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Studies on the Selective S-oxidation of Albendazole, Fenbendazole, Triclabendazole, and Other Benzimidazole Sulfides

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Abstract. The selective *S*-oxidation of albendazole, fenbendazole, and other benzimidazole sulfides with sodium periodate in acid medium, afforded the corresponding sulfoxides or sulfones. In contrast, triclabendazole and other 2-methylthiobenzimidazole derivatives could not be *S*-oxidized under the same smooth conditions with this reagent, but with MCPBA, a stronger oxidizing agent.
Keywords: Albendazole, fenbendazole, triclabendazole, metabolites, *S*-oxidation.

Resumen. La oxidación selectiva de albendazol, fenbendazol, y otros sulfuros bencimidazólicos con peryodato de sodio en medio ácido da los correspondientes sulfóxidos y sulfonas. En contraste, triclabendazol y otros derivados de 2-metiltiobencimidazoles no pueden ser oxidados bajo las mismas condiciones suaves con este reactivo, pero sí con un agente oxidante fuerte como MCPBA.
Palabras clave: Albendazol, fenbendazol, triclabendazol, metabolitos, *S*-oxidación.

Introduction

A large group of wide spectrum, high efficiency anthelmintics, such as the benzimidazole 2-carbamates (BZC), is marketed worldwide for the control of helminthiasis. It has been reported that benzimidazole anthelmintics with a sulfide group are the most active against intestinal nematodes in humans, as well as in animals [1-3]. Included among these anthelmintics are albendazole **1**, fenbendazole **2** and triclabendazole **3** (Figure 1).

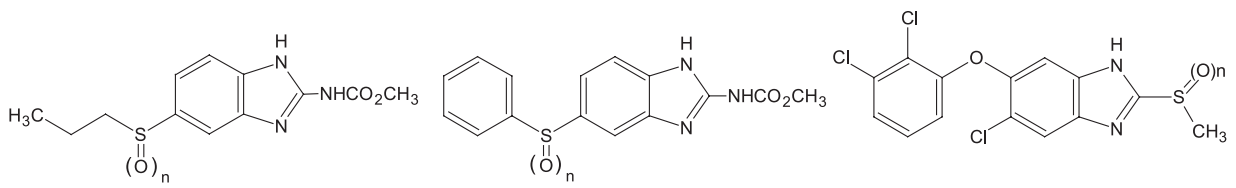
Benzimidazole sulfides **1**, **2**, and **3** undergo first pass biotransformation in the organism, where the sulphur atom is oxidized to produce the active antiparasitic sulfoxides **4** [1,4-5], **6** [6-7], and **8** [8-9], respectively. Further oxidation produces the inactive sulfones **5**, **7** or **9**.

Metabolites **4**, **5** and **7** are commercially available but not easily affordable. Not so for **6**, which is easily available at a relatively low price. Although there are reports in the pertinent literature for the synthesis of **4**, **5**[1,10-12]; **6**, **7** [2]; and **8**, **9** [13], in addition to the general methods of *S*-oxidation [13], these are not easy to carry out, or fail, due to insolubility problems in **1**-**3**, which often leads to mixtures of sulfoxides and sulfones that are difficult to separate. The need of these metabolites in helminthiasis chemotherapy research [2,3,5] makes the development of new preparation methods highly desirable, in particular, those that employ common reagents, mild reaction conditions and convenient working procedures.

In this paper we present an efficient, high yield method for the selective *S*-oxidation of **1**, **2** and **3** to obtain **4**, **6** and **8**, as well as the selective *S*-oxidation of other benzimidazole sulfides **10**, **12** and **17** to obtain **11**, **13** and **18**, respectively (cf. Figures 2 and Scheme). In these studies, sodium periodate in acid medium was used as the oxidizing agent. This reagent does not over-oxidize **1** under low temperature conditions [15-17]. In addition, aqueous mixtures of acetic acid-acetonitrile were used as solvent, which allowed carrying out the reactions at different temperature conditions for better control, thus avoiding over oxidation.

Results and Discussion

The results of the oxidation reactions of **1-3**, **10, 12** and **17** are shown in Table 1.



