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Design, synthesis and biological evaluation of novel 4-hydroxybenzene acrylic acid derivatives

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ABSTRACT

A series of 4-hydroxybenzene acrylic acid derivatives were designed and synthesized based on the ferulic acid of natural active ingredients. The tested compound **5a**, **5f** and **6a** have significant anti-inflammatory activity with suppression rates of 45.29%, 44.75% and 24.11%, respectively, compared with that of indomethacin, and their cardiac toxicity was not observed. The structure–function relationship shows that the *p*-hydroxyl group on the α-position benzene ring, particularly if acetylated, contributes to the considerable anti-inflammatory activity; that the carboxyl group on the double bond, if esterified, also contributes to the anti-inflammatory activity; that the *p*-methylsulfonyl group on the other benzene ring, whose introduction is due to the COX-2 selectivity, also contributes to anti-inflammatory activity surprisingly.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used drugs, having anti-inflammatory, analgesic, and antipyretic effects. There are more than 50 kinds of NSAIDs on the market, of which the main products include aspirin, diclofenac, ibuprofen, naproxen, indomethacin and so on, but gastrointestinal disorders and cardiovascular risks remain to be the most common side effects in those who use these drugs long-term.[1] The newly developed cyclooxygenase (COX-2) inhibitors obviously reduce the incidences of ulcers and hemorrhages, being effective as the relief of pain and inflammation. On the other hand, they increase the incidence of cardiovascular risk.[2]

Ferulic acid, which derived from 4-hydroxybenzene acrylic acid (*para*-hydroxycinnamic acid), is the main active ingredient of angelica and white peony root, both of which are traditional Chinese herbaceous drugs. The ferulic acid has not only anti-inflammatory and antibacterial effects, but lowers lipid levels significantly in the serum, prevents thrombosis, and advances coronary artery disease, however, no obvious toxicity is observed. Sodium ferulate, the sodium salt of ferulic acid, is to treat cardiovascular and cerebrovascular diseases and to prevent thrombosis.[3] The efficacy of sodium ferulate in the treatment of focal cerebral infarction was about 83.3% in a 36 case clinical trials.[4] Liu et al. found that better anti-inflammatory and anti-cancer activities by acetylation of the hydroxyl group of the ferulic acid (Fig. 2, **2a**).[5,6] Mou et al. revealed that compounds similar to α-phenylcinnamic acid (Fig. 2, **2b**) had powerful vasodilatory activity, in addition to displaying a certain degree of potassium-channel activation, and were promising for prevention and treatment of hypertension.[7]

4-Hydroxybenzene acrylic acid derivatives of formula (Fig. 1, **1**) are on the basis of ferulic acid of natural active ingredients, introducing the cyclooxygenase and lipoxygenase structure–activity group. The compound (Fig. 1), **5a** is one of the typical derivatives, its structure is characterized by two benzene rings being '*cis*' to each other across the unsaturated bridge in the α- and β-position of the derivatives, The benzene ring in the α-position has the methylsulfonyl or aminosulfonyl group, and the benzene ring in the β-position has the *p*-hydroxyl group, which form *para*-hydroxy styrene structure with unsaturated double bond, and which furthermore form *para*-hydroxybenzene acrylic acid with the carbonyl group.

In the compounds of formula (**1**), *para*-hydroxystyrene derivatives (Fig. 2, 2c) have excellent activities.[8,9] The *p*-hydroxyl group on the ring is essential for activity as an inhibitor of PGS, and lack of it exhibits a striking loss of anti-inflammatory activity and a decrease in PGS inhibitory activity. The double bond of the styrene has a conjugated system combined with an arachidonic acid, which enhances the activity, and saturation of the double bond decreases the activity. The methylsulfonyl group on the other benzene ring is due to the COX-2 selectivity.[10] Furthermore, these compounds also

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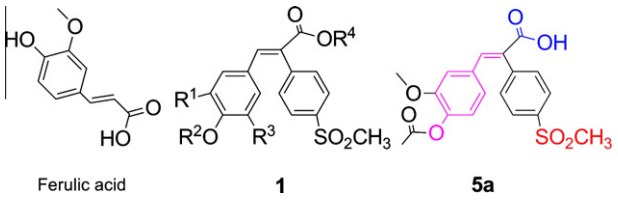


Figure 1. Ferulic acid and the new derivatives designed.

