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# Antagonists of inhibitor of apoptosis proteins based on thiazole amide isosteres

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ABSTRACT

A series of IAP antagonists based on thiazole or benzothiazole amide isosteres was designed and synthesized. These compounds were tested for binding to the XIAP-BIR3 and ML-IAP BIR using a fluorescence polarization assay. The most potent of these compounds, **19a** and **33b**, were found to have $K_i$'s of 20–30 nM against ML-IAP and 50–60 nM against XIAP-BIR3.



Programmed cell death, or apoptosis, is a crucial process in development for maintaining homeostasis and for the removal of damaged or malignant cells. This pathway is tightly controlled by a number of positive and negative regulatory elements. The inhibitor of apoptosis (IAPs) proteins negatively regulate this process through a variety of mechanisms including direct inhibition of effector caspase enzymes and modulation of TNF receptor-mediated signaling pathways.[1] Members of the IAP protein family are upregulated in various cancers and promote resistance to chemotherapy. Thus inhibition of these proteins may be a new therapeutic mechanism for treating cancer.[2]

Following the discovery that short peptides could disrupt the interaction of the IAPs with the amino terminus of caspases,[3,4] there have been multiple efforts to develop molecules with reduced peptide character that possess the appropriate potency, permeability and pharmacokinetic properties to be a useful therapeutic agent.[5–7] In our effort to develop such a molecule, we began with the modified peptide Ala-Val-Pro-2,2-diphenethylamine (**1**).[8] This lead binds to the third XIAP baculoviral inhibitor of apoptosis repeat (BIR3) domain with a $K_i$ of 345 nM and to the MLXBIR3SG (a chimeric BIR domain that preserves the native ML-IAP peptide-binding site[9]) with a $K_i$ of 43 nM.[6] The 2.3 Å resolution crystal structure (PDB 3F7G) of **1** bound to the ML-IAP BIR domain (Fig. 1A) revealed that the NH and carbonyl of the P2 valine make specific contacts with the backbone of the BIR domain (Fig. 1B).

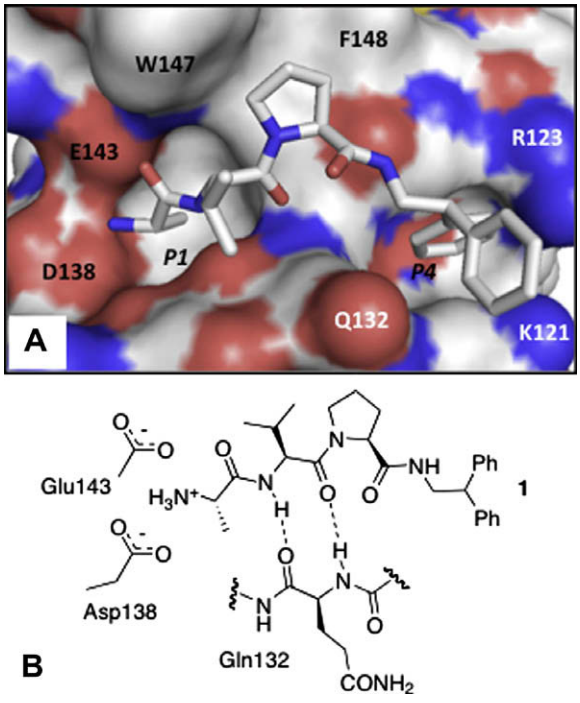


**Figure 1.** (A) Crystal structure of peptide **1** in complex with MLXBIR3SG at 2.3 Å resolution. The key P1 and P4 binding pockets are labeled (PDB 3F7G). (B) Illustration of key electrostatic and hydrogen bonds.

