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Bimodal Therapeutic Agents against Glioblastoma, one of the most Lethal Cancer

Marcos Couto,[a],[b] Catalina Alamón,[a] Susana Nievas,[c] Marina Perona,[d] María Alejandra Dagrosa,[d] Francesc Teixidor,[b] Pablo Cabral,[e] Clara Viñas,*[b] and Hugo Cerecetto*[a],[e]

[a] Dr. M. Couto, C. Alamón, Prof. Dr. H. Cerecetto
Grupo de Química Orgánica Medicinal
Instituto de Química Biológica (IQB), Facultad de Ciencias, Universidad de la República
Iguá 4225, 11400 Montevideo (Uruguay)
E-mail: hcerecetto@cin.edu.uy
[b] Prof. Dr. F. Teixidor, Prof. Dr. C. Viñas
Institut de Ciències dels Materials de Barcelona
Consejo Superior de Investigaciones Científicas (CSIC)
Campus UAB, 08193 Bellaterra (Spain)
E-mail: clara@icmab.es
[c] MSc. S. Nievas
Department of Boron Neutron Capture Therapy
National Atomic Energy Commission (CNEA)
Buenos Aires (Argentina)
[d] Dr. M. Perona, Dr. M. A. Dagrosa
Department of Radiobiology
CNEA
Buenos Aires (Argentina)
[e] Prof. Dr. P. Cabral, Prof. Dr. H. Cerecetto
Área de Radiofarmacia
Centro de Investigaciones Nucleares (CIN), Facultad de Ciencias, Universidad de la República
Mataojo 2055, 11400 Montevideo (Uruguay)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:

Abstract: About 95 % of people diagnosed with glioblastoma die within five years. Glioblastoma is the most aggressive central nervous system tumour. It is necessary to make progress in the glioblastoma treatment so that advanced chemotherapy drugs or radiation therapy or, ideally, two-in-one hybrid systems should be implemented. Tyrosine kinase receptors-inhibitors and boron neutron capture therapy (BNCT), together, could provide a therapeutic strategy. In this work, sunitinib decorated-carborane hybrids were prepared and biologically evaluated identifying excellent antitumoral- and BNCT-agents. One of the selected hybrids was studied against glioma-cells finding that it was 4-times more cytotoxic than sunitinib and 1.7-times more effective than ^{10}B-boronophenylalanine fructose complex when the cells were irradiated with neutrons.

Glioblastoma is the most frequent and the most malignant type of brain tumour among infiltrative gliomas, a group of primary tumours arising from the central nervous system. Due to its diffuse infiltration capacity and its extreme resistance to standard radio/chemo therapies, it has the worst prognosis, with a scarcely 2-year survival rate for 3 % – 5 % of the patients.[1] The current treatment includes surgery, radiotherapy, tumour treating fields (TTF) therapy, photodynamic therapy (PDT), boron neutron capture therapy (BNCT), chemotherapy (i.e angiogenesis inhibition), or combined therapies. Regarding chemotherapy, temozolomide (**Tmz**, Chart 1), an oral alkylated and reticulum endoplasmic stress promoter agent, is the first-line chemotherapeutic agent. However, its drug resistance in human patients make frequently treatment failure.[2] Since glioblastoma expresses vascular endothelial growth factor (VEGF), its tyrosine kinase receptors VEGFR1 and VEGFR2, and angiogenesis-genes (PDFGR-α and KIT), some tyrosine kinase receptor inhibitors are used as second-line chemotherapeutic treatments.[3] Sunitinib (**Sun**, Chart 1) is classified as a multi-targeted inhibitor, that targets several receptor tyrosine kinases, including VEGFR1, 2 and 3, PDGFR-α and -β, stem-cell growth factor receptor (KIT), fms-related tyrosine kinase 3 (FLT3), rearranged during transfection (RET) proto-oncogene, and colony stimulating factor receptor 1 (CSF1R), among others.[4] **Sun** is indicated for the treatment of renal carcinoma, gastrointestinal sarcoma and neuroendocrine tumours. In neuroendocrine tumours preclinical studies, **Sun** produces anti-proliferative, anti-angiogenic and pro-apoptotic effects decreasing the invasive capacity of glioma cells implanted into the brain.[4] However, minimal anti-glioblastoma activity and high toxicity were evidenced in phase II studies.[5] On the other hand, BNCT is a next generation non-invasive binary cancer therapy approach that involves the irradiation with low energy thermal neutrons of non-radioactive ^{10}B-enriched tumour, to yield high linear energy particles ($^{4}He^{2+}$ and $^{7}Li^{3+}$).[6] Because these particles have a linear path similar to the diameter of a cell, the post-neutron-irradiation BNCT damage is selectively confined within the tumour if the drug is delivered into the targeted cells. Tyrosine kinase receptor inhibitor erlotinib (**Erl**, Chart 1) decorated with a single boron atom, as boronic acid moiety, have been exploited as boron-containing drug targeting within glioma cells, though their BNCT applications limited due to the low concentration of boron in the cells.[7] Based on all these points and following our previous research (Figure 1),[8] herein we report on the development of a new hybrid compounds family that offering the possibility of dual action (drug + radiotherapy combination) may result into significant clinical benefits. This new hybrid compounds combine two fragments: the multi-

