# Design, Synthesis, and Evaluation of Tricyclic, Conformationally Constrained Small-Molecule Mimetics of Second Mitochondria-Derived Activator of Caspases

Bin Zhang,[§] Zaneta Nikolovska-Coleska,[‡,#] Yan Zhang,[§] Longchuan Bai,[‡,#] Su Qiu,[‡,#] Chao-Yie Yang,[‡,#] Haiying Sun,[‡,#] Shaomeng Wang,*[,‡,#,†,¶] and Yikang Wu*[,§]

*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China, and Comprehensive Cancer Center and Departments of Internal Medicine, Pharmacology, and Medicinal Chemistry, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor, Michigan 48109*

*Received September 12, 2008*

**Abstract:** A series of tricyclic, conformationally constrained Smac mimetics have been designed, synthesized, and evaluated. The most potent compound **6** (WS-5) binds to XIAP, cIAP-1, and cIAP-2 with $K_i$ of 18, 1.1, and 4.2 nM, respectively. Compound **6** antagonizes XIAP in a functional assay, induces cIAP-1 degradation, inhibits cell growth with an $IC_{50}$ of 68 nM in the MDA-MB-231 cancer cell line, and effectively induces cancer cells to undergo apoptosis.

Evasion of apoptosis, or programmed cell death, is commonly recognized as a hallmark of all cancers.[1,2] Targeting critical apoptosis regulators with a goal to promote apoptosis in cancer cells is an attractive new cancer therapeutic strategy.[2]

Inhibitors of apoptosis proteins (IAPs[a]) are a class of key apoptosis regulators characterized by the presence of one to three domains known as baculoviral IAP repeat (BIR) domains.[3,4] Among these IAP proteins, X-linked IAP (XIAP) inhibits apoptosis by binding to and inhibition of two effectors, caspase-3/-7 and initiator caspase-9.[4] While the third BIR domain (BIR3) of XIAP selectively targets caspase-9, the BIR2 domain, together with the linker immediately preceding it, inhibits caspase-3/-7.[4,5] Cellular IAP-1 (cIAP-1) and cIAP-2 play a critical role in regulation of tumor necrosis factor (TNF) receptor-mediated apoptosis.[4] Because of their central role in regulation of apoptosis, these IAP proteins are considered as promising new cancer therapeutic targets.[5,6]

Smac (second mitochondria-derived activator of caspases) was discovered as a potent proapoptotic protein and an endogenous antagonist of IAP proteins.[7,8] Through direct binding, Smac antagonizes XIAP and abrogates the inhibition of caspase-3/-7 and caspase-9 by XIAP.[7,9] Smac also binds to cIAP-1/2[9] and can reduce the levels of cIAP-1/2 in cells.[10]

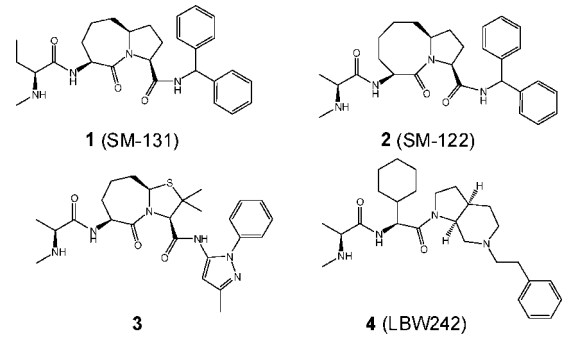



**Figure 1.** Examples of reported Smac mimetics.

**Table 1.** Binding Affinities of Smac Mimetics to XIAP, cIAP-1, and cIAP-2 BIR3 Proteins, As Determined Using Competitive Fluorescence-Polarization Assays[a]

| | $K_i \pm$ SD, nM | | |
|---|---|---|---|
| compd | XIAP BIR3 | cIAP-1 BIR3 | cIAP-2 BIR3 |
| **1** | 61 ± 6.0 | 1.3 ± 0.2 | 4.8 ± 1.2 |
| **5** | 30 ± 4.4 | 3.0 ± 0.5 | 5.9 ± 1.0 |
| **6** | 18 ± 10 | 1.1 ± 0.5 | 4.2 ± 1.1 |
| **7** | 1200 ± 500 | 150 ± 35 | 370 ± 30 |
| **8** | 690 ± 200 | 13 ± 2 | 20 ± 10 |

[a] $K_i$ and standard deviation (SD) values were determined by three to five independent experiments.

