

# Medicinal Electronomics Bricolage Design of Hypoxia-targeting Antineoplastic Drugs and Invention of Boron Tracedrugs as Innovative Future-architectural Drugs

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**Abstract.** We describe herein for the first time our medicinal electronomics bricolage design of hypoxia-targeting antineoplastic drugs and boron tracedrugs as newly emerging drug classes. A new area of antineoplastic drugs and treatments has recently focused on neoplastic cells of the tumor environment/microenvironment involving accessory cells. This tumor hypoxic environment is now considered as a major factor that influences not only the response to antineoplastic therapies but also the potential for malignant progression and metastasis. We review our medicinal electronomics bricolage design of hypoxia-targeting drugs, antiangiogenic hypoxic cell radiosensitizers, sugar-hybrid hypoxic cell radiosensitizers, and hypoxia-targeting  $^{10}\text{B}$  delivery agents, in which we design drug candidates based on their electronic structures obtained by molecular orbital calculations, not based solely on pharmacophore development. These drugs include an antiangiogenic hypoxic cell radiosensitizer TX-2036, a sugar-hybrid hypoxic cell radiosensitizer TX-2244, new hypoxia-targeting indoleamine 2,3-dioxygenase (IDO) inhibitors, and a hypoxia-targeting BNCT agent, BSH (sodium borocaptate- $^{10}\text{B}$ )-hypoxic cytotoxin tirapazamine (TPZ) hybrid drug TX-2100. We then discuss the concept of boron tracedrugs as a new drug class having broad potential in many areas.

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Most current cancer therapies target tumor cells directly. Recently, a newly emerging area of cancer or neoplastic therapeutics focuses instead on targeting cells of the tumor-specific environment or microenvironment (1). The hypoxic tumor environment is now considered a major factor that influences not only the response to antineoplastic therapies but also the potential for malignant progression and metastasis. For three decades, we have been concentrating much effort on the development of chemical modifiers of cancer treatment (2), including hypoxic cell radiosensitizers, hypoxic cytotoxins, hypoxia-targeting antineoplastic drugs (3), and Gc protein-derived macrophage-activating factors (4, 5). We provide here a thorough review of our strategy and tactics for drug design as a medicinal electronomics bricolage. In particular, we review our current progress in the development of hypoxia-targeting drugs, such as antiangiogenic hypoxic cell radiosensitizers, sugar-hybrid hypoxic cell radiosensitizers, and hypoxia-targeting  $^{10}\text{B}$  delivery agents, in which we design drug candidates based on their electronic structures obtained by molecular orbital calculations, not based solely on pharmacophore elucidation. We also present here our development of an *in vivo* developing chick embryo model to evaluate the radiosensitizing activity of compounds against solid neoplasms. We also describe our design and syntheses of new compounds that target hypoxic-neoplastic cells by functioning as indoleamine 2,3-dioxygenase (IDO) inhibitors. We further show that our hypoxia-targeting boron neutron capture therapy (BNCT) agents are promising boron-10 carrier candidates for BNCT. Finally, we present here our concept of what we call ‘boron tracedrugs’ as a new drug class with broad potential and also as next-generation pharmaceutical drugs. Boron tracedrugs are designed to have persistent traceability anytime during their lifetime. The key structural feature of these drugs consists of having multiple boron atoms firmly embedded in their scaffold or skeleton located at a position that will have little or no influence on other functional group moiety or pharmacophores.

