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ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 1726–1730
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Short communication

Improved synthesis of seven aromatic Baylis–Hillman adducts (BHA): Evaluation against *Artemia salina* Leach. and *Leishmania chagasi*

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Received 16 June 2007; received in revised form 29 February 2008; accepted 6 March 2008
Available online 29 March 2008

Abstract

We described a very efficient procedure to prepare seven aromatic compounds (**1**–**7**), a new class of antileishmanial substances, through Baylis–Hillman reaction (BHR). With one, all the Baylis–Hillman adducts were prepared in quantitative yields by reaction of the corresponding aromatic aldehydes in acrylonitrile at 0 °C in only 10–40 min reaction time. We present our results about the toxicities of these compounds evaluated on the microcrustaceous *Artemia salina* Leach. and against promastigote *Leishmania chagasi*. All substances evaluated in this work have showed high bioactivity. The 3-hydroxy-2-methylene-3-(4-bromopheny)propanenitrile (**4**) ($LC_{50} = 30.9$ μg/mL on *A. salina*; $IC_{50} = 25.2$ μM on *L. chagasi*) was the most active compound evaluated on *A. salina* Leach. and on promastigote *L. chagasi*. The 2-[hydroxy(pyridin-4-yl)methyl]acrylonitrile (**7**) ($LC_{50} = 30.9$ μg/mL on *A. salina* Leach.; $IC_{50} = 4.8$ μg/mL on *L. chagasi*) was also a very active substance evaluated in this work on promastigote *L. chagasi*.

Keywords: Baylis–Hillman adducts; Green chemistry; *Leishmania chagasi*; *Artemia salina* Leach.

1. Introduction

The leishmaniasis are a complex of diseases caused by different species of the protozoan parasite *Leishmania* and a major public health problem in many developing countries where 350 million people live at risk of infection [1]. The parasite exists in two forms: the flagellate promastigote in the female phlebotomine sandfly vector, and the amastigote in the mammalian host. The disease has been traditionally classified into three different clinical forms, visceral (VL), cutaneous (CL) and mucocutaneous leishmaniasis (MCL), which have different immunopathologies and degrees of morbidity and mortality [2]. There is so far no approved vaccine for clinical use. Toxicity and resistance to the pentavalent antimonies (for examples Glucantime® and Pentostan®), which have been the mainstay of the treatment of both visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL) during the last 60 years are critical problems [3]. Although new drugs have become available in recent years, including lipid formulations of amphotericin B, the oral drug miltefosine for VL, and topical paromomycin for CL, these are not entirely satisfactory due to the high cost, reported side effects or ineffectiveness [4,5]. Thus, the currently available chemotherapy is far from being satisfactory, urging the search for new safe, affordable and effective drugs.

Recently, we described that 16 aromatic Baylis–Hillman adducts (BHA) showed selective activity against *Leishmania*

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doi:10.1016/j.ejmech.2008.03.016

amazonensis in vitro [6]. Among them, the compound 2-[hydroxy(4-bromophenyl)methyl]acrylonitrile (**4**, Fig. 1) presents two necessary qualities for a potential drug: to present very antileishmanial activity ($IC_{50} = 12.5$ μM) and to be a safer compound (0.0 (0.9); % macrophage LDH release), being up to now, our lead compound. The BHA **3** was the most efficient among the evaluated compounds against *L. amazonensis* ($IC_{50} = 7.9$ μM) but presented some cytotoxicity on uninfected adherent mouse peritoneal macrophages [6]. Compounds **2**, **3**, **5**–**7** (Fig. 1) were never evaluated against *Leishmania* parasites [7].

In our continuing search for bioactive substances [8–11], in connection with our efforts towards the study of the reactivity of Baylis–Hillman reaction and our interest in extending the scope of this new class of Leishmanicides, our group has dedicated efforts aiming to discover a practical synthetic methodology objectifying to obtain great quantities of these compounds, potential drugs against several species of *Leishmania*.

