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Novel Peptidomimetics of the Antifungal Cyclic Peptide Rhodopeptin: Design of Mimetics Utilizing Scaffolding Methodology

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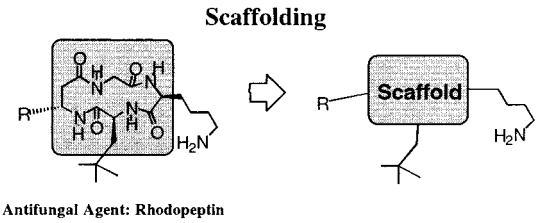
ABSTRACT



Novel nonpeptide peptidomimetics of the antifungal cyclic peptide Rhodopeptin were designed utilizing hydantoin, benzimidazole, D-glucosamine, quinolone, and benzodiazepine units as scaffolds. The scaffolds were chosen on the basis of their potential to improve the physiochemical properties of the peptidomimetics as well as their ability to bear the requisite Rhodopeptin side-chain moieties with the proper three-dimensional orientation.

Although peptides have long served as one of the most useful leads for pharmaceutical compounds, they frequently suffer from undesirable physiochemical properties such as poor bioavailability, low solubility, and low stability against enzymes. Peptidomimetic scaffolding[1] hasemerged as a powerful method for mimicking peptide-based structures in order to minimize such undesirable profiles. The strategy is particularly effective in cases where side chains, rather than the peptide backbone, are largely responsible for the critical binding interactions with target proteins.

Rhodopeptins, novel cyclic tetrapeptides composed of one β-amino acid and three α-amino acids (Figure 1), exhibit antifungal activity against *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*.[2] In recent years, there has been a significant increase in the occurrence of opportunistic fungal infections among immunocompromised patients. Only a few drugs (amphotericin B and several azoles) are available for systemic fungal infections, andthus-the urgent need for the development of new effective antifungal agents has intensified.[3]

We have been examining the synthesis and structure activity relationship (SAR) of novel analogues of Rhodo-

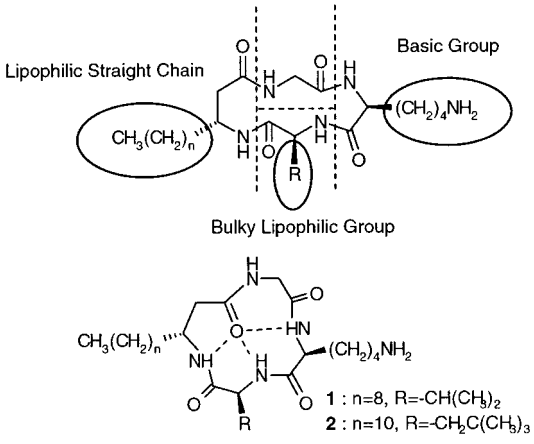


Figure 1. Rhodopeptin analogues.

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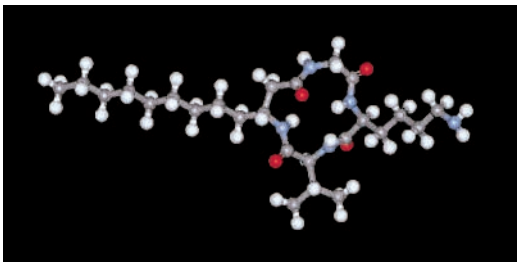

Figure 2. Most Stable Conformation of Rhodopeptin Analogue **1**.

peptin. From our SAR studies, it was found that three side chains, a lipophilic straight chain ranging from 9 to 11 carbons, a bulky lipophilic group, and a basic group on the cyclic peptide backbone, play a critical role in the antifungal activity. In addition, NMR spectroscopic studies[4] and molecular dynamics[5] of Rhodopeptin analogue **1** revealed that three out of four amide protons of the peptide backbone faced the inside of the cyclic structure, with internal hydrogen bonding between the amide proton of valine and the carbonyl group of the β-amino acid present in solution (Figure 1). A similar conformation was indicated as the most stable by QUANTA97 analysis[6] (Figure 2).

