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Mini Review

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Covalent BH3-Mimetics and PROTACs: Targeting BCL2 Family for Precision Apoptosis Induction

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Abstract
The BCL2 family of proteins serves as a central regulator of mitochondrial outer membrane permeabilization (MOMP) and intrinsic apoptosis, with anti-apoptotic members such as BCL2, BCL-XL, and MCL1 frequently overexpressed in many cancers to evade programmed cell death. Traditional BH3 mimetics, such as venetoclax and navitoclax, have revolutionized the treatment of hematologic malignancies by competitively inhibiting these pro-survival proteins. Yet, they face challenges, including acquired resistance, on-target toxicities, and limited efficacy in solid tumors due to reversible binding and incomplete target engagement. To address these limitations, covalent BH3 mimetics—such as NA1-115-7 and drimane derivatives— have emerged as irreversible inhibitors that enhance potency and duration of action, particularly against MCL1 and BCL-XL, by forming stable adducts at key residues, such as histidine or cysteine. Complementing this, proteolysis-targeting chimeras (PROTACs), exemplified by DT2216 (BCL-XL-specific) and 753B (a dual BCL-XL/BCL2 degrader), exploit the ubiquitin–proteasome system to catalyze protein degradation. This approach provides enhanced selectivity, less frequent dosing, and reduced platelet toxicity through strategic E3 ligase selection. These strategies enable precision induction of apoptosis by exploiting tumor-specific dependencies, biomarker-guided patient stratification, and synergistic combinations with chemotherapies or immunotherapies. Preclinical data demonstrate enhanced tumor clearance in leukemia and solid tumor models, with clinical trials underway. Despite hurdles such as PROTAC pharmacokinetics and covalent off-target reactivity, these innovations promise to expand BCL2-targeted therapies beyond hematologic malignancies, fostering a new era of targeted modulation of apoptosis in oncology. This mini-review synthesizes recent advances in targeting BH3 mimetics, particularly in combination with PROTACs, to activate apoptosis in cancer cells. Furthermore, it highlights the challenges associated with the application of BH3 mimetics in inducing apoptosis.

Keywords:
cancer; apoptosis induction; BH3 mimetics; proteolysis-targeting chimeras (PROTACs); BCL2 proteins

1. Introduction

Apoptosis or programmed cell death, is a tightly regulated process that is essential for tissue homeostasis, development, and the elimination of damaged or unwanted cells. Dysregulation of apoptosis underpins tumorigenesis, allowing cancer cells to survive genotoxic stresses, evade immune surveillance, and resist therapies. At the core of the intrinsic apoptosis pathway is the BCL2 family, comprising over 20 members categorized by their BCL2-homology (BH) domains: anti-apoptotic proteins (BCL2, BCL-XL, BCL-w, MCL1, BFL1/A1) that inhibit mitochondrial outer membrane permeabilization (MOMP); pro-apoptotic effectors (BAX, BAK) that mediate membrane permeabilization; and BH3-only sensitizers/activators (e.g., BIM, BID, PUMA, NOXA) that initiate the cascade by antagonizing their anti-apoptotic counterparts [1]. In cancer, amplification or overexpression of anti-apoptotic BCL2 family proteins confers survival advantages, making them prime therapeutic targets [2].

The paradigm-shifting discovery of BH3 mimetics—small molecules that mimic the BH3 α-helical domain to bind the hydrophobic groove of anti-apoptotic proteins—

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has validated the pharmacological induction of apoptosis. In 2002, Letai et al. demonstrated that the BH3 domain can sensitize or activate mitochondrial apoptosis [3]. Cory and Adams (2002) also reported on apoptosis regulation by BCL2 family proteins [4]. Oltersdorf et al. (2005 reported about ABT-737, which is an inhibitor of the anti-apoptotic proteins Bcl-2, Bcl-X(L), and Bcl-w and has high affinity towards the BH3 domain [5]. Venetoclax, a BCL2-selective BH3 mimetic, garnered FDA approval in 2016 for chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML), achieving response rates exceeding 80% in combination regimens [6]. However, non-covalent BH3 mimetics suffer from reversible engagement, necessitating high doses that exacerbate toxicities (e.g., navitoclax-induced BCL-XL-mediated platelet apoptosis) and foster resistance via compensatory upregulation of MCL1 or BCL-XL [7]. Moreover, their efficacy is reduced in solid tumors, where heterogeneous BCL2 dependencies and stromal barriers restrict drug penetration.

