An evaluation of Catalyst's conformational search algorithm with regard to conformational diversity and conformational energy penalties

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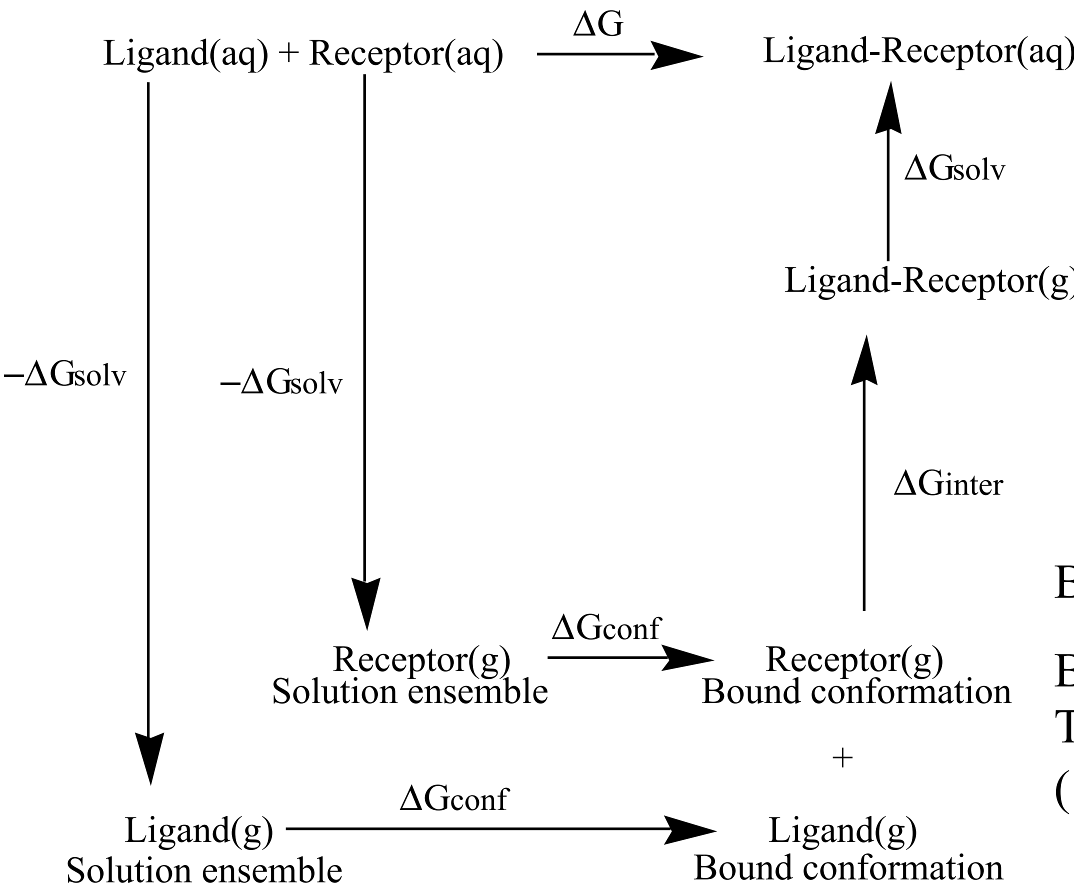
Conformational energy



$$\Delta G = -RT \ln K$$

ΔG_{conf}(Ligand) ~ ΔH_{conf}(Ligand Bound conf-Global min)

Bioactive Conformation < 12.6kJ/mol

Bostrom, J., Norrby, P.O., and Liljefors, T., J. Comput.-Aided Mol. Design (1998) 383.

$$\Delta G = \Delta G_{solv}(\text{Ligand-Receptor}) - \Delta G_{solv}(\text{Ligand}) - \Delta G_{solv}(\text{Receptor}) + \Delta G_{conf}(\text{Ligand}) + \Delta G_{conf}(\text{Receptor}) + \Delta G_{inter}$$

Catalyst

The aim of Catalysts conformation generation module is:
"Comprehensive coverage of the low-energy conformational space"
http://www.accelrys.com/

Catalyst searches feature space. More diverse sampling than other conformational search algorithms.

