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FIRST REACTIONS

Abiotic Main Group Pharmacophore Renders a New Class of Antimicrobial Agents

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A boron cluster is used to template a hybrid molecular scaffold capable of killing multiple pathogenic and antibiotic-resistant bacterial strains.

In the early 1950s, chemists made the remarkable discovery of a new class of stable catenated molecules made out of primarily boron and hydrogen (Figure 1a).[1] Since then, these compounds, termed polyhedral boron clusters, have been investigated both in academic and corporate research laboratories and applied in diverse ways ranging from polymer building blocks to nuclear medicine.[2] The unique stability profile of polyhedral boron clusters compared to that of conventional borane species (e.g., BH_4^-) results from the electron delocalization of bonding electrons in these molecules, or three-dimensional (3D) aromaticity. Because of these unique electronic properties, icosahedral clusters such as $B_{12}H_{12}^{2-}$ show no decomposition in aqueous acids and bases within the pH range from 1 to 14, can withstand harsh oxidants and reducing agents, and stay intact in biological serum media. Furthermore, $B_{12}H_{12}^{2-}$ displays very low *in vivo* toxicity, highlighting its potential to interface with biological systems.[3,4] Not surprisingly, investigators have made a number of recent strides in utilizing boron clusters as pharmacophores (Figure 1b) that can mimic aryl and large carbon-based functional groups (e.g., adamantane).[5] The potential application of boron clusters as building blocks for novel antimicrobials has been hypothesized as early as the 1980s.[6] Advancement of these ideas stalled for some time, and while investigators have begun explorations into this molecular space for antimicrobials within the past decade, only a few studies currently exist where biologically active antimicrobial boron cluster-based molecules have been investigated.[7] Among these studies, the molecular design of the bioactive scaffolds is limited to scenarios with a cluster as a pendant group attached to an organic-based fragment or as a spacer between two such fragments. Ultimately, the realm of bioactive molecules where these boron clusters serve as unique three-dimensional templates for positioning organic scaffolds has remained fundamentally underdeveloped.[4]

In this issue of *ACS Central Science*, Varkhedkar and colleagues showcase the first hybrid system where three adjacent vertices on an abiotic boron cage serve as a 3D template on which different organic functional groups may be positioned.[3] This work rests on key fundamental B–H functionalization chemistry that the authors and others have been developing over the past decade.[8] On the surface, these transformations may be viewed as trivial given the parallels between B–H and C–H bond activation chemistry, but the reality is that boron clusters are challenging substrates due to their large steric bulk and dianionic charge. The synthetic sequence Varkhedkar and co-workers employ here in their work is elegant, yet simple: a functional group is preinstalled onto the cage which then directs concomitant, intramolecular B–O and intermolecular B–C bond formation reactions in one pot (Figure 1c). This results in the formation of a 3D shell appended to a triangular face of the boron cluster icosahedron. Importantly, the radial density and 3D topology of these substituents cannot be achieved by using existing carbon-based scaffolds, thereby constituting a unique approach to small-molecule drug design.

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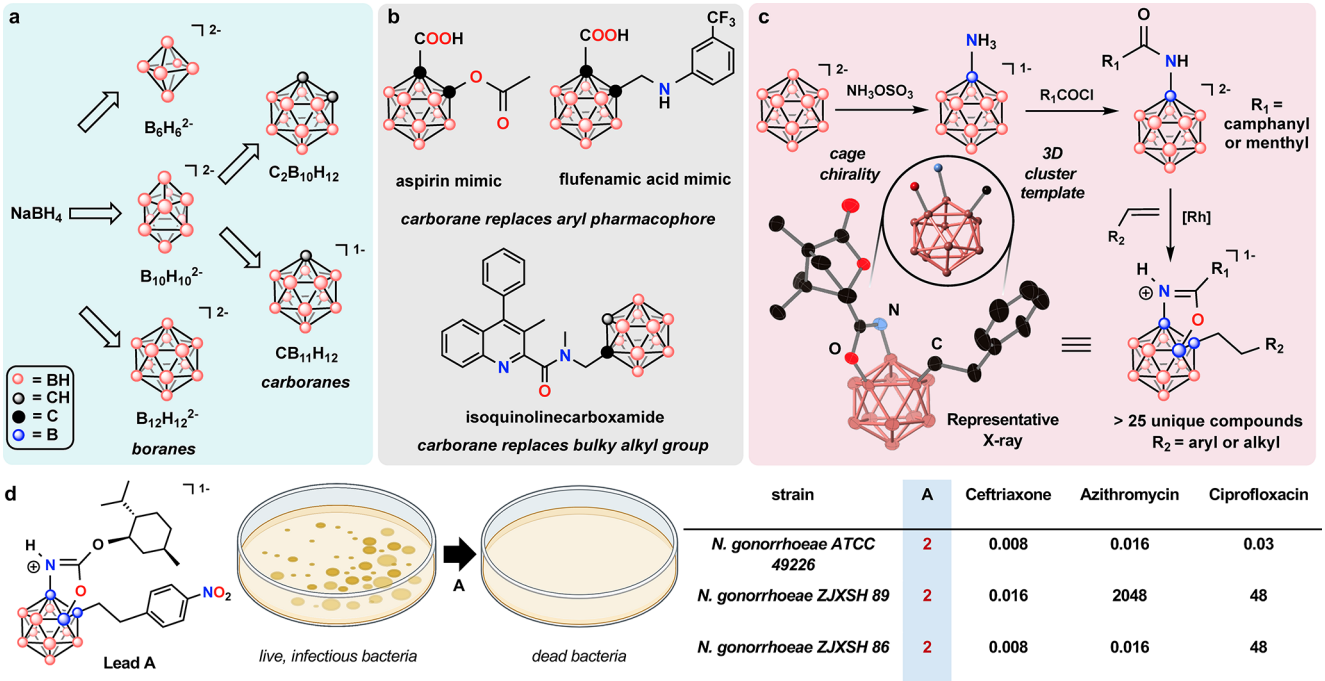

