Supporting Information for

Aldehyde Oxidase: Reaction Mechanism and Prediction of Site of Metabolism

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Definitions. In Table S1-S1, *BS1* corresponds to energies determined with the BS1 basis set; *BS2* corresponds to energies determined with the BS2 basis set; *ZPE* includes zero-point vibrational energy corrections at BS1 level in addition to BS2 energies; $\varepsilon = 4$ and $\varepsilon = 80$ includes solvent corrections in addition to BS2 and ZPE corrections.

Table S6. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for quinazoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S7. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for phthalazine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S8. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for quinoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S9. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for 2-amino-9-methylpurine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S10. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for 4-methylacridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S11. B3LYP (A) and B3LYP-D3 (B) transition state energies (kJ/mol) and distances (Å) for a concerted reaction (Fig. 1, Reaction 1) for phenanthridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

Table S12. Fast methods to predict the site of metabolism for quinazoline (A), 2-amino-9-methylpurine (B), 4-methylacridine (C), phenanhtridine (D), phthalazine (E) and quinoline (F). All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the sum of the MoCo and substrate energies.

Figure S1. Reaction mechanisms of 4-quinazolinones (A) and negatively charged xanthine (B). studied in this work.

Figure S2. Reactions for formation of 1) the products, 2) the hydroxylated tetrahedral intermediate, and 3) the cation intermediate.

Figure S3. Transition state energies versus estimates of the reactivity based on DFT calculated properties. The correlation coefficients R^2 are given in Table 2.

Figure S4. Distribution of transition state energies and reactivity based on DFT calculated properties. Red bars show the values for the SOMs and blue for the other aromatic C atoms.

Table S1-A. B3LYP transition state energies (kJ/mol) and distances (Å) for the concerted reaction (Fig. 1, Reaction 1) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
NO_2	React. Compl	-84.9	-73.5	-70.3	-21.4	3.4	1.96	3.22	1.10	3.38
	TS	73.8	100.4	93.3	142.1	165.7	2.19	1.45	1.43	1.57
	Prod. Compl	-27.8	-8.4	-11.5	28.8	49.0	4.08	1.33	5.61	1.36
	MoCo + Prod.	48.8	58.3	55.1	54.9	55.3	-		-	
CF_3	React. Compl	-74.4	-63.6	-60.6	-16.8	4.8	1.95	3.21	1.10	3.34
	TS	90.1	117.0	109.4	152.1	172.0	2.18	1.46	1.41	1.58
	Prod. Compl	-10.2	13.0	10.5	42.7	57.8	2.67	1.34	3.82	1.36
	MoCo + Prod.	50.2	59.6	56.4	56.5	57.2	-		-	
Cl	React. Compl	-69.8	-58.4	-55.4	-15.8	3.6	1.95	3.31	1.10	3.45
	TS	100.2	127.4	119.8	157.6	174.8	2.18	1.47	1.40	1.59
	Prod. Compl	-4.3	19.2	17.4	44.6	57.0	2.59	1.35	3.78	1.36
	MoCo + Prod.	52.2	61.5	58.2	58.3	105.6	-		-	
H	React. Compl	-61.9	-49.8	-47.2	-11.8	5.2	1.95	3.24	1.10	3.57
	TS	108.4	136.3	128.6	161.9	176.7	2.17	1.48	1.39	1.60
	Prod. Compl	1.6	25.8	24.1	47.4	57.6	2.59	1.35	3.78	1.36
	MoCo + Prod.	51.9	61.1	57.9	88.6	105.5	-		-	
CH_3	React. Compl	-60.4	-48.9	-46.0	-11.6	4.5	1.95	3.26	1.10	3.39
	TS	111.7	140.4	132.1	164.3	178.0	2.17	1.48	1.38	1.61
	Prod. Compl	5.1	29.6	27.6	49.8	59.7	2.57	1.35	3.77	1.36
	MoCo + Prod.	52.7	62.0	58.7	59.1	61.6	-		-	
OCH_3	React. Compl	-57.9	-46.0	-43.1	-10.2	5.1	1.95	3.36	1.10	3.53
	TS	115.9	143.8	135.6	166.0	178.4	2.17	1.48	1.38	1.61
	Prod. Compl	7.8	31.9	30.1	50.9	59.7	2.57	1.35	3.77	1.36
	MoCo + Prod.	54.6	63.8	60.4	60.8	61.6	-		-	
NH_2	React. Compl	-53.5	-43.5	-40.4	-9.7	4.2	1.95	3.34	1.10	3.45
	TS	122.0	148.2	140.7	167.7	177.5	2.17	1.49	1.37	1.61
	Prod. Compl	12.1	35.0	34.0	52.4	59.7	2.54	1.35	3.76	1.36
	MoCo + Prod.	56.1	64.9	61.7	62.3	63.2	-		-	

Table S1-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for the concerted reaction (Fig. 1, Reaction 1) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
NO_2	React. Compl	-106.5	-92.8	-89.0	-39.8	-14.9	1.96	3.31	1.10	3.56
	TS	48.4	74.8	67.8	116.9	140.9	2.19	1.45	1.42	1.58
	Prod. Compl	-50.4	-28.2	-30.2	12.3	33.8	3.65	1.33	5.55	1.36
	MoCo + Prod.	49.6	58.9	55.5	55.4	55.4				
CF_3	React. Compl	-96.3	-82.7	-79.0	-35.4	-13.8	1.96	3.33	1.10	3.58
	TS	65.1	91.7	84.2	127.3	147.5	2.18	1.46	1.40	1.59
	Prod. Compl	-34.1	-10.8	-12.7	19.5	34.6	2.60	1.34	3.83	1.36
	MoCo + Prod.	51.0	60.3	56.9	57.2	57.2				
Cl	React. Compl	-90.1	-76.3	-72.7	-33.2	-13.9	1.96	3.33	1.10	3.62
	TS	75.3	102.3	94.8	133.1	150.6	2.18	1.47	1.39	1.60
	Prod. Compl	-27.1	-3.4	-5.3	22.4	35.0	2.57	1.34	3.78	1.36
	MoCo + Prod.	53.0	62.1	58.6	59.1	59.1				
H	React. Compl	-73.7	-65.2	-63.0	-29.4	-13.5	1.94	2.92	1.09	2.94
	TS	83.7	111.5	103.8	137.7	152.8	2.17	1.48	1.38	1.61
	Prod. Compl	-21.0	3.2	1.6	24.9	35.1	2.54	1.35	3.76	1.36
	MoCo + Prod.	52.7	61.8	58.4	59.3	59.3				
CH_3	React. Compl	-80.3	-65.9	-62.4	-28.5	-12.6	1.95	3.36	1.10	3.57
	TS	86.9	115.0	107.2	139.8	153.8	2.17	1.48	1.37	1.61
	Prod. Compl	-17.5	7.2	5.1	27.4	36.7	2.54	1.35	3.75	1.36
	MoCo + Prod.	53.5	62.7	59.2	60.1	60.1				
OCH_3	React. Compl	-77.4	-63.3	-60.0	-27.5	-12.4	1.96	3.33	1.10	3.61
	TS	91.2	119.0	110.9	141.7	154.4	2.17	1.48	1.37	1.62
	Prod. Compl	-14.8	9.4	7.6	28.4	37.1	2.53	1.35	3.75	1.36
	MoCo + Prod.	55.4	64.5	60.9	61.7	61.7				
NH_2	React. Compl	-72.7	-60.3	-56.3	-26.2	-12.7	1.95	3.37	1.10	3.54
	TS	97.4	123.4	115.9	143.5	153.6	2.17	1.49	1.36	1.62
	Prod. Compl	-10.5	12.5	11.4	30.0	37.3	2.52	1.35	3.74	1.36
	MoCo + Prod.	56.9	65.6	62.1	63.4	63.4				