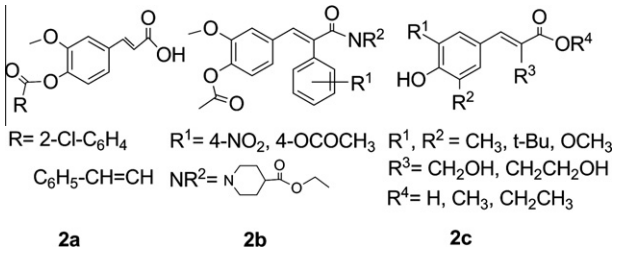


Figure 2. Active *p*-hydroxycinnamic acid derivatives reported.

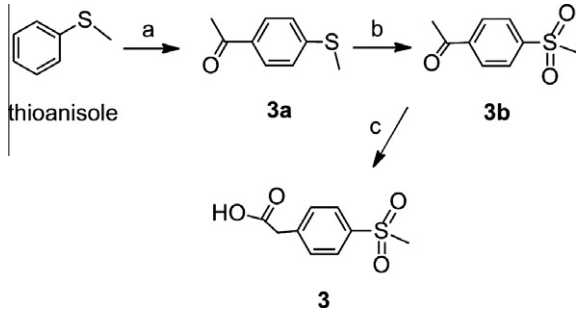
represent strong 5-LOX inhibitory effect.[11,12] Dual inhibitors of the COX-2 and 5-LOX pathways may provide safer NSAIDs, and the simultaneous modulation of them may reduce the cardiovascular risk of COX inhibitors.[13–15]

For the synthesis of *p*-hydroxybenzene acrylic acid derivatives, substituted phenylacetic acids are condensated with substituted benzaldehydes to give α-phenylcinnamic acid derivatives through the amine-catalyzed Perkin condensation.[16,17]

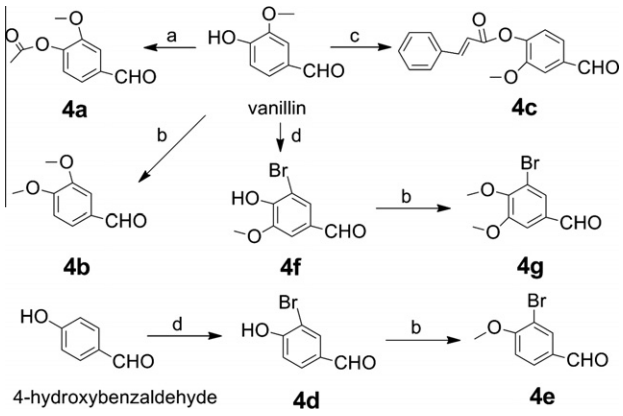
4-Methylsulfonylphenylacetic acid (**3**) is an important intermediate, prepared by the way as shown in Scheme 1. It was carried out by converting acetophenone to phenylacetic acid through the Willgerodt rearrangement.[18,19] 4-Methylmercaptoacetophenone (**3a**) was prepared by acidation of thioanisole on the *para*-position through the Friedel–Crafts reaction, then oxidized to 4-methylsulfonylacetophenone (**3b**).[20–22] A mixture of **3b**, sulfur, and morpholine was refluxed for 10 h, and then treated with sodium hydroxide for 10 hours, finally acidified, gave the 4-methylsulfonylphenylacetic acid.[23]

The synthesis of substituted benzaldehydes is depicted in Scheme 2. Acylation of vanillin with acetyl chloride gave **4a**.[24] Similarly treatment with cinnamic acid and thionyl chloride yielded **4c**. Alkylation of vanillin with dimethyl sulfate in alkaline conditions gave **4b**.[25] Bromination of 4-hydroxybenzaldehydes with bromine in methanol at low temperature yielded **4d** and **4f**,[26,27] which was followed by treatment with dimethyl sulfate to give **4e** and **4g**.

