Figure 1

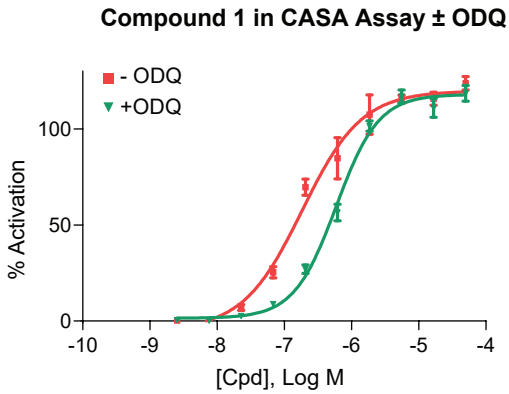
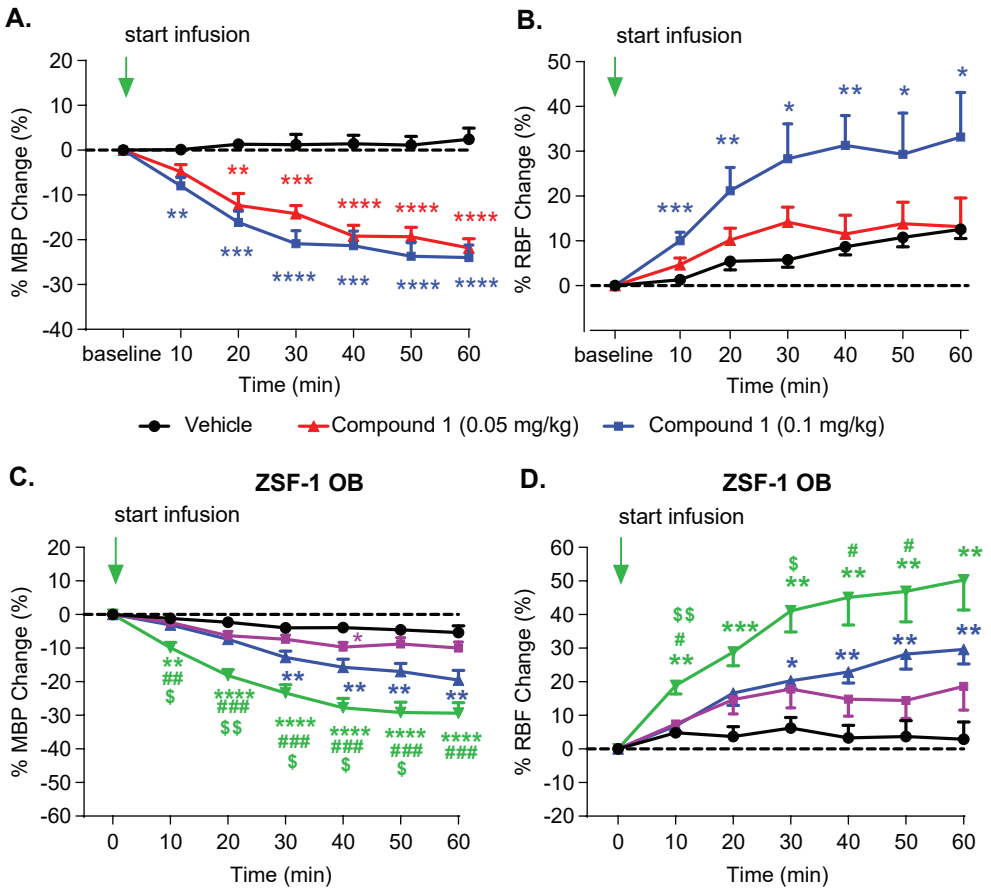
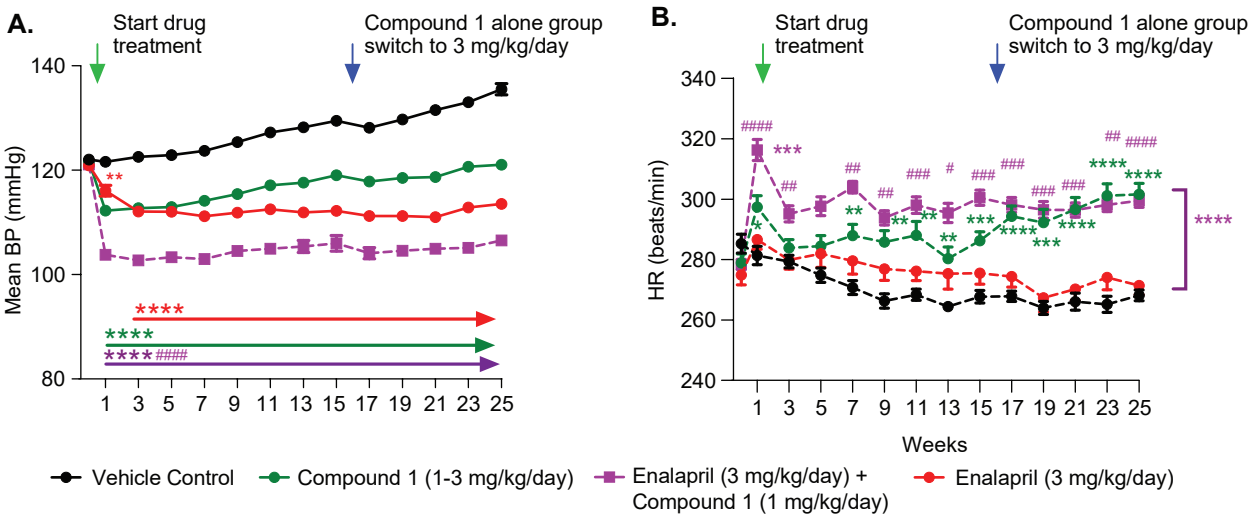

