CHARMM General Force Field (CGenFF) Compass: A Lexical Dictionary Bridge from Functional Groups to their Atom Types

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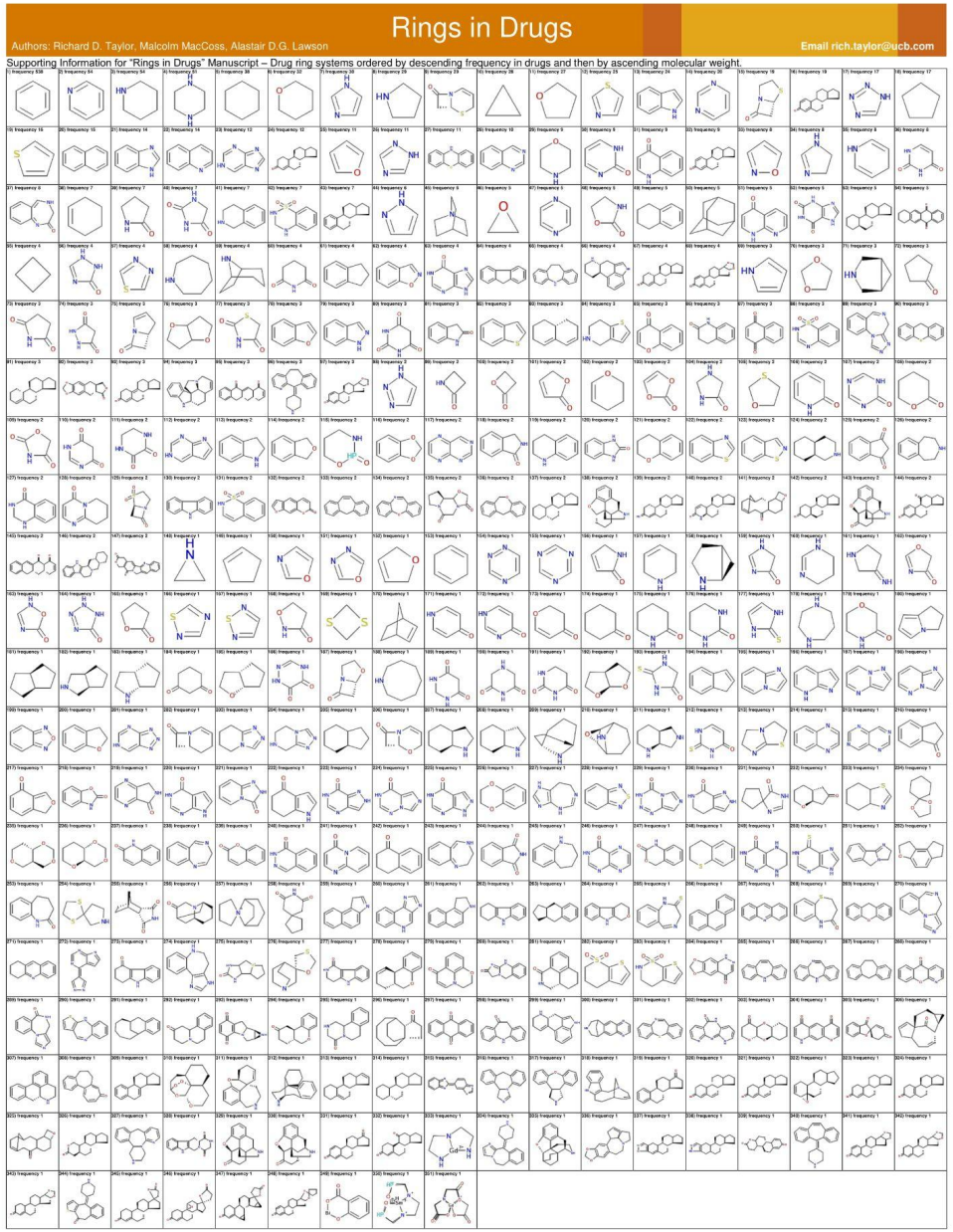
Overview & Problem

