Peptidomimetic Library

Medicinal and Computational Chemistry Dept., ChemDiv, Inc., 6605 Nancy Ridge Drive, San Diego, CA 92121 USA, Service: +1 877 ChemDiv, Tel: +1 858-794-4860, Fax: +1 858-794-4931, Email: ChemDiv@chemdiv.com

Preamble

"*In a really valiant effort to partially mimic the complex interaction between natural peptide molecules and their inner biological targets, a number of diverse small molecule organic compounds with functionalities similar to the side-chains of the amino acid residues of the original peptide prototype critical to binding have been increasingly developing*"

1. A brief introduction in protein-protein interactions

Peptides, as neurotransmitters, neuromodulators, and hormones, influence a multitude of physiological processes by signal transduction mediated through receptors. In addition, during the last 20 years their role in the appearance or maintenance of various diseases could be unequivocally proven. Agents that can imitate or block the biological functions of bioactive peptides (agonists or antagonists, respectively) can be considered as aids for the investigation of peptidergic systems and also as therapeutic agents. The suitability of bioactive peptides as therapeutic agents was examined after preliminary pharmacological experiments. It was thereby shown that based on their pharmacological properties, for example degradation by peptidases or poor bioavailability, they could be employed as drugs in only a few cases. To solve this problem peptidomimetics, compounds that act as substitutes for peptides in their interaction with receptors, have been synthesized. In comparison with native peptides they show higher metabolic stability, better bioavailability, and longer duration of action. Peptidomimetics with antagonistic properties were also developed within the range of these investigations. As a result, new types of treatment and therapy for a series of diseases are possible. Although peptidomimetics have been developed largely by empirical methods (e.g. modification of native peptides, optimization of lead structures), methods for rational design based on investigations into the structure of peptide-peptide receptor complexes and studies of conformation energies, among others, are gradually being established.

Proteins are ubiquitous macromolecules that play key roles in biological processes ranging from catalysis of chemical reactions to providing structural support of cells to the transcription of deoxyribonucleic acid (DNA). Central to the intrigue of proteins is how they interact with one another.

Although the proteins primary, secondary, tertiary, and quaternary structural forms are important to how they interact with one another, only the primary and secondary structures are generally targets for mimicry. Linus Pauling and Robert Corey, through their exhaustive X-ray diffractive studies of fibrous proteins, generalized the protein structures as falling into three secondary types: the α-pattern, the β-pattern, and the collagen pattern.[i]

Nussinov and coworkers define a protein-protein interface as an area, within a distance threshold, of interacting amino acid residues between at least two protein chains.[ii] Precisely which residues constitute an interface varies from study to study.[iii] Interface areas are calculated based on crystal structures of monomeric proteins and complexed proteins. In the complexed state, a certain percentage of the total area is "buried" by the interaction. This interface area was found by Janin and coworkers[3,iv] to be from 670 to 4890 $Å^2$ while Jones and Thornton[3] discovered a slightly wider range, from 368 to 4761 $Å^2$. Within these interfaces there often exist critical binding points known as hot spots. Although no predictions can be made with regard to whether or not particular sites are hot spots, polar residues do tend to be conserved at these sites.[2,v] X-ray crystallography revealed that hot spots are highly structural with side chains of amino
acid residues from one surface fitting into the cavities and crevices on the opposite surface.[vi] These residues are so important in binding that when mutated to alanine cause a dramatic decrease in the binding constant, usually tenfold or higher.[vii]

2. Protein secondary structures: α-helices and β-turns

The secondary motifs that seem to recur often in mediating protein-protein interactions are the α-helices and β-turns (Figure 1).[viii] The R-, L-, and 3.10 α-helices and the type I and type II β-turns are of particular interest because of their well-known status in the literature. The R and L denote whether the helix is coiling to the right or left, respectively, and the 3.10 denotes 3 residues per turn of the helix, a total of 10 atoms from the oxygen of the carbonyl group (hydrogen bond donor) of the *i* residue to the hydrogen of the amide group (hydrogen bond acceptor) of the *i+3* group.[ix] A type I β-turn has the carbonyl oxygen from the amide bond between the *i+1* and *i+2* oriented away from the observer while in a type II turn it is oriented toward the observer.[x]

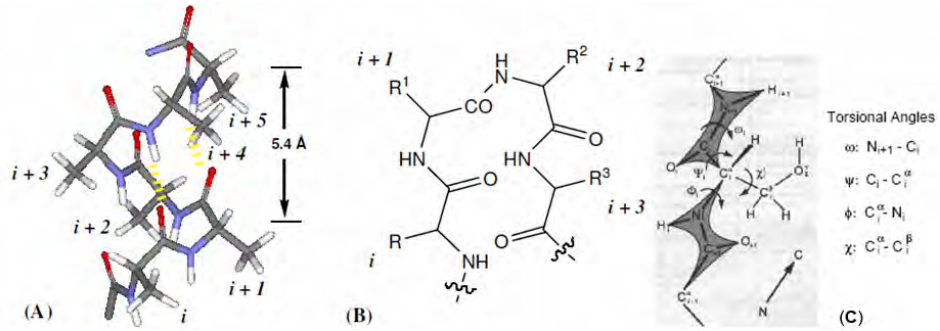


Figure 1. (**A**) General structure of an α-helix (naturally occurring R-α-helix shown). Each turn of the helix incorporates 3.6 residues. (**B**) General structure of a β-turn; (**C**) peptide's active conformational parameters

3. Peptidomimetics

As the name implies, peptidomimetics are organic molecules that mimic the action of peptides. These molecules may structurally resemble peptides but are distinctly different in terms of their side chains or their molecular backbones. Since the mode of action for a small-molecule and a peptidomimetic is similar, confusion sometimes arises with regard to the classification of the molecule as being a peptidomimetic or simply a small organic molecular mimic. Nevertheless, interactions with proteins can be mediated by other molecules with intermediate molecular masses instead of the low molecular weights associated with small-molecules or peptidomimetics.

Mimicking or disrupting protein-protein interactions using small molecules is a well-known topic in the literature. *In vitro* and *in vivo* evidence has particularly shown that cancerous cells that metastasize depend on selectin-, integrin-, and chemokine-mediated vascular adhesion events.[xi] It was recently discovered that the chemokine receptor CXCR4 was deeply involved in attracting tumor metastases to the bone marrow,[xii] and that AMD3100, a small molecule antagonist, binds the receptor thereby preventing the spread of the tumor to the site.[xiii] On a similar note, a mimic of the second mitochondria-derived activator of caspases (Smac), a protein involved in apoptosis, was just as effective as the native ligand at 105 to 106-fold lower concentrations.[xiv] The mannose-binding lectin (MBL) plays a very important role in the lectin complement pathway which is responsible for the development of the immune response in early childhood and the inflammatory response on oxidatively stressed endothethial cells.[xv] A decapeptide with the sequence SFGSGFGGGY was found to mimic the known ligand of MBL, Nacetyl-D-glucosamine (GlcNAc).[15] Arguably one of the most extensively studied and important biological interactions are those between integrins and cell adhesion molecules (CAMs).[xvi] Integrins are a large family of heterodimeric (consisting of an α subunit and a β-subunit) surface receptors on cellular plasma membranes that mediate cell-matrix and cell-cell interactions.[16b,c] Thus far, the protein-protein interactions antagonized by 4 small molecules that involve integrins, intracellular adhesion molecules

(ICAMs), and vascular cellular adhesion molecules (VCAMs) known are avb3/vitronectin, avb3/MMP2, VLA4/VCAM, and LFA-1/ICAM.19,20,21 BXT-51072, a glutathione peroxidase (GPx) mimic, has been shown to inhibit ICAM-1 and VCAM-1 expressions by tumor necrosis factor-α (TNFα).[xvii] Since the discovery of the residues within ICAM-1 that are important for the interaction with LFA-1, Gadek and co-workers developed a LFA-1 antagonist with an IC_{50} of 1.4 nM.[xviii] Figure 2 shows the structures of all the representative small molecule PMs mentioned above.

