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SYNTHESIS AND BIOLOGICAL EVALUATION OF 5,6-DIARYLIMIDAZO[2.1-b]THIAZOLE AS SELECTIVE COX-2 INHIBITORS

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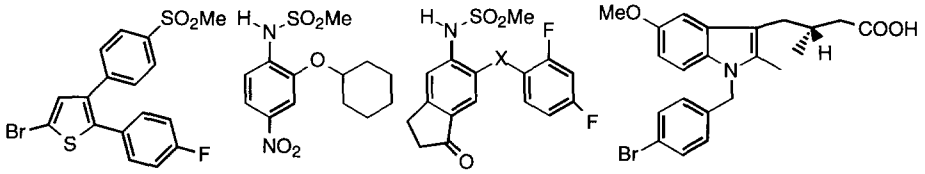
Abstract: A series of 5,6-diarylimidazo[2.1-b]thiazole compounds were prepared and their inhibitory potencies against COX-2 and Cox-1 enzymes were measured. This led to the identification of L-766,112 as a potent, orally active and selective inhibitor of the COX-2 enzyme. Copyright © 1996 Elsevier Science Ltd

Prostaglandins (PGs) are well known to be mediators of inflammation, pain and swelling.[1] They are produced by the action of the cyclooxygenase (COX) enzyme on arachidonic acid. Todays nonsteroidal antiinflammatory drugs (NSAIDs) act through the inhibition of the COX reaction. However, the fact that some PGs are cytoprotective in the gastrointestinal tract severely limits the usefulness of these NSAIDs because of side effects such as ulceration, perforation and hemorrhage.[2] The recent discovery of an inducible isoform of cyclooxygenase (COX-2)[3] that is associated primarily with inflammation has led to the hypothesis that the antiinflammatory effect of NSAIDs is due to the inhibition of COX-2 and that NSAIDs induced GI toxicity may be caused by the inhibition of the cytoprotective COX-1 enzyme and that has obviously produced significant interest. Compounds that selectively inhibit the COX-2 enzyme have been shown to possess antiinflammatory properties and reduced ulcerogenicity[4a,b] in animal models and would have tremendous therapeutic potential if these properties translated in humans.

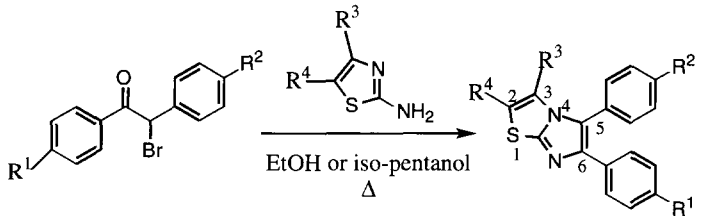
Several research groups are actively pursuing the development of COX-2 selective inhibitor.[4] A number of classes of selective COX-2 inhibitors have emerged such as the tricyclic class best represented by the cyclopentene class,[5a] Dup 697,[5b] the sulfonamide class with NS-398,[5c] Flosulide[5d] and L-745,337,[5e] and the indole class with L-761,066.[5f] Recently, Gauthier[4a] and Leblanc,[6a] from our laboratory have reported the study of the substitution and replacement of the thiophene ring of Dup 697. As a further diversification of the heterocyclic template, we report the identification of L-766,112 (**2a**) as a potent, orally active and selective COX-2 inhibitor, where the thiophene ring of Dup 697 is replaced by an imidazo[2.1-b]thiazole bicyclic system.



Synthesis

The 5,6-diarylimidazo[2.1-b]thiazoles were prepared by the condensation of α-bromodiarylethanones **1**[6] with appropriately substituted 2-aminothiazoles (all commercially available) in refluxing ethanol or iso-pentanol[7] (Scheme 1). The carboxylic acid **2p** was obtained by the hydrolysis of ester **2o** (Scheme 2), which was prepared according to Scheme 1. Chlorinated analog **2q** was prepared by treatment of compound **2a** with sulfuryl chloride followed by DBU. Upon treatment of **2q** with sulfuryl chloride the trichloro-compound **2r** was obtained (Scheme 3).