strain	A	Ceftriaxone	Azithromycin	Ciprofloxacin
N. gonorrhoeae ATCC 49226	2	0.008	0.016	0.03
N. gonorrhoeae ZJXSH 89	2	0.016	2048	48
N. gonorrhoeae ZJXSH 86	2	0.008	0.016	48

Figure 1. (a) Key representative structures of polyhedral boron clusters. (b) Representative examples of biologically active compounds containing boron cluster pharmacophores.[5] (c) Synthetic scheme leading to the library of dodecaborate-based antimicrobials synthesized by Varkhedkar and colleagues. Inset shows a representative single crystal X-ray structure of the synthesized compound with an appended camphanyl substituent (50% thermal ellipsoids are shown, H atoms are omitted for clarity, and only one diastereomer is shown). (d) Structure of lead compound A showing promising minimum inhibitory concentrations (MICs, reported in μM) compared to those of three antibiotics used to target multidrug-resistant bacteria.

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Varkhedkar et al. then screened the resulting library of compounds for antimicrobial activity against both Gram-positive and Gram-negative bacterial strains and found that several of them possess high bactericidal activity.[3] Among these, lead compound A exhibited strong bactericidal activity against antibiotic-resistant strains of *Neisseria gonorrhoeae* and *Staphylococcus aureus*. In both cases, treatment of bacterial culture with lead compound A significantly reduced colony forming units (CFUs) within 1 h of treatment (Figure 1d). The widespread availability and use of antibiotics since the discovery of penicillin in the early 1900s has also coincided with the rapid mutation of bacterial strains with resistance to treatment.[9] Multidrug-resistant bacteria within this "resistome" are of particular concern since there are few remaining options for treatment after infection, and these bacteria are often most prevalent in environments and near populations easily susceptible to infection, such as in hospitals. While the mechanisms behind antibiotic resistance are extremely complex with over 20 000 bacterial genes currently implicated in the process, it is clear that novel antimicrobials with activity against these "superbugs" are urgently needed. The boron clusters constructed by Varkhedkar and colleagues fill this potentially promising niche as novel compounds that exhibit high bactericidal activity against *N. gonorrhoeae* and *S. aureus*, two multidrug-resistant bacteria of concern. Importantly, the choice of organic and natural product-derived functional groups attached to the cluster vertices along with their precise and modular combination proves vital in changing the functionality and antimicrobial activity of the product boron cluster antimicrobials.[3]

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While the full mechanistic picture for the mode of action of lead compound A remains to be further elucidated, authors note that, as with small-molecule drugs, the observed effect of the boron cluster is structural, and no

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apparent toxicity is seen from the building blocks themselves. It is therefore enticing to think about all of the opportunities where a boron cluster can be used as a three-dimensional template to assemble abiotic yet bioactive small molecules. It also remains to be seen whether cage chirality imparts any significant effect on the bioactivity considering the authors were not able to separate the diastereomers of lead compound A and associated compounds. Regardless, given that boron clusters come in various forms of polyhedral shapes and sizes, the 3D nature of these molecules can be distinctively controlled by the cluster template itself. In order to accomplish this task, more elaborate chemistry that can programmably install functional groups in a vertex-specific manner is needed. Furthermore, finding new strategies for the synthesis of enantiopure boron clusters with defined cage chirality represents the next largely uncharted frontier in this area. With the availability of such techniques, it would be possible to graft boron clusters with a diverse array of functional groups, effectively designing small molecules with sophisticated topologies reminiscent of complex natural products.

There have been numerous discussions among the practitioners working in medicinal and pharmaceutical chemistry about the existence of a molecular flatland and the need to overcome this building block limitation.[10] While much of the effort has historically centered on developing new carbon-based pharmacophores, perhaps it is a good time to follow the work by Varkhedkar et al. and look outside of the "carbon box."

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Notes

The authors declare the following competing financial interest(s): A.M.S. is a scientific advisor for Cavea Technologies, which is start-up company aiming to develop boron cluster pharmaceuticals.

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The cell plates seen in the table of content graphic and Figure 1D were created with BioRender.com.

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