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Vinylogous Hydroxamic Acids: 5-Lipoxygenase Inhibitors

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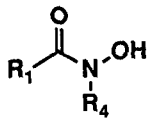
Key Words: Vinylogous hydroxamic acid; lipoxygenase inhibitor; hydroxylamine.

Abstract: Vinylogous hydroxamic acids were prepared as inhibitors of 5-lipoxygenase. The synthesis and preliminary SAR of these relatively unexplored compounds are described. These compounds are potent 5-lipoxygenase inhibitors which do not inhibit other enzymes of the arachidonic acid cascade.

Hydroxamic acids have recently received considerable attention as enzyme inhibitors, particularly of the enzyme 5-lipoxygenase, which is believed to play a key role in mediating certain inflammatory diseases.[1] While hydroxamic acids (**1**) are well known and characterized compounds, the corresponding vinylogous hydroxamic acids, 3-(*N*-hydroxy-*N*-alkylamino)-2-propene-1-ones (VHAs, **2**), represent an almost entirely unknown class of compounds.[2] In analogy to vinylogous acids, VHAs would be expected to have chemical properties similar to those of hydroxamic acids. For example, VHAs could be able to form a bidentate chelate with transition metal ions, such as iron (III). The olefin in the VHAs allows additional substituents to be incorporated into the molecule. The greater diversity of structures than is possible with simple hydroxamic acids could confer additional interesting chemical and/or biological properties to the molecule.



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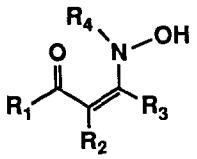

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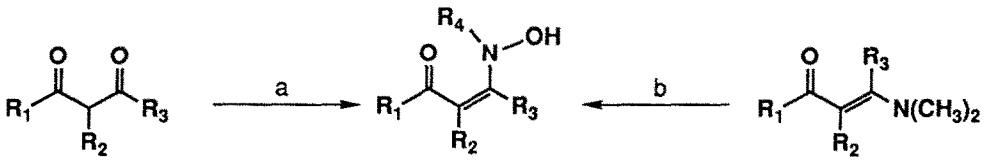
To prepare these agents, we devised two synthetic routes (Methods A and B; Scheme 1). The synthesis of VHAs from appropriately substituted 1,3-dicarbonyl compounds (**3**)[3] and hydroxylamines (R_4NHOH)[4] was convenient (Method A) and provided a simple and inexpensive entry into this series.[5] The reaction occurred

rapidly at 25° and proceeded best in protic solvents, particularly methanol, where the analytically pure VHAs usually crystallized directly from the reaction mixture. The reaction of 1,3-dicarbonyl compounds and hydroxylamines to give **2** also occurred in aprotic solvents such as chloroform, dichloromethane and THF.

Method B provided a convenient route to the VHAs by employing an exchange reaction of Me_2NH with hydroxylamines.[6] The reaction of *E*-3-(*N*,*N*-dimethylamino)-2-propen-1-ones (**4**) with hydroxylamines to give **2** occurred rapidly in the presence of one equivalent of acid, usually *p*-toluenesulfonic or hydrochloric acid, in protic solvents. Methanol was the solvent of choice, as the VHAs generally precipitated directly from the reaction mixture in pure form. The reaction of **4** with hydroxylamines would not proceed to form **2** in the absence of acid.[7]

Scheme 1



3 **2** **4**

(a) Method A: R_4NHOH, CH_3OH, 25°; (b) Method B: R_4NHOH, *p*-TsOH, CH_3OH, 25°.

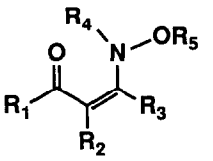
Method A: 1-(4-Fluorophenyl)-3-(*N*-hydroxy-*N*-cyclohexyl)amino-2-propen-1-one (**2b**). A solution of 1-(4-fluorophenyl)-3-oxopropan-1-one (**3**, R_1 = 4-FC_6H_4; $R_2 = R_3 = H$)[8] (3.32 g, 20 mmol) in 10 mL of methanol was heated to 40° and then treated at 40° with a solution of 2.30 g (20 mmol) of *N*-cyclohexylhydroxylamine in 20 mL of methanol. Crystals began to separate at once. The solution was allowed to cool to 25° during 1 hour. The product was filtered, washed with methanol and dried to afford 4.10 g (78%) of **2b** as yellow crystals, mp 117° - 119°. ^1H NMR ($CDCl_3$): δ 7.79 (m, 2 H); 7.04 (t, 2 H); 7.01 (d, J = 6.4 Hz, 1 H); 5.34 (d, J = 6.4 Hz, 1 H); 3.66 (m, 1 H); 2.11 - 1.62 (m, 7 H); 1.41 - 1.18 (m, 3 H). The OH proton exchanged with D_2O. ^{13}C NMR (C_6D_6): δ = 173.5, 165.9, 139.3, 129.6, 129.3, 115.0, 114.3, 69.3, 30.4, 26.5, 26.4. CIMS (NH_3): *m/z* = 264 (M + H^+); 248 (M + H^+ - O). IR (KBr pellet): 3500 cm^{-1} (OH, weak); 1620 cm^{-1} (C=O, strong); 1590 cm^{-1} (C=C, strong). UV (EtOH): λ_{max} = 362 nm (log e = 4.29). Analysis: Calc'd for $C_{15}H_{18}FNO_2$: C 68.42%; H 6.89%; N 5.32%; Found C 68.59%; H 6.80%; N 5.13%.

