Towards privileged, natural-like spiro compounds

This article describes the importance of spiro compounds as natural products and as marketed drugs or late-stage clinical candidates, as well as outlining their significance in medicinal chemistry. A number of innovative and original chemotypes, including examples from academia, are described.

The concept of 'privileged structures', originally introduced in the late 1980s by Merck & Co, Inc during the course of work on CCK antagonists,[1] has since emerged as a key principle of modern drug discovery. Privileged structures or scaffolds usually consist of semi-rigid molecular frameworks able to provide, upon the attachment of appropriate functional groups, useful high-affinity ligands for structurally- and functionally-discrete biological receptors.

Initially introduced to describe the benzodiazepine chemotype, the principle has since been extended more recently to other families of structures or sub-structures, including benzopyrans,[2] biphenyls, 1,4-dihydropyridines and spiro phenylpiperidines,[3] amongst others (Fig 1).

The latter family belongs to the wider class of 'spiro compounds', which are defined as ring systems having two or more rings linked by one common atom. This structural superfamily comprises many interesting representatives showing biological activities relevant to the drug discovery and medicinal chemistry fields (Fig 2).

Spiro compounds in natural products

The sterically-constrained spiro structure is present in many natural products, which means this class of compounds has various important biological properties. For example, the neurotoxic properties of the poison-dart frog's Histrionicotoxin have been shown to arise from both the chiral nature of the central spiro carbon atom and from the 6-6 spiro system itself. Other closely-related 6-6 spiro perhydro compounds retain these neurotoxic properties. Horsfiline, another spiro compound, belongs to the oxindole family and has been isolated from *Horsfieldia superba*, a tree found in Malaysia, the extracts of which are commonly used in local medicine (Fig 3).

Spiro compounds in medicinal chemistry

The polysubstituted central atom common to the rings of spiro compounds confers on the overall molecular framework unique 3D properties that were recognised early on by medicinal chemists. In the simplest two-ring system, the well-defined position of the rings almost orthogonal one to the other can be used to mimic structural motifs found in proteins, thus increasing the probability of interactions with biological systems of interest. For example, spiro-oxindole compounds have been successfully used to disrupt protein-protein interactions in a promising strategy for anticancer drug design (Fig 4).[4]

This specific, potent, non-peptide small-molecule inhibitor mimics the alpha-helix recognition motif of the p53-MDM2 complex, therefore efficiently reactivating p53 tumour suppressor activity by inhibiting MDM2. In this elegant example, the 5-5 spiro core system allows for a defined arrangement of functional groups in the surrounding space. Spiro systems have also been used as beta-turn surrogates.[4]

In addition to a very specific spatial arrangement of functional groups, the spiro moiety also brings a high degree of rigidity to the overall structure and reduces the number of rotatable bonds. The overall entropic price paid to reach the correct spatial arrangement in a ligand-target complex can potentially be decreased, and the probability of an acceptable oral bioavailability is increased. All these biorelevant properties of spiro compounds make them very attractive targets for non-biased, innovative hit-finding screening collections.

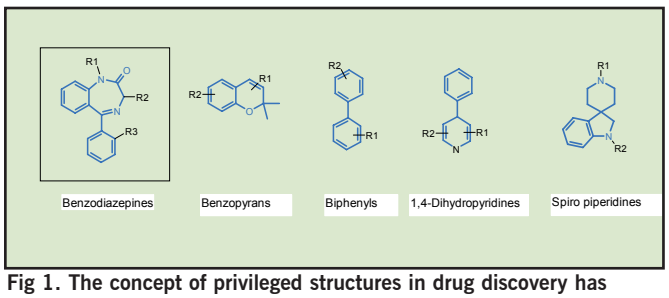

Fig 1. The concept of privileged structures in drug discovery has recently been extended to benzopyrans, biphenyls, 1,4-dihydropyridines and spiro phenylpiperidines, amongst others.

Hit-finding spiro compound collections

When addressing the challenge of developing hit-finding collections of natural product-like spiro compounds, various parameters must be considered such as:

Chemical accessibility: Spiro structures as synthetic targets can be challenging to reach, notably due to the specific nature of the central spiro atom. Indeed, tetra-substituted carbon atoms are usually considered difficult to obtain for reasons of both steric constraint and chirality control (ie when all four

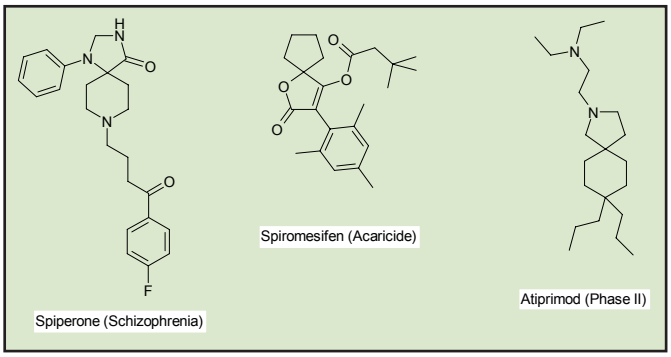

Fig 2. Examples of biologically-active spiro compounds on the market.