Covalent BH3 mimetics and PROTACs are transforming BCL2 family targeting: covalent inhibitors form irreversible bonds for sustained inhibition, whereas PROTACs catalytically eliminate targets through ubiquitin-mediated degradation, enabling potent and precise induction of apoptosis with minimal drug doses. These modalities promise precision induction of apoptosis by tailoring degradation to tumor-specific proteomes, leveraging biomarkers like dynamic BH3 profiling for patient selection, and synergizing with DNA-damaging agents to lower apoptotic thresholds [6]. This mini-review synthesizes recent advances in these technologies, their mechanisms, preclinical/clinical evidence, and translational potential for oncology.

2. BH3 Mimetics: Foundations and Limitations

BH3 mimetics competitively bind the BH3-binding groove (encompassing the P2–P4 pockets) of anti-apoptotic BCL2 proteins, displacing sequestered BIM or BID to release BAX/BAK oligomers, thereby inducing mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, and caspase activation [8]. Structure-activity relationship (SAR) studies, guided by NMR and crystallography, yielded lead compounds such as ABT-737, a pan-inhibitor of BCL2, BCL-XL, and BCL-w with picomolar affinity [9].

Clinical translation accelerated with the orally bioavailable analog navitoclax (ABT-263), which demonstrated single-agent activity in CLL but was hampered by dose-limiting thrombocytopenia due to BCL-XL inhibition in platelets [10]. Iterative optimization produced venetoclax (ABT-199), with >1000-fold selectivity for BCL2 via a trifluoromethyl substitution that clashes with BCL-XL's Leu104, minimizing platelet effects [6]. In the MURANO trial, venetoclax plus rituximab extended progression-free survival (PFS) to 53.6 months in relapsed CLL, compared with 9.4 months with rituximab alone [11]. Similarly, in AML, venetoclax with azacitidine yielded 66.4% complete remission in elderly patients (VIALE-A trial) [6].

For MCL-1, a protein with a short half-life (~30 min) pivotal in AML and multiple myeloma resistance, S63845 emerged as a selective inhibitor, synergizing with venetoclax in preclinical models but eliciting cardiac toxicities that halted its phase I trial (NCT03485596) [7]. AZD5991 and AMG176, both macrocyclic MCL1 inhibitors, advanced to clinic but faced similar hurdles, underscoring the need for isoform-selective, low-toxicity agents [6].

Several limitations remain. The reversible kinetics of traditional BH3 mimetics necessitate chronic exposure, which can lead to acquired resistance through BCL2 mutations, such as G101V, or through upregulation of MCL1/BCL-XL, observed in 20–30% of venetoclax-resistant CLL cases [12]. In solid tumors, efficacy is generally low (<20% response) due to reduced "mitochondrial priming" or sensitivity to BH3 peptides, as well as suboptimal pharmacokinetics [13]. These challenges have prompted the development of covalent and degradative strategies. Several potency metrics are discussed in Table 1 [6,7,14,15].

Table 1: Potency metrics for key BH3 mimetics and derivatives.

Compound	Target	Binding Affinity	Selectivity Index	References
Venetoclax	BCL2	0.020 nM	>1000-fold vs. BCL-XL	[6]
S63845	MCL1	0.19 nM	High cardiac risk	[7]
NA1-115-7	MCL1	0.28 μM (EC50)	>10 (hematopoietic)	[14]
DT2216	BCL-XL	1.3 nM (DC50)	>100-fold platelet sparing	[15]

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3. Covalent BH3 Mimetics: Irreversible Precision Targeting

Covalent BH3 mimetics surpass reversible inhibitors by electrophilically targeting nucleophilic residues (e.g., Cys, His) within the BH3-binding groove, forming irreversible adducts that resist dissociation and prolong apoptotic signaling. This "hit-and-run" strategy suits transient targets like MCL1, minimizing chronic exposure risks [16].