targeted inhibitor **Sun** and an icosahedral boron-cluster derived subunits (Figure 1).

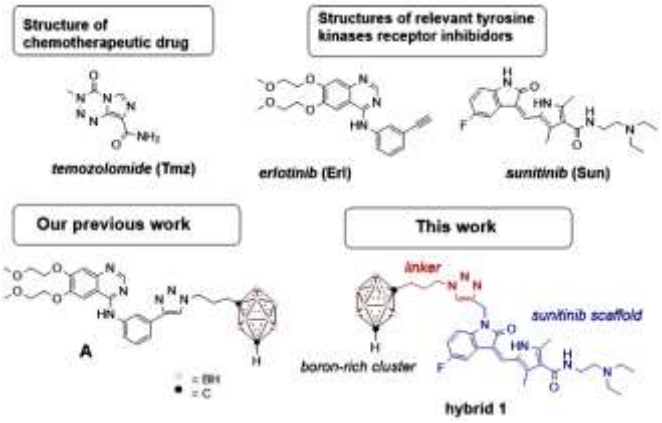
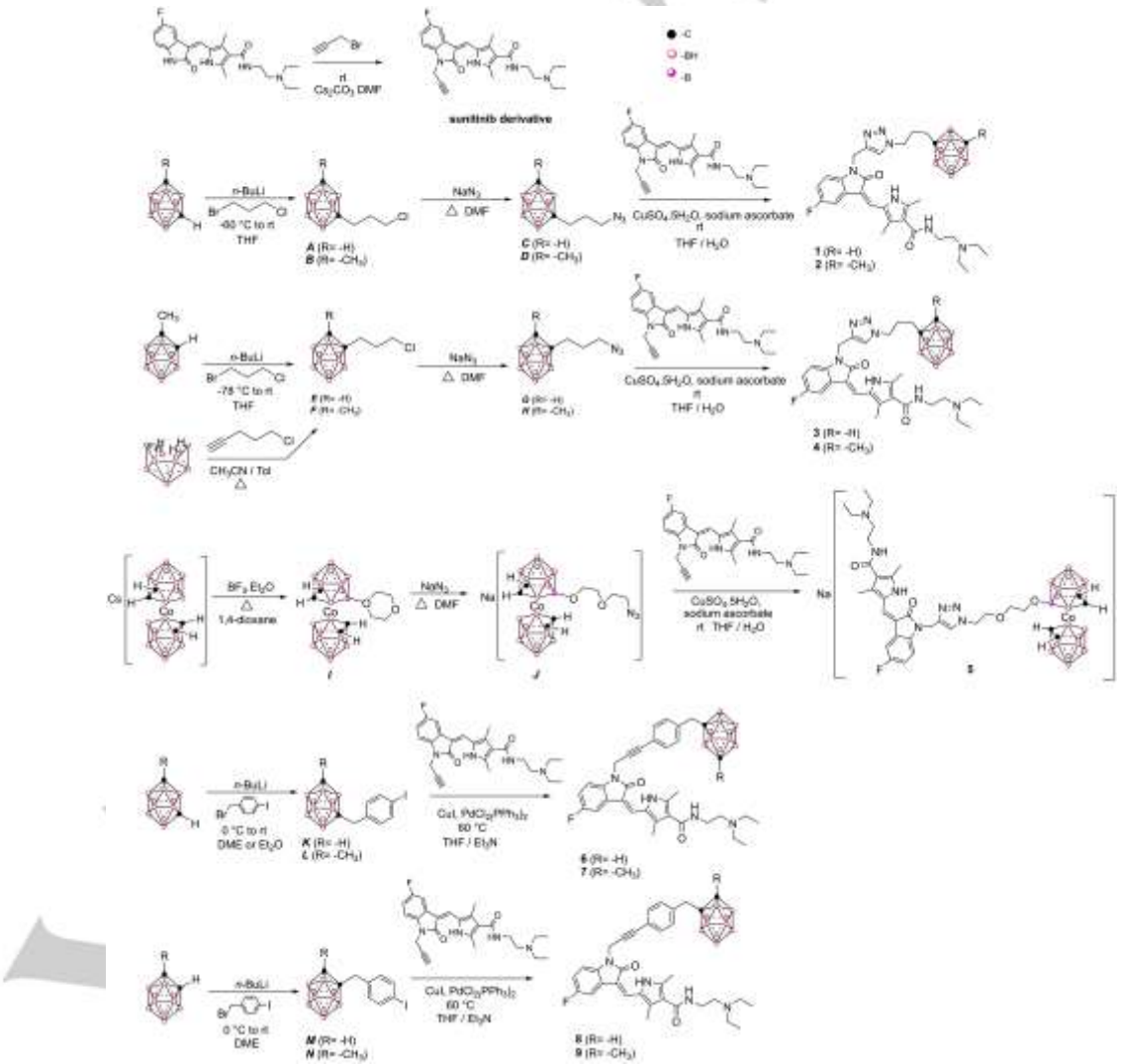


