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ADVANCES AT THE INTERFACE OF POLYHEDRAL BORANE CHEMISTRY AND MEDICINE

M. Frederick Hawthorne[a]
[a] International Institute of Nano and Molecular Medicine, University of Missouri, Columbia, MO, USA

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ADVANCES AT THE INTERFACE OF POLYHEDRAL BORANE CHEMISTRY AND MEDICINE

M. FREDERICK HAWTHORNE

International Institute of Nano and Molecular Medicine, University of Missouri, Columbia, MO, USA

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I first met Gordon during the autumn of 1960 when we were both located at Harvard. Gordon was an Assistant Professor of Inorganic Chemistry while I was on temporary appointment as a Visiting Lecturer teaching Paul Bartlett's graduate course on organic chemistry. My stay at Harvard was made possible by a leave of absence from the Rohm and Haas Company, Redstone Arsenal Research Division. Gordon's research at the time was concerned with the study of the NMR phenomena associated with the acid-base complexes of boranes and Lewis bases. He was just beginning to enter the emerging field of modern organometallic chemistry. My interests at that time, and since, were centered upon the exploratory chemistry of the larger boranes, polyhedral borane anions and the carboranes. I had not yet discovered metallacarborane chemistry, an event of 1965. Both Gordon and I interacted scientifically with Bill Lipscomb during our time at Harvard. This was a truly exciting era since Lipscomb was developing his bonding theory for boranes and rapidly determining the structures of a variety of borane derivatives made available by the research community. Early in 1961 I returned to my industrial position and in 1962 I became a Professor of Chemistry at the University of California, Riverside. Gordon returned to England as a Professor of Inorganic Chemistry at Queen Mary College, the University of London. Later, Gordon became a Professor of

Address correspondence to M. Frederick Hawthorne, 1514 Research Park Dr., Columbia, MO 65211, USA. E-mail: hawthornem@missouri.edu

Inorganic Chemistry at the University of Bristol with astounding success.

Throughout the years Gordon has always provided me with invitations to participate in important scientific meetings and lectures in Britain. The first instance in which Gordon entertained me occurred in 1963 when he arranged my appointment as a special lecturer at the University of London and several other universities. The number of invitations which Gordon has extended to me over the years is too large to recall, but I shall always be grateful for his friendship and help extended to me in the earliest part of my career. Consequently, I am extremely grateful for the opportunity to attend this meeting in Waco and to interact with my old friend, Gordon Stone. I wish him well even though he insists upon drawing dicarbollide-containing structures "upside-down"!

Keywords: carboranes, closomers, metallacarboranes, polyhedral boranes

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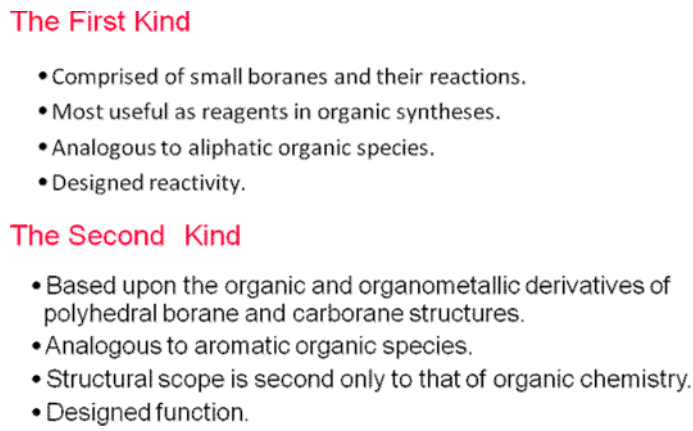
POLYHEDRAL BORANE AND CARBORANE CHEMISTRY

Since the late 1950s the chemistry of boranes has been on a new track. The original borane chemistry (Borane Chemistry of the First Kind) was immensely amplified and made nearly unrecognizable by the discovery of extremely stable polyhedral ions and molecules based upon Archimedean structures and having formal connections to $B_nH_n^{2-}$ species by substitution of cage BH groups by heteroatom-containing vertices chiefly comprised of CH and metallic elements from throughout the periodic table. These are conveniently grouped in Borane Chemistry of the Second Kind. In addition to these generalities, it is also obvious that boron and carbon bear a special relationship to each other as neighbors in the periodic table. Approximately, one might expect the catenation properties of carbon chemistry to be reflected in the chemistry of boron and this qualitative expectation is met by the ubiquitous appearance of polyhedral borane chemistry. Consequently much of what my research has entailed beyond the discovery stage has been aimed at the utilization of second kind borane chemistry in advancing the medical arts and materials science.

