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# Gibbilimbol analogues as antiparasitic agents—Synthesis and biological activity against *Trypanosoma cruzi* and *Leishmania* (*L.*) *infantum*

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ABSTRACT

The essential oils from leaves of *Piper malacophyllum* (Piperaceae) showed to be mainly composed by two alkenylphenol derivatives: gibbilimbols A and B. After isolation and structural characterization by NMR and MS data analysis, both compounds were evaluated against promastigote/amastigote forms of *Leishmania* (*L.*) *infantum* as well as trypomastigote/amastigote forms of *Trypanosoma cruzi*. The obtained results indicated that gibbilimbol B displayed potential against the tested parasites and low toxicity to mammalian cells, stimulating the preparation of several quite simple synthetic analogues in order to improve its activity and to explore the preliminary structure–activity relationships (SAR) data. Among the prepared derivatives, compound **LINS03003** (*n*-octyl-4-hydroxybenzylamine) displayed the most potent $IC_{50}$ values of 5.5 and 1.8 μM against amastigotes of *T. cruzi* and *L.* (*L.*) *infantum*, respectively, indicating higher activity than the natural prototype. In addition, this compound showed remarkable selectivity index (SI) towards the intracellular forms of *Leishmania* (SI = 13.1) and *T. cruzi* (SI = 4.3). Therefore, this work indicated that preparation of synthetic compounds structurally based in the bioactive natural products could be an interesting source of novel and selective compounds against these protozoan parasites.

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Leishmaniasis and American trypanosomiasis (Chagas disease) are tropical diseases caused by protozoan parasites belonging to *Leishmania* and *Trypanosoma* genus.[1–4] Nowadays there is a reduced number of drugs to the treat these diseases, which include highly toxic compounds such as pentamidine, amphotericin B, miltefosine and nitroheterocyclic compounds (benznidazole and nifurtimox), demonstrating the urgent necessity of novel and alternative treatments.[5–7] Prospection of pharmacologically active metabolites from plant species could be considered an interesting approach to discovery of prototypes to be used in the development of the new drugs to the treatment of parasitic diseases, mainly those used in the ethnopharmacological point of view.[8–10] In a previous work,[11] our group reported the antiparasitic activity of gibbilimbol B, an alkylphenol derivative isolated from leaves of *Piper malacophyllum* (Piperaceae) against promastigotes and amastigotes of *Leishmania* (*L.*) *infantum*, as well as *Trypanosoma cruzi* trypomastigotes. Our previous studies demonstrated that gibbilimbol B affected the permeability of plasma membrane of *L.* (*L.*) *infantum*, leading to cell death, a similar effect observed by the clinical used drug amphotericin B. This action may be attributed to its amphipathic characteristic that resembles membrane phospholipids, where the phenolic hydroxyl can be directed to the aqueous layer and the alkyl chain to the hydrophobic environment of membrane.

In continuation to our studies with *P. malacophyllum*, the essential oil from leaves showed to be composed by additional amounts of gibbilimbol B as well as by its isomeric derivative gibbilimbol A (Fig. 1). After several chromatographic steps,[12] both compounds were separated and their antiparasitic activities were individually evaluated. As can be seen in Table 1, gibbilimbol A displayed weak activity against amastigote forms of *L.* (*L.*) *infantum* and trypomastigote forms of *T. cruzi*, with $IC_{50}$ of 135.7 and 102.5 μM, respectively. Otherwise, gibbilimbol B, an isomeric derivative of gibbilimbol A (with double bond at C-4′ instead of C-3′) displayed higher activity against the tested parasites and low toxicity to mammalian cells. The result suggests the presence of unsaturation close to aromatic ring leads to improved activity, and thus other

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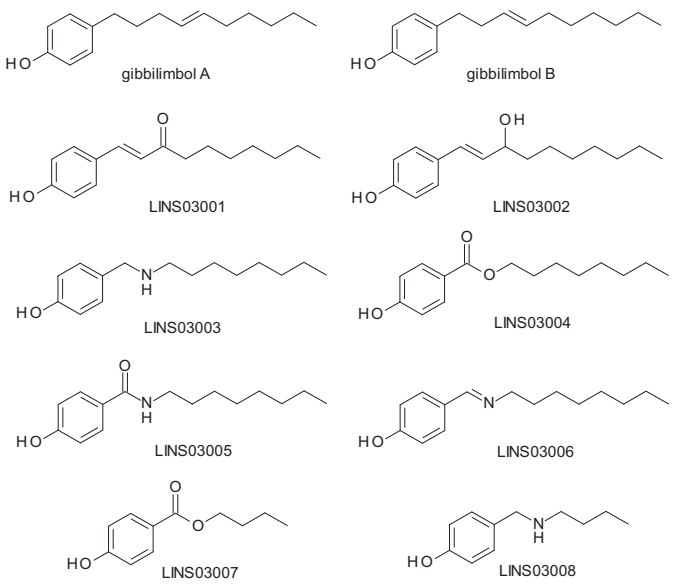



