ORIGINAL ARTICLE

ASSESSING THE POTENTIAL OF HYPOXIA-TARGETING AGENTS AS GSTP1 INHIBITORS IN OVERCOMING CANCER DRUG RESISTANCE

Kanser İlaç Direncini Aşmada Hipoksi Hedefli Ajanların GSTP1 İnhibitörleri Olarak Potansiyellerinin Değerlendirilmesi

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ABSTRACT

Objective: The persistent challenge of drug resistance in cancer therapy is closely linked to the detoxification activity of glutathione S-transferase P1 (GSTP1). This study aims to assess the potential of hypoxia-targeting agents as GSTP1 inhibitors to address drug resistance mechanisms in cancer.

Material and Methods: Molecular docking simulations were performed using the crystal structure of GSTP1 (PDB ID: 2GSS). Eight hypoxia-targeting agents were tested, including BAY 87-2243, Vadimezan, SLC-0111, Acriflavine, PX-478, Evofosfamide, Bevacizumab, and the reference GSTP1 inhibitor ethacrynic acid. Binding affinities were calculated using AutoDock Vina, and interaction profiles were visualized with Discovery Studio.

Results: Among the tested compounds, BAY 87-2243 exhibited the highest binding affinity to GSTP1 with a binding energy of -9.1 kcal/mol, surpassing ethacrynic acid (-6.7 kcal/mol). Vadimezan (-7.9 kcal/mol) and SLC-0111 (-7.2 kcal/mol) also demonstrated strong inhibitory potential. Key interactions included hydrogen bonds with residues GLN A:51 and ARG A:13 and hydrophobic interactions with PHE A:8. Other compounds displayed lower binding affinities, ranging from -6.6 to -5.7 kcal/mol.

Conclusion: Hypoxia-targeting agents, particularly BAY 87-2243, Vadimezan, and SLC-0111, show promising GSTP1 inhibition potential, offering dual functionality to modulate tumor hypoxia and counteract drug resistance. These findings warrant further in vitro and in vivo studies to explore their clinical application in cancer therapy.

Keywords: *Hypoxia; GSTP1; Drug Resistance; Molecular Docking*

ÖZET

Amaç: Kanser tedavisinde ilaç direncinin kalıcı zorluğu, glutatyon S-transferaz P1 (GSTP1) enziminin detoksifikasyon aktivitesi ile yakından ilişkilidir. Bu çalışma, kanser tedavisinde ilaç direnci mekanizmalarını hedeflemek amacıyla hipoksi odaklı ajanların GSTP1 inhibitörleri olarak potansiyelini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Moleküler yerleştirme simülasyonları, GSTP1'in kristal yapısı (PDB ID: 2GSS) kullanılarak gerçekleştirildi. BAY 87-2243, Vadimezan, SLC-0111, Akflavin, PX-478, Evofosfamid, Bevacizumab ve referans GSTP1 inhibitörü olan etakrinik asit dahil olmak üzere sekiz hipoksi odaklı ajan test edildi. Bağlanma afiniteleri AutoDock Vina kullanılarak hesaplandı ve etkileşim profilleri Discovery Studio ile görselleştirildi.

Bulgular: Test edilen bileşikler arasında BAY 87-2243, -9,1 kcal/mol bağlanma enerjisi ile GSTP1'e en yüksek bağlanma afinitesini gösterdi ve etakrinik asiti (-6,7 kcal/mol) geride bıraktı. Vadimezan (-7,9 kcal/mol) ve SLC-0111 (-7,2 kcal/mol) de güçlü inhibitör potansiyeli sergiledi. Önemli etkileşimler arasında GLN A:51 ve ARG A:13 kalıntıları ile hidrojen bağları ve PHE A:8 ile hidrofobik etkileşimler yer aldı. Diğer bileşikler, -6,6 ile -5,7 kcal/mol arasında değişen daha düşük bağlanma afiniteleri gösterdi.

Sonuç: Hipoksi odaklı ajanlar, özellikle BAY 87-2243, Vadimezan ve SLC-0111, GSTP1 inhibisyon potansiyeli göstererek tümör hipoksisini modüle etme ve ilaç direncini azaltmada çift işlevli bir yaklaşım sunmaktadır. Bu bulgular, kanser tedavisinde klinik uygulamalarını keşfetmek için ileri in vitro ve in vivo çalışmaların yapılmasını gerektirmektedir.

