

# Design of Molecular Ligands for Nuclear Imaging

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JASS 2006

## Outline

- I. Radiopharmaceuticals (RP)**
- II. Ligands as Radiopharmaceuticals (RP)**
- III. Design of RP Molecular Ligands**
- IV. Conclusion**

## Definition of Radiopharmaceuticals:

*Radiopharmaceuticals are radioactive agents used in the field of nuclear medicine as tracers for nuclear imaging.*

**What are the objectives?**

**diagnosis**

**therapy**

## I. Radiopharmaceuticals

II. Ligands as RP

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## ➤ Nuclides for Nuclear Imaging

Technetium  $^{99m}\text{Tc}$

Iodine  $^{123}\text{I}$  /  $^{125}\text{I}$

Indium  $^{111}\text{In}$

Gadolinium  $^{67}\text{Ga}$

Thallium  $^{201}\text{Tl}$

Krypton  $^{81m}\text{Kr}$

Fluorine  $^{18}\text{F}$

Carbon  $^{11}\text{C}$

Nitrogen  $^{15}\text{N}$

Rhenium  $^{188}\text{Re}$

Yttrium  $^{90}\text{Y}$

Lutetium  $^{177}\text{Lu}$

## ➤ Dosage

1 Bq (Becquerel) = one decay event per second

1 Bq =  $2.7 \cdot 10^{-11}$  Ci

5  $\mu\text{Ci}$  – 35 mCi

## ➤ Considerations

allergy, pregnancy, breast-feeding, age, intake of other medicine, other medical problems

## I. Radiopharmaceuticals

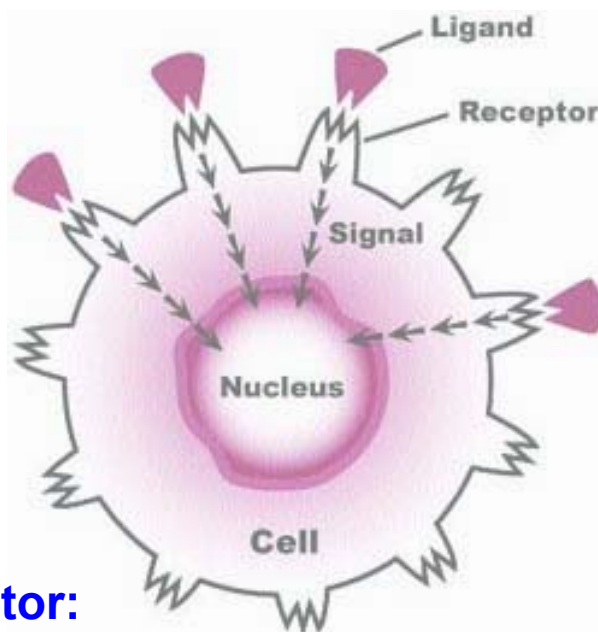
II. Ligands as RP

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### Definition of Ligand:

*In biology a ligand is an extracellular substance which binds in a highly specific manner to its receptor.*



### Definition of Receptor:

*In biology a receptor is a protein on the cell membrane or within the cytoplasm or cell nucleus that binds to its ligand and initiates the cellular response to the ligand.*

I. Radiopharmaceuticals

## II. Ligands as RP

Structure

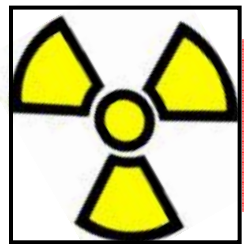
Characteristics

Used Molecules

Detected Diseases

III. Design of RP Ligands

IV. Conclusion



bioactive  
molecule

receptor

target

I. Radiopharmaceuticals

II. Ligands as RP

**Structure**

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IV. Conclusion

- **Binding to pathologically occurring molecules**
- **No uptake in non-target organs/tissue**
- **Rapid localization at target**
- **Rapid blood-pool clearance**
- **Uptake ~ strength of disease**
- **Accessibility from the outside of the cell**
- **Easy to radiolabel**
- **Storage in kit with long shelf-life**
- **Cheap**
- **Reasonable dosimetry**
- **Minimal immunological response**

I. Radiopharmaceuticals

II. Ligands as RP

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**Characteristics**

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➤ **Peptide-based molecules**

antibodies

Fab-fragments

scFv-fragments

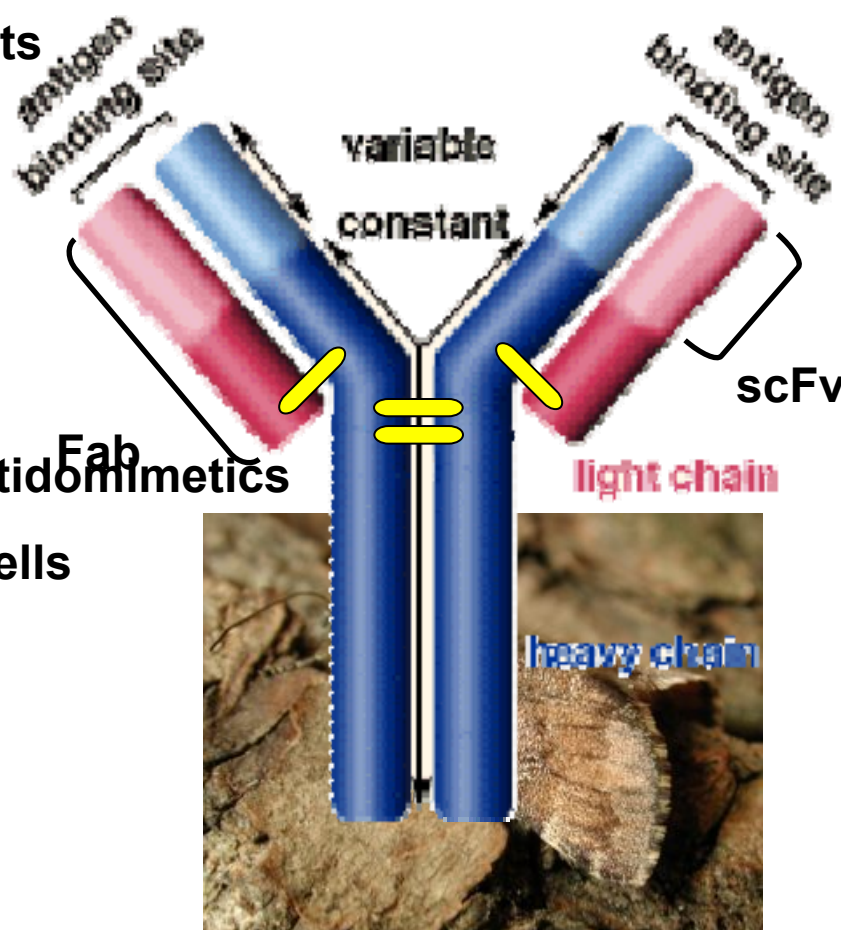
affibodies

peptides

➤ **Non-peptidic**

synthetic peptidomimetics

white blood cells



I. Radiopharmaceuticals

II. Ligands as RP

Structure

Characteristics

**Used Molecules**

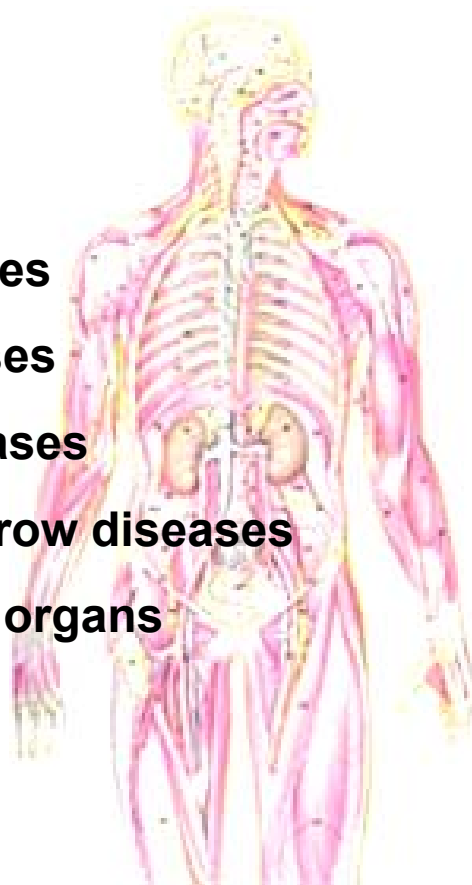
Detected Diseases

III. Design of RP Ligands

IV. Conclusion



- **Tumors**
- **Infections**
- **Inflammations**
- **Neurological diseases**
- **Blood vessel diseases**
- **Red blood cell diseases**
- **Bone and bone marrow diseases**
- **Diseases of several organs**



