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Synthesis of (S)-2-(3-Arylacrylamido)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)ethoxy]phenyl}propanoic Acids

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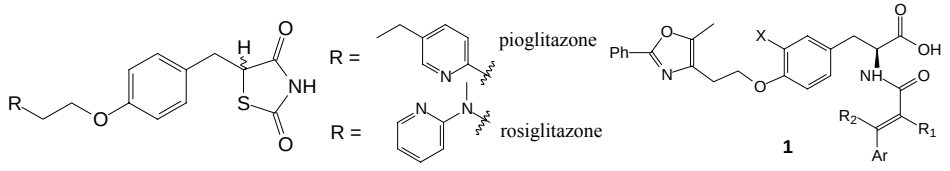
Abstract: The synthesis of (S)-2-(3-arylacrylamido)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acids is described. Their structures were confirmed by ^{1}H-NMR.

Keywords: (S)-2-(3-Arylacrylamido)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenylpropanoic acids, synthesis.

Peroxisome proliferator-activated receptors (PPARs) have been the subject of intense research following the discovery of their physiological roles in the regulation glucose and lipid homeostasis[1]. PPARγ is the molecular target for the thiazolidinedione (TZD) class of insulin sensitizing antihyperglycemic agents. Two of the TZDs, pioglitazone and rosiglitazone, have been used for treatment of type 2 diabetes[2]. PPARα is the molecular target for the fibrates (*e.g.* fenofibrate and clofibrate) which primarily decrease serum triglyceride levels and increase HDL cholesterol (HDLc) levels[3]. New dual PPAR-α/γ agonists, designed to combine the beneficial effects of insulin sensitizers and fibrates, might reduce the weight gain associated with adipogenesis resulting from PPARγ activetion through the simultaneous stimulation of lipid oxidation and decreased adiposity observed after PPARα activation. Here we report a series of tyrosine-based (S)-2-(3-arylacrylamido)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acids (**1**, **Figure 1**) that are potent and efficacious PPARa/γ dual agonists.

The process for preparing new derivatives was shown in **Scheme 1**: The key intermediate, 2-(5-methyl-2-phenyloxazol-4-yl)ethanol for **4** was prepared, following exposure of benzamide to methyl 4-bromo-3-oxopentanoate **2**[5] in hot toluene followed



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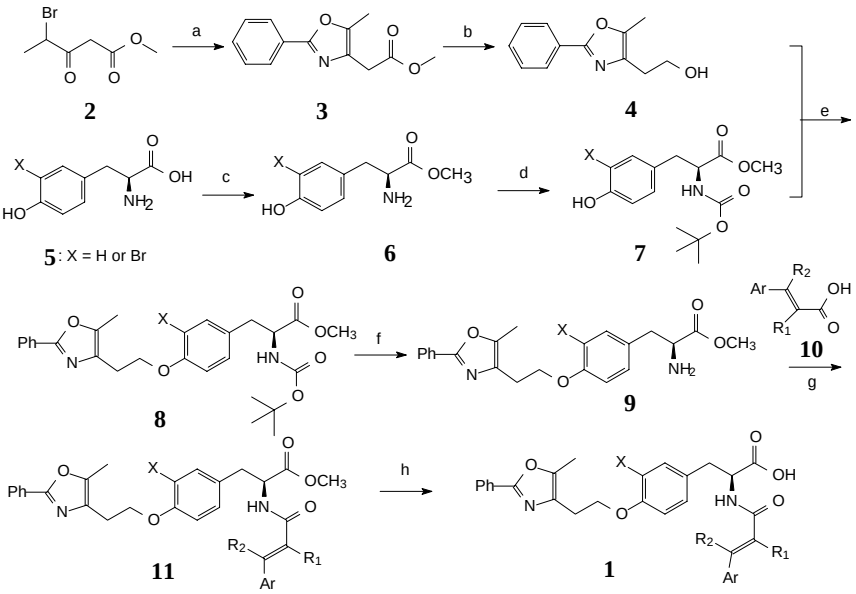
by ester reduction with LAH in THF. The other intermediate **7** was prepared by amidation of compounds **5** followed with BOC_2O. Mitsunobu reaction between **4** and **7** using triphenylphosphine and diisopropylazodicarboxylate in toluene was followed by removal of the BOC protecting group with CF_3COOH in dichloromethane to afford the amine **9**. Intermediate **9** is derivatized on the tyrosine nitrogen to provide the targeted set of analogues following saponification with LiOH. Reaction of the amine **9** with **10** provided the (*S*)-methyl-2-(3-arylacrylamido)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl) ethoxy]phenyl}propanoates **11**. Saponification with aqueous LiOH in THF provided **1**.

