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Synthesis and Pharmacodynamics of Ibuprofen-1-acetoxyethyl Ester

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Abstract Ibuprofen(IBU) and its derivatives are widely used in treating many diseases, such as depression, glomerulonephritis, fever caused by common cold or influenza, and rheumatoid arthritis. While in clinical trials, IBU was found to have many side effects. To weaken and prevent these side effects, a derivative called ibuprofen-1-acetoxyethyl ester was synthesized in this paper. The maximum concentration(c_{max}) in a shorter time was compared with IBU at the same dose.

Keywords Ibuprofen; Ibuprofen-1-acetoxyethyl ester; Pharmacodynamic research

1 Introduction

Ibuprofen(IBU), 2-(4-isobutylphenyl)propionic acid, is the most widely used non-steroidal anti-inflammatory drug. It inhibits hypothalamic cyclooxygenase(COX) to reduce the synthesis of prostaglandin E2 to achieve anti-inflammatory, analgesic and antipyretic effects[1]. Because the inhibition of IBU on COX-1 is stronger than on COX-2, long-term service can cause serious gastrointestinal side effects, such as bleeding, perforation, or pyloric obstruction[2]. Moreover, IBU has low bioavailability and short half-life because of its insolubility in water[1].

Many modifications have been conducted to ensure the efficacy of IBU and reduce its side effects[3—5]. A substituted benzamido group was introduced to the 3-position of the phenyl ring of IBU(**1**) to occupy the side pocket in cox-2 to enhance ibuprofen derivatives affinity for COX-2[6]. Subsequently, IBU sugar derivatives(**2**) were prepared to decrease the side effects and increase the bioavailability of IBU. These derivatives were synthesized using the amino or hydroxyl of several typical monosaccharides and disaccharides as glycosyl donor acylation with IBU acid chloride[7]. Furthermore, IBU eugenol ester(**3**) was synthesized from IBU acid chloride and eugenol. Eugenol as raw material can reduce the common side effects induced by this classic anti-inflammatory drug[8]. 9-*O*-Ibuprofen berberine ester(**4**) was produced from berberabine and ibuprofen acid chloride. Compound **4** has antibacterial, anti-inflammatory, anti-heart failure, and anti-platelet aggregation effects; it is also used to treat hypertension by lowering blood pressure, and to treat peptic ulcer and diabetes[9]. Fan *et al.*[10] reported the synthetic method of phillygenin IBU ester(**5**), in which the raw materials were phillygenin and IBU acid chloride. This compound has an excellent anti-virus effect. Ibuprofen polyethylene glycol ester(IPE, **6**) was synthesized from IBU and polyethylene glycol(PEG). The compound has good effects in anti-inflammation and analgesia[11].

As shown in Fig.1, the structures of the six IBU derivatives exhibited drastic changes by coupling or esterification; thus, their efficacies were also reduced. In the *in vivo* metabolic process of ibuprofen derivatives, it proved that anti-inflammatory or analgesic effects were decreased. However, the compounds of ketoprofen, suloprofen, phenoxy IBU with halobenzene derivatives and cyanoacetate derivatives have been shown to enhance pharmacological effects such as analgesia or anti-inflammatory, but adverse gastrointestinal reactions are increased due to the drug toxicity change. Moreover, arginine, as the solvent for preparing the mixed solution of IBU arginine injection[12—14], requires not only a strong saline dilution to avoid injection of hemolysis but also strict pH in diluting the physiological saline. Otherwise, the active ingredient IBU will be precipitated or degraded. The stability of the injection is also affected by temperature, which limits the sterilization conditions and effects. Therefore, a medicament that

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retains the therapeutic effects of IBU and inhibits its side effects should be developed. This medicament should be chemically stable and ensure that the active ingredient of the drug is available for intravenous injection. To avoid the aforementioned side effects, some novel IBU-based compounds were used; in particular, ibuprofen-1-acetoxyethyl ester(IAE, **8**), including (*R*)-(–)-ibprofen-1-acetoxyethyl ester(**8**a) and (*S*)-(+)-ibupro- fen-1-acetoxyethyl ester(**8**b).

These compounds were used to prepare non-steroidal anti-inflammatory medicine.

