

## Terphenyl-Based Bak BH3 $\alpha$ -Helical Proteomimetics as Low-Molecular-Weight Antagonists of Bcl-x<sub>L</sub>

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**Abstract:** We describe a general method for the mimicry of one face of an  $\alpha$ -helix based on a terphenyl scaffold that spatially projects functionality in a manner similar to that of two turns of an  $\alpha$ -helix. The synthetic scaffold reduces the flexibility and molecular weight of the mimicked protein secondary structure. We have applied this design to the development of antagonists of the  $\alpha$ -helix binding protein Bcl-x<sub>L</sub>. Using a sequential synthetic strategy, we have prepared a library of terphenyl derivatives to mimic the helical region of the Bak BH3 domain that binds Bcl-x<sub>L</sub>. Fluorescence polarization assays were carried out to evaluate the ability of terphenyl derivatives to displace the Bcl-x<sub>L</sub>-bound Bak peptide. Terphenyl **14** exhibited good in vitro affinity with a K<sub>i</sub> value of 0.114  $\mu$ M. These terphenyl derivatives were more selective at disrupting the Bcl-x<sub>L</sub>/Bak over the HDM2/p53 interaction, which involves binding of the N-terminal  $\alpha$ -helix of p53 to HDM2. Structural studies using NMR spectroscopy and computer-aided docking simulations suggested that the helix binding area on the surface of Bcl-x<sub>L</sub> is the target for the synthetic ligands. Treatment of human embryonic kidney 293 (HEK293) cells with terphenyl derivatives resulted in the disruption of the binding of Bcl-x<sub>L</sub> to Bax in intact cells.

### Introduction

The development of low-molecular-weight agents that disrupt protein–protein interactions is still a challenging goal in medicinal chemistry because the protein interfacial surfaces involved are relatively large and featureless compared to those of enzyme active sites.<sup>1</sup> Conventional methods for identifying inhibitors of protein–protein interactions have generally involved the preparation and screening of chemical libraries to discover lead compounds although often with little success.<sup>2</sup> The rational design of such inhibitors offers a compelling alternative as it can often be based on a structural knowledge of the interface. In particular, synthetic scaffolds that mimic the key elements of a protein surface can potentially lead to small molecules with the full activity of a protein domain, a fraction of the molecular weight, and no peptide bonds.

$\alpha$ -Helices are the most common protein secondary structure, accounting for over 40% of polypeptide amino acids in natural proteins.<sup>3</sup> The pharmaceutical potential for synthetic mimics of  $\alpha$ -helices is immense because  $\alpha$ -helices play pivotal roles in

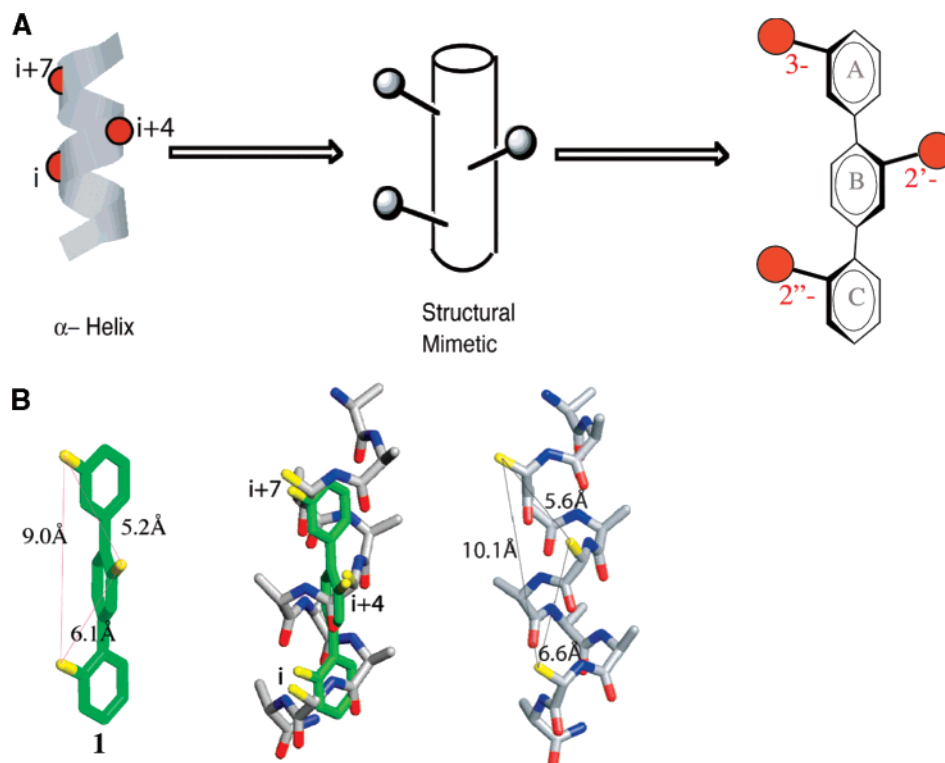
many protein–protein interfaces.<sup>2,4</sup> However, only a few examples of such molecules have been prepared. In pioneering work, functionalized indanes have been shown to match the *i* and *i* + 1 residues of an  $\alpha$ -helix and give potent inhibitors of the tachykinin receptors.<sup>5</sup> Kahne et al. reported an  $\alpha$ -helix mimic, based on an oligosaccharide scaffold, which binds the minor groove of DNA with selectivity over RNA.<sup>6</sup> We have recently introduced a proteomimetic strategy based on molecules that mimic the structure and recognition function of discontinuous stretches of an  $\alpha$ -helix.<sup>7</sup> We have extended this notion by using a terphenyl scaffold with appended functionality to mimic substituents projecting from the surface of an  $\alpha$ -helix.<sup>8–10</sup> In this design, the terphenyl is expected to adopt a staggered conformation and closely reproduce the position and angular