Anahtar Kelimeler: *Hipoksi; GSTP1; İlaç Direnci; Moleküler Yerleştirme*

INTRODUCTION

The persistent challenge of drug resistance in cancer therapy remains one of the most significant barriers to effective treatment. Among various mechanisms contributing to this resistance, the detoxification of chemotherapeutic agents by enzymes such as glutathione S-transferase P1 (GSTP1) has been extensively studied. GSTP1, a member of the glutathione S-transferase family, plays a crucial role in cellular defense against oxidative stress and toxic xenobiotics. By conjugating reduced glutathione to electrophilic compounds, GSTP1 facilitates the detoxification process, reducing the efficacy of many anti-cancer drugs (1, 2). Thus, targeting GSTP1 holds promise for overcoming drug resistance and enhancing therapeutic outcomes in cancer treatment.

Recent advances in cancer research have emphasized the importance of hypoxia as a central feature of the tumor microenvironment. Hypoxic conditions not only drive tumor progression but also contribute to resistance against conventional treatments, including chemotherapy and radiotherapy (3, 4). To address these challenges, researchers have explored hypoxia-targeting therapeutics as a novel strategy for cancer therapy. Compounds such as BAY 87-2243, Vadimezan, SLC-0111, Evofosfamide, PX-478, Acriflavine, and Bevacizumab have emerged as potential candidates for modulating the hypoxic tumor microenvironment (5-9). While these agents' primary mechanisms of action are well-documented, their possible interactions with GSTP1 remain an area of scientific curiosity and speculation.

BAY 87-2243 and Vadimezan are known for disrupting hypoxia pathways, but their potential roles in drug resistance mechanisms remain unclear (8, 10, 11). Similarly, SLC-0111, a carbonic anhydrase IX (CAIX) inhibitor, shows promise in targeting the acidic tumor microenvironment, yet its indirect effects on detoxification enzymes warrant further investigation (7, 12). Evofosfamide, a hypoxia-activated prodrug, demonstrates selective cytotoxicity under hypoxic conditions, raising questions about its impact on oxidative stress responses. Acriflavine and PX-478, both exhibiting antitumor activity through hypoxia-related mechanisms, underscore the importance of exploring their broader implications in resistance pathways (7). Bevacizumab, an anti-angiogenic agent targeting vascular endothelial growth factor (VEGF), is widely used in cancer therapy, but its role in hypoxia-driven resistance processes remains an important yet underexplored area (9). Investigating the interactions of these hypoxia-targeting agents with GSTP1, an enzyme prominently linked to drug-resistant cancer, could provide a foundation for overcoming and better understanding the mechanisms of drug resistance.

The intricate relationship between hypoxia, drug resistance, and GSTP1 remains a largely underexplored area in cancer research. While hypoxia-targeting compounds have demonstrated therapeutic efficacy in various preclinical and clinical settings, their potential to modulate GSTP1 activity indirectly has yet to be fully investigated. Understanding these interactions could pave the way for novel approaches to overcoming drug resistance and enhancing cancer therapies. In this study, molecular docking was utilized to analyze the binding affinities and interactions of hypoxia-targeting agents with GSTP1. Compounds such as BAY 87-2243, Vadimezan, and SLC-0111 emerged with promising GSTP1 inhibitor potential, surpassing the binding efficiency of ethacrynic acid, a known GSTP1 inhibitor. These findings suggest that hypoxia-targeting agents may play a dual role, influencing the tumor microenvironment and modulating key resistance pathways, offering valuable insights for future therapeutic strategies.

MATERIALS AND METHODS

The molecular structures of the selected compounds, along with the GSTP1 inhibitor ethacrynic acid, were obtained from the PubChem database (13). The compounds included BAY 87-2243 (PubChem CID: 67377767), Vadimezan (CID: 123964), SLC-0111 (CID: 310360), Acriflavine (CID: 6842), Bevacizumab (CID: 24801581), PX-478 (CID: 11234795), Evofosfamide (CID: 11984561), and Ethacrynic Acid (CID: 3278). Prior to molecular docking, energy minimization was conducted using Avogadro software to optimize the conformations of the compounds, ensuring their suitability for the docking process (14).

