Theoretical studies of several small-ring precursors to (+)-JQ1

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Background

The molecule (+)-JQ1 has shown promise in cancer research as well as a potential male birth control. It functions as a bromodomain inhibitor, and it is active on the BRD4 bromodomain. A total synthesis has been conducted by Bradner et. al., but more investigation into the synthesis needs to be conducted. The first synthesis (Figure 1) produces a racemic mixture of JQ-1. This is not synthetically useful since only the (+) enantiomer has shown promise and is desired for research. A stereospecific synthesis has been proposed (Figure 2) and is the subject of further investigation. The following data will be used to support colleagues conducting this synthesis.
DFT calculations using accurate basis sets [6-311+G(d,p)] were carried out to determine the geometry, electrostatic potential, Raman and IR (scaled harmonic frequencies), and NMR spectra for each precursor. Optimized geometries for each precursor can be seen to the right. The NMR spectra calculated using the DFT method are done so at 0 K by default, so individual chemical shifts must be interpreted with this in mind. As a result these spectra have been omitted since they are holistically inconclusive. The Raman and IR spectra are more useful for comparative purposes to experimental data. This will be done as the data become available. Furthermore, electrostatic potentials are highly useful in determining the reactivity of each molecule. The location and concentration of electrons relative to the nuclei in the molecule hints at the further chemistry that can be performed on each molecule in each step of the synthesis. The electrostatic potential can be seen for each molecule.

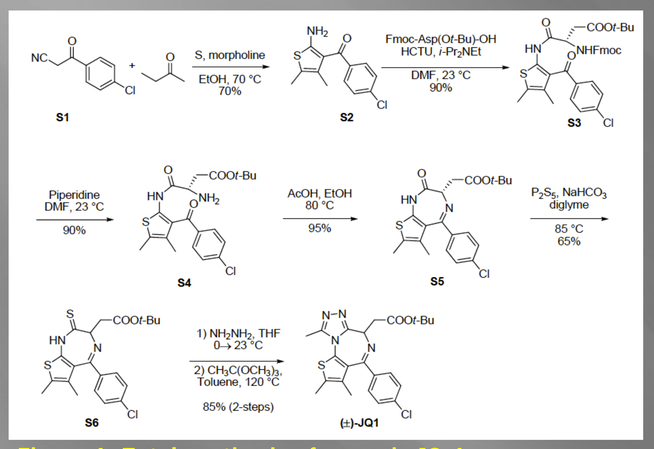


Figure 1: Total synthesis of racemic JQ-1

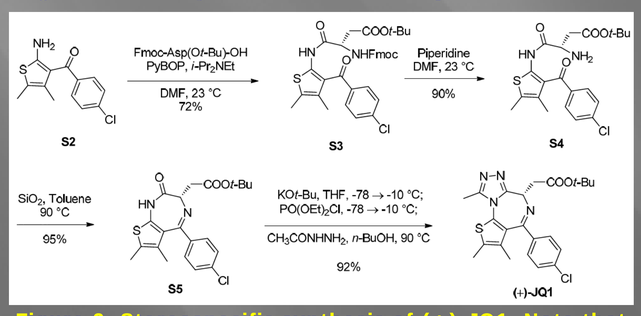
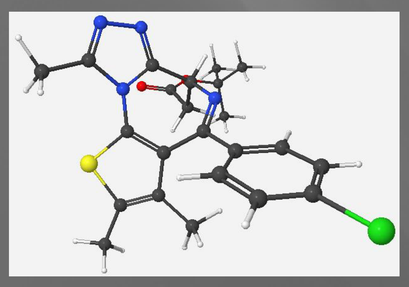
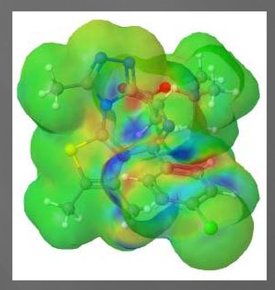


Figure 2: Stereospecific synthesis of (+)-JQ1. Note that the first step is the same for the S1 -> S2 conversion, and thus this step has been omitted.



