1,2-DICARBA-*closo*-DODECABORANYL GROUP-CONTAINING ANALOGUES OF 4-IODO-*N*-[2-(1-PIPERIDINYL)ETHYL]BENZAMIDE (IPAB)†

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† This paper is dedicated to the memory of Professor Drago Kolar

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Abstract

Using 4-iodo-*N*-[2-(1-piperidinyl)ethyl]benzamide (IPAB) as the lead compound we prepared five new 1,2-dicarba-*closo*-dodecaborane skeleton-containing analogues with the aim of finding new therapeutic agents for Boron Neutron Capture Therapy (BNCT) of malignant melanoma and breast cancer.

Key words: boron neutron capture therapy (BNCT); 1,2-dicarba-*closo*-dodecaborane; IPAB analogues

Introduction

Soon after the discovery of neutron and its nuclear reaction called neutron capture in early thirties, the idea of a binary weapon against cancer cells was formulated. Neutron Capture Therapy (NCT) is based on utilization of two nontoxic components, a compound, containing an atom with as large as possible nuclear cross-section, and a beam of thermal neutrons. Neither the compound nor the neutron beam causes significant effect on a tissue. When combined, however, the nuclear reaction occurs, leading to a new isotope in the nuclear excited state. The atom in the excited state is not stable and decays in two or more high-energy nuclear particles. These particles cause radiation damage to the neighboring cells.[1] While nuclear technology has developed sufficiently to enable production of X-ray-free, beams of clean thermal or epithermal neutrons, the problem of selective delivery of the second component to the tumor has still not been solved. A compound, which would selectively deliver the selected atom with as large as possible nuclear cross-section to the tumor, has to be prepared. The most abundant elements in living tissue have relatively small nuclear cross-sections, ranging from 1.8×10^{-4} (O) to 32.68 barn (Cl). Isotopes of other elements have larger nuclear

cross-sections of which ^{10}B is the most interesting one. Relatively large nuclear cross-section (3838 barn) and chemical properties, which enable the synthesis of stable organic molecules,[3] made ^{10}B the element of choice for the application in NTC. If using boron compounds, this method is referred to as Boron Neutron Capture Therapy (BNCT). For a successful application of BNCT it is of outmost importance that the boron-containing compound selectively accumulates in or on the tumor cells while its concentration in the neighboring tissue or plasma remains as low as possible. With a high tumor to neighboring tissue (plasma) ratio the damage upon radiation would be limited to the tumor tissue. A variety of boron compounds were tested in oncology with a moderate success. The major problems, which were detected, were an inappropriate selection of the compound to deliver boron and the inability of the thermal neutron beam to reach deeper positioned tumors.[2,4] Quite promising results were obtained with BSH ($Na_2B_{12}H_{11}SH$). The molecule contains 12 boron atoms arranged in a cage-like structure. It thus delivers twelve boron atoms at a time, which is desirable for BNCT.[5] On the other hand; more specific accumulation of the boron conveyer compound in the tumor would be desirable.

From a variety of boron-containing compounds dicarba-*closo*-dodecaborane derivatives stand out as potential agents in BNCT. Dicarba-*closo*-dodecaboranes have structures similar to BSH, except that carbons replace two boron atoms.

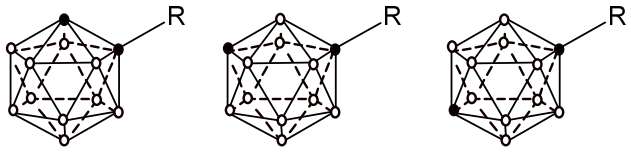
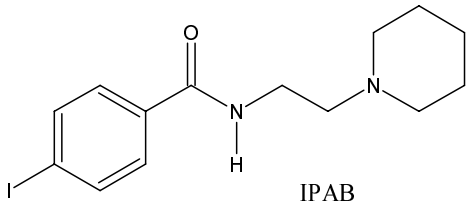


Figure 1. Three possible isomers of dicarba-*closo*-dodecaboranes (*ortho, meta, para*). Filled circles represent carbon and open circles boron atoms.

They are capable of delivering ten boron atoms at a time to the tumor and common organic transformations can be performed in order to attain the selectivity of accumulation.[6]

It is impossible to design a compound, which would be recognized by all physiologically diverse tumors. Malignant melanoma and breast cancer cells share a

common feature. Namely, in the membranes of both cell types σ-receptors are expressed. In the beginning it was believed that σ-receptors are just another opioid receptor subgroup.[7] Later it has been established that substrates, which bind to these receptors can be very diverse in chemical structure. It has been also found that not only in the CNS, but also elsewhere in the body these receptors can be found. Based on these findings 4-iodo-*N*-[2-(1-piperidinyl)ethyl]benzamide (IPAB) has been prepared.