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**Figure 1.** (A) Proteomimetics. (B) Overlay of a polyaniline  $\alpha$ -helix and the energetically minimized conformation of 3,2',2''-trimethylterphenylene (**1**; RMSD = 0.851).

orientation of functionality on the surface of an  $\alpha$ -helix. We have reported functionalized terphenyls as mimetics of the  $\alpha$ -helical region of the Bak BH3 domain involved in apoptosis.<sup>10</sup> In a further extension of this approach, we have developed other low-molecular-weight helical mimetics, such as terephthalamide and oligoamide-foldamer derivatives, as inhibitors of the Bcl-x<sub>L</sub>/Bak interaction.<sup>11</sup>

Apoptosis (programmed cell death) is essential in many physiological processes.<sup>12</sup> The B-cell lymphoma-2 (Bcl-2) protein family, composed of pro-apoptotic (Bak, Bax, Bad, Bid) and antiapoptotic subfamilies (Bcl-2, Bcl-x<sub>L</sub>), are critical regulators of apoptosis.<sup>13,14</sup> The sensitivity of cells to apoptotic stimuli depends on the balance of pro- and antiapoptotic Bcl-2 proteins. The heterodimerization of anti- and proapoptotic Bcl-2 proteins leads to the formation of pores in the mitochondrial membrane, resulting in the release of cytochrome *c*, which in turn activates the caspase cascade.<sup>15</sup> Previous studies have shown that overexpressed Bcl-2 or Bcl-x<sub>L</sub> can block the apoptotic pathway and impede the functions of many anticancer agents.<sup>16</sup> Mimicking the function of the proapoptotic Bcl-2 proteins could lead to a new class of anticancer agents and thus is of immense interest in medicinal chemistry. Recently, the groups of Schep-

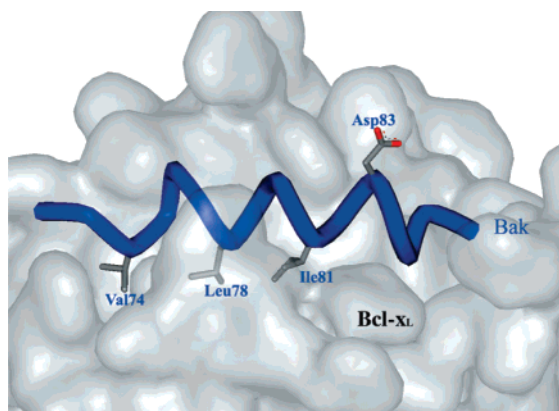
artz and Verdine have successfully developed constrained peptides that mimic the  $\alpha$ -helical region of the death-promoting Bak BH3 domain;<sup>17</sup> the rational design of low-molecular-weight inhibitors that recognize the Bak-binding region on Bcl-x<sub>L</sub> with high specificity remains a challenging goal.

As an extension of our previous study,<sup>10</sup> we herein report a group of Bcl-x<sub>L</sub> antagonists, based on the terphenyl scaffold, designed to mimic the Bak BH3 peptide. Using a fluorescence polarization assay, we have observed high in vitro inhibitory potencies in disrupting the Bcl-x<sub>L</sub>/Bak complexation. NMR spectroscopic analyses and computer-aided docking simulations suggested that the helix binding area on the surface of Bcl-x<sub>L</sub> is the target for the synthetic ligands. Cellular assays demonstrated that the terphenyl derivatives are effective in disrupting the Bcl-x<sub>L</sub>/Bax interaction in intact cells.

