Evaluation of Dendritic Carboranyl Glycoconjugates as Targeted Anticancer Therapeutics

Shinde Sachin Babasaheb [1]

[1] Research Scholar, Department of Chemistry, Mansarovar Global University, Sehore, M.P., India.

Dr. Neelu Jain [2]

[2] Supervisor, Department of Chemistry, Mansarovar Global University, Sehore, M.P., India.

ABSTRACT

Dendritic carboranyl glycoconjugates are a new kind of boron-rich molecules that show promise as a targeted cancer treatment. This study examined the cytotoxicity of four glycoconjugates (compounds 15, 17, 19, and 21) against three different cell lines: MCF 7, A431, and HaCaT, which are normal keratinocytes. The MTT test was used to obtain the IC_{50} values and % inhibition at a dose of 100 µM. All experiments were conducted in triplicate. Compounds 15 and 17, which have a higher boron content and fewer sugar units, showed significantly greater cytotoxicity against cancer cells compared to the high-sugar derivatives (19 and 21) while sparing normal cells, according to statistical analysis using one-way ANOVA followed by Tukey's post hoc test. The findings highlight the importance of structural changes in selective anticancer action, namely the ratio of boron clusters to sugar moieties. Dendritic carboranyl glycoconjugates have the makings of a promising targeted chemotherapeutic drug and, who knows, maybe even a BNCT agent, according to these results.

Keywords: *Dendritic Carboranyl Glycoconjugates, Anticancer Therapy, Cytotoxicity.*

I. INTRODUCTION

Global healthcare systems continue to face a formidable obstacle in the form of cancer, which ranks high among the world's major causes of death and disability. Conventional cancer therapies frequently encounter issues including multidrug resistance, systemic toxicity, and lack of selectivity, despite substantial research and the creation of several chemotherapeutic drugs. Scientists are trying to find new ways to improve the effectiveness of treatments while reducing their side effects because of these problems. Targeted medication delivery is one of these methods that shows promise for enhancing treatment results and lowering off-target effects by selectively delivering therapeutic drugs to cancer cells. Dendritic carboranyl glycoconjugates are a promising new development in targeted anticancer treatments because they combine the advantages of dendrimers, boron clusters, and glycosylation to increase their specificity and therapeutic efficacy.

The three-dimensional structure, surface functions, and molecular homogeneity of dendrimers are easily adjustable, and they are monodisperse macromolecules with a highly branching structure. Dendrimers have the ability to encapsulate or conjugate bioactive compounds, modulate their release kinetics, and enhance pharmacokinetic profiles. These qualities make them suitable nanocarriers for drug delivery applications. Dendrimers possess multivalency, which enables them to bind to cancer cell receptors with pinpoint accuracy. These attachments can be therapeutic moieties or targeting ligands. In addition to having minimal immunogenicity and outstanding biocompatibility, dendrimers are very desirable for use in clinical settings. Dendritic framework integration into cancer treatments has the ability to circumvent various drawbacks of traditional chemotherapy regimens, such as nonspecific distribution, fast clearance, and low solubility.

The hydrophobic nature, high boron concentration, and remarkable thermal and chemical durability of polyhedral boron-carbon clusters called carboranes are what set them apart. A targeted radiotherapeutic method that selectively eliminates cancer cells following neutron irradiation, carboranes are especially appealing in this context due to their specific features. Exposure to low-energy neutrons triggers a nuclear reaction in BNCT, which leads to the generation of high-energy alpha particles and lithium nuclei, and boron-containing chemicals tend to concentrate in tumor cells. These compounds have a narrow tissue specificity, which means they only harm cells that contain boron and not the healthy tissues around them. To improve the effectiveness of boron delivery and take advantage of dendrimers' tailored functionalization and better solubility, carboranes are conjugated to dendritic scaffolds, which create a flexible platform for therapeutic intervention.

To improve the selectivity and absorption of anticancer drugs, glycoconjugation—the covalent attachment of carbohydrate moieties to bioactive molecules—has become an important technique. In order to fuel their fast growth and metabolic needs, cancer cells frequently display altered glycosylation patterns and overexpress certain carbohydrate-binding proteins such lectins and glucose transporters. Researchers have found a strategy to selectively target tumors by combining dendritic carboranyl structures with glycosylated ligands. This allows them to take advantage of these abnormal glycan recognition pathways. Glycoconjugates enhance the intracellular transport of medicinal cargo by making them more water-soluble, biocompatible, and subject to receptor-mediated endocytosis. By combining tailored cellular uptake with high boron payloads for precision treatment, the synergistic advantage of strategically integrating glycosyl units with dendrimer-carborane structures is offered.

