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Mini-review

Progress of the synthesis of condensed pyrazole derivatives (from 2010 to mid-2013)

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ABSTRACT

Condensed pyrazole derivatives are important heterocyclic compounds due to their excellent biological activities and have been widely applied in pharmaceutical and agromedical fields. In recent years, numerous condensed pyrazole derivatives have been synthesized and advanced to clinic studies with various biological activities. In this review, we summarized the reported synthesis methods of condensed pyrazole derivatives from 2010 until now. All compounds are divided into three parts according to the rings connected to pyrazole-ring, i.e. [5, 5], [5,F 6], and [5, 7]-condensed pyrazole derivatives. The biological activities and applications in pharmaceutical fields are briefly introduced to offer an orientation for the design and synthesis of condensed pyrazole derivatives with good biological activities.

1. Introduction

As one of the most important heterocyclic compounds, pyrazoles exhibit significant biological properties such as antispasmodic [1], anti-inflammatory [2], antibacterial [3], analgesis [4], antihyperglycemic [5], hypoglycemic [6], antineoplastic [7], antidepressive activities [8], and have been widely used in biopharmaceutical and pesticides. Among the several FDA approved pharmaceutical drugs, the pyrazole core was found in Celebrex [9], Sildenafil [10] and Rimonabant (Fig. 1) [11]. As a new type of heterocyclic compounds, condensed pyrazole derivatives are designed and synthesized through biomimicry or splice. Since pyrazole ring and other important heterocyclic active structural units both exist in these compounds, the compounds always exhibit more outstanding biological activities. Boyer et al. have reported a series of condensed pyrazole derivatives with four-fold of antibacterial activities against Gram-positive as well as Gram-negative compared with general pyrazole compounds [12].

Because of the excellent bioactivity and wide range of application of pyrazole derivatives, thousands of papers concerning the synthesis or bioactivities of pyrazole derivatives have been reported. Furthermore, the methodology for the synthesis of pyrazole derivatives have been summarized in some reviews occasionally. Makino et al. reported the synthetic progress of pyrazoles from 1981 to 1999 in two reviews [13,14]; in 2011, Fustero et al. reported the synthetic progress of pyrazoles from 2000 to mid-2010 [15]; and then a mini-review involving the synthesis of functionalized tetrasubstituted pyrazoles was reported by Dadiboyena et al. [16]; in 2012, Janin summarized the preparation and chemistry of 3/5-halogenopyrazoles [17], which are usually the precursors of various derivatives. Yet, all these papers mainly focused on the construction of pyrazole core but the chemistry of condensed pyrazole derivatives exhibiting more outstanding bioactivities was less concerned. Here we briefly introduce the bioactivities and summarize the synthesis progress of condensed pyrazole derivatives investigated by us and others from 2010 to mid-2013. As we know in the existing literature, common condensed pyrazole derivatives mainly included: pyrazolopyridines, pyrazolopyrimidine, pyrazolopyrazine, pyrazolopyrane, pyrrolopyrazole and so on. In this review, all compounds are divided into different parts according to the type of the ring connected to the pyrazole ring. If a five-membered ring is connected to the pyrazole ring, the compound belongs to [5, 5]-condensed pyrazole derivatives, and if the connected ring is a six-membered or seven-membered ring, the compound belongs to [5, 6]-condensed pyrazole derivatives or [5, 7]-condensed pyrazole derivatives.

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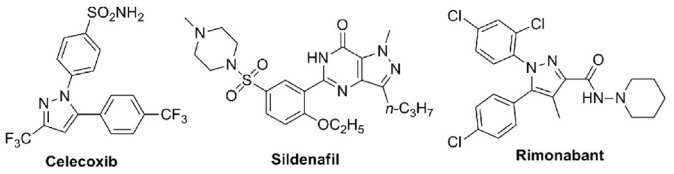


Fig. 1. Examples of several pharmaceutical drugs containing pyrazole core.

