Chinese Chemical Letters Vol. 10, No. 6, pp. 469–472, 1999

Selective Cyclooxygenase-2 Inhibitors: Design and Synthesis

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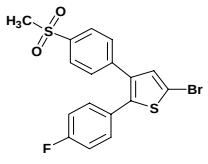
Abstract : The discovery of COX-2 provides a novel target developing more effective NSAIDs with fewer side effects . On the basis of results from the structure-activity relationships (SAR) of selective COX-2 inhibitors, we have designed and synthesized some promising compounds .

Keywords: Cyclooxygenase;cyclooxygenase-2 inhibitor selective**.**

Introduction

Owing to inhibition of prostaglandin production, non-steroids anti-inflammatory drugs (NSAIDs) have been widely used for treatment of both acute and chronic inflammatory diseases[1]. These compounds, however, exhibit serious side effects with significantly limit their use in a large proportion of the patients[2]. Arachidonic acid is a converted to prostaglandin (PGs) by at least two isoforms of the enzyme cyclooxygenase[3]. The constitutive form of the enzyme (COX-1) is responsible for the normal production of PGs. An inductive form of cyclooxygenase (COX-2) is primarily related to the production of PGs at the inflammatory sites. Currently marketed NSAIDs inhibiter both enzymes and consequently function as anti-inflammatory agents with concomitant gastric and renal toxicity. Therefore, selective inhibitors of COX-2 possess anti-inflammatory active without or with reduced toxicity side effects. There have been a few reports of selective COX-2 inhibitors, which are activity in animal models of inflammation without the normal toxicity associated with COX-1 inhibition[4-6]. The typical selective COX-2 inhibitors with "tri-cyclic" structure are interesting to us because of their similar pharmacophore conformation, as shown in **Figure 1**.

Figure 1.



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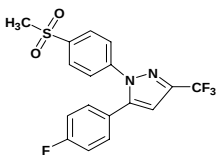

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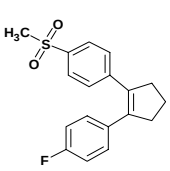

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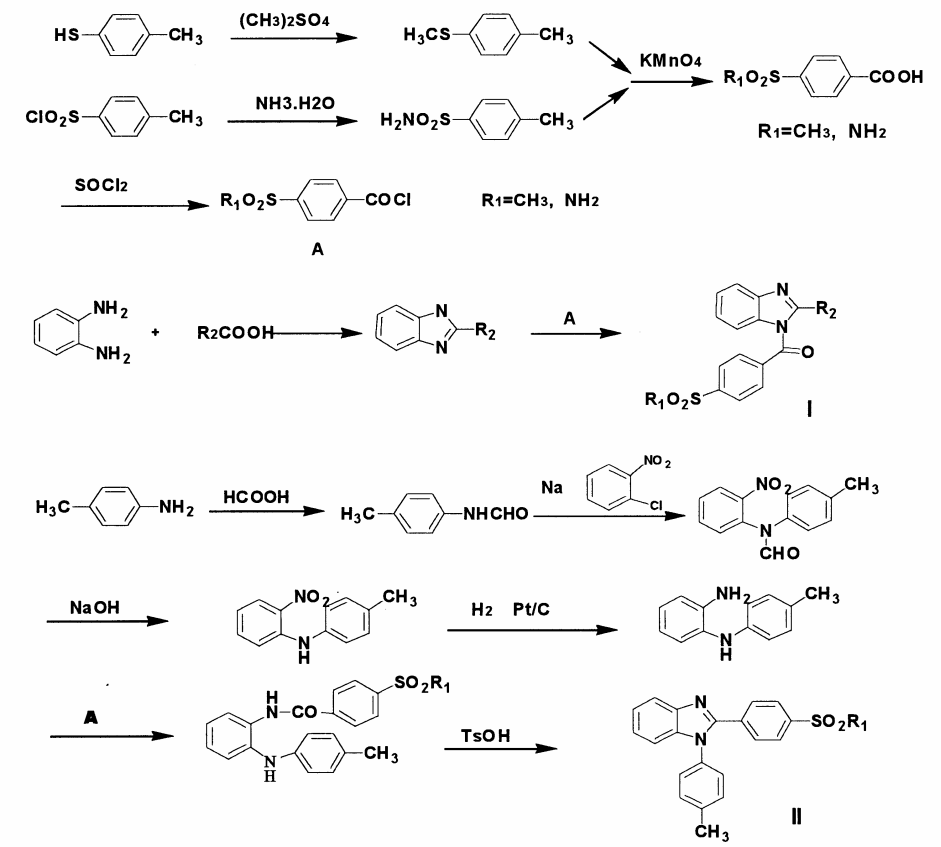
Design and Synthesis

The structure-activity relationship (SAR) of the "tri-cyclic " inhibitors revealed that: (1) a methyl-sulfonyl or aminosulfonyl group attached to one of the aryl rings is essential; (2) the two aryl rings are located in Z configuration; (3) the centroid ring linking the two aryl

