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Original article

Synthesis and biological activity of imidazopyridine anticoccidial agents: Part II

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Abstract

Coccidiosis is the major cause of morbidity and mortality in the poultry industry. Protozoan parasites of the genus *Eimeria* invade the intestinal lining of the avian host causing tissue pathology, poor weight gain, and in some cases mortality. Resistance to current anticoccidials has prompted the search for new therapeutic agents with potent in vitro and in vivo activity against *Eimeria*. Recently, we reported the synthesis and biological activity of potent imidazo[1,2-*a*]pyridine anticoccidial agents. Antiparasitic activity is due to inhibition of a parasite specific cGMP-dependent protein kinase (PKG). In this study, we report the synthesis and anticoccidial activity of a second set of such compounds, focusing on derivatization of the amine side chain at the imidazopyridine 7-position. From this series, several compounds showed subnanomolar in vitro activity and commercial levels of in vivo activity. However, the potential genotoxicity of these compounds precludes them from further development.

Keywords: Coccidiosis; Antiparasitic; Antiprotozoal; Kinase; Imidazopyridine

1. Introduction

Coccidiosis is a parasitic disease which is the major cause of morbidity and mortality in the poultry industry. It is a disease of the avian intestinal lining due to invasion by protozoan parasites of the genus *Eimeria* [1]. Some of the most significant *Eimeria* species in poultry are *Eimeria tenella*, *Eimeria acervulina*, *Eimeria necartrix*, *Eimeria brunetti, Eimeria mitis*, and *Eimeria maxima*. Over 35 billion chickens are raised annually worldwide, and all major poultry operations use anticoccidial agents prophylactically. Resistance to current coccidiostats is becoming widespread, and new broad spectrum drugs directed at novel biochemical targets are needed. Genetic studies in *Toxoplasma gondii*, a protozoan parasite closely related to *Eimeria*, demonstrate that cGMP-dependent protein kinase (PKG) is essential for survival and represents a desirable therapeutic target [2]. It was reported recently that inhibition of a novel PKG, isolated from these parasites, stops the parasite proliferation by blocking parasite invasion [2,3]. High throughput screening of known kinase inhibitors resulted in the discovery of imidazopyridine analogs as PKG inhibitors and broad spectrum anticoccidial agents [4]. Recently, we reported the synthesis and biological activity of imidazo[1,2-*a*]pyridines with diversity introduced at the 2-aryl and 3-aryl rings [4,5]. Herein, we report PKG inhibition, synthesis, evaluation, optimization, and in vivo anticoccidial activities of imidazopyridines possessing optimal functionality at the 2-aryl and 3-aryl rings, and with diversity introduced at the amine side chain of the imidazopyridine 7-position.

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2. Results and discussions

2.1. Chemistry

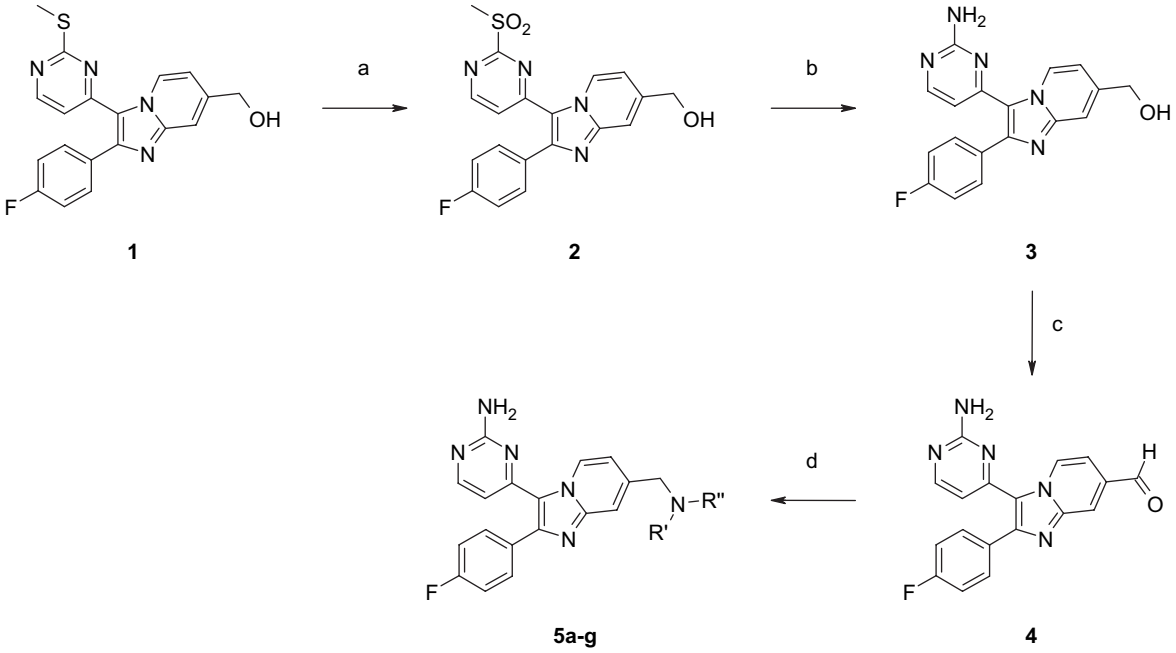
Introduction of functionality on a benzylic amine nitrogen at the imidazopyridine 7-position was accomplished as shown in Scheme 1. The synthesis of sulfide **1** is presented in a companion publication [5]. Oxidation of sulfide **1** with OXONE® gave sulfone **2**. Subsequent treatment with ammonia afforded 2-aminopyrimidine **3**. Oxidation of the benzylic alcohol with manganese(IV) oxide yielded aldehyde **4** [6]. Treatment of **4** with various amines and sodium triacetoxyborohydride ultimately yielded benzylic amines **5a–g** [7].

