Synthesis and anti-inflammatory activity of 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)- and 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone derivatives

L. Labanauskas[1], A. Brukštus[1], E. Udrėnaitė[1], P. Gaidelis[2] and V. Bučinskaitė[1]

[1] Faculty of Chemistry, Vilnius University, Naugarduko 24, LT-2006 Vilnius, Lithuania
[2] Faculty of Medicine, Vilnius University, M. K. Čiurlionio 21, LT-2009 Vilnius, Lithuania

A series of 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone and 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone derivatives were synthesized. The structure – anti-inflammatory activity relationship was studied.

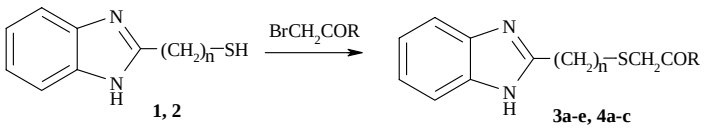
Key words: 1*H*-Benzo[*d*]imidazole derivatives, 2-bromo-1-(3,4-dialkoxyphenyl)-1-ethanones, 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones, 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones, anti-inflammatory activity

INTRODUCTION

1*H*-Benzo[*d*]imidazole derivatives are well known for their biological activity [1]. Previously we have found that various compounds containing 1*H*-benzo[*d*]imidazole or a related ring system may exhibit anti-inflammatory activity [2–4]. So, as an extension of our interest in studies of the structure–activity relationship of 1*H*-benzo[*d*]imidazoles, a series of 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone and 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone derivatives (**3 a–e** and **4 a–c**, respectively) were synthesized and investigated for their anti-inflammatory activity.

RESULTS AND DISCUSSION

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (**3 a–e**) and 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (**4 a–c**) were synthesized by the alkylation of 1*H*-benzo[*d*]imidazole-2-thiol (**1**) or 1*H*-benzo[*d*]imidazol-2-ylmethanethiol (**2**) with various 1-aryl-2-bromoethanones:



1, 2 **3a-e, 4a-c**

n = 0 (1, 3); 1 (2, 4);

R = 3,4-methylenedioxyphenyl (a); 3,4-ethylenedioxyphenyl (b); 3,4-trimethylenedioxyphenyl (c); 3,4-dimethoxyphenyl (d); 3,4-diethoxyphenyl (e);

The structure of newly the synthesized compounds **3 a–e** and **4 a–c** is in agreement with their IR and ^{1}H NMR spectral and elemental analysis data. 1*H*-Benzo[*d*]imidazol-2-ylmethanethiol was obtained by condensation of 1,2-diaminobenzene with thioglycolic acid as described in [5]. 1-(1,3-Benzodioxol-5-yl)-2-bromo-1-ethanone, 2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethanone, 2-bromo-1-(3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)-1-ethanone, 2-bromo-1-(3,4-dimethoxyphenyl)-1-ethanone and 2-bromo-1-(3,4-diethoxyphenyl)-1-ethanone were ob-

tained by bromination of the corresponding acetophenones according to the procedure described in [6]. The alkylation conditions of compounds **1** and **2** were investigated. The yields of compounds **3 a–e** were higher when the reaction proceeded for a longer time without heating. The yields of compounds **4 a–c** were higher when absolute methanol was used.

The anti-inflammatory activity of 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (**3 a–e**) was higher than that of 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (**4 a–c**). Compounds containing the cyclic dialkoxy substituent **1 a–c** were more active than the analoguous acyclic dialkoxyderivatives **1 d**, **e**. Compounds with larger cyclic dialkoxy substituents **3c** and **4c** were more active than their analogues **3 a**, **b** and **4 a**, **b** with smaller ones (Table). Compounds **3 b–d** and **4a** exhibit a moderate anti-inflammatory activity equal to or higher than that of acetylsalicylic acid and ibuprofen and a low acute toxicity.

Table. **Data on anti-inflammatory activity of compounds 3 a–e, 4 a–c and reference drugs (50 mg/kg *per os*)**

Compound	Inhibition of right hind paw oedema (%) over control in rats	
	Carrageenin-induced	Bentonite-induced
3a	24.4	9.6
3b*	36.7	38.9
3c*	51.1	57.9
3d*	39.9	32.2
3e	19.5	13.5
4a*	42.8	22.9
4b	19.2	18.7
4c	30.1	29.4
Acetylsalicylic acid	16.0	15.2
Ibuprofen	39.6	18.9

