Supplementary Data

Potential dissociative glucocorticoid receptor activity for protopanaxadiol and protopanaxatriol

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1. Quantification of the PPD- and PPT- induced GFPGR nuclear translocation in HeLa transfected cells

Quantifications of the GR nuclear localization in GFPGR transfected HeLa cells treated with the PPD and PPT compounds at a concentration range from 0.1 μM to 20 μM was performed by the use of the ImageJ v1.47 program (NIH, Bethesda, MD, USA). Briefly, for the assessment of the relative nuclear staining in each individual cell two areas of interest were drawn. One based on total green fluorescence staining (total) and the other based on Hoechst staining (nuclear). Mean green fluorescence and integrated density was measured along with several adjacent background readings. The total corrected fluorescence of area of interest (TCF) = integrated density – (selected area × mean fluorescence of background readings), was calculated. Relative GR nuclear localization is expressed as percentage of the nuclear TCF of the GFPGR staining per the TFC of total GFPGR cellular staining.

Analysis of the results by independent t-test or by one way analysis of variance followed by Tukeys's post-hoc test using StatPlus software showed that 1 μM DEX, as well as PPD and PPT compounds at concentration range from 0.1 μM το 20 μM, exhibited statistically significant induction in GFPGR nuclear translocation compared to control vehicle treated cells ($F=40.8$; $F_{crit}=1.8$; $DF_{between\ groups}=13$; $DF_{within\ groups}= 53$; $DF_{total} =166$, $^*p<0.001$). In addition, a tendency of a dose dependent increase in GR nuclear translocation, by the more effective, as regard repression of the NF-κB activity, PPT compound, was observed, which is considered statistically significant upon analysis by one way ANOVA followed by Fisher LSD test. The maximum activation of GR, at a broad range of concentration of PPD and PPT, resembles that of DEX at concentration range from 0.1 μM to 1 μM, as regards induction of nuclear translocation [26], as well as induction in GR transcriptional activation (concentration range of 10 nM to 1 μM) [64]. The difference in the magnitude of GR translocation in GFPGR overexpressing cells compared to that of the endogenous expressed GR in HeLa cells may indicate that the GFP-tagged GR experiment is likely to amplify the signal since this is an overexpression line, thus making the system more sensitive. Additionally, it limits background fluorescence, since GFP fluorescence is directly proportionally to the number of GFPGR molecules present in the cytosol and nucleus and not altered by potential artifacts of antibody-incubation, background staining and non-specific interactions of primary and secondary antibodies used in immunocytochemistry. Thus, studies on GR transfected cells may constitute a better approach to evaluate the efficiency of potential glucocorticoid receptor modulators in nuclear translocation induction.

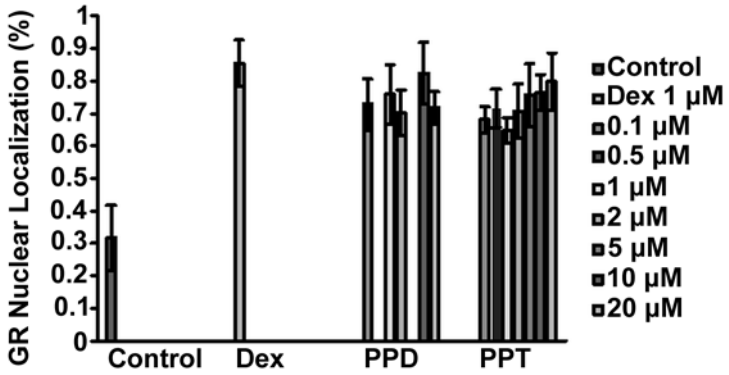

Figure S1. Quantification of the PPD- and PPT- induced nuclear translocation of the GFPGR in HeLa transfected cells. 1μM DEX and PPD and PPT compounds at concentration range from 0.1 μM to 20 μM exhibited statistically significant induction in GFPGR nuclear translocation compared to control vehicle treated cells. Results are expressed as means ± SD, n>10,**p*<0.001). No statistical significance was observed between groups of cells treated with various concentration of each compound, analysed by one way ANOVA followed by Tukeys' post-hoc test. However, statistical analysis of the results by one way ANOVA followed by Fisher LSD test showed statistical significant increase in nuclear GFPGR localization in cells treated with various concentrations of PPD and PPT as indicated below (Paragraph 4, Full statistics).

2. *Cytotoxicity assay- Effect of PPD and PPT on cell growth inhibition*

Cytotoxicity of the PPD and PPT compounds was assessed by applying the sulphorodamine B (SRB) assay according to Vichai & Kirtikara (2006)[39] with some modifications. Briefly, HeLa cells were seeded in 96 plates at a density of 1.1 X 10^4 cells per well. After 24 hrs cells, in wells in triplicates, were treated with increasing concentrations of PPD and PPT (1 μM – 20 μM) or 1 μM DEX, in DMEM growth medium supplemented with 2 mM glutamine, and 5% FBS, as indicated in supplementary Figure S2. Control cells were treated with vehicle (1/1000 EtOH, 1/1000 DMSO). After further incubation of the cells for 48 hrs, growth medium was removed and cells were fixed in trichloroacetic acid (TCA) at a final concentration of 10%. Following incubation of the cells for one hour at 4°C, TCA was removed, plates was washed four times with ddH_20, excess ddH_20 was removed and plate was allowed to dry at room temperature. After TCA-fixation cells were stained with 0.4 % SRB in 1% acetic acid, for 30 minutes. Subsequently, cells were washed with 1% acetic acid, for 4 times, and then the plates was allowed to air-dried. Bound-dye became soluble in 10 mM Tris-Base, upon incubation for 10 minutes, at 37 °C, followed by shaking on a shaker, for 2 minutes. Absorbance was measured at 540 nm in a microplate reader (BIO TEK Instruments, EL 311, Winooski, Vermont, United States). Statistical analysis of the results with one way ANOVA followed by Tukeys' post-hoc test showed no statistical significant effect ($F=1.2$; $F_{crit}=2$; $DF_{between\ groups}=11$; $DF_{within\ groups}=39$; $DF_{total}=50$, $P=0.34$)