Figure 1. Chemical structures of glioblastoma drug temozolomide (**Tmz**), some relevant tyrosine kinase receptor inhibitors, erlotinib (**Erl**) and sunitinib (**Sun**), previous developed hybrid **Erl**-boron cluster, **A**,[8b-d] and the best hybrid sunitinib-boron cluster described herein, **1**.

To achieve this goal, hybrid compounds (**1**-**9**, Scheme 1) were designed, synthesized and fully characterized. Further, all compounds were evaluated against different tyrosine kinases-overexpressing tumoral cells and the proof of concept for their use as BNCT agents was performed using hybrid **1**.

Besides the standalone nature of the boron atoms crucial for BNCT, the icosahedral boron-clusters provide chemical and thermal stability, hydrophilicity/lipophilicity character, and, a globular architecture of convenient molecular size to establish interactions in a 3D space that have grown the researchers interest in exploring their use as pharmacophores.[9]

Two structural features are required for effective kinases inhibition by **Sun**: i) the substituent at the C-3-indol system that plays relevant role in the protein binding but, especially in the compound solubility,[10] ii) the indolin-2-one motive that plays a key role in the proteins-binding processes.[11] In this regard, icosahedral boron-clusters can establish special hydrogen and dihydrogen bonds, such as C-H···X and B-H ···H-X (X = N, C, O, and S), as well as B-H ···π and C-H···π hydrogen bonds,[12] which could provide extra beneficial interactions with the target receptors through these non-classical interactions exploring unique regions of chemical space that cannot be achieved with purely organic compounds.



Scheme 1. Synthetic procedures for preparation of hybrids **1-9**.

