· 研究论文 ·

Synthesis of phenyloxyisobutyric acid derivatives and their antidiabetic activity *in vitro*

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Abstract **Aim** To design and synthesize new phenyloxyisobutyric acid analogues as antidiabetic compounds. **Methods** Eight new target compounds were synthesized by combination of lipophilic moieties and acidic moiety with nucleophilic replacement or Mitsunobu condensation. The eight compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR and MS. **Results** *In vitro* insulin-sensitizing activity (3T3-L1 adipocyte) demonstrated, that the cultured glucose concentration of up-clear solution detected with GOD-POD assay were 5.942, 6.339, 6.226 and 6.512 mmol·L^{-1}, respectively, when rosiglitazone, pioglitazone, compounds **A** and **B** were added to the insulin-resistant system. **Conclusion** *In vitro* insulin-sensitizing activity of target compound **A** is in between that of rosiglitazone and pioglitazone, and activity of target compound **B** is slightly less than that of pioglitazone.

Key words: insulin sensitizers; antidiabetic activity; phenyloxyisobutyric acid derivatives; 3T3-L1 adipocytes; GOD-POD method

CLC number: R916.2 **Document code**: A **Article ID**: 0513-4870(2006)02-0108-07

苯氧异丁酸类化合物的合成及其体外抗糖尿病活性

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摘要: 目的 设计及合成新型苯氧异丁酸类抗糖尿病化合物。方法 关键步骤采用亲核取代反应或 Mitsunobu 缩合反应把亲脂性片段和酸性片段连接成一体, 共合成了 8 个新目标物。用核磁共振、红外、质谱进行结构确认。结果 体外胰岛素增敏活性测试(3T3-L1 脂肪细胞)结果显示, 分别将罗格列酮、吡格列酮、目标物 **A** 和 **B** 加入已经存在胰岛素抵抗脂肪细胞培养液中, 用 GOD-POD 方法分析得到上清液葡萄糖浓度分别为 5.942, 6.339, 6.226 和 6.512 mmol·L^{-1}。结论 目标物 **A** 在胰岛素抵抗实验(3T3-L1 脂肪细胞)中抗糖尿病活性介于市售 PPARγ 激动剂罗格列酮和吡格列酮之间, 而目标物 **B** 的活性略低于吡格列酮。

关键词: 胰岛素增敏剂; 抗糖尿病活性; 苯氧异丁酸类化合物; 3T3-L1 脂肪细胞; GOD-POD 方法

Diabetes mellitus is a polygenic metabolic disorder that afflicts 154.4 millions people worldwide at 2000 and the number is increasing rapidly according to the WHO reports. In common, about 90% of the diabetic population is classified as non-insulin-dependent diabetes (NIDDM or type 2 diabetes). Type 2 diabetes is characterized by hyperglycemia, which is mainly due to insulin resistance and leads to several complications, such as neuropathy, nephropathy, retinopathy, and atherosclerosis[1-3]. The commonly used oral hypogly-