Scheme 1



a) $PhCONH_2$, $PhCH_3$, reflux; b) LAH, Et_2O, r.t.; c) $SOCl_2$, MeOH, reflux; d) BOC_2O, Et_3N, CH_3CN, r.t.; e) PPh_3, DEAD, $PhCH_3$, r.t.; f) CF_3COOH, CH_2Cl_2; g) CDI, CH_2Cl_2, r.t.; h) LiOH, THF-H_2O, r.t..

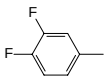
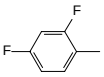
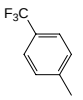
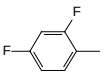
Experimental

Melting points were determined on RY-1 instrument, and the themometer was uncorrected. ^{1}H-NMR spectrum was recorded on a Brucker JMM-ECA-300 spectrometer. Rotatory value was measured with PE-243B polarimeter.

Preparation of 2-(5-methyl-2-phenyloxazol-4-yl)ethanol, **4**. A solution of 2.32 g (11.1 mmol) of benzamide and 2 g (16.7 mmol) of methyl 4-bromo-3-pentanoate in 40 mL of dry toluene was heated at 120℃ for 18 h. The solvent was removed *in vacuo.* Purification of the residue by silica gel chromatography using hexane/EtOAc (4/1) as eluent to afford 560 mg (22%) of **3** as a clear oil.

To a solution of 231 mg (1 mmol) of **3** in 5 mL of Et_2O at 0℃ was added dropwise 1 mL (1 mmol) of 1.0 mol/L LAH in Et_2O solution. The solution was stirred at r.t. for 16 hr, quenched by the addition of 0.04 mL of water, 0.04 mL of 15% NaOH solution

Table 1 Structure, mp , rotatory value and ^{1}H-NMR of the compounds

1	X	R_1	R_2	Ar	Mp(℃)	$[\alpha]_D^{20}$	^{1}H-NMR (DMSO-d_6, δ ppm, J Hz)
a	H	H	H		207-209	+80.0	8.29 (d, 1H, J=8.1), 7.91-7.89 (m, 2H), 7.52-7.38 (m, 10H), 7.15-7.13 (m, 2H), 6.85-6.83 (m, 2H), 6.71 (d, 2H, J=16), 4.50 (m, 1H), 4.17 (t, 2H, J=6.7), 3.06-2.82 (m, 4H), 2.33 (s, 3H)
b	H	F	H		174-176	+37.3	12.87 (brs, 1H), 8.79 (d, 1H, J=8.1), 7.91~7.88 (m, 2H), 7.64-7.62 (m, 2H), 7.52-7.36 (m, 6H), 7.19-7.17 (d, 2H, J=8.4), 6.86-6.84 (m, 3H), 4.54-4.48 (m, 1H), 4.16 (t, 2H, J=6.8), 3.13-2.97 (m, 2H), 2.91 (t, 2H), 2.33 (s, 3H)
c	H	H	H		188-190	+68.3	8.36 (1H, d, J=7.7), 7.90-7.88 (m, 2H), 7.75 (m, 4H), 7.49-7.42 (m, 4H), 7.15-7.13 (d, 2H, J=8.8), 6.85-6.82 (m, 3H), 4.52 (m, 1H), 4.15 (t, 2H, J=6.7), 3.08-2.84 (m, 4H), 2.33 (s, 3H)
d	H	H	H		170-172	+60.0	12.55 (brs, 1H), 8.42 (d, 1H, J=8.0), 7.89 (m, 2H), 7.81-7.44 (m, 8H), 7.13 (d, 2H,J=8.8), 6.86-6.75 (m, 3H), 4.54 (m, 1H), 4.18 (t, 2H, J=6.6), 3.08-2.82 (m, 4H), 2.33 (s, 3H)
e	H	H	H		204-206	+75.0	8.28 (d, 1H, J=8.2), 7.89 (m, 2H), 7.60 (s, 1H), 7.49-7.40 (m, 7H), 7.13-6.78 (m, 2H), 6.86 (m, 3H), 4.50 (m, 1H), 4.17 (t, 2H, J=6.6), 3.28 (s, 1H), 3.05 (m, 1H), 2.90 (m, 3H), 2.34 (s, 3H)
f	H	H	H		203-205	+26.5	12.68 (brs, 1H), 8.27 (d, 1H, J=8.0), 7.91-7.88 (m, 2H), 7.65-7.60 (m, 1H), 7.50-7.33 (m, 6H), 7.15 (d, 2H, J=8.6), 6.85-6.83 (d, 2H, J=8.6), 6.66 (d, 1H, J=16), 4.55-4.49 (m, 1H), 4.17 (t, 2H, J=6.6), 3.07-2.83 (m, 4H), 2.34 (s, 3H)
g	H	H	H		199-201	+23.3	12.79 (brs, 1H), 8.47 (d, 1H, J=8.1), 7.92-7.89 (m, 2H), 7.74-7.66 (m, 1H), 7.55-7.30 (m, 5H), 7.20-7.10 (m, 3H), 6.88-6.70 (m, 3H), 4.50 (m, 1H), 4.18 (t, 2H, J=6.7), 3.10-2.80 (m, 4H), 2.34 (s, 3H)
h	H	H	H		198-200	+18.2	12.66 (brs, 1H), 8.37 (d, 1H, J=8.1), 7.91-7.89 (m, 2H), 7.75 (d, 1H, J=1.7), 7.50-7.46 (m, 3H), 7.19-7.13 (m, 3H), 6.85 (d, 2H, J=8.7), 6.75-6.74 (m, 1H), 6.57-6.56 (m, 1H), 6.49 (d, 1H, J=16), 4.49-4.48 (m, 1H), 4.17 (t, 2H), 3.04-3.00 (m, 1H), 2.91 (t, 2H), 2.86-2.82 (m, 1H), 2.34 (s, 3H)
i	Br	H	H		243-245	+38.1	12.77 (brs, 1H), 8.42 (d, 1H, J=8.0), 7.90-7.88 (m, 2H), 7.77-7.76 (m, 4H), 7.50-7.43 (m, 5H), 7.20-7.17 (m, 1H), 7.07 (d, 1H, J=8.6), 4.55 (m, 1H), 4.24 (t, 2H), 3.08-3.03 (m, 1H), 2.94-2.84 (m, 3H), 2.35 (s, 3H)
j	Br	H	H		221-223	+60.4	12.76 (brs, 1H), 8.43 (d, 1H, J=8.2), 7.91-7.88 (m, 2H), 7.72-7.70 (m, 1H), 7.51-7.28 (m, 6H), 7.06 (d, 1H, J=8.4), 6.76 (d, 1H, J=16), 4.55-4.49 (m, 1H), 4.24 (t, 2H, J=6.7), 3.07-3.02, 2.88-2.83 (m, 2H), 2.91 (t, 2H, J=6.7), 2.35 (s, 3H)

