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27. Xyloketal Derivatives from Xylaria sp. as Structural Leads for Dual MYC-BCL2 Axis Modulation review 1

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Xyloketal Derivatives from *Xylaria sp.* as Structural Leads for Dual MYC/BCL2 Axis Modulation for Double-Hit High-Grade B-Cell Lymphoma: A Docking-Based Investigation

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Abstract

High-grade B-cell lymphoma with concurrent MYC and BCL2 rearrangements, commonly referred to as double-hit lymphoma, represents an aggressive malignancy characterized by rapid proliferation, apoptotic resistance, and poor clinical outcomes. Therapeutic strategies capable of simultaneously disrupting MYC-driven transcriptional programs and BCL2-mediated apoptotic escape remain limited. In this study, xyloketal derivatives isolated from Xylaria species were evaluated as potential dual modulators of the MYC/BCL2 oncogenic axis using a structure-based pharmacoinformatic approach. Twenty-one natural and semi-synthetic xyloketal derivatives were subjected to molecular docking against BCL2 (BH3-binding groove) and the MYC/MAX heterodimer (leucine zipper interface). Docking scores, three-dimensional binding poses, and two-dimensional interaction maps were analyzed to elucidate binding affinity, interaction mechanisms, and structure–activity relationships. Xyloketal A emerged as the most promising dual-target candidate, exhibiting strong predicted affinity for BCL2 and meaningful engagement of the MYC/MAX interface. Xyloketal J demonstrated a complementary MYC-biased interaction profile while retaining relevant BCL2 affinity. Interaction analyses revealed that xyloketals exploit hydrophobic pocket occupancy for BCL2 inhibition and surface-level polar and hydrophobic contacts to destabilize MYC/MAX dimerization. These findings identify xyloketals as structurally competent scaffolds for dual-axis modulation and provide a computational foundation for further optimization and experimental validation toward therapeutic development for double-hit high-grade B-cell lymphoma.

Keywords: Xylaria sp, Xyloketal derivatives, Anti-cancer, Lymphoma, MYC/BCL2

Abstrak

Limfoma sel B tingkat tinggi dengan rearrangement MYC dan BCL2 secara bersamaan, yang umumnya dikenal sebagai limfoma double-hit, merupakan neoplasma agresif yang ditandai dengan proliferasi cepat, resistensi terhadap apoptosis, dan hasil klinis yang buruk. Strategi terapeutik yang mampu secara bersamaan mengganggu program transkripsional yang didorong oleh MYC dan pelarian apoptosis yang dimediasi oleh BCL2 masih terbatas. Dalam studi ini, turunan xyloketal yang diisolasi dari spesies Xylaria dievaluasi sebagai modulator ganda potensial dari sumbu onkogenik MYC/BCL2 menggunakan pendekatan farmakoinformatika berbasis struktur. Dua puluh satu turunan xyloketal alami dan semi-sintetik diuji melalui docking molekuler terhadap BCL2 (celah pengikatan BH3) dan heterodimer MYC/MAX (antarmuka zipper leusin). Skor docking, pose ikatan tiga dimensi, dan peta interaksi dua dimensi dianalisis untuk mengungkap afinitas ikatan, mekanisme interaksi, dan hubungan struktur-aktivitas. Xyloketal A muncul sebagai kandidat dual-target paling menjanjikan, menunjukkan afinitas prediksi yang kuat terhadap BCL2 dan interaksi yang signifikan pada antarmuka MYC/MAX. Xyloketal J menunjukkan profil interaksi yang berorientasi pada MYC secara komplementer sambil mempertahankan afinitas BCL2 yang relevan. Analisis interaksi mengungkapkan bahwa xyloketals memanfaatkan okupansi kantong hidrofobik untuk menghambat BCL2 dan kontak polar dan hidrofobik permukaan untuk mengganggu dimerisasi MYC/MAX. Temuan ini mengidentifikasi xyloketals sebagai kerangka struktural yang kompeten untuk modulasi dual-axis dan menyediakan dasar komputasional untuk optimasi lebih lanjut dan validasi eksperimental menuju pengembangan terapeutik untuk limfoma sel B tingkat tinggi dengan dua target.

