Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 2, pp 393–396, 1997

PII: S0968-0896(96)00255-6
0968-0896/97 $17.00+0.00

Conversion of Cyclooxygenase Inhibitors into Hydroxythiazole 5-Lipoxygenase Inhibitors

Francis A. J. Kerdesky, Clint D. W. Brooks,*,† Keren I. Hulkower, Jennifer B. Bouska and Randy L. Bell

Immunoscience Research, D-47K, AP-10, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, U.S.A.

Abstract—Representative examples of NSAID cyclooxygenase inhibitors such as naproxen, ibufenac, ibuprofen, and butibufen have been transformed into 5-lipoxygenase inhibitors by replacement of the carboxylic acid moiety with a 4-hydroxythiazole group. © 1997, Elsevier Science Ltd. All rights reserved.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) offer therapeutic benefit for various inflammatory conditions.[1] This well-established therapy acting via inhibition of the enzyme cyclooxygenase (COX) has side effects mechanistically linked to interfering with the physiological properties of prostaglandins.[2] The alternative pathway for arachidonic acid metabolism initiated by 5-lipoxygenase (5-LO) results in the biosynthesis of leukotrienes.[3] Numerous studies support the role of leukotrienes as important mediators of inflammation.[4] The selective 5-LO inhibitor zileuton[5,6] has demonstrated efficacy in asthmatics for this promising new therapeutic intervention.[7] Further studies will continue to elucidate the role of leukotrienes in pathophysiological events. The derivatization of NSAIDs as hydroxamates to provide dual inhibitors of both COX and 5-LO has been reported.[8] The addition of a quinolylmethoxy substituent on the naphthalene ring of naproxen transformed the inhibitory activity profile to favor 5-LO inhibition over COX inhibition.[9]

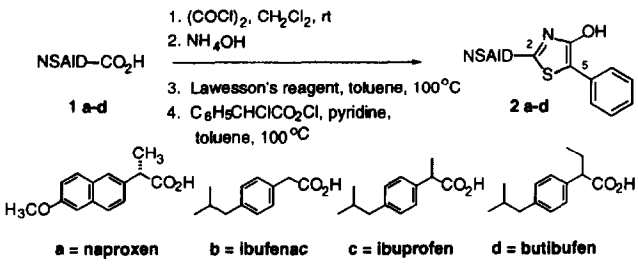
We previously described a series of 4-hydroxythiazoles as potent and selective inhibitors of 5-LO that lacked oral bioavailability.[10] Realizing that the hydroxythiazole heterocycle can be readily prepared from a carboxylic acid function, we explored the hypothesis of using clinically useful orally administered NSAIDs as templates for the design of a new series of 5-LO inhibitors. The strategic objectives were as follows: (1) to established whether the conversion of the carboxyl group of an arylpropionate NSAID into a 4-hydroxythiazole analogue would impart 5-LO inhibitory activity, (2) to determine what level of COX inhibitory activity would be retained in these new compounds, and (3) to determine whether these hydroxythiazole-NSAID analogues would have satisfactory oral bioavailability.

Results and Discussion

Chemistry

The common NSAIDs, naproxen (**1a**), ibufenac (**1b**), ibuprofen (**1c**), and butibufen (**1d**) were transformed into the respective 2-NSAID-4-hydoxy-5-phenylthiazole analogs[11] by the synthetic procedures outlined in Scheme 1. The NSAIDs **1a–d** were converted to the corresponding thioamide in a standard manner by successive treatment with (1) oxalyl chloride, (2) ammonium hydroxide, and (3) Lawesson's reagent. Reaction of the intermediate thioamides with α-chlorophenylacetylchloride and pyridine provided the desired 2-NSAID-4-hydroxy-5-phenylthiazole analogues **2a–d**.

The synthesis of the alternative prototype **5** in which the naproxen template is incorporated at C5 of the 4-hydroxythiazole heterocycle is outlined in Scheme 2. Reaction of 2-acetyl-6-methoxynaphthalene (**3**) with the anion of methyl diethylphosphonoacetate provided the intermediate unsaturated ester that was reduced by hydrogenation with Pd on carbon catalyst. Saponification of the ester followed by treatment of the carboxylate intermediate with Br_2 and PBr_3 provided the



Scheme 1.

†Formerly known as Dee W. Brooks.