Compound 1 in CASA Assay ± ODQ
- ODQ
+ODQ
% Activation
100
50
0
-10
-9
-8
-7
-6
-5
-4
[Cpd], Log M

Figure 2



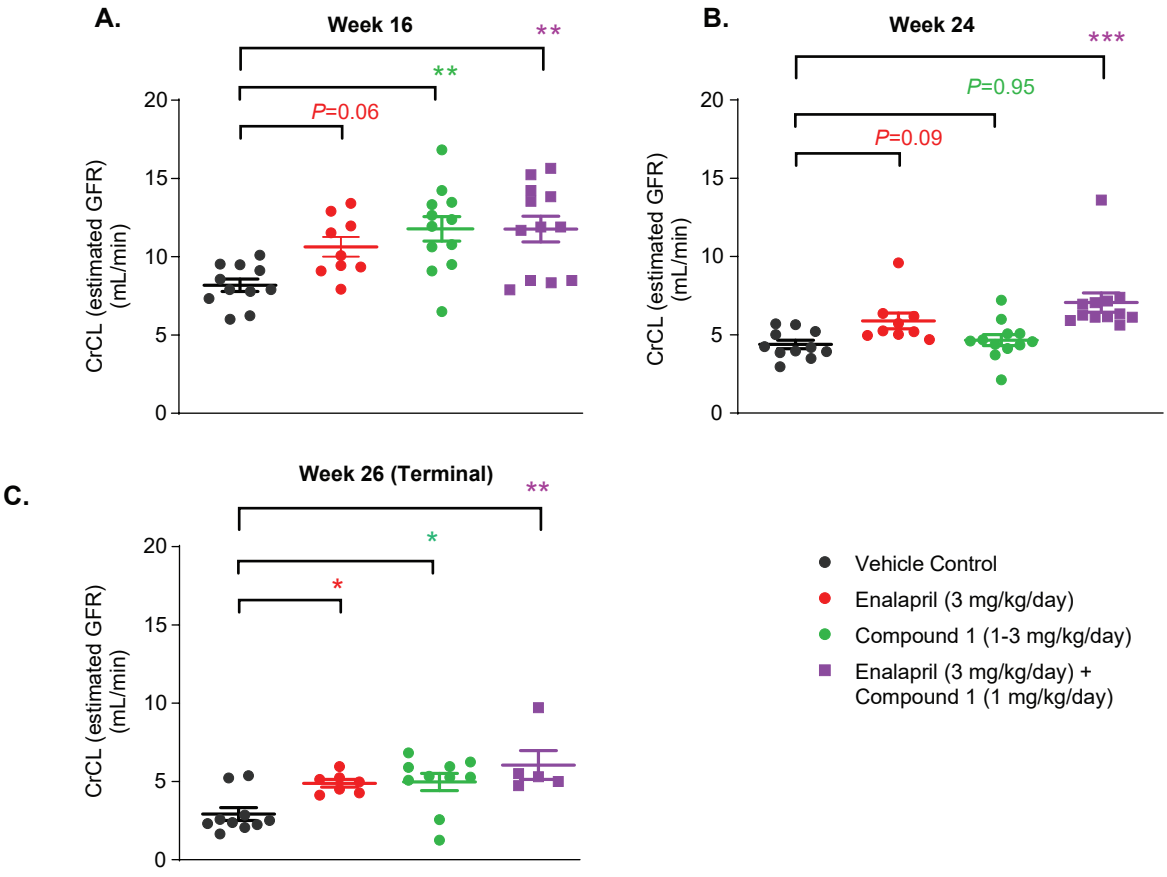
*P<0.05 **P<0.01, ***P<0.001, ****P<0.0001 vs vehicle control, # vs ENA. $ vs compound 1. Two-way ANOVA multiple comparisons RM followed by Turkey test

