Comprehensive Assessment of Torsional Strain in Crystal Structures of Small Molecules and Protein-ligand Complexes using *ab initio* Calculations

Brajesh K. Rai[*,1], *Vishnu Sresht*[1], *Qingyi Yang*[2], *Ray Unwalla*[2], *Meihua Tu*[2], *Alan M. Mathiowetz*[2], *and Gregory A. Bakken*[3]

[1]Simulation and Modeling Sciences and [2]Medicine Design, Pfizer Worldwide Research and Development, 610 Main Street, Cambridge, Massachusetts 02139, United States

[3]Simulation and Modeling Sciences, Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States

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ABSTRACT

The energetics of rotation around single bonds (torsions) is a key determinant of the 3D shape that drug-like molecules adopt in solution, the solid state, and in different biological environments, which in turn defines their unique physical and pharmacological properties. Therefore, accurate characterization of torsion angle preference and energetics is essential for the success of computational drug discovery and design. Here, we analyze torsional strain in crystal structures of

drug-like molecules in CSD and bioactive ligand conformations in PDB, expressing the total strain energy as a sum of strain energy from constituent rotatable bonds. We utilized Cloud computing to generate torsion scan profiles of a very large collection of chemically diverse neutral fragments at DFT(B3LYP)/6-31G*//6-31G** or DFT(B3LYP)/6-31+G*//6-31+G** (for sulfur-containing molecule). With the data generated from these *ab initio* calculations, we performed rigorous analysis of strain due to deviation of observed torsion angles relative to their ideal gas-phase geometries. Contrary to the previous studies based on molecular mechanics, we find that in the crystalline-state molecules generally adopt low-strain conformations, with median per-torsion strain energy in CSD and PDB under $1/10^{th}$ and $1/3^{rd}$ of a kcal/mol, respectively. However, for a small fraction (<5%) of motifs, external effects such as steric hinderance and hydrogen bonds result in strain penalty exceeding 2.5 kcal/mol. We find that due to poor quality of PDB structures in general, bioactive structures tend to have higher torsional strain compared to small molecule crystal conformations. However, in the absence of structural fitting artifacts in PDB structures, protein-induced strain in bioactive conformations is quantitatively similar to those due to the packing forces in small molecule crystal structures. This analysis allows us to establish strain energy thresholds to help to identify biologically relevant conformers in a given ensemble. The work presented here is the most comprehensive study to date that demonstrates the utility and feasibility of gas-phase QM calculations to study conformational preference and energetics of drug-size molecules. Potential applications of this study in computational lead discovery and structure-based design are discussed.

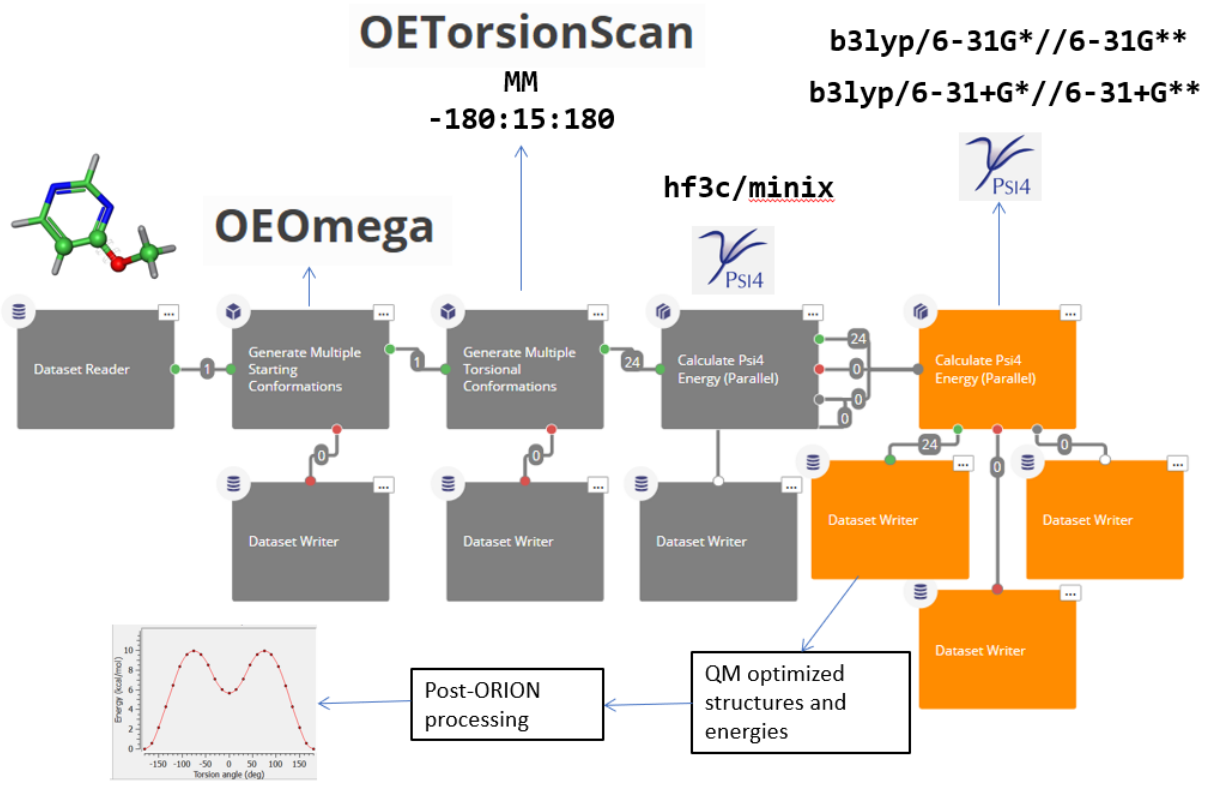


Figure S1: Screenshot of Orion floe that was used to perform torsion scan calculations. Each rectangular box in this figure represents an Orion Cube, which performs a specific task.