The crystal structure of Glutathione S-transferase P1 (GSTP1) was retrieved from the Protein Data Bank (PDB) with the ID 2GSS. This structure has a resolution

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of 1.9 Å and R-factor and R-free values of 0.209 and 0.229, respectively (15). For docking preparation, water molecules and other non-protein components were removed, hydrogen atoms were added, and Gasteiger charges were applied to the protein to ensure accurate docking results. The active site of GSTP1 was identified by examining the binding pocket of ethacrynic acid, a known GSTP1 inhibitor. The active site coordinates were defined as x = 9.07595, y = 1.00542, and z = 26.9067. A cubic grid of 15 Å × 15 Å × 15 Å was centered around this region to facilitate the docking simulations. Docking was carried out using AutoDock Vina (version 1.2.5), applying the Lamarckian Genetic Algorithm with default settings to calculate the binding affinities of each ligand (16, 17).

After the docking analysis, the molecular interactions between GSTP1 and the compounds were examined in detail. Visualization and thorough analysis of these interactions were performed using Discovery Studio software. The focus was on identifying hydrogen bonds, hydrophobic interactions, and other significant binding interactions, which offered valuable insights into the molecular dynamics and binding characteristics between GSTP1 and the various compounds.

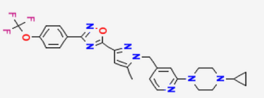
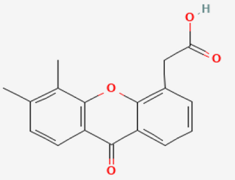
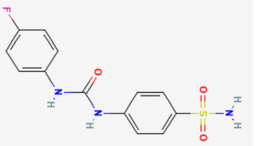
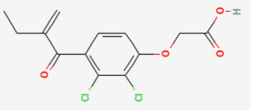
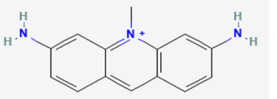
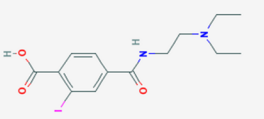
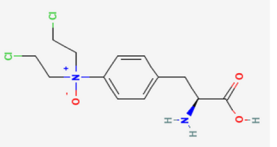
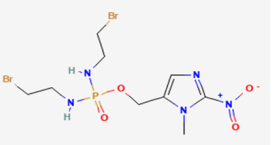
Energy minimization of the compounds was performed using Avogadro, which applies the default MMFF94 force field to optimize molecular geometries, ensuring stable conformations before docking. This process includes default statistical methods to assess the stability and energy profiles of the minimized structures. Docking analyses were conducted using AutoDock Vina, which uses its default Lamarckian Genetic Algorithm to compute binding affinities based on energy and geometric complementarity. The docking process also incorporated default statistical methods to evaluate the reliability and significance of the calculated binding affinities. Visualization of the docking results was done using Discovery Studio, which provides default features for assessing binding affinities and interaction frequencies. This software allows for the identification of key interactions, such as hydrogen bonds and hydrophobic contacts, while applying default statistical analyses to gain insights into the distribution and significance of these interactions.

This study was approved by the Non-Interventional Research Ethics Committee of Afyonkarahisar Health Sciences University (Meeting No: 2025/2, Date: 07.02.2025).

RESULTS

The binding energies of the compounds and ethacrynic acid to GSTP1 are presented in Table 1. Among the compounds tested, BAY 87-2243 showed the strongest binding affinity with a binding

Table 1. Binding energies of the compounds and ethacrynic acid to GSTP1

Compounds	Molecular structure	Binding energy (kcal/mol)
BAY 87-2243		-9.1
Vadimezan		-7.9
SLC-0111		-7.2
Ethacrynic acid		-6.7
Acriflavine		-6.6
Bevacizumab		-6.3
PX-478		-6.0
Evofosfamide		-5.7

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energy of -9.1 kcal/mol, followed by Vadimezan at -7.9 kcal/mol and SLC-0111 at -7.2 kcal/mol. Ethacrynic acid, a known GSTP1 inhibitor, demonstrated a binding energy of -6.7 kcal/mol. Other compounds, including Acriflavine, Bevacizumab, PX-478, and Evofosfamide, exhibited progressively weaker binding affinities, with binding energies ranging from -6.6 to -5.7 kcal/mol. These results suggest that BAY 87-2243, Vadimezan, and SLC-0111 may have significant potential as GSTP1 inhibitors, surpassing the binding affinity of ethacrynic acid.

