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Fibrane the reduced derivative of fenofibrate

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Keywords

Fibrate; Fibrane

1. Introduction

Catalytic activities of Aldo-Keto reductase (AKR) protein family members, AKR1B10 and Aldose Reductase are decreased by the fibrate class of compounds [1–3]. Among all the first generation fibrates, Fenofibrate is most potent inhibitor against the enzyme activities of AKR family of proteins [1–3]. However, fibrates were previously believed to act as agonists for the nuclear receptor, peroxisome proliferator-activated receptor α (PPARα) and were consequently used clinically as therapeutic agents in the treatment of hyperlipidemia, heart disease and diabetic complications [4–8]. The ability of fibrate to target both AKR and PPARαfamily of proteins necessitate a need to generate a specific derivative of it that can selectively target only AKR family rather than nuclear receptor to avoid complications and hence reduce the side-effects or show cross interaction with molecules that leads to undesired health consequences. Absence of an electronegative atom, Oxygen, will alter the physical and chemical properties of fibrate derivative under physiological condition. Lack of this heteroatomis very critical because AKR family of proteins and nuclear receptors are two distinct classes of protein families with different cellular role and function. We describe herein a method for the preparation of chemically modified derivative of the pro-drug, Fenofibrate from itself in a single step and characterization of the derivative by spectroscopy techniques.

2. Materials andmethod

2.1. General chemicals, procedures and instruments

Reagentswere obtained commercially fromSigma-Aldrich and used without any further purification. The reaction was conducted at room temperature, unless otherwise noted [9]. The ^{1}H and ^{13}C NMR were recorded on a Bruker Advance II 400MHz NMR spectrometer with an indirect detection probe. Chemical shifts were reported in parts per million (ppm)

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Declaration of competing interest

The authors declare no competing financial interests.

from a standard of tetramethylsilane (TMS) in CDCl3 (0.1% *w/v* TMS) and coupling constants (J) are labeled in Hertz. Infrared spectrum was taken on a Thermo Electron Corporation IR 200 spectrophotometer and analyzed using EZ-OMNIC software.

2.2. Formation of isopropyl 2-(4-(4-chlorobenzyl)phenoxy)-2-methylpropanoate (Fibrane) (2) from isopropyl 2-(4-(4-chlorobenzoyl) phenoxy)-2-methylpropanoate (Fenofibrate) (1)

To an oven-dried, 100 mL round bottomed flask, fitted with magnetic stir-bar, 0.529 g (0.146 mmol) of Fenofibrate (1) was added, when dissolved in 5 mL of concentrated glacial acetic acid, 0.156 g of 10% Pd-C was slowly added [9–11]. Then ammonium formate (0.571 g, 9 mmol) was added and allowed to stir under reflux at 60 °C for 5 h [9]. Progress of the reaction was monitored by TLC (93:7 hexane/ethyl acetate) which revealed a spot with the Rf=0.63 [9]. The reaction was allowed to cool in an icewater bath after completion. To this reaction mixture, 10 mL of CH_2Cl_2 and a 0.5–1.0 g of Celite were added, filtered through celite bed using a long stemmed glass funnel plugged with cotton. An additional 10 mL of CH_2Cl_2 was added, rinsed, filtrated and was placed in a separatory funnel with 8 mL of deionized water. To the organic layer separated from the reaction mixture, 8 mL of saturated aqueous sodium bicarbonate was added and swirled in the separatory funnel. After the initial neutralization, the organic layer was separated and again 8 mL of saturated aqueous sodium bicarbonate was added. The organic layer was separated, dried over $MgSO_4$ and filtered using a Whatman #1 filter pad. The solvent was removed *in vacuo* resulting in a 40.1% final yield as a brownish syrup and is over about 81% pure.

