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Mini-review

Recent advances in the chemistry and biology of pyridopyrimidines

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ABSTRACT

The interest in pyridopyrimidine cores for pharmaceutical products makes this scaffold a highly useful building block for organic chemistry. These derivatives have found applications in various areas of medicine such as anticancer, CNS, fungicidal, antiviral, anti-inflammatory, antimicrobial, and antibacterial therapies. This review mainly focuses on the progress achieved since 2004 in the chemistry and biological activity of pyridopyrimidines.

1. Introduction

Pyridopyrimidines are fused 6,6-bicyclic heterocycles consisting of a pyridine ring fused to a pyrimidine. Depending on the position of the nitrogen atom in the pyridine moiety, four isomeric structures of pyridopyrimidines **1**–**4** are available (Scheme 1). These scaffolds, which are nitrogen bioisosters of quinoxaline, are associated with a diverse range of biological activities such as anticancer, CNS disorders, and antiviral agents. They have been widely used in medicinal chemistry due to their five possible substitution sites and potentially accessible products which cover a large chemical diversity space. In the literature, previous reviews have mainly dealt with the chemistry of pyridopyrimidines, with only a minor interest in their pharmacological properties [1–5] and another review has investigated recent developments in the chemistry of pyridopyrimidines with one bridgehead nitrogen atom [6]. In the present account, new developments over the last ten years in pyridopyrimidine synthesis (excluding pyridopyrimidinone derivatives) with a focus on pharmacological properties will be discussed. These derivatives are considered as a key framework for target interaction and are platforms which orient substituents in a tridimensional manner. During the period covered in this review, few synthetic methods were investigated and, more specifically, most of the chemical developments were devoted to the regioselective introduction of various substituents.

To give an overview of the potential of pyridopyrimidines, the review is structured as follows. First the useful chemistry leading to the skeletons is depicted. Several building strategies are listed for each regioisomer. The regioselective functionalization of these scaffolds is the presented followed by the biological development of drugs which contain the pyridopyrimidine moiety.

2. Chemistry of pyridopyrimidines

The synthesis of pyridopyrimidine derivatives has markedly increased in the literature. The number of references containing the pyridopyrimidine core soared over the period 1975–2014 (Fig. 1). Several methods have been developed and two main cyclization strategies are commonly used to access these scaffolds. The first strategy involves ring closure by formation of the pyrimidine and the second strategy ring closure by formation of the pyridine.

2.1. Synthesis by ring closure

2.1.1. Synthesis by formation of the pyrimidine ring

Wu et al. synthesized 8-cyano-7-methoxy pyrido[4,3-*d*]pyrimidines **8** by pyrimidine ring closure in order to test cytotoxic activity [7]. Formamidate **6**, prepared from the reaction of the aminopyridine derivative **5** with triethyl orthoformate, cyclized smoothly in the presence of ammonia or primary amines, generating either the 4-methyl-8-cyano-7-methoxy pyrido[4,3-*d*]pyrimidine **7** or the 4-methylene-8-cyano-7-methoxy-3,4-dihydropyrido[4,3-*d*]

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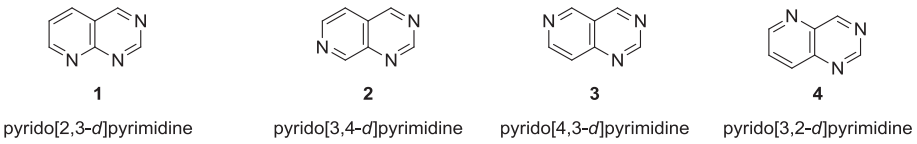


Scheme 1. Structures of pyridopyrimidines.

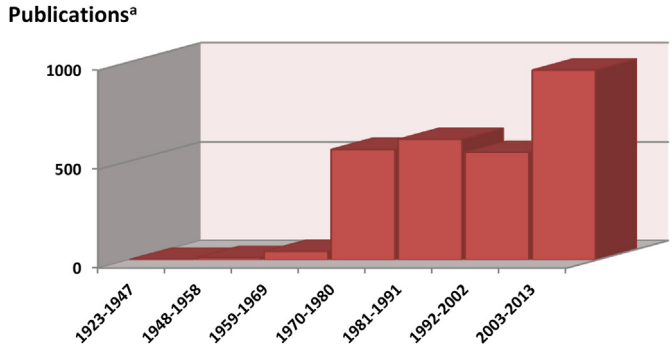


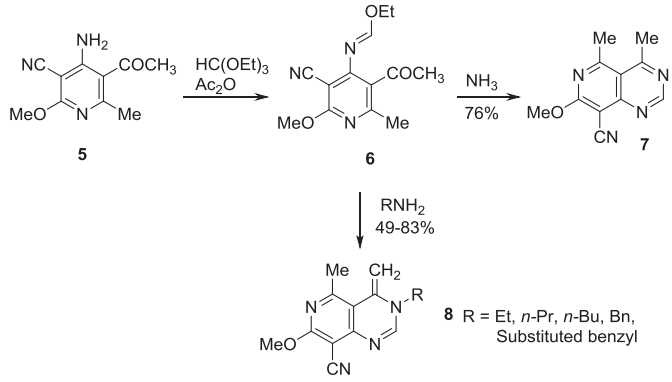
Fig. 1. Number of references containing the pyridopyrimidine core over the period 1923–2014. [a] Search performed on 20 January 2015 by Scifinder Research Topic using pyridopyrimidine as keyword.

pyrimidine **8** respectively in moderate to good yields (Scheme 2).