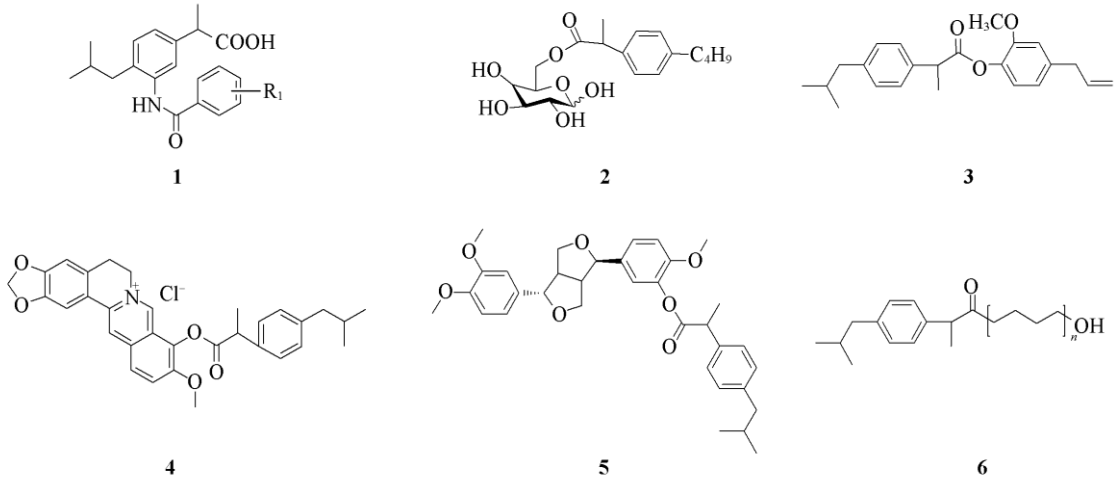


Fig.1 Structures of compounds 1—6

2 Experimental

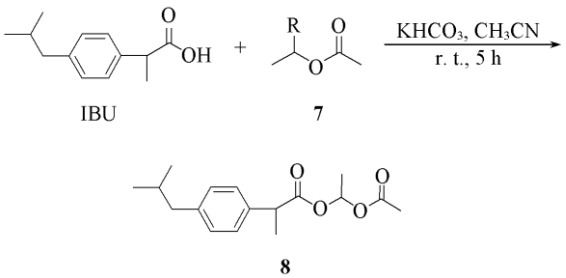
2.1 Instruments and Reagents

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained with an LC/MS 1100 spectrometer from Agilent Technology. WZZ-1S digital automatic polarimeter was from Shanghai Physical Optics Instrument Factory. Melting points were determined by using an X-4 digital microscope. Column chromatography was generally performed on silica gel(300—400 mesh), and thin-layer chromatography inspections were conducted on silica gel GF_{254} plates.

All commercial chemicals were of analytical grade and purchased from Beijing Chemical Reagent Co.(China) and used without further purification.

2.2 Synthesis of IAE

The synthetic route of IAE is shown in Scheme 1.



Scheme 1 Synthetic route of IAE

At 25 °C, IBU(0.05 mmol) in acetonitrile(110 mL) was added to $KHCO_3$(0.08 mmol) and compound **7**(0.08 mmol), and stirred for 5 h. Ethyl acetate(200 mL) was added to the mixture at room temperature. The organic phase was washed with saturated sodium carbonate solution(100 mL×2) and dried over anhydrous sodium sulfate. Active carbon was added for decolorization under reflux; after filtration, the fraction was concentrated at 164—166 °C/101 kPa to afford compound **8**: as a colorless oil, yield 91%; b. p. 164—166 °C; IR, $\tilde{\nu}$/cm^{-1}: 2968, 2862, 1735, 1516, 1450, 1370, 1118, 950, 760. ^{1}H NMR(300 MHz, $CDCl_3$), δ: 0.89(d, *J*=6.6 Hz, 6H), 1.41(d, *J*=5.4, 22.2 Hz, 3H), 1.48(d, *J*=7.2 Hz, 3H), 1.84(m, 1H), 2.01(d, *J*=31.5 Hz, 2H), 2.44(d, *J*=7.2 Hz, 2H), 3.68(m, 1H), 6.85(m, 1H), 7.09(m, 2H), 7.18(m, 2H). ESI-MS, *m/z* calcd. for $C_{17}H_{24}O_4$([M+Na$^+$]): 315; found: 315.

