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# Substituent Effects on the Basicity of Patriscabrin A and Lettucenin A: Evolution Favors the Aromatic?

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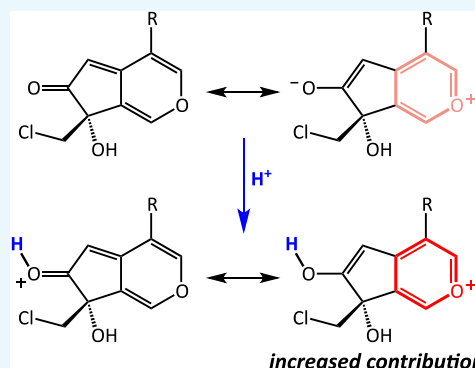


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**ABSTRACT:** Basicities for derivatives of patriscabrin A and lettucenin A were calculated with density functional theory. A significant correlation is observed between the basicity and Hammett  $\sigma$  parameters. Protonation increases the aromatic character of the cyclic moieties of each natural product. The naturally occurring structures are predicted to be the most aromatic.



## INTRODUCTION

Natural products have proven themselves extremely useful within the fields of drug discovery and pharmacotherapy toward the treatment of major diseases and disorders, such as cancer.<sup>1–4</sup> This is in no small part due to the fact that natural products possess both high structural diversity and a broad range of biological activities and functions as a result of natural selection.<sup>5</sup> A detailed understanding of differences in structural and energetic properties of the neutral versus protonated and deprotonated forms of natural products can be key to understanding their properties, as participants in proton-transfer reactions<sup>6,7</sup> but also as partners in noncovalent interactions. Here, we explore how the basicity of several natural products is tied to changes in aromaticity.<sup>8,9</sup>

Exploration of the fundamental thermochemistry of (*de*)-protonated species informs our understanding of chemical transformations and, in some cases, drives the design of new reactions, substrates, and reagents.<sup>10–12</sup> The intrinsic acidity and basicity of natural products provide clues to both their binding properties and reactivity, and the observation of these acids and bases often aids in structure elucidation via mass spectrometry.<sup>13</sup> A key quantity is the gas-phase basicity.<sup>14</sup> Probing basicity in the gas phase, an environment free from any solvent interactions, provides a measure of the fundamental basicity,<sup>15</sup> a standard against which the effects of solvent, membranes, protein binding pockets, etc. can be evaluated.

Gas-phase basicities are typically measured by means of high-pressure mass spectrometry (MS),<sup>16,17</sup> ion-cyclotron resonance (ICR)<sup>18</sup> techniques, and flowing-afterglow experiments,<sup>19</sup> but connecting these results to subtle structural

features is not always straightforward.<sup>20,21</sup> Fortunately, there exists a myriad of theoretical approaches that can be employed to provide insights into the structures of these neutral and ionized species.<sup>22–27</sup> For example, Hehre and co-workers previously studied substituent effects on the basicity of benzene and benzene derivatives,<sup>23,24</sup> mainly by way of isodesmic proton-transfer reactions.<sup>28–30</sup> In this work, it was found that the relative extent of protonation depends on the temperature and solvent (which also plays an instrumental role in determining the site of protonation). In another example, a complete set of theoretical basicity values was obtained at the MP2/6-31+G(d,p) and B3LYP/6-31+G(d,p) levels of theory for the entire series of  $\alpha$ -amino acids.<sup>15,31,32</sup>

