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2-Substituted Quinoline Alkaloids as Potential Antileishmanial Drugs

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Ten 2-substituted quinoline alkaloids isolated from a plant used for treatment of New World cutaneous leishmaniasis have antileishmanial in vitro activities against the extracellular forms of *Leishmania* spp. BALB/c mice infected with *Leishmania amazonensis* PH8 or H-142 or *Leishmania venezuelensis* were treated 1 day after the parasitic infection with a quinoline alkaloid (100 mg/kg of body weight per day) or with reference drug *N*-methylglucamine antimonate (Glucantime) (56 mg of pentavalent antimony [Sb^V] per kg per day) for 14 days. Lesion development was the criterium used to assess disease severity. Two three-carbon chain quinolines [2-*n*-propylquinoline and 2-(1′,2′-*trans*-epoxypropyl)quinoline (chimanine D)] were more potent than *N*-methylglucamine antimonate against *L. amazonensis* PH8, and five quinoline alkaloids [2-(3,4-methylenedioxyphenylethyl)quinoline, cusparine, 2-(3,4-dimethoxyphenylethyl)quinoline, 2-(*E*)-prop-1′-enylquinoline (chimanine B), and skimmianine] were as effective as the reference drug. Single treatment near the site of infection, 14 days after infection with *L. amazonensis*, with 2-*n*-propylquinoline or chimanine B reduced the severity of lesions but less notably than *N*-methylglucamine antimonate. 2-*n*-Propylquinoline exhibited significant activity against the virulent strain *L. venezuelensis*. The active products did not show any apparent toxicities during the experiment. This study is, to our knowledge, the first to show the activity of 2-substituted quinoline alkaloids for experimental treatment of New World cutaneous leishmaniasis. Further investigations of these compounds might yet prove helpful for the development of new antileishmanial drugs.

Cutaneous leishmaniasis and mucocutaneous leishmaniasis are endemic diseases in South America, particularly in the sub-Andean areas of the humid lowlands of Bolivia. Leishmaniasis is initiated by inoculation of *Leishmania* species into the skin during sand fly bites. Drugs currently used to cure leishmaniasis are derivatives of pentavalent antimony (Sb^V) (sodium stibogluconate [Pentostam] and *N*-methylglucamine antimonate [Glucantime]); pentamidine, and amphotericin B (14). These drugs are potentially toxic and generally administered via the parenteral route in a hospital setting for relatively long periods (3). In the endemic regions of Bolivia, the classic treatments are too expensive or unavailable to the population suffering from cutaneous leishmaniasis (espundia). The impact of this disease was accentuated in sub-Andean tropical areas by the influx of people descending from higher areas. In Bolivia, the Instituto Boliviano de Biologia de Altura and the French Institute of Scientific Research for the Development in Cooperation (ORSTOM) have initiated and developed original investigations of alternative compounds for the treatment of leishmaniasis. In previous studies (7), we have described the in vitro activity against the promastigote forms of *Leishmania* species and the isolation and chemical characterization of active compounds (8, 9) from a Bolivian plant used locally for treatment of cutaneous leishmaniasis and identified as *Galipea longiflora* Krause of the *Rutaceae* family. These active products were identified spectroscopically as 12 2-substituted quinoline alkaloids. The aims of this study were to evaluate and demonstrate the activities of these quinoline alkaloids in BALB/c mice infected with New World strains causing cutaneous leishmaniasis. We have used two isolates of *Leishmania amazonensis* (MHOM/IFLA/B4/67/PH8 and MHOM/GF/84/CAY-H-142) with different degrees of infectivity and a virulent strain from Venezuela, *Leishmania venezuelensis*, producing severe lesions in human infection (notably single and multiple cutaneous lesions) (4, 10) and rapid growth of lesions. The mouse footpad infection has been used as a model for the experiments (1, 6), and *N*-methylglucamine antimonate has been used as a reference drug.

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MATERIALS AND METHODS

Chemicals. The 2-substituted quinoline alkaloids were isolated from the root barks, stem barks, and leaves of *G. longiflora* by fractionation and purification monitored by bioassay, as previously described (7), using chromatographic methods. Physical and spectral data (proton magnetic resonance and mass spectrometry) were used to determine the chemical structures of the compounds (8, 9). The structures of these products are shown in Fig. 1. *N*-methylglucamine antimonate with a pentavalent antimony (Sb^V) content of 28% by weight was purchased from Rhône-Poulenc, Paris, France.

