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Synthesis and antiprotozoal activity of novel 1-methylbenzimidazole derivatives

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ABSTRACT

In this paper are reported the synthesis and antiprotozoal activity in vitro of 24 1-methylbenzimidazole derivatives (**13–36**) substituted at position 2 with aminocarbonyl, *N*-methylaminocarbonyl, *N*,*N*-dimethylaminocarbonyl, ethoxycarbonyl, 1-hydroxyethyl and acetyl groups, some of them with chlorine atoms at the benzenoid ring. Compounds **13–36** were more active than metronidazole, the choice drug against *Giardia intestinalis* and most of them against *Trichomonas vaginalis*. The most active group of compounds for both parasites was that with a 2-ethoxycarbonyl group (**16**, **22**, **28**, **34**), independently of the substitution pattern at the benzenoid ring.

1. Introduction

Parasitic infections still remain a mayor health threat in underdeveloped countries. According to WHO, more than 2 billion people of the world are infected with intestinal parasites.[1] Among these, *Giardia intestinalis*, causative agent of the disease named giardiosis, mainly affects the infant population causing severe retardation of growth and development.[2] On the other hand, *Trichomonas vaginalis* causes the sexually transmitted disease trichomonosis, with an incidence of 8 million cases in North America and 170 million infections worldwide.[3] Trichomonosis in women can be asymptomatic and have been associated with preterm labor and low-birth weight. The choice drug for the treatment of both protozoan diseases, giardiosis and trichomonosis, is metronidazole, a nitroimidazole that has been on the market for more than 40 years. Although an excellent therapeutic agent, metronidazole has undesirable side effects that limit its use; in addition, resistant strains have developed against this drug.[4] Nitazoxanide is a relatively new nitroheterocyclic drug that has been successfully used in the treatment of giardiosis;[5] however, due to different individual response to drugs, it is still important to have more options of treatment. Therefore, the search for new giardicidal and trichomonicidal agents is of great importance. In this respect, there has been a growing interest in our research group during the past decade to synthesize and test several series of benzimidazole derivatives as antiparasitic agents, including both giardicidal and trichomonicidal activity.[6–9] As part of our research program aimed at determining the structural requirements that a benzimidazole must have for antiparasitic activity, a series of 1-methylbenzimidazoles substituted at position 2 with aminocarbonyl, *N*-methylaminocarbonyl, *N*,*N*-dimethylaminocarbonyl, ethoxycarbonyl, hydroxyethyl and acetyl groups have been synthesized (Table 1). These compounds were tested in vitro against *G. intestinalis* and *T. vaginalis*.

2. Chemistry

Target molecules were synthesized according to the sequence of reactions shown in Scheme 1. As a start, the proper *N*-methyl-1,2-phenylenediamine (**1–4**) through a Phillips cyclocondensation[10] with glycolic acid cleanly afforded the corresponding 2-(hydroxymethyl)-1-methyl-1*H*-benzimidazole derivative (**5–8**).[11] Then, **5–8** were oxidized with commercial activated manganese dioxide[12] to give the expected 1-methyl-1*H*-benzimidazole-2-carbaldehyde derivative (**9–12**). For the preparation of the final amides, a method was adapted from the literature.[13] Cold isopropanol was saturated with ammonia, methylamine or dimethylamine, and to the solution was added carbaldehyde **9–12**, activated manganese dioxide and NaCN to afford 1-methyl-1*H*-benzimidazole-2-carboxamides (**13, 19, 25, 31**), *N*,1-dimethyl-1*H*-benzimidazole-2-carboxamides (**14, 20, 26, 32**) or *N*,*N*,1-trimethyl-1*H*-benzimidazole-2-carboxamides (**15, 21, 27, 33**), respectively. Ethyl 1-methyl-1*H*-benzimidazole-2-carboxylates (**16, 22, 28, 34**) were prepared in a similar manner by adding the crude carbaldehyde and activated manganese dioxide to a cold solution of NaCN in anhydrous ethanol.[13] On the other hand, a Phillips cyclocondensation of **1–4** with lactic acid afforded the corresponding 2-(1-hydroxyethyl)-1-methyl-1*H*-

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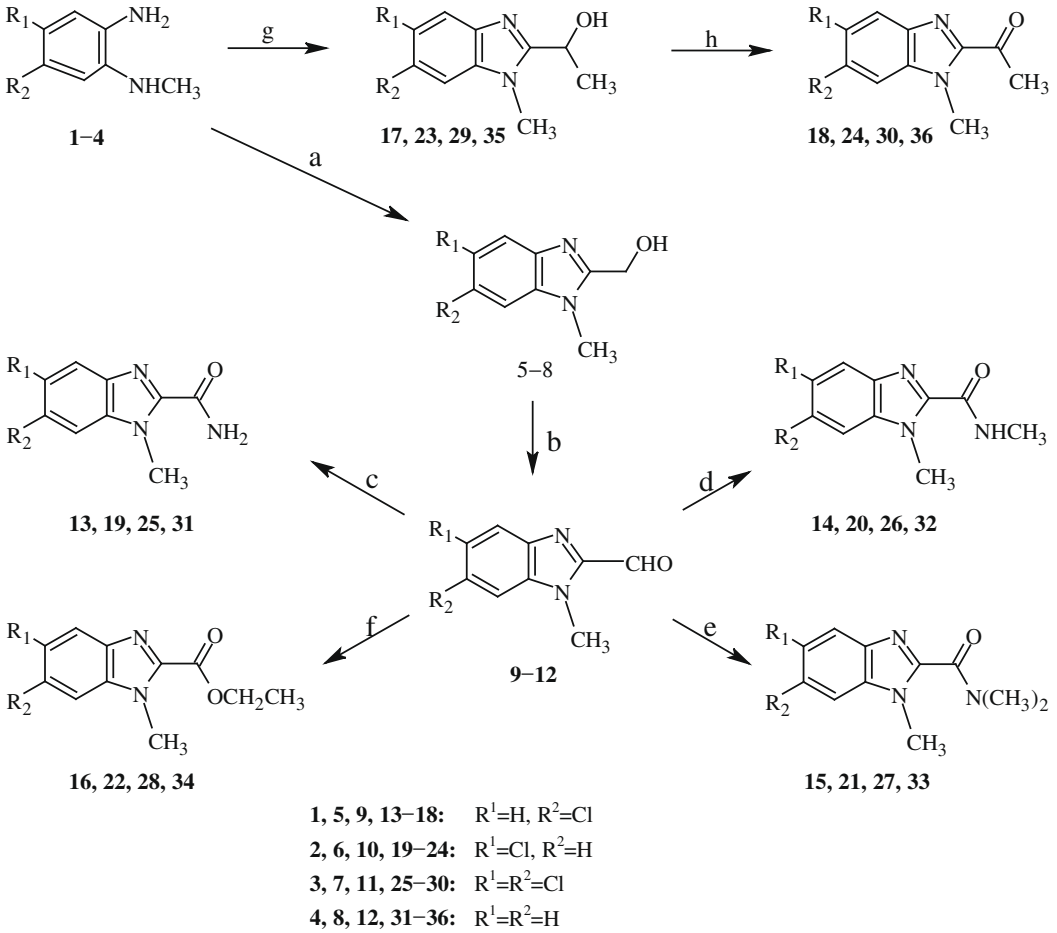


