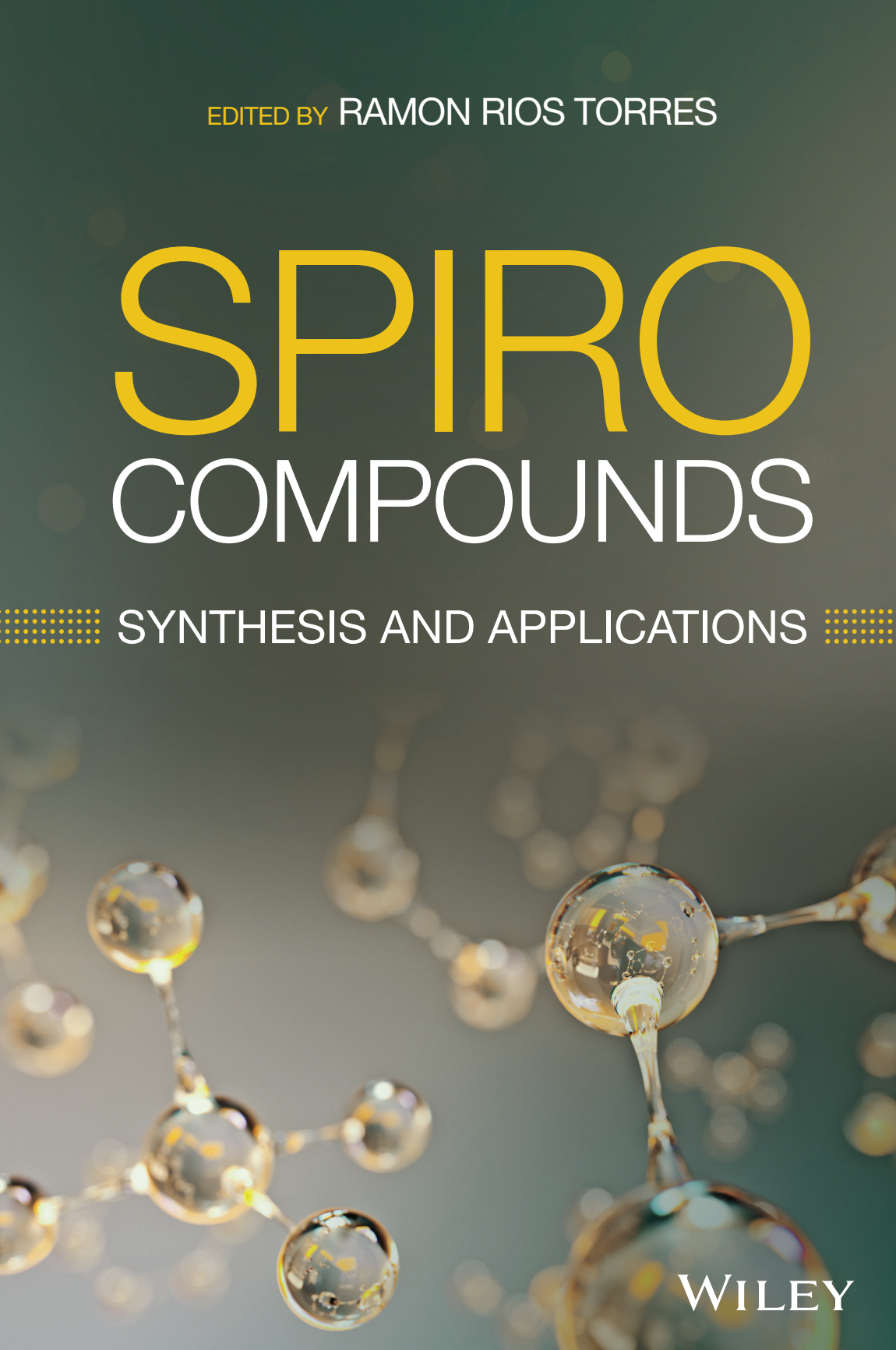
EDITED BY RAMON RIOS TORRES

SPIRO COMPOUNDS

SYNTHESIS AND APPLICATIONS



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Spiro Compounds

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Synthesis and Applications

Edited by

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Preface

When I was a kid, I dreamt to be an engineer and build planes, cars, etc. However, in high school, I felt in love with Organic Chemistry. I changed my dreams of building things for how to assemble C, H, N, and other atoms to form molecules. I was always astonished of the inherent difficulty of **organic** structures, not only for their diversity and ordered assembly but also for their 3D shape. With time, I enjoyed learning Organic Chemistry: starting from my bachelor in organic chemistry, followed by a PhD in organometallic chemistry, and several postdocs in organometallic chemistry and organocatalysis. Later on, as academic, I have always tried to develop new reactions that can allow to obtain difficult structures in an enantiopure form. However, one of the greatest challenges that I faced has been the synthesis of spiro compounds. My own way to be interested in the synthesis of spiro compounds first started in the synthesis of quaternary carbons in an enantiopure fashion. Precisely, while studying how to synthesize quaternary carbons, I developed an interest in spiro compounds, how difficult it will be to join two cycles by a single atom, and do it enantioselectively. In my research group, we have been lucky enough to develop several