

## Supplementary Figures

**Suppl. Figure 1** Dose-dependent inhibition by 2-CE of Sf9 cell membrane preparations containing human tmAC II (A) or V (B), respectively. Adenylyl cyclase activity was assayed in duplicate in the presence of the indicated concentration of 2-CE (■) or estrogen (▲).

**Suppl. Figure 2** Dose-dependent inhibition of the soluble catalytic domains of human tmAC VII by 2-CE in presence (■) and absence (▲) of 100  $\mu$ M forskolin.

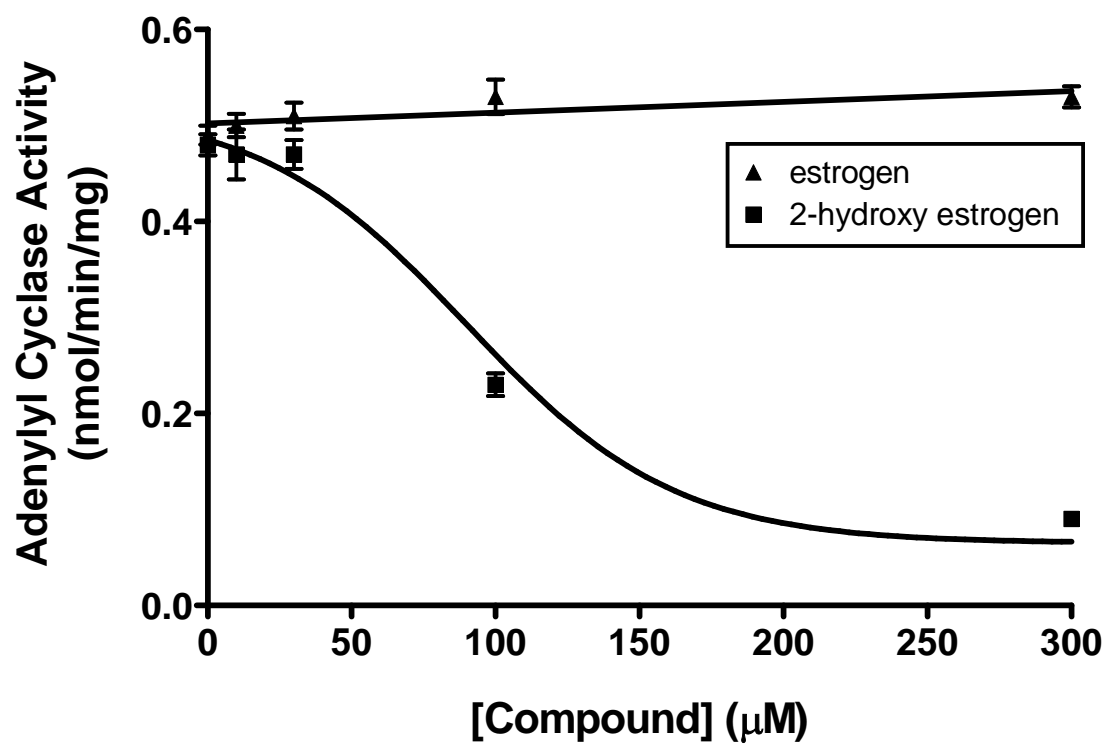
**Suppl. Figure 3** Dose-dependent inhibition of the cyanobacterial sAC homolog CyaC by 2-CE (◇) and 4-CE (□).

**Suppl. Figure 4** Alignment of human sAC, the sAC homolog CyaC, and the nine human tmAC enzymes. Secondary structure elements are indicated on top for CyaC and at the bottom for a structurally characterized tmAC, respectively. CE interacting residues are labeled (▼). Conserved residues are shown in yellow, and positions with conserved physicochemical properties in red.

**Suppl. Figure 5** Chemical structures of compounds that have been studied in this work or previously for their ability to inhibit soluble adenylyl cyclase activity. Shown on top are efficient inhibitors, whereas the compounds on bottom show no strong inhibition.

