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HDL Therapeutics for the treatment of atherosclerosis: a brief overview of the synthetic approaches

Manojit Pal *

New Drug Discovery, R&D Center, Matrix Laboratories Limited, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak District, Andhra Pradesh 502325, India

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Abbreviations: CHD, coronary heart diseases; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; TG, triglyceride; RCT, reverse cholesterol transport; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Ureido-TiBA, urea-substituted thioisobutyric acid; Fmoc, 9-fluorenylmethoxycarbonyl; DMAP, 4-dimethylaminopyridine; TFA, trifluoroacetic acid; SAR, structure–activity relationship; OEA, oleylethanolamide; LXR, liver X receptor; ABC, adenosine triphosphate binding cassette; SREBP-1c, sterol response element binding protein-1c; FAS, fatty acid synthase; CETP, cholesteryl ester transfer protein; DIEA, diisopropylethylamine; DIC, *N*,*N*-diisopropylcarbodiimide; HOBT, hydroxybenzotriazole; *m*-CPBA, *m*-chloroperbenzoic acid; TMS, trimethylsilyl; rt, room temperature; DCM, dichloromethane.

* Fax: +91 08458 279305.
E-mail address: manojitpal@rediffmail.com

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1. Introduction

Cholesterol (a combination of steroid and alcohol, i.e., sterol) is a lipid found in the cell membranes of all tissues and plays a central role in many biochemical processes, such as the composition of cell membranes and the synthesis of steroid hormones. It is insoluble in blood and is transported in the circulatory system by carriers called lipoproteins (spherical particles, which have an exterior composed of water-soluble proteins). Lipoproteins that carry cholesterol from and to the liver can be classified into two types, namely low-density lipoprotein (LDL) and high-density lipoprotein (HDL).[1–3] These two types of lipids, along with triglycerides and Lp(a) cholesterol (a genetic variation of LDL), make up the total cholesterol count. Circulation of excessive LDL cholesterol in the blood helps in building atherosclerotic plaques in the inner walls of the arteries, thereby causing narrowing and leading to a disease condition called atherosclerosis (blockage of a narrowed artery via formation of a clot often results in heart attack or stroke), whereas a high level of HDL in the blood is beneficial as it prevents heart attack or coronary heart diseases (CHD). Essentially, HDL acts as a scavenger that moves the lipids (mainly cholesterol) from the blood vessels to the liver for excretion into bile (a process called reverse cholesterol transport or RCT), from where they are then excreted from the body. Thus, low levels of HDL (<40 mg/dl) also increase the risk of heart disease. While this inverse relationship between HDL and the risk of CHD has been supported by several cardiovascular studies, currently no potent HDL elevators are available for the treatment of patients suffering from CHD. Among the currently marketed drugs, statins (about 5%), fibrates (~15%) and niacin (~20–30%) have been shown to elevate HDL significantly.[4–7] Therefore, efforts are underway to develop potent and better HDL elevators for the prevention of cardiovascular disease. The targeted therapeutics that are in the pipeline for HDL elevation, e.g., macromolecules, peptides and small molecules, have been reviewed recently.[8] The present review will therefore focus mainly on the chemical approaches and methodologies utilised and challenges encountered during the synthesis of small molecules as new HDL elevators. Based on their mechanism of action, small molecules can be subdivided into (1) PPARα ligands, (2) LXR ligands, (3) CETP inhibitors, (4) PPARδ ligands and (5) agents having miscellaneous mechanisms.

