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Design, Synthesis and *in vitro* Evaluation of a New Class of Novel Cyclooxygenase-2 Inhibitors: 3, 4-diaryl-3-pyrrolin-2-ones

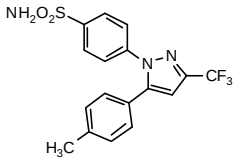
Ai Ping BAI, Zong Ru GUO*, Wen Hui HU, Fang SHEN, Gui Fang CHENG

Institute of Materia Medica, Chinese Academy of Medical Science and
Peking Union Medical College, Beijing 100050

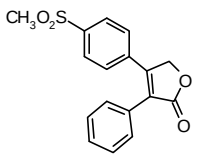
Abstract: design, synthesis and *in vivo* evaluation of a new class of COX-2 inhibitors 3, 4-diaryl-3-pyrrolin-2-ones are reported.

Keywords: Cyclooxyenase-2, inhibitor, NSAIDs (non-steroidal anti-inflammatory drugs).

COX-2 inhibitors as anti-inflammatory and analgesic agents that lack the gastro-intestinal damage and hematologic liabilities exhibited by currently marketed NSAIDs. This fact has led to the launching of two diarylheterocycle inhibitors, Celecoxib and Rofecoxib[1-3].



Celecoxib

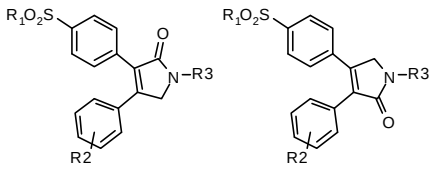


Rofecoxib

Design and synthesis

Common structures of most COX-2 inhibitors are characterized by the presence of two aryl rings in-*cis* position of a bridged hetercyclic ring, one of aromatic moiety being substituted by a sulfonyl group (methyl-sulfonyl or aminosulfonyl group)[4-6]. The centroid ring linking the two arylcycles can tolerate structural modification to a large extent. To innovate novel inhibitor with a bridged lactam, analyze the effects of the position of sulfonylphenyl group relative to the lactam carbonyl group on the activity, and the influence of different substituents on the nitrogen atom of the bridged lactam, two isomeric types of COX-2 inhibitors I and II were designed.

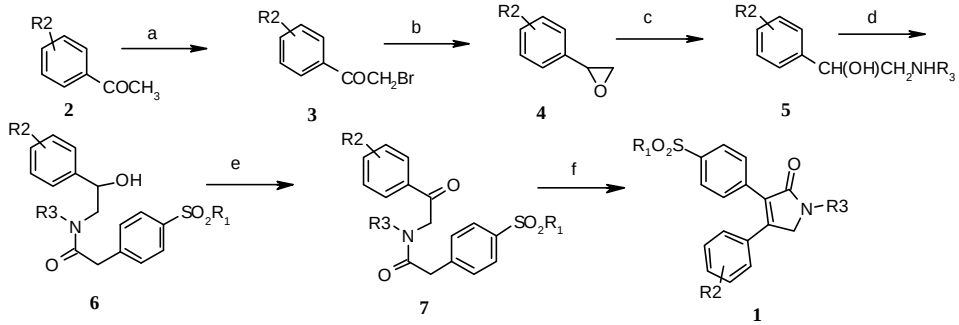
* E-mail: zrguo@imm.ac.cn



I II

The general method for preparing I and II is outlined in **scheme 1**.

Scheme 1



a. Br_2, AcOH 70-80%; b. $NaBH_4$, CH_3OH 50-80%; c. NH_2R_3, CH_3OH 40-70%; d. $R_1SO_2CH_2COCl$, Et_3N, THF 60-75%; e. CrO_3, H_2SO_4 80-90%; f. *t*-BuOK, *t*-BuOH, 50-85%

Table 1 *in vitro* COX-2 enzyme data for substituted 3,4-diaryl-3-pyrrolin-2-ones

