Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 1794–1800
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Short communication

Synthesis and *in vitro* cysticidal activity of new benzimidazole derivatives

Francisca Palomares-Alonso [a,c], Helgi Jung-Cook [a,c], Jaime Pérez-Villanueva [c], Juan Carlos Piliado [a], Sergio Rodríguez-Morales [c], Guadalupe Palencia-Hernández [b], Nayeli López-Balbiaux [c], Alicia Hernández-Campos [c], Rafael Castillo [c], Francisco Hernández-Luis [c,*]

[a] *Laboratorio de Neuropsicofarmacología, Instituto Nacional de Neurología y Neurocirugía, México DF 14269, Mexico*
[b] *Laboratorio de Neuroinmunología, Instituto Nacional de Neurología y Neurocirugía, México DF 14269, Mexico*
[c] *Facultad de Química, Departamento de Farmacia, Universidad Nacional Autónoma de México, México DF 04510, Mexico*

Received 14 November 2007; received in revised form 18 April 2008; accepted 5 May 2008
Available online 15 May 2008

Abstract

Despite albendazole being the drug of choice in neurocysticercosis treatment, its low solubility limits its bioavailability; therefore, more research is required in order to find new molecules with cestocidal activity and adequate aqueous solubility. A set of 13 benzimidazole derivatives were synthesized and their *in vitro* activities were evaluated against *Taenia crassiceps* cysts, using albendazole sulfoxide as reference molecule, showing that two of them exhibited good activity. Molecular modelling revealed that the cysticidal efficacy depends on the presence on the molecule of an H in the 1-position, a planar carbamate group at 2-position, and if the substituent in 5-position is voluminous, it should be orthogonal to the benzimidazole ring.

Keywords: Benzimidazole analogues; Cysticidal activity; Molecular modelling

1. Introduction

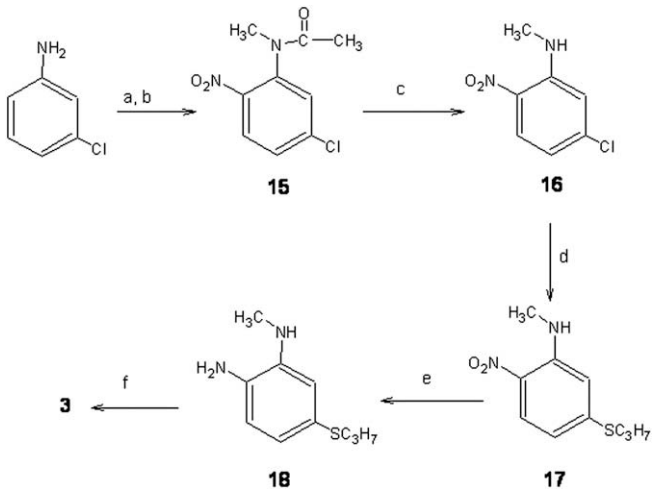
Cysticercosis, the infection caused by the larval stage of the tapeworm *Taenia solium*, is the most common parasitic disease of the nervous system in humans and the single most common cause of acquired epileptic seizures in the developing world, specially Latin America, India, Africa, and China [1,2]. The treatment of neurocysticercosis has evolved from surgical therapy in the past to anticysticercal chemotherapy. Praziquantel and albendazole (ABZ) are the drugs commonly used for the treatment of this disease [3,4], and both undergo extensive metabolism by cytochrome P450 [5,6]. Up-to-date ABZ is the drug of choice for neurocysticercosis treatment, however, its bioavailability is limited by its low solubility in the gastrointestinal tract; therefore, a high inter-individual variability in plasma levels and in efficacy has been found [7]. Considering that the search for new alternatives is still necessary, we synthesized 13 benzimidazole derivatives and their activities against *Taenia crassiceps* cysts were evaluated using albendazole sulfoxide **1**, which is the active metabolite of ABZ [8], as reference molecule. Also to understand the requirements for activity a molecular modelling study was performed.

2. Chemistry

Compound **1** was obtained by the treatment of ABZ with 3-chloroperbenzoic acid. Compound **2** was prepared by the methylation of ABZ with methyl iodide in methanol in the presence of potassium hydroxide. For the synthesis of compound **3**, the

* Corresponding author. Tel.: +55 56063822.
E-mail addresses: ingpalomares@yahoo.com.mx (F. Palomares-Alonso), franher@servidor.unam.mx (F. Hernández-Luis).

