

Supplemental Material 1: Supplemental methods

Molecular Docking Methods

Receptor and Ligand Preparation

In this study, AGR2 was selected as the receptor, and its structure file was preprocessed and saved in PDBQT format (AGR2.pdbqt). Four candidate compounds—Ciclosporin, Dexamethasone, Dobutamine, and Fenoterol—were prepared as ligands. All ligands were protonated, energy-minimized, and converted into PDBQT format under standard preparation procedures. During receptor preparation, crystallographic water molecules were removed and polar hydrogens were added.

Docking Parameter Settings

Molecular docking was performed using AutoDock Vina. The grid box parameters were configured as follows:

Grid center coordinates:

- center_x = 0.106
- center_y = 2.241
- center_z = 17.429

Grid dimensions (Å):

- size_x = 38
- size_y = 56
- size_z = 70

The docking search parameters were:

- energy_range = 5
- num_modes = 10 (generating up to 10 candidate poses for each docking run)

This grid box fully encompassed the major predicted binding pocket of AGR2, and all ligands were docked using identical parameters.

Pose Selection and Interaction Analysis

For each ligand, the pose with the lowest binding energy (highest Vina score) was selected for subsequent analysis. Hydrogen-bond interactions between the ligand and AGR2 were identified using molecular visualization tools, and key hydrogen-bond distances and residue names were recorded.

Summary of Key Hydrogen-Bond Interactions

Ciclosporin

- SER-45: 2.6 Å

Dexamethasone

- TRP-54: 2.0 Å
- TRP-54: 3.1 Å
- GLU-60: 2.7 Å
- LYS-64: 2.1 Å
- THR-55: 2.8 Å

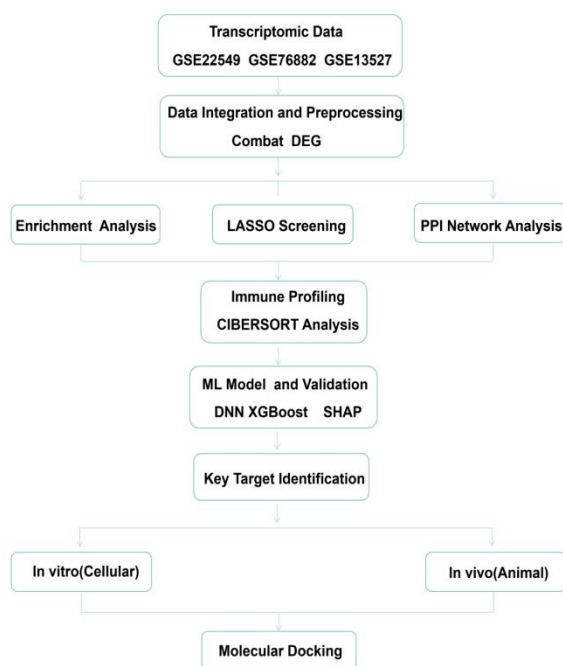
Dobutamine

- PHE-104: 2.5 Å
- GLU-102: 2.5 Å

Fenoterol

- PRO-71: 2.2 Å
- GLN-103: 2.3 Å

These interactions provide structural evidence for the potential binding modes of the four drugs with AGR2.



Supplemental Figure 1. Workflow of the integrated analytical pipeline for biomarker identification.

Supplemental Table 1. Sequence of siRNA

Gene name	Sequence
si-NC	Sense: UUCUCCGAACGUGUCACGUTT
	Antisense: ACGUGACACGUUCGGAGAATT
si-AGR2	Sense: CCAAAAAGGACCCAAAGGATT
	Antisense: UCCUUUGGGUCCUUUUUGGTT
si-DOCK2	Sense: AUGUACGACCUGAUGGAAUTT
	Antisense: AUUCCAUCAGGUCGUACAUTT