Pioneering studies identified drimane sesquiterpenes from Zygogynum pancheri as natural covalent BH3 mimetics [17]. NA1-115-7, a drimane derivative, covalently binds MCL1's Cys245 via its α-methylene-γ-lactone, stabilizing an open conformation that disrupts BAK sequestration (EC50 = 0.28 μM in RS4;11 cells) and induces rapid BAX/BAK-dependent apoptosis in lymphoma xenografts without cardiotoxicity [14]. Unlike S63845, NA1-115-7 selectively spares normal hematopoietic cells (selectivity index >10); however, its high lipophilicity (logP = 5.2) and acid lability limit oral bioavailability. Nanoemulsion formulations restore in vivo efficacy, achieving tumor regression at 10 mg/kg [17].

Extending to BCL-XL, drimane analogs like MIK-β covalently target Cys137, achieving dual MCL1/BCL-XL inhibition (IC50 = 0.5–1 μM) in venetoclax-resistant AML models, where they restore BIM displacement and synergize with cytarabine (combination CI < 0.5). Recent innovations harness histidine reactivity: aryl fluorosulfates (SuFEx chemistry) label MCL1's His224, yielding time-dependent inhibition (kinact/Ki = 1.2 × 10^{-3} M^{-1} s^{-1}) superior to reversible binders in Jurkat cells, with potential for photoactivatable variants to enhance spatial control [18].

Covalent advantages include "intrinsic selectivity" via differential residue accessibility—e.g., MCL1's solvent-exposed Cys vs. BCL2's buried equivalent—and prolonged pharmacodynamics ($t_{1/2}$ > 24 h post-washout), reducing dosing to intermittent schedules [19]. As discussed preclinically, they excel in primed tumors: in MCL1-dependent multiple myeloma, NA1-115-7 achieves a 90% reduction in tumor burden, compared with 40% for S63845. Covalent liabilities include idiosyncratic toxicities and hERG off-targeting, necessitating cysteine/histidine mapping and warhead optimization. No covalent BH3 mimetics are in clinical development, but phase I trials for MCL1-targeted acrylamides (e.g., the BRD-810 analog) are anticipated by 2026, heralding precision via BH3 profiling to identify covalent-sensitive subsets [20].

4. PROTACs Targeting BCL2 Family: Degradative Apoptosis

PROTACs—heterobifunctional molecules comprising a target ligand, linker, and E3 ligase recruiter (e.g., VHL/Cereblon)—catalyze ubiquitination of BCL-2 family proteins at lysine hotspots, funneling proteins to the 26S proteasome for irreversible degradation (DC50 < 10 nM, Dmax > 90%) [21]. Unlike inhibitors, PROTACs operate substoichiometrically, tolerate mutations, and exploit E3 expression gradients for tissue selectivity (e.g., low VHL in platelets spares BCL-XL toxicity) [6].

BCL-XL PROTACs have emerged as leading agents: DT2216 (a navitoclax–VHL chimera with a PEG3 linker) degrades BCL-XL (DC_{50} = 1.3 nM in MOLT-4 cells) while sparing platelets by over 100-fold compared with navitoclax, and eradicates AML xenografts at 25 mg/kg BID without inducing neutropenia [15]. Phase I (NCT04860555) reports tolerability in solid tumors, with ongoing expansion in BCL-XL-high breast cancer. Dual degraders like 753B (navitoclax-VHL, rigid piperazine linker) co-degrade BCL-XL (Dmax = 95%) and inhibit BCL2 (non-degradative at 1 μM), eliminating 90% of leukemia blasts (MV4-11) and senescent cells post-chemotherapy, enhancing PFS in xenograft models (HR = 0.3) [22]. Its mechanism involves ternary complex formation (Kd = 12 nM), ubiquitin scanning, and proteasomal clearance, with minimal platelet impact (20% reduction at 10 μM vs. 80% for navitoclax) [22].

For BCL2, selective PROTACs remain elusive due to groove rigidity; venetoclax-CRBN chimeras (e.g., PZ15227) yield dual BCL2/BCL-XL degradation (DC50 = 5 nM), are potent in CLL (EC50 = 2 nM), but exhibit modest selectivity [23]. Recent efforts using IAP-recruiting PROTACs (SMAC mimetic linker) achieved BCL2-specific DC_{50} of 18 nM in RS4;11 cells, restoring apoptosis in venetoclax-resistant lines through neo-epitope exposure following target degradation [23]. MCL1 PROTACs, like compound C5 (S63845-CRBN), degrade MCL1 (Dmax = 85%) in 4 h, synergizing with venetoclax (FI = 0.1) in myeloma, though cardiac liabilities persist [6]. XZ338, a BCL-XL degrader (navitoclax-CRBN), boasts oral bioavailability (F = 42%) and brain penetration, active in glioblastoma models (tumor regression 70%) [24].

