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A facile and chemoselectivity in synthesis of 4-chloro-N-(4-((1-hydroxy-2-methylpropan-2-yl)oxy)phenethyl)benzamide, the alcohol derivative of Bezafibrate

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Abstract

A facile method for the reduction of carboxylic acid group of Bezafibrate, an approved drug, is described. The selective reduction of carboxylic acid group to corresponding alcohol was carried out by activation of the carboxylic acid moiety via mixed anhydride followed by the addition of stoichiometric amount of $NaBH_4$ and methanol to obtain the first alcohol variant of Bezafibrate. The reaction was completed in 5–10 min in excellent yield and purity. The new alcohol derivative was characterized by spectroscopic methods. This is the first report on this new molecule.

Keywords

Bezafibrate; Chemoselectivity; Reduction of carboxylic acid; Sodium borohydride; Mixed anhydride

Introduction

Bezafibrate, a member of fibrate class of compounds, is in clinical use as an anti-diabetes agent and for lowering lipid levels. It is believed that fibrates are agonist of peroxisome proliferator-activated receptors (PPARs) [1,2]. In addition, molecular action of fibrates includes, aldo–keto reductase family of proteins, aldose reductase and AKR1B10 targets [3-6]. Though members of fibrate class share noticeable physiological and clinical outcomes

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100417.

CRediT authorship contribution statement

Greesha N. Majethia: Conceptualization, Methodology, Investigation, Resources, Data curation. **Wahajul Haq:** Conceptualization, Methodology, Investigation, Resources, Data curation. **Ganesaratnam K. Balendiran:** Conceptualization, Methodology, Investigation, Resources, Data curation.

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.

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their chemical scaffold contains significantly divergent fragment(s). Though most of the fibrates contain several fragments that are same, amide group is present only in Bezafibrate. Moreover, Bezafibrate is clinically administrated as carboxylic acid derivative rather than an ester. Therefore, Bezafibrate may occur in different ionic states in the initial stage soon after its administration because the pH is 4–7 in small intestine, and it is 7.3–7.45 in blood. This causes Bezafibrate to have a shorter half-life in biophase and excreted by kidney rapidly. Here we present the synthesis of Bezol, a new structural variant of Bezafibrate, 4-chloro-*N*-(4-((1-hydroxy-2-methylpropan-2-yl) oxy)phenethyl)benzamide (**I**) Fig. 1.

Materials and method

The required reagents and solvents were procured from Sigma-Aldrich and used without further purification. The reaction of the carboxylic group reduction was carried out at −15 °C in acetone dry ice bath. The ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Advance II 400 MHz NMR spectrometer with an indirect detection probe. Chemical shifts were reported in parts per million (ppm) from a standard of tetramethylsilane (TMS) in $CDCl_3$ (0.1% w/v TMS) and coupling constants (J) are reported in Hertz. The mass spectrum was recorded on Esquire-LC_00135 spectrometer and Infrared spectrum was taken on a Thermo Electron Corporation IR 200 spectrophotometer and analyzed using EZ-OMNIC software. Melting point is recorded on Stuart-SMP10 melting point apparatus and reported uncorrected.

The synthesis of compound **I** was carried out starting from the Bezafibrate obtained from Sigma-Aldrich chemical company, USA. A solution of Bezafibrate 1.5 gm (4.3 mmol) in dry THF (15 ml) was placed in a flame-dried, round-bottomed flask fitted with magnetic stirring bar and moisture guard tube. The reaction mixture was kept under stirring at −15 °C in acetone: dry ice bath. To this chilled and stirred solution N-methyl morpholine (0.5 ml, 5 mmol) was added followed by the addition of isobutyl chloroformate (0.7 ml, 5 mmol). The stirring was continued for 4–5 min and the reaction temperature was maintained at −15 °C. After 5 min, solid sodium borohydride (0.35 g, 9 mmole) was added to the reaction mixture followed by the dropwise addition of methanol (2 ml). The reaction was stirred maintaining the reaction temperature strictly at −15 °C for additional 5 min followed by the quenching of the reaction by the addition of 2 ml of 1 M hydrochloric acid to the reaction mixture. The reaction mixture was allowed to reach room temperature and the solvent was removed under reduced pressure. The residue was taken in ethyl acetate (35 ml) and washed with brine until neutral to pH. The organic layer was dried over anhydrous magnesium sulfate and filtered using a filter paper. The filtrate was concentrated under reduced pressure to obtain chromatographically homogeneous white solid product. Yield 1.37 gm, 91 %. M.P. 120–121 °C, ^{1}H NMR: δ = ^{1}H NMR (400 MHz $CDCl_3$): δ 1.49 (s, 6H, isopropyl), 2.88 (t, 2H J = 7.0 Hz, methylene-tyramine), 3.75 (s, 2H, Hydroxy methylene), 3.47 (q, 2H, J = 6.7 Hz, NH-methylene), 6.12 (bs, 1H, NH proton), 6.7 (d, 2H, Ar J = 8.10 Hz, Ar-Tyramine), 6.92 (d, 2H Ar, J = 8.00 Hz Ar-Tyramine), 7.5 (d, 2H Ar J = 8.10 Hz), 7.82 (d, 2H Ar J = 8.10 Hz). ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 34.88, 41.02, 41.29, 50.88, 81.54, 121.55, 128.25, 128.84, 129.54, 132.95, 133.57, 137.70, 152.99, 166.42, 174.71. ESI Mass Calculated for $C_{19}H_{22}ClNO_3$ = 347.13, $[M + Na]^+$ = 370.1 observed.

