Special topic

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Half- and mixed-sandwich metallacarboranes for potential applications in medicine

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Abstract: Today, medicinal chemistry is still clearly dominated by organic chemistry, and commercially available boron-based drugs are rare. In contrast to hydrocarbons, boranes prefer the formation of polyhedral clusters via delocalized 3c2e bonds, such as polyhedral dicarba-*closo*-dodecaborane(12) (*closo*-$C_2B_{10}H_{12}$). These clusters have remarkable biological stability, and the three isomers, 1,2- (*ortho*), 1,7- (*meta*), and 1,12-dicarba-*closo*-dodecaborane(12) (*para*), have attracted much interest due to their unique structural features. Furthermore, anionic *nido* clusters ($[7,8\text{-}C_2B_9H_{11}]^{2-}$), derived from the neutral icosahedral *closo* cluster 1,2-dicarba-*closo*-dodecaborane(12) by deboronation followed by deprotonation are suitable ligands for transition metals and offer the possibility to form metallacarboranes, for example via coordination through the upper pentagonal face of the cluster. The isolobal analogy between the cyclopentadienyl(–1) ligand (Cp^-) and $[C_2B_9H_{11}]^{2-}$ clusters (dicarbollide anion, Cb^{2-}) is the motivation in using Cb^{2-} as ligand for coordination to a metal center to design compounds for various applications. This review focuses on potential applications of half- and mixed-sandwich-type transition metal complexes in medicine.

Keywords: biomedical applications; carboranes; Distinguished Women in Chemistry and Chemical Engineering; medicinal chemistry; metallacarboranes.

Introduction

Today, medicinal chemistry is still clearly dominated by organic chemistry, and commercially available boron-based drugs are rare [1]. Besides bortezomib, tavaborole (AN2690), crisaborole (AN2728), epetraborole (AN3365), and SCYX-7158 (AN5568) [2–13], L-4-(dihydroxyboryl)phenylalanine (BPA) and sodium mercaptoundecahydro-*closo*-dodecaborate (BSH) are used as drugs in boron neutron capture therapy (BNCT) [14–17].

Like carbon, boron readily forms compounds with covalent boron–hydrogen bonds and boron–boron interactions. However, in contrast to hydrocarbons, boranes prefer the formation of polyhedral clusters via delocalized 3c2e bonds [18]. Polyhedral dicarba-*closo*-dodecaborane(12) (also known as carboranes, carbaboranes or *closo*-$C_2B_{10}H_{12}$),[1] in which two BH^- units of *closo*-$B_{12}H_{12}^{2-}$ are replaced by two CH vertices [19], have

1 Nomenclature adopted for carborane clusters (according to IUPAC convention): *closo* = 12-vertex icosahedral cluster, with (n – 1) skeletal electron pairs (n = total number of vertices); *nido* = 11-vertex open-face cluster, with (n – 2) skeletal electron pairs (n = total number of vertices); *ortho*-, *meta*-, *para*- = 1,2-, 1,7-, 1,12-dicarba-*closo*-dodecaborane(12), respectively.

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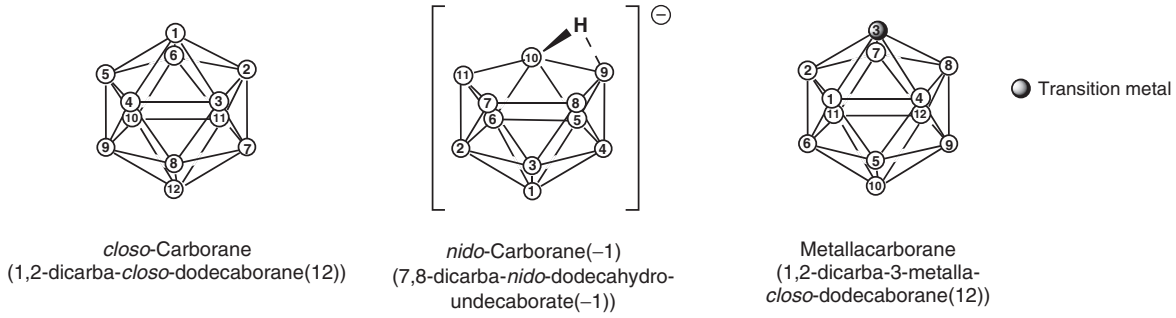


Fig. 1: Numbering scheme for *closo*-carborane (left), *nido*-carborane(–1) (center) and metallacarboranes (right). Only one isomer of the *nido*-carborane(–1) and of the metallacarborane-type structures are shown.

