Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 75–80

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DISCOVERY OF FR115092 : A NOVEL ANTINEPHRITIC AGENT

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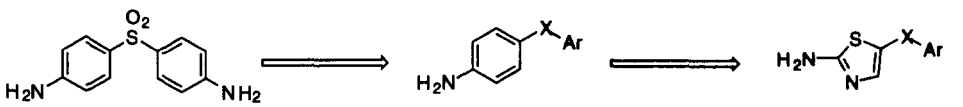
Received 16 October 1997; accepted 17 November 1997

Abstract. A series of dapsone-related 4-aminophenyl and 2-aminothiazolyl derivatives was prepared, and their antinephritic activity and blood toxicity were evaluated. 5-(2-Pyridylsulfonyl)-2-thiazolamine (FR115092, **26**) was effective against two nephritis models, namely graft-*versus*-host disease (GVHD) and autoimmune W/BF_1 mice, and showed none of the blood toxicity observed with dapsone.

Introduction: Dapsone **1** has been clinically used for the treatment of leprosy and dermatitis herpetiformis. Recent reports have shown that **1** is also effective against rheumatoid arthritis,[1,2] systemic lupus erythematosus (SLE),[3] thrombocytopenia,[4,5] and dementia.[6] Several lines of evidence suggest that the anti-inflammatory properties of **1** are partially due to suppression of leukocyte chemotactic and cytotoxic functions; *e.g.*, inhibition of neutrophil adherence,[7] suppression of myeloperoxidase and eosinophil peroxidase,[8] and prevention of the generation of 5-lipoxygenase metabolites.[9] However, the clinical application of **1** has been limited by its variety of side effects; especially, blood toxicity such as hemolytic anemia and methemoglobinemia is the dose-limiting factor.[10]

On the other hand, only corticosteroids such as prednisolone and immunosuppressants such as cyclophosphamide are available for the treatment of nephritis.[11] During our attempts to discover novel and safer antinephritic agents, we found that **1** was effective against chronic GVHD, which was considered as an experimental model for human lupus nephritis of SLE.[12] Reported here are the chemical modification of **1**, representing the structures of **2** and **3** in Scheme 1, and the identification of **26** as the optimal compound.

Scheme 1



Dapsone (**1**) **2** **3**

26 (X = SO_2, Ar = 2-pyr.)

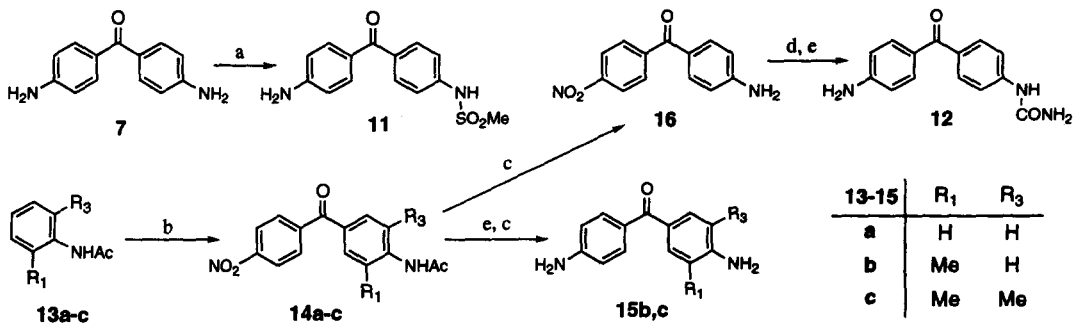
Synthesis: Compounds **1**,[13] **4**,[14] **5**,[15] **6**,[16] **7**,[17] **8**,[18] **9**,[19] **10**,[20] and **17**[21] (Tables 1, 2) were prepared according to the indicated literature, respectively. The benzophenone derivatives (**11**,**12**,**15**) could be obtained as described in Scheme 2. Methylsulfonylation of **7** gave **11**.[22] The key intermediates **14** were

0960-894X/98/$19.00
PII: S0960-894X(97)10192-5

synthesized by the Friedel-Crafts reaction between the acetanilides **13** and 4-nitrobenzoyl chloride. The urea derivative **12** was prepared by hydrolysis of **14a**, carbamoylation with chlorosulfonyl isocyanate, and subsequent reduction. Reduction of **14b,c** with iron and acid hydrolysis afforded the methyl derivatives **15b,c**.