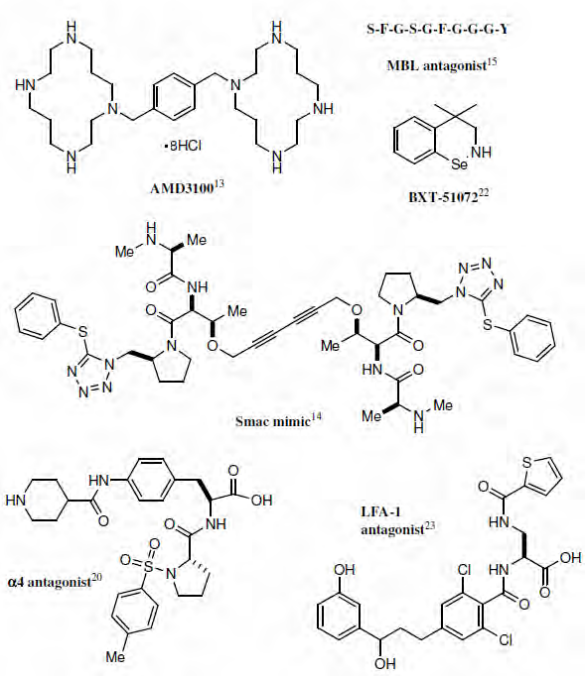


Figure 2. Representative examples of small molecule organic compounds that mimic or disrupt protein-protein interactions

3.1. α-Helix and β-turn peptidomimetics

As mentioned above, α-helices and β-turns are among the most abundant secondary structures that can be found mediating protein-protein interactions. As with all conceptual designs, the target protein serves as the model which fuels innovations. This subsection will briefly touch upon the various published designs of α-helix and β-turn peptidomimetics.[xix] Figure 3A depicts examples of β-turn peptidomimetics that have been published in the literature.[xx] Figure 3B shows a couple of specific peptidomimetic examples that are neither α-helix nor β-turn mimics, but are potent inhibitors of herpes virus[16a] and adenovirus. Of particular interest is the Burgess design which provided useful lead compounds, D3 and MPT18, each of which binds TK type A and TK type C, respectively (Figure 3C).[xxi] Designing peptidomimetics to mimic the behavior of α-helices are much more difficult as most of the designs are more prone to conformational changes than those for β-turns. Nevertheless, successful attempts have been made and published (Figure 3D).[xxii] The distances between the residues in the α-helices are unique in a sense that the distance between *i* and *i*+*n* are not necessarily larger than the

distance between *i* and *i+(n-1)*. For instance, the distance from *i* to *i+3* is 7.89 Å and from *i* to *i+2* is 7.94 Å for an α-helix. Since the distances vary slightly between R- and L-α-helices. In addition, the helices were constructed using only alanine amino acids, and all the measurements were taken from the α carbons between the residues.

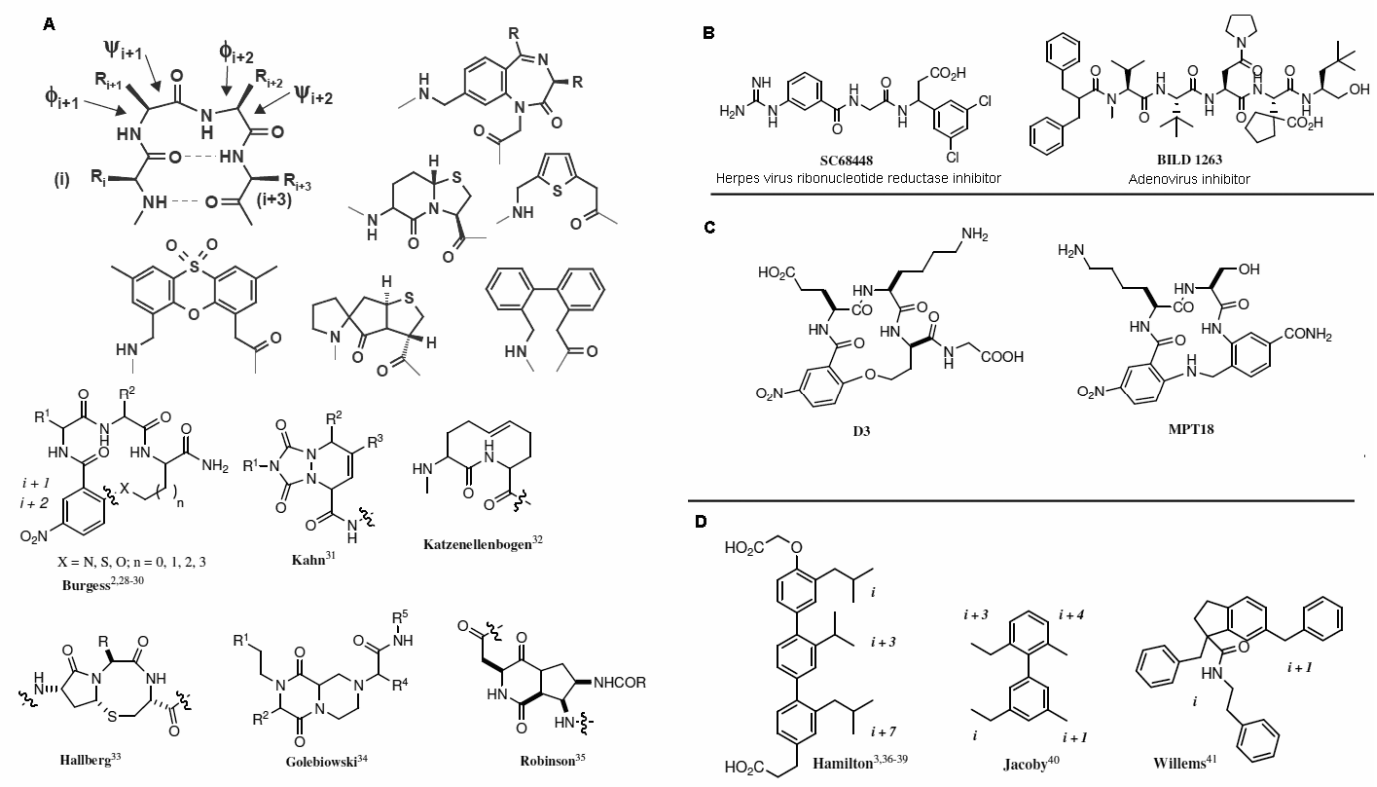


Figure 3. (**A**) Examples of β-turn peptidomimetic developed by various research groups; (**B**) PMs that are neither α-helix nor β-turn mimics; (**C**) β-turn peptidomimetics that bind tyrosine kinase A and C receptors; (**D**) Terphenyl, biphenyl, and indane as α-helical mimetics

It is interesting that**,** accounting for nearly one-third of all known protein structures,[xxiii] the α-helix is definitely a vital structural motif for molecular design and organic syntheses. Its prominence can be seen at interfaces in viral/bacterial proteins such as HIV-1 gp41, EcoR1, and human papillomaviruses (HPVs); in transcription factors such as homodimers of bHLH TF E47, Jun, and cancer-linked ESX and Sur-2/DRIP130; and in cellular proteins such as HER2/neu, Bcl-XL-Bak, and p53-MDM2.37,[xxiv] Alpha helical mimicry has been reviewed by Hamilton[xxv] and Fairlie.[xxvi] However, constraining molecules into helix-type conformations are very difficult.

