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Small-molecule Kinase Inhibitors-loaded Boron Cluster as Hybrid Agents for Glioma Cell-targeting Therapy.

Marcos Couto,[a,b,c] Ignacio Mastandrea,[d,e] Mauricio Cabrera,[d] Pablo Cabral,[c] Francesc Teixidor,[b] Hugo Cerecetto*[a,c] and Clara Viñas,*[b]

Abstract: The reported new anilinoquinazoline-icosahedral borane hybrids have been evaluated as glioma-targeting for potential use in cancer therapy. Their anti-glioma activity depends on hybrids' lipophilicity; the most powerful compound against glioma cells, a 1,7-*closo*-derivative, displays at least 3.3-times higher activity, than the parent drug erlotinib. According to the cytotoxic effects on normal glia cells, the hybrids were selective for EGFR-overexpressed tumoural cells. These boron carriers could be used to enrich glioma cancer cells with boron for cancer therapy.

Glioblastoma multiforme (GBM) is the most common primary central nervous system tumour in USA and Europe: WHO reported more than 50 % of diagnosed gliomas corresponded to grade IV ones, the most malignant form.[1] The aetiology and the predisposing factors of GBM are still poorly understood being the exposure to ionizing radiation, such as children irradiated for leukaemia, one of the few proven environmental risk factor.[2] Despite GBM being a genetically heterogeneous tumour, there has been some common molecular characteristic described such as the loss of heterozygosity on chromosome 10,[3] and the amplification of epidermal growth factor receptor (EGFR) gene on chromosome 7, often in the form of double minutes.[4] EGFR overexpression is more common in primary GBM (40-60%) than in secondary ones (less than 10%). EGFR, also known as erb-B1 or Her-1, is a member of ErbB family of transmembrane tyrosine kinase receptor (TKR)[5] involved in enhancing growth, proliferation, migration, tumour neovascularization, and resistance to chemotherapies.[6] The GBM standard treatment is surgical resection of the tumour followed by a combination of radiation and chemotherapy to kill any remaining tumour cells infiltrated in the brain parenchyma.[7a] However, the current therapeutic success is still limited.[7b] For this reason new chemotherapies (antiangiogenic, immune and gene therapies, drugs to overcome resistance, radiation-enhancement, targeted-molecular therapies,[7c,d] and boron neutron capture therapy (BNCT)) are under investigation. EGFR and other TKRs are among the most studied pathways for the development of new targeted molecular agents. In this sense, small-molecules porting the 4-anilinoquinazoline pharmacophore have been described as TKRs-inhibitors.[8] The 4-anilinoquinazoline TKRs-inhibitors, like erlotinib (approved for clinical treatment as Tarceva, Figure 1),[9] competitively binds to the ATP binding site of the protein kinases intracellularly located in the transmembrane receptor.[10] On the other hand, BNCT relies upon the production of the high linear energy transfer particles ($^4He^{2+}$ and $^7Li^{3+}$) formed by the capture of thermal neutrons by a non-radioactive drug that contains in its structure ^{10}B isotopes.[11] Due to these particles having a linear path trajectory similar to the diameter of a cell, the BNCT damage is selectively confined in the tumour when the drug is selectively delivered in its cells. The current BNCT boronated clinical agents for GBM are BPA (*p*-boronophenylalanine) and BSH (mercaptoundecahydro-*closo*-dodecaborate) (Figure 1). Nevertheless, none of them selectively target tumour cells, which results in cytotoxicity and limits their application.[12] Recently, TK inhibitors incorporating a single boron atom, as boronic acid moiety, have been exploited as boron-containing drug targeting within glioma cells,[13] though their BNCT applications could be limited due to the low concentration of boron in the cells. Contrarily, the incorporation of the anionic dodecaborate cage present in BSH contributes with twelve boron atoms per molecule. In this sense, the use of neutral *closo*-carborane (1,2-*closo*-$C_2B_{10}H_{11}$, 1,7-*closo*-$C_2B_{10}H_{11}$) and anionic *closo*-borane ($[B_{12}H_{12}]^{2-}$) and cobaltabisdicarbollide ($[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11}]^-$) moieties may offer distinct advantages in BNCT medicinal chemistry, i.e. are inert to metabolic degradation, which increases their bioavailability, promote hydrophobic interactions with biological molecules, which are possible drug targets, and could be incorporated to organic framework.[11,14]

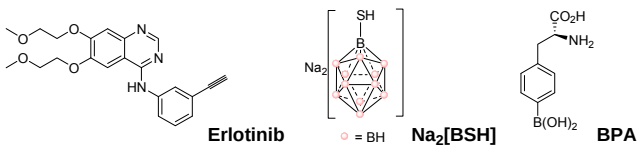

Figure 1. TKRs-inhibitor and boronated agents used for clinical treatment of GBM.

