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ORIGINAL PAPER

Synthesis and Crystal Structure of Ethyl 2-[4-(acetylamino)phenoxy]-2-methylpropanoate, A Potential Anti-inflammatory and Antidyslipidemic Hybrid

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Abstract The compound ethyl 2-[4-(acetylamino)phenoxy]-2-methylpropanoate (acetamidofibrate) was prepared by reaction of paracetamol with ethyl 2-bromo-2-methylpropionate. It was characterized by elemental analysis, NMR (^{1}H, ^{13}C) spectroscopy, and single-crystal X-ray diffraction. This compound is of interest with respect to its potential bioactivity as analgesic and antidyslipidemic agent. The compound crystallizes in the monoclinic space group P2(1)/c with unit cell dimensions $a = 8.2435(8)$, $b = 9.3390(9)$, $c = 18.2823(18)$ Å, $\beta = 91.123(2)°$, V = 1407.2(2) Å^3, Z = 4, $R_1 = 0.0465$, and $wR_2 = 0.1055$. The crystal structure is stabilized by N–H···O = C and C–H···O hydrogen-bonding interactions that interconnect molecules into chains running along *b* axis. The preliminary *in silico* screening shown that title compound could posse's antidiabetic, anti-inflammatory, hypolipemiant and anti-atherosclerosis effects.

Keywords Fibrates · Antidislypidemic activity · Crystal structure · Hydrogen bonds

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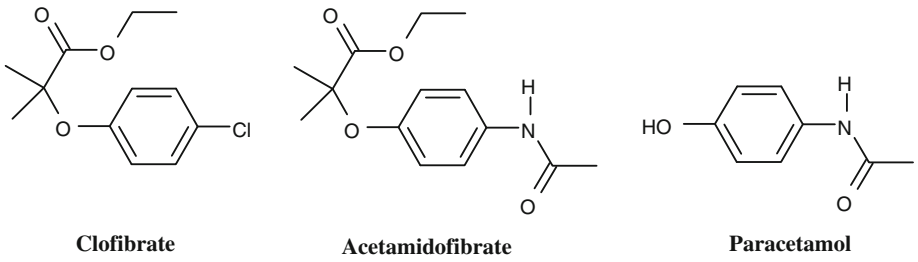
Introduction

Fibrates, such as bezafibrate, clofibrate and fenofibrate, which are ligands for the nuclear receptor PPAR α (Peroxisome Proliferator-Activated Receptor), are used as therapeutic agents in the treatment of dyslipidemia, heart disease and diabetic complications in humans. The fibrates are a widely used class of lipid-modifying agents that decrease plasma triglycerides [1–3]. The fibrate pharmacophore has been of interest to medicinal chemists ever since the initial discovery that ethyl chlorophenoxyisobutyrate possessed hypolipidemic properties [4]. On the other hand, paracetamol is widely used over-the-counter analgesic and antipyretic agent [5].

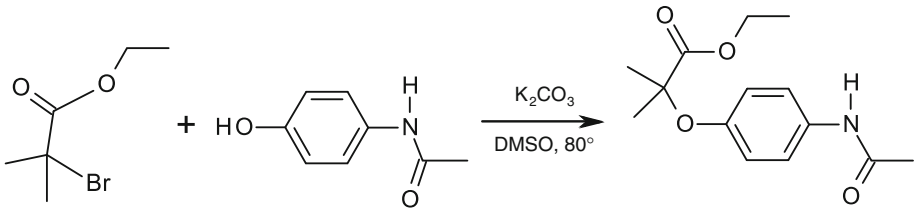
In order to assist our knowledge about the electronic and steric requirements from these kinds of molecules to shown antihyperlipidemic activity, we have synthesized and determined the crystal structure of two closed-related nitro and thio-fibrate analogues [6, 7]. In our ongoing research on fibrate derivatives with antihyperlipidemic activity, we have synthesized the compound ethyl 2-[4-(acetylamino)phenoxy]-2-methylpropanoate (acetamidofibrate), which is a bioisoster of clofibrate, with an acetamide group instead of chlorine atom. Also, the structure resembles to paracetamol, a well-known analgesic and antipyretic agent (Scheme 1).

