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Biomolecular Chemistry of Isopropyl Fibrates

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Abstract

Isopropyl 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoic acid and isopropyl 2-(4-chlorophenoxy)-2-methylpropanoate, also known as fenofibrate and isopropyl clofibrate, are hypolipidemic agents of the fibrate family. In a previously reported triclinic structure of fenofibrate (polymorph I) the methyl groups of the isopropyl moiety (iPr) are located symmetrically about the carboxylate group. We report a new monoclinic form (polymorph II) of fenofibrate and a first structural description of isopropyl clofibrate, and in these the methyl groups are placed asymmetrically about the carboxylate group. In particular the dihedral (torsion) angle between the hydrogen atom on the secondary C and the C atom of the carboxyl group makes a 2.74° angle about the ester O-C bond in the symmetric fenofibrate structure of polymorph I, whereas the same dihedral angle is 45.94° in polymorph II and -30.9° in the crystal structure of isopropyl clofibrate. Gas phase DFT geometry minimizations of fenofibrate and isopropyl clofibrate result in lowest energy conformations for both molecules with a value of about $\pm 30^\circ$ for this same angle between the O=C-O-C plane and the C-H bond of the iPr group. A survey of crystal structures containing an iPr ester group reveals that the asymmetric conformation is predominant. Although the hydrogen atom on the secondary C atom of the isopropyl group is located at a comparable distance from the carbonyl oxygen in the symmetric and asymmetric fenofibrate (2.52 and 2.28 Å) and the isopropyl clofibrate (2.36 Å) structures, this hydrogen atom participates in a puckered five membered ring arrangement in the latter two that is unlike the planar arrangement found in symmetric fenofibrate (polymorph I). Polar molecular surface area (PSA) values indicate fenofibrate and isopropyl clofibrate are less able to act as acceptors of hydrogen bonds than their corresponding acid derivatives. Surface area calculations show dynamic polar molecular surface area (PSA_d) values of the iPr esters of the fibrates are lower than those of their acids, implying that the fibrates have better membrane permeability and a higher absorbability and hence are better prodrugs when these agents need to be orally administered.

Keywords

Fibrates; Polymorph; Puckered; Surface Area; Packing energy

INTRODUCTION

Chemically and structurally diverse fibrates (Figure 1) are used as therapeutic agents in the treatment of hyperlipidemia, heart disease and diabetic complications¹⁻³. The lipid

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regulating agent fenofibrate, the isopropyl ester of fenofibric acid, is rapidly hydrolyzed by esterases to its active metabolite, fenofibric acid, following oral administration. Unmetabolized fenofibrate has been reported to be undetectable in plasma samples following an oral dose ⁴. *In vitro*, fibrate esters have been shown to exhibit different specificities than their corresponding acids. Fibrate esters antagonize the liver X receptors (LXR)s, whereas the fibric acids are specific agonists (inhibitors) for the peroxisome proliferator-activated receptor α , (PPAR α) ^{5,6}. There are various mechanisms by which isopropyl substitution of the carboxylic acid moieties of the fibrates may result in these observed differences in binding specificities, including the loss of a hydrogen bond donor, the obstruction of a hydrogen bond acceptor, the addition of a large, bulky substituent, or other factors such as e.g. the torsion angle of the iPr group about the ester bond, *vide infra*.

These factors cannot, however, fully account for the pattern of fibrate ester and acid binding affinities to their recently identified targets, aldose reductase (AR) and aldo-keto reductase AKR1B10 ⁷⁻¹². Fenofibrate is a more potent inhibitor of aldose reductase and AKR1B10 than its corresponding acid, fenofibric acid, but the contrary is true for the isopropyl clofibrate and clofibric acid pair. This exchange of substrate recognition pattern may be due to properties of the isopropyl moiety that are unique to fenofibrate or isopropyl clofibrate. In a previously reported ¹³ triclinic crystal structure of fenofibrate (Polymorph I), the atoms of the ester carbonyl and oxygen and the directly bonded C-H group form a nearly planar five-membered ring arrangement, with the isopropyl methyl groups roughly placed symmetrical on either side of this plane. This symmetrical arrangement, if unique to fenofibrate, might contribute to its affinity for AR and AKR1B10. To further investigate the role of fibrate isopropyl moieties, several structural and theoretical studies were performed. In this report, the first crystal structure of isopropyl clofibrate (Figure 2) and of a new polymorph of fenofibrate (asymmetric with respect to the ester carbonyl and C-H torsion angle, Polymorph II) are presented and discussed in relation to DFT calculations of the isopropyl rotamer conformations and compared to iPr ester entries in the Cambridge Structural Database (CSD). These iPr fibrates are also compared to the structures of their corresponding acids: to a structure of fenofibric acid that has already been reported ⁽⁷⁾, CSD entry code QANHUI), and to the structure of clofibric acid, previously reported by Kennard and coworkers at room temperature ⁽¹⁴⁾, CSD entry code BEFVAJ) and re-determined here at 100K.

The Rule of Five, or Lipinski's rule ¹⁵, is based on generalized 2D descriptors and gives relatively rough and sometimes limited predictions concerning membrane permeability ¹⁶. Dynamic PSA (PSA_d) measurements, however, estimate membrane permeability using an approach based on the 3D shape and flexibility of the molecule and factor in the effects of internal hydrogen bonding and steric hindrance ¹⁶. This method revealed a strong correlation between PSA_d and intestinal epithelial permeabilities in a homologous series of drugs measured *in vitro* ^{17,18}. The PSA_d method also showed a strong relationship with the fraction absorbed after oral administration of a series of chemically and structurally diverse drugs to humans ¹⁹. This may be due to the fact that PSA_d provides a better description of the energetically costly process of transferring polar groups into the apolar regions of the cell membranes ²⁰. On the other hand, non-polar substituents facilitate membrane transport and compounds which are more lipophilic generally have higher membrane permeabilities than hydrophilic compounds with similar hydrogen bonding properties ²¹. Overall combination of polar and non-polar surface areas documented to be much more suitable for *in vitro* intestinal epithelial permeability to a series of oligopeptide derivatives than the use of single surface properties alone ²⁰. Total, polar, and non-polar PSA_d values calculated for fenofibrate, isopropyl clofibrate, and their corresponding acids begins to shed light on the pharmacological relationship of these molecules.

