Neurotrophins and their Receptors

Marta Blanco
Marta Badia
Adrián Mallén
Hugo Ramos

Summary

1.1. DEFINITION AND FUNCTION

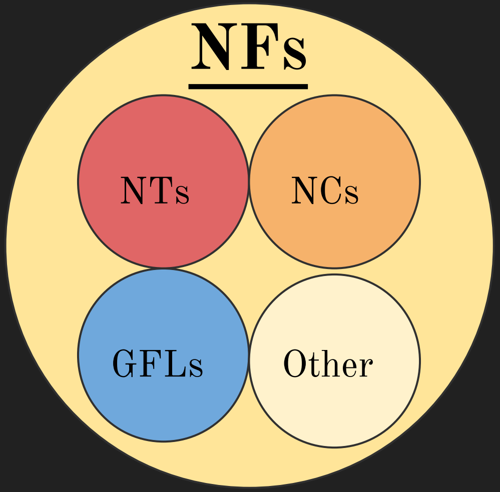
Neurotrophins family

→ closely related proteins involved in: **survival**, **development**, and **function** of neurons (in CNS and PNS)

→ ≠ **neurotrophic factors**

→ **secreted** by: **neurons** or **surrounding glia**

→ **target cells: neurons**



Different signaling pathways for each subfamily

1.1. DEFINITION AND FUNCTION

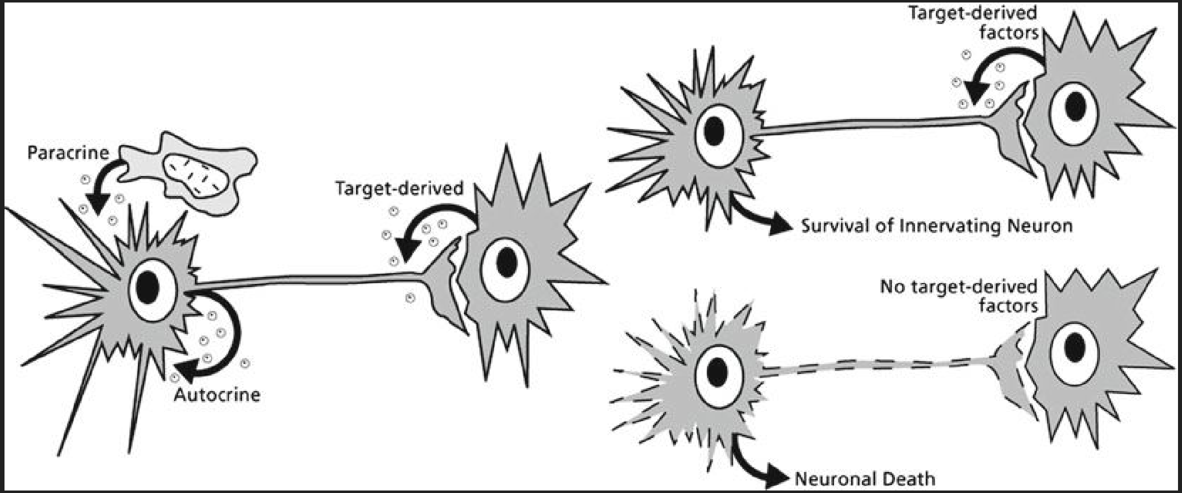


Figure 1 - **Neurotrophins secretion**: Skaper SD. *Meth Mol Biol.* 2012

Their function becomes crucial in the development of the vertebrate nervous system.

1.2. Members and their receptors

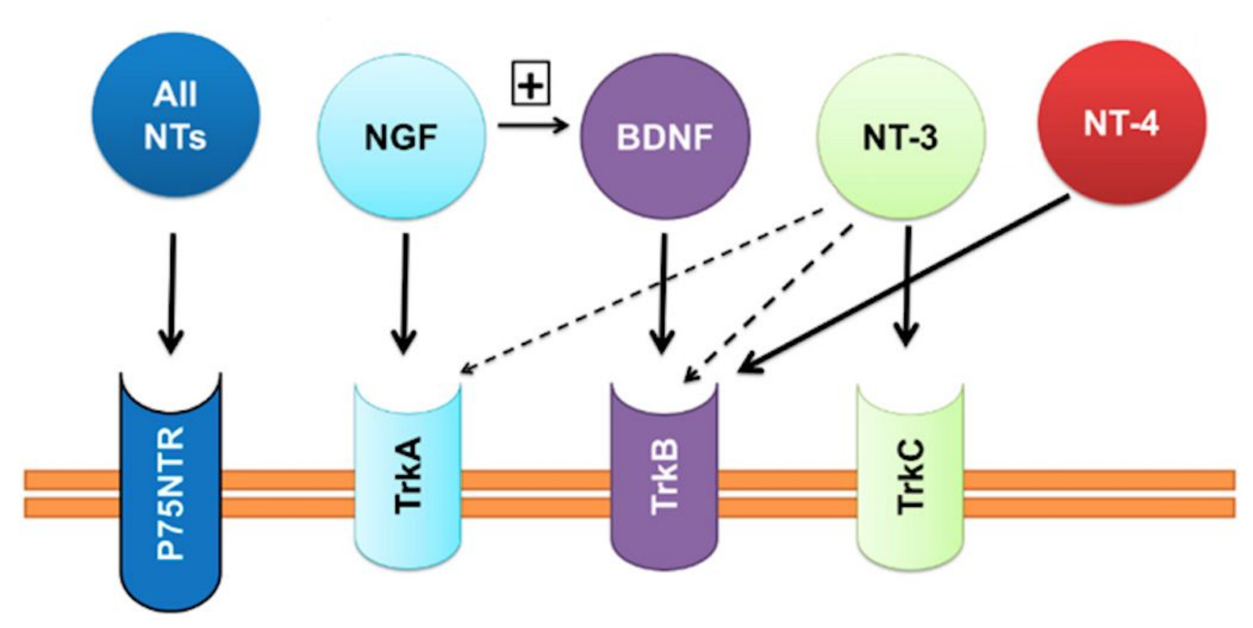


Figure 2 - **Neurotrophins and their receptors:** Khan N, Smith TM. *Molecules* 2015.

1.3. Consequent signaling pathways

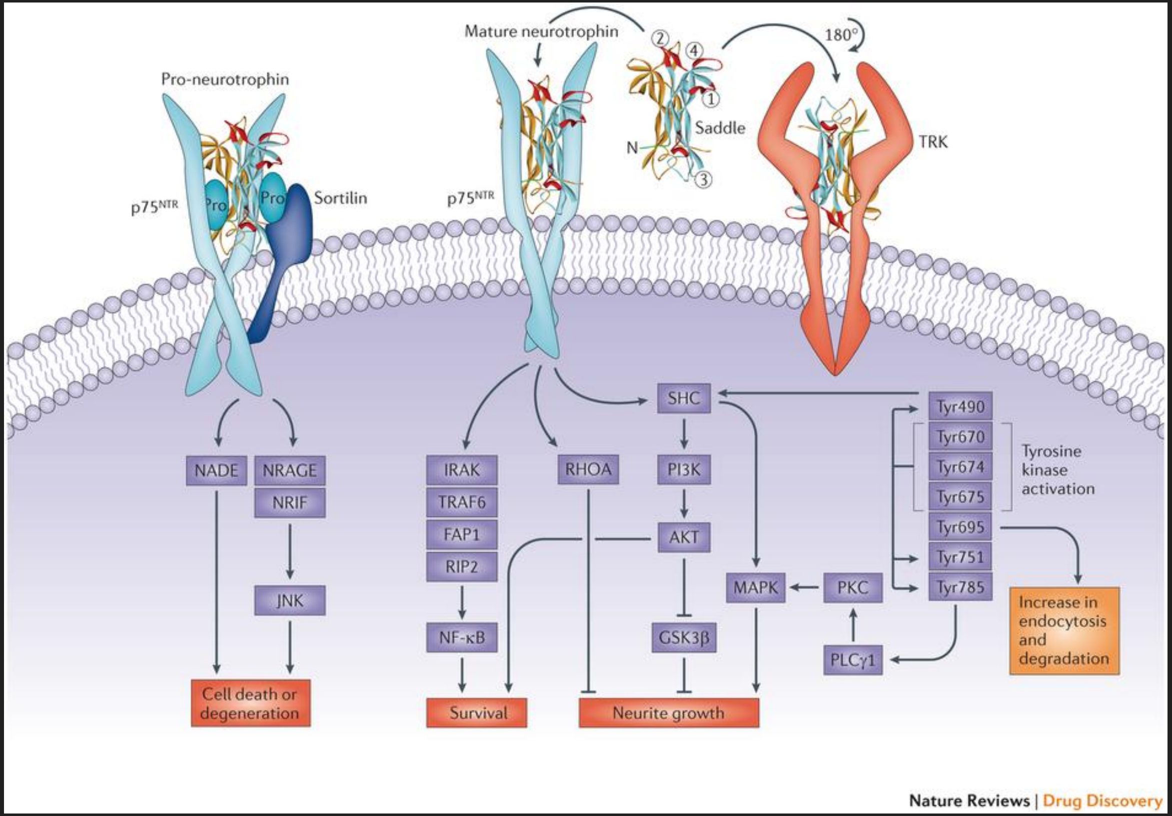
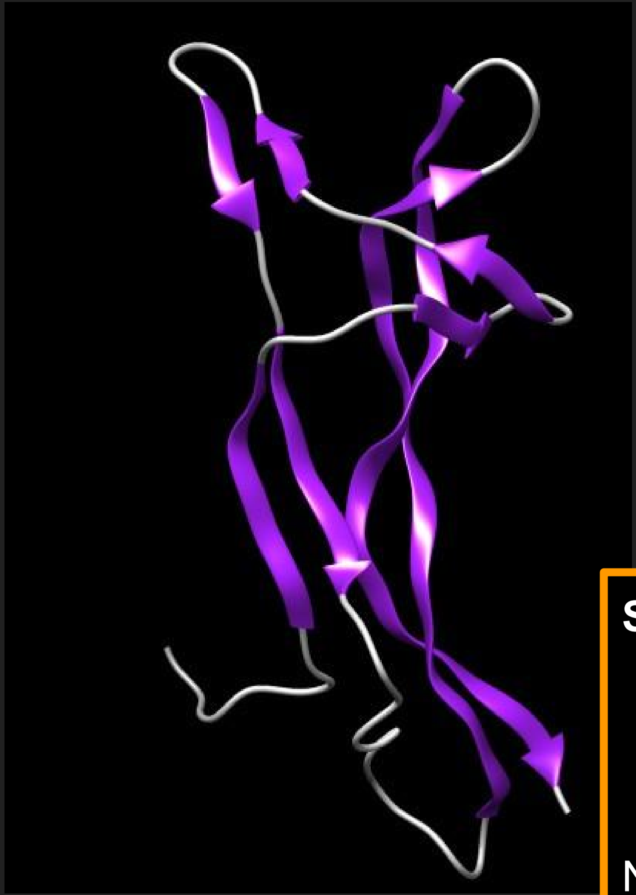


Figure 3 - **Neurotrophins Pathways:** Longo FM, Massa SM. *Nat Rev Drug Discov*. 2013.

2. Neurotrophins



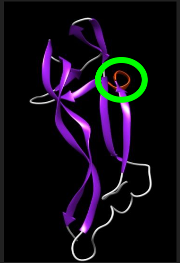
Domains and Secondary Structure

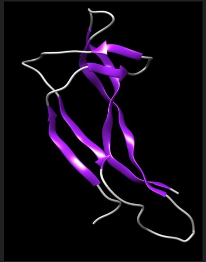
- Mainly beta
- Ribbon
- Superfamily: cystine-knot cytokines

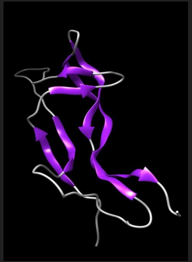
SCOP CLASSIFICATION

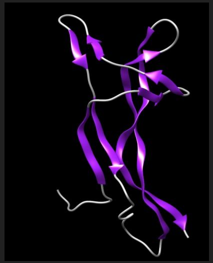
CLASS: Small Proteins
FOLD: Cystine-knot cytokines
SUPERFAMILY: Cystine-knot cytokines
FAMILY: Neurotrophin (NGF,
NT3, NT4 or BDNF)

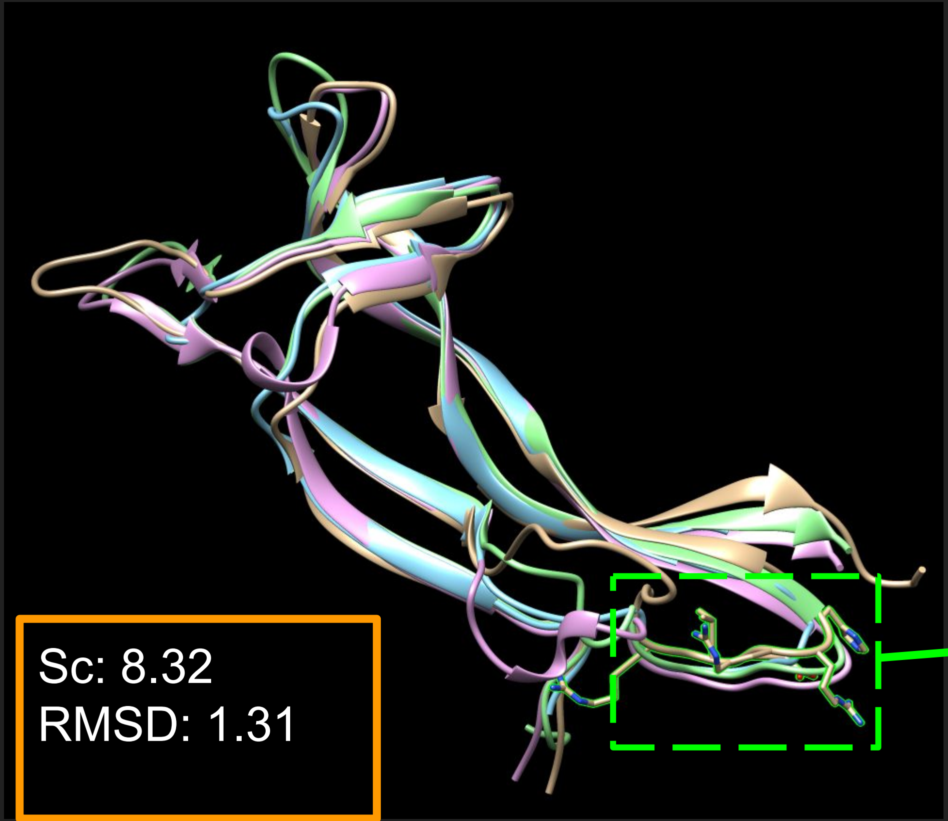
2. 1.Superimposition of Neurotrophins

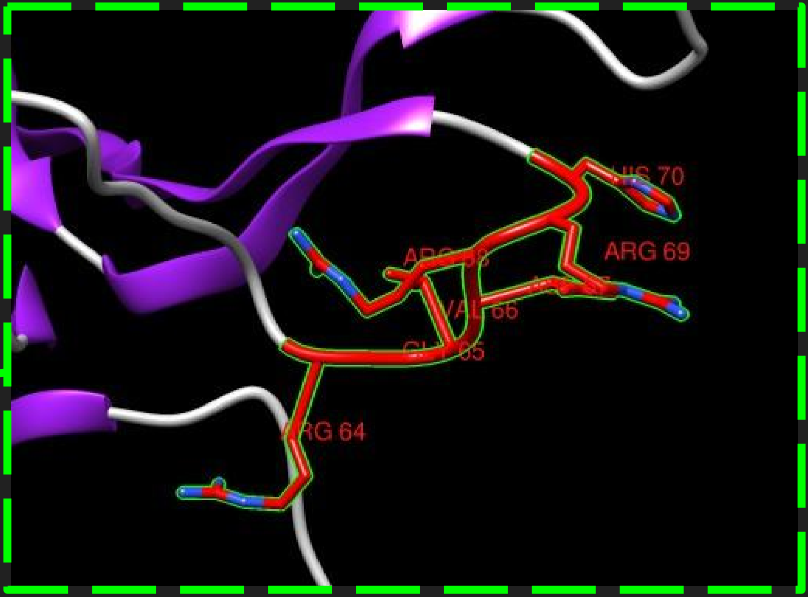

BDNF


NT3


NT4


NGF


Sc: 8.32
RMSD: 1.31



3. NEUROTROPHINS RECEPTORS (TRK)

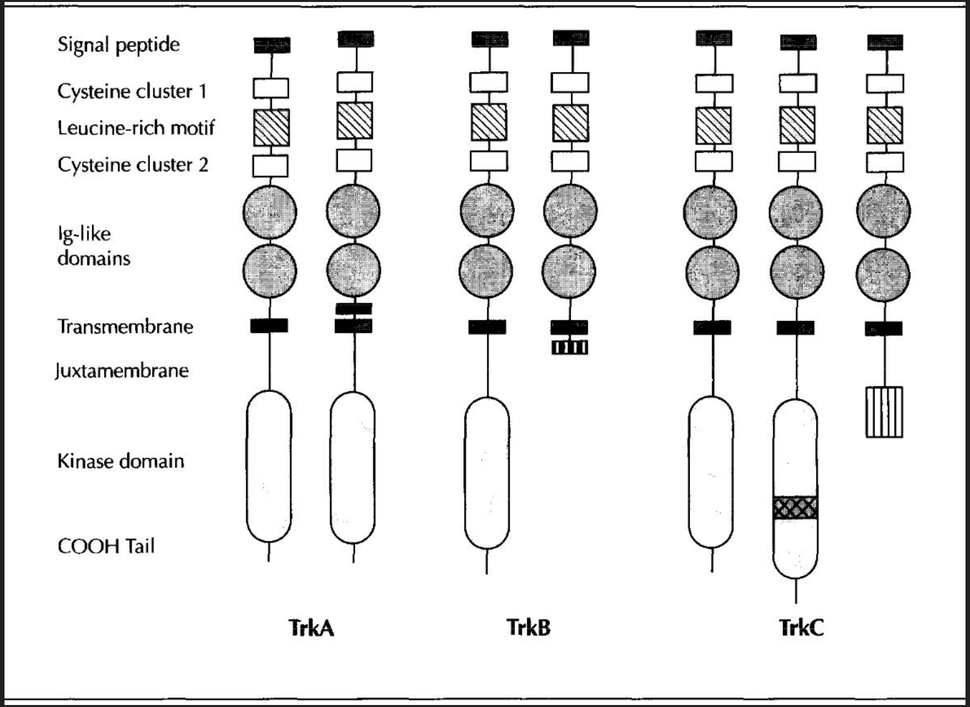
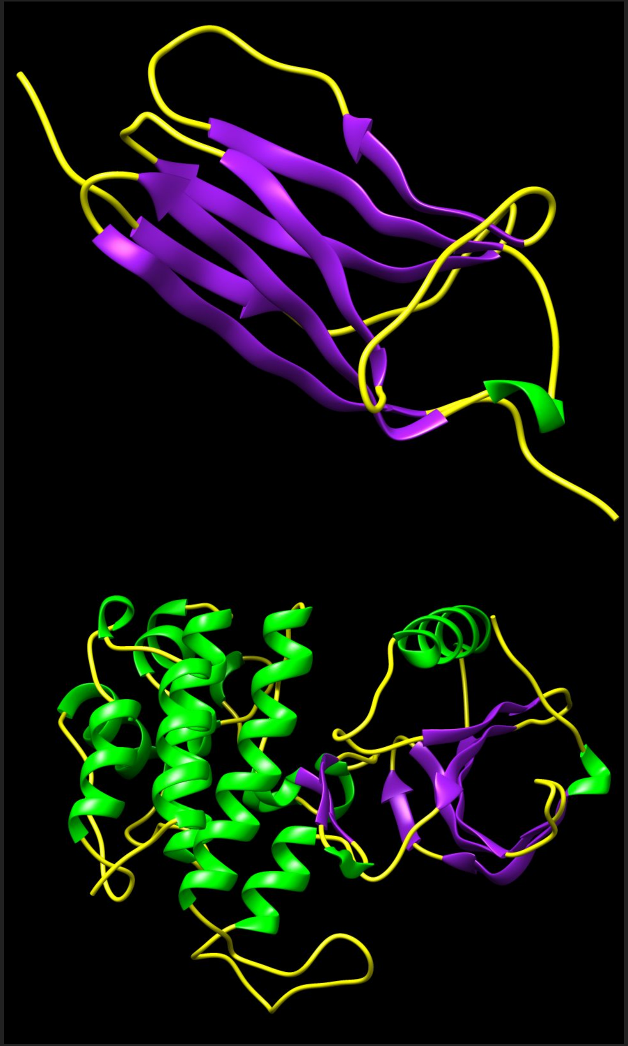


Figure 4 - **Receptors Domains:** Barbacid M. *Cell Biol,* 1995.

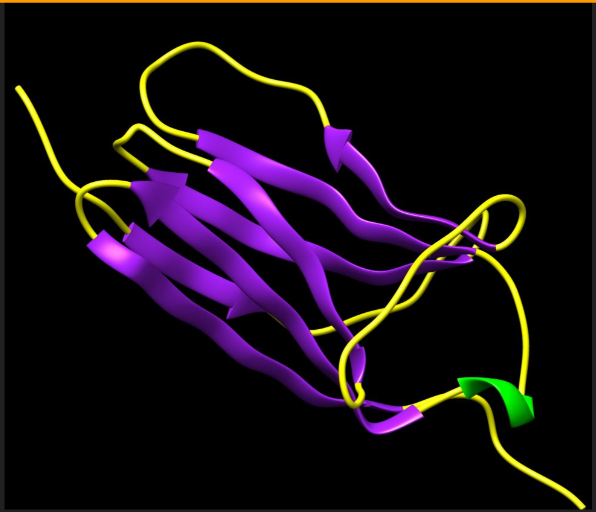


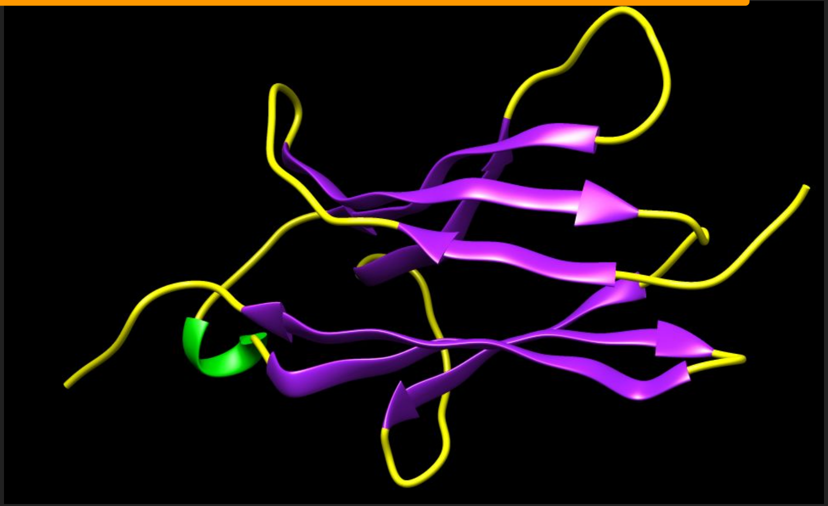
3.NEUROTROPHINS RECEPTORS (TRK)

BINDING DOMAIN

SCOP CLASIFICATION

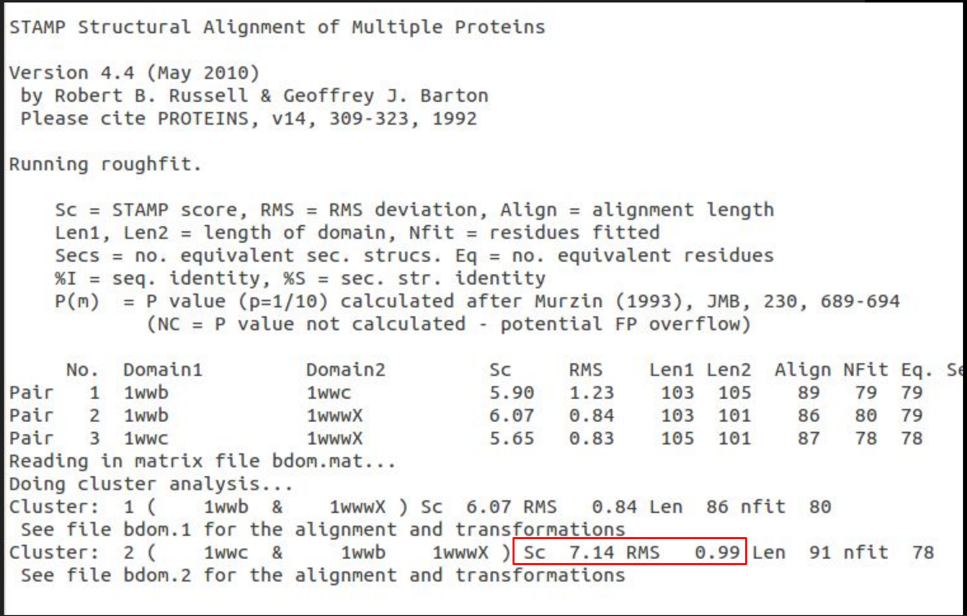
- CLASS: All-beta proteins
  - FOLD: Immunoglobulin-like beta sandwich
    - SUPERFAMILY: Immunoglobulin
      - FAMILY: I set domains
        - DOMAIN: High affinity nerve growth factor receptor TrkA



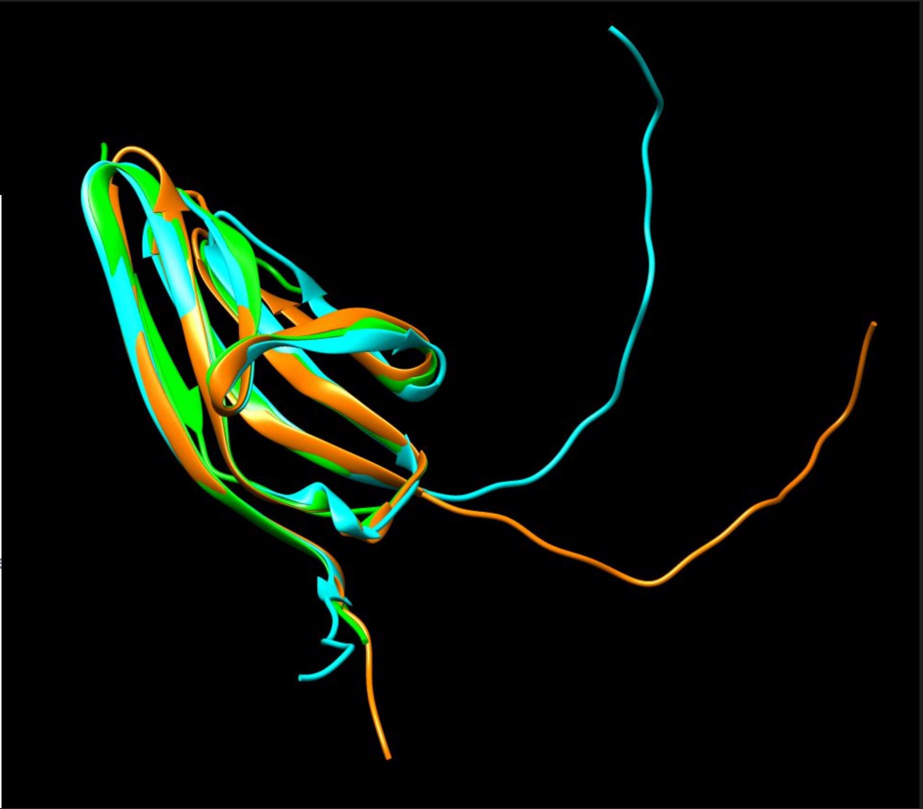


3.NEUROTROPHINS RECEPTORS (TRK)

BINDING DOMAIN



```
STAMP Structural Alignment of Multiple Proteins

Version 4.4 (May 2010)
 by Robert B. Russell & Geoffrey J. Barton
 Please cite PROTEINS, v14, 309-323, 1992

Running roughfit.

    Sc = STAMP score, RMS = RMS deviation, Align = alignment length
    Len1, Len2 = length of domain, Nfit = residues fitted
    Secs = no. equivalent sec. strucs. Eq = no. equivalent residues
    %I = seq. identity, %S = sec. str. identity
    P(m)  = P value (p=1/10) calculated after Murzin (1993), JMB, 230, 689-694
            (NC = P value not calculated - potential FP overflow)

     No.  Domain1         Domain2         Sc     RMS    Len1 Len2  Align NFit Eq. Se
Pair   1  1wwb            1wwc            5.90   1.23    103  105    89   79  79
Pair   2  1wwb            1wwwX           6.07   0.84    103  101    86   80  79
Pair   3  1wwc            1wwwX           5.65   0.83    105  101    87   78  78
Reading in matrix file bdom.mat...
Doing cluster analysis...
Cluster:  1 (    1wwb  &    1wwwX ) Sc  6.07 RMS   0.84 Len  86 nfit  80
 See file bdom.1 for the alignment and transformations
Cluster:  2 (    1wwc  &     1wwb    1wwwX ) Sc  7.14 RMS   0.99 Len  91 nfit  78
 See file bdom.2 for the alignment and transformations
```



