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Synthesis and biological evaluation of 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives as novel COX-1/2 and 5-LOX inhibitors

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ABSTRACT

Fourteen new 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives were synthesized. Six compounds displayed potent inhibitory activities against COX-1/2 and 5-LOX with IC_{50} in the range of 0.10–9.87 μM. Particularly, **10f** exhibited well balanced inhibitory action on these enzymes (IC_{50} = 0.10–0.56 μM). More importantly, **10f** and several other compounds had comparable or stronger anti-inflammatory and analgesic activities, but better gastric tolerability in vivo, as compared with darbufelone mesilate and tenidap sodium. Therefore, our findings may aid in the design of new and safe anti-inflammatory reagents for the intervention of painful inflammatory diseases, such as rheumatoid arthritis at clinic.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one kind of the medications widely used in the world because of their high efficacy in reducing pain and inhibiting inflammation.[1] Many NSAIDs can inhibit the activity of cyclooxygenase enzymes (COX-1 and COX-2), which catalyze the biotransformation of arachidonic acid to prostaglandins (PGs).[2] However, clinical studies revealed that continual treatment with NSAIDs is associated with numerous side effects, such as gastrointestinal (GI) bleeding,[3] myocardial infarction and stroke.[4] The adverse effects of NSAIDs are likely attributed to the reduced production of COX-1-related PGs that are critical regulators of the maintenance of GI mucosal integrity,[5] and to the imbalance of thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) production,[6,7] two opposite actors in regulating the homeostasis of coagulation.[8] Hence, development and discovery of new reagents that can modulate COX-1 and COX-2 activity will be of importance for the controlled inflammation.

Notably, arachidonic acid can also be metabolized through the lipoxygenase (LOX) pathway, particularly by 5-lipoxygenase (5-LOX) to form hydroperoxy eicosanoic acid, leading to the production of leukotrienes (LTs), which are potent inflammatory mediators.[9] The LTs have been associated with the development of NSAIDs-related gastrointestinal side effects.[10,11] Furthermore, increased levels of LTB_4 are detected in the gastric mucosa of NSAID-treated patients[12] and high levels of LTs may contribute to the development of atherosclerosis, myocardial infarction, and stroke.[13,14] Apparently, simultaneous inhibition of COX and 5-LOX should inhibit inflammation and mitigate the NSAIDs-related adverse effects.[15]

Indole skeleton exists in a variety of natural products and is the precursor to many pharmaceuticals, such as indomethacin and tenidap (Chart 1). Tenidap is a cytokine modulator and COX/5-LOX inhibitor,[16] which was more effective in the clinical treatment of rheumatic arthritis than traditional NSAIDs such as piroxicam and diclofenac.[17,18] However, it entered market only for a short time in Europe because of the liver and kidney toxicity, which

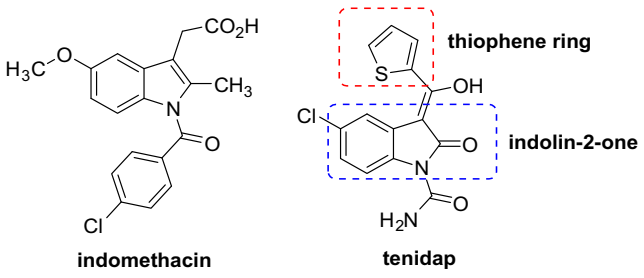

Chart 1. Chemical structures of indomethacin and tenidap.

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was likely attributed to its reactive oxidative metabolites of thiophene moiety.[19–21]

To develop alternative anti-inflammatory agents, we conducted exploratory research focusing on replacement of thiophene ring in tenidap molecule with aminosulfonylphenyl or methylsulfonylphenyl moiety, the common pharmacophores of some anti-inflammatory agents.[22–24] We hypothesized that this modification may be beneficial to enhance COX/5-LOX inhibitory activities and abolish the toxicity of thiophene moiety.

