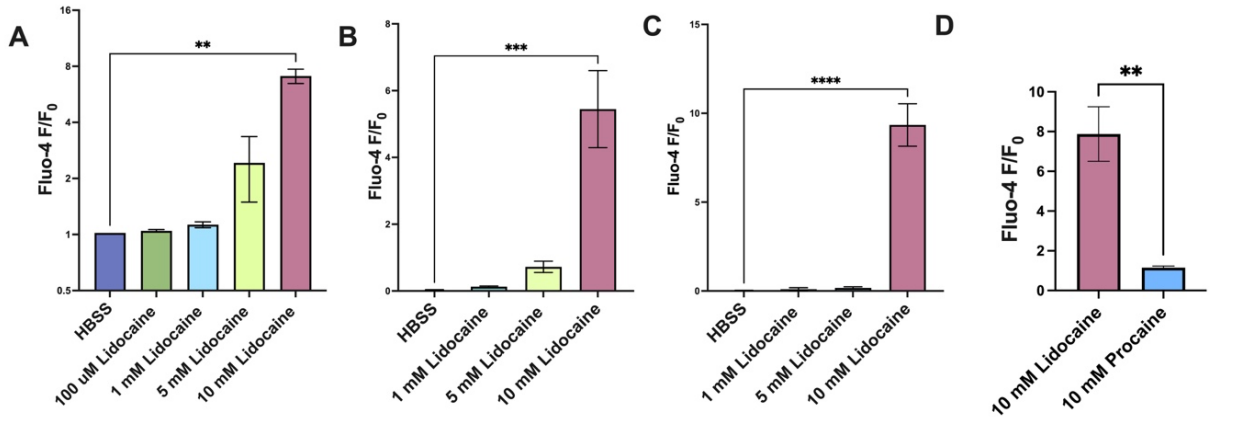
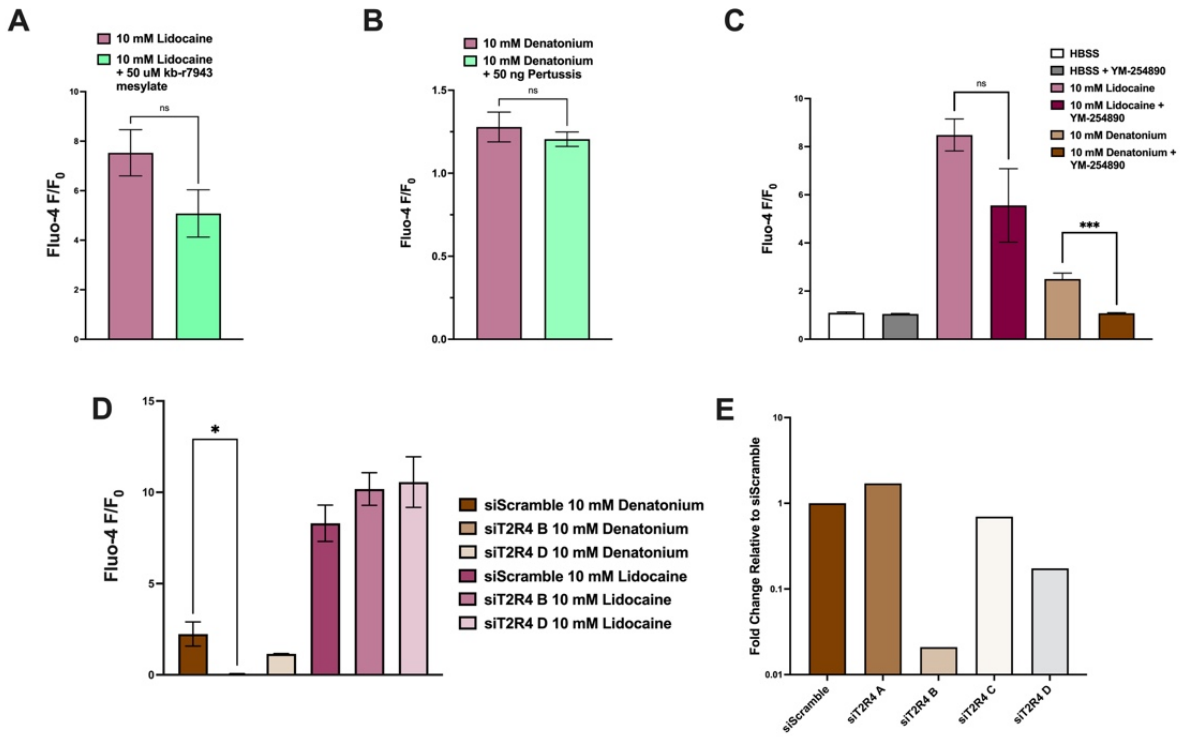
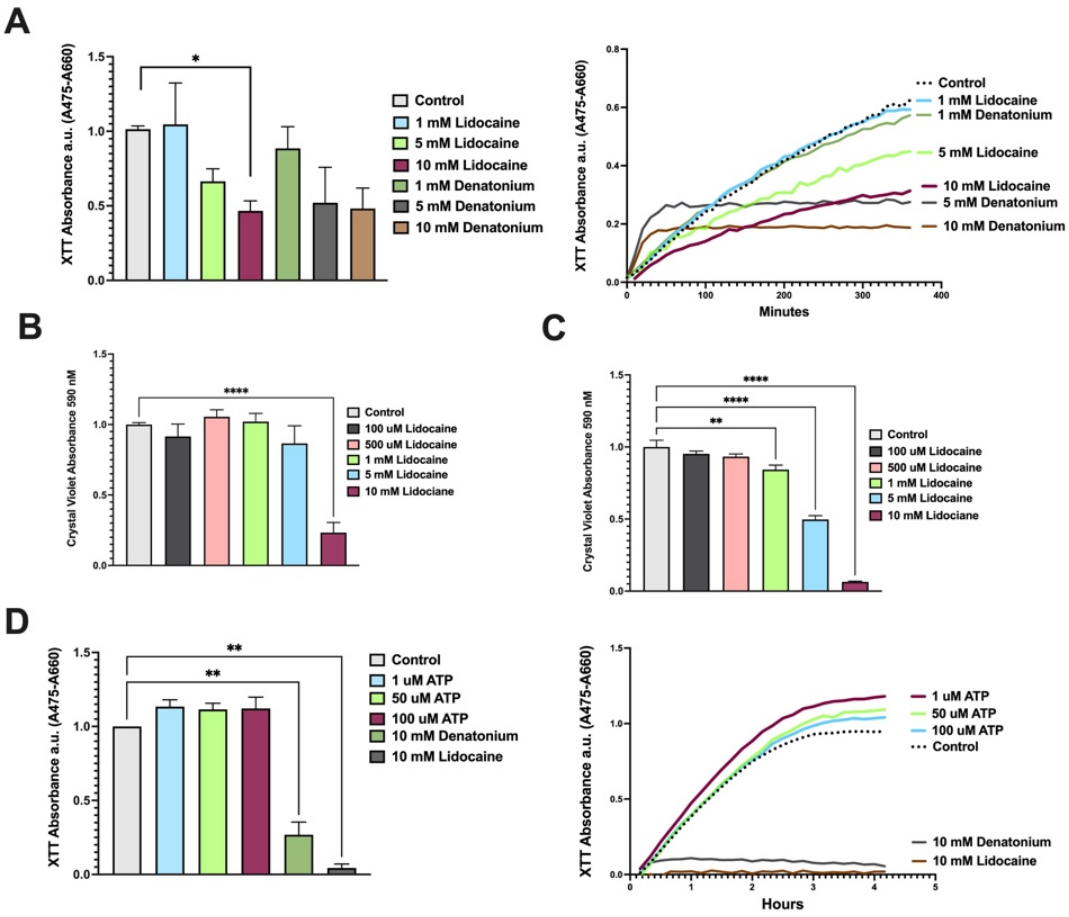


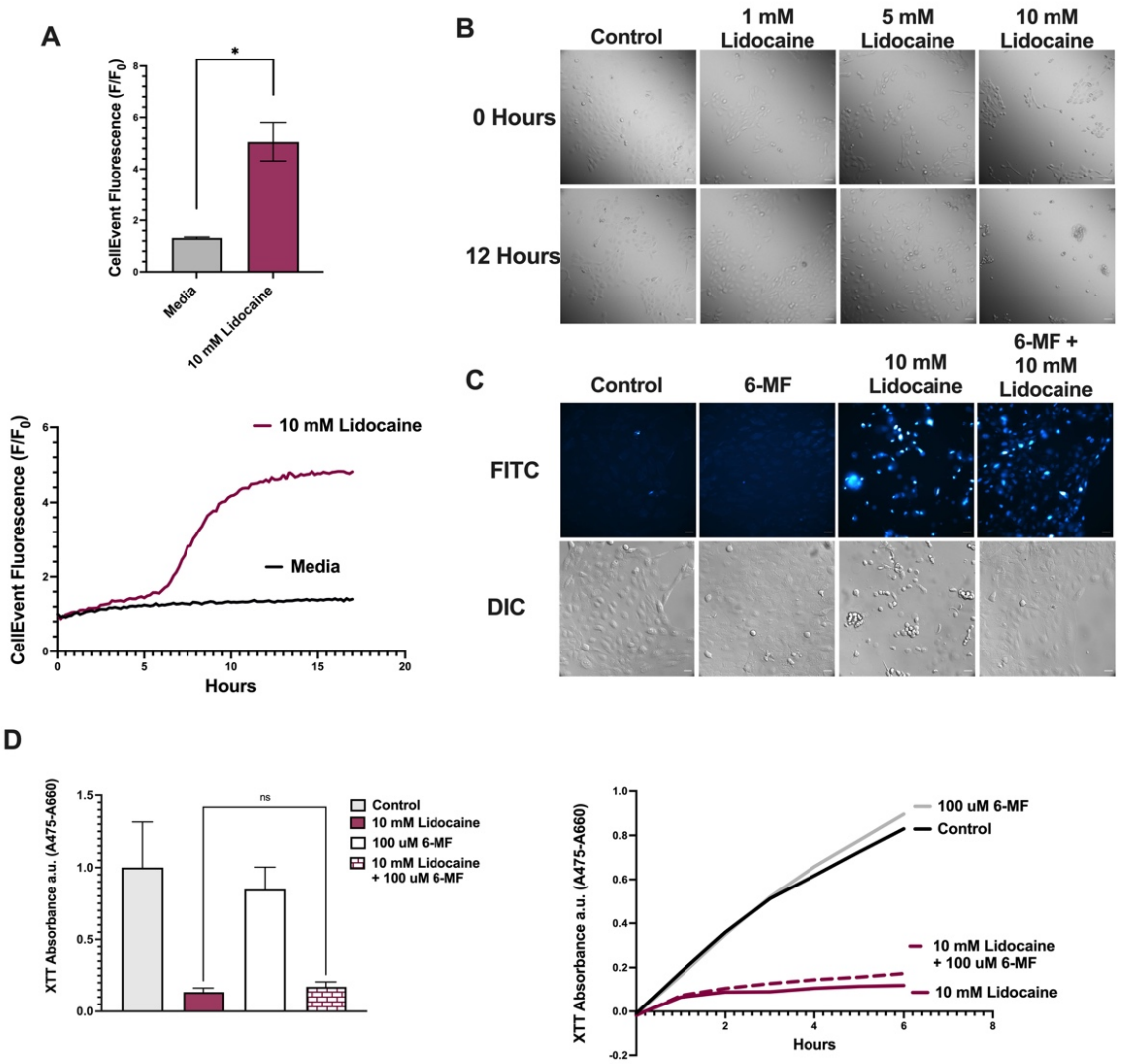
Supplemental Figure 1. Lidocaine dose response in HNSCC cell lines. SCC 4, SCC 47, SCC 90 and FaDu cells loaded with Fluo-4 were imaged for subsequent Ca^{2+} responses with 0 – 10 mM lidocaine. **A)** SCC 4 peak fluorescent Ca^{2+} responses with 0 – 10 mM lidocaine. **B)** SCC 90 peak fluorescent Ca^{2+} responses with 0 – 10 mM lidocaine. **C)** FaDu peak fluorescent Ca^{2+} responses with 0 – 10 mM lidocaine. **D)** SCC 47 peak fluorescent Ca^{2+} responses with 10 mM lidocaine or 10 mM procaine. Peak fluorescence mean +/- SEM with >3 experiments using separate cultures. Significance by 1-way ANOVA with Bonferroni posttest comparing HBSS to each agonist. $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***), and no statistical significance (ns or no indication).



