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Supplementary Information

Mechanistic Study of Hydrolytic Degradation and Protonation of Temozolomide

Saber Mirzaei[a], *M. H. Khalilian*[a], *and Avat (Arman) Taherpour*[a,b*]

[a]*Faculty of Chemistry, Razi University, P.O.Box: 67149-67346, Kermanshah, Iran.*

[b]*Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.*

E-mail: avatarman.taherpour@gmail.com

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Figure S1. The path-1 relative energy profile of TMZ decomposition for rotamer B (also see table s1).

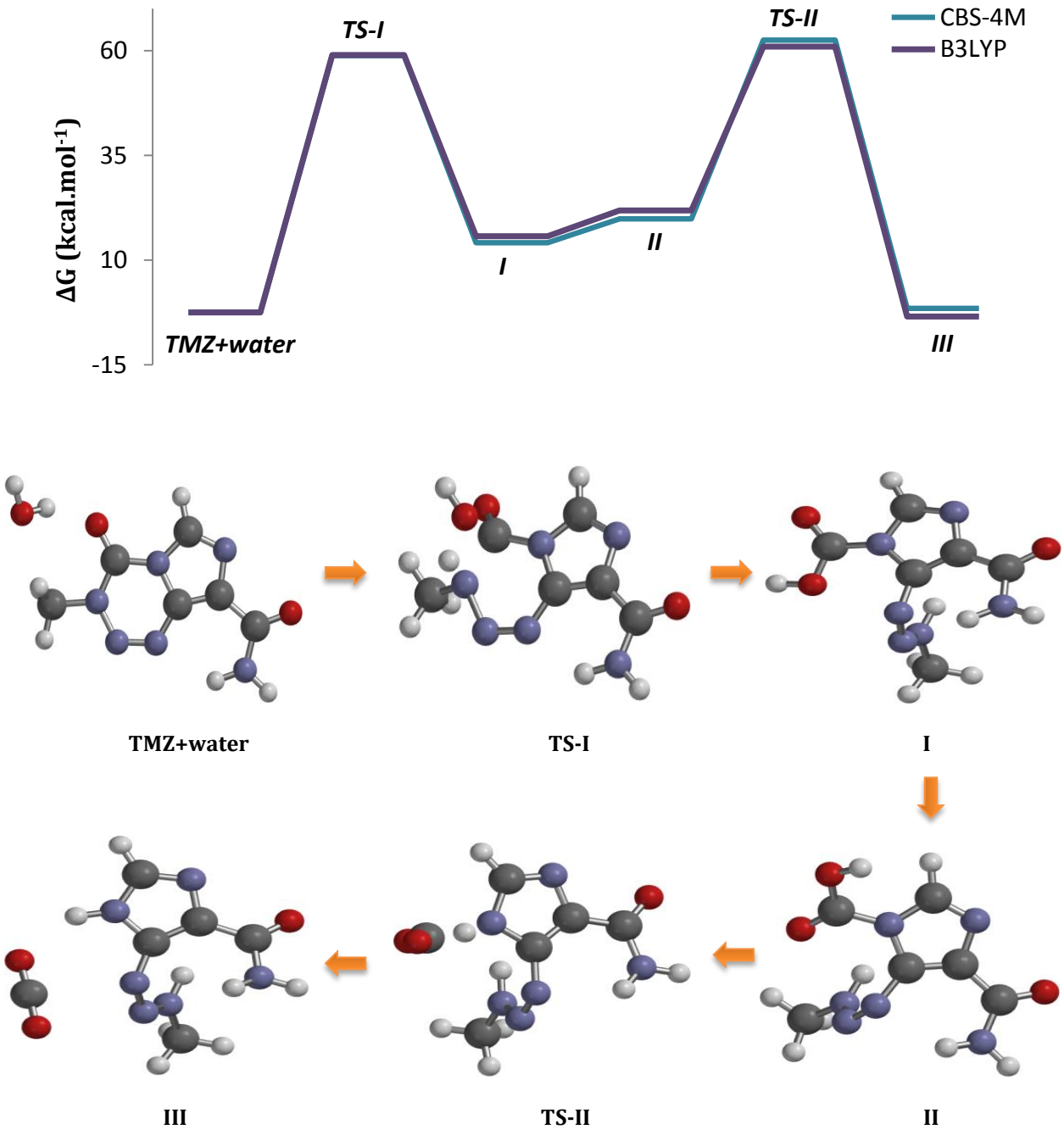


Figure S2. The path-2 relative energy profile of TMZ decomposition for rotamer B (also see table s1).

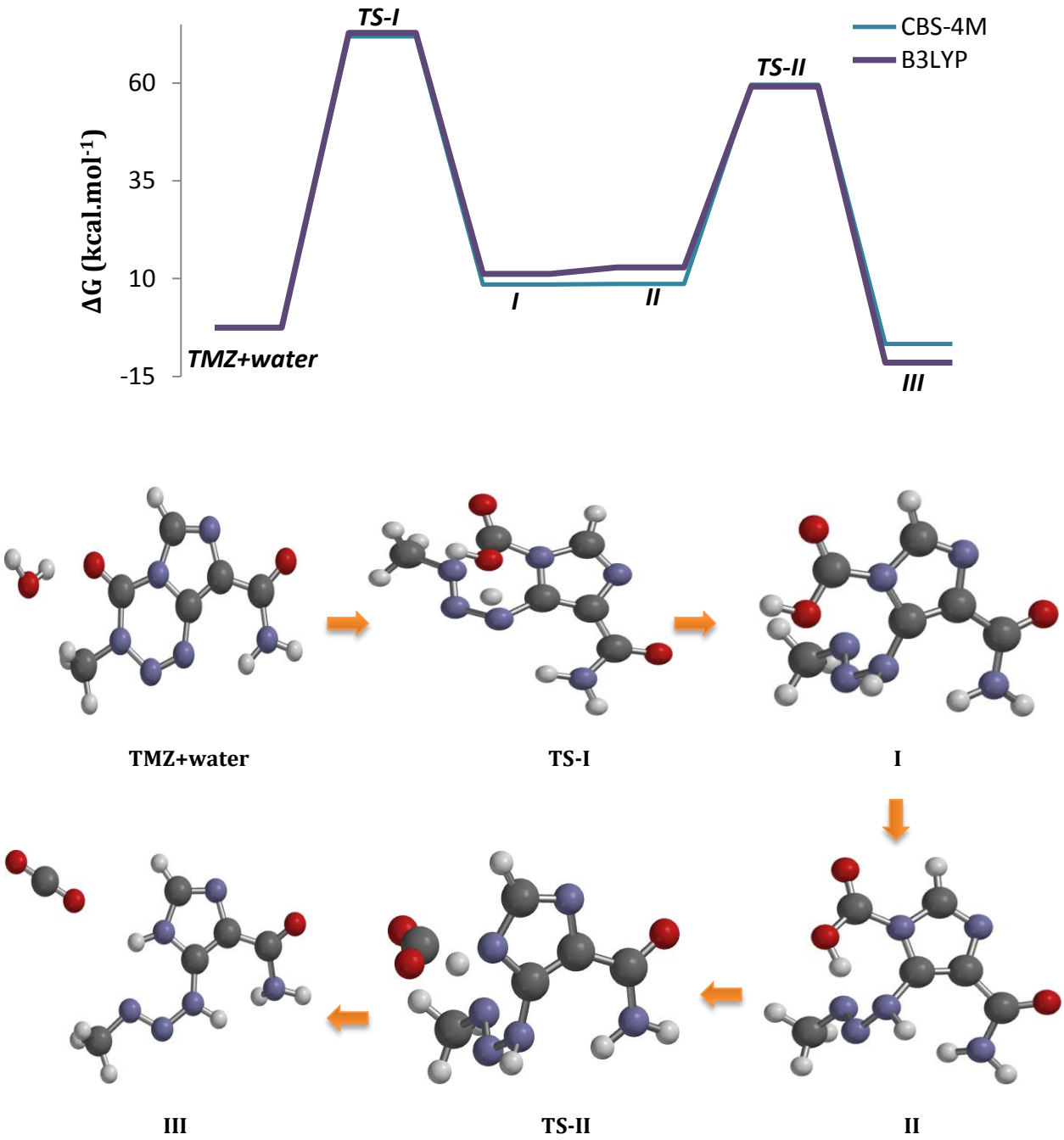
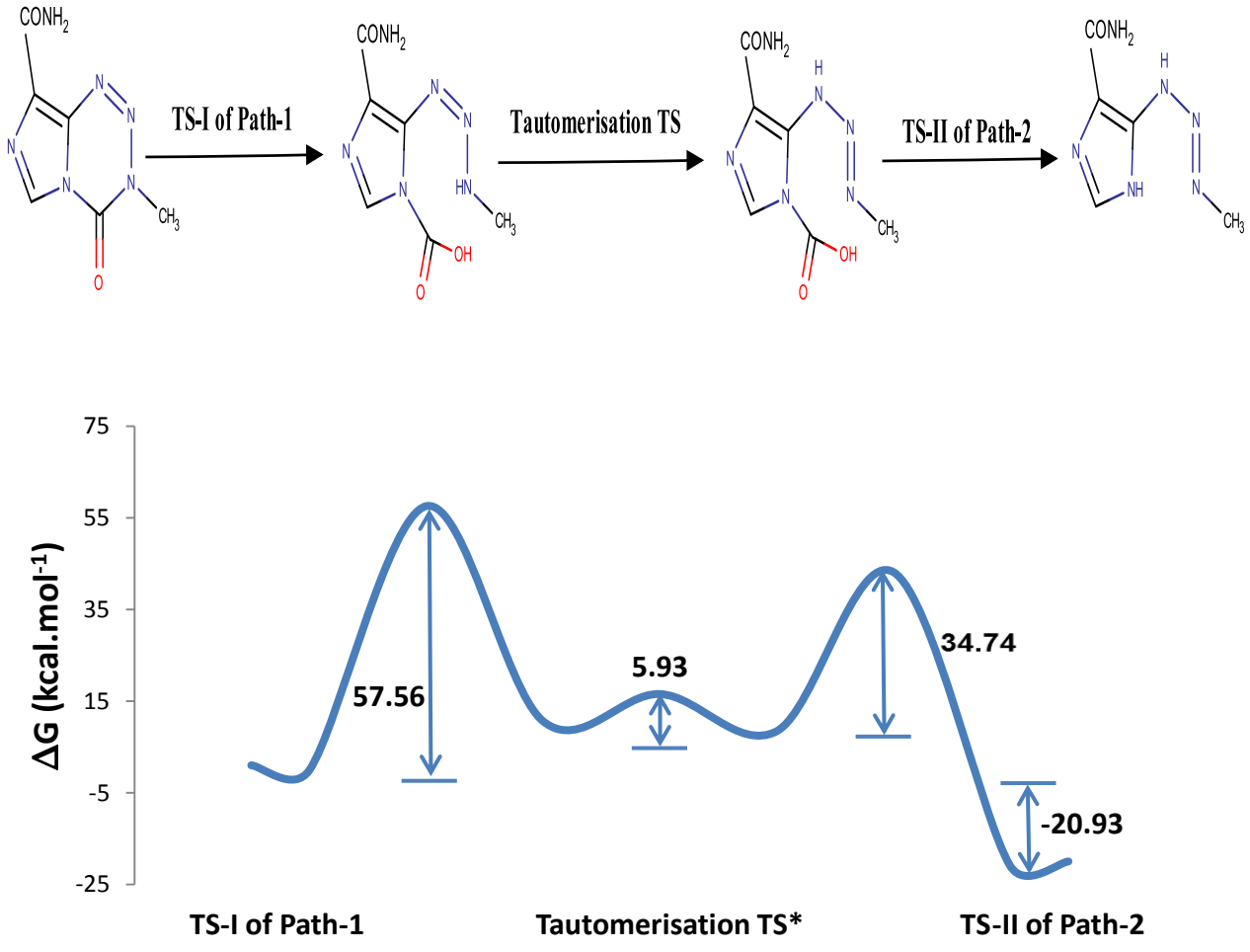


Table S1. Calculated relative free energies (ΔG) for both TMZ-B degradation paths (in kcal.mol^{-1})

	PATH-1		PATH-2	
Structure[a]	CBS-4M	B3LYP/6-31+G(d)	CBS-4M	B3LYP/6-31+G(d)
SR[b]	-7.71	-3.61	-7.71	-3.61
TS-I	58.82	58.94	71.96	72.85
I	14.15	15.68	8.53	11.23
II	19.83	21.87	8.66	12.87
TS-II	62.51	60.97	59.59	59.12
III	-1.49	-3.43	-6.67	-11.47

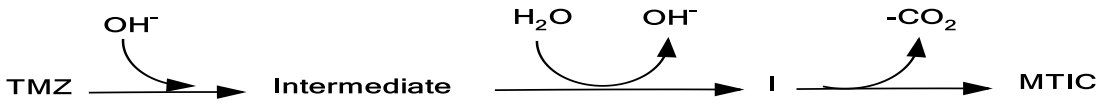
[a] The TMZ+water structure has been optimized as a reactant and all other energies were compared to this structure relatively.
[b] Separated reactants.

