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Electronic supplementary information (ESI)

Computational Designed p-Coumaric Acid Analogs: Searching for Neuroprotective Antioxidants

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Table S1. p-Coumaric acid derivatives designed in this work.

	R_1	R_2	R_3	R_4	R_5	R_6
*p*CA	H	H	H	H	H	H
*p*CA-1	H	H	H	H	NH_2	COOH
*p*CA-2	H	H	H	H	NH_2	SH
*p*CA-3	H	H	H	H	COOH	NH_2
*p*CA-4	H	H	H	H	NH_2	NH_2
*p*CA-5	H	H	H	H	OH	NH_2
*p*CA-6	H	H	H	H	SH	NH_2
*p*CA-7	H	H	H	H	NH_2	OH
*p*CA-8	H	COOH	H	H	NH_2	H
*p*CA-9	H	NH_2	H	H	NH_2	H
*p*CA-10	H	OH	H	H	NH_2	H
*p*CA-11	H	SH	H	H	NH_2	H
*p*CA-12	H	H	H	H	NH_2	H
*p*CA-13	COOH	H	H	H	NH_2	H
*p*CA-14	NH_2	H	H	H	NH_2	H
*p*CA-15	OH	H	H	H	NH_2	H
*p*CA-17	H	COOH	H	H	H	NH_2
*p*CA-18	H	NH_2	H	H	H	NH_2
*p*CA-19	H	OH	H	H	H	NH_2
*p*CA-20	H	SH	H	H	H	NH_2
*p*CA-21	H	H	H	H	H	NH_2
*p*CA-22	COOH	H	H	H	H	NH_2
*p*CA-23	NH_2	H	H	H	H	NH_2
*p*CA-26	NH_2	COOH	H	H	H	H
*p*CA-27	NH_2	H	H	H	H	H
*p*CA-28	COOH	NH_2	H	H	H	H
*p*CA-29	NH_2	NH_2	H	H	H	H
*p*CA-30	OH	NH_2	H	H	H	H
*p*CA-32	NH_2	SH	H	H	H	H
*p*CA-33	H	NH_2	H	H	COOH	H
*p*CA-34	H	NH_2	H	H	OH	H
*p*CA-35	H	NH_2	H	H	SH	H
*p*CA-36	H	NH_2	H	H	H	COOH
*p*CA-37	COOH	H	NH_2	H	H	H
*p*CA-38	NH_2	H	NH_2	H	H	H
*p*CA-39	OH	H	NH_2	H	H	H
*p*CA-41	H	COOH	NH_2	H	H	H
*p*CA-42	H	NH_2	NH_2	H	H	H
*p*CA-43	H	OH	NH_2	H	H	H
*p*CA-45	H	NH_2	H	H	H	H

*p*CA-46	H	COOH	H	NH_2	H	H
*p*CA-47	NH_2	H	COOH	H	H	H
*p*CA-48	NH_2	H	SH	H	H	H
*p*CA-50	NH_2	H	H	NH_2	H	H
*p*CA-51	OH	H	H	NH_2	H	H
*p*CA-52	SH	H	H	NH_2	H	H
*p*CA-53	NH_2	H	H	H	COOH	H
*p*CA-54	NH_2	H	H	H	OH	H
*p*CA-55	NH_2	H	H	H	SH	H
*p*CA-56	H	H	H	NH_2	H	COOH
*p*CA-57	NH_2	H	H	H	H	H
*p*CA-58	NH_2	H	H	H	H	OH
*p*CA-59	NH_2	H	H	H	H	SH
*p*CA-60	H	NH_2	H	H	H	OH
*p*CA-61	H	NH_2	H	H	H	SH
*p*CA-62	H	COOH	H	H	H	COOH
*p*CA-63	H	H	H	H	H	COOH
*p*CA-65	H	H	H	H	H	COOH
*p*CA-66	COOH	H	H	H	H	COOH
*p*CA-67	OH	H	H	H	H	COOH
*p*CA-69	H	H	H	H	COOH	COOH
*p*CA-70	H	H	H	H	OH	COOH
*p*CA-71	H	H	H	H	SH	COOH
*p*CA-72	H	COOH	H	H	H	OH
*p*CA-73	H	OH	H	H	H	OH
*p*CA-75	H	H	H	H	H	OH
*p*CA-76	COOH	H	H	H	H	OH
*p*CA-77	OH	H	H	H	H	OH
*p*CA-79	H	COOH	H	H	H	OH
*p*CA-80	H	OH	H	H	H	SH
*p*CA-81	H	SH	H	H	H	SH
*p*CA-82	H	H	H	H	H	SH
*p*CA-83	COOH	H	H	H	H	SH
*p*CA-84	OH	H	H	H	H	SH
*p*CA-85	SH	H	H	H	H	SH
*p*CA-86	H	H	H	H	COOH	SH
*p*CA-87	H	H	H	H	OH	SH
*p*CA-88	H	H	H	H	SH	SH
*p*CA-89	H	H	H	H	COOH	SH
*p*CA-90	H	H	H	H	OH	SH
*p*CA-91	H	H	H	H	SH	SH
*p*CA-92	H	COOH	H	H	COOH	H
*p*CA-93	H	OH	H	H	COOH	H

