Bioorganic & Medicinal Chemistry 21 (2013) 4885–4892

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of polysubstituted benzofuran derivatives as novel inhibitors of parasitic growth

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ARTICLE INFO

Article history:
Received 25 April 2013
Revised 25 June 2013
Accepted 1 July 2013
Available online 12 July 2013

Keywords:
Benzofurans
Sonogashira coupling reaction
Antiparasitic
T. brucei
P. falciparum

ABSTRACT

A series of polysubstituted benzofuran derivatives was easily and rapidly prepared using a tandem Sonogashira coupling/cyclization reaction. Subsequent acylation afforded a small library of 39 new compounds that were assayed in cellulo on *Plasmodium falciparum* and *Trypanosoma brucei* parasites. Some of them exhibited good inhibitory activity on *T. brucei* proliferation.

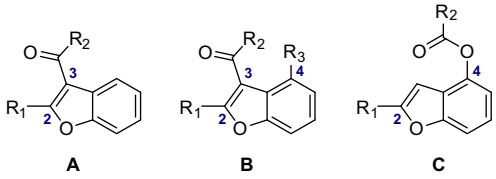
1. Introduction

According to WHO reports, *Plasmodium falciparum* is the major cause of malaria in humans, with 200–300 million individuals affected annually, causing 200–250 thousand deaths,[1] while *Trypanosoma brucei*, responsible for the African sleeping sickness, concerns 30 thousand persons and is lethal in absence of any treatment.[2] Currently resistance phenomena to established therapeutics against these diseases has dramatically developed. Hence new efficient antiparasitic agents are deeply needed.

In the course of our search for new active molecules, we synthesized intermediate benzofuran derivatives that displayed good antiparasitic activity. Benzofuran containing molecules have already been described to possess many biological properties as antiinflammatory,[3,4] antivasoconstriction,[5] antimicrobial[6] or antifungal.[7,8] However, to the best of our knowledge, few authors studied their potential antiparasitic activity.[9–13] From the chemical standpoint, many syntheses of molecules possessing a benzofuran motif have been developed. Recently rapid metal-catalyzed methods yielding benzofurans from phenols were described.[14–17] As well, Singh and Wirth published an efficient metal-free cyclization of *o*-hydroxystilbenes to benzofurans catalyzed by hypervalent iodine.[18] Nevertheless 2,3-, 2,4- and 2,3,4-trisubstituted benzofurans herein reported have rarely been studied. For all these reasons we decided to create a library of polysubstituted benzofuran derivatives to evaluate their antiproliferative effects on *P. falciparum* and on *T. brucei*.

Thus we synthesized benzofuran derivatives substituted at position 2 by an aryl or cyclopropyl group. These compounds were either *C*-acylated at position 3 (**A** and **B**, Fig. 1) or *O*-acylated at position 4 (**C**, Fig. 1), the acyl substituent R_2 being an aryl moiety bearing various substituents. In order to increase the molecular diversity in the *C*-acylated series, R_3 at position 4 is either a hydrogen atom (**A** series), a hydroxyl group or a methoxy substituent (**B** series).

Herein, we describe an easy and rapid synthesis of polysubstituted benzofuran derivatives along with their biological evaluation on *P. falciparum* and *T. brucei* proliferation.



R_1 = aryl, cyclopropyl
R_2 = aryl
R_3= OH, OMe

Figure 1. General structures of benzofuran derivatives.

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http://dx.doi.org/10.1016/j.bmc.2013.07.002

2. Chemistry

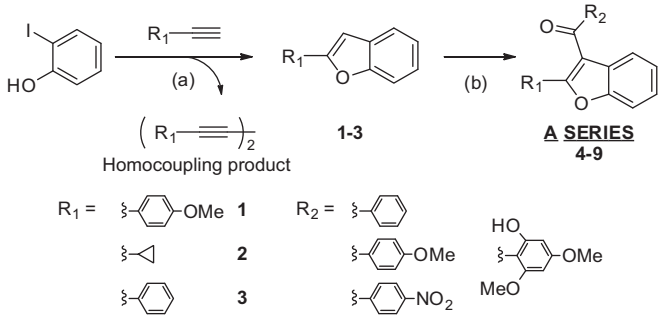
2.1. Tandem Sonogashira coupling/cyclization reaction

2-Substituted benzofurans **1**–**3** and **11**–**14** were synthesized via a tandem Sonogashira coupling/cyclization reaction from the commercially available 2-iodophenol (Scheme 1) and from the prepared 2-iodoresorcinol (Scheme 2), respectively. The substituent R_1 (aryl or cyclopropyl) was brought about by acetylene derivatives. Though this same Sonogashira coupling reaction has already been reported with 2-iodoresorcinol,[19] it was only obtained with hexyl or phenyl R_1 substituent in 50% and 60% yield, respectively. Therefore we tried to optimize this coupling reaction. Our major aim was to avoid the Glaser coupling affording the dimer products from terminal alkynes.[20–22] Thus we found that a perfectly degassed solvent by using the freeze-pump-thaw method could minimize this homocoupling reaction.