Received date: 2005-03-16

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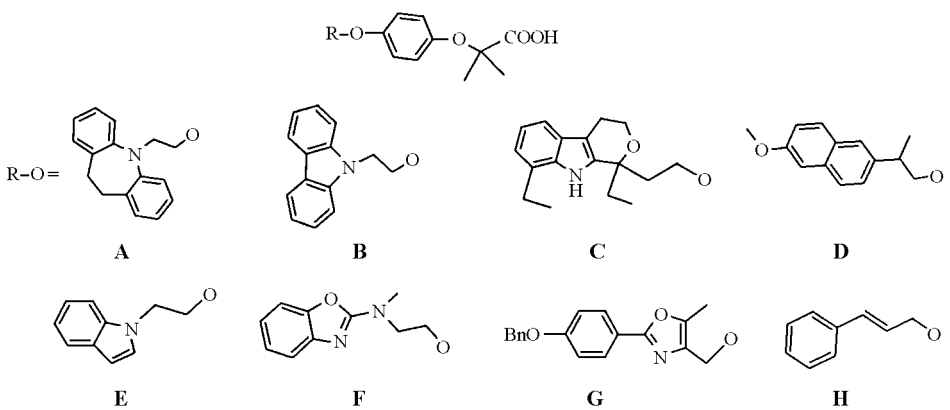
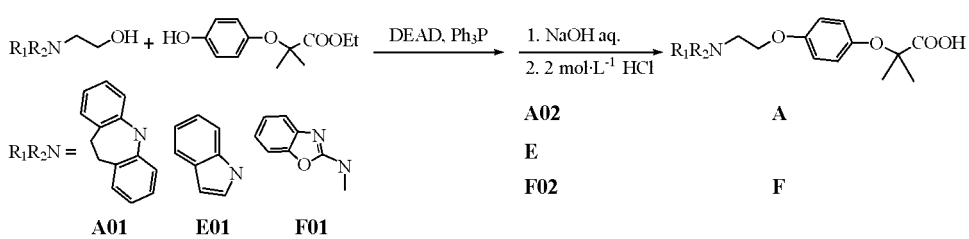
cemics for Type 2 diabetes are sulfonylureas and biguanides. But they have some flaws: sulfonylureas as insulin secretagogues probably induce serious hypoglycemia; biguanides, typified by metformin, occasionly result in lactic acid poisoning. Now two insulin sensitizers, pioglitazone[4] and rosiglitazone[5] are marketed, but TZDs (2, 4-thiazolidinedione, glitazone) insulin sensitizers usually cause patients to gain body weight and to be edematous. Thus development of new non-TZD insulin sensitizers is required. The molecular structures of insulin sensitizers are commonly composed of acidic pharmacophores, lipophilic moieties and binding chains. Lipophilic moieties are various, but the discovered pharmacophores for insulin sensitizers are limited in alkoxyphenylpropanoic acid[6], phenyloxy-isobutyric acid[7], phenylacetic acid, *N*-alkyl phenylalanine[8], and so on. Phenyloxy-isobutyric acid is the pharmacophore of fibrates[9]. Tricyclic moieties, such as carbazole, combined with alkoxyphenylpropoinic acid were discovered as dual PPARα/γ agonists, a kind of insulin sensitizers[6]. Now we manage to combine phenyloxyisobutyric acid pharmacophore with some cyclic moieties, which is designed from three to two, then to one cyclic moiety. Thus, eight new compounds were designed (Scheme 1) and their insulin sensitizing activities are screened on 3T3-L1 adipocytes by glucose-oxidase peroxidase-optical-density assay (abbreviated as GOD-POD assay)[10]. GOD-POD assay is adopted in clinical detection for glucose. The concentration of the resulted red quinones is directly proportional to that of glucose, and the quinone can be detected by optical density, so the unknown glucose concentration can also be obtained by comparison optical density with that of the known glucose sample.

In the convergent step, six desired compounds were synthesized by the alkylation of *p*-hydroxyphenyloxyisobutyrate with mesylates, tosylates (compound **B**, **C**, **D** and **H**, Scheme 3) or chloride (Scheme 4, compound **G**). In preliminary experiments, we found compounds **A**, **E** and **F** could not be prepared by nucleic attack process, but could be synthesized by condensation of *p*-hydroxyphenyloxyisobutyrate and alcohol under Mitsunobu conditions using triphenylphosphine and diethyl azodicarboxylate (DEAD). Their preparation procedure and characterized data are shown in Scheme 2.

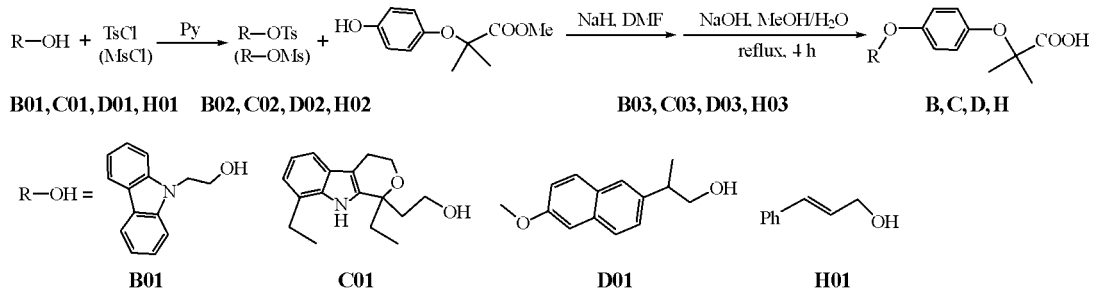
Insulin sensitizing experimental data are shown in Table 1. The glucose concentration of up clear cultured solution for non-insulin-resistant adipocytes and insulin-resistant adipocytes are 6.028 mmol·L^{-1} and 8.890 mmol·L^{-1}, respectively. When rosiglitazone, pioglitazone, compound **A** and **B** were added to the insulin-resistant system, the glucose concentration of up-clear solution cultured are 5.942, 6.339, 6.226 and 6.512 mmol·L^{-1}, respectively. These data distinctly