*p*CA-95	H	H	H	H	COOH	H
*p*CA-96	H	H	H	COOH	COOH	H
*p*CA-97	OH	H	H	H	COOH	H
*p*CA-99	H	COOH	H	H	OH	H
*p*CA-100	H	OH	H	H	OH	H
*p*CA-101	H	SH	H	H	OH	H
*p*CA-103	COOH	H	H	H	OH	H
*p*CA-104	OH	H	H	H	OH	H
*p*CA-106	H	COOH	H	H	SH	H
*p*CA-107	H	OH	H	H	SH	H
*p*CA-108	H	SH	H	H	SH	H
*p*CA-109	H	H	H	H	SH	H
*p*CA-110	COOH	H	H	H	SH	H
*p*CA-111	OH	H	H	H	SH	H
*p*CA-112	SH	H	H	H	SH	H
*p*CA-113	COOH	H	H	COOH	H	H
*p*CA-114	COOH	H	H	OH	H	H
*p*CA-115	OH	H	H	OH	H	H
*p*CA-116	SH	H	H	OH	H	H
*p*CA-119	H	COOH	COOH	H	H	H
*p*CA-120	H	COOH	H	COOH	H	H
*p*CA-121	H	COOH	H	OH	H	H
*p*CA-123	H	COOH	OH	H	H	H
*p*CA-124	H	OH	OH	H	H	H
*p*CA-125	H	SH	OH	H	H	H
*p*CA-126	COOH	H	OH	H	H	H
*p*CA-127	OH	H	OH	H	H	H
*p*CA-132	OH	H	SH	H	H	H
*p*CA-134	H	COOH	H	H	H	H
*p*CA-135	COOH	COOH	H	H	H	H
*p*CA-136	OH	COOH	H	H	H	H
*p*CA-138	H	OH	H	H	H	H
*p*CA-139	COOH	OH	H	H	H	H
*p*CA-140	OH	H	OH	H	H	H
*p*CA-142	H	SH	H	H	H	H
*p*CA-144	OH	SH	H	H	H	H
*p*CA-146	COOH	H	H	H	H	H
*p*CA-147	OH	H	H	H	H	H
*p*CA-148	OH	OH	H	H	H	H
*p*CA-149	OH	H	OH	H	OH	H
*p*CA-150	SH	OH	H	NH_2	H	H
*p*CA-151	OH	OH	H	NH_2	H	H
*p*CA-152	OH	H	OH	H	H	NH_2

*p*CA-153	NH_2	OH	H	H	H	OH
*p*CA-154	NH_2	H	OH	H	H	OH
*p*CA-155	OH	OH	H	OH	H	H
*p*CA-156	OH	OHJ	H		OH	H

Table S2. Values of the ADME properties, toxicity and synthetic accessibility for the designed p-Coumaric acid derivatives. Toxicity and molecular descriptors for p-Coumaric acid derived molecules. Oral rat 50 percent lethal dose (LD50), Ames mutagenicity (M) and synthetic accessibility (SA). Log P, topological polar surface area (TPSA), number of heavy atoms (XAt), molecular weight (MW), number of hydrogen bond acceptors (HB(a)), number of hydrogen bond donors (HB(d)), rotatable bonds (RB), and molar refractivity (MR). It is also presented the FT value for each case.

	logP	PSA	^{x}A	MW	HB^{A}	HB^{D}	RB	^{M}R	LD$_{50}$	M	SA	F_T
*p*CA	1.43	57.53	12	164.16	3	2	2	48.80	2827.23	0.22	2.03	3.68
*p*CA-1	-0.48	120.8	16	223.18	6	5	3	58.43	3989.62	0.27	3.10	3.40
*p*CA-2	0.38	83.6	14	211.24	4	4	2	60.45	647.59	0.28	3.01	3.14
*p*CA-3	-0.30	120.8	16	223.18	6	5	3	58.43	3651.79	0.18	3.14	3.59
*p*CA-4	-0.15	109.6	14	194.19	5	6	2	55.98	2496.49	0.25	3.00	3.33
*p*CA-5	1.21	103.8	14	195.17	5	5	2	54.03	2443.99	0.07	2.78	3.76
*p*CA-6	0.76	83.6	14	211.24	4	4	2	60.45	2269.86	0.29	3.01	3.40
*p*CA-7	0.00	103.8	14	195.17	5	5	2	54.03	3353.22	0.08	2.97	3.77
*p*CA-8	0.72	120.8	16	223.18	6	5	3	58.35	3744.15	0.12	3.18	3.68
*p*CA-9	0.00	109.6	14	194.19	5	6	2	55.90	1066.54	0.41	2.81	3.07
*p*CA-10	-0.16	103.8	14	195.17	5	5	2	53.96	2594.90	0.24	2.79	3.51
*p*CA-11	0.75	83.6	14	211.24	4	4	2	60.37	1390.64	0.18	2.84	3.43
*p*CA-12	0.33	83.6	13	179.18	4	4	2	52.35	1486.18	0.13	2.76	3.52
*p*CA-13	-0.17	120.8	16	223.18	6	5	3	58.35	4660.08	0.17	3.18	3.65
*p*CA-14	-0.26	109.6	14	194.19	5	6	2	55.90	1561.56	0.19	2.78	3.32
*p*CA-15	0.25	103.8	14	195.17	5	5	2	53.96	3895.28	0.06	2.76	3.90
*p*CA-17	1.34	120.8	16	223.18	6	5	3	58.43	3293.76	0.31	3.14	3.45
*p*CA-18	0.62	109.6	14	194.19	5	6	2	55.98	1700.30	0.21	2.68	3.34
*p*CA-19	0.46	103.8	14	195.17	5	5	2	54.03	2988.02	0.20	2.57	3.61
*p*CA-20	1.37	83.6	14	211.24	4	4	2	60.45	1209.97	0.15	2.75	3.45
*p*CA-21	0.95	83.6	13	179.18	4	4	2	52.43	1725.36	0.10	2.52	3.65
*p*CA-22	0.27	120.8	16	223.18	6	5	3	58.43	4042.58	0.22	3.15	3.57
*p*CA-23	0.18	109.6	14	194.19	5	6	2	55.98	2547.19	0.21	2.74	3.41
*p*CA-26	0.63	120.8	16	223.18	6	5	3	58.35	4249.69	0.12	3.19	3.71
*p*CA-27	0.40	103.8	14	195.17	5	5	2	53.96	3269.95	0.17	2.77	3.63
*p*CA-28	0.42	120.8	16	223.18	6	5	3	58.35	3727.72	0.29	3.22	3.48
*p*CA-29	0.33	109.6	14	194.19	5	6	2	55.90	1575.58	0.27	2.78	3.25
*p*CA-30	0.63	103.8	14	195.17	5	5	2	53.96	2740.69	0.11	2.77	3.69
*p*CA-32	1.08	83.6	14	211.24	4	4	2	60.37	1686.93	0.29	2.80	3.37
*p*CA-33	-0.15	120.8	16	223.18	6	5	3	58.35	1130.79	0.34	3.00	3.22
*p*CA-34	1.36	103.8	14	195.17	5	5	2	53.96	3025.05	0.14	2.68	3.67
*p*CA-35	0.91	83.6	14	211.24	4	4	2	60.37	1382.07	0.33	2.83	3.29
*p*CA-36	0.29	120.8	16	223.18	6	5	3	58.43	2602.22	0.19	2.88	3.54
*p*CA-37	0.42	120.8	16	223.18	6	5	3	58.35	3976.91	0.30	3.16	3.50