Mice. Female and male BALB/c mice were supplied by the Charles Rivers Breeding Laboratory and bred at Instituto Boliviano de Biologia de Altura, La Paz, Bolivia. Mice

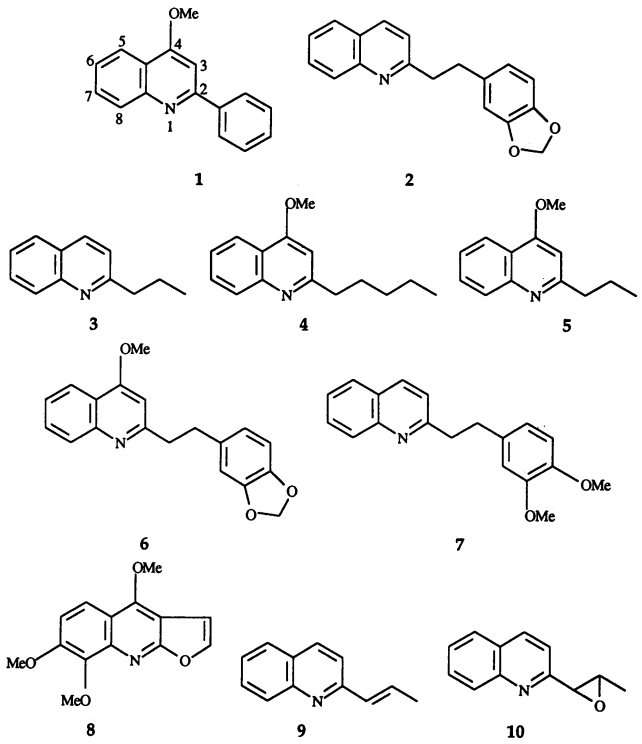

FIG. 1. Structures of 2-substituted quinoline alkaloids. 1, 4-methoxy-2-phenylquinoline; 2, 2-(3,4-methylenedioxyphenylethyl)quinoline; 3, 2-*n*-propylquinoline; 4, 4-methoxy-2-*n*-pentylquinoline; 5, chimanine A; 6, cusparine; 7, 2-(3,4-dimethoxyphenylethyl)quinoline; 8, skimmianine; 9, chimanine B; 10, chimanine D.

weighed between 18 and 20 g and were 8 weeks old when experiments were initiated.

Parasites. *L. amazonensis* MHOM/IFLA/BR/67/PH8 and MHOM/GF/84/CAY-H-142 and *L. venezuelensis* MHOM/VE/74/PM-H3 were used. The source and history of the *L. venezuelensis* isolate has been previously described (4). All strains were maintained by passage every 6 to 8 weeks in hamsters. BALB/c mice (*n*, 10, 8, or 6) were infected subcutaneously in the right rear footpad with 10^6 amastigotes obtained from donor hamsters. The parasites were delivered in 200 μl of phosphate-buffered saline (PBS).

The growth of lesions was determined weekly by measuring the diameters of both rear feet with a direct-reading vernier caliper (Kroelin 1ODI 00T6). The size of the lesion in millimeters (index of leishmaniasis) was calculated by subtracting the measurement of the uninfected foot from that of the infected foot. Measurements commenced 1 day prior to the inoculation of amastigotes and were continued for 8 or 9 weeks. For each experiment, the mean and standard error of the mean were calculated.

Drug treatment. Two experiments were conducted. Mice in the first experiment were treated by the subcutaneous route. *N*-Methylglucamine antimonate was given at a dose of 56 mg of Sb^V per kg of body weight daily, and 2-substituted quinoline alkaloids were given at 100 mg/kg daily. The quinoline alkaloids were dissolved in 40 μl of polysorbate (Tween 80; Prolabo). *N*-Methylglucamine antimonate was dissolved in PBS, and untreated mice received PBS and Tween 80. Drug treatment commenced 1 day after the inoculation of amastigotes and was continued once daily for 14 days.

In the second experiment, mice were treated directly on the infected rear footpad with a single dose 14 days after the inoculation of parasites. For this experiment, mice were treated with *N*-methylglucamine antimonate at 112 mg of Sb^V per kg and with quinoline alkaloids at 200 mg/kg.