PROTACs enable precision by avoiding the "hook effect" (optimal linker length 10–15 Å) and by activating prodrugs (e.g., tumor protease-cleavable masks), thereby reducing systemic exposure [25]. In SCLC, dual BCL-XL/BCL-2 PROTACs, such as ARV-471 analogs, overcome RB1 loss–mediated resistance, achieving up to 85% tumor cell kill [26]. Challenges include large MW (>900

Da), which hinder permeability and cause hook effects at high doses, addressed by truncated recruiters and lymphatic delivery. Figure 1 illustrates the mechanism of action of PROTAC-mediated degradation of anti-apoptotic protein BCL2.

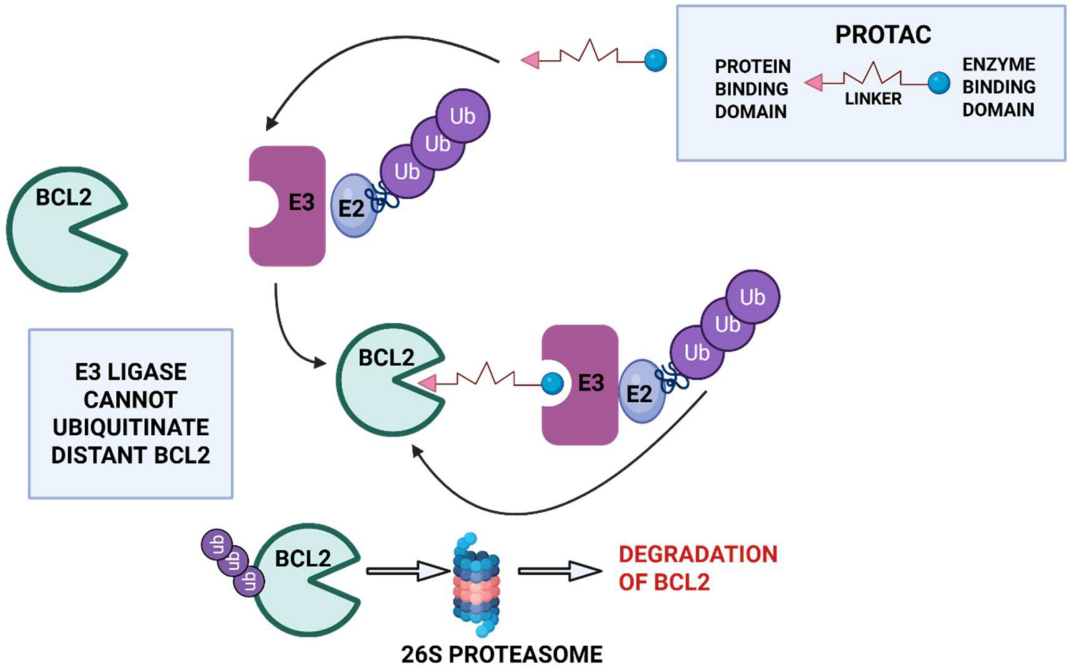

Figure 1: A PROTAC contains a target-binding domain and an E3 ligase–binding domain joined by a linker. PROTAC links the E3 ubiquitin ligase and BCL2, and BCL2 is ubiquitinated. Ubiquitinated BCL2 is degraded by the 26S proteasome.

5. Comparative Landscape: Covalent BH3 Mimetics vs. PROTACs

Covalent BH3 mimetics and PROTAC degraders represent two distinct and emerging strategies for targeting anti-apoptotic BCL-2 family proteins to reactivate apoptosis in cancer cells. Although both classes aim to neutralize pro-survival proteins such as BCL-2, BCL-XL, and MCL1, they differ significantly in their biochemical mechanisms, pharmacology, resistance profiles, and clinical readiness. Table 2 presents a comparative analysis of covalent BH3 mimetics and PROTAC degraders for apoptosis induction [10,16,18,22,27].