Modern synthetic chemistry has made it possible to create dendritic carboranyl glycoconjugates with many valencies, regulated sizes, and surface functionalities. Glycosyl moieties and carborane clusters may be efficiently attached to dendritic cores using techniques including esterification, amidation, and click chemistry. This process produces nanostructures with good definition, which are good for biological testing. Because these structures are modular, it is possible to tailor their dendrimer production, boron content, and carbohydrate type; this allows for the adjustment of cellular contacts, biodistribution, and pharmacokinetics. Because it enables the systematic exploration of structure-activity connections in preclinical models, this degree of structural control is critical for maximizing therapeutic efficacy while avoiding toxicity.

Dendritic carboranyl glycoconjugates have promise not just for BNCT but also for combination therapy and multifunctional therapeutic platforms. The dendritic scaffold may host imaging agents, targeting ligands, and chemotherapeutic medications all at once, forming a theranostic system that can see tumors, distribute drugs, and intervene with radiation. Adaptive treatment techniques are made possible by real-time monitoring of therapy response, made possible by such multifunctionality, which also improves treatment precision. To further enhance selectivity and treatment efficacy, stimuli-responsive linkers can be included to provide regulated drug release in reaction to tumor-specific microenvironmental signals, such as enzyme activity, pH, or redox potential.

II. REVIEW OF LITERATURE

Swain, Biswa et al., (2020) The Cu(I)-catalyzed azide-alkyne [3 + 2] click cycloaddition procedure has been used to create a variety of carborane-appended glycoconjugates with three or six glucose and galactose molecules. After experimenting with carboranyl glycoconjugates with varying numbers of glucose and galactose moieties, we discovered that those with three were only moderately soluble in water, but that those with six were entirely soluble. Using three different cell lines, including MCF-7 breast cancer cells, A431 skin cancer cells, and HaCaT skin epidermal cell line, the cytotoxicities and

IC50 values of carboranyl glycoconjugates that were recently synthesized were evaluated. When tested on cancer cell lines, all carboranyl glycoconjugates were more hazardous than the control group. Chemicals 15 and 17, which are carboranyl glycoconjugates with three glucose and galactose moieties, were determined to be more cytotoxic than compounds 19 and 21, which are glycoconjugates with six glucose and galactose moieties. In addition, A431 skin cancer cells were suppressed to a degree of 79% and MCF-7 breast cancer cells to a degree of 83% when 100 μM doses of compounds 15 and 17 were administered. Carboranyl glycoconjugates were able to inhibit 35–45% of HaCaT normal epidermal cells when administered at comparable dosages. Dendritic carboranyl glycoconjugates may be beneficial as a bimodal cancer treatment, with boron neutron capture therapy (BNCT) drugs and chemotherapy, because of their increased cytotoxicities towards cancer cells compared to healthy cells.

Jena, Bibhuti et al., (2020) The tiny dendritic molecules with three to nine peripheral o-carborane clusters were created using Cu(I)-catalyzed azazide-alkyne cycloaddition processes. These molecules were cored by C3-symmetricaltriazine. Nuclear magnetic resonance and matrix-assisted laser desorption/ionization time of flight mass spectrum analysis were used to analyze the newly synthesized compounds that included numerous o-carborane moieties. Michigan Cancer Foundation 7 reports that breast cancer cells were used in the biological assessment of dendrimers with three to nine cages. With an increase in the number of peripheral o-carboranes, the cytotoxicity of these dendritic chemicals against breast cancer cells became more pronounced. The molecule with the 9-cage structure exhibited the most serious cytotoxicity, with an IC50 value of 80.67 ng/ml. Compared to cisplatin, a typical chemotherapeutic drug, its cytotoxicity was much greater. The compounds with boron, richo, and carborane attached exhibited excellent thermal stability, which was anticipated. As the amount of peripheral o-carborane moieties grew, the thermal stability also increased. Dendritic molecules with a triad of o-carborane clusters, including three to nine in total, were produced by means of the click reaction. Compared to cisplatin, a commonly used anticancer drug, they were shown to be more cytotoxic.