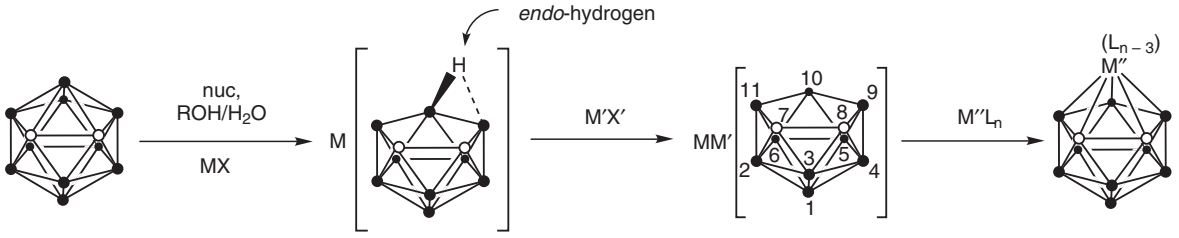
remarkable biological stability, and the three isomers, 1,2- (*ortho*), 1,7- (*meta*), and 1,12-dicarba-*closo*-dodecaborane(12) (*para*), have attracted much interest due to their unique structural features (Fig. 1). Mainly due to their high hydrophobicity [20], their inorganic nature, which prevents enzymatic degradation, and their generally low systemic toxicity, carboranes offer tremendous potential for medicinal applications, e.g. as BNCT agents [21–28], as scaffolds for diagnostic and therapeutic labelling [29], or as pharmacophores [30–40]. Furthermore, anionic *nido* clusters ($[7,8\text{-}C_2B_9H_{11}]^{2-}$), derived from the neutral icosahedral *closo* cluster 1,2-dicarba-*closo*-dodecaborane(12) by deboronation followed by deprotonation (see "Synthesis of Metallacarboranes" below), are suitable ligands for transition metals and offer the possibility to form metallacarboranes, for example via coordination through the upper pentagonal face of the cluster (Fig. 1, right) [41].

The isolobal analogy between the cyclopentadienyl(–1) ligand (Cp^-) and $[C_2B_9H_{11}]^{2-}$ clusters (dicarbollide anion, Cb^{2-}) was, and still is, the motivation in using Cb^{2-} as ligand for coordination to a metal center to design compounds for applications in either catalysis [42] or medicine [43]. Cb^{2-} and Cp^- ligands can both donate six electrons to the metal center, and can both coordinate via the pentagonal face [42, 44, 45]. However, Cp^- and Cb^{2-} show rather dissimilar coordination properties, due to differences in charge (–1 for Cp^- vs. –2 for Cb^{2-}) and symmetry (D_{5h} for Cp^- vs. C_s for Cb^{2-}). This means that the resulting metallacarborane complexes have different properties than the corresponding Cp-based purely organometallic complexes. This is the case, for example, of the ionization potential of ferrocene and ferrocene analogue $[CpFeCb]^-$, i.e. the mixed-sandwich complex, where one of the two Cp^- ligands of ferrocene is substituted by a Cb^{2-}, as described by Brown et al. [44, 45]. The first ionization energy drops to 7.45 eV in the $[CpFeCb]^-$ complex, from the 9.68 eV in ferrocene, although the iron center is in oxidation state +II in both complexes.

Half-, mixed- and full-sandwich as well as bent-metallocene-type structures are found throughout the chemistry of metallacarboranes [46, 47]. Previous reviews of metallacarboranes of 11-vertex clusters have covered full-, half- and mixed-sandwich complexes, often together with *exo*-coordinated metal complexes [48, 49]. Here, the focus is on half- and mixed-sandwich metallacarborane complexes with dicarbollide ligands with potential biological relevance. Their synthesis, chemical reactivity and mode of action in biological media can differ significantly from, for example, the COSAN-type structures [i.e. cobalt(III) bis(dicarbollide) sandwich complexes] [50–52].