Table 2: Comparative overview of covalent BH3 mimetics and PROTACs targeting BCL2 family.

Feature	Covalent BH3 Mimetics	PROTAC Degraders	References
Mechanism	Irreversible inhibition of anti-apoptotic BCL2 proteins through covalent bonding to residues such as Cys245 or His224	Catalytic ubiquitin-dependent degradation via ternary complex formation with E3 ligases such as VHL or CRBN	[22]
Duration	Long-lasting inhibition due to irreversible adduct formation, enabling prolonged MCL1/BCL-XL suppression	Duration depends on proteasomal turnover rate and E3 ligase recycling	[18]
Overcoming resistance	Partially effective; sensitive to mutations in BH3-binding groove and compensatory MCL1/BCL-XL upregulation	Strong; bypasses point mutations and overcomes adaptive resistance via complete protein degradation	[16]

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Table 2: *Cont.*

Feature	Covalent BH3 Mimetics	PROTAC Degraders	References
Platelet toxicity	BCL-XL covalent inhibitors may still induce platelet apoptosis due to BCL-XL dependence	VHL-recruiting degraders (e.g., DT2216) spare platelets due to low VHL expression	[27]
Challenges	Off-target reactivity, limited oral bioavailability, warhead instability and delivery issues	High molecular weight, poor permeability, immunogenicity risks, hook effect	[10]
Clinical status	Preclinical/early development; no covalent BH3 mimetic yet in clinical trials	Multiple degraders (e.g., DT2216, 753B) in Phase I/II clinical trials.	[27]

6. Precision Apoptosis Induction: Clinical Translation and Synergies

Precision hinges on dissecting BCL2 dependencies via BH3 profiling—ex vivo peptide exposure revealing priming scores (>50% cytochrome c release predicts response), thereby stratifying patients for covalent and PROTAC trials [28]. In CLL, venetoclax priming correlates with PFS (HR = 0.4), guiding MCL1 co-targeting [6]. NA1-115-7 sensitizes low-primed solid tumors (e.g., ovarian, priming ≈ 20%) through sustained MCL1 inhibition, inducing approximately 60% apoptosis in patient-derived xenografts [14].

PROTAC753B clears therapy-induced senescent cells (SASPs, drivers of relapse), boosting doxorubicin efficacy in AML (tumor-free survival >60 days) [22]. DT2216 + PD-1 blockade—enhances T-cell infiltration by apoptotic efferocytosis, doubling responses in NSCLC models [11]. Biomarker panels integrating proteomics (MCL1/BCL-XL ratio) and genomics (BCL2 amplification) will refine cohorts, as in ongoing DT2216 expansion (NCT04860555) [29].

Toxicity mitigation via platelet-sparing (VHL PROTACs) and cardiac monitoring (troponin for MCL1) is pivotal. Covalent warheads require GSH competition assays for safety [6]. In solid tumors, intratumoral priming via metabolic stressors (e.g., glutaminase inhibitors) primes for BH3 modalities, as in TNBC, where MCL1 addiction yields 75% regression with drimanes + carboplatin [30]. Table 3 summarizes the clinical trials of BH3 mimetics and PROTACs [31–34].

Table 3: Summary of Ongoing Clinical Trials for BH3 Mimetics and PROTACs.

Agent	Target	Phase	Type(s)	Key Outcomes/Status	NCT Identifier	Reference
Venetoclax	BCL2	III	AML/CLL	66.4% CR in elderly AML (VIALE-A); PFS 53.6 mo (MURANO)	NCT03467199	[31]
S63845	MCL1	II	AML/MM	Halted due to cardiac toxicity; 20% ORR in MM	NCT03485596	[32]
AZD5991	MCL1	I/II	Solid tumors	Dose-limiting cardiac events; modest responses	NCT03218683	[32]
DT2216	BCL-XL	I	Solid/AML	Tolerable; expansions in BCL-XL-high breast; no thrombocytopenia	NCT04886622	[33]
ABBV-467	MCL1	I	MM/NHL	Troponin elevations; antitumor activity in MM	NCT05730181	[34]