NO.	R_1	R_2	R_3	MS: (M^+)	Mp. °C	COX-2 IC_{50}* (mol/L)
I-1	CH_3	*m*-Cl	CH_3	361	171.1-172.4	4.20 E-07
I-2	CH_3	*p*-F	n-Pr	373	150.0-152.0	6.11 E-07
I-3	CH_3	H	cyclohexyl	395	183.0-185.0	1.79 E-06
I-4	NH_2	*m*-Cl	n-Pr	390	149.0-150.0	4.82 E-07
I-5	NH_2	*m*-Br	n-Pr	435	162.0-163.0	9.98 E-07
I-6	NH_2	*m*-F	n-Pr	374	188.5-190.4	5.64 E-07
I-7	CH_3	CH_3	CH_3	341	183.9-185.1	7.82 E-07
I-8	CH_3	*p*-Cl	cyclopropyl	387	107.0-109.0	4.21 E-07
II-1	CH_3	*m*-Cl	CH_3	361	168.0-169.6	1.03 E-08
II-2	CH_3	*p*-F	n-Pr	373	120.0-121.0	2.86 E-08
II-3	CH_3	*p*-Cl	CH_3	361	129.0-131.0	2.42 E-08
II-4	CH_3	*p*-Cl	cyclohexyl	429	141.9-143.5	2.07 E-05
II-5	NH_2	*m*-CH_3	cyclopropyl	368	206.0-208.0	1.87 E-08
II-6	CH_3	*p*-CH_3	n-Pr	369	161.0-163.0	1.50 E-08
II-7	CH_3	*m*-CH_3	cyclopropyl	367	136.5-137.4	1.55 E-08
II-8	CH_3	*p*-Br	CH_3	406	161.0-163.0	1.18 E-08
Rofeco-xib						9.57 E-09

* Male C57 mice weighing between 16 and 18 g were induced with FTG (1ml/mouse, i.p.), half and three days later, the peritoneal macrophages were isolated and purified further by plating in 48-well plastic tissue culture plates in RPMI 1640 containing antibiotics and allowing cells to adhere at 37°C for 2 hr. Nonadherent cells were removed by washing with RPMI 1640. The adherent cells were induced with stimulus for 10 hr. Compounds were added 30 min before stimulated. Supernatants were stored frozen at −20°C until assay for PGE_2. PGE_2 was assayed by RIA. The IC_{50} was calculated with LOGIT method.

Series I A substituted acetophenone **2** was brominated at the α-carbonyl position to give rise to α-bromoketone **3**, which was successively reduced and cyclized by sodium boron- hydride to afford styrene oxide **4**. Alkylation of a variety of appropriate amines by 4 gave hydroxyamines **5**, which in turn were acylated by variety of p-methanesulfonyl- or p-amino-sulfonyl-phenyl acetyl chloride. The resulting amides **6** were oxidized by CrO_3 to yield the ketoneamide **7**, which was treated by potassium t-butoxide to give the target lactam in moderate to high yield.

Series II II was prepared in the similar manner to series I. The starting material, however, **2** was altered to β-amino/methylsulfonylacetophenone, and in step d, a variety of substituted phenylacetyl chloride were used.

Conclusion

The data of **Table 1**, show that most of series II compounds exhibit the comparable inhibitory activity to Rofecoxib, series I compounds, however, show activities 10-100 times less than Rofecoxib, indicating that the relative position of the two phenyl rings on the unsaturated lactam convey a significant effect on COX-2 inhibition, and the substituent group's bulk on the pyrrolin' s N atom should not larger than cyclopropyl. The further study is in progress.