Figure 3



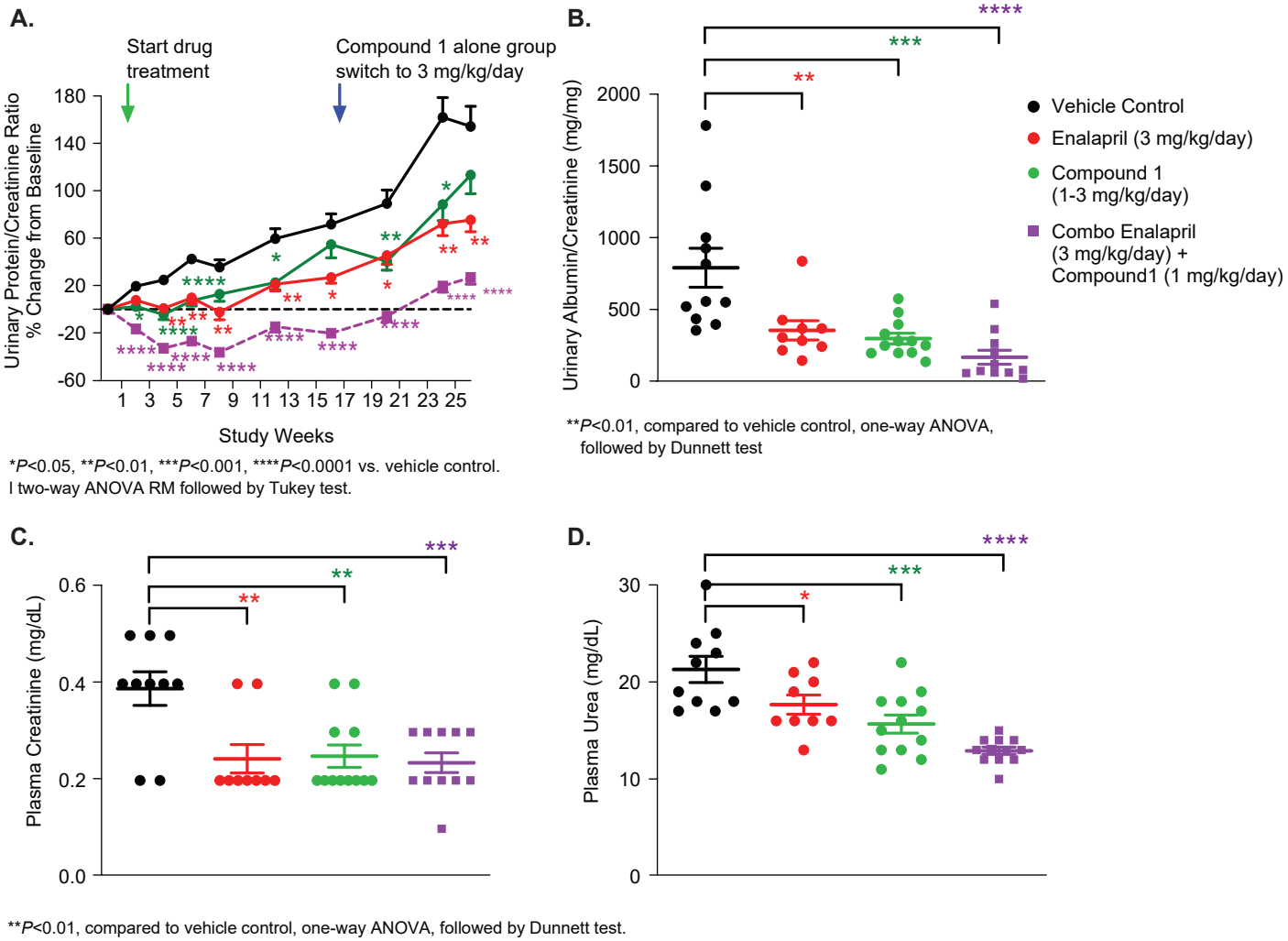
**P<0.01, ***P<0.001, ****P<0.0001, compared to vehicle control, # vs. ENA. Two-way repeat measurement ANOVA, followed by Tukey test.

Figure 4



*P<0.05, **P<0.01, vs vehicle. One-way ANOVA followed by Dunnett test.

Figure 5

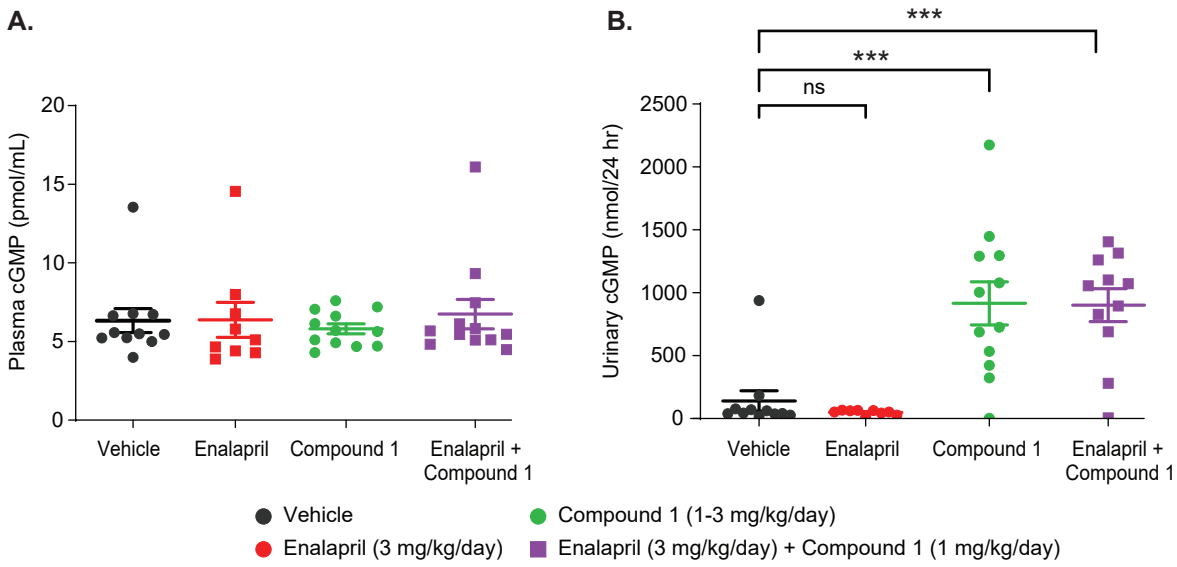


*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 vs. vehicle control. I two-way ANOVA RM followed by Tukey test.