Mimicking protein-protein interactions poses a very challenging feat in medicinal chemistry. To be considered effective, a small-molecule or peptidomimetic must, at the least, interact with the protein in a way that is similar to the native ligand. Three factors need consideration before embarking on the task of designing such a molecule: the comparable binding orientation of the molecule with the native

ligand, the synthetic feasibility of the designed molecule, and the binding strength. Therefore, various computational approaches are desperately needed to design small molecule peptidomimetics based on the fundamental concept of *in silico* drug design and combinatorial library profiling.

4. Computational approaches to the design of novel PMs

Choosing structures that are most likely to have a predefined target-specific activity of interest from the vast assortment of structurally dissimilar molecules is a particular challenge in compound selection. This challenge has been tackled with powerful computational methodologies, such as docking available structures into the receptor site and pharmacophore searching for particular geometric relations among elements thought critical for biological activity. Both methodologies focus on conformational flexibility of both target and ligand, which is a complex and computationally intense problem. With the emergence of more powerful computers not to mention the wealth of 3D structural data of proteins currently available for meticulous scrutiny, these methods have become almost a standard protocol in the pharmaceutical industry for designing novel drugs.[xxvii] Marathon efforts and research have been made to "fine-tune" the simulation of ligand-protein interactions using these computational techniques and compare the result to natural systems from which it tries to emulate.[xxviii] The latest developments in this field pave the way to wide industrial application of these technologies in drug design and discovery, though the limits of computational power and time still restrict the practical library size selected by these methods.

Assessing predictions of protein-protein interactions using the docking methodology is a complex and time-consuming process requiring collaborations between many research groups. For most docking algorithms, however, a docking calculation usually involves three basic steps: prepare the system, that is, assign receptor and ligand potentials and create a docking assembly; perform the calculation, fill in parameters, set energy cut-offs, and launch the job; and analyze the results.[xxix] In selecting what program to use, two factors need to be considered: parameterization and score functions.[xxx] Parameterization refers to the set of parameters used to describe a molecule (such as bond lengths, bond angles, energy of bond types, etc.) and score functions refer to a set of conditions a program uses to either accept or reject a docking result, often comparing the free Gibbs energy of binding (ΔG^0).[30] There are many programs available to simulate docking, each one offers its unique approach and perspective. It is important to note that most programs are search algorithms, designed to scour for molecular structures in known databases, such as the Chemical Abstracts (CA), the American Chemicals Directory (ACD), or the National Cancer Institute (NCI),[xxxi] that seem to dock well onto the receptor. In the present study we have used SurflexDock computational program [http://www.optive.com] developed by Tripos to design of our PM-library.

Another popular approach to virtual screening is based on ligand structure and consists of selecting compounds structurally related to hits identified from the initial screening of the existing commercial libraries and active molecules reported in research articles and patents. In addition, there are specific statistical data mining methods, which are able to extract information from knowledge databases of active compounds. This common category comprises a wide range of QSAR computational tools, including artificial neural-nets, various mapping techniques, PCA and SVM, recursive partitioning as well as various algorithms for 2D- and 3D-similarity assessment. In the current study we have effectively used a Tanimoto similarity algorithm implemented in ChemoSoft™ software [ChemDiv, Inc.: www.chemdiv.com] to recruit ChemDiv compounds into our unique PM-library.

It should be especially noted that as a `strike-force` combination these methods have been providing a plethora of drugs released nowadays on the market.

Concept and Applications

PM-library design at CDL involves:

• *A combined profiling methodology based on several advanced computational tools*:

1. Bioisosteric morphing and funneling procedures in designing novel potential peptidomimetics with high IP value. We apply CDL's proprietary Chemosoft™ software and commercially available solutions from Accelrys, MOE, Daylight and other platforms.

2. A molecular docking approach to PM-library design.

3. Computational-based `*in silico*` ADME/Tox assessment for novel compounds includes prediction of human CYP P450-mediated metabolism and toxicity as well as many pharmacokinetic parameters, such as Brain-Blood Barrier (BBB) permeability, Human Intestinal Absorption (HIA), Plasma Protein binding (PPB), Plasma half-life time ($T_{1/2}$), Volume of distribution in human plasma (V_d), etc.

The fundamentals for these applications are described in a series of our recent articles on the design of exploratory small molecule chemistry for bioscreening [for related data visit ChemDiv. Inc. online source: www.chemdiv.com].

• *Synthesis, biological evaluation and SAR study for the selected structures*:

1. High-throughput synthesis with multiple parallel library validation. Synthetic protocols, building blocks and chemical strategies are available.

2. Library activity validation via bioscreening; SAR is implemented in the next library generation.

We practice a multi-step approach for building our PM-library:

Several factors were kept in mind when designing peptidomimetics. One of the most obvious is the need to keep the molecules simple, thus synthetically facile should the need to make them arise. In

addition, the designed compounds should take after molecular scaffolds often found in known drugs. Therefore, if the compounds were found to be active, then perhaps they will exhibit low toxicity and high bioavailability reducing the time spent in clinical trials.

Initially, we have selected a set of small molecule compounds (more than 5,600 cmpds) that possess the structural elements closely mimicking the peptide-like moieties, including carboxamide fragment as well as its bioisosteric analogues and various cyclic structures that, in general, provide the conformational stability of peptidomimetics (Figure 4). We have also used a specific structural filter based on different privileged core fragments, all of them contained the key structural moieties that were very similar to that observed within template-peptide molecules.

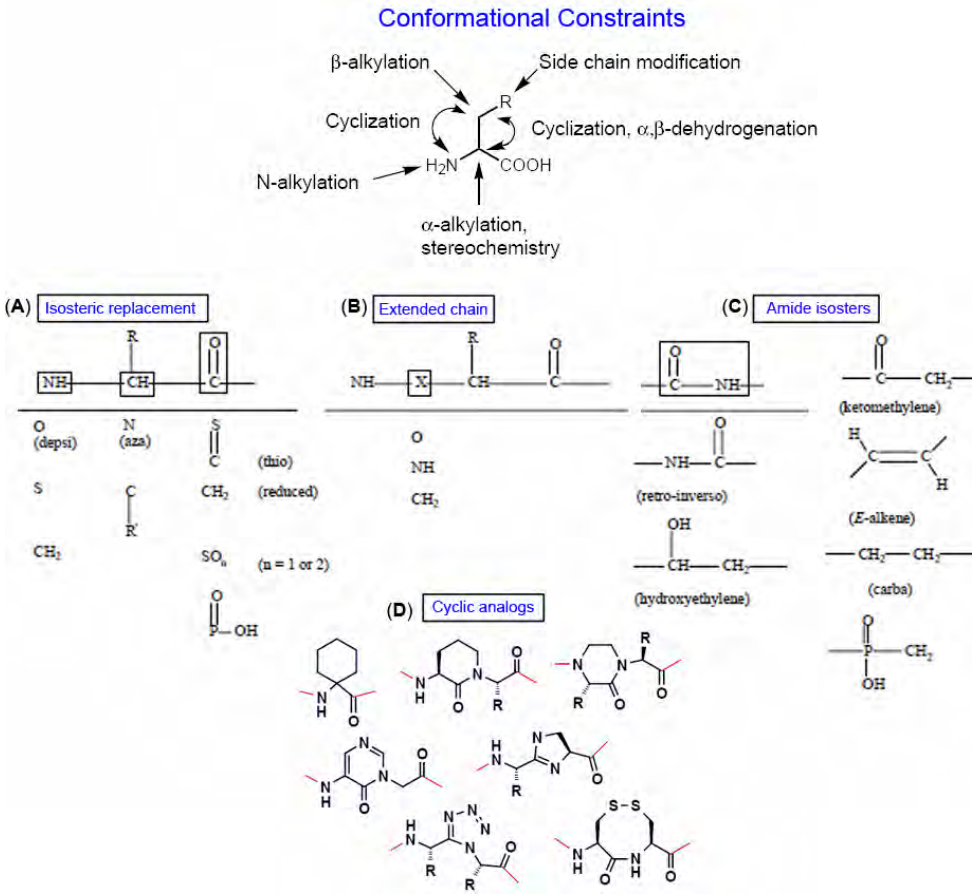


Figure 4. Examples of structural modifications and bioisosteric rules applied for Chemdiv PM-library design, including peptide bond replacement (**A-C**), and various cyclic analogues (**D**)

After a `first-generation` focused library was successfully collected, we have selected a series of biological targets (peptide-based molecules) and the related protein-based ligands that bind directly to the target peptides, leading to a therapeutically relevant physiological response (Figure 5).

