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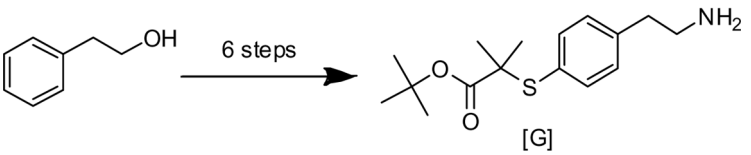
NOVEL AND EFFICIENT SYNTHESIS OF *TERT*-BUTYL-2-(4-(2-AMINOETHYL)PHENYLTHIO)-2-METHYLPROPANOATE, A KEY INTERMEDIATE IN THE SYNTHESIS OF UREIDO THIOISOBUTYRIC ACID

Jigar Desai, Anil Argade, Sanjay Gite, Kiran Shah, Laxmikant Pavase, Pravin Thombare, and Pankaj Patel
Medicinal Chemistry Division, Zydus Research Centre, Ahmedabad, Gujarat, India

GRAPHICAL ABSTRACT



Abstract *A convenient and cost-effective synthesis of pharmacologically important* tert-*butyl-2-(4-2-aminoethyl)phenylthio)-2-methylpropanoate from commercially available 2-2-phenyl-1-ethanol is described.*

Keywords Fibrates; hyperlipidemia; thioisobutyric acid

Hyperlipidemia is associated with an increased risk of coronary heart disease, the leading cause of death in the western world.[1] Drug therapy with fibrate is one way to effectively lower triglyceride and low-density lipoprotein and raise high-density lipoprotein in human. Fibric acid analogs such as clofibrate, fenofibrate, and bezafibrate are effective in the treatment of hyperlipidemia in humans[2] (Fig. 1).

Fibrates are relatively weak PPARα agonists and mediate their lipid-lowering activity through PPARα activation. Ureido fibrate analogs showed moderate PPARα selectivity on both murin and human receptors. Earlier studies showed that ureido fibrate analogs with modified urea substituents do not increase PPARα selectivity.[3]

However, modification of the fibrate headgroup to thioisobutyric acid (TiBA) increased PPARα activity relative to PPARγ and δ. Ureido-TiBA (GW-9578) is a

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Address correspondence to Jigar Desai, Medicinal Chemistry Division, Zydus Research Centre, Ahmedabad, Gujarat, India. E-mail: jigarndesai@rediffmail.com

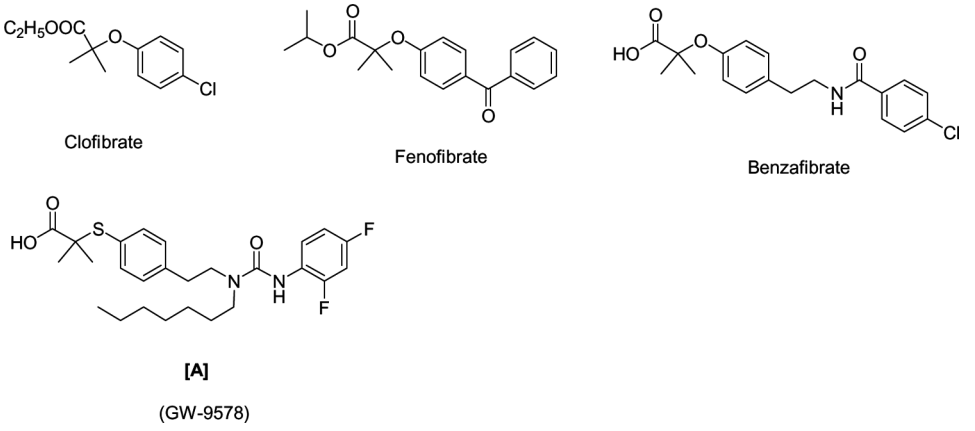


Figure 1. Fibrate analogues reported in literature.

potent PPARα agonist with 300-fold selectivity on the murin receptors and 20-fold selectivity on human receptors.

