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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, known as double-hit lymphoma, shows rapid tumor growth, strong resistance to apoptosis, and poor response to current therapies, largely because available treatments fail to target both oncogenic drivers at once. This study aimed to identify potential dual modulators of the MYC/BCL2 axis by evaluating xyloketal derivatives using a structure-based pharmacoinformatic approach. A total of twenty-one natural and semi-synthetic xyloketal compounds were prepared and analyzed through molecular docking against BCL2 at the BH3-binding groove (PDB: 4MAN) and the MYC/MAX heterodimer at the leucine zipper interface (PDB: 1NKP). Binding affinity, interaction profiles, and structure–activity relationships were examined using AutoDock Vina and Discovery Studio. The results showed that Xyloketal A achieved the strongest BCL2 binding affinity (−9.1 kcal/mol) while maintaining stable interactions with the MYC/MAX interface (−7.0 kcal/mol), supported by hydrogen bonding with Arg143 and Asp108 and hydrophobic contacts within the BH3 groove. Xyloketal J displayed the highest MYC/MAX affinity (−7.4 kcal/mol) with consistent BCL2 engagement, indicating a MYC-biased but still dual-target profile. Several derivatives, including Xyloketal A, Xyloketal J, and Xyloketal B cinnamyl ether, demonstrated balanced activity across both targets. These findings confirm that xyloketal scaffolds can engage both the BCL2 hydrophobic pocket and the MYC/MAX protein–protein interface, suggesting their potential as dual-target inhibitors. This study provides a clear computational foundation for the design and optimization of multi-target therapeutics aimed at overcoming the aggressive biology of 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 dikenal sebagai limfoma double-hit, menunjukkan pertumbuhan tumor yang cepat, resistensi yang kuat terhadap apoptosis, dan respons yang buruk terhadap terapi saat ini, terutama karena pengobatan yang tersedia gagal menargetkan kedua faktor pendorong onkogenik tersebut secara bersamaan. Penelitian ini bertujuan untuk mengidentifikasi modulator ganda potensial dari sumbu MYC/BCL2 dengan mengevaluasi turunan xyloketal menggunakan pendekatan farmakoinformatika berbasis struktur. Dua puluh satu senyawa xyloketal alami dan semi-sintetik disiapkan dan dianalisis melalui docking molekuler terhadap BCL2 pada celah pengikatan BH3 (PDB: 4MAN) dan heterodimer MYC/MAX pada antarmuka leucine zipper (PDB: 1NKP). Afinitas ikatan, profil interaksi, dan hubungan struktur-aktivitas dievaluasi menggunakan AutoDock Vina dan Discovery Studio. Hasil menunjukkan bahwa Xyloketal A mencapai afinitas ikatan BCL2 terkuat (−9,1 kcal/mol) sambil mempertahankan interaksi stabil dengan antarmuka MYC/MAX (−7,0 kcal/mol), didukung oleh ikatan hidrogen dengan Arg143 dan Asp108 serta kontak hidrofobik di dalam celah BH3. Xyloketal J menunjukkan afinitas MYC/MAX tertinggi (−7,4 kcal/mol) dengan keterlibatan BCL2 yang konsisten, menunjukkan profil yang condong ke MYC namun tetap bersifat dual-target. Beberapa turunan, termasuk Xyloketal A, Xyloketal J, dan Xyloketal B cinnamyl ether, menunjukkan aktivitas yang seimbang pada kedua target. Temuan ini mengonfirmasi bahwa kerangka xyloketal dapat berinteraksi dengan kantong hidrofobik BCL2 dan antarmuka protein-protein MYC/MAX, menunjukkan potensinya sebagai inhibitor dua target. Studi ini memberikan landasan komputasional yang jelas untuk desain dan optimasi terapi multi-target yang bertujuan mengatasi biologi agresif limfoma sel B tingkat tinggi dengan mekanisme ganda.

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

1. Introduction

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). This aggressive clinical behaviour is attributable to the simultaneous deregulation of key oncogenic pathways driven by MYC and BCL2, which cooperatively promote cell proliferation, inhibit apoptosis, and enhance genomic instability (Yuan et al., 2021). Specifically, MYC acts as a potent transcriptional activator, driving cell proliferation and metabolism, while BCL2, an anti-apoptotic regulator, confers resistance to cell death, collectively fostering an aggressive oncogenic synergy (Uchida et al., 2018).

