About OMICS Group

- OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

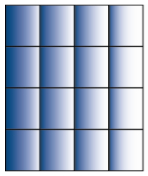
OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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

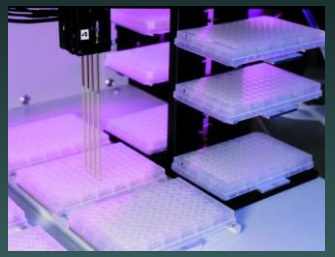
Torrey Pines Institute for Molecular Studies
Port Saint Lucie, FL 34987



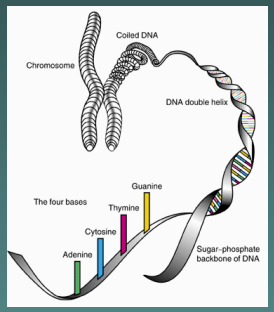
TORREY PINES INSTITUTE FOR MOLECULAR STUDIES

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

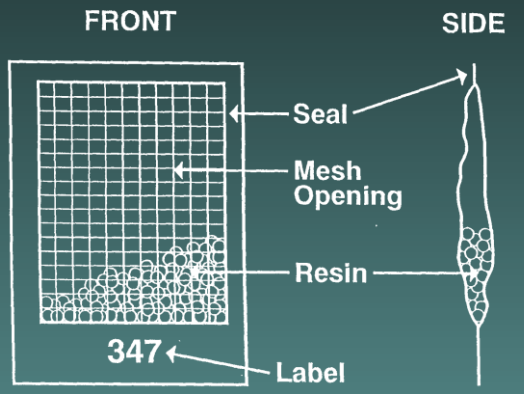
→

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



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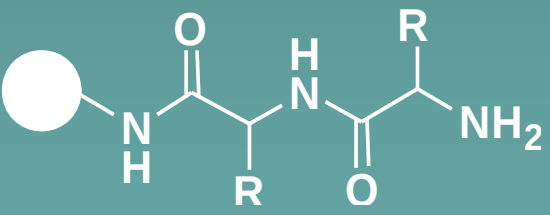
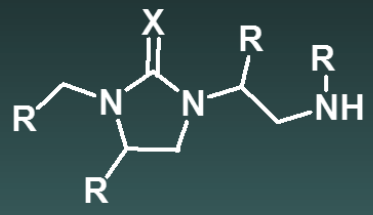
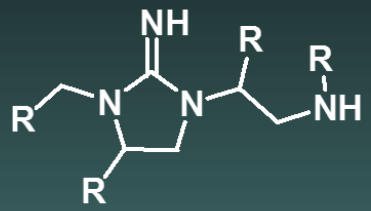
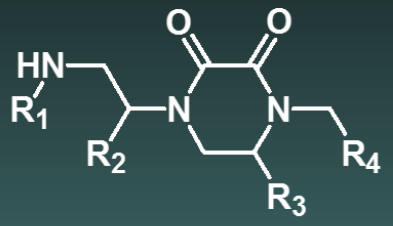




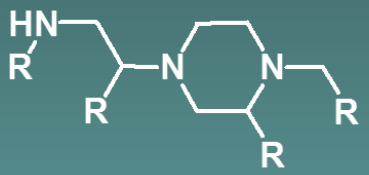
Cyclic ureas and thioureas



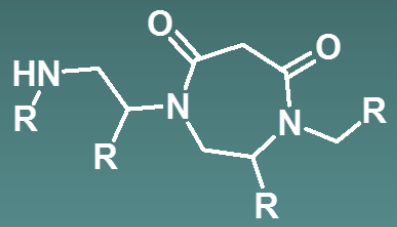
Cyclic guanidines



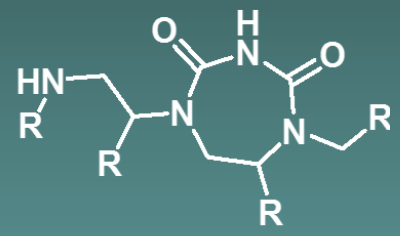
Diketopiperazines



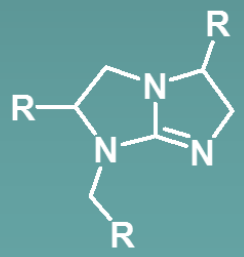
Piperazines



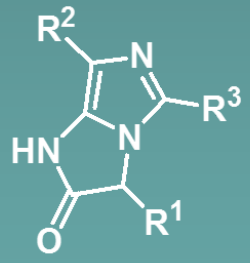
Diazepinediones



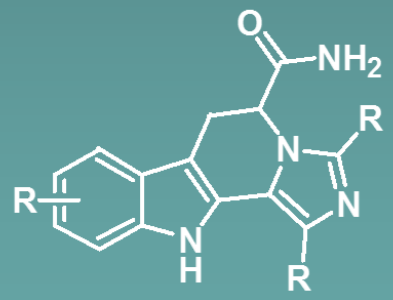
Triazepinediones



Bicyclic guanidines

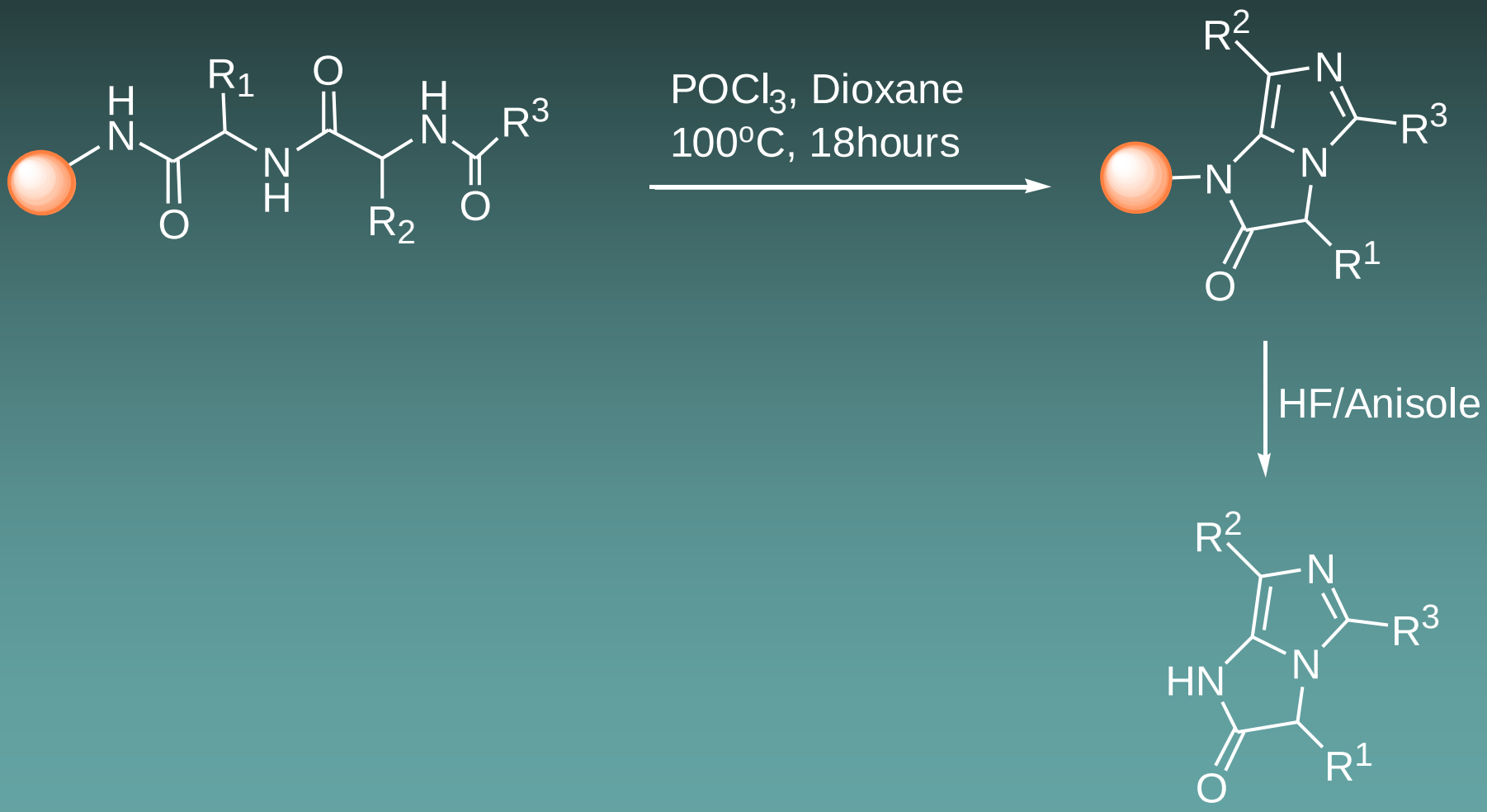


Benzimidazo-benzimidazolone



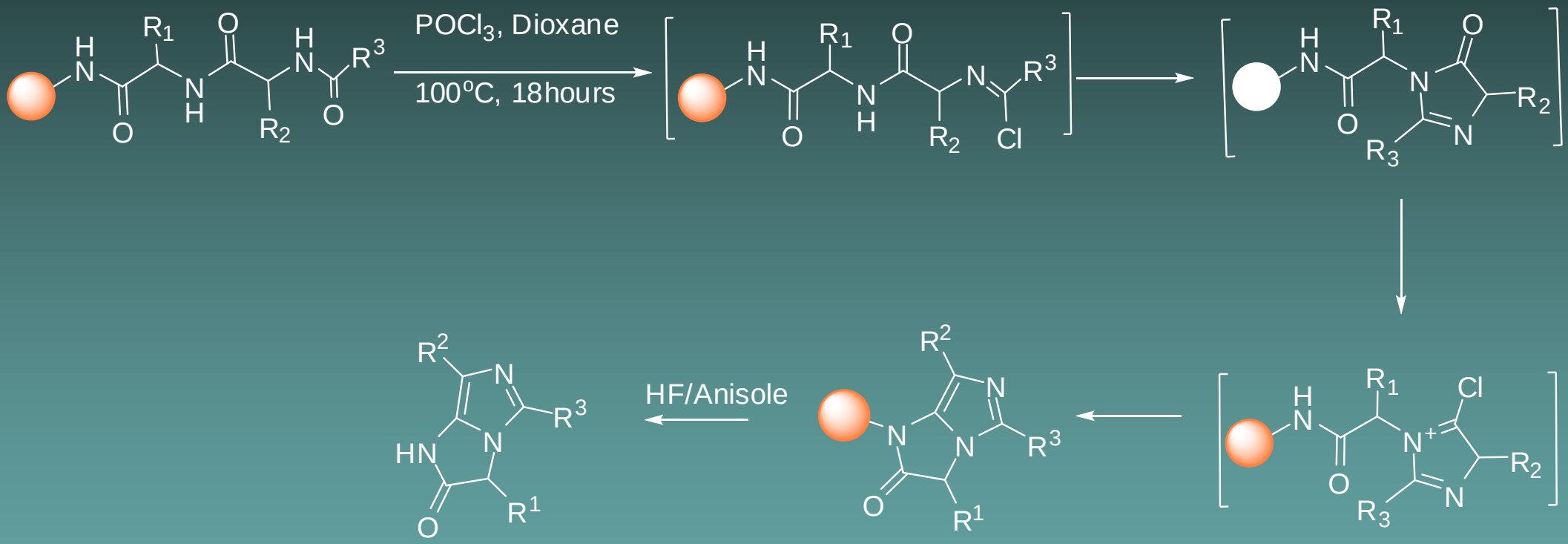
Indole-pyrido-imidazoles

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

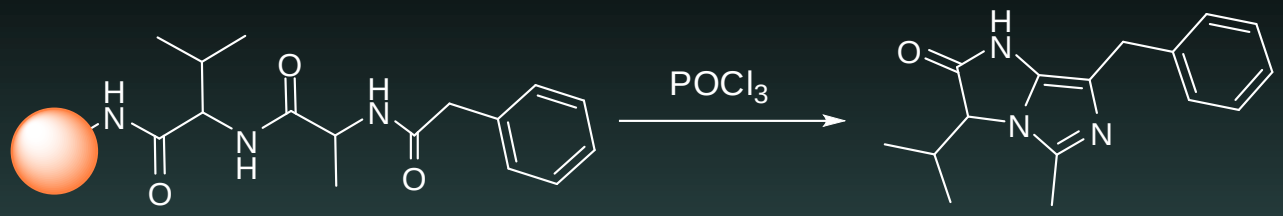


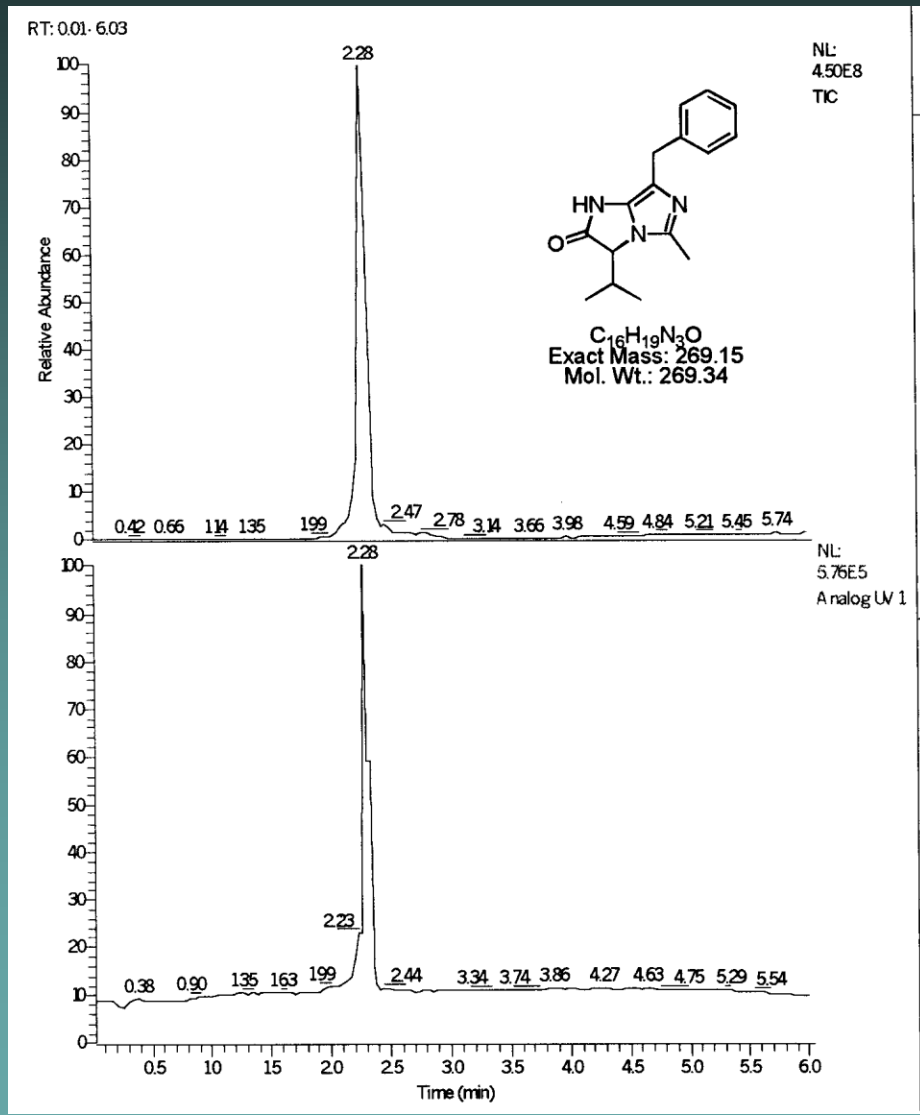
J. Org. Chem. 2004, 69:3603-3609.

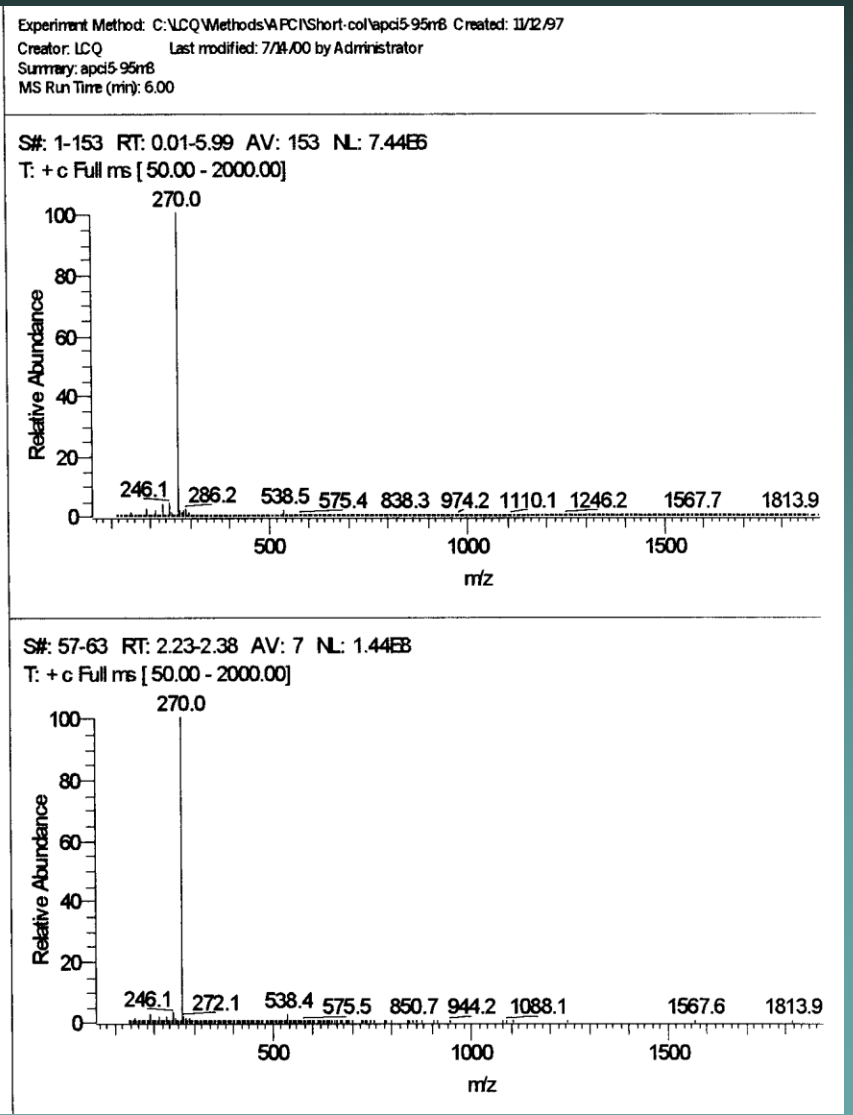
Synthesis of [3,5,7]-1H-Imidazo[1,5a]imidazol-2(3H)-ones