Method B: 1-(4-Fluorophenyl)-3-(*N*-hydroxy-*N*-benzyl)amino-2-propen-1-one (**2d**). *N*-Benzyl-hydroxylamine (0.616 g, 5.0 mmol) and *p*-TsOH • H_2O (0.856 g, 4.5 mmol) were dissolved in 4 mL of 9:1 methanol:water and 0.966 g (5.0 mmol) of *E*-1-(4-fluorophenyl)-3-(*N*,*N*-dimethylamino)-2-propen-1-one (**4**, R_1 = 4-FC_6H_4; $R_2 = R_3 = H$)[9] was added at 25°. The mixture was kept at 25° for 1 h, then cooled to -20°. Scratching induced crystal growth which was allowed to proceed for 20 min. The crystals were then filtered, washed with cold 9:1 methanol:water and dried to provide 0.433 g (34%) of **2d** as yellow crystals, mp 98° - 100°. ^1H NMR ($CDCl_3$): δ 8.04 (d, J = 6.1 Hz, 1 H); 7.82 (m, 2 H); 7.44 - 7.23 (m, 5 H); 7.03 (t, 2 H); 4.99 (s, 2 H); 4.82 (d, J = 6.1 Hz, 1 H). The OH proton exchanged with D_2O. ^{13}C NMR ($CDCl_3$): δ = 174.9, 165.7, 153.7, 133.8, 131.2, 129.3,

128.3, 126.4, 125.9, 114.9, 92.2, 63.9. CIMS (CH_4): *m/z* = 272 (M + H^+); 256 (M + H^+ - O). IR (KBr pellet): 3500 cm^{-1} (OH, weak); 1620 cm^{-1} (C=O, strong); 1590 cm^{-1} (C=C, strong). UV (EtOH): λ_{max} = 365 nm (log e = 4.27). Analysis: Calc'd for $C_{16}H_{14}FNO_2$: C 70.84%; H 5.20%; N 5.16%; Found: C 70.58%; H 5.04%; N 5.03%.

The VHAs were examined for their ability to inhibit various enzymes in the arachidonic acid cascade thought to play a role in inflammatory diseases. They were found as a class to be inactive as inhibitors of cyclooxgenase (bovine seminal vesicles, IC_{50} generally > 750 μM)[10] and PLA_2 (*Croatalus adamanteus*, IC_{50} generally > 1mM).[11] As anticipated (Table 1), they were active as inhibitors of 5-lipoxygenase (rat basophilic leukemia cells).[12] A comparison of the *in vitro* activities of selected VHAs and some standard drugs is given in Table 2. The hydroxamic acid A64077 (Zileuton, **5**)[13] was chosen as a selective 5-lipoxygenase inhibitor, while phenidone (**6**) was selected as a dual 5-LO/CO inhibitor.

Table 1: Physical Data and 5-Lipoxygenase Inhibitory Activity of VHAs (**2**)



Entry	R_1	R_2	R_3	R_4	R_5	5-LO, IC_{50}	Yield[a]	Method	mp, °C[b]
2a	4-FC_6H_4	H	H	CH_3	H	5.0 μM	20%	B	81 - 83
2b	4-FC_6H_4	H	H	c-C_6H_{11}	H	0.27 μM	78%	A	117 - 119
2c	4-FC_6H_4	H	H	C_6H_5	H	0.20 μM	50%	A	157 - 159
2d	4-FC_6H_4	H	H	$CH_2C_6H_5$	H	0.15 μM	34%	B	98 - 100
2e	4-FC_6H_4	H	H	CH_2(4-Ph)C_6H_4	H	3.0 μM	72%	A	159 - 161
2f	4-FC_6H_4	CH_3	H	$CH_2C_6H_5$	H	0.30 μM	30%	A	198 - 200
2g	4-FC_6H_4	H	CH_3	$CH_2C_6H_5$	H	0.25 μM	14%	A	95 - 97
2h	4-FC_6H_4	H	H	$CH_2C_6H_5$	$COCH_3$	> 25 μM	44%	--[c]	115 - 117
2i	4-FC_6H_4	H	H	$CH_2C_6H_5$	CH_3	> 25 μM	45%	A[d]	76 – 78
2j	4-PhC_6H_4	H	H	CH_3	H	0.06 μM	65%	B	143 - 145

