Supporting Information

Development and Validation of a Computational Model for Androgen Receptor Activity

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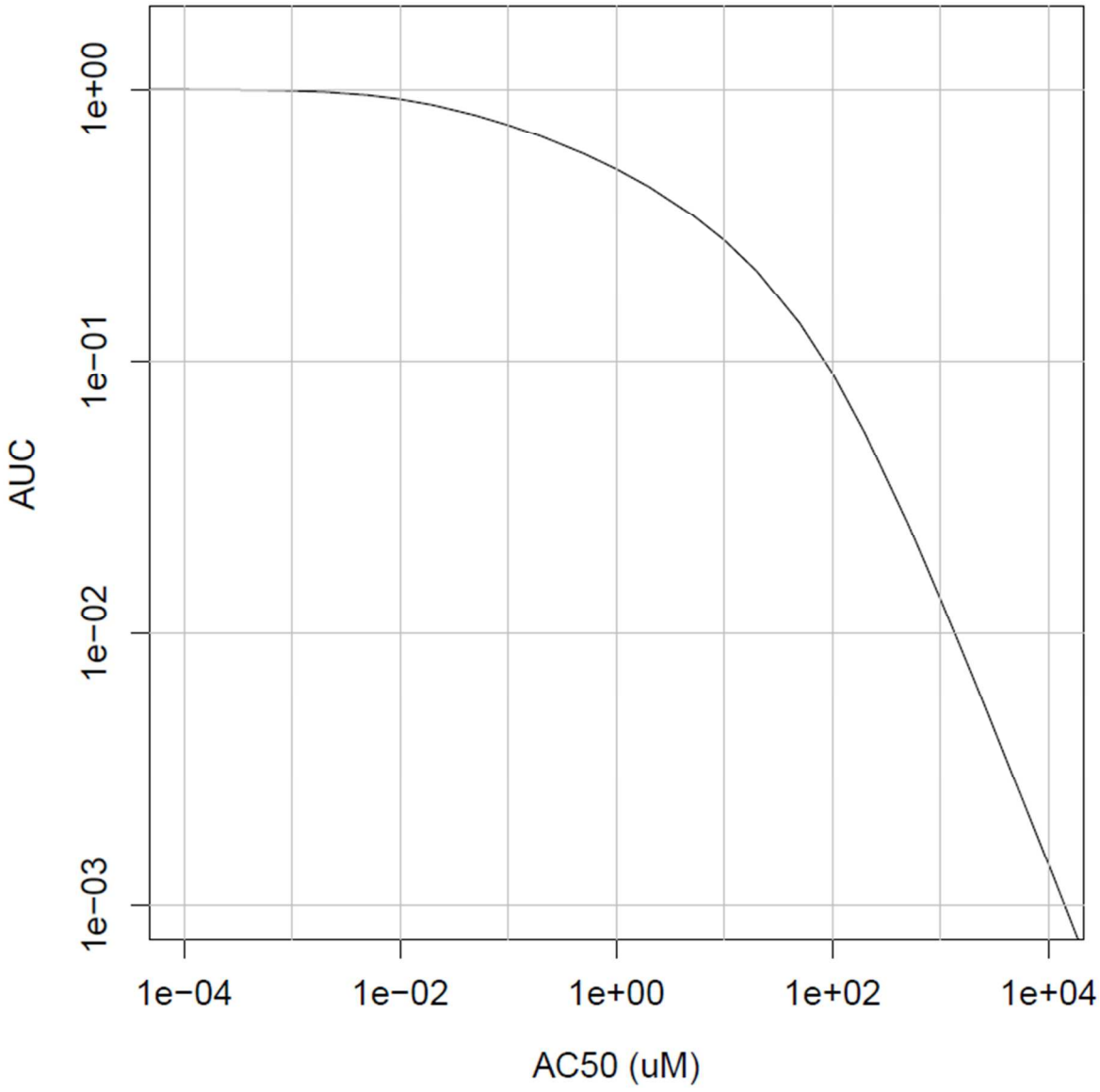
antagonism, and interference) for all 1855 chemicals. Model summary results are shown in the first tab and detailed results for each assay are shown in the second tab.