MATERIALS AND METHODS

X-ray crystal structure determinations, all structures

The known crystal structures of clofibric acid and fenofibrate (symmetric polymorph I) had been collected at room temperature and 193 K, respectively. For better comparison the structures of isopropyl clofibrate, the new polymorph of fenofibrate, polymorph I of fenofibrate and clofibric acid were recollected at 100K.

Crystals suitable for structure determination for all compounds were obtained by crystallization of the respective compounds at room temperature from a mixture of toluene and chloroform (clofibrate and clofibric acid), from methanol (fenofibrate, symmetric polymorph I), and ethanol (fenofibrate, asymmetric polymorph II). Single crystals were glued to glass fibers (clofibrate) or mounted on Mitegen microsmesh mounts (all others) in a random orientation. Initial examination and data collection were performed at 100(2) K using either Bruker Apex2 (clofibrate) or Bruker SMART APEX CCD single crystal X-ray diffractometers with graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) using the Bruker Apex2 and SAINT software packages²² for data collection and integration. Preliminary unit cell constants were determined with a set of 36 narrow frames. Intensity data were collected using ω and ϕ scans at a crystal to detector distance of 4.00 cm. The collected frames were integrated using an orientation matrix determined from the narrow frame scans. Final cell constants were determined by global refinement of xyz centroids of threshold reflections from the complete data set. Collected data were corrected for absorption and other systematic errors using SADABS²³ by multi-scan methods based on the Laue symmetry using equivalent reflections. Structure solution and refinement were carried out using the SHELXTL-PLUS or SHELXTL 6.14 software packages²⁴. The structures were determined by direct methods and refined by full matrix least-squares refinement by minimizing $w(F_o^2 - F_c^2)^2$. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located from difference Fourier maps and were refined freely using isotropic thermal parameters following the procedure established in the fenofibric acid structure determination^{7,24}. Crystal data, data collection parameters and details of the refinement parameters are listed in Table 1. Complete listings of geometrical parameters, positional and isotropic displacement coefficients for hydrogen atoms and anisotropic displacement coefficients for the non-hydrogen atoms are deposited as supplementary material. Tables of calculated and observed structure factors are available in electronic format. CIF files were deposited with the Cambridge Crystallographic Data Centre as CCDC – to be determined. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DFT Calculations

All calculations were performed with the Gaussian03 (version C02) software package installed on the Ohio Supercomputer Glenn cluster and the Gaussian03W (version 6.0)²⁵/GaussView 3.0²⁶ software package on an Athlon PC. The crystal structures reported here for isopropyl clofibrate, clofibric acid, polymorph I and II for fenofibrate and fenofibric acid that was reported previously were minimized at the B3LYP/6-31G(d) level and used as input for relaxed potential energy surface (PES) scans of rotations around the ester oxygen – isopropyl carbon bond in both fenofibrate and isopropyl clofibrate (scanned every 10° of a complete rotation of 360°). The PES calculations were also performed using the B3LYP theoretical method, which combines Becke's three parameter exchange function^{27,28} with the Lee-Yang-Parr correlation functional²⁹. The split valence, polarizable basis set 6-31G(d) was used for the scans³⁰. Geometries at the minima and maxima of the DFT scans were optimized at the B3LYP/6-31G(d) level with tight convergence criteria (opt=tight, int=ultrafine) specified for all the optimizations. Conformers were found via the

synchronous transit-guided quasi-Newton method (opt=qst2 or qst3)^{31,32}. Frequency calculations were performed on the optimized structures in order to determine the number of imaginary frequencies present, and only minima with no imaginary frequencies and conformers with one imaginary frequency were retained. Large basis set energy calculations were then performed at the B3LYP/6-311+G(d,p) level on the optimized geometries with tight SCF convergence criteria (SCF=tight) resulting in single point energies for the structures.

UNI Force Field Packing Interaction Calculations

Intermolecular interactions and packing arrangements in the crystal structures were investigated using UNI force field calculations using the PIXEL method as implemented in the program Mercury of the Cambridge Crystallographic Data centre Mercury CSD 2.4 (Build RC5)^{33,34}. This method allows the calculation of lattice energies in good agreement with crystal sublimation enthalpies for a wide selection of organic compounds, and also performs well in energy ranking for polymorphs of organic crystal structures³⁵. The quality of the Pixel results is often similar to that of quantum chemical calculations, at a fraction of the computational cost³⁶. The crystal structures were used as input, but hydrogen atom positions were normalized prior to the calculations to standard values obtained by neutron diffraction. Detailed results of the calculations, including total packing energies and calculated intermolecular potentials, are given in the supporting material.

RESULTS

Isopropyl 2-(4-chlorophenoxy)-2-methylpropanoate (isopropyl clofibrate) (Figure 1) crystallizes in the centrosymmetric triclinic space group $P\bar{1}$. A projection view of the isopropyl ester of clofibric acid is presented in Figure 2, and the geometrical parameters are shown in Table 1. Clofibric acid crystallizes in the monoclinic space group, $P2_1/n$ with one unique molecule in the asymmetric unit as reported previously¹⁴. However, the hydrogen atoms for the room temperature clofibric acid entry, BEFVAJ, in the Cambridge Structural Database (CSD) are not clearly resolved, and the structure of fenofibrate reported previously¹³ had been determined at 193 K. Therefore, both clofibric acid and the known form (polymorph I) of fenofibrate were crystallized and their structures (Figure 2) re-determined at 100 K in order to allow for uniform comparisons. Data for clofibric acid are given in Figure 2 and Table 1, those for fenofibrate polymorph I in the supporting material and Table 1. In addition, different from the reported triclinic polymorph I¹³, fenofibrate was crystallized as a monoclinic polymorph (II) and its structure (Figure 2) in the new crystal form provides better understanding of the iPr group conformation.