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Results and discussions

The reduction of carboxylic group of Bezafibrate is not straightforward due to the presence of amide carbonyl moiety in the molecule. However, new methodology is being developed for high chemoselectivity reduction of amides [7]. In addition the direct reduction of the carboxylic acid can be done by the use of strong and sophisticated reagents, to name a few, reagents with appropriate catalyst [8], by using Vitride reagent [9], by catalytic hydrogenation [10]. Another successful approach comprises the reduction after the activation of carboxylic acid to its corresponding alcohol using easily accessible and bench stable catalyst like sodium borohydride under mild experimental conditions. The activation of the carboxylic group can be achieved prior to reduction or reduction is performed by *in situ* activation of carboxylic acid [11-14]. Recent reports indicate that the catalytic hydrogenation require specific catalyst otherwise uncontrolled side reactions will be generated [15,16].

Synthesis of 4-chloro-N-(4-((1-hydroxy-2-methylpropan-2-yl)oxy) phenethyl)benzamide (I)

In the present study we have developed a facile method for the reduction of Bezafibrate via activating the carboxylic group by mixed anhydride followed by the reductions of the activated mixed anhydride using sodium borohydride and methanol as a reducing agent under mild condition. The choice on the use of the mixed anhydride is based on the consideration of the selective −15 °C reduction of carbonyl in the Bezafibrate molecule. The mixed anhydride/borohydride/methanol system is greener approach as it does not create any solid byproducts and does not require tedious purification procedures. The reduction is very facile and completed in few minutes in almost quantitative yield as summarized in Scheme 1.

The procedure shown in the Scheme 1 utilizes very commonly available reagents for the development of an exceptionally facile, expeditious and cost effective method for the preparation of compound **I** in high yield and purity. The mixed anhydride is generated *in situ* by reaction of Bezafibrate with isobutyl chloroformate and N-methyl morpholine at −15 °C. After five minutes 2 M equivalent of sodium borohydride was added maintaining the temperature around −15 °C followed by the addition of methanol to the reaction mixture. After the addition of methanol, the cooling bath is removed and allowed to come to the room temperature. The reaction mixture was quenched by the addition of 1 M hydrochloric acid and followed by usual work up resulted in the formation compound-**I** as chromatographically homogeneous glassy solid. The reduced product was characterized by spectroscopic methods as 4-chloro-*N*-(4-((1-hydroxy-2-methylpropan-2-yl) oxy)phenethyl)benzamide in excellent yield and purity without chromatographic purification. Additional singlet presence at 3.58 ppm in ^{1}H NMR corresponding to hydroxy methylene protons and absence of carboxylic acid carbonyl region between 180 and 185 ppm in ^{13}C NMR confirms the formation of compound (I).