Consequently, it may assume that the carborane cages could be located in the target-pocket, i.e. in the **Sun** indolin-2-one region, in the new hybrid compounds (**Sun** + boron-cluster), establishing extra-interactions with the kinases.[8] As connector, between indolin-2-one system and boron clusters, we selected two types of substructures: i) flexible and polar backbones (methyl-1,2,3-triazolylalkyl moieties) and, ii) a rigid and hydrophobic system (2-propynylphenylmethyl linker). Additionally, with the aim of introducing chemical diversity into the target, three different icosahedral boron clusters were chosen: the neutral *o*- and *m*-carboranes, and the anionic cobaltabis(dicarbollide). The designed hybrid compounds, **1**-**9**, were synthesized as shown in Scheme 1. **Sun** was selectively propargylated in the indolin-2-one nitrogen (sunitinib derivative in Scheme 1) to subsequently apply "click" or Sonogashira cross-coupling reaction with adequate functionalized boron cluster. The selective *N*-alkylation of indolin-2-one was achieved in the presence of cesium carbonate and non-anhydrous DMF. From this alkyne, 1,3-dipolar cycloaddition reactions, employing cluster containing azide groups (**C**, **D**, **G**, **H**, and **J**),[8d,13a] were performed obtaining desired hybrid compounds **1-5** in good to excellent yields. Besides, the cross-coupling reaction catalyzed by palladium between the alkyne and the boron cluster containing iodo-derivatives (**K**, **L**, **M**, and **N**)[8d,13b] generates the hybrids **6-9** in moderate yields. The new hybrid compounds were evaluated *in vitro* against murine C6 and human U87 MG glioma cell lines (Table 1). Derivatives **1**, **2** and **4**, bearing the triazolylpropyl system as a linker, were identified as novel *in vitro* anti-glioblastoma agents (Table 1). Additionally, compounds **1**, **2** and **4** also showed to be potent growth inhibitors of the HT-29 cell lines (Table S1, see Supporting Information for details), an overexpressing EGFR tumoral cell line derived from *Homo sapiens* colorectal adenocarcinoma.[14] The best biological results for this current family of hybrid compounds are observed when the linker is the triazolylpropyl group, this result goes in parallel with what it was previously observed for the family of **Erl**-icosahedral boron cluster hybrids.[8] However, the **6**-**9** derivatives with a 2-propynylphenylmethyl-linker showed null or lower activity. This biological behavior could be the result of their different lipophilicities; having hybrid **1** the best value for the studied compounds (expressed as R_M, Figure 2). Within the triazolylpropyl *m*-carborane derivatives, **1** and **2**, resulted in the best cellular inhibition against the three studied tumoral cells. However, unlike our previous results with **Erl** containing hybrids,[8] the cobaltabis(dicarbollide) derivative **5** was not active in the current assayed conditions.

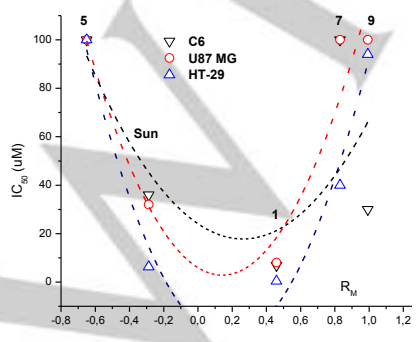
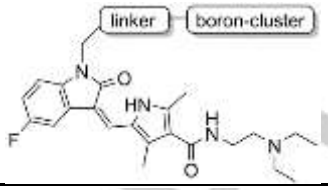
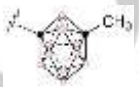
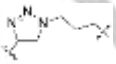
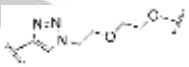
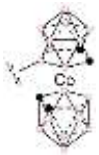
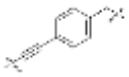
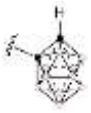


Figure 2. Relationship between IC_{50} and lipophilicity (expressed as R_M). The number of the studied compounds and cell lines name are indicated inset the graphic. The dotted lines show tendencies.

Table 1. In vitro activity of hybrids **1-9** as IC_{50} (μM) or the percentage of cells survival at 100 μM on C6 and U87 MG glioma cells.



