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Review Article

Selective Small Molecule Myeloid Cell Leukemia-1 (MCL-1) Inhibitors: Novel Agents in Cancer Therapy

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ABSTRACT

Apoptosis is a normal physiological process, which is very crucial to maintain tissue homeostasis. Dysregulated apoptosis can lead to various diseases as cancer. Thus, the evasion of apoptosis stands out as a key hallmark of cancer cells. BCL-2 family of proteins is the key modulator of the mitochondrial apoptotic pathway. Therefore, the balance between the anti-apoptotic (BCL-2, BCL-XL, and MCL-1) and pro-apoptotic (BAK, BAX, BAD, PUMA, and NOXA) members of this family will govern cell fate. Overexpression of anti-apoptotic BCL-2 members including MCL-1 is implicated in the progression of many human cancers as well as the emerging resistance to various anti-cancer agents including targeted therapies. Indeed, inhibition of the anti-apoptotic BCL-2 members by small-molecule BH3 mimetics may provide an excellent approach in cancer therapy. Unfortunately, it was reported that MCL-1 overexpression is linked to Venetoclax, first FDA approved BCL-2 selective inhibitor, resistance in AML. Thus, inhibition of MCL-1 with a selective small-molecule inhibitor may provide an attractive strategy in cancer targeted therapy. Recently, several small-molecule MCL-1 selective inhibitors have been developed and few are being tested in clinical trials. Herein, we will discuss the recent advances in the development of selective small-molecule MCL-1 inhibitors.

Keywords: Apoptosis; BCL-2; MCL-1; BH3 mimetics; Bax; Bak.

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1. INTRODUCTION

Cancer is a fatal disease, which is characterized by uncontrolled cell growth that leads to the formation of tumors. Cancerous cells can spread to other tissues and body organs via metastasis. For the cancer cell to become immortal and malignant, it must develop several mechanisms to assure its survival. These mechanisms are described and defined as the hallmarks of cancer. These biological hallmarks are factors that appear in almost all different

types of cancer, including continuous proliferation, evading growth suppressor signals, induction of angiogenesis, resisting cell death, avoiding immune destruction, tissue invasion and metastasis [1-3]. One of the key hallmarks of the cancerous cell is its ability to evade apoptosis and to resist cell death. Therefore, targeting apoptotic pathways became one of the most promising strategies in cancer-targeted therapy.

Apoptosis is a normal physiological process of programmed cell death, which is very crucial

to maintain homeostasis and normal development [4]. It plays a critical role in both physiological and pathological conditions, so it must be precisely regulated. Defective apoptosis can lead to various diseases as cancer, viral infections, and autoimmune disorders, while excessive apoptosis may lead to neurodegenerative disorders [5-7]. Many stress-inducing conditions can trigger apoptosis including DNA damage and uncontrolled proliferation [8, 9]. Apoptosis is highly controlled and regulated via two main apoptotic pathways: the extrinsic (death receptor) pathway and the intrinsic (mitochondrial or BCL-2 regulated) pathway (Fig. 1) [10].

Both the extrinsic and intrinsic pathways lead to the activation of a family of proteases called caspases. They are cysteine, aspartate-specific proteases that have a cysteine residue at their active site and cleave the protein substrate at aspartic acid residues, so the name caspases. Normally, they are synthesized within the cell as inactive procaspases, which are activated by other caspases in a cascade manner. Once they are activated, lead to the activation of other caspases which in turn resulting in the destruction of different cellular proteins thereby leading to apoptosis [11-13].

By understanding the different factors involved in the regulation of the apoptotic pathways, many of these factors may be exploited as prime targets for cancer therapy development.

BCL-2 family of proteins stands out as the key regulator of the mitochondrial apoptotic pathway. This family of proteins comprises three subfamilies which are classified according to their function and structure into pro-apoptotic BH3 only, pro-apoptotic multi-domain and pro-survival (anti-apoptotic) proteins. The pro-apoptotic BH3-only proteins include BAD, BIM, BID, BIK, NOXA and PUMA that contain only the BH3 homology domain which is very crucial

for the interactions of these proteins with other members of the BCL-2 family. On the other hand, the pro-apoptotic multi-domain proteins (the effectors) have three BH domains (BH1-BH3) which include BAK and BAX. The pro-survival (anti-apoptotic) members include BCL-2, BCL-XL, MCL-1, BCL-W and BFL-1/A-1 which have four BH domains (BH1-BH4) except for MCL-1 which have only three BH domains (BH1-BH3) [14-16].

