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A facile synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid: Metabolite of anti-hyperlipidemic drug Fenofibrate

Greesha N Majethia,

Wahajul Haq,

Ganesaratnam K. Balendiran*

Department of Chemistry, Youngstown State University, One University Plaza, Youngstown, OH, USA

Abstract

Synthesis and characterization of drug metabolites has emerged as an important area of research in consideration to the significant contribution of studies on metabolites in drug research. The present work comprises synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid, a metabolite of anti-hyperlipidemic drug fenofibrate. The desired compound was prepared by two different synthetic routes. The ketone group of fenofibric acid was reduced using sodium borohydride in one route whereas the hydrolysis of isopropyl ester of the reduced fenofibrate was achieved by the mild alkaline hydrolysis in the other path. Both the ways of synthesis furnished the desired compound in excellent yield and purity. The new synthetic congener was characterized by spectroscopic methods.

Keywords

Fenofibrate; Synthetic metabolites; Alkaline hydrolysis; Sodium borohydride reduction

Introduction

The fibrate class of drugs are in clinical use since their discovery without severe adverse effects [1]. These molecules are reported to have attractive diverse pharmacological properties [2–9]. In addition to the anti-hyperlipidemic regimen the fibrates are also under investigation for other therapeutic applications due to their high safety index [10–12].

*Corresponding author. gkbalendiran@ysu.edu (G.K. Balendiran).

CRediT authorship contribution statement

Greesha N Majethia:. **Wahajul Haq:** Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ganesaratnam K. Balendiran:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2023.101282.

Recent reports suggest that the fibrate class of drugs are being explored for the repurposing approach to address other diseases, diabetes, cardiovascular disorder and cancer [13,14]. Also there are articles on developing new formulation for improving therapeutic efficacy of fibrates [15,16].

There are a variety of approaches being explored for the discovery of new drugs and therapeutic treatment but in the recent past the drug metabolism studies namely, pharmokinetics played an important role towards the development of new drugs as well as drug formulations. Over the past few decades remarkable progress in the understanding of drug metabolism and pharmacokinetics suggest the significance of metabolites in the mechanism of action as well toxicity of the drugs in the research area of drug discovery and development [17]. The methodology for the comprehension of drug metabolism, identification of metabolites, bioavailability are developing rapidly with advanced analytical techniques too. Recently quantitative analysis of organelle-level absolute quantification through mass spectrometry imaging is reported [18]. The metabolomics studies are highly relevant to recognizing metabolism in biological milieu also facilitate the exploration of drug repurposing and drug-drug interactions [19,20]. Drug molecules undergo various chemical modifications at different organs and flow through different pathways in the human body following its administration, resulting in metabolites which can have toxicological or functional characteristics that are distinct from their parent drugs. Recently this is reported as a new area of drug metabolism caused by factors including gut microbiome [21].

Fibrates are known to reduce the catalytic activity of Aldo-Keto Reductase (AKR) family of proteins, AKR1B10 and Aldose reductase where the latter is implicated in diabetes and related complications [22–26]. Furthermore, it has been believed that fenofibrates regulate the lipid metabolism by augmenting the involvement of PPAR-α receptors and AKR family enzymes [25]. Fenofibrate is converted to its active metabolites, fenofibric acid, reduced fenofibrate and reduced fenofibric acid in its mode of action [27]. The metabolism of fenofibrate was investigated in different species, rats, dogs and monkey. The data with the administration of fenofibrate in Sprague-Dawley (SD) rats revealed the presence of above mentioned metabolites as well as identification of additional metabolites, fenofibric acid taurine and reduced fenofibric acid [28]. Similar studies were described for Cynomolgus monkeys, Sprague-Dawley (SD) rats and beagle dogs and in all of these cases presences of the metabolites reported confirm the operation of proposed metabolic pathways. Metabolomics approach reveals the effects of antihypertensives and lipid-lowering drugs on the human metabolism [28,29]. The chemical structure of the important metabolites of fenofibrate are shown in Fig. 1.

