March 2008 Volume 4 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(3), 2008 [187-194]

Synthesis and characterization of promising carboranylquinazolines for boron neutron capture therapy of tumors

Afaf R.Genady

Department of Chemistry, Faculty of Science, University of Tanta, 31527-Tanta, (EGYPT)

Tel: +20-40-3297974; Fax: +20-40-3350804

E-mail: afafgenady@hotmail.com

Received: 30th December, 2007 ; Accepted: 4th January, 2008

ABSTRACT

Novel classes of structurally different boronated quinazolines were designed bearing 22-37% boron by weight for potential application in BNCT of tumors. Firstly, the o-carborane cage was linked to quinazoline at C-2 position via thioether linker: 2-S-(1,2-dicarba-closo-dodecaboran(12)-1-yl)-3-phenylquinazolin-4(3H)-one. Secondly, the o-carborane cage connected to quinazoline moiety at C-4 position through an ether linkage: 4-O-(o-carboran-1-yl)-2-methylquinazoline. Finally, carborane moieties were also linked to the C-6 position of quinazoline: 6-[N-{3-(2-methyl-1,2-dicarba-closo-dodecaboran(12)-1-yl)methyl}benzylidinamino]quinazolin-4(3H)-one and 6-[N-{3,5-di(2-methyl-1,2-dicarba-closo-dodecaboran(12)-1 yl)methyl}benzylidinamino]quinazolin-4(3H)-one. The water solubility was achieved by the degradative conversion of the o-carboranylquinazolines to the corresponding potassium nido-carboranylquinazolines: 2-S-(1,2-dicarba-nido-undecacarborate-1-yl)-3-phenylquinazolin-4(3H)-one, 4-O-(1,2-dicarba-nido-undecacarborate-1-yl)-2-methylquinazoline, 6-[N-{3-(2-methyl-1,2-dicarba-nido-undecacarborate-1-yl)methyl}benzylidinamino] quinazolin-4(3H)-one and 6-[N-{3,5-di(2-methyl-1,2-dicarba-nido-undecacarborate-1-yl)methyl}benzylidinamino]quinazolin-4(3H)-one. The products were confirmed by NMR, elemental analysis, IR, and mass spectrometry. The compounds described here can be considered as new candidates for BNCT.

KEYWORDS

Quinazolines;
NMR spectroscopy;
BNCT;
Carboranes;
Antitumor agents.

INTRODUCTION

Boron neutron capture therapy (BNCT) is an anticancer treatment that involves the irradiation of[10] B-rich tumors with low energy neutrons[1,2]. Subsequent productions of high linear energy transfer particles[4], He_2 (α-particle) and[7] Li_3, cause severe damage to tumor cells through ionization process. The advantage of this binary approach is in the differential dose that can be established between the tumor and its surrounding normal tissue, provided that the compound, which carries the target atom, is avidly taken up in tumor, yielding a high tumor to normal tissue ratio. To achieve that objective, boron-containing analogues of various cellular building blocks have been synthesized[2-6]. Numerous heterocyclic compounds which are analogues of natu-

ral substances, may be used as transporters for anti-cancer agents to cancer cells. For example, heterocyclic analogues of neucleo-bases have been used for this goal[7]. The use of pyrimidine bases as a transport vehicle for the delivery of active molecules or their fragments is caused by an easier metabolism of pyrimidines in tumoral cells than in healthy tissues.

Quinazolines as hydrophobic analogues of pyrimidine bases, have great biological significance[8,9]. Many of them showed biological activities such as anti-bacterial, anti-inflamatory, anti-tumor anti-cancer and CNS depressant[8-10]. The anti-carcinogenic action of quenazolines is related to their ability to be included in nucleic acids of tumoral cells. The first boronated quinazolines were prepared by incorporating the hydroxyboryl group into the pyrimidine ring, but such a ring structure does not possess the needed hydrolytic stability and suffered from the low content of boron atoms per molecule[11]. Additionally, these compounds were found to be biologically unstable, and they failed to become incorporated selectively into tumor cells or into nucleic acids.

The polyhedral *o*-carboranes appear to meet the requirements of possessing high boron percentages, and for this reason, there has been significant effort in the area of compound development directed toward the incorporation of such entities into organic structures [12-16]. Interest persists in such structures because of their inherent stability and their potential for incorporating various organic moieties into these clusters. Carboranes, especially those containing the $C_2B_{10}H_{12}$ nucleus, are very organic in nature, and the method of their incorporation into various organic/biochemical substrates has now become well developed[17]. The advantage of this cage is that it contains ten boron atoms and that it can be chemically degraded to yield a hydrophilic, open-caged nido-carborane moiety[18].

Taken in consideration the last facts, we investigated the synthesis of several classes of carboranyl quinazolines starting with 2-mercapto-3-phenyl quinazolin-4(3H)-one, 4-chloro-2-methylquinazoline, and 6-aminoquinazolin-4(3H)-one(Figure 1). The advantage may be that if the boronated compounds possess comparable molar toxicity, higher boron concentrations could be administrated with those having multiple boron atoms and thereby higher tumor concentrations may be achieved.