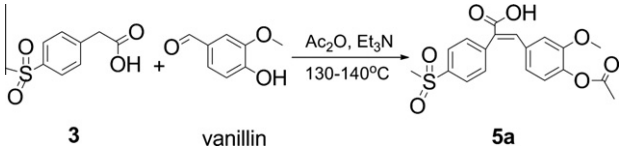
The synthesis of (*E*)-2-(4-methylsulphonylphenyl)-3-(3-methoxyl-4-acetoxylphenyl) acroleic acid (**5a**) is shown in Scheme 3.



Scheme 1. Synthesis of 4-methylsulfonylphenylacetic acid (**3**). Reagents and conditions: (a) $AlCl_3$, CH_3COCl, $CHCl_3$, rt, 2 h, **3a** 90.0% (mp 80–81 °C); (b) H_2O_2, H_3PO_4, CH_3COOH, reflux, 3 h, **3b** 96% (mp 126–127 °C); (d) (i) S, morpholine, 130 °C, 10 h; (ii) NaOH solution, 85 °C, 10 h, **3** 52% (mp 135–136 °C).



Scheme 2. Synthesis of substituted benzaldehydes. Reagents and conditions: (a) CH_3COCl, alcohol, 80 °C, 1 h, **4a** 91% (mp 77–78 °C); (b) methyl sulfate, 10%NaOH solution, reflux, 2 h, **4b** 78% (mp 42–43 °C), **4e** 94% (mp 43–44 °C), **4g** 82% (mp 60–61 °C); (c) cinnamic acid, $SOCl_2$, 80 °C, 3 h, **4c** 85% (mp 89–90 °C); (d) Br_2, methanol, rt, 3 h, **4d** 65% (mp 123–124 °C), **4f** 86.5% (mp 163–164 °C).



Scheme 3. Perkin condensation of phenylacetic acids with benzaldehydes.

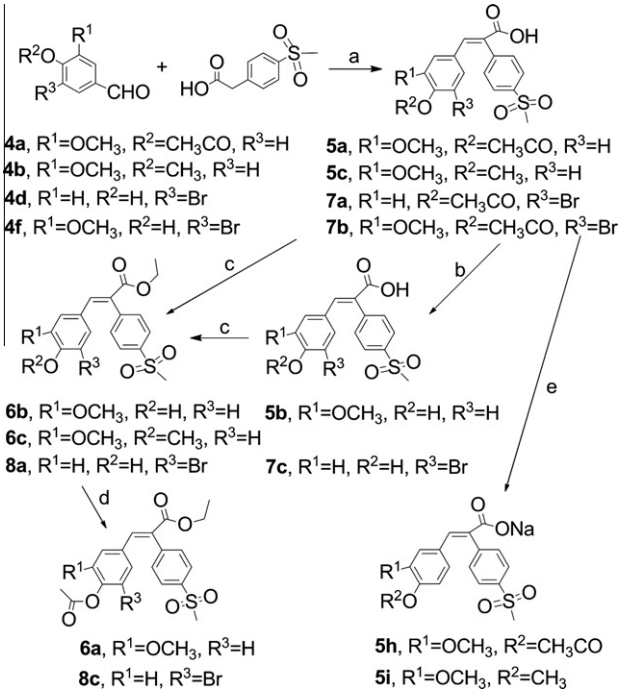
A mixture of **3**, **4a**, acetic anhydride, and triethylamine was heated to 140 °C and then acidified, filtered and dried, gave **5a** as a off-white solid, and **5a** was also obtained by condensated **3** with vanillin in the similar conditions. If **5a** was hydrolyzed in the solution of sodium hydroxide, then the acetyl was eliminated and **5b** was achieved. Compound **5c** was achieved from **3** and **4b** in the similar conditions.