The purpose of this short communication is to present a very efficient ''one-pot'' procedure that can prepare compounds **1**–**7** (Fig. 1) under green conditions [12] and to present our results on evaluations of the toxicities of **1**–**7** compounds against *Artemia salina* Leach. [13] and promastigote form of *Leishmania chagasi*, the pivotal parasite in this endemic disease in Brazil [14].

2. Chemical synthesis

Baylis–Hillman reaction (BHR) was first reported in 1972 [15], and involves the coupling of alkenes containing electron withdrawing groups (EWG) with aldehydes, ketones and imines (among others), using tertiary amines as nucleophilic catalysts, e.g. the 1,4-diazabicyclo[2.2.2]octane (DABCO), the most frequently employed catalyst (Scheme 1).

This reaction affords adducts, such as **1** (Fig. 1), from the simple starting materials (e.g. 2-nitro-benzaldehyde and acrylonitrile to prepare **1**) where all the atoms in the substrate are present in the product (a total atom economy). Due to the synthetic utility of these adducts, several protocols have been proposed to improve this reaction, such as the use of microwaves, ultrasound, salt and metal addition, high pressure and ionic liquids [16].

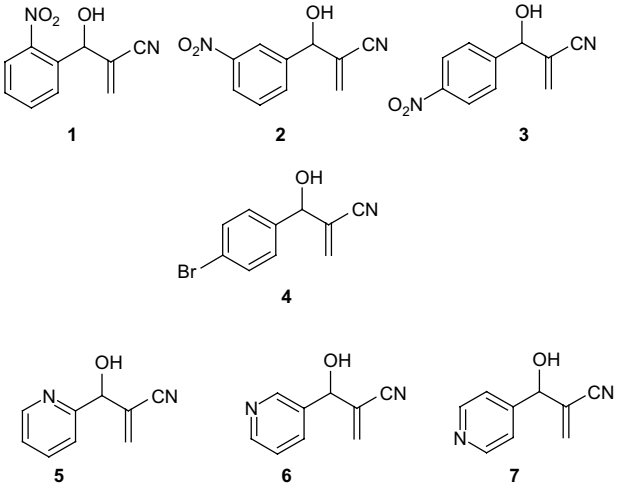
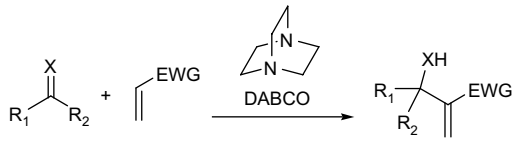


Fig. 1. The selected BH adducts prepared and evaluated in this paper.



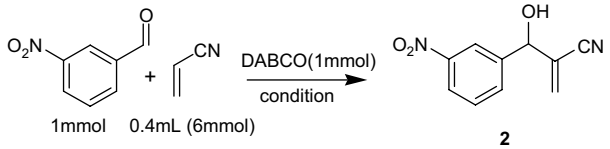
Scheme 1. The Morita–Baylis–Hillman reaction: R_1 = alkyl, aryl, heteroaryl; R_2 = H, CO_2R, alkyl, X = O, NTs, NSO_2Ph; EWG = electron withdrawing group: COR, CHO, CN, CO_2R.

2.1. About the procedures

We initiated our synthetic work into the preparation of **2** because the 3-nitro-benzaldehyde substrate is a good electrophile and the cheapest one in our selected group of aldehydes. Several solvents, temperatures and additives were first evaluated in our work, but all of them were inefficient to prepare pure **2** on reasonable yield. We present in Table 1 the most important results aiming to increase yields and minimize co-products in the preparation of BHA **2**.

In Table 1 we can note that the use of ultrasound does not significantly increase yields and not minimize the reaction time (entry 1 versus 2 and 3 versus 4, Table 1) [17]. In our case, the use of ultrasound retards the reaction time (3 versus 4). We observe that compound **2** was prepared in quantitative yield, in 20 min at 0 °C (entry 3, Table 1). It is important to point out that no co-product was observed on the medium reaction. In fact, no further chromatography purification was necessary by using this procedure. We noted that these efficiences reactions (rates and yields) were better in cold (0 °C) than at room temperature. This effect was already described by Rafel and Leahy [18] and also by us [19,20] on reaction using methyl acrylate as Michael acceptor and *p*-nitrobenzaldehyde as an electrophile. This has been explained based on the proposed mechanism for this reaction [20–24]. We present in Table 2 our results aiming the preparation of compounds **1**–**7**.

