

SUPPORTING INFORMATION

Design and Synthesis of Potent Inhibitor of Apoptosis (IAP) Protein Antagonists Bearing a Octahydropyrrolo[1,2-*a*]pyrazine Scaffold as a Novel Proline Mimetic

Kentaro Hashimoto,[‡] Bunnai Saito,[‡] Naoki Miyamoto,[‡] Yuya Oguro,[‡] Daisuke Tomita,[‡] Zenyu Shiokawa,[‡] Moriteru Asano,[‡] Hiroyuki Kakei,[‡] Naohiro Taya,[‡] Masanori Kawasaki,[‡] Hiroyuki Sumi,[‡] Masato Yabuki,[‡] Kenichi Iwai,[‡] Sei Yoshida,[‡] Mie Yoshimatsu,[‡] Kazunobu Aoyama,[‡] Yohei Kosugi,[‡] Takashi Kojima,[‡] Nao Morishita,[‡] Douglas R. Dougan,[†] Gyorgy P. Snell,[†] Shinichi Imamura,[‡] and Tomoyasu Ishikawa*,[‡]*

[‡] Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited: 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan

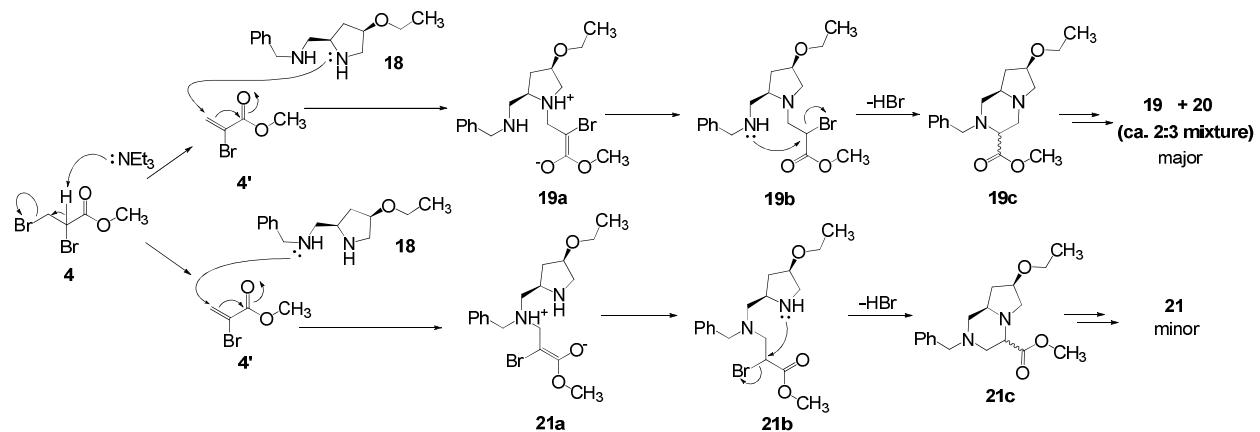
[†]Structural Biology, Takeda California, Inc., 10410 Science Center Drive, San Diego, California 92121, USA

* (B.S.) phone: +81-466-32-1162. E-mail: bunnai.saito@takeda.com; (T.I.) phone: +81-466-32-1155. E-Mail: tomoyasu.ishikawa@takeda.com

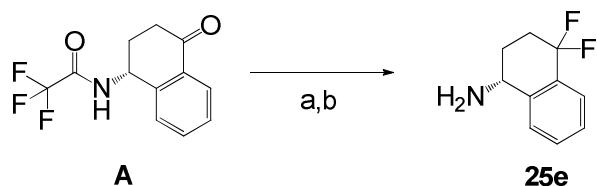
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Plausible mechanism for regioselective cyclization