If the **3** was first esterified, gave ethyl 4-methylsulfonyphenylacetate, and then condensated with vanillin, but somehow **6a** or **6b** can not be obtained. Therefore, **6b** was first achieved by esterification of **5a** or **5b** in ethanol catalyzed by concentrated sulfuric acid, subsequent treatment with acetic anhydride, ultimately yielded **6a**. Compound **6f** was obtained by esterification of **5a** in methanol similar to **6b**. Compounds **5h** and **5i** were obtained from treatment of **5a** and **5c** at appropriate temperature and basic conditions. Other α-phenylcinnamic acid derivatives were accomplished by the amine-catalyzed Perkin condensation of phenylacetic acids with benzaldehydes according to the corresponding methods as shown in Scheme 4.

In order to observe the activity of methylsulfonyl group of the α-position benzene ring and the *p*-hydroxyl group of the β-position benzene ring, no methylsulfonyl group of **9a**, **9b**, **9c** and no *p*-hydroxyl group of **9d** were synthesized. **9a** was obtained from phenylacetic acid and vanillin by a procedure similar to **5a**, then hydrolyzed in the solution of sodium hydroxide gave **9b**, and then methylated with dimethyl sulfate in alkaline conditions gave **9c**. Compound **9d** was obtained from **3** and benzaldehyde by a procedure also similar to **5a**.

Based on the ferulic acid, a series of 4-hydroxybenzene acrylic acid derivatives (Table 1) were designed and synthesized, and 26 of them were not reported in literatures. These compounds were determined by spectra, and they are the (*E*)-isomers, bearing a α,β-double bond of acrylic acid bridging the two aromatic rings in a *cis*-position. The (*Z*)-isomers have not been obtained.

Ketcham et al. reported that the triethylamine-catalyzed phenylacetic acids with benzaldehydes in acetic anhydride, afforded



Scheme 4. Synthesis of target compounds. Reagents and conditions: (a) Ac_2O, Et_3N, 130–140 °C, 3 h; (b) NaOH solution, 80 °C, 0.5 h; (c) alcohol, 98% H_2SO_4, 90 °C, 5 h; (d) Ac_2O, 130–140 °C, 3 h; (e) NaOH solution, 30 °C, 0.5 h.

'*trans*-isomer' of α-phenylcinnamic acids, but in about half of the condensations reported none of the '*cis*-isomer' has been obtained.[16] The '*trans*-isomer' had a lower solubility and a higher melting point than the '*cis*-isomer' in each pair. The '*trans*-isomer', which was ambiguous as it may refer to the structure of cinnamic acid in his literature, and which was just corresponding to the (*E*)-isomer rather than the (*Z*)-isomer, was precisely the structure of two aromatic rings in a *cis*-position of double bond. The structure can be proved by the data that the melting point of compound (I), α-phenylcinnamic acid, '*trans*-isomer' was 172–173 °C in his literature, which was matched with the '*cis*-isomer' (172–173 °C) in the other literature.[28] The compound **9b** synthesized by the reaction system has a melting point of 186–188 °C, also reported as the (*E*)-isomer.[29]

In addition, it is quite possible to perform analysis of the structure by the ^{1}H NMR. The isolated hydrogen of the double bond (Ph–CH=C–Ph) in the α-phenylcinnamic acid has a displacement in the (*E*)-isomer is larger than in the (*Z*)-isomer, its displacement is about 7.95 (D_2O) or 7.80 (DMSO), single for the (*E*)-isomer more than 7.08 (D_2O), single for the (*Z*)-isomer.[30,31] About these target compounds, the isolated hydrogen have a similar displacement about 7.85 (DMSO) in **5a** by the 2D NMR of HMQC analysis as shown in Figure 3, 7.74 (DMSO) in **5b** (deacetylated from **5a**), 7.85 ($CDCl_3$) in **6b** (esterified from **5a**), 7.87 ($CDCl_3$) in **6f** (esterified from **5a**), and 7.56 (D_2O) in **5h** (the salt of **5a**), which are very close to the data of the (*E*)-isomer.[32]