Supplemental Figure 2. Lidocaine activates separate intracellular Ca^{2+} pathway than denatonium benzoate. HNSSC cell lines, SCC 47 and SCC 90, were loaded with Fluo-4 and imaged for subsequent Ca^{2+} responses with 10 mM lidocaine or 10 mM denatonium. **A)** SCC 47 peak fluorescent Ca^{2+} response with 10 mM lidocaine with or without prior 2 minute stimulation with 50 μM kb-r7943. **B)** SCC 47 peak fluorescent Ca^{2+} response with 10 mM denatonium with or without prior 18 hour pertussis toxin incubation. Peak fluorescent mean +/- SEM with >3 separate cultures. Significance by unpaired t-test. **C)** SCC 47 peak fluorescent Ca^{2+} responses with HBSS, 10 mM lidocaine, or 10 mM denatonium benzoate with or without prior 1 hour incubation with 1 μM YM-254890. Peak fluorescent mean +/- SEM with >3 separate cultures. Significance by unpaired t-test between bitter agonist response and bitter agonist response with YM-254890. **D)** SCC 90 siT2R4 peak fluorescent Ca^{2+} responses with 10 mM lidocaine or 10 mM denatonium. Peak fluorescence mean +/- SEM with >3 experiments using separate cultures. Significance by 1-way ANOVA with Bonferroni posttest comparing siScramble response with 10 mM lidocaine or denatonium to each siT2R4 B or D with respective bitter agonist. **E)** T2R4 mRNA expression in SCC 90 siT2R4 cells relative to siScramble. $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***), and no statistical significance (ns or no indication).



Supplemental Figure 3. Lidocaine decreases cell viability and proliferation. SCC 4 cells were incubated with bitter agonists with XTT dye, an indicator of NADH production. A decrease in the difference of absorbance (475 nm – 660 nm) indicates reduced NADH production. **A)** SCC 4 XTT absorbance values (475 nm – 660 nm) after 120 minutes of incubation with media, 1 – 10 mM lidocaine, or 1 -10 denatonium benzoate. Absorbance values were measured over six hours as seen in representative traces. SCC 47 cells were incubated with 0 – 10 mM lidocaine for 6 or 24 hours and stained with crystal violet to determine cell proliferation. **B)** SCC 47 crystal violet stain absorbance values (590 nm) after 6 hours with 0 – 10 mM lidocaine. **C)** SCC 47 crystal violet stain absorbance values (590 nm) after 24 hours with 0 - 10 mM lidocaine. **D)** SCC 47 XTT absorbance values (475 nm – 660 nm) after 6 hours of incubation with 10 mM lidocaine, 10 mM denatonium, or 1 μM – 100 μM ATP. Absorbance values were measured over six hours as seen in representative traces. Absorbance mean +/- SEM with >3 separate cultures. Significance by 1-way ANOVA with Bonferroni posttest comparing each treatment to media/control. $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***), and no statistical significance (ns or no indication).



Supplemental Figure 4. 6-methoxyflavanone maintains cell morphology in the presence of lidocaine. FaDu cells were incubated with 10 mM lidocaine with CellEvent fluorescent dye, which fluoresces upon caspase-3 and caspase-7 cleavage. **A)** FaDu CellEvent fluorescence at 17 hours with 10 mM lidocaine. Representative trace of CellEvent fluorescence over 17 hours with 10 mM lidocaine. Fluorescent mean +/- SEM with >3 separate cultures. Significance determined by paired t-test between untreated and treated cells. **B)** SCC 47 representative DIC images at 0 and 12 hours with 0 – 10 mM lidocaine. Scale bars = 30 μm. **C)** SCC 47 representative DIC and FITC (measuring CellEvent fluorescence and showing cell morphology) images with 10 mM lidocaine with or without 100 μM 6-MF after 12 hours. Scale bars = 30 μm. **D)** SCC 47 XTT absorbance values (475 nm – 660 nm) after 6 hours of incubation with 10 mM lidocaine with or without prior incubation with 100 μM 6-MF. Absorbance values were measured over six hours as seen in representative traces. $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***), and no statistical significance (ns or no indication).