Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2707–2710

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Antiviral/Antiproliferative Activity of Some *N*-Sulphonylbenzimidazoles

Laura Garuti,[a,*] Marinella Roberti[a] and Erik De Clercq[b]

[a]*Department of Pharmaceutical Science, University of Bologna, via Belmeloro 6, I-40126 Bologna, Italy*
[b]*Rega Institute of Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

Received 1 March 2002; revised 22 May 2002; accepted 5 July 2002

Abstract—Some benzimidazolyl sulphones were synthesized and evaluated for their antiviral and antiproliferative properties. Compound **10** displayed significant and selective activity against human cytomegalovirus (CMV), compound **14** showed activity against varicella zoster virus (VZV). The compounds were further evaluated for inhibitory effect on the proliferation of murine leukemia cells and human T-lymphocyte cells. Marked cytotoxicity was noted with different derivatives. Some structure–activity relationships are discussed.

Arylsulphones are a promising class of non-nucleoside antiviral agents. Compounds such as Enviroxime and Enviradene have been extensively studied and many related analogues showed potent broad-spectrum antiviral activity against a range of both rhinoviruses and enteroviruses.[1–6] Aryl indolyl[7–10] and aryl pyrrolylsulphones[10–12] appeared to be effective HIV-1 RT inhibitors, that is, L-737–126 **1**, its derivative **2** and the pyrrole **3**. Recently some arylsulphonylthiophenes[13] have been shown to display interesting antiviral and antitumor activities. Previously we have synthesized a series of *N*-benzenesulphonylbenzimidazoles related to general structure **4**.[14,15] Two of them, **5** and **6** showed good activity against two RNA viruses at micromolar concentrations and were active against human tumor cell lines. The presence of the ethylenic chain between the two heterocycles and the position of the nitro group in the benzenesulphonyl moiety may play a significant role in their biological activity. Following this line of research, we have synthesized other benzimidazolyl sulphones to gain further information about the structure–activity relationship of this type of compounds. It appeared interesting to study both the effect of shifting of nitro group from para to meta position of the benzenesulphonyl moiety and the presence of two nitro groups. Moreover, considering that the isopropylsulphonyl function is the best substituent at the 1-position in many benzimidazoles,[1–6] we introduced in some derivatives this moiety. In view of importance of an alkoxycarbonyl group in some pyrrolyl aryl sulphones,[10] we replaced in four derivatives the 2-pyridylethyl moiety at the 2-position of the benzimidazole ring by an ester function. We report herein the synthesis of some *N*-sulphonylbenzimidazoles and the results of their antiviral and antiproliferative activity.

Chemistry

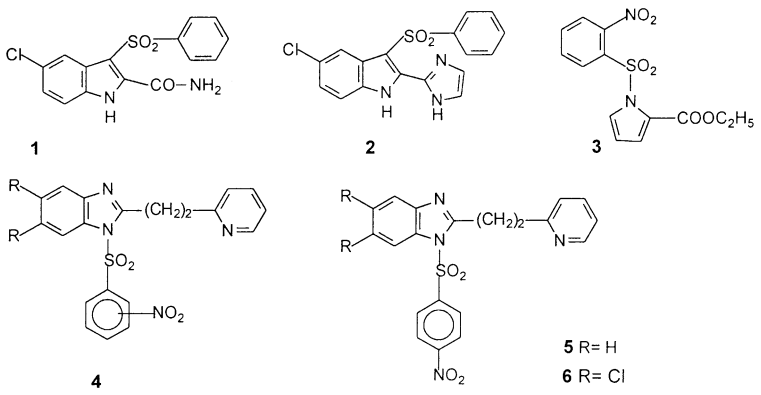
The synthesis of compound **5**,[14] namely, 2-(2-pyridylethyl)-*N*-(4-nitrobenzenesulphonyl)-benzimidazole and of the corresponding 5,6 dichloro derivative **6**[15] was described previously. The reaction of **7** and **8**[15] with isopropylsulphonylchloride in pyridine at 0 °C gave the *N*-isopropylsulphonylated benzimidazoles **9** and **10**.

The sulphonates **11**–**14** were obtained by phase-transfer condensation of **7**, **8** with the appropriate benzenesulphonyl chlorides in the presence of potassium *tert*-butoxide and 18-crown-6 (Scheme 1).