The studies of drug metabolites have been an important area of new drug development strategy due to the integrated role of metabolites to understand the efficacy and toxicity of the therapeutically significant molecules. In addition, the various biochemical and biological studies of the metabolites, the chemical synthesis of these attractive molecules remains an interesting area of research for exploration. The chemical synthesis of these molecules are challenging as the metabolites are sophisticated molecules which are generated as a consequence of drug metabolism in the biophase. In recent past synthesis of several novel drug metabolites that are reported in the literature employed de novo chemical synthesis

of the metabolites using wide range of chemical reactions describing innovative chemical transformations, functional group tolerance, orthogonally compatible reactions including chiral reactions [30–33].

The synthesis of reduced fenofibric acid (**4**), the inadequately investigated metabolite of fenofibrate, is challenging if the molecule is prepared by total synthesis approach especially when sufficient quantity is expected to be available for better characterization. However, a facile expeditious synthesis of this molecule can be achieved by late-stage derivatization approach. The late-stage functionalization comprises the introduction of a chemical group or transforming a functional group at the last-stage of the synthesis starting with a commonly available and characterized molecule. This approach has the potential to speed up the preparation of novel chemical entities and expand and diverse chemical libraries and will have major impact on drug discovery. Functional group tolerance and mild conditions allows access to new molecules not easily accessible by conventional approaches without the need for laborious de novo chemical synthesis. Number of literature reports suggest that the late-stage derivatization/transformation is an attractive approach for the facile synthesis of complex molecules like natural product analogs, immuniosuppressive drug and drug metabolites [34–37]. In view of the above discussion, the present work comprises development of a facile synthesis and characterization of a unique secondary metabolite of fenofibrate. The main objective of the present work comprises the first synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid (**4**) an underexplored metabolite of the fenofibrate. Since the synthesis of compound **4** has not been reported so far, here we present the work comprises of the synthesis and characterization of the novel metabolite of fenofibrate, 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid.

Materials and methods

The reduced fenofibric acid can be prepared by either reduction of already known metabolites like fenofibric acid (**3**) (Scheme 1) or by the hydrolysis of reduced fenofibrate (**2**) (Scheme 2). It is important to note that starting material for both the routes are not available commercially and therefore they required to be prepared from fenofibrate (**1**) and fully characterized before these can be used as starting materials. Our laboratory has already standardized the synthesis of fenofibric acid (**3**) and reduced fenofibrate (**2**) and therefore, the synthesis of these molecules needed as starting materials are prepared in gram quantities in highly pure form following the procedures reported recently [38–42]. The synthesis of the desired product (**4**) is carried out by both the routes to standardize the optimized route of synthesis to get best yield and purity. The experimental details of both the routes are described in the following text.

Synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid (4) from fenofibric acid (3)

As mentioned the required starting material, fenofibric Acid (**3**), is not commercially available therefore the needed starting compound **3** is prepared in the laboratory and characterized by spectroscopic methods according to the methods previously reported [34].

Briefly, fenofibric acid (**3**) was prepared by the mild alkaline hydrolysis of fenofibrate. The fenofibrate was stirred in equimolar amount of aqueous 1 N NaOH at 50–60 °C for 2–3 hrs. After completion of reaction as monitored by TLC the reaction mixture was evaporated under reduced pressure, acidified to pH 2 by aq. HCl and the precipitate is extracted in ethyl acetate. The organic layer is concentrated and the desired compound is precipitated by addition of hexane to get chromatographically homogeneous solid in excellent yield. The compound is characterized by spectroscopic methods.

The Synthesis of reduced fenofibric acid (**4**) was carried out from fenofibric acid as shown in Scheme 1. A solution of fenofibrate was treated with sodium borohydride at 0–5 °C and the reaction mixture was stirred for a period of 10 min or till the completion of the reaction as monitored by TLC. The reaction mixture was quenched with dilute HCl and after usual work up the desired compound **4** was obtained as chromatographically pure white solid as shown in Scheme-1.