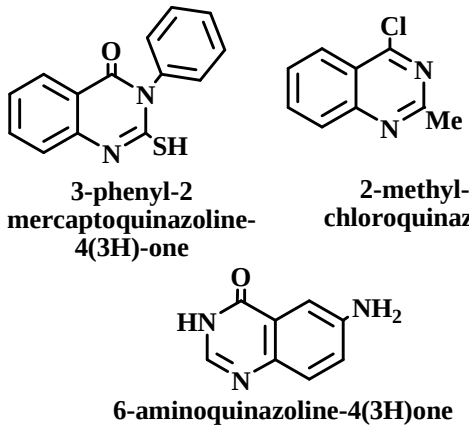
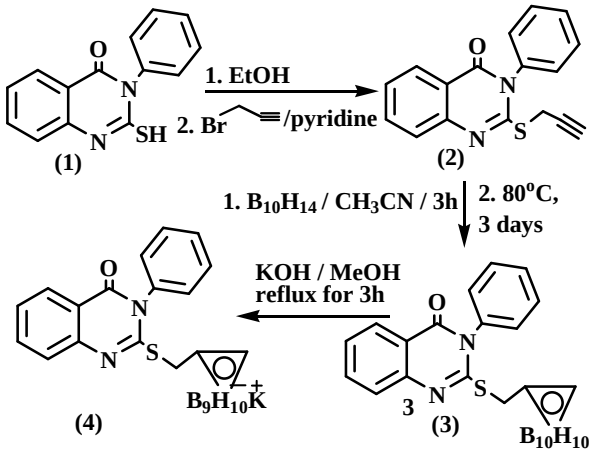


Figure 1: Building blocks for the synthesis of boronated quinazolines



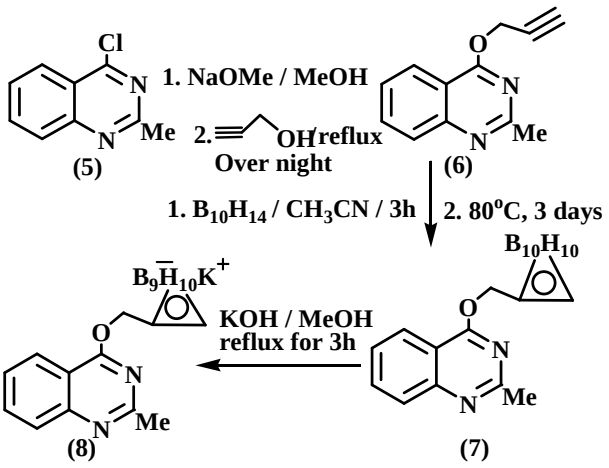
SCHEME 1

RESULTS AND DISCUSSION

One problem with the previousely used boronated quinazoline is their unstability under hydrolytic conditions. The other, when their stability are enhanced by placing bulky or aromatic groups on boron, the compounds cease to emulate biochemically, the normally occurring substances. To overcome this problems we planned three fold strategies: the first stratgy aimed to prepare o-carborane cage linked to the 2-position of quinazoline via thioester linker. The reaction of 3-phenyl-2-mercaptoquinazolin-4(3H)-one 1[19], with propargyl bromide in the presence of ethanol and catalytic amount of pyridine gave 2-S-propargyl-3-phenylquinazolin-4(3H)-one **(2)** (SCHEME 1)[20]. In

the ^{1}H NMR spectrum, a singlet from CH proton in the ethine moiety of compound **(2)** is observed at δ=1.76 ppm, while a doublet of CH_2 group protons is observed at 3.83 ppm. Moreover, compound **(2)** showed a mass spectrum with an intense molecular ion peak (M^+) with m/z =292. Reaction of 2 with the bis(acetonitrile) decaborane complex led to the formation of the carboranylquinazoline 3(SCHEME 1). Chromatography was performed by column using $CHCl_3$ and acetone(1:5) as eluent gave compound **(3)** in 63% yield. The ^{1}H NMR spectrum of compound **(3)** showed two singlets at δ = 4.05 and 4.3 ppm corresponding to carborane CH and the methylene group (CH_2S), respectively. However, another broad singlet appears at 1.5-3.4 ppm due to the B-H protons. Moreover, ^{13}C NMR chemical shifts reflected the connection of quinazoline moiety by the carborane cluster via thioether linker as shown in figure 2. Additionally, the assignments of ^{13}C NMR signals were based on DEPT experiments and chemical shift arguments. The carborane cage was then degraded in order to achieve water-solubility by using methanolic KOH to produce the nido-carboranyl quinazoline **(4)**. The ^{1}H NMR spectrum of compound 4 in dimethylsulfoxide (DMSO), typically shows the B-H proton on the open face of the nido-carborane upfield shifted at -2.30 and the remaining BHs at 1.61ppm (Figure 3). The CH-carborane proton adjacent to the open face, appeared shifted at 2.18ppm and the quinazoline protons remain essentially unchanged (Δδ less than 0.3ppm).

