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SYNTHESIS AND EFFECTS OF NOVEL THIAZOLE DERIVATIVES AGAINST THROMBOCYTOPENIA

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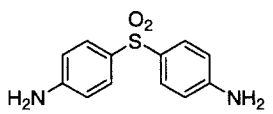
Abstract: 5-(2-Pyridylsulfonyl)-2-thiazolamine (**2**) was effective both in mitomycin C (MMC)-induced thrombocytopenia and in an animal model of idiopathic thrombocytopenic purpura (ITP). It also suppressed the increase of autoantibodies against platelets in the ITP model and showed no blood toxicity. Chemical modification of **2** led to the discovery of more potent compounds against MMC-induced thrombocytopenia.

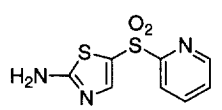
Introduction

Thrombocytopenia is a major side effect of cancer chemotherapy and radiotherapy.[1] Development of effective therapies for autoimmune thrombocytopenia such as idiopathic thrombocytopenic purpura (ITP) is also of importance.[2,3] Several cytokines such as interleukin (IL)-6,[4,5] IL-3,[6] IL-1[7] and PIXY321[8] have been evaluated for stimulation of megakaryocyte proliferation and maturation, but to date, only IL-11[1,9] and thrombopoietin[10,11] have demonstrated significant clinical efficacy.[12] Lower molecular–weight compounds, *e.g.*, leustroducsins,[13] conagenin,[14] Y-25510,[15] KT6352,[16] TAN-1511 analogue[17,18] and FK565,[19] have also been reported as thrombopoietic agents. But their clinical usefulness is not yet clear.

Recent reports have shown that dapsone **1** is effective against autoimmune thrombocytopenia.[20–27] However, dose-intensive therapy of **1** is limited by a variety of toxicities, including hemolytic anemia and methemoglobinemia.[28] In the course of research on new antinephritic agents, we found compound **2** (FR115092) possessed a similar potency and pharmacological profile to **1**, but devoid of any blood toxicity.[29] Thus, we focused on the development of a novel agent for thrombocytopenia, based on the structure of **2**. Reported here are the effects of **2** against thrombocytopenia in mice, and the synthesis and pharmacological evaluation of **2**-related compounds.



dapsone (1)



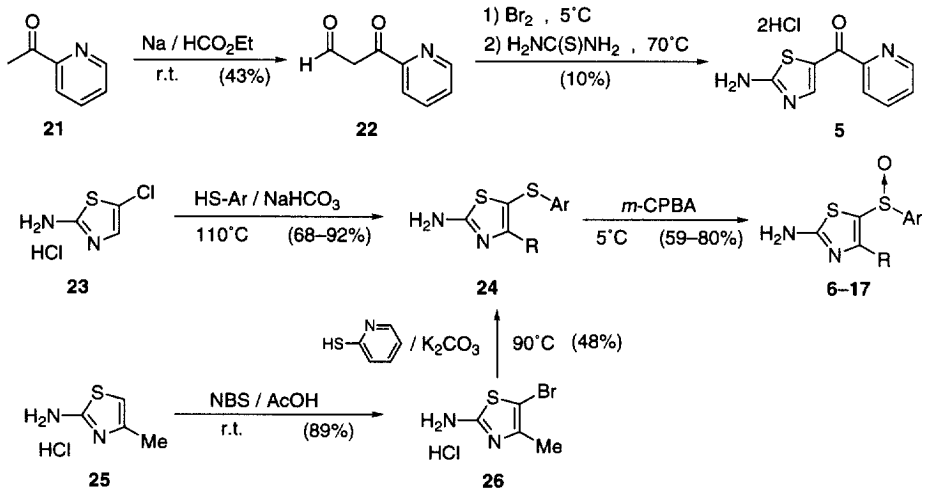
FR115092 (2)