Supplemental Table 2: Results of Drug Enrichment Analysis

ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	geneID	Count
dexamethasone CTD 00005779	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4ctd&id=5779	6/25	421/19646	1.17141928101793e-05	0.00664310173816583	0.00350976538697206	CYBB/HLA-DPB1/FPRI/AGR2/EGF/SOST	6
isotretinoin HL60 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=1002	4/25	136/19646	2.48246021532053e-05	0.00664310173816583	0.00350976538697206	PLEK/CYBB/CCR2/CD300A	4
diphenylpyraline BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1068	4/25	168/19646	5.67242584303721e-05	0.00664310173816583	0.00350976538697206	HLA-DPB1/CFB/CCR2/PVALB	4
XENON BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1947	2/25	10/19646	6.95224634519874e-05	0.00664310173816583	0.00350976538697206	CFB/PVALB	2
4-aminobutyric acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=753	4/25	180/19646	7.4166203803745e-05	0.00664310173816583	0.00350976538697206	CFB/SLC1A3/EGF/PVALB	4
Ethylparaben BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=509	4/25	186/19646	8.42187585621697e-05	0.00664310173816583	0.00350976538697206	CYBB/CFB/EGF/PVALB	4
Erythorbic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=636	4/25	187/19646	8.59859208668699e-05	0.00664310173816583	0.00350976538697206	CYBB/CFB/EGF/PVALB	4
hydrogen peroxide BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1796	4/25	189/19646	8.96011188070381e-05	0.00664310173816583	0.00350976538697206	CYBB/CFB/EGF/PVALB	4
D-Norepinephrine d-bitartrate BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=643	4/25	190/19646	9.14496564984576e-05	0.00664310173816583	0.00350976538697206	CYBB/CFB/EGF/PVALB	4
L-glutamine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=922	4/25	190/19646	9.14496564984576e-05	0.00664310173816583	0.00350976538697206	CFB/SLC1A3/EGF/PVALB	4
nitric oxide BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1147	4/25	191/19646	9.33258226306821e-05	0.00664310173816583	0.00350976538697206	CYBB/CFB/EGF/PVALB	4
Acetylcholine bromide BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=197	4/25	198/19646	0.000107253918545167	0.00699831818507216	0.00369743771826761	CYBB/CFB/EGF/PVALB	4
Chloroethylene BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1631	2/25	15/19646	0.000161587336091415	0.00973252955073678	0.00514200996630981	CFB/PVALB	2
thioridazine HL60 DOWN	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=1844	2/25	18/19646	0.000234905360102463	0.0131379212114449	0.00694118846017051	CCR2/FPRI	2
RUTHENIUM BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1690	2/25	21/19646	0.000321665473169416	0.0162843801675809	0.00860356443618914	CFB/PVALB	2
SODIUM BICARBONATE BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1739	3/25	108/19646	0.00034024862143482	0.0162843801675809	0.00860356443618914	CFB/EGF/PVALB	3
lasalocid HL60 DOWN	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=1038	2/25	22/19646	0.000353556146678002	0.0162843801675809	0.00860356443618914	CCR2/FPRI	2
rimexolone HL60 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=1650	2/25	23/19646	0.000386926266870281	0.0168312926088572	0.00889251595789593	CCR2/FPRI	2
ETHYLENE GLYCOL BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=311	3/25	116/19646	0.000419593902171694	0.0172702074035906	0.00912440883190307	CFB/EGF/PVALB	3
Ethylene dimethylacrylate BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1974	3/25	118/19646	0.000441129180168342	0.0172702074035906	0.00912440883190307	CFB/EGF/PVALB	3
dobutamine PC3 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=655	2/25	27/19646	0.000535131027149262	0.0199527425837082	0.0105416788806847	AGR2/ISG20	2
acetaldehyde CTD 00005293	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4ctd&id=5293	3/25	129/19646	0.000572317089417325	0.0203692855006257	0.0107617519684693	CYBB/CCR2/EGF	3
pergolide HL60 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=1398	4/25	312/19646	0.000606464288282201	0.0204091042254249	0.0107827894879236	CYBB/FPRI/ISG20/FCER1G	4
ACRYLAMIDE BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1575	3/25	133/19646	0.000625566413039842	0.0204091042254249	0.0107827894879236	CFB/EGF/PVALB	3
Deuterium hydride BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=690	2/25	35/19646	0.000901491445880294	0.0250215234032455	0.0132196796363185	CFB/PVALB	2
nitrate BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1903	3/25	152/19646	0.00092165879889143	0.0250215234032455	0.0132196796363185	CYBB/CFB/PVALB	3
ammonia BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=315	3/25	163/19646	0.00112767175503496	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