Secondly, the introduction of o-carborane cage takes place through quinazoline moiety by ether linkage: in this case, 4-Chloro-2-methylquinazoline **(5)** was synthesized by treating 2,3-dimethylquinazolin-4(3H)-one with PCl_5/PCl_3 according to the literature procedure[21]. The reaction of chloroquinazoline **(5)** with propargyl alcohol in the presence of alkali gave the corresponding alkoxy derivative **(6)**, which was isolated in 67% yield from **(5)** (SCHEME 2). ^{1}H NMR spectrum of 4-O-(o-carboran-1-yl)-3-methylquinazoline **(6)** confirmed the nucleophilic substitution of chlorine atom of 5 with propyloxy group, where it showed two singlets at 4.53 and 2.73ppm due to the methylene and acetylenic protons, respectively. Moreover, the methyl protons attached to the diazine ring resonates at 2.34ppm. Addition of compound **(6)** to solution of decaborane



SCHEME 2

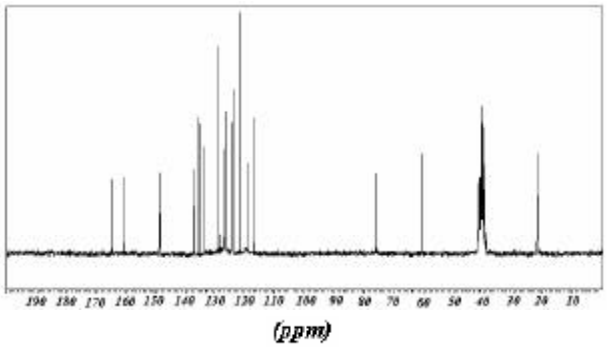


Figure 2 : 200 MHz ^{13}C NMR spectrum of compound 3 in d_6-DMSO

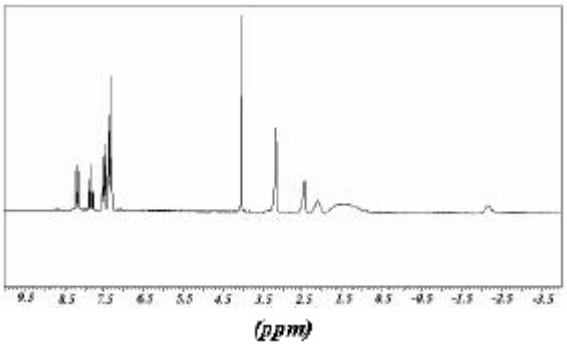
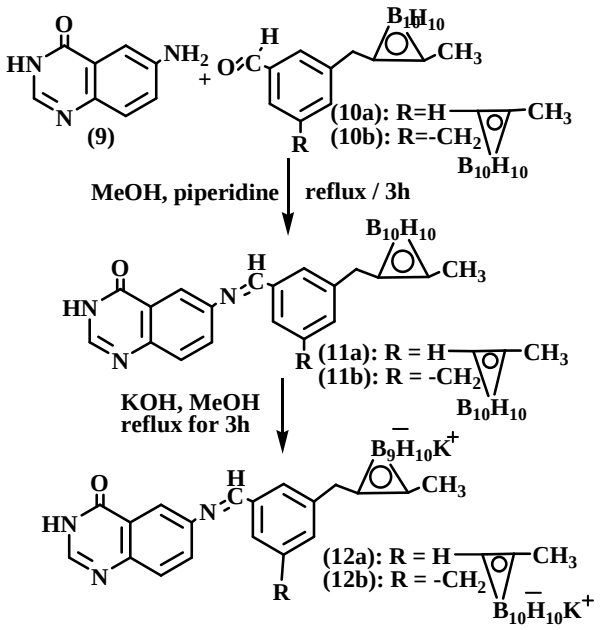


Figure 3 : 200 MHz ^{1}H NMR spectrum of compound 4 in d_6-DMSO

($B_{10}H_{14}$) in acetonitrile furnished the corresponding carborane **(7)** as shown by elemental analysis, IR, NMR and mass spectroscopy. Degradation of the carborane cage of boronated quinazoline **(7)** gave the nido-carboranyl quinazoline **(8)**.

The third route, which includes the attachment of o-carborane at 6-position of quinazoline, starts with 6-aminoquinazoline-4(3H)-one **(9)**, which was prepared

Full Paper



SCHEME 3

by a multi-step reaction according to the literature[9]. The synthesis of Schiff bases of boronated aldehydes 3-[(1-methyl-o-carboran-2-yl)methyl]benzaldehyde[22] **(10a)** and 3,5-di[(1-methyl-o-carboran-2-yl)methyl] benzaldehyde[22] **(10b)** was our strategy to get 6-aminocarboranylquinazolines **(11a)** and **(11b)**, respectively (SCHEME 3). The reaction of compound **(9)** with aldehydes **(10a)** and **(10b)** in methanol in the presence of catalytic amount of piperdine gave in high yield the suggested compound **(11a)** and **(11b)**, respectively. The ^{1}H NMR spectra of the Schiff bases **(11a)** and **(11b)** in DMSO contained singlet signals of the N=CH proton at 8.53 and 8.68ppm, respectively. The BH protons of carborane appeared in the range 1.48-3.32 ppm, while the aromatic protons resonate at 7.25-7.56 ppm. The ^{13}C NMR spectra of these compounds confirmed the presence of the imine carbon at 166.32 and 164.42ppm. However, the carborane carbons of the cluster appear at 72.34-73.91ppm.