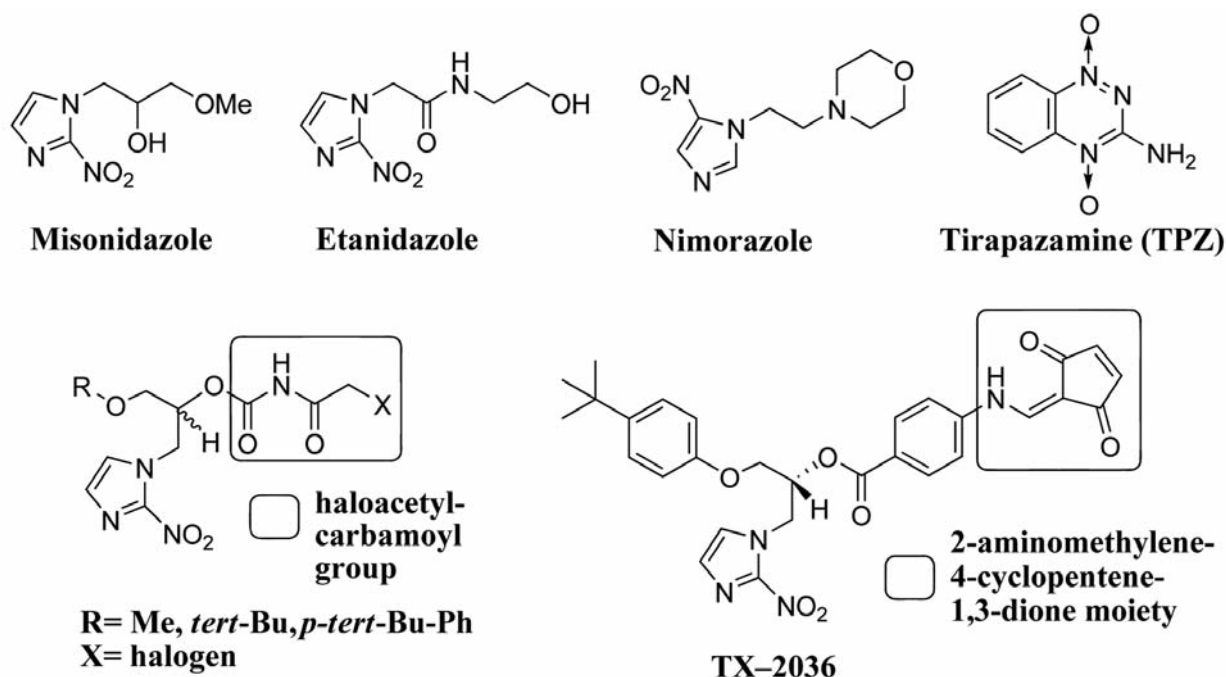


Figure 1. Representative hypoxic cell radiosensitizers and hypoxic cytotoxins.

### Hypoxia-targeting Antineoplastic Drugs

**Antiangiogenic hypoxic cell radiosensitizers.** The hypoxic nature of tumor cells is a critical consideration for the development of anticancer drugs. Thus, hypoxia was recently reported to inhibit differentiation and to facilitate 'tumor stem cell' maintenance (6-8). Hypoxic tumors are aggressive and exhibit stem cell-like characteristics. A highly tumorigenic fraction of side population (SP) cells is frequently localized in the hypoxic regions of solid tumors. Moreover, hypoxic cells that exist in many human solid tumors are generally characterized by radioresistance and this is a major complicating factor in cancer therapy. Indeed, the development of drugs that can sensitize hypoxic tumor cells to radiation has been an important goal for medicinal chemists in radiation oncology (9). Misonidazole and etanidazole (Figure 1) are well-known hypoxic cell radiosensitizers, but these have had limited therapeutic impact on radiotherapy due to clinical problems that include dose-limiting side-effects such as neurotoxicity (9). Nimorazole (Figure 1), used locally in Denmark for radiotherapy of head and neck cancer, is the only hypoxic cell radiosensitizer currently in clinical use (9). The hypoxic cytotoxin, tirapazamine (TPZ, SR4233) (Figure 1), has attracted considerable attention, including clinical trials, because of its selective toxicity to hypoxic cells in the absence of radiation (9). Our own research has been directed towards exploring a newly emerging strategy for the

development of more effective hypoxia-targeting drugs, including radiosensitizers (10, 11) and hypoxic cytotoxins (12-15), for clinical development. One of our strategies is to develop drugs that have dual actions as radiosensitizers and antiangiogenic agents.

**Angiogenesis as a drug target.** For a neoplastic cell to metastasize, there are a series of steps that it must go through (16). Each step is rate-determining in the sense that until each step is completed, the cell is limited and the subsequent step in the metastatic process will not occur. Thus, failure to complete any of the steps prevents tumor cells from undergoing metastasis. Angiogenesis is the first of these rate-determining steps and is also a prerequisite for neoplastic growth. Since a neoplasm is composed of neoplastic cells, capillary blood vessels, and connective tissue (17), antiangiogenic agents can also be considered to be antineoplastic agents. Inefficient vascular supply and the resultant hypoxia in tumor tissue often lead to neovascularization to satisfy the needs of surviving tumor tissues. Bevacizumab (Avastin<sup>®</sup>) approved by the U.S. Food and Drug Administration (FDA) for colon cancer, is the first drug to demonstrate prolongation of survival in patients with advanced cancer (18, 19). It is an antivascular endothelial growth factor (anti-VEGF) antibody, and the story of its discovery and manufacture describes a monumental achievement. There are about 200 different types of human cancer, and some 60% of these express VEGF. Many types of cancer, however, produce other angiogenic proteins as well.

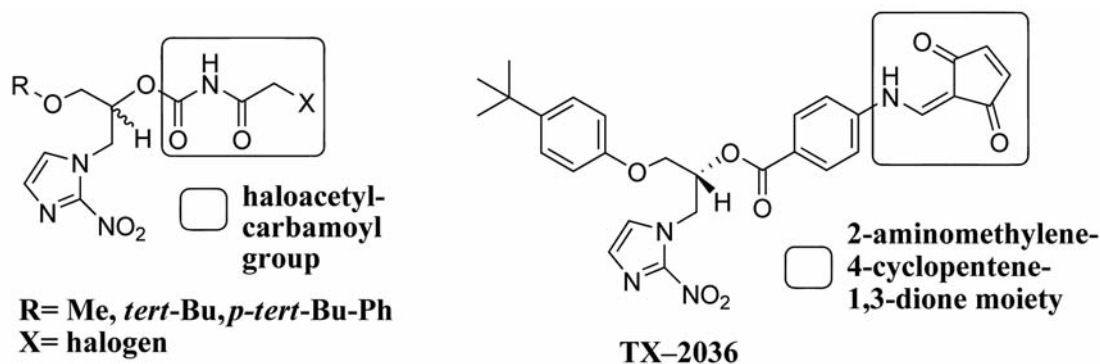


Figure 2. Hypoxia-targeting drugs: Antiangiogenic hypoxic cell radiosensitizers, chiral 2-nitroimidazole compounds, containing either a haloacetylcarbamoyl group (left side) or 2-aminomethylene-4-cyclopentene-1,3-dione moiety (right side).