Experimental

A solution of fenofibric Acid (640 mg, 2 mmol) in methanol (15 ml) was stirred in a round bottom flask on a magnetic stirrer maintaining the temperature between 0 and 4 °C. To this stirred solution sodium borohydride (200 mg) was added in potions. After complete addition the stirring was continued for additional 15 min or till the reaction come to culmination as monitored by TLC. The excess methanol was removed under reduced pressure and residue was diluted with cold water (10 ml) followed by the addition of 2 N HCl until the reaction mixture reaches pH 2. The acidified mixture was extracted with ethyl acetate (2 ×15 ml), and the combined organic layer was washed with brine until neutral and dried over anhydrous magnesium sulphate. The organic layer is separated by filtration and the clear filtrate is evaporated under reduced pressure to obtain a gummy matter which gave a white solid from ethyl acetate and hexane mixture. Yield: 580 mg, (90 %). Melting point: 133–135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (S, 6H: -$(CH_3)_2$), 5.68 (S,1H: –C<u>H</u>-OH), 6.83, 6.84 (d, *J*=8.6 Hz, 2H: Ar), 7.19, 7.20 (d, *J*=8.6 Hz, 2H: Ar), 7.24, 7.26 (d, *J*= 8.6 Hz, 2H: Ar), 7.30, 7.32 (d, *J*= 8.6 Hz, 2H: Ar).

^{13}C NMR (125 MHz $CDCl_3$): δ 23.23, 25.21, 25.25, 39.47, 39.64, 39.81, 39.98, 74.22, 77.13, 77.39, 77.64, 78.79, 118.84, 123.70, 127.22, 127.44, 127.86, 128.06, 132.26, 137.90, 143.54, 154.68, 176.16.

ES-MS: Calculated for $C_{17}H_{17}ClO_4$ $[M + H]^+$=320.77 Observed 320, $[M + Na]^+$= 343.

Synthesis of reduced fenofibric acid (4) by the hydrolysis of compound 2—

Synthesis of reduced fenofibric acid (**4**) was carried out by the mild alkaline hydrolysis of reduced fenofibrate as starting material. The required starting material is not commercially available, therefore the starting material (compound **2**) was prepared and characterized in the laboratory according to the procedure reported earlier by the mild reduction [36]. Briefly, fenofibrate was stirred in methanol followed by the addition for 4–5 M excess of sodium borohydride at room temperature. After complete addition the reaction mixture was

quenched by the addition of dilute HCl and after usual work up the compound **2** is isolated as oily material in almost quantitative yield.

The reduced fenofibrate (**2**), thus obtained was subjected to alkaline hydrolysis by the treatment of **2** with equimolar amount of aqueous 1 N NaOH at 50–60 °C for 2–3 hrs. After completion of the reaction, it was acidified to pH 2 by aq HCl and the precipitate is extracted in ethyl acetate. The organic layer is concentrated and the desired compound is isolated as chromatographically homogeneous white powder as shown in Scheme-2.

Experimental

To a solution of compound **2** (724 mg, 2 mmol) in methanol (10 ml), 1 N NaOH (2.5 ml, 2.5 mmol) was added dropwise and the reaction mixture was magnetically mixed at 50–60° for 2–3 h in a round bottom flask. The reaction mixture was monitored on TLC and after completion of the reaction, solvent was evaporated under reduced pressure on a rotavapor. The residue was taken in water and acidified with 2 N HCl up to pH 2. The reaction was extracted in ethyl acetate 10 ml x 3 times and the combined organic layer was washed with brine until neutral and dried over $MgSO_4$ and filtered. The ethyl acetate layer was concentrated at reduced pressure to get chromatographically homogeneous gummy solid. Upon purification the product was obtained as solid white powder from ethyl acetate and hexane mixture. Yield 565 mg (88 %). Melting point: 134–135 °C.

