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Antiparasitic properties of homoallylamines and related compounds

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Abstract

A study of some antiparasitic properties of several homoallylamines and related tetrahydroquinolines and quinolines, previously described, was carried out using *in vitro* activity assays against the epimastigote form of *Trypanosoma cruzi* and against *Trichomonas vaginalis*. Unspecific cytotoxicity against murine macrophages was also studied. Although the antichagasic and trichomonacidal activities are not comparable to those of the standard drugs, nifurtimox and metronidazole, some of the compounds exhibit an interesting specific antiparasitic activity.

Key words

Homoallylamines, tetrahydroquinolines, quinolines, antichagasic, trichomonacidal, unspecific cytotoxicity

Introduction

Parasitic diseases are among the most widespread of human diseases. In 1997, of a global total of 52.2 million deaths, 17.3 million were due to infectious diseases, followed by circulatory diseases, cancer, and respiratory diseases (Tracy and Wester 2001). American trypanosomiasis, caused by the protozoan parasite *Trypanosoma cruzi*, is widespread in Latin America, where 16 to 18 million people are estimated to be infected (Organización Panamericana de la Salud 1994). Since the beginning of the 1970s, benznidazole and nifurtimox have been used for the treatment of Chagas disease, although the commercialization of nifurtimox has been discontinued in Brazil, Argentina, Chile and Uruguay. Controversial results to the use of both drugs are well known and have been recently reviewed (Coura and de Castro 2002). Clinical phase of Chagas disease, parasite strain, period of treatment, dose, age and geographical origin of the patients (Andrade *et al*. 1985, Filardi and Brener 1987, Toledo *et al*. 1997) are the main factors responsible for the different degrees of success achieved. This variable susceptibility, side effects and contraindications for benznidazole and nifurtimox treatment, reinforce the need to find more efficient and less toxic drugs.

On the other hand, trichomoniasis is a common, sexually transmitted infection that affects about 170 million of people worldwide, more than the combination of infections produced by gonorrhea, syphilis, and chlamydia (World Health Organization 1995). The 5-nitroimidazole drugs, of which metronidazole is the most prescribed, are the only approved, effective drugs to treat trichomoniasis. Resistance against metronidazole (Dunne *et al*. 2003) is frequently reported, and cross-resistance among the family of 5-nitroimidazole drugs is also common. Moreover, resistant organisms are cosmopolitan in distribution and are of considerable concern as *Trichomonas* infection are linked to vaginal HIV transmission (Sorvillo and Kerndt 1998, Lo *et al*. 2002). Some reports even suggest that its eradication may be the single most effective step in HIV incidence reduction (Bowden and Garnett 1999, Sorvillo *et al*. 2001).

Both, controversial findings on the use of benznidazole and nifurtimox for the treatment of trypanosomiasis (Cancado 2002, Coura and de Castro 2002) and the increase in the recognition of metronidazole-resistant trichomoniasis (Crowell *et al*. 2003) justify the screening of new antiparasitic agents. During our investigations on the *N*-substituted homoallylamine (Kouznetsov *et al*. 1998a, b) we found that diverse homoallylamines containing aryl or heteroaryl rings at the

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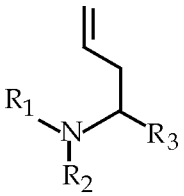
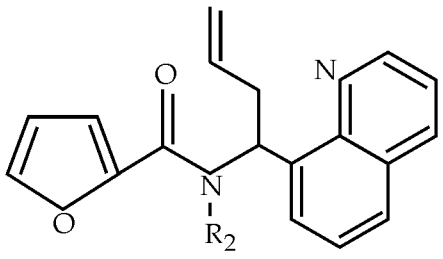
C-4 of butene displayed significant activity (MIC < 50 µg/ml) against some pathogenic dermatophytes (Urbina *et al*. 2000, Vargas *et al*. 2003). This fact encouraged us to investigate netsov *et al*. 2004). Among quinolines, Jonckers *et al*. (2002) have assayed some neocryptolepine derivatives that appear as promising antimalarial and antitrypanosomal agents.