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.05.005



Scheme 1. Synthesis of compound **3**. Reagents and conditions: (a) $(CH_3CO)_2O$, HNO_3; (b) $(CH_3)_2SO_4$/NaOH; (c) H_2SO_4, Δ; (d) C_3H_7SH; (e) H_2/C–Pd 5%; (f) 2-methyl-2-thiopseudourea hemisulfate salt, methyl chloroformate, pH = 8, Δ.

sequence shown in Scheme 1 was followed. The synthesis began with the nitration of 3-chloroaniline by using fuming nitric acid and acetic anhydride, the product was treated with dimethyl sulfate and KOH to give the *N*-methylated acetamide **15**. The hydrolysis of this compound with H_2SO_4 led to *N*-methyl-2-nitroaniline **16**. Aromatic nucleophilic substitution in **16** with 1-propanethiol afforded **17** which upon catalytic reduction with hydrogen and C–Pd 5% gave 1,2-phenylenediamine **18**. Reaction of this compound with 2-methyl-2-thiopseudourea hemisulfate salt, methyl chloroformate and NaOH yielded **3**. Compounds **4**–**9** were prepared as described in Scheme 2. The required substituted 1,2-phenylenediamines (**23**–**26**) were prepared by the reduction of the corresponding 2-nitroanilines (**19**–**22**) with hydrogen in the presence of 5% palladium on carbon. The products of reduction without isolation were cyclocondensed with 2-methyl-2-thiopseudourea hemisulfate salt, methyl chloroformate and NaOH to give the corresponding methyl benzimidazole-2-carbamates **4**, **8**, **9** and **27**. Compound **27** was converted to acylchlorides with $SOCl_2$ and then dehydrohalogenation between this acylchloride and 4-nitrobenzyl alcohol or piperidine or diethylamine gave **5**, **6** or **7**, respectively. Finally compounds **8**–**14** were prepared by known procedures [9,10,14].

3. Results and discussion

All compounds synthesized (**1**–**14**) were obtained as solids with sharp melting points and their structures were established by IR, ^{1}H NMR and MS. Compounds **1**, **8**–**14** were characterized and the melting points and spectroscopic data were compared with those previously reported by our group [11–14].

3.1. In vitro cysticidal activity

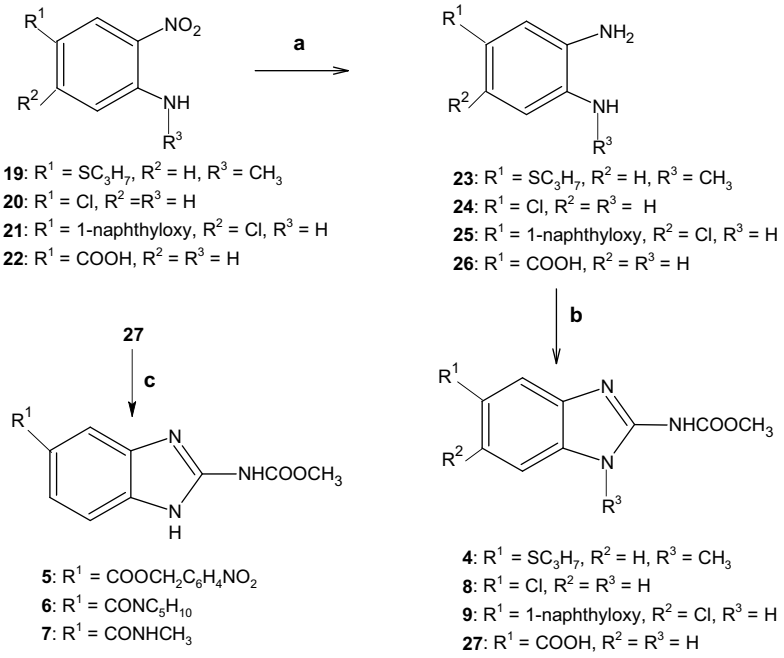
The *in vitro* cysticidal activity evaluations were performed on *T. crassiceps* cysts (ORF strain), which have been previously used as a model for the evaluation of cestocidal drugs [15], and albendazole sulfoxide **1** was used as the standard drug. We found that among the 13 investigated compounds, only **5**, **6** and **8** showed activity against *T. crassiceps* cysts of ORF strain (Table 1). The cysticidal activity of **5** and **6** was close to that exhibited by **1**; while **8** showed a lower activity. Compound **9** was not evaluated due to its insolubility in the culture media. Those compounds that exhibited activity against *T. crassiceps* cysts of ORF strain were evaluated on WFU strain (which has scolex). We found that **5**, **6** and **8** also exhibited activity against *T. crassiceps* of WFU strain. To note, **5** behaved similarly as **1**, while the activity of **6** and **8** was lower. Interestingly the activity of compounds in this strain was lower. This fact could be due to the size of the cysts, since cysts of WFU strain are larger (3–5 mm) than ORF cysts (2–3 mm) or due to the presence of the scolex, which has been suggested to have a specialized nutritional function and could help the parasite to resist the drugs' action [16,17].