Scheme 1. Reagents and conditions: (a) $HOCH_2COOH$, HCl, heat; (b) MnO_2 (act.), CH_2Cl_2; (c) (1) NH_3 in isopropanol, 0 °C (2) MnO_2 (act.), NaCN, 0 °C; (d) (1) NH_2CH_3 in isopropanol, 0 °C (2) MnO_2 (act.), NaCN, 0 °C; (e) (1) $NH(CH_3)_2$ in isopropanol, 0 °C (2) MnO_2 (act.), NaCN, 0 °C; (f) (1) MnO_2 (act.), NaCN, ethanol, 0 °C; (g) $CH_3(HO)CHCOOH$, HCl, heat; (h) MnO_2 (act.), CH_2Cl_2.

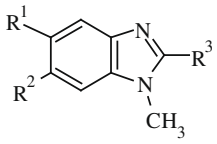
benzimidazole derivative (**17, 23, 29, 35**) which upon oxidation with activated manganese dioxide gave the 2-acetyl derivatives (**18, 24, 30, 36**). All the intermediates and final compounds were characterized by nuclear magnetic resonance (^1H and ^{13}C NMR) and elemental analysis.

3. Results and discussion

Compounds **13–36** were obtained in fair yields and purity as solids with sharp melting points. All the spectrometric and spectroscopic data for these compounds are in agreement with the expected structures. With the exception of compounds **31**,[14] **34**,[15] **35–36**,[16] most of the synthesized compounds (20) resulted in new structures. At the beginning of the synthetic work, we tried to synthesize the final compounds from the corresponding 1-methyl-1*H*-benzimidazole-2-carboxylic acid followed by activation to give the acid derivate targets;[17] however; decarboxylation in situ of the 1-methylcarboxylic acid precluded the use of this synthetic route. Aldehyde preparation by mild alcohol oxidation with activated manganese dioxide in the presence of sodium cyanide followed by addition of the amine derivative or alcohol led to the designed final compounds. The reaction mechanism seems to proceed by cyanohydrin formation, which is oxidized to acyl cyanide by manganese dioxide. The reaction of this intermediate with an amine or alcohol yields the amide or ester with a displacement of the cyanide ion.[13] The synthesis of alcohols **17, 23, 29, 35** and the oxidation of these to obtain 2-acetyl derivatives **18, 24, 30, 36** with activated manganese dioxide in CH_2Cl_2 proceeded with no complications.

Benzimidazole 2-carbamates, such as albendazole and mebendazole, are well known as anthelmintic agents. In the early 90s it was reported that these compounds were also active against the protozoa *G. intestinalis* and *T. vaginalis*.[18] The mechanism of action seems to be related to the selective inhibition of parasite tubulin polymerization;[19] for this to occur it is required that the benzimidazole nucleus have a 2-methylcarbamate group and a hydrogen at position 1.[7,20] The present study is an extension of our previous projects with benzimidazole derivatives that are non 2-methylcarbamates as antiparasitic agents.[21] The biological assays for compounds **13–36** were carried out exactly as reported before.[7] The results of these studies are presented in Table 1. In general, all of the tested compounds have good antiparasitic activity. They were more active than metronidazole against *G. intestinalis* and, with the exception of **20** and **33**, against *T. vaginalis*. On the other hand, compounds **19**, **21**, **28** and **29** were more active than albendazole against *G. intestinalis* and all of them were more active than albendazole against *T. vaginalis*. The most active compounds against *G. intestinalis* were dichloro derivatives **28** and **29**, while esters **16**, **22**, and **28** were the most active against *T. vaginalis*. For both parasites the most active compound was the dichloro ethyl ester **28**. These results increase our data bank of antiparasitic activity of benzimidazole derivatives for further QSAR studies.

