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SYNTHESIS AND CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITORY ACTIVITY OF SOME THIAZOLIDENE-4-ONE ANALOGS OF MECLOFENAMIC ACID

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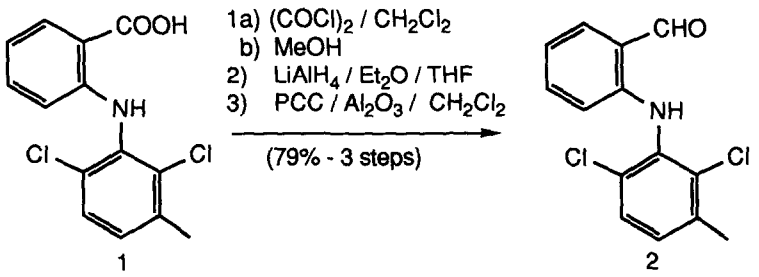
Abstract: *Replacement of the carboxylic acid functionality of meclofenamic acid with select heterocycles converted this cyclooxygenase (CO) inhibitor into dual inhibitors of CO and 5-lipoxygenase (5-LO).*

The anti-inflammatory agent meclofenamic acid, **1**, belongs to the fenamate (N-aryl-anthranilic acid) class of non-steroidal anti-inflammatory drugs (NSAIDs)[1]. NSAIDs reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. An undesirable side effect of the chronic use of NSAIDs is the formation of gastric ulcers[2]. This adverse event may be minimized in the presence of an inhibitor of 5-lipoxygenase (5-LO), another enzyme in the arachidonic acid cascade. Several dual inhibitors of CO and 5-LO are currently under investigation for the treatment of arthritis[3].

We recently reported that replacing the carboxylic acid functionality of meclofenamic acid with a heterocycle incorporated 5-lipoxygenase inhibitory activity into the NSAID pharmacophore. The heterocycles described previously were 1,3,4-oxadiazole-2-thiones or 1,3,4-thiadiazole-2-thiones[4]. We now report the preparation and *in vitro* evaluation of meclofenamic acid analogs where a rhodanine derivative is attached to the fenamate core via a double bond.

The required key intermediate, the corresponding aldehyde of meclofenamic acid, was readily prepared in 3 steps, as shown in scheme 1. Esterification of meclofenamic acid followed by reduction provided the corresponding alcohol. Oxidation of the alcohol with pyridinium chlorochromate in the presence of alumina gave the desired aldehyde **2** in good yield[5].

Scheme 1

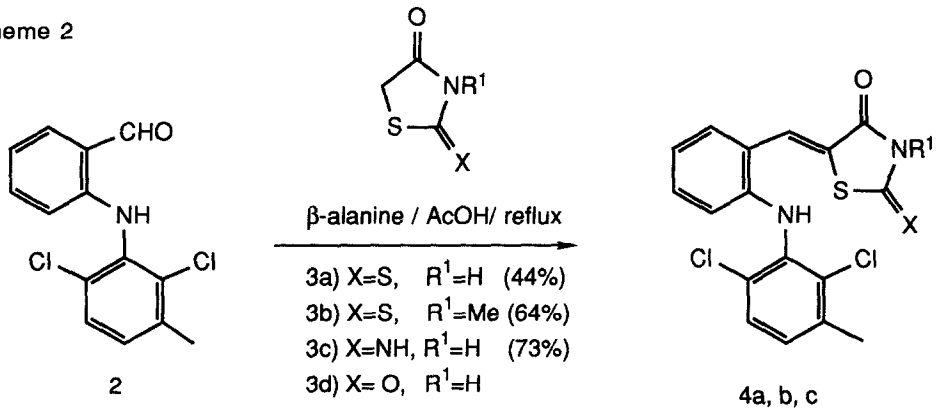


1 2

With aldehyde **2** in hand several attempts were made to condense this material with rhodanine (**3a**). Only by using the modified Knoevenagel reaction conditions shown in scheme 2 could **4a** be cleanly isolated [6]. In a similar fashion, condensation of **2** with 3-methylrhodanine (**3b**) and with pseudothiohydantoin (**3c**) provided **4b** and **4c** respectively.

Analog **4a,** which contains an acidic heterocycle, inhibited both CO and 5-LO. However, **4b**, the 3-methyl analog of **4a**, was inactive against 5-LO and only weakly inhibited CO. Analog **4c**, which contains a basic heterocycle, also showed only marginal activity. The values obtained for these compounds in an intact RBL-1 cell line assay for the inhibition of CO and 5-LO activity are presented in Table 1.