The molecular docking results display the binding interactions of various compounds with a target protein's active site, arranged in separate panels (Figure 1). The protein's secondary structure is depicted as brown ribbons, while the ligand molecules are highlighted in green stick representations for clarity. The compounds analyzed include BAY 87-2243, Vadimezan, SLC-0111, and Ethacrynic acid in the top row, alongside Acriflavine, Bevacizumab, PX-478, and Evofosfamide in the bottom row. Each ligand exhibits a distinct binding pose, aligning within the protein's binding pocket through molecular interactions such as hydrogen bonds, hydrophobic interactions, and other molecular forces. Ethacrynic acid, used as a reference inhibitor, demonstrates its specific positioning and interaction profile, serving as a comparison point for the other ligands. These results provide insights into the structural compatibility and potential inhibitory strength of each compound, contributing to a deeper understanding of their binding efficacy.

The interaction diagrams showcase the detailed molecular interactions of top hits compounds (BAY 87-2243, vadimezan, SLC-0111) and reference compounds (ethacrynic acid) with the active site of GSTP1 (Figure 2). Each compound forms specific bonds, including conventional hydrogen bonds, van der Waals forces, pi-anion, alkyl, and pi-sigma interactions, as indicated by color-coded lines. BAY 87-2243 establishes multiple hydrogen bonds with residues like GLN A:51 and ARG A:13, while also exhibiting alkyl and pi-anion interactions with residues such as PHE A:8 and VAL A:35. Vadimezan shows prominent pi-anion interactions with TYR A:108 and PHE A:8, alongside hydrogen bonds with ARG A:13 and TYR A:7, suggesting a balanced interaction network. SLC-0111 interacts extensively via hydrogen bonds with residues like ARG A:13, GLN A:51, and TYR A:108, while maintaining pi-anion interactions with PHE A:8. Finally, Ethacrynic acid displays multiple hydrogen bonds with residues such as TYR A:108 and ARG A:13, in addition to van der Waals interactions with surrounding residues. These results highlight

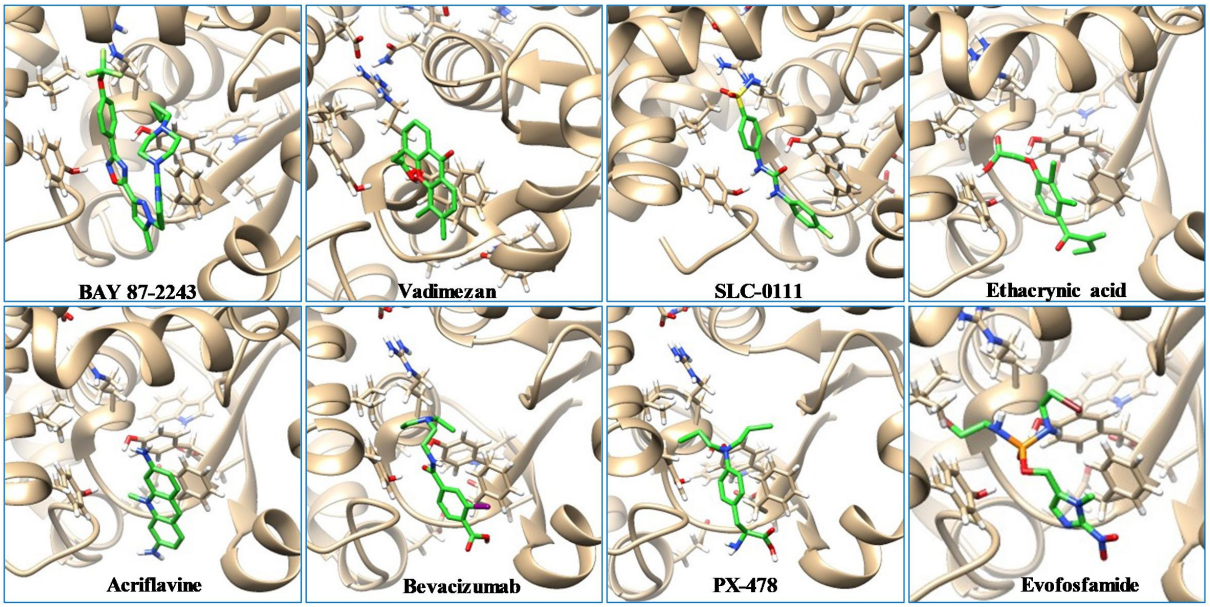

Figure 1. The arrangement of compounds (BAY 87-2243, vadimezan, SLC-0111 and ethacrynic acid) within the active site of GSTP1 (Glutathione S-transferase P1). The GSTP1 protein is illustrated in brown, with the compound structures displayed in green.