Some tumors may initially produce only VEGF but over time can express redundant angiogenic proteins owing to new mutations. At least six angiogenic proteins have been reported for some types of breast cancer. In the future, therefore, as more patients respond well to bevacizumab therapy and as bevacizumab receives FDA approval for other tumor types, treatment may be enhanced by co-administration of other antiangiogenic agents as adjuvant therapeutics for tumor growth/inhibition and antimetastasis (19).

Shweiki *et al.* (20) reported in 1992 that hypoxia induced the production of VEGF, which mediates hypoxia-initiated angiogenesis. Since this report, the link between tumor tissue hypoxia and angiogenesis gradually became firmly established (21-23). Since antiangiogenic agents contribute to hypoxia to normalize tumor vasculature, leading to increased blood flow and oxygenation, they should also benefit radiotherapy (24-26). Based on these considerations, there are apparent advantages to be gained by sensitizing hypoxic cells to radiotherapy while, at the same time, inhibiting angiogenic activity. This combination of radiosensitizing and antiangiogenic activity would be expected to provide a synergistic interaction between hypoxic cell radiosensitizers and antiangiogenic agents which target hypoxia-initiated neovasculature. Our research has focused on the design and synthesis of compounds that can function as combination drugs containing both radiosensitizing and antiangiogenic activities.

In the tumor microenvironment, there are soft nucleophiles such as non-protein thiols and thiol proteases that we targeted for alkylation with soft electrophiles. To exploit the strategy of combining a potential antiangiogenic pharmacophore with a radiosensitizer, we previously designed, synthesised, and evaluated racemic and enantiomerically pure (chiral) haloacetylcarbamoyl-2-nitroimidazoles, including chloro- and bromo-derivatives (27). We further developed novel 2-nitroimidazole derivatives that incorporate an aminomethylenecyclopentenedione moiety, a soft electrophile 2-methylene-4-cyclopentene-1,3-dione pharmacophoric des-

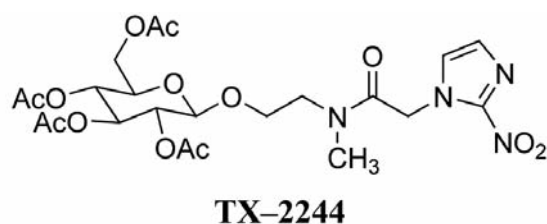


Figure 3. Hypoxia-targeting drugs: Sugar-hybrid hypoxic cell radiosensitizer TX-2244.

criptor (28) (Figure 2), as new antiangiogenic and antitumor functional groups (29). We considered two potential benefits of having a chiral center in our hypoxic cell radiosensitizers: i) this would provide us with two molecular structures expected to exhibit different intrinsic biological activities from the same synthetic route, and ii) each enantiomer would possess a specific pharmacokinetic property, as well as a specific pharmacodynamic property. These proved to be the first-ever examples of antiangiogenic hypoxic cell radiosensitizers.

We found the antiangiogenic hypoxic cell radiosensitizer TX-2036 to be the most promising candidate, based on its high hypoxic cell radiosensitizing activity [Enhancement ratio (ER)=1.79 at 1  $\mu$ M], its potent EGFR kinase inhibitory activity [50% inhibitory concentration ( $IC_{50}$ )=1.8  $\mu$ M], its anti-proliferatory activity ( $IC_{50}$ =0.81  $\mu$ M) to RLE cells, and its strong *in vivo* antiangiogenic activity using a chick embryo chorioallantoic membrane (CAM) assay (inhibition of 64% at 1  $\mu$ g per CAM) (29). TX-2036 is now under investigation as a very promising hypoxic cell radiosensitizer candidate for further development. As an extension of this research, we are also developing the *in vivo* CAM antiangiogenesis assay for more general applications in *in vivo* pharmacological studies that relate to our concept of symmetric or symmetrical translatability in drug discovery research as translational research between bench and bedside.

