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Combinatorial Libraries of Bipodal Binders of the Insulin Receptor

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Irena Selicharová, Benjamin Fabre, María Soledad Garre Hernández, Marta Lubos, Jan Pícha, Zdeněk Voburka, Katarína Mitrová and Jiří Jiráček
Institute of Organic Chemistry and Biochemistry, AS CR, Prague, Czech Republic

Background

Treatment of diabetes with insulin is complicated by its narrow therapeutic index. Efforts are devoted to develop insulin analogs/mimetics with altered properties that would bring better comfort to patients.

We designed and prepared combinatorial libraries of bipodal compounds consisting of two distinct peptides linked to a molecular scaffold. The libraries were searched for specific insulin receptor (IR) binders.

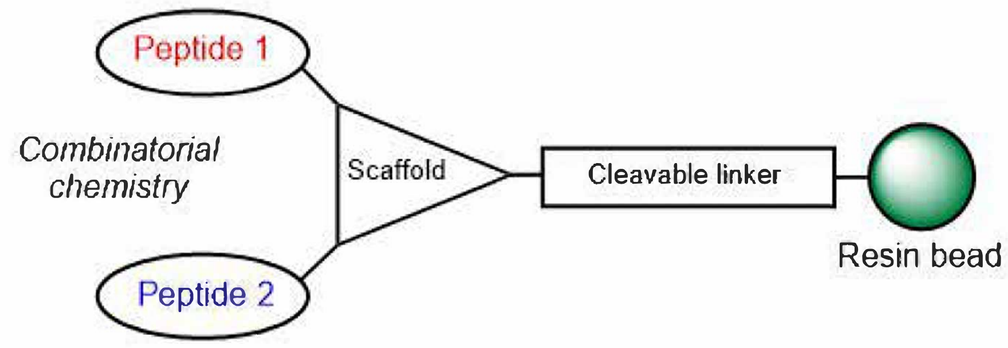
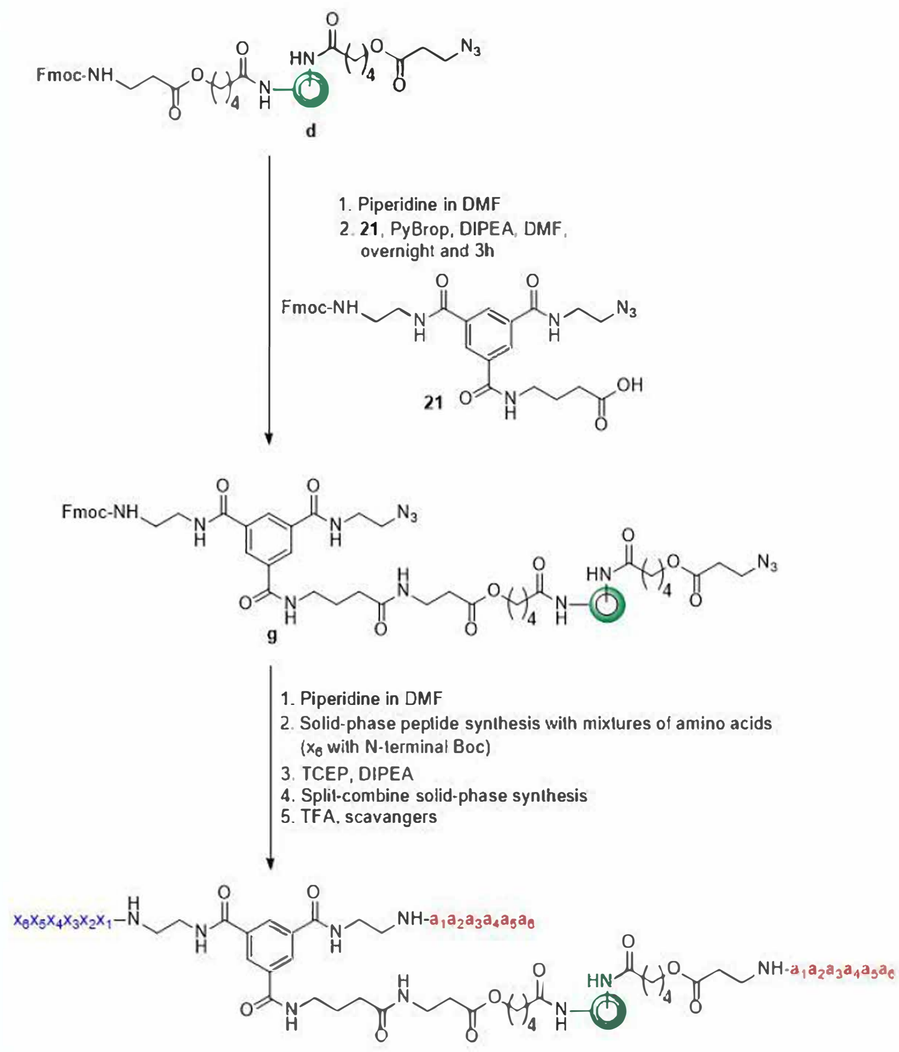


Figure 1. General structure of resin-bound construct.

Synthesis of Library

Trimesic-acid scaffold was attached to bi-layered TentaGel beads and modified with equimolar mixture of D-amino acids (x1-x6). Azido groups of the scaffold and reporter linker (inner sphere) were reduced to amines and modified by a split-combine technique to yield unique peptide sequence on each bead (a1-a6).

