Supporting Information

A Computer-Assisted Systematic Search for Melatonin Derivatives with High Potential as Antioxidants

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Running Title: New melatonin-derivatives with antioxidant potential.

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Table S1. Pole strength (PS) values for the EPT approximation (P3) used to calculated ionization energies and electron affinities.

	PS (EI)	PS (EA)
Protonated		
dM-10	0.880	0.963
dM-11	0.881	0.968
dM-81	0.880	0.965
Neutral		
Melatonin	0.879	0.975
dM-3	0.881	0.975
dM-6	0.883	0.974
dM-7	0.882	0.974
dM-8	0.881	0.974
dM-10	0.881	0.975
dM-11	0.881	0.975
dM-34	0.880	0.972
dM-38	0.881	0.975
dM-61	0.879	0.975
dM-72	0.878	0.971
dM-81	0.881	0.975
dM-114	0.879	0.975
dM-115	0.881	0.975
Anionic		
dM-3	0.879	0.978
dM-6	0.885	0.976
dM-7	0.884	0.978
dM-8	0.885	0.979
dM-34	0.885	0.980
dM-38	0.886	0.979
dM-61	0.886	0.979
dM-64	0.881	0.979
dM-72	0.877	0.977
dM-81	0.880	0.980
dM-92	0.876	0.982

dM-94	0.877	0.982
dM-104	0.877	0.977
dM-114	0.884	0.978
dM-115	0.887	0.978
Di-anionic		
dM-64	0.885	0.982
dM-92	0.877	0.980
dM-94	0.881	0.983
dM-96	0.875	0.983
dM-100	0.875	0.983
dM-104	0.877	0.982
dM-112	0.878	0.982
dM-115	0.883	0.983

Table S2. Estimated ADME properties for the reference set of molecules. Partition coefficient octanol/water (LogP), polar surface area (PSA), number of non-hydrogen atoms (^{X}At), molecular weight (MW), H bond acceptors (HB^{A}), H bond donors (HB^{D}), rotatable bonds (RB), molar refractivity (^{M}R).

	LogP	PSA	^{X}At	MW	HB^{A}	HB^{D}	RB	^{M}R
Acetylcarnitine	-5.33	66.43	14	203.24	5	0	6	197.76
Amantadine	2.65	26.02	11	151.25	1	2	0	159.20
Apomorphine	2.89	43.69	20	267.33	3	2	0	246.38
Baclofen	-0.42	63.32	14	213.66	3	3	4	186.30
Benserazide	-2.22	148.06	18	257.25	8	8	5	221.62
Benztropine	4.27	12.47	23	307.44	2	0	4	306.62
Biperiden	4.44	23.47	23	311.47	2	1	5	317.94
Bromocriptine	3.61	118.21	43	654.61	10	3	5	546.41
Cabergoline	3.44	71.67	33	451.62	7	2	8	442.37
Carbidopa	-2.82	115.81	16	226.23	6	6	4	200.64
Curcumin	3.05	96.22	27	368.39	6	3	7	331.83
Dantrolene	1.75	120.74	23	314.26	9	1	4	252.73
Donepezil	4.10	38.78	28	379.50	4	0	6	367.90
Entacapone	1.64	130.38	22	305.29	8	2	5	266.18
Galantamine	1.54	41.93	21	287.36	4	1	1	268.19
Ladostigil	2.08	41.57	20	272.35	4	1	5	265.77
L-DOPA	-2.20	103.78	14	197.19	5	5	3	172.00
Lisuride	3.16	51.37	25	338.46	5	2	3	326.25
Masitinib	4.55	73.39	36	498.66	7	2	7	456.31
Melatonin	1.45	54.12	17	232.28	4	2	4	220.12
Memantine	2.77	26.02	13	179.31	1	2	0	191.67
Modafinil	1.22	60.17	19	273.36	3	2	5	245.03
Piribedil	1.93	50.73	22	298.35	6	0	3	269.80
Pramipexole	2.09	50.94	14	211.33	3	3	3	200.85
Procyclidine	4.33	23.47	21	287.45	2	1	5	301.31
Remacemide	2.56	55.12	20	268.36	3	3	5	264.80
Riluzole	2.92	48.15	15	234.20	3	2	2	166.16
Rivastigmine	2.28	32.78	18	250.34	4	0	5	254.01

Ropinirole	3.03	32.34	19	260.38	3	1	7	268.11
Selegiline	2.64	3.24	14	187.29	1	0	4	202.64
Tacrine	3.05	38.92	15	198.27	2	2	0	191.53
Tetrabenazine	2.86	38.78	23	317.43	4	0	4	312.83
Tizanidine	2.03	62.20	16	253.72	5	2	2	194.80
Tolcapone	2.99	103.35	20	273.24	6	2	3	230.37
Trihexyphenidyl	4.83	23.47	22	301.47	2	1	5	318.12
Average	2.09	59.75	21	286.64	4	2	4	267.56
Maximum	4.83	148.06	43	654.61	10	8	8	546.41
Minimum	-5.33	3.24	11	151.25	1	0	0	159.20
SD*	2.23	36.14	6.740	96.57	2.3	1.7	2.1	85.94

* Standard deviation.

Table S3. Estimated toxicity, expressed as LD_{50} and Ames mutagenicity (M); and synthetic accessibility (SA) for the reference set of molecules.

	LD_{50}	M	SA
Acetylcarnitine	3082.83	NA	3.33
Amantadine	437.53	0.29 (–)	2.81
Apomorphine	436.08	1.03 (+)	4.41
Baclofen	391.53	0.09 (–)	2.85
Benserazide	1787.30	0.77 (+)	4.07
Benztropine	551.15	0.21 (-)	4.68
Biperiden	523.61	0.00 (–)	5.63
Bromocriptine	44.98	-0.10 (–)	6.96
Cabergoline	581.87	0.63 (+)	6.76
Carbidopa	1917.02	0.59 (+)	3.65
Curcumin	1144.30	0.05 (–)	3.99
Dantrolene	680.21	0.72 (+)	3.77
Donepezil	390.45	0.28 (–)	5.02
Entacapone	1168.63	0.95 (+)	3.76
Galantamine	471.43	0.42 (–)	5.76
Ladostigil	251.93	0.27 (–)	4.65
L-DOPA	3205.31	0.31 (–)	2.83
Lisuride	227.35	0.75 (+)	5.98
Masitinib	1393.72	0.57 (+)	4.05
Melatonin	1298.11	0.05 (–)	2.46
Memantine	564.23	0.11 (–)	5.28
Modafinil	2358.41	0.45 (–)	3.41
Piribedil	572.13	0.01 (–)	3.51
Pramipexole	1739.75	0.60 (–)	4.70
Procyclidine	442.97	0.16 (–)	4.14
Remacemide	922.71	0.12 (–)	4.17
Riluzole	218.42	0.81(+)	3.41
Rivastigmine	287.67	0.66(+)	4.27
Ropinirole	916.27	0.39 (–)	3.58