IPAB

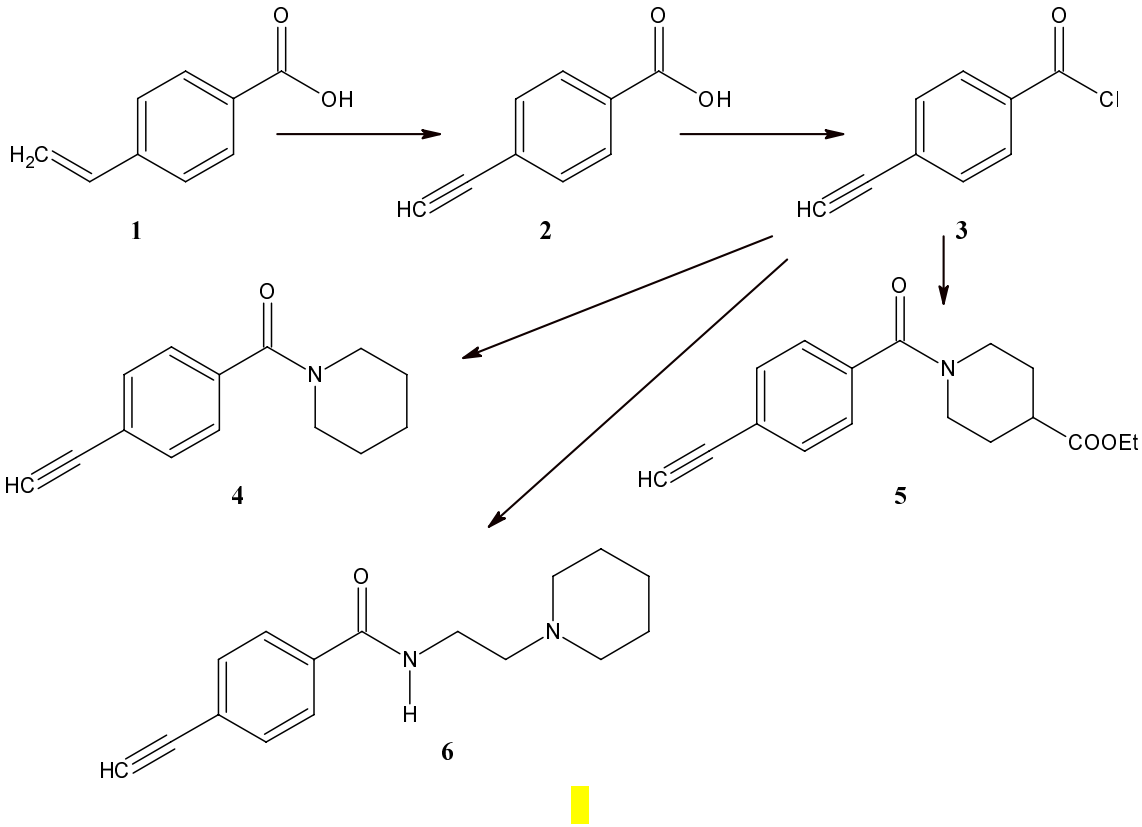
The compound was labeled with radioactive ^{125}I and used in Single Photon Emission Computer-averaged Tomography (SPECT) investigation of breast cancer and malignant melanoma.[8] The application was based on relatively tight binding of IPAB to the σ-receptors, found on the respective cancer cells. SAR studies on a series of ligands for σ-receptors showed that the introduction of a lipophilic group in the aromatic ring increases the selectivity and affinity of binding.[7]

Based on the above facts we envisaged the preparation of a new class of compounds for BNCT of malignant melanoma and breast cancer. We decided to try to modify the IPAB molecule with dicarba-*closo*-dodecaborane structural element. The two constituents would supply the two necessary features to the new molecule: binding specificity and the required atoms (^{10}B), respectively.

Results and discussion

The new potential agents for BNCT derived from the structure of IPAB were prepared by a formal substitution of the iodine atom or more drastically, replacing the whole 4-iodophenyl group by dicarba-*closo*-dodecaborane skeleton. The amide portion of IPAB structure was also varied by using *N*-(2-ethylamino)piperidine, ethyl isonipecotate or piperidine as the amine compound in the amide group formation reaction.

The synthetic pathway to the IPAB derivatives with iodine replaced with the dicarba-*closo*-dodecaborane skeleton is presented in the Schemes 1 and 2.

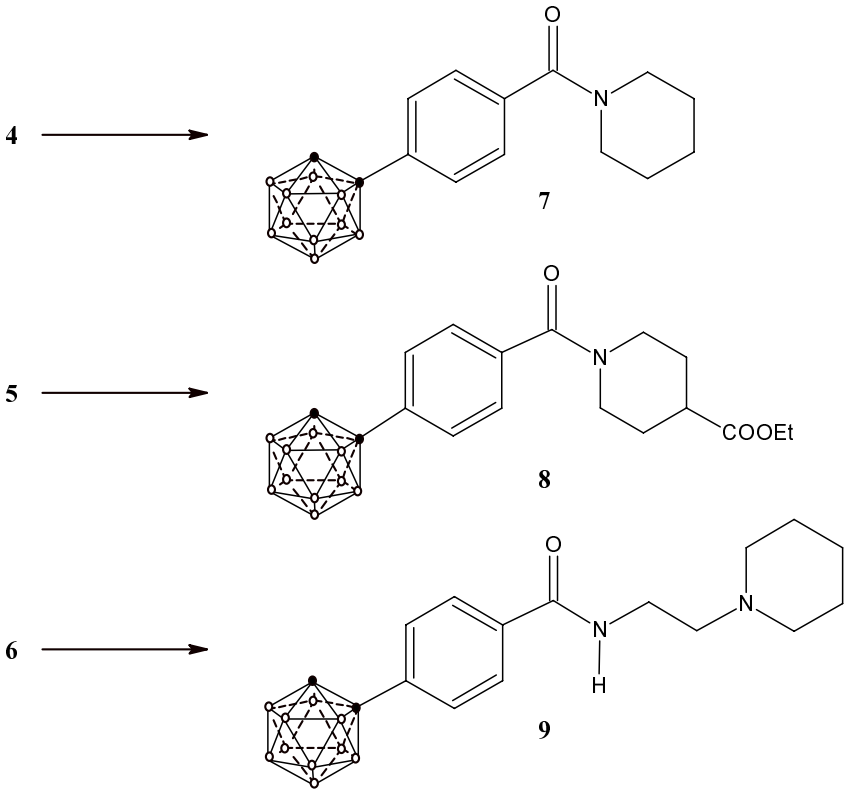


Scheme 1.

First we prepared alkynes, which are necessary for the dicarba-*closo*-dodecaborane skeleton formation. In the preparation of *p*-ethynylbenzoic acid (**2**) we found that the published procedures for elimination[9] of HBr from the product of bromine addition to *p*-vinylbenzoic acid (**1**) did not give satisfactory results. Leaving the suspension of the intermediate *p*-(1,2-dibromoethyl)-benzoic acid and sodium amide in liquid ammonia in an open container in a fume hood to slowly evaporate overnight gave the acid **2** in 91% yield. To prevent spontaneous polymerization of the acid **2** at RT, we transformed it into sodium salt. Besides allowing for longer storage at RT the salt form was used in the transformation into the acid chloride **3**. The latter was used immediately in the next step without purification. Reacting the chloride **3** with piperidine, ethyl

isonipecotate, or *N*-(2-ethylamino)piperidine resulted in the formation of amides **4**, **5**, and **6**, respectively.