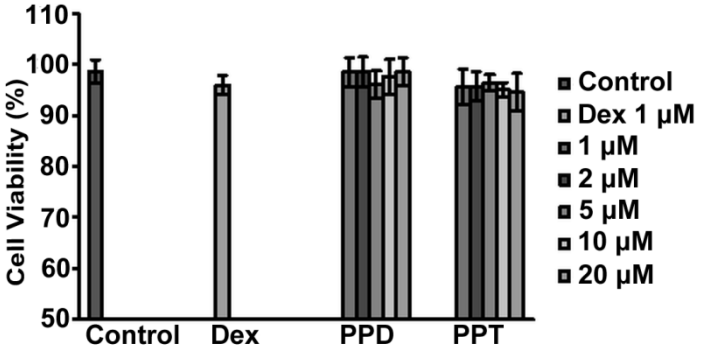

Figure S2. Effect of PPD and PPT on HeLa cell growth inhibition. Cell viability was determined by SRB assay and expressed as % viability compared to control vehicle treated cells. Results are expressed as means ± SD, n>3. No statistically significant effect of PPD and PPT on cells viability was observed.

3. Quantification of the effect of the PPD and PPT compound on PEPCK and GR protein levels in HepG2 cells

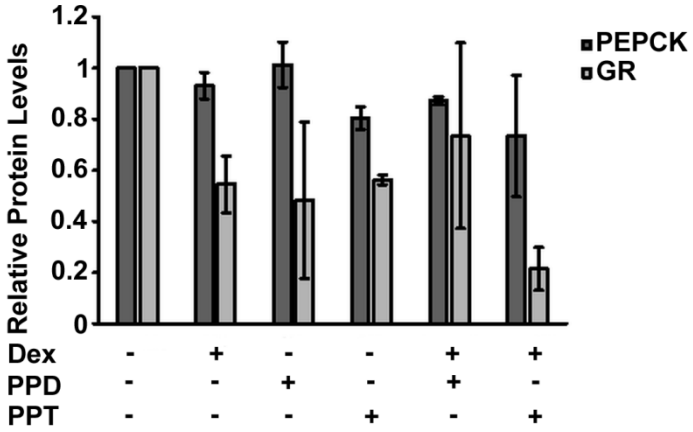

Figure S3. Quantification of the results from Western blot analysis of GR, PEPCK and β-actin protein levels in HepG2 cells treated with 10 μM of PPD or PPT in combination or not with 1 μM DEX. Relative protein levels indicate the mean ± S.D. of ratios resulting from normalization of PEPCK or GR protein levels against β-actin from two independent experiments. Quantifications of protein bands was performed by ImageJ v1.47 program (NIH, Bethesda, MD, USA)

4. Full statistics - Details on the Statistical analysis of the results

Statistical report is followed

Full Statistics

Figure 3 B

ANOVA							
Source of Variation	**d.f.**	**SS**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Between Groups	3	4,77875	1,59292	143,28126	0,	2,6903	0,7951
Within Groups	106	1,17845	0,01112				
Total	109	5,9572					
Hartley Fmax	6,31005	Degrees of Freedom	4	29			
Cochran C	0,36748	Degrees of Freedom	4	29			
Bartlett Chi-square	22,70227	Degrees of Freedom	3	*p-value*	0,00005		

Comparisons among groups (Factor 1-Factor)

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs DEX	-0,54569	28,10569	-0,00002	*Yes*
Control vs PPD	-0,13853	6,48474	0,00005	*Yes*
Control vs PPT	-0,3048	15,69847	-0,00002	*Yes*
DEX vs PPD	0,40716	19,19381	-0,00002	*Yes*
DEX vs PPT	0,24089	12,51372	-0,00002	*Yes*
PPD vs PPT	-0,16626	7,8378	-0,00002	*Yes*

Figure 5 A

Summary	
Response	GR Transcriptional Activity
Factor #1	Triterpene
Factor #2	DEX

Factor	Group
Triterpene	Control
Triterpene	PPD
Triterpene	PPT
DEX	+
DEX	-
Triterpene x DEX	Control x +
Triterpene x DEX	Control x -
Triterpene x DEX	PPD x +
Triterpene x DEX	PPD x -
Triterpene x DEX	PPT x +
Triterpene x DEX	PPT x -

ANOVA							
Source of Variation	**SS**	**d.f.**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Factor #1 (Triterpene)	9,16673	2	4,58337	1,0543	0,35354	3,11864	0,00048
Factor #2 (DEX)	588,02917	1	588,02917	135,26332	0,	3,96847	0,5977
Factor #1 + #2 (Triterpene x DEX)	48,9615	2	24,48075	5,63126	0,00527	3,11864	0,04123
Within Groups	326,04691	75	4,34729				
Total	972,20431	80	12,15255				
Omega squared for combined effect	0,63941						

1) Comparisons among groups of factor 2 (DEX) within each factor 1 (Triterpene) level

a) Factor 1 (Triterpene) = Control

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	7,51981	11,56684	0,00007	Yes

b) Factor 1 (Triterpene) = PPD

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	5,01522	9,12771	0,00007	Yes

c) Factor 1 (Triterpene) = PPT

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	4,78825	8,71463	0,00007	Yes

2) Comparisons among groups of factor 1 (Triterpene) within each factor 2 (DEX) level

a) Factor 2 (DEX) = +

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs PPD	2,95428	4,90832	0,00249	Yes
Control vs PPT	2,32748	3,86693	0,02102	Yes
PPD vs PPT	-0,6268	1,27544	0,64082	No

b) Factor 2 (DEX) = -

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs PPD	0,44969	0,74713	0,85774	No
Control vs PPT	-0,40408	0,67136	0,88342	No
PPD vs PPT	-0,85377	1,41848	0,57729	No