Propelling isopropyl group

In the previously known form of fenofibrate, the carbonyl oxygen (O4), sp^2 hybridized carbonyl carbon (C7), carboxylate oxygen (O2) and the carbon atom of the isopropyl group form a coplanar arrangement. The hydrogen atom (H15) of the isopropyl group is situated in this plane and the C-H bond is almost parallel to the C=O bond, making a planar five membered ring with a distance of 2.28 Å of the H atom from the carbonyl oxygen (O4). Because of this planar organization, the isopropyl moiety is placed approximately even with respect to the five membered ring, with the methyl groups of the isopropyl moiety being symmetrically arranged about the ester bond. Torsion angles of the hydrogen atom and the methyl groups of the isopropyl moiety about the bond τ_1 are 2.74° (H15-C18-O2-C7), 122.47° (C20-C18-O2-C7) and 117.87° (C19-C18-O2-C7) about the carboxylate bond (Figure 3, Table 2). In the (polymorph II) asymmetric form of fenofibrate reported here, the corresponding hydrogen atom, H18, is 2.52 Å away from the carbonyl oxygen, O3 (Figure 2), and the methyl groups are asymmetrically arranged about the ester bond. The torsion

angles (about the bond ν_1) of the equivalent hydrogen atom and methyl groups of the isopropyl moiety are 45.94° (H18-C18-O4-C17), -74.73° (C19-C18-O4-C17) and 164.60° (C20-C18-O4-C17) about the ester bond (Figure 3, Table 2).

Similar to the new asymmetrical fenofibrate structure, the related atoms O2, C10, O3 and C11 in isopropyl clofibrate form a planar arrangement, and the analogous hydrogen atom (H11) of the isopropyl group occupies a non-planar position to form a puckered five membered ring with a non-bonded distance of 2.36 Å from the carbonyl oxygen (O2) (Figure 2). Rotation of the isopropyl group about the ester bond (ν_1) (O3-C11) leads to the hydrogen atom placed out of the plane and the methyl groups of the isopropyl group being asymmetric about the carboxylate moiety. Torsion angles of the hydrogen atom and methyl groups of the isopropyl moiety are -30.93° (H11-C11-O3-C10), -149.60° (C13-C11-O3-C10) and 87.63° (C12-C11-O3-C10) (Table 2). The fact that both isopropyl clofibrate and fenofibrate (polymorph II) achieve a puckered geometry as found in the asymmetric conformations of their respective crystal structures implies formation of lower energy conformation present in solid phase that is independent of fibric acid type. In addition the relative free rotation of the iPr group in the fibrate esters may contribute to the differences in their conformations, their shape and hence reflects differences in the stability and molecular recognition properties of clofibrate and asymmetric fenofibrate when compared to the symmetric fenofibrate ester.

Conformational change induced by isopropyl group

The 4-chlorophenoxy, ether, dimethyl methyl and carboxylate moieties are common amid the fibric acid derivatives, and the iPr moiety is also common among their iPr esters. Although the chemical structures within the fibrate series differ the disposition of some of the common moieties can be compared. The 4-chlorophenoxy ring of isopropyl clofibrate is almost coplanar with that of the ether group (C7-O1-C4). Superposition of the dimethyl groups and the carboxyl moiety of isopropyl clofibrate with that of clofibric acid reveals that the 4-chlorophenoxy ring is rotated away from the C7-O1-C4 plane in clofibric acid. Rotation (about ν_3) of the 4-chlorophenoxy ring seen in clofibric acid is larger than that of the phenoxy ring observed in fenofibric acid when the dimethyl and carboxyl moieties of isopropyl clofibric acid and fenofibric acid are overlaid. However, when the dimethyl and carboxyl moieties of isopropyl clofibrate are placed on top of fenofibrate, the phenoxy ring is rotated (about ν_2) in the opposite direction compared to fenofibric acid and clofibric acid (Figure 4a). As shown in Table 2 and Figure 3 these movements are reflected in the corresponding torsion angles of -56.14° (C10-C7-O1-C4) and 7.03° (C7-O1-C4-C3) for isopropyl clofibrate; -78.96° (C8-C7-O1-C1) and 54.30° (C7-O1-C1-C6) for clofibric acid; -68.95° (C15-C14-O2-C11) and 18.30° (C14-O2-C11-C12) for fenofibric acid and 67.48° (C7-C12-O1-C2) and -23.32° (C12-O1-C2-C3) for symmetric fenofibrate.

Similarly when the phenoxy rings of isopropyl clofibrate, clofibric acid, fenofibric acid and fenofibrate are superimposed and viewed from the carboxyl end of the molecules, all the carboxyl moieties are on one side of the ether bond except for fenofibrate polymorph I (Figure 4b). The isopropyl substitution of clofibric acid causes the carboxyl group to move by approximately 1.5 Å, whereas in the case of fenofibric acid, the isopropyl group results in a 4.3 Å movement of the carbonyl moiety. This movement leads to the rotation of the carboxyl moiety about the phenoxy ester bond and places the carboxyl moiety in a different location. Furthermore, congruent with the conformational change, the dimethyl groups also swing in the opposite direction. The alpha carbon of the dimethyl methyl groups in clofibric acid moves by only 0.9 Å, whereas the same moiety moves by 2.0 Å in fenofibric acid due to the isopropyl group.

Superposition of the moiety formed by the atoms O2, C14, C15, C16 and C17 of the asymmetric polymorph II with the corresponding atoms of the symmetric polymorph I of

fenofibrate has an RMS deviation of 0.076 Å. Overlay of the group formed by the O4, C18, C19 and C20 atoms of the asymmetric polymorph with the related atoms of the symmetric polymorph has an RMS of 0.027 Å but inclusion of C17 in the comparison increased the RMS deviation to 0.266 Å among these pairs.

