# Desarrollo en nuevos trazadores en cáncer de próstata

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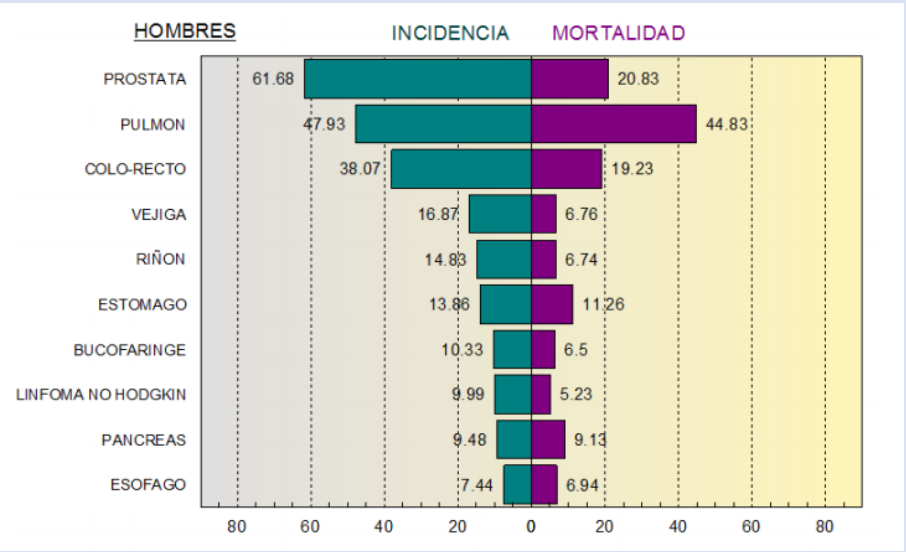
# CÁNCER DE PRÓSTATA

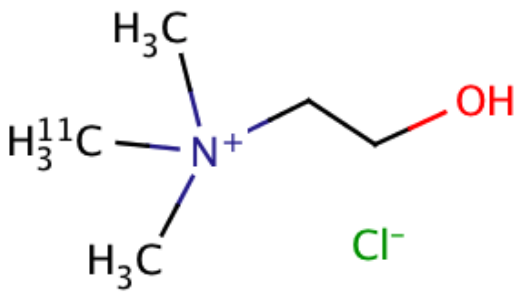


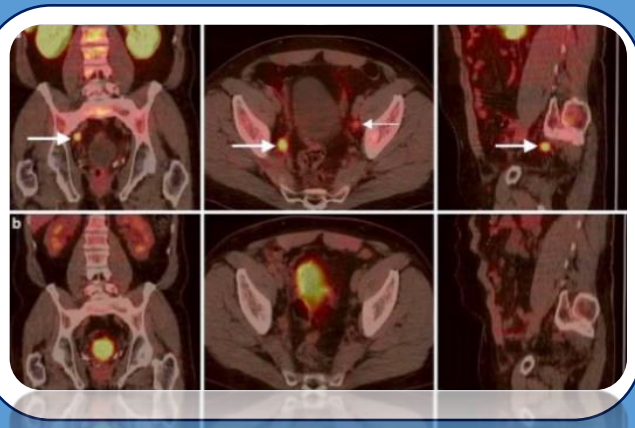

- Mayor incidencia en Uruguay en hombres
- 1 hombre cada 7 será diagnosticado durante su vida.
- 6 de cada 10 casos son diagnosticados en hombres de 65 años o mayores
- Edad promedio de diagnóstico: 66 años
- En EE.UU hay más de 2,9 millones de hombres que han sido diagnsoticados en algún punto de sus vidas y siguen vivos.

# ALGUNOS RADIOFÁRMACOS ESTUDIADOS

| | | | |
|---|---|---|---|
| [$^{11}$C] Colina | [$^{18}$] Flurorometilcolina | [$^{18}$F] Etilcolina | [$^{11}$C] Metilcolina |
| [$^{11}$C] Etanolamina | [$^{18}$F] FDHT | [$^{18}$F] DCFBC | [$^{18}$F] MAU |
| [$^{68}$Ga] Bombesina | [$^{18}$F ] Bombesina | [$^{18}$F ] FACBC | [$^{11}$C ] Acetato |
| [$^{18}$F ] Acetato | [$^{18}$ ] FDG | Antagonistas de PSMA | Anticuerpos marcados anti-PSMA |

# [$^{11}$C] Colina

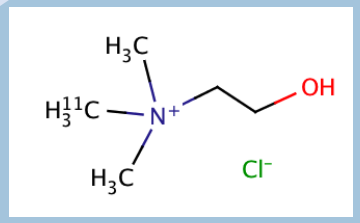


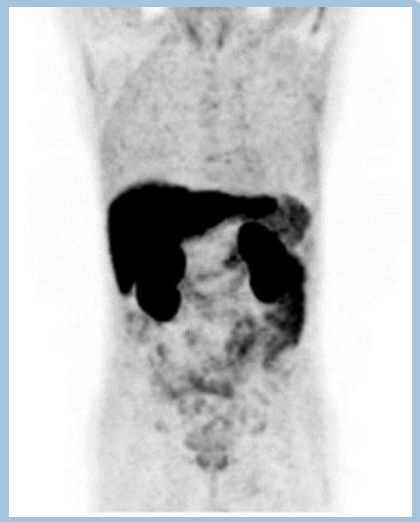



Paciente 55 años con niveles PSA (1,43 ug/L) , 27 meses post prostectomia (Gleason score: 8)
Imágenes fuisionadas PET/CT: coronal (izq), axial (medio y sagital (der).
Richter et al;.Mol Imaging Biol (2009)

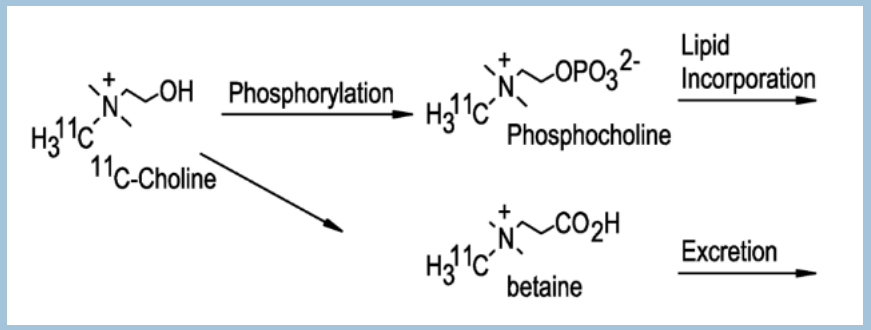
- $T_{1/2}$= 20,3 min
- Se incorpora en la célula tumoral por transporte activo
- Se fosforila mediante la colina kinasa (upregulated en tumores )
- La $^{11}$C fosforilcolina se integra a los fosfolípidos de la membrana celular como parte de la fosfatidil colina
- Como las células tumorales proliferan en una proporción incrementada, hay más captación de colina marcada.
- Tiempo de semidesintedración de $^{11}$C, lo restringe a uso en centros con ciclotrón.

# [$^{11}$C] COLINA



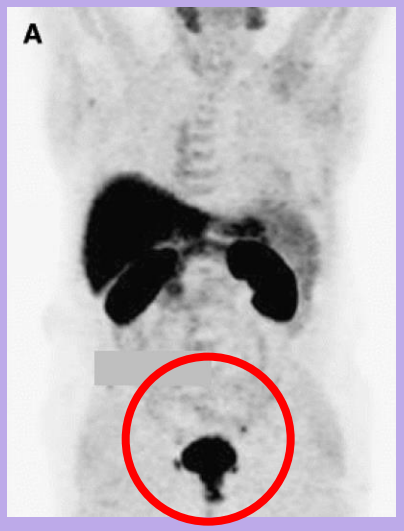



$T_{1/2}$ = 20 min
Aprobada FDA 2012
Excreción hepática (ppal)




Yanagawa T et al. JCAT 2003 and Courtesy of Dr. Bernd J. Krause, University of Rostock, Germany

# $^{18}$FCH



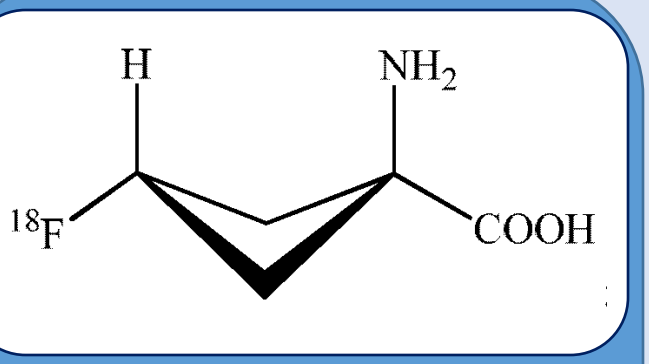


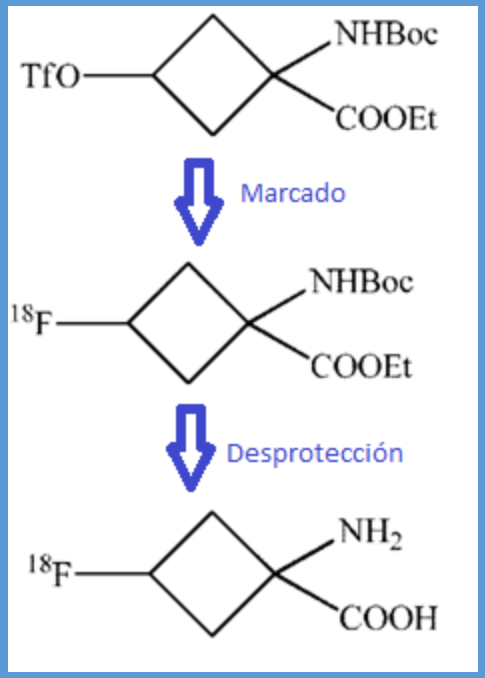
$T_{1/2}$ = 109,7 min
Excreción urinaria
Se aclara de sangre rápidamente, obtiene buen T/NT

2001 DeGrado et al. reportó que el $^{18}$FCH sirve para cancer de próstata (glándula y metástasis).

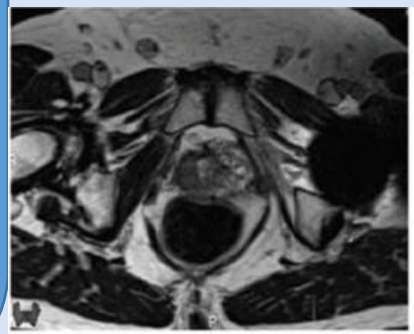
Beheshti M. Mol Imaging Biol 2009 and Courtesy of Dr. Bernd J. Krause, University of Rostock, Germany

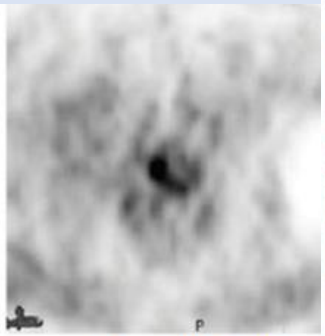
# [$^{18}$F] FACBC

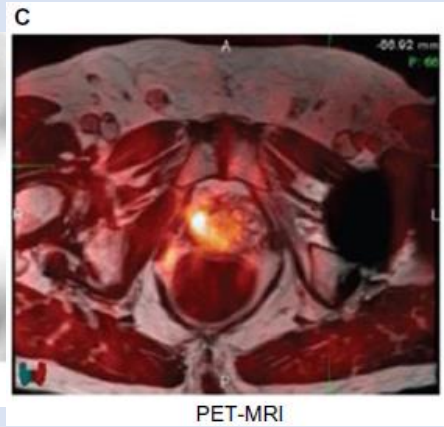



- Aprobado el 27 de Mayo de 2016
- $^{18}$F-fluciclovine o FACBC (anti-1-amino-3-[$^{18}$F]fluorocyclobutane-1-carboxylic acid)
- $T_{1/2}$= 109,7 min
- Es un radiotrazador PET análogo de leucina
- La molécula detecta la regulación al alza de transporte de aminoácidos que se produce en el cáncer de próstata.

