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Biphenyls as Potential Mimetics of Protein α-Helix

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Abstract—Based on theoretical arguments, 2,6,3′,5′-substituted biphenyl analogues are proposed as protein α-helix mimetics superimposing the side chains of the residues *i*, *i*+1, *i*+3 and *i*+4. Knowing that many protein–protein interactions of therapeutical relevance involve α-helix contacts, the communication outlines how this novel category of scaffolds might potentially open access to such targets.

Protein–protein interactions are fundamental to biology and constitute an interesting target class for medicinal chemistry projects investigating cell adhesion, signal transduction, proteolysis or protein-folding diseases.[1,2] Mimicking binding epitopes and protein-minimization, together with depeptidization (removal of amide bonds), are general medicinal chemistry approaches used today to try to interfere within such molecular recognition events.[3] Despite numerous efforts, there are today only few success stories where chemists have redirected the complex nature of protein–protein interactions.[1,3] Main challenges are that protein–protein interactions are built-up by discontinuous protein-sequence and protein-surface elements, and that multi-protein complexes are highly co-operative systems.[3] The majority of the success stories correspond to scenarios of bimolecular complexes built by the interactions of regular protein secondary-structure elements, like surface exposed extended β-strand segments (e.g., S1–S2–S3 type inhibitors of trypsin-like serine proteases)[3,4] and β-turns (e.g., α4β1 integrin antagonists,[5] somatostatin GPCR antagonists[6]). Correspondingly, the design of strand and turn mimetics—non-peptide drug-like molecules retaining the orientation of the amino acid side chains—has progressed to an established medicinal chemistry discipline.[3,7,8] Surprisingly however, there are today only few examples of small molecules mimicking the Pauling protein α-helix, which is the most abundant regular protein secondary-structure element.[9] Currently followed strategies towards α-helix mimetics[3] involve the covalent or noncovalent stabilization of a 12–20-mer peptide in helical conformation, either through initiation or capping templation,[10,11] through side chain contacts[12,13] or through the use of β-peptides.[14,15] The first entirely nonpeptidic scaffolds were only discovered recently by using 3, 2′,2″-trisubstituted terphenyl derivatives, mimicking the substituents *i*, *i*+3, and *i*+7—one ridge—of a 12-mer α-helical peptide.[16]

This situation led us to investigate by molecular modeling, including conformational and superimposition analyses, potential small molecule α-helix mimetics. The α-helix was postulated in 1951 by Pauling using theoretical models as the first secondary-structure element of proteins.[17] The predicted structure was then observed experimentally in the crystal and solution states of proteins. Small molecule helix mimetics should maintain the essential features of the natural model, including: (1) helical shape; (2) the sterical orientation of the amino acid side chains as defined by relative orientation of the Cα–Cβ bond vectors; and (3) the N-cap to C-cap helix dipole moment.[18] Organic molecules containing a chiral axis, like biphenyls, allenes, alkylidene cycloalkanes and spiranes (Scheme 1), are structures with helical shape;[19] however, not all of these, or heterocyclic variants of them, can easily fulfill the other criteria of the α-helix or qualify as drug-like. The structural superimpositions of the correspondingly substituted scaffolds on the 5-residue-long polyalanine α-helix, which is considered herein as reference model, show that 2,3′-diethyl-6,5′-dimethylbiphenyl allows a quasi-perfect superimposition of the biphenyl substituents with the Cα–Cβ bonds of the peptide residues *i*, *i*+1, *i*+3 and *i*+4 (Fig. 1). For all other above considered templates, which differ in size and twist angle, the fit, as measured by the RMS deviation of the Cα–Cβ atoms, is of lower quality. Mimicking

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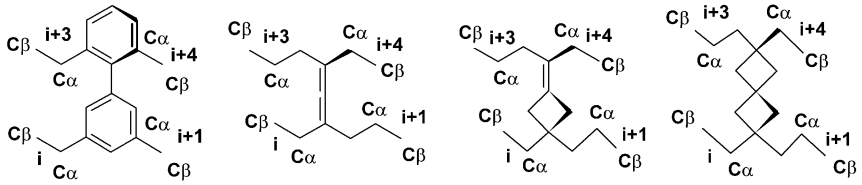

Scheme 1. Organic molecules with helical shape: biphenyls, allenes, alkylidene cycloalkanes and spiranes. Bonds corresponding to Cα–Cβ bonds in the 5-residue-long polyalanine α-helix are indicated.

