

# Leveraging a Low-Affinity Diazaspiro Orthosteric Fragment to Reduce Dopamine D3 Receptor (D<sub>3</sub>R) Ligand Promiscuity across Highly Conserved Aminergic G-Protein-Coupled Receptors (GPCRs)

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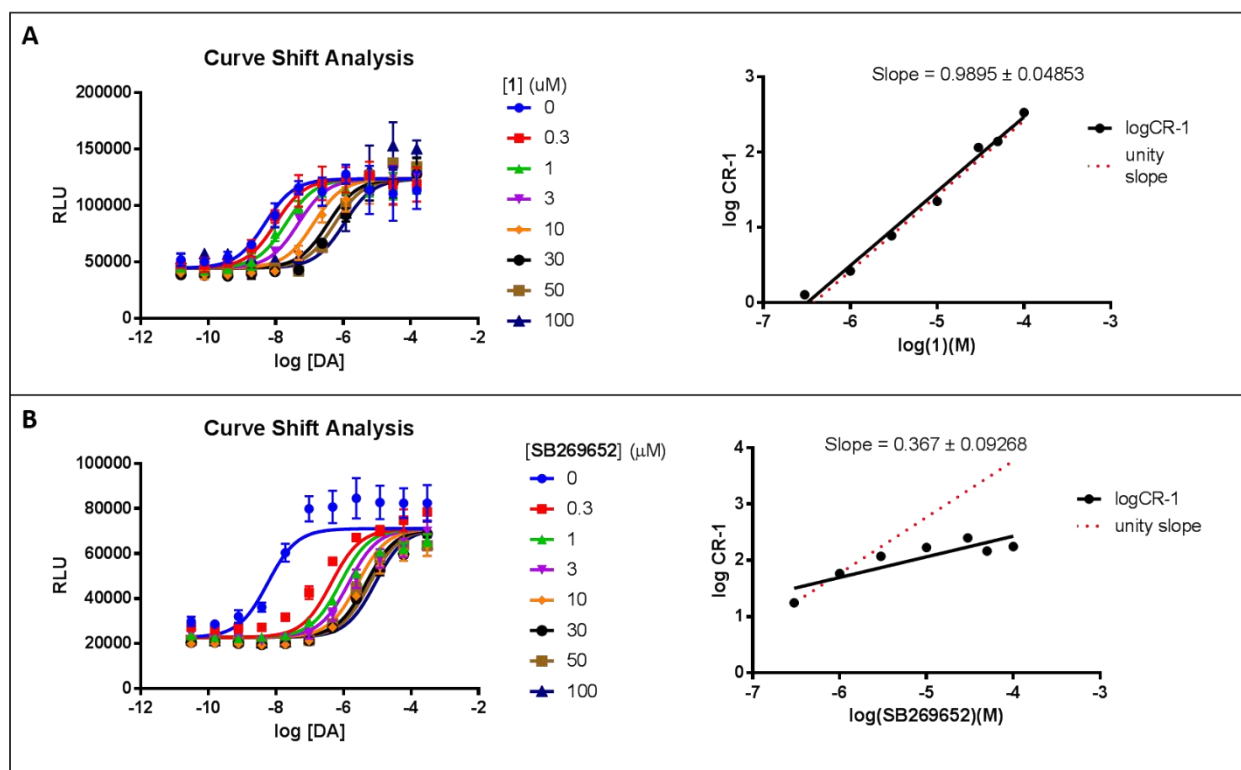
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## Supporting Information