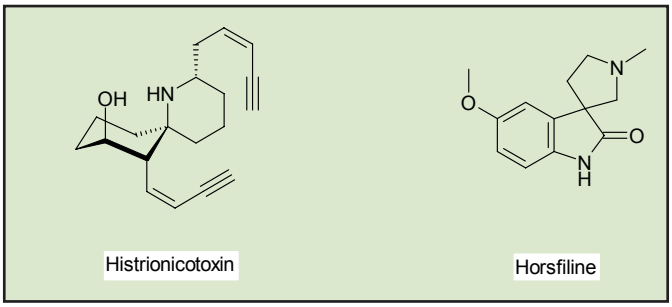

Fig 3. The sterically-constrained spiro structure is present in many natural products, including the poison Histrionicotoxin obtained from a species of frog, and Horsfiline, a medicine extracted from a Malaysian tree.

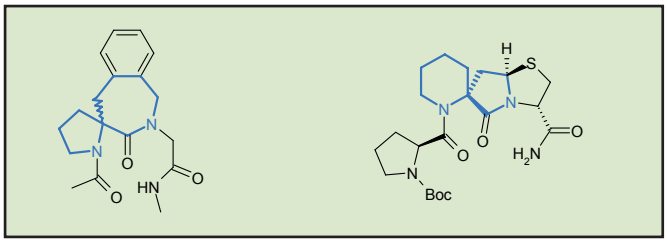

Fig 5. In addition to a very specific spatial arrangement of functional groups, the spiro moiety also brings a degree of rigidity to the overall structure and reduces the number of rotatable bonds.

substituents of the central atom are different). On the other hand, hit-finding collections should ideally be prepared in a few steps of robust chemistry, allowing for reliable access to final products (and potential downstream analogues) from commercially-available building blocks, and allowing a timely resupply of additional amounts when needed.

Novelty: Novelty guarantees the application patentability of the chemotype once hits are identified, and is usually considered as one of the key criteria when prioritising hits for potential follow-up.

Diversity points: Three or four points of variability would allow for efficient space exploration once hits are confirmed, aiming at rapid determination of reliable SAR data during the hit exploration and/or lead optimisation stages.

Physchem properties: Since the emergence of the rule-of-five parameters, different physicochemical properties are usually calculated based on the targeted structures in order to evaluate as accurately as possible the potential of the compounds in the library.

Purity: Systematic purification and further LC/MS quality control of each compound are nowadays a prerequisite of any high-quality hit-finding screening collection.

With its most recent additions to its natural product-like Keymical Collections™ series, Edelris has taken into account all of the above parameters to provide innovative, non-exclusive, reliable hit-finding collections. These two new series, named Key017 and Key019, have been carefully designed and

MW	CLogP	HBA	HBD	N	O	X	Rot B	C*
390	1.3	4.4	1.2	2.0	5.4	0.1	7.0	1.9

Table 1. Average hysicochemical properties of Keymical Collections™ Key017 and Key019 of spiro compounds from Edelris.

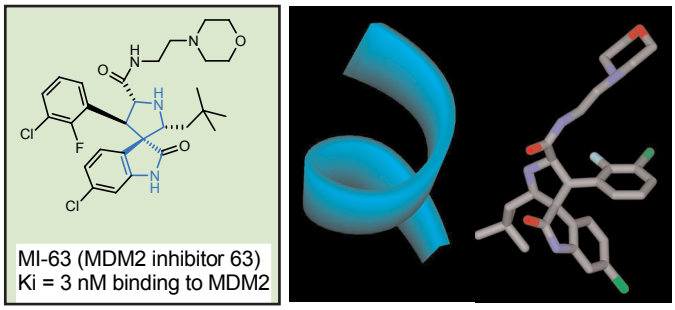

Fig 4. Spiro-oxindole compounds have been successfully used to disrupt protein-protein interactions in a promising strategy for anticancer drug design.

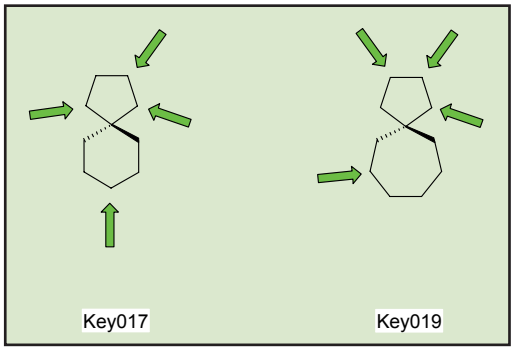

Fig 6. Schematic frameworks of the Keymical Collections™ Key017 and Key019 from Edelris.

produced within the company's laboratories to complement existing pharma companies' and biotech companies' in-house collections, bringing enhanced 3D features through spiro bicyclic structures. The schematic frameworks of these series, along with the sites of variations highlighted as green arrows, are illustrated in Fig 6.

The number of chiral centres ranges from one to three in the different series, and these are controlled in order to carefully avoid diastereomeric mixtures when more than one stereocentre is present. All compounds are available as racemates and can be obtained if required in enantiomerically-pure form. The average calculated physicochemical properties are shown in Table 1. Compounds from these two Keymical Collections™ series are available for evaluation from Edelris.[5] sp²

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