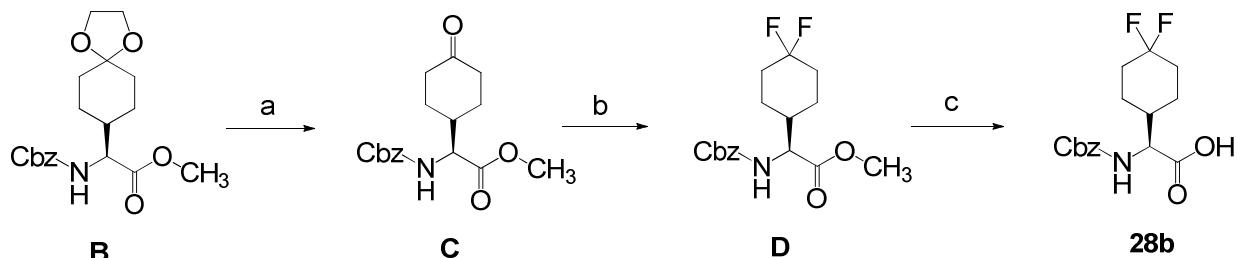
Synthesis of 25e



^a Reagents and Conditions: (a) Deoxo-Fluor®, 0 °C to 85 °C; (b) 8 M NaOH, EtOH, room temp, 3% (2 steps).

2,2,2-Trifluoro-*N*-[(1*R*)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl]acetamide¹ (**A**, 1.71 g, 6.65 mmol) and Deoxo-Fluor® (2.21 g, 9.99 mmol) were mixed at 0°C, and the mixture was stirred at 85°C for 24 h. The mixture was allowed to cool at room temperature, and then partitioned between EtOAc (30 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in hexane) to give brown oil. This oil was dissolved in ethanol (7 mL), and to the solution was added 8M NaOH (1 mL). After being stirred at room temperature for 2 h, the mixture was partitioned between EtOAc (30 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10-100% methanol in EtOAc) to give **25e** (32.1 mg, 3%) as brown oil; ¹H NMR (DMSO-*d*₆, 300 MHz): *δ* 1.64–1.80 (1H, m), 2.01–2.31 (2H, m), 2.39–2.59 (1H, m), 3.85–3.93 (1H, m), 7.33–7.40 (1H, m), 7.48 (1H, t, *J* = 7.6 Hz), 7.55 (1H, d, *J* = 7.7 Hz), 7.63 (1H, d, *J* = 7.7 Hz).

Synthesis of 28b



^a Reagents and Conditions: (a) dichloroacetic acid, acetic acid, THF/H₂O, 30 °C, 83%; (b) DAST, CH₂Cl₂, 0 °C to room temp, 62%; (c) LiOH-H₂O, THF/H₂O, 50 °C, 95%.

Methyl (2S)-{(benzyloxy)carbonyl}amino}(4-oxocyclohexyl)ethanoate C

Dichloroacetic acid (3.57 g, 26.7 mmol) was added to a solution of methyl (2S)-{(benzyloxy)carbonyl}amino}(1,4-dioxaspiro[4.5]dec-8-yl)ethanoate **B** (3.40 g, 9.36 mmol) and acetic acid (16 mL) in THF/water (2:1, 8.4 mL) at room temperature, and the mixture was stirred at 30 °C for 3 h. To the mixture was added dropwise 6M NaOH (40 mL) below 20 °C, and the mixture was extracted with EtOAc (100 mL). The organic layer was washed with brine (60 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20-50% EtOAc in *n*-hexane) to give **C** (2.48 g, 83%) as colorless oil; ¹H NMR (CDCl₃, 500 MHz): δ 1.50–1.65 (2H, m), 1.88–1.97 (1H, m), 2.02–2.10 (1H, m), 2.24–2.39 (3H, m), 2.39–2.47 (2H, m), 3.77 (3H, s), 4.48 (1H, dd, *J* = 4.5, 8.7 Hz), 5.11 (2H, s), 5.37 (1H, d, *J* = 8.7 Hz), 7.30–7.40 (5H, m).

