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CYCLIC ARYL HYDROXAMIC ACIDS: SYNTHESIS AND INHIBITION OF 5-LIPOXYGENASE

Raj N. Misra*, Catherine M. Botti, Martin F. Haslanger[1],
Jeffrey R. Engebrecht, Eileen M. Mahoney and Carl P. Ciosek, Jr.

Bristol-Myers Squibb Pharmaceutical Research Institute
PO Box 4000, Princeton, NJ 08543-4000

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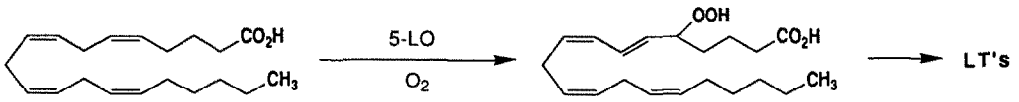
Abstract: Cyclic aryl hydroxamic acids **11** were prepared and found to be significantly less potent in inhibiting 5-lipoxygenase than their acyclic analogs **8**. This finding provides support to the hypothesis that hydroxamic acids may be inhibiting 5-LO by a mechanism other than simple iron (III) binding.

5-Lipoxygenase (5-LO) is an iron-containing enzyme[2] responsible for the conversion of arachidonic acid, **1**, to 5-hydroperoxyeicosotetraenoic acid (5-HPETE), **2**, a key step in the synthesis of biologically active leukotienes LTA_4, LTB_4, LTC_4 and LTD_4. The role of leukotrienes as potential mediators in disease[3] has



1 **2** (5-HPETE)

prompted efforts to regulate their biosynthesis[4] with considerable effort focusing on the development of 5-LO inhibitors. Several groups have recognized that iron (III) binding ligands, in particular, hydroxamic acids[5] may have the ability to inhibit 5-LO and have subsequently realized the successful development of potent lipophilic enzyme inhibitors with diverse structures based on this hypothesis.[6] Despite its rational appeal, we have been unable to extend this approach to the development of similarily lipophilic 8-hydroxyquinolines as 5-LO inhibitors.