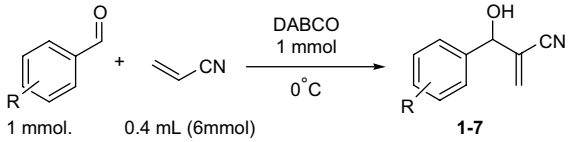
Table 1
Preparation of the adduct **2**



Entry	Condition	Reaction time (min)	Isolated yield (%)
1	25 °C	20	85[a]
2	25 °C, ultrasound	70	90[a]
3	0 °C	20	100
4	0 °C, ultrasound	40	84[a]

[a] A dimeric co-product was also observed.

Table 2
BH adducts' preparation in acrylonitrile at low temperature



Entry	Adduct	Reaction time (min)	Isolated yield (%)[a]
1	**1**	40	100
2	**2**	25	100
3	**3**	15	100
4	**4**	240	98
5	**5**	30	100
6	**6**	50	100
7	**7**	10	100

[a] No purification by chromatography was necessary.

This experimental procedure directly leads to substances **1–7** in quantitative yields (no co-products were detected in the reaction media), avoiding further chromatography purification. We found that this protocol is also adaptable to the preparation of the bioactives BHA **1–7** on scale up. These crude products are fully purified after a simple filtration on silica gel using hexane–acetate (8:2) as solvent.

2.2. Experimental section

Commercially available reagents were purchased from Aldrich and used without further purification. The compounds synthesized in this work are not new. The adducts **1–7** were characterized using NMR by comparison with the compounds described in literature [10,19,25–29]. ^{1}H and ^{13}C NMR spectra were obtained by using a Mercury Spectra AC 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) in $CDCl_3$ or Varian Spectra VNMR S-500 (100 MHz for ^{13}C). The IR spectra were obtained using spectrophotometer 1600 FT-IR and 2000 FT-IR (Perkin–Elmer). TLC was done by using silica gel Kieselgel 60 (E. Merck) and spots were visualized with short wavelength UV light.

2.3. Experimental procedure

Reactions were carried out using the corresponding aldehydes (1 mmol), 0.4 mL of acrylonitrile (6 mmol) and 1 mmol of DABCO at 0 °C for *x* min (Table 2). After the end of the reaction, the reaction media was directly filtered on silica gel, using AcOEt–hexane (2:8) as solvent and the reaction products were concentrated under reduced pressure. The products are ready to be bioevaluated as they are by using this procedure.

2.4. A scale up procedure to BHA

Reactions were also carried out using, for example, *m*-nitrobenzaldehyde 0.1 mol (15.1 g), 40 mL of acrylonitrile and 1 equiv. of DABCO at 0 °C for 30 min. The reaction mixture was filtered into silica gel (150 g), using EtOAc–hexane (1 L; 2:8 to 1:1, respectively, of the solvent) and concentrated under reduced pressure (20.2 g of **2**; 100% yield). After, DABCO could be easily recycled through silica gel using 500 mL of ethanol 96° as solvent and concentrated under reduced pressure (95% recyclable of DABCO).

2.5. Spectroscopic data

2.5.1. 2-[Hydroxy(2-nitrophenyl)methyl]acrylonitrile (*1*)

IR (KBr): 3345, 2228, 1348, 1609, 1520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (dd, $J = 8.0/1.4$ Hz, 1H); 7.84 (dd, $J = 6.0/1.8$, 1H); 7.72 (ddd, $J = 8.0/1.8/1.4$ Hz, 1H); 7.52 (ddd, $J = 8.0/1.6/1.4$ Hz, 1H); 6.12 (d, $J = 1.4$ Hz, 1H); 6.09 (d, $J = 1.2$ Hz, 1H); 5.98 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.13 (1C), 116.51 (1C), 124.30 (1C), 125.07 (1C), 129.11 (1C), 129.71 (1C), 132.03 (1C), 134.16 (1C), 134.30 (1C), 147.93 (1C).

