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Biopharmaceutic evaluation of novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives

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Abstract

Benzimidazole 2-carbamates, such as albendazole (ABZ) and mebendazole (MBZ), used for the treatment of helmintic infections, have low aqueous solubility and poor bioavailability, both of which lead to high interindividual variability when used for human systemic helmintiosis; therefore, it is necessary to search for new anthelmintics with better biopharmaceutical properties. In the present study the solubility, pK_a, log P and apparent permeability in the Caco-2 cells system of four novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives (compounds **1**–**4**) with a 2-methylthyo group were evaluated. Also the pharmacokinetic parameters of compound **1** which in previous studies showed activity similar to ABZ against *T. spirallis,* was evaluated in BALB/c mice, as a representative molecule of the series. The novel anthelmintics, showed better solubility than ABZ in aqueous acid pH and in organic solvents. The log P, P_{app} and Caco-2 data indicate that the **4** derivatives are highly permeable drugs, but it is possible that an efflux system could be involved in the transport of these compounds. Plasma levels of compound **1** and its sulfoxide (compound **5**) were high after the first 5 min. This fact strongly suggests that compound **1** is rapidly metabolized in the small intestine. On the other hand, the sulfone metabolite (compound **6**) levels were lower than those of compound **5**. The half life and mean residence time (MRT) of compound **1** and its main metabolites indicate that their elimination is very rapid.

More studies in mammalian species are necessary in order to understand the pharmacokinetic behavior of these novel compounds.

Keywords: Permeability; Pharmacokinetics; Benzimidazole; Biopharmaceutics; Caco-2; Solubility

1. Introduction

Intestinal helmintiosis is still a major health problem mainly in developing countries. The economic importance of helmintic infections has long been recognized in the field of animal husbandry. For this reason the most important advances in the chemotherapy of helmintiosis have probably come from the animal health area (Horton, 1990). Although the development of vaccines in the long term could be an ideal strategy for the control of these parasitic infections, at the present time and in the near future, the control of helmintiosis relies on the use of anthelmintics. Helminth parasites that have an intra and extra intestinal phase are able to infect humans as well as animals. The treatment for intestinal helmintiosis is usually carried out with benzimidazole 2-carbamate drugs (BZC), which have a wide spectrum of activity such as albendazole (ABZ) and mebendazole (MBZ); however, the treatment of systemic parasitosis with these types of drugs requires high doses and long treatments because of their poor solubility in body fluids; this decreases their absorption and bioavailability (Cook, 1990). In clinical trials, these drugs have shown a high interindividual variability (Sharma, 1994). Although ABZ is currently used as the drug of first choice for the treatment of neurocisticercosis, it is far from being the ideal drug because of the mentioned absorption problems (Jung et al., 1998). In addition, there are other experimental anthelmintics with a benzimidazole nucleus, among

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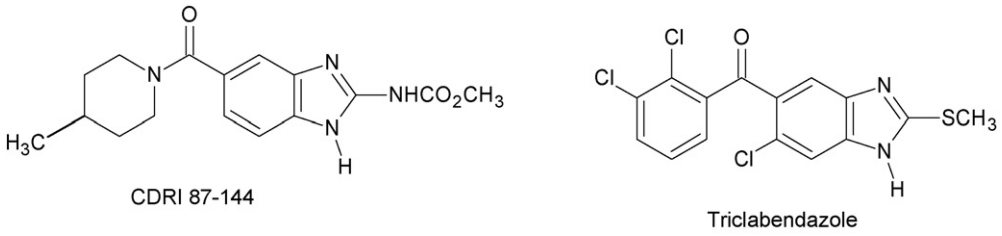


Fig. 1. Structure of CDRI 87-144 and Triclabendazole.

which is compound CDRI 87-144 (Fig. 1), which with a methylcarbamate at position 2 and a carboxamide group at position 5(6), was found to be active against infections from a wide variety of helminthes such as *Ancylostoma ceylanicum, Nippostrongylus brasiliensis, Syphacia obvelata* and *Himenolepis nana,* adults and larvae (Gupta et al., 1990). Another systemic anthelmintic is triclabendazole (TCB), the preferred drug for the treatment of animals infected with the liver fluke *Fasciola hepatica* (Sharma, 1994; Sanyal, 1995), and recently approved for use on humans (Fairweather, 2005). This fasciolicide, which is also a benzimidazole derivative, has a 2-methylthio group instead of a 2-methylcarbamate group, which increases its lipophilicity, absorption and bioavailability.