**P<0.01, compared to vehicle control, one-way ANOVA, followed by Dunnett test

**P<0.01, compared to vehicle control, one-way ANOVA, followed by Dunnett test.

Figure 6



*P<0.05, **P<0.01, vs. vehicle, one-way ANOVA followed by Dunnett test.

Figure 7

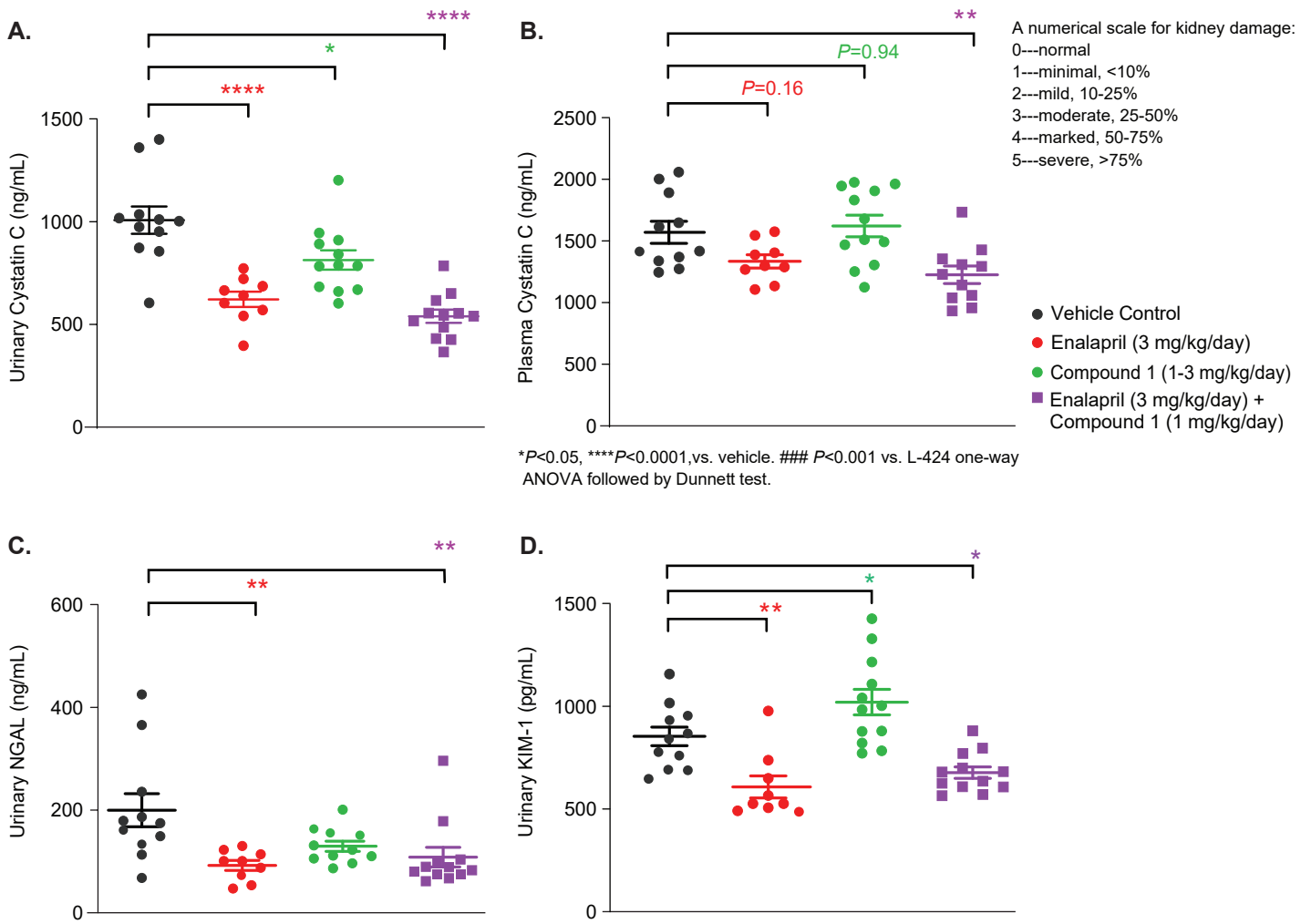
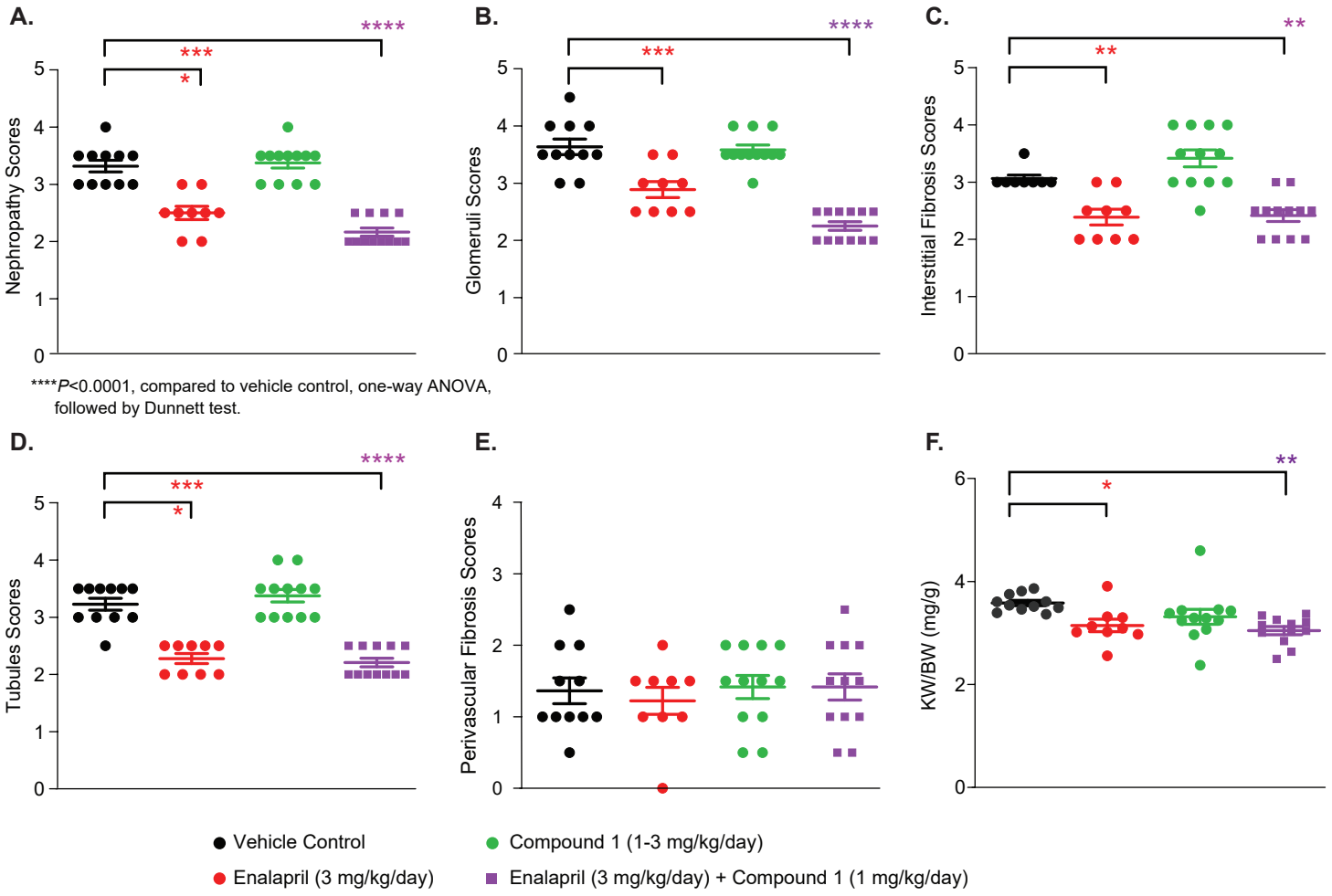

