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A convenient synthesis of ezetimibe analogs as cholesterol absorption inhibitors

Jian Feng Ji [a], Hui Bin Zhang [a], Wen Long Huang [a,*], Hai Qian [a,*], Jin Pei Zhou [b]

[a] Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, China
[b] Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

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Abstract

A convenient method for the synthesis of ezetimibe analogs as cholesterol absorption inhibitors was described. The key step in the synthesis was the intramolecular ring formation through Mitsunobu reaction. Furthermore, a new series of analogs was designed and synthesized.

Keywords: Ezetimibe; Synthesis; Cholesterol absorption inhibitor

Ezetimibe [1], as shown in Fig. 1, is the first of the cholesterol absorption inhibitors, a novel class of lipid modifying drugs, which inhibits the absorption of dietary or recycled cholesterol in the intestine and can be used either alone or in combination with a statin. Some approaches have been reported for the synthesis of ezetimibe. The significant difference of various synthesis methods was the lactam ring formation step. One general synthesis was afforded by reaction of acyl chloride and imine which was synthesized from aromatic amine and aromatic aldehyde, to give *trans* β-lactams.

Through retrosynthesis of ezetimibe, a new convenient route was proposed, which contained general reagents and moderate conditions. The key intermediate **6**, was synthesized through this method (Scheme 1).

In the previous work of our laboratory, the polarity and the length of C-3 side chain was modified by introducing ester or amide groups to the C-3 side chain. And several ester or amide analogs have shown some interesting cholesterol absorption inhibition activity [2]. In order to further investigate the effect of these groups, the ester analogs (**8a**–**g**) with substituents of different polarity or electrophilicity on phenyl groups were designed and synthesized, as shown in Scheme 2.

General procedure for synthesis of compound **6** was as follows: 4-Methoxybenzoyl chloride **1** and ethyl acetoacetate were disposed with NaOH (33% aq.) in petroleum ether and then treated with NH_4Cl to provide β-ketoester **2** [3]. Then the ketoester was heated on an oil bath at 140 °C together with 4-fluorobenzenamine in xylene by continuously distilling ethanol to give amide **3**. The Michael addition of amide **3** and methyl acrylate was quite fast, within 2 h. In anhydrous THF, the yield was 99%, which was a little higher than in THF containing about 2% water,

* Corresponding authors.
E-mail addresses: ydhuangwenlong@126.com (W.L. Huang), qianhai24@126.com (H. Qian).

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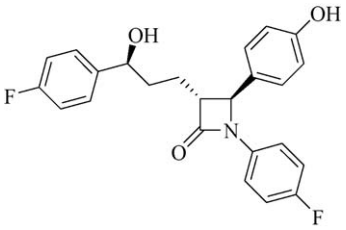
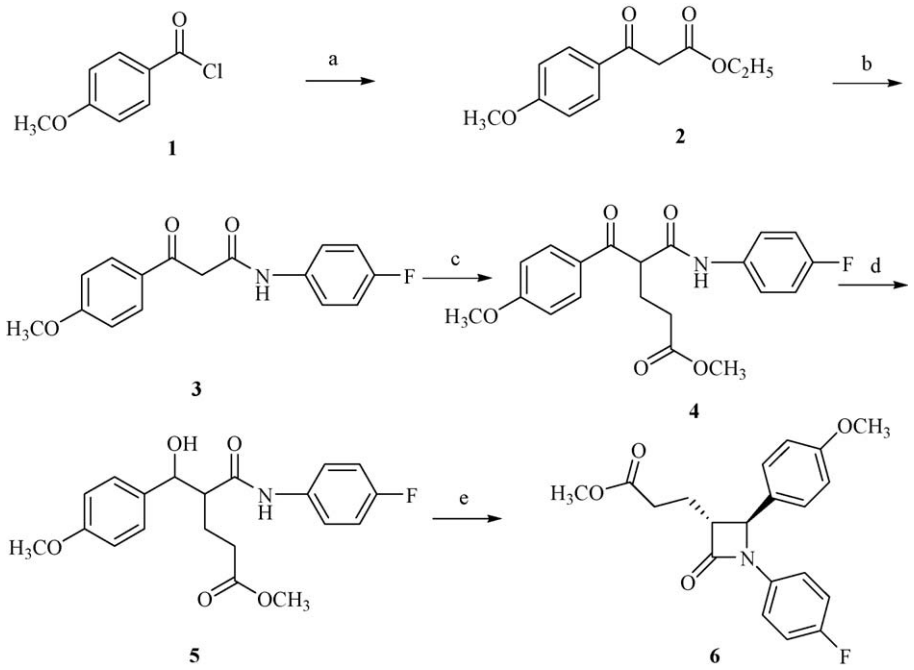
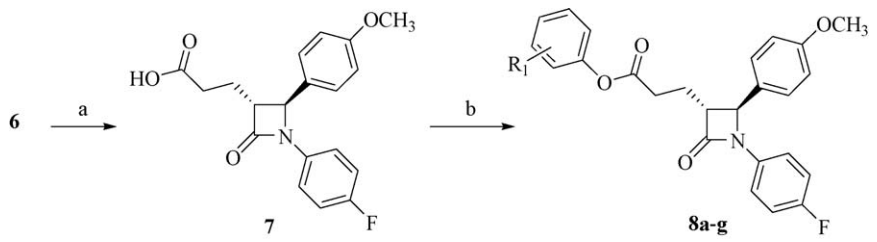


Fig. 1. Structure of ezetimibe.