Previous studies have firmly established that Smac interacts with XIAP and cIAP-1/2 proteins via its AVPI tetrapeptide motif.[9,11−14] In the past few years, a number of laboratories, including ours, have engaged in the design of small molecules, which are called Smac mimetics, to mimic the AVPI binding motif as antagonists of IAP proteins.[15−24] Two types of Smac mimetics have been reported, namely, monovalent and bivalent Smac mimetics. While monovalent Smac mimetics are designed to mimic the binding of a single AVPI binding motif to IAP proteins,[16−20] bivalent compounds contain two AVPI binding motif mimetics tethered together through a linker.[15,21−24] We have shown that bivalent Smac mimetics can achieve much higher affinities to XIAP and can be much more potent than their corresponding monovalent Smac mimetic in induction of apoptosis in tumor cells.[21] However, monovalent Smac mimetics may hold certain advantages as potential drug candidates because of their small molecular weight (~500). Furthermore, monovalent Smac mimetics provide the basic templates for the design of bivalent Smac mimetics. Herein, we report the design, synthesis and evaluation of a series of conformationally constrained Smac mimetics containing a tricyclic core structure.

In our previous study, we showed that **1** (Figure 1), which contains a [7,5] bicyclic core structure, binds to the XIAP BIR3 protein with a $K_i$ of 61 nM.[19] Our subsequent binding studies determined that **1** binds to cIAP-1 and cIAP-2 BIR3 proteins with very high affinities and has $K_i$ of 1.3 and 4.8 nM, respectively (Table 1). Furthermore, **1** potently inhibits cell growth and effectively induces apoptosis in the MDA-MB-231 breast cancer cell line but shows minimal toxicity to normal cells.[19] Hence, **1** represents a promising lead compound for further design and optimization.

Our predicted binding model of **1** in complex with XIAP BIR3 based on the crystal structure of Smac in complex with XIAP BIR3 (PDB code 1G73)[11] showed that the seven-membered ring in **1** has van der Waals contacts with Trp323 in

* To whom correspondence should be addressed. For S.W.: phone, +1-734-615-0362; fax, +1-734-647-9647; e-mail, shaomeng@umich.edu. For Y.W.: phone, +86 21 54925115; fax, +86 21 64166128; e-mail, yikangwu@mail.sioc.ac.cn.

§ Shanghai Institute of Organic Chemistry.

‡ Comprehensive Cancer Center.

# Department of Internal Medicine.

† Department of Pharmacology.

¶ Department of Medicinal Chemistry.

[a] Abbreviations: IAP, inhibitor of apoptosis protein; XIAP, X-linked IAP; cIAP-1/-2, cellular IAP 1/2; Smac, second mitochondria-derived activator of caspases; BIR, baculoviral IAP repeats domain; BIR2, the second BIR domain; BIR3, the third BIR domain; TNF, tumor necrosis factor; FP, fluorescence polarization.