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, most commonly involving translocation of the MYC locus on chromosome 8 to immunoglobulin enhancer regions such as IgH on chromosome 14 [t(8;14)], place MYC under constitutive enhancer control (Figure 1A), resulting in uncontrolled transcription of genes involved in cell cycle progression, ribosome biogenesis, and metabolic reprogramming (Dhanasekaran et al., 2022). Similarly, BCL2 rearrangements, typically involving t(14;18), lead to constitutive anti-apoptotic signaling (Figure 1B). 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.

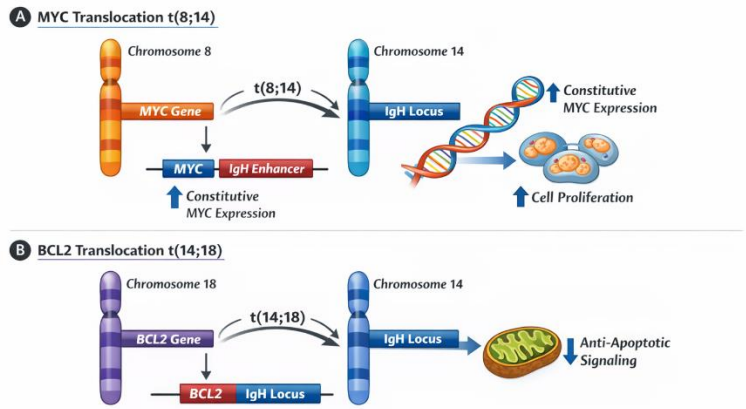

Figure 1. Genomic rearrangements underlying double-hit lymphoma (HGBL-DHL).
(A) MYC translocation, most commonly t (8;14), juxtaposes MYC with immunoglobulin heavy chain (IgH) enhancer elements, resulting in constitutive MYC overexpression and enhanced cellular proliferation. (B) BCL2 translocation, typically t (14;18), places BCL2 under control of the IgH locus, leading to sustained anti-apoptotic signaling through inhibition of mitochondrial-mediated apoptosis.

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. This

necessitates therapeutic strategies capable of concurrently targeting MYC-driven cellular processes and BCL2-mediated anti-apoptotic mechanisms to achieve durable responses, whether through rational combination regimens or the development of multi-target agents within a single molecular framework (Liu et al., 2024).

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. This research is motivated by the lack of effective therapeutic strategies capable of simultaneously disrupting proliferative signaling and apoptosis resistance in double-hit lymphoma, where current approaches remain largely limited to single-target inhibition or empiric drug combinations with suboptimal durability. Despite increasing interest in MYC as a therapeutic target, its intrinsically disordered structure and reliance on protein–protein interactions, particularly with MAX, continue to limit the development of clinically viable inhibitors. To address these challenges, molecular docking analyses were performed to assess binding affinity, characterize key intermolecular interactions, and identify structure–activity relationships relevant to dual-target engagement. Unlike prior studies that focus on either BCL2 or MYC independently, this work provides the first systematic computational evaluation of xyloketal scaffolds against the MYC/MAX–BCL2 oncogenic axis. By integrating natural product-based chemical diversity with dual-target modeling, this study offers a mechanistically grounded framework for the design of multi-functional inhibitors and establishes a rational basis for subsequent experimental validation and medicinal chemistry optimization in aggressive B-cell lymphomas.

2. Methodology

2.1. Ligand Preparation.

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.

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., 2023b). 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.

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.

2.4 Interaction and Pharmacophore Analysis

Docked ligand–protein complexes were analyzed using BIOVIA Discovery Studio Visualizer. Intermolecular interactions, including hydrogen bonds, hydrophobic contacts, and π–π interactions, were identified and recorded for both BCL2 and MYC/MAX complexes. Comparative analysis was performed across top-ranked ligands to identify recurring interaction patterns. Pharmacophoric features were extracted and aligned to determine common structural elements associated with ligand binding.

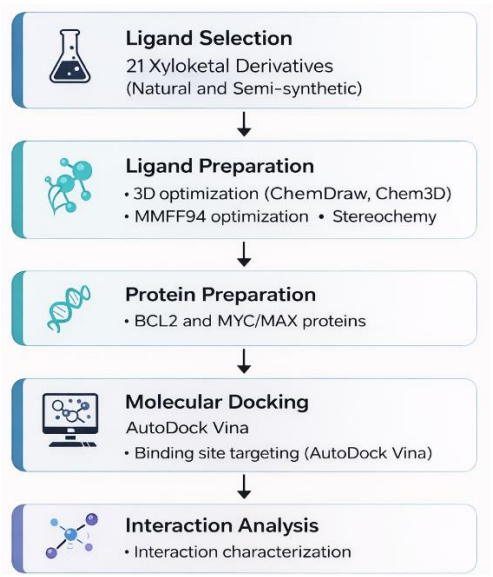

Figure 2. Structure-based pharmacoinformatic workflow for dual-target evaluation of xyloketal derivatives.

