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Review Article

Evading Apoptosis: Small Molecule Inhibitors for Targeting BCL-2

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ABSTRACT

The condition known as cancer may arise from the excessive growth of cells, or it may occur due to the accumulation of cells resulting from a blockage in the process of apoptosis. A significant number of cancer cells manage to evade the signaling mechanisms that trigger apoptosis. The BCL-2 family of proteins plays a well-established role in the regulation of apoptosis. In nearly all types of cancer, it has been observed that the anti-apoptotic BCL-2 proteins are overexpressed, rendering them resistant to cytotoxic agents. Although BCL-2 family proteins do not directly contribute to cell proliferation, their overexpression can lead to cancer by inhibiting programmed cell death (PCD).The evasion of PCD is recognized as one of the primary hallmarks of cancer. All cells, upon reaching maturity and fulfilling their functions, must undergo apoptosis, as any dysfunctional or unwanted cells should not persist in the tissues, as this may result in cancer. The regulation of the apoptotic pathway through the use of potent, newly developed BCL-2 inhibitors presents a promising future in the fight against cancer. This review focuses on the currently available small molecules, their mechanisms of action, and the potential binding sites, which could enhance our understanding of the function of BCL-2 proteins, the key players in the intrinsic pathway of apoptosis.

INTRODUCTION

Apoptosis, which is the physiological mechanism by which a cell undergoes death, is referred to as Programmed Cell Death (PCD).[1,2]

This process involves a predisposition of cells towards death and occurs through cascades of molecular events that are irreversible.[3] Any dysfunction within the apoptosis pathway can result in severe diseases such as cancer, autoimmune disorders (characterized by low apoptosis), and degenerative disorders (associated with excessive apoptosis).[4] To maintain homeostasis between cell proliferation and cell death, apoptosis is crucial.

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Apoptosis is an active and endergonic cytological process that entails the activation of cysteine-aspartic proteases known as caspases, and it represents a morphologically distinct form of cell death.[5] This process is characterized by cell shrinkage, chromatin condensation, pyknosis, bleb formation, karyorrhexis, and the separation of apoptotic bodies, which are subsequently phagocytosed by tangible body macrophages.[6,7] There are two primary pathways for apoptosis: the extrinsic pathway, also known as the death receptor pathway, and the intrinsic pathway, referred to as the mitochondrial pathway. Additionally, there exists an auxiliary pathway that requires cytotoxic T cells and perforin-granzyme-dependent mechanisms for the killing of cells.[8]

The extrinsic pathway necessitates the activation of transmembrane receptors that belong to the Tumour Necrosis Factor Receptor (TNFR) gene family.[9,10] These receptors are referred to as death receptors or pro-apoptotic receptors, and they are activated through the stimulation of death ligands or pro-apoptotic ligands.

Death receptors possess cysteine-rich extracellular domains along with an 80 amino acid domain known as the death domain, which binds to the ligand and forms a cluster that results in the formation of the Death Inducing Signal Complex (DISC).[11] There are various types of death receptors, among which CD95 (also known as Apo 1 or Fas) and TNFR1 (also referred to as p55 or CD120) are well characterized.[12,13]

A protein named Fas Associated Death Domain (FADD) binds to the DISC.[14] FADD also contains an effector domain that interacts with a death-promoting proteolytic enzyme known as caspases (Cysteine-Aspartic proteases).[15] This aspartate-specific cysteinyl protease facilitates the proteolysis of cells. Caspases are categorized into two types: initiator or apical (Caspases 2, 8, 9, 10) and executioner or effector (Caspases 3, 6, 7). The effectors are responsible for all cellular proteolysis and activate Caspase Activated DNAse (CAD). In the extrinsic pathway, initiator caspase 8 is activated first, leading to the subsequent activation of effector caspase 3.

The intrinsic pathway within the mitochondria is regulated by a gene known as BCL-2, which is part of a group of oncogenes that inhibit programmed cell death. This pathway facilitates the formation of pores in the outer mitochondrial membrane, which signals for cell death.[16] The pro-apoptotic initiator subgroup of the Bcl-2 family detects apoptosis signals, such as cellular stress, and activates the pro-apoptotic effector proteins of the same family. This activation results in oligomerization and pore formation in the outer mitochondrial membrane. Consequently, this leads to increased mitochondrial permeability and a decrease in membrane potential, resulting in the leakage of cytochrome c from the mitochondria. The apoptotic protease activating factor then binds to cytochrome c, forming a complex that activates initiator caspases, thereby triggering apoptosis. Members of the Bcl-2 family play a significant role in apoptosis through protein-protein interactions, making them a versatile and challenging target for chemotherapy.