Overview

Catalyst

Best }
Fast }

Generate Ensemble

{ Ensemble
{ Global E. Minima

Average energy of ensemble generated by various energy limits

Average energy of ensemble

MacroModel

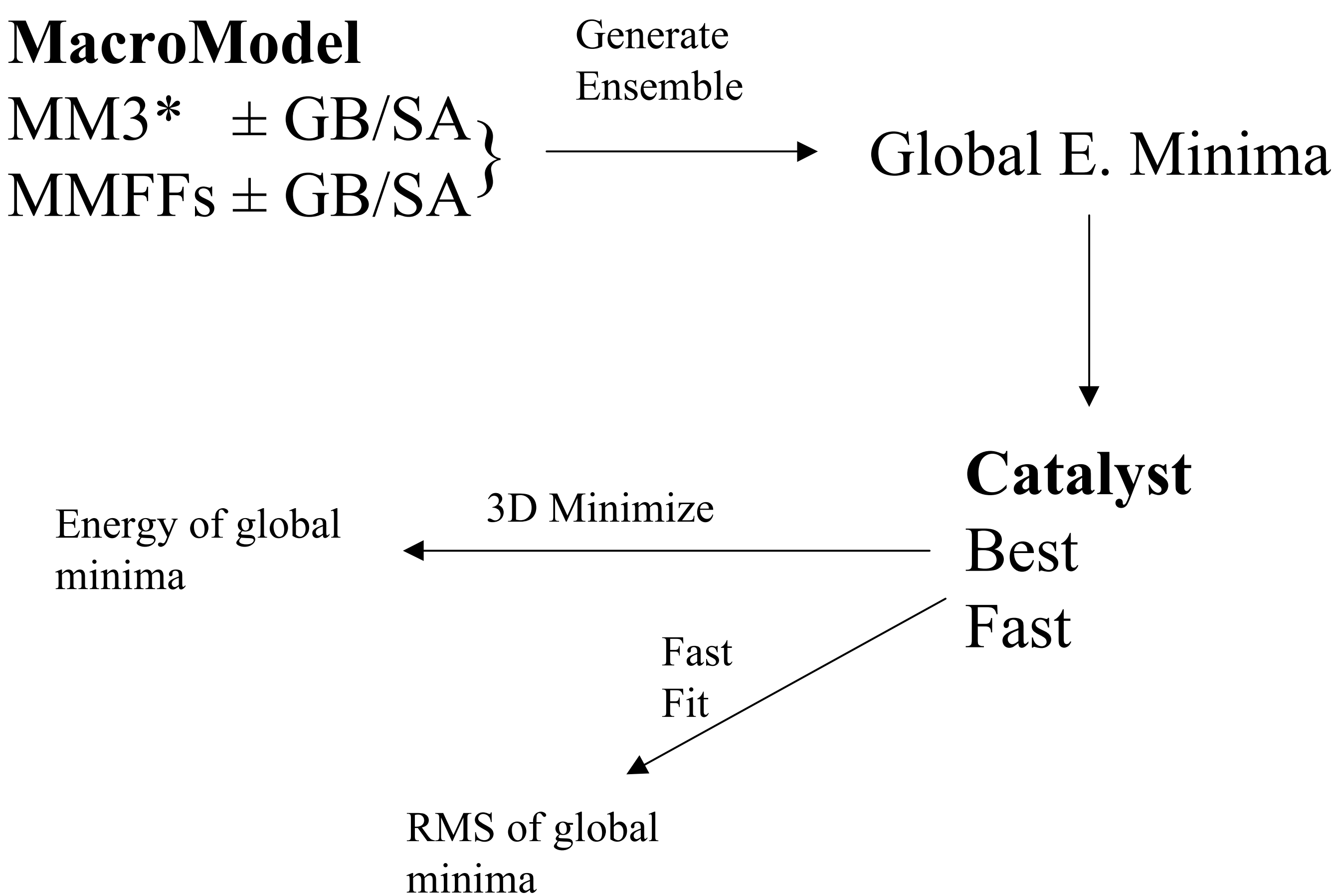
MM3* ± GB/SA }
MMFFs ± GB/SA }

Minimise

Ensemble
Global E. Minima

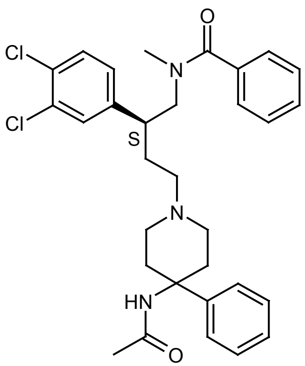
Energy and RMS of global minima

Overview



MacroModel
MM3* ± GB/SA
MMFFs ± GB/SA
Generate
Ensemble
Global E. Minima
Catalyst
Best
Fast
3D Minimize
Energy of global
minima
Fast
Fit
RMS of global
minima

Compounds



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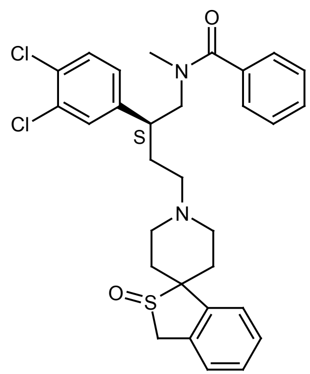

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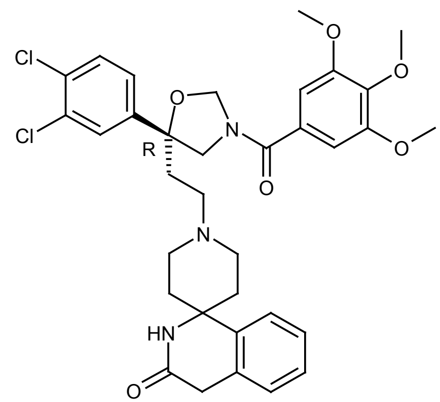

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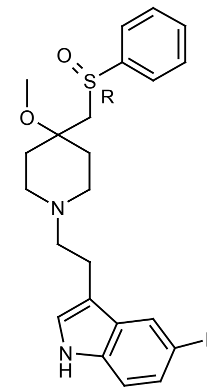

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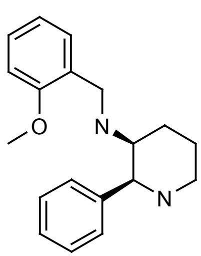

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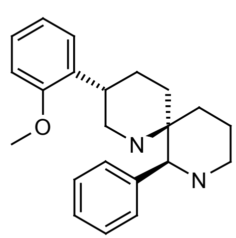

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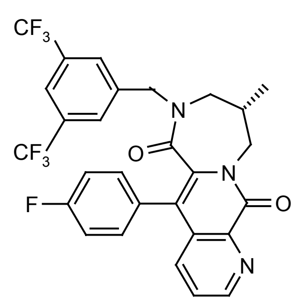

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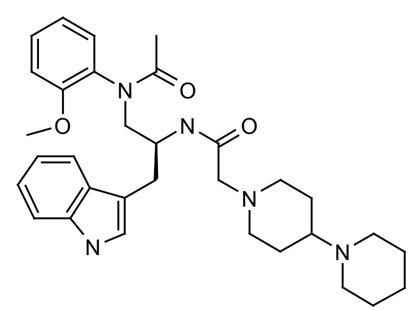

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Selective NK1 and NK2 antagonists. Dual NK1 and NK2 antagonists.
Varying degree of flexibility