Figure S3. The overall mechanism of TMZ decomposition.



*The energy of tautomerization TS is adopted from ref.36 (Doucet, K. G.; Glister, J. F.; Pye, C. C., Can. J. Chem. 2010).

Figure S4. The base-catalysed degradation of TMZ.



	TS-I	Intermediate	I	II	TS-II	III
ΔG (kcal.mol^{-1})*	7.23 (20.58)**	-29.49	30.23	36.57	75.41	14.29

*Calculated at CBS-4M. **For second detected transition state.

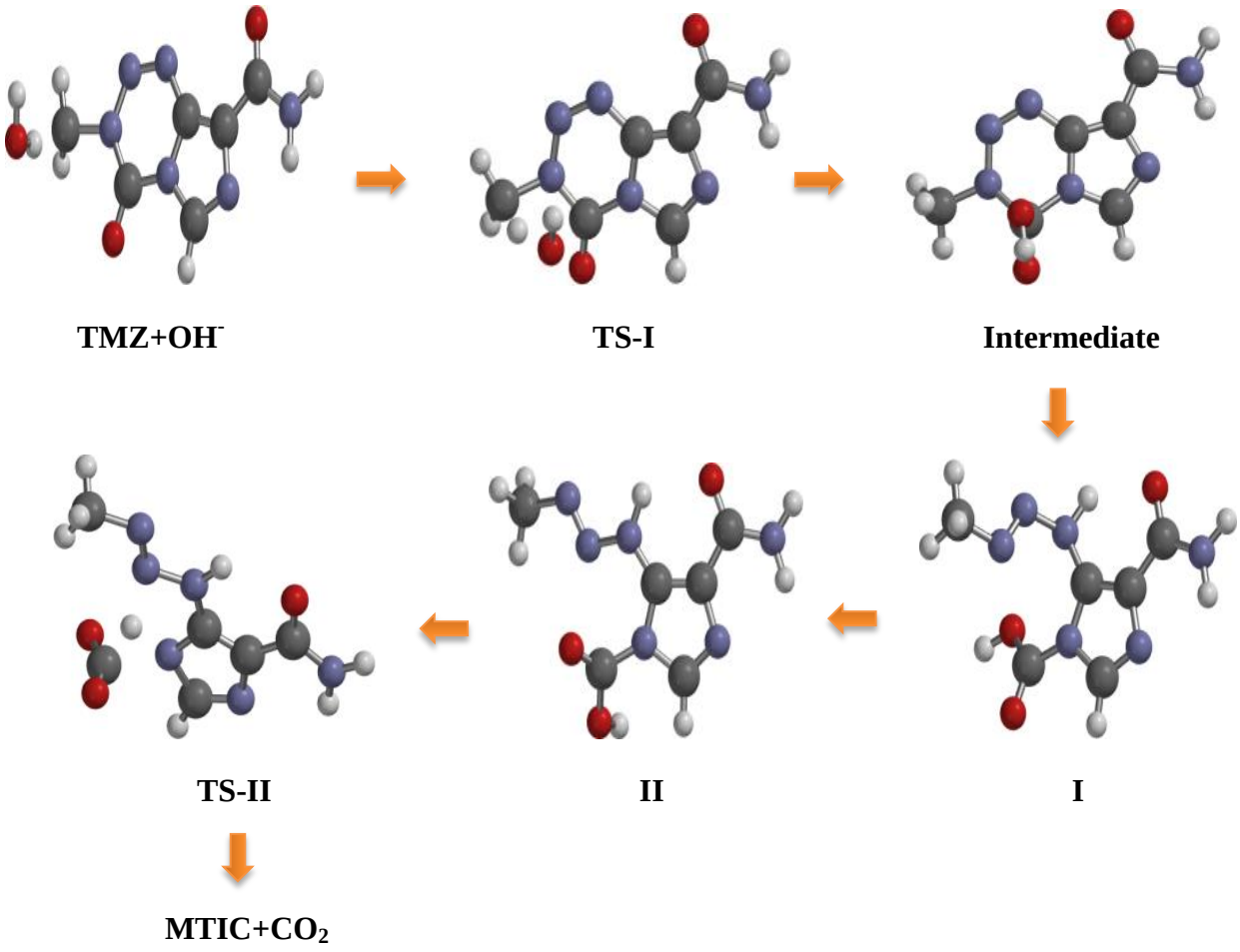


Figure S5. Atom numbering assignment of TMZ.

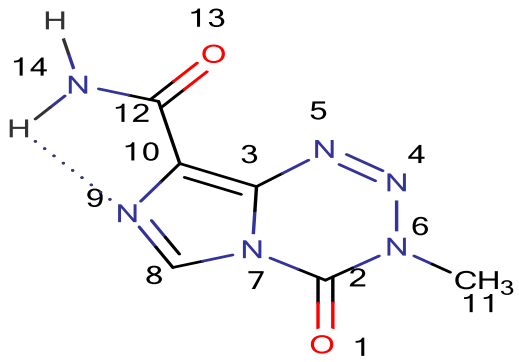


Table S2. Protonation free energies for all protonated atoms.

	B3LYP/6-311++g(2d,p)		CBS-4M	
Position	**TMZA**	**TMZB**	**TMZA**	**TMZB**
O13	-217.83	-219.44	-215.99	-217.72
N-9	-205.72	-217.21	-205.13	-216.61
N-5	-210.61	-196.14	-209.32	-195.21
N-6	-210.62	------	-206.35	-----
N-14	-201.59	-200.61	-200.66	-200.59
N-4	-197.06	------	-191.99	-185.31
O-1	-186.45	-184.01	-183.59	-180.68
N-7	-153.20	-152.80	-150.97	-149.79

Table S3. NPA partial atomic charges for TMZ.

Atom	TMZ-A	TMZ-B	O13-A	O13-B	N9-B
O1	-0.591	-0.582	-0.513	-0.516	-0.512
C2	0.830	0.832	0.833	0.832	0.833
C3	0.289	0.270	0.351	0.356	0.309
N4	0.009	0.011	0.084	0.077	0.077
N5	-0.174	-0.237	-0.292	-0.268	-0.223
N6	-0.309	-0.308	-0.258	-0.259	-0.276
N7	-0.448	-0.452	-0.440	-0.438	-0.414
C8	0.255	0.255	0.286	0.288	0.320
N9	-0.476	-0.413	-0.427	-0.452	-0.439
C10	0.059	0.065	-0.019	-0.021	0.107
C11	-0.352	-0.351	-0.354	-0.355	-0.354
C12	0.640	0.641	0.682	0.684	0.635
O13	-0.608	-0.595	-0.611	-0.596	-0.595
N14	-0.795	-0.806	-0.672	-0.681	-0.755

Table S4. Absolute free energies (a.u.) for both TMZ degradation paths of rotamer A.

Structure	PATH-1				PATH-2			
	CBS-4M (gas)	**B3LYP/6-31+g* (gas)**	**B3LYP/6-31+g* (PCM)**	**B3LYP/6-31+g* (SM8)**	**CBS-4M (gas)**	**B3LYP/6-31+g* (gas)**	**B3LYP/6-31+g* (PCM)**	**B3LYP/6-31+g* (SM8)**
TMZ+water	-786.646167	-787.518630	-787.548922	-787.549956	-786.646167	-787.518630	-787.548922	-787.549956
TS-I	-786.545939	-787.426907	-787.457139	-787.455377	-786.523393	-787.403733	-787.438539	-787.438138
I	-786.618428	-787.501717	-787.532145	-787.528112	-786.634829	-787.512654	-787.537259	-787.536004
II	-786.603787	-787.481047	-787.516100	-787.516491	-786.624735	-787.505216	-787.532861	-787.534928
TS-II	-786.536257	-787.419554	-787.448036	-787.447824	-786.562884	-787.449846	-787.471182	-787.473231
III	-786.636772	-787.521400	-787.553524	-787.543671	-786.660227	-787.551999	-787.577221	-787.566180

Table S5. Absolute free energies (a.u.) for the gas and water-mediated interconversion between N9 and O13 protonated forms of Temozolomide.

Structure	G3MP2	CBS-4M	B3LYP/6-311++G(2d,p)
O13	-710.601333	-710.627420	-711.644300
TS-1	-710.580392	-710.607327	-711.624740
N9	-710.597618	-710.625645	-711.640749
O13w	-786.972511	-787.001170	-788.108999
TSw	-786.962851	-786.994410	-788.102395
N9w	-786.970553	-787.002554	-788.107598

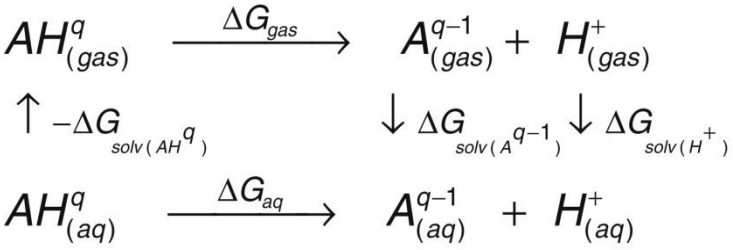
Table S6. Absolute free energies (a.u.) for all protonated atoms.

	B3LYP/6-311++g(2d,p)		CBS-4M	
Position	**TMZA**	**TMZB**	**TMZA**	**TMZB**
O13	-711.644159	-711.644300	-710.627151	-710.627420
N-9	-711.624863	-711.640749	-710.609854	-710.625645
N-5	-711.632656	-711.607161	-710.616524	-710.591552
N-6	-711.632668	------	-710.611783	-----
N-14	-711.618276	-711.614288	-710.602727	-710.600124
N-4	-711.611060	------	-710.588907	-710.575774
O-1	-711.594145	-711.587837	-710.575510	-710.568389
N-7	-711.541160	-711.538096	-710.523529	-710.519158

position	O13	N9	N5	O1
G3MP2 / TMZA	-710.601291	-710.581320	-710.587670	-710.552008
G3MP2 / TMZB	-710.601333	-710.597618	-710.562370	-710.545997

S1. pK_a calculations procedure and methods.

The reported pK_a values were obtained using the direct thermodynamic cycle (as follows).[1]



On the basis of this cycle the ΔG obtained by this formula:

$$\Delta G_{aq} = G_{gas}(H^+) + G_{gas}(A^{q-1}) - G_{gas}(AH^q)$$
$$+\Delta G_{solv}(H^+) + \Delta G_{solv}(A^{q-1}) - \Delta G_{solv}(AH^q) + RT \ln 24.46$$

Eventually, from the ΔG, the pK_a could be achieved. Following methods were used for this calculation:

The B3LYP/6-31+G(d,p) level was used for both solvation and gas phase calculations. The -265.9 kcal.mol^{-1} value was used for free energy of solvation of H^+ from Tissandier and coworkers.[2] It should be mentioned that the mono-hydrated TMZs were used for these computations to give better results.

As there is no experimental data available for pK_a of TMZ, imidazole ring is selected to see the certainty of the used methods. The calculated imidazole pK_a is 7.35, which is in notable agreement to the experimental, 6.97, value.

	Exp. pK_a	**Calc. pK_a**
Imidazole	6.97	7.35
TMZ	---	-2.625*

* Average value of O13 and N9 protonated species.

[1]R. Casasnovas, J. Ortega-Castro, J. Frau, J. Donoso, F. Muñoz. Int. J. Quantum Chem., 2014.

