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Synthesis and biological evaluation of amide derivatives of diflunisal as potential anti-inflammatory agents

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ABSTRACT

To improve the medicinal activity, the structure of diflunisal has been modified. Twenty-one amide derivatives of diflunisal were synthesized starting from diflunisal in three steps with total yields from 72% to 89%. All compounds were identified by ^{1}H NMR, MS, and elemental analysis. The anti-inflammatory and analgesic activities for 19 compounds were evaluated. It was found that **5m** possesses an excellent anti-inflammatory activity and a good analgesic activity, maybe a potential anti-inflammatory agent.

Fluorine-containing non-steroid anti-inflammatory drugs have been attractive for their special properties.[1–3] Diflunisal (**1**, CAS 22494-42-4), 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid, has been approved worldwide as therapeutics for the treatment of inflammation and pain.[4,5] Recently, the modifications of the chemical structure of **1** were studied. For example, 3-(1,3-dihydro-2*H*-isoindol-2-ylcarbonyl)-2′,4′-difluorobiphenyl-4-ol was synthesized and reported to have the H3P-90 inhibition, and H3P-90 in abnormal cells, such as in cancer cells would damage the regulation of signal transduction network.[6] Yu reported that esterification or amidation of **1** could increase their solubility and absorption in vivo, and some of them have even better analgesic activity than that of dilunisal.[7] Some changes in the carboxyl group of **1** also showed good antimycobacterial, antiviral and antimicrobial activities.[8] Roberts found that *O*-aryl esters of **1**, especially lipophilic esters, possess large permeability surface area and tissue distribution value.[9]

Our group have studied the synthesis and the SAR of fluorine-containing non-steroid anti-inflammatory drugs, and patented that some amides of fluorine-containing benzoic acid possessed good anti-inflammatory activity.[10,11]

In continuation of our research, the modification of diflunisal was studied by esterification of the hydroxyl group and amidation of the carboxylic group. We designed and synthesized 17 amide derivatives of *O*-acetyldiflunisal or *O*-benzoyldiflunisal, **5a–5q,** and evaluated their anti-inflammatory and analgesic activity. Accidentally, four amide derivatives of **1**, **5r–5u**, were obtained in the same way when **3a** (R = CH_3) was reacted with a secondary amine in amidation, such as dimethylamine, diethylamine, *N*-methylpiperazine or *N*-ethylpiperazine, because the four secondary amines are stronger alkaline and promoted the hydrolyzation of acetates. The 21 amides were synthesized from 72% to 89% in total yield. The synthetic route is shown in Scheme 1. Starting from 1, esterification of phenolic hydroxy group and amidation of carboxylic acid gave desired product 5. The preparations are summarized in Table 1. The structures of all compounds were identified by IR, ^{1}H NMR, MS, and elemental analysis (Table 2).[12,13] The crystal structure of **5a** was determined by X-ray.[14]

The anti-inflammatory and analgesic activities for these compounds (**2**, **5a–5q**) were evaluated by xylene induced mice ear edema and acetic acid induced mice writhing models for male and female Kunming mice (weight 20–26 g). The substances were administrated via the oral route at the dose of 40 mg kg^{-1}. The diflunisal, a registered anti-inflammatory drug, ED_{50} 59.6 mg kg^{-1} on carragegenin-induced paw edema in rats,[15,16] was used as a positive control. The results of the evaluation of anti-inflammatory and analgesic activity are summarized on Table 3. The ED_{50} on active compounds was determined and the results were listed in Table 4. The ED_{50} for **5m** and **5p** on xylene induced mice ear edema model is 24.24 and 25.69 mg kg^{-1} and for **5m** and **5q** on acetic acid induced mice writhing model is 43.79 and 11.58 mg kg^{-1}.

