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Small molecules targeting Mcl-1: The search for a silver bullet in cancer therapy†

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Mcl-1 (Myeloid-cell-leukemia-sequence-1) is a pro-survival member of the Bcl-2 family of proteins. Mcl-1 has been shown to be critical to the survival of a variety of cancer cells and to mediate resistance to conventional and targeted chemotherapeutics. Whilst potent and selective small molecule inhibitors of Bcl-2 and Bcl-X_L have been developed, the discovery of selective inhibitors of Mcl-1 has proven more problematic and only very recently have potent and selective inhibitors been described. In this review we outline key features of Mcl-1 biology, and chemical approaches and outcomes of inhibiting this important survival protein for the treatment of cancers.

Introduction

Apoptosis is an elegant and highly ordered process of cell removal that occurs in normal development and tissue homeostasis.[1, 2] Cells can be programmed to undergo apoptosis by death receptors (known as the extrinsic pathway) or disruption of mitochondrial integrity (the intrinsic pathway), with both routes leading to activation of caspases which irreversibly execute cell death.[3] In the context of cancer, cells can hijack these inherent pro-survival mechanisms to escape elimination,[4] and thus, evasion of apoptosis is defined as a hallmark of cancer.[3] Significant effort has therefore been invested into finding inducers of apoptosis for treatment of cancer.

The key regulators of the intrinsic apoptosis pathway belong to the Bcl-2 protein family, which comprise pro-survival and pro-apoptotic sets of proteins (**Figure 1**).[5] The *pro-survival* proteins consist of Bcl-2 and the homologs Bcl-X_L, Bcl-w, Bcl-2 A1, and Mcl-1. The *pro-apoptotic* proteins are categorised into two groups: the BH3-only proteins including Bim, Noxa, Puma, Bid and Bik (the sensors of apoptosis stimuli); and the multidomain proteins Bax, Bak and Bok.[6,7]

The BH3 domain residing in the apoptotic proteins plays a critical role, not only in defining affinity and specificity for binding to the pro-survival partners, but also in effecting cell-killing.[8] Thus, in response to apoptotic signals, pairing of the BH3-only proteins with pro-survival proteins releases the death effectors Bax and Bak. Oligomerization of these two proteins drives permeabilization of the mitochondrial outer membrane leading to cytochrome *c* release into the cytosol, activation of caspase 3 (via formation of the apoptosome complex) and thence the downstream caspase-cleavage cascade. This sequence of events is the signature of cells undergoing apoptosis *via* the intrinsic pathway.[9]

Dysregulation of the cellular levels of pro-survival proteins is the main mechanism for evasion of apoptosis, and drugs inhibiting the pro-survival activity of Bcl-2 proteins to restore cell death may therefore be valuable as cancer therapeutics. As a consequence the discovery of small molecules which either structurally or functionally mimic BH3-only proteins has been a significant focus in recent years.[10,11] The discovery of ABT-737, a potent tool compound antagonising Bcl-2, Bcl-w

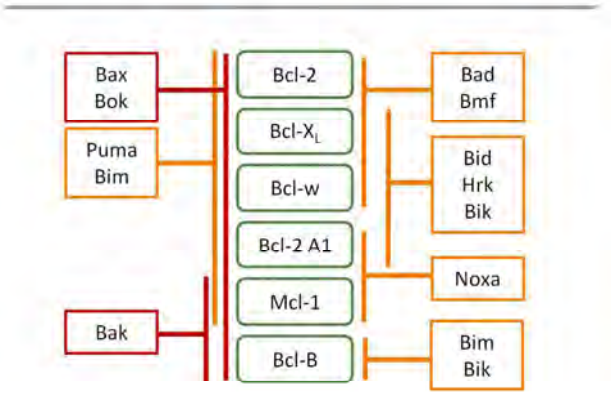

Figure 1. BCL-2 family proteins and the selectivity of their interactions. Initiators of apoptosis in orange; guardians in green; and, effectors of apoptosis in red.

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and Bcl-X_L represented a landmark achievement in this field.[12] The subsequent development of clinical candidates ABT-263 (navitoclax)[13] (Bcl-2/Bcl-X_L inhibitor) and ABT-199/GDC-0199 (venetoclax)[14] (selective Bcl-2 inhibitor), and the probe Bcl-X_L inhibitors WEHI-539,[15] A-1155463[16] and A-1331852,[17] have demonstrated the potential of highly potent small molecules targeting Bcl-2 proteins as cancer therapeutics.[18-21]

The development of equally potent BH3 mimetics specific for Mcl-1, however, has been slower despite its clear role in cancer progression and drug resistance (vide infra). This is in part a consequence of the binding site for Mcl-1 which is predicted to be shallower and less flexible.[22] Nevertheless, Mcl-1 inhibitors from various chemotypes and with differing properties with respect to potency, selectivity and efficacy, have been reported in the literature. In this review we critically assess compounds that have been reported to directly inhibit MCL-1's pro-survival activity[23] and discuss those compounds that are bona fide Mcl-1 inhibitors and those that are suitable leads for further medicinal chemistry optimization.

Role of Mcl-1 in cancer and therapeutic potential of targeting Mcl-1

Increased levels of Mcl-1 protein have been implicated in the initiation and maintenance in both haematological cancers and solid tumours. Thus, there is expanding literature which documents the pivotal role of Mcl-1 in haematological malignancies including acute myeloid leukaemia (AML),[24] multiple myeloma (MM),[25] and acute lymphoblastic lymphoma (ALL)[26] amongst others.[26, 27] The seminal study by Glaser *et.al* demonstrated that genetic deletion of one Mcl-1 allele in AML-reconstituted mice was sufficient to eradicate AML cells whereas blocking other pro-survival proteins, including Bcl-2 and Bcl-X_L, was not.[24] Amplification of Mcl-1 was also shown to be prerequisite to transform and sustain leukemic B cells expressing BCR-ABL fusion, a form of ALL with poor treatment outcome.[28] Although a critical role for Mcl-1 in development and maintenance of solid tumours has not been definitively established, knockdown of Mcl-1 with siRNA has been reported to induce apoptosis in prostate[29] and pancreatic[30] cell lines amongst others.[31] High-resolution analysis of somatic copy-number alterations from human cancer specimens identified amplifications in the *MCL1* gene in 10.9% of cancers including breast and lung cancer.[32] These findings indicate that targeting Mcl-1 to combat these cancers may be beneficial.

A role for Mcl-1 in chemoresistance has also been demonstrated. For example, cancer cells may hijack Mcl-1 to survive when other pro-survival Bcl-2 proteins have been blocked. Upregulation of Mcl-1 has been observed in various cancer cell lines that have developed resistance to ABT-263 and ABT-737.[33-35] Further, elevated levels of Mcl-1 have been documented following genotoxic drug treatments of patients with chronic lymphocytic leukemia (CLL) and correlated with increased cell viability and consequently relapse and treatment failure.[36-38] Over-expression of Mcl-1 has been attributed to the failure of solid tumour cell lines to undergo chemotherapy-induced senescence,[39] whilst gene silencing of Mcl-1 has been shown to circumvent drug-resistance in glioblastoma,[40] colon cancer and lung cancer in preclinical models.[41] Taken together, these data indicate that effective targeting of Mcl-1 may address mechanisms of relapse and chemo-resistance which are significant obstacles in effective cancer treatment.