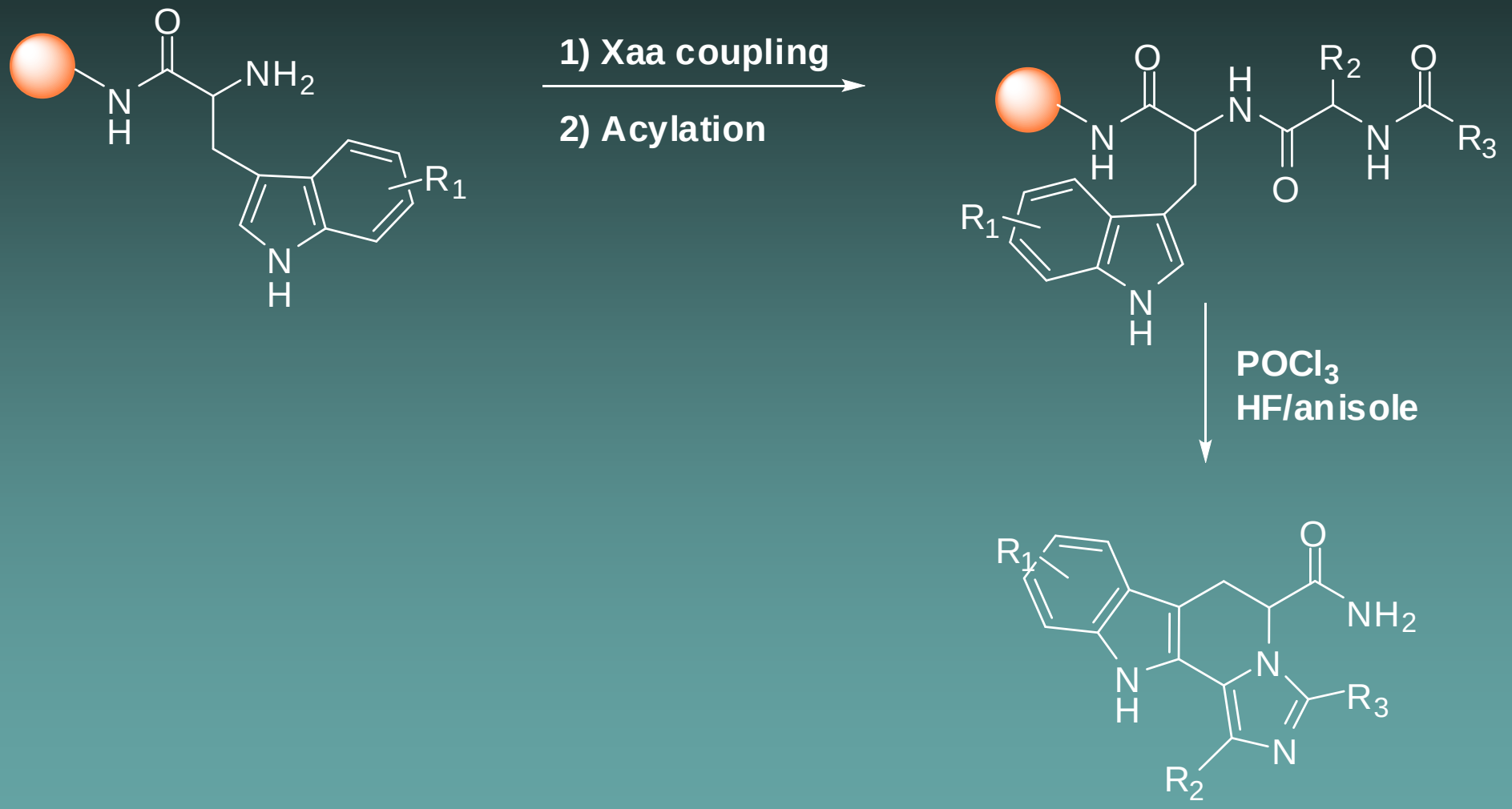
J. Org. Chem. 2004, 69:3603-3609.


POCl3

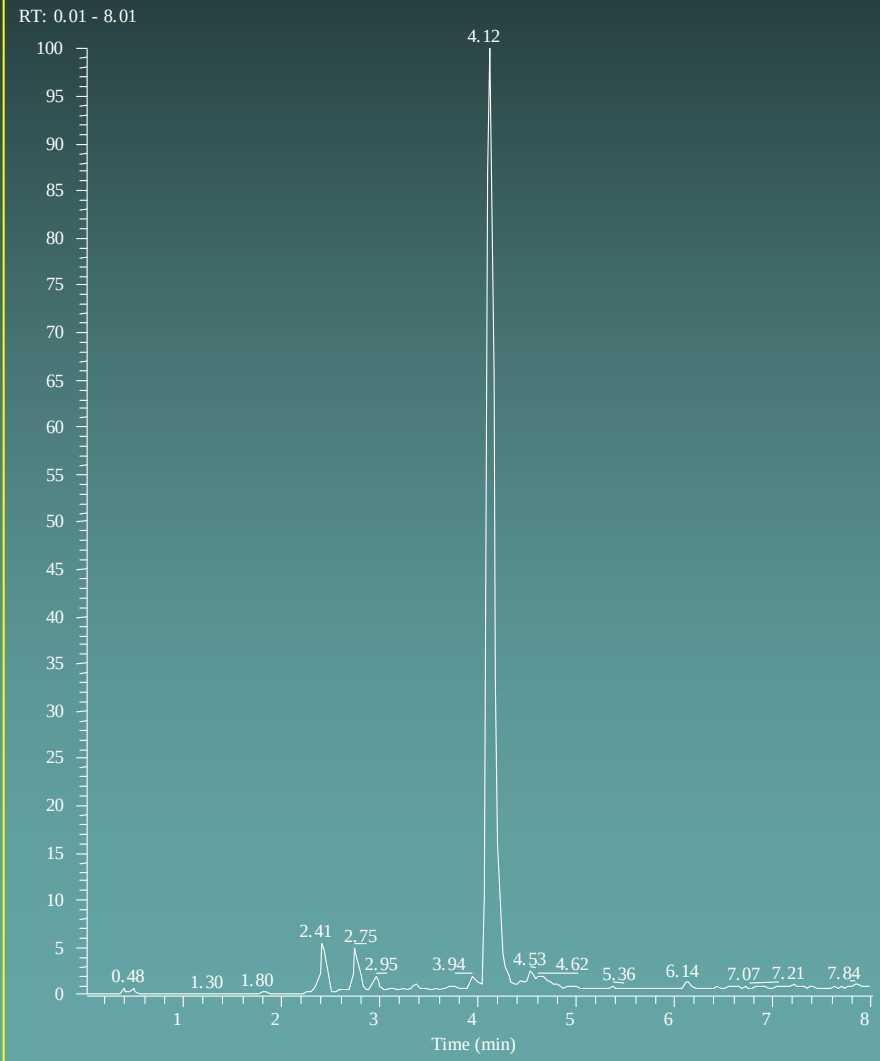

RT: 0.01 - 6.03
NL:
4.50E8
TIC
Relative Abundance
2.28
0.42 0.66 1.14 1.35 1.99 2.47 2.78 3.14 3.66 3.98 4.59 4.84 5.21 5.45 5.74
HN
N
O
N
C16H19N3O
Exact Mass: 269.15
Mol. Wt.: 269.34
NL:
5.76E5
Analog UV 1
2.28
2.23
0.38 0.90 1.35 1.63 1.99 2.44 3.34 3.74 3.86 4.27 4.63 4.75 5.29 5.54
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Time (min)

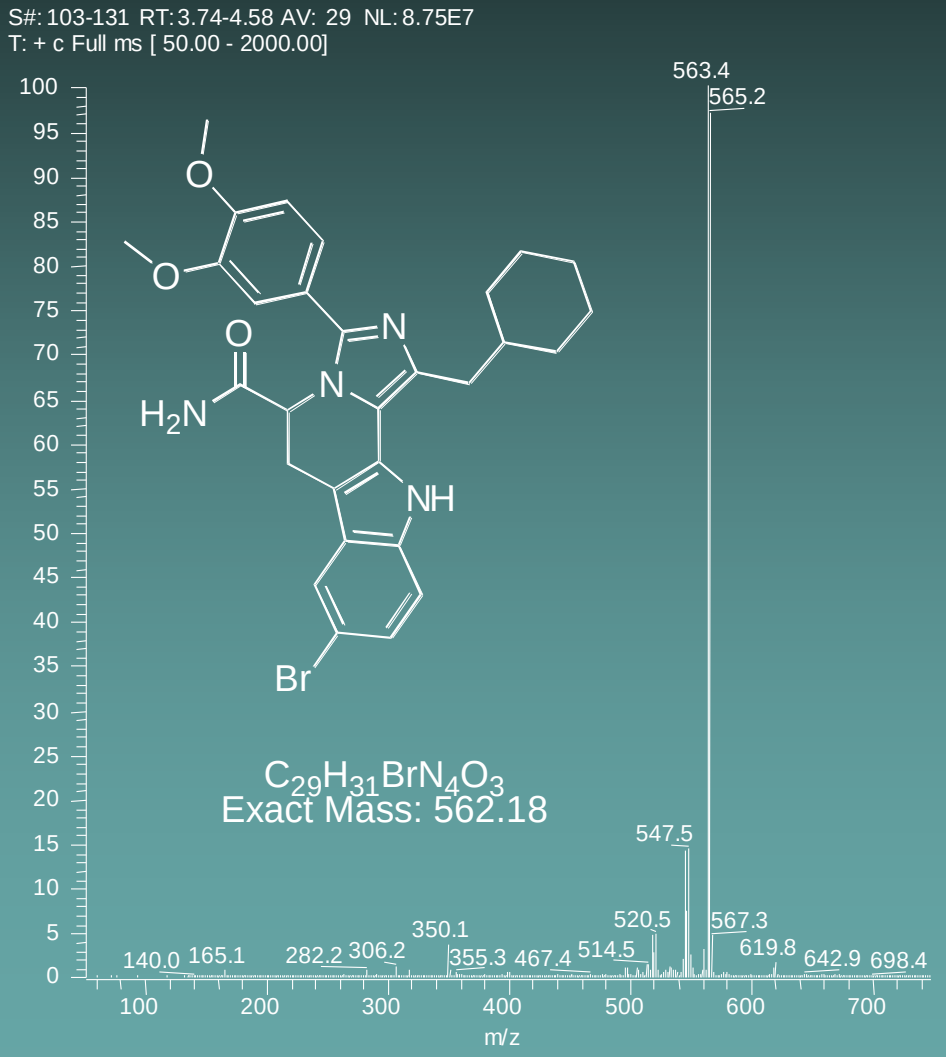

Experiment Method: C:\LCQ\Methods\APCI\Short-col\apci5-95m8 Created: 11/12/97
Creator: LCQ Last modified: 7/14/00 by Administrator
Summary: apci5-95m8
MS Run Time (min): 6.00
S#: 1-153 RT: 0.01-5.99 AV: 153 NL: 7.44E6
T: + c Full ms [50.00 - 2000.00]
270.0
Relative Abundance
246.1 286.2 538.5 575.4 838.3 974.2 1110.1 1246.2 1567.7 1813.9
500 1000 1500
m/z
S#: 57-63 RT: 2.23-2.38 AV: 7 NL: 1.44E8
T: + c Full ms [50.00 - 2000.00]
270.0
Relative Abundance
246.1 272.1 538.4 575.5 850.7 944.2 1088.1 1567.6 1813.9
500 1000 1500
m/z

Solid-Phase Synthesis of Fused Tricyclic Imidazopyridoindole

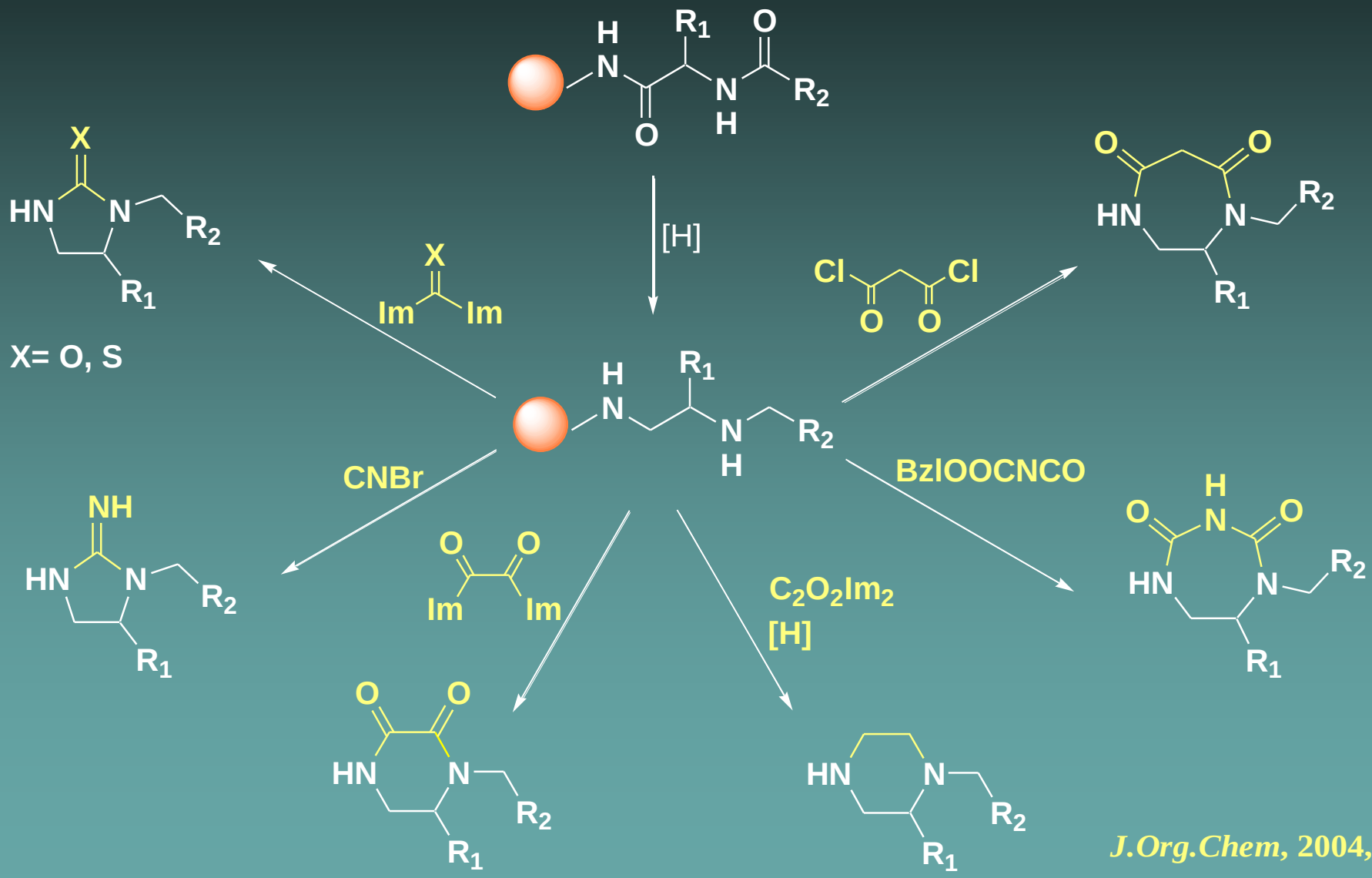



Br
O
N
H
H
N
O
N
H
O
O
O
N
H


RT: 0.01 - 8.01
4.12
0.48
1.30
1.80
2.41
2.75
2.95
3.94
4.53
4.62
5.36
6.14
7.07
7.21
7.84
Time (min)

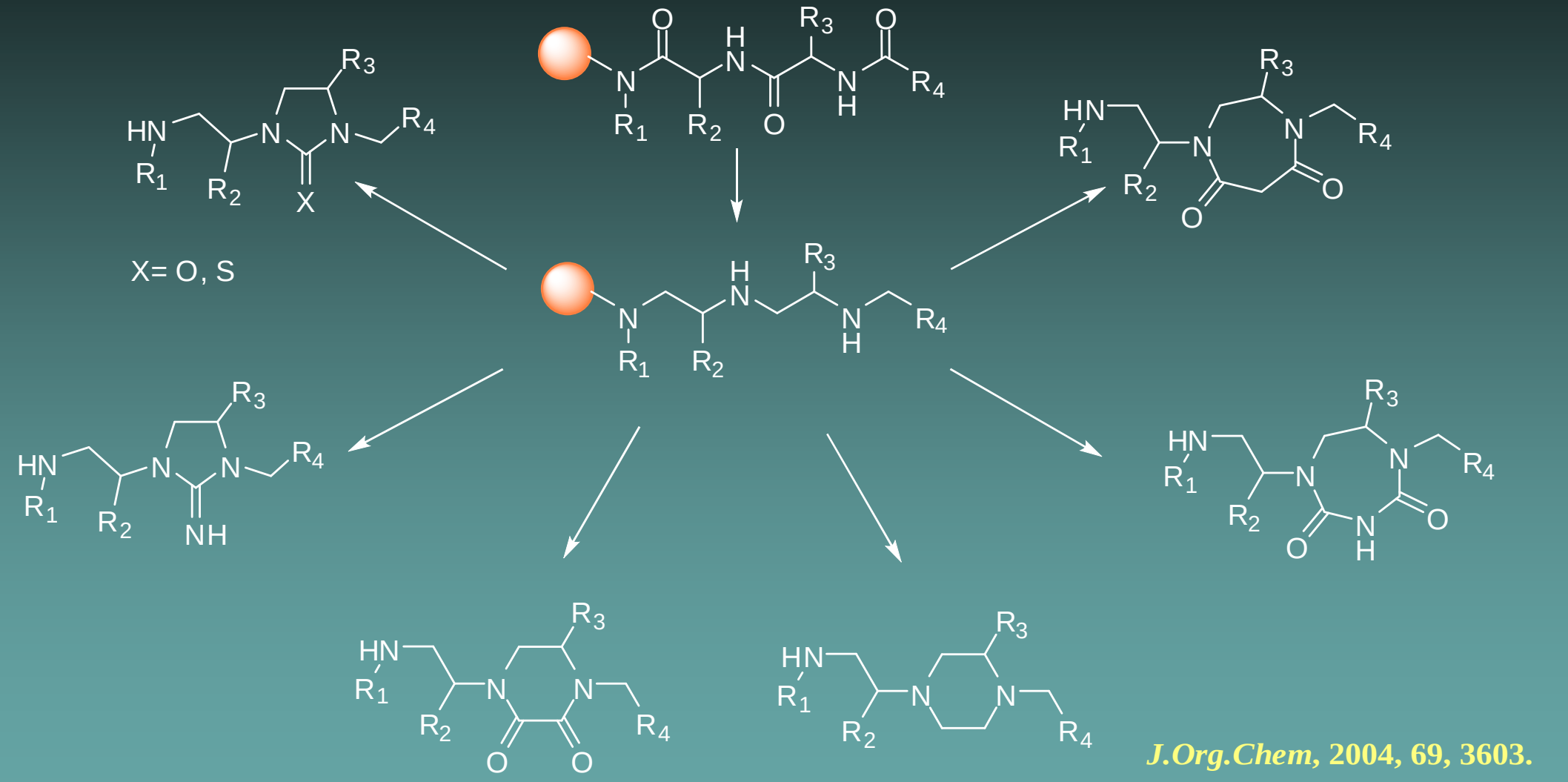

S#: 103-131 RT: 3.74-4.58 AV: 29 NL: 8.75E7
T: + c Full ms [50.00 - 2000.00]
563.4
565.2
O
O
O
N
N
H2N
NH
Br
C29H31BrN4O3
Exact Mass: 562.18
547.5
520.5
567.3
350.1
619.8
140.0
165.1
282.2
306.2
355.3
467.4
514.5
642.9
698.4
m/z

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



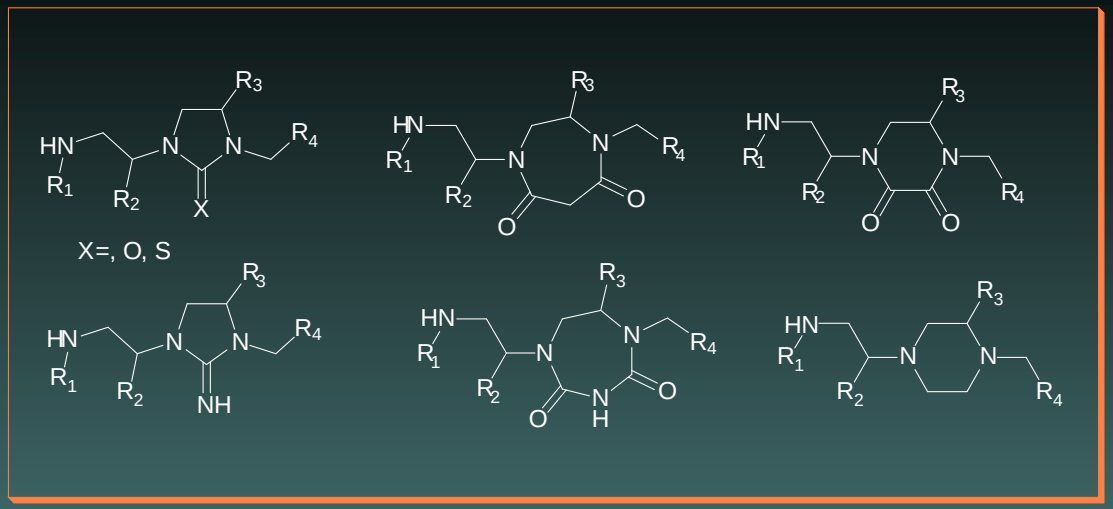
J.Org.Chem, 2004, 69, 3603.

