

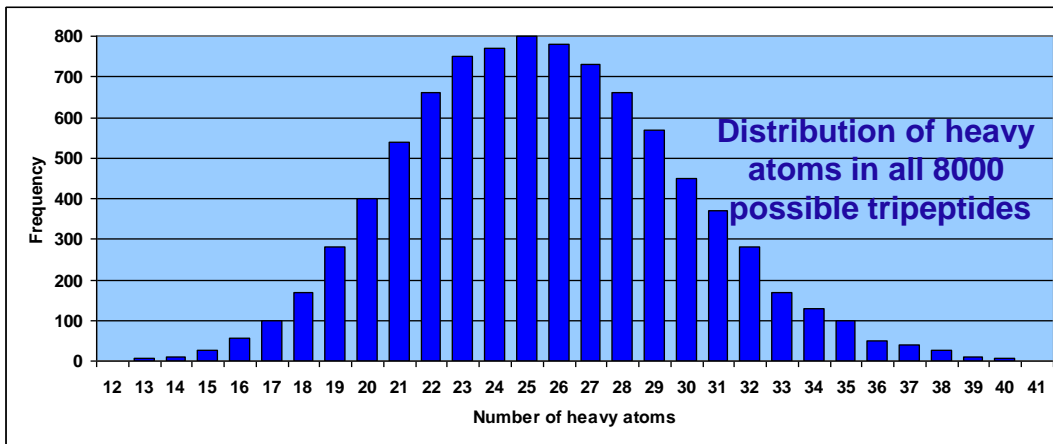
PPI Inhibitors Tripeptide Mimetics. Design of New Scaffolds

**February 2012
ChemDiv, Inc.**

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Senior Director of Medicinal chemistry

TRIPEPTIDE MOTIFS in BIOLOGY

- **Three contiguous amino acids represent an optimal if not minimal size for biological signaling [*]**
- **Clearly not all 8000 possible contiguous tripeptides are likely to have biological importance, but substantial number of them play significant roles in biology**
- **25 heavy atoms (HA) gave optimal ligand affinity or “maximal efficacy” [**]**
- **Given that the average number of heavy (nonhydrogen) atoms in the natural amino acids is 8.3, three residues would on average contribute 25 heavy atoms**



- **The distribution of heavy atoms across all 8000 possible tripeptides shows the peak of the distribution close to 25 heavy atoms**

Tripeptide motifs represent potentially important starting points for design of small molecule biological modulators

BIOLOGICALLY RELEVANT TRIPEPTIDE MOTIFS

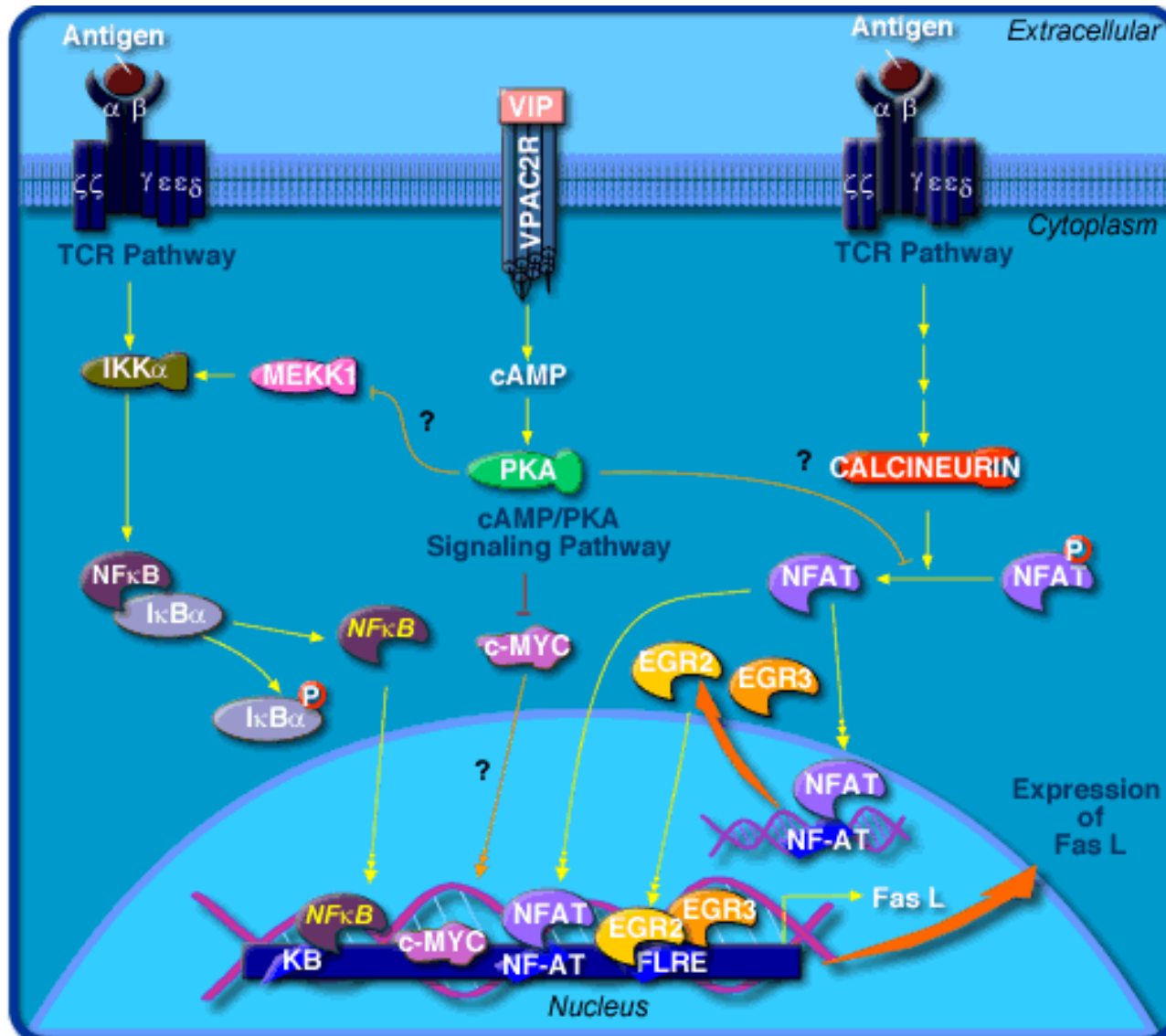
Endogenous tripeptides include the following:

- (1) **ECG** (**Glu-Cys-Gly**) - (glutathione), antioxidant, cofactor;
- (2) **EHP** (**Glu-His-Pro**) - stimulates pituitary gland controlling thyroid-stimulating hormone secretion
- (3) **FEG** (**Phe-Glu-Gly**) - inhibition of anaphylaxis, anti-inflammatory, modulates leukocyte adhesion
- (4) **GHK** (**Gly-His-Lys**) - tissue remodeling and wound healing
- (5) **PLG** (**Pro-Leu-Gly**) - modulator of the dopamine D2 receptor

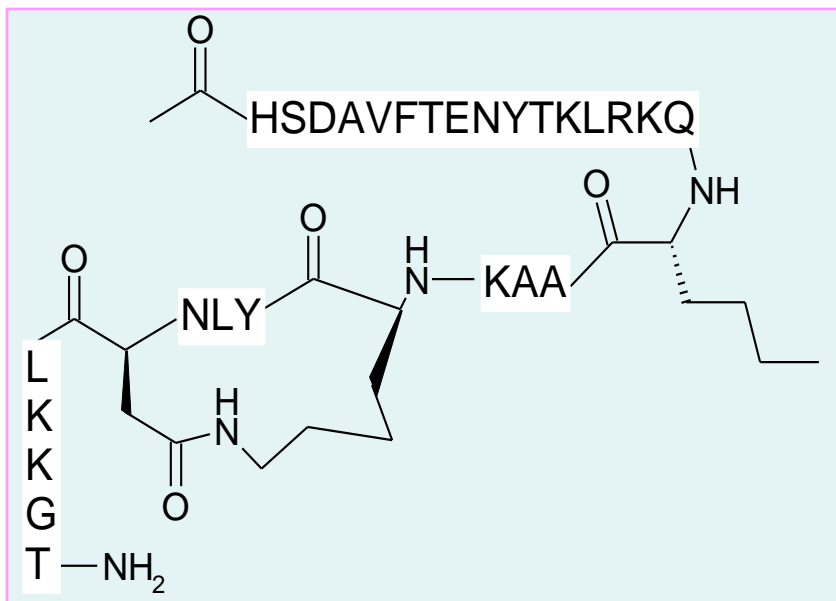
Tripeptide motifs in proteins include the following:

- (6) **DLF/SLF** (**Asp<Ser>-Leu-Phe**) - inhibition of β protein of bacterial replisome, antimicrobial
- (7) **ELR** (**Glu-Leu-Arg**) - chemokine, growth factor binding motif
- (8) **GGQ** (**Gly-Cys-Gln**) - release factor, stop codon recognition
- (9) **GPE** (**Gly-Pro-Arg**), neuroprotection
- (10) **HAV** (**His-Ala-Val**) - cadherin motif, cell-cell interactions, and adhesion
- (11) **HGK** (**His-Gly-Lys**) - vitronectin inhibition
- (12) **HPQ** (**His-Pro-Gln**) - streptavidin binding motif
- (13) **KPV** (**Lys-Pro-Val**) - anti-inflammatory properties
- (14) **LDV** (**Leu-Asp-Val**) - vascular cell adhesion molecule 1 (VCAM-1)/fibronectin adhesion motif
- (15) **RGD** (**Arg-Gly-Asp**) - cell adhesion signal
- (16) **SKL** (**Ser-Lys-Leu**) - peroxisomal targeting
- (17) **KYL** (**Lys-Tyr-Leu**) - vasoactive intestinal peptide (VIP) motif
- (18) **RER** (**Arg-Glu-Arg**) – sAPP motif, neuroprotection

Vasoactive Intestinal Peptide (VIP) Receptor Non-peptide Antagonist Design



- Member of the Secretin Family of Peptides
- Interacts with GPCRs:
 - VPAC1 and VPAC2 .
- Diverse Patho-Physiological Role
 - cancer cell growth,
 - diabetes,
 - septic shock
 - CNS [*].