Synthesis of metallacarboranes

The synthesis of *nido*-$[7,8\text{-}C_2B_9H_9R_2]^{2-}$ (dicarbollide anion) derivatives starts from the commercially available *ortho*-*closo*-carborane, 1,2-dicarba-*closo*-dodecaborane(12), and a suitable nucleophile [53]. The most electropositive BH group is removed from the 12-vertex cluster by regioselective deboronation [39], followed by removal of the so-called *endo*-hydrogen (Scheme 1). This can be abstracted either by reaction with a suitable metal complex fragment ($M'' L_n$), that incorporates ligands which can remove the proton to form stable, volatile by-products, or by reaction with a base, such as *n*-BuLi, NaH, KOH/TlOAc and TlOEt [46]. The deprotonated C_2B_3



nuc = nucleophile
X/X′ = anion
M = $[PPN]^+$, $[PMePh_3]^+$, Na^+, K^+, Cs^+, Tl^+
M′ = in general a main group metal
M″ = in general a transition metal
L = any, depending on the metal and the application
n = number of ligands L
R = any (organic) residue

○ CH or CR
● BH or BR

Scheme 1: Two-step reaction for the formation of the dicarbollide followed by complexation to a transition metal M″. The *endo*-hydrogen is shown.

face becomes, therefore, available for coordination to metal ions. The choice of the dicarbollide precursor, i.e. $M'_2[C_2B_9H_9R_2]$ in Scheme 1, depends on the transition metal and its co-ligands, since the cluster $M'_2[C_2B_9H_9R_2]$ shows different strength of covalent-ion pair interactions in solution, and therefore reactivities, according to the nature of M′ (Li^+, K^+, Na^+ or Tl^+), as reported by Fox et al. [54] and Manning et al. [55].

According to the type(s) of substituent(s) at the cage vertices, several different methods have been developed for the deboronation of *ortho*- and *meta*-carborane clusters, since the pioneering work of Hawthorne and co-workers [53], employing nucleophiles such as amines, fluorides, alkoxides and combinations thereof [39, 56, 57]. Especially, the use of fluorides (NaF, CsF) in polar protic solvents (EtOH or $EtOH/H_2O$) was shown to promote selective deboronation without cleavage of the *C*-bound groups for a multitude of substituents, such as alkylene spacers [58, 59], amide [60] carboxyl and hydroxyl groups [61], which is a frequent challenge for the appropriate treatment of the *closo*-carborane cluster. A less general synthetic approach is the reaction of 1,2-bis(phosphanyl)-1,2-dicarba-*closo*-dodecaboranes with platinum(II) [62], palladium(II) [62, 63], copper(I) [64] or silver(I) [65] complexes, which results in partial deboronation and formation of the respective *nido* clusters which act as *P,P* chelate ligands for the respective metal cations. Similarly, partial deboronation in 1,2-dithio-1,2-dicarba-*closo*-dodecaboranes is observed with copper(I) or silver(I) complexes [66]. Even hydrogenperoxide deboronates 1,2-bis(diphenylphosphanyl)-1,2-dicarba-*closo*-dodecaborane, resulting in the corresponding bis(diphenylphosphineoxide)-substituted *nido* cluster [67].

One noteworthy feature of the complexation of a dicarbollide anion to a metal center is that in some cases isomerization of *nido*-carboranes to cage systems in which the second carbon atom occupies a position on the lower boron belt can take place, due to steric effects and the conditions of the complexation reaction itself [29, 68]. In some cases, microwave heating or simply heating at reflux temperature has led to formation of 2, 1, 8 and 1, 7, 9 isomers of the metallacarborane complex, instead of the expected 3, 2, 1 isomers with all carbon atoms located on the upper face [29, 59, 60, 69].

Biologically active metallacarboranes

In this article, the focus is on half- and mixed-sandwich transition metal complexes with a pentahapto-coordinating $[C_2B_9H_9R_2]^{2-}$ or $[C_3B_8H_8R_3]^-$ ligand [69–72]. Like Cp^-, the Cb^{2-} ligand can also coordinate in an η^1 or η^3 coordination mode to transition metals, but none of these complexes was designed or tested for

biological application and are, therefore, not covered in this review. *nido*-Carborane conjugates of biomolecules were already described by Grimes [73]. These include non-classical antifolates [74] and derivatives of 5,10,15,20-tetraphenylporphyrins [75] as antibacterial and anticancer agents, thymidine analogues [76], adenosine conjugates [77], imaging, radio-imaging and radiotherapeutic agents [29], and carbon nanotubes with appended *nido*-carborane [78] as potential BNCT agents. Recently, Leśnikowski published a detailed review on the most recent developments in drug design, based on the use of boron clusters [32]. Many examples of biologically active compounds are described, ranging from substituted *closo-ortho*-carboranes, appended *nido*-carboranes, to a few examples of metallacarboranes of the COSAN type [79].