*Acute toxicity (LD_{50}) in mice >1500 mg/kg

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) in nujol and ^{1}H-NMR spectra on a BS-587A (80 MHz, Tesla, Brno, Czech Republic) with TMS as internal standart. Chemical shifts (δ) are reported in ppm.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (3 a–e). To a solution prepared from 0.52 g (3.5 mmol) 1*H*-benzo[d]imidazol-2-ylthiol (**1**), 0.15 g (3.8 mmol) sodium hydroxide and 10 ml ethanol 3.5 mmol of the corresponding 2-bromo-1-(3,4-dialkoxyphenyl)-1-ethanone was dissolved under stirring. The reaction mixture was kept for 16 h at room temperature. The crystalline solid was filtered off, washed with distilled water, dried and recrystallized from 2-propanol.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-methylenedioxyphenyl)-1-ethanone (3a). Yield 52%, m. p. 164–165 °C. IR ν (cm^{-1}): 3335 (NH), 1670 (CO). ^{1}H NMR (Acetone-D_6): 5.11 (2H, s, SCH_2CO), 6.26 (2H, s, OCH_2O), 7.00–7.96 (7H, m, ArH). Found, %: C 61.09; H 3.53; N 8.70. $C_{16}H_{12}N_2O_3S$. Calculated, %: C 61.53; H 3.87; N 8.97.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-ethylenedioxyphenyl)-1-ethanone (3b). Yield 72%, m. p. 102–103 °C. IR ν (cm^{-1}): 3327 (NH), 1674 (CO). ^{1}H NMR (Acetone-D_6): 4.31 (4H, s, OCH_2CH_2O), 4.95 (2H, s, SCH_2CO), 6.83–7.64 (7H, m, ArH). Found, %: C 62.33; H 4.53; N 8.20. $C_{17}H_{14}N_2O_3S$. Calculated, %: C 62.56; H 4.32; N 8.56.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-trimethylenedioxyphenyl)-1-ethanone (3c). Yield 67%, m. p. 160–162 °C. IR ν (cm^{-1}): 3368 (NH), 1677 (CO). ^{1}H NMR (Acetone-D_6): 2.34 (2H, qt, 5Hz, CH_2) 4.26–4.54 (6H, m, SCH_2CO, OCH_2), 7.04–7.93 (7H, m, ArH). Found, %: C 63.33; H 4.23; N 8.14. $C_{18}H_{16}N_2O_3S$. Calculated, %: C 63.51; H 4.74; N 8.23.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-dimethoxyphenyl)-1-ethanone (3d). Yield 64%, m. p. 87–88 °C. IR ν (cm^{-1}): 3321 (NH), 1665 (CO). ^{1}H NMR (Acetone-D_6): 3.96 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 5.12 (2H, s, SCH_2CO), 7.04–7.99 (7H, m, ArH). Found, %: C 62.42; H 4.84; N 8.67. $C_{17}H_{16}N_2O_3S$. Calculated, %: C 62.18; H 4.91; N 8.53.

2-(1*H*-Benzo[*d*]imidazol-2-ylsulfanyl)-1-(3,4-diethoxyphenyl)-1-ethanone (3e). Yield 66%, m. p. 117–118 °C. IR ν (cm^{-1}): 3296 (NH), 1669 (CO). ^{1}H NMR (Acetone-D_6): 1.10–1.69 (6H, m, CH_3), 3.81–4.51 (4H, m, OCH_2), 5.09 (2H, s, SCH_2CO), 7.03–7.93 (7H, m, ArH). Found, %: C 63.85; H 5.32; N 8.02. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 64.02; H 5.66; N 7.86.

2-(1*H*-Benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanones (4 a–c). A solution of 1.0 g (6.1 mmol) 1*H*-benzo[*d*]imidazol-2-ylmethanethiol (**2**), 0.15 g (6.1 mmol) sodium and 30 ml abs. methanol was prepared. The corresponding 2-bromo-1-(3,4-dialkoxyphenyl)-1-ethanone (6.1 mmol) was added and dissolved under stirring. The reaction mixture was kept at room temperature for 16 h. The obtained crystalline solid was filtered off, washed with distilled water, dried and recrystallized from 2-propanol.

2-(1*H*-Benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-methylenedioxyphenyl)-1-ethanone (4a). Yield

72%, m. p. 174–175 °C. IR ν (cm^{-1}): 3303 (NH), 1660 (CO). ^{1}H NMR (DMSO-D_6 + CF_3COOD): 4.31 (2H, s, CH_2S), 4.35 (2H, s, SCH_2CO), 6.12 (2H, s, OCH_2O), 6.47–7.96 (7H, m, ArH). Found, %: C 62.19; H 3.98; N 8.75. $C_{17}H_{14}N_2O_3S$. Calculated, %: C 62.56; H 4.32; N 8.58.

2-(1*H*-Benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-ethylenedioxyphenyl)-1-ethanone (**4b**). Yield 78%, m. p. 142–143 °C. IR ν (cm^{-1}): 3298 (NH), 1668 (CO). ^{1}H NMR (DMSO-D_6): 3.99 (2H, s, CH_2S), 4.14 (2H, s, SCH_2CO), 4.33 (2H, s, OCH_2CH_2O), 6.87–7.39 (7H, m, ArH), 12.20 (1H, s, NH). Found, %: C 63.86; H 4.89; N 8.25. $C_{18}H_{16}N_2O_3S$. Calculated, %: C 63.51; H 4.74; N 8.23.