Table 1
Benzimidazole derivatives (**13**–**36**) synthesized and tested in vitro against *G. intestinalis* and *T. vaginalis*



Compound	R^1	R^2	R^3	IC_{50} *G. intestinalis* (μM)[a]	IC_{50} *T. vaginalis* (μM)[a]
13	H	Cl	$CONH_2$	0.0763 ± 0.0014	0.1094 ± 0.0040
14	H	Cl	$CONHCH_3$	0.0715 ± 0.0089	0.1051 ± 0.0112
15	H	Cl	$CON(CH_3)_2$	0.0400 ± 0.0063	0.2383 ± 0.0232
16	H	Cl	$CO_2CH_2CH_3$	0.0482 ± 0.0063	0.0189 ± 0.0021
17	H	Cl	$CH(OH)CH_3$	0.0712 ± 0.0047	0.1091 ± 0.0047
18	H	Cl	$COCH_3$	0.0670 ± 0.0048	0.2276 ± 0.0071
19	Cl	H	$CONH_2$	0.2338 ± 0.0001	0.1860 ± 0.0001
20	Cl	H	$CONHCH_3$	0.3577 ± 0.0089	0.3577 ± 0.0089
21	Cl	H	$CON(CH_3)_2$	0.2440 ± 0.0084	0.2104 ± 0.0084
22	Cl	H	$CO_2CH_2CH_3$	0.0398 ± 0.0020	0.0272 ± 0.0063
23	Cl	H	$CH(OH)CH_3$	0.0379 ± 0.0000	0.0949 ± 0.0047
24	Cl	H	$COCH_3$	0.0503 ± 0.0002	0.1318 ± 0.0071
25	Cl	Cl	$CONH_2$	0.4619 ± 0.0513	0.1339 ± 0.0089
26	Cl	Cl	$CONHCH_3$	0.1511 ± 0.0116	0.2247 ± 0.0155
27	Cl	Cl	$CON(CH_3)_2$	0.0735 ± 0.0037	0.0753 ± 0.0055
28	Cl	Cl	$CO_2CH_2CH_3$	0.0275 ± 0.0001	0.0293 ± 0.0001
29	Cl	Cl	$CH(OH)CH_3$	0.0203 ± 0.0040	0.0407 ± 0.0040
30	Cl	Cl	$COCH_3$	0.0349 ± 0.0020	0.0637 ± 0.0061
31	H	H	$CONH_2$	0.0942 ± 0.0029	0.1655 ± 0.0143
32	H	H	$CONHCH_3$	0.0608 ± 0.0132	0.1084 ± 0.0079
33	H	H	$CON(CH_3)_2$	0.5117 ± 0.0541	0.4305 ± 0.0271
34	H	H	$CO_2CH_2CH_3$	0.0686 ± 0.0098	0.0857 ± 0.0024
35	H	H	$CH(OH)CH_3$	0.0681 ± 0.0057	0.1674 ± 0.0085
36	H	H	$COCH_3$	0.0861 ± 0.0057	0.2095 ± 0.0028
Albendazole				0.0370 ± 0.0030	1.5905 ± 0.0113
Metronidazole				1.2260 ± 0.1250	0.2360 ± 0.0160

[a] Values are means of duplicates of three experiments ± Standard Error of Measurement S.E.M.

4. Conclusions

Carboxylic acid derivatives **13–28**, esters and amides, were synthesized by the oxidation of the precursor cyanohydrins followed by displacement of the cyanide ion by the proper amine or ethanol in one pot-reaction. Most of these compounds (20) resulted in new structures that were active against both protozoan parasites: *G. intestinalis* and *T. vaginalis.* These compounds showed better activity than metronidazole, the choice drug for these infections, especially, the group of ester compounds (**16**, **22**, **28, 34)** which was the most active, independently of the substitution pattern.

It is confirmed that the 2-methylcarbamate group and the hydrogen at position 1 are not required for antiprotozoal activity against *G. intestinalis* and *T. vaginalis*.[7,21] Further QSAR studies are in progress based on the activity of these new compounds and some other 1-methylbenzimidazole derivatives previously synthesized and tested.

5. Experimental

5.1. Chemistry

Melting points were determined on a Büchi B-450 melting-point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were measured on a Varian EM-390 (300, 400 and 75.5 MHz) and a Varian Unity 300 (300 and 75.4 MHz) spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (Me_4Si, $\delta = 0$) used as internal reference in $CDCl_3$ or DMSO-d_6; *J* values are given in hertz. Splitting patterns have been designated as follows: s, singlet; br s, broad singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qt, quintuplet; m, multiplet. Mass spectra were recorded on a JEOL JMS-SX102A and JEOL 1AX505HA spectrometer at the Instituto de Química, UNAM; *m/z* (% rel. int.). Elemental analyses were performed on a Fisons EA1108 instrument. Catalytic hydrogenations were carried out on a Parr hydrogenation apparatus. Reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F_{254} plates (Merck). Starting materials 1–4 were synthesized in our laboratory from available commercial 2-nitroaniline, 3-chloroaniline, 4-chloroaniline and 3,4-dichloroaniline (Aldrich), respectively, via acetylation, nitration, methylation and hydrolysis.

5.2. General method of synthesis

5.2.1. 2-(Hydroxymethyl)-1-methyl-1*H*-benzimidazole (5–8) [11]

The appropriate *N*-methyl-1,2-phenylenediamine **1–4** (0.082 mol), 1.5 equivalents of glycolic acid and 10 mL of concentrated HCl were heated under a N_2 atmosphere at 95 °C for 12 h; then, the reaction mixture was neutralized with a saturated $NaHCO_3$ solution, and the crude product was isolated by vacuum filtration.

5.2.2. 1-Methyl-1*H*-benzimidazole-2-carbaldehyde (9–12) [22–24]

Crude 2-hydroxymethyl intermediates (**5–8**), (0.012 mol), 1.0 equiv of activated manganese dioxide and 250 mL of dichloromethane were magnetically stirred at room temperature for 3 days. During this time, the reaction mixture was filtered through a small bed of celite every 24 h to remove manganese salts. The filtered solution was then treated with a 1.0 equiv of MnO_2. When the reaction was completed, the mixture was filtered twice, first

through a small bed of celite, and then through a small column packed with silica gel, which was washed with ethyl acetate in order to remove the compounds from the residual MnO_2 and polar compounds.

