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Chinese Chemical Letters 22 (2011) 409–412
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Diclofenac derivatives with insulin-sensitizing activity

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Received 15 July 2010
Available online 17 January 2011

Abstract

A series of diclofenac derivatives were synthesized. The insulin-sensitizing activity of 28 new compounds was evaluated in 3T3-L1 cells. The compounds **10a** and **10f** exhibited similar insulin-sensitizing activity with positive drug rosiglitazone.

Keywords: Diclofenac derivatives; Synthesis; Insulin-sensitizing activity

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia as well as insulin resistance. Recently T2DM was also presumed as a chronic inflammation disease [1]. Studies showed that inflammatory cytokines such as C-reactive protein (C-RP), interleukins (ILs), tumor necrosis factor-alpha (TNF-α), plasminogen activator inhibitor type 1 (PAI-1) probably play a major role in the development of insulin resistance, which is known as important pathologic factor that lead to T2DM [2]. Improving insulin sensitivity can not only effectively keep blood glucose at an appropriate level, but also postpone or avoid the occurrence of undesired complications.

Some recent studies have revealed that non-steroidal anti-inflammatory drugs (NSAIDs) possessed some extent of insulin-sensitizing activity [3]. Studies showed that NSAIDs can control inflammation by inhibiting the expression of inflammatory factors and mediators of inflammation [4]. These findings aroused our interest to search new insulin sensitizers by structure modification of NSAIDs. In our preliminary work, NSAIDs diclofenac's derivative **10a** was found having a similar insulin-sensitizing activity with positive control rosiglitazone [5]. However, compound **10a** only showed a weak agonist activity on peroxisome proliferator-activated receptor γ (PPARγ), which is a common target receptor of many kinds of insulin-sensitizers. This result suggests that diclofenac acid derivatives might have different insulin-sensitizing mechanisms. Herein we reported the synthesis and insulin-sensitizing activities of more diclofenac derivatives.

Synthetic route of diclofenac derivatives was shown in Scheme 1. According to different substitute positions on the phenyl cycle of the target compounds, *p*-nitrophenol or *m*-nitrophenol was used as the starting material. The key intermediate **7** was prepared referring to the synthesis of diclofenac through 7 steps of reaction. Compound **8** was

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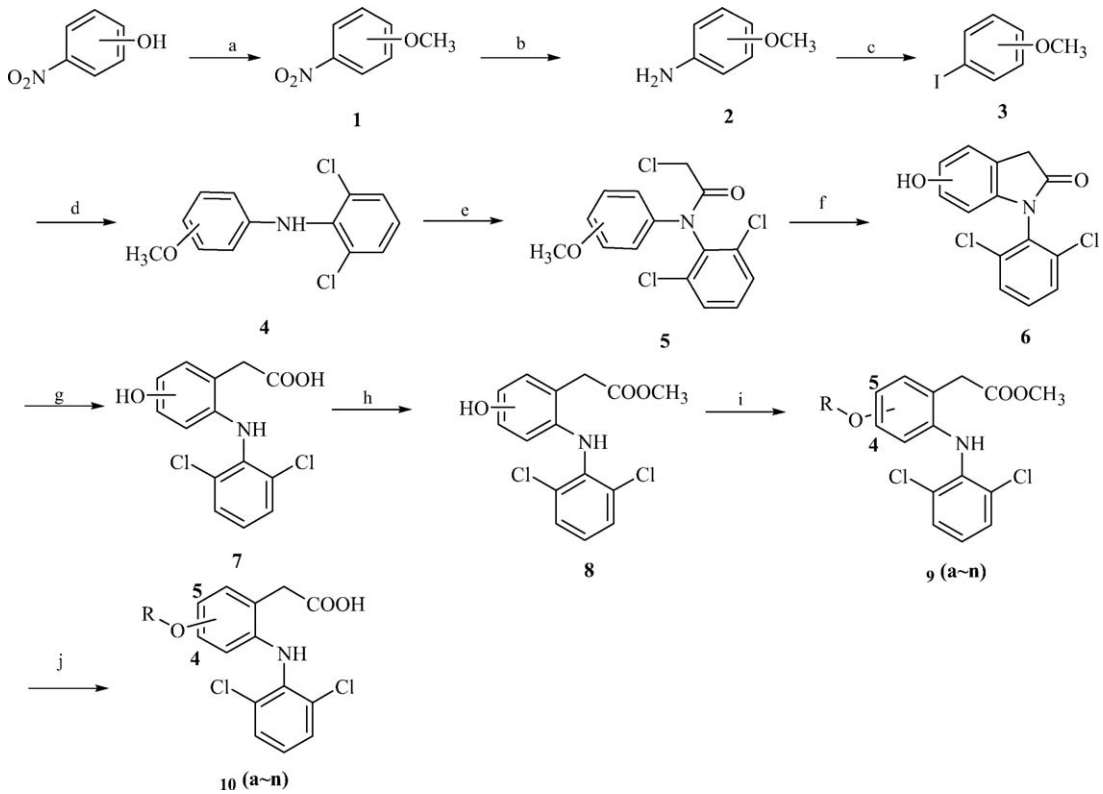
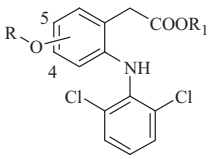
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.11.008