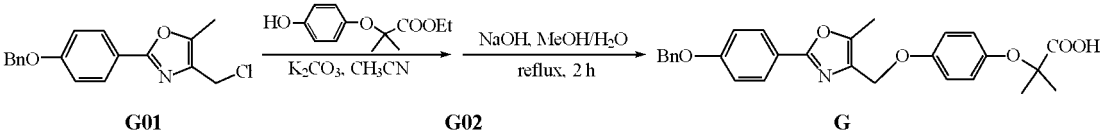
Scheme 1 Designed phenyloxyisobutyric acid derivatives for PPARα/γ dual agonists



Scheme 2 Synthesis of target compounds **A**, **E** and **H** by Mitsunobu condensation



Scheme 3 Synthesis of target compounds **B**, **C**, **D** and **H** by tosylates or mesylates



Scheme 4 Synthesis of target compound **G** by chloride

illustrate the *in vitro* antidiabetic activity of targeted compound **A** is in between that of rosiglitazone and pioglitazone, and compound **B** has a little lower activity than that of pioglitazone. Unfortunately, other seven compounds have hardly insulin sensitizing activity.

In summary, the known pharmacophore phenyloxyisobutyric acid is adopted in the work. Eight lipophilic moieties were designed. The pharmocophore and lipophilic moieties were combined into eight new desired compounds. Eight compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and MS. The *in vitro* antidiabetic activities of the eight desired compounds were screened on 3T3-L1 adipocytes by GOD-POD assay[10]. The anti-diabetic activity of target compound **A** is in between that of rosiglitazone and pioglitazone, and compound **B** shows less activity than pioglitazone.

Table 1 The antidiabetic activities of the target compounds **A** to **H** on 3T3-L1 adipocytes (*in vitro*)

Sample	Glucose conc. of up-clear solution/mmol·L^{-1}
Non-insulin-resistant adipocytes	6.028
Insulin-resistant adipocytes	8.890
Rosiglitazone	5.942
Pioglitazone	6.339
Compound **A**	6.226
Compound **B**	6.512
Compound **C** to **H**	> 8.0

The concentration of the test compounds: 0.1 mmol·L^{-1}

Experimental

Melting points were taken in open capillaries on an Electro-thermal digital melting point apparatus and which was not corrected. Electrospray ionization mass (ESI-MS) spectra (positive and negative mode) were recorded using a Finnigan LCQ^{DECA} mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3COCD_3 or DMSO-d_6 on a Bruker Avance 600 MHz spectrometer. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer (KBr discs).

10, 11-Dihydro-5H-dibenzo[b, f]azepine, 2-chlorobenzooxazole, butane-2, 3-dione monooxime, benzyloxyphenol, isobutyric acid, NaH, KOBu^t, $LiAlH_4$, Cs_2CO_3 were bought from Acros, other reagents were analytical reagents and bought from China.

Ethyl *p*-hydroxyphenyloxyisobutyrate was synthesized according to literature[11]. Compound **A01**, **B01** and **G01** were prepared according to literature[7]. **E01** was synthesized according to literature[12]. Compound **F01** was synthesized according to literature[6].

1 Antidiabetic activity screening procedure

3T3-L1 preadipocytes were grown and maintained in Dulbecco's modified Eagle's medium (DMEM), which contains 10% fetal calf serum in a humidified atmosphere composed of 95% air and 5% CO_2 at 37 ℃. When the cells were transferred to six-well plates and combined, cells were induced to differentiate into adipocytes by 0.25 μmol·L^{-1} dexamethasone (Dex), 0.5 mmol·L^{-1} isobutyl methylxanthine (IBMX) and 5 μg·mL^{-1} insulin for two days. Then Dex and IBMX were removed, and the cells were further treated with insulin till cells were completely differentiated and showed the characteristics of adipocytes. The differentiated adipocytes were incubated in 10% fetal calf serum, phenolsulfonphtha-

lein-free DMEM, and treated with 50 mmol· L^{-1} insulin and the tested compounds for 37 hours, then 10 μL up-clear cultured solution was transferred to 150 μL calibration liquid to test the content of glucose by GOD-POD assay[10].