Compounds **15**, **16**[16] and **17**[17] have been reported in the literature. Treatment of **17** with methanol in boiling solution led to the ester **18**. *N*-sulphonylated derivatives **19**–**22** were prepared by the same method used for the synthesis of **11**–**14** (Scheme 2). All the compounds were

*Corresponding author. Tel.: +39-051-2099715; fax: +39-051-2099734; e-mail: lauga@alma.unibo.it

0960-894X/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(02)00535-8

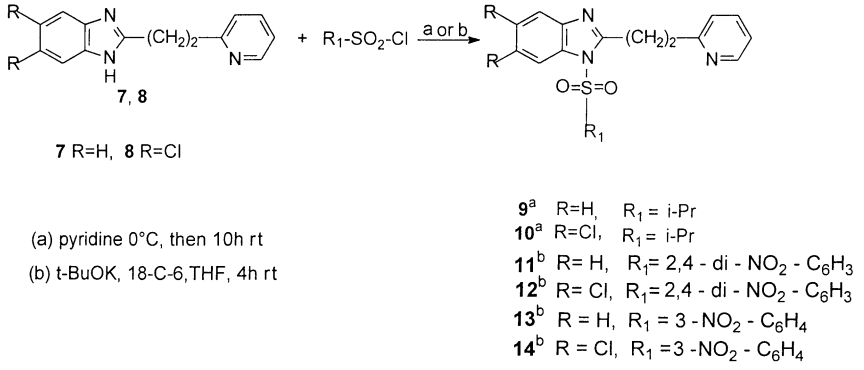


purified by column chromatography using ethyl acetate/petroleum ether 1/1 as eluent and were characterized by NMR spectra and elemental analyses.

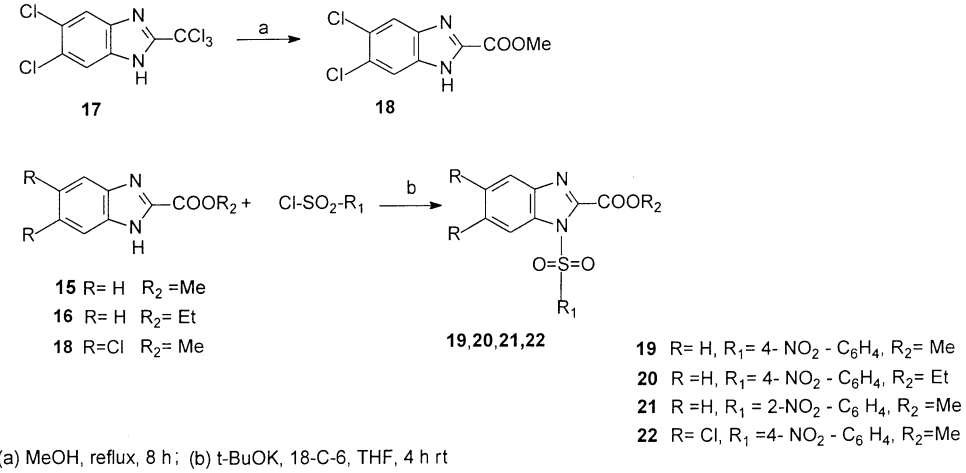
Results and Discussion

Antiviral activity

The *N*-sulphonylated benzimidazoles were evaluated for their antiviral activity against Coxsackie B4 virus, influenza A (H_2, N_2, H_3, N_2), B and respiratory syncytial virus (RSV). However, no antiviral activity was noted against any of these viruses. The compounds were also evaluated against human cytomegalovirus (CMV, strains AD-169 and Davis) and varicella-zoster virus (VZV, strains OKA, YS, 07/1 and YS/R). As shown in Table 1, compound **10** showed significant activity against CMV with an IC_{50} values of 1.6 and 1.1 μg/mL (strains AD-169 and Davis, respectively), and CC_{50} of 37 μg/mL. The selectivity index (CC_{50}/IC_{50}) of **10** was approximately 25 (range 15–20). Compound **14** was inhibitory to VZV at IC_{50} values ranking between 2–4 μg/mL with CC_{50} of 11 μg/mL. The selectivity index of **14** ranged between 5 and 10.