2. PPARα ligands

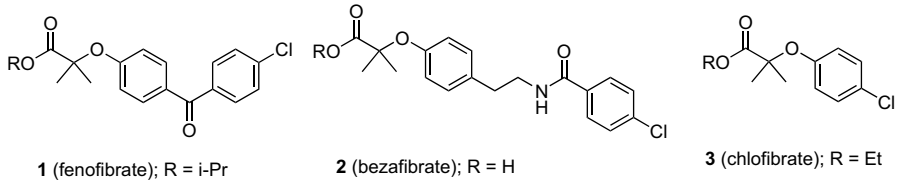
The PPARs or peroxisome proliferator-activated receptors are a group of nuclear receptor proteins that function as transcription factors (a protein sometimes called a sequence-specific DNA-binding factor that binds to specific parts of DNA using DNA-binding domains and is part of the system that controls the transfer (or transcription) of genetic information from DNA to RNA) regulating the expression of genes. PPARs play essential roles in the regulation of cellular differentiation, development and metabolism (carbohydrate, lipid and protein) of higher organisms. Three distinct PPAR subtypes or isoforms, e.g., PPARα, PPARγ and PPARδ, have been identified in most mammalian species. PPARα, one of these three isoforms, is expressed predominantly in the metabolically active tissues like liver and others, e.g., muscle, heart, kidney and intestine. PPARα was recognised to be the target receptor for the fibrate class of anti-hyperlipidemic drugs, whereas PPARγ was shown to function as the cellular receptor of the thiazolidinedione (TZD) class of insulin-sensitising drugs. Notably, a recent study has shown that all the TZDs are not necessarily activators of PPARγ.[9] In contrast to PPARα and PPARγ, there are no marketed drugs that target PPARδ, and the physiological role of PPARδ remains largely mysterious due, in part, to the lack of selective ligands as chemical tools to study its pharmacology (see Section 6 for a discussion on PPARδ agonists).

2.1. Synthesis of fibrates

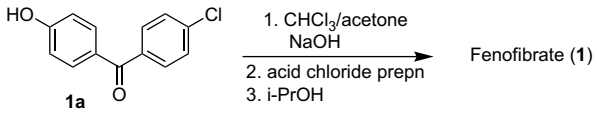
Fibrates, e.g., carboxylic acid derivatives **1**–**3** (Scheme 1), are a class of drugs that increase HDL cholesterol (HDL-C) via activation of PPARα, as indicated by several studies.[10,11] As a result of PPARα-associated mechanisms, fibrates stimulate triglyceride breakdown, i.e., they activate lipoprotein lipase (LPL) and also reduce ApoCIII expression (an inhibitor of LPL); as a consequence, they raise HDL-cholesterol levels.

Various synthetic methods for the well-known members of the fibrate family, e.g., fenofibrate (**1**), bezafibrate (**2**) and chlofibrate (**3**), have been reported. For example, chlofibrate (**3**) can be prepared via the reaction of 4-chlorophenol with an acetone/chloroform mixture in the presence of sodium hydroxide followed by esterification of the resulting carboxylic acid with ethanol.[12] Similarly, fenofibrate (**1**) can be prepared by reacting (4-chlorophenyl)-(4-hydroxyphenyl)methanone (**1a**) with an acetone/chloroform mixture followed by esterification via conversion of the resulting acid into the acid chloride and then treating it with isopropyl alcohol (Scheme 2).[13,14]

Fenofibrate can also be prepared directly under solvent-free conditions by reacting **1a** with 2-bromo-2-methylpropionic acid ester (**1b**) in the presence of excess K_2CO_3 at higher temperatures.[15] This process was extended to the synthesis of bezafibrate **2** that involves the reaction of 4-[*N*-(4-chlorobenzoyl)-2-aminoethyl]-



Scheme 1. Structures of fibrates.



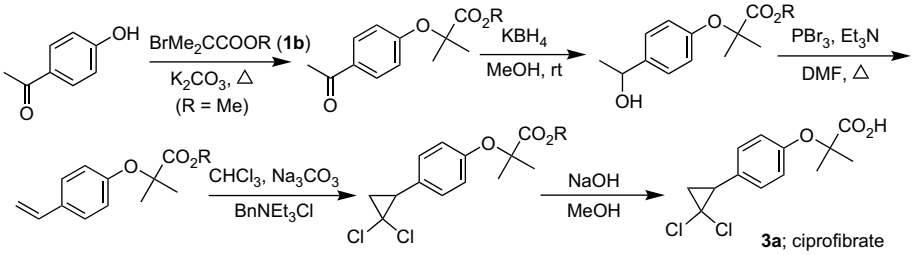
Scheme 2. Synthesis of fenofibrate.

phenol with **1b** followed by hydrolysis of the resulting ester. Furthermore, the utility of this solvent-free process was demonstrated in the synthesis of ciprofibrate (**3a**), another member of the fibrate family that acts as an HDL elevator, in high yield (Scheme 3).