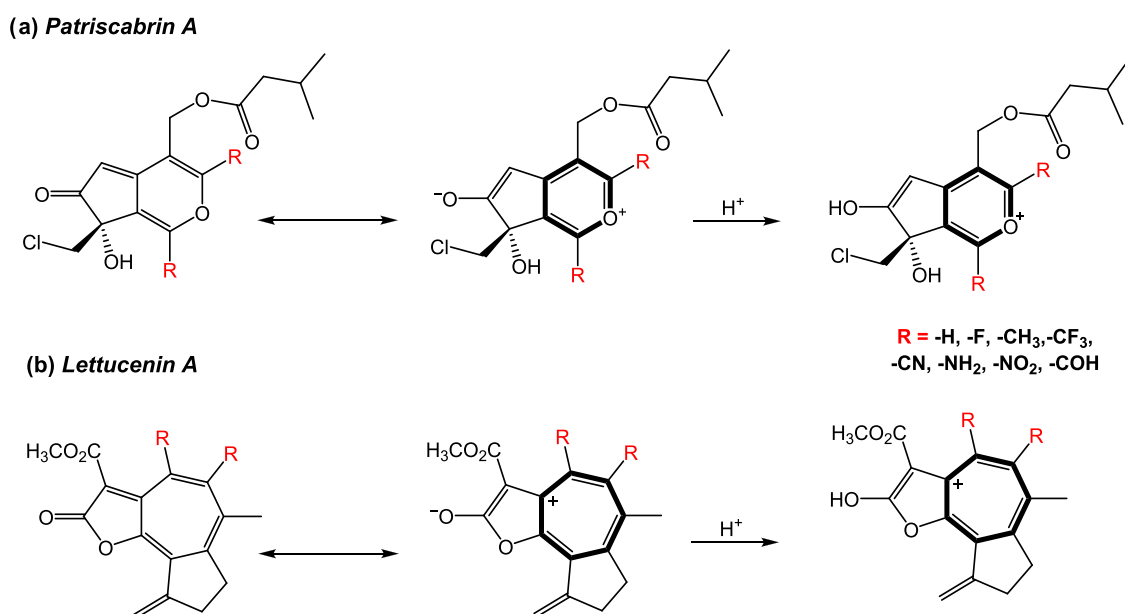
Herein, we assess the effects of substituents on the basicity of two natural products, patriscabrin A and lettucenin A,<sup>33,34</sup> that we anticipate have a significant zwitterionic character as a result of containing potentially aromatic substructures (*cf.* Figure 1). Nature arrived at these particular secondary metabolites as a result of evolution. In this work, we probe how the properties of these molecules would be different if different substituents had been included. While we do not endeavor to elucidate the evolutionary pathways to the natural products in question, we do intend to shine a light on the

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**Figure 1.** Schematic representation of the protonation of substituted (a) patriscabrin A and (b) lettucenin A under investigation in the present work, where R = -H, -F, -Me, -CF<sub>3</sub>, -CN, -NH<sub>2</sub>, -NO<sub>2</sub>, and -COH. The aromatic moieties are shown in bold.

unique features of these evolutionary endpoints, contrasting what is with what might have been.

## ■ COMPUTATIONAL METHODS

The optimized structural coordinates and harmonic vibrational frequency data reported in this work have been obtained using the *Gaussian 09* suite of programs (G09).<sup>35</sup> These quantities were computed using the B3LYP functional,<sup>36,37</sup> as it is known to reproduce the experimental results well (in addition to being in good agreement with those reported at the CCSD(T) and G2 levels<sup>38,39</sup>) for intrinsic acid/base properties.<sup>40,41</sup> Supplementary geometrical, frequency, and energy calculations were also performed with the M06-2X method to investigate the robustness of our chosen method (see the [Supporting Information \(SI\)](#));<sup>42</sup> our overall qualitative conclusions persist with this method.

We calculated basicities ( $B_{NP}$ ) of natural products and analogues (NP) using a proton-transfer reaction between each NP and water (eq 1). We chose this method to avoid problems with reliably modeling the solvation energy of a proton.<sup>43,44</sup> While the absolute  $B_{NP}$  values have no convenient experimental counterparts, they are useful in a relative sense. More negative values correspond to more basic NPs.

$$B_{NP} = E(NPH^+ + H_2O) - E(NP + H_3O^+) \quad (1)$$

In the present work, the site of protonation was chosen to be the oxygen on the carbonyl for both natural products. To accurately obtain the basicities, we chose to use the correlation-consistent triple- $\zeta$  (cc-pVTZ) basis set,<sup>45,46</sup> as previous studies on calculating basicities have used related basis sets.<sup>47,48</sup> This choice of the basis set was also used previously in accurately obtaining the similar values of the naturally occurring amino acids.<sup>15</sup>

Nucleus independent chemical shift (NICS) analyses also were carried out in this work as a tool for assessing aromaticity.<sup>49–51</sup> The  $NICS_{zz}$  values for planar rings were calculated (at and directly above the ring center) using the gauge-independent atomic orbital (GIAO) method<sup>52,53</sup> at the

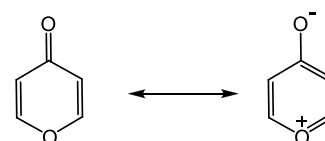
B3LYP/cc-pVTZ level of theory. The values were calculated from the ring center (0.0 Å) through to 8.0 Å above center in 0.2 Å increments.