File S3: "Supplemental File 3_allchem_results.pdf": PDF file with results of the AR Pathway Model for all 1855 chemicals. For each chemical, the left-hand panel shows the concentration response data for the 11 in vitro assays, colored by assay group as defined in the legend (Text Figure 8). The right-hand panel shows the magnitude of the modeled "receptor" responses, where the agonist pathway (R1) is in blue and the antagonist pathway (R2) is in red, and the other interference pathways (R3-R7) are colored as defined in the legend. Model AUC values are displayed below the chemical name and literature-based reference classifications are displayed in the plot. The median cytotoxic concentration for each chemical is indicated by a vertical red line, and the cytotoxicity region (representing 3 median absolute deviations) is indicated by the gray shaded region. A green horizontal bar indicates the median-AC50 of the active assays.

File S4: "Supplemental File 4_AR_CytoFilter_Comparison.xlsx": Excel file with cytotoxicity filtering information and additional filtering approaches that were both more permissive (no exclusion) and more restrictive (exclusion of AC50s within 20% of the cytotoxicity AC50), and the corresponding results for the AR pathway model (as well as paired cytotoxicity data).

File S5: "Supplemental File 5_Tier1_AR Binding_List1_ICCVAM.xlsx": Excel file with data on comparisons between EDSP Tier 1 binding assays and AR Pathway model results.

Figure S1



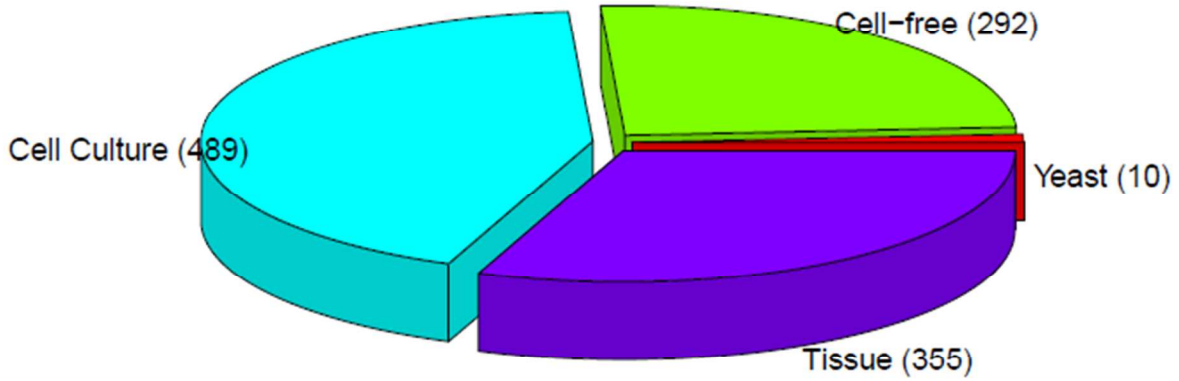
Calibration curve between AR pathway model AUC score (y-axis) and AC50 in µM. An AUC of 0.1 corresponds to predicted AR pathway activity of ~100 µM.

Figure S2

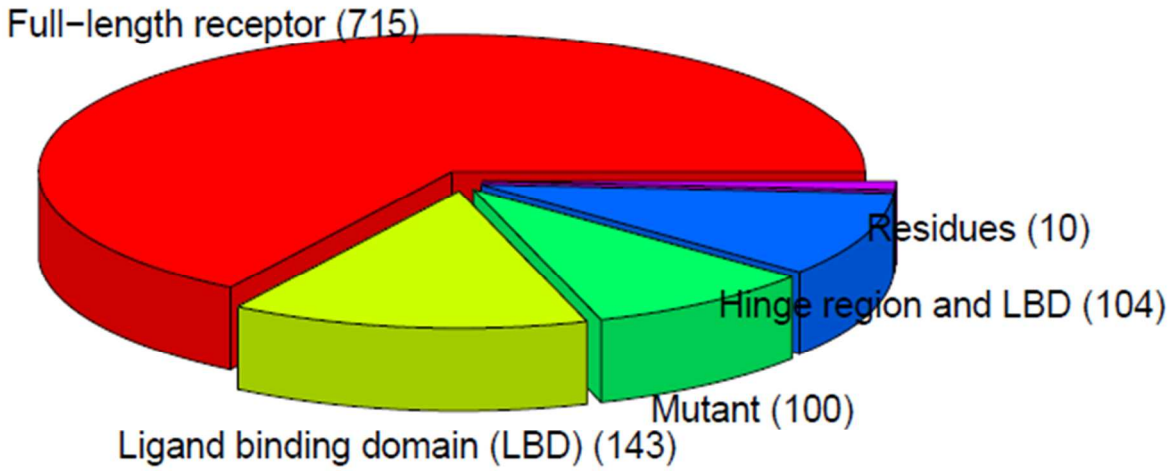
SEE FILE: “Figure S2_AR model and CI.pdf”

