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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

NOVEL PEPTIDES AS AGONISTS/ANTAGONISTS OF FPR2 FOR THE TREATMENT OF INTESTINAL DISEASE

VITALITY

Università degli Studi di Urbino
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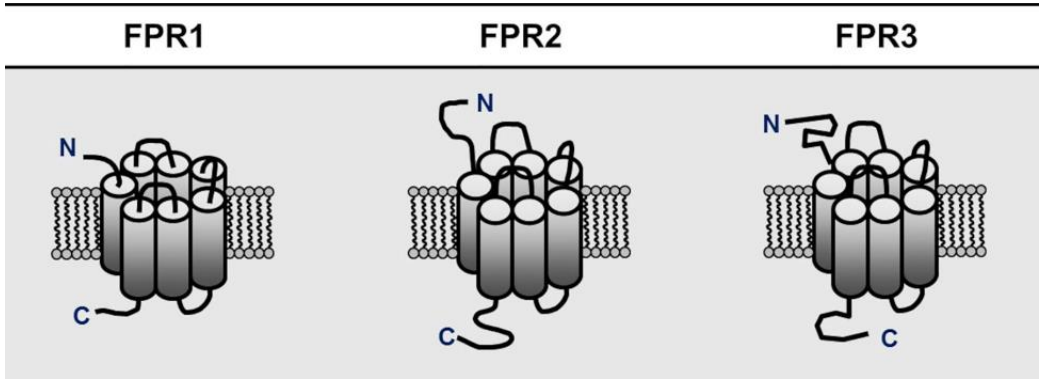
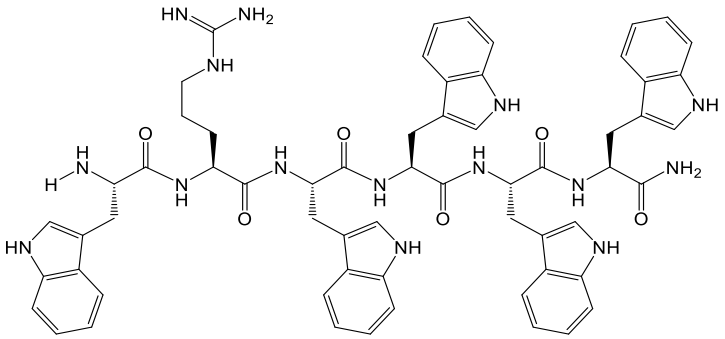
Receptors FPR

- G protein-coupled receptor
- 3 isoforms: FPR1, FPR2, FPR3
- Are involved in chemotaxis ⟶ infection and inflammation
- Inflammatory bowel disease, including ulcerative colitis and Crohn's disease
- Mediating inflammatory response

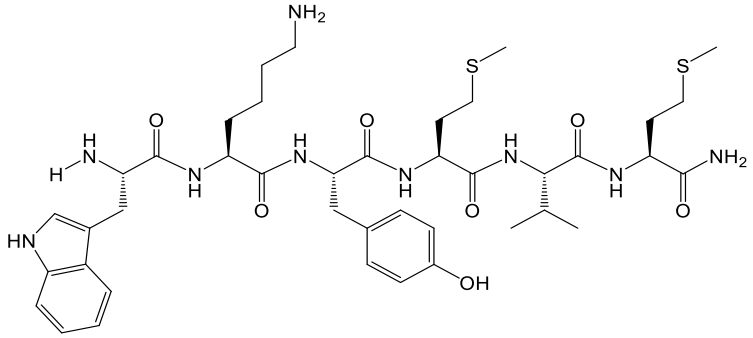


Antagonist: WRWWWW (AMGS3)



Inhibits only binding between agonist and FPR2

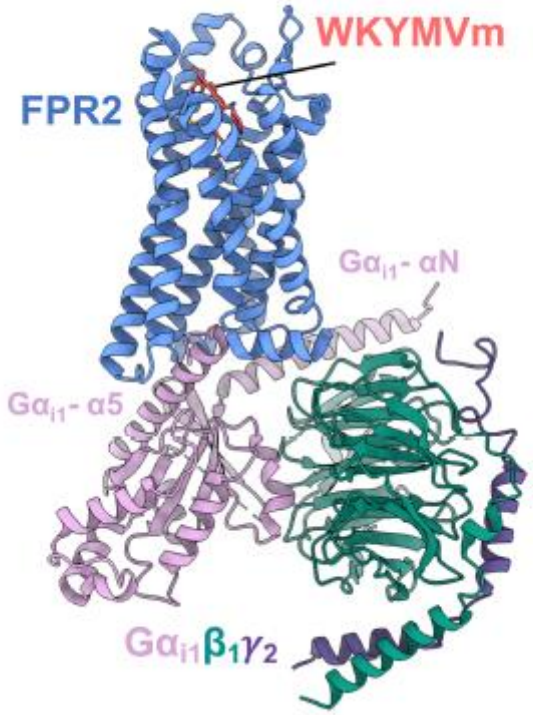
Agonist: WKYMVm (AMGS10)

