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Hybrid synthetic approach and biological characterization of a branched heterodimer for overcoming prostate cancer heterogeneity

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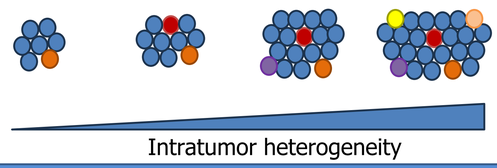
BACKGROUND

Prostate cancer is the fifth cause of cancer-related death in men over the world (375 000 cases in 2020) ⟶ 5-year survival rate of 31% at the late stage.[1]

Radiolabelled Prostate-Specific Membrane Antigen (PSMA) inhibitors entry in clinical practice for imaging (**[^{68}Ga]Ga-PSMA-11**) and therapy (**[^{177}Lu]Lu-PSMA-617**).[2]

80% of prostate cancers show high heterogeneity ⟶ low expression of PSMA and presence of multiple distinct tumour foci.[3]



AIM OF THE RESEARCH

Development of heterodimers addressing two distinct targets expressed by tumoral prostate tissues.[4]

Neurotensin (NT) system was found to be involved in the growth of prostate cancer cells.

NTS1 ⟶ valid onco-target for imaging and therapy of PSMA-negative prostate cancer lesions.

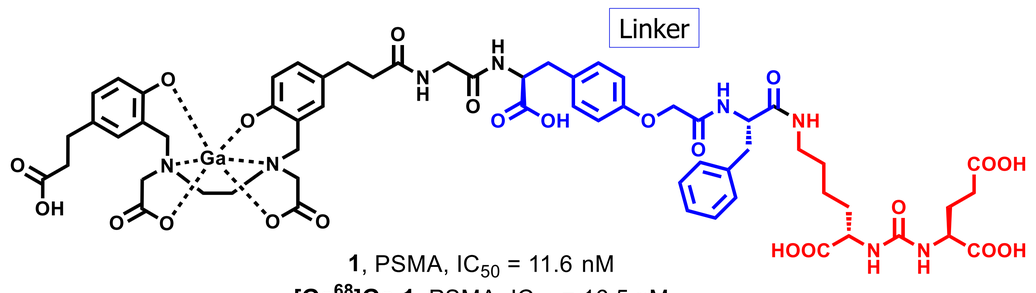
pGlu-Leu- Tyr-Glu-Asn- Lys-Pro-**Arg^{8}-Arg^{9}-Pro^{10}-Tyr^{11}- Ile^{12}-Leu^{13}-OH**

⇩

H-Arg^{8}-Arg^{9}-Pro^{10}-Tyr^{11}- Ile^{12}-Leu^{13}-OH ⟹ **H-Lys^{8}-Lys^{9}-Pro^{10}-Tyr^{11}- Ile^{12}-Leu^{13}-OH**

NT8-13 -> NTS1, K_i = 1.5 nM — **JMV 438** -> NTS1, K_i = 4 nM

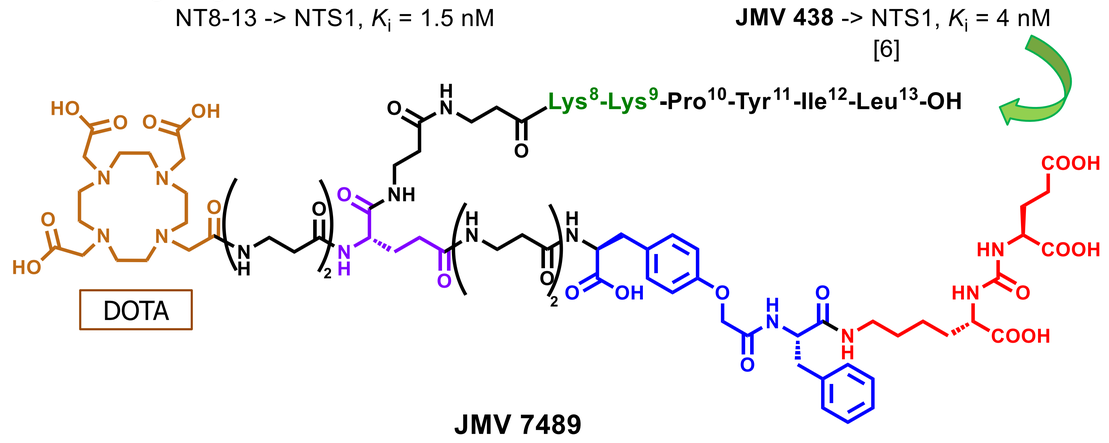
[6]