From Table 3, it could be found that the inhibition on xylene induced mice ear edema model of **5m**, **5p**, **5a**, and **5i** is 68.86%, 65.20%, 48.83%, and 41.37% relatively, superior to diflunisal 39.85% at the dose of 40 mg kg^{-1}. Comparing **2b**, **5m**, **5n**, and **5o** with **2a**, **5a**, **5e**, and **5f** relatively, the biological activity of **5m** is superior to **5a** in both anti-inflammatory and analgesic activity

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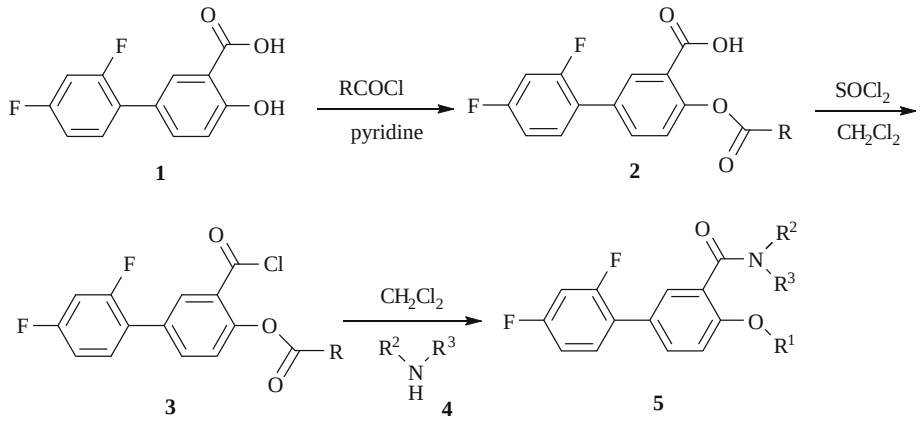

Scheme 1. Route of synthesis.

Table 1
Synthesis of compounds (**5**)

Compound	R^1	R^2	R^3	Yield (%)	Mp (°C)
5a	$COCH_3$	H	CH_3	81	157–160
5b	$COCH_3$	H	CH_2CH_3	77	110–112
5c	$COCH_3$	H	Cyclohexyl	73	159–162
5d	$COCH_3$	H	$CH_2C_6H_5$	81	134–136
5e	$COCH_3$	H	C_6H_5	87	152–155
5f	$COCH_3$	H	*o*-$C_6H_4CH_3$	85	166–169
5g	$COCH_3$	H	*m*-$C_6H_4CH_3$	81	123–125
5h	$COCH_3$	H	*p*-$C_6H_4CH_3$	89	164–167
5i	$COCH_3$	H	*o*-C_6H_4Cl	84	159–163
5j	$COCH_3$	H	*p*-C_6H_4Cl	84	183–186
5k	$COCH_3$	H	2,5-$(CH_3)_2C_6H_3$	81	109–112
5l	$COCH_3$	H	Morpholine-4-yl	76	124–126
5m	COC_6H_5	H	CH_3	75	147–150
5n	COC_6H_5	H	C_6H_5	84	139–140
5o	COC_6H_5	H	*o*-$C_6H_4CH_3$	86	165–168
5p	COC_6H_5	CH_2CH_3	CH_2CH_3	72	125–128
5q	COC_6H_5		4-Methylpiperazin-1-yl	83	154–157
5r	H	CH_3	CH_3	76	123–125
5s	H	CH_2CH_3	CH_2CH_3	73	139–141
5t	H		4-Methylpiperazin-1-yl	74	95–97
5u	H		4-Ethylpiperazin-1-yl	77	142–143

and others are nearly equal to each partner. Therefore, the compound containing *O*-benzoyl group may have a good biological activity.

Additionally, it indicates that the substituted groups on amide could affect the anti-inflammatory activity. It was found that the alkyl group benefits as increase as following: $CH_3 > CH_2C_6H_5 > CH_2CH_3$, and the aryl group are more complex. It was discovered that the compounds with such electron-donating group (CH_3 group) seems to benefit as increase as following: *para* > *ortho* > *meta*, and the compounds with electro-withdrawing group (Cl group) is *ortho* > *para*. But it needs more data to find the relationship.

From Table 3, it could also be found that the inhibition on acetic acid induced mice writhing model of **5q** and **5m** is 88.33% and 47.50% at the dose of 40 mg kg^{-1}. Additionally, it indicates that the substituted groups on amide could also affect the analgesic activity and the compound with hetero-atom on amide group is better than others in analgesic activity. The effect of substituted group on the analgesic activity seems more complex than on the anti-inflammatory activity.

