

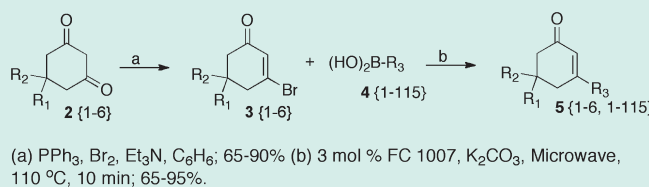
Design, Synthesis, and Diversification of 3,5-Substituted Enone Library

Juhienah Khalaf,[†] Maria E. Estrella-Jimenez,[†] Matthew J. Shashack,[†] Sharangdhar S. Phatak,^{‡,§} Shuxing Zhang,[‡] and Scott R. Gilbertson^{*,†}[†]Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States[‡]Integrated Molecular Discovery Laboratory, Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston Texas 77030, United States[§]School of Biomedical Informatics, The University of Texas Health Science Center, 7000 Fannin Street, Houston, Texas 77030, United States

Supporting Information

ABSTRACT: This paper describes the synthesis of a 300 member library of 3,5-substituted enones. The synthesis starts with 6 different bromoenones that are accessed from the corresponding 1,3-diones. These bromides are then diversified by Suzuki coupling with a variety of aromatic and vinyl boronic acids. Additionally a small series of triazoles was synthesized by a Sonogashira coupling reaction dipolar cycloaddition sequence. The library was analyzed by principal component analysis to examine its diversity.

KEYWORDS: enone, Suzuki, library

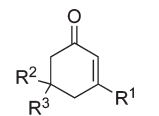


The ever-increasing demand for novel medicinally active compounds has resulted in a continuous search for simple and efficient methods for the generation of libraries to be examined in biological systems. With that in mind, and as a continuation of an effort to develop small molecule inhibitors of anthrax edema factor,¹ a library of cyclohexenones has been developed. In an earlier paper it was reported that mono substituted cyclohexenones possess activity against the adenyl cyclase inhibitor, anthrax edema factor.¹ In an attempt to improve the activity, a new series of cyclohexenones (**1**) has been developed possessing substituents at the 3 and 5 positions (Figure 1).

For generation of ensembles of the desired molecules, the Suzuki reaction was an ideal choice in generating libraries with the basic structure **1**.^{2,3} Diversity at position R¹ was obtained by reaction of bromoenones (Scheme 1) with commercially available boronic acids (diversity reagent **4**).

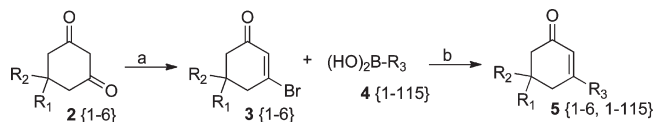
Six different bromoenones (Figure 2, diversity reagent **3**) were used. These consisted of five with aromatic substituents at position 5 and one with dimethyl substitution at that location. The necessary bromoenones were prepared in good to excellent yield from 1,3-diones in a single step through bromination with triphenylphosphine and bromine (Scheme 1).⁴ These types of bromides are excellent substrates for the Suzuki coupling to a variety of boronic acids in generally good to excellent yields.^{1,2}

The boronic acids are predominantly aryl with only four vinyl boronic acids being used in the library (Figure 3). However, the variety of aromatic boronic acids is extensive; oxygen, nitrogen, and sulfur heterocycles were used. Substituents on the benzene rings were varied from ethers, bromides, chlorides, iodides as



R¹ = aryl, vinyl, alkynyl or triazole
R² = aryl or alkyl
R³ = alkyl or H

Figure 1

Scheme 1^a

well as acids, esters, amides, aldehydes, nitriles, trifluoromethyl groups, and alkyl groups. Polycyclic aromatic rings such as naphthalene, phenanthrene, indole, thiophene, benzofuran, and quinoline were also included. While all possible combinations of elements **3** and **4** are not represented, three hundred unique

Received: April 13, 2011

Revised: June 3, 2011

Published: June 07, 2011

compounds were prepared. The examples that were synthesized are represented in Table 1.

