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A NOVEL SERIES OF HIGHLY POTENT 5-LIPOXYGENASE INHIBITORS; 2-ARYLDIENYLBENZOXAZOLES

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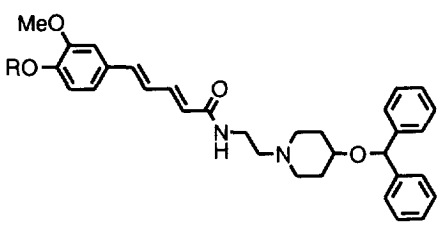
Abstract: A series of 2-(4-arylbutadienyl)benzoxazole derivatives and an oxazolopyridine derivative were prepared and their 5-lipoxygenase inhibitory activities were evaluated. A number of compounds showed 50 % inhibition in the range of 10^{-8} ~10^{-7} M.

The leukotrienes (LTs) are products derived from arachidonic acid via the 5-lipoxygenase (5-LO) pathway and have been recognized to be important chemical mediators[1]. A number of compounds targeting inhibitors of 5-LO and/or LT antagonists have been synthesized[2]. Among them, several kinds of 5-LO inhibitors have been evaluated for clinical investigation in such areas as asthma[3], allergic rhinitis[4], rheumatoid arthritis[5], inflammatory bowel disease[6], and psoriasis[7].

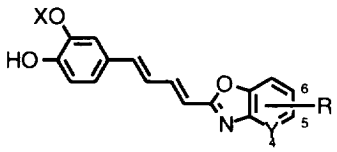
In this paper we report our preliminal results of a new series of aryldienylbenzoxazoles as highly potent 5-LO inhibitors. In 1984, it was reported that caffeic acid and its methyl ester have 5-LO inhibitory activity[8]. There have also been some research reports on 5-LO inhibitors around caffeic acid[9] and catechol derivatives[10]. Among them, TMK-777 has been found to be a strong 5-LO inhibitor along with having anti-histaminic properties[11]. Its ethoxycarbonylated pro-drug, TMK-688 has been developed for clinical evaluation.



R= CO_2Et TMK-688
H TMK-777

In overviewing the structure of TMK-777, we hypothesized that some kinds of aromatics, such as benzoxazoles substituted with hydroxyaryldienyl groups, might be a selective 5-LO inhibitor without antihistaminic activity. Also we expected the benzoxazole derivatives to be stable against hydrolysis by amidases since, unlike the amides, the oxazole skeleton does not serve as a substrate for enzymatic hydrolysis.

Table 1. Inhibition of 5-Lipoxygenase by benzoxazole derivatives.



compd.	X	Y	R	IC_{50} (μM)
1a	Me	H	H	0.33
1b	Me	H	5-Me	0.29
1c	Me	H	5-Cl	0.38
1d	Me	H	4,5-CH=CH-CH=CH	0.17
1e	Me	H	5-CO_2Et	0.25
1f	Me	H	6-CO_2Et	0.13
1g	H	H	H	0.03
1h	H	H	5-CO_2Et	0.02
1i	Me	H	5-CO_2H	5.8
1j	Me	H	5-CH_2OH	0.26
1k	Me	H	6-CH_2OH	0.30
9	Me	N	H	0.37
ethyl caffeate				1.15
TMK-777				0.15

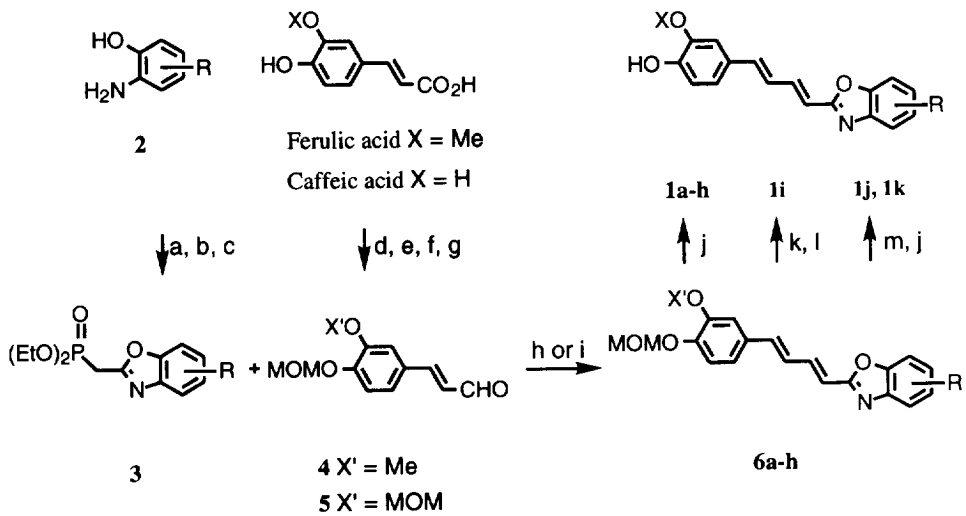
The above compounds were evaluated for 5-LO inhibition using the cytosolic enzymes prepared from rat basophilic leukemia cells and the IC_{50} values were determined based on the production of 5-hydroxyeicosatetraenoic acid (5-HETE)[12]. All of the test compounds except **1i** inhibited 5-LO strongly with an IC_{50} of below 1 μM. Ethyl caffeate as a positive reference had an IC_{50} value of 1.15 μM in this assay. Compounds **1b**, **1c**, **1e**, **1j** and **1k** with various substituents (methyl, chloro, 5-ethoxycarbonyl, hydroxymethyl) on the benzene ring fused to oxazole did not show significantly different inhibitory activities. Oxazolopyridine analog **9** is almost equipotent with **1a**. Naphthoxazole analog **1d** and 6-ethoxycarbonyl analog **1f** showed a little enhanced potency. The carboxylic acid derivative **1i** was 20-fold less potent than the corresponding ester **1e**.