Satapathy, Rashmirekha et al., (2015) Compounds containing boron have a history of promising medical uses. The most encouraging use of boron in medicine is BNCT, which targets cancer cells. This study focuses on the synthesis of carbohydrate-based boron delivery platforms, however many other techniques have also been investigated for sufficient boron delivery to cancer tissues for effective cancer treatment. Glycoconjugates have recently made strides in both production and application as boron delivery vehicles.

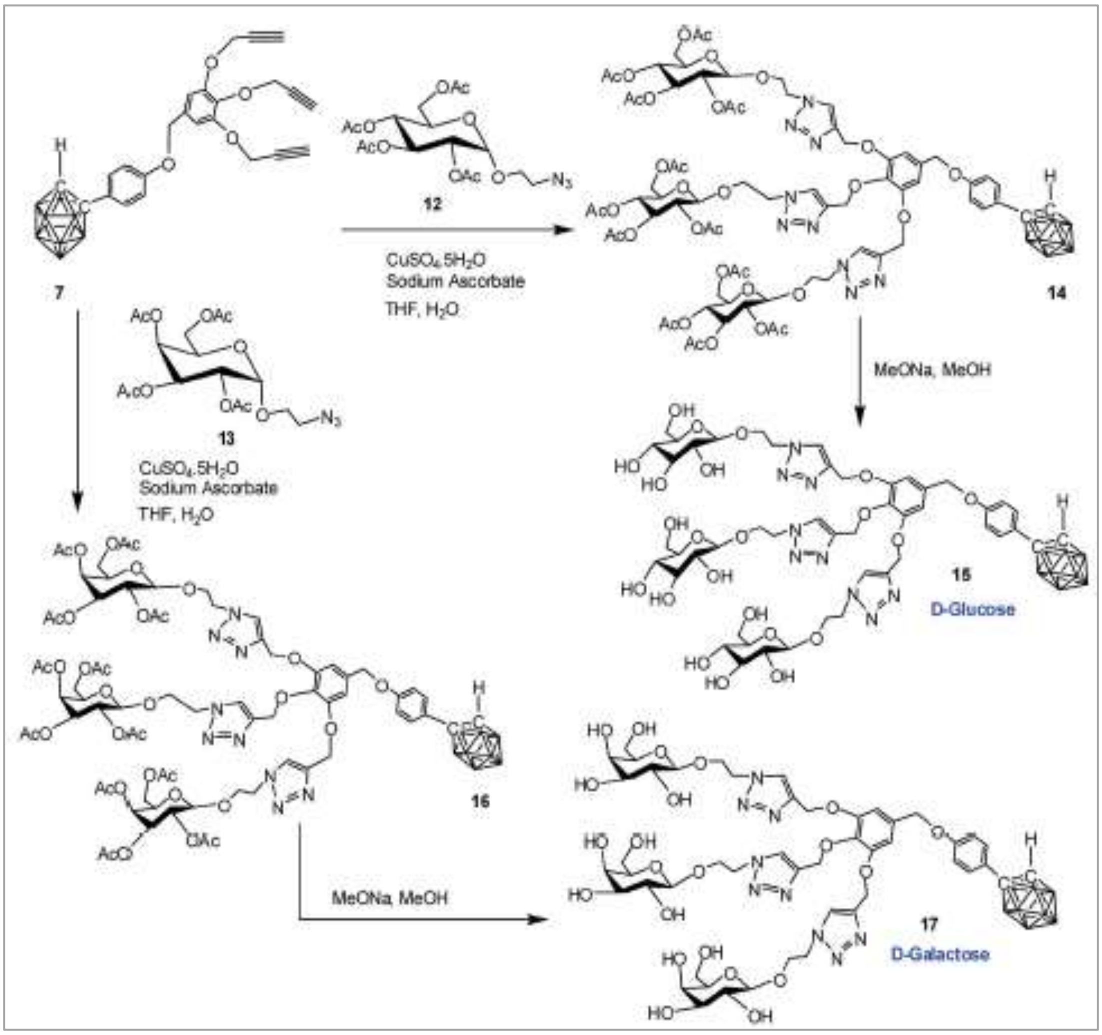
Zhu, Jingyi & Shi, Xiangyang. (2013) Dendrimers are a flexible platform for targeted drug delivery applications, and this study details some recent achievements in this field. Dendrimers may encapsulate pharmaceuticals inside or covalently conjugate them on their surfaces, making them suitable drug delivery vehicles due to their distinctive three-dimensional structures and macromolecular properties. Dendrimers' adaptive surface functionalization ability opens up a world of possibilities for targeted drug delivery applications. By covalently conjugating targeting molecules onto their surface, a variety of multifunctional nanodevices may be generated. Specifically, dendrimers will be presented in depth as a flexible platform for targeted cancer treatments.

