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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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0040-4039/

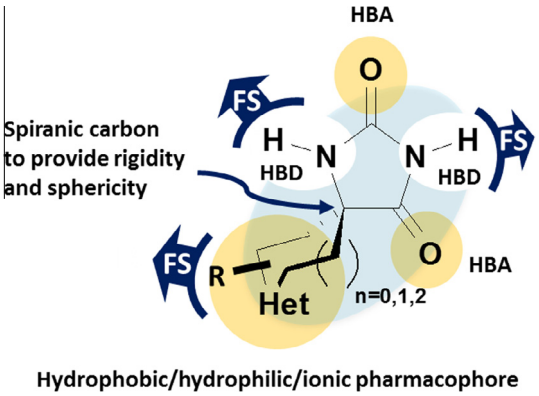
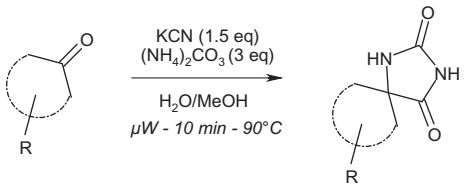
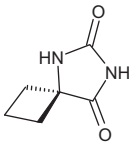
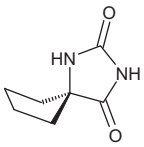
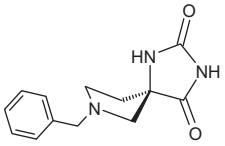
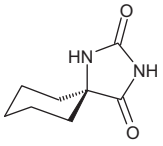
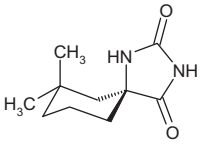
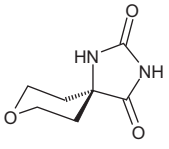


Figure 1. Structure of the spirohydantoin privileged fragment scaffold (HBA: H-bond acceptor, HBD: H-bond donor, FS: functionalization site).

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

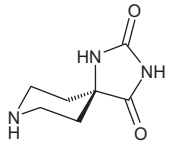
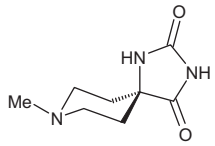
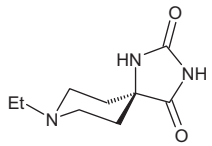
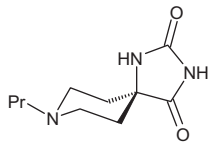
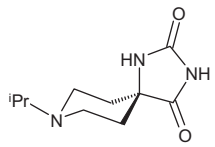
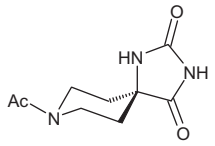
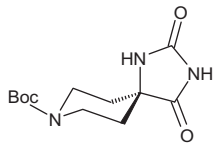
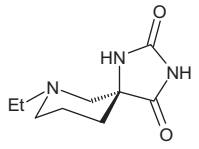
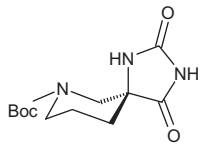
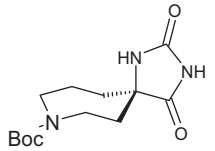
Table 1
Functionalized spirohydantoins synthesized using microwave-assisted Bucherer–Berg reaction



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

(*continued on next page*)

Table 1 (*continued*)

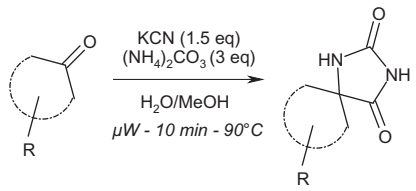
Entry	Compd	Structure	Yield[a] (%)	Solubility[b] (mM)
7	**1g**		76	0.4
8	**1h**		98	>1
9	**1i**		100	>1
10	**1j**		75	>1
11	**1k**		75	>1
12	**1l**		80	>1
13	**1m**		100	>1
14	**1n**		58*	>1
15	**1o**		55*	>1
16	**1p**		97*	>1