On the whole, it seems a trend that the substituted groups on the either amide or ester could affect on the inflammatory activity

Table 2
Elemental analysis (calcd data in parentheses) and ^{1}H NMR data (in $CDCl_3$) of new compounds

Compound	Elemental analysis (%)			^{1}H NMR (δ, ppm)
	C	H	N	
5a	62.86 (62.95)	4.36 (4.29)	4.49 (4.59)	2.36 (s, 3H, $COCH_3$), 2.99 (d, 3H, *J* = 4.8 Hz, N-CH_3), 6.25 (s, 1H, –NH), 6.94 (m, 2H, 3′,5′-CH), 7.18 (d, 1H, *J* = 8.4 Hz, 5-CH), 7.40 (q, 1H, *J* = 7.6 Hz, 6′-CH), 7.59 (d, 1H, *J* = 8.4 Hz, 6-CH), 7.84 (s, 1H, 2-CH)
5b	63.83 (63.95)	4.82 (4.74)	4.31 (4.39)	1.24 (t, 3H, *J* = 7.2 Hz, –CH_3), 2.34 (s, 3H, –$COCH_3$), 3.47 (m, 2H, –CH_2), 6.25 (s, 1H, –NH), 6.94 (m, 2H, 3′,5′-CH), 7.17 (d, 1H, *J* = 8.4 Hz, 5-CH), 7.40 (q, 1H, *J* = 7.6 Hz, 6′-CH), 7.59 (d, 1H, *J* = 8.4 Hz, 6-CH), 7.84 (s, 1H, 2-CH)
5c	67.43 (67.55)	5.73 (5.67)	3.67 (3.75)	1.24 (m, 3H, 3″,4″,5″-CH), 1.44 (q, 2H, *J* = 5.0 Hz, 3″,5″-CH), 1.66 (m, 1H, 4″-CH), 1.74 (m, 2H, 2″,6″-CH), 2.02 (m, 2H, 2″,6″-CH), 2.36 (s, 3H, –CH_3), 3.96 (m, 1H, 1″-CH), 6.13 (d, 1H, *J* = 7.5 Hz, –NH), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.96 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.16 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.41 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.58 (d, 1H, *J* = 8.5 Hz, 6-CH), 7.84 (s, 1H, 2-CH)
5d	69.22 (69.29)	4.55 (4.49)	3.56 (3.67)	2.08 (s, 3H, –CH_3), 4.61 (d, 2H, *J* = 5.5 Hz, –CH_2), 6.63 (s, 1H, N-H), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.97 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.16 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.35 (q, 1H, *J* = 8.5 Hz, 6′-CH), 7.38 (m, 5H, –C_6H_5), 7.59 (s, 1H, 2-CH), 7.94 (d, 1H, *J* = 8.4 Hz, 6-CH)
5e	68.60 (68.66)	4.19 (4.12)	3.75 (3.81)	2.37 (s, 3H, –CH_3), 6.94 (m, 2H, 3′,5′-CH), 7.17 (d, 1H, *J* = 8.0 Hz, 5-CH), 7.25 (q, 1H, *J* = 8.0 Hz, 4″-CH), 7.40 (m, 3H, 6′,3″,5″-CH), 7.64 (m, 3H, 6, 2″,6″-CH), 7.98 (s, 1H, 2-CH), 8.07 (s, 1H, –NH)
5f	69.23 (69.29)	4.54 (4.49)	3.60 (3.67)	2.34 (s, 3H, –CH_3), 2.37 (s, 3H, –CH_3), 6.95 (t, 1H, *J* = 8.5 Hz, 3′-CH), 7.00 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.15 (t, 1H, *J* = 7.5 Hz, 4″-CH), 7.25 (d, 1H, *J* = 7.5 Hz, 5-CH), 7.27 (d, 1H, *J* = 8.5 Hz, 6″-CH), 7.28 (t, 1H, *J* = 8.5 Hz, 5″-CH), 7.46 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.67 (d, 1H, *J* = 8.5 Hz, 3″-CH), 7.83 (s, 1H, 2-CH), 7.95 (d, 1H, *J* = 7.5 Hz, 6-CH), 8.00 (s, 1H, –NH)
5g	69.23 (69.29)	4.55 (4.49)	3.58 (3.67)	2.36 (s, 3H, –CH_3), 2.37 (s, 3H, –CH_3), 6.95 (m, 2H, 3′,5′-CH), 6.99 (d, 1H, *J* = 7.6 Hz, 4″-CH), 7.24 (d, 1H, *J* = 8.0 Hz, 5-CH), 7.27 (t, 1H, *J* = 7.6 Hz, 4″-CH), 7.36 (d, 1H, *J* = 7.6 Hz, 6″-CH), 7.43 (q, 1H, *J* = 7.6 Hz, 6′-CH), 7.51 (s, 1H, 2″-CH), 7.65 (d, 1H, *J* = 8.4 Hz, 6-CH), 7.97 (s, 1H, 2-CH), 8.01 (s, 1H, –NH)
5h	69.21 (69.29)	4.54 (4.49)	3.61 (3.67)	2.36 (s, 3H, –CH_3), 2.38 (s, 3H, –CH_3), 6.95 (m, 2H, 3′,5′-CH), 7.19 (d, 2H, *J* = 7.6 Hz, 3″,5″-CH), 7.25 (d, 1H, *J* = 8.0 Hz, 5-CH), 7.43 (q, 1H, *J* = 7.6 Hz, 6′-CH), 7.51 (d, 2H, *J* = 8.0 Hz, 2″,6″-CH), 7.65 (d, 1H, *J* = 8.4 Hz, 6-CH), 7.99 (s, 1H, 2-CH), 8.01 (s, 1H, –NH)