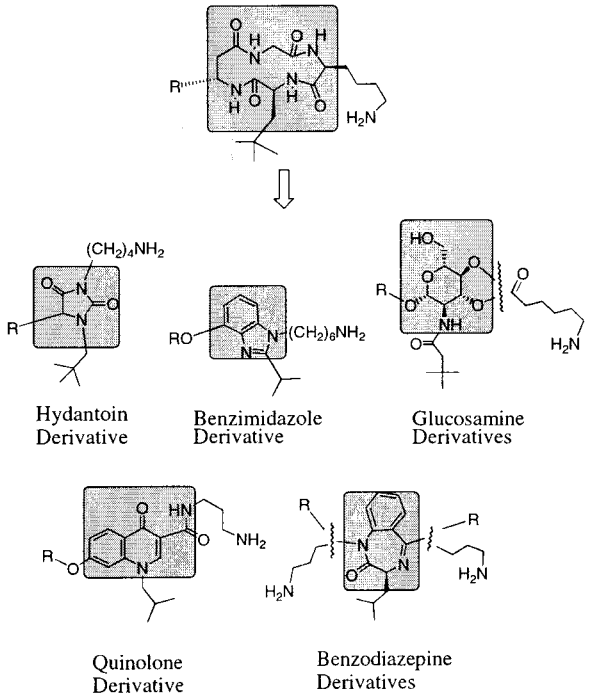

Figure 3. Conversion of cyclic peptide backbone to a variety of scaffolds.

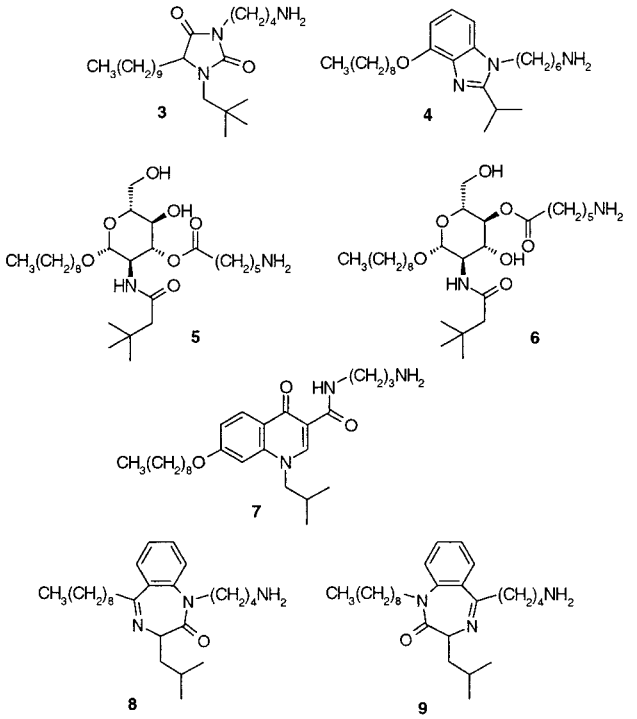

Figure 4. Structures of designed molecules by scaffolding.

On the basis of this structural knowledge, we have applied the scaffolding methodology to the cyclic peptide in an effortto identify biologically active peptidomimetics exhibiting superior physiochemical properties.

Our strategy toward the generation of these peptidomimetics involved the initial screening of several scaffold candidates by molecular modeling. First, scaffolds were selected on the basis of their lack of inherent biological activity (e.g., sugars) or their demonstrated attractive physiochemical properties in other pharmaceutic compounds (e.g., hydantoin, benzimidazole, quinolones, and benzodiazepines). Next, the three critical Rhodopeptin side chains were placed on the scaffolds, presumably in the proper positions. Finally, three-dimensional structures with someconformational analysis were generated to confirm the structural similarity with the parent cyclic peptides. If theorientation of the three sidechains was found to be

(1) (a) Belanger, P. C.; Dufresne, C. *Can. J. Chem.* **1986**, *64*, 1514. (b) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc*. **1992**, *114*, 9217. (c) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. A.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550. (d) Hirschmann, R.; Hynes, J., Jr.; Cichy, M. A.; van Rijn, R. D.; Sprengeler, P. A.; Spoors, P. G.; Shakespeare, W. C.; Pietranico, S.; Barbosa, J.; Liu, J.; Yao, W.; Rohrer, S.; Smith, A. B., III. *J. Med. Chem*. **1998**, *41*, 1382. (e) Olson, G. L.; Cheung, H.-C.; Chiang, E.; Madison, V. S.; Sepinwall, J.; Vincent, G. P.; Winokur, A.; Gary, K. A. *J. Med. Chem.* **1995**, *38*, 2866.

incorrect, the structure was discarded and the side chains were moved to alternate positions on the scaffold. Repeated cycles of this type generated the five types of compounds depicted in Figure 3.

The structures of designed molecules are depicted in Figure 4. Considering the synthetic accessibility, the isopropyl group was chosen in place of the neopentyl group as the bulky lipophilic group for benzimidazole, quinolone, and benzodiazepine.