Table S2-A. B3LYP transition state energies (kJ/mol) and distances (Å) for the concerted reaction with deprotonated MoCo (Fig. 1, Reaction 2) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
NO_2	React. Compl	-200.8	184.1	-185.7	-90.8	-28.3	1.74	3.06	1.10	3.58
	TS	-171.2	-140.9	-150.6	-24.4	60.8	1.97	1.35	1.33	1.71
	Prod. Compl	-295.8	-268.0	-271.6	-125.6	-66.4	2.14	1.26	3.29	1.36
CF_3	React. Compl	-173.2	-157.4	-159.2	-81.4	-24.2	1.74	3.02	1.11	3.54
	TS	-122.4	-91.3	-102.3	8.3	82.9	1.97	1.36	1.32	1.73
	Prod. Compl	-254.1	-226.4	-230.8	-125.6	-53.8	2.17	1.26	3.22	1.36
Cl	React. Compl	-162.1	-146.2	-147.4	-78.5	-25.6	1.74	3.04	1.10	3.55
	TS	-95.0	-63.4	-73.7	24.1	92.0	1.96	1.37	1.31	1.75
	Prod. Compl	-231.8	-203.8	-208.1	-114.7	-48.7	2.17	1.26	3.29	1.36
H	React. Compl	-146.6	-129.5	-130.5	-70.5	-22.9	1.74	3.06	1.10	3.56
	TS	-70.0	-36.6	-46.9	39.4	100.2	1.96	1.38	1.29	1.78
	Prod. Compl	-210.0	-180.6	-185.4	-102.7	-43.3	2.17	1.26	3.26	1.36
CH_3	React. Compl	-143.3	-125.8	-126.8	-69.6	-24.2	1.74	3.06	1.10	3.56
	TS	-64.4	-29.6	-40.9	44.4	103.4	1.96	1.38	1.30	1.77
	Prod. Compl	-204.4	-173.9	-179.3	-97.8	-39.8	2.17	1.26	3.28	1.36
OCH_3	React. Compl	-138.9	-122.0	-123.2	-68.6	-23.4	1.74	3.06	1.10	3.55
	TS	-56.9	-23.1	-34.3	48.3	107.0	1.96	1.38	1.29	1.77
	Prod. Compl	-198.0	-168.3	-173.5	-94.9	-37.1	2.18	1.26	3.41	1.36
NH_2	React. Compl	-130.4	-116.2	-116.4	-66.3	-24.1	1.74	3.07	1.10	3.57
	TS	-42.7	-13.2	-23.4	55.4	111.6	1.96	1.38	1.29	1.77
	Prod. Compl	-185.3	-159.5	-163.8	-88.6	-33.1	2.17	1.26	3.25	1.36

Table S2-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for the concerted reaction with deprotonated MoCo (Fig. 1, Reaction 2) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
NO_2	React. Compl	-217.7	-201.1	-202.6	-107.3	-44.4	1.74	3.02	1.10	3.61
	TS	-191.7	-161.9	-170.9	-43.9	41.6	1.97	1.36	1.32	1.73
	Prod. Compl	-314.4	-287.4	-291.1	-168.4	-87.0	2.13	1.26	3.15	1.36
CF_3	React. Compl	-190.3	-174.4	-176.1	-97.8	-40.4	1.74	2.99	1.10	3.57
	TS	-143.0	-112.3	-122.7	-11.9	62.7	1.97	1.37	1.31	1.75
	Prod. Compl	-186.8	-159.8	-164.2	-59.7	11.7	2.17	1.26	3.24	1.36
Cl	React. Compl	-179.1	-163.1	-164.3	-94.7	-41.5	1.74	3.00	1.10	3.58
	TS	-115.7	-84.6	-94.6	3.0	70.8	1.96	1.37	1.30	1.76
	Prod. Compl	-250.6	-223.1	-227.3	-134.3	-68.6	2.17	1.26	3.19	1.36
H	React. Compl	-159.2	-145.2	-146.8	-88.2	-41.9	1.74	2.97	1.10	3.27
	TS	-90.7	-57.7	-67.8	18.4	79.1	1.96	1.38	1.29	1.78
	Prod. Compl	-228.9	-200.0	-204.6	-122.3	-63.2	2.17	1.26	3.20	1.36
CH_3	React. Compl	-160.0	-142.4	-143.5	-85.7	-40.0	1.74	3.02	1.10	3.57
	TS	-85.2	-50.8	-61.8	23.5	82.5	1.96	1.38	1.29	1.77
	Prod. Compl	-224.4	-194.6	-199.5	-118.6	-61.1	2.17	1.26	3.13	1.36
OCH_3	React. Compl	-155.5	-138.7	-139.9	-85.0	-39.6	1.74	3.03	1.10	3.57
	TS	-77.6	-44.1	-54.9	28.0	86.8	1.96	1.38	1.29	1.79
	Prod. Compl	-216.6	-187.7	-192.9	-114.6	-57.0	2.17	1.26	3.11	1.36
NH_2	React. Compl	-147.0	-132.9	-133.0	-82.3	-39.8	1.74	3.03	1.10	3.60
	TS	-63.4	-34.2	-43.9	34.9	91.0	1.96	1.39	1.29	1.78
	Prod. Compl	-204.1	-178.8	-183.0	-108.4	-53.1	2.17	1.26	3.16	1.36