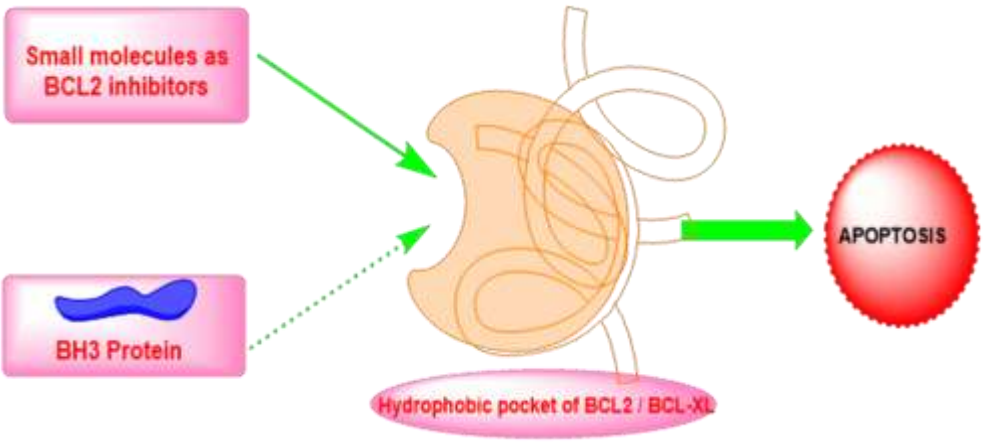


Figure 1: Apoptosis

BCL-2 FAMILY

BCL-2 proteins constitute a family of proteins located in the outer membrane of mitochondria and the endoplasmic reticulum. They play a role in both the negative and positive signaling mechanisms of apoptosis.[17] These proteins are evolutionarily conserved and may possess Bcl-2 homology (BH) domains. The Bcl-2 proteins are categorized into three primary classes based on their functions. These include pro-apoptotic effector proteins (e.g., Bax, Bak, Bok), anti-apoptotic or pro-survival proteins (e.g., Bcl-2, Bcl-xl, Bcl-w, Mcl-1), and pro-apoptotic BH3-only proteins (e.g., Bad, Bik, Bim, Bid, Bmf, NOXA), which serve as initiators of apoptosis.[18,19]

Prosurvival and proapoptotic effector proteins belong to a multi-domain family. They possess all four Bcl-2 homology domains (BH1-BH4). In contrast, BH3 proteins are characterized by a single domain. Nearly all members of this family feature a transmembrane domain at their C-terminal, facilitating interaction with mitochondria. The structure is composed of two central amphipathic alpha helices (predominantly hydrophobic), which are encircled by seven additional amphipathic alpha helices. Proapoptotic members exhibit a prominent hydrophobic groove on their surface. This groove serves as the binding site for the peptides of BH3 mimetics from various proapoptotic members, such as Bax.

Upon receiving death stimuli, the BH3-only protein will attach to the groove of the prosurvival proteins. This interaction between proteins results in the activation of pro-apoptotic members, leading to the extrusion of cytochrome c from the intermembrane space. Consequently, this activates initiator caspases, followed by the activation of effector caspases.