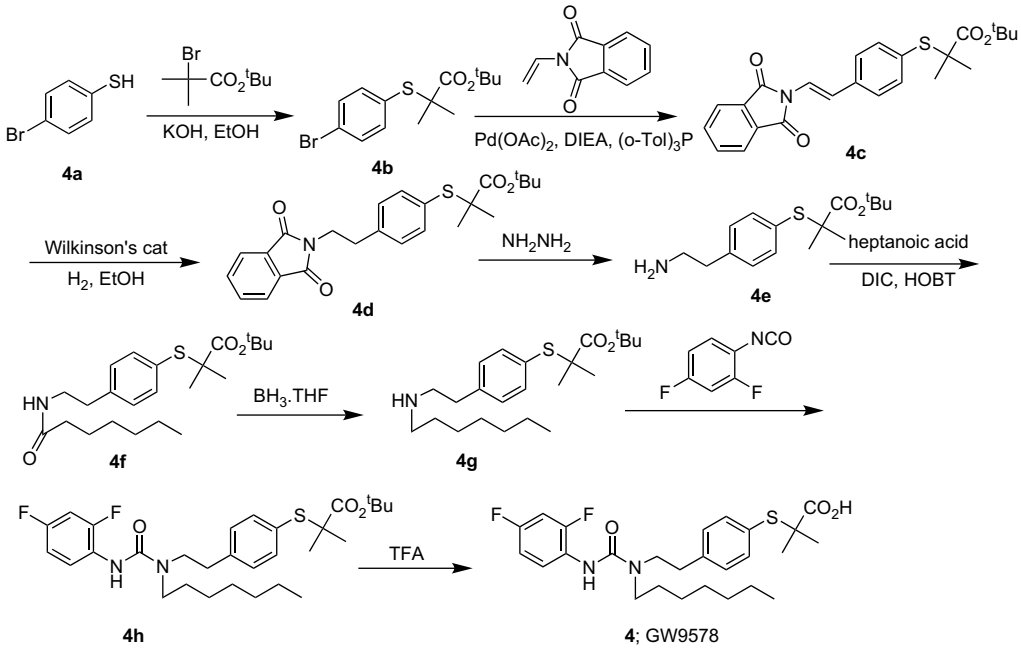
2.2. Synthesis of ureido-fibrates

Although fibrates have been identified as HDL elevators, in humans, a high dose (about 300–1200 mg/kg) of these compounds was needed to achieve the desired pharmacological effect. Since the HDL-elevating properties of fibrates were thought to be due to their activation of the PPARα receptor, efforts were devoted to develop potent and selective PPARα agonists. Thus, a series of ureido-fibrates were synthesised in order to evaluate their pharmacological properties, eventually leading to the identification of a urea-substituted thioisobutyric acid (Ureido-TiBA) **4** or GW9578.[16] A synthesis of Ureido-TiBA **4** is shown in Scheme 4. The process involves the reaction of 4-bromothiophenol (**4a**) with *tert*-butyl bromoisobutyrate to give the bromo ester **4b**, which, on Heck coupling with vinylphthalimide followed by hydrogenation of the resulting olefin **4c**, afforded compound **4d**. After phthalimide deprotection the resulting amine **4e** was reacted with heptanoic acid to furnish the amide **4f**, which was then converted into the secondary amine **4g** required for the construction of the urea moiety. The reaction of **4g** with 2,4-difluorophenyl isocyanate followed by cleavage of the *tert*-butyl ester moiety of **4h** yielded Ureido-TiBA **4**. Compared to all the fibrates, compound **4** showed a high selectivity towards PPARα when assayed for agonist activity in vitro, e.g., the EC_{50} values (the concentration of test compound that gave 50% of the maximal receptor activity) for PPARα human receptor activity for chlofibrate, fenofibrate, bezafibrate and compound **4** were found to be 55, 30, 50 and 0.05 μM, respectively.[16]