The *in vitro* study results showed that the introduction of a methyl group instead of an H moiety at 1-position completely abolished the activity (**3** and **4**). In the case of **2** when the H atom in the *N*-carbamate was replaced with a methyl group, the activity decreased drastically, indicating that the protons in *N*-carbamate and in 1-position are necessary for the cysticidal activity. Also the derivatives containing methylthio instead of *N*-carbamate group (**10**–**13**) at 2-position were all inactive, confirming the importance of this group for the activity of the molecule. When the effect of the substituents at the 5-position was evaluated, we found that when the propylthio group at 5-position was replaced with larger groups such as 4-nitrobenzoyl carboxylate or piperidinyl-carboxamide (**5** or **6**) the activity was conserved and was close to that exhibited by **1**. In the case of **8**, the presence of a chlorine atom in the benzimidazole ring reduced the activity significantly; while the introduction of the *N*-methylcarboxamide abolished the activity of **7**.

3.2. Molecular modelling studies

In an attempt to identify the structural requirements for the cysticidal activity, molecular studies were performed on compounds **1**–**9**. Compounds **10**–**14** were excluded since these molecules with methylthio group at 2-position were ineffective. Although compounds **2**–**4** resulted ineffective, they were included in the analysis due to the presence of the methyl carbamate group at 2-position.

The conformational analysis was performed and the main molecular descriptors were obtained. All the molecular descriptors were correlated with the *in vitro* activity against *T. crassiceps* cysts using the QSAR module in Sybyl V. 7.3. Fig. 1 represents the lowest energy conformer of compounds **1**–**4** for comparison of the substituents at 1- and 2-positions. Fig. 2 shows the lowest energy conformer of compounds **1** and **5**–**9**. These figures provide visual evidence for the structural similarities and differences between these compounds. It can be seen that the introduction of the methyl group in both positions, *N*-carbamate (**2**) or at benzimidazole 1-position



Scheme 2. Synthesis of compounds **4**–**9**. Reagents and conditions: (a) H_2/C–Pd 5%; (b) 2-methyl-2-thiopseudourea hemisulfate salt, methyl chloroformate, pH = 8, Δ (c) thionyl chloride.

(compounds **3** and **4**) (Fig. 1a), precludes the planarity of the carbamate group which is observed in **1** (Fig. 1b). This feature could be important since the theoretical studies have shown that a planar conformation of **1** could facilitate its accommodation into the cleft of the *Haemonchus contortus* β-tubulin model [18].

We also found that the cysticidal activity was maintained when groups at 5-position could adopt the orthogonal conformation to the plane of the benzimidazole ring [4-nitrobenzyl carboxylate (**5**) and piperidinyl-carboxamide (**6**) (Fig. 2a)]. Our data are in agreement with those obtained by McCracken and Lipkowitz, in *Hymenolepis diminuta* [19], who found that those anthelmintics which have substituents at 5-position twisted out-of-plane are more active than those which have substituents at 5-position in plane. Although, in compound **8** (Fig. 2a), the substituent in 5-position was planar, the modest cysticidal activity could be explained considering that the chlorine atom could accommodate into the β-tubulin cleft. Compound **7** resulted to be inactive mainly due to the presence of the group *N*-methylcarboxamide at 5-position of the benzimidazole ring that is not orthogonal in the plane. Although the conformational study showed that **9** complied with the presence of the protons in *N*-carbamate and in 1-position of benzimidazole ring as well as with the "L" shape at 5-position (Fig. 2b), its activity was limited due to its low solubility. This characteristic is very common in benzimidazoles and should also be considered in the design of new derivatives.

The molecular descriptors of **1** and **5**–**9** are listed in Table 2. Correlations of descriptors with determined experimental activity were performed in order to identify which molecular features have influence on the cysticidal activity, and only a weak correlation with HOMO was found ($r = 0.399$). These results did not agree with a previous study realized by McCracken and Lipkowitz in *H. diminuta* [19], which reported a good correlation between the HOMO and PSA descriptors with the anthelmintic activity. This fact could be due to the differences in the biological evaluation parameters used, since the authors of Ref. (9) used the dose that is required to reduce the worm burden by 75%, while we used a fixed concentration of all compounds. Other factors could be due to the differences between the cestodes. More studies should be done with the active compounds in order to evaluate the molecular descriptors for cysticidal activity.

4. Conclusion

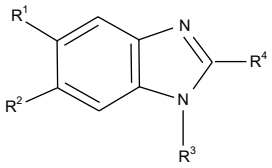
In summary we found that among the investigated compounds, **5** and **6** showed good cysticidal activity. These outcomes are very promising and our current efforts will focus on further evaluation to explore their *in vivo* efficacy. Additionally our results suggest that for cysticidal activity the molecule must have an H at 1-position, a methyl carbamate group at 2-position and an orthogonal substituent at 5-position.