1, PSMA, IC_{50} = 11.6 nM

[Ga^{68}]Ga-1, PSMA, IC_{50} = 16.5 nM

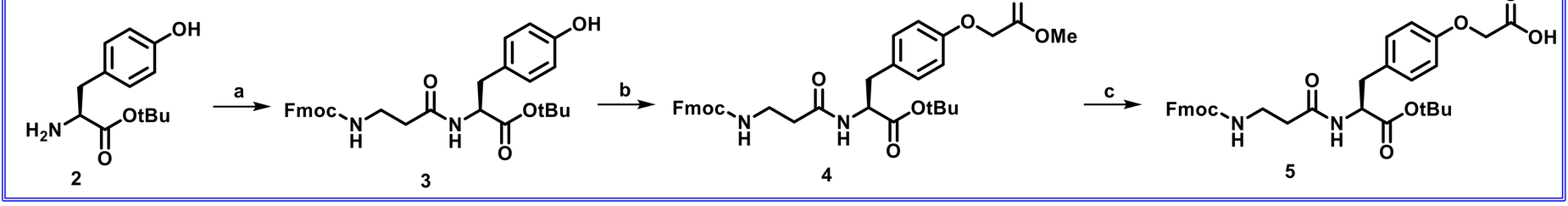
[5]