The RMS deviation between the common non-hydrogen atoms of 1) fenofibric acid and fenofibrate polymorph I (0.178 Å), 2) fenofibric acid and fenofibrate polymorph II (0.054 Å) and 3) fenofibrates polymorph I and polymorph II (0.136 Å – including 16 atoms from Cl to phenoxy O) indicate significant structural changes are occurring at the carboxyl moiety part of these molecules. The conformation of polymorph II (excluding the iPr group) resembles very much that of its acid derivative whereas polymorph I deviates more from polymorph II and fenofibric acid (QANHUIJ). Overall the chloro biphenyl moiety in polymorph I and II of fenofibrate and in the fenofibric acid structures have a highly conserved conformation (Figure 5) in all the known crystal forms as indicated by the RMS values. This observation suggests that hydrolysis of polymorph I results in a larger conformational change than that of polymorph II. Consequently the presence of the iPr group has a smaller effect on polymorph II as it deviates less from its acid.

Crystal packing of isopropyl clofibrate, clofibric acid, fenofibrate and fenofibric acid

There are eight molecules packed in the orthorhombic, *Pbca*, crystal form of fenofibric acid which are arranged in the form of dimers related by inversion centers. This packing arrangement is a rare acid-to-ketone hydrogen bonding dimerization pattern⁷ rather than the more prevalent $R^2_2(8)$ hydrogen bonding motif most predominant for carboxylic acid dimers^{37,38}. Clofibric acid, on the other hand, does form acid-to-acid hydrogen bonded dimers with the commonly observed $R^2_2(8)$ graph set motif rather than the unusual acid to ketone dimers. Fenofibrate and isopropyl clofibrate, on the other hand, lack the ability to form intermolecular hydrogen bonding dimers due to the lack of acidic protons which greatly influences the way the fenofibrates and clofibrates pack when compared to their corresponding acid derivatives. To quantify intermolecular interactions and packing arrangements in the crystal structures we performed UNI force field calculations on the crystal structures. For both clofibric acid and fenofibric acid the largest intermolecular potential was each found for the pairs of molecules connected through O-H...O hydrogen bonds, with -48.5 kJ/mol for clofibric acid and -65.7 kJ/mol for fenofibric acid (other stabilizing interactions also contribute to the total intermolecular potential between the molecules, thus rising the interaction potential above the value expected for only the hydrogen bonding energy). No such strong or directional forces are found for the fibrate esters. The strongest intermolecular potential for clofibrate, dominated by a slipped π - π interaction (Figure 6), is with -38.1 kJ/mol over 10 kJ/mol weaker than that found in clofibric acid. The total packing energy in isopropyl clofibrate is, despite of the higher molecular mass, lower than that for clofibric acid (-121.9 kJ/mol vs. -114.47 kJ/mol). A similar pattern is found for fenofibric acid vs the fenofibrates. The total packing energy of the acid is with -174.61 kJ/mol again over 10 kJ/mol stronger than that for the fenofibrates (-155.64 kJ/mol for polymorph I and -162.27 kJ/mol for polymorph II, *vide infra* for a discussion of the relative stabilities of fenofibrate polymorphs I and II). The larger intermolecular attraction between the acid vs the ester molecules in the crystal structures is also evident from the densities of these compounds which are 1.396 g/cm³ for clofibric acid and 1.389 g/cm³ for fenofibric acid, but only 1.279 g/cm³ for isopropyl clofibrate and 1.304 g/cm³ for the two fenofibrates.

Theoretical basis of conformations in iPr fibrates

Results of the B3LYP/6-311+G(d,p) based calculations for the four molecules, fenofibric acid, isopropyl clofibrate and clofibric acid are summarized in Table 3. As summarized in

Table 3 and shown in Figure 7 (only for clofibrate), both fenofibrate and isopropyl clofibrate have a similar characteristic pattern of ester bond rotation. The rotation plot has the expected low energy “well” with two minima (labeled *A* and *B*) separated by a small rotational barrier (*AB'*) as well as a higher energy minimum (*C*) separated from the well by larger rotational barriers (*BC'* and *CA'*). The low energy conformations in the well correspond to the isopropyl hydrogen being rotated by 33-37° out of the ester plane as defined in the crystal structures mentioned here. The conformer between these states occurs when the isopropyl hydrogen aligns with the ester plane, making a planar, five-membered ring. The *C* minimum, approximately 12.1 kJ/mol higher in energy than the *A* minimum, corresponds to a conformation with the isopropyl hydrogen rotated by about 180° out of the ester plane and away from the carboxyl oxygen. The energy barriers relating to this conformational rotation are approximately 28-29 kJ/mol for both iPr esters, fenofibrate and isopropyl clofibrate. Because this barrier is easily surmountable at room temperature, concentrations of the various minima can be expected to equilibrate in solution. Boltzmann distribution analysis of these minima indicates that the *A* and *B* minima should be present relative to the *C* minimum in about a 210:1 ratio in the absence of other forces such as solid state packing interactions.