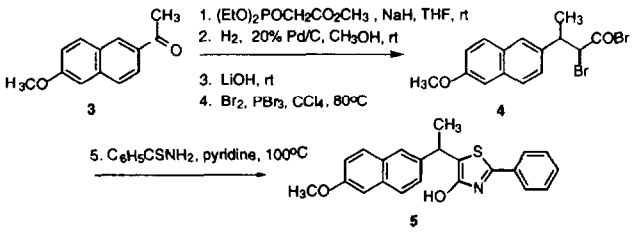
α-haloester intermediate **4** that was then treated with phenylthioamide to provide the 5-NSAID-4-hydroxy-2-phenylthiazole analogue **5**.

Evaluation of inhibitory activity

The NSAID-4-hydroxythiazole analogues were evaluated for inhibitory activity in three 5-LO inhibition assays: (1) a broken cell assay expressing 5-LO activity as measured by 5-HETE formation which utilized a 20000 *g* supernatant of sonicated rat basophilic leukemia cells, (2) an intact cell assay using purified human polynuclear leukocytes (HPMN) stimulated with calcium ionophore (A23187) to produce LTB_4, and (3) calcium ionophore (A23187) stimulated LTB_4 formation in whole human blood.[6] The 5-LO inhibition results are shown in Table 1. The 5-LO inhibitory activity of two reference compounds: 2,5-diphenyl-4-hydroxythiazole (**6**) and zileuton **7** are also shown in Table 1 for comparison.

All the hydroxythiazole analogues **2a–d** and **5** were found to possess potent 5-LO inhibitory activity in the broken cell assay with compound **2d** being particularly potent with an IC_{50} of 60 nM. Changing the position of the NSAID template from C_2 to C_5 of the 4-hydroxythiazole (comparing compounds **2a** and **5**) had little effect on inhibitory activity in the different 5-LO assays. In general, the NSAID-hydroxythiazoles had attenuated inhibitory activity in human whole blood compared to the broken cell assay, which may be due to plasma protein binding interference.

Interestingly, the potent cyclooxgenase activity of the parent NSAID template was not retained when the carboxylic acid function was converted to a hydroxythiazole group. No significant inhibition of human recombinant COX-1 and COX-2 was observed for **2a–d** and **5** at concentrations below 10 μM. Oral administration of **2b** (200 μmol kg^{-1}) to rats did not reveal any detectable plasma concentrations of compounds between 1 and 8 h post dose. Thus, these NSAID-hydroxythiazole congeners did not demonstrate satisfactory oral bioavailability in the rat.



Scheme 2.

Conclusion

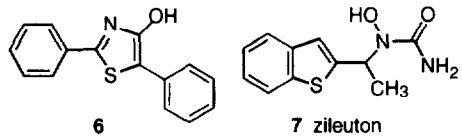
This study showed that carboxylate containing NSAID cyclooxygenase inhibitors were converted into potent 5-LO inhibitors by replacing the carboxylate function with the 4-hydroxythiazole pharmacophore. However, utilization of the NSAID templates did not result in 5-LO inhibiting congeners with satisfactory oral bioavailability and thus precluded further pharmacological investigation of these inhibitors.

Experimental

General

Melting points were determined in open glass capillaries and are uncorrected. ^1H NMR spectra chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an internal standard. Elemental analyses (C, H, and N) were performed at Abbott Laboratories or Robertson Microlit Laboratories, Inc. Madison, NJ. Silica gel 60 (E. Merck, 230–400 mesh) was used for prep. CC. THF was freshly distilled from sodium benzophenone ketyl. Other solvents were HPLC grade. Reagents were obtained commercially and used without further purification. Chemical yields reported are unoptimized

Table 1. Leukotriene inhibitory activities of NSAID-4-hydroxythiazole congeners



Compound	Broken cell (RBL-1) 5-LO IC_{50} μM[a]	Human Neutrophil 5-LO IC_{50} μM[a]	Human Blood 5-LO IC_{50} μM[a]
2a	0.42 (0.36–0.47)	0.79 (0.61–0.98)	4.7 (3.0–6.4)
2b	1.1 (1.00–1.20)	4.83 (3.87–6.08)	—
2c	0.71 (0.68–0.74)	0.56 (0.49–0.63)	2.2 (1.3–3.6)
2d	0.06 (0.05–0.07)	0.13 (0.13–0.14)	2.3 (1.2–3.9)
5	0.9 (0.60–1.20)	0.71 (0.55–0.91)	1.5 (1.4–1.7)
6[10]	0.53 (0.52–0.55)	—	—
7 (zileuton)[6]	0.5	0.60	0.74

[a]Assays run in duplicate with 95% confidence limits in parentheses.

specific examples of one preparation. Analytical TLC was conducted with E. Merck F254 commercial plates to follow the course of reactions.

