Peptides as leads for medicinal chemistry - the Ups and Downs of Peptidomimetic Research.

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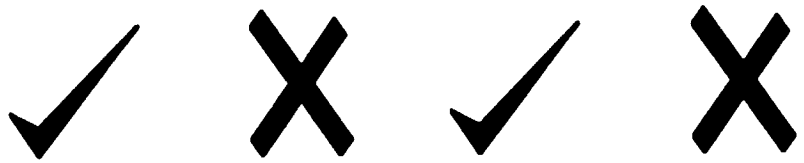

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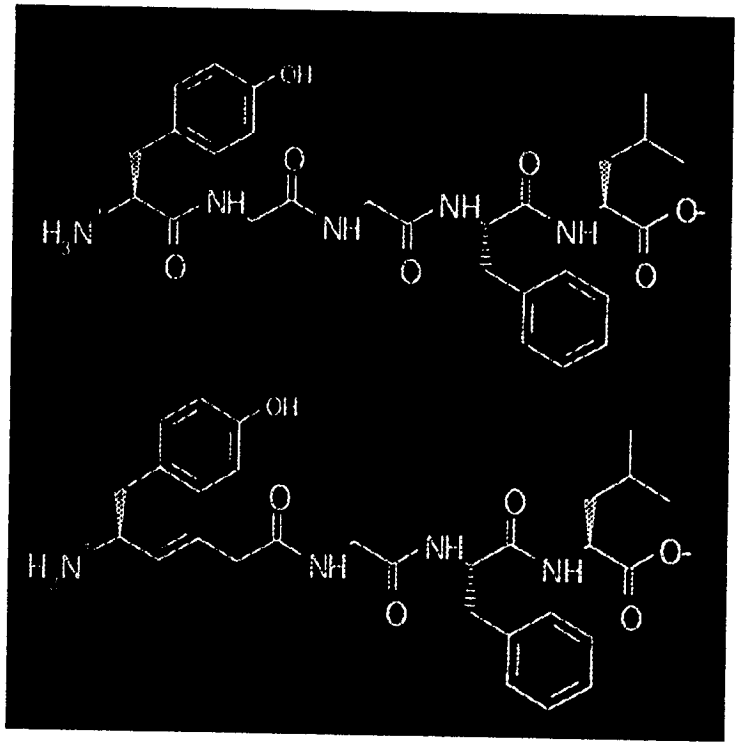
Enkephalins

- Replacement of amide bonds by carbon carbon double bonds
- Stable to amino peptidase
- Higher logP



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Angiotensin II - attempt 1

- Asp-Arg-Val-Tyr-Ile-His-Pro-Phe
- analogues based on His-Pro-Phe
- synthesis failed
- selected screening based on lipophilic acids
- no success
  - lack of capacity
  - lack of samples

X

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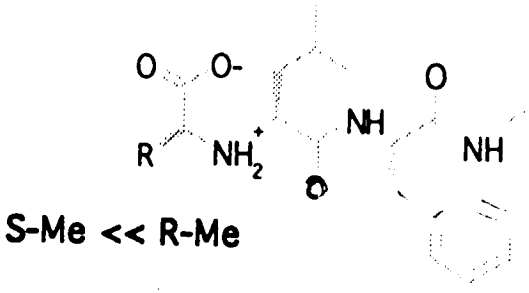
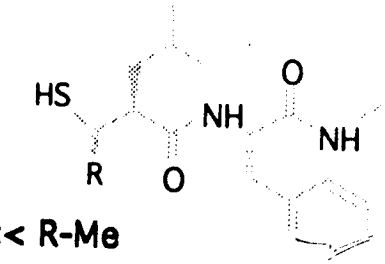
Collagenase Inhibition

- Collagenase model based on Thermolysin
- Potency enhancement of Methyl
- Conformational analysis
- identification of solvent "direction" ✓
- in vitro problems ✗
- X-ray structure
  - confirms TLN homology
  - Bioactive conformation correct



S-Me << R-Me



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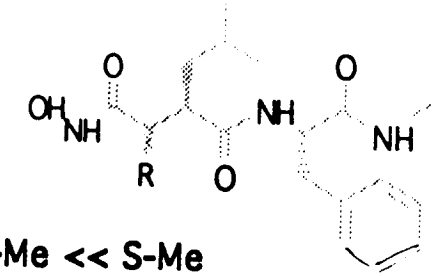

R-Me << S-Me

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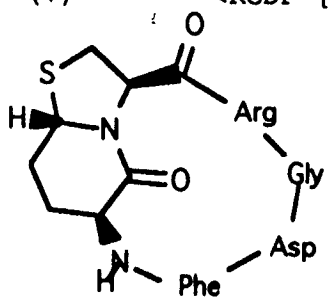
Fibrinogen antagonists

