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SYNTHESIS AND ANTIRHEUMATIC ACTIVITY OF NOVEL TETRAHYDROQUINOLINE-8-CARBOXYLIC ACID DERIVATIVES

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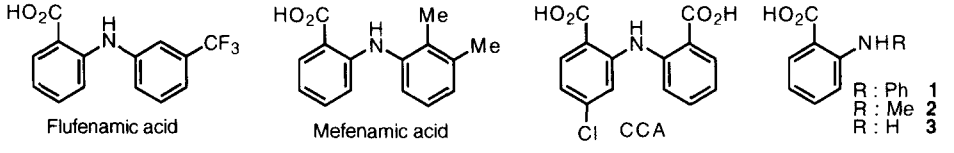
Abstract: A study of the modification of *N*-alkylanthranilic acids to develop novel DMARDs is detailed. 1,2,3,4-Tetrahydroquinoline-8-carboxylic acid derivatives were found to exhibit a therapeutic effect on adjuvant arthritis and a suppressive effect on bone destruction. © 1997 Elsevier Science Ltd.

Although Flufenamic acid, Mefenamic acid, and CCA are much alike in structure, there is an important difference in the pharmacology of CCA (Fig. 1). While Flufenamic- and Mefenamic acid exhibit cyclooxygenase (COX) inhibitory activity and are classified as nonsteroidal antiinflammatory drugs (NSAIDs), CCA shows no COX inhibition and is classified as a disease-modifying antirheumatic drug (DMARD). To our knowledge, CCA is the sole antirheumatic drug of anthranilic acid type. This suggests that anthranilic acid derivatives, typically utilized as NSAIDs, might be useful in other roles as well, and in particular that anthranilic acids lacking COX inhibition, like CCA, might have potential as DMARDs. Based on the above expectation, we attempted to investigate the antirheumatic activity of anthranilic acids.[1]

Fig. 1

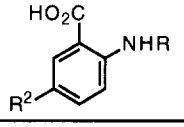


During our preliminary examining of the COX inhibitory activity of *N*-phenylanthranilic acid (**1**), *N*-methylanthranilic acid (**2**), and anthranilic acid (**3**), we found that only **1** showed COX inhibition.[2] Thus, *N*-methylanthranilic acid (**2**) and anthranilic acid (**3**), lacking COX inhibition, might make suitable lead compounds in the development of DMARDs.[1] Accordingly, we focused our research on the modification and antirheumatic acitivity of compounds of the *N*-alkylanthranilic acid-type, such as **2** and **3**.

First, anthranilic acids were synthesized and tested for their effects on adjuvant arthritis in rats. As expected, 5-nitroanthranilic acid (**4b**) and *N*-methyl-5-nitroanthranilic acid (**4c**) moderately reduced arthritic swelling of non-injected rat paws[3] without COX inhibitory activity (Table 1). Since it was

obvious that *N*-alkylanthranilic acid-type compounds had potential as antirheumatic agents, we continued the conversion of lead compounds. However, the activity of the synthesized derivatives on adjuvant arthritis was low, and it seemed that simple modifications such as *N*-alkylation and the introduction of substituents to the benzene ring were limited in their enhancement of antirheumatic activity.

Table 1

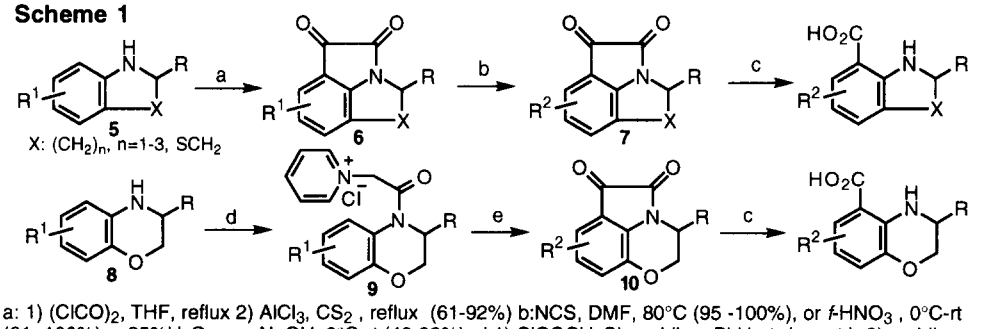


Compound	R	R^2	Inhibitory effect on adjuvant arthritis*
4 a	H	Cl	-
4 b	H	NO_2	+ (10)
4 c	Me	NO_2	++ (50)
4 d	CH_2Ph	NO_2	-

*) Edema suppression rates were calculated as percentages with respect to the control value; 0-20%=-, 21-30%=+, 31-40%=++. ( ): Dose (mg/kg).