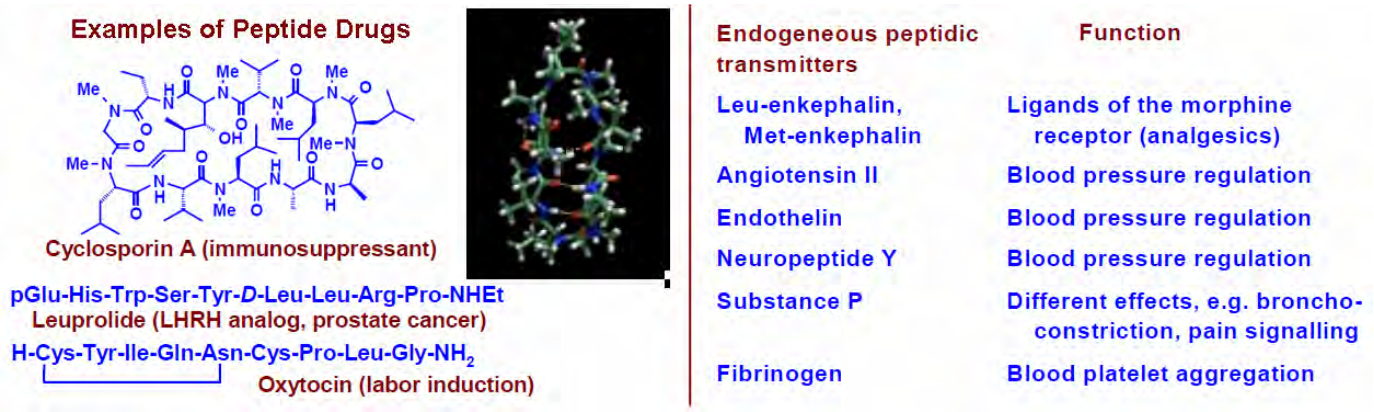


Figure 5. Representative examples of peptide drugs and the key functions of several endogenous peptide-based transmitters

Because of the nonpolar nature and steric bulkiness of its side chain, phenylalanine is one of the preferred residues in peptidomimetics when the biological targets are known to have hydrophobic binding sites. For example, almost every aspartyl protease for which substrate specificities have been studied (e.g., HIV protease, renin, cathepsins D and E, etc.) has a preference for hydrophobic amino acid side chains at the P1 position. It is not surprising that most of the HIV protease inhibitors on the market or in clinical studies have phenylalanine or other bulky hydrophobic groups at the P1 position. Also, to increase the oral bioavailability of compounds derived from peptidomimetic approaches, amino acid residues with bulky and hydrophobic side chains are often left unchanged where other residues are modified. In this regard, phenylalanine or other amino acids with nonpolar aromatic side chains are considered to be key pharmacophores in many biologically important peptide-like molecules. To design a focused library of peptidomimetics containing phenylalanine as the key pharmacophore, the most efficient way would be to use bioisosteric morphing and the related privileged structures (Figure 6).

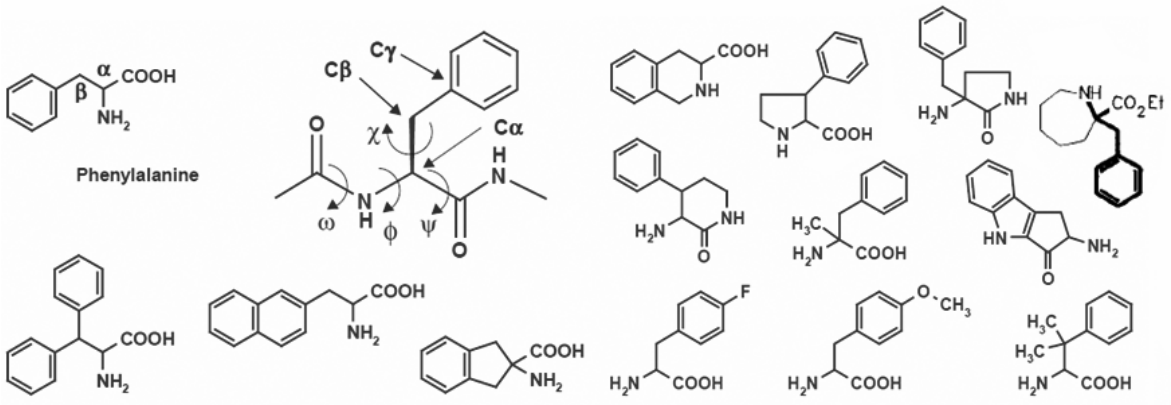


Figure 6. Representative structural analogues of phenylalanine entered in our PM-library

A huge number of scientific publications describing the successful application of molecular docking approach to the design of novel peptidomimetics are currently available. Among them, docking

studies especially focused on a particular protein-protein interaction, in many cases it means a peptide-based active molecule binding to the active site of protein-based biological target/receptor. For example, small molecules that mimic or disrupt NGF – TK type A interactions are by no means absent in the literature. In addition to the Burgess TK type A agonist, D3 (see Figure 3(**C**)), many other small molecule agents were recently developed and comprehensively scored using a molecular docking technique[xxxii]. Thus, Figure 7 shows the proposed molecules superimposed over the helical part of NGF and docked onto TK type A. Molecules **1** and **2** are indole derivatives. Indoles are attractive targets because they appear in many important natural products and are prominent in known drugs.[xxxiii] Cyclopentadienone **3**, furan **4**, and pyrazolidine **5** derivatives are strikingly simple structurally, almost drug-like. Biphenyltype compounds **6** and **7**, utilizing triazines and pyrazolidines, were fathomed because of their structural intrigue and the synthetic routes to obtaining them could possibly be facile. Diketopiperazines and their derivatives are well known in the literature. Molecule **8** was proposed because the chemical routes to procure it are easily accessible. The figures show the proposed molecules superimposed over the helical part of NGF that encompasses H4 and I6 (blue sticks).

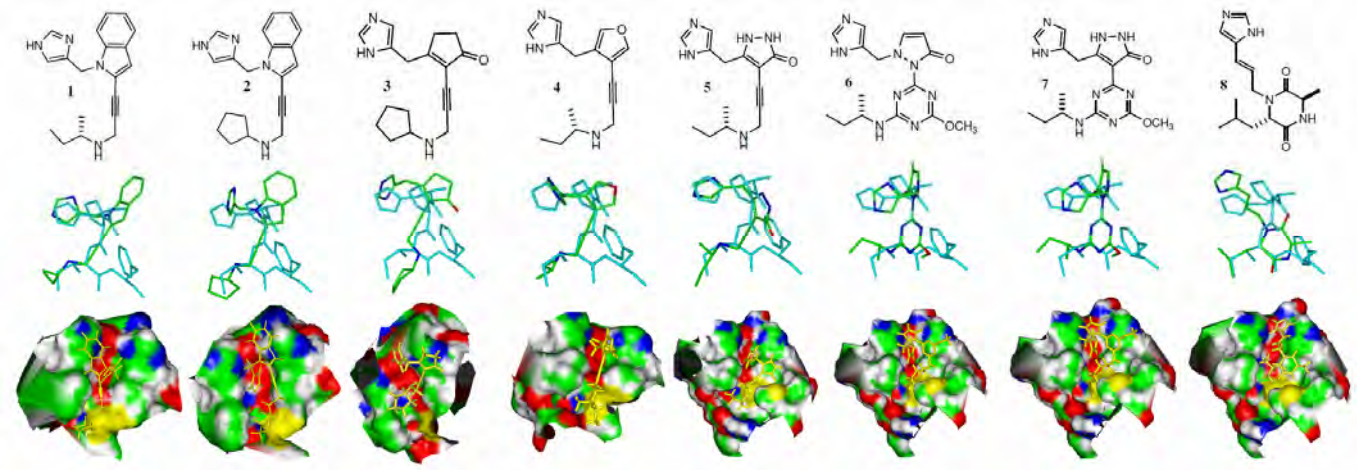


Figure 7. Designed molecules superimposed over the helical part of NGF containing H4 and I6 residues (blue sticks) and docked onto TK type A (Connolly surface).