JMV 7489

SYNTHESIS

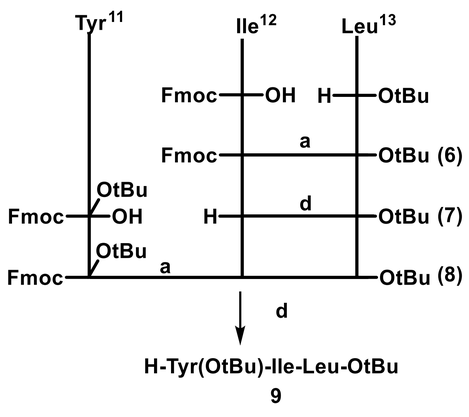
Synthesis of PMSA linker in solution

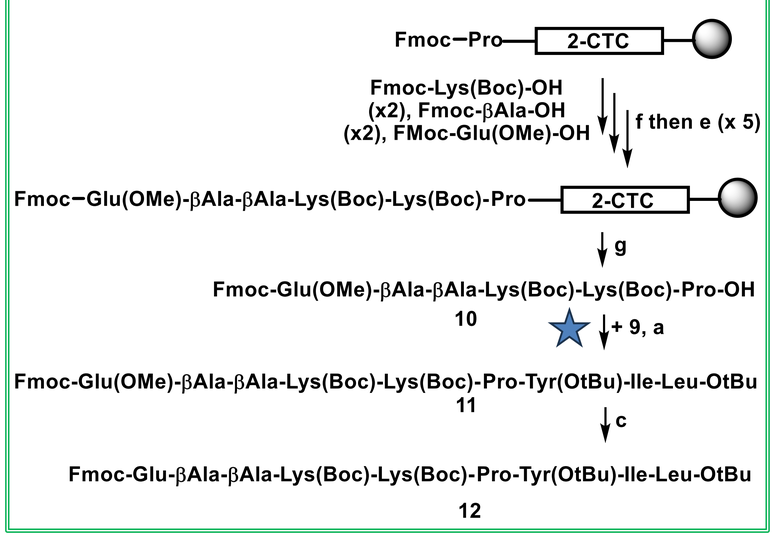


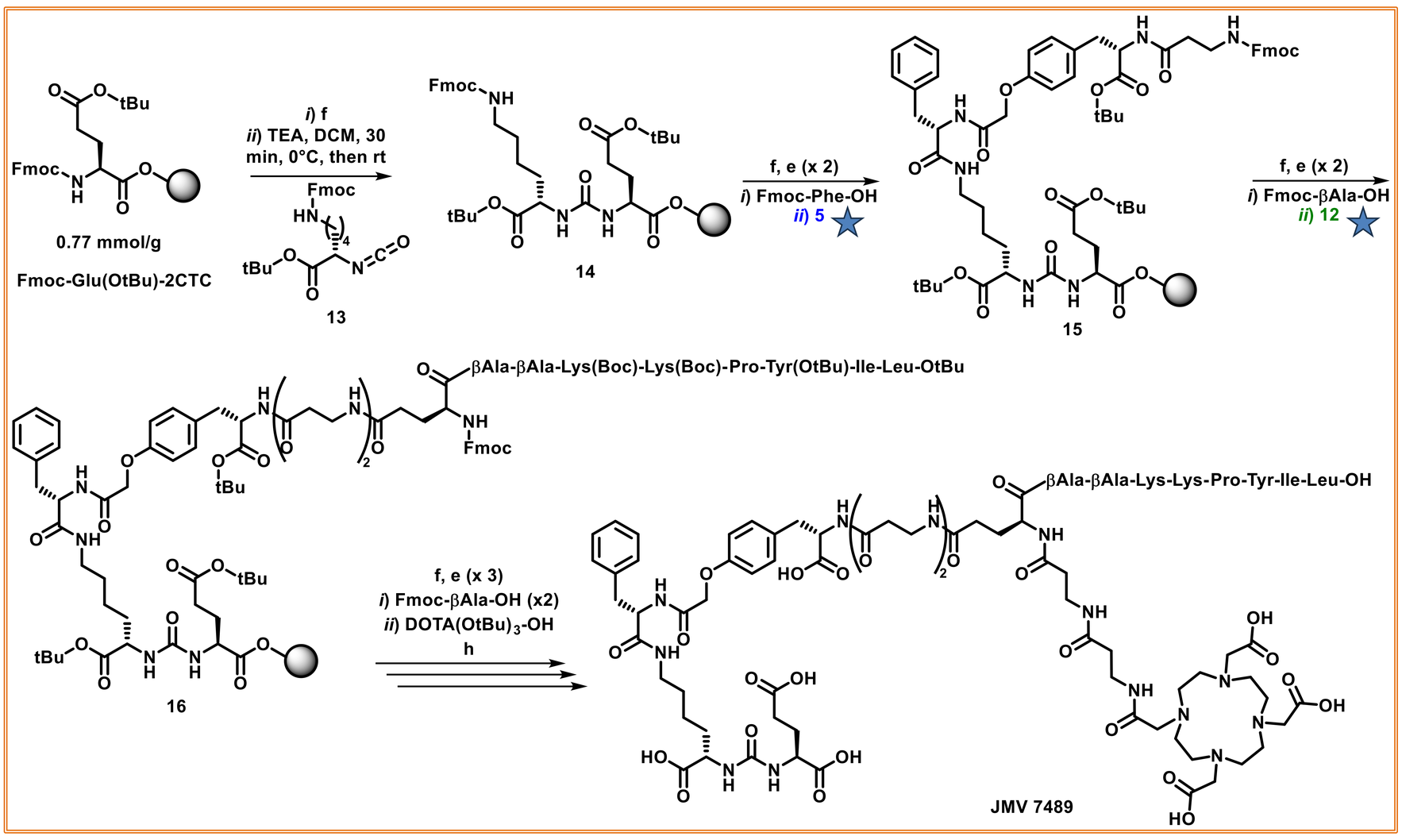
a = HATU, DIPEA, DMF, rt, on
b = Methyl bromoacetate, K_2CO_3, ACN, rt, on
c = NaOH, $CaCl_2$, ISA/H2O 7:3, rt, TLC mon.
d = 20% piperidine in DMF, rt, 1h
e = HATU, DIPEA, DMF, 45 min
f = 20% piperidine in DMF, 5 min (x 3)
g = TFE/DCM/AcOH (8:1:1), 4h
h = TFA/H_2O/TIS (95:2.5:2.5), 7h

