Supporting information

Synthesis, structural characterization, in silico ADMET and molecular docking studies of Schiff base derived from 4-hydroxybenzaldehyde and 4-aminobenzoic acid

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Melting point

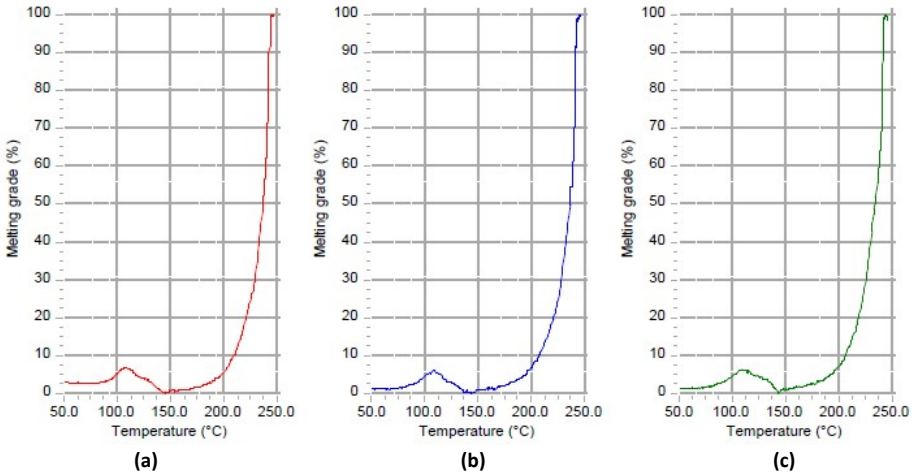


Fig. S1. Melting grade curves for the title compound. Measurements were conducted simultaneously on three samples (a-c) with a gradient of 1°C/min.