Overlaid three-dimensional structures of the parent cyclic peptide (**1**, blue) and peptidomimetics **3**−**9** bearing theminimum requirement for overlapping and structural similarity are shown in Figures 5−7.[7]

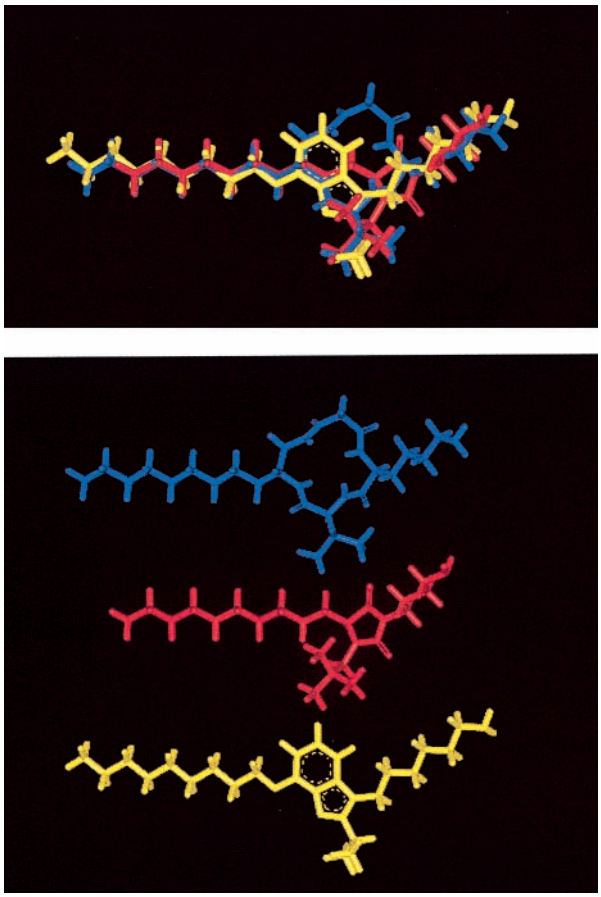

Figure 5. Overlaid 3D-Structures of compound **1**, hydantoin and benzimidazole derivatives. Compound **1**; blue, Compound **3**; red, Compound **4**; yellow.

Encouraged by these molecular modeling results, we initiated the synthesis of those molecules. The synthesis of those mimetics and their antifungal activity and 3D structure−activity relationship are described in the following paper.[8]

In summary, we embarked on a strategy to address the limitation of the antifungal cyclic peptide Rhodopeptin by

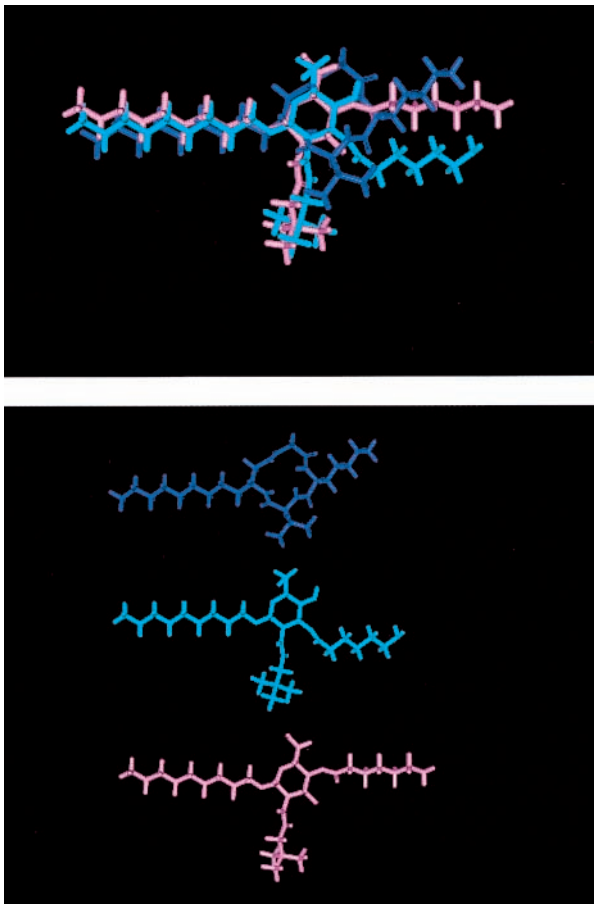

Figure 6. Overlaid 3D-structures of compound **1**, and glucosamine derivatives. Compound **1**; blue, Compound **5**; light blue, Compound **6**; right purple.

employing nonclassical peptidomimetic design, namely scaffolding. Classical peptidomimetic involves searching for structural motifs that mimic some aspect of peptide secondary structure such as β-turns, etc., striving to map onto the peptide bachbone. The nonclassical approach assumes that backbone interactions are either not involved with binding to the receptor or are of low importance and strives to find structures that hold the peptide side chains in a similar conformation. The risk/reward factor of this latter approach

(2) (a) Chiba, H.; Agematu, H.; Kaneto, R.; Terasawa, T.; Sakai, K.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 695. (b) Chiba, H.; Agematu, H.; Dobashi, K.; Yoshioka, T. *J. Antibiotics* **1999**, *52*, 700. (c) Chiba, H.; Agematu, H.; Sakai, K.; Dobashi, K.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 710. (d) Kawato, H. C.; Nakayama, K.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 973. (e) Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977.

