

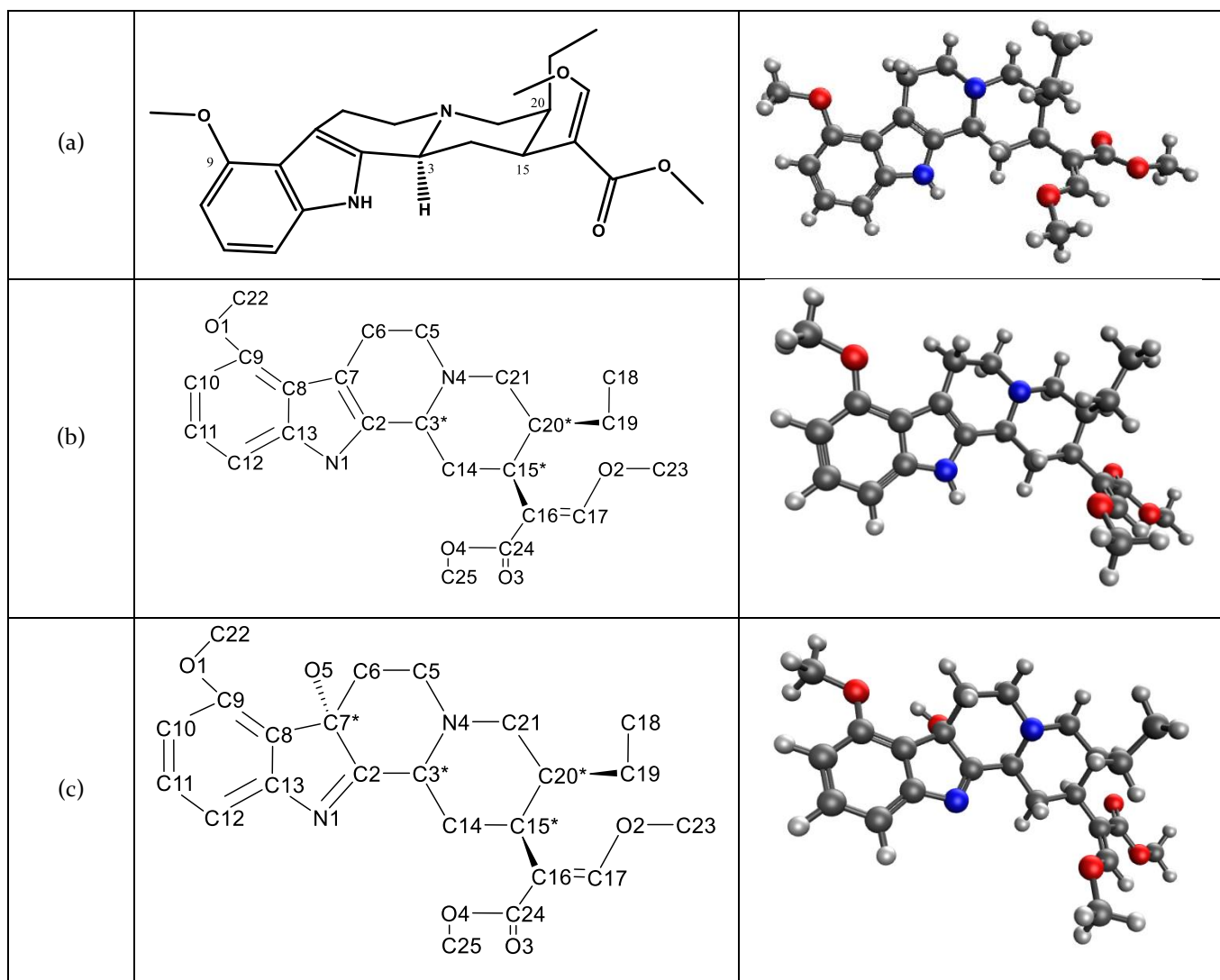


FIGURE 1S (a) Structure of mitragynine by Carvalho *et al.* (16) (b) Calculated lowest-energy structure of mitragynine (M_mmm) and (c) Calculated lowest-energy structure of 7-hydroxymitragynine (H_mmm)

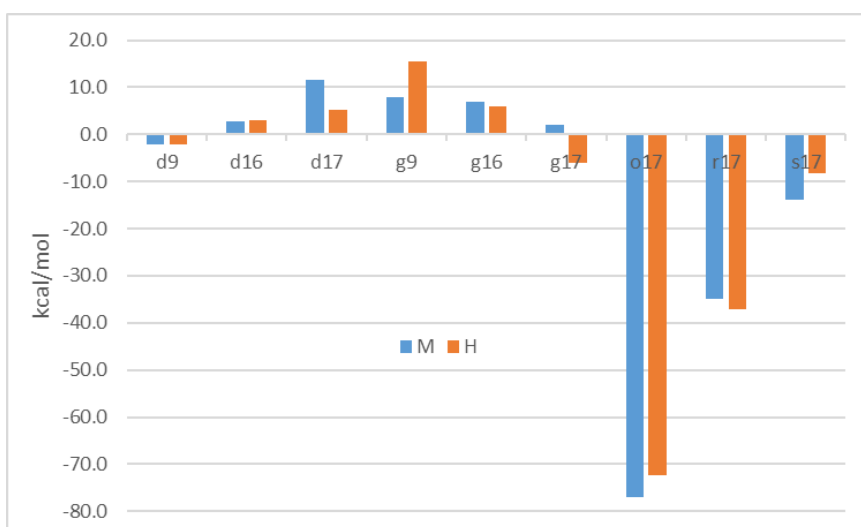


FIGURE 2S Average standard Gibbs energies of reaction for demethylation (d), conjugation to a glucuronide (g), oxidation (o), reduction (r), conjugation to sulfate (s) at different positions in mitragynine (M) and 7-hydroxymitragynine (H).

