

## The Use of Carboranes in Cancer Drug Development

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### Abstract

Over the past decade, there has been a rising interest in the use of carboranes as a potential pharmacophoric moiety in the development of new drugs for the treatment of various types of cancer. The unique physical and chemical properties of carboranes make their use attractive in drug development. In several instances, the inclusion of carboranes into a drug structure has increased the agent's binding affinity, potency, or bioavailability. The purpose of this review is to highlight applications of carboranes to the medicinal chemistry of cancer.

**Keywords:** Carboranes; Cancer; Pharmacophoric; Drugs

### Introduction

Cancer is the second leading cause of death in the United States, exceeded only by heart disease. It is estimated that 1,685,210 new diagnoses and 595,690 American deaths will be due to cancer this year [1]. The fight against cancer involving early detection and new methods of treatment are crucial. Since their initial discovery during the 1960's, researchers have utilized carboranes in the search for new and effective treatments for cancer [2,3]. Formally named dicarbalo-dodecaboranes, carboranes containing two carbon atoms are icosahedral clusters containing carbon, boron, and hydrogen and exist as *ortho*-1, *meta*-2, and *para*-3 isomers, depending on the relative position of the two carbon atoms (Figure 1). Carboranes have a general formula of  $C_2B_{10}H_{12}$  and possess unique chemical and physical properties that suggest their potential use as a moiety for the design of new drug candidates with enhanced activity and/or target selectivity [3]. Some of these properties include high oxidative and thermal stability, hydrophobicity, and low toxicity [4]. Owing to their stability, carboranes also may increase the *in vivo* stability and bioavailability of pharmaceuticals that might otherwise rapidly metabolize [5].

Furthermore, selective chemical substitution of each carbon or boron atom in these clusters allows for their use as rigid, three dimensional scaffolds upon which to construct new drug molecules.

Nearly all past biomedical research involving carboranes has focused on their use in the design of boron delivery agents for Boron Neutron Capture Therapy (BNCT) [2]. This binary radiation therapy depends on the selective delivery of a high concentration of boron-10 atoms to targeted tissues. It is generally accepted that a minimum concentration of 30 ppm boron is required for successful BNCT therapy and this concentration is equivalent to the delivery of approximately  $10^9$  boron atoms to each targeted cell [6]. As BNCT human clinical trials have been attempted nearly continuously for the past five decades, there is a large body of literature associated with the use of carboranes for the development of BNCT boron agents. There are several good reviews and books covering that work [6-13]. While BNCT requires the delivery of large quantities of boron to diseased tissue, (requiring concentrations of boron in the low millimolar range) there is an increasing interest to use carboranes to synthesize new and highly potent drugs which operate at the opposite extreme of the concentration range, namely nanomolar, to picomolar [14].

*Ortho*-carborane and its carbon-functionalized derivatives may be prepared by reacting acetylene (or functionalized acetylene) with the decaborane derivative  $B_{10}H_{12}L_2$ , where L is a weak Lewis base, such as acetonitrile or diethylsulfide [3,15]. The acetylenes used in such reactions include a wide range of functional groups such as esters,

halides, carbamates, ethers, and nitro groups; however, such reactions are not successful in the presence of nucleophilic species such as alcohols, acids, or amines. Under an inert atmosphere, *ortho*-carborane will thermally isomerize to *meta*-carborane at temperatures ranging from 400-500°C and to the most thermodynamically stable isomer, *para*-carborane, at 600-700°C [2]. The CH groups in the carboranes are weakly acidic and can be deprotonated using a strong base, such as butyllithium to produce nucleophiles [5]. The pKa values for *ortho*-, *meta*- and *para*-carborane are 22.0, 25.6, and 26.8 respectively [16,17]. Separately, the boron vertices may be functionalized by reactive electrophiles. In turn, a wide range of carborane derivatives may be synthesized regioselectively without the need for complex protecting groups. Bases, such as pyrrolidine or fluoride, may be used to generate *nido*-carboranes 4, 5, and 6 (Figure 1) [18-22]. Such reactions convert the extremely hydrophobic *closo*-carboranes to the hydrophilic *nido*-carboranes [23-25].

### Carboranes as Pharmacophores

Pharmacophore approaches involving various ligand-based and structure-based methods have evolved to be one of the most successful concepts in medicinal chemistry. A pharmacophore was defined in 1909 by Ehrlich as a molecular framework that carries the essential features responsible for a drug's biological activity [26]. Considerable progress has been made on pharmacophore technology in the past two decades and has made pharmacophore approaches a major tool in drug discovery. Recent developments have expanded the boron carrier approach of carboranes for BNCT to be used as frameworks in developing newly improved pharmacophores.

Compared to aryl rings, the superior synthetic diversity and three dimensional complexities of carboranes allow them to be extremely useful in fine tuning the pharmacokinetics of newly developed drug candidates [5]. They are optimal for chemical modification by functionalizing the weakly acidic CH groups and boron atoms, and have the ability to employ various isomers (1-3) to optimize the binding affinity with other substituents [27]. The same preparation methods can

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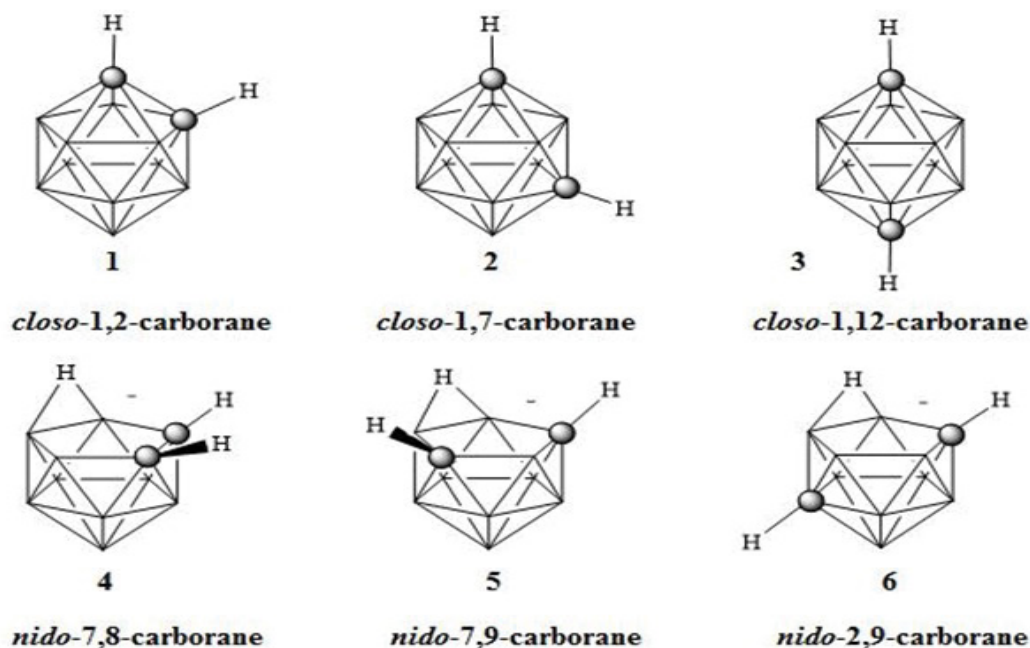


Figure 1: Ortho-(1), meta-(2), para-carborane (3), and nido-carboranes (4-6).

typically be used to synthesize any of the three carborane isomers, while in contrast the synthesis of the *ortho*, *meta*, and *para* isomers in aryl rings is much more challenging [5]. The *closo*-carboranes are both air and moisture stable and are known to possess “superhydrophobicity.” Their high partition coefficient values are known to surpass common bioisosteres such as aryl, cycloalkyl, and adamantyl groups [5]. Moreover, their high stability and low toxicity towards cells make them interesting compounds for therapeutic applications [2]. The interactions between carborane pharmacophores and the active sites of biological targets are often stronger than those of the aryl, cycloalkyl, or adamantyl pharmacophore counterparts. Several studies have been performed in an attempt to elucidate the underlying mechanism behind these interactions. In addition to the three dimensional shape and hydrophobicity which results in more points of interaction with the active site, the carborane cage can form dihydrogen bonds. The formation and characteristics of the dihydrogen bonds were explored by Fanfrik et al. through the use of molecular dynamic simulations between carboranes and various amino and nucleic acids [28]. Dihydrogen bonding, also named proton-hydride bonding, typically occurs between a positively charged hydrogen atom of a proton donor AH (A=N, O, S, C, halogen) and an MH proton acceptor (M=boron, alkali metal, or transition metal). In the case of carboranes and biological molecules these bonds form between NH--HB, CH--HB, and SH--HB. Such bonds are calculated to exhibit strong stabilization energies between 6.1 to 7.6 kcal mol<sup>-1</sup>, compared with 1 to 5 kcal mol<sup>-1</sup> for typical biomolecular hydrogen bond strengths, and H--H distances between 1.7 to 2.2 Å [28]. These interactions can potentially be used to improve the binding of carboranes over the more conventional pharmacophores containing aromatic groups such as aryl, or cycloalkyl, or adamantyl.