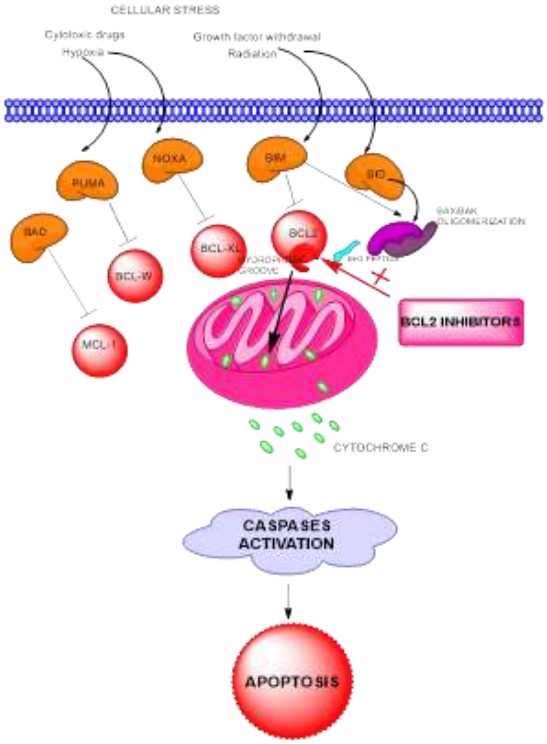


Figure 2: Mechanism of apoptosis

The strategy of targeting BCL-2 proteins for cancer therapy is evolving continuously. One of the initial approaches employs antisense oligonucleotides such as Oblimersen, which can attach to the complementary mRNA of BCL-2.[20] This attachment leads to the suppression of protein expression. Although this antisense oligonucleotide progressed to phase III clinical trials, it was not approved by the FDA as a standalone treatment due to significant adverse effects. However, it demonstrates considerable synergistic efficacy when used in combination therapy with Dacarbazine for melanoma treatment, and several antisense oligonucleotides have been reported to show good efficacy in combination therapies. Unfortunately, none of these have received FDA approval. Another approach involves the use of peptides targeting BCL-2 proteins. In this method, BH3-only protein mimetic peptides are utilized to bind to BCL-2 with a higher affinity than proapoptotic proteins. Consequently, proapoptotic proteins are released and can homodimerize to initiate apoptotic events. The limitations of these peptides include a high degree of metabolic instability, degradation by various cellular enzymes such as proteases, and very low cell permeability, with none of this category advancing to clinical trials. The most significant and contemporary strategy is the development of small-molecule inhibitors of antiapoptotic BCL-2 proteins, which can disrupt protein-protein interactions by binding to the hydrophobic groove of BCL-2. These inhibitors primarily impede the protein-protein interactions of heterodimer complexes formed between antiapoptotic proteins and proapoptotic members.

The antiapoptotic BCL-2 proteins exhibit a globular configuration and comprise a cluster of eight to nine hydrophobic α helices.[21] Among these, the two largest hydrophobic α helices serve as the structural backbone of the protein, encircled by six to seven amphipathic α helices. A long hydrophobic groove, extending to 20 A˚, is formed by these proteins on the surface, functioning as the binding site for the BH3 peptides. The binding cavity is primarily constituted by the α3 and α4 helices, with α5 and α6 positioned at the centre. Although the antiapoptotic proteins BCL-2 and BCL-xl share approximately 49% sequence similarity, they are identical in their three-dimensional structures. The principal distinction between BCL-2 and Bcl-xl is observed in the helical fold of the α3 helix, which creates a wider groove in BCL-2 compared to Bcl-xl. The second significant difference lies within the binding groove itself, where three notable variations occur in the amino acid sequences at positions 104, 108, and 122. At position 104, Ala is found in Bcl-xl, whereas Asp is present in BCL-2. At position 108, Leu is located in Bcl-xl, while Met is found in BCL-2. In the 122nd position, Ser is present in Bcl-xl, in contrast to Arg in BCL-2. The Met at the 108th position of BCL-2 is situated at the centre of the α3 helix, allowing small molecules to penetrate deeper into the hydrophobic pocket of the binding cavity compared to Leu in Bcl-xl.

BCL-2 INHIBITORS FROM NATURE

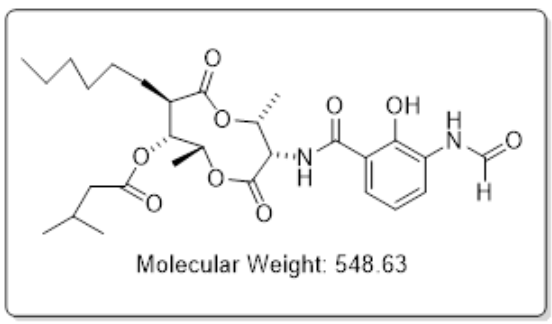
Nature serves as the largest pharmacy in the world for treating various ailments. Natural products exhibit greater chemical diversity, enhanced biochemical selectivity, and other molecular characteristics that position them as promising candidates for drug discovery.