Solvation effects were studied using an implicit solvation model. For all species examined in solution, geometry optimizations and frequency analyses were carried out using the solvation model based on density (SMD).<sup>54</sup> This model was selected on the basis of its reliable performance in other investigations into similar systems and properties.<sup>54</sup> Chloroform and water (with  $\epsilon = 4.71$  and 78.36, respectively) were considered. Chloroform, in particular, was chosen, as its dielectric constant is similar to that found within the interior of a protein (an admittedly crude model but a useful one nonetheless).<sup>55,56</sup> Additional calculations using the polarizable continuum model (PCM)<sup>57,58</sup> also were performed and can be found in the [Supporting Information](#). All molecular representations were generated using the *Chemdraw*<sup>59</sup> and *Chemcraft*<sup>60</sup> programs.

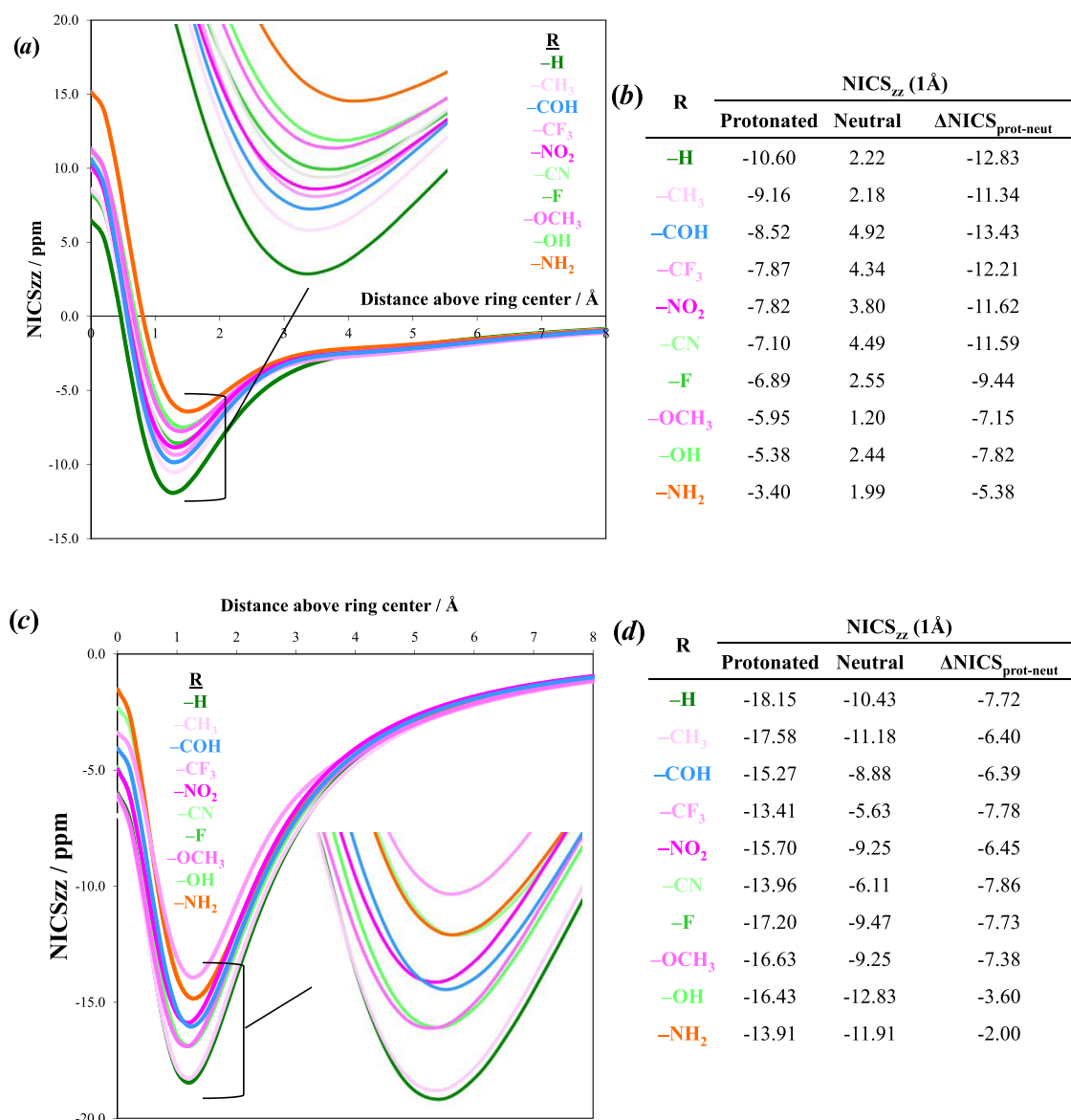
## ■ RESULTS AND DISCUSSION

**Aromaticity.** For patriscabrin A, which was isolated in 2018,<sup>34</sup> one can draw a resonance form that is zwitterionic and contains an aromatic substructure, a pyrylium ion (Figure 1).<sup>61,62</sup> The extended  $\pi$ -system in patriscabrin A also can be viewed as a vinylogous pyrone (Figure 2).