We focus our attention on metallacarborane complexes, which were designed and tested for applications as potential novel metal-based drugs and theranostic agents.

Metallacarboranes as pharmacophores for metal-based drugs

Studies on the cytotoxic activity or enzyme inhibition properties of metallacarboranes are rare; only a few examples are found in Russell Grimes' monography on carboranes [80]. In contrast to the vast literature available on cobalt(III) bis(dicarbollide) sandwich complexes, i.e. COSAN-type icosahedral metallacarboranes [50, 79, 81], examples of metallacarboranes that were screened for cytotoxic activity are only found in a recent review on the use of carboranes in medicine [43].

A small library of bent-metallocene-type tantalum(V) and niobium(V) complexes, incorporating a mixed ligand system of cyclopentadienyl(–1) and 6-vertex sub-icosahedral dicarbollide, $[C(R)C(R')B_4H_4]^{2-}$ (R = R′ = Me, Et, $SiMe_3$), was tested with several tumour cell lines (P388, HI-60, murine L1210, etc.) and showed moderate to potent activity in vitro [82]. However, these studies apparently were not continued based on the available literature.

Bis(dicarbollide) complexes and mixed-sandwich ferracarborane complexes were studied as potential novel isoform-selective nitric oxide synthase (NOS) inhibitors [69]. Three isoforms of human NOS are known, each of which is located in different tissues and has specific physiological functions [83]: neuronal NOS (nNOS) [84], inducible NOS (iNOS) [85], and endothelial NOS (eNOS) [83]. All three isoforms catalyse the conversion of L-arginine to L-citrulline and nitric oxide (NO). Overproduction of nitric oxide (NO) by nNOS is associated with a variety of neuronal pathologies, such as Alzheimer's, Parkinson's and Huntington's diseases, whereas NO overproduction by iNOS is associated with the inflammatory status of the immune system, such as arthritis [85]. The development of NOS inhibitors has received increasing interest since the 1990s [83]. As NO is implicated in many different and independent physiological functions, according to the specific synthase enzyme, the development of isoform-specific inhibitors is highly important [85].

Kaplánek and co-workers used an icosahedral metallacarborane fragment for the synthesis of potentially selective NOS inhibitors, which target the region just outside the binding pocket and not the catalytic cavities of the enzymes [69]. The possibility of regioselective three-dimensional functionalization of the carborane cage could allow modulation of the biological activity based on different specific binding interactions with the different NOS isoforms. The two mixed-sandwich ferracarborane complexes tested (**1a,b**, Fig. 2) showed very different biological activity. Particularly complex **1a**, bearing an NH_2 group in *para* position with respect to the iron center, showed no inhibition of NOS activity, neither under competitive nor under non-competitive binding assay conditions, regardless of the specific isoform. On the contrary, complex **1b**, with a guanidine substituent, showed complete inhibition of all NOS isoforms at 10 μM concentration, albeit in a non-specific manner. Compounds **2a–d** all showed binding affinities for the NOS enzymes, with a slightly preferential binding affinity for the eNOS isoform over the other two. Several types of basic binding motifs (guanidines, urea, alkyl amines, etc.) were selected (Fig. 2), and several substitution patterns at the clusters were explored. The presence of a basic amine was proven to be beneficial for increasing inhibitory potency and selectivity towards nNOS over both iNOS and eNOS [85].