The library was subjected to principal component analysis (PCA) to characterize its diversity.⁵ Members of the library were

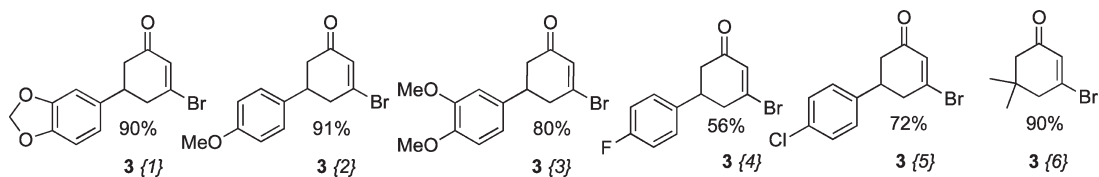


Figure 2. Diversity Reagent 3 {1–6}.

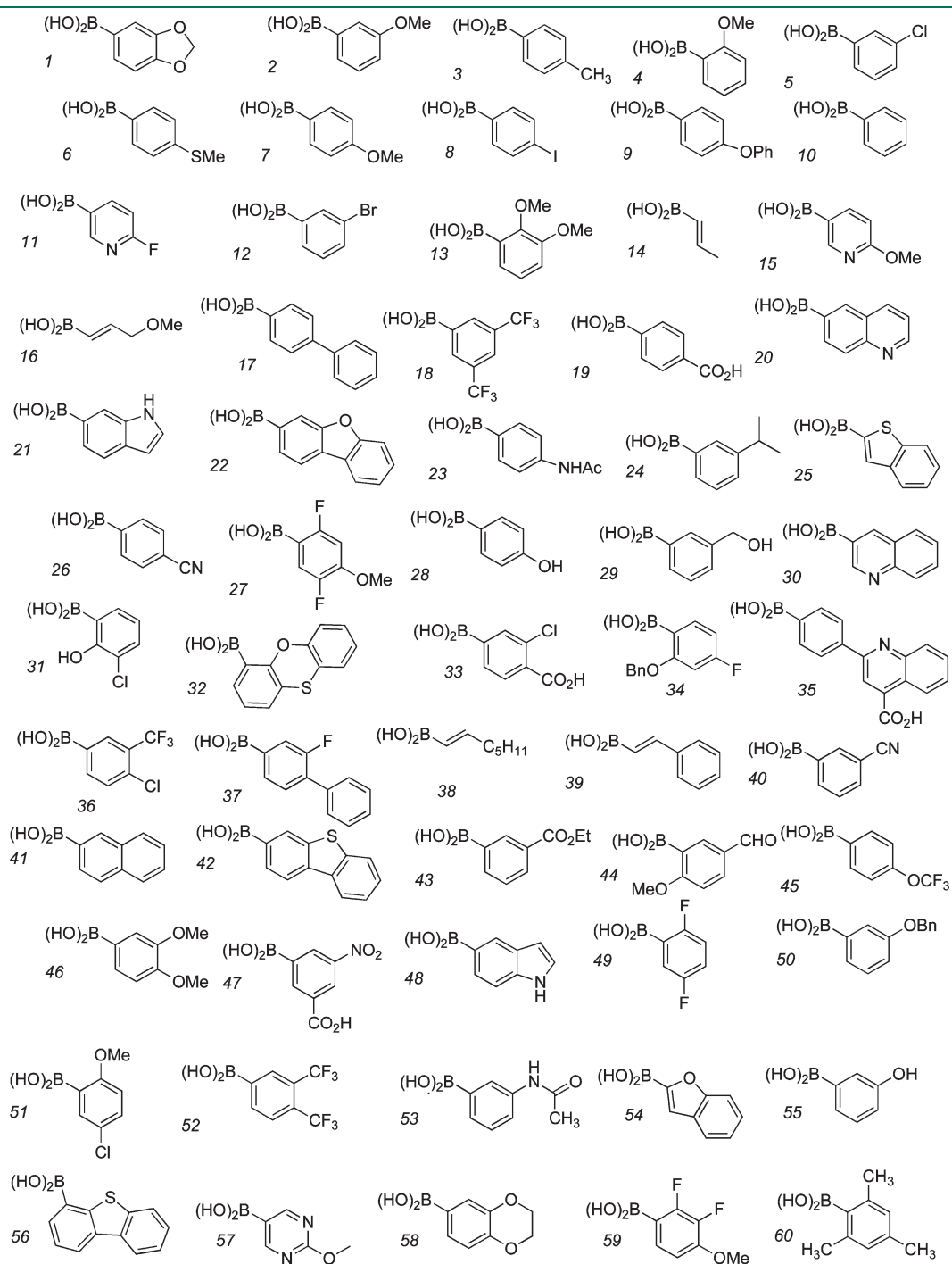


Figure 3. Continued

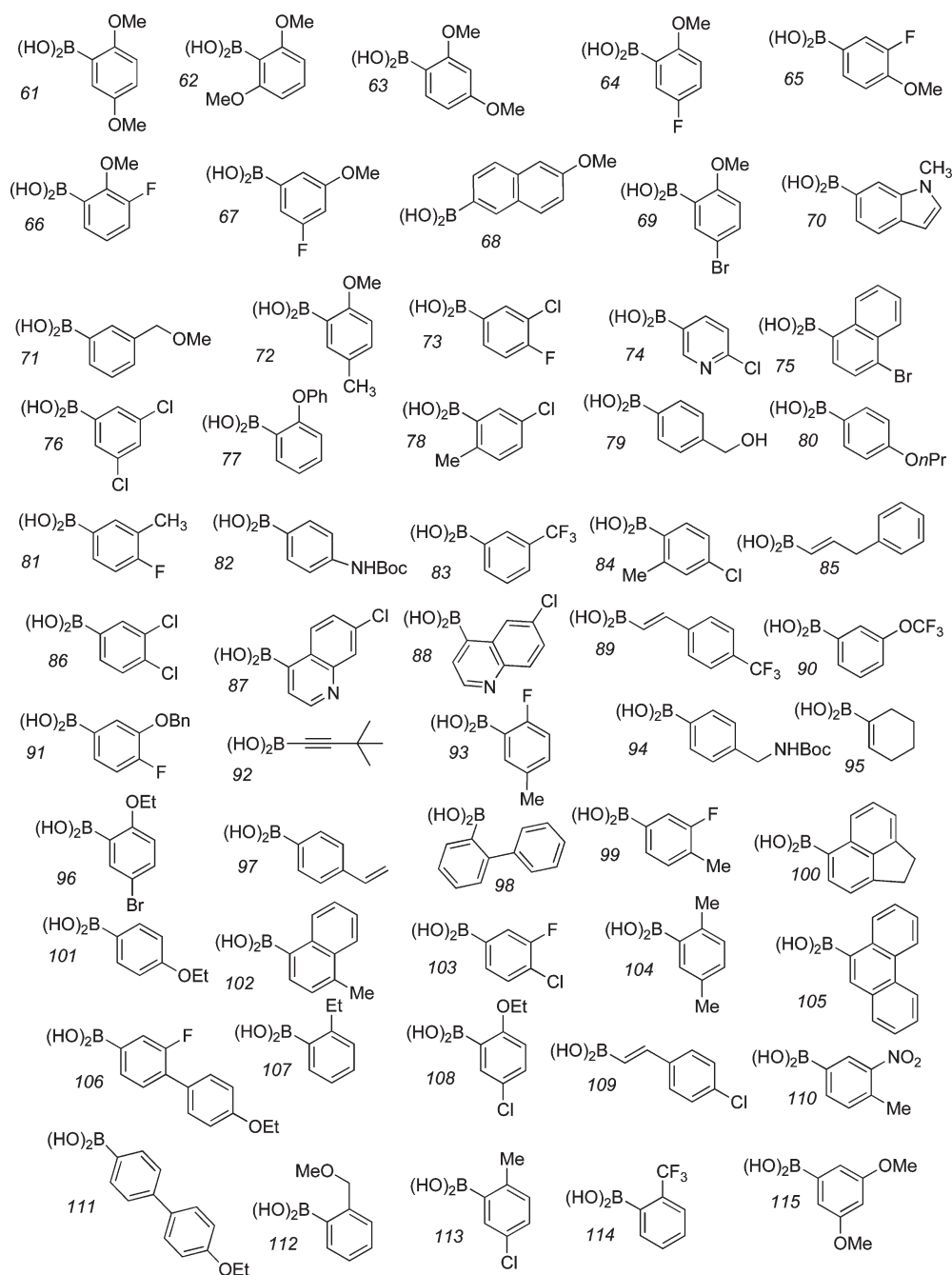
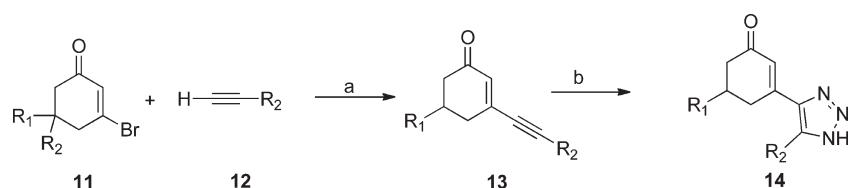


