Chemical Physics Letters 706 (2018) 729–735

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Research paper

Well-Tempered MetaDynamics based method to evaluate universal peptidomimetics

Enrico Gandini [a], Federico Dapiaggi [a], Francesco Oliva [a], Stefano Pieraccini [a,b,*], Maurizio Sironi [a,b,*]

[a] Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy
[b] Istituto di Scienze e Tecnologie Molecolari (INSTM), CNR, and INSTM, UdR Milano, Via Golgi 19, 20133 Milano, Italy

ARTICLE INFO

Article history:
Received 22 May 2018
In final form 12 July 2018
Available online 20 July 2018

Keywords:
Minimalist mimics
Universal mimics
Peptidomimetics
Metadynamics
Well-tempered metadynamics

ABSTRACT

Peptidomimetics are a broad family of compounds designed to mimic the main structural features of peptides, avoiding their metabolic drawbacks. In particular, universal peptidomimetics use only peptide side-chain analogs to mimic different secondary structures. In this work, a novel method is proposed to identify universal peptidomimetics. It is based on a single Meta-Dynamics simulation which allows the reconstruction of the Free Energy Surface of the compound of interest. Subsequently, cluster analysis is carried out to obtain representative structures. Such conformers are then compared to ideal secondary structures to assess their mimicking ability. This protocol was validated against known universal peptidomimetics.

1. Introduction

Peptides are an important family of molecules, having an essential role in numerous biological processes, ranging from cell signaling to immune response. Accordingly, they are thoroughly investigated as potential bioactive agents [1–4]. Natural peptides are generally not considered as optimal drug candidates by the medicinal chemistry community [5], because of their limited stability toward proteolysis and the generally poor transport properties across body barriers. Moreover, their inherent flexibility enables interaction with multiple receptors besides the desired target, increasing the risk of undesired side effects [6]. Thus, it is expedient to design small peptide-like chains encompassing their pharmacophore while improving their pharmacokinetic and pharmacodynamic properties. Such molecules are called "peptidomimetics" [7]. Peptidomimetics have been broadly studied at theoretical and experimental level [8–10].

Many peptidomimetics closely resemble peptides, mimicking both backbone and side chains. Usually, they are actually peptides containing modified, non-natural residues to constrain their structure in the relevant active conformations, e.g. by applying peripheral groups [11,12] or by making a cyclic peptide [13,14].

Another interesting type of peptidomimetics are compounds that achieve mimicry using only side chains analogs. The first example of this type of compounds are the β turn mimics by Hirschmann and Smith [15–17]. This type of peptidomimetics were thoroughly studied by several authors [18–23], and has been defined as minimalist peptidomimetics [18]. Even though minimalist peptidomimetics only mimic peptide side chains, they have the potential to mimic hot-spots residues at protein-protein interfaces [24–26], since side chain substituents account for about 80% of the interactions [27–29].

Minimalist peptidomimetics should be synthetically accessible with different side chains, should display thermodynamically and kinetically accessible conformations for induced fit and finally side chains orientation should depend on a limited number of significant degrees of freedom [18].

Recently, a subset of the minimalist peptidomimetics family, comprising molecules that are flexible enough to mimic different kinds of secondary structures, has been identified [18]. These compounds have been labeled universal peptidomimetics. Burgess and coworkers also developed a protocol to evaluate the performance of a compound as a potential universal peptidomimetic [21]. This protocol is based on Density Functional Theory (DFT) calculations to evaluate the energy barriers between relevant conformations, and on Quenched Molecular Dynamics (QMD) and cluster analysis to explore the conformational ensemble of the molecules.

* Corresponding authors at: Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy.
E-mail addresses: stefano.pieraccini@unimi.it (S. Pieraccini), maurizio.sironi@unimi.it (M. Sironi).

