1

Spiro Compounds: A Brief History

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Policyclic molecules containing at least two rings joined together by a single atom, mostly a carbon atom, previously named spiranes, are called spiro compounds or spirocycles, and the single central atom is referred to as the spiro atom [1]. We should mention that apart from carbon, other elements such as nitrogen, phosphorus, and arsenic may represent the spiro atom.

The term was coined by the German chemist Nobel laureate Adolf von Baeyer who created the first spirane in 1900 [2].

This peculiar structural feature is present in natural products and has long been the subject of methodological studies and synthetic efforts [3].

Several synthetic procedures for spiro compounds have been developed and will be extensively discussed in the next chapters. However, the asymmetric synthesis of spirocycles that allow the creation of stereogenic quaternary centers represent a demanding task for organic chemists. Even the concepts of spiro aromaticity and spiro antiaromaticity can be applied when spiroconjugation is possible [4].

The search for the key term "spiro" in SciFinder^{n} database, at the end of October 2019, resulted in more than 40 700 references with an exponential growth starting from the middle of the last century and an increasing attention to this subject is expected in the future (Figure 1.1).

These massive research efforts cover a wide range of fields from organic and medicinal chemistry to material sciences and engineering, to name a few.

The enormous interest in spiro compounds rely on their distinctive properties often associated with the three-dimensional stereochemical features, reflecting on their pharmacological properties that include, among others, bactericidal, fungicidal, anticancer, cytotoxic, antidepressant, antihypertensive, insecticidal, herbicidal, and plant growth regulatory effects [5]. These properties are due to the tetrahedral nature of the spiro carbon and consequent asymmetric features associated with it.

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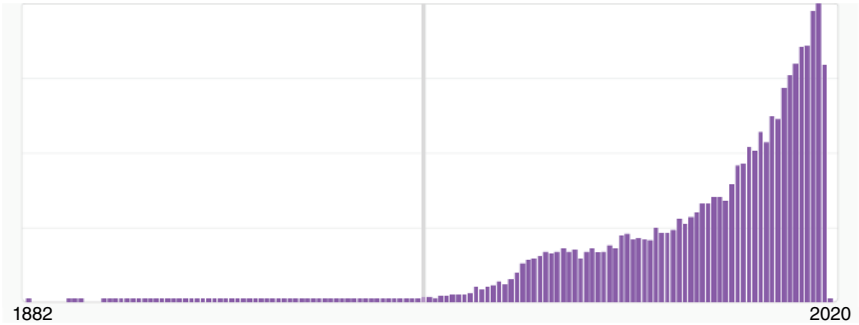

Figure 1.1 Growing interest in spiro compounds in chemical literature.

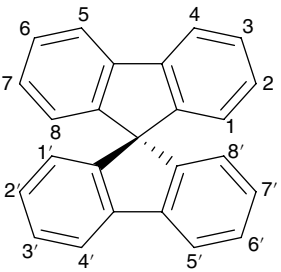

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Figure 1.2 Dye sensitizer 9,9-spirobifluorene. *Source:* Lupo et al. [7].

In addition, many other practical utilizations include optoelectronic devices, ophthalmic lenses, and solar cells [6]. Compounds like 9,9-spirobifluorene **1** (Figure 1.2) have application in dye-sensitized solar cells (DSCs) and represent the most efficient alternative to the current solar cell technologies [7].

Spirocyclic compounds find technological application as efficient charge-transfer molecules due to their intramolecular donor–acceptor structural feature amplified by spiroconjugation. The desired optical properties can be achieved by careful design of the spiro donor–acceptor characteristic as illustrated in Figure 1.3 [8]. When structural characteristics make it possible, spiro compounds can equilibrate with their non-spiro analogues exhibiting photochemical phenomena like photochemical memory.