Energy of Global energy minima calculated by other force fields

Catalyst —Conf. Model→ Global Minima —Export→ MacroModel —Minimise→ Energy

Compound	Catalyst Method	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA	MM3* Constr.	MM3* GB/SA Constr.	MMFFs Constr.	MMFFs GB/SA Constr.
1	BEST	37.5	24.7	39.1	20.2	41.0	33.0	50.6	39.0
1	FAST	26.3	9.6	37.6	4.8	29.9	16.8	39.7	14.6
2	BEST	13.6	8.2	22.3	10.0	14.1	10.5	22.6	17.9
2	FAST	28.6	13.4	37.9	4.5	30.6	16.8	40.5	8.8
3	BEST	16.7	6.1	15.1	3.2	28.4	18.4	44.8	33.4
3	FAST	34.3	24.8	57.6	24.6	61.9	60.5	70.0	55.4
4	BEST	11.4	4.5	33.5	14.7	12.3	6.3	39.4	18.1
4	FAST	18.1	10.7	21.3	5.6	32.5	18.0	51.2	21.9
5	BEST	28.5	23.0	13.7	1.5	30.8	25.0	16.0	3.2
5	FAST	28.2	20.6	24.2	6.7	33.5	25.8	31.9	14.5
6	BEST	4.9	9.0	17.1	10.3	8.6	13.8	27.6	22.8
6	FAST	24.6	37.4	61.4	63.0	71.1	81.3	86.7	90.3
7	BEST	0.3	1.0	0.1	0.3	48.0	34.2	24.4	4.9
7	FAST	0.1	1.0	4.5	0.3	26.9	18.9	17.1	6.6
8	BEST	46.0	33.0	49.0	32.5	40.0	32.9	103.9	81.1
8	FAST	31.7	14.8	28.6	10.1	18.9	13.2	33.2	20.6
Average	BEST	19.9	13.7	23.7	11.6	27.9	21.8	41.2	27.6
Average	FAST	24.0	16.5	34.1	15.0	38.2	31.4	46.3	29.1

Red	Within 4.2 kJ
Green	Within 8.4 kJ
Cyan	Within 12.6 kJ

Best lower in energy than Fast

Only fully minimised structures low in energy

Structure of Global energy minima, minimised by other force fields

Catalyst —Conf. Model→ Global Minima —Export→ MacroModel —Minimise→ RMS

Compound	Catalyst Method	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA	MM3* Constr.	MM3* GB/SA Constr.	MMFFs Constr.	MMFFs GB/SA Constr.
1	BEST	1.259	1.016	0.899	0.747	0.139	0.140	0.139	0.139
1	FAST	0.539	0.506	0.473	0.413	0.124	0.124	0.131	0.131
2	BEST	0.355	0.398	0.405	0.417	0.129	0.128	0.134	0.128
2	FAST	0.368	0.338	0.484	0.373	0.130	0.126	0.130	0.131
3	BEST	0.800	0.886	1.077	1.086	0.147	0.147	0.143	0.144
3	FAST	1.371	1.107	0.581	1.018	0.130	0.132	0.146	0.147
4	BEST	0.409	0.407	0.594	0.476	0.127	0.139	0.142	0.139
4	FAST	0.648	0.699	0.596	0.560	0.139	0.138	0.139	0.138
5	BEST	0.580	0.523	0.579	0.468	0.126	0.125	0.127	0.124
5	FAST	0.736	0.660	0.362	0.339	0.139	0.135	0.132	0.134
6	BEST	0.404	0.454	0.541	0.569	0.129	0.130	0.142	0.141
6	FAST	1.797	1.797	0.680	0.723	0.143	0.144	0.149	0.150
7	BEST	0.905	0.875	0.920	0.774	0.104	0.106	0.124	0.125
7	FAST	0.607	0.567	0.613	0.504	0.122	0.121	0.123	0.123
8	BEST	0.519	0.579	2.598	2.547	0.148	0.145	0.155	0.155
8	FAST	0.527	0.841	0.652	0.716	0.131	0.131	0.148	0.147
Average	BEST	0.654	0.642	0.952	0.886	0.131	0.133	0.138	0.137
Average	FAST	0.824	0.814	0.555	0.581	0.132	0.131	0.137	0.138