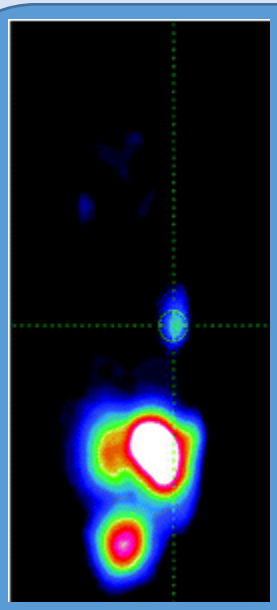

MRI

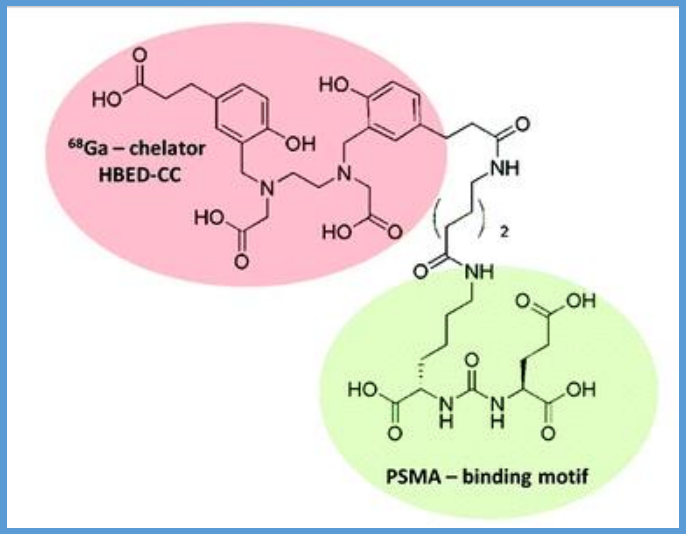

Anti-3-($^{18}$F) FACBC PET



PET-MRI

# ANTAGONISTA DE PSMA






•El HBED-CC fue seleccionado por su naturaleza lipofílica

•Se encontró que el "sitio de unión activo" de PSMA se compone de dos motivos estructurales, uno que representa un bolsillo lipófilo y el otro que puede interactuar con inhibidores basados en la urea

•PSMA: Antígeno de membrana especifico prostático

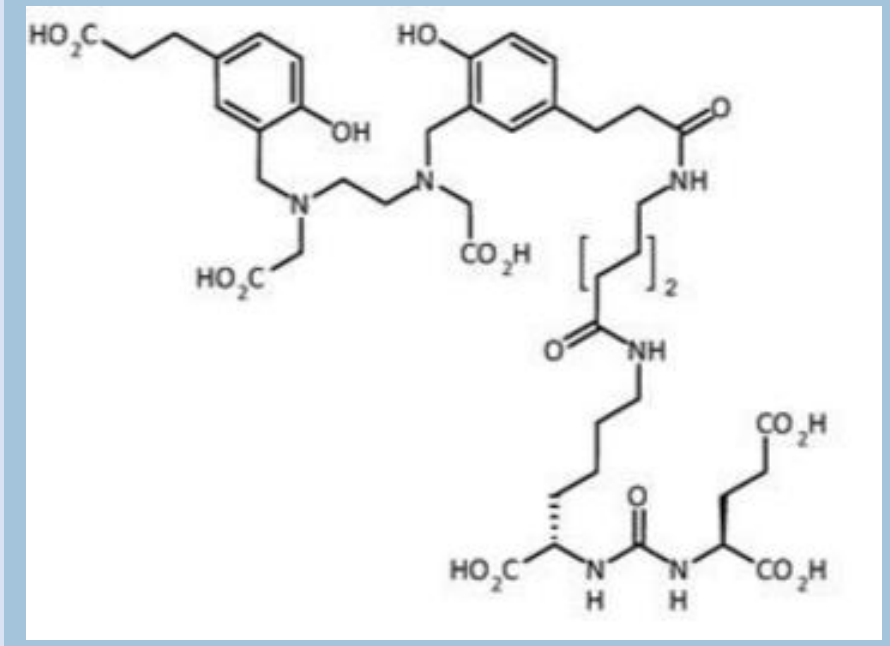
•Proteína transmembrana, sobreexpresada en cáncer de próstata .

•Se expresa en tejidos noramles de riñón, intestino delgado, glándulas salivares.

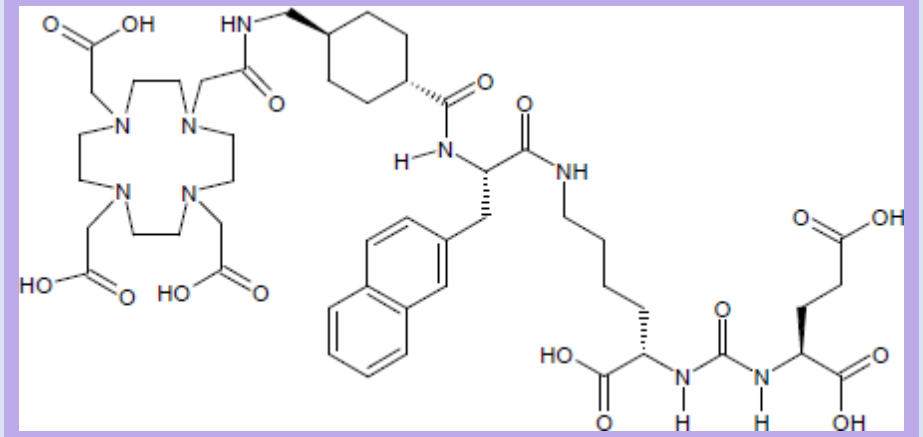
•Luego de la unión del sustrato al PSMA , estos son internalizados.

# PSMA

## [$^{68}$Ga]Ga-HBED-CC-PSMA



## [$^{177}$Lu]Lu-DOTA-PSMA-617



# ALGUNOS RADIOFÁRMACOS ESTUDIADOS

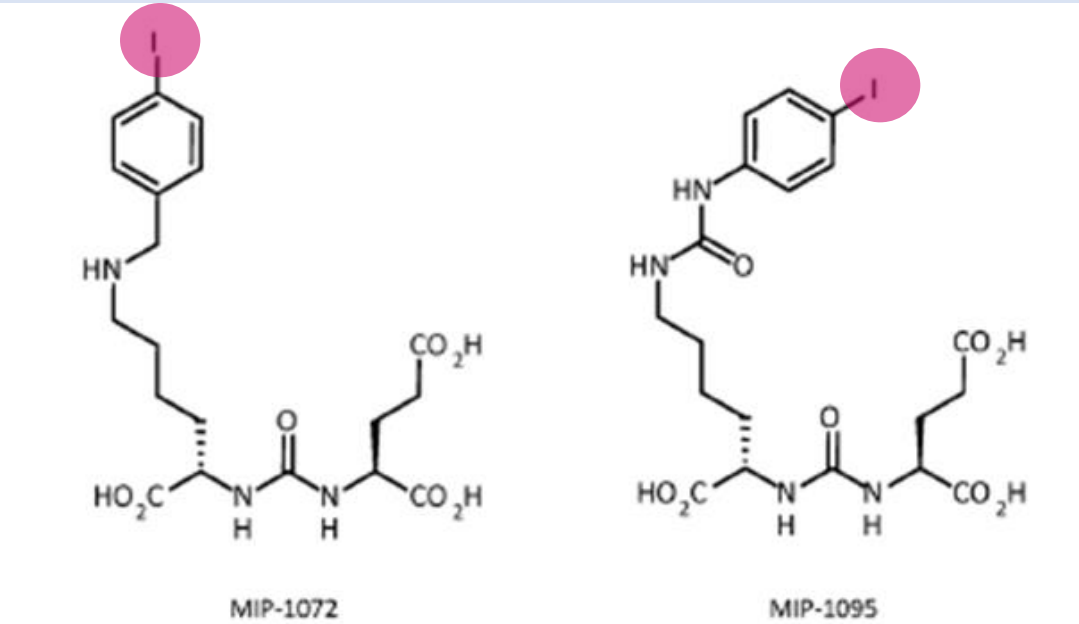
| | | | |
|---|---|---|---|
| [$^{11}$C] Colina | [$^{18}$] Flurorometilcolina | [$^{18}$F] Etilcolina | [$^{11}$C] Metilcolina |
| [$^{11}$C] Etanolamina | [illegible] | [illegible] | [$^{18}$F] MAU |
| [$^{68}$Ga] Bombesina | [$^{18}$F ] Bombesina | [$^{18}$F ] FACBC | [$^{11}$C ] Acetato |
| [$^{18}$F ] Acetato | [$^{18}$ ] FDG | Antagonistas de PSMA | Anticuerpos marcados anti-PSMA |

PET

# NUEVOS TRAZADORES II

## $^{123}$I-MIP-1072

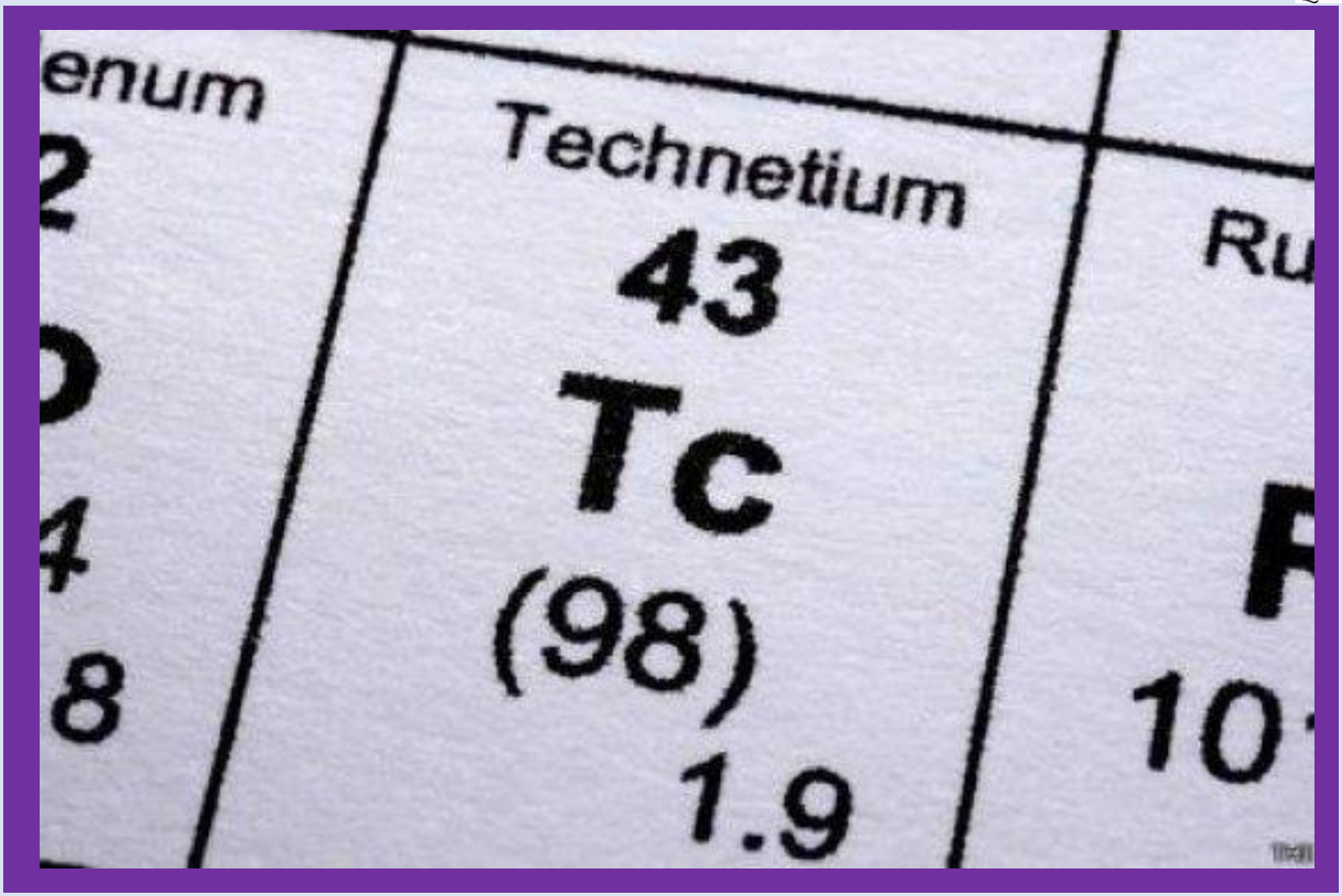
Se une específicamente y con alta especificidad a PSMA. Se depura rápidamente de tejido no target y es principalmente excretado en orina.