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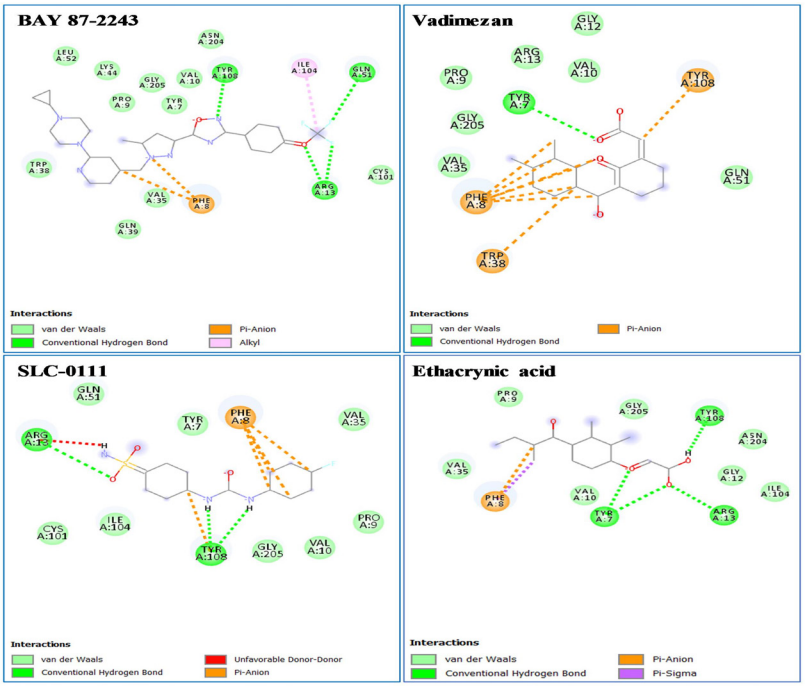

Figure 2. 2D Interaction diagrams of top hits (BAY 87-2243, vadimezan and SLC-0111) and reference compound (ethacrynic acid) with GSTP1 (Glutathione S-transferase P1). The amino acid residues involved in the interactions include Arginine (ARG), Asparagine (ASN), Cysteine (CYS), Glutamine (GLN), Glycine (GLY), Isoleucine (ILE), Leucine (LEU), Phenylalanine (PHE), Proline (PRO), Tyrosine (TYR), Tryptophan (TRP), and Valine (VAL).

each compound's unique binding characteristics and interaction strengths, emphasizing their potential to engage effectively with GSTP1's active site.

DISCUSSION

The findings of this study shed light on the potential dual functionality of hypoxia-targeting agents, not only as modulators of the tumor microenvironment but also as inhibitors of GSTP1, a pivotal enzyme in drug resistance mechanisms. GSTP1 has long been recognized for its role in detoxifying chemotherapeutic agents and reducing their efficacy (1, 2, 18-20). In this study, compounds such as BAY 87-2243, Vadimezan, and SLC-0111 demonstrated stronger binding affinities to GSTP1 compared to the reference inhibitor, ethacrynic acid. These results suggest that targeting hypoxia-associated pathways could inadvertently address resistance mechanisms mediated by GSTP1.

The role of GSTP1 in cancer therapy has been extensively documented, with the enzyme often highlighted as a key player in cellular defense against oxidative stress and xenobiotics (1, 2). Ethacrynic acid, a well-known GSTP1 inhibitor, has been investigated in previous studies for its potential to combat drug resistance; however, its clinical application is still limited due to side effects. (21) . Compared to ethacrynic acid, BAY 87-2243 demonstrated a markedly higher binding affinity in this study, forming multiple hydrogen bonds and pi-anion interactions with key residues in the GSTP1 active site. These findings are consistent with the emerging literature emphasizing the need for more selective GSTP1 inhibitors with dual-targeting potential.

The interplay between hypoxia and drug resistance has been a growing focus in cancer research (22, 23). Hypoxia induces profound changes in tumor biology, including increased oxidative stress, activation of detoxification enzymes like GSTP1, and promotion of resistance to conventional therapies (20, 24) . BAY 87-2243, previously reported to inhibit hypoxia-inducible factor (HIF) activity and improve radiation response (8), demonstrated the strongest GSTP1 inhibition in this study. This suggests that the compound could act as a dual-function agent, targeting both the hypoxic

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environment and detoxification pathways, which could significantly enhance therapeutic outcomes.

