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4-Aryl/cycloalkyl-5-phenyloxazole Derivatives as Selective COX-2 Inhibitors

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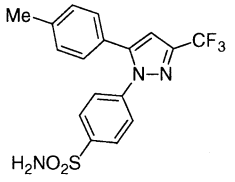
Abstract—A series of 4-aryl/cycloalkyl-5-phenyloxazole derivatives was synthesized and evaluated for their ability to inhibit cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1). These compounds were found to be potent and selective COX-2 inhibitors.

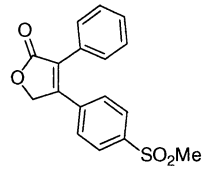
Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin have been widely used for the treatment of inflammatory diseases. However, the clinical use of these drugs has been limited by unfavorable side effects such as gastrointestinal damage.[1] Both the anti-inflammatory effect and the side effects of NSAIDs are known to be due to inhibition of cyclooxygenase (COX) which converts arachidonic acid to prostanoids (PGs) that are important mediators of inflammation but also keep physiological functions such as gastric mucosal protection and platelet aggregation.[2]

In 1991, it was discovered that there are two isoforms of COX.[3] One isoform, COX-1, is constitutively expressed and produces physiologically important PGs. On the other hand, the second isoform, COX-2, is induced significantly under inflammatory conditions. The classical NSAIDs inhibit COX-1 more strongly than COX-2. These findings led to a scenario that a selective COX-2 inhibitor may offer a new generation of NSAIDs with diminished side effects.[4]

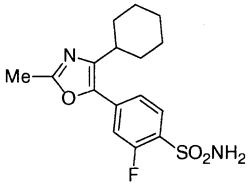
Many efforts have been made to find COX-2 selective inhibitors and now vicinal diaryl heterocyclic compounds bearing methylsulfonyl or sulfonamide group are known to be selective COX-2 inhibitors.[5] From this class of compounds, two drugs, celecoxib[6] and rofecoxib,[7] are now on the market. We and another group have independently found oxazole derivatives of this class.[8] Our work led to the discovery of JTE-522,[9] which is now under clinical investigation. In this paper, we report the synthesis and SAR study of a series of 4-aryl/cycloalkyl-5-phenyloxazoles **1** as selective COX-2 inhibitors.



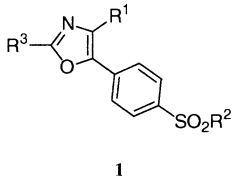
Celecoxib



Rofecoxib



JTE-522



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Synthesis

A series of 5-(4-alkylsulfonylphenyl)-4-aryl/cycloalkyl oxazoles were synthesized as shown in Scheme 1.[10] 4-(Alkylsulfonyl)benzylbromides **2** were coupled with an appropriate acid chloride **3** in the presence of zinc powder and catalytic amount of tetrakis(triphenylphosphin)palladium(0) in 1,2-dimethoxyethane to give benzyl ketones **4**.[11] The benzyl ketones were converted to α-acetoxy ketones **5** ($R^3 = Me$) by the reaction with

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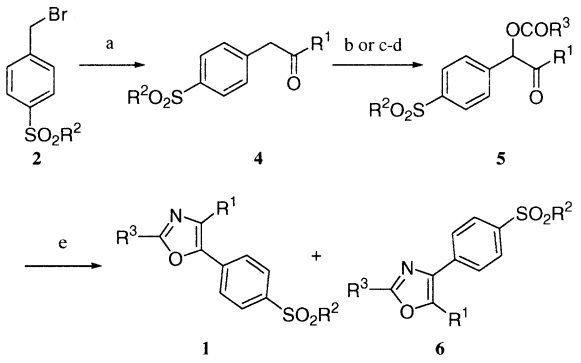
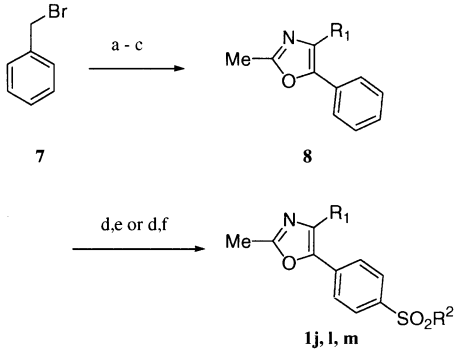


Scheme 1. Reagents and conditions: (a) R^1COCl (**3**), Zn, 5–10 mol% $Pd(PPh_3)_4$, DME, 0 °C to rt; (b) $Pb(OAc)_4$, AcOH reflux; (c) Br_2, toluene–$CHCl_3$, rt; (d) R^3COONa, EtOH reflux; (e) NH_4OAc, AcOH reflux.