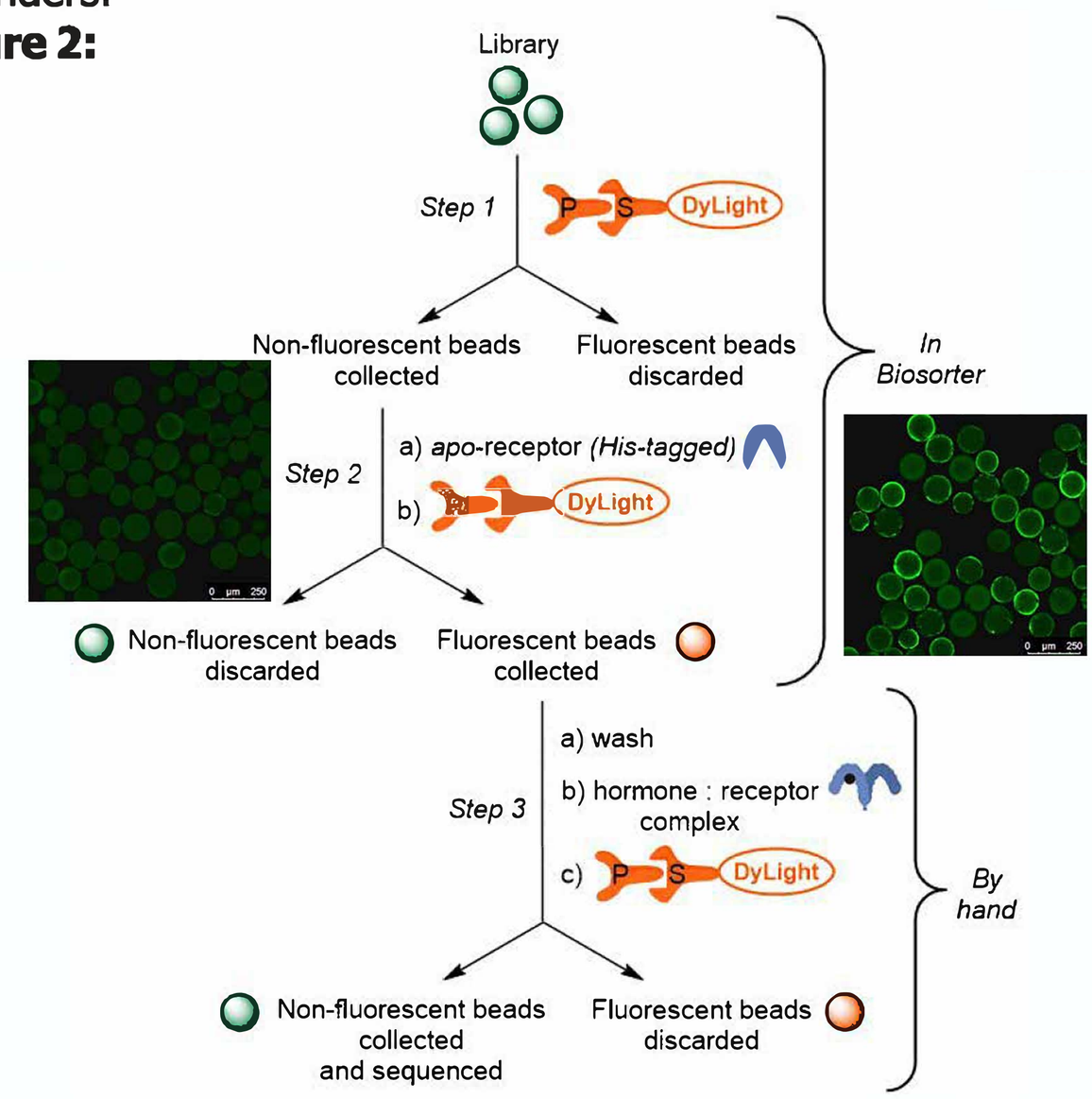
Scheme 1:



Active beads selection workflow

Beads modified with compound libraries were incubated with IR and fluorescent antibody sandwich and sorted on large-particle BioSorter. Fluorescent beads were manually re-sorted for specific IR binders.

Figure 2:



New IR binding compounds

- Peptides „slyfys" (IR Site-1) **Figure 3**, „GeeepaGG" (IR Site-2) and „yyaypGG" (IR Site-2) were discovered within libraries of nearly 3 x 10_6 peptides.
- Similarity with peptides discovered through phage display Ac-FYDFWERQ (IR Site-1) and SLEEEWAQ (IR Site-2)

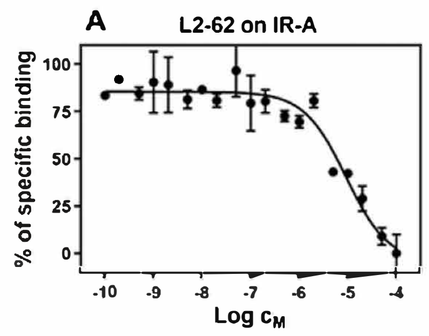


Figure 3: IR-A binding of L2-62 having a slyfys sequence of one arm of the trimesic acid scaffold and all possible hexapeptide sequences (selection of 12 D-amino acids).

Challenges encountered

- Robust non-specific interactions with basic and hydrophobic peptides.
- Inevitable looses of beads throught the selection proces.
- No highly potent compounds were found.

Reference: Selicharova et al., ChemMedChem 2024, 19, e202400145

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