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Herein, we describe the development of new hybrid molecules with potential dual action (drug-radiotherapy combinations) to result in significant clinical benefits. For this purpose, the synthesis of new boron-containing quinazolines (Figure 2) has been achieved and their *in vitro* activities toward glioma cells assessed. These new compounds combine the 4-anilinoquinazolinyl moiety that possesses the capability to interact intracellularly with EGFR, with the icosahedral boron clusters, as the source of boron. Moreover, the different icosahedral boron clusters that have different lipophilicity[10,15] could provide different bio-activity to the boron-containing anilinoquinazoline derivatives.

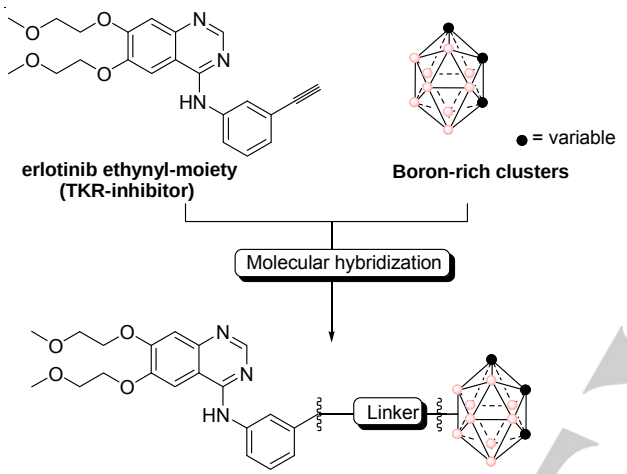

Figure 2. General design of the hybrid agents.

To enhance the interaction between the quinazoline derivatives and the EGFR, by increasing lipophilicity,[10,15] we selected the erlotinib ethynyl-moiety as synthon of structural modifications. The direct reaction between ethynyl-erlotinib and decaborane via decaborane-acetonitrile adduct formation followed by alkyne insertion was first attempted. However, the coordination capability of the nitrogen from the quinazoline produced a complex mixture but not the desired compounds as previously reported for the synthesis of 1-(C_5H_4N)-1,2-*closo*-$C_2B_{10}H_{11}$.[16] Consequently, the ethynyl moiety was used as connector to design several families with a linker between TKR-interacting group and the icosahedral boron cluster. Scheme 1 shows the synthesis of the new anilinoquinazoline-icosahedralborane cluster hybrids. The first approach consisted in the use of [1,2,3]triazolylpropyl connector generated by 1,3-dipolar cycloaddition,[17] in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate, affording hybrids **5**, **6**, **11**, and **12** in good yield (69-78 % after purification). The intermediate carboranylazides (**3**,[18a] **4**,[18b] **9**, and **10**) were selected to introduce chemodiversity to the final compounds, i.e. un-substituted and methyl-substituted 1,2- and 1,7-*closo*-carboranyl frameworks. The second approach involved the transformation of ethynyl-erlotinib group into an erlotinib-ethynylbenzyl connector (Scheme 1), via Sonogashira cross-coupling in presence of CuI and $[PdCl_2(PPh_3)_2]$, generating compounds **15**, **16**, **19**, and **20** in 35-49 % yield, after purification. Again, the iodophenyl intermediates (**13**, **14**, **17**, and **18**) introduced chemodiversity.

The anionic boron-containing [1,2,3]triazole derivatives **23** and **26** were obtained in 79 and 71 %, respectively, after purification via 1,3-dipolar cycloaddition between ethynyl-erlotinib and azides **22**[19a] and **25**[19b] (Scheme 2).

Finally, we focused on the confirmation of the relevance of carboranyl moiety in the displayed bioactivity. For that, and according to the bioisosterism proposed by Armstrong and Valliant,[14b,20] we prepared the phenyl-analogue, **28** (Scheme 3), of the two most active derivatives, i.e. **5** and **11** (see below).