Protein-protein interaction (PPI) between the pro-apoptotic and pro-survival members of the BCL-2 family plays a pivotal role in governing the cell fate. This interaction is mediated via the BH3 domain of the pro-apoptotic members and the hydrophobic binding groove on the surface of the anti-apoptotic proteins. Any aberrations in the balance between the pro-apoptotic and anti-apoptotic proteins may result in dysregulated apoptosis. This imbalance mainly results from overexpression of one or more pro-survival proteins [17, 18].

One of the major approaches for anti-apoptotic BCL-2 proteins inhibition is the development of small molecule inhibitors (BH3 mimetics) which mimic the BH3-only pro-apoptotic proteins and have the ability to bind to the BH3 hydrophobic binding groove on the surface of the anti-apoptotic proteins and thus inhibit its action and activate apoptosis by the release of BH3-only proteins (BAK, BAX) [20, 21].

Recently, a series of BH3 mimetics have been reported, ABT-737 (1) and its orally available analog Navitoclax (ABT-263) (2) are representing the first prime advance in small molecule inhibitors targeting BCL-2 anti-apoptotic proteins. They showed activity against BCL-2, BCL-XL, and BCL-W but had no activity against MCL-1 or BFL-1/A-1. Navitoclax (2) has shown very promising results in clinical trials

except for its dose-limiting side effect thrombocytopenia due to co-inhibition of BCL-XL [22]. More recently, Venetoclax (ABT-199) (3) has been approved for the treatment of chronic lymphocytic leukemia. Venetoclax is considered as the first selective BCL-2 inhibitor thus lacks Navitoclax's side effect, thrombocytopenia [23] (Fig. 2).

Unfortunately, neither Navitoclax nor Venetoclax can inhibit MCL-1 anti-apoptotic protein and it was found that a high level of MCL-1 is the main contributor to the Venetoclax resistance in acute myeloid leukemia (AML) [24].

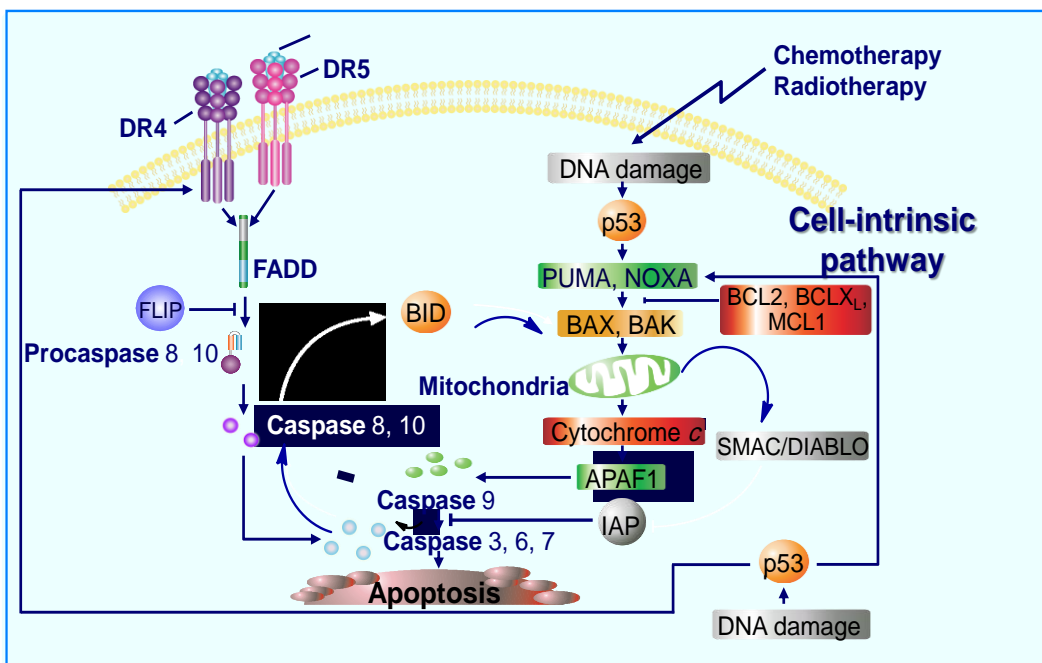


Fig. 1. Schematic diagram illustrating the two major apoptotic pathways [10]