The dicarba-*closo*-dodecaborane skeleton formation is usually achieved by reacting an appropriate acetylenic compound with decaborane in acetontrile. It has been proposed that first a complex between decaborane and acetonitrile is formed. In the second step this complex adds to the triple bond.[10] An improved procedure in which *N,N*-dimethylaniline replaces acetonitrile gives higher yields of dicarba-*closo*-dodecaboranes in shorter reaction time.[11] In this manner we prepared derivatives **7**, **8** and **9**.



Scheme 2.

To prove that the carborane cage has not rearranged during the reactions, and that we were dealing with the *ortho*- and not with the isomeric *meta*- or *para*-caborane derivatives, we performed a single crystal X-ray analysis of compounds **8** and **14**.

The asymmetric unit of **8** is shown in Fig. 2. It contains two molecules (**a** and **b**) of ethyl 1-[4-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoyl]-4-piperidinecarboxylate. Bond lengths (Table 2) and angles are similar and are within the normal ranges for this

type of molecules. The main difference between the conformation of molecules **a** and **b** is in the orientation of the piperidinecarboxylate group regarding to the aromatic ring. Bond lengths and displacement parameters in carborane cage confirm that **a** and **b** molecules are *ortho*-carborane derivatives. Carbon to boron bond distances (average 1.71(1) Å in **a** and 1.70(1) Å in **b**) are significantly longer than C(16)-C(17) bond length (1.648(7) Å in **a** and 1.635(7) Å in **b**) and significantly shorter than boron to boron bond distances (average 1.765(7) Å in **a** and 1.76(1) Å in **b**). This is in an agreement also with reported bond lengths in the literature.[12]

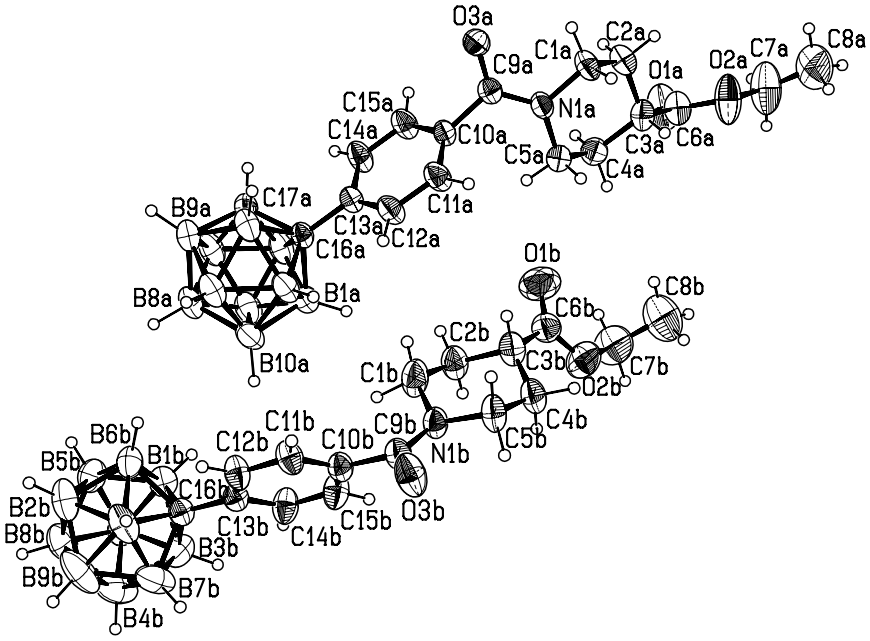


Figure 2. OrtepII view of the asymmetric unit of **8**, showing the labeling of the non-hydrogen atoms. The displacement ellipsoids are shown at the 40% probability level.

To prepare IPAB analogues lacking the phenyl ring first methyl propiolate was reacted with decaborane to give the ester **10**. The ester was isolated from the reaction mixture and purified by sublimation. Sublimation proved to be superior isolation technique giving methyl 1,2-dicarba-*closo*-dodecaboran-1-yl carboxylate in 95% yield. To prevent the decomposition of the carborane skeleton during hydrolysis,[13] mild reaction conditions were used to prepare the acid **11**. The acid was converted into the