A.
Urinary Cystatin C (ng/mL)
1500
1000
500
0
****
*
****
B.
Plasma Cystatin C (ng/mL)
2500
2000
1500
1000
500
0
**
P=0.94
P=0.16
A numerical scale for kidney damage:
0---normal
1---minimal, <10%
2---mild, 10-25%
3---moderate, 25-50%
4---marked, 50-75%
5---severe, >75%
Vehicle Control
Enalapril (3 mg/kg/day)
Compound 1 (1-3 mg/kg/day)
Enalapril (3 mg/kg/day) + Compound 1 (1 mg/kg/day)
*P<0.05, ****P<0.0001,vs. vehicle. ### P<0.001 vs. L-424 one-way ANOVA followed by Dunnett test.
C.
Urinary NGAL (ng/mL)
600
400
200
0
**
**
D.
Urinary KIM-1 (pg/mL)
1500
1000
500
0
**
*
*

Figure 8



****P<0.0001, compared to vehicle control, one-way ANOVA, followed by Dunnett test.

Figure 9

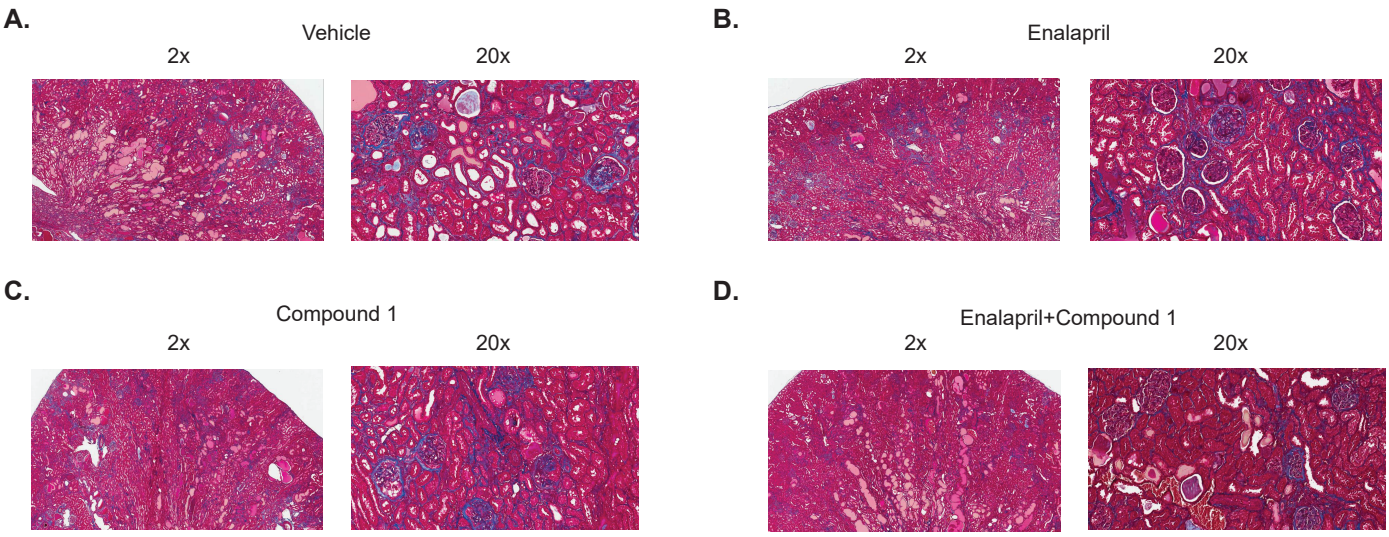