The successful design and implementation of a pharmacophore requires a careful study of the drug candidate's pharmacokinetics. In cancer therapy, the agent's biodistribution is an especially important characteristic. The design and use of carborane containing

pharmacophores is a relatively recent endeavour [29-31]. Past research efforts described in the literature explored the design of various carborane-based anti-cancer pharmacophores and their relative potencies. However, a majority of this preliminary work was limited to studies conducted *in vitro*. Nonetheless, there are some important examples in the literature where carborane containing pharmacophores were successfully translated into small animal models. While these experiments were not associated with cancer, it is interesting to note that the enzyme Nampt is highly implicated in many different cancers, including the most aggressive and the most refractory to treatment [32].

Much of what is known regarding the administration, biodistribution, tumor targeting and *in vivo* stability of carborane derivatives is derived from studies where carboranes were used to develop boron-rich agents for BNCT [7-13]. The concentration of boron required for effective BNCT is several orders of magnitude higher than those typically administered during conventional chemotherapy. However, many of the observations made during BNCT animal studies are still highly relevant to the use of carboranes as a pharmacophore in conventional drugs. Carboranes and substituted carboranes have been observed to be highly stable *in vivo*. For example, the molecule 2,4-( $\alpha,\beta$ -dihydroxyethyl) deuterioporphyrin (BOPP) is a porphyrin bearing four *ortho*-carboranyl moieties attached through ester linkages [33]. Several animal studies have been conducted using this molecule, most often using isotonic saline solutions of the potassium salt at a concentration of 10 mg/ml [33]. Solutions of BOPP containing BNCT-relevant doses, typically between 5-50 mg/kg, have been administered to both mice and rat models of glioma cancer through intraperitoneal, intravenous, or tail vein injections [34]. In those studies, doses as high as 200 mg/kg were well tolerated, causing no apparent signs of morbidity and no mortality. In a separate bio distribution study, 35 mg/kg of BOPP in saline was administered to dogs intravenously and the animals were monitored for up to 28 days [35]. The compound exhibited a long plasma half-life and accumulation in liver, lymph nodes, adrenal and kidney was observed.

Kreimann et al. explored the biodistribution of a carborane containing porphyrin in a therapeutic study using hamster mouth cancer models. In a multidose protocol they determined the boron uptake in a variety of tissues, as well as tumor, including normal mouth tissues, blood, liver, spleen, and brain over the course of several days [36]. They observed statistically significant differences in accumulation between tissues. The tumor/normal tissue maximum mean ratios were 11.9/1 after three days and the tumor/blood ratios of 235/1 after 4 days [36]. Liposomal formulations of carborane based lipid conjugates have also been extensively studied in both mouse xenograft and chemically induced hamster cancer models. For example, suspensions of small, boron-rich unilamellar vesicles were administered to hamsters as intravenous bolus injections and the distribution of boron was measured in several tissues over a 72-hour period [37]. A long plasma half-life was observed (approximately 30 hours), along with high tumor, liver, and spleen accumulations. At 54 hours post injection, both the tumor accumulation and specificity were remarkable, with a tumor/normal surrounding tissue ratio of nearly 28:1 [37]. Boron-rich carborane-containing oligomers, referred to as Oligomeric Phosphate Diesters (OPDs) were shown to accumulate in tumor tissue when administered to mice bearing EMT6 tumors via tail vein injections [38].

### Estrogen receptor

It has been apparent for close to a century that the steroid estrogen has played a major role in breast cancer [39]. When molecules, such as estrogen hormones, bind to the ligand binding domain of the estrogen receptor the protein forms a dimer. The dimerized form of the estrogen receptor binds to DNA promoter elements which results in the initiation of gene transcription [2,5]. Antagonism of the estrogen receptor is a mechanism used for the treatment of hormone responsive cancers [40-44]. The molecules depicted in Figure 2 represent the hormone 17  $\beta$ -estradiol 7 and the estrogen receptor alpha (ER $\alpha$ ) antagonist's tamoxifen 8 and 4-hydroxytamoxifen 9. Endo et al. synthesized a

number of carborane containing estrogen receptor agonists 10a-g and antagonists 11-12 depicted in Figure 2 [40,41].

The activities of the estrogen agonist's 10a-g were analysed, the carborane derivative 10c exhibited at least 10-fold greater potency than 17 $\beta$ -estradiol 7 both *in vitro* and *in vivo* [41].

Remarkably, in comparison with the natural molecule, these carborane containing agonists are quite simple in both structure and synthesis, containing no carbon stereocenters. Based on the inhibition of ER $\alpha$ , derivative 12 demonstrated the greatest antiestrogen response, exhibiting an activity that was comparable to tamoxifen [40].

The estrogenic response of these compounds in the uterine and bone tissues of ovariectomized mice was measured. The assays measured the inhibition of 17 $\beta$ -estradiol binding to the ER $\alpha$  receptor at concentrations of  $1 \times 10^{-9}$  M. The binding affinity for the ER $\alpha$  receptor for 7, 11, and 12 were 0.1 nM, 1.0 nM, and 60 nM respectively [40]. The most potent inhibition of the transcriptional response to 17 $\beta$ -estradiol was exhibited by 12, thus the authors noted that the antagonistic response does not directly correlate with the drugs binding affinity. They also noted that while inducing an agonistic effect on the estrogen receptor in the bone tissue of the mice, 11 exhibited antagonistic effects on the estrogen receptor in the uterine tissue. This observation supports the potential of using similar carborane-based compounds for the long term prevention of estrogen dependent malignancy without inducing negative anti-estrogenic responses such as bone loss [40].

### Dihydrofolate reductase

Folate metabolism is involved in processes critical in cell proliferation and DNA synthesis. The enzyme Dihydrofolate Reductase (DHFR) regulates cellular levels of tetrahydrofolate [3]. The dysregulation of the folate metabolic process reduces the metabolism of purine and pyrimidine, as well as the methylation of DNA, each of which are crucial processes in the cells [45]. Thus, the inhibition of the

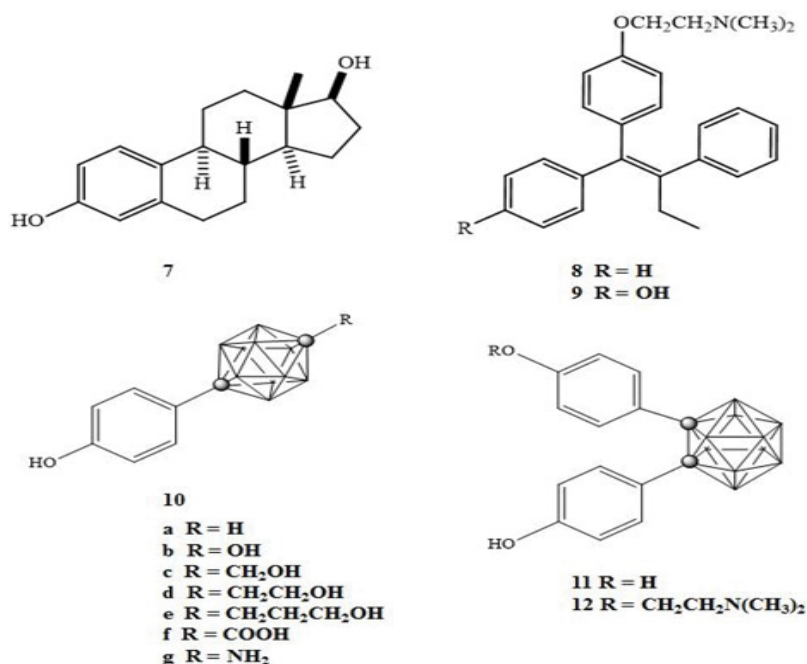


Figure 2: Hormone and ER $\alpha$  antagonists (7-9), estrogen receptor agonist carborane derivatives (10a-g), and estrogen receptor antagonist carborane derivatives (11-12).

dihydrofolate reductase enzyme is an area of much interest for cancer therapy [46].

Known inhibitors of this enzyme include the anticancer agent methotrexate (MXT) 13 and the antimicrobial agent trimethoprim (TMP) 14 (Figure 3) [45]. Also depicted in Figure 3 is the carborane containing inhibitor 15. The DHFR inhibition activity of these compounds was measured on various cancer cell lines and their half maximal inhibitory concentrations ( $IC_{50}$ ) were reported by Reynolds et al. [47]. The *closo*-carborane derivative 15 demonstrated up to 10-fold and 100-fold greater activity in comparison with MXT 13 and TMP 14 respectively, for several of the cancer cell lines [47]. The increased activity for these carborane containing drug candidates offers excellent potential in the treatment of a variety of cancers. These preliminary *in vitro* results suggest that further investigations of these small molecules are warranted using small animal models.

### Translocator protein

The Translocator Protein, (TSPO) also referred to as the peripheral benzodiazepine receptor, regulates the transmembrane functions of the mitochondria. The translocator protein has been shown to be overexpressed in tumor cells, making this an intriguing target for selective therapeutic and diagnostic applications [48]. Normally, TSPO actively opens and closes the pore in the mitochondria membrane. However, if the pore remains open for prolonged periods of time apoptotic factors can escape the mitochondria and enter the cytosol. This can lead to swelling of the mitochondrial matrix, interference with both ATP synthesis and oxidative phosphorylation, leading to apoptosis and necrosis of the cell [49].