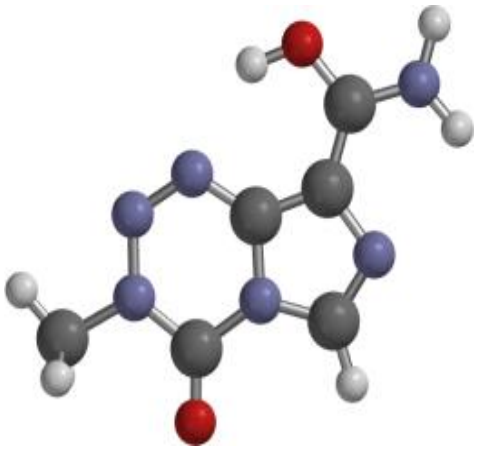
[2] M.D. Tissandier, K.A. Cowen, W.Y. Feng, E. Gundlach, M.H. Cohen, A.D. Earhart, J.V. Coe, J. Phys. Chem. A., 1998.

S2. Figure and Cartesian coordinates of all optimized protonated species at the B3LYP/6-311++G(2d,p) level of theory.

O13A

V1=74.22* cm^{-1}

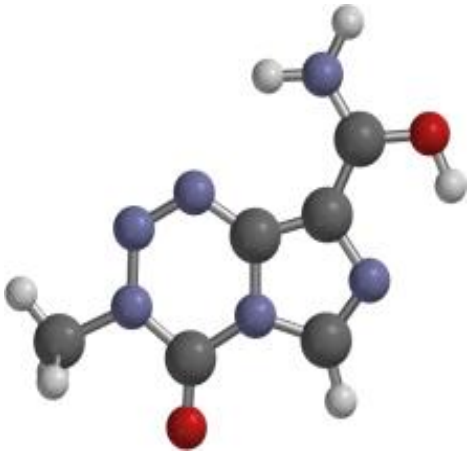
O	-2.76842800	1.60403200	0.00024800
C	-1.96531100	0.72198900	0.00022400
C	0.27338500	-0.17452100	-0.00017000
N	-1.41259700	-1.68051400	-0.00018900
N	-0.15657000	-1.45969800	-0.00027000
N	-2.27916700	-0.65175500	0.00004200
N	-0.56983400	0.90559000	-0.00008800
C	0.22228700	2.04412700	-0.00037500
N	1.48794300	1.72711700	0.00014900
C	1.55209000	0.35450400	0.00003100
C	-3.70606900	-1.01987900	0.00002400
C	2.76648400	-0.40231900	0.00015100
O	2.74825300	-1.70863700	0.00030300
N	3.93406700	0.18822300	-0.00008300
H	-0.19932200	3.03675600	-0.00043100
H	-4.18398800	-0.61061200	0.88841000
H	-3.75478200	-2.10414900	-0.00055500
H	-4.18420900	-0.60963400	-0.88778700
H	4.78780600	-0.35552300	-0.00008500
H	3.97943400	1.19982700	-0.00004300
H	1.83237200	-2.06597100	-0.00016500



O13B

V1=73.73 cm^{-1}

O	2.74830600	1.62624600	0.00075600
C	1.97067400	0.72067600	0.00074300
C	-0.25600000	-0.22874200	-0.00051400
N	1.46884400	-1.68916400	-0.00051300
N	0.20745200	-1.50322900	-0.00069100
N	2.31585800	-0.64099500	0.00013500
N	0.56998400	0.86925800	0.00018700
C	-0.22918600	1.99835300	-0.00023700
N	-1.49019800	1.66362300	-0.00054700
C	-1.54103600	0.29051900	-0.00019500
C	3.74943400	-0.97903200	0.00010800
C	-2.80560500	-0.37928100	0.00001800
O	-3.89948600	0.32951100	0.00030800
N	-2.92231500	-1.68427400	0.00012800
H	0.18114000	2.99557600	-0.00012500
H	4.21939300	-0.55937700	-0.88777400
H	3.82070300	-2.06206200	-0.00013400
H	4.21930800	-0.55976500	0.88821400
H	-3.83918700	-2.11365800	0.00038100
H	-2.09412200	-2.27043600	0.00025100
H	-3.67486000	1.28218400	0.00024900

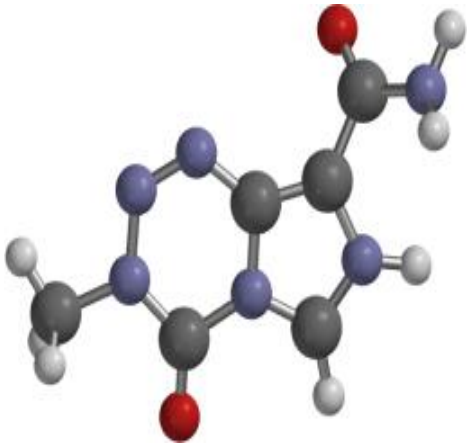


*The lowest frequency from the optimized structure.

N9 A

V1=39.34 cm^{-1}

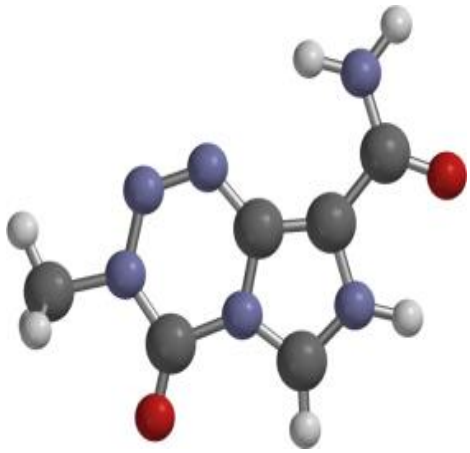
O	2.73409500	1.62364300	-0.11205800
C	1.99607200	0.68744500	-0.03510200
C	-0.27848600	-0.26526400	0.03969700
N	1.45984600	-1.70692000	0.17377800
N	0.21194400	-1.53254500	0.15916700
N	2.33023500	-0.64368500	0.06985900
N	0.57038700	0.83480300	-0.04143800
C	-0.14503400	1.95893000	-0.13364000
N	-1.42857200	1.59377900	-0.09804100
C	-1.56567500	0.22217100	0.00253800
C	3.75839200	-1.00364500	0.08812200
C	-2.87877300	-0.51216200	-0.08306200
O	-2.96639400	-1.46682700	-0.81342000
N	-3.89950400	0.05326200	0.62339600
H	0.25167600	2.95662500	-0.22875600
H	4.22776600	-0.67288900	-0.83686300
H	3.80930200	-2.08427900	0.17902000
H	4.24419900	-0.52213600	0.93517400
H	-4.78277700	-0.44126700	0.58638600
H	-3.71494700	0.55513400	1.48042300
H	-2.20615000	2.23856600	-0.18992000



N9 B

V1=70.15 cm^{-1}

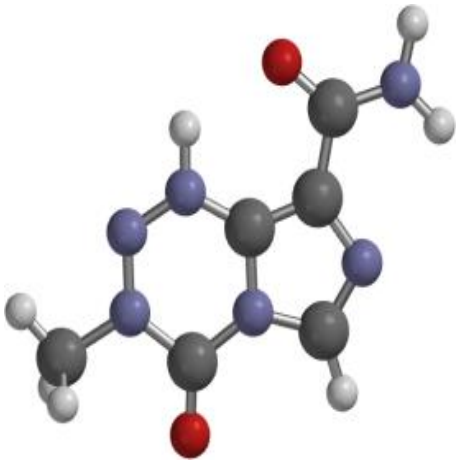
O	-2.73032700	1.63304900	0.00006000
C	-1.98337700	0.70263100	-0.00021900
C	0.27769400	-0.26037000	-0.00001500
N	-1.46461500	-1.70521700	-0.00003900
N	-0.21259800	-1.53125600	-0.00005800
N	-2.32261900	-0.64033400	-0.00007800
N	-0.56246300	0.84902700	-0.00008600
C	0.17441500	1.97081500	0.00006700
N	1.44609000	1.58667100	-0.00001800
C	1.56588900	0.21820900	0.00004200
C	-3.75515100	-0.98850400	0.00015300
C	2.95006400	-0.35198100	0.00008000
O	3.86955300	0.44672800	0.00002600
N	3.04636700	-1.69013100	0.00002100
H	-0.20949000	2.97805200	0.00007200
H	-4.22813200	-0.57591100	0.88966500
H	-3.81625200	-2.07229200	-0.00034300
H	-4.22857300	-0.57504800	-0.88871700
H	3.96763100	-2.10504000	-0.00005900
H	2.23593400	-2.29296100	-0.00007700
H	2.27673400	2.17885600	-0.00006400



N5-A

V1=70.96 cm^{-1}

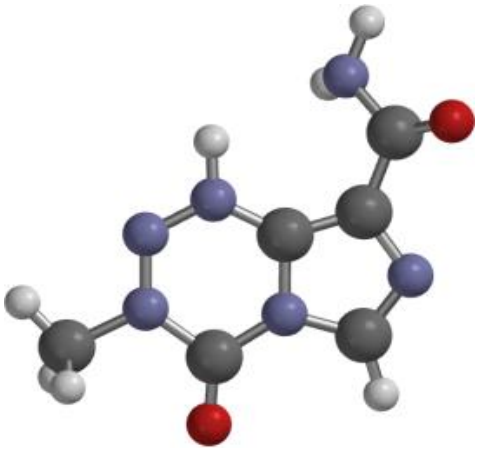
O	-2.74788500	1.60019900	-0.00012700
C	-1.92221600	0.74653200	-0.00019100
C	0.33684700	-0.13306300	0.00004700
N	-1.42457300	-1.66620100	0.00013700
N	-0.17251000	-1.39512300	0.00015500
N	-2.26015900	-0.65444700	-0.00000700
N	-0.53918100	0.93583000	-0.00010400
C	0.25099400	2.06769200	-0.00006800
N	1.52304600	1.74472100	0.00017600
C	1.60772700	0.38155700	0.00002800
C	-3.69822100	-0.99850900	0.00012000
C	2.79900800	-0.50482800	0.00006000
O	2.58660800	-1.71735500	-0.00048500
N	3.99937900	0.08213900	0.00018800
H	-0.16943000	3.06093500	-0.00009600
H	-4.16295900	-0.57688300	0.88935000
H	-3.76924200	-2.08157800	-0.00009700
H	-4.16317200	-0.57650100	-0.88881300
H	4.82983700	-0.49272800	0.00000900
H	4.09119800	1.08725900	0.00043700
H	0.50713700	-2.16796900	0.00032100



N5-B

V1=56.98 cm^{-1}

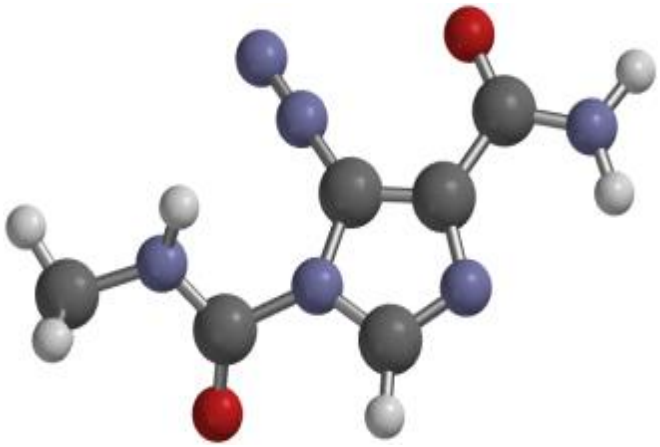
O	-2.78213000	1.53699900	0.05981200
C	-1.93685500	0.70346700	0.03166000
C	0.35850400	-0.12051300	0.05899000
N	-1.38641500	-1.68563800	-0.12244100
N	-0.13821200	-1.38951200	-0.05466000
N	-2.24606100	-0.70078300	-0.07468700
N	-0.56181200	0.91902700	0.08987500
C	0.18671000	2.07595700	0.14736300
N	1.46674800	1.80351400	0.13872400
C	1.61283300	0.44672300	0.08911200
C	-3.67493900	-1.07402300	-0.15326100
C	2.92101500	-0.26972800	-0.07140200
O	3.78086500	0.15214100	-0.79581800
N	2.94346000	-1.51101600	0.55696300
H	-0.27009600	3.05228900	0.19420500
H	-4.18123700	-0.72195700	0.74346100
H	-3.72185800	-2.15582200	-0.22853500
H	-4.11556500	-0.60183400	-1.02931500
H	3.82914800	-1.99373500	0.43983800
H	2.61559800	-1.53260200	1.51633600
H	0.50655800	-2.17990700	-0.09912600