Compound (*R*)-(–)-ibuprofen-1-acetoxy-ethyl ester(**8**a): $[\alpha]_D^{20}$ =–34.5°(*c* 0.03, CH_3OH).

Compound (*S*)-(+)-ibuprofen-1-acetoxy-ethyl ester(**8**b): $[\alpha]_D^{20}$ =34.5°(*c* 0.03, CH_3OH).

2.3 Pharmacodynamic Research in Beagle Dogs

We examined the self-cultivation in 12 experimental beagle dogs(mass 8—12 kg, female-to-male same size ratio). The dogs were randomly divided into test groups 1 and 2 and control groups 1 and 2; each group consisted of three dogs. Pre-medication fasting was conducted for 12 h, while drinking water was unstinted. Then, IBU(100 μL) was injected to each dog at a dose of 12.5 mg/kg based on the dose of 400 mg/kg for an adult. For test group 1, the dose was injected within 0.17 h and for test group 2, the dose was administered orally. After the same time interval, blood samples were collected from the small saphenous vein on the back legs of the dogs in the two test groups. Blood samples were added to the bile ducts with lipase inhibitor[15]. The blood sample(100 μL), felbinac(100 μL) and acetonitrile(400 μL) were mixed and placed into a turbine mixer for 1 min and then kept static for 10 min. The supernatant was collected in another test tube. Time-concentration curves were drawn according to the test results by LC-MS/MS. The results are listed in Tables 1—3.

Table 1 Pharmacokinetic parameters of intravenous infusion of IBU

t/h	c_1/(μg·mL^{-1})	c_2/(μg·mL^{-1})	c_3/(μg·mL^{-1})	$\bar{c}$/(μg·mL^{-1})	SD
0	0	0	0	0	0
0.033	25.3	16.5	18.2	20.0	4.7
0.083	39.7	20.5	—*	30.1	13.6
0.117	47.2	—*	36.1	41.7	7.8
0.17	64.7	35.9	36.8	45.8	16.4
0.33	80.5	50.1	69.7	66.8	15.4
0.5	67.3	44.9	64.0	58.7	12.1
0.75	64.5	35.4	46.6	48.8	14.7
1.0	52.6	30.4	34.8	39.3	11.8
2.0	41.0	26.2	—*	33.6	10.5
3.0	25.1	18.7	—*	21.9	4.5
5.0	11.5	8.76	13.4	11.2	2.3
7.0	5.7	4.9	8.3	6.3	1.8
12.0	1.5	15.3	2.4	1.8	0.5
24.0	0.5	10.4	0.5	0.7	0.3
$AUC_{0\text{-}t}$/(μg·mL^{-1}·h^{-1})(t=24 h)	225.4	160.1	210.7	198.7	34.2
c_{max}/(μg·mL^{-1})	80.5	50.1	69.7	66.8	15.4
$t_{1/2}$/h	4.47	6.68	4.05	4.92	6.62

* The data were not detected.

Table 2 Pharmacokinetic parameters of intravenous infusion of IAE for test group 1

t/h	c_1/(μg·mL^{-1})	c_2/(μg·mL^{-1})	c_3/(μg·mL^{-1})	$\bar{c}$/(μg·mL^{-1})	SD
0	0	0	0	0	0
0.033	76.8	52.7	75.5	68.3	13.6
0.083	55.6	—*	60.7	58.2	3.6
0.17	55.5	46.7	55.9	52.7	5.2
0.33	49.4	39.1	51.4	46.6	6.6
0.5	44.3	36.2	44.1	41.5	4.6
0.75	34.5	39.3	34.6	36.1	2.7
1.0	31.1	30.8	32.6	31.5	0.9
2.0	26.5	17.0	25.2	22.9	5.2
3.0	20.5	10.5	17.0	16.0	5.1
5.0	14.7	4.7	9.3	9.5	5.0
7.0	9.6	2.7	5.8	6.0	3.4
12.0	2.5	0.7	1.4	1.5	0.9
24.0	0.6	0.2	0.2	0.3	0.2
$AUC_{0\text{-}t}$/(μg·mL^{-1}·h^{-1})(t=24 h)	204.0	112.7	163.2	159.9	45.7
c_{max}/(μg·mL^{-1})	76.8	52.7	75.5	68.3	13.6
$t_{1/2}$/h	4.17	4.06	3.38	3.87	0.43

* The data were not detected.