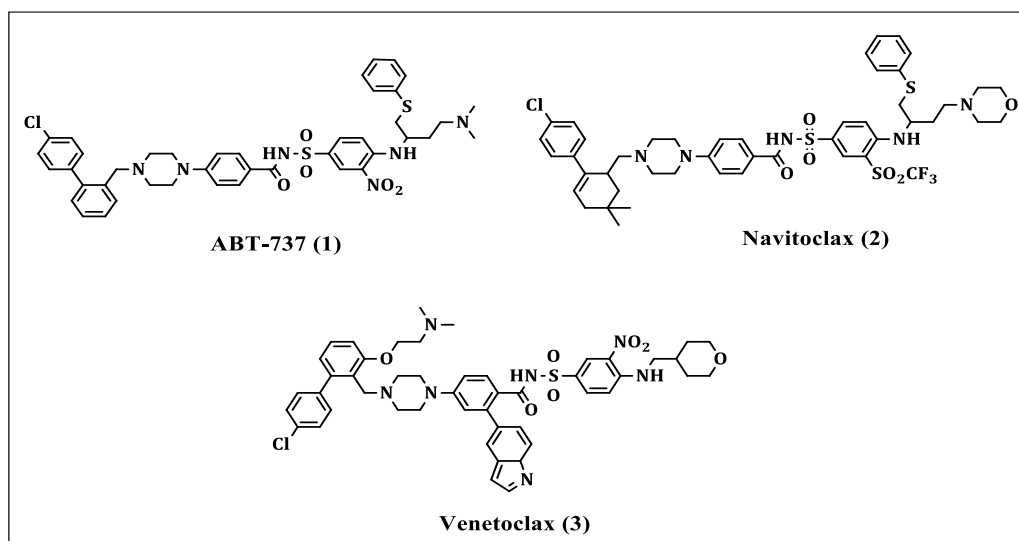


Fig. 2. Chemical structure of ABT-737, Navitoclax, and Venetoclax

2. Targeting the anti-apoptotic protein MCL-1 in cancer therapy

MCL-1 is a member of the anti-apoptotic BCL-2 family of proteins, which is normally expressed within the tissues. It plays a pivotal role in maintaining homeostasis [25, 26].

Several studies have shown that MCL-1 is overexpressed in a vast number of human tumors, including breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and non-small cell lung cancer [27-32].

Additionally, overexpression of MCL-1 has been reported in some hematological cancer, including B-lymphoma and myeloblastic leukemia [33-35]. This high expression level contributes to the emerging resistance of various chemotherapeutic agents including cisplatin, erlotinib, taxol, and many other anticancer agents [36, 37]. Accordingly, inhibition of MCL-1 and downregulation of its expression may be advantageous and may increase the sensitivity of cancer cells to chemotherapeutics. Thus targeting MCL-1 by small-molecule inhibitors, either as a single agent or in combination may offer an effective therapeutic strategy for the treatment of different cancers. Recently, several small-molecule MCL-1 inhibitors have been developed; some have been entered clinical trials. Herein, we focus on the most potent selective small-molecule MCL-1 inhibitors.

3. Selective small molecule MCL-1 inhibitors

Recently, there is a great advance in the development of small molecule MCL-1 inhibitors. Several selective and highly potent inhibitors have been reported including:

3.1. Marinopyrrol A (Maritoclax)

Marinopyrrol A (4) (Fig. 3) is a bi-pyrrole derivative which is first isolated from the marine *Streptomyces sp.* CNQ-418.

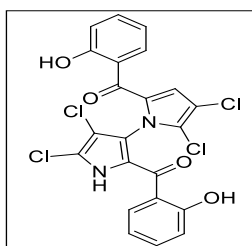


Fig. 3. Marinopyrrol A (4)

It was used for its powerful anti-microbial activity against MRSA. Marinopyrrol A is the first discovered selective MCL-1 inhibitor with IC_{50} of 10.1 μ M, its inhibitory activity against MCL-1 was discovered during the screening of small library [38-40]. It has the efficacy to induce apoptosis in MCL-1-dependent lymphoma and leukemia cell lines [41].

3.2. MIM1, A substituted pyrogallol derivative

MIM1 (5) (Fig. 4) was discovered through high throughput screening technique that used a fluorescently labeled MCL-1 stapled BCL-2 domain α -helix. It exhibits a moderate activity against MCL-1 with an IC_{50} of 4.8 μ M and can induce Bax/Bak-dependent apoptosis in leukemia cell lines [42]. Because of its moderate activity and selectivity, further optimization is now in progress using structure-activity relationship studies (SAR) [43].