Molecular Structure of (+)-JQ1



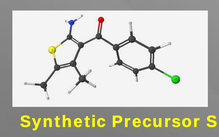
Summary

We present the results of DFT(B3LYP) calculations
on several precursors to (+)-JQ1 using an accurate basis set,
including a report of conformational analysis, thermochemistry, optimized geometries and electrostatic potentials, and calculated IR and Raman spectra.

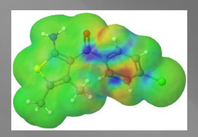
Species include
(I) 1*H*-1,4-diazepin-2(3*H*)-imine,
(II) 9*H*-[1,2,4]triazolo[4,3-a][1,4]diazepine,
(III) 6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine,
and (IV) 4-(4-chlorophenyl)-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine;

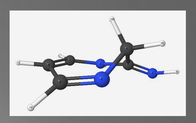
Studies are also reported on monobrominated (II)-(IV) substituted at the chiral center of the seven member ring, including a comparison of the energetics of equatorial versus axial bromination of the parent precursor. Implications with regard to the larger structure of (+)-JQ1 are discussed.

Molecular Structures



Synthetic Precursor S2





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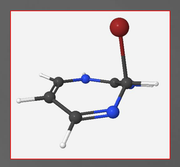

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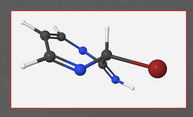

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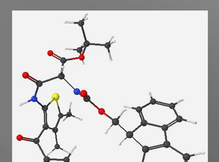

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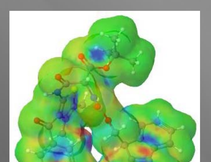

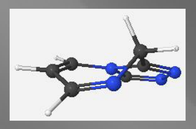

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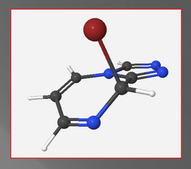

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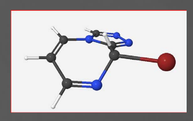

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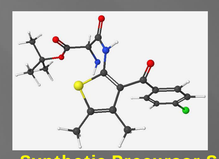
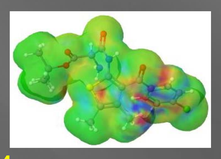
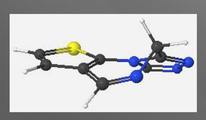


Synthetic Precursor S4





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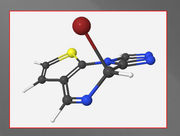

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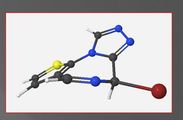

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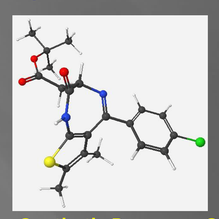

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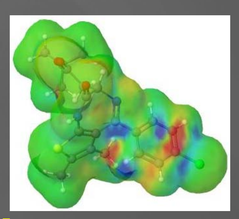

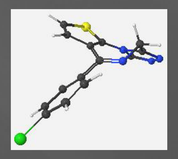

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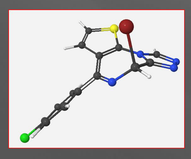

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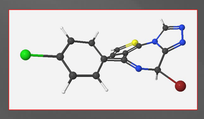

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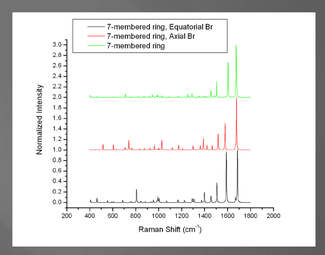
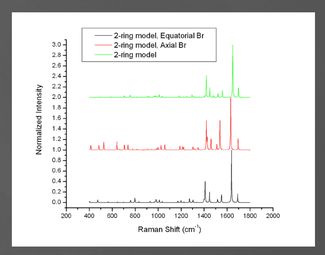
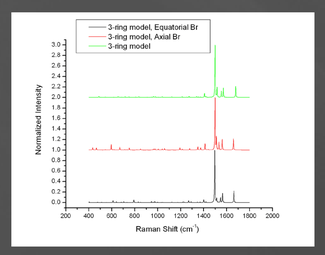