Survey of CSD entries

We have performed a survey of all the structural entries with an iPr ester moiety deposited in the Cambridge structural database (CSD V5.32, updates until May 2011). The search retrieved 220 compounds with determined isopropyl atom positions. 8 of these entries were double entries and only the higher quality entry was retained. For compounds in which the isopropyl group is disordered only the major conformer was used. Inclusion of structures containing one or more iPr ester groups and single or multiple molecules per crystallographic asymmetric unit resulted in 348 individual iPr groups. A polar histogram showing the distribution of the torsion angles, (τ_1) C-O-C-H, is given in Figure 8. As can be seen the large majority of the compounds surveyed show values between 20 and 50° for the absolute value of the torsion angle with clear maxima at around 40 and -40°. The ester torsion angle was found to be less than 20° in only 14.9% of the cases (52 absolute); one quarter of the torsion angles is larger than 41 or smaller than -41°, and values are between 20° and 40° for most (60.1%) of the iPr ester groups, which roughly coincides with the theoretical rotational energy predictions (Figures 7). Only three compounds, or less than 1% of all isopropyl esters surveyed, have an absolute torsion angle of three degrees or less among them is symmetric fenofibrate with a torsion angle of 2.75°, though the equivalent torsion angle is 45.94° in the asymmetric fenofibrate crystal structure (polymorph II). The other two compounds that show similar small torsion angles are isopropyl 3-oxo-2-(triphenylphosphoranylidene)butyrate (CSD code GUKVEN³⁹, torsion angle = -2.28°) and (+)-syn-isopropyl 4-(1,1,1,3,3,3-hexafluoropropan-2-yloxy)-1-hydroxy-3-methyl-2-(prop-1-ynyl)cyclopent-2-enecarboxylate (FOVLOS⁴⁰, -2.34°).

Surface area

PSA (polar molecular surface area), which is the sum of the fractional contributions to the surface area of all nitrogen and oxygen atoms, reflects the hydrogen bonding capacity of a molecule and partly the energy involved in the membrane transport of a compound. Table 4 contains the highest and lowest total, polar and non-polar MSA and ASA values and the corresponding C-O-C-H ester bond torsion angle (τ_1) at which the values for the above molecular descriptors are calculated (Figure 9). In most of the calculations, the solvent accessibility values increased by similar amounts upon the addition of an iPr ester group to the fibric acids, but the highest total MSA values increased much more for the change from fenofibric acid to fenofibrate (320 to 365 Å²) than when changing from clofibric acid to isopropyl clofibrate (223 to 268 Å²) (Table 4). The highest total MSA values of the

molecules are also differently affected by addition of the iPr ester moiety. Fenofibrate has an $\sim 145 \text{ \AA}^2$ larger highest total MSA than fenofibric acid, but isopropyl clofibrate has only an $\sim 45 \text{ \AA}^2$ larger highest total MSA.

DISCUSSION

In drug design various commonly applied rules play important roles⁴¹. However, when a given molecule with drug like properties crystallizes in two or more different lattice arrangements (i.e. when crystalline polymorphs exist) almost all of these predictions start to break down. In general three-dimensional structure (conformation) and properties (solubility, adsorption, permeability, melting point, density, hardness, crystal shape, chemical reactivity) of different polymorphs of a given compound are as different as they would be for crystals of two chemically different compounds. It thus is possible to obtain different crystal forms of a drug and by doing so affect the performance properties for that compound. As a result a large number of patents are issued based on the ability to selectively produce a clinically favorable polymorph. When a metastable polymorph of a drug is used it can undergo phase conversion to a more stable polymorph. This may result in a number of significant problems like 1) different physical properties such as kinetic or thermodynamic solubility (thus severely affecting the drug's pharmacokinetics), 2) undesirable particle size distribution, 3) inability to produce uniform suspensions by shaking, and 4) unacceptable products in which the active ingredient is unevenly distributed, to mention just a few. The present work demonstrates that the previously reported fenofibrate polymorph I with a symmetrical iPr ester has a very unique conformation that is not replicated in isopropyl clofibrate, or in the “asymmetric” polymorph II of fenofibrate reported here. The iPr groups of isopropyl clofibrate and “asymmetric” fenofibrate presented here have conformations similar to the majority of other reported iPr ester structures that also correspond more closely to the minima obtained in the DFT calculations. Based upon the crystal structures reported here, the DFT calculations and results from the survey of the CSD, iPr ester moieties, including those of fenofibrate and isopropyl clofibrate, prefer “puckered” conformations, where the C-O-C-H torsion angle (τ_1) is ± 30 – 40° . These observations reinforce the fact that the puckered conformation reported here in the crystal structures with about $\pm 30^\circ$ is energetically more stable, but the conformation can be altered by external factors, such as crystal packing effects or the shape of the inner binding cavity in the target.

PSA varies for fenofibrate and isopropyl clofibrate based on the iPr group rotation about the torsion angle τ_1 . In the absence of an iPr group PSA_d values go up for fenofibrate and isopropyl clofibrate. PSA_d for fenofibrate is higher than that for isopropyl clofibrate, a reflection of the fact that the former has an additional heteroatom O than isopropyl clofibrate. Thus, though addition of the isopropyl groups may not result in a substantially different solid state conformation for fenofibrate and isopropyl clofibrate, the iPr moieties may have altered the pharmacokinetics of their respective acids' by changing their electronic, molecular and solvent accessibility properties, which could partially explain their ability to discriminate different target molecules with varying binding patterns and affinities. The difference between the highest total MSA for fenofibrate and total MSA for fenofibric acid and the lowest total MSA for fenofibrate and total MSA for fenofibric acid is almost equal to the difference in value between highest and lowest total MSA for fenofibrate. This trend is maintained for total ASA, PSA_d , polar ASA, non-polar MSA and non-polar ASA for between fenofibrate and isopropyl clofibrate and their fibric acids. A previously established relationship between PSA_d and absorbed fraction after oral administration of conventional drugs to humans indicates¹⁹ that drugs with $\text{PSA}_d < 60 \text{ \AA}^2$ are predicted to be completely ($>90\%$) absorbed whereas drugs with $\text{PSA}_d > 140 \text{ \AA}^2$ should be absorbed to less than 10%. As shown in Table 4 both fenofibrate and isopropyl clofibrate have PSA_d values

that are less than $60 \text{ \AA}^2$ implying that these molecules have a high tendency to be absorbed when administered orally. Consistent with previous studies⁴², when this relationship is applied to the endothelin receptor antagonists, an oral absorption of $< 20\%$ is predicted and found for the low permeability endothelin receptor antagonists ($\text{PSA}_d > 120 \text{ \AA}^2$) while an oral absorption of 40-70% is estimated and observed for the high permeability endothelin receptor antagonists ($\text{PSA}_d 78\text{-}104 \text{ \AA}^2$).