Keywords: Xylaria sp, Xyloketal, Anti-Kanker, Lymphoma, MYC/BCL2

1. Introduction

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• Purpose: State the purpose of the research clearly and specifically.
• Methods: Describe the research methods used, including data types, data collection techniques, and data analysis techniques.
• Results: Present the main findings of the study concisely and concisely.
• Conclusion: Draw conclusions from the research findings and emphasize the contribution of the research to the related field of science

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High-grade B-cell lymphoma with concurrent MYC and BCL2 rearrangements, commonly referred to as double-hit lymphoma (HGBL-DHL), represents one of the most aggressive and treatment-refractory subtypes of mature B-cell malignancies. Clinically, this entity is characterized by rapid tumor progression, early relapse, and limited responsiveness to standard immunochemotherapy regimens such as R-CHOP. Median survival remains poor, even with intensified treatment strategies, underscoring the urgent need for mechanism-driven therapeutic approaches rather than empirical escalation of cytotoxic therapy (Alaggio et al., 2022; Somasundaram & Abramson, 2025).

At the molecular level, the aggressive phenotype of HGBL-DHL is driven by functional co-dependence between MYC-mediated transcriptional amplification and BCL2-mediated suppression of apoptosis. MYC rearrangements result in uncontrolled transcription of genes involved in cell cycle progression, ribosome biogenesis, and metabolic reprogramming, creating a state of sustained proliferative pressure (Dhanasekaran et al., 2022). Under normal conditions, such oncogenic stress would trigger intrinsic apoptotic pathways. However, aberrant BCL2 overexpression stabilizes mitochondrial membranes, blocks cytochrome c release, and neutralizes pro-apoptotic BH3-only proteins, thereby uncoupling proliferation from cell death (King, Hohorst, & García-Sáez, 2023). This coordinated survival program allows malignant B cells to tolerate extreme metabolic and replicative stress, contributing directly to therapy resistance and disease relapse.

Despite its central oncogenic role, MYC has long been considered a challenging therapeutic target. Its intrinsically disordered regions and reliance on protein–protein interactions, particularly MYC/MAX heterodimerization, limit the applicability of classical small-molecule inhibition (Donati & Amati, 2022). Recent strategies have therefore focused on disrupting the MYC/MAX interface or destabilizing the leucine zipper domain to indirectly suppress MYC-driven transcriptional programs (Casacuberta-Serra, González-Larreategui, Capitán-Leo, & Soucek, 2024). In contrast, BCL2 is structurally well defined and pharmacologically tractable. The presence of a hydrophobic BH3-binding groove has enabled the development of BH3 mimetics, such as venetoclax, which validate BCL2 as a clinically actionable target (Vom Stein & Frenzel, 2025). However, selective BCL2 inhibition alone has shown limited durability in double-hit lymphoma, highlighting the need for therapeutic paradigms capable of addressing both oncogenic drivers simultaneously.

Natural products continue to serve as a valuable source of structurally diverse scaffolds with inherent multi-target potential. Xyloketals, a class of polycyclic ether metabolites isolated from fungi of the genus *Xylaria*, are distinguished by rigid three-dimensional frameworks enriched with oxygenated functional groups (W. Chen et al., 2024). Unlike flat aromatic compounds commonly explored in transcription factor inhibition, xyloketals possess spatial complexity that may favor engagement with both deep ligand-binding pockets and extended protein–protein interfaces. Previous studies have reported antioxidant, protein-modulatory, and neuroprotective activities for several xyloketal analogues, suggesting a capacity for precise molecular recognition (W. Chen et al., 2024; Gong, Bandura, Wang, Feng, & Sun, 2022). However, their relevance in hematologic malignancies, particularly in the context of oncogenic transcriptional and apoptotic signaling, has not been systematically investigated.

