

Badania *in silico* struktury wybranych białek błonowych oraz specyfiki ich oddziaływania z biomolekułami tworzącymi z nimi kompleksy o potencjale terapeutycznym

Magdalena J. Ślusarz

Publikacje wchodzące w skład osiągnięcia:

- H1.** Ślusarz MJ Sikorska E, Ślusarz R, Ciarkowski J. Molecular docking-based study of vasopressin analogues modified at positions 2 and 3 with N-methylphenylalanine: Influence on receptor-bound conformations and interactions with vasopressin and oxytocin receptors, *Journal of Medicinal Chemistry*, 2006, 49, 2463–2469. IF = 5,115
- H2.** Ślusarz R., Sikorska E., Ślusarz M.J., Theoretical study on interactions of bicyclic vasopressin analogues with human neurohypophyseal hormone receptors, *QSAR & Combinatorial Science*, 2008, 27, 834-840. IF = 2,594
- H3.** Ślusarz R., Ślusarz M.J., An influence of the aromatic side chains conformations in positions 2 and 3 of vasopressin analogs on interactions with vasopressin and oxytocin receptors, *QSAR & Combinatorial Science*, 2009, 28, 1166-1175. IF = 3,027
- H4.** Ślusarz MJ.: Molecular modeling study of the opioid receptor interactions with series of cyclic deltorphin analogues, *Journal of Peptide Science*, 2011, 17, 554-564. IF = 1,799
- H5.** Ślusarz MJ, Sikorska E., Ślusarz R.: Interactions of vasopressin and oxytocin receptors with vasopressin analogues substituted in position 2 with 3,3'-diphenylalanine - a molecular docking study, *Journal of Peptide Science*, 2013, 19, 118-126. IF = 1,862
- H6.** Karska N., Graul M., Sikorska E., Zhukov I., Ślusarz MJ., Kasprzykowski F., Lipińska A., Rodziewicz-Motowidło S.: Structure determination of UL49.5 transmembrane protein from bovine herpesvirus 1 by NMR spectroscopy and molecular dynamics, *Biochimica et Biophysica Acta - Biomembranes*, 2019, 1861, 926-938. IF = 3,411
- H7.** Karska N., Graul M., Sikorska E., Ślusarz MJ., Zhukov I., Kasprzykowski F., Kubiś A., Lipińska A., Rodziewicz-Motowidło S.: Investigation of the effects of primary structure modifications within the RRE motif on the conformation of synthetic bovine herpesvirus 1-encoded UL49.5 protein fragments, *Chemistry & Biodiversity*, 2021, 18, e2000883. IF = 2,745
- H8.** Ślusarz MJ., Molecular insights into the mechanism of the sugar-modified enkephalin binding to the opioid receptors, *Computational Biology and Chemistry*, 2022, 101, 107783. IF = 3,100
- H9.** Ślusarz MJ, How kelch domain-containing protein 3 distinguishes between the C-end degon of bovine viral protein UL49.5 and its mutants – insights from a molecular dynamics, *Bioorganic and Medicinal Chemistry*, 2024, 109, 117795. IF = 3,300
- H10.** Ślusarz MJ, Ślusarz MJ., Lipińska AD. An intrinsic network of polar interactions is responsible for binding of UL49.5 C-degron by the CRL2KLHDC3 ubiquitin ligase, *Proteins: Structure, Function and Bioinformatics*, 2024, 92, 610-622. IF = 3,200
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Badane białka błonowe

RECEPTORY WAZOPRESYNY I OKSYTOCYNY
V1aR, V2R, OTR

RECEPTORY OPIOIDOWE
MOR (μ), DOR (δ)

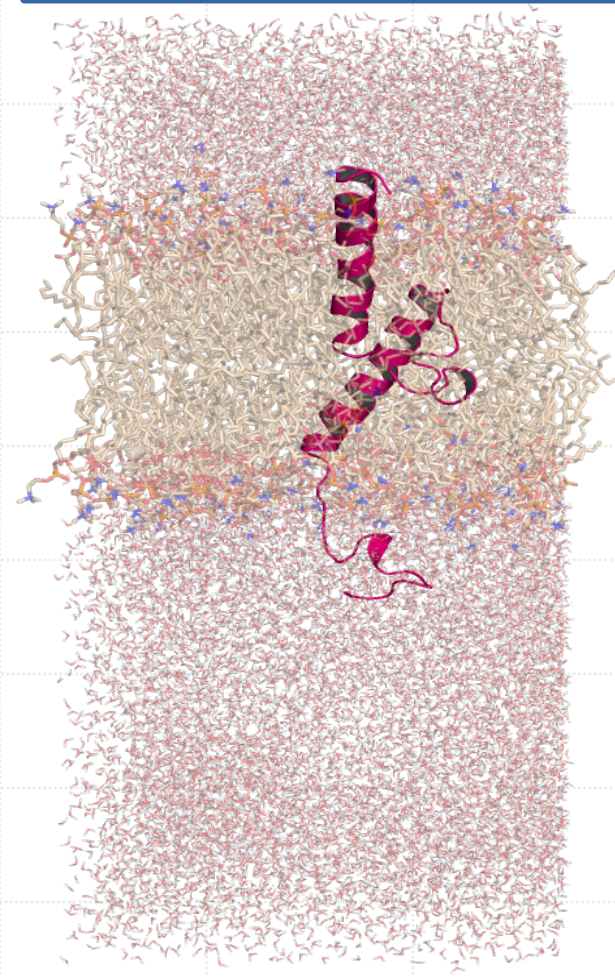
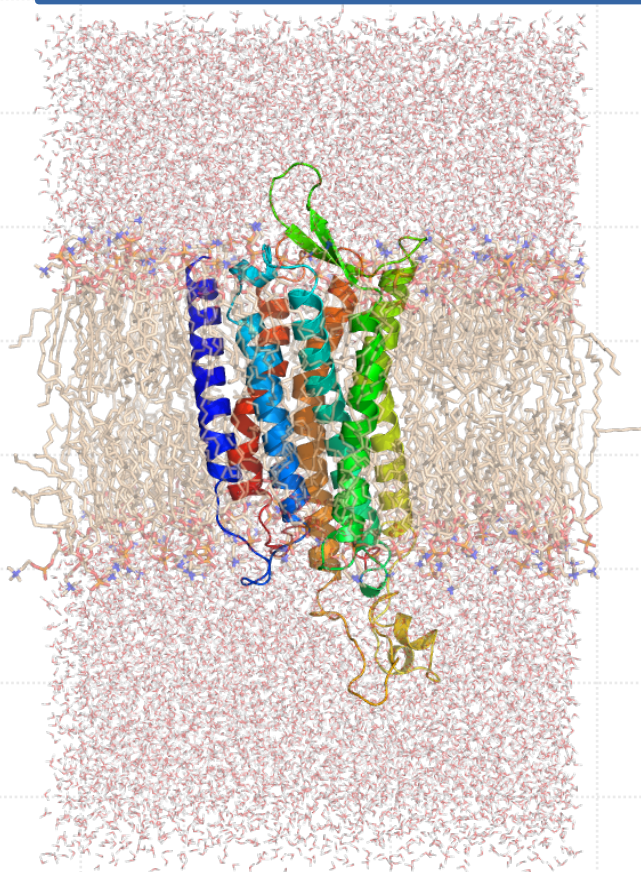
BIAŁKO UL49.5

H1–H5, H8

Receptory sprzężone
z białkiem G (GPCR)

H6–H7, H9–H10

Białko wirusowe



Przedmiot badań

RECEPTORY WAZOPRESYNY I OKSYTOCYNY V1aR, V2R, OTR

[D-MePhe^{2,3}]AVP
[D-MePhe²,MePhe³]AVP
[MePhe²,D-MePhe³]AVP
[MePhe^{2,3}]AVP
c-(4-9)-[Mpa¹, Lys⁴]AVP
c-(4-9)-[Mpa¹, Orn⁴]AVP
c-(4-9)-[Mpa¹, Dab⁴]AVP
c-(4-9)-[Mpa¹, Dap⁴]AVP
[Mpa¹,Dpa²,Val⁴,D-Arg⁸]VP
[Mpa¹,D-Dpa²,Val⁴,D-Arg⁸]VP
[D-Dpa²,D-Arg⁸]VP
[Mpa¹,D-Dpa²,D-Arg⁸]VP

[Aic²]AVP
[Mpa¹,Aic²]AVP
[Aic²,D-Arg⁸]VP
[Mpa¹,Aic²,D-Arg⁸]VP
[Aic²,Val⁴]AVP
[Mpa¹,Aic²,Val⁴,D-Arg⁸]VP
[Aic³]AVP
[Mpa¹,Aic³]AVP
[Aic³,D-Arg⁸]VP

RECEPTORY OPIOIDOWE MOR (μ), DOR (δ)