1. R_1 = phenyl, R_2 = H, R_3 = 3-pyridyl
2. R_1 = *p*-tolyl, R_2 = H, R_3 = 3-pyridyl
3. R_1= *p*-MeO-phenyl, R_2 = H, R_3 = 3-pyridyl
4. R_1 = *p*-F-phenyl, R_2 = H, R_3 = 3-pyridyl
5. R_1= *p*-Cl-phenyl, R_2 = H, R_3 = 3-pyridyl
6. R_1 = *p*-Br-phenyl, R_2 = H, R_3 = 3-pyridyl
7. R_1 = *o*-I-phenyl, R_2 = H, R_3 = 3-pyridyl
8. R_1 = 2,4-di-F-phenyl, R_2 = H, R_3 = 3-pyridyl
9. R_1 = *o*-isopropylphenyl, R_2 = H, R_3 = 3-pyridyl
10. R_1 = methylendioxyphenyl, R_2 = H, R_3 = 3-pyridyl
11. R_1 = *p*-tolyl, R_2 = H, R_3 = 2-pyridyl
12. R_1 = *p*-tolyl, R_2 = H, R_3 = 4-pyridyl
13. R_1 = R_3 = phenyl, R_2 = H
14. R_1 = phenyl, R_2 = H, R_3 = *p*-MeO-phenyl
15. R_1 = phenyl, R_2 = H, R_3 = phenethyl
16. R_1 = *p*-tolyl, R_2 = H, R_3 = phenyl
17. R_1 = *p*-tolyl, R_2 = CH_2CO_2Et, R_3 = phenyl
18. R_1 = *p*-tolyl, R_2 = H, R_3 = phenethyl
19. R_1= *o*-tolyl, R_2 = H, R_3 = phenyl
20. R_1 = *o*-tolyl, R_2 =H, R_3 = propyl
21. R_1 = *o*-tolyl, R_2 = H, R_3 = phenethyl
22. R_1 = *p*-MeO-phenyl, R_2 = H, R_3 = phenyl
23. R_1 = *m*-MeO-phenyl, R_2 = H, R_3 = phenyl
24. R_1= *p*-MeO-phenyl, R_2 = Ac, R_3 = phenyl
25. R_1 = *p*-MeO-phenyl, R_2 = H, R_3 = propyl
26. R_1 = *p*-MeO-phenyl, R_2 = H, R_3 = phenethyl
27. R_1 = *o*,*p*-di-MeO-phenyl, R_2 = H, R_3 = phenyl
28. R_1 = *p*-F-phenyl, R_2 = H, R_3 = propyl
29. R_1 = *p*-F-phenyl, R_2 = H, R_3 = phenethyl
30. R_1 = *p*-Cl-phenyl, R_2 = H, R_3 = phenyl
31. R_1 = *p*-Cl-phenyl, R_2 = H, R_3 = *p*-$N(Me)_2$-phenyl
32. R_1 = *p*-Br-phenyl, R_2 = H, R_3 = phenyl
33. R_1 = *p*-Br-phenyl, R_2 = H, R_3 = propyl
34. R_1 = *p*-Br-phenyl, R_2 = H, R_3 = phenethyl
35. R_1 = *o*-isopropylphenyl, R_2 = H, R_3 = phenyl
36. R_1 = 3,4-methylendioxyphenyl, R_2 = H, R_3 = *p*-MeO-phenyl



68. R_2 = *p*-Cl-phenyl
69. R_2 = *p*-EtO-phenyl

Fig. 1. Chemical structures of homoallylamines assayed

other possible antimicrobial activities of these homoallylamines and related hydroquinoline and quinoline derivatives. So, we have recently reported the antiparasitic properties of some 5-nitro(amino)-2-pyridylquinoline derivatives (Kouz-

In this paper we report the *in vitro* antichagasic and trichomonacidal activities, and unspecific cytotoxicity against macrophages of the previously synthesized (Urbina *et al*. 2000, Vargas *et al*. 2003) homoallylamines 1–36, 68 and 69

