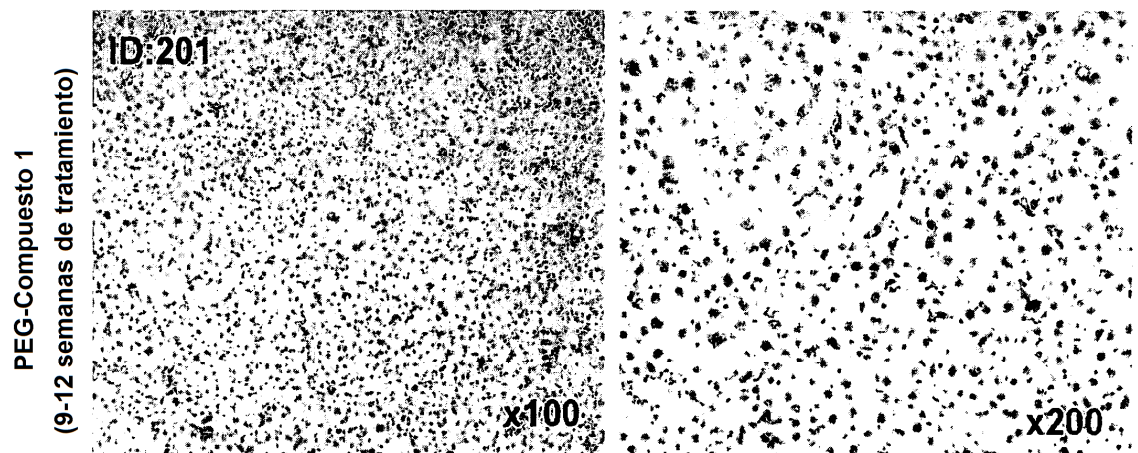


FIG. 57C

FIG. 57D

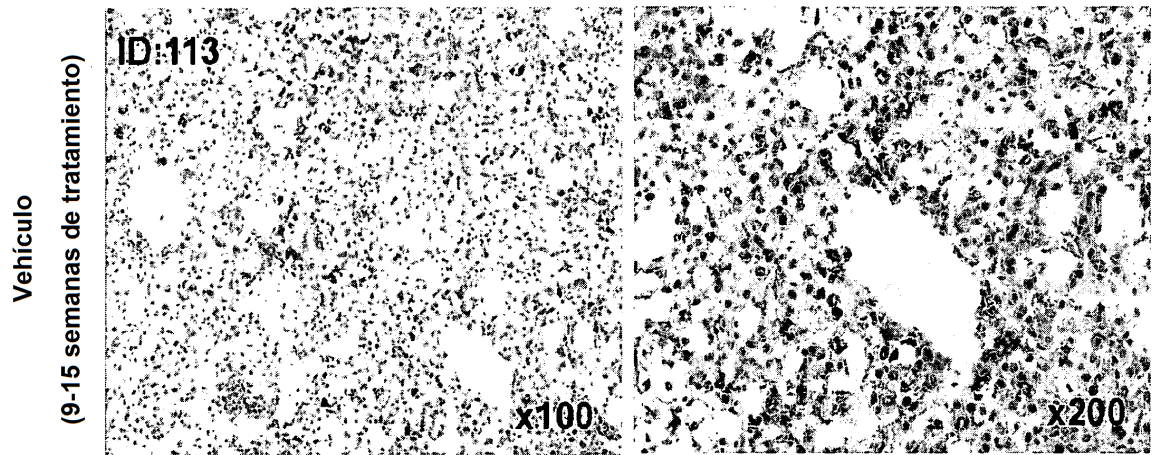


FIG. 57E

FIG. 57F

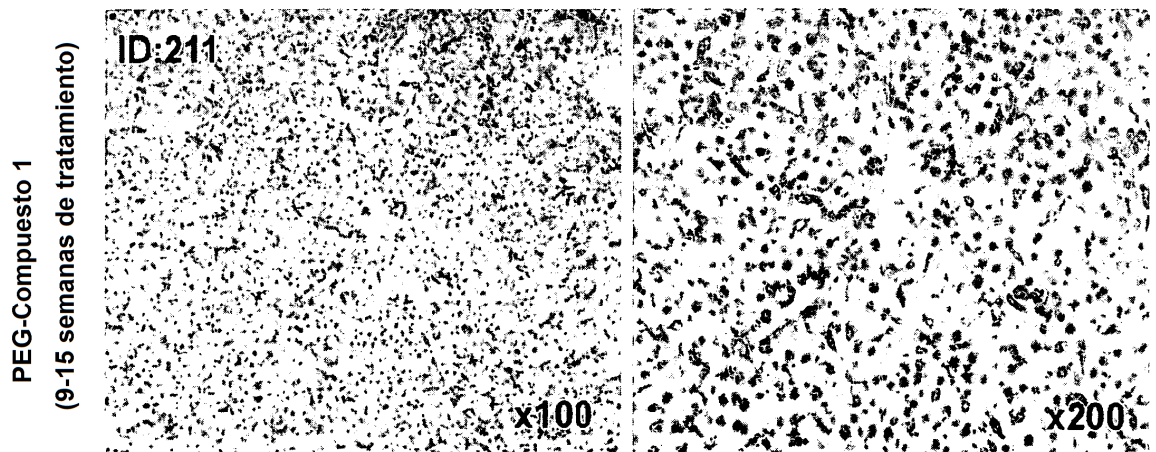


FIG. 57G

FIG. 57H

FIG. 58A

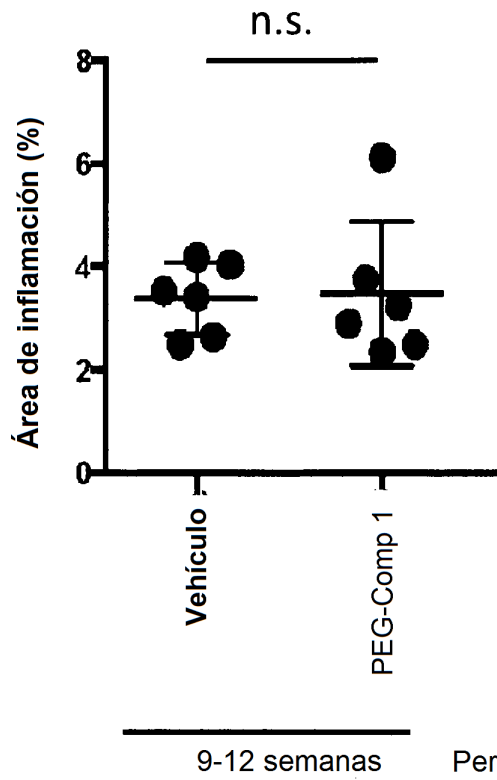
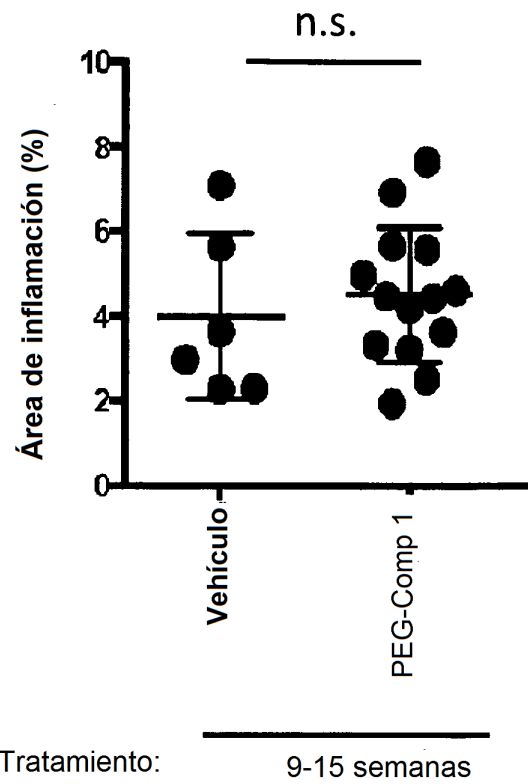