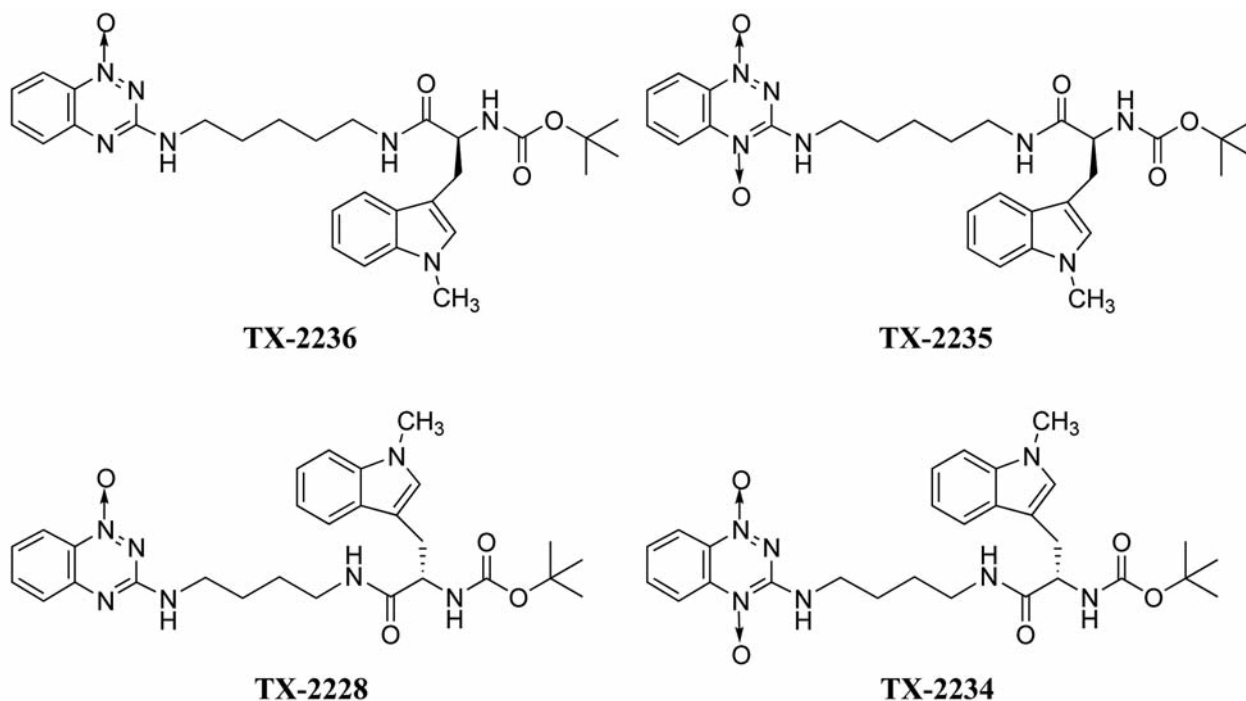


Figure 4. Hypoxia-targeting drugs: 1MT-TPZ-hybrid IDO inhibitors

**Sugar-hybrid Hypoxic Cell Radiosensitizers.** The sugar moiety has been used effectively in drug design to improve water solubility and for molecular recognition. An additional factor relevant to this study is the significant increase of glucose uptake into tumor tissue that has been ascribed to enhanced tumor glycolysis, known as the Warburg effect, or aerobic glycolysis (30, 31). As a medicinal bricolage to improve drug delivery to the tumors, we designed glycosylated conjugates of radiosensitizers with neoplastic favored glycolytic substrates, such as glucose and galactose, to create sugar-hybrid hypoxic cell radiosensitizers targeting neoplastic cells (32). As a hypoxic cell radiosensitizer to be linked to sugars, we developed TX-1877, to use as a more potent and promising hypoxic cell radiosensitizer. TX-1877 has many additional biological activities such as antimetastatic properties, and immunopotentiating activity (33-36). The fully acetylated glucose-containing hypoxic cell radiosensitizer, TX-2244, the most active radiosensitizer we found, had both higher *in vitro* radiosensitizing activity and lower hydrophobicity compared to misonidazole, a well-known classical hypoxic cell radiosensitizer (32).

TX-2244 has acetylated glucose moieties (Figure 3). Since the acetyl group is a hydrolytically labile functional group, it is possible that intracellular glucose metabolism could contribute to the radiosensitizing activity of this derivative. Interestingly, TX-2244 not only has lower hydrophobicity (n-octanol/water partition coefficient  $P_{\text{oct}}=1.05 \times 10^{-1}$ ) but also

has higher radiosensitizing activity ( $\text{ER}=2.30$  at 1 mM) than misonidazole ( $P_{\text{oct}}=4.22 \times 10^{-1}$ ,  $\text{ER}=1.72$  at 1 mM), and it also has a higher radiosensitizing activity than its "aglycone" parent compound TX-1877 ( $\text{ER}=1.75$ ) (32), an observation that should be further investigated. In any case, we have successfully achieved the medicinal bricolage design of a sugar-hybrid hypoxic cell radiosensitizer having increased radiosensitizing activity along with controlled hydrophobicity.

**Hypoxia-targeting IDO Inhibitors.** Indoleamine 2,3-dioxygenase (IDO) is a monomeric 45 kDa heme-containing dioxygenase that catalyzes the initial and rate-limiting step of L-tryptophan (L-Trp) catabolism in the kynurenine pathway (37-39). This step involves the oxidative cleavage of the 2,3 double bond in the indole moiety, resulting in the production of *N*-formylkynurenine. Heme iron that exists in the active site of IDO is active in its ferrous ( $\text{Fe}^{2+}$ ) form, whereas the ferric ( $\text{Fe}^{3+}$ ) form is inactive. These kynurenine pathway metabolites, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid, anthranilic acid, and quinolinic acid, suppress T-cell proliferation and differentiation, and accelerate T-cell apoptosis (40%). Allogenic fetal rejection by pregnant maternal mice is prevented by IDO-mediated tryptophan catabolism (41%). For this reason, IDO is associated with immunosuppression and immunotolerance. Expression of IDO has been reported in various neoplastic cells, such as lung, prostatic, pancreatic, and colorectal



