# Síntesi i aplicació de ψ-dipèptids amb estructura de 3 aminopiperidona. Síntesi de ψ-melanotans

Jordi Mas Pons

**ADVERTIMENT**. La consulta d'aquesta tesi queda condicionada a l'acceptació de les següents condicions d'ús: La difusió d'aquesta tesi per mitjà del servei TDX (**www.tdx.cat**) ha estat autoritzada pels titulars dels drets de propietat intel·lectual únicament per a usos privats emmarcats en activitats d'investigació i docència. No s'autoritza la seva reproducció amb finalitats de lucre ni la seva difusió i posada a disposició des d'un lloc aliè al servei TDX. No s'autoritza la presentació del seu contingut en una finestra o marc aliè a TDX (framing). Aquesta reserva de drets afecta tant al resum de presentació de la tesi com als seus continguts. En la utilització o cita de parts de la tesi és obligat indicar el nom de la persona autora.

**ADVERTENCIA**. La consulta de esta tesis queda condicionada a la aceptación de las siguientes condiciones de uso: La difusión de esta tesis por medio del servicio TDR (**www.tdx.cat**) ha sido autorizada por los titulares de los derechos de propiedad intelectual únicamente para usos privados enmarcados en actividades de investigación y docencia. No se autoriza su reproducción con finalidades de lucro ni su difusión y puesta a disposición desde un sitio ajeno al servicio TDR. No se autoriza la presentación de su contenido en una ventana o marco ajeno a TDR (framing). Esta reserva de derechos afecta tanto al resumen de presentación de la tesis como a sus contenidos. En la utilización o cita de partes de la tesis es obligado indicar el nombre de la persona autora.

**WARNING**. On having consulted this thesis you're accepting the following use conditions: Spreading this thesis by the TDX (**www.tdx.cat**) service has been authorized by the titular of the intellectual property rights only for private uses placed in investigation and teaching activities. Reproduction with lucrative aims is not authorized neither its spreading and availability from a site foreign to the TDX service. Introducing its content in a window or frame foreign to the TDX service is not authorized (framing). This rights affect to the presentation summary of the thesis as well as to its contents. In the using or citation of parts of the thesis it's obliged to indicate the name of the author.

**UNIVERSITAT DE BARCELONA**

**FACULTAT DE FARMÀCIA**

**DEPARTAMENT DE FARMACOLOGIA I QUÍMICA TERAPÈUTICA**

# SÍNTESI I APLICACIÓ DE ψ-DIPÈPTIDS AMB ESTRUCTURA DE 3-AMINOPIPERIDONA. SÍNTESI DE ψ-MELANOTANS

**JORDI MAS PONS**

**2010**

# SUMMARY & CONCLUSIONS

# CHAPTER 6. SUMMARY & CONCLUSIONS

1. We have obtained 7 melanotan derivatives, all including conformation-restrained dipeptides. To select the best set of modifications we have performed molecular dynamic simulations using the lactam molecule **13** as the template.

2. Five scaffolds have been synthesized:

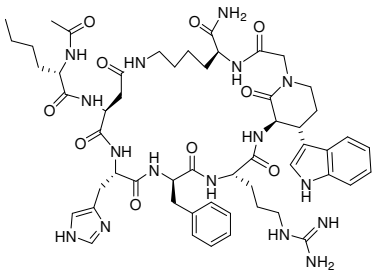
- the lactamic pseudodipeptide **13** as Trp surrogate. This compound is obtained from compound **21** by a Michael addition of indole.
- the oxazolopiperidone **15** which is a β-turn mimetic and we have adapted their structure to the solid phase peptide synthesis.
- Azadipeptides {azaSer}-Phe **85** and **88** and {azaArg}-Phe **91** properly protected for the Boc/Bn solid phase synthesis.
- The diazanorbornanes dipeptides {azaSer-Phe} **86** and {azaArg}Phe **108** protected with Fmoc for their use in solid phase peptide synthesis using the Fmoc/$^{t}$Bu strategy.
- The tripeptide **110** in solution by coupling Fmoc-Trp(Boc)-OH to azadipeptide **90a** in order to confirm the capacity of norbornane dipeptides for the peptide synthesis. PyBOP and HOAt are required to achieve the coupling reaction.