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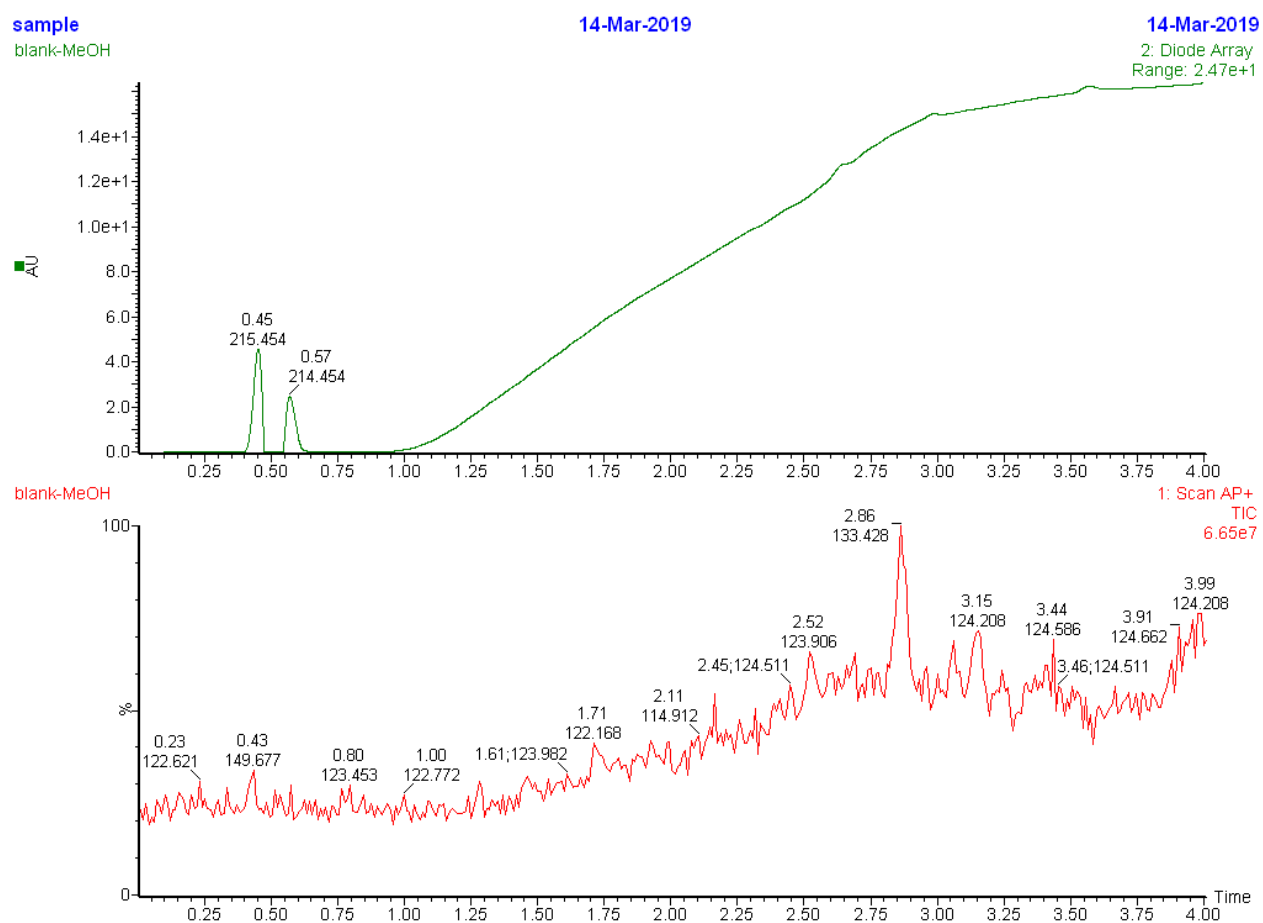
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## Schild Plot Slopes for 1 and SB269,652

