

EXAMPLE

1

The Structural Modification of 6,8-Diprenylaromadendrin, An Approach to Improve the Anti-HIV Properties of this Natural Product

Abstract

The human immunodeficiency virus (HIV), the causative agent for Acquired Immunodeficiency Syndrome (AIDS), has been a target for therapeutic intervention for more than twenty years. Great strides have been made in the treatment of AIDS¹, but drug resistance is still prevalent, warranting further investigation into new therapies.² Moreover, though the pharmaceutical industry once had a keen interest in developing drugs for treating HIV infection, in recent years, their research efforts have been concentrated in areas such as oncology, inflammation, diabetes, neuroscience, cardiovascular disease, and obesity. Unfortunately, for a variety of reasons, major pharmaceutical companies have markedly reduced their commitment to infectious disease research.³ New therapies with novel mechanisms of action are still very much needed to ensure AIDS does not re-establish itself as the scourge it once was.

The immediate, near-term goal of this research is to establish the chemistry required to optimize the known anti-HIV activity of the natural product, 6,8-diprenylaromadendrin (6,8-DAD; see Figure 1 below).⁴ Defining the antiviral mechanism of 6,8-DAD potentially can offer an innovative means for controlling the viral replication of HIV.⁵

This research project, to be initiated in the very near future, will rely upon traditional medicinal chemistry for structure optimization, and the use of external collaborations for evaluating the biological activity of novel compounds.⁶ The short- and long-term goals of this project will be able to answer the following questions⁷:

- a) Can more potent analogs of the original natural product be prepared?
- b) Can we use these new analogs to identify the molecular target of the drug and therefore identify its mechanism of action?

c) If the target of this antiviral agent is novel, is it “druggable”?⁸

Additionally, this project will serve as an excellent pedagogical device for undergraduate science majors⁹ and as the foundation of a broader application for external funding.

On the basis of the conclusions drawn from this research and the extent to which the aforementioned questions are answered, at the very least, one or more publications in well-respected, high-impact journals such as the *Journal of Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry*, and the *Journal of Virology* can be expected.¹⁰ Moreover, and equally important, if tangible evidence of improved biological and drug-like properties are established, patent protection for the new analogs would be sought promptly. Lastly, this project will serve as the basis for external grant proposals to such prestigious institutions as the National Institutes of Health and the National Science Foundation.

Background

Prior to returning to Fordham University in July 2010, I spent the past sixteen years working as a medicinal chemist in the pharmaceutical industry, where I contributed to, and have lead research teams in the areas of inflammation^{11a}, cancer^{11c}, and antiviral^{11b,d} research. I am the coauthor of twenty research papers and a co-inventor of more than twenty patent applications. Previous to this, I spent two years at Memorial Sloan-Kettering Cancer Center, working on the total synthesis of the anticancer agent Taxol,[®] where I honed my skills as a synthetic organic chemist.¹² I obtained my BS from Fordham University (Chemistry, FCRH, '84), my MS and PhD from New York University (Chemistry, 1986, and 1990).

Contribution

As mentioned in the abstract, the 3-hydroxyflavanone, 6,8-diprenylaromadendrin (6,8-DAD; Figure 1) is reported to possess anti-HIV activity.⁴ However, little is known about the viral target of this compound or the structural requirements for its potency. This core is quite common and several related, less-substituted analogs possessing similar biological activity have been disclosed. Potential sites within

the 6,8-DAD framework for structural modification are highlighted in color in Figure 1. This program will prepare structural analogs of this natural product with the intent of defining how these alterations impact potency. The correlation of molecular structure with biological activity is known as a structure-activity relationship (SAR) and is an essential part of any medicinal chemistry program. To harness the power of SARs, an iterative paradigm¹³ will be implemented to allow for the refinement of the subtle molecular properties for potency.^{14,15}

