**Recent Advances in the Synthesis of Spirocyclic Compounds**

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ABSTRACT

The synthesis of spirocycles has attracted organic chemists over recent years due to their broad range of biological activities and the difficulty in synthesizing them. The aim of this chapter is to summarize potent biological activities exhibited by spirocyclic compounds and the recent diverse chemical approaches used in their synthesis. This may pave the way for superior approaches towards the synthesis of these compounds and thus, help in further drug development.

Keywords—heterocyclic compounds; spirocycles; quaternary carbon

# INTRODUCTION

With its origins rooted in organic synthesis and medicinal chemistry, heterocyclic compounds constitute a major class of organic compounds containing at least one heteroatom such as oxygen, nitrogen and sulphur incorporated in the ring. They are present throughout the nature in various forms and are the building blocks of numerous natural products. Moreover heterocyclic compounds are the fundamentals of life such as DNA, RNA, haeme derivatives in blood and chlorophyll for photosynthesis [1]. During the last decades, synthesis and transformations of heterocyclic fused rings, especially that of spirocycle, have received considerable attention owing to their remarkable and expanded applications and poised them as cornerstones in the field of pharmaceutical chemistry. The main basis of extensive applications of heterocyclic compounds is that their structure can be formulated as required and these structural changes lead to some fruitful biological activities of the compounds.

Spirocyclic compounds are three dimensional bicyclic molecules that present a twisted structure of two ring systems with just one shared atom between two rings (the spiroatom). The presence of the tetrahedral sp3 spiro carbon leads to the orthogonal arrangement of the planes of the two spirocyclic rings. Spirocyclic structure was first created by Von Bayer in 1900 as a bicyclic hydrocarbon connected by a single carbon atom and proposed the name of the synthesized compound as spirocyclane [2]. Due to asymmetric characteristic of the molecule, spiro heterocycles have been found to play fundamental roles in many biological processes and have exhibited diversified biological activity and pharmacological and therapeutic properties. Compared to an analogous monocyclic ring system, a spirocyclic ring system tends to have decreased lipophilicity which correlates with more desirable pharmacokinetic and safety properties in drug candidates and fewer low energy conformations for the ring system and its substituents [3,4]. Additionally, spirocyclic compounds exhibit improved metabolic stability and solubility in aqueous solutions as compared to their monocyclic structures [5]. These factors have contributed significant advances towards the controlled synthesis of spirocyclic compounds. Spirocyclic compounds are conformationally rigid and at the same time, they are flexible enough, which relieves them from permeability and absorption issues [6,7]. This facilitates their incorporation in molecules which exhibits striking pharmacological properties such as anticancer, anti-Alzheimer’s, antioxidant [8-10]. Spirocyclic scaffolds are present in a variety of architecturally complex natural products which display excellent pharmacological activity against various biological targets including receptors and enzymes as well as against acute thrombosis [11], hypertension [12], and tumor growth [13]. A broad overview of the related activities is discussed below:

# BIOLOGICAL ACTIVITIES OF SPIROCYCLIC COMPOUNDS

## **Antimicrobial activity**

Spirocyclic moieties present in both natural and pharmaceutical compounds display broad spectrum antibacterial activity. Exiguaquinol(**1**)is the first natural product that was isolated from Australian sponge *Neopetrosia exigua* and has the potential to inhibit *Helicobacter pylori glutamate racemase MurI* [14]. Gamma-rubromycin (**2**), isolated from the culture broth of *Streptomyces sp. Al* originating from orange grove soil samples collected from Israel, showed marked inhibitory function against a range of Gram-positive bacteria, particularly *Bacillus subtilis* and *Staphylococcus aureus* as well as Gram-negative bacteria such as *Escherichia coli* (Figure 1) [15,16].Purpuromycin (**3**), containing a spiroketal ring system, was first isolated from *Actinoplanes ianthinogenes* and was found to exhibit antimicrobial activity against various bacterial strains including *Staphylococcus aureus*, fungi and protozoa [17]. In fungi, the activity is due to inhibition of RNA synthesis. The compound displays excellent activity against *Gardnerellavaginalis, Trichomonasvaginalis* and *Candia albicans*, the three main pathogenic agents of common vaginal infections [18]. Phomopsichalasin (**4**), isolated from *Phomopsis sp.*, is also known for its antimicrobial and antifungal activities (Figure 1) [19].