Our design is based on an extended 3,2',2''-trisubstituted terphenylene scaffold in which the para-coupling of a series of ortho-substituted aryl subunits results in molecules that mimic the functionality at  $i$ ,  $i + 4$ , and  $i + 7$  positions of an  $\alpha$ -helix (Figure 1A). Although there is some flexibility due to aryl-aryl bond rotation, the scaffold balances this with a rigid core structure allowing some optimization of binding interactions due to induction of fit. Energy minimization of 3,2',2''-trimethylterphenylene (**1**) showed that the terphenyl scaffold takes up a staggered conformation, with the projected ortho-substituents in a good agreement with the targeted amino acid side chains at the  $i$ ,  $i + 4$ , and  $i + 7$  positions of an  $\alpha$ -helix (Figure 1B).<sup>18</sup>

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**Figure 2.** Interface of the Bcl-x<sub>L</sub>/Bak BH3 domain complex. Hydrophobic residues (V74, L78, I81) and D83 of the Bak BH3 domain play critical roles in the binding.

The distances between the methyl groups are 5.2 (3, 2'), 6.1 (2', 2''), and 9.0 (3, 2'') Å, closely corresponding to the side chains at  $i$ ,  $i + 4$ , and  $i + 7$  positions in an  $\alpha$ -helix (5.6, 6.6, and 10.1 Å, respectively). Aryl–aryl torsion angles of 56.0° (A–B) and 55.9° (B–C) give a conformation with close correspondence of the positions of the three ortho-substituents and the  $i$ ,  $i + 4$ , and  $i + 7$  side chains in an  $\alpha$ -helix. Computational modeling shows the superimposition of **1** on the  $i$ ,  $i + 4$ , and  $i + 7$  side chains of a polyalanine  $\alpha$ -helix with a root-mean-square deviation (RMSD) value of 0.851 Å, suggesting good stereochemical similarity between the pair (Figure 1B).

The NMR-derived structure of the Bcl-x<sub>L</sub>/Bak BH3 domain complex indicated that the Bak peptide is an amphipathic  $\alpha$ -helix that interacts with Bcl-x<sub>L</sub> by projecting its side chains of V74, L78, and I81, on one face of the helical backbone, into a hydrophobic cleft of Bcl-x<sub>L</sub> (Figure 2).<sup>19</sup> In addition, Bak D83 forms an ion pair with a lysine residue of Bcl-x<sub>L</sub>. A 26-mer peptide, derived from the related protein Bad, binds even better to Bcl-x<sub>L</sub>,<sup>20,21</sup> exploiting larger hydrophobic residues (Y, F) to induce a slight structural change in the binding region of Bcl-x<sub>L</sub>. Furthermore, it has been shown that the  $\alpha$ -helical propensity of these peptides is decisive for strong binding to Bcl-x<sub>L</sub>.<sup>20</sup> On the basis of these structural requirements, we designed a series of terphenyl molecules containing alkyl or aryl substituents on the three ortho-positions to mimic the key hydrophobic substituents on the helical exterior of Bak and carboxylic acid substituents on one or both ends to mimic the additional ion pair.

## Results and Discussion

**Synthesis and Crystallographic Analysis.** A flexible and modular synthesis was developed using *O*-alkylated phenols as building blocks. The terphenyl backbone was synthesized by sequential Suzuki aryl–aryl cross-coupling of the corresponding *p*-methoxyphenylboronate and phenyltriflate derivatives. Carboxyl groups were attached on one or both ends of the terphenyl backbone in order to mimic the D83 residues in the Bak BH3 peptide. Scheme 1 shows a modular synthesis of terphenyl derivative **14**. A 2-cyanoethyl substituent was introduced at the 4-position of 4-iodo-2-isobutyl-1-anisole (**3**) using a Heck reaction, followed by the reduction of the resulting olefin to generate

propionitrile **5**. The phenol group was deprotected using BBr<sub>3</sub> and activated to triflate **7**, which in turn underwent a Suzuki cross-coupling reaction with 2-(4-methoxy-3-naphthalen-1-ylmethyl-phenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane.