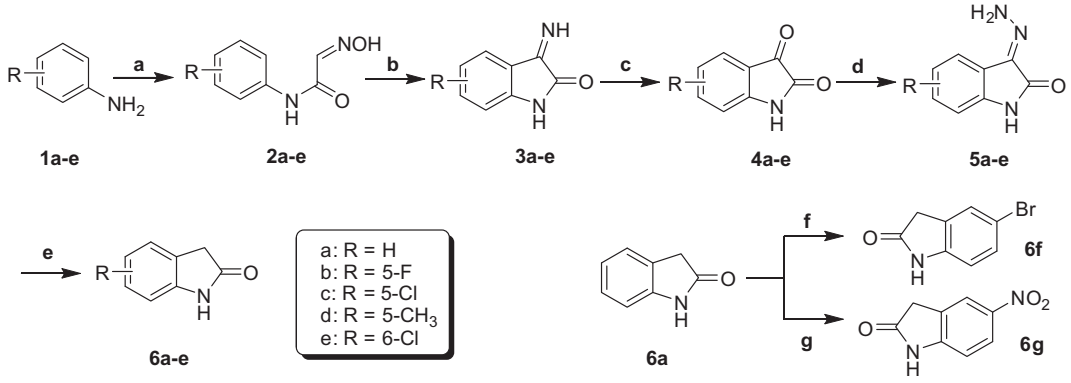
Herein, we report the synthesis of 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives and their biological activities.

For synthesis of the target compounds, indolin-2-ones **6a–e** were synthesized from appropriate anilines according to the reported procedures (Scheme 1).[25,26] Briefly, isonitrosoacetanilides **2a–e** were prepared by the condensation of appropriate anilines **1a–e** with chloral hydrate and oxammonium hydrochloride, respectively, in 70–90% yields. The subsequent cyclization of **2a–e** in the presence of concentrated sulfuric acid afforded 3-iminoindolin-2-ones **3a–e**, which were directly hydrolyzed to generate isatins **4a–e** in 45–85% yields. Finally, indolin-2-ones **6a–e** were obtained by a Wolff–Kishner–Huang reduction of **4a–e** in 50–90% yields. 5-Bromoindolin-2-one **6f** was obtained by the bromination of indolin-2-one **6a** with bromine in hot water,[27] and 5-nitroindolin-2-one **6g** from nitration of indolin-2-one **6a** at −5 to 0 °C followed by recrystallization in aqueous acetic acid.[28]

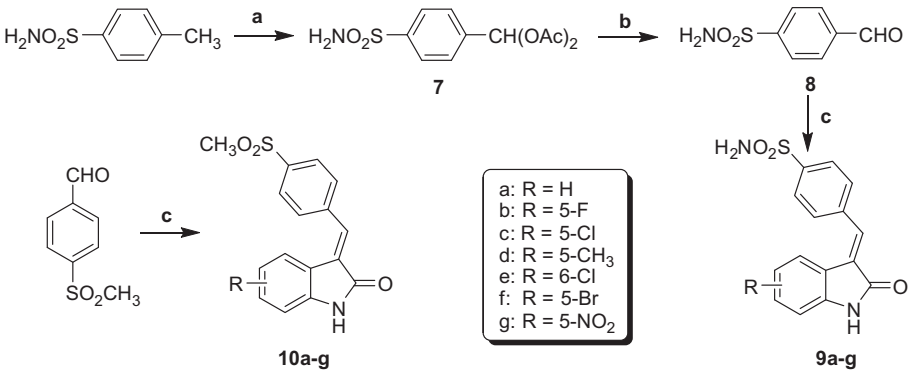
The target compounds **9a–g** and **10a–g** were synthesized by Knoevenagel condensation of indolin-2-ones **6a–g** with 4-sulfamoylbenzaldehyde **8** or the commercially available 4-methylsulfonylbenzaldehyde, as illustrated in Scheme 2. The oxidation of 4-toluenesulfonamide using chromic oxide in the mixture of acetic acid, acetic anhydride, and concentrated sulfuric acid afforded 4-[bis(acetyloxy)methyl]benzenesulfonamide **7**, which was hydrolyzed in the refluxing mixture of alcohol, water and concentrated sulfuric acid to furnish 4-sulfamoylbenzaldehyde **8** in 40% yield.[29] Initially, the target compounds were synthesized via the Knoevenagel reaction using piperidine as catalyst in methanol or ethanol to generate a mixture of *E* and *Z* geometrical isomers (described as follows), which were difficult to be separated.[30] Alternatively, the target compounds were prepared by refluxing in acetic acid in the presence of sodium acetate.