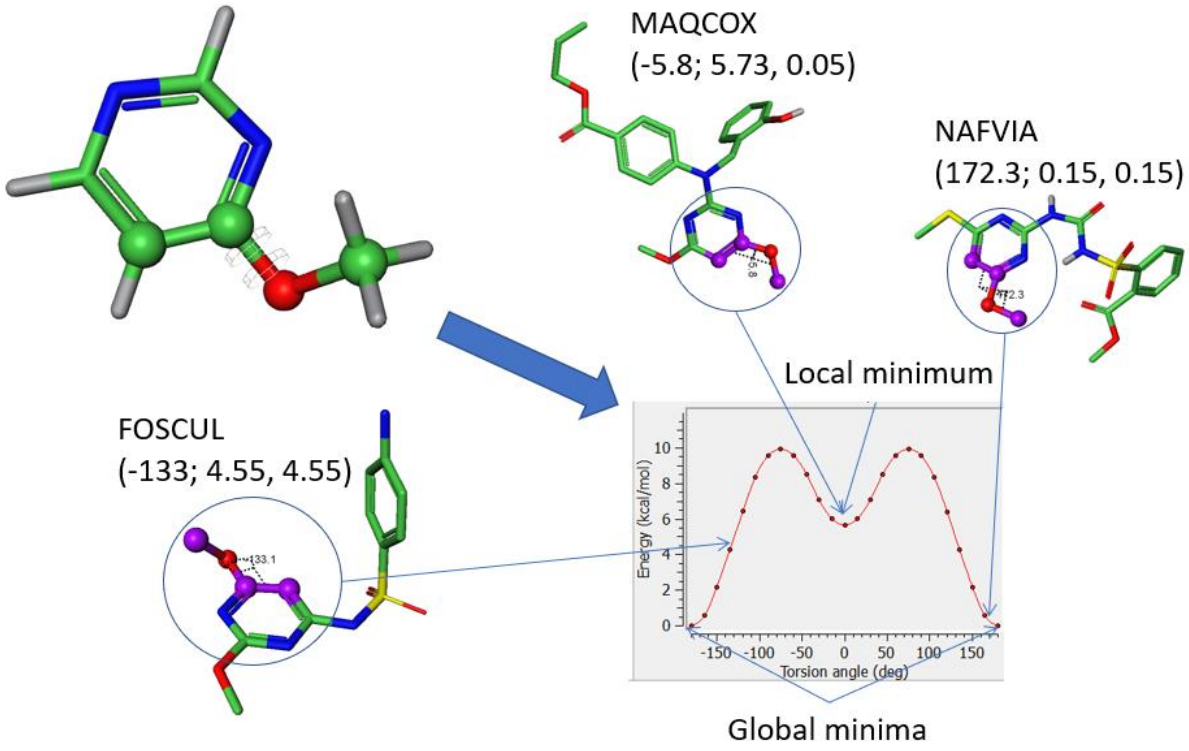


Figure S2: Illustrative example showing calculation of global and local torsion strain energy.

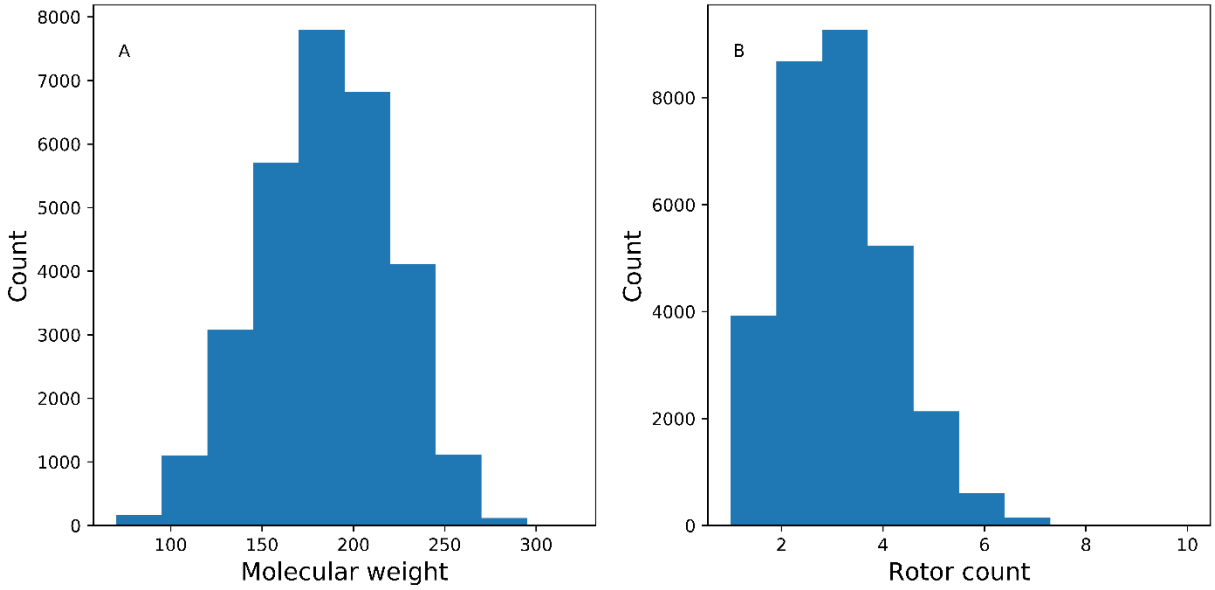


Figure S3: Distribution of molecule weight (A) and number of rotatable bonds (B) of the fragments used in this study.