FIG. 58B



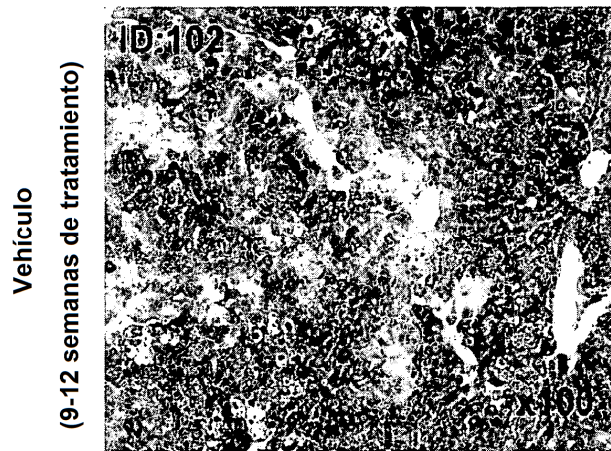


FIG. 59A

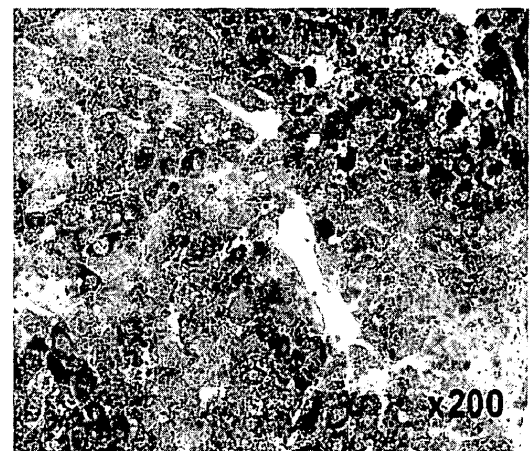


FIG. 59B

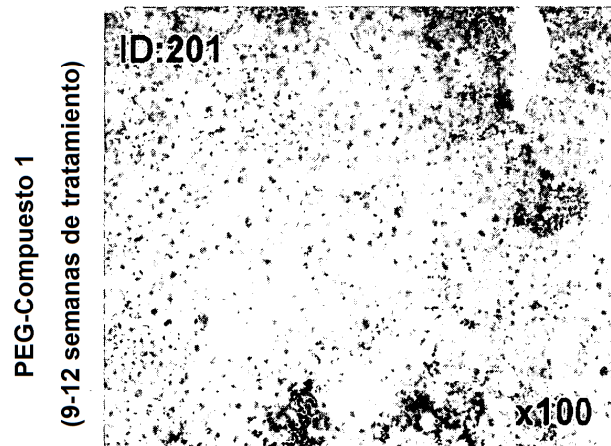


FIG. 59C

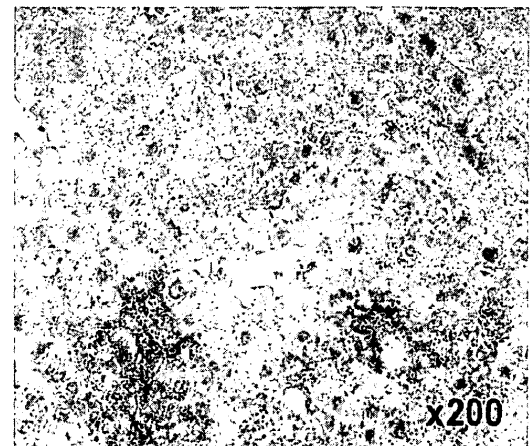


FIG. 59D

Vehículo
(9-15 semanas de tratamiento)

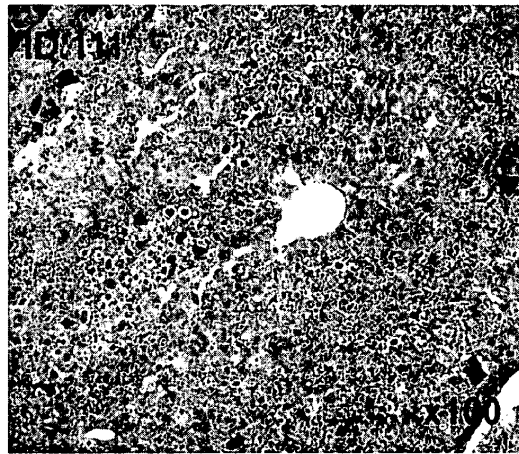


FIG. 59E

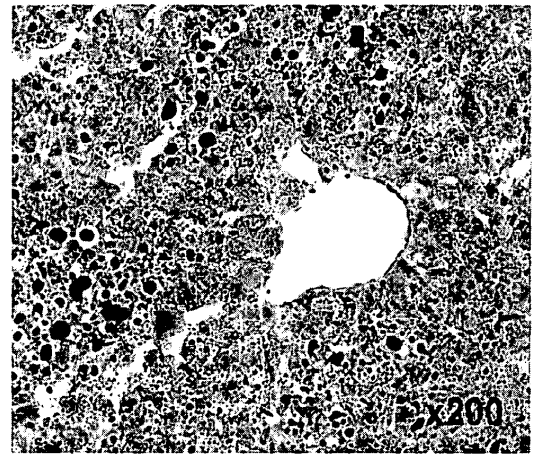


FIG. 59F

PEG-Compuesto 1
(9-15 semanas de tratamiento)