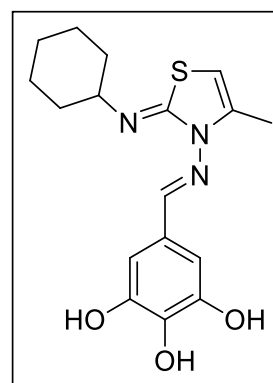


Fig. 4. MIM1 (5), Pyrogallol derivative

3.3. 8-Hydroxyquinoline based inhibitors

A high throughput screening of a small molecule library has been carried out by the Scripps Research Institute in collaboration with Eutropics Pharmaceuticals Company for the discovery of novel MCL-1 inhibitors. This screening resulted in the discovery of a selective MCL-1 inhibitor (6) with an IC_{50} value of 2.4 μ M. Further structure-activity relationship (SAR) studies were conducted, which resulted in the discovery of hydroxyquinoline derivative (7). These studies have shown that the removal of the carboxylic acid group and the 4-chloro group may improve the drug-like properties. It was found that compound (7) binds more potently and selectively to MCL-1 with an IC_{50} value of 0.31 μ M [44] (Fig. 5).

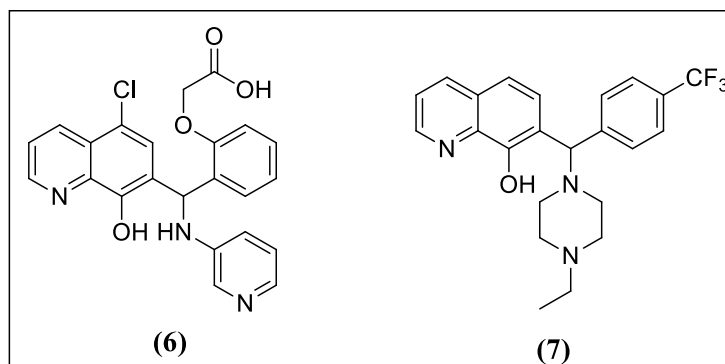


Fig. 5. 8- Hydroxyquinoline MCL-1 inhibitors

3.4. Substituted 6,5- fused heterocycles-2-carboxylic acid-based inhibitors (Merged compounds)

An NMR-based screening of a large fragment library has been carried out for novel potent MCL-1 inhibitors by Friberg and coworkers which is then followed by NMR-guided molecular docking, culminated in the discovery of two chemically distinct groups of fragments, the first one contains 5, 6- fused heterocyclic-2-carboxylic acids, for example, compound (8) which inhibit MCL-1 with a K_i value of 131 μM , and the second group contains hydrophobic aromatic compounds linked to a polar group, for example, compound (9) which inhibit MCL-1 with a K_i value of 60 μM . Based on these studies, one fragment from each group was chemically linked, that

is lead to an impressive increase in the binding affinity and potency as compared to each fragment. This merging strategy is carried out by Fesik's group, thus merging fragment (8) and (9) led to the discovery of (10) with dramatically enhanced K_i value of 0.32 μM against MCL-1 [45].

Further optimization and SAR studies rustled in the identification of compound (11), in which the benzothiophene ring is replaced by indole ring, with more enhanced potency (K_i value of 55 nM) and selectivity over other anti-apoptotic members.

Additionally, Fesik's group discovered a tricyclic indole carboxylic acid fragment during their screening, which was furtherly optimized to lead to the discovery of compound (12) that inhibits MCL-1 with a K_i value of 3 nM [46] (Fig. 6).

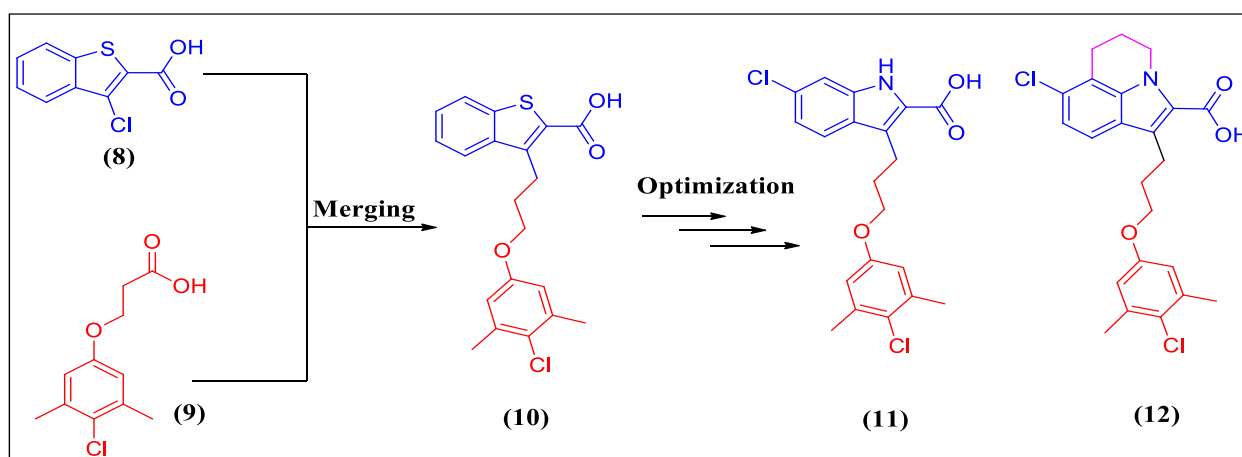


Fig. 6. Merging fragments from two distinct classes produced a compound with significantly improved MCL-1 inhibitory activity