Scheme 1 summarizes the field of organoborane chemistry as I see it at the moment, while Scheme 2 lists unique functions of borane of the second kind.



Scheme 1. Two kinds of organoborane chemistries. (Figure appears in color online.)

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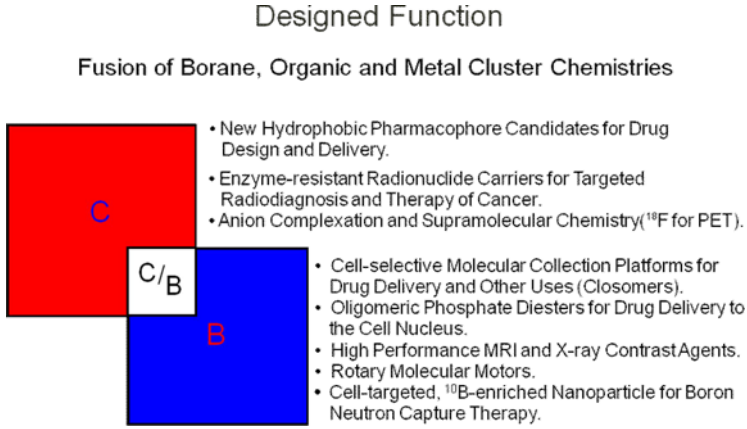
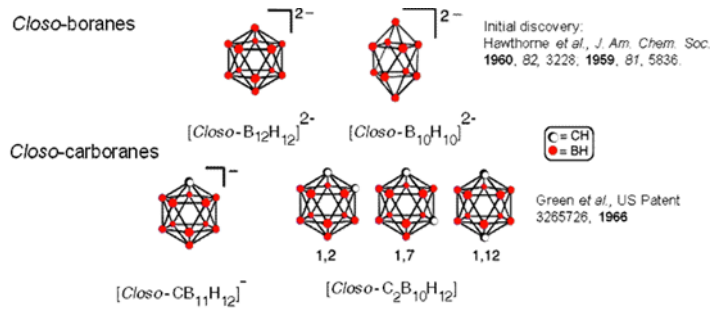
Examples of molecular building blocks utilized in this work are explained in Schemes 3 and 4 in which the icosahedron and Archimedean bicapped anti-prism are the models for structural design of the most commonly used borane components.

BORON NEUTRON CAPTURE THERAPY (BNCT)

Scheme 5 illustrates the rudiments of the BNCT method for cancer therapy. This highly selective and effective method has been studied since 1954 when neutrons became available for peaceful purposes.



Scheme 2. Unique functions of boranes of the second kind. (Figure appears in color online.)



Scheme 3. Aromatic *closo*-borane and -carborane construction modules. (Figure appears in color online.)

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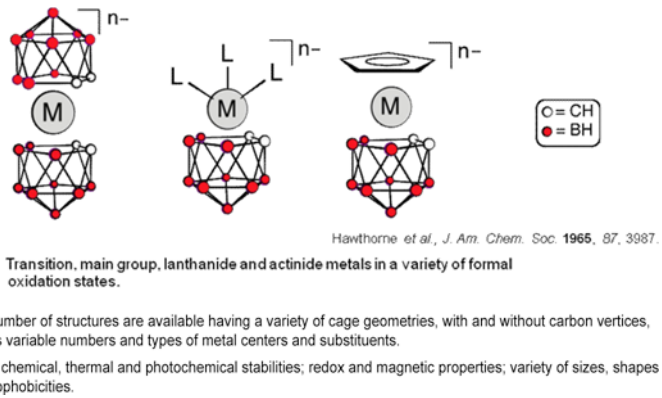
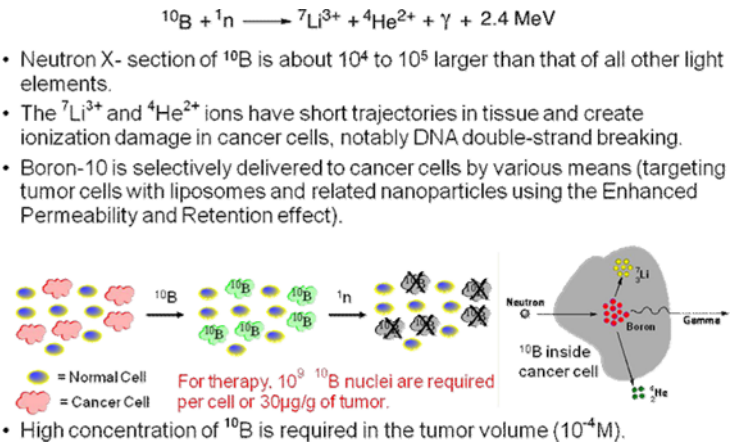
The basis of the method is the high nuclear capture cross-section for ^{10}B (ca 4000 Barns) compared to other light elementals that comprise living tissue ($10^5 - 10^4$ smaller). The reason BNCT is not available today is due to: (a) poor selection of cancer target for validation (Glioblastoma Multiforme, GBM), an incurable brain cancer; (b) the inability of agent synthesis to be carried through to evaluation of efficacy; and (c) the high cellular concentration of ^{10}B required for targeting tumors (10^{-3} to 10^{-4} M). My recent move to the University of Missouri, Columbia,