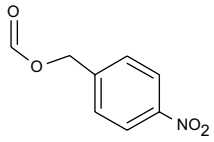
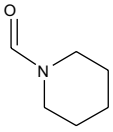
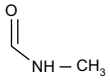
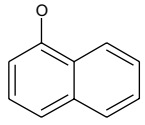
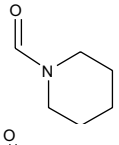
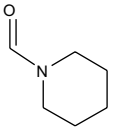
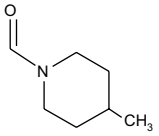
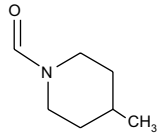
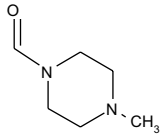
5. Experimental protocols

5.1. Chemistry

Melting points were determined in one-end open capillary tubes on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F254 plates (E. Merck). The spots were visualized under ultraviolet lamp. IR spectra were recorded on a Perkin Elmer FT-IR-1600 spectrophotometer as potassium bromide discs. ^{1}H NMR and ^{13}C NMR spectra were measured with a Varian EM-390 (300 and 75.5 MHz)

Table 1
Structure and biological activity of compounds **1**−**14** against *T. crassiceps* ORF and WFU strains



Compound	R^1	R^2	R^3	R^4	Cysts' mortality (%)			
					ORF strain		WFU strain	
					0.28 μM	1.70 μM	0.28 μM	1.70 μM
1	$S(O)C_3H_7$	H	H	$NHCO_2CH_3$	46 ± 5	88 ± 7	25 ± 2.3	35 ± 2.3
2	SC_3H_7	H	H	$N(CH_3)CO_2CH_3$	0	0	ND	ND
3	H	SC_3H_7	CH_3	$NHCO_2CH_3$	0	0	ND	ND
4	SC_3H_7	H	CH_3	$NHCO_2CH_3$	0	0	ND	ND
5		H	H	$NHCO_2CH_3$	41 ± 4.6	68 ± 7	22.6 ± 2.3	26 ± 4
6		H	H	$NHCO_2CH_3$	37 ± 6.1	62 ± 8	9.3 ± 2.3	16.7 ± 3
7		H	H	$NHCO_2CH_3$	0	0	ND	ND
8	Cl	H	H	$NHCO_2CH_3$	15 ± 2.3	23 ± 2.3	5 ± 2.3	8 ± 0
9		Cl	H	$NHCO_2CH_3$	ND	ND	ND	ND
10		H	H	SCH_3	0	0	ND	ND
11		Cl	H	SCH_3	0	0	ND	ND
12		H	H	SCH_3	0	0	ND	ND
13		Cl	H	SCH_3	0	0	ND	ND
14		H	H	SCH_3	0	0	ND	ND

"ND" indicates that the *in vitro* activity was not determined.

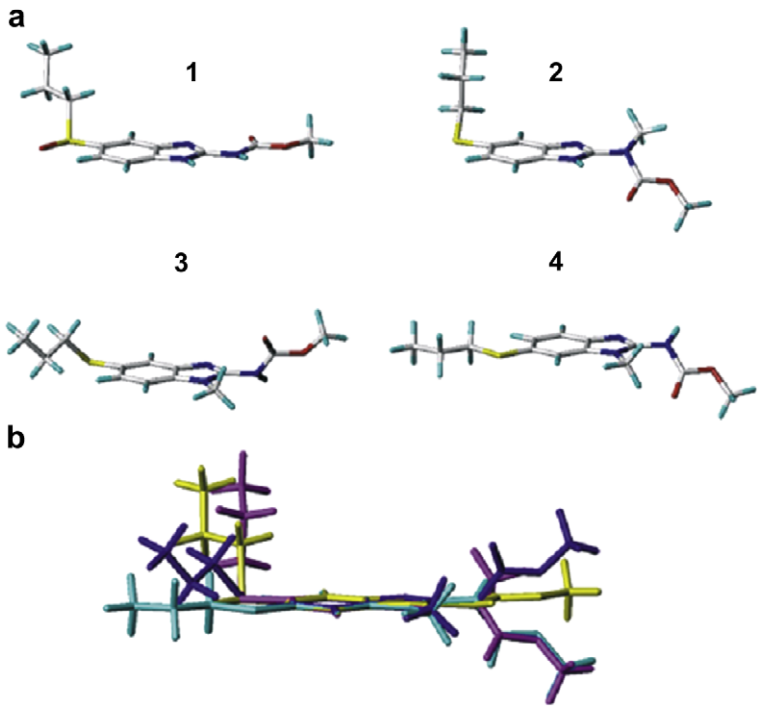


Fig. 1. Lowest energy conformer of compounds **1**–**4**. (a) Compounds modelled. (b) Superimposition of **1** (yellow), **2** (magenta), **3** (cyan) and **4** (purple), which were colored for better understanding. Methyl carbamate group of benzimidazole is planar, while the carbamate group of compounds **2**–**4** is outside the plane due to the steric effect of methyl group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