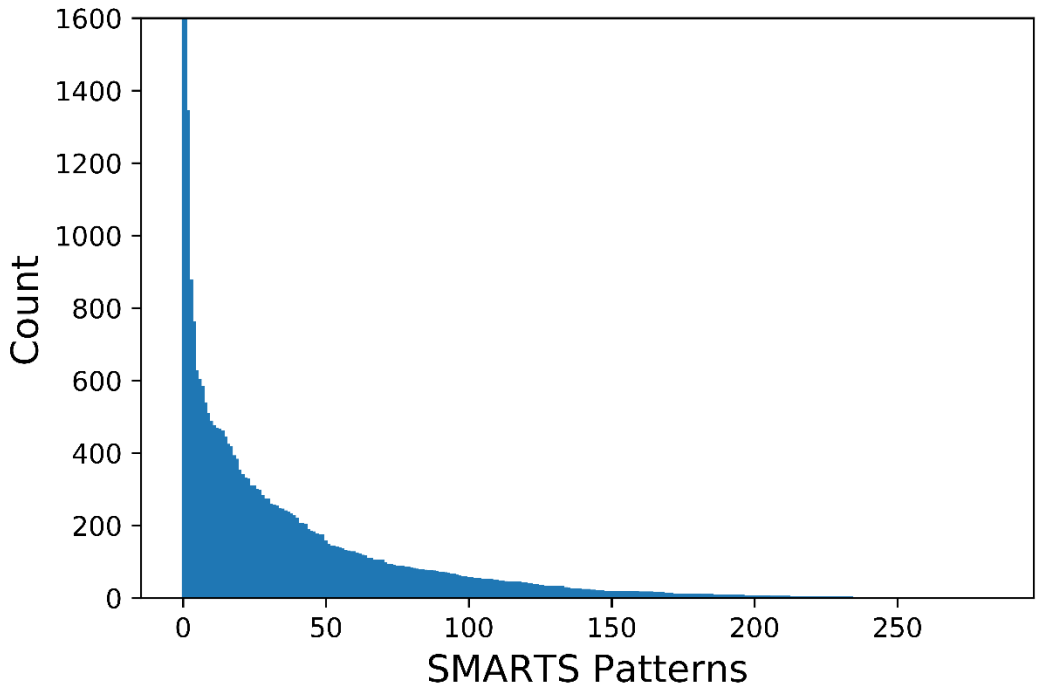


Figure S4: Frequency of occurrence of SMARTS patterns in the set of torsion motifs used to analyze dihedral angle preference and torsion strain

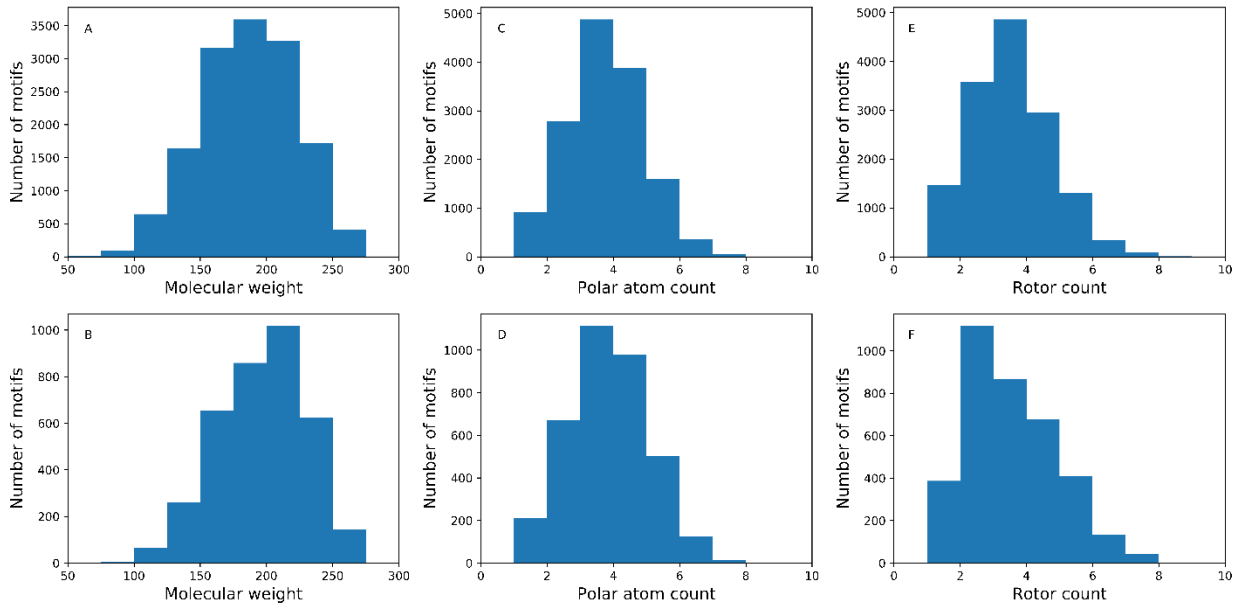


Figure S5: Distribution of molecular weight (A and B), polar atom count (C and D), and rotor count (E and F) of motifs in the CSD set. (Top row) low-strain motifs. (Bottom row) high-strain motifs.