Deprotection and triflation of the resulting biphenyl **8** was followed by a second Suzuki coupling, giving the terphenyl **11**. The final steps involved deprotection and alkylation of the hydroxyl group with chloroacetonitrile, affording (cyanomethoxy)-terphenyl **13**. Hydrolysis of the terminal cyano groups produced **14** with two carboxyl groups on both ends of the terphenyl backbone. The resulting acid groups were converted into their corresponding ammonium salts to increase the solubility of the terphenyl derivatives in aqueous solution.

Crystallographic analysis has confirmed that in the solid state the terphenyl derivatives take up a staggered conformation similar to that in Figure 1B.<sup>8</sup> Figure 3 shows that 3,2',2''-trimethyl-4-nitro-4''-hydroxyterphenyl (**2**) projects all three ortho-side chains on the same face. The distances between these side chains are 5.10, 6.28, and 8.83 Å, which compare to those of the side chains at the  $i$ ,  $i + 4$ , and  $i + 7$  positions in an  $\alpha$ -helical peptide (5.6, 6.6, and 10.1 Å, respectively). This solid-state structure shows that terphenyl derivatives of this type can adopt a conformation that reproduces the spatial arrangement of the side chains in  $\alpha$ -helices. However, the aryl–aryl bond rotational barrier is low, suggesting that minor conformational changes can occur to optimize contact to the helix-binding domain of a protein target.<sup>22</sup>

**In Vitro Evaluation.** The inhibitory effects of these terphenyl derivatives on the Bcl-x<sub>L</sub>/Bak complex were evaluated using a previously reported fluorescence polarization assay.<sup>23</sup> The Bak BH3 peptide was labeled with fluorescein as the probe to monitor the competitive binding of the terphenyl compounds to Bcl-x<sub>L</sub>. Regression analysis was conducted to determine the IC<sub>50</sub> values, which in turn can be related to the known affinity of the 16-mer Bak BH3 peptide to acquire the inhibitory constant ( $K_i$ ) of the inhibitors.<sup>10,24</sup> To test the validity of this assay, we used a nonlabeled Bak BH3 peptide as the competitive inhibitor to bind Bcl-x<sub>L</sub>, giving  $K_i = 0.122 \mu\text{M}$ , which closely corresponds to the  $K_d$  value (0.120  $\mu\text{M}$ ) obtained from a saturation titration experiment.

Structure–activity studies have shown that the terphenyl derivatives recognize the Bak-binding site through specific binding. Terphenyl derivative **14**, with an isobutyl, 1-naphthylmethyl, isobutyl side chain sequence, was identified as a potent inhibitor of Bcl-x<sub>L</sub> with  $K_i = 0.114 \mu\text{M}$  (Table 1). Analogues **15** and **16**, which contain smaller side chains, showed lower activities ( $K_i = 2.09$  and  $1.82 \mu\text{M}$ , respectively), indicating that hydrophobic surface area is critical for binding to the helix-binding cleft on Bcl-x<sub>L</sub>. Compound **19**, an isomer with a different arrangement of the same side chains as **14**, is significantly less potent, confirming the importance of effective shape complementarity. Nonspecific binding by the terphenyl backbone does not appear to be significant since **22** lacking the interacting side chains shows only weak binding to Bcl-x<sub>L</sub>.

We have further studied the role of the carboxyl groups by converting them to ammonium groups (**24**), which gave lowered