**Figure 1.** Structures of gibbilimbols A/B and related analogues (**1**–**8**).

functional groups in this region should be explored. Therefore, this work aimed the preparation of synthetic compounds structurally related to gibbilimbol B and the evaluation of the antiparasitic activity against *L.* (*L.*) *infantum*/*T. cruzi*, extracellular and intracellular forms and mammalian cytotoxicity, as well as to explore the structure–activity relationships (SAR).

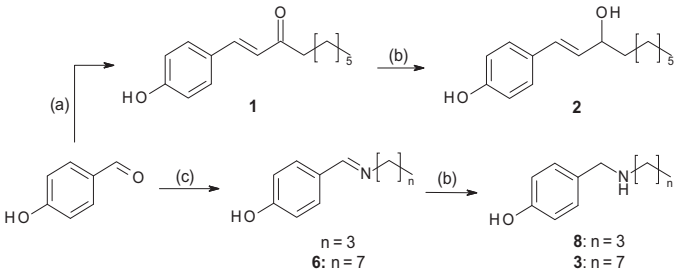
Considering the alkyl side chain nature of gibbilimbol derivatives and the previous reported targeting ability to *Leishmania* plasma membrane,[11] interactions with specific membrane components such as ergosterol could be plausible effect of these compounds. Thus, eight analogues of gibbilimbols (LINS0300**X**, **1**–**8**) were designed (Fig. 1) to evaluate possible interactions by hydrogen-bonding and the role of the length of side chain (alkenyl or alkyl) in the activity. Polar functional groups were inserted in this moiety to provide additional interaction sites, so derivatives possessing carbonyl (**1**), hydroxyl (**2**) and amine (**3**) groups were designed. As metabolic deactivation is also desirable in a future drug to avoid excessive toxicity to mammalian cells,[13] ester (**4**), amide (**5**) and imine (**6**) derivatives were also proposed, since they can be easily hydrolyzed in vivo. Moreover, lower homologues of these compounds (**7** and **8**) were also synthesized and evaluated.

Compounds **1**–**8** were synthesized according to the Schemes 1 and 2, through classical methods which conducted to excellent yields.[14] Compound **1** was obtained through aldol condensation of 4-hydroxybenzaldehyde and 2-nonanone under basic conditions.[15] This compound was then used to obtain **2** by reduction of carbonyl group using sodium triacetoxyborohydride (STAB) prepared in situ prior to reduction.[16] Interestingly, only the product of 1,2-reduction was observed. Generally α,β-unsaturated ketones can be reduced to both 1,2- and 1,4-reduction products when reacted with borohydride.[17] However, the distribution of these products is variable. It is well known STAB is a 1,2-selective agent in the α,β-unsaturated aldehydes reduction. However it is not a good reducing agent for α,β-unsaturated ketones.[18] Possibly the extended conjugation to the aromatic ring played the role to obtain selectively the 1,2-reduction product **2**.

**Table 1**
Antiparasitic activities of gibbilimbols A/B, and of the synthetic derivatives **1**–**8** against trypomastigote/amastigote forms of *T. cruzi* and promastigote/amastigote forms of *L.* (*L.*) *infantum*