## $^{123}$I-MIP-1095

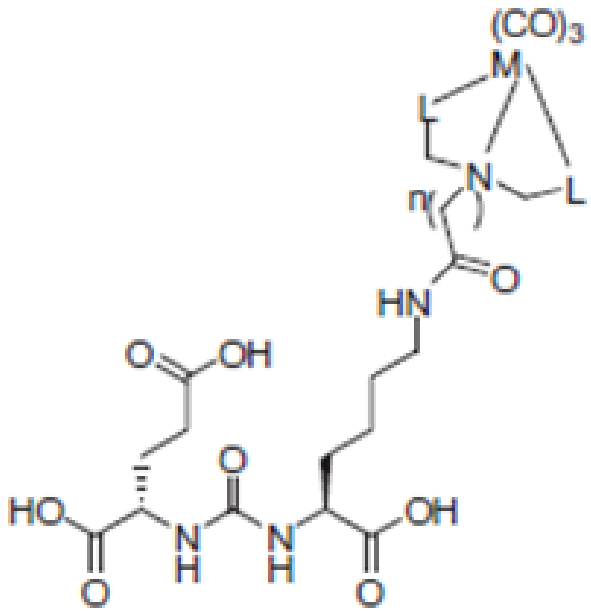
Captación en glándulas salivares, paratiroides, glándulas lagrimales.
La captación tumoral se puede observar en las primeras 24 horas post administración.

# TECNECIO ?



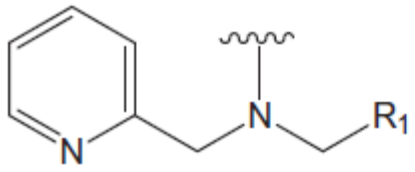
# NUEVOS RADIOFÁRMACOS DE $^{99m}Tc$

## $^{99m}Tc$ o Re -Glu-urea-Lys-X

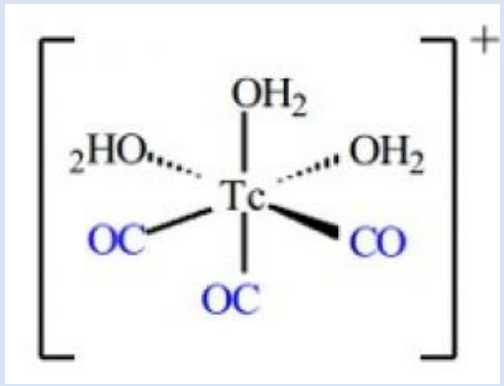



M = Re or $^{99m}Tc$

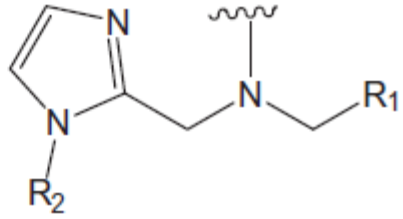
SAAC (First Generation) Ligand




$R_1$ = 2-pyridyl (Dp derivative)
$R_1$ = COOH (PAMA derivative)



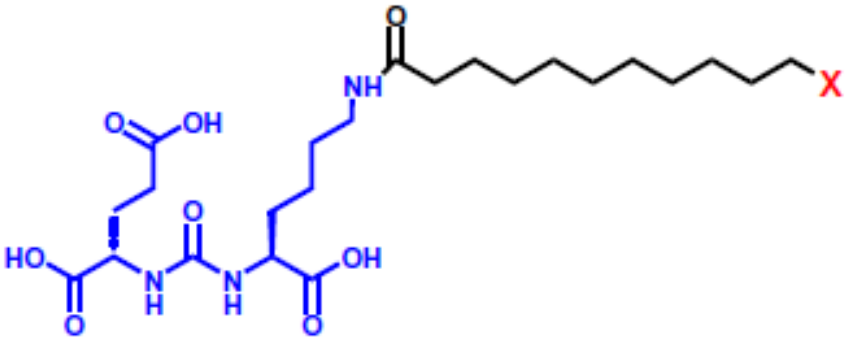

SAAC II (Second Generation) Ligand



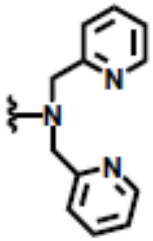
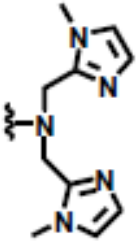
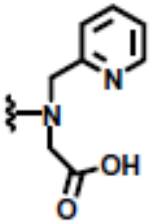
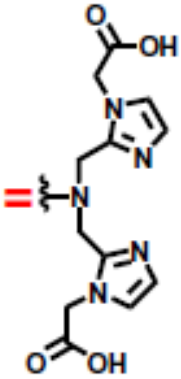
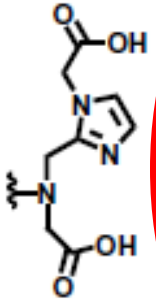
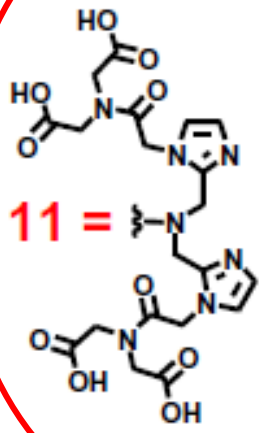

$R_1$ = imidazole (symmetric) or COOH
$R_2$ = polar functionality

*K.P. Maresca et al /Inorganica Chimica Acta 389 (2012) 168–175*

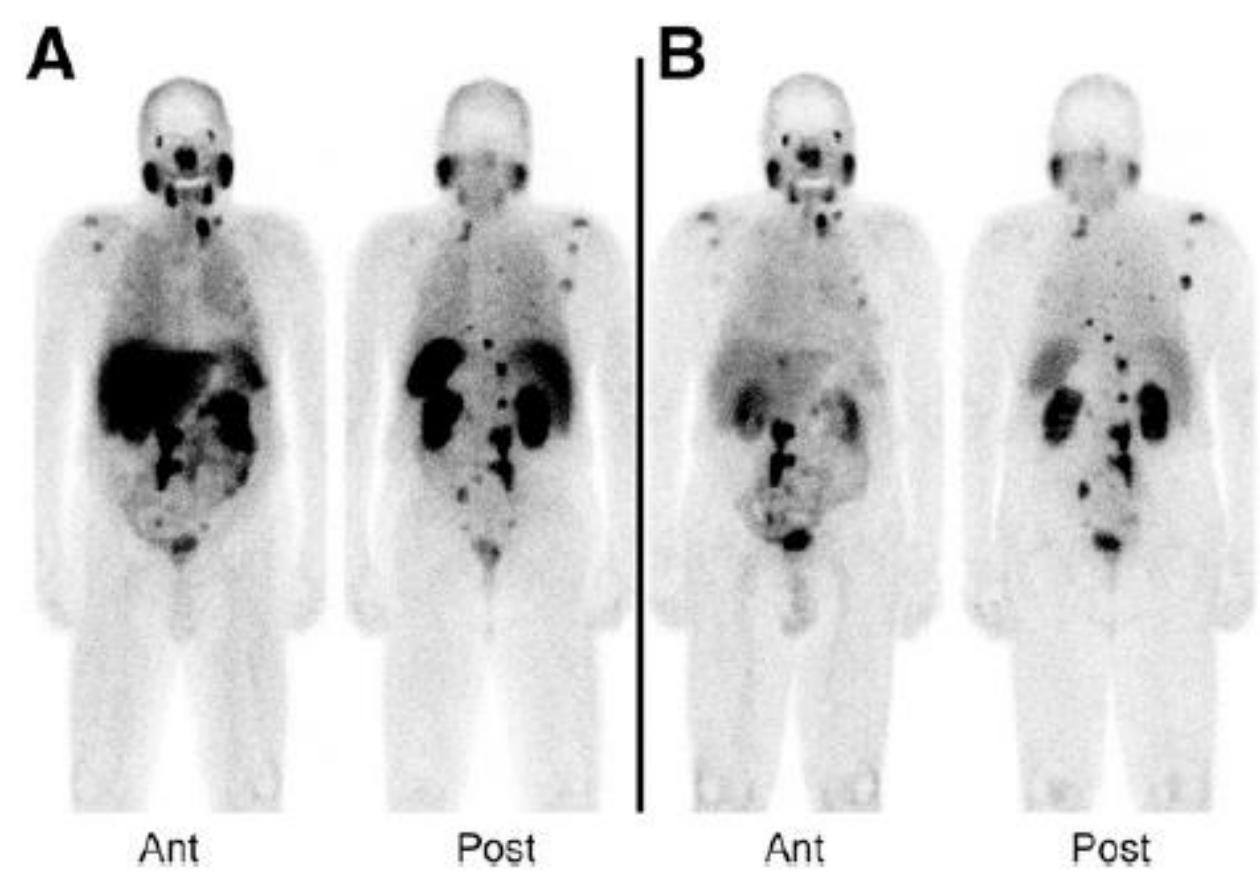
# RADIOFÁRMACOS I



SAAC II

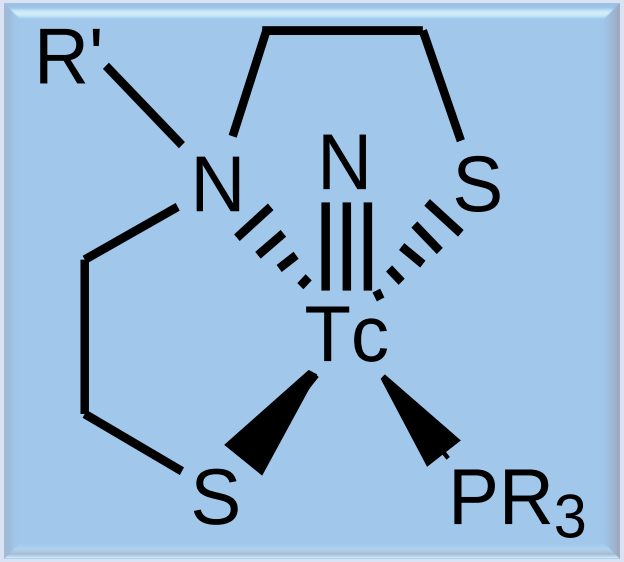
X = 6= 
7 = 
8 = 
9 = 
10 = 
11 = 

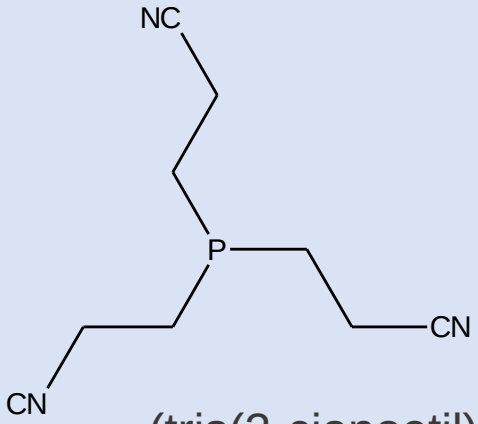
# CONT.