Selegiline	403.04	0.50 (–)	3.75
Tacrine	1060.16	0.89 (+)	2.55
Tetrabenazine	526.51	0.33 (–)	4.11
Tizanidine	386.25	0.26 (–)	4.01
Tolcapone	2742.17	0.47 (–)	3.14
Trihexyphenidyl	500.94	0.38 (–)	4.21
Average	960.77	0.41 (–)	4.16
Maximum	3205.31	1.03 (+)	6.96
Minimum	44.98	-0.10 (–)	2.46
SD*	836.37	0.30	1.09

* Standard deviation.

Table S4. Melatonin derivatives designed in this work.

Label	R_1	R_2	R_3	R_4
Melatonin	H	H	H	H
dM-1	H	H	H	OH
dM-2	OH	H	H	H
dM-3	H	OH	H	H
dM-4	H	H	OH	H
dM-5	H	H	H	SH
dM-6	SH	H	H	H
dM-7	H	SH	H	H
dM-8	H	H	SH	H
dM-9	H	H	H	NH_2
dM-10	NH_2	H	H	H
dM-11	H	NH_2	H	H
dM-12	H	H	NH_2	H
dM-13	H	H	H	COOH
dM-14	COOH	H	H	H
dM-15	H	COOH	H	H
dM-16	H	H	COOH	H
dM-17	OH	H	H	OH
dM-18	SH	H	H	OH
dM-19	NH_2	H	H	OH
dM-20	COOH	H	H	OH
dM-21	H	OH	H	OH
dM-22	H	SH	H	OH
dM-23	H	NH_2	H	OH
dM-24	H	COOH	H	OH
dM-25	H	H	OH	OH
dM-26	H	H	SH	OH
dM-27	H	H	NH_2	OH
dM-28	H	H	COOH	OH
dM-29	OH	OH	H	H

dM-30	OH	SH	H	H
dM-31	OH	NH_2	H	H
dM-32	OH	COOH	H	H
dM-33	OH	H	OH	H
dM-34	OH	H	SH	H
dM-35	OH	H	NH2	H
dM-36	OH	H	COOH	H
dM-37	H	OH	OH	H
dM-38	H	OH	SH	H
dM-39	H	OH	NH_2	H
dM-40	H	OH	COOH	H
dM-41	OH	H	H	SH
dM-42	SH	H	H	SH
dM-43	NH_2	H	H	SH
dM-44	COOH	H	H	SH
dM-45	H	OH	H	SH
dM-46	H	SH	H	SH
dM-47	H	NH_2	H	SH
dM-48	H	COOH	H	SH
dM-49	H	H	OH	SH
dM-50	H	H	SH	SH
dM-51	H	H	NH_2	SH
dM-52	H	H	COOH	SH
dM-53	SH	OH	H	H
dM-54	SH	SH	H	H
dM-55	SH	NH_2	H	H
dM-56	SH	COOH	H	H
dM-57	SH	H	OH	H
dM-58	SH	H	SH	H
dM-59	SH	H	NH_2	H
dM-60	SH	H	COOH	H
dM-61	H	SH	OH	H

dM-62	H	SH	SH	H
dM-63	H	SH	NH_2	H
dM-64	H	SH	COOH	H
dM-65	OH	H	H	NH_2
dM-66	SH	H	H	NH_2
dM-67	NH_2	H	H	NH_2
dM-68	COOH	H	H	NH_2
dM-69	H	OH	H	NH_2
dM-70	H	SH	H	NH_2
dM-71	H	NH_2	H	NH_2
dM-72	H	COOH	H	NH_2
dM-73	H	H	OH	NH_2
dM-74	H	H	SH	NH_2
dM-75	H	H	NH_2	NH_2
dM-76	H	H	COOH	NH_2
dM-77	NH_2	OH	H	H
dM-78	NH_2	SH	H	H
dM-79	NH_2	NH_2	H	H
dM-80	NH_2	COOH	H	H
dM-81	NH_2	H	OH	H
dM-82	NH_2	H	SH	H
dM-83	NH_2	H	NH_2	H
dM-84	NH_2	H	COOH	H
dM-85	H	NH2	OH	H
dM-86	H	NH_2	SH	H
dM-87	H	NH_2	NH_2	H
dM-88	H	NH_2	COOH	H
dM-89	OH	H	H	COOH
dM-90	SH	H	H	COOH
dM-91	NH_2	H	H	COOH
dM-92	COOH	H	H	COOH
dM-93	H	OH	H	COOH

dM-94	H	SH	H	COOH
dM-95	H	NH_2	H	COOH
dM-96	H	COOH	H	COOH
dM-97	H	H	OH	COOH
dM-98	H	H	SH	COOH
dM-99	H	H	NH_2	COOH
dM-100	H	H	COOH	COOH
dM-101	COOH	OH	H	H
dM-102	COOH	SH	H	H
dM-103	COOH	NH_2	H	H
dM-104	COOH	COOH	H	H
dM-105	COOH	H	OH	H
dM-106	COOH	H	SH	H
dM-107	COOH	H	NH_2	H
dM-108	COOH	H	COOH	H
dM-109	H	COOH	OH	H
dM-110	H	COOH	SH	H
dM-111	H	COOH	NH_2	H
dM-112	H	COOH	COOH	H
dM-113	OH	SH	COOH	H
dM-114	OH	SH	OH	H
dM-115	OH	OH	SH	H
dM-116	COOH	COOH	OH	H

