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Mini-review

Cycloadditions and condensations as essential tools in spiropyrazoline synthesis

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ABSTRACT

Heterocycles with potential bioactive properties are of greater interest to researchers engaged in the areas of natural product synthesis and heterocyclic methodology. Several FDA (Food and Drug Administration) approved pharmaceutical drugs incorporate a heterocyclic motif in their core structure. Spiroisoxazolines and spiropyrazolines belong to the class of five membered heterocycles that have received greater attention over the past four decades. Spiropyrazolines structurally resemble naturally occurring spiroisoxazolines, have extra nitrogen in place of isoxazoline oxygen, and offer the viability to construct useful analogs for the exploration of possible bioactivity. As of today, no reports on the construction of these spiropyrazolines were available and the current review is aimed at providing a comprehensive discussion of the protocols applied in the synthesis of functionalized spiropyrazolines.

1. Introduction

The exploitation of a small molecule to a desirable extent is a valuable contribution in the field of synthetic organic and medicinal chemistry. Bioactive heterocyclic compounds are of potential interest to researchers engaged in the areas of natural product synthesis and heterocyclic methodology [1–9]. In addition to the potential bioactive properties rendered by these heterocyclic compounds, they are actively sought in the agrochemical and pharmaceutical sectors [6,7,10–15]. A few examples of the pharmaceutical drugs that incorporated a heterocyclic scaffold include celecoxib (celebrex) **1** [14], rimonabant **2** [16–18], raloxifene **3** [15], lipitor **4** [19,20], and cialis **5** [21–23]. Of the several heterocycles, five membered isoxazole (isoxazoline) and pyrazole (pyrazoline) based motifs have garnered greater attention and are conveniently accessed in few steps [24–36]. These five membered heterocycles exhibited several biological properties including antiviral [37,38], antitubulin [39,40], anti-inflammatory [41], antibacterial [42,43], antifungal [44,45], and antidepressant activity [46]. However, when an isoxazoline or pyrazoline is joined to another ring at one carbon atom, they are termed as spiroisoxazolines and spiropyrazolines [28,29,32,47,48].

The spirocyclic molecular framework is of substantial interest to medicinal chemists [49–51], and the synthesis of these spirocycles is a daunting task, due to the non-availability of the convenient protocols and starting materials. Spiroisoxazolines and spiropyrazolines belong to the class of five membered heterocyclic compounds, and an array of methodologies were designed and executed adopting various synthetic pathways [47,48,–52–62]. While the major structural core of several bromotyrosinated natural products **6**–**11** is spiroisoxazoline [49–59], spiropyrazolines with extra nitrogen (in place of isoxazoline oxygen) present the flexibility to synthesize additional analogs for the investigation of possible bioactivity (Fig. 1) [31,48,53,54]. In general, the spiropyrazolines have a basic structure derived from the pyrazoline and are exemplified by unique spiro junction at the C-5 position of a pyrazoline [47,48]. These spiropyrazoline based templates are attractive targets for synthesis based upon the intriguing spirocyclic skeleton rendered with potential bioactive applications.

A variety of methods exist for the synthesis of the functionalized spiropyrazolines. General and classical syntheses of the spiropyrazolines rendered protocols based on 1,3-dipolar cycloaddition [1,6,61–65] or condensation as an essential step [66–71]. Spiropyrazolines with several sites for modification present the

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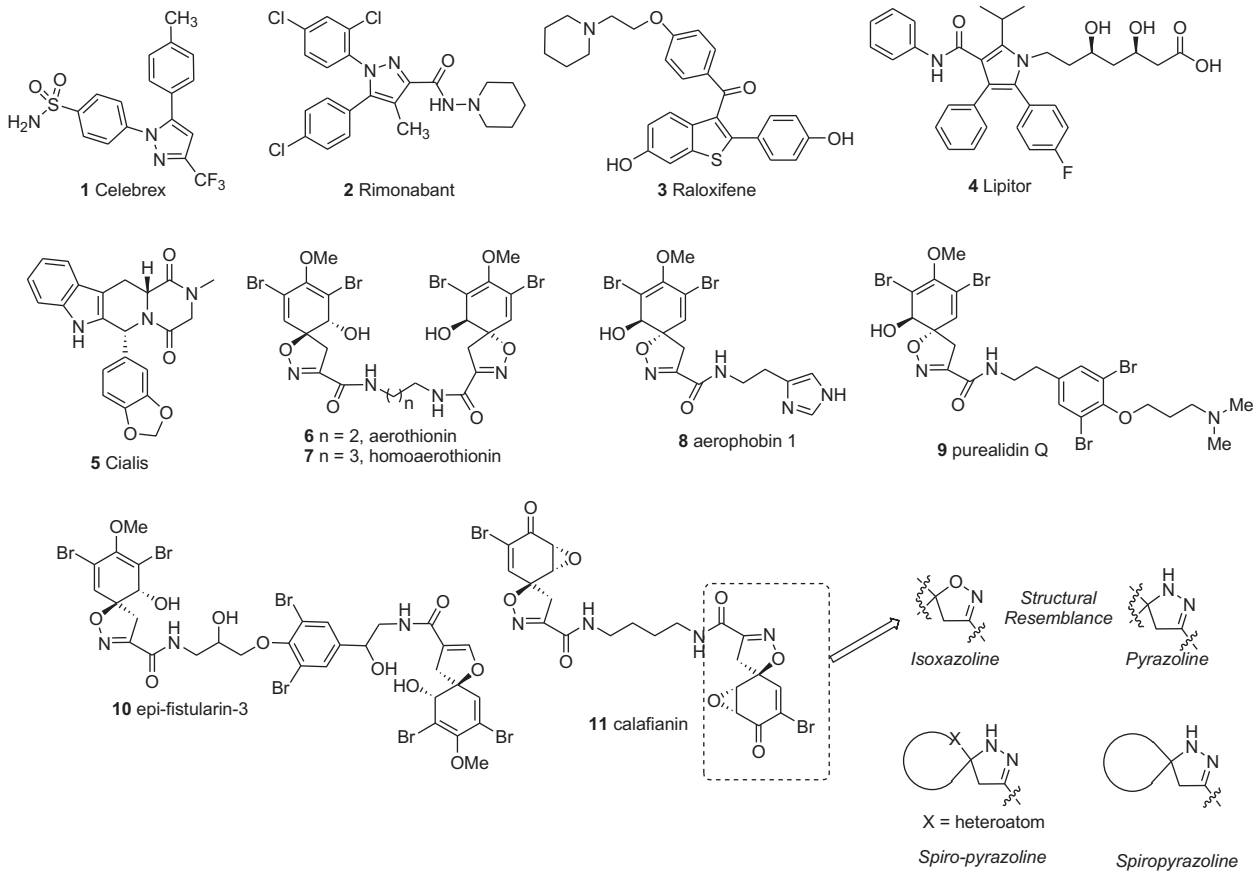