spectrometer. Chemical shifts (δ) are given in parts per million (ppm) using tetramethylsilane (Me_4Si) as an internal standard; J values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublet; t, triplet; m, multiplet; bs, broad signal. MS were recorded on a JEOL JMS-SX102A spectrometer by electron impact (EI) or fast atomic bombarded (FAB). Starting materials 3-chloroaniline, **20**, **22** and ABZ were purchased from Sigma Aldrich Company.

*5.1.1. Methyl methyl[5-(propylthio)-1H-benzimidazol-2-yl]carbamate (**2**)*

M.p. 80–82 °C. IR ν: 3333.18, 2956.25, 2870.21, 1702.88, 1546.67, 1454.16, 1198.50, 1165.06, 1107.82 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 0.935 (t, 3H, $CH_3CH_2CH_2S$, $J = 7.2$ Hz), 1.524 (m, 2H, $CH_3CH_2CH_2S$, $J = 6.8$ Hz), 2.848 (t, 2H, $CH_3CH_2CH_2S$, $J = 7.2$ Hz), 3.469 (s, 3H, CH_3), 3.839 (s, 3H, OCH_3), 7.112 (dd, 1H, H-6, $J_{6,7} = 8.4$, $J_{6,4} = 1.6$ Hz), 7.394 (d, 1H, H-7, $J = 8.1$ Hz), 7.476 (d, 1H, H-4, $J = 1.6$ Hz), 11.992 (s, 1H, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.99, 22.078, 33.661, 36.487, 53.768, 111.914, 113.361, 117.544, 119.164, 124.106, 127.078, 132.526, 134.033, 139.626, 141.283, 148.961, 154.203 ppm; EI-MS *m/z*: 279 $[M]^+$ (100%).

*5.1.2. Methyl [1-methyl-6-(propylthio)-1H-benzimidazol-2-yl]carbamate (**3**)*

M.p. 142.1–143.4 °C. IR ν: 3255.97, 2964.50, 2869.96, 1628.59, 1590.14, 1450.93, 1219.37, 1173.80, 1088.48 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.022 (t, 3H, $CH_3CH_2CH_2S$, $J = 7.2$ Hz), 1.650 (m, 2H, $CH_3CH_2CH_2S$, $J = 7.5$ Hz), 2.904 (t, 2H, $CH_3CH_2CH_2S$, $J = 7.2$ Hz), 3.660 (s, 3H, CH_3), 3.796 (s, 3H, OCH_3), 7.226 (d, 1H, H-4, $J = 7.8$ Hz), 7.249 (dd, 1H, H-5, $J_{5,4} = 7.5$, $J_{5,7} = 1.2$ Hz), 7.286 (d, 1H, H-7, $J_{5,7} = 1.2$ Hz), 9.631 (s, 1H, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.283, 22.500, 28.581, 37.501, 52.755, 111.126, 111.314, 125.886, 127.062, 131.010, 131.170, 153.673, 163.238 ppm; FAB-MS *m/z*: 280 $[M + 1]^+$.

*5.1.3. Methyl [1-methyl-5-(propylthio)-1H-benzimidazol-2-yl]carbamate (**4**)*

M.p. 120.5–122.1 °C. IR ν: 3286.98, 2956.08, 2929.46, 2868.25, 1631.18, 1490.64, 1451.44, 1217.44, 1172.07, 1086.47 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 0.938 (t, 3H, $CH_3CH_2CH_2S$, $J = 7.5$ Hz), 1.532 (m, 2H, $CH_3CH_2CH_2S$, $J = 7.5$ Hz), 2.858 (t, 2H, $CH_3CH_2CH_2S$, $J = 6.9$ Hz), 3.468 (s, 3H, CH_3), 3.607 (s, 3H, OCH_3), 7.190 (dd, 1H, H-6, $J_{6,7} = 8.4$, $J_{6,4} = 1.5$ Hz), 7.326 (d, 1H, H-7, $J = 8.4$ Hz), 7.427 (d, 1H, H-4, $J = 1.4$ Hz), 11.981 (s, 1H, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) δ: 13.019, 21.994, 28.035, 36.162, 51.722, 109.645, 112.782, 124.351, 128.713, 129.214, 129.562, 153.511, 162.517 ppm; FAB-MS *m/z*: 280 $[M + 1]^+$.