We have recently shown that the combination of a dicarbollide ligand with a ruthenium(II)–arene fragment exhibits promising cytotoxic properties. Mixed-sandwich ruthenacarborane complexes with a variety of arene ligands were prepared [86] to combine the known, well-studied cytotoxic activity of ruthenium(II)–arene

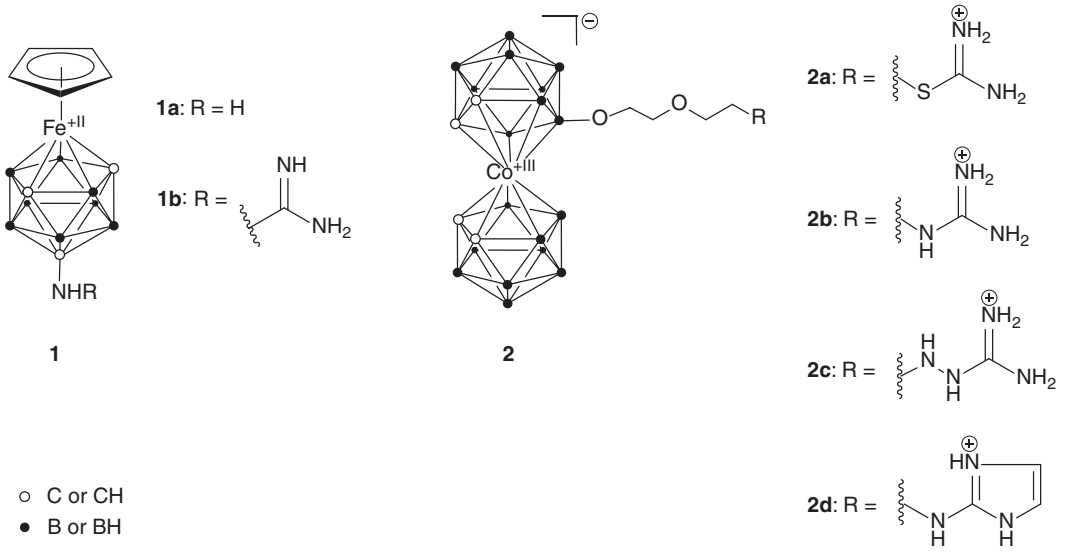


Fig. 2: Selected examples of mixed-sandwich ferracarborane (**1a,b**) and full-sandwich cobaltacarborane (**2a–d**) complexes tested as NOS inhibitors [69].

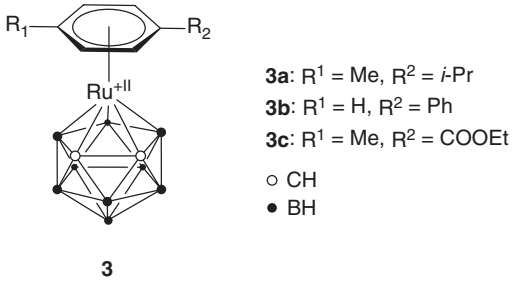


Fig. 3: Ruthenacarborane complexes (**3a–c**) with different arene ligands, tested as cytotoxic agents.

fragments (arene = benzene, *p*-cymene, biphenyl, tetrahydroanthracene, etc.) [87–89] with a dicarbollide ligand. Complexes **3a–c** (Fig. 3) were tested on three types of tumorigenic cell lines, namely B16 (murine skin metastatic melanoma), HCT116 (human colorectal carcinoma) and MCF-7 (human hormone-dependent breast adenocarcinoma), and three non-tumorigenic cell lines, i.e. human MRC-5 (human fetal fibroblasts), murine MLEC (murine lung endothelial cells) and peritoneal Mf (murine peritoneal macrophages). The three complexes **3a–c** were active against HCT116 and MCF-7 cell lines, with IC_{50} values in the low micromolar range (6–32 μM), whereas viability of the non-tumorigenic cell lines was not significantly impaired. No significant influence of the different arene ligands on the cytotoxic activity was observed. Further investigations on the mode of action are currently being carried out; preliminary results suggest a caspase-dependent apoptotic cell-death pathway [86].

In summary, metallacarboranes are emerging as highly interesting compounds for medical applications. Their attractive properties, such as biological stability, their amphiphilic nature and the possible exoskeletal functionalizations, and the promising results obtained upon studying the biological activity of such complexes certainly encourage further studies.

Metallacarboranes as radio-imaging and radiotherapeutic agents

The development of radio-imaging agents is important for many interdisciplinary areas, ranging from biochemistry to chemistry, materials science and imaging technologies [90, 91].

One of the approaches that have been explored most extensively in the last two decades is the development of so-called molecular imaging probes (MIPs), agents used to visualize, characterize and quantify biological processes in vivo at the molecular and cellular levels [90]. The agent producing the signal for image detection can be a radionuclide (e.g. ^{125}I, ^{99m}Tc), a fluorescent molecule or a magnetic moiety [90]. Positron emission spectroscopy (PET), single-photon emission computed spectroscopy (SPECT) and magnetic resonance imaging (MRI) technologies are employed as routine primary diagnostic methods. In particular, bioorganometallic target-specific radio-imaging agents are being extensively studied as potential novel MIPs [92].