[a] All yields reported are for purified products. [b] All compounds gave satisfactory ^1H NMR, CIMS, and elemental analyses. [c] Prepared by the acetylation of **2d** with Ac_2O (1.1 eq) and Et_3N (1.3 eq) in CH_2Cl_2 at 20 °C for 2 h.[14] [d] Prepared from N-methoxybenzylamine.[15,16]

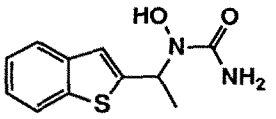
From the results in Table 1, it may be noted that the NOH moiety is critical for lipoxygenase inhibition. Acylation (**2h**, $R_5 = COCH_3$) or alkylation (**2i**, $R_5 = CH_3$) of the hydroxylamine oxygen results in the complete loss of inhibitory activity. This may be due to the reversal of the olefin geometry from *Z* (**2a** - **d**, J ≈ 6 Hz) to *E* (**2h** and **2i**, J ≈ 12 to 18 Hz). The substitution of various groups on the hydroxylamine nitrogen (R_4) appears to

be well tolerated, with the *in vitro* potency increasing as R_4 becomes more lipophilic. Likewise, increasing the lipophilicity of R_1 also affords increased *in vitro* potency (**2j** vs. **2a**). An extreme increase in lipophilicity, however, is detrimental and enzyme inhibition is decreased (**2e**).[17] The loss of potency observed with **2e** may also be attributed, wholly or in part, to the increased steric demands of the substituent R_4 in **2e**. Placing substituents on the olefin (**2f** and **2g**) results in a slight loss of potency *in vitro*. Studies are currently in progress to examine the biological properties of the VHAs *in vivo* and to determine the mechanism by which they inhibit lipoxygenase.

Table 2: *In Vitro* Profiles of Standard Drugs and Selected VHAs (**2**)

Compound	PLA_2[a] IC_{50}[d]	CO[b] IC_{50}[d]	5-LO[c] IC_{50}[d]
A64077	> 1000	> 750	0.14
Phenidone	> 1000	6.9	0.48
2b	> 1000	> 750	0.27
2d	> 1000	> 750	0.15
2h	> 1000	> 750	> 25
2i	> 1000	> 750	> 25

[a] PLA_2 inhibition. [b] Cyclooxygenase inhibition. [c] 5-Lipoxygenase inhibition. [d] Values listed in μM concentration; averages of two or more determinations.



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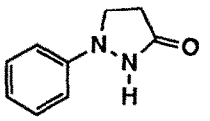

6

References and Notes

1. (a) Corey, E. J.; Cashman, J. R.; Kantner, S. S.; Wright, S.W. *J. Am. Chem. Soc.* **1984**, *106*, 1503; (b) Summers, J. B.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Dyer, R. D.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 574-580; (c) Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, P. R.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 2121-2126; (d) Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, P. R.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W.; Martin, J. G. *J. Med. Chem.* **1988**, *31*, 3-5; (e) Summers, J. B.; Gunn, B. P.; Martin, J. G.; Martin, M. B.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1960-1964; (f) Jackson, W. P.; Islip, P. J.; Kneen, G.; Pugh, A.; Wates, P. J. *J. Med. Chem.* **1988**, *31*, 500-503; (g) Huang, F.-C.; Shoupe, T. S.; Lin, C. J.; Lee, T. D. Y.; Chan, W.-K.; Tan, J.; Schnapper,

M.; Suh, J. T.; Gordon, R. J.; Sonnino, P. A.; Sutherland, C. A.; Van Inwegen, R. G.; Coutts, S. M. *J. Med. Chem.* **1989**, *32*, 1836-1842.