Figure 3. Diversity Reagent 4 {1–60} and {61–115}.

Scheme 2^a



^a (a) Pd(PPh₃)₂Cl₂, CuI, Et₃N, DMF, 110 °C, μ W; (65–86%) (b) NaN₃, DMF, 100 °C; (45–65%).

characterized with 185 2D descriptors derived from Molecular Operating Environment (MOE version 2010.10).⁶ PCA was

performed on the matrix to reduce the dimensionality of chemical space. The three-dimensional plot of the top three

Table 1. Library Members^a

| | | | | | | | | | | | |
|----------|----------|-----------|----------|-----------|-----------|----------|----------|----------|-----------|----------|----------|
| 5 {1,1} | 5 {1,27} | 5 {1,81} | 5 {2,39} | 5 {2,73} | 5 {2,104} | 5 {3,18} | 5 {4,9} | 5 {4,47} | 5 {4,93} | 5 {5,25} | 5 {6,10} |
| 5 {1,2} | 5 {1,28} | 5 {1,87} | 5 {2,40} | 5 {2,74} | 5 {2,105} | 5 {3,19} | 5 {4,11} | 5 {4,48} | 5 {4,94} | 5 {5,26} | 5 {6,11} |
| 5 {1,3} | 5 {1,29} | 5 {1,111} | 5 {2,41} | 5 {2,75} | 5 {2,107} | 5 {3,20} | 5 {4,12} | 5 {4,49} | 5 {4,111} | 5 {5,27} | 5 {6,13} |
| 5 {1,4} | 5 {1,30} | 5 {1,114} | 5 {2,42} | 5 {2,76} | 5 {2,108} | 5 {3,21} | 5 {4,13} | 5 {4,51} | 5 {4,112} | 5 {5,28} | 5 {6,14} |
| 5 {1,5} | 5 {1,31} | 5 {2,1} | 5 {2,43} | 5 {2,77} | 5 {2,109} | 5 {3,22} | 5 {4,14} | 5 {4,55} | 5 {4,113} | 5 {5,29} | 5 {6,17} |
| 5 {1,6} | 5 {1,32} | 5 {2,2} | 5 {2,44} | 5 {2,78} | 5 {2,110} | 5 {3,23} | 5 {4,17} | 5 {4,58} | 5 {5,1} | 5 {5,31} | 5 {6,19} |
| 5 {1,7} | 5 {1,33} | 5 {2,3} | 5 {2,45} | 5 {2,79} | 5 {2,112} | 5 {3,25} | 5 {4,19} | 5 {4,59} | 5 {5,2} | 5 {5,32} | 5 {6,20} |
| 5 {1,8} | 5 {1,34} | 5 {2,5} | 5 {2,46} | 5 {2,80} | 5 {2,113} | 5 {3,27} | 5 {4,20} | 5 {4,61} | 5 {5,3} | 5 {5,34} | 5 {6,23} |
| 5 {1,9} | 5 {1,36} | 5 {2,6} | 5 {2,48} | 5 {2,81} | 5 {2,114} | 5 {3,28} | 5 {4,22} | 5 {4,62} | 5 {5,4} | 5 {5,36} | 5 {6,27} |
| 5 {1,10} | 5 {1,37} | 5 {2,7} | 5 {2,50} | 5 {2,83} | 5 {3,1} | 5 {3,29} | 5 {4,23} | 5 {4,63} | 5 {5,5} | 5 {5,37} | 5 {6,29} |