Table S3-A. B3LYP transition state energies (kJ/mol) and distances (Å) for initial proton transfer and a subsequent concerted reaction with deprotonated MoCo (Fig. 1, Reaction 3) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O_1	Mo – O_2	H_{Moco}-O_1	H_{Moco}– N	O_2 – C	C – H_{Sub}	H_{Sub} – S
NO_2	R	-56.0	-40.3	-35.0	-8.0	5.9	1.92	1.71	0.98	2.02	3.03	1.10	1.92
	TS-1	9.4	37.5	36.0	85.6	110.9	1.84	1.82	1.08	1.50	1.71	1.10	3.12
	Int-1	-88.2	-58.2	-46.3	2.3	27.4	1.70	1.98	2.26	1.02	1.39	1.11	2.87
	TS-2	-16.1	17.6	13.8	53.8	72.1	1.70	2.03	2.28	1.02	1.30	1.48	1.59
	P	-107.2	-75.7	-75.3	-49.4	-40.1	1.72	2.23	1.65	1.06	1.23	3.51	1.36
CF_3	R	-49.2	-33.3	-27.9	-6.3	4.5	1.92	1.71	0.98	2.00	3.08	1.10	2.70
	TS-1	25.4	53.7	49.1	86.6	104.7	1.83	1.82	1.14	1.36	1.79	1.10	3.26
	Int-1	-72.6	-42.6	-31.1	12.0	34.0	1.70	1.97	2.30	1.02	1.39	1.11	2.86
	TS-2	-1.4	32.6	28.7	63.6	79.0	1.70	2.04	2.21	1.02	1.31	1.46	1.61
	P	-95.1	-63.7	-63.3	-45.2	-38.2	1.72	2.26	1.63	1.06	1.24	3.48	1.36
Cl	R	-44.5	-28.4	-23.1	-5.0	4.0	1.92	1.71	0.98	1.99	3.10	1.10	2.73
	TS-1	31.9	59.2	56.1	75.2	83.0	1.81	1.80	1.28	1.21	1.97	1.09	3.00
	Int-1	-60.7	-30.3	-18.8	20.3	40.1	1.70	1.97	2.32	1.02	1.40	1.11	2.86
	TS-2	8.3	42.4	38.0	66.1	77.7	1.69	2.03	2.46	1.02	1.31	1.47	1.60
	P	-87.7	-56.4	-55.9	-41.7	-36.6	1.73	2.26	1.63	1.06	1.24	3.39	1.36
H	R	-39.5	-22.5	-17.1	-3.8	2.5	1.92	1.71	0.98	1.96	3.13	1.10	2.75
	TS-1	36.9	63.9	62.6	70.5	71.9	1.80	1.79	1.35	1.16	2.04	1.09	2.93

	Int-1	-53.0	-21.8	-10.5	24.1	41.5	1.70	1.97	2.34	1.02	1.40	1.11	2.85
	TS-2	13.4	48.2	44.1	69.0	78.9	1.70	2.03	2.40	1.02	1.31	1.45	1.61
	P	84.5	-52.8	-51.7	-42.0	-39.9	1.72	2.26	1.66	1.06	1.24	3.49	1.36
CH_3	R	-36.7	-19.5	-14.7	-2.5	2.9	1.92	1.71	0.98	1.96	3.14	1.10	2.76
	TS-1	40.5	67.9	65.2	74.3	76.3	1.80	1.79	1.31	1.18	2.00	1.09	3.19
	Int-1	-48.3	-16.4	-5.7	28.5	45.5	1.70	1.97	2.35	1.02	1.40	1.11	2.85
	TS-2	17.6	52.8	48.3	72.3	81.4	1.70	2.03	2.42	1.02	1.31	1.44	1.61
	P	-81.0	-49.1	-48.5	-39.5	-37.3	1.72	2.26	1.65	1.06	1.24	3.41	1.36
OCH_3	R	-36.6	-19.7	-14.5	-3.3	1.8	1.92	1.71	0.98	1.96	3.16	1.10	2.78
	TS-1	42.2	69.0	67.3	72.8	73.0	1.80	1.79	1.34	1.17	2.04	1.09	3.03
	Int-1	-42.9	-11.6	-0.8	32,4	48.8	1.70	1.96	2.35	1.02	1.40	1.11	2.84
	TS-2	22.6	57.0	52.4	73.7	81.4	1.69	2.03	2.53	1.02	1.31	1.45	1.61
	P	-77.8	-46.1	-45.2	-37.6	-35.8	1.72	2.26	1.66	1.05	1.24	3.48	1.36
NH_2	R	-33.0	-17.1	-11.3	-2.3	1.3	1.92	1.71	0.99	1.96	3.16	1.10	2.79
	TS-1	46.1	71.6	73.0	72.4	69.0	1.79	1.79	1.41	1.13	2.07	1.09	2.92
	Int-1	-35.2	-6.1	5.4	37.1	52.8	1.70	1.96	2.37	1.02	1.40	1.11	2.85
	TS-2	29.8	62.6	58.5	78.0	84.2	1.69	2.03	2.46	1.02	1.31	1.44	1.62
	P	-72.0	-41.8	-40.4	-35.8	-36.0	1.72	2.25	1.68	1.05	1.24	3.35	1.36

Table S3-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for initial proton transfer and a subsequent concerted reaction with deprotonated MoCo (Fig. 1, Reaction 3) for 6-substituted 4-quinazolinones. All energy contributions are given relative to the sum of the MoCo and substrate energies.