Solid Phase Synthesis of Heterocyclic Compounds from Acylated Reduced Dipeptides

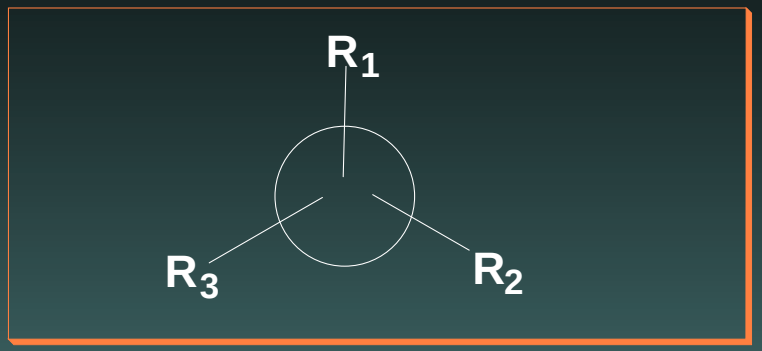


J.Org.Chem, 2004, 69, 3603.

Tetrahedron. (2000), 56, 3319-3326.



Diversity of Scaffolds

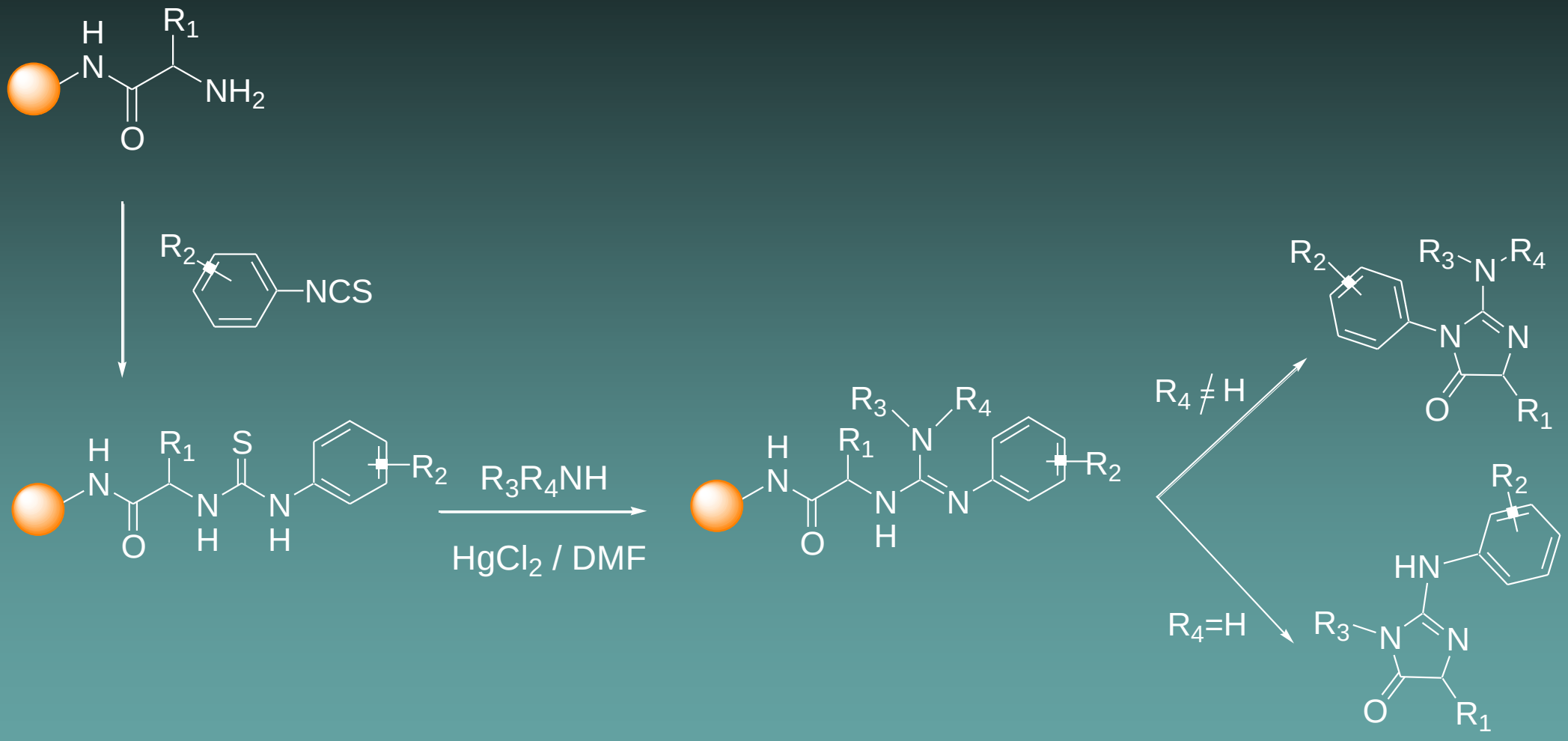


Diversity of Functional Groups around each Scaffold

Structure Activity Relationship

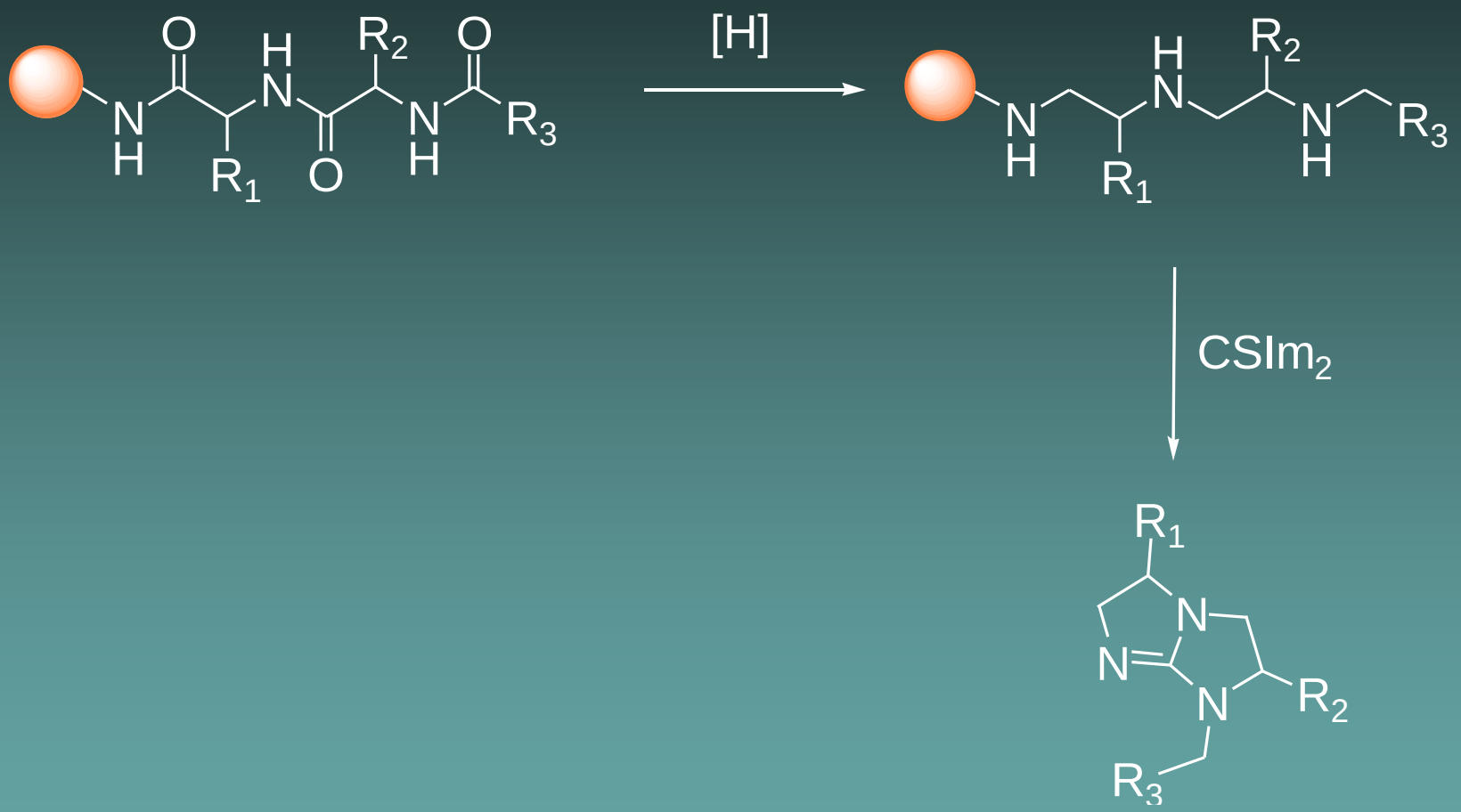
Optimal Scaffold Having Optimal Functional Groups

Solid-Phase Synthesis of Trisubstituted Imidazolones

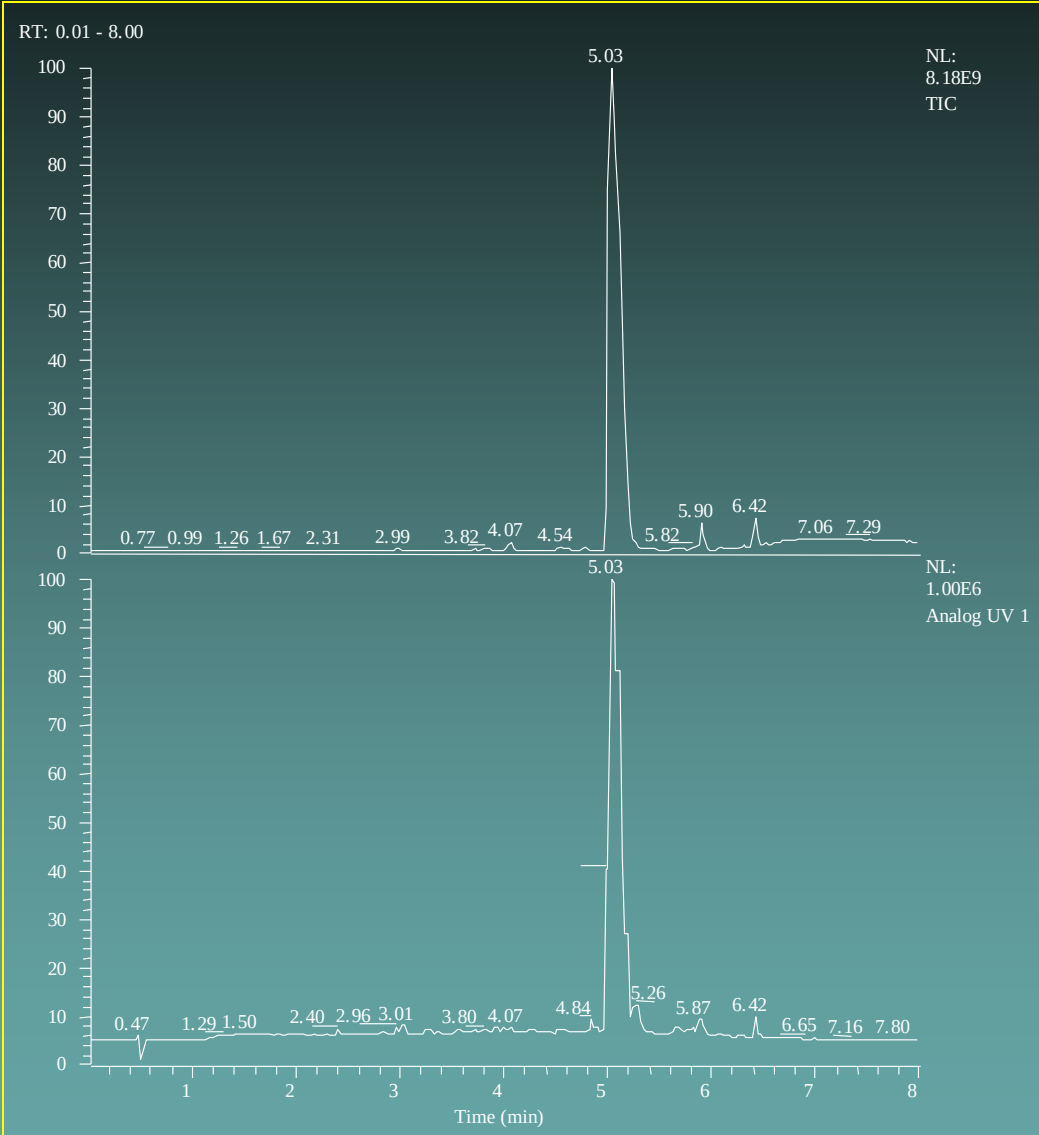


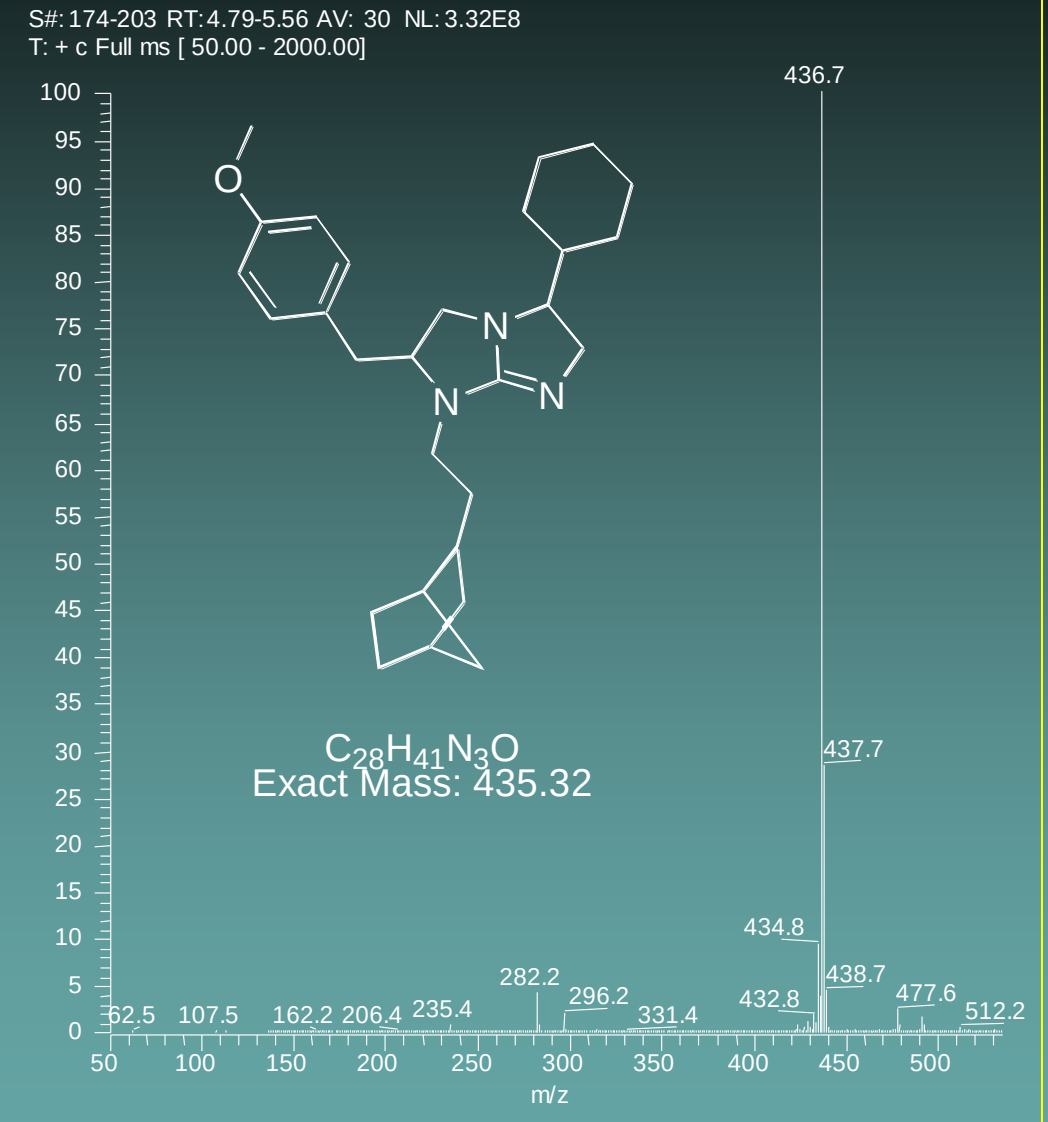
1R01AI105836-01A1 Piedrafita/Nefzi (PIs)
Novel RORgamma antagonists for inflammation and autoimmune disease