5.2.3. 1-Methyl-1*H*-benzimidazole-2-carboxamide derivatives (13–15, 19–21, 25–27, 31–33)

Cold isopropyl alcohol (10 mL) was saturated with dry NH_3, NH_2CH_3 or $NH(CH_3)_2$. Then, NaCN (5 mmol) was added, and after 5 min stirring, carbaldehyde **9–12** (1 mmol) and MnO_2 (20 mmol) were incorporated. The reaction mixture was stirred for 4 h at 0 °C and then for 24 h at 25 °C. Purification of the corresponding compounds was carried out by diluting the reaction mixture with CH_2Cl_2 and filtering twice, first through a small bed of celite, and then, through a small column packed with silica gel that was washed as before.

5.2.4. Ethyl 1-methyl-1*H*-benzimidazole-2-carboxylates (16, 22, 28, 34)

Into a cold solution of NaCN (5 mmol) in absolute ethanol (50 mL) at 0 °C was added carbaldehyde **9–12** (1 mmol) and manganese dioxide (20 mmol). The reaction mixture was stirred for 4 h at 0 °C and then for 24 h at 25 °C. Purification of the corresponding compound was carried out by diluting the reaction mixture with CH_2Cl_2 and filtering twice, first through a small bed of celite, and then, through a small column packed with silica gel that was washed as before.

5.2.5. 2-(1-Hydroxyethyl)-1-methyl-1*H*-benzimidazole derivatives (17, 23, 29, 35)

The appropriate *N*-methyl-1,2-phenylenediamine **1–4** (0.053 mol), 1.3 equiv of lactic acid and 10 mL of concentrated HCl were heated under a N_2 atmosphere at 95 °C for 12 h; then, the reaction mixture was neutralized with saturated $NaHCO_3$ solution, and the crude product was isolated by vacuum filtration.

5.2.6. 2-Acetyl-1-methyl-1*H*-benzimidazole (18, 24, 30, 36)

The appropriate 2-(1-hydroxyethyl)-1-methyl-1*H*-benzimidazole, (0.0094 mol), 10 equiv of activated manganese dioxide and 250 mL of dichloromethane were magnetically stirred at room temperature for 1 day. After the reaction was completed, the mixture was filtered twice, first through a small bed of celite to remove manganese salts, and then through a small column packed with silica gel, which was washed with ethyl acetate in order to remove the compounds from the residual MnO_2 and polar compounds.

5.2.7. 6-Chloro-1-methyl-1*H*-benzimidazole-2-carboxamide (13)

Recrystallized from water, 56% yield of light brown solid, mp 246.8-247.3 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.08 (s, 3H, NCH_3), 7.29 (dd, 1H, C-5, J = 1.9 Hz, J = 8.5 Hz), 7.71 (d, 1H, H-4, J = 8.7 Hz), 7.81 (d, 1H, H-7, J = 1.5 Hz), 7.87 and 8.28 (s, 2H, NH_2, exch. D_2O); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 31.99 (NCH_3), 111.25 (C-7), 121.30 (C-4), 123.31 (C-5), 128.60 (C-6), 137.33 (C-7a), 139.30 (C-3a), 144.93 (C-2), 161.06 (CO); EIMS: 209 (M^+, 100), 165 (50), 152 (30). Anal. Calcd for $C_9H_8ClN_3O$ (209.63): C, 51.56; H; 3.86; N, 20.04. Found: C, 51.83; H, 4.01; N, 19.71.

5.2.8. 6-Chloro-*N*,1-dimethyl-1*H*-benzimidazole-2-carboxamide (14)

Recrystallized from ethanol, 46% yield of light brown solid, mp 171–171.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.03 (d, 3H, $NHCH_3$, J = 5.2, s with D_2O), 4.21 (s, 3H, NCH_3), 7.33 (dd, 1H, H-5, J = 1.8 Hz, J = 8.6 Hz), 7.45 (d, 1H, H-7, J = 1.6 Hz), 7.68 (d, 1H, H-4, J = 8.4 Hz), 7.88 (s, 1H, NH, exch. D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 25.90 ($NHCH_3$), 32.10 (NCH_3), 110.47 (C-7), 121.19 (C-4), 124.36 (C-5), 130.42 (C-6), 137.24 (C-7a), 139.08 (C-3a), 144.06 (C-2), 159.75 (CO); EIMS: 223 (M^+, 47), 166 (100), 165 (48). Anal. Calcd for $C_{10}H_{10}ClN_3O$ (223.65): C, 53.70; H; 4.51; N, 18.79. Found: C, 53.72; H, 4.49; N, 18.64.

5.2.9. 6-Chloro-*N*,*N*,1-trimethyl-1*H*-benzimidazole-2-carboxamide (15)

Recrystallized from ethanol, 46% yield of white solid, mp 108.8–109.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.17 and 3.34 (s, 3H + 3H, $N(CH_3)_2$, 3.90 (s, 3H, NCH_3), 7.27 (dd, 1H, H-5, J = 2.0 Hz, J = 8.8 Hz), 7.40 (d, 1H, H-7, J = 1.6 Hz), 7.69 (d, 1H, H-4, J = 8.8 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 109.95 (C-7), 121.42 (C-4), 123.56 (C-5), 129.84 (C-6), 135.94 (C-7a), 139.95 (C-3a), 145.92 (C-2), 160.80 (CO); EIMS: 237 (M^+, 12), 180 (70), 166 (100), 165 (40). Anal. Calcd for $C_{11}H_{12}ClN_3O$ (237.68): C, 55.59; H, 5.09; N, 17.68. Found: C, 55.70; H, 5.46; N, 17.74.