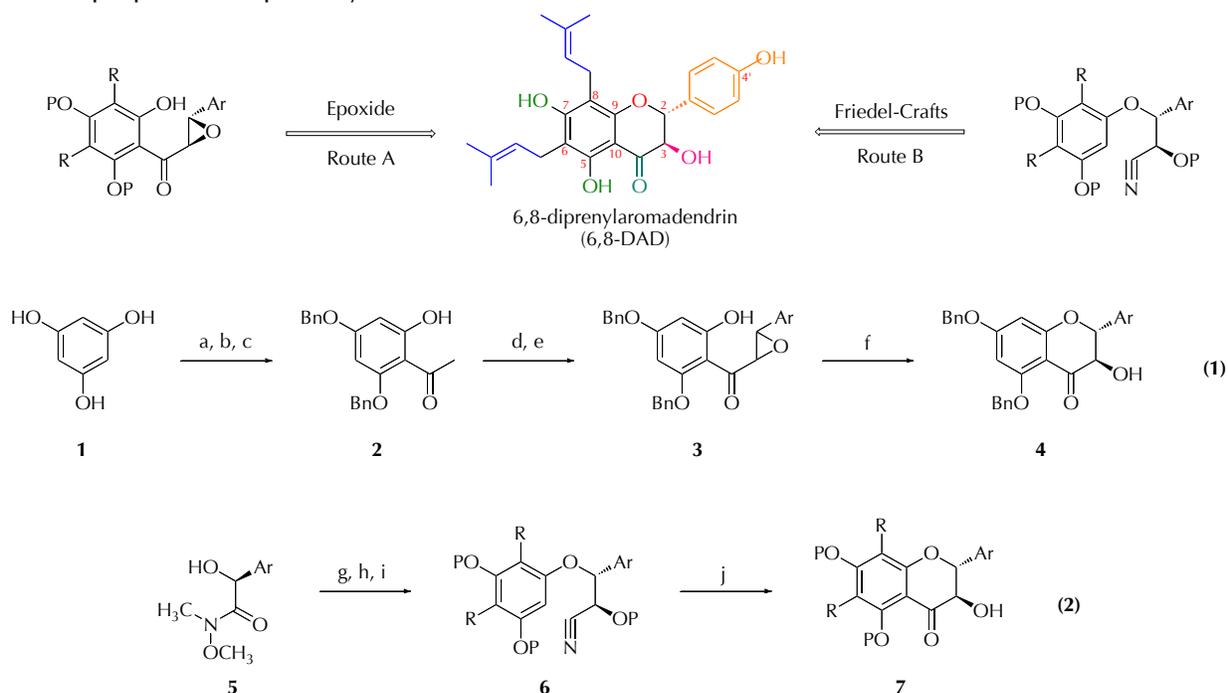


Figure 1: The Structure of 6,8-diprenylaromadendrin and proposed synthetic routes.

Reagents: (a) K_2CO_3 , $BnBr$; (b) $AcOH$, $(CF_3CO)_2O$; (c) $TiCl_4$; (d) $ArCHO$, KOH ; (e) $DMDO$; (f) $0.12\ M\ HCl$, $aq\ EtOH$; (g) $phenol$, $DEAD$, Ph_3P ; (h) $LiAlH_4$; (i) $TMSCN$; (j) $ZnCl_2$, HCl .

Numerous syntheses of the 3-hydroxyflavanone skeleton have been reported¹⁶ and this program will build on these published results. The use of literature precedent should minimize some of the risk associated with research (ie, the published routes are likely to permit the preparation of analogs without requiring extensive modification), allowing focus to be maintained on answering the aforementioned questions. As to the benefit to undergraduate researchers, by applying the tenets learned in their introductory organic chemistry course, they would gain valuable laboratory experience through the use of published strategies, learn to make use of primary references to support their work, and explore the

synthetic chemistry of new related analogs in order to ascertain the structural requirements for activity against HIV. Additionally, this will build confidence and self-reliance, foster critical thinking, and serve as a strong foundation for a career as an independent researcher.

With respect to the proposed chemistry, the described routes would allow the variation of the substituents on the core structure rather easily. In particular, the routes would allow (a) the optimization of the hydrocarbon chains at C(6) and C(8) and one or both of the phenols at C(5) and C(7); (b) an analysis of the stereochemical requirements at C(2) and C(3); (c) the determination of the C(3) substituent requirements; and (d) the assessment of the C(2) and C(4) functional group requirements. In addition, the use of isosteres¹⁷ will be explored to address potential liabilities in the lead compound.