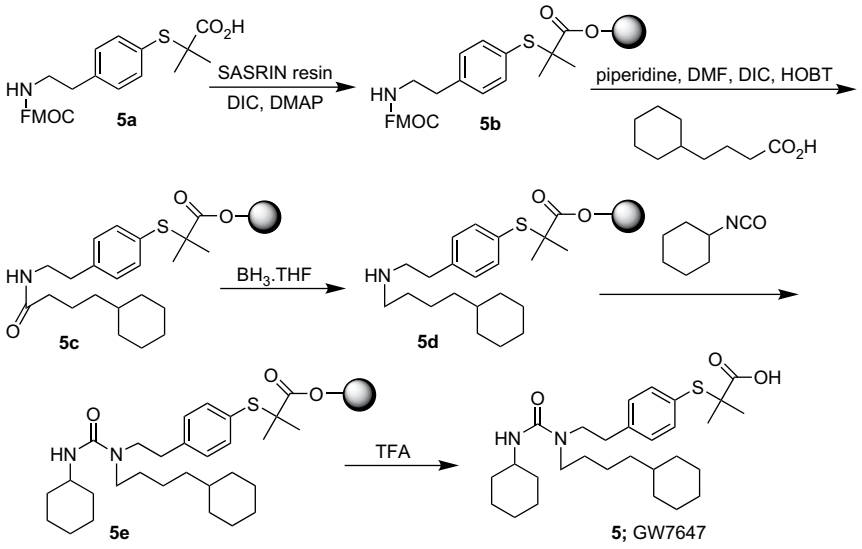
Although compound **4**, which existed as a viscous oil or foam, was found to be effective in rodents, it appeared to be less promising when tested on human receptors. Thus, the lack of expected pharmacological effects, coupled with the poor physical properties of compound **4**, triggered further research activities, especially in the area of medicinal chemistry. As a result, a solid-phase, parallel-array synthesis was employed that led to the identification of another ureido-fibrate, i.e., Ureido-TiBA **5** (GW7647).[17] Compound **5** showed an EC_{50} value of 0.001 μM on murine PPARα and the administration of **5** (3 mg/kg po bid) to cholesterol/cholic acid-fed rats for 4 days resulted in a 60% increase in HDL-cholesterol. The solid-phase synthesis[17] of compound **5** (Scheme 5) was carried out using a strategy similar to that applied to **4**, which required loading of the FMOC-substituted TiBA **5a** onto the solid phase, i.e., SASRIN resin, to generate **5b** in the initial step. Deprotection of the FMOC



Scheme 3. Synthesis of ciprofibrate.



Scheme 4. Synthesis of Ureido-TiBA **4** (GW9578).



Scheme 5. Synthesis of Ureido-TiBA **5** (GW7647).

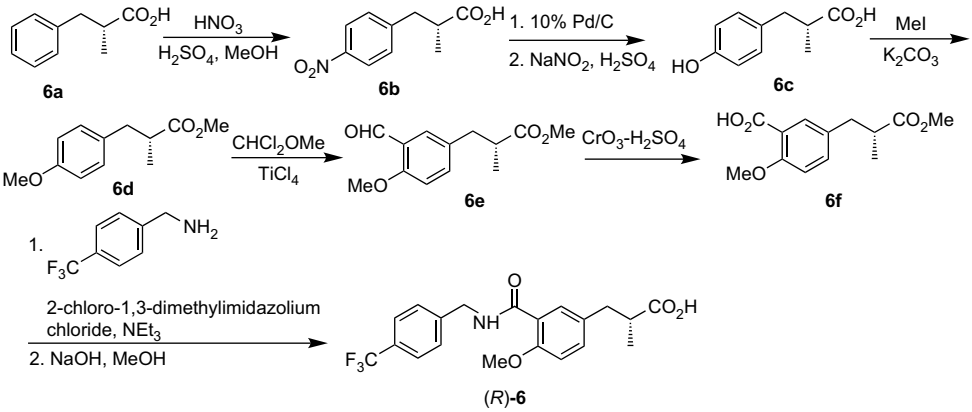
group (piperazine/DMF), followed by coupling with an appropriate carboxylic acid, afforded the intermediate resin-bound amide **5c**, which was reduced in situ with borane to generate the resin-bound secondary amine **5d**. Reaction of the amine with cyclohexyl isocyanate to provide **5e**, followed by cleavage with 10% TFA, afforded the Ureido-TiBA **5**.