**A-Captación tumoral del $^{99m}$TcMIP 1404 (4 hs)**
**B- Captación tumoral del $^{99m}$Tc-MIP-1405 (4 hs)**

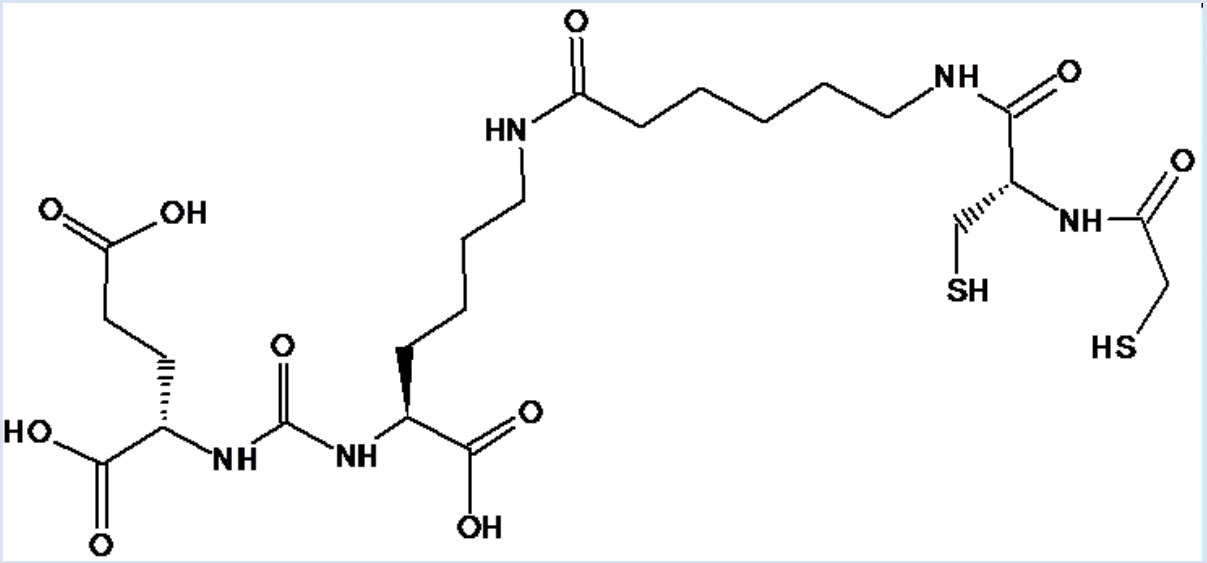
# TRABAJO DE INVESTIGACIÓN CÁTEDRA




(tris(2-cianoetil) fosina)

**DERIVADO DE GLU-UREA-LYS**



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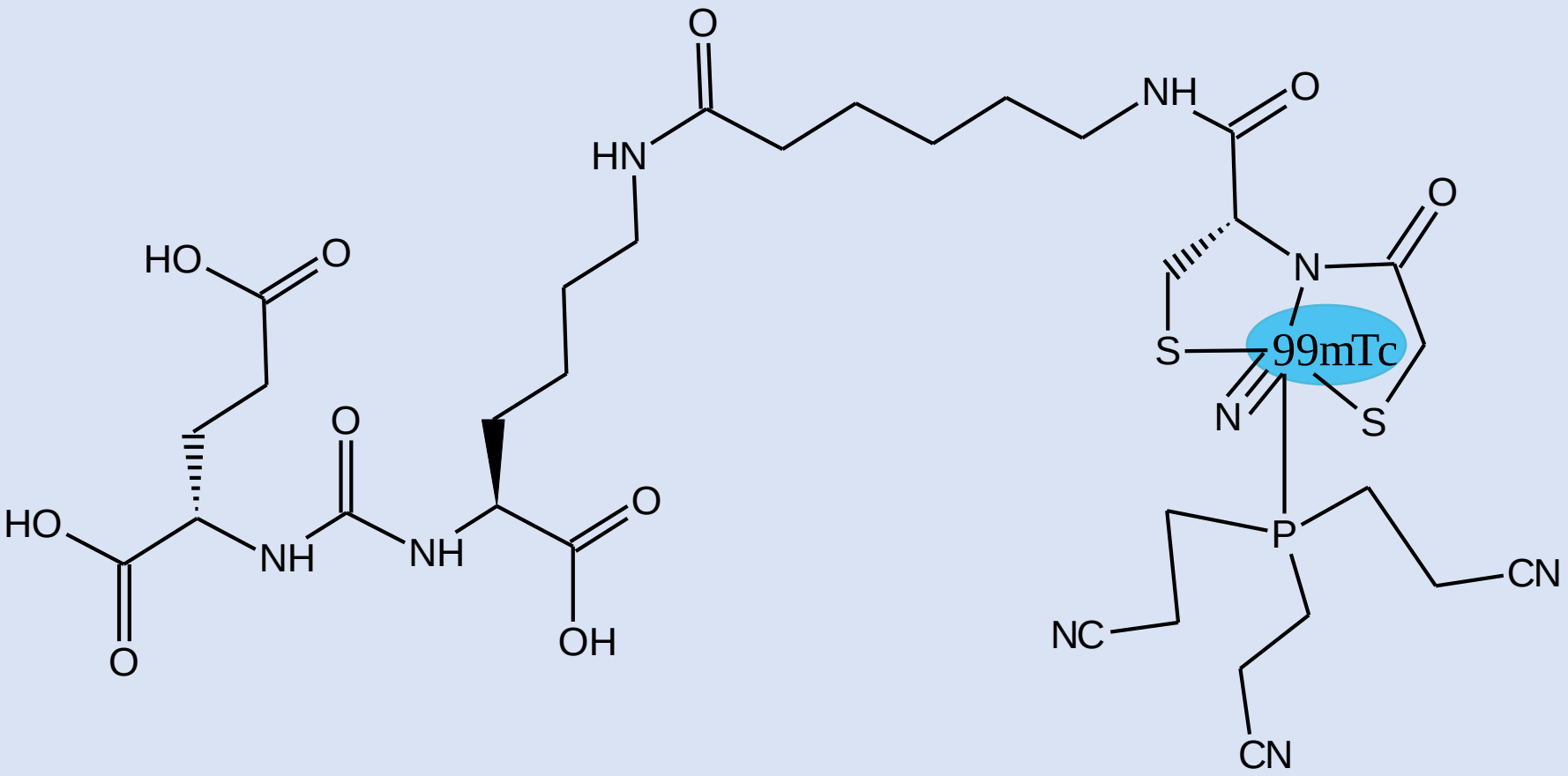


**También para $^{188}Re$**

# Desarrollo de nuevos fármacos antiandrógenos

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Área Radioquímica
Facultad de Química

RQ

U D E L A R
FQ
FACULTAD DE QUIMICA

SUBIMN
SOCIEDAD URUGUAYA DE BIOLOGIA Y MEDICINA NUCLEAR

# INTRODUCCIÓN

Aproximadamente el 80-90% de los cánceres de próstata al momento del diagnóstico inicial son andrógeno dependientes.

El receptor de andrógenos (AR) está presente en la mayoría de cánceres de próstata y se cree que tiene un papel crítico en su desarrollo.

Hoy en día , el tratamiento de cáncer de próstata se realiza por la inhibición del receptor de andrógeno usando antiandrógenos.

Synthesis and biological evaluation of a nonsteroidal bromine-76-labeled androgen receptor ligand 3-[$^{76}$Br]bromo-hydroxyflutamide

Ephraim E. Parent[a], Carl Jenks[b], Terry Sharp[b], Michael J. Welch[b], John A. Katzenellenbogen[a,*]

[a]Department of Chemistry, University of Illinois, Urbana, IL 61801, USA
[b]Washington University School of Medicine, St. Louis, MO 63110, USA

Received 28 April 2006; received in revised form 25 May 2006; accepted 30 May 2006

**1. Introduction**

Prostate cancer is the second leading cause of cancer deaths in men in the United States [1]. The androgen receptor (AR) has been shown to regulate multiple genes that are capable of augmenting or inhibiting tumor cell growth, including cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors [2,3]. Androgen ablation causes cancer regression because, without androgens, the rate of tumor cell proliferation is lower and the rate of cell death is increased, leading to extinction of these cells [4].

**A novel $^{99m}$Tc-labeled testosterone derivative as a potential agent for targeting androgen receptors**

Tapas Das, Sharmila Banerjee,* Grace Samuel, Ketaki Bapat, Suresh Subramanian, Maroor R. A. Pillai* and Meera Venkatesh

*Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai 400085, India*

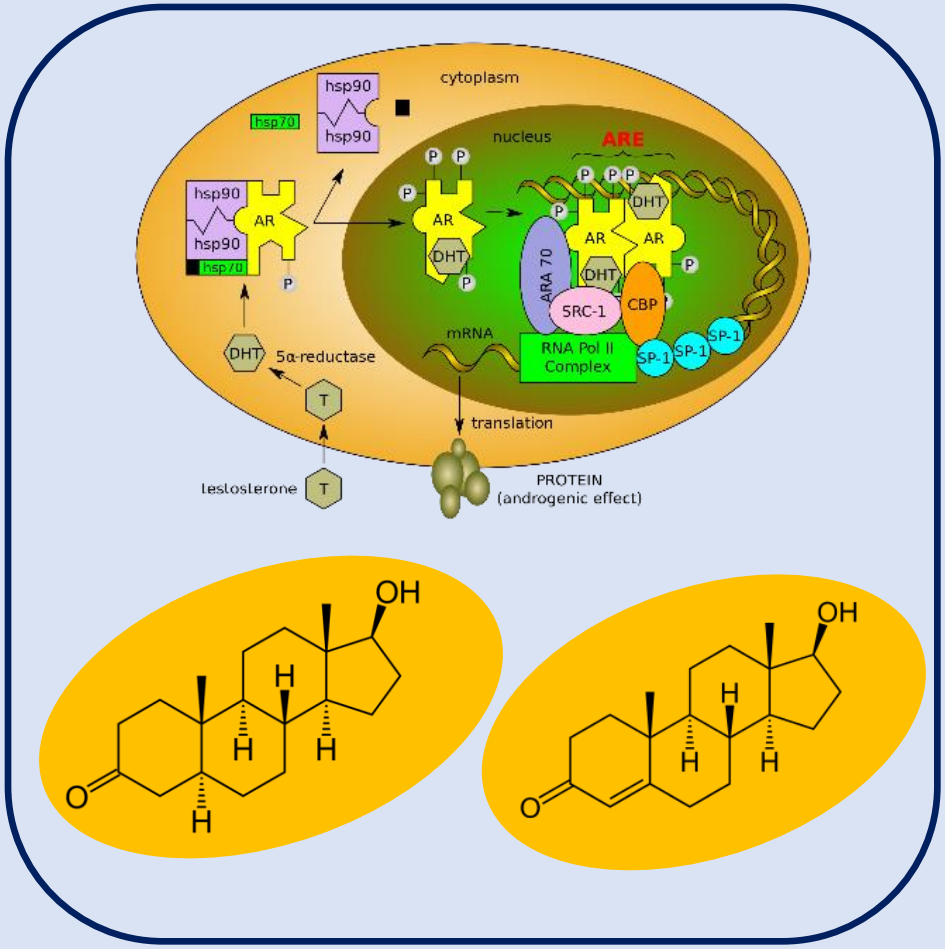
Received 23 May 2006; revised 4 August 2006; accepted 17 August 2006
Available online 1 September 2006

Several methods of radiolabeling steroidal substrates with radioisotopes of choice for targeting specific receptors over-expressed in target tissues in diseased states have been reported.[1–3] Testosterone is a steroidal hormone which binds to androgenic receptors which are over-expressed in cancerous regions of the prostate.[1] Agents to image the prostate or tumors therein, based on the androgen content, serve as a useful tool in staging of the disease and monitoring the course of therapy.[4]

# ANTIANDRÓGENOS

Los antiandrógenos son medicamentos que inhiben la síntesis de testosterona o bloquean el receptor androgénico.