1: n=0 **2:** n=0 **3:** n=0

4: n=1 **6:** n=1 **8:** n=1

5: n=2 **7:** n=2 **9:** n=2

Fig. 1. Structure of albendazole **1**, fenbendazole **2**, triclabendazole **3**, and their metabolites.

Table 1. Oxidation reactions, conditions and results

Compound	$NaIO_4$ Equivalents	Solvent	Temperature (°C)	Product	Yield (%)
1	1.00	CH_3COOH/H_2O	0-5	**4**	97
1	2.50	CH_3COOH/H_2O	25	**5**	90
2	1.10	$CH_3COOH/CH_3CN/H_2O$	15	**6**	95
2	2.80	$CH_3COOH/CH_3CN/H_2O$	60	**7**	67
3	1.00	$CH_3COOH/CH_3CN/H_2O$	60	**8**	0
10	1.09	$CH_3COOH/CH_3CN/H_2O$	0-5	**11**	90
12	1.00	$CH_3COOH/CH_3CN/H_2O$	60	**13**	0
17	1.00	$CH_3COOH/CH_3CN/H_2O$	0-5	**18**	80

Oxidation of **1** with sodium periodate in acetic acid to obtain albendazole sulfoxide **4** was studied under several temperature conditions. At -10°C it was necessary to add acetonitrile as co-solvent to avoid precipitation of **1** and to complete its oxidation; however, the reaction was incomplete. On the other hand, at 25°C, a mixture of **1**, **4** and **5** was produced. The best results were obtained when the reaction was carried out in acetic acid-water at 0-5°C, in this case, **4** was obtained as the only product in a 97% yield. Its ^{1}H NMR spectrum showed a multiplet at 2.72-2.86 ppm, characteristic of the diastereotopic α-methylene hydrogens next to the chiral sulfoxide. The mass spectrum showed a peak at *m/z* 281, which is in agreement with the molecular ion of **4**. The purity of **4** was confirmed by HPLC. Only one peak with a 6.75 min retention time was observed.

When **1** was oxidized with excess of sodium periodate at 25°C for longer periods of time, sulfone **5** was the only product obtained in a 90% yield. The ^{1}H NMR spectrum now showed a triplet at 3.21 ppm for the nondiastereotopic α-methylene hydrogens next to the sulfone group. The mass spectrum showed the molecular ion peak of **5** at *m/z* 297. The purity was confirmed by HPLC, a single peak with a 5.21 min retention time was observed.

Encouraged by these results, we decided to test the periodate oxidation method with compounds **2**, **3** and other benzimidazole sulfides, **10** and **12**, which are currently being studied as experimental new antiparasitic agents (Figure 2).

Oxidation of **2** at 15°C gave sulfoxide **6** in a 95% yield. Its structure was confirmed by mass spectrometry. When the temperature and the equivalents were increased (60°C, 2.8 eq.), sulfone **7** was obtained as the only product in a 67% yield.

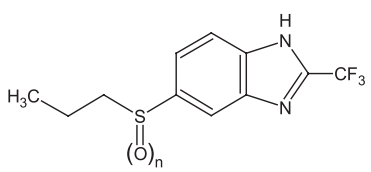
In order to increase the solubility of **3** and prevent its precipitation, the oxidation reaction with sodium periodate was undertaken with acetonitrile as co-solvent; however, although a solution was attained, no change in **3** was observed, even at 20°C. In this case, we had to use *m*-chloroperbenzoic acid (MCPBA), a stronger oxidizing agent, and obtained **8** at 0-5°C [18].

In the case of compound **10**, the oxidation with sodium periodate in acetic acid-acetonitrile proceeded smoothly at 0-5°C to afford sulfoxide **11** in a 90% yield.

The oxidation of **12** to the sulfoxide **13** also failed with sodium periodate, but it was easily achieved with MCPBA. The lower reactivity of sulfides such as **3** and **12** can be attributed to a reduced electron density on sulfur because of the inductive effect of the imidazole ring nitrogen atoms. This contention is supported by the regiospecific and high yielding oxidation of the bis-sulfide **17** (Scheme 1[19, 20]; see Experimental section for details of synthesis) to the monosulfoxide **18**, and by electron density calculations (Fig. 3).