N6-A

V1=46.13 cm^{-1}

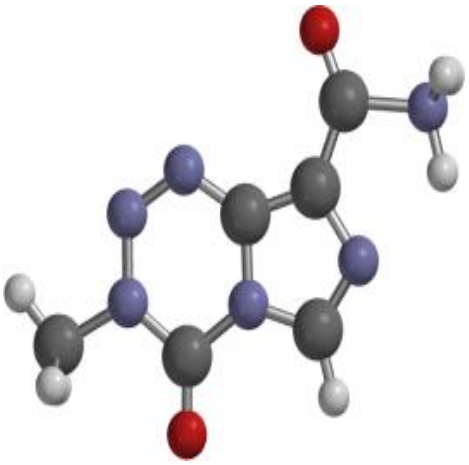
O	2.70389100	-1.41389500	0.81805100
C	2.15094500	-0.59058400	0.15223400
C	-0.34795400	0.24461000	0.01586000
N	-0.00597200	2.63487700	0.42092700
N	-0.16071900	1.55261000	0.23631700
N	2.65772900	0.48368600	-0.47562100
N	0.66790900	-0.70646600	-0.00662800
C	0.02419800	-1.89088900	-0.10094200
N	-1.29848900	-1.76029000	-0.15859400
C	-1.56041400	-0.45257200	-0.07654700
C	4.10481000	0.74553400	-0.41926800
C	-2.89404800	0.22567600	-0.06031400
O	-2.89743400	1.44307300	0.03478600
N	-3.95767100	-0.58166600	-0.15103000
H	0.56837000	-2.82366900	-0.12553600
H	4.45114100	0.58043200	0.59783700
H	4.27595600	1.78284600	-0.69774700
H	4.65019200	0.08523300	-1.09444900
H	-4.88349400	-0.17772200	-0.13921300
H	-3.85376300	-1.58358600	-0.21673200
H	2.15521200	0.85312800	-1.27059400



N14-A

V1=67.49 cm^{-1}

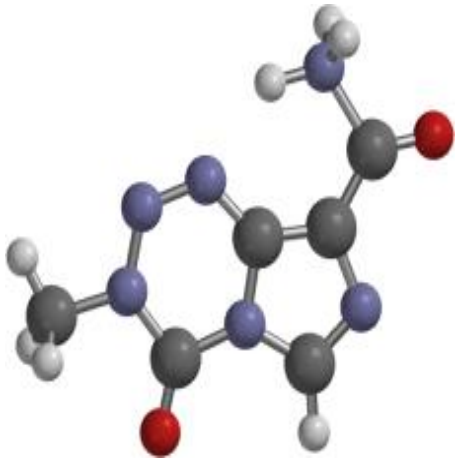
O	2.68766600	1.71095700	0.00003200
C	1.97701300	0.74975900	-0.00027600
C	-0.20161400	-0.33178500	-0.00004000
N	1.61079400	-1.67860300	-0.00002500
N	0.34236600	-1.57436200	-0.00008800
N	2.40241500	-0.57962100	-0.00003900
N	0.56720500	0.80863800	-0.00010000
C	-0.27526200	1.90089700	0.00001900
N	-1.51987500	1.51336900	0.00012900
C	-1.51729800	0.13198000	-0.00000800
C	3.85085900	-0.83905500	0.00019400
C	-2.74185700	-0.60857700	-0.00002100
O	-3.00601000	-1.75950500	0.00003100
N	-3.97029900	0.41180900	0.00003400
H	0.09363100	2.91410200	0.00003300
H	4.29828900	-0.39584600	-0.88799800
H	3.97969900	-1.91686300	0.00064000
H	4.29812700	-0.39511900	0.88810100
H	-4.54516300	0.23819000	0.82830100
H	-3.61179900	1.37792000	-0.00006500
H	-4.54532000	0.23807700	-0.82809300



N14-B

V1=63.06 cm^{-1}

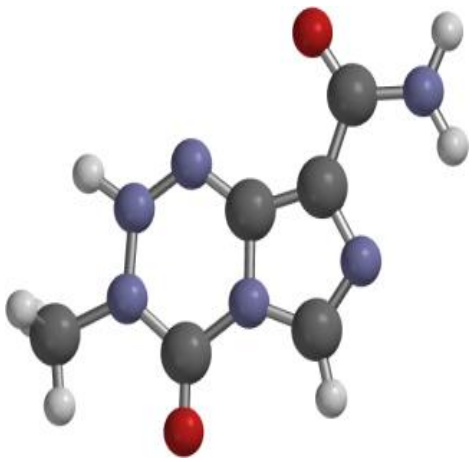
O	-2.81706500	1.52893000	-0.00000600
C	-1.97456800	0.68466600	0.00004700
C	0.30991700	-0.10412000	0.00009200
N	-1.32138700	-1.68600900	0.00007100
N	-0.07587900	-1.40673300	0.00011500
N	-2.23219100	-0.70267100	0.00001500
N	-0.59086400	0.92836500	-0.00001800
C	0.14010000	2.10979400	-0.00001200
N	1.41765000	1.86599300	-0.00014600
C	1.56624900	0.49855600	-0.00006300
C	-3.64201300	-1.13063200	-0.00003900
C	2.85326500	-0.14195200	-0.00003200
O	3.95375600	0.28307400	0.00025100
N	2.72653900	-1.73266500	-0.00018400
H	-0.33769100	3.07698100	-0.00002800
H	-4.13653800	-0.74143000	0.88830300
H	-3.64642700	-2.21598400	-0.00109600
H	-4.13695700	-0.73964800	-0.88735100
H	3.21945600	-2.08557700	0.82474400
H	1.74053600	-2.06696200	-0.00013800
H	3.21932700	-2.08525000	-0.82531200



N4-A

V1=50.26 cm^{-1}

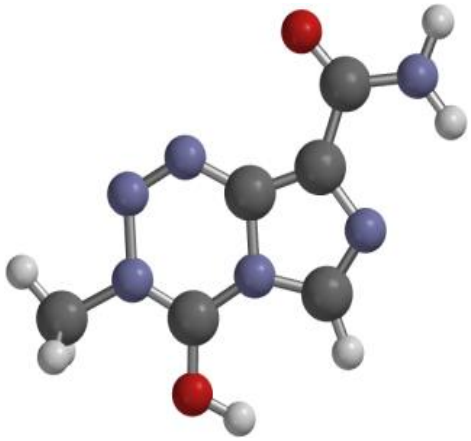
O	-2.67231500	1.71657800	0.00003100
C	-1.93551700	0.77937800	0.00000800
C	0.31974200	-0.25278600	0.00005700
N	-1.43705700	-1.58413700	-0.00005500
N	-0.17105900	-1.48326200	-0.00001500
N	-2.35036500	-0.55489000	-0.00012100
N	-0.52780700	0.87228300	0.00009200
C	0.27023200	1.96246700	0.00014100
N	1.55344800	1.61764800	0.00010800
C	1.62342500	0.27325200	0.00004500
C	-3.77374000	-0.92478100	-0.00011100
C	2.90098700	-0.51784900	-0.00000300
O	2.84706900	-1.73153100	0.00041300
N	4.01714300	0.23583900	-0.00053700
H	-0.11963700	2.96932200	0.00018400
H	-4.00936900	-1.49414200	0.89949200
H	-4.00921200	-1.49457700	-0.89947400
H	-4.33826100	0.00313000	-0.00037000
H	4.91387400	-0.22748500	-0.00013200
H	3.97606300	1.24348800	-0.00027600
H	-1.83239800	-2.52256500	-0.00010500



O1-A

V1=47.79 cm^{-1}

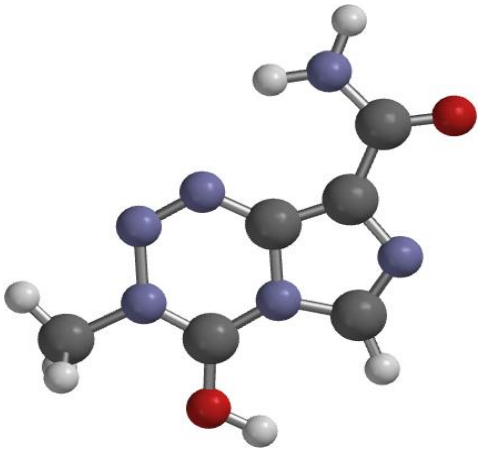
O	-2.77546200	1.57214900	0.00002800
C	-1.88869100	0.61097200	-0.00000300
C	0.33621700	-0.28402900	0.00000000
N	-1.37340500	-1.78275300	0.00001400
N	-0.15755700	-1.54148400	0.00003000
N	-2.29835000	-0.62959100	-0.00002600
N	-0.54964400	0.83069300	-0.00002700
C	0.24869500	1.95550400	-0.00006800
N	1.50988300	1.62448800	0.00008200
C	1.60422800	0.25846400	-0.00001200
C	-3.71844900	-1.01336700	0.00000400
C	2.90670700	-0.49252100	0.00002000
O	2.90065000	-1.70515200	-0.00004200
N	3.99983200	0.29924500	0.00001100
H	-0.13426000	2.96544200	-0.00008000
H	-4.20548200	-0.62606100	0.89356100
H	-3.73928000	-2.09965700	-0.00097400
H	-4.20596200	-0.62441300	-0.89256500
H	4.90906800	-0.13849300	-0.00001900
H	3.93058700	1.30462200	0.00000800
H	-2.40371900	2.46826200	-0.00005500



O1B

V1=31.94 cm^{-1}

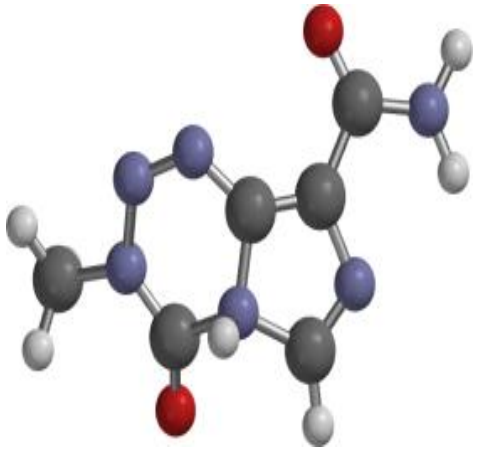
O	2.82306200	1.50138300	0.00013100
C	1.89059200	0.58755800	0.00025200
C	-0.35313700	-0.22237400	-0.00032700
N	1.31387100	-1.77318300	0.00000000
N	0.09542200	-1.49195100	-0.00012900
N	2.25224600	-0.67695500	0.00024700
N	0.56809400	0.86305800	-0.00017100
C	-0.21012800	2.00790000	-0.00095000
N	-1.47640100	1.70831700	0.00035800
C	-1.61070700	0.34760000	-0.00034700
C	3.66504500	-1.10091000	0.00026500
C	-2.98863600	-0.28040500	-0.00004000
O	-3.96069500	0.43674900	0.00031400
N	-3.01401200	-1.63447400	0.00014500
H	0.19709400	3.00859200	-0.00098100
H	4.16118200	-0.72522700	-0.89290100
H	3.65531300	-2.18685900	0.00020500
H	4.16109900	-0.72531400	0.89351300
H	-3.91780300	-2.08407800	0.00051800
H	-2.18512600	-2.20753100	-0.00003700
H	2.49659300	2.41546600	-0.00013300



N7-A

V1=50.31 cm^{-1}

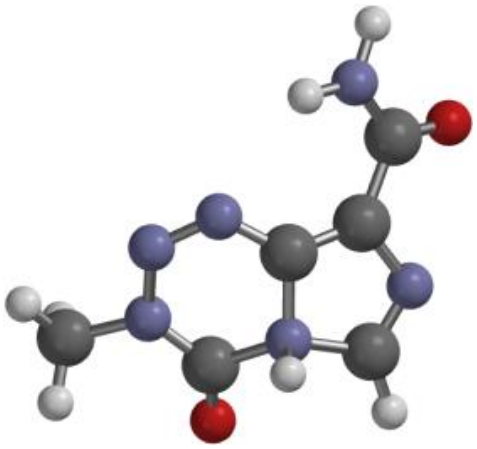
O	2.45812300	1.64793600	-0.57415500
C	1.90874100	0.70311400	-0.11860500
C	-0.31370300	-0.23769900	0.51856800
N	1.43891600	-1.67031500	0.42670400
N	0.23022300	-1.48339200	0.66519000
N	2.23768100	-0.60076900	-0.06725900
N	0.57289200	0.92863800	0.68260400
C	-0.31826700	2.05877300	0.29403700
N	-1.47733200	1.64405300	0.00965100
C	-1.51637000	0.23413200	0.11597400
C	3.53214900	-1.03626100	-0.63267800
C	-2.73125400	-0.58205100	-0.23299700
O	-2.65384000	-1.79059700	-0.21316600
N	-3.82173200	0.15108600	-0.54000000
H	0.05910000	3.07099600	0.33051000
H	3.47106700	-1.06202200	-1.71964400
H	3.72093900	-2.03304800	-0.24378600
H	4.31044000	-0.34504600	-0.31795000
H	-4.67379000	-0.33619400	-0.77813800
H	-3.81287700	1.15907100	-0.54192900
H	0.85854900	1.06238700	1.66548100