<sup>63</sup> For lettucenin A, which was first isolated in 1985,<sup>33</sup> one can draw a resonance form that is zwitterionic and contains an aromatic tropylium ion substructure (Figure 1).<sup>64,65</sup>

To assess the aromatic character of the 6- and 7-membered rings in patriscabrin A and lettucenin A, we computed  $NICS_{zz}$



**Figure 2.** Resonance structures of 4-pyrone.



**Figure 3.** NICS<sub>zz</sub> values obtained using the B3LYP-optimized geometries in water of (a) patriscabrin A and (c) lettucein A. Tables in (b) and (d) show the NICS<sub>zz</sub> values obtained at 1 Å above the surface of the pyrylium and tropylium rings in patriscabrin A and lettucein A, respectively.

values (Figure 3).<sup>66</sup> For patriscabrin A, the neutral form does not show significant aromatic character, even in water, where the zwitterionic character is favored.<sup>66,67</sup> For completeness, we include the gas-phase results in the Supporting Information.<sup>68</sup>

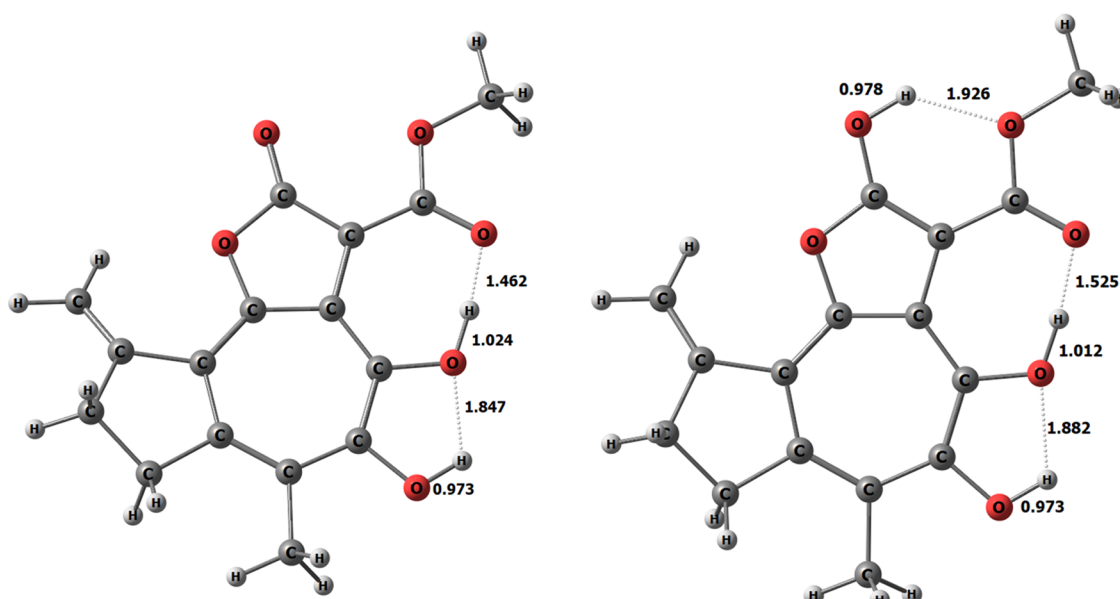
O-Protonated patriscabrin A, however, is predicted to have aromatic character but significantly less than that of benzene and pyrylium (NICS<sub>zz</sub> (1 Å) at the same level of theory: -29.69 and -24.56, respectively). Adding substituents to the six-membered ring, whether  $\pi$ -donating or -withdrawing, reduces the magnitude of the computed NICS<sub>zz</sub> values.