The target compounds **9a–g** and **10a–g** could exist as either *E* or *Z*-isomers due to the exocyclic double bond. To determine the configuration of the target compounds, **10f** was characterized by a nuclear Overhauser effect (NOE) experiment. Obviously, if **10f** belongs to the *Z*-isomer, NOE analysis would reveal interaction between the vinyl proton and H-4 on the indolin-2-one ring. In fact, there was no interaction between the vinyl proton and H-4 in the spectrum. However, the strong interaction between H-4 and H-2′ or H-6′ proton was observed (Supplementary data), indicating that **10f** was *E*-isomer with the chemical shifts of H-2′ and H-6′ protons in the range 7.94–7.96 ppm (Chart 2).

Notably, the target compounds we first obtained were a mixture of *E* and *Z*-isomers when piperidine was employed as the catalyst as described above. We analyzed that the chemical shifts of H-2′ and H-6′ protons for the *Z* but not *E*-isomer would go downfield due to the deshielding effect of the carbonyl group. Indeed, ^{1}H NMR spectra data revealed that the chemical shifts of H-2′ and H-6′ for the *Z*-isomer of **10f** were at 8.48–8.50 ppm (Supplementary data), which were much higher than 7.94–7.96 ppm for



Scheme 1. The synthetic pathway of indolin-2-ones **6a–g**. Reagents and conditions: (a) $Cl_3CCH(OH)_2$, $NH_2OH{\cdot}HCl$, Na_2SO_4, HCl, H_2O, 60–70 °C; (b) concd H_2SO_4, 80–90 °C; (c) H_2O, H_2SO_4; (d) 85% hydrazine hydrate, C_2H_5OH, reflux; (e) NaOH, C_2H_5OH, H_2O, reflux; (f) Br_2, KBr, H_2O, 90 °C; (g) concd H_2SO_4, fuming HNO_3, −5 to 0 °C.



Scheme 2. The synthetic pathway of the target compounds 9**a–g** and **10a–g**. Reagents and conditions: (a) Cr_2O_3, concd H_2SO_4, HOAc, Ac_2O, 5–10 °C; (b) concd H_2SO_4, CH_3OH, H_2O, reflux; (c) **6a–g**, NaOAc, HOAc, ruflux.

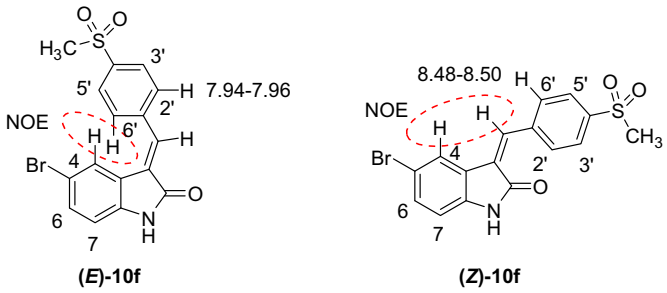


Chart 2. Determination of **10f** configuration by NOE analysis. Data shown are the chemical shifts of H-2′ and H-6′ protons of **10f**.

the *E*-isomer, consistent with the previous reports.[30,31] In this regard, the chemical shifts of phenyl H-2′ and H-6′ protons for other target compounds (**9a–g**, **10a–e**, and **10g**) were in the range of 7.86–8.03 ppm, which were similar to that of **10f** *E*-isomer (7.94–7.96 ppm), suggesting that the configurations of other target compounds were the *E*-isomer.