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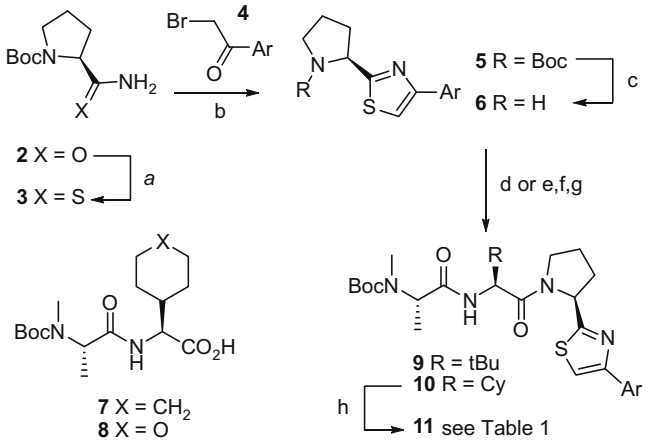



**Scheme 1.** Synthesis of thiazole amide isosteres. Reagents and conditions: (a) Lawesson's reagent, toluene, 50 °C, 1 h (90%); (b) 0.95 equiv pyridine, MeCN, 50 °C; (c) TFA, $CH_2Cl_2$; (d) **7** or **8**, DIC, HOAt, $CH_2Cl_2$; (e) Boc-*t*-Leu-OH, HATU, DIPEA, DMF; (f) TFA, $CH_2Cl_2$; (g) Boc-*N*-Me-Ala-OH, EDC, HOBT; (h) TFA, HPLC.

By contrast, the P3–P4 amide bond does not make any specific contacts with the protein, and thus was a good candidate for replacement with a heterocycle. Several potential heterocycles were evaluated for geometric fit, modular synthesis, and drug-likeness. From this analysis a thiazole appeared attractive, as did a 4-substituted benzothiazole.[10]

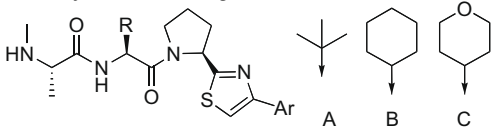
The synthesis of the thiazole-containing antagonists (Scheme 1) began with Boc-proline amide **2**, which was converted to the thioamide **3** with Lawesson's reagent in toluene at 50 °C. Use of higher temperatures led to complete racemization. Condensation with bromomethyl ketones proceeded smoothly under optimized conditions with 0.95 equiv of pyridine. Use of more pyridine or a stronger base prevented the dehydration step of the condensation and led to isolation of the hydroxy thiazoline intermediate, while use of less base resulted in significant removal of the Boc group and degradation of the product. After intermediate **6** was purified by chromatography, the Boc group could be cleanly removed. The antagonists were rapidly completed using the convergent peptide coupling procedure of Carpino.[11] Thus dipeptides **7** or **8** could be coupled in high yield with no evidence of epimerization of the P2 residue. Antagonists containing the *tert*-leucine residue at P2 were assembled stepwise with Boc-*t*-Leu, then Boc-*N*-Me-Ala. Finally, the Boc group was removed with trifluoroacetic acid in DCM, and the product purified by reverse-phase HPLC. The structures of these analogs are listed in Table 1.

Antagonists were assayed for binding to the BIR3 domain of XIAP and MLXBIR3SG using a previously reported fluorescence polarization assay (Table 1).[6] The simple phenyl analog **11a** lost significant affinity for MLXBIR3SG relative to our design starting point **1**, while a slight increase in affinity for XIAP-BIR3 was observed. Extending the P4 group to a naphthyl substituent dramatically increased affinity of the corresponding analog for both BIR domains. Further gains in affinity were found by substituting the naphthyl group with a small electron-withdrawing group at the 4-position as in **11e–g**. Affinity for the BIR domains could also be increased by adding a 5,6-fused ring system such as benzofuran in **11h–i** or benzothiophene **11k**.