Scheme 1. Synthetic route for declofenac derivatives. Reagents: (a) CH_3I, K_2CO_3, acetone, reflux, 4–6 h, 96–98%; (b) Fe–HCl, EtOH, reflux, 4–6.5 h, 87.8–95.5%; (c) (1) H_2SO_4, THF, 0 °C; (2) H_2SO_4, $NaNO_2$ aqueous, 0 °C, 0.5 h; (3) KI aqueous, 0 °C, 1 h, reflux, 2 h, 49.7–72.1%; (d) 2,6-dichlorobenzenamine, Cu, CuI, K_2CO_3, NMP, 160 °C, 40 h, 45.1–56.8%; (e) 2-chloroacetyl chloride, 105 °C, 1.5 h, 71.3–88.5%; (f) $AlCl_3$, N_2, 250 °C, 0.5 h, 160 °C, 2 h, 74.3–84.9%; (g) 10% NaOH aqueous, reflux, 2 h, 71–75%; (h) methanol, *p*-methylbenzenesulfonic acid, 80 °C, 3 h, 68–72%; (i) R–OH, Ph_3P, diethyl azodicarboxylate, Et_2O, r.t., 16–30 h, 31.5–77.3%; (j) THF–NaOH, HCl aqueous, r.t., 6–24 h, 27.9–72.1%.

Table 1
Increasing percentage of triglyceride in 3T3-L1 cell.



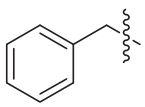
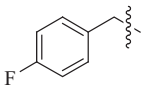
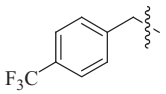
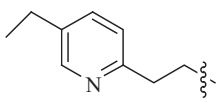
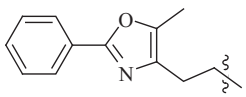
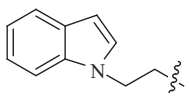
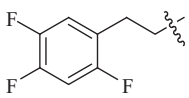
Compound	R	R-position	R_1	Insulin-sensitizing activity	
				10^{-9} mol/L	10^{-5} mol/L
9a		4	CH_3	4.8 ± 3.8	88.7 ± 22.4
10a		4	H	5.1 ± 0.6	92.1 ± 21.7
9b		5	CH_3	4.2 ± 1.5	35.3 ± 2.0
10b		5	H	5.0 ± 1.5	79.8 ± 6.5
9c		4	CH_3	3.5 ± 1.7	35.2 ± 9.6
10c		4	H	4.4 ± 4.1	59.6 ± 24.4
9d		5	CH_3	4.9 ± 0.9	46.5 ± 16.5
10d		5	H	5.0 ± 2.6	67.7 ± 5.8

Table 1 (*Continued*)