From a structural standpoint, xyloketal derivatives present features well suited for dual-target modulation. Their polycyclic cores may accommodate insertion into the hydrophobic BH3 groove of BCL2, while their conformational rigidity and surface topology could support interaction with the elongated MYC/MAX coiled-coil interface(Olbromski et al., 2023). These characteristics support a hypothesis-driven exploration of xyloketals as dual modulators of the MYC/BCL2 axis, a strategy that directly addresses the molecular basis of double-hit lymphoma rather than downstream consequences(Song et al., 2025).

In this study, we apply a structure-based pharmacoinformatic workflow to evaluate twenty-one natural and semi-synthetic xyloketal derivatives as potential dual inhibitors of BCL2 and MYC/MAX. Molecular docking analyses were performed to assess binding affinity, characterize key intermolecular interactions, and identify structure–activity relationships relevant to dual-target engagement. By providing the first systematic computational assessment of xyloketal scaffolds against the MYC/BCL2 oncogenic axis, this work aims to establish a rational foundation for subsequent experimental validation and medicinal chemistry optimization in aggressive B-cell lymphomas.

2.Methodology

2.1. Ligand Preparation.

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Twenty-one xyloketal derivatives were selected based on previously reported chemical and biosynthetic studies of secondary metabolites isolated from Xylaria species (S. Chen, Cai, Liu, Cui, & She, 2022; W. Chen et al., 2024). Two-dimensional chemical structures were drawn using ChemDraw and converted into three-dimensional conformations using Chem3D. Geometry optimization was performed employing the MMFF94 force field, which is widely applied for small-molecule minimization in structure-based studies (Lai et al.). Reported stereochemical configurations were preserved to maintain the native conformational features of the natural products and their semi-synthetic analogues. The optimized ligand structures were exported in suitable formats for molecular docking analysis.

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2.2. Protein Preparation.

The crystal structure of BCL2 containing a well-resolved BH3-binding groove (PDB ID: 4MAN) was selected due to its relevance in modeling ligand-mediated disruption of anti-apoptotic function (Xu et al., 2023a). To represent MYC-driven transcriptional regulation, the MYC/MAX heterodimer structure (PDB ID: 1NKP) was employed, focusing on the leucine-zipper interface essential for dimerization and transcriptional activity (Dhanasekaran et al., 2022; Schutz et al., 2024). Protein preparation was carried out using AutoDockTools. Crystallographic water molecules and non-essential heteroatoms were removed, polar hydrogens were added, and Gasteiger partial charges were assigned in accordance with standard docking protocols (T. Chen, Shu, Zhou, Beckford, & Misir, 2023). Prepared protein structures were saved in PDBQT format for subsequent docking simulations.

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2.3 Docking Procedure

Molecular docking simulations were performed using AutoDock Vina, which applies a gradient-based conformational search algorithm combined with an empirical scoring function to estimate binding affinity (Tang et al., 2024). A rigid-receptor and flexible-ligand approach was adopted for both targets. For BCL2, the docking grid was centered on the canonical BH3-binding groove encompassing residues critical for interaction with pro-apoptotic BH3-only proteins (Mukherjee, Sheetz, & Shellman, 2025). For the MYC/MAX complex, the grid box was positioned over the leucine-zipper dimerization interface to assess ligand binding at the protein–protein interaction surface (Edaibis, Akel, & Shin, 2025). Grid dimensions were selected to fully cover the relevant interaction regions while permitting adequate ligand flexibility. Docking exhaustiveness was set to 24 to enhance pose sampling and improve prediction reliability. The top-ranked poses were selected based on binding affinity scores and structural plausibility.

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2.4 Interaction and Pharmacophore Analysis

Docked ligand–protein complexes were analyzed using BIOVIA Discovery Studio Visualizer. Intermolecular interactions, including hydrogen bonds, hydrophobic contacts, π–π stacking, and steric complementarity, were systematically examined for both BCL2 and MYC/MAX complexes (Baroroh et al., 2023). Comparative interaction profiling was conducted across high-affinity ligands to identify recurring structural features associated with favorable binding. Pharmacophoric elements were extracted and aligned to determine conserved interaction motifs supporting dual-target engagement. These analyses facilitated structure–activity interpretation and prioritization of xyloketal scaffolds with potential relevance for simultaneous modulation of the MYC/BCL2 axis.