I. Radiopharmaceuticals

II. Ligands as RP

Structure

Characteristics

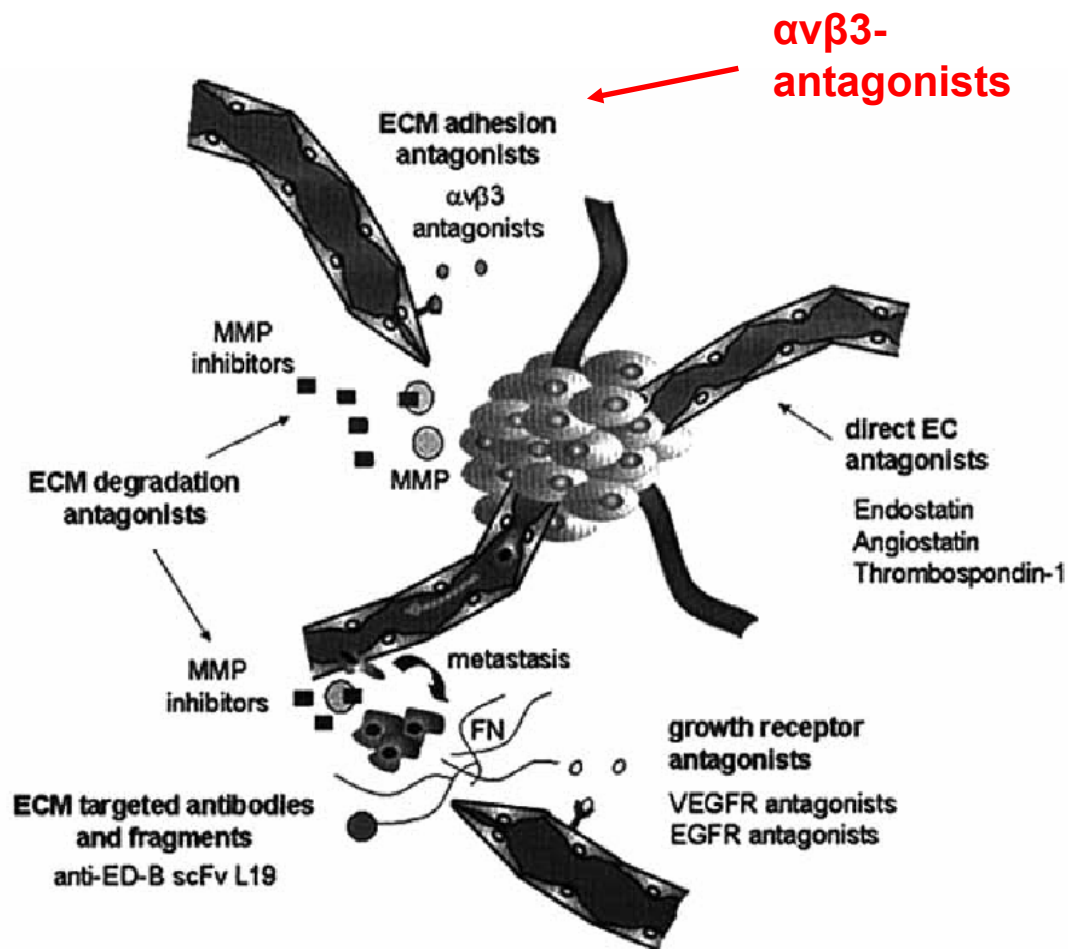
Used Molecules

**Detected Diseases**

III. Design of RP Ligands

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## Tumor-induced angiogenesis



I. Radiopharmaceuticals

II. Ligands as RP

### III. Design of RP Ligands

1. Direct Labeling
2. Carbohydrates
3. Hydrophilic Tetrapeptides
4. Radiometal Labeling
5. Phage Display
6. Linear Peptides
7. Peptidomimetics
8. Hetero-/Homomultimer

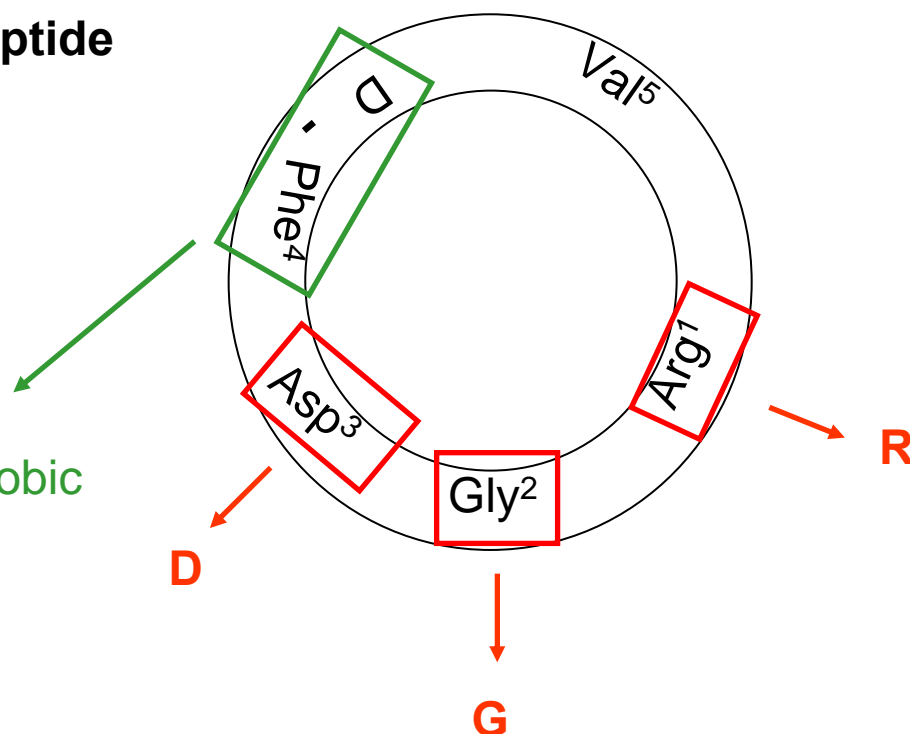
IV. Conclusion

## $\alpha\beta 3$ Integrin Antagonists

**Aim: lead structure is needed**

**RGD-peptide**

hydrophobic



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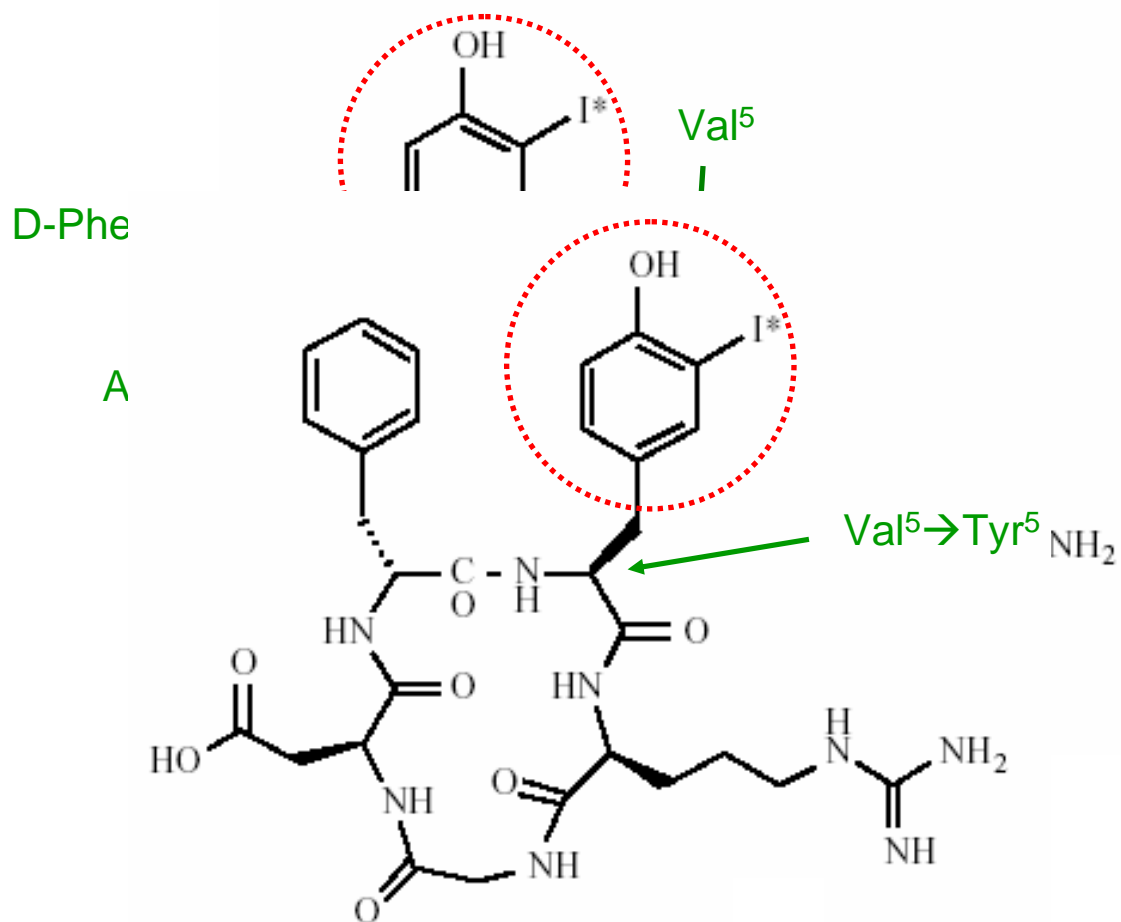
6. Linear Peptides