As part of our research project aimed at determining the structural requirements for antiparasitic activity in order to obtain structures with better biopharmaceutical properties to increase bioavailability, a series of four compounds with hybridized structural characteristics of CDRI 87-144 and TCB have been synthesized. These compounds, tested for antiparasitic activity were found to be active in vitro against the systemic phase of *Trichinella spiralis*. In order to enhance the ADME information, in the present study we evaluated some of the physicochemical properties and the apparent permeability in Caco-2 cells of these compounds, as well as the pharmacokinetic behavior of compound **1** in rodents, as a representative molecule of the series.

2. Materials and methods

2.1. Reagents and solvents

Table 1 shows the structure of compounds **1**–**4** evaluated in this study. Compounds **5** and **6** (sulfoxide and sulfone metabolites of compound **1**) were also synthesized in the laboratory by a procedure previously described (Soria-Arteche et al., 2005). Atenolol and propranolol, used as low and high permeability standards respectively (Artursson and Karlsson, 1991), were purchased from Sigma–Aldrich. ABZ was donated by Glaxo Smith Kline (México).

Methanol, ethanol, acetonitrile (ACN), dimethylsulfoxide (DMSO), carbon tetrachloride, *n*-Octanol, hydrochloric acid, sodium hidroxide, sodium chloride, potassium cloride, sodium hydrogen phosphate and sodium dihydrogen phosphate were of analytical grade (J.T. Baker). Intestinal and Gastric Simulated Medium (SIF and SGF) without enzymes were prepared as indicated in the USP XXVII.

2.2. Solubility

Solubility was determined according to the procedure of Yalkowski et al. (1983). The solvents used were carbon tetrachloride, ACN, methanol, *n*-Octanol, ethanol, DMSO, pH 7.4 phosphate buffer solution, distilled water, 1% sodium lauryl sulfate (SLS), 0.1 M hydrochloric acid, SIF and SGF. Tubes containing each compound at appropriate concentrations were shaken at 100 strokes min^{-1} at 25 °C for 3 h. At this time a sample was collected and filtered through a 0.45 μm nylon filter. Drug concentration was determined by HPLC.

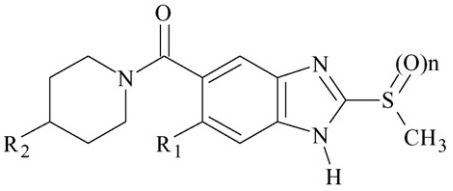
2.3. pK_a determination

Because of their high molar extinction coefficients, the pK_a values of all compounds were determined by means of a spectrophotometric study in the ultraviolet region. Fresh double distilled water was employed for all experiments.

2.3.1. Calibration of glass electrode and pK_a assay

The electrode was calibrated as mentioned Gans et al. (1999) using the Strong-pH worksheet (Protonic Software, Hyperquad Co. UK). To determine pK_a values, 0.1N HCl and 0.1N NaOH solutions containing 0.1 M NaCl to maintain constant ionic strength were prepared. A stock solution of each derivative (2×10^{-4} M) was prepared by previously dissolving a suitable quantity of drug in 1 mL of methanol and completion to the volume of 50 mL with water. An aliquot of the stock solution was added to 0.1N HCl with 0.15 M NaCl to a final drug concentration of 2×10^{-5} M (solution A). Solution B was prepared at

Table 1
Evaluated (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives



Compound	R_1	R_2	*N*
1	H	H	0
2	Cl	H	0
3	H	CH_3	0
4	Cl	CH_3	0
5	H	H	1
6	H	H	2

the same drug concentration with 0.1 NaOH containing 0.15 M NaCl. Then, solution A was titrated with solution B using the Accumet 950 potentiometer and a Titrino equipment model 716 DMS (Metrohm, USA) used as dosifier. Samples were collected every 0.5 pH units and allowed to repose for 4 h at 25 °C. Then, the pH value was measured twice. The absorbance readings and spectra were recorded in the ultraviolet range at 25 °C using a Hewlett Packard 8453 spectrophotometer (Hewlett Packard, USA). The analytical wavelengths were located, absorbance values being plotted with their pH values (Albert and Serjeant, 1971). The determination of pK_a values was performed by fitting the obtained data using the Origin software (Origin ver. 4.0, Microal Inc., MA, USA) to the equation:

$$A_{obs} = \frac{[A_i + A_m(10^{pH-pK_a})]}{(1 + 10^{pH-pK_a})},$$

where A_{obs}, A_i and A_m are the observed absorbance, the absorbance of the neutral species and the absorbance of the anionic form respectively. The obtained values were confirmed using pHab Software (Protonic Software, Hyperquad Co.) (Gans et al., 1999).