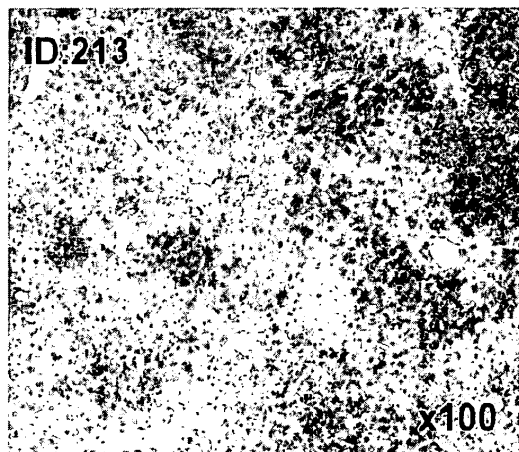


FIG. 59G

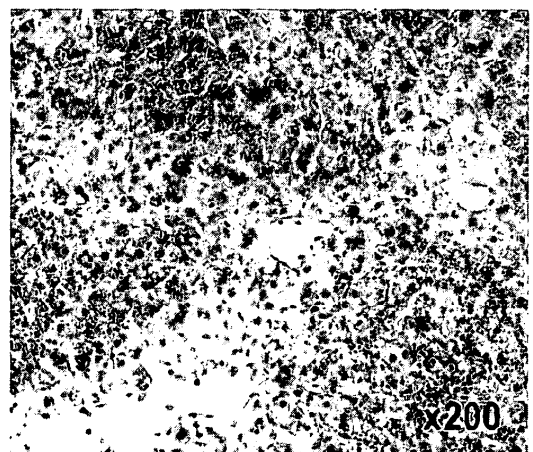


FIG. 59H

FIG. 60A

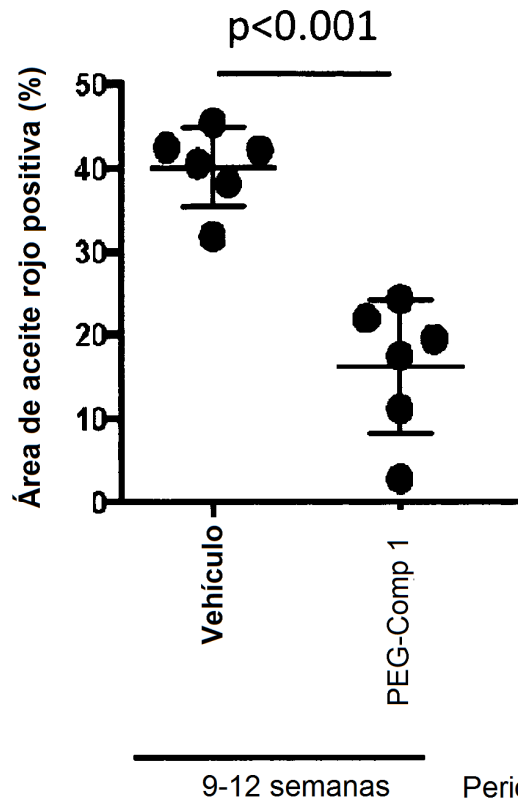


FIG. 60B

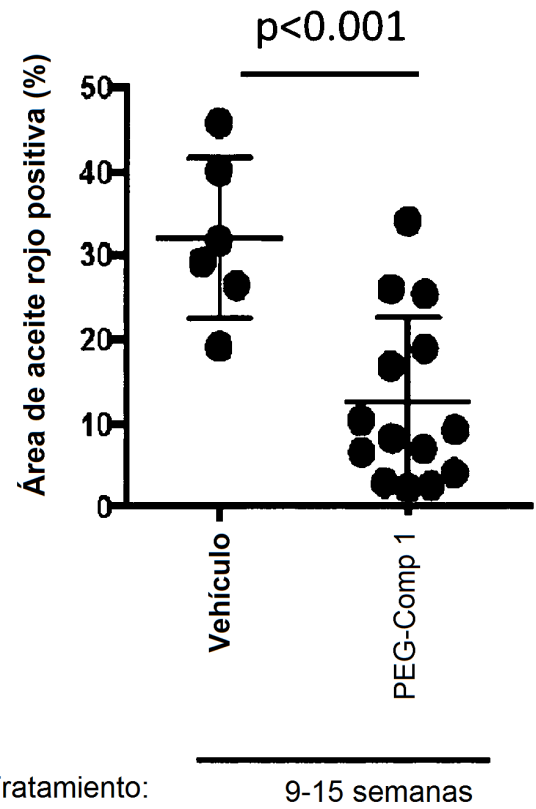
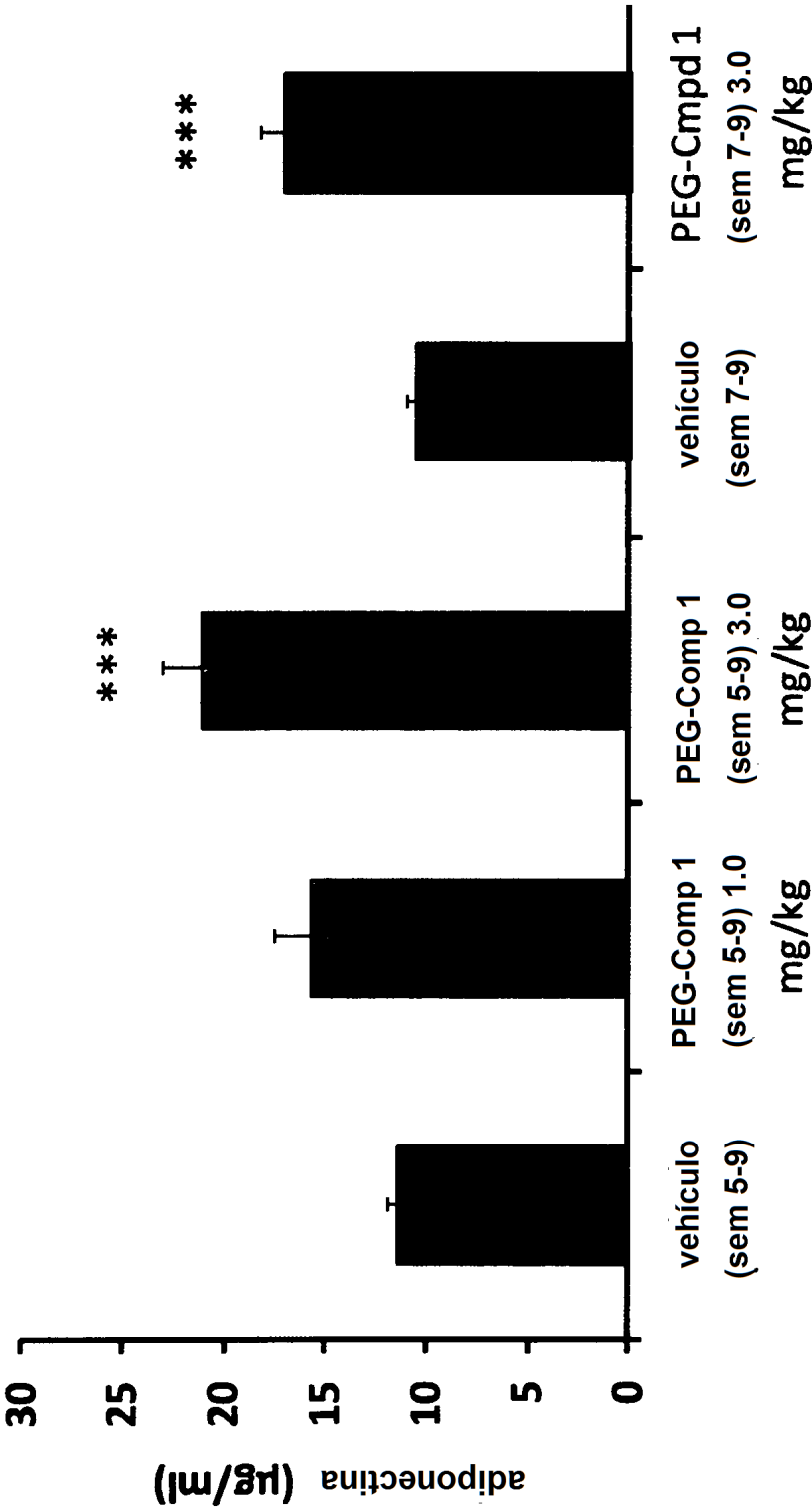
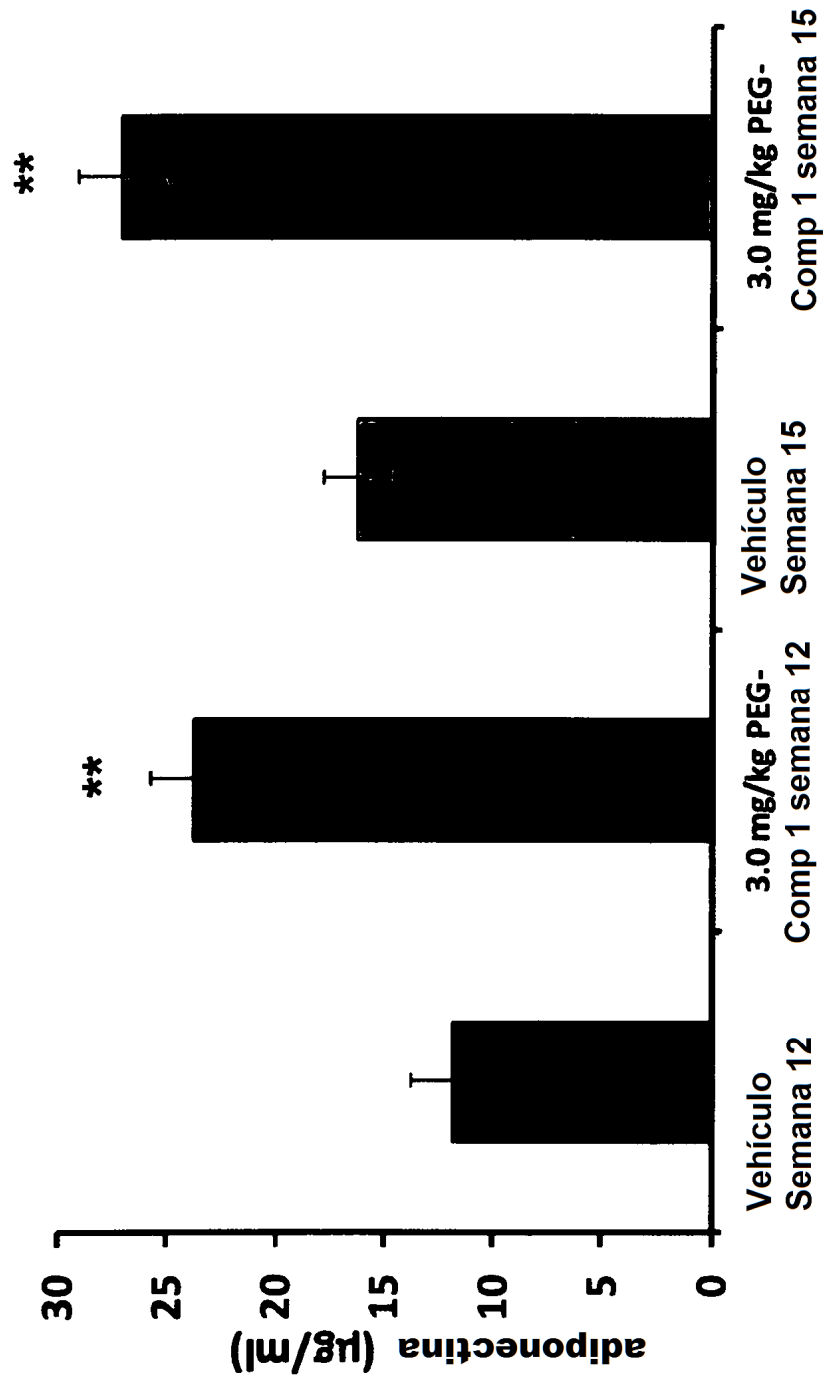