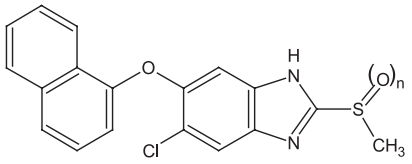
Conclusions

A practical, mild and efficient method for the *S*-oxidation of albendazole **1**, fenbendazole **2**, and benzimidazole sulfide **10** was developed. The method consists in treating a cold solu-



10: n=0

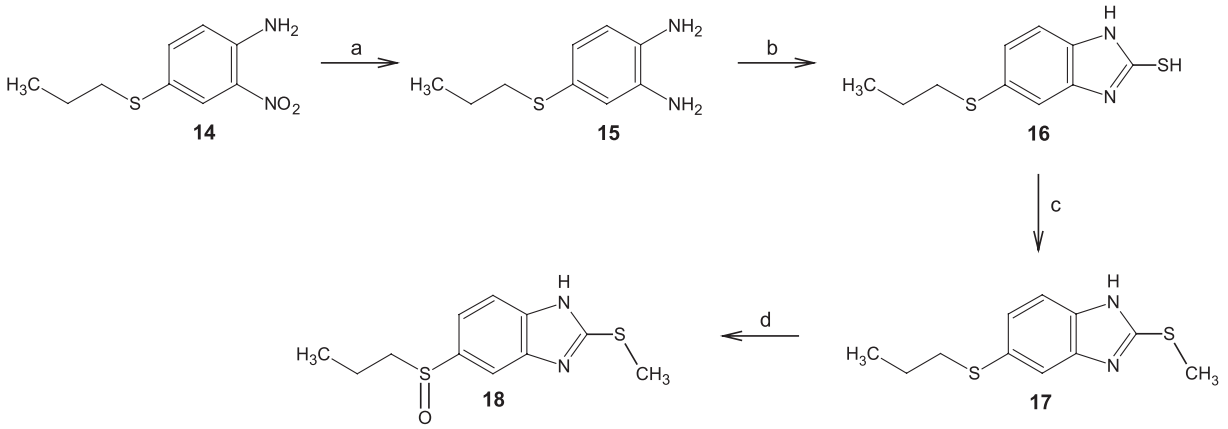
11: n=1



12: n=0

13: n=1

Fig. 2. Benzimidazole sulfides used as experimental antiparasitic agents and their sulfoxides.



Scheme 1. Reagents: (a) $SnCl_2 \cdot 2H_2O$, EtOH; (b) CS_2, KOH, EtOH; (c) CH_3I, KOH, CH_3COCH_3; (d) $NaIO_4$.

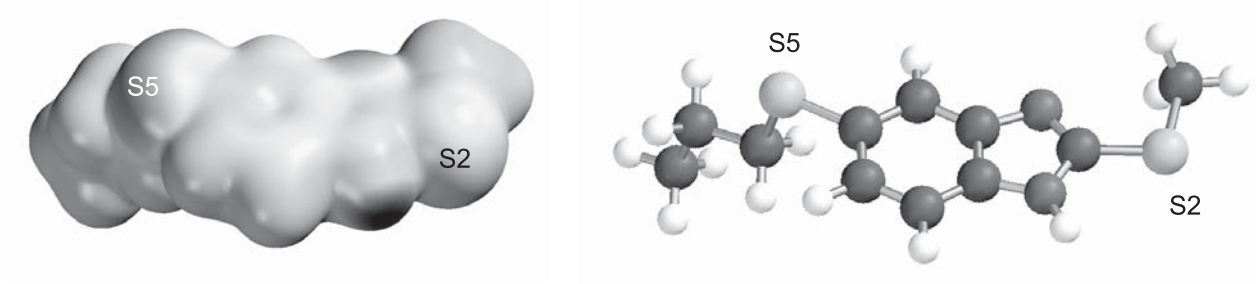


Fig. 3. Molecular surface of **17** showing the potential energy calculated at RHF/6-31G(*d*,*p*) level. Darker zones represent either more positive or more negative regions. The sulphur atom of the propylthio group (S5, charge -0.366) corresponds to a darker zone than the sulphur atom of the methylthio group (S2, charge -0.211).

tion of these compounds with sodium periodate to generate the corresponding sulfoxides. The related sulfones were obtained at higher temperatures. In the case of 2-(methylthio)benzimidazoles, such as triclabendazole **3**, the *S*-oxidation was achieved with MCPBA, a stronger oxidizing agent.