reactions that led to spiro compounds in an enantiopure form (or almost enantiopure), but I still remember the first time that we got a spiro compound in an enantiopure form as an incredible feeling of achievement. Now, several years later, I decided to honor this type of compounds by editing a book, summarizing the achievements that Organic Chemists have been done in the last decades.

I also want to dedicate this book to Professor Dieter Enders who left us during the writing of this book. He was always a source of inspiration, since his early success with RAMP and SAMP chemistry, until the development of highly complex domino reactions, showing a commitment and brilliance to organic chemistry that inspired me in my career. I still remember his kind hospitality in The Domino cat symposium in Aachen. Professor Enders, you left a huge footprint in organic and synthetic chemistry.

Finally, I want to thanks all the authors for their work and commitment in those difficult COVID times.

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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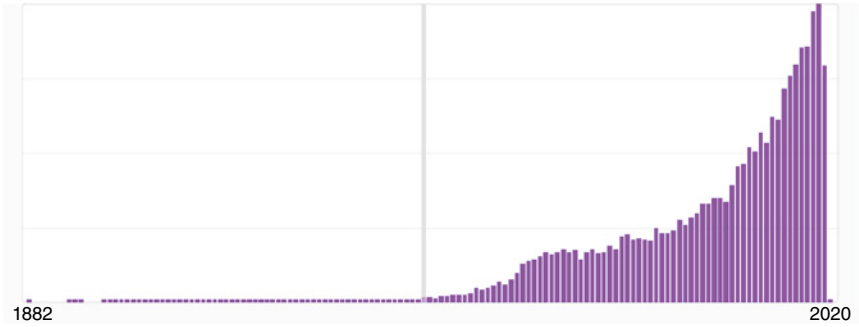
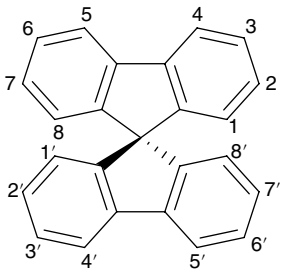


Figure 1.1 Growing interest in spiro compounds in chemical literature.



1

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

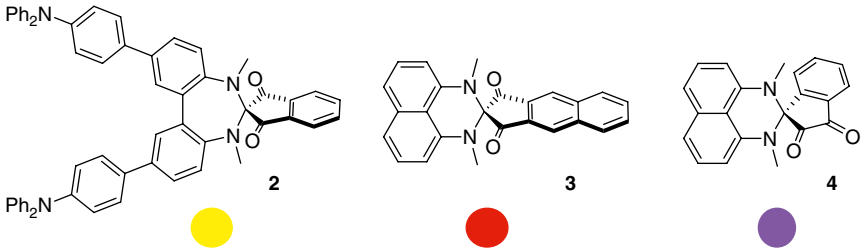


Figure 1.3 Donor–acceptor spiro compounds and colors displayed by them. *Source:* Wössner et al. [8].

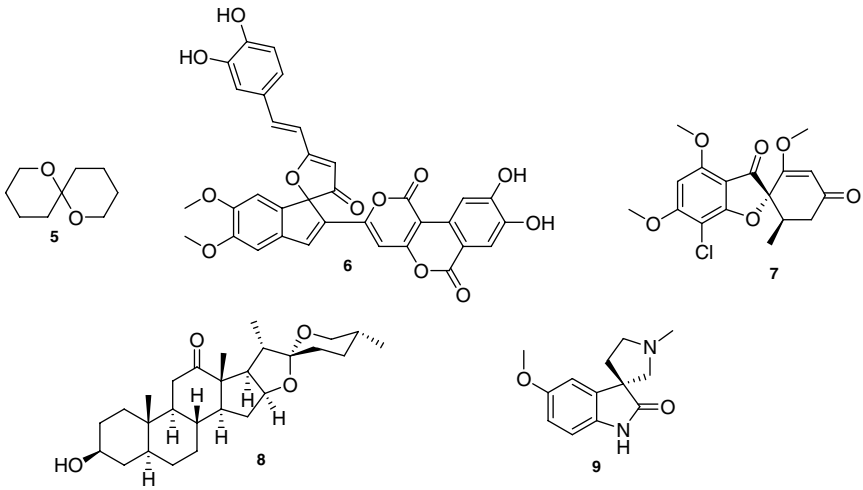


Figure 1.4 Examples of naturally occurring compounds containing the spiro moiety.