A.
Vehicle
2x
20x
B.
Enalapril
2x
20x
C.
Compound 1
2x
20x
D.
Enalapril+Compound 1
2x
20x

Figure 10

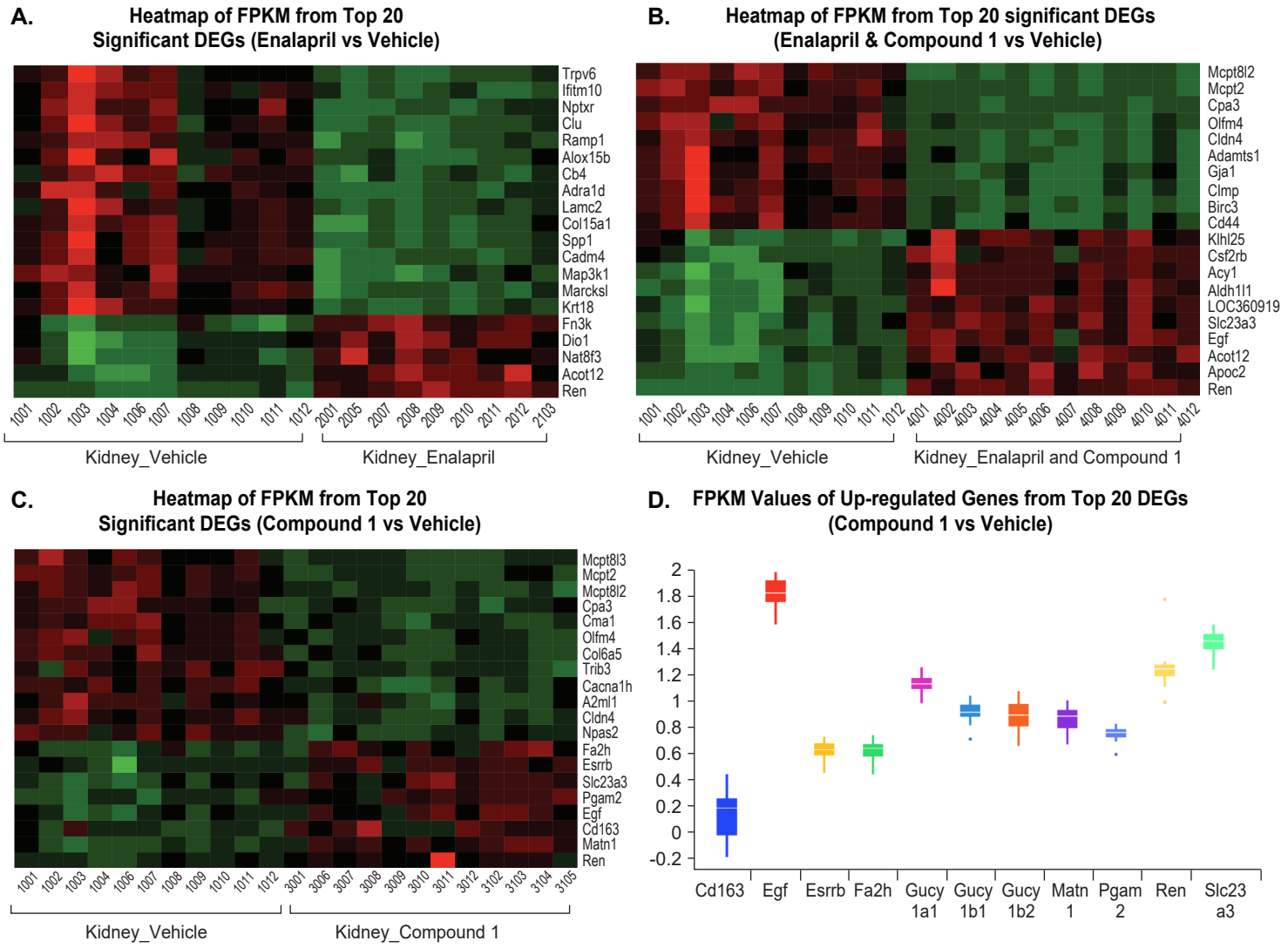
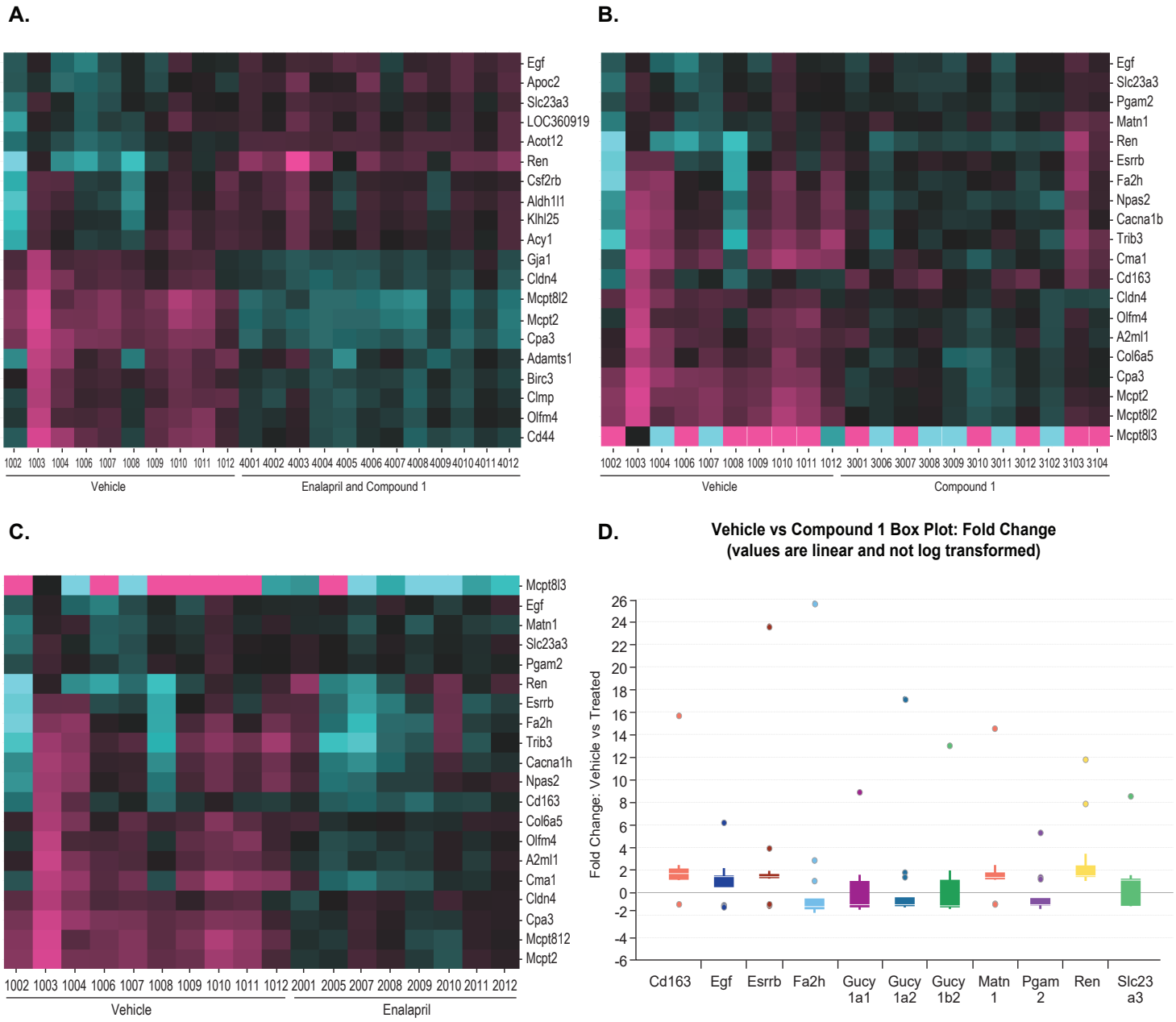

A.
Heatmap of FPKM from Top 20 Significant DEGs (Enalapril vs Vehicle)
Trpv6
Ifitm10
Nptxr
Clu
Ramp1
Alox15b
Cb4
Adra1d
Lamc2
Col15a1
Spp1
Cadm4
Map3k1
Marcksl
Krt18
Fn3k
Dio1
Nat8f3
Acot12
Ren
1001 1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 2001 2005 2007 2008 2009 2010 2011 2012 2103
Kidney_Vehicle
Kidney_Enalapril
B.
Heatmap of FPKM from Top 20 significant DEGs (Enalapril & Compound 1 vs Vehicle)
Mcpt8l2
Mcpt2
Cpa3
Olfm4
Cldn4
Adamts1
Gja1
Clmp
Birc3
Cd44
Klhl25
Csf2rb
Acy1
Aldh1l1
LOC360919
Slc23a3
Egf
Acot12
Apoc2
Ren
1001 1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 4001 4002 4003 4004 4005 4006 4007 4008 4009 4010 4011 4012
Kidney_Vehicle
Kidney_Enalapril and Compound 1
C.
Heatmap of FPKM from Top 20 Significant DEGs (Compound 1 vs Vehicle)
Mcpt8l3
Mcpt2
Mcpt8l2
Cpa3
Cma1
Olfm4
Col6a5
Trib3
Cacna1h
A2ml1
Cldn4
Npas2
Fa2h
Esrrb
Slc23a3
Pgam2
Egf
Cd163
Matn1
Ren
1001 1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 3001 3006 3007 3008 3009 3010 3011 3012 3102 3103 3104 3105
Kidney_Vehicle
Kidney_Compound 1
D.
FPKM Values of Up-regulated Genes from Top 20 DEGs (Compound 1 vs Vehicle)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
Cd163
Egf
Esrrb
Fa2h
Gucy 1a1
Gucy 1b1
Gucy 1b2
Matn 1
Pgam 2
Ren
Slc23 a3