https://doi.org/10.1016/j.cplett.2018.07.029
0009-2614/

In this work we propose an alternative method to identify universal peptidomimetics based on MetaDynamics (MetaD) [30–32] and cluster analysis. MetaD is an enhanced sampling technique based on phase space coarse graining through the identification of collective variables describing the system that allows the reconstruction of its free energy surface [33–37]. In particular, Well-Tempered MetaD (WTMetaD) [38] has been employed to explore the conformational space of the investigated compounds and to estimate the energy barriers between the most populated conformers, whereas subsequent cluster analysis has been used to identify representative conformations from the Free Energy Surfaces (FESs) minima. To evaluate the ability of the studied compounds to mimic typical secondary structure elements, the C_α-C_β vectors (as defined in Fig. 1) of the relevant conformations were overlaid on the corresponding atoms of ideal secondary structures. Our protocol requires just one production phase simulation for every tested compound and provides thermodynamically relevant conformations that effectively mimic secondary structures elements. To validate our protocol, we tested it on two universal peptidomimetic scaffolds proposed and previously studied by Ko et al. We investigated their conformational and energetic properties, considering the effect of the scaffold structure and sidechains variability, defining which secondary structure elements are better reproduced. Our results, coherent with previous observations, assess the viability of the proposed protocol as a validation tool for universal peptidomimetics.

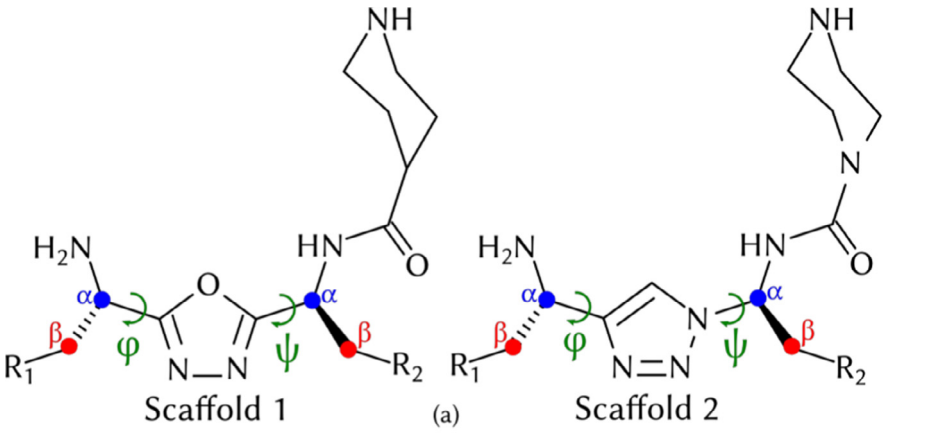
2. Materials and methods

The peptidomimetic scaffolds considered in this work are presented in Fig. 1 Panel (a). Scaffold 1 is based on a 1,3,4-oxadiazole, whereas Scaffold 2 is based on a 1,2,3-triazole. These two scaffolds were proposed by Ko et al. [18] as universal peptidomimetics. In particular Scaffold 1 was also synthesized with a variety of side chains, reported in Fig. 1 Panel (b). We simulated compounds based on Scaffold 1 and 2 with the combinations of side chains R_1 and R_2 reported in Fig. 1 Panel (b).

In order to investigate the steric hindrance and charge effects of substituents R_1 and R_2 we tested, as limiting cases, scaffolds 1 and 2 with side chains of Alanine and Tryptophan or Arginine and Aspartic Acid respectively.

Therefore, we considered twenty-one side chain combinations, and two scaffolds, amounting to forty-two molecules Fig. 1 Panel (b). We will henceforth reference to these compounds with the following nomenclature: NR_1R_2, where N is the number of the Scaffold, and R_1, R_2 are letters, identical to the one-letter codes of the amino acids. (*i.e.* 1YE is the compound based on Scaffold 1, with R_1 and R_2 the side chains of Tyrosine and Glutamic Acid respectively).

The molecules were initially optimized with Gaussian 09 (Revision D.01) [39] using Restricted Hartree-Fock (RHF) with basis set 6-31G(d). Each optimized structure has been solvated in a cubic box of 4 nm with TIP3P water. Every system has been submitted



Amino Acid	Side Chain	Amino Acid	Side Chain
A	–H	I	
S	–OH	T	–OH
W		Y	–OH
D	–COO⁻	E	–COO⁻
R		K	–NH₃⁺

(b)

R_1	R_2	R_1	R_2
A	A	W	W
R	D	D	R
I	S	K	D
K	E	K	I
K	S	K	Y
A	K	S	D
S	E	S	K
S	Y	T	K
A	S	Y	D
Y	E	Y	K
Y	S		

Fig. 1. (a) Peptidomimetic scaffolds that were considered; C_α atoms in blue, C_β atoms in red, and in green, the degrees of freedom used as CVs for the WT-MetaD simulation. (b) On the left, structure and nomenclature of the amino acid side chains that were considered. On the right, side chain combinations that were used to construct the peptidomimetic molecules for both scaffolds 1 and 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)