3.NEUROTROPHINS RECEPTORS (TRK)

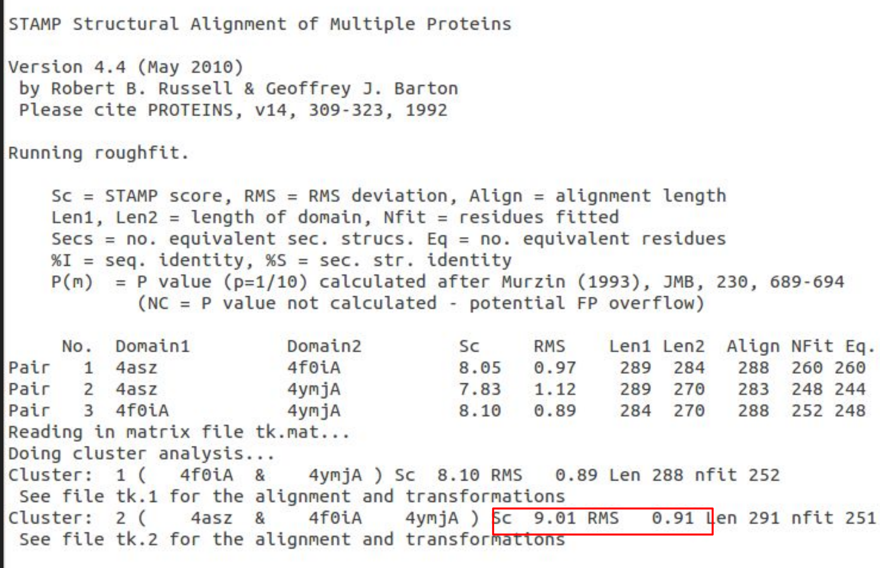
TYROSINE KINASE DOMAIN

- Mainly alpha
- Orthogonal bundle
- Superfamily: phosphotransferase

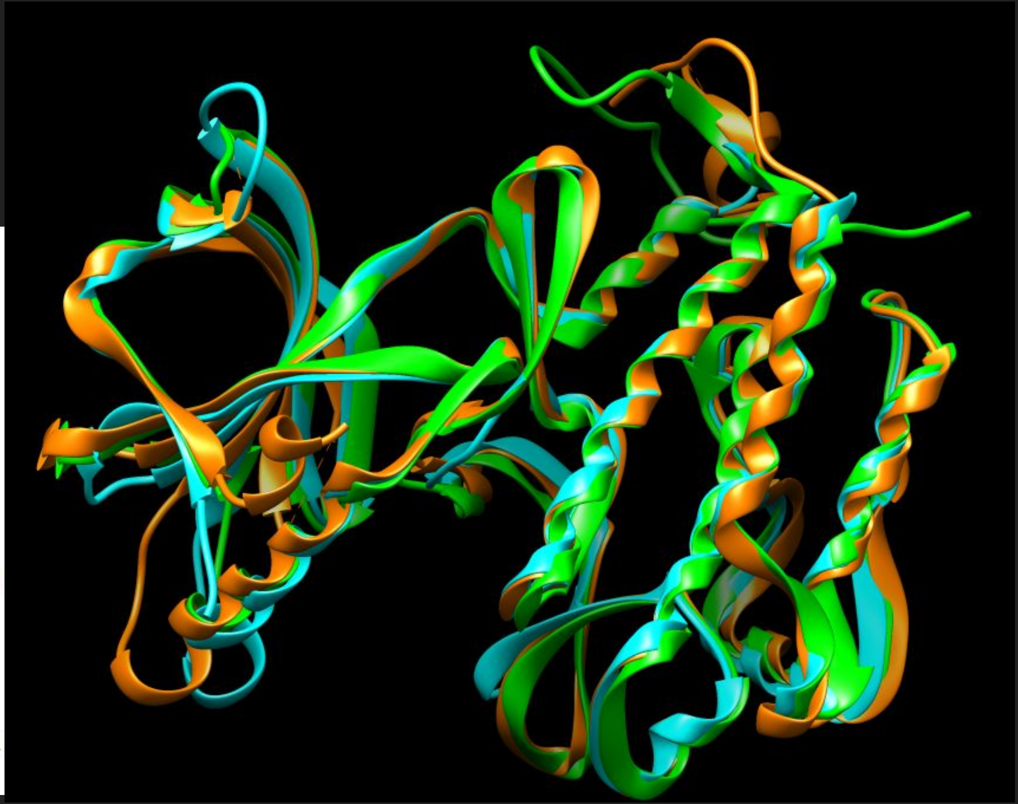
- Alpha and beta
- 2-Layer sandwich
- Superfamily: phosphotransferase

3.NEUROTROPHINS RECEPTORS (TRK)

TIROSIN KINASE DOMAIN



```
STAMP Structural Alignment of Multiple Proteins

Version 4.4 (May 2010)
 by Robert B. Russell & Geoffrey J. Barton
 Please cite PROTEINS, v14, 309-323, 1992

Running roughfit.

    Sc = STAMP score, RMS = RMS deviation, Align = alignment length
    Len1, Len2 = length of domain, Nfit = residues fitted
    Secs = no. equivalent sec. strucs. Eq = no. equivalent residues
    %I = seq. identity, %S = sec. str. identity
    P(m)  = P value (p=1/10) calculated after Murzin (1993), JMB, 230, 689-694
            (NC = P value not calculated - potential FP overflow)

     No.  Domain1         Domain2         Sc     RMS     Len1 Len2  Align NFit Eq.
Pair   1  4asz            4f0iA           8.05   0.97     289  284   288  260 260
Pair   2  4asz            4ymjA           7.83   1.12     289  270   283  248 244
Pair   3  4f0iA           4ymjA           8.10   0.89     284  270   288  252 248
Reading in matrix file tk.mat...
Doing cluster analysis...
Cluster:  1 (    4f0iA  &    4ymjA ) Sc  8.10 RMS   0.89 Len 288 nfit 252
 See file tk.1 for the alignment and transformations
Cluster:  2 (    4asz  &    4f0iA    4ymjA ) Sc  9.01 RMS   0.91 Len 291 nfit 251
 See file tk.2 for the alignment and transformations
```



3.NEUROTROPHINS RECEPTORS (P75)

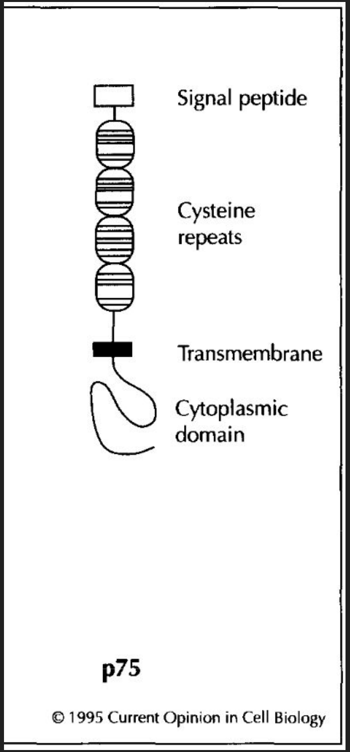


Figure 5 - **Receptors Domains:** Barbacid M. *Cell Biol* ,1995

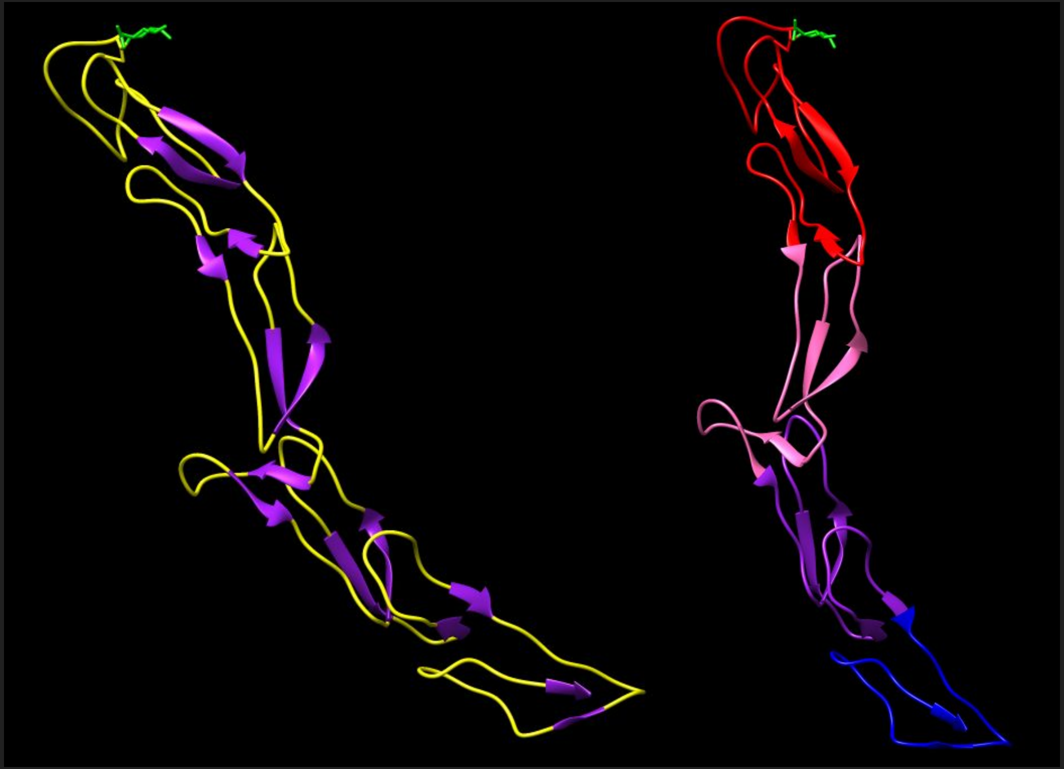
SCOP CLASIFICATION

- CLASS: Small Proteins
  - FOLD: TNF Receptor-Like
    - SUPERFAMILY: TNF Receptor-Like
      - FAMILY: TNF Receptor-Like
        - DOMAIN: Low Affinity Neurotrophin Receptor p75NTR

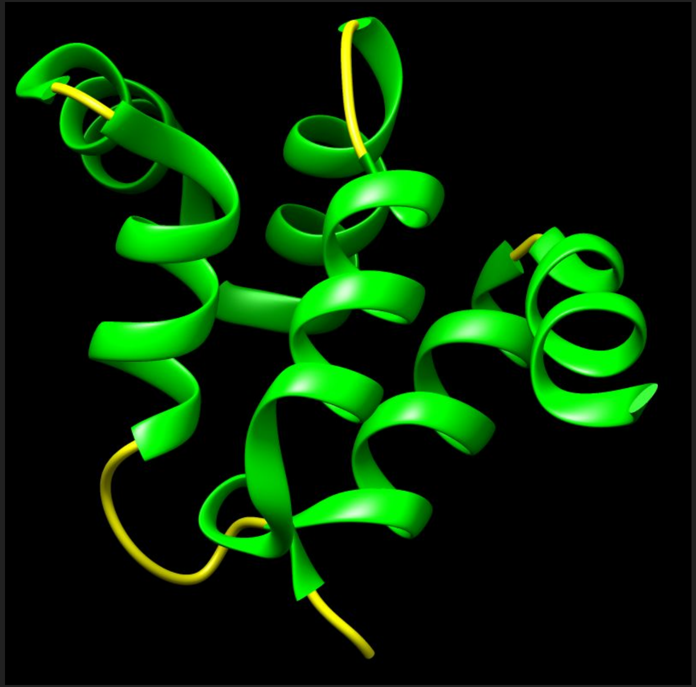
SCOP CLASIFICATION

- CLASS: All alpha proteins
  - FOLD: Death domain
    - SUPERFAMILY: Death domain
      - FAMILY: Death domain
        - DOMAIN: Low Affinity Neurotrophin Receptor p75

3.NEUROTROPHINS RECEPTORS (P75)