Degradation of **(11a)** and **(11b)** gave the nido-carboranyl analogues **(12a)** and **(12b)**, respectively. The proton NMR spectra of the 12a and 12b, in d_6-DMSO, showed the B-H protons the open face of the nido-carboranes at -2.3 and -2.53 ppm and the remaining BHs absorb at 1.3 and 1.56 ppm, respectively. The methyl protons, adjacent to the open face, appeared upfield shifted at 1.8 and 2.1 ppm, respectively.

The IR spectra of compounds **(3,4,11, and 12)** showed strong absorption bands within the 1662-1682cm^{-1} region characteristics for CO of carbonyl group. For all compounds, the vibrational frequencies of B-H band ν(B-H) and the B-B band ν(B-B) of o-carborane or nido-carborane cluster were not found to be sensitive to the connection of quinazoline moieties indicating that the intracluster bonding is not perturbed by its connection with quinazoline ring.

EXPERIMENTAL

Materials and methods

All reagents, dry solvents, and $B_{10}H_{14}$ were commercially obtained from chemical companies. Quinazolines(e.g. 3-phenyl-2 mercaptoquinazoline-4(3H)-one, 2-methyl-4-chloroquinazoline, and 6-aminoquinazoline-4(3H)one), 3-[(1-methyl-o-carboran -2-yl)methyl]benzaldehyde **(10a)** and 3,5-di[(1-methyl-o-carboran-2-yl)methyl]benzaldehyde **(10b)** were prepared according to the literature methods.[9,19,22] Column chromatography was conducted on silica gel 60 (Fluka). Plate chromatography was conducted on TLC plates, silica gel on aluminum, 20X (Aldrich). Elemental analyses were performed by a Perkin-Elmer 2400 automatic elemental analyzer. All compounds gave elemental analysis within ± 0.4%. The measurements for NMR(^{11}B, ^{1}H and ^{13}C) were carried out on a Bruker DPX 200 spectrometer. The chemical shifts δ are given in ppm relative to Ξ = 100MHz for (^{1}H) (nominally $SiMe_4$), Ξ = 50 MHz for δ (^{13}C) (nominally $SiMe_4$), and Ξ = 32.083MHz for δ (^{11}B) (nominally F_3BOEt_2) in d_6-DMSO. IR(cm^{-1}) spectra were determined as KBr disc on a Bruker Vector 22 spectrometer. Mass spectrometric data were measured using a Finnigan MAT 8222 instrument, either (a) by fast-atom bombardment ionization (FAB) with glycerol or nitrobenzylalcohol (NBA) as matrix. Only the signal with the highest intensity of the boron isotopic pattern is listed and compared with distribution of isotopes calculated by ISOFORM program. Melting points determination were performed by the open capillary method using a MEL-TEMP11 melting point apparatus and are reported uncorrected.

Synthesis of 2-propargylthio-3-phenylquinazolin-

4(3H)-one (2)

Propargyl bromide (0.32ml, 3.6mmol) and 0.21ml pyridine were added to a solution of quinazoline **(1)**(0.5g, 2.0mmol) in 10ml dry ethanol. The reaction mixture was refluxed for 20 min, then the solution was cooled to room temperature and stirred for 2h. The resulting precipitate was filtered off and recrystallized from ethanol to yield a faint yellow solid substance.

Yield: (75%, 0.42g, m.p. 186-188°C); IR ν_{max}(KBr disc)/cm^{-1}: 2122s(C≡C), 1672s (C=O), 1580m (C=N); δ_H(200MHz; d_6-DMSO; $SiMe_4$) 1.76(s, 1H, $CH_{acetylenic}$) 3.83(s, 2H, SCH_2), 7.25-8.02(m, 9H, H_{arom}); δc(50MHz; d_6-DMSO; $SiMe_4$) ; 17.6(CH_2, CH_2S), 69.2(CH, $CH_{acetylenic}$), 75.8(C, $C_{acetylenic}$), 118.23(CH, C_{arom}), 120(CH, C_{arom}), 122.5 (2CH, C_{arom}), 123.6(C, C_{arom}), 127.3(CH, C_{arom}), 128.7(2CH, C_{arom}), 134(CH, C_{arom}), 135(CH, C_{arom}), 136.6(C, C_{arom}), 148(C, C_{arom}), 161.3(C=O), 164.6(C, C_{arom}); (FAB^+): *m/z*(%) = 294(26) $[M + 2H]^+$, 293(55) $[M +H]^+$, 292 (98) $[M^+]$; elemental analysis calcd(%) for $C_{17}H_{12}N_2OS$: C 69.84, H 4.14, N 9.58; Found: C 69.71, H 4.04, N 9.49.