We report here some examples of carbocyclic and heterocyclic naturally occurring compounds containing the spiro moiety (Figure 1.4). One of the simplest compounds is the pheromone of the olive fly *Dacus oleae* **5**. Phelligridin G **6** from the fungus *Phellinus igniarius* has been long used in Traditional Chinese Medicine for the treatment of gonorrhea [9]. The antimycotic drug griseofulvin **7**, isolated from a penicillium mold in 1939, found application in the treatment of fungal skin

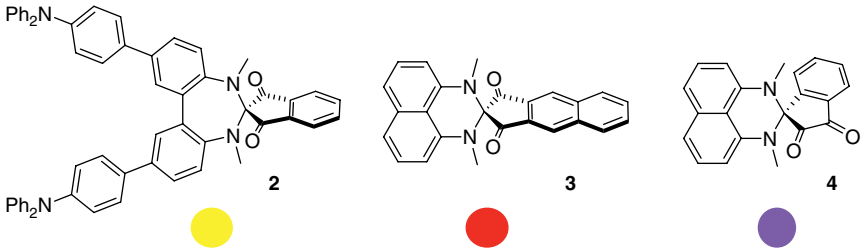


Figure 1.3 Donor–acceptor spiro compounds and colors displayed by them. *Source:* Wössner et al. [8].

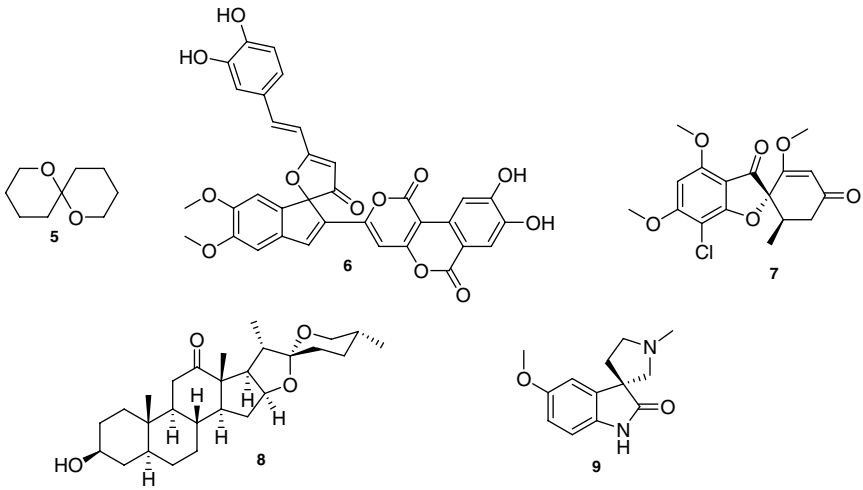


Figure 1.4 Examples of naturally occurring compounds containing the spiro moiety.

infections since 1957. Hecogenin **8**, the aglycone part of a steroid saponin found in the plant Agave sisalana, is responsible for many therapeutic effects and is also used as a starting material in the synthesis of corticosteroids [10]. Horsfiline **9** is an oxindole alkaloid having analgesic effect, isolated from the plant *Horsfieldia superba* [11].

A classic example of the importance of the presence of a spiro functionality is the retention of the biological activity of perhydrohistrionicotoxin **10**, the completely reduced analogue of the potent nicotinic receptor antagonist alkaloid (−)-histrionicotoxin **11**, isolated from "dart-poison" frogs, that clearly suggests the fundamental role of the spiropiperidine moiety in determining a strong receptor binding. The massive synthetic efforts on this topic are collected in a book chapter [12] (Figure 1.5).

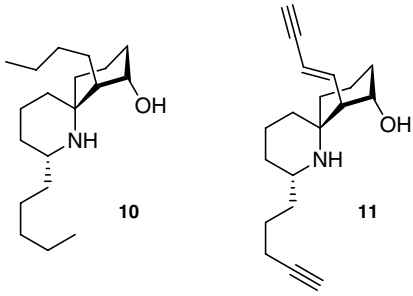


Figure 1.5 Spiro functionality in nicotinic receptor antagonists. *Source:* Hart [12].