Both hybridized pharmacophoric groups into the acetamidofibrate, could retain the bioactivities mentioned before, and the structure of the acetamidofibrate, could be a promise of a new biologically active chemical entity. The design of the compounds was based on the biological activity predictions made by the computer software PASS® (Prediction of Activity Spectra for Substances). This software illustrates the predicted activity spectrum of a compound as probable activity (*Pa*) and probable

Scheme 1 Structures of clofibrate, paracetamol and the hybrid designed



Scheme 2 Synthesis of acetamidofibrate



inactivity (*Pi*) with the accuracy of prediction reported to be as high as 85% [8].

In view of these facts and in order to search for new compounds with improved biological activity, the present investigation deals with the synthesis of acetamidofibrate, as outlined in Scheme 2, which might have useful biological and therapeutic activities. The crystal structure of title compound determined by single-crystal X-ray diffraction, and a theoretical and predictive bioactivity spectrum are also reported.

Experimental

Materials and Measurements

All starting materials and reagents were obtained commercially and were used as received. Melting point was determined on an EZ-Melt MPA120 automated melting point apparatus from Stanford Research Systems and is uncorrected. Reactions were monitored by TLC on 0.2 mm precoated silica gel 60 F254 plates (E.Merck). NMR studies were carried out with a Varian Mercury 200 instrument. Chemical shifts (δ_H, δ_C) and coupling constants values (*J*) values are given in ppm and Hz, respectively. Standard reference was used: TMS ($\delta_H = 0$, $\delta_C = 0$) in DMSO-d_6. The following abbreviations are used: s, singlet; d, doublet; q, quartet; t, triplet; bs, broad signal. Mass spectra was recorded on a Jeol JMS-700 equipment. Elemental analysis has been carried out on an Elementar Vario ELIII instrument. Predictive values of biological activities were also investigated using the chemistry software server PASS (http://195.178.207.233/PASS/).

Synthesis of Ethyl 2-[4-(Acetylamino)phenoxy]-2-methylpropanoate

Paracetamol (2.5 g, 0.013 mol) and potassium carbonate (4.57 g, 0.033 mol) were dissolved in the minimum amount of dimethyl sulfoxide and were heated at 40 °C. After 20 min, the ethyl 2-bromo-2-methylpropionate (3.19 mL, 0.0210 mol) was added dropwise and the reaction mixture was heated to reflux (80 °C) and monitored by TLC (Scheme 2). After the reaction completion (15 h), the reaction mixture was filtered and solid residue was washed off with acetone (10 mL). The total mother liquors were concentrated under reduced pressure and then poured into water and extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and partially evaporated under reduced pressure. The residues crystallized as a white solid. The crystals were washed with cold acetone, yielding 2.3 g after crystallization (53.4%), m. p. 90–93°C. Elemental analysis (Found: C, 63.38; H, 7.07; N 5.52. Calc. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28). ^{1}H NMR data (200 MHz; DMSO-d_6; Me_4Si) δ: 1.17 (3H, t, $J = 7.3$, H-12), 1.47 (6H, s, H-9 and H-10), 2.00 (3H, s, H-14), 4.15 (2H, q, $J = 7.3$, H-11), 6.75 (2H, d, $J = 8.7$, H-2 and H-6), 7.45 (2H, d, $J = 8.7$, H-3 and H-5), 9.83 (1H, bs, N–H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 14.62 (C-12), 24.50 (C-14), 25.71 (C-9, C-10), 61.61 (C-11), 79.55 (C-7), 120.30 (C-2, C-6), 120.67 (C-3, C-5), 134.73 (C-4), 150.98 (C-1), 168.44 (C-13), 173.77 (C-8). EI-MS: *m/z* (rel. int.) 265 (M^+, 25%).

