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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
Diversity Oriented Synthesis of Low Molecular Weight Acyclic and Heterocyclic Compounds from Resin-bound Polyamides: Application for Drug Discovery

Adel Nefzi

Torrey Pines Institute for Molecular Studies
Port Saint Lucie, FL 34987
Drug discovery and development

High-throughput screening (HTS)

The mapping of the human genome (30,000 genes: therapeutic targets)
Bioinformatics

Need for new Compounds
- Natural Products
- Synthetic Products

Combinatorial Chemistry
- Solid Phase Organic Synthesis
- Parallel Synthesis
- Diversity Oriented Synthesis
- Mixture based Libraries

Computational Chemistry (Virtual Screening)
Solid Phase Synthesis of Heterocyclic Compounds from Modified Resin-Bound Peptides
Synthesis of [3,5,7]-1H-Imidazo[1,5a]imidazol-2(3H)-ones

Synthesis of [3,5,7]-1H-Imidazo[1,5a]imidazol-2(3H)-ones

Solid-Phase Synthesis of Fused Tricyclic Imidazopyridinoindole

1) Xaa coupling
2) Acylation

POCl₃
HF/anisole
S#: 103-131  RT: 3.74-4.58  AV: 29  NL: 8.75E7
T: + c Full ms [50.00 - 2000.00]

C$_{29}$H$_{31}$BrN$_4$O$_3$
Exact Mass: 562.18

RT: 0.01 - 8.01

Time (min)

m/z

563.4  565.2
547.5  567.3
520.5  619.8
514.5  629.2
350.1  642.9
355.3  698.4
467.4
306.2
282.2
165.1
224.1
7.21
7.84
7.07
6.14
5.36
4.53
2.75
3.94
2.41
1.80
1.10
0.38

H$_2$N

Br

NH

N

NO

H$_2$N

O

O

C$_2$9H$_{31}$BrN$_4$O$_3$

Exact Mass: 562.18
Solid-Phase Synthesis of Heterocyclic Compounds from Reduced Acylated Amino Acids

Solid-Phase Synthesis of Heterocyclic Compounds from Reduced Acylated Amino Acids

Solid Phase Synthesis of Heterocyclic Compounds from Acylated Reduced Dipeptides

\[ \text{Solid Phase Synthesis of Heterocyclic Compounds from Acylated Reduced Dipeptides} \]

\[ \text{J.Org.Chem, 2004, 69, 3603.} \]

\[ \text{Tetrahedron. (2000), 56, 3319-3326.} \]
Diversity of Scaffolds

Diversity of Functional Groups around each Scaffold

Structure Activity Relationship

Optimal Scaffold Having Optimal Functional Groups
Solid-Phase Synthesis of Trisubstituted Imidazolones

Novel RORgamma antagonists for inflammation and autoimmune disease

1R01AI105836-01A1 Piedrafita/Nefzi (PIs)
Solid-Phase Synthesis of Trisubstituted Bicyclic Guanidines

C_{28}H_{41}N_{3}O
Exact Mass: 435.32
Solid Phase Synthesis of Bis Heterocyclic Compounds from Resin Bound Orthogonally Protected Lysine

Solid Phase Synthesis

\[ \text{NHBocl} \rightarrow \text{[H]} \rightarrow \text{NHNH} \]

C\text{XIm}_2, \text{C}_2\text{O}_2\text{Im}_2

\text{J. Comb. Chem. 2001, 3, 68-70.}
Solid-Phase Synthesis of Bis Heterocyclic Compounds from Reduced Tripeptides

Pyrrolidine containing bis-heterocyclic compounds

\[
\begin{align*}
R_1 &= 26 \\
R_2 &= 26 \\
R_3 &= 26 \\
R_4 &= 42
\end{align*}
\]
MRSA
MIC < 2.5 µg

(Antitubercular)
% inhibition: 95
MIC = 2 µg/ml

Mu opioid receptor binding activity
79.3 nM

PTHrP inhibitor
TPI1634-104
Synthesis of hexahydro-diimidazo[1,2-d:1',2'-g][1,4]diazepines

Parallel Synthesis of Hexahydrodiimidazodiazepines Heterocyclic Peptidomimetics and Their in Vitro and in Vivo Activities at $\mu$ (MOR), $\delta$ (DOR), and $\kappa$ (KOR) Opioid Receptors

Identification of potent and highly selective chiral tri-amine and tetra-amine \( \mu \) receptors ligands

\[
\]
Small-molecule XIAP inhibitors derepress downstream effector caspases and induce apoptosis of acute myeloid leukemia cells


1) [H]
2) PhNCO

89865 compounds
135 mixtures

1396-11
1396-34
Representative Small Molecular Libraries: Libraries for Probe, Hit and Lead Identification