Fibrane (2) has the following spectroscopic properties: ^{1}H NMR: δ 1.24 (d, 6H, ^{3}J = 6.32 Hz), 1.59 (s, 6H), 3.94 (s, 2H), 5.10 (septet, 1H, ^{3}J = 6.29 Hz), 6.79 (pd) (^{3}J = 8.62 Hz, 2H), 7.06 (pd) (^{3}J = 8.80 Hz, 2H), 7.18 (pd) (^{3}J = 7.80 Hz, 2H), 7.29 (pd) (^{3}J = 7.82 Hz, 2H); ^{13}C NMR: δ 21.57,25.39,41.09, 68.88, 79.03, 119.5,126.02, 128.42,128.89, 129.51, 134.63, 141.35, 153.90, 173.86; [R spectrum (cm^{-1}): 2976, 1757,1245,1146,901.

3. Results and discussions

A multistep synthesis of isopropyl 2-(4-(4-chlorobenzyl)phenoxy)-2-methyl-propanoate from p-cresol has been reported by Guo et al. [10] though the aim of our study [9] is to generate a derivative of Fenofibrate where the carbonyl group is reduced in a single step selectively over the ester carbonyl. There are a number of documented chemical methods available to convert carbonyl group of a ketone to methylene derivatives. As reviewed by Ram and Ehrenkaufer [11] use of ammonium formate as a catalytic hydrogen transfer agent demonstrated to be an effective synthetic condition for such single step chemical conversions (Scheme 1).

3.1. Synthesis of Fibrane (2)

Following the procedure established for the reduction of aromatic ketones [12], Fenofibrate (1) dissolved in concentrated glacial acetic acid with a catalytic amount of 10% Pd-C and ammonium formate was allowed to stir under reflux at 60 °C for 5 h [9]. TLC (93:7 hexane/ethyl acetate) monitoring showed complete consumption of starting material and the appearance of a UV-active spot with a slightly higher R_f value than the starting material, (1).

Formation of the new alkane, (2) was supported by (a) the signals at 3.94 ppm in its ^{1}H NMR (Fig. 1a) for two protons, (b) absence of the peak at 194.0 ppm in ^{13}C NMR (Fig. 1b), (c) presence of peak at 41.09 ppm in its ^{13}C NMR (Fig. 1b), (d) an appearance of an absorption band at 3028 cm^{-1} (Fig. 1c) as well as (e) disappearance of carbonyl bending at 1597 cm^{-1} and 1651 cm^{-1}in its IR spectra (Fig. 1c).

Experimentally observed NMR signals are consistent with the appearance of a singlet corresponding to two protons at 3.66 ppm and a signal at 41.1 ppm as anticipated ^{1}H NMR and ^{13}C NMR spectrum, respectively of the product Fibrane. Moreover the IR data of Fenofibrate show that the ketone carbonyl stretching band of 1651 cm^{-1} and ester carbonyl stretching band of1728 cm^{-1} are present in experimental vibrational spectra. These spectral data further reconfirms formation of reduced product of Fenofibrate under experimental condition.

4. Conclusion

In summary, we have developed a one-step synthetic route to generate reduced derivative of Fenofibrate. This synthetic method is expected to be useful in preparing alkanes of ketone moiety of Fenofibrate. Unlike the known derivatives of Fenofibrate, alkane of Fenofibrate lacks the carbonyl group in the middle part of the molecule. Hence this design may alter binding specificities towards competing targets, PPARα and AKR family, differently. Absence of such moiety is expected to make the new derivative function distinctively compared to parent generation of Fenofibrate in the molecular interactions and recognition and as a result lead to affect the drug-target selection and show altered Pharmacological behavior under Physiological environment.

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Abbreviations and acronyms

CNS	central nervous system
J	coupling constants
d	doublet
dd	doublet of doublets
MS	mass spectra
m	multiplet
ppm	parts per million
pd	pseudo doublet
RT	room temperature
s	singlet