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00404-1

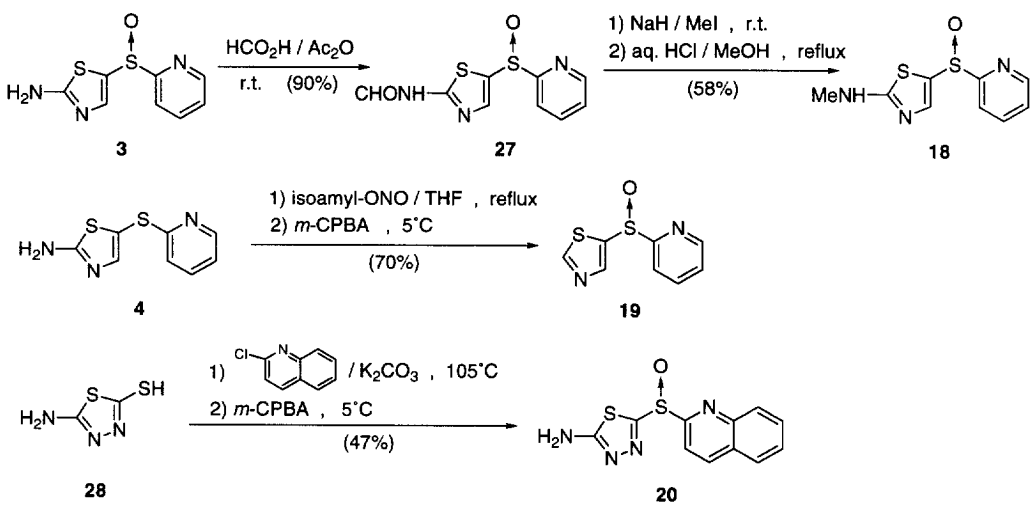
Chemistry

Synthetic routes to the 2-aminothiazole derivatives **5–17** (Tables 1–3) are summarized in Scheme 1. Commercially available 2-acetylpyridine **21** was converted to unstable aldehyde **22**, which was brominated and treated with thiourea to give 5-(2-pyridylcarbonyl)-2-thiazolamine **5**. The sulfoxides **6–17** were synthesized by careful oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) from the corresponding sulfides **24**. The key intermediates **24** were obtained by the coupling reaction between 5-halothiazoles (**23**,**26**) and thiols in the presence of $NaHCO_3$ or K_2CO_3. Syntheses of miscellaneous compounds **18–20** are shown in Scheme 2.

Scheme 1



Scheme 2



2-Methylaminothiazole and 2-desaminothiazole derivatives **18**, **19** were prepared from **3** or **4** (previously reported in ref. 29) using a conventional methylation or deamination method, respectively. Successive treatment of 2-amino-5-mercapto-1,3,4-thiadiazole **28** with 2-chloroquinoline and *m*-CPBA afforded **20**.

Biological results and discussion

Dapsone (**1**) and FR115092 (**2**) were given orally to mitomycin C (MMC)-induced thrombocytopenic mice[30]

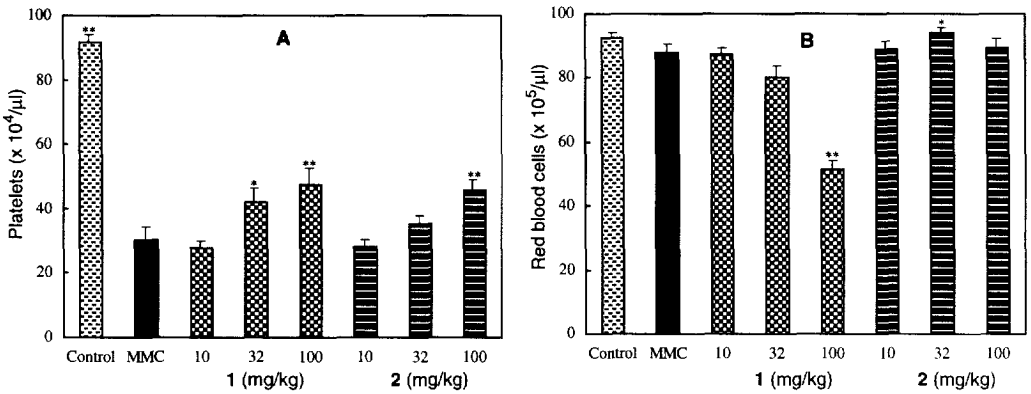
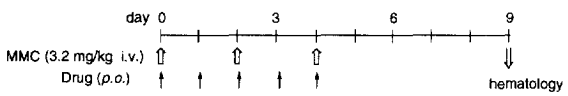


Fig. 1 Effects of **1** and **2** on the Number of Platelets (A) and Red Blood Cells (B) in MMC-induced Thrombocytopenic Mice



* p<0.05, ** p<0.01 *vs.* MMC control (Student's *t*-test).

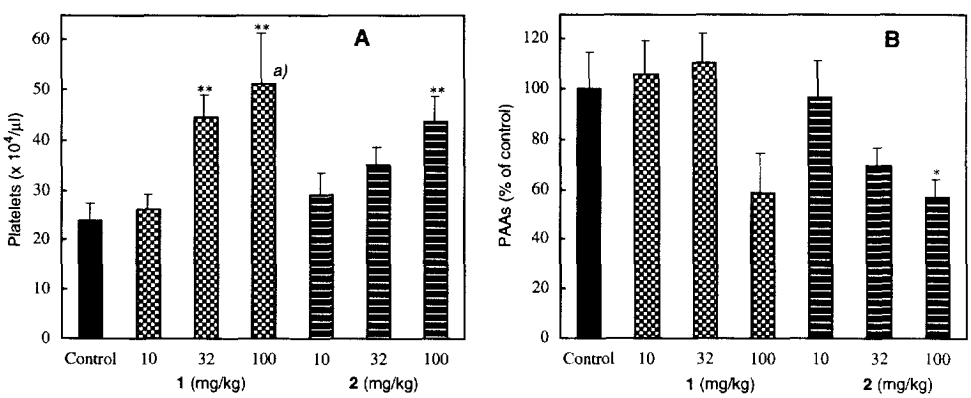
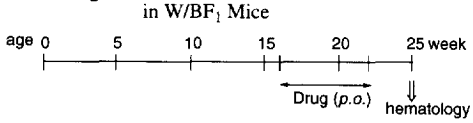


Fig. 2 Effects of **1** and **2** on the Number of Platelets (A) and Platelet-associated Antibodies (B) in W/BF$_1$ Mice



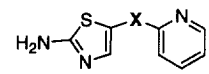
* p<0.05, ** p<0.01 *vs.* control (Dunnett's test).

a) Toxic (21/29 mice died.)