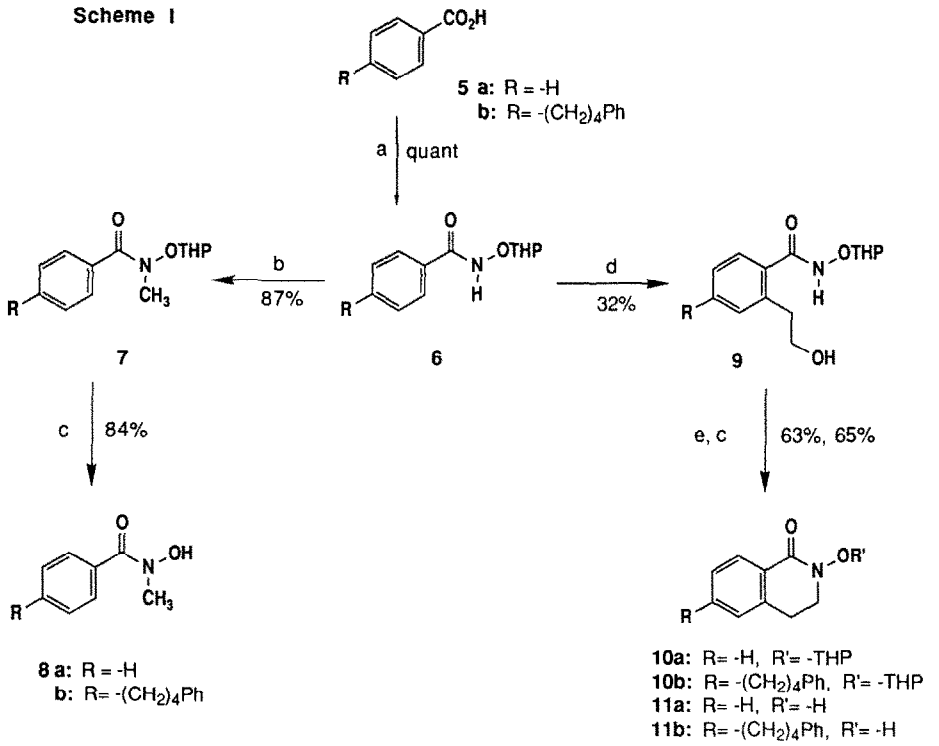
3 **4**

Thus, 8-hydroxyquinolines **3** and **4**[7,9] exhibited no significant inhibition of 5-LO.[10] The inability of **3** and **4** to inhibit 5-LO was surprising since both 8-hydroxyquinolines and hydroxamic acids are known to be effective chelators of iron (III).[11] In order to gain insight into the mechanistic nature by which hydroxamic acids act to inhibit 5-LO, previously disclosed hydroxamic acids **8**[6b] and their cyclic analogs **11** were prepared. Anticipating an iron chelation mechanism of inhibition, we expected that cyclic aryl hydroxamic acids **11** would be more potent inhibitors of 5-LO than their acyclic analogs **8** due to the restricted *syn* geometry of the metal chelating

functionality.

The syntheses of **8** and **11** are shown in Scheme I. The yields indicated are for the example where R= -$(CH_2)_4$Ph. Thus, DCC coupling of acid **5b**[12a] with THP-hydroxylamine[12b] gave amide **6b** in quantitative yield. Clean N-alkylation of the sodium salt of **6b** with iodomethane in toluene[6b] followed by removal of the THP-group[13] afforded acyclic aryl hydroxamic acid **8b**.[14] The analogous cyclic aryl hydroxamic acids were prepared by *ortho* metalation[15] of **6b** (n-BuLi, 2.2 eq, THF, 0 to 25°, 15 min) followed by low temperature

Scheme I



a. DCC, HOBT (1.2 eq) H_2NOTHP (2 eq)/CH_2Cl_2, 25°; b. NaH (1 eq)/toluene then CH_3I, 110°; c. PPTS (1.1 eq)/ aq MeOH, 65°; d nBuLi (2.2 eq)/THF, 0 to 25°, 15 min then ethylene oxide (1.1 eq), -78° followed by BF_3 OEt_2 (1.1 eq); e NaH/benzene, TsCl, 25°.

quenching of the resulting dianion with ethylene oxide/boron trifluoride etherate[16] to give carbinol **9b**. Cyclization of **9b** was accomplished with excess sodium hydride/p-toluenesulfonyl chloride in benzene to afford **10b**. A minor amount (~15%) of the product resulting from cyclization on oxygen was also obtained. The products from N vs. O cyclization were distinguishable on the basis of their ^{1}H NMR spectra ($CDCl_3$) which exhibited characteristic resonances at δ3.92 (t, *J* =6, 2H, -CH_2N-) and δ4.36 (t, *J* =6, 2H, -CH_2O-), respectively. Uneventful PPTS deprotection[13] of **10b** gave desired crystalline cyclic hydroxamic acid **11b**.[17]

The results of *in vitro* evaluation of **8** and **11** are shown in Table 1. Surprisingly, cyclic hydroxamic acids **11** were significantly less active than their acyclic analogs **8** in both a whole cell[18] and cell-free enzyme[19] assay. This finding, in addition to the inability of 8-hydroxyquinolines to inhibit 5-LO suggests that it may be

Table 1: *In Vitro* Biological Evaluation of Hydroxamic Acids[18,19]

Hydroxamic Acid	Mouse Macrophage LTC_4 I_{40} (μM)	RBL-1 5-LO HETE I_{50} (μM)
8a	7.0	9.0
11a	>100	82
8b	0.043	0.040
11b	3.0	0.29

necessary to re-examine the hypothesis that hydroxamic acid inhibitors of 5-LO act by a primary mechanism involving simple binding to an active site iron.[20]

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Notes and References

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7. Prepared from 4-methyl-8-hydroxyquinoline[8] by benzylic deprotonation followed by alkylation (LDA, 2 eq/THF. 0°, 24 h then excess RBr, -78 to 25°) in 40-50% yield: **3**, mp 67-68° (MeOH); **4**, mp 100-102° (pet ether).