10.1021/jm801146d CCC: $40.75 
Published on Web 11/14/2008

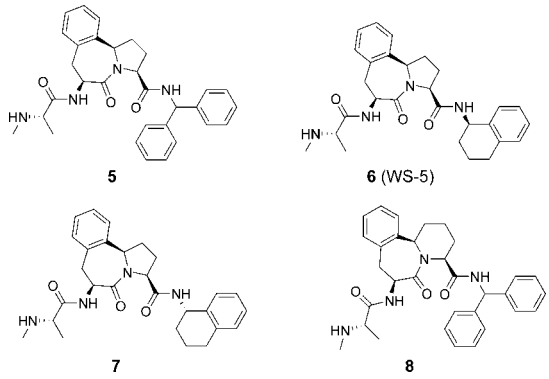



**Figure 2.** Chemical structures of new Smac mimetics.

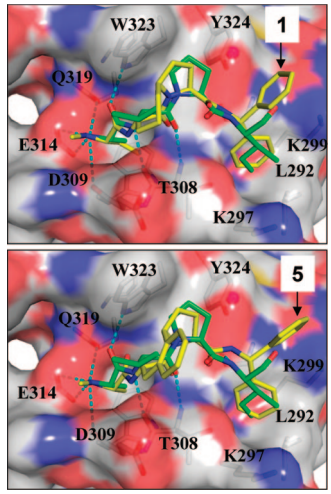



**Figure 3.** Predicted binding models of **1** and **5** in complex with XIAP BIR3, in superposition on the crystal structure of Smac in complex with XIAP BIR3. Protein is displayed in surface model with key binding residues shown and labeled. Compounds **1**, **5**, and AVPI peptide are shown in stick. Carbon atoms of AVPI peptide are depicted in green, and carbon atoms of **1** and **5** are depicted in yellow. Oxygen and nitrogen atoms in these compounds are shown in red and blue, respectively.

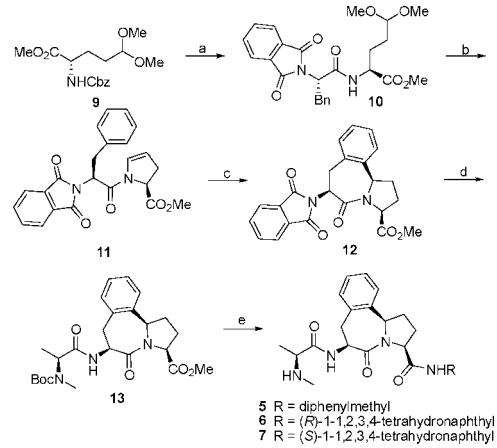
XIAP BIR3 and may contribute to its high binding affinity (Figure 3). We have designed **5** (Figure 2), which has a phenyl ring fused to the seven-membered ring, to investigate if further conformational restriction is tolerated and if this phenyl ring can further enhance the binding to XIAP.

Compound **5** was synthesized (Scheme 1) and evaluated for its binding to XIAP, cIAP-1, and cIAP-2 BIR3 proteins using fluorescence-polarization based binding assays.[25] Compound **5** binds to these three IAP proteins with high affinities, having $K_i$ of 30, 3.0, and 5.9 nM to XIAP, cIAP-1, and cIAP-2, respectively (Table 1). Hence, the high binding affinities of **5** to XIAP and cIAP-1/2 clearly indicated that further conformational restriction of the [7,5] core structure in **1** by a fused phenyl ring is not detrimental for binding to these IAP proteins.

Compound **5** was evaluated for its ability to inhibit cancer cell growth in the MDA-MB-231 breast cancer cell line, a sensitive cell line used in previous studies.[18−20] Indeed, **5** potently inhibits cell growth in this cell line with an $IC_{50}$ of 468 nM (Figure 4). Hence, **5** is a potent and cell-permeable Smac mimetic and a promising new lead compound for optimization and structure−activity relationship studies.

We next investigated if the diphenylmethyl group in **5** can be replaced by a tetrahydronaphthyl group, which was first employed in the design of potent Smac peptidomimetics.[18]

**Scheme 1.** Synthesis of Compounds **5**−**7**[a]




[a] Reagents and conditions: (a) (i) $H_2$, 10% Pd−C, methanol; (ii) *N*-phthaloyl-L-phenylpropanoic acid, EDC, HOBt, *N*-methylmorpholine, $CH_2Cl_2$−DMF 1:1, 0 °C to room temp, overnight, 92% over two steps; (b) $CF_3COOH$, 4 Å molecular sieves, $CHCl_3$, reflux, 88%; (c) trifluorosulfonic acid, trifluorosulfonic anhydride, $CH_2Cl_2$, 98%; (d) (i) hydrazine hydrate, methanol, 3 days; (ii) L-*N*-Boc-*N*-methylalanine, EDC, HOBt, *N*-methylmorpholine, $CH_2Cl_2$−DMF 1:1, 0 °C to room temp, overnight, 92% over two steps; (e) (i) 2 N LiOH, then 1 N HCl; (ii) amine, EDC, HOBt, *N*-methylmorpholine, $CH_2Cl_2$−DMF 1:1, 0 °C to room temp, overnight; (iii) $ZnBr_2$, $CH_2Cl_2$.