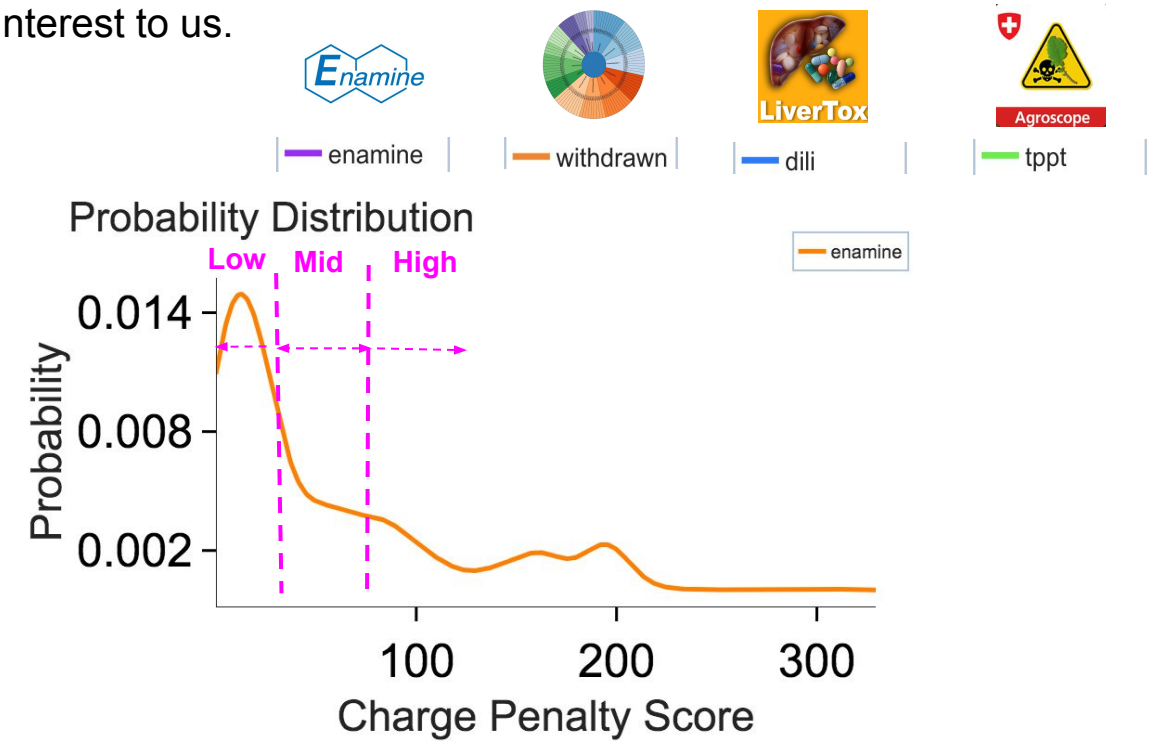
A central component of any successful force field is the small molecules used to define the initial atom type engine. The CHARMM General Force Field (CGenFF) was created based on a selection criteria that consists of a wide range heterocycles and simple functional groups (1).

More recently a study, Rings in Drugs, was published and highlighted that each year 28% of new therapeutics contain a new novel ring system (2). So this percentage could be significantly higher if we included non-ring functional groups. This presents a problem: in a nearly infinite chemical space how do we select the most important functional groups to conduct time-consuming force field parameterization that maximizes our representation of molecules most likely to be considered in drug design?