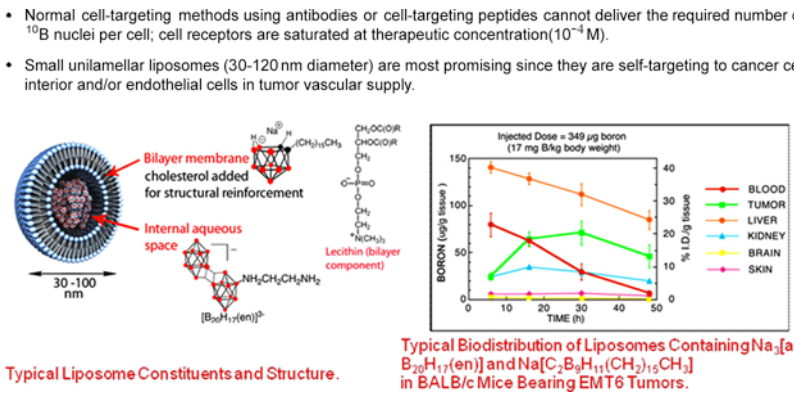


Scheme 4. Metallacarborane construction modules. (Figure appears in color online.)



Scheme 5. Boron neutron capture therapy of cancer. (Figure appears in color online.)

with its 10 MW nuclear reactor, a new neutron beam and the establishment of an institute (International Institute of Nano and Molecular Medicine), which, for the first time, brings together chemistry, medicine, and nuclear capability in one location, will allow us to establish a renaissance of BNCT research, which is based upon less demanding tumor models than GBM and at the same time utilizes targeted nanoparticle delivery of ^{10}B to tumor cells. Scheme 6 illustrates the preliminary biodistribution data obtained using liposomes as nano delivery vehicles. Research at Missouri will soon begin.



Scheme 6. Boron-containing liposomes as nanoparticle delivery vehicles. (Figure appears in color online.)

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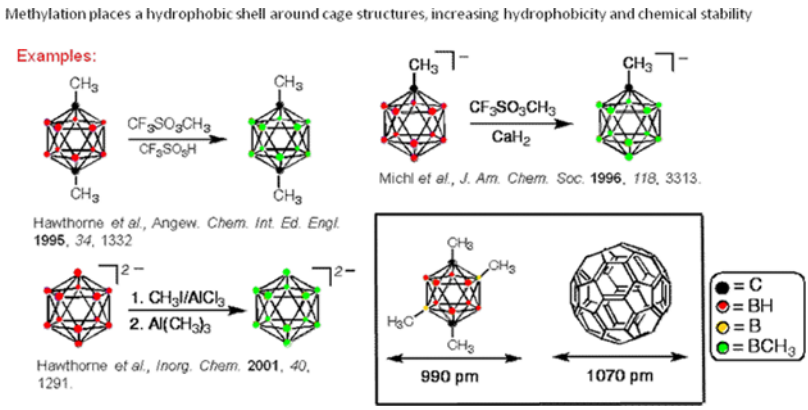

Scheme 7. Permethylation of icosahedral borane derivatives. (Figure appears in color online.)