Most of catalysts global energy minima changes conformation upon minimization

Far from local minima
High conformational energy

(cyan) Within 0.5 Å

Average energy of ensemble calculated by other force fields

Catalyst —Conf. Model→ Ensemble —Export→ MacroModel —Minimise→ Energy

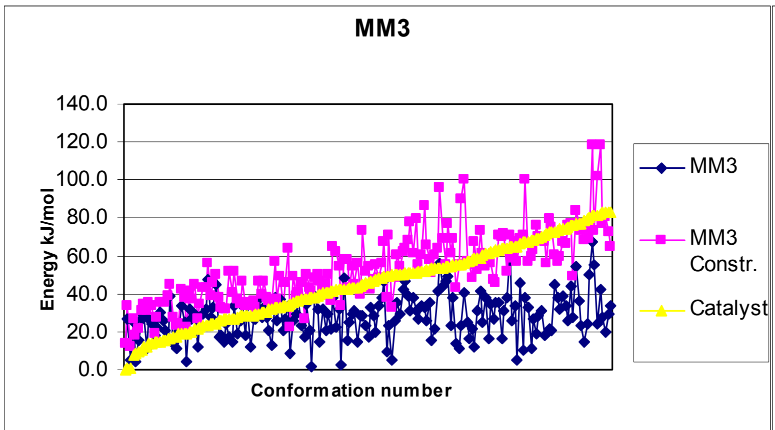
Compound	Catalyst Method	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA	MM3* Constr.	MM3* GB/SA Constr.	MMFFs Constr.	MMFFs GB/SA Constr.	Catalyst	Number of Conf.
1	BEST	40.4	35.2	39.0	28.9	66.8	62.1	77.9	68.8	47.8	192
1	FAST	37.2	29.2	40.7	24.8	53.7	45.5	66.3	51.1	48.3	199
2	BEST	27.7	25.0	33.5	20.4	53.1	50.0	73.7	62.3	45.3	183
2	FAST	33.8	29.0	42.0	24.8	49.7	45.1	65.0	49.1	55.3	100
3	BEST	39.1	35.0	39.6	25.6	56.4	52.1	74.7	65.7	44.5	107
3	FAST	45.3	38.3	54.0	32.3	78.1	71.6	89.8	70.4	49.8	225
4	BEST	25.7	22.5	41.9	33.9	49.0	45.3	81.6	70.7	43.7	230
4	FAST	36.1	32.0	44.3	36.7	55.4	51.8	77.0	65.0	41.6	225
5	BEST	31.5	26.7	27.5	15.2	54.9	48.8	60.7	46.8	49.7	71
5	FAST	27.6	22.7	15.8	7.0	40.4	35.4	38.9	29.3	25.3	10
6	BEST	30.5	38.4	45.1	44.4	59.3	66.6	79.0	75.4	54.2	56
6	FAST	24.7	35.8	52.6	58.1	71.1	81.3	93.0	97.4	44.2	5
7	BEST	10.8	3.3	9.7	2.8	41.9	33.1	47.1	27.7	32.8	140
7	FAST	11.5	4.7	15.2	3.6	42.3	36.2	40.7	25.3	29.7	67
8	BEST	54.0	41.7	66.2	47.3	76.9	66.2	125.6	96.6	41.1	202
8	FAST	55.8	42.4	72.6	46.7	65.3	53.8	110.8	77.0	47.2	216
Average	BEST	32.5	28.5	37.8	27.3	57.3	53.0	77.5	64.3	44.9	147.6
Average	FAST	34.0	29.3	42.2	29.2	57.0	52.6	72.7	58.1	42.7	130.9

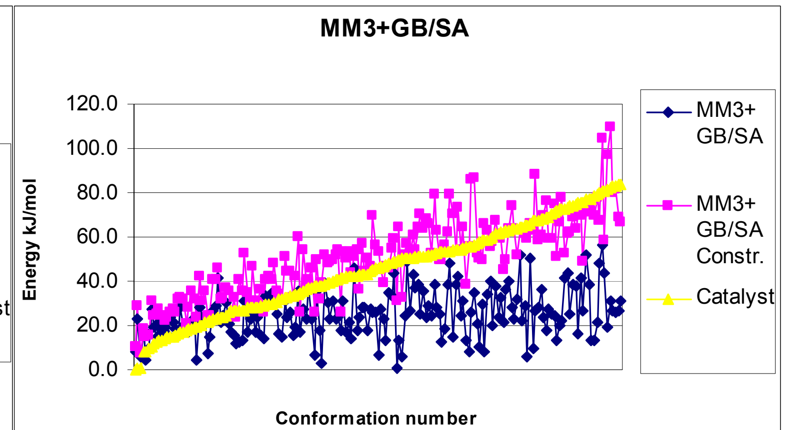
(red)	Below Glob. min.
(green)	Within 4.2 kJ/mol of glob. min.
(cyan)	Within 8.4 kJ/mol of glob. min.

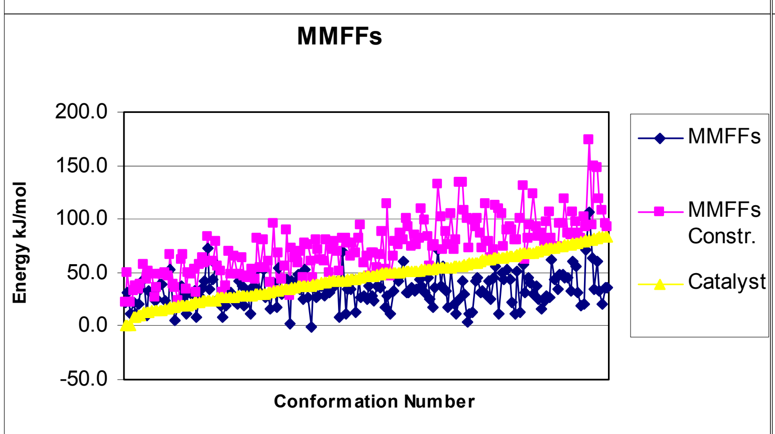
Generally within the standard 84kJ energy limit. Fast and Best equal in energy.

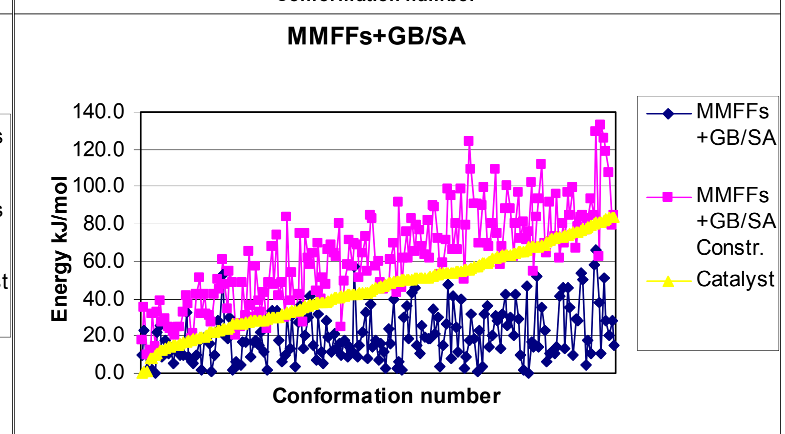
Average energy comparable to Global minima

