Acylpyrogallols as Inhibitors of Antiapoptotic Bcl-2 Proteins

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Abstract: A series of acylpyrogallols were designed, synthesized, and evaluated as small-molecule inhibitors of antiapoptotic Bcl-2 proteins. The most potent compound **9** (TM-179) binds to Bcl-2 with an IC_{50} of 170 nM and to Mcl-1 with a K_i of 37 nM. Compound **9** potently inhibits cell growth and induces apoptosis in human breast and prostate cancer cell lines.

Apoptosis, or programmed cell death, is a cellular process critical to normal development and homeostasis of multicellular organisms. It is now recognized that dysfunction of the apoptosis machinery is a hallmark of cancer.[1–3] Defects in the apoptosis machinery confer apoptosis resistance to therapeutic agents on cancer cells and makes current anticancer therapies less effective, leading ultimately to their failure. Targeting critical apoptosis regulators as a means of overcoming apoptosis resistance of cancer cells is a promising strategy in cancer therapy.

The Bcl-2 family proteins comprise a class of central arbiters of apoptosis and include antiapoptotic members Bcl-2, Bcl-xL, and Mcl-1 and proapoptotic members Bim, Bid, Bad, Bak, and Bax.[4–7] The antiapoptotic Bcl-2 proteins, including Bcl-2, Bcl-xL, and Mcl-1, are overexpressed in many cancer cell lines and human cancer tissues. Such overexpression protects cancer cells from the apoptosis caused by current anticancer therapies and plays a role in the failure of conventional anticancer drugs.[4–7] These antiapoptotic Bcl-2 proteins are therefore considered to be promising molecular targets for the design of novel anticancer drugs.

Although the precise mechanism by which Bcl-2 proteins regulate apoptosis in cells is still under intense investigation and not completely understood,[8] it is clear that antiapoptotic Bcl-2 proteins effectively inhibit apoptosis, at least in part by directly binding to proapoptotic Bcl-2 proteins such as Bim, Bid, and Bad. Experimentally determined three-dimensional structures of Bcl-2, Bcl-xL, and Mcl-1 show that these proteins contain a well-defined hydrophobic surface binding groove, known as the BH3 binding groove, into which Bid, Bim, Bad, or Noxa binds.[9–11] Small molecules designed to bind to the BH3 binding groove in these antiapoptotic Bcl-2 proteins and to block their interactions with proapoptotic Bcl-2 members are predicted to promote apoptosis in cancer cells and represent a promising new cancer therapeutic strategy. Although a number of groups, including ours, have reported the discovery and design of nonpeptidic inhibitors of the antiapoptotic Bcl-2 proteins (Figure 1),[12–22] design and development of potent and druglike small-molecule inhibitors against these antiapoptotic Bcl-2 proteins remain as one of the most challenging tasks in modern drug discovery and medicinal chemistry. In this paper, we report the design, synthesis, and evaluation of a series of acylpyrogallol analogues as inhibitors of the antiapoptotic Bcl-2 proteins.

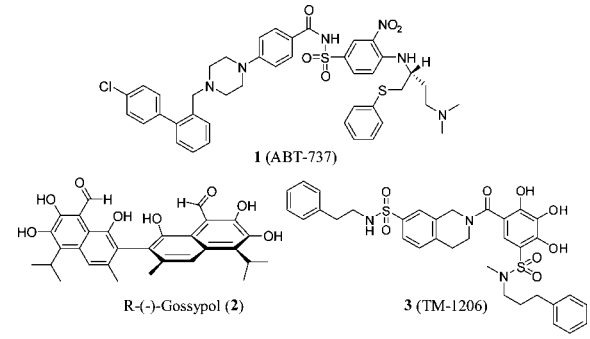

Figure 1. Representative small-molecule inhibitors of Bcl-2 proteins.