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IV. Conclusion

## ➤ Iodine-Labeling <sup>125</sup>I



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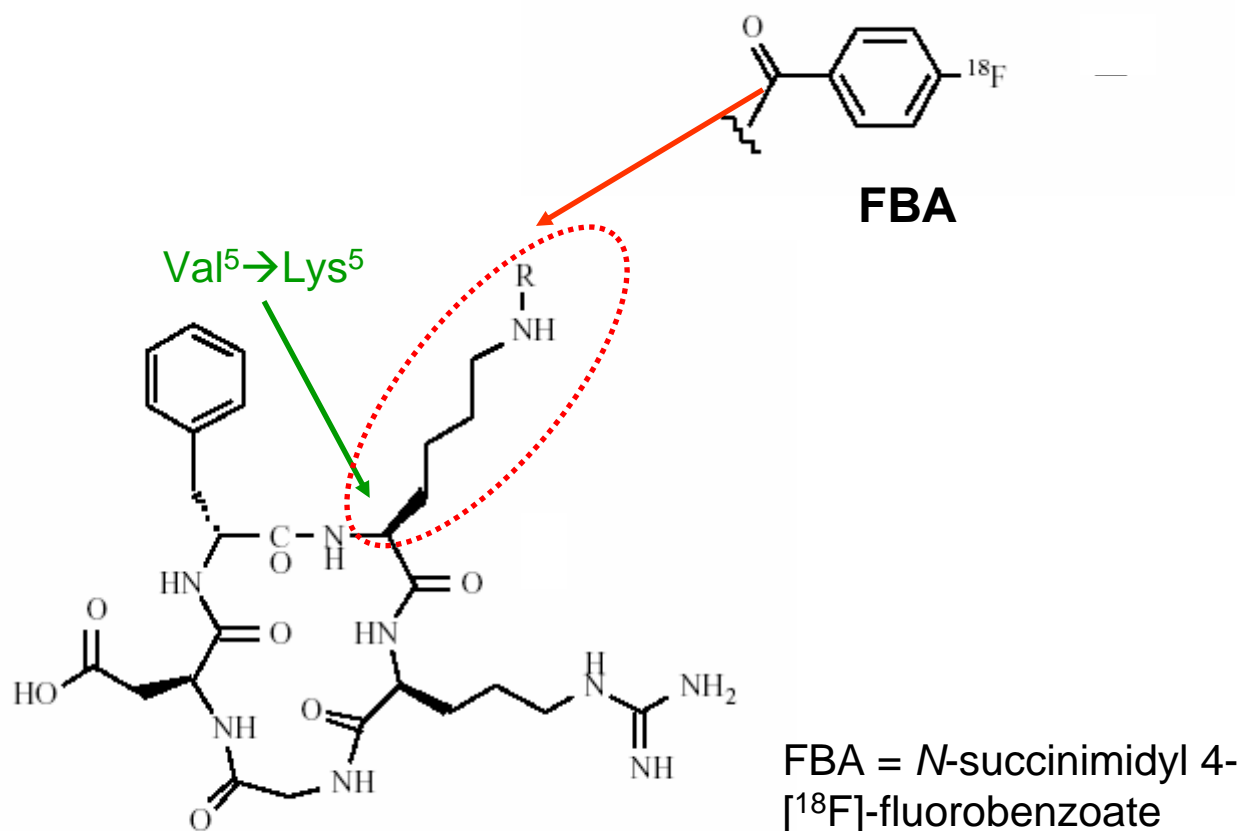
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## ➤ Fluorine-Labeling $^{18}\text{F}$

a) No-carrier-added

→ via prosthetic groups



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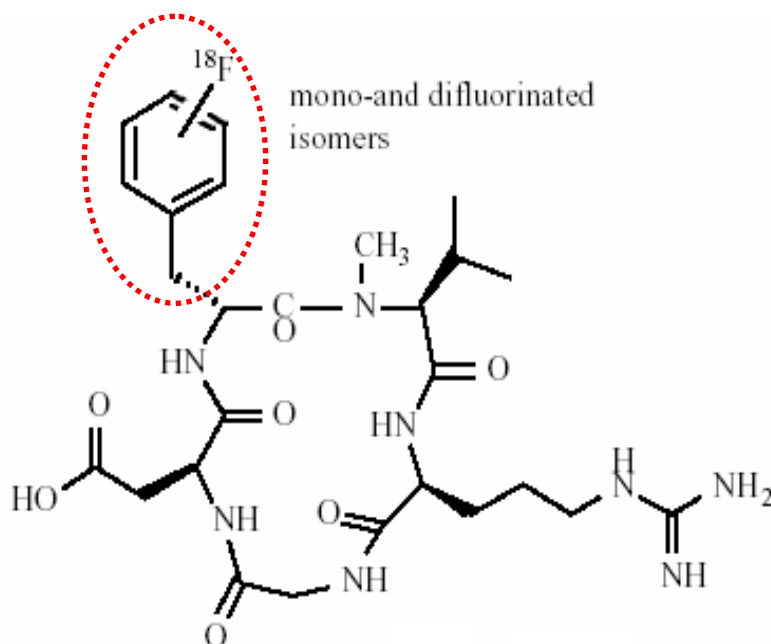
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## ➤ Fluorine-Labeling $^{18}\text{F}$

### b) Carrier-added

→ via  $^{18}\text{F}$ AcOF



AcOF =  $^{18}\text{F}$ -Acetylhypofluoride

$\text{CH}_3\text{CO}_2^{18}\text{F}$

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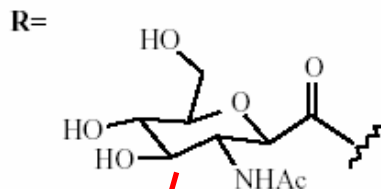
IV. Conclusion

**Aim: Bioavailability↑**

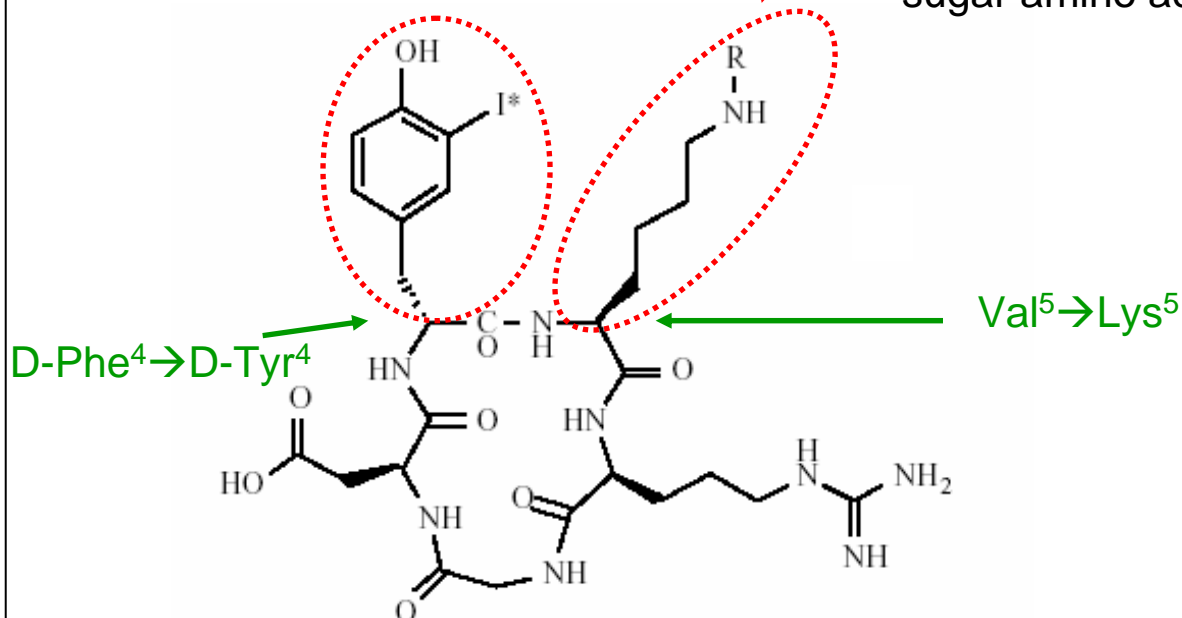
**Solubility↑**

**Resistance↑**

**Glucose**



Glucose-based sugar amino acid



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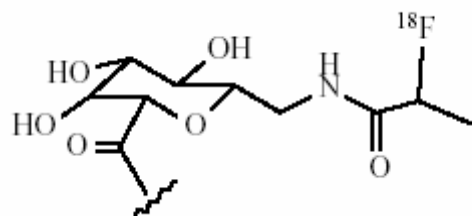
6. Linear Peptides