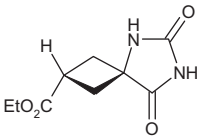
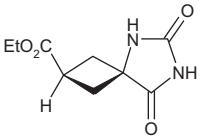
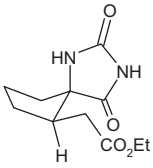
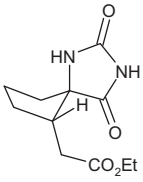
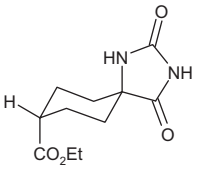
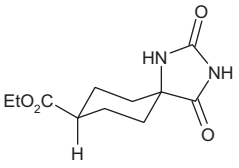
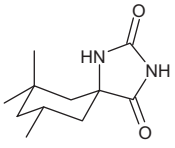
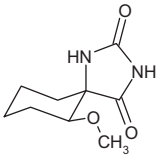
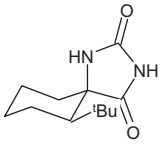
[a] Isolated yield after purification.
[b] Measured solubility in PBS at pH 7.4.
* Compound obtained as a racemic mixture.

same reaction under thermal conditions required 4 h. In addition, the reaction mixture was more complex and its purification led to the desired compound with a significantly lower yield (63%). These optimized microwave-assisted conditions were then applied to a broad range of commercially available cyclic ketones with different ring sizes and substituents.

16 spirohydantoins (Table 1) with four (entry 1, **1a**), five (entries 2 and 3, **1b**, **1c**), six (entries 4–15, **1d**–**1o**) or seven

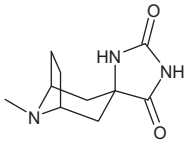
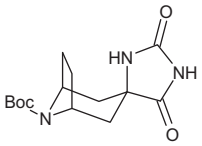
Table 2
Spirohydantoin privileged fragments synthesized starting from substituted and hindered cyclic ketones



Entry	Compd	Structure	Ratio[a] (%)	Yield[b] (%)	Solubility[c] (mM)
1	**2a**		28	22	0.8
	2a′		72	49	>1
2	**2b**		74	50*	0.8
	2b′		26	16*	>1
3	**2c**		25	10	>1
	2c′		75	61	>1
4	**2d**		>98	93*	0.1
5	**2e**		>98	76*	0.8
6	**2f**		>98	3*	0.9

(*continued on next page*)

Table 2 (*continued*)

Entry	Compd	Structure	Ratio[a] (%)	Yield[b] (%)	Solubility[c] (mM)
7	**2g**		100	40	>1
8	**2h**		100	60	0.9

[a] Ratio determined by LC/MS.
[b] Isolated yield after purification.
[c] Measured solubility in PBS at pH 7.4.
[*] Compound obtained as a racemic mixture.

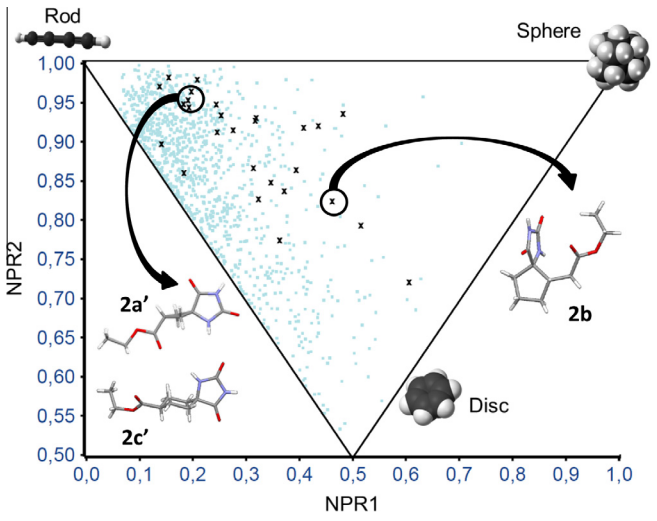


Figure 2. Molecular shape analysis of the spirohydantoin set using normalized principal moment of inertia (PMI).

membered-ring (entry 16, **1p**) were obtained with good to excellent yields. In addition, Boc or benzyl protected *N*-heterocycles were also introduced (entries 3, 13, 15 and 16). The use of free nitrogen-containing cyclic ketone was also tolerated, as example the use of piperidinone led to compound **1g** with a 76% yield (entry 7).