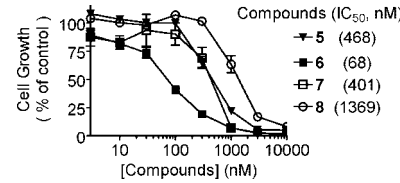



**Figure 4.** Inhibition of cell growth by Smac mimetics in the MDA-MB-231 human breast cancer cell line. Cells were treated for 4 days, and cell growth was determined using a WST-8 assay.

Modeling showed that the 1-(*R*)-tetrahydronaphthyl group, but not the (*S*)-isomer, can effectively interact with the hydrophobic pocket in XIAP BIR3 (Supporting Information). To test the modeling prediction, **6** and **7** with the (*R*)- or the (*S*)-tetrahydronaphthyl group were synthesized and evaluated.

Compounds **6** and **7** bind to XIAP BIR3 with $K_i$ of 18 and 1200 nM, respectively. Thus, **6** is 67 times more potent than **7** in binding to XIAP. Furthermore, **6** binds to cIAP-1 and cIAP-2 proteins with $K_i$ of 1.1 and 4.2 nM, respectively, and is >80 times more potent than **7**. Consistent with its high binding affinity to these IAP proteins, **6** achieves an $IC_{50}$ of 68 nM in inhibition of cell growth in the MDA-MB-231 cell line, while **7** has an $IC_{50}$ of 401 nM (Figure 4).

We next designed and synthesized **8**, in which the five-membered proline ring in **5** is replaced by a six-membered ring, to investigate the importance of the ring size. Modeling showed that replacement of the five-membered proline ring in **5** by a six-membered ring in **8** significantly weakens the contacts of **5** with Trp323, although all the hydrogen bonds are maintained (Figure S2 of Supporting Information). Consistent with modeling prediction, **8** binds to XIAP, cIAP-1, and cIAP-2 proteins with $K_i$ of 692, 13, and 20 nM, respectively, substantially less potent than **5**. These data showed that the five-membered ring in **5** is critical in maintaining the optimal conformation for interactions with these IAP proteins. Compound **8** is 20 times less potent than **6** in cell growth inhibition in the MDA-MB-231 cancer cell line (Figure 4).

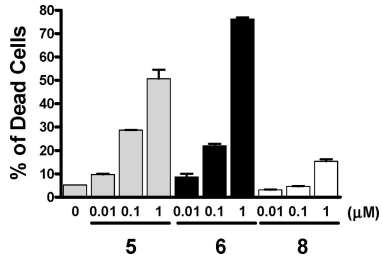



**Figure 5.** Induction of cell death by **5**, **6**, and **8** in the MDA-MB-231 breast cancer cell line. Cells were treated with different concentrations of the compounds for 48 h. Cell viability was determined using a trypan blue exclusion assay.

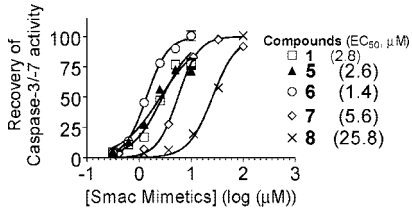



**Figure 6.** Functional antagonism of Smac mimetics against XIAP BIR3 in a cell-free functional assay. Addition of dATP and cytochrome *c* into the MDA-MB-231 cell lysates induced activation of caspase-3/-7 and XIAP BIR3 at 500 nM completely inhibited the caspase-3/-7 activity. Compounds **1** and **5**−**8** dose-dependently recovered the caspase activity.

We next investigated if **5**, **6**, and **8** can effectively induce cell death in the MDA-MB-231 cell line. Our data showed that while these three Smac mimetics are capable of inducing cell death in a dose-dependent manner, **6** is most effective and **8** is least effective (Figure 5). Treatment of the MDA-MB-231 cancer cells with 1 $\mu$M **6** for 48 h induced 75% of cells to undergo cell death but the treatment by **8** caused less than 20% of the cells to die. Thus, our data showed that **6** is a potent and effective inducer of cell death in the MDA-MB-231 cancer cell line.

These new Smac mimetics were evaluated as antagonists of XIAP in a cell-free functional assay. While the XIAP BIR3 protein effectively inhibits the activity of caspase-9 and caspase-3/-7, these Smac mimetics dose-dependently antagonize the inhibition of XIAP to caspase activity (Figure 6). Consistent with their binding affinity data, **5** and **6** are the most potent Smac mimetics in relieving the inhibition of XIAP in this functional assay while **8** is the least potent.