Table 1. Fractional Coordinates and Equivalent Displacement Factors (Å^2) for **8**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
O(1a)	1.2407(4)	0.4555(4)	–0.2522(3)	0.115(2)
O(2a)	1.1059(3)	0.4276(3)	–0.4065(3)	0.110(2)
O(3a)	0.9124(3)	0.0194(2)	–0.2371(2)	0.058(1)
O(1b)	0.8416(5)	0.4164(4)	–0.0800(4)	0.127(3)
O(2b)	0.7544(4)	0.5291(3)	–0.0939(4)	0.102(2)
O(3b)	0.2317(3)	0.2445(3)	–0.0529(2)	0.091(2)
N(1a)	0.9153(3)	0.1727(2)	–0.2490(2)	0.053(1)
N(1b)	0.4401(3)	0.3129(3)	–0.0135(2)	0.059(2)
C(1a)	0.9215(5)	0.1536(4)	–0.3467(3)	0.061(2)
C(2a)	1.0331(5)	0.2335(4)	–0.3460(4)	0.064(2)
C(3a)	1.0291(4)	0.3362(3)	–0.3127(3)	0.060(2)
C(4a)	1.0295(5)	0.3523(4)	–0.2088(3)	0.064(2)
C(5a)	0.9181(5)	0.2722(3)	–0.2097(4)	0.060(2)
C(6a)	1.1364(5)	0.4139(4)	–0.3171(4)	0.072(2)
C(7a)	1.2002(7)	0.4953(7)	–0.4283(7)	0.128(4)
C(8a)	1.1589(8)	0.4803(6)	–0.5317(7)	0.133(5)
C(9a)	0.9060(3)	0.1012(3)	–0.2040(3)	0.047(2)
C(10a)	0.8831(3)	0.1150(3)	–0.1106(3)	0.048(2)
C(11a)	0.9707(4)	0.1102(4)	–0.0233(3)	0.065(2)
C(12a)	0.9464(4)	0.1099(4)	0.0605(3)	0.066(2)
C(13a)	0.8315(3)	0.1114(3)	0.0580(3)	0.048(2)
C(14a)	0.7443(4)	0.1163(4)	–0.0293(3)	0.063(2)
C(15a)	0.7701(4)	0.1183(4)	–0.1123(3)	0.065(2)
C(16a)	0.8022(3)	0.1092(3)	0.1478(3)	0.048(2)
C(17a)	0.8621(4)	0.0463(3)	0.2223(3)	0.060(2)
C(1b)	0.5602(5)	0.2976(5)	0.0319(5)	0.089(3)
C(2b)	0.6690(5)	0.3709(5)	0.0276(4)	0.074(3)
C(3b)	0.6397(5)	0.3797(4)	0.0793(4)	0.073(2)
C(4b)	0.5207(5)	0.4006(4)	–0.1188(4)	0.071(2)
C(5b)	0.4100(5)	0.3265(4)	–0.1146(4)	0.070(2)
C(6b)	0.7547(5)	0.4434(4)	–0.0838(4)	0.071(2)
C(7b)	0.8676(8)	0.6010(6)	–0.0898(8)	0.126(5)
C(8b)	0.8611(9)	0.5934(7)	–0.1902(8)	0.154(6)
C(9b)	0.3421(4)	0.2714(3)	0.0077(3)	0.060(2)
C(10b)	0.3704(4)	0.2626(3)	0.1125(3)	0.056(2)
C(11b)	0.3138(4)	0.1723(4)	0.1254(3)	0.063(2)
C(12b)	0.3304(4)	0.1637(3)	0.2201(3)	0.064(2)
C(13b)	0.4025(4)	0.2450(3)	0.3036(3)	0.051(2)
C(14b)	0.4593(5)	0.3349(4)	0.2906(3)	0.071(2)
C(15b)	0.4440(5)	0.3430(4)	0.1963(4)	0.074(2)
C(16b)	0.4242(4)	0.2357(3)	0.4073(3)	0.053(2)
C(17b)	0.3220(4)	0.1454(4)	0.4209(3)	0.076(2)
B(1a)	0.7928(5)	0.2100(4)	0.2166(4)	0.063(2)
B(2a)	0.8992(5)	0.1002(5)	0.3438(4)	0.070(3)
B(3a)	0.6582(5)	0.1008(4)	0.1452(4)	0.063(2)
B(4a)	0.6326(5)	0.0291(5)	0.2254(4)	0.070(3)

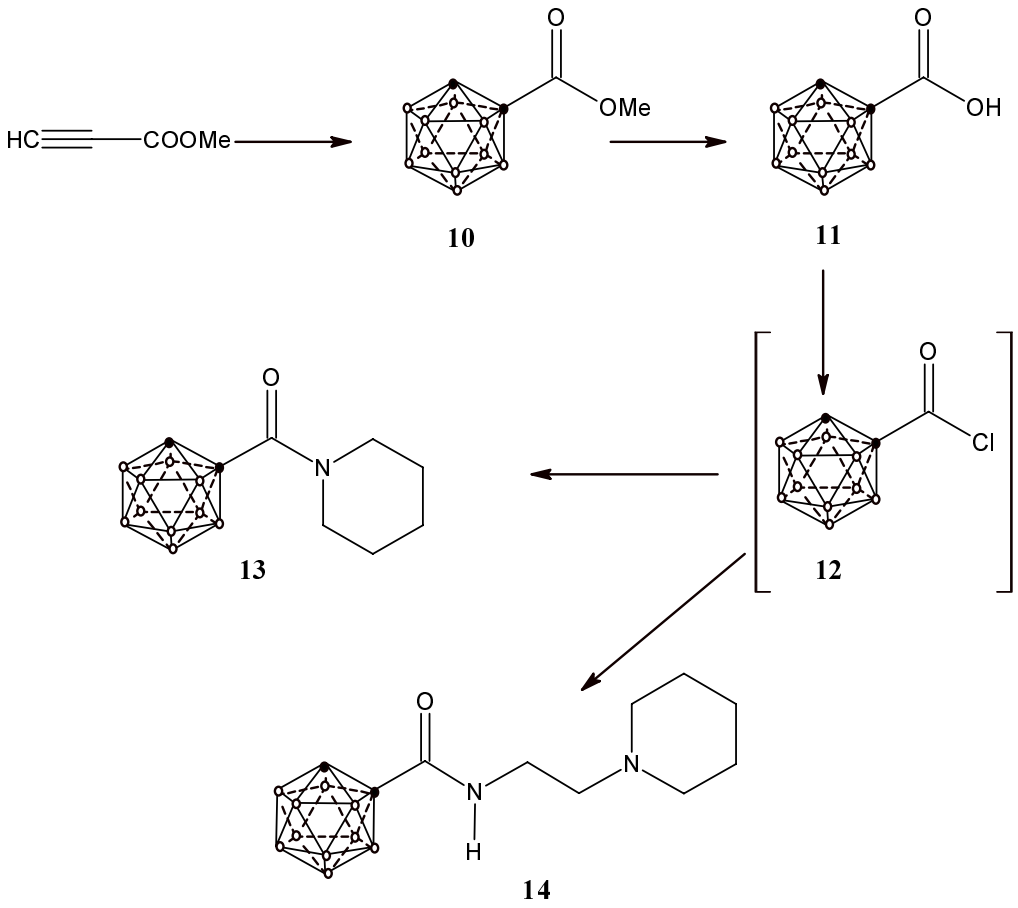
Table 1 continued.