RESULTS

Treatment (14 days) of mice infected with *L. amazonensis* PH8. Table 1 shows the antileishmanial data for 10 2-substituted quinoline alkaloids given for 14 days to BALB/c mice infected with *L. amazonensis* PH8. As previously described, the use of either *N*-methylglucamine antimonate or any other drug had no preventive drug action on the development of lesions but reduced their severity (6). Preliminary toxicological evaluations of quinoline alkaloids given to BALB/c mice indicated that the drugs had reasonable therapeutic indices, with an acute intraperitoneal 50% lethal dose greater than 400 mg/kg. No apparent signs of drug toxicity, weight loss, or hair loss were observed in any experiment; only an

TABLE 1. Fourteen-day-treatment effects of *N*-methylglucamine antimonate and 10 2-substituted quinoline alkaloids on the development of *L. amazonensis* PH8 in BALB/c mice

Drug[a]	Lesion diam (mm)[b] the following no. of wk postinfection:			
	2	4	6	8
4-Methoxy-2-phenylquinoline (1)	0.50 ± 0.08	1.27 ± 0.21	3.77 ± 0.36	5.01 ± 0.50
2-(3,4-Methylenedioxyphenylethyl)quinoline (2)	0.46 ± 0.10	0.83 ± 0.16	3.10 ± 0.40	4.62 ± 0.48
2-*n*-Propylquinoline (3)	0.48 ± 0.11	0.72 ± 0.18	2.10 ± 0.35	3.42 ± 0.26
4-Methoxy-2-*n*-pentylquinoline (4)	0.40 ± 0.09	1.16 ± 0.13	3.61 ± 0.41	4.94 ± 0.51
Chimanine A (5)	0.47 ± 0.19	1.83 ± 0.36	3.54 ± 0.69	4.88 ± 0.67
Cusparine (6)	0.62 ± 0.11	1.12 ± 0.26	2.85 ± 0.45	4.15 ± 0.68
2-(3,4-Dimethoxyphenylethyl)quinoline (7)	0.33 ± 0.11	0.82 ± 0.17	3.21 ± 0.34	4.44 ± 0.60
Skimmianine (8)	0.36 ± 0.08	1.26 ± 0.33	2.93 ± 0.41	4.25 ± 0.48
Chimanine B (9)	0.35 ± 0.11	0.92 ± 0.28	2.35 ± 0.40	4.39 ± 0.50
Chimanine D (10)	0.35 ± 0.08	1.04 ± 0.29	1.68 ± 0.43	2.60 ± 0.66
N-Methylglucamine antimonate[c]	0.17 ± 0.07	0.48 ± 0.15	2.35 ± 0.34	4.02 ± 0.41
None	0.53 ± 0.14	1.25 ± 0.16	3.80 ± 0.41	6.60 ± 0.67

[a] Given for 14 days starting 1 day after the inoculation of *L. amazonensis*. Dosages: *N*-methylglucamine, 56 mg of Sb^V per kg per day; all other drugs, 100 mg/kg/day. Numbers in parentheses refer to structures depicted in Fig. 1.

[b] Calculated by subtracting the measurement for the uninfected footpad from the measurement for the infected footpad. The data are means ± standard errors of the means for groups of 10 mice each.

[c] Standard drug.

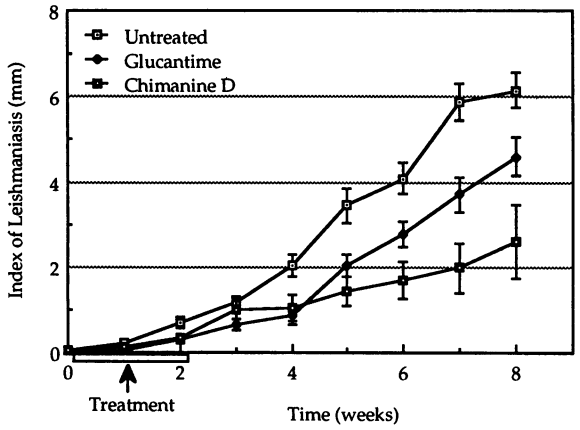

FIG. 2. Effects of chimanine D (100 mg/kg/day) and *N*-methylglucamine antimonate (Glucantime) (56 mg of Sb^v per kg per day) on the development of *L. amazonensis* PH8 in BALB/c mice. Treatments were given for 14 days, commencing 1 day after inoculation with *L. amazonensis*. Datum points represent the average measurements for groups of 10 mice each. Lesion diameter was expressed as the thickness of the infected footpad minus the thickness of the contralateral uninfected footpad. Bars, standard errors of the means.