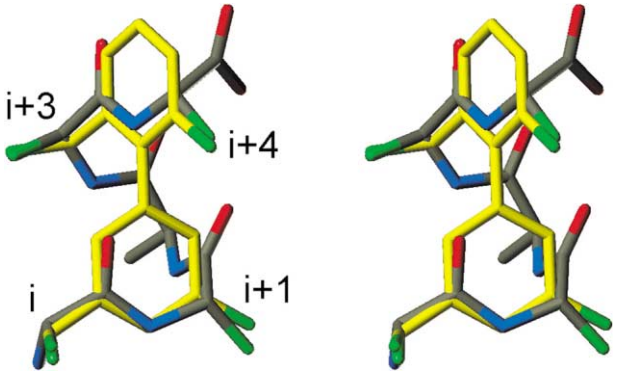

Figure 1. Stereoview of the superimposition of a 5-residue-long polyalanine α-helix with the proposed mimetic 2,3′-diethyl-6,5′-dimethylbiphenyl. The quasi-perfect superimposition of the Cα–Cβ bonds of the peptide residues *i*, $i+1$, $i+3$ and $i+4$ with the biphenyl substituents is observed; Cβ atoms and equivalents are indicated in green. The biphenyl twist angle is −83°. The reference penta-L-Ala protein α-helix was built within Tripos Sybyl™ (6.7) software using the Pauling α-helix definitions for φ,ψ dihedral angles. Iterative conformational adjustments, geometry optimizations, and fittings were performed. The geometries of the considered α-helix mimetics were optimized with MOPAC PM3 using the keywords FULL and PRECISE. Superimpositions were done by fitting on the Cα–Cβ bonds using Sybyl Fit-Atoms. RMS deviations on Cα and Cβ atoms for the four considered scaffolds are: biphenyl 0.47 Å, allene 0.75 Å, alkylidene cycloalkane 0.63 Å and spirane 0.95 Å.

the peptide residue $i+2$ is never accessible. 2,3′-Diethyl-6,5′-dimethylbiphenyl is thus proposed based on theoretical arguments as an α-helix mimetic scaffold; to mimic a given α-helical peptide, the substituents correspond to the side chain groups of the amino acids beyond the Cβ atoms. Introduction of the α-helix dipole moment appears possible through heterocyclic variations, which might also be indicated in the perspective of drug-likeness given the strong lipophilicity of the 2,3′-diethyl-6,5′-dimethylbiphenyl fragment (Clog P[20] equals 6.5). The here introduced 2,3′-diethyl-6,5′-dimethylbiphenyl template mimics thus one turn of a 5-mer α-helical peptide and differs thus from the above mentioned trisubstituted terphenyl α-helix template[16] and also from the previously introduced disubstituted biphenyl hair-pin and β-turn templates.[21,22]

Compared to other scaffolds containing a chiral axis, the biphenyl is a typical drug-like scaffold. In a retrospective statistical analysis of privileged scaffolds of pharmacologically active molecules, the biphenyl was found to be present in 2.1% of reference drug molecules.[23] Corroboratively, biphenyls were identified from NMR-based screening as privileged molecules for protein binding and it was suggested to use the biphenyl motif as template for the discovery and design of therapeutics with high affinity and specificity for a broad range of protein targets.[24] This preference for biphenyls was rationalized by the degree of flexibility about the aromatic linkage or because the biphenyl motif is simply of a size and shape that may conform to a wide variety of protein pockets. In this perspective, it is interesting to note that the Protein Data Bank (PDB)[25] contains 14 ligand–receptor complexes where the ligand are referenced as biphenyls. Most of these complexes correspond to serine-proteinases and metalloproteinases; none of these binding sites does, however, correspond to an α-helix recognition site. It is also noteworthy that none of the around 100 in the Comprehensive Medicinal Chemistry Database (CMC)[26] contained biphenyls is comparable to the here proposed scaffold. The 2,6,3′,5′ substitution pattern is observed in bulbocapnine,[27] which is an apomorphine type structure and which because of its fused polycyclic nature has a rather planar shape. Most of the CMC biphenyl drugs are mono- or disubstituted biphenyls and the *ortho* and *para* positions, as typically observed in angiotensin AT_1 GPCR antagonists like Diovan™,[28] are the most frequent substitution sites.