Stereochemistry of double bond in these compounds can also be determined spectroscopically. The displacement of olefinic proton is 7.87 ($CDCl_3$), and the methyl esters is 3.82 ($CDCl_3$) in **6f**.[33] The correlation between olefinic proton and methyl ester in **6f** (esterified from **5a**) typically reveal two benzene rings being '*cis*' to each other and the stereochemistry of the (*E*)-isomer by the 2D NMR of NOESY analysis as shown in Figure 4.

The anti-inflammatory activity of compounds were tested through a xylene-induced ear edema mouse model method.[34] Kunming mice, consisting of both males and females, each weighing

Table 1
Structure and melting point of compounds designed

Compd	R^1	R^{2a}	R^3	R^4	R^5	Mp (°C)
*Formula (**1**)*						
5a	CH_3O	$CH_3C(=O)O$	H	H	SO_2CH_3	225–226
5b	CH_3O	HO	H	H	SO_2CH_3	222–223
5c	CH_3O	CH_3O	H	H	SO_2CH_3	232–233
5d	CH_3O		H	H	SO_2CH_3	250–251
5e	CH_3O	H	CH_3O	H	SO_2CH_3	220–221
5f	H	$CH_3C(=O)O$	H	H	SO_2CH_3	213–214
5g	H	HO	H	H	SO_2CH_3	219–220
5h	CH_3O	$CH_3C(=O)O$	H	Na	SO_2CH_3	197–199
5i	CH_3O	CH_3O	H	Na	SO_2CH_3	251–253
6a	CH_3O	$CH_3C(=O)O$	H	CH_2CH_3	SO_2CH_3	129–130
6b	CH_3O	HO	H	CH_2CH_3	SO_2CH_3	178–179
6c	CH_3O	CH_3O	H	CH_2CH_3	SO_2CH_3	163–164
6d	CH_3O		H	CH_2CH_3	SO_2CH_3	171–173
6e	CH_3O	H	CH_3O	CH_2CH_3	SO_2CH_3	134–135
6f	CH_3O	HO	H	CH_3	SO_2CH_3	170–171
7a	H	$CH_3C(=O)O$	Br	H	SO_2CH_3	210–212
7b	CH_3O	$CH_3C(=O)O$	Br	H	SO_2CH_3	224–226
7c	H	HO	Br	H	SO_2CH_3	216–218
7d	CH_3O	HO	Br	H	SO_2CH_3	225–227
8a	H	HO	Br	CH_2CH_3	SO_2CH_3	110–111
8b	CH_3O	HO	Br	CH_2CH_3	SO_2CH_3	171–172
8c	H	$CH_3C(=O)O$	Br	CH_2CH_3	SO_2CH_3	103–105
8d	CH_3O	$CH_3C(=O)O$	Br	CH_2CH_3	SO_2CH_3	148–150
9a	CH_3O	$CH_3C(=O)O$	H	H	H	205–207
9b	CH_3O	HO	H	H	H	186–188
9c	CH_3O	CH_3O	H	H	H	228–229
9d	H	H	H	H	SO_2CH_3	229–230

[a] $R^{2\prime} = OR^2$, in Figure 1, formula (1).

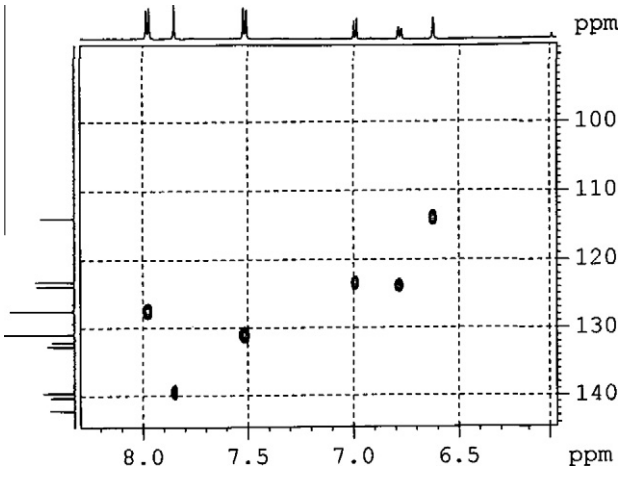


Figure 3. 2D NMR of HMQC analysis of **5a**.