R		BS1	BS2	ZPE	ε=4	ε=80	Mo – O_1	Mo – O_2	H_{Moco}-O_1	H_{Moco}– N	O_2 – C	C – H_{Sub}	H_{Sub} – S
NO_2	R	-82.3	-65.1	-59.6	-32.0	-18.0	1.92	1.71	0.98	1.94	2.90	1.10	2.61
	TS-1	-19.8	8.4	7.3	57.8	83.7	1.84	1.83	1.07	1.51	1.69	1.10	3.03
	Int-1	-117.2	-87.8	-76.0	-28.5	-3.8	1.70	1.98	2.30	1.02	1.39	1.11	2.86
	TS-2	-42.0	-8.5	-12.3	27.9	46.3	1.70	2.03	2.27	1.02	1.31	1.47	1.60
	P	-129.4	-98.2	-97.8	-71.9	-62.6	1.72	2.22	1.64	1.06	1.24	3.42	1.36
CF_3	R	-75.0	-57.6	-52.0	-30.5	-19.8	1.92	1.71	0.99	1.91	2.97	1.10	2.64
	TS-1	-4.6	22.5	18.4	43.0	53.7	1.81	1.80	1.26	1.23	1.95	1.09	3.11
	Int-1	-101.5	-72.2	-60.9	-18.6	3.8	1.70	1.97	2.34	1.02	1.39	1.11	2.86
	TS-2	-27.6	6.0	1.9	36.5	51.8	1.70	2.04	2.25	1.02	1.31	1.46	1.61
	P	-117.3	-86.2	-85.8	-67.9	-61.0	1.72	2.25	1.63	1.06	1.23	3.45	1.36
Cl	R	-70.0	-52.5	-46.9	-29.4	-20.8	1.92	1.71	0.99	1.91	3.01	1.10	2.68
	TS-1	0.9	27.7	25.4	40.3	45.8	1.80	1.79	1.31	1.19	2.03	1.09	2.94
	Int-1	-90.0	-60.1	-48.7	-10.3	9.3	1.70	1.97	2.30	1.02	1.40	1.11	2.88
	TS-2	-17.5	16.4	11.9	40.3	52.0	1.69	2.03	2.45	1.02	1.31	1.46	1.60
	P	-109.9	-78.9	-78.4	-64.4	-59.4	1.72	2.25	1.63	1.06	1.24	3.34	1.36
H	R	-64.8	-46.6	-40.9	-27.6	-21.4	1.92	1.71	0.99	1.90	3.03	1.10	2.70

	TS-1	5.8	32.8	31.7	39.1	40.3	1.80	1.79	1.35	1.16	2.06	1.09	2.90
	Int-1	-82.1	-51.3	-40.0	-6.0	11.0	1.70	1.96	2.33	1.02	1.40	1.11	2.87
	TS-2	-12.3	22.1	17.8	43.0	53.1	1.70	2.03	2.35	1.02	1.31	1.45	1.62
	P	-106.8	-75.3	-74,2	-64.5	-61.8	1.72	2.25	1.66	1.06	1.24	3.46	1.36
CH_3	R	-61.9	-43.5	-38.4	-26.3	-21.0	1.92	1.71	0.99	1.89	3.04	1.10	2.71
	TS-1	8.1	35.3	34.0	40.7	41.4	1.80	1.79	1.35	1.16	2.04	1.09	2.98
	Int-1	-78.1	-46.7	-35.6	-2.2	14.3	1.70	1.96	2.33	1.02	1.40	1.11	2.87
	TS-2	-8.3	26.6	22.2	46.3	55.5	1.69	2.03	2.40	1.02	1.31	1.44	1.62
	P	-103.2	-71.5	-71.0	-62.2	-60.1	1.72	2.25	1.65	1.06	1.24	3.35	1.36
OCH_3	R	-61.9	-43.7	-38.1	-27.1	-22.1	1.92	1.71	0.99	1.88	3.05	1.10	2.74
	TS-1	10.8	37.6	37.4	41.7	41.3	1.79	1.79	1.38	1.14	2.06	1.09	2.92
	Int-1	-72.4	-41.7	-30.8	1.7	17.7	1.70	1.96	2.35	1.02	1.40	1.11	2.86
	TS-2	-3.4	31.0	26.4	48.8	57.1	1.69	2.03	2.48	1.02	1.31	1.43	1.62
	P	-100.0	-68.5	-67.7	-60.0	-58.2	1.72	2.26	1.65	1.06	1.24	3.41	1.36
NH_2	R	-58.2	-41.0	-34.8	-26.0	-22.7	1.92	1.71	0.99	1.88	3.06	1.10	2.74
	TS-1	14.8	40.1	41.5	41.3	38.1	1.79	1.79	1.40	1.13	2.07	1.09	2.95
	Int-1	-64.8	-36.1	-24.6	6.6	21.9	1.70	1.96	2.35	1.02	1.40	1.11	2.87
	TS-2	3.8	36.5	32.4	52.4	59.0	1.69	2.03	2.41	1.02	1.31	1.44	1.62
	P	-94.3	-64.3	-62.9	-58.3	-58.5	1.72	2.25	1.67	1.05	1.24	3.32	1.36

Table S4-A. B3LYP transition state energies (kJ/mol) and distances (Å) for initial proton transfer and a subsequent stepwise reaction (Fig. 1, Reaction 4) for negatively charged xanthine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – H_{Moco}	H_{Moco}– N	O – C	C – H_{Sub}	H_{Sub} – S
Reactant	123.1	141.5	145.6	43.8	-3.5	1.88	1.01	1.81	3.36	1.09	2.87
TS1	140.9	168.1	164.5	47.3	-7.3	1.79	1.33	1.18	3.09	1.10	2.53
Interm 1	140.1	166.6	170.8	49.7	-6.8	1.77	1.50	1.10	3.07	1.11	2.40
TS2	185.3	210.5	217.4	109.6	62.0	1.83	2.87	1.01	1.81	1.11	2.29
Interm 2	168.6	195.4	104.0	106.9	66.0	1.93	2.69	1.01	1.44	1.12	2.44
TS3	193.3	228.9	223.5	123.3	80.1	2.00	2.68	1.01	1.36	1.33	1.70
Product	92.2	123.8	125.1	19.6	-26.8	2.18	2.68	1.01	1.24	2.92	1.37

Table S4-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for initial proton transfer and a subsequent stepwise reaction (Fig. 1, Reaction 4) for negatively charged xanthine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – H_{Moco}	H_{Moco}– N	O – C	C – H_{Sub}	H_{Sub} – S
Reactant	105.2	124.9	129.1	25.9	-21.9	1.88	1.01	1.73	3.35	1.09	2.84
TS1	122.0	149.3	145.9	28.3	-26.5	1.79	1.33	1.18	3.10	1.10	2.51
Interm 1	121.1	147.9	152.1	31.1	-25.4	1.78	1.50	1.10	3.08	1.11	2.40
TS2	165.2	190.2	197.0	89.5	42.1	1.82	2.84	1.01	1.81	1.11	2.29
Interm 2	146.6	172.5	181.7	84.2	43.1	1.92	2.65	1.01	1.44	1.12	2.48
TS3	173.6	208.9	203.4	103.0	59.6	2.00	2.78	1.01	1.36	1.33	1.69
Product	122.3	155.7	159.0	57.2	13.2	2.24	2.66	1.01	1.25	3.31	1.36