The differences between the acids and iPr esters of fibrate derivatives are readily explainable based on the absence and presence of strong directional O-H...O hydrogen bonds. The analyses of the forces that govern the crystallization patterns of the two polymorphs of fenofibrate, on the other hand, are less easily discernable. This is however of eminent importance, especially for a pharmaceutical such as fenofibrate, as different polymorphs might also carry distinctively different physical properties. When administered orally in solid form the presence of a different polymorph can, for example, severely affect pharmacokinetic properties if e.g. dissolution rates of the two polymorphs are substantially different. The difference in the packing energy for the two fenofibrate polymorphs estimated using UNI force field calculations is quite large with values of -155.64 and -162.27 kJ/mol for the triclinic and monoclinic forms, respectively. This substantial variation outweighs possible contributions of conformational variations between the molecules present in the two structures, such as e.g. isopropyl rotation (with an estimated energy difference between conformers of around 2 kJ/mol , *vide supra*), or rotation around any of the other flexible torsion angles. Neglecting conformational differences between the two forms of fenofibrate the asymmetric monoclinic form (polymorph II) is the thermodynamically more stable one by over 6 kJ/mol . The less stable triclinic form (polymorph I) is however obtained on a regular basis when crystallizing fenofibrate from alcoholic solutions (such as ethanol or methanol), with only occasional appearance of the thermodynamically more stable monoclinic form (which was also obtained from ethanol here). While a more thorough investigation of crystallization conditions that lead to the formation of one polymorph over the other is clearly warranted, the observations thus far point toward kinetic reasons for the apparently preferred formation of the triclinic over the monoclinic form. One possible explanation for this observation could be the formation of π -stacked dimers in solution that might serve as nucleation points for the formation of the triclinic crystal form. Note that only the thermodynamically less stable triclinic form exhibits any π - π stacking interactions. The interplanar separation between the two chlorobenzene rings is with $3.486 \text{ \AA}$ in the typical range of a strong π - π stacking interaction. For this crystal form this π - π stacking interaction is also the by far strongest single interaction with a calculated UNI force field intermolecular potential of -38.7 kJ/mol . This interaction energy is substantially more than what is obtained for a typical arene-arene interaction alone (e.g. -8.5 kJ/mol for the benzene dimer at a distance of $3.6 \text{ \AA}$,⁴³ or -18 kJ/mol for chlorobenzene,³⁶), but other interactions such as between the ketone and the aromatic ring or between one of the C-H groups and the chloro atom also contribute to the rather large intermolecular potential (see Figure 6). Formation of the monoclinic crystal form, which does not contain any such π -stacked dimers, could be limited if a significant fraction of fenofibrate molecules are present in solution in the form of π -stacked dimers that would have to first dissociate prior to being able to be incorporated into a monoclinic crystal lattice. The substantially different packing energies of fenofibrate polymorphs I and II might play an important role for the biological and pharmacological properties of fenofibrate as solubility and dissolution rates might be affected, and an in depth analysis of the properties of the two polymorphs will have to be conducted in order to guarantee that pharmacokinetic properties are not affected by the possible presence of a thermodynamically more stable polymorph. Once in solution, formation of π -stacked dimers should not play any pharmacological role as concentrations in the body are by far too low for any dimerization to be maintained. However, other metabolites including protein targets present in the physiological condition may have

aromatic groups to form π -stacking with fenofibrate to cause its conformation to be identical to that found in polymorph I.

Comparison of the common non-hydrogen atoms in polymorph I, polymorph II and fenofibric acid structures indicate polymorph I deviates most from fenofibric acid while polymorph II is very close in its conformation to that of the acid. This observation implies the targets that are capable of selectively binding fenofibrate in a polymorph I like conformation will show no or less binding towards a flipped conformation such as found in polymorph II and fenofibric acid. Under such a situation the iPr group may not have a significant role to play in the pharmacological properties through such targets. However if the targets preferentially bind molecules in a conformation close to that of polymorph II then a diminished or a lack of interaction would be expected for a polymorph I like conformation. In this case the iPr group may or may not play a physiological function because fenofibric acid has a similar molecular conformation and therefore can bind the targets with an only slightly altered affinity.

The most noticeable difference between the two types of conformers comes from the relative orientation of the carboxyl group with respect to the carbonyl group of symmetric fenofibrate (polymorph I) compared to these groups in asymmetric fenofibrate (polymorph II) and fenofibric acid. Target molecules that are capable of binding symmetric fenofibrate through the polar interactions that are on the opposite side of the fenofibrate derivative will show a lower or reduced affinity towards the asymmetric form of the fenofibrate or fenofibric acid because in these conformations the polar atoms are on the same side and behind the molecule. Although the conformation of asymmetric fenofibrate very closely resembles that of fenofibric acid, the differences in their target selectivity indicate that the affinity resides predominantly within the presence of the iPr group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CSD	Cambridge Structural Database
CCD	Charge Coupled Device
iPr	isopropyl
LXR	liver X receptor
PPARα	peroxisome proliferator-activated receptor α
SA	surface area
MSA	molecular surface area
ASA	accessible surface area
PSA_d	dynamic polar molecular surface area

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Figure 1.

Chemical structures of (I) fenofibric acid, (2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoic acid); (II) fenofibrate, (isopropyl 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methylpropanoic acid); (III) clofibric acid, (2-(4-chlorophenoxy)-2-methylpropionic acid); and (IV) isopropyl clofibrate, (isopropyl 2-(4-chlorophenoxy)-2-methylpropanoate).

Figure 2.

Crystal structures of fibrates in the Thermal Ellipsoid Plot representation. Atom labels and numbering shown are same as what was deposited in the CSD and used in the text. 2a. Isopropyl clofibrate (50% probability thermal ellipsoids),. Isopropyl group is asymmetric about the ester bond. 2b. Redetermined crystal structure of Clofibric acid. 2c. Redetermined crystal structure of fenofibrate in the symmetric polymorph I. Isopropyl group is symmetric about the ester bond in the triclinic crystal form. 2d. Crystal structure of fenofibrate in the new asymmetric polymorph II. Isopropyl group is asymmetric about the ester bond in the monoclinic crystal form.