Table S5. Values of the ADME properties, toxicity and synthetic accessibility for the designed melatonin derivatives

	logP	PSA	^{x}A	MW	HB^{A}	HB^{D}	RB	^{M}R	LD_{50}	M	SA
Melatonin	1.45	54.12	17	232.28	4	2	4	69.38	1298.11	0.05(-)	2.46
dM-1	1.35	74.35	18	248.28	5	3	4	70.45	1091.26	0.17(-)	3.73
dM-2	0.96	74.35	18	248.28	5	3	4	70.98	1509.78	0.19(-)	3.71
dM-3	0.73	74.35	18	248.28	5	3	4	70.98	1405.53	0.12(-)	3.70
dM-4	1.16	74.35	18	248.28	5	3	4	70.98	1293.03	0.20(-)	3.65
dM-5	1.96	54.12	18	264.35	4	2	4	76.87	1518.87	-0.02(-)	3.74
dM-6	1.60	54.12	18	264.35	4	2	4	77.40	952.29	0.00(-)	3.74
dM-7	1.60	54.12	18	264.35	4	2	4	77.40	863.07	0.00(-)	3.74
dM-8	1.60	54.12	18	264.35	4	2	4	77.40	530.67	0.00(-)	3.74
dM-9	1.05	80.15	18	247.30	5	4	4	72.40	2401.95	0.30(-)	3.73
dM-10	0.86	80.15	18	247.30	5	4	4	72.93	1415.00	0.12(-)	3.72
dM-11	0.86	80.15	18	247.30	5	4	4	72.93	1309.70	0.03(-)	3.71
dM-12	0.86	80.15	18	247.30	5	4	4	72.93	1455.54	0.15(-)	3.70
dM-13	1.26	91.42	20	276.29	6	3	5	76.68	540.19	0.19(-)	3.93
dM-14	0.95	91.42	20	276.29	6	3	5	75.38	418.14	0.18(-)	4.02
dM-15	1.37	91.42	20	276.29	6	3	5	75.38	2743.45	0.4(-)	4.01
dM-16	0.95	91.42	20	276.29	6	3	5	75.38	1161.83	0.18(-)	3.98
dM-17	0.86	94.58	19	264.28	6	4	4	72.06	1951.83	0.32(-)	3.81
dM-18	1.51	74.35	19	280.35	5	3	4	78.47	959.36	0.11(-)	3.84
dM-19	0.76	100.37	19	263.30	6	5	4	74.00	1629.65	0.34(-)	3.82
dM-20	0.85	111.65	21	292.29	7	4	5	76.45	392.33	0.23(-)	4.11
dM-21	0.63	94.58	19	264.28	6	4	4	72.06	1592.29	0.15(-)	3.80
dM-22	1.51	74.35	19	280.35	5	3	4	78.47	747.02	0.09(-)	3.84
dM-23	0.76	100.37	19	263.30	6	5	4	74.00	1940.61	0.41(-)	3.81
dM-24	1.27	111.65	21	292.29	7	4	5	76.45	610.27	0.31(-)	4.11
dM-25	1.06	94.58	19	264.28	6	4	4	72.06	955.98	0.38(-)	3.79
dM-26	1.51	74.35	19	280.35	5	3	4	78.47	1443.42	0.16(-)	3.84
dM-27	0.76	100.37	19	263.30	6	5	4	74.00	1615.78	0.20(-)	3.81
dM-28	0.85	111.65	21	292.29	7	4	5	76.45	645.32	0.21(-)	4.07
dM-29	0.64	94.58	19	264.28	6	4	4	72.59	1026.78	0.27(-)	3.78
dM-30	1.31	74.35	19	280.35	5	3	4	79.00	461.57	0.13(-)	3.82
dM-31	0.57	100.37	19	263.30	6	5	4	74.53	1432.71	0.31(-)	3.79

dM-32	1.08	111.65	21	292.29	7	4	5	76.98	1045.89	0.19(-)	4.09
dM-33	0.67	94.58	19	264.28	6	4	4	72.59	1137.47	0.23(-)	3.77
dM-34	1.12	74.35	19	280.35	5	3	4	79.00	1622.24	0.13(-)	3.82
dM-35	0.37	100.37	19	263.30	6	5	4	74.53	1337.40	0.24(-)	3.78
dM-36	0.46	111.65	21	292.29	7	4	5	76.98	887.65	0.26(-)	4.05
dM-37	0.67	94.58	19	264.28	6	4	4	72.59	921.29	0.34(-)	3.78
dM-38	1.12	74.35	19	280.35	5	3	4	79.00	664.47	0.02(-)	3.81
dM-39	0.37	100.37	19	263.30	6	5	4	74.53	1801.88	0.28(-)	3.78
dM-40	0.46	111.65	21	292.29	7	4	5	76.98	1947.08	0.38(-)	4.05
dM-41	1.47	74.35	19	280.35	5	3	4	78.47	475.98	0.07(-)	3.82
dM-42	2.12	54.12	19	296.42	4	2	4	84.89	995.19	N/A	3.85
dM-43	1.37	80.15	19	279.37	5	4	4	80.42	1300.56	0.57 (+)	3.83
dM-44	1.46	91.42	21	308.36	6	3	5	82.87	685.57	-0.12 (-)	4.12
dM-45	1.25	74.35	19	280.35	5	3	4	78.47	1554.43	-0.09 (-)	3.81
dM-46	2.12	54.12	19	296.42	4	2	4	84.89	879.34	N/A	3.85
dM-47	1.37	80.15	19	279.37	5	4	4	80.42	1204.46	0.26 (-)	3.82
dM-48	1.88	91.42	21	308.36	6	3	5	82.87	1703.84	-0.12 (-)	4.12
dM-49	1.67	74.35	19	280.35	5	3	4	78.47	849.35	-0.03 (-)	3.80
dM-50	2.12	54.12	19	296.42	4	2	4	84.89	1305.53	N/A	3.85
dM-51	1.37	80.15	19	279.37	5	4	4	80.42	565.71	0.36(-)	3.81
dM-52	1.46	91.42	21	308.36	6	3	5	82.87	2223.78	-0.27(-)	4.08
dM-53	1.08	74.35	19	280.35	5	3	4	79.00	1787.60	-0.03(-)	3.81
dM-54	1.76	54.12	19	296.42	4	2	4	85.42	2143.48	N/A	3.85
dM-55	1.01	80.15	19	279.37	5	4	4	80.95	1103.09	0.42(-)	3.82
dM-56	1.52	91.42	21	308.36	6	3	5	83.40	2012.85	-0.20(-)	4.12
dM-57	1.31	74.35	19	280.35	5	3	4	79.00	2555.44	-0.03(-)	3.80
dM-58	1.76	54.12	19	296.42	4	2	4	85.42	1962.93	N/A	3.85
dM-59	1.01	80.15	19	279.37	5	4	4	80.95	966.50	0.31(-)	3.82
dM-60	1.10	91.42	21	308.36	6	3	5	83.40	2122.54	-0.21(-)	4.08
dM-61	1.31	74.35	19	280.35	5	3	4	79.00	862.81	0.02(-)	3.80
dM-62	1.76	54.12	19	296.42	4	2	4	85.42	990.00	N/A	3.85
dM-63	1.01	80.15	19	279.37	5	4	4	80.95	1268.87	0.37(-)	3.82
dM-64	1.10	91.42	21	308.36	6	3	5	83.40	1660.68	0.01(-)	4.08
dM-65	0.56	100.37	19	263.30	6	5	4	74.00	2163.83	0.21(-)	3.81