5.2.10. Ethyl 6-chloro-1-methyl-1*H*-benzimidazole-2-carboxylate (16)

Recrystallized from ethanol, 50% yield of white solid, mp 142.6–143.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.48 (t, 3H, CH_3, J = 6.9 Hz), 4.11 (s, 3H, NCH_3), 4.50 (q, 2H, CH_2, J = 6.9 Hz), 7.29 (dd, 1H, H-5, J = 1.8, Hz, J = 8.7 Hz), 7.42 (dd, 1H, H-7, J = 0.6 Hz, J = 1.9 Hz), 7.8 (dd, 1H, H-4, J = 0.6 Hz, J = 8.7 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.19 (CH_3), 32.21 (NCH_3), 62.31 (CH_2), 110.34 (C-7), 122.74 (C-4), 124.65 (C-5), 131.39 (C-6), 137.09 (C-7a), 140.07 (C-3a), 141.65 (C-2), 159.74 (CO); FABMS: 238 (M^+, 35), 193 (10), 166 (100), 165 (30). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$ (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.45; H, 4.63; N, 11.70.

5.2.11. 6-Chloro-2-(1-hydroxyethyl)-1-methyl-1*H*-benzimidazole (17)

Recrystallized from ethanol, yield 85% of white solid, mp 175.5–176.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.57 (d, 3H, CH_3, J = 6.6 Hz), 3.84 (s, 3H, NCH_3), 5.03 (qt, 1H, CH, J = 6.0 Hz, becomes q with D_2O), 5.65 (d, 1H, OH, J = 6.0 Hz, exch. D_2O), 7.18 (dd, 1H, H-5, J = 3.0 Hz, J = 9.0 Hz), 7.59 (d, 1H, H-4, J = 9.0 Hz), 7.68 (d, 1H, H-7, J = 3.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.21 (CH_3), 30.24 (NCH_3), 63.03 (CH), 109.46 (C-7), 119.51 (C-4), 122.90 (C-5), 128.68 (C-6), 136.29 (C-7a), 139.09 (C-3a), 157.04 (C-2); EIMS: *m/z* (% rel. int.); 210(M^+, 62), 208 (34), 195(100), 193 (38), 167 (57), 165 (54). Anal. Calcd for $C_{10}H_{11}ClN_2O$ (210.66): C, 57.01; H; 5.26; N, 13.30. Found: C, 57.52; H, 5.24; N, 13.15.

5.2.12. 2-Acetyl-6-chloro-1-methyl-1*H*-benzimidazole (18)

Recrystallized from ethyl acetate, yield 73% of white solid, mp 188.5–189.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (s, 3H, $COCH_3$), 4.08 (s, 3H, NCH_3), 7.31 (dd, 1H, H-5, J = 1.8 Hz, J = 8.7 Hz), 7.41 (d, 1H, H-7, J = 2.1 Hz), 7.78 (d, 1H, H-4, J = 8.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 27.99 (CH_3), 32.42 (NCH_3), 110.48 (C-7), 122.72 (C-4), 124.73 (C-5), 131.79 (C-6), 137.35 (7a), 139.92 (C-3a), 146.64 (C-2), 192.93 (CO); EIMS: *m/z* (% rel. int.): 208 (M^+, 100), 180 (32), 165 (96). Anal. Calcd for $C_{10}H_9ClN_2O$ (208.64): C, 57.57; H; 4.35; N, 13.43. Found: C, 57.91; H, 4.43; N, 13.47.

5.2.13. 5-Chloro-1-methyl-1*H*-benzimidazole-2-carboxamide (19)

Recrystallized from ethanol, 30% yield of white solid, mp 184.7–185.1 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.09 (s, 3H, NCH_3), 7.37 (dd, 1H, H-6, J = 2.1 Hz, J = 8.7 Hz), 7.68 (dd, 1H, H-7, J = 0.6 Hz, J = 8.8 Hz), 7.75 (dd, 1H, H-4, J = 0.3 Hz, J = 2.1 Hz), 7.86 and 8.25 (s, 2H, NH_2, exch. D_2O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 32.33 (NCH_3) 111.37 (C-7), 120.39 (C-4), 125.50 (C-6), 129.21 (C-5), 135.58 (C-7a), 141.58 (C-3a), 143.56 (C-2), 161.28 (CO); FABMS: 210 (MH^+,100), 209 (M^+, 22), 193 (30), 154 (65). Anal. Calcd for

$C_9H_8ClN_3O$ (209.63): C, 51.56; H, 3.85; N, 20.04. Found: C, 51.52; H, 3.72; N, 19.79.

5.2.14. 5-Chloro-*N*,1-dimethyl-1*H*-benzimidazole-2-carboxamide (20)

Recrystallized from ethanol, 56% yield of light brown solid, mp 190.3–191.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.79 (d, 3H, $NHCH_3$, J = 5.1, becomes s with D_2O), 4.09 (s, 3H, NCH_3), 7.36 (dd, 1H, H-6, J = 1.8 Hz, J = 8.8 Hz), 7.69 (d, 1H, H-7, J = 8.7 Hz), 7.73 (d, 1H, H-4, J = 1.8 Hz), 8.96 (d, 1H, NH, J = 4.8 Hz, exch. D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 26.13 ($NHCH_3$) 32.46 (NCH_3), 111.60 (C-7), 119.49 (C-4), 125.78 (C-6), 130.04 (C-5), 134.80 (C-7a), 139.65 (C-3a), 143.59 (C-2), 158.96 (CO); FABMS: 224 (MH^+,100), 223 (M^+,15), 193 (12), 154 (58). Anal. Calcd for $C_{10}H_{10}ClN_3O$ (223.65): C, 53.70; H, 4.51; N, 18.79. Found: C, 53.80; H, 4.48; N, 18.69.