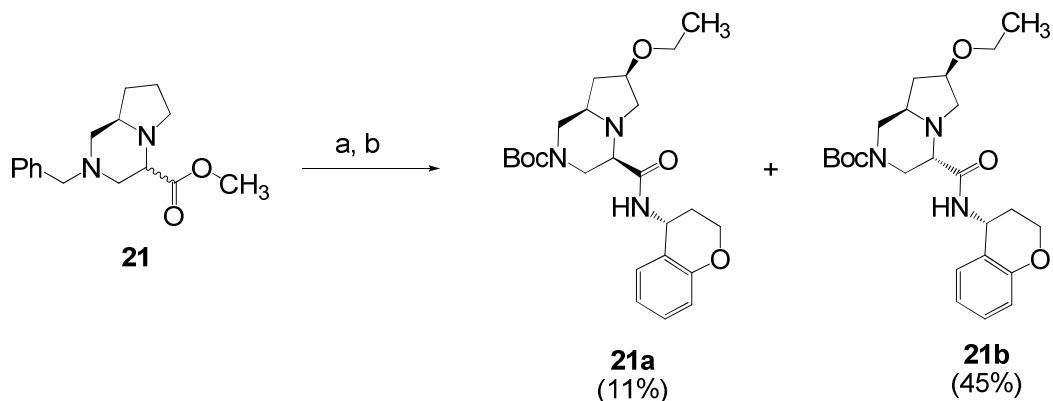
Methyl (2S)-{(benzyloxy)carbonyl}amino}(4,4-difluorocyclohexyl)ethanoate D

Diethylaminosulfur trifluoride (63.0 g, 391 mmol) was added to a solution of **C** (54.2 g, 170 mmol) in dichloromethane (310 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. To the mixture was added methanol/water (1/1, 35 mL) at 0 °C. The organic layer was successively washed with water (200 mL), sat.NaHCO₃ (250 mL x 2) and brine (250

mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was dissolved in acetonitrile (150 mL) and water (130 mL), and to the solution were successively added ruthenium chloride (166 mg, 0.800 mmol) and sodium periodate (25.5 g, 119 mmol) at 0°C. After being stirred at room temperature for 5 h, the mixture was partitioned between EtOAc (1.0 L) and water (250 mL). The organic layer was washed with aqueous sodium thiosulfate (250 mL) and brine (250 mL), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-17% EtOAc in hexane) to give **D** (36.1 g, 62%) as colorless oil; ^1H NMR (CDCl_3 , 500 MHz): δ 1.37–1.51 (2H, m), 1.60–1.81 (4H, m), 1.84–1.94 (1H, m), 2.07–2.17 (2H, m), 3.76 (3H, s), 4.40 (1H, dd, J = 5.0, 8.5 Hz), 5.07–5.15 (2H, m), 5.33 (1H, d, J = 8.5 Hz), 7.31–7.40 (5H, m).

(2*S*)-{[(Benzyl oxy)carbonyl]amino}(4,4-difluorocyclohexyl)ethanoic acid **28b** Lithium hydroxide monohydrate (17.8 g, 424 mmol) was added to a solution of **D** (36.1 g, 106 mmol) in THF (588 mL) and water (295 mL) at 0 °C and the reaction mixture was stirred at 5°C for 1 h. Additional lithium hydroxide monohydrate (2.92 g, 69.6 mmol) was added to the mixture, and the mixture was stirred at room temperature for 1 h. The mixture was neutralized with 1M HCl (405 mL), followed by the addition of 1M HCl (105 mL). The resulting precipitate was collected by filtration and the collected solid was dissolved in EtOAc (500 mL). The solution was dried over MgSO_4 and concentrated under reduced pressure. The obtained colorless solid (38.1 g) was subjected to slurry washing with EtOAc/hexane (350 mL, 1:19) to give **28b** (33.1 g, 95%) as white amorphous solid; ^1H NMR (CDCl_3 , 500 MHz): δ 1.23–1.35 (1H, m), 1.37–1.48 (1H, m), 1.57–1.93 (5H, m), 1.94–2.05 (2H, m), 3.99 (1H, dd, J = 6.0, 8.5 Hz), 5.03 (2H, s), 7.29–7.40 (5H, m), 7.65 (1H, d, J = 8.5 Hz), 12.78 (1H, br s).