Solid-Phase Synthesis of Trisubstituted Bicyclic Guanidines



J. Org. Chem. 1998, 63, 8622-8623.

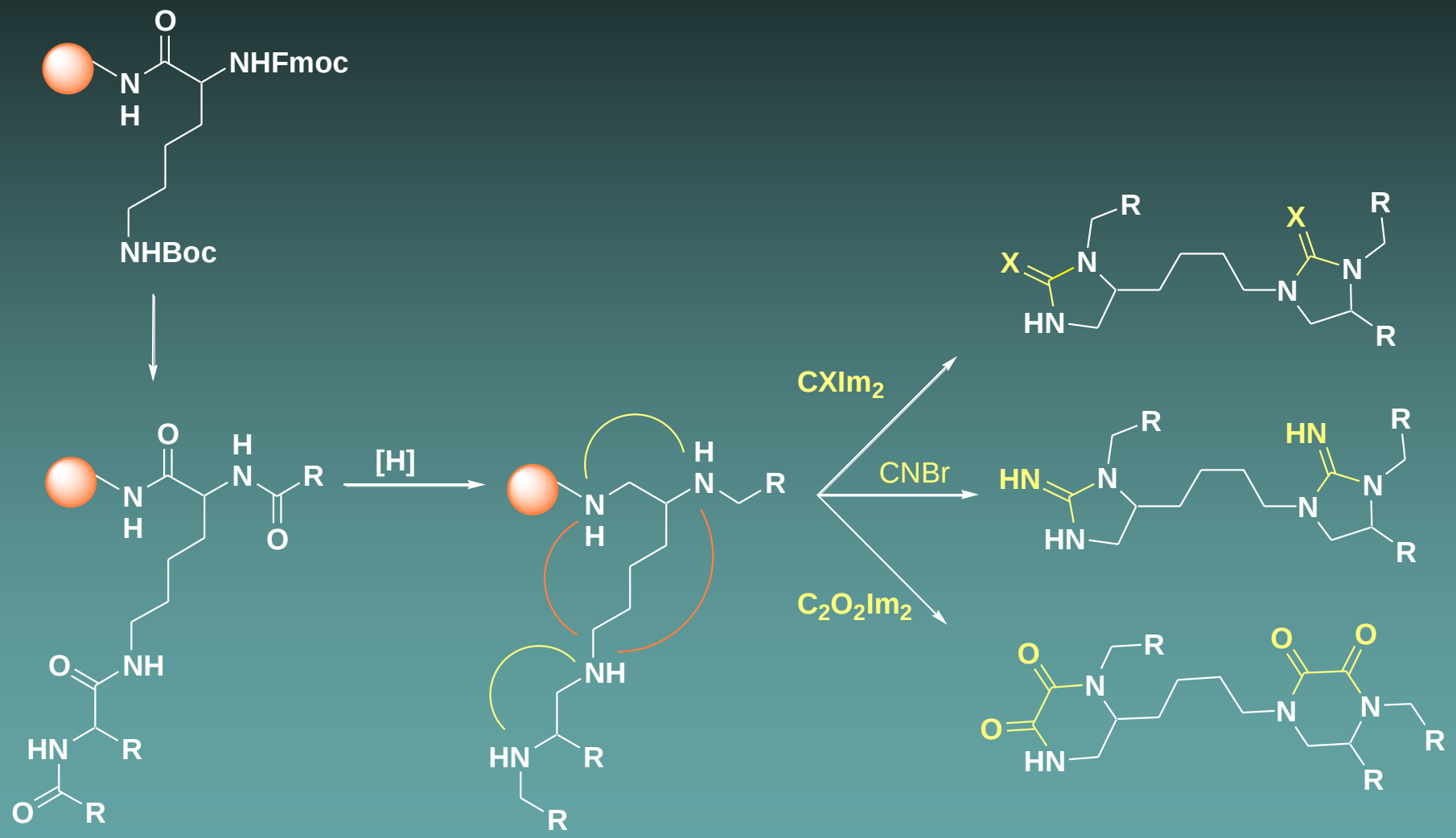




$C_{28}H_{41}N_3O$

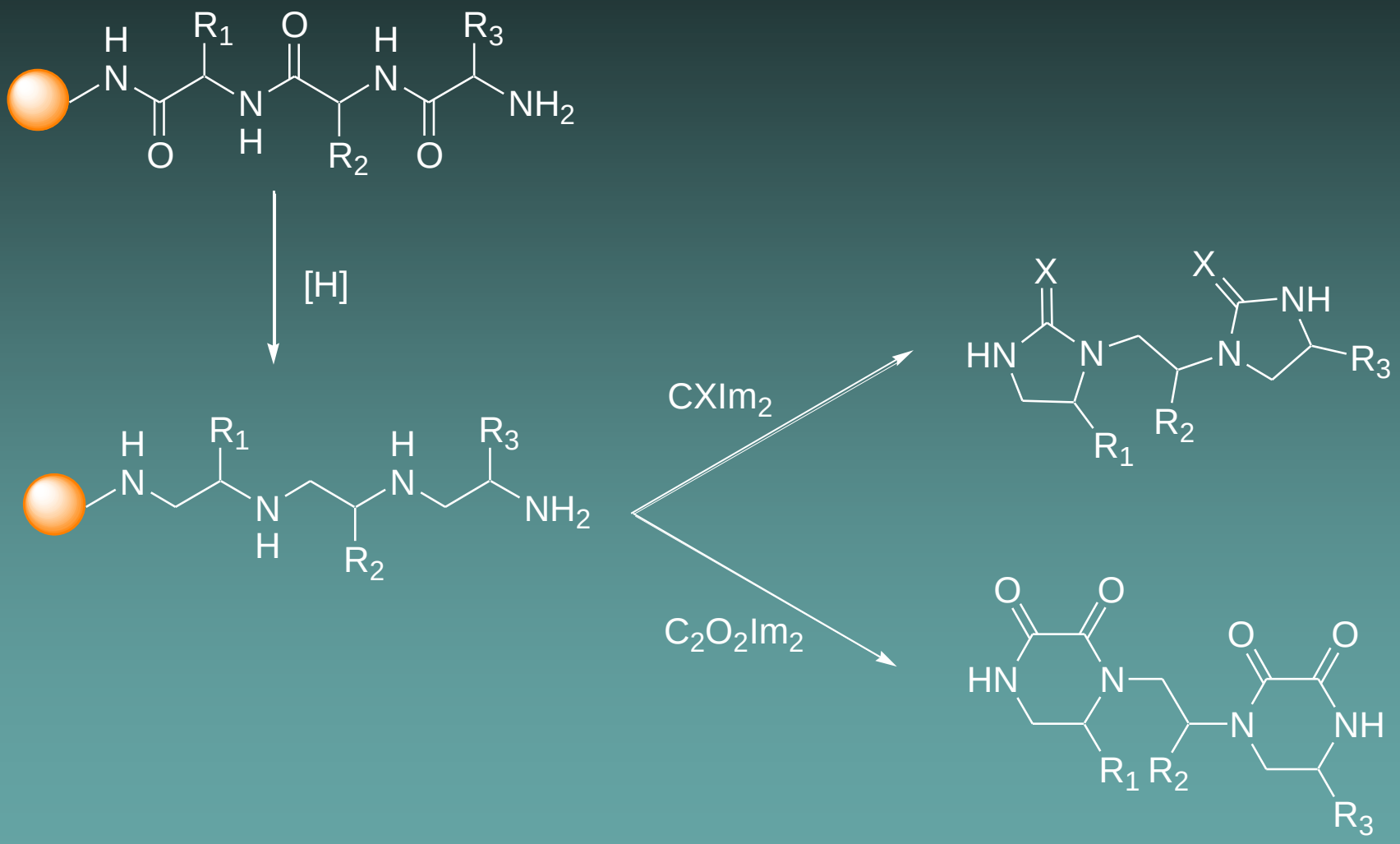
Exact Mass: 435.32

Solid Phase Synthesis of Bis Heterocyclic Compounds from Resin Bound Orthogonally Protected Lysine



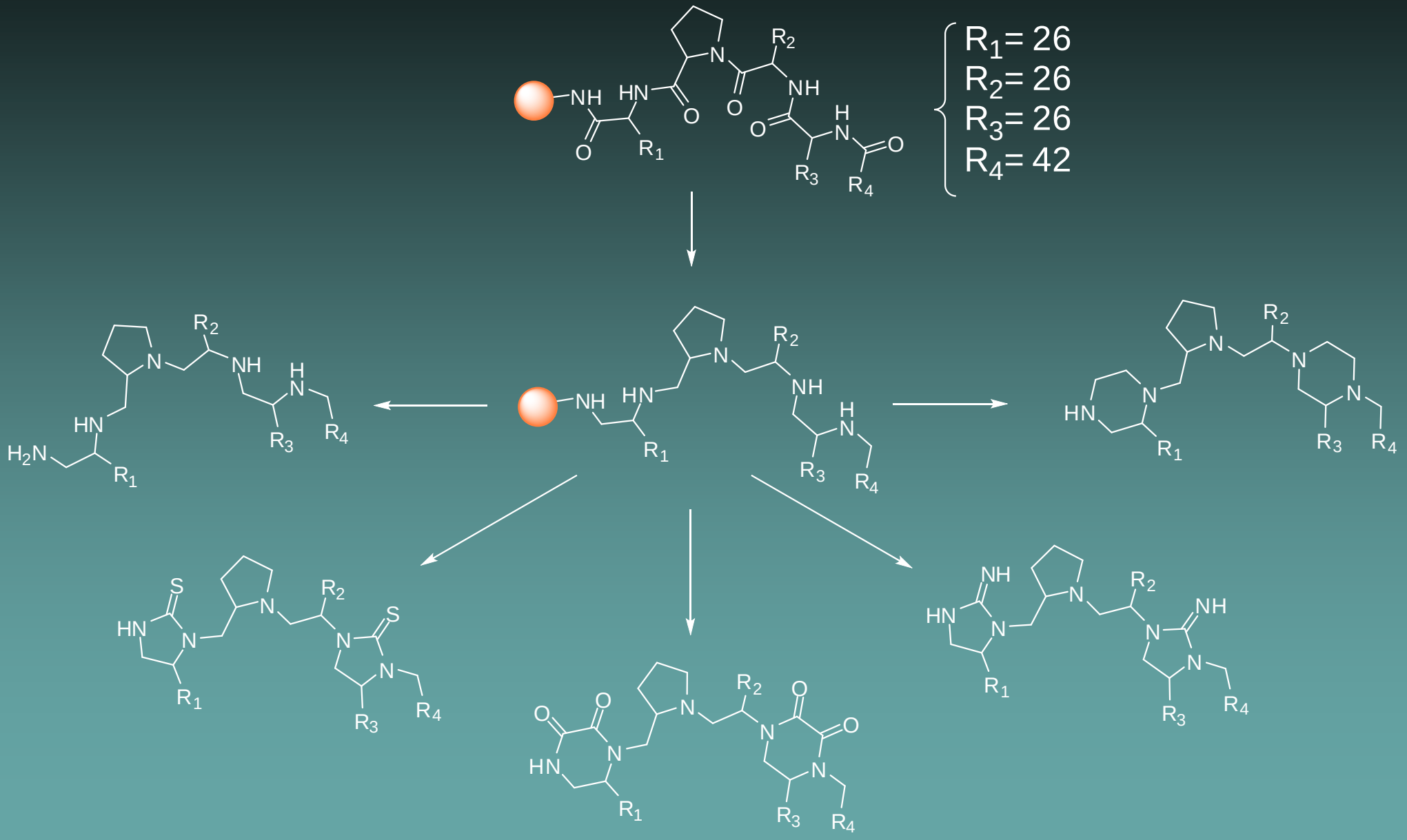
J. Comb. Chem. 2001, 3, 68-70.

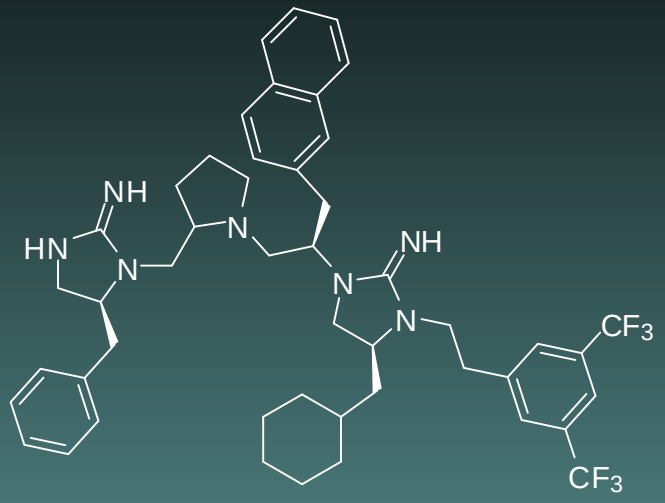
Solid-Phase Synthesis of Bis Heterocyclic Compounds from Reduced Tripeptides



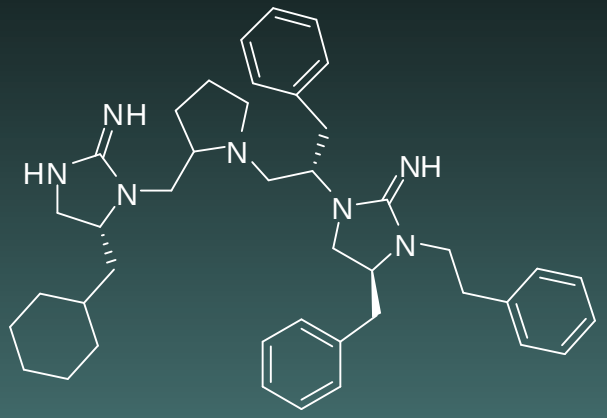
Org. Lett. (2001), 2, 3349.

Pyrrolidine containing bis-heterocyclic compounds

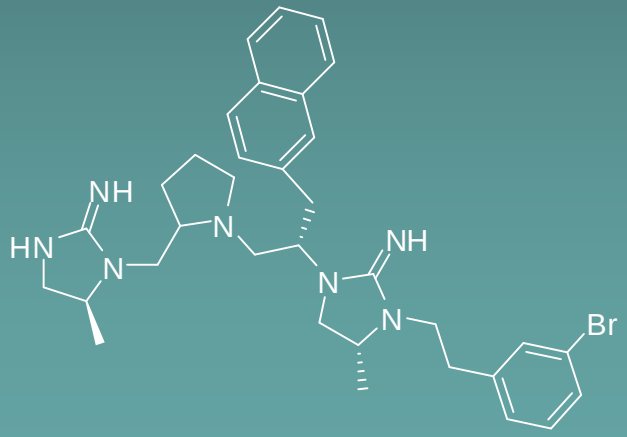




MRSA
MIC < 2.5 µg

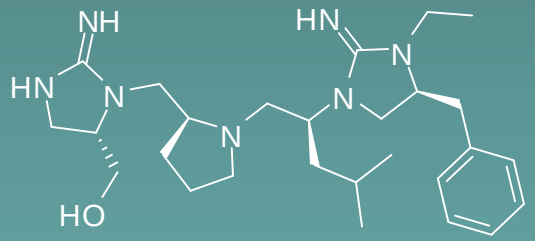


(Antitubercular)
% inhibition: 95
MIC = 2 µg/ml



Mu opioid receptor binding activity

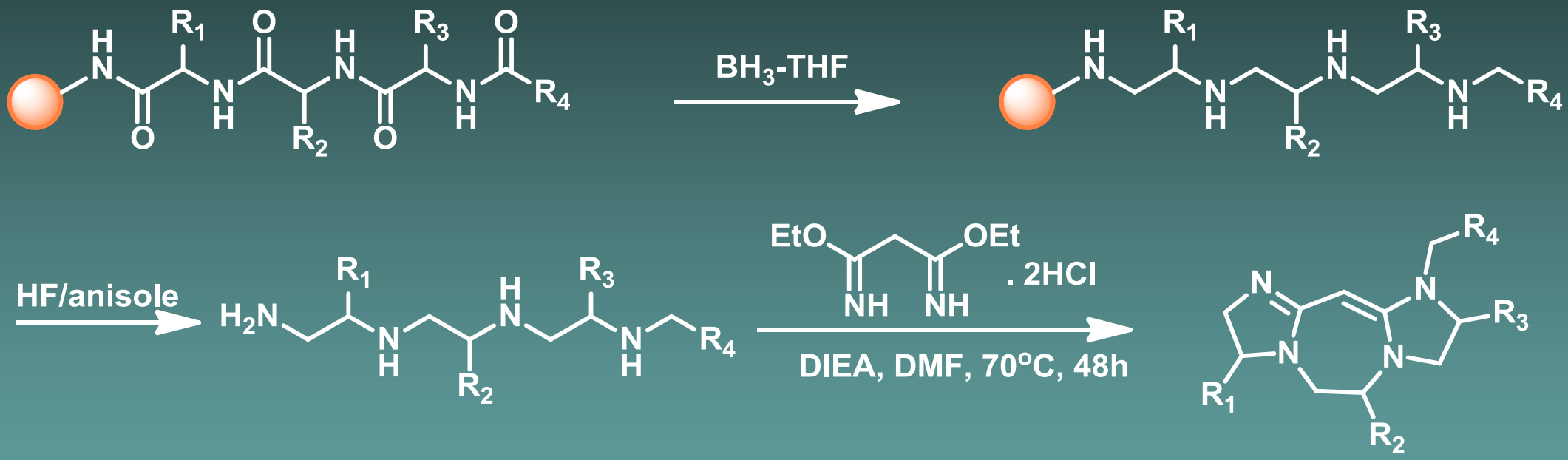
79.3 nM



PTHrP inhibitor

TPI1634-104

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



J. Med. Chem. 2015, 58, 4905-4917.

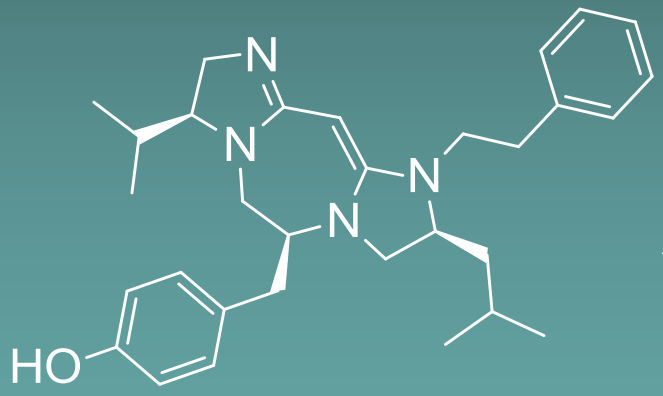
Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Parallel Synthesis of Hexahydrodiimidazodiazepines Heterocyclic Peptidomimetics and Their in Vitro and in Vivo Activities at μ (MOR), δ (DOR), and κ (KOR) Opioid Receptors

Shainnel O. Eans, Michelle L. Ganno, Elisa Mizrachi, Richard A. Houghten, Colette T. Dooley, Jay P. McLaughlin, and Adel Nefzi*

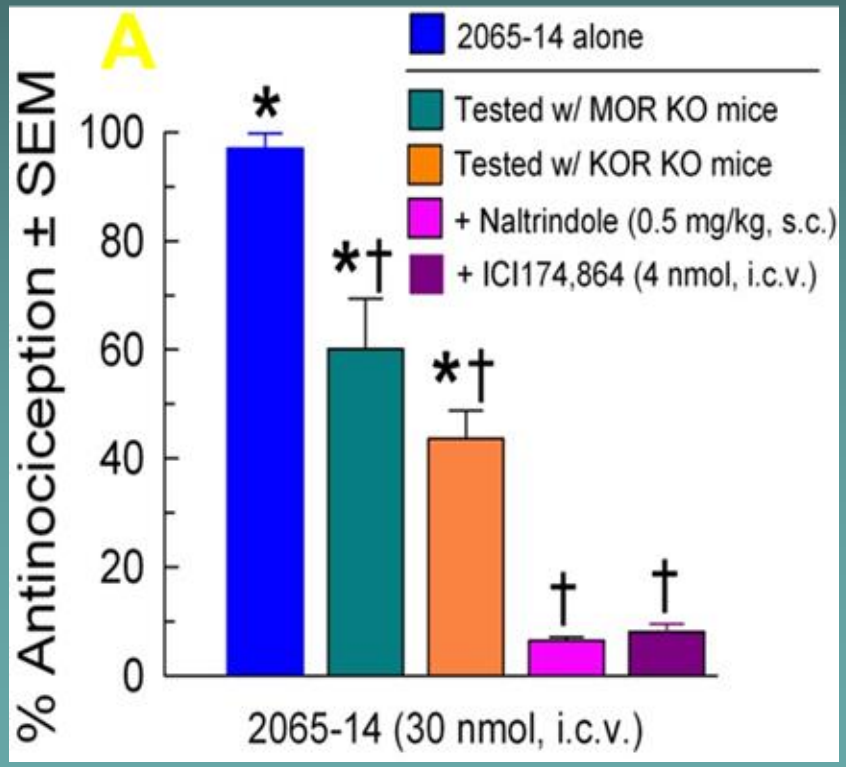


2065-14

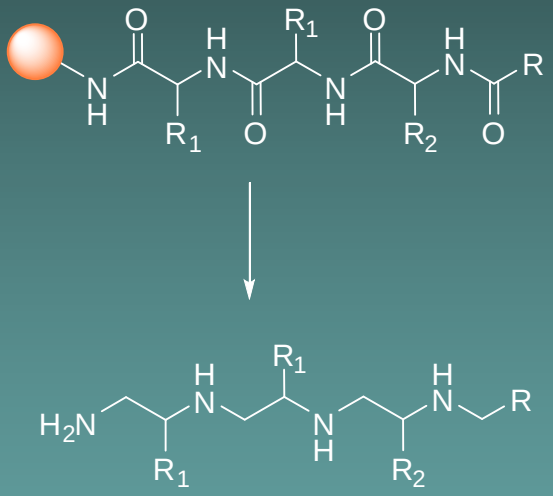
μ= Ki: 721 ± 35 nM

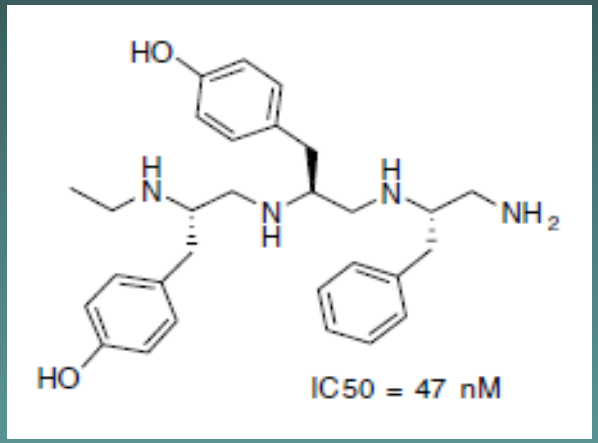
κ= Ki: 23 ± 12 nM

δ: Ki= 32 ± 6 nM

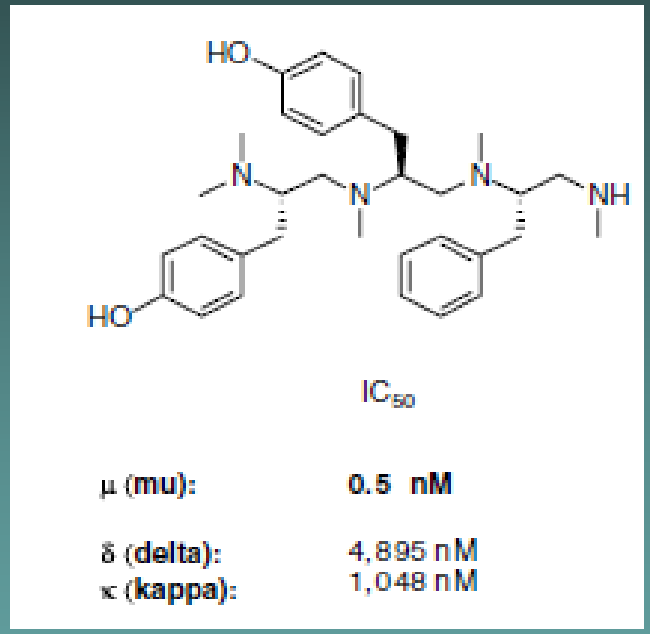


Identification of potent and highly selective chiral tri-amine and tetra-amine μ receptors ligands