Table S5-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for 6-substituted quinazolines. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
6-NO_2-Quinazoline (C2)**	88.3	117.1	110.4	143.1	154.7	2.19	1.45	1.40	1.59
6-NO_2-Quinazoline (C4)*	85.2	113.4	107.3	142.8	158.4	2.20	1.45	1.39	1.59
6-NH_2-Quinazoline (C2)**	148.7	176.8	169.9	178.9	174.8	2.17	1.48	1.34	1.65
6-NH_2-Quinazoline (C4)*	116.4	142.9	137.3	161.0	170.7	2.17	1.49	1.34	1.66

Table S5-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for 6-substituted quinazolines. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
6-NO_2-Quinazoline (C2)**	66.4	95.0	88.4	121.0	132.4	2.19	1.45	1.39	1.59
6-NO_2-Quinazoline (C4)*	54.1	82.1	76.1	111.4	126.8	2.20	1.45	1.39	1.60
6-NH_2-Quinazoline (C2)**	127.3	155.3	148.4	158.3	154.8	2.17	1.48	1.33	1.67
6-NH_2-Quinazoline (C4)*	85.0	111.3	106.0	130.1	140.2	2.17	1.49	1.33	1.66

Table S6-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, reaction 1) for quinazoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
C2**	Reactant	-4.9	1.1	2.2	9.3	9.6	1.94	2.93	1.10	2.86
	TS	131.0	161.5	154.2	169.5	170.8	2.17	1.47	1.36	1.63
	Product	44.5	69.6	68.9	61.9	53.2	2.43	1.34	2.90	1.36
C4*	Reactant	-40.1	-29.5	-26.3	-2.0	9.6	1.97	3.38	1.10	4.39
	TS	109.4	137.8	131.9	157.8	169.2	2.18	1.48	1.35	1.64
	Product	25.1	48.0	49.2	56.1	57.5	2.40	1.35	2.83	1.36
C5	Reactant	-43.0	-32.2	-29.5	-4.3	7.5	1.96	3.25	1.09	2.98
	TS	151.6	178.2	169.2	188.3	193.3	2.17	1.49	1.38	1.60
	Product	69.4	90.4	89.7	95.6	95.6	2.39	1.36	2.80	1.36
C6	Reactant	-36.0	-28.3	-25.9	-4.3	7.5	1.96	3.16	1.09	3.81
	TS	156.9	182.4	172.3	191.3	195.7	2.16	1.50	1.39	1.61
	Product	65.2	84.7	83.4	86.8	85.6	2.37	1.36	2.82	1.36
C7	Reactant	-35.9	-27.7	-25.1	-1.6	9.7	1.96	3.21	1.09	4.24
	TS	150.2	174.0	164.6	185.2	191.5	2.16	1.50	1.38	1.60
	Product	61.6	80.8	79.5	82.3	80.7	2.36	1.36	2.85	1.36
C8	Reactant	-40.0	-30.5	-28.0	-4.0	7.3	1.95	4.38	1.09	6.54
	TS	170.6	201.1	191.1	202.2	199.3	2.18	1.48	1.38	1.60
	Product	40.9	60.3	58.0	84.7	95.1	4.55	1.33	5.81	1.36

Table S6-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for quinazoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

		BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
C2**	Reactant	-31.2	-20.4	-19.5	-8.2	-4.4	1.94	3.27	1.10	3.43
	TS	109.5	139.9	132.6	148.2	149.7	2.17	1.47	1.35	1.64
	Product	24.5	49.8	49.2	40.4	30.2	2.38	1.34	2.76	1.36
C4*	Reactant	-56.3	-48.5	-46.7	-23.1	-12.0	1.94	2.95	1.10	2.86
	TS	79.5	107.7	101.7	127.5	138.7	2.18	1.48	1.35	1.64
	Product	-5.2	18.1	19.7	26.4	27.6	2.39	1.35	2.69	1.36
C5	Reactant	-65.1	-51.9	-48.1	-23.3	-12.1	1.96	3.33	1.09	3.63
	TS	120.4	147.5	138.5	155.9	159.9	2.17	1.49	1.38	1.60
	Product	37.8	58.8	58.9	62.6	61.0	2.35	1.36	2.62	1.36
C6	Reactant	-50.6	-44.7	-43.2	-18.6	-7.0	1.94	3.03	1.09	3.01
	TS	132.4	158.1	147.9	166.0	169.9	2.15	1.50	1.38	1.60
	Product	41.0	60.3	59.0	61.4	59.6	2.34	1.36	2.71	1.36
C7	Reactant	-53.2	-46.2	-43.9	-19.2	-7.6	1.95	3.12	1.09	3.27
	TS	125.5	149.0	139.7	159.6	165.4	2.16	1.49	1.38	1.60
	Product	35.5	53.7	52.5	53.0	50.0	2.32	1.36	2.87	1.37
C8	Reactant	-51.2	-39.5	-37.5	-18.2	-10.6	1.94	3.27	1.09	3.53
	TS	143.0	173.7	163.7	173.6	170.0	2.17	1.48	1.38	1.60
	Product	12.2	34.2	32.8	58.3	69.7	4.24	1.34	4.79	1.36

Table S7-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for phthalazine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Phthalazine (C4)*	126.7	158.6	152.1	179.1	189.9	2.18	1.47	1.32	1.68
Phthalazine (C5)	146.0	170.7	161.1	184.1	191.8	2.17	1.49	1.40	1.59
Phthalazine (C6)	150.5	177.6	168.3	188.6	193.1	2.16	1.50	1.40	1.59

Table S7-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for phthalazine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Phthalazine (C4)*	70.1	101.8	95.6	123.1	134.3	2.19	1.48	1.31	1.69
Phthalazine (C5)	94.8	119.4	109.7	133.4	141.6	2.17	1.48	1.39	1.59
Phthalazine (C6)	93.4	120.8	111.5	131.0	135.0	2.16	1.50	1.38	1.60