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Small molecule antagonists of Mcl-1

This review discusses Mcl-1 inhibitors reported in the peer-reviewed literature up to mid-2015. We have assessed each compound series based on published data and assessed compounds based on their biochemical and cellular data with particular focus on cellular potency and selectivity. In addition, chemical structures and functionality known to be reactive or lead to assay artefacts are also flagged.[42]

Peptide and oligomeric inhibitors

The successful design of non-natural peptides (foldamers) as mimetics of the BH3-only pro-apoptotic proteins to engage the apoptotic response has recently been demonstrated.[24, 43] A Bim variant, Bimα_s2A and a Puma-like peptide with high affinity for Mcl-1, were able to elicit apoptosis in AML and MEF cell lines.[24, 43] Stapled peptides based on the BH3 template of Noxa, exploiting the inherent specificity of this BH3-only protein towards Mcl-1, have been reported to possess enhanced stability and cell penetration.[44, 45] The activity of these peptide inhibitors to induce Bax/Bak dependent apoptosis[44] lends support to the specificity of this type of antagonist, however the role of the staple in the activity of these compounds has been questioned.[46]

Oligomeric small molecules that act as α-helix mimetics have also been reported, such as the water-soluble oligoamide JY-1-106 (**1**) (**Figure 2**) which weakly neutralized Mcl-1 at low micromolar ranges.[47] JY- 1- 1061) was able to disrupt Mcl- 1/Bak dimers, restore apoptosis and inhibit tumour growth in a lung cancer xenograft mouse model with no apparent toxicity issues.[48]

JY-1-106 and other similar terphenyl compounds are designed to replicate the side chain trajectory of an ideal isolated α-helix, however, as the actual conformation of the compounds in the cellular milieu may be different, the mechanism of action of these molecules needs further validation.

Pan inhibitors of pro-survival proteins

A number of the BH3 mimetics developed to date possess measurable binding affinity against Mcl-1 (**Table 1**).

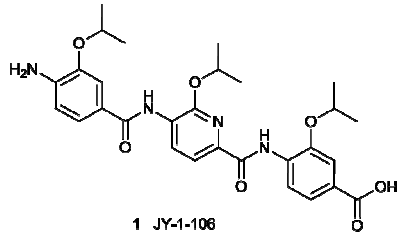

Figure 2. Pan inhibitor JY-1-106 (**1**)[55]

Table 1. Binding affinity of pan-inhibitors of members of Bcl-2 family

Compound	In vitro activity (K_i, μM)[a]			Ref
	Mcl-1	Bcl-2	Bcl-X_L	
ABT-737	>1[a]	0.12	0.064	13
ABT-263	0.5[a]	<0.001	<0.0005	13
ABT-199	>0.444	<0.0001	0.048	14
2a (-)-Gossypol	1.75[a]	0.28[a]	3.03[a]	49,50
2b (-)-Apogossypol	2.60	2.80	3.69	55
2c BI79C1	0.20[a]	0.32[a]	0.31[a]	56
3 Obatoclax	2.90[a]	1.11[a]	4.69[a]	60,66
4 BI112D1	0.025[a]	0.031[a]	0.076[a]	56,57
5a	4.10	0.76	1.50	23
5b	3.11	0.80	1.27	
6 (S1)	0.058	0.310		45,68
7a	0.050	0.190	0.165	72
7b	0.010	0.020	0.018	
8	0.160	-	-	71
9 DCBL55	6.4	3.1	3.4	73
10 BCL-LZH 40	0.2	0.53	0.017	76
13	0.088[a]	-	0.0037[a]	78

[a]Values were obtained under different experimental conditions. Comparison of absolute affinities may be misleading. [b]IC_{50} value

*Pan BH3-mimetics in clinical studies (**Figure 3**):* Gossypol **2a** and obatoclax **3** are the only two pan Bcl-2 inhibitors reported to antagonise Mcl-1 that have advanced to phase II clinical trials. Isolated from the plant *Gossypium*, (-)-Gossypol (AT-101) (**1a**) binds Bcl-X_L, Bcl-2, Mcl-1 and Bcl-w at low micromolar affinity and induces apoptosis in various human cancer cell lines.[49-53] Despite the potency reported for **2a** and its derivatives such as apogossypol (**2b-c**) and apogossypolone BI112D1 (**4**),[54, 55, 56] the cytotoxicity is not wholly Mcl-1 dependent as these compounds were active on Bax/Bak deficient fibroblasts.[57,58] Given that Bax/Bak are essential for cells to undergo apoptosis via the intrinsic pathway,[59] this outcome suggests that the single-agent efficacy effects observed in transformed cells are not solely due to inhibition of pro-survival proteins.[60, 61] Likewise, obatoclax (**3**), which displays a similar binding profile to **2a**,[62] also killed Bax/Bak deficient fibroblasts again indicating off-target effects.[58, 63, 64] In clinical studies in patients with AML, ALL and CLL both **2a** and **3** have not demonstrated significant benefit due to dose limiting toxicity that may be a consequence of their non-selectivity.[65, 66]

*Pan BH3-mimetics in pre-clinical development (**Figures 4, 5**):* The compound series **5**, a truncated version of ABT-737, was designed to mimic the trajectory of two key residues of the BH3-only protein Bim.[22] These compounds were weakly active and exhibited low micromolar affinity to Mcl-1 in binding assays while cellular cytotoxicity was observed only at very high concentrations (IC_{50} 10-40 μM).[67] The planar heterocyclic compound S1 (**6**) was reported to potently neutralize both Bcl-2 and Mcl-1 and mediate Bax/Bak dependent apoptosis *in vivo*;[45, 68, 69] however, subsequent studies indicated that induction of Noxa was responsible for the cell death response.[70] Moreover, although related systems **7a-b** and the acyclic cyanoacrylamide **8**,[71] derived from **6**,[72] were reported to possess sub-micromolar binding affinity towards Mcl-1, further studies are required to validate their activity as bona fide BH3-mimetics. Compound **9**, identified from virtual screening as a moderate Mcl-1 binder,[73] was shown to induce cell death *via* mechanisms unrelated to pro-survival proteins,[73] possibly in part related to the reactive rhodanine-like scaffold present in this compound.[74, 75] In light of this data, the related compound BCL-LZH 40 (**10**), reported as a nanomolar Mcl-1 inhibitor [76, 77] requires further investigation in cellular systems. Tanaka and colleagues prepared pyrazolopyridine **11** which was found to bind to Mcl-1 with submicromolar potency (IC_{50}

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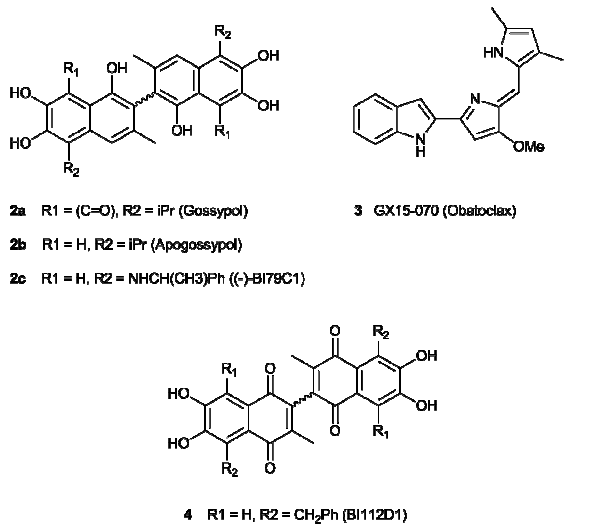

Figure 3: Clinically studied pan inhibitors of Bcl-2 proteins and their derivatives

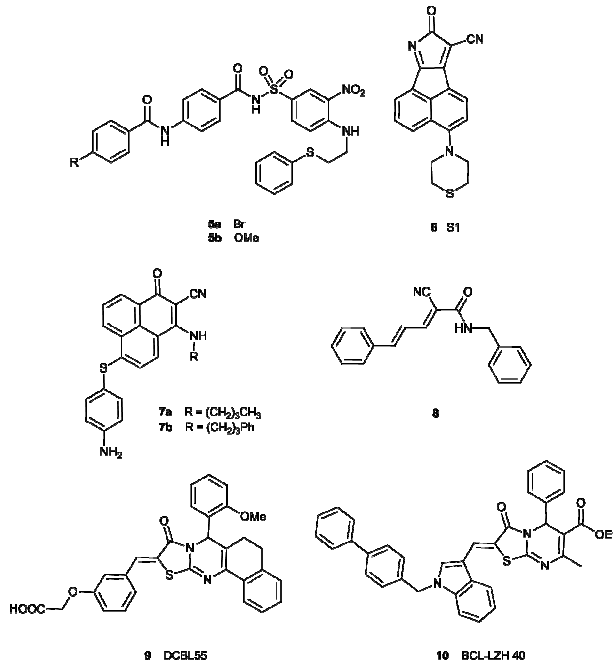

Figure 4: Pan-inhibitors in preclinical development

0.54 µM).[78] Binding studies of fragments of ABT-263 led to the selection of acylsulfonamide **12** (IC_{50} 0.15µM) for the development of hybrid structures as dual Mcl-1/Bcl-X_L inhibitors. Thus, the pyrazolopyridine fragment of **11** was joined to **12** *via* a linker (**Figure 5**). This resulted in the discovery of **13** which exhibits 6-fold and 40-fold enhancement in binding affinity towards Mcl-1 and Bcl-X_L, respectively, over the individual components.