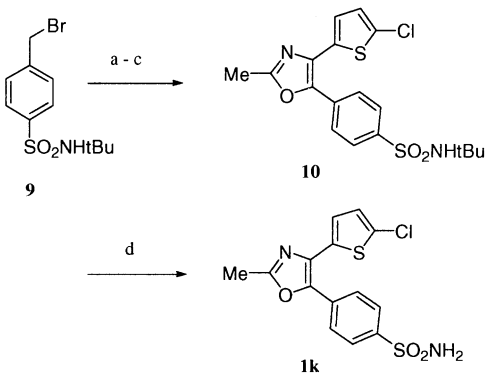
lead tetraacetate in refluxing acetic acid.[12] Other α-acyloxy ketones were prepared from **4** in two steps; first, bromination by Br_2 in toluene–$CHCl_3$, and second, reaction with the corresponding acid sodium salt in refluxing EtOH. Heating the α-acyloxy ketones **5** in refluxing AcOH in the presence of NH_4OAc[13] afforded oxazoles **1** and its regio isomers **6**. These isomers were separable by flash chromatography. When R^1 is phenyl or thienyl ring, **1** was obtained as a major isomer with **6** as a minor isomer (<10%), but in the case that R^1 is cycloalkyl group, only one isomer **1** was observed.

Preparation route for 5-(4-aminosulfonyl)phenyl-4-cyclohexyl or phenyl oxazoles **1j**, **l**, **m** is shown in Scheme 2. Starting from benzylbromide **7**, oxazoles **8** were obtained by using the same procedure for the preparation of **1** shown in Scheme 1. The oxazoles **8** were reacted with chlorosulfonic acid in refluxing $CHCl_3$ followed the treatment with 28% ammonia in THF to give sulfonamides **1j** and **1l**. *N*-Methylsulfonamide **1m** was obtained by treating with $MeNH_2$ instead of ammonia in the last step.

5-(Aminosulfonyl)phenyl-4-(5-chloro-thien-2-yl)-2-methyl oxazole **1k** was prepared as shown in Scheme 3. Benzylbromide **9** was converted to an oxazole **10** in three steps by the same method as shown in Scheme 1. Deprotection of the *N*-*tert*-butyl group of sulfonamide was performed by treating the oxazole **10** with trifluoroacetic acid to give 4-thienyl oxazole **1k**.



Scheme 2. Reagents and conditions: (a)–(c) same as shown in Scheme 1; (d) $ClSO_3H$, $CHCl_3$, reflux; (e) 28% NH_4OH, THF, rt; (f) $MeNH_2{\cdot}HCl$, Et_3N, dioxane–H_2O, rt.



Scheme 3. Reagents and conditions: (a) 5-chloro-2-thiophenecarbonyl chloride, Zn, 5–10 mol% $Pd(PPh_3)_4$, DME, 0 °C to rt; (b) $Pb(OAc)_4$, AcOH reflux; (c) NH_4OAc, AcOH reflux; (d) CF_3COOH, 50 °C.

Results and Discussion

The compounds synthesized in this study were tested for their ability to inhibit human COX-2 and COX-1 enzymes in vitro.[14] The results of 2-methyloxazoles are summarized in Table 1. First, we examined 2-methy-5-(4-methylsulfonyl)phenyl-4-phenyl oxazole **1a** as a vicinal diaryl type of compound and found that it is a very potent COX-2 inhibitor ($IC_{50}=0.09$ μM) with high selectivity (COX-1: $IC_{50}>100$ μM). Introduction of a fluorine atom on the 4-position of the phenyl group (**1b**) also showed high potency for COX-2 but reduced selectivity. Changing the position of the two aromatic rings on the oxazole, the regioisomer **6b** showed reduced activity. This was also observed in the case of thienyl derivatives, **1c** versus **6c**. To see the substituent effect of the 4-position on the oxazole, other rings instead of phenyl ring were examined.[15] Thienyl compounds (**1c**–**e**) showed high potency. It seems that thienyl type is more potent. Cyclohexyl (**1g**) imparts as much activity as phenyl ring, whereas cycloheptyl (**1f**) is less active and cyclopentyl (**1h**) is weakly active. Notably, cycloalkyls are highly selective for COX-2. It is interesting to note

Table 1. In vitro human COX-2[a] and COX-1[b] enzyme inhibitory concentrations of 2-methyl oxazole derivatives

Compd	R^1	R^2	COX-2 IC_{50} (μM)[c]	COX-1 IC_{50} (μM)[c]
1a	Ph	Me	0.09	>100
1b	4-F-Ph	Me	0.07	42
6b	4-F-Ph	Me	2.1	>100
1c	5-Cl-2-thienyl	Me	0.03	12.5
6c	5-Cl-2-thienyl	Me	1.2	93
1d	5-Me-2-thienyl	Me	0.04	47.5
1e	5-Et-2-thienyl	Me	0.14	>100
1f	Cyclopentyl	Me	18	>100
1g	Cyclohexyl	Me	0.07	>100
1h	Cycloheptyl	Me	0.28	>100
1i	4-F-Ph	Et	38	>100
1j	4-F-Ph	NH_2	0.024	4.7
1k	5-Cl-2-thienyl	NH_2	0.02	0.6
1l	Cyclohexyl	NH_2	0.07	47.5
1m	Cyclohexyl	NHMe	3.1	>100
Indomethacin			2.4	0.15

[a]Human recombinant COX-2 enzyme.
[b]Human COX-1 enzyme from human platelets.
[c]Values are means of at least three experiments.