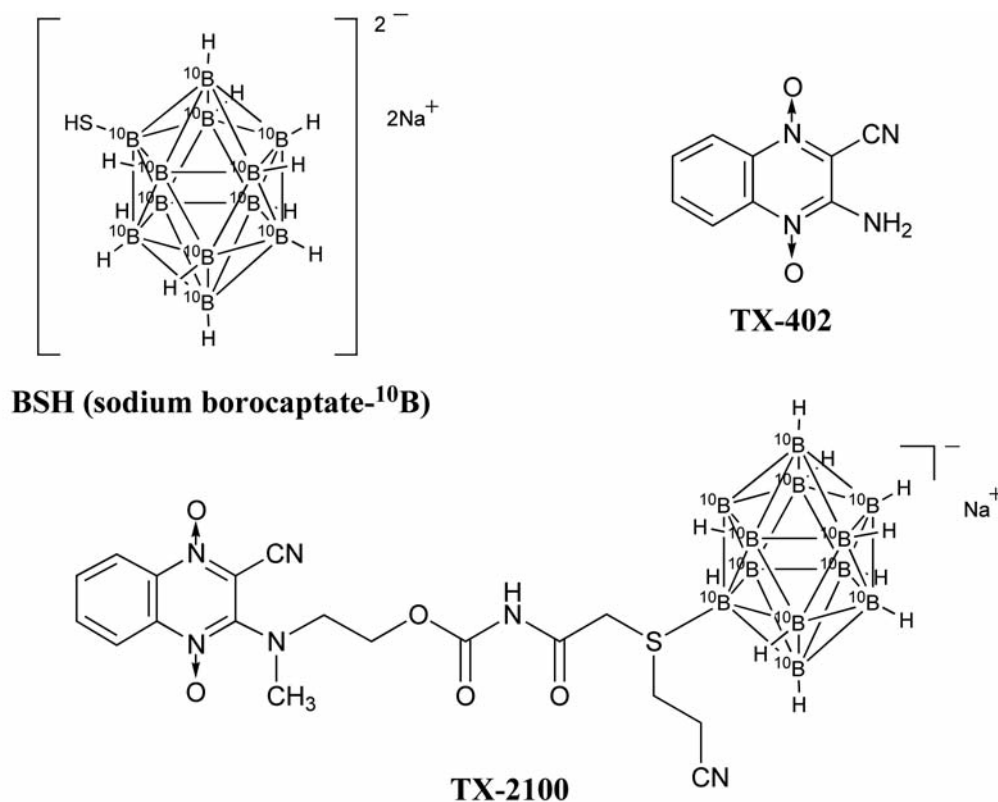


Figure 5. Hypoxia-targeting drugs: BSH, TX-402, and hypoxia-targeting BNCT agent, TX-2100.

carcinoma. Consequently, developments of IDO inhibitors such as 1-methyl-tryptophan (1MT) have been initiated (39). 1MT is a competitive inhibitor of IDO with a  $K_i=19 \mu\text{M}$ . TPZ is a hypoxic cytotoxin, which is currently under phase II/III clinical trials in combination with radiotherapy and cisplatin-based chemotherapy. It is reduced by one-electron reductases such as cytochrome P450 reductase to form a radical, which mediates the induction of lethal double-strand breaks in cellular DNA. Further metabolism produces the TPZ-monoxide. From the above considerations, we reasoned that a hybrid molecule possessing both IDO inhibitory activity and hypoxia-selective cytotoxicity could be an effective and novel antineoplastic agent. To develop IDO-specific inhibitors, we chose the substrate (L-Trp) analog 1MT as the IDO inhibitory unit for our designed hybrids. We designed the first-ever examples of hypoxia-targeting 1MT-TPZ hybrid IDO inhibitors, including TX-2236, TX-2235, TX-2228, and TX-2234 (Figure 4) (42).

IDO is activated only after its heme iron is reduced from the ferric form to the ferrous form. This reduction takes place more easily in reductive or hypoxic conditions. However, IDO needs molecular oxygen or superoxide for the catalytic reaction, concentrations of which are normally low in hypoxic conditions (hypoxia  $p\text{O}_2$  less than 5 mmHg). We reasoned

that the hypoxic tumor environment may stabilize the active ferrous form of IDO, and catalyzes tryptophan degradation by using molecular oxygen or superoxide existing in the hypoxic neoplastic cells. Because of the oxygen affinity of rhIDO with  $K_d^{O_2}=54 \mu\text{M}$ , IDO can still function in hypoxic conditions. In anoxic environments, this catalytic reaction does not take place because of the lack of molecular oxygen. In addition, hypoxic cytotoxins undergo one-electron reduction to produce cytotoxic radicals, but do not undergo one-electron reduction in aerobic conditions. We found that hypoxic cytotoxicities of TPZ hybrids TX-2235 and TX-2234 were up to 1.5-fold higher compared to their lead compound TPZ, and we observed preferential hypoxic cytotoxicities (42). As a result, we proposed the following explanation: TPZ hybrids TX-2235 are taken into hypoxic cells and suffer one-electron reduction by reductases to generate hydroxyl radicals or TPZ radicals that cause DNA double-strand breaks. At the same time, TPZ hybrid TX-2235 is metabolized to TPZ-monoxide hybrid TX-2236, which is a stronger IDO inhibitor compared to the parent TPZ hybrid TX-2235. TPZ hybrid TX-2234 also functions in the same manner as TX-2235. TPZ hybrids TX-2235 and TX-2234 can attack hypoxic cells as dual antineoplastic agents, functioning as hypoxic cytotoxins and IDO inhibitors (42). We further designed, as a unique