2.5.2. 2-[Hydroxy(3-nitrophenyl)methyl]acrylonitrile (*2*)

IR (KBr): 3345, 3105, 2239, 1583, 1520, 1348 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (dd, $J = 1.8/1.6$ Hz, 1H); 8.18 (ddd, $J = 8.0/1.0/1.2$ Hz, 1H); 7.57 (t, $J = 8.0$ Hz, 1H); 7.75 (ddd, $J = 7.8/1.6$ Hz, 1H); 6.09 (d, $J = 0.8$ Hz, 1H); 6.20 (d, $J = 1.6$ Hz, 1H); 5.43 (s, 1H); 3.02 (br s, 1H, CH*OH*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.66 (1C), 116.31 (1C), 121.14 (1C), 123.35 (1C), 125.01 (1C), 129.73 (1C), 131.52 (1C), 132.53 (1C), 141.21 (1C), 147.98 (1C).

2.5.3. 2-[Hydroxy(4-nitrophenyl)methyl]acrylonitrile (*3*)

IR (KBr): 3447, 3115, 2228, 1599, 1520, 1348, 736 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21(d, $J = 8.8$ Hz, 2H); 7.58 (d, $J = 9.0$ Hz, 2H); 6.07 (d, $J = 0.8$ Hz, 1H); 6.16 (d, $J = 0.6$ Hz, 1H); 5.42 (s, 1H); 3.23 (br s,1H, CH*OH*). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 73.01; 116.62; 123.92 (2C); 126.13; 127.34 (2C); 130.51; 146.80; 147.82.

2.5.4. 2-[Hydroxy(4-bromophenyl)methyl]acrylonitrile (*4*)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.54 (dd, $J = 6.0/2.0$ Hz, 2H); 7.28 (dd, $J = 6.0/1.8$ Hz, 2H); 6.11 (d, $J = 1.6$ Hz, 1H); 6.04 (d, $J = 1.0$ Hz, 1H); 5.27 (s, 1H); 2.71 (s, CH*OH*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 73.29 (1C); 116.66 (1C); 122.74 (1C); 125.77 (1C); 128.10 (2C); 130.34 (1C); 131.89 (2C); 138.12 (1C).

2.5.5. 2-[Hydroxy(pyridin-2-yl)methyl]acrylonitrile (*5*)

IR (film) 3200, 2225, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.56 (ddd, $J = 8.0/1.4$ Hz, 1H); 7.75 (ddd, $J = 7.8/7.6/1.6$ Hz, 2H); 7.37 (d, $J = 7.8$ Hz, 1H); 7.29 (ddd, $J = 0.8/1.0/1.2$ Hz, 1H); 5.28 (s,1H); 6.21 (s, 1H); 6.05 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.89 (1C), 116.69 (1C), 121.19 (1C), 123.67 (1C), 125.82 (1C), 130.86 (1C), 137.43, 148.47 (1C), 156.09 (1C).

2.5.6. 2-[Hydroxy(pyridin-3-yl)methyl]acrylonitrile (*6*)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.41 (m, 2H); 7.79 (ddd, $J = 7.8/1.8/1.6$ Hz, 1H); 7.33 (dd, $J = 8.0$ Hz, 1H); 6.05 (d,

$J = 1.0$ Hz, 1H); 6.17 (d, $J = 1.2$, 1H); 5.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.51 (1C), 116.69 (1C), 124.09 (1C), 125.99 (1C), 130.39 (1C), 135.04 (1C), 136.13 (1C), 147.40 (1C), 148.94 (1C).

*2.5.7. 2-[Hydroxy(pyridin-4-yl)methyl]acrylonitrile (**7**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.50 (d, $J = 6$ Hz, 2H); 7.36 (d, $J = 5.8$ Hz, 2H); 5.31(s, 1H); 6.16 (d, $J = 0.6$ Hz, 1H); 6.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.48 (1C), 116.50 (1C), 121.42 (2C), 125.67 (1C), 130.63 (1C), 149.14 (1C), 149.58 (2C).