Table S8-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for quinoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Quinoline (C2)*	137.4	163.8	156.2	175.4	180.5	2.15	1.51	1.33	1.67
Quinoline (C3)	168.0	193.3	183.2	197.6	198.6	2.16	1.51	1.38	1.60
Quinoline (C4)	149.9	176.0	167.1	183.5	188.0	2.16	1.49	1.40	1.59
Quinoline (C5)	160.5	187.8	178.6	192.9	194.9	2.16	1.50	1.36	1.63
Quinoline (C6)	167.6	192.8	182.5	196.0	196.2	2.15	1.51	1.37	1.61
Quinoline (C7)	168.7	193.2	183.0	195.8	195.8	2.15	1.51	1.37	1.62
Quinoline (C8)	182.2	212.7	202.4	205.7	197.6	2.17	1.48	1.39	1.60

Table S8-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for quinoline. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Quinoline (C2)*	113.9	140.0	132.4	152.1	157.6	2.15	1.51	1.32	1.68
Quinoline (C3)	144.1	169.3	159.4	173.7	174.7	2.16	1.51	1.37	1.61
Quinoline (C4)	118.5	144.7	135.9	151.4	155.5	2.16	1.49	1.39	1.59
Quinoline (C5)	128.4	155.7	146.5	160.5	162.4	2.16	1.50	1.36	1.63
Quinoline (C6)	143.1	168.4	158.0	170.6	170.2	2.15	1.51	1.37	1.62
Quinoline (C7)	144.1	168.3	158.0	170.8	170.9	2.15	1.51	1.36	1.62
Quinoline (C8)	154.4	184.9	174.9	178.3	170.3	2.17	1.48	1.37	1.61

Table S9-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, reaction 1) for 2-amino-9-methylpurine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Famciclovir (C6)*	149.0	176.8	172.0	179.5	177.1	2.18	1.48	1.38	1.60
Famciclovir (C8)**	127.1	157.0	151.9	172.5	179.9	2.21	1.46	1.38	1.61

Table S9-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for 2-amino-9-methylpurine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Famciclovir (C6)*	125.9	153.5	148.8	156.8	154.8	2.17	1.48	1.36	1.61
Famciclovir (C8)**	97.1	127.3	122.5	144.1	152.2	2.21	1.46	1.38	1.61

Table S10-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for 4-methylacridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
DACA (C1)	153.7	181.9	172.5	189.5	191.4	2.17	1.49	1.36	1.63
DACA (C2)	158.8	186.0	176.1	190.6	190.1	2.17	1.49	1.37	1.62
DACA (C3)	160.0	188.7	178.7	192.3	191.4	2.17	1.49	1.37	1.62
DACA (C5)	169.4	201.0	190.0	203.2	200.7	2.18	1.47	1.36	1.63
DACA (C6)	157.5	183.9	173.9	187.6	187.1	2.17	1.49	1.38	1.61
DACA (C7)	159.1	186.2	176.1	191.0	191.0	2.17	1.50	1.37	1.62
DACA (C8)	151.5	179.4	170.0	188.5	191.9	2.17	1.49	1.36	1.63
DACA (C9)*	130.6	162.1	153.7	174.6	180.2	2.19	1.47	1.42	1.58

Table S10-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for 4-methylacridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
DACA (C1)	120.0	148.5	139.3	156.0	157.7	2.17	1.49	1.35	1.64
DACA (C2)	133.6	160.6	150.8	166.1	166.0	2.17	1.49	1.36	1.62
DACA (C3)	128.6	157.0	146.8	160.3	159.3	2.16	1.49	1.37	1.62
DACA (C5)	122.0	158.6	152.0	175.8	179.6	2.23	1.45	1.27	1.75
DACA (C6)	132.5	158.7	148.7	163.2	163.2	2.16	1.49	1.37	1.62
DACA (C7)	134.3	161.2	151.2	166.4	166.4	2.17	1.49	1.37	1.62
DACA (C8)	117.9	146.1	136.9	154.8	157.9	2.17	1.49	1.35	1.63
DACA (C9)*	90.2	121.6	113.6	134.0	139.5	2.18	1.46	1.40	1.58

Table S11-A. B3LYP transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for phenanthridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Phenanthridine (C1)	170.1	200.2	190.7	205.3	207.0	2.18	1.52	1.39	1.62
Phenanthridine (C2)	166.4	193.2	182.3	193.6	191.7	2.16	1.50	1.39	1.50
Phenanthridine (C3)	171.6	197.6	186.9	197.1	193.7	2.15	1.51	1.38	1.60
Phenanthridine (C4)	183.9	214.7	203.9	208.0	199.5	2.17	1.48	1.38	1.60
Phenanthridine (C6)*	127.6	157.6	150.7	174.6	181.7	2.17	1.50	1.31	1.68
Phenanthridine (C7)	163.5	190.6	180.7	195.4	195.3	2.17	1.50	1.39	1.60
Phenanthridine (C8)	164.1	189.9	179.6	194.2	194.4	2.16	1.51	1.38	1.60
Phenanthridine (C9)	155.8	181.6	171.3	186.7	188.5	2.16	1.50	1.40	1.59
Phenanthridine (C10)	167.8	198.1	188.7	204.2	206.0	2.18	1.51	1.39	1.61

Table S11-B. B3LYP-D3 transition state energies (kJ/mol) and distances (Å) for concerted reaction (Fig. 1, Reaction 1) for phenanthridine. All energy contributions are given relative to the sum of the MoCo and substrate energies.

	BS1	BS2	ZPE	ε=4	ε=80	Mo – O	O – C	C – H	H – S
Phenanthridine (C1)	129.9	160.0	150.4	165.4	167.3	2.16	1.52	1.38	1.62
Phenanthridine (C2)	141.2	167.9	157.3	169.2	167.6	2.15	1.50	1.38	1.61
Phenanthridine (C3)	146.8	172.6	162.0	172.1	168.6	2.15	1.50	1.38	1.61
Phenanthridine (C4)	155.4	186.5	175.2	178.8	170.1	2.16	1.48	1.37	1.61
Phenanthridine (C6)*	96.2	126.0	119.4	143.7	151.1	2.18	1.50	1.31	1.69
Phenanthridine (C7)	131.9	159.1	149.2	163.3	162.8	2.16	1.49	1.38	1.60
Phenanthridine (C8)	139.4	164.9	154.6	168.8	168.7	2.16	1.50	1.38	1.60
Phenanthridine (C9)	130.4	156.0	145.7	161.1	163.0	2.15	1.50	1.39	1.59
Phenanthridine (C10)	128.0	158.3	148.7	164.7	166.8	2.17	1.51	1.38	1.61