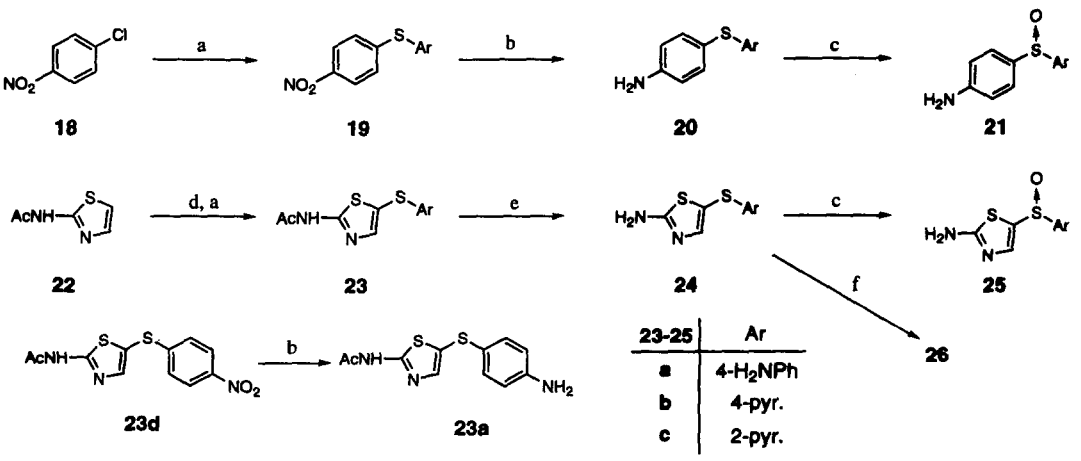
The syntheses of the sulfides, sulfoxides, and sulfone (**21,24,25,26**) are summarized in Scheme 3. Treatment of **18** with the thiols in the presence of K_2CO_3 gave the sulfides **19**, which were reduced with iron and oxidized with *m*-chloroperbenzoic acid (mCPBA) to afford the 4-aminophenyl sulfoxides **21**. The thiazole derivatives **23** were synthesized by chlorination of **22** with *N*-chlorosuccinimide (NCS) and subsequent

Scheme 2



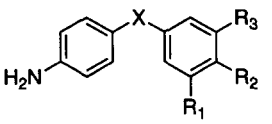
a) $MeSO_2Cl$, pyr., 5°C, 25%; b) 4-nitrobenzoyl chloride, $AlCl_3$, nitrobenzene, 100°C, 67-100%; c) conc. HCl, EtOH, reflux, 49-75%; d) $ClSO_2NCO$, MeCN, r.t., 63%; e) Fe, NH_4Cl, EtOH, H_2O, reflux, 64-100%.

Scheme 3



a) ArSH, K_2CO_3, DMF, 100-120°C, 50-100%; b) Fe, NH_4Cl, EtOH, H_2O, reflux, 72-93%; c) mCPBA(1eq.), $CHCl_3$, 5°C, 37-79%; d) NCS, AcOH, 55°C, 84%; e) HCl, H_2O, AcOH, reflux, 70-91%; f) mCPBA(2.6eq.), DMF, r.t., 73%.

Table 1. Antinephritic activity and blood toxicity of dapsone (**1**) and related compounds



Compd.	X	R_1	R_2	R_3	GVH nephritis[a] % inhibition (100mg/kg p.o.)	Incidence of RBC decrease[b] (100mg/kg p.o.)
1	SO_2	H	NH_2	H	95*	3/15
4	S	H	NH_2	H	70	8/8
5	S(O)	H	NH_2	H	95**	0/10
6	O	H	NH_2	H	93**	4/5
7	CO	H	NH_2	H	95**	0/9
8	SO_2NH	H	NH_2	H	54	0/8
9	CONH	H	NH_2	H	c)	0/10
10	CO	NH_2	H	H	c)	0/10
11	CO	H	$NHSO_2Me$	H	c)	0/9
12	CO	H	$NHCONH_2$	H	c)	0/9
15b	CO	Me	NH_2	H	100*	0/9
15c	CO	Me	NH_2	Me	99*	0/10

a) ** $p<0.01$, * $p<0.05$, significant difference from control(Student's t-test). See ref. 23 for the experimental detail.

b) The number of mice with decreased red blood cells (< 80% of the control mice) / the number of tested mice. See ref. 24 for the experimental detail. c) Less than 50% inhibition.