3.5. S1 and S1 derivatives based inhibitors

S1 compound (13) (Fig. 7) was discovered through screening by Song and coworkers who found that S1 has the ability to inhibit BCL-2 and MCL-1 in a nanomolar concentration (for BCL-2, $K_d = 58$ nM and MCL-1, $K_d = 310$ nM) and disrupting their interaction with pro-apoptotic proteins (Bak and Bax) leading to induction of apoptosis [47, 48].

Using scaffold hopping approaches, several derivatives of S1 (13) have been discovered, which possess more potent inhibitory activity against anti-apoptotic proteins. For example, compound (14) inhibits MCL-1, BCL-2, and BCL-XL with IC_{50} of 10 nM, 20 nM and 18 nM, respectively.

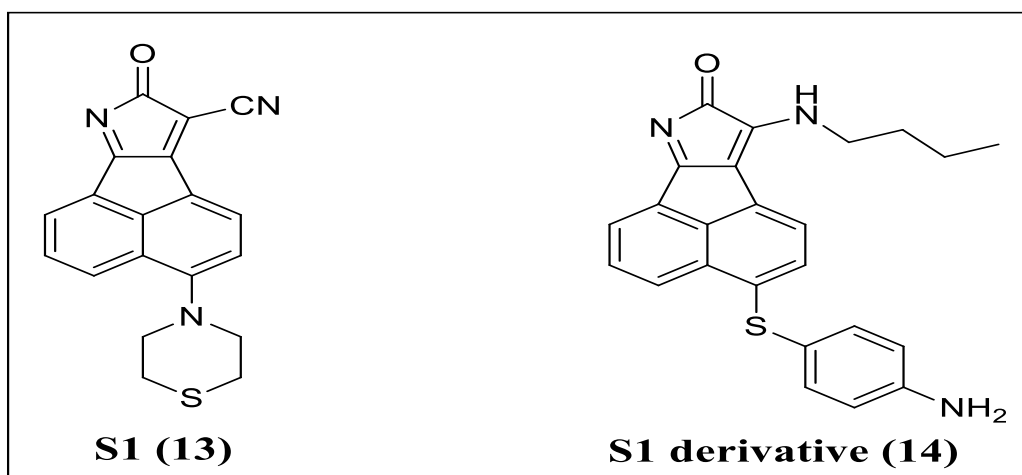


Fig. 7. S1 and S1 derivative, Pan- BCL-2 inhibitors

More recently, Zhang and coworkers discovered two novel MCL-1 selective small-molecule inhibitors based on SAR and screening studies of several S1 derivatives. The first one is

compound (16), which binds MCL-1 with K_d value of 160 nM and the second one is compound (17), which inhibits MCL-1 with an IC_{50} value of 54 nM [49, 50] (Fig. 8).

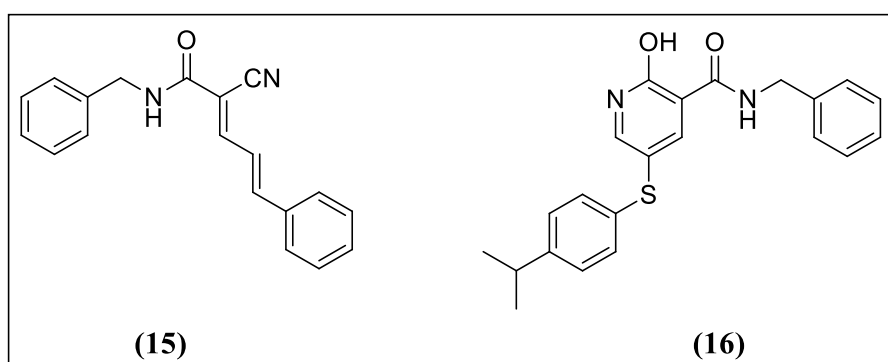


Fig. 8. Selective MCL-1 inhibitors based on S1 (13) compound

3.6. N-(4-hydroxy naphthalen-1-yl) aryl sulfonamide based inhibitors

This class of MCL-1 inhibitors was developed by Nikolovska-Coleska's laboratory using fluorescence polarization high throughput screening approaches. UMI-59 (17) was the first hit identified in this class with a K_i value of 1.55 μ M against MCL-1 [51]. Further structure-based optimization of UMI-59 (17) resulted in a more potent inhibitor (18) with improved K_i value of 180 nM. Additionally, compound (18)

selectively inhibit cell growth and induce apoptosis in MCL-1- dependent leukemia cell lines (HL-60 and MV4-11).