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).

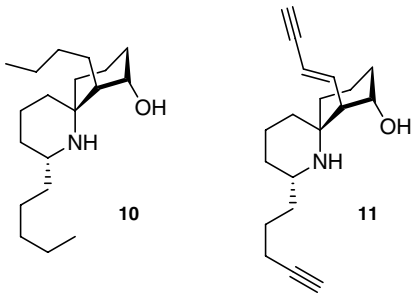


Figure 1.5 Spiro functionality in nicotinic receptor antagonists. *Source:* Hart [12].

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).

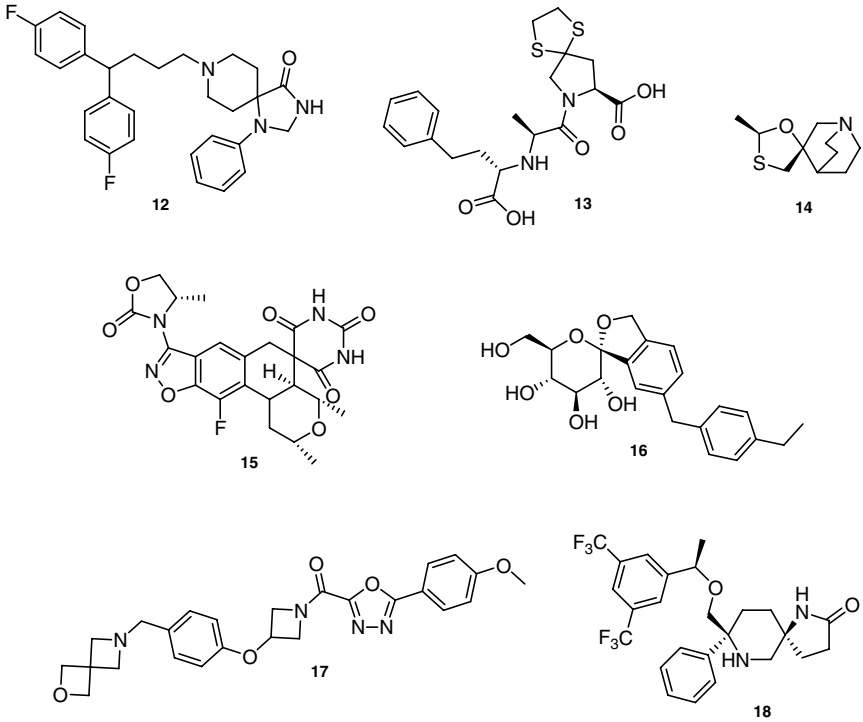


Figure 1.6 Examples of marketed spiro compound drugs. *Sources:* Based on Zheng and Tice [13]; Zheng et al. [14].

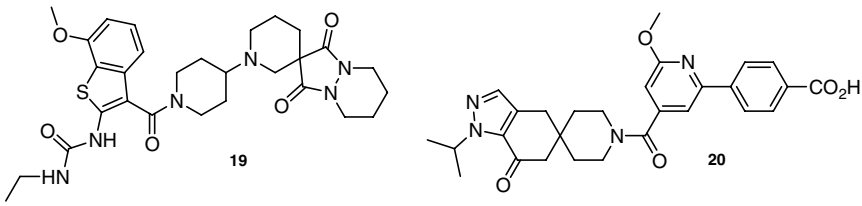


Figure 1.7 ACC inhibitors of pharmaceutical interest. *Sources:* Based on Bourbeau and Bartberger [16a]; Esler and Bence [16b].

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).

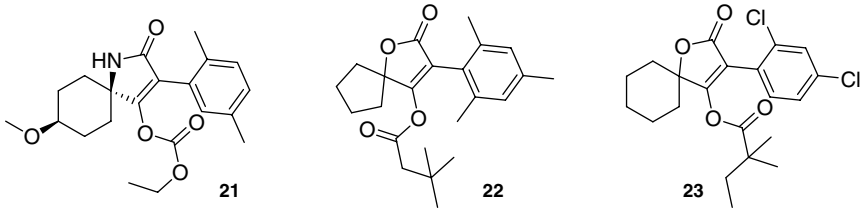


Figure 1.8 Commercial spirocyclic insecticide/acaricide products. *Source:* Jeschke et al. [17].