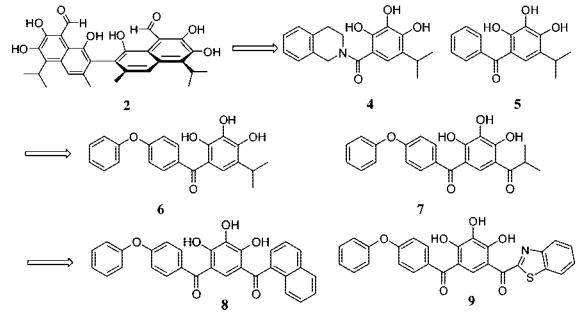

Figure 2. Design of acylpyrogallols as new inhibitors of the Bcl-2 proteins.

Previously, we have reported the discovery of (−)-gossypol (**2**) as a pan inhibitor of Bcl-2, Bcl-xL, and Mcl-1, with K_i values of 320, 480, and 180 nM, respectively.[19] Using **2** as the initial lead compound and a structure-based strategy, we also designed several new classes of small-molecule inhibitors, including **3**, to target Bcl-2, Bcl-xL, and Mcl-1 proteins.[20–22] We report herein structure-based design, synthesis, and evaluation of acylpyrogallols as new inhibitors of the antiapoptotic Bcl-2 proteins.

Our computational modeling studies predicted that **2** forms a hydrogen bonding network with residues Arg146 and Asn143 in Bcl-2 through its aldehyde group and the adjacent hydroxyl groups on one of its naphthalene rings, while the isopropyl group on the same naphthalene ring is inserted into a hydrophobic pocket in Bcl-2.[20,21] These groups in part mimic the interactions of Asp99, Phe101, and Asn102 in the Bim peptide with Bcl-2 protein. On the basis of the predicted binding model for **2**, pyrogallol **4** was designed to mimic the hydrogen bonding and part of the hydrophobic interactions between **2** and Bcl-2 (Figures 2 and 3).[21] Compound **4** was previously used as the starting point for the design of **3**.[21]

The predicted binding model showed that the carbonyl group in **4** forms a hydrogen bond with Y108 in Bcl-2 (Figure 3). We investigated if the tetrahydroisoquinoline amide in **4** can be replaced by a benzoyl group, which led to the design of **5**. Modeling predicted that the binding of **5** to Bcl-2 is similar to that of **4**. While the carbonyl group in **5** forms a hydrogen bond with Y108, the phenyl ring inserts into a hydrophobic pocket in the protein (Figure 3). To test our prediction, **5** was

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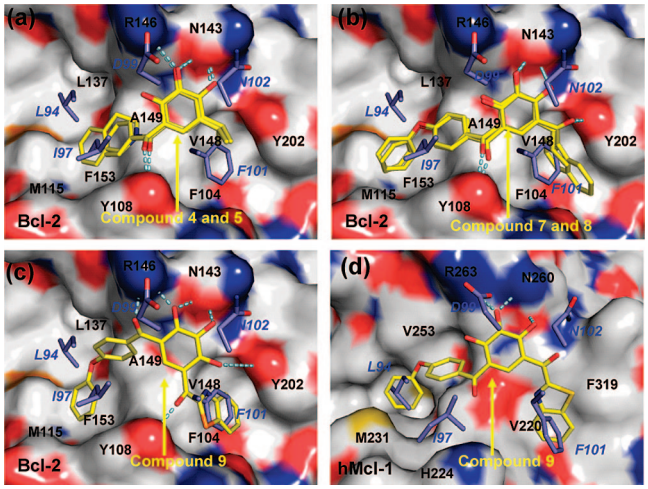
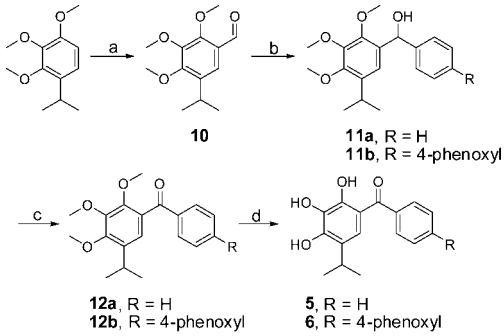


Figure 3. Predicted binding models of Bcl-2 in complex with (a) **4** and **5**, (b) **7** and **8**, (c) **9**, and (d) hMcl-1 and **9**. Bcl-2 and hMcl-1 are shown in surface representation where carbon, oxygen, nitrogen, and sulfur atoms are in gray, red, blue, and orange, respectively. Carbon and oxygen atoms in all designed compounds are in yellow and red, respectively. The key residues in Bim BH3 peptide are shown and labeled in light-blue and labeled in italic. Hydrogen bonds are depicted as dashed lines in cyan.