Referring to the phenolic part, catechols **1g** and **1h** showed 10-fold stronger activity than their corresponding o-methoxyphenols, **1a** and **1e**.

Earlier work has suggested that the introduction of the hydrophilic hydroxyl groups in the side chain of

catechol derivatives decreases the inhibitory activity[9]. Also it has been reported on caffeic acid that the methyl ester derivative has stronger inhibitory activity than caffeic acid itself[8]. The resulting significant loss of inhibitory activity on carboxylic acid **1 i** is in accordance with the previous findings, however, it is noteworthy that the hydroxymethyl substituent in the benzoxazole in **1 j** and **1 k** did not show any reduction in inhibitory activity compared to **1 a** and **1 b**. Even though the reason is unclear, it can be considered that the acidity of the substituents on the benzene ring fusing to oxazole might significantly affect the inhibitory activity in this series of compounds.

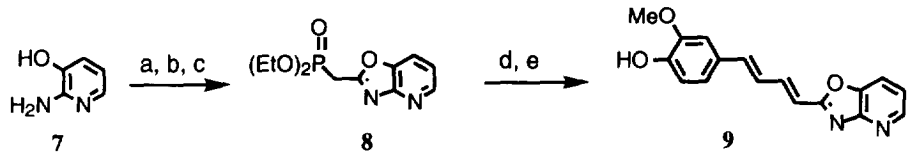
Since the ester or hydroxymethyl group can serve as a clue for the introduction of various kinds of functionalities in the skeleton, compounds such as **1 e**, **1 f**, **1 h**, **1 j** and **1 k** are very attractive for further investigation.



Scheme 1: (a) $ClCH_2COCl$, $NaHCO_3$, acetone, rt, 73-81 %; (b) ethyl polyphosphate, $ClCH_2CH_2Cl$, reflux, 50-77 %; (c) $(EtO)_3P$, 150 °C, 91-100 %; (d) EtOH, H_2SO_4, reflux, 96 %: (e) MOMCl, iPr_2NEt, CH_2Cl_2, rt, 96-98 %; (f) DIBAH, THF, -78 °C, 80-88 %; (g) MnO_2, CH_2Cl_2, rt, 75-78 %; (h) NaH, 4A Sieves, THF, -10-0 °C, 50-79 %; (i) NaOH, nBu_4NBr, H_2O, CH_2Cl_2, rt, 70 % (**6 g**); (j) aq. 4 M HCl, THF, rt, 43-70 %; (k) aq. LiOH, CH_2Cl_2-MeOH, rt, 65 %; (l) 50 % aq. AcOH, 70 °C, 73 %; (m) DIBAH, THF, -78 °C, 91-93 %.

The compounds in Table 1[13] were prepared as outlined in Schemes 1 and 2. *o*-Aminophenols **2** were chloroacetylated, cyclized by ethyl polyphosphate[14] and subjected to the Arbuzov reaction to give phosphonates **3**. The aldehyde **4** or **5** was prepared starting from ferulic acid or caffeic acid in 4 steps. Condensation of **3** with **4** or **5** by the Horner-Wadsworth-Emmons reaction under homogeneous or heterogeneous[15] conditions afforded **6 a-h**, each of which was deprotected under acidic conditions to give **1 a-h**.

Hydrolysis of the ester moiety in **6 e** and subsequent deprotection afforded the corresponding carboxylic acid **1i** (conditions k and l). The hydoxymethyl derivative **1 j** or **1 k** was obtained each from **6 e** or **6 f** by reducing the ester group with DIBAH and subsequent deprotection (conditions m and j).



7 8 9

Scheme 2: (a) $MeC(OEt)_3$, 100 °C, 86 %; (b) trichloroisocyanuric acid, CH_2Cl_2, 40 °C, 27 %; (c) $(EtO)_3P$, 150 °C, 64 %; (d) **4**, NaOH, nBu_4NBr, H_2O, CH_2Cl_2, rt, 47 %; (e) aq. 4 M HCl, THF, rt, 75 %.