Figure 6

Summary	
Response	NFkbeta Activity
Factor #1	TNF
Factor #2	Treatment

Factor	**Group**
TNF	+
TNF	-
Treatment	Control
Treatment	DEX
Treatment	PPD
Treatment	PPT
TNF x Treatment	+ x Control
TNF x Treatment	+ x DEX
TNF x Treatment	+ x PPD
TNF x Treatment	+ x PPT
TNF x Treatment	- x Control
TNF x Treatment	- x DEX
TNF x Treatment	- x PPD
TNF x Treatment	- x PPT

Figure 6 A

ANOVA							
Source of Variation	**SS**	**d.f.**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Factor #1 (TNF)	12,17724	1	12,17724	214,3615	1,09806E-10	4,494	0,45263
Factor #2 (Treatment)	7,62998	3	2,54333	44,77132	5,23506E-8	3,23887	0,27857
Factor #1 + #2 (TNF x Treatment)	6,00491	3	2,00164	35,2357	2,79888E-7	3,23887	0,21788
Within Groups	0,90891	16	0,05681				
Total	26,72104	23	1,16178				
Omega squared for combined effect	0,94909						

1) Comparisons among groups (Factor 2 - Treatment)

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
DEX vs PPT (df = 2)	-0,10382	1,06697	0,66747	No
PPD vs PPT (df = 3)	-0,51323	5,27461	0,00691	Yes
Control vs PPT (df = 4)	-1,4301	14,69741	0,00003	Yes
DEX vs PPD (df = 2)	-0,40942	4,20764	0,02454	Yes
Control vs DEX (df = 3)	-1,32628	13,63044	0,00005	Yes
Control vs PPD (df = 2)	-0,91686	9,4228	0,00008	Yes

2) Comparisons among groups of factor 2 (Treatment) within each factor 1 (TNF) level

a) Factor 1 (TNF) = +

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
DEX vs PPT (df = 2)	-0,39553	2,87432	0,13827	No
PPD vs PPT (df = 3)	-0,86522	6,28762	0,00159	Yes
Control vs PPT (df = 4)	-2,75818	20,04392	0,00003	Yes
DEX vs PPD (df = 2)	-0,46969	3,4133	0,07134	No
Control vs DEX (df = 3)	-2,36266	17,1696	0,00005	Yes
Control vs PPD (df = 2)	-1,89296	13,7563	0,00007	Yes

b) Factor 1 (TNF) = -

Tukey B				
Groups	Difference	Test Statistic	p-value	Significant
DEX vs PPT (df = 2)	-0,18789	1,3654	0,55965	No
Control vs DEX (df = 3)	-0,2899	2,10675	0,39395	No
DEX vs PPD (df = 4)	-0,34914	2,53721	0,31181	No
Control vs PPT (df = 2)	-0,10202	0,74135	0,77963	No
PPD vs PPT (df = 3)	-0,16125	1,17181	0,76573	No
Control vs PPD (df = 2)	-0,05923	0,43045	0,8773	No

3) Comparisons among groups of factor 1 (TNF) within each factor 2 (Treatment) level

a) Factor 2 (Treatment) = Control

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-3,0949	22,49086	0,00011	Yes

b) Factor 2 (Treatment) = DEX

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-1,02215	7,42801	0,00018	Yes

c) Factor 2 (Treatment) = PPD

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-1,1427	8,3041	0,00013	Yes

d) Factor 2 (Treatment) = PPT

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-0,43873	3,18829	0,03856	Yes

Figure 6 B

ANOVA							
Source of Variation	**SS**	**d.f.**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Factor #1 (TNF)	13,48348	1	13,48348	78,06254	0,	3,94454	0,37115
Factor #2 (Treatment)	0,69183	3	0,23061	1,33511	0,26782	2,70359	0,00484
Factor #1 + #2 (TNF x Treatment)	5,62435	3	1,87478	10,85404	3,58932E-6	2,70359	0,14238
Within Groups	15,89085	92	0,17273				
Total	35,69051	99	0,36051				
Omega squared for combined effect	0,51837						

1) Comparisons among groups of factor 2 (Treatment) within each factor 1 (TNF) level

a) Factor 1 (TNF) = +

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	0,85808	4,61671	0,00828	Yes
Control vs PPD	0,87068	4,50073	0,0106	Yes
Control vs PPT	1,40078	7,44178	-0,00001	Yes
Dex vs PPD	0,0126	0,10503	0,99987	No
Dex vs PPT	0,5427	4,87341	0,00471	Yes
PPD vs PPT	0,5301	4,28844	0,01643	Yes

b) Factor 1 (TNF) = -

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	0,3021	2,90191	0,17682	No
Control vs PPD	0,22013	2,11452	0,44458	No
Control vs PPT	0,14545	1,3127	0,78985	No
Dex vs PPD	-0,08197	0,76387	0,94903	No
Dex vs PPT	-0,15665	1,37633	0,76504	No
PPD vs PPT	-0,07468	0,65615	0,96677	No

2) Comparisons among groups of factor 1 (TNF) within each factor 2 (Treatment) level

a) Factor 2 (Treatment) = Control

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	1,55468	8,44784	0,00006	Yes

b) Factor 2 (Treatment) = DEX

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	0,9987	9,30683	0,00006	Yes

c) Factor 2 (Treatment) = PPD

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	0,90413	7,53602	0,00006	Yes

d) Factor 2 (Treatment) = PPT

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	0,29935	2,54454	0,0753	No

Figure 6 C

ANOVA							
Source of Variation	**SS**	**d.f.**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Factor #1 (TNF)	757,85656	1	757,85656	276,43168	1,61694E-11	4,494	0,86076
Factor #2 (Treatment)	36,3362	3	12,11207	4,41793	0,01914	3,23887	0,03204
Factor #1 + #2 (TNF x Treatment)	36,46459	3	12,15486	4,43354	0,01891	3,23887	0,03219
Within Groups	43,86511	16	2,74157				
Total	874,52246	23	38,02272				
Omega squared for combined effect	0,925						