| 5 {1,11} | 5 {1,38} | 5 {2,8} | 5 {2,51} | 5 {2,84} | 5 {3,2} | 5 {3,31} | 5 {4,24} | 5 {4,65} | 5 {5,6} | 5 {5,38} | 5 {6,31} |
| 5 {1,12} | 5 {1,39} | 5 {2,10} | 5 {2,58} | 5 {2,85} | 5 {3,3} | 5 {3,32} | 5 {4,25} | 5 {4,66} | 5 {5,7} | 5 {5,39} | 5 {6,32} |
| 5 {1,13} | 5 {1,48} | 5 {2,12} | 5 {2,59} | 5 {2,86} | 5 {3,4} | 5 {3,36} | 5 {4,26} | 5 {4,67} | 5 {5,8} | 5 {5,41} | 5 {6,34} |
| 5 {1,14} | 5 {1,50} | 5 {2,14} | 5 {2,60} | 5 {2,87} | 5 {3,5} | 5 {3,37} | 5 {4,27} | 5 {4,69} | 5 {5,9} | 5 {5,42} | 5 {6,36} |
| 5 {1,15} | 5 {1,60} | 5 {2,15} | 5 {2,61} | 5 {2,89} | 5 {3,6} | 5 {3,38} | 5 {4,29} | 5 {4,70} | 5 {5,10} | 5 {5,43} | 5 {6,37} |
| 5 {1,16} | 5 {1,61} | 5 {2,18} | 5 {2,62} | 5 {2,90} | 5 {3,7} | 5 {3,42} | 5 {4,34} | 5 {4,71} | 5 {5,12} | 5 {5,44} | 5 {6,38} |
| 5 {1,17} | 5 {1,62} | 5 {2,20} | 5 {2,63} | 5 {2,92} | 5 {3,8} | 5 {3,45} | 5 {4,36} | 5 {4,72} | 5 {5,14} | 5 {5,45} | 5 {6,39} |
| 5 {1,18} | 5 {1,64} | 5 {2,24} | 5 {2,64} | 5 {2,94} | 5 {3,9} | 5 {3,49} | 5 {4,37} | 5 {4,73} | 5 {5,15} | 5 {5,46} | 5 {6,41} |
| 5 {1,19} | 5 {1,66} | 5 {2,25} | 5 {2,65} | 5 {2,95} | 5 {3,10} | 5 {3,52} | 5 {4,38} | 5 {4,75} | 5 {5,17} | 5 {5,49} | 5 {6,43} |
| 5 {1,20} | 5 {1,69} | 5 {2,29} | 5 {2,66} | 5 {2,96} | 5 {3,11} | 5 {4,1} | 5 {4,39} | 5 {4,76} | 5 {5,18} | 5 {6,2} | 5 {6,45} |
| 5 {1,22} | 5 {1,74} | 5 {2,32} | 5 {2,67} | 5 {2,97} | 5 {3,12} | 5 {4,2} | 5 {4,41} | 5 {4,77} | 5 {5,19} | 5 {6,3} | 5 {6,46} |
| 5 {1,23} | 5 {1,75} | 5 {2,34} | 5 {2,69} | 5 {2,98} | 5 {3,13} | 5 {4,3} | 5 {4,42} | 5 {4,78} | 5 {5,20} | 5 {6,4} | 5 {6,49} |
| 5 {1,24} | 5 {1,76} | 5 {2,36} | 5 {2,70} | 5 {2,100} | 5 {3,14} | 5 {4,4} | 5 {4,43} | 5 {4,79} | 5 {5,21} | 5 {6,7} | 5 {6,55} |
| 5 {1,25} | 5 {1,77} | 5 {2,37} | 5 {2,71} | 5 {2,101} | 5 {3,15} | 5 {4,5} | 5 {4,45} | 5 {4,81} | 5 {5,22} | 5 {6,8} | 5 {6,56} |
| 5 {1,26} | 5 {1,79} | 5 {2,38} | 5 {2,72} | 5 {2,102} | 5 {3,17} | 5 {4,6} | 5 {4,46} | 5 {4,84} | 5 {5,23} | 5 {6,9} | 5 {6,57} |

