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SHORT COMMUNICATION

Activity of natural and synthetic polygodial derivatives against *Trypanosoma cruzi* amastigotes, trypomastigotes and epimastigotes

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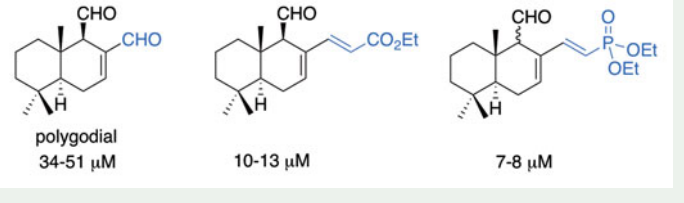
ABSTRACT

Our laboratories have been investigating biological effects of a sesquiterpenoid polygodial and its natural and synthetic analogues. Herein, we report the evaluation of these compounds against the three forms of *Trypanosoma cruzi,* amastigotes, trypomastigotes and epimastigotes. Although polygodial was found to be poorly active, its natural congener epipolygodial and synthetic Wittig-derived analogues showed low micromolar potency against all three forms of the parasite. Synthetic α,β-unsaturated phosphonate **9** compared favorably with clinically approved drugs benznidazole and nifurtimox, and was effective against trypomastigotes, toward which benznidazole showed no activity.



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Trypanosoma cruzi; polygodial; anti-parasitic; phosphonate; Wittig derivatives; terpenes

1. Introduction

According to the World Health Organization, Chagas disease is one of the seventeen neglected tropical diseases (NTD). Although discovered over a century ago, Chagas disease is treated with only two drugs, benznidazole and nifurtimox, which have limited efficacy (Brener 1979). Thus, there is an urgent need to develop novel more effective therapeutic agents. Natural products have been intensely scrutinized as potential anti-Chagas agents (Charneau et al. 2015; Fritis et al. 2013; Izumi et al. 2011; Lopes et al. 2008; Nkwengoua et al. 2009; Pontual et al. 2017), however, very few

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reports describe activity against the three forms of *T. cruzi*, amastigotes, trypomastigotes and epimastigotes, possibly due to differences in their morphological and functional characteristics (Kollien and Schaub 2000) and difficulty to obtain each in quantity and quality (Fonseca-Berzal et al. 2018).

A bicyclic sesquiterpene polygodial (**1**) was first isolated from *Polygonum hydropiper* L. (Polygonaceae). It contains a characteristic α,β-unsaturated 1,4-dialdehyde functionality that is also shared by over 80 terpenoids isolated from a variety of natural sources (Jonassohn and Sterner 1997). Evidently, these natural products protect the producing organisms from predators (Jonassohn and Sterner 1997), which is consistent with their hot taste to the human tongue and antifeedant activities (Caprioli et al. 1987).

In the course of our studies of biological effects of the polygodial family of compounds, we have isolated (Just et al. 2015; Deans et al. 2014) and prepared (Just et al. 2015; Dasari et al. 2015; De La Chapa et al. 2018) several natural and synthetic polygodial derivatives. Herein, we report the results of this investigation involving the discovery of a synthetic compound rivalling both approved drugs, benznidazole and nifurtimox, in its antiproliferative potency.

2. Results and discussion

Compounds **1–9** were evaluated for growth inhibition against the three forms of CL tdTomato (DTU TcVI) *T. cruzi*, generated as described in Supplementary Material (Fonseca-Berzal et al. 2018; Canavaci et al, 2010) (Table S1). Polygodial (**1**) and 1β-acetoxypolygodial (**3**) showed moderate to poor potency. In contrast, the C9-epimer epipolygodial (**2**) was significantly more potent with the GI_{50} values approaching single micromolar digits against all three forms of the parasite. Clearly, the presence of the dialdehyde structural motif alone is not sufficient for activity and other features, such as the configuration at C9, are also important. Drimendiol (**4**) and (–)-drimenol (**5**), both possessing the unfavorable stereochemistry at C9 and lacking the aldehyde groups, were also poorly active or completely inactive. Although Wittig product **6** was poorly active, compounds **7–9** all showed single digit growth inhibitory potencies, demonstrating that the incorporation of an α,β-unsaturated system can be beneficial for antiparasitic activity. The low micromolar potencies of compounds **7**–**9** compare favourably with other compounds reported in the recent literature (Fritis et al. 2013; Lopes et al. 2008), but the fact that they maintain this potency across all three forms of *T. cruzi* gives them a significant advantage.

Polygodial-derived α,β-unsaturated phosphonate **9** was selected for competition assay against the clinically approved anti-trypanosomal drugs benznidazole and nifurtimox. Figure S1 shows the antiproliferative activity of compound **9**, benznidazole and nifurtimox at 7–8 μM, concentrations representing the GI_{50} values of **9** against epimastigotes, amastigotes and trypomastigotes. Compound **9** was found to be slightly more potent than benznidazole against epimastigotes and amastigotes and significantly more potent against trypomastigotes, for which benznidazole was completely ineffective. Although less potent against epimastigotes and amastigotes than nifurtimox, compound **9** was equally effective at inhibiting growth of trypomastigotes. Overall, the

results show that phosphonate **9** compares favorably with the clinically used anti-trypanosomal drugs, especially against trypomastigotes, the infective form.