Compound	R	R-position	R_1	Insulin-sensitizing activity	
				10^{-9} mol/L	10^{-5} mol/L
9e		4	CH_3	4.5 ± 1.4	33.3 ± 12.5
10e		4	H	4.8 ± 3.7	75.7 ± 24.9
9f		5	CH_3	5.0 ± 1.2	80.5 ± 5.3
10f		5	H	5.5 ± 1.0	92.3 ± 7.6
9g		4	CH_3	4.2 ± 7.0	25.4 ± 10.0
10g		4	H	5.2 ± 1.2	43.9 ± 12.2
9h		5	CH_3	4.6 ± 1.5	80.4 ± 4.8
10h		5	H	5.9 ± 1.3	78.4 ± 4.5
9i		4	CH_3	4.0 ± 3.0	58.7 ± 15.6
10i		4	H	7.0 ± 4.8	81.4 ± 6.1
9j		5	CH_3	5.3 ± 1.4	19.5 ± 16.0
10j		5	H	6.0 ± 1.5	89.7 ± 8.6
9k		4	CH_3	2.1 ± 3.5	39.8 ± 20.8
10k		4	H	3.9 ± 1.5	40.0 ± 5.8
9l		5	CH_3	3.7 ± 1.4	74.5 ± 8.7
10l		5	H	2.8 ± 4.5	68.5 ± 3.9
9m		4	CH_3	5.0 ± 2.1	64.1 ± 17.0
10m		4	H	4.3 ± 1.6	42.6 ± 5.1
9n		5	CH_3	0.7 ± 2.2	65.3 ± 23.1
10n		5	H	4.5 ± 1.2	47.3 ± 2.7
Rosiglitazone				5.3 ± 1.9	93.7 ± 9.8

obtained via methyl esterification of **7** [5]. Condensation of **8** with desired alcohol via Mitsunobu reaction provided compounds **9a–n**. Saponification of **9a–n** with NaOH (aq.) to give the target compounds **10a–n**, respectively [6].

All synthesized compounds were screened for insulin-sensitizing activity by measuring the triglyceride accumulation resulting from insulin-regulated differentiation of 3T3-L1 cells [7]. The marketed insulin-sensitizing drug rosiglitazone was selected as positive control. The activities data are presented in Table 1. As indicated in Table 1, at concentration of 10^{-5} mol/L, compounds **10a** and **10f** showed similar promoting differentiation activity with positive drug rosiglitazone. There is no obvious activity regularity by comparing compounds with substitution on 4- or 5-position of the phenyl cycle. In most cases, the activities of those compounds with a free carboxyl group were higher than their corresponding methyl ester derivatives.

In summary, we have discovered a novel class of diclofenac derivatives which possess potent insulin-sensitizing activity, and they may be used as candidate compounds in the development of antidiabetic agents. The inhibiting activity test of diclofenac derivatives on the expression of inflammatory factors is ongoing presently.

Acknowledgments

The research work was supported by National Natural Science Foundation (No. 30960462), Guizhou Social Development Scientific Foundation (No. 2008-3039), Governor's Foundation for Excellent Scientific and Educational Talents of Guizhou (No. 2009-81) and Excellent Youth Scientific Talents Foundation of Guizhou (No. 2009-24).