Although this protein is a potential target for therapeutic agents, a majority of the work described in the literature focuses on targeting applications of the TSPO. Derivatives of the TSPO binding ligands have been synthesized and their  $IC_{50}$  concentrations were reported by Cappelli et al. [50]. The molecules depicted in Figure 4 represent PK11195 TSPO receptor ligand 16, isoquinolinecarboxamide derivative

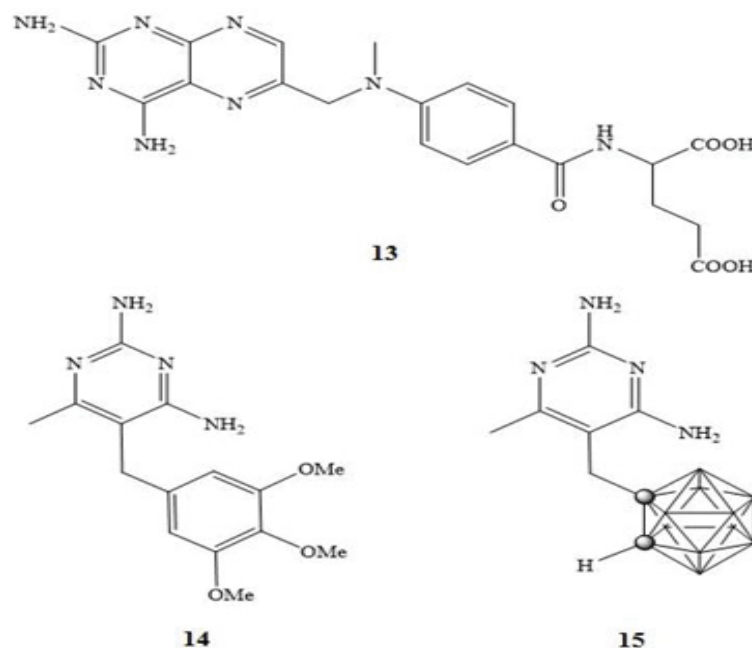
17, and the carborane containing derivative 18. The binding constants and  $IC_{50}$  values for these ligands were 2.5 nM, 0.11 nM, and 73 nM for 16, 17, and 18 respectively. Although the TSPO binding strength and  $IC_{50}$  values were lower for the carborane derivative of 18, the carborane cage has the potential for incorporation of additional diagnostic and therapeutic moieties [50].

### Protein kinase C

Protein Kinase C (PKC) is a signal transduction protein involved in tumor promotion activity when bound to phorbol esters; potent modulators of PKC are thus appealing anticancer targets [51]. 2,3,51 PKC has been shown to modulate proliferation of cancer cells, either increasing or decreasing, dependent on the type of cancer.51 Many studies have shown that PKC acts as a promoter of cancer cell proliferation and a suppressor of apoptosis.51 PKC inhibitors such as benzolactam-V8-310 (BL-V8-310) 19, depicted in Figure 5, have been studied both *in vivo* and *in vitro* and their effects on various cancer cell lines have been reported [52]. In many types of cancers, inhibition of PKC resulted in a decrease of tumor growth. It is believed that this is perhaps the result of many processes including: reduced angiogenesis, increases in apoptosis, and decreases in cell proliferation [51,52]. The comparative dose response and PKC binding constants for 19 and its carborane derivative 20a-c were analyzed using bioassays of HL-60 cells. The median effective dose ( $ED_{50}$ ) values for 19 and 20 were  $5 \times 10^{-9}$  M and  $7 \times 10^{-9}$  M respectively. The binding constants for 19 and 20a-c reported as  $K_i=1.8$  nM and  $K_i=2.0$  nM, 1.4 nM, and 1.8 12 nM [52]. The  $ED_{50}$  concentrations and binding constants illustrate the potency of these carborane derivatives as PKC inhibitors, further demonstrating the potential use of carboranes in the medicinal chemistry of new molecules for the treatment of cancer.

### Prostate specific membrane antigen

A membrane bound glycoprotein known as Prostate Specific Membrane Antigen (PSMA) is overexpressed in prostate cancer as well as newly formed vascular networks of most tumors. This cell surface



**Figure 3:** MXT (13), TMP (14), and carborane DHFR inhibitor (15).



protein is a target for imaging and therapy because it is expressed at levels 1,000-fold greater than in other tissues. Through immuno-fluorescence analysis, it has been shown biochemically that PSMA or a PSMA-antibody complex internalizes by receptor mediated endocytosis through clathrin coated pits [53].

Much work has been done in developing potent ligands for PSMA through the use of carboranes; El-Zaria et al. compared *closo*-, *nido*-, and *iodo*-carborane conjugates *in vitro* against known PSMA inhibitor 2-(Phosphonomethyl)-Pentanedioic Acid (PMPA) [54]. The water soluble iodinated carborane cluster 21 (Figure 6) exhibited the highest affinity with an  $IC_{50}$  concentration of 73.2 nM which was comparable to PMPA with a value of 63.9 nM [55-58]. However, *in vivo* studies exhibited lower than desired selectivity due to off target binding to areas such as the liver and gall bladder [54].

The initial diagnosis of prostate cancer is dependent on androgen levels through the androgen receptor (AR). Androgen induced transcriptional activity involves binding of testosterone 22 and 5 $\alpha$ -dihydrotestosterone (DHT) 23 to AR. The interaction of AR with coregulators and phosphorylation of AR results in the modulation of AR transcriptional activity. Inhibition of AR and the resultant reduction of serum androgens is the basis of endocrine therapy for the treatment of prostate cancer. This has been achieved clinically using the antagonists flutamide 24 and (R)-bicalutamide 26 [55]. However, androgen ablation therapy ultimately fails and prostate cancer progresses to a hormone refractory state capable of transcriptional activity. Clinical evidence suggests the advancement of prostate cancer through several processes. These include mutations of AR that enable it to become transcriptionally active in response to ligands, alterations in expression of AR coregulators, and alterations of normal androgen axis by dysregulation of AR activity. Therefore, inhibition of AR activity and reduction of DHT concentrations (androgen ablation) may delay cancer progression [56-58].

Potential drugs that could be used to treat AR disorders include novel biologically active non-steroidal AR ligands containing *closo*-carboranes [3,44]. Goto et al. investigated *para*-carborane containing ligands in developing potent AR antagonists as depicted in Figure 7 [59]. Compounds 27 and 28 exhibited lower  $IC_{50}$  concentrations of  $3.8 \times 10^{-7}$  M and  $4.2 \times 10^{-7}$  M, respectively, against LNCaP cells in comparison to the clinically used AR full antagonist (R)-bicalutamide 26 with an  $IC_{50}$  of  $8.7 \times 10^{-7}$  M [59].

Fujii et al. developed compounds demonstrating anti-androgenic activity through novel derivatives of ten-vertex and twelve-vertex *para*-carborane [55]. These were tested against androgen-dependent SC-3 cells. One of the most potent ten-vertex derivatives 29a (Figure 7) bearing a 3-cyano group exhibited a higher potency than hydroxyflutamide 25 with an  $IC_{50}$  of  $7.6 \times 10^{-7}$  M [55]. Derivative 29b bearing a 4-cyano group exhibited lower affinity with an  $IC_{50}$  of  $1.6 \times 10^{-5}$  M. With regard to cyclohexanone derivatives, 30 exhibited an  $IC_{50}$  concentration of  $6.1 \times 10^{-6}$  M. The twelve-vertex derivatives 31a, 31b, and 32 exhibited  $IC_{50}$  concentrations of  $1.9 \times 10^{-6}$  M,  $1.0 \times 10^{-5}$  M, and  $9.7 \times 10^{-6}$  M, respectively. The study was a further demonstration of the potential use of carboranes as a hydrophobic core structure of biologically active molecules [55].

### Purinergic receptors

Purinergic receptors are signaling receptors involved in the process of neurotransmission. Activation of a specific subtype of the purinergic receptor results in the influx of  $Na^+$  and  $Ca^{2+}$  across the cell membrane and the release of  $K^+$  ions. The P2Y and P2X receptor subtypes have

been linked to processes such as cell proliferation, differentiation, and apoptosis [60]. When exposed to high concentrations of ATP for a sufficient period of time, the cation channel of the P2X7 receptor can be converted to a nonspecific transmembrane pore that allows the passage of small molecules as large as 900 daltons [61]. This process, along with the involvement of the caspase enzyme system, has been associated with apoptosis of the cell [60,62].

The P2X7 receptor has been implicated in ATP mediated cell death, regulation of receptor trafficking, and inflammation; it is a potential target for cancer therapies. An agonistic response of the receptor is required to facilitate apoptosis. BzATP is one such molecule that has a larger binding constant than that of ATP to the binding site of the P2X7 receptor and has been used in assays determining the state of the transmembrane pore associated with P2X7 activation [60,63]. Adenosine 33 and 2'-deoxyadenosine 34 are known agonists of the P2X7 receptor. Olejniczak et al. prepared the carborane derivatives 35-37 shown in Figure 8 [64]. The carborane derivatives 35-47 each had a greater agonistic effect than 33 or 34 [65]. This increase in agonistic effect improves the potential of drug candidates targeting the purinergic receptors for cancer treatment. However, establishing their potencies using small animal experiments will be necessary.