^a All compounds in Table 1 were produced in greater than 20 mg quantities. The Suzuki used to produce these libraries proceeded in yields from 95% to 35% with 78% being the average yield.

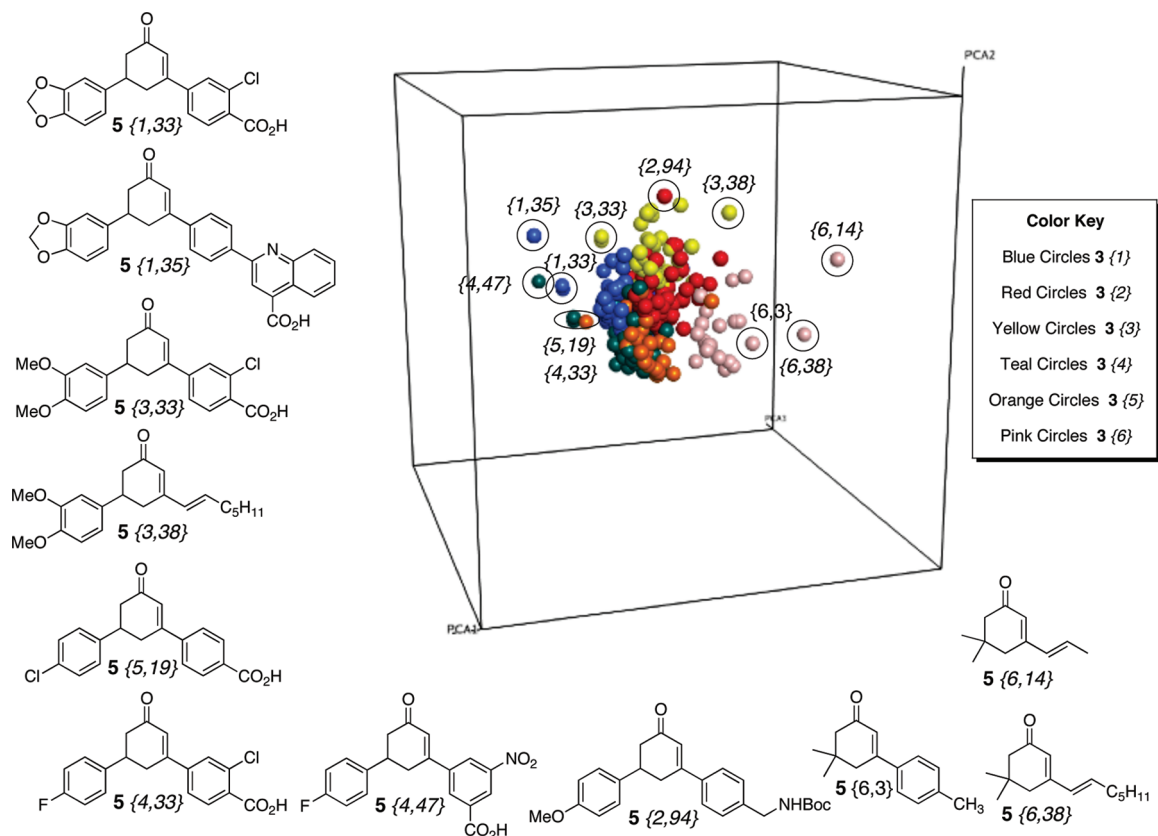
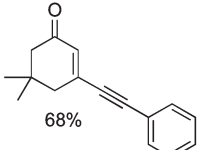
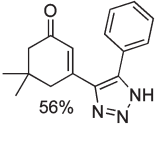
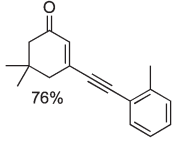
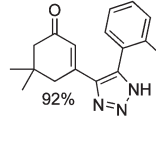
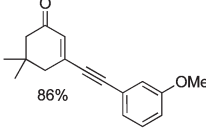
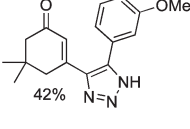
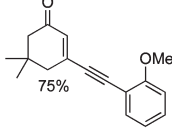
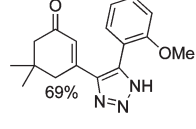
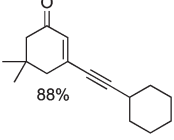
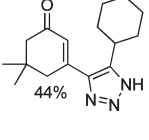
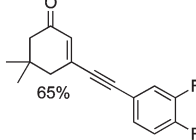