Results of the AR Pathway model for all 1855 chemicals with uncertainty bounds. For each chemical, the AUC point estimates (circles) and 95% confidence intervals (error bars) are indicated for the AR agonist (red), antagonist (black), and interference (blue) pathways. Chemicals are sorted by the maximum of the AUC point estimate for the agonist and antagonist pathways. Interference pathway point estimates and confidence intervals are drawn for all interference pathways where the upper end of the confidence interval is greater than 0.1, while agonist and antagonist values are plotted for all chemicals regardless of confidence interval range.

Figure S3



(a)

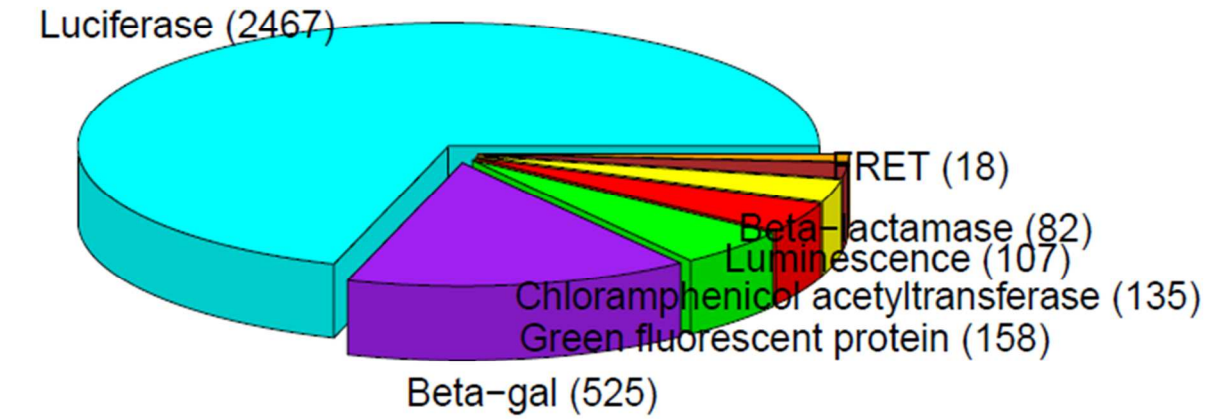


(b)

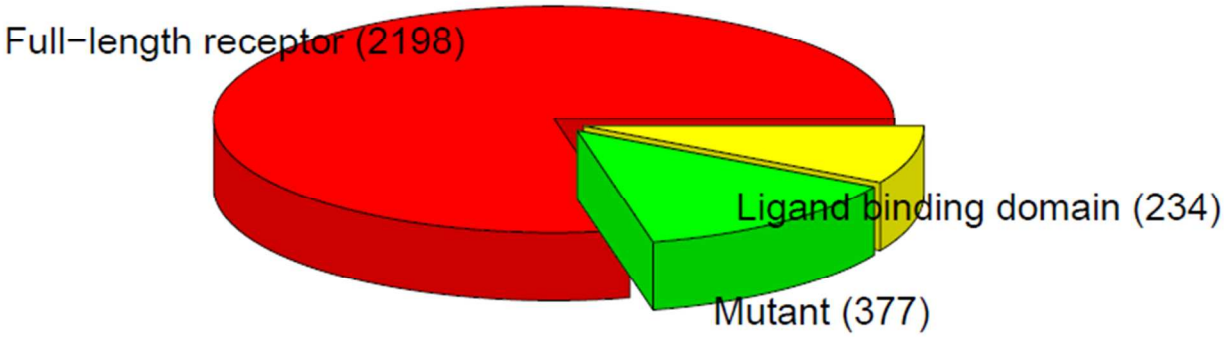
Abbreviation: AR = androgen receptor. The number of experiments conducted using each assay type is shown in parentheses.