In general, the nature of the P2 residue had little effect on affinity. The cyclohexyl group provided an opportunity to modify molecular properties. For instance, the substitution of a pyran for the cyclohexyl lowers the *c*Log *P* of **11c** from 4.9 to 2.5 for **11d**.[12]

Chemistry was developed to investigate the effect of substituents at the 5-position of the thiazole (Scheme 2). Deprotonation of naphthyl thiazole **12** with *n*-BuLi followed by treatment with

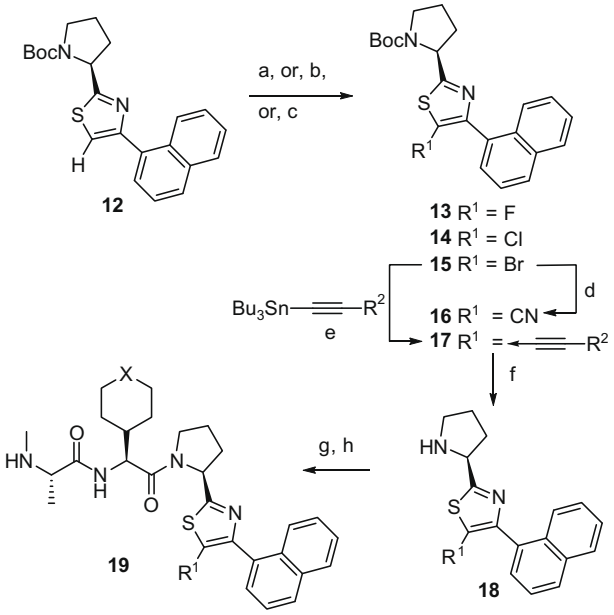
**Table 1**
Structure and affinity for thiazole antagonists[a]




| Compd | Ar | R | $K_i$[b] (mM) | |
|---|---|---|---|---|
| | | | XIAP-BIR3 | MLXBIR3SG |
| **11a** | Ph | B | 0.19 | 1.2 |
| **11b** | X = CH | A | 0.068 | 0.22 |
| **11c** | | B | 0.068 | 0.11 |
| **11d** | | C | 0.035 | 0.10 |
| **11e** | X = CF | B | 0.019 | 0.068 |
| **11f** | | C | 0.140 | 0.040 |
| **11g** | X = N | B | 0.075 | 0.045 |
| **11h** | | A | 0.13 | 0.18 |
| **11i** | | B | 0.10 | 0.20 |
| **11j** | | B | 0.12 | 0.13 |
| **11k** | | A | 0.047 | 0.12 |

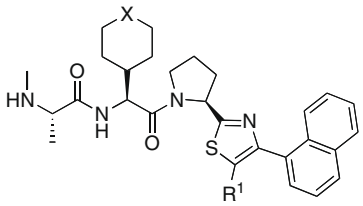
[a] $K_i$ determined as described in Ref. 6.
[b] Average of two measurements.

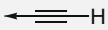
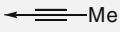
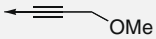
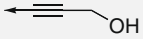
$(PhSO_2)_2NF$ yielded, after separation from residual starting material, the fluorinated derivative **13**.[13] While direct fluorination was unsuccessful, direct halogenation of **12** with NCS or NBS yielded chloro or bromo derivatives **14** or **15** in moderate yield. Bromo derivative **15** could be further elaborated by coupling with $Zn(CN)_2$




**Scheme 2.** Synthesis of 5-subsituted thiazoles. Reagents and conditions: (a) *n*-BuLi $(PhSO_2)_2NF$, THF −78 °C (18%); (b) NCS, 1:1 $CH_2Cl_2$/hexanes (50%); (c) NBS, $CH_2Cl_2$ (66%); (d) $Zn(CN)_2$, $PdCl_2DPPF$ DMF, $H_2O$, mWave, 130 °C 75%; (e) $Bu_3SnCCR_2$, $Pd(PPh_3)_4$, LiCl, PhMe, D (60%); (f) TFA, DCM (quant.); (g) **7** or **8**, DIC, HOAt, $CH_2Cl_s$; (h) TFA, HPLC (30–60%, two steps).