(Fig. 1), and male (NZW x BXSB)F_1 mice (W/BF_1 mice) which are well-known as an animal model for ITP[31] (Fig. 2). Both compounds inhibited the reduction of the number of platelets in the MMC-induced model as shown in Fig. 1–A. In addition, although **1** induced a decrease in the number of peripheral red blood cells, **2** did not (Fig. 1–B). Both **1** and **2** also significantly prevented the development of thrombocytopenia and suppressed the increase in circulating autoantibodies against platelets (PAAs) in W/BF_1 mice (Fig. 2). Compound **2** also encouraged the growth and maturation of megakaryocytes in bone marrow in both models (data not shown).[32] The above results indicated that **2** was effective against thrombocytopenia, without induction of hemolytic anemia.

In order to clarify further the structure–activity relationship of analogues of **2** and to find more potent compounds, we chemically modified the connecting link, the pyridine, and the 2-aminothiazole moieties of **2**. The test results, % of the number of platelets for the treated *versus* MMC control group in the MMC-induced thrombocytopenic mice, are summarized in Tables 1–3. As a first step, we tested a series of compounds (**3–5**), which had various connecting links (X) as a surrogate for the sulfone group in **2**. As shown in Table 1, the sulfoxide **3** was the most active in the series and we selected **3** as a lead compound for further modification. As a surrogate for the 2-pyridyl group, some condensed-heterocycles showed excellent activity, especially benzimidazole and quinoline derivatives **10**–

Table 1. Investigation of Connecting Links (**X**)

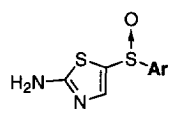


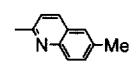
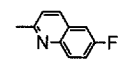
Compd.	X	Number of platelets [a] (% of MMC control)
2 [b]	SO_2	139**
3 [b]	S(O)	154**
4 [b,c]	S	147*
5 [c]	CO	140

a) Dose : 100 mg/kg *p.o.* ; ** $p<0.01$, * $p<0.05$ *vs.* MMC control (Student's *t*-test). See ref. 30 for experimental detail.

b) Ref. 29. *c)* 2HCl salt.

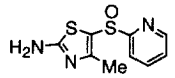
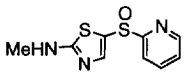
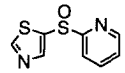
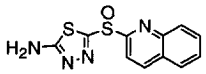
Table 2. Investigation of 5-(Arylsulfinyl)-2-thiazolamines



Compd.	Ar	Number of platelets [a] (% of MMC control)
6		115 [b]
7		116 [b]
8		146*
9		138
10		165**
11		188*
12		181*
13		146**
14		162**
15		131*
16		130 [b]

a) Dose : 100 mg/kg *p.o.*, unless otherwise noted ; ** $p<0.01$, * $p<0.05$ *vs.* MMC control. *b)* 32 mg/kg.

Table 3. Investigation of Miscellaneous Derivatives

Compd.	Structure	Number of platelets [a] (% of MMC control)
17		118
18		132
19		148*
20		102

a) Dose : 32 mg/kg *p.o.* ; * p<0.05 *vs.* MMC control.

Table 4. Dose–response Study

Compd.	Number of platelets (% of MMC control) [a] 10 mg/kg	32 mg/kg	100 mg/kg
10	92	112	165**
11	116	123*	188*
12	138*	153*	181*
19	124	148*	171**
1	91	125*	150*
2	94	143*	139**

a) ** p<0.01, * p<0.05 *vs.* MMC control (Student's *t*-test).

12 were more active than **3** (Table 2). Interestingly, desamino compound **19** also exhibited potent activity (Table 3). But incorporation of a methyl moiety (**17**,**18**) or replacement of thiazole with thiadiazole (**20**) resulted in loss of activity.

Based on the dose–response study shown in Table 4, compounds **12** and **19** were confirmed to be superior to **1** or **2**. The activities described in this paper suggest that thiazole derivatives such as **2**, **12** or **19** have potential as a new agent for various types of thrombocytopenic diseases. Full details of the chemistry and pharmacology of this novel series of compounds will be published in due course.

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References and Notes

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30. The platelet count-increasing activity was determined using mice whose number of platelets was depleted as a result of MMC administration. Test compounds were administered orally once a day for 5 days to male ddY mice (n = 10). MMC (3.2 mg/kg) was administered intravenously to mice on days 0, 2 and 4 after the initial dosing with the test compound. The number of platelets was counted 5 days after the final dosing with the test compound with an automatic blood analyzer (Sysmex E-4000).
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