2.3. Synthesis of phenylpropionic acid derivative

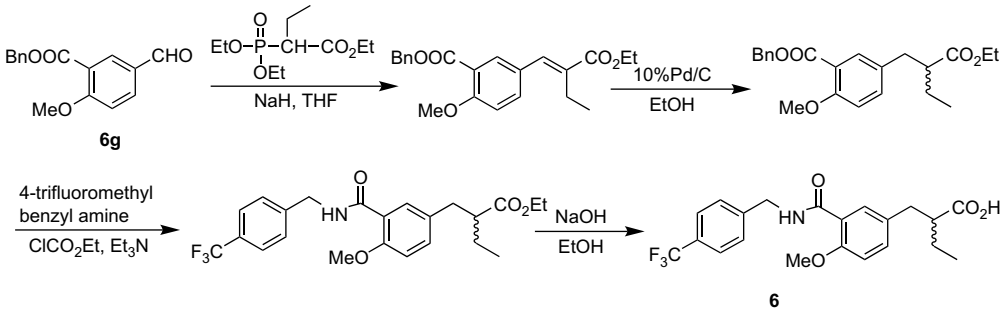
In another approach to obtain non-fibrate-based HDL elevators having a superior clinical profile, a phenylpropionic acid derivative **6** (Scheme 6) has been reported as a potent PPARα agonist.[18] This compound was derived from KRP-297 (MK-767), a non-selective PPAR agonist that belongs to the thiazolidine-2,4-dione (TZD) class of insulin sensitisers like glitazones (e.g., troglitazone, pioglitazone and rosiglitazone),[19] by replacing the thiazolidine-2,4-dione ring by an α-substituted carboxylic acid moiety. Compound **6** (EC_{50}=0.04 μM) was found to be more potent towards PPARα activation compared to KRP-297 (EC_{50}=1.0 μM) and bezafibrate (EC_{50}>78 μM) when screened for agonist activity in vitro. The presence of an asymmetric centre at the α-position of the carboxylic group was found to be critical, as (*S*)-**6** exhibited more potency than (*R*)-**6** and the absolute configuration was determined by the preparation of (*R*)-**6**. The synthesis of optically active **6** was achieved by using (*R*)-2-benzylbutanoic acid (**6a**) as the starting material as shown in Scheme 6.[20] Thus, nitration of **6a**, followed by the reduction of **6b** and then treatment of the resulting aniline derivative with nitrous acid, provided the phenol-based carboxylic acid intermediate **6c**. One-pot methylation of the phenolic OH and carboxylic acid moiety provided the ester **6d**, which on *ortho*-formylation of the anisole moiety in the presence of $TiCl_4$ provided **6e**. The oxidation of **6e** afforded the acid ester **6f**. Coupling the acid moiety of **6f** with 4-trifluoromethylbenzylamine followed by ester hydrolysis provided the desired *R*-enantiomer of **6**. The preparation of racemic **6**, outlined in Scheme 7, requires four steps from the aldehyde **6g**.[18] Compound **6g**, prepared from 5-formylsalicylic acid, was treated with the Wadsworth–Emmons reagent, followed by hydrogenolysis, condensation with 4-trifluoromethylbenzylamine and alkaline hydrolysis to afford the racemic **6**. Each enantiomer of compound **6** was, however, obtained by optical resolution of the corresponding 4-(*S*)-benzyloxazolidinoneimide derivative of **6**, which was prepared by the reaction of racemic **6** and 4-(*S*)-benzyloxazolidinone via the mixed-anhydride method (reagents: pivaloyl chloride, NEt_3 followed by 4-(*S*)-benzyloxazolidinone, *t*-BuOK in THF), followed by alkaline removal of the chiral auxiliary (reagents: LiOH, 30% H_2O_2, MeOH).[18,20]

2.4. Synthesis of triazolone derivatives

Prompted by the observed PPARα-mediated elevation of HDL-cholesterol levels caused by fibrates and the identification of GW9578 (**4**), GW7647 (**5**) and non-fibrate phenylpropanoic acid (**6**)



Scheme 6. Synthesis of (*R*)-enantiomer of phenylpropionic acid **6**.



