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An Efficient and Scalable Synthesis of Hydroxyglimepiride and Carboxyl Glimepiride: Main Metabolites of Glimepiride

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ABSTRACT A facile and scalable synthetic route for preparing metabolites of glimepiride is disclosed here. Starting from commercially available materials **4** and **6**, hydroxyglimepiride (2) and carboxyl glimepiride (3) were synthesized on a gram scale with 64% and 67% overall yields, respectively, in a four-step sequence. *N*, *N*'-carbonyldiimidazole, and $NaBH_4$ were used in the reduction of carboxyl glimepiride (3) to hydroxyglimepiride (2), which makes the process safer and more convenient. Besides, excellent purity of product (99.34%) was achieved without purification over column chromatography.

KEYWORDS Glimepiride, Metabolites, Facile synthesis.

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INTRODUCTION

Glimepiride **1**, a third-generation sulfonylurea agent, which exhibits a potent anti-hyperglycemic activity with a low risk of inducing hypoglycemia,[1,2] is commonly used in the treatment of type II diabetes. Metabolic processes of drugs are always the subject of intense scrutiny in pharmaceutical companies and research institutions. Isolation, identification, synthesis, and pharmacological/toxicological studies of metabolites not only are necessary during early-stage drug development but also plays an important role in drug discovery.[3] Glimepiride is mainly metabolized by hepatic oxidative biotransformation to an active metabolite hydroxyglimepiride **2**, which contributes about 33% of lowering glucose effect of the parent compound, and an inactive metabolite carboxyl glimepiride **3 [Figure 1]**.[4,5] Both metabolites showed good safety in animal toxicology studies.[6]

RESULTS AND DISCUSSION

Gurjar *et al* previously reported a synthetic route for preparing hydroxyglimepiride **[Scheme 1]**.[7] The hydroxymethyl moiety was introduced by Wittig reaction of cyclohexanedione *mono*-ethylene ketal and subsequent hydroboration–oxidation reaction. After protecting the free hydroxy group with PMB, acidic cleavage of ethylene ketal group, treatment with hydroxylamine hydrochloride and reduction of oxime, cyclohexylamine intermediate was obtained in both *cis* and *trans* forms. Separation of this mixture was difficult and they continued their work with the mixture and accomplished separation at later stage. The sulfonylurea unit was provided by condensation reaction between the corresponding isocyanate and sulfonamide **4** in the presence of base. After deprotection of the PMB group and separation of the *cis* and *trans* mixture by preparative HPLC, the *cis*- and *trans*-isomer of hydroxyglimepiride were provided. The method is straightforward but the route is tedious including 9 steps with 12% overall yield. Separation of isomers by preparative HPLC is another issue which limits its applications in scalable synthesis.

As one of our cooperative projects to synthesize both hydroxyglimepiride and carboxyglimepiride, and their derivatives on a gram scale, a new synthetic route was designed in our recent study **[Scheme 2]**.

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8.37 (t, *J* = 5.8 Hz, 1H, -CONH-), 7.81 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.32 (d, *J* = 7.7 Hz, 1H, -CONH-), 4.17 (s, 2H, $-CH_2-$), 3.57 (s, 3H, $-COOCH_3$), 3.50 (m, 2H, $-CH_2-$), 3.23 (m, 1H, -CH-), 2.90 (t, *J* = 7.2 Hz, 2H, $-CH_2$-Ar), 2.15–2.26 (m, 3H, $-CH_2-$ and -CH-), 2.01 (s, 3H, $-CH_3$), 1.84 (m, 2H, $-CH_2-$), 1.74 (m, 2H, $-CH_2-$), 1.32 (m, 2H, $-CH_2-$), 1.15 (m, 2H, $-CH_2-$), 0.98 (t, *J* = 7.5 Hz, 3H, $-CH_3$). ^{13}C NMR (126 MHz, DMSO-d_6): δ 175.03, 171.84, 152.04, 151.65, 150.54, 144.96, 138.19, 131.93, 129.17, 127.33, 51.88, 51.31, 47.87, 41.16, 35.15, 31.12, 27.29, 15.98, 12.82, 12.70. HRMS (ESI), *m/z* calcd 535.2221 for $C_{25}H_{35}N_4O_7S$ $[M + H]^+$, found 535.2230.