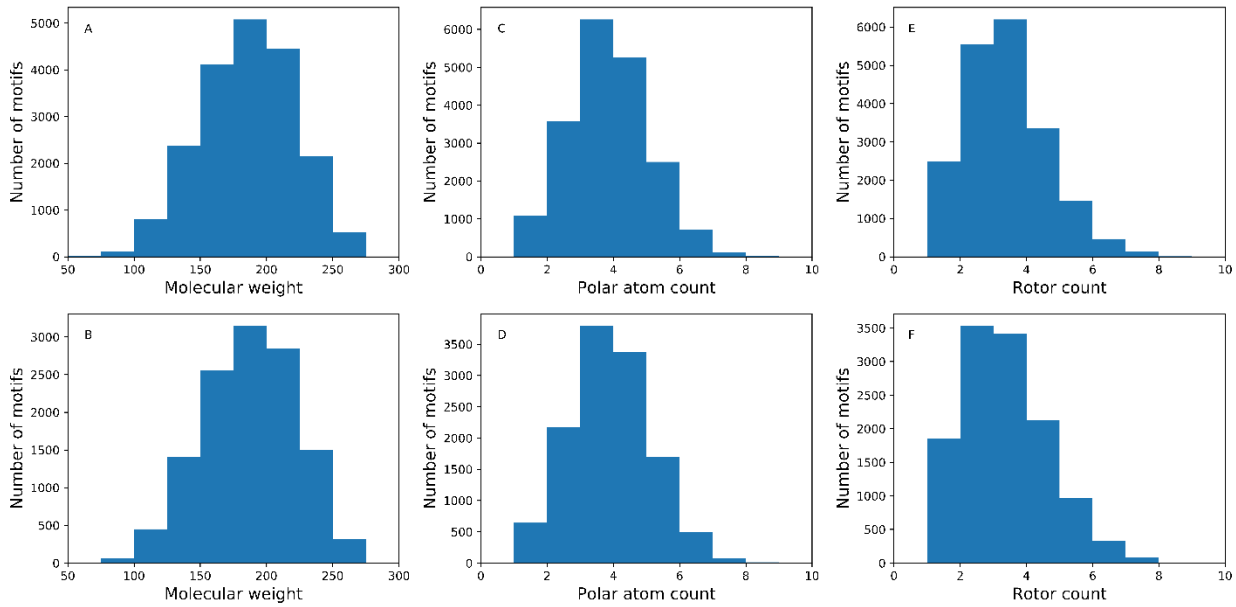


Figure S6: Distribution of molecular weight (A and B), polar atom count (C and D), and rotor count (E and F) of motifs in the PDB set. (Top row) low-strain motifs. (Bottom row) high-strain motifs.

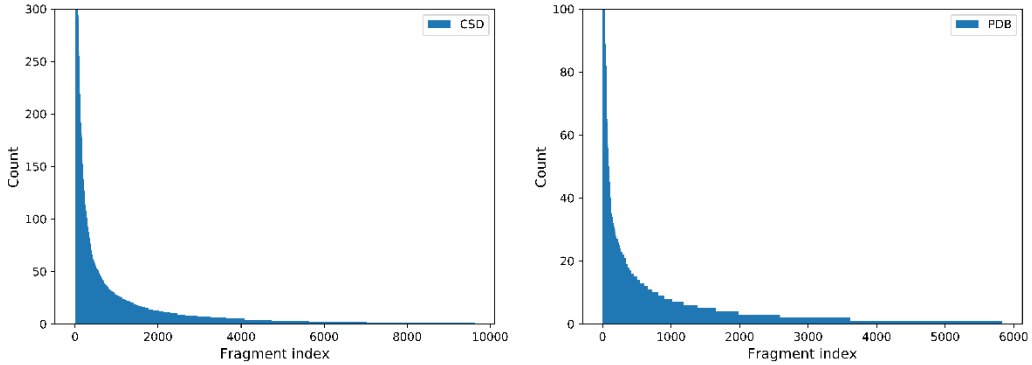
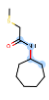


Figure S7: Frequency of occurrence of torsion motifs in the drug-like collection of CSD (left) and PDB (left) structures used in the present work. Simpler motifs, such as anisole, butyl etc., are represented more frequently compared to other fragments. Nonetheless, despite an over

representation of such frequently occurring motifs, they account for only a small fraction of the entire set—less than 10% for top 10 in CSD- and PDB- set.

Table S1: List of SMARTS patterns represented in the torsion motifs collection used in the present study. For each SMARTS pattern, a representative torsion motif is shown along with the frequency of occurrence of the pattern.

	SMARTS		Count
1	[!#1:1][CX4:2]!@[CX4:3][!#1:4]		2452
2	[!#1:1][CX4H2:2]!@[CX4H2:3][!#1:4]		1897
3	[O:1]=[CX3:2]!@[NX3H1:3][!#1:4]		1346
4	[a:1][c:2]!@[CX4H2:3][N,O:4]		880
5	[O:1]=[CX3:2]!@[NX3H0:3][!#1:4]		763
6	O=[C:1][NX3H1:2]!@[CX4H1:3][H:4]		629
7	O=[C:1][NX3H0:2]!@[CX4H2:3][!#1:4]		605

