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Synthesis and activity of novel homodimers of Morita–Baylis–Hillman adducts against *Leishmania donovani*: A twin drug approach

Wagner A. V. da Silva [a], Daniele C. Rodrigues [a], Ramon G. de Oliveira [a], Rhuan K. S. Mendes [a], Tayná R. Olegário [a], Juliana C. Rocha [b], Tatjana S. L. Keesen [b], Claudio G. Lima-Junior [a,*], Mário L. A. A. Vasconcellos [a,*]

[a] Departamento de Química, Universidade Federal da Paraíba, Campus I, 58059-900 João Pessoa, PB, Brazil
[b] Departamento de Biotecnologia, Universidade Federal da Paraíba, Campus I, 58059-900 João Pessoa, PB, Brazil

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ABSTRACT

It is reported here the synthesis of novel Homodimers **12–19** of Morita–Baylis–Hillman adducts (MBHA) from one-pot Morita–Baylis–Hillman Reaction (MBHR) between aromatic aldehydes as eletrophiles and ethylene glycol diacrylate as Michael acceptor (35–94% yields) using cheap and *green* conditions. The bioactivities were evaluated against promastigote form of *Leishmania donovani*. All homodimers showed to be more potent than corresponding monomers. It is worth highlighting that the halogenated homodimers **17** and **18** (0.50 μM) is almost 400 times more active than the corresponding monomer **10** and 1.24 times more potent than the second-line drug amphotericin B (0.62 μM). Moreover, the selectivity index to **18** is very high (SI_{rb} > 400) far better than amphotericin B (SI_{rb} = 18.73). This is the first report of twin drugs strategy applied on Morita–Baylis–Hillman adducts.

Leishmaniasis is an infectious disease caused by protozoan *Leishmania*, and affects millions worldwide. As this parasite infection leads to an immunological imbalance outcome. Deeper studies on the new treatments and mechanisms involved in intracellular pathogen control are essential. Infection with the protozoa parasite *Leishmania* can cause several clinical forms of disease such as tegumentary or visceral forms,[1–3] this last one is the severe form and the major cause of mortality. This clinical form is caused by *Leishmania donovani*[2] and the development of new drugs and treatments is a necessity due to the resistance and cytotoxicity of commercial drugs used in treatment of human visceral leishmaniasis (HVL). In this context, the Morita–Baylis–Hillman reaction (MBHR) is an important chemical transformation which allows not only access to poly-functionalized molecules with considerable synthetic potential as also promising biological profile.[4,5] Several Morita–Baylis–Hillman adducts (MBHA) have been reported as bioactive compounds against neglected diseases such as leishmaniasis, schistosomiasis, malaria and Chagas disease.[6]

In connection with our continuum interest in synthesis of new Morita–Baylis–Hillman adducts with potent antiparasitic activity[6–8] herein we report the synthesis of homodimers of Morita–Baylis–Hillman adducts based on twin drug approach.

This approach is supported by an association of two identical pharmacophoric entities generating an 'identical twin drug' which is equivalent to a homodimer derivative.[9–11] Some authors have been suggested that administration of twin drugs can be favorable when compared with two separated drugs presenting own pharmacokinetic and pharmacodynamics proprieties.[10–12]

The antiparasitic piperaquine (**1**), bis-aminoacridine (**2**) and potent acetyl cholinesterase inhibitor bis-tacrine (**3**) are some examples of twin drugs (homodimers) present in literature (Fig. 1).[12–14]

The design of new homodimers of Morita–Baylis–Hillman adducts was based on compounds **4–11** presented in Figure 2. Except **9**, all Morita–Baylis–Hillman adducts already presented activity against promastigote s and amastigotes forms of *Leishmania amazonensis* and *Leishmania chagasi*.[7,15] The structure of eight new homodimers synthesized in this work are presented in Figure 3.

We began our experimental work preparing ethylene glycol diacrylate **20** (Scheme 1). This compound was synthetized by reaction between acrylic acid, ethylene glycol under *p*-toluene sulfonic acid catalysis at 110 °C. The diacrylate **20** was obtained in 86% after 6 h of reflux.[16] ^{1}H NMR and ^{13}C NMR analysis confirmed the structure **20** (see supplementary data).

Due to higher reactivity of 2-nitrobenzaldehyde and bioactivity against leishmaniasis of MBHA derivatives of this starting material,

* Corresponding authors.
E-mail addresses: claudio@quimica.ufpb.br (C.G. Lima-Junior), mlaav@quimica.ufpb.br (M.L.A.A. Vasconcellos).

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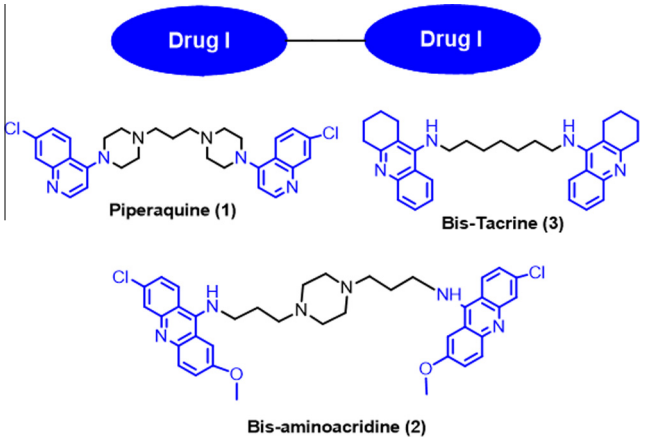


Figure 1. Synthetic bioactive homodimers as twin drugs.