2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole (2a). Oxalyl chloride (1.9 mL, 22 mmol) was added dropwise to naproxen (5 g, 22 mmol) and DMF (0.02 mL) in CH_2Cl_2 (100 mL) at 5 °C. The mixture was stirred at rt for 8 h, then cooled with an ice bath and concd NH_4OH (10 mL) was slowly added. After stirring for 1 h the volatile organics were removed in vacuo and H_2O (200 mL) was added to the residue resulting in a precipitated solid which was collected by filtration and recrystallized from CH_2Cl_2:MeOH to afford the corresponding amide (4.2 g, 85%, mp 177–178 °C). To this amide (3 g, 9 mmol) suspended in toluene (100 mL) was added Lawesson's reagent (1.8 g, 4.5 mmol) and the mixture was stirred at 100 °C for 4 h, cooled to rt, concd in vacuo and chromatographed (silica gel, CH_2Cl_2) to provide the corresponding thioamide (1.5 g, 72%, mp 144–145 °C). To a mixture of the thioamide (1.0 g, 4 mmol) in toluene (100 mL) and pyridine (0.65 mL, 8 mmol) was added dropwise α-chlorophenylacetylchloride (0.65 mL, 4.1 mmol). The mixture was refluxed for 4 h, cooled to rt and concd in vacuo. The residue was recrystallized from Et_2O:EtOH to provide **2a** (0.3 g, 27%). Mp 245–246 °C; ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.61 (3H, d, J=7 Hz), 3.81 (3H, s), 4.21 (1H, q, J=7 Hz), 7.1–8.0 (11H, m), 10.41 (1H, s); MS: 361 (M^+). Anal. calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.29; N, 3.87. Found C, 73.28; H, 5.24; N, 3.92.

2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole (2b). Prepared according to the method of **2a** using ibufenac instead of naproxen. Mp 196–197 °C; ^{1}H NMR (60 MHz, DMSO-d_6): δ 0.81 (6H, d, J=7 Hz), 1.75 (1H, m), 2.44 (2H, d, J=7 Hz), 3.78 (2H, s), 7.0–8.0 (9H, m), 10.55 (1H, s); MS: 323 (M^+). Anal. calcd for $C_{20}H_{21}NOS$: C, 74.23; H, 6.54; N, 4.33. Found: C, 74.68; H, 6.47; N, 4.37.

2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxythiazole (2c). Prepared according to the method of **2a** using ibuprofen instead of naproxen. Mp 185–186 °C; ^{1}H NMR (60 MHz, DMSO-d_6): δ 0.85 (6H, d, J=7 Hz), 1.60 (3H, d, J=7 Hz), 1.85 (1H, m), 2.45 (2H, d, J=7 Hz), 4.01 (1H, q, J=7 Hz), 7.0–8.0 (9H, m), 10.27 (1H, s); MS: 337 (M^+). Anal. calcd for $C_{21}H_{23}NOS$: C, 74.73; H, 6.86; N, 4.15. Found: C, 74.39; H, 6.85; N, 4.51.

2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole (2d). Prepared according to the method of **2a** using butibufen instead of naproxen. Mp 168–169 °C; ^{1}H NMR (60 MHz, DMSO-d_6): δ 0.85 (3H, d, J=7 Hz), 0.91 (3H, t, J=7 Hz), 1.58 (2H, m), 1.85 (1H, m), 2.45 (2H, d, J=7 Hz), 4.02 (1H, t, J=7 Hz), 7.0–8.0 (9H, m), 10.55 (1H, s); MS: 351 (M^+). Anal. calcd for $C_{22}H_{25}NOS$: C, 75.17; H, 7.16; N, 3.98. Found: C, 74.98; H, 7.14; N, 4.10.