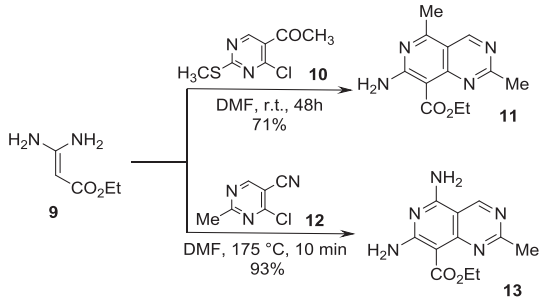
An amino pyridine framework can be fused to the prebuilt pyrimidine ring. To this end, cyclocondensation with imine derivatives was used by Lobanov et al. for the design of pyrido[4,3-*d*]pyrimidines. 1-(4-Chloro-2-methylsulfanyl-pyrimidin-5-yl)ethanone **10** reacted with ethyl 3,3-diaminoprop-2-enoate **9** to produce the pyrido[4,3-*d*]pyrimidine derivative **11** in 71% yield at room temperature in DMF. At elevated temperature (175 °C), the same reaction with chloropyrimidine **12** led in a few minutes to the bisamino derivative **13** in good yield (Scheme 3) [8,9].

Recently, a new synthetic approach to 4-aminopyrido[2,3-*d*] or [3,2-*d*]pyrimidines was described by Maes et al. [10]. The authors investigated the use of Pd-catalyzed cross coupling reactions between *N*-(bromopyridyl)amidines **15** and secondary or tertiary isocyanides to efficiently access disubstituted pyridopyrimidines **16** in moderate yields (Scheme 4).

Elneairy et al. investigated the use of a Dimroth rearrangement for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives [11]. Pyridin-2-(1*H*)-thione **17** reacted with phenyl isothiocyanate in refluxing pyridine to give substituted pyrido[2,3-*d*]pyrimidine **19** in 59% yield as the result of intermediate **18** rearrangement.



Scheme 2. Synthesis of pyrido[4,3-*d*]pyrimidines *via* imidate.



Scheme 3. Synthesis of pyrido[4,3-*d*]pyrimidines *via* an imine.

Compound **19** then reacted with various halides such as chloroacetonitrile in DMF in the presence of potassium hydroxide to give thioalkyl derivatives **20**. Interestingly, these derivatives were subjected to a second intramolecular thiophenyl ring creation leading to thieno[3′,5′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **21** (Scheme 5).

2.1.2. Synthesis by formation of the pyridine ring

2.1.2.1. Pyrido[2,3-d]pyrimidines. Dorokov et al. studied a Friedländer strategy to access pyrido[2,3-*d*]pyrimidines [12]. The reaction of 2,6-disubstituted-5-acetyl-4-aminopyrimidine hydrochloride **22** in refluxing acetylacetone afforded 6-acetyl pyrido[2,3-*d*]pyrimidine **23** in 55% yield. When a phenyl substituent was adjacent to the keto group, the cyclization of the enamine intermediate required the addition of DBU in order to cyclize into compound **25** (53% yield). Using sodium methoxide led to compound **26** with concomitant deacetylation. The use of ethyl acetoacetate instead of acetylacetone led to ethyl pyrido[2,3-*d*]pyrimidine-6-carboxylate **27** in lower yield (Scheme 6).

Using the method of Gangjee [13–15], 2,4,6-triaminopyrimidine **28** reacted with bromomalondialdehyde in acidic conditions. A further protection of the 2,4-diamino-6-bromopyrido[2,3-*d*]pyrimidine with the pivaloyl group increased solubility and facilitated purification of the final compound. Under these conditions, bis pivaloyl derivative **29** was obtained in a global yield of 39% (Scheme 7).

2.1.2.2. Pyrido[3,2-d]pyrimidines. Recently, Quattropani et al. reported an efficient route to 2,4,8-trichloropyrido[*3,2-d*]pyrimidine derivatives [16]. Aminouracil **30** and 3-substituted 3-alkoxyacrylic acid ethyl ester were heated at 140 °C in isopropanol under microwave irradiation, yielding enamines **31** as a mixture of ethyl and isopropyl esters having *E* and *Z* configurations. The mixture was cyclized into the 6-substituted 2,4,8-trihydroxypyrido[*3,2-d*]pyrimidines at 250 °C under microwave irradiation in a mixture of 1,2-dichlorobenzene and dimethylacetamide. Chlorination with excess of $POCl_3$ in *N,N*-diethylaniline or in neat $POCl_3$ produced the highly valuable platform **32** (Scheme 8).

2.1.2.3. Pyrido[3,4-d]pyrimidines. Malhotra et al. described the only convenient process to prepare pyrido[3,4-*d*]pyrimidines [17].