The target compounds **9a–g** and **10a–g** were preliminarily evaluated in vitro for their ability to inhibit 5-LOX and COX activities by measuring the formation of LTB_4 (a product of 5-LOX) and 12-hydroxyheptadecatrienoic acid (12-HHTrE, a product of COX) in rabbit peripheral venous blood samples stimulated with the calcium ionophore A23187 alone or in combination with lipopolysaccharide (LPS).[32] Two well-known COX/5-LOX dual inhibitors, darbufelone mesilate (DBF)[33] and tenidap sodium (TND), were used as reference standards. As shown in Table 1, DBF displayed potent inhibitory activity against COX-2/5-LOX but relatively weak against COX-1, while TND inhibited COX-1 activity more potently than COX-2, which were consistent with previous reports.[16,33] Six target compounds (**9b**, **9c**, **9g**, and **10e**–**g**) exhibited potent inhibitory action on these three enzymes, and their anti-COX-1 and anti-5-LOX activities were more potent than DBF and TND, respectively. Particularly, **10f** showed excellent inhibitory activity against COX-1 (IC_{50} = 0.11 μM), COX-2 (IC_{50} = 0.10 μM), and 5-LOX (IC_{50} = 0.56 μM), respectively, and its inhibitory activities were well balanced for these enzymes. Compound **9b** also had strong inhibitory activity against COX-1 (IC_{50} = 0.62 μM) and COX-2 (IC_{50} = 0.18 μM), which had the highest COX-2 selectivity among the target compounds tested. These novel compounds with potent inhibitory activity were worthwhile for further bioactivities evaluation in vivo.

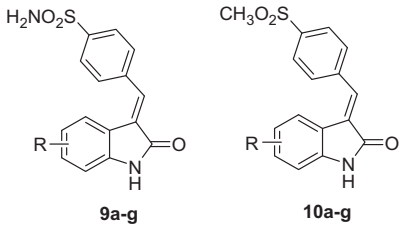
Furthermore, the in vivo anti-inflammation activities of aminosulfonyl derivatives (**9b**, **9c**, and **9g**) and methylsufonyl derivatives (**10a**, **10c**, and **10e**–**g**) were evaluated using a well-known rat model of the carrageenan-induced paw oedema.[34] Male Wistar rats were randomized for oral treatment with DBF (13.0 mg/kg body weight), with an equimolar dose of TND, or individual compounds (n = 10 per group). One hour after treatment, the rats were injected with 0.1 mL of 1% carrageenan in saline in right footpad and the volumes of the paw for individual rats were measured using a plethysmometer at 0, 1, 3, and 6 h post-carrageenan treatment (Table 2). Injection with carrageenan-induced inflammation and increased the volume of the paw at 1 h post-injection. The volume of the paw further increased with time. In contrast, treatment with most of the target compounds significantly mitigated the carrageenan-induced inflammation in rats. Notably, the inhibitory effects of **9b**, **10a**, **10e**, and **10f** were stronger than that of DBF and TND, especially for **10f**. These data clearly demonstrated that these compounds have strong anti-inflammatory activity in vivo.

Next, the compounds at an equimolar dose of DBF (26.0 mg/kg body weight) were evaluated for their analgesic activities using the acetic acid induced writhing assay in mice.[35] As shown in Table 3, treatment with each of the target compounds significantly reduced the numbers of writhes in mice (P <0.01), indicating that these compounds displayed strong analgesic activity. Especially, **9c**, **10f**, and **10g** had more potent analgesic activity than TND, while similar to DBF.

To determine the potential ulcerogenic effect, groups of male Wistar rats were treated orally with vehicle control or individual compounds daily for consecutive 7 days, respectively. The total numbers and areas of gastric ulcers in the stomachs of individual rats were examined (Table 4). Treatment with the test compounds, but not the control, did induce various sizes of ulcers in the stomachs of these rats. All target compounds tested caused fewer gastric ulceration than TND (P <0.01). Notably, the total areas of gastric ulcers in the groups of rats received some compounds were similar to that of the DBF-treated rats, while the total areas of gastric ulcers in the **9b**, **9c**, **9g** and **10f** treated rats were significantly smaller than that of the DBF-treated rats (P <0.05). Given that DBF had been shown to have less gastric adverse effect in human,[33] our data clearly indicated that these new compounds may be better gastrically tolerized in human.