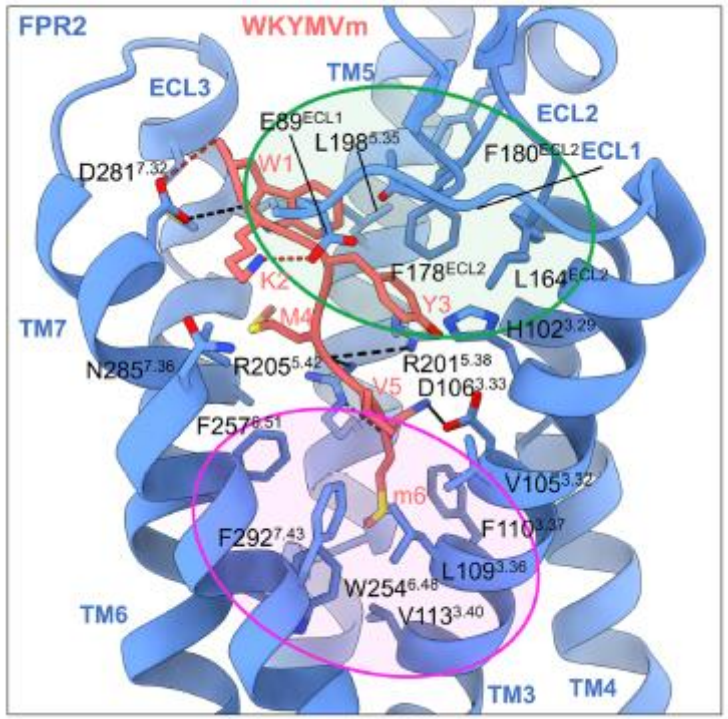


- ✓ Binds FPR1 and FPR2
- ✓ Stimulates phagocyte activity
- ✓ Promotes proliferation
- ✓ Inhibits intestinal permeability

[Mormile, Rossi, Prevete , Granata, Pucino, De Paulis "The N-Formyl Peptide Receptors and Rheumatoid Arthritis: A Dangerous Liaison or Confusing Relationship?"]

Receptor FPR2

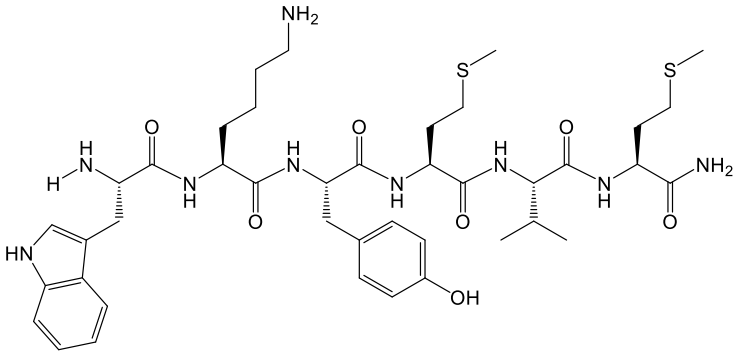




Two hydrophobic clusters:

- **At the top** → **W1 and Y3**
- **At the base** → **V5 and D-Met6**

Agonist AMGS10

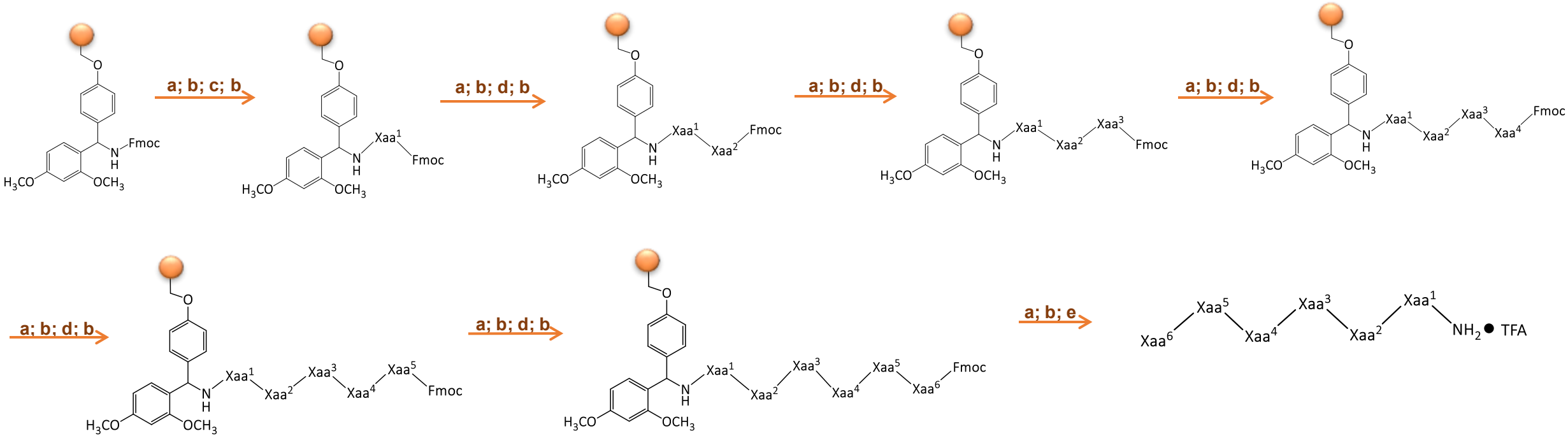


W K Y M V m

- Hydrophobic interactions
- Polar interactions
- Hydrogen bonds
- Salt bridges
- Van der Waals

[Cheng Xue Qin, Lucy V. Norling, Elizabeth A. Vecchio, Eoin P. Brennan, Lauren T. May, Denise Wootten, Catherine Godson, Mauro Perretti, Rebecca H. Ritchie "Formylpeptide receptor 2: Nomenclature, structure, signalling and translational perspectives: IUPHAR review 35"]

Synthesis SPPS

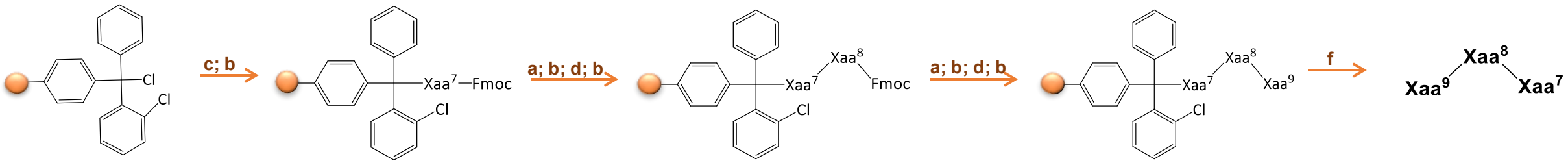


Reagents and conditions:

a) Piperidine 20% DMF;
b) Wash: DMF x3, MeOH x 3, DCM x3;
c) Xaa1 (3 eq.), HOBt (3 eq.), DIPEA (6 eq.), TBTU (3 eq.), DMF (6mL), overnight r.t.;
d) Coupling aminoacid (3 eq.), HOBt (3 eq.), DIPEA (6 eq.), TBTU (3 eq.), DMF (6mL), 2h r.t.;
e) TFA:H_2O:TIPS (95:2.5:2.5), 3h r.t.

PRODUCT	Xaa^1	Xaa^2	Xaa^3	Xaa^4	Xaa^5	Xaa^6
AMGS1	D-Met	L-Trp-(Boc)	L-Met	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS2	L-Met	L-Trp-(Boc)	L-Met	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS3	L-Trp-(Boc)	L-Trp-(Boc)	L-Trp-(Boc)	L-Trp-(Boc)	L-Arg-(Pbf)	L-Trp-(Boc)
AMGS4	D-Met	L-Trp-(Boc)	L-Met	L-Tyr-(tBut)	L-Lys-(Boc)	L-Tyr-(tBut)
AMGS5	L-Trp-(Boc)	L-Lys-(Boc)	L-Tyr-(tBut)	L-Met	L-Leu	For-Met
AMGS6	L-Trp-(Boc)	L-Lys-(Boc)	L-Tyr-(tBut)	L-Met	L-Val	For-Met
AMGS9	D-Met	L-Leu	L-Met	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS10	D-Met	L-Val	L-Met	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS11	D-Met	L-Leu	L-Phe	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS12	D-Met	L-Val	L-Phe	L-Tyr-(tBut)	L-Lys-(Boc)	L-Trp-(Boc)
AMGS13	L-Trp-(Boc)	L-Lys-(Boc)	L-Tyr-(tBut)	L-Phe	L-Leu	For-Met
AMGS14	L-Trp-(Boc)	L-Lys-(Boc)	L-Tyr-(tBut)	L-Phe	L-Val	For-Met

Synthesis SPPS



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d) Coupling aminoacid (3 eq.), HOBt (3 eq.), DIPEA (6 eq.), TBTU (3 eq.), DMF (6mL), 2h r.t.;
f) 1% TFA/DCM

PRODUCT	Xaa^7	Xaa^8	Xaa^9
AMGS7	L-Phe	L-Leu	For-Met
AMGS8	L-Phe	L-Leu	Boc-Met

Analyses and purification

Semipreparative HPLC

Mass spectrometer

H-NMR

- Yields 30%-50%
- Purity ≥95%

BIOLOGICAL TESTS


Thank you
for your attention