Results and discussion

Traditionally, drug metabolites have been both difficult and highly challenging to synthesize but are favourably important for biochemical and pharmacological studies as well as understanding the mode of their action. Conventional methods for metabolite synthesis, such as those engage the use of microsomes or multistep synthetic chemistry, are extremely costly and time consuming. Also the environmental waste generated by such processes face another level of negative consequences including health and or environmental hazards. The present work comprises a first report for a facile and efficient synthesis of a secondary metabolite (compound **4**) by late-stage functionalization/derivatization strategy to obtain the desired compound in single step in high yield and purity under mild experimental conditions. The compound **4** was successfully prepared by two different synthetic routes and using different starting material under different experimental conditions. The required starting material (compounds **2** and **3**) are not commercially available hence these compounds are also prepared in the laboratory and fully characterized by the procedures already reported. The products, obtained by both the different routes, were analysed using spectroscopic methods and found identical in terms of their spectroscopic data and the yields and purity of the products were also matching. Thus, it is evident that both routes gave similar quality product and successful development of new routes for the synthesis of reduced fenofibric acid, a metabolite of fenofibrate. The ^{1}H NMR data of compound 4 show a sharp singlet at ~ 5.68 corresponding to the proton generated after the reduction of the ketone carbonyl. The ^{13}C data clearly show the presence of only one carbonyl peak at 176.16 ppm whereas a sharp peak around 195 ppm corresponding to the benzophenone carbonyl is absent in compound 4.

Finally the base peak corresponding to the $[M + Na]^+$ at 343 further supports the structure of 2-(4-((4-chlorophenyl) (hydroxy) methyl) phenoxy)-2-methylpropanoic acid (**4**).

Conclusion

In summary, a facile and efficient synthesis of compound **4** was successfully developed by late-stage derivatization methodology. The synthetic transformations were carried out under mild experimental conditions in high yields by two different routes. The synthetic metabolite will be highly useful for the *in vivo* and *in vitro* studies pending so far due to unattainability of this compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Data availability

All the data/results/information associated with this study is disclosed and not is withheld.