| Compounds | $IC_{50}$ μM (95% CI) | | | | $CC_{50}$ μM (95% CI) | SI[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *T. cruzi* trypomastigotes | *T. cruzi* amastigotes | *L. (L.) infantum* promastigotes | *L. (L.) infantum* amastigotes | NCTC cells[a] | TCT | TCA | LIP | LIA |
| **1** | 11.8 (10.1–13.1) | 22.5 (19.1–26.5) | 82.7 (74.3–92.2) | NA | 82.8 (66.5–103.1) | 7.0 | 3.7 | 1.0 | – |
| **2** | 6.1 (5.5–6.7) | NA | 125.1 (90.3–174.4) | NA | 49.5 (32.9–74.4) | 8.1 | – | 0.4 | – |
| **3** | 17.0 (14.0–20.8) | 5.5 (4.6–6.5) | 28.6 (25.3–32.6) | 1.8 (1.1–2.9) | 23.5 (15.5–82.9) | 1.4 | 4.3 | 0.8 | 13.1 |
| **4** | 4.5 (3.7–5.4) | NA | 123.4 (114.0–133.0) | NA | 130.3 (107.9–157.4) | 29.0 | – | 1.1 | – |
| **5** | 26.5 (22.6–31.2) | NA | 45.1 (38.8–52.3) | NA | 45.4 (27.3–75.3) | 1.7 | – | 1.0 | – |
| **6** | NA | NA | 19.9 (17.5–22.6) | NA | 99.2 (79.3–124.3) | – | – | 5.0 | – |
| **7** | NA | 26.4 (20.4–33.3) | NA | NA | 167.8 (98.3–286.4) | – | 6.4 | – | – |
| **8** | NA | NA | 31.6 (24.1–41.5) | NA | >300 | – | – | 9.5 | – |
| Gibbilimbol A | 102.5 (74.5–122.7) | NA | NA | 135.7 (92.1–163.5) | 224.6 (201.3–256.9) | 2.2 | – | – | 1.7 |
| Gibbilimbol B[c] | 75.3 (62.3–90.9) | NA | 100.4 (82.6–121.8) | 94.9 (73.2–123.2) | 254.1 (217.9–296.3) | 3.4 | – | 2.5 | 2.7 |
| Miltefosine | ND | ND | 16.7 (13.0–21.5) | 16.4 (15.4–17.4) | 241.4 (206.9–281.6) | – | – | 14.5 | 14.7 |
| Benznidazole | 440.7 (406.1–478.3) | 230.3 (176.2–301.1) | – | – | 269.9 (414.9–532.1) | 0.6 | 1.2 | – | – |

$IC_{50}$: 50% inhibitory concentration.
NA: not active.
ND: not determined.
[a] $CC_{50}$: 50% cytotoxic concentration.
[b] SI: selectivity index calculated from $CC_{50}/IC_{50}$ (TCT: *T. cruzi* trypomastigotes, TCA: *T. cruzi* amastigotes, LIP: *L.* (*L.*) *infantum* promastigotes, LIA: *L.* (*L.*) *infantum* amastigotes).
[c] Available from Oliveira et al.[11]




**Scheme 1.** Reagents and conditions of preparation of compounds **1**–**3**, **6** and **8**. (a) 2-nonanone, NaOH 40%, overnight; (b) STAB, AcOH, 4 h; (c) butylamine or octylamine, THF, 60 °C, 1 h.

To obtain the imine derivatives **6** and **8**, 4-hydroxybenzaldehyde and the corresponding amines were mixed together in equimolar amounts, under ultrasonic irradiation.[19] This reaction led to quantitative conversion of the products and obviously excellent yields. Starting from **6** the compound **3** was obtained through reduction of the imine group using STAB.[16] The lower homologue **8** was also obtained by the same way.

Finally, the esters **4** and **7** were obtained through classical Fischer esterification using the 4-hydroxybenzoic acid and the corresponding alcohol.[20] In case of compound **4**, 1-octanol was used in excess in toluene, while 1-butanol was used as solvent in the synthesis of **7**. Otherwise, amide derivative **5** was obtained by the reaction of 1-octylamine with the acyl chloride previously obtained reacting the 4-hydroxybenzoic acid with thionyl chloride.[21]

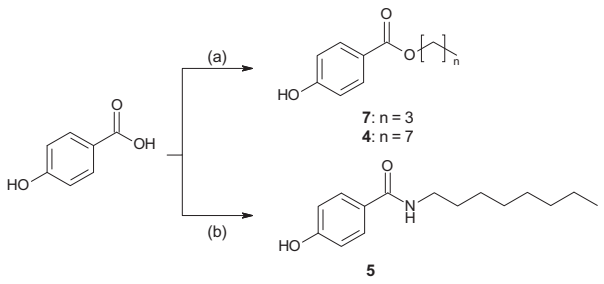
The antiprotozoal activity of gibbilimbol A and compounds **1**–**8** was evaluated in vitro against trypomastigote/amastigote forms of *T. cruzi* as well as promastigote/amastigote forms of *L.* (*L.*) *infantum* using the method from Oliveira et al.[11] Benznidazole and miltefosine were used as positive control against *T. cruzi* and *L.* (*L.*) *infantum*, respectively. Cytotoxicity was determined in mammalian NCTC clone 929 cells as previously described.[11]