The use of substituted and hindered cyclic ketones was also possible and this led to 11 new spirohydantoins (entries 1–8, Table 2). Compounds **2a** and **2a′** were synthesized in two steps starting from 3-oxocyclobutanecarboxylic acid then esterified using thionyl chloride in ethanol. Interestingly, the presence of ester functions (entries 2 and 3) did not affect the reactivity and mixtures of diastereoisomers **2b**, **2b′**, **2c** and **2c′** were obtained with overall good yields. In the cyclohexane series, when the carbon in α or β position of the ketone function was substituted (entries 4–6) only one diastereoisomer (**2d**, **2e** or **2f**) was formed and isolated. This may be explained by the steric hindrance that constrained the nucleophilic attack of cyanide on the less hindered face of the intermediate cyclic imine. This phenomenon was also observed with the *N*-methyl or N-Boc tropinone that led to **2g** and **2h** with quantitative diastereoisomeric excess. These spirohydantoins were obtained with good yields except for compound **2f** where the *tert*-butyl group may limit the accessibility to the electrophilic center due to steric hindrance.

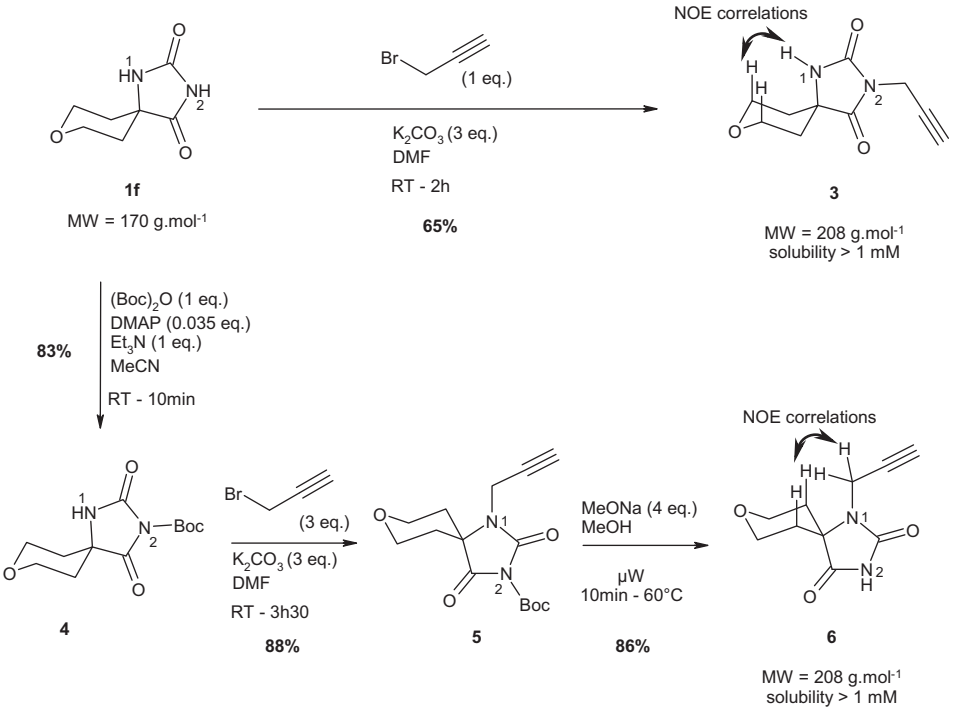
As hydantoins are known to possess low water solubility[21] we evaluated the impact of the introduction of a spiranic center on this physico-chemical property. Water solubility of the 27 spirohydantoins synthesized was measured (Tables 1 and 2). Interestingly, 24 functionalized spirohydantoins, including the most hydrophobic compounds **1d**, **1e**, **2f,** and **2h** display high solubility >0.8 mM. This first observation is in agreement with our hypothesis that incorporation of a spiranic center into the structures of our privileged fragments may be beneficial for the solubility.