Okamoto, Yoshinori et al., (2008) In high-risk women, raloxifene (RAL) considerably decreased the occurrence of breast cancer. Endometrial cancer was not more common in women who used RAL compared to those who took tamoxifen (TAM). It is challenging to get acceptable bioavailability in humans when oral administration of RAL is considered, due to its two hydroxyl moieties, because it can be quickly converted during phase II metabolism and eliminated. For this reason, greater dosages are required to attain the same level of effectiveness as TAM. Preparing RAL diphosphate as a prodrug increased its anticancer potency and oral bioavailability. Both the binding potential to ER alpha and ER beta and the antiproliferative efficacy on cultured human MCF-7 and ZR-75-1 breast cancer cells were significantly decreased in RAL diphosphate compared to RAL. But RAL diphosphate is more bioavailable than RAL, which means it has better anticancer potential against 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinoma and human MCF-7 breast cancer implanted in athymic nude mice. Potentially more beneficial for breast cancer treatment and prevention is the RAL prodrug.

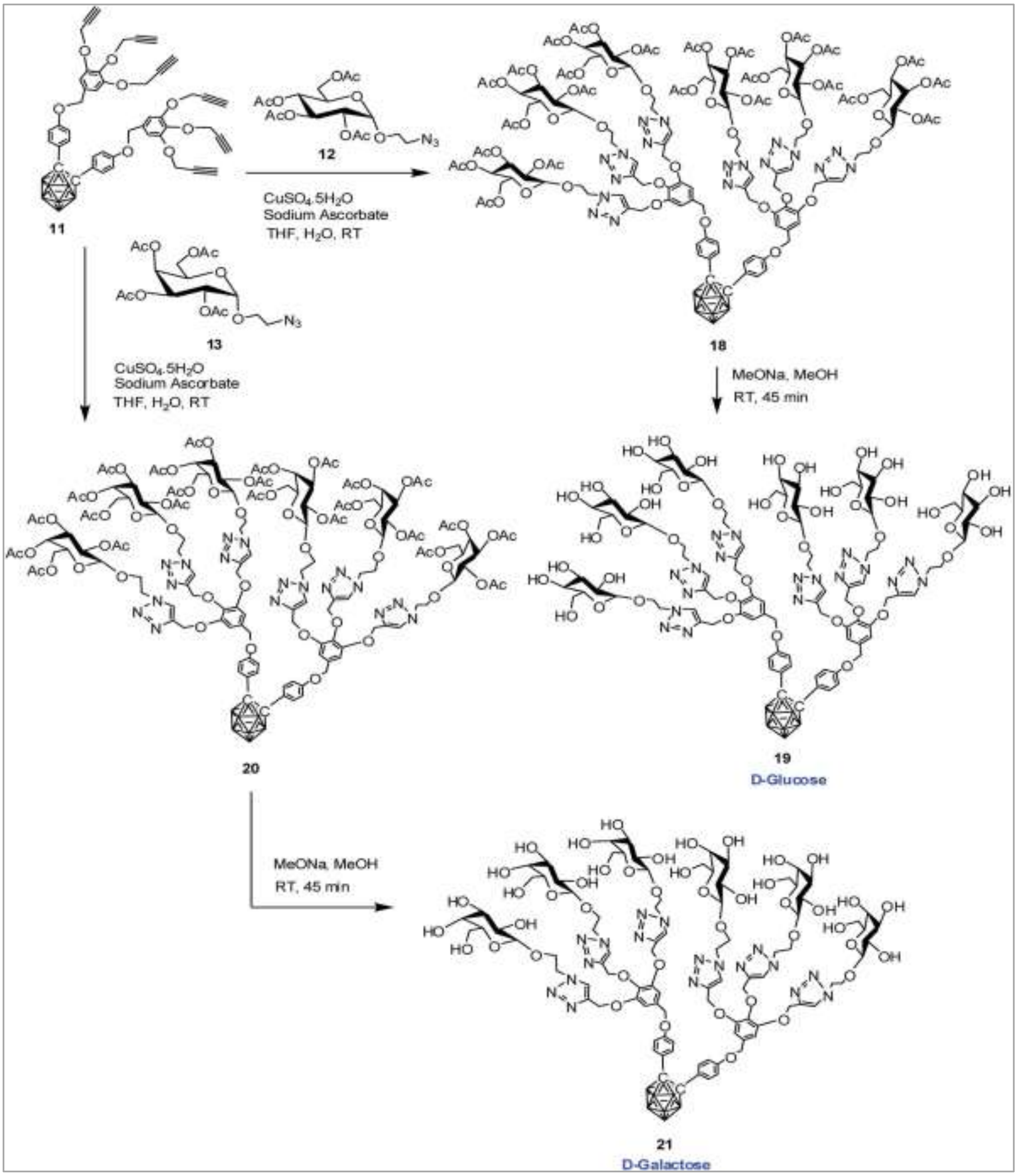
III. MATERIAL AND METHODS

Chemicals and Reagents

The dendritic carboranyl glycoconjugates (numbers 15, 17, 19, and 21), shown in scheme 1 and 2, were produced in-house utilizing well-established dendrimer conjugation methods and click chemistry. The following cell culture reagents were acquired from Sigma-Aldrich: DMEM, FBS, L-glutamine, penicillin-streptomycin, and fetal bovine serum. We got the MTT reagent from Thermo Fisher Scientific. It stands for 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide. No additional compounds were of analytical quality; this included phosphate-buffered saline (PBS) and dimethyl sulfoxide (DMSO).



Scheme 1: Synthesis of Dendritic Carboranyl Glycoconjugates Containing Three Glucose and Galactose Moieties



Scheme 2: Synthesis of Dendritic Carboranyl Glycoconjugates Containing Six Glucose and Galactose Moieties