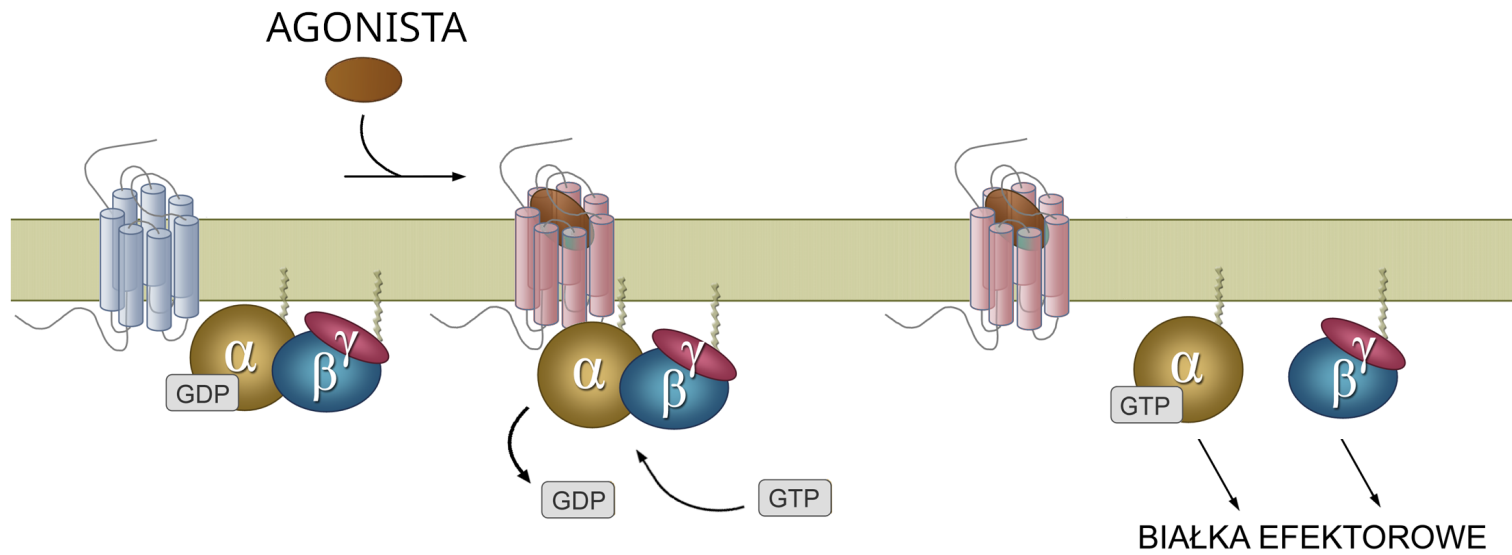
c-(2-4)-Tyr¹-Lys²-Phe³-Dab⁴-Val⁵-Val⁶-Gly⁷-NH₂ Leu⁵-ENK
c-(2-4)-Tyr¹-Lys²-Phe³-Dap⁴-Val⁵-Val⁶-Gly⁷-NH₂ Leu⁵-ENK-GlcA
c-(2-4)-Tyr¹-Orn²-Phe³-Dap⁴-Val⁵-Val⁶-Gly⁷-NH₂
c-(2-4)-Tyr¹-Lys²-Phe³-Orn⁴-Val⁵-Val⁶-Gly⁷-NH₂
c-(2-4)-Tyr¹-D-Orn²-Phe³-Orn⁴-Val⁵-Val⁶-Gly⁷-NH₂
c-(2-4)-Tyr¹-Lys²-Phe³-Dab⁴-NH₂
c-(2-4)-Tyr¹-Lys²-Phe³-Dap⁴-NH₂
c-(2-4)-Tyr¹-Orn²-Phe³-Dap⁴-NH₂
c-(2-4)-Tyr¹-Lys²-Phe³-Orn⁴-NH₂
c-(2-4)-Tyr¹-D-Orn²-Phe³-Orn⁴-NH₂

BIAŁKO UL49.5

MUTANTY: E11G, RRE(9-11)GGG, RRE(9-11)AAA, R95K, R93K, R96D

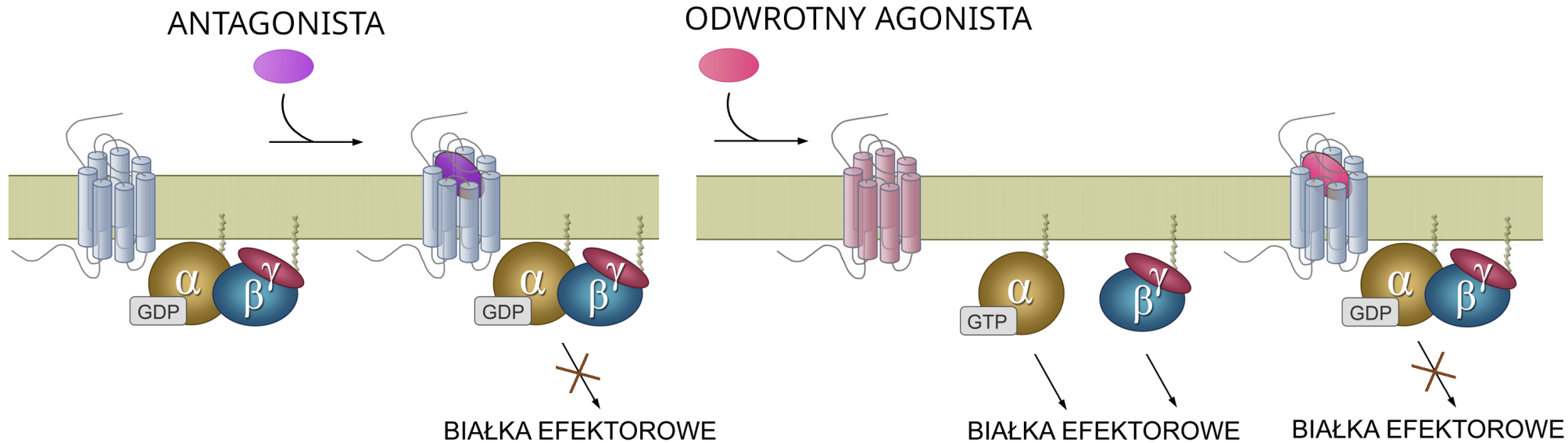
KLHDC3

Receptory sprzężone z białkiem G (GPCR)



V1aR → presyjne
V2R → antydiuretyczne
OTR → tokolityczne; galaktokinetyczne

MOR (μ) → analgetyczne
DOR (δ) → analgetyczne



Receptory sprzężone z białkiem G (GPCR) → potencjał terapeutyczny

V2R

- moczówka prosta ośrodkowa
- moczenie nocne
- zespół Schwartz-Bartera
- moczówka prosta nerkowa (AVPR2)

V1aR

- zespół wątrobowo nerkowy
- silne krwawienia

OTR

- wywoływanie/hamowanie akcji porodowej
- niedorozwój mięśnia sercowego

MOR (μ) DOR (δ)

- umiarkowany i silny ból
- kaszel

Efekty uboczne:

- tolerancja
- uzależnienie
- zaburzenia oddychania
- nudności
- wymioty
- zaparcia

**EPIDEMIA
OPIOIDOWA**

H1

Receptory wazopresyny i oksytocyny

[D-MePhe^{2,3}]AVP

[D-MePhe²,MePhe³]AVP

[MePhe²,D-MePhe³]AVP

[MePhe^{2,3}]AVP

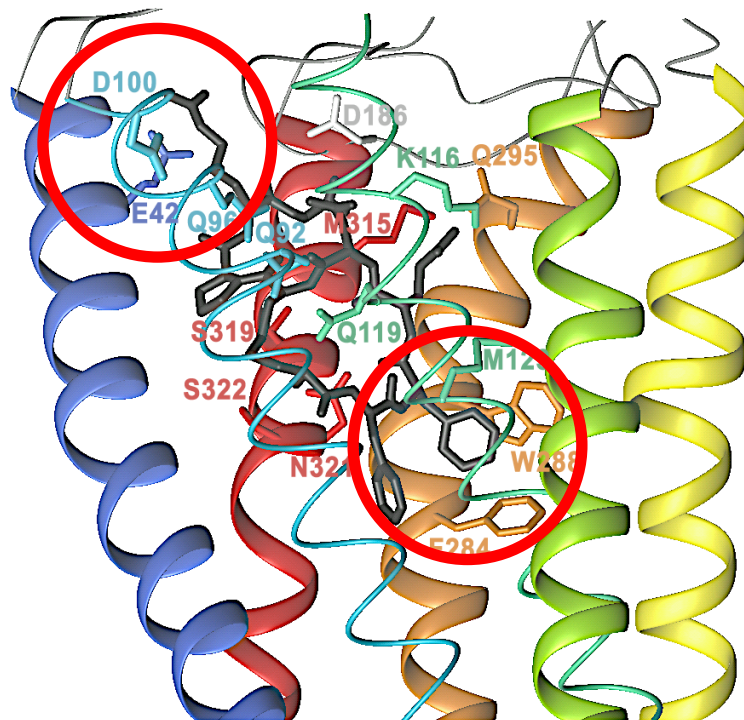
N-metylo-L/D-fenylalanina

DZIAŁANIE ANTAGONISTYCZNE

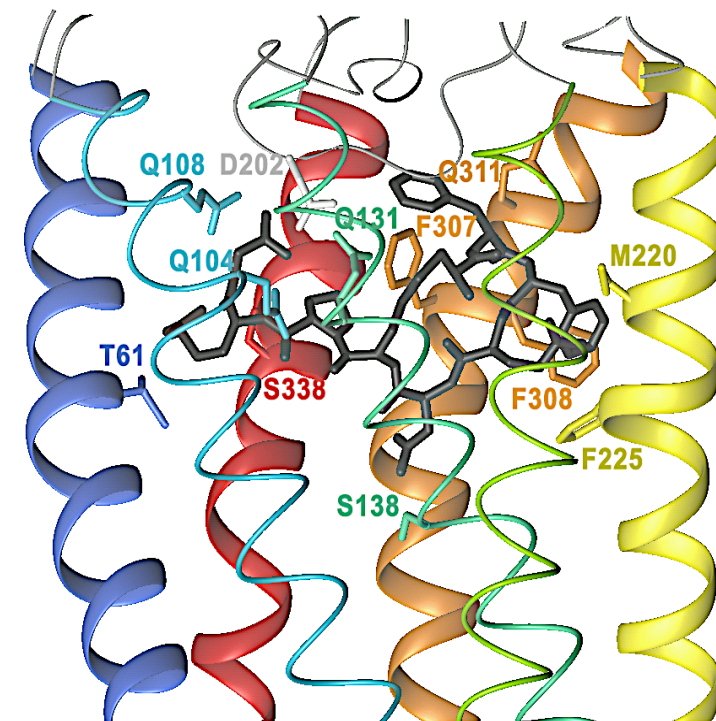
Słabe oddziaływanie z V2 → (D/K2.65)

Oddziaływanie z TM6 → krytyczne

LIGAND / pA ₂	OTR	V1aR	V2R
[D-MePhe ^{2,3}]AVP	6.4	0	0
[D-MePhe ² ,MePhe ³]AVP	6.6	¹ 5.8	0
[MePhe ² ,D-MePhe ³]AVP	0	0	0
[MePhe ^{2,3}]AVP	0	0	0