The Valliant group has pioneered research on Re^{I}- and ^{99m}Tc^{I}-based metallacarboranes as target-specific radio-imaging agents [29]. They have applied the so-called bioisosteric replacement strategy, replacing a Cp ring in known promising radiopharmaceuticals with a dicarbollide cluster while preserving and/or modulating the biological activity. Bioisosteric replacement is nowadays a very common approach in drug design, and numerous examples can be found in the literature on medicinal organic chemistry [93] and polyhedral boron clusters [32, 39, 73].

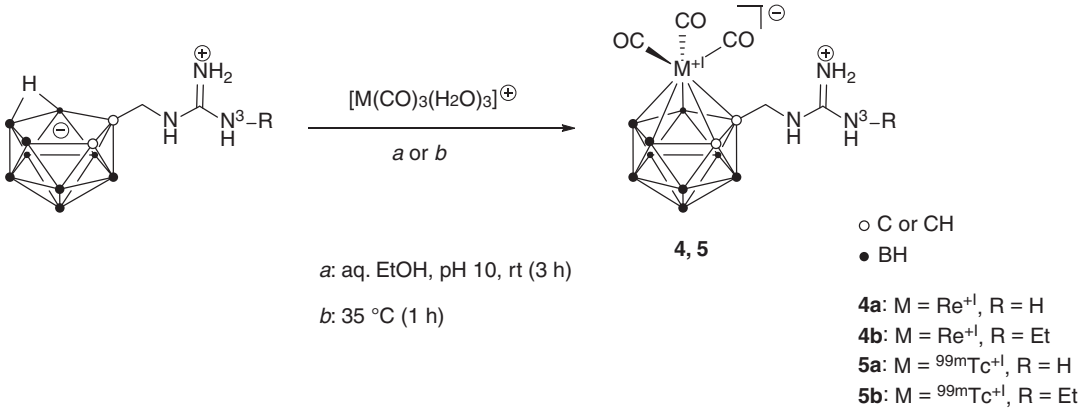
Most of the early work of the Valliant group has already been thoroughly reviewed by Grimes [94] and Armstrong and Valliant [29], including rhena- and technetacarborane complexes designed as probes for estrogen receptors [95] or incorporating an iodine-labelled bipyridyl ligand and a nitrosyl group at the metal center, designed to enhance transport across the blood-brain barrier (BBB) [70].

A small library of anionic Re^{I}- and ^{99m}Tc^{I}-dicarbollide complexes has been prepared over the past decade. Typically, the complexation to the $[M(CO)_3]^+$ (M = Re,^{99m}Tc) fragment is performed in aqueous solution under microwave heating (150–200 °C), starting from the respective *nido*-carborane precursor and $[M(CO)_3(H_2O)_3]Br$ [29]. Many of these complexes have been specifically designed and tested for interactions with chosen biological targets [58, 60].

The presence of an ancillary base at the cluster can lower the reaction temperature of the complexation reaction. Thus, Re^{I}- and ^{99m}Tc^{I}-dicarbollide complexes bearing a guanidine substituent at the *C*-vertex can be obtained under mild reaction conditions (Scheme 2) [96], giving access to radiolabelled metallacarborane complexes with a wider spectrum of vectors. Unsubstituted and *N*-alkyl-substituted guanidine derivatives afforded the target Re^{I}- and ^{99m}Tc^{I}-dicarbollide complexes in moderate yields (30–69 %) [96].

Biodistribution studies were carried out on healthy female CD1 mice with **5a,b**. Both compounds rapidly cleared from the bloodstream, but showed different tissue accumulation profiles. Compound **5a** showed highest accumulation in the gall bladder (42.11 ± 16.99 %ID/g at 4 h), whereas **5b** accumulated preferentially in the bladder [96], suggesting different clearance pathways, which may be due to the different guanidine substituents at the clusters, as all other factors were equal.