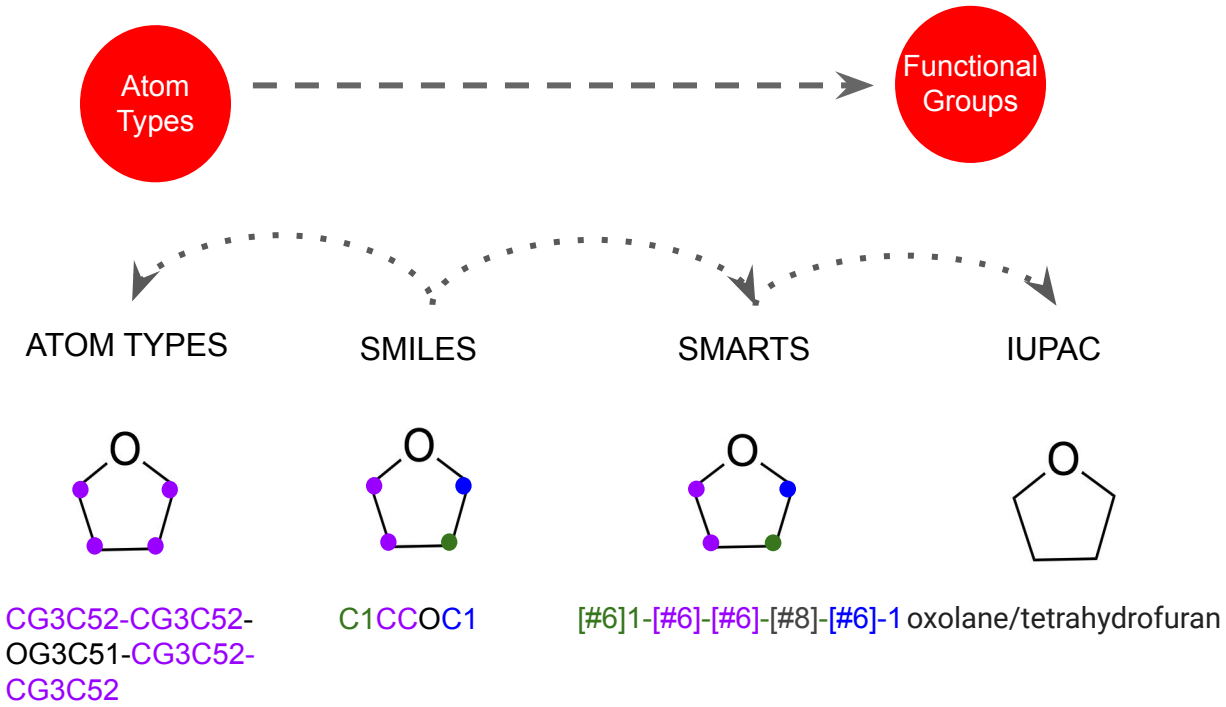
Philosophy

CGenFF is unique in its ability to quantify the quality of the assigned charges and bonded parameters of a compound based on compounds in the FF and it's decision tree. This penalty score allows for the distribution of well vs. poorly predicted compounds to be determined. Using the penalty values clusters in the charge probability distribution were identified and denoted "No", "Low", "Mid", "High". To visualize this classification scheme, we applied the sunburst to a variety of existing chemical databases that was of interest to us.



Linguistic Schematic

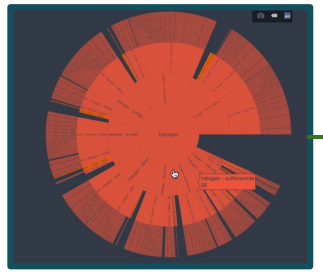
To visualize what atoms and associated atom types had the highest penalties, thereby requiring parameter optimization,we correlated the atom language using a series of key value dictionaries to something readable by medicinal chemists, IUPAC.

