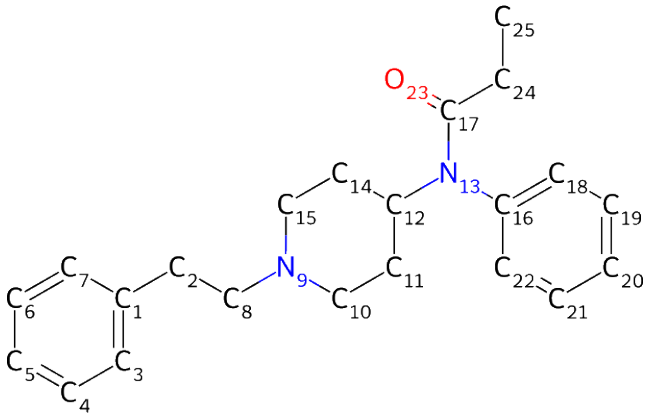
C-oxidation BDE Energy Report for: 142_fentanyl-out

This report covers the results for bond dissociation enthalpies (BDE) and solvent accessible surface area (SASA) calculations performed for 142_fentanyl-out. Oxidation propensity is established using C-H BDE. The lower the C-H BDE values the higher the propensity for C-oxidation. Details for the density functional theory (DFT) calculations and overall workflow are explained at the end of this document.

BDE and SASA



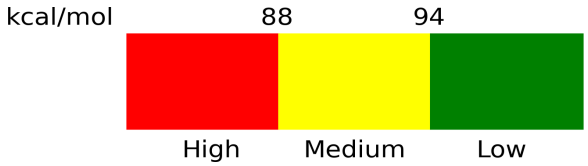
Atom	BDE (kcal/mol)	Propensity
C2	85.59	High
C3	111.76	Low
C4	111.95	Low
C5	112.31	Low
C6	111.8	Low
C7	111.25	Low
C8	90.8	Moderate
C10	90.76	Moderate
C11	99.19	Low
C12	92.81	Moderate
C14	99.32	Low
C15	90.95	Moderate
C18	112.6	Low
C19	112.17	Low
C20	112.74	Low
C21	112.18	Low

C22	112.63	Low
C24	91.07	Moderate
C25	101.49	Low

Missing Sites:

None

Risk Scale:



Calculation Details

Conformational search calculations were performed only for the base ground state molecule. The lowest energy conformer was selected to generate radicals and run optimization DFT calculations. DFT calculations were performed using Gaussian with B3LYP level of theory and 6-31G(d,p) basis set. The BDE protocol was adapted from: *Lienard, P., Gavartin, J., Boccardi, G., & Meunier, M. (2015). Predicting drug substances autoxidation. Pharmaceutical research, 32, 300-310.*