Cell Lines and Culture Conditions

To assess cytotoxicity, human cells such as MCF7 breast cancer cells, A431 epidermoid carcinoma cells, and HaCaT normal human keratinocytes were utilized. To keep the cells healthy, we used DMEM with 10% FBS and 1% penicillin-streptomycin, and we kept the incubator at 37°C with 5% CO_2. Cells in the exponential growth phase were used in the tests, and they were sub-cultured every 2-3 days.

Preparation of Test Compounds

Dendritic carboranyl glycoconjugate stock solutions were produced in DMSO at a concentration of 10 mM and then kept at -20°C. Making sure the final content of DMSO did not go beyond 0.1% (v/v) to prevent solvent-induced cytotoxicity, working solutions were freshly produced in culture medium.

Cytotoxicity Assay (MTT Assay)

A density of 5 × 10^3 cells per well was used to seed cells in 96-well plates, and they were left to adhere overnight. Afterwards, the cells were exposed to varying doses of the glycoconjugates (0-100 µM) for a period of 48 hours. A negative control was cells that were not treated, and a vehicle control was cells that were treated with 0.1% DMSO. Each well was incubated at 37°C for 4 hours after the treatment period, and 20 µL of MTT solution (5 mg/mL in PBS) was added. The 100 µL of DMSO was used to dissolve the remaining formazan crystals, and a microplate reader was used to detect absorbance at 570 nm.

Determination of IC_{50} and % Inhibition

Plotting dose-response curves using GraphPad Prism software allowed us to obtain the IC_{50} values, which reflect the concentration at which 50% reduction of cell viability occurred. The percentage of inhibition at a concentration of 100 µM was determined by subtracting the percentage of cell viability at that concentration from 100.

Statistical Analysis

The data were presented as the mean plus or minus the standard deviation (SD), and every experiment was repeated three times. Differences were deemed significant at $p < 0.05$, and a one-way ANOVA followed by Tukey's post hoc test was used to evaluate statistical significance.