*p*CA-38	0.33	109.6	14	194.19	5	6	2	55.90	1703.85	0.28	2.73	3.27
*p*CA-39	0.84	103.8	14	195.17	5	5	2	53.96	3976.80	0.12	2.71	3.76
*p*CA-41	1.02	120.8	16	223.18	6	5	3	58.35	4739.50	0.23	3.09	3.60
*p*CA-42	0.51	109.6	14	194.19	5	6	2	55.90	2311.43	0.29	2.63	3.34
*p*CA-43	0.58	103.8	14	195.17	5	5	2	53.96	3031.54	0.16	2.67	3.65
*p*CA-45	1.10	83.6	13	179.18	4	4	2	52.35	2642.11	0.20	2.49	3.60
*p*CA-46	1.05	120.8	16	223.18	6	5	3	58.35	3836.93	0.13	3.14	3.67
*p*CA-47	0.17	103.8	14	195.17	5	5	2	53.96	2974.43	0.10	2.64	3.75
*p*CA-48	1.08	83.6	14	211.24	4	4	2	60.37	1394.96	0.29	2.76	3.34
*p*CA-50	0.07	109.6	14	194.19	5	6	2	55.90	1596.44	0.42	2.65	3.18
*p*CA-51	0.58	103.8	14	195.17	5	5	2	53.96	3758.90	0.13	2.66	3.74
*p*CA-52	0.82	83.6	14	211.24	4	4	2	60.37	1286.26	0.01	2.71	4.06
*p*CA-53	-0.41	120.8	16	223.18	6	5	3	58.35	1437.49	0.21	2.99	3.25
*p*CA-54	1.10	103.8	14	195.17	5	5	2	53.96	2830.12	0.16	2.68	3.63
*p*CA-55	0.65	83.6	14	211.24	4	4	2	60.37	2082.77	0.33	2.80	3.39
*p*CA-56	-0.16	120.8	16	223.18	6	5	3	58.43	2466.86	0.22	2.92	3.49
*p*CA-57	0.66	83.6	13	179.18	4	4	2	52.35	2492.58	0.13	2.54	3.67
*p*CA-58	0.33	103.8	14	195.17	5	5	2	54.03	2835.99	0.05	2.77	3.87
*p*CA-59	0.71	83.6	14	211.24	4	4	2	60.45	4016.92	0.36	2.77	3.52
*p*CA-60	0.77	103.8	14	195.17	5	5	2	54.03	3774.13	0.22	2.74	3.61
*p*CA-61	1.15	83.6	14	211.24	4	4	2	60.45	1941.66	0.29	2.75	3.41
*p*CA-62	1.00	132.1	18	252.18	7	4	4	60.88	3948.50	0.31	3.29	3.47
*p*CA-63	0.13	115.1	16	224.17	6	4	3	56.48	5361.82	0.26	2.84	3.64
*p*CA-65	0.61	94.8	15	208.17	5	3	3	54.88	1816.17	0.32	2.69	3.38
*p*CA-66	-0.07	132.1	18	252.18	7	4	4	60.88	4067.77	0.32	3.33	3.46
*p*CA-67	0.35	115.1	16	224.17	6	4	3	56.48	4320.82	0.13	2.83	3.74
*p*CA-69	-0.64	132.1	18	252.18	7	4	4	60.88	5184.22	0.34	3.30	3.38
*p*CA-70	0.87	115.1	16	224.17	6	4	3	56.48	3821.94	0.15	2.88	3.68
*p*CA-71	0.43	94.8	16	240.24	5	3	3	62.90	914.82	0.23	3.10	3.24
*p*CA-72	1.49	115.1	16	224.17	6	4	3	56.48	4770.48	0.23	3.12	3.60
*p*CA-73	0.61	98.0	14	196.16	5	4	2	52.09	4846.68	0.17	2.70	3.73
*p*CA-75	1.10	77.8	13	180.16	4	3	2	50.48	4198.64	0.20	2.59	3.68
*p*CA-76	0.42	115.1	16	224.17	6	4	3	56.48	2822.90	0.32	3.15	3.41
*p*CA-77	0.83	98.0	14	196.16	5	4	2	52.09	4128.79	0.03	2.72	4.07
*p*CA-79	1.87	94.8	16	240.24	5	3	3	62.90	5450.55	0.31	3.12	3.56
*p*CA-80	0.99	77.8	14	212.23	4	3	2	58.50	3116.70	0.21	2.70	3.59
*p*CA-81	1.90	57.5	14	228.29	3	2	2	64.92	1188.79	0.10	2.75	3.53
*p*CA-82	1.48	57.5	13	196.23	3	2	2	56.90	2411.47	0.12	2.59	3.67
*p*CA-83	0.80	94.8	16	240.24	5	3	3	62.90	2346.42	0.15	3.15	3.53
*p*CA-84	1.22	77.8	14	212.23	4	3	2	58.50	2450.23	0.26	2.73	3.49
*p*CA-85	1.46	57.5	14	228.29	3	2	2	64.92	1055.18	0.23	2.78	3.32
*p*CA-86	-0.15	115.1	16	224.17	6	4	3	56.48	3850.17	0.41	3.09	3.43
*p*CA-87	1.36	98.0	14	196.16	5	4	2	52.09	3764.27	0.17	2.72	3.67