2.4. Partition coefficient

The octanol–water partition coefficient was determined by the traditional shake-flask technique. To 2 mL of a buffer solution (pH 7.4) containing 100 μM of each compound, 2 mL of *n*-Octanol, previously saturated with buffer solution, were added. The mixture was shaken for 40 min, centrifuged and the aqueous and organic phases were separated. Samples were assayed by HPLC as indicated in section 2.6. The partition coefficient (log *P*) was calculated according to the following equation:

$$\text{Log } P = \log \frac{[\text{drug}]_o}{[\text{drug}]_{aq}},$$

where $[\text{drug}]_o$ is the drug concentration in the organic phase and $[\text{drug}]_{aq}$ is the drug concentration in the aqueous phase. In addition, Clog *P* values were calculated with ACDLAB Software (ACD Labs System).

2.5. Culture of Caco-2 cell line

The Caco-2 cell line (donated by Dr. I. Hidalgo, Absorption Systems, USA at passage 55) was maintained at 37 °C in DMEM/high glucose supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 2 mM nonessential aminoacids, 2 mM sodium pyruvate (all of them from Gibco) and 100 U/mL penicillin and 100 μg/mL streptomycin (Sigma–Aldrich) in a 5% CO_2 atmosphere with 90% relative humidity. Cells were grown and routinely seeded. For transport experiments, 60,000 cells/cm^2 were seeded onto 12 mm Transwell polycarbonate filters (area of 1.13 cm^2, a mean pore size of 0.4 μm) on 12-well plates (Corning Costar Corp.). The medium was changed every 48 h for 6 days and every 24 h thereafter. The monolayers were used after 26–30 days of growth and between passages 58–65. Before starting the experiments the monolayer integrity was verified with transepithelial electrical resistance (TEER) measurements showing a value between 250–300 Ωcm^2 (Artursson and Karlsson, 1991; Balimane et al., 2004).

2.6. Bidirectional transport studies in Caco-2 monolayers

Stock solutions (10 mM) of compounds **1**–**4**, propranolol and atenolol were prepared by dissolving each compound in ethanol. For transport experiments, working solutions (100 μM) were prepared from stock solutions dissolved in the transport medium (Hank's Balanced salt solution, HBSS at pH 7.4). ABZ was dissolved in DMSO (10 mM), and then, a working solution (50 μM) was prepared in the transport medium. The pH of both apical and basolateral compartment was 7.4. For apical-to-basolateral ($J_{A\rightarrow B}$) transport experiments, the cells were incubated in the apical compartment with 500 μL of the transport medium containing the drug and 1500 μL of the fresh medium in the basolateral compartment. During incubation at regular intervals (15 min) each insert was changed to a new well with fresh transport medium. A sample of 1000 μL was removed at 15, 30, 45, 60 and 90 min from the basolateral compartment. For basolateral-to-apical transport ($J_{B\rightarrow A}$), the cells were incubated with 500 μL of the fresh transport medium on the apical compartment and 1500 μL of the transport medium containing the drug in the basolateral compartment. Samples of 200 μL were removed from the apical side and replaced with fresh medium every 15 min. Transport studies were carried out twice in triplicate and the monolayer integrity was determined by using Lucifer-Yellow (LY) in apical to basolateral transport (Watanabe et al., 1999). Samples (100 μL) were injected directly into a high performance liquid chromatography system (SPD-10 A, Shimadzu), equipped with a variable wavelength detector at 305 nm using a symmetry C18 250 mm × 4.5 mm analytical column and methanol–water (60:40) as mobile phase was used for compounds **1**–**3**. In the case of compound **4**, the mobile phase used was methanol–water (70:30). The flow was maintained at 1 mL min^{-1}. All corresponding methods were previously validated. Sensitivity was 0.5 μM (0.137 μg/mL) and the maximum intraday coefficient of variation was 6.0%. The recovery ranged between 94.5 and 100%. The Apparent Permeability Coefficient (P_{app}) was calculated according to the following equation:

$$P_{app} = \frac{dQ}{dt} \times \frac{1}{C_O A},$$

where dQ/dt is the slope of the concentration versus time curve, C_O the initial concentration for the drug in the donor compartment and A is the area of the insert.