Analysis of structure–activity relationship (SAR) revealed that compounds **10a**, **10e**, and **10f** with a methylsulfonyl substituent had stronger inhibitory activity against COX-1/2 and 5-LOX than that of the corresponding sulfamoyl analogs **9a**, **9e**, and **9f**. Furthermore, introduction of methyl (an electron-donating group) into the C-5 position of the indolin-2-one ring reduced their inhibitory activities (e.g., **9a** vs **9d**, **10a** vs **10d**). In contrast, introduction of

Table 1
Inhibitory activity of the target compounds against COX-1/COX-2 and 5-LOX in vitro



Compound	R	IC_{50}[a] (μM)			COX-2 S. I.[b]
		COX-1	COX-2	5-LOX	
DBF[c]	—	37.60	0.11	0.61	341.82
TND[d]	—	2.56	8.40	36.70	0.31
9a	H	>50	>50	>50	n.d.
9b	5-F	0.62	0.18	9.87	3.44
9c	5-Cl	0.16	3.31	3.37	0.05
9d	5-CH_3	>50	>50	>50	n.d.
9e	6-Cl	>50	>50	>50	n.d.
9f	5-Br	24.63	20.88	10.55	1.18
9g	5-NO_2	0.14	3.72	3.06	0.04
10a	H	9.32	5.52	9.51	1.69
10b	5-F	8.99	>50	9.42	n.d.
10c	5-Cl	>50	3.82	>50	n.d.
10d	5-CH_3	>50	>50	>50	n.d.
10e	6-Cl	0.24	2.39	2.99	0.10
10f	5-Br	0.11	0.10	0.56	1.10
10g	5-NO_2	0.50	3.29	3.91	0.15

n.d. not determined.
[a] The concentration (μM) of test compound causing 50% inhibition of LTB_4 (5-LOX), 12-HHTrE (after 30 min incubation with A23187 alone) for COX-1, or 12-HHTrE (after 24 h incubation with A23187 plus LPS) for COX-2, determined by HPLC. Data are expressed as the mean from the dose–response curves of at least three independent experiments and intra-group variation was less than 12%. Vehicle control had no inhibitory effect on these enzymes (data not shown).
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] Darbufelone mesilate.
[d] Tenidap sodium.

Table 2
Anti-inflammatory activity of the target compounds against the carrageenan-induced paw edema in rats ($n = 10$)

Compound	Dose (mg/kg)	Increase in paw volume[a] (mL)			Inhibition rate (%)		
		1 h	3 h	6 h	1 h	3 h	6 h
Vehicle	—	0.21 ± 0.07	0.36 ± 0.08	0.51 ± 0.07	—	—	—
DBF	13.00	0.17 ± 0.04**	0.23 ± 0.08**	0.42 ± 0.06**	19.05	36.11	17.65
TND	10.38	0.16 ± 0.04**	0.22 ± 0.06**	0.41 ± 0.04**	23.81	38.89	19.61
9b	9.65	0.14 ± 0.04**	0.20 ± 0.05**	0.37 ± 0.06*	33.33	44.44	27.45
9c	10.15	0.17 ± 0.05**	0.24 ± 0.04**	0.41 ± 0.08*	19.05	33.33	19.61
9g	10.47	0.19 ± 0.04ns	0.28 ± 0.08*	0.44 ± 0.09ns	9.52	22.22	13.73
10a	9.08	0.15 ± 0.06**	0.22 ± 0.06**	0.40 ± 0.04**	28.57	38.89	21.57
10c	10.12	0.18 ± 0.07*	0.29 ± 0.05**	0.43 ± 6.59*	14.29	19.44	15.69
10e	10.12	0.16 ± 0.07**	0.21 ± 0.10**	0.40 ± 0.05**	23.81	41.67	21.57
10f	11.48	0.14 ± 0.05**	0.19 ± 0.05**	0.36 ± 0.05**	33.33	47.22	29.41
10g	10.44	0.15 ± 0.05**	0.24 ± 0.05**	0.39 ± 0.09**	28.57	33.33	23.53