2 Procedure for synthesis of the desired compounds from compound A to H

2.1 Synthesis of compound A

2-{4-[2-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (**A02**)

Ph_3P (0.8 mmol), compound **A01** (0.4 mmol) and ethyl *p*-hydroxyphenyloxy-isobutyrate (0.4 mmol) were added into 25 mL dry THF stirring under ice bath. Then to the cooled solution, a solution of DEAD (0.8 mmol) in 3 mL dry THF was added slowly. After complete addition, the mixture was stirred overnight under room temperature. After removing the solvent, the resulting residue was purified by column chromatograph using petroleum ether and ethyl acetate as eluent on silica gel. A pale yellow thick liquid **A02** was obtained with yield of 65.0%. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27(t, 3H, *J* = 7.2 Hz), 1.52 (s, 6H), 2.18(s, 4H), 4.04(t, 2H, *J* = 6.0 Hz), 4.18(t, 2H, *J* = 6.0 Hz), 4.24(q, 2H, *J* = 7.2 Hz), 6.67(d, 2H, *J* = 9.0 Hz), 6.78(d, 2H, *J* = 9.0 Hz), 6.96(t, 2H, *J* = 7.2 Hz), 7.12(d, 2H, *J* = 7.2 Hz), 7.15(t, 2H, *J* = 7.2 Hz), 7.21(d, 2H, *J* = 7.8 Hz).

2-{4-[2-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid (**A**)

Referring to the hydrolyzation procedure of compound **B03** into compound **B**, pale red crystal **A** was prepared with 70% - 80% yield. Mp 112 - 114 ℃. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.51(s, 6H), 3.17 (s, 4H), 4.06(t, 2H, *J* = 6.0 Hz), 4.19(t, 2H, *J* = 6.0 Hz), 6.70(d, 2H, *J* = 9.0 Hz), 6.85(d, 2H, *J* = 9.0 Hz), 6.96(t, 2H, *J* = 7.2 Hz), 7.12(d, 2H, *J* = 7.2 Hz), 7.15(t, 2H, *J* = 7.2 Hz), 7.22(d, 2H, *J* = 7.8 Hz). ^{13}C NMR (CDCl$_3$, 600 MHz) δ 176.18, 155.58, 147.95, 147.42, 134.90, 130.20, 126.73, 123.24, 120.53, 115.34, 80.79, 66.11, 50.90, 32.31, 24.94. IR (KBr) υ(cm^{-1}): 3 420, 3 009, 2 917, 1 706, 1 593, 1 507, 1 488, 1 456, 1 333, 1 303, 1 220, 1 166, 1 105, 1 047, 845, 761, 749. ESI-MS(+), *m*/*z* (rel. int.): 418([M+H]$^+$, 100).

2.2 Synthesis of compound B

Toluene-4-sulfonic acid 2-carbazol-9-yl-ethyl ester (**B02**)

To a solution of 2.271 g(0.011 mol) compound **B01** in 10 mL dry pyridine in ice bath, 2.1 g TsCl was added. Then the mixture was stirred overnight at room temperature. The resulting mixture was acidified to pH 3 - 4 with 2 mol· L^{-1} HCl, and then extracted with 40 mL ethyl acetate. The organic layer was washed by water and saturated NaCl solution, and then dried with anhydrous $MgSO_4$. After the solvent was removed, the resulting residue was purified by column chromatograph with petroleum ether and ethyl acetate as eluent. 3.16 g white solid **B02** was obtained with 78.7% yield. Mp 111 - 113 ℃. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.25 (s, 3H), 4.39(t, 2H, *J* = 5.4 Hz), 4.50(t, 2H, *J* = 5.4 Hz), 6.82(d, 2H, *J* = 8.1 Hz), 7.20 - 7.27(m, 6H), 7.38 - 7.44(m, 2H), 8.00(d, 2H, *J* = 7.8 Hz).

2-[4-(2-Carbazol-9-yl-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester (**B03**)

To a solution of 0.278 g(1.24 mmol) ethyl *p*-hydroxyphenyloxyisobutyrate, 0.566 g(1.55 mmol) compound **B02** in 20 mL dry DMF, 0.5 g Cs_2CO_3 was added, respectively. The mixture was stirred at 55 ℃ overnight. After work-up and purification, 0.392 g white crystal was obtained with 75.8% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.26(t, 3H, *J* = 7.2 Hz), 1.51(s, 6H), 4.22(q, 2H, *J* = 7.2 Hz), 4.31(t, 2H, *J* = 6.0 Hz), 4.71(t, 2H, *J* = 6.0 Hz), 6.74 (dd, 4H, J_1 = 28.5 Hz, J_2 = 9.3 Hz), 7.24 - 7.28 (m, 2H), 7.46 - 7.50(m, 4H), 8.11(d, 2H, *J* = 7.8 Hz).