More recent examples of anionic Re^{I}- and ^{99m}Tc^{I}-dicarbollide complexes as potential MIPs include a group of complexes in which the dicarbollide ligand bears a 1-(methoxyphenyl)piperazine substituent [58, 60]



Scheme 2: Synthesis of complexes **4a,b** and **5a,b** [96]. The position of the nitrogen atom N^3 of the guanidine group is labelled.

(Fig. 4) and complexes in which the cluster is regioselectively substituted at the B(8) vertex with a tailored tether (see below) [70, 71].

The 1-(2-methoxyphenyl)piperazine group is well known as a rather potent and selective inhibitor of the 5-HT1A sub-type of the serotonin receptor, primarily located in brain tissues [97] and has, therefore, often been incorporated as the targeting vector within molecules designed as potential inhibitors or MIPs of serotonin receptors (Fig. 4) [98, 99]. The rhenium(I) complexes **6**, **8** and **10** and the corresponding technetium(I)-99m complexes **7**, **9** and **11** (Fig. 4) were prepared in an attempt to obtain highly selective MIPs for serotonin receptors (5-HT*x* class) [100]. An increased lipophilicity of the target complexes [39, 58] compared to analogous Cp-based molecular imaging probes [97] and the necessary stability of the MIP agent in biological media to reach the target unaltered [58, 60] are important features of the complexes. Typically, for a radiotracer to be considered as a potential efficient molecular imaging probe, partition coefficients (log*D*) should range from 2.0 to 3.5 [101]. For the $^{99m}Tc^{I}$-dicarbollide complexes **7**, **9** and **11**, log*D* values between *n*-octanol and a phosphate buffer (0.02 M, pH 7.4) between 2.26 and 2.6 were found suggesting potential effective transport across the BBB [58].

Compounds **6**, **8** and **10** were screened for binding affinity towards several key receptors found in the central nervous system (CNS), including serotonin (5HT*x* series) and α-adrenergic receptors. In comparison

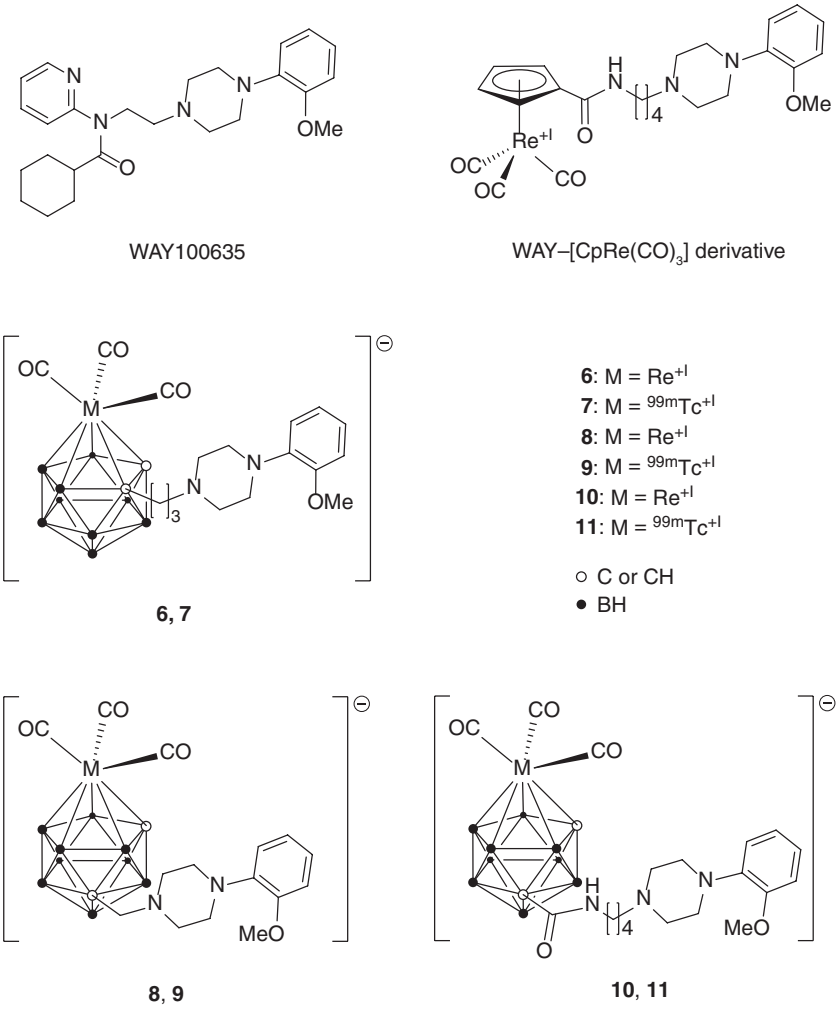
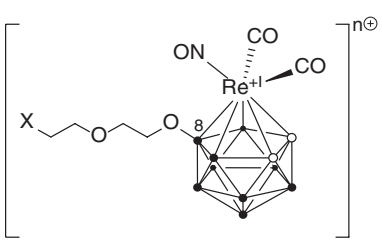