N7-B

V1=13.65 cm^{-1}

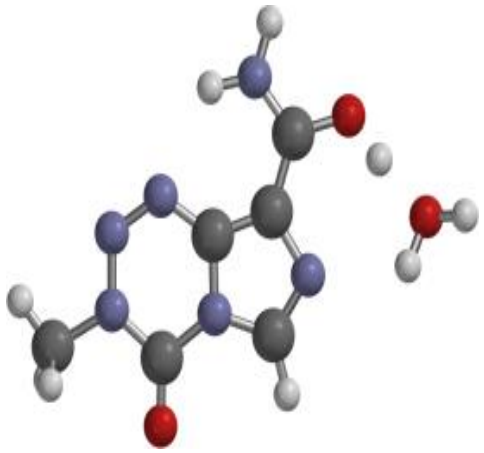
O	-2.54675800	1.57805500	0.50176800
C	-1.92778500	0.65911100	0.08387600
C	0.33321500	-0.19671200	-0.49978400
N	-1.34466600	-1.71422500	-0.30005400
N	-0.14045300	-1.47627000	-0.54786800
N	-2.20164300	-0.66952100	0.07871300
N	-0.60797500	0.92060700	-0.68690700
C	0.26454400	2.10134100	-0.33661500
N	1.44079100	1.73367700	-0.07732100
C	1.53202400	0.32676400	-0.15356600
C	-3.49948900	-1.12354800	0.62528900
C	2.81928900	-0.34038900	0.28341700
O	3.59806200	0.31365800	0.93711700
N	2.97242000	-1.62832200	-0.08789700
H	-0.15168100	3.09703800	-0.40026600
H	-3.48455400	-1.06023800	1.71229600
H	-3.62706200	-2.15488200	0.30937500
H	-4.29282300	-0.49607700	0.22618500
H	3.80318800	-2.11178300	0.22326500
H	2.25886400	-2.15355200	-0.56976500
H	-0.87647500	1.02477400	-1.67852800



O13w

V1=41.93 cm^{-1}

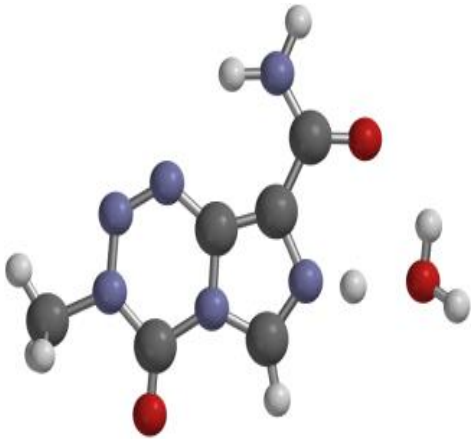
O	2.80268200	-1.96291800	-0.01742900
C	2.20463000	-0.92846100	-0.00742900
C	0.18000100	0.40612900	-0.00790500
N	2.14643800	1.53068400	0.02875500
N	0.87496200	1.57379600	0.01568700
N	2.79164500	0.34332800	0.01948700
N	0.80110100	-0.82041000	-0.02134600
C	-0.18201900	-1.78214000	-0.04837400
N	-1.36746800	-1.22977700	-0.05307600
C	-1.18035100	0.13423100	-0.02606000
C	4.26174900	0.41786200	0.03795200
C	-2.25929900	1.10449200	-0.02243900
N	-1.97112300	2.39071800	-0.02445500
O	-3.49979900	0.77995900	-0.02192900
O	-4.19080800	-1.62853900	0.16208100
H	-3.41454800	-2.17207800	-0.03891100
H	-4.95560500	-1.99014100	-0.30291900
H	-1.00693500	2.70878800	-0.02384400
H	-2.72521900	3.06473300	-0.01279900
H	4.63919900	-0.09160200	0.92294000
H	4.52654500	1.47033500	0.05686400
H	4.66035800	-0.06513400	-0.85257800
H	0.04422400	-2.83618700	-0.06309800
H	-3.74176300	-0.22776900	0.02271400



N9w

V1=56.65 cm^{-1}

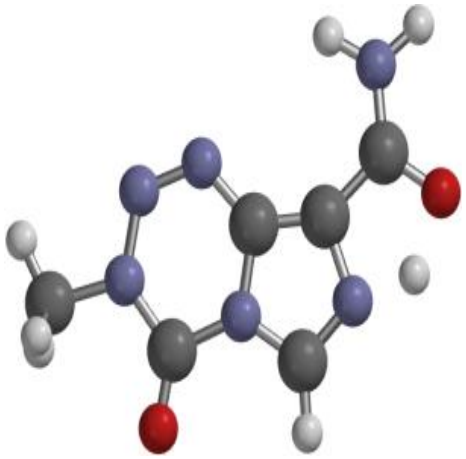
O	2.69608400	-1.99880100	-0.00925100
C	2.15846000	-0.93259800	-0.00479100
C	0.15738500	0.48408400	-0.00913600
N	2.16655100	1.52998000	0.01314300
N	0.90562600	1.62273700	0.00396900
N	2.77818400	0.30781300	0.00952000
N	0.74394100	-0.77401500	-0.01421800
C	-0.22348100	-1.70880900	-0.02508400
N	-1.38747700	-1.07692800	-0.02890500
C	-1.20499500	0.28745200	-0.01800300
C	4.25091200	0.34258300	0.02228900
C	-2.37442000	1.21916400	-0.01062200
O	-3.50516900	0.75693900	-0.00986700
N	-2.07405500	2.52746600	-0.00542600
O	-3.84801800	-2.01781300	0.10796500
H	-4.37802500	-2.67415100	-0.35912000
H	-0.05982700	-2.77394300	-0.02750600
H	-2.34802600	-1.54502600	-0.03124400
H	4.61826900	-0.16793500	0.91088200
H	4.63352000	-0.15596200	-0.86665000
H	4.54215900	1.38824500	0.03189500
H	-2.83579800	3.19077600	0.00450200
H	-1.12221400	2.86740800	-0.00260800
H	-4.30578000	-1.16264800	0.05456200



TS-1

V1= -1398.73 cm^{-1}

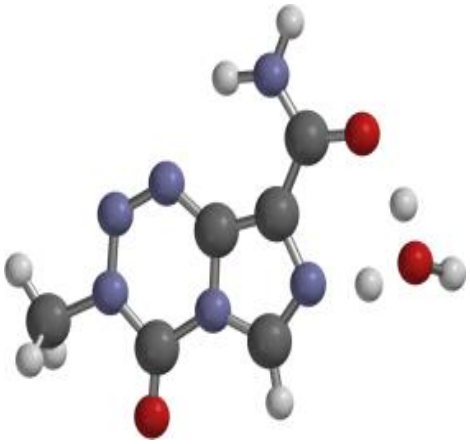
O	2.67132000	1.69357900	0.00004000
C	1.96672200	0.72966300	0.00002000
C	-0.22212300	-0.36379900	0.00001500
N	1.59800000	-1.70505200	0.00003500
N	0.33422500	-1.60515200	0.00003500
N	2.38817800	-0.59728000	0.00001400
N	0.54930200	0.79426200	-0.00000800
C	-0.27132300	1.88193700	-0.00003100
N	-1.51031200	1.44480100	-0.00002000
C	-1.52243900	0.07628200	0.00000300
C	3.83838900	-0.85652300	0.00006700
C	-2.93595700	-0.34869200	-0.00004100
O	-3.70644700	0.64554300	-0.00010500
N	-3.32177200	-1.60810200	-0.00002000
H	0.07342900	2.90313600	-0.00004600
H	4.28577300	-0.41363800	-0.88814800
H	3.96691400	-1.93434700	-0.00062000
H	4.28554100	-0.41482000	0.88899400
H	-4.30955000	-1.82758300	-0.00005900
H	-2.65186200	-2.36453400	0.00003300
H	-2.75218200	1.56124900	-0.00008500



TSw

V1= -488.87 cm^{-1}

O	2.76717900	-1.93726900	0.00367000
C	2.17816500	-0.89746400	0.00214100
C	0.13148200	0.43370300	0.00633100
N	2.09706800	1.56249500	-0.00444100
N	0.83101800	1.60269000	0.00103900
N	2.75356500	0.36949200	-0.00457900
N	0.76589800	-0.79544200	0.00757300
C	-0.18349700	-1.76446100	0.01188900
N	-1.37446600	-1.20182000	0.01527100
C	-1.22302300	0.17024700	0.01077600
C	4.22320300	0.45815300	-0.01212100
C	-2.37790400	1.10551400	0.00563200
O	-3.54813300	0.69340700	-0.00053600
N	-2.08362100	2.40696100	0.00960900
O	-3.76971300	-1.79632400	-0.10879300
H	-4.23033500	-2.25443700	0.60888700
H	0.03785800	-2.81933200	0.00963200
H	-2.63121400	-1.73407200	-0.00466600
H	4.62135400	-0.03057700	0.87546200
H	4.61238600	-0.03500400	-0.90123500
H	4.47696000	1.51357500	-0.01608900
H	-2.84639000	3.06960800	-0.00053300
H	-1.12897300	2.74373400	0.01065400
H	-3.92308100	-0.77678700	-0.05604200



S3. Cartesian coordinates of all optimized structures of Temozolomide degradation at the B3LYP/6-31+G(d) level of theory.

TMZ+water (rotamer A)
V1= 29.69 cm^{-1}

C	0.39914700	-0.18320400	-0.30449400
N	-0.41418800	0.94150800	-0.15115800
C	0.40149100	2.00615000	0.11593900
N	1.66436700	1.63420600	0.13032900
C	1.69636100	0.28152700	-0.12335700
C	-1.81084800	0.86340300	-0.21687700
N	-2.21560500	-0.41870600	-0.53679800
N	-1.39769100	-1.52948500	-0.67763400
N	-0.14073800	-1.41180000	-0.56796200
C	-3.64905200	-0.70259600	-0.59781900
O	-2.55238000	1.80949000	-0.03750300
C	2.97726600	-0.47839300	-0.16147100
N	4.08000300	0.30646000	0.00325300
O	3.02225900	-1.69380700	-0.32219800
H	0.01534700	3.00111100	0.28256300
H	-4.13378100	-0.01044800	-1.28967000
H	-4.09423300	-0.59126500	0.39510800
H	-3.75504800	-1.72965900	-0.94606500
H	4.99037600	-0.13126600	0.00133200
H	3.99298700	1.30322900	0.14889900
H	-0.76754200	-1.79968300	2.31114300
O	-1.24694300	-0.95832700	2.37555000
H	-1.15080600	-0.67745500	3.29815600

TS-I of path-1(rotamer A)
V1= -1305.02 cm^{-1}

N	-0.03863900	1.59295300	0.01752500
N	2.18200300	0.77912300	0.06341900
N	0.37178100	-0.79091100	-0.14608000
C	1.80112100	-0.70769400	-0.13674500
C	-0.48288600	0.29742800	-0.00885400
N	1.16273100	1.90141200	-0.00603100
C	-1.76837500	-0.23418600	-0.05516400
N	-1.69325900	-1.59403300	-0.21271900
C	-0.40869700	-1.89674300	-0.26945100
O	2.50857000	-1.47320800	-0.75536600
C	3.38840700	1.19612400	-0.67953300
C	-3.08148300	0.47589300	0.03084600
O	-3.16565200	1.68860600	0.18532700
N	-4.15160600	-0.35849000	-0.08099600
H	0.01145000	-2.88526600	-0.38955500
H	4.22265300	0.55687400	-0.38903700
H	3.59006300	2.23458700	-0.41376800
H	3.21851600	1.10684200	-1.75496400
H	-5.08054000	0.03258800	-0.01040600
H	-4.02497400	-1.35627500	-0.18695600
H	2.37203900	0.45319700	1.18809300
O	2.07556900	-0.75162000	1.73400200
H	2.82328900	-1.34807000	1.91247600