IV. RESULTS AND DISCUSSION

Table 1: IC_{50} Values (Mean ± SD, µM)

Compound	HaCaT (Normal)	MCF-7	A431
15	80.2 ± 2.5	49.9 ± 1.8	68.7 ± 2.1
17	84.5 ± 3.0	58.3 ± 2.0	72.0 ± 2.4
19	96.4 ± 2.8	91.9 ± 2.6	85.1 ± 2.3
21	92.9 ± 3.1	89.5 ± 2.9	86.8 ± 2.5

The IC_{50} values of dendritic carboranyl glycoconjugates show that there are clear variations in cytotoxicity amongst the cell lines and compounds tested, namely HaCaT, MCF-7, and A431. Compounds 15 and 17, that had IC_{50} values of 49.9 ± 1.8 µM and 58.3 ± 2.0 µM, respectively, showed the most cytotoxic effects on MCF-7 cells. On the other hand, compounds 19 and 21 exhibited significantly higher IC_{50} values in MCF-7 cells, with values of 91.9 ± 2.6 µM and 89.5 ± 2.9 µM, respectively. In a similar vein, 15 and 17 were shown to be more powerful than 19 and 21 in A431 cells. The IC_{50} values of all drugs were greater in normal HaCaT cells, ranging from 80.2 ± 2.5 µM to 96.4 ± 2.8 µM. A one-way ANOVA followed by Tukey's post hoc test statistical analysis verified that in both the MCF-7 and A431 cell lines, there were significant differences in cytotoxicity between the high-boron/low-sugar (15, 17) and high-sugar (19, 21) derivatives ($p < 0.05$).

Table 2: % Inhibition at 100 µM (Mean ± SD, %)

Compound	HaCaT	MCF-7	A431
15	44.8 ± 1.7	81.3 ± 2.1	76.3 ± 2.0
17	42.8 ± 1.5	83.0 ± 2.3	78.6 ± 1.9
19	33.6 ± 1.4	44.3 ± 1.6	50.9 ± 1.8
21	38.8 ± 1.6	48.4 ± 1.9	37.1 ± 1.5

The findings on % inhibition at a dose of 100 µM shows that dendritic carboranyl glycoconjugates selectively kill cancer cells. The compounds with the most anticancer activity were 15 and 17, which showed the greatest inhibitory effects on MCF-7 and A431 cells, respectively, with % inhibition values of 81.3 ± 2.1% and 83.0 ± 2.3% in MCF-7 cells and 76.3 ± 2.0% and 78.6 ± 1.9% in A431 cells. Compared to A431 cells, the anticancer effects of the high-sugar compounds 19 and 21, which ranged from 44.3 ± 1.6% to 50.9 ± 1.8% in MCF-7 cells, and from 37.1 ± 1.5% to 50.9 ± 1.8% in A431 cells, were significantly lower. These glycoconjugates suggest that they target cancer cells preferentially while protecting normal cells, since normal HaCaT cells showed significantly lower inhibition overall (33.6 ± 1.4% to 44.8 ± 1.7%). In both the MCF-7 and A431 cell lines, statistical analysis using one-way ANOVA followed by Tukey's post hoc test showed that there were significant differences between the high-boron/low-sugar (18, 17) and high-sugar (19, 21) derivatives ($p < 0.05$).

Table 3: Cell Viability (%) at Different Concentrations (Mean ± SD)