Structural determination of **21**



^a Reagents and Conditions: (a) LiOH-H₂O, MeOH/H₂O, 50 °C; (b) (R)-chroman-4-amine hydrochloride, EDC-HCl, HOBT, *i*-Pr₂NEt, DMF, 0 °C to room temp.

Since the compound **21** was an inseparable diastereomers, it was converted to the amide **21a** and **21b** according to the procedure in Scheme 4. The stereochemistry of each amide was determined by 1D- and 2D-NMR (NOESY) experiment.

Compound **21a** and **21b** were prepared by the similar method to that described for **30** using **21** (mixture of isomers, 657 mg, 2.00 mmol), lithium hydroxide monohydrate (134 mg, 3.20 mmol), (4*R*)-3,4-dihydro-2*H*-chromen-4-amine hydrochloride (390 mg, 2.10 mmol), DIPEA (0.70 mL, 4.40 mmol), HOBT (270 mg, 2.00 mmol) and EDC (498 mg, 2.60 mmol). Yield: 11% (**21a**), 45% (**21b**), white amorphous solid (98 mg for **21a**, 401 mg for **21b**).

21a: ¹H NMR (DMSO-*d*₆, 600 MHz): δ 1.03 (3H, t, *J* = 6.6 Hz), 1.24 (1H, td, *J* = 11.7, 4.8 Hz), 1.39 (9H, s), 1.82-1.96 (2H, m), 1.98-2.08 (1H, m), 2.11 (1H, t, *J* = 7.7 Hz), 2.15-2.23 (1H, m), 2.52-2.98 (2H, m), 2.60 (1H, dd, *J* = 10.8, 3.1 Hz), 3.01 (1H, d, *J* = 9.9 Hz), 3.30 (2H, dd, *J* = 6.8, 3.1 Hz), 3.77-4.09 (3H, m), 4.20 (2H, t, *J* = 5.0 Hz), 4.84-5.06 (1H, m), 6.79 (1H, d, *J* = 8.1 Hz), 6.87 (1H, t, *J* = 7.0 Hz), 7.13 (1H, d, *J* = 7.3 Hz), 7.16 (1H, t, *J* = 7.7 Hz), 8.09-8.48 (1H, m).

21b: ^1H NMR (DMSO- d_6 , 600 MHz): δ 1.08 (3H, t, J = 7.0 Hz), 1.13-1.26 (1H, m), 1.38 (9H, s), 1.75-2.09 (2H, m), 2.09-2.25 (1H, m), 2.54-3.55 (8H, m), 3.63-3.91 (1H, m), 3.93-4.02 (2H, m), 4.12-4.32 (2H, m), 4.97 (1H, dd, J = 13.8, 6.1 Hz), 6.77 (1H, d, J = 8.1 Hz), 6.82-6.90 (1H, m), 7.08 (1H, d, J = 7.3 Hz), 7.14 (1H, t, J = 7.2 Hz), 8.25 (1H, br s).

Recrystallization of 45

The crystals **45** (5.00 g, 8.25 mmol) was dissolved in 2-butanone (25 mL) at 77°C (internal temperature 60 °C). Heptane (40 mL) was added dropwise to the mixture at 77°C (internal temperature >60°C). The mixture was stirred at 77°C for 1 h (internal temperature 65 °C). Heptane (60 mL) was added dropwise at 77°C (inside temperature was above 60 °C) and the suspension was cooled to 5 °C slowly. The resulting crystals were collected by filtration, washed with heptane (30 mL) and dried under reduced pressure (70 °C for 1 h) to give **45** (4.56 g, 91%) as colorless crystals; mp 179 °C.; ^1H NMR (300 MHz, DMSO- d_6) : δ 1.01–1.15 (6H, m), 1.15–1.38 (3H, m), 1.54–2.29 (16H, m), 2.63–3.64 (7H, m), 3.88–4.48 (4H, m), 4.59–5.15 (3H, m), 6.70–6.80 (1H, m), 6.80–6.92 (1H, m), 7.07–7.30 (2H, m), 7.88–8.12 (1H, m), 8.12–8.33 (1H, m); Anal. Calcd for $\text{C}_{31}\text{H}_{45}\text{F}_2\text{N}_5\text{O}_5$: C, 61.47; H, 7.49 N, 11.56. Found: C, 61.52; H, 7.54; N, 11.45.