18–22 g, are divided into groups of 10 at random. The tested compounds and indomethacin which are made into suspensions using 5‰ CMC-Na are administered orally to the dose group and the positive control group, respectively, while the base control group is treated with only 5‰ CMC-Na. One hour later after administration,

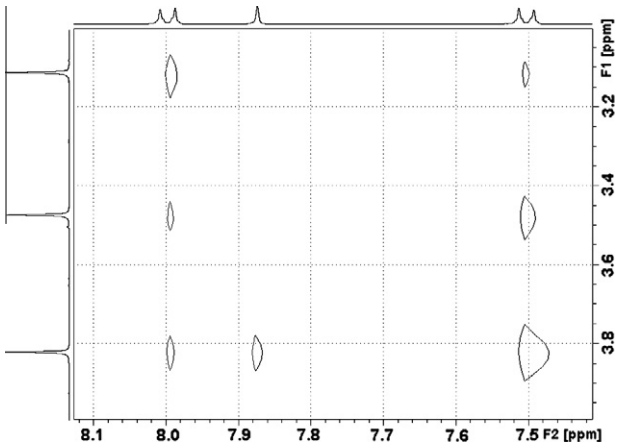


Figure 4. 2D NMR of NOESY analysis of **6f** (esterified from **5a**).

Table 2
Anti-inflammatory activity of the test compounds

Compd	Dose (mg/kg)	Mice	Ear swelling levels	Suppression rates (%)
Base control	—	9	22.36 ± 3.30	—
Indometacin	100	10	14.08 ± 3.94**	37.03
5a	300	10	10.87 ± 1.79**	45.29
	150	10	14.68 ± 4.16*	26.12
	75	10	17.41 ± 4.82	12.38
5f	300	10	12.35 ± 3.22**	44.75
	150	10	15.01 ± 2.45**	32.87
	75	10	17.14 ± 2.51*	23.34
5b	300	9	21.14 ± 3.7	9.97
5c	300	10	18.74 ± 1.82*	15.92
5e	300	10	16.70 ± 2.63	10.60
6a	300	10	15.74 ± 1.43**	24.11
6b	300	10	15.35 ± 4.26*	34.62
8c	75	10	20.97 ± 2.77	0
9a	300	10	17.47 ± 3.29*	21.86
9d	300	10	18.45 ± 2.81*	17.49

Results are expressed in mean ± SD, significance levels.
* P <0.05.
** P <0.01, as compared with the base control group. Experiments were completed in twice.

Table 3
Cardiac toxicity of the test compounds

Compd	Dose* (mg/kg)	Mice	Toxic deaths	Toxic signs	Myocardial lesions
Base control	—	10	1/10	NTS[a]	NTS
Indometacin	100	10	0/10	NTS	NTS
5a	150	10	0/10	NTS	NTS
6a	150	10	1/10	NTS	NTS

NTS: no tangible symptoms.
[a] Single, every other day, a total of six times.

50 μL of xylene is applied to both sides of right ears of the mice, while left ears are left untreated as control. Another hour later after swelling is induced, mice were killed and each of the two auricles from a mouse is fetched with an 8 mm punching device and weighed. The anti-inflammatory activity of each tested compound is assessed through the suppression rate of ear swelling level.

The structure–function relationship, as revealed by the anti-inflammatory activity from animal experiments associated with the test compounds (Table 2), may be summarized as follows.