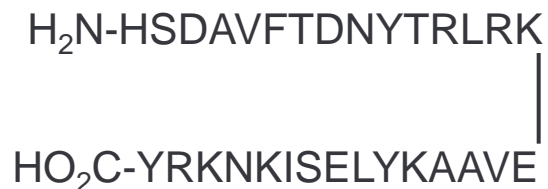
Ro-25-1553 (Preclinical), Roche

Target: VPAC₂ agonist

Problems: Poor bioavailability and stability

Therapeutic Group: Bronchodilators, Chronic obstructive Pulmonary Diseases, treatment of Antiallergy/antiasthmatic drugs

Assessing the Landscape Known Lead Compounds



BAY-55-9837 (Preclinical) Bayer

VPAC₂ agonist

Acts as insulin secretagogue - poor water solubility and short lifespan *in vivo*.

Type 2 Diabetes

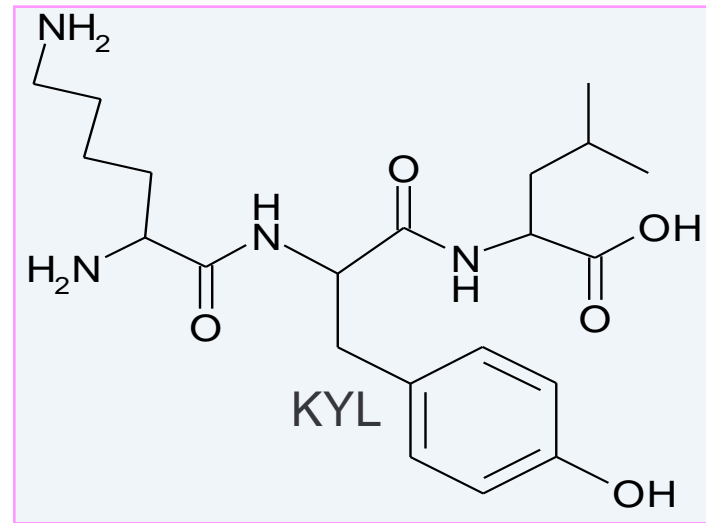
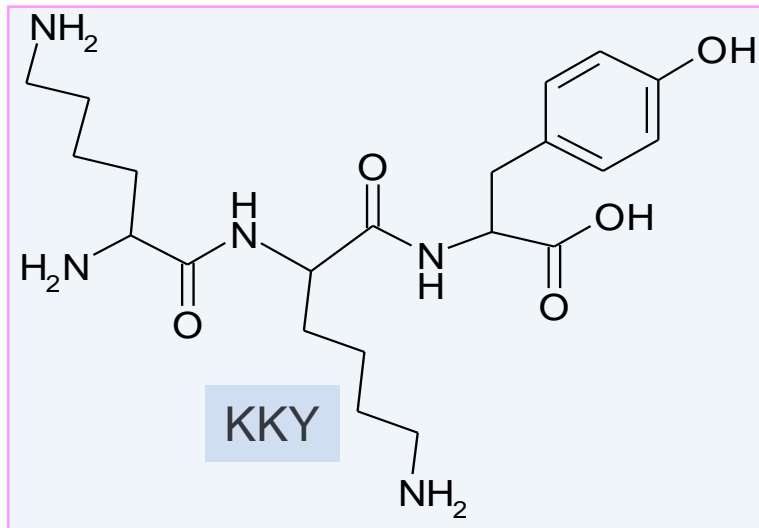
***other active compounds are similar cyclic peptides, peptide fragments of VIP, or modified VIPs (Ala/Gly replacements of key residues)**

VIP and Region Selected for Scaffold Design

Native VIP: **HSDAVFTDNYTRLRKQMAV**²⁰**KKYL**²³**NSILN**

Stearyl-K-K-Y-L: same neurotrophic effects as entire 28-aa VIP [*]

Tripeptide Motifs Selected for Peptidomimetic Design:

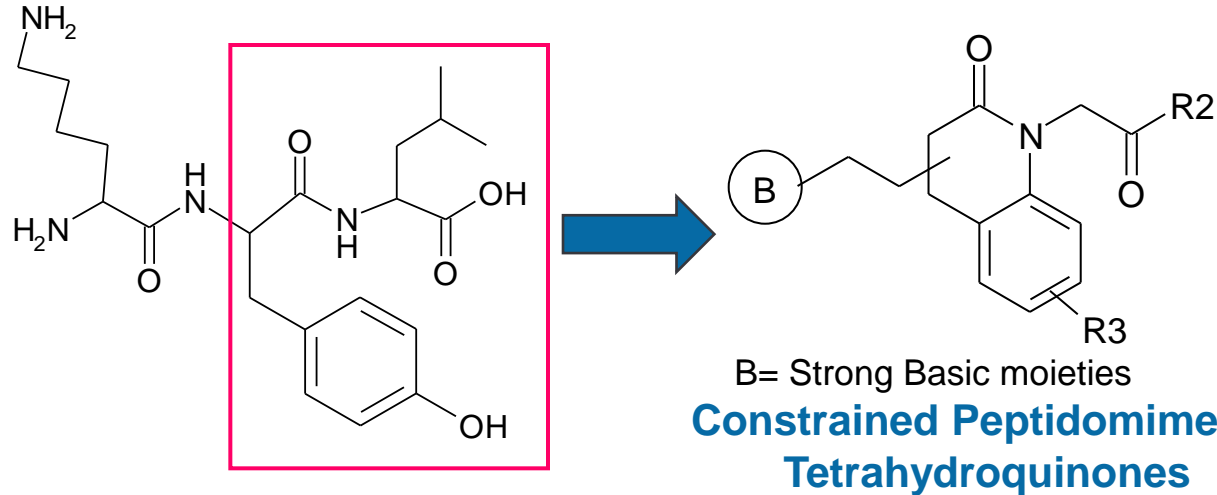


[*] PNAS. 1999; 96: 4143

Selection of Small Molecule Scaffold

Selected Trimers: 20 22 21 23
 K K Y K Y L

Studies have shown residues in the N-terminus are important for receptor binding: Lys²¹ and Leu²³ show high affinity for VPAC₁ binding [1-3], whereas Tyr²² and Leu²³ are essential for VPAC₂ binding [2,3].



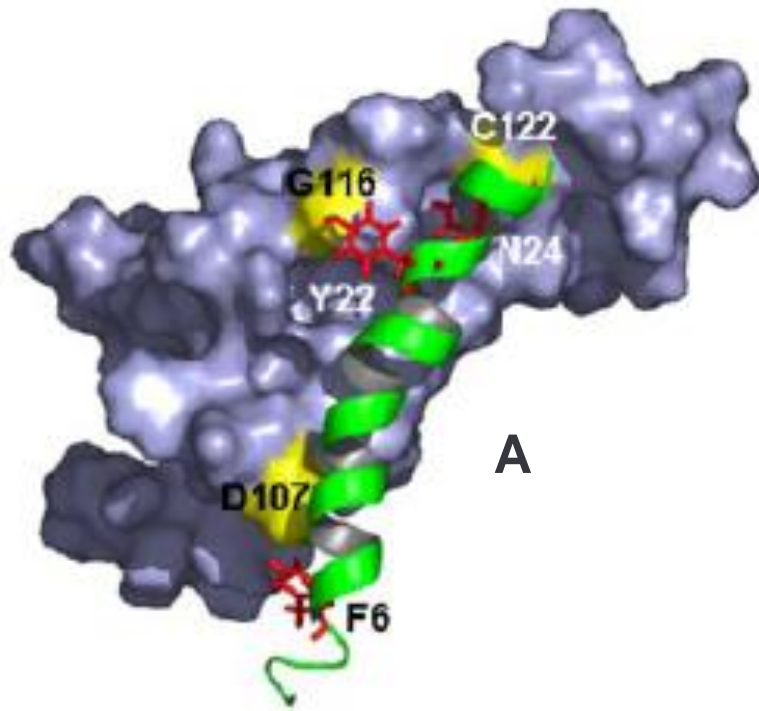
Since Leu²³ is an important residue for binding both receptors, concentrate scaffold design on this end of tripeptide