Compounds were characterized by multinuclear NMR and FT-IR spectroscopic techniques, mass spectrometry and elemental analysis (see the Supporting Information).

The cytotoxicity of anilinoquinazoline-carboranyl and dodecaboranyl derivatives was evaluated by conducting sulforhodamine B assays on C6 cells from rat glioma.[21] It has been demonstrated that this kind of cells overexpress of EGFR21f (see own results, Supporting Information, Figure S1), even in brain tumours derived from C6 cultures. The results revealed that some boron-containing compounds had a concentration dependent cytotoxic effect on glioma cells (Table 1). Good to excellent biological results were obtained for some boron-containing derivatives when they were compared with the parent erlotinib. Compounds **5** and **11** were the most active being **11** at least 3.3-times more active than erlotinib. Additionally, **23** was at least 2.3-times more active than the parent compound. On the other hand, all the derivatives belonging to ethynylbenzyl-connector series (**15**, **16**, **19**, **20**) as well as the dianionic compound **26**, were inactive at the assayed doses. To emphasize that phenyl-analogue **28** was not as active as its bioisosters (**5** and **11)**.

To find out the selectivity toward tumoural cells, cytotoxicities of the most active compounds (**5**, **11**, and **23**) and parent erlotinib were evaluated on a mixed primary glial cell culture and these results were compared with C6 cells (SI, Table 1). Clearly, the results showed that these compounds were at least 2.3-times more cytotoxic for gliomas than for the normal glial cells.