### Nicotinamide phosphoribosyl transferase

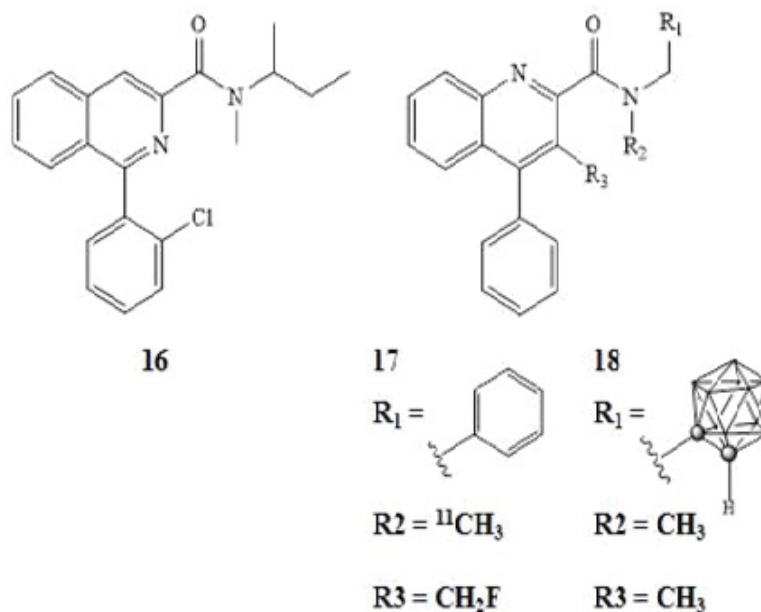
NAD<sup>+</sup> is a vital cofactor used throughout cellular respiration. In addition to its role in glycolysis, the TCA cycle, and the reaction linking this cycle with oxidative phosphorylation, NAD<sup>+</sup> is consumed as a substrate by more than 300 known NAD-dependent enzymes. Mammals possess a unique NAD<sup>+</sup> recycling pathway, which converts nicotinamide to NAD<sup>+</sup>. The first and rate-limiting step in this pathway is catalyzed by the enzyme Nicotinamide phosphoribosyltransferase (Nampt). Nampt has been shown to be upregulated in many/most cancers [66-73] and its overexpression is highest in aggressive and refractory cancers, making it a promising target for the treatment of various cancers [74,75].

FK866 38 is the first known small molecule inhibitor of Nampt and has been investigated in several Phase I/II clinical trials against several cancers [76,77]. Recently, we reported the synthesis and anticancer activity of several carborane-containing derivatives, where the benzoylpiperazine of 38 was replaced by a number of different moieties, including adamantyl, *ortho*-, *meta*-, or *para*-carborane [78-80]. Of the new agents reported, a derivative containing a *meta*-carborane 39 exhibited a 100-fold greater inhibition of Nampt and a 10-fold increase in potency with respect to FK866 in several human cancer cell lines *in vitro* (Figure 9).

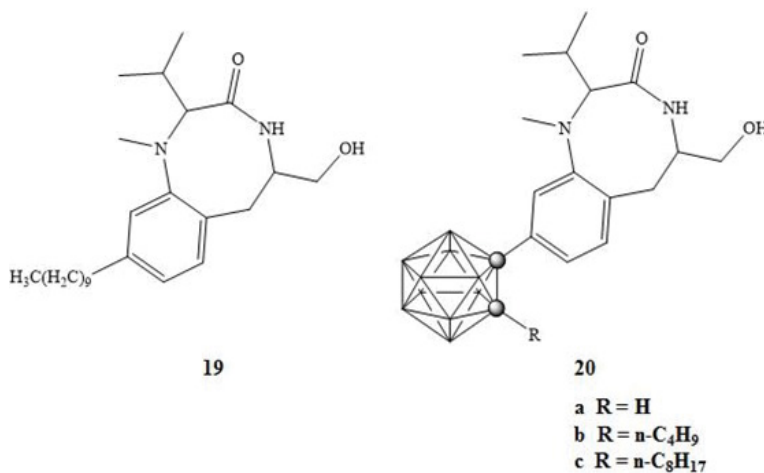
The carborane-based inhibitor 39 demonstrated low, to sub-nanomolar potencies against human lung, colon, and breast cancers *in vitro* and the hydrophobic carborane moiety was shown to significantly increase agent potency over other, similarly sized organic moieties [78-80]. Recently, the synthesis of a new derivative of 39, bearing a hydroxymethyl group attached to the carborane cluster was reported, allowing for the covalent attachment of the drug to various targeting groups through the use of facile click chemistry reactions.

### Hypoxia inducible factors

The relationship between hypoxia inducible factors HIF-1 $\alpha$  and HIF-2 $\alpha$  has been an area of much interest. The levels of these proteins are closely related to the oxygen content of the cells [81]. These proteins are expressed in low oxygen environments and have been linked to angiogenesis [82]. Due to the higher metabolic rates of cancer cells,



**Figure 4:** PK11195 TPSO receptor ligand (16), isoquinolinecarboxamide derivative (17), and carborane derivative (18).

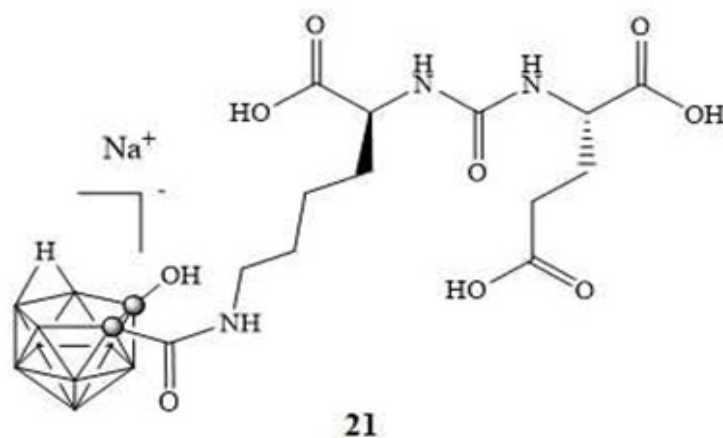


**Figure 5:** PKC inhibitor BL-V8-310 (19) and carborane derivative (20a-c).

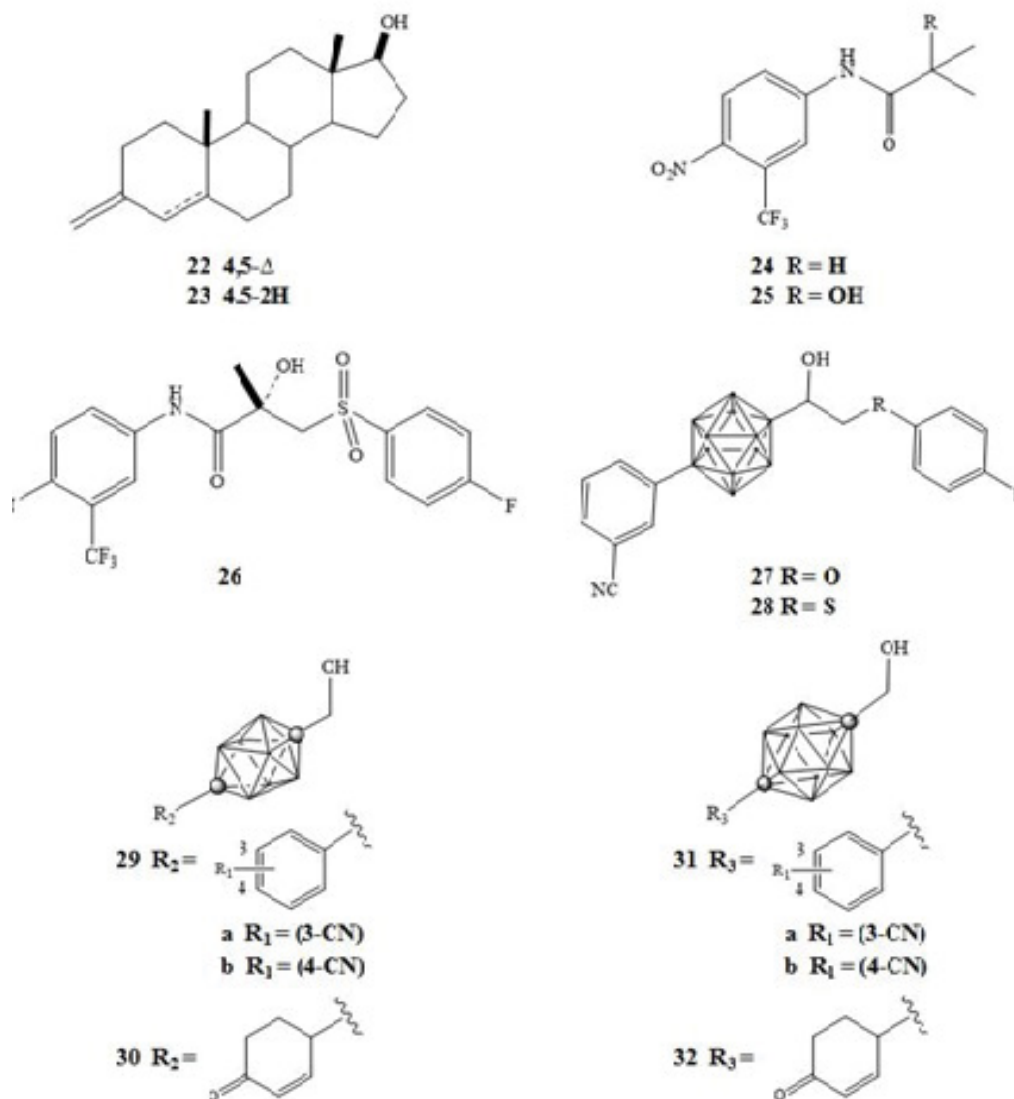
tumors typically have lower oxygen content than normal tissues, resulting in increased levels of HIF-1 $\alpha$  and HIF-2 $\alpha$  in cancerous tissues [81]. Others have probed the relationship between tumor growth and metastasis and many of these studies suggest that these proteins have a profound effect on the survival and growth of cancerous tissues [82]. This protein has therefore been a target of interest for the treatment of various types of cancer. Nakamura et al. developed carboranyl derivatives of the LW6 drug molecule 40 depicted in Figure 10 for HIF-1 inhibition. The activity of these molecules was measured in HeLa cells and the growth inhibition  $\text{IC}_{50}$  concentrations were reported [83]. The carborane derivative GN26361 41 exhibited a 10-fold increase in activity compared with LW6 40. The results of this study support the use of carborane derivatives for the design of inhibitors of this protein. In principle, molecules such as these could be used to combat the angiogenesis of growing tumors [84,85].