dM-66	1.21	80.15	19	279.37	5	4	4	80.42	1051.73	0.50(-)	3.84
dM-67	0.46	106.17	19	262.31	6	6	4	75.95	1996.82	0.39(-)	3.82
dM-68	0.55	117.45	21	291.31	7	5	5	78.40	1588.32	0.21(-)	4.11
dM-69	0.34	100.37	19	263.30	6	5	4	74.00	1347.03	0.27(-)	3.80
dM-70	1.21	80.15	19	279.37	5	4	4	80.42	1639.15	0.26(-)	3.84
dM-71	0.46	106.17	19	262.31	6	6	4	75.95	1307.64	0.39(-)	3.81
dM-72	0.97	117.45	21	291.31	7	5	5	78.40	2892.93	0.22(-)	4.11
dM-73	0.76	100.37	19	263.30	6	5	4	74.00	1748.03	0.19(-)	3.79
dM-74	1.21	80.15	19	279.37	5	4	4	80.42	1110.11	0.47(-)	3.84
dM-75	0.46	106.17	19	262.31	6	6	4	75.95	1915.40	0.40(-)	3.80
dM-76	0.55	117.45	21	291.31	7	5	5	78.40	860.88	0.29(-)	4.07
dM-77	0.34	100.37	19	263.30	6	5	4	74.53	1678.55	0.31(-)	3.79
dM-78	1.01	80.15	19	279.37	5	4	4	80.95	794.36	0.44(-)	3.83
dM-79	0.27	106.17	19	262.31	6	6	4	76.48	1418.52	0.34(-)	3.80
dM-80	0.78	117.45	21	291.31	7	5	5	78.93	2561.37	0.36(-)	4.10
dM-81	0.57	100.37	19	263.30	6	5	4	74.53	2039.07	0.17(-)	3.78
dM-82	1.01	80.15	19	279.37	5	4	4	80.95	1640.45	0.59(+)	3.83
dM-83	0.27	106.17	19	262.31	6	6	4	76.48	1553.96	0.35(-)	3.79
dM-84	0.36	117.45	21	291.31	7	5	5	78.93	986.33	0.08(-)	4.06
dM-85	0.57	100.37	19	263.30	6	5	4	74.53	1947.22	0.24(-)	3.78
dM-86	1.01	80.15	19	279.37	5	4	4	80.95	689.06	0.57(+)	3.82
dM-87	0.27	106.17	19	262.31	6	6	4	76.48	2246.48	0.33(-)	3.80
dM-88	0.36	117.45	21	291.31	7	5	5	78.93	797.88	0.17(-)	4.06
dM-89	0.77	111.65	21	292.29	7	4	5	78.29	408.80	0.15(-)	4.01
dM-90	1.42	91.42	21	308.36	6	3	5	84.70	710.80	0.06(-)	4.04
dM-91	0.67	117.45	21	291.31	7	5	5	80.23	430.93	0.16(-)	4.02
dM-92	0.76	128.72	23	320.30	8	4	6	82.68	2093.23	0.11(-)	4.22
dM-93	0.54	111.65	21	292.29	7	4	5	78.29	405.71	0.28(-)	4.00
dM-94	1.42	91.42	21	308.36	6	3	5	84.70	2399.65	0.18(-)	4.04
dM-95	0.67	117.45	21	291.31	7	5	5	80.23	600.66	0.24(-)	4.01
dM-96	1.18	128.72	23	320.30	8	4	6	82.68	4733.46	0.3(-)	4.29
dM-97	0.97	111.65	21	292.29	7	4	5	78.29	439.32	0.15(-)	3.99
dM-98	1.42	91.42	21	308.36	6	3	5	84.70	753.65	0.06(-)	4.04
dM-99	0.67	117.45	21	291.31	7	5	5	80.23	477.68	0.19(-)	4.01

dM-100	0.76	128.72	23	320.30	8	4	6	82.68	2303.16	0.13(-)	4.26
dM-101	0.43	111.65	21	292.29	7	4	5	76.98	885.91	0.30(-)	4.08
dM-102	1.10	91.42	21	308.36	6	3	5	83.40	1067.96	-0.13(-)	4.12
dM-103	0.36	117.45	21	291.31	7	5	5	78.93	943.15	0.23(-)	4.09
dM-104	0.87	128.72	23	320.30	8	4	6	81.38	6960.49	0.26(-)	4.29
dM-105	0.66	111.65	21	292.29	7	4	5	76.98	315.55	0.37(-)	4.07
dM-106	1.10	91.42	21	308.36	6	3	5	83.40	3633.05	-0.14(-)	4.12
dM-107	0.36	117.45	21	291.31	7	5	5	78.93	512.86	0.25(-)	4.09
dM-108	0.45	128.72	23	320.30	8	4	6	81.38	2693.87	0.2(-)	4.28
dM-109	0.66	111.65	21	292.29	7	4	5	76.98	1201.18	0.25(-)	4.08
dM-110	1.10	91.42	21	308.36	6	3	5	83.40	2189.77	-0.10(-)	4.12
dM-111	0.36	117.45	21	291.31	7	5	5	78.93	805.52	0.35(-)	4.09
dM-112	0.45	128.72	23	320.30	8	4	6	81.38	2861.76	0.16(-)	4.28
dM-113	0.81	111.65	22	324.36	7	4	5	85.00	1035.58	0.28(-)	4.15
dM-114	1.02	94.58	20	296.35	6	4	4	80.61	1511.46	0.09(-)	3.88
dM-115	1.02	94.58	20	296.35	6	4	4	80.61	2072.78	0.10(-)	3.89
dM-116	0.16	148.95	24	336.30	9	5	6	82.98	2194.63	0.11(-)	4.35

Table S6. Elimination scores for the subset of melatonin derivatives chosen as the most promising, according to S^S.