When researchers sought an antiapoptotic antagonist to function as an anticancer agent, they screened the existing natural library for potential leads. They identified various natural agents capable of targeting antiapoptotic proteins.

TETROCARCIN A

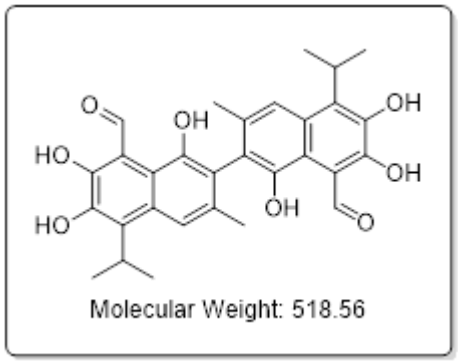
Tetrocarcin A, recognized as the first reported BCL-2 inhibitor, is an antibiotic derived from Actinomycete (Micromonospora chalcea NRRL11289) that inhibits the antiapoptotic function of the BCL-2 family.[22] Chemically, it is classified as a spirotetronate belonging to the polyketide family and is categorized as a medium-sized spirotetronate, featuring a 13-membered carbon macrocyclic structure. It contains a tetronate moiety that is spirolinked to a cyclohexene ring and connected to a trans-decalin system via a carbonyl group. These compounds are biosynthesized by type I polyketide synthase, with the incorporation of trans-decalin occurring through a Diels-Alder reaction. They exhibit weak acidity and are lipophilic in nature. These molecules demonstrate a dose-dependent cytotoxic effect on various cell lines that overexpress BCL-2 proteins. Depending on the specific cell type, they disrupt different antiapoptotic pathways. In HeLa cells, for instance, they exert an antiapoptotic effect by inhibiting mitochondrial functions associated with the BCL-2 protein family, thereby inducing apoptosis. In lymphoma cells, they trigger apoptosis directly through a caspase-dependent pathway. Furthermore, they can suppress mitochondrial functions mediated by BCL-2 proteins. Consequently, they inhibit the antiapoptotic activities of BCL-2 family proteins across various cell death signaling pathways.

ANTIMYCIN A



Another natural inhibitor of the BCL-2 protein is Antimycin A, which is synthesized by Streptomyces species. It acts as an inhibitor of mitochondrial electron transport by interfering with the electron flow from cytochrome b to cytochrome c within complex III. The inhibition of BCL-2, as reported by Tzung et al., occurs due to its capacity to competitively bind with the ligands for the hydrophobic groove of Bcl-xl. This binding results in the disruption of the pore formation function of Bcl-xl, potentially leading to mitochondrial swelling. Studies have indicated that Antimycin preferentially binds to the wild-type protein rather than the mutated variant. Manion et al. demonstrated that Antimycin specifically induces cell death in murine hepatocytes that overexpress BCL-xl or BCL-2. Additionally, their derivative, 2-methoxy antimycin A3, also exhibits specificity towards the BCL-2 protein.[23,24]

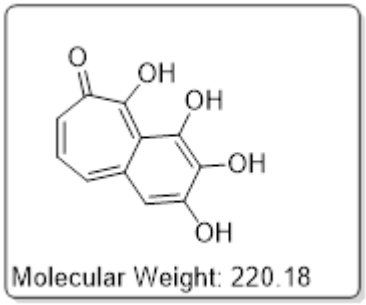
GOSSYPOL



Gossypol, also referred to as BL-193, is a yellow pigment derived from cotton seeds (Gossypium malvacea). This compound is classified as a terpenoid aldehyde and exists in three isoforms: + BL-193, - BL-193, and a racemic mixture. In nature, it predominantly occurs as a racemic mixture. The isoform with the highest cytotoxic potency is - BL-193. The anticancer properties of gossypol were first documented by Tuszynski and Cossu. Based on findings from nuclear magnetic

resonance spectroscopy, cell-based assays, and fluorescence polarization displacement assays, researchers have established that gossypol acts as a BH3 mimetic, binding to Bcl-2/Bcl-xl at the mitochondria and obstructing the function of Bcl-2. This molecule exhibits inhibitory effects against a broad spectrum of cancer cell lines. It has been reported to inhibit the heterodimerization of the Bcl-2/Bcl-xl complex in PC-3 prostate cancer cells. Studies involving CLL and HT-29 colon cancer cells have demonstrated that gossypol can downregulate the anti-apoptotic members of the Bcl-2 family. Gossypol acetic acid, known as AT-101 from Ascent Therapeutics, is currently undergoing clinical trials (phase II). These lead compounds provide structural insights that are crucial for the development and design of new candidates aimed at combating cancer.[25]