*p*CA-88	0.91	77.8	14	212.23	4	3	2	58.50	2571.01	0.30	2.97	3.43
*p*CA-89	0.23	94.8	16	240.24	5	3	3	62.90	585.03	0.14	3.11	3.25
*p*CA-90	1.74	77.8	14	212.23	4	3	2	58.50	3542.86	0.33	2.74	3.51
*p*CA-91	1.29	57.5	14	228.29	3	2	2	64.92	1177.96	0.23	3.00	3.31
*p*CA-92	0.57	132.1	18	252.18	7	4	4	60.80	1793.99	0.34	3.36	3.27
*p*CA-93	-0.31	115.1	16	224.17	6	4	3	56.41	4240.79	0.34	2.94	3.51
*p*CA-95	0.18	94.8	15	208.17	5	3	3	54.80	3924.94	0.22	2.89	3.60
*p*CA-96	-0.32	132.1	18	252.18	7	4	4	60.80	1469.86	0.39	3.42	3.19
*p*CA-97	0.10	115.1	16	224.17	6	4	3	56.41	4722.35	0.18	2.89	3.68
*p*CA-99	2.08	115.1	16	224.17	6	4	3	56.41	4177.14	0.17	2.97	3.66
*p*CA-100	1.20	98.0	14	196.16	5	4	2	52.02	1523.23	0.08	2.61	3.66
*p*CA-101	2.11	77.8	14	212.23	4	3	2	58.43	1881.37	0.05	2.67	3.80
*p*CA-103	1.19	115.1	16	224.17	6	4	3	56.41	3583.22	0.19	3.07	3.59
*p*CA-104	1.61	98.0	14	196.16	5	4	2	52.02	4226.62	0.15	2.61	3.74
*p*CA-106	1.63	94.8	16	240.24	5	3	3	62.82	1989.64	0.26	3.18	3.37
*p*CA-107	0.75	77.8	14	212.23	4	3	2	58.43	3532.56	0.43	2.79	3.45
*p*CA-108	1.66	57.5	14	228.29	3	2	2	64.84	775.77	0.32	2.84	3.17
*p*CA-109	1.24	57.5	13	196.23	3	2	2	56.82	4386.52	0.24	2.76	3.62
*p*CA-110	0.74	94.8	16	240.24	5	3	3	62.82	2778.04	0.14	3.18	3.58
*p*CA-111	1.16	77.8	14	212.23	4	3	2	58.43	2589.03	0.32	2.76	3.45
*p*CA-112	1.40	57.5	14	228.29	3	2	2	64.84	1176.44	0.12	2.82	3.48
*p*CA-113	0.25	132.1	18	252.18	7	4	4	60.80	5970.65	0.25	3.32	3.60
*p*CA-114	0.67	115.1	16	224.17	6	4	3	56.41	5399.39	0.48	3.06	3.47
*p*CA-115	1.08	98.0	14	196.16	5	4	2	52.02	4431.22	0.12	2.61	3.80
*p*CA-116	1.32	77.8	14	212.23	4	3	2	58.43	1177.95	0.20	2.68	3.39
*p*CA-119	1.53	132.1	18	252.18	7	4	4	60.80	5891.15	0.14	3.23	3.74
*p*CA-120	1.14	132.1	18	252.18	7	4	4	60.80	5648.01	0.26	3.44	3.57
*p*CA-121	1.56	115.1	16	224.17	6	4	3	56.41	6419.52	0.22	3.04	3.68
*p*CA-123	1.09	115.1	16	224.17	6	4	3	56.41	5492.59	0.34	3.04	3.56
*p*CA-124	0.65	98.0	14	196.16	5	4	2	52.02	4509.95	0.19	2.50	3.72
*p*CA-125	1.33	77.8	14	212.23	4	3	2	58.43	1209.25	0.07	2.68	3.62
*p*CA-126	0.26	115.1	16	224.17	6	4	3	56.41	4070.05	0.35	3.08	3.48
*p*CA-127	0.68	98.0	14	196.16	5	4	2	52.02	5352.51	0.15	2.62	3.79
*p*CA-132	1.58	77.8	14	212.23	4	3	2	58.43	1636.57	0.18	2.74	3.48
*p*CA-134	1.82	94.8	15	208.17	5	3	3	54.80	3968.78	0.22	2.91	3.60
*p*CA-135	0.72	132.1	18	252.18	7	4	4	60.80	5548.99	0.22	3.43	3.60
*p*CA-136	0.93	115.1	16	224.17	6	4	3	56.41	5414.31	0.25	3.08	3.61
*p*CA-138	0.94	77.8	13	180.16	4	3	2	50.41	2708.93	0.26	2.08	3.62
*p*CA-139	0.49	115.1	16	224.17	6	4	3	56.41	3069.89	0.39	3.17	3.38
*p*CA-140	0.70	98.0	14	196.16	5	4	2	52.02	5329.47	0.20	2.69	3.72
*p*CA-142	1.85	57.5	13	196.23	3	2	2	56.82	985.20	0.14	2.51	3.46
*p*CA-144	1.38	77.8	14	212.23	4	3	2	58.43	1627.05	0.31	2.78	3.35
*p*CA-146	0.75	94.8	15	208.17	5	3	3	54.80	3803.33	0.18	2.94	3.63

*p*CA-147	1.17	77.8	13	180.16	4	3	2	50.41	3278.75	0.22	2.43	3.64
*p*CA-148	0.37	118.2	15	212.16	6	5	2	53.70	3191.86	0.11	2.93	3.70
*p*CA-149	0.34	118.2	15	212.16	6	5	2	53.70	4255.61	0.08	2.90	3.84
*p*CA-150	0.56	103.8	15	227.24	5	5	2	61.98	2738.38	0.41	2.92	3.38
*p*CA-151	-0.22	124.0	15	211.17	6	6	2	55.56	5386.84	0.25	2.97	3.50
*p*CA-152	-0.24	124.0	15	211.17	6	6	2	55.56	5304.50	0.20	2.92	3.56
*p*CA-153	0.07	124.0	15	211.17	6	6	2	55.64	4112.59	0.23	2.98	3.46
*p*CA-154	-0.16	124.0	15	211.17	6	6	2	55.64	4615.11	0.26	2.91	3.47
*p*CA-155	0.62	118.2	15	212.16	6	5	2	53.62	3593.19	0.27	2.87	3.54
*p*CA-156	0.62	118.2	15	212.16	6	5	2	53.62	3593.19	0.27	2.87	3.54

Table S3. Elimination scores for the subset of p-coumaric acid derivatives chosen as the most promising, according to SS.