Hirshfield surface

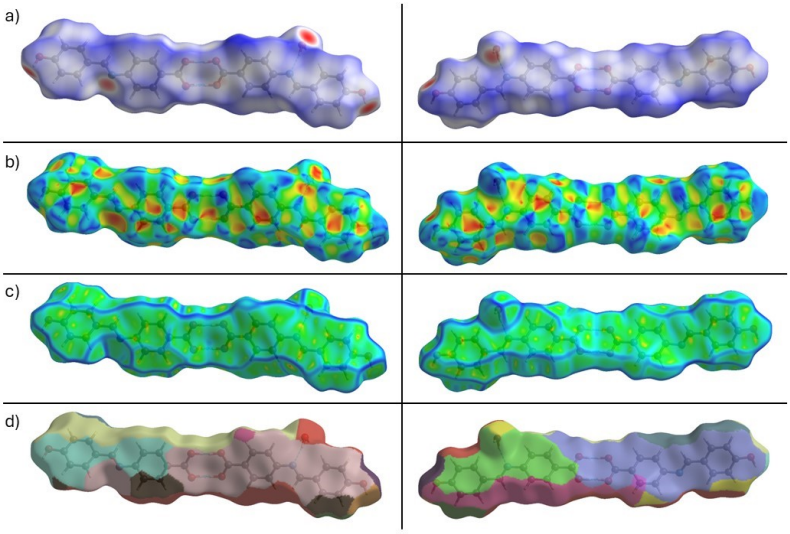
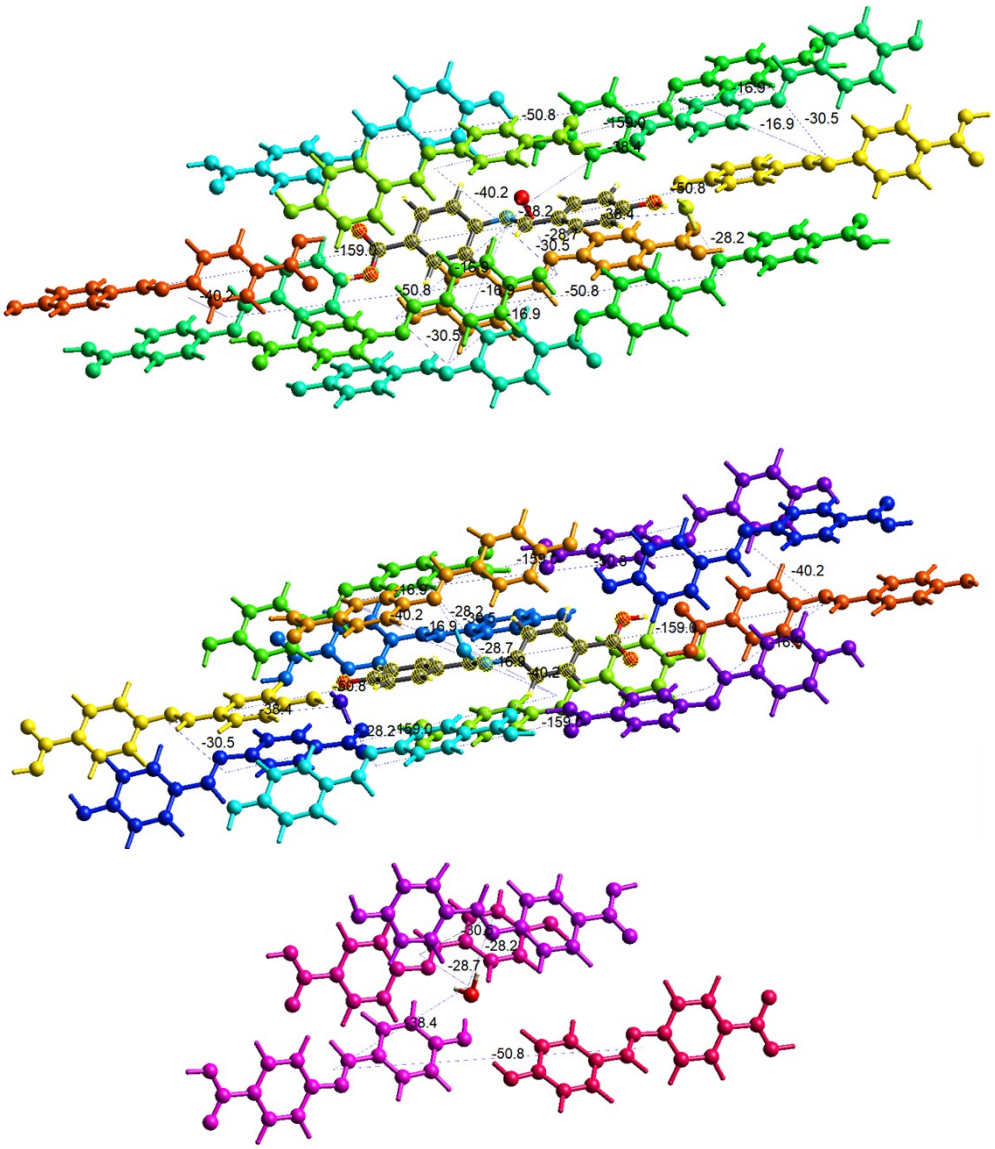


Fig. S2. Visualization of Hirshfeld surface for the asymmetric unit of obtained compound using the parameters: d_{norm} (a), shape index (b), curvedness (c), and fragment patch (d).