			
8	[!#1:1][CH2:2]!@[n:3][cH0:4]		586
			
9	[O:1]=[C:2]!@[O:3]~[C:4]		540
			
10	[cH0:1][c:2]!@[CX4H2:3][N,O,S:4]		511
			
11	[C:1][CX4H2:2]!@[OX2:3][c:4]		488
			
12	O=[C:1][NX3H1:2]!@[CX4H2:3][!#1:4]		477
			
13	[OX2:1][CX4:2]!@[CX4:3][N:4]		469
			
14	[a:1][c:2]!@[CX4H1:3][N,O:4]		468
			
15	[O:1]=[CX3:2](a)!@[NX3H0:3][!#1:4]		462
			
16	[C:1][CH2:2]!@[O:3][CX4:4]		446

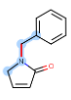
			
17	[C:1][CX4:2]!@[CX3:3]=[O:4]		425
			
18	[cH1:1][c:2]([cH1])!@[NX3H1:3][C,c:4]		418
			
19	[C:1][CX4:2]!@[NX3:3][C:4]		394
			
20	[!#1:1][CX4H2:2]!@[NX3H1:3][!#1:4]		384
			
21	[a:1][a:2]!@[NH1:3][C,c:4]		355
			
22	[cH0:1][c:2]([cH1])!@[O:3][C:4]		342
			
23	[CX4:1][CX4H2:2]!@[NX3:3][CX4:4]		333
			
24	[!#1:1][CX4H2:2]!@[NX3:3][!#1:4]		330
			
25	[c:1][c:2]!@[c:3][s,o,nX3H1:4]		311

			
26	[a:1][c:2]!@[C:3]([NH0])=[O:4]		311
			
27	[cH1:1][c:2]([cH1])!@[O:3][C:4]		301
			
28	O=[C:1][NX3H0:2]!@[CX4H1:3][H:4]		298
			
29	[a:1][c:2]!@[C:3]([NH1,NH2])=[O:4]		284
			
30	[OX2:1][CX4:2]!@[CX4:3][OX2:4]		275
			
31	[c:1][c:2]!@[c:3][nX2H0:4]		274
			
32	[cH0:1][c:2]!@[CX4H2:3][CX4:4]		260
			
33	[a:1][c:2]!@[CX4H2:3][CX4:4]		257
			
34	[NH1:1][CX4:2]!@[CX3:3]=[O:4]		255

			
35	[cH1:1][c:2]([cH1])!@[CX4H2:3][CX4:4]		248
			
36	[N:1][CX4:2]!@[CX3:3]=[O:4]		247
			
37	[O:1][CX4:2]!@[CX3:3]=[O:4]		242
			
38	O=[C:1][O:2]!@[CH2:3]~[C:4]		239
			
39	[cH1,nX2H0:1][c:2]([cH1,nX2H0])!@[NX3r:3][*:4]		233
			
40	[cH0:1][c:2]([cH,nX2H0])!@[NX3H0:3][CX4:4]		228
			
41	[cH0:1][c:2]([cH1])!@[NX3H1:3][C,c:4]		222
			
42	[a:1][c:2]!@[CX4H2:3][a:4]		208
			
43	[!#1:1][CX4:2]!@[NX3:3][!#1:4]		206

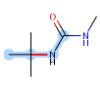
			
44	[cH0:1][c:2]([nX2H0])!@[NX3H1:3][C,c:4]		205
			
45	O=[C:1][NX3:2]!@[!#1:3][!#1:4]		191
			
46	[cH1:1][c:2]([cH1])!@[C:3]([NH1,NH2])=[O:4]		186
			
47	[a:1][a:2]!@[NX3:3][!#1:4]		184
			
48	[a:1][c:2]!@[CX4H1:3][H:4]		179
			
49	[cH0:1][c:2]!@[CX4H1:3][CX4:4]		175
			
50	[H:1][CX4H1:2]!@[OX2:3][!#1:4]		175
			
51	[*:1][CX4:2]!@[O:3][CX4:4]		160
			
52	[c:1][CX4H2:2]!@[OX2:3][c:4]		149

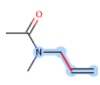
			
53	[a:1][a:2]!@[CX3:3]=[CX3H1:4]		145
			
54	[nX2H0:1][c:2]([nX2H0])!@[NX3H1:3][C,c:4]		144
			
55	[c:1][c:2]([cH0])!@[c:3][nX2H0:4]		143
			
56	[C:1][CX4H2:2]!@[CX3:3]=[O:4]		139
			
57	N[C:2](=[O:1])!@[CH2:3][N:4]		138
			
58	[cH0:1][c:2]([cH1])!@[c:3]([cH1:4])[cH1]		132
			
59	[O:1]=[C:2]!@[NX3H1:3]([H:4])(cn)		131
			
60	[a:1][c:2]!@[CX4H0:3][CX4:4]		129
			
61	[!#1:1][CX4H2:2]!@[CX3:3]=[O:4]		129

			
62	[O:1]=[CX3:2]([NH1])!@[CH2:3][C:4]		126
			
63	[*:1]~[CX4:2]!@[n:3]~[*:4]		122
			
64	[c:1][CX4H2:2]!@[CX3:3]=[O:4]		119
			
65	[*:1]~[CX3:2]!@[CX3:3]~[*:4]		117
			
66	[O:1]=[CX3:2]([NX3H1]C)!@[NX3H1:3][!#1:4]		110
			
67	O=[C:1][NX3H1:2]!@[CX4H2:3][c:4]([cH,nX2H0])[cH,nX2H0]		110
			
68	[cH1,n:1][c:2]!@[O:3][CRH1:4]		107
			
69	O=[C:1][NX3H0:2]!@[CX4H2:3][c:4]([cH,nX2H0])[cH,nX2H0]		107
			
70	[O:1]=[C:2]([N])!@[O:3]~[C:4]		106

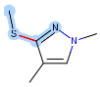
			
71	[cH1:1][c:2](cO)!@[O:3][C:4]		105
			
72	[cH0:1][c:2]([cH1])!@[CX3:3]([NX3H1])=[O:4]		99
			
73	[aH0:1][c:2]!@[OX2:3][!#1:4]		95
			