2-[4-(2-Carbazol-9-yl-ethoxy)-phenoxy]-2-methyl-propionic acid (**B**)

0.356 g compound **B03** (0.2 mmol) was resolved in 20 mL solution of methanol and water (1∶1) containing 0.6 mol NaOH. The mixture was stirred in reflux for 4 hours. After work-up, 0.300 g white solid was obtained with 90.3% yield. Mp 188 - 189 ℃. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.50(s, 6H), 4.34 (t, 2H, *J* = 6.0 Hz), 4.74(t, 2H, *J* = 6.0 Hz), 6.73 (d, 2H, *J* = 9.0 Hz), 6.86(d, 2H, *J* = 9.0 Hz), 7.26 - 7.28(m, 2H), 7.29 - 7.54(m, 4H), 8.13 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (CDCl$_3$, 600 MHz) δ 155.19, 140.73, 125.96, 123.38, 123.23, 120.59, 119.43, 115.15, 108.94, 66.51, 42.76, 31.17, 24.89; IR (KBr) υ(cm^{-1}): 3 435, 1 697, 1 627, 1 504, 1 485, 1 457, 1 229, 1 153, 831, 753, 725; ESI-MS (negative), *m*/*z*: 389(M - H)$^-$, 388(M - 2H)$^-$, 777(2M - H)$^-$.

2.3 Synthesis of compound C

Methanesulfonic acid 2-(1, 8-diethyl-1, 3, 4, 9-tetrahydro-pyrano [3, 4-b] indol-1-yl)-ethyl ester (**C02**)

1.407 g(4.87 mmol) Etodolac was reduced with 0.9 g $LiAlH_4$ in 25 mL THF under reflux. After work-up, compound **C01** reacted with 0.5 mL MsCl in 5 mL pyridine. After work-up, the resulting brown solid residue was recrystalized with hexane/ethyl acetate, and 1.187 g pale yellow solid was obtained with 69.4% yield. Mp 121 - 122 ℃ (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.2 Hz), 1.38 (t, 3H, *J* = 7.5 Hz), 1.81 - 1.91 (m, 1H), 1.94 - 2.04 (m, 1H), 2.28 - 2.38 (m, 2H), 2.69 - 2.89 (m, 4H), 2.72 (s, 3H), 3.95 - 4.04 (m, 2H), 4.08 - 4.16 (m, 1H), 4.32 - 4.40 (m, 1H), 7.01 - 7.11 (m, 2H), 7.35 (d, 1H, *J* = 7.5 Hz), 7.76 (s, 1H). ESI-MS (positive), *m/z*: 352 $(M+H)^+$. IR (KBr), υ (cm^{-1}): 3 365, 3 019, 1 467, 1 342, 1 175, 1 076, 1 049, 984, 965, 947, 923, 847, 750, 531.

2-{4-[2-(1, 8-Diethyl-1, 3, 4, 9-tetrahydro-pyrano [3, 4-b] indol-1-yl)-ethoxy]-phenoxy}-2-methyl-propionic acid (**C**)

200 mg(0.55 mmol) compound **C02**, 112 mg (0.5 mmol) ethyl *p*-hydroxyphenyloxy- isobutyrate, 0.2 g K_2CO_3 and 20 mL CH_3CN were added into 50 mL flask. The mixture was stirred for 8 hours under reflux. After work-up, the crude **C03** was hydrolyzed similar to the hydrolyzation procedure of compound **B03**. After purification by chromatograph, 58 mg yellow thick liquid, target compound **C** was obtained in 25.7% yield in two steps. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 7.2 Hz), 1.52 (s, 6H), 1.92 - 1.95 (m, 1H), 2.00 - 2.06 (m, 1H), 2.31 - 2.39 (m, 2H), 2.76 - 2.80 (m, 4H), 3.84 - 3.87 (m, 2H), 4.02 - 4.12 (m, 2H), 6.74 (d, 2H, *J* = 9.0 Hz), 6.87 (d, 2H, *J* = 9.0 Hz), 7.01 (d, 1H, *J* = 7.2 Hz), 7.08 (t, 1H, *J* = 7.2 Hz), 7.37 (d, 1H, *J* = 7.2 Hz).