Scheme 1.



rings can tolerate structural modification to a large extent. On the basis of the results from the SAR, we designed and synthesized two novel types of compounds with potential bioactivity in order to study to what extent the centroid ring may be modified. At first, the centroid ring is opened, and the two aryl rings are linked by an N-alkyl amide linkage. To increase the hydrophobicity in the region of the amide bond, and to keep the two aryl rings in *cis*-conformation, we have synthesized the 2-alkyl-N-benzoylbenzimidazoles. In addition, manipulation of the bulk of the centroid ring ,resulted in the second type. The synthetic routes of the compounds are shown in **Scheme 1**.

Results and Discussion

All of the compounds were identified by MS or ^{1}H nmr (300MHz or 500MHz).The spectral data and activity data of some compounds as examples are shown in **Table 1:**

Table 1. Structures and the spectral data and biological activity data of some compounds

compound No.	R_1	R_2	Mp. ^{0}C	MS	PEG2 Inhibitor rate(10^{-5}M)	^{1}H nmr
I1	CH_3	CH_3CH_2	185-186	M+:329	13.5	100MHZ (D_3CCOCD_3,D_2O): δ 8.2-8.0, (ArH, dd); 7.7 (Ar'H, 1H,d) ;7.3 (Ar'H. 1H,t); 7.1 (Ar'H. 1H, t); 6.7 (Ar'H. 1H, d); 3.0 (CH_2, q); 1.4 (CH_3, t)
I2	CH_3	C_4H_9	143-144	M+:356	0	500MHZ ($CDCl_3$): δ 8.2-8.0, (ArH, dd); 7.8 (Ar'H, 1H, d);7.3 (Ar'H.1H,t); 1 (Ar'H.1H, t); 6.6 (Ar'H.1H, d); 3.15 (SO_2, CH_3,S); 3.10(CH_2,t); 1.9 (CH_2 ,m); 1.4 (CH_2, m) ; 0.9 (CH_3, t)
I3	CH_3	CH_2Ph	157-158	M+:390	0	300MHZ ($CDCl_3$): δ 8.0-7.8, (ArH, dd); 7.8 (Ar'H, 1H, d) ; 7.3 (Ar'H.1H, t); 7.2 (Ar'H.1H, t); 7.1 (Ar'H.1H, d); 6.6 (Ar'H.1H, d); 4.6 (CH_2, s); 3.1 (SO_2,CH_3, t)
I4	NH_2	CH_2Ph	198-199	M+:391	9.1	300MHZ (D_3CCOCD_3,D_2O): δ 8.0-8.0, (ArH, dd); 7 (Ar'H, 1H, d) ;7.3 (Ar'H.1H, t); 7.2 (Ar'H.1H, t); 7.1 (Ar'H.1H, d); 6.7 (Ar'H.1H, d); 4.5 (CH_2,s);
I5	CH_3	CH_2CH_2P	120-121	M+:404	14.8	300MHZ ($CDCl_3$): δ 8.1-7.8, (ArH, dd); 7.8 (Ar'H, 1H, d);7.3 (Ar'H.1H, t); 7.2 (Ar'H.5H, t); 7.1(Ar'H.1H,t); 6.5 (Ar'H.1H, d); 3.5 (CH_2, t); 3.5 (CH_2, t); 3.1 (SO_2, CH_3, s)
II6	NH_2	/	188-189	M+:363	100.0	300MHZ (D_3CCOCD_3, D_2O): δ 7.9-7.8, (ArH, dd); 7.5-7.3(Ar'H, dd); 7.4-7.2 (Ar'H. dd); 2.5 (Ar"CH_3,s)
II7	CH_3	/	269-271	M+:362	97.2	500MHZ (D_3CCOCD_3, D_2O): δ7.95-7.85, (ArH, dd); 7.78 (Ar'H, 1H,d); 7.43-7.34 (Ar'H. 1H,t); 7.35-7.30 (Ar'H. dt); 7.23 (Ar'H. dd); 3.15 (SO_2, CH_3,s); 2.45 (Ar"CH_3,s)

The results from preliminary pharmacological evaluation suggested that the centroid ring of the "tri-cyclic" inhibitor might not be replaced by the amide bond even if the hydrophobicity in the bridge was augmented. However , it seems to be allowed to enlarge the bulk of the centroid . For example, compound **6** and **7** shown potent activity and significant selectivity for inhibition of COX-2 over COX-1 (compound **6** :IC_{50}:3.6×10^{-8}/1.2×10^{-4}mol/l; compound **7**; IC_{50}:3.9×10^{-9}/9.35×10^{-9} mol/l). The further study is in progress.

Acknowledgment

This project supported by the National Natural Science Foundation of China, No 39770877

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Received 24 March 1999