3. Toxicity against *A. salina* Leach.

The brine shrimp assay has been established as a safe, practical, and economic method for the synthetic compounds bioactivity determination [10,13]. The brine shrimp lethality bioassay was performed following the reported procedure [13]. The growth medium was prepared with filtered sea water in a small tank divided into two compartments. The shrimp eggs were added to the covered compartment and a lamp was placed above the open side of the tank to attract hatched shrimps through perforations in the partition wall. After 48 h, the shrimps mature as nauplii (*A. salina* Leach.) and are ready for the assay. Stock solutions of the test compounds were prepared by dissolving 25 mg in 2 mL of DMSO, and filtered sea water to complete 5 mL of the total volume. Appropriate volumes were then added to tubes with sea water containing 10 nauplii to afford four different drug concentrations in quadruplicate for each one. The control samples containing sea water and DMSO, under the same conditions, do not cause significant brine shrimp mortality. After 24 h of incubation under light, the number of dead and survivor brine shrimps in each tube was counted. The LC_{50} values were calculated by graphics of concentration drug versus lethality percentage using a probit adjust scale. Data analysis was performed with Origin 6.0 software. Tested compounds are considered inactive when $LC_{50} > 1000$ μg/mL [30,31]. We present in Table 3 the results of the toxicities of **1**–**7** in *A. salina* Leach.

4. Bioevaluation on *L. chagasi*

4.1. Results

The compounds of Baylis–Hillman **1**–**7** in the present work showed strong antileishmanial activity against promastigote forms of *L. chagasi* (Fig. 2).

Table 3
Toxicity against *Artemia salina* of the Baylis–Hillman adducts

Adduct	LC_{50} (μg/mL)	LC_{50} (μM)
1	87.8	430.39
2	96.1	471.07
3	36.8	180.39
4	30.9	129.83
5	87.2	545.00
6	88.8	555.00
7	70.9	443.12

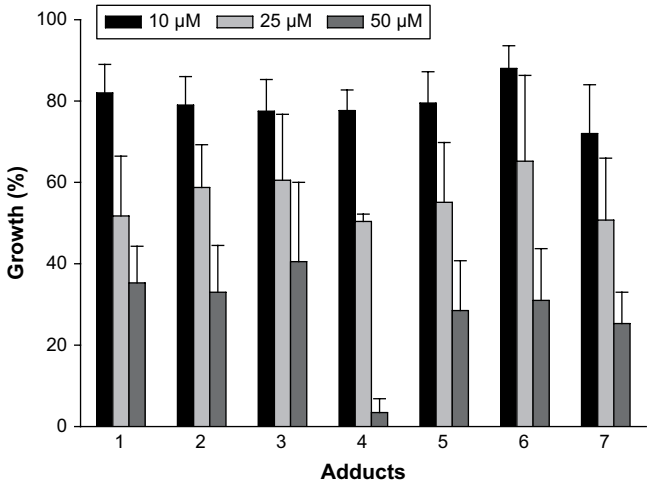


Fig. 2. Effect of different concentrations of Baylis–Hillman adducts against promastigote forms of *L. chagasi*. The parasites were cultivated in Schneider medium at 26 °C for 72 h. The initial number of cells was 1×10^6 promastigotes/mL. The graph represents the meaning of three independent experiments performed in triplicate.

Following a 72 h parasite culture in the presence of the adducts, *L. chagasi* growth was inhibited with IC_{50} values between 25.2 and 38.8 μM (Table 4), **4** being the most active compound ($IC_{50} = 25.2$ μM). Note in Table 4 that all seven adducts revealed high antipromastigote activity.