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9. New compounds exhibited spectral data (IR, MS, ^1H and/or ^{13}C NMR) consistent with proposed structures.

10. Evaluated to 15 μM for inhibition of LTC_4 synthesis in mouse peritoneal macrophages.

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12. a. Prepared in 3 steps by reaction of the ylide of (4-phenylpropyl)triphenylphosphonium bromide, 1.25 eq (generated *in situ* with KO-t-amylate, 1.1 eq, THF, 0°, 45 min) with commercially-available methyl-4-formylbenzoate (1.0 eq, THF, 0 to 10°, 60 h) followed by hydrogenation (5% Pd-C, MeOH) and then saponification (NaOH/aq MeOH/THF, reflux) in 68% overall yield.
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14. Physical data for **8a**: oil; IR (film) 3.16, 3.42, 6.23, 6.37 μ; 270 MHz ^1H NMR ($CDCl_3$) δ 3.31 (s, 3H), 7.30 (m, 5H), 8.6 (br s, 1H). Physical data for **8b**: white crystals (EtOAc/hexane), mp 77-78°; IR (KBr) 3.18, 3.27, 5.65 μ; 270 MHz ^1H NMR ($CDCl_3$) δ 1.68 (m, 4H), 2.65 (m, 4H), 3.38 (s, 3H), 7.20 (m, 7H), 7.43 (d, *J* =8, 2H), 8.8 (br s, 1H); MS(CI): 284 $(M+H)^+$.

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17. Physical data for **11a**: white crystals (EtOAc/pet ether), mp 95-96°; IR (KBr) 2.91, 3.43 (broad), 6.05, 6.35, 6.74, 6.94, 7.49 μ; 270 MHz ^1H NMR ($CDCl_3$) δ 3.20 (t, *J* =7, 2H), 3.92 (t, *J* =7, 2H), 7.21 (d, *J* =7, 1H), 7.34 (dd, *J* =8,8, 1H), 7.45 (dd, *J* = 7,7, 1H), 8.06 (d, *J* =6, 1H); MS(CI): 164 $(M+H)^+$; TLC: R_f(silica gel, 1:19 MeOH/CH_2Cl_2) = 0.31, UV. Physical data for **11b**: white powder (EtOAc/pet ether), mp 82-83°; IR (KBr) 2.92, 3.26 (broad), 6.07, 6.15, 6.20, 6.37, 6.74, 6.88, 7.50 μ; 270 MHz ^1H NMR ($CDCl_3$) δ 1.66 (m, 4H), 2.64 (m, 4H), 3.14 (t, *J* =7, 2H), 3.88 (t, *J* =7, 2H, -CH_2N-), 6.98 (s, 1H), 7.10-7.35 (m, 6H), 7.95 (d, *J* =8, 1H), 8.38 (br s, 1H); MS(CI): 296 $(M+H)^+$; TLC: R_f(silica gel, 1:9 MeOH/CH_2Cl_2) = 0.61, UV.

18. Mouse macrophage assay used was similar to that described by Scott, W. A.; Pawlowski, N. A.; Murray, H. W.; Andreach, M.; Cohn, Z. A. *J. Exp Med.* **1982**, *155*, 1148. The I_{40} for NDGA was 1 μM and Corey's 5-LO inhibitor 5[6a] was 0.16 μM in this assay.

19. Enzyme assay used was similar to that described by Jakschik, B. A.; Lee, L. H. *Nature*, **1980**, *28*, 51. The I_{50} for NDGA was 0.2 μM and Corey's 5-LO inhibitor 5[6a] was 0.3 μM in this assay.

20. An alternate mechanism may involve a redox-associated process which is likely occurring with other potent inhibitors of 5-LO (*i.e.* hydroquinones, benzoquinones, catechols and *p*- and *o*-aminophenols).[4]