Selective inhibitors of Mcl-1

Preclinical and clinical studies of the dual Bcl-2/Bcl-X_L inhibitor ABT-263 indicate that inhibition of Bcl-X_L results in toxicity to platelets.[14,79] The development of Mcl-1 inhibitors with improved selectivity over Bcl-X_L should therefore avoid this side effect. Despite the topological and sequence similarity between Mcl-1 and the other Bcl-2 family members, the nature of the binding groove of Mcl-1 appears to be more open and less flexible compared to the other pro-survival proteins.[22] A tabulation of reported selective small-molecule antagonists of Mcl-1 is presented in **Table 2**.

Compounds identified from chemical screening (***Figure 6***): Screening for small molecules selectively disrupting Mcl-1–BH3 peptide complexes have identified potential Mcl-1 antagonists of varied chemotypes from libraries of natural and synthetic compounds. The plant metabolite gambogic acid (**14**)[80] and the marine *Streptomyces* metabolite, marinopyrrole A (referred to as maritoclax) (**15a**), displaced the counterpart Bim-BH3 peptide from Mcl-1 more effectively than from other Bcl-2 homologs.[81, 82] Inhibition of tumour angiogenesis has been reported for gambogic acid (**14**) in xenograft models of prostate and glioma malignancies with few side effects.[80] Treatment of Mcl-1 dependent human leukaemia[82] and melanoma[83] cell lines with **15a** led to caspase-dependent apoptosis. Elaborated marinopyrrole analogues, such as **15c**,[84] also possess low micromolar binding affinity for Mcl-1, as do the cyclic analogues **16a,b**.[85,86] Both **14** and **15a**, however, have displayed additional activities, namely proteasome associated mechanisms responsible for modulation of Mcl-1 levels that interestingly may synergise with their primary effects on Mcl-1 binding.[83, 87, 88]

Library screening has also led to the discovery of the thiazolyl derivative Mcl-1 inhibitor molecule 1 (MIM-1) **17**[89] and the hydroxyquinoline **18**.[90] Initial reports documented that these compounds preferentially disrupted Mcl-1/Bax and Mcl-1/Bim heterodimers compared to the corresponding Bcl-X_L dimers. In cellular assays, only modest activities were observed for the putative Mcl-1 inhibitor **17**, although the apoptosis observed was Bax/Bak dependent implying selectivity for Mcl-1.[57, 89] The high concentrations of these compounds required to elicit apoptosis does not preclude the possibility of off-target driven cellular toxicity. For example, the structural features of **17** and **18**, particularly their ability to chelate metals and generate

Table 2: Binding affinity (FP-based assay) of reported selective Mcl-1 antagonists

Compound	Activity (IC_{50}, µM)	Ref
Compounds identified from chemical screening		
14 Gambogic acid	0.79	80
15a	10	81-83
16a	1.4[a]	85
17 MIM-1	4.78	89
18	0.31	90
Compounds identified from structure-guided hit-to-lead optimization		
19 Tw-37	0.26	50
20a UMI-77	1.87[b]	94
20b-d	0.17-0.29	94
21a	6.9	96,97
21b	8	
Compounds derived from fragment-based screening		
22	0.18 (66% inhibition)[b]	100
23	0.03	101
25a	0.05-35[b]	102
25b	0.12- 1.6[b]	
26a	0.00043[c]	103
26b	0.00045[c]	

[a]ELISA assay IC_{50} value. [b]K_i value from Fluorescence Polarization-based assay. [c]K_i value from TR-FRET assay

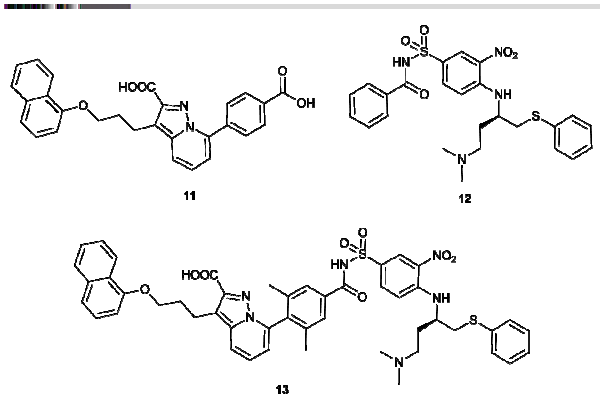

Figure 5: Hybrid compound 12 as dual Bcl-xL/Mcl-1 inhibitor and component parts

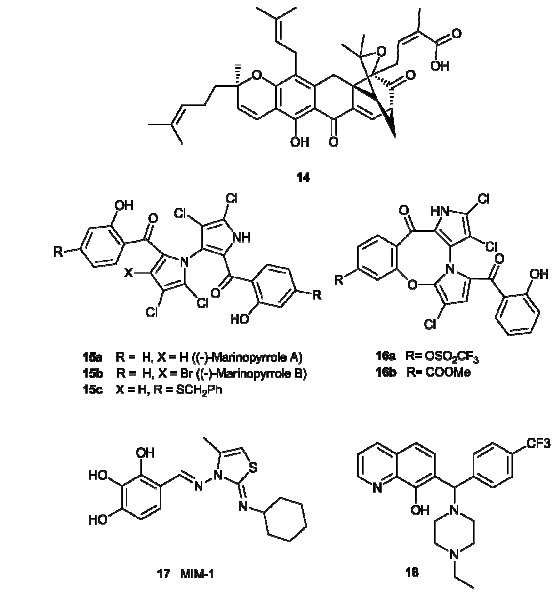

Figure 6: Mcl-1 inhibitors identified from chemical screening and SAR optimization

redox active species[91,92] may result in other biological activities, and therefore further validation is necessary to confirm their function as a bona fide BH3-mimetics.[74]

Compounds identified from structure-guided hit-to-lead optimization (***Figure 7***): Several compounds from structure-guided hit-to-lead optimization programs have been reported to be specific Mcl-1 inhibitors. The benzenesulfonyl derivative TW-37 (**19**) was discovered using computational-aided design and NMR studies, inspired by molecular docking of (-)-Gossypol (**2a**).[48] Compound **19** displaced Bax and t-Bid from human recombinant Mcl-1 and Bcl-2 with comparable binding affinity (<0.3 μM)[93] but induced Bax/Bak dependent apoptosis only in Mcl-1 dependent cell lines.[57] Although the high concentration required (≥10 μM) is sub-optimal for therapeutic application, **19** may serve as a valuable lead for further optimization of Mcl-1 selective inhibitors. In competition assays with fluorescently labelled Bid-BH3 peptide and recombinant Bax, UMI-77 (**20a**) selectively bound to Mcl-1 and also disrupted Mcl-1:Noxa dimers in cell lysate.[94] Compound **20a** induced apoptosis in pancreatic cancer cell lines with high Mcl-1 expression whereas the compound was less active in Bcl-X_L-amplified or Mcl-1 silenced cell lines.[94] Treatment with **20a** also caused more cell death in wild-type than in Bax/Bak double knockout (DKO) MEFs (60% *versus* 16%). These results support that the compound does indeed act as an Mcl-1 inhibitor; however its activity in Mcl-1 deficient cells, Bax/Bak DKO and wild-type MEFs indicates that additional mechanisms of action are contributing to its cytotoxicity. Exploiting an ionic interaction between **20a** and an additional hydrophobic pocket of Mcl-1 afforded high nanomolar binders **20b-d**. Their efficacies were confirmed in apoptosis assays where both analogues induced Bax/Bak-dependent cell death, accompanied by caspase activation in human AML cell lines and in Eμ-Myc lymphoma cell lines over-expressing Mcl-1 and Bcl-2.[95]