Figure 11

A.
Top 15 Significant KEGG and IPA Pathways (Enalapril vs Vehicle)
FRX/RXR activation
LPS/IL-1 mediated inhibition of RXR function
Protein digestion and absorption
Granulocyte adhesion and diapedesis
Tryptophan metabolism
Atherosclerosis signaling
Agranulocyte adhesion and diapedesis
Xenobiotic metabolism signaling
Renin-angiotensin system
Hematopoietic cell lineage
Cell cycle: G2/M DNA damage checkpoint regulation
Staphylococcus aureus infection
Viral protein interaction with cytokine and cytokine receptor
HOTAIR regulatory pathway
Bile secretion
Altered T cell and B cell signaling in rheumatoid arthritis
Hepatic fibrosis/hepatic stellate cell activation
LXR/RXR activation
Nicotine degradation II
Chemical carcinogenesis
Complement and coagulation cascades
Retinol metabolism
T helper cell differentiation
Thyroid hormone metabolism I (via deiodination)
Thyronamine and Iodothyronamine metabolism
Cytokine-cytokine receptor interaction
Glutathione metabolism
Amoebiasis
Histidine metabolism
Biosynthesis of cofactors
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6
IPA
KEGG
B.
Top 15 Significant KEGG and IPA Pathways (Enalapril and Compound 1 vs Vehicle)
Cytokine-cytokine receptor interaction
Hematopoietic cell lineage
FXR/RXR activation
Tryptophan metabolism
Glutathione metabolism
LPS/IL-1 mediated inhibition of RXR function
Hepatic cholestasis
Glucocorticoid receptor signaling
NRF2-mediated oxidative stress response
Œ≥glutamyl cycle
LXR/RXR activation
Glutathione biosynthesis
Granulocyte adhesion and diapedesis
Nicotine degradation II
Protein digestion and absorption
Bile secretion
Xenobiotic metabolism signaling
Viral protein interaction with cytokine and cytokine receptor
JAK-STAT signaling pathway
Renin-angiotensin system
Role of JAK1 and JAK3 in Œ≥c cytokine signaling
Atherosclerosis signaling
STAT3 pathway
VDR/RXR activation
Cysteine and methionine metabolism
Glycine, serine, and threonine metabolism
Serotonergic synapse
Biosynthesis of cofactors
Amoebiasis
Complement and coagulation cascades
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5
C.
Significant (Padj <0.05) KEGG Pathways (Compound 1 vs Vehicle)
Renin-angiotensin system
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5
-log(Padj)
D.
Overlap of KEGG Pathways
Enalapril & Compound 1
Enalapril
Compound 1
7
10
4
1
0
0
0
E.
Overlap of IPA Pathways
Enalapril & Compound 1
Enalapril
58
17
18

Supp Fig 1


A.
Egf
Apoc2
Slc23a3
LOC360919
Acot12
Ren
Csf2rb
Aldh1l1
Klhl25
Acy1
Gja1
Cldn4
Mcpt8l2
Mcpt2
Cpa3
Adamts1
Birc3
Clmp
Olfm4
Cd44
1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 4001 4002 4003 4004 4005 4006 4007 4008 4009 4010 4011 4012
Vehicle
Enalapril and Compound 1
B.
Egf
Slc23a3
Pgam2
Matn1
Ren
Esrrb
Fa2h
Npas2
Cacna1b
Trib3
Cma1
Cd163
Cldn4
Olfm4
A2ml1
Col6a5
Cpa3
Mcpt2
Mcpt8l2
Mcpt8l3
1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 3001 3006 3007 3008 3009 3010 3011 3012 3102 3103 3104
Vehicle
Compound 1
C.
Mcpt8l3
Egf
Matn1
Slc23a3
Pgam2
Ren
Esrrb
Fa2h
Trib3
Cacna1h
Npas2
Cd163
Col6a5
Olfm4
A2ml1
Cma1
Cldn4
Cpa3
Mcpt812
Mcpt2
1002 1003 1004 1006 1007 1008 1009 1010 1011 1012 2001 2005 2007 2008 2009 2010 2011 2012
Vehicle
Enalapril
D.
Vehicle vs Compound 1 Box Plot: Fold Change
(values are linear and not log transformed)
Fold Change: Vehicle vs Treated
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
-4
-6
Cd163
Egf
Esrrb
Fa2h
Gucy 1a1
Gucy 1a2
Gucy 1b2
Matn 1
Pgam 2
Ren
Slc23 a3