B(5a)	0.8524(6)	0.2040(5)	0.3418(4)	0.072(3)
B(6a)	0.9234(5)	0.1732(4)	0.2642(4)	0.062(2)
B(7a)	0.7036(5)	–0.0034(4)	0.1461(4)	0.062(2)
B(8a)	0.7532(5)	0.0926(5)	0.3470(4)	0.068(3)
B(9a)	0.7637(6)	–0.0083(5)	0.2718(4)	0.070(3)
B(10a)	0.6866(6)	0.1607(5)	0.2690(4)	0.072(3)
B(1b)	0.5717(5)	0.2576(4)	0.4968(4)	0.064(2)
B(2b)	0.3911(6)	0.0998(5)	0.5151(4)	0.086(3)
B(3b)	0.4893(6)	0.3369(5)	0.5108(4)	0.078(3)
B(4b)	0.4141(8)	0.3010(7)	0.5886(4)	0.103(4)
B(5b)	0.5508(6)	0.1741(4)	0.5676(4)	0.073(3)
B(6b)	0.4634(5)	0.1355(4)	0.4362(4)	0.066(2)
B(7b)	0.3251(7)	0.2622(7)	0.4573(5)	0.096(4)
B(8b)	0.4527(6)	0.2000(6)	0.6244(4)	0.084(3)
B(9b)	0.3047(6)	0.1749(8)	0.5271(4)	0.110(4)
B(10b)	0.5651(6)	0.2970(4)	0.6125(4)	0.072(3)

Table 2. Bond lengths (Å) for **a** and **b** molecules of the compound **8**.

	a	**b**		**a**	**b**
O(1)-C(6)	1.193(5)	1.206(9)	C(17)-B(2)	1.695(7)	1.697(9)
O(2)-C(6)	1.314(7)	1.282(8)	C(17)-B(6)	1.706(7)	1.694(9)
O(2)-C(7)	1.46(1)	1.45(1)	C(17)-B(7)	1.710(6)	1.69(1)
O(3)-C(9)	1.249(5)	1.225(5)	C(17)-B(9)	1.699(9)	1.67(1)
N(1)-C(1)	1.470(6)	1.466(7)	B(1)-B(3)	1.768(6)	1.75(1)
N(1)-C(5)	1.462(6)	1.478(7)	B(1)-B(5)	1.772(8)	1.757(9)
N(1)-C(9)	1.327(6)	1.344(7)	B(1)-B(6)	1.755(9)	1.751(7)
C(1)-C(2)	1.519(7)	1.480(9)	B(1)-B(10)	1.78(1)	1.765(9)
C(2)-C(3)	1.519(8)	1.540(8)	B(2)-B(5)	1.76(1)	1.741(8)
C(3)-C(4)	1.527(8)	1.487(8)	B(2)-B(6)	1.761(9)	1.76(1)
C(3)-C(6)	1.502(7)	1.477(8)	B(2)-B(8)	1.76(1)	1.769(9)
C(4)-C(5)	1.516(7)	1.501(8)	B(2)-B(9)	1.769(7)	1.74(1)
C(7)-C(8)	1.40(1)	1.45(2)	B(3)-B(4)	1.761(9)	1.77(1)
C(9)-C(10)	1.506(6)	1.511(7)	B(3)-B(7)	1.752(9)	1.784(9)
C(10)-C(11)	1.383(6)	1.384(7)	B(3)-B(10)	1.777(8)	1.750(9)
C(10)-C(15)	1.373(7)	1.378(5)	B(4)-B(7)	1.77(1)	1.768(8)
C(11)-C(12)	1.381(8)	1.385(7)	B(4)-B(8)	1.766(6)	1.77(1)
C(12)-C(13)	1.384(7)	1.380(5)	B(4)-B(9)	1.76(1)	1.80(1)
C(13)-C(14)	1.381(6)	1.381(7)	B(4)-B(10)	1.773(9)	1.75(1)
C(13)-C(16)	1.504(6)	1.508(6)	B(5)-B(6)	1.74(1)	1.768(7)
C(14)-C(15)	1.382(8)	1.379(8)	B(5)-B(8)	1.766(9)	1.77(1)
C(16)-C(17)	1.648(7)	1.635(7)	B(5)-B(10)	1.774(8)	1.747(9)
C(16)-B(1)	1.708(8)	1.712(6)	B(7)-B(9)	1.774(8)	1.79(1)
C(16)-B(3)	1.700(8)	1.718(6)	B(8)-B(9)	1.76(1)	1.753(9)
C(16)-B(6)	1.721(5)	1.726(8)	B(8)-B(10)	1.77(1)	1.75(1)
C(16)-B(7)	1.735(7)	1.71(1)			

acid chloride **12**, which was reacted without purification with piperidine or *N*-(2-ethylamino)piperidine to yield IPAB analogues **13** and **14**, respectively, containing the 1,2-dicarba-*closo*-dodecaborane and lacking the aromatic ring (Scheme 3).



Scheme 3.

Table 3. Crystal data, data collection and refinement summary for the compound **8**.

Asymmetric unit formula	$(C_{17}H_{29}B_{10}NO_3)_2$
Formula weight	807.06
Crystal color, habit	colorless, plate
Crystal size (mm^3)	0.42×0.40×0.15
Crystal system	triclinic
a (Å)	12.103(3)
b (Å)	14.574(1)
c (Å)	14.901(1)
α (°)	99.16(1)
β (°)	110.77(1)
γ (°)	105.91(1)
V ($Å^3$)	2265.3(7)

Table 3 continued.

Z	2
Space group	P -1 (No. 2)
D_c (Mgm^{-3})	1.183
No. of refl. for cell parameters	75
θ range (°) for cell parameters	9.98–14.42
T (°C)	20(1)
λ (MoK_α) (Å)	0.71069
Scan type	ω-2θ
θ_{max} (°)	28
Intensity decay (%)	1.22
R_{int}	0.021
μ(MoK_α) (mm^{-1})	0.0701
No. of measured reflections	21956
No. of unique reflections	10924
No. of observed reflections (I >2.5σ(I))	4210
No. of contributing reflect. (in refinement)	7636
No. of parameters	756
Weighting scheme	calculated
Extinction method	Zachariasen
Extinction coefficient	$6(1).10^4$
R (on F)	0.069
R_w (on F)	0.077
$(\Delta/\sigma)_{max}$	0.01
$\Delta\rho_{max}$ ($eÅ^{-3}$)	0.73
$\Delta\rho_{min}$($eÅ^{-3}$)	-0.42

Conclusions

Based on the structure of IPAB, the compound that showed specific binding to σ-receptors, also found in malignant melanoma and breast cancer cells, we prepared five new 1,2-dicarba-*closo*-dodecaborane cage containing analogues with the intention to obtain new agents for BNCT. In three of the new analogues the iodine atom in IPAB and in two the whole 4-iodophenyl groups were formally replaced by the 1,2-dicarba-*closo*-dodecaborane cage. With this modification we introduced ten boron atoms in the molecule, which is most favorable for potential use in BNCT. We also varied the length and polarity of the amide side chain for better accommodation of the new derivatives in the σ-receptors and increased polarity and, consequently, better water solubility.