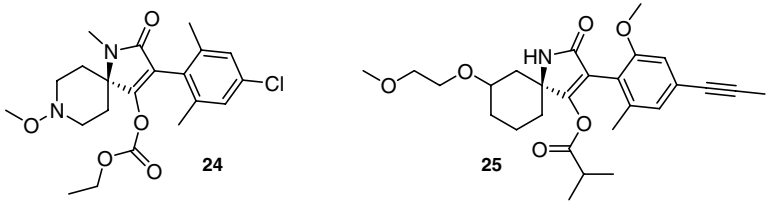
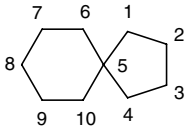


Figure 1.9 Recently patented spiro compound of agrochemical interest.



26

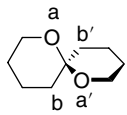
Figure 1.10 Example of numbering of spirocyclic compounds.

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.

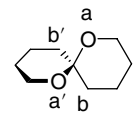
1.1 Notes on IUPAC Rules for Spiro Compounds

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.



(*R*)-1,7-dioxaspiro[5.5]undecane



(*S*)-1,7-dioxaspiro[5.5]undecane

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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2

Selected Applications of Spirocycles in Medicinal Chemistry

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2.1 Introduction

Spiro compounds contain two rings, connected by a single sp^3 hybridized quaternary center, the "spiroatom" [1]. The latter is often a carbon, although a number of quaternary *N*-spiro ammoniums have also been reported. Trospium chloride (**1**) (Table 2.1) is a good example, and its spiro ammonium motif can be readily prepared by double *N*-alkylation of endo-nortropine [3]. Spirocyclic systems are found in a wide range of natural products [4], including spiro-ketals [5, 6], lactones [7], lactams [8, 9], and oxindoles [10–12]. An early and illustrative example of spirocyclic natural product which has attracted the attention of medicinal chemists is the antibiotic platensimycin (**2**). It is a metabolite from *Streptomyces platensis* which represents a structurally unusual example of bioactive molecule containing a carbaspirocyclic scaffold. Its antibiotic activity was reported by Merck in 2006, as part of a screening campaign to identify inhibitors of beta-ketoacyl synthases I/II (FabF/B) enzymes [13]. Inhibition of FAB enzymes by platensimycin leads to impaired biosynthesis of key fatty acids required bacterial cell membrane integrity [14]. Platensimycin displays activity against a range of Gram-positive bacteria, including strains showing resistance to other potent antibiotics such as methicillin, vancomycin, linezolid, or macrolide. Structural studies on an *Escherichia coli* FabF(C163Q) in complex with platensimycin highlighted important interactions underlying complex formation. The shape complementarity and conformational restriction provided by the spiro motif are important contributors to the potency of platensimycin, allowing polar interactions and hydrophobic contacts at the binding site entrance (Figure 2.1) [13]. The first total synthesis of racemic platensimycin was reported by Nicolaou on the same year (Scheme 2.1) [15], involving a key ruthenium-catalyzed enyne cycloisomerization [16]. Since then, stereoselective syntheses of platensimycin spirocyclic core based on rhodium-catalyzed asymmetric cycloisomerization and hypervalent iodine-mediated de-aromatizing cyclization [17], decarboxylative allylation [18], and intramolecular Diels–Alder [19] have been reported.

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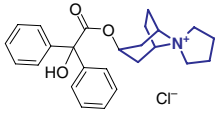
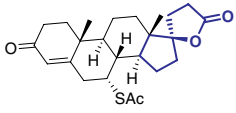
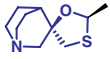
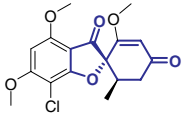
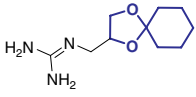
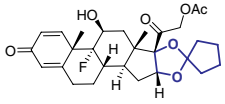
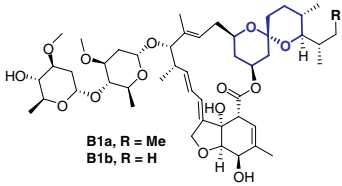
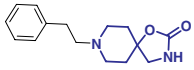
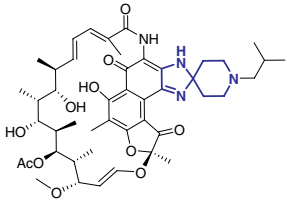
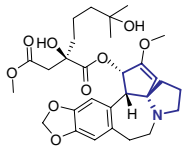
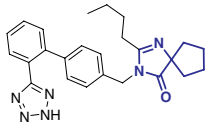
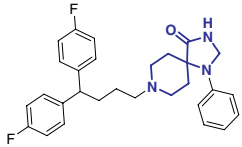
Table 2.1 Selected examples of FDA- approved drugs containing spirocyclic motifs.