Experimental

Melting points were determined on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F_{254} plates (E. Merck). Infra-red spectra were recorded in a Perkin-Elmer FT-IR-1600 spectrometer on KBr pellets, the absorption bands are given cm^{-1}. MS were recorded on a JEOL JMS-SX102A spectrometer by electron impact (EI) of low and high resolution (HR-MS), and FAB^+. ^1H NMR spectra were measured with a Varian model EM-390 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to Me_4Si ($\delta = 0$) used as internal standard. The solvent employed was DMSO-d_6 , except for **11** and **17** that was $CDCl_3$. *J* values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; sext, sextuplet; m, multiplet; bs, broad signal. HPLC analyses were performed in a Perkin Elmer serie 200LC, UV 785A detector: column C-8, mobile phase: CH_3OH-H_2O-CH_3CN-CH_3COOH (40:40:19.4:0.6). Starting materials **1**, **2**, and **3** were obtained commercially, where as **10**, **12**, and **14** were synthesized in our laboratories.

General method for the synthesis of propylsulfinyl derivatives (4, 6, 11 and **18) and propylsulfonyl derivatives (5, 7)**. Into a stirred solution of **1, 2, 10,** or **17** in AcOH or AcOH/CH_3CN (1:1) was slowly added, dropwise, a solution of $NaIO_4$ in a mixture of H_2O/AcOH. The mixture was stirred, then, the solvent removed *in vacuo* without heating. The progress of the reaction was monitored by TLC. The residue was suspended in brine and neutralized with a saturated solution of potassium carbonate, the resulting suspension was filtered, and the residue washed with water and air dried.

Methyl 5-[(propylsulfinyl)-1*H*-benzimidazol-2-yl]carbamate (4). Following the general procedure, **1** (0.5 g, 1.89 mmol,) in 6.5 mL AcOH and $NaIO_4$ (0.403 g, 1.89 mmol) in 14 mL of H_2O/AcOH (5:2) were stirred at 0-5ºC for 2 h and gave **4**

(0.514 g, 97%) as a white powder. Mp 218-220ºC. TLC (Toluene-THF-AcOH, 5:1:1). IR ν_{max} 3169 (NH), 1730 (C=O), and 1028 (SO). MS EI (*m/z*): 281 (M^+), HRMS (EI) Calcd for $C_{12}H_{15}N_3O_3S$ (M^+) *m/z*: 281.0834, found: 281.0820. ^{1}H-NMR: δ 0.95 (3H, t, *J*= 7.20, C$\underline{H}_3$CH$_2$CH$_2$SO), 1.42-1.66 (2H, m, C$\underline{H}_2$CH$_2$SO), 2.72-2.86 (2H, m, C$\underline{H}_2$SO), 3.79 (3H, s, C$\underline{H}_3$O), 7.33 (1H, dd, *J* = 8.0, *J* = 1.4, H-6), 7.57 (1H, d, *J* = 8.0, H-7), 7.72 (1H, d, *J* = 1.4, H-4), and 11.90 (H, bs, NH, int. D_2O). HPLC: rt: 6.75 min.

Methyl [5-(propylsulfonyl)-1*H*-benzimidazol-2-yl]carbamate (5). Following the general procedure, **1** (1.0 g, 3.76 mmol) in 15 mL of AcOH and $NaIO_4$ (2.015 g, 9.42 mmol, 2.5 eq.) in 25 mL of H_2O/AcOH (4:1) were stirred at 25°C for 22 h and gave **11** (1.01 g, 90%) as a white powder. Mp: 226-227°C. IR ν_{max} 3352 (NH), 1731 (C=O), 1276 and 1131. MS (EI) (*m/z*): 297 (M^+). H-RMS (EI) calcd for $C_{12}H_{15}N_3O_4S$ (M^+) 297.0783. Found: 297.0792. ^{1}HNMR: δ 0.89 (3H, t, *J* = 7.5, C$\underline{H}_3$CH$_2$CH$_2$SO$_2$), 1.55 (2H, sext, *J* = 7.5, C$\underline{H}_2$CH$_2$SO$_2$), 3.22 (2H, t, *J* = 7.5, C$\underline{H}_2$SO$_2$), 3.80 (3H, s, C$\underline{H}_3$O), 7.58 (1H, dd, *J* = 8.2; *J* = 1.5, H-6); 7.62 (1H, d, *J* = 8.2, H-7), 7.91 (1H, s, H-4); and 12.06 (bs, NH, int. D_2O). HPLC: rt: 5.21 min.