The oxazolopyridine derivative **8** was prepared starting from **7** by one-step methylbenzoxazole formation, chlorination of the methyl group, and finally an Arbuzov reaction. Thus obtained, **8** was condensed with **4** followed by deprotection to give **9**.

In conclusion, we demonstrated that a new series of aryldienylbenzoxazole derivatives had high potency as an 5-LO inhibitor. Especially the catechol derivatives showed strong inhibition with nearly a 50-fold enhancement compared with ethyl caffeate. Since various substituents can be introduced onto the heteroaromatic rings, another property could be added to this series of compounds without loss of basic 5-LO inhibitory activity. A further study of this series of aryldienylbenzoxazoles is now in progress.

References and Notes

1. a) Dahlén, S.-E.; Hedqvist, P.; Hammarström, S.; Samuelsson, B. *Nature* **1980**, *288*, 484; b) Ford-Hutchinson, A. W. *Fed. Proc.* **1985**, *44*, 25.
2. For recent reviews about 5-lipoxygenase inhibitors, see: a) Musser, J. H.; Kreft, A. F. *J. Med. Chem.* **1992**, *35*, 2501; b) Kreft, A. F.; Marshall, L. A.; Wong, A. *Drugs Future* **1994**, *19*, 255.
3. a) Israel, E.; Rubin, P.; Kemp, J. P.; Grossman, J.; Pierson, W.; Siegel, S. C.; Tinkelman, D.; Murray, J. J.; Busse, W.; Segal, A. T.; Fish, J.; Kaiser, H. B.; Ledford, D.; Wenzel, S.; Rosenthal, R.; Cohn, J.; Lanni, C.; Pearlman, H.; Karahalios, P.; Drazen, J. M. *Ann. Intern. Med.* **1993**, *119*, 1059; b) Israel, E.; Drazen, J. M.; Pearlman, H.; Cohn, J.; Rubin, P. *J. Allergy, Clin. Immunol.* **1992**, *89*, 236; c) Israel, E.; Dermarkarian, R. M.; Rosenberg, M.; Sperling, R.; Taylor, G.; Rubin, P.; Drazen, J. M. *N. Engl. J. Med.* **1990**, *323*, 1740.
4. Knapp, H. R. *N. Engl. J. Med.* **1990**, *323*, 1745.
5. Weinblatt, M.; Kremer, J.; Helfgott, S.; Coblyn, J.; Maier, A.; Sperling, R.; Petrillo, G.; Kesterson, J.; Dube, L.; Henson, B.; Teoh, N.; Rubin, P. *Arthritis Rheum.* **1990**, *33*, S152.
6. Lauritsen, K.; Laursen, L. S.; Rask-Madsen, J.; Jacobsen, O.; Naesdal, J.; Stenson, W.; Cort, D.; Goebell, H.; Peskar, B.; Hanauer, S.; Rubin, P.; Swanson, L.; Kesterson, J. *Gastroenterology* **1990**, *98*, A185.
7. Black, A. K.; Camp, R. D. R.; Mallet, A. I.; Cunningham, F. M.; Hofbrauer, M.; Greaves, M. W. *J. Invest. Dermatol.* **1990**, *95*, 50.
8. Koshihara, Y.; Neichi, T.; Murota, S.; Lao, A.; Fujimoto, Y; Tatsuno, T. *Biochim. Biophys. Acta* **1984**, *792*, 92.
9. Naito, Y.; Sugiura, M.; Yamaura, Y.; Fukaya, C.; Yokoyama, K.; Nakagawa, Y.; Ikeda, T.; Senda, M.; Fujita, T. *Chem. Pharm. Bull.* **1991**, *39*, 1736.
10. LeMahieu, R. A.; Carson, M.; Han, R.-J.; Will, P. C.; Thomas, T. K.; Nagy, C.; Cominelli, F. *BioMed. Chem. Lett.* **1994**, *4*, 339.
11. Wakabayashi, T.; Ozawa, S; Arai, J.; Takai, M.; Koshihara, Y.; Murota, S. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1987**, *17A*, 186.
12. Matsumoto, K.; Morita, I.; Hibino, H.; Murota, S. *Prostagrandins Leukotrienes Essen. Fatty Acids* **1993**, *49*, 861.
13. Satisfactory analytical data for all compounds have been obtained (^{1}H NMR, IR, HRMS, EIMS).
14. Kanaoka, Y; Hamada, T. Yonemitsu, O. *Chem. Pharm. Bull.*, **1970**, *18*, 587.
15. a) Piechucki, C. *Synthesis*, **1974**, 869; b)Wakabayashi, T.; Watanabe, K. *Tetrahedron Lett.*, **1978**, 361.

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