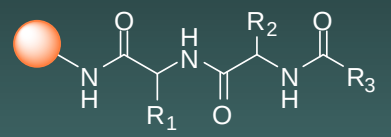
SAR



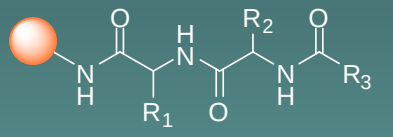
Bioorg. Med. Chem. Lett. 2006, 16, 4331-4338.

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

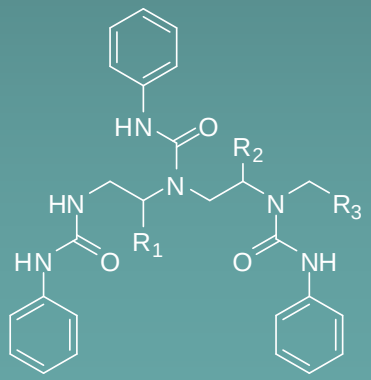
Bing Z. Carter, Marcela Gronda, Zhiliang Wang, Kate Welsh, Clemencia Pinilla, Michael Andreeff, Wendy D. Schober, Adel Nefzi, Gregory R. Pond, Imtiaz A. Mawji, Richard A. Houghten, John Ostresh, Joseph Brandwein, Mark D. Minden, Andre C. Schuh, Richard A. Wells, Hans Messner, Kathy Chun, John C. Reed, and Aaron D. Schimmer



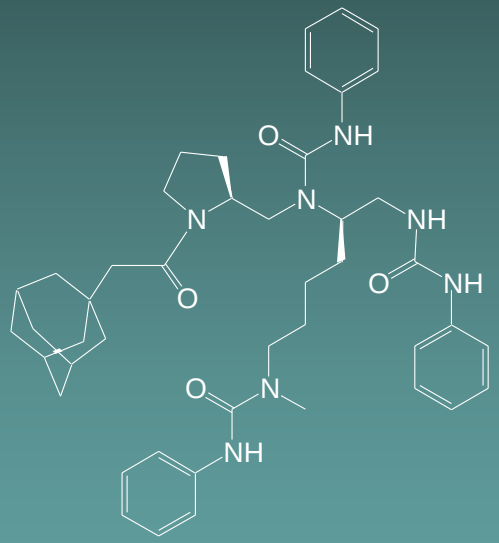
1) [H]
2) PhNCO



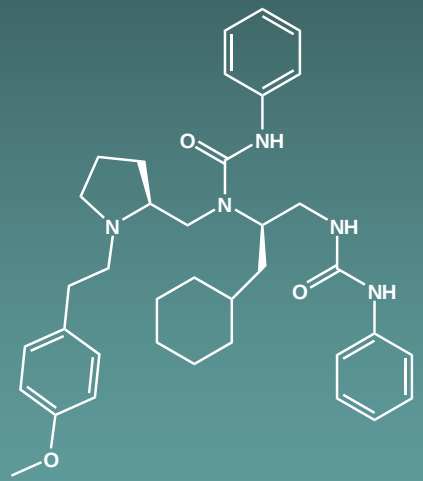
HF



89865 compounds
135 mixtures

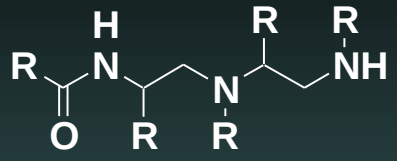


1396-11

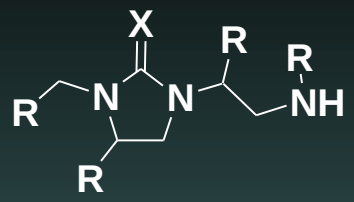


1396-34

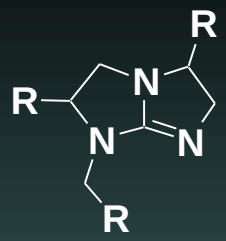
Representative Small Molecular Libraries: Libraries for Probe, Hit and Lead Identification



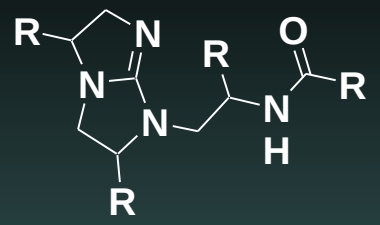
N-acyl triamines
(450,000)



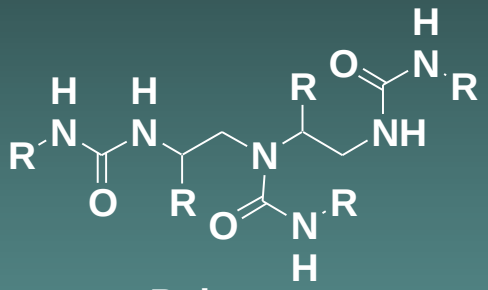
Cyclic ureas and thioureas
(472,000; X= O, S)



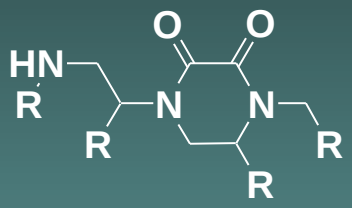
Bicyclic guanidines
(100,000)



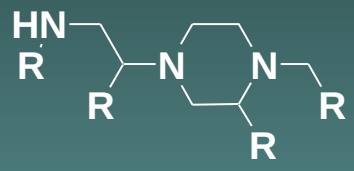
Acyl-bicyclic guanidines
(1,300,000)



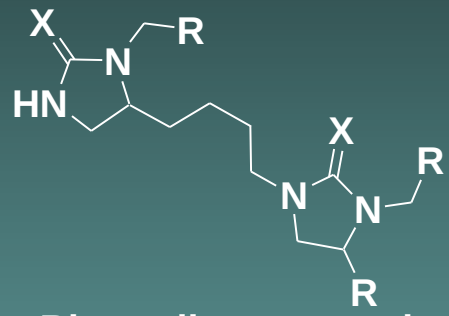
Polyureas
(160,000)



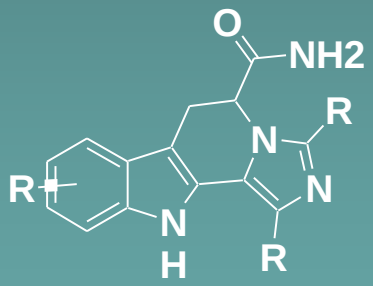
Diketopiperazines
(80,000)



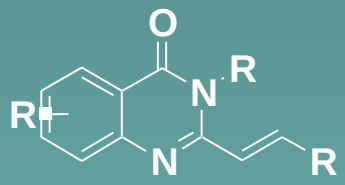
Piperazines
(80,000)



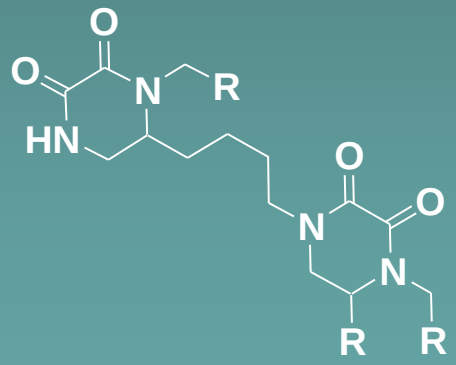
Bis-cyclic ureas and
Bis-cyclic thioureas
(72,000)



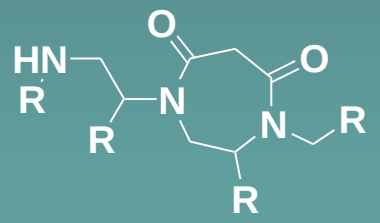
Indole-pyrido-imidazoles
(45,000)



Styryl quinazolinones
(122,000)



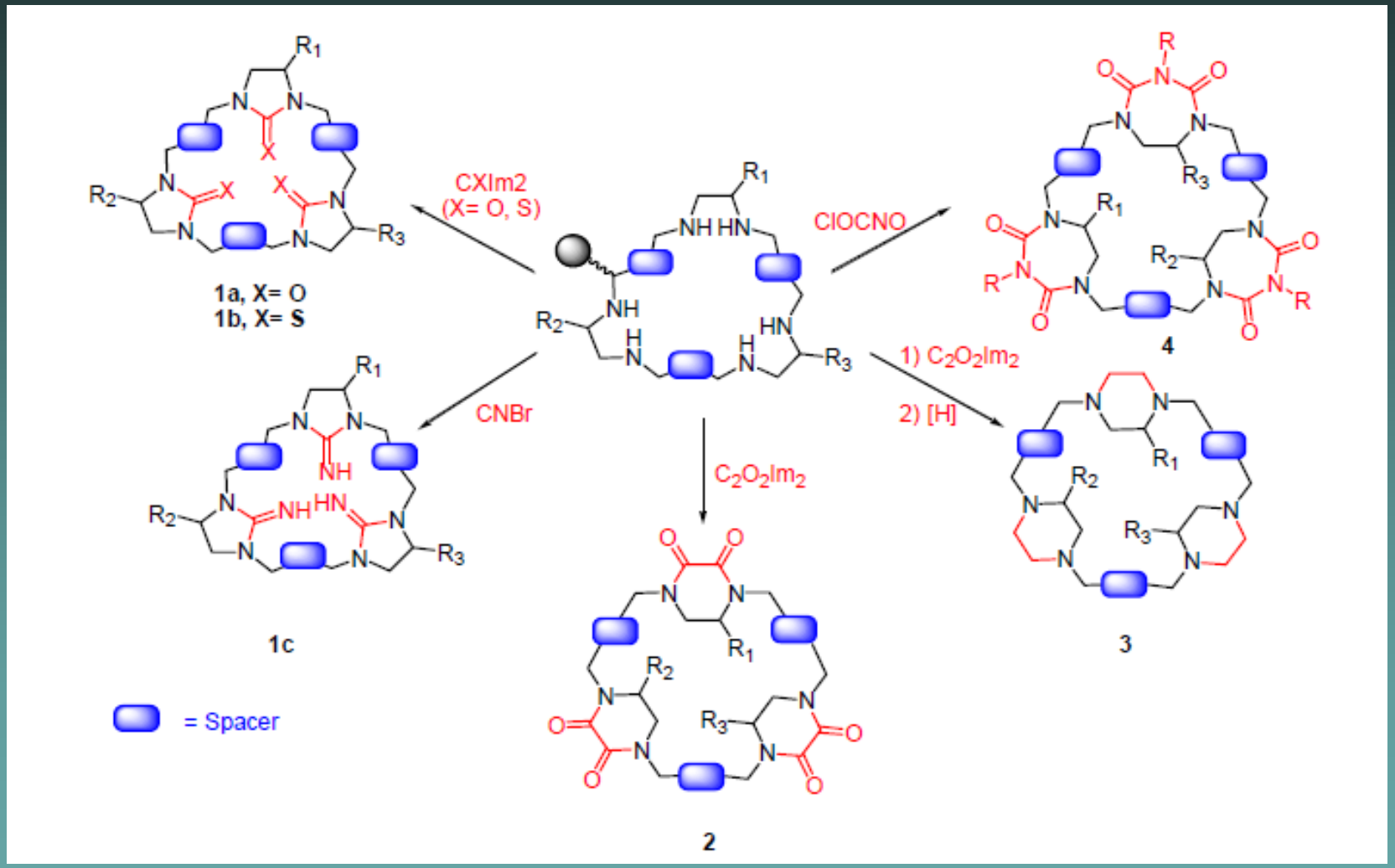
Bis-diketopiperazines
(72,000)



Diazepinediones
(80,000)

A versatile access to new macrocyclic oligoheterocycles (MOH)

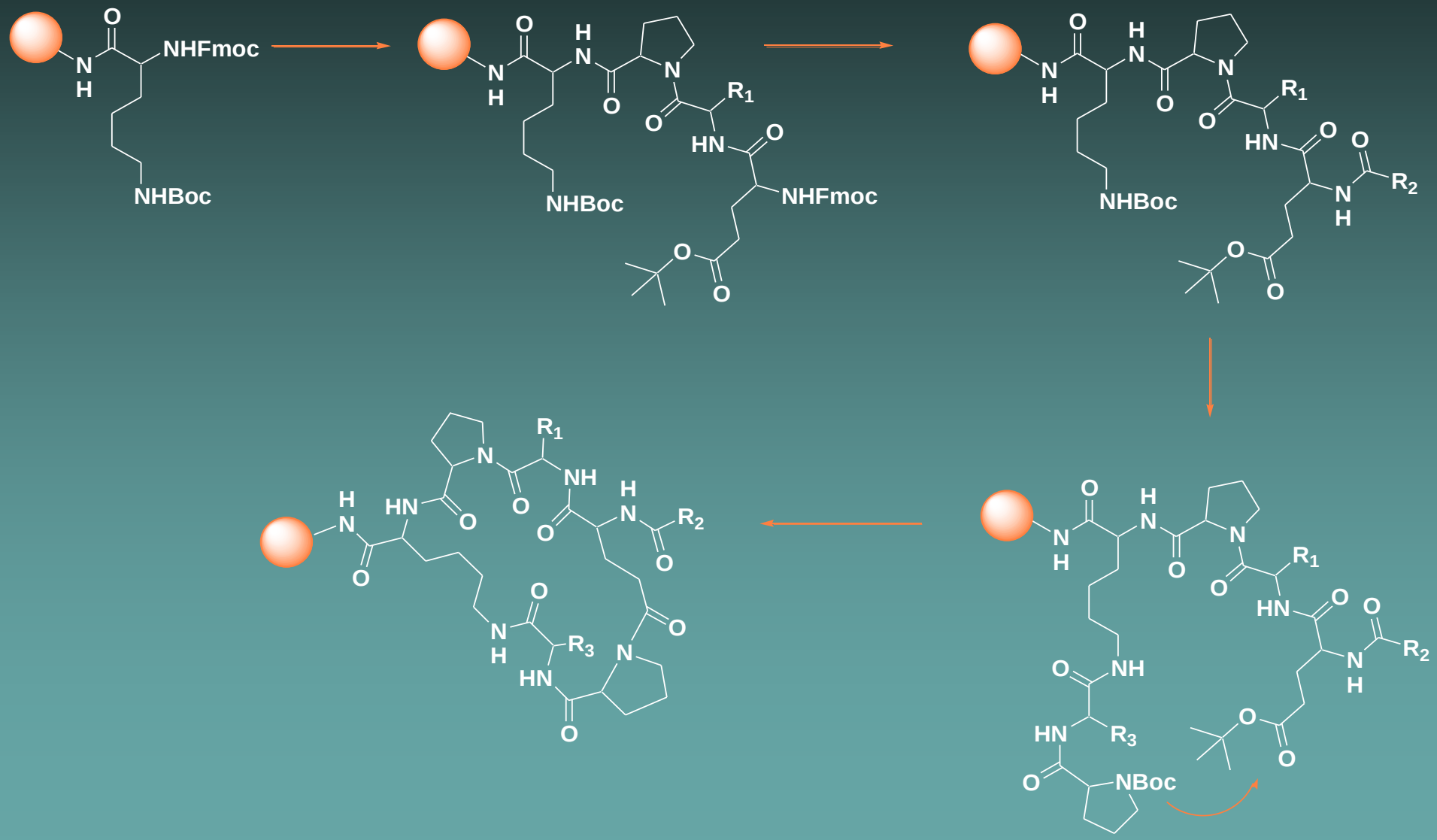
Adel Nefzi* and Rodegar T. Santos



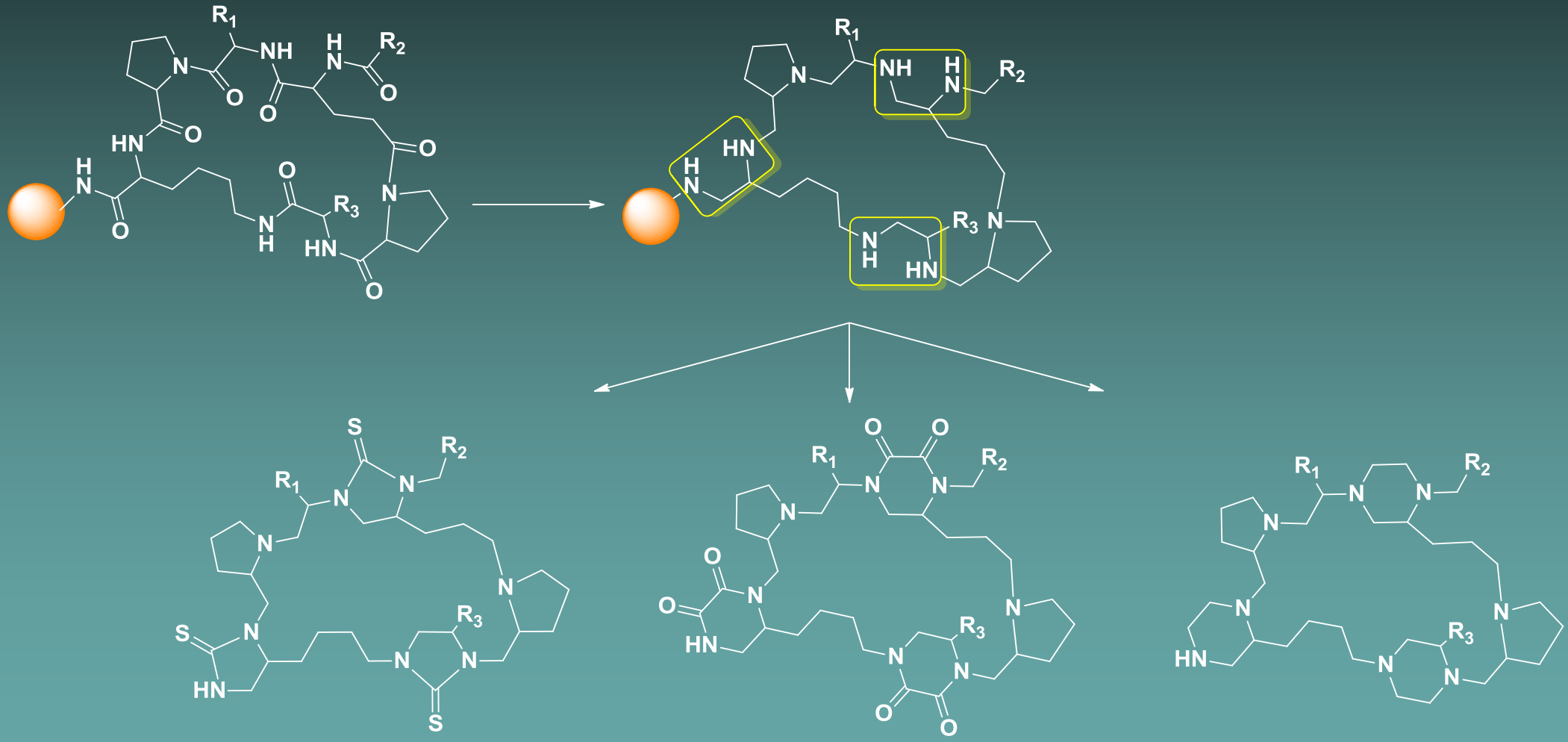
Bioorg. Med .Chem. Lett. 2006, 16:3358-3361.