Our next trial was centered on the novel type of anthranilic acid analogs. Bicyclic anthranilic acid analogs, such as indoline-7-carboxylic acids, 1,2,3,4-tetrahydroquinoline-8-carboxylic acids, benzazepine-9-carboxylic acids, 1,4-benzothiazine-5-carboxylic acids, and 1,4-benzoxazine-5-carboxylic acids, can be regarded as an structural extension of *N*-methylanthranilic acid. These analogs were prepared by a sequence involving (1) transformation of amines (**5** and **8**) to the corresponding key isatin analogs (**6** and **10**); (2) introduction of substituent groups to the key intermediates, if necessary and; (3) conversion of **7** and **10** to acids by oxidative cleavage reaction (Scheme 1). In the case of the synthesis of benzoxazine analogs, the ether bond of the amide derivative obtained by oxalyl chloride treatment of **8** was easily cleaved by successive $AlCl_3$ treatment. Therefore, isatin analogs of benzoxazine were synthesized by applying the method of Heinisch.[4]

Scheme 1

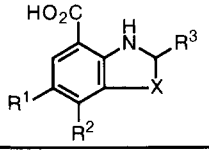


a: 1) $(ClCO)_2$, THF, reflux 2) $AlCl_3$, CS_2, reflux (61-92%) b:NCS, DMF, 80°C (95 -100%), or *f*-HNO_3, 0°C-rt (61- 100%) c: 35%H_2O_2, aq. NaOH, 0°C-rt (49-93%) d:1) $ClCOCH_2Cl$, pyridine, PhH, rt (quant.) 2) pyridine, reflux (quant.) e: 1) *N,N*-dimethyl-p-nitrosoaniline, DMF, aq. NaOH, rt (95 -100%) 2) c-HCl, rt (30- 58%) 3) NBS, DMF, 80°C (90%), or *f*-HNO_3, 0°C-rt (73%)

As depicted in Table 2, the activity of indoline **11** and benzothiazine derivatives **15a** and **15b** was low, but some of the derivatives displayed effects on adjuvant arthritis in rats. None of these compounds displayed any COX inhibitory activity.

Among compounds extrapolated from *N*-methyl-5-nitroanthranilic acid (**4c**), tetrahydroquinoline **12a** and the benzazepine analog **13a** exhibited good activity. This was especially true of 6-nitro-1,2,3,4-tetrahydroquinoline-8-carboxylic acid (**12a**), which was twice as effective on adjuvant arthritis as the parent compound **4c**. In addition to the nitro compounds **4c**, **12a**, and **13a**, tetrahydroquinoline-6,8-dicarboxylic acid **12b**, and 8-carboxyl-1,2,3,4-tetrahydro-6-quinolineacetic acid (**12c**), 7-methylsulfonylamino-benzazepine-9-carboxylic acid **13b**, and 3-phenyl-1,4-benzoxazine-5-carboxylic acid **14c** also exhibited the therapeutic effect on the chronic inflammatory model. The activity of these anthranilic acid analogs on adjuvant arthritis was much more effective than that of CCA, and the effect continued even after discontinuation of therapy.

Table 2



Compound	X	R^1	R^2	R^3	Inhibitory effect on adjuvant arthritis*
11	CH_2	NO_2	H	H	-
12 a	$(CH_2)_2$	NO_2	H	H	++++ (50)
12 b	$(CH_2)_2$	CO_2H	H	H	++ (10)
12 c	$(CH_2)_2$	CH_2CO_2H	H	H	+++ (10)
12 d	$(CH_2)_2$	NO_2	H	Ph	-
13 a	$(CH_2)_3$	NO_2	H	H	+ (10)
13 b	$(CH_2)_3$	NHMs	H	H	++ (50)
14 a	OCH_2	NO_2	H	H	-
14 b	OCH_2	Br	Cl	H	+ (50)
14 c	OCH_2	H	H	Ph	++ (10)
15 a	SCH_2	Cl	H	H	-
15 b	SCH_2	CO_2H	H	H	-

*) Edema suppression rates were calculated as percentages with respect to the control value; 0- 20%=-, 21-30%=+, 31-40%=++, 41-50%=+++, more than 50%=++++. ( ): Dose (mg/kg).