X-Ray Crystallography

X-ray diffraction studies were performed on a Bruker-APEX diffractometer equipped with a CCD area detector

($\lambda = 0.71073$ Å, monochromator: graphite). Frames were collected at $T = 293$ K via ω/ϕ-rotation at 10 s per frame (SMART) [12]. The measured intensities were reduced to F^2 and corrected for absorption with SADABS (SAINT-NT) [13]. Corrections were made for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL-NT program package [14, 15]. Non-hydrogen atoms were refined anisotropically. N–H hydrogen atom has been localized by difference Fourier map and could be refined, resulting in N–H distance of 0.85(2) Å. Nevertheless, the aryl, methylene and methyl H atoms were constrained using a riding model approximation. The crystallographic data for the compound are summarized in Table 1. Selected bond lengths, and bond angles are listed in Table 2. Hydrogen bonding interactions are listed in Table 3. Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-737613.

Table 1 Crystal data and refinement parameters for the compound

CCDC	737613
Molecular formula	C_{14} H_{19} N O_4
Molecular weight	265.30
Crystal system	Monoclinic
Space group	P2(1)/c
Temperature	273(2) K
a (Å)	8.2435(8)
b (Å)	9.3390(9)
c (Å)	18.2823(18)
β (°)	91.123(2)
V (Å^3)	1407.2(2)
Z	4
D_{calc} (Mg/m^3)	1.252
Crystal dimensions (mm); colour	0.31 × 0.15 × 0.12, colourless
Absorption coefficient (mm$^{-1)}$	0.092
Radiation λ	Mo Kα (0.71073 Å)
T_{min}/T_{max}	0.972/0.989
Reflections measured	9,973
Range/indices (h, k, l)	−9, 9; −10, 11; −21, 21
θ limit (°)	2.23 to 25.0
Total no. of unique data	2,480 [$R_{int} = 0.0275$]
No. of observed data, $I > 2\sigma(I)$	2,292
No. of variables	180
No. of restraints	0
Goodness-of-fit on F^2	1.134
R_1, wR_2 [I > $2\sigma(I)$]	0.0465, 0.1035
R_1, wR_2 (all data)	0.0504, 0.1055

Table 2 Bond distances (Å) and angles (°) for the compound

Bond distances			
C1–O1	1.3811(19)	C7–C10	1.513(3)
C1–C6	1.388(2)	C7–C8	1.540(2)
C1–C2	1.391(2)	C8–O2	1.202(2)
C2–C3	1.380(2)	C8–O3	1.331(2)
C3–C4	1.395(2)	C11–O3	1.458(2)
C4–C5	1.385(2)	C11–C12	1.504(3)
C4–N1	1.423(2)	C13–O4	1.224(2)
C5–C6	1.389(2)	C13–N1	1.350(2)
C7–O1	1.441(2)	C13–C14	1.505(2)
C7–C9	1.526(2)	N1–H1	0.85(2)
Bond angles			
O1–C1–C6	126.20(15)	C9–C7–C8	107.86(14)
O1–C1–C2	114.50(14)	C10–C7–C8	111.38(14)
C6–C1–C2	119.30(15)	O2–C8–O3	124.66(16)
C3–C2–C1	120.98(15)	O2–C8–C7	123.76(16)
C2–C3–C4	119.97(15)	O3–C8–C7	111.50(14)
C5–C4–C3	118.89(15)	O3–C11–C12	109.75(14)
C5–C4–N1	118.80(15)	O4–C13–N1	122.76(16)
C3–C4–N1	122.26(15)	O4–C13–C14	121.81(15)
C4–C5–C6	121.30(15)	N1–C13–C14	115.42(15)
C1–C6–C5	119.55(15)	C13–N1–C4	125.87(15)
O1–C7–C9	103.91(14)	C13–N1–H1	116.2(13)
O1–C7–C10	112.29(14)	C4–N1–H1	116.4(13)
C9–C7–C10	110.05(15)	C1–O1–C7	121.45(13)
O1–C7–C8	111.00(13)	C8–O3–C11	117.04(14)
Torsion angles [°] for Compound			
O4–C13–N1–C4	−2.0(3)	C12–C11–O3–C8	88.08(18)
C8–C7–O1–C1	58.30(19)	O2–C8–O3–C11	5.6(2)
O1–C7–C8–O3	40.99(18)	C9–C7–O1–C1	173.99(14)