Synthesis of 2-S-(1,2-di-closo-dodecaboran(12)-1-yl)-3-phenylquinazolin-4(3H)-one (3)

A solution of $B_{10}H_{14}$ (1.4g, 11.7mmol) in acetonitrile (40ml) was refluxed for 2h to obtain the bis(acetonitrile)decaborane. Then, quinazolinylacetylene **(2)** (2.9g, 10.1mmol) was added followed by reflux for 4h. After cooling, the solvent was evaporated and a yellow solid was obtained. Methanol (20ml) was added and evolved H_2 was observed from the decomposition of excess bis(acetonitrile)decaborane. After 5 h, the MeOH was evaporated in vacuum and the yellow residue washed with hexane (3×20 ml) and purified by column chromatography (acetone/$CHCl_3$, 1:5) to give compound 3 as a yellow solid substance.

Yield: (63%, 2.3g, R_f = 0.58, m.p. = 170-172°C); IR ν_{max}(KBr disc)/cm^{-1}: 2560s (BH), 1682s(C=O), 1586(C=N); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) 1.5-3.4(bs, BH), 4.05 (bs, 1H, $CH_{carborane}$), 4.3(s, 2H, SCH_2), 7.25-7.69 (m, 7H, H_{arom}), 7.79 (t, J = 2.6 ,1H, $H_{arom)}$, 8.16(d, J = 2.4 ,1H, $H_{arom)}$; δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 16.1(CH_2, CH_2S), 60.9 (CH, $CH_{carborane}$), 75.4(C, $C_{carborane}$), 117.8(CH_{arom}), 119.6 (CH_{arom}), 123.1($2CH_{arom}$), 123.3 (C_{arom}), 127.1 (CH_{arom}), 128.6($2CH_{arom}$), 134.2(CH_{arom}), 135.3 (CH_{arom}), 136.9(C_{arom}), 148.7(C_{arom}), 161.7(C=O), 165.1(C_{arom}); δ_B(33.083 MHz; d_6-DMSO; $SiMe_4$) -2.96(1B), -4.65(1B), -9.12(2B), -11.14 (2B), -12.78 (4B); FAB^+): m/z(%) =411(59) $[M + H]^+$, 410(89) $[M^+]$; elemental analysis calcd(%) for $B_{10}C_{17}H_{22}N_2OS$: C 49.73, H 5.4, N 6.82; Found: C 49.52, H 5.12, N 6.62.

Synthesis of potassium 2-S-(1,2-dicarbadode caborater-1-yl)-3-phenylquinazolin-4(3H)-one (4)

A solution of compound **(3)** (0.41g, 1.0 mmol) in methanolic KOH (20ml, 0.5M) was refluxed for 3h. The resulting *nido*-carboranylquinazoline **(4)** was purified using preparative TLC (0.1% CH_3CO_2H in 3:1 acetone/$CHCl_3$) as a yellow solid substance.

Yield: (58%, 0.23g, R_f = 0.3, m.p. =255-256 °C); IR ν_{max}(KBr disc)/cm^{-1}: 2508s (BH), 1673s(C=O), 1589m(C=N); δ_H (200 MHz; d_6-DMSO; $SiMe_4$) -2.3 (bs, 1H, BH), 1.61 (bs, 9H, BH), 2.18 (bs, 1H, $CH_{carboborane}$), 4.05 (s, 2H, SCH_2), 7.41-7.72 (m, 7H, H_{arom}), 7.85(t, J = 2.3 ,1H, $H_{arom)}$, 8.23(d, J = 2.4 ,1H, $H_{arom)}$; δ_C (50 MHz; d_6-DMSO; $SiMe_4$) 16.2(SCH_2), 57.3($CH_{carborane}$), 69.8 ($C_{carborane}$), 117.2(CH_{arom}), 119.9 (CH_{arom}), 123.5 ($2CH_{arom}$), 123.4(C_{arom}), 127.4 (CH_{arom}), 128.5($2CH_{arom}$), 134.1(CH_{arom}), 135.6 (CH_{arom}), 136.7(C_{arom}), 148.6(C_{arom}), 161.3 (C=O), 165.8 (C_{arom}); δ_B(33.083MHz; d_6-DMSO; $SiMe_4$)-9.92(1B), -10.71(2B), -11.19(2B), -14.62(1B), -22.71 (1B), -32.91 (2B); $(FAB)^-$: m/z(%)= 399(85) $[M^-]$; elemental analysis calcd(%) for $B_9C_{17}H_{22}N_2OSK$: C 46.53, H, 5.05, N 6.38; Found: C 46.22, H 4.89, N 6.14.

Synthesis of 4-O-propargyl-2-methylquinazoline (6)

To a solution of quinazoline (5) (0.66g, 3.5mmol) in 20ml NaOMe/MeOH, propargyl alcohol (2.23ml, 4.0mmol) was added and refluxed for 2 days. After cooling the precipitate formed was filtered and washed with methanol followed by purification with column chromatography using $CHCl_3$ as eluent to give compound **(6)** as a colorless solid.