Literature review results for AR binding data on potential reference chemicals: (a) assay types and (b) receptor types

Figure S4



(a)

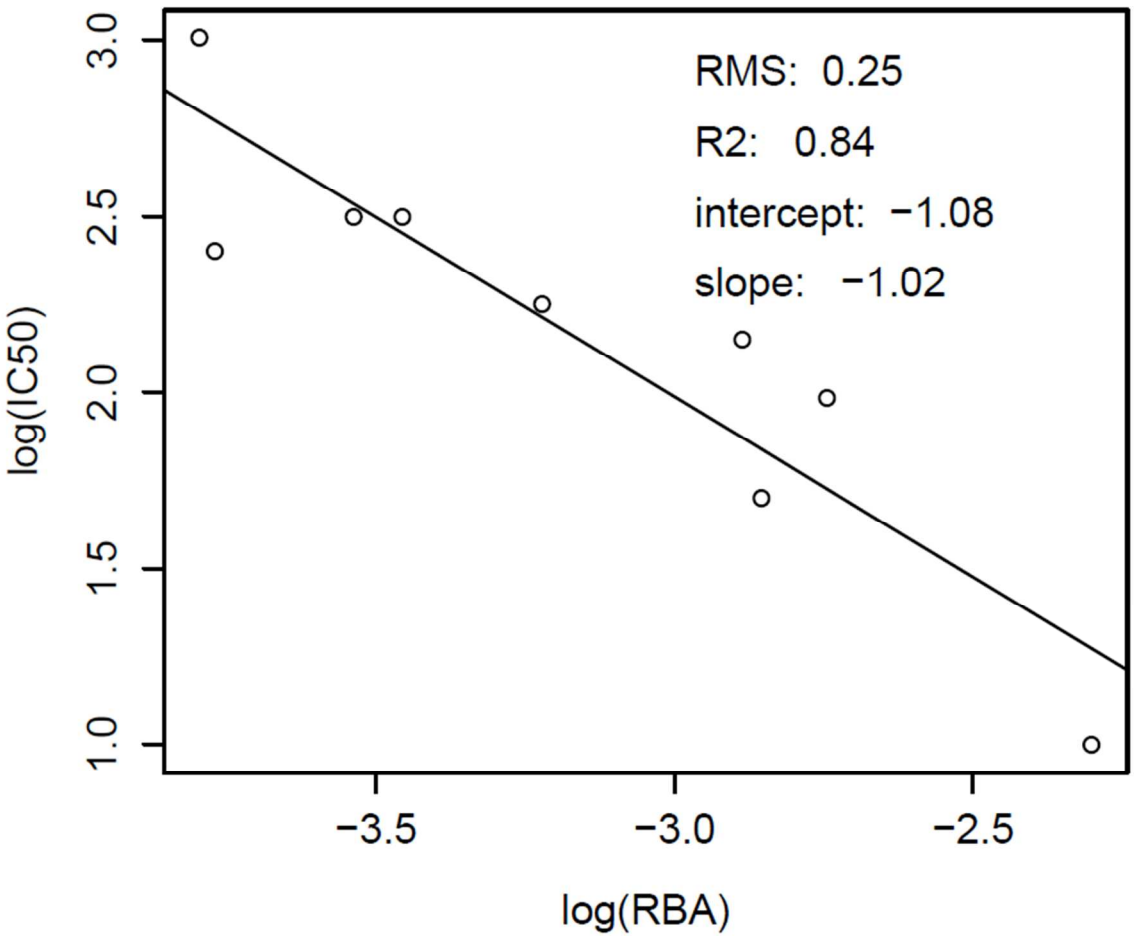


(b)

Abbreviation: AR = androgen receptor, FRET = fluorescence resonance energy transfer. The number of experiments conducted using each assay type is shown in parentheses.