5.2.15. 5-Chloro-*N*,*N*,1-trimethyl-1*H*-benzimidazole-2-carboxamide (21)

Recrystallized from ethanol, 48% yield of white solid, mp 161.6–162.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.18 and 3.34 (s, 3H + 3H, $N(CH_3)_2$, 3.94 (s, 3H, NCH_3), 7.34 (m, 2H, H-6 and H-7,), 7.77–7.78 (m, 1H, H-4,); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 31.50 (NCH_3), 35.56 and 39.06 ($N(CH_3)_2$), 10.77 (C-7), 120.29 (C-4), 124.63 (C-6), 128.46 (C-5), 134.03 (C-7a), 142.17 (C-3a), 146.33 (C-2), 160.92 (CO); EIMS: 237 (M^+, 12), 180 (72), 166 (100). Anal. Calcd for $C_{11}H_{12}ClN_3O$ (237.68): C, 55.59; H, 5.09; N, 17.68. Found: C, 55.60; H, 5.16; N, 17.71.

5.2.16. Ethyl 5-chloro-1-methyl-1*H*-benzimidazole-2-carboxylate (22)

Recrystallized from ethanol, 46% yield of white solid, mp 150.2–151.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.49 (t, 3H, CH_3, J = 7.2 Hz), 4.12 (s, 3H, NCH_3), 4.52 (q, 2H, CH_2, J = 7.2 Hz), 7.32 (dd, 1H, H-6, J = 2.0 Hz, J = 8.4 Hz), 7.44 (dd, 1H, H-4, J = 0.4 Hz, J = 2.0 Hz), 7.81 (dd, 1H, H-7, J = 0.4 Hz, J = 8.8 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.23 (CH_3), 32.29 (NCH_3), 62.44 (CH_2), 110.42 (C-7), 122.71 (C-4), 124.82 (C-6), 131.51 (C-5), 137.04 (C-7a), 139.82 (C-3a), 141.53 (C-2), 159.65 (CO); EIMS: 238 (M^+, 40), 193 (8), 166 (100), 165 (32). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$ (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.69; H, 4.65; N, 11.82.

5.2.17. 5-Chloro-2-(1-hydroxyethyl)-1-methyl-1*H*-benzimidazole (23)

Recrystallized from water/ethanol, 4:1, yield 75% of brown solid, mp 95.5–96.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.56 (d, 3H, CH_3, J = 6.0 Hz), 3.85 (s, 3H, NCH_3), 5.05 (qt, 1H, CH, J = 6.6 Hz, becomes q with D_2O), 5.70 (d, 1H, OH, 6.0 Hz, exch. D_2O), 7.24 (dd, 1H, H-6, J = 2.1, Hz, J = 8.7 Hz), 7.54 (d, 1H, H-7, J = 8.7 Hz), 7.64 (d, H, H-4, J = 1.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 21.36 (CH_3), 30.17 (NCH_3), 61.93 (CH), 111.27 (C-7), 118.34 (C-4), 122.06 (C-6), 125.73 (C-5), 135.02 (C-7a), 142.42 (C-3a), 158.06 (C-2); EIMS: *m/z* (% rel. int.) 210 (M^+, 10), 195 (30), 167(100), 165(65). Anal. Calcd for $C_{10}H_{11}ClN_2O$ (210.66): C, 57.01; H; 5.26; N, 13.30. Found: C, 56.98; H, 5.35; N, 13.32.

5.2.18. 2-Acetyl-5-chloro-1-methyl-1*H*-benzimidazole (24)

Recrystallized from ethanol, yield 65% of white solid, mp 97.4–97.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (s, 3H, CH_3), 4.08 (s, 3H, NCH_3), 7.31 (dd, 1H, H-7, J = 0.6 Hz, J = 8.7 Hz), 7.36 (dd, 1H, H-6, J = 1.8 Hz, J = 8.7 Hz), 7.82 (dd, 1H, H-4,, J = 0.6 Hz, J = 1.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.09 (CH_3), 32.47 (NCH_3), 111.42 (C-7), 121.17 (C-4), 126.57 (C-6), 129.42 (C-5), 135.28 (7a), 141.73 (C-3a), 146.67 (C-2), 192.92 (CO); EIMS: *m/z* (% rel. int.); 208 (M^+, 54), 180 (32), 165 (100). Anal. Calcd for $C_{10}H_9ClN_2O$ (208.64): C, 57.57; H; 4.35; N, 13.43. Found: C, 57.39; H, 4.16; N, 13.45.

5.2.19. 5,6-Dichloro-1-methyl-1*H*-benzimidazole-2-carboxamide (25)

Recrystallized from ethanol, 61% yield of brown solid, mp 245.8–246.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.07 (s, 3H, NCH_3), 7.92 (s, 1H, H-4), 8.03 (s, 1H, H-7), 7.92 and 8.30 (s, 1H + 1H, NH_2, exch. D_2O); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 32.30 (NCH_3) 113.19 (C-7), 120.98 (C-4), 125.49 (C-5), 126.64 (C-6), 136.07 (C-7a), 139.91 (C-3a), 146.02 (C-2), 160.78 (CO); EIMS: 243 (M^+, 100), 199 (56), 186 (28). Anal. Calcd for $C_9H_7Cl_2N_3O$ (244.07): C, 44.29; H, 2.89; N, 17.22. Found: C, 44.46; H, 3.14; N, 17.02.

5.2.20. 5,6-Dichloro-*N*,1-dimethyl-1*H*-benzimidazole-2-carboxamide (26)

Recrystallized from ethanol, 71% yield of brown solid, mp 213.4–214.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.05 (d, 3H, $NHCH_3$, J = 5.2 Hz, becomes s with D_2O), 4.26 (s, 3H, NCH_3), 7.64 (s, 1H, H-4), 7.94 (s, 1H, H-7), 8.38 (s, 1H, NH, exch. D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 26.33 ($NHCH_3$) 32.87 (NCH_3), 112.45 (C-7), 120.35 (C-4), 129.76 (C-5), 129.89 (C-6), 130.38 (C-7a), 136.21 (C-3a), 143.45 (C-2), 157.72 (CO); FABMS: 258 (70), 257 (M^+, 13), 154 (100), 136 (72). Anal. Calcd for $C_{10}H_9Cl_2N_3O$ (258.10). C, 46.53; H, 3.51; N, 16.28. Found: C, 46.87; H, 3.56; N, 16.03.