FIG. 61



*** p<0.001 contra vehículo respectivo, Prueba T de Dunnett

FIG. 62



**p<0.005 contra Prueba T de Dunnett del vehículo

FIG. 63

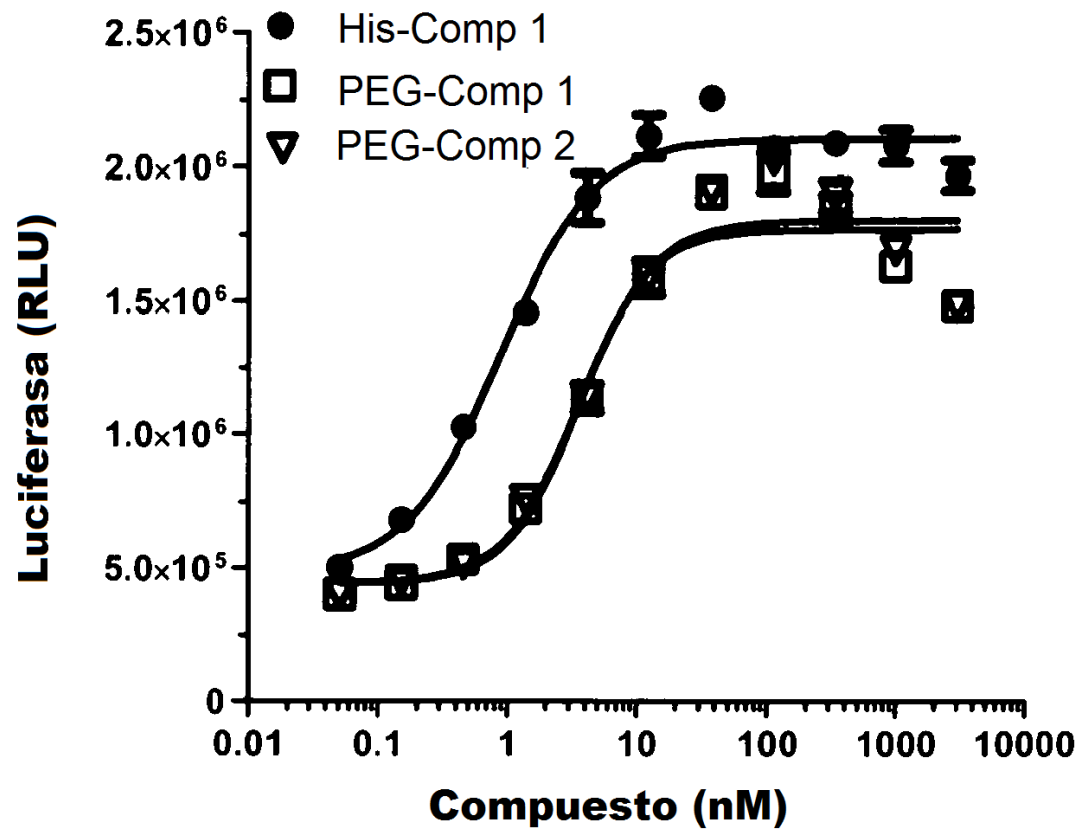


FIG. 64

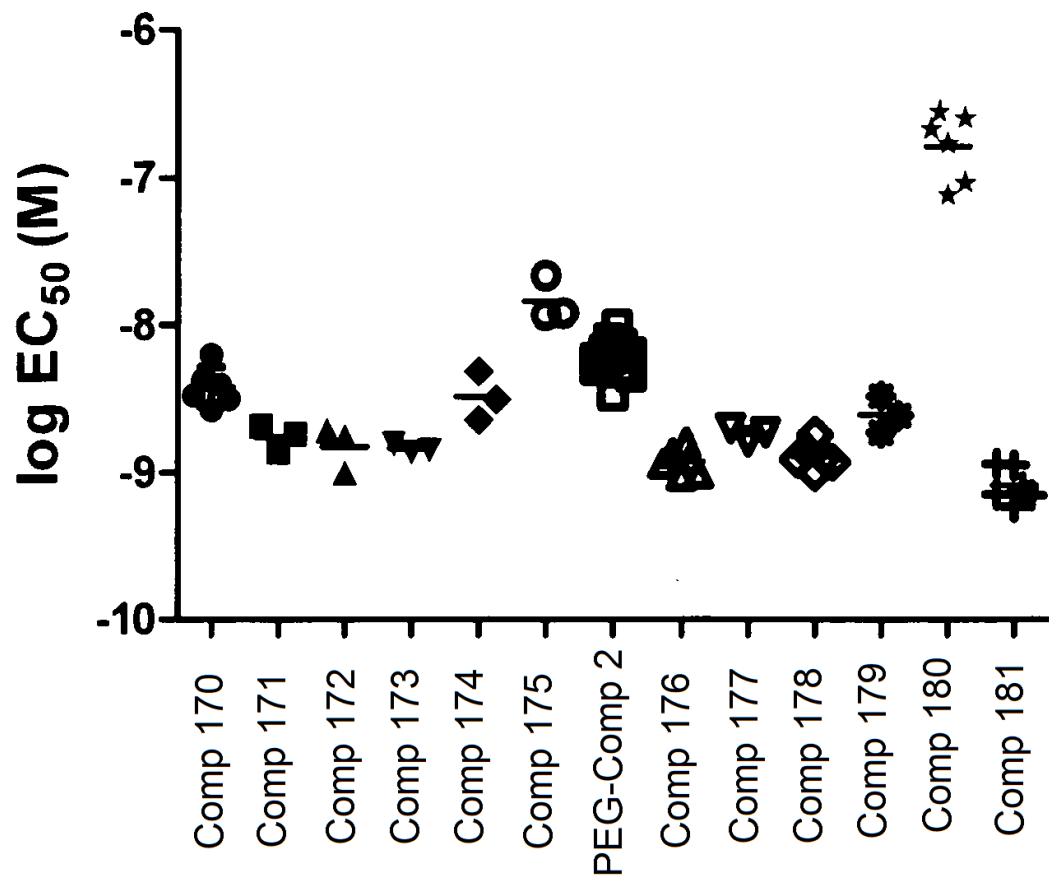
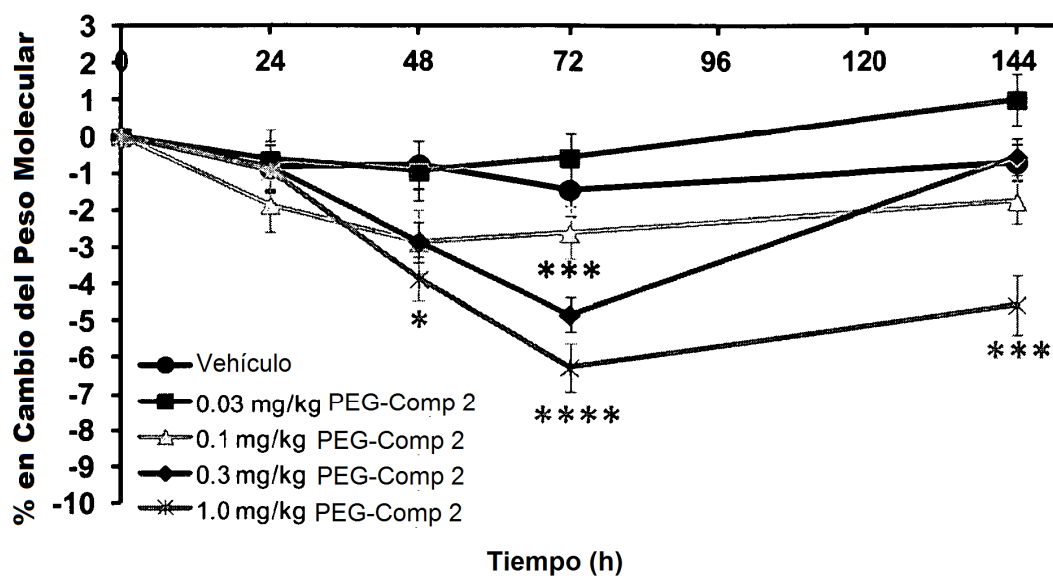
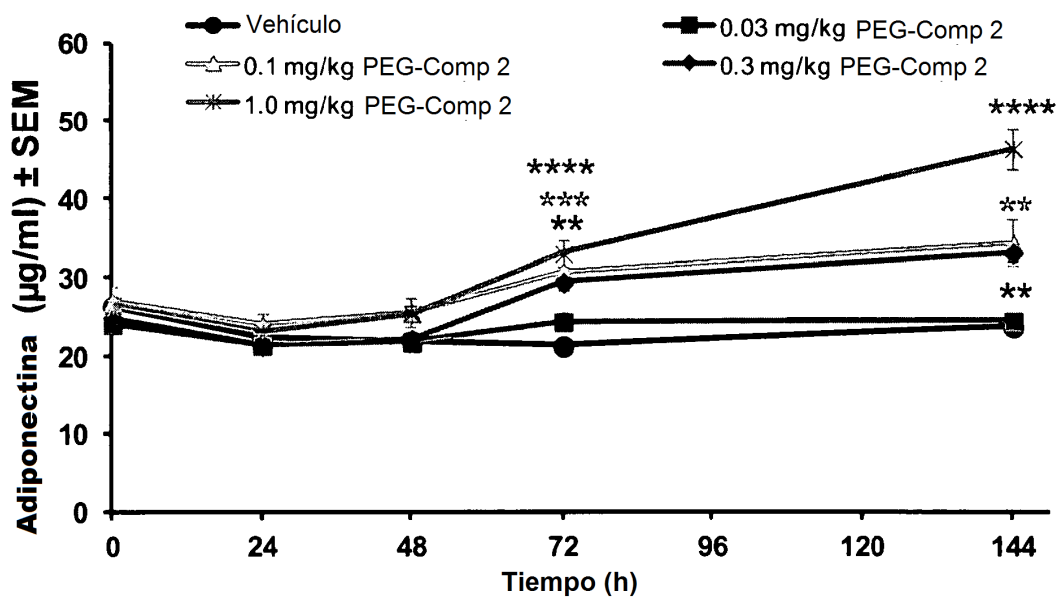


FIG. 65



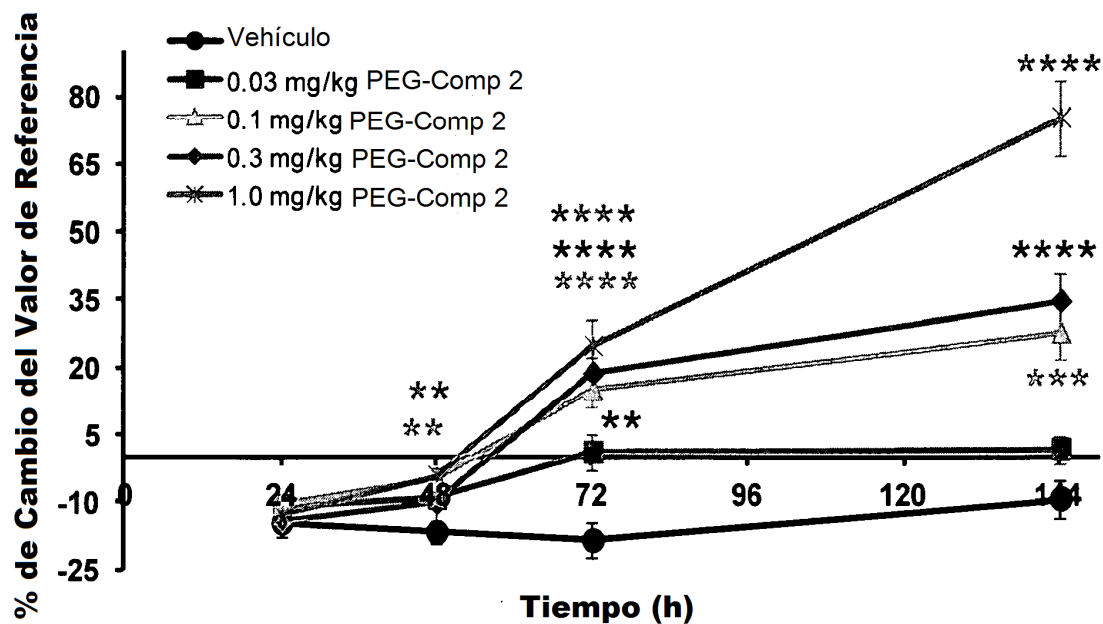
* p<0.05, *** p<0.0005, **** p<0.0001 contra la Prueba T de Dunnett del vehículo