OTR - [D-MePhe²,MePhe³]AVP



V1aR - [D-MePhe^{2,3}]AVP

H2

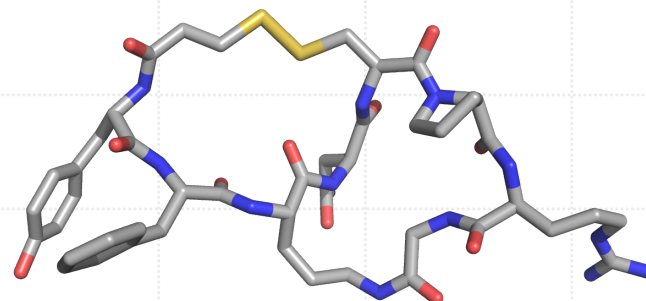
Receptory wazopresyny i oksytocyny

c-(4-9)-[Mpa¹, Lys⁴]AVP

c-(4-9)-[Mpa¹, Orn⁴]AVP

c-(4-9)-[Mpa¹, Dab⁴]AVP

c-(4-9)-[Mpa¹, Dap⁴]AVP

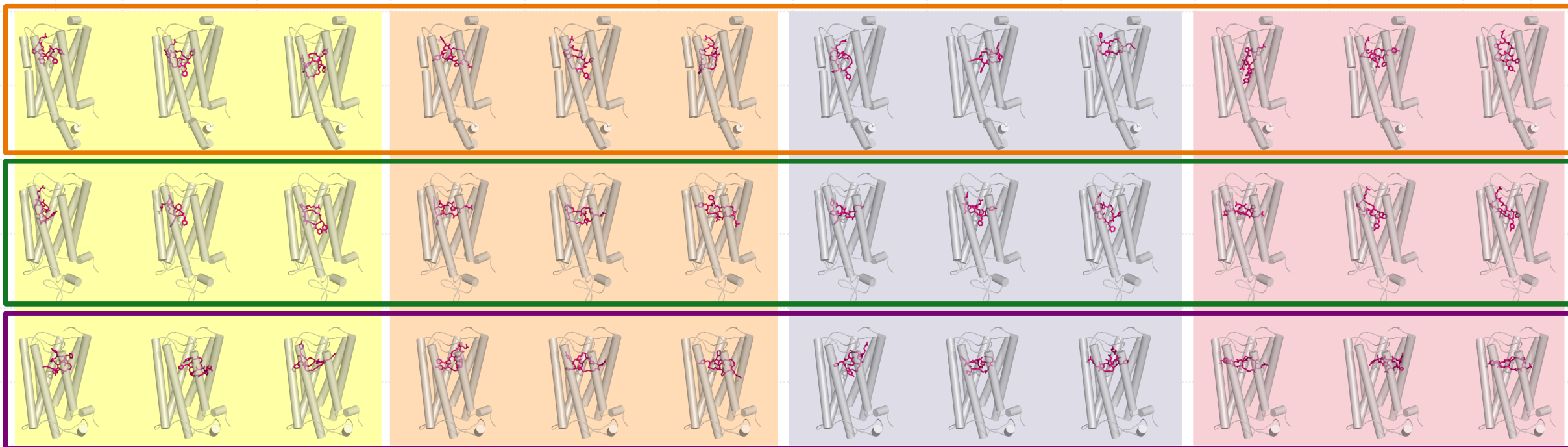


Brak ważnych oddziaływań kotwiczących

Brak preferencji ułożenia w kieszeni receptora, orientacja ↓

Analog 2 – wielkość pierścienia akceptowalna → modyfikacje

cyklizacja 4-9



c-(4-9)-[Mpa¹, Lys⁴]AVP

c-(4-9)-[Mpa¹, Orn⁴]AVP

c-(4-9)-[Mpa¹, Dab⁴]AVP

c-(4-9)-[Mpa¹, Dap⁴]AVP

Receptory wazopresyny i oksytocyny

[Aic²]AVP

[Mpa¹,Aic²]AVP

[Aic²,D-Arg⁸]VP

[Mpa¹,Aic²,D-Arg⁸]VP

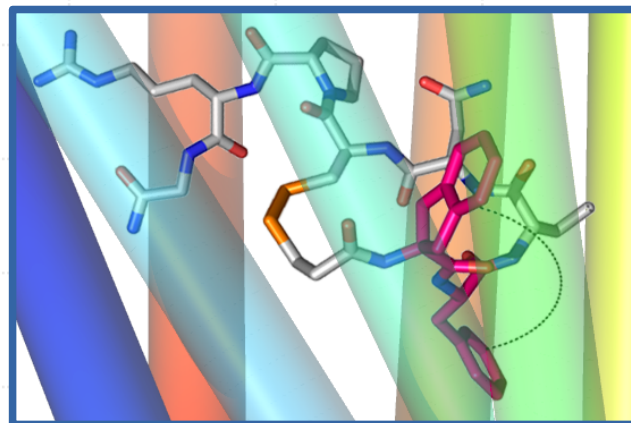
[Aic²,Val⁴]AVP

[Mpa¹,Aic²,Val⁴,D-Arg⁸]VP

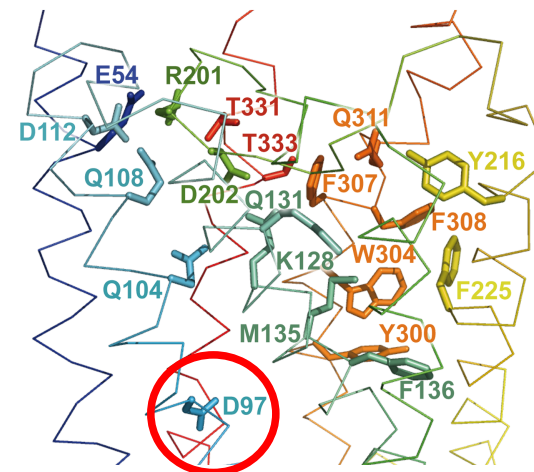
Aic³]AVP

[Mpa¹,Aic³]AVP

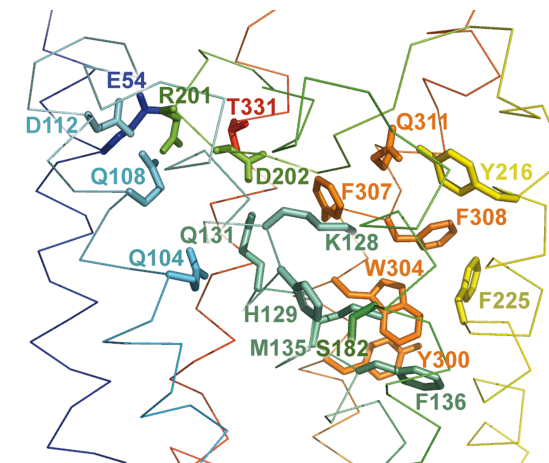
[Aic³,D-Arg⁸]VP



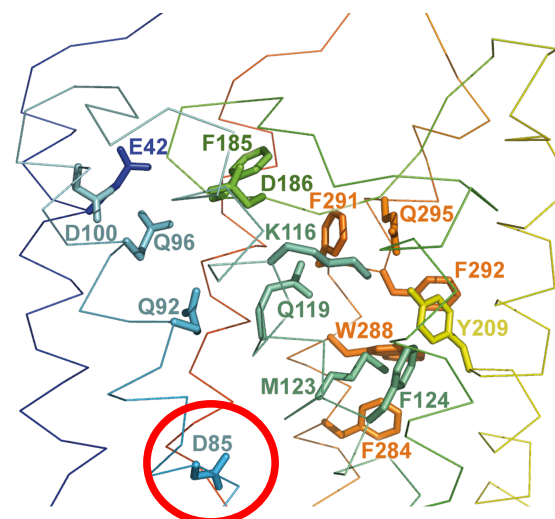
V1aR - antagonista



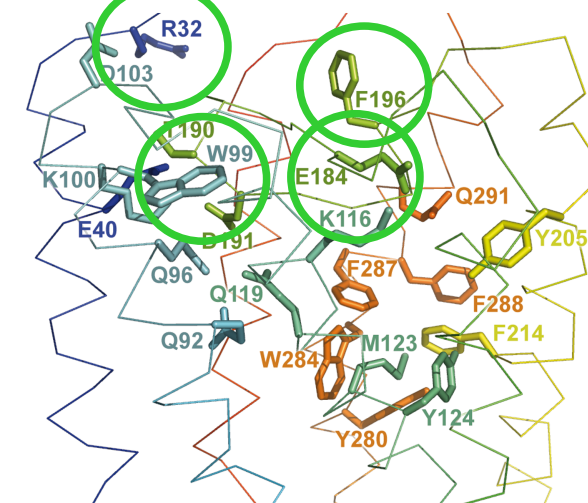
V1aR - agonista



OTR - antagonista



V2R - agonista



kwas 2-aminoindano-2-karboksylowy

DZIAŁANIE ANTAGONISTYCZNE/AGONISTYCZNE

Utrata aktywności po podstawieniu Aic w pozycji 3

analogue	oxytotic	pressor	antidiuretic
AVP	17	412	465
[Aic ²]AVP	pA ₂ = 7.27 ± 0.22	9.4 ± 2.8	~450 (45 000)
[Mpa ¹ ,Aic ²]AVP	pA ₂ = 7.50 ± 0.16	5.3 ± 2.5	~450 (45 000)
[Aic ² ,D-Arg ⁸]VP	pA ₂ = 6.86 ± 0.17	0	~45 (4500)
[Mpa ¹ ,Aic ² ,D-Arg ⁸]VP	pA ₂ = 7.31 ± 0.25	pA ₂ = 5.60	~450 (45 000)
[Aic ² ,Val ⁴]AVP	pA ₂ = 7.93 ± 0.17	0	~450 (45 000)
[Mpa ¹ ,Aic ² ,Val ⁴ ,D-Arg ⁸]VP	pA ₂ = 8.06 ± 0.11	pA ₂ = 6.25	~4500 (450 000)