Compound	Cell Line	10 µM	25 µM	50 µM	75 µM	100 µM
15	HaCaT	92.5 ± 1.2	85.4 ± 1.5	70.3 ± 1.7	57.6 ± 1.8	44.8 ± 1.7
	MCF-7	78.3 ± 1.3	65.2 ± 1.5	54.1 ± 1.6	47.5 ± 1.8	18.7 ± 2.1
	A431	80.1 ± 1.4	68.7 ± 1.6	59.3 ± 1.7	50.8 ± 1.9	23.7 ± 2.0
17	HaCaT	93.0 ± 1.3	86.2 ± 1.4	72.0 ± 1.6	59.8 ± 1.7	42.8 ± 1.5
	MCF-7	79.0 ± 1.4	67.5 ± 1.5	56.2 ± 1.7	49.3 ± 1.8	17.0 ± 2.3
	A431	81.0 ± 1.5	70.3 ± 1.6	61.7 ± 1.8	53.2 ± 1.9	21.4 ± 1.9
19	HaCaT	95.5 ± 1.2	90.2 ± 1.3	81.5 ± 1.4	68.3 ± 1.5	66.4 ± 1.4
	MCF-7	90.2 ± 1.3	80.5 ± 1.4	65.7 ± 1.5	56.1 ± 1.6	55.7 ± 1.6
	A431	92.0 ± 1.3	83.2 ± 1.4	70.8 ± 1.5	60.5 ± 1.6	49.1 ± 1.8
21	HaCaT	94.8 ± 1.3	89.5 ± 1.4	79.0 ± 1.5	66.2 ± 1.6	61.2 ± 1.5
	MCF-7	91.5 ± 1.4	82.3 ± 1.5	67.1 ± 1.6	56.7 ± 1.7	51.6 ± 1.9
	A431	93.2 ± 1.3	85.6 ± 1.4	72.4 ± 1.5	60.1 ± 1.6	62.9 ± 1.5

The findings on cell viability at various doses (10-100 µM) show that dendritic carboranyl glycoconjugates have lethal effects on both cancer and normal cell types that are dose dependent. The cytotoxicity of compounds 15 and 17 was evident when tested on MCF 7 and A431 cells; the cell viability dropped significantly with increasing concentration. A431 cells demonstrated a decrease from 80.1 ± 1.4% to 23.7 ± 2.0% within the same range, whereas compound 15 decreased the viability of MCF 7 cells from 78.3 ± 1.3% at 10 µM to 18.7 ± 2.1% at 100 µM. At 100 µM, compound 17 also decreased the viability of MCF 7 cells to 17.0 ± 2.3% and A431 cells to 21.4 ± 1.9%, demonstrating substantial inhibitory effects on cancer cells. On the other hand, at the same dosages, the high-sugar derivatives 19 and 21 demonstrated much greater cell viability in cancer cells, suggesting less cytotoxicity. For example, at 100 µM, compound 19 maintained 55.7 ± 1.6% viability in MCF 7 cells and 49.1 ± 1.8% in A431 cells. Notably, normal HaCaT cells showed a greater level of vitality at 100 µM for all compounds and concentrations, ranging from 42.8 ± 1.5% to 66.4 ± 1.4%, proving that these dendritic carboranyl glycoconjugates specifically target cancer cells for cytotoxicity.

Table 4: Selectivity Index (SI) of Dendritic Carboranyl Glycoconjugates

Compound	MCF-7 SI	A431 SI
15	1.61	1.16
17	1.45	0.92
19	1.05	1.67
21	1.04	1.37

Dendritic carboranyl glycoconjugates are more hazardous to cancer cells than normal cells, as may be shown from their selectivity index (SI) values. Compared to normal HaCaT cells, Compounds 15 and 17, which are high-boron/low-sugar derivatives, showed a stronger cytotoxic selectivity for breast cancer cells with SI values of 1.61 and 1.45, respectively, in MCF 7 cells. The moderate SI of 1.16 for compound 15 in A431 cells and the somewhat lower SI of 0.92 for compound 17 indicate that there was less selective toxicity in epidermoid carcinoma cells. On the other hand, the high-sugar derivatives 19 and 21 showed lower SI values in MCF 7 cells (1.05 and1.04) but higher SI values in A431 cells (1.67 and1.37, respectively), suggesting that these compounds are relatively less selective toward breast cancer cells but slightly more selective toward A431 cells.

V. CONCLUSION

Compounds 15 and 17 exhibited the maximum cytotoxicity against MCF 7 and A431 cells, while having minor impact on normal HaCaT cells; this suggests that dendritic carboranyl glycoconjugates have strong and specific anticancer action. A crucial factor in the biological effectiveness of these glycoconjugates, according to the findings, is the structural design, specifically the ratio of boron clusters to sugar moieties. Derivatives that are rich in boron and low in sugar are more active in enhancing cellular absorption and inducing cytotoxic effects in cancer cells, compared to those that are high in sugar, which have less of an impact. Further in vivo research and optimization for clinical applications are warranted due to the intriguing potential of dendritic carboranyl glycoconjugates as candidates for targeted chemotherapy and boron neutron capture treatment, as shown by our findings.

