Antileishmanial and Antimalarial Chalcones: Synthesis, Efficacy and Cytotoxicity of Pyridinyl and Naphthalenyl Analogs

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Abstract: The antileishmanial and antimalarial activity of methoxy-substituted chalcones (1,3-diphenyl-2-propen-1-ones) is well established. The few analogs prepared to date where the 3-phenyl group is replaced by either a pyridine or naphthalene suggest these modifications are potency enhancing. To explore this hypothesis, sixteen 3-naphthalenyl-1-phenyl-2-prop-1-enones and ten 1-phenyl-3-pyridinyl-2-prop-1-enones were synthesized and their *in vitro* efficacies against *Leishmania donovani* and *Plasmodium falciparum* determined. One inhibitor with submicromolar efficacy against *L. donovani* was identified (IC_{50} = 0.95 μM), along with three other potent compounds (IC_{50} < 5 μM), all of which were 3-pyridin-2-yl derivatives. No inhibitors with submicromolar efficacy against *P. falciparum* were identified, though several potent compounds were found (IC_{50} < 5 μM). The cytotoxicity of the five most active *L. donovani* inhibitors was assessed. At best the IC_{50} against a primary kidney cell line was around two-fold higher than against *L. donovani*. Being more active than pentamidine, the 1-phenyl-3-pyridin-2-yl-2-propen-1-ones have potential for further development against leishmaniasis; however it will be essential in such a program to address not only efficacy but also their potential for toxicity.

Key Words: Leishmaniasis, malaria, chalcone, propenone, structure activity relationship, cytotoxicity.

INTRODUCTION

Each year around 100,000 people die from leishmaniasis [1] and more than 1 million people from malaria [2]. The parasites responsible for most of these deaths are *Leishmania donovani* and *Plasmodium falciparum*, respectively. Since both have developed resistance to most available drugs there is an urgent need for novel and affordable products to combat the diseases they cause [1, 2]. Chalcones (1,3-diphenyl-2-propen-1-ones) and their carbocyclic and heterocyclic analogs display a wide range of biological activities including both antileishmanial [3-7] and antimalarial [4, 8-11] activity. Interest in the series began with the report that the natural product Licochalcone A possesses good *in vitro* efficacy against *L. donovani* (IC_{50} = 13 μM) and *P. falciparum* 3D7 (IC_{50} = 5.6 μM) [4]. A range of synthetic chalcones have been prepared and the structure-activity relationships explored [4-7, 9-11].

The activity of chalcone analogs tested against *L. donovani* varies, with IC_{50}s ranging from >30 μM to 1.4 μM. Many of the more active compounds (IC_{50} < 5 μM) are substituted with methoxy and/or hydroxyl groups [4-7]. A few 3-pyridinyl- and 3-naphthalenyl-derivatives have been prepared, and are amongst the most potent antileishmanial chalcone analogs identified described to date [4-7].

The activity of the analogs tested against *P. falciparum* is even more variable, with IC_{50}s ranging from 600 μM to 0.23 μM. As with *Leishmania*, many of the more active compounds against *Plasmodium* (IC_{50} < 5 μM) are substituted with methoxy and/or hydroxyl groups [4, 9-11]. Additionally halo-substituents are potency enhancing against *Plasmodium*, which is not usually the case against *Leishmania*. The 3-pyridinyl- and 3-naphthalenyl-derivatives possess moderate antimalarial activity, and are not among the most potent antimalarial 1-phenyl-2-propen-1-ones prepared to date [4].

It has emerged that mammalian cells are inhibited by the compounds at concentrations approaching those required to inhibit parasites. Until recently, amongst the more potent antileishmanial compounds (IC_{50} < 5 μM), the difference in these concentrations was typically less than two-fold, and at best only four-fold [4, 5]. Differences in the structure activity relationships for the antileishmanial activity and the toxicity may allow the development of selective antiparasitic agents. Indeed, substitution of the 3-phenyl group with either a 3-nitro or a 4-fluoro group has just been shown to dramatically improve the selectivity of a series of chalcone analogs [6].