5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole (3). Methyl diethylphosphonoacetate (1.6 g, 7.5 mmol) and NaH (0.19 g, 7.5 mmol) in THF (25 mL) was added to 2-acetyl-6-methoxynaphthalene (**3**) (1.5 g, 7.5 mmol) in THF (50 mL) at 23 °C under nitrogen. After refluxing for 20 h, the reaction mixture was cooled, satd NH_4Cl added, and the mixture was poured into water. The solution was extracted with Et_2O and the organic extracts were dried ($MgSO_4$) and the solvent evapd. Chromatography (silica gel, Et_2O/pentane) afforded methyl 3-(6-methoxy-2-naphthyl)-2-butenoate (0.75 g). This intermediate (0.51 g, 2 mmol) in MeOH (50 mL) was hydrogenated with 20% Pd/C (50 mg) at 3 atm at 23 °C until the theoretical amount of hydrogen was taken up. Removal of solvent and catalyst gave the crude ester which was dissolved in isopropanol:water, 2:1 (40 mL). LiOH (82 mg, 2 mmol) was added and the mixture stirred at 23 °C for 1 h. Saturated NH_4Cl was added, the mixture was extracted with EtOAc, concd in vacuo and the residue was recrystallized from MeOH:H_2O to afford 3-(6-methoxy-2-naphthyl) butyric acid (0.45 g). Bromine (3 mL of a 1 M soln in CCl_4, 3 mmol) was added slowly to the acid (0.37 g, 1.5 mmol) and PBr_3 (0.4 g, 1.5 mmol) in CCl_4 (20 mL) at 23 °C under nitrogen. The mixture was heated at 80 °C for 20 h, cooled to rt, poured into ice water, extracted with benzene, dried (Na_2SO_4), and concd in vacuo to provide a residue which was distilled to afford 2-bromo-3-(6-methoxy-2-naphthyl)butyrylbromide (**4**) (0.55 g). To a soln of **4** (386 mg, 1 mmol) in toluene (20 mL) was added thiobenzamide (137 mg, 1 mmol) and pyridine (0.16 mL, 2 mmol) in toluene (60 mL) at 23 °C. The reaction mixture was heated at 100 °C for 4 h, then cooled to rt and concd in vacuo. Recrystallization of the residue from EtOH:Et_2O provided **3** (128 mg). Mp 224–226 °C, ^{1}H NMR (60 MHz, DMSO-d_6): δ 1.30 (3H, d, J=7 Hz), 3.82 (3H, s), 3.92 (1H, q, J=7 Hz), 7.1–8.0 (11H, m), 10.55 (1H, s); MS: 361 (M^+). Anal. calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.29; N, 3.87. Found: C, 72.89; H, 5.27; N, 4.01.

Biological assays

The detailed procedures for the biological assays presented in Table 1 are described in ref 6.

Recombinant human PGHS-1 and PGHS-2 assays

Compound (3.3% DMSO final concentration) was preincubated for 60 min with aliquots of CHAPS (3-[3-cholamidopropyl)dimethylammonio]-1-propanesulfonate) solubilized microsomes prepared from baculovirus infected Sf9 insect cells expressing recombinant human prostaglandin H synthase 1 or 2 in a reaction mixture containing hematin and phenol cofactors. Arachidonic acid (10 μM final concentration; Nu-Chek Prep Inc., Elysian, MN) was added to start the reactions. Following an incubation time of 2.5 min at 25 °C, the reactions were quenched with HCl and neutralized with NaOH. PGE_2 production by the

reaction mixtures was measured by EIA (Cayman Chemicals, Ann Arbor, MI).

References

1. Lombardino, J. G. *Nonsteroidal Antiinflammatory Drugs*; Wiley-Interscience: New York, 1985.

2. Vane, J. R. *Nature (Lond.)* **1971**, *231*, 232.

3. Samuelsson, B. *Science* **1983**, *220*, 568.

4. (a) Lewis, R. A.; Austen, K. F.; Soberman, R. J. *New Engl. J. Med.* **1990**, *323*, 645. (b) Henderson, W. R. *Ann. Intern. Med.* **1994**, *121*, 684.

5. Brooks, D. W.; Carter, G. W. In *The Search for Anti-Inflammatory Drugs*; Merluzzi, V. J.; Adams, J., Eds.; Birkhauser: Boston, 1995; Chapter 5, pp 129–160.

6. Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. *J. Pharmacol. Exp. Ther.* **1991**, *256*, 929.

7. 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.; Perlman, H.; Karahalios, P.; Drasen, J. M. *Ann. Intern. Med.* **1993**, *119*, 1059.

8. Walsh, D. A.; Lo, Y. S.; Shamblee, D. A.; Welstead, W. J.; Nolan, J. C.; Graff, G. *J. Med. Chem.* **1990**, *33*, 2070.

9. Musser, J. H.; Kreft, A. F. *J. Med. Chem.* **1992**, *35*, 2502.

10. Kerdesky, F. A. J.; Holms, J. H.; Moore, J. L.; Bell, R. L.; Dyer, R. D.; Carter, G. W.; Brooks, D. W. *J. Med. Chem.* **1991**, *34*, 2158.

11. Brooks, D. W.; Kerdesky, F. A. J. U.S. Patent 5,032,588, 16 July 1991.

(*Received in U.S.A.* 1 *August* 1996; *accepted* 26 *September* 1996)