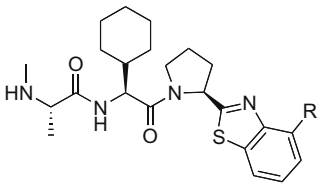
**Table 2**
Structure and affinity of 5-substituted thiazoles[a]

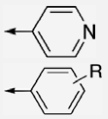


| Compd | X | $R^1$ | $K_i$[b] (mM) | |
|---|---|---|---|---|
| | | | XIAP-BIR3 | MLXBIR 3SG |
| **19a** | O | F | 0.024 | 0.068 |
| **19b** | $CH_2$ | Cl | 0.035 | 0.21 |
| **19c** | O | CN | 0.032 | 0.069 |
| **19d** | O |  | 0.031 | 0.16 |
| **19e** | O |  | 0.038 | 0.16 |
| **19f** | O |  | 0.031 | 0.14 |
| **19g** | O |  | 0.031 | 0.14 |

[a] $K_i$ determined as described in Ref. 6.
[b] Average of two measurements.

**Table 3**
Structure and affinity of benzothiazoles[a]



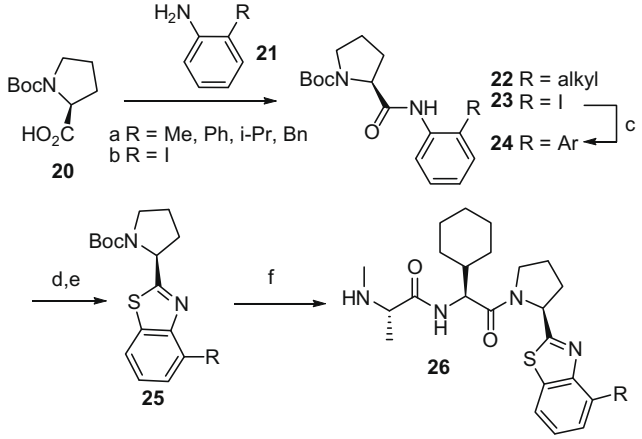
| Compd | R | $K_i$[b] (mM) | |
|---|---|---|---|
| | | XIAP-BIR3 | MLXBIR3SG |
| **26a** | Me | 0.94 | 2.7 |
| **26b** | *i*-Pr | 0.19 | 2.8 |
| **26c** | Bn | 0.15 | 0.71 |
| **26d** | Ph | 0.036 | 0.053 |
| **26e** |  | 0.05 | 0.20 |
| **26f** |  | 0.06 | 0.46 |
| **26g** | 2-Cl | 0.16 | 0.73 |
| **26h** | 3-Cl | 0.055 | 0.14 |
| **26i** | 4-Cl | 0.058 | 0.068 |
| **26j** | 2-F | 0.046 | 0.13 |
| **26k** | 3-F | 0.049 | 0.13 |
| **26l** | 4-F | 0.045 | 0.044 |

[a] $K_i$ determined as described in Ref. 6.
[b] Average of two measurements.

or an alkynyl stannane under palladium catalysis. These elaborated thiazoles were deprotected and coupled to dipeptides **7** or **8** as described in Scheme 2.

Analogs substituted with F and CN (**19a**, **19c**) had higher affinity for both the XIAP-BIR3 and MLXBIR3SG domains (Table 2). The larger chloro and alkyne substituents retained affinity for XIAP-BIR3, but lost affinity for MLXBIR3SG. These were small, but reproducible, variations for which the structural basis was not clear (vide infra).

Having succeeded in replacing the P3–P4 amide bond with a thiazole, we were encouraged to also try a benzothiazole. These were synthesized as shown in Scheme 3. Boc-proline was coupled to 2-substituted anilines using standard peptide coupling conditions. Subsequent Suzuki–Miyaura coupling gave access to a variety of 2-aryl substituted analogs to probe the P4 pocket. Conversion to the thioamide using Lawesson's reagent at 80 °C gave moderate yields and resulted in some racemization of the proline. These thioamides were oxidatively cyclized to the benzothiazole using basic potassium ferricyanide.[14] The antagonists were completed using the previously described fragment coupling and deprotection sequence. Purification by reverse-phase HPLC removed the minor diastereomer generated during formation of the thioamide and gave rise to analogs **26a–l**, for which binding affinities for both XIAP-BIR3 and MLXBIR3SG are shown in Table 3.