Cpd	linker	boron-cluster	$IC_{50,C6}$[a]	$IC_{50,U98\ MG}$[b]
1			6.9 ± 0.5	8.0 ± 0.3
2			5.2 ± 0.5	8.0 ± 0.4
3			78.3 ± 0.8	> 100 (95 ± 5 %)
4			4.4 ± 0.5	8.0 ± 0.5
5[b]			> 100 (100 ± 5 %)	> 100 (100 ± 4 %)
6			> 100 (65 ± 5 %)	> 100 (100 ± 5 %)
7			> 100 (100 ± 5 %)	> 100 (64 ± 4 %)
8			80 ± 4	> 100 (100 ± 5 %)
9			30 ± 5	> 100 (94 ± 6 %)
Sun	-	-	36 ± 10	32 ± 4
A	-	-	30 ± 5	70 ± 5
Erl	-	-	> 100	63 ± 5
Tmz	-	-	ns[c]	> 100

[a] Values in parenthesis are the percent of cells survival at 100 μM. [b] As sodium salt. [c] ns: not studied.

Hybrid **1**, besides being better cell-growth inhibitor than the tyrosine kinase receptor inhibitor **Erl** and the hybrid **A** (Figure 1), was at least 4 times and 12 times more active against glioblastoma cells U87 MG than the parent compound **Sun** and the classical therapeutic agent **Tmz** (Table 1), respectively. The

selective accumulation of hybrid **1** in tumoral cells was evaluated measuring boron on normal glial and tumor cells (see below).

To study the potential of hybrid **1** as *in vivo* BNCT agent, the cellular uptake against normal murine astrocytes and *Rattus norvegicus* brain glioma-derived F98 cells was analyzed by using inductively-coupled plasma optical emission spectroscopy (ICP-OES).[15] The cells were incubated with hybrid **1** at a sub-lethal (IC_{50}/80) dose and with ^{10}B-boronophenylalanine fructose complex (**^{10}BPA-fr**), which was taken as reference, after varying times of incubation (1, 2 and 4 h). The boron accumulation after uptake in F98 cells treated with **^{10}BPA-fr** displays an uptake value of 13.6 μg of B/mg protein[16] after 1 h incubation. The uptake decreases with time, being 4.4 μg of B/mg protein after 4 h, probably because of the efflux by the extracellular amino acids exchange.[17] By the opposite, hybrid **1** shows smaller boron accumulation value than **^{10}BPA-fr** at the beginning, but it progressively increases with the duration of the experiment (0-4 h); it reaches its maximum (6 μg of B/mg protein) after 4 h of incubation (Figure 3a). Additionally, hybrid **1** was able to accumulate boron on HT-29 EGFR-overexpressing cells (Figure S1, see Supporting Information for details). On the other hand, selective increased boron accumulation on F98-glioma cells with respect to astrocytes is observed along the studied incubation time period; being a significant boron accumulation glioma/astrocyte ratio of 2.12 after 4 h incubation (Figure 3b). This information allowed us to perform *in vitro* neutron irradiation experiments.

In this sense, the murine glioma cells were incubated with both hybrid **1** and **^{10}BPA-fr** and irradiated with a neutron flux of 3 × 10^{10} neutrons/cm^{-2} min receiving a dose of 2 Gy, according to dosimetric studies shown in Table 2.[15,18] Both compounds, **1** and **^{10}BPA-fr**, were studied on F98-glioma cells at doses equivalents to 10.0 ppm of ^{10}B. The effect of *in vitro* BNCT by hybrid **1** was extremely interesting observing a marked decrease in the surviving cell fraction in the irradiated group and being significantly higher than the effect produced by the irradiation with neutrons alone on F98-glioma cells (Figure 3c).