Scheme 1



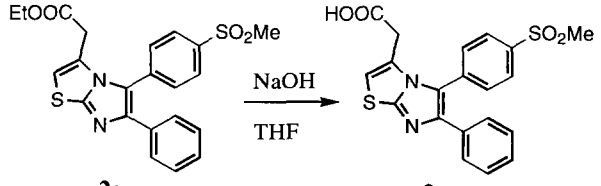
1

R^1 = H, SMe, SO_2Me, F
R^2 = H, SMe, SO_2Me
R^3, R^4 = H, Me, COOMe, COOH,Ph

2

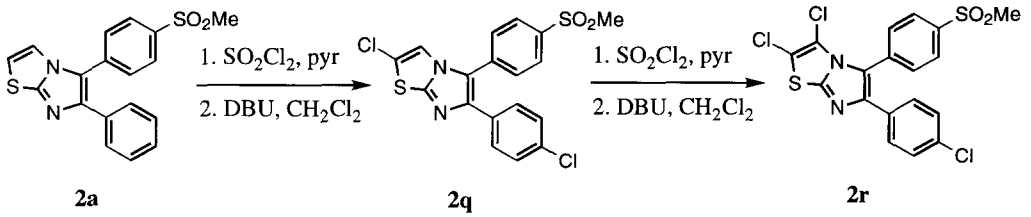
R^1 = H, SMe, SO_2Me, F
R^2 = H, SMe, SO_2Me
R^3, R^4 = H, Me, COOMe, COOH,Ph

Scheme 2



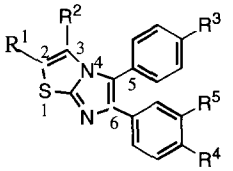
2o **2p**

Scheme 3



2a **2q** **2r**

Table I: Inhibition of Cox-2 and Cox-1 enzyme by 5,6-diarylimidazo[2.1-b]thiazole.



Compd	R^1	R^2	R^3	R^4	R^5	COX-2 (IC_{50} μM)	COX-1 (IC_{50} μM)
2a	H	H	4-$MeSO_2$	H	H	0.016	>50
2b	H	H	H	4-MeS	H	5.0	0.078
2c	H	H	H	4-$MeSO_2$	H	3.21	>50
2d	H	H	4-MeS	H	H	0.42	0.32
2e	Me	H	H	4-$MeSO_2$	H	0.14	>50
2f	H	H	4-$MeSO_2$	F	H	0.014	>50
2g	H	H	4-$MeSO_2$	F	F	0.012	>50
2h	Me	H	4-$MeSO_2$	H	H	0.012	>50
2i	H	Me	4-$MeSO_2$	H	H	3.0	>50
2j	Me	Me	4-$MeSO_2$	H	H	5.0	>50
2k	Me	Me	H	4-$MeSO_2$	H	>5.0	>50
2l	H	Me	H	4-$MeSO_2$	H	1.0	>50
2m	-CH=CH-CH=CH-		4-$MeSO_2$	H	H	>5.0	>50
2n	-CH=CH-CH=CH-		H	4-$MeSO_2$	H	>5.0	>50
2o	H	CH_2COOEt	4-$MeSO_2$	H	H	0.9	>50
2p	H	CH_2COOH	4-$MeSO_2$	H	H	>5	>50
2q	Cl	H	4-$MeSO_2$	Cl	H	0.016	>50
2r	Cl	Cl	4-$MeSO_2$	Cl	H	3.6	>50

IC_{50} values for the inhibition of the production of PGE_2 in arachidonic acid stimulated chinese hamster ovary (CHO) cells transfected with human COX-1 or COX-2.[8]

Discussion

In our pursuit of a selective COX-2 inhibitor, we have studied extensively the replacement of the thiophene center ring of Dup 697 with various 5- and 6-membered heterocycles. Our attention was then turned towards 5,6- and 5,5-bicyclic systems. A number of different bicyclic systems were prepared and evaluated and the imidazo[2.1-b]thiazole turned out to be one of the most potent and selective series of COX-2 inhibitors. Compounds **2a-2r** were tested in vitro for their ability to inhibit the arachidonic acid-dependent production of PGE_2 mediated by the COX-1 and COX-2 enzymes in chinese hamster ovary cells[8] as the primary screen and the results are reported in Table I. In general the SAR was quite tight. As with other tricyclic inhibitors[6b] of the same class the methyl sulfone proved to be essential for good COX-2 activity and selectivity, demonstrated with compounds **2a** vs. **2d** and **2c** vs. **2b**. All compounds other than **2b** and **2d** were inactive against COX-1 under the conditions evaluated.