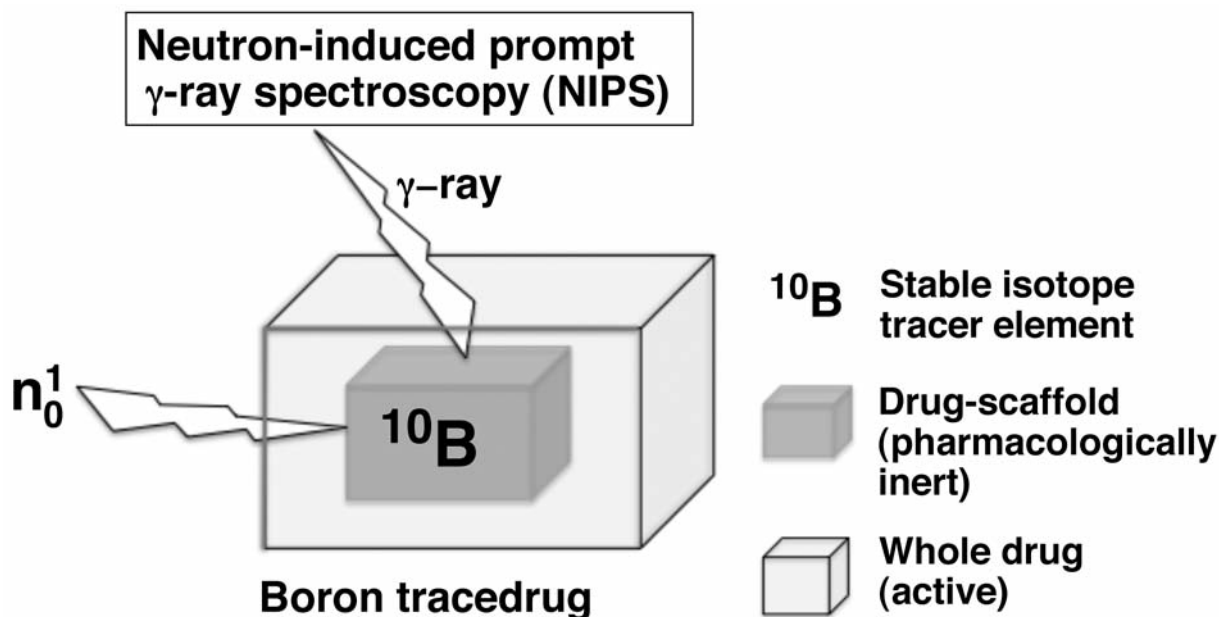


Figure 6. Illustration of designed boron tracedrug.

class of hybrid drugs, hypoxia-targeting IDO hybrid inhibitors conjugated with an unsubstituted L-Trp as an IDO affinity moiety not possessing the inhibitor IMT. TPZ-monoxide hybrids were good competitive IDO inhibitors, while TPZ hybrids were uncompetitive IDO inhibitors. Among them, the TPZ-monoxide hybrid TX-2236 has the strongest IDO inhibitory activity (43).

**Hypoxia-targeting BSH-TPZ Hybrid BNCT Agents.** BNCT is a targeted radiation therapy that significantly increases the therapeutic ratio relative to conventional radiotherapeutic modalities (44). In BNCT, when a therapeutic amount of  $^{10}\text{B}$  can be distributed throughout the target tumor, two particles generated through the neutron capture reaction in boron [ $^{10}\text{B}(n, \alpha)^7\text{Li}$ ] carry a high linear energy transfer (LET) if a sufficient number of very-low-energy thermal neutrons can be delivered. Thus, they can damage both hypoxic tumor cells and aerobic tumor cells very efficiently. However, it is difficult to distribute a therapeutically effective amount of  $^{10}\text{B}$  homogeneously throughout target tumors, including hypoxic areas, using a conventional  $^{10}\text{B}$ -carrier [Sodium borocaptate- $^{10}\text{B}$  (BSH) or boronophenylalanine- $^{10}\text{B}$  (BPA)] (Figure 5) (43). It is especially difficult to deliver  $^{10}\text{B}$  from BPA. Therefore, the presence of hypoxic tumor cells is also associated with resistance to BNCT. For efficient tumor-selective  $^{10}\text{B}$  delivery agents (B-10 carriers) which are of pivotal importance for success of BNCT for cancer treatment, we conjugated hypoxia-targeting BNCT agents, such as 2-

nitroimidazole-type hypoxic cell radiosensitizers (46, 47) and the hypoxic cytotoxin TX-402 [3-amino-2-quinoxaline-carbonitrile 1,4-dioxide; a hypoxic cytotoxin developed by us (48-50)] (Figure 5) (49-51) to (51, 52) BSH. The TX-402 conjugate (TX-2100) had the most favorable characteristics, having high concentrations of  $^{10}\text{B}$  in tumors and during irradiation. TX-2100 also showed a significantly stronger *in vitro* radiosensitizing effect than BSH when irradiated with a neutron beam. We have proposed that our hypoxia-targeting hybrid B-10 carriers, especially TX-2100, may be useful and promising B-10 carrier candidates for BNCT.