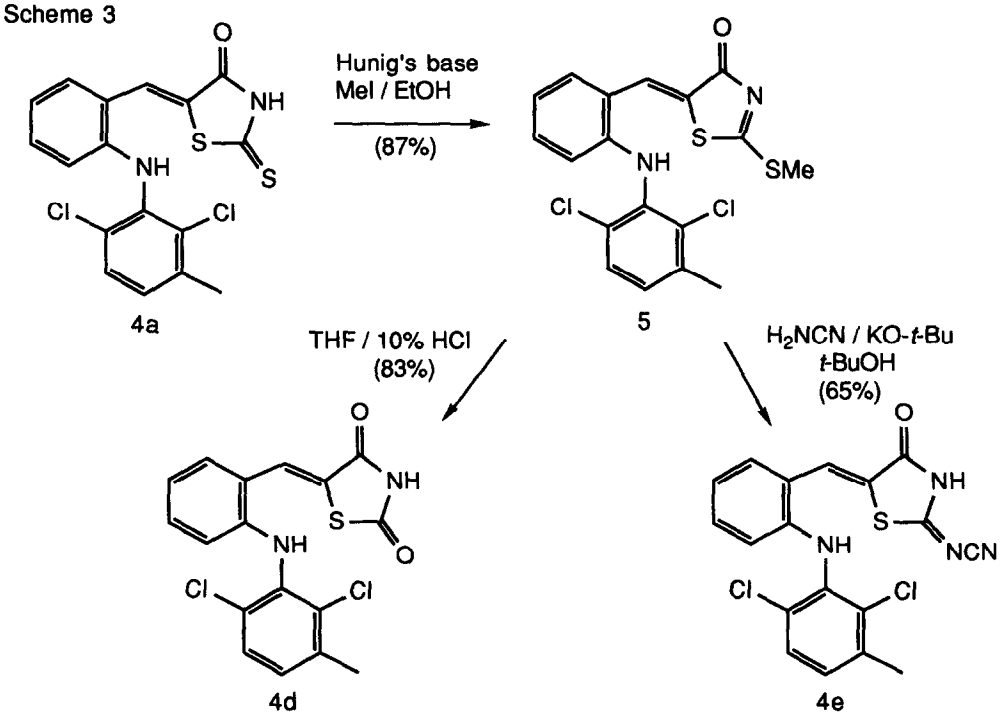
Scheme 2



All attempts to prepare analog **4d** via direct condensation of aldehyde **2** with 2,4-thiazolidenedione (**3d**) under a variety of conditions were not successful. The route depicted in scheme 3 was therefore followed. When **4a** was treated with Hunig's base in EtOH followed by iodomethane a mixture of the SMe analog **5** and the NMe analog **4b** was obtained. The two isomers were easily separated by flash chromatography. Acidic hydrolysis of **5** provided the desired dione **4d**. Disappointingly, **4d** showed no activity against CO and only minimal activity against 5-LO.

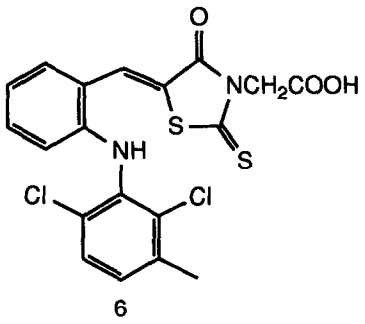
The cyanoimino group (=NCN) has been shown to be a bioisosteric replacement for a thione (=S)[7]. The cyanoimino analog, **4e**, was prepared via treatment of **5** with cyanamide under basic conditions. While **4e** was found to be a dual inhibitor, it was less active than **4a** in inhibiting both CO and 5-LO.

Scheme 3



One derivative of meclofenamic acid was prepared where the carboxylic acid is replaced by a heterocycle that in turn contains a carboxylic acid. Condensation of **2** with rhodanine-3-acetic acid gave a 78% yield of **6**. This acidic analog was a potent inhibitor of 5-LO.

We have extended this work to other NSAIDs. The indomethacin analog **7** was prepared and was found to be a balanced dual inhibitor. We are continuing to examine other heterocyclic analogs of NSAIDs as inhibitors of CO and 5-LO.



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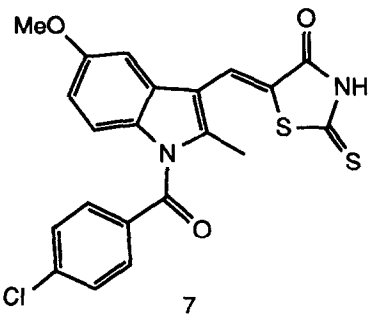

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Table 1: Inhibition of 5-Lipoxygenase (5-LO) and of Cyclooxygenase (CO)[8]

Compound	5-LO[a]	CO[a]
Meclofenamic acid (1)	24	0.10
4a	0.82	6.0
4b	NA[b]	32%
4c	35%	20%
4d	30%	NA[b]
4e	1.5	10.2
6	2.2	33%
Indomethacin	>100	0.50
7	1.4	2.0

a) Values reported as either an IC_{50} (μM) or the percent inhibition at 10 μM.
b) Less than 5% inhibition at 10 μM is reported as NA (not active).

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References and Notes

1) For an SAR study of the fenamates see: Kaltenbronn, J. S.; Scherrer, R. A.; Short, F. W.; Jones, E. M.; Beatty, H. R.; Saka, M. M.; Winder, C. V.; Wax, J.; Willamson, W. R. N., *Arzeim. Forsch. / Drug Res.* **1983**, 33, 621.

2) Gabriel, S. E. ; Bombardier, C., *J. Rheumatol.***1990**, 17,1.

3) For a review on dual inhibitors see: Carty, T. J.; Marfat, A.; Masamune, H., in *Annual Reports in Medicinal Chemistry* **1988**, 23, 181.

4) Boschelli, D. H.; Connor, D. T.; Bornemeier, D. A.; Dyer, R. D., *Bio. Med. Chem. Lett.* **1992**, 2, 69.

5) The route used to prepare **2** was reported previously, U. S. Patent 4,981,865.

6) New compounds exhibited spectral data (IR, MS, ^{1}H NMR) and combustion data (CHN) consistent with their proposed structures.

7) Durant, G. J; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R., *J. Med. Chem.* **1977**, 20, 901. Chiu, W.-H.; Klein, T. H.; Wolff, M. E., *J. Med. Chem.* **1979**, 22, 119.

8) The procedure used to determine the inhibition of 5-LO and of CO has been described previously, see: Flynn, D. L.; Capiris, T.; Cetenko, W. J.; Connor, D. T.; Dyer, R. D.; Kostlan, C. R.; Nies, D. E.; Schrier, D. J.; Sircar, J. C., *J. Med. Chem.* **1990**, 33, 2070.