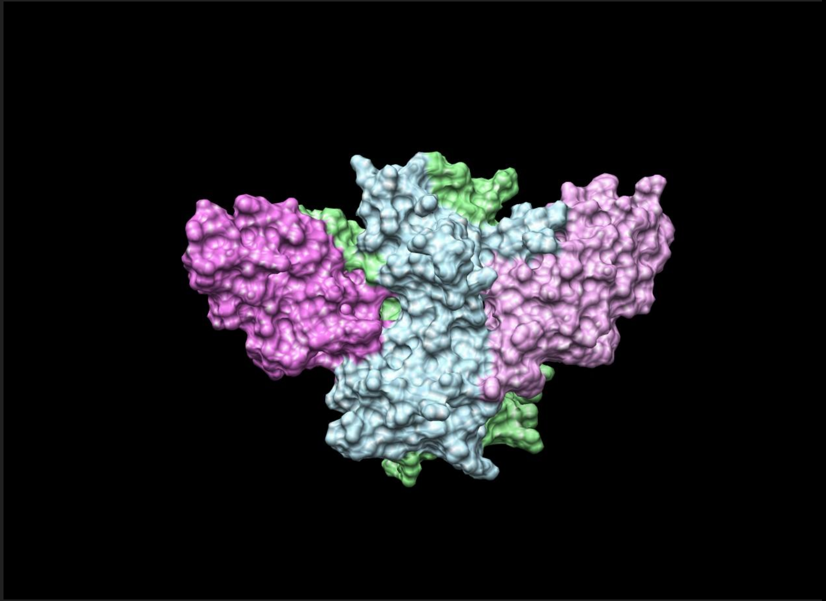
Mainly Beta

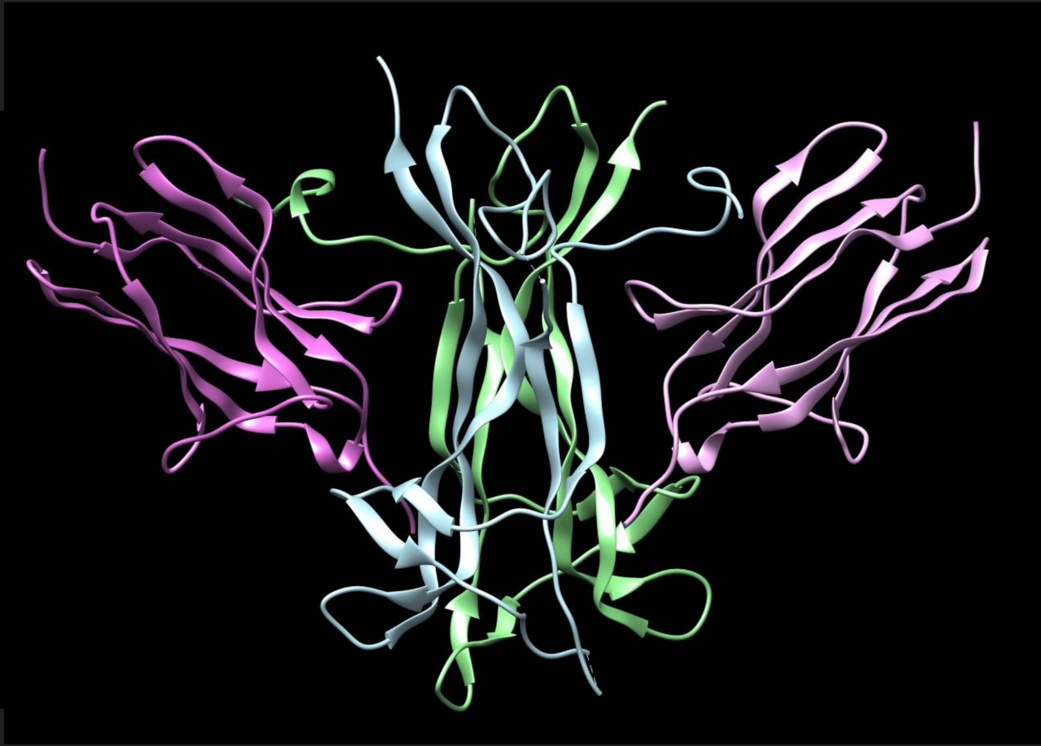


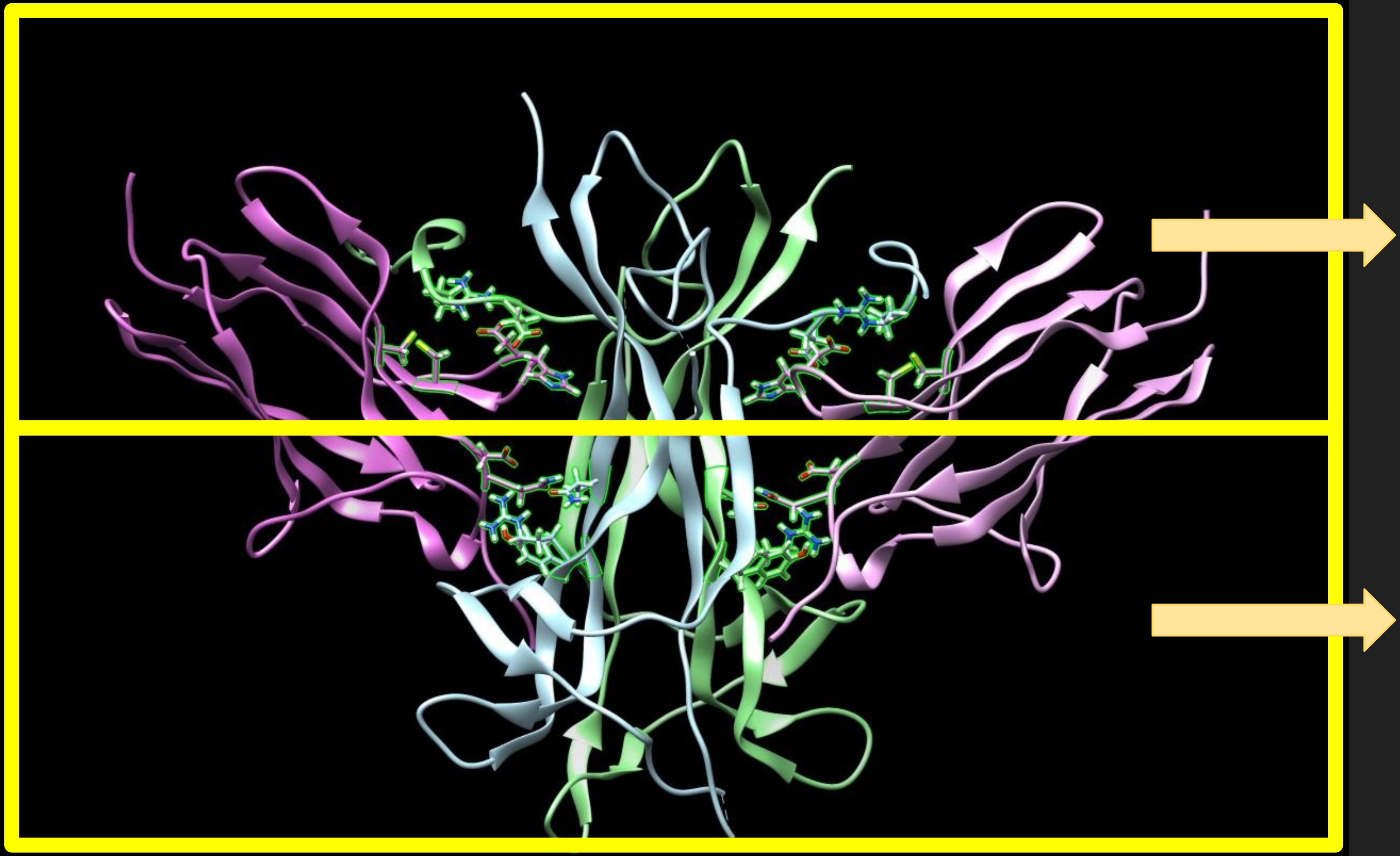
6 helices closed bundled
Greek-key

4. EXAMPLE A: NT 4/5 INTERACTIon WITH TRKB

Secondary structure of the complex







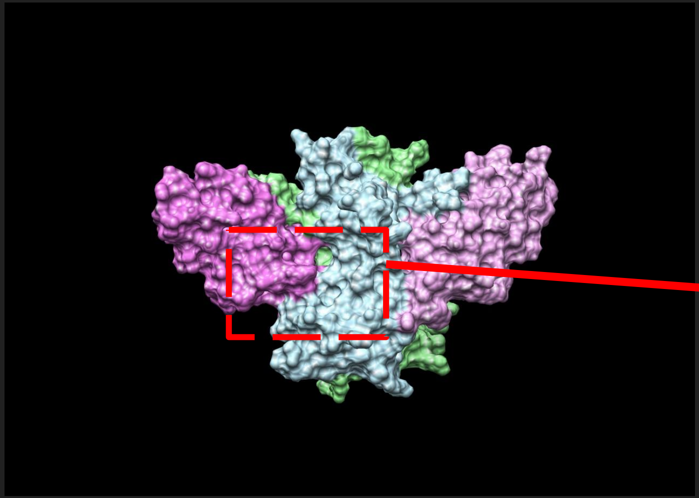
Specific Patch

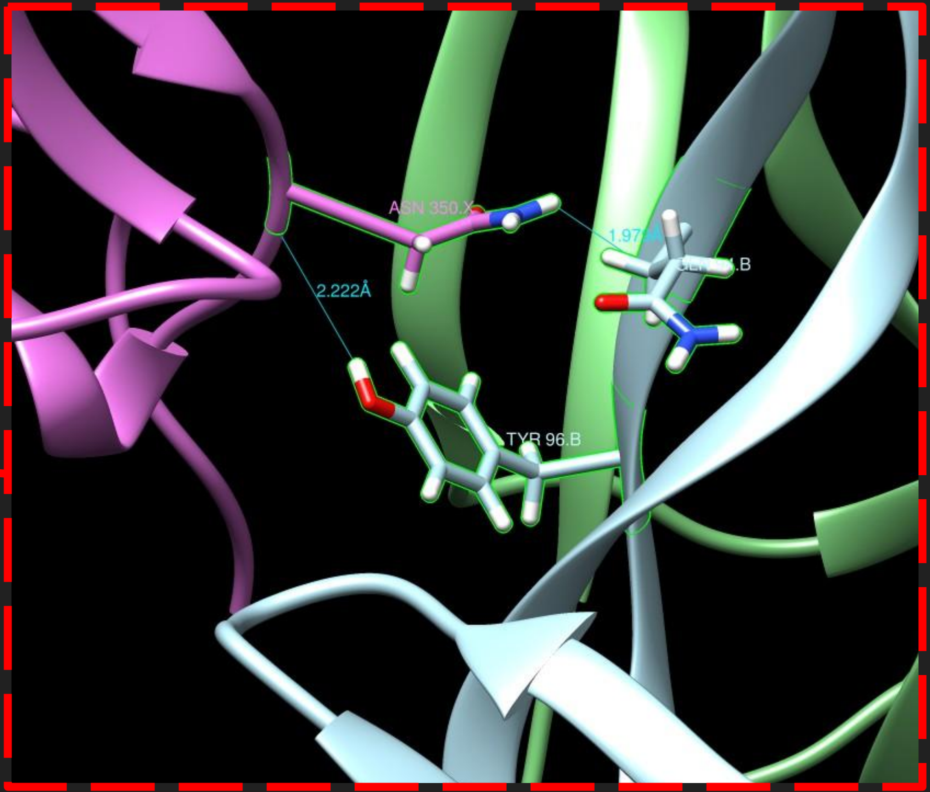
Conserved Patch

INTERACTIONS

HYDROGEN BONDS

TYR96 - ASN350
GLY94 - ASN350

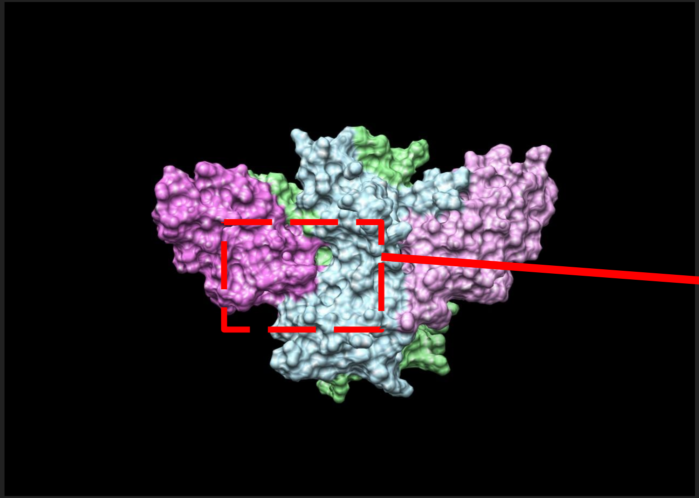


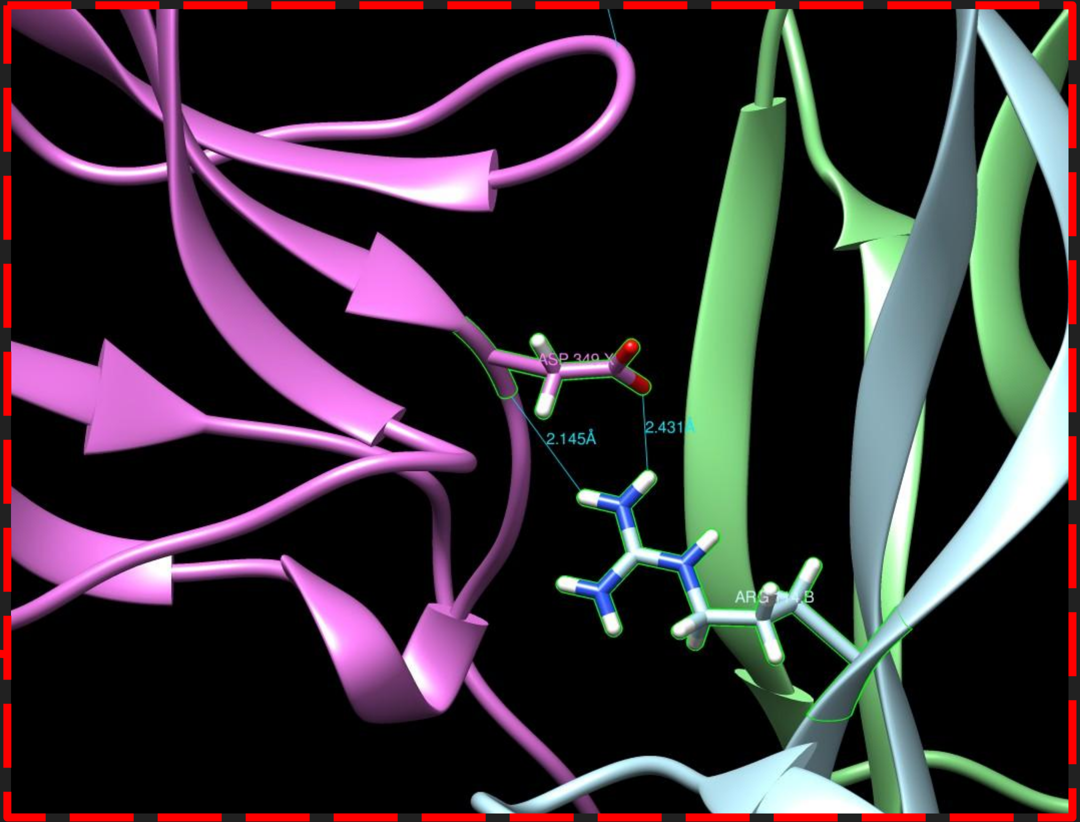


INTERACTIONS

HYDROGEN BONDS

ARG114 - ASP349

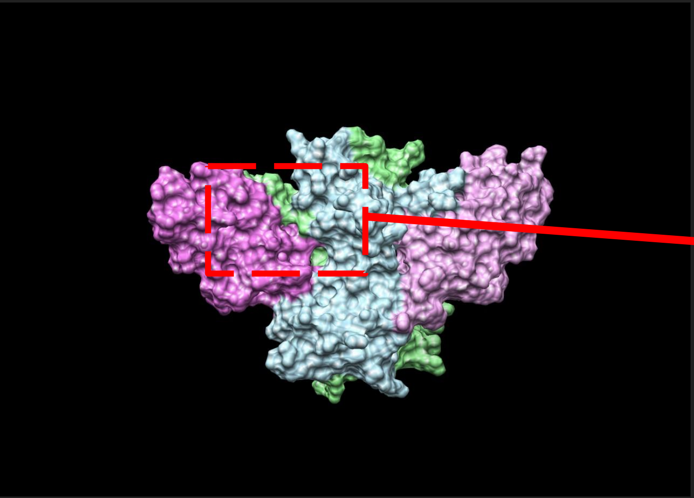


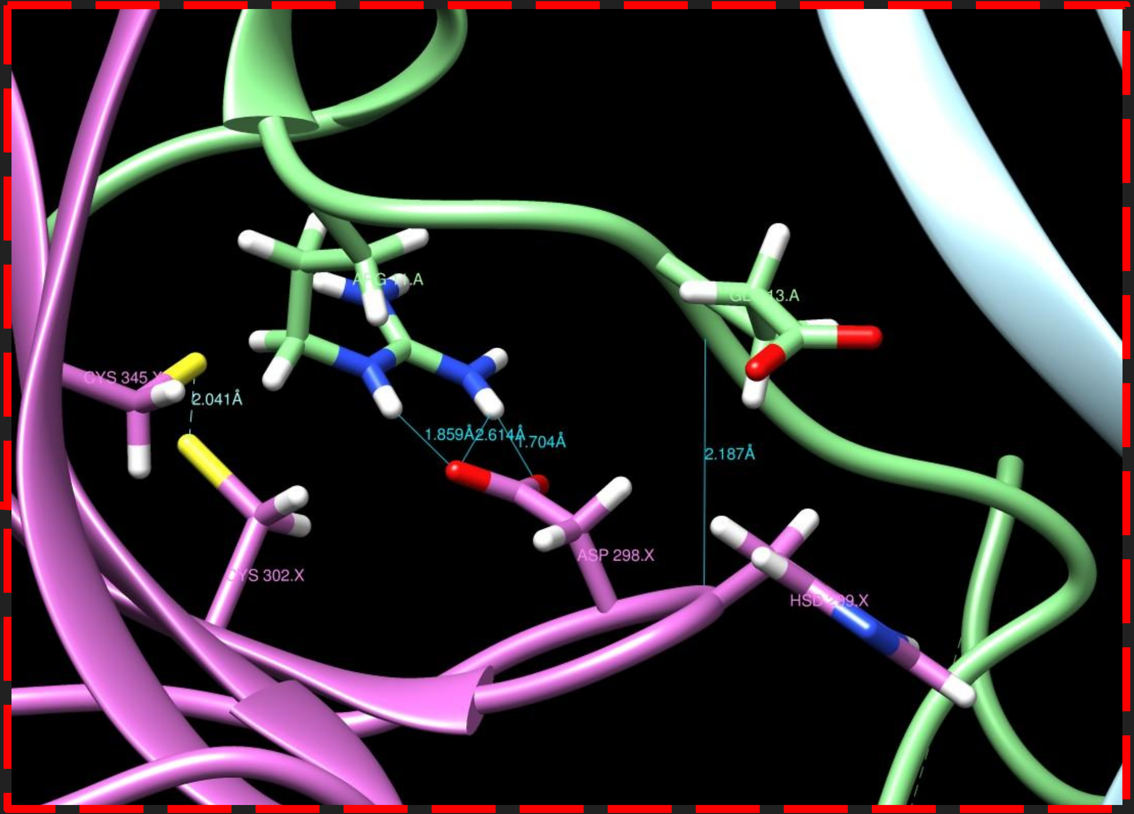


INTERACTIONS

HYDROGEN BONDS

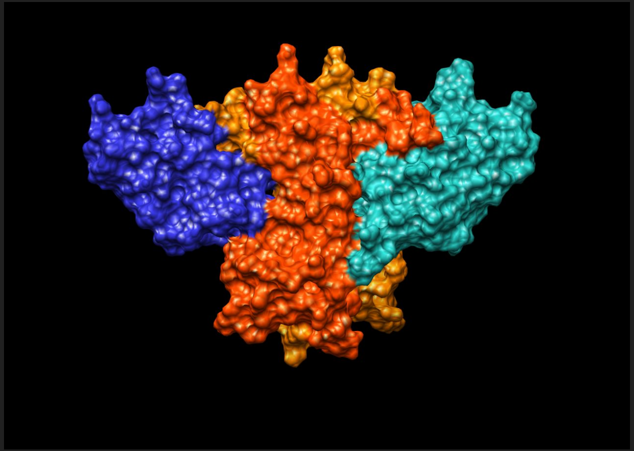
ARG11 - ASP298
GLU13 - HSD299

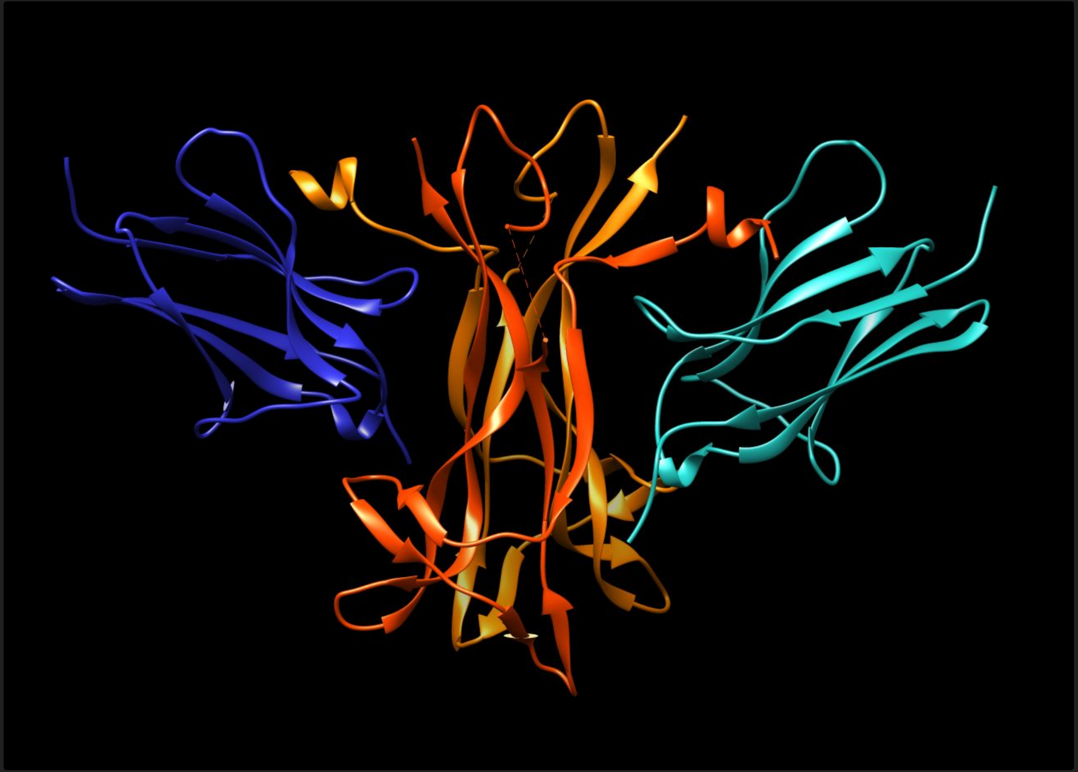




5. EXAMPLE B: NERVE GROWTH FACTOR INTERACTS WITH TRKa

Secondary structure of the complex

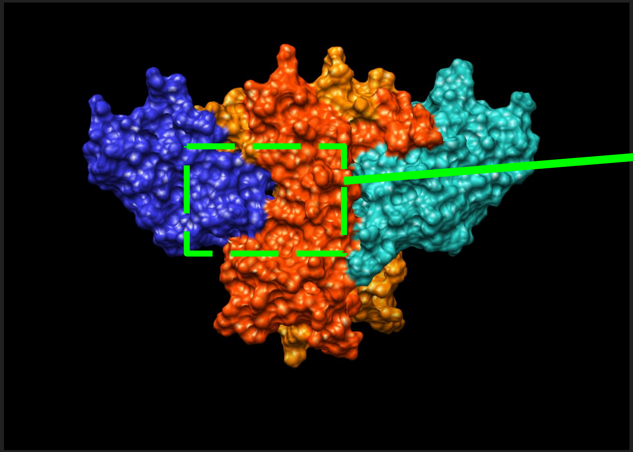


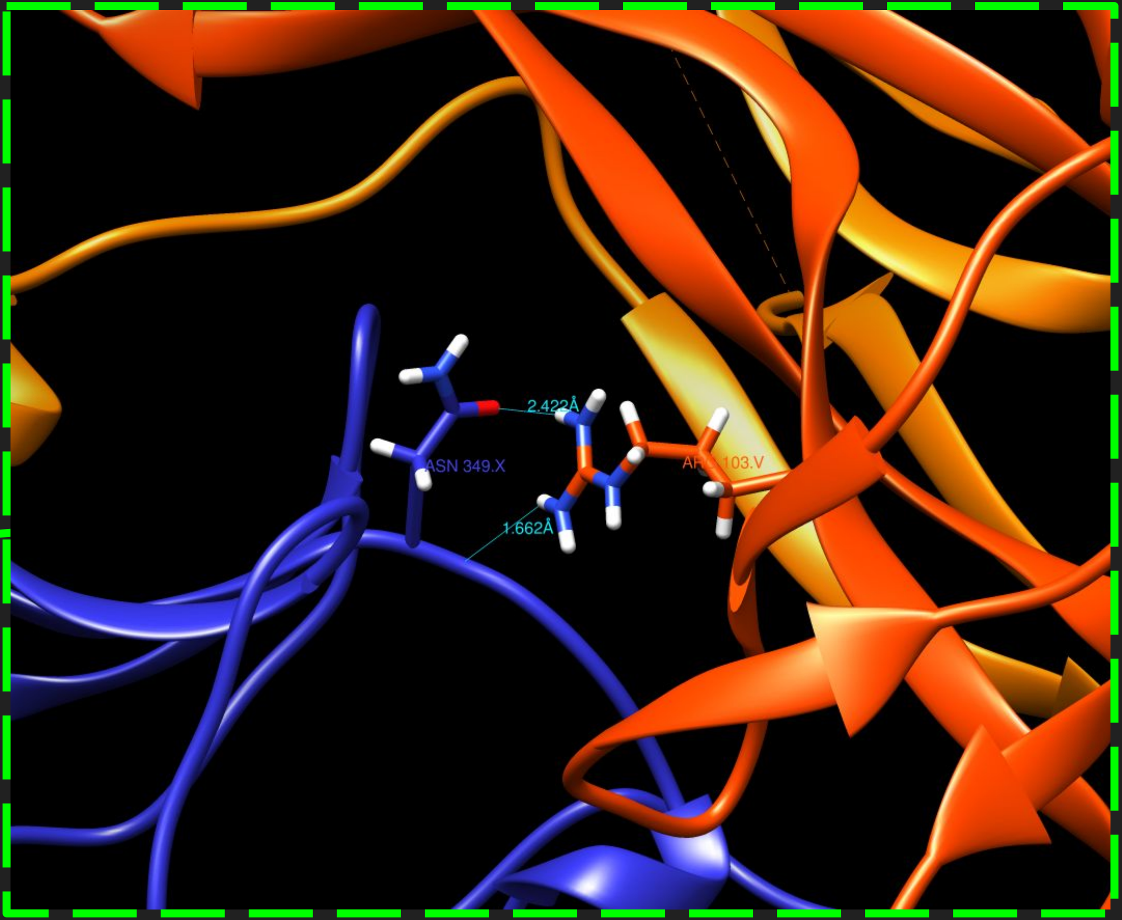


INTERACTIONS

HYDROGEN BONDS

ARG103 - ASN349

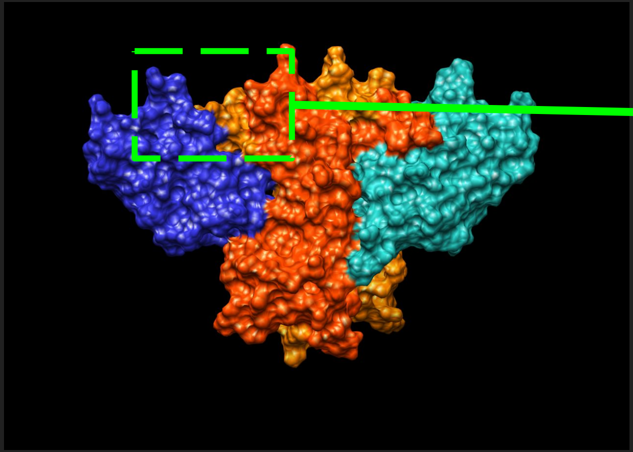


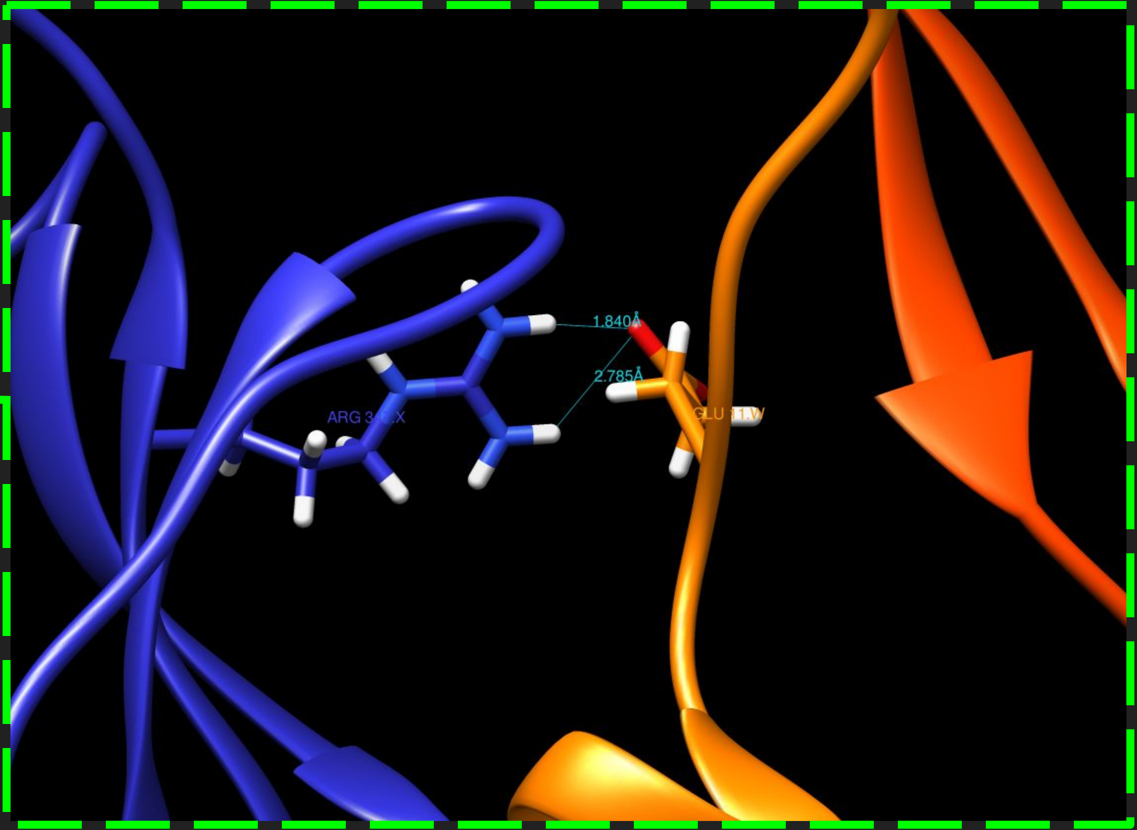


INTERACTIONS

HYDROGEN BONDS

GLU11 - ARG347

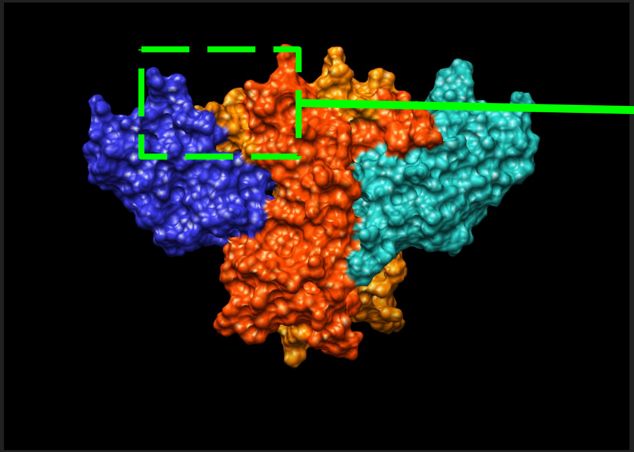


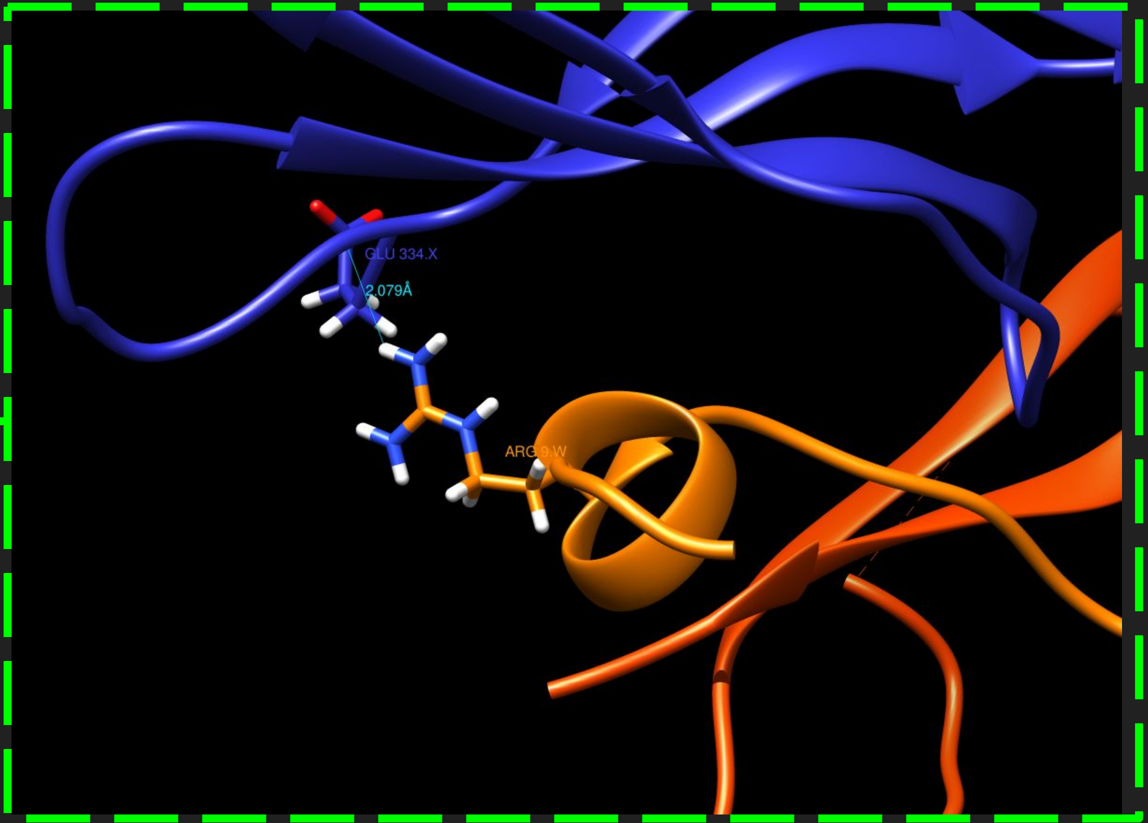


INTERACTIONS

HYDROGEN BOND

ARG9 - GLU334

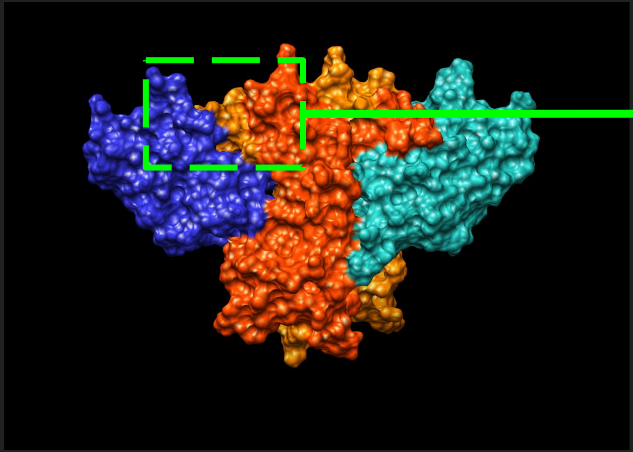


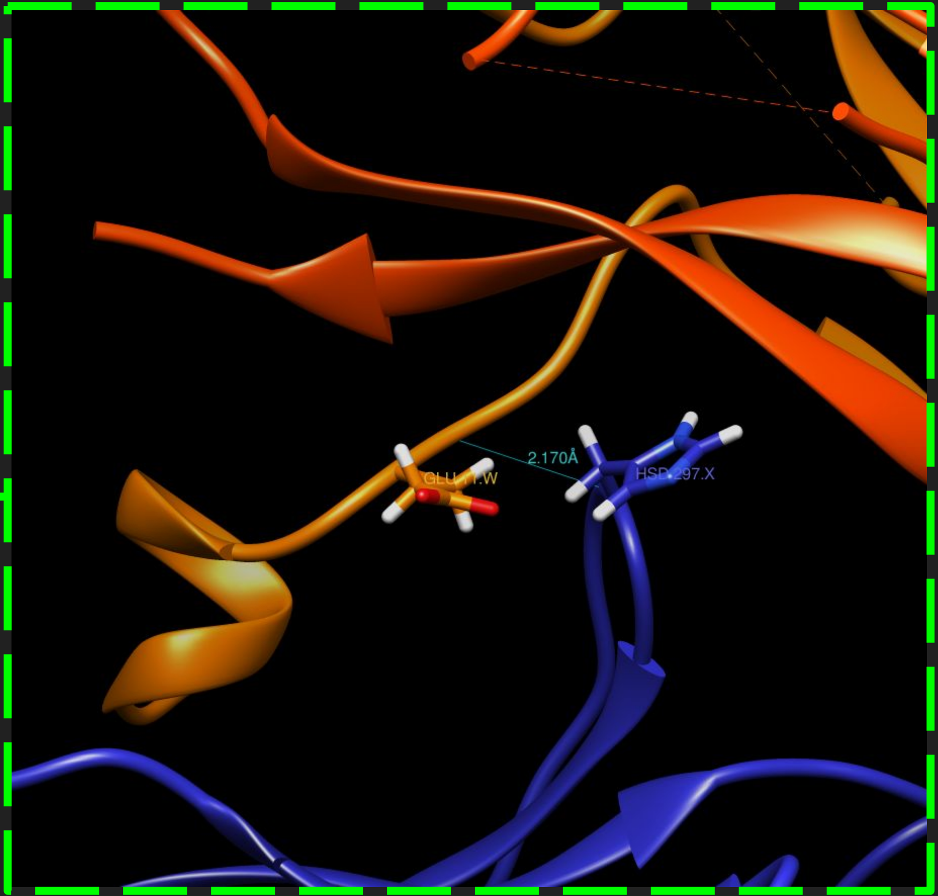


INTERACTIONS

HYDROGEN BOND

GLU11 - HIS297

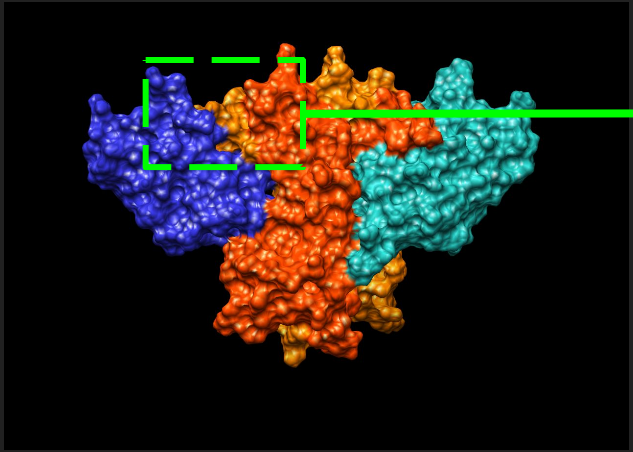


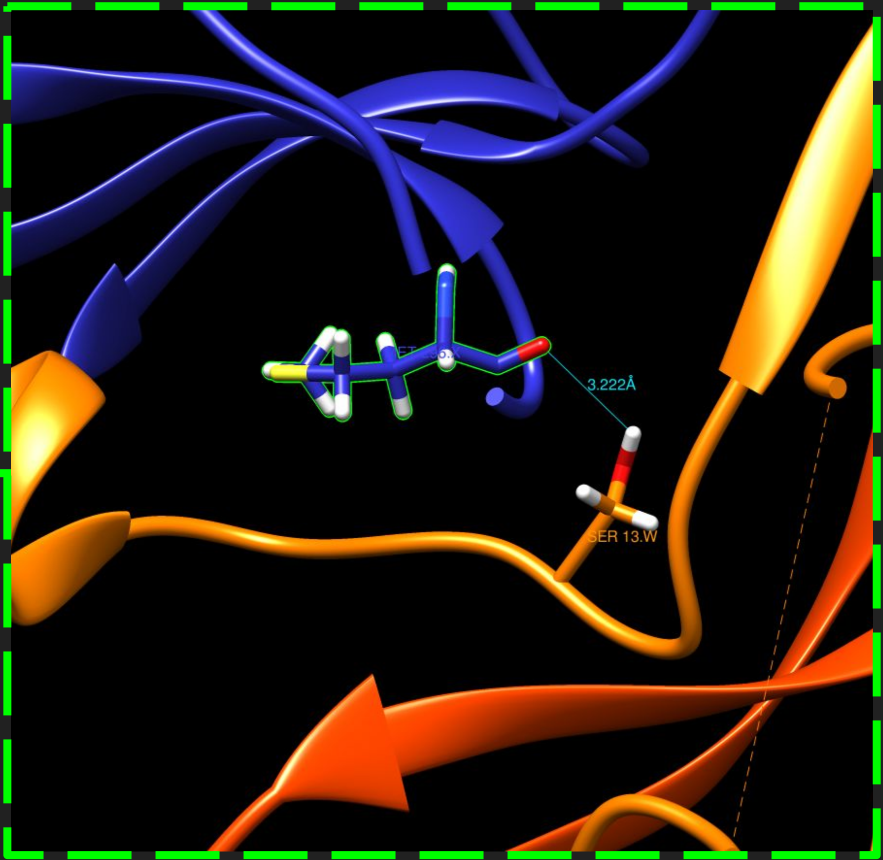


INTERACTIONS

HYDROGEN BOND

SER13 - MET296

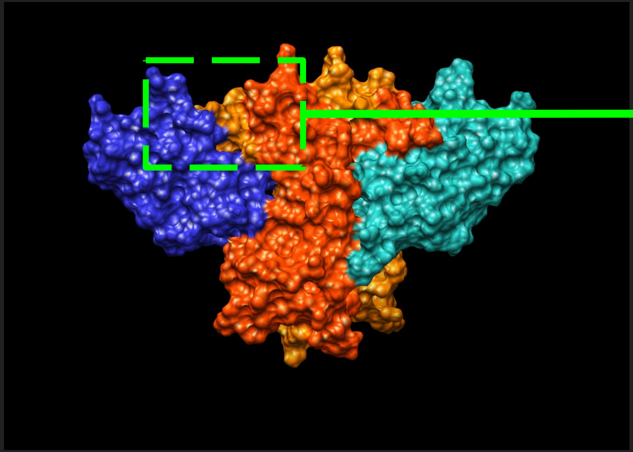


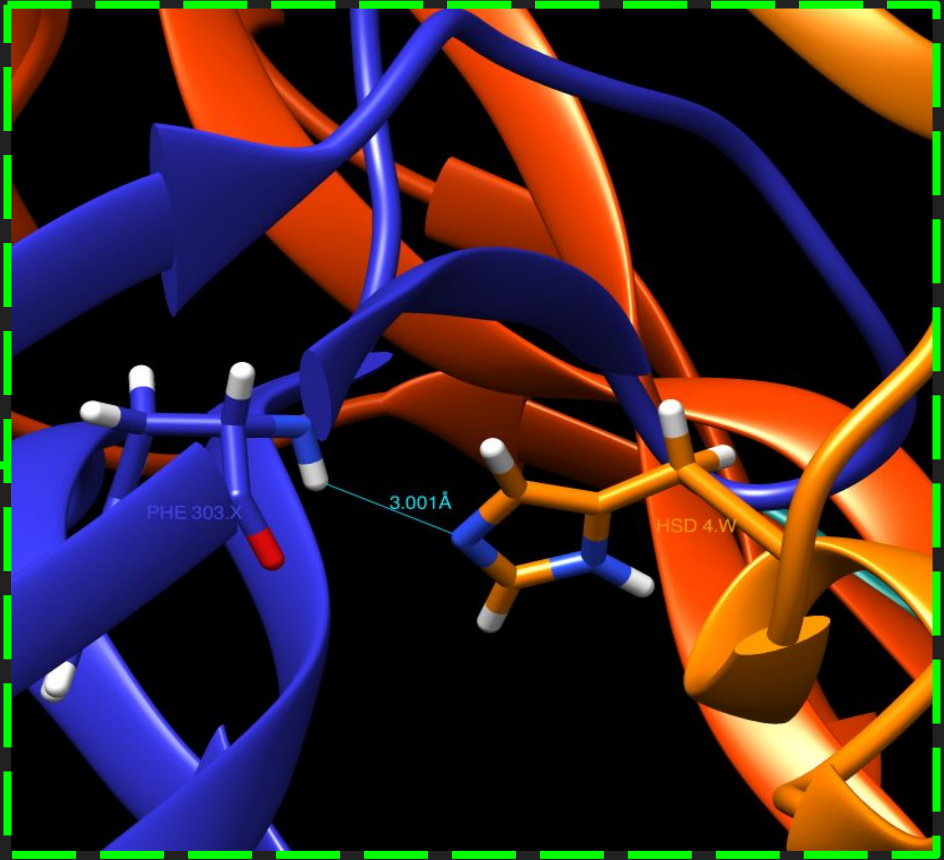


INTERACTIONS

HYDROGEN BOND

HIS4 - PHE303

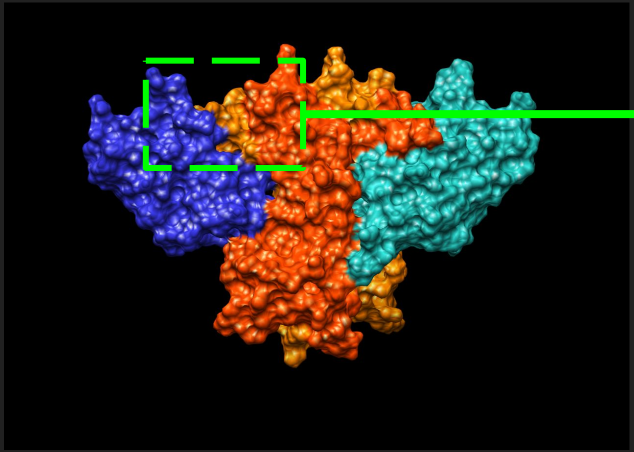


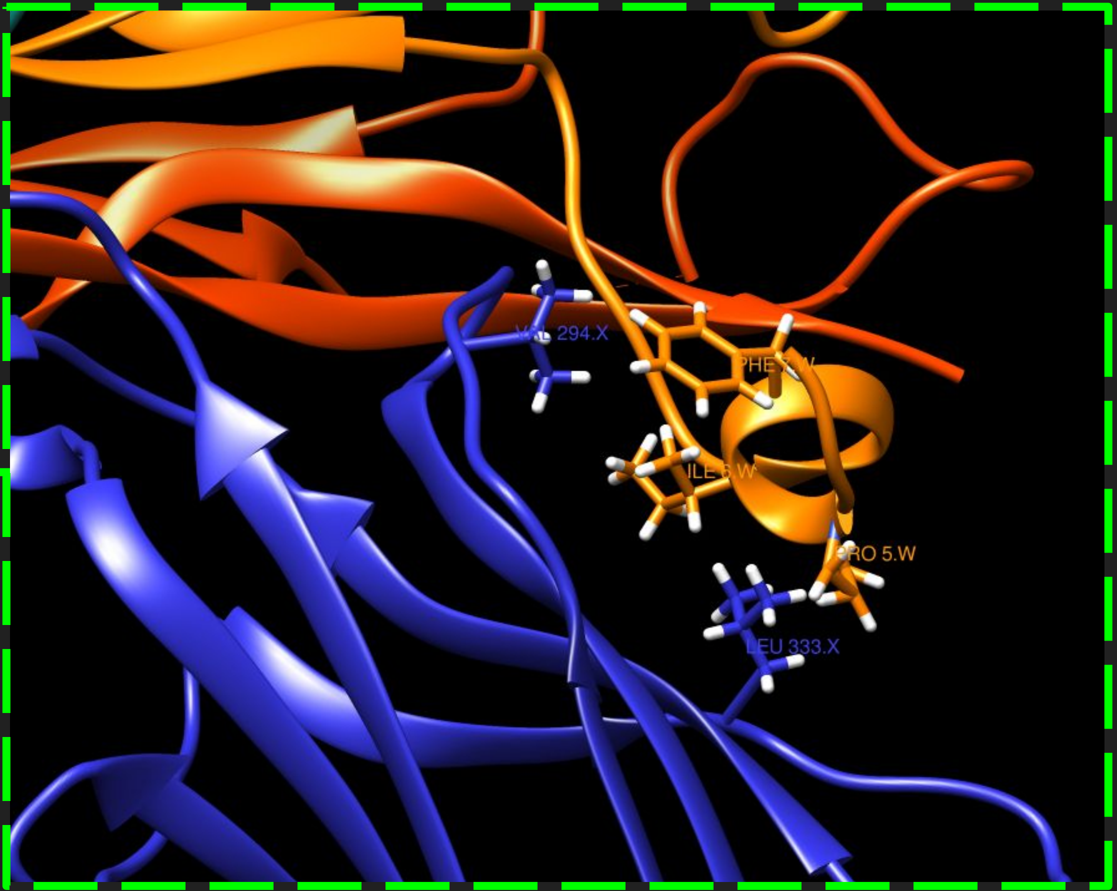


INTERACTIONS

HYDROPHOBIC INTERACTION

PRO5 ILE6 PHE7 - VAL294 LEU333

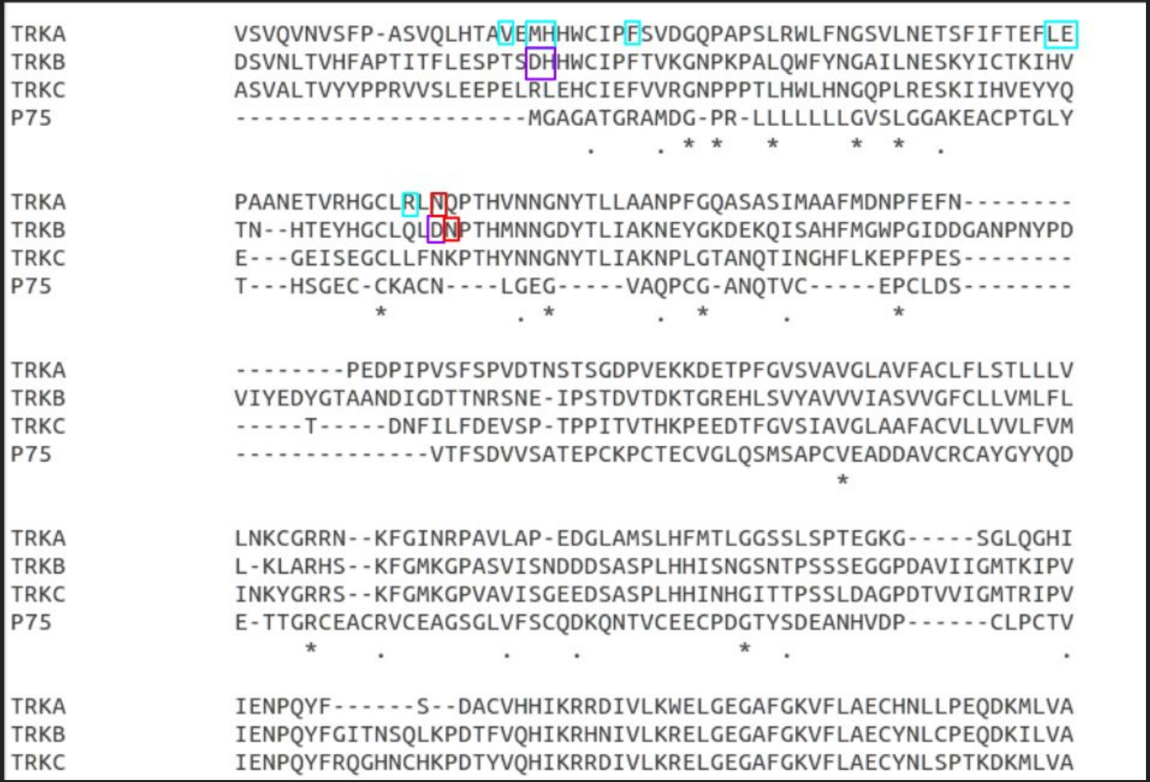




NEUROTROPHINS SEQUENCE ALIGNMENT

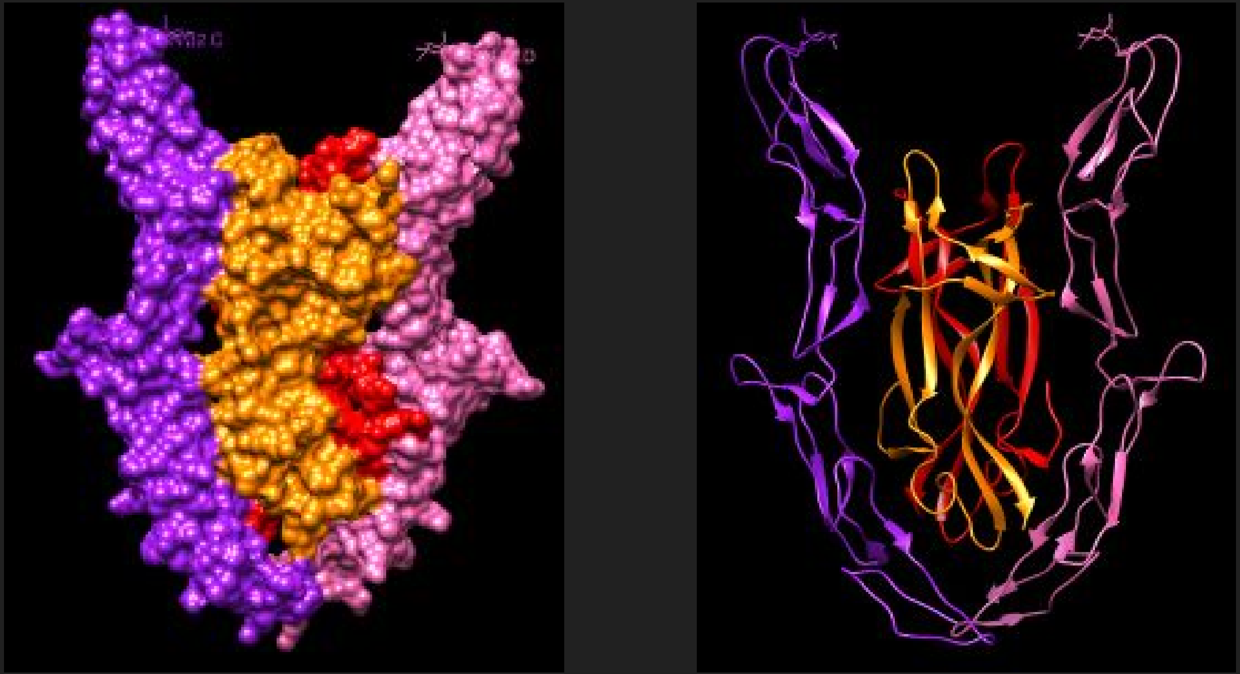
```
BDNF_HUMAN      MTILFLTMVISYFGCMKAAPMKEANIRGQG--GLAYPGVRTHGTLESVN-----GPKAGS
NGF_HUMAN       MSMLFYTLITAFLIGIQAEPHSESNVPAG------HTIPQAHWTK---------LQHSLD
NTF3_HUMAN      MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF4_HUMAN      ------------------------------------------------------MLPLPS


BDNF_HUMAN      RGLTSLADTFEHVIEELLD---EDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLL
NGF_HUMAN       TALRRARS--APAAAIAARVAGQTRNITVDPRLFKKRRLRSPRVLFSTQPPREAADTQDL
NTF3_HUMAN      STLPKAEAPREPERGGPAKSAFQPVIAMDTELLRQQRRYNSPRVLLSDSTPLEPPPLYLM
NTF4_HUMAN      CSLPILLLFLLPSVPIES----QPPPSTLPPFLAPEWDLLSPRVVLSRGAPAGPPLLFLL
                  *                   .                 . **. *   *        .

BDNF_HUMAN      EEYKN---YLDAANMSMRVRRHSDP--ARRGELSVCDSISEWVTAADKKTAVDMSGGTVT
NGF_HUMAN       DFEVG---GAAPFNRTHRSKRSSSHPIFHRGEFSVCDSVSVWVG--DKTTATDIKGKEVM
NTF3_HUMAN      EDYVG---SPVVANRTSRRKRYAEH-KSHRGEYSVCDSESLWVT--DKSSAIDIRGHQVT
NTF4_HUMAN      EAGAFRESAGAPANRS-RRGVSETAPASRRGELAVCDAVSGWVT--DRRTAVDLRGREVE
                .            * . *          .*** .***. * **   *. .* *. *  *

BDNF_HUMAN      VLEKVPVSK-GQLKQYFYETKCNPMGYTKEG-------CRGIDKRHWNSQCRTTQSYVRA
