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CONVERSION OF NSAIDS INTO BALANCED DUAL INHIBITORS OF CYCLOOXYGENASE AND 5-LIPOXYGENASE

Diane H. Boschelli *# , David T. Connor#, Milton Hoefle#,
Dirk A. Bornemeier% and Richard D. Dyer%
Departments of Chemistry# and Biochemistry%
Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company
2800 Plymouth Rd., Ann Arbor, MI 48105

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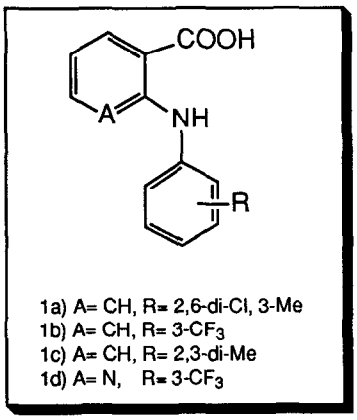
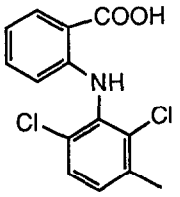
ABSTRACT *By replacing the carboxylic acid functionality of several fenamates with 1,3,4-oxadiazole-2-thiones and 1,3,4-thiadiazole-2-thiones we converted selective cyclooxygenase (CO) inhibitors into dual inhibitors of both CO and 5-lipoxygenase (5-LO).*

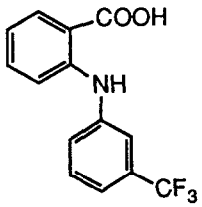
Non-steroidal anti-inflammatory drugs (NSAIDS) block the metabolism of arachidonic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. While classical NSAIDS are effective at reducing the pain and swelling associated with arthritis, their chronic use is estimated to induce gastric ulcers in 20% of patients[1]. Inhibition of 5-lipoxygenase (5-LO), another enzyme in the arachidonic acid cascade, may provide protection against this untoward side effect. Dual inhibitors of CO and 5-LO are predicted to be ideal drugs for the treatment of arthritis[2].



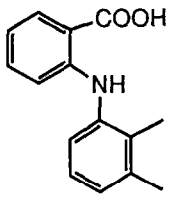
1a) A= CH, R= 2,6-di-Cl, 3-Me
1b) A= CH, R= 3-CF_3
1c) A= CH, R= 2,3-di-Me
1d) A= N, R= 3-CF_3



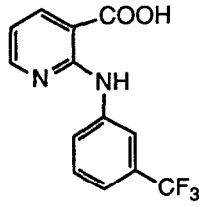
1a) meclofenamic acid



1b) flufenamic acid



1c) mefenamic acid



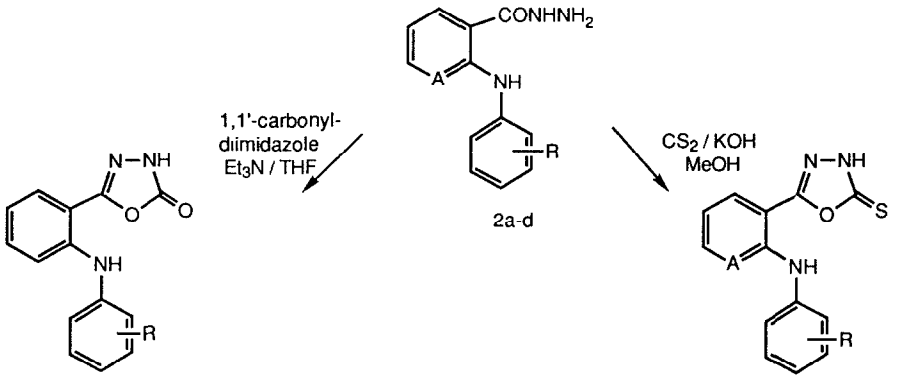
1d) niflumic acid

The fenamates (1a-d) are potent inhibitors of CO[3]. Over 20 years ago, Juby and coworkers prepared fenamate analogs where the carboxylic acid was replaced by a tetrazole and reported

that these derivatives had anti-inflammatory properties[4]. We found that the tetrazole analog of (1a) not only inhibited CO but also increased the level of inhibition of 5-LO[5]. In an attempt to find potent balanced dual inhibitors we replaced the carboxylic acid functionality of several fenamates with other acidic heterocycles.

Scheme 1 depicts the one step conversion of hydrazides 2(a-d) into 1,3,4-oxadiazol-2-ones (3a and 3c) and 1,3,4-oxadiazole-2-thiones (4a-d). We found that 4a-d were well balanced potent dual inhibitors of CO and 5-LO, while compounds 3a and 3c were inactive, see Table 1.