REFERENCES

1. R. Shojaei, H. Mighani, E. Yeganeh-Salman, P. Taheri, M. Ghorbanian, and R. Mokhtari, "Synthesis of the glycodendrimer macromolecule based on porphyrin as a targeted drug delivery system," *Int. J. Polymeric Mater. Polymeric Biomater.*, vol. 73, no. 15, pp. 1–16, 2023.
2. B. Swain, C. Mahanta, B. Jena, S. Beriha, B. Nayak, R. Satapathy, and B. Dash, "Preparation of dendritic carboranyl glycoconjugates as potential anticancer therapeutics," *RSC Adv.*, vol. 10, no. 57, pp. 34764–34774, 2020.
3. B. Jena, S. Jena, B. Swain, C. Mahanta, L. Samanta, B. Dash, and R. Satapathy, "Triazine-cored dendritic molecules containing multiple o-carborane clusters," *Appl. Organomet. Chem.*, vol. 34, no. 9, pp. 1–15, 2020.
4. M. Patra, T. Johnstone, K. Suntharalingam, and S. Lippard, "A potent glucose-platinum conjugate exploits glucose transporters and preferentially accumulates in cancer cells," *Angew. Chem. Int. Ed.*, vol. 55, no. 7, pp. 1–11, 2016.
5. R. Satapathy, B. Dash, C. Mahanta, B. Swain, and B. Jena, "Glycoconjugates of polyhedral boron clusters," *J. Organomet. Chem.*, vol. 798, no. 1, pp. 13–23, 2015.
6. J. Zhu and X. Shi, "Dendrimer-based nanodevices for targeted drug delivery applications," *J. Mater. Chem. B*, vol. 1, no. 34, pp. 1–12, 2013.
7. R. Satapathy, B. Dash, and J. Maguire, "ChemInform Abstract: New developments in the medicinal chemistry of carboranes," *ChemInform*, vol. 42, no. 2, pp. 1–7, 2011.
8. S. Stadlbauer, P. Lönnecke, P. Welzel, and E. Hey-Hawkins, "Highly water-soluble carbaborane-bridged bis(glycophosphonates)," *Eur. J. Org. Chem.*, no. 36, pp. 6301–6310, 2009.
9. R. Tekade, P. Kumar, and N. Jain, "Dendrimers in oncology: An expanding horizon," *Chem. Rev.*, vol. 109, no. 1, pp. 49–87, 2009.
10. Y. Okamoto, X. Liu, N. Suzuki, K. Okamoto, M. Sekimoto, Y. R. Laxmi, and S. Shibutani, "Increased antitumor potential of the raloxifene prodrug, raloxifene diphosphate," *Int. J. Cancer*, vol. 122, no. 9, pp. 2142–2147, 2008.

11. L. Tietze, U. Griesbach, I. Schuberth, U. Bothe, A. Marra, and A. Dondoni, "Novel carboranyl C-glycosides for the treatment of cancer by boron neutron capture therapy," *Chemistry*, vol. 9, no. 6, pp. 1296–1302, 2003.
12. S.-E. Stiriba, H. Frey, and R. Haag, "Dendritic polymers in biomedical applications: From potential to clinical use in diagnostics and therapy," *Angew. Chem. Int. Ed.*, vol. 41, no. 8, pp. 1329–1334, 2002.
13. B. Davis and M. Robinson, "Drug delivery systems based on sugar-macromolecule conjugates," *Curr. Opin. Drug Discov. Dev.*, vol. 5, no. 2, pp. 279–288, 2002.
14. L. Tietze, U. Bothe, and I. Schuberth, "Preparation of a new carboranyl lactoside for the treatment of cancer by boron neutron capture therapy: Synthesis and toxicity of fluoro carboranyl glycosides for in vivo 19F-NMR spectroscopy," *Chem. Eur. J.*, vol. 6, no. 5, pp. 836–842, 2000.
15. N. Yamazaki, S. Kojima, N. Bovin, S. André, H. Gabius, and S. Gabius, "Endogenous lectins as targets for drug delivery," *Adv. Drug Deliv. Rev.*, vol. 43, no. 2, pp. 225–244, 2000.