2.7. Pharmacokinetic evaluation of compound *1*

To perform the study, 8 week-old male BALB/c mice of 25–27 g were used. A single oral dose of 30 mg/kg body weight of compound **1** (200 μL) was administered with a bucco-gastric tube. After administration, blood samples were collected individually in Eppendorf tubes with a CDPA buffer

(Sigma–Aldrich) at 0, 0.08, 0.17, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0 and 8.0 h. Plasma was separated by centrifugation and stored at −20 °C until assay.

The concentrations of compound **1** and its metabolites were determined by HPLC with ultraviolet detection as follows: 250 μL of plasma were extracted by being passed through a preconditioned Strata C18-E cartridge. The sample was washed with 2 mL of deionized water and eluted with 2 mL of methanol. The organic phase was evaporated under a nitrogen stream until dryness and reconstituted with 250 μL of 0.01 M HCl containing compound **3** (External standard at 1 μg/mL, ES) and 50 μL were injected into the HPLC system. The chromatographic conditions were 0.01 M phosphate buffer pH 6.5:ACN 95:5 as mobile phase, a Waters Spherisorb S5 CN column (200 mm × 4.6 mm) and a flow rate of 1 mL min^{-1}. Absorbance was determined at 295 nm. Under these conditions, retention times for compounds **6**, **5**, **1** and **3** (ES) were 5.5, 6.5, 11 and 13.7 min respectively. The method was linear in the range of 18.75–600 ng/mL for compounds **1** and **6** and 39.0–1200 ng/mL for compound **5**. The recovery was higher than 90% and the intraday coefficient of variation was less than 10.0, 13.0 and 12.0% for compounds **1**, **6** and **5** respectively.

3. Results

The solubility of the compounds **1**–**4** and ABZ in both aqueous and organic solvents at 25 °C is shown in Table 2. Solubility of the new benzimidazole derivatives in aqueous solvents such as distilled water, SIF and pH 7.4 phosphate buffer was very low (between 0.014 and 0.028 mg/mL) while with a tensoactive agent (1% SLS) it increased slightly (between 0.41 and 1.0 mg/mL). In acid media (GSF and 0.1 M HCl) it increased significantly (1–9 mg/mL). In organic solvents such as DMSO, methanol, ethanol and octanol the solubility ranged from 2.8 to 58 mg/mL; however, in carbon tetrachloride it was relatively low (0.3–2.8 mg/mL). Table 3 summarizes the pK_a values obtained for each compound showing that for compounds **1** and **3**, pK_a values were close to 4 and 10.4 while for compounds **2** and **4**, which have a chlorine atom in position 6, the pK_a values were close to 3.3 and 10.

Table 2
Solubility of novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives (25 °C)

Solvent	Compound (mg/mL)				ABZ
	1	**3**	**2**	**4**	
CCl_4	0.30	1.60	0.33	2.80	0.071
n-Octanol	15.50	2.95	2.18	15.00	0.13
Ethanol	44.00	11.50	36.00	44.00	0.36
Methanol	12.40	22.00	27.00	42.00	0.57
CAN	8.22	1.02	16.00	6.00	0.16
DMSO	25.00	18.66	24.00	58.00	6.25
SSL 1%	0.41	0.43	0.241	1.13	0.09
Buffer pH 7.4	0.028	0.013	0.013	0.016	ND
SIF	0.024	0.016	0.015	0.016	ND
Water	0.019	0.018	0.014	0.015	ND
SGF	9.00	3.80	1.00	2.80	0.058
HCl 0.1 M	9.20	8.00	2.43	1.06	0.04

*ND: not detected.