Yield: (67%, 0.46g, R_f = 0.41, m.p.=185-186 °C); IR ν_{max}(KBr disc)/cm^{-1}: 2134s (C≡C), 1563s(C=N); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) 2.34(s, 3H, CH_3), 2.73(s, 1H, $CH_{acetylenic}$), 4.53(s, 2H, OCH_2), 7.73(t,

1H, H_{arom}), 7.91(m, 2H, H_{arom}), 8.05(m, 1H, H_{arom}); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 27.3(CH_3), 58.2 (OCH_2), 78.2($CH_{acetylenic}$), 79.0 ($C_{acetylenic}$), 114.1 (C_{arom}), 120(CH_{arom}), 126(CH_{arom}), 128(C_{arom}), 135 (CH_{arom}), 167 (C_{arom}), 180(C_{arom}); (FAB^+): m/z(%) =199 (76) $[M + H]^+$, 198(92) $[M^+]$; elemental analysis calcd (%) for $C_{12}H_{10}N_2O$: C 72.71, H 5.08, N 14.13; Found: C 72.53, H 4.89, N 13.91.

Synthesis of 4-O-(1,2-dicarba-closo-dodecaboran (12)-1-yl)-2-methylquinazoline (7)

Compound **(7)** was prepared with the same procedure as in compound **(3)**. The purification was carried out by TLC using $CHCl_3$ as eluent to yield a colorless solid substance.

Yield: (76%, 2.4g, R_f=0.61, m.p.=192-193 °C); IR ν_{max}(KBr disc)/cm^{-1}: 2573s (BH),1558s (C=N); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) 1.46-3.51(bs, BH), 2.38(s, 3H, CH_3), 4.12(bs, 1H, carborane CH), 4.2(s, 2H, OCH_2), 7.38-7.94(m, 4H, $H_{aromatic}$); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 26.3(CH_3), 57.3(OCH_2), 62.0($CH_{carborane}$), 75.8 ($C_{carborane}$), 113.92(C_{arom}), 121.05(CH_{arom}), 127.14(CH_{arom}), 128.52(C_{arom}), 135.47(CH_{arom}), 167.09 (C_{arom}), 180.91(C_{arom}); δ_B (33.083 MHz; d_6-DMSO; $SiMe_4$) -2.92 (1B), -4.58 (1B), -8.99 (2B), -10.97(2B), -12.59(4B); (FAB^+): m/z(%) = 317 (59) $[M+H]^+$, 316 (78) $[M^+]$; elemental analysis calcd(%) for $B_{10}C_{12}H_{20}N_2O$: C 45.55, H 6.37, N 8.85; Found: C 45.31, H 6.17, N 8.59.

Synthesis of potassium 4-O-(1,2-dicarba-nido-undecarborate-1-yl)-2-methylquinazoline (8)

Compound **(8)** was prepared with the same procedure as in compound **(4)**. The resulting substance was purified by TLC (0.1% CH_3CO_2H in 1:1 acetone/ $CHCl_3$) as a colorless solid substance.

Yield: (63%, 0.19g, R_f = 0.27, m.p. = 233-234°C); IR ν_{max}(KBr disc)/cm^{-1}: 2520s (BH), 1551s(C=N); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) -1.92(bs, 2H, BH), 2.13(br, 8H, BH), 2.24(s, 3H, CH_3), 2.17(bs, 1H, $CH_{carborane}$), 4.06(s, 2H, OCH_2), 7.26-7.74(m, 4H, H_{arom}); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 26.3(CH_3), 56.3(OCH_2), 56.87($CH_{carborane}$), 67.96 ($C_{carborane}$), 113.56(C_{arom}), 121.24(CH_{arom}), 127.61(CH_{arom}), 128.74(C_{arom}), 135.21(CH_{arom}), 167.11(C_{arom}), 180.02 (C_{arom}); δ_B (33.083 MHz; d_6-DMSO; $SiMe_4$) -9.89 (1B), -10.69 (2B), -11.17(2B), -14.59(1B), -22.71 (1B),-32.96 (2B); (FAB^-): m/z(%) = 305(87) $[M^-]$; elemental analysis calcd(%) for $B_9C_{12}H_{20}N_2OK$: C 41.81, H 5.85, N 8.13; Found: C 41.53, H 5.46, N 7.96.

Synthesis of 6-[N-{3-(2-methyl-1,2-dicarba-closo-dodecaboran(12)-1-yl)methyl}benzylidine amino]quinazoline-4(3H)-one (11a), 6-[N-{3,5-di(2-methyl-1,2-dicarba-closo-dodecaboran(12)-1-yl)methyl}benzylidine amino]quinazoline-4(3H)-one (11b)

To a solution of 6-aminoquinazoline-4(3H)one **(9)**(1.6g, 10mmol) in 20ml methanol, carboranylbenza ldehyde **(10a)** or 10b (11.0mmol) and piperidine (1ml) were added. The reaction mixture was heated under reflux for 3h. After cooling, the deposited solid product was collected by filtration, washed with methanol and purified by column chromatography using acetone-chloroform 1:1 as eluent to give compounds **(11a)** or **(11b)**.