TMS	tetramethylsilane
t	triplet

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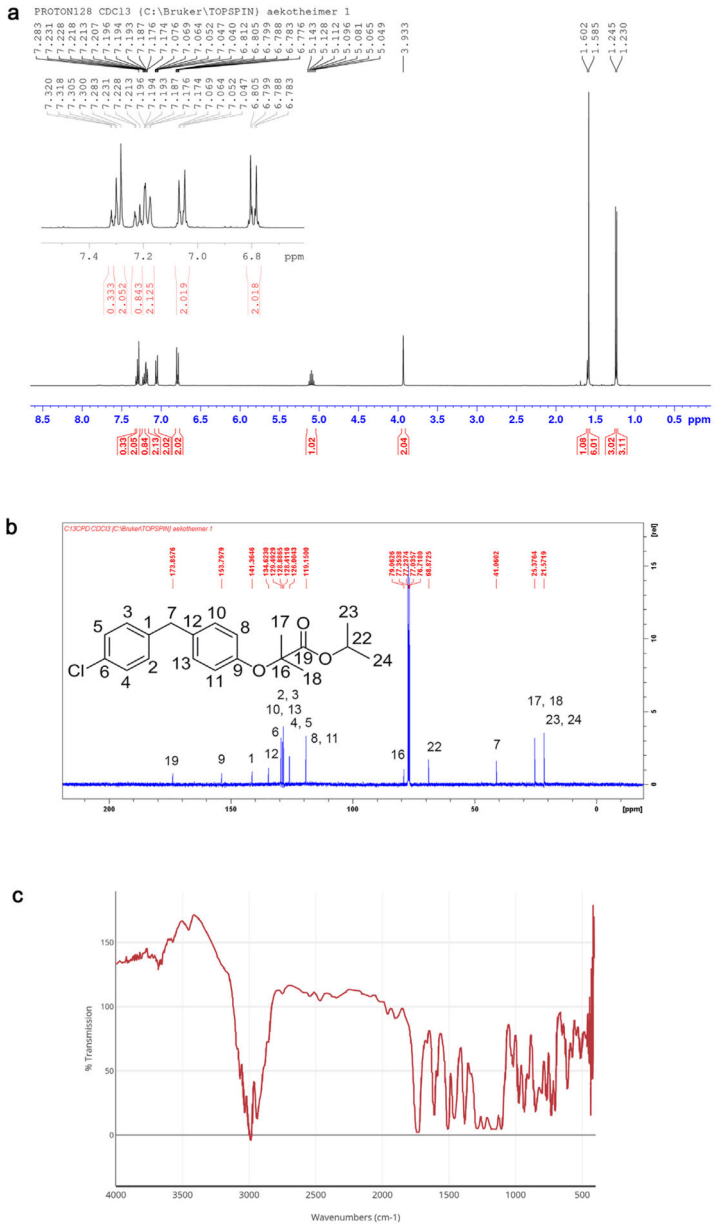
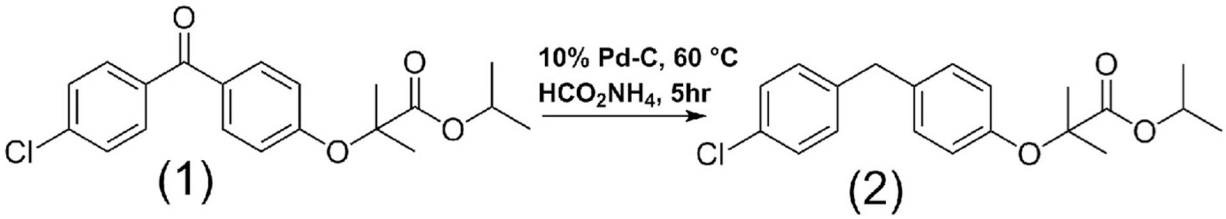


Fig. 1.

a. The ^{1}H NMR spectrum of Fibrane (2) shown in ppm of chemical shift was recorded on a Bruker Advance II400 MHz NMR spectrometer. Peak integration shown in red reflects number of protons in Fibrane. b. The ^{13}C NMR spectrum of Fibrane (2) shown in ppm of chemical shift was recorded on a Bruker Advance II100 MHz NMR spectrometer. The numbers shown in the NMR spectrum correspond to the atom labeling in the chemical structure. c. Experimental IR Spectrum of Fibrane (2). The lack of absorption band at 1651 cm^{-1} indicates the nonexistence of ketone carbonyl group and presence of 1728 cm^{-1} band implies unaltered ester carbonyl group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Scheme 1.
Pd-C catalyzed chemical conversion of Fenofibrate (1) to Fibrane (2).