74	[N:1][C:2](=O)!@[CX4H2:3][CX4H2:4]		93
			
75	[!#1:1][CH2:2]!@[n:3][a:4]		91
			
76	[cH1:1][c:2]([cH1])!@[CX3:3]=[O:4]		90
			
77	[*:1]~[CX3:2]!@[NX3:3]~[*:4]		89
			
78	O=[C:1][O:2]!@[CH1:3][H:4]		89
			
79	[c:1][c:2]!@[c:3]([cH0])[nX2H0:4]		87

			
80	[O:1]=[C:2]!@[O:3]~[CH0:4]		87
			
81	[H:1][CX4H1:2]!@[O:3][CX4:4]		84
			
82	[OX2:1][CX4H2:2]!@[CX4H2:3][N:4]		83
			
83	[!#1:1][CX4H0:2]!@[OX2:3][!#1:4]		81
			
84	[a:1][c:2]!@[C:3](=[N:4])		80
			
85	[a:1][a:2]!@[CX3:3]=[O:4]		79
			
86	[cH1:1][c:2]([nX2])!@[O:3][C:4]		78
			
87	[cH1:1][c:2]([cH1])!@[c:3]([cH1:4])[cH1]		77
			
88	[cH0:1][c:2]([cH1])!@[CX3:3]=[O:4]		77

			
89	[cH1:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH0])		76
			
90	[nX2H0:1][c:2]!@[c:3][nX2H0:4]		75
			
91	[cH1,n:1][c:2]!@[O:3][CH1:4]		72
			
92	[O:1]=[CX3:2]!@[CX4H1r3:3][H:4]		72
			
93	[cH0:1][c:2]!@[CX4H0:3][*:4]		71
			
94	[!#1:1][CX4:2]!@[SX2:3][!#1:4]		70
			
95	[a:1][c:2]!@[CX3:3]=[CX3H0:4]		68
			
96	O=[C:1][NX3H1:2]!@[CX4H0:3][C:4]		68
			
97	[cH0:1][c:2]([cH0])!@[O:3][C:4]		65

			
98	[C:1][CX4H2:2]!@[NX3:3][C:4]		63
			
99	[cH0:1][c:2]([nX2])!@[O:3][C:4]		60
			
100	[O:1]=[C:2]!@[NX3H0:3]([a:4])[A]		60
			
101	[cH1:1][c:2]([cH1])!@[O:3][c:4]		58
			
102	[OX2:1][CX4H2:2]!@[CX4H2:3][Nr:4]		57
			
103	[cH1:1][c:2]([cH0])!@[O:3][c:4]		56
			
104	[c:1]([NH1,NH2])[c:2]!@[CX3:3](=[O:4])([!O])		56
			
105	[CX3:1]=[CX3:2]!@[CH2:3][!#1:4]		56
			
106	[c:1][CX4:2]!@[CX3:3]=[O:4]		53

			
107	[OH1:1][CX4:2]!@[CX3:3]=[O:4]		53
			
108	[*:1]~[cX3:2]!@[NX2:3]~[*:4]		53
			
109	[O:1]=[C:2]!@[O:3]~[!#1:4]		52
			
110	[c:1][cr6:2]!@[cr5:3][c:4]		51
			
111	[a:1][c:2]!@[CX4H2:3][CX3:4]		50
			
112	[cH0:1][c:2]!@[CX4H2:3][a:4]		49
			
113	[O:1]=[C:2]!@[NX3:3](C=O)[*:4]		49
			
114	[nX2H0:1][c:2]!@[c:3][nX3H1:4]		47
			
115	[cH0:1][c:2]([cH1])!@[CX3:3]([NX3H0])=[O:4]		46

			
116	[OX2:1][CX4H2:2]!@[CX4H2:3][OX2:4]		46
			
117	[*:1]~[NX3:2]!@[NX2:3]~[*:4]		46
			
118	[cH1:1][c:2]([cH1])!@[CX3:3](c)=[O:4]		45
			
119	[aH0:1][c:2]([aH0])!@[SX2:3][!#1:4]		45
			
120	[cH1:1][a:2]([cH1])!@[a:3]([cH1])[cH0:4]		43
			
121	[a:1][c:2]!@[CX4H0:3][a:4]		43
			
122	[a:1][c:2]!@[CX4H0:3][*:4]		42
			
123	[a:1][ar6:2]!@[ar5:3][a:4]		42
			
124	[cH0:1][c:2]([cH0])!@[c:3]([cH1:4])[cH1]		38

125 [c:1][c:2]!@[c:3][c:4]!@c 38

126 [a:1][c:2]!@[CX4H2:3][!#1:4] 37

127 [a:1][c:2]!@[CX4H0:3][CX3:4] 36

128 [cH1:1][a:2]([cH1])!@[a:3]([cH0])[cH0:4] 34

129 [cH0:1][c:2]([cH0])!@[CX3:3]=[O:4] 34

130 [cH0:1]([CX3])[c:2]([cH1])!@[O:3][C:4] 33

131 [c:1][CX4H2:2]!@[OX2:3][C:4] 33

132 [aH1:1][c:2]([aH1])!@[SX4:3][!#1:4] 33

133 [a:1][c:2]!@[CX4H1:3][a:4] 33

			
134	[!#1:1][CX4r:2]!@[CX4r:3][!#1:4]		33
			
135	[CX3:1]=[CX3:2]!@[CH2:3][C:4]		30
			
136	[!#1:1][CX4:2]!@[CX3H0:3][!#1:4]		29
			
137	[cH0:1][c:2]([cH0])!@[NX3H1:3][C,c:4]		27
			
138	[CX3:1]=[CX3:2]!@[CH2:3][OX2:4]		27
			
139	O=[C:1][O:2]!@[c:3]~[*:4]		27
			
140	[cH0:1][c:2]!@[c:3]([cH0])[nX2H0:4]		26
			
141	[cH0:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH1])		25
			
142	[O:1]=[CX3:2]!@[CX4r3:3]!@[!#1:4]		25

			
143	[O:1]=[C:2]!@[NX3H1:3](C=O)[H:4]		25
			
144	[cH0:1][c:2]!@[C:3](=[N:4])		23
			