2.4 Synthesis of compound D

The synthetic process of compound **D01** was similar to that of compound **E01**. And a yield of 68.7% was obtained. Mp 124 - 125 ℃. The synthesis of compound **D02** was according to the procedure of compound **B02**, yield 95.1%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (d, 3H, *J* = 6.9 Hz), 2.79 (s, 3H), 3.31 (q, 1H, *J* = 6.9 Hz), 3.91 (s, 3H), 4.34 (m, 3H), 7.11 - 7.16 (m, 2H), 7.33 (d, 1H, *J* = 8.4 Hz), 7.60 (s, 1H), 7.66 - 7.73 (m, 2H). ESI-MS (positive), *m/z*: 295 $(M+H)^+$, 317 $(M+Na)^+$.

Similar to the procedure of compound **B03**, compound **D03** was obtained with 82.5% yield.

2-{4-[2-(6-Methoxy-naphthalen-2-yl)-propoxy]-phenoxy}-2-methyl-propionic acid (**D**)

The hydrolyzation procedure of compound **B03** into target compound **D** was analogous to that of compound **B**. A white solid was obtained with 60% - 70% yield. Mp: 58 - 60 ℃. ^{1}H NMR (600 MHz, CD_3COCD_3) δ 1.45 (d, 3H, *J* = 7.2 Hz), 1.48 (s, 6H), 2.85 (br, 1H), 3.35 (m, 1H), 3.90 (s, 3H), 4.06 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.2 Hz), 4.16 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.2 Hz), 6.82 - 6.89 (m, 1H), 6.84 (d, 2H, *J* = 9.0 Hz), 6.88 (d, 2H, *J* = 9.0 Hz), 7.26 (d, 1H, *J* = 2.4 Hz), 7.48 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.75 - 7.77 (m, 3H). ^{13}C NMR (600 MHz, CD_3COCD_3) δ 17.7, 24.6, 39.4, 54.7, 73.5, 79.2, 105.5, 114.8, 118.6, 121.6, 125.5, 126.5, 126.8, 129.0, 129.1, 133.7, 139.1, 149.1, 154.7, 157.5, 174.6. IR (KBr), υ (cm^{-1}): 3 435, 3 043, 1 723, 1 632, 1 606, 1 505, 1 465, 1 393, 1 214, 1 162, 1 030, 853, 820.

2.5 Synthesis of compound E

Compound **E01** was synthesized according to the procedure of compound **B01**, and the pale yellow thick oil was obtained with 40% - 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (br, 1H), 3.88 (t, 2H, *J* = 5.1 Hz), 6.54 (d, 1H, *J* = 3.0 Hz), 7.12 - 7.16 (m, 2H), 7.23 (d, 1H, *J* = 7.8 Hz), 7.38 (d, 1H, *J* = 7.8 Hz), 7.66 (d, 1H, *J* = 7.8 Hz).

2-[4-(2-Indol-1-yl-ethoxy)-phenoxy]-2-methyl-propionic acid ethyl ester (**E**)

The target compound **E** was synthesized according to the procedure of compound **A02**. After work up and purification by column chromatograph, pale yellow thick liquid was obtained with yield of 15% - 25%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.2 Hz), 1.52 (s, 6H), 4.23 (m, 4H), 4.50 (t, 2H, *J* = 6.0 Hz), 6.52 (d, 1H, *J* = 9.0 Hz), 6.72 (d, 2H, *J* = 9.0 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 7.11 (t, 1H, *J* = 7.2 Hz), 7.21 - 7.24 (m, 2H), 7.40 (d, 1H, *J* = 7.8 Hz), 7.64 (d, 1H, *J* = 7.8 Hz). ^{13}C NMR (600 MHz, $CDCl_3$) δ 14.1, 14.2, 25.2, 45.7, 61.3, 67.2, 79.6, 101.6, 109.1, 114.9, 119.4, 121.0, 121.5, 121.6, 128.3, 128.6, 136.0, 149.4, 153.8, 174.2. ESI-MS (negative mode), *m/z*: 366 $(M-H)^-$. IR (neat), υ (cm^{-1}): 3 049, 1 732, 1 641, 1 610, 1 510, 1 464, 1 216, 1 139, 742.