1) Comparisons among groups (Factor 2 - Treatment)

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
DEX vs PPT (df = 2)	-0,86584	1,28089	0,59024	No
DEX vs PPD (df = 3)	-2,32366	3,43755	0,08879	No
Control vs DEX (df = 4)	-3,16012	4,67498	0,02093	Yes
PPD vs PPT (df = 2)	-1,45783	2,15666	0,29671	No
Control vs PPT (df = 3)	-2,29429	3,39409	0,09388	No
Control vs PPD (df = 2)	-0,83646	1,23743	0,60603	No

2) Comparisons among groups of factor 2 (Treatment) within each factor 1 (TNF) level

a) Factor 1 (TNF) = +

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
DEX vs PPT (df = 2)	-1,63557	1,71093	0,43691	No
DEX vs PPD (df = 3)	-4,46083	4,66634	0,01657	Yes
Control vs DEX (df = 4)	-6,36043	6,65346	0,00121	Yes
PPD vs PPT (df = 2)	-2,82525	2,95542	0,12567	No
Control vs PPT (df = 3)	-4,72486	4,94253	0,01115	Yes
Control vs PPD (df = 2)	-1,8996	1,98712	0,34674	No

b) Factor 1 (TNF) = -

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs DEX (df = 2)	-0,04018	0,04204	0,98838	No
Control vs PPT (df = 3)	-0,13628	0,14256	0,99707	No
Control vs PPD (df = 4)	-0,22668	0,23713	0,99832	No
DEX vs PPT (df = 2)	-0,0961	0,10053	0,97206	No
DEX vs PPD (df = 3)	-0,1865	0,19509	0,99437	No
PPD vs PPT (df = 2)	-0,0904	0,09456	0,97372	No

3) Comparisons among groups of factor 1 (TNF) within each factor 2 (Treatment) level

a) Factor 2 (Treatment) = Control

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-14,58576	15,25773	0,00011	Yes

b) Factor 2 (Treatment) = DEX

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-8,18514	8,56224	0,00012	Yes

c) Factor 2 (Treatment) = PPD

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-12,45947	13,03349	0,00011	Yes

d) Factor 2 (Treatment) = PPT

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs - (df = 2)	-9,72462	10,17264	0,00011	Yes

Figure 6 D

ANOVA							
Source of Variation	**SS**	**d.f.**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Factor #1 (TNF)	77,25888	1	77,25888	87,40489	1,20238E-7	4,54308	0,77352
Factor #2 (Treatment)	2,11304	3	0,70435	0,79684	0,5146	3,28738	0,
Factor #1 + #2 (TNF x Treatment)	5,22244	3	1,74081	1,96943	0,16194	3,28738	0,02604
Within Groups	13,25879	15	0,88392				
Total	97,85315	22	4,44787				
Omega squared for combined effect	0,7941						

1) Comparisons among groups of factor 2 (Treatment) within each factor 1 (TNF) level

a) Factor 1 (TNF) = +

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	-0,53714	0,98955	0,89566	No
Control vs PPD	-1,47805	2,72297	0,2592	No
Control vs PPT	0,02409	0,0397	0,99999	No
Dex vs PPD	-0,94091	1,73341	0,62095	No
Dex vs PPT	0,56123	0,92478	0,91261	No
PPD vs PPT	1,50214	2,4752	0,33389	No

b) Factor 1 (TNF) = -

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	0,10703	0,19718	0,99905	No
Control vs PPD	-0,14174	0,26113	0,99773	No
Control vs PPT	-1,18371	2,18073	0,43879	No
Dex vs PPD	-0,24877	0,4583	0,98782	No
Dex vs PPT	-1,29074	2,3779	0,36673	No
PPD vs PPT	-1,04197	1,9196	0,54314	No

2) Comparisons among groups of factor 1 (TNF) within each factor 2 (Treatment) level

a) Factor 2 (Treatment) = Control

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	3,42842	6,31609	0,00055	Yes

b) Factor 2 (Treatment) = DEX

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	4,07259	7,50282	0,00019	Yes

c) Factor 2 (Treatment) = PPD

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	4,76473	8,77793	0,00013	Yes

d) Factor 2 (Treatment) = PPT

Tukey Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
+ vs -	2,22061	3,65908	0,02063	Yes

Figure S1

1) Comparison among Control and Dex

ANOVA							
Source of Variation	**d.f.**	**SS**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Between Groups	1	2,98605	2,98605	442,45748	0,	4,06705	0,90749
Within Groups	43	0,2902	0,00675				
Total	44	3,27625					
Hartley Fmax	1,95256	Degrees of Freedom	2	28			
Cochran C	0,66131	Degrees of Freedom	2	28			
Bartlett Chi-square	2,2408	Degrees of Freedom	1	p-value	0,13441		

Comparisons among groups (Control-Dex)

Tukey B				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex (df = 2)	-0,53814	26,20252	0,00007	*Yes*

2) Comparison among group, which indicated in the table

Groups
Control
Dex
PPD 0,1 μM
PPD 1 μM
PPD 2 μM
PPD 10 μM
PPD 20 μM
PPT 0,1 μM
PPT 0,5 μM
PPT 1 μM
PPT 2 μM
PPT 5 μM
PPT 10 μM
PPT 20 μM

ANOVA							
Source of Variation	**d.f.**	**SS**	**MS**	**F**	**p-value**	**F crit**	**Omega Sqr.**
Between Groups	13	3,57358	0,27489	40,80358	0,	1,78461	0,75601
Within Groups	153	1,03075	0,00674				
Total	166	4,60433					
Hartley Fmax	8,4545	Degrees of Freedom	14	28			
Cochran C	0,13879	Degrees of Freedom	14	28			
Bartlett Chi-square	17,46755	Degrees of Freedom	13	p-value	0,1788		