Energy of ensemble calculated by various force fields

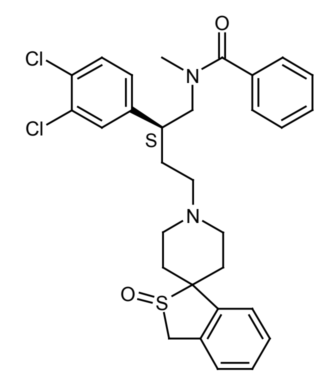








Energy penalty calculated by Catalyst is almost a random number



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Energy of Global energy minima found by other force fields

MacroModel —Conf. Model→ Global Minima —Export→ Catalyst —3D Minimize→ Energy

Compound	Catalyst Fast	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA
1	13.7	4.2	-2.6	14.6	9.9
2	16.4	18.4	1.8	25.7	12.8
3	56.6	18.1	-0.5	65.4	37.4
4	9.5	6.2	2.0	5.5	7.5
5	7.6	-2.3	-2.3	-0.4	0.1
6	63.4	16.9	-5.7	0.4	1.0
7	2.6	2.5	2.5	1.7	2.4
8	-4.8	3.2	1.9	5.6	6.9
Average	20.6	8.4	-0.4	14.8	9.8

(red)	High conf. energy
(cyan)	Negative conf. energy

Catalysts force field are not comparable to MM3* and MMFFs

Catalyst does not find the global minima in its own forcefield

Structure of Global energy minima found by other force fields

MacroModel —Conf. Model→ Global Minima —Export→ Catalyst —Fast Fit→ RMS

	Catalyst Best search					Catalyst Fast search				
Compound	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA	Catalyst Fast	MM3*	MM3* GB/SA	MMFFs	MMFFs GB/SA	Catalyst Best
1	1.440	1.657	1.323	1.694	1.700	1.203	1.633	1.358	1.633	1.977
2	1.494	1.594	1.121	1.360	1.287	1.871	1.970	0.938	1.358	1.505
3	1.945	1.935	1.820	1.985	1.060	2.477	1.231	1.697	1.773	1.346
4	1.395	0.751	0.723	1.005	1.601	1.553	1.364	1.648	1.716	1.606
5	0.767	0.754	1.306	1.307	0.987	1.289	1.295	1.260	1.237	1.361
6	0.736	0.409	0.577	0.592	0.824	1.657	1.551	1.714	1.709	1.559
7	0.547	1.065	0.482	1.201	0.197	0.759	0.877	0.597	0.666	0.483
8	1.942	1.909	1.548	1.889	1.952	1.685	1.776	1.182	1.802	2.446
Average	1.283	1.259	1.113	1.379	1.201	1.562	1.462	1.299	1.487	1.535

(red)	Within 0.5 Å
(cyan)	Within 1 Å

Trend: Fast search gives higher RMS than Best search

Global energy minima found by other methods generally not precent in catalysts ensemble

Energy limits for conformational search

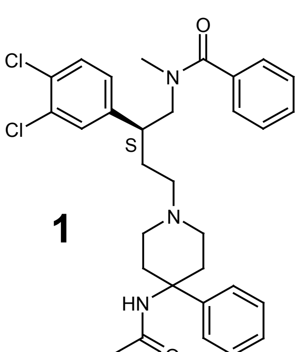
The mean energies of the poled set were somewhat higher than those of the unpoled set, consistent with our goal of covering conformational space with respect to a user-defined energy threshold rather than just elucidating local minima.

A. Smellie et al., J. Comp. Chem., Vol. 16, No. 2, 171-187 (1995)

Energy limits for conformational search

Catalyst —Conf. Model→ Ensemble —Export→ MacroModel —Minimise→ Energy

	Catalyst Fast search				Catalyst Best search			
Energy limmit	MMFFs	MMSFFs Constr	Catalyst	Number of conf.	MMFFs	MMSFFs Constr	Catalyst	Number of conf.
2.1	15.0	31.2	0.2	2	20.4	31.6	0.6	2
4.2	14.7	32.5	1.3	2	26.1	32.7	1.3	3
8.4	41.1	51.6	2.8	2	34.9	40.9	4.2	7
12.6	41.1	43.2	1.4	2	26.7	34.6	7.7	9
16.8	30.2	44.0	9.7	19	29.7	36.9	8.2	10
21	31.7	45.4	14.5	77	27.6	36	9.6	12
42	32.0	51.8	22.6	74	39.2	54.3	19.3	44
63	32.1	55.1	37.7	185	39.5	69.5	34.1	134
84	34.4	60.1	43.6	236	34.9	74.9	43.8	197



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Low E limit insufficient coverage of conf. space