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3. Results and Discussion

The Docking scores for the twenty-one xyloketal derivatives against BCL2 and the MYC/MAX heterodimer are summarized in Table 1. Across the dataset, binding affinities were consistently stronger for BCL2 than for MYC/MAX. Predicted BCL2 binding energies ranged from −9.1 to −6.0 kcal/mol, whereas MYC/MAX scores were distributed within a narrower and weaker range from −7.4 to −5.3 kcal/mol. This divergence reflects fundamental structural differences between the two targets. BCL2 presents a deep, well-defined BH3-binding groove optimized for small-molecule engagement, while MYC/MAX represents a shallow, solvent-exposed protein–protein interaction interface dominated by coiled-coil geometry (Ji et al., 2022; Qian et al., 2022; Xu et al., 2023b). The observed docking trends are therefore consistent with established challenges in small-molecule modulation of transcription factor dimers (Taylor, Davies, Wilson, & Thomas, 2023).

Table 1. Binding Affinity Ranking of Xyloketal Derivatives toward MYC/BCL2

No	Compound	Binding Energy (kcal/mol)	
		BCL-2	MYC
1	Xyloketal A	-9.1	-7.0
16	Xyloketal B Cinnamyl Ether	-8.6	-7.0
8	Xyloketal J	-8.4	-7.4
3	Xyloketal C	-8.1	-6.5
9	Xyloketal B Formamide	-8.1	-6.9
21	Dehydroxy Xyloketal B	-8.1	-6.7
5	Xyloketal E	-8.0	-7.0
12	Methyl xyloketal B	-8.0	-6.8
2	Xyloketal B	-7.9	-6.3
15	Xyloketal B Hexyl Ether	-7.9	-5.5
13	Xyloketal B Propargyl Ether	-7.7	-6.0
20	Xyloketal B Methyl Formate	-7.5	-7.0
11	Xyloketal B Propyl Ether	-7.4	-6.2
18	Xyloketal B Acid	-7.4	-6.2
19	Xyloketal B Methyl Ether	-7.3	-6.3
10	Xyloketal B Butyl Ether	-7.2	-6.2
17	Xyloketal H Dimethyl Ester	-6.6	-5.3
6	Xyloketal G	-6.5	-5.9
4	Xyloketal D	-6.1	-5.8
7	Xyloketal H	-6.0	-5.4
14	Dehydroxy Xyloketal H	-6.0	-5.7

Among all evaluated compounds, Xyloketal A exhibited the strongest predicted affinity for BCL2, with a docking score of −9.1 kcal/mol. This value lies within the affinity range reported for clinically validated BH3 mimetics, such as venetoclax, supporting the feasibility of competitive inhibition at the anti-apoptotic groove (Kater et al., 2024; Mukherjee et al., 2025). Xyloketal B cinnamyl ether (−8.6 kcal/mol) and Xyloketal J (−8.4 kcal/mol) followed closely, while several derivatives clustered between −8.1 and −8.0 kcal/mol. This clustering indicates that the xyloketal core scaffold inherently favors engagement with the BH3-binding cleft, with peripheral substitutions exerting only a secondary effect on BCL2 affinity.

Three-dimensional visualization of the Xyloketal A–BCL2 complex (Figure 1b) revealed deep insertion into the hydrophobic groove, stabilized by hydrogen bonds with Arg143 and Asp108. These residues are known anchoring points for BH3-domain peptides and small-molecule inhibitors (Croce et al., 2025; Wei et al., 2023). Additional hydrophobic contacts with Phe101, Leu137, Val153, and Gly145 reinforced ligand burial within the pocket, a hallmark of effective BCL2 antagonists.