RESULTS AND DISCUSSION

In a quest for novel antimalarial agents we had previously prepared a series of 3-naphthalenyl-1-phenyl-2-prop-1-enones using the sodium hydroxide–mediated condensation shown in Scheme **1** [11]. In the present study we prepared an analogous series of 1-phenyl-3-pyridinyl-2-prop-1-enones using a related barium hydroxide–mediated condensation, since the sodium hydroxide method failed to yield the desired propenones. Such a one step synthesis ensures that the cost of therapy by these compounds would be affordable.

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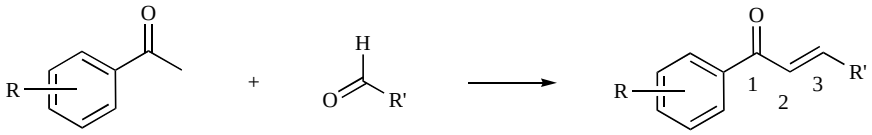


Scheme 1. excess 50% aq. NaOH, EtOH or 1.2 eq. $Ba(OH)_2 \cdot 8H_2O$, MeOH.

The majority of compounds (**1**-**26**, Table **1**) prepared were active against both *L. donovani* (IC_{50} < 20 μM) and *P. falciparum* (IC_{50} < 10 μM). The series of compounds was designed to assess the impact of methoxy substitution on the 1-phenyl group, and of the structure of the C3-substituent, on the antiparasitic activity of 1-phenyl-2-prop-1-enones. It complements earlier studies where two methoxylated naphthalene-derivatives (including **3**), and a total of ten other hydroxylated naphthalene- and pyridine-derivatives were assessed [4, 6].

The modest antimalarial activity of the 3-naphthalenyl-derivatives (**1**-**16**) has been reported by us previously [11]. Their antileishmanial activity, reported herein, is of greater interest. Six of the new derivatives (**5**, **7**, **8**, **11**, **13**, **15**) are likely more active than both the most potent known methoxylated-naphthalene (**3**) and Licochalcone A (IC_{50} = 13 μM), though differences in assays complicate comparison (e.g. (**3**) has reported ED_{50} = 4.37 μM, here IC_{50} = 15 μM) [4]. Two or three methoxy substituents appear to be required for activity, with the specific location of these groups on the 1-phenyl group influencing activity over a three fold range. The results show that a naphthalen-1-yl-derivative is generally about three-fold more potent against leishmaniasis than the corresponding naphthalen-2-yl-isomer. Regression analysis showed there is a loose correlation between the antileishmanial and antimalarial activities of this series of naphthalenyl-derivatives (R^2 = 0.66), a trend which is not usually observed amongst the substituted 2-propen-1-ones [4]. Although there is the possibility of developing dual acting therapeutics from this series, the modest activity of the naphthalenyl-derivatives against *P. falciparum* makes this unlikely.

Generally the pyridine-derivatives (**17**-**26**) were more active against *P. falciparum* than the naphthalene-derivatives, and all were devoid of significant cross-resistance (Resistance Indices ≈ 1). The most potent 3-pyridinyl-derivative (**23**) was only about six-fold less active than the best antimalarial 2-propen-1-one described to date [10]. The connectivity of the 3-pyridinyl substituent did not influence activity significantly, though the pyridin-2-yl-analogs were invariably the most active (**17** *cf* **18**, **19**; **20** *cf* **21**, **22**; **24** *cf* **25**, **26**). Only the 3-pyridin-2-yl-isomers were therefore tested against *L. donovani*, and all proved to be very active (IC_{50} < 5 μM). Three are more potent than the clinically useful antileishmanial drug pentamidine (**20**, **23**, **24**), including one with submicromolar efficacy (**23**) which has an IC_{50} lower than any reported to date for 2-propen-1-ones. As in the naphthalenyl series, analogs with two or three methoxy substituents on the 1-phenyl ring were more active than those with just one. The fact that the 3-pyridinyl-derivatives prepared were about ten-fold more active than the corresponding 3-naphthalenyl-derivatives is consistent with the previous finding that the 3-substituent has a large influence on antileishmanial activity (more than the 1-substituent) [4, 5]. The comparative activity of the less lipophilic pyridinyl-derivatives (lower clog*P*), compared to the more lipophilic naphthalenes (higher clog*P*), supports the opinion that lipophilicity is not a requirement for antileishmanial activity in chalcone analogs [4], in contrast to previous findings [7].