Table 3
pK_a, log *P* and Clog *P* values of novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives

Compound	pK_{a1}	pK_{a2}	log *P*	Clog *P*
1	3.97 ± 0.07	10.62 ± 0.08	1.97 ± 0.02	1.7 ± 0.75
2	3.35 ± 0.05	9.96 ± 0.02	2.37 ± 0.17	2.02 ± 0.77
3	3.93 ± 0.04	10.81 ± 0.04	1.85 ± 0.10	2.19 ± 0.75
4	3.37 ± 0.01	10.17 ± 0.16	1.97 ± 0.14	2.51 ± 0.77
ABZ	2.80[a]	10.20[a]	3.46 ± 0.12	3.0 ± 0.64

[a] Reported by Jung et al. (1998).

Table 4
Apparent Permeability Coefficients (P_{app}) of novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives using the Caco-2 model

Compound	P_{app} Caco-2 (10^{-6} cm/s)		BA/AB ratio
	$J_{A\rightarrow B}$	$J_{B\rightarrow A}$	
1	45.0 ± 5.24	99.4 ± 1.67	2.21
2	11.1 ± 0.9	37.7 ± 1.26	3.40
3	28.6 ± 5.56	63.9 ± 2.99	2.23
4	167.0 ± 13.3	114.0 ± 40.9	0.68
ABZ	6.5 ± 0.87	3.21 ± 0.92	0.49
Atenolol	2.6 ± 1.1	3.1 ± 0.26	1.19
Propranolol	31.4 ± 0.25	52.3 ± 1.22	1.67

The data are the mean ± S.E.M. of three determinations.

Log *P* and Clog *P* values were close to 2.0, ABZ having the highest values (3.46 and 3 respectively). The P_{app} values obtained in the Caco-2 cell line for all compounds as well as the $J_{A\rightarrow B}/J_{B\rightarrow A}$ ratio (BA/AB) are shown in Table 4.

Fig. 2 shows the observed mean plasma concentration profile of compound **1** and its metabolites. Compound **1** showed an initial mean concentration of 8 μg/mL, which rapidly decreased to reach the lowest concentration (near 0.019 μg/mL) at 2 h post-administration. Our results show that compound **1** was rapidly metabolized to sulfoxide and sulfone. The concentration of both metabolites also decreased rapidly and 4 h after administration, they could no longer be detected. The pharmacokinetic parameters are shown in Table 5.

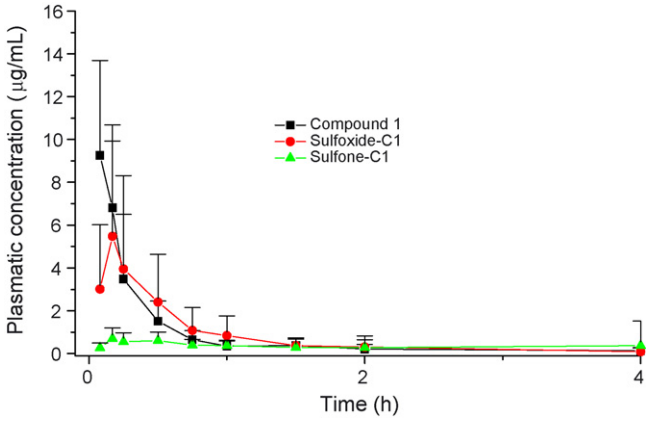


Fig. 2. Pharmacokinetic profile of compound **1** and its metabolites, sulfoxide and sulfone, after oral administration of 30 mg/kg of compound **1** in male BALB/c mice.

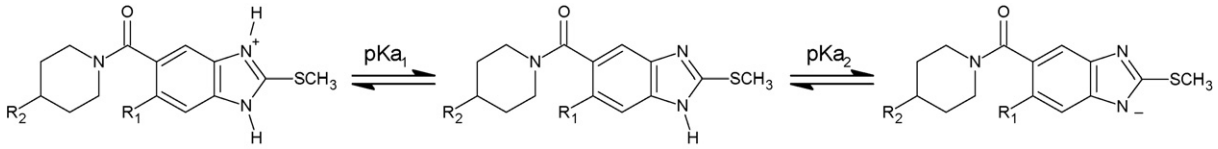


Fig. 3. Ionization of novel anthelmintic compounds.