	$S^{E,ADME2}$	$S^{E,ADME8}$	$S^{E,ADMET}$	$S^{E,ADMETSA}$
melatonin	0.85	2.20	3.81	5.36
dM-3	1.01	3.14	4.64	5.06
dM-6	0.45	1.36	2.74	3.12
dM-7	0.45	1.36	2.85	3.23
dM-8	0.45	1.36	3.24	3.63
dM-10	0.96	3.76	5.28	5.68
dM-11	0.96	3.76	5.45	5.86
dM-34	0.50	2.20	3.92	4.23
dM-38	0.50	2.20	3.85	4.18
dM-61	0.41	2.11	3.53	3.86
dM-64	0.67	3.51	5.68	5.76
dM-72	0.55	5.80	8.75	8.80
dM-81	0.93	5.09	7.19	7.53
dM-92	0.95	7.02	9.38	9.43
dM-94	0.53	3.42	5.91	6.02
dM-96	0.76	6.83	11.71	11.83
dM-100	0.95	7.02	9.56	9.65
dM-104	0.90	6.99	14.66	14.78
dM-112	1.09	7.17	10.28	10.39
dM-114	0.58	3.64	5.37	5.62
dM-115	0.58	3.64	6.01	6.25

Table S7. Zero-point bond dissociation energies (BDE, in kcal/mol) for melatonin and its derivatives.

	a	***b***	***c***	***d***	**R_1**	**R_2**	**R_3**
Protonated							
dM-10	98.57	90.48	95.76	96.84	-	-	-
dM-11	99.12	89.45	96.44	97.22	-	-	-
dM-81	98.6	91.84	97.16	96.84	-	-	80.62 (OH)
Neutral							
MEL	98.04	89.33	96.55	97.11	-	-	-
dM-3	98.09	86.4	92.37	97.2	-	77.76 (OH)	-
dM-6	97.37	87.74	94.06	97.02	74.33 (SH)	-	-
dM-7	98.32	88.29	95.51	97.36	-	73.24 (SH)	-
dM-8	98.27	89.41	96.78	97.19	-	-	73.46 (SH)
dM-10	96.68	86.75	92.78	97.31	-	-	-
dM-11	97.74	88.18	96.55	97.15	-	-	-
dM-34	97.53	85.54	91.68	96.26	72.53 (OH)	66.68 (SH)	-
dM-38	98.86	88.36	96.64	96.96	-	75.46 (OH)	71.51 (SH)
dM-61	98.48	89.68	96.56	97.24	-	69.14 (SH)	76.01 (OH)
dM-72	98.36	89.15	97.21	97.3	-	-	-
dM-81	97.07	91.25	95.9	103.86	-	-	63.65 (OH)
dM-114	97.49	93.37	96.44	97.41	76.42 (OH)	68.32 (SH)	69.56 (OH)
dM-115	98.24	93.91	93.9	97.06	76.88 (OH)	76.54 (OH)	67.54 (SH)
Anionic							
dM-3	97.04	87.37	91.92	101.45	-	-	-
dM-6	96.13	84.91	91.39	103.69	-	-	-
dM-7	96.68	87.48	95.93	101.64	-	-	-
dM-8	97.84	88.56	95.95	108.11	-	-	-
dM-34	96.75	85.99	92.55	100.09	61.8 (OH)	-	-
dM-38	98.07	88.46	95.6	105.12	-	68.31 (OH)	-
dM-61	96.92	86.25	96.46	103.98	-	-	70.75 (OH)
dM-64	98.4	89.36	93.23	97.16	-	78.19 (SH)	-
dM-72	97.52	88.21	92.71	97.4	-	-	-
dM-81	96.08	90.55	95.77	87.86	-	-	-
dM-92	97.68	93.98	97.14	96.66	-	-	-

dM-94	98.49	88.5	90.66	97.03	73.87 (SH)	-	-
dM-104	97.38	90.17	97.44	97.09	-	-	-
dM-114	96.7	88.61	96.06	95.14	69.83 (OH)	-	70.19 (OH)
dM-115	97.6	89.46	93.79	89.04	63.09 (OH)	66.16 (OH)	-
Dianionic							
dM-64	96.92	88.35	96.64	101.47	-	-	-
dM-92	97.03	88.16	95.14	96.92	-	-	-
dM-94	96.64	87.70	93.21	103.39	-	-	-
dM-96	97.83	88.83	97.25	97.07	-	-	-
dM-100	97.96	88.81	93.38	97.11	-	-	-
dM-104	96.65	85.91	90.50	97.12	-	-	-
dM-112	97.65	89.13	92.84	97.07	-	-	-
dM-115	96.83	85.35	115.18	86.73	-	59.50 (OH)	-