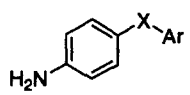
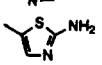
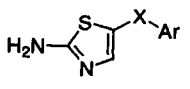
treatment with the thiols. The amino intermediate **23a** was obtained from the nitro compound **23d** by reduction. Acid hydrolysis of **23** gave the sulfides **24**, and successive oxidation with mCPBA produced the sulfoxides **25a-c** and the sulfone **26**.

Results and discussion: Severe immune complex glomerulonephritis is a major symptom of chronic GVHD in mice. The animals have elevated protein excretion in the urine, hypoalbuminemia, and frequently, ascites and edema. Since all of the histological patterns occurring in human lupus nephritis can be seen in these animals, murine chronic GVHD can be used as an experimental model for human lupus nephritis.[12] The disease can be induced experimentally and develops relatively rapidly. We, therefore, chose this GVHD model in the search for novel antinephritic agents.[23] Additionally, the number of red blood cells (RBC)[24] and platelets[25] were counted to check the blood toxicity of the compounds. The test results, % inhibition of proteinuria in the GVHD model and incidence of the mice with a decreased number of RBC, are summarized in Tables 1 and 2.

As a first step in the chemical modification of **1**, we designed a series of compounds (**4-9**), which had various connecting links (X) as a surrogate of the sulfone group in **1** (Table 1). This modification of X could change the physicochemical properties as well as the steric conformation of the whole molecule and the basicity of the amino moiety, which seemed to be one of the essential pharmacophores in the molecule. As shown in Table 1, compounds **5-7** showed potent antinephritic activity comparable to **1**. On the other hand, the amides (**8,9**) were weak or inactive. The sulfoxide and ketone (**5,7**) were also devoid of the blood toxicity and we selected **5** and **7** as lead compounds for further modification.

The positional isomer (**10**) and the methylsulfonyl and carbamoyl derivatives (**11,12**) of **7** were inactive (Table 1). However, incorporation of methyl moieties (**15b,c**) and replacement of one of the aminophenyl group with heterocyclic groups (**17,21b,25a** ; Table 2) resulted in a variety of active compounds. Unfortunately, these active compounds showed mutagenicity in an Ames test or an *in vitro* chromosome aberration test.[26] The aminophenyl structure of the above compounds was hypothesized to cause the mutagenicity, and so, we shifted our focus to replacement of the remaining aminophenyl group. This led us to the aminothiazole analogues (**24c,25b,c,26** ; Table 2). Interestingly, the sulfide (**24c**) and sulfone (**26**) as well as sulfoxide (**25b,c**) derivatives exhibited no blood toxicity, different from **1** and **4**. Because of the lethal toxicity of **25b**, mutagenicity in an Ames test of **24c** and metabolic conversion of **25c** to **24c**, the sulfone derivative **26** was selected for development. In the dose-response studies against GVHD, both **26** and **1** were

Table 2. Antinephritic activity and blood toxicity of 4-aminophenyl and 2-aminothiazolyl derivatives

	Compd.	X	Ar	GVH nephritis[a] % inhibition (100mg/kg p.o.)	Incidence of RBC decrease[b] (100mg/kg p.o.)
	**17**	CO		89*	0/9
	21a	S(O)		e)	NT
	21b	S(O)		99*	0/10
	21c [d]	S(O)		c)	NT
	25a	S(O)		79	0/10
	**25b**	S(O)		100* [f]	0/9
	25c	S(O)		98**	0/10
	24c [d]	S		90*	0/10
	26	SO_2		92**	0/10

a), b), c) : refer to Table 1. d) 2HCl salt. e) 9/10 mice died. f) 8/10 mice died. NT : Not tested.