*5.1.4. 4-Nitrobenzyl-2-[(methoxycarbonyl)amino]-1H-benzimidazole-5-carboxylate (**5**)*

M.p. 319.6–320.3 °C. IR ν: 3382.02, 1708.07, 1652.23, 1272.12, 1186.56, 852.11 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.776 (s, 3H, OCH_3), 5.496 (s, 2H, CH_2O), 7.491 (dd, 1H, H-6, $J_{6,7} = 8.5$, $J_{6,4} = 1.0$ Hz), 7.752 (d, 2H, H-2′, $J = 8.6$ Hz), 7.801 (d, 1H, H-7, $J = 8.5$ Hz), 8.119 (d, 1H, H-4, $J = 1.0$ Hz), 8.274 (d, 2H, H-3′, $J = 8.6$ Hz), 11.981

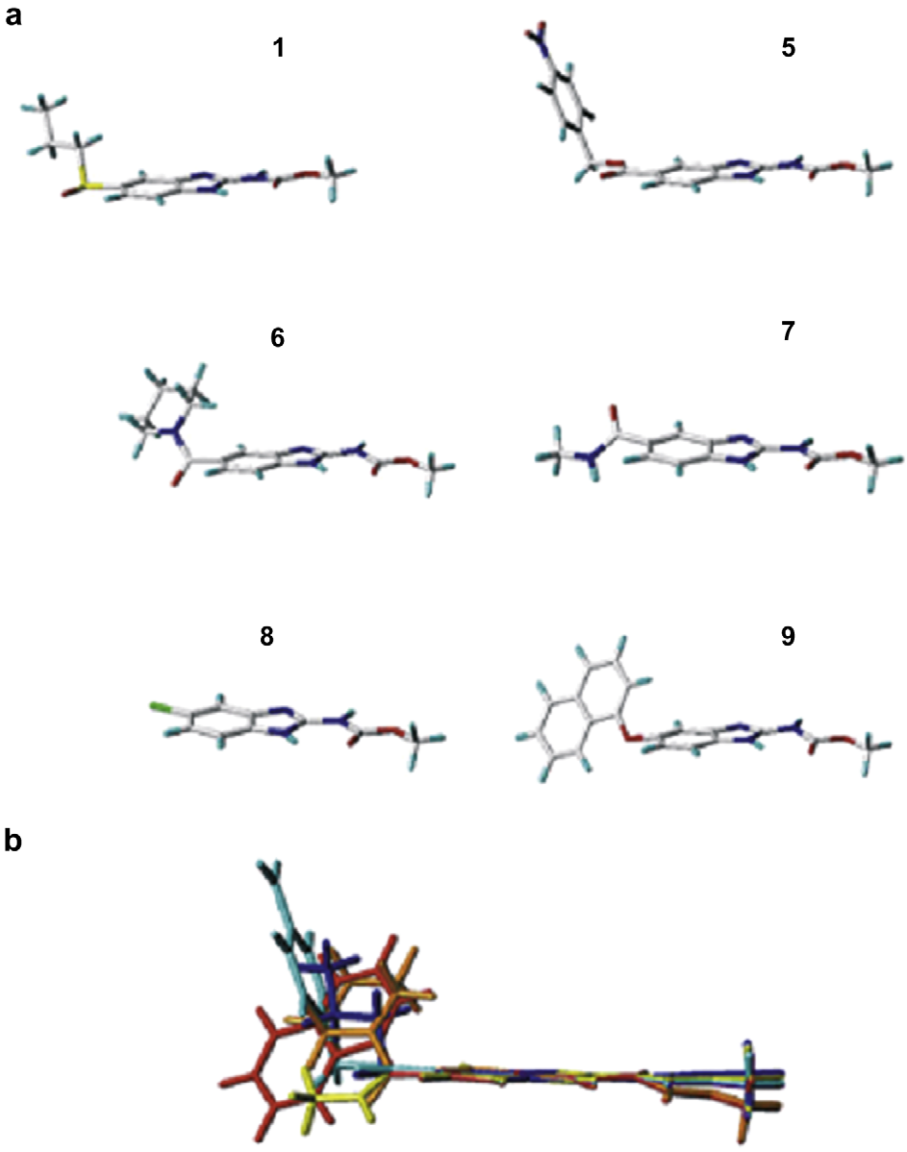


Fig. 2. Lowest energy conformer of compounds **1** and **5**–**9**. (a) Compounds modelled. (b) Superimposition of **1** (blue), **5** (cyan), **6** (orange), **7** (yellow), **8** (violet) and **9** (red), which were colored for better understanding. In all the molecules, except **7** and **8**, substituent at 5-position was orthogonal to benzimidazole ring. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(bs, 1H, exchangeable with D_2O) ppm; FAB-MS *m/z*: 371 $[M + 1]^+$.