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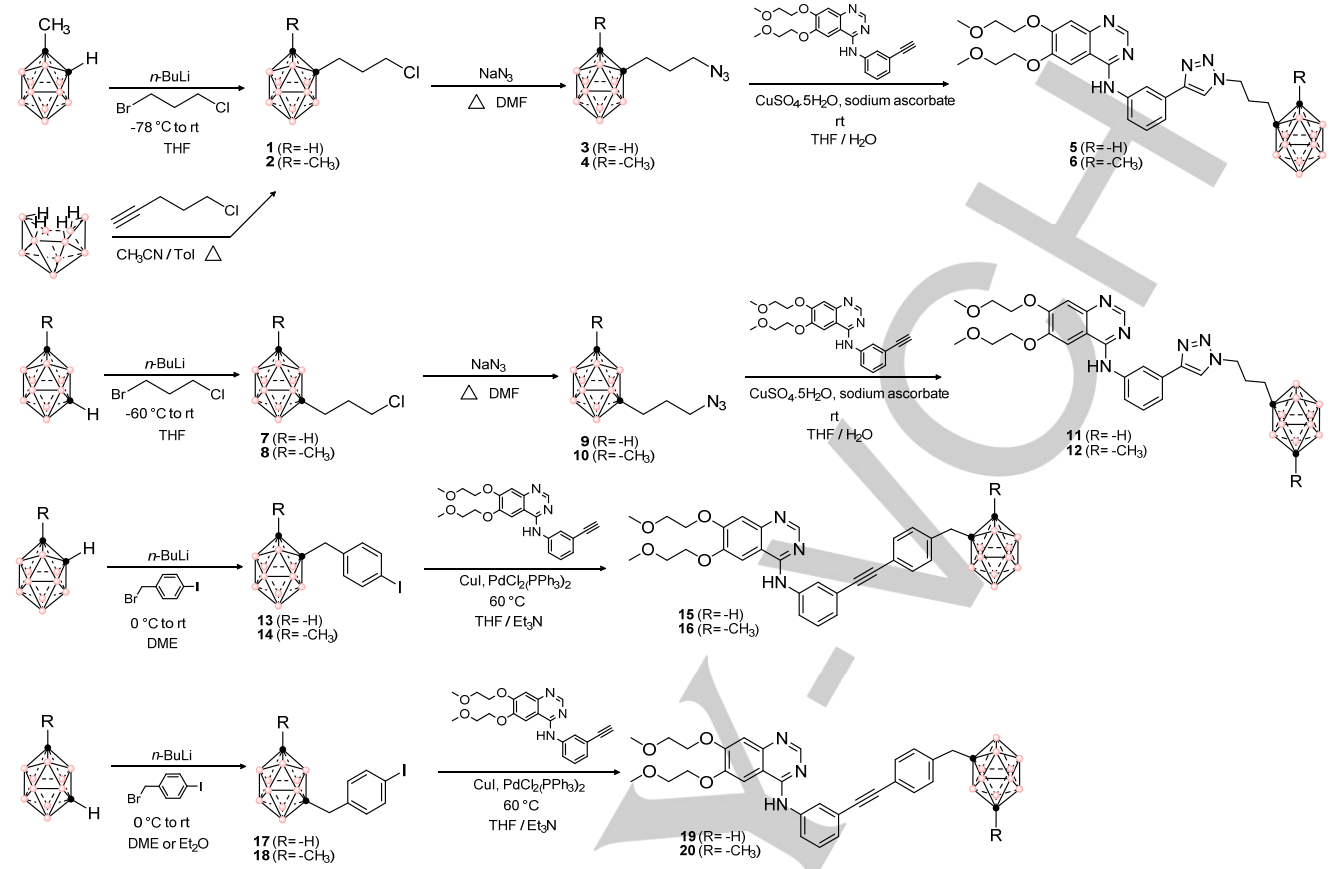
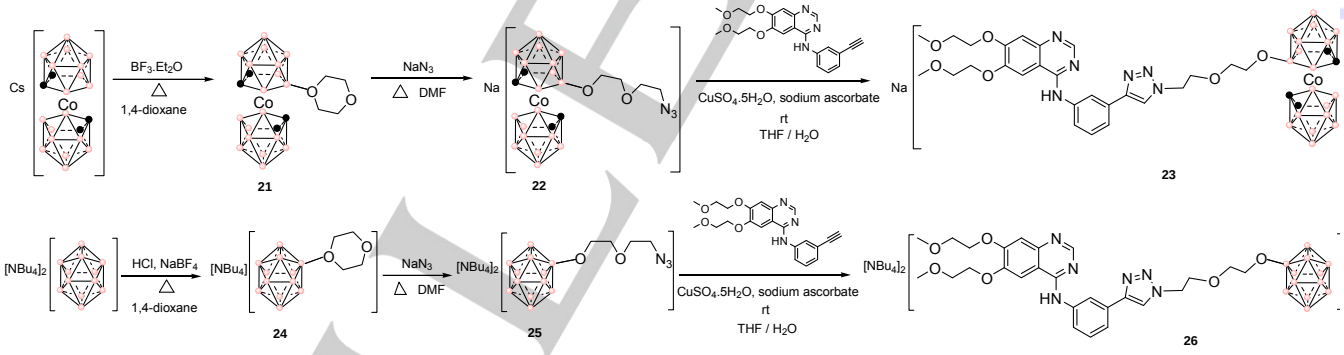
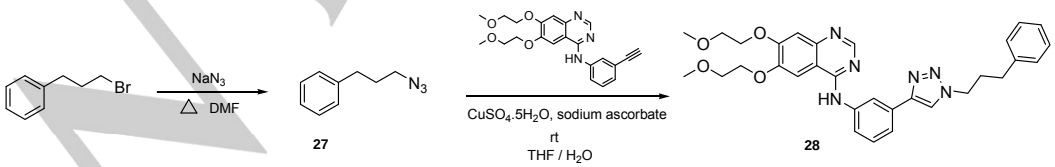


Scheme 1. Synthesis of *closo*-carboranylquinazoline.



Scheme 2. Synthesis of anionic cobaltabisdicarbollidequinazoline (**23**) and dodecaboranylquinazoline (**26**).



Scheme 3. Synthesis of bioisoster **28**.

Interesting, structure-activity relationship has been assumed for the *closo*-carboranylquinazoline series. On one hand, the methyl-substitution, in the *ortho* or the *meta* position, i.e. compounds **6** and **12**, produced a decrease of the cytotoxicity on glioma cells (compare activities of pair of compounds **5** and **6**, and **11** and **12**, see the Supporting Information, Figure S2). This relationship was independent of the linker used between quinazolinyl and carboranyl cluster showing ethynylbenzyl-connector derivatives, i.e. **15**, **16**, **19** and **20**, the same tendency but slightly lower values (see the Supporting Information, Figure S3). On the other hand, when we compared the *ortho* and *meta* isomers, i.e. couple of isomers **5** and **11** or isomers **6** and **12** (see the Supporting Information, Figure S2), *meta*-carboranyl compounds were more active than the *ortho* analogues. The influence of the lipophilicity was studied to explain the observed bioactivities. In this sense, lipophilicities were determined in terms of R_M.[22] As observed in Table 1, compounds with the highest hydrophilicities, **26** and the parent erlotinib, or compounds with the highest lipophilicities, **15**, **16**, **19** and **20**, were inactive. When the R_M values were plotted *vs* the IC_{50} against C6 cells quadratic curve was obtained although the results were not statistically robust. When only the structural related compounds were considered, i.e. triazole-connector derivatives **5**, **6**, **11**, **12**, **23**, **26**, and erlotinib, a statistic quadratic fitted curve was obtained (r^2_{adj}= 0.9815, Figure 3). This kind of behaviour, with an optimum lipophilicity, is typical of compounds that interact with a bio-molecule.[23] As one could expect the phenyl triazole-derivative **28** did not fit to this relationship, it was an outlier (Figure 3).