Experimental

NMR spectra were recorded on a Bruker DPX 300 or Varian EM 360C spectrometers. ^1H chemical shifts are quoted in parts per million (ppm) downfield from TMS as internal standard and coupling constants are given in Hz. Melting points were

determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were determined at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana using a Perkin-Elmer 2400 CHN elemental analyzer. IR spectra were recorded on a Perkin Elmer 727B spectrometer. Mass spectra were recorded by Dr. B. Kralj and Dr. D. Žigon at the Mass Spectrometry Center, Jožef Stefan Institute. Radial chromatography was performed using Chromatotron (Harrison Research, 840 Moana Court, Palo Alto, CA 94306). The rotors were prepared as recommended by Harrison Research using E. Merck Silica Gel (Cat. No. 7749-3), with 1 or 2 mm layer thickness.

4-Ethynylbenzoic acid (2).

A solution of 4-vinylbenzoic acid (**1**, 2 g, 13.5 mmol) in dichloromethane (50 cm^3) was cooled to 0 °C and a solution of bromine was added dropwise (0.75 cm^3, 14,17 mmol in 20 cm^3 of dichloromethane). After the addition volatiles were removed at low temperature undre reduced pressure. The residue was dissolved in minimum amount of ether and the solution was added dropwise to a solution of sodium amide (2.1 g, 54 mmol) in liquid ammonia (125 cm^3). The reaction mixture was left in a hood to evaporate at RT overnight. To the residue water was added, acidified with 2 M HCl to pH 3 and extracted with ethyl acetate. After drying and removal of the solvent 4-ethynylbenzoic acid (**2**, 1.8 g, 91%), of was obtained. mp 222–223 °C dec., (lit.:[14] 224–225 °C); IR (KBr): 3260 cm^{-1} (C≡C-H), 1670 cm^{-1} (-CO-); ^{1}H NMR (60 MHz; $CDCl_3$) δ: 4.45 1H, s, C≡C-H), 7.8 (2H, d, 2-H, 6-H, J 8.3), 8.2 (2H, d, 3-H, 5-H, J 8.3); m/z 146 (M^+), $C_9H_6O_2$ requires 146.14.

4-Ethynylbenzoyl chloride (3).

In a solution of sodium methylate in methanol (11.9 cm^3, 1M) 4-ethynylbenzoic acid (**2**, 1.74 g, 11.9 mmol) was dissolved and the solvent was removed in vacuo. The remaining solid was suspended in dichloromethane (40 cm^3), the suspension was cooled to 0 °C and oxalyl chloride (2.12 cm^3, 25 mmol) was added dropwise. The solution was allowed to warm to RT and was stirred for additional 1.5 h. The solvent and excess of the

reagent were removed in vacuo. Raw product (1.75 g, 89%) was used in the next step without purification. IR (KBr) 3250 cm^{-1} (C≡C-H), 2090 cm^{-1} (-C≡C-), 1775 cm^{-1}, 1715 cm^{-1} (-CO-).

1-(4-Ethynylbenzoyl)piperidine (4).

To a solution of 4-ethynylbenzoyl chloride (**3**, 560 mg, 3.4 mmol) in chloroform (20 cm^3) piperidine (1 cm^3, 10 mmol) was added followed by dropwise addition of triethylamine (1 cm^3). The reaction mixture was stirred at RT for 21 h, washed with water, the organic layer was dried and evaporated. The residue was chromatographed by radial chromatography (2 mm SiO_2, 5% MeOH in acetone) to give yellow-brown oil which later crystallized (480 mg, 66%). mp 120–121°C (from petroleum ether); (Found C, 76.88; H, 5.11; N, 6.35. $C_{14}H_{15}NO$ requires C, 78.84; H, 7.09; N, 6.57);[15] ^{1}H- NMR (300 MHz, $CDCl_3$) δ: 1.51–1.78 (6H, m, piperidine 3-H, 4-H, 5-H), 3.12 (1H, s, C≡C-H), 3.32 (2H, bs, piperidine 2a-H, 6a-H), 3.70 (2H, bs, piperidine 2e-H, 6e-H), 7.35 (2H, bd, J 8.3, Ar-H), 7,52 (2H, bd, J 8.3, Ar-H).

Ethyl 1-(4-ethynylbenzoyl)-4-piperidinecarboxylate (5).

To a solution of 4-ethynylbenzoyl chloride (**3**, 230 mg, 1.4 mmol) in chloroform (15 cm^3) ethyl isonipecotate (0.54 cm^3, 3.5 mmol) was added followed by dropwise addition of triethylamine (1 cm^3). The reaction mixture was stirred at RT for 24 h, washed with water, the organic layer was dried and evaporated. The residue was chromatographed by radial chromatography (2 mm SiO_2, 30% tetrachloromethane in diethyl ether) to give yellow-brown oil (256 mg, 64%). mp 83–84 °C (from benzene – petroleum ether); (Found C, 70.85; H, 6.72; N, 4.87. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91);[15] ^{1}H- NMR (300 MHz, $CDCl_3$) δ: 1.26 (3H, t , J 7.1, CH_3), 1.60–2.00 (4H, m, piperidine 3-H, 5-H), 2.58 (1H, m, piperidine 4-H), 3.05 (2H, t, J 11.3, piperidine 2a-H, 6a-H), 3.22 (1H, s, C≡C-H), 3.70 and 4.49 (2H, bs, piperidine 2e-H, 6e-H), 4.,16 (2H, q, J 7.1, -OCH_2-), 7.35 (2H, bd, J 8.5, Ar-H), 7.52 (2H, bd, J 8.5, Ar-H).

4-Ethynyl-*N*-[2-(1-piperidinyl)ethyl]benzamide (6).