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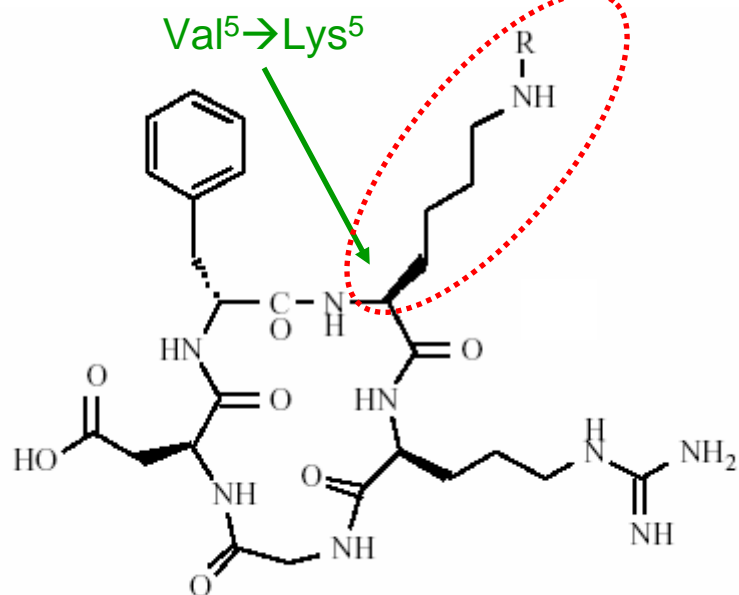
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## Galactose



Galactose-based sugar

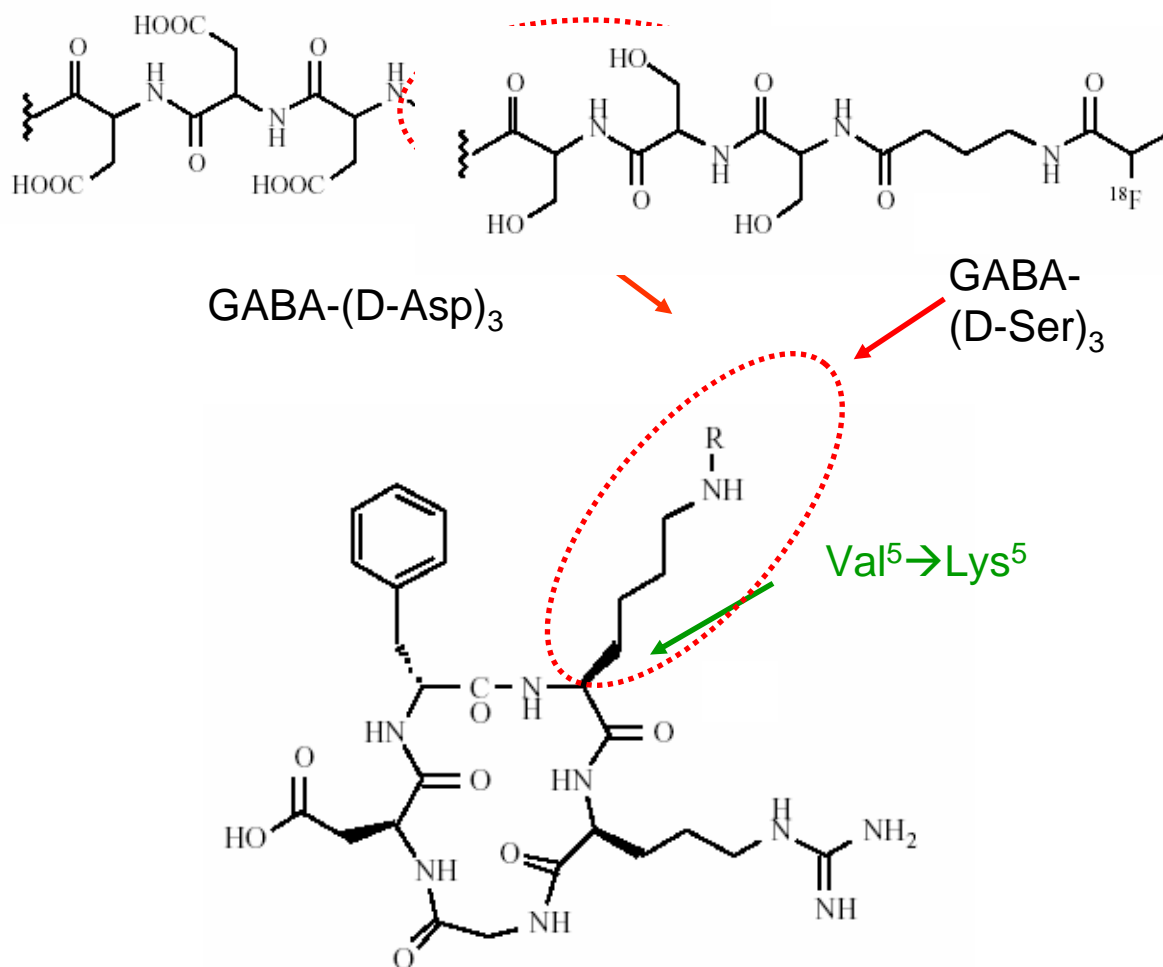


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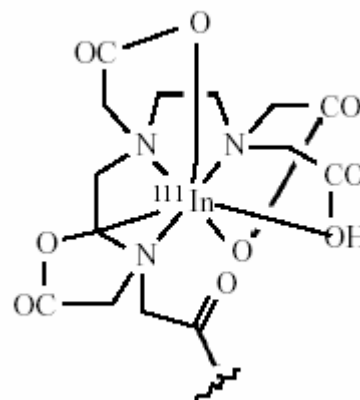


**Aim: Positive effect of hydrophilicity on pharmacokinetic**  
**Use of D-amino acids allows in vivo „fine tuning“**

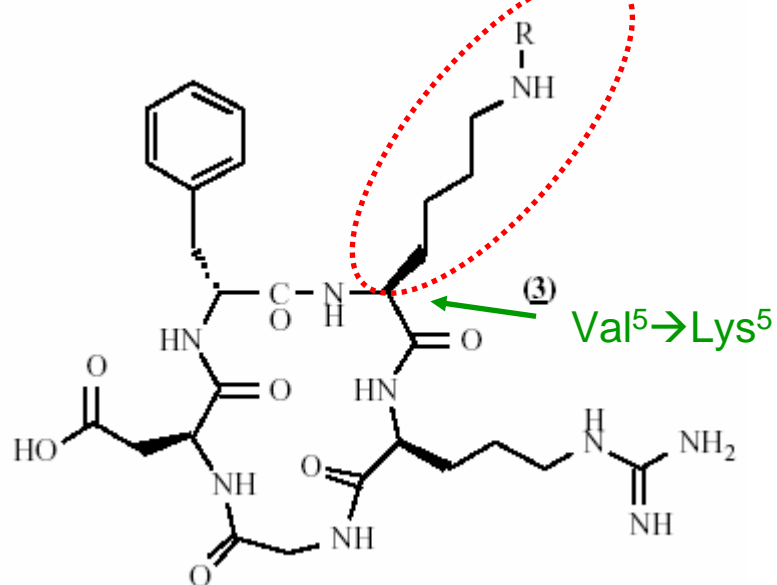


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## $^{111}\text{In}$ Indium-labeling via DTPA