Energy frameworks data



	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	0	-	3.49	B3LYP/6-31G(d,p)	-51.3	-11.4	-13.6	74.9	-28.2
	0	-	14.32	B3LYP/6-31G(d,p)	-114.1	-36.9	-12.7	0.0	-159.0
	0	-	4.76	B3LYP/6-31G(d,p)	-2.3	-2.0	-43.2	18.0	-30.5
	0	-	14.82	B3LYP/6-31G(d,p)	-30.9	-10.5	-11.8	0.0	-50.8
	0	-	8.53	B3LYP/6-31G(d,p)	-71.2	-16.6	-6.3	88.5	-38.4
	0	-	4.02	B3LYP/6-31G(d,p)	-3.6	-3.3	-64.9	36.5	-40.2
	0	-	7.60	B3LYP/6-31G(d,p)	-7.5	-1.7	-24.6	22.1	-16.9
	0	-x+1/2, y+1/2, -z+1/2	10.88	B3LYP/6-31G(d,p)	-5.7	-1.4	-15.9	17.5	-10.1
	0	x+1/2, -y+1/2, z+1/2	12.87	B3LYP/6-31G(d,p)	3.3	-1.8	-12.2	0.0	-8.4
	0	-x, -y, -z	6.27	B3LYP/6-31G(d,p)	-4.3	-1.0	-19.6	8.8	-16.9
	0	-	8.42	B3LYP/6-31G(d,p)	-3.1	-2.3	-12.4	6.7	-11.6
	0	-	3.58	B3LYP/6-31G(d,p)	-40.1	-8.7	-11.7	49.2	-28.7
	0	-x, -y, -z	7.43	B3LYP/6-31G(d,p)	0.9	-0.7	-14.3	6.1	-8.2
	0	x+1/2, -y+1/2, z+1/2	12.80	B3LYP/6-31G(d,p)	9.1	-1.2	-12.7	0.0	-2.4
	0	-	7.93	B3LYP/6-31G(d,p)	-9.1	-1.2	-2.1	1.7	-11.3
	0	-x+1/2, y+1/2, -z+1/2	10.49	B3LYP/6-31G(d,p)	-5.1	-2.2	-12.0	8.0	-12.5
	0	-	3.49	B3LYP/6-31G(d,p)	-51.3	-11.4	-13.6	74.9	-28.2
	0	-	8.53	B3LYP/6-31G(d,p)	-71.2	-16.6	-6.3	88.5	-38.4
	0	-	3.58	B3LYP/6-31G(d,p)	-40.1	-8.7	-11.7	49.2	-28.7
	0	-	7.93	B3LYP/6-31G(d,p)	-9.1	-1.2	-2.1	1.7	-11.3

Fig. S3. Energy values between molecular pairs for each independent molecule in asymmetric unit. For clarity, only interactions with $-E <$ 15 kJ/mol are displayed.

Crystallographic data

Tab. S1. Crystal data and structure refinement for title compound.

Compound	hemihydrate of 4-(4-hydroxybenzylidene)aminobenzoic acid
Chemical formula	$C_{28}H_{22}N_2O_6 \cdot H_2O$
FW/g·mol^{-1}	500.51
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.6372(3)
b/Å	11.4481(4)
c/Å	24.7299(9)
α/°	90
β/°	94.210(3)
γ/°	90
V/Å^3	2438.70(14)
Z	4
T/K	291(2)
λ_{Mo}/Å	0.71073
ρ_{calc}/g·cm^{-3}	1.363
$F(000)$	1048
μ/mm^{-1}	0.099
ϑ range/°	3.30-25.00
Completeness of ϑ/%	99.8
Reflections collected	35631
Reflections unique	4288 [R_{int} = 0.0520]
Data/restraints/parameters	4288 / 4 / 420
Goodness of fit on F^2	1.095
Final R_1 value (I>2σ(I))	0.0496
Final wR_2 value (I>2σ(I))	0.1113
Final R_1 value (all data)	0.0763
Final wR_2 value (all data)	0.1235
Largest diff. peak and hole/ e· Å^{-3}	0.3395 and -0.2880
CCDC number	2352237

Tab. S2. Hydrogen bonds geometry for title compound.