[Mpa¹,Dpa²,Val⁴,D-Arg⁸]VP

[Mpa¹,D-Dpa²,Val⁴,D-Arg⁸]VP

[D-Dpa²,D-Arg⁸]VP

[Mpa¹,D-Dpa²,D-Arg⁸]VP

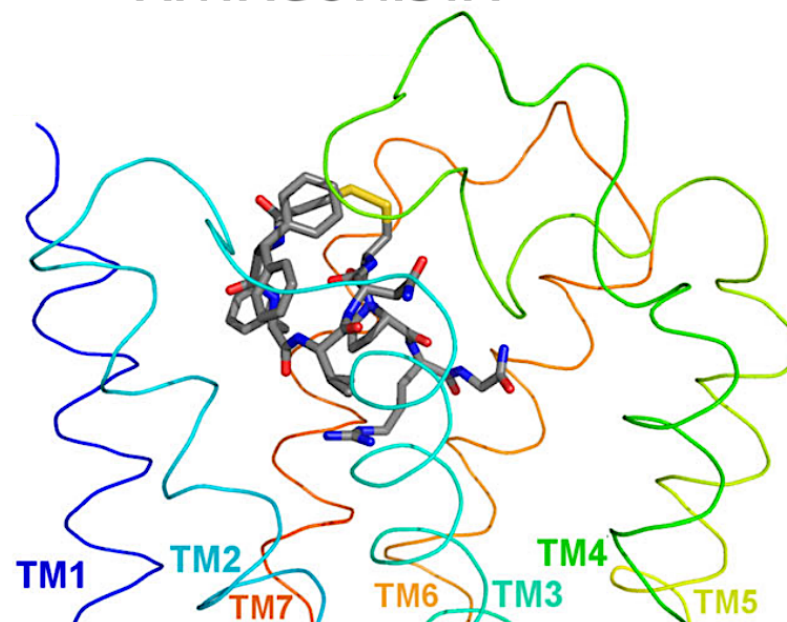
L/D-difenyloalanina

DZIAŁANIE ANTAGONISTYCZNE
/AGONISTYCZNE

V1aR – brak aktywności

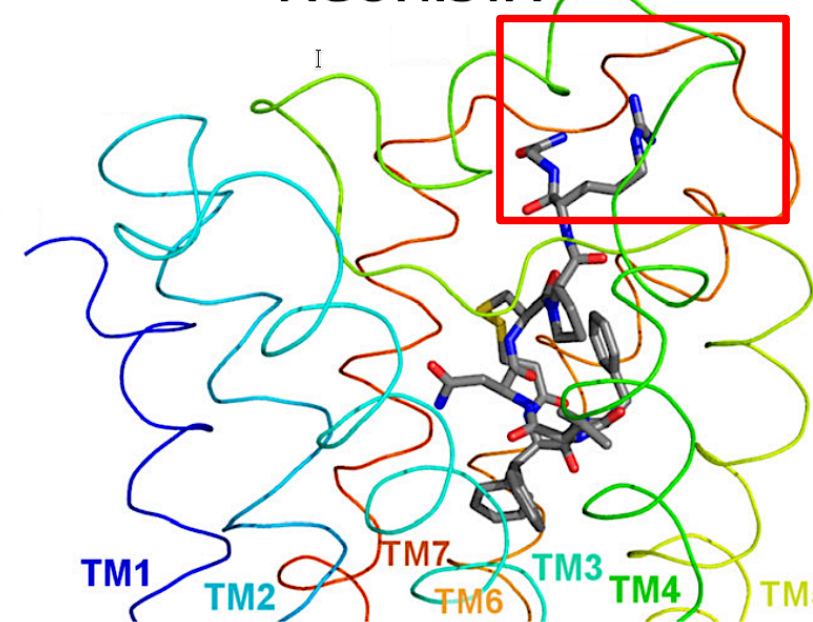
	OTR [pA ₂]	V1aR [pA ₂]	V2R (IU/mg)
[Mpa ¹ ,Dpa ² ,Val ⁴ ,D-Arg ⁸]VP (I)	0.24 ± 0.12	0	100
[Mpa ¹ ,D-Dpa ² ,Val ⁴ ,D-Arg ⁸]VP (II)	7.78 ± 0.08	<5.8	9000
[D-Dpa ² ,D-Arg ⁸]VP (III)	7.83 ± 0.08	0	1000
[Mpa ¹ ,D-Dpa ²]VP (IV)	7.80 ± 0.14	0	4500
AVP	17	412	450

ANTAGONISTA

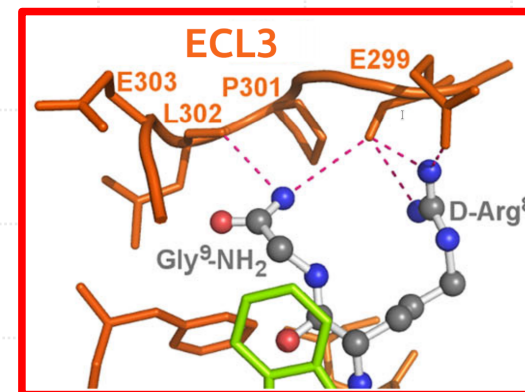


OTR - [Mpa¹,D-Dpa²,Val⁴,D-Arg⁸]VP

AGONISTA



V2R - [Mpa¹,D-Dpa²,Val⁴,D-Arg⁸]VP



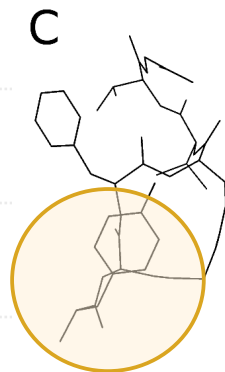
H4

Receptory opioidowe

- c-(2-4)-Tyr¹-Lys²-Phe³-Dab⁴-Val⁵-Val⁶-Gly⁷-NH₂
- c-(2-4)-Tyr¹-Lys²-Phe³-Dap⁴-Val⁵-Val⁶-Gly⁷-NH₂
- c-(2-4)-Tyr¹-Orn²-Phe³-Dap⁴-Val⁵-Val⁶-Gly⁷-NH₂
- c-(2-4)-Tyr¹-Lys²-Phe³-Orn⁴-Val⁵-Val⁶-Gly⁷-NH₂
- c-(2-4)-Tyr¹-D-Orn²-Phe³-Orn⁴-Val⁵-Val⁶-Gly⁷-NH₂
- c-(2-4)-Tyr¹-Lys²-Phe³-Dab⁴-NH₂
- c-(2-4)-Tyr¹-Lys²-Phe³-Dap⁴-NH₂
- c-(2-4)-Tyr¹-Orn²-Phe³-Dap⁴-NH₂
- c-(2-4)-Tyr¹-Lys²-Phe³-Orn⁴-NH₂
- c-(2-4)-Tyr¹-D-Orn²-Phe³-Orn⁴-NH₂

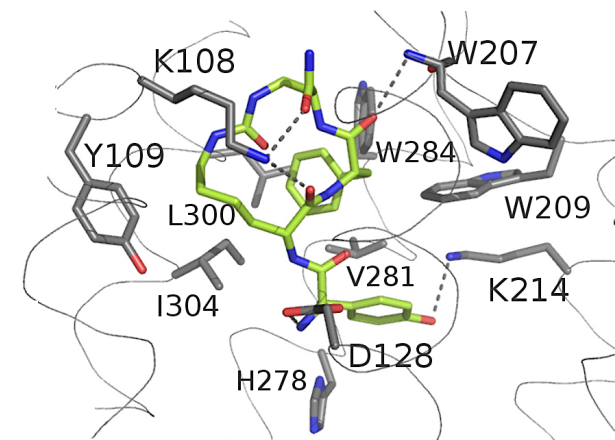
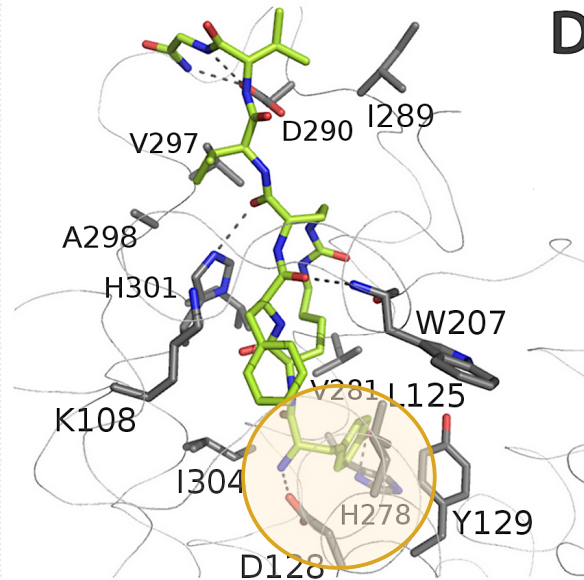
deltorfina: Tyr-D-Ala-Phe-Asp/Glu-Val-Val-Gly-NH₂

Ligand	Daa ²	Daa ⁴	GPI IC ₅₀ (nM)	MVD IC ₅₀ (nM)	GPI/MVD ratio
A	Lys	Dab	65.4 ± 9.6	0.640 ± 0.043	102
B	Lys	Dap	25.4 ± 2.0	0.483 ± 0.065	52.6
C	Orn	Dap	>10,000	27.1 ± 3.1	>369
D	Lys	Orn	>10,000	67.0 ± 6.9	>149
E	Orn	Orn	159 ± 23	0.814 ± 0.054	88
a	Lys	Dab	1.17 ± 0.25	5.02 ± 1.39	4.29
b	Lys	Dap	4.15 ± 0.36	19.5 ± 2.3	4.70
c	Orn	Dap	3.37 ± 0.09	7.76 ± 1.27	2.30
d	Lys	Orn	15.6 ± 1.6	47.1 ± 3.5	3.01
e	Orn	Orn	4.77 ± 0.71	11.4 ± 1.5	2.39
[Leu ⁵]enk			246 ± 39	11.4 ± 1.1	21.4

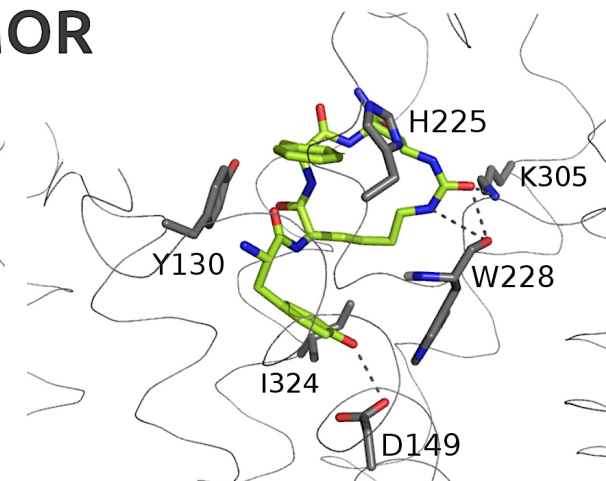
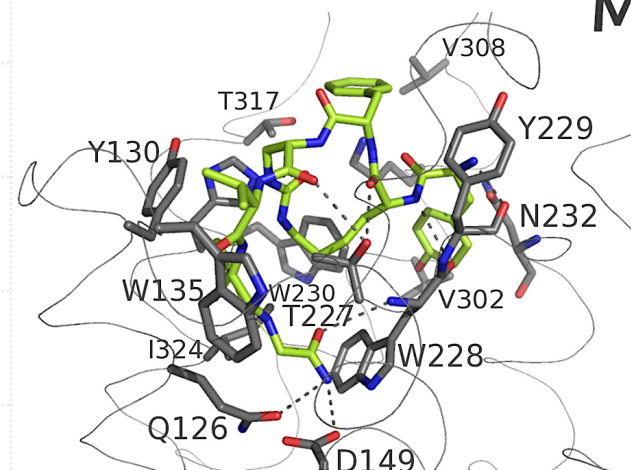


D3.32

DOR



MOR



HEPTA-

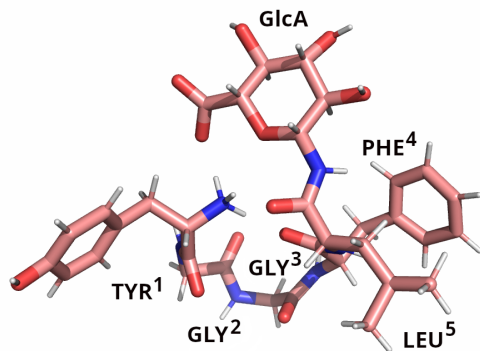
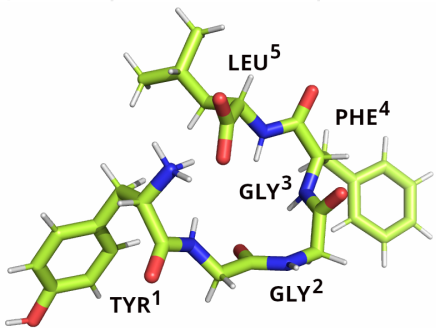
TETRA-