Another inhibitor from this class is UMI-77 (19), which was developed by structure-based modification of UMI-59 (17). UMI-77 (19) binds to MCL-1 with K_i value of 490 nM. Also inhibits cell growth and induces apoptosis in a pancreatic cancer xenograft model (BxPC-3) [52] (Fig. 9).

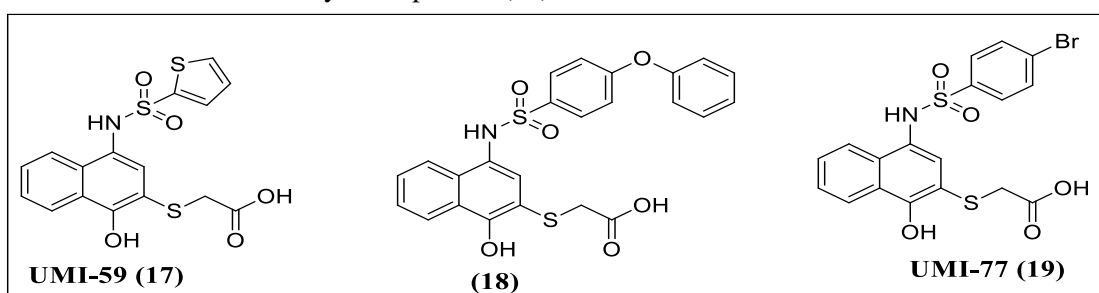


Fig. 9. N-(4-hydroxy naphthalen-1-yl) aryl sulfonamide selective MCL-1 inhibitors

More recently; another potent selective MCL-1 inhibitor (**20**) based on 1-hydroxy-2-naphthoic acid scaffold has been reported with a K_i value of 31 nM [53] (Fig. 10).

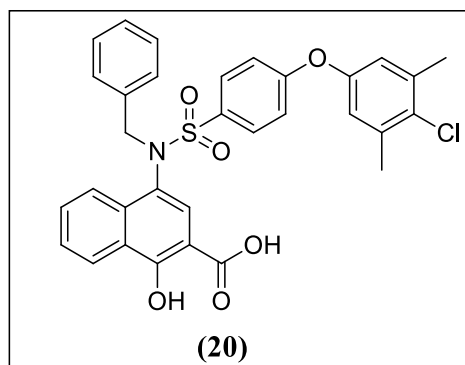


Fig. 10. 1-Hydroxy-2-naphthoic acid-based MCL-1 inhibitor

3.7. 2-(Arylsulfonamido) Benzoate and Salicylate based inhibitors

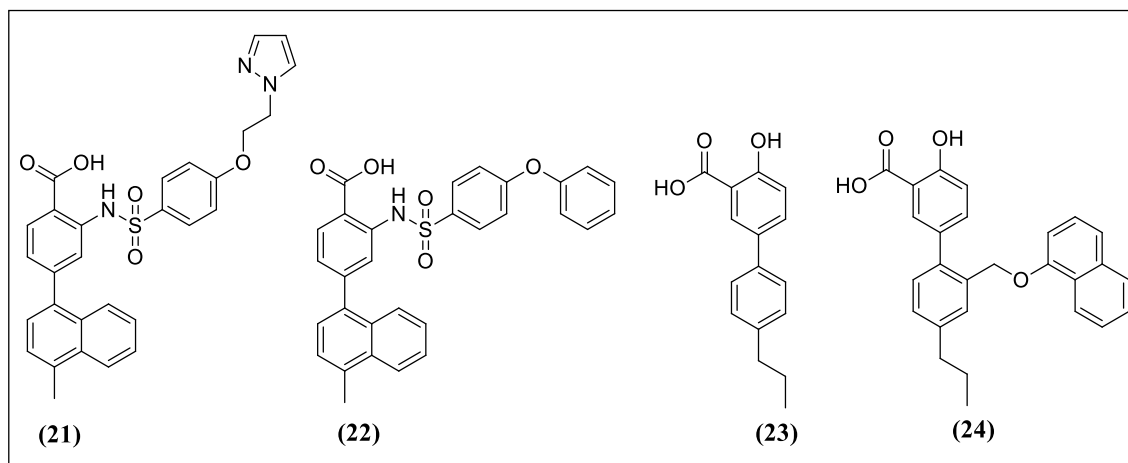


Fig. 11. Aryl sulfonamides and salicylates based MCL-1 inhibitors

3.8. Indol-2- Carboxylic acid-based inhibitors

Recently, several indol-2-carboxylic acid-based MCL-1 inhibitors were reported by AbbVie [55, 56]. This class of inhibitors sharing a structural similarity with Fesik's inhibitors with additional chain linked to the indole and benzene rings.