Cost

The cost associated with this research project is estimated below:

Category	Description	Expense
Personnel	2 Undergraduate Research Assistants	\$1820.00
Other Services	SRI ⁶ – Screening of compounds	\$2150.00
Supplies	Chemicals and glassware	\$2500.00
Total Proposed Expenses		\$6470.00

The expenses were proposed based on the following plan of action. Two undergraduate researchers would be hired at a rate of \$14/h and expected to work at least 5 h/week over the course of a semester (13 weeks). These students are very likely going to be juniors or seniors and thus the rate was assigned based on the suggested rate given in the supporting documentation for this grant application.

As mentioned in earlier, I have worked in the past with the SRI as a contract organization for screening compounds in cells for activity against HIV.⁶ At this stage, I plan to use them once again and I assigned a budget of \$2150 for this purpose. Other screening services will also be explored.

The last item included in the expenses for this project is for chemicals and glassware. Presently, my laboratory is devoid of both and as such, I will be starting from scratch. Chemicals and glassware are unfortunately expensive and therefore I have assigned \$2500 for their purchase. Although I would

have difficulty specifying my exact needs for each, I can offer the following estimate as to what would be required.

Glassware needs:

- a) A complete set of round bottom flasks in assorted sizes for running reactions;
- b) Test tubes for collecting fractions during purification;
- c) Separatory funnels, reflux condensers, Erlenmeyer flasks, all of assorted sizes (these are general purpose glassware);

Chemical needs:

- a) Reagents and catalysts for the preparation of new analogs;
- b) Various solvents to use in reactions as well as purification of new products;
- c) Inert gases for instrumentation and reactions which cannot be run in the presence of oxygen

Conclusion

Through the use of synthesis, structural modifications of the natural product, 6,8-DAD, will be realized. Screening of these analogs for biological activity will hopefully identify more potent analogs against HIV and define SARs for this series. Undergraduates will be well trained in art of medicinal chemistry, while applying their acquired interdisciplinary science knowledge toward problem solving. Moreover, the science will continually stimulate them and they will acquire confidence as an independent thinker and researcher. The results established in this early stage of the project, made possible by a Faculty Research Grant, would serve as the basis for a much larger, more encompassing external research grant proposal.

EXAMPLE

2

**Symbolic Candidacies and the Significance of Third Parties:
A Historic Analysis of African Americans Seeking Executive Office, 1872-2008**

Abstract

If awarded, a First Year at Fordham Faculty Research Grant would provide me with able research assistants and the necessary materials to successfully launch my second manuscript project. Unlike most academic treatises and mainstream media on the subject, this post-Obama election project is not focused on the absence of a black *president* over the past one and half centuries since the abolition of slavery, but the plethora of black *presidential candidates* that have appeared over that period's duration. By examining in detail how over thirty African American presidential candidates have been incorporated into the electoral process at the executive level, this project introduces the importance of the presidential campaigns of African Americans to US electoral politics generally. Although the participation of African American candidates on the national level may have seemed like far-flung and self-serving endeavors for many of these third party and independent candidates, important institutional mechanisms arose from their inclusion into the electoral system at this elite level. These candidates implemented grass roots organizing on local levels in diverse locales, altered party rules, and groomed local campaign workers for local-level and state-wide offices. Their quest for the executive office not only contributed to an increase in African American elected officials on local levels, but also directly and indirectly enabled the success of the Obama campaign some 136 years after Frederick Douglass's name first appeared on a presidential ballot.

This project is in the genesis stage of research. With the assistance of this grant, background research will be gathered pertaining to the role of African Americans in third parties, symbolic candidacies, and the political party participation of African American elected officials. This pilot data will enable me to prepare and implement a qualitative survey throughout the spring, summer, and fall of 2010. Once the survey data is collected, I plan to

publish an article based on my findings,¹ which will also provide a platform to apply for external support. With the data collected, the following summer I will submit applications for a grant proposal to such prestigious organizations as the Russell Sage Foundation, the Ford Foundation, the Mellon Foundation, and the National Science Foundation (NSF).

Background

African American candidates for President of the United States have represented various political parties and affiliations, but more than two thirds represented independent parties, a trend that provides potential insight into the historical limitations of the dominant two-party system for African Americans. However, despite this trend, African American politicians have also historically depended on an established party as a way to achieve their own political party status.² This process may have ironically undermined the perceived independence and authority of these new political parties, helping to explain why several independent and third party candidates received little to no traction during their national campaigns.