Pueden clasificarse en esteroides (ciproterona, espironolactona) y no esteroides (flutamida) .



# ANTIANDRÓGENOS

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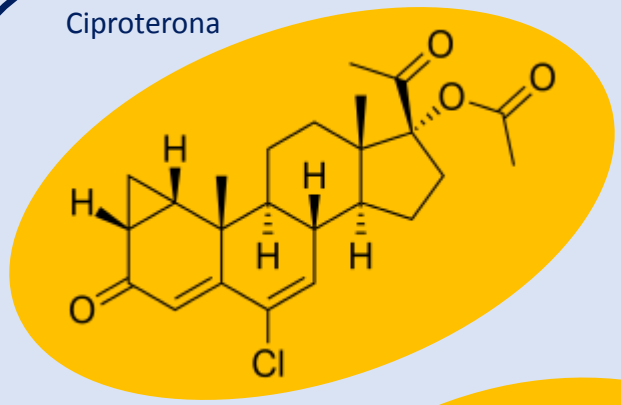
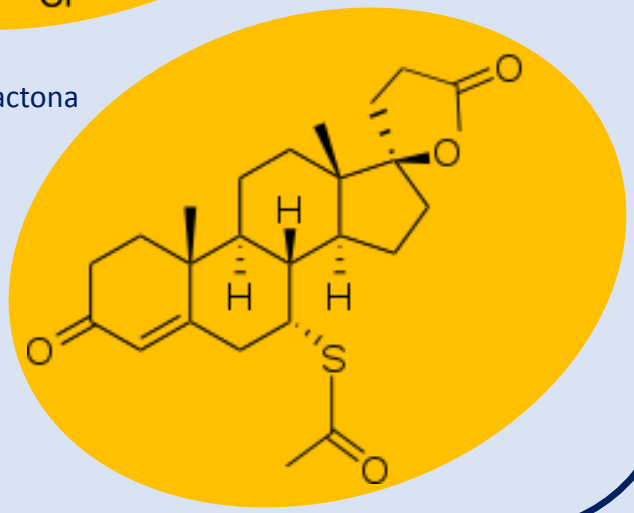
Ciproterona




Espironolactona



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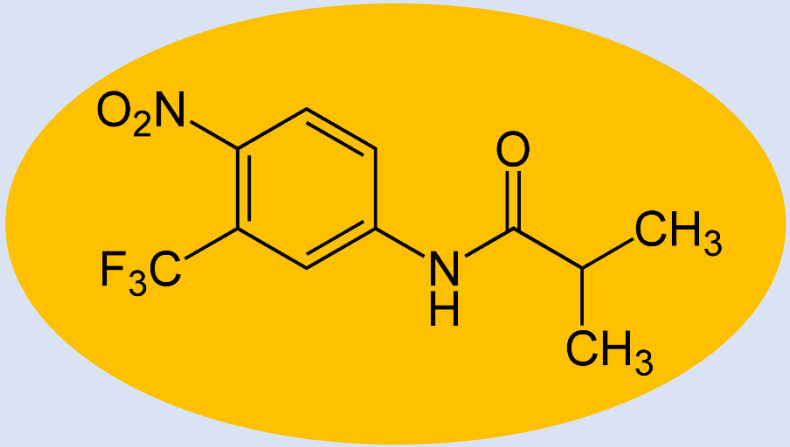
Pueden clasificarse en esteroides (ciproterona, espironolactona) y no esteroides (flutamida).

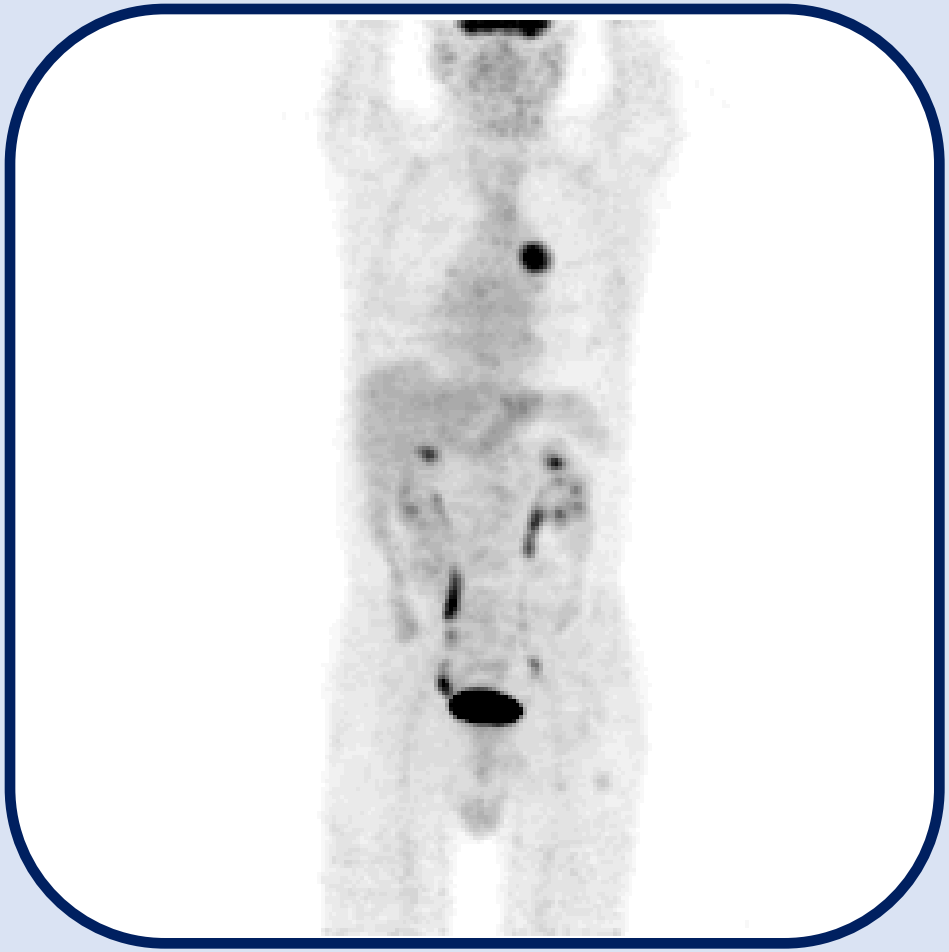
Flutamida



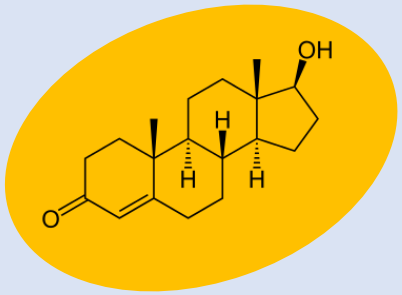
# ANTIANDRÓGENOS

Actualmente no hay técnicas de imagen no invasivas para detectar, orientar y supervisar el tratamiento específico de pacientes AR positivo.

Están en desarrollo varios compuestos para imagen de receptores de andrógenos de derivados esteroideos y no esteroides, empleando radionucleidos emisores PET y SPECT.



# ANTIANDRÓGENOS ESTEROIDEOS




## Fully-automated synthesis of 16β-$^{18}$F-fluoro-5α-dihydrotestosterone (FDHT) on the ELIXYS radiosynthesizer

Mark Lazari [a,b,c], Serge K. Lyashchenko [d], Eva M. Burnazi [d], Jason S. Lewis [d,e], R. Michael van Dam [a,b,c], Jennifer M. Murphy [b,c,*]

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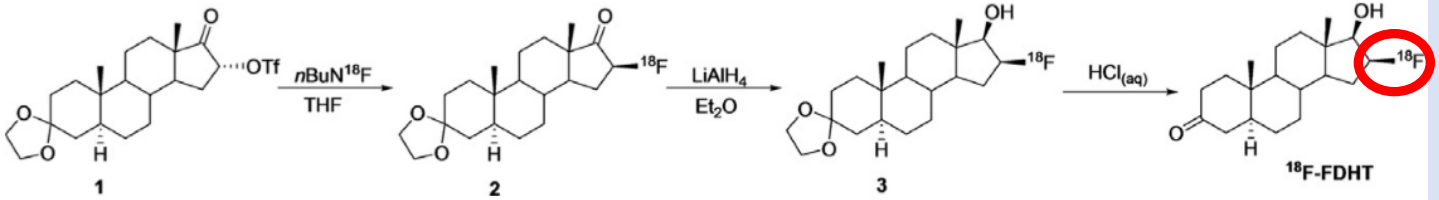
### 5. Conclusion

The radiosynthesis of $^{18}$F-FDHT has been adapted for full automation on the ELIXYS radiosynthesizer resulting in good yields, high purity and good specific activity suitable for clinical use. In addition to the advantages of automation, the use of disposable kits on ELIXYS will enable the creation of reagent kits to simplify the overall protocol and facilitate routine production of $^{18}$F-FDHT. Ultimately, we hope that the automated synthesis of $^{18}$F-FDHT will be adopted by others and accelerate research by enabling widespread access to this promising PET tracer, potentially aiding in the clinical management of metastatic prostate cancer.