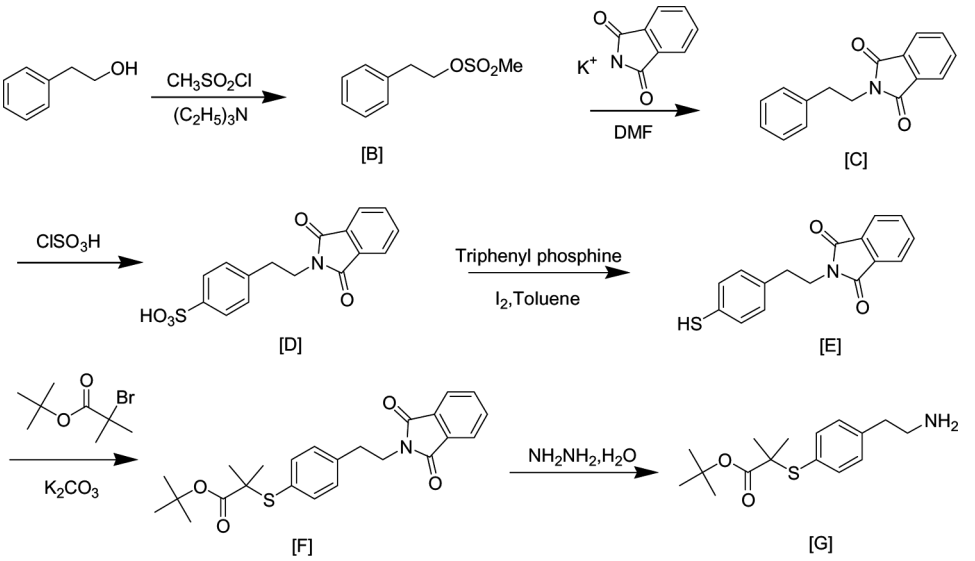
Considering the potential of GW-9578, a selective PPARα agonist, different synthetic approaches have been published in the literature.

Brown et al.[4] reported synthesis of ureido-thio isobutyric acid (**A**) (GW-9578), a subtype of selective PPARα agonist with potent lipid-lowering activity. This synthetic approach suffers from various drawbacks such as the use of toxic and expensive palladium acetate, transition-metal catalyst (Wilkinson's), and the use of malodorous thio phenols.

Boros et al.[5] reported an improved process for the synthesis of compound **A**. This procedure describes reduction of the sulfonyl chloride derivative to disulfide by using sodium bisulfide with a small amount of sodium iodide at 90 °C. Iodine generated *in situ* was repeatedly removed by titration with aqueous $NaHSO_3$. Solid iodine generated during the reaction sublimates and sometimates clogs the condenser. Methyl isothio butyrate moiety was introduced by the use of methyl trimethyl silyl dimethyl keten acetal. The latter reaction was performed at −78 °C. Chlorine displacement from methyl isothio butyrate derivative with potassium phthalimide required 0.5 eq of 18-crown-6 followed by deprotection of phthalimide with hydrazine hydrate to give the amine compound in 26% overall yield.

We report an easy and convenient approach for the synthesis of a key intermediate of GW-9578 analog starting with cheap and commercially available 2-phenyl-1-ethanol (Scheme 1). 2-Phenyl-1-ethanol was converted to mesylate derivative (**B**) using methane sulfonyl chloride. Mesylate derivative (**B**) was reacted with potassium phthalimide to give intermediate **C**. Chlorosulfonation of **C** gave sulfonic acid derivative (**D**), which was then reduced to thiol analog (**E**) using triphenyl phosphine and iodine. Thiol analog (**E**) was treated with *tert*-butyl bromoisobutyrate followed by reaction with hydrazine hydrate to give amine compound (**G**) in excellent yield.

The reported procedure represents a novel approach of using an innovative step for the reduction of aryl sulfonic acid derivative (**D**) to its aryl thiol derivative



Scheme 1. Synthesis of key intermediate ureido fibrate analogue (**G**).