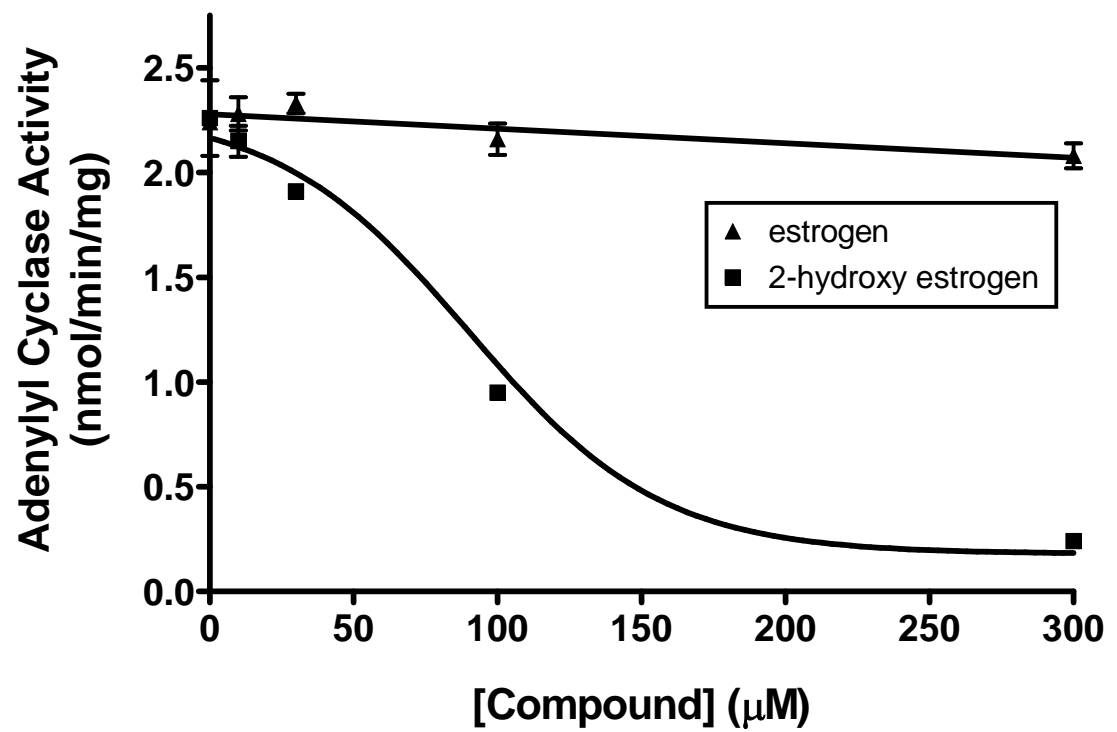
# Supplementary Figure 1

A

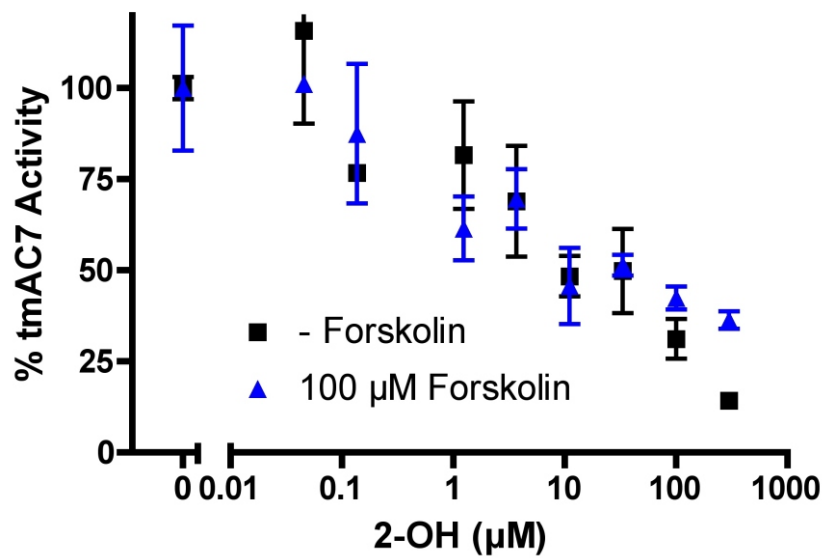


## Supplementary Figure 1

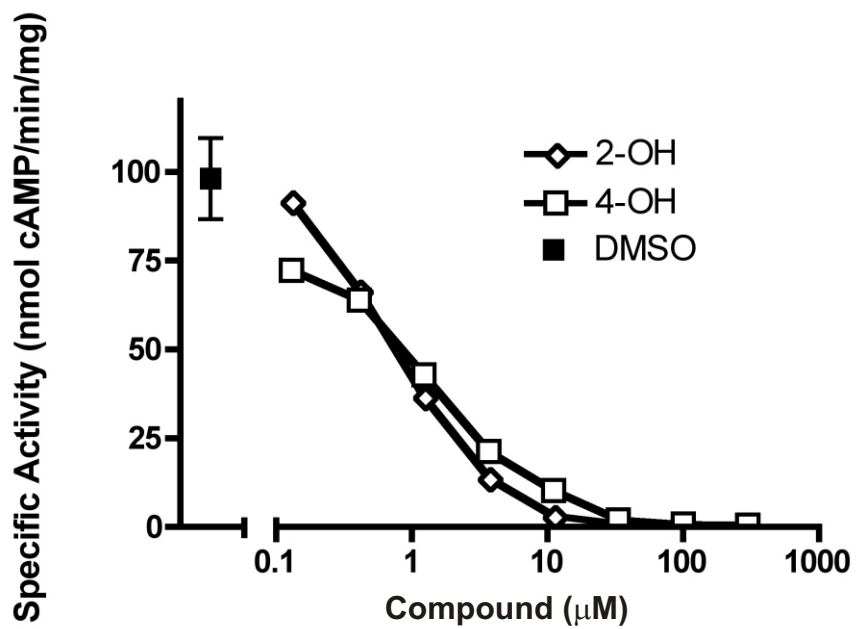
**B**



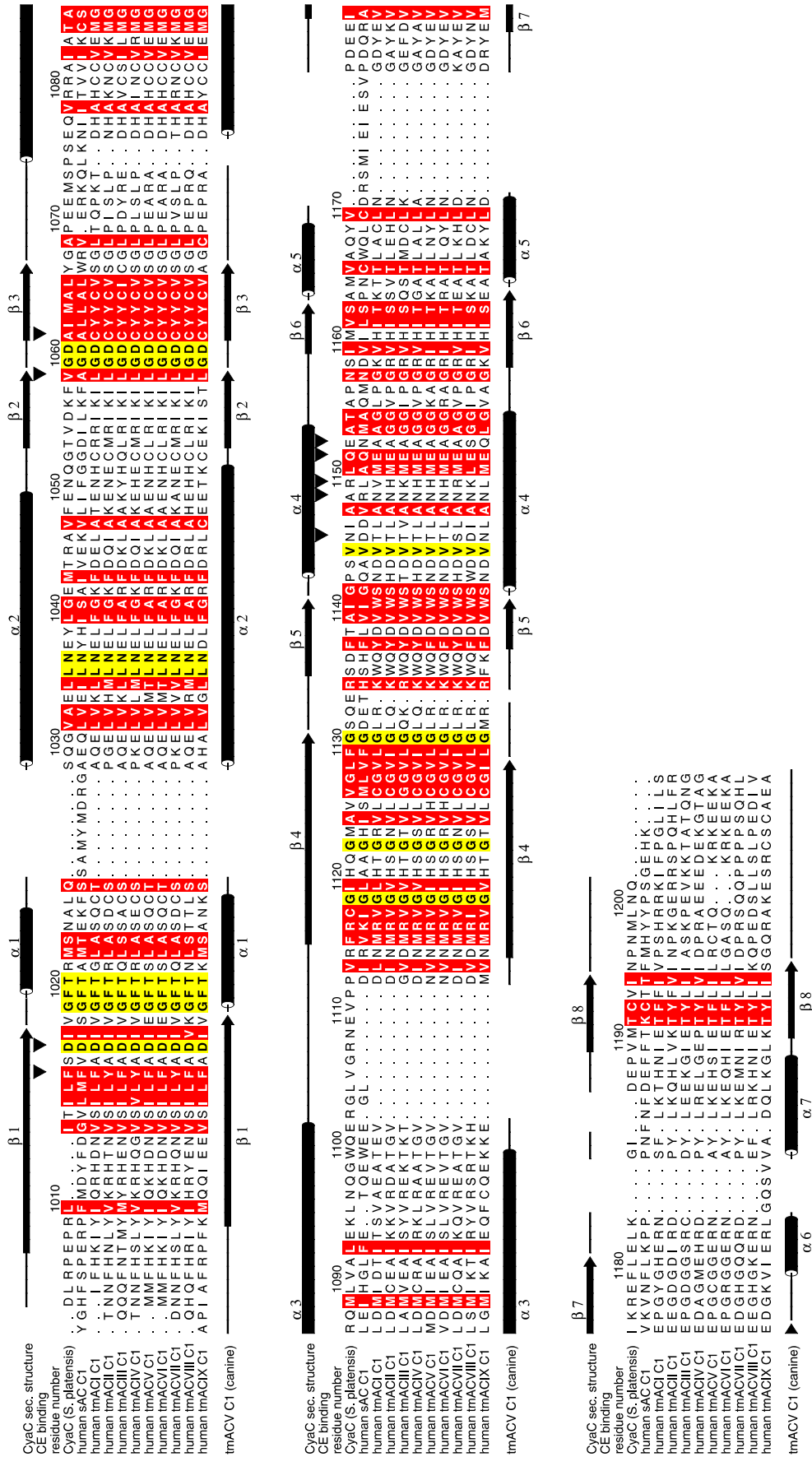
## Supplementary Figure 2



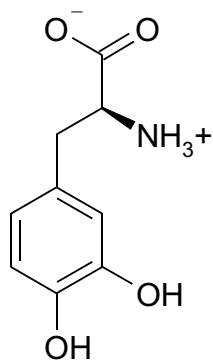
## Supplementary Figure 3



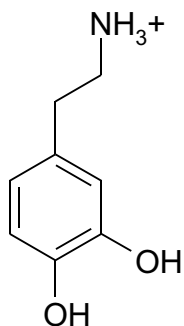