The same methodology has been effectively used for ChemDiv PM-library design. Thus, we have selected several biological protein-based targets (their structures were obtained from www.rcsb.org) for which corresponding protein-based or peptidomimetic ligands as well as related binding sites were known. For example, we have used a unique data obtained previously for cyclo-RGDf-N-MeV binding to integrin αvβ3 (Figure 8)[xxxiv] for our PD-library design.

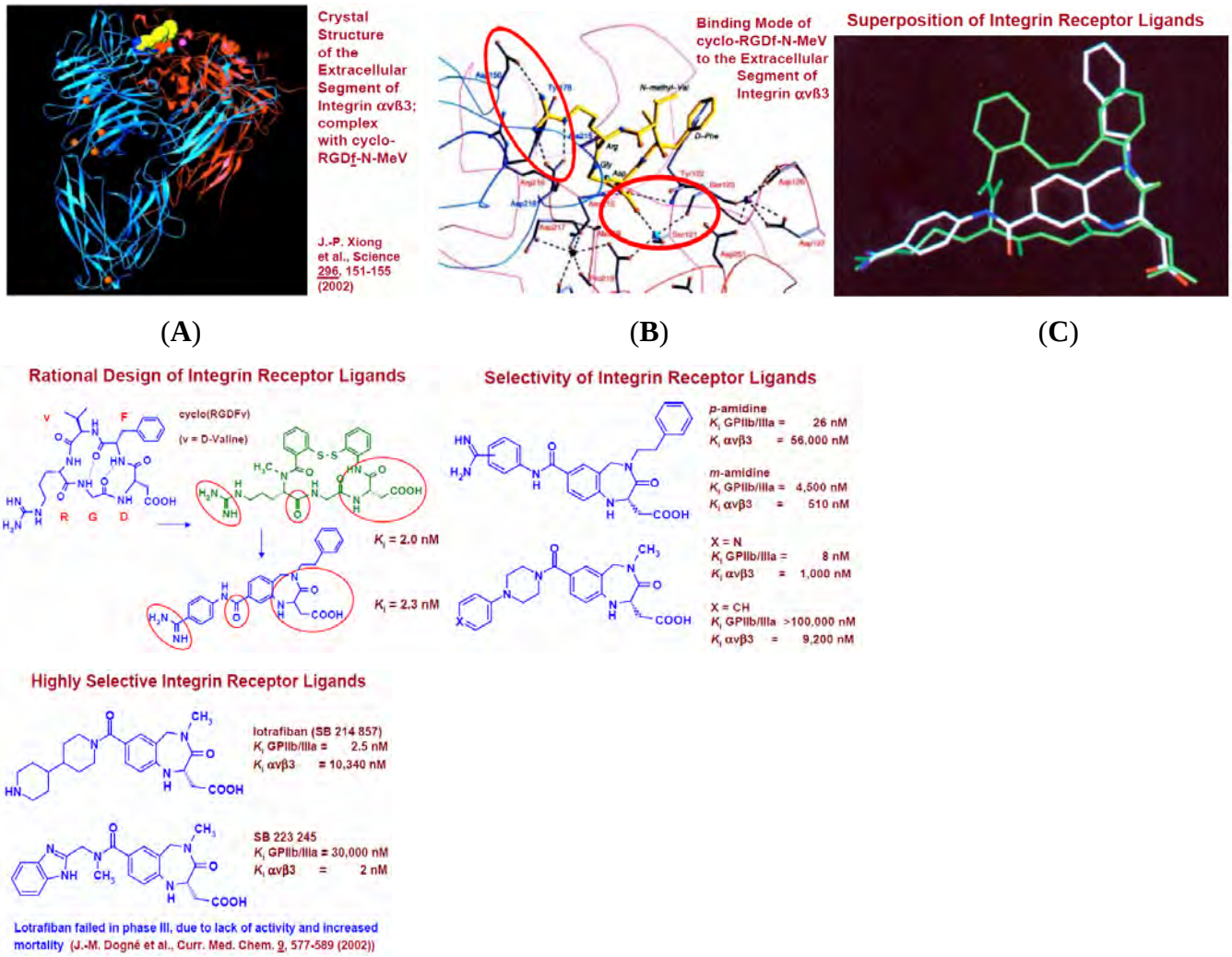
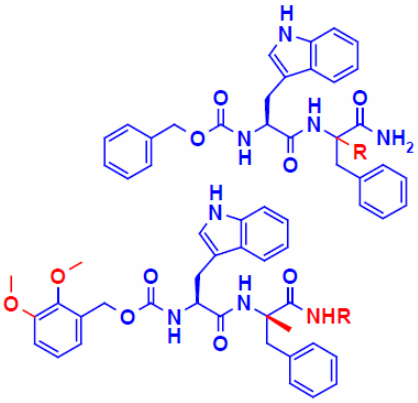


Figure 8. The crystal structure (**A**) and binding mode (**B**) of cyclo-RGDf-N-MeV - integrin αvβ3 interaction; (**C**) superposition of integrin receptor ligands; (**D**) recent advances achieved in the design of integrin-targeted peptidomimetics

Figure 9 summarizes the representative structures of known peptidomimetics that were recently developed and biologically evaluated. We have used these data to design our PM-library based on the fundamental bioisosteric rules.

ChemDiv
The chemistry of cures℠

Rational Design of NK_2 Receptor Antagonists



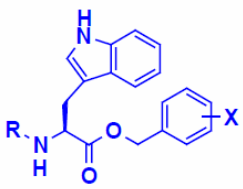
R = H
K_i = 2,700 nM

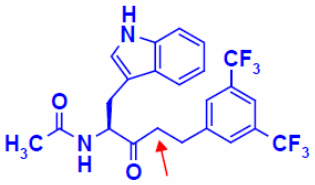
R = CH_3
K_i = 327 nM

R = H
K_i = 17.2 nM

R = CH_2CONH_2
K_i = 1.4 nM

Optimization of an NK1 Receptor Antagonist



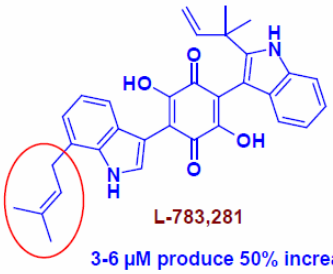


orally available analog
IC_{50} = 3 nM

R = Et, X = H	IC_{50} = 3,800 nM
R = H, X = H	IC_{50} >10,000 nM
R = H, X = 3,5-di-CH_3	IC_{50} = 1,533 nM
R = Ac, X = 3,5-di-CH_3	IC_{50} = 67 nM
R = Ac, X = 3,5-di-CF_3	IC_{50} = 1.6 nM

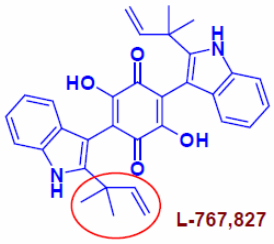
A Small Molecule Insulin Mimetic

screening of > 50,000 mixtures of synthetics and natural products yielded the insulin mimetic L-783,281