Methyl [5-(phenylsulfinyl)-1*H*-benzimidazol-2-yl]carbamate (6). Following the general procedure, **2** (0.5 g, 1.67 mmol) in 13 mL of AcOH/CH_3CN and $NaIO_4$ (0.393 g, 1.84 mmol) in 6 mL of H_2O/AcOH (5:2) were stirred at 15ºC for 2 h and gave **6** (0.527 g, 95%) as a pale pink solid, after recrystallization from $CHCl_3$. Mp 253.9ºC. TLC (Toluene-THF-AcOH, 5:1:1). IR ν_{max} 3388 (NH), 1721 (C=O), 1047. MS (EI) (*m/z*): 315 (M^+). HR-MS (EI) calcd for $C_{20}H_{13}N_3O_3S$ (M^+) *m/z*: 315.0678. Found: 315.0677. ^{1}HNMR δ 3.76 (3H, s, C$\underline{H}_3$O), 7.36 (1H, dd, *J* = 8.4; *J*= 1.35, H-6), 7.4-7.55 (5H, m, H-2', H-3', H4', H5', H-6'), 7.66 (1H, d, *J* = 8.4, H-7), 7.73 (1H, d, *J* = 1.35, H-4), and 11.86 (s, NH, int. D_2O).

Methyl [5-(phenylsulfonyl)-1*H*-benzimidazol-2-yl]carbamate (7). Following the general procedure, **2** (0.16 g, 0.54 mmol) in 15 mL of AcOH/CH_3CN and $NaIO_4$ (0.285 g, 1.34 mmol) in 4.5 mL of H_2O/AcOH (4:1) were stirred at 60°C for 24 h and gave **7** (0.113 g, 67%) as a pale pink solid. Mp: 319.8-321.1°C. TLC (Toluene-THF-AcOH, 5:1:1). IR ν_{max} 3342 (NH), 1731 (C=O), 1268, and 1047 (SO_2). MS (FAB) (*m/z*): 332 (M+1), HR-MS calcd for $C_{15}H_{14}N_3O_4S$ (M^+) *m/z*: 331.0627, found: 332.0726. ^{1}H-NMR: δ 3.74 (3H, s, C$\underline{H}_3$O), 7.36 (1H, dd, *J* = 8.4, *J* = 1.8, H-6), 7.48-7.53 (3H, m, H-3', H-4', H-5'), 7.49 (1H, dd, *J* = 8.4, *J* = 0.6, H-7), 7.73 (1H, d, *J* = 1.8, H-4), and 11.81 (s, NH, int. D_2O).

5-(Propylsulfinyl)-2-(trifluoromethyl)-1*H*-benzimidazole (11). Following the general procedure, **10** (0.40 g, 1.54 mmol) in 8 mL of AcOH/CH_3CN and $NaIO_4$ (0.328 g, 1.69 mmol, 1.09 eq.) in 16 mL of H_2O/AcOH (5:2) were stirred at 60°C for 2 h and gave **11** (0.381 g, 90%) as a white powder, after recrystallization from cyclohexane-toluene. Mp: 123.2-125.2 °C. IR ν_{max} 3425 (NH), 1015 (SO). MS (*m/z*): 276 (M^+), HR-MS (EI) calcd for $C_{11}H_{11}F_3N_2OS$ (M^+) *m/z* 276.0544, found: 276.0546. ^{1}H-NMR: δ 1.06 (3H, t, *J* = 7.34, C$\underline{H}_3$CH$_2$CH$_2$SO), 1.60-1.90 (2H, m, C$\underline{H}_2$CH$_2$SO), 2.83-3.0 (2H, m, C$\underline{H}_2$SO), 7.48 (1H, d, *J* = 7.9, H-6), 7.89 (1H, d, *J* = 7.9, H-7), 8.25 (1H, s, H-4), and 10.58 (1H, bs, NH int. D_2O).