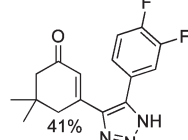
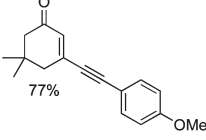
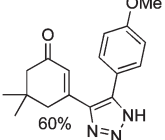
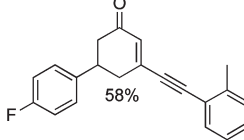
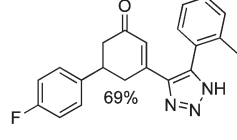
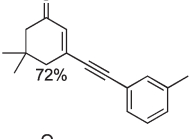
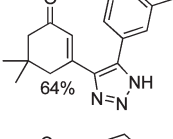
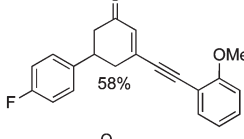
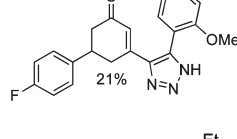
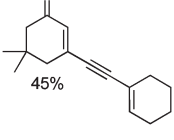
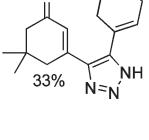
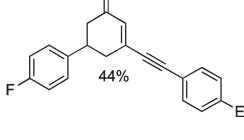
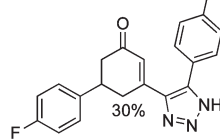
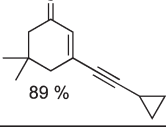
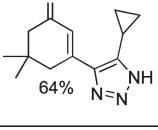
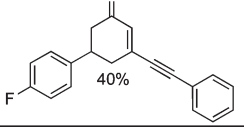
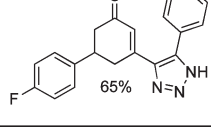