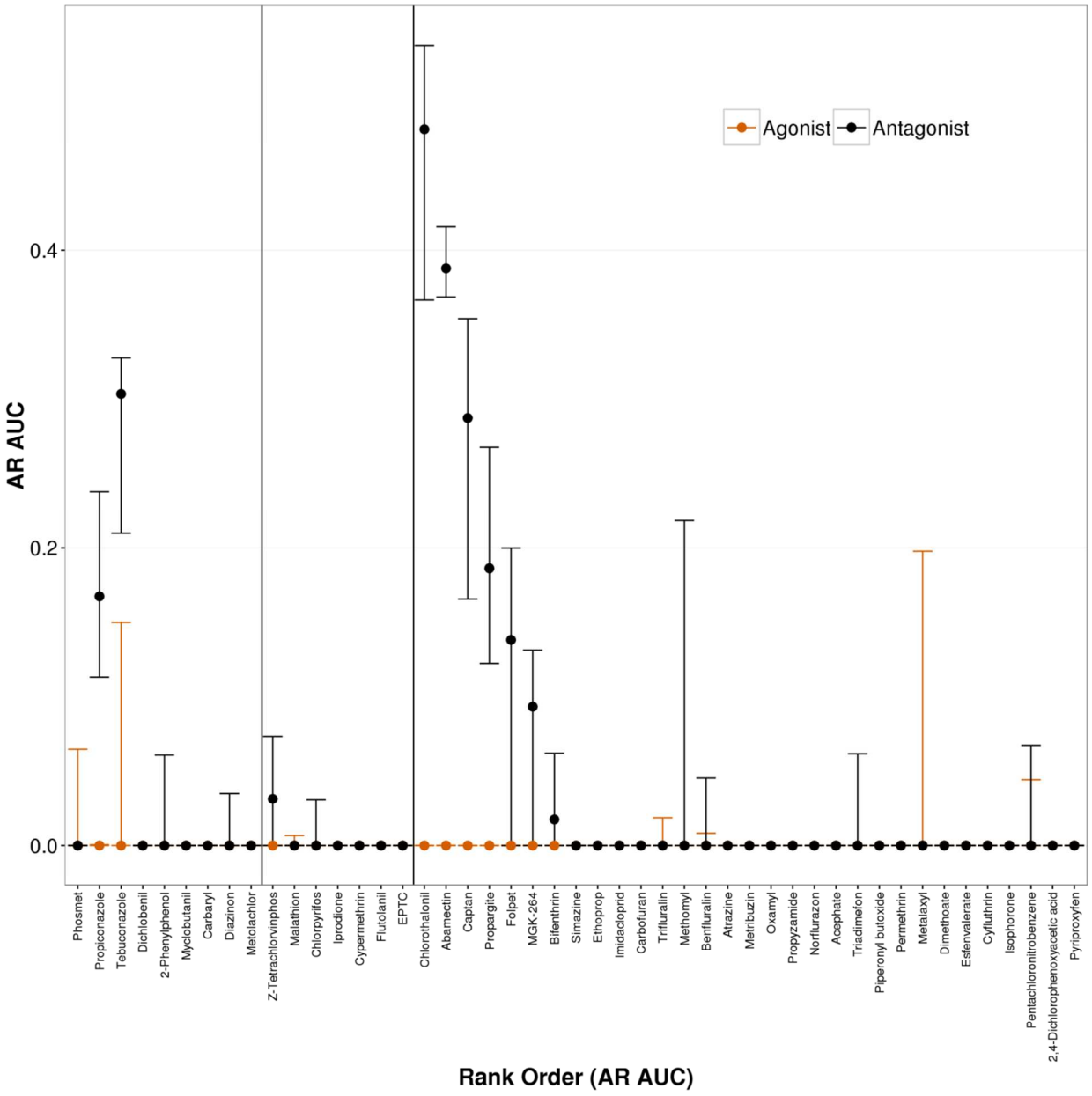
Literature review results for AR transactivation data on potential reference chemicals: (a) assay types and (b) receptor types