4.2. Experimental section

Promastigote forms of *L. chagasi* (MCAN/BR/99/JP15) in the log phase of growth (1×10^6 parasites/mL) were incubated at 26 °C in Schneider's Drosophila medium supplemented with 20% of FBS in the presence or absence of different concentrations of **1**–**7** Baylis–Hillman adducts. The reference drug Glucantime® was used as control. After 72 h, parasites were collected, fixed on isotonic solution (10.5 g citric acid, 7.0 g NaCl, 5.0 mL formalin and 1000 mL distilled water) and examined under light microscopy. The inhibitory effect of the fraction on cell growth was estimated by cell counting using a Neubauer chamber. The concentration that inhibits 50% of the growth (IC_{50}) was determined by regression analysis using the program SPSS 8.0 for Windows. All

Table 4
Promastigote antileishmania activity of Baylis–Hillman adducts **1**–**7**

Compounds	IC_{50} (μM)[a]	IC_{50} (μg/mL)
1	38.8	7.9
2	34.6	7.1
3	37.4	7.6
4	25.2	6.0
5	32.0	5.1
6	36.9	5.9
7	30.1	4.8
Glucantime®	–	1620.3[b]

[a] IC_{50} values obtained from a minimum of three separate experiments performed in triplicate are shown.

[b] The reference drug (Glucantime®) used in this study does not show *in vitro* activity on the promastigote forms of *L. chagasi*.

experiments were done at least three times and each experiment was performed in triplicate.

5. Conclusion

We presented in this short communication a very efficient procedure to prepare compounds **1**–**7** (10–40 min reaction time, 0 °C, 98–100%) a new class of antileishmanial compounds. The results reveal the biological activity of seven aromatic Baylis–Hillman adducts **1**–**7** against the promastigote form of *L. chagasi* parasites. The compound 2-[hydroxy(4-bromophenyl)methyl]acrylonitrile (**4**) presented the most toxicity against *A. salina* Leach. indicating that the use of *A. salina* Leach. was efficient to the biological replay control, in our search for antileishmanial substances. The fact of 2-[hydroxy(4-bromophenyl)methyl]acrylonitrile (**4**) was also a very active and safe compound on *L. amazonensis* in our previous article [6], focusing our attention on these new potential drugs on *L. chagasi* ($IC_{50} = 25.2$ μM or 6.0 μg/mL). Finally, we could detach the interesting profile of the pyridine nucleus on **5**, **6** and **7** ($LC_{50} = 5.1$, 5.9 and 4.8 μg/mL, respectively) and the nitro compounds **1**, **2** and **3** ($LC_{50} = 7.9, 7.1$ and 7.6 μg/mL, respectively) as very active ones against the promastigote form of *L. chagasi*.

Acknowledgment

FAPESQ (Fundação de Amparo à Pesquisa do Estado da Paraíba) and CNPq (conselho Nacional de Desenvolvimento Científico e Tecnológico).