I of path-1(rotamer A)
V1= 48.75 cm^{-1}

N	-0.03423300	-1.20569300	0.85123500
N	-1.83706700	-1.74071700	-0.40830000
N	1.62236200	0.25757900	-0.00724100
C	2.65866000	-0.69767200	-0.05142600
C	0.25272000	0.00507900	0.21933100
N	-0.98419100	-1.99686100	0.57826500
C	-0.34496500	1.24803500	0.01441500
N	0.60607900	2.21040900	-0.31023200
C	1.75405200	1.60384000	-0.31790100
O	2.51602100	-1.88683500	-0.15888100
C	-2.96878800	-2.65696600	-0.49958400
C	-1.76329800	1.63903000	0.10973000
O	-2.68290700	0.81125700	0.20854300
N	-1.98889700	2.97485500	0.06394900
H	2.71203900	2.03889800	-0.56109900
H	-3.33490700	-2.66236500	-1.53014800
H	-3.78418400	-2.35884900	0.17228800
H	-2.62681200	-3.65892700	-0.23345500
H	-2.94310300	3.30669700	0.06009100
H	-1.22206500	3.61703000	-0.08757900
H	-2.06724400	-0.74858500	-0.55446600
O	3.85538100	-0.06502000	0.02190500
H	4.53964200	-0.75420200	-0.05929500

II of path-1(rotamer A)
V1= 50.12 cm^{-1}

N	0.16318700	1.10950200	-1.12516000
N	-1.01303100	2.55925500	0.18218100
N	1.35369300	-0.66015000	-0.03754200
C	2.62836700	-0.02400500	0.00500400
C	0.13940400	-0.01850400	-0.31488800
N	-0.44422600	2.20285600	-0.95212400
C	-0.83062700	-0.97005600	-0.01345000
N	-0.24037200	-2.13652200	0.45805300
C	1.04365500	-1.93419800	0.43875800
O	2.78947200	1.12048800	0.32432200
C	-0.90861700	1.96663200	1.51163800
C	-2.28996700	-0.86016900	-0.21116900
O	-2.82758000	0.18805400	-0.57504000
N	-2.98367100	-2.00506700	0.05031500
H	1.80182100	-2.61050200	0.81236700
H	-1.55608300	1.09278100	1.62017000
H	-1.21776400	2.73498600	2.22484100
H	0.12974200	1.69139100	1.72246600
H	-3.98451700	-2.00756400	-0.08543400
H	-2.50526900	-2.84989900	0.33186100
H	-1.44642900	3.46738100	0.09140300
O	3.65091900	-0.84860300	-0.30862800
H	3.33364900	-1.64540400	-0.76832300

TS-II of path-1(rotamer A)
V1= -1874.66 cm^{-1}

C	0.12974500	-0.10432600	-0.48217700
N	1.30531500	-0.88833500	-0.33169300
C	0.86046000	-2.10215100	0.23501300
N	-0.42327300	-2.14807900	0.37996900
C	-0.91568500	-0.90906100	-0.06219900
N	0.25619100	1.05104900	-1.22678600
N	-0.27210700	2.18330000	-1.00958000
C	2.81335200	-0.13234900	0.21894900
O	3.43673600	-0.42603900	-0.84057100
O	2.89829400	0.39991700	1.26948300
C	-2.36491900	-0.63792700	-0.13052400
O	-2.81367200	0.44404600	-0.51692000
H	1.55828700	-2.88932400	0.49268000
H	2.31424700	-0.88253700	-1.17941300
N	-0.77985600	2.54197800	0.15139400
H	-1.15350000	3.47970000	0.09777200
C	-0.63982400	1.92764700	1.46715100
H	-0.84588700	2.70811400	2.20371400
H	0.38489300	1.56923100	1.61283400
H	-1.34009700	1.10108000	1.61050100
N	-3.15493700	-1.67343300	0.27650200
H	-4.15668200	-1.58000800	0.18458200
H	-2.75022600	-2.56599100	0.52548200

III of path-1(rotamer A)
V1= 20.95 cm^{-1}

C	-0.05145500	-0.41768900	0.16751600
N	0.46068300	-1.58045600	0.70676600
C	-0.54661400	-2.50562600	0.76034500
N	-1.66650000	-2.02272600	0.27944500
C	-1.38783900	-0.72154900	-0.10821300
N	0.86497000	0.56460900	-0.21769600
N	0.75356100	1.81775000	-0.05853700
C	3.75728900	-0.28248400	-0.50562400
O	3.49693500	-1.13168200	0.26225600
O	4.07121000	0.54279100	-1.26545000
C	-2.38724500	0.10624200	-0.80980700
O	-2.15113800	1.25677800	-1.18969600
H	-0.40414500	-3.49848700	1.16558800
H	1.44106700	-1.71174800	0.92849100
N	-0.14009900	2.39607400	0.72531100
H	-0.05644700	3.40101400	0.66520400
C	-0.97089300	1.84095800	1.78862300
H	-1.25131000	2.67610500	2.43592100
H	-0.40224900	1.11531500	2.37932600
H	-1.87442700	1.36497600	1.40228300
N	-3.59693300	-0.50267300	-0.98908500
H	-4.28538300	-0.03870000	-1.56447100
H	-3.71238900	-1.47871800	-0.74968600

TMZ+water (rotamer B)
V1= 8.69 cm^{-1}

C	-0.83546000	0.23249600	-0.04113300
N	0.16887300	-0.72405300	-0.20926600
C	-0.45613200	-1.94654400	-0.24536100
N	-1.75823800	-1.81804900	-0.11386300
C	-2.02871800	-0.47985100	0.01552500
C	1.51330000	-0.36244600	-0.30487100
O	2.41689600	-1.16833100	-0.45443800
C	-3.42911800	0.02773700	0.18627900
N	-3.53738800	1.38429900	0.30052800
O	-4.38822800	-0.73014700	0.21741800
N	-0.53898200	1.56137700	0.03170200
N	0.66615600	1.94864200	-0.05249700
N	1.67494500	1.00886600	-0.21534300
C	3.02688200	1.57763700	-0.31609900
H	0.09254500	-2.86899600	-0.36836300
H	-2.73586300	2.00353900	0.27161800
H	-4.46257700	1.77418700	0.41796000
H	3.66657700	1.18631100	0.47774000
H	2.91642100	2.65744100	-0.22585000
H	3.46309100	1.32111000	-1.28487900
H	5.50054600	-1.49388600	1.19611700
O	4.95453000	-0.75771200	0.88487700
H	4.22158500	-1.15193500	0.37793200

TS-I of path-1(rotamer B)
V1= -1355.74 cm^{-1}

N	-0.13879500	1.50590900	0.04321900
N	2.10344800	0.84776200	0.05618000
N	0.39014000	-0.85334800	-0.13904300
C	1.80921500	-0.69566100	-0.10992900
C	-0.50982700	0.19255500	0.00240200
N	1.05180000	1.88832100	0.00949500
C	-1.78018900	-0.38557900	-0.06865200
N	-1.65089100	-1.73339400	-0.24243600
C	-0.35538000	-1.98501000	-0.28711900
O	2.57231800	-1.41277300	-0.71893600
C	3.27863700	1.31318900	-0.70996800
C	-3.13494500	0.26187300	0.00631900
O	-4.16040000	-0.40252500	-0.03356200
N	-3.12331000	1.62132800	0.12337900
H	0.09980000	-2.95672500	-0.41855100
H	4.13741600	0.69630200	-0.44537000
H	3.45518200	2.35482100	-0.43867700
H	3.08597600	1.22838800	-1.78205100
H	-4.01419800	2.09640800	0.17569700
H	-2.26649400	2.16104800	0.14303300
H	2.33154900	0.51899300	1.18509300
O	2.09235400	-0.68402100	1.71873500
H	2.86479200	-1.24892400	1.89706100

I of path-1 (rotamer B)
V1= 23.70 cm^{-1}

N	-0.02140000	0.89902000	-1.17985300
N	-0.38782500	2.18568500	0.63173400
N	-1.00259400	-1.06317900	0.02031400
C	-2.38733000	-0.92555700	-0.16850500
C	0.08251500	-0.24396100	-0.35169400
N	-0.22289800	2.04443300	-0.67023200
C	1.20764800	-0.92604700	0.06830000
N	0.85191900	-2.11354500	0.69715800
C	-0.44119900	-2.17943300	0.64721400
O	-3.18325900	-1.78178500	0.14365700
C	-0.40938900	3.52764300	1.19263100
C	2.64571300	-0.54937100	-0.08729000
O	3.53621600	-1.12117100	0.52787100
N	2.89115800	0.49663500	-0.94221800
H	-1.07101000	-2.97121700	1.02687200
H	0.57178000	3.81175000	1.59244200
H	-1.15487800	3.57821900	1.99179400
H	-0.68689500	4.21938000	0.39533500
H	3.86242100	0.67491800	-1.16320200
H	2.18531400	0.81938000	-1.59479600
H	-0.19028200	1.38835700	1.23975200
O	-2.70207800	0.25892800	-0.71603600
H	-3.66975100	0.26845100	-0.83439400

II of path-1 (rotamer B)
V1= 33.36 cm^{-1}

C	-0.19696000	-0.18403000	0.30688500
N	0.71618100	-1.20721500	0.00140300
C	-0.02956100	-2.21430700	-0.61977300
N	-1.28579700	-1.90305600	-0.71338400
C	-1.42511000	-0.65848000	-0.12020200
N	0.09636600	0.89829600	1.16855500
N	0.61205900	1.97633300	0.72973300
N	0.88247100	2.13227000	-0.54271000
C	1.64280100	3.29638100	-0.96715600
C	2.12468300	-1.16443300	0.17694900
O	2.69122300	-2.37095700	0.37514400
O	2.76516400	-0.14859600	0.12645200
C	-2.77344100	-0.02394900	0.00817500
O	-3.74526200	-0.43802400	-0.61116500
N	-2.83139500	1.05463500	0.84969100
H	0.43640600	-3.10092800	-1.03187000
H	0.79205300	1.33435800	-1.17240300
H	1.54160200	4.06230500	-0.19634600
H	1.23744000	3.67347200	-1.91072700
H	2.70273300	3.04663900	-1.09487900
H	2.03100800	-3.04634500	0.60945000
H	-3.74709100	1.44192400	1.03540300
H	-2.06682100	1.28325500	1.47564500

TS-II of path-1(rotamer B)
V1= -1869.44 cm^{-1}

C	-0.20610900	-0.30307000	0.49170200
N	0.77509300	-1.30492800	0.28015900
C	0.09006600	-2.29519800	-0.47018300
N	-1.15137300	-2.01252800	-0.67790000
C	-1.37030700	-0.76644400	-0.07084000
N	0.05298000	0.78810000	1.35100600
N	0.48501500	1.89341800	0.88463500
N	0.67904600	2.05632000	-0.40303500
C	1.22351300	3.30930400	-0.89825500
C	2.47281900	-0.94699400	-0.07973800
O	2.89602600	-1.52567700	0.96105200
O	2.79680900	-0.34428300	-1.04302000
C	-2.72660800	-0.13919100	-0.09024300
O	-3.60825300	-0.52235000	-0.84777900
N	-2.89218200	0.90995400	0.77640900
H	0.60135500	-3.19217500	-0.79873400
H	0.49542300	1.28560000	-1.04753400
H	1.31101000	3.99117700	-0.05071100
H	0.55390600	3.74358700	-1.64805600
H	2.21239600	3.14923300	-1.34201200
H	1.66330100	-1.68924100	1.17245000
H	-3.82678000	1.28802900	0.86107900
H	-2.22755700	1.09947900	1.51792500

III of path-1(rotamer B)
V1= 20.19 cm^{-1}

C	-0.07602000	-0.62616600	-0.10826800
N	0.49801000	-1.74192900	-0.67355200
C	-0.48867600	-2.67687500	-0.83741300
N	-1.64849400	-2.24122300	-0.40972400
C	-1.42191600	-0.96486800	0.06517100
N	0.78246800	0.42869900	0.27599300
N	0.57823100	1.62651600	-0.11327600
N	-0.42449600	1.92806500	-0.91195600
C	-0.66996100	3.31893600	-1.24671900
C	3.75200500	-0.19513300	0.44467800
O	3.51710300	-1.08458000	-0.28394400
O	4.03593200	0.67511200	1.16572600
C	-2.51732700	-0.19064100	0.71117300
O	-3.70101500	-0.36235700	0.44935700
N	-2.09893200	0.78269100	1.59605700
H	-0.30041000	-3.64754900	-1.27647500
H	-1.09538700	1.20917100	-1.18167900
H	0.21172500	3.89406600	-0.95743800
H	-1.54677000	3.70397500	-0.71211800
H	-0.83188600	3.42087400	-2.32464400
H	1.48674400	-1.82498900	-0.88293600
H	-2.83097100	1.22292100	2.14017000
H	-1.18534400	0.72486700	2.02949500