Table 2. In vitro human COX-2[a] and COX-1[b] enzyme inhibitory concentration of 4-cyclohexyl-5-(4-methylsulfonylphenyl) oxazole derivatives

Compd	R^3	COX-2 IC_{50} (μM)[c]	COX-1 IC_{50} (μM)[c]
1g	Me	0.07	>100
1n	Et	0.27	60
1o	Ph	>100	>100

[a]Human recombinant COX-2 enzyme.
[b]Human COX-1 enzyme from human platelets.
[c]Values are means of at least three experiments.

that cyclohexyl ring successfully worked as a bioisostere of pheny ring in this case.

Both methylsulfone and sulfonamide are well recognized to be important moieties for COX-2 inhibition,[6,16] and it is generally seen that sulfonamides are more potent than methylsulfones, but less selective COX-2 inhibitors.[16,17] This phenomenon was also seen in our oxazole derivatives as shown in Table 1. Sulfonamides **1j–l** were equally or slightly more potent for COX-2 compared to the corresponding methysulfones but the selectivities are reduced. To investigate the effect of steric bulkiness in this moiety, ethylsulfone **1i** and *N*-methylsulfonamide **1m** were examined. Both compounds exhibit markedly reduced activity. Therefore, the COX-2 activity is very sensitive to the steric bulkiness of R^2.

Next, we examined the effect of the substituent size at the 2-position of the oxazole. As shown in Table 2, ethyl group (**1n**) instead of methyl showed reduced activity and phenyl (**1o**) is no more active. COX-2 activity is very sensitive to the bulkiness of the substituent at this position.

Conclusion

We have designed and synthesized a series of 4-aryl/cycloalkyl-5-phenyl oxazole derivatives and showed that they are potent and selective COX-2 inhibitors. The structure–activity relationship study suggests that (1) a phenyl ring of vicinal diaryl heterocyclic compound can be replaced by cyclohexyl or thienyl ring in the oxazole case, (2) sulfonamides are slightly more potent but less selective inhibitors than methylsulfones, and (3) COX-2 activity is very sensitive to the substituent size at sulfonyl moiety and 2-position of the oxazole ring.

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10. Syntheses of these compounds were performed by the method described in ref 5 as follows.

Cyclohexyl (4-methylsulfonyl)benzyl ketone 4g. To a solution of cyclohexanecarbonyl chloride (6.18 g), 2.32 g of tetrakis(triphenylphosphine)palladium(0) and zinc powder (3.42 g) in 1,2-DME (200 mL) was added a solution of (4-methylsulfonyl)benzylbromide (10.00 g) in DME (100 mL) dropwise at room temperature. After stirring for 2 h, the insoluble material was removed by filtration. The filtrate was concentrated in vacuo and the residue dissolved in AcOEt. The solution was washed with 2 N aq HCl and brine and was dried over Na_2SO_4. The solvent was removed by evaporation in vacuo. The residue was precipitated in AcOEt–iPr$_2$O. The precipitates were collected by filtration to give 5.42 g (48%) of **4g**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2–1.4 (m, 5H), 1.7 (m, 1H), 1.8–1.9 (m, 4H), 2.47 (m, 1H), 3.05 (s, 3H), 3.85 (s, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 2H).

2-Cyclohexyl-1-(4-methylsulfonylphenyl)-2-oxo ethyl acetate 5g. A solution of **4g** (1.48 g) and lead tetraacetate (2.50 g) in AcOH (20 mL) was heated at reflux for 3 h. The solvent was removed by evaporation in vacuo. The residue was diluted with AcOEt and washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography (SiO_2, hexane/AcOEt = 5/2) to give 0.52 g (29%) of **5g**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1–1.4 (m, 5H), 1.6–2.0 (m, 5H), 2.19 (s, 3H), 2.47 (m, 1H), 3.07 (s, 3H), 6.16 (s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H).

4-Cyclohexyl-2-methyl-5-(4-methylsulfonyl)phenyl oxazole 1g. A solution of **5g** (0.52 g) and NH_4Cl (0.29 g) in AcOH (10 mL) was heated at reflux for 4 h. The solvent was removed by evaporation in vacuo. The residue was purified by flash chromatography (SiO_2, hexane/AcOEt = 1/1) to give 0.38 g (77%) of **1g**. mp 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.98 (m, 10H), 2.51 (s, 3H), 2.82 (m, 1H), 3.08 (s, 3H), 7.72 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H). IR (cm^{-1}): 2927, 2853, 1602, 1578, 1308, 1152. MS (FAB^+): 320 (MH). Anal. ($C_{17}H_{21}NO_3S$): calcd: C; 63.92, H; 6.63, N; 4.39. Found: C; 63.83, H; 6.69, N; 4.19.

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