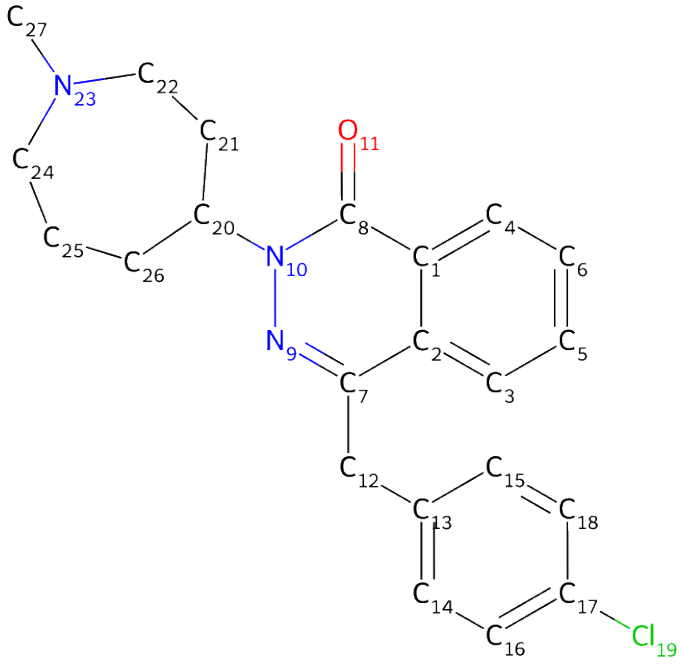
C-oxidation BDE Energy Report for: 061_azelastine-out

This report covers the results for bond dissociation enthalpies (BDE) and solvent accessible surface area (SASA) calculations performed for 061_azelastine-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



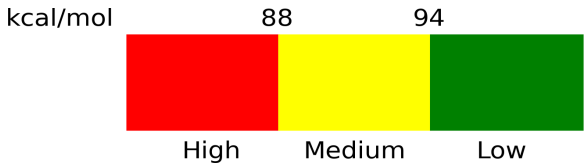
Atom	BDE (kcal/mol)	Propensity	SASA (Å²)
C3	111.68	Low	8.19
C4	114.85	Low	14.67
C5	112.35	Low	16.22
C6	112.67	Low	16.83
C12	78.23	High	1.26
C14	112.24	Low	7.77
C15	112.23	Low	7.42
C16	113.68	Low	12.19
C18	113.68	Low	12.43
C20	90.16	Moderate	0.00

C21	96.27	Low	0.39
C22	91.14	Moderate	0.38
C24	90.15	Moderate	0.58
C25	97.48	Low	0.66
C26	96.2	Low	0.43
C27	92.32	Moderate	6.82

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.*