TMZ+water (rotamer A)
V1= 29.69 cm^{-1}

C	0.39914700	-0.18320400	-0.30449400
N	-0.41418800	0.94150800	-0.15115800
C	0.40149100	2.00615000	0.11593900
N	1.66436700	1.63420600	0.13032900
C	1.69636100	0.28152700	-0.12335700
C	-1.81084800	0.86340300	-0.21687700
N	-2.21560500	-0.41870600	-0.53679800
N	-1.39769100	-1.52948500	-0.67763400
N	-0.14073800	-1.41180000	-0.56796200
C	-3.64905200	-0.70259600	-0.59781900
O	-2.55238000	1.80949000	-0.03750300
C	2.97726600	-0.47839300	-0.16147100
N	4.08000300	0.30646000	0.00325300
O	3.02225900	-1.69380700	-0.32219800
H	0.01534700	3.00111100	0.28256300
H	-4.13378100	-0.01044800	-1.28967000
H	-4.09423300	-0.59126500	0.39510800
H	-3.75504800	-1.72965900	-0.94606500
H	4.99037600	-0.13126600	0.00133200
H	3.99298700	1.30322900	0.14889900
H	-0.76754200	-1.79968300	2.31114300
O	-1.24694300	-0.95832700	2.37555000
H	-1.15080600	-0.67745500	3.29815600

TS-I of path-2(rotamer A)
V1= -1503.41 cm^{-1}

N	-0.18805300	-1.44683200	0.44717600
N	-2.06715000	-0.69611100	-0.50208200
N	-0.39336600	0.90237500	-0.02767600
C	-1.78482900	0.71700300	0.21169800
C	0.42033300	-0.20954200	0.10636400
N	-1.33682500	-1.70775800	-0.28065700
C	1.70757800	0.25009600	-0.08262500
N	1.66594800	1.61456600	-0.33369300
C	0.40812700	1.98524500	-0.28381200
O	-2.65236200	1.55586600	0.11981400
C	-3.32405700	-0.86440800	-1.23050600
C	2.99101000	-0.50170500	-0.05433200
O	3.05078800	-1.70764400	0.16645000
N	4.08378900	0.27697300	-0.29977500
H	0.01362900	2.97952700	-0.43681800
H	-3.47343900	-1.93024500	-1.40552000
H	-3.26155800	-0.32090100	-2.17736300
H	-4.13226700	-0.43248000	-0.63636500
H	4.99810900	-0.15174500	-0.28176500
H	3.98752600	1.27046300	-0.46119200
H	-0.82357500	-0.99907000	1.43851700
O	-1.60707800	0.02089800	1.81621000
H	-2.49857700	-0.23112900	2.11694200

I of path-2(rotamer A)
V1= 40.78 cm^{-1}

N	0.12554900	1.17844700	0.85535900
N	1.78972300	1.43736000	-0.58657500
N	0.45150100	-1.14073600	0.00638100
C	1.79550800	-1.45357500	0.29671300
C	-0.32027400	-0.01598700	0.29852400
N	1.06888100	1.99568200	0.26020100
C	-1.60513100	-0.35649800	-0.07013700
N	-1.64234000	-1.64235000	-0.59046800
C	-0.41674400	-2.07793700	-0.54983500
O	2.38992100	-2.34882900	-0.25713900
C	2.77694100	2.35120300	-1.15902600
C	-2.79202200	0.50513300	0.08162900
O	-2.72264700	1.60327100	0.65073000
N	-3.94021700	0.00282800	-0.43940900
H	-0.05226200	-3.03915200	-0.88167100
H	2.69654100	3.36229000	-0.74262200
H	2.62954100	2.37673700	-2.24455600
H	3.77813900	1.94533400	-0.97146800
H	-4.79808000	0.52573000	-0.33267100
H	-3.95399500	-0.91672200	-0.86064700
H	-0.65766400	1.74280300	1.18481200
O	2.27636600	-0.70075700	1.29407300
H	3.20730800	-0.95916200	1.42186100

II of path-2(rotamer A)
V1= 46.97 cm^{-1}

N	0.39715900	-1.10071700	0.29555400
N	2.20090100	-2.26383700	-0.04078300
N	0.13410700	1.30228900	-0.08510700
C	1.42331400	1.80756600	0.30273600
C	-0.36204100	0.01834000	0.09238000
N	1.68871100	-1.13178700	-0.13900900
C	-1.73742000	0.12353600	-0.02634800
N	-2.09939000	1.44428100	-0.24992800
C	-0.99308600	2.12282600	-0.28425000
O	2.00878200	1.46927400	1.28883200
C	3.58703400	-2.28958700	-0.49717500
C	-2.67281700	-1.00440600	0.04960900
O	-2.26653200	-2.15512300	0.27034000
N	-3.98296500	-0.69854500	-0.14106300
H	-0.89605500	3.19403700	-0.40000200
H	3.92911800	-1.31111500	-0.85485900
H	3.67191500	-3.03668400	-1.29462000
H	4.21473400	-2.62409200	0.33690900
H	-4.67325500	-1.43211500	-0.06422600
H	-4.27418300	0.25847900	-0.28813600
H	-0.12000800	-1.97556900	0.43158400
O	1.87389300	2.76557200	-0.53349500
H	1.37902100	2.75783700	-1.37143200

TS-II of path-2(rotamer A)
V1= -1783.59 cm^{-1}

N	-0.30642300	1.15257100	-0.11532000
N	-2.18622600	2.23987800	-0.05185100
N	-0.12877700	-1.26042600	-0.41952900
C	-1.73169300	-1.84678500	0.40345300
C	0.42643800	0.00180800	-0.19657400
N	-1.65678000	1.11237900	-0.15878700
C	1.79192100	-0.15299600	-0.09261000
N	2.12104300	-1.50666200	-0.23065300
C	0.99484900	-2.12334100	-0.40486900
O	-1.84527400	-1.88262200	1.56655400
C	-3.64311200	2.18003600	-0.09523600
C	2.75058600	0.93250800	0.12400600
O	2.36543800	2.10779500	0.23314300
N	4.05744400	0.56577000	0.19399500
O	-2.23591800	-2.06974400	-0.72840500
H	0.20054600	2.02951000	0.04212000
H	0.87335000	-3.18978900	-0.54809300
H	-4.03260800	2.60320400	0.83812600
H	-3.98910700	2.81998300	-0.91529400
H	-4.01960300	1.15885700	-0.23020200
H	4.75887000	1.27483000	0.35432100
H	4.32696600	-0.40498000	0.10740700
H	-1.22828100	-1.60699500	-1.17272300

III of path-2(rotamer A)
V1= 12.48 cm^{-1}

N	0.30199200	1.14006900	0.00104600
N	-1.36261200	2.53366400	0.00317600
N	0.11675000	-1.28363400	0.00795300
C	-3.96923500	-1.40533700	-0.00626800
C	0.83961200	-0.12266500	0.00283900
N	-1.03244800	1.32531000	0.00419100
C	2.17347300	-0.50453600	0.00020700
N	2.26277200	-1.88823900	0.00381700
C	1.02926900	-2.32305100	0.00797100
O	-4.98741400	-0.83689300	-0.01339900
C	-2.80738300	2.72391000	0.00633700
C	3.30657300	0.42093200	-0.00486200
O	3.12991000	1.65073500	-0.00742300
N	4.53913300	-0.15304500	-0.00658000
O	-2.94973000	-1.98289400	0.00093400
H	0.95359200	1.93053700	-0.00168400
H	0.71401800	-3.35729600	0.01146500
H	-3.07877800	3.31496600	0.88910000
H	-3.08335100	3.31024000	-0.87818500
H	-3.36049600	1.77599900	0.01024000
H	5.35786300	0.43810600	-0.00992500
H	4.63563100	-1.15964800	-0.00416000
H	-0.89356600	-1.35488100	0.00969400

TMZ+water (rotamer B)
V1= 8.69 cm^{-1}

C	-0.83546000	0.23249600	-0.04113300
N	0.16887300	-0.72405300	-0.20926600
C	-0.45613200	-1.94654400	-0.24536100
N	-1.75823800	-1.81804900	-0.11386300
C	-2.02871800	-0.47985100	0.01552500
C	1.51330000	-0.36244600	-0.30487100
O	2.41689600	-1.16833100	-0.45443800
C	-3.42911800	0.02773700	0.18627900
N	-3.53738800	1.38429900	0.30052800
O	-4.38822800	-0.73014700	0.21741800
N	-0.53898200	1.56137700	0.03170200
N	0.66615600	1.94864200	-0.05249700
N	1.67494500	1.00886600	-0.21534300
C	3.02688200	1.57763700	-0.31609900
H	0.09254500	-2.86899600	-0.36836300
H	-2.73586300	2.00353900	0.27161800
H	-4.46257700	1.77418700	0.41796000
H	3.66657700	1.18631100	0.47774000
H	2.91642100	2.65744100	-0.22585000
H	3.46309100	1.32111000	-1.28487900
H	5.50054600	-1.49388600	1.19611700
O	4.95453000	-0.75771200	0.88487700
H	4.22158500	-1.15193500	0.37793200

TS-I of path-2(rotamer B)
V1= -1543.36 cm^{-1}

N	-0.06847900	-1.36684600	0.47051200
N	-1.97811000	-0.76765500	-0.50552300
N	-0.41667900	0.96946700	-0.01353600
C	-1.78840200	0.71122400	0.23105700
C	0.45609700	-0.09529000	0.11215300
N	-1.18598000	-1.72317200	-0.28295400
C	1.71864700	0.41326800	-0.11031100
N	1.61229600	1.76777500	-0.37599400
C	0.34378600	2.08292300	-0.30525500
O	-2.71656400	1.47375100	0.12295900
C	-3.21192000	-1.01236800	-1.24915700
C	3.03301600	-0.29644500	-0.10132900
O	4.09102400	0.27349900	-0.33390800
N	2.95254000	-1.63282400	0.18450100
H	-0.09497500	3.05741300	-0.46582700
H	-3.30976000	-2.08586900	-1.41533300
H	-3.16154200	-0.47584400	-2.20100000
H	-4.04880400	-0.61183200	-0.67244100
H	3.81262100	-2.16278500	0.20654700
H	2.07124400	-2.09375600	0.38097900
H	-0.76146600	-0.93485700	1.45091300
O	-1.59351200	0.00962800	1.81205300
H	-2.47136100	-0.29459000	2.10534700

I of path-2(rotamer B)
V1= 28.55 cm^{-1}

N	-0.05094500	0.94996500	-1.13815400
N	-0.50342800	2.05060700	0.73217100
N	-0.88201900	-1.10522700	0.01888500
C	-2.26728400	-1.08516900	-0.18464900
C	0.14776100	-0.24925800	-0.43188200
N	-0.54445100	2.09874500	-0.50522200
C	1.31147000	-0.79911100	0.05352400
N	1.04288000	-1.95506900	0.76984800
C	-0.24644600	-2.10900600	0.73944400
O	-3.03412300	-1.84595800	0.35795800
C	-0.94828700	3.29511000	1.35708500
C	2.72926000	-0.32448100	-0.08939700
O	3.65543500	-0.90390100	0.46118000
N	2.90885800	0.77353100	-0.88309800
H	-0.81427100	-2.91368900	1.18515600
H	-1.26400200	4.04367900	0.62070100
H	-0.12233600	3.68457500	1.96273100
H	-1.77254000	3.05759000	2.03845400
H	3.84399900	1.15011700	-0.95599400
H	2.12644300	1.28622600	-1.26958700
H	-0.48365700	0.88296600	-2.05267900
O	-2.62979200	-0.13378700	-1.07014000
H	-3.60090200	-0.17865900	-1.14652900

