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A Convenient Synthesis of the Substituted 2, 3-Diarylindole the Potent Selective COX-2 Inhibitors

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Abstract: Phenyl sulfone-containing 2, 3-diarylindole derivatives were designed and identified to be selective COX-2 inhibitors. A convenient synthetic route was also developed for the synthesis of the novel inhibitors.

Keywords: Nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, substituted 2, 3-diarylindole, pharmacophore.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed drugs worldwide for the treatment of inflammatory conditions. The mechanism of action was through their inhibition of prostaglandin biosynthesis *via* the enzyme cyclooxygenase-2 (COX-2)[1]. COX-2 and COX-1 are the two similar but distinct isoforms of cyclooxygenase (COX). COX-2 is induced upon inflammatory stimuli and is responsible for progression of inflammation, whereas COX-1 is a constitutively expressed isoforms and responsible for the maintenance of physiological homestasis, such as gastrointestinal integrity and renal function. Thus selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities, comparing with the traditional NSAIDs.

Current research has focused on developing the safer NSAIDs—selective COX-2 inhibitors[2-7]. Celecoxib[8] and Rofecoxib[9] have been recently marketed as a new generation of NSAIDs by Searle and Merck & Co., Inc., respectively, and phenyl sulfone-containing *cis*-1, 2-diaryl-alkenes or their structural equivalents are known to be their pharmacophore. We herein designed the substituted phenyl sulfone-containing 2, 3-diarylindole **1** and **2** and the initially synthesized two compounds **1a** and **1b** were documented to be the potent selective COX-2 inhibitors *via* the biological evaluation (outlined in **Table 1**).

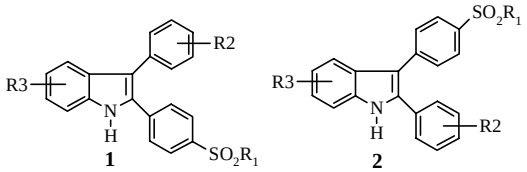

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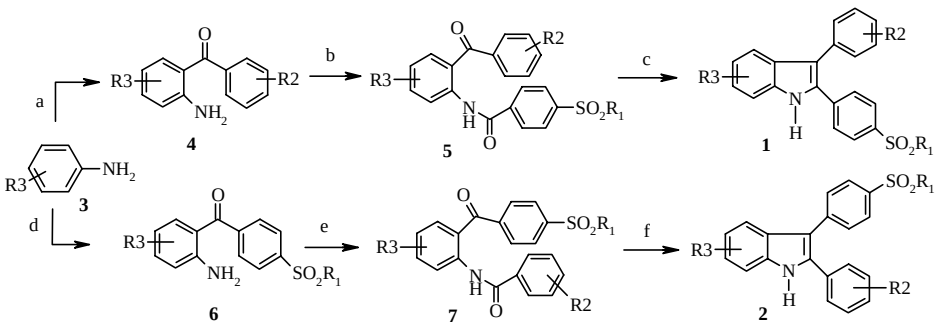
Table 1 *In vitro and in vivo* activity of compound **1a** and **1b**

				in vitro IC_{50} (M)		*in vivo*[b] ED_{50} (mg/kg)	
No.	R_1	R_2	R_3	COX-2	COX-1	3 h	4 h
1(a)	CH_3	H	H	6.0×10^{-10}	$\geqslant10^{-5}$	12.17	9.44
1(b)	NH_2	H	H	9.1×10^{-11}	$\geqslant10^{-5}$	6.02	5.22
celecoxib				8.2×10^{-9}	$\geqslant10^{-5}$	9.30	11.28

[a] Cell level.
[b] Rat carrageenan-induced foot pad edema assay.