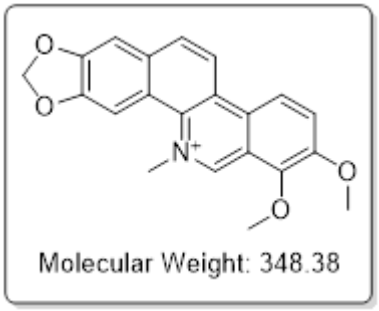
PURPUROGALLIN



Purpurogallin is a natural product that contains benzotropolone and is utilized as an antioxidant in edible oil derived from the nutgalls of Quercus spp and oak barks.

Studies indicate that this molecule can inhibit the BCL-2 protein by binding to the BH3 binding site of Bcl-xl/Bcl-2. The mechanism underlying its antitumor activity involves its capacity to inactivate the BCL-2 protein. Researchers have also examined the activity of various analogues of Purpurogallins and concluded that the presence of two hydroxyl groups and the hydrogen-donating nature of phenolic groups are crucial for its antitumor activity.[26] We can modify the R5 site with different small substituents. Therefore, this small natural polyphenol hit molecule provides valuable insights for the further development of leads.[27]

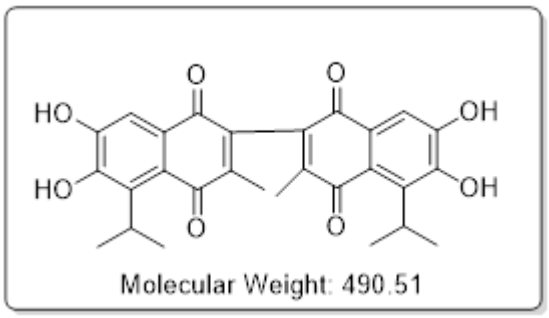
CHELERYTHRINE



Chelerythrine is a benzophenanthridine alkaloid derived from the plant Cheledonium majus. High-throughput screening utilizing fluorescence polymerization binding assays indicates that this compound can directly interact with mitochondria and impede the heterodimerization of the Bcl-xl-Bak BH3 peptide. Consequently, it can facilitate the release of cytochrome c from the mitochondria. There is evidence demonstrating that this molecule exhibits in vivo activity against squamous carcinomas of the head and neck.

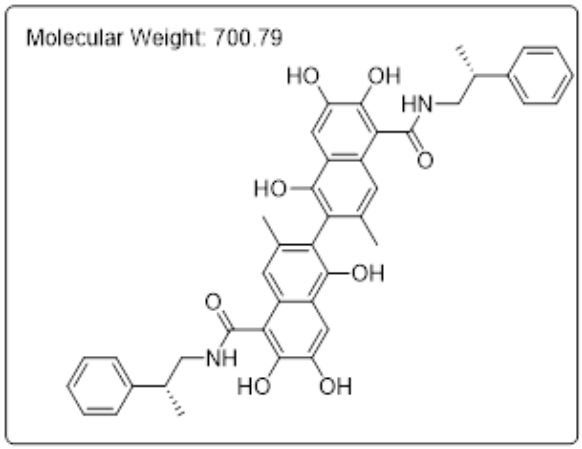
Furthermore, certain catechins such as epigallocatechin gallate, epicatechin gallate, and gallocatechin gallate, along with specific theaflavins including theaflavin digallate and theaflavin-3' gallate, have also been documented to interact with the Bcl-xl protein and exhibit antiapoptotic properties.[28]