5.2.21. 5,6-Dichloro-*N*,*N*,1-trimethyl-1*H*-benzimidazole-2-carboxamide (27)

Recrystallized from ethanol, 60% yield of white solid, mp 176.2–176.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.18 and 3.33 (s, 3H + 3H, $N(CH_3)_2$), 3.92 (s, 3H, NCH_3), 7.53 (s, 1H, H-4), 7.88 (s, 1H, H-7); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.73 (NCH_3), 35.68 and 39.09 ($N(CH_3)_2$), 111.44 (C-7), 121.73 (C-4), 127.26 (C-5), 128.49 (C-6), 134.58 (C-7a), 140.43 (C-3a), 146.85 (C-2), 160.41 (CO); FABMS: 272 (MH^+, 100), 271 (M^+, 7), 154 (50), 136 (28). Anal. Calcd for $C_{11}H_{11}Cl_2N_3O$ (272.13): C, 48.55; H, 4.07; N, 15.44. Found: C, 48.42; H, 4.27; N, 15.72.

5.2.22. Ethyl 5,6-dichloro-1-methyl-1*H*-benzimidazole-2-carboxylate (28)

Recrystallized from ethanol, 64% yield of brown solid, mp 152–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (t, 3H, CH_3, J = 7.2 Hz), 4.14 (s, 3H, NCH_3), 4.53 (q, 2H, CH_2, J = 6.8 Hz), 7.58 (s, 1H, H-7), 7.99 (s, 1H, H-4); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.21 (CH_3) 32.52 (NCH_3), 62.67 (CH_2), 111.87 (C-7), 122.79 (C-4), 128.28 (C-5), 130.03 (C-7a), 135.65 (C-6), 140.48 (C-3a), 142.51 (C-2), 159.48 (CO); FABMS: 273 (100), 272 (M^+, 13), 154 (60), 136 (44). Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_2$ (273.11): C, 48.37; H, 3.69; N, 10.26. Found: C, 48.42; H, 3.37; N, 10.36.

5.2.23. 5,6-Dichloro-2-(1-hydroxyethyl)-1-methyl-1*H*-benzimidazole (29)

Recrystallized from ethanol, yield 70% of brown solid, mp 181–182.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.56 (d, 3H, CH_3, J = 6.6 Hz), 3.83 (s, 3H, NCH_3), 5.02 (qt, 1H, CH, J = 6.6 Hz, becomes q with D_2O), 5.66 (d, 1H, OH, 6 Hz, exch. D_2O), 7.82 (s, 1H, H-4), 7.86 (s, 1H, H-7); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 21.28 (CH_3), 30.44 (NCH_3), 61.88 (CH), 111.82 (C-7), 120.06 (C-4), 123.84 (C-5), 124.56 (C-6), 135.79 (C-7a), 141.09 (C-3a), 159.09(C-2); EIMS: *m/z* (% rel. int.) 244 (M^+, 50), 230 (60), 229 (100), 201 (45), 199 (20). Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$ (244.01): C, 49.00; H; 4.11; N, 11.43. Found: C, 48.89; H, 4.19; N, 11.40.

5.2.24. 2-Acetyl-5,6-dichloro-1-methyl-1*H*-benzimidazole (30)

Recrystallized from ethanol, yield 69% of white solid, mp 182.6–183.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.82 (s, 3H, CH_3), 4.08 (s, 3H, NCH_3), 7.52 (s, 1H, H-4), 7.94 (s, 1H, H-7); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.02 (CH_3), 32.59 (NCH_3), 111.85 (C-7), 122.78 (C-4), 127.98 (C-5), 130.13 (C-6), 135.91 (7a), 140.53 (C-3a), 147.41 (C-2), 192.89 (C=O); EIMS: *m/z* (% rel. int.); 242 (M^+, 100), 227 (10), 214 (24),199 (48). Anal. Calcd for $C_{10}H_8Cl_2N_2O$ (243.08.64): C, 49.41; H; 3.32; N, 11.52. Found: C, 49.42; H, 3.50; N, 11.53.

5.2.25. 1-Methyl-1*H*-benzimidazole-2-carboxamide (31)[14]

Recrystallized from ethanol, 36% yield of yellow solid, mp 202–202.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.23 (s, 3H, NCH_3), 5.87 and 7.73 (s, 1H + 1H, NH_2, exch. D_2O), 7.35–7.47 (m, 3H, H-4, H-5 and H-6), 7.79 (ddd, 1H, H-7, J = 0.8 Hz, J = 1.2 Hz, J = 8.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 32.15 (NCH_3), 110.53 (C-7), 120.64 (C-4), 123.70 (C-5), 124.94 (C-6), 136.91 (C-7a), 140.69 (C-3a), 142.49 (C-2), 161.59 (CO); EIMS: 175 (M^+, 100), 131 (49), 118 (27), 104 (15). Anal. Calcd for $C_9H_9N_3O$ (175.18): C, 61.70; H, 5.18; N, 23.99. Found: C, 62.07; H, 5.25; N, 23.95.

5.2.26. *N*,1-Dimethyl-1*H*-benzimidazole-2-carboxamide (32)

Recrystallized from water, 55% yield of brown solid, mp 94.7–96.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.81 (d, 3H, $NHCH_3$, J = 5.1 Hz, s with D_2O), 4.10 (s, 3H, NCH_3), 7.26–7.38 (m, 2H, H-5 and H-6), 7.62 (d, 1H, H-4, J = 7.8 Hz), 7.70 (d, 1H, H-7, J = 7.8 Hz), 8.90 (d, 1H, NH, J = 4.2 Hz, exch. D_2O); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 25.80 ($NHCH_3$), 31.66 (NCH_3), 111.20 (C-7), 119.87 (C-4), 122.91 (C-5), 123.97 (C-6), 136.54 (C-7a), 140.66 (C-3a), 143.98 (C-2), 159.89 (CO); EIMS: 189 (M^+, 55), 160 (22), 132 (100). Anal. Calcd for $C_{10}H_{11}N_3O$ (189.21). C, 63.48; H, 5.86; N, 22.21. Found: C, 63.78; H, 5.81; N, 21.93.