To a solution of 4-ethynylbenzoyl chloride (**3**, 115 mg, 0.7 mmol) in chloroform (10 cm^3) *N*-(2-ethylamino)piperidine (0.1 cm^3) and triethylamine (10 cm^3) were added and the reaction mixture was stirred at RT for 24 h, washed with 2% solution of sodium bicarbonate, dried and evaporated. The residue was chromatographed by radial chromatography (1 mm SiO_2, 5% MeOH in dichloromethane) to give yellow oil (96 mg, 53%). mp 107 °C; (Found C, 74.52; H, 7.90; N, 11.14. $C_{16}H_{28}N_2O$ requires C, 74.97; H, 7.86; N, 10.93); IR (KBr) 3340 cm^{-1} (-NH-), 2090 cm^{-1} (-C≡C-), 1630 and 1540 cm^{-1} (NH-CO-); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44–1.50 (2H, m, piperidine 4-H), 1.56 – 1.63 (4H, m, piperidine 3-H, 5-H), 2.43 (4H, t, J 4.9, piperidine 2-H, 6-H), 2.55 (2H, t, J 6.0, -CH_2-N-), 3.18 (1H, s, C≡C-H), 3.50 (2H, dt, J 1.5, 4.9, NH$\underline{CH_2}$), 6.97 (1H, bs, -NHCO-), 7.55 (2H, bd, J 8.3, Ar-H), 7,74 (2H, bd, J 8.3, Ar-H); *m/z* (FAB) 257 (MH^+), $C_{16}H_{28}N_2O$ requires 256.35.

General procedure for the preparation of 1,2-dicarba-*closo*-dodecaborane derivatives. A mixture of ethynylbenzoic acid derivative, *N,N*-diethylaniline, and decaborane (2 mmol each) was dissolved in toluene (10 cm^3) and refluxed for 3 h. The solvent was removed in vacuo and the residue was extracted with diethyl ether. Evaporation of ether gave solid, which was recrystallized from benzene – petroleum ether.

4-(1,2-Dicarba-*closo*-dodecaboran-1-yl)-*N*-[2-(1-piperidinyl)ethyl]benzamide (7).

White solid (185 mg, 25%). mp 146–148 °C; (Found C, 51.24; H, 8.33; N, 7.50. $C_{16}H_{30}B_{10}N_2O$ requires C, 51.31; H, 8.07; N, 7.48); IR (KBr): 2550 cm^{-1} (B - H); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.2–3.2 (10H, b, B-H), 1.47–1.63 (6H, m, piperidine), 2.44 (4H,bs, piperidine), 2.55 (2H, t, J 6.0, -CH_2-N), 3.51 (2H, dt, J 1.5 Hz, 4.9, -NH-$\underline{CH_2}$), 3.91 (1H, bs, H-C-B), 7.03 (1H, bs, -NH-), 7.55 (2H, bd, J 8.3, Ar-H), 7.74 (2H, bd, J 8.3, Ar-H); *m/z* (FAB): 375 (MH^+), $C_{16}H_{30}B_{10}N_2O$ requires 374.53.

Ethyl 1-[4-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoyl]-4-piperidinecarboxylate (8).

White solid (55 mg, 30%). mp 176–177 °C; (Found C, 50.80; H, 7.51; N, 3.70. $C_{17}H_{29}B_{10}NO_3$ requires C, 50.60; H, 7.24; N, 3.47); IR (KBr): 2600 cm^{-1} (B-H), 1725 cm^{-1} (-CO-O-), 1630 cm^{-1} and 1590 cm^{-1} (-CO-NH-); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (3H, t, J 7.1, $-CH_3$), 1.60–2.00 (4H, m, piperidine 3-H, 5-H), 1.2–3.2 (10H, b, B-H), 2.58 (1H, m, piperidine 4-H), 3.07 (2H, t, J 11.3, piperidine 2a-H, 6a-H), 3.65 and 4.47 (2H, bs, piperidine 2e-H, 6e-H), 3.96 (1H, bs, H-C-B), 7.35 (2H, ddd, J 1.9, 1.9, 8.5, Ar-H), 7,53 (2H, ddd, J 1.9, 1.9, 8.5, Ar-H).

1-[4-(1,2-Dicarba-*closo*-dodecaboran-1-yl)benzoyl]piperidine (9).

White solid (21 mg, 23%). mp 192–193 °C; (Found C, 50.56; H, 7.91; N, 4.33. $C_{14}H_{25}B_{10}NO$ requires C, 50.73; H, 7.60; N, 4.23); IR (KBr): 2600 cm^{-1} (B-H), 1620 cm^{-1} (-CO-NH-); ^{1}H-NMR (300 MHz. $CDCl_3$) δ: 1.2–3.5 (10H, b, B-H), 1.55–1.68 (6H, m, piperidine), 3.30 (2H, bs, piperidine 2a-H, 6a-H H), 3.69 (2H, bs, piperidine 2e-H, 6e-H), 3.96 (1H, bs, H-C-B), 7.35 (2H, ddd, J 1.7, 1.7, 8.3, Ar-H), 7,52 (2H, ddd, J 1.7, 1.7, 8.3, Ar-H).

Methyl 1,2-dicarba-*closo*-dodecaboran-1-yl carboxylate (10).

Following the above general procedure on a 10 millimolar scale methyl propiolate gave yellow oil from which the product was isolated by sublimation at 50 °C (1.88 g, 93%). mp 71–73 °C (lit.:[11] 73 °C); IR (KBr): 2600 cm^{-1} (B-H), 1740 cm^{-1} (-CO-); ^{1}H-NMR (300 MHz. $CDCl_3$) δ: 1.25–3.4 (10H, b, B-H), 3.85 (3H, s, CH_3), 4.10 (1H, bs, H-C-B).

1,2-Dicarba-*closo*-dodecaboran-1-yl carboxylic acid (11).

The ester **10** (160 mg, 0.8 mmol) was dissolved in MeOH (1.6 cm^3), added to a 2% NaOH (4 cm^3) and stirred at RT for 72 h. The solvent was removed; the residual water solution was acidified with 2M HCl and extracted with dichloromethane. The organic layer was dried and evaporated to leave the acid **11** (105 mg, 70%). mp 150 °C (from

petroleum ether; lit.:[13] 148–150 °C); IR (KBr): 3200 cm^{-1} (-OH), 2620 cm^{-1}–2550 cm^{-1} (m, B-H), 1740 cm^{-1} (-CO-); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25–3.4 (10H, b, B-H), 4.05 (1H, bs, H-C-B); *m/z*: 188 (M^+), $C_3H_{12}B_{10}O_2$ requires 188.24.