References

[1] World Health Organization, Division of Control of Tropical Diseases, <http://www.whoint/tdr/diseases/leish/diseaseinfo.html>, 2007 (accessed May 2007).
[2] B.L. Herwaldt, Lancet 354 (1999) 1191–1199.
[3] S.L. Croft, S. Sundar, A.H. Fairlamb, Clin. Microbiol. Rev. 19 (2006) 111–126.
[4] S.L. Croft, G.H. Coombs, Trends Parasitol. 19 (2003) 502–508.
[5] J.A. Valderrama, C. Zamorano, M.F. González, E. Prina, A. Fournet, Bioorg. Med. Chem. 13 (2005) 4153–4159.
[6] R.O.M.A. de Souza, V.L.P. Pereira, M.F. Muzitano, C.A.B. Falcão, B. Rossi-Bergmann, E.B.A. Filho, M.L.A.A. Vasconcellos, Eur. J. Med. Chem. 42 (2007) 99–102.
[7] M.K. Kundu, N. Sundar, S.K. Kumar, S.V. Bhat, S. Biswas, N. Valecha, Bioorg. Med. Chem. Lett. 9 (1999) 731–736.
[8] L.S.M. Miranda, B.G. Marinho, S.G. Leitão, M.E. Matheus, P.D. Fernandes, M.L.A.A. Vasconcellos, Bioorg. Med. Chem. Lett. 14 (2004) 1573–1575.
[9] L.S.M. Miranda, B.G. Marinho, S.G. Leitão, M.E. Matheus, P.D. Fernandes, M.L.A.A. Vasconcellos, N.M. Gomes, Eur. J. Pharmacol. 550 (2006) 47–53.
[10] M.L.A.A. Vasconcellos, T.M.S. Silva, C.A. Câmara, R.M. Martins, K.M. Lacerda, H.M. Lopes, V.L.P. Pereira, R.O.M.A. de Souza, L.T.C. Crespo, Pest. Manag. Sci. 62 (2006) 288–292.
[11] R.O.M.A. de Souza, B.A. Meireles, L.S. Sequeira, M.L.A.A. Vasconcellos, Synthesis (2004) 1595–1600.
[12] R.O.M.A. de Souza, P.H. Fregadolli, L.C. Aguiar, K.M. Gonçalves, V.L.P. Pereira, L.C. Filho, P.M. Esteves, M.L.A.A. Vasconcellos, O.A.C. Antunes, Lett. Org. Chem. 3 (2006) 936–939.
[13] T.P. Barbosa, C.A. Camara, T.M.S. Silva, R.M. Martins, A.C. Pinto, M.D. Vargas, Bioorg. Med. Chem. 13 (2005) 6464–6469.
[14] A.J.M. Caldas, D.R.C. Silva, C.C.R. Pereira, P.M.S. Nunes, B.P. Silva, A.A.M. Silva, A. Barral, J.M.L. Costa, Rev. Soc. Bras. Med. Trop. 34 (2001) 445–451.
[15] A.B. Baylis, M.E.D. Hillman, Chem. Abstr. 77 (1972) 34174q1; German Patent 2155113, 1972.
[16] D. Basavaiah, J. Rao, T. Satyanarayana, Chem. Rev. 103 (2003) 811–891.
[17] F. Coelho, W.P. Almeida, D. Veronese, C.R. Mateus, E.C.S. Lopes, R.C. Rossi, G.P.C. Silveira, C.H. Pavam, Tetrahedron 58 (2002) 7437–7447.
[18] S. Rafel, J.W. Leahy, J. Org. Chem. 62 (1997) 1521–1522.
[19] R.O.M.A. de Souza, M.L.A.A. Vasconcellos, Synth. Commun. 33 (2003) 1383–1389.
[20] R.O.M.A. de Souza, M.L.A.A. Vasconcellos, Catal. Commun. 5 (2004) 21–24.
[21] L.S. Santos, C.H. Pavam, W.P. Almeida, F. Coelho, M.N. Eberlin, Angew. Chem., Int. Ed. 43 (2004) 4330–4333.
[22] J.S. Hill, N.S. Isaacs, Tetrahedron Lett. 27 (1986) 5007–5010.
[23] K.E. Price, S.J. Broadwater, B.J. Walker, D.T. McQuade, J. Org. Chem. 70 (2005) 3980–3987.
[24] V.K. Aggarwal, S.Y. Fulford, G.C. Lloyd-Jones, Angew. Chem., Int. Ed. 44 (2005) 1706–1708.
[25] C. Yu, B. Liu, L. Hu, J. Org. Chem. 66 (2001) 5413–5418.
[26] Z. San-Hu, C. Zhao-Bin, Synth. Commun. 35 (2005) 3045–3053.
[27] M. Shi, C.-Q. Li, J.-K. Jiang, Tetrahedron 59 (2003) 1181–1189.
[28] Z. Sanhu, C. Zhaobin, Synth. Commun. 35 (2005) 121–127.
[29] P. VanHaeke, G. Persoone, Colloq. Inst. Natl. Saute Rec. Med. 106 (1982) 359–361.
[30] M.F. Cavalcante, M.C.C. de Oliveira, J.R. Velandia, A. Echevarria, Quim. Nova 23 (2000) 20–22.
[31] B.N. Meyer, N.R. Ferrigini, J.E. Putnan, L.B. Jacobsen, D.E. Nichols, J.L. McLaughlin, J. Med. Plant. Res. 45 (1982) 31–34.