145	[!#1:1][CX4:2]!@[CX3:3]=[O:4]		23
			
146	[cH0:1][c:2]!@[CX4H2:3][CX3:4]		22
			
147	[nX2:1][c:2]([nX2])!@[O:3][C:4]		21
			
148	[cH0:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH0])		21
			
149	[cH1:1][c:2]([cH1])!@[NX3:3][CX4:4]		20
			
150	[cH0:1][c:2]!@[CX4H0:3][N,O,S:4]		20
			
151	[c:1]([OH1])[c:2]!@[CX3:3](=[O:4])([!O])		20

152 [aH1:1][c:2]([aH0])!@[SX2:3][!#1:4] 20

153 [aH0:1][c:2]([aH1])!@[SX4:3][!#1:4] 20

154 [a:1][c:2]!@[C:3](=[NH0:4][CX4]) 20

155 [!#1:1][CX4:2]!@[SX4:3][!#1:4] 20

156 [nX3H1:1][a:2]!@[CX3:3]=[O:4] 19

157 [aH1:1][c:2]([aH1])!@[SX2:3][!#1:4] 19

158 [O:1]=[CX3:2]!@[nX3:3]([aH0:4])([aH0]) 19

159 [C:1][CX4H2:2]!@[OX2:3][!#1:4] 19

160 [*:1]~[OX2:2]!@[P:3]~[*:4] 19

161 [cH1:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH1]) 18

162 [cH0:1]([OH0])[c:2]([cH1])!@[C:3](=O)[NH1:4] 18

163 [a:1][a:2]!@[CX3:3](a)=[O:4] 18

164 [*:1]~[NX2:2]!@[OX2:3]~[*:4] 18

165 O=[C:1][NX3H1:2]!@[CX3:3]=[NX2:4] 18

166 [nX2H0:1][c:2](a(a)(a))!@[c:3][nX2H0:4] 17

167 [!#1:1][CX3:2](=S)!@[NX3H1:3][!#1:4] 17

168 [cH0:1][c:2]!@[CX4H0:3][CX4:4] 16

169 [c:1]([NH1,NH2])[c:2]!@[CX3:3](=[O:4])([O]) 16

170 [cH0:1][c:2]([cH1])!@[c:3]([cH0:4])[cH1] 15

171 [O:1]=[CX3:2]!@[nX3:3][aH1:4] 14

172 [C:1][S:2](=O)(=O)!@[NX3H1:3][C:4] 14

173 [s:1][c:2]!@[C:3]([NH1])=[O:4] 13

174 [a:1][c:2]!@[C:3](=[N:4][!#1])(N[!#1]) 13

175 [a:1]([NH1,NH2])[a:2]!@[CX3:3](=[O:4])([NX3H0,CX4H0,c]) 13

176 [O:1]=[CX3:2]!@[CX3:3]=[O:4] 13

177 [H:1][CX4H1:2]!@[SX4:3][!#1:4] 13

178 [*:1]~[cX3:2]!@[P:3]~[*:4] 13

179 [cH1:1][c:2]([nX3])!@[O:3][C:4] 12

180 [O:1]=[C:2]!@[NX3H1:3]([H:4])(c([nX2H0])([nX2H0])) 12

181 [*:1][CX4:2]!@[O:3][CX3:4](=[!O]) 12

182 [!#1:1][CX3:2]!@[SX2:3][!#1:4] 12

183 [cH1:1][c:2]([nX3H1])!@[NX3H1:3][C,c:4] 11

184 [cH0:1][c:2]([cH1])!@[CX3:3](c)=[O:4] 11

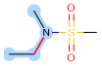
185 [a:1][c:2]([a])!@[O:3][CX4H0:4] 11

186 [*:1]~[CX3:2]!@[OX2:3]~[*:4] 11

187 [cH0:1][c:2]([cH0])!@[O:3][c:4] 10

188 [a:1][c:2]!@[C:3](=[N:4][CX4])(N[CX4]) 10

189 O=[S:1](=O)[NX3H0:2]!@[CX4H2:3][!#1:4] 10



190 [nX2H0:1][c:2](c)!@[CX3:3]([!O])=[O:4] 9

191 [cH1:1][c:2]([cH1])!@[CX3:3]([CX3H0])=[O:4] 9

192 [cH0:1][c:2]([nX3H1])!@[NX3H1:3][C,c:4] 9

193 [c:1][cr6:2]!@[cr6:3][c:4] 9

194 [c:1][CX4H2:2]!@[OX2:3][!#1:4] 9

195 [O:1][CX4:2]!@[O:3][CX4:4] 9

196 [*:1]~[CX4:2]!@[P:3]~[*:4] 9

			
197	[*:1][S:2](=O)(=O)!@[NX3H0r:3][*:4]		9
			
198	[nX2H0:1][c:2]([nX3H1])!@[NX3H1:3][C,c:4]		8
			
199	[cH1:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4])		8
			
200	[O:1]=[C:2]([NH1])!@[NX3H1:3](C=O)[H:4]		8
			
201	[C]\[CX3:1]([H])=[CX3:2]([H])!@\[CH2:3][C:4]		8
			
202	[cH0:1][c:2]([cH0])!@[C:3](=[N:4])		7
			
203	[cH0:1](Cl)[c:2]([cH1])!@[CX3:3]([NX3H1])=[O:4]		7
			
204	[a:1]([OH1])[a:2]!@[CX3:3](=[O:4])([NX3H0,CX4H0,c])		7
			
205	[C]\[CX3:1]([H])=[CX3:2]([H])!@/[CH2:3][C:4]		7

			
206	[*:1]~[CX3:2]!@[NX2:3]~[*:4]		7
			
207	[cH1:1][c:2]([cH1])!@[CX4H2:3][CX4H1:4]C(=O)(O)		6
			
208	[cH0:1][c:2]!@[CX4H1:3][a:4]		6
			
209	[c:1]([OH1])[c:2]!@[CX3:3](=[O:4])([O])		6
			
210	[CX3:1]=[CX3:2]!@[CH2:3][c:4]		6
			
211	[CX3:1]=[CX3:2]!@[CH1:3](C)[C:4]		6
			