Applied radiation and Isotopes , 21/05/2015

**Scheme 1.** Three-step synthesis of $^{18}$F-FDHT.

nature REVIEWS

January 2014

**KEY ADVANCES IN MEDICINE**

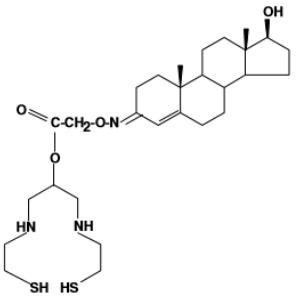
Androgen deprivation therapy is the standard of care for patients with recurrent or metastatic disease, but all patients eventually develop castration-resistant prostate cancer (CRPC). Considerable molecular heterogeneity underlies the biology of CRPC, with continued reliance on androgen receptor (AR)-mediated signalling that frequently gives rise to AR-independent, c-MYC-driven neuroendocrine prostate cancer (NEPC) as a treatment-emergent adaptive response.[7] Although no currently available biomarkers are able to readily identify and predict subsets of patients who are most likely to respond to continued AR-directed therapy, new PET-based molecular imaging approaches might offer a suitable alternative and have the potential to accurately distinguish AR-dependent prostate cancer from treatment-emergent NEPC. Indeed, $^{18}$F-fluoro-5α-dihydrotestosterone ($^{18}$F-FDHT)-PET was used as a pharmacodynamic biomarker of AR ligand binding in the early phase clinical trials of the second-generation AR antagonists ARN-509 and enzalutamide, and helped guide the recommended phase II dose selection of these two agents.[8]

## A novel $^{99m}$Tc-labeled testosterone derivative as a potential agent for targeting androgen receptors

Tapas Das, Sharmila Banerjee,* Grace Samuel, Ketaki Bapat, Suresh Subramanian, Maroor R. A. Pillai† and Meera Venkatesh

*Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai 400085, India*

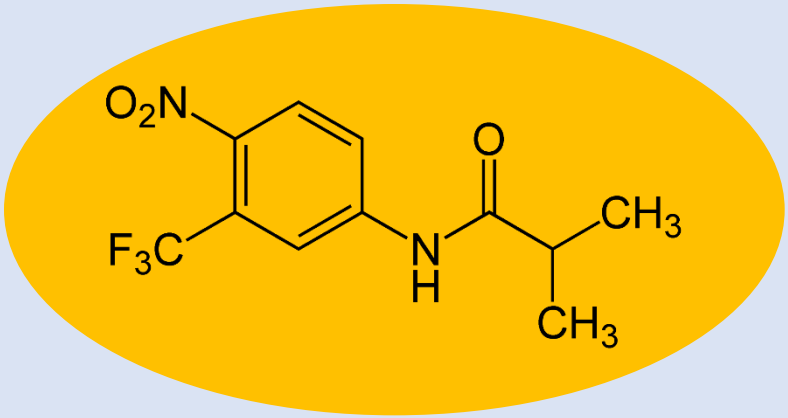
Received 23 May 2006; revised 4 August 2006; accepted 17 August 2006
Available online 1 September 2006




DAHPES-testosterone conjugate

01/09/2006

# DERIVADOS ANTIANDRÓGENOS




La flutamida es un antiandrógeno puro, sin actividad esteroidea intrínseca. Su mecanismo de acción es ser antagonista del receptor androgénico.

## Synthesis and biological evaluation of a nonsteroidal bromine-76-labeled androgen receptor ligand 3-[$^{76}$Br]bromo-hydroxyflutamide

Ephraim E. Parent[a], Carl Jenks[b], Terry Sharp[b], Michael J. Welch[b], John A. Katzenellenbogen[a,*]

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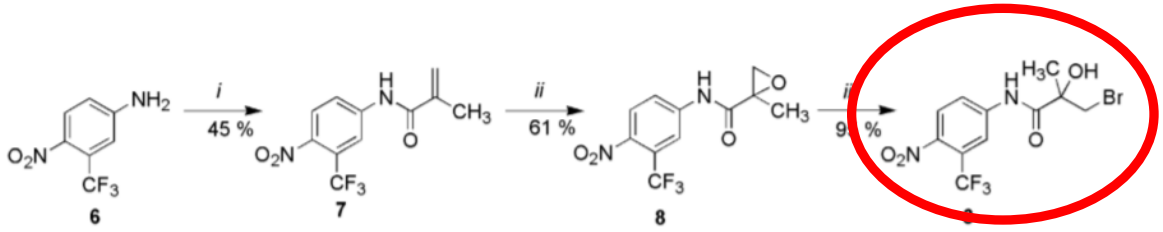
[b]*Washington University School of Medicine, St. Louis, MO 63110, USA*

Received 28 April 2006; received in revised form 25 May 2006; accepted 30 May 2006




Scheme 1. Synthesis of 3-bromo-hydroxyflutamide from an epoxide intermediate, Compound (**8**). (i) Methacryloyl chloride, $Et_3N$, $CH_2Cl_2$. (ii) Formic acid, $H_2O_2$. THF. (iii) Ammonium bromide, acetone.

Table 2
Tissue distribution of activity from $^{76}$Br-**3**

| Tissue | % Injected dose/g | | |
|---|---|---|---|
| | 1 h | 1-h block[a] | 4 h |
| Blood | 0.21±0.038 | 0.26±0.035 | 0.46±0.032 |
| Liver | 0.44±0.082 | 0.58±0.11 | 0.33±0.028 |
| Kidney | 0.28±0.045 | 0.37±0.055 | 0.36±0.042 |
| Muscle | 0.13±0.059 | 0.16±0.025 | 0.12±0.0095 |
| Bone | 0.10±0.024 | 0.14±0.039 | 0.14±0.018 |
| Prostate | 0.33±0.19 | 0.37±0.065 | 0.38±0.046 |

[a] Animals were cotreated with 36 μg of testosterone acetate to block AR-mediated uptake.

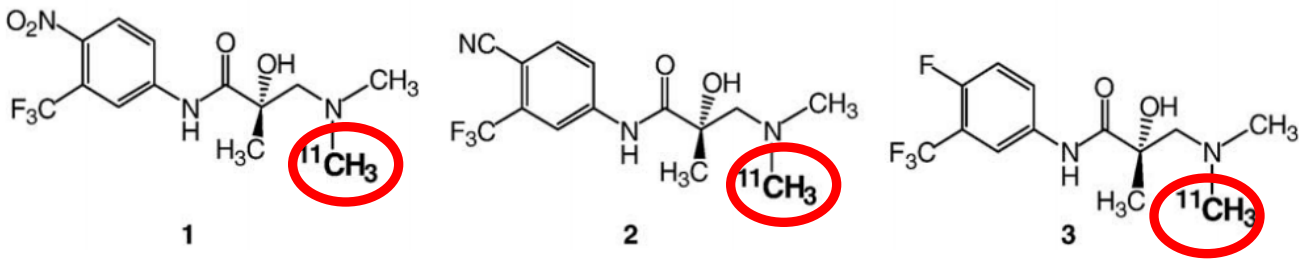
The bromine label in $^{76}$Br-**3**, however, proved to be metabolically unstable in vivo in rats, so that in tissue distribution studies, prostate uptake levels were very low and nonspecific, and could not be blocked by coinjection of an excess of a high-affinity unlabeled androgen. Thus, in humans, this compound is also likely to be metabolized too rapidly for an effective imaging of prostate cancer.

Nuclear Medicine and Biology, 30/05/2006

# DERIVADOS ANTIANDRÓGENOS

## Chiral dimethylamine flutamide derivatives—modeling, synthesis, androgen receptor affinities and carbon-11 labeling

Orit Jacobson[a], Desideriu Laky[a], Kathryn E. Carlson[b], Sharona Elgavish[c], Michael Gozin[d], Einat Even-Sapir[e], Ilan Leibovitc[f], Mordechai Gutman[g], Roland Chisin[a], John A. Katzenellenbogen[b], Eyal Mishani[a,*]




### 5. Conclusions

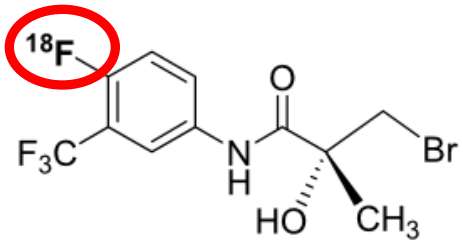
Novel AR ligands have been designed based on molecular modeling, indicating their higher interaction with the receptor over 3-bromo-hydroxyflutamide and hydroxy-flutamide. These compounds were synthesized and have demonstrated higher or similar affinities to the AR than the currently used commercial drugs. Unlike other reported nonsteroidal radiolabeled AR ligands, these compounds have an electron-rich group (dimethylamine) located on the methyl moiety, which may confer a better stability to the molecule and, in addition, serve as an anchor for carbon-11 labeling in a more straightforward approach than labeling with fluorine-18 or bromine-76. An automated radiosynthetic route for the preparation of these novel $^{11}$C-containing hydroxyflutamide derivatives was developed. If these compounds demonstrate an antagonist effect on the AR, they may also be superior therapeutic endocrine agents for prostate cancer than the currently used drugs.

Nuclear Medicine and Biology, 28/05/2006

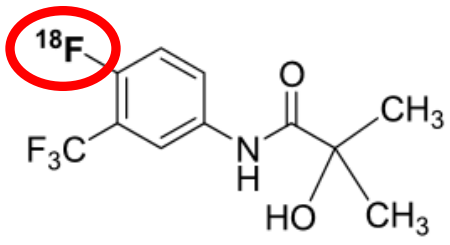
# DERIVADOS ANTIANDRÓGENOS

## Prostate cancer PET bioprobes: Synthesis of [$^{18}$F]-radiolabeled hydroxyflutamide derivatives

Orit Jacobson,[a] Yossi Bechor,[b] Avi Icar,[b] Nurit Novak,[b] Atalia Birman,[b] Hanit Marom,[b] Ludmila Fadeeva,[b] Elizabeth Golan,[b] Ilan Leibovitch,[c] Mordechai Gutman,[d] Einat Even-Sapir,[c] Roland Chisin,[a] Michael Gozin[b,*] and Eyal Mishani[a,*]




[$^{18}$F]-1




[$^{18}$F]-2

**Figure 2.** $^{18}$F-radiolabeled nonsteroidal antiandrogen derivatives.

### 3. Conclusions

The objective of the described work was to develop radiosynthetic methodologies for the preparation of novel $^{18}$F-containing hydroxyflutamide derivatives, with potential affinity for the androgen receptor. These compounds may present a better alternative to radiolabeled steroid-based androgen ligands for noninvasive molecular imaging of AR-dependent prostate cancer using PET. This developed methodology for nonsteroidal anilide-type $^{18}$F-labelled radiopharmaceuticals can serve as a platform for the preparation of a wide spectrum of specific prostate cancer PET imaging agents and may lead to image-guided treatment of prostate cancer.

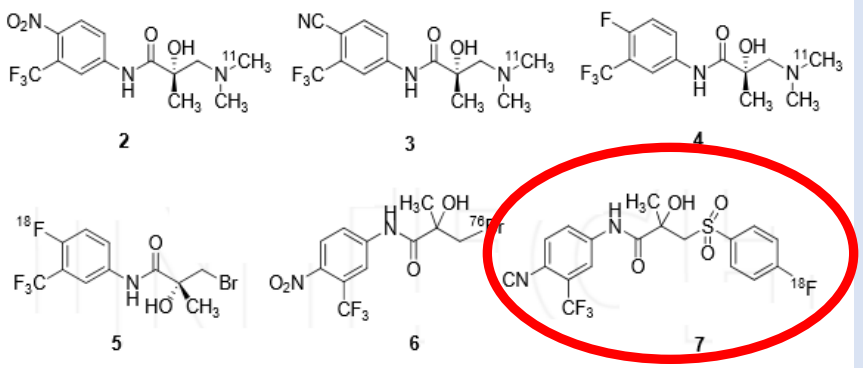
Bioorganic & Medicinal and Chemistry, 17/06/2005

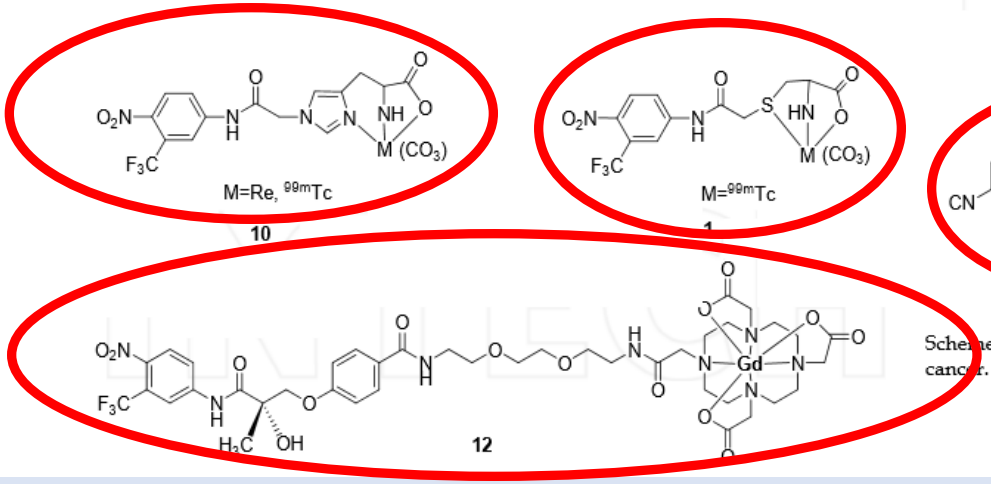
# DERIVADOS ANTIANDRÓGENOS

## Recent Development and Trends in Molecular Imaging Probes for Prostate Cancer

Wenbin Zeng[1,2], Zhiguo Liu[1,2] and Wei Wang[2,3]