[1] J Biol Chem. 2000; 275(31): 24003

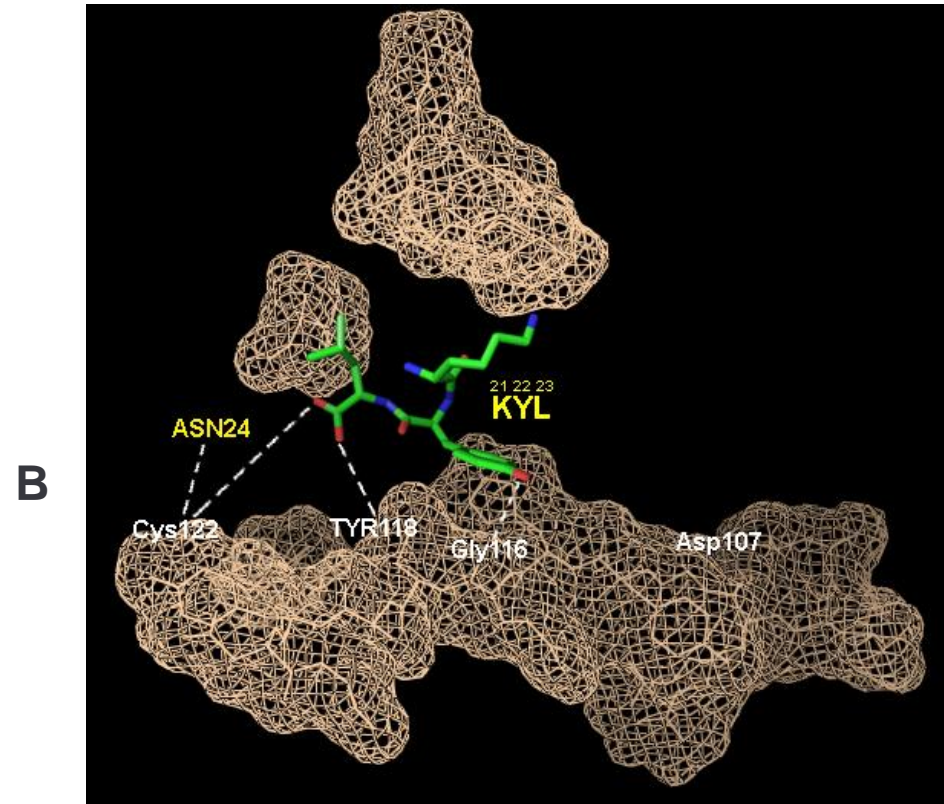
[2] J Pharmacol Exp Ther. 2002; 303(2): 445

[3] Front Med Chem. 2005; 2: 393

Molecular Docking of VIP and the Core KYL Fragment Into the Active Site of hVPAC1



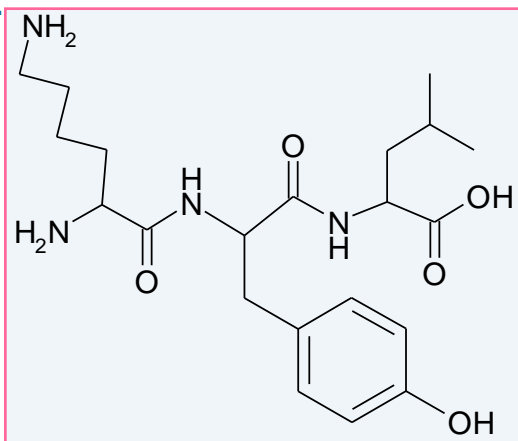
(A) Molecular docking of VIP into the *N*-ted of *hVPAC1* receptor. VIP is represented in *green*, and *N*-ted is represented in *blue*. *Red*, side chains of Phe⁶, Tyr²², and Asn²⁴ of VIP; *yellow*, target residues of *hVPAC1* identified by photoaffinity experiments and Edman degradation, *i.e.* Asp¹⁰⁷, Gly¹¹⁶, and Cys¹²²



(B) The critical interactions between KYL and residues of *hVPAC1* active site

Scaffolds vip-1A & vip-1B for Synthesis of Discovery Library

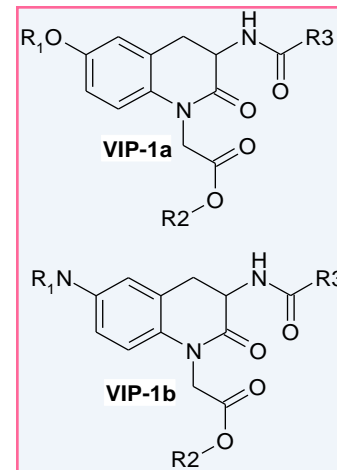
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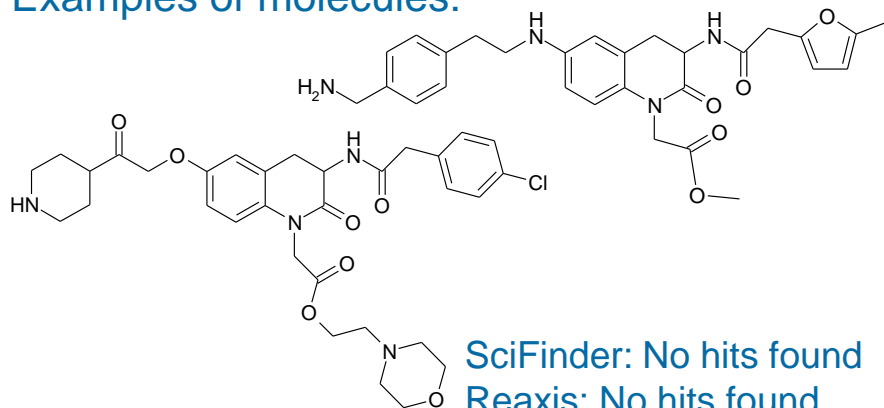
Introduce constrained quinone ring as peptide mimic, basic moieties for lysine replacement

Libraries:

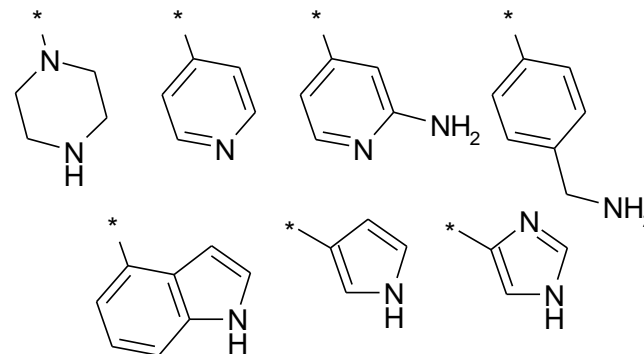
Diverse substituents looking at donating/withdrawing properties, H-bond acceptor/donors, solubility



Examples of molecules:

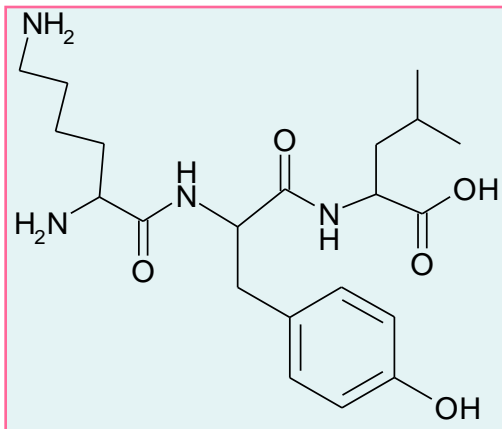


R1 =alkyl, aryl/hetaryl amines, Strong bases:



Scaffolds vip-2A & vip-2B for Synthesis of Discovery Library

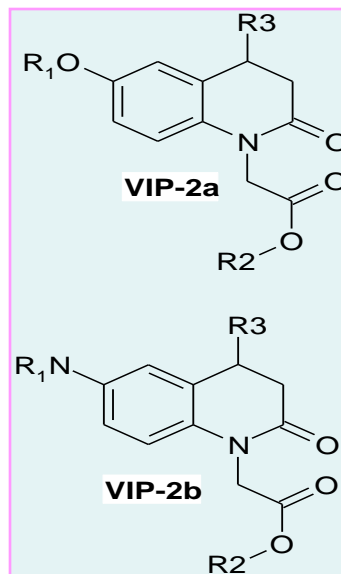
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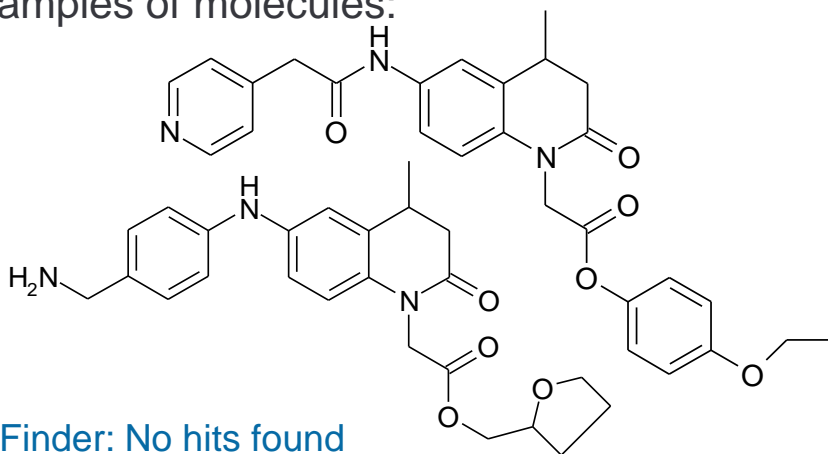
Introduce constrained quinone ring as peptide mimic, basic moieties for lysine replacement

Libraries:

Diverse substituents looking at donating/withdrawing properties, H-bond acceptor/donors, solubility

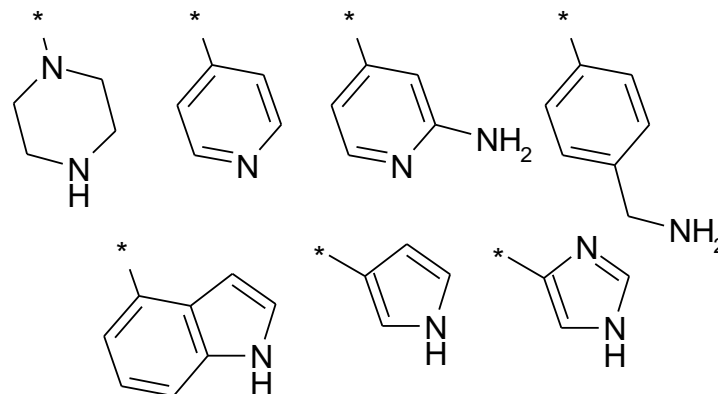


Examples of molecules:

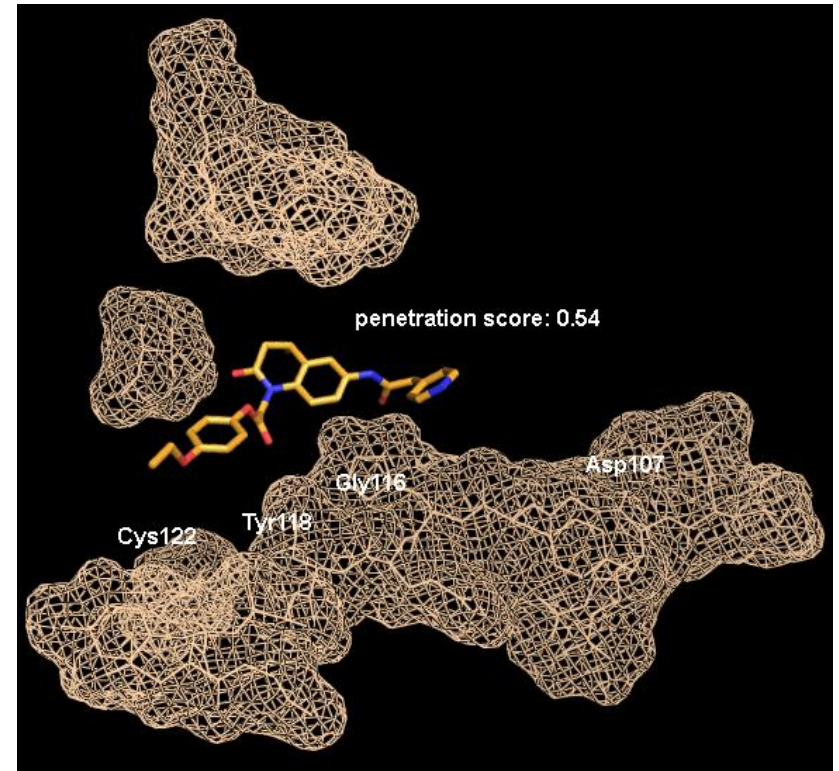
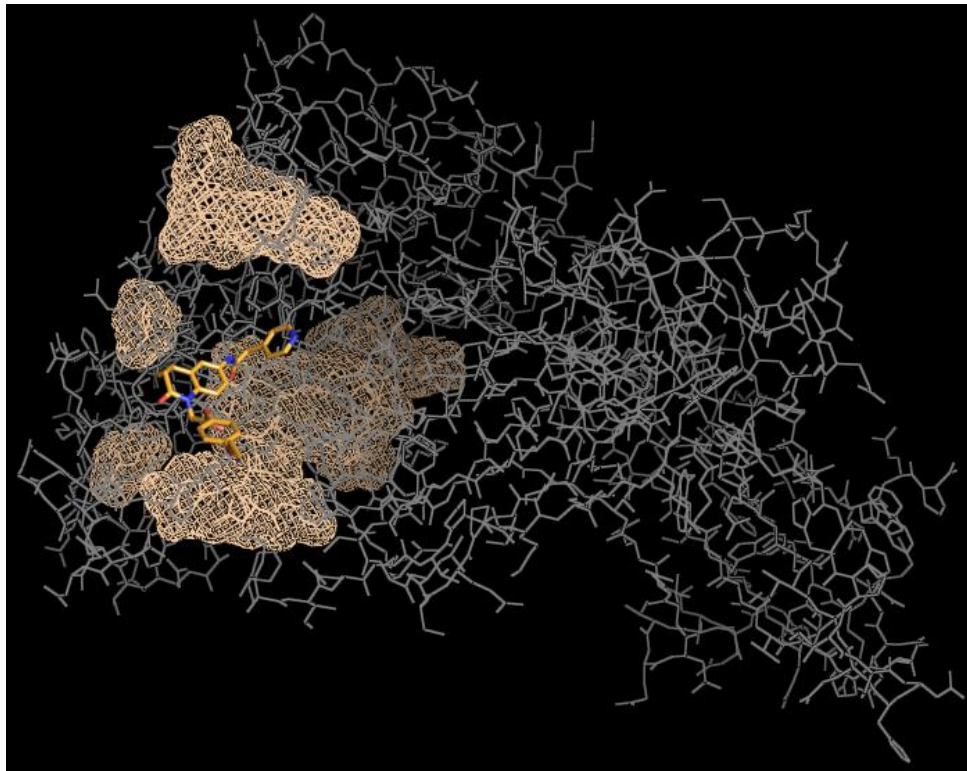


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Reaxis: No hits found

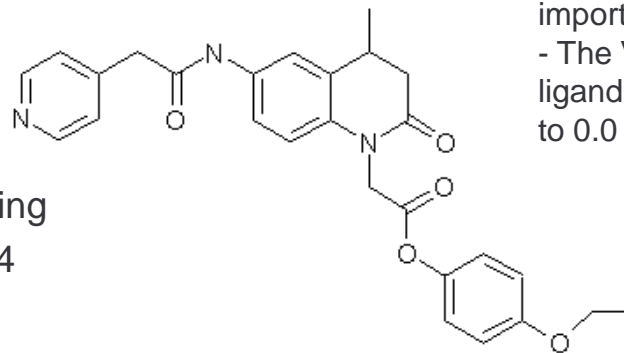
R1 =alkyl, aryl/hetaryl amines Strong bases:



Molecular Docking of Potential Small Molecule Inhibitors of hVPAC1 Receptor from Discovery Libraries VIP-2



VIP2 example

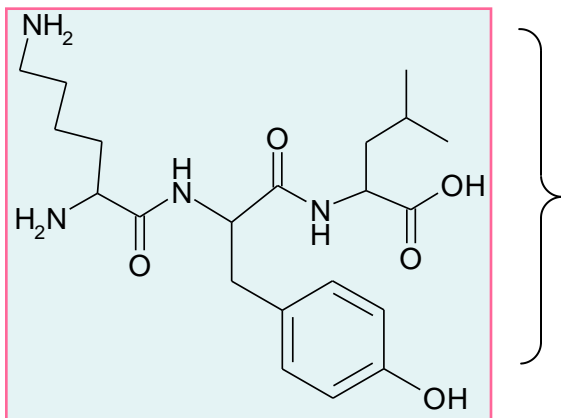


- Beige area designates the amino acid residues important for VIP binding
- The VLS ("penetration") score is the measure of ligand protein interaction VLS scores that are close to 0.0 are favorable.