For lettucein A, the NICS<sub>zz</sub> data indicates that both the neutral and protonated forms have significant aromatic character in water, with the 7-membered ring in the protonated form approaching that of isolated tropylium (NICS<sub>zz</sub> at the same level of theory: -26.86). Again, adding substituents reduces aromatic character.

The difference in the neutral NICS<sub>zz</sub> values between R = -OH and R = -OCH<sub>3</sub> in Figure 3d can be attributed to a proximity effect that facilitates a stabilizing (and, seemingly, aromaticizing) interaction with the hydroxy substituent in the

lowest-energy conformer of lettucein A (Figure 4).<sup>69–73</sup> A hydrogen bond between the OH group and the carbonyl oxygen atom of the adjacent ester group is present in both the neutral and protonated forms, but this hydrogen bond is weakened in the protonated version as a competing hydrogen bond is present between the now-protonated oxygen and the ester.

**Basicity.** Computed basicities for patriscabrin A and lettucein A are collected in Table 1. In addition to gas-phase values, basicities for chloroform and water are included. Not surprisingly, since protonation converts a neutral structure to an ion in the cases examined here, basicities uniformly increase with solvent polarity. In other words, both natural products are most basic in water and least basic in the gas phase. In line with expectations, the amino-substituted systems are predicted to possess the highest basicities and the trifluoromethyl-substituted systems are predicted to be the least basic for lettucein A. On the other hand, the hydroxy-substituted systems are predicted to possess the highest basicities and the nitro-substituted systems are predicted to be



**Figure 4.** Top views of the neutral (left) and ionic (right) forms of lettucein A for R = -OH, calculated using the B3LYP/cc-pVTZ level of theory in water. This phenomenon persists even at the M06-2X/cc-pVTZ level of theory.

**Table 1.** Computed Basicities,  $B_{NP}$ , in kcal mol<sup>-1</sup>, of Patriscabrin A and Lettucenin A, Calculated at the B3LYP/cc-pVTZ Level of Theory, as a Function of the Substituent on the Ring and the Solvent Environment, Where R = -CF<sub>3</sub>, -CH<sub>3</sub>, -CN, -COH, -F, -H, -NH<sub>2</sub>, -NO<sub>2</sub>, -OH, and -OMe

R	patriscabrin A			lettucenin A		
	$\epsilon = 1.00$	$\epsilon = 4.71$	$\epsilon = 78.36$	$\epsilon = 1.00$	$\epsilon = 4.71$	$\epsilon = 78.36$
-NO <sub>2</sub>	-42.03	-78.12	-90.76	-51.94	-83.94	-93.98
-CN	-43.14	-80.67	-93.06	-51.30	-83.82	-92.30
-CF <sub>3</sub>	-49.07	-83.78	-94.69	-48.48	-81.96	-91.10
-COH	-51.85	-85.90	-95.75	-56.31	-87.39	-94.25
-F	-53.52	-88.48	-98.15	-54.39	-86.38	-93.77
-H	-57.71	-92.31	-100.55	-64.13	-92.88	-97.61
-CH <sub>3</sub>	-63.32	-95.94	-102.62	-68.06	-95.28	-99.22
-OCH <sub>3</sub>	-64.72	-96.63	-104.27	-64.62	-93.06	-98.78
-OH	-66.48	-99.86	-108.39	-68.44	-95.12	-98.89
-NH <sub>2</sub>	-65.82	-99.53	-107.79	-75.04	-101.10	-103.43

the least basic for patriscabrin A. This effect, however, does not track with the changes in aromatic character (assessed via NICS calculations) described above.

To put the observed trend on firmer footing, we deployed the venerable Hammett  $\sigma$  constants.<sup>74,75</sup> Figure 5 shows the computed basicities as a function of the *meta* and *para* Hammett  $\sigma$  constants ( $\sigma_m$  and  $\sigma_p$ ) for both patriscabrin A and lettucein A. Better fits are achieved with  $\sigma_p$  values, and the best correlation is observed for patriscabrin A.