A-1210477 (**25**), (Fig. 12) is the most potent and selective inhibitor identified in this class, it inhibits MCL-1 with an IC_{50} value of 26.2 nM and exhibits a higher binding affinity and selectivity over other anti-apoptotic proteins. Several studies have demonstrated that A-1210477 inhibits MCL-1 dependent cells and triggers apoptosis in non-small-cell lung cancer cell lines. Additionally, it has an excellent synergistic

effect when combined with Navitoclax (**2**) in different cancer cell lines [55 - 57].

An NMR-based fragment-screening assay has been utilized to screen a fragment library for the discovery of new selective MCL-1 inhibitors. This assay resulted in the identification of two groups of MCL-1 inhibitors which considered as hits for further optimization, the first one based on aryl sulfonamides and the second one based on salicylates scaffold [54] (Fig. 11). Structure-based optimization of the initially discovered hits led to the identification of compound (**21**) which inhibits MCL-1 with an IC_{50} value of 30 nM, representing the most potent inhibitor in this class. Another analog was compound (**22**), which has an IC_{50} value of 500 nM [54]. Similarly, Structure-based rational optimization along with molecular modeling studies led to the identification of salicylate inhibitors (**23**) and (**24**). Salicylates inhibitor (**24**) is considered the most potent with IC_{50} values of 0.57 μ M [54].

effect when combined with Navitoclax (**2**) in different cancer cell lines [55 - 57].

VU-661013 (**26**) is another indole based MCL-1 inhibitor, which was discovered by the use of fragment-based approaches and structure optimization of compounds in this series. It selectively inhibits MCL-1 with a K_i value of 97 pM. *In vitro* studies have shown that its ability to kill cells by induction of apoptosis with an IC_{50} value of 150 nM in a set of AML cell lines. Moreover, *in vivo* studies revealed that VU-661013 (**26**) has synergistic anti-tumor activity in combination with Ventoclax (**3**) in several mice xenograft models of AML [57-59].

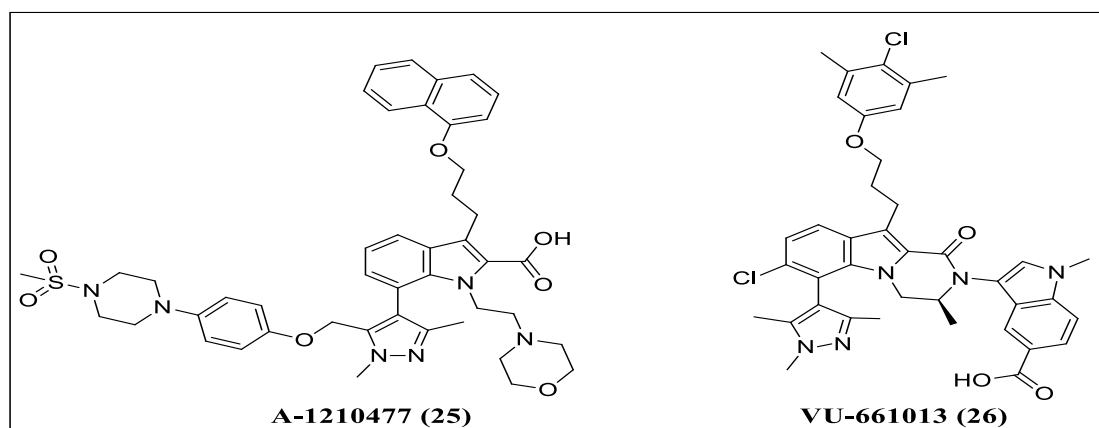


Fig. 12. Indol-2- Carboxylic acid-based MCL-1 inhibitors

Table 1. Selective MCL-1 inhibitors in clinical trials [57]

MCL-1 inhibitor	Phase	Disease	NCT number
MIK665/S64315 (28)	Phase I	Lymphoma or Multiple myeloma Acute myeloid leukemia	NCT02992483 NCT02979366
AMG -176 (29)	Phase I	Acute myeloid leukemia Multiple myeloma	NCT02675452
AZD5991 (30)	Phase I	Hematological malignancies	NCT03218683

3.9. Miscellaneous selective MCL-1 inhibitors

Recently, several potent and selective small-molecule MCL-1 inhibitors have been reported, few inhibitors have advanced into early-stage clinical trials [57] (Table. 1) including:

3.9.1. S63845 (27)

It is a highly potent and selective MCL-1 inhibitor, which was discovered by collaboration between Servier and Vernalis. It exhibits a high-affinity binding with a K_d value of .19 nM. It exhibits a potent anti-tumor activity in different cancer cell lines as well as in animal models [60, 61]. Its combination with Ventoclast (3) has demonstrated an excellent anti-tumor activity on a panel of patient-derived xenografts models of MCL [62] (Fig. 13).