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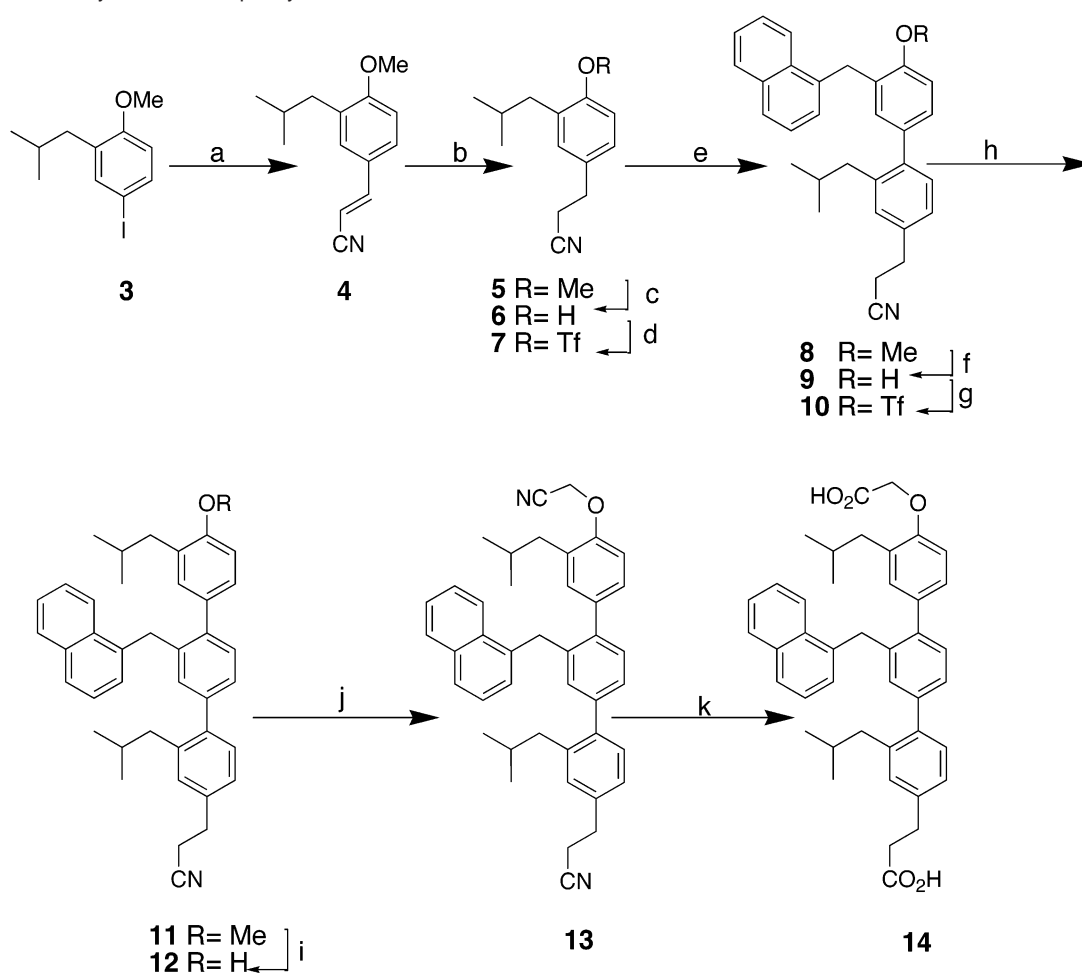
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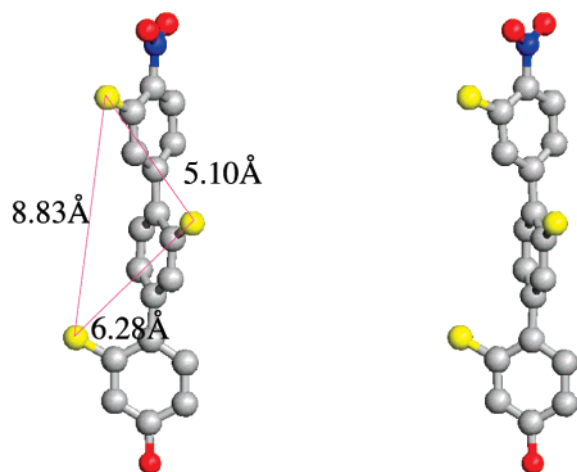
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Scheme 1. Modular Synthesis of Terphenyl Derivative 14<sup>a</sup>

<sup>a</sup> (a) Acrylonitrile, Pd(OAc)<sub>2</sub>, Bu<sub>4</sub>NCl, KOAc, DMF, 63%. (b) Mg, MeOH, 100%. (c) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 98%. (d) Tf<sub>2</sub>O, DIEA, CH<sub>2</sub>Cl<sub>2</sub>, 90%. (e) 2-(4-Methoxy-3-naphthalen-1-ylmethyl-phenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane, Pd(PPh<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, DMF, 78%. (f) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 85%. (g) Tf<sub>2</sub>O, DIEA, CH<sub>2</sub>Cl<sub>2</sub>, 82%. (h) 2-(3-Isobutyl-4-methoxyphenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane, Pd(PPh<sub>3</sub>)<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, DMF, 47%. (i) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 76%. (j) ClCH<sub>2</sub>CN, K<sub>2</sub>CO<sub>3</sub>, DMF, 96%. (k) NaOH, Bu<sub>4</sub>NOH(aq.), 1,4-dioxane, 100%.