### Tumor necrosis factor $\alpha$

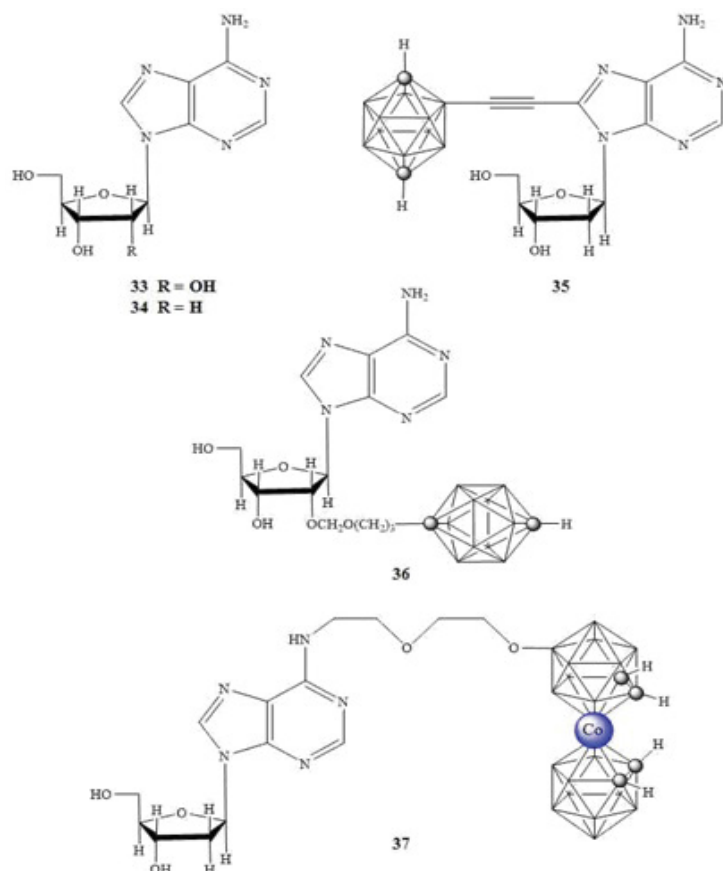
The Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ) is a protein involved in the early steps of a complex pathway that has been linked to inflammatory responses and cell survival including apoptosis. There are multiple ways in which the TNF- $\alpha$  protein can promote tumor growth. The TNF- $\alpha$  interacts with adjacent cells in an autocrine manner. Autocrine processes have been linked to increased damage of genetic material in malignant cells or cells with malignant potential, as well as the improved survivability of malignant cells. The expression of TNF- $\alpha$  leads to the production of cytokines and chemokines which when combined, can lead to an angiogenic response [2,86]. The inhibition of this protein and the resulting effects on cancer cell growth have been explored [87,88]. Phthalimides are regulators of the TNF- $\alpha$  protein; under specific conditions, these molecules have been shown to inhibit the production



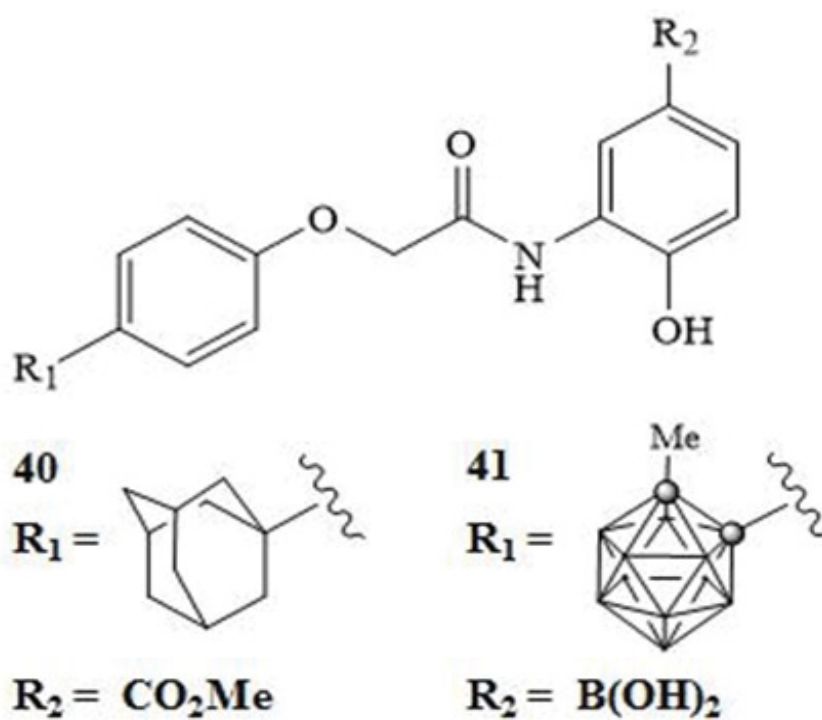
**Figure 6:** Water soluble iodinated carborane cluster.



**Figure 7:** Testosterone (22), DHT (23), flutamide (24), hydroxyflutamide (25), (R)-bicalutamide (26), pure AR antagonists with *para*-carborane cage as hydrophobic pharmacophore (27-28), ten-vertex carborane derivatives (29-30), and twelve-vertex carborane derivatives (31-32).



**Figure 8:** Purinergic receptor agonists adenosine (33) and 2'-deoxyadenosine (34), and carborane containing P2X7 agonist derivatives (35-37).



**Figure 9:** FK866 (38) and *meta*-carborane derivative of FK866 (39).



of TNF- $\alpha$  and therefore have been explored to treat a variety of diseases including cancers [86]. The N-phenylphthalimides 42a-c and adamantyl substituted phthalimide 43 drug molecules along with carborane derivatives 21 of these phthalimide compounds, depicted in Figure 11, were prepared and TNF- $\alpha$  inhibition was measured [89]. The N-(1,2-dicarba-closo-dodecaboran-1-yl-methyl)phthalimide 44 and the N-(1,2-dicarba-closo-dodecaboran-1-yl)-4,5,6,7-tetra-fluorophthalimide 45 were analyzed to determine their relative potency for TNF- $\alpha$  inhibition [89]. The carborane derivative 45 demonstrated a 100-fold greater inhibitory response when compared with 42a-c and 43 [89]. The combination of significantly greater inhibitory activity and less complex synthesis of the carborane containing phthalimide derivative in comparison with 42a-c suggests that additional work, including small animal studies is warranted.