7. Challenges

Achieving selective inhibition or degradation of individual BCL-2 family members remains a major challenge. On-target toxicities pose a significant barrier, particularly for multi-family targeting. Acquired resistance undermines long-term efficacy. In covalent BH3 mimetics, point mutations in the BH3-binding groove (e.g., G101V in BCL-2) or upregulation of compensatory anti-apoptotic proteins such as BCL-XL reduce binding affinity, reflect-

ing resistance patterns similar to those observed with non-covalent venetoclax. The structural demands of these agents hinder clinical translation. Covalent BH3 mimetics frequently violate Lipinski's rule of five due to their bulky warheads and linkers, resulting in poor oral bioavailability and rapid clearance, as exemplified by the use of nanoemulsion formulations of NA1-115-7 to improve tumor penetration [6]. For PROTACs, chronic exposure leads to genomic alterations in E3 ligase components, such as CRBN mutations, that impede ternary complex formation and degradation, as modeled in BET-PROTAC systems adaptable to BCL-2 contexts [27]. Covalent BH3 mimetics face challenges related to warhead reactivity, including thiol trapping, as well as delivery; future generations may leverage bioorthogonal click chemistry for in situ activation [35]. PROTACs face ADME challenges-including low solubility and efflux-but lymphatic-optimized linkers and oral CRBN variants, including XZ338, continue to advance pipelines [35]. Resistance arising from UPS adaptation, including PSMB5 upregulation, may be mitigated by using HDAC6 inhibitors to enhance aggresome-mediated protein clearance.

Acquired resistance to BH3 mimetics via BCL2 mutations (e.g., G101V) or MCL1 upregulation occurs in 20–30% of cases. Apart from PROTACs, other strategies include BH3 switching—for example, from venetoclax to MCL1 inhibitors—and combinatorial approaches. Sabutoclax, a pan-BH3 mimetic, synergizes with docetaxel, highlighting the potential for precision therapy guided by BH3 profiling [36]. Combinatorial BH3 approaches mitigate resistance and extend tumor clearance by 60% in models [7].

Despite the great promise of PROTACs against the BCL2 family for precision apoptosis induction, a series of underexplored limitations generally restricts their broader clinical successes, especially in solid tumors. The immunogenicity associated with the large heterobifunctional structure of PROTACs can lead to anti-drug antibodies or anti-PEG antibodies and initiate adaptive immune responses, as observed across preclinical and early clinical studies with multiple PROTAC scaffolds [37,38]. TME barriers significantly hinder the efficacy of PROTACs in solid tumors: hypoxia, dense stroma, and high interstitial fluid pressure hamper tumor penetration and retention, leading to a deficiency in intracellular concentrations required for effective ternary complex formation; hypoxia-activated or nanoparticle-encapsulated BCL-XL PROTACs have thus been developed to partially surmount these barriers, although stromal sequestration still limits target engagement in breast and pancreatic cancer models [39,40]. Finally, pharmacodynamic complexities arise from variable ternary complex stability, heterogeneous E3 ligase expression, and the "hook effect" at higher doses, resulting in non-linear degradation kinetics and unpredictable BCL2-family protein depletion in patients [41,42]. Addressing these challenges through next-generation delivery systems, immune-silent linkers, and patient-stratified dosing regimens will be essential to translate the full potential of BCL2-targeted PROTACs into durable clinical responses.

However, there are some controversies that exist in the field of research. Some studies show that blocking MCL1 rapidly causes heart damage in heart muscle cells, which is why several clinical trials of MCL1 inhibitors (S63845, AZD5991, AMG176) were stopped or heavily dose-limited due to elevated troponin levels in patients. However, other groups report that newer MCL1-targeted compounds (e.g., shorter-acting or more selective molecules) do not harm the heart in animal models and suggest that the toxicity may be manageable with intermittent dosing or cardiac monitoring [6]. The field has not yet reached agreement on whether MCL1 can be safely drugged in humans. Although PROTACs are designed to degrade the intended BCL2-family protein selectively, several reports indicate that they can inadvertently degrade off-target proteins or elicit immune responses against the PROTAC molecule itself. At the same time, some researchers argue that these off-target effects are rare and generally benign, particularly when VHL is employed as the E3 ligase. This disagreement makes clinicians cautious about long-term PROTAC use, particularly in patients who need many months of treatment [43].