SEMISYNTHETIC AND SYNTHETIC SMALL MOLECULE INHIBITORS OF BCL-2:APOG2



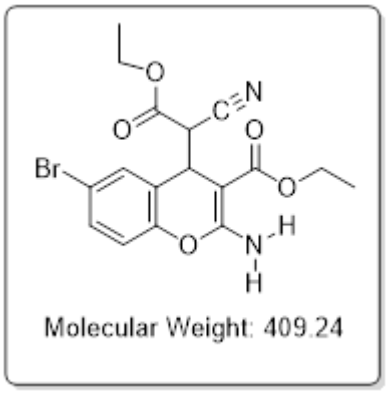
ApoG2 is a semisynthetic derivative of gossypol, referred to as apogossypolone, which has been synthesized by Ascenta Therapeutics.[29] This molecule contains a ketone group in place of the two hydroxyl groups found in gossypol. Research has demonstrated that it can bind to the BCL-2 and MCL-1 proteins. Additionally, it inhibits the binding of Bim to BCL-2 and promotes apoptosis. There are two isoforms, both of which exhibit equal activity. They possess lower toxicity compared to gossypol and are more potent. Furthermore, they display stereoselective cytotoxic differences across various cell lines when compared to gossypol.[30]

BI-97C1 (SABUTOCLAX)



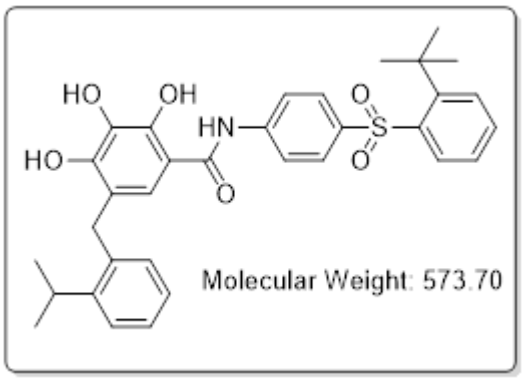
BI-97C1 is a pure optical derivative of Appogossypol. It has the ability to inhibit the interaction of the BH3 peptide with Bcl-xl, BCL-2, and MCL-1.[31] The molecule has been extensively researched in prostate cancer utilizing M2182 cell lines, a tumorigenic variant of the normal prostate cells P69, where Mcl-1 is overexpressed, demonstrating significant efficacy in suppressing tumor growth. In vivo studies conducted in xenograft models indicate its considerable potential in prostate cancer. Additionally, the molecule exhibits synergistic effects when combined with the drug Docetaxel. Research has also been conducted on this molecule in the context of colorectal cancer and lung cancer. It represents a promising candidate for further development and derivatization into novel antiapoptotic drugs.[32]

HA14-1



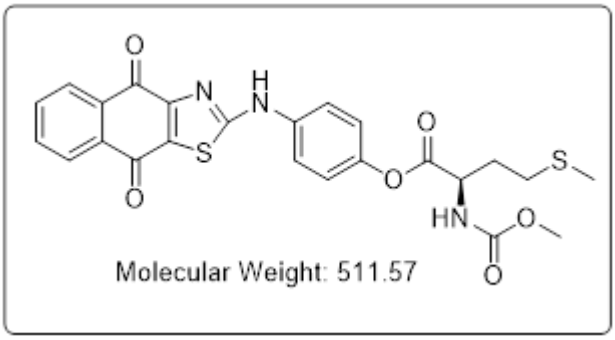
HA14-1 is the inaugural molecule identified through an in-silico strategy in the context of de novo drug discovery, based on the predicted structure of BCL-2. It is a nonpeptide organic compound known to function as a BCL-2 inhibitor. This molecule exhibits a strong affinity for binding to the surface pocket of the Bcl-xl protein. The molecule induces a reduction in mitochondrial membrane potential. Consequently, it can obstruct the antiapoptotic action, leading to the activation of caspase 9, which is subsequently followed by the activation of caspase 3. HA14-1 represents a promising lead compound for further development and modification to create a more potent and selective antiapoptotic inhibitor.[33]