D–H···A	***d*(D–H)[Å]**	***d*(H···A)[Å]**	***d*(D···A [Å]**	**∠D–H···A [°]**
O(1W)–H(2W)···N(1)	0.91(2)	1.94(2)	2.835(2)	167(2)
O(1W)–H(1W)···N(21)^{i}	0.87(3)	2.06(3)	2.915(2)	167(3)
O(15)–H(15)···O(36)	0.87(4)	1.79(4)	2.654(2)	177(6)
O(16)–H(16)···O(35)	0.86(4)	1.78(4)	2.625(2)	170(4)
O(17)–H(17)···O(1W)^{ii}	0.95(3)	1.64(3)	2.582(2)	171(3)
O(35)–H(35)···O(16)	0.87(4)	1.76(4)	2.625(2)	175(3)
O(36)–H(36)···O(15)	0.86(5)	1.80(5)	2.654(2)	171(6)
O(37)–H(37)···O(17)^{iii}	0.95(2)	1.76(2)	2.695(2)	170(3)
C(3)–H(3)···O(1W)	1.16(3)	2.31(3)	3.411(4)	158(2)
C(7)–H(7)···O(37)^{iv}	1.09(3)	2.40(3)	3.464(3)	166(3)
Symmetry code: (i) 3/2+x.1/2-y.1/2+z; (ii) 1/2-x.-1/2+y.3/2-z; (iii) -2+x.y.-1+z; (iv) -3/2-x.-1/2+y.1/2-z				

Tab. S3. C–H···π interactions geometry for obtained compound.

C–H···Cg	***d*(H···Cg) [Å]**	***d*(C···Cg) [Å]**	**∠C–H···Cg [°]**
C21–H21···Cg2	3.08	3.56	107.7
C9–H9···Cg1	3.79	3.72	78.0
C26–H26···Cg2	3.47	3.47	87.2
C4–H4···Cg2	3.63	3.85	93.1
C29–H29···Cg1	3.58	3.91	64.1

Cg represents the centre of gravity of the aromatic ring.

Tab. S4. N···π interaction geometry for obtained compound.

Y=X···Cg[a]	***d*(Y···Cg) [Å]**	***d*(X···Cg) [Å]**	**∠X–Y···Cg [°]**
C1=N1···Cg2	3.79	3.74	78.2

Cg represents the centre of gravity of the aromatic ring.

Tab. S5. C–O···π interactions geometry for obtained compound.

X–Y···Cg[a]	***d*(Y···Cg) [Å]**	***d*(X···Cg) [Å]**	**∠X–Y···Cg [°]**
C34–O35···Cg1	3.38	3.60	89.4
C14–O16···Cg1	3.43	3.64	70.4

Symmetry code: (i) 1-x, -y, 1-z.

Cg represents the centre of gravity of the aromatic ring.

ADME data

Tab. S6. Drug-likeness parameters for obtained Schiff base ligand.

Physicochemical Properties	
Formula	$C_{14}H_{11}NO_3$
Molecular weight (MW)	241.24
Num. heavy atoms	18
Num. arom. heavy atoms	12
Num. rotatable bonds	3
Num. H-bond acceptors	4
Num. H-bond donors	2
Molar refractivity (MR)	69.12
Topological polar surface area (TPSA)	69.89
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.79
Log $P_{o/w}$ (XLOGP3)	2.39
Log $P_{o/w}$ (WLOGP)	2.84
Log $P_{o/w}$ (MLOGP)	2.14
Log $P_{o/w}$ (SILICOS-IT)	2.77
Consensus Log $P_{o/w}$	2.39
Water Solubility	
Log S (ESOL)	-3.14
Solubility	1.76e-01 mg/ml ; 7.30e-04 mol/l
Class	Soluble
Log S (Ali)	-3.50
Solubility	7.65e-02 mg/ml ; 3.17e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-3.81
Solubility	3.71e-02 mg/ml ; 1.54e-04 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.07 cm/s
Druglikeness	
Bioavailibity Score	0.85
Medicinal Chemistry	
PAINS	0
Brenk	1
Leadlikeness	No
Synthetic accessibility	2.09

Tab. S7. Drug-likeness parameters for 4-{(E)-[(4-hydroxyphenyl)methylidene]amino benzenesulfonamide.