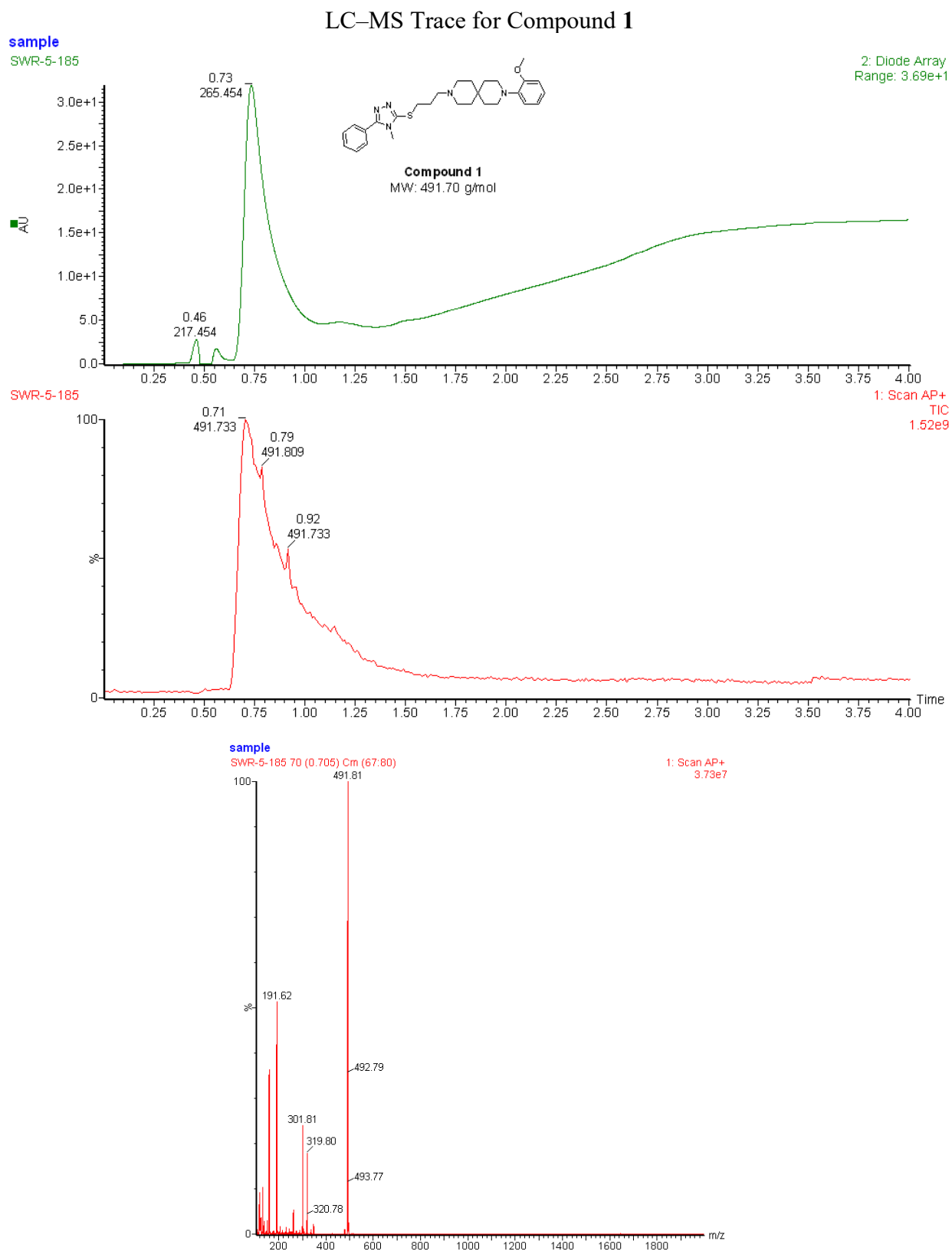


**Figure S1.** (A) Curve shift analysis of dopamine at the D<sub>3</sub>R with or without the presence of increasing concentrations of **1** in a  $\beta$ -arrestin 2 recruitment assay. A Schild plot generated from the concentration-response (CR) curves affords a near linear slope of 1, indicating **1** acts as a competitive antagonist at the receptor. (B) Curve shift analysis of dopamine at the D<sub>3</sub>R with or without the presence of increasing concentrations of SB269,652 in a  $\beta$ -arrestin 2 recruitment assay. A Schild plot generated from the concentration-response (CR) curves affords a slope that deviates significantly from unity, consistent with the allosteric pharmacology of SB269,652 at the receptor. Data points represent the mean  $\pm$  SEM obtained from seven to sixteen replicates.