Table 5
Pharmacokinetic parameters of compound **1** and its metabolites sulfoxide (compound 5) and Sulfone (compound 6)

	Compound **1**	Compound **5**	Compound **6**
K_e (1 h^{-1})	1.08	1.56	1.15
$T_{1/2}$ (h)	0.78	0.52	0.73
T_{max} (h)	0.12*	0.16	0.24*
C_{max} (ng/mL)	10,570.93*	5359.73	802.00*
$AUC_{o\ to\ inf}$ (h ng/mL)	3398.39*	2983.74	859.47*
AUC/AUC C1	1.0	0.8485	0.25
V_d/F (mL)	212.519	–	–
Cl/F (mL/h)	192.59	–	–
$MRT_{0\ to\ inf}$ (h)	0.85	0.78	1.37

Abbreviations: K_e, elimination constant; $T_{1/2}$, half life time; C_{max}, maximal concentration; T_{max}, maximal concentration time; AUC, area under the curve; V_d, distribution volume; Cl, clearance; F, absorbed fraction; MRT, mean residence time.

* $p < 0.005$.

4. Discussion

From the obtained results, it can be concluded that all novel compounds are amphiprotic (Fig. 3). The pK_{a1} values between 3 and 4 are attributable to the protonation of the amine group at position 3 while the pK_{a2} values between 10 and 10.6 are attributable to the loss of the proton of the amine group in position 1. Although all compounds have the same ionization equilibrium, the pK_a values for compounds **2** and **4** are lower than those of compounds **1** and **3** because of the inductive effect of the chlorine atom, with no significant effect on solubility properties. Fig. 4 shows the relationship between the charged species and the pH, thus, suggesting that between pH 5 and 9 they remain as neutral species which support a high absorption in the intestinal region. Although in earlier reports other benzimidazole compounds have shown low solubility (Jung et al., 1998; Domanska and Bogel-Lukasik, 2003), we found that compounds **1**–**4** are more soluble than ABZ in aqueous solvents. When the solubility data of organic solvents were related to the dielectric constant and the polar surface area of the organic solvents (Fig. 5), we found that all derivatives were dissolved at higher amounts in solvents with an intermediate constant dielectric value (methanol, ethanol and DMSO), probably due to the formation of hydrogen bonding at different sites of the carboxamides. This relation indicates that there are polar interactions between the novel anthelmintic carboxamide derivatives and the solvent molecules, thus, permitting the depletion of intermolecular hydrogen bonding between compound molecules and consequently the promotion of the solvation and solubilization process. It is important to note that in ACN, the intermolecular hydrogen bonding in the benzimidazole core prevents solvation and the solubility is, thus, lower.

The log P values obtained in the present study (Table 3) indicate strong lipophilic properties similar to other benzimidazolic compounds such as Fenbendazole (3.93), Mebendazole (3.73), Oxfendazole (2.6) and Thiabendazole (2.5) as previously reported (Mottier et al., 2003).

The P_{app} values ($J_{A\rightarrow B}$) were higher than ABZ and similar to those obtained for propranolol (31.4×10^{-6} cm/s). The decreasing order of permeability was compound **2** < compound **1** < compound **3** < compound **4**. The results are in agreement with their log P and Clog P values indicating that compounds **1**–**4** have a high permeability and consequently may have good bioavailability (Artursson and Karlsson, 1991). ABZ showed low P_{app}, which contrasts with the high lipophilicity predicted by log P and Clog P, which could be due to the precipitation of the drug during permeability assays, as previously

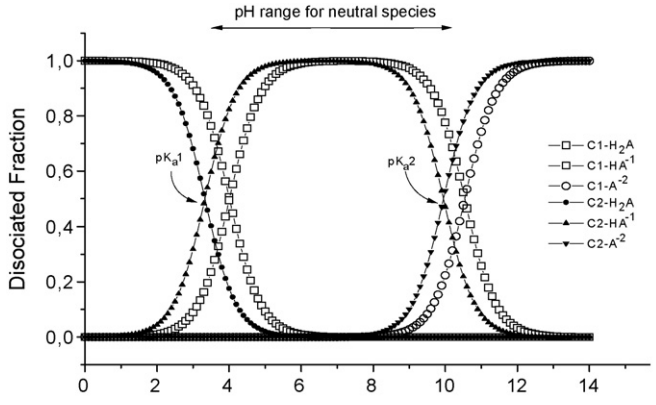


Fig. 4. Distribution species diagram of compound **1** (C1) and compound **2** (C2).

