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Letter

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Synthesis of a 2(1*H*)-Pyridone Library via Rhodium-Catalyzed Formation of Isomunchones

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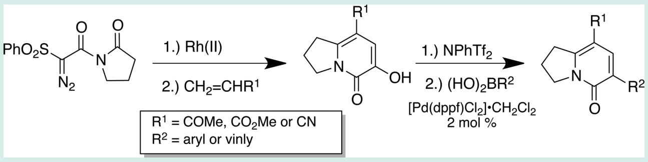
Supporting Information

ABSTRACT: Through the use of the dipolar cycloaddition of isomunchones with olefins the 2(1*H*)-pyridone ring system has been synthesized.[1] The use of different cyclization partners followed by diversification of the initial scaffold has provded libraries of 4-hydroxy-2(1*H*)-pyridones. There are no examples of this ring system in either PubChem or the MLSMR



KEYWORDS: *pyridone, rhodium, carbene, isomunchone*

The 2(1*H*)-pyridone structure is found in a large number of natural products such as camptothecin (**1**),[2] as well as synthetic elastase and thrombin inhibitors. Both antibacterial and antifungal activities have been ascribed to molecules with this functionality. The 4-hydroxy-2(1*H*)-pyridones such as pyridoxatin (**2**)[3] and huperzine A[4] have been investigated as potential therapeutics and pyridone acids (**3**) obtained from fermentation have been found to be angiotensin-converting-enzyme (ACE) inhibitors by Eli Lilly.[5] Tricyclic pyridones have been identified as subtype-selective GABAA receptor agonists, and therefore have potential as nonsedating anxiolytics.[6] Despite its documented activity, this ring system is nearly completely unrepresented in PubChem and the Molecular Library Small Molecule Repository (MLSMR) of the NIH, with only twelve compounds being identified as 90% similar to **4**.

While there are numerous methods for the preparation of substituted 2-pyridones the chemistry developed by Padwa was selected for access to the desired molecules.[1] This approach provides highly functionalized 4-hydroxy-2(1*H*)-pyridones (**9**) from readily available starting materials. The method involves the rhodium-catalyzed formation of an isomunchone (**6**) that then undergoes a dipolar cycloaddition with an olefin to form intermediate **8** which then decomposes to form 2(1*H*)-pyridone **9**. A strength of this approach is that a variety of alkenes can be used in the cycloaddition to the isomunchones, allowing for the introduction of different groups in the 5 position. While both electron-rich and electron-deficient alkenes have been reported to proceed in high yield and with good selectivity, the most useful examples are with electron deficient versions (Scheme 1). Another important feature is the availability of the starting diazoimides. By appropriate selection of the diazo precursor (**5**) and dipolarophile (**7**), various groups can be introduced into the C6−C8 positions from the diazo compound and C-4 and C-5 positions from the dipolarophile (olefin). Moreover, substituents can be introduced at C-3 by conversion of the hydroxyl functionality to a triflate group, followed by a palladium-catalyzed cross-coupling and amination reactions.[1,6c7]

The reported library was synthesized from one diazoimide (**5**) and three different electron defficient olefins (**7**{*1*−*3*}). The rhodium catalyzed reactions followed by triflate formation proceeded in 40%, 55%, and 45%, respectively. Following the formation of the 4-hydroxy-2(1*H*)-pyridones, the compounds (**9** {*1*−*3*}) with the free hydroxyl, were found to be somewhat labile so they were immediately converted to their respective triflates (**10**{*1*−*3*}). Additional diversity was then introduced by Suzuki reaction on the triflate formed from the initially formed 4-hydroxy-2(1*H*)-pyridones (Table 1). All compounds in Table 1 were produced in greater than 20 mg quantity. The Suzuki reaction used to produce these libraries proceeded in yields from 95% to 35% with 78% being the average yield.

To visualize the diversity of the library, it was subjected to principal component analysis (PCA).[8] The chemical compounds were characterized with 186 2D descriptors derived from Molecular Operating Environment (MOE version 2010.10).[9] PCA was performed on the descriptor matrix to reduce the dimensionality of chemical space as described previously.[10] The three-dimensional plots of the top three principal components illustrate that within each set of compounds there are members of the library that differ considerably from the aggregate. The labeled circles represent the examples that fall the farthest from the cluster center of each chemical series (Figure 2). The LogP for the library ranged from 0.33 to 4.82 with a mean value of 2.64. The molecular weight of the compounds on average is about 313.10 varying from 242.30 to 424.46, while the total