As stated before, spirocycles are present in successfully developed medications and represent attractive synthetic targets included in chemical libraries for diversity-oriented synthesis within drug discovery projects. In this context, the spiro moiety has been and can be employed both as core structure and as an activity modulator, appended to decorate the peripheral part of the molecule [13].

The major advantage of spirocycles in biological applications as core structure or pharmacophores originates from their 3-D nature and the associated conformational features that allow for a better ability to interact with the target protein enzyme. The tetrahedral feature of the spiro atom renders the two ring planes nearly perpendicular to each other with a limited number of potential conformations. When added in the periphery of the molecule, the spirocycle acts as a modulator of physicochemical properties such as log P and water solubility, as well as affecting the metabolic stability of the molecule. Not least, from an intellectual property perspective, the introduction of spirocycles offers the possibility of obtaining a free patent space in a me-too research approach.

Prominent examples of marketed spirocompounds, illustrating these concepts, include fluspirilene **12**, spiraprilat **13,** and cevimeline **14**, while experimental compounds in different stages of clinical development are ETX0914 **15,** a DNA gyrase inhibitor; tofoglifozin CSG452 **16,** an inhibitor of hSGLT2 for the treatment of Type 2 diabetes; AZD1979 **17,** an antagonist of melanin-concentrating hormone receptor; and rolapitant **18,** a neurokinine 1 receptor antagonist [13, 14] (Figure 1.6).

We wish once more to draw the attention of the readers on the potential usefulness and uniqueness of the spiro motif in the interaction with a specific biological target spanning from drugs to agrochemicals.

The enzyme Acetyl-coenzyme A carboxylases (ACCs) have crucial roles in fatty acid metabolism in most living organisms, among which include humans, insects, and plants. The experimental ACC inhibitor compounds for the treatment of human metabolic disease contain a spirocyclic moiety as in Takeda compound **19** [15] and in Pfizer PF-05221304 **20**. The last one is currently in phase II clinical trials for the treatment of Non-Alcoholic Steatohepatitis (NASH) [16] (Figure 1.7).

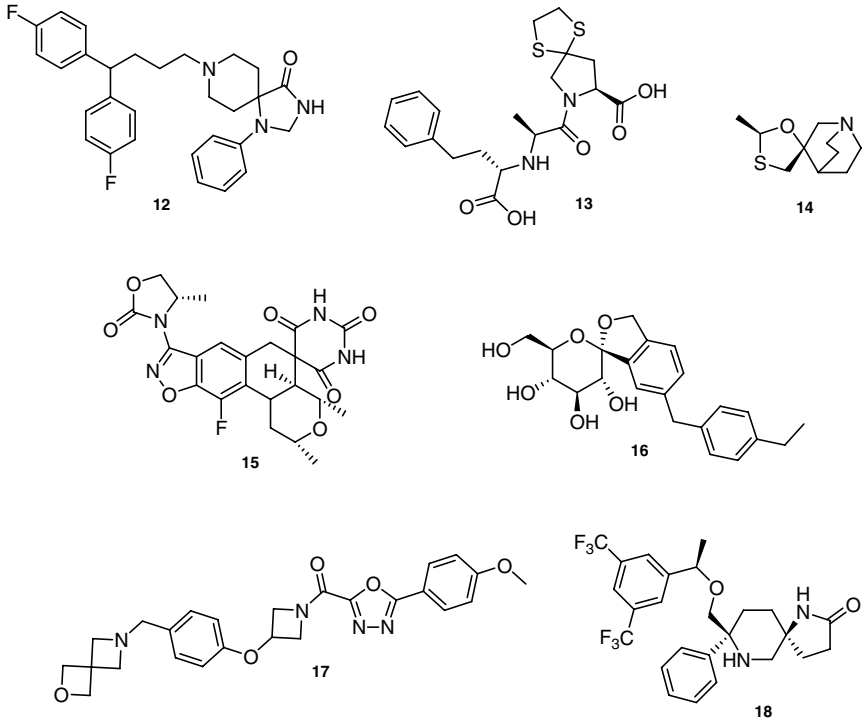


Figure 1.6 Examples of marketed spiro compound drugs. *Sources:* Based on Zheng and Tice [13]; Zheng et al. [14].