Trans-4-(3-((4-(2-(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamido)ethyl)phenyl)sulfonyl)ureido) cyclohexane-1-carboxylic acid (3)

To a stirred solution of **8 (**3.5 g, 6.55 mmol) in THF (35 mL) was added 1 *M* aqueous LiOH (19.7 mL, 19.70 mmol). The reaction was stirred at room temperature for 4 h until complete consumption of **8**, as monitored by TLC analysis. Water and methyl *tert*-butyl ether were added. The aqueous layer was separated, acidified with 1 *M* HCl until pH reached to 2~3. The resulting white solid was filtered, washed with water and dried in vacuum at 50°C to obtain 2.79 g of carboxyl glimepiride **3**. Yield: 82%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.03 (s, 1H, -COOH), 10.33 (s, 1H, $-SO_2NH-$), 8.37 (t, *J* = 5.7 Hz, 1H, -CONH-), 7.81 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.32 (d, *J* = 7.7 Hz, 1H, -CONH-), 4.17 (s, 2H, $-CH_2-$), 3.53–3.47 (m, 2H, $-CH_2-$), 3.22 (m, 1H, -CH-), 2.90 (t, *J* = 7.2 Hz, 2H, $-CH_2$-Ar), 2.18 (q, *J* = 7.6 Hz, 2H, $-CH_2-$), 2.11 (m, 1H, -CH-), 2.01 (s, 3H, $-CH_3$), 1.87–1.81 (m, 2H, $-CH_2-$), 1.77–1.70 (m, 2H, $-CH_2-$), 1.34–1.24 (m, 2H, $-CH_2-$), 1.19–1.08 (m, 2H, $-CH_2-$), 0.98 (t, *J* = 7.6 Hz, 3H, $-CH_3$). ^{13}C NMR (126 MHz, DMSO-d_6): δ 176.29, 171.84, 152.04, 151.66, 150.53, 144.97, 138.19, 131.94, 129.18, 127.33, 51.88, 48.00, 41.33, 35.15, 31.26, 30.66, 27.36, 15.99, 12.83, 12.70. HRMS (ESI), *m/z* calcd 521.2064 for $C_{24}H_{33}N_4O_7S$ $[M + H]^+$, found 521.2062.

3-Ethyl-N-(4-(N-((trans-4-(hydroxymethyl)cyclohexyl) carbamoyl)sulfamoyl)phenethyl)-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (2)

To a solution of carboxyl glimepiride **3 (**2.1 g, 4.03 mmol) in THF (20 mL) at room temperature was added *N*, *N*'-carbonyldiimidazole (1.44 g, 8.88 mmol). The reaction was stirred for 3 h before cooled in an ice-bath and added $NaBH_4$ (0.46 g, 12.16 mmol) and water (2.9 mL) portion wise. After continuous stirring for 1 h, 1 *M* HCl (aq) was added to adjust the pH to 2~3. DCM was added and the organic layer was separated, washed with water and dried over Na_2SO_4, filtered, and concentrated. The crude product was stirred in acetone (6.5 mL) at room temperature for 2 h, filtered, dried in vacuum at 45 °C for 2 h to afford 1.94 g of hydroxyglimepiride **2**. Yield: 95%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (t, *J* = 5.8 Hz, 1H, -CONH-), 7.82 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.74 (brs, 1H, -OH), 7.41 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.41 (d, *J* = 8.0 Hz, 1H, -CONH-), 4.19 (s, 2H, $-CH_2-$), 3.50–3.65 (m, 3H, $-CH_2-$ and -CH-), 3.45 (d, *J* = 6.4 Hz, 2H, $-CH_2O-$), 2.97 (t, *J* = 7.3 Hz, 2H, $-CH_2$-Ar), 2.27 (q, *J* = 7.6 Hz, 2H, $-CH_2-$), 2.05 (s, 3H, $-CH_3$), 1.97 (d, *J* = 12.0 Hz, 2H, $-CH_2-$), 1.83 (d, *J* = 12.9 Hz, 2H, $-CH_2-$), 1.45 (m, 1H, -CH-), 1.17 (m, 2H, $-CH_2-$), 0.98–1.11 (m, 5H, $-CH_3$ and $-CH_2-$). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.77, 152.77, 150.69, 150.32, 146.01, 137.73, 134.00, 129.93, 127.35, 68.08, 52.35, 49.96, 40.63, 39.57, 36.25, 32.56, 28.14, 16.78, 13.32, 12.95. HRMS (ESI), *m/z* calcd 507.2272 for $C_{24}H_{35}N_4O_6S$ $[M + H]^+$, found 507.2283. The spectral data were consistent with literature.[7] HPLC purity: 99.3%, retention time of 5.78 min.

CONCLUSION

We have established an efficient, facile, and scalable route for the preparation of both hydroxyglimepiride and carboxyl glimepiride in overall yields of 64% and 67%, respectively. The process has several advantages over previously reported approach: Short steps, simplicity of product purification, good yields, and avoid of the utilization of dangerous and hazardous reagents. Further evaluations of compounds **2**, **3** and their derivatives in bioactivities and drug-like properties are ongoing.

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