References and notes

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7. ^{1}H-NMR (300MHZ) data for **I-1** ($CDCl_3$, δ ppm): 8.04-7.59 (dd, 4H, J=8.4; 8.4, ArH); 7.24-7.00 (m, 4H, ArH); 4.33 (s, 2H, CH_2); 3.19 (s, 3H, NCH_3,); 3.06 (s, 3H, CH_3SO_2). **I-2** ($CDCl_3$, δ ppm): 7.93-7.61 (dd, 4H, J=8.4; 8.4, ArH); 7.35-6.91 (m, 4H, ArH); 4.33 (s, 2H, CH_2); 3.56 (t, 2H, J=7.2, NCH_2); 3.06 (s, 3H, CH_3SO_2,); 1.71 (m, 2H, CH_2); 1.02-0.97(t, 3H, J=7.2, CH_3). **I-3** ($CDCl_3$, δ ppm): 7.90-7.64 (dd, 4H, J=8.4; 8.4, ArH); 7.36-7.22 (m, 5H, ArH); 4.31 (s, 2H, CH_2); 4.16 (m, 1H, NCH); 3.05 (s, 3H, CH_3SO_2); 1.92-1.19 (m, 10H, $(CH_2)_5$). **I-4** ($CDCl_3$, δ ppm): 7.90-7.55 (dd, 4H, J=9.0; 9.0, ArH); 7.35-7.05 (m, 4H, ArH); 4.91 (s, 2H, NH_2); 4.32 (s, 2H, CH_2); 3.56 (t, 2H, J=7.2, NCH_2); 1.71(m, 2H, CH_2); 1.00 (t, 3H, J=7.2, CH_3). **I-5** ($CDCl_3$, δ ppm): 7.90-7.57 (dd, 4H, J=8.1; 8.1, ArH); 7.50-7.11 (m, 4H, ArH); 4.99 (s, 2H, NH_2); 4.32 (s, 2H, CH_2); 3.56 (t, 2H, J=7.2,NCH_2); 1.71(CH_2, m); 1.02 (t, 3H, J=7.2, CH_3). **I-6** ($CDCl_3$, δ ppm): 7.91-7.56 (dd, 4H, J=8.1; 8.1, ArH); 7.33-6.95 (m, 4H, ArH); 4.91 (s, 2H, NH_2); 4.32 (s, 2H, CH_2); 3.56 (t, 2H, J=7.5,NCH_2); 1.72(m, 2H, CH_2); 1.00 (t, 3H, J=7.5, CH_3). **I-7** ($CDCl_3$, δ ppm): 7.92-7.61 (dd, 4H, J=8.4; 8.4, ArH); 7.12 (broad, 4H, ArH); 4.33 (s, 2H, CH_2); 3.18 (s, 3H, NCH_3); 3.06 (s, 3H, CH_3SO_2); 2.36 (s, 3H, CH_3). **I-8** ($CDCl_3$, δ ppm): 7.92-7.58 (dd, 4H, J=8.4; 8.4, ArH); 7.31-7.14 (dd, 4H, J=8.7;8.7, ArH); 4.27 (s, 2H, CH_2); 3.06 (s, 3H, CH_3SO_2); 2.88 (m, 1H, NCH), 0.94-0.88 (m, 4H, $(CH_2)_2$). **II-1** ($CDCl_3$, δ ppm): 7.90-7.44 (dd, 4H, J=8.4; 8.4, ArH); 7.34-7.16 (m, 4H, ArH); 4.32 (s, 2H, CH_2); 3.20 (s, 3H, NCH_3); 3.08 (s, 3H, CH_3SO_2). **II-2** ($CDCl_3$, δ ppm): 7.86-7.43 (dd, 4H, J=8.4; 8.4, ArH); 7.39-6.99 (m, 4H, ArH); 4.30 (s, 2H, CH_2); 3.53 (t, 2H, J=7.5, NCH_2); 3.05 (s, 3H, CH_3SO_2); 1.76-1.63 (m, 2H, CH_2); 0.97(t, 3H, J=7.8, CH_3). **II-3** ($CDCl_3$, δ ppm):

7.90-7.43 (dd, 4H, J=8.4; 8.4, ArH); 7.41-7.20 (m, 4H, ArH); 4.34 (s, 2H, CH_2); 3.20 (s, 3H, NCH_3); 3.08 (s, 3H, CH_3SO_2). **II-4** ($CDCl_3$, δ ppm): 7.89-7.45 (dd, 4H, J=8.4; 8.4, ArH); 7.34 (broad, 4H, ArH); 4.28 (s, 2H, CH_2); 4.16-4.10 (m, 1H, NCH); 3.07 (s, 3H, CH_3SO_2); 1.915-1.185 (m, 10H, $(CH_2)_5$). **II-5** (CD_3COCD_3, δ ppm): 7.82-7.48 (dd, 4H, J=8.4; 8.4, ArH); 7.34-7.06 (m, 4H, ArH); 4.40 (s, 2H, CH_2); 2.28 (s, 3H, CH_3); 0.97-0.77 (m, 4H, $(CH_2)_2$). **II-6** ($CDCl_3$, δ ppm): 7.86-7.46 (dd, 4H, J=8.1; 8.1, ArH); 7.25-7.07 (m, 4H, ArH); 4.32 (s, 2H, CH_2); 3.56 (t, 2H, J=7.2, NCH_2); 3.06 (s, 3H, CH_3SO_2); 2.33 (m, 3H, CH_3); 1.75-1.65 (m, 2H, CH_2); 1.00 (t, 3H, J=7.2, CH_3). **II-7** ($CDCl_3$, δ ppm): 7.85-7.44 (dd, 4H, J=7.8; 7.8, ArH); 7.24-7.05 (m, 4H, ArH); 3.05 (s, 3H, CH_3SO_2); 2.90 (m, 1H, NCH); 2.32 (s, 3H, CH_3); 0.89 (m, 4H, $(CH_2)_2$). **II-8** ($CDCl_3$, δ ppm): 7.90-7.48 (dd, 4H, J=8.4; 8.4, ArH); 7.47-7.25 (dd, 4H, J=8.4; 8.4, ArH); 4.32 (s, 2H, CH_2); 3.20 (s, 3H, NCH_3); 3.08 (s, 3H, CH_3SO_2).

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