Synthesis of Proline Containing Cyclic Peptides

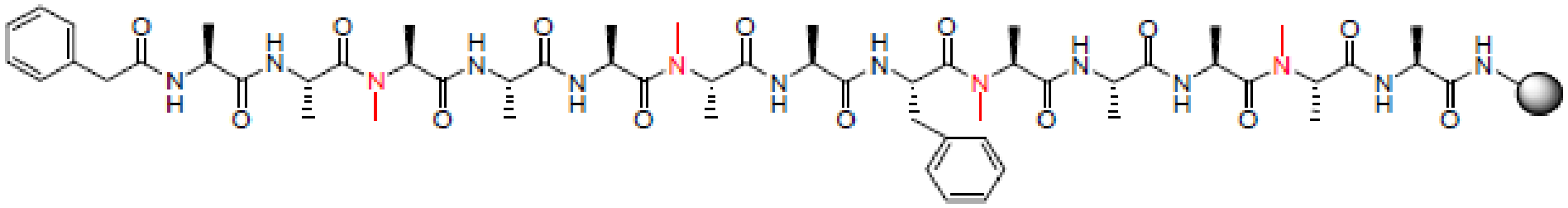
A versatile access to new macrocyclic oligoheterocycles (MOH)



Cyclic Multiple Heterocyclics from Proline Containing Cyclic Peptides

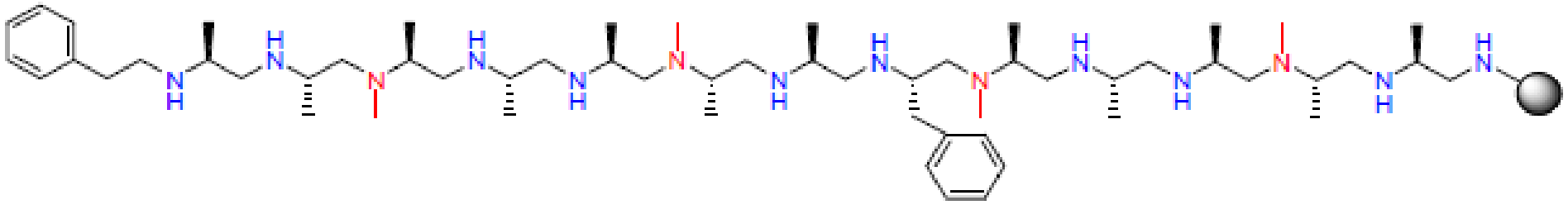


Oligoheterocyclic Compounds



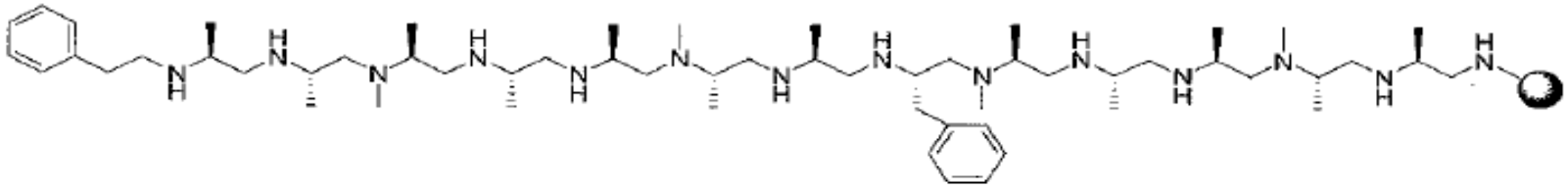
(Utilization of N-Me-Alanine as a spacer: Alternation of two secondary amides and one tertiary amide)

1) BH_3-THF
2) Piperidine



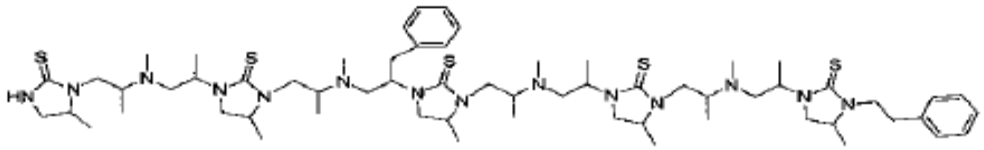
Generation of resin-bound spacially separated pairs of secondary amines

Oligoheterocyclic Compounds



Generation of resin-bound spacially separated pairs of secondary amines

Scheme 3



$C_{62}H_{104}N_{14}S_5$
Exact Mass: 1204.72

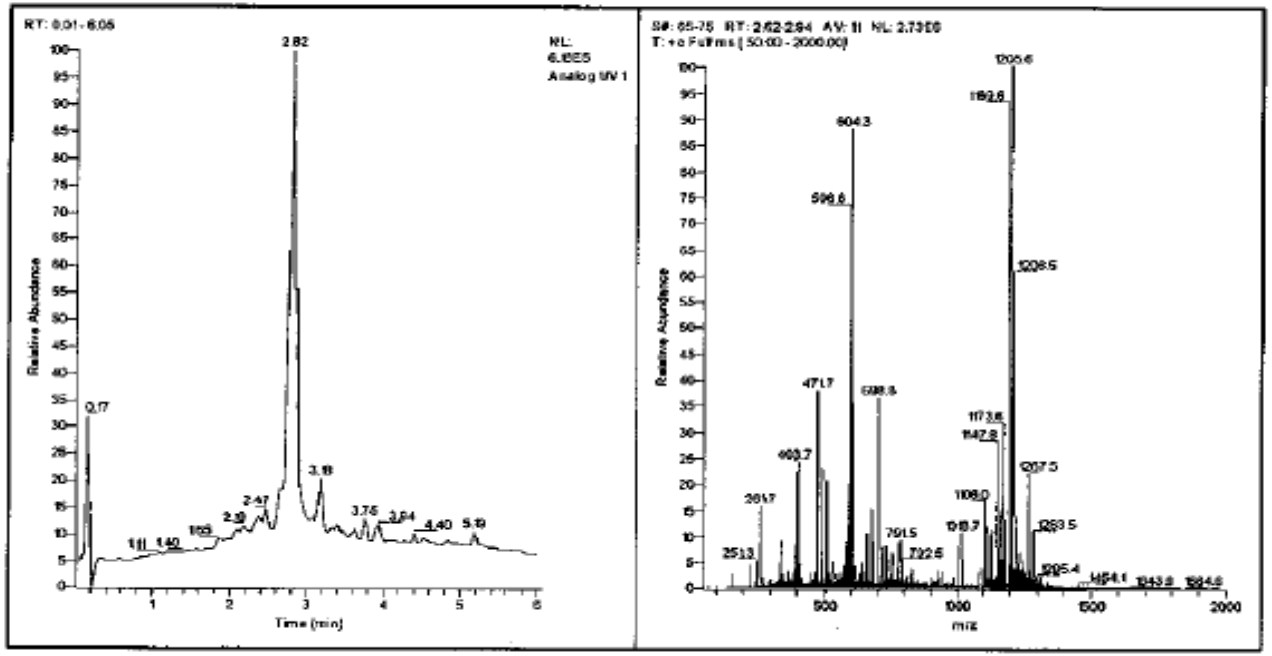
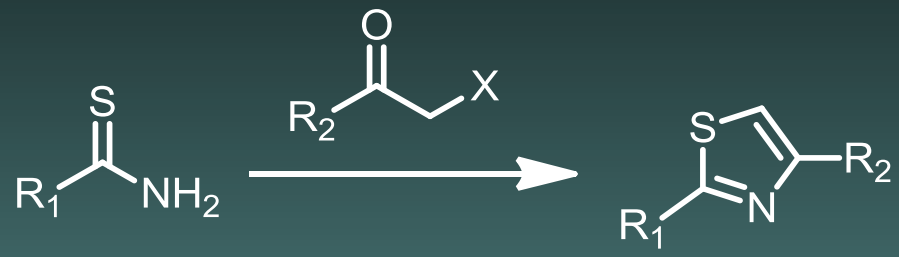
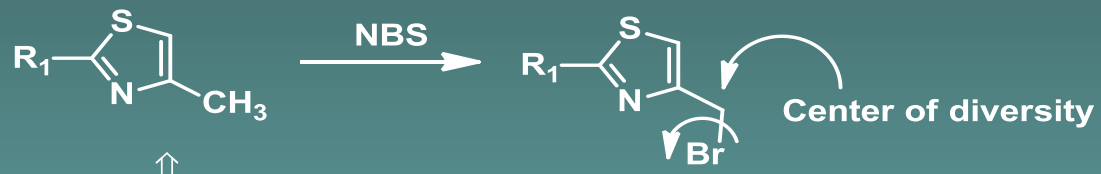


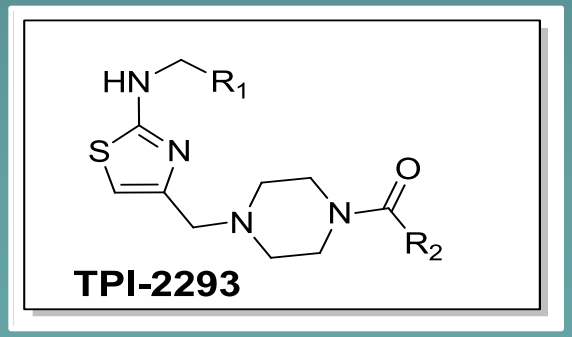
Figure 2

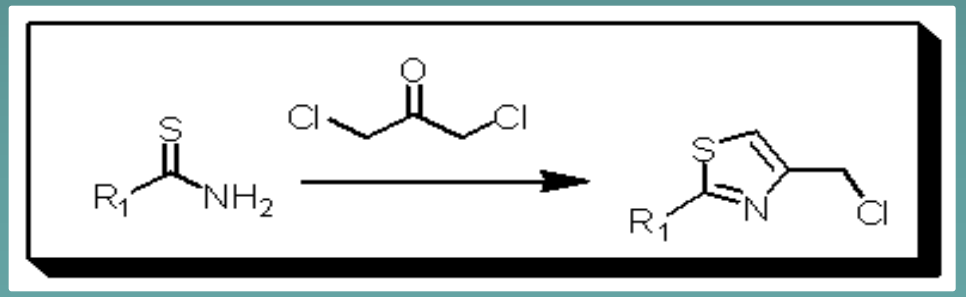
Hantzsch Based Macrocyclization Approach for the Synthesis of Thiazole Containing Cyclopeptides



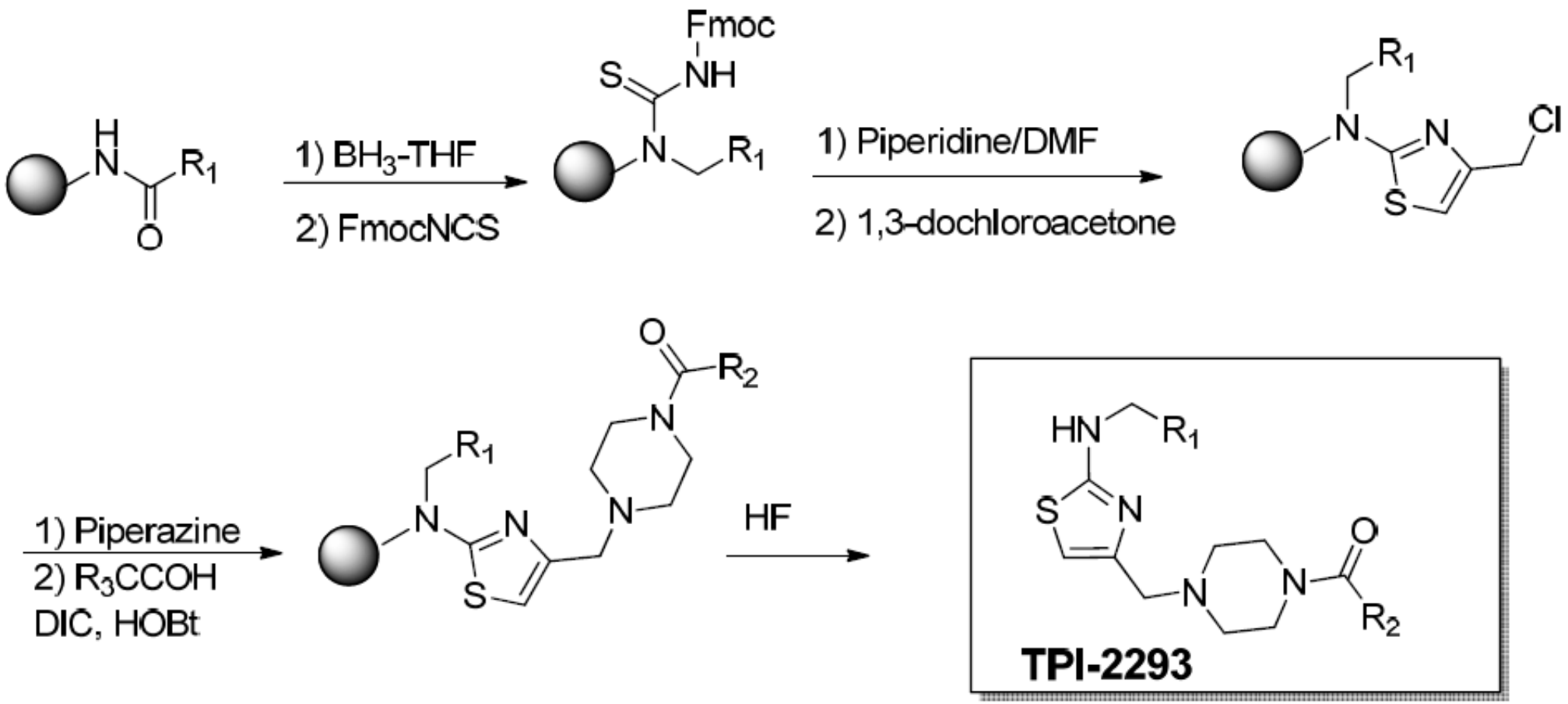
Hantzsch reaction



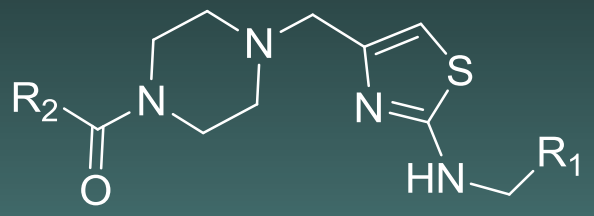




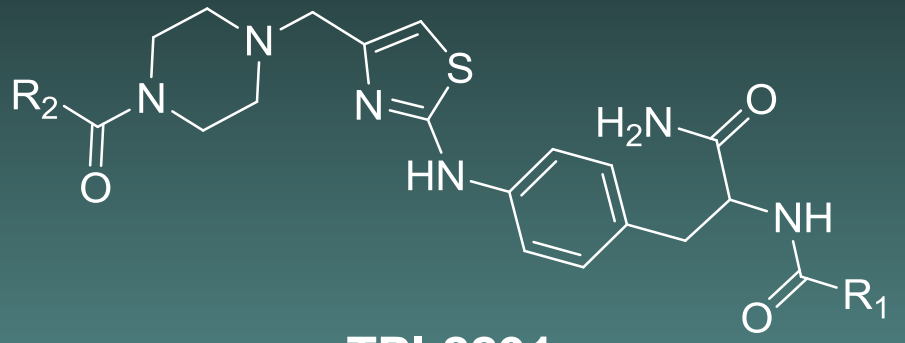
Synthesis of Thiazole tethered Piperazine Library