TW-37



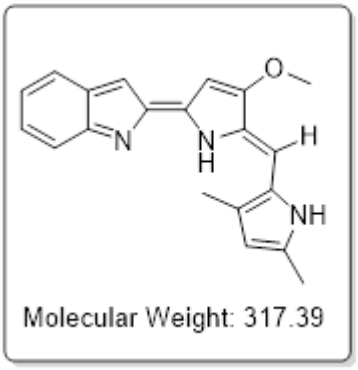
TW-37 was developed utilising a structure-based drug design approach, with gossypol serving as the template. Molecular modelling studies suggest that TW-37 will competitively bind to the BH3 binding groove of the BCL-2 protein.[34,35] Experimental results, obtained through enzyme-linked immunosorbent assay and fluorescence polarization binding studies, indicate that this molecule can simultaneously inhibit BCL-2, Bcl-xl, and MCL-1, thereby effectively inducing apoptosis in cancer cells, particularly in melanoma-derived tumors. The molecule exhibits activity across various cell lines within the nanomolar range.[36]

YC-137



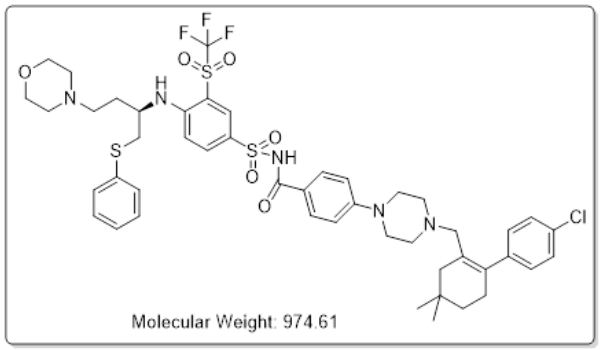
YC-137 was created by Real et al. utilizing a structure-based computational drug design approach. They investigated the impact of the drug on MB435 breast cancer cells as well as other breast cancer cell lines such as MB435L, MB231, and MCF7, discovering that cell death is triggered by the release of cytochrome c, which subsequently activates caspases through selective binding to BCL-2. It was found that they inhibit the binding of the Bid-BH3 peptide to the hydrophobic groove of BCL-2.[37]

OBATOCLAX (GX015-070)



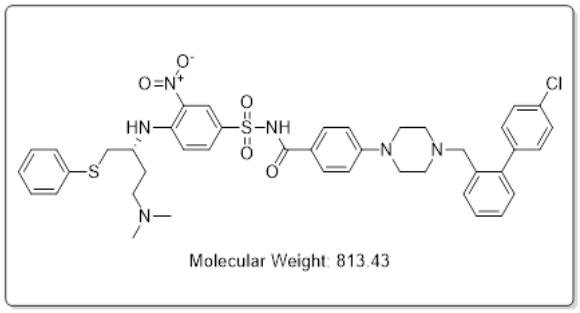
This medication was created by Gemin X as a polypyrole and subsequently transferred to Cephalon, which was later acquired by Teva Pharmaceuticals. It functions as a BCL-2 family inhibitor, exhibiting potential pro-apoptotic and anti-neoplastic properties. This compound operates by obstructing the interaction of anti-apoptotic proteins with pro-apoptotic Bax and Bak, thereby triggering the apoptotic process in cells with overexpressed BCL-2. It underwent screening for both haematological and solid tumours. Reports indicate that obatoclax can directly activate Bax.[38]

ABT-263



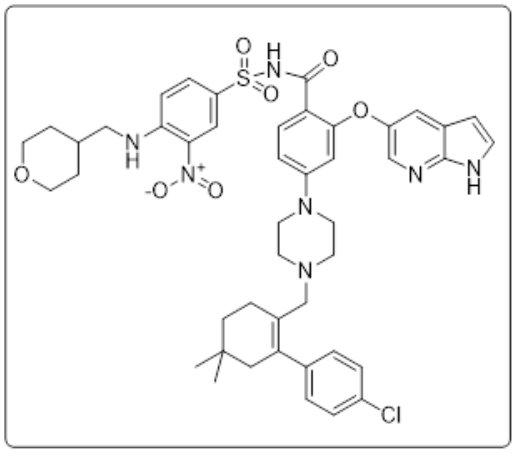
ABT-263, an orally available small molecule, was developed by Abbott Laboratories and is also known as Navitoclax. It was created using a structure-based computational drug discovery approach.[39] The active site of Bcl-xl was identified through NMR, and an alanine scan of the Bak BH3 peptide revealed the residues essential for strong binding to Bcl-xl. This was followed by NMR fragment screening, which led to the identification of the lead molecule for the development of Navitoclax.[40,41] The mechanism of action of this compound involves the inhibition of Bc-2, Bcl-xl, and Bcl-w. These proteins can disrupt the protein-protein interactions between pro-apoptotic proteins, such as Bim, thereby inducing apoptosis. Extensive testing against a wide range of lung cancer cell lines has demonstrated excellent activity without any off-target effects.[42] Furthermore, it has been shown to enhance the clinical efficacy of bortezomib and rituximab. Clinical studies (Phase I/II) commenced in 2009 for lymphatic leukemia and lung cancer. However, since it inhibits Bcl-xl, it reduces platelet lifespan, which can lead to thrombocytopenia.[43]