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	-0,53814	29,7737	0,74636	*No*
Control vs PPD 0,1 µM	-0,41141	18,5621	0,74636	*No*
Control vs PPD 1 µM	-0,44223	20,82078	0,74636	*No*
Control vs PPD 10 µM	-0,50741	25,44497	0,74636	*No*
Control vs PPD 2 µM	-0,38526	15,9311	0,74636	*No*
Control vs PPD 20 µM	-0,44072	18,22457	0,74636	*No*
Control vs PPT 0,1 µM	-0,34699	13,19316	0,74636	*No*
Control vs PPT 0,5 µM	-0,30705	10,32582	0,74636	*No*
Control vs PPT 1 µM	-0,33095	14,14551	0,74636	*No*
Control vs PPT 10 µM	-0,44886	17,8605	0,74636	*No*
Control vs PPT 2 µM	-0,39082	17,63333	0,74636	*No*
Control vs PPT 20 µM	-0,48145	20,57805	0,74636	*No*
Control vs PPT 5 µM	-0,44035	17,52203	0,74636	*No*
Dex vs PPD 0,1 µM	0,12673	6,36173	0,74651	*No*
Dex vs PPD 1 µM	0,09591	5,07779	0,75214	*No*
Dex vs PPD 10 µM	0,03073	1,76445	0,99842	*No*
Dex vs PPD 2 µM	0,15288	6,90358	0,74639	*No*
Dex vs PPD 20 µM	0,09742	4,39914	0,77214	*No*
Dex vs PPT 0,1 µM	0,19115	7,82082	0,74637	*No*
Dex vs PPT 0,5 µM	0,23109	8,22274	0,74636	*No*
Dex vs PPT 1 µM	0,20719	9,73471	0,74636	*No*

Dex vs PPT 10 μM	0,08928	3,85203	0,81342	*No*
Dex vs PPT 2 μM	0,14732	7,39505	0,74637	*No*
Dex vs PPT 20 μM	0,0567	2,6638	0,95837	*No*
Dex vs PPT 5 μM	0,09779	4,21903	0,78281	*No*
PPD 0,1 μM vs PPT 1 μM	-0,03082	1,35005	0,9999	*No*
PPD 0,1 μM vs PPD 10 μM	-0,09601	4,43862	0,77042	*No*
PPD 0,1 μM vs PPD 2 μM	0,02615	1,02177	1,	*No*
PPD 0,1 μM vs PPD 20 μM	-0,02931	1,14535	0,99998	*No*
PPD 0,1 μM vs PPT 0,1 μ M	0,06441	2,33363	0,98293	*No*
PPD 0,1 μM vs PPT 0,5 μM	0,10436	3,37806	0,87028	*No*
PPD 0,1 μM vs PPT 1 μM	0,08046	3,23765	0,88915	*No*
PPD 0,1 μM vs PPT 10 μM	-0,03745	1,41379	0,99983	*No*
PPD 0,1 μM vs PPT 2 μM	0,02059	0,86878	1,	*No*
PPD 0,1 μM vs PPT 20 μM	-0,07004	2,81838	0,94233	*No*
PPD 0,1 μM vs PPT 5 μM	-0,02895	1,09269	0,99999	*No*
PPD 1 μM vs PPD 10 μM	-0,06518	3,1516	0,90071	*No*
PPD 1 μM vs PPD 2 μM	0,05697	2,29765	0,98479	*No*
PPD 1 μM vs PPD 20 μM	0,00151	0,06098	1,	*No*
PPD 1 μM vs PPT 0,1 μ M	0,09524	3,5449	0,84864	*No*
PPD 1 μM vs PPT 0,5 μM	0,13518	4,47076	0,76892	*No*
PPD 1 μM vs PPT 1 μM	0,11128	4,63092	0,76251	*No*
PPD 1 μM vs PPT 10 μM	-0,00663	0,25766	1,	*No*
PPD 1 μM vs PPT 2 μM	0,05141	2,25163	0,98696	*No*
PPD 1 μM vs PPT 20 μM	-0,03921	1,63186	0,99926	*No*
PPD 1 μM vs PPT 5 μM	0,00188	0,07302	1,	*No*
PPD 10 μM vs PPD 2 μM	0,12216	5,15552	0,75112	*No*
PPD 10 μM vs PPD 20 μM	0,06669	2,81476	0,94273	*No*
PPD 10 μM vs PPT 0,1 μM	0,16042	6,20525	0,74661	*No*
PPD 10 μM vs PPT 0,5 μM	0,20037	6,8291	0,74639	*No*
PPD 10 μM vs PPT 1 μM	0,17646	7,70896	0,74637	*No*
PPD10 μM vs PPT 10 μM	0,05855	2,37427	0,98064	*No*
PPD 10 μM vs PPT 2 μM	0,11659	5,39032	0,74891	*No*
PPD 10 μM vs PPT 20 μM	0,02597	1,13441	0,99999	*No*
PPD 10 μM vs PPT 5 μM	0,06706	2,71919	0,95293	*No*
PPD 2 μM vs PPD 20 μM	-0,05546	2,02716	0,99445	*No*
PPD 2 μM vs PPT 0,1 μ M	0,03826	1,30826	0,99993	*No*
PPD 2 μM vs PPT 0,5 μM	0,07821	2,41595	0,97808	*No*
PPD 2 μM vs PPT 1 μM	0,05431	2,03653	0,99423	*No*
PPD 2 μM vs PPT 10 μM	-0,0636	2,25527	0,9868	*No*
PPD 2 μM vs PPT 2 μM	-0,00556	0,21744	1,	*No*
PPD 2 μM vs PPT 20 μM	-0,09619	3,60703	0,84092	*No*