To further assess the potential of the compounds as antileishmanial therapeutics, the five compounds most active against *L. donovani* were assessed for mammalian cytotoxicity (**5**, **17**, **20**, **23**, **24**). The IC_{50} against Vero cells was found in each case to be similar to those against *L. donovani*. At best the IC_{50} for the mammalian cells was two-fold higher than for the parasite cells. These modest selectivities are comparable to those of most 1-phenyl-2-propen-1-ones described to date [4, 5].

In conclusion, the 1-phenyl-3-pyridin-2-yl-2-propen-1-ones described herein possess *in vitro* IC_{50}s against leishmaniasis lower than any previously reported for chalcone-analogs and lower than the clinically useful antileishmanial drug pentamidine. However, preliminary results suggest the selectivity of their inhibition of parasites over mammalian cells is minimal.

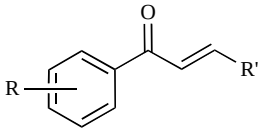
Analogs containing a 3-nitro or a 4-fluoro substituent in the 3-pyridin-2-yl-group are currently being prepared, since these will have improved selectivity if results comparable to those in a related 3-phenyl series are obtained [6]. Considerable experimentation will likely be required to achieve successful synthesis of these potentially selective analogs, since Claisen-Schmidt condensations involving strongly electron deficient aldehydes like those required are prone to side reaction [12]. However, improved selectivity will be critical if the 1-phenyl-3-pyridin-2-yl-2-propen-1-ones are to be developed into a therapy for leishmaniasis.

EXPERIMENTAL

Chemistry

Compounds were prepared by the condensation of substituted methyl ketones with substituted aldehydes as shown in Scheme **1**. All spectroscopic and analytical data recorded was consistent with the structure proposed. Each derivative was homogeneous by thin layer chromatography and had purity > 95%, evidenced by ^{1}H-Nuclear Magnetic Resonance (NMR) spectral integration and ^{13}C-NMR. NMR data (from spectra recorded in deuteriochloroform on a Jeol 400 MHz NMR) and melting points (which are uncorrected and were measured on a Hover Capillary Melting Point Apparatus) are provided for compounds not previously reported. The following procedure is representative of those used to prepare the naphthaldehyde-derived compounds (**1**-**16**).

Table 1. *In Vitro* Efficacy Against *P. falciparum* W2 and D6 and Against *L. donovani* and Cytotoxicity Against Mammalian Cells