	$S^{E,ADME2}$	$S^{E,ADME8}$	$S^{E,ADMET}$	$S^{E,ADMETSA}$
*p*CA	1.56	5.67	8.55	10.49
*p*CA-5	1.34	7.59	10.50	11.76
*p*CA-7	1.89	8.13	12.10	13.19
*p*CA-15	1.77	8.02	12.70	13.98
*p*CA-52	1.35	6.07	7.79	9.12
*p*CA-58	1.74	7.98	11.43	12.71
*p*CA-77	1.50	7.08	12.14	13.45
*p*CA-101	0.78	4.82	7.13	8.49
*p*CA-115	1.39	6.97	12.09	13.50
*p*CA-127	1.57	7.15	13.27	14.68
*p*CA-149	1.55	8.50	13.54	14.69
Average	1.49	7.09	11.02	12.37

Table S4. Reactivity indexes, their acronyms, calculation method and interpretation.

	Acronym	Calculation*	Interpretation
First (vertical) ionization energy	IE	P3, EPT	Directly related to the capability of donating one electron. The lower the IE the most likely the antioxidant protection, via electron transfer.
First (vertical) electron affinity	EA	P3, EPT	Directly related to the capability of accepting one electron. The higher the EA the most likely the antioxidant protection, by converting $O_2^{\bullet-}$ into $^3O_2$, via electron transfer.
Electrophilicity	ω	$\frac{(IE+EA)^2}{8(IE-EA)}$	In a chemical reaction, involving two molecules, that with the higher ω is expected to act as the electrophile, while the other will behave as the nucleophile.[1,2]
Electrodonating power	ω^-	$\frac{(3IE+EA)^2}{16(IE-EA)}$	Measures the capability of a chemical system to donate a fractional amount of charge. The lower the ω^- the most likely the molecule would act as an electron donor during weak interactions with other species.[3,4]
Electroaccepting power	ω^+	$\frac{(IE+3EA)^2}{16(IE-EA)}$	Measures the capability of a chemical system to accept a fractional amount of charge. The higher the ω^+ the most likely the molecule would act as an electron acceptor during weak interactions with other species.[3,4]
Chemical potential	μ	$-\left(\frac{IE+EA}{2}\right)$	Electrons will flow from regions of high μ to regions of low μ. The number of electrons that flow would be proportional to differences in μ, while the associated stabilization energy would be proportional to its μ^2.
Chemical hardness	η	$\frac{IE-EA}{2}$	Measures the resistance to change in electron number, or to deformation of the electron cloud. It rules the Pearson's hard and soft acids and bases and maximum hardness principles.[5,6]
Bond dissociation energies	BDE	$E(D)+E(H)-E(DH)$	Measures the energy necessary for breaking donor(D)-H bonds. The lower the BDE, the higher the antioxidant activity, via H transfer.

*The expressions for ω, μ and η correspond to the commonly used finite difference approximation.

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Table S5. Pole strength (PS) values for the EPT approximation (P3) used to calculated ionization energies and electron affinities.

	PS (EI)	PS (EA)
Neutral		
*p*CA	0.880	0.972
*p*CA-5	0.882	0.970
*p*CA-7	0.882	0.973
*p*CA-15	0.883	0.970
*p*CA-115	0.881	0.972
*p*CA-127	0.879	0.968
Anionic		
*p*CA	0.882	0.974
*p*CA-5	0.887	0.975
*p*CA-7	0.887	0.975
*p*CA-15	0.885	0.975
*p*CA-52	0.881	0.973
*p*CA-58	0.884	0.974
*p*CA-77	0.884	0.974
*p*CA-101	0.880	0.973
*p*CA-115	0.883	0.974
*p*CA-127	0.881	0.974
*p*CA-149	0.883	0.975
Di-anionic		
*p*CA-5	0.878	0.976
*p*CA-7	0.878	0.976
*p*CA-15	0.879	0.976
*p*CA-52	0.885	0.974
*p*CA-58	0.878	0.975
*p*CA-77	0.879	0.974
*p*CA-101	0.885	0.973
*p*CA-115	0.880	0.975
*p*CA-127	0.879	0.975
*p*CA-149	0.880	0.975

Table S6. Equations concerning SS construction.

$$S^{S} = S^{ADME} + S^{T} + S^{SA}$$

where

$$S^{ADME} = \frac{S^{logP} + S^{HB^{D}} + S^{HB^{A}} + S^{MW} + S^{{}^{M}R} + S^{{}^{X}A} + S^{RB} + S^{PSA}}{8}$$

$$S^{T} = \frac{S^{LD_{50}} + S^{M}}{2}$$

with

$$S^{logP} = \begin{cases} 1, & \text{if } -0.4 \leq logP \leq 5.0 \\ 0, & \text{otherwise} \end{cases} \qquad S^{HB^{D}} = \begin{cases} 1, & \text{if } HB^{D} \leq 5 \\ 0, & \text{otherwise} \end{cases}$$

$$S^{HB^{A}} = \begin{cases} 1, & \text{if } HB^{A} \leq 10 \\ 0, & \text{otherwise} \end{cases} \qquad S^{MW} = \begin{cases} 1, & \text{if } 160 \leq MW \leq 480 \\ 0, & \text{otherwise} \end{cases}$$