(11a) Yield: (87%, 3.5g, R_f = 0.35, m.p. =189-191 °C); IR ν_{max}(KBr disc)/cm^{-1}: 2572s (BH), 1668s(C=O), 1628s(C=N), 1585m(C=C); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) 1.51-3.32(bs, BH), 2.19(s, 3H, CH_3), 3.4(s, 2H, CH_2), 7.25-7.56(m, 6H, H_{arom}), 7.73(s, 1H, H_{arom}), 8.53(s, 1H, CH=N), 11.87(bs, 1H, NH); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 14.92 (CH_3), 31.21 (CH_2), 72.34, 73.91($C_{carborane}$), 105.06, 107.14, 109.07, 121.13, 127.42(CH_{arom}), 123.61, 140.05($3C_{arom}$), 142.43 (CH_{arom}), 147.02, 162.73($2C_{arom}$), 166.32 (CH=N); δ_B(33.083 MHz; d_6-DMSO; $SiMe_4$) -2.91 (1B), -4.55 (1B), -9.24(2B), -11.15 (2B), -12.69 (4B); (FAB^+): m/z(%)=(92) 420 $[M+H]^+$, 419(79) $[M^+]$; elemental analysis calcd(%) for $B_{10}C_{19}H_{25}N_3O$: C 54.39, H 6.01, N 10.02; Found: C 54.16, H 6.41, N 10.38.

(11b) Yield: (72%, 4.2g, R_f = 0.38, m.p. = 205-206 °C); IR ν_{max}(KBr disc)/cm^{-1}: 2575vs (BH), 1662s(C=O), 1632s (C=N), 1579m(C=C); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) 1.48-3.18(bs, BH), 2.21(s, 6H, $2CH_3$), 3.56(s, 4H, $2CH_2$), 7.30-7.48(m, 6H, H_{arom}), 7.82 (s, 1H, H_{arom}), 8.68(s, 1H, CH=N), 11.91 (bs, 1H, NH); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 15.02($2CH_3$), 30.82 ($2CH_2$), 72.51, 73.61($4C_{carborane}$), 105.25, 108.19, 109.56, 121.74, 123.61, 127.32 ($6CH_{arom}$), 142.51(C_{arom}), 143.21(CH_{arom}), 147.82, 161.98($2C_{arom}$), 164.42 (CH=N); δ_B(33.083 MHz; d_6-

DMSO; $SiMe_4$) -2.85(2B), -4.55(2B), -8.94(4B), -11.06 (4B), -12.54 (8B); (FAB^+): m/z(%) =590(95) ($[M+H]^+$, 589 (81) $[M^+]$; elemental analysis calcd(%) for $B_{20}C_{23}H_{39}N_3O$: C 46.84, H 6.66, N 7.12; Found: C 46.53, H 6.31, N 6.91.

Synthesis of 6-[N-{3-(2-methyl-nido-carborate-1-yl)methyl}benzylidine amino]quinazoline-4(3H)-one (12a), 6-[N-{3,5-di(2-methyl-nido-carborate-1-yl)methyl}benzylidine amino]quinazoline-4(3H)-one (12b)

The conversion of compounds **(11a)** and 11b to their nido-forms **(12a)** and **(12b)** was performed as described for compounds **(3)**. Pure compounds were obtained after using TLC (0.1% CH_3CO_2H in 2:1 acetone/$CHCl_3$) to yield colorless solid substances.

(12a) Yield: (79%, 0.35g, R_f = 0.24, m.p. =263-264°C); IR ν_{max}(KBr disc)/cm^{-1}: 2521s (BH), 1673s (C=O), 1619s(C=N), 1584m (C=C); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) -2.3 (bs, 2H, BH), 1.3(bs, 8H, BH), 1.8 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 7.29-7.58 (m, 6H, H_{arom}), 7.71(s, 1H, H_{arom}), 8.56(s, 1H, CH=N), 11.79 (bs, 1H, NH); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 14.83 (CH_3), 30.72 (CH_2), 58.21, 57.95 ($C_{carborane}$), 105.15, 106.26, 109.95, 122.01, 126.97(CH_{arom}), 123.24, 141.27($3C_{arom}$), 142.65(CH_{arom}), 147.12, 162.65 ($2C_{arom}$), 168.11(CH=N); δ_B(33.083 MHz; d_6-DMSO; $SiMe_4$) -9.91(1B), -10.57 (2B), -11.21 (2B), -14.65 (1B), -22.79(1B), -32.91(2B); (FAB^-): m/z(%) = 408(67) $[M^-]$; elemental analysis calcd(%) for $B_9C_{19}H_{25}N_3OK$: C 50.96, H 5.63, N 9.38; Found: C 50.64, H 5.14, N 9.02.