Cmpd. No.	R	R'	P.f. W2 IC_{50}, µM [a]	P.f. D6 IC_{50}, µM [a]	Resistance Index [b]	L.d. IC_{50}, µM [c]	Cytotoxicity IC_{50}, µM [d]	cLog*P* [e]
1	4-MeO-	naphthalen-1-yl-	10	9.1	1.1	>200	-	5.01
2	4-MeO-	naphthalen-2-yl-	>17	>17	-	>200	-	4.97
3	2,4-diMeO-	naphthalen-1-yl-	4.6	4.9	0.94	15 ± 2	-	4.91
4	2,4-diMeO-	naphthalen-2-yl-	>16	8.7	-	32 ± 1	-	4.88
5	2,5-diMeO-	naphthalen-1-yl-	2.8	2.9	0.97	5.1 ± 1	5.7 ± 1	4.90
6	2,5-diMeO-	naphthalen-2-yl-	5.0	5.5	0.91	16 ± 1	-	4.87
7	2,6-diMeO-	naphthalen-1-yl-	3.1	3.2	0.97	7.5 ± 1.1	-	4.80
8	2,6-diMeO-	naphthalen-2-yl-	3.3	3.4	0.97	10 ± 2	-	4.77
9	3,4-diMeO-	naphthalen-1-yl-	5.0	5.2	0.96	15 ± 1	-	4.90
10	3,4-diMeO-	naphthalen-2-yl-	7.7	9.8	0.79	>200	-	4.87
11	3,5-diMeO-	naphthalen-1-yl-	4.3	4.5	0.96	6.9 ± 1.1	-	4.98
12	3,5-diMeO-	naphthalen-2-yl-	9.5	7.4	1.3	26 ± 2	-	4.95
13	2,3,4-triMeO-	naphthalen-1-yl-	5.8	4.3	1.3	9.5 ± 1.4	-	4.76
14	2,3,4-triMeO-	naphthalen-2-yl-	>14	>14	-	30 ± 1	-	4.73
15	3,4,5-triMeO-	naphthalen-1-yl-	4.8	5.2	0.92	6.9 ± 0.5	-	4.81
16	3,4,5-triMeO-	naphthalen-2-yl-	6.0	6.6	0.91	23 ± 5	-	4.79
17	4-MeO-	pyridin-2-yl-	12	9.7	1.2	3.6 ± 0.9	4.2 ± 1.0	2.72
18	4-MeO-	pyridin-3-yl-	10	7.1	1.4	-	-	2.58
19	4-MeO-	pyridin-4-yl-	12	12	1.0	-	-	2.56
20	2,4-diMeO-	pyridin-2-yl-	1.7	1.3	1.3	1.9 ± 0.4	2.3 ± 0.4	2.65
21	2,4-diMeO-	pyridin-3-yl-	2.7	3.1	0.87	-	-	2.51
22	2,4-diMeO-	pyridin-4-yl-	>19	>19	-	-	-	2.49
23	2,5-diMeO-	pyridin-2-yl-	1.4	2.0	0.70	0.95 ± 0.24	1.7 ± 0.1	2.65
24	2,3,4-triMeO-	pyridin-2-yl-	2.3	2.4	0.96	1.8 ± 0.4	2.5 ± 0.5	2.51
25	2,3,4-triMeO-	pyridin-3-yl-	3.9	3.2	1.2	-	-	2.38
26	2,3,4-triMeO-	pyridin-4-yl-	3.2	2.8	1.1	-	-	2.36
chloroquine			0.24	0.013	18.5	-	-	-
pentamidine			-	-	-	2.9 ± 0.3	69 ± 18	-

[a] Inhibition of [^{3}H] hypoxanthine uptake by *P. falciparum* strains W2 (chloroquine resistant) and D6 (chloroquine sensitive); values from one experiment. [b] IC_{50} against W2 / IC_{50} against D6. [c] Inhibition of *L. donovani* axenic amastigote-like forms; values are means of three experiments ± standard deviation. [d] Inhibition of African Green Monkey kidney (Vero) cells; values are means of three experiments ± standard deviation. [e] Calculated using Advanced Chemistry Development ACD/Log*D* Sol Suite.

(*E*)-1-(2,5-Dimethoxy-phenyl)-3-naphthalen-1-yl-propenone (5)

3',5'-Dimethoxyacetophenone (360 mg, 2.00 mmol) and 1-naphthaldehyde (312 mg, 2.00 mmol) were reacted in ethanol (3.0 mL) with 50% aqueous sodium hydroxide solution (1 mL). After stirring for five minutes, ice water was added. Filtration and recrystallization from ethanol yielded Compound (**5**) as a yellow solid (320 mg, 50 %) m.p. 90-91°C; ^{1}H-NMR δ 8.53 (1H, d, *J* = 15.6 Hz); 8.27 (1H, d); 7.96-7.85 (3H, m); 7.64-7.50 (4H, m); 7.30 (1H, d); 7.09 (1H, dd); 6.98 (1H, d); 3.91(3H, s); 3.90 ppm (3H, s); ^{13}C-NMR δ 192.16; 153.59; 152.68; 139.89; 133.67; 132.54; 131.72; 130.46; 129.55; 129.38; 128.69; 126.78; 126.17; 125.45; 125.12; 123.56; 119.42; 114.43; 113.30; 56.42; 55.83 ppm.