Table 1. Effect of the hybrids on C6 glioma cells, lipophilicities determined in terms of R_M and effect of the most active hybrids (**5**, **11**, and **23**) on mix of primary glial cells.

Compds	IC_{50},C6 (μM)[a]	R_M	Compds	IC_{50},mix (μM)[b,c]	SI[d]
5	34 ± 7	0.738	**5**	> 100	> 2.9
6	> 100	0.857	**11**	> 100	> 3.3
11	30 ± 4	0.766	**23**	> 100	> 2.3
12	99 ± 4	0.966	**Erlotinib**	> 100	-
15	> 100	1.420			
16	> 100	1.370			
19	> 100	1.440			
20	> 100	1.320			
23	44 ± 6	0.150			
26	> 100	-0.857			
28	79 ± 4	0.209			
Erlotinib	> 100	-0.209			

[a] Compound concentrations required to inhibit the C6 growth by 50 % were determined from dose–response plots. Assays were run in triplicate. [b] Compound concentrations required to inhibit mix of primary glial cell culture growth by 50 %. Assays were run in triplicate. [c] Higher doses than 100 μM could not be evaluated due to solubility problems. [d] SI: Selectivity index, defined as $IC_{50,mix\ of\ primary\ glial\ cells}$ / $IC_{50,C6\ cells}$.

In conclusion, new anilinoquinazoline-icosahedralborane hybrids have been synthesized and the *in vitro* cytotoxic effects toward EGFR-overexpressing C6 glioma cells evaluated. The overall results showed that the hybrids are highly promising antitumour agents with dual action, targeting EGFR and for potential BNCT application.

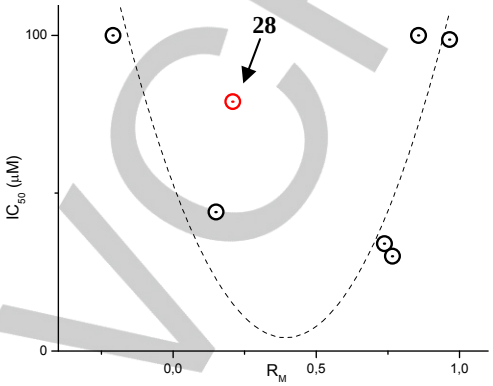


Figure 3. Relationship between IC_{50} and lipophilicity (expressed as R_M).

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Keywords: 4-anilinoquinazoline • carborane • glioblastoma multiforme • 1,3-dipolar cycloaddition • Sonogashira cross-coupling

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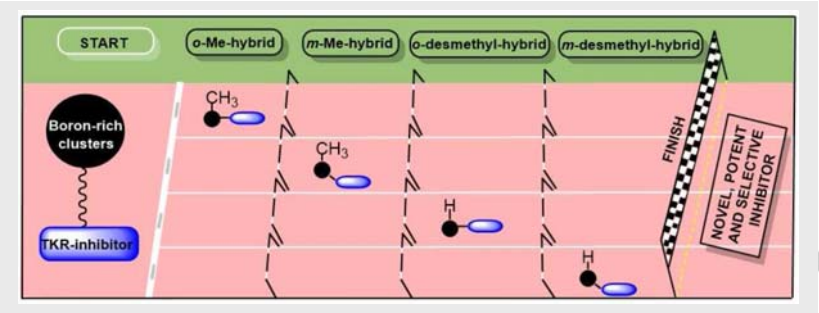

We report the syntheses of anilinoquinazoline-icosahedral borane hybrids and their anti-glioma activities

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Small-molecule kinase inhibitors-loaded boron cluster as hybrid agents for glioma cell-targeting therapy.