**Figure 1: Spirocyclic compounds exhibiting antimicrobial property**

**B. Chemotherapeutic property**

Spiro compounds are also known for their cytotoxicity and are of prime importance in cancer chemotherapy. Cephalostatin I (**5**), isolated from the South African (Indian Ocean) marine worm *Cephalodiscus gilchristi*, contains two highly oxygenated steroidal spiroketal units linked by a central pyrazine ring and display potent cytotoxic activity [20]. Solamargine (**6**), a steroidal alkaloid glycoside, is highly efficacious against melanomas in preliminary clinical trials without signiﬁcant side effects or recurrence of cancer 10 years after treatment [21]. The promising anticancer activity of solamargine (**6**) along with unique mode of action implies its applicability in the treatment of drug-resistant cancers (Figure 2).



**Figure 2: Spirocyclic compounds exhibiting chemotherapeutic property**

**C. Anti-inflammatory property**

Cynandione B (**7**), isolated from the rhizome of *Cynanchum taiwanianum*, is a 6,6-monobenzannulated spiroketal exhibiting potent anti-inflammatory activity through inhibition of neutrophil activation [22]. A synthetic spirocyclic compound 8 is a potent CCR1 (chemokine receptor) antagonists that participates actively in the treatment of chronic inflammatory diseases (Figure 3) [23].



**Figure 3: Spirocyclic compounds exhibiting anti-inflammatory property**

**D.** **Anti-HCV property**

Hepatitis C is a liver infection and is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. MK-8831 (**9**), possessing a novel spirocyclic-proline motif, is a potential hepatitis C (HCV) protease inhibitor [24]. Another synthetic spirocycle **10** is a potent HCV NS5A inhibitor and represents a different type of therapy for treatment of hepatitis C viral infection (Figure 4) [25].



**Figure 4: Examples of some spirocyclic compounds exhibiting anti-HCV property**

**E.** **Photochromic property**

Spiropyrans are one of the most widely studied classes of photochromic materials due to their equilibrating cyclic and acyclic structuresand the intense absorption of the colored form in the visible region [26,27]. The unique property of spiropyrans **11** and **12** to exhibit photochromism when irradiated by photons, has been exploited to study liquid crystals [28]. Photolysis of light-yellow solution of spirobenzothiapyran **13** in polar solvents like methanol and acetone results in color change of the solution to blue-green (Figure 5) [29].



**Figure 5: Examples of some spirocyclic compounds exhibiting photochromic property**

**III. Reported procedures for the synthesis of spirocyclic compounds**

Over the years, organic chemists are in continuous resonance for the synthesis of the myriad of biologically important moieties containing spirocyclic framework. Several strategies have been developed towards the synthesis of these spirocyclic scaffolds, which includes (a) metal-catalyzed spirocyclization, (b) intermolecular double substitutions, (c) intramolecular substitutions, (d) cycloaddition reactions, (e) intramolecular arrangements, and (f) radical cyclizations. In order to provide flavor of these reports, few fruitful recent results on fabrication of various spirocyclic building blocks of valuable molecules by utilizing various reaction strategies have been discussed below.

In a very recent report, Chen and group carried out visible-light induced cyclization of biaryl ynones **14** with diselenides **15** to produce selenated spiro[5.5]trienones **16** under green conditions (Scheme 1) [30].

**Scheme 1: Synthesis of selenated spiro[5.5]trienones by treating biaryl ynones with diselenides**

In a report by [Kalaitzakis](https://pubs.rsc.org/en/results?searchtext=Author%3ADimitris%20Kalaitzakis) and team, photocatalyzed [2 + 2]-cycloadditions was carried out between γ-alkylidene–γ-lactams **17** and unsaturated substrates **18** leading to the formation of saturated spirocyclic compounds **19** (Scheme 2) [31].