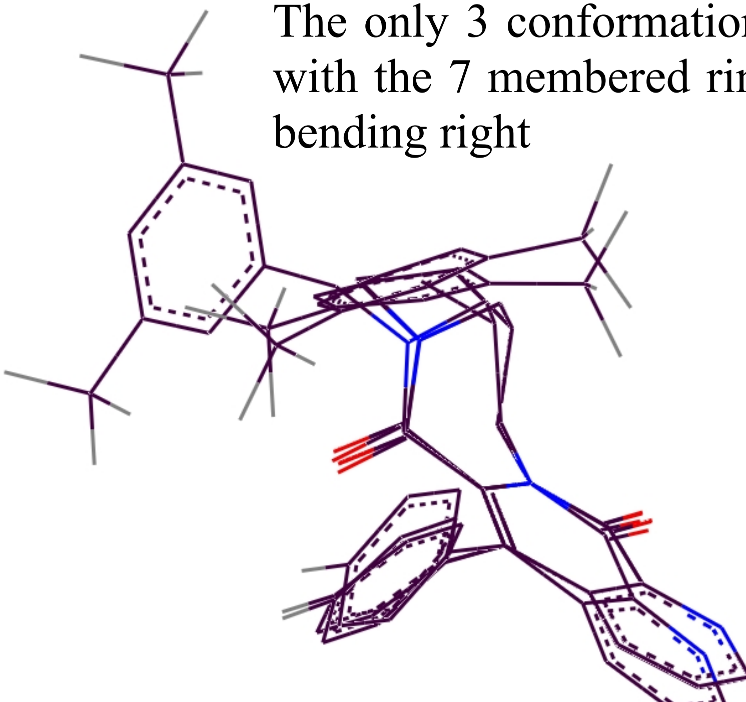
Conformational diversity

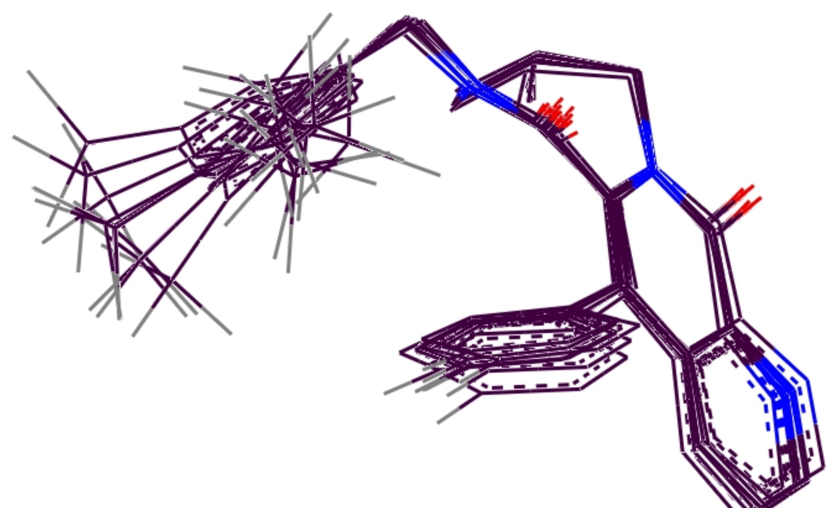
The 7 membered ring can bend to the left or right of the tricyclic ring system

Method	Right	Left
Catalyst Best	3	137
Catalyst Fast	24	43
MMFFs	29	24
MMFFs+GB/SA	30	47
MM3*	9	8
MM3*+GB/SA	9	7

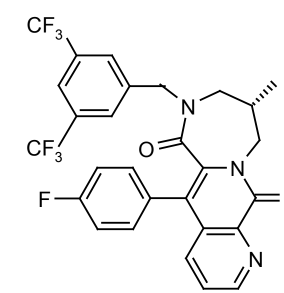
Catalyst Best Search

The only 3 conformations with the 7 membered ring bending right





10 first conf. in ensemble



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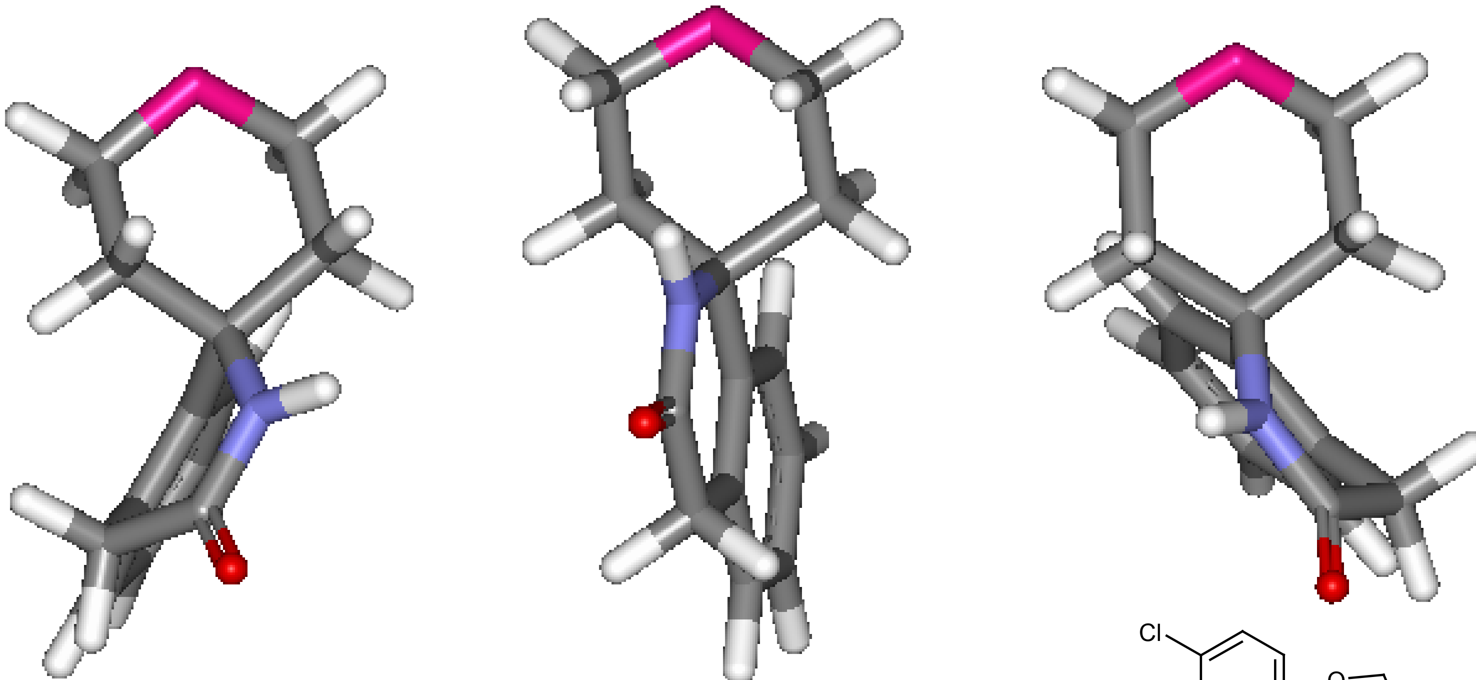
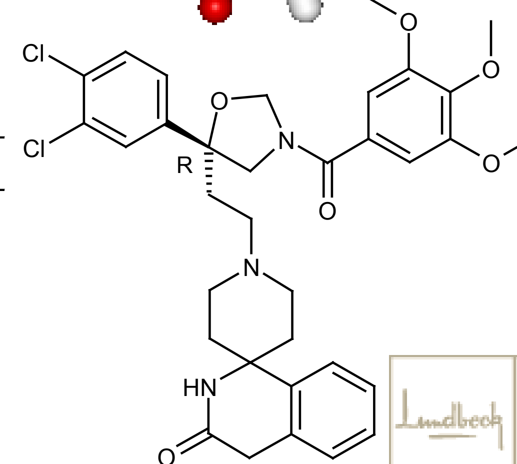
Conformational diversity