Fig. 4: WAY100635 [N-{2,1-[4-(2-methoxyphenyl)piperazinyl]ethyl}]-N-(2-pyridinyl)cyclohexanecarboxamide] (top left), a potent and selective 5-HT1A receptor antagonist, WAY–[CpRe(CO)$_3$] derivative (top right), and Valliant's Re^{I}- and $^{99m}Tc^{I}$-dicarbollide complexes **6–11**. The counterions (Na^{+}) of **6–11** are omitted.



12

12a: X = I, n = 0
12b: X = OTf, n = 0
(OTf = triflate)
12c: X = OBn, n = 0
(Bn = benzyl)
12d: X = OH, n = 0
12e: X = NH_3^+, n = 1

○ CH
● B or BH

Fig. 5: Rhenacarborane complexes **12a–e** with a nitrosyl ligand at the rhenium(I) center and an oxygen-based tether at the B(8) vertex [70, 71]. The $[BF_4]^-$ counterion of **12e** is omitted.

with the positive control WAY100635, a potent and selective 5-HT1A inhibitor [102], none of the tested rhenacarborane complexes showed competitive binding affinities with either of the serotonin receptors. Complex **10**, which bears an amide group between the cluster carbon atom and the aryl piperazine unit, showed instead high affinities for α_{1A}, α_{1D} and α_{2C} adrenergic receptors, in the low nanomolar range.

Modifying the B(8) vertex via introduction of a tailored tether gives access to rhenacarborane complexes which can easily be conjugated to biologically relevant vectors [70, 71]. First, a tether is regioselectively attached at B(8) of the $[Re(CO)_3(Cb)]^+$ core, followed by targeted modification of the terminal group of the tether according to the desired biological function of the complex. An example is the ring-opening reaction of the cyclic oxonium species [3,3,3-$(CO)_3$-*closo*-Re(8-$O(CH_2)_3CH_2$-3,1,2-$C_2B_9H_{10}$)] with an appropriate nucleophile (organic halides, LiOBn, $NMe_4OH \cdot 5H_2O$, AgOTf, etc.) [70]. Subsequent nitrosylation gave a variety of new complexes (Fig. 5) [71].

Complex **12a** could be labelled with ^{131}I (instead of non-radioactive iodine) and thus used as a marker for biodistribution studies on the rhenacarborane complex. Compounds **12d** and **12e** can be used for the synthesis of amino acid and peptide conjugates [71]. Furthermore, rhenacarborane complexes based on ^{188}Re could potentially be used as radiotherapeutic agents [29]. Therefore, the synthesis of Re^I- and $^{99m}Tc^I$-complexes is often carried out in parallel, with the idea of achieving a synergistic combination of target-selective radioimaging and radiotherapeutic agents (theranostic approach).

In summary, these examples of rhenacarboranes and technetacarboranes as potential selective radioimaging agents show that drug design strategies employed in medicinal organic and organometallic chemistry, such as the bioisosteric replacement approach, can be successfully extended also to metallacarborane-based medicinal chemistry. Furthermore, the inherent properties of the C_2B_9 clusters, e.g. regioselective functionalization, robustness, biocompatibility, etc., can lead to biologically active hybrid organic–inorganic compounds with unexpected binding modes to the biological target and unprecedented modulation of the biological activity of the parent organic compound [36, 60].

Conclusions

Several potential applications in medicine can be envisioned for metallacarboranes, ranging from BNCT to pharmacophores in drug design, to radio-imaging applications and combinations thereof. Furthermore, the dicarbollide ligand offers a wide range of structural diversity through different substitution patterns for various applications. While the presented studies are very promising, only a small number of known metallacarboranes has been tested for potential biological or medicinal applications. Thus, there is a vast potential for further research and improvement.

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