3.9.2. MIK665/S64315 (28)

Although It is an analog to S63845 (27), there is a very little about S64315 (28) data has been revealed. It has been launched into 2 clinical trials (phase I), the first one is to be used in a patient with acute myeloid leukemia and the other one is to be used in patients with lymphoma or multiple myeloma to evaluate its tolerated dose and toxicity [61] (Fig. 13).

3.9.3. AMG176 (29)

It was discovered by Amgen following a screening of a large library of compounds and structure-based lead optimization. It is a selective MCL-1 inhibitor with a K_i value of ≤ 1 nM. Presently, it is evaluated in phase I clinical trials in patients with myeloid leukemia [63] (Fig. 13).

3.9.4. AZD5991 (30)

It is a potent and selective MCL-1 inhibitor with an IC_{50} value of 10 nM, which is discovered by AstraZeneca. Currently, it is evaluated in phase I clinical trials in patients with hematological malignancies [64, 65] (Fig. 13).

Conclusion

In summary, MCL-1 is a member of the anti-apoptotic BCL-2 family of proteins; its overexpression was implicated in various human tumors and hematological cancers and the emerging resistance to different anti-cancer agents, making it a very promising target in cancer therapy development. In recent years, a great effort was focused to develop potent and selective small-molecule MCL-1 inhibitors that culminated in the discovery of several selective

inhibitors from different chemical classes with promising preclinical activity. Currently, some of these inhibitors are undergoing early-stage clinical trials that may culminate in a novel approved selective MCL-1

inhibitor. Making, MCL-1 selective small molecule inhibitors, valuable and promising agents in cancer therapy.

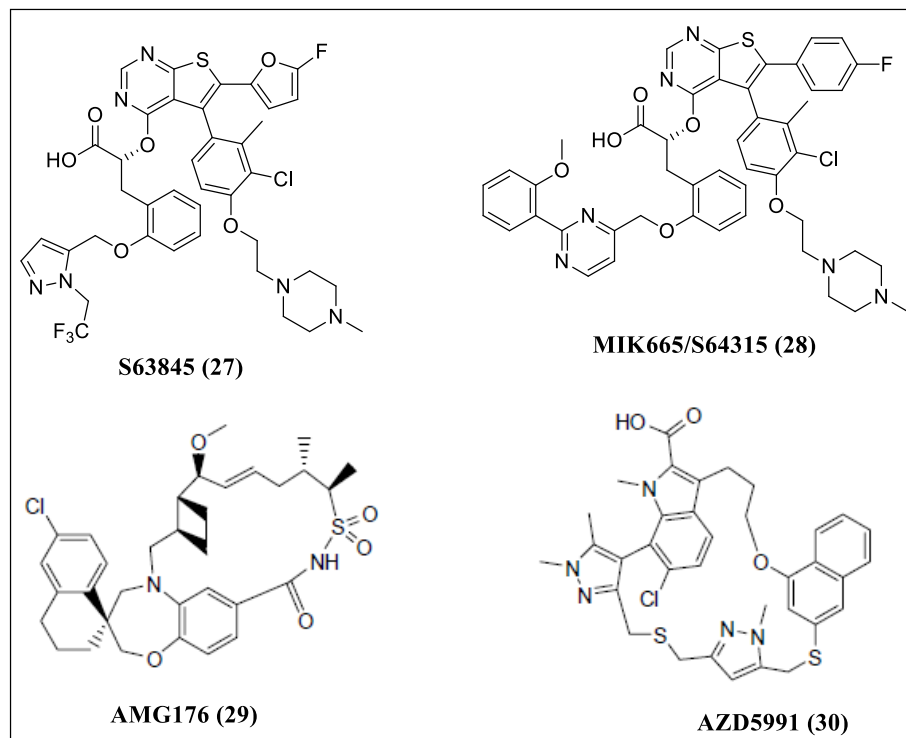


Fig. 13. Miscellaneous selective MCL-1 inhibitors

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

The authors declare that no competing interests exist.

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Authors' contributions

The manuscript was drafted and written by Hoda S. Ibrahim, Deena S. Lasheen, Rabah A. Taha and Dalal A. Abou El Ella have provided comments and contributed to revising the manuscript. All authors have read and approved the final manuscript.

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