(*continued on next page*)

Table 2 (*continued*)

Compound	Elemental analysis (%)			^{1}H NMR (δ, ppm)
	C	H	N	
5i	62.70 (62.78)	3.56 (3.51)	3.43 (3.49)	2.41 (s, 3H, $-CH_3$), 6.96 (m, 2H, 3′,5′-CH), 7.10 (t, 1H, *J* = 7.6 Hz, 4″-CH), 7.28 (d, 1H, *J* = 8.0 Hz, 5-CH), 7.34 (t, 1H, *J* = 8.0 Hz, 5″-CH), 7.44 (m, 2H, *J* = 8.0 Hz, 6′,3″-CH), 7.68 (d, 1H, *J* = 8.4 Hz, 6-CH), 8.10 (s, 1H, 2-CH), 8.58 (d, 1H, *J* = 8.4 Hz, 6″-CH), 8.78 (s, 1H, –NH)
5j	62.71 (62.78)	3.57 (3.51)	3.42 (3.49)	2.36 (s, 3H, $-CH_3$), 6.95 (m, 2H, 3′,5′-CH), 7.25 (d, 1H, *J* = 8.0 Hz, 5-CH), 7.34 (d, 2H, *J* = 8.4 Hz, 3″,5″-CH), 7.43 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.57 (d, 2H, *J* = 8.4 Hz, 2″,6″-CH), 7.66 (d, 1H, *J* = 8.0 Hz, 6-CH), 7.97 (s, 1H, 2-CH), 8.06 (s, 1H, –NH)
5k	69.78 (69.87)	4.92 (4.84)	3.43 (3.54)	2.29 (s, 3H, CO-CH_3), 2.37 (s, 6H, Ph-CH_3), 6.94 (d, 1H, *J* = 8.5 Hz, 3′-CH), 6.96 (d, 1H, *J* = 8.0 Hz, 4″-CH), 7.00 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.13 (d, 1H, *J* = 8.0 Hz, 3″ –CH), 7.26 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.46 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.67 (d, 1H, *J* = 8.0 Hz, 6-CH), 7.79 (s, 2H, 2,6″-CH), 8.00 (s, 1H, –NH)
5l	63.04 (63.15)	4.83 (4.74)	3.79 (3.88)	2.32 (s, 3H, $-CH_3$), 3.40 (t, 2H, *J* = 5.0 Hz, 2″,6″-CH), 3.63 (t, 2H, *J* = 5.0 Hz, 2″,6″-CH), 3.75 (m, 4H, 3″,5″-CH_2), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.97 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.26 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.36 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.43 (s, 1H, 2-CH), 7.55 (d, 1H, *J* = 8.5 Hz, 6-CH)
5m	68.49 (68.66)	4.14 (4.12)	3.70 (3.81)	2.89 (d, 3H, *J* = 4.8 Hz, CH_3), 6.36 (s, 1H, NH), 6.94 (t, 1H, *J* = 8.4 Hz, 3′-H), 7.00 (t, 1H, *J* = 8.2 Hz, 5′-H), 7.31 (d, 1H, *J* = 8.4 Hz, 5-H), 7.45 (q, 1H, *J* = 7.6 Hz, 7.56 (t, 2H, *J* = 7.6 Hz, 3″,5″-H), 7.65 (d, 1H, *J* = 8.4 Hz, 6-H), 7.69 (t, 1H, *J* = 7.6 Hz, 4″-H), 7.94 (s, 1H, 2-H), 8.27 (d, 2H, *J* = 6.8 Hz, 2″,6″-H)
5n	72.59 (72.72)	4.01 (3.99)	3.19 (3.26)	6.96 (t, 1H, *J* = 8.4 Hz, 3′-H), 7.00 (t, 1H, *J* = 8.4 Hz, 5′-H), 7.08 (t, 1H, *J* = 7.6 Hz, 4‴-H), 7.26 (t, 2H, *J* = 8.0 Hz, 3‴,5‴-H), 7.37 (d, 1H, *J* = 8.0 Hz, 5-H), 7.45 (d, 2H, *J* = 7.6 Hz, 2‴,6‴-H), 7.47 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.55 (t, 2H, *J* = 7.6 Hz, 3″,5″-H), 7.69 (t, 1H, *J* = 7.6 Hz, 4″-H), 7.72 (d, 1H, *J* = 8.0 Hz, 6-H), 8.10 (s, 1H, 2-H), 8.23 (s, 1H, NH), 8.24 (d, 2H, *J* = 7.2 Hz, 2″,6″-H)
