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Microwave-assisted synthesis of functionalized spirohydantoins as 3-D privileged fragments for scouting the chemical space

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ABSTRACT

Fragment-based drug design has been successfully applied to a large set of proteins, however in order to expand this concept to the most demanding targets, such as protein–protein interactions, it is required to enrich current fragment libraries with new and original 3D privileged fragments. Our goal was to develop a rapid microwave-assisted synthesis of 27 new privileged spirohydantoin fragments. Among them 24 compounds showed a high water solubility. These molecules were plotted according to the normalized principal moments of inertia of their minimized conformers, and most of the compounds were prone to occupy under-populated regions of the triangular plot. Finally we demonstrated that the hydantoin ring can be selectively *N*-monoalkylated providing the access to rapid functionalization for further elaboration.

Introduction

Fragment-based lead discovery relies on the screening of low-molecular-weight molecules, that show lower complexity in contrast to lead-like or drug-like libraries commonly used in High Throughput Screening. Fragment hits are then optimized using rational design to improve not only their affinity toward the targeted protein but also all other required drug properties.[1–4] In this process, the selection of fragments is a key element to ensure novelty, high hit-rates and chemical tractability. Rules such as the accepted Rule of 3 (Ro3) proposed by Congreve et al.[5] are now commonly used to select fragments based on their physicochemical properties (MW < 300, clog$P \leqslant 3$, the number of hydrogen bond donors and acceptors each $\leqslant$3). More recently these rules have been relaxed and incorporation of functional groups to help further optimization has also been suggested.[6] Solubility is also important because fragments, of low expected affinity or potency, are generally tested at high concentrations (0.1–1 mM). Finally, in order to fit diverse biological targets and pockets, a fragment collection of diverse shapes and chemical functions is essential. Many fragment libraries contain mostly planar aromatic scaffolds. This lack of geometrical and chemical diversity jeopardizes the success in discovering hits for more challenging targets,[7] such as protein–protein interactions. Therefore, an increase in the proportion of fragments that contain sp^3 Carbon atoms has been proposed to raise the number of more complex[8] motifs compared to highly aromatic compounds.[9]

In that purpose, spirocyclic scaffolds show today a significant interest due to the conformational restriction that is imposed by the spiranic center.[10] In addition, a careful selection of these spirocyclic scaffolds can provide a rapid access to 3-D diversity.[11–14] Therefore, we report here an illustration of this concept of privileged structures[15] in the context of fragments.

The concept of privileged fragments lies on the use of a minimal central scaffold, here based on a spirohydantoin motif that can provide/accept H-bonds, together with the presence of a spiranic carbon atom able to provide rigidity and sphericity and to spread pharmacophores in the three dimensions (Fig. 1). In this work we explored a straightforward microwave-assisted synthetic pathway for the preparation and functionalization of spirohydantoins. We also illustrated how the selective modifications of these building blocks might result in a wider range of lead-like compounds that cover more efficiently the 3-D chemical space.

Results and discussion

The first synthesis of hydantoins was described by Bucherer and Bergs in 1934 and consisted in reacting carbonyl compounds with sodium cyanide and ammonium carbonate in a refluxing mixture of ethanol and water. This method was then applied for the

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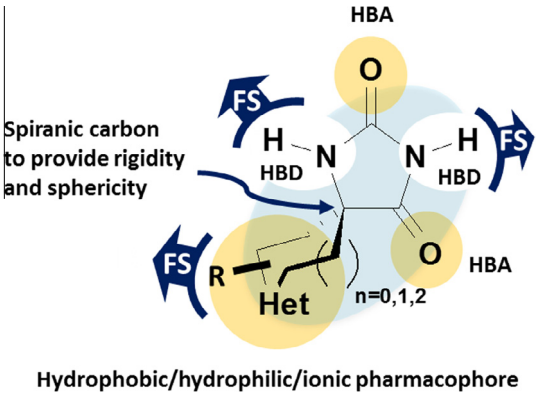
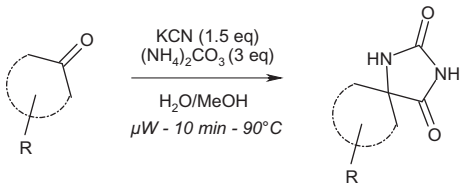
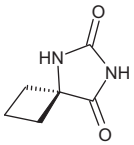
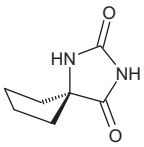
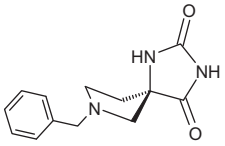
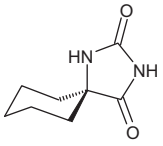
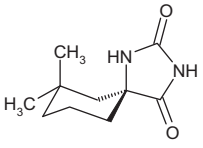
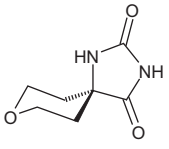


Figure 1. Structure of the spirohydantoin privileged fragment scaffold (HBA: H-bond acceptor, HBD: H-bond donor, FS: functionalization site).

synthesis of spirohydantoins.[16–18] However, long reaction time, high temperature and large quantities of cyanide are required to get acceptable yields. This limits the use of less stable chemical functions and could lead to the formation of toxic hydrogen cyanide. In order to circumvent these drawbacks, we report the optimization of a microwave-assisted synthesis using milder conditions and we extend its scope to quickly and quantitatively obtain a set of original functionalized spirohydantoins. The experimental conditions were optimized using the cyclohexanone as starting material.[19,20] The desired spirohydantoin **1d** was obtained by reacting the cyclohexanone with 3 equiv of ammonium carbonate and only 1.5 equiv of potassium cyanide in a 1:1 mixture of methanol and water. The solution was heated in a sealed tube under microwave irradiation at 90 °C. Under these conditions, the reaction was complete after only 10 min and led to the desired spirohydantoin with a 98% yield. A shorter reaction time did not lead to full conversion and the replacement of methanol by ethanol led to a lower conversion. As a comparison, the completion of the

Table 1
Functionalized spirohydantoins synthesized using microwave-assisted Bucherer–Berg reaction



Entry	Compd	Structure	Yield[a] (%)	Solubility[b] (mM)
1	**1a**		60	0.7
2	**1b**		91	0.8
3	**1c**		50*	>1
4	**1d**		98	0.8
5	**1e**		71*	0.9
6	**1f**		95	>1

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