2-(Methylthio)-5-(propylsulfinyl)-1*H*-benzimidazole (18). Following the general procedure, **17** (0.105 g, 0.44 mmol)) in 10 mL of AcOH/CH_3CN and $NaIO_4$ (0.094 g, 0.44 mmol) in 2 mL of H_2O/AcOH were stirred for 2 h and gave **18** (0.900 g, 80%) as a white powder, after recrystallization from AcOEt-Et$_2$O. Mp: 100.1-100.5 °C. TLC ($CHCl_3$-CH_3OH, 95.5:0.5). IR ν_{max} 3392 (NH) and 1083 (S=O). MS (EI) *m/z* 254 (M^+). HRMS (EI) calcd for $C_{11}H_{14}N_2OS_2$ (M^+) *m/z* 254.0548. Found: 254.0560. ^{1}HNMR: δ0.99 (3H, t, *J*= 7.34, C$\underline{H}_3$CH$_2$CH$_2$SO), 1.47- 1.79 (2H, m, C$\underline{H}_2$CH$_2$SO), 2.75 (3H, s, C$\underline{H}_3$S), 2.68-2.87 (2H, m, C$\underline{H}_2$SO), 7.38 (1H, dd, *J*= 8.4, *J*= 1.5, H-6), 7.58 (1H, dd, *J* = 8.4, *J* = 0.6, H-7), and 7.69 (1H, dd, *J* = 1.5, *J* = 0.6, H-4), and 13.2 (bs, NH, int. D_2O).

5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylsulfinyl)-1*H*-benzimidazole (8). To a stirred solution of **3** (0.50 g, 1.37 mmol) in 50 mL of $CHCl_3$ was slowly added, dropwise, a solution of MCPBA (0.338g, 1.37 mmol) in 4 mL of $CHCl_3$ at 0-5°C. The progress of the reaction was monitored by TLC ($CHCl_3$-MeOH, 95.5:0.5). At the end of the reaction the solvent was removed *in vacuo* without heating, the residue was suspended in brine and neutralized with a saturated solution of potassium carbonate. The mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and evaporated *in vacuo* to give **8** (0.389 g, 75%) of a white soapy powder. Mp: 176-178°C. IR ν_{max}: 3168 (NH), 1050 (SO). MS (EI) (*m/z*): 376 (M^+). HRMS (EI) Calcd for $C_{14}H_9Cl_3N_2O_2S$ (M^+) *m/z* 375.9450. Found: 375. 9422. ^{1}HNMR: δ3.08 (3H, s, CH_3SO), 6.75 (1H, d, *J* = 8.4, H-6'), 7.28 (1H, t, *J* = 8.0, *J* = 8.4, H-5'), 7.40 (1H, dd, *J* = 8.0, *J* = 0.8, H-4'), 7.47 (1H, s, H-7), 7.93 (1H, s, H-4), and 13.82 (bs, NH, int. D_2O).

5-Chloro-2-(methylsulfinyl)-5-(1-naphtyloxy)-1*H*-benzimidazole (13). Into a stirred solution of **12** (0.50 g, 1.476 mmol) in 20 mL of $CHCl_3$ was slowly added, dropwise, a solution of MCPBA (0.394 g, 1.37 mmol) in 15 mL of $CHCl_3$ at 0-5°C. The progress of the reaction was monitored by TLC ($CHCl_3$-MeOH, 97:3). When the reaction was completed, it was treated with a solution of $NaHCO_3$ until pH 7. Afterwards, the mixture was extracted with $CHCl_3$ (3 × 3 mL). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and evaporated *in vacuo* to give **13** as a white soapy powder. The solid was recrystallized from ethanol-benzene 1:1 to give 0.381 g (72.43%) of a white powder. Mp 189-190°C. IR ν_{max} 3422 (NH), 1048 (SO). MS (EI) (*m/z*): 356 (M^+). HRMS (EI) Calcd for $C_{18}H_{13}ClN_2O_2S$ (M^+) *m/z* 356.0386 Found: 356.0380 ^{1}H NMR: δ 3.08 (3H, s, CH_3SO), 6.702 (1H, d, *J* = 7.5, H-2'), 7.376 (1H, s, H-4), 7.403 (1H, t, *J* = 8.1, H-3'), 7.568-7.638 (2H, m, H-6', H-7'), 7.69 (1H, d,

J = 8.4, H-4'), 7.97 (1H, s, H-7), 7.99-8.00 (1H, m, H-5'), 8.18-8.21 (1H, m, H-8'), and 14.12 (bs, NH, int. D_2O).