5o	73.27 (73.13)	4.40 (4.32)	3.13 (3.16)	2.18 (s, 3H, CH_3), 6.96 (t, *J* = 8.4 Hz, 1H, 3′-H), 7.00 (t, 1H, *J* = 8.0 Hz, 5′-H), 7.07 (t, 1H, *J* = 7.2 Hz, 4‴-H), 7.14 (d, 1H, *J* = 7.6 Hz, 3‴-H), 7.20 (t, 1H, *J* = 6.8 Hz, 5‴-H), 7.36 (d, 1H, *J* = 8.4 Hz, 5-H), 7.48 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.53 (t, 2H, *J* = 7.6 Hz, 3″,5″-H), 7.68 (t, 1H, *J* = 7.6 Hz, 4″-H), 7.72 (d, 1H, *J* = 8.4 Hz, 6-H), 7.85 (d, 1H, *J* = 8.4 Hz, 6‴-H), 7.90 (s, 1H, –NH), 8.09 (s, 1H, 2-H), 8.22 (d, 2H, *J* = 7.2 Hz, 2″,6″-H)
5p	70.48 (70.41)	5.08 (5.17)	3.30 (3.42)	1.02, 1.08 (t, t, 6H, *J* = 7.2 Hz, CH_3), 3.24 (m, 4H, CH_2), 6.94 (t, 1H, *J* = 8.4 Hz, 3′-H), 6.98 (t, 1H, *J* = 8.4 Hz, 5′-H), 7.43 (d, 1H, *J* = 8.4 Hz, 5-H), 7.43 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.50 (t, 3H, *J* = 7.6 Hz, 2,3″,5″-H), 7.58 (d, 1H, *J* = 8.0 Hz, 6-H), 7.64 (t, 1H, *J* = 8.0 Hz, 4″-H), 8.18 (d, 2H, *J* = 7.2 Hz, 2″,6″-H)
5q	66.37 (66.51)	5.30 (5.13)	9.16 (9.31)	2.20 (s, 3H, $-CH_3$), 2.28 (t, 4H, *J* = 4.2 Hz, 3‴-CH_2), 3.38, 3.720 (t, t, 4H, *J* = 4.8 Hz, 2‴-CH_2), 6.94 (t, 1H, *J* = 8.0 Hz, 3′-H), 6.97 (t, 1H, *J* = 8.0 Hz, 5′-H), 7.42 (d, 1H, *J* = 8.4 Hz, 5-H), 7.42 (q, 1H, *J* = 8.0 Hz, 6′-H), 7.49 (s, 1H, 2-H), 7.51 (t, 2H, *J* = 8.0 Hz, 3″,5″-H), 7.60 (d, 1H, *J* = 8.0 Hz, 6-H), 7.65 (t, 1H, *J* = 7.6 Hz, 4″-H), 8.18 (d, 2H, *J* = 8.0, 2″-H);
5r	64.92 (64.98)	4.78 (4.73)	4.97 (5.05)	3.21 (s, 6H, N-CH_3), 6.93 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.95 (d, 1H, *J* = 8.5 Hz, 5′-CH), 7.10 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.36 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.46 (d, 1H, *J* = 8.5 Hz, 6-CH), 7.50 (s, 1H, 2-CH), 10.08 (s, 1H, OH)
5s	66.80 (66.87)	5.69 (5.61)	4.52 (4.59)	1.31 (t, 6H, *J* = 7.0 Hz, $-CH_3$), 3.59 (q, 4H, *J* = 7.0 Hz, N-CH_2), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.96 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.10 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.36 (q, 1H, *J* = 8.0 Hz, 6′-CH), 7.45 (d, 1H, *J* = 8.5 Hz, 6-CH), 7.49 (s, 1H, 2-CH), 10.08 (s, 1H, OH)
5t	64.98 (65.05)	5.56 (5.46)	8.38 (8.43)	2.35 (s, 3H, $-CH_3$), 2.50 (t, 4H, *J* = 5.0 Hz, 3″,5″-CH_2), 3.80 (t, 4H, *J* = 5.0 Hz, 2″,6″-CH_2), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.96 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.09 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.36 (q, 1H, *J* = 8.5 Hz, 6′-CH), 7.43 (s, 1H, 2-CH), 7.47 (d, 1H, *J* = 8.5 Hz, 6-CH), 9.74 (s, 1H, OH)
5u	65.81 (65.88)	5.91 (5.82)	8.02 (8.09)	1.12 (t, 3H, *J* = 7.0 Hz, $-CH_3$), 2.48 (q, 2H, *J* = 7.0 Hz, $-CH_2$), 2.53 (t, 4H, *J* = 5.0 Hz, 3″,5″-CH_2), 3.81 (t, 4H, *J* = 5.0 Hz, 2″,6″-CH_2), 6.92 (t, 1H, *J* = 8.5 Hz, 3′-CH), 6.96 (d, 1H, *J* = 8.0 Hz, 5′-CH), 7.09 (d, 1H, *J* = 8.5 Hz, 5-CH), 7.35 (q, 1H, *J* = 8.5 Hz, 6′-CH), 7.44 (s, 1H, 2-CH), 7.45 (d, 1H, *J* = 8.5 Hz, 6-CH), 9.79 (s, 1H, OH)