II of path-2(rotamer B)
V1= 39.01 cm^{-1}

N	-0.15500500	0.86272000	-1.16011300
N	-0.86588800	2.01214000	0.60181000
N	-0.83155500	-1.14838900	0.06423500
C	-2.23752200	-1.18413500	-0.21899900
C	0.15883100	-0.25937800	-0.35858400
N	-0.42528600	2.12048400	-0.54851100
C	1.34481400	-0.75267900	0.14402500
N	1.11105600	-1.91364000	0.85584300
C	-0.17790600	-2.11366500	0.80682300
O	-2.95898900	-1.97284800	0.33233300
C	-1.20949300	3.29937100	1.20407700
C	2.73375800	-0.24569000	-0.06916300
O	3.70345900	-0.98518600	-0.08681600
N	2.83164300	1.11105300	-0.33432500
H	-0.72405600	-2.92449600	1.26694500
H	-0.99033600	4.14419900	0.54142400
H	-0.65429000	3.39000400	2.14363000
H	-2.27609100	3.27613900	1.45262000
H	3.78373400	1.45866300	-0.37573900
H	2.16247800	1.74603700	0.08421800
H	0.50444700	1.03329300	-1.91422700
O	-2.64929600	-0.30868200	-1.13640600
H	-1.89691700	0.23637900	-1.47341500

TS-II of path-2(rotamer B)
V1= -1811.96 cm^{-1}

N	0.01460700	0.85032700	1.29689500
N	0.76613700	1.95624700	-0.46371500
N	0.68671700	-1.30816300	0.28484900
C	2.48519900	-1.00757800	-0.08782900
C	-0.27394300	-0.30165900	0.53659400
N	0.73095800	1.93331200	0.77493500
C	-1.44226900	-0.70147900	-0.05915200
N	-1.25579900	-1.92831300	-0.69914400
C	-0.01621400	-2.24472400	-0.48937100
O	2.84949800	-0.47175800	-1.06327300
C	1.47229800	3.12328800	-0.98660900
C	-2.78709700	-0.03651200	-0.10175700
O	-3.70756600	-0.49418800	-0.76487400
N	-2.90893300	1.09201000	0.66021100
H	0.46496300	-3.14836200	-0.84564600
H	1.84466100	3.77929800	-0.19071300
H	0.78441500	3.67090500	-1.64039300
H	2.30201800	2.76453500	-1.60535000
H	-3.77482800	1.60936400	0.59235500
H	-2.11131200	1.51087100	1.12147500
H	0.26817600	0.72543100	2.27079700
O	2.82369400	-1.57727300	0.98898600
H	1.63326000	-1.72224200	1.16129200

III of path-2(rotamer B)
V1= 3.53 cm^{-1}

N	1.18729100	1.50770400	-0.02979600
N	-0.91842400	2.16910800	-0.05000600
N	-0.23787400	-0.47801100	0.02676500
C	-4.59307700	-1.19783600	0.04461000
C	0.98560200	0.13361000	0.02836300
N	0.29070800	2.50874500	-0.11227500
C	1.92914900	-0.89811000	0.03445000
N	1.27596300	-2.11299900	0.02434100
C	-0.00333300	-1.83329100	0.02899400
O	-5.69339000	-1.58665200	0.05467100
C	-1.81142100	3.32254400	-0.13342400
C	3.39834900	-0.77859800	-0.02759600
O	4.13742000	-1.59909800	-0.54675700
N	3.89653600	0.43311900	0.49416700
H	-0.81130600	-2.55125100	0.04267100
H	-1.25822900	4.26342900	-0.23828700
H	-2.43106100	3.35379900	0.77067700
H	-2.48082200	3.18712900	-0.99111400
H	4.91293200	0.45101000	0.49367600
H	3.50931700	0.71427900	1.39126300
H	2.14615400	1.81551800	-0.14605700
O	-3.48932300	-0.80780600	0.03453300
H	-1.11565700	0.03097400	0.01283300

S4. Cartesian coordinates of all optimized transition states of Temozolomide reaction with different nucleophiles at the CBS-4M level of theory.

OH^- first detected transition state

V1= -1069.25 cm^{-1} ΔG (kcal.mol^{-1}) = 7.23

C	-0.52420600	-0.33347700	-0.19796500
N	0.32621500	0.74044000	-0.30636400
C	-0.41600200	1.88389000	-0.19307500
N	-1.66691900	1.58467300	-0.03471600
C	-1.76803500	0.19537900	-0.03903300
C	1.70668500	0.61844400	-0.47818100
N	2.08782200	-0.70679300	-0.49648100
N	1.23181700	-1.76368100	-0.37091900
N	-0.02143500	-1.61234800	-0.25852200
C	3.50690400	-0.96178400	-0.02447400
O	2.39644100	1.56445500	-0.75359400
C	-3.06292400	-0.46546700	0.11484400
N	-4.07873300	0.42100200	0.27640000
O	-3.23372700	-1.67395300	0.09931200
H	0.02944300	2.84619800	-0.22779200
H	3.31460600	-0.29379600	1.09032400
H	4.18151900	-0.55981200	-0.76965500
H	3.60236600	-2.03843100	0.03191100
H	-5.00398800	0.07619500	0.39680500
H	-3.88584000	1.39787300	0.28870500
O	2.56978100	0.42472500	1.89919900
H	2.09603400	-0.21500500	2.47187800

OH^- second detected transition state

V1= -432.30 cm^{-1} ΔG (kcal.mol^{-1}) = 20.58

C	-0.36367600	-0.13591500	-0.10541400
N	0.48825800	0.91225200	-0.39484700
C	-0.28744600	2.07208100	-0.33498500
N	-1.52844700	1.78264400	-0.20400000
C	-1.63366700	0.37882500	-0.10699400
C	1.81030600	0.70575200	-0.05733500
N	2.18430300	-0.60558300	-0.37821300
N	1.28428900	-1.66503200	-0.48356100
N	0.06872400	-1.44731700	-0.34787900
C	3.55155500	-1.02864800	-0.11545300
O	2.62898500	1.56935000	0.16967700
C	-2.90624700	-0.30401300	-0.00175200
N	-2.81367400	-1.66819100	0.03318600
O	-3.99809700	0.25214100	0.04183200
H	0.14903900	3.03537500	-0.43223200
H	3.69875800	-1.19731200	0.94487300
H	4.22269200	-0.25285600	-0.44543900
H	3.73078900	-1.94253800	-0.66074600
H	-3.66055000	-2.18442800	0.11274900
H	-1.93807300	-2.13952600	-0.04029800
O	0.65183400	-0.05088300	1.65881400
H	0.72644300	-0.77348500	2.31730800

MeOH

V1= -1661.35 cm^{-1} ΔG ($kcal.mol^{-1}$) = 55.91

N	-0.38714900	1.64315900	0.37494800
N	1.86207600	1.14055700	-0.02639100
N	0.21485000	-0.55539800	-0.41644000
C	1.62410900	-0.35188900	-0.40889000
C	-0.72376800	0.35503000	0.02026600
N	0.75762400	2.08488900	0.32822900
C	-1.92725200	-0.25963600	-0.10080900
N	-1.73552400	-1.52468900	-0.61012300
C	-0.45209200	-1.67501200	-0.79554400
O	2.36019500	-0.90949400	-1.21648900
C	2.83556700	1.85380600	-0.88952000
C	-3.27642800	0.25661500	0.21166000
O	-3.46777200	1.36851400	0.66586300
N	-4.24650700	-0.63780900	-0.06042300
H	0.04487500	-2.52833900	-1.18643400
H	3.67572000	1.20199600	-1.05650700
H	3.13338800	2.75489000	-0.37854200
H	2.37506100	2.09909900	-1.83507300
H	-5.19524400	-0.39153600	0.11688200
H	-4.01815700	-1.53332200	-0.43323200
H	2.26681000	0.55607000	1.02689900
O	2.04255900	-0.64102200	1.16837600
C	2.87633800	-1.77933100	1.47120100
H	3.26805300	-2.16267300	0.53917600
H	3.68804700	-1.46367300	2.11087900
H	2.28515200	-2.52896000	1.97517500

$MeNH_2$

V1= -1787.00 cm^{-1} ΔG ($kcal.mol^{-1}$) = 53.86

N	-0.45209900	1.63517300	0.38240000
N	1.80130600	1.20480200	-0.03088700
N	0.20067200	-0.60632200	-0.29658200
C	1.63867700	-0.40649600	-0.31450000
C	-0.75194800	0.32261600	0.07064500
N	0.68032200	2.11204900	0.30557800
C	-1.95266500	-0.30122500	-0.06163600
N	-1.74723700	-1.57982300	-0.52695100
C	-0.45787100	-1.73203900	-0.67199400
O	2.32309100	-0.89363400	-1.22858000
C	2.69005600	1.89958900	-0.99252100
C	-3.31121900	0.21854000	0.19874000
O	-3.52275000	1.33302800	0.63794100
N	-4.27159700	-0.67971300	-0.09903300
H	0.04877100	-2.59278500	-1.03377200
H	3.54550500	1.27179400	-1.17301000
H	2.98146300	2.84534100	-0.56339100
H	2.16624300	2.06155100	-1.92338600
H	-5.22602900	-0.43098900	0.03960400
H	-4.02950700	-1.57685800	-0.45872900
H	2.29228300	0.65210500	1.00835100
N	2.16303400	-0.64975700	1.16221500
H	1.41630800	-0.88740300	1.79769200
C	3.31372600	-1.58327900	1.26039900
H	2.97546700	-2.59519400	1.44165400
H	3.82814400	-1.55167100	0.31408800
H	3.96526500	-1.27214600	2.06402700

CH_3COOH

V1= -484.75 cm^{-1} ΔG (kcal.mol^{-1}) = 55.10

N	1.00492900	1.68023100	-0.60570900
N	0.14519400	-0.12021200	0.73580500
N	-1.27108800	1.64251400	0.01910100
C	-1.16207400	0.37482100	0.84925200
N	-0.02526200	2.32833500	-0.61490700
C	1.16340100	0.46096500	-0.00362600
C	2.23348100	-0.35934500	0.11983000
N	1.89015900	-1.42878900	0.91412900
C	0.64715700	-1.26414000	1.27326400
C	3.59196900	-0.20664100	-0.45257900
N	4.41002000	-1.21972400	-0.12064600
O	3.89682800	0.74582900	-1.14265300
C	-2.10264300	2.71277500	0.64995600
O	-1.88084700	0.16667400	1.79048100
C	-2.84238900	-1.26691700	-0.94651300
O	-3.74156600	-1.11854700	-1.74141400
O	-1.88177400	-0.36263600	-0.75951100
C	-2.70879000	-2.48546200	-0.05747900
H	0.06907300	-1.90482700	1.89247900
H	5.34687400	-1.21658900	-0.46053700
H	4.08655500	-1.97026800	0.45012300
H	-3.04919900	2.28240100	0.92839400
H	-2.22695200	3.49307500	-0.08167800
H	-1.59185100	3.08759900	1.52214000
H	-1.76440300	1.11798800	-0.79276000
H	-1.74458300	-2.95212200	-0.22368700
H	-2.76623900	-2.17477900	0.97968500
H	-3.49872300	-3.18585100	-0.27640800

CH_3COOH product

V1= 22.93 cm^{-1} ΔG (kcal.mol^{-1}) = 40.11

N	0.83916600	1.36193100	-1.03884200
N	0.01547800	-0.17496600	0.62249500
N	-1.13684300	1.83802800	0.13096900
C	-1.38364300	0.24391800	0.56811200
N	-0.10847800	2.12956100	-1.00109300
C	1.02073300	0.29149600	-0.19589700
C	2.12040200	-0.45426200	0.09368800
N	1.80060400	-1.35791500	1.07454400
C	0.53669300	-1.17000400	1.37162300
C	3.48514400	-0.36007400	-0.47137600
N	4.31804700	-1.28824900	0.03369000
O	3.79201300	0.47598900	-1.29921900
C	-0.82548700	2.68587100	1.32491300
O	-2.06510500	0.10933300	1.59614200
C	-2.92666600	-1.05832400	-0.89270600
O	-3.68997300	-0.86105700	-1.78846700
O	-1.88927000	-0.15242800	-0.70341200
C	-2.93495600	-2.23671500	0.03734500
H	-0.03577400	-1.70100500	2.09149000
H	5.26227900	-1.31614100	-0.28298100
H	3.99657200	-1.93750000	0.71827200
H	-1.54492700	2.42865100	2.08524800
H	-0.88378600	3.72721200	1.05059600
H	0.16942900	2.44332000	1.66285600
H	-2.00740800	2.11630600	-0.30162300
H	-1.99202900	-2.76589700	-0.04330200
H	-3.04961400	-1.88837700	1.05269100
H	-3.74519700	-2.89142500	-0.24013700