4-(Propylthio)-*o*-phenylenediamine (**15**). A stirred mixture of **14** (0.5 g, 2.35 mmol), $SnCl_2 \cdot 2H_2O$ (3.18 g, 14.13 mmol) and 5 mL of absolute ethanol was heated at 80°C under N_2 for 2 h. The progress of the reaction was monitored by TLC ($CHCl_3$-MeOH, 95.5:0.5), and once finished, it was allowed to reach room temperature, then, it was neutralized with a 50% NaOH solution and filtered. The residue of tin salts was dried under vacuum and extracted with AcOEt (3x10 mL). The combined organic extracts were washed with brine, and dried with anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, a brown viscous liquid was obtained. The crude product was immediately used in the next reaction without any purification.

5-(Propylthio)-1*H*-benzimidazole-2-thiol (16). A stirred mixture of **15** (0.429 g, 1.912 mmol), EtOH (6 mL), KOH (0.233 g, 3.53 mmol) in water (1 mL) and CS_2 (0.2 mL, 3.532 mmol) was heated at 50°C under N_2 for 3 h. Then, the reaction was left 12 h at room temperature. The progress of the reaction was monitored by TLC ($CHCl_3$-MeOH, 95.5:0.5). The yellow precipitate formed was poured into water and treated with 20% AcOH solution to pH 6. The solid was separated by filtration, washed with water and air dried to obtain **16** (0.391 g, 74%) of a slightly yellow powder. Mp: 216.1-217.8°C. IR ν_{max} 3439 (NH). MS (*m/z*): 224 (M^+). HRMS (EI) Calcd for $C_{10}H_{12}Cl_3N_2O_2S$ (M^+) *m/z* 224.0442, found: 375. 9422. ^{1}H-NMR: δ 0.99 (3H, t, *J* = 7.28, C<u>H</u>$_3$CH$_2$CH$_2$S), 1.60 (2H, sext, *J* = 7.28, CH$_3$C<u>H</u>$_2$CH$_2$S), 2.84 (2H, t, *J* = 7.28, CH$_3$CH$_2$C<u>H</u>$_2$S), 7.14 (1H, s, H-7), 7.15 (1H, s, H-6), 7.25 (1H, m, H-4), and 9.55 (bs, NH, int. D_2O).

2-(Methylthio)-5-(propylthio)-1*H*-benzimidazole (17). Into a stirred, dark solution, of **16** (1.2 g, 5.33 mmol) in 4.5 mL of acetone and KOH (0.351 g, 6.27 mmol) in 0.5 mL of water, was slowly added, under N_2, CH_3I (0.4 mL, 5.33 mmol) at 0°C. Then, the mixture was stirred for 30 min at 10°C. The progress of the reaction was monitored by TLC ($CHCl_3$-MeOH, 95.5:0.5) and once finished it was neutralized with a 20% HCl solution and concentrated under vacuum. The residue was taken up with AcOEt, the extract washed with brine, dried with anhydrous Na_2SO_4 and half concentrated under vacuum. Addition of MeOH allowed the formation of **14** (1.22 g, 96%) of a white powder. Mp: 142.7-142.9°C. IR ν_{max} 3426 (NH). MS (EI) *m/z*: 238 (M^+). HRMS (EI) Calcd for $C_{11}H_{14}N_2S_2$ (M^+) *m/z* 238.0598, found: 238.0582. ^{1}HNMR: δ 0.97 (3H, t, *J* = 7.5, C<u>H</u>$_3$CH$_2$CH$_2$S), 1.61 (2H, sext., *J* = 7.5 Hz, CH$_3$C<u>H</u>$_2$CH$_2$S), 2.85 (3H, s, C<u>H</u>$_3$S), 2.85 (2H, t, *J* = 7.5, C<u>H</u>$_2$SO), 7.24 (1H, dd, *J* = 8.4, *J* = 1.5, H-6), 7.42 (1H, d, *J* = 8.4, H-7), 7.55 (1H, d, *J* = 1.2, H-4), and 10.21 (bs, NH, int. D_2O).