$^{111}\text{InDTPA}$

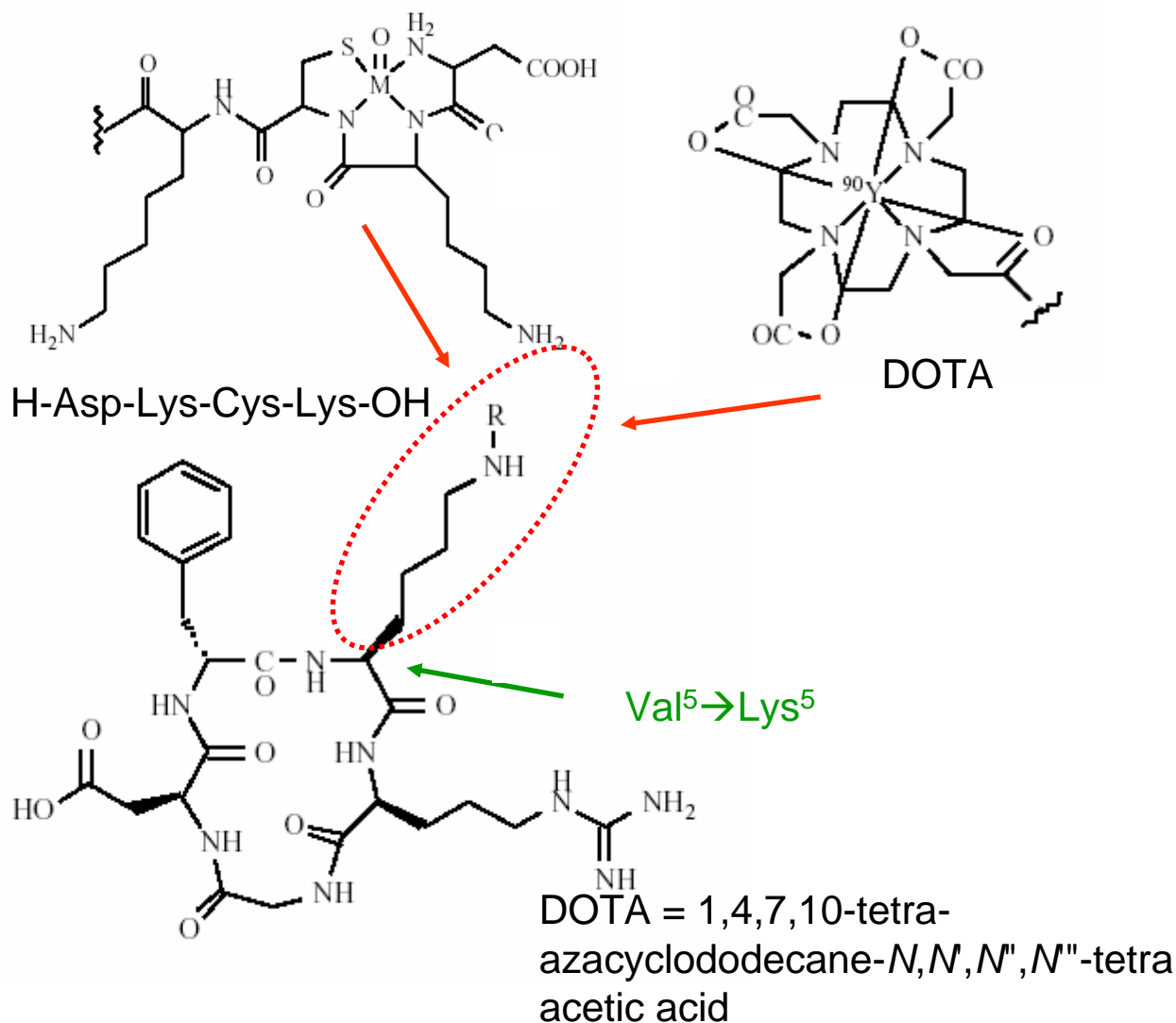


DTPA =  
diethylenetriamine-  
pentaacetic acid

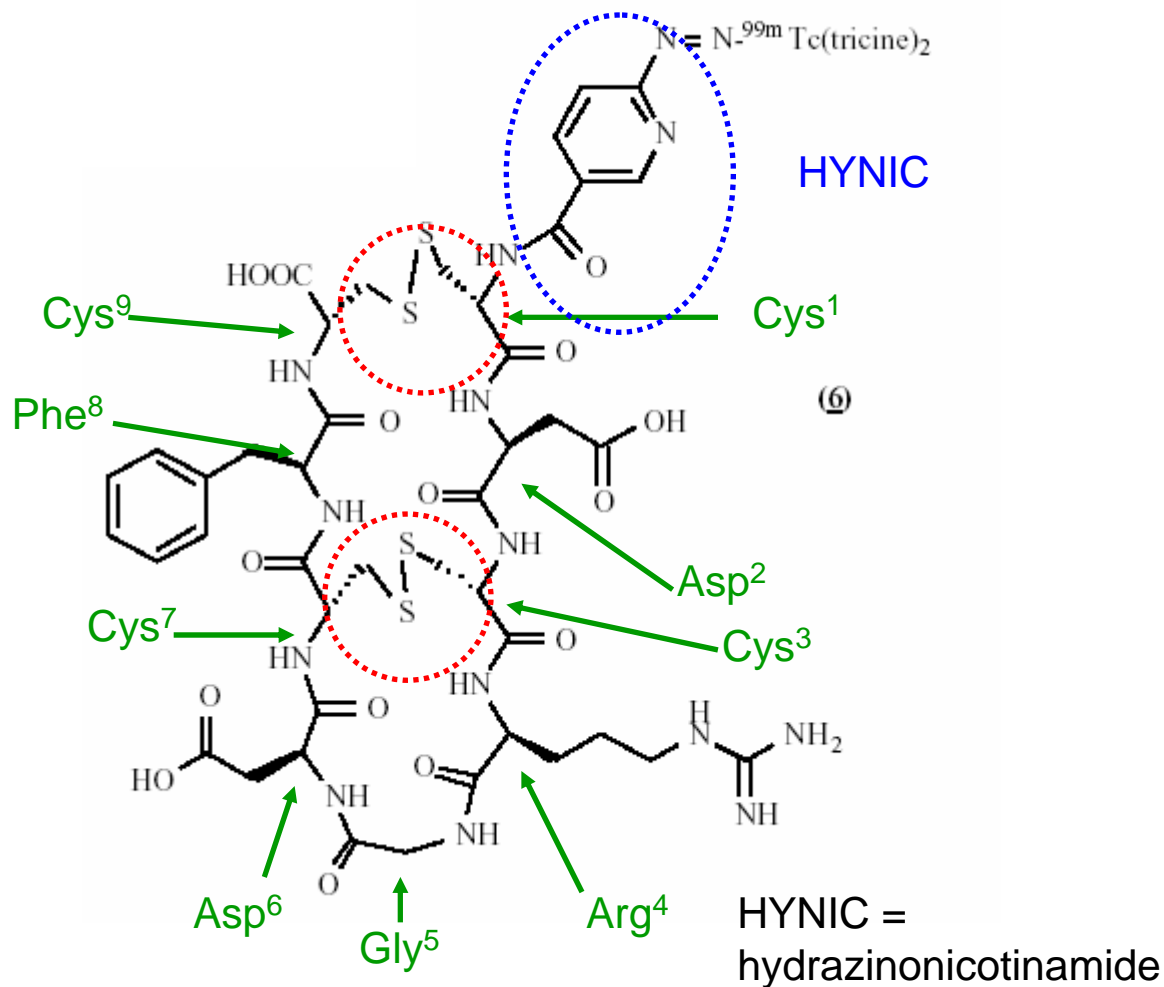
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## IV. Conclusion

## $^{99m}\text{Tc}$ -, $^{188}\text{Re}$ - and $^{90}\text{Y}$ -labeling via tetrapeptide or DOTA



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**Important: check influence of radiolabeling and modification on affinity**

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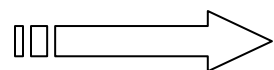
**Aim: tumor accumulation ↑**

## <sup>18</sup>F-labeling

H-Lys-Pro-Gln-Val-Thr-Arg-Gly-Asp-Val-Phe-  
Phe-Glu-Gly-NH<sub>2</sub>

## <sup>99m</sup>Tc-labeling

H-Arg-Gly-Asp-Ser-Cys-Arg-Gly-Asp-Ser-  
Tyr-OH

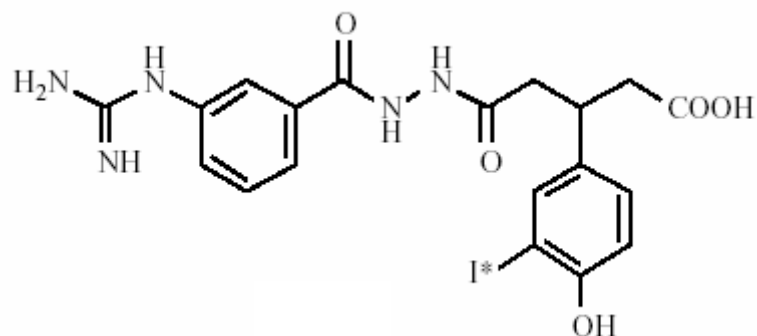


**Increased affinity by introducing two RGD motifs**

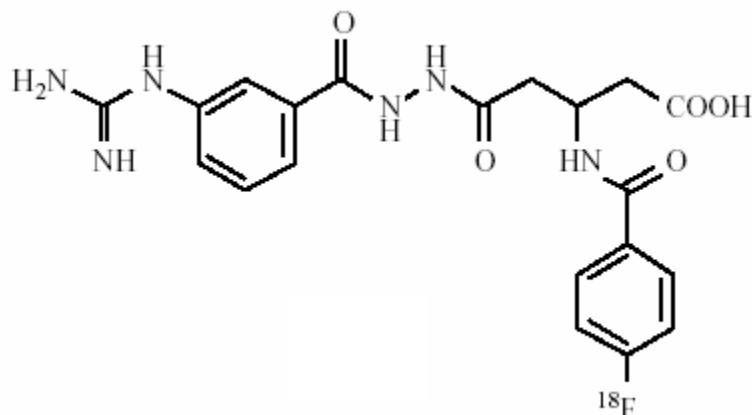
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**Aim: Oral bioavailability ↑**