FIG. 66A



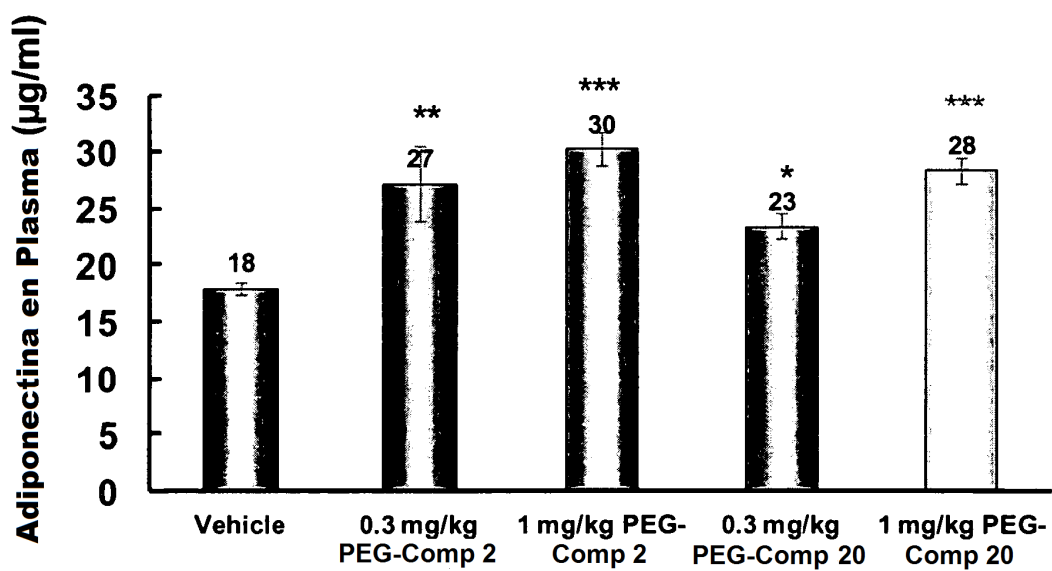
p<0.01, * p<0.001, ****p<0.0001 contra Prueba T de Dunnett del vehículo

FIG. 66B



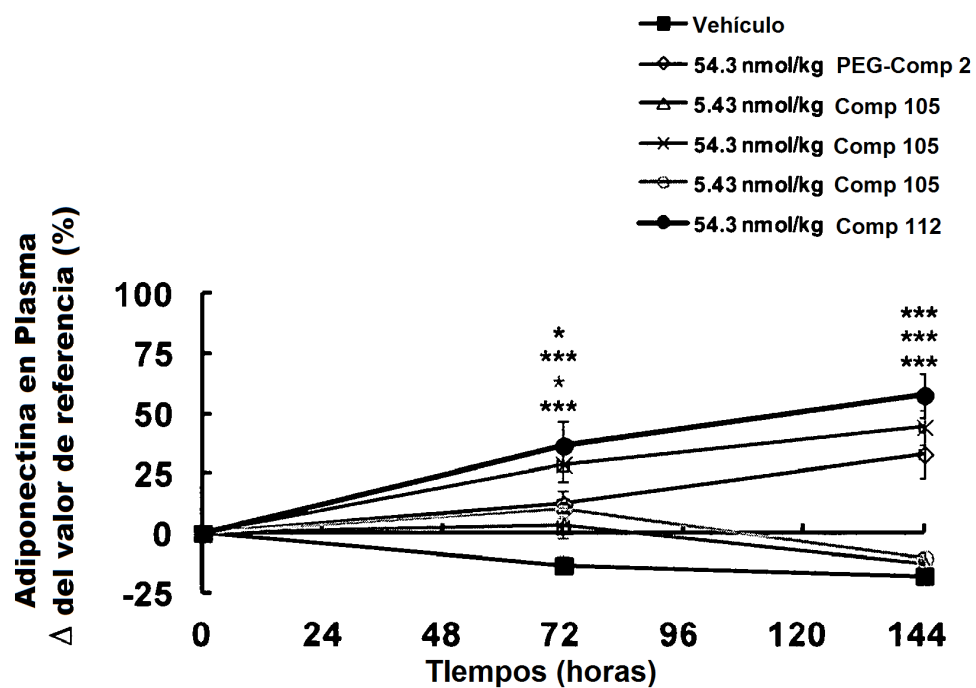
** p<0.01, *** p<0.001, **** p<0.0001 contra Prueba T de Dunnett del vehículo

FIG. 67A.



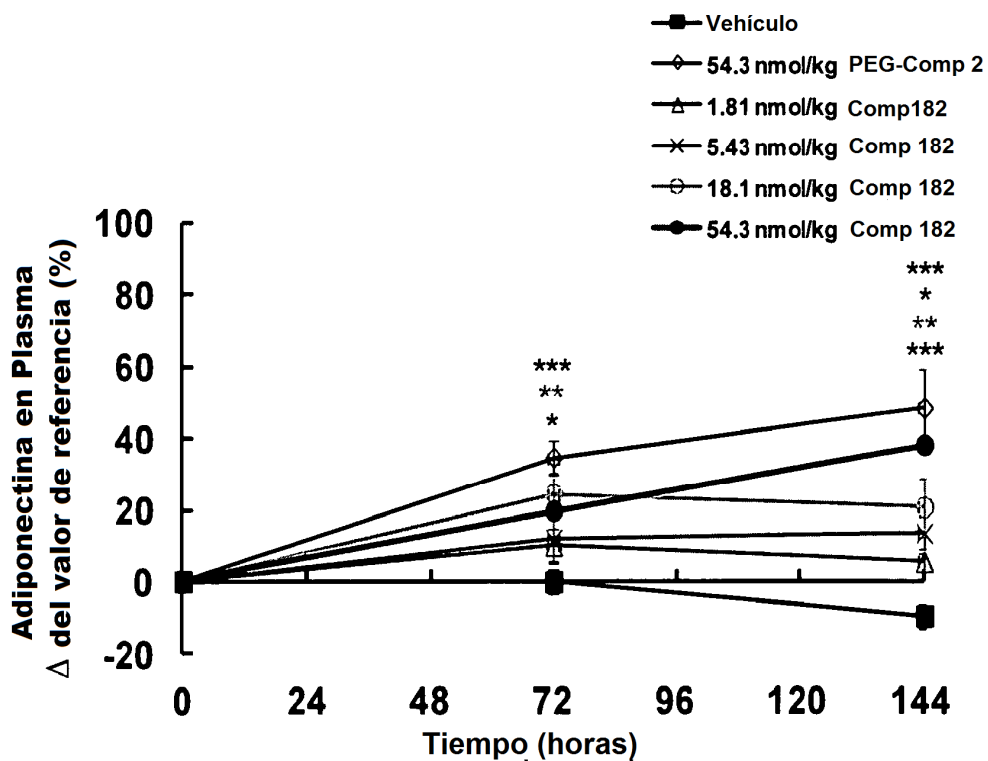
* p<0.05, ** p<0.01, *** p<0.001 contra vehículo ANOVA seguido por el Método de Dunnett

FIG. 67B.



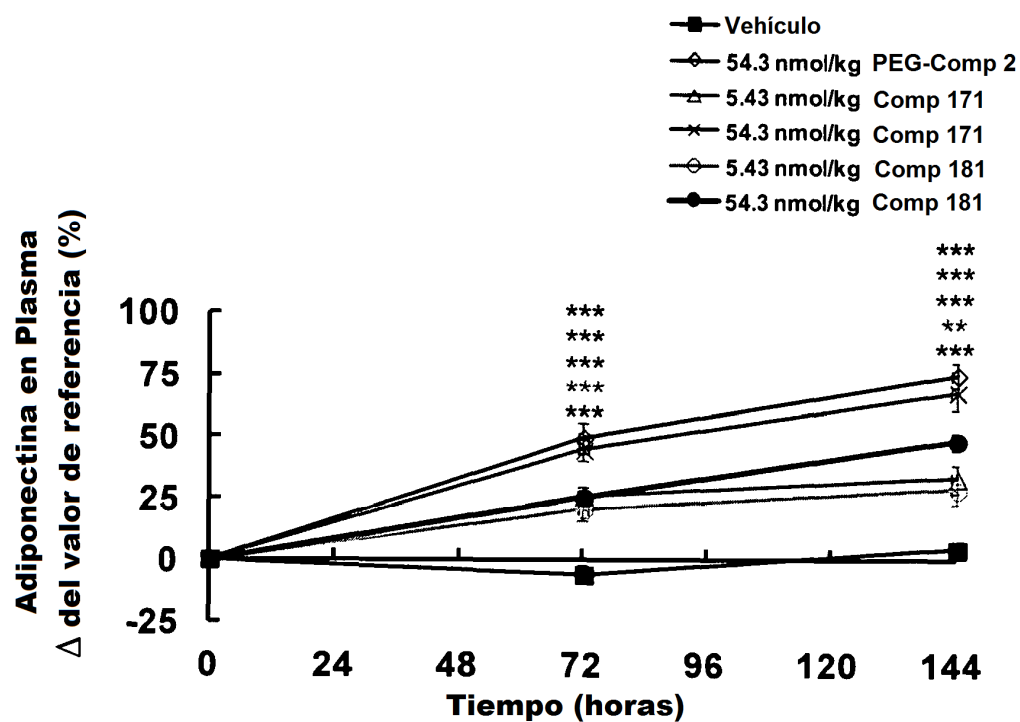
* $p < 0.05$, *** $p < 0.001$ contra vehículo ANOVA seguido por el Método de Dunnett

FIG. 67C.