### Creation of Boron Tracedrugs as Innovative Emerging Pharmaceutical Drug Classes

**Design Concept of 'Boron Tracedrugs'.** Traceability data management of the flow of goods, information and other resources is integral to present logistics information systems. However, many materials, such as drugs and chemicals themselves, as yet have no general tags which enable their traceability. Thus, when these drugs need to be traced, the only option for tracking them is to analyze them by their appropriate analytical method. For tracking data management of next-generation pharmaceutical drugs and chemicals, we present here our strategy and tactics of boron tracedrugs as next-generation pharmaceuticals, based on our BNCT  $^{10}\text{B}$ -carrier drug design. We propose boron tracedrugs as entities that will possess persistent traceability throughout their lifetime.

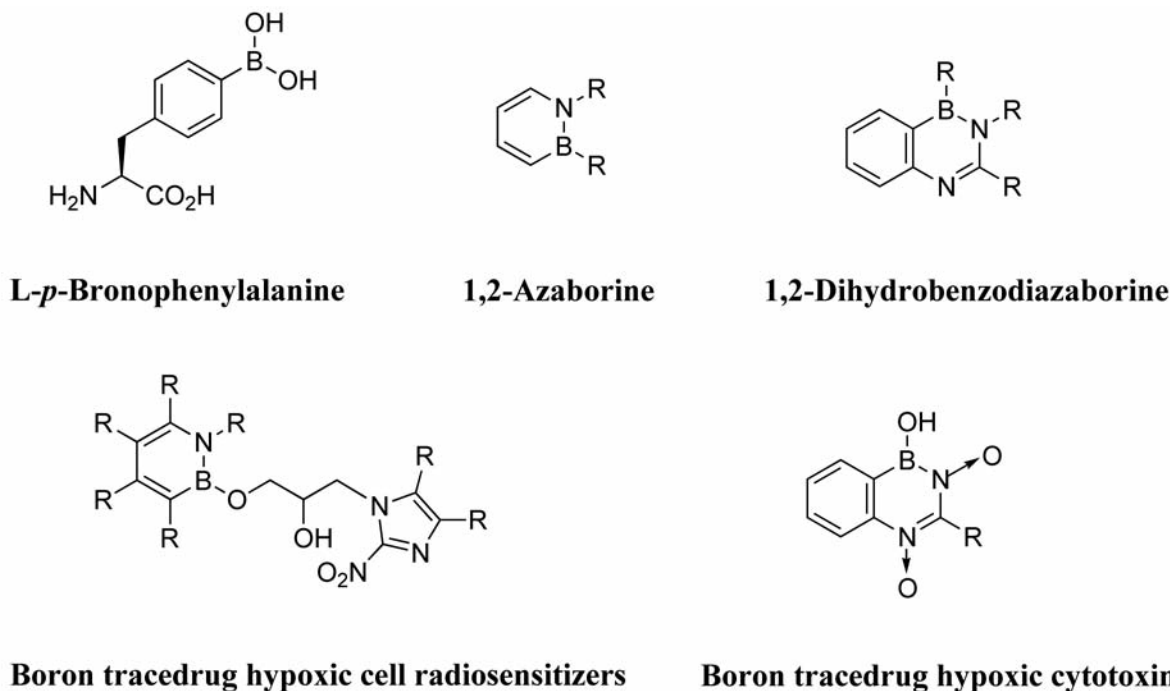


Figure 7. L-p-Boronophenylalanine (BPA) and boron tracedrug scaffolds such as 1,2-azaborine and 1,2-dihydro-benzodiazaborine, and boron tracedrug hypoxic cell radiosensitizers and hypoxic cytotoxins.

*Boron Tracedrugs Having Boron Heterocyclic Moieties as their Scaffolds.* The key design element of boron tracedrugs consists of their containing multiple boron atoms firmly embedded in their scaffold or skeleton at a position that will have little or no influence on other functional group(s) and pharmacophore(s). The traceability of 'boron tracedrugs' is based on the neutron capture activity of the stable isotope boron-10 embedded in the drug. Thus, newly designed boron tracedrugs would be novel pharmaceuticals, the structures of which would always include natural boron (B-11, 80.4%; B-10, 19.6%), as tracers, embedded deeply in their skeletons or scaffolds, as shown in Figure 6.