Table 3
The anti-inflammatory and analgesic activities of compounds

Compound	The inhibitory effect on xylene induced mice ear edema		The inhibitory effect on acetic acid induced mice writhing	
	Dose/(mg kg^{-1})	Inhibition/%	Dose/(mg kg^{-1})	Inhibition/%
2a	40	13.65	40	0
2b	40	16.06	40	7.97
5a	40	48.83	40	29.87
5b	40	5.38	40	23.86
5c	40	0	40	15.63
5d	40	34.12	40	16.58
5e	40	23.16	40	8.90
5f	40	19.58	40	12.30
5g	40	12.78	40	18.96
5h	40	36.40	40	30.96
5i	40	41.37	40	11.74
5j	40	0	40	29.87
5k	40	22.03	40	13.20
5l	40	0	40	28.52
5m	40	68.86	40	47.50
5n	40	19.79	40	5.57
5o	40	21.40	40	20.79
5p	40	65.20	40	0
5q	40	27.47	40	88.33
1	40	39.85	40	8.33

and analgesic activity. So these results will provide a good idea to design and research the SAR in the future.

Fortunately, because of possessing an excellent anti-inflammatory activity and a good analgesic activity, **5m** may be a potential anti-inflammatory agent.

Table 4
The ED_{50} of compound **5m**, **5p**, and **5q**

Compound	Test model	ED_{50}/(mg kg^{-1})
5m	On xylene induced mice ear edema	24.24
5p	On xylene induced mice ear edema	25.69
5m	On acetic acid induced mice writhing	43.79
5q	On acetic acid induced mice writhing	11.58