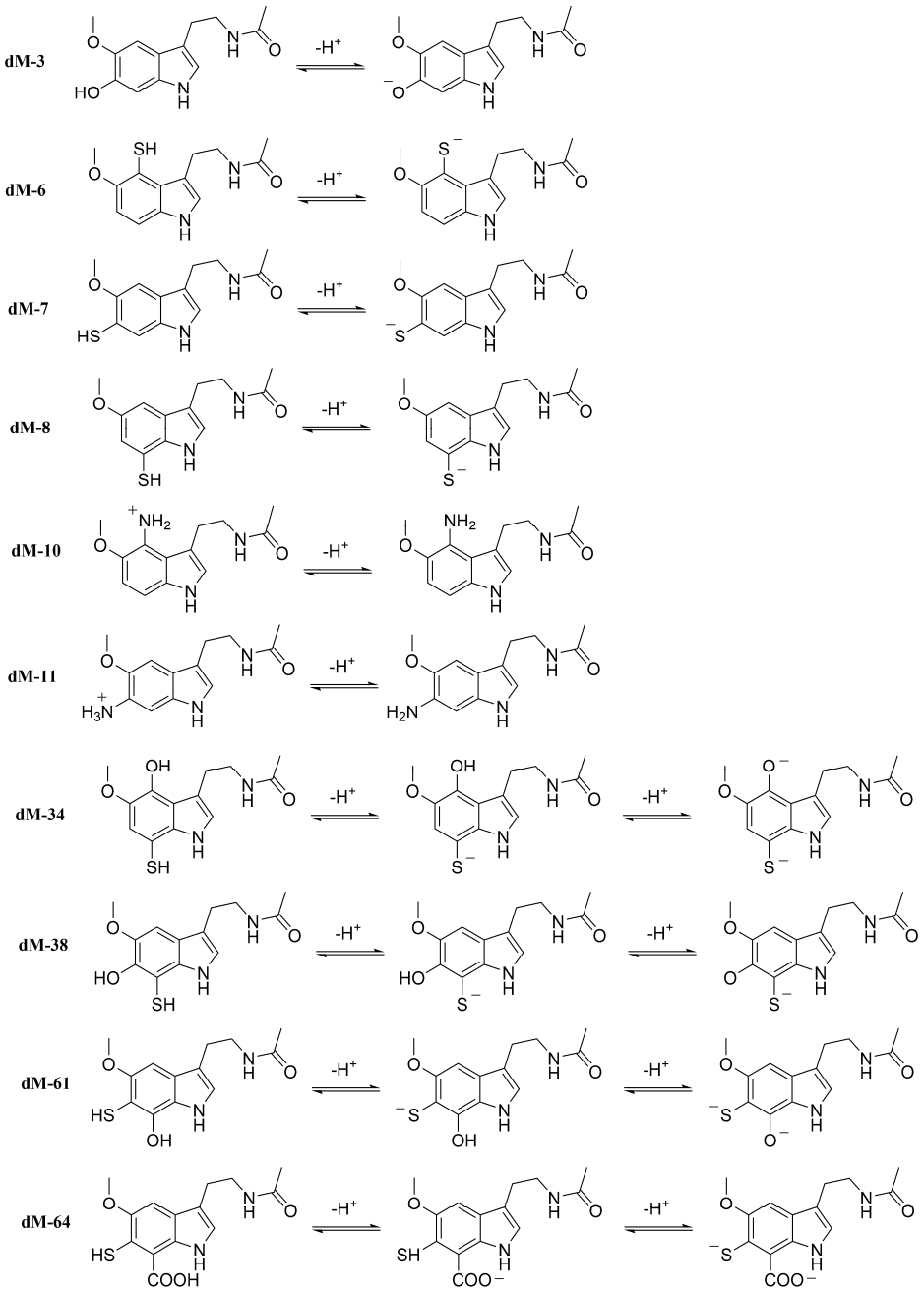

Figure S1. Deprotonation routes for the subset of melatonin derivatives chosen as the most promising, from their drug-lile behavior (Part 1).

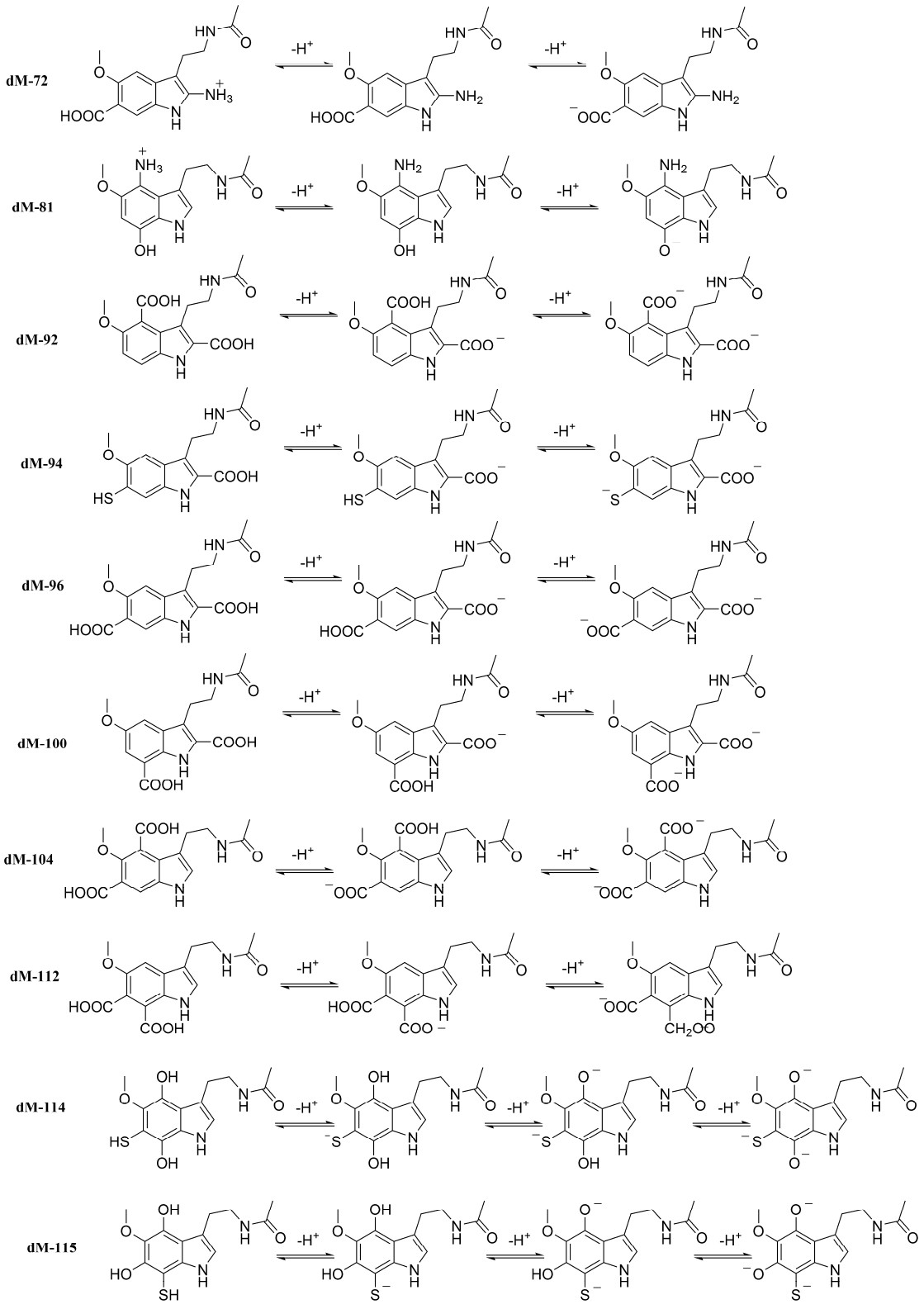

Figure S1. Deprotonation routes for the subset of melatonin derivatives chosen as the most promising, from their drug-lile behavior (Part 2).