2.6 Synthesis of compound F

2-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (**F02**)

180 mg (0.80 mmol) ethyl *p*-hydroxyphenyloxyisobutyrate, 102 mg (0.53 mmol) compound **F01** and 524 mg (2.0 mmol) Ph_3P were added into a 50 mL flask with 2.5 mL dry THF. The flask was put in ice-salt bath on a magnetic stirrer. 348 mg (2 mmol) DEAD was added drop-wise into the flask. Then the mixture was stirred overnight. The solvent was evaporated under reduced pressure to dry, and the resulting residue was put on silica gel column-chromatograph using petroleum ether and ethyl acetate as eluent. 86 mg white thick oil was obtained with 40.8% yield. ^{1}H NMR (600 MHz, CD_3COCD_3) δ: 1.22 (t, 3H, J = 7.2 Hz), 1.47 (s, 6H), 3.31 (s, 3H), 3.95 (t, 2H, J = 5.4 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.26 (t, 2H, J = 5.4 Hz), 6.81-6.86 (m, 4H), 6.99 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.13 (td, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.25 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 7.8 Hz). ESI-MS (positive), m/z: 399 $(M+H)^+$; (negative), m/z: 397 $(M-H)^-$.

2-{4-[2-(Benzooxazol-2-yl-methyl-amino)-ethoxy]-phenoxy}-2-methyl-propionic acid (**F**)

According to the synthetic procedure for target compound **B**, 63 mg (0.16 mmol) compound **F02** was put into the reaction, and 45 mg white solid was obtained with 76.8% yield after purification. Mp 66-68 ℃. ^{1}H NMR (600 MHz, CD_3COCD_3 + DMSO-d_6) δ: 1.44 (s, 3H), 1.46 (s, 3H), 3.29 (s, 3H), 3.93 (t, 2H, J = 5.4 Hz), 4.24 (t, 2H, J = 5.4 Hz), 6.68 (d, 2H, J = 12.6 Hz), 6.79 (d, 2H, J = 12.6 Hz), 6.97-7.32 (m, 4H). ^{13}C NMR (600 MHz, CD_3COCD_3 + DMSO-d_6) D: 24.8, 36.2, 49.6, 65.9, 79.1, 108.6, 114.9, 115.8, 120.1, 121.9, 123.8, 143.9, 148.0, 149.6, 153.3, 154.1, 175.2. ESI-MS (positive mode), m/z: 371 $(M+H)^+$; (negative mode), m/z: 369 $(M-H)^-$, 387 $(M+H_2O-H)^-$. IR (KBr), T (cm^{-1}): 1 705, 1 645, 1 586, 1 505, 1 464, 1 216, 1 148, 142.

2.7 Synthesis of compound G

2-{4-[2-(4-Benzyloxy-phenyl)-5-methyl-oxazol-4-ylmethoxy]-phenoxy}-2-methyl-propionic acid ethyl ester (**G02**)

To a solution of 0.1390 g (1.174 mmol) ethyl *p*-hydroxyphenyloxyisobutyrate and 0.1521 g (1.166 mmol) compound **G01** in 10 mL dry DMF, excessive NaH was added. The resulting mixture was stirred overnight at room temperature. After work-up and purification by column chromatagraph using petroleum ether and ethyl acetate, 0.1672 g white solid was obtained with 77.10% yield. ^{1}H NMR (300 MHz, $CDCl_3$) D: 1.29 (t, 3H, J = 7.2 Hz), 1.55 (s, 6H), 2.40 (s, 3H), 4.25 (q, 2H, J = 7.2 Hz), 4.92 (s, 2H), 5.12 (s, 2H), 6.83-6.92 (m, 4H), 7.04 (d, 2H, J = 8.7 Hz), 7.37-7.44 (m, 5H), 7.97 (d, 2H, J = 8.7 Hz).

2-{4-[2-(4-Benzyloxy-phenyl)-5-methyl-oxazol-4-ylmethoxy]-phenoxy}-2-methyl-propionic acid (**G**)

Target compound **G** was synthesized according to synthetic procedure of compound **B**. After work-up and purification, 0.1293 g white solid was obtained with 84.19% yield. Mp: 164-165 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) D: 1.55 (s, 6H), 2.20 (s, 1H), 2.44 (s, 3H), 4.95 (s, 2H), 5.14 (s, 2H), 6.91-6.95 (m, 4H), 7.06 (d, 2H, J = 9.0 Hz), 7.37-7.47 (m, 5H), 7.98 (d, 2H, J = 9.0 Hz). ^{13}C NMR (600 MHz, $CDCl_3$) D: 10.6, 25.0, 31.1, 62.6, 70.2, 115.2, 115.6, 122.9, 127.7, 128.1, 128.3, 128.8, 136.6, 160.0. IR (KBr), T (cm^{-1}): 3 435, 1 717, 1 611, 1 583, 1 500, 1 465, 1 384, 1 252, 1 216, 1 177, 1 149, 1 009, 840.