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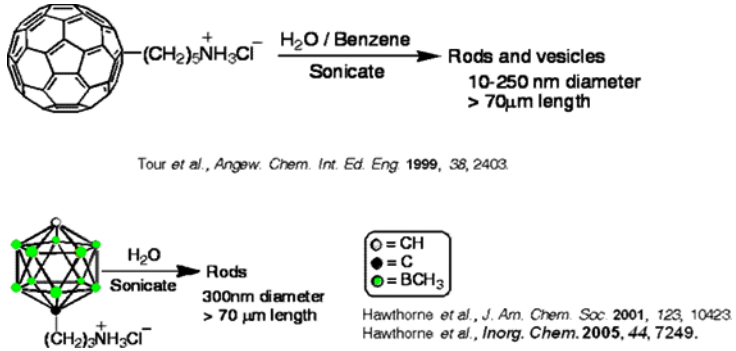
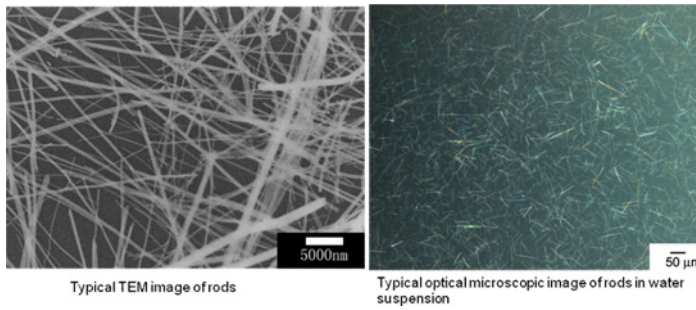
HYDROPHILIC CARBORANE SURROGATES FOR C_{60}

The near spherical shape of the icosahedron and the ready availability of the carboranes suggested that the decoration of the carborane surface with methyl groups would increase the effective size of the carborane cage to near that of C_{60}. Scheme 7 describes this approach and points out the similarity in size of the fully methylated carborane and the C_{60} molecules.

In order to test this hypothesis we carried out the comparison of the C_{60} chemistry of Tour and that of a similar carborane derivative.



Scheme 8. Self-assembly of rod structures. (Figure appears in color online.)



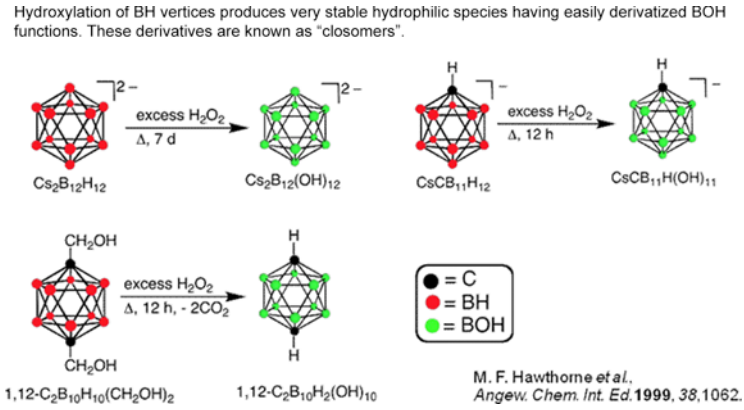
Scheme 9. TEM and optical images of self-assembled rods. (Figure appears in color online.)

Scheme 8 describes this approach and Scheme 9 presents TEM and optical images of the resulting self-assembled rod product.

This result strongly emphasizes the size and reactivity similarity of the two polyhedral structures.

HYDROPHILIC HYDROXYLATED POLYHEDRAL BORANES

Having amply demonstrated the ability to enhance the hydrophilicity of the icosahedral carborane by permethylation of all vertices, it became a challenge to obtain a perhydroxylated species having enhanced hydrophilicity and an array of functional BOH vertices. Scheme 10 illustrates the use of hot 30% H_2O_2 to accomplish the hydroxylation of BH vertices in a



Scheme 10. Perhydroxylation of icosahedral borane and carborane derivatives. (Figure appears in color online.)