Docking study was performed using
"SurFlex Docking", Version 1.24
(BioPharmics LLC)

Scaffolds vip-3A & vip-3B for Synthesis of Discovery Library

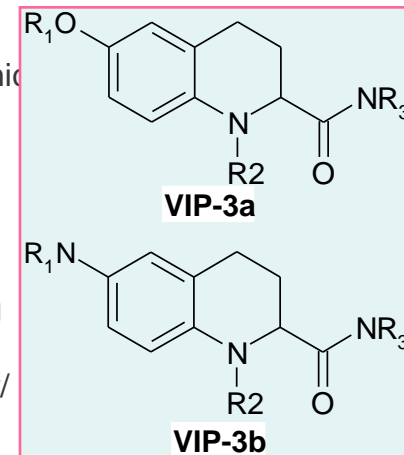
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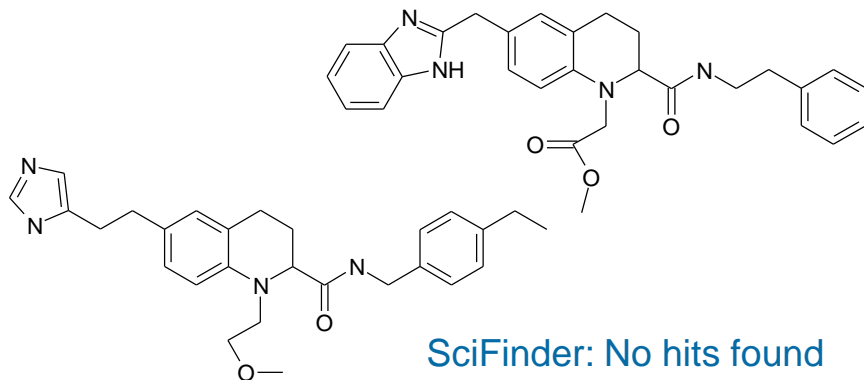
Introduce constrained quinone ring as peptide mimic basic moieties for lysine replacement

Libraries:

Diverse substituents looking at donating/withdrawing properties, H-bond acceptor/donors, solubility

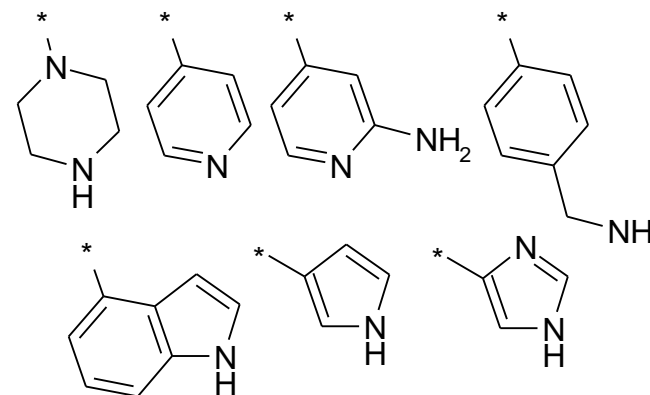


Examples of molecules:

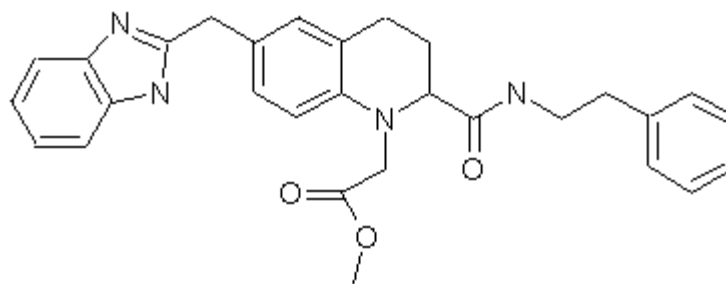
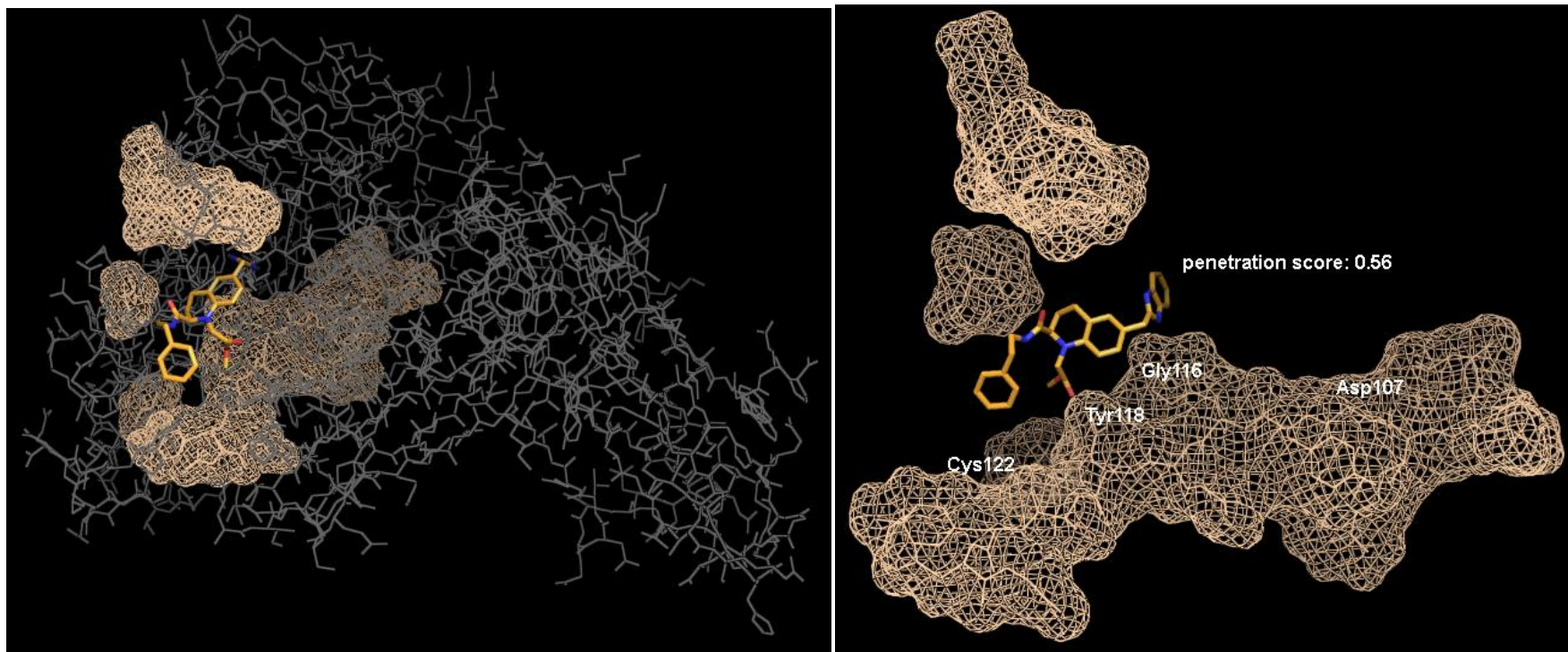


SciFinder: No hits found
Reaxis: No hits found

R1 =alkyl, aryl/hetaryl amines Strong bases:

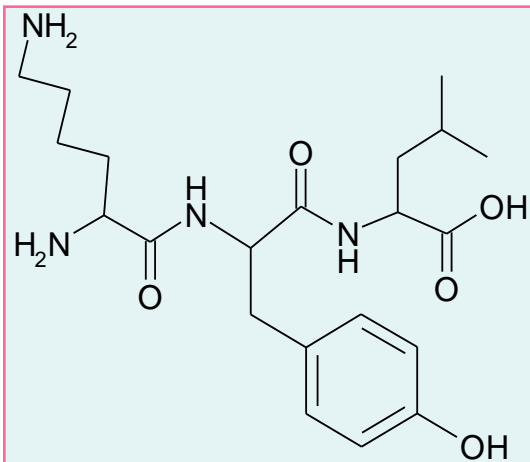


Molecular Docking of Potential Small Molecule Inhibitors of hVPAC1 Receptor from Discovery Libraries VIP-3



VIP-3 example

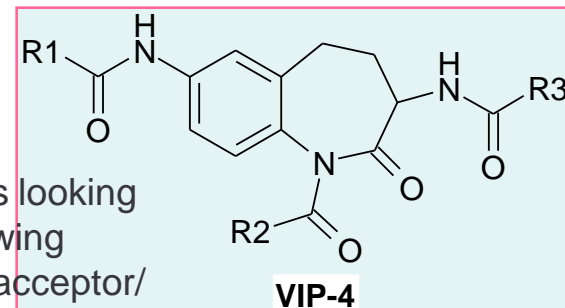
Proposal: Scaffold vip-4 for Synthesis of Discovery Library



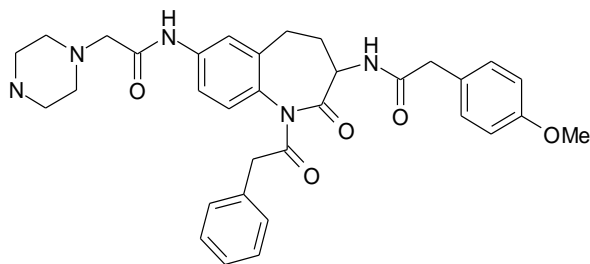
Introduce larger, constrained quinone ring as peptide mimic, basic moieties for lysine replacement