## GBHO derivatives



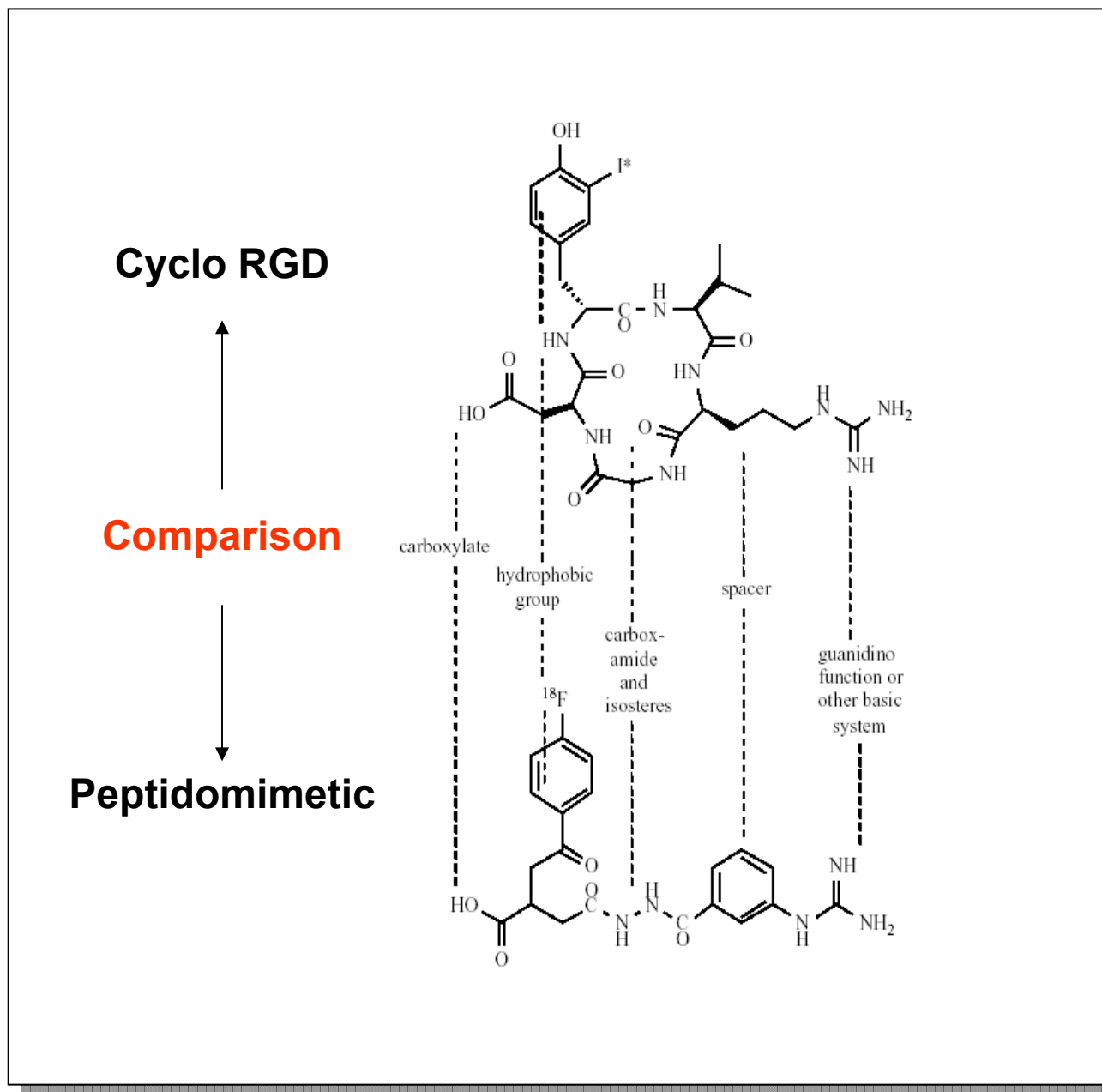
**Iodine**



**Fluorine**

GBHO = guanidinobenzoyl  
hydrazino oxopentanoic acid

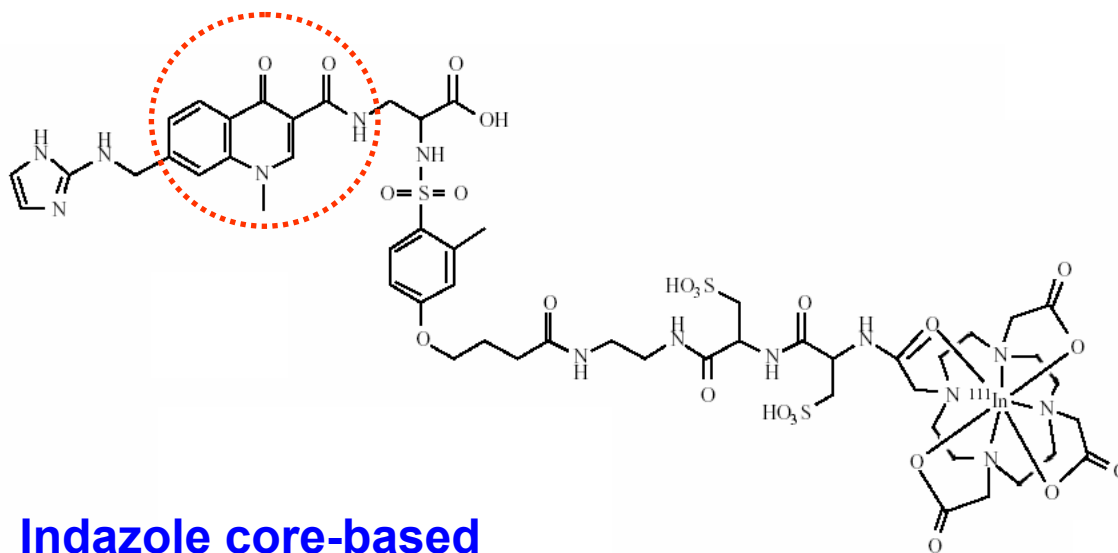
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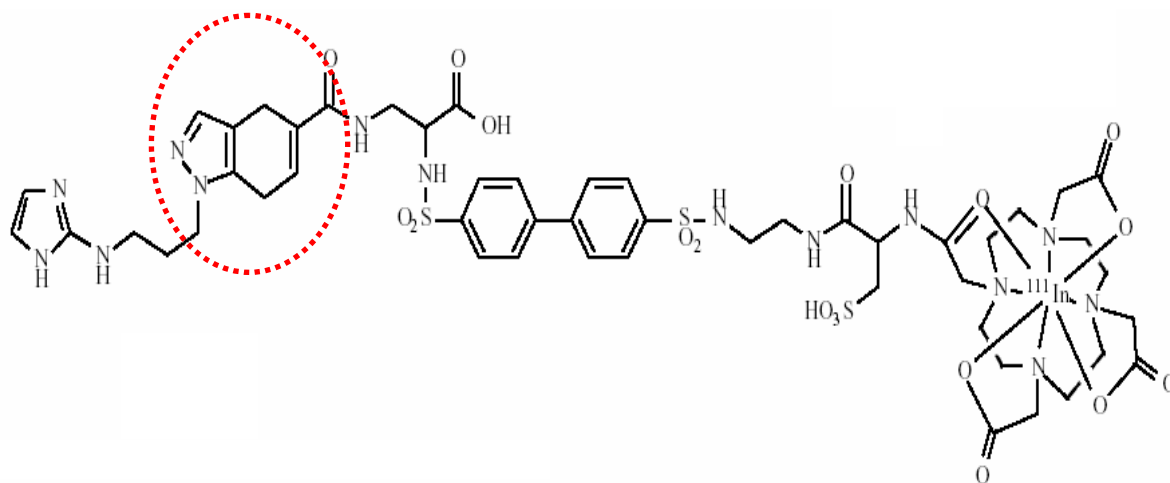
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## Quinolone core-based