Figure 3.

Schematic drawing of the chemical structure of fenofibrate. Atom numbering shown is based on the asymmetric crystal polymorph II of fenofibrate and as employed in the crystal structures that are indicated in the relevant OTEP diagrams above (Figure 2). To avoid crowding only selected atoms numbers are shown here. Arrows indicate the rotation about bonds corresponding to the torsion angles τ_1 , τ_2 and τ_3 .

Figure 4.

Overlay of fibrates. 4a. Left and 4b. right correspond to superimposition of dimethyl and phenyl ring groups, respectively of isopropyl clofibrate (magenta), fenofibrate (yellow), fenofibric acid (purple), redetermined clofibric acid (white) and fenofibrate II (tan). Only non-hydrogen atoms are shown. C atoms are colored as indicated in parentheses based on the compound. To provide better contrast from the color of the C skeleton O atoms are kept in red and Cl in green or pink.

Figure 5.

Superimposition of fenofibrate polymorphs and fenofibric acid. Crystal structure of the symmetric form of fenofibrate (TADLIU), asymmetric form of fenofibrate and fenofibric acid (QANHUI) were overlaid in yellow, green and orange color, respectively. Hydrogen and oxygen atoms are shown in white and red while chlorine is marked in green (fenofibrate polymorph II and fenofibric acid) and purple (fenofibrate polymorph I).

Figure 6. π -stacking and dimer formation in the triclinic form of fenofibrate. The calculated interaction energy for the shown pair of molecules is -38.7 kJ/mol, the interplanar separation between the two chlorobenzene rings is 3.486 Å.

Figure 7.

Energy profile and related conformation. a. Relaxed PES scan of the isopropyl ester of clofibrate at the B3LYP/6-31G(d) level with minima and conformers labeled. b. Only selected conformations about the ester bond rotation with molecular structures, carbon (grey), hydrogen (white), oxygen (red), and chlorine (green) are shown. The carbonyl oxygen O(3) is omitted for clarity. The angle measured is the dihedral angle of H(28)-C(15)-O(4)-C(14). Conformations with the H atom of the isopropyl group with larger torsion angles have lower energy than those with smaller angles.

Figure 8.

Polar Histogram plot of the isopropyl ester torsion angle, (τ_1) C-O-C-H, based on a CSD database search (CSD V5.32, updates until May 2011). Total of 212 compounds were included in the study after removal of 8 double entries. For compounds in which the isopropyl group is disordered only the major conformer was retained. The total number of isopropyl ester groups considered was 348 in the survey.

Figure 9. Change of surface area (Å²) relative to the ester bond torsion angle ν_1 in iPr fibrate derivatives. Total ASA and MSA for fenofibrate and iPr clofibrate are broken down into their polar and nonpolar components.

Table 1

Crystal data and structure refinement.

Compound	Isopropyl clofibrate	Clofibric acid	Clofibric acid
Reference	Current study	Current study	¹⁴
CSD Entry			BEFVAJ
Empirical formula	C ₁₃ H ₁₇ Cl O ₃	C ₁₀ H ₁₁ Cl O ₃	C ₁₀ H ₁₁ Cl O ₃
Formula weight	256.72	214.64	214.7
Temperature	100(2) K	100(2) K	RT (283–303)
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	— <i>P</i> 1	<i>P</i> 2 ₁ /n	<i>P</i> 2 ₁ /n
Unit cell dimensions	a = 8.6352(5) Å b = 8.6684(6) Å c = 9.7478(6) Å α = 76.242(4)° β = 73.777(4)° γ = 75.333(4)°	a = 6.2132(5) Å b = 7.7970(6) Å c = 21.0796(13) Å α = 90° β = 90.351(3)° γ = 90°	21.127(8) Å 7.966(5) Å 6.329(3) Å α = 90° β = 90.05(4)° γ = 90°
Volume	666.72(7) Å ³	1021.17(13) Å ³	1065.2 Å ³
Z	2	4	4
Density (calculated)	1.279 Mg/m ³	1.396 Mg/m ³	1.338 Mg/m ³
Absorption coefficient	0.281 mm ⁻¹	0.352 mm ⁻¹	0.352 mm ⁻¹
F(000)	272	448	488
Crystal size (mm ³)	0.46 × 0.37 × 0.19	0.33 × 0.31 × 0.29	0.25 × 0.40 × 0.31
Theta range for data collection	2.21 to 26.00°	2.79 to 35.63°	25.0°
Reflections collected	11785	37930	1272
Independent reflections	2575 [R(int) = 0.035]	4707 [R(int) = 0.040]	1272
Completeness (to theta)	98.4 % (26.00°)	100.0 % (35.63°)	Not reported
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	None
Max. and min. transmission	0.9486 and 0.8817	0.9049 and 0.8928	Not reported
Refinement method	^a Full-matrix least-squares on F ²	^a Full-matrix least-squares on F ²	^b Full-matrix least-squares
Data / restraints / parameters	2575 / 12 / 223	4707 / 0 / 171	955
Goodness-of-fit on F ²	1.075	1.036	Not reported
Final R indices [I > 2σ(I)]	R1 = 0.0417, wR2 = 0.1059	R1 = 0.0357, wR2 = 0.0930	0.060
R indices (all data)	R1 = 0.0500, wR2 = 0.1109	R1 = 0.0444, wR2 = 0.0983	Not reported
Largest diff. peak and hole	0.373 and -0.475 e.Å ⁻³	0.473 and -0.329 e.Å ⁻³	Not reported