NGF_HUMAN       VLGEVNINN-SVFKQYFFETKCRDPNPVDSG-------CRGIDSKHWNSYCTTTHTFVKA
NTF3_HUMAN      VLGEIKTGN-SPVKQYFYETRCKEARPVKNG-------CRGIDDKHWNSQCKTSQTYVRA
NTF4_HUMAN      VLGEVPAAGGSPLRQYFFETRCKADNAEEGGPGAGGGGCRGVDRRHWVSECKAKQSYVRA
                **  .        .***.**.*        *       ***.* .** * * . ...*.*

BDNF_HUMAN      LTMDSKKRIGWRFIRIDTSCVCTLTIKRGR-
NGF_HUMAN       LTMDG-KQAAWRFIRIDTACVCVLSRKAVRR
NTF3_HUMAN      LTSENNKLVGWRWIRIDTSCVCALSRKIGRT
NTF4_HUMAN      LTADAQGRVGWRWIRIDTACVCTLLSRTGRA
                ** .      ** *****.*** *  .  *
```

NEUROTROPHINS RECEPTORS (TRK)
SEQUENCE ALIGNMENT

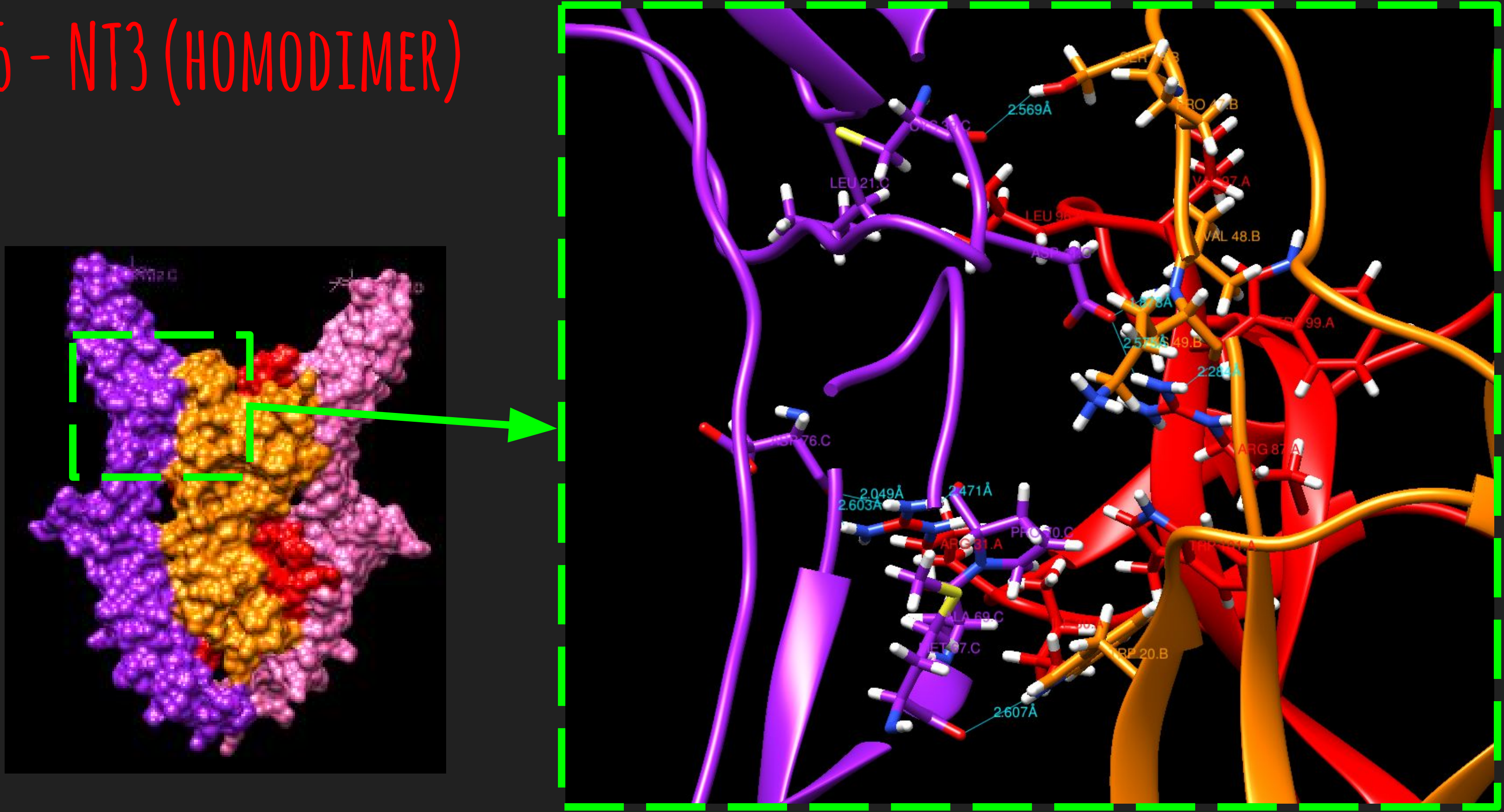


```
TRKA            VSVQVNVSFP-ASVQLHTAVEMHHWCIPFSVDGQPAPSLRWLFNGSVLNETSFIFTEFLE
TRKB            DSVNLTVHFAPTITFLESPTSDHHWCIPFTVKGNPKPALQWFYNGAILNESKYICTKIHV
TRKC            ASVALTVYYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLHWLHNGQPLRESKIIHVEYYQ
P75             ---------------------MGAGATGRAMDG-PR-LLLLLLLGVSLGGAKEACPTGLY
                                         .    . * *   *     *  *  .

TRKA            PAANETVRHGCLRLNQPTHVNNGNYTLLAANPFGQASASIMAAFMDNPFEFN--------
TRKB            TN--HTEYHGCLQLDNPTHMNNGDYTLIAKNEYGKDEKQISAHFMGWPGIDDGANPNYPD
TRKC            E---GEISEGCLLFNKPTHYNNGNYTLIAKNPLGTANQTINGHFLKEPFPES--------
P75             T---HSGEC-CKACN----LGEG-----VAQPCG-ANQTVC-----EPCLDS--------
                          *         . *       .  *     .       *

TRKA            --------PEDPIPVSFSPVDTNSTSGDPVEKKDETPFGVSVAVGLAVFACLFLSTLLLV
TRKB            VIYEDYGTAANDIGDTTNRSNE-IPSTDVTDKTGREHLSVYAVVVIASVVGFCLLVMLFL
TRKC            -----T-----DNFILFDEVSP-TPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFVM
P75             --------------VTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQD
                                                           *

TRKA            LNKCGRRN--KFGINRPAVLAP-EDGLAMSLHFMTLGGSSLSPTEGKG-----SGLQGHI
TRKB            L-KLARHS--KFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPV
TRKC            INKYGRRS--KFGMKGPVAVISGEEDSASPLHHINHGITTPSSLDAGPDTVVIGMTRIPV
P75             E-TTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDP------CLPCTV
                     *    .        .    .           *  .                   .

TRKA            IENPQYF------S--DACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVA
TRKB            IENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVA
TRKC            IENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVA
```

6. Example C: NT3 interaction with p-75



P-75 - NT3 (HOMODIMER)



SITE 1

SALT BRIDGE

ARG87 - ASP41

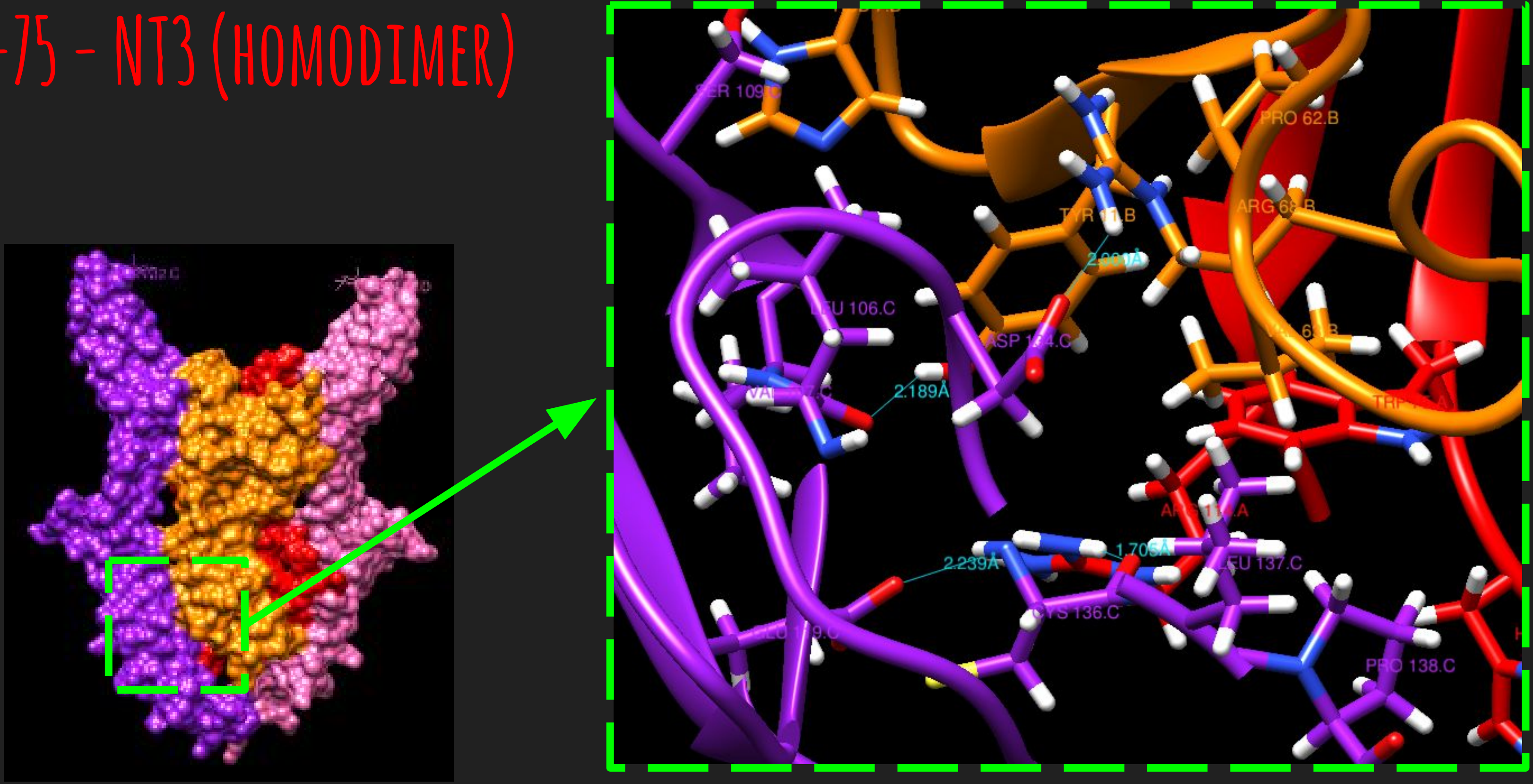
HYDROGEN BONDS

LYS49 - ASP41
ARG31 - ASP76
TRP20 - MET67
ARG31 - PRO70

HYDROPHOBIC CONTACTS

LEU96 - LEU21
ILE30, TRP101 - ALA69, PRO70

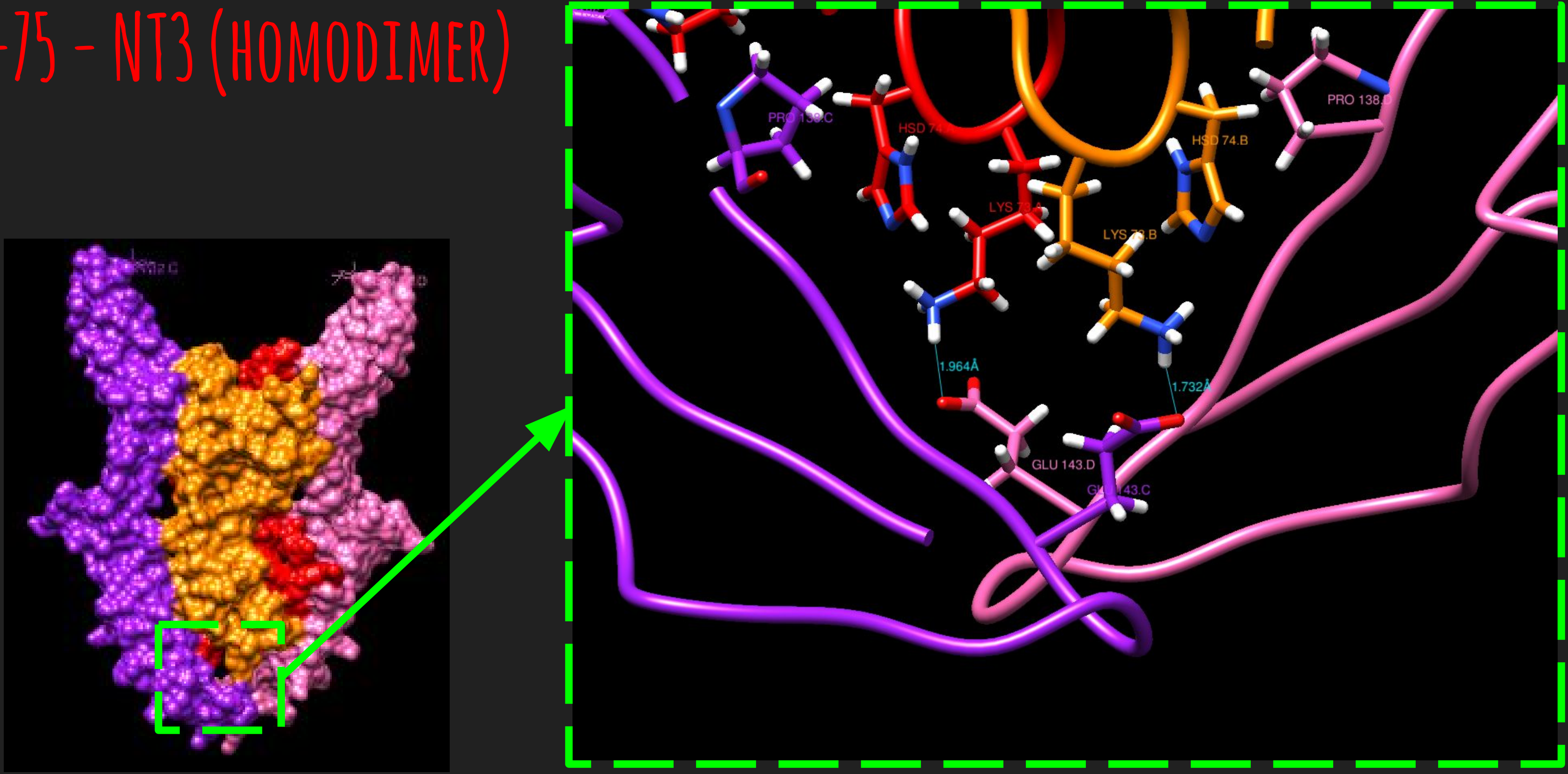
P-75 - NT3 (HOMODIMER)



SITE 2

SALT BRIDGES	HYDROGEN BONDS	HYDROPHOBIC CONTACTS
ARG114 - GLU119	TYR11 - LEU106	TRP75, VAL63 - LEU137
ARG68 - ASP134	ARG114 - CYS136	

P-75 - NT3 (HOMODIMER)



SITE 3

SALT BRIDGE

LYS73 - GLU143

HYDROPHOBIC CONTACTS

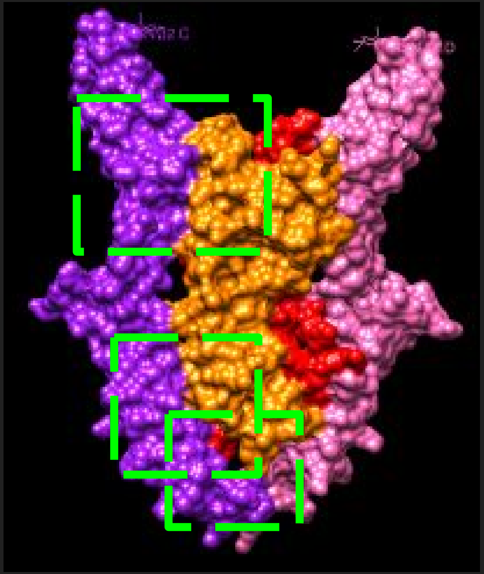
HSD74 - PRO138

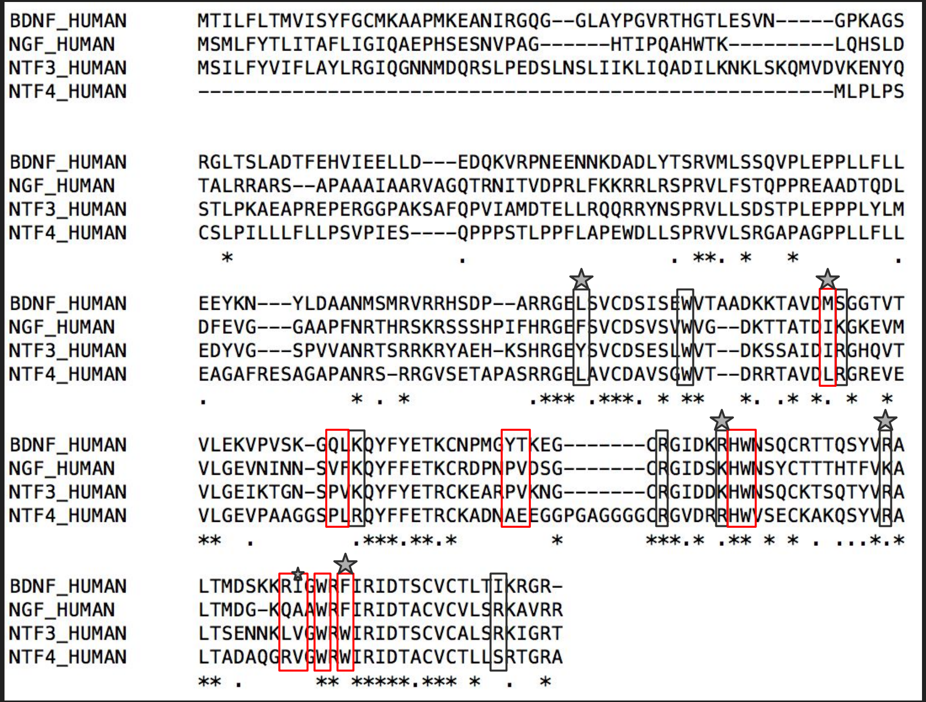
P-75 - NT3 (HOMODIMER)