Calculations for thermodynamic stability of 19 and 20

Theoretical calculations for thermodynamic stability have been carried out to investigate the mechanism of epimerization depicted in Scheme 5. First of all, conformations of **19** and **20** were generated by Omega2 and geometrically optimized by MultiMinimization function of Macromodel where MMFF94s as the force field, 80 as the dielectric constant, and GB/SA for the

solvation model were used, respectively. Then, each of minimum energy was selected to calculate the energy difference between **19** and **20**.

Preparations of proteins, peptides and reagents

The recombinant BIR3 domain (residues 250-350) of human cIAP1 protein fused to His-tag (cIAP_BIR3) was prepared in Discovery Research Center. The *N*-terminal His-tagged BIR3 domain (residues 252-356) of recombinant human XIAP protein (XIAP_BIR3) and Smac-N7 peptide (AVPIAQK; Smac-N7) were purchased from R&D Systems, Inc., and EMD Chemicals Inc. (Calbiochem), respectively. A C-terminally biotinylated Smac-N7 peptide (AVPIAQ-K(biotin)-NH₂; biotinyl-Smac) was synthesized at Peptide Institute Inc. Europium cryptate (Eu³⁺ cryptate) -conjugated mouse monoclonal antibody anti-6-Histidine (Anti-6HIS Cryptate), high grade XL665-conjugated streptavidin (SA-XL^{ent!}), and HTRF detection buffer were purchased from Sceti Medical Labo K.K. (cisbio). Anti-6HIS Cryptate and SA-XL^{ent!} were dissolved in distilled water, and stored at -30°C, according to the manufacturer's protocol. Other reagents used were obtained from Wako Pure Chemicals and were of analytical grade or comparable.

Binding activities using homogeneous time-resolved fluorescence resonance energy transfer (HTRF) technology.

Binding experiments were performed in white low-volume 384-well plates (Greiner, #784075). A 5 µL of IAP proteins (40 nM for XIAP_BIR3, 8 nM for cIAP_BIR3) and 5 µL of increasing concentration of compounds were added to wells in the assay buffer (25 mM HEPES, 100 mM NaCl, 0.1% BSA, 0.1% Triton X-100, pH 7.5). After shaking at room temperature, 5 µL of biotinyl-Smac (20 nM for XIAP_BIR3 and 80 nM for cIAP_BIR3, dissolved in assay buffer)

added to the well, followed by adding 5 μ L of mixture of Anti-6HIS Cryptate and SA-XL^{ent!}, 100 times diluted with HTRF detection buffer, respectively. In some case, the condition of 40 nM cIAP_BIR3 and 20 nM biotinyl-Smac was used for the compound evaluation.

After overnight incubation at room temperature in the dark, HTRF measurement was carried out on a multi-label reader (EnVision, PerkinElmer Life And Analytical Sciences, Inc.) with the following settings:

Measurement mode: Time-Resolved Fluorescence

Excitation: 320 nm

Emission Donor: 615 nm

Emission Acceptor: 665 nm

Measurement Height: 6.5 mm

Cycle: 2000

Delay: 90 ms

Number of flashes: 280 μ s.

Fluorescence collected at 615 nm ($F_{615\text{nm}}$) is the total europium cryptate signal, and fluorescence collected at 665 nm ($F_{665\text{nm}}$) is the FRET signal. The ratio = $(F_{665\text{nm}} / F_{615\text{nm}}) \times 10000$ was calculated and IC_{50} values were determined using the ratio by nonlinear regression curve fitting with the program Prism (Graph Pad Software).