It has been reported that bone destruction occurs in adjuvant arthritic rats.[5] The IL-1β production by splenic adherent cells from adjuvant arthritic rats is markedly increased during the development of disease,[6] and this mediator enhances Ca release from the bones.[7] These findings suggest that the increase of IL-1β during the development of adjuvant arthritis might play a role in bone damage. In addition to the antiinflammatory effect above, it was noted that the bicyclic anthranilic acid analogs listed in Table 2, particularly 1,2,3,4-tetrahydroquinoline-8-carboxylic acid derivatives **12a** and **12c** suppress Ca release from IL-1β-stimulated bones.[8] Actually, **12a** and **12c** exhibited a suppression of bone damage in the non-injected paws of established adjuvant arthritic rats.[9] Thus, **12c**-treated rats had an average bone destruction score of 3.5, much lower than the scores of 6.2 and 5.4 for adjuvant control and CCA-treated rats,

respectively. Rheumatoid arthritis (RA) is a chronic autoimmune disease with joint destruction. Accordingly, the suppressive effect on bone destruction exhibited by **12a** and **12c** is of great import to the treatment of this disease. Moreover, both agents were found to inhibit the appearance of anti-sheep erythrocyte IgM antibody-producing cells *in vitro* and *in vivo* (data not shown).

In conclusion, antirheumatic activity was enhanced by the transformation of *N*-alkylanthranilic acids to bicyclic anthranilic acid analogs. The novel antirheumatic agents, 6-nitro-1,2,3,4-tetrahydroquinoline-8-carboxylic acid (**12a**) and 8-carboxy-1,2,3,4-tetrahydro-6-quinolineacetic acid (**12c**) showed not only potent antirheumatic activity but also a suppressive effect on bone destruction. The pharmacological properties of both agents are distinct from those of ordinary DMARDs. These properties are now under further investigation.

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References and Notes

1. If the test compounds had COX inhibition, it would be vague whether their effects on adjuvant arthritis exhibited by COX inhibition or immunomodulating activity. In order to distinguish DMARDs from NSAIDs definitely, we selected the compounds without COX inhibition.
2. Inhibitory avtivity on COX was measured according to the method of Hiroi et al.: Hiroi J.; Ohara K.; Fujitsu T.; Hirai O.; Satoh S.; Ochi T.; Senoh H.; Mori J.; Kikuchi H., *Folia Parmacol. Japan*, **86**, 441 (1985). IC_{50} of Flufenamic acid was 1.5×10^{-5} M and its value was about three times that of *N*-phenylanthranilic acid (**1**). In contrast, acids **2** and **3** did not suppress malondialdehyde production at a concentration of 9×10^{-5} M.
3. Adjuvant arthritis was induced in SD rats according to the method of Kameyama et al.: Kameyama, T.; Nabeshima T.; Yamada S.; Sato M., *Arzneim-Forsch/Drug Res.*, **37**, 19 (1987). After the adjuvant injection, drug treatment (10 mg/kg and 50 mg/kg p.o.) was started on Day 14 and continued until Day 20 (once daily, 7 treatments). Suppressive rates on edema were calculated on Day 21. Some of the compounds listed in Table 1 and 2 did not show a dose-dependent suppression. In order to simplify comparison of the inhibitory effects, Table 1 and 2 were expressed by better inhibitory effect obtained at the above doses.
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5. (a) Pozo E. D.; Graeber M.; Elford P.; Payne T., *Arth. Rheum.*, **33**, 247 (1990). (b) Binderup L., *Acta Pharmacol. Toxicol.*, **59**, 228 (1986).
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8. The bone resorption was measured according to a modification of the method described by Tsuda et al.: Tsuda M.; Kitazaki T.; Ito T.; Fujita T., *J. Bone Miner. Res.*, **1**, 207 (1986).
9. On day 24, radiographic assessments of non-injected paws were done by a modification of the method of Tanaka et al.: Tanaka A.; Kakushi H.; Shike T.; Yoshida T.; Kojima Y.; Nishiyama S.; Yahara I., *Oyo Yakuri-Pharmacometrics*, **24**, 571 (1982). Bone damage was assessed blindly on a scale of 0-4+ (with 0 equaling normal and 4+ equaling severe changes) for metatarsus, tarsus, calcaneum, and the end of the distal tibia of the non-injected paw. The maximum total severity score by this method was 16+.

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