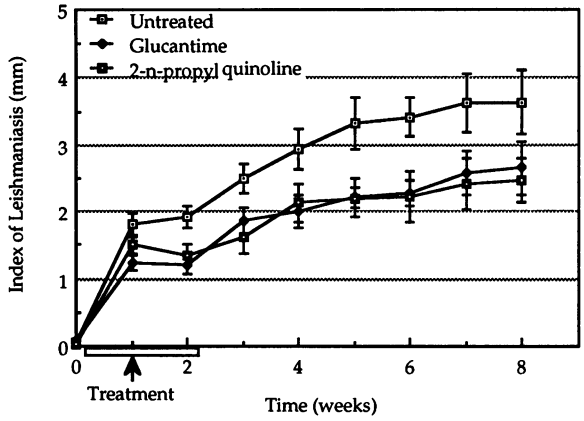

FIG. 3. Effects of 2-*n*-propylquinoline (100 mg/kg/day) and *N*-methylglucamine antimonate (Glucantime) (56 mg of Sb^v per kg per day) on the development of *L. amazonensis* H-142 in BALB/c mice. Treatments were given for 14 days, commencing 1 day after inoculation with *L. amazonensis*. Datum points represent the average measurements for groups of 10 mice each. Lesion diameter was expressed as the thickness of the infected footpad minus the thickness of the contralateral uninfected footpad. Bars, standard errors of the means.

inflammatory effect near the site of administration of the drug was observed. Two quinoline alkaloids, 2-*n*-propylquinoline and chimanine D (Fig. 1, compounds 3 and 10, respectively, and Fig. 2), were more active than the reference antileishmanial drug, *N*-methylglucamine antimonate, after the 8 weeks of the experiment. Both compounds are three-carbon chain 2-substituted quinolines with a propyl group and a propyl *trans*-epoxy-1′2′ group, respectively. The following five quinoline alkaloids were approximately as effective as *N*-methylglucamine antimonate in this model: three substituted 2-phenylethyl compounds [2-(3,4-methylenedioxyphenylethyl)quinoline, cusparine and 2-(3,4-dimethoxyphenylethyl)quinoline (Fig. 1, compounds 2, 6, and 7, respectively)], a furo(2,3,*b*)quinoline alkaloid, skimmianine (Fig. 1, compound 8), and a three-carbon chain 2-substituted quinoline, chimanine B (Fig. 1, compound 9). The following three compounds exhibited moderate activities: 4-methoxy-2-phenylquinoline, 4-methoxy-2-*n*-pentylquinoline, and chimanine A (or 4-methoxy-2-*n*-propylquinoline) (Fig. 1, compounds 1, 4, and 5, respectively). The presence of a 4-methoxy group in these alkaloids produced a decrease in antileishmanial activity.

Treatment (14 days) of mice infected with *L. amazonensis* H-142. The effects of four quinoline alkaloids and *N*-methylglucamine antimonate on the development of *L. amazonensis* H-142-caused lesions in mice are presented in Table 2. After 8 weeks, treatment with 2-*n*-propylquinoline (Fig. 1, structure 3) was as effective as that with the reference drug (Fig. 3). The remaining compounds, 2-(3,4-methylenedioxyphenylethyl)quinoline, chimanine A, and cusparine (Fig. 1, compounds 1, 5, and 6, respectively), did not exhibit any effect. With this model, we have noted a slow development of lesion growth in each group of mice. The difference between the diameters of the lesions in the untreated mice and the diameters of the lesions in those mice treated with *N*-methylglucamine antimonate was only 1 mm. After 9 or 10 weeks, we observed a beginning of ulceration of lesions followed by autocicatrization in the untreated mice.