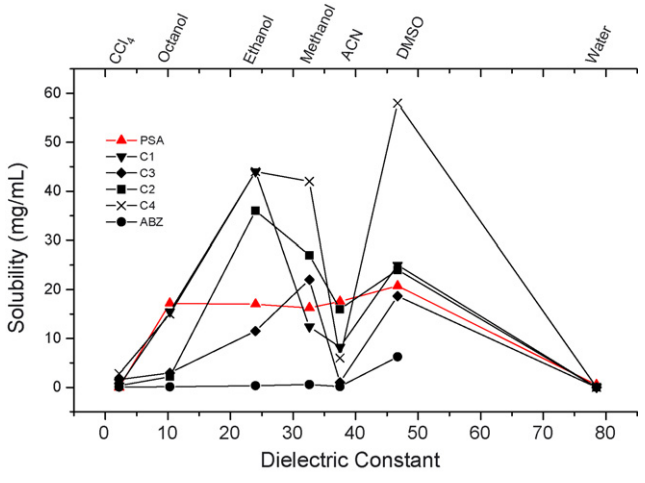


Fig. 5. Relationship between solubility of novel anthelmintic compounds **1**–**4** versus dielectric constant of tested organic solvents.

reported Kobayashi et al. (2001) using a continuous dissolution/permeability system.

Interestingly, the BA/AB ratio for compounds **1**–**3** was higher than **1**, suggesting that an efflux mechanism could be involved in the transport of these compounds through Caco-2 cells. Merino et al. (2005) found that ABZ sulfoxide (ABZSO) and oxfendazol (OXF) were transported by the breast cancer resistance protein (ABCG2/BCRP), however, no association was found between albendazol (Merino et al., 2002) and BCRP or *P*-glycoprotein. Thus, more detailed studies are required in order to explain the behavior of these benzimidazolic derivatives.

Considering that compound **1** showed the highest activity against *T. spirallis* which was similar to ABZ, it was selected as a representative molecule of the series to perform the pharmacokinetic assay. Our results showed that in mice the highest plasma levels of compound **1** were found as early as 5 min, indicating a rapid and effective absorption. compounds **5** and **6** (sulfoxide and sulfone derivatives) were also found at high concentrations soon after administration of compound **1**; however, the levels of compound **6** were lower than those obtained for the sulfoxide. Rawden et al. (2000) have shown that benzimidazole derivatives which have a sulfur atom in their structure such as ABZ are extensively oxidized to first metabolite sulfoxide, by FMO and mainly by CYP3A4 localized in the small intestine (Villaverde et al., 1995; Merino et al., 2005). The second metabolite, compound **6** is probably produced by a reaction catalyzed mainly by a metabolic system CYP 450 as mentioned by Virkel et al. (2006) in relation to metabolism of TCB. Our pharmacokinetic data suggest that compound **1** could also be metabolized to its sulfoxide in the small intestine. The $AUC_{0\rightarrow\infty}$ of compound **1** was equivalent to the compound **5** ($AUC_{met}/AUC_{C1} = 0.84$) and higher than the compound **6** ($AUC_{met}/AUC_{C1} = 0.24$), which might indicate that the second metabolite was formed only from compound **5**, producing low levels in the blood.

On the other hand, it is important to indicate that although compound **1** and its metabolites showed a short mean residence time (TMR) and half life in mice (Table 5), other benzimidazole derivatives that have shown a relatively small half lives in rodents (ABZ 4 h in rats and 2 h in mice) (García et al., 2003), displayed a longer plasma half life in humans (Dayan, 2003), or in ruminant species (Kinabo and Bogan, 1989). Considering that compound **1** showed a better solubility than ABZ, which could increase its bioavailability, it would be important to evaluate its pharmacokinetic behavior in other species.

In conclusion, it was found that the novel anthelmintic (1*H*-benzimidazol-5(6)-yl)carboxamide derivatives were more soluble than ABZ in aqueous and organic solvents. Data of log *P* and P_{app} in Caco-2 cells indicate that these compounds should be highly absorbed in vivo although some active transport mechanism might be involved. The pharmacokinetic study showed that like TCB and ABZ, compound **1** is metabolized to sulfoxide and sulfone metabolites. Considering that compound **1** is as active as ABZ, it would be of interest to establish whether this derivative has an active transport or a passive one. In addition, it would be of value to determine its pharmacokinetic behavior in other species to establish its therapeutic potential.

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