L-783,281

3-6 µM produce 50% increase of the maximal effect of insulin (in mice)

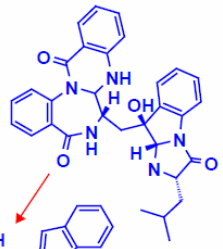


L-767,827

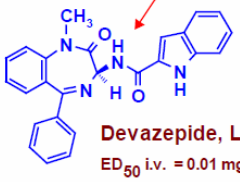
less active by a factor of 100

B. Zhang et al., Science 284, 974-977 (1999)

Asperlicin (microbial product)



ED_{50} i.v. = 14.8 mg/kg
ED_{50} p.o. > 300 mg/kg



Devazepide, L-364 718

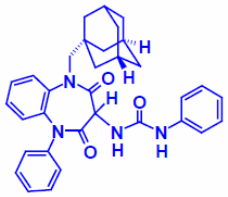
ED_{50} i.v. = 0.01 mg/kg
ED_{50} p.o. = 0.04 mg/kg

K_i CCK-A (rat) = 1,480 nM
K_i CCK-B (human) = 0.15 nM

CCK-A and CCK-B Antagonists

A. Ursini et al., J. Med. Chem. 43, 3596-3613 (2000)

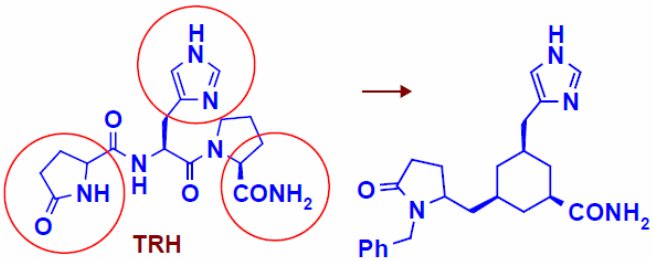
cf.



GV 150 013

K_i CCK-A (rat) = 0.37 nM
K_i CCK-B (human) = 29.5 nM

Design of an Orally Active TRH Mimetic



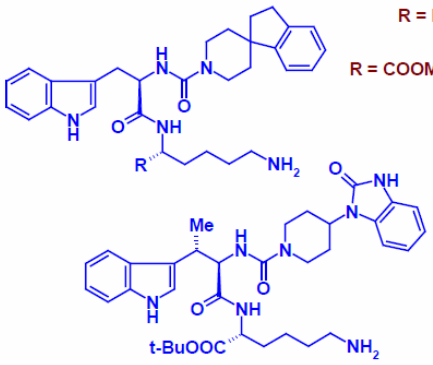
TRH

metabolically not stable, no oral bioavailability

peptidomimetic, orally bioavailable, sufficient half-life time

G. L. Olson et al., J. Med. Chem. 36, 3039-3049 (1993)

Amino Acid Amides as Somatostatin Mimics

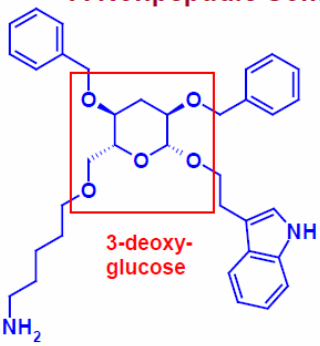


R = H	sst2	K_i = 5.9 nM
R = COOMe	sst1	K_i = 3,794 nM
	sst2	K_i = 1.0 nM
	sst3	K_i = 360 nM
	sst4	K_i = 2,402 nM
	sst5	K_i = 2,105 nM

	sst1	K_i = 2,392 nM
	sst2	K_i = 0.01 nM
	sst3	K_i = 31 nM
	sst4	K_i = 81 nM
	sst5	K_i = 163 nM

L. Yang et al., Proc. Natl. Acad. Sci. USA 95, 10836-10841 (1998)

A Nonpeptidic Somatostatin Mimic



3-deoxy-glucose

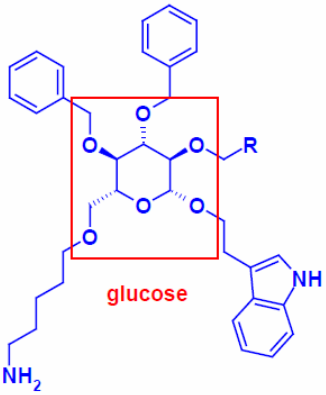
mimic of the receptor-recognizing ß-turn Phe7-Trp8-Lys9-Thr10 of somatostatin.

IC_{50} = 1.3 µM (pituitary somatostatin receptor)

agonist activity in a functional assay at 3 µM

K. C. Nicolaou et al., Peptide Chem. Struct. Biol., Proceedings of the 11th Am. Peptide Symp., 1990, pp. 881-884; C. Wermuth, The Practice of Medicinal Chemistry, 1996, pp. 571 ff.

A Subtype-Specific Somatostatin Mimic



glucose

R = phenyl
non-selective, weak sst-receptor partial agonist

R = imidazol-4-yl
100 nM, selective sst4-receptor agonist

R. Hirschmann et al., J. Med. Chem. 41, 1382-1391 (1998).

ChemDiv, Inc. 6605 Nancy Ridge Drive, San Diego, CA 92121 USA
PHONE: +1 858-794-4860 FAX: +1 858-794-4931
EMAIL: chemdiv@chemdiv.com, www.chemdiv.com