Single treatments on the footpads of mice infected with *L. amazonensis* PH8. In this experiment, the treatments were administered at the site of parasitic infection. The results obtained are shown in Table 3. Each of the two 2-substituted three-carbon chain compounds 2-*n*-propylquinoline and chimanine B [or 2-(*E*)-prop-1′-enylquinoline] (Fig. 1, compounds 3 and 9, respectively) reduced the severity of lesions in this model but to a lower extent than the standard antimony treatment, which appeared to be much more effective. The following four quinoline alkaloids did not

TABLE 2. Fourteen-day-treatment effects of *N*-methylglucamine antimonate and three 2-substituted quinoline alkaloids on the development of *L. amazonensis* H-142 in BALB/c mice

Drug[a]	Lesion diam (mm)[b] the following no. of wk postinfection:			
	2	4	6	9
2-(3,4-Methylenedioxyphenylethyl)quinoline (2)	0.35 ± 0.11	0.97 ± 0.13	1.42 ± 0.22	2.65 ± 0.42
Chimanine A (5)	0.46 ± 0.10	0.61 ± 0.15	1.01 ± 0.21	2.80 ± 0.52
Cusparine (6)	0.43 ± 0.04	0.73 ± 0.07	1.04 ± 0.36	2.96 ± 0.58
N-Methylglucamine antimonate[c]	0.42 ± 0.10	0.67 ± 0.18	0.66 ± 0.24	1.98 ± 0.34
None	0.53 ± 0.12	0.88 ± 0.12	1.43 ± 0.44	2.96 ± 0.46

[a] See Table 1, footnote *a*.
[b] See Table 1, footnote *b*.
[c] Standard drug.

TABLE 3. Single-administration effects of *N*-methylglucamine antimonate and six 2-substituted quinoline alkaloids on the development of *L. amazonensis* PH8 in BALB/c mice

Drug[a]	Lesion diam (mm)[b] the following no. of wk postinfection:			
	2	4	6	8
2-(3,4-Methylenedioxyphenylethyl)quinoline (2)	0.40 ± 0.18	1.20 ± 0.19	2.71 ± 0.48	5.22 ± 0.78
2-*n*-Propylquinoline (3)	0.45 ± 0.12	1.41 ± 0.31	2.37 ± 0.65	3.68 ± 0.84
Cusparine (6)	0.37 ± 0.12	1.27 ± 0.31	2.90 ± 0.62	5.03 ± 0.77
Skimmianine (8)	0.38 ± 0.04	1.51 ± 0.35	2.95 ± 0.36	4.98 ± 0.36
Chimanine B (9)	0.28 ± 0.07	1.75 ± 0.57	1.78 ± 0.52	3.67 ± 0.82
Chimanine D (10)	0.38 ± 0.08	1.40 ± 0.18	2.65 ± 0.47	4.90 ± 0.72
N-Methylglucamine antimonate[c]	0.45 ± 0.06	0.53 ± 0.23	1.52 ± 0.38	2.83 ± 0.58
None	0.35 ± 0.08	1.01 ± 0.20	2.87 ± 0.29	4.90 ± 0.42

[a] Single administration on the infected rear footpad 14 days after the inoculation of *L. amazonensis*. Doses: *N*-methylglucamine antimonate, 112 mg of Sb^V per kg; all other drugs, 200 mg/kg. Numbers in parentheses refer to structures depicted in Fig. 1.
[b] Calculated by subtracting the measurement for the uninfected footpad from the measurement for the infected footpad. The data are means ± standard errors of the means for groups of six mice each.
[c] Standard drug.

show any effect: 2-(3,4-methylenedioxyphenylethyl)quinoline (Fig. 1, compound 2), cusparine (compound 6), a furoquinoline alkaloid, skimmianine (compound 8), and the most active product in the first experiment (14-day treatment), chimanine D (compound 10).

Treatment of *L. venezuelensis* infection. With the virulent strain *L. venezuelensis*, two quinoline alkaloids, 2-(3,4-methylenedioxyphenylethyl)quinoline and 2-*n*-propylquinoline (Fig. 1, compounds 2 and 3, respectively), have been tested. The results obtained with this model are presented in Table 4. After 8 weeks, the substituted 2-propyl chain compound (Fig. 1, compound 3) was as effective as the reference drug and showed the same inhibitory effect as that against *L. amazonensis*. Some untreated BALB/c mice infected with *L. venezuelensis* presented multiple cutaneous nodules on the ears.