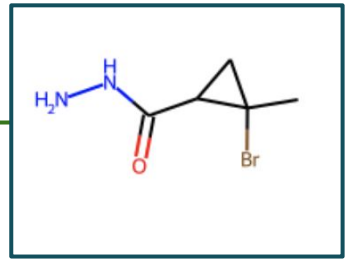


Sunburst

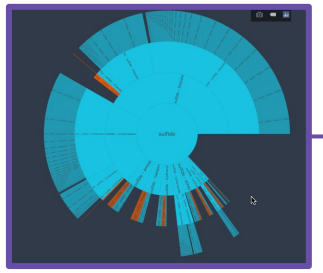
Compound Selection

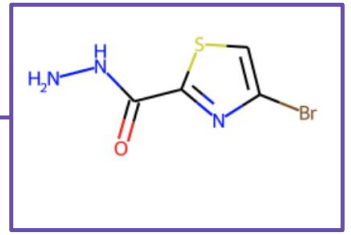
Query: Halogen - Cyclopropane, High, NG2S1



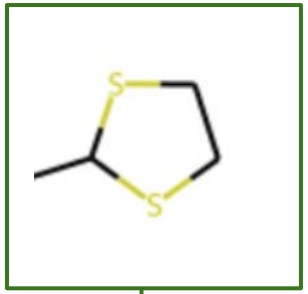


Query: Thiazole - Sulfide, High, SG311

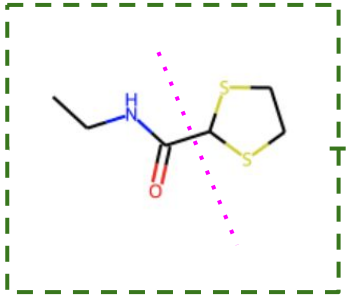




1,3-Dithiolane

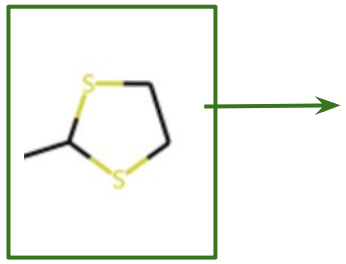


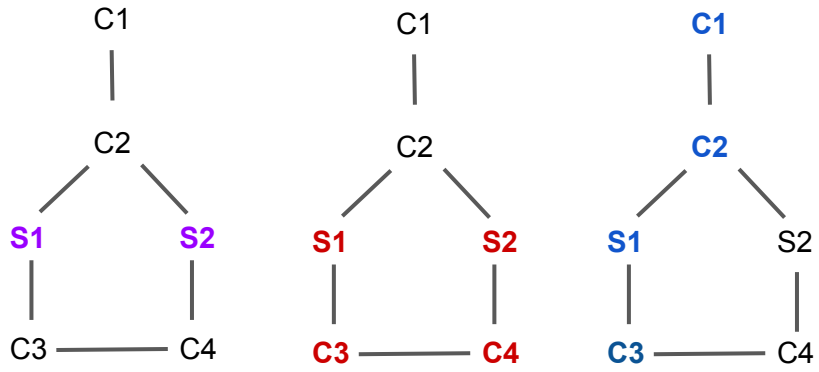
Query: Amide - Sulfide, High, SG311



Parameterization

1,3-Dithiolane

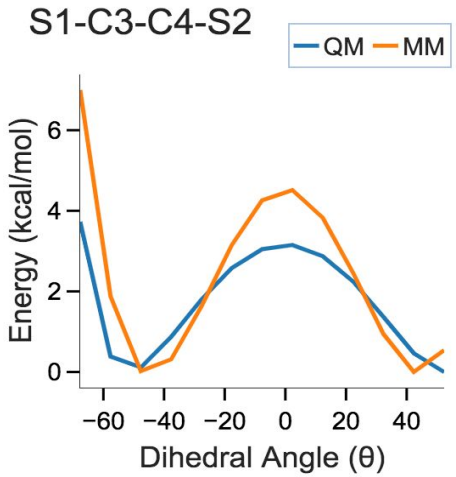


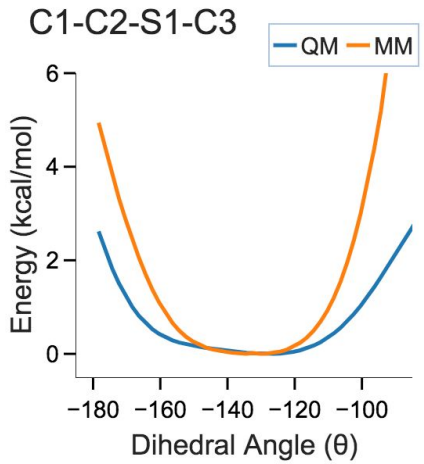


High Penalty Dihedrals	Atom Types	Penalty
S1-C3-C4-S2	SG311-CG352-CG352-SG311	232.2
C1-C2-S1-C4	CG201-CG331-SG311-CG352	146
High Penalty Atom Charges	**Atom Types**	**Penalty**
S1, S2	SG311	151.339
C1	CG201	71.459
C2	CG331	138.768
C3, C4	CG352	124.574

Major parameter corrections were:

- **S1-C3-C4-S2:** dihedral required a high force constant at only a multiplicity of 3.
- **C1-C2-S1-C4:** required a lower force constraint at multiple mutilpliticities.
- **S1-S2:** Water interaction energies were evaluated, Monte Carlo Simulating Annealing was applied to bring the overall dipole to < 0.5 kcal/mol difference

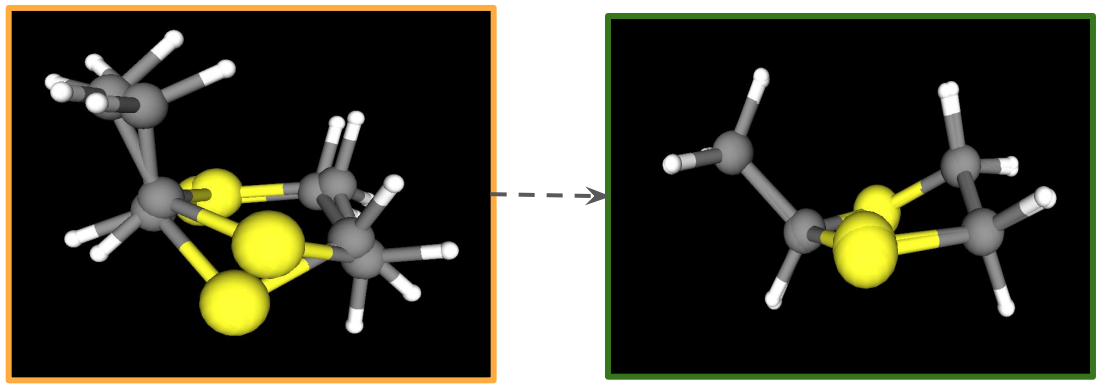




Conclusions