Table 3 Distances (Å) and angles (°) involving hydrogen bonding of the compound

D–H···A	D(D–H) (Å)	D(H···A) (Å)	D(D···A) (Å)	∠(D–H···A)
N1–H1···O4^{i}	0.85(2)	2.03(2)	2.864(2)	169(2)
C5–H5···O2^{ii}	0.93	2.57	3.182(2)	124
C6–H6···O2^{ii}	0.93	2.58	3.184(2)	123
C14–H14B···O4^{i}	0.96	2.60	3.406(2)	142

Symmetry codes: (i) 2 − x, −1/2 + y, ½ − z; (ii) 1 − x, −y, 1 − z

In Silico Bioactivity Predictions

Before the establishment of an in vitro bioassay, we obtained predictive values concerning biological activities by comparing the chemical structures of the compound designed, with structures or substructures of more than

46,000 well-known biologically active drugs included in the database of software named Prediction of Activity Spectra for Substances (PASS) [8–11]. Thus, PASS-based computer pre-screening of large databases of diverse compounds can increase the probability of finding bioactive new chemical agents, and reduce the number of compounds that have to be synthesized and tested experimentally. The results of prediction, estimate that compounds will be active respect to the probability *Pa*. For *Pa* values >0.7, the corresponding compound is very likely to reveal this activity in experiments, but in that case, the chance of the compound being the analogue of a known pharmaceutical agent is also high. For *Pa* values between 0.5 and 0.7, the compound is likely to reveal this activity in experiments and the compound exhibits less similarity to the known pharmaceutical agents. For *Pa* values lower than 0.5, the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in experiments, the compound might be a new biologically active chemical entity.

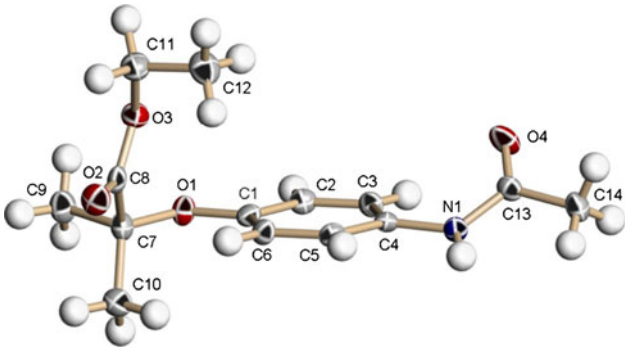


Fig. 1 Molecular structure of the compound. Displacements ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii; numbering according to Table 2

Results and Discussion

Single crystal of acetamidofibrate was grown at room temperature by slow evaporation of ethyl acetate solution. Figure 1 gives perspective view of the compound with the atomic labeling system.

Crystal Structure Description

All the bond lengths in the compound are within normal ranges [16], and comparable to those of the similar compounds [6, 7]. The dihedral angle between