Figure S5



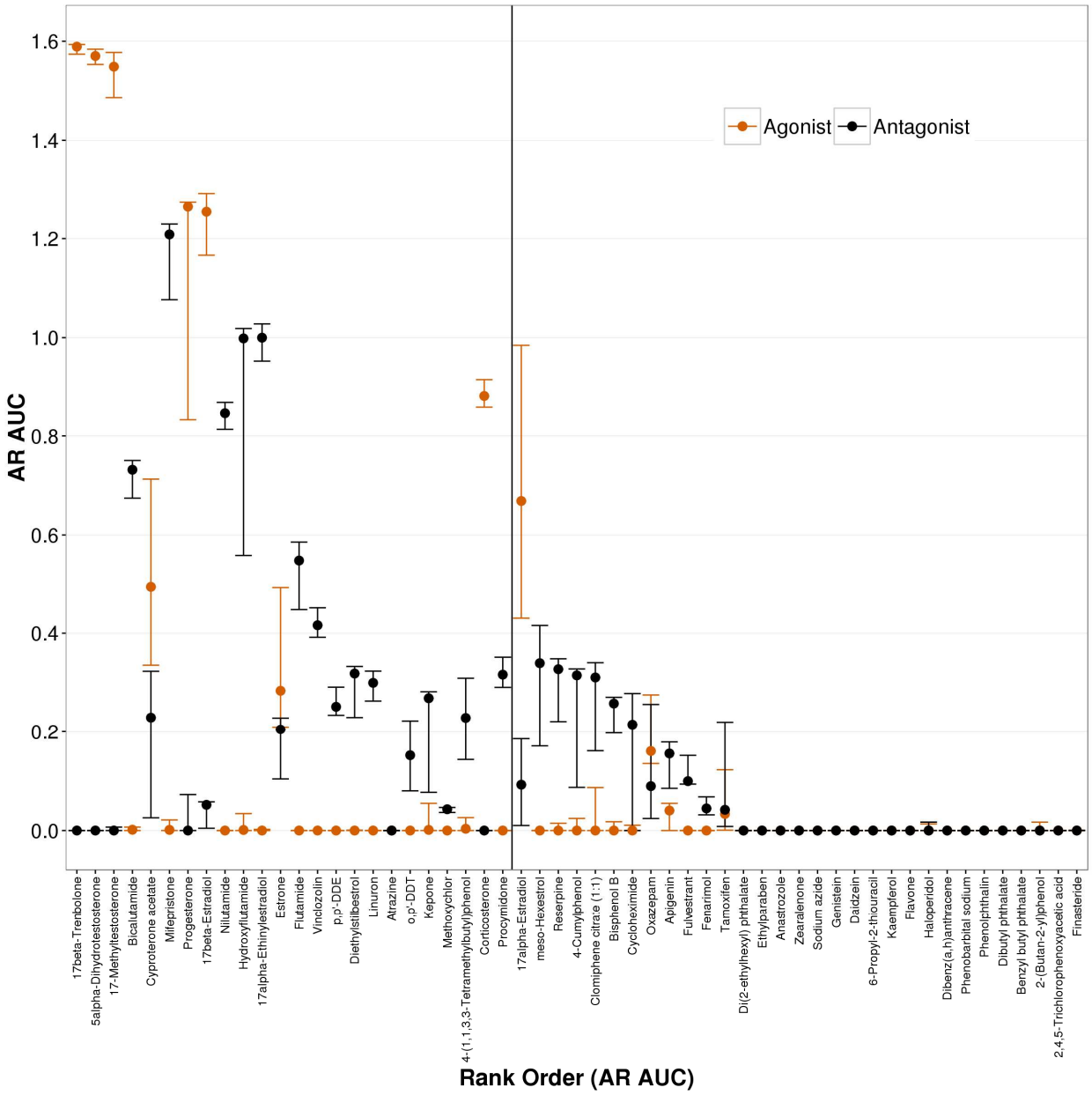
Calibration curve using the AR Tier 1 binding data from U.S. EPA EDSP List 1 chemicals, allowing the estimation of IC50 values from RBAs. RMS represents root-mean-square error and R^2 represents goodness of fit.

Figure S6



Results of the AR Pathway model for all 47 chemicals in List 1 with uncertainties. For each chemical, the AUC point estimates (circles) and 95% confidence intervals (error bars) are indicated for the AR agonist (red) and antagonist (black) pathways. The two vertical lines mark the List 1 Tier 1 binding activity: the left most region contains active chemicals, the middle region are those with equivocal results, and the rightmost are inactive. List 1 actives are sorted by the estimated potency from the List 1 results. Chemicals in the equivocal and inactive regions are sorted by the maximum of the AR Pathway model AUC agonist and antagonist values.

Figure S7



Results of the AR Pathway model for all 55 chemicals in ICCVAM with uncertainties. For each chemical, the AUC point estimates (circles) and 95% confidence intervals (error bars) are indicated for the AR agonist (red) and antagonist (black) pathways. The vertical line marks the ICCVAM Tier 1 binding activity: chemicals left of the line are active while chemicals to the right of the line are inactive. ICCVAM actives are sorted by the estimated potency from the ICCVAM results. Chemicals in the inactive region are sorted by the maximum of the AR Pathway model AUC agonist and antagonist values.