TABLE 1S Standard Gibbs energies of reaction for Mitragynine and 7-hydroxymitragynine metabolic pathways

Reactions	ΔG_{soln} kcal/mol	ΔG_{gas} kcal/mol	Step Number	Reaction	Position
d					
$\text{M_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_dmm}$	-2.2	0.3	1	d	9
$\text{M_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_mdm}$	2.3	8.3	1	d	16
$\text{M_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_mmd}$	11.0	16.6	1	d	17
$\text{M_mdm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_ddm}$	-1.2	1.6	2	d	9
$\text{M_mmd} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_dmd}$	-1.1	1.6	2	d	9
$\text{M_dmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_ddm}$	3.3	9.6	2	d	16
$\text{M_dmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_dmd}$	12.1	17.8	2	d	17
$\text{M_mmo} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_dmo}$	-4.4	-4.8	3	d	9
$\text{M_mgm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{M_dgm}$	-1.6	0.4	3	d	9
$\text{H_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_dmm}$	-1.9	-0.6	1	d	9
$\text{H_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_mdm}$	3.0	8.9	1	d	16
$\text{H_mmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_mmd}$	5.3	10.2	1	d	17
$\text{H_mdm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_ddm}$	-1.9	-0.5	2	d	9
$\text{H_mmd} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_dmd}$	-1.9	-0.1	2	d	9
$\text{H_dmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_ddm}$	3.0	9.0	2	d	16
$\text{H_dmm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_dmd}$	5.2	10.8	2	d	17
$\text{H_mmo} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_dmo}$	-2.0	-0.3	3	d	9
$\text{H_mgm} + \text{H}_2\text{O} \rightarrow \text{CH}_4\text{O} + \text{H_dgm}$	-2.5	0.1	3	d	9
g					
$\text{M_dmm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{M_gmm}$	4.2	-1.7	2	g	9
$\text{M_mdm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{M_mgm}$	7.1	-1.1	2	g	16
$\text{M_ddm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{M_dgm}$	6.6	-2.3	3	g	16
$\text{M_mmr} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{M_mmG}$	2.0	-4.2	3	g	17
$\text{M_dmr} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{M_gmr}$	11.6	6.9	4	g	9
$\text{H_dmm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{H_gmm}$	4.9	3.4	2	g	9
$\text{H_mdm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{H_mgm}$	6.3	-1.4	2	g	16
$\text{H_ddm} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{H_dgm}$	5.7	-0.8	3	g	16
$\text{H_mmr} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{H_mmG}$	-6.0	-14.6	3	g	17
$\text{H_dmr} + \text{C}_6\text{H}_{10}\text{O}_7 \rightarrow \text{H}_2\text{O} + \text{H_gmr}$	26.0	21.6	4	g	9
s					
$\text{M_dmm} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{M_smm}$	-8.8	-409.6	2	s	9
$\text{M_ddm} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{M_sdm}$	-18.2	-423.9	3	s	9
$\text{M_dmr} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{M_smr}$	-14.9	-421.5	4	s	9
$\text{H_dmm} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{H_smm}$	-10.8	-412.7	2	s	9
$\text{H_ddm} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{H_sdm}$	-15.3	-419.6	3	s	9
$\text{H_dmr} + 2\text{H}_3\text{O}^+ + \text{SO}_4^{2-} \rightarrow 3\text{H}_2\text{O} + \text{H_smr}$	1.3	-401.9	4	s	9
r					
$\text{M_mmd} + \text{C}_6\text{H}_8\text{N}_2\text{O} + \text{H}_3\text{O}^+ \rightarrow \text{C}_6\text{H}_7\text{N}_2\text{O}^+ + \text{H}_2\text{O} + \text{M_mmr}$	-32.7	-67.4	2	r	17
$\text{M_dmd} + \text{C}_6\text{H}_8\text{N}_2\text{O} + \text{H}_3\text{O}^+ \rightarrow \text{C}_6\text{H}_7\text{N}_2\text{O}^+ + \text{H}_2\text{O} + \text{M_dmr}$	-37.3	-70.5	2	r	17
$\text{H_mmd} + \text{C}_6\text{H}_8\text{N}_2\text{O} + \text{H}_3\text{O}^+ \rightarrow \text{C}_6\text{H}_7\text{N}_2\text{O}^+ + \text{H}_2\text{O} + \text{H_mmr}$	-29.9	-61.8	2	r	17
$\text{H_dmd} + \text{C}_6\text{H}_8\text{N}_2\text{O} + \text{H}_3\text{O}^+ \rightarrow \text{C}_6\text{H}_7\text{N}_2\text{O}^+ + \text{H}_2\text{O} + \text{H_dmr}$	-44.5	-80.0	2	r	17
o					
$\text{M_mmd} + 1/2\text{O}_2 \rightarrow \text{M_mmo}$	-75.2	-70.0	2	o	17
$\text{M_dmd} + 1/2\text{O}_2 \rightarrow \text{M_dmo}$	-78.6	-76.3	2	o	17
$\text{H_mmd} + 1/2\text{O}_2 \rightarrow \text{H_mmo}$	-72.4	-69.9	2	o	17
$\text{H_dmd} + 1/2\text{O}_2 \rightarrow \text{H_dmo}$	-72.4	-70.1	2	o	17