### Retinoic acid receptor and retinoid X receptor

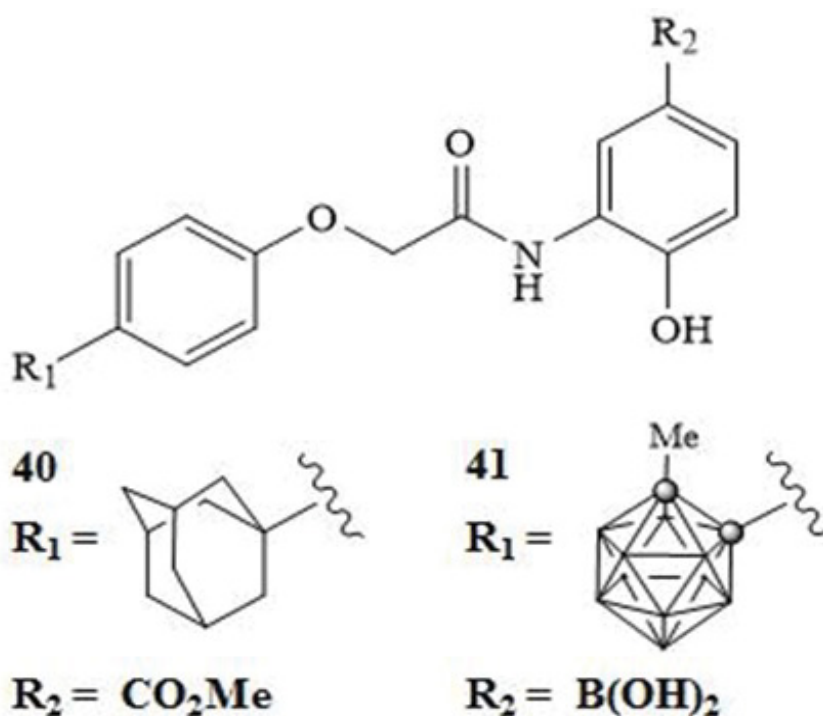
The Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR) have recently been implicated in the regulation of gene networks involved in the control of cell growth, differentiation, survival, and death. These two receptor proteins, when bound to their corresponding ligands, form the RAR-RXR heterodimer [3,90]. The RAR and RXR binding ligands include all-trans-retinoic acid 46 and 9-cis-retinoic acid 49, respectively. The RAR-RXR heterodimer can be activated by an RAR agonist, such as AM80 47, but not by an RXR agonist. The presence of an RXR agonist, such as PA024 48, can increase activity of an RAR agonist and thus promote transcriptional activity of the RAR-RXR heterodimer, even when RAR agonist concentrations are low [90,91]. The retinoid X receptor can form heterodimers with other nuclear receptors; some of these heterodimers can become transcriptionally active in the presence of RXR ligands alone [92].

The amount of cell differentiation and the half maximal effective concentrations (EC<sub>50</sub>) of the carborane containing agonist derivatives

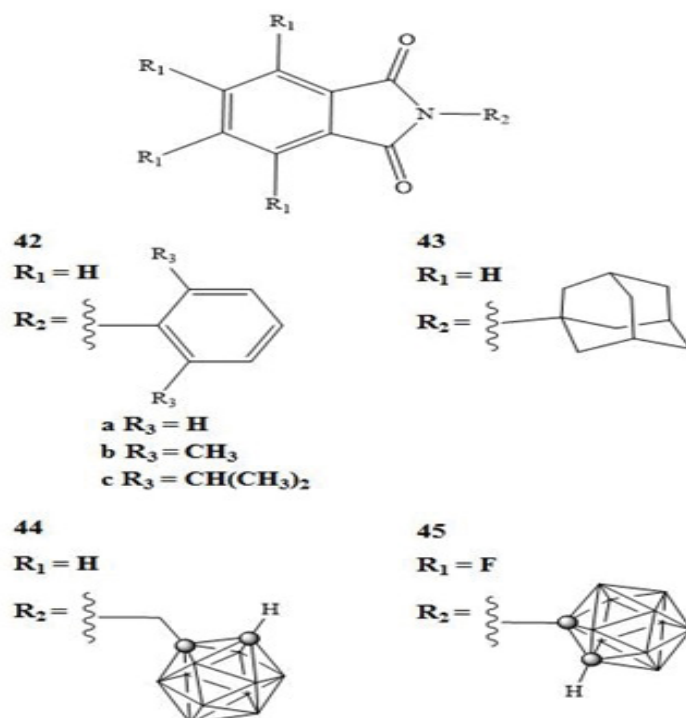
51a-f were reported [91]. The EC<sub>50</sub> for the carborane derivative 51d shown in Figure 12 was  $1.5 \times 10^{-9}$  M, which is comparable to the activity of the all-trans-retinoic acid [91]. The activities of carborane RXR antagonists 52a-e were measured in HL<sup>60</sup> cancer cells in the presence of the RXR and RAR binding ligands Am80 and PA024, both at concentrations of  $1 \times 10^{-10}$  M. The inhibition of cell differentiation was measured and EC<sub>50</sub> concentrations were reported. The carborane derivative 52b exhibited higher potency than the RXR antagonist PA452 50 by almost an order of magnitude, suggesting their potential as anticancer agents [91]. Additional studies are warranted using small animal tumor models.

### Future Directions

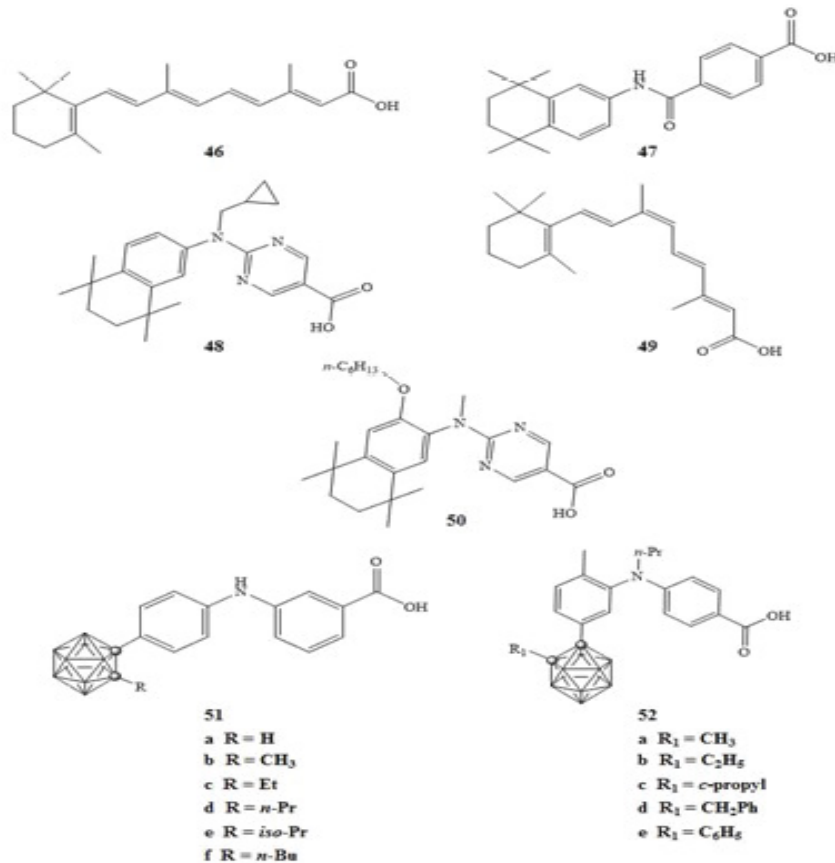
The initial research exploring the use of carboranes as pharmacophores has clearly demonstrated their potential to improve the binding and potency of small molecule anticancer agents. Their synthetic diversity and chemical stability make carboranes powerful agents for use in drug discovery. Carboranes show great promise in their ability to improve the biological activity of small molecules. However, much work remains to be completed before this research can be translated into the clinics. The biodistribution studies of carborane-based BNCT agents have shown favorable accumulation in tumor tissues [33-38]. Although these results are encouraging, the biodistribution of carborane pharmacophores needs to be extensively studied at concentrations relevant to those typically employed for pharmaceuticals in order to progress these agents towards clinical trials. Further developments in modern techniques will allow researchers to more rapidly prepare and identify potent carborane derivatives. We believe that success in advancing potent and effective pharmacophores will be instrumental in the treatment of a variety of diseases. While much work is still required in this emerging field, the use of carboranes as pharmacophores is an exciting and promising area in the fight against cancer.



**Figure 10:** Hypoxia inducible factor HIF-1 $\alpha$  inhibitor LW6 (40) and carborane derivative GN26361 (41).



**Figure 11:** Phthalimide compounds used in TNF- $\alpha$  regulation (42-43) and carborane derivatives of phthalimides (44-45).



**Figure 12:** RAR binding ligand all-*trans*-retinoic acid (46), RAR agonist Am80 (47), RXR agonist PA024 (48), RXR binding ligand 9-*cis*-retinoic acid (49), RXR antagonists PA452 (50), carborane derivatives of RAR agonists (51a-f), and carborane derivatives of RXR antagonists (52a-e).