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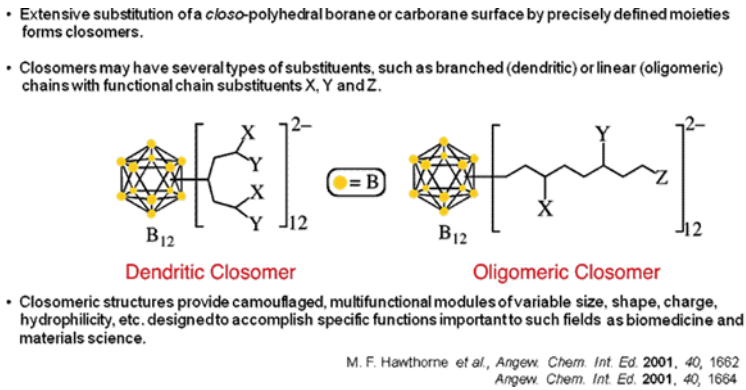

Scheme 11. Closomers represent new motifs in molecular architecture. (Figure appears in color online.)

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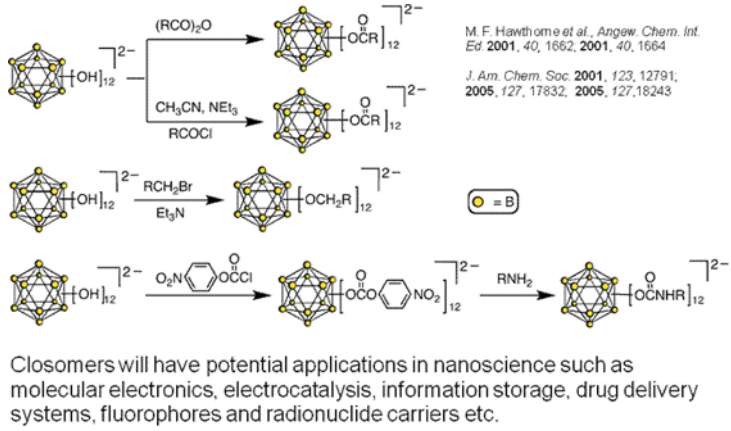
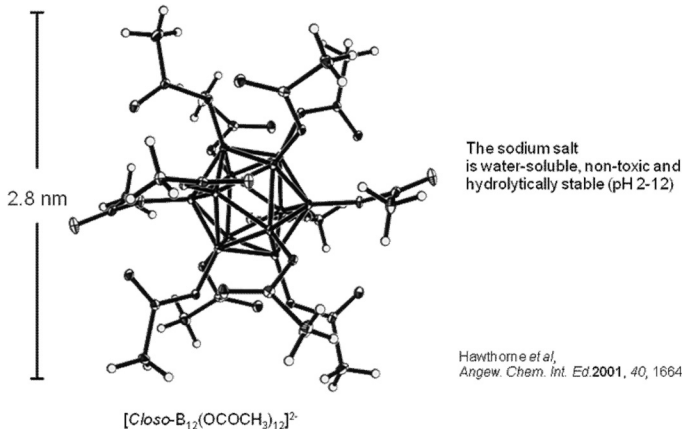
variety of environments. Most important is the high-yield synthesis of the $B_{12}(OH)_{12}^{2-}$ ion whose chemistry is still under development.

Scheme 11 outlines methods for the utilization of the 12-fold functionality of the $B_{12}(OH)_{12}^{2-}$ ion, an effective platform for the collection of functional varieties for use in medicine and materials science. Scheme 12 illustrates the versatile reactivity of the icosahedral perhydroxyl closomer.

Schemes 13 and 14 display the structures of the simplest 12-fold acetate ester closomer and the space-filling view of the 12-fold benzyl ether, respectively.



Scheme 12. Synthesis of closomers. (Figure appears in color online.)



Scheme 13. Representative closomer ester structure.