Libraries:

Diverse substituents looking at donating/withdrawing properties, H-bond acceptor/donors, solubility

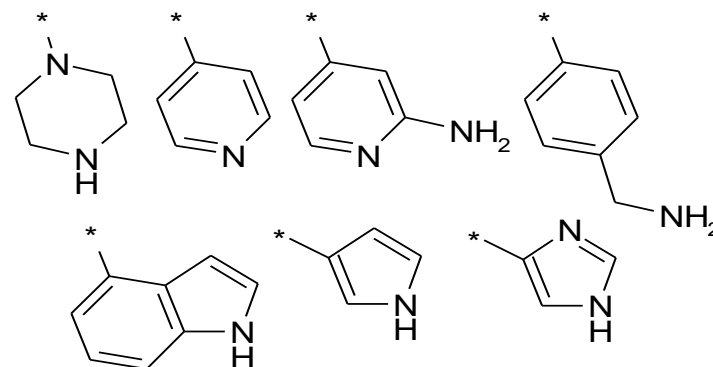


Examples of molecules:

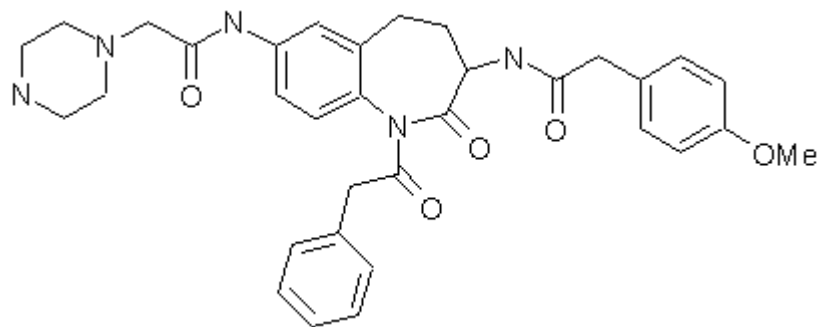
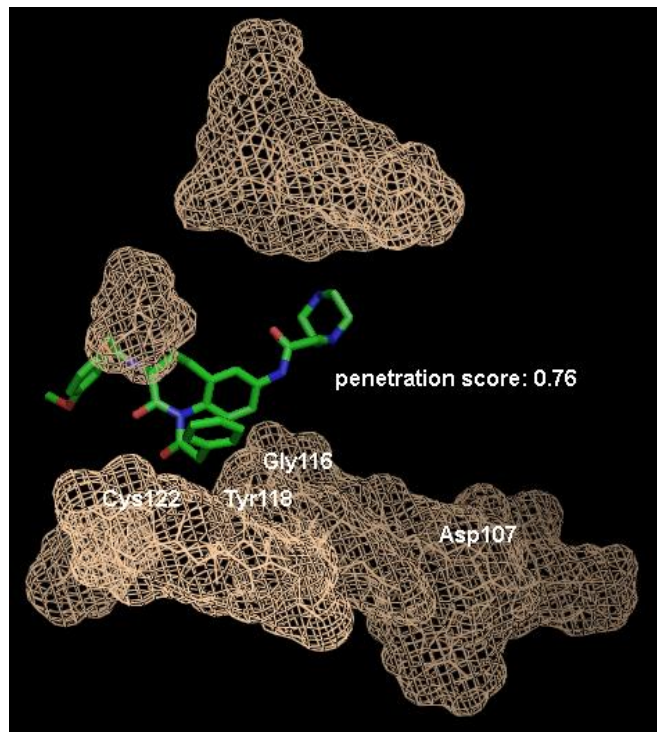
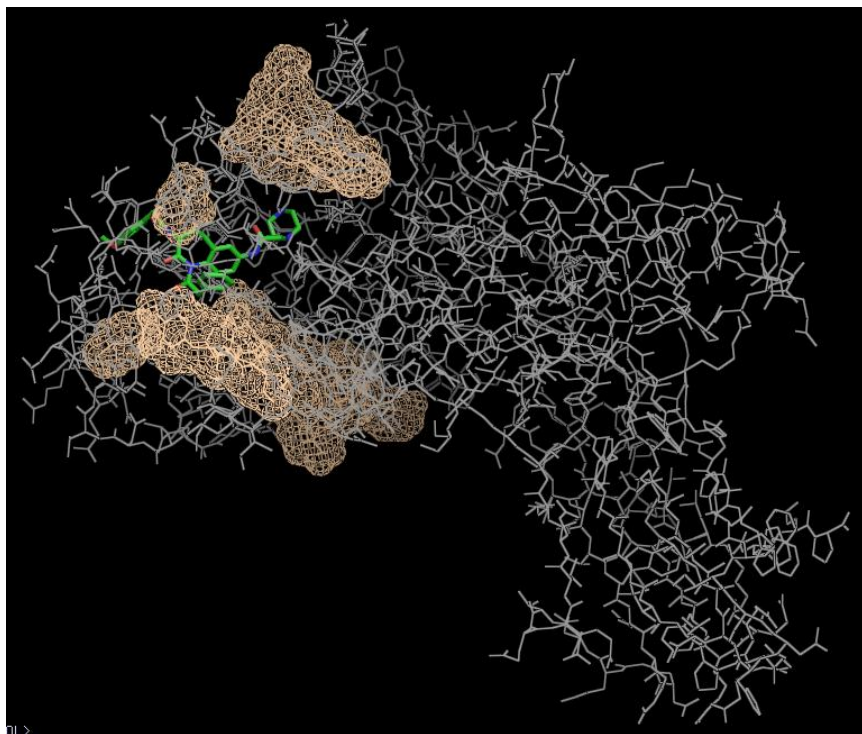


SciFinder: No hits found
Reaxis: No hits found

R1 =alkyl, aryl/hetaryl amines, Strong bases:



Molecular Docking of Potential Small Molecule Inhibitors of hVPAC1 Receptor from Discovery Libraries VIP-4

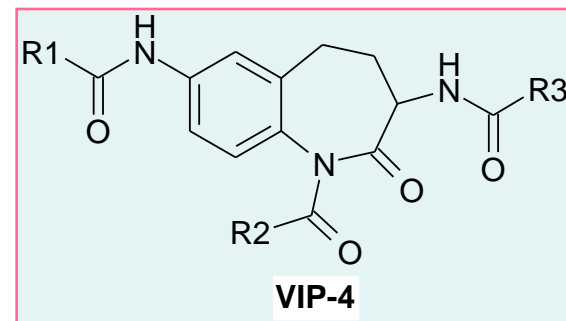
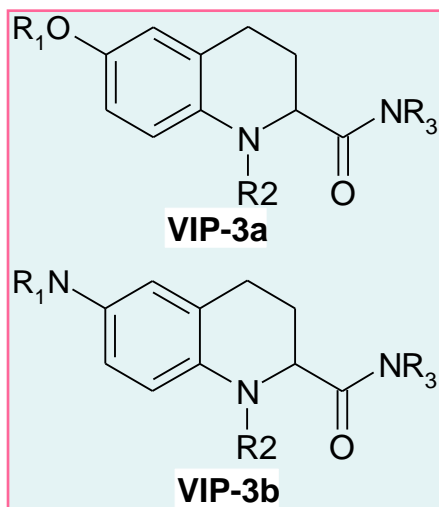
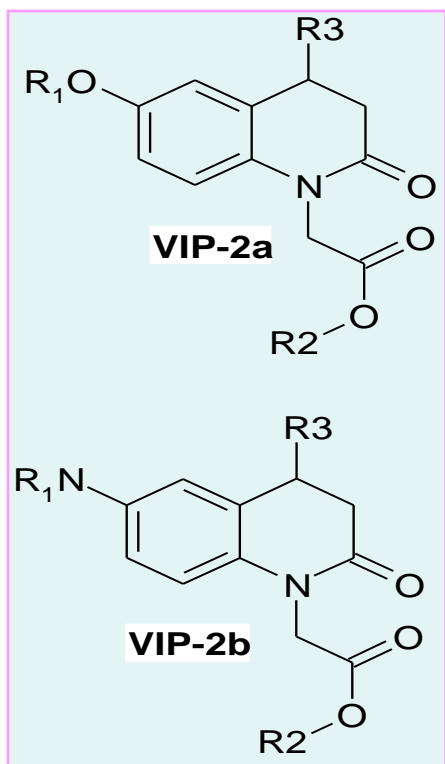


VIP-4 example

Selected VIP-Scaffolds for Synthesis of Discovery Library

Scaffolds selected for synthesis possess:

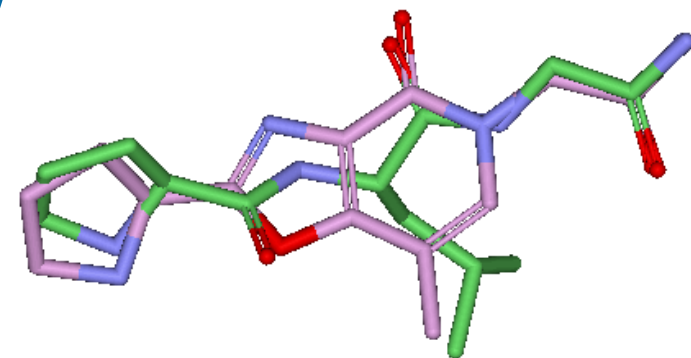
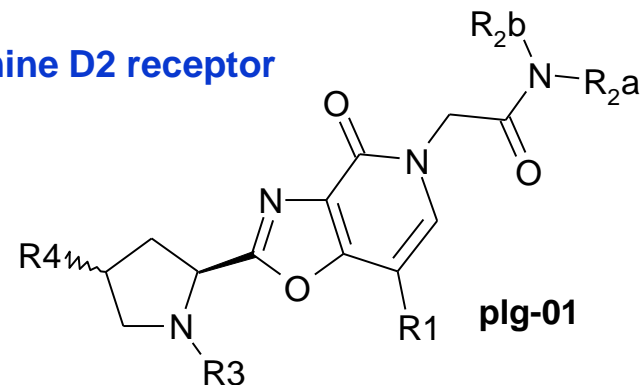
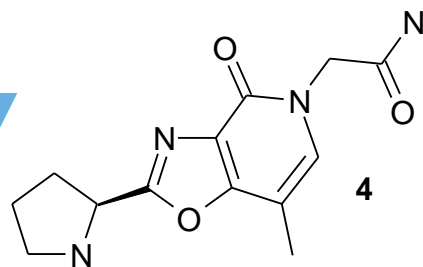
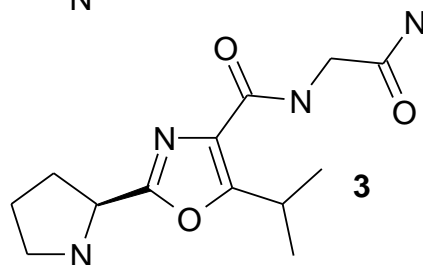
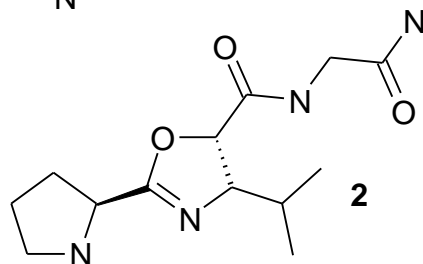
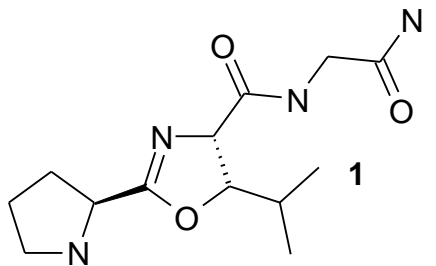
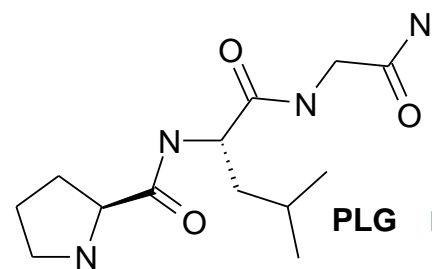
- ❖ Proper spatial arrangement in the VIP binding site and are bound to 2-4 amino acid residues critical for complex formation
- ❖ High synthetic feasibility
- ❖ High IP potential
- ❖ Drug-like and tractable



Other Tripeptide Mimetics. Design of New Scaffolds

SYNTHETIC APPROACH to NEW PLG-MIMETICS

Design of Novel Scaffolds - 1



Core alignment:

Green – starting PLG

violet – plg-01 scaffold

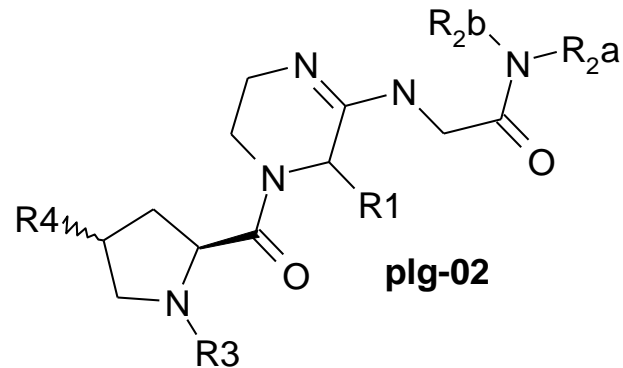
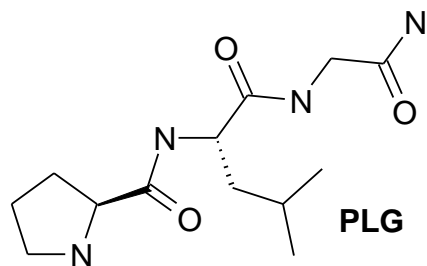
New Library
(20-50 compounds)

Drug-likeness

Synthetic feasibility

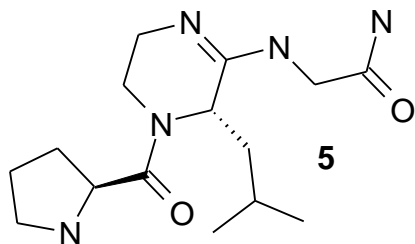
SYNTHETIC APPROACH to NEW PLG-MIMETICS

Design of Novel Scaffolds - 2

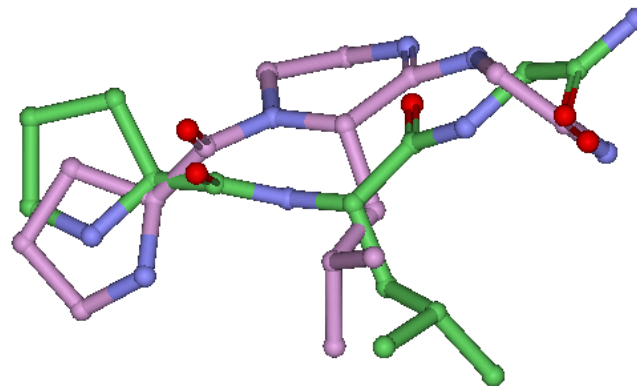


Drug-likeness

Unique
validated
chemistry



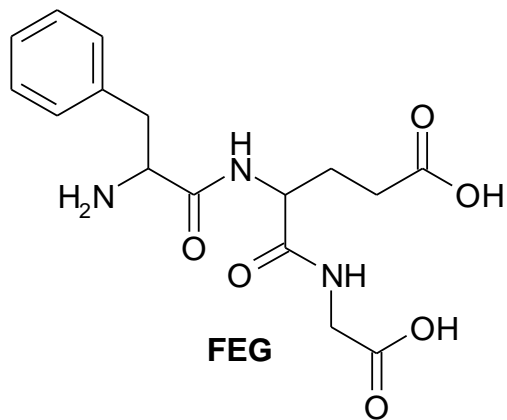
New Library
(20-50 compounds)