The rhodanine derivatives **21a,b** have also been reported as Mcl-1 inhibitors [96,97] from screening a small library of analogues based on the Bcl-X_L inhibitor BH3I-1;[98] however, as stated previously, the potential issues with rhodanine derivatives raises concerns over the usefulness of these compounds as drug leads.[75,99]

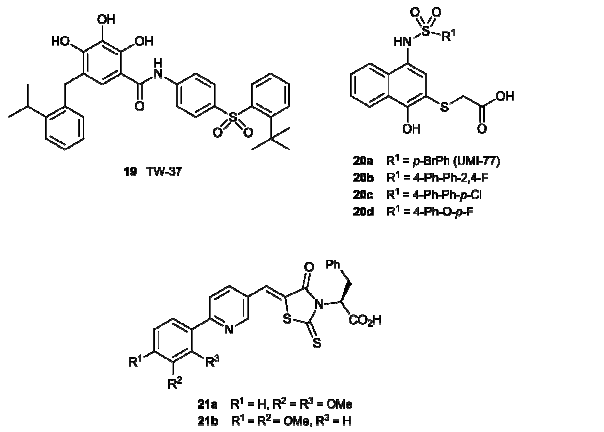

Figure 7: Mcl-1 inhibitors developed by structure-guided hit to lead optimization

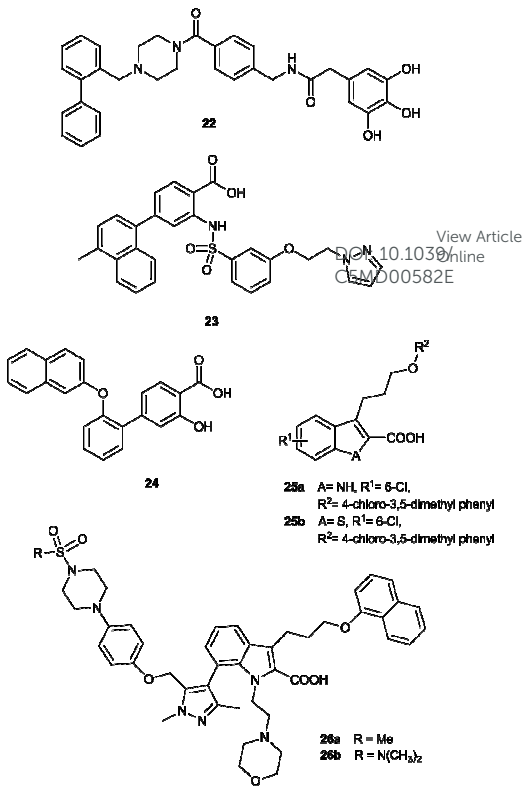

Figure 8: Mcl-1 inhibitors developed by fragment-based screening

Compounds derived from fragment-based-screening (***Figure 8***): Several research groups have undertaken fragment-based screens to identify selective Mcl-1 inhibitors. The benzylpiperazines, such as **22** (IC_{50} 0.18 μM), inhibited Mcl-1 without cross-binding to Bcl-2 and Bcl-X_L.[100] Similar potencies were observed for compounds identified from an NMR-based fragment screening study that identified two promising scaffolds represented by the arylsulfonamide **23** (IC_{50} 0.03 μM) and salicyclic acid **24** (IC_{50} 0.57 μM). The naphthyl moiety of **24** occupied the same space as the conserved isoleucine residue of Bim, Noxa and Puma as determined by X-ray crystallography.[101] An alternate hit series which displayed Mcl-1 selectivity are the indoles (e.g. **25a**) and benzothiophenes (e.g. **25b**).[102] Cellular activity of these compounds has, however, not been reported. Researchers at AbbVie have studied related systems based on the indole-2-carboxylic scaffold and have obtained significant potency improvements with the sulfonamides **26a,b** that possess picomolar Mcl-1 inhibition.[103] Importantly, these compounds induce the hallmarks of apoptosis in Mcl-1 dependent cell lines without cytotoxicity in MEF cells lacking Bax/Bak.[104] In addition, synergy was observed with co-administration of **26b** and ABT-263, to effectively kill a panel of cell lines expressing both Bcl-X_L and Mcl-1.[104] These results indicate that **26a,b** satisfy the characteristics of true BH3-mimetics and further study across a range of cell types will demonstrate the therapeutic potential of these agents in various cancers. Unfortunately these

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compounds show only low micromolar activity against Mcl-1 dependent cells presumably as a result of their zwitter-ionic nature possibly limiting cellular permeability and through high plasma-protein binding.

Targeting Mcl-1 Regulation

Mcl-1 is differentiated from other Bcl-2 family members in its regulation pathway (short half-life, degradation/stabilization mechanism) which also offers the opportunity to indirectly target this protein. Whilst beyond the scope of this review, small molecule inhibitors of both natural and synthetic origin have been reported to possess Mcl-1 dependent cellular cytotoxicity through these mechanisms. Examples include inhibitors of kinases involved in transcription such as CDK7 and CDK9;[105] spliceosome inhibitors such as the natural product FR901464;[106] and blocking Mcl-1 translation through inhibition of kinases such as Mnk1/2 and mTOR[107] or via inhibiting translation initiation with the natural product silvestrol and analogues.[108, 109]

Conclusions

Amplification of Mcl-1 expression has been implicated in commitment to transformation, maintenance of malignant cells, as well as drug resistance in various cancers. The discovery of potent and selective BH3-mimetic Mcl-1 antagonists is a significant drug design challenge. The recent disclosure of the potent Mcl-1 inhibitors **26a** and **26b** that possess selective activities within cells represents the current state-of-the-art and demonstrates that design of such compounds is indeed feasible.

As Mcl-1 plays a pivotal role in both normal and malignant cells, targeting Mcl-1 may be a double-edged sword. Recent publications have shown that genetic deletion of Mcl-1 in cardiomyocytes in mice results in impaired autophagy and mitochondria dysfunction, manifested by fatal heart failure.[110, 111] In addition, immunosuppressive regulatory T cells require Mcl-1 for survival and ablation of Mcl-1 causes lethal autoimmune disease.[112] Neutrophils are similarly also highly sensitive to Mcl-1 depletion.[113] Taken together, these findings indicate that clinical deployment of Mcl-1 inhibitors may be associated with significant on-target toxicity. Further study with potent and selective Mcl-1 inhibitors such as **26a,b** will clearly allow a greater understanding of the therapeutic potential of these agents and the potential toxicities associated with their use.