Most of the compounds **1** and **2** described herein were synthesized by using the general route outlined in **Scheme 1**, and the coupling reaction catalyzed by titanium (Ti) was employed in the key step for the indole synthesis. Aromatic acylamido carbonyl compounds can be easily cyclized to indole derivatives upon treatment with low-valent titanium reagents[10-13], and in this paper the coupling reagent "low-valent" Ti was prepared *in situ* from $TiCl_4$ and Zn in reflux THF. To prepare the intermediate substituted 2-amino-lenzophone[14] **4** and **6**, the commercial available starting material **3** was taken Friedel-Crafts reaction followed by hydrolyzed with concentrated H_2SO_4. Acylation of the intermediate **4** and **6** with substituted benzoyl chloride gave compound **5** and **7** respectively which were cyclized by intramolecular condensation in the presence of $TiCl_4$ and Zn giving rise to the final compounds **1** and **2**.

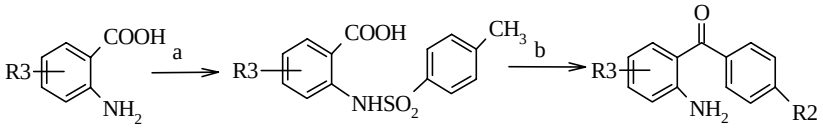
Scheme 1



Reagents: a. (ⅰ) $R_2C_6H_4COCl$, $ZnCl_2$; (ⅱ) H_2SO_4 80%; b. Et_3N, $R_1SO_2C_6H_4COCl$, THF; c. $TiCl_4$, Zn, THF. d. (ⅰ) $R_1SO_2C_6H_4COCl$, $ZnCl_2$; (ⅱ) H_2SO_4 80%; e. Et_3N, $R_2C_6H_4COCl$, THF; (f) $TiCl_4$, Zn, THF.

An alterative method to synthesize the intermediate **4** (for example the method outlined in **Scheme 2**) is to provide the final compound **1** with different groups[15]. Preparation of the substituted 2-aminolenzophone in this method commenced with substituted o-aminobenzoic acid, which was protected by tosylate and then taken Friedel-Crafts reaction followed by hydrolyzed with concentrated H_2SO_4. Fischer indole synthesis was also used for the preparation of the target compound **2**, but was less efficient than the route outlined in **Scheme 1**.

Scheme 2



Reagents: (a) TsCl, Na_2CO_3; (b) (ⅰ) ArR_2, $AlCl_3$; (ⅱ) H_2SO_4 80%.

Table 2 Melting point and elemental analysis data[a] of **1c~e** and **2a~c**.

				Yield[b]	Mp.	E. A. cacld (%)			E. A. found (%)		
No.	R1	R2	R3	(%)	(°C)	C	H	N	C	H	N
1(c)	NH_2	H	5-F	76.9	302 - 304	65.56, 4.13, 7.65			65.46, 4.16, 7.47		
1(d)	NH_2	H	5-Cl	72.3	297 - 299	62.74, 3.95, 7.32			62.65, 4.08, 7.30		
1(e)	CH_3	H	5-Cl	75.4	281 - 283	66.05, 4.22, 3.67			66.11, 4.18, 3.91		
2(a)	2-F	SO_2CH_3	5-Cl	78.1	246 - 248	63.07, 3.78, 3.50			63.30, 3.93, 3.27		
2(b)	H	SO_2CH_3	5-Cl	82.4	273 - 275	66.05, 4.22, 3.67			65.98, 4.47, 3.75		
2(c)	4-Cl	SO_2CH_3	5-Cl	77.1	269 - 271	60.58, 3.63, 3.36			60.58, 3.68, 3.07		

[a] All compounds were determined by 300 MHz ^{1}HNMR spectroscopy.
[b] Isolated yields of **1** or **2** from **5** or **7**.

In summary, phenyl sulfone-containing 2, 3-diarylindoles have been shown a novel class of selective COX-2 inhibitors, and its preparation can be easily and efficiently carried out by using the synthetic route developed herein with the advantages of easily accessible starting materials, convenient manipulation and moderate to high yields.

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