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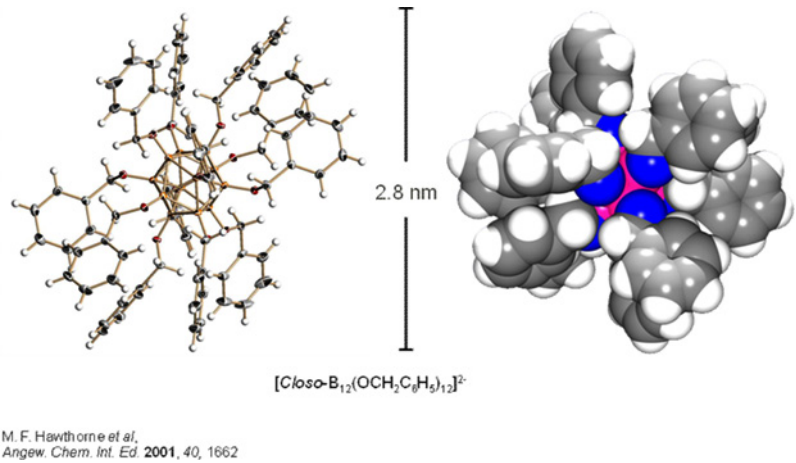
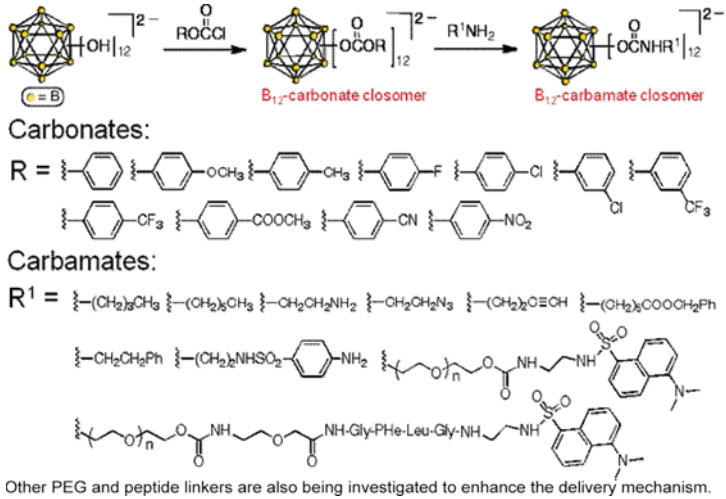
Scheme 15 illustrates the high-yield route for the formation of the 12-fold derivatives such as carbonates. The application of these reactions and reagents to biomedical challenges is obvious.

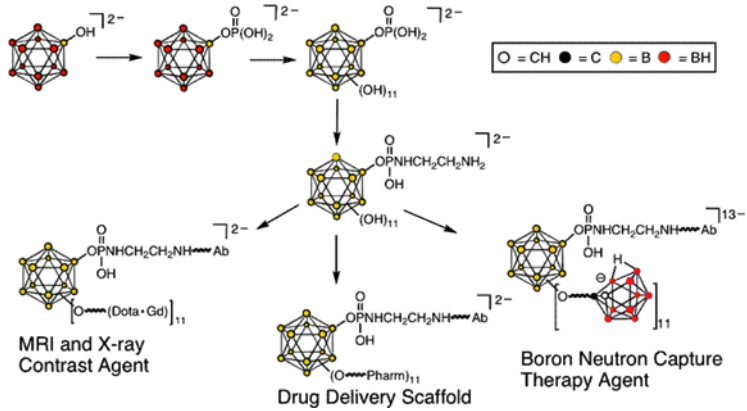
The ability to target specifically modified closomers (molecular nanoparticles) to bio-sites of interest using bioligands is of great interest and we are pursuing this objective. Scheme 16 displays applications of such systems and ways in which one might proceed.



Scheme 14. Representative closomer ether structure. (Figure appears in color online.)



Scheme 15. Closomer conjugates for drug delivery. (Figure appears in color online.)



Scheme 16. Targeted multifunctional nanostructures with diverse applications. (Figure appears in color online.)

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Dr. George Kracke	Dr. Michael Lewis	Mr. Richard Julius
Ms. Betty Tang	Ms. Karen Chain	Dr. Natasha Shlyakhtina
Dr. Lalit Goswami	Dr. Anupam Singh	Dr. Vikas Kulkarni
Dr. Peter Kueffer	Dr. Hanbaek Lee	Dr. Ram Pichaandi
Dr. Alok Paital	Mr. Arsen Gulustyan	Mr. Shuo Yang
Mr. Shatadru Chakravarty	Dr. Lixin Ma	Ms. Amanda Dennis
Dr. Yulia Sevryugina	Dr. Oscar Tutusaus	Dr. Hairong Li
Mr. Zach Houston		

Lastly, I thank the organizers of the Stone Symposium for the invitation to speak and participate in a celebration of the life of one of England's greatest chemists, my friend, Gordon Stone.

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