**Scheme 2: Synthesis of saturated spirocyclic compounds by photocatalyzed [2 + 2]-cycloadditions reaction**

Zhang and team members developed an efficient method for the one-pot three component reaction between an amine **20**, unsaturated nitro compound **21** and cyclic ketone **22** leading to the formation of spirocycloalkane fused pyrazolo[3,4-b]pyridine derivatives **23** and **24** (Scheme 3) [32].



**Scheme 3: Synthesis of spirocycloalkane fused pyrazolo[3,4-b]pyridine by reacting an amine and an unsaturated nitro compound with a cyclic ketone**

In a report by Suri and team members, a three-component domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction between 1,3-dicarbonyl **25**, ketones **26** and alkenes/alkynes **27** was carried out in the presence of magnetically separable silica (Fe3O4@SiO2) catalyst under solvent-free condition leading to the spirocyclic chromenones **28** (Scheme 4) [33].



**Scheme 4: Synthesis of spirocyclic chromenones by domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction**

In a recent report, Li and team members carried out the synthesis of spiro[4*H*-pyran-3,3’-oxindoles] **32** by reacting isatin **29** with malononitrile **30** andenol derivatives **31** catalyzed by [HMTA-Bu]Br in aqueous ethanol solution (Scheme 5) [34].



**Scheme 5: Synthesis of spiro[4*H*-pyran-3,3’-oxindoles] by reacting isatin with malononitrile and enol derivatives in the presence of [HMTA-Bu]Br catalyst**

Very recently, Gogoi and his team developed a highly efficient decarbonylative cycloaddition reaction of 3-hydroxy-2-phenylchromones **33** with alkynes **34** accelerated by Ru-catalyst to yield spiro benzofuranones **35** (Scheme 6) [35].



**Scheme 6: Synthesis of spiro benzofuranones by decarbonylative cycloaddition reaction**

A novel method was developed by Zhang and group membersfor the construction of a spectrum of spirocyclanes **38** through exo-Diels-Alder reaction of α-methylene carbonyl compounds, generated *in situ* from stable methiodide salts of Mannich bases **36**, with 2, 4-dienals **37** via trienamine activation of a chiral secondary amine (Scheme 7) [36].



**Scheme 7: Synthesis of spirocyclanes through exo-Diels-Alder reaction**

A facile 1,3-dipolar cycloaddition reaction between imine **39** and methyl-2-(oxetane/azetidine-3-ylidene)acetate **40** as dipolarophile catalyzed by silver was developed by Jones and co-workers which afforded oxetane/azetidine containing spirocycles **41** in moderate to good yield (Scheme 8) [37].



**Scheme 8: Synthesis of oxetane/azetidine containing spirocycles through 1,3-dipolar cycloaddition reaction catalyzed by silver**

Li’s group developed an efficient strategy of Rh (III)-catalyzed [3+2] annulation of cyclic N-sulfonyl or N-acyl ketimines **42** with activated alkenes **43** via C-H activation pathway to construct a library of spirocycle molecules **44** and **45** (Scheme 9) [38]. Interestingly, the stereochemistry of the product could be controlled by maintaining the temperature of the reaction.



**Scheme 9: Synthesis of spirocyclic compounds via C-H activation pathway**

Lv and group members reported an oxidant-free synthesis of spirocyclic compounds **48** by cobalt-catalyzed reaction between benzimidates **46** and maleimides **47** using nitrobenzene as promoter (Scheme 10) [39].



**Scheme 10: Cobalt catalyzed synthesis of spirocyclic compounds**

Jagadeesh and co-workers recently employed a novel BF3·OEt2 catalyzed Prins cascade strategy for the stereoselective synthesis of spiro-oxindole derivatives **51** and **52**, by coupling 4-hydroxy-N-methyl-2-methylene-N-phenylbutanamide (**49**) with aldehydes **50** (Scheme 11) [40].



**Scheme 11: Synthesis of spiro-oxindoles *via* BF3·OEt2 catalyzed Prins cascade reaction**

Due to the structural simplicity and wide range of biological activity with diverse properties, spirocyclic compounds constitute an ideal lead class of compounds for structural diversification to enhance their promising pharmacological activities and further study.

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