(1) The *p*-hydroxyl group with pharmacological activity proposed by 4-hydroxystyrene derivatives, contributes to activity, as its absence in **5e** and **9d** is associated with decreased suppression rates of 10.60% and 17.49% at a dose of 300 mg/kg, respectively, when compared with the 15.92% and 44.75% of **5c** and **5f** at the same dose, respectively. (2) Acylation of the *p*-hydroxyl group significantly improves anti-inflammatory activity, as the suppression rate of **5a** is 45.29% at a dose of 300 mg/kg, while that of **5b** is only 9.97%. (3) When the same *p*-hydroxyl group is alkylated to a methoxy in **5c**, the suppression rate of 15.92% is higher than that of the untreated **5b**, but not as high as that of the acetylated **5a**. (4) Esterification of the carboxyl group on the double bond, also on the incorporated ferulic acid, improves anti-inflammatory activity, as exemplified by the suppression rate of 34.62% of **6b**, compared with that of **5b**. (5) When bromine is introduced into the structure, anti-inflammatory activity will be lost, as shown in **8c**. (6) If the methylsulfonyl group ($-SO_2CH_3$) on the *p*-position of the ring, which is not derived from ferulic acid and which has been proved by the diaryl heterocyclic inhibitors to impart selective inhibition effects on cyclooxygenases, is removed, some anti-inflammatory activity is retained as is shown by 21.86% of **9a**, but it is clearly lower than that of **5a**.

In the cardiac toxicity experiments, the groups are administered orally every other day, a total of six times.[35] Compounds are treated similarly to anti-inflammatory activity. The growth and behavior of mice is observed, such as condition of hair coat, eating, and activities. All the mice anesthetized with sodium pentobarbital are killed by cervical dislocation at the 12th day, atria are isolated immediately after death, and are washed in phosphate buffered saline, and the left ventricular fragments are prepared for electron microscopy. The myocardial lesion is evaluated by examination on the pathologic changes of transverse and longitudinal sections of the whole ventricle between the groups. There is no tangible results for toxicity signs, such as reducing of activities, decreased eating, loose fur, loss of hair and so on between the control group and the dose groups (Table 3). The spectra of myocardial tissue are also no significant difference or abnormal changes in the groups.

In conclusion, a series of 4-hydroxybenzene acrylic acid derivatives of formula (**1**) were designed and synthesized, the presented compound **5a**, **5f** and **6a** have significant anti-inflammatory activity with suppression rates of 45.29%, 44.75% and 24.11%, respectively, compared with that of indomethacin. The structure–function relationship shows that the *p*-hydroxyl group on the α-position benzene ring, particularly if acetylated, contributes to the considerable anti-inflammatory activity; that the carboxyl group on the double bond, if esterified, also contributes to the anti-inflammatory activity; that the *p*-methylsulfonyl group on the other benzene ring, whose introduction is due to the COX-2 selectivity, also contributes to anti-inflammatory activity surprisingly.

The cardiac toxicity of the tested compounds are not observed, and the spectra of myocardial tissue are no significant difference and abnormal changes between the dose group and the base control group. The NSAIDs, especially such as rofecoxib and celecoxib, are associated with risk of cardiovascular events, which is a long slow process. The mechanism of action for the potential risk is still uncertain. To establish a feasible model for exact experiments of these compounds is difficult in short periods of time, but cardiac toxicity is not observed, it is possibly matched with anti-inflammatory and cardiovascular activity of these derivatives.

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33. Compound **6b,** ^{1}H NMR(BRUKER, 400 MHz, $CDCl_3$): δ 1.31 (3H, t, $-CH_2CH_3$), 3.10 (3H, s, $-SO_2CH_3$), 3.47 (3H, s, $-OCH_3$), 4.29 (2H, q, $-CH_2CH_3$), 7.86 (1H, s, C═C–H); **6f**, ^{1}H NMR(BRUKER, 400 MHz, $CDCl_3$): 3.11 (3H, s, $-SO_2CH_3$), 3.47 (3H, s, $-OCH_3$), 3.82 (3H, s, $-COOCH_3$), 7.87 (1H, s, C═C–H).
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