Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1171–1174

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND ACTIVITY OF SULFONAMIDE-SUBSTITUTED 4,5-DIARYL THIAZOLES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

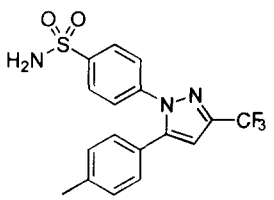
Jeffery S. Carter,* Steven Kramer, John J. Talley, Thomas Penning, Paul Collins, Matthew J. Graneto, Karen Seibert, Carol M. Koboldt, Jaime Masferrer, and Ben Zweifel

G.D.Searle-Monsanto, 700 Chesterfield Parkway North, St. Louis, MO 63198; 4901 Searle Parkway North, Skokie IL 60077, U. S. A.

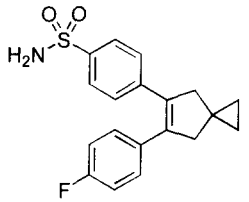
Received 8 December 1998; accepted 15 March 1999

Abstract: A series of sulfonamide-substituted 4,5-diarylthiazoles was prepared via three synthetic routes as selective COX-2 inhibitors. Recently in the synthesis of selective COX-2 inhibitors we have discovered that the sulfonamide moiety is a suitable replacement for the methylsulfonyl moiety yielding compounds with activity both in vitro and in vivo.

Nonsteroidal antiinflammatory drugs (NSAIDS) are widely used to treat pain and inflammation. These compounds inhibit the enzyme cyclooxygenase (COX) and thus prevent the formation of prostaglandins at elevated levels causing inflammation.[1] Recently it has been hypothesized that selective inhibiton of a second isoform of this enzyme, COX-2,[2] may provide the same therapeutic relief of inflammation, pain and fever without causing the gastric ulceration associated with currently marketed non-selective COX-1/COX-2 inhibitors.[3] Several classes of compounds have been reported as selective COX-2 inhibitors.[4] In diaryl heterocycles[5] (e.g., celecoxib: IC_{50}(υM), hCOX-1 = 15.0, hCOX-2 = 0.04)[5a] and spiro-cyclopentenes (e.g., **1**, IC_{50}(υM), hCOX-1 = 0.33, hCOX-2 = 0.003)[6] incorporation of a sulfonamide moiety as part of the pharmacophore has been reported to increase bioavailability[6] in addition to enhancing selectivity for COX-2 inhibition. We report the synthesis and activity of several members of sulfonamide substituted 4,5-diarylthiazoles.



Celecoxib



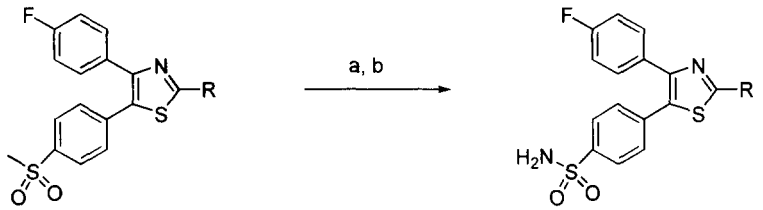
1

To rapidly test the utility of the sulfonamide moiety in the diarylthiazole class of COX-2 inhibitors we utilized the method of Huang et al.[7] for conversion of the methyl sulfone moiety to a sulfonamide as shown in Scheme 1. Deprotonation of the methylsulfonyl moiety followed by quench with triethyl borate yielded an "ate" complex which upon rearrangement yields the corresponding sulfinic acid. Treatment of the sulfinic acid

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00157-2

with hydroxylamine O-sulfonic acid yielded the sulfonamide. Due to the requirement for careful exclusion of moisture, we wished to develop more readily scalable syntheses.

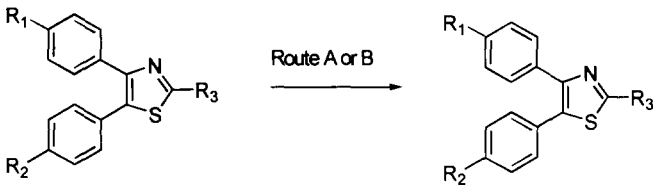
Scheme 1



Reaction conditions: (a) *n*-BuMgBr, THF, 0 °C; (b) 0 °C, $B(Et)_3$, H_2N-OSO_3H.

Alternatively, we incorporated the sulfonamide moiety by electrophilic aromatic substitution on the appropriately substituted diaryl thiazole. Our strategy was determined by the intrinsic reactivity of the 5-aryl moiety relative to the 4-aryl. As shown in Scheme 2, Route A, diphenylthiazole **4a** was treated with neat chlorosulfonic acid forming a sulfonyl chloride intermediate. Treatment of the crude sulfonyl chloride with ammonium hydroxide yielded sulfonamide **5a**.[8] Thiazole **5b** was prepared analogously from **4b**.