- constrained cyclic RGD peptides
- non-peptide "antagonists"

Cyclic RGD peptides and their Fibrinogen antagonist activity

Compound	Sequence*	Activity+
(1)	GRGDS	1.0 (standard)
(2)	<RBDFG>	>44
(3)	<RGD-(Me)FG>	>25
(4)	<RGDFG>	0.4
(5)	<RGDF-[D]PF>	0.7
(6)	<RGDF-[c65]>	0.9
(7)	<RGDF-[t65]>	0.02



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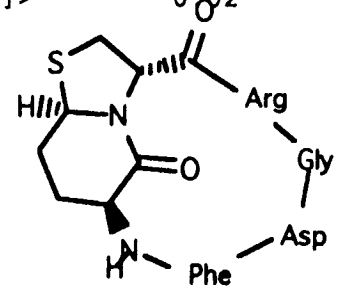

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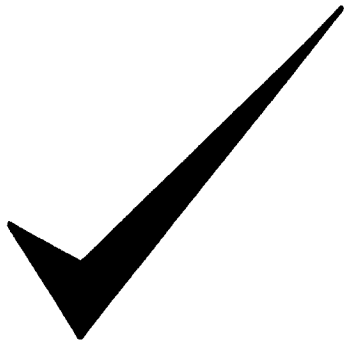
Fibrinogen - the Jewel in the Crown

- Linear Peptide
- Cyclic constraints
- Rapid identification of non-peptide lead
- Development of potent non peptide
  - GR144053
  - .....



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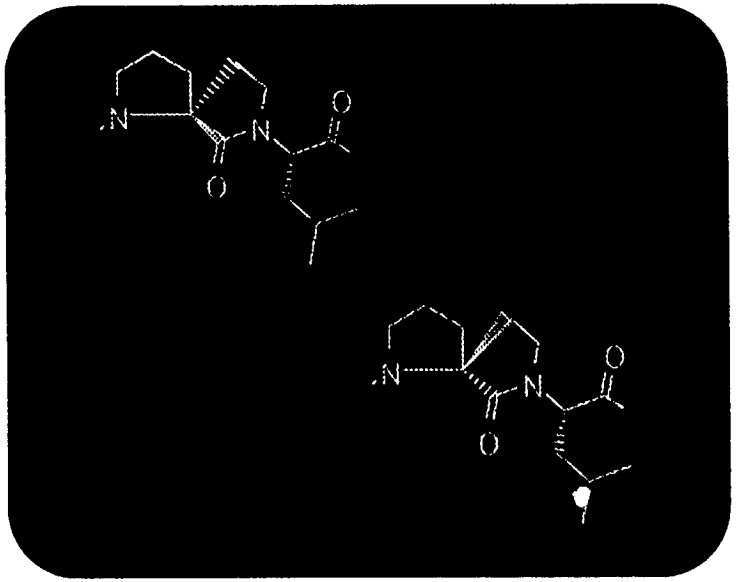
Early NK1 work

- Ava-Phe-Phe-(XY)-Met-NH2 based on SP(6-11)
- XY = Gly-Leu Substance P



(R)-spirolactam
Agonist

(S)-spirolactam
Antagonist

Ward et al J.Med.Chem 1990,3,1848

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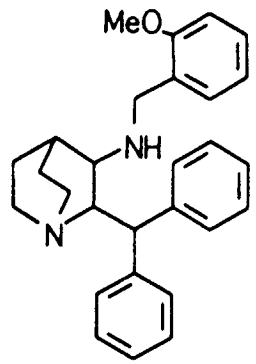
NK1 antagonism



- peptide dead end?
- loss of interest in NK1?
- Pfizer lead
  - high thoughput screening success

- reasons for failures of peptide approach?
  - antagonists dont bind at same sites as agonist despite competitative antagonism
  - mutation information
    - » JBC vol 267, 25664-25667 (1992),
    - » Biochem v33, 3007, 1994