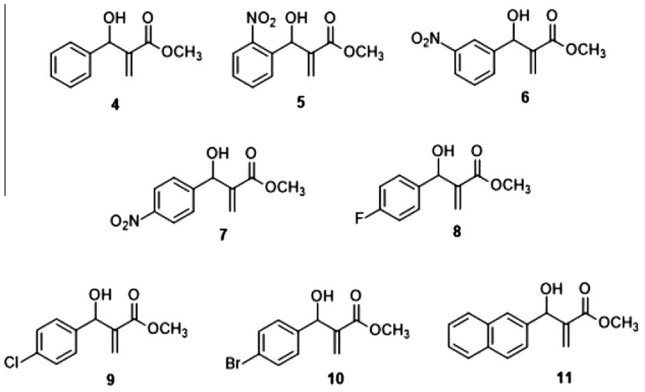
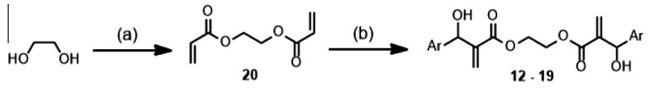


Figure 2. leishmanicides MBHA previously described by us (**4**–**8**, **10**, **11**) and described here (**9**).

we have decided to find an efficient experimental protocol to optimize the synthesis of **13**, and then apply such protocol to synthesize other MBHA **12**, **14**–**19**. Initially, to a mixture 2:1 of 2-nitrobenzaldehyde and **20** as Michael acceptor in acetonitrile, DABCO as promoter was added and stirred for 24 h at room temperature. The reaction afforded homodimeric MBHA **13** in 88%. After we have studied the solvent effect. Thus, MBHR were performed between the 2-nitrobenzaldehyde and acceptor **20** using some solvents, such as DMF, DMF: H_2O (6:4), ^tBuOH, ^tBuOH:H_2O (6:4) and DMSO. The reactions time were fixed in 24 h. It was observed that **13** was obtained in better yield using DMF (94% yield). With the solvent optimal conditions established, we investigated the influence of temperature in this reaction. Thus, reactions were performed at 80 °C under microwave irradiation and low temperature (0 °C)[17,18] in the presence of DABCO and DMF. It was observed that **13** was obtained in low yields in microwave and temperature protocols (25% yields).

With the optimal conditions for the preparation of **13**, we examined the MBHR between aromatic aldehydes as electrophile and ethylene glycol diacrylate **20** as Michael acceptor aiming to obtain new homodimers of MBHA (**12–19**). All reactions were carried out using DMF as solvent, DABCO (1 equiv) as promoter at room temperature. The results of **12–19** preparations are presented in Table 1.

It is possible to highlight in Table 1 that homodimers **12–15** were obtained in moderate to excellent yields (Table 1, entries 1–4). However, no efficient results were obtained preparing homodimers **16–19**, due to long reactions times, low yields were obtained ranging from 35 to 48% (Table 1, entries 5–8). Up to date, the Morita–Baylis–Hillman reaction with diacrylates like-**20** was reported only once in the literature.[19] The synthesis described by Shanmugam et al. performed in 35% yield using 1,6-hexanediol acrylate and isomerics pyridinecarboxaldehydes.[19] The homodimers synthesized here were characterized by spectroscopic analysis such as ^1H, ^{13}C NMR and HRMS (for detailed information see the supplementary data). The adducts **4**–**11** also were prepared using procedures recently described by us.[20] Homodimers **12**–**19** and



Scheme 1. Reagents and conditions: (a) Acrylic acid (2 equiv), TsOH (10 % mol), hydroquinone, cyclohexane, Dean–stark, 110 °C, 6 h (86%); (b) 1 equiv DABCO, Aldehydes (2 equiv), optimized conditions in Table 1 (35–94%).

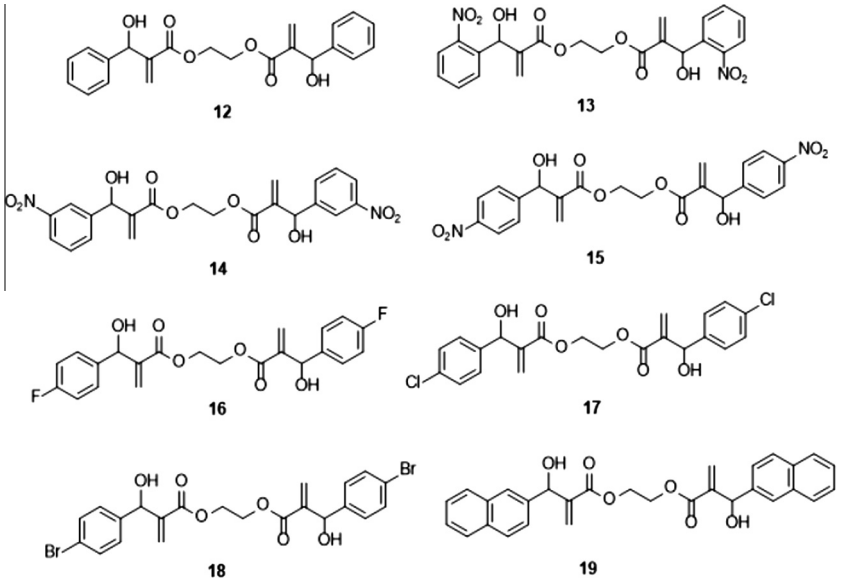


Figure 3. New Homodimers (**12**–**19**) of MBHA synthesized and biologically evaluated in this article.