37. $R_1 = R_3$ = phenyl, $R_2 = R_4 = H$
38. R = *p*-tolyl, $R_2 = R_4 = H$, R_3 = phenyl
39. R_1 = *p*-tolyl, R_2 = Ac, R_3 = phenyl, R_4 = Ac
40. R_1 = *p*-Br-phenyl, $R_2 = R_4 = H$, R_3 = phenyl
41. R_1= p-Br-phenyl, $R_2 = R_4 = H$, R_3 = propyl
42. R_1 = *o*-isopropylphenyl, $R_2 = R_4 = H$, R_3 = phenyl

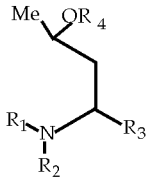


Fig. 2. Chemical structures of amine derivatives assayed

43. $R_1 = H$, R_3 = 3-pyridiyl
44. R_1 = 6-Me, R_3 = 3-pyridyl
45. R_1 = 6-MeO, R_3 = 3-pyridyl
46. R_1 = 6-F, R_3 = 3-pyridyl
47. R_1 = 6-Cl, R_3 = 3-pyridyl
48. R_1 = 6-Br, R_3 = 3-pyridyl
49. R_1 = 8-I, R_3 = 3-pyridyl
50. R_1 = 6,8-di-F, R_3 = 3-pyridyl
51. R_1 = 8-isopropyl, R_3 = 3-pyridyl
52. R_1 = 6-Me, R_3 = 2-pyridyl
53. R_1 = 6-Me, R_3 = 4-pyridyl
54. $R_1 = H$, R_3 = phenyl
55. R_1 = 6-Me, R_3 = phenyl
56. R_1 = 6-F, R_3 = propyl

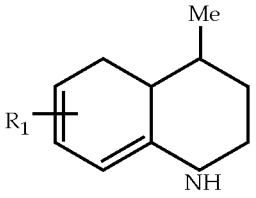


Fig. 3. Chemical structures of hydroquinolines assayed

57. $R_1 = H$, R_3 = 3-pyridyl
58. R_1 = 6-Me, R_3 = 3-pyridyl
59. R_1 = 6-Me, R_3 = 4-pyridyl
60. R_1 = 6-Me, R_3 = 2-pyridyl
61. R_1 = 6-F, R_3 = 3-pyridyl
62. R_1 = 6-Cl, R_3 = 3-pyridyl
63. R_1 = 8-isopropyl, R_3 = 3-pyridyl
64. R_1 = 6-Me,8-NO_2, R_3 = 3-pyridyl
65. R_1 = 6,8-di-F, R_3 = 3-pyridyl
66. $R_1 = H$, R_3 = propyl
67. R_1 = 6-Me, R_3 = phenyl

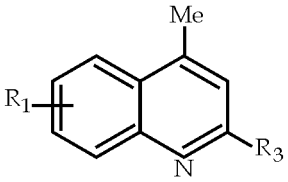


Fig. 4. Chemical structures of quinolines assayed

(Fig. 1), amine derivatives 37–42 (Fig. 2), hydroquinolines 43–56 (Fig. 3) and quinolines 57–67 (Fig. 4).

Materials and methods

Anti-*Trypanosoma cruzi* epimastigote assays

The activity of the compounds was determined on epimastigotes of *T. cruzi* strain Y, grown at 28°C in liver infusion tryptose (LIT) medium supplemented with 10% of heat inactivated fetal calf serum as described (Muelas-Serrano *et al*. 2000). Briefly, 24 well plates (Costar, Corning NY) were seeded with 900 µl of a homogeneous early log phase culture containing 500,000 epimastigotes/ml. Compounds dissolved in dimethyl sulfoxide (DMSO) were then added in triplicate at final concentrations of 100, 10 and 1 µg/ml. After 96 h of incubation at 28°C, 100 µl of a 2.5 mg/ml of MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, containing 0.22 mg/ml of PMS (phenazine methosulfate) to enhance the formazan yield (Cedillo-Rivera *et al*. 1992, Hattori and Nakanishi 1995) were added. After 75 min, formazan crystals were dissolved with 1 ml of a 10% sodium dodecyl sulfate (SDS) – 0.01 N HCl solution, and absorbances were read at 595 nm in a plate reader EL × 800 from Bio-Tek Instruments Inc. Antiepimastigote (AE) activity was calculated as:

$$\% AE = 100 \times (ODc–ODcm)–(ODe–ODec)/(ODc–ODcm)$$

where ODc represents the mean of optical densities for control wells and ODe, the mean for experimental wells. Optical density of medium (ODcm) and of every compound (ODec) were respectively subtracted. Nifurtimox (Lampit from Bayer, Argentina) was used as reference drug.

Anti-*Trichomonas vaginalis* assays

Trichomonas vaginalis strain JH31A No. 4 was cultured at 37°C with 5% CO_2 in TYM (Trypticase-Yeast extract-Maltose) medium supplemented with 10% of heat inactivated equine serum. The assays were carried out using glass tubes containing 100,000 protozoa/ml in a final volume of 2 ml. Compounds were added to the cultures 6 h after seeding. For each concentration assayed (100, 10 and 0.1 µg/ml), there were three experimental and six growth controls. Viable protozoa were assessed at 24 h after incubation in the presence of the compounds by counting in an haemocytometer. Results are expressed both as percentages of inhibition (cytostatic activity) and percentages of reduction (cytocidal activity) with respect to controls. Metronidazole (Rhône Poulenc, Courbevoie, France) was used as reference drug.

Toxicity assays

Murine macrophages J774 were seeded (70,000 cells/well) in 96 well flat bottom microplates (Sarstedt, Sarstedt Inc., Newton, NC) with 200 µl of RPMI 1640 medium (Sigma) supplemented with 20% heat inactivated fetal calf serum. Cells were allowed to attach for 24 h in a humidified 5% CO_2/95% air atmosphere at 37°C. Then, cells were exposed to the compounds (100, 10 and 1 µg/ml) for 24 h. Afterwards, cells were washed with PBS and incubated (37°C) with MTT 0.4 mg/ml for 60 min. Formazan was dissolved with DMSO (100 µl) and optical densities were measured as above. Each concentration was assayed three times and six growth controls were used in each test. Cytotoxicity percentages (%C) were determined as:

$$\%C = 100–(ODd–ODdm)/(ODc–ODcm) \times 100$$

where ODd is the mean of OD595 of wells with macrophages and different concentrations of the compounds; ODdm is the

mean of OD595 of wells with different compounds concentrations in medium; ODc is the growth control and ODcm is the mean of OD595 of wells with only medium.

Results

In order to simplify the results, only antiparasitic activity above 50% and unspecific toxicity below 50% are summarized. The *in vitro* efficacy against epimastigotes of *T. cruzi* is shown in Table I. The specific activity against *T. vaginalis* (Table II) is expressed as cytostatic activity (growth inhibition), or cytocidal activity (percentage of reduction with respect to control) in brackets. Unspecific cytotoxicity to macrophages (Table III) is expressed as cytotoxicity percentage.

Discussion

In the course of a screening program for new antifungal compounds, we have recently reported (Urbina *et al*. 2000, Vargas *et al*. 2003) the interesting antifungal properties displayed by some homoallylamines, tetrahydroquinolines and quinolines. Homoallylamines could serve as versatile precursors to obtain 2-substituted 4-methylquinolines via tetrahydroquinolines. Both type of compounds have important biological properties,

Table I. Anti-*Trypanosoma cruzi* epimastigote activity

Activity range (%)	Compound No.
100 µg/ml	
50–75	15, 20, 28, 37, 38, 56, 59, 62, 64
> 75	1–14, 16, 17, 19, 21–27, 29, 30–36, 39–55, 57, 58, 60, 61, 63, 65, 67–69
10 µg/ml	
50–75	2, 3, 7, 10, 15, 16, 22, 26, 44, 47, 48, 50–52, 55, 57, 58, 59, 65
> 75	5, 9, 25, 49, 63, 64, 68, 69
1 µg/ml	
50–75	25

Nifurtimox was assayed at 10, 2.5 and 0.5 µg/ml and reached 100, 88 and 54%, respectively.