## SUMMARY AND OUTLOOK

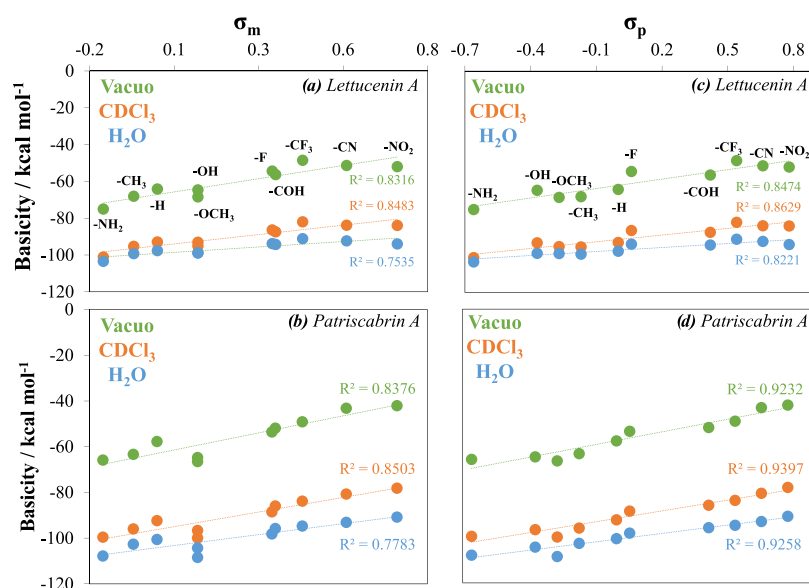
Computed basicities of patriscabrin A and lettucein A differ by 10 kcal mol<sup>-1</sup> in the gas phase, 6 kcal mol<sup>-1</sup> in chloroform, and 10 kcal mol<sup>-1</sup> in water. It appears that nature converged on maximum aromaticity in both protonated species. However, NICS<sub>zz</sub> values do not correlate with computed basicities for substituted systems, suggesting that the driving force for maximizing aromatic character is not simply modulation of basicity. Maximizing cyclic  $\pi$ -delocalization could have implications for noncovalent interactions with the natural products.<sup>76-78</sup> For example, changes in the aromatic character of a ring have been shown by Wu and co-workers to influence

the binding properties of attached substituents.<sup>72,73</sup> In analogy, enhanced hydrogen bonding with the  $\sigma,\beta$ -unsaturated carbonyl groups of patriscabrin A and lettucein A could be associated with aromaticity gain.

## CITATION DIVERSITY STATEMENT<sup>79</sup>

Studies have found, unsurprisingly, that women and other under-represented minorities remain under-cited and unacknowledged within their respective fields.<sup>80,81</sup> We aim to help rectify said disparity by attempting to accurately cite studies relevant to this study while being mindful of the gender balance of the reference list. The references contain 60% man/man, 13% woman/man, 21% man/woman, 0% woman/woman, and 5% unknown categorization (this list is unfortunately limited to binary gender identities and we are hopeful for the day when we are able to recognize, and endorse, those of intersex, transgender, and/or nonbinary identities). These percentages reflect the gender imbalances that persist across many fields of chemistry and related science, technology, engineering, and mathematics (STEM) fields.<sup>82</sup> We believe that much more needs to be done to correct this imbalance.





**Figure 5.** Proton affinity of lettuceenine A (*top*) and patriscabrin A (*bottom*) as functions of  $\sigma_p$  and  $\sigma_m$  in various environments, where R = -H, -F, -Me, -CF<sub>3</sub>, -CN, -NH<sub>2</sub>, -NO<sub>2</sub>, and -COH. The graphs share a common y-axis to illustrate the relative distribution of values. Graphs (a) and (b) share a common x-axis, as do (c) and (d). The order of data points for the R groups is identical for (a) and (b), as well as (c) and (d). To minimize congestion on the graph, data points are explicitly labeled only for (a) and (c) in water.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c04051>.

Coordinates of minima, NICS<sub>zz</sub> data, and the proton affinities at the B3LYP and M06-2X methods. Additional investigations into patriscabrin B and lettuceenine B are also included (PDF)

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### Notes

The authors declare no competing financial interest.

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