Among the eight designed analogues, compounds **1**–**5** displayed activity against the trypomastigotes of *T. cruzi* with $IC_{50}$ values in a range between 4 and 26 μM; the natural compound gibbilimbol A also presented activity, but showing a reduced potential ($IC_{50}$ = 102 μM). The active compounds **1**–**5** showed 16–97-fold more potency than the clinical used drug benznidazole against the trypomastigotes (Y strain), suggesting the presence of functional groups in the tail moiety can significantly influence the activity. Although gibbilimbol B showed the weakest potency in a previous study, it was 4-fold more active than benznidazole. Among them, compounds **1** and **3** also demonstrated activity against the intracellular amastigotes of *T. cruzi*, showing $IC_{50}$ values of 22.5 and 5.5 μM, respectively. Although compounds **2** and **4** were the most potent against the trypomastigotes, with $IC_{50}$ values of 6.1 and 4.5 μM, respectively, it showed no activity against the intracellular amastigotes. The lack of activity against intracellular forms could be ascribed to low penetration in host cells, metabolization inside macrophages generating inactive metabolites, but also to enzymatic differences between trypomastigotes and amastigotes,[22] which may have resulted in low susceptibility of the parasite to the gibbilimbol derivatives. When tested against murine fibroblasts for mammalian cytotoxicity, compounds **1**, **2** and **4** demonstrated selectivity when one considers the trypomastigotes, with an index of 7.0, 8.1 and 29.0, respectively. The latter is the most selective compound in the series regarding the trypomastigote form of *T. cruzi*. Compounds **1** and **3** demonstrated selectivity index of 3.7 and 4.3 to intracellular amastigote form. Based on the structures of most potent compounds, it is possible to suggest that the presence of functional groups in the tail moiety can significantly improve the activity, although a higher toxicity to mammalian cells was also observed when compared to the natural prototypes. However, derivatives **7** and **8** were not active in this evolutionary form of the parasite (trypomastigotes), but have also shown the lowest toxicity to mammalian cells among the designed analogues. Trypomastigotes are clinical forms of the parasite abundant in acute phase of the Chagas' disease. Furthermore, drugs that only target the replicating stages of the parasite may leave non-replicating forms, such as trypomastigotes, capable of maintaining infections long after the end of the treatment.[23]

Interestingly, the natural compound gibbilimbol B showed weak activity against trypomastigotes and was not active against *T. cruzi* amastigotes. The modifications proposed in this study improved the effectiveness of this natural prototype, since the analogues **1** and **3** presented not only activity, but also selectivity towards the intracellular amastigotes of *T. cruzi*, which are responsible for the chronic phase of the disease and a target stage considered for drug discovery studies.[24] It is expected that a good antitrypanosomal agent possess high potency ($IC_{50}$ <10 μM) against the amastigotes, together with adequate physicochemical properties to achieve the intracellular environment.[24] This can be a possible explanation to the poor activity (and also to the low cytotoxicity) of homologues **7** and **8**, since they are less lipophilic than the higher homologues and indeed may show poor penetration into the cells. Considering the effectiveness of compound **3** against both *T. cruzi* forms, further structural modifications may contribute to the improvement of the biological selectivity.

Leishmania parasites were also susceptible to gibbilimbols and their derivatives. Our data demonstrated that the isolated compound gibbilimbol A was also active against the intracellular amastigotes ($IC_{50}$ = 135.7 μM), but it was about 1.4-fold less potent than the previous reported gibbilimbol B.[11] Except for compound **7**, all derivatives demonstrated activity against the extracellular promastigotes of *L.* (*L.*) *infantum,* with $IC_{50}$ values in a range between 31 and 123 μM. The natural gibbilimbol A showed lack of activity against the promastigotes. Compound **6** demonstrated the highest activity against promastigotes, similarly to the standard drug miltefosine. Among the designed derivatives, compound **3** demonstrated potential against the intracellular amastigotes, with an $IC_{50}$ value of 1.8 μM, 52-fold higher potency against the intracellular amastigotes in comparison to natural prototype gibbilimbol B. Furthermore, a high selectivity index (SI) value of 13 was found, close to the standard drug miltefosine. Structural differences between gibbilimbol B and derivative **3** suggested an improvement on the antiparasitic effectiveness and conferred selectivity against both *Leishmania* and *T. cruzi* intracellular amastigotes. Further exploitation of **3** may contribute to improve the potency and selectivity.