Thermochemistry

Species	V	AxBr-V	EqBr-V	W	AxBr-W	EqBr-W
Dihedral (°)	0.0	26.0	24.7	0.0	24.1	20.7
ΔE (kJ/mol)	22.2	32.8	32.7	20.5	55.3	32.2
Species	**X**	**AxBr-X**	**EqBr-X**	**Y**	**AxBr-Y**	**eQBr-Y**
Dihedral (°)	0.0	18.5	19.1	5.9	9.2	7.1
ΔE (kJ/mol)	25.5	35.7	35.7	44.8	49.8	49.7

Conclusions

- Barriers to inversion of the seven- membered ring range from 20 to 50 kJ/mol.
- Our model JQ1 compound has a large barrier of 50 kJ/mol, much larger than thermal energies.
- These data suggest that JQ1 exists as a diastereomer due to (1) the optical center, and (2) the overall morphology of the molecule.

Potential Energy Surfaces

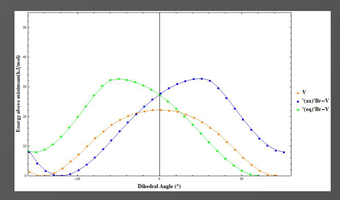


Figure 3

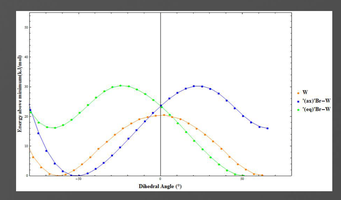


Figure 4

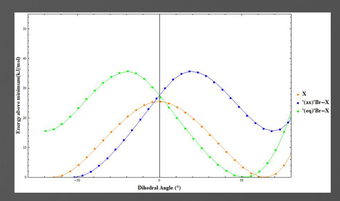


Figure 5

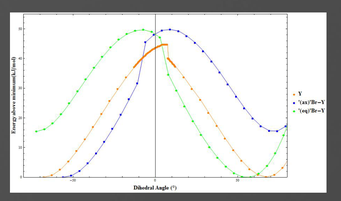
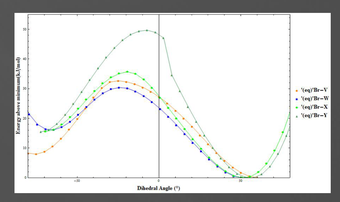


Figure 6



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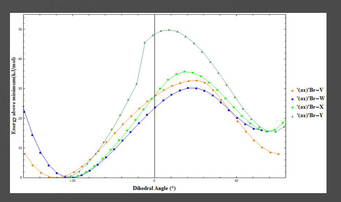

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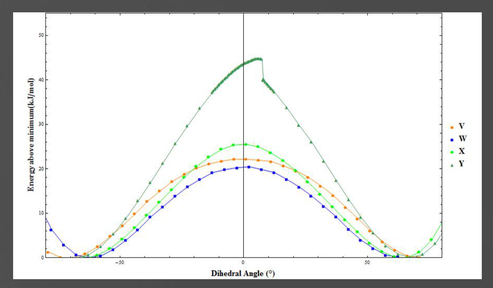

Figure 9

Figures 3 through 9 show sections of the potential energy surface in which a particular dihedral angle containing the optical center is varied systematically connecting equatorially and axially substituted species while preserving chirality.
Barriers are approximately 20 to 50 kJ/mol as the complexity of the ring system increases. The rapid change in the surface of model JQ1 compound Y is due to steric effects involving the chlorophenyl group.

References

1) P. Filippakopoulos et al., Nature 468, 1067-73 (2010).

2) Elizabeth J. O. Atkinson, Jake Hillyer, David Scheafer, and Eric Lemieux, Linfield College.

Acknowledgements

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