## Indazole core-based

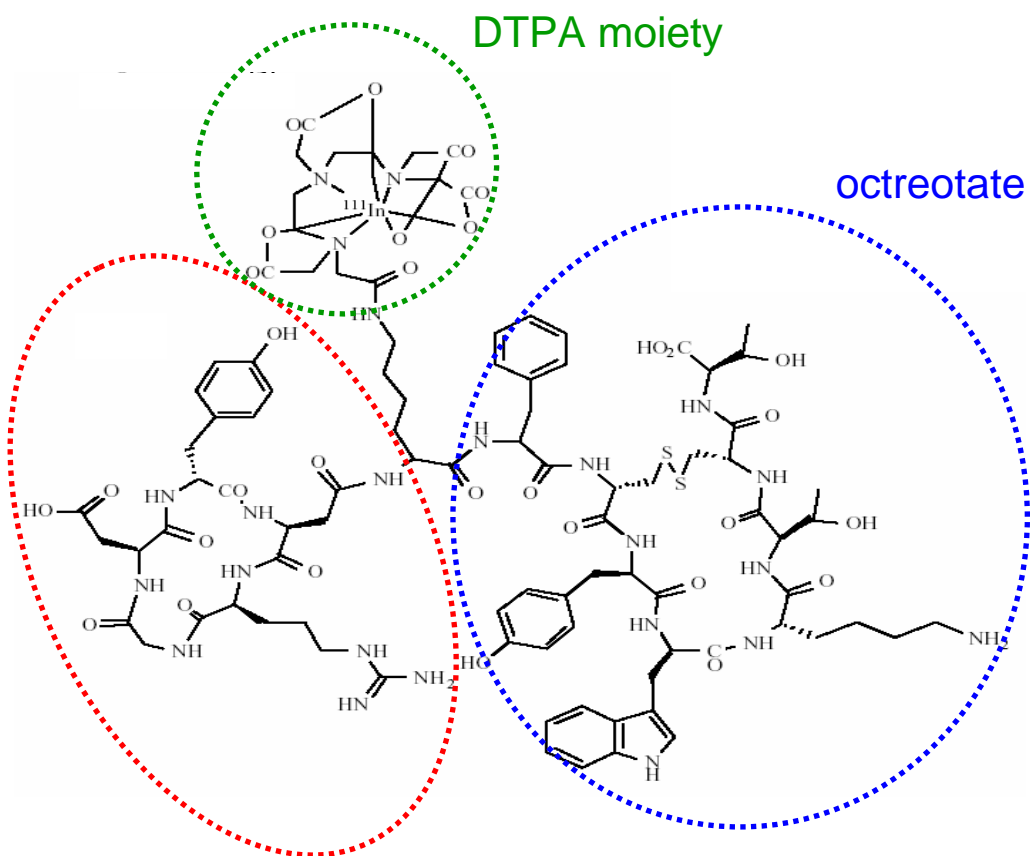


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## IV. Conclusion

## Heterogenous Dimer

**Aim: tumor accumulation ↑**



cyclo(-Arg<sup>1</sup>-Gly<sup>2</sup>-Asp<sup>3</sup>-DTyr<sup>4</sup>-Glu<sup>5</sup>-)

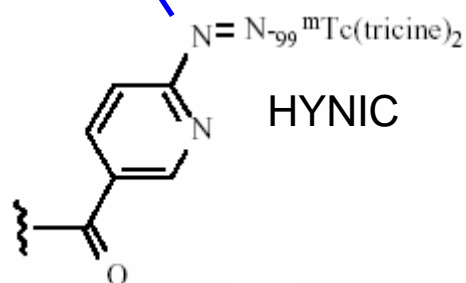
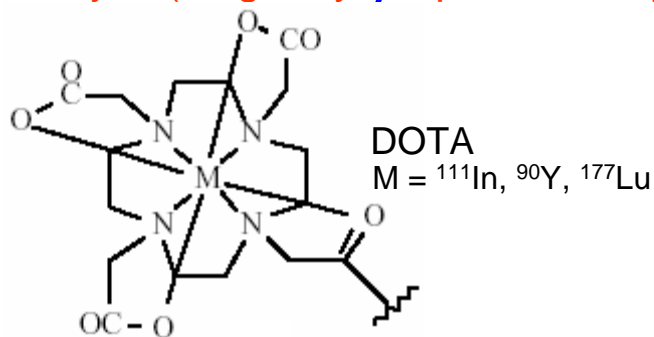
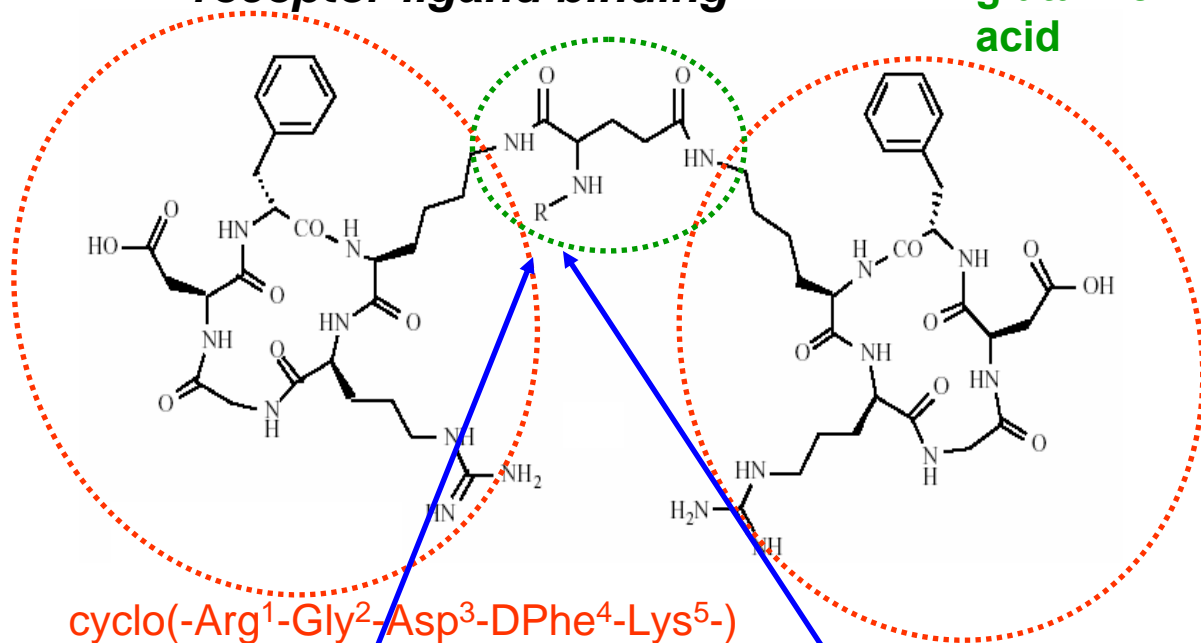
DTPA = diethylene-triamine-pentaacetic acid