Scheme 2



Compd	R_1	R_2
4a	H	H
4b	Cl	H
6a	H	Br
6b	H	Cl

Compd	R_1	R_2
5a	H	SO_2NH_2
5b	Cl	SO_2NH_2
7a	SO_2NH_2	Br
7b	SO_2NH_2	H
7c	SO_2NH_2	Cl

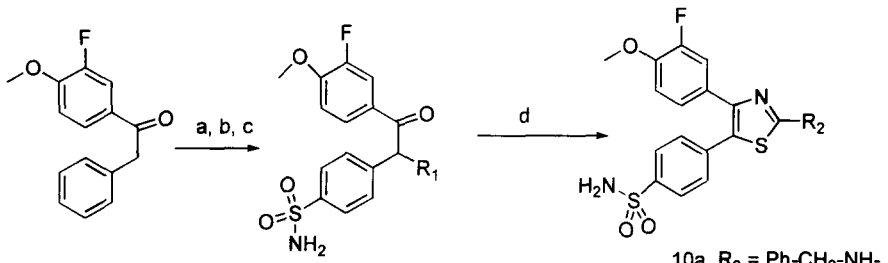
Reaction conditions: Route A: (a) $ClSO_3H$; (b) NH_4OH. *Route B:* (a) $ClSO_3H$; (b) NH_4OH; (c) H_2, Pd/C.

Scheme 2, Route B illustrates the synthesis of the regioisomeric thiazole which employs a bromine atom to selectively deactivate-protect the intrinsically more reactive 5-aryl moiety. Chlorosulfonation of **6a** followed by aminolysis of the sulfonyl chloride intermediate yielded sulfonamide **7a**. The bromine was easily removed by catalytic hydrogenolysis over Pd/C and H_2 yielding **7b**. Chlorosulfonation and aminolysis of 4-*para*-chlorophenylthiazole **6b** yielded sulfonamide **7c**.

We next incorporated the sulfonamide moiety prior to formation of the thiazole nucleus as shown in Scheme 3. In this case, chlorosulfonation and aminolysis of deoxybenzoin **8**[9] yielded the desired sulfonamide **9a**. In this approach, the aryl bearing the acyl moiety is relatively deactivated toward chlorosulfonation thus allowing selective chlorosulfonation. Treatment of **9a** with Br_2 and HBr in HOAc yielded bromoketone **9b**.

Using the Hantzch thiazole synthesis,[10] condensation of **9b** with the appropriate thioureas or thioamides yielded the sulfonamide substituted diarylthiazoles **10a**, **10b**, and **10c**.

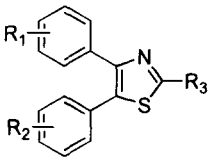
Scheme 3



Reaction conditions: (a) $ClSO_3H$; (b) NH_4OH, (c) Br_2, HBr, HOAc; (d) R_3-CS-NH_2.

The in vitro enzyme activity[11] of the analogs prepared in the two regioisomeric series of thiazoles is shown in Table 1. Within the 5-(4-aminosulfonylphenyl)thiazole series, analogs bearing larger moieties in the 2-position (e.g., **3a** and **10a**) display enhanced inhibitory activity against hCOX-1 (human cyclooxygenase-1). Analogs **3a** and **10b** show the sensitivity to alteration of the 4-aryl moiety. The 2-methyl substitutent provides analogs with very good selectivity for hCOX-2 inhibition. Thus, minimal substitution on the non-sulfonamide aryl moiety and smaller 2-position substituents provide the greatest COX-2 selectivity and potency. These analogs are orally bioavailable and provide good in vivo activity as determined by the rat air pouch assay (AP).[3a] Analog **5a** provides both in vitro selectivity and in vivo activity (AP [2mpk] 59 % inhibition).

Table 1.



Comp d	R_1	R_2	R_3	hCOX-1 (μM)	hCOX-2 (μM)	AP (2mpk)
3a	4-F-	4-SO_2NH_2	2-Cl-Ph-	0.80	0.013	50 %
3b	4-F-	4-SO_2NH_2	3,5-diClPh-O-CH_2-	0.12	0.009	NT
5a	H-	4-SO_2NH_2	CH_3-	34.0	0.038	59 %
5b	4-Cl-	4-SO_2NH_2	CH_3-	1.84	0.005	42 %
7a	4-SO_2NH_2	4-Br	CH_3-	115	0.024	NT
7b	4-SO_2NH_2	4-H	CH_3-	72.5	0.029	7%
7c	4-SO_2NH_2	4-Cl	CH_3-	35.6	0.018	30 %
10a	4-MeO-3-F-	4-SO_2NH_2	Ph-CH_2-NH-	0.010	0.059	NT
10b	4-MeO-3-F-	4-SO_2NH_2	2-Cl-Ph-	>100	2.48	33 %
10c	4-MeO-3-F-	4-SO_2NH_2	CH_3-	4.18	0.028	NT

NT = not tested

Good selectivity was maintained in the regioisomeric 4-(4-aminosulfonylphenyl)thiazoles. The 2-methyl moiety and simple or no substitution of the 5-aryl moiety provides excellent in vitro potency and

selectivity. Interestingly this series displays poorer oral activity in vivo. Most striking is the very weak in vivo activity of **7b** while regioisomer **5a** was potent both in vitro and in vivo.