Method	Left	Center	Right
Catalyst Best	94%	2.6%	3.5%
Catalyst Fast	15%	85%	0%
MMFFs MMFFs+GB/SA MM3* MM3*+GB/SA	~50%	0%	~50%



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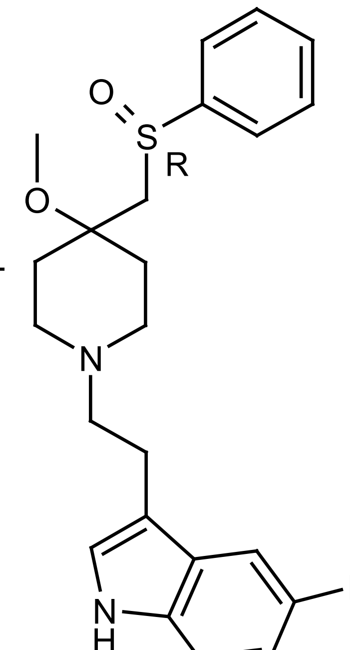
Conformational diversity

Catalyst Method	Fast	Best
Axial Chair	0 (0%)	2 (0.8%)
Axial Twist	0 (0%)	40 (17%)
Equatorial	49 (100%)	188 (81%)
No. Conformations	49	230



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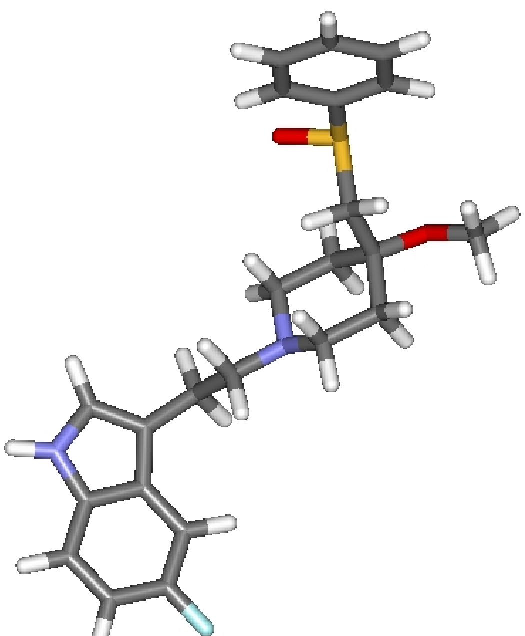
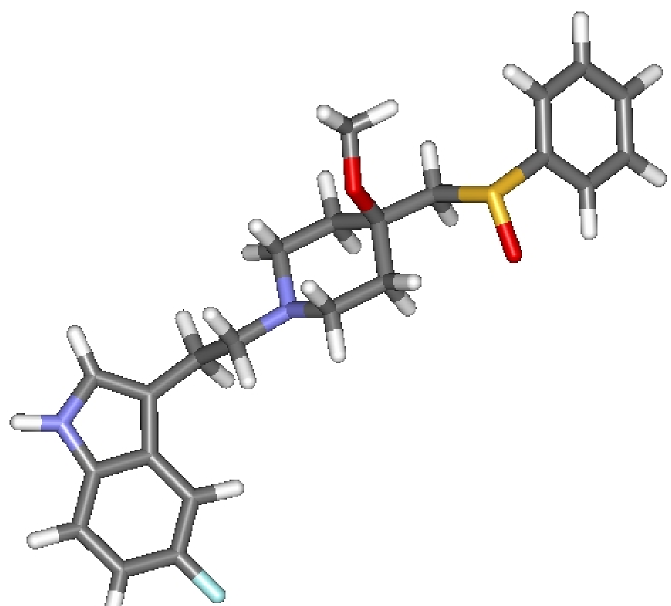
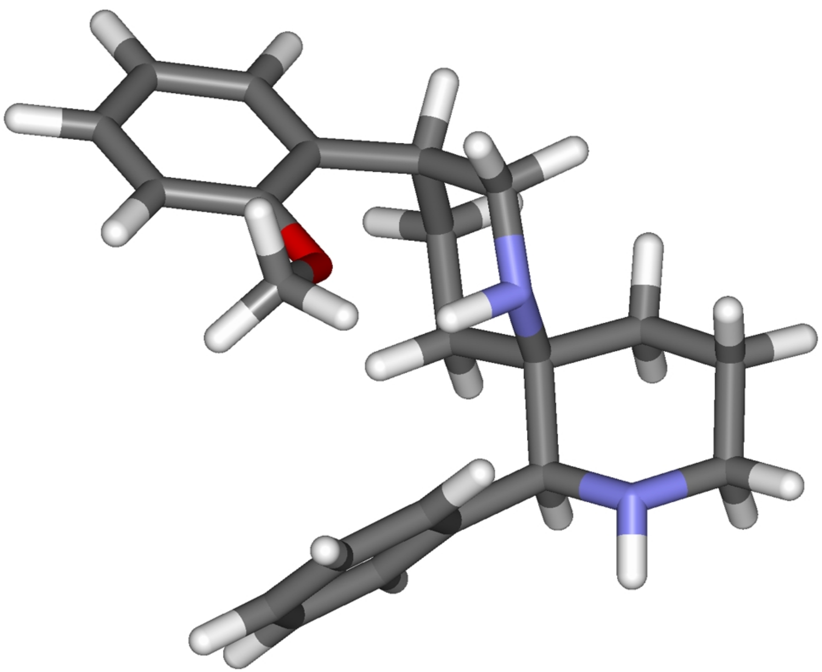
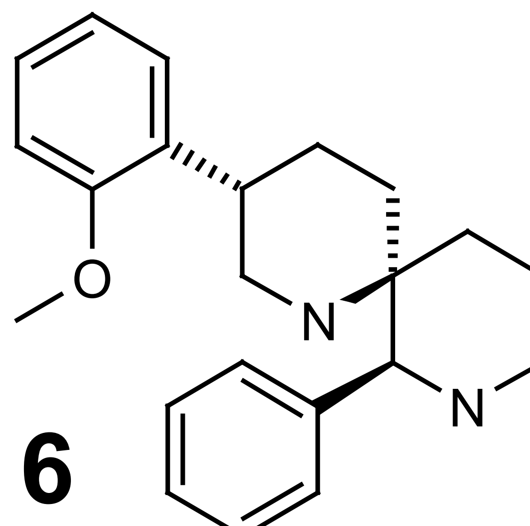