212	[C:1][CX4:2]!@[CX3:3][C:4]		6
			
213	O=[C:1][NX3H0:2]!@[CX4H0:3][C:4]		6
			
214	[nX3H1:1][a:2]!@[a:3][o,s,nX2H0:4]		5

215 [cH0:1][a:2]([cH1])!@[a:3]([sX2,o,nX2H0,nX3H1:4]) 5

216 [a:1][a:2]!@[CX3:3]=[CX3H2:4] 5

217 O[c:1][c:2](cO)!@[O:3][C:4] 5

218 [cH1:1][c:2]([cH1])!@[O:3][!C;!H:4] 4

219 [cH1:1][a:2]([cH1])!@[a:3]([cH1])[cH1:4] 4

220 [cH0:1][c:2]([cH0])!@[c:3][nX2H0:4] 4

221 [cH0:1][c:2]([cH0])!@[NX3:3][CX4:4] 4

222 [cH0:1](Cl)[c:2]([cH1])!@[CX3:3]=[O:4] 4

223 [aH0:1][c:2]([aH0])!@[SX4:3][!#1:4] 4

224 [a:1][ar5:2]!@[ar5:3][a:4] 4

225 [O:1]=[CX3:2]([NH1])!@[CH2:3][CX3:4]=O 4

226 [O:1]=[C:2]([!NH1])!@[NX3H1:3]([H:4])(c([nX2H0])([nX2H0])) 4

227 [C]\[CX3:1]([H])=[CX3:2]([H])!@\[CH1:3](C)[C:4] 4

228 [CX3:1]=[CX3:2]!@[CX3:3]=[CX3:4] 4

229 [C:1][S:2](=O)(=O)!@[NX3H0:3][C:4] 4

230 [*:1]~[OX2:2]!@[SX4:3]~[*:4] 4

231 [*:1]~[NX2:2]!@[nX3:3]~[*:4] 4

232 [*:1]~[CX4:2]!@[NX2:3]~[*:4] 4

233	[!#1:1][CX3:2](=S)!@[NX3H0:3][!#1:4]	4

234	O=[S:1](=O)[NX3H1:2]!@[CX4H2:3][!#1:4]	4

235	O=[C:1][NX3H1:2]!@[CX3:3]=[*H1:4]	4

236	[nX2H0:1][a:2]([nX2H0])!@[CX3:3]=[O:4]	3

238	[cH0:1][c:2]!@[CX4H0:3][CX3:4]	3

239	[cH0:1][a:2]([cH0])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH0])	3

240	[cH0:1](F)[c:2]([cH1])!@[CX3:3]=[O:4]	3

241	[c:1][S:2](=O)(=O)!@[NX3H1:3][C:4]	3

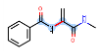
242	[c:1][S:2](=O)(=O)!@[NX3H0:3][C:4]	3

			
243	[*:1]~[nX3:2]!@[OX2:3]~[*:4]		3
			
244	[*:1]~[CX3:2]!@[cX3:3]~[*:4]		3
			
245	[*:1][S:2](=O)(=O)!@[NX3H0:3][*:4]		3
			
246	[!#1:1][c:2]!@[SX3:3][!#1:4]		3
			
247	[!#1:1][CX4H2:2]!@[OX2:3][c:4]		3
			
248	[!#1:1][CX4H2:2]!@[OX2:3][C:4]		3
			
249	O=[S:1](=O)[NX3H1:2]!@[CX4H1:3][H:4]		3
			
250	[nX2:1][c:2]([nX3])!@[O:3][C:4]		2
			
251	[nX2:1][c:2]!@[NX2:3]=[C:4]([NX3])N		2

			
252	[cH:1][c:2]([cH])!@[O:3][C:4](F)(F)[F]		2
			
254	[cH0:1][c:2]!@[CX4H2:3][!#1:4]		2
			
255	[cH0:1][c:2]!@[CX4H1:3][CX3:4]		2
			
256	[cH0:1][a:2]([cH0])!@[a:3]([sX2,o,nX2H0,nX3H1:4])([cH1])		2
			
257	[cH0:1](F)[c:2]([cH1])!@[CX3:3]([NX3H1])=[O:4]		2
			
258	[C]\[CX3:1]([H])=[CX3:2]([C])!@\[CH2:3][C:4]		2
			
259	[CH0:1][NX3:2]([CH0])!@[c:3][a:4]		2
			
260	[*:1]~[CX4:2]!@[CX3:3]~[*:4]		2
			
261	[*:1][S:2](=O)(=O)!@[NX3H1:3][*:4]		2

			
263	[cH1:1][c:2]([cH1])!@[O:3][S:4]		1
			
264	[cH1:1][c:2]([cH1])!@[NX3:3][a:4]		1
			
266	[cH0:1][c:2]([cH1])!@[O:3][!C;!H:4]		1
			
267	[cH0:1][c:2]([cH0])!@[CX3:3](c)=[O:4]		1
			
268	[cH0:1][c:2]!@[CX4H1:3][H:4]		1
			
269	[cH0:1]([CX3])[c:2]([cH1])!@[CX3:3](c)=[O:4]		1
			
270	[c:1][cr6:2]!@[cr6:3][cH0:4]		1
			
271	[c:1][CX4:2]!@[CX3:3][c:4]		1
			
272	[a:1][a:2]!@[a:3][a:4]!@a		1

			
273	[C:1][S:2](=O)(=O)!@[NX3H1:3][c:4]		1
			
274	[*:1]~[NX3:2]!@[NX3:3]~[*:4]		1
			
275	[!#1:1][CX4H2:2]!@[OX2:3][!#1:4]		1
			
276	[!#1:1][CX4:2]!@[SX3:3][!#1:4]		1
			
277	O=[S:1](=O)[NX3H0:2]!@[CX4H1:3][H:4]		1
			
278	O=[S:1](=O)[NH1:2]!@[c:3]([cH1])[cH1:4]		1
			
279	O=[S:1](=O)[NH1:2]!@[c:3]([cH1])[cH0:4]		1
			
280	O=[S:1](=O)[NH0:2]!@[c:3]([cH1])[cH1:4]		1
			
281	O=[S:1](=O)[N:2]!@[c:3][a:4]		1

			
282	O=[C:1][NX3H1:2]!@[CX3:3]=[*H2:4]		1
			
283	O=[C:1][NX3H1:2]!@[CX3:3]=[*H0:4]		1