(**E**) by using triphenyl phosphine and a catalytic amount of iodine.[6] This step is a fast and simple reduction of sulfonic acid without formation of aryl disulfide side product.

EXPERIMENTAL

All the raw materials were obtained commercially and used without further purification. ^{1}H NMR spectra were recorded using $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard on a Bruker 300-MHz instruments. *J* values are expressed in hertz. Infrared (IR) spectrum was recorded on a Fourier transform (FT)–IR-8300 Shimadzu instrument using $CHCl_3$ as solvent. Electronspray ionization–mass spectra (ESI-MS) were recorded on a Shimadzu LC-MS-2010A instrument.

Synthesis of Methanesulfonic Acid Phenethyl Ester [B]

2-Phenyl-1-ethanol (10 g, 82 mmol) was dissolved in dichloromethane (100 mL), and triethyl amine (16.5 g, 163 mmol) was added dropwise to the mixture at 25 °C. The reaction mixture was cooled to 10 °C, and methane sulfonyl chloride (11.26 g, 98.3 mmol) was added dropwise. The mixture was allowed to stir at 25 °C for 4 h. Completion of reaction was monitored by thin-layer chromatography (TLC). The mixture was quenched in water (100 mL). The organic layer was separated, washed with water (50 mL), dried over sodium sulfate, and evaporated under reduced pressure to get mesilate derivative (**B**) as a liquid (14 g, 85.8%). ^{1}H NMR ($CDCl_3$): δ 2.82 (3H, s), 3.05 (2H, *t*, $J = 6.81$), 4.41 (2H, *t*, $J = 6.9$), 7.22–7.35 (5H, m). ESI-MS (*m*/*z*) 218 ($M + NH_4^+$, 100%). IR ($CHCl_3$) 3030, 1355, 1172 cm^{-1}.

Synthesis of 2-Phenethyl-isoindole-1,3-dione [C]

Mesilate derivative (**B**) (2.0 g, 10 mmol) was dissolved in dimethyl formamide (10 mL), and potassium phthalimide (2.2 g, 12 mmol) was added to the mixture. The reaction mixture was heated to 50 °C for 4 h. Completion of reaction was monitored by TLC. The mixture was quenched in water (100 mL). The solid compound was filtered, washed with water (100 mL), and dried to afford the solid compound (2.2 g, 88%). ^{1}H NMR ($CDCl_3$): 2.99 (2H, t, $J = 7.5$), 3.92 (2H, t, $J = 7.5$), 7.21–7.31 (5H, m), 7.70 (2H, dd, $J = 3.09, 5.34$), 7.82 (2H, dd, $J = 3.09, 5.5$). ESI-MS (m/z): 252 ($M + H^+$, 100%). IR (KBr) 1708, 1396, 1101, 709 cm^{-1}.

Synthesis of 4-[2-(1,3-Dioxo-1,3-dihydro-Isoindol-2-yl)-ethyl]-benzenesulfonic Acid [D]

Isoindol derivative (**C**) (2.5 g, 10 mmol) was added in parts to a solution of chlorosulfonic acid (2.3 g, 20 mmol) precooled at 0–5 °C. The reaction mixture was stirred for 2 h at the same temperature. Completion of the reaction was monitored by TLC. The reaction mixture was poured in ice-cold water (150 mL). The solid obtained was filtered, washed with water (100 mL), and dried to get the solid product (1.2 g, 47%). ^{1}H NMR ($CDCl_3$): 3.14 (2H, t, $J = 7.2$), 3.98 (2H, t, $J = 7.2$), 7.50 (2H, d, $J = 8.3$), 7.72–7.76 (2H, m), 7.80–7.85 (2H, m); 7.94 (2H, d, $J = 8.4$). ESI-MS (m/z) 332 ($M + H^+$, 100%). IR (KBr) 1771, 1715, 1170 cm^{-1}.