Table 3 Pharmacokinetic parameters of intravenous infusion of IAE for test group 2

t/h	c_1/(μg·mL^{-1})	c_2/(μg·mL^{-1})	c_3/(μg·mL^{-1})	$\bar{c}$/(μg·mL^{-1})	SD
0	0	0	0	0	0
0.083	5.2	2.9	17.0	8.4	7.5
0.167	8.9	5.6	41.7	18.7	19.9
0.250	23.3	10.1	44.3	25.9	17.2
0.500	60.1	30.4	38.6	43.0	15.3
0.750	53.4	42.4	34.0	43.3	9.7
1.0	41.1	39.0	37.7	39.3	1.7
1.5	36.9	36.2	37.8	36.9	0.8
2.0	31.8	28.8	27.4	29.3	2.2
3.0	23.2	19.9	19.6	20.9	2.0
4.0	16.9	17.2	14.5	16.2	1.5
6.0	5.6	8.8	5.8	6.7	1.8
8.0	2.4	4.3	2.0	2.9	1.2
12.0	0.6	1.0	0.4	0.7	0.3
24.0	0.2	0.3	97.3	0.2	0.1
48.0	—*	—*	—*	0	0
$AUC_{0\text{-}t}$/(μg·mL^{-1}·h^{-1})(t=24 h)	163.9	160.9	14.7	157.3	8.9
c_{max}/(μg·mL^{-1})	60.1	42.4	44.3	48.9	9.7
$t_{1/2}$/h	3.74	4.03	3.29	3.69	0.37

* The data were not detected.

3 Results and Discussion

3.1 Optimization of Synthesis

Compound **8** was prepared through esterification of IBU and organic esters under basic conditions. Reaction conditions, including the solvents, amount of catalyst, reaction temperature and selection of catalyst and additive were optimized. The effects of different solvents and reaction temperatures in the presence of 20%(molar ratio) $KHCO_3$ were examined. The results showed that the effects of different solvents and reaction temperatures were responsible for the yields. The reaction yield was 34% when the reaction was conducted in toluene, but the yield was increased to 91% in acetone(Entries 1 and 2, Table 4). Thus, acetone was established as the best solvent for this reaction system. Meanwhile, when the temperature was decreased to –20 °C, the reaction did not proceed(Entry 6, Table 4). Therefore, the best temperature was 25 °C.

Table 4 Screening of solvents and temperature for synthesis of IAE[a]

Entry	R	Solvent	Temperature/°C	Catalyst	Yield[b](%)
1	Br	Toluene	25	$KHCO_3$	34
2	Br	CH_3CN	25	$KHCO_3$	91
3	Br	THF	25	$KHCO_3$	20
4	Br	CH_3CN	25	NaOH	18
5	Br	CH_3CN	25	$NaHCO_3$	10
6	Br	CH_3CN	−20	$KHCO_3$	—
7	Cl	CH_3CN	25	$KHCO_3$	75
8	CH_3COO	CH_3CN	25	$KHCO_3$	72

a. Reactions were conducted using IBU(5 mmol), ester(0.8 mmol), and cat.(0.5 mmol) in solvent(1 mL) for 5 h; *b*. isolated yield after column purification.

Quantitative structure-activity relationship modeling software was used to predict absorption, distribution, metabolism, excretion and toxicological(ADMET) properties of the compounds. Based on these data, the druggability rates of the compounds were also evaluated[12].

The structures of the four compounds are shown in Fig.2. The pharmacological properties of the compounds were evaluated according to the built-in drug evaluation criteria.

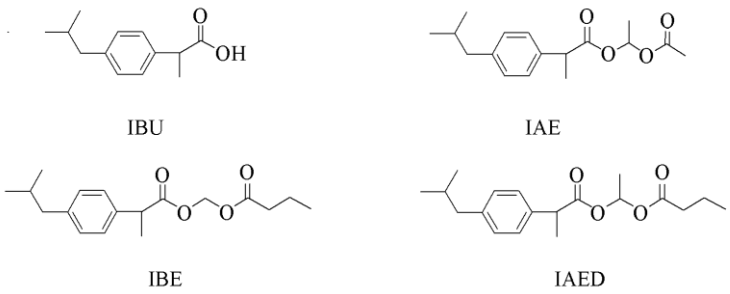


Fig.2 Structures of compounds tested by ADMET Predictor

According to the software prediction and calculation, IBU has the lowest ADMET-risk coefficient of 1.7, followed by IAE, IBE and IAED. Among them, IBE and IAED have a risk factor of more than 5; therefore, their druggability rates are poor. The druggability of IAE is actually better than that of IBE mentioned in American patent[16] and has significant potential for development. Pharmacological risk prediction results are listed in Table 5.