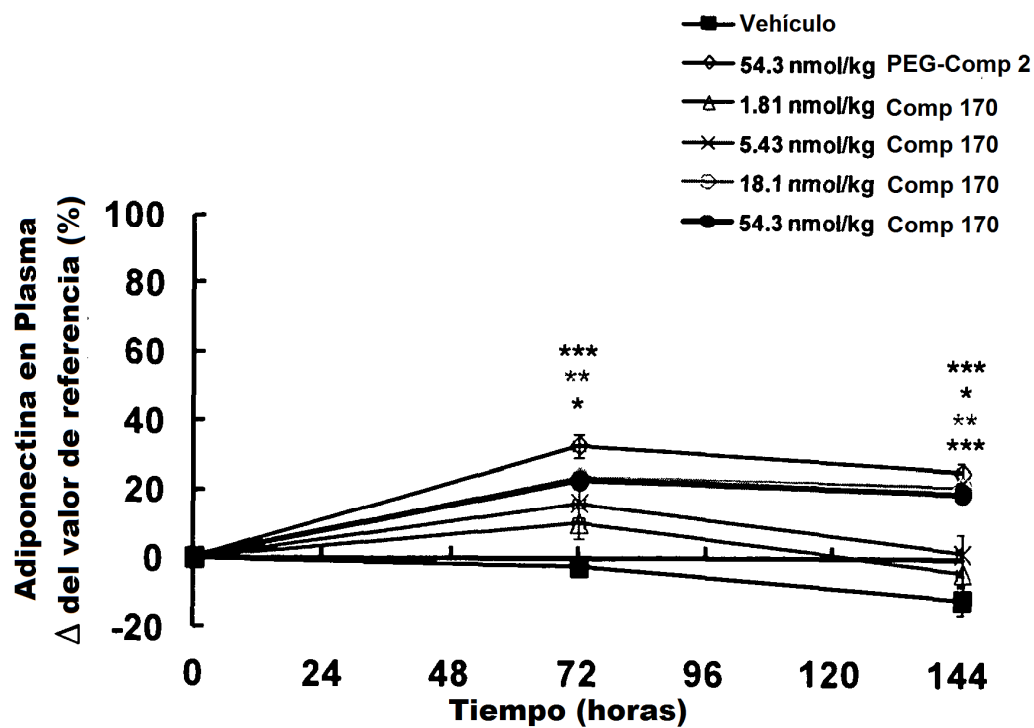
* $p < 0.05$, *** $p < 0.001$ contra Vehículo ANOVA seguido por el Método de Dunnett

FIG. 67D.



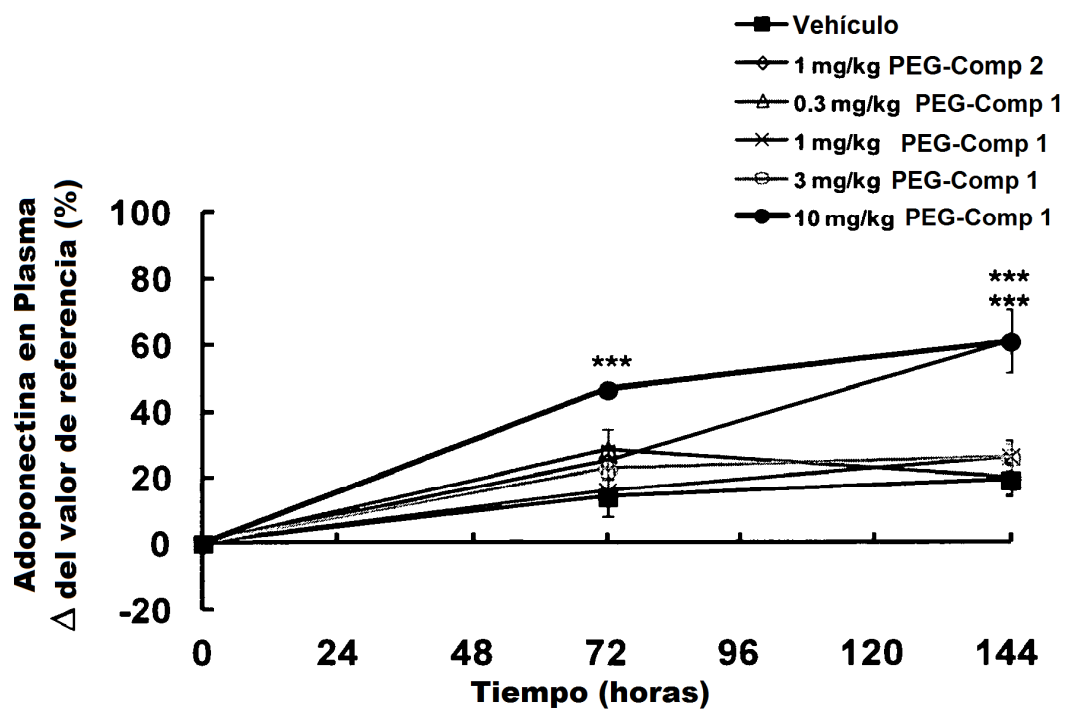
** $p < 0.01$, *** $p < 0.001$ contra vehículo ANOVA seguido por el Método de Dunnett

FIG. 67E.



* $p < 0.05$, *** $p < 0.001$ contra vehículo ANOVA seguido por el Método de Dunnett

FIG. 67F.



*** $p < 0.001$ contra vehículo ANOVA seguido por el Método de Dunnett

FIG. 68.

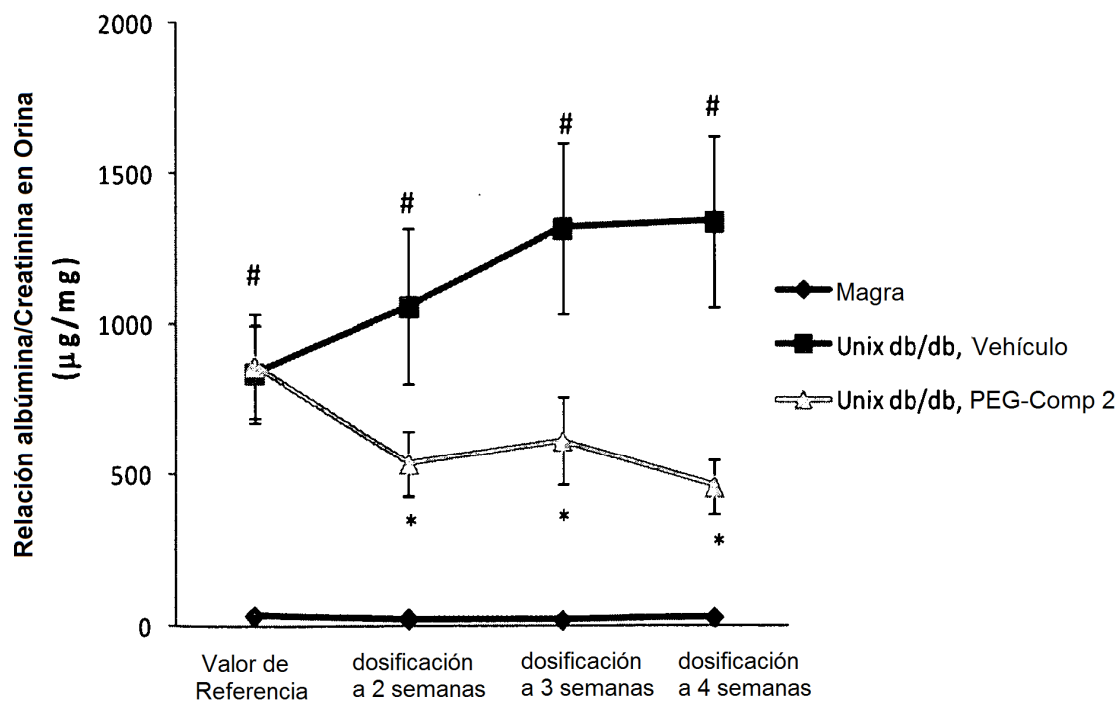


FIG. 69.