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## Homogenous Dimer

**Aim: *improvement of targeting by cooperative receptor-ligand binding***

glutamic acid

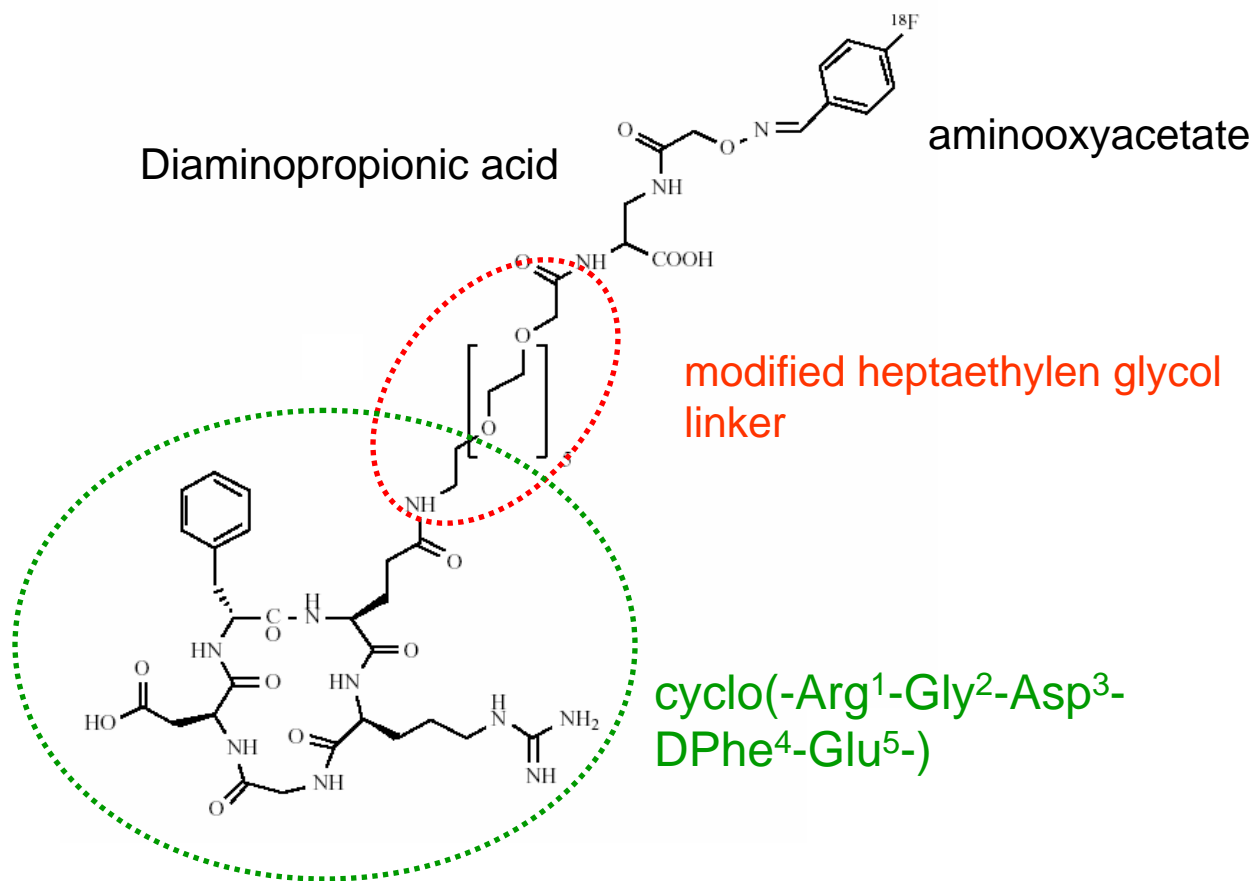


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## IV. Conclusion

## Homogenous Multimer

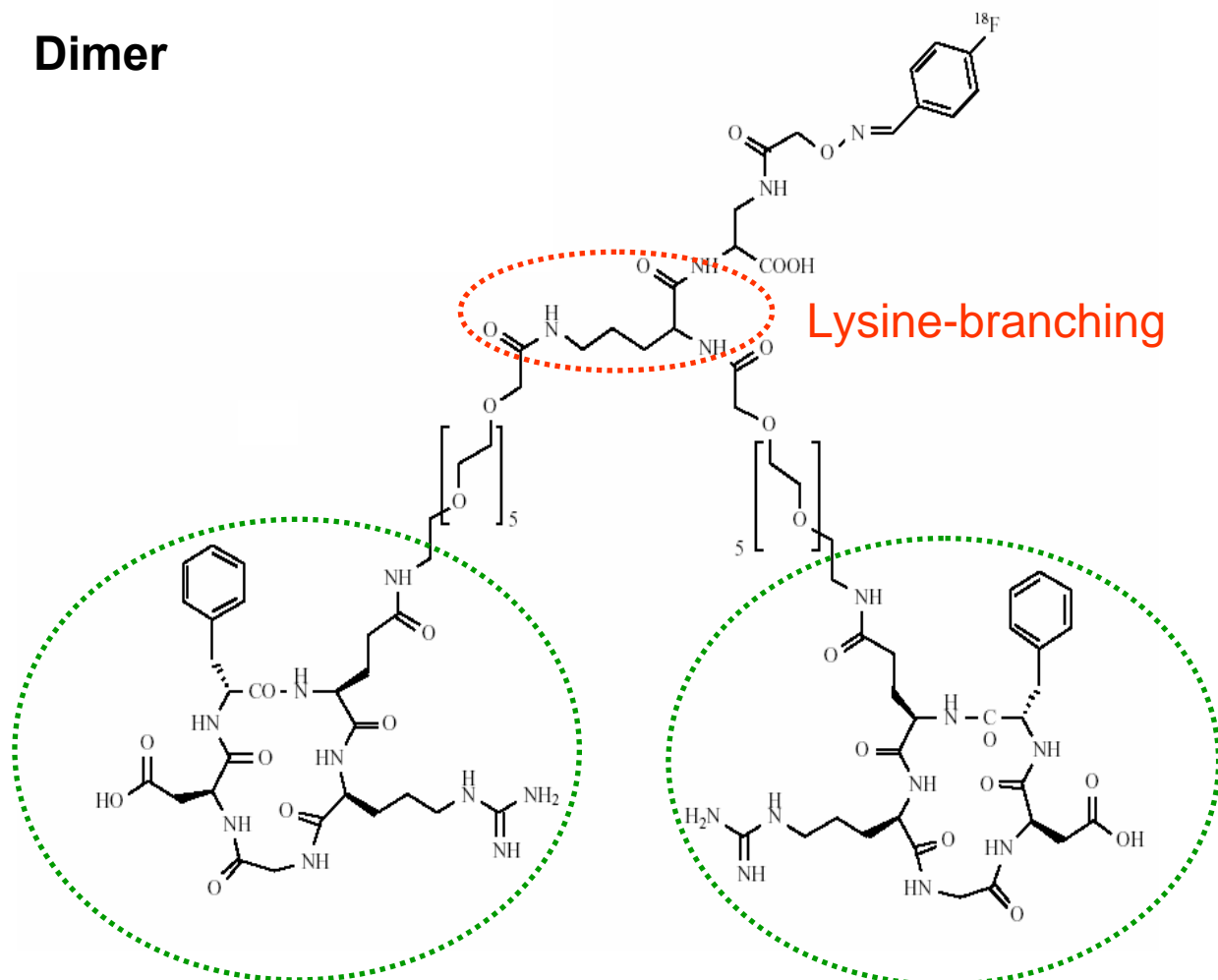
### Monomer



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## Homogenous Multimer

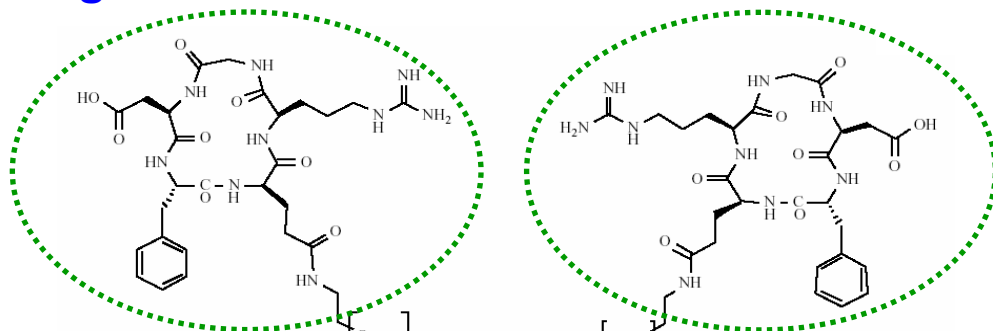
### Dimer



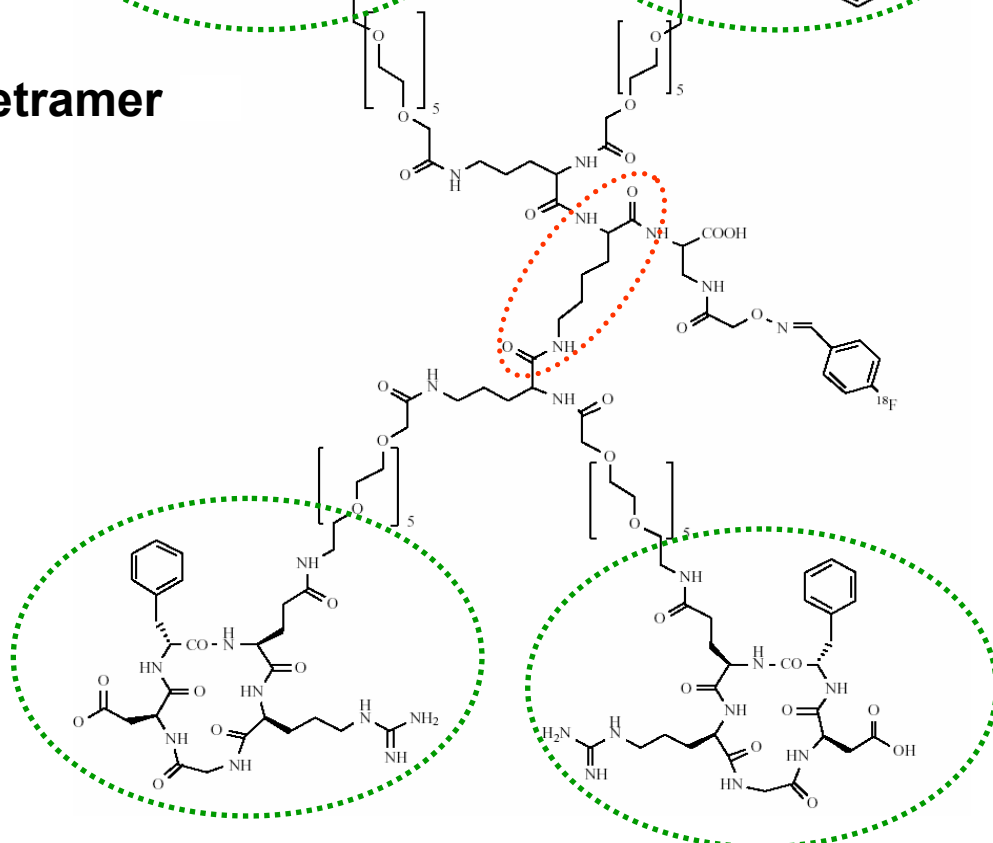
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## Homogenous Multimer

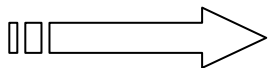


## Tetramer



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- Requirement of **Lead Structure**
- **Direct Labeling easy**, but uptake of lipophilic structures by liver
- **Modification with Carbohydrates:**  
→ no more uptake in liver
- **Modification with hydrophilic tetrapeptide:**  
→ good tumor-to-background ratios
- **Radiometal-Labeling:**  
→ Uptake in kidney
- **Non-peptidic Substances** with high affinities
- **Multimerization** can improve tumor uptake



**No gold standard**

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# Acknowledgements

- **Prof. Dr. Horst Kessler**
- **Franz Hagn**
- **Everybody who helped organizing JASS 2006**





# References

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**Thanks for  
your  
attention**