3. Synthesis of peptides

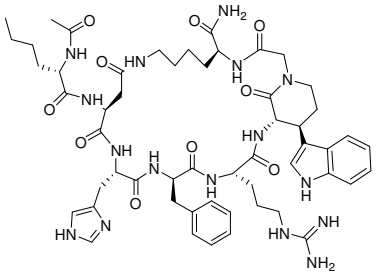
- We have prepared the model peptide **MT2** as reference for the synthesis, conformational studies and future biological assays.
- We have used compounds **13** and **108** to synthesise pseudopeptides in which the active site of **MT2** was modified. Peptide **121** was obtained as a mixture of diastereomers which were separated by semipreparative HPLC. Pseudomelanotan **121a** was obtained with 99% purity and **121b** with 88% purity. Pseudopeptide **120** which includes the {azaArg} **108** was obtained with a purity of 95%.
- Pseudopeptide **122** in which the central residues of β-turn was replaced by oxazolopiperidone **15** was obtained with a purity higher than 99%.
- Three psedopeptides with modifications in the flexible part of **MT2** were sobtained. Compound **15** was used for the synthesis of pseudomelanotan **123** which was obtained with 98% purity. Pseudoazapeptides **124** (94% purity) and **125** (95% purity) were prepared by replacing the Lys residue of **MT2** with

diazanorbornanes **101b** and **114**. However these peptides were obtained in low yields.

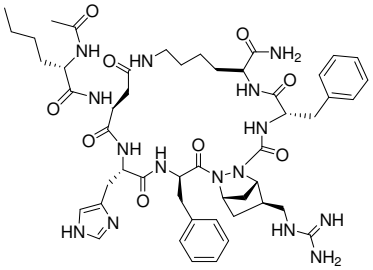
- All peptides were characterized by analitic HPLC, MALDI and NMR.



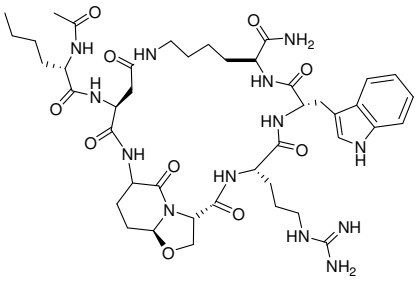
**121a**
Yield 19%
Purity 99%



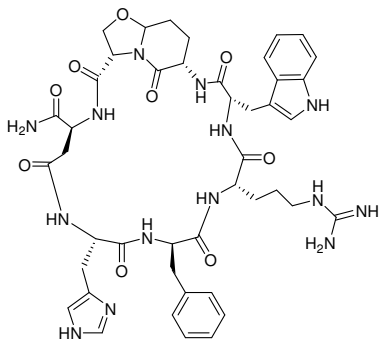
**121b**
Yield 20%
Purity 88%



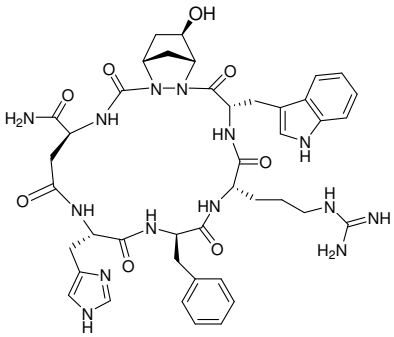
**120**
Yield 19%
Purity 95%



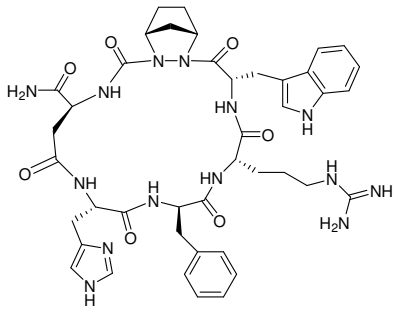
**122**
Yield 44%
Purity 99%



**123**
Yield 46%
Purity 98%



**124**
Yield 3%
Purity 92%



**125**
Yield 1%
Purity 95%

4. All peptides have been studied by NMR to determine their conformation in solution.