## References

- Siegel RL, Miller KD, Jemal A (2016) Cancer statistics. *Cancer J Clin* 66: 7-30.
- Valliant JF, Guenther KJ, King AS, Morel P, Schaffer P, et al. (2002) The medicinal chemistry of carboranes. *Coord Chem Rev* 232: 173-230.
- Issa F, Kassiou M, Rendina LM (2011) Boron in drug discovery: carboranes as unique pharmacophores in biologically active compounds. *Chem Rev* 111: 5701-5722.
- Fein MM, Bobinski J, Mayes N, Schwartz N, Cohen MS (1963) Carboranes I: The preparation and chemistry of 1-isopropenylcarborane and its derivatives (a new family of stable clovoboranes). *Inorg Chem* 2: 1111-1115.
- Armstrong AF, Valliant JF (2007) The bioinorganic and medicinal chemistry of carboranes: from new drug discovery to molecular imaging and therapy. *Dalton Trans* 38: 4240-4251.
- Grimes RN (2016) Carboranes. 3rd edn. Academic Press, London, San Diego, Cambridge, Oxford.
- Barth RF, Coderre JA, Vicente MG, Blue TE (2005) Boron neutron capture therapy of cancer: current status and future prospects. *Clin Cancer Res* 11: 3987-4002.
- Barth RF, Soloway AH, Fairchild RG (1990) Boron neutron capture therapy for cancer. *Sci Am* 263: 100-107.
- Laramore G (1997) The use of neutrons in cancer therapy: a historical perspective through the modern era. *Semin Oncol* 24: 672-685.
- Coderre JA, Morris GM (1999) The radiation biology of boron neutron capture therapy. *Radiat Res* 151: 1-18.
- Moss RL (2014) Critical review, with an optimistic outlook, on Boron Neutron Capture Therapy (BNCT). *Appl Radiat Isot* 88: 2-11.
- Hawthorne MF, Lee MW (2003) A critical assessment of boron target compounds for boron neutron capture therapy. *J Neurooncol* 62: 33-45.
- Hosmane NS, Maguire JA, Zhu Y (2012) Boron and gadolinium neutron capture therapy for cancer treatment. *World Scientific*.
- Grimes RN (2011) Carboranes. 2nd edn. Academic Press: London, San Diego, Cambridge, Oxford, pp: 1053-1082.
- Stanko VI, Chapovskii YA, Brattsev VA, Zakharkin LI (1965) The Chemistry of decaborane and its derivatives. *Russ Chem Rev* 34: 424-439.
- Kashin AN, Butin KP, Stanko VI, Beletskaya IP (1969) Acidity of ortho-, meta-, and para-boranes. *Bull Acad Sci USSR, Div Chem Sci* 18: 1775-1777.
- Leites LA (1992) Vibrational spectroscopy of carboranes and parent boranes and its capabilities in carborane chemistry. *Chem Rev* 92: 279-323.
- Wiesboeck RA, Hawthorne MF (1964) Dicarbaundecaborane 13 and derivatives. *J Am Chem Soc* 86: 1642-1643.
- Hawthorne MF, Young DC, Garrett PM, Owen DA, Schwerin SG, et al. (1968) The preparation and characterization of the (3)-1,2- and (3)-1,7-dicarbadodecahydroundecaborate(-1) ions. *J Am Chem Soc* 90: 862-868.
- Zakharkin LI, Kirillova VS (1975) Cleavage of o-carboranes to (3)-1,2-dicarbaundecaborates by amines. *Bull Acad Sci USSR, Div Chem Sci* 24: 2484-2486.
- Maurer JL, Serino AJ, Hawthorne MF (1988) Hydrophilically augmented glucosyl carborane derivatives for incorporation in antibody conjugation reagents. *Organometallics* 7: 2519-2524.
- Tomita H, Luu H, Onak T (1991) Cage opening of parent closo cage carboranes with fluoride ion: formation of 5-fluoro-hexahydro-nido-2,4-dicarbahexaborate(1-) ([5-F-nido-2,4-C2B4H6]-). *Inorg Chem* 30: 812-815.
- Davidson MG, Hibbert TG, Howard JA, Mackinnon A, Wade K (1996) Definitive crystal structures of ortho-, meta- and para-carboranes: supramolecular structures directed solely by C-H...O hydrogen bonding to hmpa. *Chem Commun* 19: 2285-2286.
- Hermanek S (1992) Boron-11 NMR spectra of boranes, main-group heteroboranes, and substituted derivatives. Factors influencing chemical shifts of skeletal atoms. *Chem Rev* 92: 325-362.
- Yamamoto K, Endo Y (2001) Utility of boron clusters for drug design. Hansch-fujita hydrophobic parameters  $\pi$  of dicarba-closo-dodecaboranyl groups. *Bioorg Med Chem Lett* 11: 2389-2392.
- Yang SY (2010) Pharmacophore modelling and applications in drug discovery: challenges and recent advances. *Drug Discov Today* 15: 444-450.
- Frank R, Ahrens V, Boehnke S, Hofmann S, Kellert M, et al. (2015) Carboranes-more than just phenyl mimetics. *Pure Appl Chem* 87: 163-171.
- Fanfrik J, Lepsik M, Horinek D, Havlas Z, Hobza P (2006) Interaction of carboranes with biomolecules: formation of dihydrogen bonds. *Chemphyschem Eur J Chem Phys Physical Chem* 7: 1100-1105.
- Fanfrik J, Hnyk D, Lepsik M, Hobza P (2007) Interaction of heteroboranes with biomolecules. *Phys Chem Chem Phys* 9: 2085-2093.
- Fanfrik J, Holub J, Ruzickova Z, Rezac J, Lane PD, et al. (2016) Competition between halogen, hydrogen and dihydrogen bonding in brominated carboranes. *Chem Phys Chem* 17: 3373-3376.
- Pecina A, Lepsik M, Rezac J, Brynda J, Mader P, et al. (2013) QM/MM calculations reveal the different nature of the interaction of two carborane-based sulfamide inhibitors of human carbonic anhydrase II. *The Journal of Physical Chemistry B* 117: 16096-16104.
- Huang P, Lee MW, Sadrafi K, Heruth DP, Zhang LQ, et al. (2017) MC-PPEA as a new and more potent inhibitor of CLP-induced sepsis and pulmonary inflammation than FK866. *Drug Des Devel Ther* 11: 629-641.
- Kahl SB, Koo MS (1990) Synthesis of tetrakis-carborane-carboxylate esters of 2, 4-bis-( $\alpha$ ,  $\beta$ -dihydroxyethyl)-deuteroporphyrin IX. *Journal of the Chemical Society, Chemical Communications* 1: 1769-1771.
- Hill JS, Kahl SB, Syll SS, Nakamura Y, Koo M, et al. (1995) Selective tumor kill of cerebral glioma by photodynamic therapy using a boronated porphyrin photosensitizer. *Proc Natl Acad Sci* 92: 12126-12130.
- Tibbitts J, Sambol NC, Fike JR, Bauer WF, Kahl SB (2000) Plasma pharmacokinetics and tissue biodistribution of boron following administration of a boronated porphyrin in dogs. *J Pharm Sci* 89: 469-477.
- Kreimann EL, Miura M, Itoiz ME, Heber E, Garavaglia RN, et al. (2003) Biodistribution of a carborane-containing porphyrin as a targeting agent for Boron Neutron Capture Therapy of oral cancer in the hamster cheek pouch. *Arch Oral Biol* 48: 223-232.
- Heber E, Kueffer P, Lee MW, Hawthorne MF, Garabalino M, et al. (2012) Boron delivery with liposomes for boron neutron capture therapy (BNCT): biodistribution studies in an experimental model of oral cancer demonstrating therapeutic potential. *Rad Environ Biophys* 51: 195-204.
- Lee MW, Shelly K, Kane R, Hawthorne MF (2006) Continued biological investigations of boron-rich oligomeric phosphate diesters (OPDs): Tumor-selective boron agents for BNCT. *Adv neutron capture ther, Proceedings of 12th international congress on neutron capture therapy, Japan*.
- Sommer S, Fuqua SA (2001) Estrogen receptor and breast cancer. *Semin Cancer Biol* 11: 339-352.
- Endo Y, Yoshimi T, Miyaura C (2009) Boron clusters for medicinal drug design: Selective estrogen receptor modulators bearing carborane. *Pure Appl Chem* 75: 1197-1205.
- Endo Y, Iijima T, Yamakoshi Y, Fukasawa H, Miyaura C, et al. (2001) Potent estrogen agonists based on carborane as a hydrophobic skeletal structure. A new medicinal application of boron clusters. *Chem Biol* 8: 341-355.
- Endo Y, Yamamoto K, Kagechika H (2003) Utility of boron clusters for drug design. Relation between estrogen receptor binding affinity and hydrophobicity of phenols bearing various types of carboranyl groups. *Bioorg Med Chem Lett* 13: 4089-4092.
- Kwon O, Jung YW, Jee JG, Byun Y (2013) Facile Docking and Scoring Studies of Carborane Ligands with Estrogen Receptor. *Bull Korean Chem Soc* 34: 1051-1054.
- Hosmane NS (2016) Boron Science: New Technologies and Applications; CRC Press, Boca Raton, United States.
- Fotoohi K, Jansen G, Assaraf YG, Rothen L, Stark M, et al. (2004) Disparate mechanisms of antifolate resistance provoked by methotrexate and its metabolite 7-hydroxymethotrexate in leukemia cells: implications for efficacy of methotrexate therapy. *Blood* 104: 4194-4201.
- Ryan BM, Weir DG (2001) Relevance of folate metabolism in the pathogenesis of colorectal cancer. *J Lab Clin Med* 138: 164-176.