$$S^{{}^{M}R} = \begin{cases} 1, & \text{if } 40 \leq {}^{M}R \leq 130 \\ 0, & \text{otherwise} \end{cases} \qquad S^{{}^{X}A} = \begin{cases} 1, & \text{if } {}^{X}A \leq 70 \\ 0, & \text{otherwise} \end{cases}$$

$$S^{RB} = \begin{cases} 1, & \text{if } RB \leq 10 \\ 0, & \text{otherwise} \end{cases} \qquad S^{PSA} = \begin{cases} 1, & \text{if } PSA \leq 140 \\ 0, & \text{otherwise} \end{cases}$$

$$S^{LD_{50}} = 1 + \log\left(\frac{LD_{50}{}^{dM}}{LD_{50}{}^{\overline{RefSet}}}\right) \qquad S^{M} = 1 + \log\left(\frac{M^{\overline{RefSet}}}{M^{dM}}\right) \qquad S^{SA} = 1 + \log\left(\frac{SA^{\overline{RefSet}}}{SA^{dM}}\right)$$

Table S7. Exclusion scores (S^E) equations.

$$S^{E,ADME2} = \left| \frac{\log P_{\overline{RefSet}} - \log P_{dM}}{SD_{\log P}} \right| + \left| \frac{MW_{\overline{RefSet}} - MW_{dM}}{SD_{MW}} \right|$$

$$S^{E,ADME8} = S^{E,ADME2} + \left| \frac{PSA_{\overline{RefSet}} - PSA_{dM}}{SD_{PSA}} \right| + \left| \frac{{}^{X}A_{\overline{RefSet}} - {}^{X}A_{dM}}{SD_{{}^{X}A}} \right| + \left| \frac{{HB^{A}}_{\overline{RefSet}} - {HB^{A}}_{dM}}{SD_{HB^{A}}} \right| + \left| \frac{{HB^{D}}_{\overline{RefSet}} - {HB^{D}}_{dM}}{SD_{HB^{D}}} \right| + \left| \frac{RB_{\overline{RefSet}} - RB_{dM}}{SD_{RB}} \right| + \left| \frac{{}^{M}R_{\overline{RefSet}} - {}^{M}R_{dM}}{SD_{{}^{M}R}} \right|$$

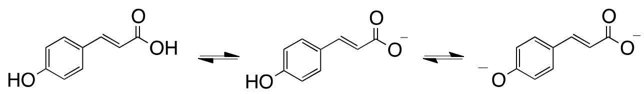
$$S^{E,ADMET} = S^{E,ADME8} + \left| \frac{LD_{50\,\overline{RefSet}} - LD_{50\,dM}}{SD_{LD_{50}}} \right| + \left| \frac{M_{\overline{RefSet}} - M_{dM}}{SD_{M}} \right|$$

$$S^{E,ADMETSA} = S^{E,ADMET} + \left| \frac{SA_{\overline{RefSet}} - SA_{dM}}{SD_{SA}} \right|$$

Table S8. Zero-point bond dissociation energies (BDE, in kcal/mol) for p-coumaric acid and its derivatives.

	1O	R_1	R_2	R_3	R_4	R_5	R_6
Neutral							
CA	87.02	-	-	-	-	-	-
CA-5	90.42	-	-	-	-	95.10 (OH)	-
CA-7	89.05	-	-	-	-	-	70.88 (OH)
CA-15	88.62	-	-	-	87.55 (OH)	-	-
CA-115	88.31	88.65 (OH)	-	-	88.84 (OH)	-	-
CA-127	80.12	81.75 (OH)	-	79.39 (OH)	-	-	-
Anionic							
CA	84.42	-	-	-	-	-	-
CA-5	74.64	-	-	-	-	70.88 (OH)	-
CA-7	79.01	-	-	-	-	-	68.68 (OH)
CA-15	87.53	-	-	-	86.83 (OH)	-	-
CA-52	85.66	78.66 (SH)	-	-	-	-	-
CA-58	79.59	-	-	-	-	-	77.49 (OH)
CA-77	80.26	81.25 (OH)	-	-	-	-	78.89 (OH)
CA-101	82.30	-	74.47 (SH)	-	-	90.81 (OH)	-
CA-115	85.00	86.51 (OH)	-	-	86.50 (OH)	-	-
CA-127	77.69	79.98 (OH)	-	77.88 (OH)	-	-	-
CA-149	74.44	76.75 (OH)	-	76.13 (OH)	-	-	78.18 (OH)
Di-anionic							
CA-5	-	-	-	-	-	69.65 (OH)	-
CA-7	-	-	-	-	-	-	67.01 (OH)
CA-15	-	-	-	-	81.15 (OH)	-	-
CA-52	81.12	-	-	-	-	-	-
CA-58	-	-	-	-	-	-	70.51 (OH)
CA-77	74.42	-	-	-	-	-	72.46 (OH)
CA-101	76.94	-	-	-	-	90.99 (OH)	-
CA-115	80.74	81.08 (OH)	-	-	-	-	-
CA-127	-	73.02 (OH)	-	73.23 (OH)	-	-	-
CA-149	-	69.89 (OH)	-	71.37 (OH)	-	-	70.82 (OH)

CA



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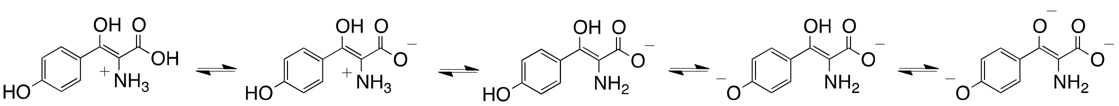

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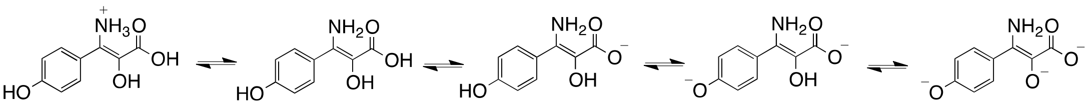