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., 2023a). 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).

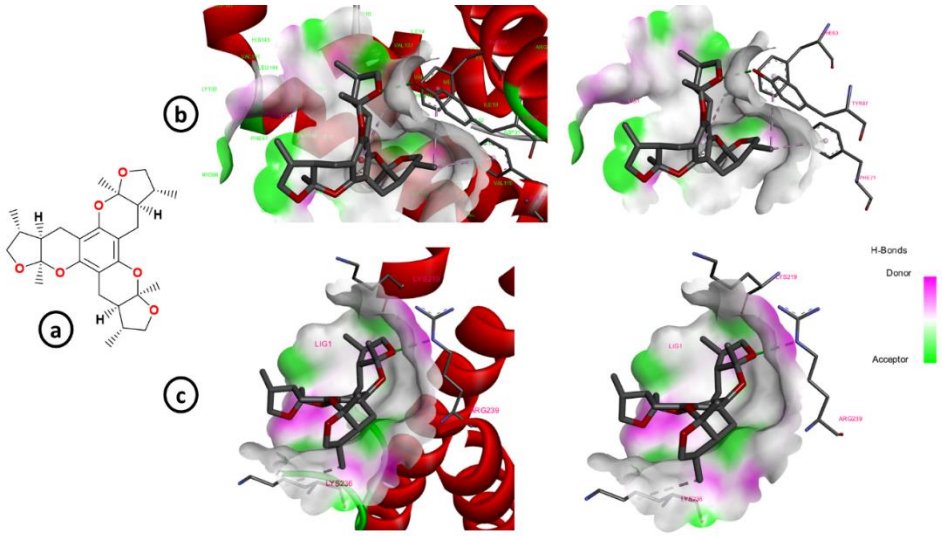

Figure 1. (a) Chemical Structure of Xyloketal A, and 3D Binding Interaction between Xyloketal A toward. (b) BCL2, and (c) MYCMAX

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.

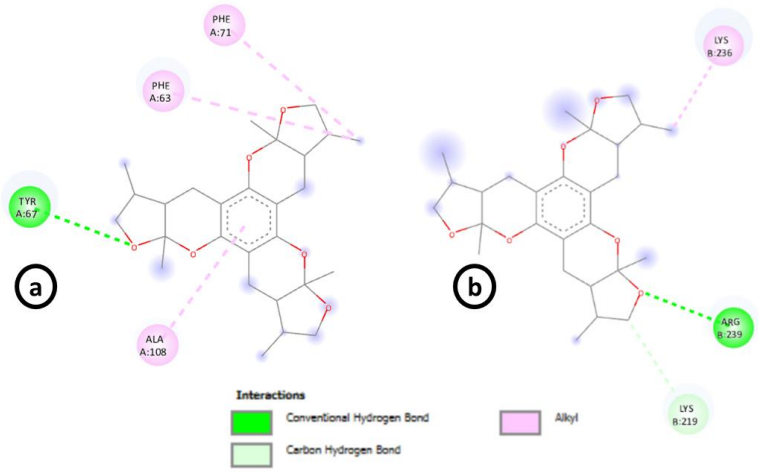

Figure 2. 2D Binding Interaction between Xyloketal A toward (a) BCL2 and (b) MYCMAX

4. Conclusion

This study provides the first systematic pharmacoinformatic evaluation of xyloketal derivatives as dual modulators of the MYC/BCL2 survival axis in double-hit high-grade B-cell lymphoma. Molecular docking and interaction analysis show that xyloketals can engage both targets through distinct binding modes. Xyloketal A emerged as the most promising candidate, demonstrating BH3-like binding to the BCL2 hydrophobic groove alongside stable interaction at the MYC/MAX interface. The rigid polycyclic ether core supports BCL2 affinity, while peripheral substituents influence compatibility with the MYC/MAX protein–protein interaction surface. Xyloketal J further highlights scaffold flexibility with improved MYC/MAX engagement while retaining dual-target activity. These findings support the potential of xyloketals as dual-target scaffolds addressing coordinated proliferation and apoptosis resistance in double-hit lymphoma. Although limited to computational analysis, this work establishes a structural basis for further validation through molecular dynamics, binding free-energy studies, and experimental investigation.

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