H8

Leu⁵-ENK

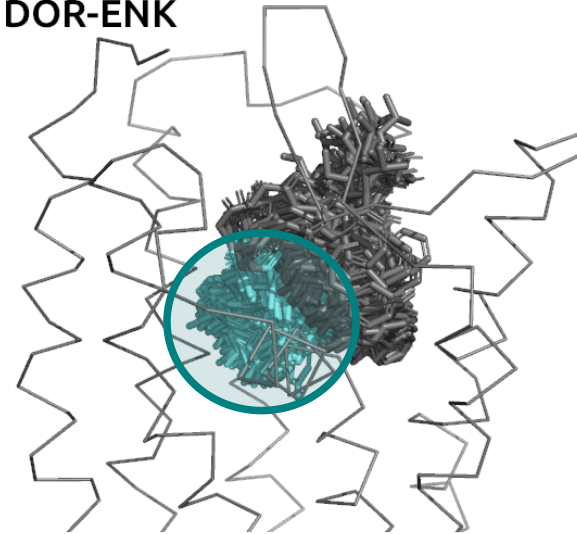
Leu⁵-ENK-GlcA

kwasy β-D-glukuronowe

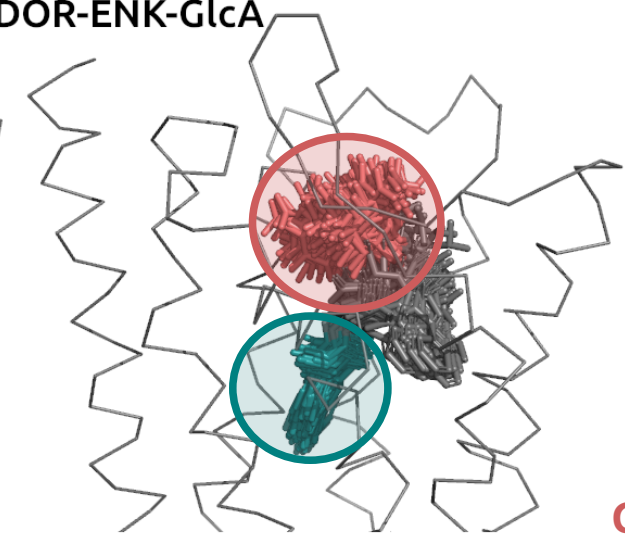


Receptory opioidowe

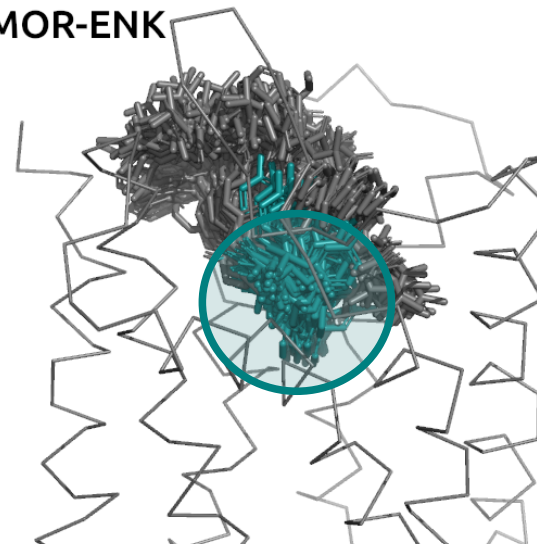
DOR-ENK



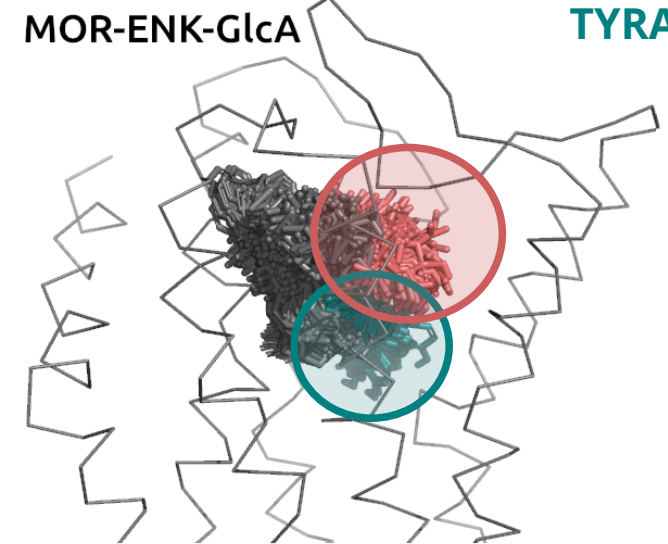
DOR-ENK-GlcA



MOR-ENK



MOR-ENK-GlcA



Testy GPI I MVD:

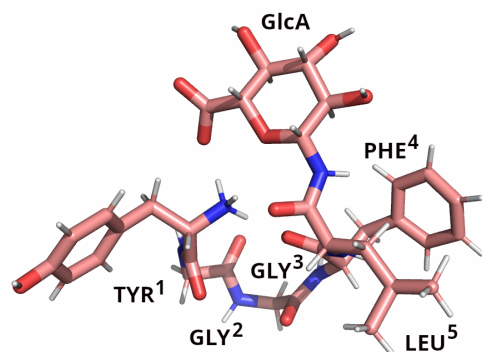
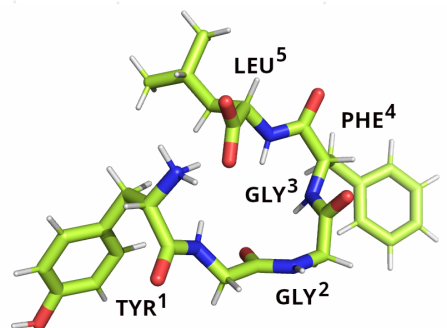
Leu⁵-ENK-GlcA 40 razy bardziej aktywny niż Leu5-ENK; ↑ selektywność

H8

Leu⁵-ENK

Leu⁵-ENK-GlcA

kwask β-D-glukuronowy

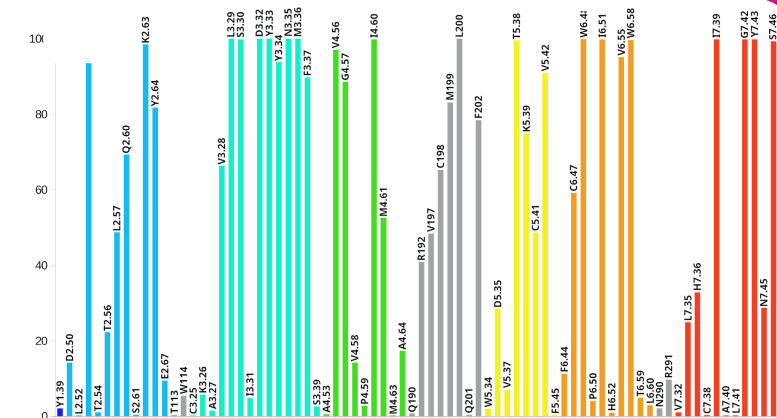
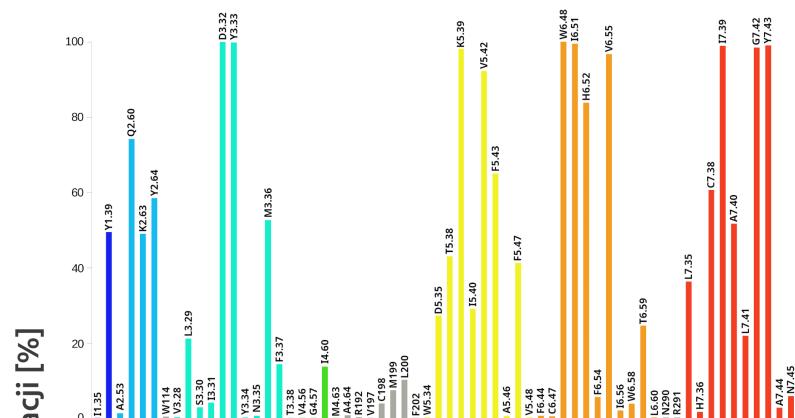


Receptory opioidowe

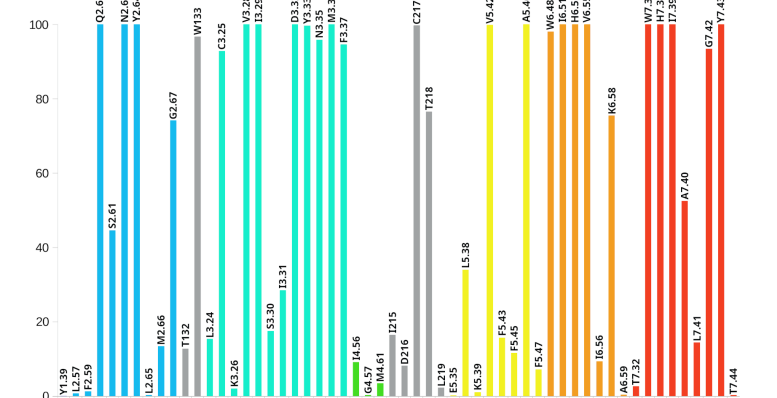
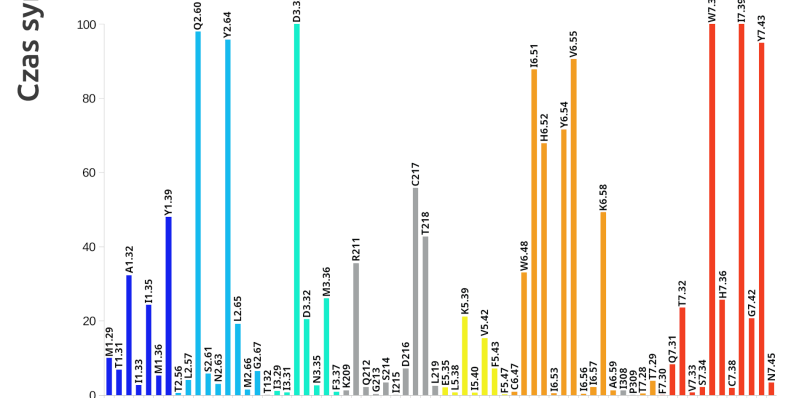
Leu⁵-ENK

