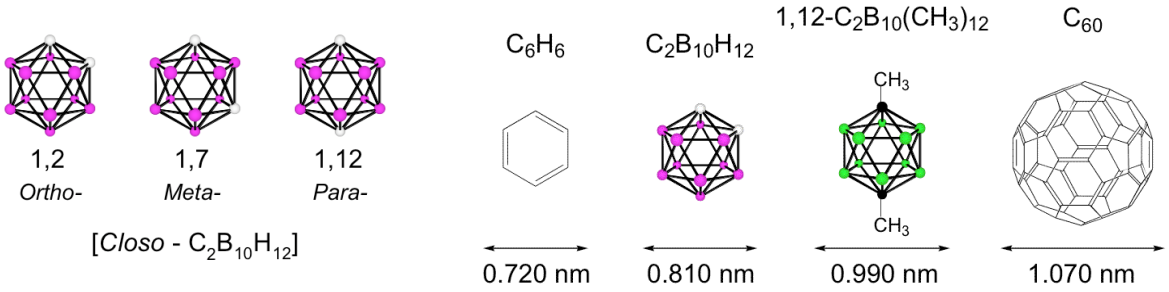
Carboranes as Novel and Versatile Pharmaceutical Building Blocks

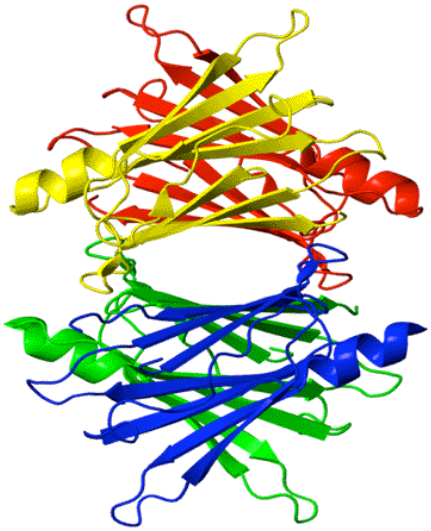
The three isomeric dicarba-*closo*-dodecaboranes (carboranes); *closo*-1,2-C2B10H12, *closo*-1,7-C2B10H12 and *closo*-1,12-C2B10H12, commonly known as *ortho*, *meta* and *para*-carborane respectively, are icosahedral carbon-containing boron clusters that share approximately the same volume as a rotated phenyl ring and may be described as three-dimensional analogs of aromatic hydrocarbons.



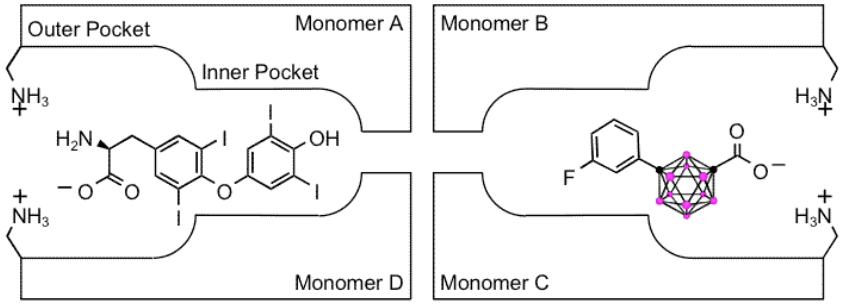
Much of the extensive chemistry of carboranes has been utilized to further their exploration as agents of high boron-content for use in Boron Neutron Capture Therapy (BNCT), thus providing a wealth of information indicating the biocompatibility and resistance to catabolism of a variety of carborane-supported structures. Recently, the use of carboranes as novel pharmacophores has garnered increasing interest, primarily due to their extraordinary characteristic properties; such as resistance to catabolism, kinetic inertness to reagents and elevated hydrophobicity. These varied properties have facilitated the application of the carborane moiety in an exceptionally diverse variety of biological targets including HIV protease inhibitors, potent retinoid antagonists and estrogen agonists, insect neuropeptides and a-human thrombin inhibition as well as analogs of the anti-estrogen tamoxifen, the controversial drug thalidomide and the antifolate trimethoprim. In an effort to expand the medicinal chemistry of carboranes, we have endeavored to identify further biological targets where the unique properties of carboranes may prove to be beneficial.

Transthyretin Amyloidosis

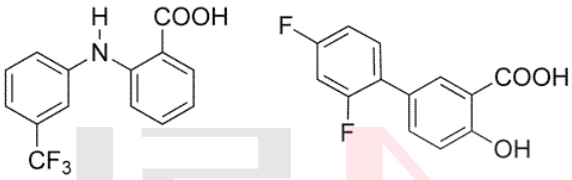
Transthyretin (TTR) is a homotetrameric transport protein found in the blood at a concentration of approximately 3.6 μM. In some people, TTR is known to dissociate and subsequently aggregate into cytotoxic amyloid fibril formations. It was found that this amyloid plaque buildup was prevented by the binding of thyroxine (T4), the natural substrate for TTR, into the pocket of TTR. This stabilization can also be afforded by the use of small molecules such as diflunisal and flufenamic acid, but at the cost of side effects (cardiovascular events, gastrointestinal irritation) due to their inhibition of the cyclooxygenase enzyme (COX) in the body. It was hypothesized that a bulky carborane analog of these drugs may inhibit TTR amyloid formation while not inhibiting the COX enzyme, leading to reduced side effects.



TTR

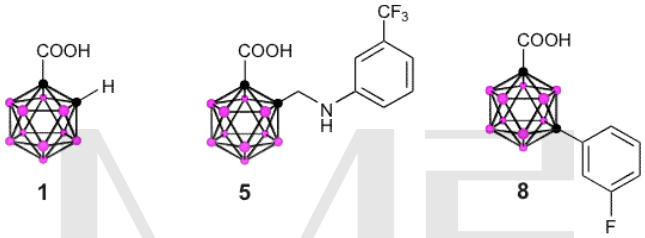


Binding of T4 and carborane-based drug to TTR

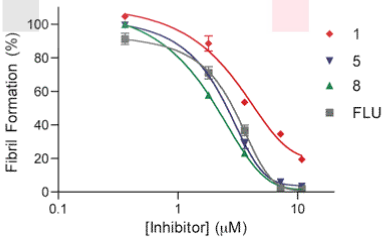


Flufenamic Acid Diflunisal

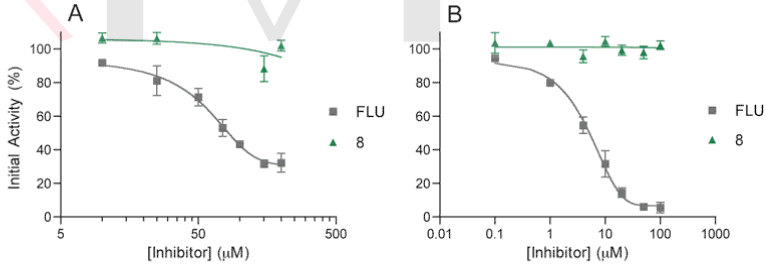
Known TTR fibril inhibitors



Carborane-based TTR fibril inhibitors



Carborane-based analogs inhibit TTR fibril formation as well as known inhibitors



Carboranes-based analogs exhibit virtually no COX-1 (A) or COX-2 (B) inhibition