The good results with hybrid **1** at 10.0 ppm of ^{10}B encouraged us to carry out studies at lower doses, equivalents to 0.1 and 1.0 ppm of ^{10}B, which could be beneficial in the future thinking in a multitherapy treatment. Hybrid **1** displayed the same cytotoxic effects at the lower doses, 200-times lower than the recommended one,[6] i.e. 20 ppm of ^{10}B (Figure 3c). In contrast, in the same conditions, 2 Gy and 0.1, 1.0, and 10.0 ppm of ^{10}B, **^{10}BPA-fr** group produced a surviving cell fraction significantly higher than hybrid **1** (Figure 3c) resulting hybrid **1** 1.7 times more effective than **^{10}BPA-fr**, at all the studied doses, in the *in vitro* model of BNCT. At 48 h post-neutron-irradiation with 2 Gy and at 1.0 ppm dose of ^{10}B, the effect of both hybrid **1** and **^{10}BPA-fr** on F98-cell death levels, was analyzed by fluorescence microscopy (Figure 4 and Figure S2, see Supporting Information for details). There was an increase in apoptotic cells and mitotic catastrophe (MC) in the hybrid **1**-irradiated group compared to the untreated control cells group and **^{10}BPA-fr**-treated group . These results suggest that although only 19.6 % of the boron in the carborane cage was ^{10}B, this amount is sufficient for the success in an *in vitro* model of BNCT.

Hybrid **1** with selective *in vitro* uptake by glioma cells and remarkable cytotoxic effect against tyrosine-kinase overexpress cells has been identified as a promising candidate to apply bimodal (chemo + BNCT) therapies. Hybrid **1** that belongs to a new hybrid compounds family, which combines the multi-targeted TKR inhibitor sunitinib and a boron-cluster, have been synthesized in a high yield and fully characterized together with other congeners. Hybrid **1** revealed to be significantly higher active in BNCT than **^{10}BPA-fr**. These results point out not only that hybrid **1** might be useful to rational development of TK inhibitors with improved potency but that together with its BNCT action may result into significant clinical benefits. More research is going on in this sense in our laboratories.

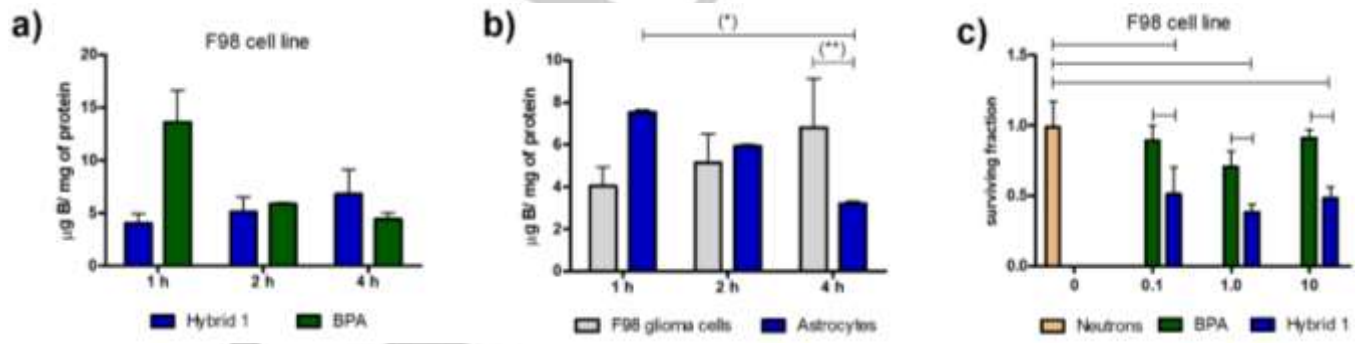


Figure 3. a) Average boron concentration, obtained by ICP-OES, in F98 cells treated with hybrid **1** or **^{10}BPA-fr** by 4 h at a sub-lethal dose (IC_{50}/80) for hybrid **1** and at 0.925 mM for **^{10}BPA-fr**. b) Average boron concentration, obtained by ICP-OES, in F98 and astrocyte cells treated with hybrid **1** at 0.1 μM by 4 h. (*) $p < 0.001$; (**) $p < 0.12$. c) Effect on F98-cell survival without and with hybrid **1-** or **^{10}BPA-fr**-after post-neutron-irradiation (2 Gy). Compounds were studied at doses equivalents to 0.1, 1.0, and 10.0 ppm of ^{10}B. All bars indicate $p < 0.001$.