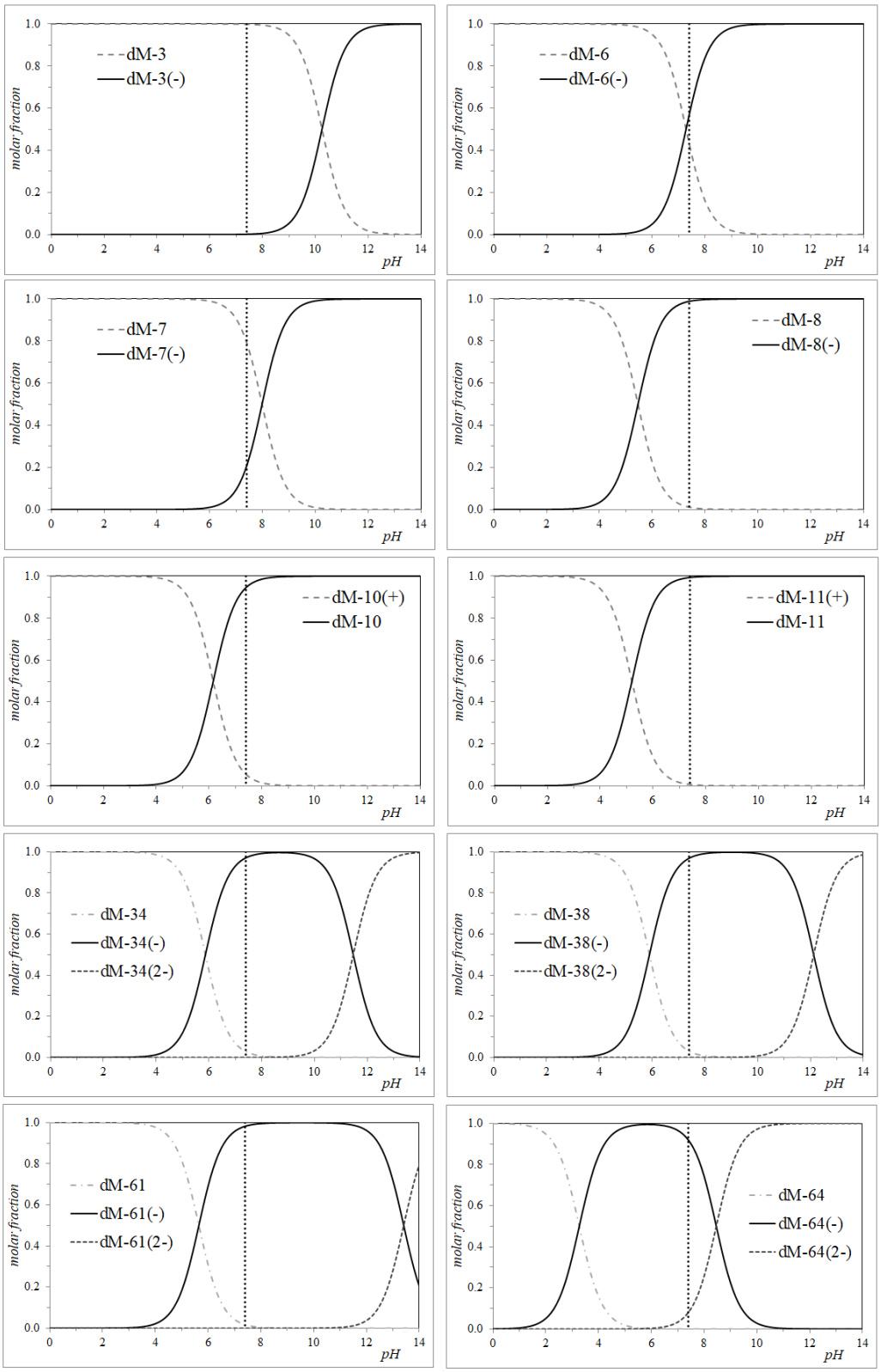

Figure S2. Distribution diagram of the acid-base species of melatonin derivatives. The vertical line landmarks the physiological pH (pH=7.4). (Part 1).