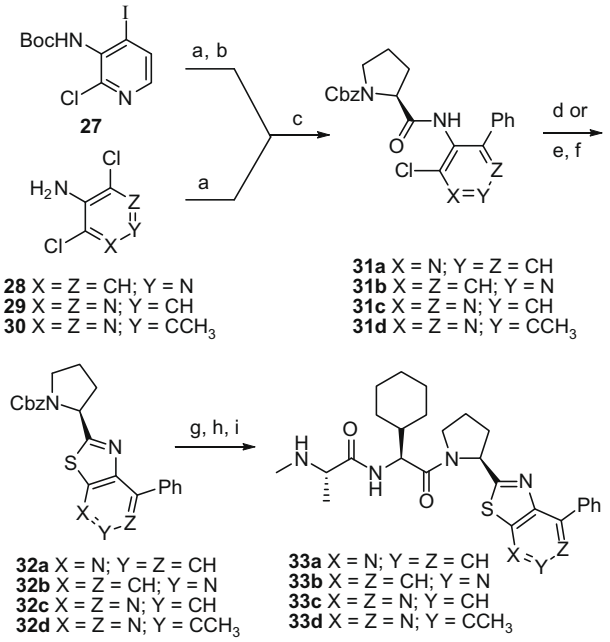

**Scheme 3.** Reagents and conditions: (a) HATU, DIPEA, DMF, 50 °C; (b) cyanuric fluoride, pyridine, $CH_2Cl_2$; (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, DMF, $H_2O$; (d) Lawesson's reagent, toluene, 80 °C; (e) $K_3Fe(CN)_6$, NaOH, $H_2O$, 85 °C; (f) TFA, toluene, $CH_2Cl_2$; (g) **7**, DIC, HOAt, $CH_2Cl_2$; (h) TFA, toluene, $CH_2Cl_2$, HPLC.

From our initial set of analogs we determined that an unsubstituted phenyl ring in the 4-position of the benzothiazole (**26d**), gave the highest affinity for both BIR domains. Replacement with an isopropyl (**26b**) or benzyl (**26c**) group reduced the affinity 4–5-fold, and a simple methyl group in the P4 pocket resulted in a 26-fold reduction in affinity (**26a**). Substituting the phenyl ring in the P4 pocket revealed more subtle variations in the SAR. The 3-pyridyl compound **26e** was only slightly less potent than **26d**, and the 4-pyridyl compound **26f** was equipotent in binding the BIR3 domain of XIAP, but bound to MLXBIR3SG with eightfold less affinity.

We continued to assess the binding preferences of the P4 pocket by substituting the phenyl ring exhaustively with fluorine and chlorine (**26g–l**). Most of these compounds showed very small differences in affinity from one another and from the unsubstituted **26a**. The exception was the 2-chloro substituted compound **26g**, which bound both BIR domains with significantly lower affinity. This was attributed either to an unfavorable contact between the chlorine atom and the protein or, more likely, to an increase in the torsion angle between the benzothiazole and the 2-chlorophenyl rings which, in turn, produces a less favorable interaction with the P4 pocket.

We turned our attention to modifications of the benzothiazole itself in an effort to modify the properties of our molecules. As a consequence of the peptidic portion of our molecules, the topological polar surface area (tPSA) of **26a** was 73.8 $Å^2$, however the *c*Log *P* was 5.1, which decreases the probability of successful development.[15] We experimented with the placement of nitrogen atoms in the phenyl ring of the benzotrizole, addition of which increases the tPSA by approximately 13, while reducing the *c*Log *P* by nearly a full unit.