Cell lines

For the in vitro assay, the MDA-MB-231 cancer cell line and MRC5 normal lung fibroblasts were obtained from the ATCC (Manassas, VA, USA). The culture medium that was recommended by the suppliers was used for the cultivation of each cell line. For the in vivo study, MDA-MB-231 cells stably expressing luciferase (MDA-MB-231-Luc) were established at

Takeda Pharmaceutical Company, Ltd. (TPC, Fujisawa, Kanagawa, Japan) by transfecting a firefly luciferase expression vector (Promega Corporation, Madison, WI, USA) into MDA-MB-231 cells.

Measurement of cell viability

MDA-MB-231 cells were seeded at 3×10^3 cells/well in 96-well plates (Sumitomo Bakelite Co., Ltd., Tokyo, Japan) and cultured overnight. On the following day, test compounds were diluted in growth medium to the desired final concentration and then added to the cells. After 3 days of incubation, cell viability was measured with a CellTiter-Glo® Luminescent Cell Viability Assay® (Promega Corporation) according to the manufacturer's instructions. GI₅₀ values were determined with the ratio by nonlinear regression curve fitting with Prism.

In vivo PD study

Mice were housed and maintained within the facility at TPC in accordance with the Takeda Experimental Animal Care and Use Committee approved protocol. Athymic nude mice (BALB/cAJcl-*nu/nu*) of approximately 5 weeks of age were obtained from CLEA Japan, Inc. (Tokyo, Japan). For the subcutaneous implanted tumor xenograft models, nude mice were injected with 5×10^6 MDA-MB-231-Luc cells/mouse. When the tumor volumes reached approximately 200 mm³, mice were randomly assigned to treatment groups. Tumors were collected at 6 hr after dosing of **45**. Pharmacodynamics of compounds was assessed by measuring caspase activity in tumors (as described below).

Measurement of Caspase assay in tumor

Caspase-3/caspase-7 activities in tumors were measured with a Caspase-Glo assay kit (Promega Corporation). Cytosolic extracts from MDA-MB-231-Luc xenografts were prepared by homogenization in extraction buffer (25 mM HEPES, pH 7.5; 5 mM MgCl₂; 1 mM EDTA) and subsequently centrifuged (5 min, 10,000 rpm, 4°C). The protein concentration of the supernatant was adjusted to 1 mg/mL with extraction buffer, and an equal volume of reagents and 10 µg/mL cytosolic protein was mixed and incubated at room temperature for 30 min. The luminescence of each sample was measured in a luminometer.

In vivo efficacy study

Athymic nude mice (BALB/cAJcl-*nu/nu*) of approximately 5 weeks of age were obtained from CLEA Japan Inc. (Tokyo, Japan). For subcutaneous implanted tumor xenograft models, nude mice were injected with 5×10^6 MDA-MB-231-Luc cells/ mouse. When tumor volumes reached approximately 200 mm³, mice were randomly assigned to treatment groups. Compound **45** in 0.5% methylcellulose (Shinetsu, Japan) were administered orally at 30, 100 mg/kg B.I.D. (twice a day) for up to 14 consecutive days. Tumor volumes and body weights were measured approximately twice weekly throughout the study. Tumor volume was calculated using calipers and the equation $(L \times W^2) / 2$, where L and W refer to the larger and smaller dimensions collected at each measurement, respectively. Tumor regression rate (%) = (tumor volume on the day of start of administration - tumor volume on the day of completion of administration)/tumor volume on the day of start of administration $\times 100$.