Physicochemical Properties	
Formula	$C_{13}H_{12}N_2O_3S$
Molecular weight (MW)	276.31
Num. Heavy atoms	19
Num. Arom. Heavy atoms	12
Num. Rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	2
Molar refractivity (MR)	73.16
Topological polar surface area (TPSA)	101.13
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.52
Log $P_{o/w}$ (XLOGP3)	1.43
Log $P_{o/w}$ (WLOGP)	2.87
Log $P_{o/w}$ (MLOGP)	0.97
Log $P_{o/w}$ (SILICOS-IT)	1.45
Consensus Log $P_{o/w}$	1.65
Water Solubility	
Log S (ESOL)	-2.72
Solubility	5.22e-01 mg/ml ; 1.89e-03 mol/l
Class	Soluble
Log S (Ali)	-3.16
Solubility	1.92e-02 mg/ml ; 6.94e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-4.00
Solubility	2.78e-02 mg/ml ; 1.01e-04 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.97 cm/s
Druglikeness	
Bioavailibity Score	0.55
Medicinal Chemistry	

PAINS	0
Brenk	1
Leadlikeness	Yes
Synthetic accessibility	2.39

Protox III data

Tab. S8. Toxicology data for 4-{(*E*)-[(4-hydroxyphenyl)methylidene]amino}benzoic acid.

Classification	Target	Prediction	Probability
Organ toxicity	Hepatotoxicity	Active	0.66
Organ toxicity	Neurotoxicity	Active	0.54
Organ toxicity	Nephrotoxicity	Active	0.67
Organ toxicity	Respiratory toxicity	Active	0.64
Organ toxicity	Cardiotoxicity	Inactive	0.68
Toxicity end points	Carcinogenicity	Inactive	0.55
Toxicity end points	Immunotoxicity	Inactive	0.99
Toxicity end points	Mutagenicity	Inactive	0.55
Toxicity end points	Cytotoxicity	Inactive	0.76
Toxicity end points	BBB-barrier	Inactive	0.52
Toxicity end points	Ecotoxicity	Inactive	0.59
Toxicity end points	Clinical toxicity	Active	0.50
Toxicity end points	Nutritional toxicity	Inactive	0.82
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	Active	0.54
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	Inactive	0.85
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	Active	0.75
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	Active	0.53
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	Inactive	0.97
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Inactive	0.94
Tox21-Stress response pathways	Heat shock factor response element (HSE)	Inactive	0.94
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	Inactive	0.56
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	Inactive	0.88
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	Inactive	0.66
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	Inactive	0.90
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	Inactive	0.78
Molecular Initiating Events	Transtyretrin (TTR)	Inactive	0.97
Molecular Initiating Events	Ryanodine receptor (RYR)	Inactive	0.98
Molecular Initiating Events	GABA receptor (GABAR)	Inactive	0.96
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	Inactive	0.92
Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	Inactive	0.97
Molecular Initiating Events	Kainate receptor (KAR)	Inactive	0.99
Molecular Initiating Events	Achetylcholinesterase (AChE)	Active	0.66
Molecular Initiating Events	Constitutive androstane receptor (CAR)	Inactive	0.98
Molecular Initiating Events	Pregnane X receptor (PXR)	Inactive	0.92
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	Inactive	0.97
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	Inactive	0.95

Molecular Initiating Events	Na+/I- symporter (NIS)	Inactive	0.98
Metabolism	Cytochrome CYP1A2	Inactive	0.63
Metabolism	Cytochrome CYP2C19	Inactive	0.75
Metabolism	Cytochrome CYP2C9	Inactive	0.65
Metabolism	Cytochrome CYP2D6	Inactive	0.83
Metabolism	Cytochrome CYP3A4	Inactive	0.83
Metabolism	Cytochrome CYP2E1	Inactive	0.99

Tab. S9. Toxicology data for 4-{(E)-[(4-hydroxyphenyl)methylidene]amino}benzenesulfonamide.