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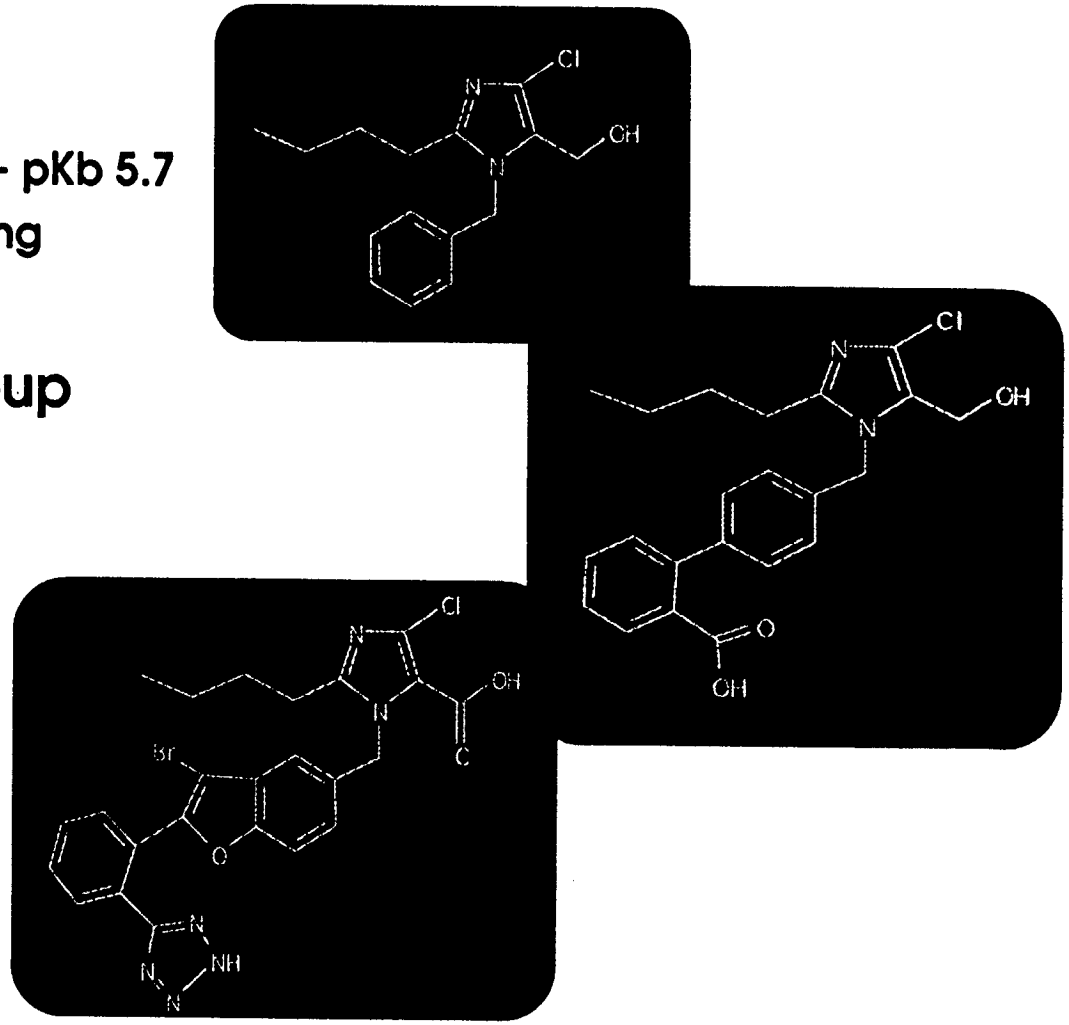
Angiotensin II - attempt 2

- Takeda patent
  - "weak" AII antagonism - pKb 5.7
  - high throughput screening
- Dupont add acid group
  - potent AII antagonism
- Glaxo - GR117289
  - » pKb 9.8



✓

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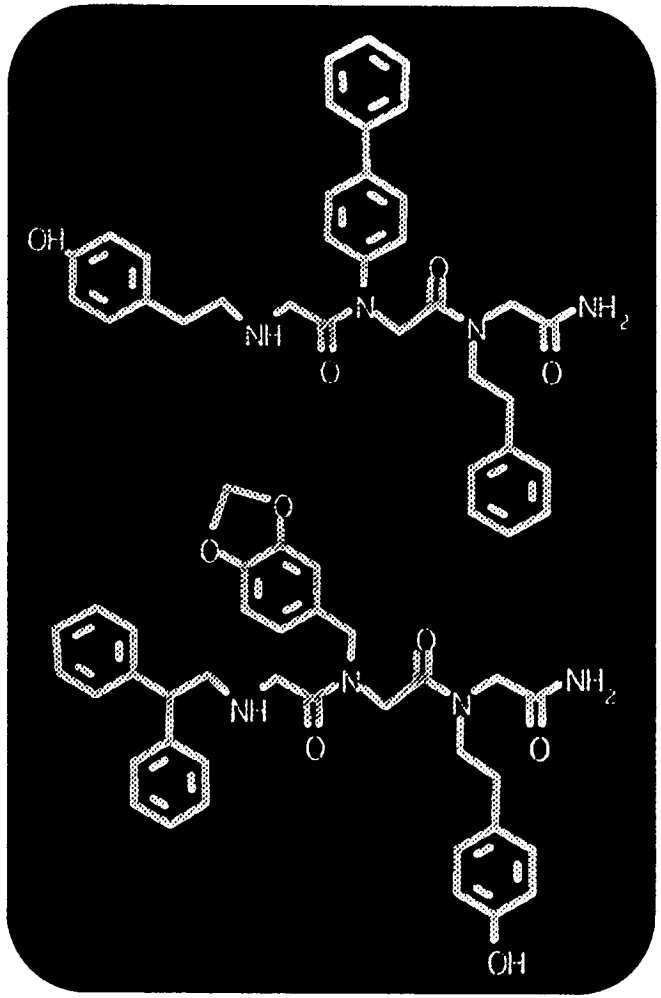
Non peptide AII and NK1 antagonists