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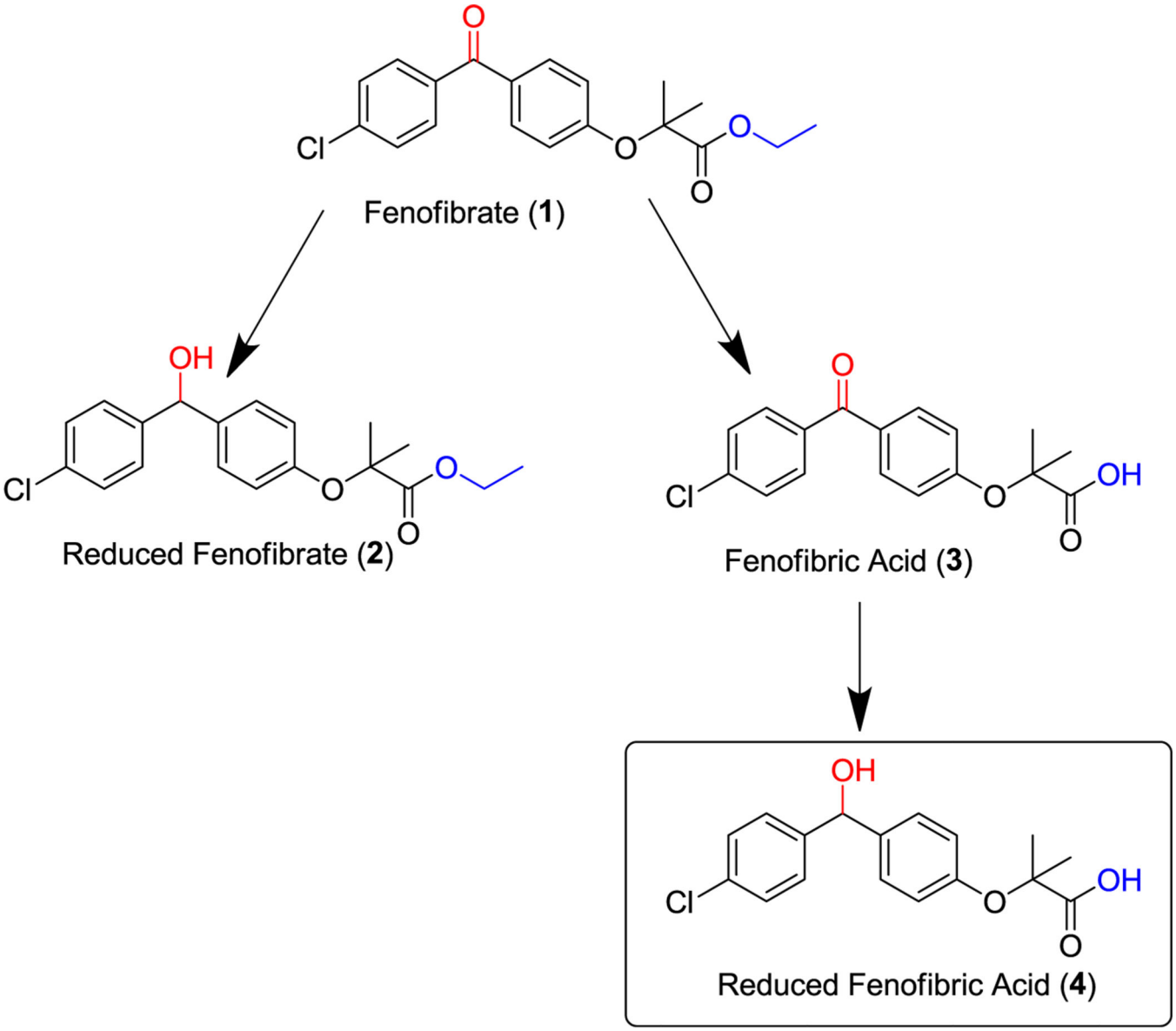
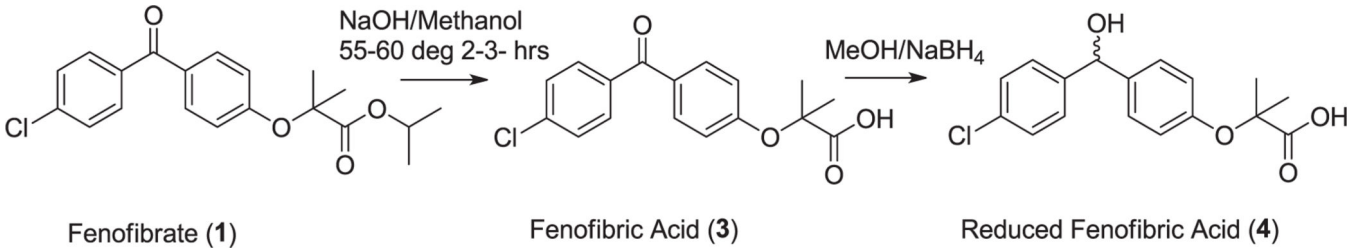
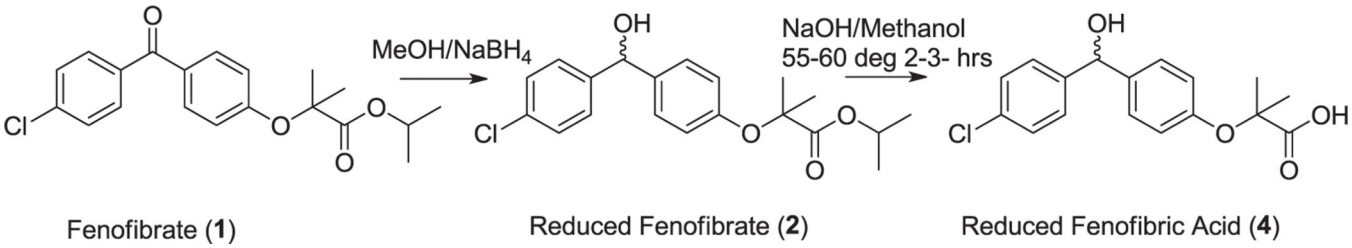


Fig. 1.
Chemical structure of fenofibrate and its prominent metabolites.



Scheme 1.

Synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid (4) from Fenofibric acid (**3**).



Scheme 2.

Synthesis of 2-(4-((4-chlorophenyl)(hydroxy)methyl) phenoxy)-2-methylpropanoic acid (4) from compound **2**.