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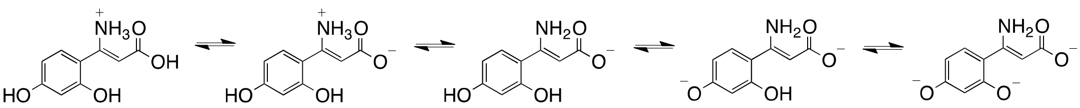

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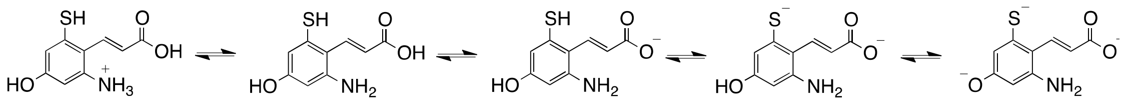

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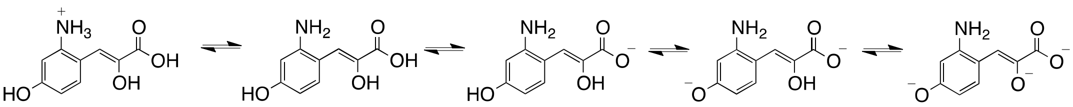

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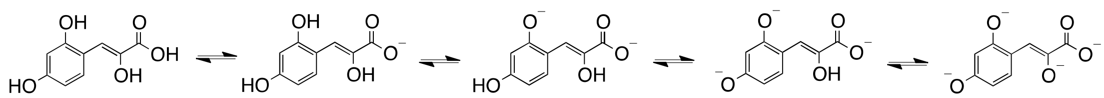

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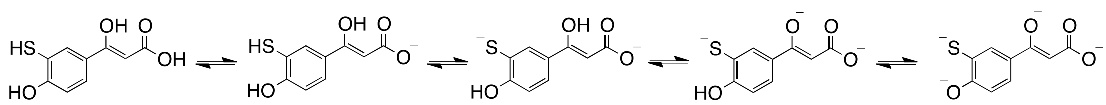

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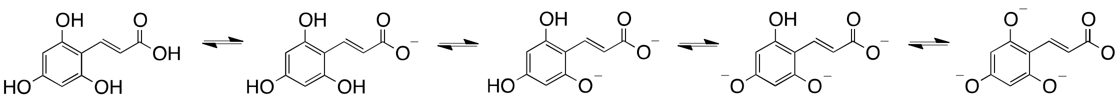
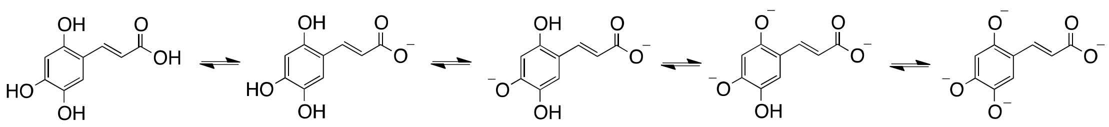


Figure S1. Deprotonation routes for the subset of p-coumaric acid derivatives chosen as the most promising, from their drug-like behavior (Part 1).

CA-127



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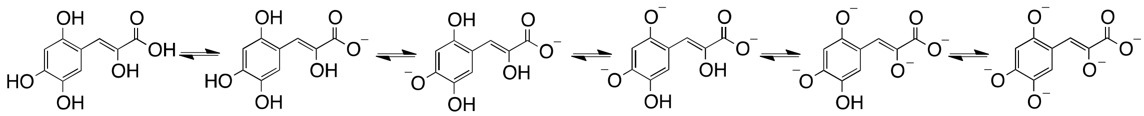

Figure S1 (cont…). Deprotonation routes for the subset of p-coumaric acid derivatives chosen as the most promising, from their drug-like behavior.