Leu⁵-ENK-GlcA

DOR



MOR



Reszty aminokwasowe receptora

Testy GPI I MVD:

Leu⁵-ENK-GlcA 40 razy bardziej aktywny niż Leu⁵-ENK; ↑ selektywność

H8

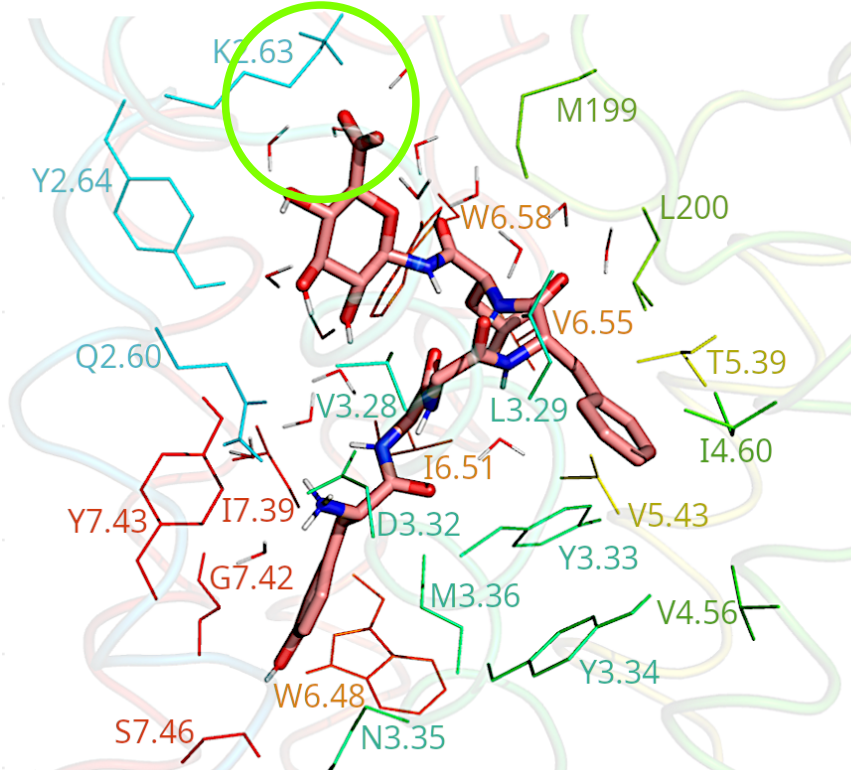
Leu⁵-ENK

Leu⁵-ENK-GlcA

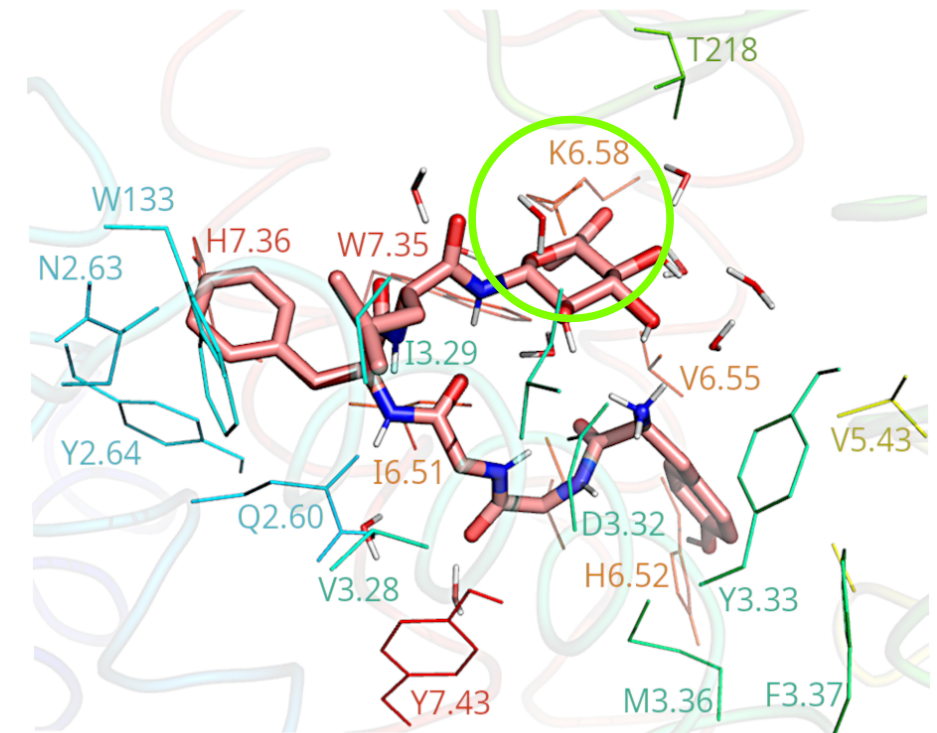
kwasy β-D-glukuronowe

Receptory opioidowe

DOR



MOR



DLACZEGO WYŻSZA SELEKTYWNOŚĆ ENK-GlcA:

K2.63/N2.63 vs W6.58/K6.58

Testy GPI I MVD:

Leu⁵-ENK-GlcA 40 razy bardziej aktywny niż Leu⁵-ENK; ↑ selektywność

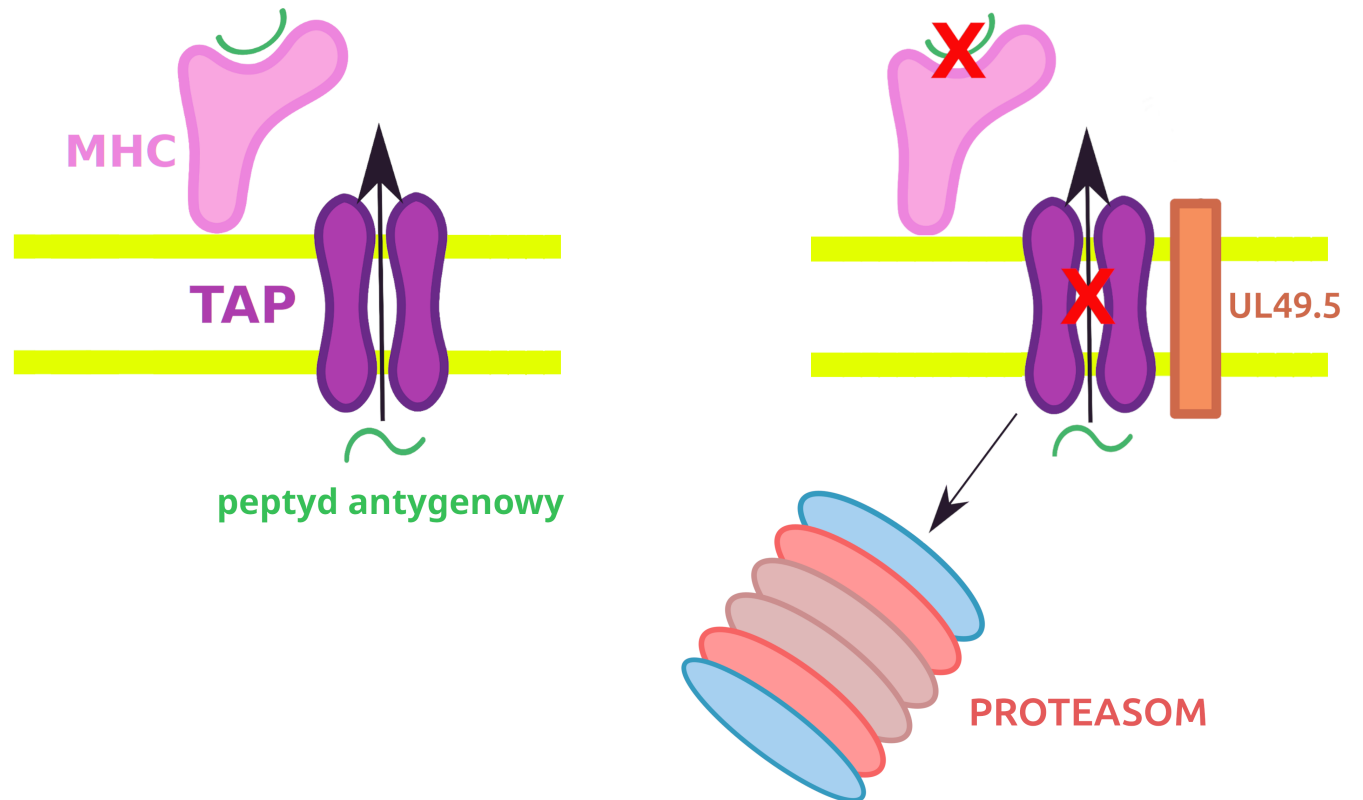
Białko UL49.5

- białko BoHV-1 → wirusy z rodzaju *Varicellovirus* (*Alphaherpesviridae*)
- 96 reszt aminokwasowych, jednohelikalne, transbłonowe
- brak struktur eksperymentalnych

INHIBICJA TAP
DEGRADACJA TAP

POTENCJAŁ TERAPEUTYCZNY:

- LEKI PRZECIWWIRUSOWE
- LEKI PRZECIWNOWOTWOROWE
- PROTAC



H6 H7

UL49.5 wt

E11G

RRE(9-11)GGG

RRE(9-11)AAA

SYNTEZA PEPTYDÓW

BADANIA STRUKTURALNE PEPTYDÓW: NMR, CD

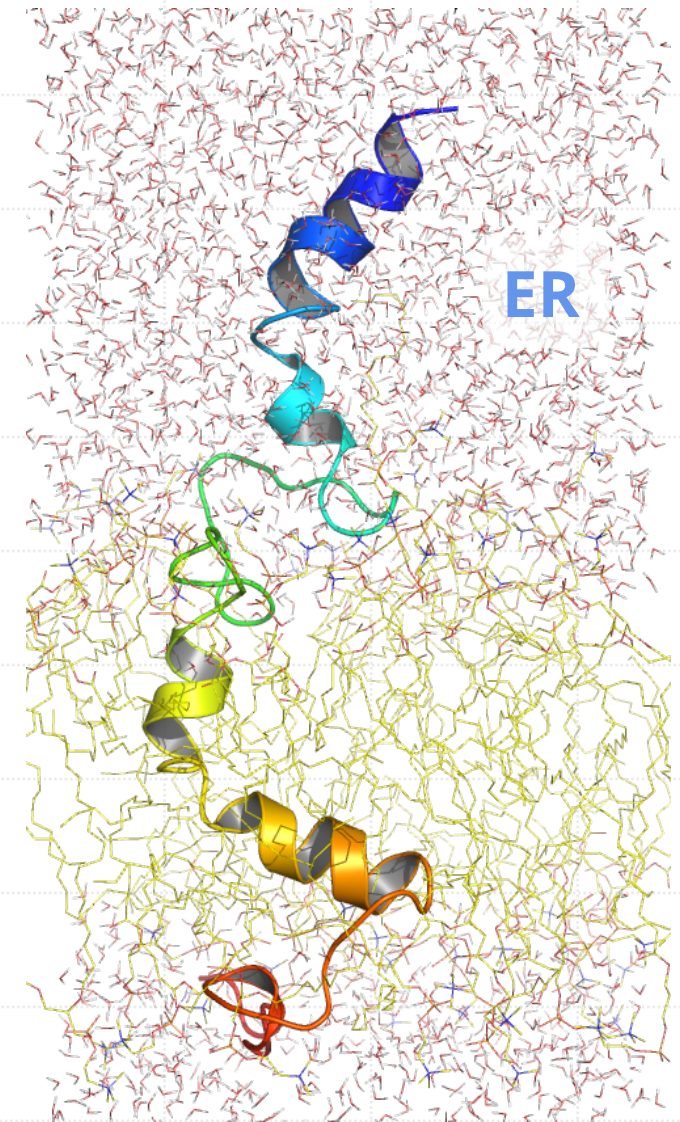
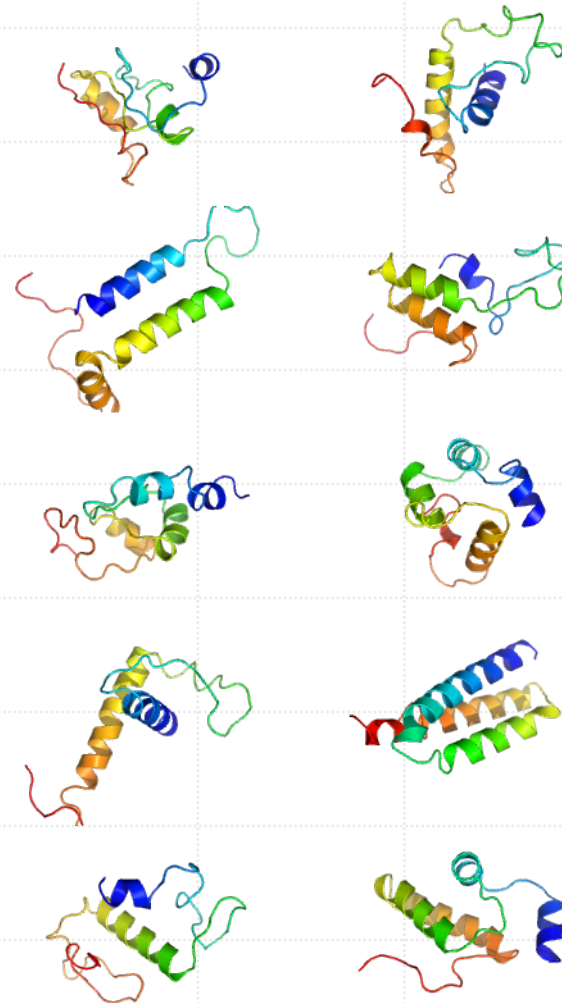
BADANIA ATYWNOŚCI BIOLOGICZNEJ

KONSTRUKCJA MODELU BIAŁKA Z PEPTYDÓW

KONSTRUKCJA MUTANTÓW

DYNAMIKA MOLEKULARNA BIAŁKA I MUTANTÓW

Białko UL49.5



H6 H7

UL49.5

E11G

RRE(9-11)GGG

RRE(9-11)AAA

SYNTEZA PEPTYDÓW

BADANIA STRUKTURALNE PEPTYDÓW: NMR, CD

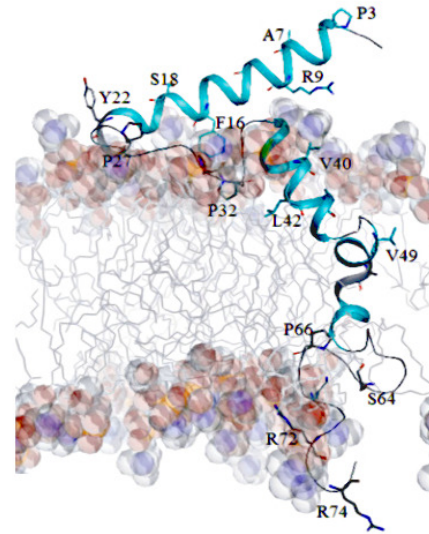
BADANIA ATYWNOŚCI BIOLOGICZNEJ

KONSTRUKCJA MODELU BIAŁKA Z PEPTYDÓW

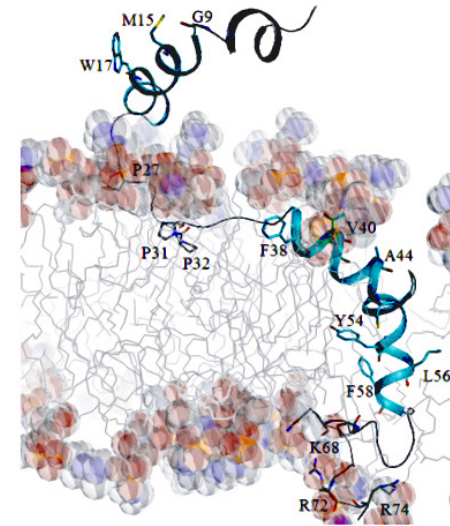
KONSTRUKCJA MUTANTÓW

DYNAMIKA MOLEKULARNA BIAŁKA I MUTANTÓW

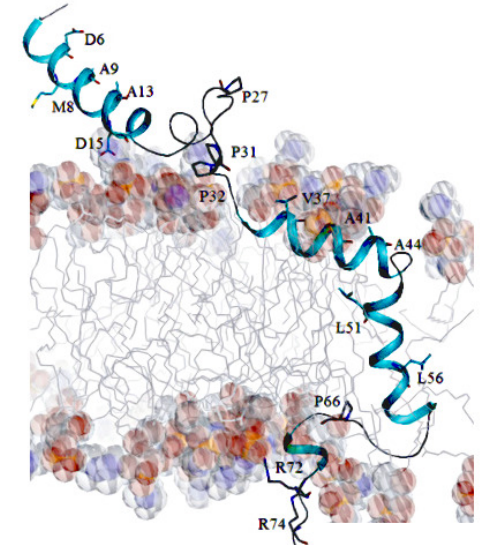
Białko UL49.5



E11G

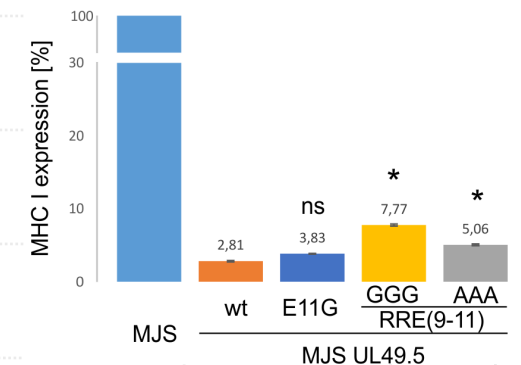


RRE(9-11)GGG



RRE(9-11)AAA

- niewielki wpływ na aktywność
- niewielki wpływ na strukturę całego białka
- większa ruchliwość domeny N-terminalnej



H9

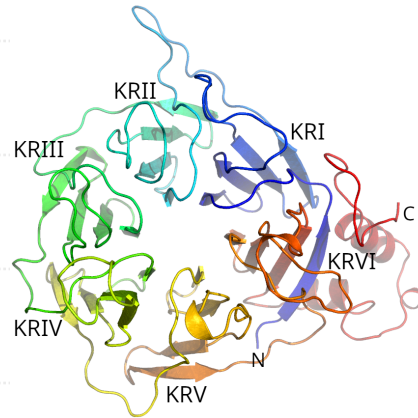
UL49.5 (87-96)

UL49.5 (87-96) R95K

UL49.5 (87-96) R93K

UL49.5 (87-96) R96D

KLHDC3



Białko UL49.5

ligaza ubikwityny E3

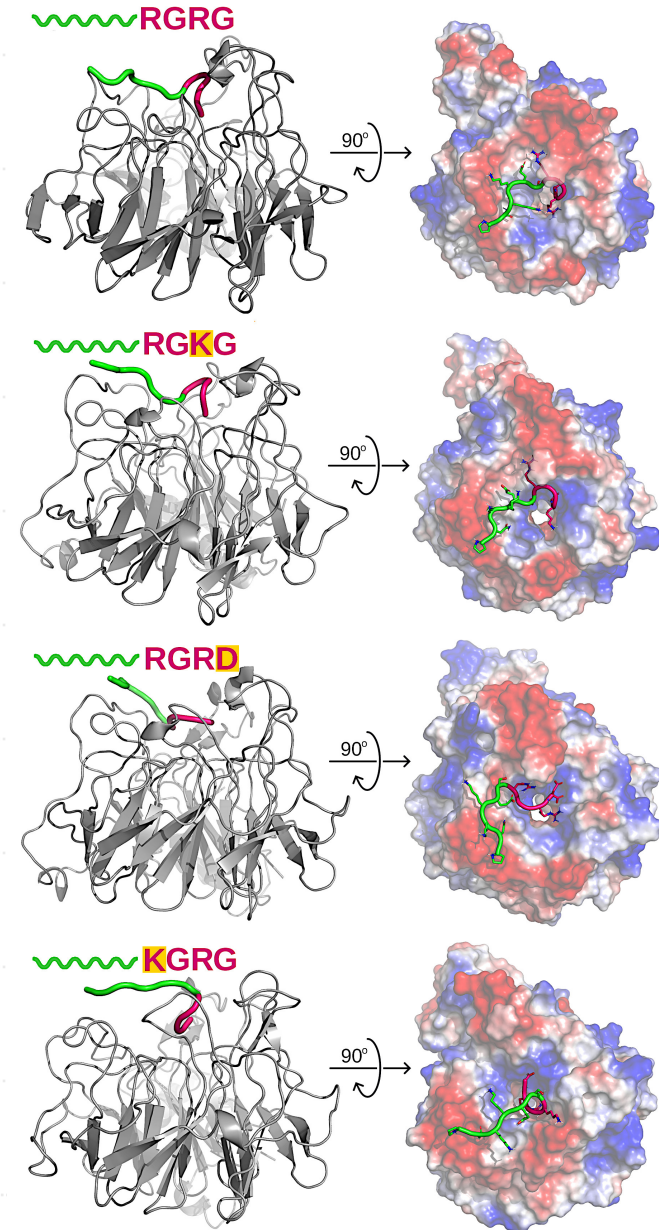
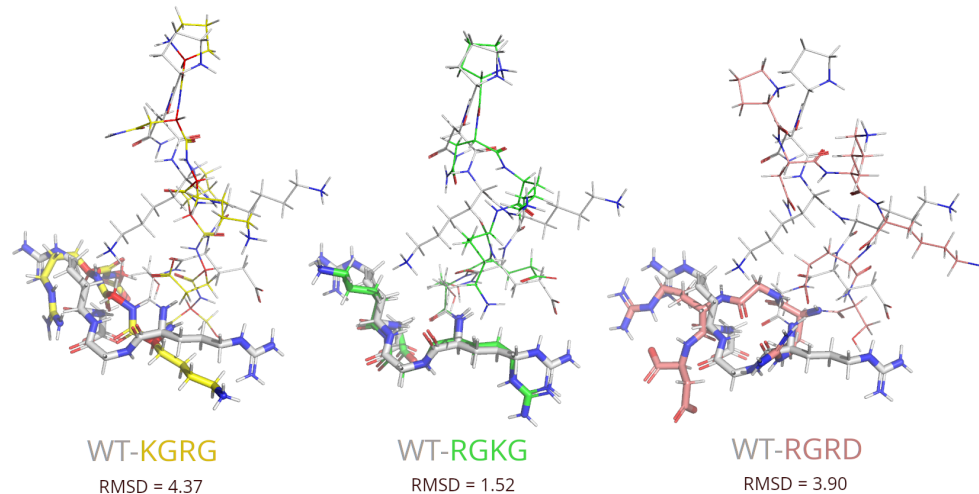
C - degron
- RGRG