Table 5 Pharmacological risk prediction results of IBU, IAE, IBE and IAED

Compd.	S+Absn_Risk	S+Absn_Code	CYP_Risk	CYP_Code	ADMET_Risk*	ADMET_Code
IBU	0	—	1.25	C9, D6	1.70	fu, C9, D6
IAE	0.91	ow	2.45	1A, C9, 19	3.36	ow, 1A, C9, 19
IBE	2.23	RB, ow, Sw	3.00	1A, C9, 19	5.56	RB, ow, Sw, fu, 1A
IAED	2.44	RB, ow, Sw	3.44	1A, C9, 19, 3A	6.49	RB, ow, Sw, fu, 1A

* ADMET_Risk represents the total ADMET risk factor. The larger the value is the worse the druggability is. In general, the ADMET risk factor of the marked drugs is less than 5.

3.2 Preclinical Pharmacodynamics Research on IBU and IAE

The four compounds, IBU, IAE, IBE and IAEO, were prepared into fat emulsion by high-pressure homogenization techniques and then their pharmacokinetics were studied in beagle dogs[17]. An LC-MS/MS method to determine IBU in plasma was established. The pharmacokinetics of IBU in beagle dogs given the same dose of IBU arginine salt injection and IBU ester intralipid was investigated. The linear range for IBU was from 0.1 μg/mL to 100 μg/mL with a quantitation limit of 0.1 μg/mL. The main pharmacokinetic parameters for intravenous infusion of IBU and IAE intralipid were as follows: $t_{1/2}$=(4.92±6.62) and (3.87±0.43) h; c_{max}=(66.676±15.411) and (68.333±13.554) μg/mL; $AUC_{0\text{-}24}$=(198.714±34.222) and (159.978±45.77) $\mu g \cdot mL^{-1} \cdot h^{-1}$. The experimental results of IBU and IAE are listed in Fig.3. As can be seen from Fig.3, IAE is superior to IBU in some experimental parameters. IAE intralipid can easily spread across the cell membrane, which promotes the rapid absorption of the drug. At the same time, IAE can be easily hydrolyzed into IBU *in vivo*. Due to the

changes of the IAE structure, the vascular irritation is smaller and $t_{1/2}$ is shorter than the intravenous infusion of IBU when the two drugs were bioequivalent. And compared with some works[18,19], we will try the applications of IAE in other fields.

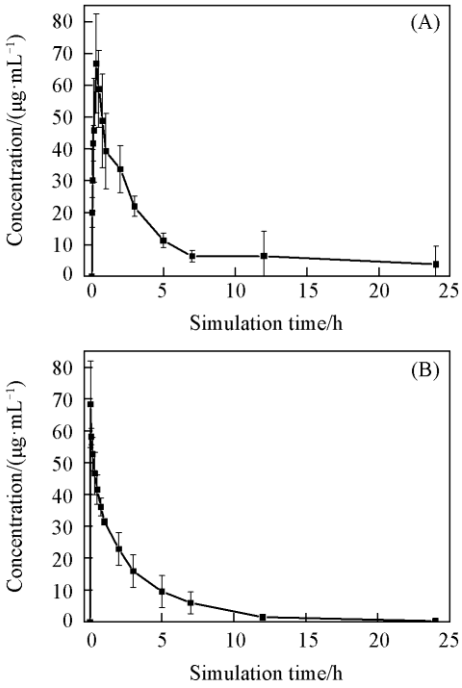


Fig.3 Simulated drug curves of IBU(A) and IAE(B) intralipid in beagle dogs

4 Conclusions

Ibuprofen-1-acetoxyethyl ester exhibited good effects both in the oral and injection experiments. Although the structure changed, ibuprofen-1-acetoxyethyl ester was bioequivalent with IBU at the same dose. In addition, it could reach c_{max} in a shorter time compared with IBU. We believe that this finding may have wide applications in the development of new drugs.

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