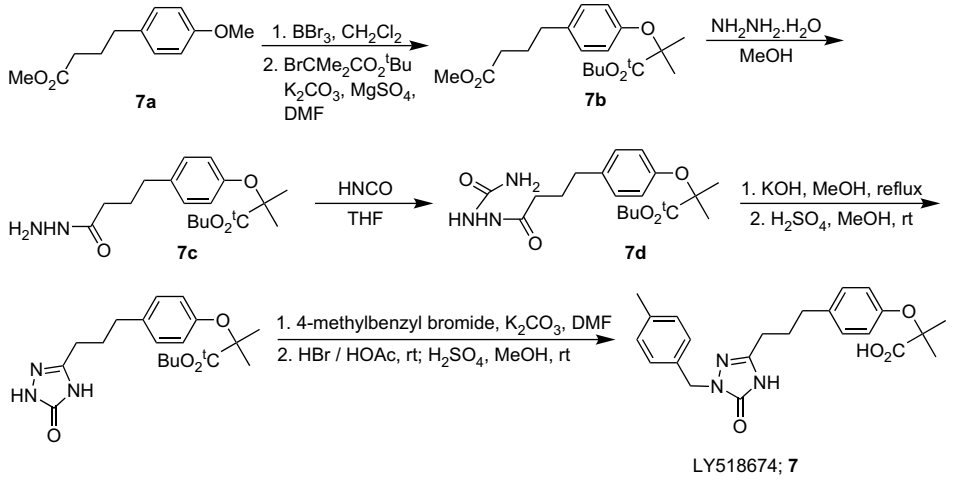
Scheme 7. Synthesis of racemic mixture of compound **6**.

as potent human PPARα agonists, a new series of hPPARα agonists containing a 2,4-dihydro-3*H*-1,2,4-triazol-3-one (triazolone) core has been reported.[21] The triazolone core is the unique structural feature of this class and SAR (structure–activity relationship) work on this class has led to the discovery of **7** (LY518674), a highly potent and selective PPARα agonist (EC_{50}=42 nM) that is presently in clinical evaluation. After oral administration in human apo A-I transgenic mice once daily at 3 mg/kg for one week, compound **7** produced a 208% elevation in HDL cholesterol, compared to fenofibrate's 120% increase. Compound **7** also showed good pharmacokinetic properties (oral bioavailability >50%) when tested in Beagle dogs and F344 rats. The synthetic approach adopted for the preparation of triazolone **8** is shown in Scheme 8. Demethylation of ether **7a** followed by alkylation with methyl or *tert*-butyl bromoisobutyrate provided the diester **7b**, which, upon treatment with hydrazine hydrate, afforded hydrazide **7c**. Next, **7c** was converted into the acylsemicarbazide **7d**, which, on ring construction under KOH/MeOH, followed by hydrolysis of the *tert*-butyl ester, afforded the triazolone derivative **7**.

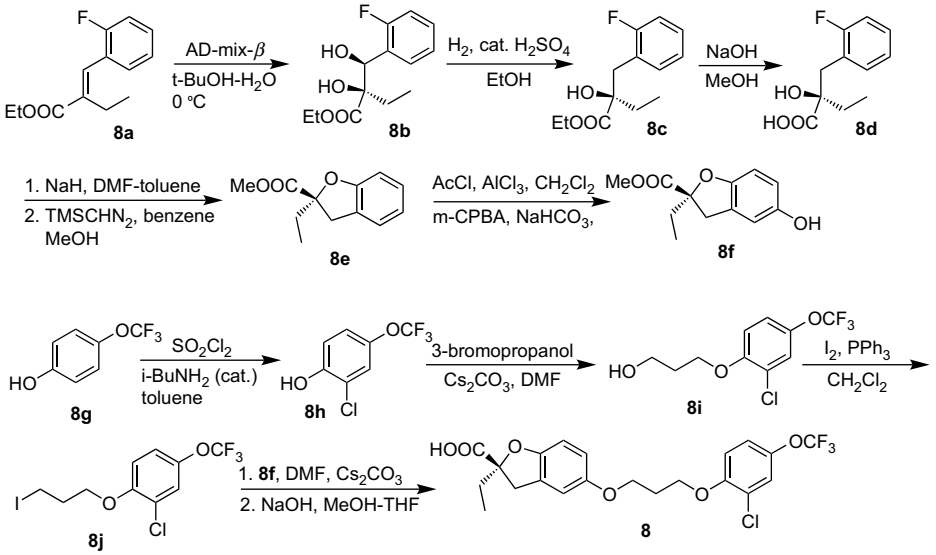
2.5. Synthesis of 2,3-dihydrobenzofuran-2-carboxylic acid derivative