Scheme 1. (a) Pyridine 0 °C, then 10 h rt, (b) t-BuOK, 18-C-6, THF, 4 h rt.



Scheme 2. (a) MeOH, reflux, 8 h; (b) t-BuOK, 18-C-6, THF, 4 h rt.

Table 1. Activity of *N*-sulphonylbenzimidazoles against human cytomegalovirus (CMV) and varicella-zoster virus (VZV) in human embryonic lung (HEL) cells

	Antiviral activity IC_{50} (μg/mL)[a]						Cytotoxicity (μg/mL)			
	CMV		TK^+ VZV		TK^-VZV		Cell morphology (MCC)[b]		Cell growth (CC_{50})[c]	
Compd	AD-169	Davis	YS	OKA	07/1	YS/R				
5	13	13	13	>20	>20	3	>50	≥20	>50	>50
6	>5	>5	>5	>5	>5	>2	20	≥5	>50	>50
9	12	11	>20	>20	>20	>20	>50	50	>50	>50
10	1.6 2.5	1.1 2.0	>5	>5	>5	2	≥50 50	20	37	37
11	30	32	>20	>20	>20	>20	>50	50	32	32
12	9	8	>5	>5	>5	>5	50	20	7	7
13	14	20	>2	>2	>2	>2	50	5	50	50
14	20	>20	4	3	4	2	50	20	11	11
19	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
20	>50	>50	>50	>50	43	20	>50	>50	>50	>50
21	>50	50	50	>50	>20	20	>50	>50	>50	>50
22	>50	>50	>50	>50	>50	>50	>50	>50	>50	50
Ganciclovir	0.3	0.4					>50		>50	
Cidofovir	0.1	0.3					>50		>50	
Acyclovir			0.38	0.35	6.5	3.1		>50		>200
Brivudin			0.003	0.002	6.8	6.4		>50		>200

[a]Concentration required to reduce virus plaque formation by 50%. Virus imput was 100 plaque forming units (PFU) for CMV and 20 PFU for VZV.
[b]Minimum cytotoxic concentration that causes a microscopically detectable alteration of normal cell morphology.
[c]Cytotoxic concentration required to reduce cell growth by 50%.

These results lead to some considerations. The importance of substituents at the 2-position of the benzimidazole ring is once more confirmed. The replacement of the 2-pyridylethyl moiety with an ester function completely abolishes the biological activity (**19**–**22**). The presence of two chlorine atoms at the 5 and 6 positions is crucial; only the 5,6 dichloroderivatives (**10** and **14**) are active. With regard to the N-1 position, the presence of the isopropylsulphonyl group is suitable for antiviral activity; compound **10** displays inhibitory activity against CMV. In the *N*-benzenesulphonylated derivatives, the position of the nitro group plays a significant role; the active compound **14** bears this moiety at 3-position of the phenyl ring. Lack of activity is observed when the nitro is shifted to position 4 (compare **6** with **14**; the IC_{50} for **6** could not adequately be interpreted at concentrations >2 μg/mL because of interference with the normal cell morphology at these concentrations). The presence of two nitro groups results in complete abrogation of activity.

Antiproliferative activity

The compounds were further evaluated for their inhibitory effects on the proliferation of murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt 4 /C8 and CEM/0).[18]

The results of this study are shown in Table 2. Marked cytostatic activity was noted with different derivatives, in particular **6**, **10**, **11**, **12** and **14**. The compounds bearing a dinitrobenzenesulphonyl group (**11** and **12**), had the most potent antiproliferative action. This activity might be related to the reduction of the nitro groups to an electrophilic nitrogen that induces oxidative damage to DNA with a relatively high AT content. In the mononitro series (**6** and **14**), the presence of the chlorine atoms at 5 and 6 position was essential; the corresponding nonhalogenated derivatives were inactive. The position of the nitro group was an important feature; replacement of this moiety from para to meta position increased the inhibitory effect. The isopropylsulphonyl moiety also has a significant influence on the proliferation of humam T-lymphocyte cells, but only in the 5,6 dichlorobenzimidazole.