8. Conclusions and Future Direction

Despite significant advancements in covalent BH3 mimetics and PROTACs for targeting the BCL2 family, several research gaps persist that hinder their full clinical potential. This review highlights several research gaps, including the mechanisms of resistance, biomarker development for diagnostic purposes, and the roles of less well-characterized BH3 family proteins, such as BCL2A1 and BFK, in apoptosis. A significant gap remains in understanding the mechanisms of resistance, particularly in solid tumors, where BH3 mimetics demonstrate modest efficacy due to heterogeneous BCL2 dependencies and the poor correlation between BCL2 family RNA expression and drug sensitivity. The role of compensatory upregulation of MCL1/BCL-XL and non-canonical BCL2 functions remains underexplored. Covalent inhibitors, while promising for prolonged engagement, face gaps in warhead selectivity because off-target reactivity to non-cysteine residues risks idiosyncratic toxicities and inadequate phar-

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macokinetic profiles in vivo. PROTACs, though catalytic and platelet-sparing, suffer from high molecular weights (>900 Da), which impede oral bioavailability and brain penetration, alongside undefined "hook effects" at high doses and UPS adaptation in resistant cells.

Another critical gap is biomarker development: whereas BH3 profiling predicts priming, its standardization for covalent/PROTAC responses is lagging, and genomic complexity, for example, TP53 and NOTCH1 mutations, only partially correlates with outcomes. Lastly, the relative resistance mediated by understudied and less commonly targeted BCL2 family members, such as BCL2A1 or BFK, speaks to the need for isoform-specific, comprehensive targeting. These challenges are further compounded in solid tumors, where stromal barriers and generally low mitochondrial priming hinder the translation of successes achieved in hematologic malignancies.

To bridge these gaps, future directions should prioritize innovative modalities and combinations for enhanced precision. Multivalent PROTACs co-degrading BCL2, MCL1, and BCL-XL, guided by AI-driven linker design, offer the potential for pan-inhibition while avoiding toxicities, such as the cardiac effects associated with MCL1 inhibitors. Biomarker-guided strategies integrating proteomics with dynamic BH3 profiling will enable patient stratification, as demonstrated in venetoclax trials. Beyond oncology, applications in senescence clearance and neurodegeneration represent untapped avenues. Developing AI and computational tools for precision drug targeting can open new avenues for eradicating cancer in the future.

The next decade of BCL2-family-targeted therapy should follow a clear, prioritized roadmap to translate covalent BH3 mimetics and PROTACs from promising preclinical agents into widely effective therapies, particularly for solid tumors. Firstly, resistance-proof multi-modal degraders must be developed. Tumor-microenvironment-responsive delivery platforms are urgently needed. Hypoxia- or protease-activatable PROTACs, nanoparticle-encapsulated covalent mimetics, and lymphatic-targeted formulations may overcome stromal barriers and poor penetration that currently limit efficacy in pancreatic, ovarian, and triple-negative breast cancers. Next-generation biomarkers beyond static BH3 profiling, such as real-time proteomic monitoring of BCL2-family stoichiometry, E3 ligase expression mapping, and liquid-biopsy detection of circulating ubiquitin-tagged fragments, and machine-learning integration of genomic and metabolic signatures, will enable precise patient stratification and adaptive dosing. Addressing these will propel precision apoptosis induction, transforming outcomes in BCL2-driven cancers in the future.

List of Abbreviations

PROTAC	Proteolysis-targeting chimeras
BCL2	B-Cell Lymphoma2
MCL1	Myeloid Cell Leukemia 1
BH3	BCL2 Homology 3
AML	Acute Myeloid Leukemia
BCL-XL	B-Cell Lymphoma-extra large
NOTCH1	Neurogenic locus notch homolog protein 1
TME	Tumor Microenvironment

Author Contributions

The author is solely responsible for conceptualization, investigation, writing—original draft, writing—review and editing, and visualization of the manuscript. The author has reviewed and accepted the published version of the manuscript.

Consent for Publication

No consent for publication is required, as the manuscript does not involve any individual personal data, images, videos, or other materials that would necessitate consent.

Conflicts of Interest

The author declares no conflicts of interest.

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AI Declaration

"Grammarly web portal" has been used for language correction. No other AI Tools has been used for Data Generation.

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