The protein–protein interactions observed in the examples of: (1) activated nuclear receptors with their co-activators;[29] (2) the tumor suppressor protein p53 with the oncoprotein MDM2;[30] and (3) self-assembly of HIV gp41[31] are just three cases where α-helical recognition is evidenced by crystal structure analysis and which highlight the potential relevance of α-helix mimetic scaffolds for therapeutical applications. In conclusion, based on molecular modeling investigations, we propose here 2,6,3′,5′-substituted biphenyl analogues as α-helix mimetics superimposing the side chains of the residues *i*, $i+1$, $i+3$ and $i+4$. Knowing that many protein–protein interactions of potential therapeutical relevance involve α-helix contacts, this category of scaffolds opens potentially a novel way to interfere within such targets and contributes potentially to enlarge the scope of peptidomimetic chemistry.

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References and Notes

1. Cochran, A. G. *Chem. Biol.* **2000**, *7*, R85.
2. Xenarios, I.; Fernandez, E.; Salwinski, L.; Duan, X. J.; Thompson, M. J.; Marcotte, E. M. *Nucleic Acids Res.* **2001**, *29*, 239.

3. Fairlie, D. P.; West, M.; Wong, A. K. *Curr. Med. Chem.* **1998**, *5*, 29.
4. Leungm, D.; Abbenante, G.; Fairlie, D. *J. Med. Chem.* **2000**, *43*, 305.
5. Souers, A. J.; Virgilio, A. A.; Schurer, S. S.; Ellman, J. A.; Kogan, T. P.; West, H. E.; Ankener, W.; Vanderslice, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2297.
6. Souers, A. J.; Virgilio, A. A.; Rosenquist, S. A.; Fenuik, W.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 1817.
7. Gillespie, P.; Cicariello, J.; Olson, G. L. *Biopolymers* **1997**, *43*, 191.
8. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, D. *Tetrahedron* **1997**, *53*, 12789.
9. Creighton, T. E. In *Proteins. Structures and Molecular Properties*, 2nd ed.; Creighton, T. E., Ed.; W.H. Freeman and Company: New York, 1993; p 255.
10. Kemp, D. S.; Allen, T. J.; Oslick, S. L.; Boyd, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 4240.
11. Maison, W.; Arce, E.; Renold, P.; Kennedy, R. J.; Kemp, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 10245.
12. Jackson, D. Y.; King, D. S.; Chmielewski, J.; Singh, S.; Schultz, P. *J. Am. Chem. Soc.* **1991**, *113*, 9391.
13. Albert, J. S.; Hamilton, A. D. *Biochemistry* **1995**, *34*, 984.
14. Deechongkit, S.; Kennedy, R. J.; Tsang, K. Y.; Renold, P.; Kemp, D. S. *Tetrahedron Lett.* **2000**, *41*, 9679.
15. Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
16. Orner, B. P.; Ernst, J. T.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 5482.
17. Pauling, L.; Corey, R. B.; Branson, H. R. *Proc. Natl. Acad. Sci. U.S.A* **1951**, *37*, 205.
18. Hol, W. G.; van Duijnen, P. T.; Berendsen, H. G. *Nature* **1978**, *273*, 443.
19. Smith, M. B.; March, J. In *March's Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 5th ed.; Smith, M. B.; March, J., Eds.; John Wiley & Sons: New York, 2001; p 127.
20. CLOPG software is available from Daylight Chemical Information Systems, Inc., Santa Fe, NM, USA.
21. Kemp, D. S.; Allen, T. J.; Oslick, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 6641.
22. Nesloney, C. L.; Kelly, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 5836.
23. Bemis, G. W.; Murcko, M. *J. Med. Chem.* **1996**, *39*, 2887.
24. Hajduk, P. H.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443.
25. Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. *Nucleic Acids Res.* **2000**, *28*, 235.
26. Comprehensive Medicinal Chemistry (CMC-3-D) Release 01.1 is available from MDL Information Systems Inc., San Leandro, CA, USA.
27. Ribar, B.; Meszaros, C.; Gasic, O.; Kanyo, I.; Engel, P. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1991**, *C47*, 2612.
28. Buhlmayer, P.; Furet, P.; Criscione, L.; de Gasparo, M.; Whitebread, S.; Schmidlin, T.; Lattmann, R.; Wood, J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 29.
29. Shiau, A. K.; Barstad, D.; Loria, P. M.; Cheng, L.; Kushner, P. J.; Agard, D. A.; Greene, G. L. *Cell* **1998**, *95*, 927.
30. Kussie, P. H.; Gorina, G.; Marechal, V.; Elenbaas, B.; Moreau, J.; Levine, A. J.; Pavletich, N. P. *Science* **1996**, *274*, 948.
31. Chan, D. C.; Chutkowski, C. T.; Kim, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15613.