🟥 HYDROPHOBIC CONTACTS

■ HYDROGEN BOND AND SALT BRIDGE

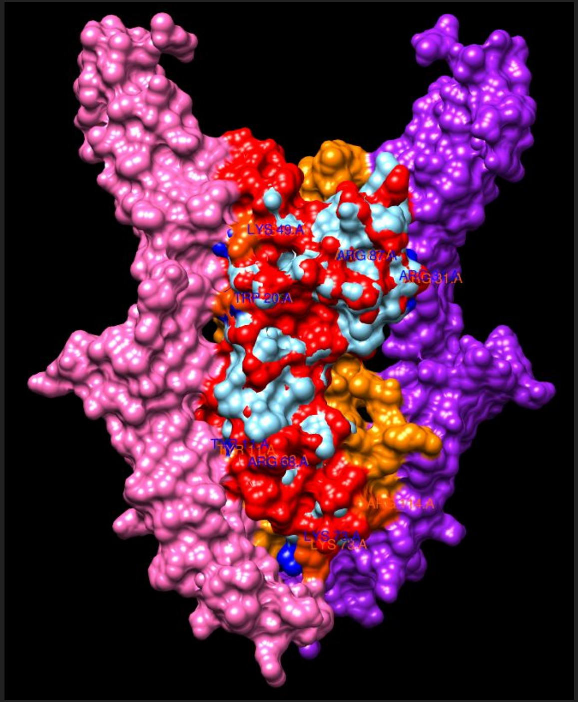
★ CONSERVATIVELY SUBSTITUTED

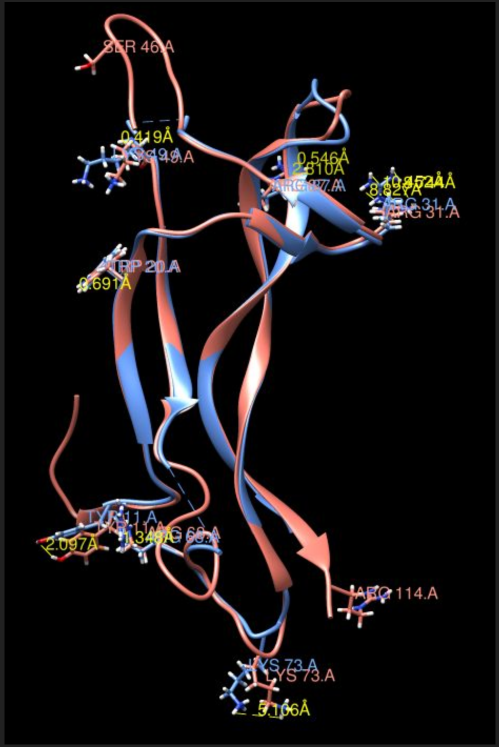


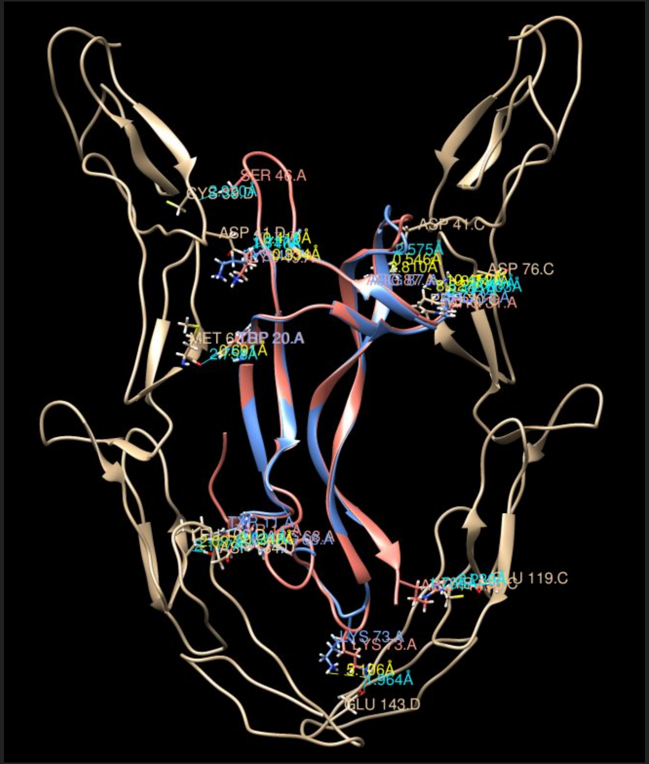


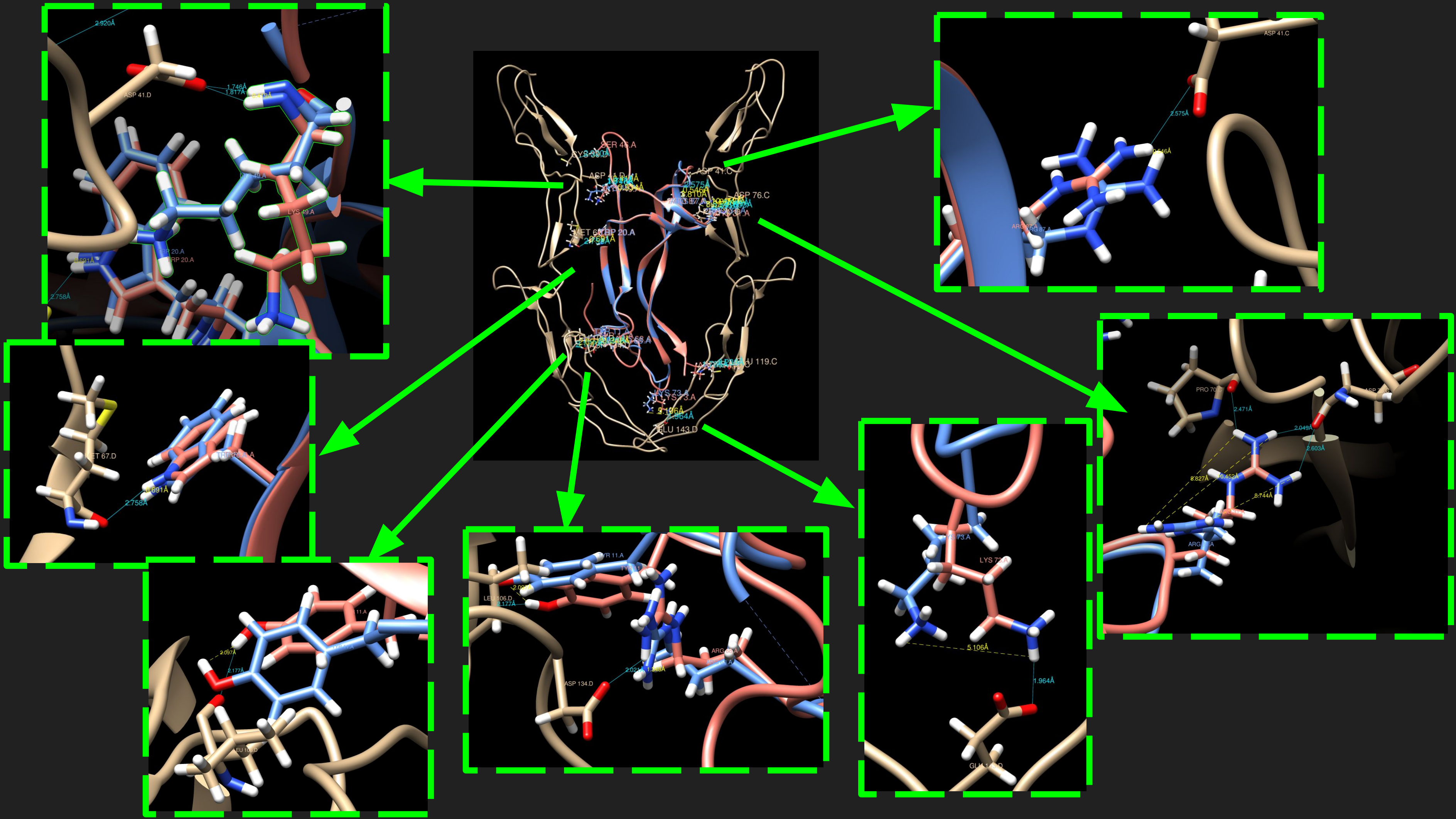
```
BDNF_HUMAN      MTILFLTMVISYFGCMKAAPMKEANIRGQG--GLAYPGVRTHGTLESVN-----GPKAGS
NGF_HUMAN       MSMLFYTLITAFLIGIQAEPHSESNVPAG------HTIPQAHWTK---------LQHSLD
NTF3_HUMAN      MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF4_HUMAN      ------------------------------------------------------MLPLPS


BDNF_HUMAN      RGLTSLADTFEHVIEELLD---EDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLL
NGF_HUMAN       TALRRARS--APAAAIAARVAGQTRNITVDPRLFKKRRLRSPRVLFSTQPPREAADTQDL
NTF3_HUMAN      STLPKAEAPREPERGGPAKSAFQPVIAMDTELLRQQRRYNSPRVLLSDSTPLEPPPLYLM
NTF4_HUMAN      CSLPILLLFLLPSVPIES----QPPPSTLPPFLAPEWDLLSPRVVLSRGAPAGPPLLFLL
                  *                   .                 . **. *   *        .

BDNF_HUMAN      EEYKN---YLDAANMSMRVRRHSDP--ARRGELSVCDSISEWVTAADKKTAVDMSGGTVT
NGF_HUMAN       DFEVG---GAAPFNRTHRSKRSSSHPIFHRGEFSVCDSVSVWVG--DKTTATDIKGKEVM
NTF3_HUMAN      EDYVG---SPVVANRTSRRKRYAEH-KSHRGEYSVCDSESLWVT--DKSSAIDIRGHQVT
NTF4_HUMAN      EAGAFRESAGAPANRS-RRGVSETAPASRRGELAVCDAVSGWVT--DRRTAVDLRGREVE
                .            * . *          .*** .***. * **   *. .* *. *  *

BDNF_HUMAN      VLEKVPVSK-GQLKQYFYETKCNPMGYTKEG-------CRGIDKRHWNSQCRTTQSYVRA
NGF_HUMAN       VLGEVNINN-SVFKQYFFETKCRDPNPVDSG-------CRGIDSKHWNSYCTTTHTFVKA
NTF3_HUMAN      VLGEIKTGN-SPVKQYFYETRCKEARPVKNG-------CRGIDDKHWNSQCKTSQTYVRA
NTF4_HUMAN      VLGEVPAAGGSPLRQYFFETRCKADNAEEGGPGAGGGGCRGVDRRHWVSECKAKQSYVRA
                **  .        .***.**.*        *       ***.* .** * * . ...*.*

BDNF_HUMAN      LTMDSKKRIGWRFIRIDTSCVCTLTIKRGR-
NGF_HUMAN       LTMDG-KQAAWRFIRIDTACVCVLSRKAVRR
NTF3_HUMAN      LTSENNKLVGWRWIRIDTSCVCALSRKIGRT
NTF4_HUMAN      LTADAQGRVGWRWIRIDTACVCTLLSRTGRA
                ** .      ** *****.*** *  .  *
```

Conformational changes

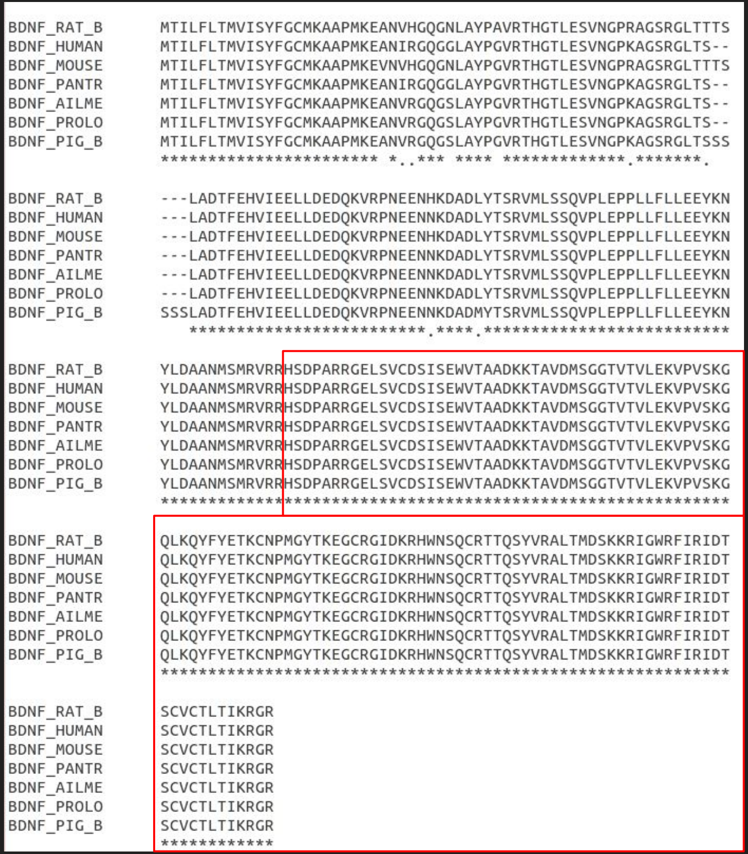




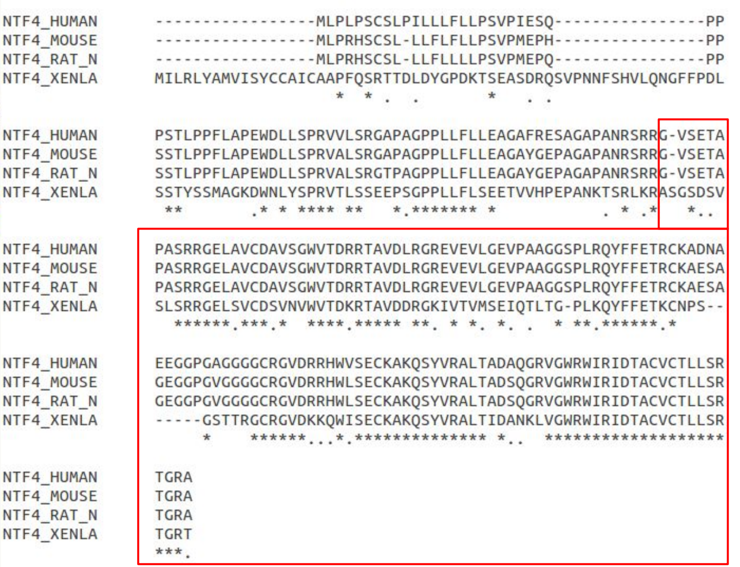



2.920Å
ASP 41.D
1.746Å
1.817Å
LYS 49.A
TRP 20.A
2.758Å
SER 46.A
CYS 39.D
ASP 41.C
ASP 76.C
MET 67.D
GLU 119.C
LYS 73.A
5.106Å
1.964Å
GLU 143.D
2.575Å
0.546Å
ARG 87.A
PRO 70
2.471Å
2.049Å
2.603Å
8.827Å
10.452Å
8.744Å
LEU 106.D
2.177Å
2.097Å
TYR 11.A
ASP 134.D
2.021Å
1.348Å

7. NEUROTROPHINS IN OTHER SPECIES: BDNF AND NT4



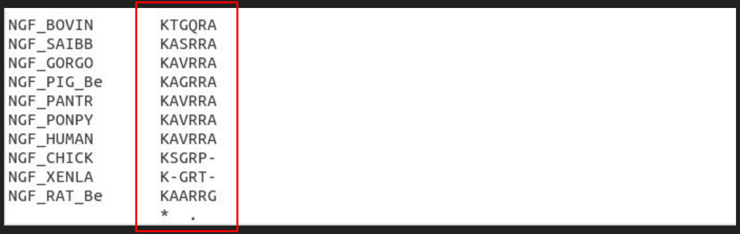
```
BDNF_RAT_B      MTILFLTMVISYFGCMKAAPMKEANVHGQGNLAYPAVRTHGTLESVNGPRAGSRGLTTTS
BDNF_HUMAN      MTILFLTMVISYFGCMKAAPMKEANIRGQGGLAYPGVRTHGTLESVNGPKAGSRGLTS--
BDNF_MOUSE      MTILFLTMVISYFGCMKAAPMKEVNVHGQGNLAYPGVRTHGTLESVNGPRAGSRGLTTTS
BDNF_PANTR      MTILFLTMVISYFGCMKAAPMKEANIRGQGGLAYPGVRTHGTLESVNGPKAGSRGLTS--
BDNF_AILME      MTILFLTMVISYFGCMKAAPMKEANVRGQGSLAYPGVRTHGTLESVNGPKAGSRGLTS--
BDNF_PROLO      MTILFLTMVISYFGCMKAAPMKEANVRGQGSLAYPGVRTHGTLESVNGPKAGSRGLTS--
BDNF_PIG_B      MTILFLTMVISYFGCMKAAPMKEANVRGQGSLAYPGVRTHGTLESVNGPKAGSRGLTSSS
                *********************** *..*** **** *************.*******.

BDNF_RAT_B      ---LADTFEHVIEELLDEDQKVRPNEENHKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_HUMAN      ---LADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_MOUSE      ---LADTFEHVIEELLDEDQKVRPNEENHKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_PANTR      ---LADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_AILME      ---LADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_PROLO      ---LADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEYKN
BDNF_PIG_B      SSSLADTFEHVIEELLDEDQKVRPNEENNKDADMYTSRVMLSSQVPLEPPLLFLLEEYKN
                   *************************.****.**************************

BDNF_RAT_B      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_HUMAN      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_MOUSE      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_PANTR      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_AILME      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_PROLO      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
BDNF_PIG_B      YLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKG
                ************************************************************

BDNF_RAT_B      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_HUMAN      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_MOUSE      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_PANTR      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_AILME      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_PROLO      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
BDNF_PIG_B      QLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDT
                ************************************************************

BDNF_RAT_B      SCVCTLTIKRGR
BDNF_HUMAN      SCVCTLTIKRGR
BDNF_MOUSE      SCVCTLTIKRGR
BDNF_PANTR      SCVCTLTIKRGR
BDNF_AILME      SCVCTLTIKRGR
BDNF_PROLO      SCVCTLTIKRGR
BDNF_PIG_B      SCVCTLTIKRGR
                ************
```



```
NTF4_HUMAN      -----------------MLPLPSCSLPILLLFLLPSVPIESQ----------------PP
NTF4_MOUSE      -----------------MLPRHSCSL-LLFLFLLPSVPMEPH----------------PP
NTF4_RAT_N      -----------------MLPRHSCSL-LLFLLLLPSVPMEPQ----------------PP
NTF4_XENLA      MILRLYAMVISYCCAICAAPFQSRTTDLDYGPDKTSEASDRQSVPNNFSHVLQNGFFPDL
                                   *  * .  .       *   . .

NTF4_HUMAN      PSTLPPFLAPEWDLLSPRVVLSRGAPAGPPLLFLLEAGAFRESAGAPANRSRRG-VSETA
NTF4_MOUSE      SSTLPPFLAPEWDLLSPRVALSRGAPAGPPLLFLLEAGAYGEPAGAPANRSRRG-VSETA
NTF4_RAT_N      SSTLPPFLAPEWDLLSPRVALSRGTPAGPPLLFLLEAGAYGEPAGAPANRSRRG-VSETA
NTF4_XENLA      SSTYSSMAGKDWNLYSPRVTLSSEEPSGPPLLFLSEETVVHPEPANKTSRLKRASGSDSV
                 **       .* * **** **   *.******* *           . * .*   *..

NTF4_HUMAN      PASRRGELAVCDAVSGWVTDRRTAVDLRGREVEVLGEVPAAGGSPLRQYFFETRCKADNA
NTF4_MOUSE      PASRRGELAVCDAVSGWVTDRRTAVDLRGREVEVLGEVPAAGGSPLRQYFFETRCKAESA
NTF4_RAT_N      PASRRGELAVCDAVSGWVTDRRTAVDLRGREVEVLGEVPAAGGSPLRQYFFETRCKAESA
NTF4_XENLA      SLSRRGELSVCDSVNVWVTDKRTAVDDRGKIVTVMSEIQTLTG-PLKQYFFETKCNPS--
                  ******.***.*  ****.***** **. * *. *. .  * **.******.*

NTF4_HUMAN      EEGGPGAGGGGCRGVDRRHWVSECKAKQSYVRALTADAQGRVGWRWIRIDTACVCTLLSR
NTF4_MOUSE      GEGGPGVGGGGCRGVDRRHWLSECKAKQSYVRALTADSQGRVGWRWIRIDTACVCTLLSR
NTF4_RAT_N      GEGGPGVGGGGCRGVDRRHWLSECKAKQSYVRALTADSQGRVGWRWIRIDTACVCTLLSR
NTF4_XENLA      -----GSTTRGCRGVDKKQWISECKAKQSYVRALTIDANKLVGWRWIRIDTACVCTLLSR
                     *    ******...*.************** *..  *******************

NTF4_HUMAN      TGRA
NTF4_MOUSE      TGRA
NTF4_RAT_N      TGRA
NTF4_XENLA      TGRT
                ***.
```

7. NEUROTROPHINS IN OTHER SPECIES: NGF

```
NGF_BOVIN       ----MSMLFYTLITALLIGIQAAPHTESNVPAGHAIPQAHWIKLQHSLDTVLRRAHSAPA
NGF_SAIBB       ----MSMLFYTLITAFLIGIQAEPHSESNVPAGHTIPQAHWTKLQHSLDTALRRARSAPA
NGF_GORGO       ----MSMLFYTLITAFLIGIQAELHSESNVPAGHTIPQAHWTKLQHSLDTALRRARSAPA
NGF_PIG_Be      ----------------LIGIQAEPHTESNVPAGHAIPQAHWTKLQHSLDTALRRAHSAPA
NGF_PANTR       ----MSMLFYTLITAFLIGTQAEPHSESNVPAGHTIPQAHWTKLQHSLDTALRRARSAPA
NGF_PONPY       ----MSMLFYTLITAFLIGIQAEPHSESNVPAGHTIPQAHWTKLQHSLDTALRRARSTPA
NGF_HUMAN       ----MSMLFYTLITAFLIGIQAEPHSESNVPAGHTIPQAHWTKLQHSLDTALRRARSAPA
NGF_CHICK       MHSVMSMLYYTLIIAFLIGTQAAPKSEDNGPLEYPAEHSLPSTQQSNGQHIAKAAPQTTH
NGF_XENLA       ----MSMLYYTLLIAILISVQAAPKTKDHAPARSSAKSRIPHHTHR------TKSLHHSH
NGF_RAT_Be      ----MSMLFYTLITAFLIGVQAEPYTDSNVPEGDSVPEAHWTKLQHSLDTALRRARSAPA
                                **  **   .  . *             .         .

NGF_BOVIN       GPIAAR-VAGQTHNITVDPKLFKKRRLRSPRVLFSTQPPPVAADTQDLDFEAGGASSFNR
NGF_SAIBB       GPIAAR-VAGQTRNITVDPKLFKKRRLRSPRVLFSTQPPPEAADTQDLDFEVAGAAPVNR
NGF_GORGO       AAIAAR-VAGQTRNITVDPRLFKKRRLRSPRVLFSTQPPPEAADTQDLDFEVGGAAPFNR
NGF_PIG_Be      GANSAR-VAGQTRNITVDPKLFKKRRLRSPRVLFSTQPPPVAADTQDPDLEASGAASFNR
NGF_PANTR       AAIAAR-VAGQTRNITVDPRLFKKRRLRSPRVLFSTQPPPEAADTQDLDFEVGGAAPFNR
NGF_PONPY       AAIAAR-VAGQTCNITVDPRLFKKRRLRSPRVLFSTQPPPEAADTQDLDFEVGGAAPFNR
NGF_HUMAN       AAIAAR-VAGQTRNITVDPRLFKKRRLRSPRVLFSTQPPREAADTQDLDFEVGGAAPFNR
NGF_CHICK       GRFAWMPDGTEDLNIAMDQNFFKKKRFRSSRVLFSTQPPPVSRKGQSTGFLSS-AVSLNR
NGF_XENLA       GKLEAK-EPSYFRNVTVDPKLFRKRKFRSPRVLFSTQPPPLSEDFQHLEYLDD-EESLNK
NGF_RAT_Be      EPIAAR-VTGQTRNITVDPKLFKKRRLRSPRVLFSTQPPPTSSDTLDLDFQAHGTISFNR
                             *...*   *.*.. ** *********  .                *.

NGF_BOVIN       THRSKRSSSHPVFHRGEFSVCDSISVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_SAIBB       THRSKRSSSHPIFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_GORGO       THRSKRSSSHPIFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_PIG_Be      THRSKRSSSHPVFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_PANTR       THRSKRSSSHPIFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_PONPY       THRSKRSSSHPIFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_HUMAN       THRSKRSSSHPIFHRGEFSVCDSVSVWVGDKTTATDIKGKEVMVLGEVNINNSVFKQYFF
NGF_CHICK       TARTKR-TAHPVLHRGEFSVCDSVSMWVGDKTTATDIKGKEVTVLGEVNINNNVFKQYFF
NGF_XENLA       TIRAKR-TVHPVLHKGEYSVCDSVSMWVGEKTKATDIKGKEVTVLGEVNINNSVFKQYFF
NGF_RAT_Be      THRSKRSSTHPVFHMGEFSVCDSVSVWVGDKTTATDIKGKEVTVLGEVNINNSVFKQYFF
                * *.** . **. * **.*****.*.***.** ********* ********* *******

NGF_BOVIN       ETKCRDPNPVDSGCRGIDAKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_SAIBB       ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_GORGO       ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_PIG_Be      ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_PANTR       ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_PONPY       ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_HUMAN       ETKCRDPNPVDSGCRGIDSKHWNSYCTTTHTFVKALTMDGKQAAWRFIRIDTACVCVLSR
NGF_CHICK       ETKCRDPRPVSSGCRGIDAKHWNSYCTTTHTFVKALTMEGKQAAWRFIRIDTACVCVLSR
NGF_XENLA       ETKCRDPKPVSSGCRGIDAKHWNSYCTTTHTFVKALTMEGKQAAWRFIRIDTACVCVLSR
NGF_RAT_Be      ETKCRAPNPVESGCRGIDSKHWNSYCTTTHTFVKALTTDDKQAAWRFIRIDTACVCVLSR
                ***** * ** *******.****************** . ********************
```