Table 2. Dosimetry for thermal neutron irradiation without and with ^{10}B.

^{10}B, ppm	Irradiation time, min	Fluence ×10^{12}, n/cm^2	Dose γ, Gy	Dose ^{14}N, Gy	Dose ^{10}B, Gy	Total absorbed dose, Gy	Relative error dose
0.0	11.27	3.9 ± 0.3	0.92 ± 0.11	1.08 ± 0.09	0.00 ± 0.00	2.0 ± 0.1	± 7 %
0.1	11.57	3.8 ± 0.3	0.90 ± 0.10	1.07 ± 0.09	0.033 ± 0.004	2.0 ± 0.1	± 7 %
1.0	10.07	3,3 ± 0.3	0.78 ± 0.091	0.93 ± 0.08	0.29 ± 0.04	2.0 ± 0.1	± 6 %
10.0	4.38	1.4 ± 0.1	0.34 ± 0.04	0.40 ± 0.03	1.3 ± 0.2	2.0 ± 0.2	± 8 %

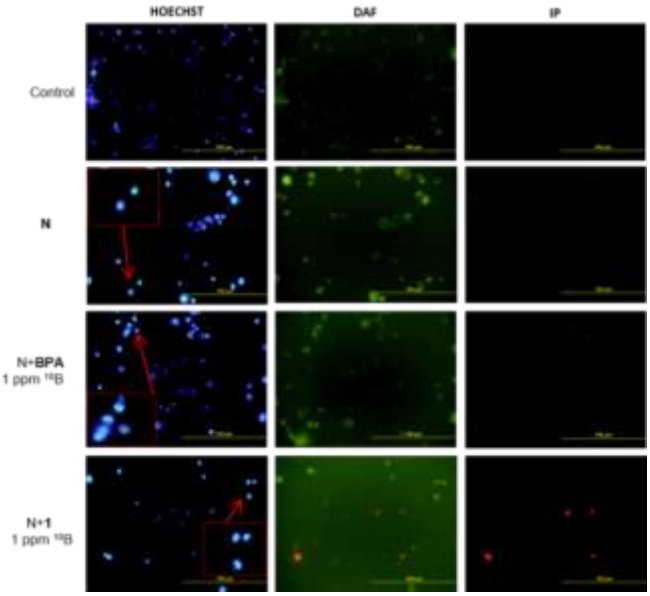


Figure 4. Analyses of apoptotic or necrotic cells evaluated, post-neutron-irradiation, by fluorescence microscopy. Representative images from stained cells 48 h after irradiation. Apoptotic nuclei labelled with Hoechst (red arrowheads and inset) exhibited peripheral chromatin clumping, blebbing in apoptosis and fragmentation; cytoplasm of living cells was labelled with DAF and necrotic cells were labelled with IP. Abbreviations: N= assay without compounds incubation and with neutron irradiation; N+**^{10}BPA-fr** 1 ppm ^{10}B = assay with **^{10}BPA-fr** incubation at a dose equivalent to 1 ppm of ^{10}B and with neutron irradiation; N+**1** 1 ppm ^{10}B = assay with hybrid **1** incubation at a dose equivalent to 1 ppm of ^{10}B and with neutron irradiation

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carborane • sunitinib • BNCT • glioblastoma • bimodal therapy

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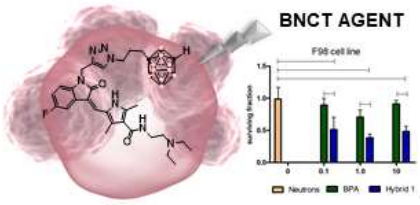

Compounds for bimodal cancer-treatment, based on tyrosine kinase receptors-inhibitors and boron neutron capture therapy (BNCT), were successfully developed. The single molecules, sunitinib decorated-carborane hybrids, could represent significant advance in cancer treatment.