Table 3. Antinephritic activity of **26** and **1** on chronic GVHD in mice (p.o.)

Compd.	% inhibition of proteinuria		
	100mg/kg	32mg/kg	10mg/kg
26	92**	29	63*
1	95*	—	—

** $p<0.01$,

* $p<0.05$, *vs.* control (Student's t-test).

— : Less than 50% inhibition.

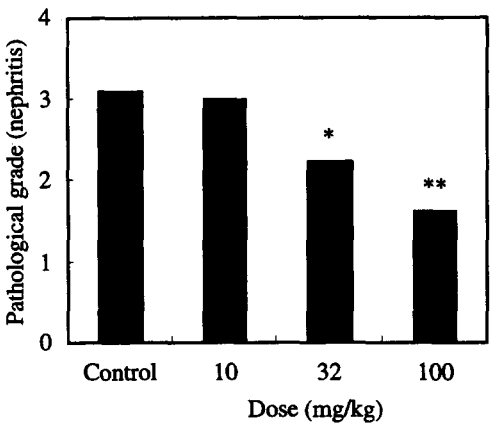


Fig. 1 Effect of **26** against lupus nephritis in W/BF_1 mice

Drug was orally administered for 6 weeks after development of established lupus disease at the age of 16 weeks. * $p<0.05$, ** $p<0.01$ compared with control (Kruskal-Wallis test).

significantly active at 100 mg/kg, but they showed marginal activities at 10 and 32 mg/kg (Table 3).

The antinephritic activity of **26** was further evaluated against spontaneous autoimmune disease, lupus nephritis, in male (NZW x BXSB)F_1 mice (W/BF_1 mice).[27,28] Compound **26** showed beneficial therapeutic effects; histological examination of kidney specimens showed that **26** suppressed the growth of mesangium cells from 32 mg/kg p.o. (Fig. 1), and the urinary protein levels and antibodies to double strand DNA were also reduced (data not shown).[29] Treatment with prednisolone (up to 3.2 mg/kg p.o.), in contrast to **26**, showed only marginal effects.

In conclusion, the chemical modification of **1** has led to a novel antinephritic compound **26** (FR115092), which possesses similar potency and pharmacological profile to **1**, but devoid of any blood toxicity and mutagenicity.[30]

Acknowledgments: The authors are grateful to Drs. H. Senoh, K. Shimomura, T. Fujii, and their colleagues in the pharmacological division for biological assays, and Drs. K. Sakane and G. W. Spears in the Medicinal Chemistry Research Laboratories for useful suggestions during the preparation of this manuscript.

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23. Six weeks old female (57BL/6 x DBA/2)F_1 and DBA/2 mice were used. Chronic GVHD was induced in (57BL/6 x DBA/2)F_1 mice with two injections of DBA/2 spleen cells given 5 days apart. Each injection contained 5 x 10^7 cells. From 3 days after the second cell injection, drug was administered orally once a day for 8 weeks. To assess the renal disease, proteinuria were measured after the last drug administration. The concentration of serum albumin in the urine was determined by the single radial immunodiffusion method using rabbit anti-mouse serum albumin antiserum. Ten mice were used per group. The activity of the compound was expressed as a % inhibition of proteinuria.
24. The test compound was given orally once a day for 5 days to female ddY mice aged 6 weeks. The number of RBC were counted 5 days after the final dosing with the test compound, in which mice were bled from the orbital plexus and the RBC were counted with an automatic blood analyzer. The incidence of RBC decrease was expressed by the number of mice with a decreased number of RBC (<80% of the control animals) *vs.* the number of tested mice.
25. Data for platelets are not shown.
26. Unpublished results of the Toxicology Research Laboratories.
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29. **1** also exhibited significant activity at 100 mg/kg similarly to **26** in W/BF_1 mice.
30. Because of the pharmacological and structural similarity between **1** and **26**, the clinical dose of **26** is estimated to be as low as that of **1** (around 100 mg/day).[1-4]