Table S12-A. DFT calculated molecular properties for quinazoline. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the sum of the substrate and MoCo energies.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C2 **	1179.3	259.7	52.5	0.90	0.30
C4 *	1174.5	228.3	46.3	0.63	0.13
C5	1281.4	270.1	98.4	0.12	-0.19
C6	1309.7	299.0	102.0	0.00	-0.22
C7	1306.5	275.3	98.8	0.15	-0.20
C8	1307.9	292.8	110.7	0.12	-0.20

Table S12-B. DFT calculated molecular properties for 2-amino-9-methylpurine. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the substrate energy.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C6 *	1139.2	285.8	60.6	0.37	0.12
C8 **	1296.7	267.4	70.8	0.42	0.27

Table 12-C. DFT calculated molecular properties for 4-methylacridine. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the substrate energy.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C1	1217.8	290.1	99.4	0.05	-0.20
C2	1234.4	292.6	101.2	0.03	-0.21
C3	1217.5	305.9	103.1	0.09	-0.22
C5	1247.7	283.9	109.8	-0.11	-0.20
C6	1238.1	280.0	101.6	0.13	-0.22
C7	1250.6	316.2	102.4	0.03	-0.22
C8	1222.4	283.9	97.8	0.06	-0.19
C9 *	1221.8	214.0	94.7	0.11	-0.13

Table S12-D. DFT calculated molecular properties for phenanthridine. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the sum of the substrate and the MoCo energies.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C1	1222.8	302.3	106.7	0.02	-0.20
C2	1264.3	304.9	100.6	0.03	-0.21
C3	1257.0	308.6	102.4	0.12	-0.22
C4	1257.6	309.8	112.0	-0.10	-0.20
C6 *	1132.6	278.6	86.0	0.48	0.12
C7	1268.2	278.5	100.1	0.07	-0.18
C8	1272.0	299.5	102.6	0.06	-0.22
C9	1275.1	277.4	98.3	0.11	-0.20
C10	1262.9	292.1	107.5	-0.08	-0.20

Table S12-E. DFT calculated molecular properties for phthalazine. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the substrate energy.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C4 *	1217.0	259.7	56.5	0.50	0.07
C5	1329.7	275.5	98.8	0.00	-0.19
C6	1307.9	269.4	96.6	0.10	-0.20

Table S12-F. DFT calculated molecular properties for quinoline. All energies (kJ/mol) are calculated at the B3LYP level of theory using BS1 and given relative to the substrate energy.

Position	Cation intermediate	Intermediate	Product	ESP charges	NBO charges
C2 *	1162.1	294.9	81.7	0.44	0.08
C3	1262.6	339.1	103.5	-0.48	-0.27
C4	1259.1	276.3	90.9	0.13	-0.16
C5	1251.1	323.7	99.1	-0.09	-0.20
C6	1287.0	346.1	101.8	-0.21	-0.22
C7	1274.5	319.6	102.2	-0.01	-0.22
C8	1276.0	322.6	110.9	-0.42	-0.20

Figure S1. Reaction mechanisms of 4-quinazolinones (A) and negatively charged xanthine (B). studied in this work.

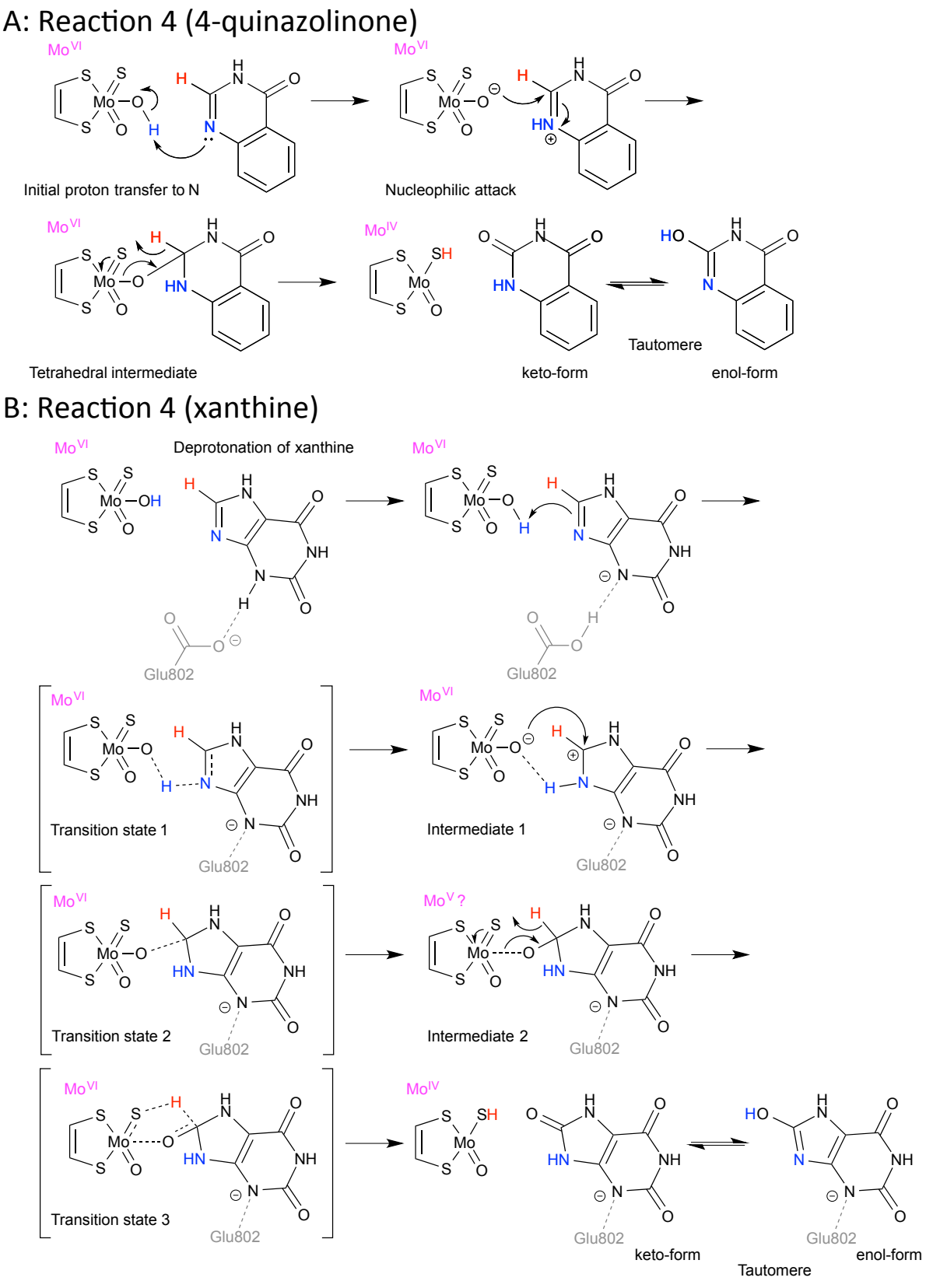

Figure S2. Reactions for formation of 1) the products, 2) the hydroxylated tetrahedral intermediate, and 3) the cation intermediate.