(3) (a) De Lucca, A. J.; Walsh, T. J. *Antimicrob. Agents Chemother*. **1999**, *43*, 1. (b) Barrett, J. F.; Klanbert, D. H. *Ann. Rep. Med. Chem*. **1992**, *27*, 149. (c) Barrett, J. F.; Hey, R. J.; Peterson, P. K. *New strategies in Fungal Disease*; Churchill Livingstone: Edinburgh, 1992. (d) Yamaguchi, H.; Kobayashi, G. S.; Takahashi, H. *Recent Progress in Antifungal Chemotherapy*; Marcell Dekker Inc.: New York, 1991. (e) Balkovec, J. M. *Exp. Opin. Invest. Drugs*. **1994**, *3*, 65.

(4) NMR studies in DMSO-d_6. Variable-temperature ^{1}H NMR studies revealed intramolecular hydrogen bonding.

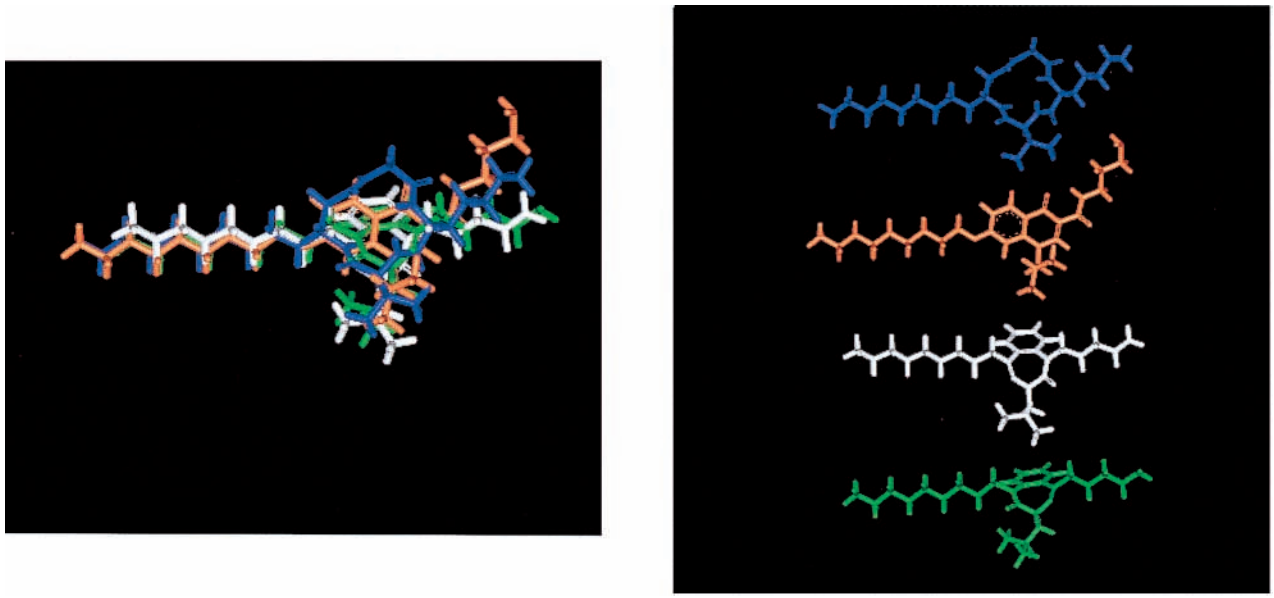

Figure 7. Overlaid 3D-structures of compound **1**, quinolone and benzodiazepine derivatives. Compound **1**; blue, Compound **7**; orange, Compound **8**; white, Compound **9**; green.

is much higher in general, since the backbone interactions indeed may prove to be important, and it is difficult to find scaffolds that have identical conformational characteristics to those of the peptide backbone which both increase risk; however, the physicochemical properties of the new compounds are likely to be very different from the lead peptide and thus the reward can also be great. The successful application and result of this design philosophy are described in the following paper.[8]

(5) Molecular dynamics calculation with the X-PLOR program on the basis of restraints derived from NMR studies.
(6) Conformational search using random sampling.
(7) Molecular modeling (molecular similarity) by QUANTA97.
(8) Nakayama, K.; Inagaki, H.; Ohta, T.; Kawato, H. C. *Org. Lett.* 2001, *3*, 3451.

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