Computational methodology

Complete optimization of the geometry of compound **17** was done with the program Spartan'02 [21] at level RHF/6-31G(*d*,*p*). The electrostatic potential map was calculated from the optimized geometry.

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References

1. Gyurik, R. J.; Chow, A. W.; Zaber, B.; Brunner, E. L.; Miller, J. A.; Villani, A. J.; Petka, L. A.; Parish, R. C. *Drug Metabolism Disposition*. **1981**, *9*, 503-508.
2. Averkin, E. A.; Beard, C. C.; Dvorak, C. A.; Edwards, J. A.; Fried, J. H.; Kilian, J. G.; Schiltz, R. A. *J. Med. Chem.* **1975**, *18*, 1164-1166.
3. Lecaillon, J. B.; Godbillon, J.; Campestrini, J.; Naquira, C.; Miranda, L.; Pacheco, R.; Mull, R.; Poltera, A. A. *J. Clin. Pharmacol.* **1998**, *45*, 601-604.
4. Alvarez, L. I.; Sánchez, S. F.; Lanusse, C. E. *J. Vet. Pharmacol. Therap*. **1999**, *22*, 77-86.
5. Virkel, G.; Lifschitz, A.; Soraci, A.; Sansinanea, A.; Lanusse, C. *Xenobiotica* **2000,** *30*, 381-393.
6. Murray, M.; Hudson, A. M.; Yassa, V. *Chem. Res. Toxicol*. **1992**, 5, 60-66.
7. Szprengier-Juszkiewicz, T.; Semeniuk, S.; Wlodarczyk, B. *Bull. Vet. Inst. Pulawy*. **2002**, *46*, 119-125.
8. Sanyal, P. K. *Indian J. Pharmacol*. **1994**, *26*, 200-203.
9. Takeba, K.; Fujinuma, K.; Sakamoto, M.; Miyazaki, T.; Oka, H.; Itoh, Y.; Nakazawa, H. *J. Chromatog. A.* **2000**, *882*, 99-107.
10. De Laurentis, N.; Milillo, M. A.; Bruno, S. *Pharm. Pharmacol. Lett*. **1996**, *6*, 51-53.
11. Xie, J.H.; Hu, Y.Z. *Xhejiang Daxue Xuebao Yixueban*. **31**, 45 (2002); *Chem. Abstr.* **138**, 73201(2002).
12. Brandon, D. L.; Binder, R. G.; Bates, A. H.; Montangue, W. C. *J. Agric. Food Chem.* **1994**, *42*, 1588-1594.
13. Iddon, B.; Kutschy, P.; Robinson, A.G.; Suschitzky, H.; Kramer, W.; Neugebauer, F.A. *J. Chem. Soc. Perkin Trans. 1*. **1992**, 3129-3134.
14. Hudlicky, M. Oxidation in Organic Chemistry. ACS Monograph 186. American Chemical Society. Washington D.C. **1990**, 252.
15. Leonard, N. J.; Johnson, C. R. *J. Org. Chem*. **1961**, *27*, 282-284.
16. Hiskey, R. G.; Harpold, M. A. *J. Org. Chem*. **1967**, 32, 3191-3194.
17. Evans, B.J.; Doi, T.; Musker, W. K. *J. Org. Chem.* **1990**, 55, 2580-2586.
18. Hay, M. P.; Wilson, W. R.; Denny, W A. *Tetrahedron* **2000**, *56*, 645-657.

19. Hernández-Campos, A.; Ibarra-Velarde, F.; Vera-Montenegro, Y.; Rivera-Fernández, N.; Castillo, R. *Chem. Pharm. Bull*. **2002**, *50*, 649-652.
20. Navarrete-Vázquez, G.; Yépez, L.; Hernández-Campos, A.; Tapia, A.; Hernández-Luis, F.; Cedillo, R.; González, J.; Martínez-Fernández, A.; Martínez-Grueiro, M.; Castillo, R. *Bioorg. Med. Chem.*, **2003**, *11*, 4615-4622**.**
21. Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Vooris, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W., Head-Gordon, M.; Pople, J. A. J. *Comput. Chem.* **2000**, *21*, 1532-1548.