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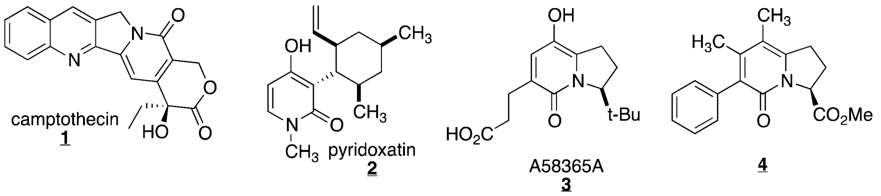
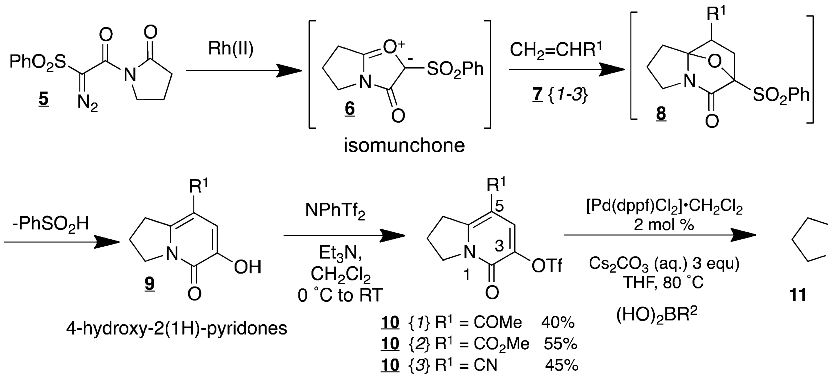


Figure 1.