This explanation may find support in scholars who argue that African American voters are inherently practical, and therefore seek to maximize their policy preferences within the dominant party system. This argument suggests that even if African American third party candidates articulated shared preferences with an African American polity, they would still fail to garner substantial support from these voters,³ as African Americans have traditionally believed that although achieving their electoral ends outright may be beyond their reach, they

¹ There are several possible journals of interest. The *Journal of Black Studies*, *Du Bois Review*, and the *Journal of Politics* are the three journals of primary interest.

² Walters, 1984.

³ Extending as far back as the mid-nineteenth century, blacks supported one of the two major parties, and not the Liberty Party, the party of abolitionists.

can act as a balance of power by throwing their support behind the “lesser of two evils” within the dominant two-party system.⁴

However, such compromises do not reflect the interests of the African American electorate through “sincere” and “straightforward” voting. This is the dilemma of the African American electorate, that it must either: 1) work within a dominant two-party system that is designed to disappoint, and thus potentially lead to African American’s alienation and withdrawal; or 2) not work within that system and guarantee their alienation as a consequence of that withdrawal.⁵ Thus by participating in the two-party system, in which roughly ninety-percent of African American voters have historically supported the Democratic Party, African Americans are seeking to *protect* their interests, but at the price of a decreased ability to *advance* their interests. As a consequence, the dominant two-party system has been crippling for African Americans.

Thus my project takes an historical approach to ask whether and how African American political power can be asserted and interests advanced without a party machine that operates within the confines of America’s dominant two-party system. I have already presented a preliminary draft of this project at the most recent meeting of the American Political Science Association in Toronto, Canada this past September 2009. The paper was entitled, “A Historical Analysis of African Americans and the Executive Office, 1872-2008” and generated interest from scholars of voting and elections, as well as scholars of American political development.

Contribution

African American allegiance to the two party system is rational in that it has provided them with a certain level of ideological stability, structural stability in terms of choices (even if

⁴ James Weldon Johnson (1924) “...How can the Negro expect any worthwhile consideration for his vote as long as politicians are always reasonably sure as to how it will be cast?”

⁵ Hamilton, 1973.

that choice is between the lesser of two evils), as well as a percentage of black political leaders and leadership.⁶ However, that same allegiance is irrational to the extent that the gained ideological stability fails to accurately reflect and advance African American interests; the structural stability it provides constitutes picking the lesser of two evils rather than a truly preferred platform; and the percentage of African American political leaders and leadership has not risen to the level of being truly representative, particularly at the national level. This tension highlights both the inherent limitations of America's dominant two-party system for African American candidates, as well as both the importance and limitations of the effects African American third-party candidates have had — and can have — on that system.

By employing mixed methods of archival, quantitative, and qualitative research, my project will thus present scholars of electoral politics, American political development, and African American Studies with an incisive examination of that tension, along with implications for its resolution that will resonate with the next generation of African American candidates and voters. To ascertain the effect of third party candidates, I will conduct a detailed analysis of African American candidates as well as the voting patterns of African Americans over the past fifty years. A national qualitative survey of past and present African American elected officials and candidates, as well as interviews with those who reside in the NYC metro region, will also be conducted to create detailed political narratives of the effects of African American third party candidates on local and state level politics. This combination of qualitative and quantitative data will help support claims pertaining to increased participation of African Americans in the US electoral process due to the long lasting effects African American candidates have had as a result of running for this nation's highest office.

⁶ Walters, 1984.


Cost

With the generous support of the First Year at Fordham Faculty Research Grant, I will be able to employ two undergraduate research assistants to conduct substantive archival research at the Schomburg Center for Research in Harlem, NY. I will also use these research assistants to edit and disseminate a national survey, the necessary supplies and equipment for which constitutes the balance of my costs. Some of this equipment, particularly the laptop, will also be necessary for me to conduct research on site at the Schomburg Center as well as interviews with subjects throughout the New York metro region.

Conclusion

To fully understand the historical significance of President Obama's election, it is necessary to shift our focus away from the absence of an African American president over the past one and half centuries in order to examine the more important issue, from which this absence distracts us: the origin, legacy and lessons of the thirty African American presidential candidates since Frederick Douglass's name first appeared on a presidential ballot. Having already generated interest from a variety of scholars at the American Political Science Association, *Symbolic Candidacies and the Significance of Third Parties* thus promises to be a valuable contribution to my career, my discipline, and the continued development of American Democracy at this historic moment.