We began our synthesis of the aza-benzothiazoles by preparing the biphenyl amides **31a–d** (Scheme 4). Inclusion of a chloro substituent *ortho* to the aniline nitrogen provided the desired aza-ben-

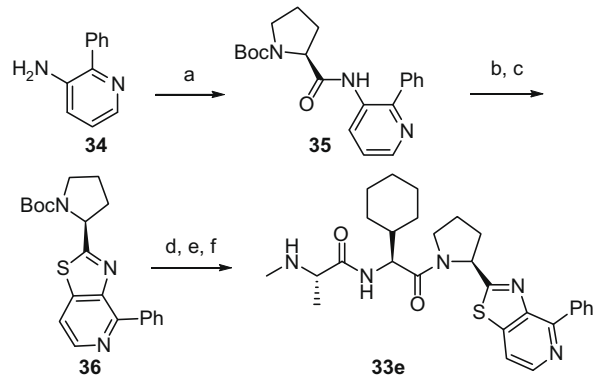



**Scheme 4.** Reagents and conditions: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, $K_2CO_3$, DMF, $H_2O$ (27–83%); (b) TFA, toluene, $CH_2Cl_2$, 40 °C (100%); (c) Cbz-Pro-COCl, pyridine, $CH_2Cl_2$, 40 °C (99%); (d) for **31a** and **31b–c**: Lawesson's reagent, toluene, 100 °C (51–75%); (e) for **31b**: $Tf_2O$, pyridine, $CH_2Cl_2$, 0 °C, then aq $(NH_4)_2S$ (35%); (f) DMF, 120 °C (96%); (g) TFA, thioanisole, 40 °C (100%); (h) **7**, DIC, HOAt, $CH_2Cl_2$; (i) TFA, HPLC (30–60%, two steps).

zothiazole[16] upon conversion to the thioamide using either Lawesson's reagent or Charette's method of conversion to the pyridinium triflate salt and subsequent cleavage with $(NH_4)_2S$.[17] Our standard peptide coupling and deprotection gave access to the compounds **33a–d**. We completed the synthesis of **33e** using a route nearly identical to that used for making our original benzothiazoles (Scheme 5).

We observed that these aza-benzothiazoles bound to both BIR domains with near equal affinity (Table 4), and were essentially equipotent to their benzothiazole analogs. The exception was diaza-benzothiazole **33c** dropped 3–7-fold in affinity. Interestingly, the affinity was recovered when the ring was substituted with a methyl group (**33d**). The basis for this improved affinity remains unclear, as this region appears to be solvent exposed in the bound state (vide infra).

To gain a more detailed understanding of the interactions between the thiazole-containing IAP antagonists and the BIR domain of ML-IAP, the crystal structures of complexes between MLX-




**Scheme 5.** Reagents and conditions: (a) Boc-Pro-OH, EDC, DIPEA; (b) Lawesson's reagent, toluene, 100 °C; (c) $K_3Fe(CN)_6$, NaOH, $H_2O$, 120 °C; (d) TFA, toluene, $CH_2Cl_2$; (e) TFA, toluene, $CH_2Cl_2$; (f) **7**, DIC, HOAt, $CH_2Cl_2$; (g) TFA, toluene, $CH_2Cl_2$, HPLC.

**Table 4**
Affinity of aza-benzothiazoles[a]

| Compound | $K_i$[b] (mM) | |
|---|---|---|
| | XIAP-BIR3 | MLXBIR3SG |
| **33a** | 0.041 | 0.036 |
| **33b** | 0.073 | 0.049 |
| **33c** | 0.26 | 0.13 |
| **33d** | 0.051 | 0.032 |
| **33e** | 0.037 | 0.024 |

[a] $K_i$ determined as described in Ref. 6.
[b] Average of two measurements.