and dried over $MgSO_4$. The mixture was filtered, the filtrate was concentrated and dried under vacuum for several hours to give 180 mg (87%) of **4** as a yellow solid.

General procedure of preparation of (2S)-3-[3-(un)substituted-4-hydroxyphenyl]-2-tert-butoxycarbonyl aminopropionic acid methyl ester **7**. To the suspension of **5** in 10

mL methanol at 0°C, 5.5 mmol of thionyl chloride was added dropwise *via* syringe.

The resulting solution was kept at reflux for 3 h. After removal of the solvent and the excess of thionyl chloride *in vacuo*, the residue was dissolved in dry acetonitrile (5 mL), then 5.5 mmol of triethylamine and 5.5 mmol of di-*tert*-butyl dicarbonate were added. The mixture was stirred for 1.5 h at r.t.. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel (heptane/EtOAc) to give **7**.

General procedure of preparation of (S)-2-(3-arylacrylamido)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acid, **1**. A solution of 22.1 mmol of diethyl azodicarboxylate and 18.5 mmol of triphenylphosphine in 30 mL of THF were added rapidly at 0°C to a stirred mixture of 18.5 mmol of **4** and 18.5 mmol of **7** in 50 mL of THF at r.t.. The reaction was stirred at r.t. for 18 h and the solvent was removed *in vacuo* to dryness. The residue was taken up in ether/water and 32.2 mmol of lithium hydroxide monohydrate added at once. After stirring for 12 h at r.t., the aqueous layer was seperated and extracted with ether, and all the organic solutions were combined and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography using hexane/EtOAc to give **8**.

To a stirred solution of 3.3 mmol of **8** in 30 mL of CH_2Cl_2 at r.t. was added 3.3 mL of trifluoroacetic acid. After stirring overnight, the reaction was quenched with 0.1 mol/L NaOH solution, and the layers were separated. The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue purified by silica gel chromatography with ($CHCl_3$/MeOH) as eluant to give **9**.

2.4 mmol of **10** was added to the solution of CDI (2.8 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at r.t. for 1 h. 2.4 mmol of **9** was added and the resulting mixture was stirred at r.t. overnight. The solution was washed with water and dried over $MgSO_4$. The solvents were removed *in vacuo* and the residue purified by silica gel chromatography with EtOAc/hexane as eluant to give **11**. **11** was dissolved in THF (6 mL) at r.t.. 1 mol/L lithium hydroxide solution (4 mL) was added and stirred for 30 min. The pH adjusted to ~3.0 with 2 mol/L hydrochloric acid. The resulting solids were filtered and dried to yield the title compounds **1**.

Acknowledgments

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References and Note

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6. The mass spectral data of compounds **1a-h** were deposited to the editorial office of CCL.

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