General procedure for the preparation of amides of 1,2-dicarba-*closo*-dodecaboran-1-yl carboxylic acid. To a solution of the acid **11** (75 mg, 0.4 mmol) in an excess of thionyl chloride (3 cm^3) DMF (10 μl) was added and the reaction mixture was refluxed for 4 h. After cooling all volatiles were removed in vacuum and the residual raw acid chloride **12** was used immediately in the next step. The raw material was dissolved in chloroform (5 cm^3) and one equivalent of the amine was added drop wise at RT. After 72 h at RT the reaction mixture was evaporated and the residue was distributed between dichloromethane and water. The organic layer was dried and evaporated. The product was isolated either by column chromatography or recrystallization.

(1,2-Dicarba-*closo*-dodecaboran-1-yl)-(1-piperidyl)methanone (13).
The product was isolated by column chromatography (SiO_2, chloroform : MeOH = 30 : 1) in 55% yield. mp 117–119 °C (from acetonitrile); (Found C, 37.10; H, 8.24; N, 6.67. $C_8H_{21}B_{10}NO$ requires C, 37.63; H, 8.29; N, 5.49);[16] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.3–3.5 (10H, b, B-H), 1.52–1.69 (6H, m, piperidine H), 3.70 (4H, bs, piperidine 2-H, 6-H), 4.79 (1H, bs, H-C-B); *m/z* (EI): 255, $C_8H_{21}B_{10}NO$ requires 255.36.

***N*-[2-((1,2-Dicarba-*closo*-dodecaboran-1-yl)carboxamido)ethyl]piperidine (14).**
The product was isolated by recrystallization from acetonitrile in 96% yield. mp 125–127 °C; IR (KBr): 3370 cm^{-1} (-NH-), 2610 cm^{-1} (B-H), 1690 cm^{-1} in 1510 cm^{-1} (CO-NH); (Found C, 40.12; H, 9.23; N, 10.05. $C_8H_{26}B_{10}N_2O$ requires C, 40.25; H, 8.78; N, 9.39);[16] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.2–3.2 (10H, b, B-H), 1.46–1.62 (6H, m, piperidine 3-H, 4-H, 5-H), 2.39 (4H, m, piperidine 2-H, 6-H), 2.45 (2H, t, J 5.9, CH_2N), 3.27 (2H, bt, J 5.9, $NHCH_2$), 4.26 (1H, bs, H-C-B), 7.09 (1H, bs, -NH-); *m/z* (FAB): 299 (MH^+), $C_8H_{26}B_{10}N_2O$ requires 298.43.

X-ray structure analysis. Diffraction data for the compound **8** were collected on Enraf Nonius CAD-4 diffractometer with graphite monochromatized MoKα radiation at RT. Intensities of reflections were corrected for decay, Lorentz-polarization effects but no for absorption (due to the low value of the linear absorption coefficient). Structure was solved by direct methods using SIR92.[17] The most of hydrogen atoms positions were obtained from difference Fourier maps. We employed full-matrix least-squares refinement on F magnitudes with anisotropic temperature factors for all non-hydrogen atoms and isotropic for hydrogen atoms, using the weighting function: $w=6.0\times W_f\times W_s$ where $W_f(|F_o|<3.52)=(|F_o|/3.52)$, $W_f(|F_o|>32)=(32/|F_o|)^{1.5}$, $W_f(3.52\leq|F_o|\leq32)=1.0$ and $W_s(\sin\theta<0.31)=(\sin\theta/0.31)^{1.1}$, $W_s(\sin\theta>0.57)=(0.57/\sin\theta)^{1.8}$ and $W_s(0.37\leq\sin\theta\leq 0.63)=1$. The parameters of hydrogen atoms attached to C(8a), C(8b), C(3b) and C(12b) were calculated and were not refined. The Xtal3.4[18] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII[19] was used to produce molecular graphics. Final atomic coordinates and equivalent isotropic thermal parameters with their e.s.d.'s are listed in Table 1. Bond lengths are presented in Table 2. Details of crystal data, data collection and refinement are given in Table 3. Final atomic coordinates, displacement parameters and geometry parameters have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: 157637. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Finally we would mention that X-ray data were collected also for the compound **14**. Unfortunately, the crystals and consequently the reflection data were of poor quality. We were able to solve the structure but the refinement resulted in large R value (0.146) and bond lengths, which deviate from expected standard geometry. Nevertheless the obtained structure is an agreement with the structural diagram of the compound **14**. Fig. 3 shows the content of asymmetric unit of this compound.

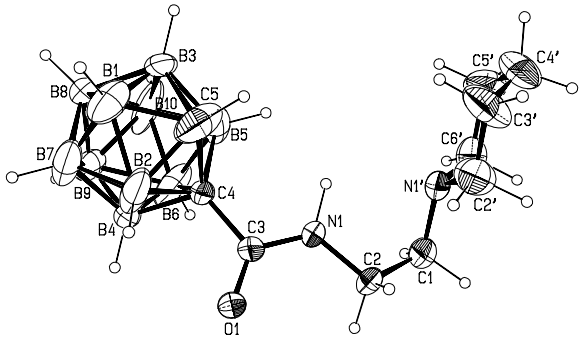


Figure 3. OrtepII view of the asymmetric unit of **14**, showing the labeling of the non-hydrogen atoms. The displacement ellipsoids are shown at the 25% probability level.

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References and Notes

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Povzetek

Spojino 4-jodo-*N*-[2-(1-piperidinil)etil]benzamid (IPAB) smo uporabili kot spojino vodnico za pripravo petih novih derivatov, ki vsebujejo 1,2-dikarba-*closo*-dodekaboransko kletko. Naš namen je bil sintetizirati nove spojine, ki bi bile uporabne za zdravljenje malignega melanoma in raka dojke z metodo BNCT.