[1] *School of Pharmaceutical Sciences, Central South University, Tongzipo Road, Changsha,*
[2] *Molecular Imaging Research Center, Central South University, Changsha,*
[3] *Cell Transplantation & Gene Therapy Institute, The Third Xiangya Hospital of Central South University, Changsha, China*



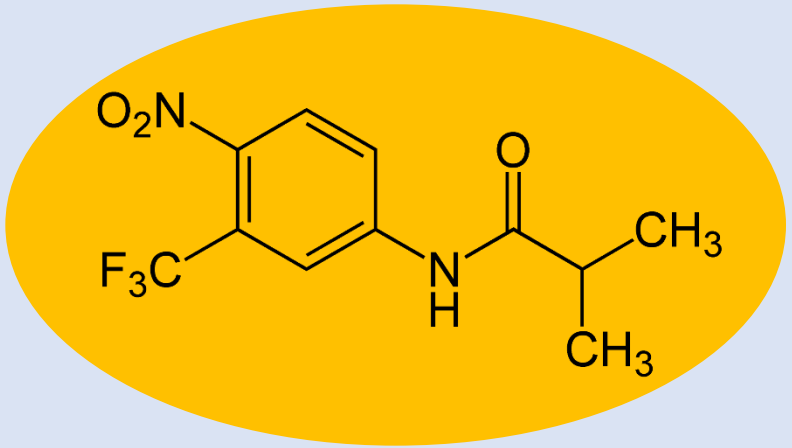




Scheme 2. Chemical structures of some nonsteroidal AR radioligands for imaging prostate cancer.

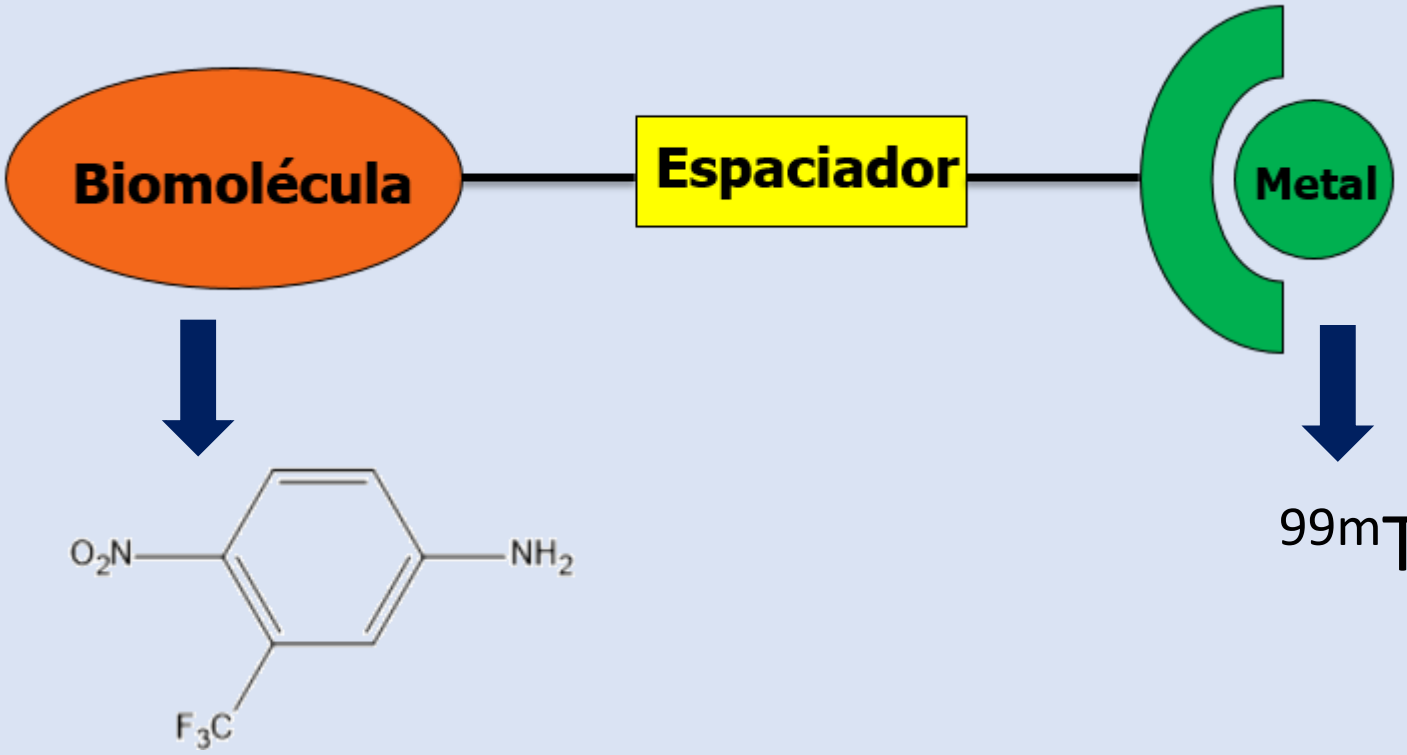
# OBJETIVO

Desarrollar potenciales radiofármacos para diagnóstico de cáncer de próstata a partir de fármacos antiandrogénicos, no esteroideos los cuales interaccionan con el receptor de andrógenos (AR), sobreexpresado en el cáncer de próstata.

Antiandrógeno

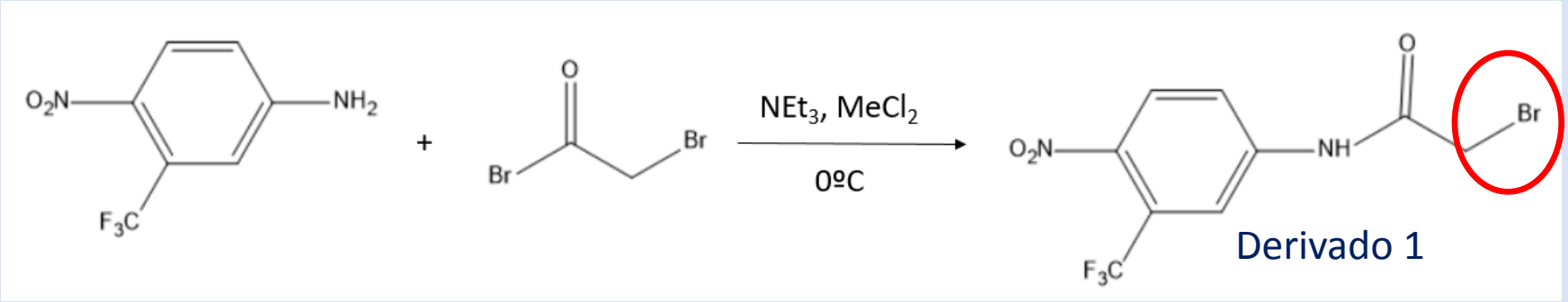


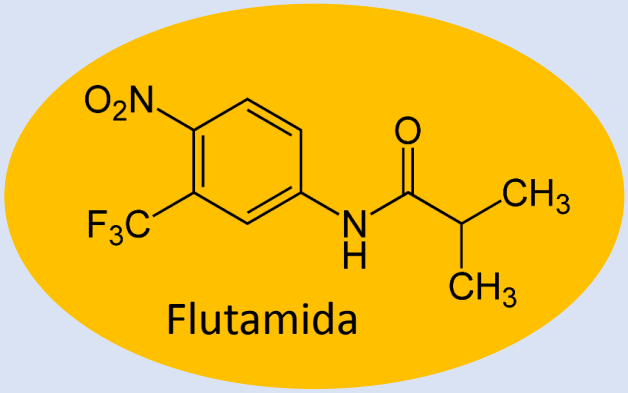
# DISEÑO DE LOS COMPLEJOS




Método “pendent approach”, que consiste en añadir a la molécula biológica mediante síntesis orgánica una serie de grupos donores de electrones capaces de coordinar al metal, la llamada unidad quelante.

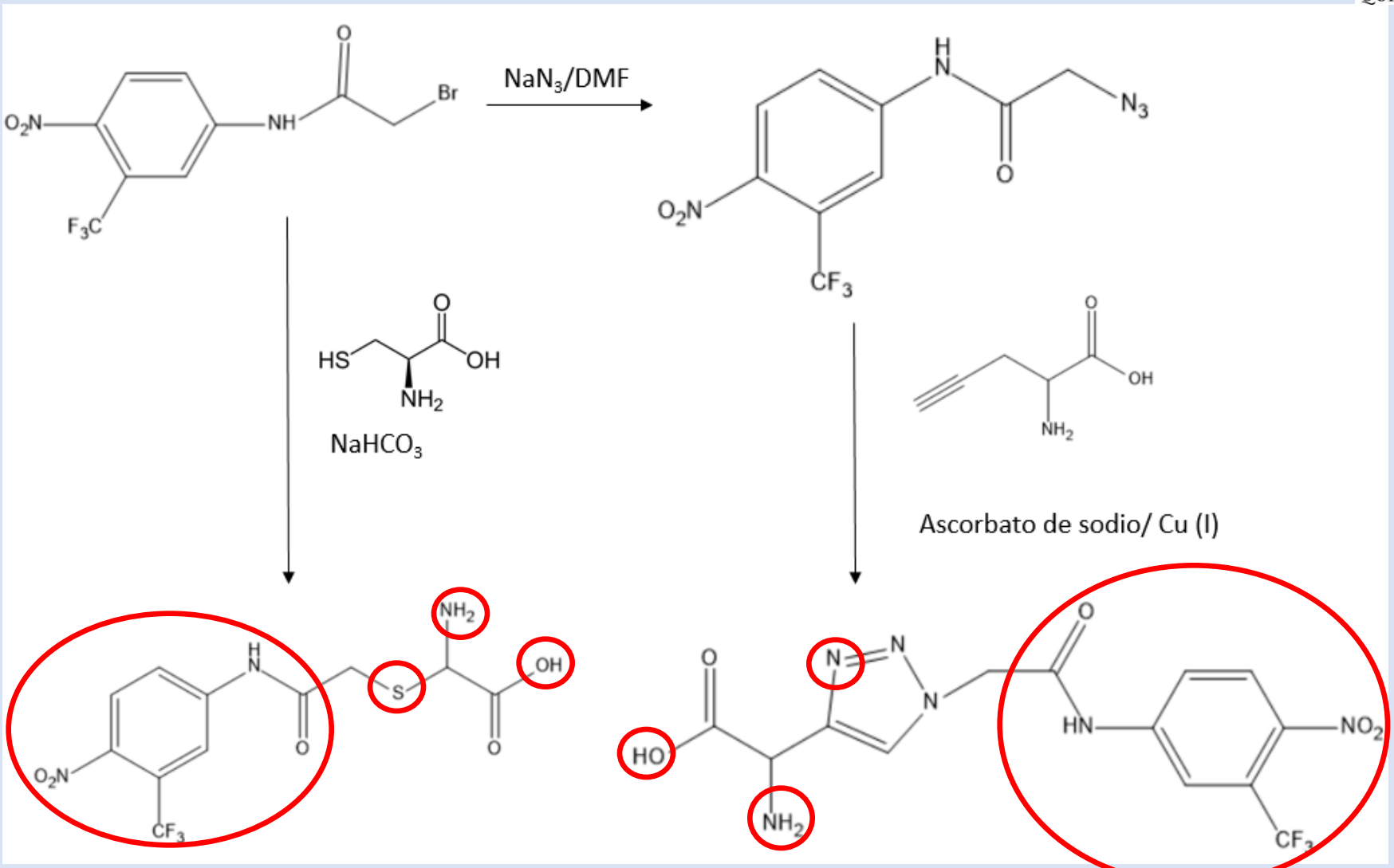
# SÍNTESIS DEL DERIVADO 1




Se realizó la síntesis del derivado 1 para luego poder derivatizarlo a fin de poder obtener los ligandos para poder realizar la marcación con $^{99m}Tc$ en diferentes estados de oxidación.