SCHEME 1



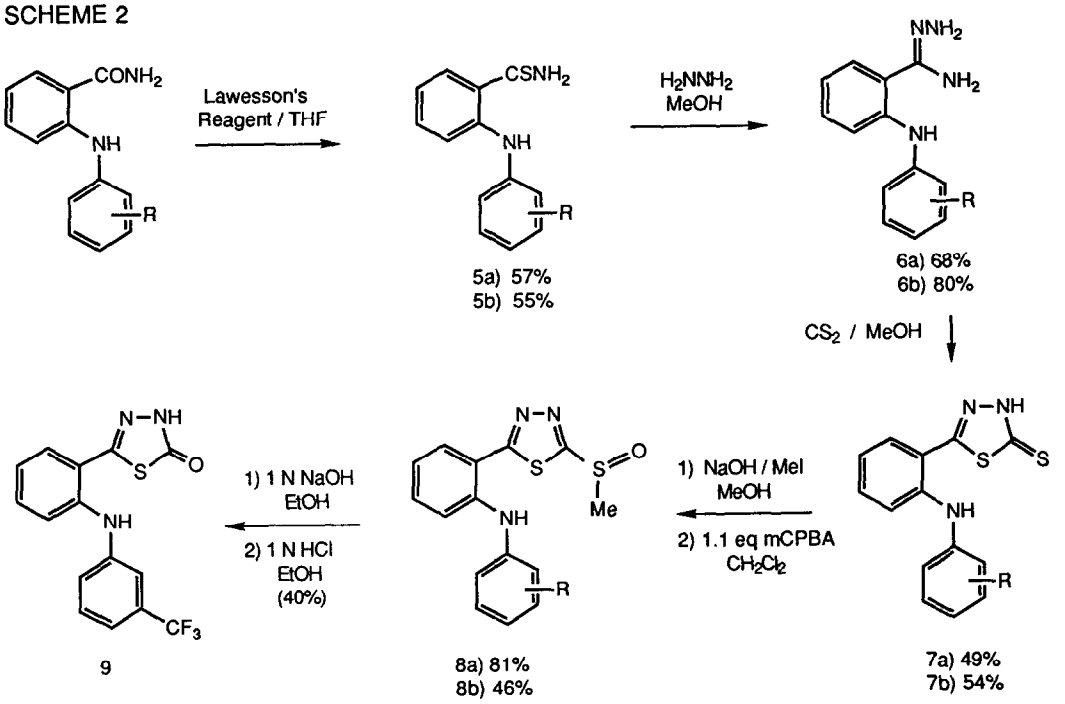
3a) 79%
3c) 85%

4a) 65%
4b) 69%
4c) 80%
4d) 74%

The disparate activity of the 1,3,4-oxadiazole-2-thiones versus the 1,3,4-oxadiazol-2-ones prompted us to prepare the corresponding 1,3,4-thiadiazoles. An attractive route to these compounds would have been via thiohydrazides analogous to 2a-d. Unfortunately attempts to prepare the desired thiohydrazides were unsuccessful and therefore the sequence of reactions depicted in Scheme 2 was utilized. The thioamides were prepared from the amides in moderate yield with either P_2S_5 or Lawesson's reagent. Under various conditions, a large amount of concomitant nitrile formation always occurred. Treatment of the thioamides with hydrazine gave amidrazones which were purified by rapid chromatography. Cyclization to 1,3,4-thiadiazol-2-thiones (7a-b) occured readily upon treatment of the unstable amidrazones with carbon disulfide.

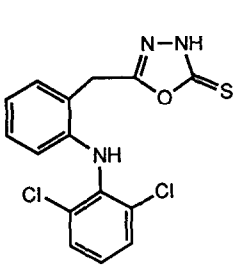
Reaction of 7a-b with base and methyl iodide gave only alkylation on the exocyclic sulfur. The thiomethyl derivative was oxidized to the sulfoxide with m-CPBA. A two step hydrolysis protocol converted 8b to the desired 1,3,4-thiadiazole-2-one (9).

SCHEME 2



As was the case in the 1,3,4-oxadiazole series, 1,3,4-thiadiazoles with an exocyclic thione (7a-b) were balanced dual inhibitors. Compound 9 was a selective inhibitor of 5-LO.

To further investigate the SAR of this series we prepared the 1,3,4-oxadiazole-2-thione analog of diclofenac, a known selective CO inhibitor and also the same heterocyclic derivative of a "meta" fenamate analog. Analogs 10 and 11 are both selective inhibitors of 5-LO. Therefore the mode of attachment of the 1,3,4-oxadiazole-2-thione to the aromatic ring is crucial for dual inhibition. We are continuing to examine other heterocyclic analogs of the fenamates as potential inhibitors of CO and 5-LO.



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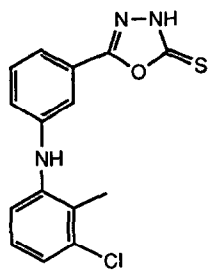

11

The values obtained for these compounds in an *in vitro* assay (either an IC_{50} μM or the % inhibition at 16 μM) are presented in Table 1.

Table 1

Compound		5-LO[8]	CO[8]
1a	meclofenamic acid	24.0	0.10
3a	1,3,4-oxadiazol-2-one	N*	N
3c	1,3,4-oxadiazol-2-one	N	N
4a	1,3,4-oxadiazole-2-thione	0.74	0.70
4b	1,3,4-oxadiazole-2-thione	0.77	0.27
4c	1,3,4-oxadiazole-2-thione	1.00	0.61
4d	1,3,4-oxadiazole-2-thione	0.99	0.19
7a	1,3,4-thiadiazole-2-thione	1.39	1.75
7b	1,3,4-thiadiazole-2-thione	0.87	0.85
9	1,3,4-thiadiazol-2-one	100%	N

* N = < 40% Inhibition @ 16μM.

REFERENCES

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

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

3) 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., and Willamson, W. R. N., *Arzeim. Forsch. / Drug Res.* 33(1), 621, 1983.

4) Juby, P. F., Hudyma, T. W., and Brown, M., *J. Med. Chem.*, 11(1), 111, 1968.

5) The tetrazole analog of meclofenamic acid was prepared by J. B. Kramer, Parke-Davis.

6) The hydrazides 2a-d are obtained by converting the fenamates to their corresponding methyl esters then heating the esters at reflux in methanolic hydrazine hydrate.

7) The amides are obtained via the methods reported by Juby-reference 4, or by reaction of the corresponding acid chloride or imidazolide with ammonium hydroxide.

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. and Sircar, J. C., *J. Med. Chem.*, 33(8), 2070 ,1990.