Core alignment:
Green – starting PLG
violet – plg-02 scaffold

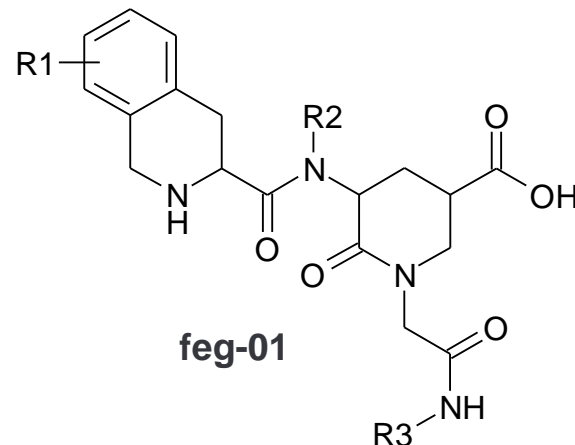
SYNTHETIC APPROACH to NEW FEG-MIMETICS

Design of New Scaffolds

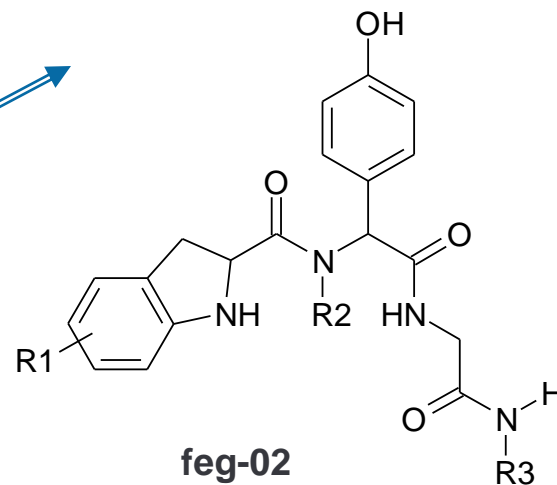
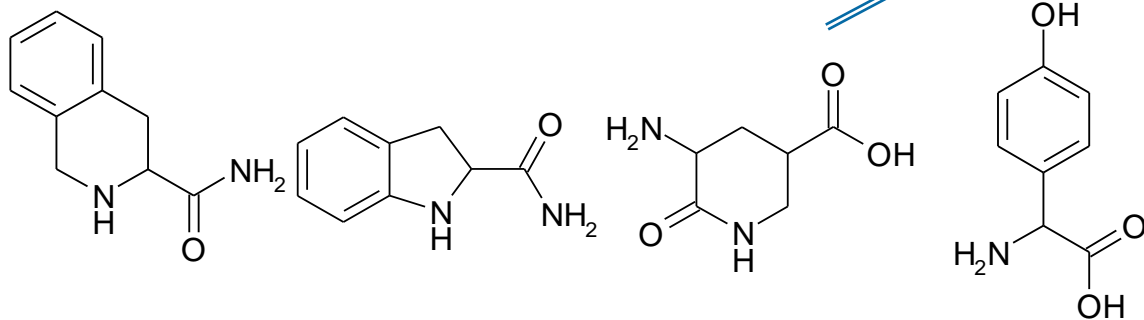


FEG

Inhibitor of anaphylaxis, anti-inflammatory, modulates cardiac leukocyte adhesion



feg-01



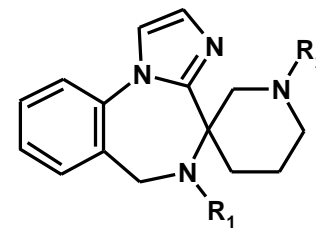
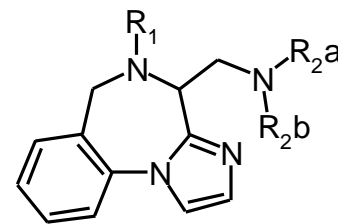
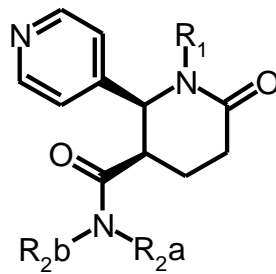
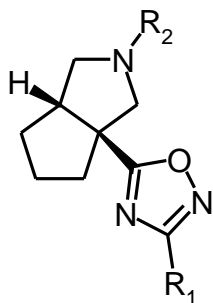
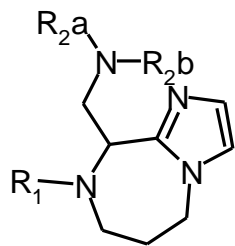
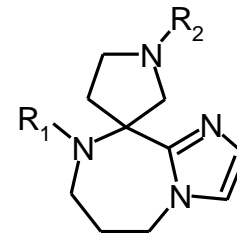
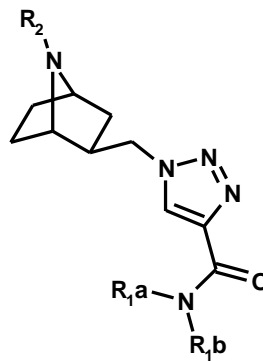
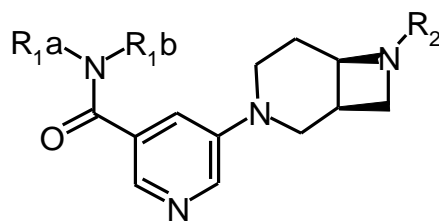
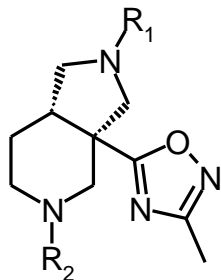
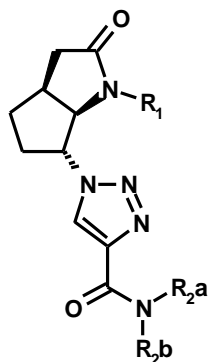
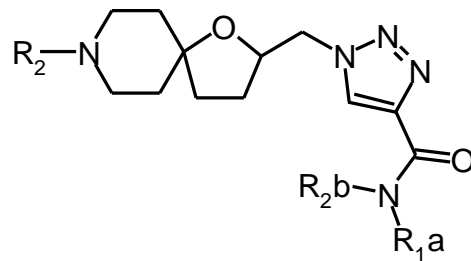
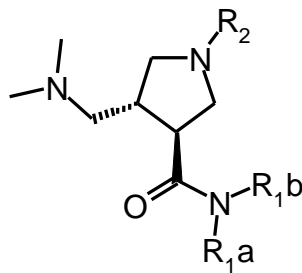
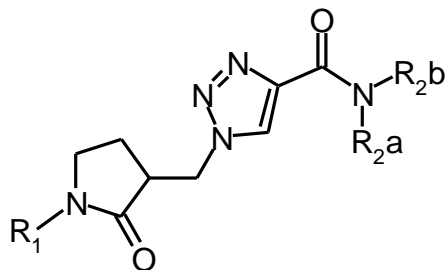
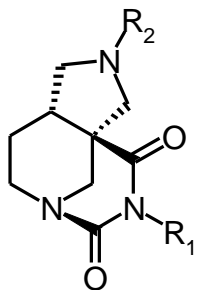
feg-02

F (Phe) - mimetic F (Phe) - mimetic E (Glu) - mimetic E (Glu) - mimetic

Other Peptidomimetics. Design of New Scaffolds

SYNTHETIC APPROACH to NEW DI- & TRI-PEPTIDE MIMETICS

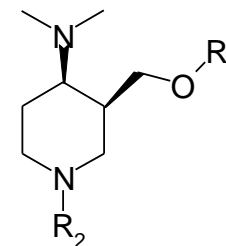
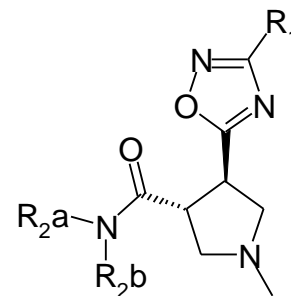
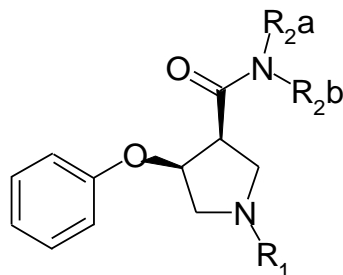
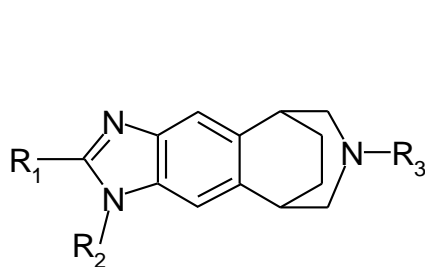
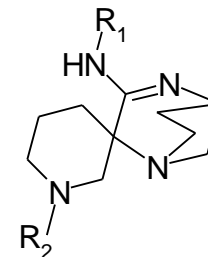
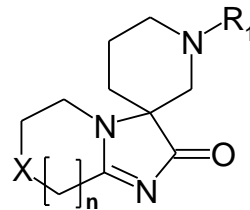
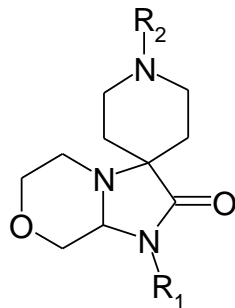
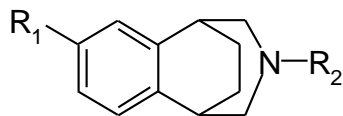
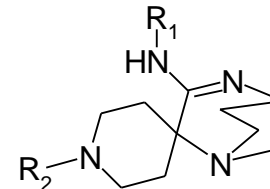
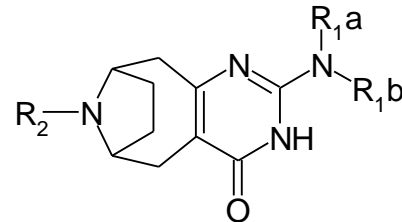
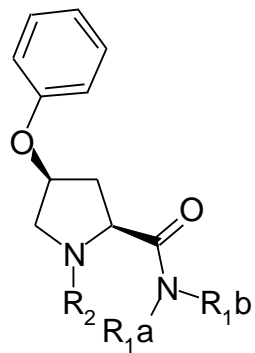
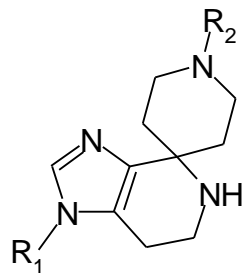
New Scaffolds 1



3D

SYNTHETIC APPROACH to NEW DI- & TRI-PEPTIDE MIMETICS

New Scaffolds 2



SYNTHETIC APPROACH to NEW DI- & TRI-PEPTIDE MIMETICS

New Scaffolds 3