Two-dimensional interaction analysis (Figure 2a) further clarified the binding logic. Alkyl and π–alkyl interactions with Phe63 and Phe71, together with a conventional hydrogen bond involving Tyr67, stabilized the ligand orientation. Contacts with Ala108 supported the 3D pose alignment observed in Figure 1b. Collectively, these interactions mirror the interaction topology reported for BH3 mimetics and confirm that Xyloketal A engages BCL2 through a combination of hydrophobic enclosure and polar anchoring (Croce et al., 2025; Mukherjee et al., 2025; Wei et al., 2023). The rigid polycyclic ether framework likely minimizes entropic penalties upon binding, further contributing to its favorable affinity.

Docking against the MYC/MAX heterodimer yielded a narrower and weaker affinity distribution, consistent with the known difficulty of targeting transcription factor protein–protein interactions (Dhimitriu, Tsimpili, & Zoidis, 2025; Taylor et al., 2023). Xyloketal J displayed the strongest predicted interaction (−7.4 kcal/mol), followed by Xyloketal A, Xyloketal B cinnamyl ether, Xyloketal E, and Xyloketal B methyl formate, each scoring near −7.0 kcal/mol. These values

suggest partial destabilization of MYC/MAX dimerization rather than complete disruption, which is a realistic outcome given the elongated, solvent-exposed nature of the leucine zipper interface (Schutz et al., 2024). Three-dimensional docking poses (Figure 1c) showed that xyloketals occupy shallow surface depressions along the coiled-coil region rather than deeply buried pockets.

Two-dimensional interaction mapping (Figure 2b) revealed that Xyloketal A forms a conventional hydrogen bond with Arg239, a residue implicated in maintaining heterodimer stability (Edaibis et al., 2025). Additional alkyl and carbon hydrogen bond interactions with Lys219 and Lys236 anchored the ligand along the interface. Unlike BCL2 binding, which is dominated by hydrophobic pocket insertion, MYC/MAX engagement relied on surface-level polar and electrostatic contacts. This interaction profile aligns with previously reported small-molecule MYC/MAX modulators that act through interface weakening rather than direct displacement (Dhimitriu et al., 2025; Edaibis et al., 2025; Schutz et al., 2024).

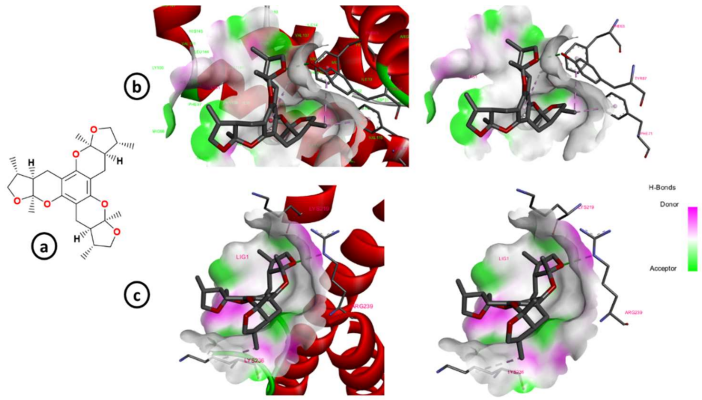

Figure 1. a) Chemical Structure of Xyloketal A, and 3D Binding Interaction between Xyloketal A toward b) BCL2 and c) MYCMAX

Comparative analysis across both targets revealed distinct structure–activity trends. BCL2 affinity remained relatively consistent across most xyloketal derivatives retaining the intact polycyclic ether core, indicating that BCL2 binding is scaffold-driven. In contrast, MYC/MAX affinity was more sensitive to peripheral substitution. Derivatives bearing extended or aromatic substituents, such as cinnamyl, methyl formate, and propyl groups, showed improved MYC/MAX docking scores, suggesting that increased surface complementarity and hydrophobic reach enhance protein–protein interface engagement (Dhimitriu et al., 2025; Wang et al., 2024).

Applying operational thresholds of ≤ −8.0 kcal/mol for BCL2 and ≤ −7.0 kcal/mol for MYC/MAX identified Xyloketal A, Xyloketal J, and Xyloketal B cinnamyl ether as top-tier dual modulators. Xyloketal E and Xyloketal B methyl formate formed a secondary tier. This stratification highlights a rational design principle in which preservation of the rigid xyloketal core supports BH3-groove binding, while peripheral elaboration governs MYC/MAX compatibility.