Our results suggest that the presence of a nitrogen atom in the position C-2′ of the side chain of phenolic derivatives significantly improved the activity against *L.* (*L.*) *infantum* promastigotes, as




**Scheme 2.** Reagents and conditions to preparation of compounds **4**, **5** and **7**. (a) 1-butanol or 1-octanol, $H_2SO_4$ (cat.), toluene, overnight; (b) $SOCl_2$, triethylamine, toluene, 60 °C, 2 h, then 1-octylamine, overnight.

observed to the compounds **3**, **5**, **6** and **8**. Other substitution patterns led to an activity close to the observed to natural gibbilimbols A and B. Conversely, compounds presenting oxygen in C-2′ position, as well as other oxygenated functions directed to outside of the tail (carbonyl or hydroxyl groups) led to poor activity. Considering the differences in the antiparasitic activity of natural prototypes and the new derivatives, future studies towards the discovery of mechanism of action may represent a tool to improve the selectivity of these compounds.

In conclusion, although the toxicity of the gibbilimbol derivatives was enhanced when compared to the natural scaffold (gibbilimbol B), our proposed modifications resulted in higher potency against both parasites, also increasing the selectivity in the clinically relevant form of these parasites (intracellular amastigotes). In addition, the insertion of functional groups close to aromatic ring led to more active compounds. Considering that gibbilimbol B is a quite simple structure, further exploratory studies regarding the mode of action of these compounds should be made, as well as additional molecular modifications to enlarge the SAR data.