Scheme 1. Reagents and conditions: (a) (1) ethyl acetoacetate, NaOH (33% aq.), petroleum ether, (2) NH_4Cl, total 35%; (b) 4-fluorobenzenamine, xylene, 140 °C, 4 h, 72%; (c) methyl acrylate, $NaOC_2H_5$, THF, 75 °C, 2 h, 96%; (d) $NaBH_4$, CH_3OH, 0 °C, 8 h, 92%; (e) Ph_3P, diethyl azodicarboxylate (DEAD), THF, 8 h, 32.7%.



Scheme 2. Reagents and conditions: (a) LiOH, acetone, H_2O, rt, 99.2%; (b) substituted phenols, DMAP, DCC, CH_2Cl_2, rt.

yielding 96%. Reduction of compound **4** by $NaBH_4$ in CH_3OH gave alcohol **5**. Under Mitsunobu [4] condition, the lactam ring was formed, to give compound **6** [5]. Between 0 and 80 °C, the yields of ring formation were quite stable, from 32% to 34%.

Spectral data of compound **6** indicated that the reaction under Mitsunobu condition afforded the *trans* β-lactam [6] because the coupling constant of C_3 and C_4 proton was 2.1 Hz, which showed significant difference compared to that of *cis* β-lactams (5–6 Hz).

Table 1
Results of *in vivo* bioactivities.

Compounds[a]	R_1	TC or reduction (%)[b]
8a	4-$COOCH_3$	10.3
8b	4-$COOC_2H_5$	18.7**
8c	4-Cl	31.2
8d	4-Br	12.5
8e	4-OCH_3	NE#
8f	2,6-CH_3	NE#
8g	4-NO_2	28.5*
High-cholesterol diet	–	13.26 ± 1.59[c]
Normal diet	–	45.1**
Ezetimibe	–	39.1**

* $P < 0.05$.
** $P < 0.01$.
\# NE: No effect.
[a] 8 rats per group.
[b] Compared to High-cholesterol diet animal group.
[c] Concentration in serum: mmol/L.

Cholesterol absorption inhibition activity was investigated in a rat model [7]. Serum cholesterol levels were determined in a kit form. The results were presented in Table 1. As can be seen from the data, some of the target compounds showed moderate effect in lowering total serum cholesterol content. Substitution of alkoxy and 2,6-dimethyl for R_1 as in compound (**8e**) and compound (**8f**) resulted in significant decrease in potency. Substitution of electrophilic groups for R_1 as in compounds **8a**, **8b**, **8c**, **8d** and **8g** results in promising activity in lowering total serum cholesterol content. These SAR trends may provide insights into the further research on novel cholesterol absorption inhibitors.

In summary, a mild and convenient procedure for the monocyclic β-lactams through Mitunobu reaction was developed. The present procedure described here offered moderate yields of products, short reaction time, and operational simplicity. Bioactivity data indicated that some of the target compounds showed moderate effect in lowering total serum cholesterol level.

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[5] Synthesis of compound **6**: To a solution of **5** (5.08 g, 13.55 mmol) and Ph_3P (3.54 g, 13.55 mmol) in THF (40 mL) at 0 °C was added dropwise, DEAD (2.47 mL, 13.55 mmol). The solution was stirred for 8 h and then evaporated. The residue was purified on Si-gel to provide 1.58 g (32.7%) of compound **6** as a white solid. Spectral data of compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–6.88 (m, 8H, –Ph–), 4.64–4.63 (d, 1H, $J = 2.1$, $–CH_2–CH–CH–$), 3.80 (s, 3H, $–Ph–OCH_3$), 3.66 (s, 3H, $–COOCH_3$), 3.14–3.08 (m, 1H, $–CH_2–CH–CH–$), 2.61–2.48 (m, 2H, $–CH_2–CH_2–COO–$), 2.26–2.18 (m, 2H, $–CH_2–CH_2–COO–$); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 167.8, 163.7, 160.5, 157.3, 133.8, 129.2, 127.5, 127.4, 127.4, 127.3, 127.2, 127.1, 118.4, 118.3, 115.9, 115.6, 115.4, 115.1, 114.6, 73.1, 61.0, 60.3, 55.3, 36.6, 24.9; IR (KBr, cm^{-1}) (υ: 2986, 2917, 1740, 1610, 1508, 1386, 1249, 1223, 1175, 1076, 833, 750; MS (70 eV) *m/z*: $[M + H]^+$ 358, $[M + Na]^+$ 380.
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