The other naphthalene-derivatives included: Compound (**6**) m.p. 121.5-122.5°C; ^{1}H-NMR δ 8.00 (1H, s); 7.92-7.83 (3H, m); 7.82-7.75 (2H, m); 7.59-7.50 (3H, m); 7.24 (1H, m); 7.07 (1H, m); 6.98 (1H, d); 3.91 (3H, s); 3.84 (3H, s); ^{13}C-NMR δ192.44; 153.57; 152.53; 143.41; 134.22; 133.30; 132.61; 130.50; 129.65; 128.59; 128.54; 127.74; 127.20; 127.01; 126.65; 123.70; 119.11; 114.35; 113.34; 56.48; 55.82 ppm; Compound (**7**) m.p. 142-142.5°C; ^{1}H-NMR δ 8.24 (1H, d, *J* = 15.9 Hz); 8.07-8.00 (1H, m); 7.94-7.82 (3H, m); 7.58-7.48 (3H, m); 7.43-7.35 (1H, m); 7.07 (1H, d, *J* = 15.9 Hz); 6.68 (2H, d); 3.85 ppm (6H, s); ^{13}C-NMR δ194.82; 157.58; 141.63; 133.56; 131.97; 131.40; 130.95; 130.95; 130.50; 128.68; 126.68; 126.05; 125.42; 125.21; 123.09; 118.42; 104.02; 55.87 ppm; Compound (**8**) m.p. 111-112°C; ^{1}H-NMR δ 7.91 (1H, s); 7.88-7.81 (3H, m); 7.72 (1H, m); 7.57-7.46 (3H, m); 7.41-7.34 (1H, m); 7.09 (1H, m, *J* = 16.1 Hz); 6.66 (2H, d); 3.91 (3H, s); 3.82 ppm (3H, s); ^{13}C-NMR δ195.25; 157.54; 145.22; 134.23; 133.21; 132.33; 130.79; 130.45; 128.79; 128.57; 128.50; 127.74; 127.24; 126.64; 123.73; 118.40; 104.03; 55.94 ppm; Compound (**11**) m.p. 99-100°C; ^{1}H-NMR δ 8.69 (1H, d, *J* = 15.4 Hz); 8.28 (1H, d); 7.98-7.88 (3H, m); 7.66-7.52 (4H, m); 7.23 (2H, d); 6.72 (1H, m); 3.90 ppm (6H, s); ^{13}C-NMR δ189.83; 160.89; 141.78; 140.10; 133.66; 132.26; 131.69; 130.81; 128.73; 126. 94; 126.27; 125.41; 125.07; 124.59; 123.43; 106.35; 105.11; 55.60 ppm; Compound (**12**) m.p. 60-62°C; ^{1}H-NMR δ 8.07 (1H, d); 8.00 (1H, d, *J* = 15.7 Hz); 7.94-7.79 (4H, m); 7.64-7.32 (3H, m); 7.21 (2H, d); 6.71 (1H, m); 3.90 ppm (6H, s); ^{13}C-NMR δ190.01; 160.86; 144.99; 140.21; 134.33; 133.28; 132.27; 130.69; 128.69; 128.61; 127.76; 127.36; 126.73; 123.61; 122.06; 106.33; 104.92; 55.60 ppm; Compound (**13**) m.p. 84-85.5°C; ^{1}H-NMR δ 8.54 (1H, d); 8.26 (1H, d); 7.91-7.86 (3H, m); 7.61-7.48 (5H, m); 6.78 (1H, d); 3.94 (3H, s); 3.93 (3H, s); 3.92 ppm (3H, s); ^{13}C-NMR δ190.62; 157.11; 153.84; 142.08; 139.68; 133.65; 132.48; 131.72; 130.42; 128.99; 128.67; 126.76; 126.71; 126.15; 125.95; 125.45; 124.97; 123.50; 107.31; 62.11; 61.05; 56.09 ppm.