Conclusion: These early results in this series of diarylthiazoles demonstrate the appreciable selectivity imparted by the *para*-sulfonamide moiety. Many of these compounds display good COX-2 selectivity and oral activity (air pouch assay). Sulfonamide-substituted diarylthiazole **5a** is noteworthy in this respect.

References:

1. Vane, J. R. *Nature (London)* **1971**, *231*, 232.

2. Holtzman, M. J.; Turk, J.; Shornick, L. P. *J. Biol. Chem.* **1992**, *267*, 21438; Masferrer, J. L.; Seibert, K.; Zweifel, B.; Needleman, P. *Proc. Nat'l Acad. Sci. U.S.A.* **1992**, *89*, 3917; O'Banion, M. K.; Sadowski, H. B.; Winn, V. D.; Young, D. A. *J. Biol. Chem.* **1991**, *266*, 23261; Meade, E. A.; Smithe, D. L.; Devitt, D. L. *J. Biol. Chem.* **1993**, *268*, 6610.

3. (a) Masferrer, J. L.; Zweifel, B. S.; Manning, P. T.; Hauser, S. D.; Leahy, K. M.; Smith, W. G.; Isakson, P. C.; Seibert, K. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3228. b)Seibert, K.; Zhang,Y.; Leahy, K.; Hauser, S.; Masferrer, J.; Perkins, W.; Lee, L.; Isakson, P. *Proc. Natl. Acad. Sci.* U.S.A. **1994**, *91*, 12013.

4. Carter, J. S. *Exp. Opin. Ther. Patents* **1997** *8(1)*,21-29. Prasit, P.; Riendeau, D., *Annu. Rep. Med. Chem.*, **1997**, *32*, 211. Talley, J. J., *Exp. Opin. Ther. Patents* **1997**, *7(1)*, 55. Reitz, D. and Seibert, K., *Annu. Rep. Med. Chem.*, **1995**, *30*, 179.

5. (a) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P.C. *J. Med. Chem.* **1997**, *40*, 1347. (b) Bertenshaw, S. R.; Talley, J. J.; Rogier, D. J.; Graneto, M. J.; Rogers, R. S.; Kramer, S. W.; Penning, T. D.; Koboldt, C. M.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E. *Biorg. Med. Chem. Lett.*,1995, *5*, 2919. (c) Bertenshaw, S. R.; Talley, J. J.; Rogier, D. J.; Graneto, M. J.; Koboldt, C. M.; Zhang, W. E.,*Biorg. Med. Chem. Lett.* **1996**, *6*, 2827. (d) Leblanc, Y.; Gauthier, J. Y.; Ethier, D.; Guay, J.; Mancini, J.; Riendeau, D.; Tagari, P.; Vickers, P.; Wong, E.; Prasit, P. *Biorg. Med. Chem. Lett.* **1995**, *5 (18)*, 2123.

6) Huang, H-C.; Li, J. J.; Garland, D. J.; Chamberlain, T. S.; Reinhard, E. J.; Manning, R. E.; Seibert, K.; Koboldt, C. M.; Gregory, S. A.; Anderson, G. D.; Veenhuizen, A. W.; Zhang, Y.; Perkins, W. E.; Burton, E. G.; Cogburn, J. N.; Isakson, P. C.; Reitz, D.B. *J. Med. Chem.* **1996** *39*, 253.

7) Huang, H-C.; Reinhard, E. J.; Reitz, D. B. *Tetrahedron Lett.* **1994**, *39*, 7201.

8) Drygala, P. F.; Kirby, A. F.; Watson, K. G. *Synthetic Commun.* **1994**, *24(5)*, 671.

9) This deoxybenzoin was prepared by Friedel-Crafts acylation of 2-fluoroanisole with phenacetyl chloride using $AlCl_3$ as the catalyst.

10) Wiley, R. H., England, D. C., Behr, L. C. "The Preparation of Thiazoles" *in Organic Reactions*, John Wiley and Sons, Inc.; Vol. 6, pp 367-409.

11) Gierse, J. K.; Hauser, S. D.; Creely, D. P.; Koboldt, C.; Rangwala, S.H.; Isakson, P.C.; Seibert, K. *Biochem. J.* **1995**, *305*, 479.