Fig. 1. Bioactive heterocyclic compounds of natural and synthetic origin.

flexibility to construct additional analogs of biomedical interest [48] and also serve as essential precursors in the synthesis of cyclopropane derivatives [72,73]. To date, there exist no review reports that provided a discussion on the synthesis of these molecules and the current review is aimed at providing a comprehensive overview of practical methodologies used to construct spiropyrazolines of biomedical interest. In addition to the spiropyrazoline synthesis, a discussion on the synthesis of cyclopropane derivatives is also provided (wherever required). The contents are discussed in four sections: (a) condensation reactions, (b) 1,3-dipolar cycloadditions, (c) related 1,3-dipolar cycloadditions, and (d) reactions of spiropyrazolines.

2. Condensation reactions

Condensation reaction is an example of organic reaction, wherein two molecules or moieties interact and unite to form one single molecule [14,27,66–68]. During the condensation process, they are normally associated with a loss of a small molecule such as H_2O, HCl, or AcOH [31,66,69–71]. These condensations find superior place in organic synthesis and are actively sought in the synthesis of heterocyclic rings of varied sizes. In this section, a brief overview of condensation reactions applied to synthesize various spiropyrazolines is provided.

Indole-2,3-dione (isatin) **12** is a valuable precursor in organic synthesis and find several applications in chemistry and biology [74–77]. In presence of a base, these indole-2,3-diones reacted with α-tetralone [78] (or) substituted acetophenones [79–82], and furnished the α,β-unsaturated carbonyl intermediates **13**–**15**. The synthesized intermediates **13**–**15** following reacted with hydrazine (or) phenylhydrazine under ethanol reflux conditions to afford the desired spiropyrazolines **16**–**19** in moderate yields (Scheme 1) [78–82].

In another report, Aoyagi and coworkers treated 3-phenacylideneindolin-2-ones **20** with hydrazine hydrate and isolated several spiro[indoline-3,3′-(5′-pyrazolin)]-2-ones **21** [82]. The synthesized spiropyrazolines on following treatment with acetic anhydride furnished the 2′-acetyl analogs **22**/**23** in high yields. Of recent, Alizadeh and Zohreh utilized the ketene aminals as essential intermediates and synthesized several spiropyrazolines incorporated with an indole-2,3-dione motif [83]. The required ketene aminals **25** were conveniently prepared through the reaction of 1,1-bis(methylthio)-2-nitroethylene with diamines or ammonia. One pot reaction of 1,1-bis(methylthio)-2-nitroethylene (ketene aminal) **25**, hydrazine hydrate and isatin **24** (1:2:2) proceeded to completion and the desired spirooxindole–pyrazolines **26** were isolated in high yields (Scheme 2) [83].

Similar to isatin, indenoquinoxalines **27** also find potential applications in organic synthesis and exhibited several bioactive properties such as antimetabolism and antitubercular properties [84,85]. Indenoquinoxaline and indenopyridopyrazine derived spiropyrazolines (**31** and **32**) were prepared through the condensation of chalcones and hydrazine in acidic conditions [81]. The chalcone intermediates **29** and **30** were prepared in two convenient steps that involved a base treatment under solvent free conditions and following dehydration using glacial AcOH and HCl. The chalcones **29**–**30** upon condensation with hydrazine hydrate under ethanol reflux conditions furnished the desired spiropyrazolines **31**/**32** in excellent yields (Scheme 3) [81].

Additional report that utilized the condensation as a key step was reported by Youssef and coworkers [86]. The desired spiropyrazolines **36a**–**c** incorporated an essential benzothienopyridazine motif.