47. Reynolds RC, Campbell SR, Fairchild RG, Kisliuk RL, Micca PL, et al. (2007) Novel Boron-Containing, Nonclassical Antifolates: Synthesis and Preliminary Biological and Structural Evaluation. *J Med Chem* 50: 3283-3289.
48. Austin CJ, Kahlert J, Kassiou M, Rendina LM (2013) The translocator protein (TSPO): a novel target for cancer chemotherapy. *Int J Biochem Cell Biol* 45: 1212-1216.
49. Mukherjee S, Das SK (2012) Translocator protein (TSPO) in breast cancer. *Curr Mol Med* 12: 443-457.
50. Cappelli A, Valenti S, Mancini A, Giuliani G, Anzini M, et al. (2010) Carborane-conjugated 2-quinolinecarboxamide ligands of the translocator protein for boron neutron capture therapy. *Bioconjug Chem* 21: 2213-2221.
51. Koivunen J, Aaltonen V, Peltonen J (2006) Protein kinase C (PKC) family in cancer progression. *Cancer Lett* 235: 1-10.
52. Endo Y, Yoshimi T, Kimura K, Itai A (1999) Protein kinase C modulators bearing dicarba-closo-dodecaborane as a hydrophobic pharmacophore. *Bioorg Med Chem Lett* 9: 2561-2564.
53. Ghosh A, Heston WD (2004) Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem* 91: 528-539.
54. El-Zaria ME, Genady AR, Janzen N, Petlura CI, Beckford VDR, et al. (2014) Preparation and evaluation of carborane-derived inhibitors of prostate specific membrane antigen (PSMA). *Dalton Trans* 43: 4950-4961.
55. Fujii S, Ohta K, Goto T, Oda A, Masuno H, et al. (2012) Development of androgen receptor ligands by application of ten-vertex para-carborane as a novel hydrophobic core structure. *Med Chem Comm* 3: 680-684.
56. Heinlein CA, Chang C (2004) Androgen receptor in prostate cancer. *Endocr Rev* 25: 276-308.
57. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, et al. (1995) Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *New England Journal of Medicine* 332: 1393-1398.
58. Fujii S, Yamada A, Tomita K, Nagano M, Goto T, et al. (2011) P-carborane-based androgen antagonists active in LNCaP cells with a mutated androgen receptor. *Med Chem Comm* 2: 877-880.
59. Goto T, Ohta K, Fujii S, Ohta S, Endo Y (2010) Design and synthesis of novel androgen receptor antagonists with sterically bulky icosahedral carboranes. *J Med Chem* 53: 4917-4926.
60. White N, Burnstock G (2006) P2 receptors and cancer. *Trends Pharmacol Sci* 27: 211-217.
61. Wilkinson SM, Gunosewoyo H, Barron ML, Boucher A, McDonnell M, et al. (2014) The first CNS-active carborane: A novel P2X7 receptor antagonist with antidepressant activity. *ACS Chem Neurosci* 5: 335-339.
62. Li WH, Qiu Y, Zhang HQ, Liu Y, You JF, et al. (2013) P2Y2 receptor promotes cell invasion and metastasis in prostate cancer cells. *Br J Cancer* 109: 1666-1675.
63. Gabel D (2015) Boron clusters in medicinal chemistry: perspectives and problems. *Pure Appl Chem* 87: 173-179.
64. Olejniczak A, Wojtczak B, Lesnikowski ZJ (2007) 2'-Deoxyadenosine Bearing Hydrophobic Carborane Pharmacophore. *Nucleosides Nucleotides Nucleic Acids* 26: 1611-1613.
65. Bednarska K, Olejniczak AB, Wojtczak BA, Sułowska Z, Leśnikowski Z (2010) Adenosine and 2'-deoxyadenosine modified with boron cluster pharmacophores as new classes of human blood platelet function modulators. *J Chem Med Chem* 5: 749-756.
66. Hufton S, Moerkerk PT, Brandwijk R, de Bruine AP, Arends JW, et al. (1999) A profile of differentially expressed genes in primary colorectal cancer using suppression subtractive hybridization. *FEBS Lett* 463: 77-82.
67. Van-Beijnum JR, Moerkerk PT, Gerbers AJ, De Bruine AP, Arends JW, et al. (2002) Target validation for genomics using peptide-specific phage antibodies: A study of five gene products overexpressed in colorectal cancer. *Int J Cancer* 101: 118-127.
68. Nahimana A, Attinger A, Aubry D, Greaney P, Ireson C, et al. (2009) The NAD biosynthesis inhibitor APO866 has potent antitumor activity against hematologic malignancies. *Blood* 113: 3276-3286.
69. Reddy PS, Umesh S, Thota B, Tandon A, Pandey P, et al. (2008) PBEF1/NAmpRTase/Visfatin: a potential malignant astrocytoma/glioblastoma serum marker with prognostic value. *Cancer Biol Ther* 7: 663-668.
70. Nakajima TE, Yamada Y, Hamano T, Furuta K, Gotoda T, et al. (2009) Adipocytokine levels in gastric cancer patients: resistin and visfatin as biomarkers of gastric cancer. *Gastroenterol* 44: 685-690.
71. Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, et al. (2010) Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Sci* 101: 1286-1291.
72. Yang H, Yang T, Baur JA, Perez E, Matsui T, et al. (2007) Nutrient-sensitive mitochondrial NAD<sup>+</sup> levels dictate cell survival. *Cell* 130: 1095-1107.
73. Patel ST, Mistry T, Brown JEP, Digby JE, Adya R, et al. (2010) A novel role for the adipokine visfatin/pre-B cell colony-enhancing factor 1 in prostate carcinogenesis. *Peptides* 31: 51-57.
74. Khan JA, Forouhar F, Tao X, Tong L (2007) Nicotinamide adenine dinucleotide metabolism as an attractive target for drug discovery. *Expert Opin Ther Targets* 11: 695-705.
75. Bi T, Che X (2010) Nampt/PBEF/visfatin and cancer. *Cancer Biol Ther* 10: 119-125.
76. Hasmann M, Schemainda I (2003) FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis. *Cancer Res* 63: 7436-7442.
77. Hohen K, Saltz LB, Hollywood E, Burk K, Hanauske AR (2008) The pharmacokinetics, toxicities, and biologic effects of FK866, a nicotinamide adenine dinucleotide biosynthesis inhibitor. *Invest New Drugs* 26: 45-51.
78. Lee MW, Sevryugina YV, Khan A, Ye SQ (2012) Carboranes increase the potency of small molecule inhibitors of nicotinamide phosphoribosyltransferase. *J Med Chem* 55: 7290-7294.
79. Sadrafi K, Zargham EO, Lee MW (2016) Improved synthesis of MC4-PPEA and the biological evaluation of its hydroxymethyl derivative. *Bioorg Med Chem Lett* 26: 618-621.
80. Sadrafi K, Mason EO, Lee MW (2018) Clickable prodrugs bearing potent and hydrolytically cleavable nicotinamide phosphoribosyl transferase inhibitors. *Drug Des Devel Ther* 12: 987-995.
81. Vaupel P, Mayer A, Hockel M (2004) Tumor hypoxia and malignant progression. *Methods Enzymol* 381: 335-354.
82. Semenza GL (2010) Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. *Oncogene* 29: 625-634.
83. Nakamura H, Yasui Y, Maruyama M, Minegishi H, Ban HS, et al. (2013) Development of hypoxia-inducible factor (HIF)-1 $\alpha$  inhibitors: effect of ortho-carborane substituents on HIF transcriptional activity under hypoxia. *Bioorg Med Chem Lett* 23: 806-810.
84. Shimizu K, Maruyama M, Yasui Y, Minegishi H, Ban HS, et al. (2010) Boron-containing phenoxyacetanilide derivatives as hypoxia-inducible factor (HIF)-1 $\alpha$  inhibitors. *Bioorg Med Chem Lett* 20: 1453-1456.
85. Minegishi H, Matsukawa T, Nakamura H (2013) Boron-containing phenoxyacetanilide derivatives as hypoxia-inducible factor (HIF)-1 $\alpha$  inhibitors. *Chem Med Chem* 8: 265-271.
86. Szlosarek P, Charles KA, Balkwill FR (2006) Tumour necrosis factor- $\alpha$  as a tumour promoter. *Eur J Cancer* 42: 745-750.
87. Miyachi H, Azuma A, Ogasawara A, Uchimura E, Watanabe N, et al. (1997) Novel biological response modifiers: phthalimides with tumor necrosis factor- $\alpha$  production-regulating activity. *J Med Chem* 40: 2858-2865.
88. Endo Y (2000) A new medicinal application of boron clusters. Potent nuclear receptor ligands bearing carborane as a hydrophobic pharmacophore. *Contemporary Boron Chemistry* 253: 139.
89. Tsuji M, Koiso Y, Takahashi H, Hashimoto Y, Endo Y (2000) Modulators of tumor necrosis factor  $\alpha$  production bearing dicarba-closo-dodecaborane as a hydrophobic pharmacophore. *Biol Pharm Bull* 23: 513-516.
90. Kagechika H, Shudo KJ (2005) Synthetic retinoids: Recent developments concerning structure and clinical utility. *J Med Chem* 48: 5875-5883.
91. Ohta K, Iijima T, Kawachi E, Kagechika H, Endo Y (2004) Novel retinoid X receptor (RXR) antagonists having a dicarba-closo-dodecaborane as a hydrophobic moiety. *Bioorg Med Chem Lett* 14: 5913-5918.
92. Altucci L, Leibowitz MD, Ogilvie KM, de Lera AR, Gronemeyer H (2007) RAR and RXR modulation in cancer and metabolic disease. *Nat Rev Drug Discov* 6: 793-810.