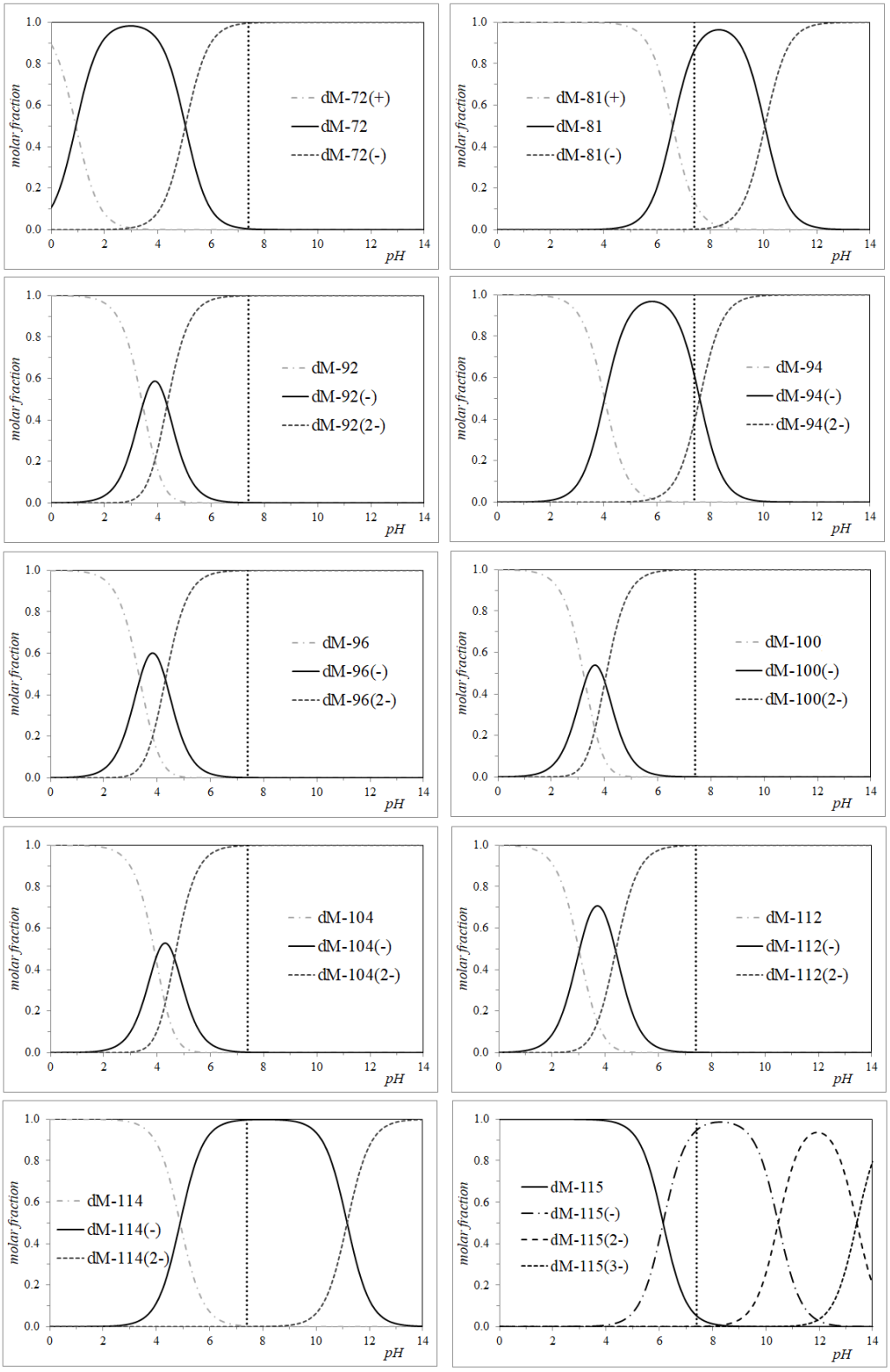

Figure S2. Distribution diagram of the acid-base species of melatonin derivatives. The vertical line landmarks the physiological pH (pH=7.4). (Part 2).

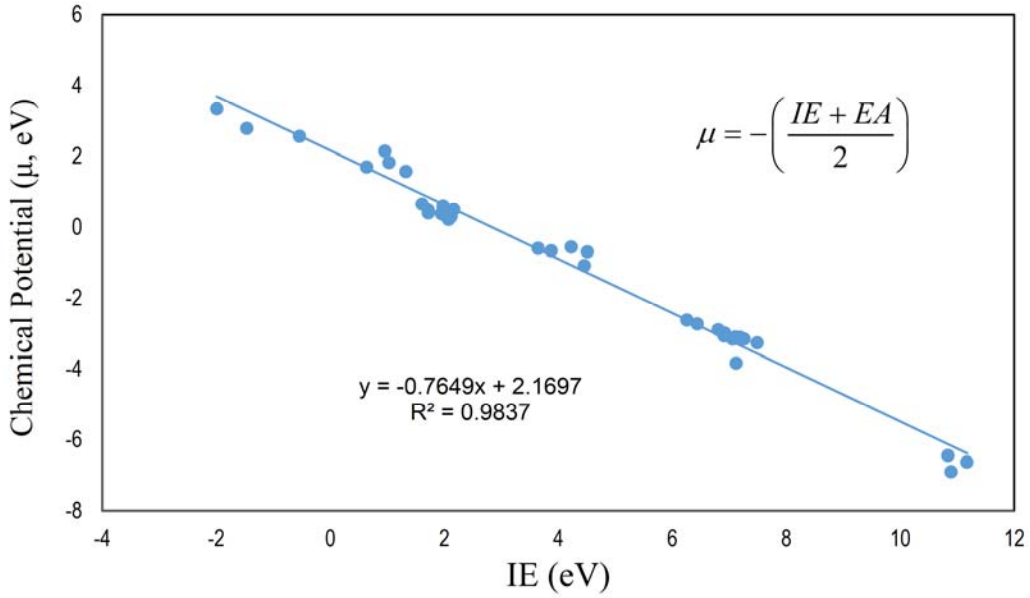

Figure S3. Linear dependence of the chemical potential with the ionization energy, for melatonin derivatives.

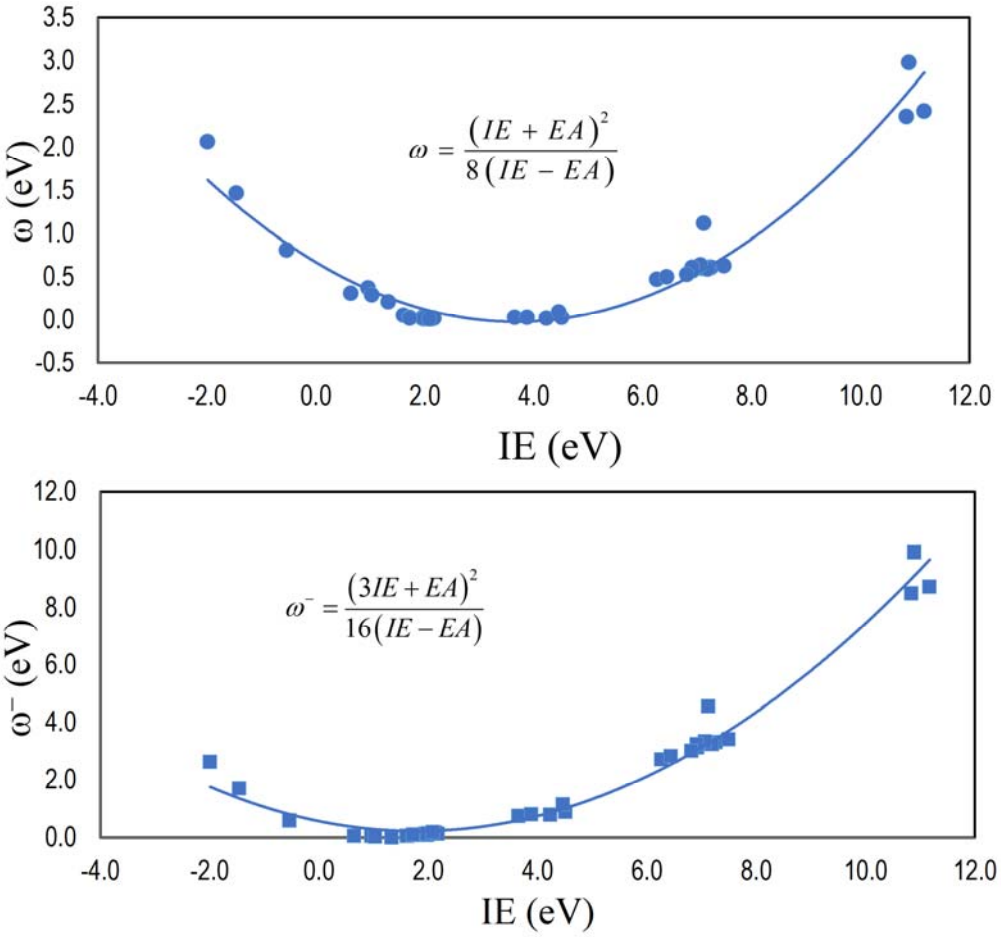

Figure S4. Non-linear dependences of the electrophilicity (ω) and electrodaonating power (ω^-) with the ionization energy, for melatonin derivatives.