- **N-acyl triamines** (450,000)
- **Cyclic ureas and thioureas** (472,000; X= O, S)
- **Bicyclic guanidines** (100,000)
- **Acyl-bicyclic guanidines** (1,300,000)
- **Polyureas** (160,000)
- **Diketopiperazaines** (80,000)
- **Piperazaines** (80,000)
- **Bis-cyclic ureas and Bis-cyclic thioureas** (72,000)
- **Indole-pyrido-imidazoles** (45,000)
- **Styryl quinazolinones** (122,000)
- **Bis-diketopiperazaines** (72,000)
- **Diazepinediones** (80,000)
A versatile access to new macrocyclic oligoheterocycles (MOH)

Adel Nefzi* and Rodegar T. Santos

Synthesis of Proline Containing Cyclic Peptides

A versatile access to new macrocyclic oligoheterocycles (MOH)
Cyclic Multiple Heterocyclics from Proline Containing Cyclic Peptides
Oligoheterocyclic Compounds

(Utilization of N-Me-Alanine as a spacer: Alternation of two secondary amides and one tertiary amide)

1) BH₃-THF
2) Piperidine

Generation of resin-bound spacially separated pairs of secondary amines
Oligoheterocyclic Compounds

Scheme 3

Figure 2
Hantzsch Based Macrocyclization Approach for the Synthesis of Thiazole Containing Cyclopeptides

Hantzsch reaction

NBS

Center of diversity

TPI-2293
Synthesis of Thiazole tethered Piperazine Library

1) BH$_3$-THF
2) FmocNCS

1) Piperidine/DMF
2) 1,3-dochloroacetone

1) Piperazine
2) R$_3$CCOH
DIC, HOBt

HF

TPI-2293
Thiazole Tethered Piperazine Libraries

TPI-2057

TPI-2291

IKKe

sAPPalpha and TrkA
Preclinical evaluation of thiazole piperazine and its analog as Alzheimer’s drugs

Fig. 8

A. AD Fibroblasts: sAPPα

B. Human neurons: sAPPα
Synthesis of polythiazole compounds

1) XCH₂COR
2) HF/anisole

Two-Steps Hantzsch Based Macro cyclization Approach for the Synthesis of Thiazole Containing Cyclopeptides
Synthesis of Thiazole Containing Cyclopeptides

1. FmocHN

2. SPPS

3. 1) FmocNCS in DMF
   2) 20% piperidine in DMF

4. Cl

5. DMF, 70 °C overnight

6. TFA/(But)₃SiH/DCM (5:5:90)

7. 1) CsOH-H₂O
   2) HF/anisole

References:
Tet. Lett. 2011, 52, 817-819
Synthesis of Macro cyclic Compounds via Thio-Methyl-Thiazole as Analog of the Disulfide Bridge
Approximate three-dimensional chemical space distribution of different cyclic peptides

Variability preserved: 96.8%
Synthesis of Thiazole Containing Cyclopeptides Application for the synthesis of DAMGO and Enkephalin Constrained Analogs

Enkephalin-analog

DAMGO-analog

DAMGO-analog

Enkephalin-analog

Enkephalin-analog

C-terminal fragment

TPI-1924-1: Tyr-Ala-Gly-Phe
TPI-1924-4: Tyr-Ala-Gly-(N-Me)Phe
TPI-1924-7: Tyr-Ala-Phe
TPI-1924-10: Tyr-Ala-Gly-(N-Me)Phe
TPI-1924-13: Tyr-Gly-Gly-Phe-Leu
TPI-1924-16: Tyr-Gly-Gly-Phe-Met
TPI-1924-19: Tyr-Gly-Phe-Leu
TPI-1924-22: Tyr-Gly-Phe-Met
TPI-1924-25: Tyr-Phe-Leu
TPI-1924-28: Tyr-Phe-Met
TPI-1936-1: [Tyr-Gly-Gly-Phe]—Met
TPI-1936-2: [Tyr-Gly-Gly]—Phe-Met
TPI-1936-3: [Tyr-Gly]—Gly-Phe-Met
TPI-1936-4: [Tyr-Gly-Phe]—Met
TPI-1936-5: [Tyr-Gly]—Phe-Met
TPI-1936-6: [Tyr-Gly-Gly-Phe]—Leu
TPI-1936-7: [Tyr-Gly-Gly]—Phe-Leu
TPI-1936-8: [Tyr-Gly]—Gly-Phe-Leu
TPI-1936-9: [Tyr-Gly-Phe]—Leu
TPI-1936-10: [Tyr-Gly]—Phe-Leu
**In vivo screening of series TPI-1924 and TPI-1936 compounds**