Scheme 1. Synthesis of Phenyl(2,3,4-trihydroxy-5-isopropyl-phenyl)methanones **5** and **6**[a]



[a] Reagents and conditions: (a) *t*-BuLi (1.5 equiv), HMPA, THF, −78 to −40 °C, then DMF, 91%; (b) substituted phenylmagnesium bromide, THF, 0 °C to room temp, 2 h, >90%; (c) Dess−Martin periodinane (1.5 equiv), CH_2Cl_2, room temp, 30 min, >76%; (d) BBr_3 (6 equiv), CH_2Cl_2, −78 to −20 °C, >72%.

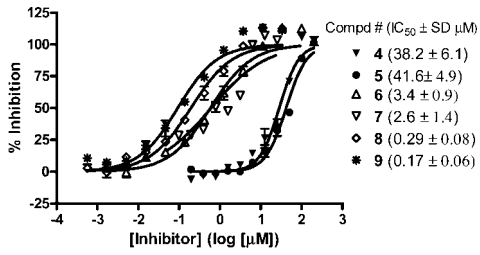
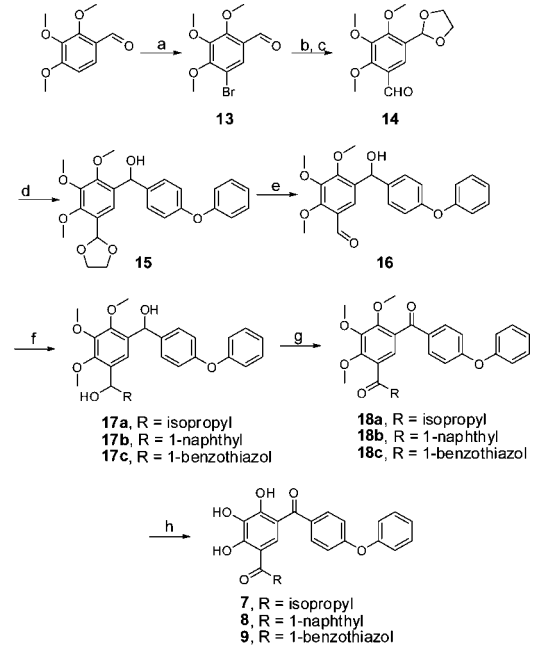


Figure 4. Competitive binding of **4**−**9** to Bcl-2 protein as determined using an ELISA assay in competition with a biotinylated Bim peptide.

synthesized (Scheme 1). Compound **5** was determined to bind to Bcl-2 with an IC_{50} of 41.6 μM in our ELISA-based binding assay and is as potent as **4** (Figure 4).

Analysis of the predicted binding models of **5** and the Bim BH3 peptide in a complex with Bcl-2 indicated that installation of a hydrophobic group on the phenyl ring to interact with the hydrophobic pocket occupied by Leu94 in the Bim BH3 peptide could significantly enhance the binding affinity. Modeling

Scheme 2. Synthesis of Compounds **7**−**9**[a]



[a] Reagents and conditions: (a) Br_2 (1.1 equiv), AcOH, room temp, 1 day, 72%; (b) ethylene glycol (3 equiv), TsOH (cat.), toluene, Dean–Stark; (c) *n*-BuLi (1.2 equiv), HMPA, THF, −78 °C, 0.5 h, then DMF, −78 °C to room temp, 81%; (d) 4-phenoxyphenylmagnesium bromide (3.0 equiv), THF, 0 °C to room temp, 3 h, 93%; (e) TsOH (cat.), acetone, 0 °C, 20 min, 86%; (f) RMgBr or RLi (3 equiv),THF, 0 °C, >82%; (g) Dess−Martin periodinane (3.0 equiv), CH_2Cl_2, room temp, 40 min, >62%; (h) BBr_3 (10 equiv), CH_2Cl_2, −78 to −20 °C, 6 h, >75%.

showed that a phenoxy group on the para position of the phenyl ring can occupy this hydrophobic pocket. We used an oxygen linker between these two phenyl rings to balance the hydrophobic and hydrophilic properties of the resulting **6**. Compound **6** was synthesized (Scheme 1) and determined to bind to Bcl-2 with an IC_{50} of 3.4 μM in the ELISA-based assay, being 11 times more potent than **5**.