Acknowledgements

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Notes and references

1. P. M. Henson and D. A. Hume, *Trends Immunol.*, 2006, **27**, 244-250.
2. H. E. Abud, *Cell Death Differ.*, 2004, **11**, 797-799.
3. S. Fulda, *Front. Oncol.*, 2011, **1**, 23.
4. S. L. Floor, J. E. Dumont, C. Maenhaut and E. Raspe, *Trends Mol. Med.*, 2012, **18**, 509-515.
5. P. E. Czabotar, G. Lessene, A. Strasser and J. M. Adams, *Nat Rev Mol Cell Biol*, 2014, **15**, 49-63.
6. P. E. Czabotar and G. Lessene, *Curr. Pharm. Des.*, 2010, **16**, 3132-3148.
7. D. Hanahan and R. A. Weinberg, *Cell*, 2011, **144**, 646-674.
8. L. Chen, S. N. Willis, A. Wei, B. J. Smith, J. I. Fletcher, M. G. Hinds, P. M. Colman, C. L. Day, J. M. Adams and D. C. Huang, *Mol. Cell*, 2005, **17**, 393-403.
9. M. J. Roy, A. Vom, P. E. Czabotar and G. Lessene, *Br. J. Pharmacol.*, 2014, **171**, 1973-1987.
10. C. Billard, *Mol. Cell Ther.*, 2013, **12**, 1691-1700.
11. G. Lessene, P. E. Czabotar and P. M. Colman, *Nature Reviews: Drug Discovery*, 2008, **7**, 989-1000.
12. T. Oltersdorf, S. W. Elmore, A. R. Shoemaker, R. C. Armstrong, D. J. Augeri, B. A. Belli, M. Bruncko, T. L. Deckwerth, J. Dinges, P. J. Hajduk, M. K. Joseph, S. Kitada, S. J. Korsmeyer, A. R. Kunzer, A. Letai, C. Li, M. J. Mitten, D. G. Nettesheim, S. Ng, P. M. Nimmer, J. M. O'Connor, A. Oleksijew, A. M. Petros, J. C. Reed, W. Shen, S. K. Tahir, C. B. Thompson, K. J. Tomaselli, B. Wang, M. D. Wendt, H. Zhang, S. W. Fesik and S. H. Rosenberg, *Nature*, 2005, **435**, 677-681.
13. C. Tse, A. R. Shoemaker, J. Adickes, M. G. Anderson, J. Chen, S. Jin, E. F. Johnson, K. C. Marsh, M. J. Mitten, P. Nimmer, L. Roberts, S. K. Tahir, Y. Xiao, X. Yang, H. Zhang, S. Fesik, S. H. Rosenberg and S. W. Elmore, *Cancer Res.*, 2008, **68**, 3421-3428.
14. A. J. Souers, J. D. Leverson, E. R. Boghaert, S. L. Ackler, N. D. Catron, J. Chen, B. D. Dayton, H. Ding, S. H. Enschede, W. J. Fairbrother, D. C. Huang, S. G. Hymowitz, S. Jin, S. L. Khaw, P. J. Kovar, L. T. Lam, J. Lee, H. L. Maecker, K. C. Marsh, K. D. Mason, M. J. Mitten, P. M. Nimmer, A. Oleksijew, C. H. Park, C. M. Park, D. C. Phillips, A. W. Roberts, D. Sampath, J. F. Seymour, M. L. Smith, G. M. Sullivan, S. K. Tahir, C. Tse, M. D. Wendt, Y. Xiao, J. C. Xue, H. Zhang, R. A. Humerickhouse, S. H. Rosenberg and S. W. Elmore, *Nat. Med.*, 2013, **19**, 202-208.
15. G. Lessene, P. E. Czabotar, B. E. Sleebs, K. Zobel, K. N. Lowes, J. M. Adams, J. B. Baell, P. M. Colman, K. Deshayes, W. J. Fairbrother, J. A. Flygare, P. Gibbons, W. J. A. Kersten, S. Kulasegaram, R. M. Moss, J. P. Parisot, B. J. Smith, I. P. Street, H. Yang, D. C. S. Huang and K. G. Watson, *Nat. Chem. Biol.*, 2013, **9**, 390-397.
16. Z.-F. Tao, L. Hasvold, L. Wang, X. Wang, A. M. Petros, C. H. Park, E. R. Boghaert, N. D. Catron, J. Chen, P. M. Colman, P. E. Czabotar, K. Deshayes, W. J. Fairbrother, J. A. Flygare, S. G. Hymowitz, S. Jin, R. A. Judge, M. F. T. Koehler, P. J. Kovar, G.

Lessene, M. J. Mitten, C. O. Ndubaku, P. Nimmer, H. E. Purkey, A. Oleksijew, D. C. Phillips, B. E. Sleebs, B. J. Smith, M. L. Smith, S. K. Tahir, K. G. Watson, Y. Xiao, J. Xue, H. Zhang, K. Zobel, S. H. Rosenberg, C. Tse, J. D. Leverson, S. W. Elmore and A. J. Souers, *ACS Med. Chem. Lett.*, 2014, **5**, 1088-1093.

17. J. D. Leverson, D. C. Phillips, M. J. Mitten, E. R. Boghaert, D. Diaz, S. K. Tahir, L. D. Belmont, P. Nimmer, Y. Xiao, X. M. Ma, K. N. Lowes, P. Kovar, J. Chen, S. Jin, M. Smith, J. Xue, H. Zhang, A. Oleksijew, T. J. Magoc, K. S. Vaidya, D. H. Albert, J. M. Tarrant, N. La, L. Wang, Z. F. Tao, M. D. Wendt, D. Sampath, S. H. Rosenberg, C. Tse, D. C. Huang, W. J. Fairbrother, S. W. Elmore and A. J. Souers, *Sci. Transl. Med.*, 2015, **7**, 279ra240.

18. S. Thomas, B. A. Quinn, S. K. Das, R. Dash, L. Emdad, S. Dasgupta, X.-Y. Wang, P. Dent, J. C. Reed, M. Pellecchia, D. Sarkar and P. B. Fisher, *Expert Opin. Ther. Targets*, 2013, **17**, 61-75.

19. N. Bajwa, C. Liao and Z. Nikolovska-Coleska, *Expert Opin. Ther. Pat.*, 2011, **22**, 37-55.

20. G. Lessene, P. E. Czabotar and P. M. Colman, *Nat. Rev. Drug Discov.*, 2008, **7**, 989-1000.

21. A. S. Azmi, Z. Wang, P. A. Philip, R. M. Mohammad and F. H. Sarkar, *Expert Opin. Emerg. Drugs*, 2011, **16**, 59-70.

22. C. H. Zheng, H. Yang, M. Zhang, S. H. Lu, D. Shi, J. Wang, X. H. Chen, X. H. Ren, J. Liu, J. G. Lv, J. Zhu and Y. J. Zhou, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 39-44.

23. J. Belmar and S. W. Fesik, *Pharmacol. Ther.*, 2015, **145**, 76-84.

24. S. P. Glaser, E. F. Lee, E. Trounson, P. Bouillet, A. Wei, W. D. Fairlie, D. J. Izon, J. Zuber, A. R. Rappaport, M. J. Herold, W. S. Alexander, S. W. Lowe, L. Robb and A. Strasser, *Genes Dev.*, 2012, **26**, 120-125.

25. B. Zhang, *Blood*, 2002, **99**, 1885-1893.

26. G. L. Kelly, S. Grabow, S. P. Glaser, L. Fitzsimmons, B. J. Aubrey, T. Okamoto, L. J. Valente, M. Robati, L. Tai, W. D. Fairlie, E. F. Lee, M. S. Lindstrom, K. G. Wiman, D. C. S. Huang, P. Bouillet, M. Rowe, A. B. Rickinson, M. J. Herold and A. Strasser, *Genes Dev.*, 2014, **28**, 58-70.

27. S. Grabow, A. R. D. Delbridge, L. J. Valente and A. Strasser, *Blood*, 2014, **124**, 3939-3946.

28. B. Koss, J. Morrison, R. M. Perciavalle, H. Singh, J. E. Rehg, R. T. Williams and J. T. Opferman, *Blood*, 2013, **122**, 1587-1598.

29. E. S. Choi, J. Y. Jung, J. S. Lee, J. H. Park, N. P. Cho and S. D. Cho, *Cancer Lett.*, 2013, **328**, 65-72.

30. H. Takahashi, M. C.Chen, H. Pham, Y. Matsuo, H. Ishiguro, H. A. Reber, H. Takeyama, O. J. Hines and G. Eibl, *Biochim. Biophys. Acta*, 2013, **1833**, 2980.

31. M. Modugno, P. Banfi, F. Gasparri, R. Borzilleri, P. Carter, L. Cornelius, M. Gottardis, V. Lee, C. Mapelli, J. G. Naglich, A. Tebben, G. Vite, W. Pastori, C. Albanese, E. Corti, D. Ballinari and A. Galvani, *Exp. Cell Res.*, 2015, **332**, 267-277.