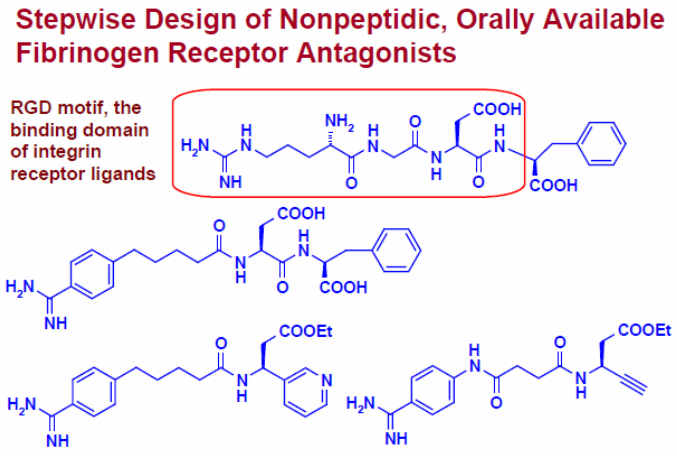


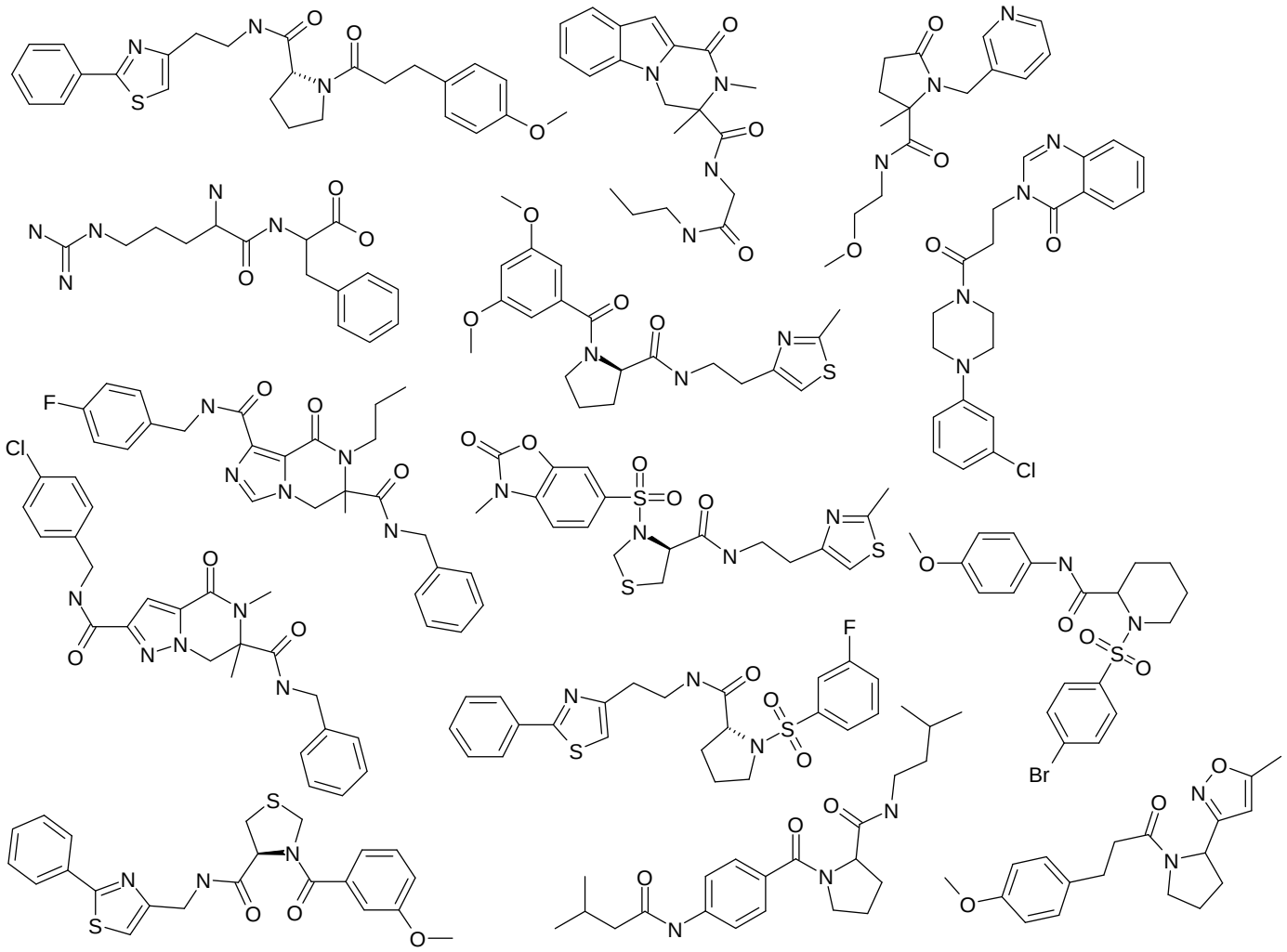
Figure 9. Representative structures of known peptidomimetics and related biological targets which were used for ChemDiv PM-libarary design

Synthesis and biological evaluation

(4) Novel PM-library is synthesized according to the above criteria and rules.

(5) The subsets of PM-library are validated by bioscreening in collaboration with academic institutions.

Our strategy has proven to be efficient for generation of protein class-targeted libraries. The higher hit rate over diverse libraries, along with identification of novel active chemotypes with optimized diversity and ADME properties, has been shown in multiple studies. Using the computational approaches listed above we have compiled PM-library consisted of more than 15,000 small molecule compounds. Representative set of peptidomimetics from ChemDiv collection is shown below. This library can be further extended up to 20K compounds.



Examples of compounds from PM-library

Conclusion

Chemotypes included into this “elementary” set represent various peptidomimetics. The main components are α-helices and β-, γ-turns mimetics based on several combinatorial templates modified with both flexible and rigid substituent. Geometry of the designed fragments was compared computationally (molecular docking study supported by MMFF94 force field) with the dihedral angles reported for several “natural” β- and γ-turn motifs to select the best match. We have also developed numerous proprietary spiro-bicyclic scaffolds to further supplement our effort in design of modular, drug-like peptidomimetics. Additional components of this 5K compound as well as of extended 15K sets include di- and tri-peptide mimetics, namely AlaPro, GlyPro, ValPro, IlePro; RGD, AVPI and PDZ-, VIP-motifs, SH2 domain mimetics based on our proprietary heterocyclic isosteres of phosphotyrosine and β-sheet mimetics. This library is recommended for interrogation of “difficult” targets (ex., receptor de-orphanization, protein-protein interactions, proteins of unknown function) and ii) identification of

novel patentable chemotypes against well-characterized targets. The latter approach was validated by us in discovery of dual specific antagonists against AT1 and ETA receptors.

References

[i] Zubay, G. L. Biochemistry, 4th ed.; Wm. C. Brown Publishers: Dubaque, Iowa, 1998.

[ii] Hu, Z.; Ma, B.; Wolfson, H.; Nussinov, R. Proteins: Structure, Function, and Genetics 2000, 39, 331-342.

[iii] Stites, W. E. Chem. Rev. 1997, 97, 1233-1250.

[iv] Conte, L. L.; Chothia, C.; Janin, J. J. Mol. Biol. 1999, 285, 2177-2198.

[v] Ma, B.; Elkayam, T.; Wolfson, H.; Nussinov, R. PNAS 2003, 100, 5772-5777.

[vi] Arkin, M. R.; Wells, J. A. Nature Reviews: Drug Discovery 2004, 3, 301-317.

[vii] DeLano, W. L. Curr. Opin. Struc. Bio. 2002, 12, 14-20.

[viii] (a) Park, C.; Burgess, K. J. Comb. Chem. 2001, 3, 257-266; (b) Orner, B. P.; Ernst, J. T.; Hamilton, A. D. J. Am. Chem. Soc. 2001, 123, 5382-5383.

[ix] (a) Marchesini, S. Secondary Protein Structure: 3.10 helix. http://www.med.unibs.it/~marchesi/310.html (accessed 9/29/05). (b) Janes, R. W. First Year: Basic Biochemistry. http://www.qmul.ac.uk/~ugbt760/bas02new.doc (accessed 9/29/05)

[x] A Server for b-Turn Types Prediction. http://bioinformatics.uams.edu/raghava/betaturns/method.html (accessed 9/29/05).

[xi] Sipkins, D. A.; Wei, X.; Wu, J. W.; Runnels, J. M.; Cote, D.; Means, T. K.; Luster, D. A.; Scadden, D. T.; Lin, C. P. Nature 2005, 435, 969-974.

[xii] Y. Lavrovsky, Y.A. Ivanenkov, K.V. Balakin, A.V. Ivachtchenko. CXCR4 receptor as a promising target for oncolytic drugs. Mini-Reviews in Medicinal Chemistry, 2008, 8, 1075-1087.

[xiii] (a) K.V. Balakin, Y.A. Ivanenkov, et al. Regulators of Chemokine Receptor Activity as Promising Anticancer Therapeutics. Current Cancer Drug Targets, 2008, 8, 299-340; (b) AMD3100: CXCR4 Chemokine Receptor Antagonist. http://www.sigmaaldrich.com/img/assets/13760/amd3100.pdf (accessed 9/29/05).

[xiv] Li, L.; Thomas, R. M.; Suzuki, H.; De Brabander, J. K.; Wang, X.; Harran, P. G. Science 2004, 305, 1471-1474.

[xv] Montalto, M. C.; Collard, C. D.; Buras, J. A.; Reenstra, W. R.; McClaine, R.; Gies, D. R.; Rother, R. P.; Stahl, G. L. J. Immunol. 2001, 166, 4148-4153.

[xvi] (a) Cochran, A. G. Chemistry & Biology. 2000, 7, R85-R94; (b) Berman, A. E.; Kozlova, N. I.; Morozevich, G. E. Biochemistry (Moscow) 2003, 68, 1284-1299; (c) Newham, P.; Humphries, M. J. Molecular Medicine Today 1996, 96, 304-313.