PPD 2 μM vs PPT 5 μM	-0,0551	1,95364	0,99597	*No*
PPD 20 μM vs PPT 0,1 μ M	0,09373	3,20449	0,89361	*No*
PPD 20 μM vs PPT 0,5 μM	0,13367	4,12921	0,78917	*No*
PPD 20 μM vs PPT 1 μM	0,10977	4,11635	0,79014	*No*
PPD 20 μM vs PPT 10 μM	-0,00814	0,28864	1,	*No*
PPD 20 μM vs PPT 2 μM	0,0499	1,94969	0,99605	*No*
PPD 20 μM vs PPT 20 μM	-0,04073	1,52721	0,99962	*No*
PPD 20 μM vs PPT 5 μM	0,00037	0,01299	1,	*No*
PPT 0,1 μ M vs PPT 0,5 μM	0,03994	1,17541	0,99998	*No*
PPT 0,1 μ M vs PPT 1 μM	0,01604	0,56091	1,	*No*
PPT 0,1 μ M vs PPT 10 μM	-0,10187	3,3913	0,86852	*No*
PPT 0,1 μ M vs PPT 2 μM	-0,04383	1,58787	0,99944	*No*
PPT 0,1 μ M vs PPT 20 μM	-0,13445	4,70088	0,76022	*No*
PPT 0,1 μ M vs PPT 5 μM	-0,09336	3,10812	0,90649	*No*
PPT 0,5 μM vs PPT 1 μM	-0,0239	0,7519	1,	*No*
PPT 0,5 μM vs PPT 10 μM	-0,14181	4,28603	0,77852	*No*
PPT 0,5 μM vs PPT 2 μM	-0,08377	2,71173	0,95368	*No*
PPT 0,5 μM vs PPT 20 μM	-0,1744	5,48611	0,7483	*No*
PPT 0,5 μM vs PPT 5 μM	-0,13331	4,02894	0,79716	*No*
PPT 1 μM vs PPT 10 μM	-0,11791	4,28295	0,77871	*No*
PPT 1 μM vs PPT 2 μM	-0,05987	2,4093	0,9785	*No*
PPT 1 μM vs PPT 20 μM	-0,1505	5,79821	0,74707	*No*
PPT t 1 μM vs PPT 5 μM	-0,1094	3,97397	0,80194	*No*
PPT 10 μM vs PPT 2 μM	0,05804	2,19085	0,98947	*No*
PPT 10 μM vs PPT 20 μM	-0,03259	1,18365	0,99998	*No*
PPT 10 μM vs PPT 5 μM	0,00851	0,29312	1,	*No*
PPT 2 μM vs PPT 20 μM	-0,09062	3,64673	0,83614	*No*
PPT 2 μM vs PPT 5 μM	-0,04953	1,86975	0,99729	*No*
PPT 20 μM vs PPT 5 μM	0,04109	1,49263	0,9997	*No*

Fisher LSD				
Group vs. Group (Contrast)	**Difference**	**Test Statistic**	**p-value**	**Significant**
Control vs Dex	-0,53814	21,05318	0,	Yes
Control vs PPD 0,1 μM	-0,41141	13,12538	0,	Yes
Control vs PPD 1 μM	-0,44223	14,72251	0,	Yes
Control vs PPD 10 μM	-0,50741	17,99231	0,	Yes
Control vs PPD 2 μM	-0,38526	11,26499	0,	Yes
Control vs PPD 20 μM	-0,44072	12,88672	0,	Yes
Control vs PPT 0,1 μM	-0,34699	9,32897	0,	Yes
Control vs PPT 0,5 μM	-0,30705	7,30146	1,39566E-11	Yes
Control vs PPT 1 μM	-0,33095	10,00239	0,	Yes
Control vs PPT 10 μM	-0,44886	12,62928	0,	Yes
Control vs PPT 2 μM	-0,39082	12,46865	0,	Yes
Control vs PPT 20 μM	-0,48145	14,55088	0,	Yes
Control vs PPT 5 μM	-0,44035	12,38994	0,	Yes
Dex vs PPD 0,1 μM	0,12673	4,49842	0,00001	Yes
Dex vs PPD 1 μM	0,09591	3,59054	0,00044	Yes
Dex vs PPD 10 μ M	0,03073	1,24766	0,21404	No
Dex vs PPD 2 μM	0,15288	4,88157	2,59373E-6	Yes
Dex vs PPD 20 μM	0,09742	3,11066	0,00222	Yes
Dex vs PPT 0,1 μM	0,19115	5,53016	1,3293E-7	Yes
Dex vs PPT 0,5 μM	0,23109	5,81436	3,36555E-8	Yes
Dex vs PPT 1 μM	0,20719	6,88348	1,36479E-10	Yes
Dex vs PPT 10 μM	0,08928	2,7238	0,00719	Yes
Dex vs PPT 2 μM	0,14732	5,22909	5,43682E-7	Yes
Dex vs PPT 20 μM	0,0567	1,88359	0,06149	No
Dex vs PPT 5 μM	0,09779	2,9833	0,00331	Yes
PPD 0,1 μM vs PPD 1 μM	-0,03082	0,95463	0,34125	No
PPD 0,1 μM vs PPD 10 μM	-0,09601	3,13858	0,00203	Yes
PPD 0,1 μM vs PPD 2 μM	0,02615	0,7225	0,47108	No
PPD 0,1 μM vs PPD 20 μM	-0,02931	0,80989	0,41925	No
PPD 0,1 μM vs PPT 0,1 μ M	0,06441	1,65012	0,10094	No
PPD 0,1 μM vs PPT 0,5 μM	0,10436	2,38865	0,01811	Yes
PPD 0,1 μM vs PPT 1 μM	0,08046	2,28936	0,02341	Yes
PPD 0,1 μM vs PPT 10 μM	-0,03745	0,9997	0,31901	No
PPD 0,1 μM vs PPT 2 μM	0,02059	0,61432	0,5399	No
PPD 0,1 μM vs PPT 20 μM	-0,07004	1,9929	0,04803	No
PPD 0,1 μM vs PPT 5 μM	-0,02895	0,77265	0,44091	No
PPD 1 μM vs PPD 10 μM	-0,06518	2,22852	0,02728	No
PPD 1 μM vs PPD 2 μM	0,05697	1,62469	0,10626	No
PPD 1 μM vs PPD 20 μM	0,00151	0,04312	0,96566	No