Conformational diversity

Catalyst Method	Fast	Best
Chair Chair	0 (0%)	3 (5.3%)
Unexpected	5 (100%)	53 (94.6%)
No. Conformations	5	56





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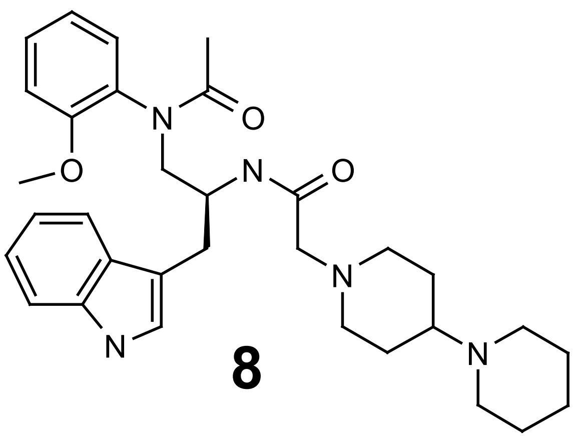
Conformational diversity

Catalyst Method	Fast	Best
Chair Chair Equatorial substituents	36 (17%)	4 (1.8%)
Chair Twist Equatorial substituents	9 (4.2%)	6 (2.7%)
Non Extended Conformations	171 (79.2%)	212 (95.5%)
No. conformations	216	222



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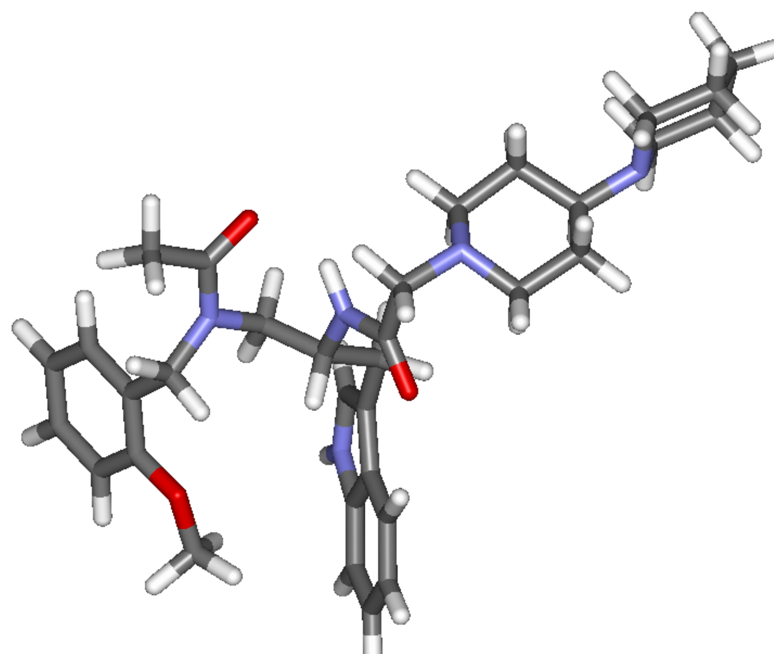

Conformational diversity

5 out of 8 conformational models generated by Catalyst are not diverse

Diversity in feature space is not the same as diversity in conformational space

Poling: Promoting Conformational Variation
A. Smellie et al., J. Comp. Chem., Vol. 16, No. 2, 171-187 (1995)

Poling: Preventing Conformational Variation

Conclusion

- Most conformations generated by Catalyst are far from a local minima and high in energy.
- The rank ordering of the conformational model is arbitrary.
- Diverse sampling of feature space does not always result in a diverse conformational model. The conformational diversity is often seen in distortions of low energy conformations. Especially for rings, high energy conformations are overrepresented in the conformational model. Sometimes so much that no low energy conformation is found for the ring system.

Conclusion

The high energy conformations are just noise that results in false positives when doing a database search. This noise is dangerous when doing automatic hypothesis generation, since it leads to wrong models.

Catalyst is a good tool for 3D database search. Substituting the conformational search algorithm for a Monte Carlo or Low mode search would greatly enhance the quality of the program.