2. (a) These compounds are the subject of a recent U. S. patent application. (b) A series of cyclic vinylogous N-hydroxy-N-methylureas have recently been described as inhibitors of 5-lipoxygenase: Flynn, G. A.; Beight, D. W. *Eur. Pat. Appl'n 90113677* (filed 17 July 90).
3. The required β-ketoaldehydes and β-diketones (**3**) were readily prepared by acylation of the appropriate ketones ($R_1COCH_2R_2$) using standard methods: House, H. O. *Modern Synthetic Reactions (2nd Ed).* Benjamin: Menlo Park, CA, 1972.
4. The *N*-alkyl substituted hydroxylamines used in this work were prepared by the reduction of the corresponding oximes[a, b] or nitro compounds,[c] or by the alkylation of a suitably protected hydroxylamine.[d] *N*-Aryl substituted hydroxylamines were prepared by the reduction of the corresponding nitro compounds.[e] (a) Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. I.* **1979**, 643-645; (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904; (c) Kabalka, G. W.; Varma, R. S. *OPPI Briefs* **1985**, *17*, 254-256; (d) Sulsky, R.; Demers, J. P. *Tetrahedron Lett.* **1989**, *30*, 31-34; (e) Ayyangar, N. R.; Brahme, K. C.; Kalkote, U. R.; Srinivasan, K. V. *Synthesis* **1984**, 938-941.
5. The preparations of three VHA by this method have been reported: Woodward, R. B.; Woodman, D. J.; Kobayashi, Y. *J. Org. Chem.* **1967**, *32*, 388-391; (b) De Sarlo, F.; Renzi, G. *J. Chem. Soc., Perkin Trans. I* **1978**, 1113-1116.
6. The preparation of one VHA by this method has been reported: Lin, Y.; Lang, S. A. Jr. *J. Heterocyclic Chem.* **1977**, *14*, 345-347. The 3-(*N,N*-dimethylamino)-2-propen-1-ones (**4**) were prepared in high yields from the corresponding ketones ($R_1COCH_2R_2$) by heating with the appropriate dimethylamide acetal: Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1.
7. The reaction of **2** with excess dimethylamine was found to furnish **4** after several hours at 25°.
8. Swaelens, G.; Anteunis, M.; Tavernier, D. *Bull. Soc. Chim. Belg.* **1970**, *79*, 441-450.
9. Dusza, J. P.; Albright, J. D.; Hardy, R. A Jr. *U.S. Patent 4,209,621* (24 June 1980).
10. (a) White, H. L.; Glassman, A. T. *Prostaglandins* **1974**, *7*, 123-129; (b) Vigdahl, R. L.; Tukey, R. H. *Biochem. Pharmacol.* **1977**, *26*, 307-311.
11. (a) Patriarca, P.; Beckerdite, S.; Elsbach, P. *Biochim. Biophys. Acta* **1972**, *260*, 593-600; (b) Davidson, F. F.; Dennis, E. A.; Powell, M.; Glenney, J. R., Jr. *J. Biol. Chem.* **1987**, *262*, 1698-705.
12. (a) Jakschik, B. A.; Lee, L. A.; Shuffer, G.; Parker, C. W. *Prostaglandins* **1978**, *16*, 733-748; (b) Jakschik, B. A.; Sun, F. F.; Lee, L. H.; Steinhoff, M. M. *Biochem. Biophys. Res. Commun.* **1980**, *95*, 103-110; (c) Jakschik, B. A.; DiSantis, D. M.; Sankarappa, S. K.; Sprecher, H. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 624-629.
13. Summers, J. B.; Gunn, B. P.; Brooks, D. W. *Eur. Pat. Appl'n 88101386* (filed 1 February 1988).
14. Spectral data for **2h**: NMR ($CDCl_3$): δ 7.89 (m, 2H); 7.83 (d, J = 12.8 Hz, 1 H); 7.34 (m, 5 H); 7.09 (t, 2 H); 6.02 (d, J = 12.5 Hz, 1 H); 4.69 (s, 2 H); 2.16 (s, 3 H). CIMS (NH_3): *m/z* = 314 ($M + H^+$). Analysis: Calc'd for $C_{18}H_{16}FNO_3$: C 69.00%; H 5.15%; N 4.47%; Found: C 68.78%; H 5.09%; N 4.46%.
15. Schaumann, E; Walter, W. *Justus Liebigs Ann. Chem.*, **1971**, *743*, 154-166.

16. Spectral data for **2i**: NMR ($CDCl_3$): δ 7.90 (m, 2 H); 7.75 (d, J = 18 Hz, 1 H); 7.36 (m, 5 H); 7.03 (t, 2 H); 6.18 (d, J = 18 Hz, 1 H); 4.55 (s, 2 H); 3.65 (s, 3 H). CIMS (NH_3): *m/z* = 286 ($M + H^+$). Analysis: Calc'd for $C_{17}H_{16}FNO_2$: C 71.56%; H 5.65%; N 4.91%; Found: C 71.41%; H 5.48%; N 4.82%.
17. Log P calculations for these compounds suggest that the optimal log P value is between 2 and 3 (**2b - d**, **2j**). In contrast, **2a** may be too hydrophilic (0.95) and **2e** may be too hydrophobic (4.25). Log P values were calculated using the MEDCHEM Software CLOGP 3 program, release 3.54 (1989) from Daylight Chemical Information Systems, Inc. (18500 Von Karman, Ste. #450, Irvine, CA 92715).