BADANIA EKSPERYMENTALNE :

R93K i **R96D** nie oddziałują z KLHDC3 → brak degradacji TAP

R95K = WT, oddziałuje z KLHDC3 → degradacja TAP

DLACZEGO?

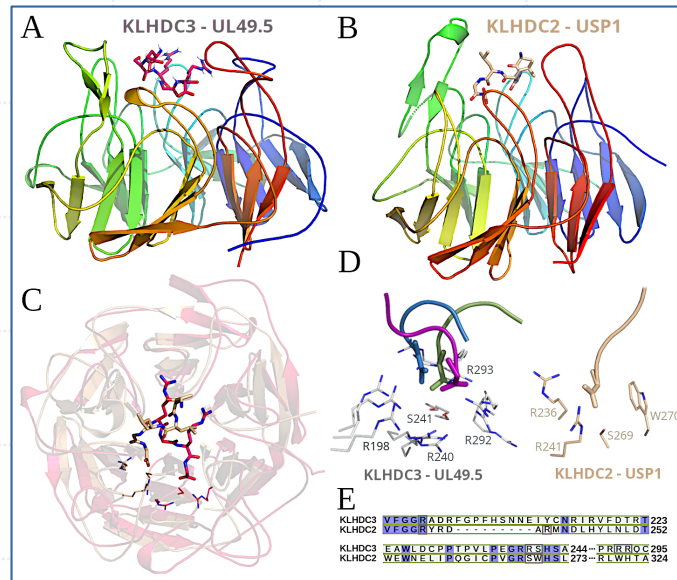
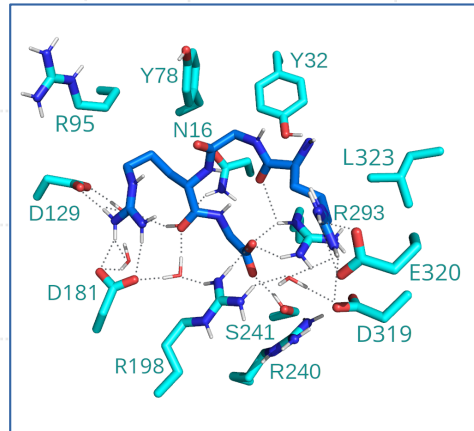


H10

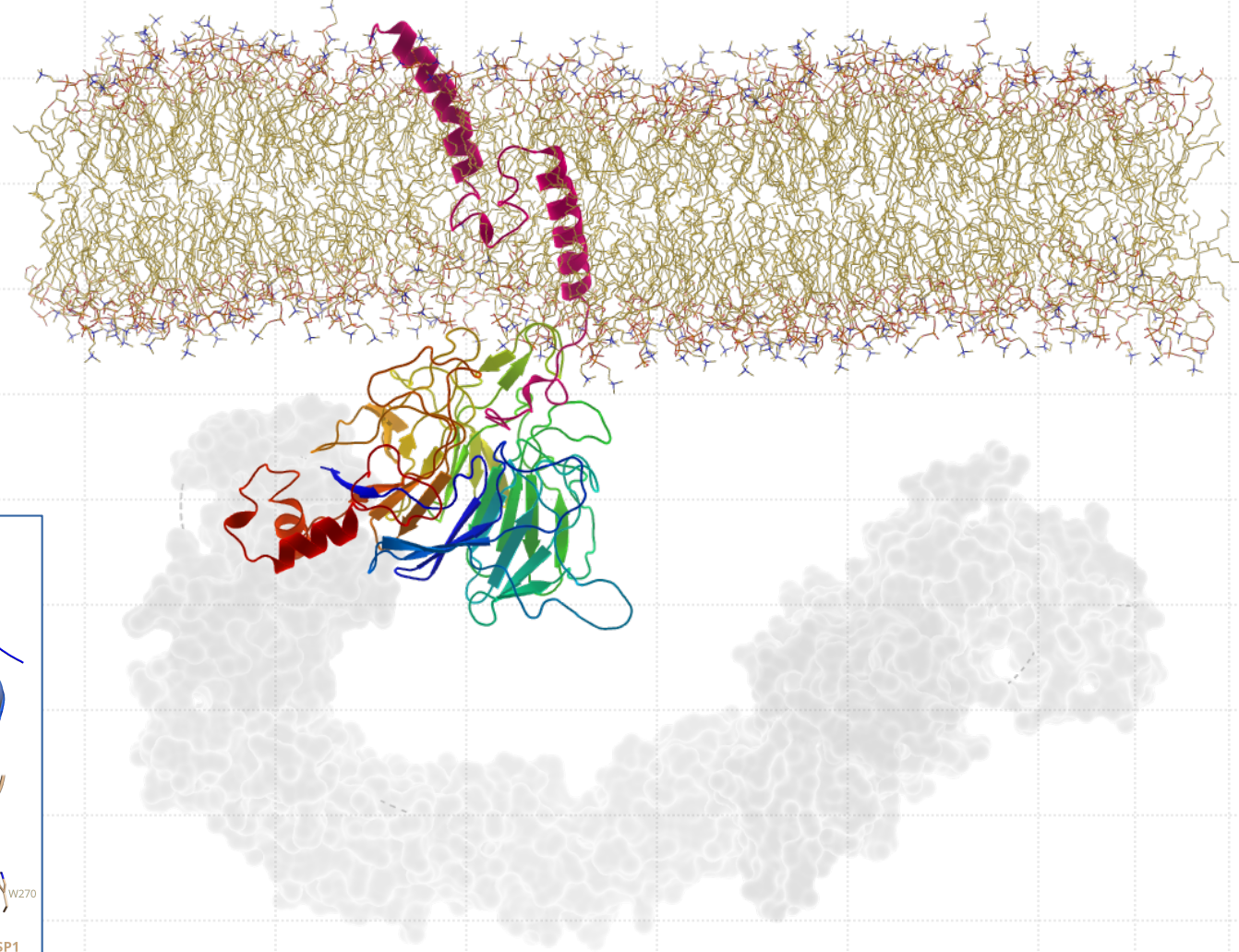
UL49.5 (87-96)

KLHDC3

- stabilna struktura kompleksu (1200 ns)
- UL49.5 → dwie helisy
- sieć polarnych oddziaływań → triada **RSR**



Białko UL49.5



Badania in silico struktury wybranych białek błonowych oraz specyfiki ich oddziaływania z biomolekułami tworzącymi z nimi kompleksy o potencjale terapeutycznym

IF: 30,153

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- H3.** Ślusarz R., Ślusarz M.J., An influence of the aromatic side chains conformations in positions 2 and 3 of vasopressin analogs on interactions with vasopressin and oxytocin receptors, *QSAR & Combinatorial Science*, 2009, 28, 1166-1175. IF = 3,027
- H4.** Ślusarz MJ.: Molecular modeling study of the opioid receptor interactions with series of cyclic deltorphin analogues, *Journal of Peptide Science*, 2011, 17, 554-564. IF = 1,799
- H5.** Ślusarz MJ, Sikorska E., Ślusarz R.: Interactions of vasopressin and oxytocin receptors with vasopressin analogues substituted in position 2 with 3,3'-diphenylalanine - a molecular docking study, *Journal of Peptide Science*, 2013, 19, 118-126. IF = 1,862
- H6.** Karska N., Graul M., Sikorska E., Zhukov I., Ślusarz MJ., Kasprzykowski F., Lipińska A., Rodziewicz-Motowidło S.: Structure determination of UL49.5 transmembrane protein from bovine herpesvirus 1 by NMR spectroscopy and molecular dynamics, *Biochimica et Biophysica Acta - Biomembranes*, 2019, 1861, 926-938. IF = 3,411
- H7.** Karska N., Graul M., Sikorska E., Ślusarz MJ., Zhukov I., Kasprzykowski F., Kubiś A., Lipińska A., Rodziewicz-Motowidło S.: Investigation of the effects of primary structure modifications within the RRE motif on the conformation of synthetic bovine herpesvirus 1-encoded UL49.5 protein fragments, *Chemistry & Biodiversity*, 2021, 18, e2000883. IF = 2,745
- H8.** Ślusarz MJ., Molecular insights into the mechanism of the sugar-modified enkephalin binding to the opioid receptors, *Computational Biology and Chemistry*, 2022, 101, 107783. IF = 3,100
- H9.** Ślusarz MJ, How kelch domain-containing protein 3 distinguishes between the C-end degon of bovine viral protein UL49.5 and its mutants – insights from a molecular dynamics, *Bioorganic and Medicinal Chemistry*, 2024, 109, 117795. IF = 3,300
- H10.** Ślusarz MJ, Ślusarz MJ., Lipińska AD. An intrinsic network of polar interactions is responsible for binding of UL49.5 C-degron by the CRL2KLHDC3 ubiquitin ligase, *Proteins: Structure, Function and Bioinformatics*, 2024, 92, 610-622. IF = 3,200

Liczba publikacji: 42	Sumaryczny IF: 124,204
H-index: 13/14/13 (Sc/GS/WoS)	Liczba cytowań: 480/591/449 (Sc/GS/WoS)

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04.2023 - 06.2023 - Wydział Farmaceutyczny Gdańskiego Uniwersytetu Medycznego

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