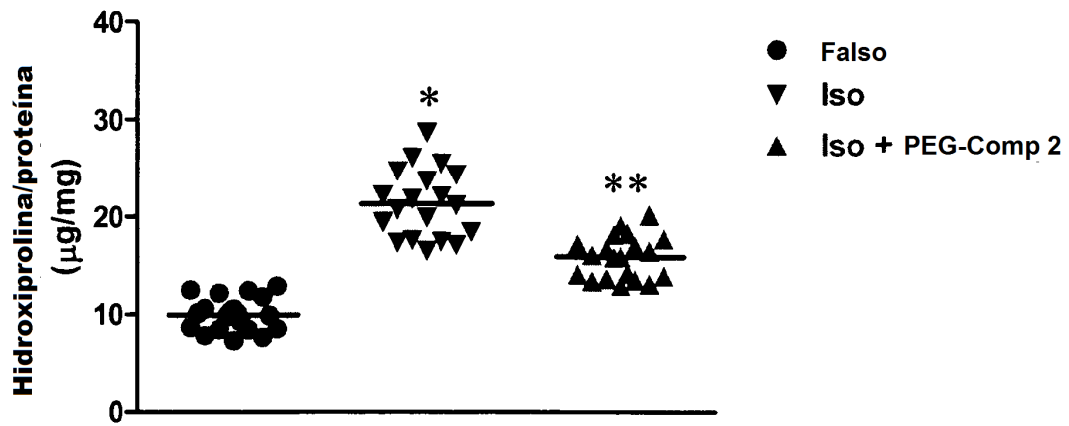
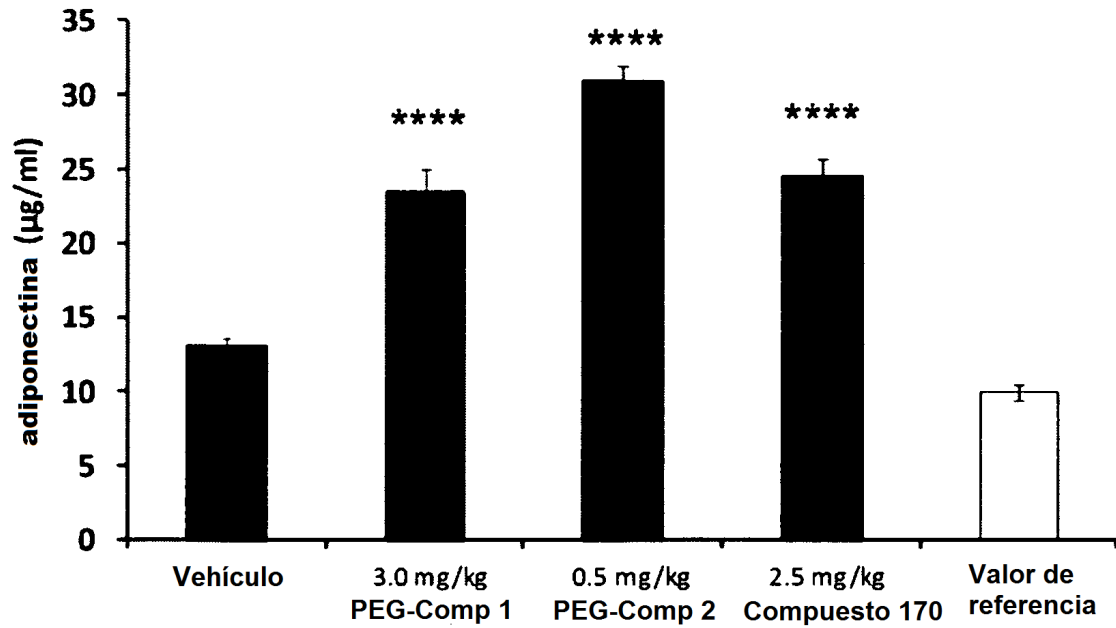
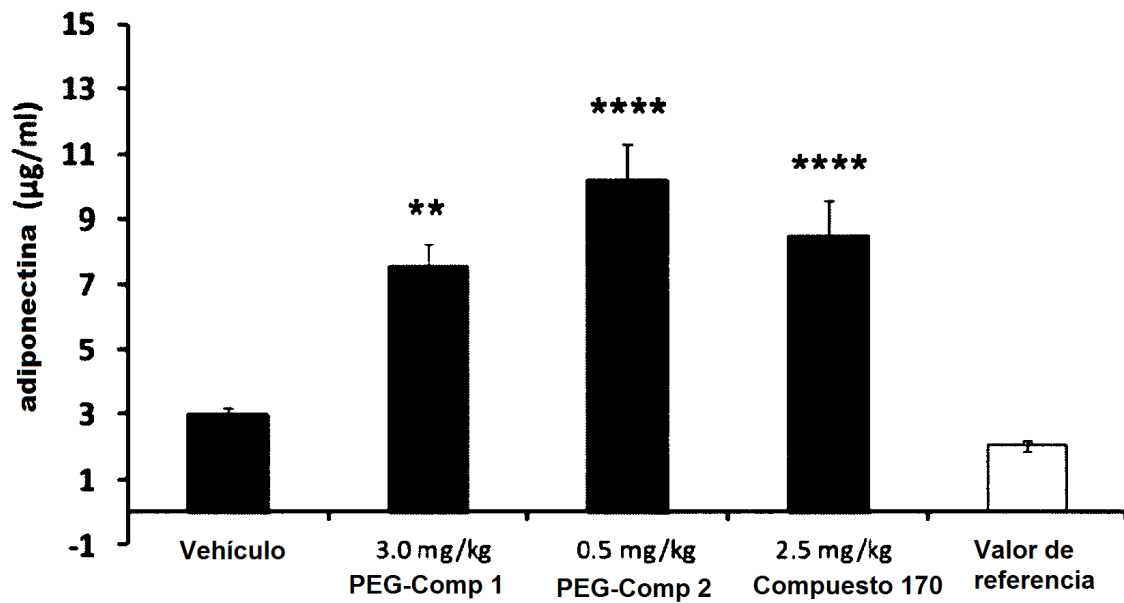


FIG. 70A



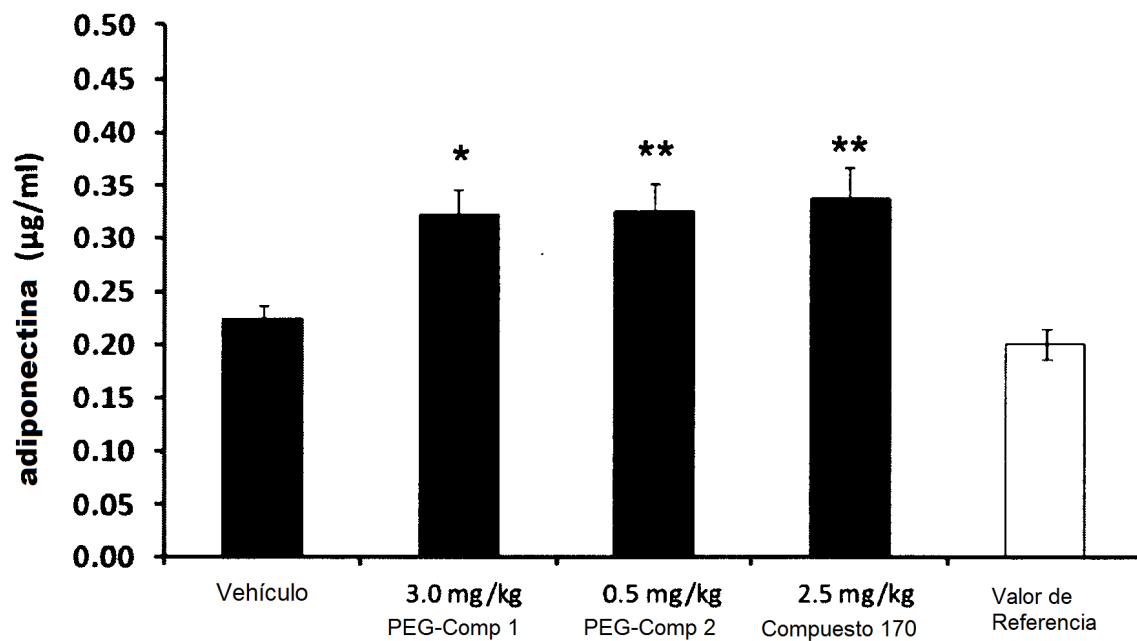
****p<0.0001 contra la Prueba T de Dunnett del vehículo

FIG. 70B



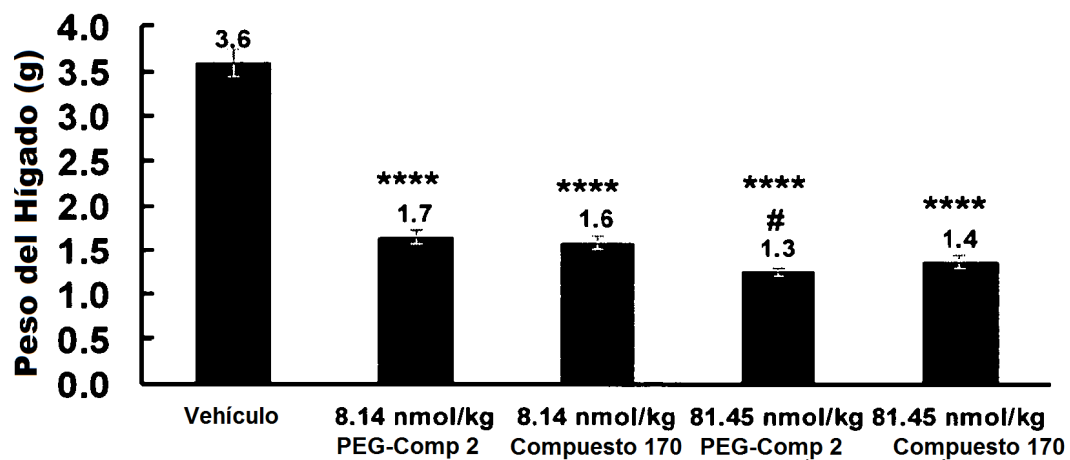
p<0.005, **p<0.0001 contra la Prueba T de Dunnett del vehículo