# Supplementary Figure 4



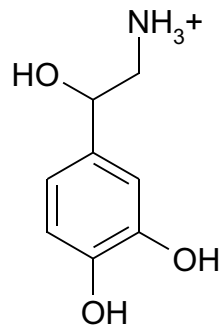
Supplementary Figure 5



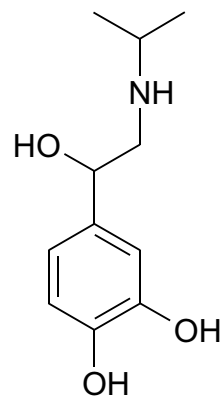
L-dopa



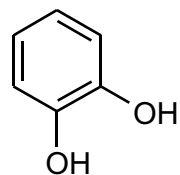
dopamine



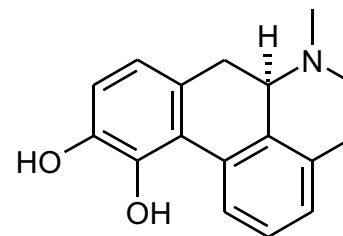
norepinephrine



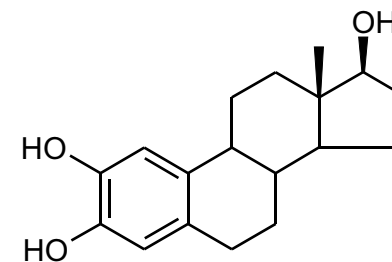
isoproterenol



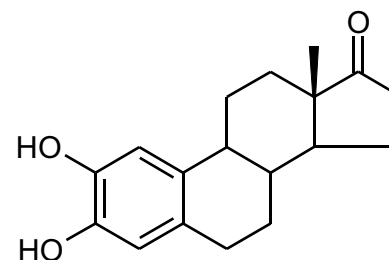
catechol