Mouse pharmacokinetic study

Animals used in the study (Tables 2-4) were female BALB/cAJcl mice (7-weeks old; CLEA Japan, Inc.). Test compounds were administered orally at a dose of 10 mg/kg and intravenously at a dose of 1 mg/mL/kg. Concentrations of compounds in the plasma were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

Metabolic stability assay

Human and mouse hepatic microsomes were purchased from Xenotech, LLC (Lenexa, KS). An incubation mixture with a final volume of 0.1 mL consisted of microsomal protein in 50 mmol/L phosphate buffer (pH 7.4) and 1 μ mol/L test compound. The concentration of hepatic microsomal protein was 0.2 mg/mL. An NADPH-generating system containing 50 mmol/L MgCl₂, 50 mmol/L glucose-6-phosphate, 5 mmol/L β -NADP⁺ and 15 unit/mL glucose-6-phosphate dehydrogenase was prepared and added to the incubation mixture with a 10% volume of the reaction mixture. After the addition of the NADPH-generating system, the mixture was incubated at 37 °C for 0 and 20 min. The reaction was terminated by the addition of acetonitrile equivalent to the volume of the reaction mixture. All incubations were made in duplicate. Test compound in the reaction mixture was measured by LC/MS/MS. For metabolic stability determinations, chromatograms were analyzed for parent compound disappearance from the reaction mixtures.

cIAP and XIAP molecular biology, protein expression, purification and crystallography

The BIR 3 domain of human cIAP1 (residues 260-352) and XIAP (residues 238-357) were over-expressed as 6xHis and GST fusion proteins respectively in E. coli. The cIAP1 protein was purified by immobilized Ni²⁺ affinity chromatography, followed by cleavage of the 6xHis tag

with TEV protease and size exclusion with a Superdex 75 column (GE Healthcare). The XIAP protein was purified through a Glutathione sepharose 4B (GE Healthcare) column. The GST tag was removed with PreScission protease and then further purified by a Superdex 75 size exclusion column. The final buffer for both proteins was 25 mM HEPES pH 7.6, 50 mM NaCl, 1 mM MgCl₂, and 0.25 mM TCEP. Prior to crystallization, purified protein mixed with 1 mM inhibitor compound was concentrated to 18 mg/ml.

Crystals suitable for data collection were obtained by vapor diffusion in sitting drops at 20 °C. Reservoirs contained 2.2-3.0 M NaCl and 100 mM TRIS (pH 8.2-8.8) for cIAP complexes and 18-20% PEG4000 and 100 mM TRIS (pH 8.2-8.8) for the XIAP complex. Crystals were immersed in mother liquor solution containing 22% ethylene glycol for cryo protection and flash frozen in liquid nitrogen. Crystals of all the IAP complexes grew in the orthorhombic space group P2₁2₁2₁. The two cIAP complexes have very similar unit cell dimensions and contain two molecules in the asymmetric unit while the XIAP complex contains eight molecules in the asymmetric unit.

Diffraction data were collected from single cryogenically protected crystals at beamline 5.0.3 of the Advanced Light Source at Lawrence Berkeley National Laboratory. Data were reduced using the HKL2000 software package.² The structures were determined by molecular replacement with either MOLREP³ or PHASER⁴ of the CCP4 program suite utilizing PDB codes 3D9T and 2OPZ as search models for cIAP and XIAP, respectively, and refined with the program REFMAC.⁵ Several cycles of model building with XtalView⁶ or COOT⁷ and refinement were performed for improving the quality of the model. Data reduction and refinement statistics are summarized in Table 4. The coordinates and structure factors have been deposited in Protein Data Bank with accession code 4HY0, 4HY4 and 4HY5.

Table 4. Data reduction and refinement statistics for the X-ray structures of the cIAP and XIAP complexes.