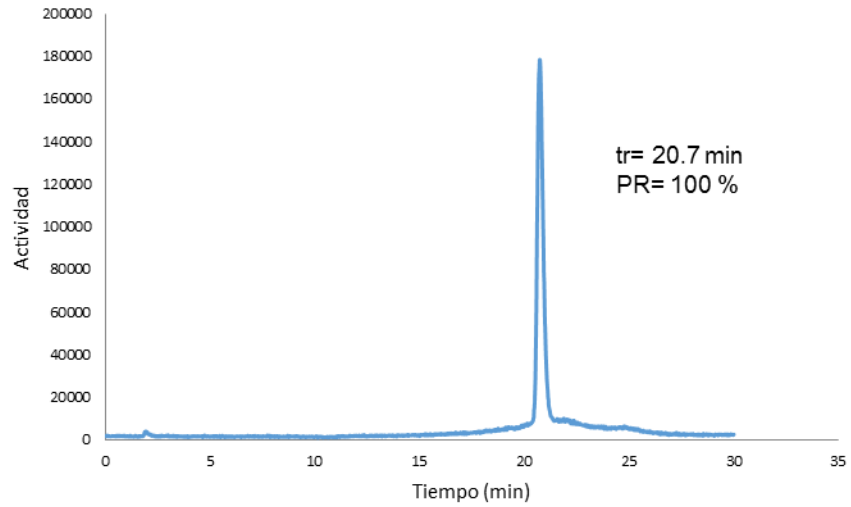
# SÍNTESIS DE LOS LIGANDOS

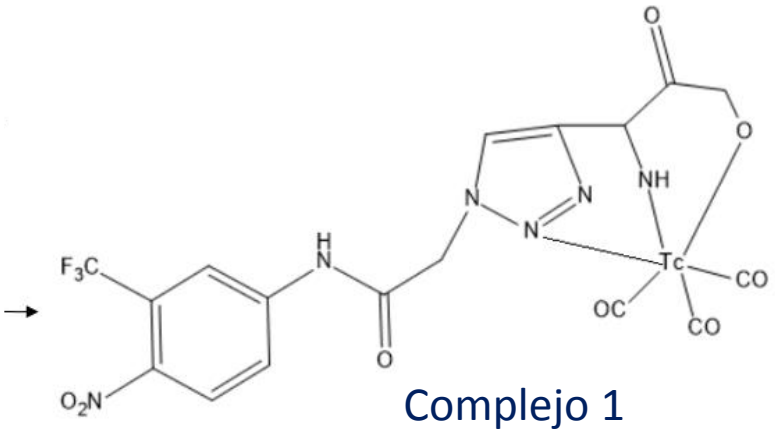


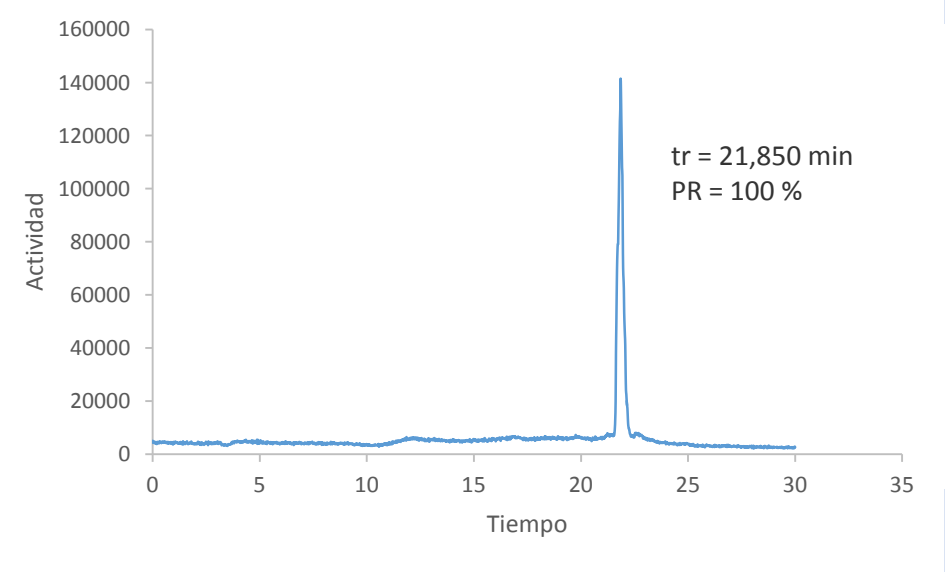

Ligando 2

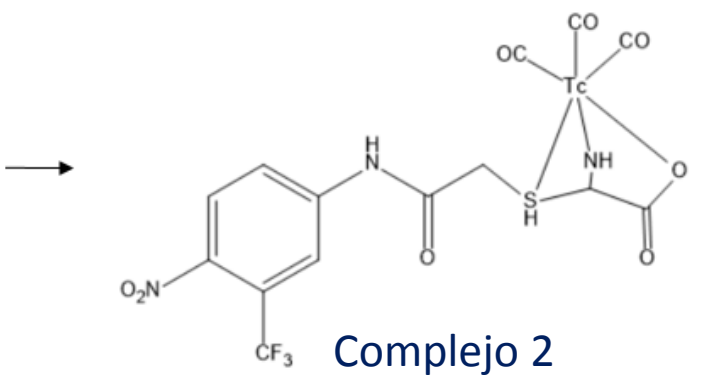
Ligando 1

# OPTIMIZACIÓN DE LA MARCACIÓN CON $^{99m}Tc$



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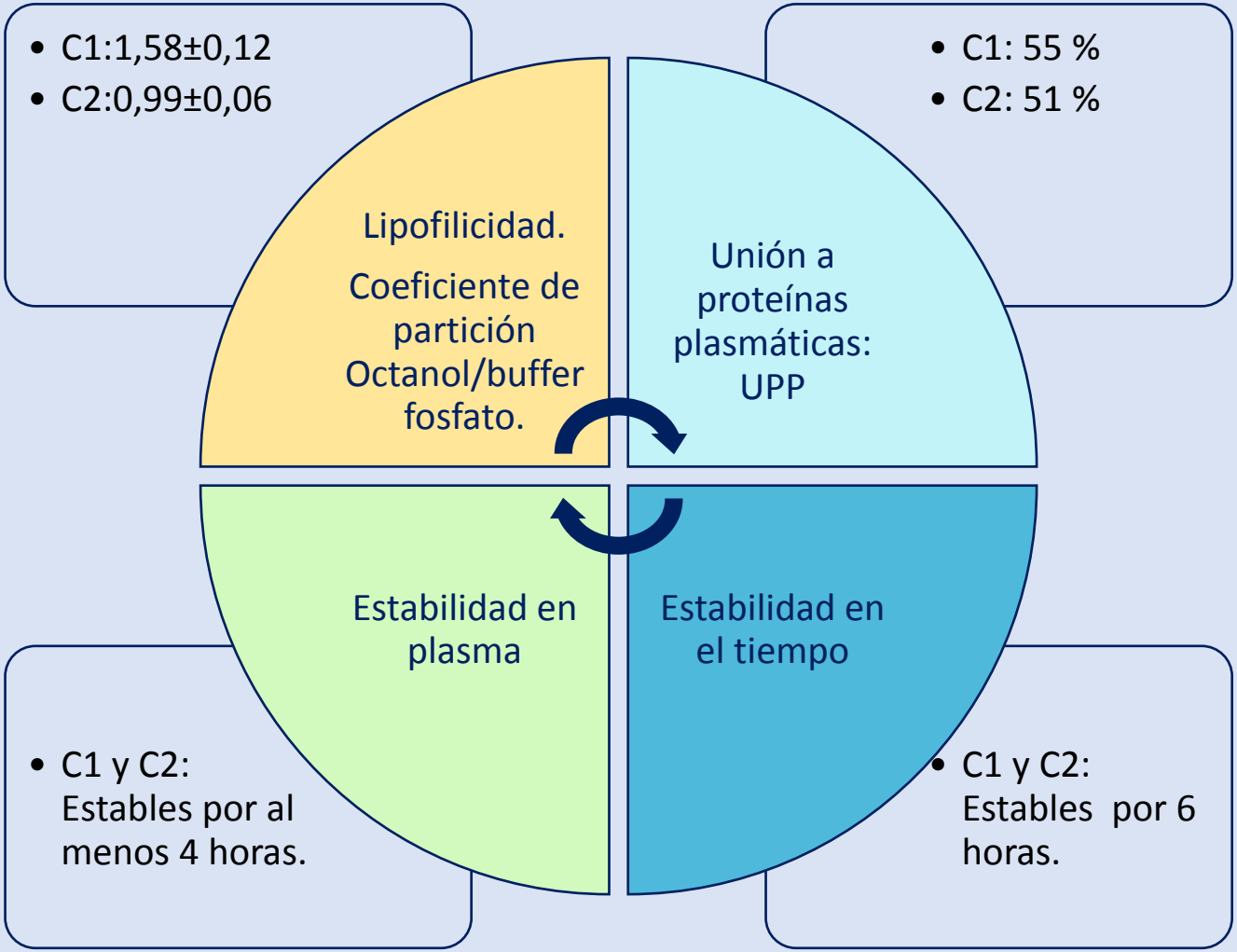
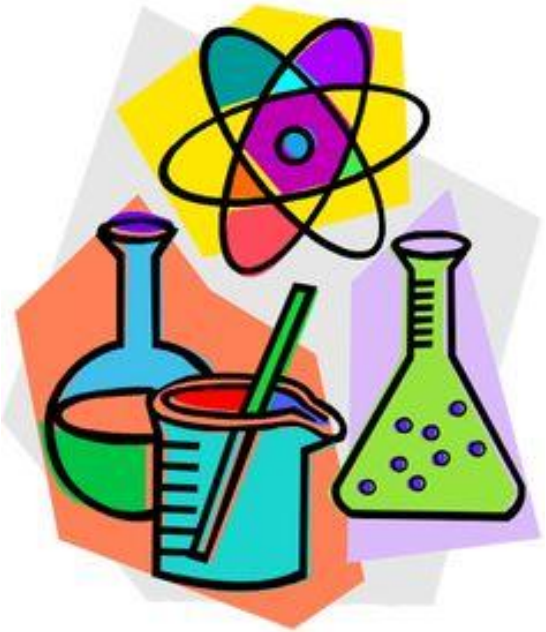


# PRESENTE Y FUTURO

Se están sintetizando nuevos ligandos derivados de antiandrógenos.

Se realizarán estudios in vitro en células en cultivo a fin de conocer la afinidad del complejo obtenido por estas células.

Se realizarán estudios en animales normales y en animales portadores de tumores de próstata



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