Compound	Fenofibrate I	Fenofibric acid	Fenofibrate II
Reference	Current study	⁷	Current study
CSD Entry		QANHUI	
Empirical formula	C ₂₀ H ₂₁ Cl O ₄	C ₁₇ H ₁₅ ClO ₄	C ₂₀ H ₂₁ ClO ₄
Formula weight	360.82	318.74	360.82

Compound	Fenofibrate I	Fenofibric acid	Fenofibrate II
Temperature	100(2) K	160(2) K	100(2)
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	— <i>P1</i>	<i>Pbca</i>	<i>P2₁/n</i>
Unit cell dimensions	a = 8.1325(15) Å b = 8.2391(15) Å c = 14.399(3) Å α = 93.978(2)° β = 105.748(2)° γ = 95.854(2)°	a = 18.2168(4) Å b = 7.5623(2) Å c = 22.1355(5) Å α = 90° β = 90° γ = 90°	a = 13.619(7) b = 7.554(4) c = 17.880(9) α = 90° β = 92.351(7)° γ = 90°
Volume	919.0(3) Å ³	3049.41(13) Å ³	1837.8 Å ³
Z	2	8	4
Density (calculated)	1.285 Mg/m ³	1.389 Mg/m ³	1.304 Mg/m ³
Absorption coefficient	0.229	0.266	0.229 mm ⁻¹
F(000)	380	1328	760
Crystal size (mm ³)	0.55 × 0.50 × 0.44	0.47 × 0.43 × 0.14	0.55 × 0.30 × 0.25
Theta range for data collection	2.5 to 29.13°	2.2 to 28.3°	1.84 to 31.23°
Reflections collected	12909	47753	30060
Independent reflections	4864 [R(int) = 0.0235]	3497 [R(int) = 0.0356]	5647 [R(int) = 0.027]
Completeness (to theta)	98.7 % (29.13°)	99.9 % (27.5°)	99.9% (28.00°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Max. and min. transmission	0.7464 and 0.6988	0.9637 and 0.8853	0.746 and 0.689
Refinement method	^a Full-matrix least-squares on F ²	^a Full-matrix least-squares on F ²	^a Full-matrix least-squares on F ²
Data / restraints / parameters	4864 / 0 / 310	3497 / 6 / 259	5647 / 0 / 310
Goodness-of-fit on F ²	1.035	1.114	1.026
Final R indices [I>2σ(I)]	R1 = 0.0391, wR2 = 0.1024	R1 = 0.0416, wR2 = 0.0957	R1 = 0.0355, wR2 = 0.0897
R indices (all data)	R1 = 0.0418, wR2 = 0.1050	R1 = 0.0485, wR2 = 0.0991	R1 = 0.0419, wR2 = 0.0953
Largest diff. peak and hole	0.509 and -0.449 e.Å ⁻³	0.32 and -0.29 e.Å ⁻³	0.47 and -0.30 e.Å ⁻³

^aFull-matrix least-squares on F²^bFull-matrix least-squares^anot on F₂.

Table 2

Torsion angles of fibric acids and their iPr esters as found in their crystal structures (Figure 2). Atom numbering is as used in the respective crystal structures as deposited in the CSD.

Bond	Clofibric acid	Isopropyl Clofibrate	Fenofibric acid	Symmetric Fenofibrate	Asymmetric Fenofibrate
τ_1 atoms angle		H11-C11-O3-C10 -30.93° C13-C11-O3-C10 -149.60° C12-C11-O3-C10 87.63°		H15-C18-O2-C7 2.74° C20-C18-O2-C7 122.47° C19-C18-O2-C7 117.87°	H18-C18-O4-C17 45.94° C19-C18-O4-C17 -74.73° C20-C18-O4-C17 164.60°
τ_2 atoms angle	C8-C7-O1-C1 -78.96°	C10-C7-O1-C4 -56.14°	C15-C14-O2-C11 -68.95°	C7-C12-O1-C2 67.48°	C17-C14-O2-C11 -62.73°
τ_3 atoms angle	C7-O1-C1-C6 54.30°	C7-O1-C4-C3 7.03°	C14-O2-C11-C12 18.30°	C12-O1-C2-C3 -23.32°	C14-O2-C11-C10 5.37°

Table 3

Minima and conformers of the isopropyl ester rotation with geometry optimized at the B3LYP/6-31G(d) level and energy calculated at the B3LYP/6-311+G(d,p) level.

Conformation	Fenofibrate		Clofibrate	
	Energy (kJ/mol, relative to lowest energy conformation)	C16-O3-C37-H38 dihedral angle (°)	Energy (kJ/mol, relative to lowest energy conformation)	C14-O4-C15-H28 dihedral angle (°)
Minimum A	1.394	-34.5	0.000	-33.3
Conformer AB'	2.113	-9.8	2.073	12.1
Minimum B	0.000	33.3	1.327	34.7
Conformer BC'	28.060	117.8	28.698	120.3
Minimum C	12.127	179.0	12.159	-179.0
Conformer CA'	28.597	-120.4	28.258	-119.0

Table 4

Total surface area Å² (above) along with its components and the corresponding ester bond torsion angle τ_1 are listed in parentheses in degrees (below). These values reported here were calculated using the procedures described in ^{44,45}.

Compound	Total MSA		Total ASA		Polar MSA(PSA _d)		Polar ASA		Non-polar MSA		Non-polar ASA	
	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest
Fenofibrate	365.26 (104)	359.55 (-106)	641.13 (104)	628.72 (-106)	31.57 (-6)	27.38 (104)	68.53 (-6)	60.05 (104)	337.87 (104)	331.26 (-96)	581.08 (104)	566.19 (-96)
Fenofibric Acid	319.51		575.50		47.35		120.65		272.17		454.85	
Isopropyl Clofibrate	267.85 (-103)	262.51 (107)	488.84 (-113)	477 (107)	18.32 (7)	14.31 (-103)	33.19 (7)	24.8 (-103)	253.54 (-103)	247.52 (107)	463.95 (-103)	449.8 (97)
Clofibric Acid	222.69		424.01		33.96		85.82		188.73		338.19	