To visualize the effects of polygodial analogues on the growth of the parasite in infected human cells, we utilized confocal microscopy. Figure S2A demonstrates that treatment of tdTomato *T. cruzi*-infected human retinal pigment epithelial (ARPE) cells with compound **7**, used at 20 μM causes a significant reduction in the intracellular parasites. Importantly, the ARPE replication/viability is not affected. Figure S2B shows that two successive treatments with compound **9**, used at 5 μM, leads to no signs of the presence of intracellular parasites 7 days after treatment, resulting in long-term cure of the cells.

3. Conclusion

The evaluation of polygodial and its natural and synthetic analogues against *T. cruzi* showed that while polygodial was poorly effective, its natural congener epipolygodial and synthetically-derived Wittig analogues produced low micromolar activity against all three forms of the parasite. Furthermore, a synthetic α,β-unsaturated phosphonate **9** compared favorably with clinically approved drugs benznidazole and nifurtimox, and was effective against trypomastigotes, toward which benznidazole showed no activity. The results of this investigation demonstrate the anti-trypanosomal potential of polygodial analogues and encourage further studies aimed at identification of a lead compound toward pre-clinical development.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Brener Z. 1979. Present status of chemotherapy and chemoprophylaxis of human trypanosomiasis in the Western Hemisphere. Pharm. Ther. 7(1):71–90.

Canavaci AM, Bustamante JM, Padilla AM, Brandan CMP, Simpson LJ, Xu D, Boehlke CL, Tarleton RL. 2010. In vitro and in vivo high-throughput assays for the testing of anti-*Trypanosoma cruzi* compounds. PLoS Negl Trop Dis. 4(7):e740.

Caprioli V, Cimino G, Colle R, Gavagnin M, Sodano G, Spinella A. 1987. Insect antifeedant activity and hot taste for humans of selected natural and synthetic 1,4-dialdehydes. J Nat Prod. 50(2): 146–151.

Charneau S, de Mesquita ML, Marques Dourado Bastos I, Santana JM, de Paula JE, Grellier P, Espindola LS. 2015. In vitro investigation of Brazilian Cerrado plant extract acitivity against Plasomium falciparum, *Trypanosoma cruzi* and *T. brucei* gambiense. Nat Prod Res. 29:1320–1326.

Dasari R, De Carvalho A, Medellin DC, Middleton KN, Hague F, Volmar MNM, Frolova LV, Rossato MF, Mathieu V, Rogelj S. 2015. Wittig derivatization of sesquiterpenoid polygodial leads to cytostatic agents with activity against drug resistant cancer cells and capable of pyrrolylation of primary amines. Eur J Med Chem. 103:226–237.

Deans RM, Gardiner MG, Horne J, Hung AC, Hyland CJT, Just J, Smith JA, Yin J. 2014. Isolation and Characterisation of 1β-Acetoxypolygodial from *Tasmannia lanceolata*. Asian J Org Chem. 3(11):1193–1196.

De La Chapa J, Singha PK, Sallaway M, Self K, Nasreldin R, Dasari R, Hart M, Kornienko A, Just J, Smith JA, et al. 2018. Novel polygodial analogs P3 and P27: efficacious therapeutic agents disrupting mitochondrial function in oral squamous cell carcinoma. Int J Oncol. 53(6):2627–2636.

Fonseca-Berzal C, Arán VJ, Escario JA, Gómez-Barrio A. 2018. Experimental models in Chagas disease: a review of the methodologies applied for screening compounds against *Trypanosoma cruzi*. Parasitol Res. 117(11):3367–3380.

Fritis MC, Lagos CR, Sobarzo NQ, Venegas IM, Sanchez CS, Altamirano HC, Catalan LE, Palma WQ. 2013. Depsides and triterpenes in *Pseudocyphellaria coriifolia* (lichens) and biological activity against *Trypanosoma cruzi*. Nat Prod Res. 27(17):1607–1610.

Izumi E, Ueda-Nakamura T, Dias Filho BP, Veiga JV, Nakamura CV. 2011. Natural products and Chagas' disease: a review of plant compounds studied for activity against *Trypanosoma cruzi*. Nat Prod Rep. 28(4):809–823.

Jonassohn M, Sterner O. 1997. Terpenoid unsaturated 1,4-dialdehydes, occurrence and biological activities. Trends Org. Chem. 6:23–43.

Just J, Jordan TB, Paull B, Bissember AC, Smith JA. 2015. Practical Isolation of Polygodial from Tasmannia lanceolata: a viable scaffold for synthesis. Org Biomol Chem. 13(46):11200–11207.

Kollien A, Schaub G. 2000. The development of *Trypanosoma cruzi* in Triatominae. Parasitol Today (Regul Ed).). 16(9):381–387.

Lopes AA, López SN, Regasini LO, Junior JMB, Ambrósio DL, Kato MJ, da Silva Bolzani V, Cicarelli RMB, Furlan M. 2008. In vitro activity of compounds isolated from *Piper crassinervum* against *Trypanosoma cruzi*. Nat Prod Res. 22(12):1040–1046.

Nkwengoua ET, Ngantchou I, Nyasse B, Denier C, Blonski C, Schneider B. 2009. In vitro inhibitory effects of palmatine from *Enantia chlorantha* on *Trypanosoma cruzi* and *Leishmania infantum*. Nat Prod Res. 23(12):1144–1150.

Pontual EV, Pires-Neto DF, Fraige K, Higino TMM, Carvalho BEA, Alves NMP, Lima TA, Zingali RB, Coelho L, Bolzani VS, et al. 2017. A trypsin inhibitor from *Moringa oleifera* flower extract is cytotoxic to *Trypanosoma cruzi* with high selectivity over mammalian cells. Nat Prod Res. 31: 1–5.