These conditions combined with the use of 3 equiv of alkynes allowed to significantly increase the reaction yield up to 77% for benzofuran-4-ol **11** (Scheme 2). Afterwards they were applied for the formation of all 2-substituted derivatives. Thus synthesis of benzofurans **1**–**3** (Scheme 1) was performed with moderate to high yield (50–88%) as well as benzofuran-4-ols **11**–**13** (Scheme 2) (70–77%). Only compound **14** possessing a xylyl group (Scheme 2) was obtained in low yield (12%). Formation of benzofurans required diluted conditions in order to minimize homocoupling reaction. Therefore, faced with a scale-up issue for derivatives **1**–**3**, we decided to use conditions described by Alami's group[23] allowing the cyclization into benzofurans from 2-iodoanisole in two steps (Scheme 3). Thus through this method, multigram scale reactions have been carried out giving 5- to 10-fold greater amounts of desired product. Moreover, formation of benzofuran **1** substituted by a 4-methoxyphenyl group was performed in quantitative yield, whereas a 50% yield was obtained using Sonogashira coupling reaction. On the contrary, much better yields were observed with the tandem reaction for the synthesis of compounds **2** and **3** with 88% and 70% yields, respectively, compared to 65% and 16% obtained in two steps, respectively.

2.2. Friedel–Crafts acylation

A standard Friedel–Crafts acylation using tin(IV) chloride was then carried out to form compounds **4**–**9** (**A** series), **19**–**25** and **26**–**31** (**B** series) bearing a hydrogen atom, a hydroxyl group and a methoxy substituent at position 4 of benzofuran motif, respectively (Scheme 2 and Table 1). The acyl chlorides used in this reaction were generally commercially available except di- and trisubstituted derivatives that were prepared just before the acylation reaction from the corresponding acid and thionyl chloride. Few derivatives of the **A** series were prepared because they early displayed low antiparasitic activity (see Table 3). Acylation yields for **A** series (Table 1) were low with *p*-nitro- and trisubstituted benzoyl chlorides (compounds **5**, **6** and **9**) and the 2-cyclopropyl-3-(*p*-nitrobenzoyl)benzofuran could not be obtained under these conditions. However, moderate to excellent yields were reached with benzoyl chloride (compounds **4**, **7** and **8**).



Scheme 1. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N (10 equiv), MeCN, 60 °C, overnight, **1**: 50%, **2**: 88%, **3**: 70%; (b) R_2–COCl (1.2 equiv), $SnCl_4$ (1.2 equiv), DCM, rt, 1–5 h, 13–86% (see Table 1).

In order to avoid esterification of the 4-OH group in the **B** series, protection of benzofuran-4-ols **11**–**14** was first carried out (Scheme 2). Hence introduction of a benzyl or a methyl group was performed yielding derivatives **15**–**18** with excellent yields (81–92%). Under acylation conditions, the benzyl protecting group was hydrolyzed affording the direct formation of 2,3,4-trisubstituted analogues **19**–**25** (Scheme 2 and Table 1). It should be noticed that only traces of 2-phenyl-3-acylbenzofurans were obtained in **B** series. Indeed, acylation of 2-phenyl derivatives was unsuccessful probably because many positions of the 2-phenyl ring were also acylated underFriedel–Crafts conditions, leading to a complex mixture where the expected derivative was generally formed as a minor product. Likewise, all reactions performed with *p*-nitrobenzoyl chloride failed leading to many side products. On the other hand, acylation of compound **18** (R_1 = *p*-methoxyphenyl, R_3 = Me) afforded benzofurans **26**–**31** (Table 1) in better yields (up to 41%). Only acylation with disubstituted benzoyl chloride was less efficient (27% yield). The *p*-methoxyphenyl group was the only R_1 substituent used in this series because of our preliminary biological results (see Table 4).

Though our first goal was to obtain rapidly a small library of polysubstituted benzofurans, we tried to optimize the acylation reaction. Thus we found that using titanium(IV) chloride or aluminium(III) chloride instead of tin(IV) chloride as Lewis acid significantly increased the yield reaction. Indeed 82% yield was obtained instead of 67% for the optimized acylation performed to get compound **26** (Table 1).

2.3. *O*-Acylation

Further *O*-acyl benzofuran derivatives **32**–**51** (**C** series) were prepared from compounds **11**–**14** bearing a free hydroxyl group, according to Scheme 2. Obtained yields (Table 2) were moderate (39–54%) for 2-phenyl-benzofuran derivatives **45**–**50**. Only acylation with *p*-chlorobenzoyl chloride afforded expected compound **49** in good yield (71%). This reaction proved to be more efficient on 2-*p*-methoxyphenyl-benzofuran leading to compounds **32**–**38** in good yield but the best results were obtained on 2-cyclopropylbenzofuran leading to compounds **39**–**44** in good to excellent yields (69–96%) except with 2-ethoxynaphthaloyl chloride. This reaction led to a modest yield only with the trisubstituted benzoyl chloride that was synthesized just before acylation (11% for compound **34**, Table 3).

3. Biology

All these benzofuran derivatives were assayed on the intra-erythrocytic stages of *P. falciparum*,[24–26] responsible for malaria and the bloodstream forms of *T. brucei gambiense*, the pathogenic agent of African sleeping sickness.[27–29] Results are summarized in Tables 3–5.

None of the 2,3-disubstituted benzofurans of the **A** series (Table 3) were active against *P. falciparum*. Their activity against *T. brucei* was moderate when R_2 was a phenyl group (compounds **4**, **7** and **8**) and compounds bearing a *p*-nitrobenzoyl moiety at position 3 (compounds **4** and **9**) were inactive. Only compound **6** where R_2 was a trisubstituted phenyl (IC_{50} = 6.7 μM) displayed a better activity.

Like 2,3-disubstituted benzofurans, **B** series derivatives (Table 4) displayed no activity against *P. falciparum*. On the other hand, better results were obtained on *T. brucei*. Almost all derivatives displayed