5.2.27. *N*,*N*,1-Trimethyl-1*H*-benzimidazole-2-carboxamide (33)

69% yield of white solid, mp 43.8–44.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.16 and 3.33 (s, 3H + 3H, $N(CH_3)_2$), 3.93 (s, 3H, NCH_3), 7.28–7.41 (m, 3H, H-4, H-5 and H-6), 7.78 (ddd, 1H, H-7, J = 0.9 Hz, J = 2.2 Hz, J = 8.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 31.15 (NCH_3), 35.39 and 38.96 ($N(CH_3)_2$), 109.83 (C-7), 120.47 (C-4), 122.75 (C-5), 123.98 (C-6), 135.28 (C-7a), 141.33 (C-3a), 145.16 (C-2), 161.26 (CO); EIMS: 203 (M^+, 10), 146 (70), 132 (100). Anal. Calcd for $C_{11}H_{13}N_3O$ (203.24): C, 65.01; H, 6.45; N, 20.68. Found: C, 65.33; H, 6.27; N, 20.23.

5.2.28. Ethyl 1-methyl-1*H*-benzimidazole-2-carboxylate (34)[15]

48% yield of yellow oil, bp 200 °C at 0.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.48 (t, 3H, CH_3, J = 7.2 Hz), 4.16 (s, 3H, NCH_3), 4.51 (q, 2H, CH_2, J = 7.2 Hz), 7.33–7.46 (m, 3H, H-4, H-5 and H-6), 7.92 (ddd, 1H, H-7, J = 0.9 Hz, J = 2.1 Hz, J = 8.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.17 (CH_3) 32.07 (NCH_3), 62.21 (CH_2), 110.32 (C-7), 121.72 (C-4), 123.83 (C-5 and C-6), 125.50 (C-6), 136.50 (C-7a), 140.80 (C-3a), 141.26 (C-2), 159.92 (CO); EIMS: 204 (M^+, 10), 132 (19), 60 (94), 43 (100); FABHRMS Calcd for $C_{11}H_{13}N_2O_2$ (MH^+) 205.0977. Found: 205.0980.

5.2.29. 2-(1-Hydroxyethyl)-1-methyl-1*H*-benzimidazole (35)[16]

Recrystallized from water, yield 74% of brown solid, mp 131.6–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.59 (d, 3H, CH_3, J = 6.8 Hz), 3.84 (s, 3H, NCH_3), 5.06 (qt, 1H, CH, J = 6.4 Hz, becomes q with D_2O), 5.69 (d, 1H, OH, 6.0 Hz, exch. D_2O), 7.15–7.25 (m, 2H, H-5, H-6), 7.55 (d, 1H, H-7, J = 7.6 Hz), 7.61 (d, 1H, H-4, J = 7.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 21.56 (CH_3), 29.98 (NCH_3), 62.11 (CH), 109.82 (C-7), 118.95 (C-4), 121.37 (C-6), 122.06 (C-5), 136.23 (C-7a), 141.59 (C-3a), 156.52 (C-2); EIMS: *m/z* (% rel. int.) 176 (M^+, 4), 174 (30), 158 (78), 157 (100), 131 (52). Anal. Calcd for $C_{10}H_{12}N_2O$ (176.21): C, 68.16; H; 6.86; N, 15.90. Found: C, 69.18; H, 7.77; N, 16.11.

5.2.30. 2-Acetyl-1-methyl-1*H*-benzimidazole (36)[16]

Recrystallized from water, yield 65% of white solid, mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.86 (s, 3H, CH_3), 4.13 (s, 3H, NCH_3), 7.35–7.49 (m, 3H, H-5, H-6, H-7), 7.91 (d, 1H, H-4, J = 8.1 Hz);^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 28.22 (CH_3), 32.32 (NCH_3), 110.57 (C-7), 121.53 (C-6), 124.05 (C-4), 126.11 (C-5), 136.60 (7a), 140.73 (C-3a), 145.54 (C-2), 192.86 (CO); EIMS: *m/z* (% rel. int.); 174 (M^+, 18), 131(19), 91 (88), 76 (100). Anal. Calcd for $C_{10}H_{10}N_2O$ (174.19): C, 68.95; H; 5.79; N; 16.08. Found: C, 68.52; H, 6.02; N, 16.13.

5.3. Biological activity

5.3.1. Parasites

T. vaginalis strain GT3, and *G. intestinalis* isolate IMSS:0981:1 were used in all the experiments. Trophozoites of *G. intestinalis* and *T. vaginalis* were maintained in TYI-S-medium supplemented with 10% calf serum and bovine bile.

5.3.2. Susceptibility assays

In vitro susceptibility assays were performed by using a method previously described.[7] Briefly, 4×10^5 trophozoites of *G. intestinalis* or 4×10^4 trophozoites of *T. vaginalis* were incubated for 48 h at 37 °C with different concentrations of the compound to be tested, each added as solutions in DMSO. For solvent control, cultures received an equivalent amount of DMSO only, while albendazole and metronidazole were used as positive controls. At the end of the treatment period, the cells were washed and subcultured for another 48 h in a fresh medium to which no drug was added.

The trophozoites were then counted with a haemocytometer and the 50% inhibitory concentration (IC_{50}), together with the respective 95% confidence limit were calculated by Probit analysis. Experiments were carried out by using duplicate tubes, being repeated three times.

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