Figure 4. Principal Component Analysis.

Table 2. Alkynes and Triazoles

| Alkyne Yield | Triazole Yield | Alkyne Yield | Triazole Yield |
|--|--|---|--|
|  68% |  56% |  76% |  92% |
|  86% |  42% |  75% |  69% |
|  88% |  44% |  65% |  41% |
|  77% |  60% |  58% |  69% |
|  72% |  64% |  58% |  21% |
|  45% |  33% |  44% |  30% |
|  89% |  64% |  40% |  65% |

principal components illustrates that within each set of compounds there are members of the library that differ considerably from the aggregate. The labeled circles (Figure 4) represent examples that fall the farthest from the center of the plot. The LogP for the library ranged between 1.16 to 6.58 with a mean value of 4.20. The library's molecular weight averaged 335 ranging from 164 to 462 while the polar surface area ranged from 17 to 103 with a mean value of 35.3. Histograms of this data are presented in the Supporting Information.

In an extension of this chemistry, a smaller series of triazoles was synthesized by a Sonogashira coupling to provide an alkyne that was then reacted with sodium azide. The coupling reaction (Scheme 2) was catalyzed by $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI and conducted under microwave conditions (250W at 110 °C for 10 min) in DMF.⁷ In all cases the samples were purified by column chromatography to remove remaining palladium catalyst and copper iodide. The corresponding alkynes were reacted with sodium azide in DMF and heated at 100 °C for 1 h.^{8,9} The reaction was concentrated and

purified by column chromatography to give 1,2,3-triazoles analogues (Table 2). In this case the library size was limited by the use of only two bromoenones and the availability of different alkynes for the first coupling step with 14 alkynes synthesized and corresponding 14 triazoles obtained.

A 300-member library was synthesized by combining six different bromoenones with boronic acids via the Suzuki coupling. The library consisted of enones where the diversity at position 3 was installed by Suzuki reaction and the diversity at position 5 originated from the six different bromoenones used as starting material. Principal component analysis (PCA) indicates that while the molecules are clustered, specific members are significantly different from the group. Additionally fourteen triazoles were synthesized through a Sonogashira coupling followed by dipolar cycloaddition of azide. All these compounds have been submitted to the NIH Molecular Library Small Molecule Repository (MLSMR) to be distributed to the NIH screening centers.

■ ASSOCIATED CONTENT

S Supporting Information. General procedures for library synthesis and ^1H NMR data for the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: srgilbe2@central.uh.edu.

Funding Sources

This work was supported by NIGMS GM079558 and GM089173, the Robert A. Welch Foundation, and the M. D. Anderson Foundation. S.S.P. was also supported by UTHealth Innovation for Cancer Prevention Research Predoctoral Fellowship, The University of Texas School of Public Health—Cancer Prevention and Research Institute of Texas Grant RP101503.

■ ACKNOWLEDGMENT

We would like to thank University of Kansas Chemical Methodologies and Library Development Center of Excellence, in particular Frank Schoenen and Benjamin Neuenswander, for providing analytical and purification support, and David Hill for chemoinformatics support.

■ REFERENCES

(1) Jimenez, M. E.; Bush, K.; Pawlik, J.; Sower, L.; Peterson, J. W.; Gilbertson, S. R. Synthesis and screening of small molecule inhibitors of anthrax edema factor. *Bioorg. Med. Chem. Lett.* **2008**, *18* (14), 4215–4218.

(2) Wang, Y.; Sauer, D. R. Use of Polymer-Supported Pd Reagents for Rapid and Efficient Suzuki Reactions Using Microwave Heating. *Org. Lett.* **2004**, *6* (16), 2793–2796.

(3) Suzuki, T.; Sato, O.; Hirama, M. Palladium Catalyzed Stereospecific Cyclization of Hydroxy Epoxides - Stereocontrolled Synthesis of Cis-2-Alkenyl and Trans-2-Alkenyl-3-Hydroxytetrahydropyrans. *Tetrahedron Lett.* **1990**, *31* (33), 4747–4750.

(4) Piers, E.; Nagakura, I. Reaction of beta-Diketones with Triphenylphosphine Dihalides: A New, Efficient Synthesis of Cyclic β -Chloro-, β -Bromo- and β -Iodo- α , β -Unsaturated Ketones. *Synth. Commun.* **1975**, *5* (3), 193–199.

(5) Tan, D. S. Diversity-oriented synthesis: exploring the intersections between chemistry and biology. *Nat. Chem. Biol.* **2005**, *1* (2), 74–84.

(6) Chemical Computing Group, M., Quebec, Canada.

(7) Petricci, E.; Radi, M.; Corelli, F.; Botta, M. Microwave-enhanced Sonogashira coupling reaction of substituted pyrimidinones and pyrimidine nucleosides. *Tetrahedron Lett.* **2005**, *44*, 9181–9184.

(8) Huisgen, R. 1,3-Dipolar Cycloadditions Past and Future. *Angew. Chem., Int. Ed. Engl.* **1963**, *2* (10), 563–598.

(9) Huisgen, R. Kinetics and Mechanism of 1,3-Dipolar Cycloadditions. *Angew. Chem., Int. Ed. Engl.* **1963**, *2* (11), 633–645.