Scheme 1



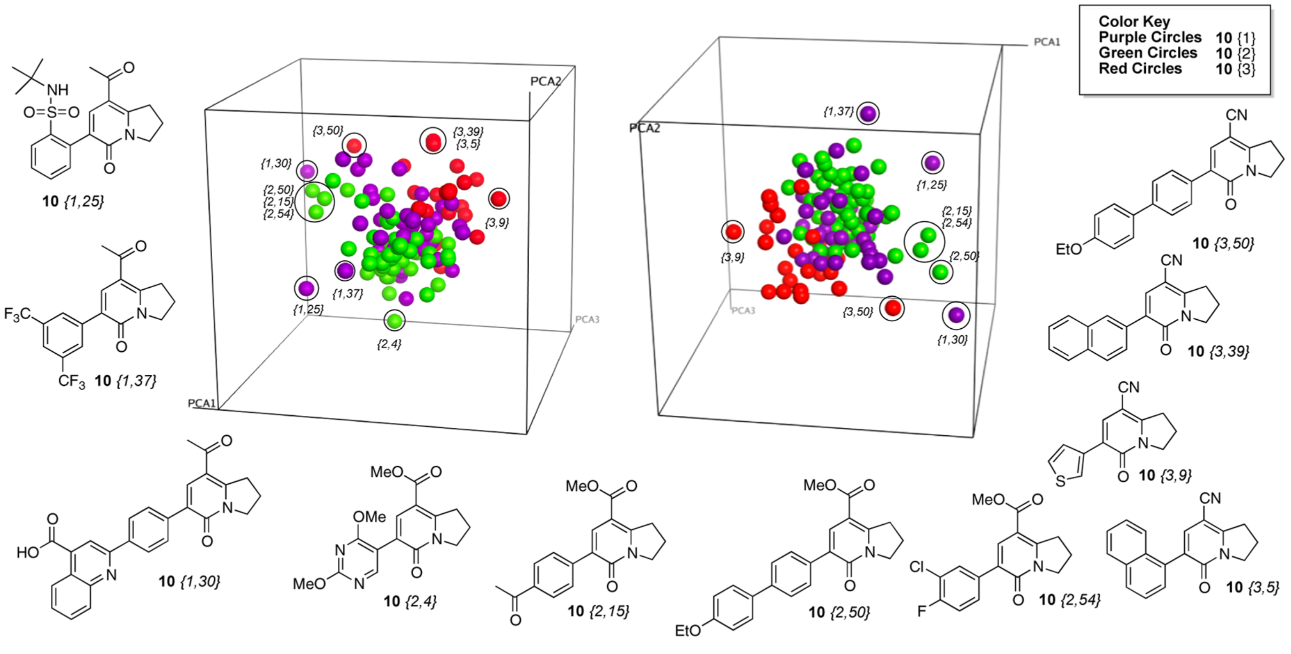


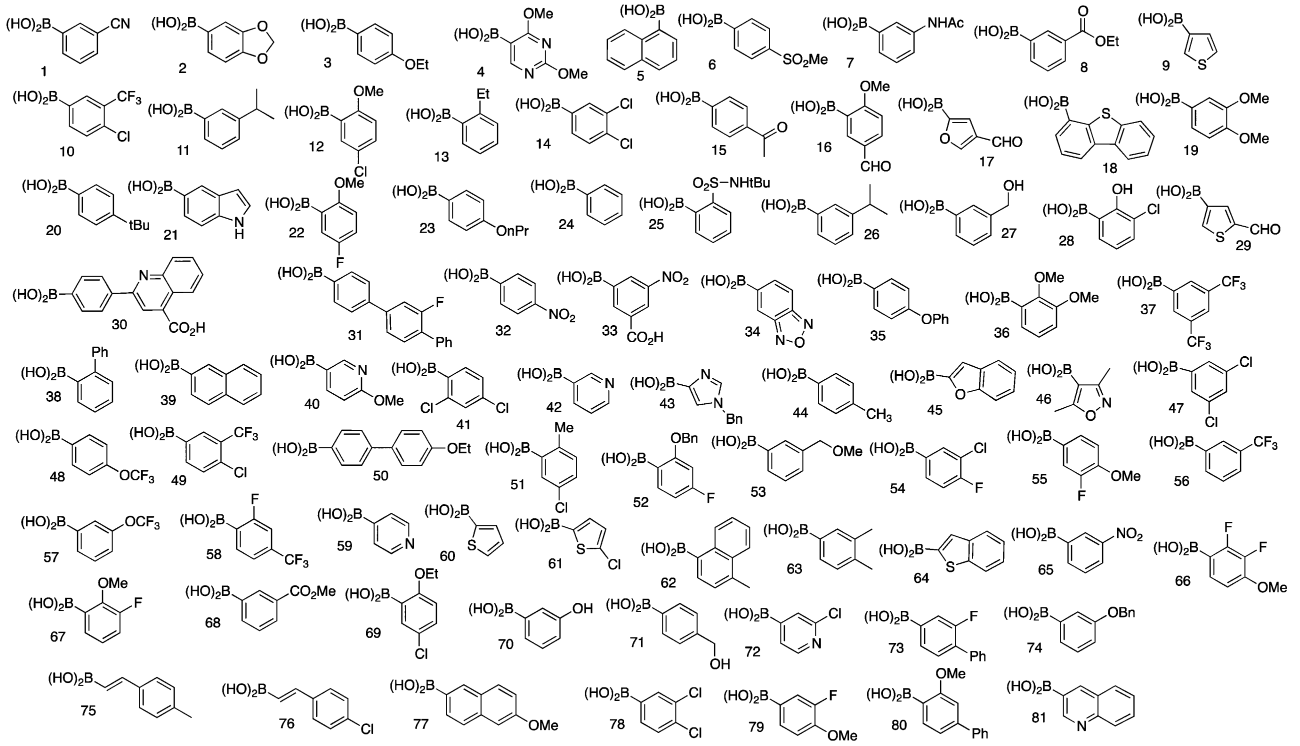
Figure 2. Principal component analysis.

polar surface area (TPSA) ranged from 37.38 Å^2 to 120.50 Å^2 with a mean value of 56.08 Å^2. Detailed methods and histograms are presented in the Supporting Information.

Thus far, 68 members of this library have gone out to the NIH screening centers. Of those, 5 have been designated as a hit in a luminescence cell-based primary high throughput screening assay to identify activators of the DAF-12 from the parasite H. contortus (hcDAF-12). This screen was carried out at The Scripps Research Institute Molecular Screening Center on a screen submitted by David Mangelsdorf from University of Texas Southwestern Medical Center.

In conclusion, a 128-member library was synthesized by combining three different olefins in isomunchone dipolar cycloadditions followed by Suzuki reaction of the resulting triflate with 81 78 boronic acids. PCA indicates that while the molecules are clustered, specific members are significantly different from the group. The molecules have been submitted to the NIH MLSMR to be distributed to the

Table 1. Library Members[a]



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[a] All members of the library were analyzed by ^{1}H and ^{13}C NMR and mass spectrometry. All compounds were found to be 95% purity of greater.

NIH screening centers. With 68 of them having been subjected to 9 assays thus far.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures for library synthesis and ^{1}H NMR data for the compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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