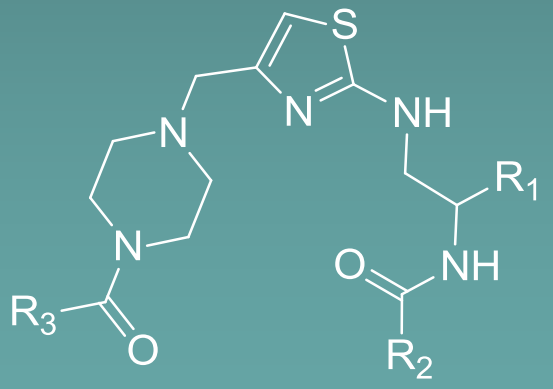
Thiazole Tethered Piperazine Libraries



TPI-2057



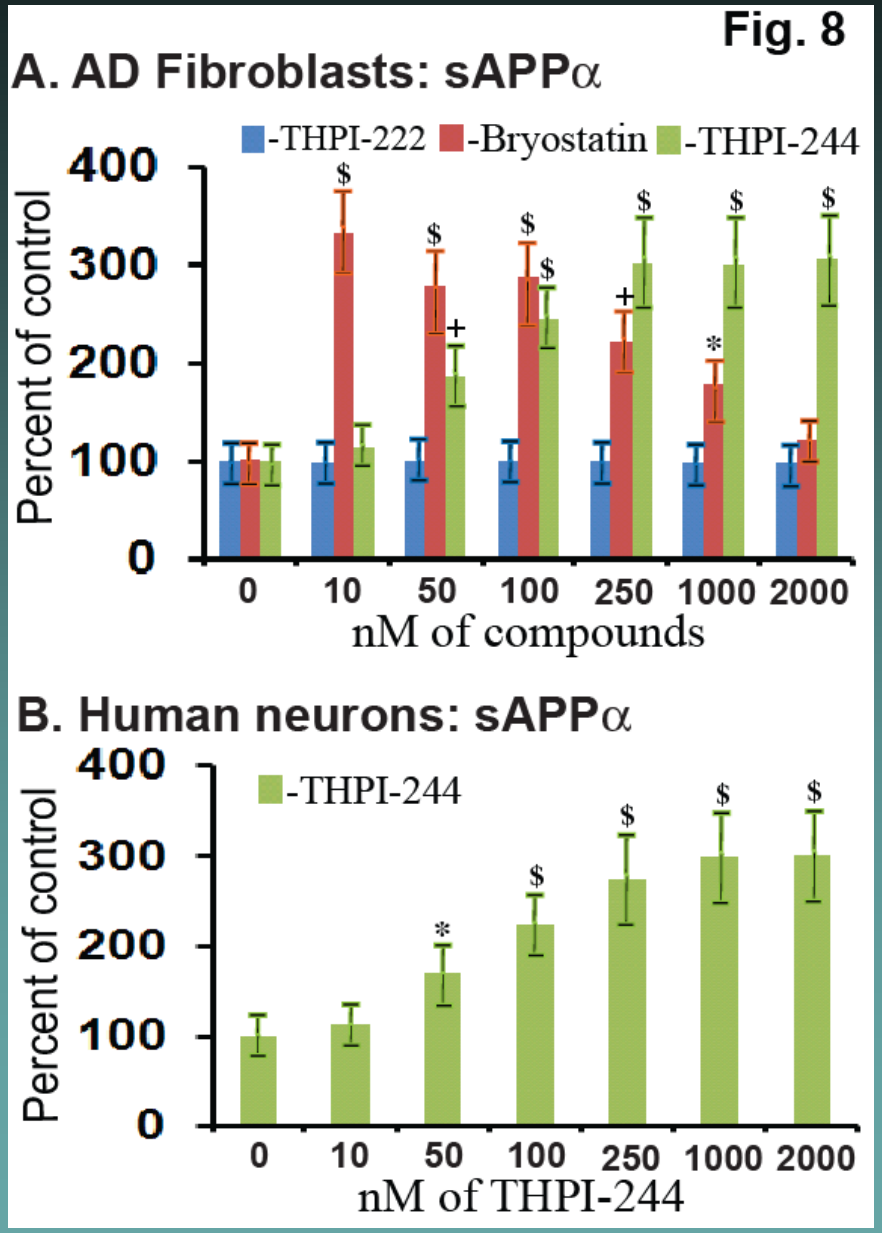
TPI-2291



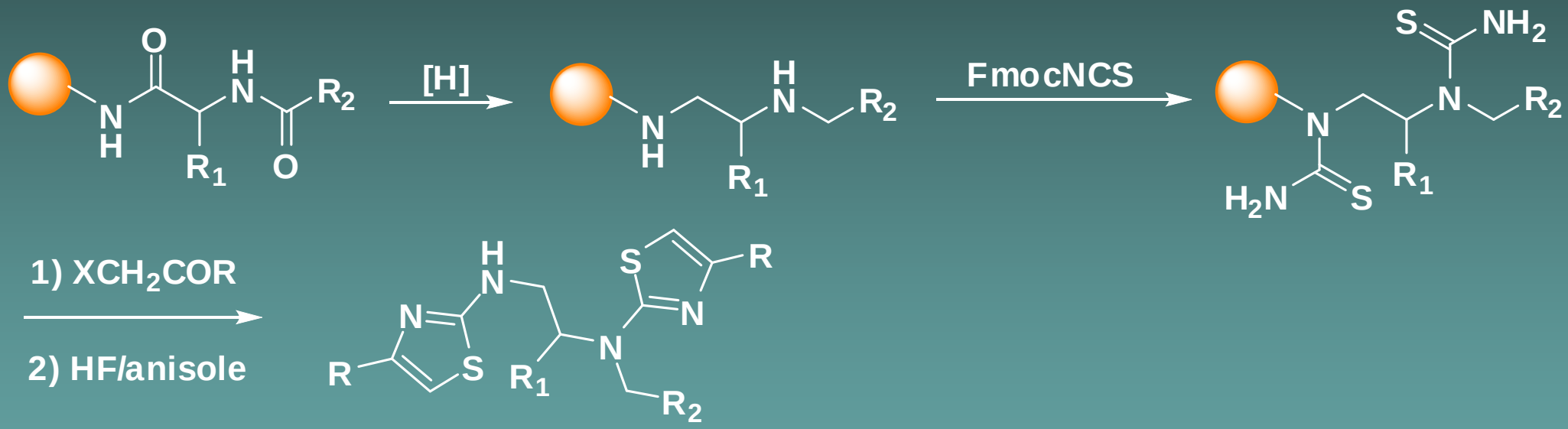
IKKe

sAPPalpha and TrkA

Preclinical evaluation of thiazole piperazine and its analog as Alzheimers drugs

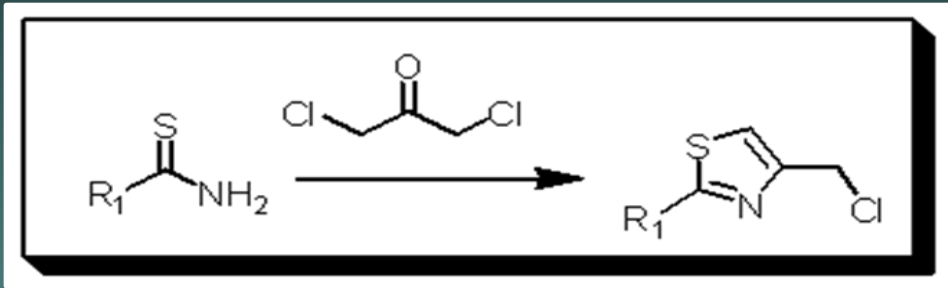


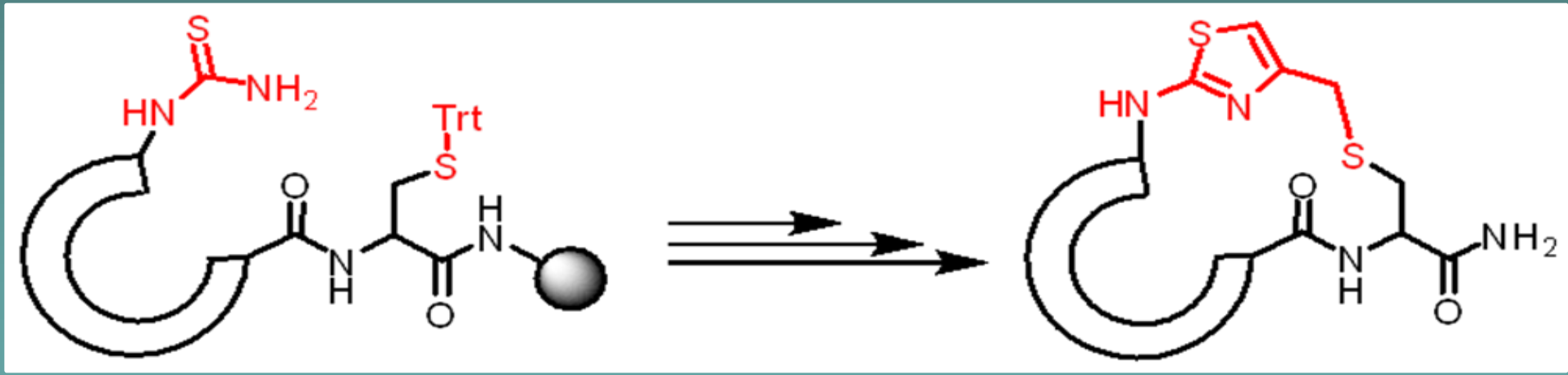
Synthesis of polythiazole compounds



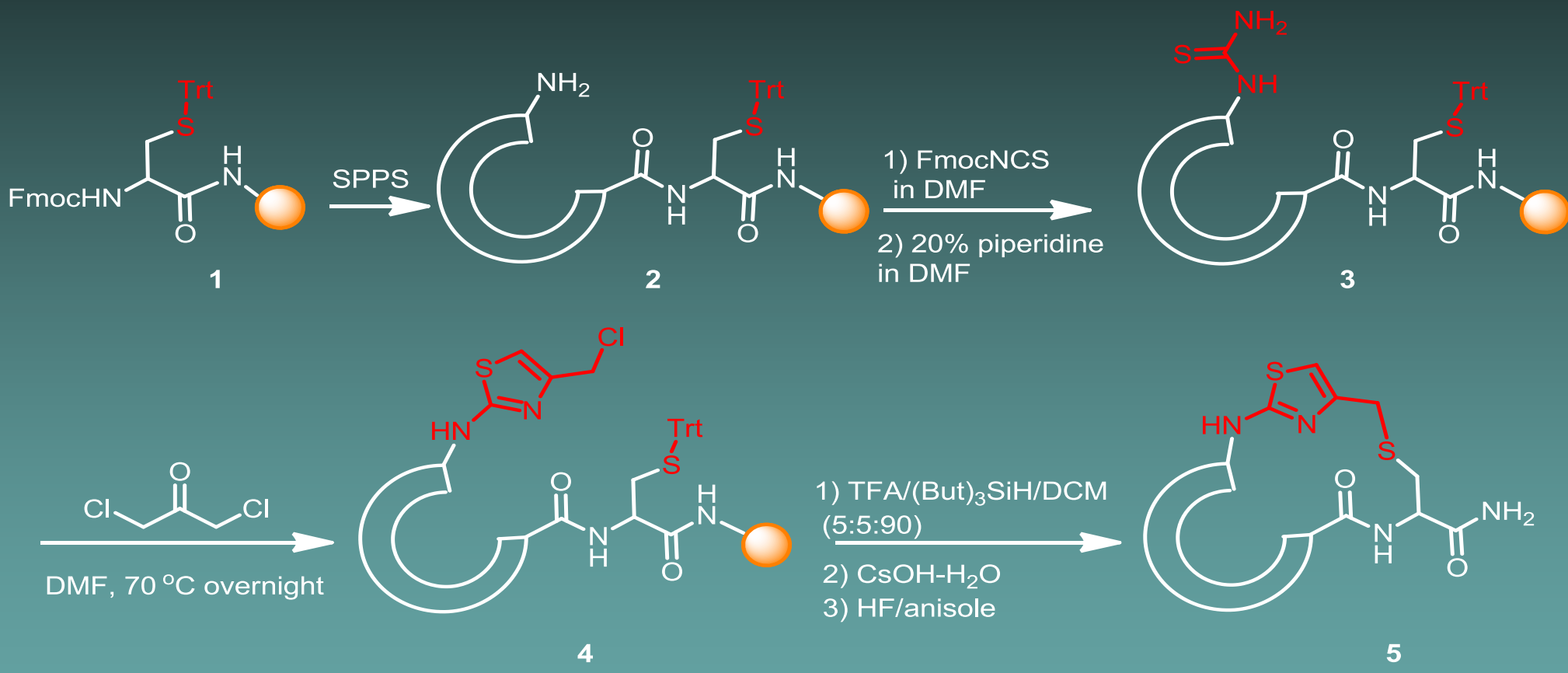
J. Com. Chem. 2010, 12, 315-317.

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



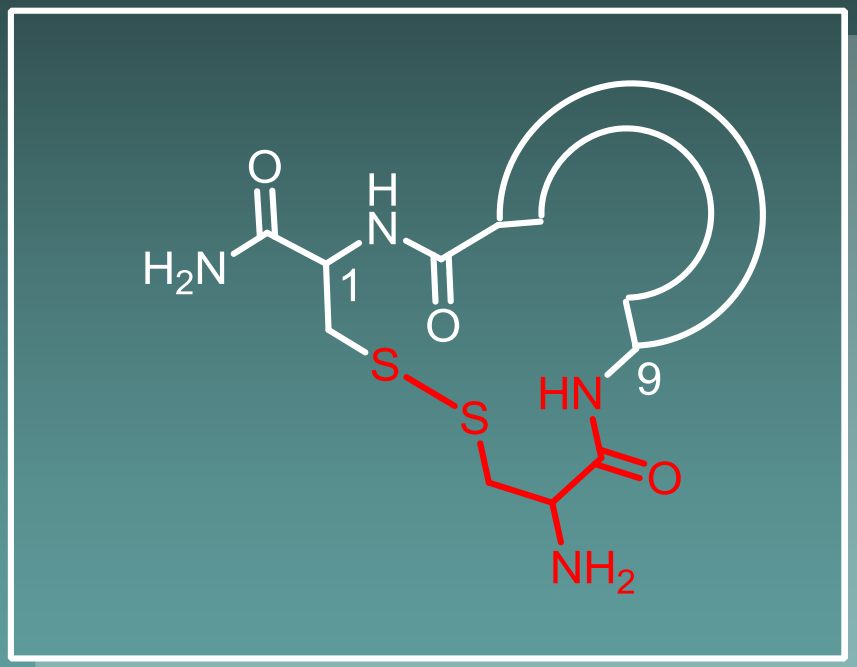


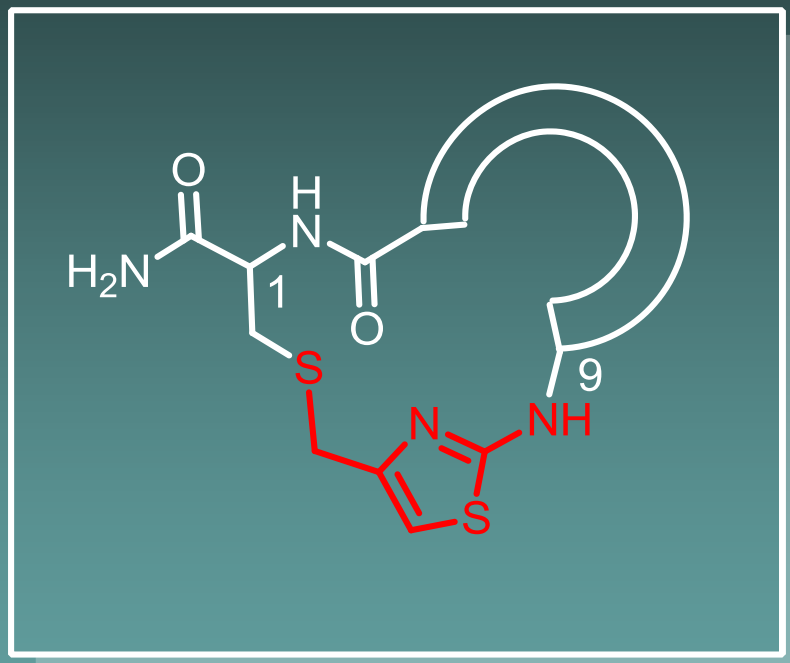
Synthesis of Thiazole Containing Cyclopeptides



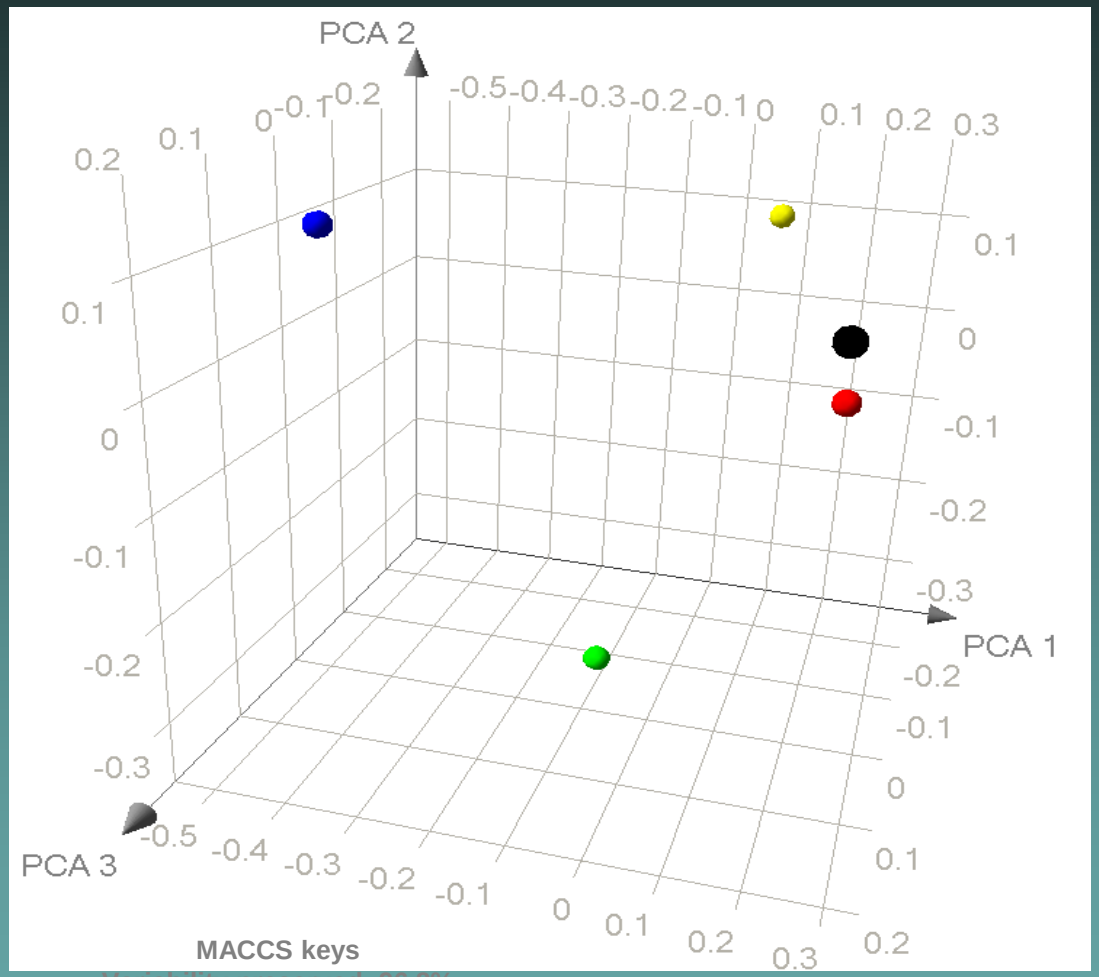
J. Org. Chem. **2010**, 75, 7939–7941
Tet. Lett. **2011**, 52, 817-819

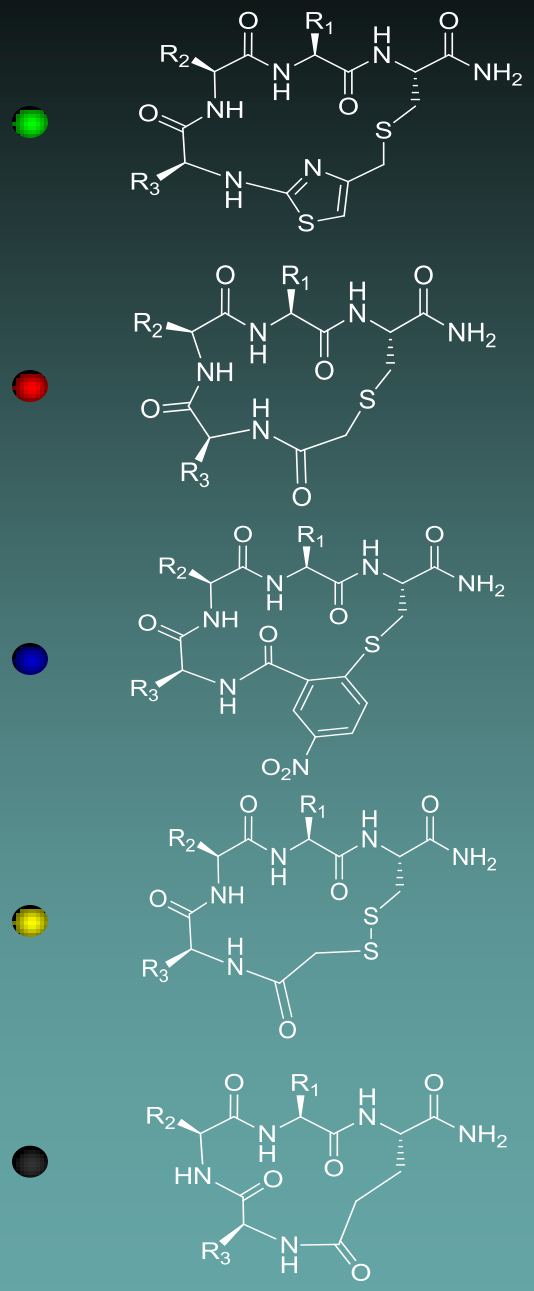
Synthesis of Macrocyclic Compounds *via* Thio-Methyl-Thiazole as Analog of the Disulfide Bridge