FIG. 70C



* $p < 0.05$, ** $p < 0.01$ contra Prueba T de Dunnett

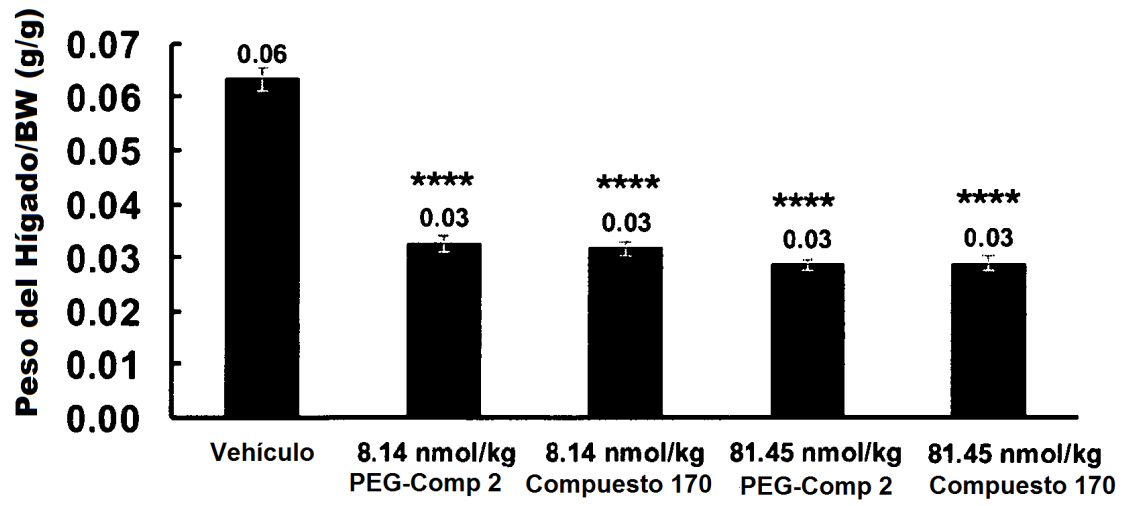
FIG. 71A



**** $p < 0.0001$ contra vehículo ANOVA seguido por el Método de Dunnett

$p < 0.05$ contra dosis inferior del mismo compuesto mediante Tukey-Kramer

FIG. 71B



****p<0.0001 contra vehículo ANOVA seguido por el Método de Dunnett.

FIG. 72A

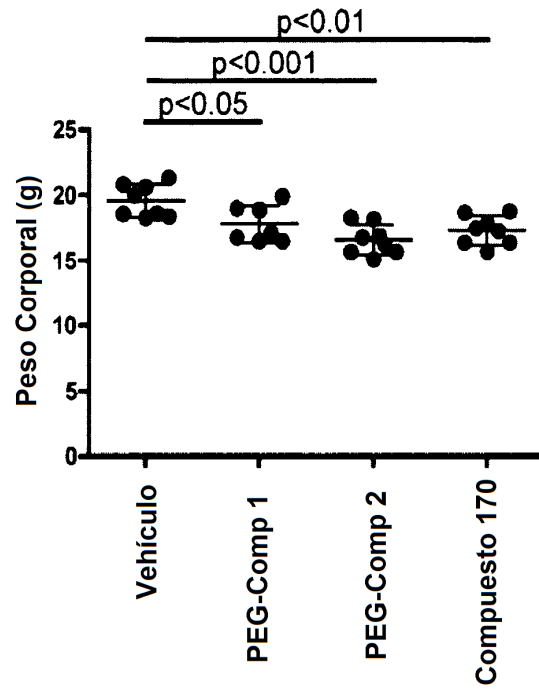


FIG. 72B

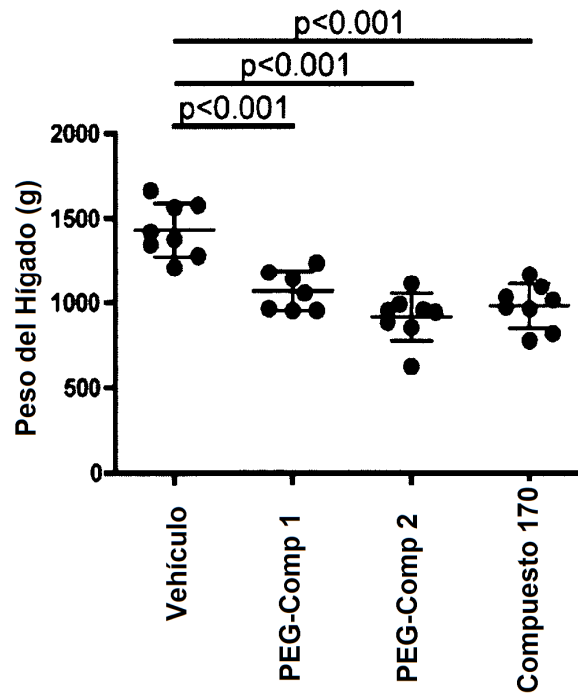


FIG. 72C

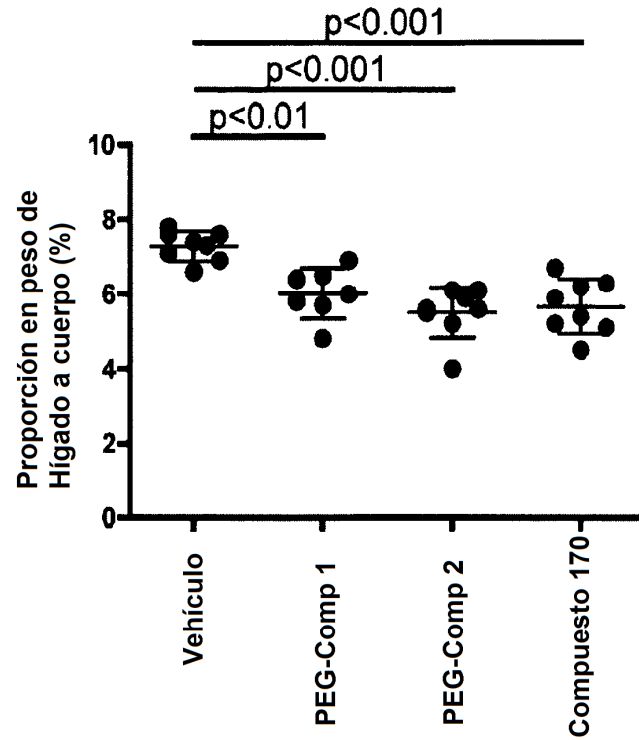


FIG. 72D

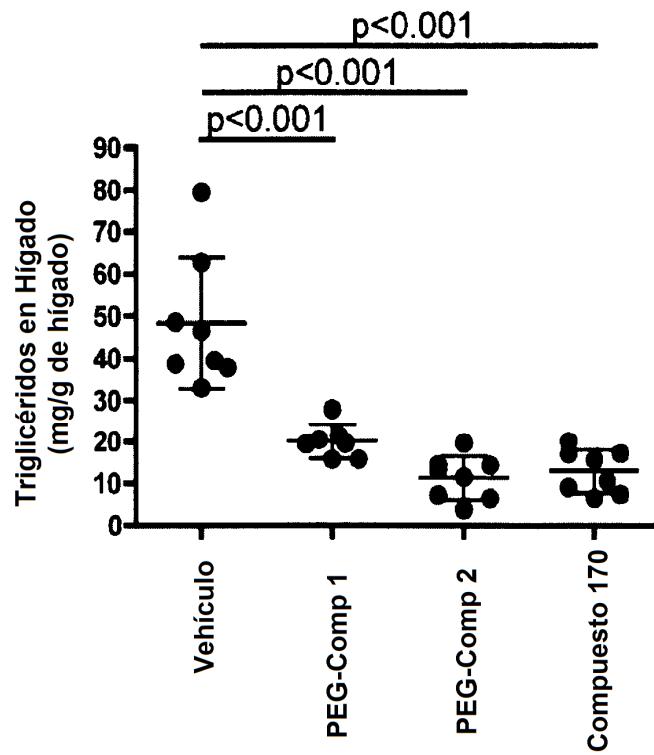


FIG. 72E

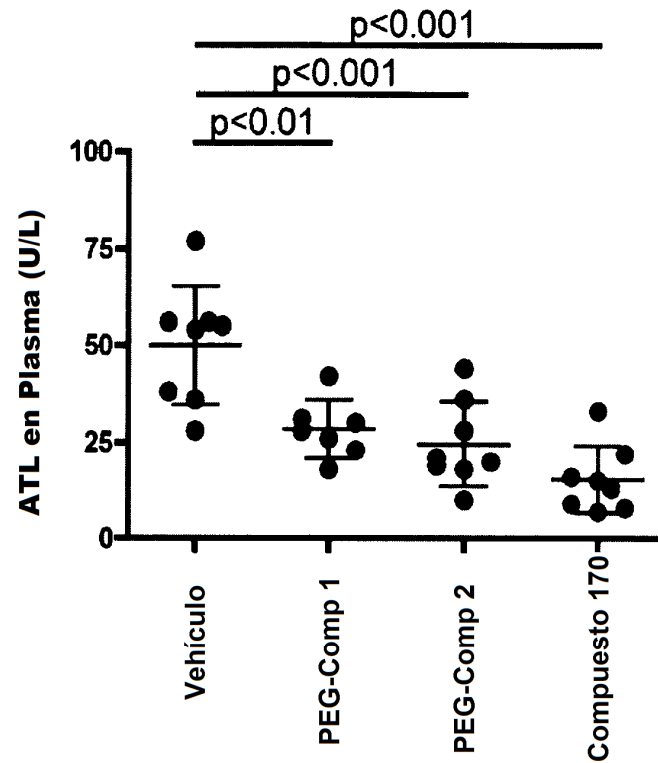


FIG. 72F

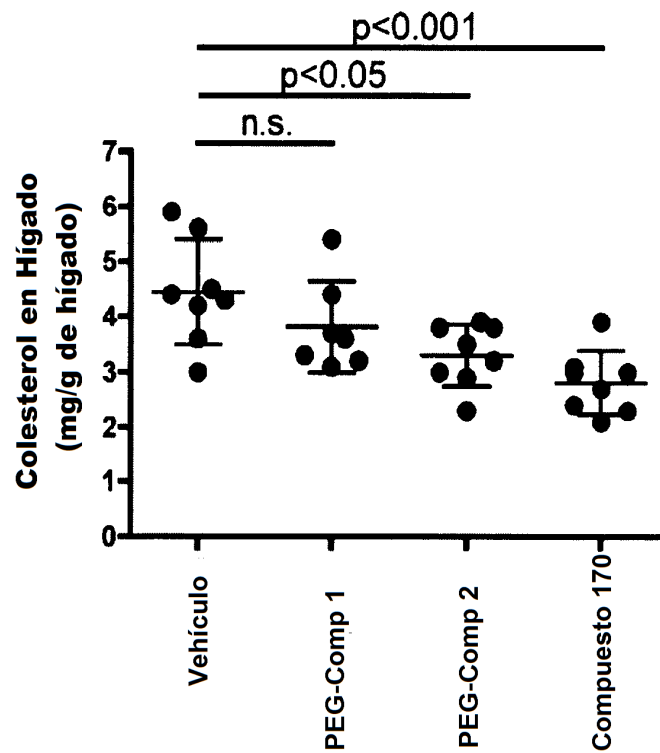


FIG. 72G