ABT -737



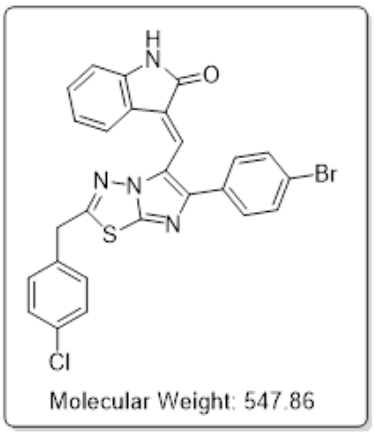
ABT-737 was created as a powerful mimetic inhibitor of the BCL-2 homology domain 3 by Abbott Laboratories in partnership with Idun Laboratories.[44] It demonstrates superior inhibition of BCL-2, Bcl-xl, and Bcl-w. However, it was ineffective in inhibiting MCL-1. Research conducted by Chen et al. revealed that the downregulation of MCL-1 enhances the sensitivity of leukemia cells to ABT-737.[45] This compound can be delivered via the parenteral route.

ABT-199



ABT-199, also known as Venatoclax, is the sole drug in the BCL-2 class that has received FDA approval. It is administered orally and is intended for the treatment of Chronic Lymphocytic Leukemia (CLL). The drug has demonstrated efficacy against various cancer cell lines, including Non-Hodgkin Lymphoma (NHL) and Multiple Myeloma. This compound is classified as a BH3 mimetic; however, it exhibits greater selectivity for BCL-2 compared to Bcl-xl, thereby avoiding the risk of thrombocytopenia.[46]

Disarib



Disarib was developed by Indian scientists at IISC, Bangalore. It was rationally designed using 3-substituted indolin-2-one (for instance, Z34), which exhibits antitumor activity. This molecule comprises four rings: an imidazothiadiazole ring at the center, along with benzyl, phenyl, and indole rings. Disarib demonstrates a high specificity for BCL-2, unlike other members of the antiapoptotic family such as BCL-xl, BCL-w, and MCL-1. It binds predominantly to the BH1 domain rather than the BH3 domain. Vartak et al. reported that the cell death induced by disarib occurs without the production of reactive oxygen species and does not involve cell cycle arrest. It can reduce mitochondrial potential and promote apoptosis in cells. They investigated the induction of tumor regression in xenograft and allograft models of mice to assess the molecule's potential as a therapeutic agent. The molecule exhibits greater efficacy compared to ABT-199.[47]

CONCLUSION

Considering that more than fifty percent of all cancer cells show an overexpression of BCL-2, it serves as a crucial therapeutic target for cancer treatment. Current chemotherapeutic agents mainly concentrate on the cell cycle and can also harm normal cells. By steering cancer cells towards apoptosis through the inhibition of antiapoptotic proteins, we can alleviate the adverse side effects of chemotherapy and address resistance. Employing small molecule inhibitors of BCL-2 to induce apoptosis has been demonstrated as an effective approach for cancer therapy. Among the various molecules categorized as BCL-2 inhibitors, only ABT-199 has been granted FDA approval in this category. The newly developed compound Disarib shows promising and superior results in vitro and in mouse xenograft models compared to ABT-199, suggesting a potential pathway for its development as a clinically viable candidate. Other drugs within the ABT series, such as ABT 263 and ABT 737, have exhibited excellent results in combination therapies. Furthermore, drug-resistant cells frequently display overexpression of Bcl-xl and MCL-1, highlighting the importance of investigating new drug candidates as BCL-2 family inhibitors with improved efficacy. Ongoing research into the creation of BCL-2 family inhibitors is anticipated to produce even more potent nanomolar range molecules with minimised off-target effects.

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