[xvii] D'Alessio, P.; Moutet, M.; Coudrier, E.; Darquenne, S.; Chaudiere, J. Free Radical Biology & Medicine 1998, 24, 979-987.

[xviii] Gadek, T. R.; Burdick, D. J.; McDowell, R. S.; Stanley, M. S.; Marsters, J. C., Jr.; Paris, K. J.; Oare, D. A.; Reynolds, M. E.; Ladner, C.; Zioncheck, K. A.; Lee, W. P.; Gribling, P.; Dennis, M. S.; Skelton, N. J.; Tumas, D. B.; Clark, K. R.; Keating, S. M.; Beresini, M. H.; Tilley, J. W.; Presta, L. G.; Bodary, S. C. Science 2002, 295, 1086-1089.

[xix] Hippenmeyer, P. J.; Ruminski, R. P.; Rico, J. G.; Sharon, H.; Lu, D.; Griggs, D. W. Anitviral Research 2002, 55, 169-178.

[xx] (a) Lee, H. B.; Zaccaro, M. C.; Pattarawarapan, M.; Roy, S.; Saragovi, H. U.; Burgess, K. J. Org. Chem. 2004, 69, 701-713; (b) Reyes, S. J.; Burgess, K. Tetrahedron: Asymmetry 2005, 16, 1061-1069; (c) Maliartchouk, S.; Feng, Y.; Ivanisevic, L.; Debeir, T.; Cuello, A. C.; Burgess, K.; Saragovi, H. U. Mol. Pharm. 2000, 57, 385-391; (d) Ogbu, C. O.; Qabar, M. N.; Boatman, P. D.; Urban, J.; Meara, J. P.; Ferguson, M. D.; Tulinsky, J.; Lum, C.; Babu, S.; Blaskovich, M. A.; Nakanishi, H.;

Ruan, F.; Cao, B.; Minarik, R.; Little, T.; Nelson, S.; Nguyen, M.; Gall, A.; Kahn, M. Bioorg. Med. Chem. Lett. 1998, 8, 2321; (e) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. J. Am. Chem. Soc. 1998, 120, 4334; (f) Johannesson, P.; Lindeberg, G.; Tong, W.; Gogoll, A.; Karlen, A.; Hallberg, A. J. Med. Chem. 1999, 42, 601; (g) Golebiowski, A.; Klopfenstein, S. R.; Chen, J. J.; Shao, X. Tet. Lett. 2000, 41, 4841-4844; (e) Pfeifer, M. E.; Moehle, K.; Linden, A.; Robinson, J. Helv. Chim. Acta 2000, 83, 444.

[xxi] (a) Pattarawarapan, M.; Burgess, K. J. Med. Chem. 2003, 46, 5277-5291; (b) Maliartchouk, S.; Feng, Y.; Ivanisevic, L.; Debeir, T.; Cuello, A. C.; Burgess, K.; Saragovi, H. U. Mol. Pharm. 2000, 57, 385-391.

[xxii] (a) Orner, B. P.; Ernst, J. T.; Hamilton, A. D. J. Am. Chem. Soc. 2001, 123, 5382-5383; (b) (36) Kutzki, O.; Park, H. S.; Ernst, J. T.; Orner, B. P.; Hamilton, A. D. J. Am. Chem. Soc. 2002, 124, 11838-11839; (c) Ernst, J. T.; Becerril, J.; Park, H. S.; Yin, H.; Hamilton, A. D. Angew. Chem. Int. Ed. 2003, 42, 535-539; (d) Yin, H.; Lee, G.; Sedey, K. A.; Rodriguez, J. M.; Wang, H.-G.; Sebti, S. M.; Hamilton, A. D. J. Am. Chem. Soc. 2005, 127, 5463-5468; (e) Yin, H.; Lee, G.; Kutzki, O.; Park, H. S.; Orner, B. P.; Ernst, J. T.; Wang, H.-G.; Sebti, S. M.; Hamilton, A. D. J. Am. Chem. Soc. 2005, 127, 10191-10196; (f) Jacoby, E. Bioorg. Med. Chem. Lett. 2002, 12, 891-893; (g) Horwell, D. C.; Howson, W.; Nolan, W. P.; Ratcliffe, G. S.; Rees, D. C.; Willems, H. Tetrahedron 1995, 51, 203-216.

[xxiii] Shepherd, N. E.; Abbenante, G.; Fairlie, D. P. Angew. Chem. Int. Ed. 2004, 43, 2687-2690.

[xxiv] (a) Calvo, J. C.; Choconta, K. C.; Diaz, D.; Orozco, O.; Bravo, M. M.; Espejo, F.; Salazar, L. M.; Guzman, F.; Patarroyo, M. E. J. Med. Chem. 2003, 46, 5389-5394; (b) Peczuh, M. W.; Hamilton, A. D. Chem. Rev. 2000, 100, 2479-2494; (c) Asada, S.; Choi, Y.; Uesugi, M. J. Am. Chem. Soc. 2003, 125, 4992-4993.

[xxv] Peczuh, M. W.; Hamilton, A. D. Chem. Rev. 2000, 100, 2479-2494.

[xxvi] Fairlie, D. P.; West, M. L.; Wong, A. K. Curr. Med. Chem. 1998, 5, 29-62.

[xxvii] (a) Marrone, T. J.; Briggs, J. M.; McCammon, J. A. Annu. Rev. Pharmacol. Toxicol. 1997, 37, 71-90; (b) Joseph-McCarthy, D. Pharmacology & Therapeutics 1999, 84, 179-191.

[xxviii] McConkey, B. J.; Sobolev, V.; Edelman M. Curr. Sci. 2002, 83, 845-856.

[xxix] (a) Affinity, December 1998. Molecular Simulations, Inc.: San Diego, 1998. (b) Janin, J. Protein Science 2005, 14, 278-283.

[xxx] (a) Marrone, T. J.; Briggs, J. M.; McCammon, J. A. Annu. Rev. Pharmacol. Toxicol. 1997, 37, 71-90; (b) Joseph-McCarthy, D. Pharmacology & Therapeutics 1999, 84, 179-191; (c) McConkey, B. J.; Sobolev, V.; Edelman M. Curr. Sci. 2002, 83, 845-856.

[xxxi] Ajay, W.; Walters, P.; Murcko, M. J. Med. Chem. 1998, 41, 3314.

[xxxii] (a) Pattarawarapan, M.; Burgess, K. J. Med. Chem. 2003, 46, 5277-5291; (b) Ito, M.; Sakai, N.; Ito, K.; Mizobe, F.; Hanada, K. J. Antibiotics 1999, 52, 224-230; (c) Owolabi, J. B.; Rizkalla, G.; Tehim, A.; Ross, G. M.; Riopelle, R. J. J. Pharm.Expt. Ther. 1999, 289, 1271-1276; (d) Labie, C.; Lafon, C.; Marmouget, C.; Saubusse, P.; Fournier, J. British J. Pharm.1999, 127, 139-144; (d) LeSauteur, L.; Cheung, N. K. V.; Lisbona, R.; Saragovi, H. U. Nature Biotech. 1996, 14, 1120-1122.

[xxxiii] Nicolaou, K. C.; Snyder, S. A. Classics in Total Synthesis II. Wiley-VCH: Weinheim, Germany, 2003, pp. 365-378.

[xxxiv] (a) Christopher P. Carron, Debra M. Meyer, Jodi A. Pegg, V. Wayne Engleman, Maureen A. Nickols, Steven L. Settle, William F. Westlin, Peter G. Ruminski, and G. Allen Nickols. Cancer Research, 1998, 58, 1930-1935; (b) C P Carron, D M Meyer, V W Engleman, J G Rico, P G Ruminski, R L Ornberg, W F Westlin and G A Nickols. Journal of Endocrinology (2000) 165, 587–598.