The dual-target binding behavior observed for selected xyloketals directly reflects the molecular pathology of double-hit high-grade B-cell lymphoma, where MYC overexpression drives unchecked proliferation and BCL2 overactivity suppresses apoptosis (Campo et al., 2022; Kumjan, Satayasoontorn, Lawongsa, & Laoruangroj, 2025). Pharmacological BCL2 inhibition lowers the apoptotic threshold, while attenuation of MYC/MAX signaling dampens transcriptional programs that sustain metabolic and proliferative demand.

Xyloketal A exemplifies this dual mechanism, demonstrating BH3-mimetic-like engagement of BCL2 alongside meaningful surface interaction with the MYC/MAX heterodimer. The capacity of a single scaffold to adopt distinct binding modes across two structurally divergent oncogenic targets is unusual and therapeutically attractive (Badria et al., 2025; Brambila et al., 2023). Xyloketal J, with its MYC-biased profile, further supports the versatility of the xyloketal framework. The integrated docking scores, three-dimensional poses, and two-dimensional interaction analyses establish xyloketals as structurally competent modulators of the MYC/BCL2 survival axis. These findings justify progression to molecular dynamics simulations, binding free-

energy calculations, and experimental validation to substantiate their therapeutic potential in double-hit lymphoma.

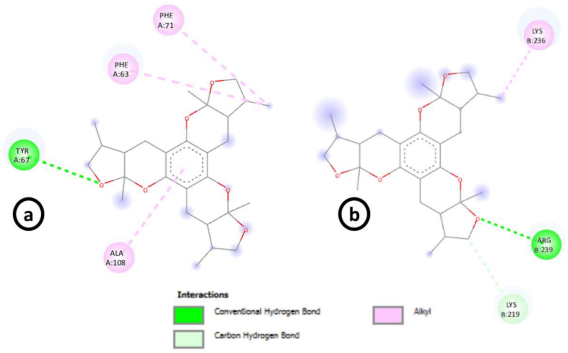

Figure 2. 2D Binding Interaction between Xyloketal A toward a) BCL2 and b) MYCMAX

4. Conclusion

This study depicted the first systematic pharmacoinformatic evaluation of xyloketal derivatives as dual modulators of the MYC/BCL2 survival axis relevant to double-hit high-grade B-cell lymphoma. Through integrated docking analysis, three-dimensional pose inspection, and residue-level interaction mapping, we demonstrate that xyloketals possess a structural architecture capable of engaging two mechanistically distinct oncogenic targets. Xyloketal A emerged as the most compelling lead compound, combining BH3-mimetic-like engagement of the BCL2 hydrophobic groove with supportive interaction at the MYC/MAX dimerization interface. The rigid polycyclic ether core proved central to BCL2 affinity, while peripheral substituents governed compatibility with the MYC/MAX protein–protein interaction surface. Xyloketal J further highlighted the adaptability of the scaffold, exhibiting enhanced MYC/MAX engagement while maintaining dual-target relevance. Importantly, the interaction patterns observed for both targets align with realistic mechanisms of partial MYC/MAX destabilization and effective BCL2 antagonism, consistent with current understanding of small-molecule modulation of these proteins. Given the cooperative role of MYC-driven transcriptional amplification and BCL2-mediated apoptotic suppression in the pathogenesis and therapeutic resistance of double-hit lymphoma, the identification of small molecules capable of addressing both pathways is of high translational relevance. While the present findings are computational in nature, they establish a strong structural and mechanistic rationale for advancing xyloketal derivatives into molecular dynamics simulations, binding free-energy analyses, and experimental validation. Collectively, this work positions xyloketals as promising natural-product-derived scaffolds for the rational development of dual-target therapeutics aimed at complex oncogenic circuitry in aggressive B-cell lymphomas.

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Acknowledgement

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