2-(1*H*-Benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-trimethylenedioxyphenyl)-1-ethanone (**4c**). Yield 68%, m. p. 207–208 °C. IR ν (cm^{-1}): 3374 (NH), 1664 (CO). ^{1}H NMR (DMSO-D_6): 2.16 (2H, qt, 5Hz, CH_2), 4.03–4.42 (8H, m, CH_2S, SCH_2CO, OCH_2), 6.85–7.76 (7H, m, ArH). Found, %: C 63.97; H 5.26; N 8.13. $C_{19}H_{18}N_2O_3S$. Calculated, %: C 64.39; H 5.12; N 7.90.

Pharmacological experiments

Adult male Wistar rats weighing 180–220 g and male BALB/C strain mices weighing 18–22 g were used. The animals were allowed food and water *ad libitum*. They were housed in rooms at 18–20 °C with a 12-h light/dark cycle and relative humidity 55–60%. The animals were randomly allocated into groups at the beginning of each experiment. All test compounds and the reference drugs were administered orally suspended in a 0.5% solution of carboxymethylcellulose. Carrageenin-induced hind paw oedema in rats was produced by the method of Winter et al. [7]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the right hind paw 1 h after administration of the test compound. Control animals received only 0.5% carboxymethylcellulose solution. Right hind paw volume was measured with an electronic oncograph immediately before and 1, 2, 3, and 5 h after the carrageenin injection. The results were matched with those in control rats. Each experiment was made with 5 groups of rats, 10 animals each (the 1st one was control). Analogously was produced and studied right hind paw oedema induced by 0.1 ml 5% suspension of bentonite [8]. The data were evaluated statistically using Student's t test. A level of $p < 0.05$ was adopted for the test of significance. The test of acute toxicity of compounds **3 b–d** and **4a** was done on mice fastened for 24 h, with water *ad libitum.* Groups of 6 mice were treated perorally with the test compound at various dose levels. The animals were watched for mortality and symptoms until day 8 [9].

CONCLUSIONS

A series of new 2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)- and 2-(1*H*-benzo[*d*]imidazol-2-ylmethylsulfanyl)-1-(3,4-dialkoxyphenyl)-1-ethanone derivatives were synthesized. Some of them exhibit a moderate anti-inflammatory activity, low acute toxicity and are more active than acetylsalicylic acid and ibuprofen.

Received 9 January 2003
Accepted 30 January 2003

References

1. R. P. Mamedov, A. Y. Malkina, B. P. Fedorov, *Azerb. Chim. Zhurn.* **3**, 61 (1695); (C. A. **64**. 2685 g (1962)).
2. L. Labanauskas, A. Brukštus, E. Udrėnaitė, P. Gaidelis, V. Daukšas, *Chim.-Farmac. Zhurn.* **32**(**2**), 15 (1998).
3. L. Labanauskas, A. Brukštus, E. Udrėnaitė, P. Gaidelis, V. Bučinskaitė, V. Daukšas, *Chim.-Farmac. Zhurn.* **34**(**7**), 16 (2000).
4. L. Labanauskas, A. Brukštus, E. Udrėnaitė, P. Gaidelis, V. Bučinskaitė, V. Daukšas, *Die Pharmazie* (**6**) 429 (2000).
5. E. S. Milner, S. Snyder, M. Joullie, J. Chem. Soc. **11,** 4151 (1994).
6. V. Daukšas, G. Milvydienė, R. Dambrauskas, *Izv. VUZ SSSR, Chimija i Chim. Technologija,* **8**(**5**) 781 (1965).
7. C. A. Winter, E. A. Risley, G. W. Nuss, Proc. Soc. Exp. Biol. Med. **3** 544 (1962).
8. J. J. Jedzinsky, *Acta Univ. Palack. Olomousciencis Fac. Med.* **103**, 175 (1982).
9. J. T. Litchfield, F. J. Wilkoxon, *Pharmacol. Exp. Ther.* **96**, 99 (1949).

L. Labanauskas, A. Brukštus, E. Udrėnaitė, P. Gaidelis, V. Bučinskaitė

2-(1*H*-BENZO[*D*]IMIDAZOL-2-ILSULFANIL)- IR 2-(1*H*-BENZO[*D*]IMIDAZOL-2-ILMETILSULFANIL)-1-(3,4-DIALKOKSIFENIL)-1-ETHANONO DARINIŲ SINTEZĖ IR PRIEŠUŽDEGIMINIS AKTYVUMAS

S a n t r a u k a

Susintetinti 2-(1*H*-benzo[*d*]imidazol-2-ilsulfanil)- ir 2-(1*H*-benzo[*d*]imidazol-2-ilmetilsulfanil)-1-(3,4-dialkoksifenil)-1-etanono dariniai ir ištirtas jų priešuždegiminis aktyvumas. Kai kurių iš jų aktyvumas prilygo arba pralenkė acetilsalicilo rūgšties ir ibuprofeno aktyvumą, o toksiškumas buvo mažesnis už šių preparatų toksiškumą.