The following procedure is representative of those used to prepare the pyridine carboxaldehyde-derived compounds (**17**-**26**).

(*E*)-1-(2,4-Dimethoxy-phenyl)-3-pyridin-2-yl-propenone (20)

2',4'-Dimethoxyacetophenone (360 mg, 2.00 mmol) and 2-pyridinecarboxaldehyde (214 mg, 2.00 mmol) were reacted in methanol (3.0 mL) with barium hydroxide octahydrate (630 mg). After stirring for 60 minutes, ice water was added to the yellow solution. Column chromatography, eluting with 25% ethyl acetate in hexane, yielded Compound (**20**) as a yellow solid (60 mg, 11 %) m.p. 47.5-49.5°C; ^{1}H-NMR δ 8.66 (1H, d); 7.97 (1H, d, *J* = 15.4 Hz); 7.78 (1H, d); 7.74-7.68 (1H, m); 7.64 (1H, d, *J* = 15.4 Hz); 7.48 (1H, d); 7.28-7.23 (1H, m); 6.55 (1H, dd); 6.49 (1H, d); 3.91 (3H, s); 3.87 ppm (3H, s); ^{13}C-NMR δ190.36; 164.41; 160.72; 153.70; 149.71; 139.84; 137.04; 132.99; 130.98; 124.73; 123.90; 121.86; 105.13; 98.49; 55.78; 55.53 ppm.

The other pyridine-derivatives included: Compound (**24**) m.p. 69.5-71.0°C; ^{1}H-NMR δ 8.66 (1H, d); 7.91 (1H, d, *J* = 15.4 Hz); 7.71 (1H, m); 7.64 (1H, d, *J* = 15.4 Hz); 7.49 (2H, m); 7.25 (1H, m); 6.74 (1H, d); 3.93 (3H, s); 3.92 (3H, s); 3.89 ppm (3H, s); ^{13}C-NMR δ190.80; 157.26; 154.00; 153.47; 149.78; 142.09; 140.75; 137.08; 130.50; 126.43; 125.93; 124.57; 124.09; 107.16; 62.03; 61.02; 56.10 ppm; Compound (**25**) m.p. 56-58°C; ^{1}H-NMR δ 8.82 (1H, d); 8.60 (1H, dd); 7.92 (1H, m); 7.62 (2H, m); 7.52 (1H, d); 7.34 (1H, dd); 6.76 (1H, d); 3.92 (3H, s); 3.91 (3H, s); 3.90 ppm (3H, s); ^{13}C-NMR δ189.81; 157.37; 153.85; 150.46; 149.65; 141.99; 138.49; 134.52; 130.98; 128.35; 126.07; 125.96; 123.72; 107.33; 61.98; 60.96; 56.04 ppm.

The clog*P* value, a predictor of lipophilicity, was calculated for each analog synthesized using Advanced Chemistry Development ACD/Log*D* Sol Suite.

Biological Assays

In vitro efficacy against *P. falciparum* was determined by a modified version of Desjardins' method, in which parasites were pre-exposed to test compound prior to measurement of their [^{3}H]-hypoxanthine uptake [10]. *In vitro* efficacy against *L. donovani* was determined by measuring the inhibition in growth of axenic amastigote-like parasites caused by the test compound, using a tetrazolium dye-based reagent [13]. The mammalian cytotoxicity of select compounds was assessed by measuring the inhibition in growth of African Green Monkey kidney (Vero) cells caused by the test compound [14].

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