*5.1.5. Methyl [5-(piperidin-1-ylcarbonyl)-1H-benzimidazol-2-yl]carbamate (**6**)*

M.p. 296–297 °C. IR *ν*: 3339.01, 2932.17, 2849.02, 1734.11, 1627.01, 1596.02, 1423.11, 1259.10, 1237.02 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 1.406 (bs, 2H, H-3′), 1.652 (bs, 4H, H-2′, H-4′), 3.551 (bs, 4H, H-1′, H-6′), 3.802 (s, 3H, OCH_3), 7.011 (dd, 1H, H-6, $J_{6,7} = 8.5$, $J_{6,4} = 1.0$ Hz), 7.452 (d, 2H, H-4), 11.670 (bs, 1H, exchangeable with D_2O) ppm; EI-MS *m/z*: 301 ($[M]^+$ 50%), 269 (100%).

*5.1.6. Methyl {5-[(methylamino)carbonyl]-1H-benzimidazol-2-yl}carbamate (**7**)*

M.p. 368 °C. IR *ν*: 3298, 2947, 1638, 1587 cm^{-1}; ^1H NMR (DMSO-d_6) *δ*: 3.520 (s, 3H, $CONHCH_3$), 3.620 (s, 3H, $NHCO_2CH_3$), 7.440 (d, 1H, H-7, $J = 8.4$ Hz), 7.810 (dd, 1H, H-6, $J_1 = 8.4$, $J_2 = 1.5$ Hz), 7.980 (d, 1H, H-4, $J = 1.2$ Hz), 8.390 (d, $J = 4.8$ Hz, 1H, exchangeable with D_2O, $NHCH_3$), 12.21 (bs, 1H, exchangeable with D_2O, $NHCO_2CH_3$) ppm; EI-MS *m/z*: 232 ($[M]^+$ 5%), 200 (100%).

5.2. In vitro activity

The *in vitro* cysticidal activity evaluations were performed on *T. crassiceps* cysts due to its similarity with *T. solium* cysts [16,20]. Cysts were obtained from experimentally infected male BALB/c mice (two months old). After three months the mice were killed by cervical dislocation and the cysts were removed from the peritoneal cavity. The parasites were washed with sterile 0.9% saline solution and only those cysts exhibiting intact bladder surface were used for the

Table 2
Molecular descriptors retrieved from molecular modelling calculations

Compound	HF (kcal/mol)	MV (Å^3)	HOMO (eV)	LUMO (eV)	IP (eV)	DM (Debye)	log *P*	PSA (Å^3)
1	−53.20	832.18	−8.88	−0.26	8.88	5.35	1.54	150.77
5	−60.45	1030.07	−9.14	−1.15	9.14	8.55	3.12	216.07
6	−50.17	899.12	−8.88	−0.32	8.88	5.00	1.65	144.19
7	−43.18	735.57	−8.93	−0.33	8.93	5.28	0.68	164.02
8	−15.71	633.97	−8.84	−0.31	8.84	3.93	2.09	112.84
9	12.65	965.00	−8.35	−0.31	8.35	3.44	3.56	115.98

HF: heat of formation, MV: molecular volumes, log *P*: water/octanol partition coefficient, IP: ionization potential, DM: dipolar moment, PSA: polar surface area.

experiments. Stock solution of each compound was prepared in dimethyl sulfoxide (DMSO), and working solutions were prepared with culture medium to obtain concentrations of 0.28 and 1.7 μM (which represent the effective concentration 50 and 99 of **1**, obtained previously by us in *T. crassiceps* cysts of strain ORF) [14]. Culture medium containing 0.25% DMSO was prepared as control. Each cell culture flask contained 25 cysts in 5 mL of culture medium and was incubated for 11 days at 37 °C, with 5% CO_2. The parasites were observed every day for 11 days with an inverted light microscope (Reichert 569) and the mortality of the cysts was registered. The criteria to assess cyst mortality *in vitro* were loss of vesicular fluid, paralysis of membrane and cyst collapse. The mortality was confirmed on day 11 using the Trypan Blue exclusion test. Each experiment was performed in triplicate.

5.3. Molecular modelling studies

Molecular modelling was performed using the Spartan 02 software (Wave function, Irvine, CA, USA). All compounds were built with the fragments method. The conformational analysis was performed with a systematic method [21], using all the rotable bonds, increment of the dihedral angle was set to 60°, and energy was calculated with Merck Molecular Force Field. After calculation, the lowest energy conformer was retrieved, and was geometry optimized with the AM1 semiempirical method [22], using the keywords: AM1, singlet, precise, full, $T = 3600$, MMOK. From these calculations the following molecular descriptors were obtained: heat of formation (HF), highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), dipole moment, log *P*, and ionization potential. Optimized molecules were exported to Sybyl V. 7.3 (Tripos, Inc., St. Louis, MI, USA), then polar surface area (PSA) and molecular volume (MV) were calculated [23] for each molecule. log *P*: water/octanol partition coefficient was calculated using the Ghose–Crippen method [24].