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[5] Q.J. Zhang, J.T. Wang, H.S. Wu, et al. Bioorg. Med. Chem. Lett. 19 (2009) 3324.
[6] Physical and spectral data for some diclofenac derivatives: **10f**: pale yellow solid, mp 125–127 °C; IR (KBr, cm^{-1}): 3335, 3200 (br), 1690, 1569, 1514, 1439, 1376; 1H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 2H), 5.15 (s, 2H), 6.33 (d, 1H, J = 8.8 Hz), 6.78 (dd, 1H, J = 2.8 Hz, 8.8 Hz), 6.92 (s, 1H), 6.98 (d, 1H, J = 2.8 Hz), 7.11 (t, 1H, J = 8.0 Hz), 7.47 (s, 1H), 7.49 (s, 1H), 7.66 (d, 2H, J = 8.0 Hz), 7.76 (d, 2H, J = 8.4 Hz), 12.75 (br, 1H); EI-MS (*m*/*z*): 469 (M+), 310, 292, 159; Anal. calcd. for $C_{22}H_{16}Cl_2F_3NO_3$: C, 56.19; H, 3.43; N, 2.98, Found: C, 56.20; H, 3.32; N, 2.95; **10h**: off-white solid, mp 139–142 °C; IR (KBr, cm^{-1}): 3344, 2965, 2947, 1712, 1615, 1586, 1517, 1454; 1H NMR (400 MHz, DMSO-d_6): δ 1.19 (t, 3H), 2.59 (q, 2H), 3.11 (t, 2H, J = 6.4 Hz), 3.68 (s, 2H), 4.13 (t, 2H, J = 6.6 Hz), 6.37 (d, 1H, J = 8.4 Hz), 6.62 (d, 1H, J = 8.4 Hz), 6.79 (s, 1H), 6.88 (t, 1H, J = 8.0 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.36–7.42 (m, 2H), 7.56 (d, 1H, J = 8.0 Hz), 8.36 (s, 1H); EI-MS (*m*/*z*): 311, 230, 133, 118; Anal. calcd. for $C_{23}H_{22}Cl_2N_2O_3$: C, 62.03; H, 4.98; N, 6.29, Found: C, 62.19; H, 5.10; N, 6.26;**10i**: off-white solid, mp 130–133 °C; IR (KBr, cm^{-1}): 3333, 3300 (br), 1703, 1616, 1588, 1518, 1453; 1H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H), 2.93 (t, 2H, J = 6.8 Hz), 3.59 (s, 2H), 4.00 (t, 2H, J = 6.7 Hz), 6.10 (d, 1H, J = 2.0 Hz), 6.49–6.51 (dd, 1H, J = 2.4 Hz, 2.0 Hz), 6.93 (s, 1H), 6.99 (m, 1H), 7.18 (d, 1H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.52 (m, 3H), 7.96 (d, 2H, J = 8.4 Hz); EI-MS (*m*/*z*): 417, 186, 104, 43; Anal. calcd. for $C_{26}H_{22}Cl_2N_2O_4$: C, 62.79; H, 4.46; N, 5.63, Found: C, 62.63; H, 4.56; N, 5.75; **10j**: off-white solid, mp 137–138 °C; IR (KBr): 3342, 3200 (br), 1741, 1623, 1580, 1506, 1450; 1H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H), 2.90 (t, 2H, J = 6.6 Hz), 3.68 (s, 2H), 4.15 (t, 2H, J = 6.4 Hz), 6.32 (d, 1H, J = 8.8 Hz), 6.70 (dd, 1H, J = 2.8 Hz, 8.8 Hz), 6.88 (d, 1H, J = 13.2 Hz), 7.06–7.10 (m, 1H), 7.46–7.51 (m, 6H), 7.92 (m, 2H), 12.85 (br, 1H); EI-MS (*m*/*z*): 478, 186, 104, 43; Anal. calcd. for $C_{26}H_{22}Cl_2N_2O_4$: C, 62.79; H, 4.46; N, 5.63, Found: C, 62.83; H, 4.49; N, 5.73.
[7] 3T3-L1 cells were obtained from Shanghai Institute of Biochemistry and Cell Biology and maintained at 37 °C in an atmosphere of 5% CO_2 in Dulbecco's modified Eagle medium (DMEM, Gibco) containing 10% fetal bovine serum (FBS). The 3T3-L1 pre-adipocytes were grown in 96-well plates until 2 days postconfluence. The differentiation was induced by addition of 5 μg/mL insulin (Lilly), 0.5 mmol/L isobutylmethylxanthine and 1 μmol/L dexamethasone (Sigma). The induction medium was removed 2 days after incubation. After an additional 2 days of incubation in DMEM supplemented with 10% FBS and 5 μg/mL insulin, the medium was changed every other day with DMEM supplemented with 10% FBS. Cells were challenged during the first 4 days of differentiation with different compounds at 10 μmol/L, with rosiglitazone as positive control and 0.1% DMSO as negative control. The addition of compounds to the medium was accomplished by dissolving the drug in DMSO and diluting the drug 1000-fold with medium. 7 days after the induction of 3T3-L1 cells, Oil Red O staining was used to detect triglyceride accumulation in 3T3-L1 cells. The precipitation of Oil Red O in 3T3-L1 adipocytes was dissolved with isopropyl alcohol, and OD value at 510 nm was determined by ELISA spectrometry. The results were based on 3 independent experiments.