Preparation of 2-[2-(4-Mercapto-phenyl)-ethyl]-isoindole-1,3-dione [E]

Sulfonic acid derivative (**D**) (2.7 g, 8.1 mmol) was dissolved in toluene (50 mL). Triphenyl phosphine (2.35 g, 8.9 mmol) was added at 25 °C followed by a catalytic amount of iodine. The mixture was heated to 35–40 °C for 4 h. The completion of the reaction was monitored by TLC. The reaction mixture was quenched in water (100 mL), and the organic layer was separated and distilled under reduced pressure. The crude compound obtained was purified through column chromatography using silica gel G, mesh size 230–400, mobile phase 30% ethyl acetate in hexane, to get a white solid product (2.1 g, 91%). ^{1}H NMR ($CDCl_3$): 2.94 (2H, t, $J = 7.89$), 3.40 (1H, s), 3.89 (2H, t, $J = 7.8$). ESI-MS (m/z) 301.2 ($M + NH_4^+$, 100%). IR (KBr) 2558, 1702, 1395, 717 cm^{-1}.

Preparation of 2-{4-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-phenylsulfanyl}-2-methyl-propionic Acid *tert*-Butyl Ester [F]

Thiol analog (**E**) (2.8 g, 9.8 mmol) was dissolved in acetone (20 mL). Anhydrous potassium carbonate (1.6 g, 12 mmol) was added to this, followed by 2-bromo-2-methyl-propionic acid *tert*-butyl ester (2.6 g, 12 mmol). The mixture was allowed to reflux for 3 h. Completion of the reaction was monitored by TLC. The mixture was cooled to 25 °C and quenched in water (200 mL). The solid obtained was filtered, washed with water (50 mL), and dried to get a solid compound (4.0 g, 88%). ^{1}H NMR ($CDCl_3$): 1.40 (15H, bs), 2.96–3.01 (2H, m), 3.88–3.94 (2H,

m), 7.22 (2H, d, $J = 8.19$), 7.43 (2H, d, $J = 8.16$), 7.71 (2H, dd, $J = 3.06, 5.46$), 7.83 (2H, dd, $J = 2.91, 5.46$). ESI-MS 443.2 $(M + NH_4)^+$. IR (KBr) 1770, 1712, 1398, 1361, 1143, 721 cm^{-1}.

Preparation of 2-[4-(2-Amino-ethyl)-phenylsulfanyl]-2-methyl-propionic Acid *tert*-Butyl Ester [G]

Isoindole derivative (**F**) (4.2 g, 9.8 mmol) was dissolved in absolute alcohol (50 mL). To this, 99% hydrazine hydrate (0.5 g, 12 mmol) was added. The reaction mixture was heated to 50 °C for 1 h. Hydrochloric acid (5 mL, 35% commercial grade) was added to the mixture, and the mixture was refluxed for 0.5 h. Completion of reaction was monitored by TLC. The white solid obtained was filtered, and the filtrate was concentrated under reduced pressure to remove excess alcohol. The pH of the solution was adjusted to 9 by adding aqueous ammonia. The compound was extracted by adding ethyl acetate (50 mL × 3). The combined organic layer was washed with water (50 mL), dried over sodium sulfate, and evaporated under reduced pressure to afford a solid product (3.0 g, 71%), mp 155–160 °C. ^{1}H NMR ($CDCl_3$): 1.42 (15H, s), 2.74 (2H, t, $J = 6.81$), 2.96 (2H, t, $J = 6.9$), 7.14 (2H, d, $J = 8.01$), 7.43 (2H, d, $J = 8.04$). ESI-MS (m/z) 296.2 ($M + H^+$, 100%). IR ($CHCl_3$) 4212, 3371, 2977, 2933, 1716, 1591, 1367, 1280, 1255, 1149, 846, 759 cm^{-1}.

CONCLUSION

The reported synthetic methodology for the synthesis of *tert*-butyl 2-(4-(2-amino ethyl)phenylthio)-2-methylpropanoate has an advantage of using cheap and commercially available 2-phenyl-1-ethanol. All the steps involved in this methodology are very facile and do not require any special conditions. It can be extended for multikilogram synthesis. The reported procedure avoids the use of expensive and poisonous metal catalysts such as Pt and Pd.

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