DISCUSSION

The data collected in this work indicate that *L. amazonensis* is reasonably susceptible to 2-substituted three-carbon chain quinoline alkaloids (2-*n*-propylquinoline and chimanine D [Fig. 1, compounds 3 and 10, respectively]) and 2-substituted aryl quinoline alkaloids. Substitution at position 4 of the quinoline by the methoxy group (Fig. 1, compounds 1, 4, and 5) results in decreased antileishmanial activity. We have observed remarkable bioavailabilities of oily quinoline alkaloids (2-substituted three-carbon chain and 2-phenylethyl quinolines) not exhibited by cristalline compounds such as 4-methoxy-2-phenylquinoline (Fig. 1, compound 1). Results of the in vivo experiments indicated that all mice treated with 100 mg of a 2-substituted quinoline alkaloid per kg daily for 14 days resisted infection with each New World cutaneous leishmaniasis-causing strain, including the virulent strains *L. amazonensis* PH8 and *L. venezuelensis* H-3. The high concentration of a 2-substituted quinoline alkaloid did not cause any obvious toxicity in the mice even at a dosage of 100 mg/kg/day for 14 days. In previous experiments, treatments with antimony drugs at 28 and 56 mg of Sb^V per kg per day for 1 week did not produce any significant difference between the untreated and treated mice. In general, all the 2-substituted quinoline alkaloids tested exhibited a minimal activity (50 to 100 μg/ml) against five strains of promastigote forms of *Leishmania* spp. and five clones of epimastigote forms of *Trypanosoma cruzi* (7). It is often difficult to correlate drug activity in vitro with that in vivo (3). Traditional use of *G. longiflora* in areas of endemic cutaneous leishmaniasis together with our clinical observations facilitated excellent evaluation of the efficacies of these active compounds.

Many aminoquinoline compounds, substituted at positions 8, 7, 6 and 4, have been synthesized at the Walter Reed Army Institute for Research and have previously been shown to be effective against cutaneous leishmaniasis and visceral leishmaniasis (11–13, 15), malaria (5), and recently, against *Pneumocystis carinii*-caused pneumonia (2). An examination of the data obtained in the present study demonstrates that interesting biological activities also exist in the 2-substituted quinoline alkaloids.

To our knowledge, this study is the first to show the activities of 2-substituted quinoline alkaloids for treating

TABLE 4. Effects of *N*-methylglucamine antimonate and three 2-substituted quinoline alkaloids on the development of *L. venezuelensis* H-3 in BALB/c mice

Drug[a]	Lesion diam (mm)[b] the following no. of wk postinfection:			
	2	4	6	8
2-(3,4-Methylenedioxyphenylethyl)quinoline (2)	0.60 ± 0.26	1.80 ± 0.44	3.78 ± 0.49	5.50 ± 0.55
2-*n*-Propylquinoline (3)	0.33 ± 0.15	1.26 ± 0.21	2.68 ± 0.39	4.12 ± 0.76
N-Methylglucamine antimonate[c]	0.45 ± 0.19	0.95 ± 0.21	2.48 ± 0.34	4.25 ± 0.44
None	0.61 ± 0.30	2.07 ± 0.19	4.12 ± 0.22	6.60 ± 0.51

[a] Given for 14 days starting 1 day after the inoculation of *L. venezuelensis*. Dosages: *N*-methylglucamine antimonate, 56 mg of Sb^V per kg per day; all other drugs, 100 mg/kg/day. Numbers in parentheses refer to structures depicted in Fig. 1.
[b] Calculated by subtracting the measurement for the uninfected footpad from the measurement for the infected footpad. The data are means ± standard errors of the means for groups of six mice each.
[c] Standard drug.

experimental New World cutaneous leishmaniasis. The activities of 2-substituted quinoline alkaloids against other strains causing New World cutaneous leishmaniasis or visceral leishmaniasis may be demonstrated with oral treatments of mice susceptible to *Leishmania* spp. The total synthesis of the compounds tested in this work together with other derived quinoline alkaloids is in progress in our laboratory. Following studies on the structure-activity relationship, we hope to improve the effectiveness of 2-substituted quinoline alkaloids for the treatment of cutaneous leishmaniasis.

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