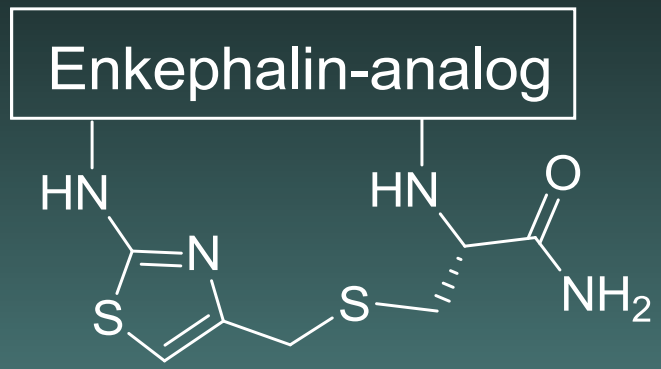


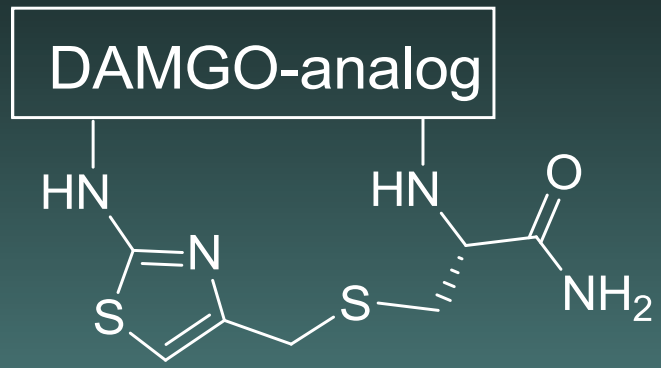
Approximate three-dimensional chemical space distribution of different cyclic peptides

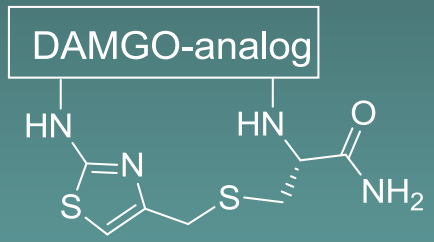




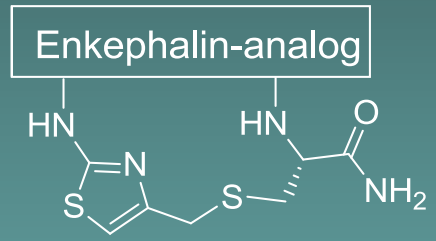
Synthesis of Thiazole Containing Cyclopeptides Application for the synthesis of DAMGO and EnkephalinConstrained Analogs



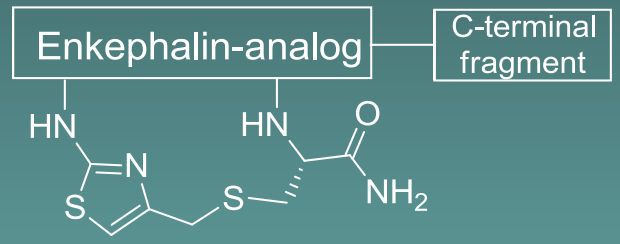




TPI-1924-1: Tyr-Ala-Gly-Phe
TPI-1924-4: Tyr-Ala-Gly-(N-Me)Phe
TPI-1924-7: Tyr-Ala-Phe
TPI-1924-10: Tyr-Ala-Gly-(N-Me)Phe

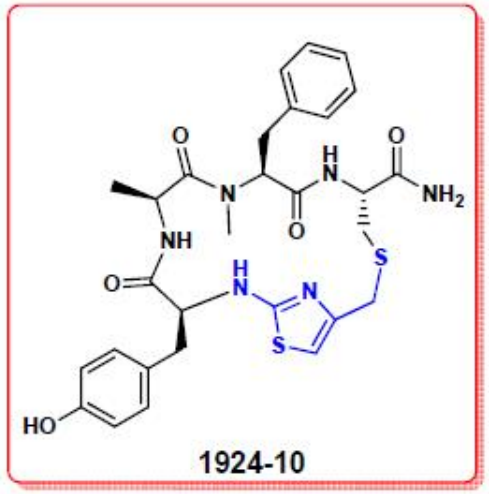


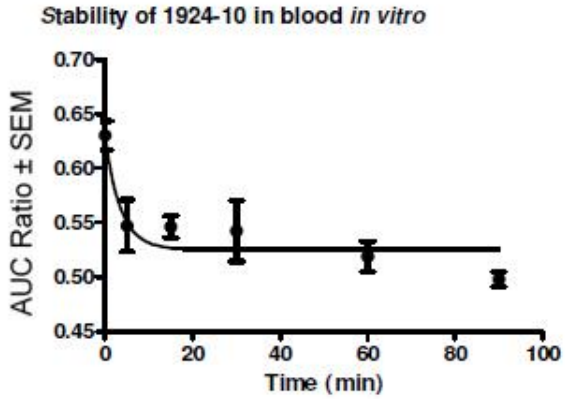
TPI-1924-13: Tyr-Gly-Gly-Phe-Leu
TPI-1924-16: Tyr-Gly-Gly-Phe-Met
TPI-1924-19: Tyr-Gly-Phe-Leu
TPI-1924-22: Tyr-Gly-Phe-Met
TPI-1924-25: Tyr-Phe-Leu
TPI-1924-28: Tyr-Phe-Met

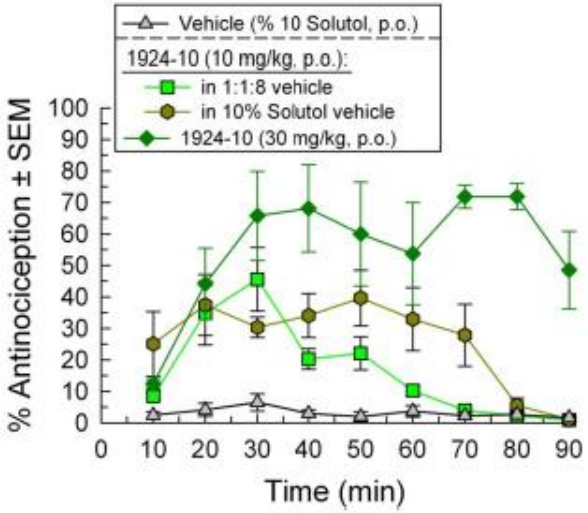


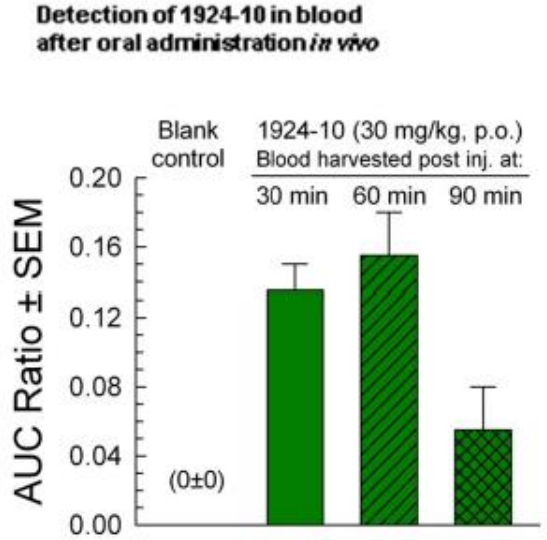
TPI-1936-1: [Tyr-Gly-Gly-Phe]—Met
TPI-1936-2: [Tyr-Gly-Gly]—Phe-Met
TPI-1936-3: [Tyr-Gly]—Gly-Phe-Met
TPI-1936-4: [Tyr-Gly-Phe]—Met
TPI-1936-5: [Tyr-Gly]—Phe-Met
TPI-1936-6: [Tyr-Gly-Gly-Phe]—Leu
TPI-1936-7: [Tyr-Gly-Gly]—Phe-Leu
TPI-1936-8: [Tyr-Gly]—Gly-Phe-Leu
TPI-1936-9: [Tyr-Gly-Phe]—Leu
TPI-1936-10: [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

O_1 X X X -NH_2
X O_2 X X -NH_2
X X O_3 X -NH_2
X X X O_4 -NH_2

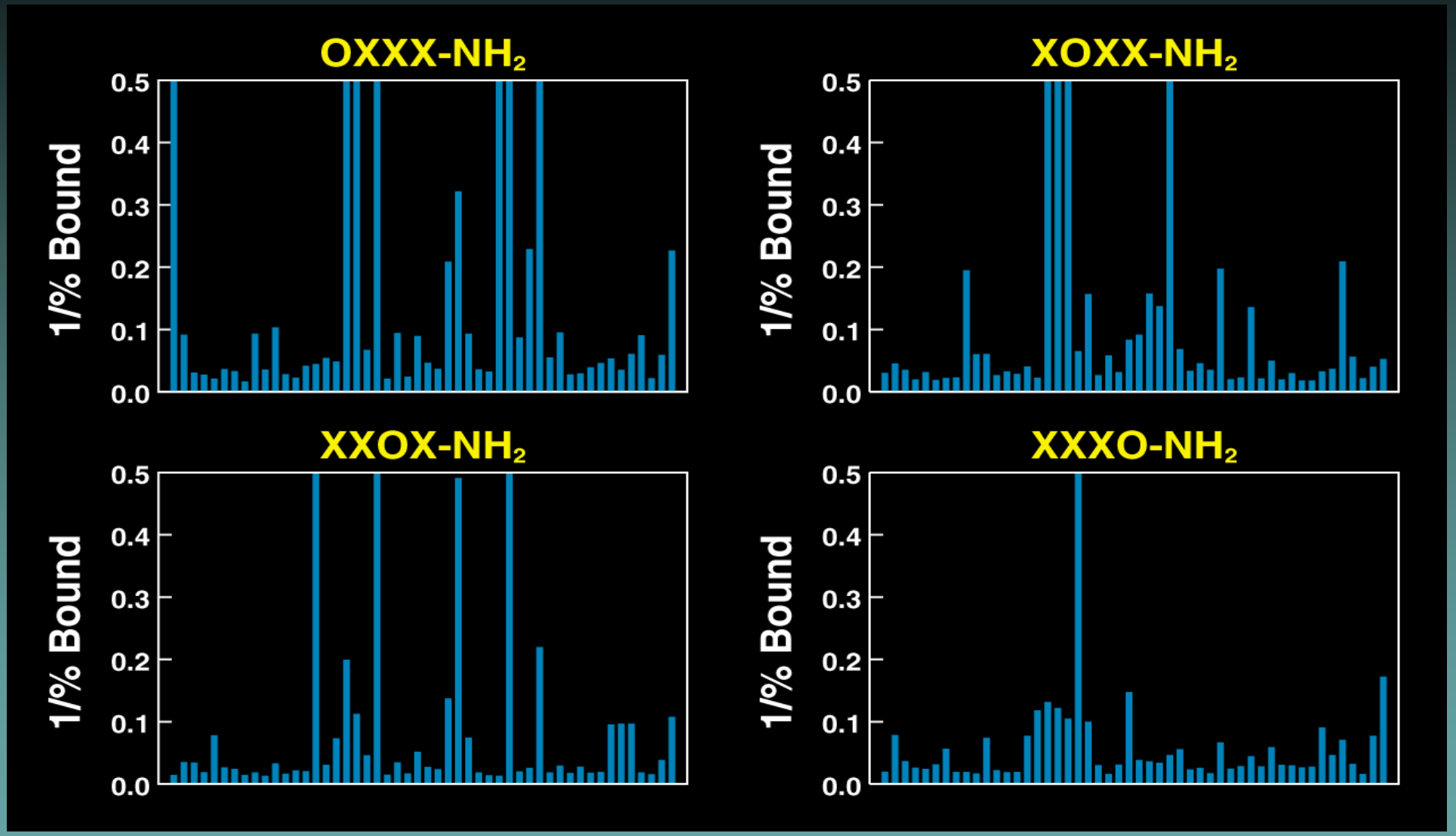
6,250,000 tetra-peptides
125,000 each mixture

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

O = individual X = mixture

Dooley, Houghten (1998) J. Biol. Chem. 273, 18848

Kappa Receptor Binding Assay



7 x 4 x 4 x 1= 96 individual tetrapeptides

Kappa Receptor Binding Assay

Positional Library	Most Active Residues	Number of Residues
OXXX-NH_2	DPhe, DNle	2
XOXX-NH_2	DPhe, DNal	2
XXOX-NH_2	DTrp, Dile, DNle	3
XXXO-NH_2	DArg, DCha	2
	Total	24

Sequence	IC_{50} (nM)
(DPhe)(DNal)(DNle)(DArg)-NH_2	1
(DPhe)(DPhe)(DNle)(DArg)-NH_2	2
(DNle)(DNal)(Dile)(DArg)-NH_2	2
(DPhe)(DPhe)(Dile)(DArg)-NH_2	2
(DNle)(DNal)(DNle)(DArg)-NH_2	3
(DPhe)(DNal)(Dile)(DArg)-NH_2	4

All Full Agonists

Kappa Receptor Selectivity

Sequence	κ U69,593 IC_{50} (nM)	μ DAMGO IC_{50} (nM)	δ DSLET IC_{50} (nM)
(DPhe)(DNal)(DNle)(DArg)-NH_2	0.7	22,630	49,640
(DPhe)(DPhe)(DNle)(DArg)-NH_2	2.0	42,963	>25,000
(DNle)(DNal)(Dile)(DArg)-NH_2	2.0	3,034	19,316
(DPhe)(DPhe)(Dile)(DArg)-NH_2	2.0	>150,000	>25,000
(DNle)(DNal)(DNle)(DArg)-NH_2	3.0	1,709	>25,000
(DPhe)(DPhe)(DNle)(DCha)-NH_2	6.0	15,000	28,932

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*


CORROSIVE
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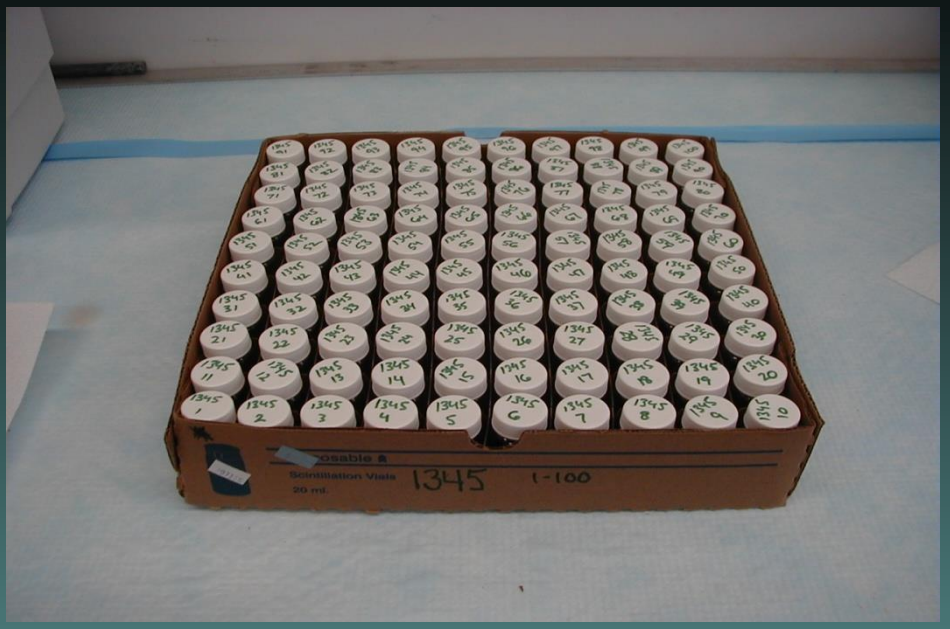
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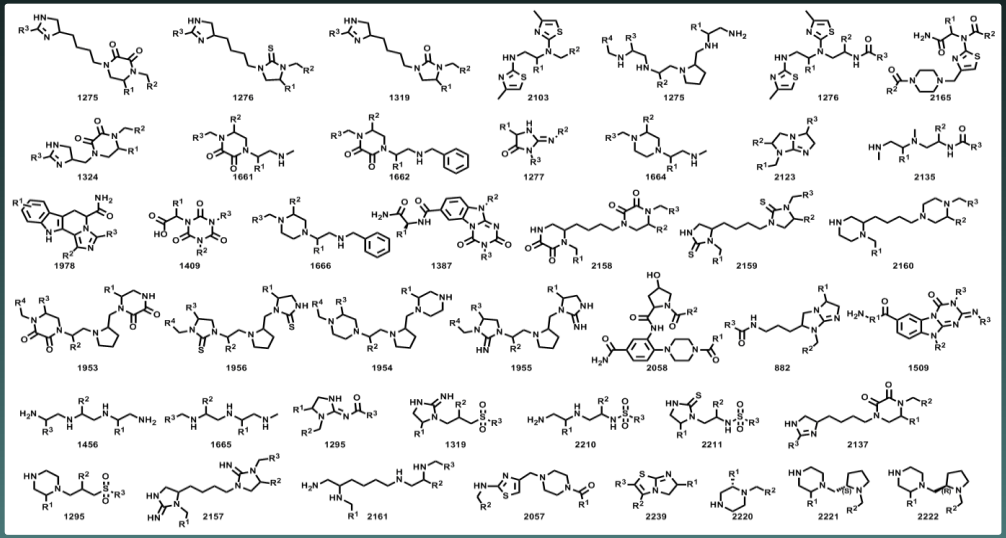
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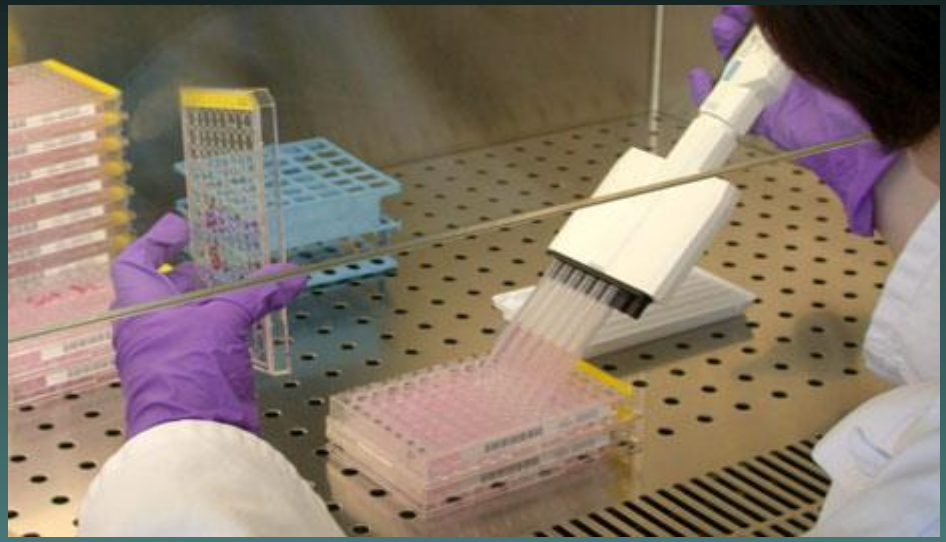

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