Our binding data showed that these Smac mimetics bind to cIAP-1 with high affinities. Several recent studies have demonstrated that Smac mimetics induce rapid cIAP-1 degradation in cells. Compounds **5**, **6**, and **8** were thus evaluated for their ability to induce cIAP-1 degradation in the MDA-MB-231 cancer cell line. Western blotting showed that these three compounds can induce cIAP-1 degradation but **6** is the most potent one (Figure 7). Compound **6** effectively induces cIAP-1 degradation at concentrations as low as 100 nM and is more potent than **5** and **8**, consistent with their binding affinities to cIAP-1. Compound **6** also potently and dose-dependently induces processing of caspase-8 and cleavage of poly(ADP-ribose) polymerase (PARP), two biochemical markers of apoptosis, at concentrations as low as 100 nM within 24 h.

The synthesis of **5**−**7** is shown in Scheme 1, whereas the synthesis of **8** is provided in Supporting Information. The synthesis of the key intermediate **13** was accomplished using a procedure similar to that published previously[26] with some modifications. Briefly, removal of the Cbz protecting group in

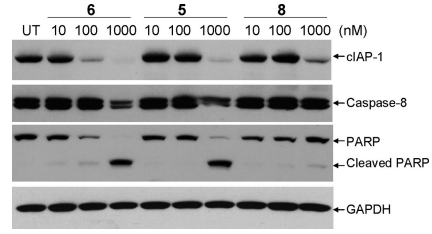



**Figure 7.** Western blot analysis of the levels of cIAP-1, caspase-8, pro-PARP, and cleaved PARP. MDA-MB-231 breast cancer cells were treated with different concentrations of Smac mimetics for 24 h, and proteins were probed with specific antibodies. GAPDH was used as the loading control.

**9** followed by condensation of the resulting amine with *N*-phthaloyl-L-phenylpropanoic acid yielded amide **10**. Cyclization of **10** under the catalytic conditions using trifluoroacetic acid furnished **11**. Cyclization of the enamide moiety with the phenyl ring in **11** in the presence of trifluorosulfonic acid and trifluorosulfonic anhydride provided **12**. Conversion of the phthalimide moiety in **12** to amine followed by condensation of this amine with L-*N*-Boc-*N*-methylalanine generated an amide **13**. Hydrolysis of the methyl ester group in **13** furnished an acid. Condensation of this acid with corresponding amines afforded three amides, which were deprotected with $ZnBr_2$ to give designed compounds **5**−**7**.

In summary, we have designed and synthesized a series of novel Smac mimetics containing a tricyclic core structure. The most potent compound **6** (WS-5) binds to XIAP, cIAP-1, and cIAP-2 with low nanomoalr affinities. Consistent with its molecular mechanism of action, **6** effectively antagonizes XIAP in a cell-free functional assay and efficiently induces the degradation of cIAP-1 in cancer cells at concentrations as low as 100 nM. Compound **6** achieves an $IC_{50}$ of 68 nM in the MDA-MB-231 cell line in a cell growth assay and effectively induces cell death at 100 nM. Taken together, these data showed that **6** is a promising Smac mimetic for further evaluations and optimization for the development of a novel class of anticancer drugs. Further in vitro and in vivo studies of **6** and its analogues are being performed, and the results will be reported in due course.

**Acknowledgment.** We are grateful for financial support from the National Natural Science Foundation of China (Grants 20672129, 20621062, 20772143), the Chinese Academy of Sciences ("Knowledge Innovation Project", Grants KJCX2.YW.H08 and KGCX2-SW-209), the National Cancer Institute, U.S. National Institutes of Health (Grant R01CA109025), the Breast Cancer Research Foundation, the Susan G. Komen Foundation, the Prostate Cancer Foundation, and the University of Michigan Cancer Center (Core Grant P30CA046592). cIAP-1 antibody is a kind gift from Dr. John Silke of La Trobe University, Victoria, Australia.

**Supporting Information Available:** Experimental section including information on the synthesis of **8**, chemical data for **5**−**8**, and details of molecular modeling, fluorescence polarization-based binding assays to XIAP, cIAP-1, and cIAP-2, the cell-free caspase functional assay, the cell growth assay, cell viability assay, and Western blot analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM801146D