32. R. Beroukhim, C. H. Mermel, D. Porter, G. Wei, S. Raychaudhuri, J. Donovan, J. Barretina, J. S. Boehm, J. Dobson, M. Urashima, K. T. Mc Henry, R. M. Pinchback, A. H. Ligon, Y.-J. Cho, L. Haery, H. Greulich, M. Reich, W. Winckler, M. S. Lawrence, B. A. Weir, K. E. Tanaka, D. Y. Chiang, A. J. Bass, A. Loo, C. Hoffman, J. Prensner, T. Liefeld, Q. Gao, D. Yecies, S. Signoretti, E. Maher, F. J. Kaye, H. Sasaki, J. E. Tepper, J. A. Fletcher, J. Tabernero, J. Baselga, M.-S. Tsao, F. Demichelis, M. A. Rubin, P. A. Janne, M. J. Daly, C. Nucera, R. L. Levine, B. L. Ebert, S. Gabriel, A. K. Rustgi, C. R. Antonescu, M. Ladanyi, A. Letai, L. A. Garraway, M. Loda, D. G. Beer, L. D. True, A. Okamoto, S. L. Pomeroy, S. Singer, T. R. Golub, E. S. Lander, G. Getz, W. R. Sellers and M. Meyerson, *Nature*, 2010, **463**, 899-905.

33. B. Wang, Z. Ni, X. Dai, L. Qin, X. Li, L. Xu, J. Lian and F. He, *Mol. Cancer*, 2014, **13**, 98-98.

34. M. Konopleva, R. Contractor, T. Tsao, I. Samudio, P. P. Ruvolo, S. Kitada, X. Deng, D. Zhai, Y.-X. Shi, T. Sneed, M. Verhaegen, M. Soengas, V. R. Ruvolo, T. McQueen, W. D. Schober, J. C. Watt, T. Jiffar, X. Ling, F. C. Marini, D. Harris, M. Dietrich, Z. Estrov, J. McCubrey, W. S. May, J. C. Reed and M. Andreeff, *Cancer Cell*, 2006, **10**, 375-388.

35. S. Mazumder, G. S. Choudhary, S. Al-Harbi and A. Almasan, *Cancer Res.*, 2012, **72**, 3069-3079.

36. Y. Pei, Q. Gao, J. Li and X. Zhao, *J. Theor. Biol.*, 2014, **360**, 200-207.

37. J. B. Johnston, J. T. Paul, N. J. Neufeld, N. Haney, D. M. Kropp, X. Hu, M. Cheang and S. B. Gibson, *Leuk. Lymphoma*, 2004, **45**, 2017-2027.

38. S. H. Kaufmann, J. E. Karp, P. A. Svingen, S. Krajewski, P. J. Burke, S. D. Gore and J. C. Reed, *Blood*, 1998, **91**, 991-1000.

39. E. Bolesta, L. W. Pfannenstiel, A. Demelash, M. L. Lesniewski, M. Tobin, S. E. Schlanger, S. C. Nallar, J. C. Papadimitriou, D. V. Kalvakolanu and B. R. Gastman, *Mol. Cell. Biol.*, 2012, **32**, 1879-1892.

40. A. C. Murphy, B. Weyhenmeyer, J. Noonan, S. M. Kilbride, S. Schimansky, K. P. Loh, D. Kogel, A. G. Letai, J. H. Prehn and B. M. Murphy, *Apoptosis*, 2014, **19**, 629-642.

41. C. Peddaboina, D. Jupiter, S. Fletcher, J. L. Yap, A. Rai, R. P. Tobin, W. Jiang, P. Rascoe, M. K. Rogers, W. R. Smythe and X. Cao, *BMC Cancer*, 2012, **12**, 541.

42. C. H. Arrowsmith, J. E. Audia, C. Austin, J. Baell, J. Bennett, J. Blagg, C. Bountra, P. E. Brennan, P. J. Brown, M. E. Bunnage, C. Buser-Doepner, R. M. Campbell, A. J. Carter, P. Cohen, R. A. Copeland, B. Cravatt, J. L. Dahlin, D. Dhanak, A. M. Edwards, M. Frederiksen, S. V. Frye, N. Gray, C. E. Grimshaw, D. Hepworth, T. Howe, K. V. M. Huber, J. Jin, S. Knapp, J. D. Kotz, R. G. Kruger, D. Lowe, M. M. Mader, B. Marsden, A. Mueller-Fahrnow, S. Muller, R. C. O'Hagan, J. P. Overington, D. R. Owen, S. H. Rosenberg, R. Ross, B. Roth, M. Schapira, S. L. Schreiber, B. Shoichet, M. Sundstrom, G. Superti-Furga, J. Taunton, L. Toledo-Sherman, C. Walpole, M. A. Walters, T. M. Willson, P. Workman, R. N. Young and W. J. Zuercher, *Nat. Chem. Biol.*, 2015, **11**, 536-541.

43. B. J. Smith, E. F. Lee, J. W. Checco, M. Evangelista, S. H. Gellman and W. D. Fairlie, *ChemBioChem*, 2013, **14**, 1564-1572.

44. M. L. Stewart, E. Fire, A. E. Keating and L. D. Walensky, *Nat. Chem. Biol.*, 2010, **6**, 595-601.

45. Z. Zhang, L. Jin, X. Qian, M. Wei, Y. Wang, J. Wang, Y. Yang, Q. Xu, Y. Xu and F. Liu, *ChemBioChem*, 2007, **8**, 113-121.

46. T. Okamoto, K. Zobel, A. Fedorova, C. Quan, H. Yang, W. J. Fairbrother, D. C. S. Huang, B. J. Smith, K. Deshayes and P. E. Czabotar, *ACS Chem. Biol.*, 2013, **8**, 297-302.

47. X. Cao, J. L. Yap, M. K. Newell-Rogers, C. Peddaboina, W. Jiang, H. T. Papaconstantinou, D. Jupitor, A. Rai, K. Y. Jung, R. P.

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DOI: 10.1039/C5MD00582E
Published Online