In general, compounds with the 4-methylsulfonylphenyl substituent at the 6-position were not very active against the COX-2 enzyme except for compound **2e**. Compounds that were unsubstituted at the 2- and 3-position, (**2a**, **2f**, and **2g**) were quite potent and selective (IC_{50} = 0.016, 0.014 and 0.016 μM vs. COX-2, respectively). Monosubstitution at the 2-position gave compounds **2e** and **2h**, which retained their potency (0.039 and 0.012 μM, respectively, against Cox-2). However, substitution at the 3-position resulted in a significant loss of potency (**2i**, **2j**, **2k**, and **2l** have an IC_{50} of 3.0, 5.0, >5.0, and 1.0 μM, respectively). Compounds **2m** and **2n**, with a fused phenyl ring at the 2,3-position, are also inactive, which is expected since substituents at the 3-position seem to be detrimental to the COX-2 inhibitory potency. Similarly, an acetate substituent at the 3-position (**2o** and **2p**), caused a major decrease in potency against COX-2. Among the compounds described in Table I, four of these stand out as candidates for further evaluation, these are compounds **2a**, **2h**, **2f**, and **2g**. They possess COX-2 activity similar to those of Dup 697 and Indomethacin. However, their selectivity is superior (Dup-697 is 0.002 and 0.059 μM against COX-2 and, COX-1, and Indomethacin is 0.026 and 0.018 against COX-2 and, COX-1, respectively). Measuring their ability to inhibit the COX-2 enzyme in human whole blood[9] identifies compounds **2a** and **2f** (IC_{50} = 0.9 and 0.4 μM, respectively) as clearly superior to compounds **2h** and **2g** (IC_{50} = 17.5 and 2.2 μM, respectively), this difference in activity might be due to protein binding in the whole blood. Also, in the COX-1 human whole blood assay these compounds, **2a** and **2f**, proved to be more selective with IC_{50} > 30 μM for **2a** and IC_{50} = 25 μM for **2f**. With an ED_{50} = 2mg/kg vs. 5 mg/kg in the carrageenin induced rat paw edema assay, compound **2a** was shown to be slightly superior to compound **2f** and also superior to Dup-697 (57% inhibition at 10 mg/kg)[10] in this model. In a GI permeability assay, when rats were dosed with compound **2a** at 100 mg/kg bid for 10 days there was no increase in the level of ^{51}Cr excreted in the feces[11], indicative of a high level of GI tolerance. Unfortunately, compound L-766,112 was found to be inactive in an adjuvant arthritis model, which might be

due to the low bioavailability, where C_{max} is 1 μM at 1 and 2 h, in rats dosed P.O. at 20 mg/kg. Furthermore, metabolism studies of L-766,112[12] (**2a**) have shown that the oxidation of the sulfur atom at the 1 position of the heterocyclic system gave a reactive metabolite that may result in potential problems. In order to address the oxidative metabolism problems, compounds (**2q** and **2r**) with electron withdrawing substituents on the heterocyclic rings were prepared. Indeed, introduction of electron withdrawing chloride substituents did significantly reduce metabolism since after incubation with rat hepatocytes compounds **2q** and **2r** were nearly quantitatively recovered, whereas **2a** is extensively metabolized. Unfortunately, the in vitro potency of compound **2q** did not translate in vivo and compound **2r** was not found to be sufficiently active.

In conclusion, we have identified a new series of selective COX-2 inhibitors that are active in vitro and in vivo. We have also identified L-766,112 as a very potent and selective COX-2 inhibitor. This potency was partially translated in vivo as shown by its activity in the rat paw edema assay. However, the poor metabolic profile of L-766,112 prompted us to investigate other tetracyclic systems. Further studies on the metabolism of L766,112 and on improving the in vivo potency are presented in the following papers.

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