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## References and notes

1. Engels, D.; Savioli, L. *Trends Parasitol.* **2006**, *22*, 363.
2. Barrett, M. P.; Croft, S. L. *Br. Med. Bull.* **2012**, *104*, 175.
3. Ketter, H.; Marjanovic, S. *Nat. Rev. Drug Disc.* **2004**, *3*, 171.
4. Den Boer, M.; Argaw, D.; Jannin, J.; Alvar, J. *Clin. Microbiol. Infect.* **2011**, *17*, 1471.
5. Soares-Bezerra, R. J.; Leon, L.; Genestra, M. *Braz. J. Pharm. Sci.* **2004**, *40*, 139.
6. Rosenthal, E.; Marty, P. *J. Postgrad. Med.* **2003**, *49*, 61.
7. Croft, S. L.; Sundar, S.; Fairlamb, A. H. *Clin. Microbiol. Rev.* **2006**, *19*, 111.
8. Schmidt, T. J.; Khalid, S. A.; Romanha, A. J.; Alves, T. M.; Biavatti, M. W.; Brun, R.; da Costa, F. B.; de Castro, S. L.; Ferreira, V. F.; Lacerda, M. V.; Lago, J. H. G.; Leon, L. L.; Lopes, N. P.; Amorim, R. C. N.; Niehues, M.; Ogungbe, O. V.; Pohlit, A. M.; Scotti, M. T.; Setzer, W. N.; Soeiro, M. N. C.; Steindel, M.; Tempone, A. *Curr. Med. Chem.* **2012**, *19*, 2128.
9. Schmidt, T. J.; Khalid, S. A.; Romanha, A. J.; Alves, T. M.; Biavatti, M. W.; Brun, R.; da Costa, F. B.; Castro, S. L.; Ferreira, V. F.; Lacerda, M. V.; Lago, J. H. G.; Leon, L. L.; Lopes, N. P.; Amorim, R. C. N.; Niehues, M.; Ogungbe, O. V.; Pohlit, A. M.; Scotti, M. T.; Setzer, W. N.; Soeiro, M. N. C.; Steindel, M.; Tempone, A. *Curr. Med. Chem.* **2012**, *19*, 2176.
10. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311.
11. Oliveira, A.; Mesquita, J. T.; Tempone, A. G.; Lago, J. H. G.; Guimarães, E. F.; Kato, M. J. *Exp. Parasitol.* **2012**, *132*, 383.
12. Fresh leaves (~100 g) of *P. malacophyllum* were subjected to hydro-distillation to afford 260 mg of crude essential oil. A portion of the leaf oil (200 mg) was submitted to column chromatography over silica gel $CH_2Cl_2$ and $CH_2Cl_2$/MeOH (99:1) to afford seven groups (A–G). Group D (65 mg) was purified by prep. TLC ($SiO_2$ coated with $AgNO_3$) to afford gibbilimbols A (3.5 mg) and B (41.1 mg). *Gibbilimbol A:* pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.05 (d, 2H, $J$ = 8.5 Hz), 6.75 (d, 2H, $J$ = 8.5 Hz), 5.41 (m, 2H), 2.54 (t, 1H, $J$ = 7.7 Hz), 2.01 (m, 4H), 1.64 (m, 2H), 1.29 (m, 6H), 0.89 (t, 3H, $J$ = 6.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 153.4, 134.9, 131.0, 129.8, 129.5, 115.0, 34.4, 32.6, 32.0, 31.6, 31.4, 29.3, 22.5, 14.1; LREIMS $m/z$ (rel. int.) 232 $[M]^+$ (19), 133 (30), 121 (16), 120 (100), 107 (68); *Gibbilimbol B:* pale yellow oil; $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.05 (d, 2H, $J$ = 8.5 Hz), 6.75 (d, 2H, $J$ = 8.5 Hz), 5.43 (m, 2H), 2.60 (t, 1H, $J$ = 7.7 Hz), 2.27 (m, 2H), 1.98 (m, 2H), 1.27 (m, 8H), 0.89 (t, 3H, $J$ = 6.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 153.4, 134.5, 131.2, 129.5, 129.3, 115.0, 35.2, 34.7, 32.6, 31.8, 29.5, 28.8, 22.6, 14.1; LREIMS $m/z$ (rel. int.) 232 $[M]^+$ (12), 204 (8), 133 (5), 120 (15), 107 (100).
13. *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: Oxford, 2008.
14. *Yields and characterization data for the compounds* **1**: yellowish solid (40%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.52 (d, 1H, $J$ = 16.1 Hz), 7.46 (d, 2H, $J$ = 8.6 Hz), 6.87 (d, 2H, $J$ = 8.6 Hz), 6.63 (d, 1H, $J$ = 16.1 Hz), 5.84 (br s, 1H), 2.64 (t, 2H, $J$ = 7.4 Hz), 1.55–1.75 (m, 2H), 1.21–1.42 (m, 8H), 0.88 (t, 3H, $J$ = 6.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 201.3, 158.0, 142.5, 130.2, 127.3, 124.0, 116.0, 40.9, 31.7, 29.3, 29.1, 24.6, 22.6, 14.1; HRMS calculated 246.1620; found 245.1560 $[M-H^+]$; **2**: yellowish oil (52%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.27 (d, 2H, $J$ = 8.0 Hz), 6.78 (d, 2H, $J$ = 8.0 Hz), 6.50 (d, 1H, $J$ = 15.6 Hz), 6.07 (dd, 1H, $J$ = 15.6, 7.1 Hz), 4.88 (br s, 1H), 4.25 (q, 1H, $J$ = 6.5 Hz), 1.50–1.72 (m, 4H), 1.16–1.48 (m, 8H), 0.88 (t, 3H, $J$ = 6.