2.8 Synthesis of compound H

2-Methyl-2-[4-(3-phenyl-allyloxy)-phenoxy]-propionic acid ethyl ester (**H01**)

135 mg (0.60 mmol) ethyl *p*-hydroxyphenyloxyisobutyrate, 300 mg (1.04 mmol) cinnamyl tosylate and 100 mg K_2CO_3 were added into a 100 mL flask with 25 mL CH_3CN. The resulting mixture was refluxed for 8 hours. After work-up, a crude product of compound **H01** was directly used for next step. IR (KBr), T (cm^{-1}): 1 732, 1 504, 1 449, 1 382, 1 283, 1 214, 1 176, 1 138, 1 019, 966.

2-Methyl-2-[4-(3-phenyl-allyloxy)-phenoxy]-propionic acid (**H**)

The target compound **H** was prepared by hydrolyzation of compound **H01** according to the procedure of compound **B**. After purification, white solid was obtained with 70% - 80% yield. Mp: 142-143 ℃. ^{1}H NMR (600 MHz, CD_3COCD_3) D: 1.50 (s, 6H), 4.69 (dd, 2H, J_1 = 5.7 Hz, J_2 = 1.5 Hz), 6.48 (t, 0.5H, J = 6.0 Hz), 6.51 (t, 0.5H, J = 6.0 Hz), 8.79 (d, 1H, J = 16.2 Hz), 6.89-6.93 (m, 2H), 7.26 (t, 1H, J = 7.2 Hz), 7.34 (t, 2H, J = 7.2 Hz), 7.48 (d, 2H, J = 7.2 Hz). ^{13}C NMR (600 MHz, CD_3COCD_3) D: 24.6, 68.6, 79.1, 115.0, 120.6, 125.1, 126.4, 127.7, 128.5, 132.3, 136.7, 149.2, 154.4, 174.6.

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2006年全国医院药学(合理用药)学术会议征文通知

随着医院药学事业的发展,医院药学模式是以病人为中心由供应型向服务型转换,临床药学作为医院药学的重要组成部分,其目的就是如何提高合理用药水平,为病人服务。因此,合理用药工作质量的好坏直接关系到医疗质量和合理用药水平。为适应新形势的需要,探讨合理用药中的新经验、新动向,更好地为病人服务,促进医院药学事业的发展,中国药学会医院药学专业委员会拟在 2006年 9月主办以研讨合理用药为主题的全国医院药学学术会议。现向全国药学各专业人员征文,有关内容如下。

1 征文内容

现代医院药学学科建设与发展;医院药学的机构设置及专业设置;医院药学的工作性质和任务;医院药学制剂室的建设、现状和发展前景;我国临床药学的现状和前途;我国医院药学的人才现状和专业人才的培养;如何开展适合我国的临床药学;药学咨询和药学服务的经验和体会;临床药学中合理用药判断标准及其他问题;医院药学研究中的新技术、新成果;其他医院药学的有关热点问题。

2 征文要求

未公开发表的论文均可作为本次会议的征文稿件。全文控制在 3 000字内,研究论文需附中、英文摘要(书写格式请按中国医院药学杂志投稿要求),综述不超过 4 000字。所有征文超过 1 000字者均需另附 800字左右的摘要,附软盘。论文截止日期: 2006年 5月 30日。论文可通过邮局寄至中国医院药学杂志编辑部,条件允许最好发电子邮件,请注明作者详细联系地址和电话。地址:武汉市胜利街 155号,邮政编码: 430014,电话: 86- 27- 82836596; E-mail: 82836596@163.com。请在信封和论文稿件及电子邮件上注明/会议征文0字样,以免同杂志正常稿件混淆。

3 说明

会议录用后均给第一作者发会议通知;会议将编辑论文集;会议设优秀论文一、二、三等奖;与会代表将获取国家继续教育学分证书。会议地点成都。

中国药学会医院药学专业委员会

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