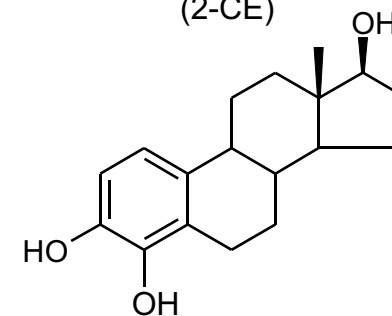
apomorphine



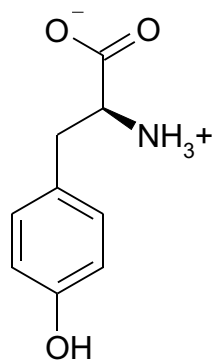
2-hydroxy-17β-estradiol  
(2-CE)



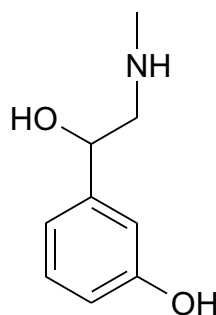
2-hydroxy estrone



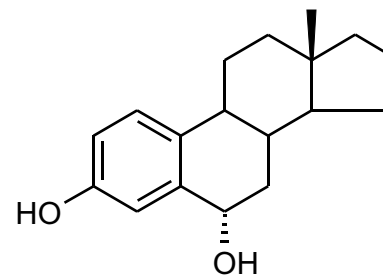
4-hydroxy-17β-estradiol  
(4-CE)



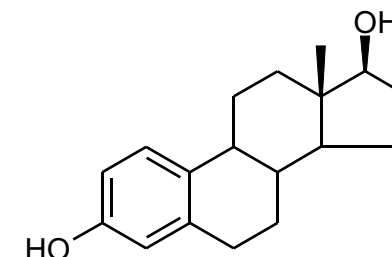
L-tyrosine



phenylephrine



6α-hydroxyestradiol



17β-estradiol (estrogen)