To further characterize the 3D shapes of representative fragments, compounds **2a′**, **2b,** and **2c′** were recrystallized in MeOH or EtOH. The 3D-structures of these three fragments were solved by X-ray crystallography (see Supplementary data). Interestingly spirohydantoins **2a′** and **2c′** spread their structure mainly in two dimensions whereas spirohydantoin **2b**, as expected, displays a more spherical structure (Fig. 2).

Next we analyzed the molecular shape of our entire set of fragments using the principal moment of inertia plots.[22] Normalized principal moments of inertia (NPR1 and NPR2) were determined. These two values were then plotted to provide the triangular chart where each corner indicates compounds that tend to have rod-like, disk-like, or sphere-like features (Fig. 2).

The data obtained for the entire set of spirohydantoins were compared to our entire library of fragments. The triangular plot shows that the majority of our commercially available fragments (pale blue squares on Fig. 2) are grouped in the left corner of the plot corresponding to structures with rod-like geometric features. Interestingly, the spirohydantoin fragments (dark crosses on Fig. 2) are more scattered in the 3-D space and show a broader diversity in terms of molecular shape. For example compound **2b** occupies the under-populated central part of the graph.

In addition to their high solubility and their tendency to populate in a broader way the 3-D chemical space, the 27 fragments fulfill the rule of three and most of them have a molecular weight less than 220 g mol^{-1}. More importantly, for all these fragments functionalization remains possible while keeping fragment properties. Therefore, we also worked on straightforward sequences that allow the selective N-monoalkylation of the hydantoin ring to provide access to fragment-like or more complex lead-like structures (Scheme 1). Compound **1f** was monoalkylated on the most acidic nitrogen atom using propargyl bromide (1 equiv) and potassium carbonate (3 equiv) in DMF to afford compound **3**. The synthesis of isomer **6**, was carried out using a three-step protocol: **1f** was first protected on the most acidic nitrogen atom with a Boc group. This reaction was complete after only 10 min at room temperature and led quantitatively to compound **4**. Then



Scheme 1. Selective preparation of *N*-monoalkylated analogs **3** and **6**.

alkylation of the free remaining Nitrogen atom with propargyl bromide (3 equiv) was performed as previously. Finally compound **5** was deprotected using sodium methoxide in MeOH under microwave irradiation to afford compound **6** in a 63% overall yield. NMR experiments (^{1}H, ^{13}C and 1D-NOESY) allowed us to confirm the structures of the two isomers **3** and **6** (Scheme 1). Finally, we confirmed that the substitution of the hydantoin ring did not impact the solubility, as the two compounds showed solubility higher than 1 mM.

The introduction of alkyne functions opens the way to further functionalization via Huisgen-type click-chemistry or Sonogashira coupling. In addition, the benzyl and Boc protecting groups of spirohydantoins **1c**, **1m**, **1o**, **1p,** and **2h** could be removed to provide a third anchoring point, making these privileged spirohydantoin fragments very useful to probe the chemical space in a broader way.

Conclusion

We report here a rapid and convenient microwave-assisted synthesis of functionalized privileged spirohydantoin fragments which are able to probe more efficiently the 3-D chemical space than flat aromatic scaffolds. The optimization of the synthetic route using microwave irradiation allowed the rapid synthesis of analogs and led to 27 compounds with moderate to excellent yields. 24 of our privileged fragments displayed an aqueous solubility higher than 0.8 mM suggesting that this physico-chemical property is generic to the spirohydantoin scaffold and warrants biological screening at high concentrations. Analysis of the shape of our privileged fragments showed that they adopt preferentially rod-like and sphere-like conformations. Moreover we were able to selectively alkylate each of the two Nitrogen atoms of the hydantoin ring providing accessibility to further functionalization. The enrichment of fragment libraries with these 3-D scaffolds may allow finding compounds that bind to a larger set of targets and hits will be of great interest to kick-start fragment-based lead discovery.

Crystallographic data

Crystallographic data for compounds **2a′** (CCDC 1465076), **2b** (CCDC 1465078) and **2c′** (CCDC 1465077) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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Supplementary data

Supplementary data (experimental procedures, analytical and spectral data of all synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.065.

References and notes

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