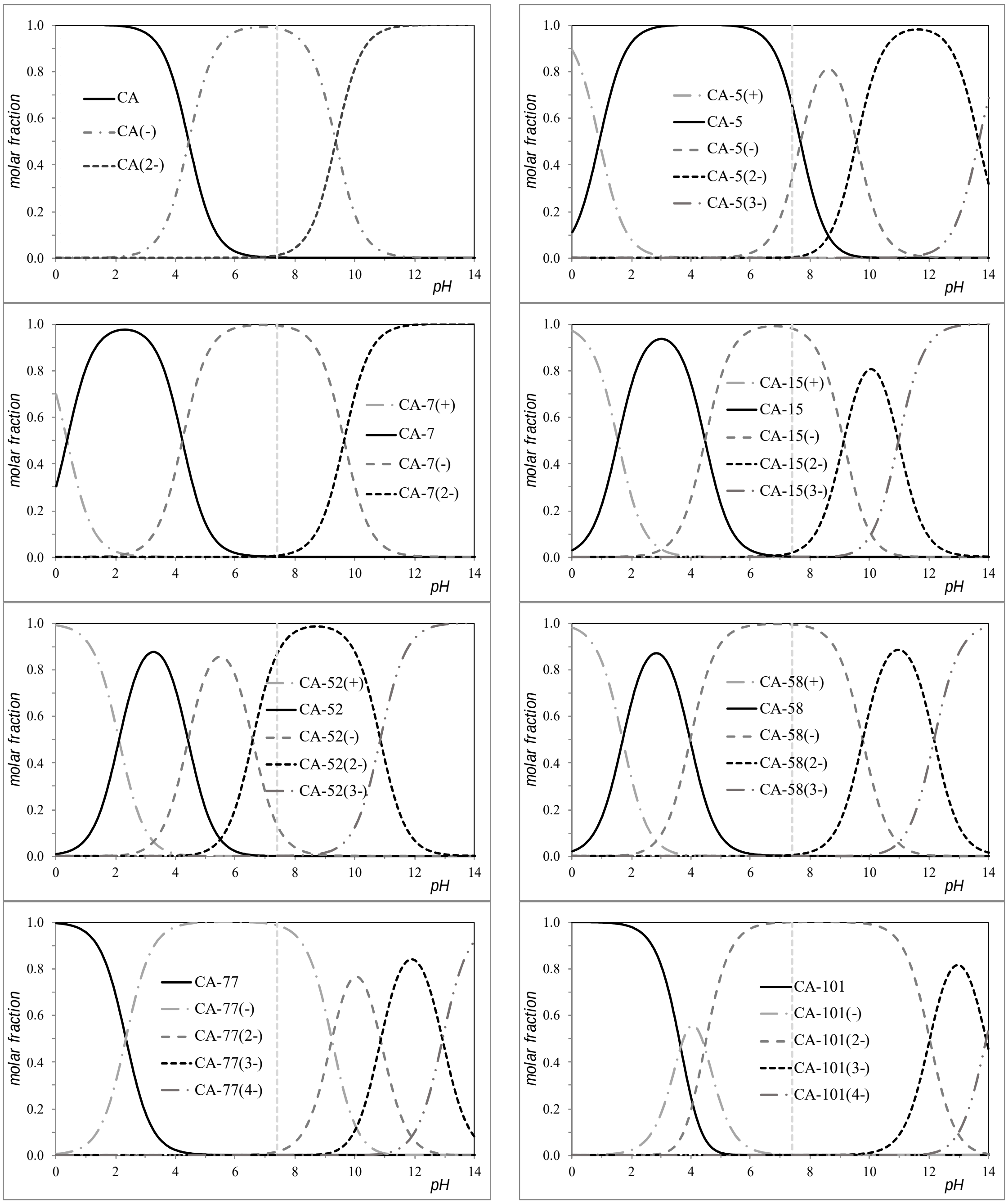

Figure S2. Distribution diagram of the acid-base species of p-coumaric acid derivatives. The vertical line landmarks the physiological pH (pH=7.4). (Part 1).

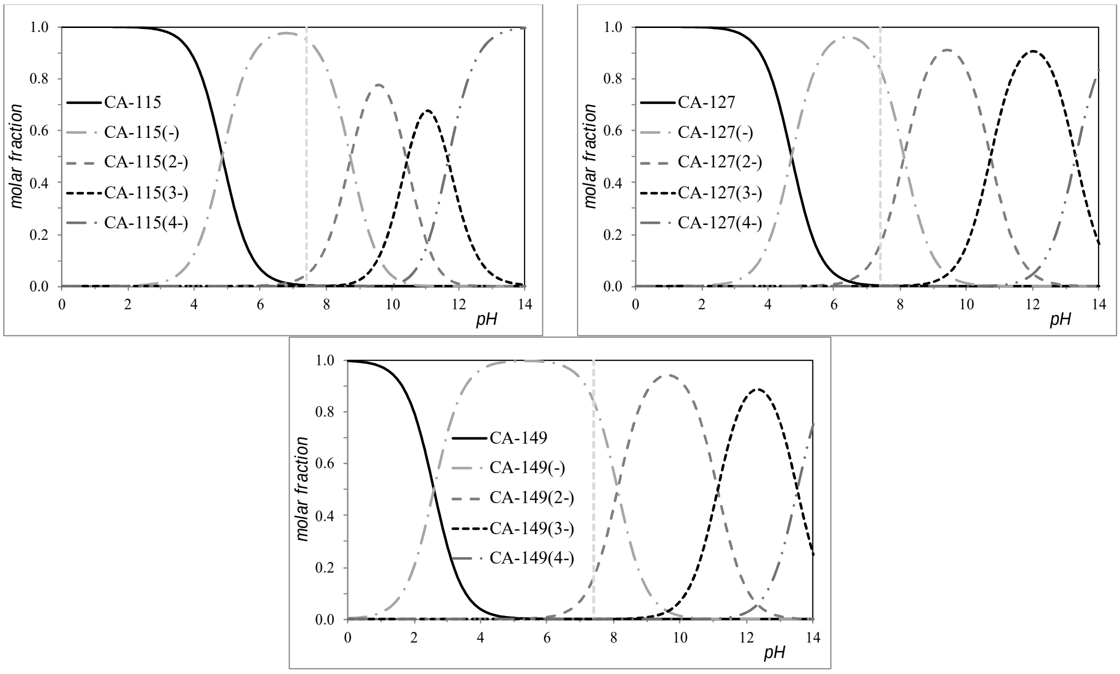

Figure S2 (cont…). Distribution diagram of the acid-base species of *p*-coumaric acid derivatives. The vertical line landmarks the physiological pH (pH=7.4).

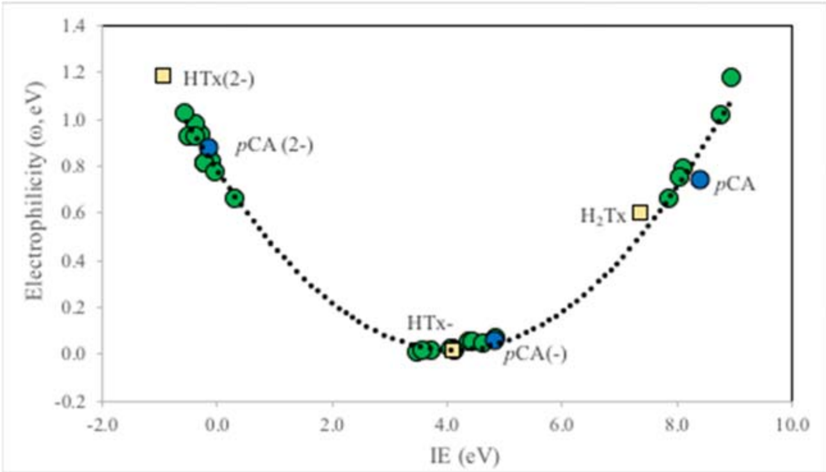

Figure S3. Non-linear dependence of the electrophilicity with the ionization energy, for p-coumaric acid derivatives.