Syntheses of compounds bearing a carbonyl group bridging the imidazopyridine 7-position to the benzylic amine are shown in Schemes 2 and 3. In Scheme 2, treatment of aldehyde **4** with hydroxylamine and trifluoroacetic acid gave nitrile **6** [8], which was hydrolyzed with potassium hydroxide to yield amide **7** [9]. Alternatively, nitrile **6** was converted to imidate **8** when treated with ethanol and hydrochloric acid [10]. Subsequent treatment of imidate **8** with dimethylamine gave amidine **9** [10]. An unexpected byproduct of this reaction was *N*,*N*-dimethylaniline **10**, which presumably resulted from elimination of ethanol from imidate **8** to give a 7-cyanoimidazopyridine, followed by dimethylamine displacement of the cyano group.

Synthesis of the corresponding 7-carboxylic acid methyl amide (**17**) is shown in Scheme 3. The synthesis of bromide **11** is presented in a companion publication [5]. Subsequent cyclization with 2-(amino)isonicotinic acid ethyl ester yielded imidazopyridine **12** [11], which upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride gave Weinreb amide **13** [12]. Oxidation of the sulfide group of **13** with OXONE® afforded sulfone **14**, which was treated with ammonia to give 2-aminopyrimidine **15** [13]. The reaction of Weinreb amide **15** with ethylmagnesium bromide gave both the expected ethyl ketone **16** [12], and 7-carboxylic acid methyl amide **17**, which likely arises from deprotonation of the Weinreb amide methoxy group by the Grignard reagent followed by E2 elimination of formaldehyde [14].

Different pathways were used to introduce one or two alkyl substituents at the benzylic carbon of a 7-(dimethylaminomethyl)imidazopyridine, shown in Schemes 4 and 5. Synthesis of analogs in which this alkyl group is a single methyl or ethyl is shown in Scheme 4. Oxidation of alcohol **1** with manganese(IV) oxide gave aldehyde **18** [6], which was treated with methylmagnesium bromide to give secondary alcohol **20a**. Similarly, treatment of Weinreb amide **13** with ethylmagnesium bromide gave ethyl ketone **19** [12], which was reduced with sodium borohydride to give alcohol **20b**. Esterification of alcohols **20a** and **20b** with methanesulfonyl chloride and triethylamine yielded methanesulfonate esters **21a** and **21b**, which was followed by treatment with dimethylamine and diisopropylethylamine to give benzylic dimethylamines **22a** and **22b**. Oxidation of sulfides **22a** and **22b** to sulfones **23a** and **23b** was performed with either OXONE® or peracetic acid and catalytic sodium tungstate hydrate, followed by treatment with sulfur dioxide to reduce any tertiary amine oxide back to the tertiary amine [15]. Subsequent displacement of sulfone by ammonia then followed to ultimately yield 2-aminopyrimidines [13] **24a** and **24b**. HPLC separation of enantiomers of **24a** was conducted on a Chiralcel OJ (Diacel) column.

A slightly different approach was used to introduce either an *n*-propyl chain or two geminal methyl groups onto the benzylic



Scheme 1. Reagents: (a) OXONE®; (b) NH_3; (c) MnO_2; (d) HNR′R″, $NaB(OAc)_3H$ where R′ and R″ are defined as part of the R substituent of compounds **5a–g** in Table 1.