BIR3SG and compounds **11b** (PDB 3GT9) and **26d** (PDB 3GTA) were determined to resolutions of 1.7 Å (Fig. 2). Key contacts observed in the structure of **1** in complex with the ML-IAP BIR domain (Fig. 1A) are conserved in the complexes with **11b** and **26d**. In particular, hydrogen bonds with the main chain of Gln132 and the side chain carboxylate of Asp138 are maintained. The hydrophobic contacts in the P4 pocket differ in our new complexes. In the case of **11b**, the 1-naphthyl group makes extensive hydrophobic contacts with the side chain of Lys121. In compound **26d**, the 4-phenyl ring makes similar hydrophobic contacts with the Lys side chain, while the six-membered ring of the benzothiazole makes a close π–π interaction with the amide of Gln132.[18] In both cases, the replacement for the P3–P4 amide successfully presents the aromatic side chain appropriately to the P4 pocket, which results in the observed high affinity binding.

Beginning from the crystal structure of peptide **1**, we were successful in replacing the P3–P4 amide bond with both a thiazole and a benzothiazole amide isostere. A series of compounds were produced to evaluate the SAR of substitutions both on the heterocycle as well as on the hydrophobic portion of the molecules extending into the P4 pocket. In the thiazole series, a naphthalene or benzothiophene in the 4-position was found to be optimal for high affin-

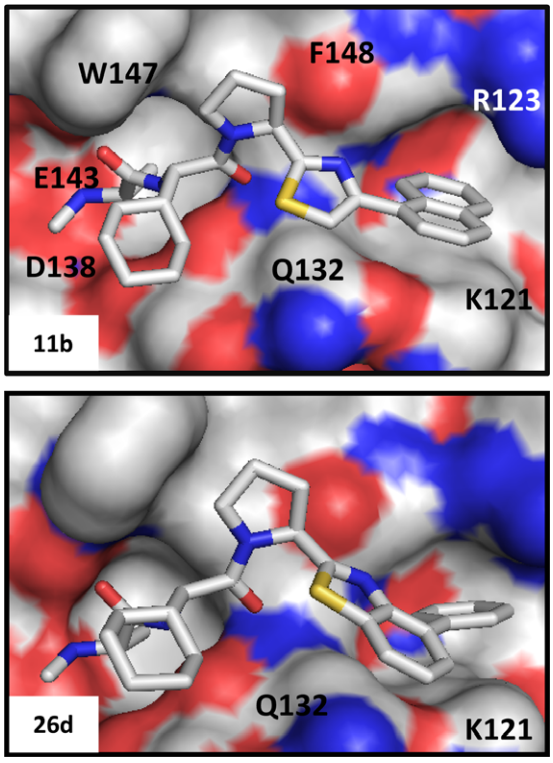



**Figure 2.** Crystal structures of **11b** (PDB 3GT9) and **26d** (PDB 3GTA) in complex with MLXBIR3SG at 1.7 Å resolution.

ity binding to either BIR domain. Affinity could be further improved through the inclusion of a small electronegative substituent at the 4-position of the naphthalene. A similar improvement in affinity was observed when the 5-position of the thiazole was substituted with electronegative functional groups. When the P3–P4 amide bond was replaced with a benzothiazole, the P4 pocket appears to accommodate a variety of aromatic rings with relatively small differences in affinity for the BIR domain of ML-IAP (MLXBIR3SG) and the BIR3 domain of XIAP. One notable exception was the reduced affinity of the 2-chloro phenyl substitution, which we believe to be the result of an alteration of the torsion angle between the benzothiazole and 2-chlorophenyl rings. Inclusion of nitrogen into the benzothiazole ring, undertaken with an eye to improving the physical properties of the molecules, did not significantly alter the affinity of these molecules for the BIR domains. Crystal structures of several of the molecules complexed to the MLXBIR3SG protein supported our hypothesis that the critical relationship for high affinity binding to this protein is the favorable presentation of an aromatic ring or rings for binding in the P4 pocket.

## Acknowledgments

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