## LCMS Chromatograms for Key Compounds 1 and 31

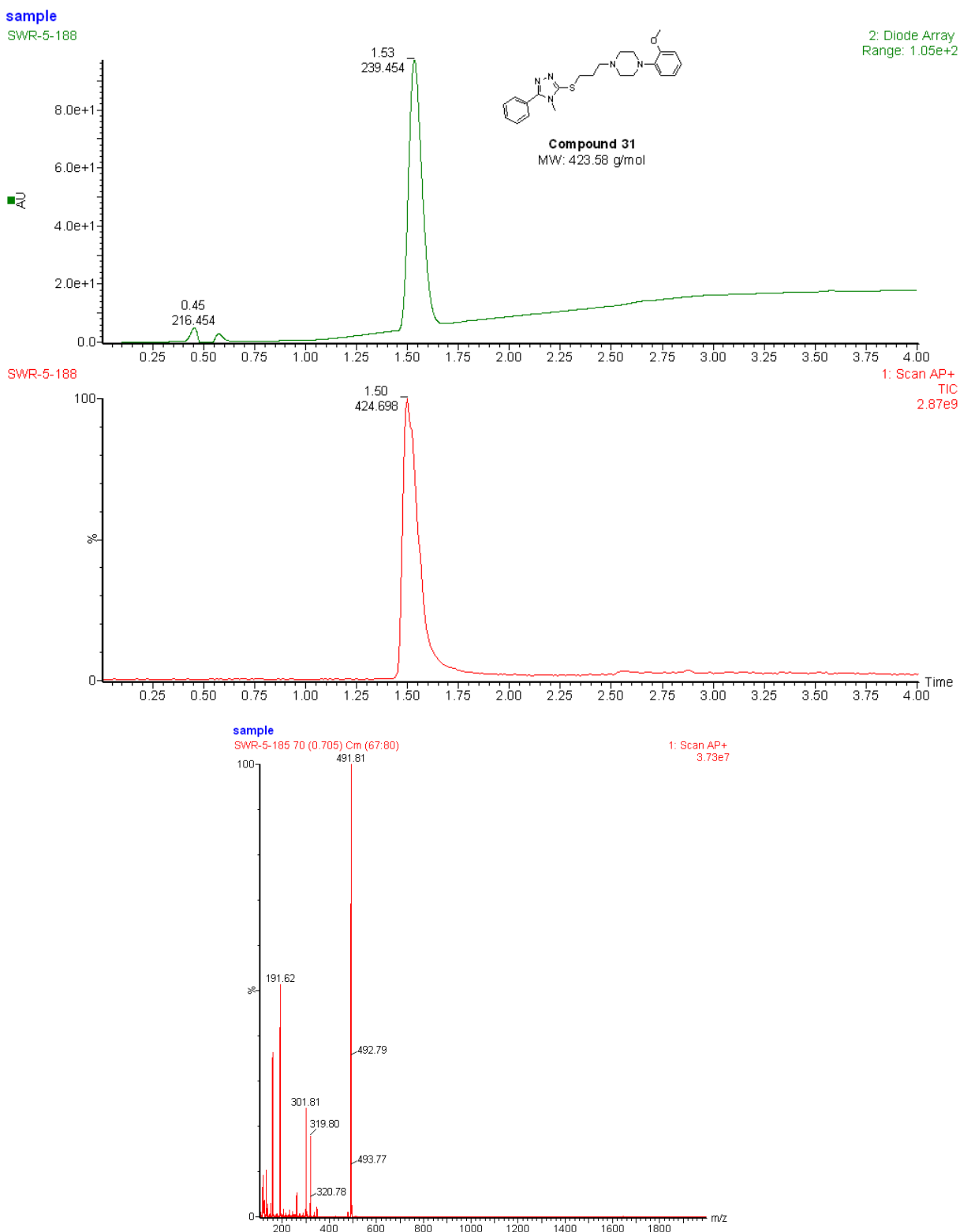


SI Figure 2: The UV and MS trace of our standard solvent methanol



**SI Figure 3: The UV and MS trace of compound 1**

# LC-MS Trace for Compound 31



SI Figure 4: The UV and MS trace of compound 31

# <sup>1</sup>H and <sup>13</sup>C Spectrum of Compounds