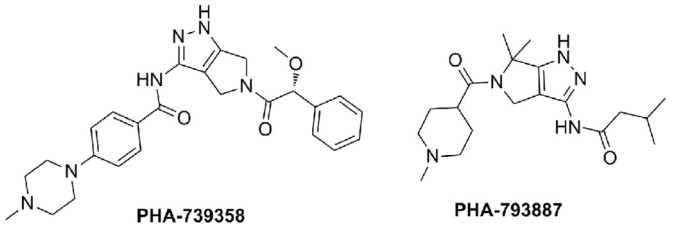


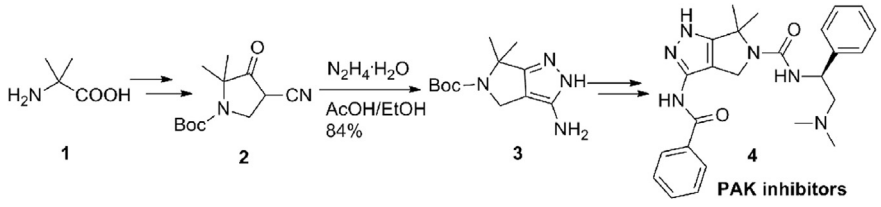
Fig. 2. Structures of compounds containing pyrrolopyrazole core.

2. [5, 5]-Condensed pyrazole derivatives

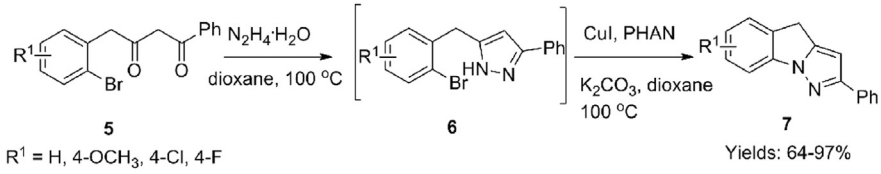
2.1. Pyrrolo[3,4-c]pyrazoles

The pyrrolopyrazole (PP), as an extension of the classic adenine mimetic pharmacophore presenting in several classes of kinase inhibitors, has been exploited as a hinge binder for numbers of protein kinase targets [18–24]. Recently, PHA-739358 (Fig. 2), an Aurora kinase inhibitor, has advanced into phase II clinical trials for the treatment of cancer because of the good pharmacokinetic properties and general safety profiles in phase I clinical study [25]. Compared with other hinge binder templates, the PP core offers efficient hydrogen bond interactions without multiple co-planar aromatic systems, which improves the physicochemical properties greatly.

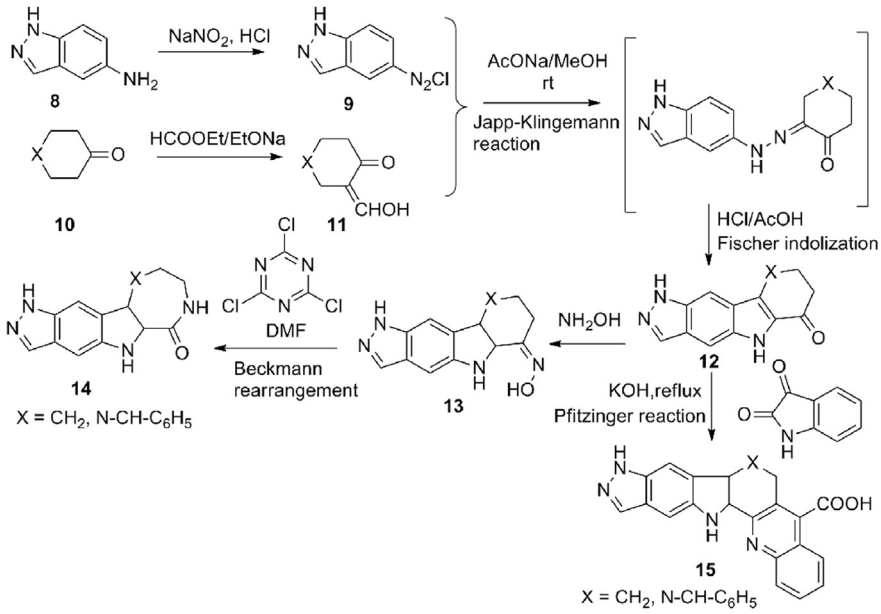
In 2010, Brasca et al. reported a potent cyclin dependent kinases (CDK) inhibitor, PHA-793887 (Fig. 2) which shows the inhibition of tumor growth in preclinical xenograft tumor models and was selected for clinical evaluation as anticancer agent [21]. Shi et al. reported the synthesis of 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazoles as Aurora-A kinase inhibitors and two of them were found to have



Scheme 1. Synthesis of PAK inhibitors.



Scheme 2. Synthesis of pyrazolo[1,5-a]indole framework *via* CuI catalyzation.



Scheme 3. Synthesis of pyrazole-condensed carbazole or azacarbazole derivatives.