Conclusion

We conclude, therefore, that in this type of compounds, the replacement of the 2-pyridylethyl moiety at the 2-position of the benzimidazole with an ester function is deleterious for both antiviral and antiproliferative activity. Moreover, the activity against CMV and VZV requires the presence of two chlorine atoms at the 5 and 6 position. These two halogens are important but non

Table 2. Antiproliferatve activity of *N*-sulphonylbenzimidazoles against murine leukemia cells and human T-lymphocyte cells

Compd	IC_{50} (μg/mL)[a]		
	L1210/0	Molt 4/C8	CEM/0
5	>200	>200	≥200
6	5.4±0.3	2.6±0.2	2.8±0.4
9	140±84	83±36	103±32
10	17 ±1	7.1±1.1	5.4±1,8
11	2.1±1.9	2.6±0.5	3.4±1.2
12	4.6 ±0.0	3.6±1.7	5.2±3.5
13	18 ±0.4	15±1	16±1
14	4.1±0.05	1.0±0.0	1.5±0.04
19	>200	>200	>200
20	172±39	170±29	98 ±14
21	≥200	155±64	158±60
22	>200	>200	>200

[a]Concentration required to inhibit cell growth by 50%.

essential for antiproliferative action. On the contrary, the position of the nitro group and the presence of two nitro groups have a significant role in the cytostatic effect.

References and Notes

1. Wikel, J. H.; Paget, C. J.; DeLong, D. C.; Nelson, J. D.; Wu, C. Y. E.; Paschal, J. W.; Dinner, A.; Templeton, R. J.; Chaney, M. O.; Jones, N. D.; Chamberlin, J. W. *J. Med. Chem.* **1980**, *23*, 386.
2. Hermann, E. C., Jr.; Hermann, J. A.; DeLong, D. C. *Antiviral Res.* **1981**, *1*, 301.
3. Victor, F.; Brown, T. J.; Campanale, K.; Heinz, B. A.; Shipley, L. A.; Su, K. S.; Tang, J.; Vance, L. M.; Spitzer, W. A. *J. Med. Chem.* **1997**, *40*, 1511.
4. Victor, F.; Loncharich, R.; Tang, J.; Spitzer, W. A. *J. Med. Chem.* **1997**, *40*, 3478.
5. Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; McKinney, E. S.; Tang, J. C. *J. Med. Chem.* **1997**, *40*, 3937.
6. Hamdouchi, C.; De Blas, J.; Del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50.
7. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O' Brien, J. A.; Sardana, V. V.; Schhleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med: Chem.* **1993**, *36*, 1291.
8. Young, S. D.; Amblard, M. C.; Britcher, S. F.; Grey, V. E.; Tran, L. O.; Lumma, W. C.; Huff, J. R.; Schleif, W. A.; Emini, E. E.; O'Brien, J. A.; Pettibone, D. J. *Bioog. Med. Chem. Lett.* **1995**, *5*, 491.
9. Artico, M.; Silvestri, M.; Stefancich, G.; Massa, S.; Pagnazzi, E.; Musu, D.; Scintu, F.; Pinna, E.; Tinti, E.; La Colla, P. *Arch. Pharm. (Weinheim)* **1995**, *328*, 223.
10. Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. *J. Med. Chem.* **1996**, *39*, 522.
11. Artico, M.; Silvestri, M.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, A. G.; Scintu, F.; La Colla, P. *J. Med. Chem.* **2000**, *43*, 1886.
12. Silvestri, R.; Artico, M.; De Martino, G.; Novellino, E.; Greco, G.; Lavecchia, A.; Massa, S.; Loi, A. G.; Doratiotto, S.; La Colla, P. *Bioorg. Med. Chem.* **2000**, *8*, 2305.
13. Stephens, C. E.; Felder, T. M.; Sowell, J. W., Sr.; Andrei, G.; Balzarini, J.; Snoeck, R.; De Clercq, E. *Bioorg. Med. Chem.* **2001**, *9*, 1123.
14. Garuti, L.; Roberti, M.; Rossi, M.; Cermelli, C.; Portolani, M.; Malagoli, M.; Castelli, M. *Anti-Cancer Drug Des.* **1998**, *13*, 397.
15. Garuti, L.; Roberti, M.; Cermelli, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2525.
16. Ennis, B. C.; Holan, G.; Samuel, E. L. *J. Chem. Soc (C)* **1967**, 30.
17. Holan, G.; Samuel, E. L.; Ennis, B. C.; Hinde, R. W. *J. Chem. Soc. (C)* **1967**, 20.
18. Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817.