Classification	**Target**	**Prediction**	**Probability**
Organ toxicity	Hepatotoxicity	Inactive	0.58
Organ toxicity	Neurotoxicity	Inactive	0.88
Organ toxicity	Nephrotoxicity	Inactive	0.6
Organ toxicity	Respiratory toxicity	Inactive	0.55
Organ toxicity	Cardiotoxicity	Inactive	0.61
Toxicity end points	Carcinogenicity	Active	0.58
Toxicity end points	Immunotoxicity	Inactive	0.99
Toxicity end points	Mutagenicity	Inactive	0.78
Toxicity end points	Cytotoxicity	Inactive	0.87
Toxicity end points	BBB-barrier	Active	0.69
Toxicity end points	Ecotoxicity	Inactive	0.72
Toxicity end points	Clinical toxicity	Active	0.51
Toxicity end points	Nutritional toxicity	Inactive	0.72
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	Inactive	0.90
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	Inactive	0.61
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	Inactive	0.88
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	Inactive	0.99
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	Inactive	0.83
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	Inactive	0.72
Molecular Initiating Events	Transtyretrin (TTR)	Inactive	0.59
Molecular Initiating Events	Ryanodine receptor (RYR)	Inactive	0.87
Molecular Initiating Events	GABA receptor (GABAR)	Inactive	0.94
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	Inactive	0.98

Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	Inactive	0.99
Molecular Initiating Events	Kainate receptor (KAR)	Inactive	1
Molecular Initiating Events	Achetylcholinesterase (AChE)	Inactive	0.85
Molecular Initiating Events	Constitutive androstane receptor (CAR)	Inactive	1
Molecular Initiating Events	Pregnane X receptor (PXR)	Inactive	0.63
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	Inactive	0.97
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	Inactive	0.56
Molecular Initiating Events	Na+/I- symporter (NIS)	Inactive	0.96
Metabolism	Cytochrome CYP1A2	Inactive	0.93
Metabolism	Cytochrome CYP2C19	Inactive	0.58
Metabolism	Cytochrome CYP2C9	Inactive	0.57
Metabolism	Cytochrome CYP2D6	Inactive	0.82
Metabolism	Cytochrome CYP3A4	Inactive	0.87
Metabolism	Cytochrome CYP2E1	Inactive	0.99

Molecular docking data

Tab. S10. Molecular docking results for AChE binding with 4-{(E)-[(4-hydroxyphenyl)methylidene]amino}benzoic acid.

Mode	Affinity (kcal/mol)	Distance from best mode	
		R.M.S.D l.b	R.M.S.D u.b
1	-8.2	0.000	0.000
2	-7.5	0.934	8.274
3	-7.4	3.894	4.626
4	-6.9	3.792	4.382
5	-6.7	4.745	6.781
6	-6.7	4.466	6.393
7	-6.5	16.805	17.514
8	-6.3	5.503	7.564
9	-6.2	25.518	26.272

Tab. S11. Molecular docking results for CA II binding with 4-{(E)-[(4-hydroxyphenyl)methylidene]amino}benzoic acid.

Mode	Affinity (kcal/mol)	Distance from best mode	
		R.M.S.D l.b	R.M.S.D u.b
1	-6.4	0.000	0.000
2	-6.3	0.812	1.898
3	-5.9	4.798	6.208
4	-5.8	5.135	5.965
5	-5.6	1.459	8.243
6	-5.6	19.510	21.079
7	-5.4	5.048	6.952
8	-5.4	26.113	28.116
9	-5.3	1.381	2.171

Tab. S12. Molecular docking results for CA II binding with 4-{(E)-[(4-hydroxyphenyl)methylidene]-amino}benzenesulfonamide.

Mode	Affinity (kcal/mol)	Distance from best mode	
		R.M.S.D l.b	R.M.S.D u.b
1	-6.8	0.000	0.000
2	-6.1	16.030	19.777
3	-5.9	5.052	8.404
4	-5.9	22.141	24.509
5	-5.9	16.141	18.715
6	-5.8	16.116	18.700
7	-5.8	29.592	29.980
8	-5.7	13.524	14.269
9	-5.7	29.354	31.431