PPD 1 μM vs PPT 0,1 μM	0,09524	2,50662	0,01322	Yes
PPD 1 μM vs PPT 0,5 μM	0,13518	3,16131	0,00189	Yes
PPD 1 μM vs PPT 1 μM	0,11128	3,27456	0,00131	Yes
PPD 1 μM vs PPT 10 μM	-0,00663	0,1822	0,85567	No
PPD 1 μM vs PPT 2 μM	0,05141	1,59214	0,11339	No
PPD 1 μM vs PPT 20 μM	-0,03921	1,1539	0,25032	No
PPD 1 μM vs PPT 5 μM	0,00188	0,05164	0,95889	No
PPD 10 μM vs PPD 2 μM	0,12216	3,64551	0,00036	Yes
PPD 10 μM vs PPD 20 μM	0,06669	1,99034	0,04831	No
PPD 10 μM vs PPT 0,1 μM	0,16042	4,38777	0,00002	Yes
PPD 10 μM vs PPT 0,5 μM	0,20037	4,82891	3,26635E-6	Yes
PPD 10 μM vs PPT 1 μM	0,17646	5,45106	1,93379E-7	Yes
PPD 10 μM vs PPT 10 μM	0,05855	1,67886	0,09519	No
PPD 10 μM vs PPT 2 μM	0,11659	3,81153	0,0002	Yes
PPD 10 μM vs PPT 20 μM	0,02597	0,80215	0,4237	No
PPD 10 μM vs PPT 5 μM	0,06706	1,92276	0,05634	No
PPD 2 μM vs PPD 20 μM	-0,05546	1,43342	0,15375	No
PPD 2 μM vs PPT 0,1 μM	0,03826	0,92508	0,35636	No
PPD 2 μM vs PPT 0,5 μM	0,07821	1,70833	0,08958	No
PPD 2 μM vs PPT 1 μM	0,05431	1,44004	0,15187	No
PPD 2 μM vs PPT 10 μM	-0,0636	1,59471	0,11281	No
PPD 2 μM vs PPT 2 μM	-0,00556	0,15375	0,87801	No
PPD 2 μM vs PPT 20 μM	-0,09619	2,55056	0,01172	Yes
PPD 2 μM vs PPT 5 μM	-0,0551	1,38144	0,16913	No
PPD 20 μM vs PPT 0,1 μM	0,09373	2,26592	0,02484	Yes
PPD 20 μM vs PPT 0,5 μM	0,13367	2,91979	0,00403	Yes
PPD 20 μM vs PPT 1 μM	0,10977	2,9107	0,00414	Yes
PPD 20 μM vs PPT 10 μM	-0,00814	0,2041	0,83855	No
PPD 20 μM vs PPT 2 μM	0,0499	1,37864	0,16999	No
PPD 20 μM vs PPT 20 μM	-0,04073	1,0799	0,28186	No
PPD 20 μM vs PPT 5 μM	0,00037	0,00918	0,99268	No
PPT 0,1 μM vs PPT 0,5 μM	0,03994	0,83114	0,40717	No
PPT 0,1 μM vs PPT 1 μM	0,01604	0,39662	0,69219	No
PPT 0,1 μM vs PPT 10 μM	-0,10187	2,39801	0,01767	Yes
PPT 0,1 μM vs PPT 2 μM	-0,04383	1,12279	0,26326	No
PPT 0,1 μM vs PPT 20 μM	-0,13445	3,32403	0,00111	Yes
PPT 0,1 μM vs PPT 5 μM	-0,09336	2,19777	0,02945	No
PPT 0,5 μM vs PPT 1 μM	-0,0239	0,53167	0,59572	No
PPT 0,5 μM vs PPT 10 μM	-0,14181	3,03068	0,00286	Yes
PPT 0,5 μM vs PPT 2 μM	-0,08377	1,91748	0,05702	No
PPT 0,5 μM vs PPT 20 μM	-0,1744	3,87927	0,00015	Yes

PPT 0,5 μM vs PPT 5 μM	-0,13331	2,84889	0,00498	Yes
PPT 1 μM vs PPT 10 μM	-0,11791	3,0285	0,00288	Yes
PPT 1 μM vs PPT 2 μM	-0,05987	1,70363	0,09045	No
PPT 1 μM vs PPT 20 μM	-0,1505	4,09995	0,00007	Yes
PPT 1 μM vs PPT 5 μM	-0,1094	2,81002	0,00559	Yes
PPT 10 μM vs PPT 2 μM	0,05804	1,54917	0,12338	No
PPT 10 μM vs PPT 20 μM	-0,03259	0,83697	0,4039	No
PPT 10 μM vs PPT 5 μM	0,00851	0,20727	0,83607	No
PPT 2 μM vs PPT 20 μM	-0,09062	2,57863	0,01085	Yes
PPT 2 μM vs PPT 5 μM	-0,04953	1,32211	0,18808	No
PPT 20 μM vs PPT 5 μM	0,04109	1,05545	0,29286	No

Figure S2

ANOVA							
Source of Variation	d.f.	SS	MS	F	p-value	F crit	Omega Sqr.
Between Groups	11	0,01052	0,00096	1,15475	0,34858	2,04425	0,0323
Within Groups	39	0,03229	0,00083				
Total	50	0,04281					
Hartley Fmax	11,04338	Degrees of Freedom	12	7			
Cochran C	0,23915	Degrees of Freedom	12	7			
Bartlett Chi-square	6,95631	Degrees of Freedom	11	p-value	0,80261		