Silica BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=2078	2/25	40/19646	0.00117719167195893	0.0250215234032455	0.0132196796363185	CFB/PVALB	2
acetaminophen BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=842	3/25	167/19646	0.001209224252888683	0.0250215234032455	0.0132196796363185	CFB/CCR2/PVALB	3
asparagine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=320	2/25	41/19646	0.00123659668841769	0.0250215234032455	0.0132196796363185	CFB/EGF	2
Aziridine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=847	2/25	42/19646	0.0012974153957935	0.0250215234032455	0.0132196796363185	CFB/EGF	2
L-aspartic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1214	3/25	173/19646	0.00133839841816488	0.0250215234032455	0.0132196796363185	CFB/SLC1A3/EGF	3
dimethyl sulfoxide BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=802	3/25	177/19646	0.00142916754307335	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
palmitic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1059	3/25	177/19646	0.00142916754307335	0.0250215234032455	0.0132196796363185	CYBB/CFB/EGF	3
2,2',3,4,4',5,5'-HEPTACHLOROBIPHENYL_CTD_00003812	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4ctd&id=3812	2/25	45/19646	0.00148831966740316	0.0250215234032455	0.0132196796363185	CCR2/SERPINA3	2
fenoterol PC3 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=774	2/25	45/19646	0.00148831966740316	0.0250215234032455	0.0132196796363185	AGR2/ISG20	2
(-)-isoprenaline HL60 UP	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=7	3/25	182/19646	0.00154796911722029	0.0250215234032455	0.0132196796363185	HLA-DPB1/FPRI/ISG20	3
L-leucine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=914	3/25	182/19646	0.00154796911722029	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
glycerol BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=877	3/25	183/19646	0.00157245066880769	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
L-alanine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1210	3/25	186/19646	0.00164735414262895	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
L-cysteine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=912	3/25	186/19646	0.00164735414262895	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
lactic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=883	3/25	186/19646	0.00164735414262895	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
methane BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1202	3/25	186/19646	0.00164735414262895	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
methanol BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1566	3/25	186/19646	0.00164735414262895	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
acetic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1008	3/25	187/19646	0.00167281123320115	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
liothyronine BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=846	3/25	187/19646	0.00167281123320115	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
sodium chloride BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1114	3/25	187/19646	0.00167281123320115	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
gossypol HL60 DOWN	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d3&id=876	2/25	48/19646	0.00169182501375537	0.0250215234032455	0.0132196796363185	MS4A6A/CCR2	2
Coke BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=63	3/25	189/19646	0.00172446465798665	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
Superoxide BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1795	3/25	189/19646	0.00172446465798665	0.0250215234032455	0.0132196796363185	CYBB/CFB/FPRI	3
glutathione BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=600	3/25	190/19646	0.0017506627596148	0.0250215234032455	0.0132196796363185	CYBB/CFB/EGF	3
HEXACHLOROETHANE BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1639	3/25	190/19646	0.0017506627596148	0.0250215234032455	0.0132196796363185	CFB/FGB/EGF	3
L-glutamic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1211	3/25	190/19646	0.0017506627596148	0.0250215234032455	0.0132196796363185	CFB/SLC1A3/PVALB	3
propionic acid BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1304	2/25	49/19646	0.00176244461071678	0.0250215234032455	0.0132196796363185	CFB/PVALB	2
Angiotensin II, human BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=136	3/25	193/19646	0.00183075314143029	0.0250215234032455	0.0132196796363185	CYBB/CCR2/EGF	3
diazepam BOSS	http://dsigdb.tanlab.org/DSigDBv1.0/displayDrug.py?db=d4boss&id=1405	3/25	193/19646	0.00183075314143029	0.0250215234032455	0.0132196796363185	CFB/EGF/PVALB	3
(+)-chelidonium HL60 DOWN	http://dsigdb.tanlab.org/DSigDBv							