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12. All the chemicals and solvents were analytical reagent and used as received, unless otherwise stated. Melting points were taken on XRC-1 apparatus and are uncorrected. IR spectra were measured on a Bio-Rad FTS-40 spectrometer (KBr); ^{1}H NMR spectra were recorded on a Brucker AC-80 spectrometer (400 MHz) or a Brucker AC-100 spectrometer (500 MHz) using TMS as the internal standard in $CDCl_3$. MS spectra were run on an HP5989B instrument.
13. General procedure for the synthesis of compound **5**.A solution of diflunisal **1** (1 equiv) and pyridine (2 equiv) in $CHCl_3$ was stirred for 30 min to protect the carboxyl group by forming a salt (mp 126–129 °C after being separated). To this reaction mixture was added dropwise a solution of RCOCl (1 equiv) in chloroform at room temperature, and the reaction was allowed to processed with stirring for an additional about 3 h (monitored by TLC). After that 1 M HCl was used to precipitate, filtrate, wash and dry to afford compound **2**. It was observed that insufficient amount of pyridine would decrease the yield. Compound **2a** (R = CH_3): yield 98%, white crystalline solid, mp 161–165 °C; MS *m/z*: 292 $[M]^+$ (2), 250 (49), 232 (100), 204 (27), 175 (23), 156 (7). Compounds **2b** (R = C_6H_5): yield 95%, white crystalline solid, mp 167–172 °C; IR (KBr, cm^{-1}): 3444, 1738, 1689, 1267, 1210, 706; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 6.96 (t, 1H, *J* = 8.0 Hz, 3′-H), 7.00 (t, 1H, *J* = 8.0 Hz, 5′-H), 7.35 (d, 1H, *J* = 7.5 Hz, 5-H), 7.46 (q, 1H, *J* = 8.0 Hz, 6′-H), 7.50 (t, 2H, *J* = 8.0 Hz, 3″,5″-H), 7.65 (t, 1H, *J* = 7.6 Hz, 4″-H), 7.80 (d, 1H, *J* = 8.0 Hz, 6-H), 8.21 (d, 2H, *J* = 7.5 Hz, 2″,6″-H), 8.25 (s, 1H, 2-H), 11.24 (s, 1H, –COOH); MS *m/z*: 354 $[M]^+$ (2), 232 (20), 175 (4), 151 (2), 122 (4), 105 (100), 77 (29), 51 (5).A mixture of compound **2** and $SOCl_2$ (2 equiv) in CH_2Cl_2 was refluxed for 4 h prior to work up to give compound **3**. The compounds **5** were prepared by reaction of **3** (1 equiv) with substituted amines **4** (2 equiv) in CH_2Cl_2 at room temperature for 3 h, in 72–89% total yields based on the diflunisal. Compound **5a**: MS *m/z*: 305 $[M]^+$ (2), 263 (77), 245 (22), 233 (23), 232 (100), 204 (24), 175 (21), 151 (9). Compound **5b**: MS *m/z*: 319 $[M]^+$ (3), 277 (73), 259 (20), 233 (28), 232 (100), 204 (17), 175 (17), 151 (6). Compound **5c**: IR (KBr, cm^{-1}): 3069, 2937, 2852, 1767, 1633, 846, 818; MS *m/z*: 373 $[M]^+$ (5), 332 (15), 249 (28), 232 (100), 204 (16), 175 (18), 151 (12), 98 (17). Compound **5d**: IR (KBr, cm^{-1}): 3069, 2863, 1765, 1634, 865, 833; MS *m/z*: 381 $[M]^+$ (3), 339 (77), 232 (18), 204 (10), 175 (11), 151 (5), 106 (18), 91 (100). Compound **5e**: MS *m/z*: 367 $[M]^+$ (4), 325 (32), 233 (39), 232 (12), 204 (8), 175 (16), 151 (10), 93 (100). Compound **5f**: IR (KBr, cm^{-1}): 3204, 2860, 1760, 1640, 875, 846; MS *m/z*: 381 $[M]^+$ (2), 339 (27), 233 (28), 204 (4), 177 (10), 175 (7), 151 (7), 107 (100). Compound **5g**: MS *m/z*: 381 $[M]^+$ (3), 339 (16), 233 (21), 204 (5), 177 (6), 175 (6), 151 (5), 107 (100). Compound **5h**: MS *m/z*: 381 $[M]^+$ (4), 339 (15), 233 (25), 204 (4), 177 (6), 175 (5), 151 (5), 107 (100). Compound **5i**: MS *m/z*: 401 $[M]^+$ (2), 359 (35), 233 (66), 232 (39), 204 (16), 175 (26), 151 (18), 127 (100). Compound **5j**: MS *m/z*: 401 $[M]^+$ (2), 359 (22), 233 (63), 232 (14), 204 (8), 175 (16), 151 (10), 127 (100). Compound **5k**: IR (KBr, cm^{-1}): 3199, 2860, 1763, 1641, 864, 857; MS *m/z*: 395 $[M]^+$ (4), 353 (29), 233 (34), 204 (4), 177 (11), 175 (8), 151 (8), 121 (100). Compound **5l**: IR (KBr, cm^{-1}): 2858, 1762, 1639, 1613, 1255, 847, 807; MS *m/z*: 361 $[M]^+$ (3), 319 (98), 275 (35), 233 (100), 204 (18), 175 (29), 151 (23), 86 (81). Compound **5m**: IR (KBr, cm^{-1}): 3392, 1719, 1665, 1611, 1481, 1272, 1213, 709; MS *m/z*: 367 $[M]^+$ (2), 245 (123), 232 (2), 204 (2), 175 (4), 151 (2), 105 (100), 77 (24). Compound **5n**: IR (KBr, cm^{-1}): 3335, 1745, 1647,1597, 1442, 1265, 1200, 707; MS *m/z*: 429 $[M]^+$ (1), 337 (4), 307 (5), 232 (2), 180 (5), 106 (8), 105 (100), 77 (23). Compound **5o**: IR (KBr, cm^{-1}): 3445, 1736, 1644), 1602, 1487, 1272, 1213, 706; MS *m/z*: 443 $[M]^+$ (1), 337 (3), 321 (5), 194 (3), 175 (3), 106 (10), 105 (100), 77 (40). Compound **5p**: IR (KBr, cm^{-1}): 1739, 1633, 1471, 1266, 1211, 710; MS *m/z*: 409 $[M]^+$ (5), 337 (2), 175 (4), 151 (2), 106 (8), 105 (100), 77 (20), 72 (18). Compound **5q**: IR (KBr, cm^{-1}): 1735, 1634, 1462, 1260, 1208, 708; MS *m/z*: 436 $[M]^+$ (7), 379 (54), 337 (7), 233 (8), 175 (6), 106 (8), 105 (100), 77 (39). Compound **5r**: MS *m/z*: 277 $[M]^+$ (100), 276 (30), 233 (56), 232 (82), 204 (27), 175 (30), 151 (23), 44 (37). Compound **5s**: MS *m/z*: 305 $[M]^+$ (65), 304 (43), 232 (57), 204 (21), 175 (23), 151 (33), 72 (100), 58 (76). Compound **5t**: MS *m/z*: 332 $[M]^+$ (33), 275 (7), 233 (18), 204 (5), 151 (11), 99 (22), 83 (18), 70 (100). Compound **5u**: MS *m/z*: 346 $[M]^+$ (39), 275 (9), 233 (33), 204 (6), 175 (8), 151 (15), 99 (19), 84 (100).
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