**Figure 3.** Stereoview of the X-ray crystal structure of 3,2',2''-trimethyl-4-nitro-4''-hydroxyterphenylene (**2**).

activity ( $K_i = 13.6 \mu\text{M}$ ), or to methyl esters (**23**), which showed poor solubility in aqueous solution. Terphenyl derivatives with a carboxyl group at only one end of the backbone, such as **25**–**30**, showed weaker binding affinity compared to the terphenyl derivatives with two flanking acid functionalities at each end of the scaffold. The second carboxyl group possibly mimics




the Bak D83 and interacts with a Bcl-x<sub>L</sub> lysine residue, enhancing the binding affinity. Compound **21** with a third carboxylic acid on the middle phenyl ring did not show strong potency in disrupting the Bcl-x<sub>L</sub>/Bak binding, ruling out the possibility that the terphenyl compounds recognize the protein by nonspecific interaction with the positive charges on the Bcl-x<sub>L</sub> exterior surface.

A key issue is whether the terphenyl scaffold could demonstrate selectivity among different helix-binding proteins. Schepartz et al. have shown that aPP-templated miniature proteins can selectively bind to Bcl-x<sub>L</sub> or Bcl-2, two paralog proteins.<sup>25</sup> To this end, we have determined the ability of the terphenyl derivatives to disrupt the binding of the N-terminal  $\alpha$ -helix of the tumor suppressor p53 to HDM2, as well as the binding of Bak BH3 to Bcl-2, a Bcl-x<sub>L</sub> homolog. Terphenyl **14** selectively binds to Bcl-x<sub>L</sub> and Bcl-2 over HDM2 (225- and 212-fold, respectively), while its isomer **17**, with a 2-naphthylmethyl side chain on the middle ring, is more potent in disrupting the p53/HDM2 interaction under the same assay conditions (Figure 4). This selectivity may provide unique applications in the recognition of a specific protein in the presence of other structurally similar targets in a complex cellular environment.


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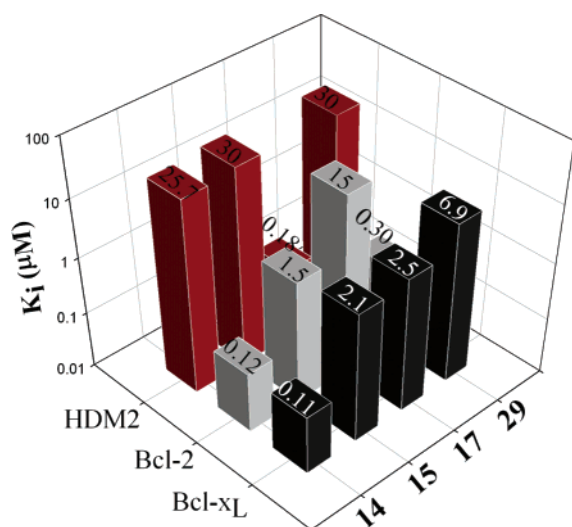


**Table 1.** Results of the Fluorescence Polarization Assay using Fluorescein-Labeled Bak (BH3 domain 72–86) Binding to Bcl-x<sub>L</sub>

X	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	K <sub>i</sub> ( $\mu$ M) <sup>24</sup>
	-iBu		-iBu	-H	<b>14</b> 0.114
	-iBu	-iPr	-iBu	-H	<b>15</b> 2.09
	-iBu	-Bn	-iBu	-H	<b>16</b> 1.82
-COOH	-iBu		-iBu	-H	<b>17</b> 2.50
	-Bn	-Bn	-iBu	-H	<b>18</b> 2.73
		-iBu	-iBu	-H	<b>19</b> 2.70
	-Bn	-Me	-Me	-Me	<b>20</b> 2.34
-COOMe	-Bn	-Me	-Me	-(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	<b>21</b> >30.0
	-H	-H	-H	-H	<b>22</b> >30.0
	-iBu	-iPr	-iBu	-H	<b>23</b> No affinity
-CH <sub>2</sub> NH <sub>4</sub> Cl	-iBu	-iPr	-iBu	-H	<b>24</b> 13.6

R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	K <sub>i</sub> ( $\mu$ M)
-Me	-Me	-Me	<b>25</b> 18.2
-iPr	-Me	-Me	<b>26</b> 10.4
-iPr	-iBu	-iBu	<b>27</b> 4.82
-Bn	-Et	-iPr	<b>28</b> 3.27
	-Et	-iPr	<b>29</b> 6.88
-H	-H	-H	<b>30</b> >30

**Figure 4.** Comparison of terphenyl derivatives that bind to different helix-binding proteins.

**Binding Mode Studies.** A computational docking simulation of **14** using the Autodock 3.0 program suggested that the binding cleft for the Bak BH3 domain on the surface of Bcl-x<sub>L</sub> is the target area for the synthetic inhibitors (Figure 5A).<sup>26</sup> The top-ranked binding modes all lie within the Bak BH3 binding pocket.