Comparisons among groups (Factor 1 - Factor)

Tukey-Kramer				
Groups	**Difference**	**Test Statistic**	**p-value**	**Significant**
CONTROL vs DEX	0,02604	1,89016	0,9686	No
CONTROL vs PPD 1 μM	0,00076	0,06139	1,	No
CONTROL vs PPD 10 μM	0,01004	0,80568	0,99999	No
CONTROL vs PPD 2 μM	0,00086	0,06906	1,	No
CONTROL vs PPD 20 μM	-0,0001	0,00767	1,	No
CONTROL vs PPD 5 μM	0,02486	1,99502	0,95436	No
CONTROL vs PPT 1 μM	0,01702	1,36582	0,99769	No
CONTROL vs PPT 10 μM	0,03585	2,87743	0,66844	No
CONTROL vs PPT 2 μM	0,02897	2,32497	0,88162	No
CONTROL vs PPT 20 μM	0,04063	3,26109	0,48955	No
CONTROL vs PPT 5 μM	0,02218	1,78017	0,97971	No
DEX vs PPD 1 μM	-0,02527	1,62623	0,98992	No

DEX vs PPD 10 μM	-0,016	1,02947	0,99983	No
DEX vs PPD 2 μM	-0,02518	1,62008	0,99022	No
DEX vs PPD 20 μM	-0,02613	1,6816	0,98687	No
DEX vs PPD 5 μM	-0,00118	0,07588	1,	No
DEX vs PPT 1 μM	-0,00902	0,58036	1,	No
DEX vs PPT 10 μM	0,00982	0,63163	1,	No
DEX vs PPT 2 μM	0,00293	0,18867	1,	No
DEX vs PPT 20 μM	0,0146	0,93924	0,99993	No
DEX vs PPT 5 μM	-0,00386	0,24814	1,	No
PPD 1 μM vs PPD 10 μM	0,00927	0,64458	1,	No
PPD 1 μM vs PPD 2 μM	0,0001	0,00665	1,	No
PPD 1 μM vs PPD 20 μM	-0,00086	0,05981	1,	No
PPD 1 μM vs PPD 5 μM	0,02409	1,67458	0,98729	No
PPD 1 μM vs PPT 1 μM	0,01625	1,12967	0,99959	No
PPD 1 μM vs PPT 10 μM	0,03509	2,43877	0,84612	No
PPD 1 μM vs PPT 2 μM	0,0282	1,96032	0,95951	No
PPD 1 μM vs PPT 20 μM	0,03987	2,77103	0,71611	No
PPD 1 μM vs PPT 5 μM	0,02141	1,48851	0,99511	No
PPD 10 μM vs PPD 2 μM	-0,00918	0,63793	1,	No
PPD 10 μM vs PPD 20 μM	-0,01013	0,70439	1,	No
PPD 10 μM vs PPD 5 μM	0,01482	1,03	0,99983	No
PPD 10 μM vs PPT 1 μM	0,00698	0,4851	1,	No
PPD 10 μM vs PPT 10 μM	0,02581	1,79419	0,97849	No
PPD 10 μM vs PPT 2 μM	0,01893	1,31574	0,99834	No
PPD 10 μM vs PPT 20 μM	0,03059	2,12645	0,93072	No
PPD 10 μM vs PPT 5 μM	0,01214	0,84393	0,99998	No
PPD 2 μM vs PPD 20 μM	-0,00096	0,06645	1,	No
PPD 2 μM vs PPD 5 μM	0,024	1,66793	0,98768	No
PPD 2 μM vs PPT 1 μM	0,01616	1,12303	0,99962	No
PPD 2 μM vs PPT 10 μM	0,03499	2,43212	0,84833	No
PPD 2 μM vs PPT 2 μM	0,02811	1,95367	0,96044	No
PPD 2 μM vs PPT 20 μM	0,03977	2,76438	0,71902	No
PPD 2 μM vs PPT 5 μM	0,02132	1,48187	0,99529	No
PPD 20 μM vs PPD 5 μM	0,02495	1,73438	0,98334	No
PPD 20 μM vs PPT 1 μM	0,01711	1,18948	0,99934	No
PPD 20 μM vs PPT 10 μM	0,03595	2,49858	0,82543	No
PPD 20 μM vs PPT 2 μM	0,02906	2,02012	0,95037	No
PPD 20 μM vs PPT 20 μM	0,04073	2,83083	0,68956	No
PPD 20 μM vs PPT 5 μM	0,02228	1,54832	0,99322	No
PPD 5 μM vs PPT 1 μM	-0,00784	0,5449	1,	No
PPD 5 μM vs PPT 10 μM	0,01099	0,76419	0,99999	No
PPD 5 μM vs PPT 2 μM	0,00411	0,28574	1,	No
PPD 5 μM vs PPT 20 μM	0,01577	1,09645	0,99969	No
PPD 5 μM vs PPT 5 μM	-0,00268	0,18606	1,	No
PPT 1 μM vs PPT 10 μM	0,01883	1,30909	0,99841	No
PPT 1 μM vs PPT 2 μM	0,01195	0,83064	0,99998	No
PPT 1 μM vs PPT 20 μM	0,02361	1,64135	0,98914	No
PPT 1 μM vs PPT 5 μM	0,00516	0,35884	1,	No
PPT 10 μM vs PPT 2 μM	-0,00688	0,47845	1,	No
PPT 10 μM vs PPT 20 μM	0,00478	0,33226	1,	No
PPT 10 μM vs PPT 5 μM	-0,01367	0,95026	0,99992	No
PPT 2 μM vs PPT 20 μM	0,01166	0,81071	0,99998	No
PPT 2 μM vs PPT 5 μM	-0,00679	0,47181	1,	No