Strategy implemented in this study emerges from “Late-Stage Diversification” concept that is known for repurposing molecules and natural products efficiently for drug development [17,18]. This notion has also been successful in the discovery of many drugs which include: 1) New antibiotics that are needed to meet the challenges of acquired bacterial

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resistance [19,20]. 2) Advanced macrolide derivatives of a highly potent Mechanistic target of rapamycin (mTOR) inhibitor and immunosuppressive drug, Rapamycin, produced and have received clinical approval due to improved therapeutic potential [21,22]. Such functionalization has resulted in the identification of novel rapalogs, Temsirolimus and Everolimus as new drugs for treatment [21,22]. The potency of Rapamycin has significantly improved by attaching additional hydroxyl groups which enhance the hydrophilicity of the highly hydrophobic Rapamycin. 3) Discovery of octreotide, a highly potent derivative of Sandostatin obtained by the conversion of C-terminal carboxylic group of threonine to corresponding alcohol [23] was developed by similar approach. 4) An alpha-glucosidase inhibitor, Voglibose is used clinically to lower post-prandial blood glucose levels in patients with Diabetes Mellitus. 5) Luseogliflozin, Sodium-glucose Cotransporter-2 (SGLT2) inhibitor has been used in clinical trials for the treatment of Diabetes Melltius, Type 2.

As reflected by growing number of drugs that contain hydroxyl fragment and are in clinical use or trials, combining hydroxyl group has been beneficial for the improvement of biological activity of hydrophobic molecules. In view of the above prospective compound **I** is designed as a new Bezafibrate derivative with reduced lipophilicity as well eliminated the acidic character of the molecule. Synthesis of newly designed compound takes advantage of late-stage derivatization strategy to obtain drug like molecule with minimal structural alteration from the parent molecule. The alcohol derivative of the Bezafibrate may have interesting biochemical properties because of its neutral character.

Conclusion

In summary, a facile method for the selective reduction of carboxylic acid group of Bezafibrate was developed. The reduction of carboxylic acid to corresponding alcohol was selectively carried out by activation of carboxylic acid via mixed anhydride followed by the addition of stoichiometric amount of sodium borohydride and methanol to obtain the new alcohol variant of Bezafibrate without any changes to the amide carbonyl group. The reaction was completed in 5–10 min in excellent yield and purity as evident from the spectroscopic data of the compound. The new alcohol derivative is an example of late-stage derivatization for obtaining novel therapeutically useful molecules. The new alcohol variant is expected to exert interesting chemical and biological properties that are different from parent compound.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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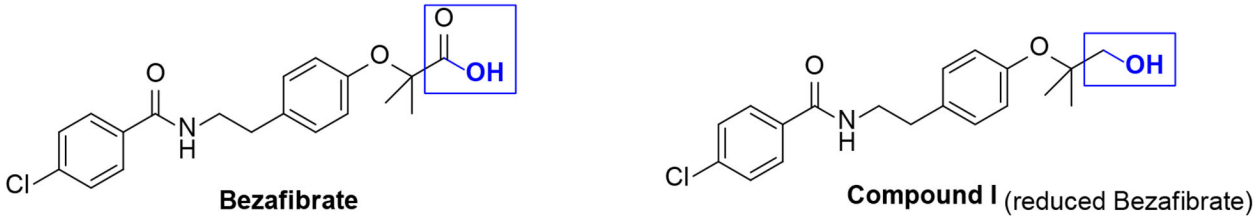

Fig. 1.

Chemical structure of Bezafibrate ($C_{19}H_{20}ClNO_4$) and its reduced derivative, 4-chloro-*N*-(4-((1-hydroxy-2-methylpropan-2-yl)oxy)phenethyl)benzamide (**I**) ($C_{19}H_{22}ClNO_3$).

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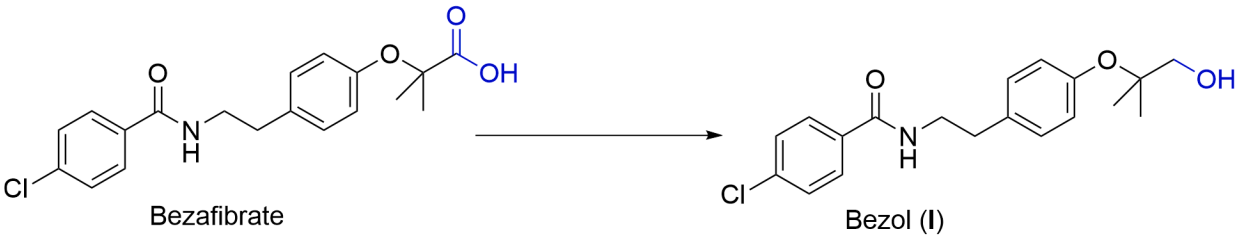

Reagents and conditions: *(i) N-methyl morpholine -15* °C *(ii), isobutyl-chloroformate (iii) Sodiumborohydride/methanol*

Scheme 1.
Synthesis of 4-chloro-*N*-(4-((1-hydroxy-2-methylpropan-2-yl)oxy)phenethyl) benzamide (**I**).

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