Modeling showed that the isopropyl group in **5** and **6** inserts into the hydrophobic pocket occupied by Phe101 in the Bim BH3 peptide (Figure 3), which can accommodate a larger hydrophobic group than isopropyl for more optimal interaction. To facilitate the synthesis of new analogues with larger hydrophobic groups, we first designed and synthesized **7** (Figure 2) to test if insertion of a carbonyl group between the isopropyl group and the pyrogallol core is tolerated. Compounds **6** and **7** were determined to have similar binding affinities to Bcl-2 (Figure 4), indicating that insertion of a carbonyl group at this site is tolerated.

Compounds **8** and **9** were designed with a naphthyl or a benzo[*d*]thiazolyl group to replace the isopropyl group in **7**. Modeling predicted that compared to **7**, both **8** and **9** have an improved hydrophobic interaction with Bcl-2. Compounds **8** and **9** were synthesized using a method similar to that used for **7** (Scheme 2). In the ELISA assay, **8** and **9** bind to Bcl-2 with IC_{50} values of 0.29 and 0.17 μM, respectively, and are thus 9–15 times more potent than **7**. Hence, **8** and **9** bind to Bcl-2 100-times more potently than the initial compound **5**.

Recent studies have demonstrated that Mcl-1 can effectively protect cancer cells from apoptosis induction when Bcl-2 and Bcl-xL proteins are inhibited by ABT-737 (**1**), a potent and specific inhibitor of Bcl-2 and Bcl-xL.[23,24] Mcl-1 emerges as an important and attractive molecular target for anticancer drug design, independent of Bcl-2 and Bcl-xL proteins. We have thus

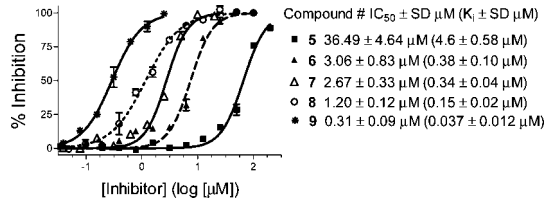


Figure 5. Competitive binding curves of designed compounds **5**−**9** to Mcl-1 protein as determined using a fluorescence-polarization assay.

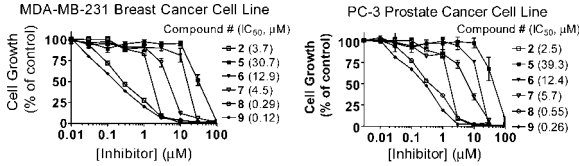


Figure 6. Inhibition of cell growth by designed small molecules in the MDA-MB-231(2LMP) breast cancer cell line and PC-3 prostate cancer cell line. Cells were treated for 4 days, and cell growth was determined by WST-based assay.

evaluated the binding affinities of **5**−**9** to Mcl-1 using our established fluorescence-polarization (FP) assay.[21] Compounds **5**, **6**, **7**, **8**, and **9** bind to Mcl-2 with K_i values of 4.6, 0.38, 0.34, 0.15, and 0.037 μM, respectively (Figure 5). We further determined that **8** and **9** bind to Bcl-xL with K_i values of 1.32 and 1.11 μM, respectively, in our FP-based Bcl-xL assay.

Compounds **2** and **5**−**9** were tested for their activity in inhibition of cell growth in the MDA-MB-231 (2LMP) human breast cancer cell line and the PC-3 human prostate cancer cell line, both of which express high levels of Bcl-2, Bcl-xL, and Mcl-1 proteins (Supporting Information). Compounds **2**, **5**, **6**, **7**, **8**, and **9** have IC_{50} values of 3.7, 30.7, 12.9, 4.5, 0.29, and 0.12 μM, respectively, in the MDA-MB-231 cell line and 2.5, 39.2, 12.4, 5.7, 0.55, and 0.26 μM, respectively, in the PC-3 cell line (Figure 6). Their potencies in inhibition of cancer cell growth in both cell lines correlate well with their binding affinities to Bcl-2 and Mcl-1 proteins.