- Input from peptidomimetic work?
- Would we have got where we are without learning the hardway through peptides?
- Can we tell in advance?
- 7TMs vs enzymes?
  - Renin, HIV-Protease!!
- where to next?

Chemical libraries

eg Chiron work:
JMedChem 1994,37,2679



18 mixtures of ca. 204 PEPTOID trimers
screening and "decoding" identified:

» **Ki=5nM at a2 adrenergic receptor**

» **Ki=6nM at m-specific opiate receptor**

✓

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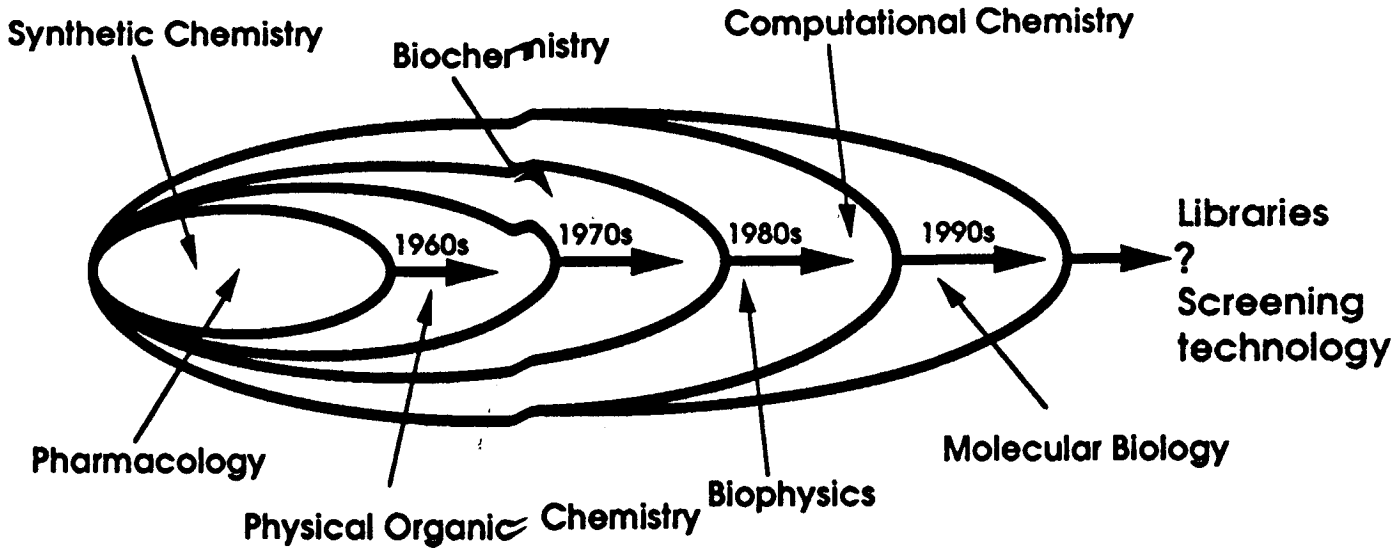
Libraries (cont'd)

- yet more peptides? ✗
- Chiron results suggest peptoids are not peptides? ✓
  - different physicochemical properties
  - metabolically more stable
- non peptide libraries?
  - benzodiazepines etc
- Capacity of screening?
- Information explosion? ✗

Modern Medicinal Chemistry



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Summary

- Peptides and peptidomimetics make useful tools for exploring biology
- No *a priori* way of knowing that the peptidomimetic approach will lead to a good drug
- Need to short circuit traditional methodology with use of "inspired" High Throughput screening of compound collections to make the strategic jump of peptide to true non-peptide
- Gaps in compound collections will be filled by libraries

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