Tubin, W. Yu, K. Vanommeslaeghe, P. T. Wilder, A. D. MacKerell, Jr., S. Fletcher and R. W. Smythe, *Mol. Cancer*, 2013, **12**, 42.
48. X. Cao, J. L. Yap, M. K. Newell-Rogers, C. Peddaboina, W. Jiang, H. T. Papaconstantinou, D. Jupitor, A. Rai, K. Y. Jung, R. P. Tubin, W. Yu, K. Vanommeslaeghe, P. T. Wilder, A. D. MacKerell, Jr., S. Fletcher and R. W. Smythe, *Mol. Cancer*, 2013, **12**, 42.
49. Y. Meng, W. Tang, Y. Dai, X. Wu, M. Liu, Q. Ji, M. Ji, K. Pienta, T. Lawrence and L. Xu, *Mol. Cancer Ther.*, 2008, **7**, 2192-2202.
50. G. Wang, Z. Nikolovska-Coleska, C. Y. Yang, R. Wang, G. Tang, J. Guo, S. Shangary, S. Qiu, W. Gao, D. Yang, J. Meagher, J. Stuckey, K. Krajewski, S. Jiang, P. P. Roller, H. O. Abaan, Y. Tomita and S. Wang, *J. Med. Chem.*, 2006, **49**, 6139-6142.
51. J. W. Jaroszewski, O. Kaplan and J. S. Cohen, *Cancer Res.*, 1990, **50**, 6936-6943.
52. M. Zhang, H. Liu, R. Guo, Y. Ling, X. Wu, B. Li, P. P. Roller, S. Wang and D. Yang, *Biochem. Pharmacol.*, 2003, **66**, 93-103.
53. G. P. Tuszynski and G. Cossu, *Cancer Res.*, 1984, **44**, 768-771.
54. S. Kitada, C. L. Kress, M. Krajewska, L. Jia, M. Pellecchia and J. C. Reed, *Blood*, 2008, **111**, 3211-3219.
55. J. Wei, S. Kitada, M. F. Rega, A. Emdadi, H. Yuan, J. Cellitti, J. L. Stebbins, D. Zhai, J. Sun, L. Yang, R. Dahl, Z. Zhang, B. Wu, S. Wang, T. A. Reed, H. G. Wang, N. Lawrence, S. Sebti, J. C. Reed and M. Pellecchia, *Mol. Cell Ther.*, 2009, **8**, 904-913.
56. J. Wei, J. L. Stebbins, S. Kitada, R. Dash, W. Placzek, M. F. Rega, B. Wu, J. Cellitti, D. Zhai, L. Yang, R. Dahl, P. B. Fisher, J. C. Reed and M. Pellecchia, *J. Med. Chem.*, 2010, **53**, 4166-4176.
57. S. Varadarajan, M. Vogler, M. Butterworth, D. Dinsdale, L. D. Walensky and G. M. Cohen, *Cell Death Differ.*, 2013, **20**, 1475-1484.
58. M. F. van Delft, A. H. Wei, K. D. Mason, C. J. Vandenberg, L. Chen, P. E. Czabotar, S. N. Willis, C. L. Scott, C. L. Day, S. Cory, J. M. Adams, A. W. Roberts and D. C. S. Huang, *Cancer Cell*, 2006, **10**, 389-399.
59. G. Dewson and R. M. Kluck, *J. Cell Sci.*, 2009, **122**, 2801-2808.
60. M. Nguyen, R. C. Marcellus, A. Roulston, M. Watson, L. Serfass, S. R. Murthy Madiraju, D. Goulet, J. Viallet, L. Belec, X. Billot, S. Acoca, E. Purisima, A. Wiegmans, L. Cluse, R. W. Johnstone, P. Beauparlant and G. C. Shore, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 19512-19517.
61. S. Trudel, Z. H. Li, J. Rauw, R. E. Tiedemann, X. Y. Wen and A. K. Stewart, *Blood*, 2007, **109**, 5430-5438.
62. K. Daïri, Y. Yao, M. Faley, S. Tripathy, E. Rioux, X. Billot, D. Rabouin, G. Gonzalez, J.-F. Lavallée and G. Attardo, *Org. Process Res. Dev.*, 2007, **11**, 1051-1054.
63. M. Vogler, D. Dinsdale, M. J. Dyer and G. M. Cohen, *Cell Death Differ.*, 2009, **16**, 360-367.
64. M. Konopleva, J. Watt, R. Contractor, T. Tsao, D. Harris, Z. Estrov, W. Bornmann, H. Kantarjian, J. Viallet, I. Samudio and M. Andreeff, *Cancer Res.*, 2008, **68**, 3413-3420.
65. J. W. Jaroszewski, O. Kaplan and J. S. Cohen, *Cancer Res.*, 1990, **50**, 6936-6943.
66. C. A. Goard and A. D. Schimmer, *Core Evid*, 2013, **8**, 15-26.
67. C. H. Zheng, H. Yang, M. Zhang, S. H. Lu, D. Shi, J. Wang, X. H. Chen, X. H. Ren, J. Liu, J. G. Lv, J. Zhu and Y. J. Zhou, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 39-44.
68. Z. Zhang, G. Wu, F. Xie, T. Song and X. Chang, *J. Med. Chem.*, 2011, **54**, 1101-1105.
69. Z. Zhang, T. Song, T. Zhang, J. Gao, G. Wu, L. An and G. Du, *Int. J. Cancer*, 2011, **128**, 1724-1735.
70. T. C. Albershardt, B. L. Salerni, R. S. Soderquist, D. J. Bates, A. A. Pletnev, A. F. Kisselev and A. Eastman, *J. Biol. Chem.*, 2011, **286**, 24882-24895.
71. Z. Zhang, T. Song, X. Li, Z. Wu, Y. Feng, F. Xie, C. Liu, J. Qin and H. Chen, *Eur. J. Med. Chem.*, 2013, **59**, 141-149.
72. T. Song, X. Li, X. Chang, X. Liang, Y. Zhao, G. Wu, S. Xie, P. Su, Z. Wu, Y. Feng and Z. Zhang, *Bioorg. Med. Chem.*, 2013, **21**, 11-20.
73. Y. Feng, X. Ding, T. Chen, L. Chen, F. Liu, X. Jia, X. Luo, X. Shen, K. Chen, H. Jiang, H. Wang, H. Liu and D. Liu, *J. Med. Chem.*, 2010, **53**, 3465-3479.
74. J. B. Baell and G. A. Holloway, *J. Med. Chem.*, 2010, **53**, 2719-2740.
75. T. Tomašić and L. Peterlin Mašič, *Expert Opin. Drug Disc.*, 2012, **7**, 549-560.
76. B. Zhou, X. Li, Y. Li, Y. Xu, Z. Zhang, M. Zhou, X. Zhang, Z. Liu, J. Zhou, C. Cao, B. Yu and R. Wang, *Chemmedchem*, 2011, **6**, 904-921.
77. Y. Xu, M. Zhou, Y. Li, C. Li, Z. Zhang, B. Yu and R. Wang, *Chemmedchem*, 2013, **8**, 1345-1352.
78. Y. Tanaka, K. Aikawa, G. Nishida, M. Homma, S. Sogabe, S. Igaki, Y. Hayano, T. Sameshima, I. Miyahisa, T. Kawamoto, M. Tawada, Y. Imai, M. Inazuka, N. Cho, Y. Imaeda and T. Ishikawa, *J. Med. Chem.*, 2013, **56**, 9635-9645.
79. K. D. Mason, M. R. Carpinelli, J. I. Fletcher, J. E. Collinge, A. A. Hilton, S. Ellis, P. N. Kelly, P. G. Ekert, D. Metcalf, A. W. Roberts, D. C. S. Huang and B. T. Kile, *Cell*, 2007, **128**, 1173-1186.
80. D. Zhai, C. Jin, C.-w. Shiau, S. Kitada, A. C. Satterthwait and J. Reed, *Mol. Cancer Ther.*, 2008, **7**, 1639-1646.
81. C. C. Hughes, A. Prieto-Davo, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 629-631.
82. K. Doi, R. Li, S. S. Sung, H. Wu, Y. Liu, W. Manieri, G. Krishnegowda, A. Awwad, A. Dewey, X. Liu, S. Amin, C. Cheng, Y. Qin, E. Schonbrunn, G. Daughdrill, T. P. Loughran, Jr., S. Sebti and H. G. Wang, *J. Biol. Chem.*, 2012, **287**, 10224-10235.
83. M. K. Pandey, K. Gowda, K. Doi, A. K. Sharma, H. G. Wang and S. Amin, *PLoS One*, 2013, **8**, e78570.
84. R. Li, C. Cheng, M. E. Balasis, Y. Liu, T. P. Garner, K. G. Daniel, J. Li, Y. Qin, E. Gavathiotis and S. M. Sebti, *Eur. J. Med. Chem.*, 2015, **90**, 315-331.
85. C. Cheng, Y. Liu, M. E. Balasis, N. L. Simmons, J. Li, H. Song, L. Pan, Y. Qin, K. C. Nicolaou, S. M. Sebti and R. Li, *Mar. Drugs*, 2014, **12**, 1335-1348.
86. R. Li, *Med. Res. Rev.*, 2016, **36**, 169-189.
87. X. Li, S. Liu, H. Huang, N. Liu, C. Zhao, S. Liao, C. Yang, Y. Liu, C. Zhao, S. Li, X. Lu, C. Liu, L. Guan, K. Zhao, X. Shi, W. Song, P. Zhou, X. Dong, H. Guo, G. Wen, C. Zhang, L. Jiang, N. Ma, B. Li, S. Wang, H. Tan, X. Wang, Q. P. Dou and J. Liu, *Cell Rep*, 2013, **3**, 211-222.
88. J. Eichhorn, S. Alford, C. Hughes, W. Fenical and T. Chambers, *Cell Death Dis.*, 2013, **4**, e880.
89. N. A. Cohen, M. L. Stewart, E. Gavathiotis, J. L. Tepper, S. R. Bruekner, B. Koss, J. T. Opferman and L. D. Walensky, *Chem. Biol.*, 2012, **19**, 1175-1186.