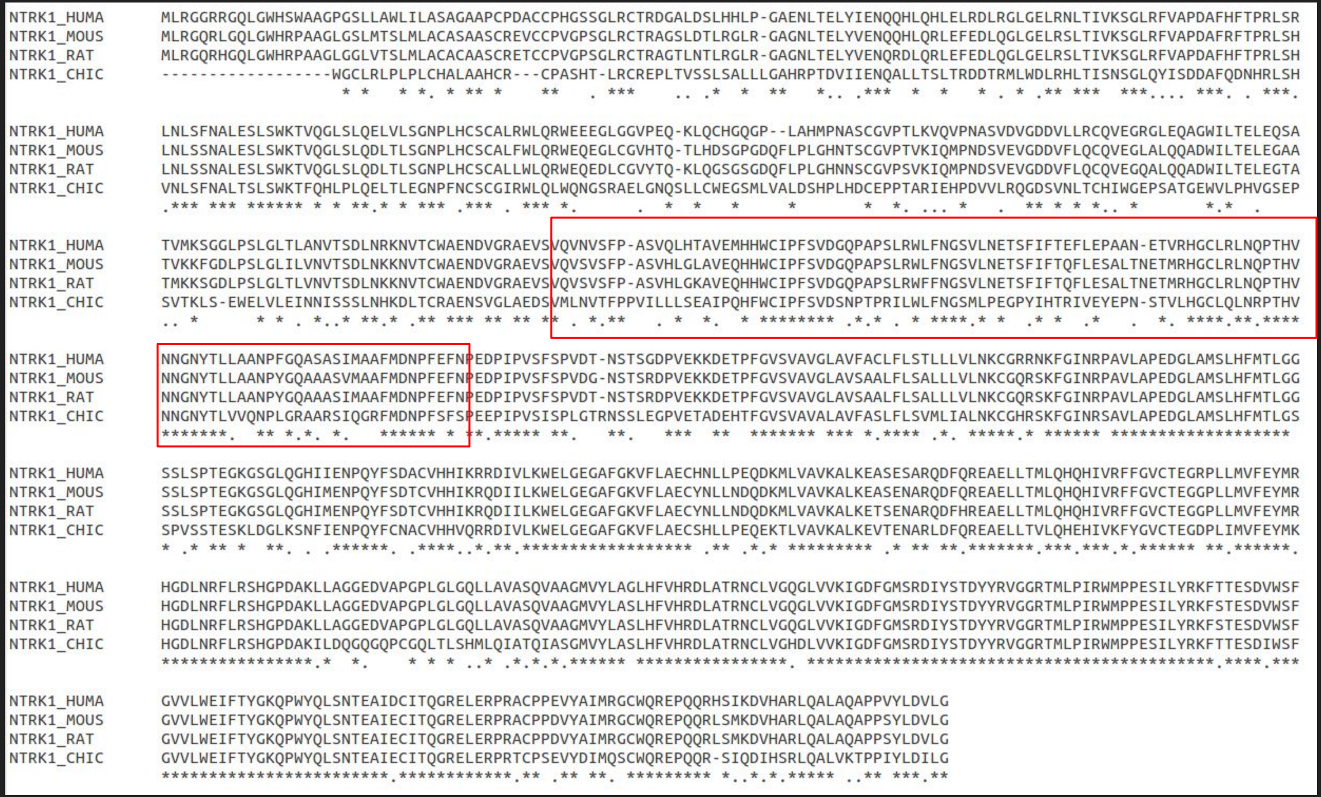


```
NGF_BOVIN       KTGQRA
NGF_SAIBB       KASRRA
NGF_GORGO       KAVRRA
NGF_PIG_Be      KAGRRA
NGF_PANTR       KAVRRA
NGF_PONPY       KAVRRA
NGF_HUMAN       KAVRRA
NGF_CHICK       KSGRP-
NGF_XENLA       K-GRT-
NGF_RAT_Be      KAARRG
                *  .
```

7. NEUROTROPHINS IN OTHER SPECIES: NT3

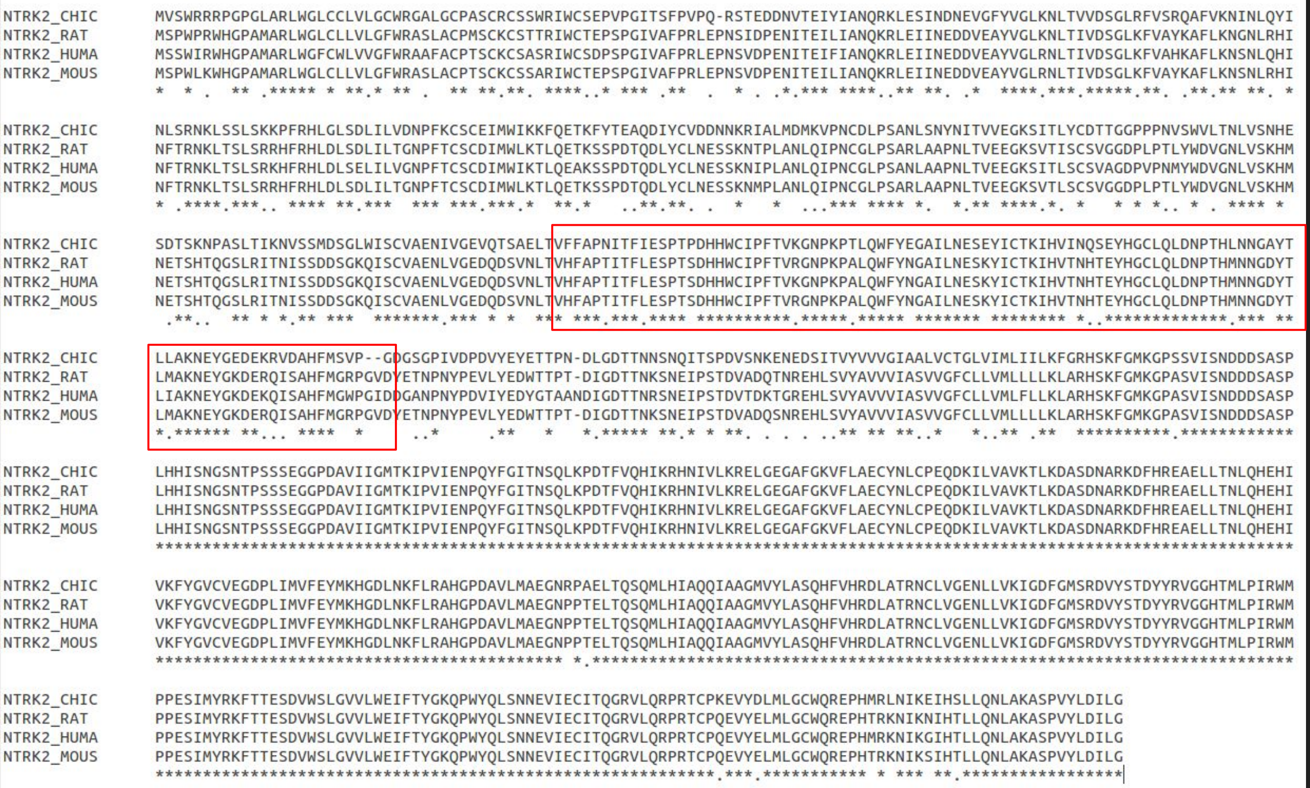
```
NTF3_BOVIN      MSILFYVMFLAYLRGVQGNSMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF3_HUMAN      MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF3_MOUSE      MSILFYVIFLAYLRGIQGNSMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF3_RAT_N      MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDVKENYQ
NTF3_FELCA      MSILFYVIFLAYLRGIQGNNMDQRSLPEDSLNSLIIKLIQADILKNKLSKQMVDLKENYQ
NTF3_PIG_N      MSILFYMIFLAYLRGIQGNSMDQRRLPEDSLNSLIIKLIQADILKNKLSKQMVDLQENYQ
NTF3_CHICK      MSILFYVIFLAYLRGIQSTNMDQRSLPEDSMNSLIIKLIRADILKNKLSKQVMDVKENYQ
NTF3_XENLA      MSILFYVMFLPYLCGIHATNMDKRNLPENSMNSLFIKLIQADLLKNKISKQTVDTKENHQ
                ******..** ** *.. . **.* *** *.*** ****.**.****.*** .* .** *

NTF3_BOVIN      STLPKAEAPPR----EPAKSEFQPVTAMGPELLRQQ--RRYSSPRVLLSDSTPLEPPPLY
NTF3_HUMAN      STLPKAEAPREPERGGPAKSAFQPVIAMDTELLRQQ--RRYNSPRVLLSDSTPLEPPPLY
NTF3_MOUSE      STLPKAEAPREPEQGEATRSEFQPMIATDTELLRQQ--RRYNSPRVLLSDSTPLEPPPLY
NTF3_RAT_N      STLPKAEAPREPEQGEATRSEFQPMIATDTELLRQQ--RRYNSPRVLLSDSTPLEPPPLY
NTF3_FELCA      STLPKAEAPREPEQGEPAKSEFQPVTAMDTELLRQQ--RRYSSPRVLLSDSTPLEPPPLY
NTF3_PIG_N      STLPKAEAPREPERGEPAKSEFQPVTAVGPEWLRHH--RRYNSPRVLLSDSTPLEPPPLY
NTF3_CHICK      NIVQKVEDHQEMDGDENVKSDFQPVISMDTDLLRQQ--RRYNSPRVLLSDNTPLEPPPLY
NTF3_XENLA      STIPKPQILLDLDGDDNMKQDFQPVISLEAELVKQQKQRRYKSPRVLLSDSLPLEPPPLY
                  . * .           .  ***. .   . ....  *** ********* ********

NTF3_BOVIN      LMEDYVGSPVAANRTS-RRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_HUMAN      LMEDYVGSPVVANRTS-RRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_MOUSE      LMEDYVGNPVVANRTSPRRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_RAT_N      LMEDYVGNPVVTNRTSPRRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_FELCA      LMEDYVGSPVAANRTS-RRKRYAEHKSHRGEYSLCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_PIG_N      LVEDYVGNPSVANRTA-RRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_CHICK      LTEDYVGSSVVLNRTS-RRKRYAEHKSHRGEYSVCDSESLWVTDKSSAIDIRGHQVTVLG
NTF3_XENLA      LMDDYIGHSTVVNNRTSRRKRFAEHKGHRGEYSVCDSESLWVTDKMNAIDIRGHQVTVLG
                * .**.*     *  . ****.**** ******.***********  *************

NTF3_BOVIN      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_HUMAN      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_MOUSE      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_RAT_N      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_FELCA      EIKSGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_PIG_N      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYFRALTSYNNKLVGW
NTF3_CHICK      EIKTGNSPVKQYFYETRCKEAKPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKLVGW
NTF3_XENLA      EIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCKTSQTYVRALTSENNKMVGW
                ***.*****************.************************ ***** ***.***

NTF3_BOVIN      RWIRIDTSCVCALSRKIGRT
NTF3_HUMAN      RWIRIDTSCVCALSRKIGRT
NTF3_MOUSE      RWIRIDTSCVCALSRKIGRT
NTF3_RAT_N      RWIRIDTSCVCALSRKIGRT
NTF3_FELCA      RWIRIDTSCVCALSRKIGRT
NTF3_PIG_N      RWIRIDTSCVCALSRKIGRT
NTF3_CHICK      RWIRIDTSCVCALSRKIGRT
NTF3_XENLA      RWIRIDTSCVCALSRKIGRS
                *******************.
```

8. NEUROTROPHINS RECEPTORS IN OTHER SPECIES: TRKA



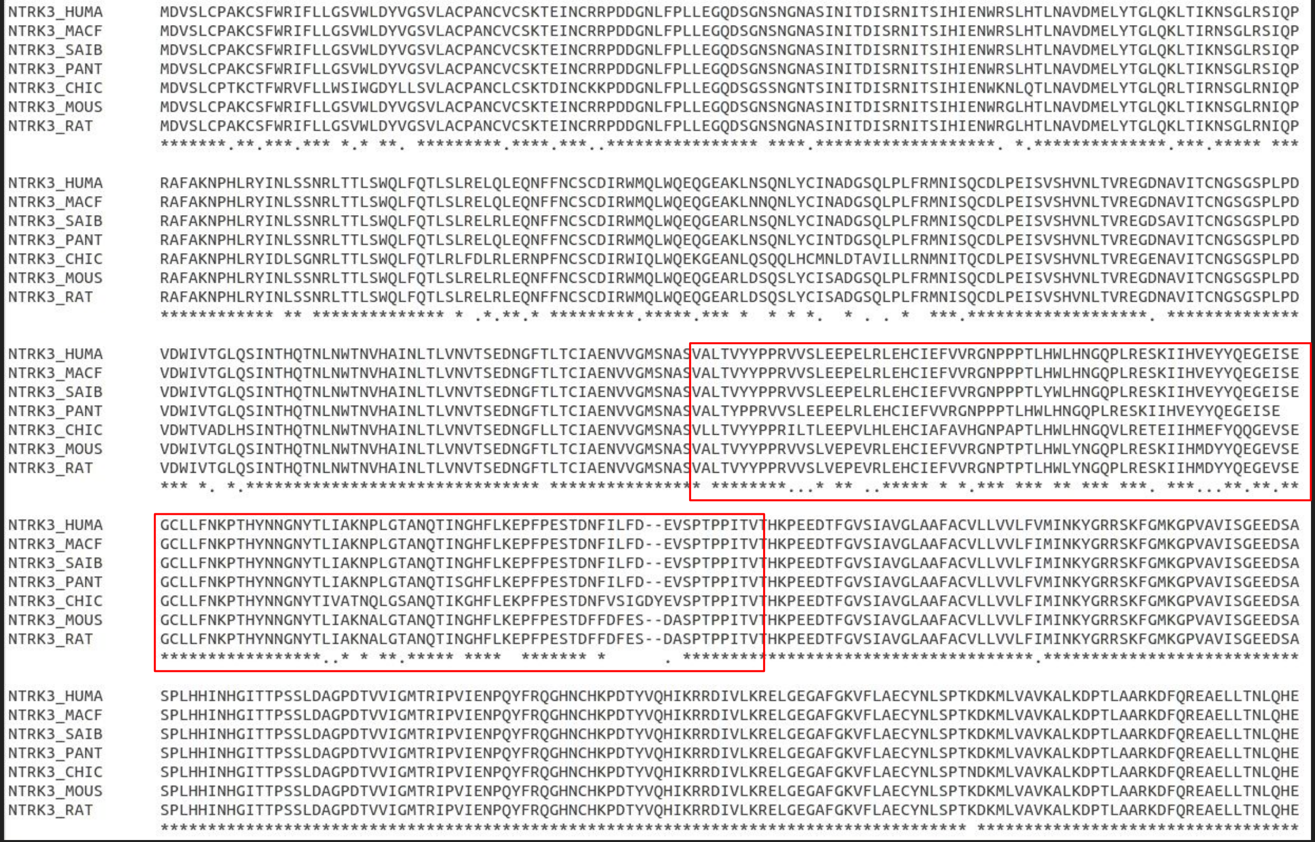
```
NTRK1_HUMA      MLRGGRRGQLGWHSWAAGPGSLLAWLILASAGAAPCPDACCPHGSSGLRCTRDGALDSLHHLP-GAENLTELYIENQQHLQHLELRDLRGLGELRNLTIVKSGLRFVAPDAFHFTPRLSR
NTRK1_MOUS      MLRGQRLGQLGWHRPAAGLGSLMTSLMLACASAASCREVCCPVGPSGLRCTRAGSLDTLRGLR-GAGNLTELYVENQQHLQRLEFEDLQGLGELRSLTIVKSGLRFVAPDAFRFTPRLSH
NTRK1_RAT       MLRGQRHGQLGWHRPAAGLGGLVTSLMLACACAASCRETCCPVGPSGLRCTRAGTLNTLRGLR-GAGNLTELYVENQRDLQRLEFEDLQGLGELRSLTIVKSGLRFVAPDAFHFTPRLSH
NTRK1_CHIC      ------------------WGCLRLPLPLCHALAAHCR---CPASHT-LRCREPLTVSSLSALLLGAHRPTDVIIENQALLTSLTRDDTRMLWDLRHLTISNSGLQYISDDAFQDNHRLSH
                                   * *   * *. * ** *    **   . ***    .. .*  *  **   *.. .***  *  *   * . * .** ***  ***.... ***. . ***.

NTRK1_HUMA      LNLSFNALESLSWKTVQGLSLQELVLSGNPLHCSCALRWLQRWEEEGLGGVPEQ-KLQCHGQGP--LAHMPNASCGVPTLKVQVPNASVDVGDDVLLRCQVEGRGLEQAGWILTELEQSA
NTRK1_MOUS      LNLSSNALESLSWKTVQGLSLQDLTLSGNPLHCSCALFWLQRWEQEGLCGVHTQ-TLHDSGPGDQFLPLGHNTSCGVPTVKIQMPNDSVEVGDDVFLQCQVEGLALQQADWILTELEGAA
NTRK1_RAT       LNLSSNALESLSWKTVQGLSLQDLTLSGNPLHCSCALLWLQRWEQEDLCGVYTQ-KLQGSGSGDQFLPLGHNNSCGVPSVKIQMPNDSVEVGDDVFLQCQVEGQALQQADWILTELEGTA
NTRK1_CHIC      VNLSFNALTSLSWKTFQHLPLQELTLEGNPFNCSCGIRWLQLWQNGSRAELGNQSLLCWEGSMLVALDSHPLHDCEPPTARIEHPDVVLRQGDSVNLTCHIWGEPSATGEWVLPHVGSEP
                .*** *** ****** * * **.* * *** .*** . *** *.      .  *  *   *     *       *  *. ... *   .  ** * * *.. *       *.*  .

NTRK1_HUMA      TVMKSGGLPSLGLTLANVTSDLNRKNVTCWAENDVGRAEVSVQVNVSFP-ASVQLHTAVEMHHWCIPFSVDGQPAPSLRWLFNGSVLNETSFIFTEFLEPAAN-ETVRHGCLRLNQPTHV
NTRK1_MOUS      TVKKFGDLPSLGLILVNVTSDLNKKNVTCWAENDVGRAEVSVQVSVSFP-ASVHLGLAVEQHHWCIPFSVDGQPAPSLRWLFNGSVLNETSFIFTQFLESALTNETMRHGCLRLNQPTHV
NTRK1_RAT       TMKKSGDLPSLGLTLVNVTSDLNKKNVTCWAENDVGRAEVSVQVSVSFP-ASVHLGKAVEQHHWCIPFSVDGQPAPSLRWFFNGSVLNETSFIFTQFLESALTNETMRHGCLRLNQPTHV
NTRK1_CHIC      SVTKLS-EWELVLEINNISSSLNHKDLTCRAENSVGLAEDSVMLNVTFPPVILLLSEAIPQHFWCIPFSVDSNPTPRILWLFNGSMLPEGPYIHTRIVEYEPN-STVLHGCLQLNRPTHV
                .. *      * * . *..* **.* .** *** ** ** ** . *.**   . *  *.  * ******** .*.* . * ****.* *  .*  .*   .  *. ****.**.****

NTRK1_HUMA      NNGNYTLLAANPFGQASASIMAAFMDNPFEFNPEDPIPVSFSPVDT-NSTSGDPVEKKDETPFGVSVAVGLAVFACLFLSTLLLVLNKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGG
NTRK1_MOUS      NNGNYTLLAANPYGQAAASVMAAFMDNPFEFNPEDPIPVSFSPVDG-NSTSRDPVEKKDETPFGVSVAVGLAVSAALFLSALLLVLNKCGQRSKFGINRPAVLAPEDGLAMSLHFMTLGG
NTRK1_RAT       NNGNYTLLAANPYGQAAASIMAAFMDNPFEFNPEDPIPVSFSPVDT-NSTSRDPVEKKDETPFGVSVAVGLAVSAALFLSALLLVLNKCGQRSKFGINRPAVLAPEDGLAMSLHFMTLGG
NTRK1_CHIC      NNGNYTLVVQNPLGRAARSIQGRFMDNPFSFSPEEPIPVSISPLGTRNSSLEGPVETADEHTFGVSVAVALAVFASLFLSVMLIALNKCGHRSKFGINRSAVLAPEDGLAMSLHFMTLGS
                *******.  ** *.*. *.   ****** * **.***** **.   **.   ***  **  ******* *** *.**** .*. *****.* ****** *******************

NTRK1_HUMA      SSLSPTEGKGSGLQGHIIENPQYFSDACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALKEASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMR
NTRK1_MOUS      SSLSPTEGKGSGLQGHIMENPQYFSDTCVHHIKRQDIILKWELGEGAFGKVFLAECYNLLNDQDKMLVAVKALKEASENARQDFQREAELLTMLQHQHIVRFFGVCTEGGPLLMVFEYMR
NTRK1_RAT       SSLSPTEGKGSGLQGHIMENPQYFSDTCVHHIKRQDIILKWELGEGAFGKVFLAECYNLLNDQDKMLVAVKALKETSENARQDFHREAELLTMLQHQHIVRFFGVCTEGGPLLMVFEYMR
NTRK1_CHIC      SPVSSTESKLDGLKSNFIENPQYFCNACVHHVQRRDIVLKWELGEGAFGKVFLAECSHLLPEQEKTLVAVKALKEVTENARLDFQREAELLTVLQHEHIVKFYGVCTEGDPLIMVFEYMK
                * .* ** *   **. . .******. .****..*.**.****************** .** .*.* ********* .* ** **.*******.***.***.*.****** **.******.

NTRK1_HUMA      HGDLNRFLRSHGPDAKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDVWSF
NTRK1_MOUS      HGDLNRFLRSHGPDAKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLASLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFSTESDVWSF
NTRK1_RAT       HGDLNRFLRSHGPDAKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLASLHFVHRDLATRNCLVGQGLVVKIGDFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFSTESDVWSF
NTRK1_CHIC      HGDLNRFLRSHGPDAKILDQGQGQPCGQLTLSHMLQIATQIASGMVYLASLHFVHRDLATRNCLVGHDLVVKIGDFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDIWSF
                ****************.*  *.    * * * ..* .*.*.*.****** ****************. *******************************************.****.***

NTRK1_HUMA      GVVLWEIFTYGKQPWYQLSNTEAIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPVYLDVLG
NTRK1_MOUS      GVVLWEIFTYGKQPWYQLSNTEAIECITQGRELERPRACPPDVYAIMRGCWQREPQQRLSMKDVHARLQALAQAPPSYLDVLG
NTRK1_RAT       GVVLWEIFTYGKQPWYQLSNTEAIECITQGRELERPRACPPDVYAIMRGCWQREPQQRLSMKDVHARLQALAQAPPSYLDVLG
NTRK1_CHIC      GVVLWEIFTYGKQPWYQLSNTEAIECITQGRELERPRTCPSEVYDIMQSCWQREPQQR-SIQDIHSRLQALVKTPPIYLDILG
                ************************.************.** .** **. ********* *..*.*.***** ..** ***.**
```

8. NEUROTROPHINS RECEPTORS IN OTHER SPECIES: TRKB



```
NTRK2_CHIC      MVSWRRRPGPGLARLWGLCCLVLGCWRGALGCPASCRCSSWRIWCSEPVPGITSFPVPQ-RSTEDDNVTEIYIANQRKLESINDNEVGFYVGLKNLTVVDSGLRFVSRQAFVKNINLQYI
NTRK2_RAT       MSPWPRWHGPAMARLWGLCLLVLGFWRASLACPMSCKCSTTRIWCTEPSPGIVAFPRLEPNSIDPENITEILIANQKRLEIINEDDVEAYVGLKNLTIVDSGLKFVAYKAFLKNGNLRHI
NTRK2_HUMA      MSSWIRWHGPAMARLWGFCWLVVGFWRAAFACPTSCKCSASRIWCSDPSPGIVAFPRLEPNSVDPENITEIFIANQKRLEIINEDDVEAYVGLRNLTIVDSGLKFVAHKAFLKNSNLQHI
NTRK2_MOUS      MSPWLKWHGPAMARLWGLCLLVLGFWRASLACPTSCKCSSARIWCTEPSPGIVAFPRLEPNSVDPENITEILIANQKRLEIINEDDVEAYVGLRNLTIVDSGLKFVAYKAFLKNSNLRHI
                *  * .  ** .***** * **.* ** .  ** **.**. ****..* *** .**  .  * . .*.*** ****..** **. .*  ****.***.*****.**. .**.** **. *

NTRK2_CHIC      NLSRNKLSSLSKKPFRHLGLSDLILVDNPFKCSCEIMWIKKFQETKFYTEAQDIYCVDDNNKRIALMDMKVPNCDLPSANLSNYNITVVEGKSITLYCDTTGGPPPNVSWVLTNLVSNHE
NTRK2_RAT       NFTRNKLTSLSRRHFRHLDLSDLILTGNPFTCSCDIMWLKTLQETKSSPDTQDLYCLNESSKNTPLANLQIPNCGLPSARLAAPNLTVEEGKSVTISCSVGGDPLPTLYWDVGNLVSKHM
NTRK2_HUMA      NFTRNKLTSLSRKHFRHLDLSELILVGNPFTCSCDIMWIKTLQEAKSSPDTQDLYCLNESSKNIPLANLQIPNCGLPSANLAAPNLTVEEGKSITLSCSVAGDPVPNMYWDVGNLVSKHM
NTRK2_MOUS      NFTRNKLTSLSRRHFRHLDLSDLILTGNPFTCSCDIMWLKTLQETKSSPDTQDLYCLNESSKNMPLANLQIPNCGLPSARLAAPNLTVEEGKSVTLSCSVGGDPLPTLYWDVGNLVSKHM
                * .****.***.. **** **.***  *** ***.***.*  **.*   ..**.**. .  *   *  ...*** **** *.  *.** ****.*. *   * * *.. * . **** *

NTRK2_CHIC      SDTSKNPASLTIKNVSSMDSGLWISCVAENIVGEVQTSAELTVFFAPNITFIESPTPDHHWCIPFTVKGNPKPTLQWFYEGAILNESEYICTKIHVINQSEYHGCLQLDNPTHLNNGAYT
NTRK2_RAT       NETSHTQGSLRITNISSDDSGKQISCVAENLVGEDQDSVNLTVHFAPTITFLESPTSDHHWCIPFTVRGNPKPALQWFYNGAILNESKYICTKIHVTNHTEYHGCLQLDNPTHMNNGDYT
NTRK2_HUMA      NETSHTQGSLRITNISSDDSGKQISCVAENLVGEDQDSVNLTVHFAPTITFLESPTSDHHWCIPFTVKGNPKPALQWFYNGAILNESKYICTKIHVTNHTEYHGCLQLDNPTHMNNGDYT
NTRK2_MOUS      NETSHTQGSLRITNISSDDSGKQISCVAENLVGEDQDSVNLTVHFAPTITFLESPTSDHHWCIPFTVRGNPKPALQWFYNGAILNESKYICTKIHVTNHTEYHGCLQLDNPTHMNNGDYT
                 .**..  ** * *.** ***  *******.*** * *  *** ***.***.**** **********.*****.***** ******* ******** *..*************.*** **

NTRK2_CHIC      LLAKNEYGEDEKRVDAHFMSVP--GDGSGPIVDPDVYEYETTPN-DLGDTTNNSNQITSPDVSNKENEDSITVYVVVGIAALVCTGLVIMLIILKFGRHSKFGMKGPSSVISNDDDSASP
NTRK2_RAT       LMAKNEYGKDERQISAHFMGRPGVDYETNPNYPEVLYEDWTTPT-DIGDTTNKSNEIPSTDVADQTNREHLSVYAVVVIASVVGFCLLVMLLLLKLARHSKFGMKGPASVISNDDDSASP
NTRK2_HUMA      LIAKNEYGKDEKQISAHFMGWPGIDDGANPNYPDVIYEDYGTAANDIGDTTNRSNEIPSTDVTDKTGREHLSVYAVVVIASVVGFCLLVMLFLLKLARHSKFGMKGPASVISNDDDSASP
NTRK2_MOUS      LMAKNEYGKDERQISAHFMGRPGVDYETNPNYPEVLYEDWTTPT-DIGDTTNKSNEIPSTDVADQSNREHLSVYAVVVIASVVGFCLLVMLLLLKLARHSKFGMKGPASVISNDDDSASP
                *.****** **... ****  *     ..*     .**   *   *.***** **.* * **. . . . ..** ** **..*   *..** .**  **********.************

NTRK2_CHIC      LHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDNARKDFHREAELLTNLQHEHI
NTRK2_RAT       LHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDNARKDFHREAELLTNLQHEHI
NTRK2_HUMA      LHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDNARKDFHREAELLTNLQHEHI
NTRK2_MOUS      LHHISNGSNTPSSSEGGPDAVIIGMTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVAVKTLKDASDNARKDFHREAELLTNLQHEHI
                ************************************************************************************************************************

NTRK2_CHIC      VKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAEGNRPAELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVYSTDYYRVGGHTMLPIRWM
NTRK2_RAT       VKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAEGNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVYSTDYYRVGGHTMLPIRWM
NTRK2_HUMA      VKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAEGNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVYSTDYYRVGGHTMLPIRWM
NTRK2_MOUS      VKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMAEGNPPTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIGDFGMSRDVYSTDYYRVGGHTMLPIRWM
                ******************************************* *.**************************************************************************

NTRK2_CHIC      PPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGRVLQRPRTCPKEVYDLMLGCWQREPHMRLNIKEIHSLLQNLAKASPVYLDILG
NTRK2_RAT       PPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGRVLQRPRTCPQEVYELMLGCWQREPHTRKNIKNIHTLLQNLAKASPVYLDILG
NTRK2_HUMA      PPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGRVLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDILG
NTRK2_MOUS      PPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGRVLQRPRTCPQEVYELMLGCWQREPHTRKNIKSIHTLLQNLAKASPVYLDILG
                ***********************************************************.***.*********** * *** **.*****************
```