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 159.3, 133.5, 130.7, 130.1, 130.0, 116.1, 71.8, 36.8, 31.9, 29.8, 29.5, 25.3, 22.7, 14.1; HRMS calculated 248.1776; found 247.1631 $[M-H^+]$; **3**: yellowish oil (70%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.08 (d, 2H, $J$ = 8.6 Hz), 6.60 (d, 2H, $J$ = 8.6 Hz), 3.68 (s, 2H), 3.64 (br s, 2H), 2.67 (t, 2H, $J$ = 7.3 Hz), 1.54 (quint., 2H, $J$ = 7.1 Hz), 1.16–1.38 (m, 10H), 0.87 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 155.8, 130.6, 129.7, 115.8, 53.5, 49.5, 31.8, 29.6, 29.5, 29.2, 27.3, 22.6, 14.1; HRMS calculated 235.1936; found 236.2008 $[M+H^+]$; **4**: colorless oil (82%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.96 (d, 2H, $J$ = 8.9 Hz), 6.87 (d, 2H, $J$ = 8.9 Hz), 6.07 (br s, 1H), 4.28 (t, 2H, $J$ = 6.7 Hz), 1.68–1.83 (m, 2H), 1.20–1.50 (m, 10H), 0.88 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 166.8, 160.0, 131.9, 121.8, 115.2, 65.1, 31.8, 29.3, 29.2, 28.7, 26.1, 22.6, 14.1; HRMS calculated 250.1568; found 249.1512 $[M-H^+]$; **5**: yellowish oil (71%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.60 (d, 2H, $J$ = 8.2 Hz), 6.87 (d, 2H, $J$ = 8.2 Hz), 6.28 (t, 1H, $J$ = 5.3 Hz), 3.42 (q, 2H, $J$ = 6.6 Hz), 1.59 (quint., 2H, $J$ = 7.2 Hz), 1.15–1.40 (m, 10H), 0.87 (t, 3H, $J$ = 6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 168.3, 160.2, 128.8, 125.6, 115.6, 40.3, 31.8, 29.3, 29.2, 27.0, 26.6, 22.6, 14.1; HRMS calculated 249.1728; found 248.1649 $[M-H^+]$; **6**: white solid (60%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 8.15 (s, 1H), 7.49 (d, 2H, $J$ = 8.6 Hz), 6.67 (d, 2H, $J$ = 8.8 Hz), 6.40 (br s, 1H), 3.57 (t, 2H, $J$ = 6.9 Hz), 1.68 (quint., 2H, $J$ = 6.9 Hz), 1.30-1.52 (m, 10H), 0.86 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 162.4, 160.4, 130.3, 126.5, 116.0, 60.8, 31.8, 30.7, 29.3, 29.2, 27.2, 22.6, 14.1; HRMS calculated 233.1779; found 232.1702 $[M-H^+]$; **7:** white solid (85%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.95 (d, 2H, $J$ = 8.1 Hz), 6.88 (d, 2H, $J$ = 8.1 Hz), 6.14 (s, 1H), 4.30 (t, 2H, $J$ = 6.6 Hz), 1.80-1.69 (m, 2H), 1.47 (sext., 2H, $J$ = 7.4 Hz), 0.97 (t, 3H, $J$ = 7.4 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 167.9, 159.9, 131.9, 122.8, 115.2, 64.8, 30.8, 19.3, 13.8; HRMS calculated 194.0942; found 193.0835 $[M-H^+]$; **8:** yellowish oil (70%); $^1$H NMR (300 MHz, $CDCl_3$, TMS, ppm) $\delta$ 7.06 (d, 2H, $J$ = 8.1 Hz), 6.59 (d, 2H, $J$ = 8.1 Hz), 5.48 (br s, 1H), 3.69 (s, 2H), 2.69 (t, 2H, $J$ = 7.4 Hz), 1.59–1.47 (m, 2H), 1.32 (sext., 2H, $J$ = 7.2 Hz), 0.89 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS, ppm) $\delta$ 156.3, 129.8, 129.7, 115.9, 53.4, 49.1, 31.5, 20.5, 13.9; HRMS calculated 179.1310; found 180.1408 $[M+H^+]$.
15. Ramachandra, M. S.; Subbaraju, G. V. *J. Asian Nat. Prod. Res.* **2006**, *8*, 683.
16. Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 158.
17. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
18. Gribble, G. W.; Abdel-Magid, A. F. *Sodium Triacetoxyborohydride in the Encyclopedia of Reagents for Organic Synthesis*, 2007. http://dx.doi.org/10.1002/9780470842898.rs112.pub2.
19. Marchand, P.; Griffe, L.; Poupot, M.; Turrin, C. O.; Bacquet, G.; Fournié, J. J.; Majoral, J. P.; Poupot, R.; Caminade, A. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3963.
20. Owen, C.; Jamos, K.; Sampson, L.; Ahmed, S. *J. Pharm. Pharmacol.* **2003**, *55*, 85.
21. Fernandes, J. P. S.; Pavan, F. R.; Leite, C. Q. F.; Felli, V. M. A. *Saudi Pharm. J.* **2013**, *22*, 376.
22. Reimão, J. Q.; Migotto, A. E.; Kossuga, M. H.; Berlinck, R. G.; Tempone, A. G. *Parasitol. Res.* **2008**, *103*, 1445.
23. Katsuno, K.; Burrows, J. N.; Duncan, K.; Huijsduijnen, R. H.; Kaneko, T.; Kita, K.; Mowbray, C. E.; Schmatz, D.; Warner, P.; Slingsby, B. T. *Nat. Rev. Drug Disc.* **2015**, *14*, 751.
24. Don, R.; Ioset, J. R. *Parasitology* **2014**, *141*, 140.