Advance Article Online DOI: 10.1039/C5MD00582E

90. D. J. Richard, R. Lena, T. Bannister, N. Blake, W. E. Pierceall, N. E. Carlson, C. E. Keller, M. Koenig, Y. He, D. Minond, J. Mishra, M. Cameron, T. Spicer, P. Hodder and M. H. Cardone, *Bioorg. Med. Chem.*, 2013, **21**, 6642-6649.
91. V. Prachayasittikul, S. Prachayasittikul, S. Ruchirawat and V. Prachayasittikul, *Drug Des. Devel. Ther.*, 2013, **7**, 1157-1178.
92. J. B. Baell, *Fut. Med. Chem.*, 2010, **2**, 1529-1546.
93. R. M. Mohammad, A. S. Goustin, A. Aboukameel, B. Chen, S. Banerjee, G. Wang, Z. Nikolovska-Coleska, S. Wang and A. Al-Katib, *Clin. Cancer Res.*, 2007, **13**, 2226-2235.
94. F. Abulwerdi, C. Liao, M. Liu, A. S. Azmi, A. Aboukameel, A. S. Mady, T. Gulappa, T. Cierpicki, S. Owens, T. Zhang, D. Sun, J. A. Stuckey, R. M. Mohammad and Z. Nikolovska-Coleska, *Mol. Cell Ther.*, 2014, **13**, 565-575.
95. F. A. Abulwerdi, C. Liao, A. S. Mady, J. Gavin, C. Shen, T. Cierpicki, J. A. Stuckey, H. D. Showalter and Z. Nikolovska-Coleska, *J. Med. Chem.*, 2014, **57**, 4111-4133.
96. P. H. Bernardo, T. Sivaraman, K. F. Wan, J. Xu, J. Krishnamoorthy, C. M. Song, L. Tian, J. S. Chin, D. S. Lim, H. Y. Mok, V. C. Yu, J. C. Tong and C. L. Chai, *J. Med. Chem.*, 2010, **53**, 2314-2318.
97. P. H. Bernardo, T. Sivaraman, K.-F. Wan, J. Xu, J. Krishnamoorthy, C. M. Song, L. Tian, J. S. F. Chin, D. S. W. Lim, H. Y. K. Mok, V. C. Yu, J. C. Tong and C. L. L. Chai, *Pure Appl. Chem.*, 2011, **83**, 723-731.
98. A. A. Lugovskoy, A. I. Degterev, A. F. Fahmy, P. Zhou, J. D. Gross, J. Yuan and G. Wagner, *J. Am. Chem. Soc.*, 2002, **124**, 1234-1240.
99. J. Baell and M. A. Walters, *Nature*, 2014, **513**, 481-483.
100. X. Ding, Y. Li, L. Lv, M. Zhou, L. Han, Z. Zhang, Q. Ba, J. Li, H. Wang, H. Liu and R. Wang, *Chemmedchem*, 2013, **8**, 1986-2014.
101. A. M. Petros, S. L. Swann, D. Song, K. Swinger, C. Park, H. Zhang, M. D. Wendt, A. R. Kunzer, A. J. Souers and C. Sun, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1484-1488.
102. A. Friberg, D. Vigil, B. Zhao, R. N. Daniels, J. P. Burke, P. M. Garcia-Barrantes, D. Camper, B. A. Chauder, T. Lee, E. T. Olejniczak and S. W. Fesik, *J. Med. Chem.*, 2013, **56**, 15-30.
103. M. Bruncko, L. Wang, G. S. Sheppard, D. C. Phillips, S. K. Tahir, J. Xue, S. Erickson, S. Fidanze, E. Fry, L. Hasvold, G. J. Jenkins, S. Jin, R. A. Judge, P. J. Kovar, D. Madar, P. Nimmer, C. Park, A. M. Petros, S. H. Rosenberg, M. L. Smith, X. Song, C. Sun, Z.-F. Tao, X. Wang, Y. Xiao, H. Zhang, C. Tse, J. D. Leverson, S. W. Elmore and A. J. Souers, *J. Med. Chem.*, 2015, **58**, 2180-2194.
104. J. D. Leverson, H. Zhang, J. Chen, S. K. Tahir, D. C. Phillips, J. Xue, P. Nimmer, S. Jin, M. Smith, Y. Xiao, P. Kovar, A. Tanaka, M. Bruncko, G. S. Sheppard, L. Wang, S. Gierke, L. Kategaya, D. J. Anderson, C. Wong, J. Eastham-Anderson, M. J. C. Ludlam, D. Sampath, W. J. Fairbrother, I. Wertz, S. H. Rosenberg, C. Tse, S. W. Elmore and A. J. Souers, *Cell Death Dis.*, 2015, **6**, e1590.
105. P. Bose, G. L. Simmons and S. Grant, *Expert Opin. Invest. Drugs*, 2013, **22**, 723-738.
106. H. Nakajima, Y. Hori, H. Terano, M. Okuhara, T. Manda, S. Matsumoto and K. Shimomura, *J. Antibiot.*, 1996, **49**, 1204-1211.
107. D. Silvera, S. C. Formenti and R. J. Schneider, *Nat. Rev. Cancer*, 2010, **10**, 254-266.
108. D. M. Lucas, R. B. Edwards, G. Lozanski, D. A. West, J. D. Shin, M. A. Vargo, M. E. Davis, D. M. Rozewski, A. J. Johnson, B. N. Su, V. M. Goettl, N. A. Heerema, T. S. Lin, A. Lehman, X. Zhang, D. Jarjoura, D. J. Newman, J. C. Byrd, A. D. Kinghorn and M. R. Grever, *Blood*, 2009, **113**, 4656-4666.
109. L. M. Lindqvist, I. Vikstrom, J. M. Chambers, K. McArthur, M. Ann Anderson, K. J. Henley, L. Happo, L. Cluse, R. W. Johnstone, A. W. Roberts, B. T. Kile, B. A. Croker, C. J. Burns, M. A. Rizzacasa, A. Strasser and D. C. Huang, *Cell Death Dis.*, 2012, **3**, e409.
110. R. L. Thomas, D. J. Roberts, D. A. Kubli, Y. Lee, M. N. Quinsay, J. B. Owens, K. M. Fischer, M. A. Sussman, S. Miyamoto and A. B. Gustafsson, *Genes Dev.*, 2013, **27**, 1365-1377.
111. X. Wang, M. Bathina, J. Lynch, B. Koss, C. Calabrese, S. Frase, J. D. Schuetz, J. E. Rehg and J. T. Opferman, *Genes Dev.*, 2013, **27**, 1351-1364.
112. W. Pierson, B. Cauwe, A. Policheni, S. M. Schlenner, D. Franckaert, J. Berges, S. Humblet-Baron, S. Schonefeldt, M. J. Herold, D. Hildeman, A. Strasser, P. Bouillet, L. F. Lu, P. Matthys, A. A. Freitas, R. J. Luther, C. T. Weaver, J. Dooley, D. H. Gray and A. Liston, *Nat. Immunol.*, 2013, **14**, 959-965.
113. A. G. Rossi, D. A. Sawatzky, A. Walker, C. Ward, T. A. Sheldrake, N. A. Riley, A. Caldicott, M. Martinez-Losa, T. R. Walker, R. Duffin, M. Gray, E. Crescenzi, M. C. Martin, H. J. Brady, J. S. Savill, I. Dransfield and C. Haslett, *Nat. Med.*, 2006, **12**, 1056-1064.

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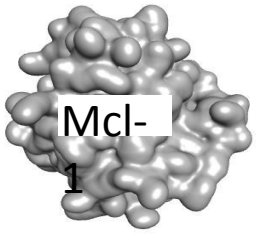

Cancer cells

- Upregulation
- Dependence
- Pro-survival
- Chemoresistance

Small Molecule Inhibitors

Progress towards the development of potent and selective inhibitors of the pro-survival protein Mcl-1 is reviewed.