Crucial steps report ★

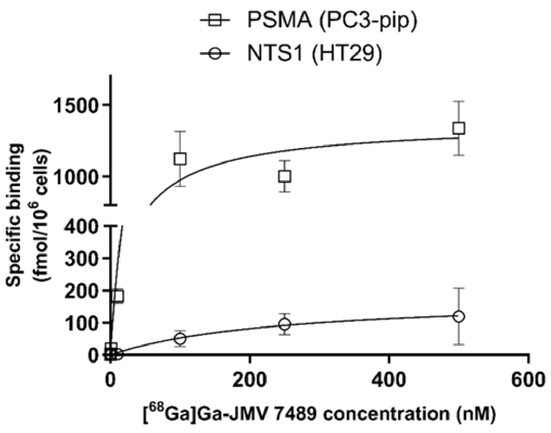
Syntesis of NT arm







BIOLOGICAL INVESTIGATION



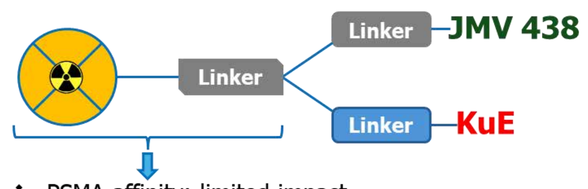
	Affinity towards NTS1 nM	Affinity towards PSMA nM
[^{68}Ga]Ga-**JMV 7489**	246 ± 1 (HT-29 cells, K_d)	53 ± 17 (PC-3 pip cells, K_d)
JMV 438	4.0 (CHO-K1 expressing hNTS1, K_i) [6]	-
[^{68}Ga]Ga-**1**	-	16.5 (IC_{50}, LnCaP cells) [5]
[^{68}Ga]Ga-**JMV 7089**	154.7 ± 13.2 (HT-29 cells, K_d)	-

⇩ DOTA-$(\beta Ala)_2$-JMV438

- ❖ Loss of affinity with respect to the monomers was observed, more evident in NTS1 binding.
- ❖ The NT monomer **JMV 7089** was synthesized using SPPS.
- ❖ **JMV 7089** showed lower affinity towards NTS1 if compared with **JMV 438**.
- ❖ The linker and the DOTA macrocycle are the main responsible for the loss of affinity.
- ❖ The integration of the NT-pharmacophore into the DOTA-β-Ala-β-Ala-NTS1-PSMA heterodimer was quite well tolerated at the NTS1 (1.6-fold decrease in affinity **JMV 7489** *versus* **JMV 7089**).

CONCLUSION AND PERSPECTIVES

- ❖ A hybrid synthetic pathway, which includes both synthesis in batch and solid phase, was successfully employed.
- ❖ The linker and chelating macrocycle play a key role for binding affinity, in particular towards NTS1.
- ❖ These findings could be taken into consideration for future development of NTS1-PSMA radiopharmaceuticals.



- ❖ PSMA affinity: limited impact
- ❖ NTS1 affinity: notable impact

FUNDINGS

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INSTITUT NATIONAL DU CANCER

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[1] Cancer.net., Prostate Cancer: Statistics, https://www.cancer.net/cancer-types/prostate-cancer/statistics; [2] Capasso G. et al., *Eur J Med Chem* **2024**, *263*, 115966; [3] Haffner M.C. et al., *Nat Rev Urol* **2021**, *18*, 79-92; [4] Schollhammer R. et al. *Cancers* **2023,** *15*, 2345; [5] Zha Z. et al., *Nucl Med Biol* **2018**, *59*, 36-47; [6] Previti S. et al., *Front Chem* **2020**, *8*, 406.