Vadimezan, another hypoxia-targeting agent, also showed promising GSTP1 inhibitory potential in this study. Known for its vascular disrupting properties (6) , Vadimezan was previously thought to exert its antitumor effects primarily through vascular collapse. However, our results suggest that its interaction with GSTP1 could represent an additional mechanism of action. By forming hydrogen bonds and pi-anion interactions with residues such as TYR A:108 (25), Vadimezan could reduce GSTP1-mediated detoxification of chemotherapeutics, a concept not widely explored in the literature.

SLC-0111, a CAIX inhibitor targeting acidic tumor microenvironments, emerged as another strong GSTP1 interactor in this study. Carbonic anhydrase inhibitors like SLC-0111 have been shown to disrupt pH regulation in tumors, sensitizing them to chemotherapy (5). The observed GSTP1 inhibition by SLC-0111 suggests a potential synergistic mechanism, where both tumor acidification and detoxification pathways are simultaneously disrupted. This aligns with findings from Mokhtari et al. (12), who advocated for combination therapies targeting multiple resistance pathways. Such dual functionality could make SLC-0111 an attractive candidate for further preclinical investigation.

Combination therapy strategies often seek to exploit vulnerabilities in tumor biology while mitigating resistance mechanisms. This study's findings complement prior research advocating for the integration of hypoxia-targeting agents with conventional chemotherapeutics (7). Evofosfamide, a hypoxia-activated prodrug, was previously noted for its selective cytotoxicity under low-oxygen conditions but demonstrated weaker GSTP1 binding affinity in this analysis. Despite this, Evofosfamide's hypoxia activation may still contribute to overcoming GSTP1-related resistance when used in combination with stronger inhibitors like BAY 87-2243. Such strategies highlight the importance of designing multidimensional therapeutic regimens that address both the tumor microenvironment and intrinsic resistance pathways.

Molecular docking has become an indispensable tool in modern drug discovery, particularly in identifying and optimizing enzyme inhibitors. This computational approach enables screening potential drug candidates before costly and time-intensive in vitro and in vivo experiments (26, 27). In the context of GSTP1 inhibition, docking studies provide valuable insights into the binding interactions of hypoxia-targeting agents, facilitating the rational design of novel therapeutics. Recent molecular docking studies have identified promising GSTP1 inhibitors with improved selectivity and binding efficiency (28-30). By comparing our findings with these studies, we highlight the potential of hypoxia-targeting compounds as dual-function agents, reinforcing their relevance in overcoming drug resistance. Integrating molecular docking with experimental validation will further strengthen the translational value of this research.

While this study provides compelling evidence of GSTP1 inhibition by hypoxia-targeting therapeutics, several limitations warrant consideration. The findings are based on molecular docking simulations, which, while robust, require validation through in vitro and in vivo experiments to confirm enzyme inhibition and downstream effects on cancer cells (31). Additionally, the impact of these compounds on non-target tissues and their potential systemic toxicity must be thoroughly evaluated. Future research should explore the pharmacokinetics and pharmacodynamics of these agents in preclinical models, as well as their efficacy in overcoming resistance in various cancer types.

The integration of hypoxia-targeting therapeutics with GSTP1 inhibition represents a promising avenue for addressing the persistent challenge of drug resistance in cancer therapy. Expanding this line of research to include high-throughput screening of other hypoxia-targeting agents may yield additional candidates with superior binding properties and therapeutic potential. Ultimately, the development of dual-function compounds tailored to individual tumor profiles could pave the way for personalized cancer treatments with enhanced efficacy and reduced resistance.

CONCLUSION

This study underscores the potential of hypoxia-targeting agents such as BAY 87-2243, Vadimezan, and SLC-0111 as dual-function inhibitors that target the hypoxic tumor microenvironment while simultaneously inhibiting GSTP1-mediated detoxification pathways. By

demonstrating higher binding affinities than ethacrynic acid, these compounds offer novel opportunities to address both tumor hypoxia and drug resistance, two critical barriers in cancer therapy. Future preclinical and clinical studies should focus on validating these findings and exploring the therapeutic potential of combining hypoxia-targeting agents with existing chemotherapeutics to improve patient outcomes.

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The authors declare that they have no conflict of interest to disclose.

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