Acknowledgment

This work was supported by grants from PAPIIT-UNAM IN210805. We are grateful to Rosa Isela del Villar, Georgina Duarte, Margarita Guzmán and Marisela Gutiérrez (Facultad de Química, UNAM) for providing all the spectra.

References

[1] G. Román, J. Sotelo, O. Del Brutto, A. Flisser, M. Dumas, N. Wadia, Bull. World Health Organ. 78 (2000) 399–406.
[2] A. Flisser, E. Sarti, M. Lightowlers, P. Schantz, Acta Trop. 87 (2003) 43–51.
[3] O. Takayanagui, Expert Rev. Neurother. 4 (2004) 129–139.
[4] O. Del Brutto, K. Ross, Ch. Coffey, H. García, Ann. Intern. Med. 145 (2006) 43–52.
[5] K.U. Buhring, H.W. Dickmann, H. Muller, A. Garbe, H.M. Nowak, Eur. J. Drug Metab. Pharmacokinet. 3 (1978) 179–190.
[6] H. Rawden, G. Kokwaro, S. Ward, G. Edwards, Br. J. Clin. Pharmacol. 49 (2000) 313–322.
[7] F. Góngora-Rivera, J.L. Soto-Hernández, D. González-Esquivel, H.J. Cook, C. Márquez-Caraveo, R. Hernández Dávila, J. Santos-Zambrano, Neurology 66 (2006) 436–438.
[8] R.O. McCracken, K.B. Lipkowitz, J. Parasitol. 76 (1990) 180–185.
[9] S. Ram, D.S. Wise, L.L. Wortring, J.M. McCall, L.B. Townsed, J. Med. Chem. 35 (1992) 539–547.
[10] C.A. Hernández, V.F. Ibarra, F.N. Vera, R. Castillo, Chem. Pharm. Bull. 50 (2002) 649–652.
[11] O. Soria-Arteche, R. Castillo, A. Hernández-Campos, M. Hurtado-de la Peña, G. Navarrete-Vázquez, J.L. Medina-Franco, K. Gómez-Flores, J. Mex. Chem. Soc. 49 (2005) 349–354.
[12] J. Valdez, R. Cedillo, A. Hernández-Campos, L. Yépez, F. Hernández-Luis, G. Navarrete-Vazquez, A. Tapia, R. Cortés, M. Hernández, R. Castillo, Bioorg. Med. Chem. 12 (2002) 2221–2224.
[13] M. Reyes, V.F. Ibarra, M.Y. Vera, A.G. Cantó, A. Hernández, C.A.A. Hernández, R. Castillo, M.A. Villa, Parasitol. Res. 102 (2008) 705–708.
[14] J.C. Rivera, L. Yépez-Mulia, A. Hernández-Campos, R. Moreno-Esparza, R. Castillo, G. Navarrete-Vázquez, I. Fuentes-Noriega, H. Jung-Cook, Int. J. Pharm. 343 (2007) 159–165.
[15] F. Palomares, G. Palencia, R. Pérez, D. González-Esquivel, N. Castro, H. Jung, Antimicrob. Agents Chemother. 48 (2004) 2302–2304.
[16] R.S. Freeman, Can. J. Zool. 40 (1962) 969–990.
[17] J.D. Smyth, D.P. McManus (Eds.), The Physiology and Biochemistry of Cestodes, Cambridge University Press, Great Britain, 1989, pp. 15–19.
[18] M.W. Robinson, N.A. Trudgett, L. Hoey, I. Fairweather, J. Mol. Graph. Model. 23 (2004) 275–284.
[19] R.O. McCracken, K.B. Lipkowitz, J. Parasitol. 76 (1990) 853–864.
[20] N. Rossi, I. Rivas, M. Hernández, H. Urdaneta, Rev. Cubana Med. Trop. 52 (2000) 157–164.
[21] A.R. Leach, in: K.B. Lipkowitz, D.B. Boyd (Eds.), Reviews in Computational Chemistry, VCH, USA, 1991, pp. 114–135.
[22] M.S.J. Dewar, E.G. Zoebisch, E.G. Healy, S.J.J.P. Stewart, J. Am. Chem. Soc. 107 (1985) 3902–3909.
[23] K.B. Lipkowitz, R.O. McCracken, Parasitol. Res. 79 (1993) 475–479.
[24] A. Ghose, G.M. Crippen, J. Comput. Chem. 7 (1986) 565–568.