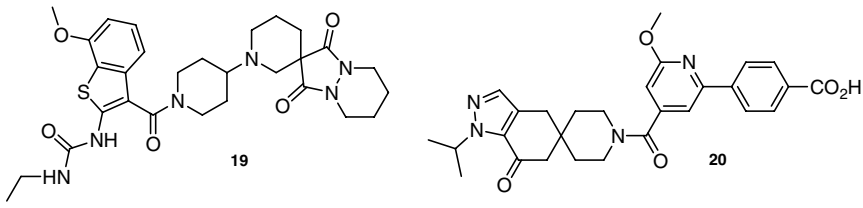


Figure 1.7 ACC inhibitors of pharmaceutical interest. *Sources:* Based on Bourbeau and Bartberger [16a]; Esler and Bence [16b].

The commercial insecticide/acaricide products spirotetramat **21**, spiromesifen **22**, and spirodiclofen **23** from Bayer CS and spiropidion **24** from Syngenta, acting as insect ACC inhibitors, all have spirocyclic structures [17] (Figure 1.8).

New spirocyclic herbicide compounds with the representative formula **25** have been recently patented [18]. It is noteworthy that compounds **21** and **24**, sharing similar molecular features with **25**, do not show any phytotoxic effect (Figure 1.9).

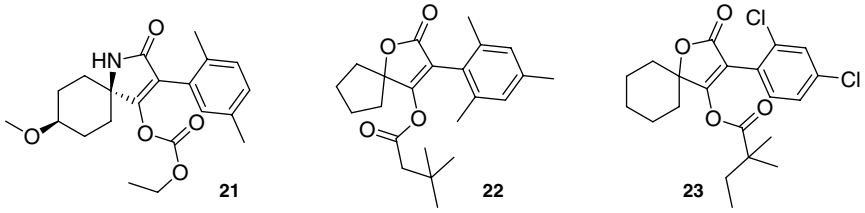


Figure 1.8 Commercial spirocyclic insecticide/acaricide products. *Source:* Jeschke et al. [17].

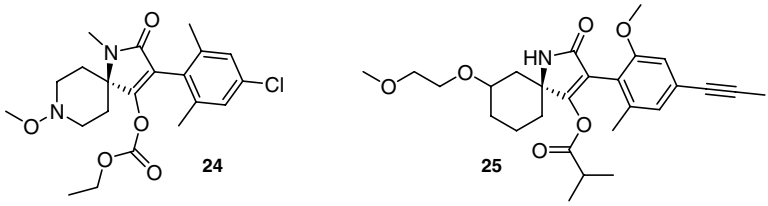
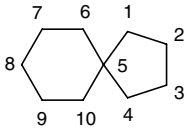


Figure 1.9 Recently patented spiro compound of agrochemical interest.



26

Figure 1.10 Example of numbering of spirocyclic compounds.

As presented in this chapter, spirocyclic scaffolds find application in a large number of sectors for their own peculiar architecture characteristics, displaying valuable application properties, or simply because of the introduction of structural novelty that guarantee patentability and intellectual property rights.

1.1 Notes on IUPAC Rules for Spiro Compounds

Naming spirocycles could be quite complex. The accepted rules are collected in the IUPAC blue book [1, 19].

Simplifying with two examples, the structure **26** is numbered starting from the smallest cycle (Figure 1.10). The name comes from the prefix spiro followed by square brackets containing the number of atoms of the two cycles starting from the smallest and excluding the spirocenter. In this case, the functional group is an alkane so that the name became spiro[4,5]decane.

Figure 1.11 Example of naming chiral spiro compounds.

When the compound is chiral because it contains a chiral center, the CIP rules are followed. In the case in which the substituents on the spirocenter are the same, but the structures display an axial chirality as in Figure 1.11, we assign arbitrarily the priority to one of the cycles and then, within each cycle the order follows the CIP rules: a>a′>b>b′.

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