Potent inhibitors of Bcl-2 and Bcl-xL Proteins

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Ji Group Literature Meeting
5/31/12
Outline

- Background
- Pharmacophore Model
- Lead Compound of pocket 1
- Linking of pocket 1 and 2
- Optimization
- Cell Death Assay
- Summary
Background

- Bcl-2, Bcl-xL anti-apoptotic proteins
- Overexpressed in many cancer cell lines
- Forms heterodimers with pro-apoptotic Bcl-2 family proteins
- Leads to increased apoptosis resistance
- Inhibition of heterodimer helps lead to apoptosis
Bcl-xL pockets

- Bcl-xL complexed with BAD BH3

Haibin Zhou; Jianfang Chen; Jennifer L. Meagher; Chao-Yie Yang; Angelo Aguilar; Liu Liu; Longchuan Bai; Xin Cong; Qian Cai; Xueliang Fang; Jeanne A. Stuckey; Shaomeng Wang; J. Med. Chem. 2012, 55, 4664-4682.
Pharmacophore Model

- Based on the three residues and structural information
- Two aromatic rings 5±1 Å apart and one hydrophobic group 6±1 Å apart from aromatic rings
- Searched an in-house 3-D database of 1410 U.S. FDA approved drugs
# 3 Scaffold Classes

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
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<tr>
<td><img src="image" alt="Methadone" /></td>
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Docking Lipitor and Celecoxib

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Site 1+2

- Fragment 4 $K_i = 78.0\ \mu M$ for Bcl-2 and $138\ \mu M$ for Bcl-xL
- Fragment 5 $K_i = \text{over} 100\mu M$ for Bcl-2 and $75\mu M$ for Bcl-xL
- Combined fragments of 7,8,9 bind with a $K_i$ less than 1 nM for Bcl-2 & Bcl-xL
- 6-11 have $IC_{50}$ value > 10µM for Mcl-1 showing specificity for Bcl-2 & Bcl-xL
- 6,8,9,10,11 show $IC_{50}$ value > 10µM for growth inhibition of cancer cell lines H146 & H1417
- 7 shows an $IC_{50}$ value of 2.0µM

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16 has $K_i < 1$ for Bcl-2 & Bcl-xL & $IC_{50}$ values of 0.43 µM and 0.65 µM for H146 and H1417.

17 shows $K_i = 1.2$ nM for Bcl-2 and $K_i < 1$ nM for Bcl-xL. Similar to 16 against the cancer cell lines.

19 showed less potency than 17 against the cancer cells.

20 shows $K_i < 1$ nM for Bcl-2 and Bcl-xL and $IC_{50}$ values of 0.34 µM and 0.55 µM for inhibition of H146 & H1417.

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21 shows $K_i < 1\text{nM}$ and $IC_{50} = 61\text{nM}$ and $90\text{nM}$.
Cell Death Evaluation

- Tested 20 & 21
- Tryptophan blue assay using H146
- 21 more potent than 20
- 21 induces > 70% cell death in 24 h at 300nM
Summary

- Designed a lead compound for site 1 through the use of the Bcl-xL crystal structure and a pharmacophore model to screen FDA approved drugs

- Linked the lead compound of site 1 to a fragment of a known inhibitor that occupied site 1 & 2

- Optimized the lead compound of the corresponding linked compound

- Obtained a potent inhibitor of Bcl-2 and Bcl-xL Ki < 1nM and inhibitor of cell growth of H 146 and H1417 with IC$_{50}$ values of 60-90nM