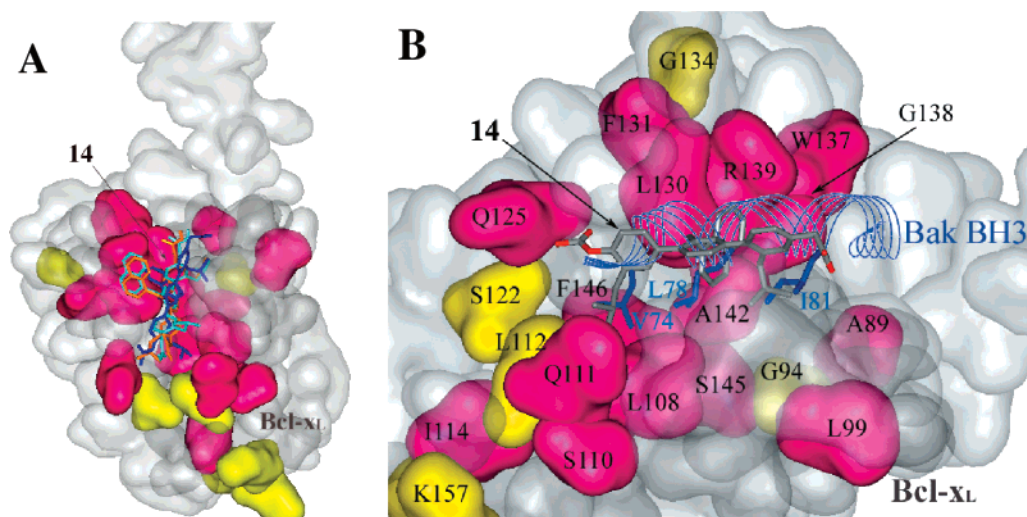
<sup>15</sup>N-HSQC experiments lent further support to the proposed binding site of the terphenyl derivatives in the Bak BH3 binding region. The residues of A89, L99, L108, T109, S110, Q111, I114, Q125, L130, F131, W137, G138, R139, I140, A142, S145,

and F146 (shown in magenta in Figure 5) showed significant chemical shift changes upon the addition of the synthetic inhibitor **14**. Some other residues, including G94, L112, S122, G134, K157, E158, M159 (shown in yellow in Figure 5) showed moderate chemical shift changes under the same conditions. These affected residues all lie near the shallow cleft on the protein surface into which the Bak BH3 helix binds. The targeted residues V74, L78, and I81 of Bak BH3 are within 4 Å distance of residues F97, R102, L108, L130, I140, A142, and F146 of Bcl-x<sub>L</sub>, most of which showed significant chemical shift changes (F97 overlapped with N5), confirming that **14** and Bak BH3 target the same area on the exterior surface of Bcl-x<sub>L</sub>. Overlay of **14** and the Bak BH3 peptide (Figure 5B) suggested that the terphenyl indeed adopts a staggered conformation, mimicking the cylindrical shape of the helix with the substituents making a series of hydrophobic contacts with the protein surface.

$\alpha$ -Helical domains achieve high selectivity for their protein targets through the precise projection of recognition groups from their surfaces. Comparison of different terphenyl derivatives (**14**, **16**–**18**) has revealed a good correlation between the terphenyl/Bcl-x<sub>L</sub> contacts and their binding affinities. Table 2 lists the amino acid residues affected within the Bak BH3 binding cleft on the Bcl-x<sub>L</sub> surface upon the ligand binding. Terphenyl **14** affected more residues in the Bak BH3 binding pocket, suggesting that its side chains recognize the target pockets with good spatial complementarity. In contrast, **17** induced fewer residues showing chemical shift changes, indicating that the weaker affinity of **17** is due to a less effective fit.

**Inhibition of the Bcl-x<sub>L</sub>/Bak Association in Intact Human Cells.** To determine if terphenyl derivatives inhibit the BH3-mediated interaction with Bcl-x<sub>L</sub> in intact cells, HEK293 cells transfected with both HA-Bcl-x<sub>L</sub> and flag-Bax (a close family member of Bak) were treated with 100  $\mu$ M of the indicated