Using CGenFF Compass, the dithiolane fragment was identified within the enamine database due to high penalty scores of the sulphur charges and of selected dihedrals.

Before **After**



CGenFF compass has enabled us to find interesting outlier patterns rapidly. This allows us to identify the most interesting compounds in the force field for parameter optimization.

Acknowledgements & References

Thank you to the following for their helpful discussions into the usability and functionality of CGenFF Compass: Payal Chatterjee, Anmol Kumar, Elena Chow, Holden Smith, Marvin Corro, Paween Mahinthichaichan, Quynh Vo, Kellie Hom, Erik Vasquez, Ronald Kasl, Chris Burke, Sameera Thakurdas, Jana Shen, and lastly, Atlantis.

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1. Vanommeslaeghe, K., et al. “CHARMM General Force Field (CGenFF): A Force Field for Drug-like Molecules Compatible with the CHARMM All-Atom Additive Biological Force Fields.” *Journal of Computational Chemistry*, vol. 31, no. 4, Mar. 2010, pp. 671–90. *PubMed Central*, doi:10.1002/jcc.21367.

2. Taylor, Richard D., et al. “Rings in Drugs.” *Journal of Medicinal Chemistry*, vol. 57, no. 14, July 2014, pp. 5845–59. *ACS Publications*, doi:10.1021/jm4017625.

3. “A Brief History of Sunburst Visualization” Corp, (c) 2008-2018 Software Ambience *DaisyDisk*,