(12b) Yield: (68%, 0.38g, R_f =0.15, m.p. =293-294°C); IR ν_{max}(KBr disc)/cm^{-1}: 2525vs (BH), 1673s (C=O), 1619s (C=N), 1583m(C=C); δ_H(200 MHz; d_6-DMSO; $SiMe_4$) -2.53 (bs, 2H, BH), 1.56(bs, 8H, BH), 2.11(s, 6H, $2CH_3$), 3.62(s, 4H, $2CH_2$), 7.31-7.47(m, 6H, H_{arom}), 7.85(s, 1H, H_{arom}), 8.64(s, 1H, CH=N), 11.86(bs, 1H, NH); δ_C(50 MHz; d_6-DMSO; $SiMe_4$) 15.12($2CH_3$), 31.65 ($2CH_2$), 59.24, 58.89($4C_{carborane}$), 105.16, 108.24, 109.34, 121.69, 123.47, 127.56($6CH_{arom}$), 142.59(C_{arom}), 143.27 (CH_{arom}), 147.83, 161.58 ($2C_{arom}$), 166.92 (CH=N); δ_B(33.083 MHz; d_6-DMSO; $SiMe_4$) -9.94 (2B), -10.71(4B), -11.09 (4B), -14.64(2B), -22.86(2B), -32.01(4B); (FAB^-) m/z(%) = 568(79) $[M^-]$; elemental analysis calcd(%) for $B_{18}C_{23}H_{39}N_3OK_2$: C 42.74, H 6.08, N 6.50; Found: C 42.65, H 5.89, N 6.19.

CONCLUSION

We have demonstrated a very simple, efficient, and practical method for the synthesis of novel water soluble boronated quinazolines in acceptable yields from readily available starting materials. Three classes of boronated quinazoline were designed bearing 22-37% boron by weight for potential application in BNCT of tumors. The reactions as well as the workup procedures and the purifications for all products were readily feasible. All compounds are highly stable at room temperature compared with previously reported boronatedquinazolines[11]. The compounds described in this report are representative of agents which can be prepared by simple coupling reactions to yield a large series of agents for experimental BNCT.

ACKNOWLEDGMENT

The author is grateful to Professor Doctor Detlef Gabel, Department of Chemistry, University of Bremen, Germany, for providing facilities for NMR and MS measurements.

REFERENCES

[1] M.F.Hawthorne; Angew.Chem.Int.Ed.Engl., **32**, 950-984 **(1993)**.
[2] A.H.Soloway, W.Tjarks, B.A.Barnum, F.G.Rong, R.F.Barth, I.M.Codogni, J.G.Wilson; Chem.Rev., **98**, 1515-1562 **(1998)**.
[3] H.Ketz, W.Tajarks, D.Gabel; Terahedron Lett., **31**, 403 **(1990)**.
[4] W.Tjarks, D.Gabel; J.Med.Chem., **34**, 315 **(1991)**.
[5] C.DiMeo, L.Panza, D.Capitani, L.Mannina, A. Banzato, M.Rondina, D.Renier, A.Rosato, V. Crescenzi; Biomacromolecules, **8**, 552-559 **(2007)**.
[6] Y.Yamato, N.Sadayori; Bioorg.Med.Chem.Lett., **6**, 9 **(1996)**.
[7] W.Tjarks; J.Organomet.Chem., **614-615**, 37-47 **(2000)**.
[8] G.A.El-Hiti, M.F.Abdel-Megeed; Heterocycles, **65**, 3007-3041 **(2005)**.
[9] N.R.El-Brollosy, M.F.Abdel-Megeed, G.A.El-Hiti,

A.R.Genady; Afinidad, **60**, 199-205 **(2003)**.

[10] I.R.Ager, D.R.Harrison, P.D.Kennewell, J.B.Taylor; J.Med.Chem., **20**, 379 **(1977)**.

[11] J-C.Zhuo, A.H.Soloway, J.C.Beeson, J.Weihua, B.A.Barnum, F-G.Rong, W.Tjarks, G.T.Jordan IV, J.Liu, S.G.Shore; J.Org.Chem., **64**, 9566-9574 **(1999)**.

[12] A.K.Bandyopadhyaya,S.Narayanasamy, R.F.Barth, W.Tjarks; Tetrahedron Lett., **48**, 4467-4469 **(2007)**.

[13] C.Naeslund, S.Ghirmai, S.Sjoberg; Tetrahedron, **61**, 1181-1186 **(2005)**.

[14] K.Ohta, H.Yamazaki, F.Pichierri, M.Kawahata, K.Yamaguchi, Y.Endo; Tetrahedron, **63**, 12160-12165 **(2007)**.

[15] Y.Q.Chen, J.Q.Wang, G.-X.Jin; J.Organometal. Chem., **692**, 5190-5194 **(2007)**.

[16] A.K.Bandyopadhyaya, R.Tiwari, W.Tjarks; Bioorg. Med.Chem., **14**, 6924-6932 **(2006)**.

[17] H.Nakamura, K.Aoyagi, B.Singaram, J.Cai, H. Nemoto, Y.Yamamoto; Angew.Chem., Int.Ed.Engl., **36**, 367 **(1997)**.

[18] M.Miura, D.Gabel, G.Oenberink, R.G.Fairchild; Tetrahedron Lett., **31**, 2247-2250 **(1990)**.

[19] M.F.Abdel-Megeed, Y.L.Ali, M.A.Saleh, I.M. Abdo, K.Smith, G.A.El-Hiti; Sulfur Lett., **19**, 129 **(1995)**.

[20] German Patent DE 2304322, **(1974)**.

[21] M.T.Bogert, C.E.May; J.Am.Chem.Soc., **31**, 507 **(1909)**.

[22] M.G.H.Vicente, S.J.Shetty, A.Wichramasinghe, K.M.Smith; Tetrahedron Lett., **41**, 7623-7627 **(2000)**.