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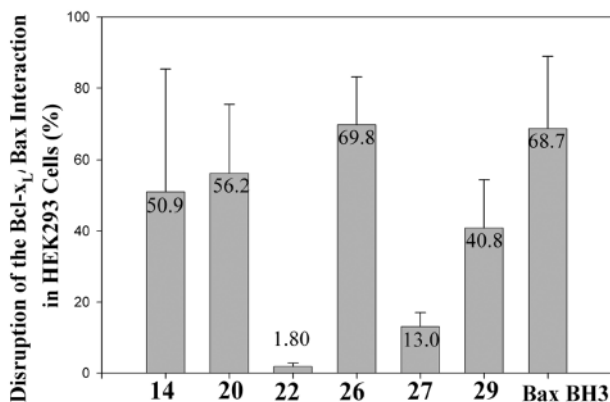


**Figure 5.** Results of the  $^{15}\text{N}$ -HSQC and the molecular-docking experiments of **14** binding to Bcl- $x_L$ . The residues that showed significant and moderate chemical shift changes upon the addition of **14** are shown in magenta and yellow, respectively. (A) The three top-ranked binding modes of **14** are shown in blue (rank 1), orange (rank 2), and cyan (rank 3). (B) Overlay of the top-ranked docking result of **14** and the Bak BH3 peptide (blue). The key hydrophobic side chains of V74, L78, and I81 are shown in stick representations.

**Table 2.** Comparison of the Amino Acid Residues Affected by Different Terphenyl Derivatives within the Bak BH3 Binding Pocket in  $^{15}\text{N}$ -HSQC Experiments

ligand	significantly shifted residues <sup>a</sup>	moderately shifted residues <sup>a</sup>
Bak peptide	S106, L112, A142, A148, A199, E202	R100, Y101, S122, R132, D133, V192, L194, A100
<b>14</b>	A89, L99, L108, T109, S110, Q111, I114, Q125, L130, F131, W137, G138, R139, I140, A142, S145, F146	G94, L112, S122, G134, K157, E158, M159
<b>16</b>	R100, F105, L108, L112, I114, Y120, L194	R100, Q121
<b>17</b>	R100, L112	D95, Q121, Q125
<b>18</b>	L112, I114, Y120, S122, F143, L194, Y195, A200	Q121, V192

<sup>a</sup>  $\Delta\omega_{\text{NH}} > 0.5\Delta\omega_{\text{NH}}^{\text{max}}$ . <sup>b</sup>  $0.5\Delta\omega_{\text{NH}}^{\text{max}} > \Delta\omega_{\text{NH}} > 0.3\Delta\omega_{\text{NH}}^{\text{max}}$ .



**Figure 6.** Inhibition of the Bcl- $x_L$ /Bax association in whole cells.

terphenyl derivatives or control Bax BH3 peptide. After 24 h incubation, the cells were harvested, lysed, and subjected to immunoprecipitation with anti-HA antibody. The resulting mixture was loaded onto a 12.5% SDS-PAGE gel, and proteins transferred to nitrocellulose for Western blot analysis. The presence of flag-Bax protein in the HA-Bcl- $x_L$  immune complexes was detected with anti-flag antibody. The inhibitory potencies of the terphenyl compounds were determined by measuring the relative intensity of flag-Bax protein co-immunoprecipitated with HA-Bcl- $x_L$ . As shown in Figure 6, the terphenyl derivative **14** blocked the Bcl- $x_L$ /Bax complexation by  $50.9 \pm 34.5\%$ . Terphenyl derivative **26**, with isopropyl, methyl, methyl side chains, showed the strongest effect with

$69.8 \pm 13.4\%$  inhibition of Bcl- $x_L$ /Bax association, which was similar to the Bax BH3 peptide, perhaps due to improved membrane permeability in **26**. Consistent with this, computational analysis of Caco-2 permeability suggested that **26** has better membrane penetration (327 nm/s) than **14** (14.5 nm/s).<sup>27</sup>

In conclusion, a strategy of helix mimicry based on a substituted terphenyl scaffold was successfully applied to the design of a Bcl- $x_L$  antagonist. Terphenyl derivative **14** exhibited binding affinity in the nanomolar range as seen in the fluorescence polarization assay. The binding modes of the terphenyl derivatives were confirmed by means of NMR spectroscopy and computational docking simulations. Co-immunoprecipitation experiments showed that terphenyl derivatives are effective in disrupting the Bcl- $x_L$ /Bax interaction in intact cells. We have also shown that the terphenyl serves as a general scaffold to mimic  $\alpha$ -helical segments with good selectivity in recognition of different helix-binding proteins.

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**Supporting Information Available:** Experimental section and complete refs 19 and 20. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(27) The permeability prediction analysis was carried out using: *QikProp V2.1*; Schrodinger Inc.: New York, 2003.