Data Collection			
Protein	cIAP	cIAP	XIAP
Compound	45 (T-3256336)	26b	45 (T-3256336)
Wavelength (Å)	0.98	0.98	0.98
Space group	P ₂ 12 ₁ 2 ₁	P ₂ 12 ₁ 2 ₁	P ₂ 12 ₁ 2 ₁
Unit cell dimensions (Å)	a=31.1, b=68.2, c=122.3, $\alpha=90^\circ$, $\beta=90^\circ$, $\gamma=90^\circ$	a=30.6, b=68.6, c=117.6, $\alpha=90^\circ$, $\beta=90^\circ$, $\gamma=90^\circ$	a=58.3, b=100.8, c=184.6, $\alpha=90^\circ$, $\beta=90^\circ$, $\gamma=90^\circ$
Resolution (Å)	1.75	1.25	2.85
Unique reflections	27152	69825	26564
Redundancy	6.0	5.5	6.6
Completeness (%)	96.3 (73.2)	99.5 (92.8)	99.0 (98.8)
I/σ(I)	19.8 (1.9)	22.6 (2.3)	20.8 (2.2)
R _{sym} ^a	0.084 (0.496)	0.065 (0.460)	0.084 (0.878)
Refinement			
Molecules in assymteric unit	2	2	8
Reflections used	24674	65816	24913
RMS Bonds (Å)	0.009	0.008	0.009
RMS Angles (°)	1.049	1.259	1.261
Average B value (Å ²)	29.9	12.2	44.2
R-value ^b	0.178	0.152	0.218
R _{free} ^b	0.211	0.170	0.278

^aR_{sym} = $\sum_{h} \sum_{j} |I(h)j| - \langle I(h)j \rangle / \sum_{h} \sum_{j} \langle I(h)j \rangle$, where $\langle I(h)j \rangle$ is the mean intensity of symmetry-related reflections. ^bR-value = $\sum |F_{\text{obs}} - F_{\text{calc}}| / \sum |F_{\text{obs}}|$. R_{free} for 5% of reflections excluded from refinement. Values in parentheses are for the highest resolution shell.

X-ray crystallography analysis of compound 45

A colorless prism (0.40 x 0.11 x 0.06 mm) was obtained by re-crystallization from hexane/ethyl acetate solution. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu-K α radiation. The structure was solved by direct methods (SHELXS-97⁸) and refined using full-matrix least-squares on F^2 (SHELXL-97⁸). All non-H atoms were refined with anisotropic displacement parameters. Crystal data; C₃₁H₄₅F₂N₅O₅, M_r = 605.72, orthorhombic, $P2_12_12_1$, a = 9.75088(19) Å, b = 11.3743(3) Å, c = 30.0068(7) Å, V = 3328.02(12) Å³, Z = 4, D_{calc} 1.209 g/cm³, R_1 = 0.0296 for 5770 reflections with $I > 2\sigma(I)$, wR = 0.0771.² The residual electron density in the solvent region was difficult to model correctly and was treated with the SQUEEZE routine in PLATON.⁹ The absolute configuration was determined based on the Flack parameter,¹⁰ 0.05(11). This result is consistent with the configuration of *L*-alanine moiety.

Table 1. Crystal structure data for compound 45

Empirical formula	C ₃₁ H ₄₅ F ₂ N ₅ O ₅	
Formula weight	605.72	
Wavelength (Å)	1.54187	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions (Å, °)	a = 9.75088(19)	α = 90
	b = 11.3743(3)	β = 90
	c = 30.0068(7)	γ = 90
Volume (Å ³)	3328.02(12)	

Z	4
Density (calculated) (Mg/m ³)	1.209
Absorption coefficient (mm ⁻¹)	0.746
<i>F</i> (000)	1296
θ range for data collection	2.95-68.24
Reflections collected	38187
Independent reflections [<i>R</i> (int)]	6028 [0.0292]
Data/ restraints/ parameters	6028/ 0/ 403
Goodness-of-fit on <i>F</i> ²	1.085
<i>R</i> ₁ , w <i>R</i> ₂ indices [<i>I</i> >2 σ (<i>I</i>)]	0.0296, 0.0762
<i>R</i> ₁ , w <i>R</i> ₂ indices (all data)	0.0307, 0.0771
Flack parameter [Friedel pairs]	0.05(11) [2604]
Final Δ <i>F</i> max/ min (e. Å ⁻³)	0.172/ -0.137

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