Dose- and time-dependent antinociceptive effect of 1924-10 after oral (p.o.) administration.
Positional Scanning: Tetra-Peptide Library

\[ \text{O}_1 \ X \ X \ X \ -\text{NH}_2 \\
\text{X} \ \text{O}_2 \ X \ X \ -\text{NH}_2 \\
\text{X} \ X \ \text{O}_3 \ X \ -\text{NH}_2 \\
\text{X} \ X \ X \ \text{O}_4 \ -\text{NH}_2 \]

6,250,000 tetra-peptides
125,000 each mixture

(50 different L-, D-, and Unnatural amino acids)

\( \text{O} = \text{individual} \quad \text{X} = \text{mixture} \)

Kappa Receptor Binding Assay

7 x 4 x 4 x 1 = 96 individual tetrapeptides
# Kappa Receptor Binding Assay

<table>
<thead>
<tr>
<th>Positional Library</th>
<th>Most Active Residues</th>
<th>Number of Residues</th>
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<tbody>
<tr>
<td>OXXX-NH₂</td>
<td>dPhe, dNle</td>
<td>2</td>
</tr>
<tr>
<td>XOXO-NH₂</td>
<td>dPhe, dNal</td>
<td>2</td>
</tr>
<tr>
<td>XXOX-NH₂</td>
<td>dTrp, dile, dNle</td>
<td>3</td>
</tr>
<tr>
<td>XXXO-OH₂</td>
<td>dArg, dCha</td>
<td>2</td>
</tr>
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**Total** 24

<table>
<thead>
<tr>
<th>Sequence</th>
<th>IC₅₀ (nM)</th>
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<tbody>
<tr>
<td>(dPhe)(dNal)(dNle)(dArg)-NH₂</td>
<td>1</td>
</tr>
<tr>
<td>(dPhe)(dPhe)(dNle)(dArg)-NH₂</td>
<td>2</td>
</tr>
<tr>
<td>(dNle)(dNal)(dile)(dArg)-NH₂</td>
<td>2</td>
</tr>
<tr>
<td>(dPhe)(dPhe)(dile)(dArg)-NH₂</td>
<td>2</td>
</tr>
<tr>
<td>(dNle)(dNal)(dNle)(dArg)-NH₂</td>
<td>3</td>
</tr>
<tr>
<td>(dPhe)(dNal)(dile)(dArg)-NH₂</td>
<td>4</td>
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</tbody>
</table>

All Full Agonists
<table>
<thead>
<tr>
<th>Sequence</th>
<th>( \kappa ) U69,593 IC\textsubscript{50} (nM)</th>
<th>( \mu ) DAMGO IC\textsubscript{50} (nM)</th>
<th>( \delta ) DSLET IC\textsubscript{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(dPhe)(dNal)(dNle)(dArg)-NH\textsubscript{2}</td>
<td>0.7</td>
<td>22,630</td>
<td>49,640</td>
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<tr>
<td>(dPhe)(dPhe)(dNle)(dArg)-NH\textsubscript{2}</td>
<td>2.0</td>
<td>42,963</td>
<td>&gt;25,000</td>
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<tr>
<td>(dNle)(dNal)(dile)(dArg)-NH\textsubscript{2}</td>
<td>2.0</td>
<td>3,034</td>
<td>19,316</td>
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<tr>
<td>(dPhe)(dPhe)(dile)(dArg)-NH\textsubscript{2}</td>
<td>2.0</td>
<td>&gt;150,000</td>
<td>&gt;25,000</td>
</tr>
<tr>
<td>(dNle)(dNal)(dNle)(dArg)-NH\textsubscript{2}</td>
<td>3.0</td>
<td>1,709</td>
<td>&gt;25,000</td>
</tr>
<tr>
<td>(dPhe)(dPhe)(dNle)(dCha)-NH\textsubscript{2}</td>
<td>6.0</td>
<td>15,000</td>
<td>28,932</td>
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**Phase III Human Trials 2014/2015**

**Cara Therapeutics**
Combinatorial Chemistry: Libraries from Libraries, the Art of the Diversity-Oriented Transformation of Resin-Bound Peptides and Chiral Polyamides to Low Molecular Weight Acyclic and Heterocyclic Compounds

Adel Nefzi, John M. Ostresh, Jongping Yu, and Richard A. Houghten*
<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Dr. Cornelia Hoesl</td>
<td>Safa Derbal</td>
<td>Richard Houghten</td>
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<td>Afef Dellai</td>
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</tr>
<tr>
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<td>Maria Martinez</td>
<td>John Ostresh</td>
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<tr>
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<td></td>
<td>Clemencia Pinilla</td>
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<td>Karina Martinez-M</td>
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<td>Allison</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diana Velosa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jennifer Davis</td>
<td></td>
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Headquarters
Florida Campus
Port St. Lucie, FL

California Campus
3550 General Atomics Court
San Diego, CA

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