Table II. Anti-*Trichomonas vaginalis* cytostatic or cytocidal (parenthesis) activity

Activity range (%)	Compound No.
100 µg/ml	
50–75	10, 15, 17, 18, 21, 23, 25–27, 31, 45, 50, 55, 62, 66, 67
> 75	1–4, (5), (6), 7, 8, (9), 11, (12), (13), 14, (16), 19, 20, 22, (24), (28), 29, 30, 32–39, (40), 41, (42), 43, 44, 47–49, (51–54), 56, 57, (58), 59–61, (63), 64, 65, 68, 69
10 µg/ml	
50–75	5, 6, 28, 29, 32, 34–36, 39, 40, 49, 53, 57–60, 63, 64, 65, 68, 69
> 75	42

Metronidazole was assayed at 2, 1 and 0.5 µg/ml and reached cytocidal activity of 100, 97.9 and 83.5, respectively.

Table III. Unspecific cytotoxicity determined on macrophages

Cytotoxicity (%)	Compound No.
100 µg/ml	
< 25	3, 11, 18, 20–23, 26, 29, 34, 37, 41, 43, 46, 59, 66
25–50	1, 2, 4, 8, 10, 12, 14, 19, 25, 27, 28, 35, 39, 44, 45, 49, 60, 64, 67
10 µg/ml	
< 25	1–4, 6, 8, 10–44, 46–63, 65–67, 69
25–50	5, 7, 9, 45, 64, 68
1 µg/ml	
< 25	1–9, 11–44, 46–50, 52–69
25–50	10, 45, 51

some have showed antileishmanial activity (Fournet *et al*. 1993). Looking for other antiparasitic effect, trypanocidal and trichomonacidal activities were assayed.

Results showed that most of the compounds tested (Table I) exhibit a trypanocidal activity of 75 to 100% at the higher concentration assayed (100 µg/ml). Since this activity could be due to unspecific cytotoxicity we compared unspecific cytotoxicity (%C) (Table III) with anti-epimastigote activity (%AE) (Table I) for each compound.

Some compounds (1–4, 8, 10, 11, 14, 21–23, 25–27, 29, 34, 35, 39, 41, 43–46, 49) present intrinsic trypanocidal activity at 100 µg/ml since their %C at this concentration is much lower than their %AE (%C<50, %AE>75), showing homoallylamines 22 and 29 the most interesting trypanocidal activity without cytotoxicity at this concentration.

Twenty-eight compounds (2, 3, 5, 7, 9, 10, 15, 16, 19, 22, 25, 26, 35, 44, 47–52, 55, 57–59, 63–65, 68 and 69) retained at least 50% of antichagasic activity at 10 µg/ml, at this concentration none unspecific cytotoxicity was shown for these compounds in most cases. Both, the homoallylamine derivative 25 (%C = 5.2) and the quinoline derivative 63 (%C = 0) showed trypanocidal activity higher than 90% at 10 µg/ml being the most interesting compounds at this concentration. Compound 25 retained even 60% of trypanocidal activity at the lower dose assayed (1 µg/ml).

Regarding trichomonacidal assays, many compounds exhibit cytocidal activity or at least an important cytostatic activity (≥75%) at 100 µg/ml: 1–9, 11–14, 16, 19, 20, 22, 24, 27–30, 32–37, 39–44, 47–49, 51–54, 56–61, 63–65, 68 and 69. However, if we discarded those with > 25% of unspecific cytotoxicity, only compounds 3, 11, 22, 29, 34, 41, 43 and 59 maintain an intrinsic trichomonacidal activity.

Although the antiparasitic activities were not comparable to those of the standard drugs, nifurtimox and metronidazole, some of the compounds could be useful as lead structures for further development.

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