Ns—not significant.
[a] Increase in paw volume was calculated as (the volume after carrageenin injection) – (the volume before injection). Data analyzed by one way ANOVA followed by Dunnett's *t*-test.
* $P < 0.05$.
** $P < 0.01$ significant difference versus vehicle control.

Table 3
Analgesic activity of the target compounds against the acetic acid induced writhing in mice

Compound	Dose (mg/kg, po)	Number of writhes in 15 min following treatment (Mean ± SD)[a]	Inhibition rate (%)
Vehicle	—	49.3 ± 10.53	—
DBF	26.00	6.8 ± 3.43**	86.2
TND	20.76	14.6 ± 2.31**	70.4
9b	19.30	22.7 ± 4.63**	54.0
9c	20.30	9.5 ± 3.16**	80.7
9g	20.94	29.2 ± 3.20**	40.8
10a	18.16	22.5 ± 2.88**	54.4
10c	20.24	18.1 ± 6.70**	63.3
10e	20.24	22.1 ± 4.15**	55.2
10f	22.96	8.5 ± 2.49**	82.8
10g	20.88	13.2 ± 3.27**	73.2

[a] Data analyzed by one way ANOVA followed by Dunnett's *t*-test.
** $P < 0.01$ significant difference vs vehicle control.

Table 4
Comparative analysis of the potential ulcerogenic effect of the target compounds in rats

Compound	Dose (mg/kg)	Gastric ulcer area[a] (mm^2)
CMC-Na	—	0
TND	10.38	3.75 ± 1.04
DBF	13.00	0.87 ± 0.26*
9b	9.65	0.45 ± 0.18*,**
9c	10.15	0.19 ± 0.12*,**
9g	10.47	0.12 ± 0.13*,**
10a	9.08	0.56 ± 0.22*
10c	10.12	0.88 ± 0.23*
10e	10.12	0.75 ± 0.38*
10f	11.48	0.44 ± 0.18*,**
10g	10.44	0.81 ± 0.26*

[a] Data analyzed by one way ANOVA followed by Dunnett's *t*-test.
* $P < 0.01$ significant difference vs TND.
** $P < 0.05$ significant difference vs DBF.

an electron-withdrawing group generally increased inhibitory activity against both COX-1/2 and 5-LOX (e.g., **9b**, **9c**, **9f**, and **9g** vs **9a**; **10e–g** vs **10a**). In addition, the position of the substituted group at C-5 or C-6 of the indolin-2-one ring obviously influenced the inhibitory activity (e.g., **9c** vs **9e**, **10c** vs **10e**). Apparently, 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives with an electron-withdrawing group at C-5/6 of the indolin-2-ones ring should have potent inhibitory activity against COX and 5-LOX. The in vivo assay demonstrated that most of the target compounds with potent inhibitory activities against COX/5-LOX displayed strong anti-inflammatory and analgesic activities as well as low gastric toxicity.

In summary, a series of 3-[4-(amino/methylsulfonyl)phenyl] methylene-indolin-2-one derivatives were synthesized and characterized as the *E* configurational isomer. Biological analysis revealed that six target compounds displayed potent activity against COX-1/COX-2 and 5-LOX with IC_{50} at low micromolar levels, particularly for **10f**. In comparison with DBF and TND, **10f** and several others exhibited comparable or stronger anti-inflammatory and analgesic activities, and better gastric tolerance in vivo. Therefore, our findings may aid in the design of new and safe anti-inflammatory reagents for the intervention of painful inflammatory diseases, such as rheumatoid arthritis at clinic.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.056.

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