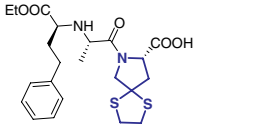
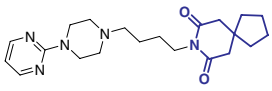
Structure	ID	Name (Trade name)	Indication
	**1**	Trospium chloride (Flotros)	Overactive bladder
	**3**	Spironolactone (Aldactone)	Heart failure, edema, hypertension
	**4**	Cevimeline (Evoxac)	Dry mouth (Sjögren's Syndrome)
	**5**	Griseofulvin (Crivicin)	Antifungal antibiotic for ringworm infections
	**6**	Guanadrel (Hylorel)	Hypertension

	**7**	Amcinonide (Cyclocort)	Inflammatory and pruritic manifestations
	**8**	Ivermectin (Ascapil)	Anti-parasitic
	**9**	Fenspiride (Eurespal)	Antitussive
	**10**	Rifabutin (Ansatipin)	Antibiotic, tuberculosis

(*Continued*)

Table 2.1 (Continued)

Structure	ID	Name (Trade name)	Indication
	**11**	Homo-harringtonine (Ceflatonin)	Chronic myeloid leukemia
	**12**	Irbesartan (Avapro)	Hypertension
	**13**	Fluspirilene (Imap)	Schizophrenia

	**14**	Spirapril (Renormax)	Hypertension
	**15**	Buspirone (Buspar)	Anxiety disorders

Source: Adapted from Knox et al. [2].

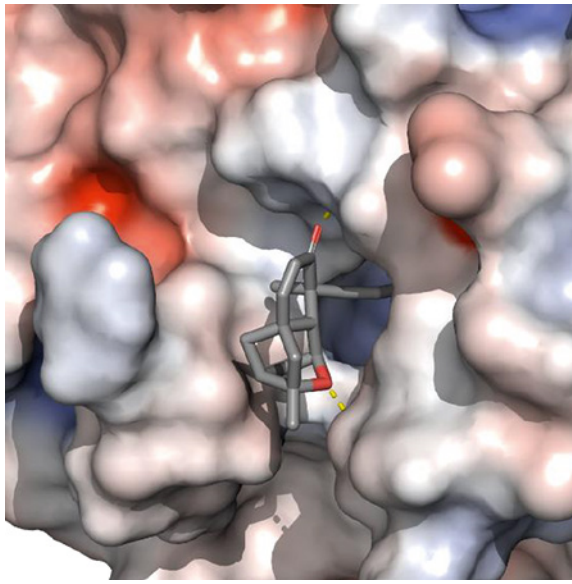
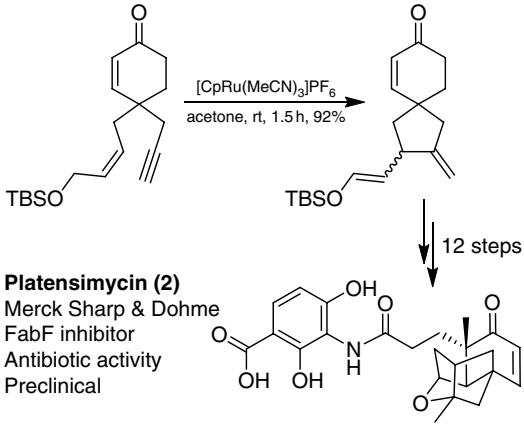


Figure 2.1 X-ray crystal structure (pdb 2gfx[12]) of Platensimycin (**2**, sticks representation) bound to the active site of FabF (surface representation) highlights hydrophobic contacts and hydrogen bonds in the complex.



Scheme 2.1 Key enyne cycloisomerization step in Nicolaou's total synthesis of platensimycin. *Source:* Adapted from Nicolaou et al. [15].

In contrast, a comparatively small number of spirocycle containing drugs have been investigated in the last decades, and spirocyclic molecules are still underrepresented in marketed drugs [2]. Selected examples of spirocycle containing drugs are shown in Table 2.1, including spironolactone **3** which has been known for over 50 years [20]. It seems fair to state that historically drug design strategies in medicinal chemistry have been heavily inspired (or biased?) by the advances in synthetic chemical methods toward new molecular scaffolds. This raises the question of chemical diversity and unconscious bias toward traditional/ubiquitous building