Our concept of boron trace drugs evolved from our previous drug design studies on the development of hypoxia-targeting B-10 carrier compounds described above. In particular, the pharmacokinetics of neutron-induced prompt gamma-ray spectroscopy (NIPS) allows measurement of B-10 concentration within a few minutes. We envisioned that if new pharmaceuticals all contained B-10 embedded in their molecular skeleton or scaffold, research and developmental facilities would be simplified and green chemistry would be facilitated. BSH described here, L-p-boronophenylalanine (BPA), and molecules with the compact B<sub>10</sub>H<sub>10</sub>C<sub>2</sub> carborane unit are all important in BNCT (44). Although boron is not an element commonly found in natural products or drugs, several bioactive boron-containing compounds are known (53). For example, the natural product boromycin and its relatives are

antibiotics and potential antivirals. Borinic esters and oxazaborolidines with antibacterial activity are known, and benzoxaborole is being studied for onychomycosis. Certain alpha-animoboronic acids and related agents have anticancer, hypolipidemic, and antifungal activity; diazaborines are antimalarial, and others are protease and proteasome inhibitors, such as bortezomib (54). Thus, boron chemistry is relevant to synthetic organic chemists and medicinal chemists.

Although the creation of a boron trace drug seemed to be a simple concept for researchers who are working on BNCT with prompt gamma ray spectroscopy, a search of the literature using PubMed and other tools revealed no previous reports of this application. Thus, this represents an unexplored area with much potential in next-generation neutron-related industrial development.

In this section, we provide more detail and examples of design of boron tracedrugs as a proposal. As examples of a lead trace drug scaffold or skeleton, we chose benzene isosteres, azaborines such as 1,2-dihydro-1,2-azaborines (55) and 2,4,1-benzodiazaborines (56) and examined their medicinal chemistry in detail. Firstly we will design hypoxia-targeting antineoplastic boron trace drugs such as nitroimidazole-type hypoxic cell radiosensitizers (etanidazole and TX-1877) and hypoxic cytotoxins (tirapazamine and TX-402) (hypoxia-targeting antineoplastic tracedrugs) using these leads of tracedrug scaffolds or skeletons. Drug

development will be based on our technology of *in vitro* clonogenic assay, general *in vivo* pharmacological assay using developing chick embryo, and especially pharmacokinetics using prompt gamma ray spectroscopy.

We suggest that boron tracedrugs will have major impact on the process of clinical drug development and open a new medicinal chemistry era without radioisotope technology. Research with such technology can be carried out in conventional laboratories without legal regulations, except those related to the measurement of pharmacokinetics using prompt gamma-ray analysis using neutrons in nuclear reactors and accelerators, including BNCT-PET now under development. Boron tracedrugs can also be designed to correspond to the era of tailor-made or personalized medicine development, because of less selected drug candidates for pharmacological assay (ADME/Tox) in the early clinical drug development. Generally, at this stage of drug development, only a few drug candidates, selected based on their preclinical investigation, should be applied to their pharmacological assay. Boron tracedrugs have the added potential of being a new class of drugs based on their destructive physical powers acquired by weak thermal neutrons used in BNCT. Possible applications include destruction of extracellular amyloid-beta deposits in the brain regions—the hallmark lesions of Alzheimer disease (57)—and other aberrant macromolecules in degenerative diseases frequently occurring in aged patients.

Boron tracedrugs research offers opportunities for research in engineering fields, in particular in nuclear engineering and neutron engineering, to develop human-friendly atomic power reactors as neutron generators. In the chemical and chemical engineering field, boron tracedrugs could contribute to process chemistry in the pharmaceutical industry where boron-containing organic compounds can be designed to constitute diversity-oriented libraries. The importance of traceability of synthetic materials and modified natural products, and biomolecules such as proteinous drugs/antibody drugs, RNA interference for gene transfer system, nanomaterials, and micromachines is apparent. However, there are no ethical discussions of the traceability of medicine(s) in patients except for a limited number of cases where drug accidents have occurred. Providing patients with drugs having high traceability is a priority for the entire area of pharmaceutical research and development in health care.

In summary, the novel characteristics of boron tracedrugs are as follows. Boron tracedrugs are designed to have boron atom(s)—highly traceable but pharmacologically inert—embedded in their scaffold or skeleton. They provide a warranty of traceability, anytime if necessary, during their lifespan. This meaning is completely different to the traceability of traditional drugs labeled with radioisotope only at the appropriate stage during the drug research and development process. We also call these boron tracedrugs ‘honnête homme’ drugs. If boron tracedrug technology is available, all drug candidates under

development could be traced to fit a developmental strategy for tailor-made drugs as well as next-generation drugs. We, in particular, selected the benzene isostere-functional and boron-containing *N*-heterocycles, such as 1,2-dihydro-1,2-azaborines and 2,4,1-benzoazaborines, as lead compounds to optimize their structures by molecular modeling based on molecular orbital calculations. A boron element embedded in their structure is supplied from boron reagents with natural abundance boron instead of the  $^{10}\text{B}$ -enriched boron compounds used for BNCT.

## Conclusion

The promise of hypoxia-targeting antineoplastic drugs for cancer treatments lies in the potential for tumor selectivity and the availability of molecular indicators of tumor susceptibility (biomarkers for diagnostics), especially in radiation therapy. Boron tracedrugs could be ideal future medicines as theragnostics, drugs possessing properties of both diagnostics and therapeutics, with the information for pharmacokinetics available from themselves directly, without the need for additional treatments. These drugs could be useful in the future world where autopsy imaging (Ai), virthopsy, or virtual biopsy, will be available for medical assessment in the detection of the cause of disease and death.

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