We next evaluated the ability of **9** to induce apoptosis and cell death in the MDA-MB-231 and PC-3 cancer cell lines (Figure 6). Compound **9** effectively induced cell death in both cancer cell lines in a time- and dose-dependent manner, as determined using the trypan blue exclusion assay (Supporting Information). For example, treatment with **9** at 0.3, 1, and 3 μM for 4 days induced 31 ± 3%, 58 ± 7%, and 86 ± 4% of cells to undergo cell death in the MDA-MB-231 cancer cell line (Supporting Information). Furthermore, **9** is very effective in induction of apoptosis in the MDA-MB-231 and PC-3 cancer cell lines, as shown by the Annexin-V/propidium iodide flow cytometric analysis (Figure 7).

The synthesis of **5** and **6** is shown in Scheme 1. Briefly, 1-isopropyl-2,3,4-trimethoxybenzene was treated with *tert*-butyllithium/HMPA and then DMF to give the benzaldehyde **10**. Reaction of **10** with a Grignard reagent afforded a secondary alcohol **11a** or **11b**, which was oxidized to the phenone **12a** or **12b** by excess Dess−Martin periodinane (DMP). The trimethyl ether **12a** or **12b** was subjected to demethylation by BBr_3 to give the pyrogallol phenone **5** or **6**.

The synthesis for **7**−**9** is shown in Scheme 2. 2,3,4-Trimethoxybenzaldehyde was brominated by Br_2 in AcOH to give **13**. The aldehyde group was protected as a 1,3-dioxolan, and a second aldehyde group was added by *n*-BuLi and DMF treatment to give **14**. The 4-phenoxyphenyl group was incorporated to give the secondary alcohol **15**, which was converted

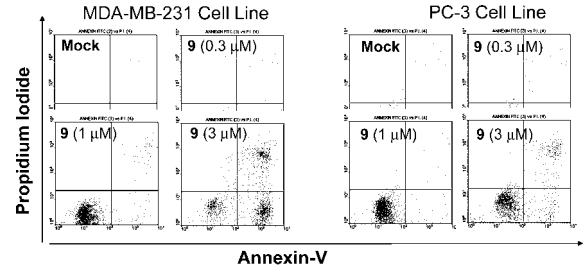


Figure 7. Induction of apoptosis by **9** in the MDA-MB-231(2LMP) breast cancer cell line and PC-3 prostate cancer cell line. Cells were treated for 4 days, and apoptosis was analyzed by annexin-V/propidium iodide staining by flow cytometry.

to the aldehyde **16** by a facile and quick deprotection with TsOH in acetone. Alcohols **17a**, **17b**, and **17c** were prepared by addition of **16** to excess isopropylmagnesium chloride, 1-naphthylmagnesium bromide, and 2-benzothiazolyl lithium solution prepared in situ, respectively. Oxidation of **17** with excess DMP yielded the phenone **18**. Demethylation of the trimethyl ethers **18a**−**c** with BBr_3 in DCM at −78 °C readily gave pyrogallols **7**−**9**, respectively.

In summary, employing a structure-based strategy, we have designed acylpyrogallols as new inhibitors of the antiapoptotic Bcl-2 proteins. The most potent compound **9** binds to Bcl-2 and Mcl-1 with high affinities (IC_{50} = 0.17 μM and K_i = 37 nM, respectively). Consistent with its high binding affinities to Bcl-2 and Mcl-1, **9** potently inhibits cell growth in the MDA-MB-231 and PC-3 cancer cell lines with IC_{50} values of 120 and 260 nM, respectively, and effectively induces cell death and apoptosis in these tumor cells. Compound **9** represents an attractive lead compound for further optimization toward development of a novel class of anticancer drugs aimed at overcoming resistance of cancer cells to apoptosis.

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Supporting Information Available: An experimental section including the chemical data for **5**−**9** and details of the fluorescence polarization based and ELISA binding assays, molecular modeling, and the cellular assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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