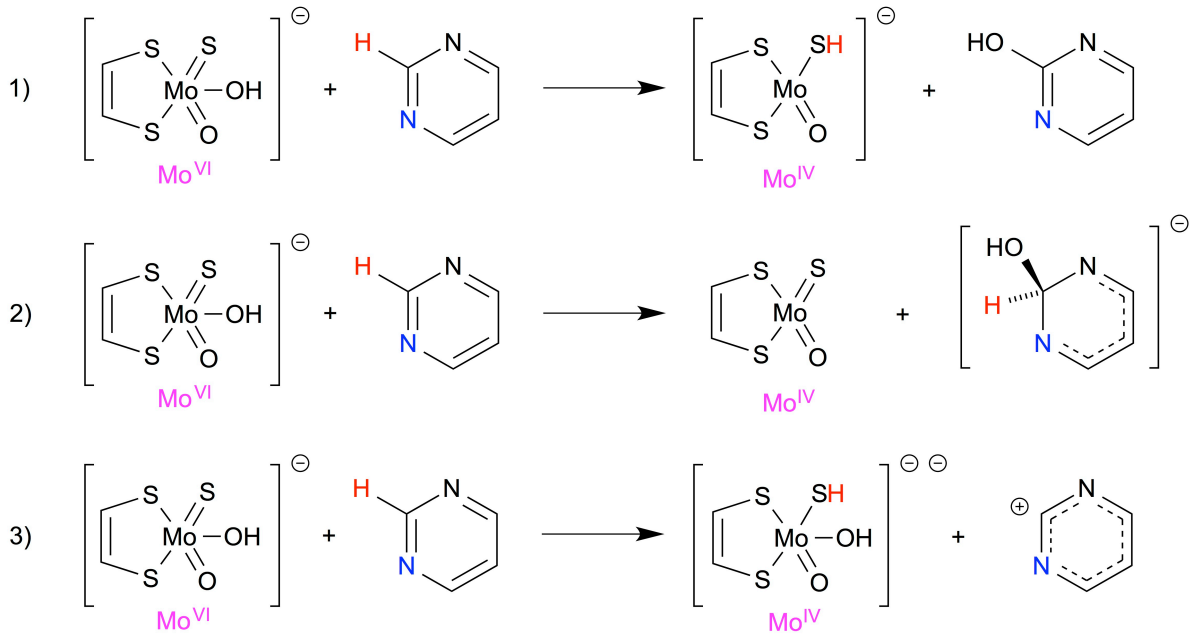

Figure S3. Transition state energies (at B3LYP level) versus estimates of the reactivity based on DFT calculated properties. Red and blue point show the SOMs/non-SOMs.

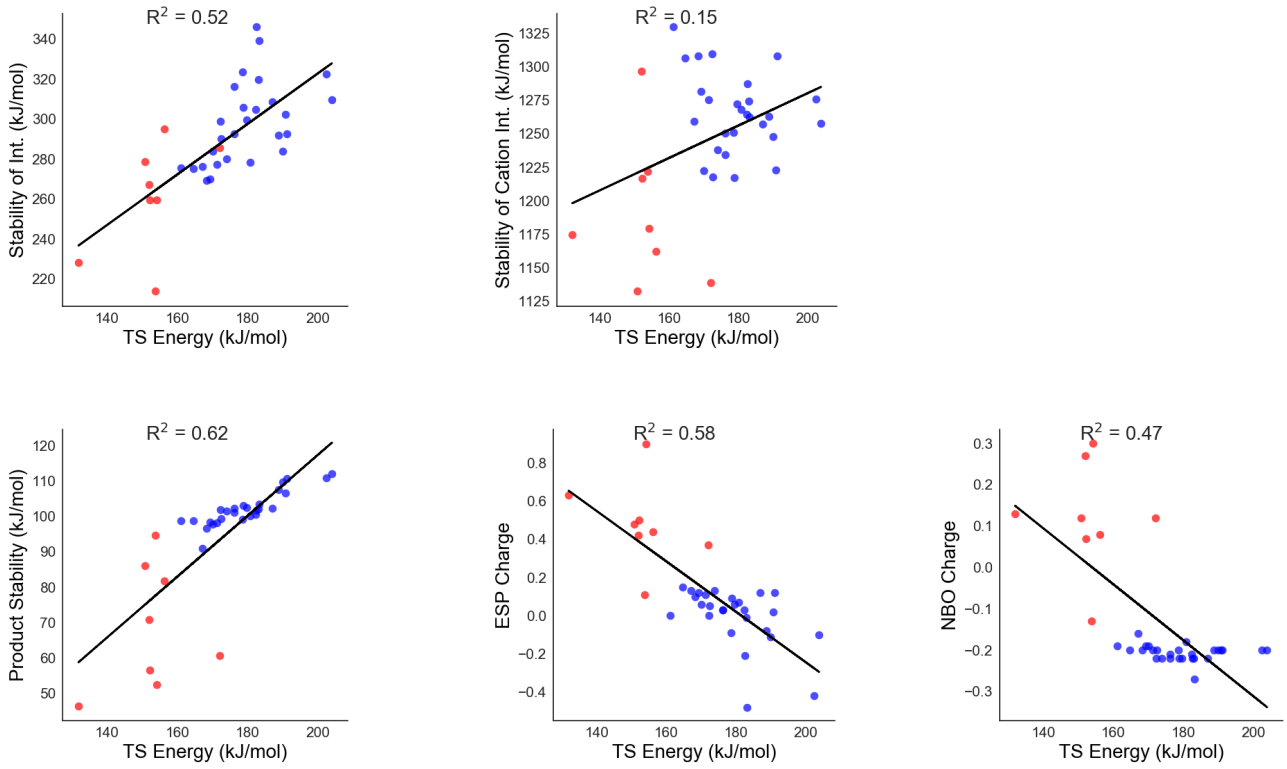

Figure S4. Distribution of transition state energies and reactivity based on DFT calculated properties. Red bars show the values for the SOMs and blue for the other aromatic C atoms.