8. NEUROTROPHINS RECEPTORS IN OTHER SPECIES: TRKC



```
NTRK3_HUMA      MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRSLHTLNAVDMELYTGLQKLTIKNSGLRSIQP
NTRK3_MACF      MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRSLHTLNAVDMELYTGLQKLTIRNSGLRSIQP
NTRK3_SAIB      MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRSLHTLNAVDMELYTGLQKLTIKNSGLRSIQP
NTRK3_PANT      MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRSLHTLNAVDMELYTGLQKLTIKNSGLRSIQP
NTRK3_CHIC      MDVSLCPTKCTFWRVFLLWSIWGDYLLSVLACPANCLCSKTDINCKKPDDGNLFPLLEGQDSGSSNGNTSINITDISRNITSIHIENWKNLQTLNAVDMELYTGLQRLTIRNSGLRNIQP
NTRK3_MOUS      MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRGLHTLNAVDMELYTGLQKLTIKNSGLRNIQP
NTRK3_RAT       MDVSLCPAKCSFWRIFLLGSVWLDYVGSVLACPANCVCSKTEINCRRPDDGNLFPLLEGQDSGNSNGNASINITDISRNITSIHIENWRGLHTLNAVDMELYTGLQKLTIKNSGLRNIQP
                *******.**.***.*** *.* **. *********.****.***..**************** ****.*******************. *.**************.***.***** ***

NTRK3_HUMA      RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELQLEQNFFNCSCDIRWMQLWQEQGEAKLNSQNLYCINADGSQLPLFRMNISQCDLPEISVSHVNLTVREGDNAVITCNGSGSPLPD
NTRK3_MACF      RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELQLEQNFFNCSCDIRWMQLWQEQGEAKLNNQNLYCINADGSQLPLFRMNISQCDLPEISVSHVNLTVREGDNAVITCNGSGSPLPD
NTRK3_SAIB      RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELRLEQNFFNCSCDIRWMQLWQEQGEARLNSQNLYCINADGSQLPLFRMNISQCDLPEISVSHVNLTVREGDSAVITCNGSGSPLPD
NTRK3_PANT      RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELQLEQNFFNCSCDIRWMQLWQEQGEAKLNSQNLYCINTDGSQLPLFRMNISQCDLPEISVSHVNLTVREGDNAVITCNGSGSPLPD
NTRK3_CHIC      RAFAKNPHLRYIDLSGNRLTTLSWQLFQTLRLFDLRLERNPFNCSCDIRWIQLWQEKGEANLQSQQLHCMNLDTAVILLRNMNITQCDLPEISVSHVNLTVREGENAVITCNGSGSPLPD
NTRK3_MOUS      RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELRLEQNFFNCSCDIRWMQLWQEQGEARLDSQSLYCISADGSQLPLFRMNISQCDLPEISVSHVNLTVREGDNAVITCNGSGSPLPD
NTRK3_RAT       RAFAKNPHLRYINLSSNRLTTLSWQLFQTLSLRELRLEQNFFNCSCDIRWMQLWQEQGEARLDSQSLYCISADGSQLPLFRMNISQCDLPEISVSHVNLTVREGDNAVITCNGSGSPLPD
                ************ ** ************** * .*.**.* *********.*****.*** *  * * *.  * . . *  ***.*******************. **************

NTRK3_HUMA      VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTVYYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLHWLHNGQPLRESKIIHVEYYQEGEISE
NTRK3_MACF      VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTVYYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLHWLHNGQPLRESKIIHVEYYQEGEISE
NTRK3_SAIB      VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTVYYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLYWLHNGQPLRESKIIHVEYYQEGEISE
NTRK3_PANT      VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLHWLHNGQPLRESKIIHVEYYQEGEISE
NTRK3_CHIC      VDWTVADLHSINTHQTNLNWTNVHAINLTLVNVTSEDNGFLLTCIAENVVGMSNASVLLTVYYPPRILTLEEPVLHLEHCIAFAVHGNPAPTLHWLHNGQVLRETEIIHMEFYQQGEVSE
NTRK3_MOUS      VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTVYYPPRVVSLVEPEVRLEHCIEFVVRGNPTPTLHWLYNGQPLRESKIIHMDYYQEGEVSE
NTRK3_RAT       VDWIVTGLQSINTHQTNLNWTNVHAINLTLVNVTSEDNGFTLTCIAENVVGMSNASVALTVYYPPRVVSLVEPEVRLEHCIEFVVRGNPTPTLHWLYNGQPLRESKIIHMDYYQEGEVSE
                *** *. *.******************************* **************** ********...* ** ..***** * *.*** *** ** *** ***. ***...**.**.**

NTRK3_HUMA      GCLLFNKPTHYNNGNYTLIAKNPLGTANQTINGHFLKEPFPESTDNFILFD--EVSPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFVMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_MACF      GCLLFNKPTHYNNGNYTLIAKNPLGTANQTINGHFLKEPFPESTDNFILFD--EVSPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFIMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_SAIB      GCLLFNKPTHYNNGNYTLIAKNPLGTANQTINGHFLKEPFPESTDNFILFD--EVSPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFIMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_PANT      GCLLFNKPTHYNNGNYTLIAKNPLGTANQTISGHFLKEPFPESTDNFILFD--EVSPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFVMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_CHIC      GCLLFNKPTHYNNGNYTIVATNQLGSANQTIKGHFLEKPFPESTDNFVSIGDYEVSPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFIMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_MOUS      GCLLFNKPTHYNNGNYTLIAKNALGTANQTINGHFLKEPFPESTDFFDFES--DASPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFIMINKYGRRSKFGMKGPVAVISGEEDSA
NTRK3_RAT       GCLLFNKPTHYNNGNYTLIAKNALGTANQTINGHFLKEPFPESTDFFDFES--DASPTPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFIMINKYGRRSKFGMKGPVAVISGEEDSA
                *****************..* * **.***** ****  ******* *      . *************************************.***************************

NTRK3_HUMA      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_MACF      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_SAIB      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_PANT      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_CHIC      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTNDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_MOUS      SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
NTRK3_RAT       SPLHHINHGITTPSSLDAGPDTVVIGMTRIPVIENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVAVKALKDPTLAARKDFQREAELLTNLQHE
                ************************************************************************************* **********************************
```

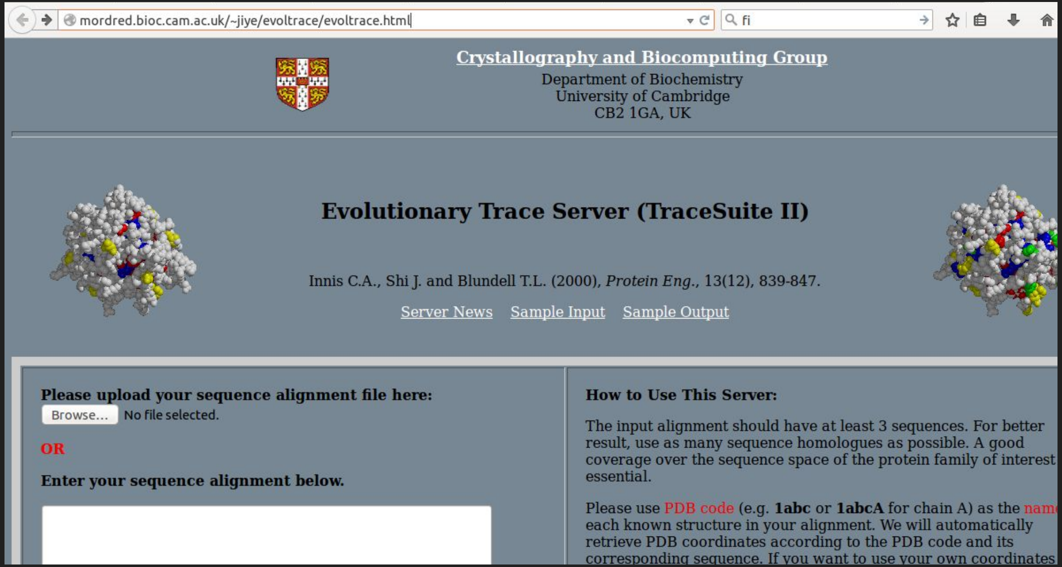
8. NEUROTROPHINS RECEPTORS IN OTHER SPECIES: TRKC

```
NTRK3_HUMA      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYRLFN----
NTRK3_MACF      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYRVG-----
NTRK3_SAIB      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPXQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCXVGANLLVKIGDFGMSRDVYSTDYYRVG-----
NTRK3_PANT      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYRVG-----
NTRK3_CHIC      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYRVG-----
NTRK3_MOUS      HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYR-------
NTRK3_RAT       HIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLRAHGPDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGANLLVKIGDFGMSRDVYSTDYYREGPYQKG
                ********************************************** **************************************** *************************

NTRK3_HUMA      ---------------------PSGNDFCIWCEVGGHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
NTRK3_MACF      ----------------------------------GHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
NTRK3_SAIB      ----------------------------------GHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
NTRK3_PANT      ----------------------------------GHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
NTRK3_CHIC      ----------------------------------GHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDIMLGCWQREPQQ
NTRK3_MOUS      --------------------------------VGGHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
NTRK3_RAT       PFSVSWQQQRLAASAASTLFNPSGNDFCIWCEVGGHTMLPIRWMPPESIMYRKFTTESDVWSFGVILWEIFTYGKQPWFQLSNTEVIECITQGRVLERPRVCPKEVYDVMLGCWQREPQQ
                                                  **************************************************************************.***********

NTRK3_HUMA      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_MACF      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_SAIB      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_PANT      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_CHIC      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_MOUS      RLNIKEIYKILHALGKATPIYLDILG
NTRK3_RAT       RLNIKEIYKILHALGKATPIYLDILG
                **************************
```

8. Neurotrophins receptors in other species: p75

```
TNR16_RAT       MRRAGAACSAMDRLRLLLLLILGVSSGGAKETCSTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDNVTFSDVVSATEPCKPCTECLGLQSMSAPCVEADDAVCRCAYGYYQDEET
TNR16_MOUS      --------MDRLRLLLLLLLLLGVSFGGAKETCSTGMYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECLGLQSMSAPCVEADDAVCRCSYGYYQDEET
TNR16_HUMA      -MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETT
TNR16_CHIC      --------MAGFVPLLLLLLPAGPTWG-SKEKCLTKMYTTSGECCKACNLGEGVVQPCGVNQTVCEPCLDSVTYSDTVSATEPCKPCTQCVGLHSMSAPCVESDDAVCRCAYGYFQDELS
                               *****  * . * .** * * .** ************** **** ********** **.** ***********.*.**.********.*******.***.*** .

TNR16_RAT       GHCEACSVCEVGSGLVFSCQDKQNTVCEECPEGTYSDEANHVDPCLPCTVCEDTERQLRECTPWADAECEEIPGRWIPRSTPPEGSDSTAPSTQEPEVPPEQDLVPSTVADMVTTVMGSS
TNR16_MOUS      GRCEACSVCGVGSGLVFSCQDKQNTVCEECPEGTYSDEANHVDPCLPCTVCEDTERQLRECTPWADAECEEIPGRWITRSTPPEGSDVTTPSTQEPEAPPERDLIASTVADTVTTVMGSS
TNR16_HUMA      GRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSS
TNR16_CHIC      GSCKECSICEVGFGLMFPCRDSQDTVCEECPEGTFSDEANFVDPCLPCTICEENEVMVKECTATSDAECRDLHPRWTTHTPSLAGSDSPEPITRDP---FNTEGMATTLADIVTTVMGSS
                * *  * .*  * **.* *.* * *******.**.***** ********.**..*  ..***  .**** ..  **  ..    ***   * *..*      . . .*.*  ********

TNR16_RAT       QPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKRWNSCKQNKQGANSRPVNQTPPPEGEKLHSDSGISVDSQSLHDQQTHTQTASGQALKGDGNLYSSLPLTKREEVEKLLN---GDTW
TNR16_MOUS      QPVVTRGTADNLIPVYCSILAAVVVGLVAYIAFKRWNSCKQNKQGANSRPVNQTPPPEGEKLHSDSGISVDSQSLHDQQTHTQTASAQALKGDGNLYSSLPLTKREEVEKLLN---GDTW
TNR16_HUMA      QPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKRWNSCKQNKQGANSRPVNQTPPPEGEKLHSDSGISVDSQSLHDQQPHTQTASGQALKGDGGLYSSLPPAKREEVEKLLNGSAGDTW
TNR16_CHIC      QPVVSRGTADNLIPVYCSILAAVVVGLVAYIAFKRWNSCKQNKQGANNRPVNQTPSPEGEKLHSDSGISVDSQSLHDQQPPNQSTQGPAPKGDGSLYASLPPSKQEEVEKLLSSSAEETW
                ****.***.************************************** ******* ***********************  .*..   * **** **.*** .*.*******     .**

TNR16_RAT       RHLAGELGYQPEHIDSFTHEACPVRALLASWGAQDSATLDALLAALRRIQRADIVESLCSESTATSPV
TNR16_MOUS      RHLAGELGYQPEHIDSFTHEACPVRALLASWGAQDSATLDALLAALRRIQRADIVESLCSESTATSPV
TNR16_HUMA      RHLAGELGYQPEHIDSFTHEACPVRALLASWATQDSATLDALLAALRRIQRADLVESLCSESTATSPV
TNR16_CHIC      RQLAGELGYKEDLIDCFTREESPARALLADWSAKETATLDALLVALRKIQRGDIAESLYSESTATSPV
                *.*******. . **.**.* .* ***** * ....******* ***.*** *. *** *********
```

9. Phylogenetic tree of neurotrophins and their receptors



mordred.bioc.cam.ac.uk/~jiye/evoltrace/evoltrace.html

Crystallography and Biocomputing Group
Department of Biochemistry
University of Cambridge
CB2 1GA, UK

Evolutionary Trace Server (TraceSuite II)

Innis C.A., Shi J. and Blundell T.L. (2000), *Protein Eng.*, 13(12), 839-847.

Please upload your sequence alignment file here:

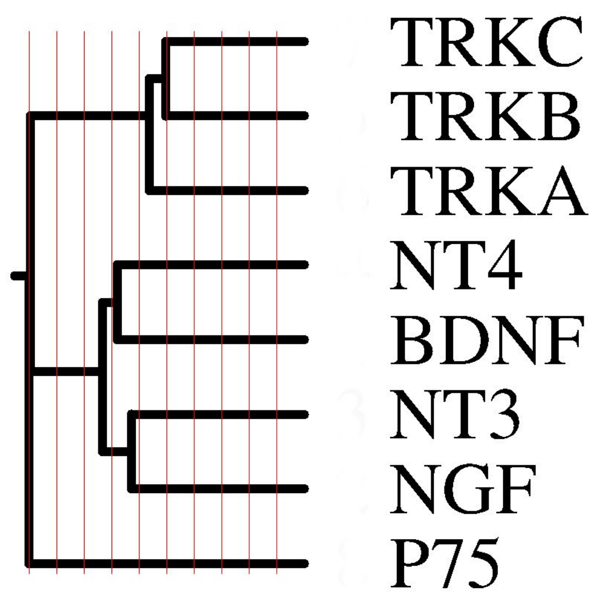
OR

Enter your sequence alignment below.

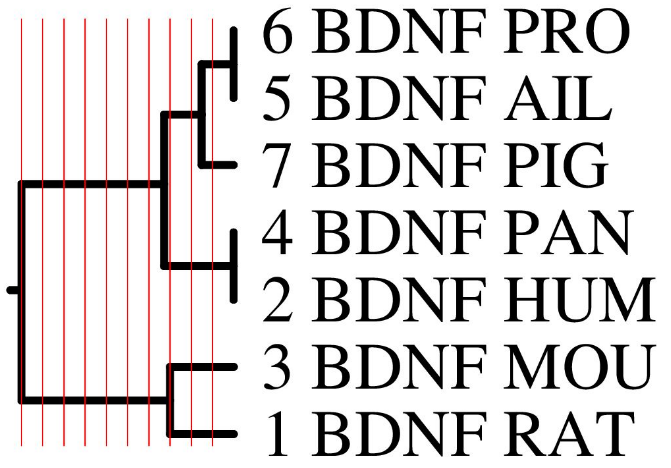
How to Use This Server:

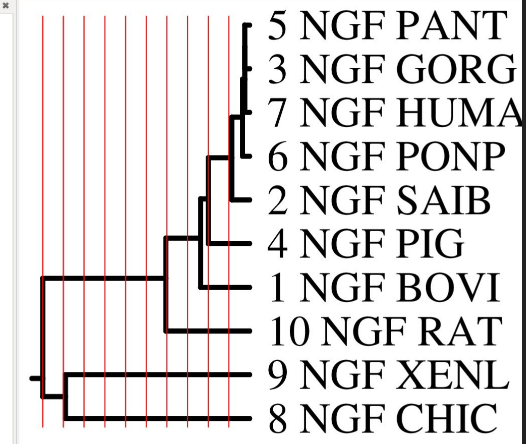
The input alignment should have at least 3 sequences. For better result, use as many sequence homologues as possible. A good coverage over the sequence space of the protein family of interest essential.

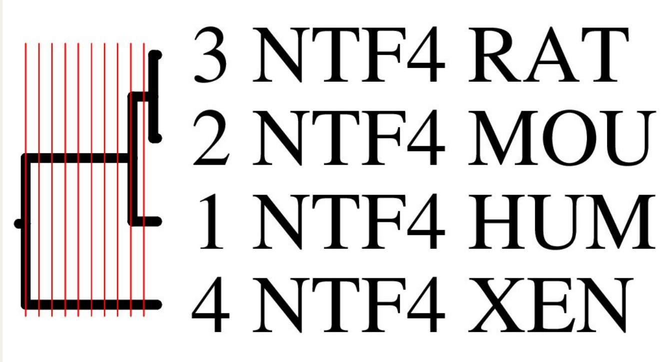
Please use PDB code (e.g. **1abc** or **1abcA** for chain A) as the nam each known structure in your alignment. We will automatically retrieve PDB coordinates according to the PDB code and its corresponding sequence. If you want to use your own coordinates

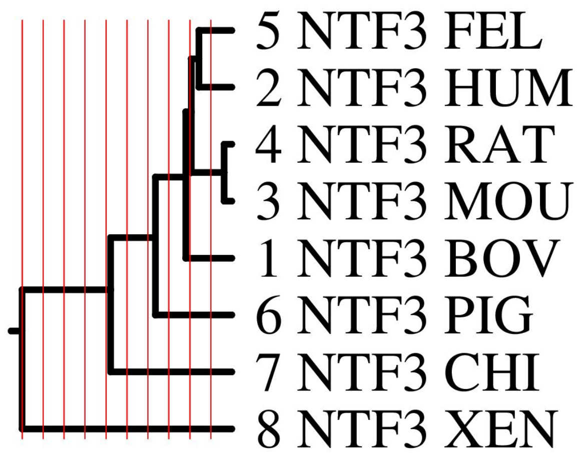


9. Neurotrophins phylogenetic tree

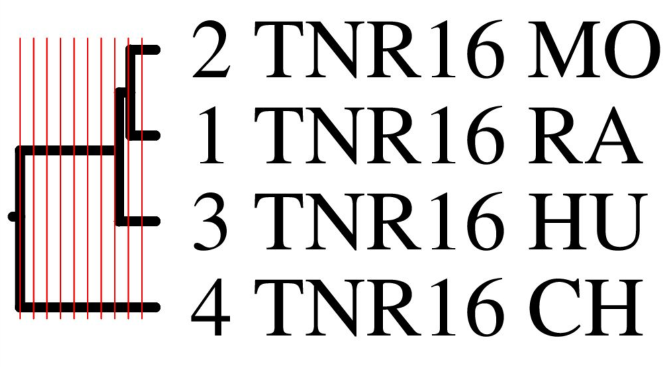


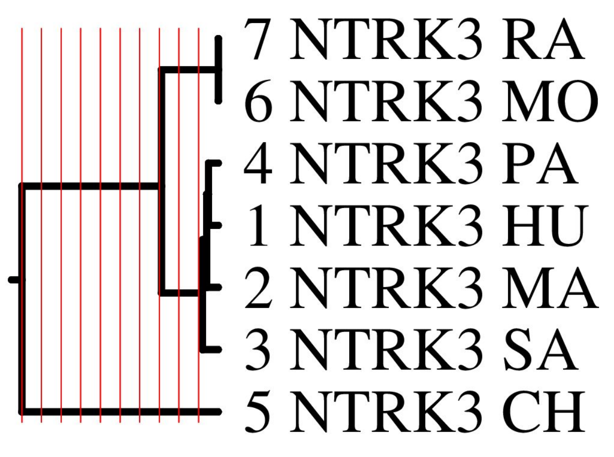


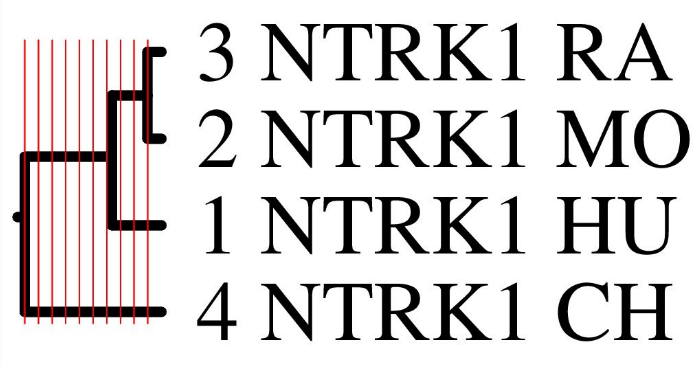


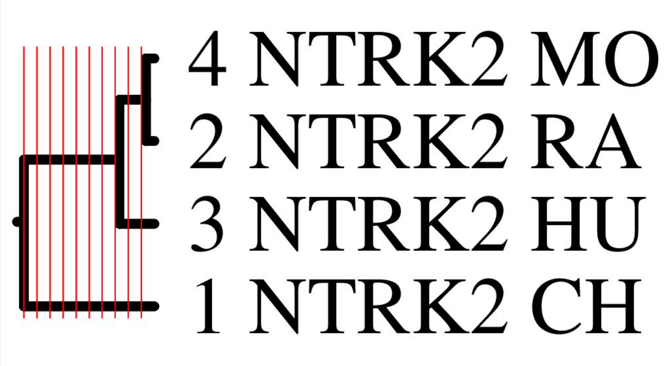


9. NEUROTROPHIC RECEPTORS PHYLOGENETIC TREE









10. CONCLUSION

- There are 4 neurotrophins (NGF, BDNF, NT3 and NT4) in humans, which can bind into several receptors (TRKA, TRKB, TRKC and p75), some of them specifically with a higher affinity.
- All neurotrophins are similar, with conserved residues.
- Neurotrophins and their receptors act as dimers. Neurotrophins can form hetero- or homodimers.
- The binding of the neurotrophin with its receptor leads to several conformational changes, stabilized by hydrophobic contacts, hydrogen bonds and salt bridges.

MULTIPLE CHOICE QUESTIONS

- Which of these receptors has low affinity for ALL the neurotrophins?

a) TRKA
b) TRKB
c) TRKC
d) p75
e) None of the above

- Which of these neurotrophin receptors contain Ig domains in its extracellular domain?

a) TRKA
b) TRKB
c) a and b
d) p75
e) All of the previous

- In which TRK domain can we observe cysteine repeats?

a) Extracellular domain
b) Transmembrane region
c) Intracellular domain
d) Extracellular and intracellular domain
e) None of above

- Which of the following sentences is correct?

a) Neurotrophin is a synonymous of neurotrophic factor
b) Neurotrophins are not modified after their synthesis
c) Only neurons synthesize neurotrophins
d) Neurotrophins can activate MAPK
e) Pro-neurotrophins bind TRK receptors

- Neurotrophins are involved in:

a) Neurons survival
b) Neurons development
c) a and b
d) Neurons function
e) All of the previous

- About the conservation of neurotrophins' sequence, select the FALSE options:

1. The pro-domain is highly maintained in all neurotrophins.
2. BDNF sequence is not maintained in other species.
3. C-terminal of BDNF is a region that is highly different in humans.
4. BDNF sequence is highly maintained in other species.

a) 1, 2 and 3
b) 1 and 3
c) 2 and 4
d) 4
e) 1, 2, 3 and 4

MULTIPLE CHOICE QUESTIONS

- The TRK receptors domain which is the responsible of the binding with neurotrophins is a:

a) Ig-like domain
b) Kinase domain
c) Transmembrane domain
d) Leucine rich motif
e) Cysteine cluster

- Which of the following molecules are neurotrophins?

a) BDNF
b) NGF
c) a and b
d) TNF16
e) All of the previous

- Which of the following sentences is TRUE?

a) TRKA has a death domain
b) Neurotrophins don’t have a SCOP classification
c) There are more alpha helices than beta strands in the binding domain
d) Neurotrophins don’t exist in rats
e) Any of them is true

- Choose the correct sentences:

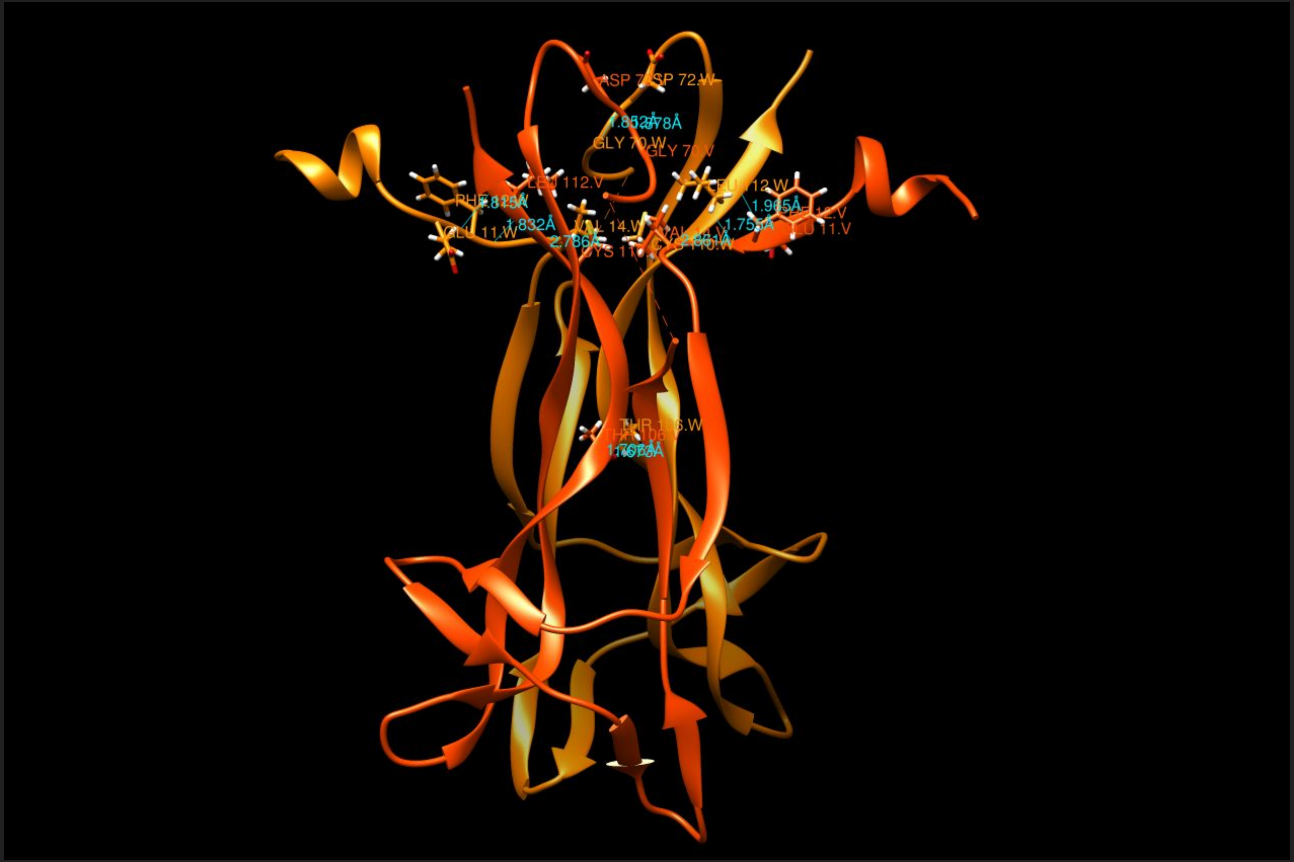
1. TRK needs to act as a dimer to transduce the signal.
2. There isn’t any conformational change when a neurotrophin binds p75 receptor.
3. p75 and NT-3 interact by 3 interaction sites.
4. NGF has high affinity for TRKC.