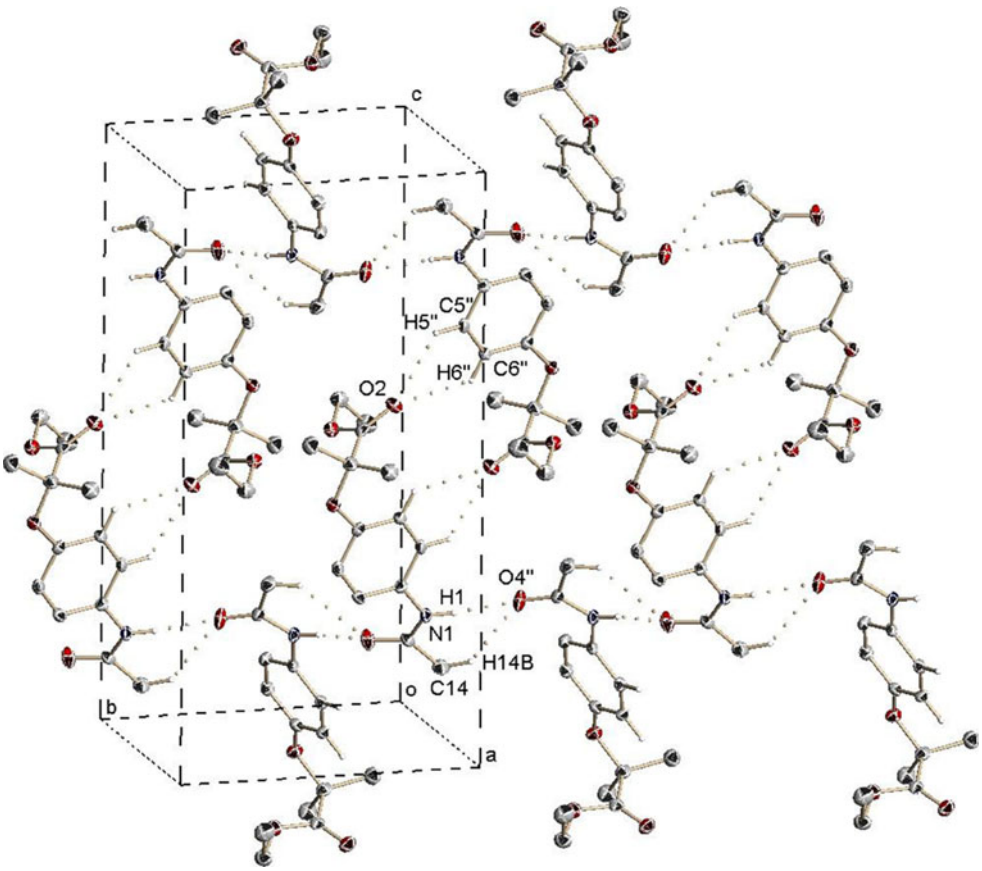


Fig. 2 Perspective view of the molecular packing of compound. The intermolecular hydrogen bonds N–H···O and C–H···O are shown as dotted lines. Most of the hydrogen atoms are omitted for clarity

Table 4 Predictive values of biological activities calculated with PASS for title compound

Antidiabetic		Anti-inflammatory		Hypolipemic		PPARα agonist		Atherosclerosis treatment	
Pa	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*	*Pa*	*Pi*
0.841	0.002	0.743	0.086	0.918	0.002	0.841	0.003	0.898	0.002

4-(acetylamino)phenoxy moiety and the ethyl-2-methyl-propanoate is 58.30(19)°. Intermolecular N1–H1···O4^{i} and C14-H14B···O4^{i} hydrogen bonds [symmetry code: (i) $2 - x$, $-1/2 + y$, $1/2 - z$], links molecules into chains running along the *b* axis (Table 3). In the crystal packing there are also weak C–H···O interactions between the aryl H atoms on C5 and C6 and the O2 atom of an adjacent molecule, forming $R_2^1(6)$ motifs [17]. Two ring structures can be identified (I and II) (Fig. 2).

In Silico PASS Screening

An approach to computer-aided prediction of the general biological activity spectra on the basis of chemical structure of a compound has been developed and marketed as computer program PASS [8]. This software is based on a robust analysis of structure–activity relationships in a heterogeneous training set [9] including many thousands of compounds from different chemical series. Using PASS predictions the number of actives in the selected compounds can be increased by up to 17-fold [10, 11].

Results presented in Table 4 describe four biological activities taken from PASS software: antidiabetic, anti-inflammatory, hypolipemiant and anti-atherosclerosis effects. *Pa* values estimated for all activities were ranging between 0.74 and 0.91. These results indicated that compound exhibited chemical levels of similarity to those of known antidiabetic, anti-inflammatory and antidislipidemic drugs, and are likely to reveal these activities in in vitro or in vivo tests. The predictions include a specific target as PPAR-α agonist.

The in silico test generated by the computational program PASS, revealed that title hybrid compound could posses all the biological activities predicted. However, experimental test should be carried out in order to corroborate these bioactivities.

Supplementary Material

CCDC-737613 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge at http://www.ccdccam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 441223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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