a) 1, 2 and 3
b) 1 and 3
c) 2 and 4
d) 4
e) 1, 2, 3 and 4

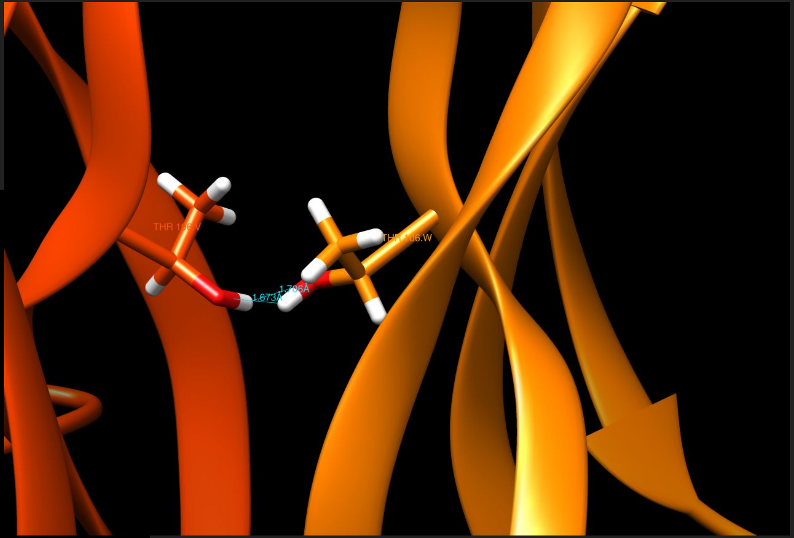
References

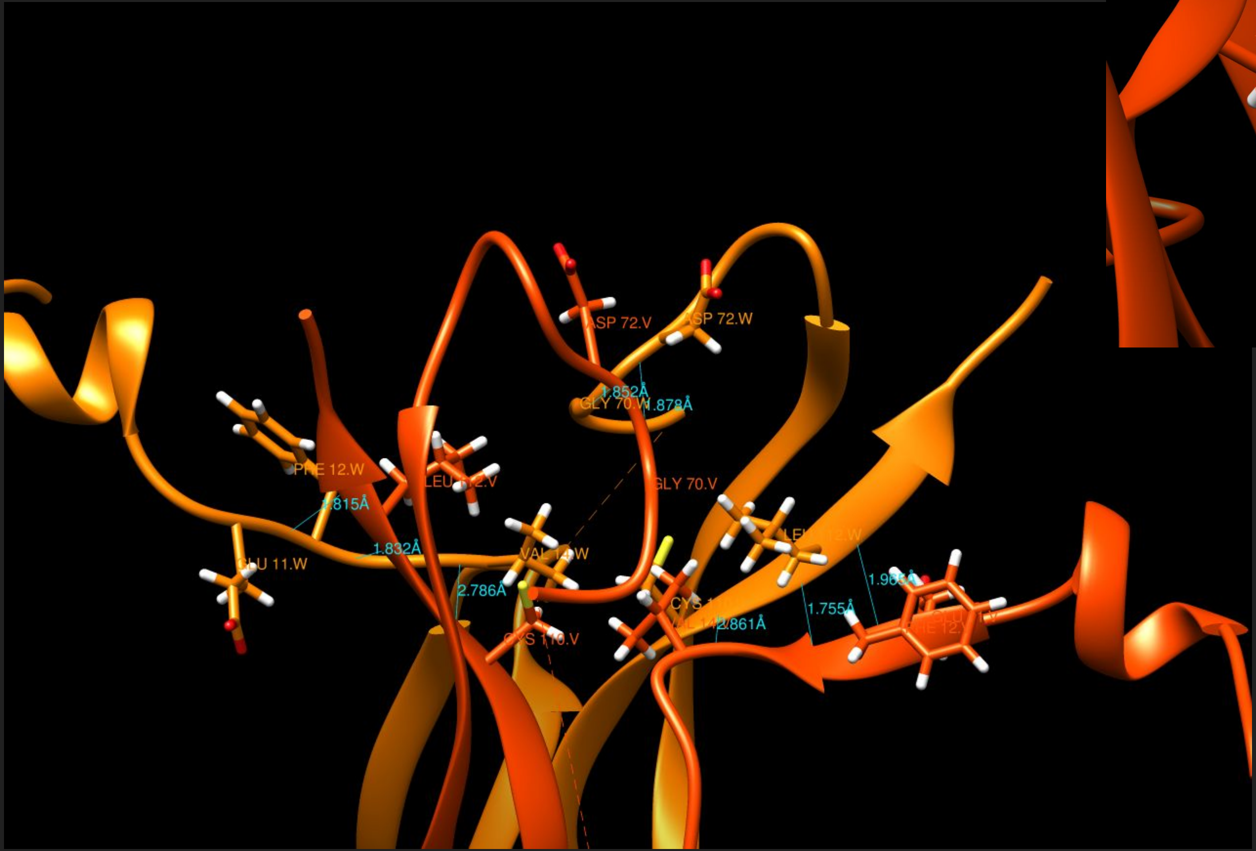
- Banfield M, Naylor R, Robertson R, Allen S et al. Specificity in Trk Receptor: Neurotrophin interactions: The Crystal Structure of TrkB-d5 in complex with Neurotrophin-4/5. *Structure* 2001; 9:1191-1199.
- Barbacid M. Neurotrophins and their receptors. *Cell Biol* 1995; 7:148-I55.
- Bertrand T, Kothe M, Liu J, Dupuy A, Rak A, Berne PF et al. The Crystal Structures of TrkA and TrkB Suggest Key Regions for Achieving Selective Inhibition. *J Mol Biol.* 2012; 423(3): 439-53.
- Gong Y, Cao P, Yu H, Jiang T. Crystal structure of the neurotrophin-3 and p75NTR symmetrical complex. Nature. Macmillan Publishers Limited. All rights reserved; 2008 Aug 7 ;454(7205):789–93.
- Khan N, Smith TM. Neurotrophins and Neuropathic Pain: Role in Pathobiology. *Molecules*. 2015; 20(6):10657-88.
- Longo FM, Massa SM. Small-molecules modulation of neurotrophin receptors: a strategy for the treatment of neurological disease. *Nat Rev Drug Discov*. 2013; 12: 507-525.
- Robinson R, Radziejewski C, Spragoon, Greenwald J, Kostura M, et al. The structures of the neurotrophin 4 homodimer and the brain-derived neurotrophic factor/neurotrophin 4 heterodimer reveal a common Trk-binding site . *Protein Science* 1999; 8:2589–2597.
- Skaper SD. The Neurotrophin Family of Neurotrophic Factors: An Overview. *Meth Mol Biol.* 2012; 846:1-12.
- Stroleru B, Popescu AM, Tache DE, Neamtu OM, Emami G,Tataranu LG et al. Tropomyosin-Receptor-Kinases Signaling in the Nervous System. *MAEDICA.* 2013; 8(1): 43-48.
- Wiesmann C, Ultsch MH, Bass SH, de Vos AM. Crystal structure of nerve growth factor in complex with the ligand-binding domain of TrkA receptor. *Nature.* 1999; 401(6749): 184-8.

EXTRA MATERIAL

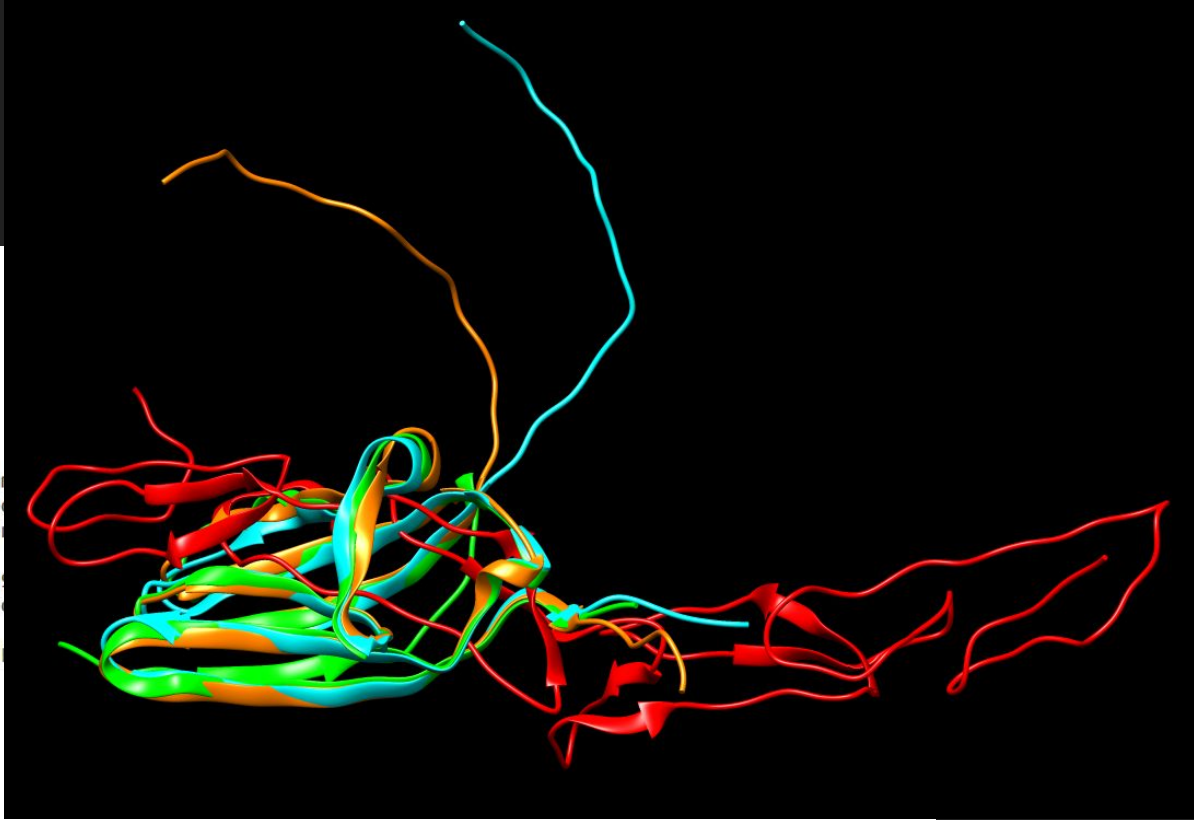


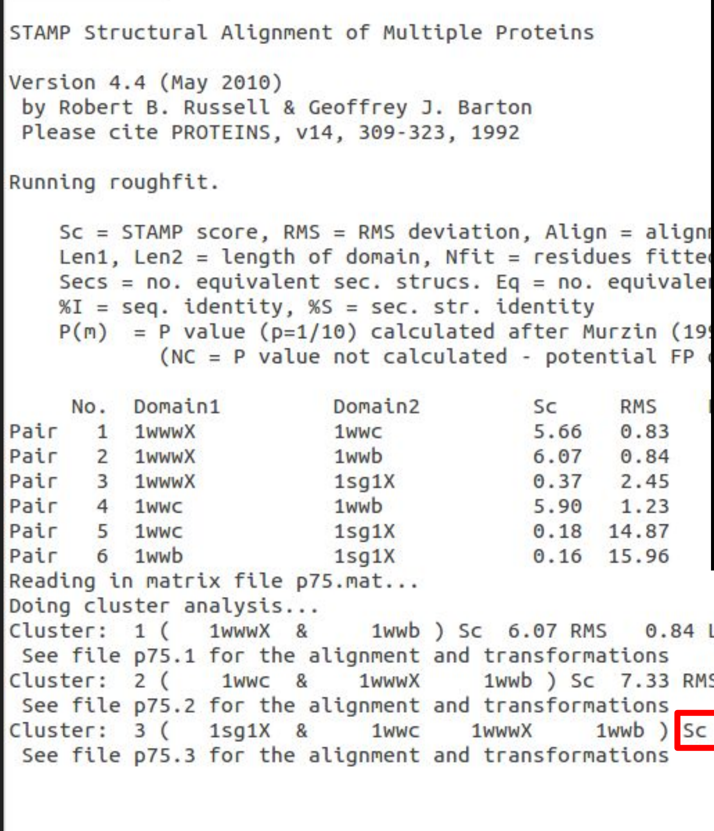
EXTRA MATERIAL





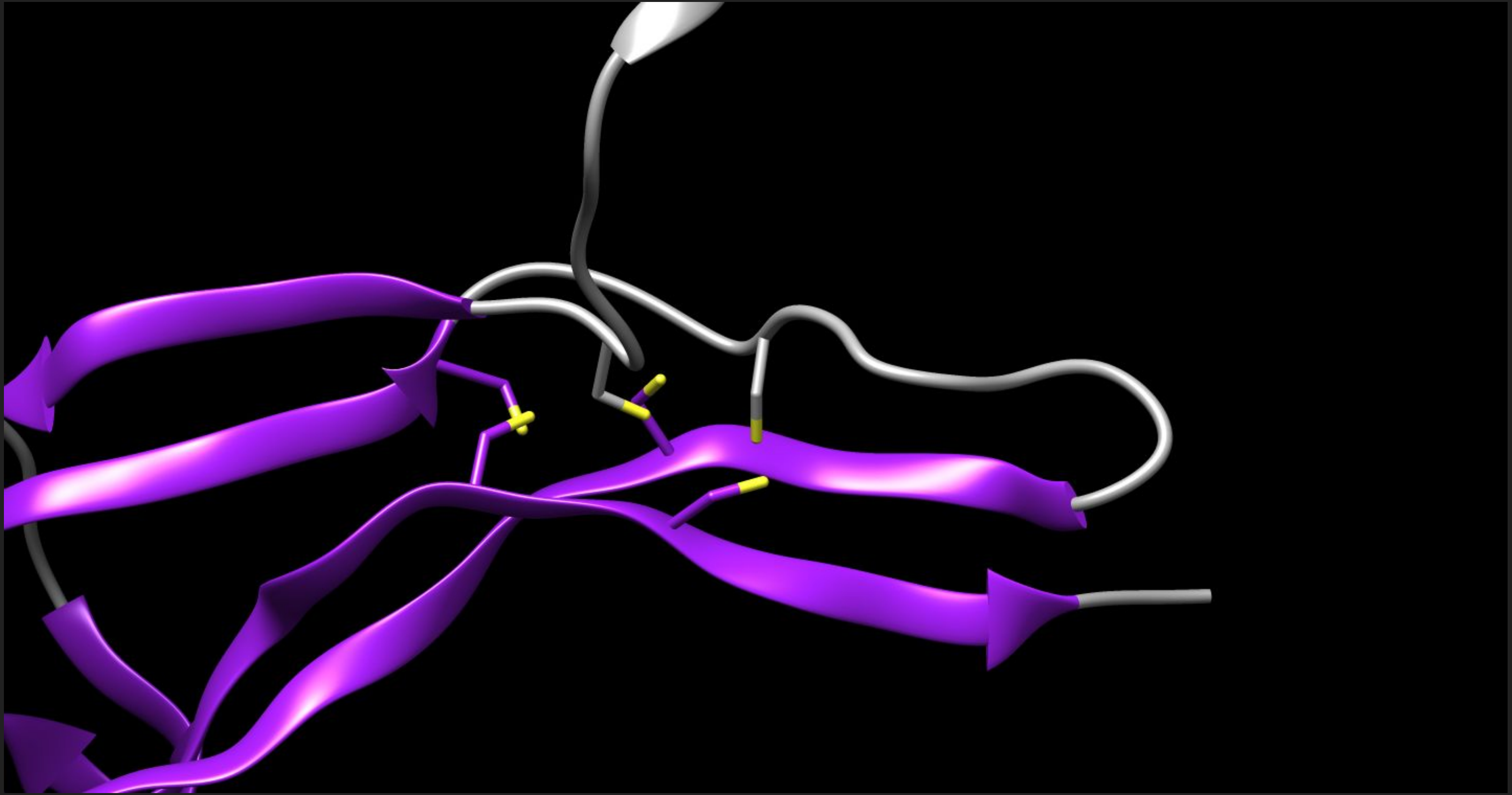
EXTRA MATERIAL



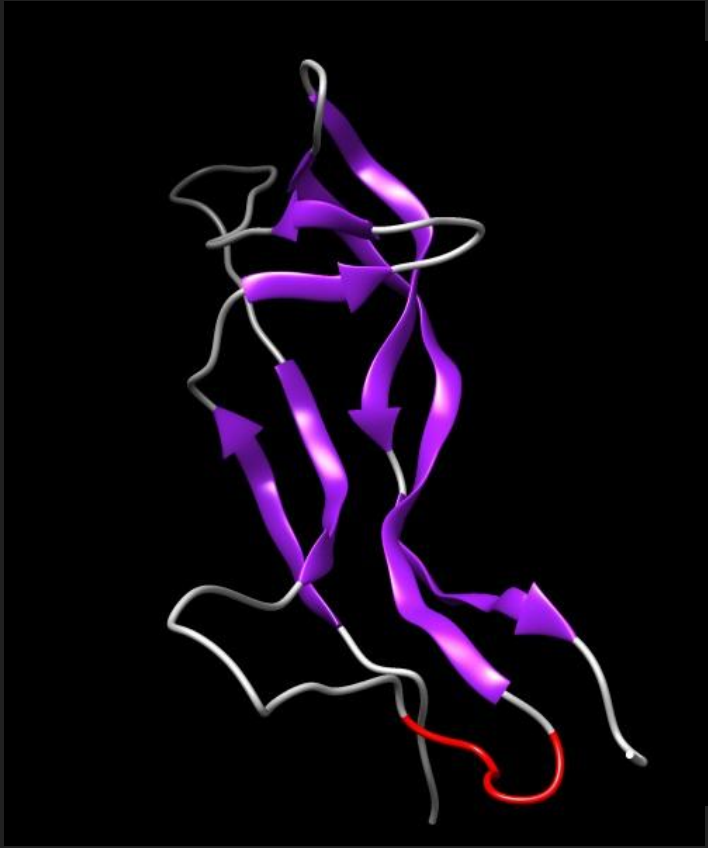


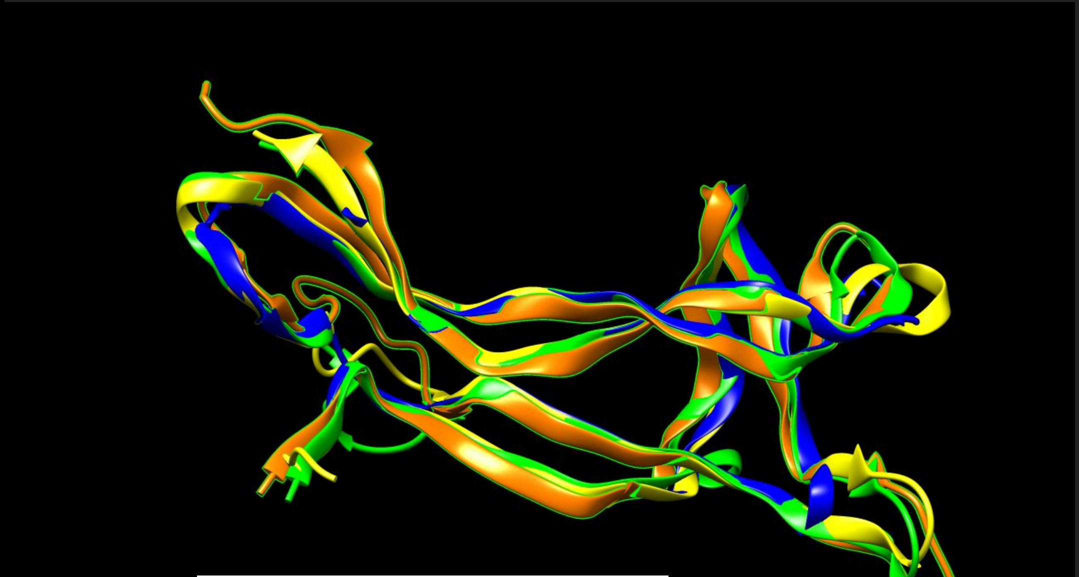
```
STAMP Structural Alignment of Multiple Proteins

Version 4.4 (May 2010)
 by Robert B. Russell & Geoffrey J. Barton
 Please cite PROTEINS, v14, 309-323, 1992

Running roughfit.

    Sc = STAMP score, RMS = RMS deviation, Align = align
    Len1, Len2 = length of domain, Nfit = residues fitte
    Secs = no. equivalent sec. strucs. Eq = no. equivale
    %I = seq. identity, %S = sec. str. identity
    P(m)  = P value (p=1/10) calculated after Murzin (19
            (NC = P value not calculated - potential FP

     No.  Domain1         Domain2         Sc     RMS
Pair   1  1wwwX           1wwc            5.66   0.83
Pair   2  1wwwX           1wwb            6.07   0.84
Pair   3  1wwwX           1sg1X           0.37   2.45
Pair   4  1wwc            1wwb            5.90   1.23
Pair   5  1wwc            1sg1X           0.18  14.87
Pair   6  1wwb            1sg1X           0.16  15.96
Reading in matrix file p75.mat...
Doing cluster analysis...
Cluster:  1 (   1wwwX  &     1wwb ) Sc  6.07 RMS   0.84 Len  87 nfit  80
 See file p75.1 for the alignment and transformations
Cluster:  2 (    1wwc  &    1wwwX     1wwb ) Sc  7.33 RMS   0.99 Len  91 nfit  78
 See file p75.2 for the alignment and transformations
Cluster:  3 (   1sg1X  &     1wwc    1wwwX     1wwb ) Sc  1.91 RMS   3.86 Len 149 nfit  30  LOW SCORE
 See file p75.3 for the alignment and transformations
```

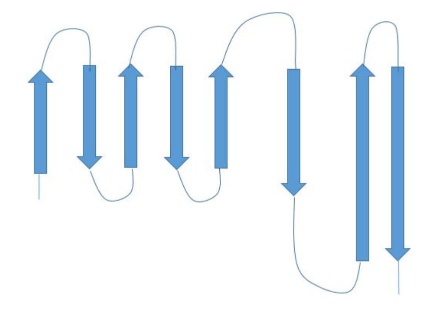
EXTRA MATERIAL



EXTRA MATERIAL



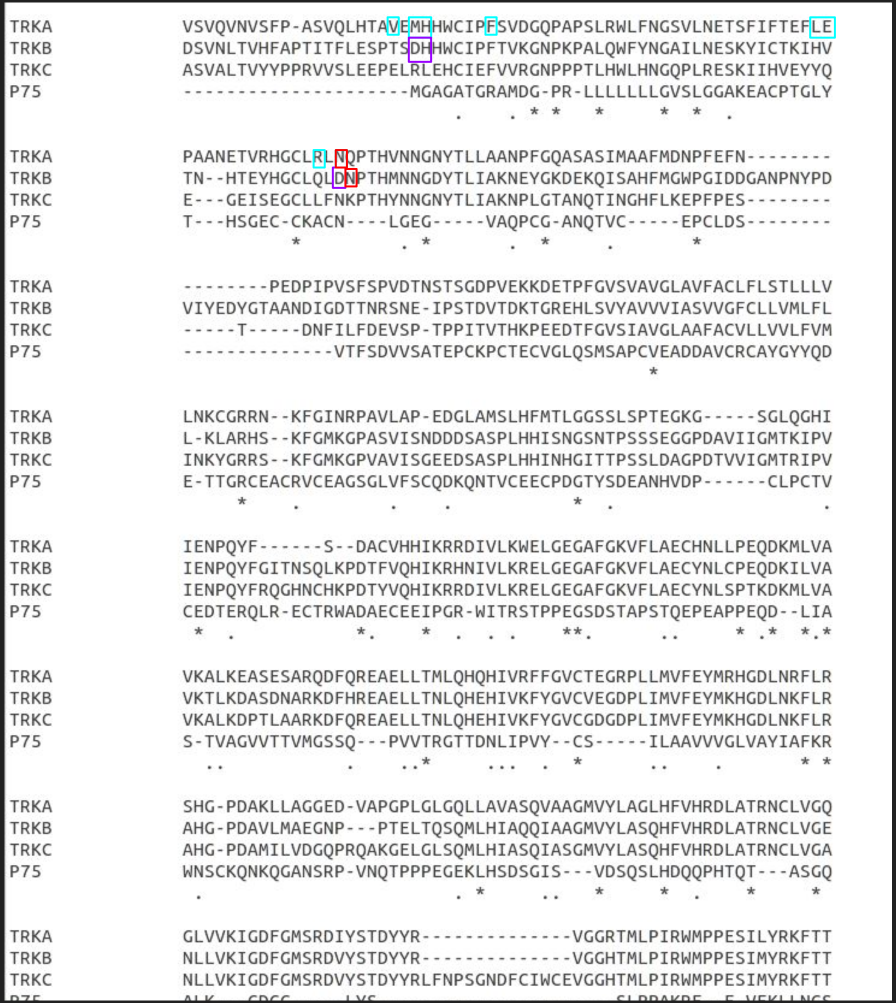




Extra material - Neurotrophins receptors alignment

```
P75             ------------------------------------------------------------
TRKC            ------------------------------------------------------------
TRKB            GAMDTFVQHIKRHNIVLKRELGE--FGKVFLAECYNLC--KILVAVKTLKDASDNARKDF
TRKA            -----CVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPDKMLVAVKALK----SARQDF


P75             ----ETCSTGLYTHSGECCKACNLGE------GVAQPCGANQTVCEPCLDNVTFS-----
TRKC            -------------------------------------------TVYYPPRVVSLE-----
TRKB            HREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLRAHGPDAVLMP-----
TRKA            QREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDV


P75             -D---VVSATEPCKPCTECLGLQSMSAPCVEADDAVCRCAYGYYQDEETGHCEACSVCEV
TRKC            -E---PELRLEHCIEFVVRGN-PPPTLHWLHNGQPLRESKIIHVEYYQEG--EISEGCLL
TRKB            -PTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGENLLVKIG--DFGMSRDV
TRKA            APGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIG--DFGMSRDI
                                             .        .          *  .      .

P75             GSGLVFSCQDKQNTVCEECP--------EGTYSDEAN-HVDPCLPCTVCEDTERQLR---
TRKC            FNKPTHYNNGNYTL-IAKNP--------LGTANQTIN-GHFLKEPFPVDE----------
TRKB            YSTDYYRVGGHTMLPIRWMPPESIMYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNE
TRKA            YSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTE
                                   *          *

P75             --ECTPWADAECE-----------------------------------------------
TRKC            ------------------------------------------------------------
TRKB            VIECITQGRVLQRPRTCPQEVYELMLGCWQREPHMRKNIKGIHTLLQNLAKASPVYLDIL
TRKA            AIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQAPPV-----


P75             -
TRKC            -
TRKB            G
TRKA            -
```

EXTRA MATERIAL



```
TRKA            VSVQVNVSFP-ASVQLHTAVEMHHWCIPFSVDGQPAPSLRWLFNGSVLNETSFIFTEFLE
TRKB            DSVNLTVHFAPTITFLESPTSDHHWCIPFTVKGNPKPALQWFYNGAILNESKYICTKIHV
TRKC            ASVALTVYYPPRVVSLEEPELRLEHCIEFVVRGNPPPTLHWLHNGQPLRESKIIHVEYYQ
P75             ---------------------MGAGATGRAMDG-PR-LLLLLLLGVSLGGAKEACPTGLY
                                         .    . * *   *     *  *  .

TRKA            PAANETVRHGCLRLNQPTHVNNGNYTLLAANPFGQASASIMAAFMDNPFEFN--------
TRKB            TN--HTEYHGCLQLDNPTHMNNGDYTLIAKNEYGKDEKQISAHFMGWPGIDDGANPNYPD
TRKC            E---GEISEGCLLFNKPTHYNNGNYTLIAKNPLGTANQTINGHFLKEPFPES--------
P75             T---HSGEC-CKACN----LGEG-----VAQPCG-ANQTVC-----EPCLDS--------
                          *         . *       .  *     .       *

TRKA            --------PEDPIPVSFSPVDTNSTSGDPVEKKDETPFGVSVAVGLAVFACLFLSTLLLV
TRKB            VIYEDYGTAANDIGDTTNRSNE-IPSTDVTDKTGREHLSVYAVVVIASVVGFCLLVMLFL
TRKC            -----T-----DNFILFDEVSP-TPPITVTHKPEEDTFGVSIAVGLAAFACVLLVVLFVM
P75             --------------VTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQD
                                                           *

TRKA            LNKCGRRN--KFGINRPAVLAP-EDGLAMSLHFMTLGGSSLSPTEGKG-----SGLQGHI
TRKB            L-KLARHS--KFGMKGPASVISNDDDSASPLHHISNGSNTPSSSEGGPDAVIIGMTKIPV
TRKC            INKYGRRS--KFGMKGPVAVISGEEDSASPLHHINHGITTPSSLDAGPDTVVIGMTRIPV
P75             E-TTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDP------CLPCTV
                     *    .        .    .           *  .                   .

TRKA            IENPQYF------S--DACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVA
TRKB            IENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFLAECYNLCPEQDKILVA
TRKC            IENPQYFRQGHNCHKPDTYVQHIKRRDIVLKRELGEGAFGKVFLAECYNLSPTKDKMLVA
P75             CEDTERQLR-ECTRWADAECEEIPGR-WITRSTPPEGSDSTAPSTQEPEAPPEQD--LIA
                 *  .           *.    *  .  . .    **.      ..     * .*  *.*

TRKA            VKALKEASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLR
TRKB            VKTLKDASDNARKDFHREAELLTNLQHEHIVKFYGVCVEGDPLIMVFEYMKHGDLNKFLR
TRKC            VKALKDPTLAARKDFQREAELLTNLQHEHIVKFYGVCGDGDPLIMVFEYMKHGDLNKFLR
P75             S-TVAGVVTTVMGSSQ---PVVTRGTTDNLIPVY--CS-----ILAAVVVGLVAYIAFKR
                  ..           .    ..*     ...  .  *      ..    .       * *

TRKA            SHG-PDAKLLAGGED-VAPGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQ
TRKB            AHG-PDAVLMAEGNP---PTELTQSQMLHIAQQIAAGMVYLASQHFVHRDLATRNCLVGE
TRKC            AHG-PDAMILVDGQPRQAKGELGLSQMLHIASQIASGMVYLASQHFVHRDLATRNCLVGA
P75             WNSCKQNKQGANSRP-VNQTPPPEGEKLHSDSGIS---VDSQSLHDQQPHTQT---ASGQ
                 .                       . *     ..   *     *  .    *     *

TRKA            GLVVKIGDFGMSRDIYSTDYYR--------------VGGRTMLPIRWMPPESILYRKFTT
TRKB            NLLVKIGDFGMSRDVYSTDYYR--------------VGGHTMLPIRWMPPESIMYRKFTT
TRKC            NLLVKIGDFGMSRDVYSTDYYRLFNPSGNDFCIWCEVGGHTMLPIRWMPPESIMYRKFTT
```