It is interesting to note that all the PPARα agonists such as fibrates **1**–**3**, ureido-based fibric acids **4** (GW9578) and **5** (GW7647), non-fibrate phenylpropanoic acid derivative **6** and α-phenoxyphenylpropanoic acid **7** (LY518674) possess a common structural feature, i.e., an acidic head-group with a carboxylic acid moiety connected through a conformationally flexible spacer to the phenyl ring. On the other hand, several non-selective agonists have been developed adopting a general strategy based on the use of a 1,3-bis(oxy)propylidene linker to connect an acidic head-group and a lipophilic tail.[22] Utilising this information, a novel class of PPARα agonists **8** (EC_{50}<10 nM) have been reported very recently that contain conformationally constrained 2,3-dihydrobenzofuran-2-carboxylic acid as an acidic head-group.[23] The *S*-enantiomer of **8** was found to be about 400-fold more potent than the *R*-enantiomer in vitro. In vivo studies in a Male Syrian hamster model comprising oral administration indicated that compound (*S*)-**8** required only about 1/500 of the exposure of fenofibrate in order to achieve a comparable lipid-lowering efficacy. The synthesis of (*S*)-**8**, as outlined in Scheme 9, requires the preparation of two key intermediates, i.e., the chiral phenol **8f** and the iodo ether **8i**, separately. The asymmetric synthesis of the required enantiomer of **8f** involves a Sharpless asymmetric dihydroxylation (AD) reaction on the α,β-unsaturated ester **8a** in the presence of AD-mix-β to give the diol **8b**. Selective removal of the benzylic hydroxyl group by catalytic hydrogenation and subsequent hydrolysis of the ester moiety of **8c** afforded the chiral hydroxy acid **8d**. Intramolecular cyclisation of **8d** in the presence of a base, followed by conversion of the carboxylic moiety into the methyl ester furnished **8e**. A two-step sequence involving a Friedel–Crafts acylation of **8e**, followed by Bayer–Villiger oxidation of the resulting ketone, afforded the chiral phenol **8f**. The absolute stereochemistry was confirmed by X-ray crystallographic data generated on a single crystal of an amide derivative of **8f**.

The iodo ether **8j** was prepared via *ortho*-chlorination of 4-trifluoromethoxyphenol (**8g**) to give **8h**, followed by reaction with 3-bromopropanol and subsequent conversion of the resulting alcohol (**8i**) into the corresponding iodide. An S_N2 coupling of the iodide **8j** with the chiral phenol **8f** yielded the target compound **8**.



Scheme 8. Synthesis of triazolone derivative **7** (LY518674).



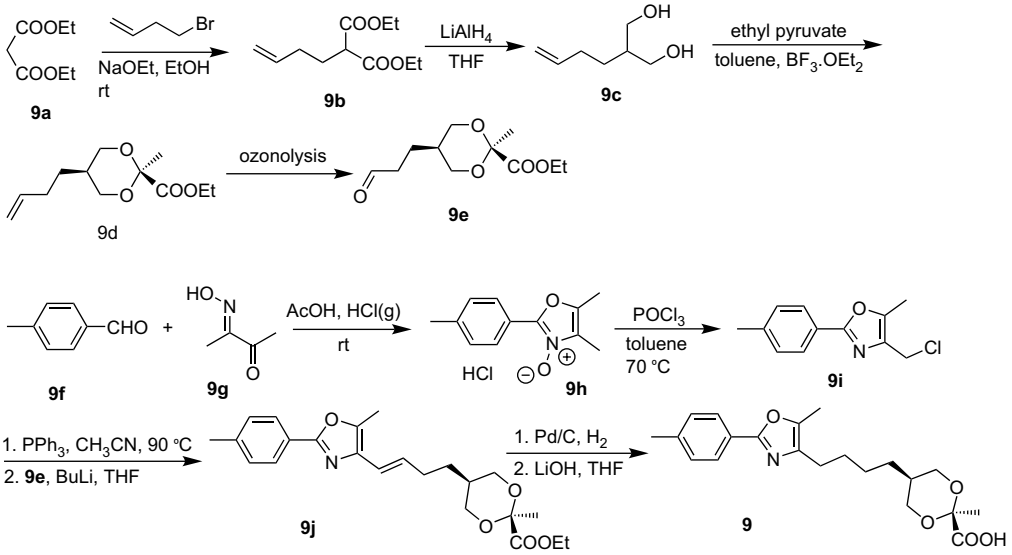
Scheme 9. Synthesis of 2,3-dihydrobenzofuran-2-carboxylic acid derivative (**8**).

2.6. Synthesis of dioxanecarboxylic acid derivative

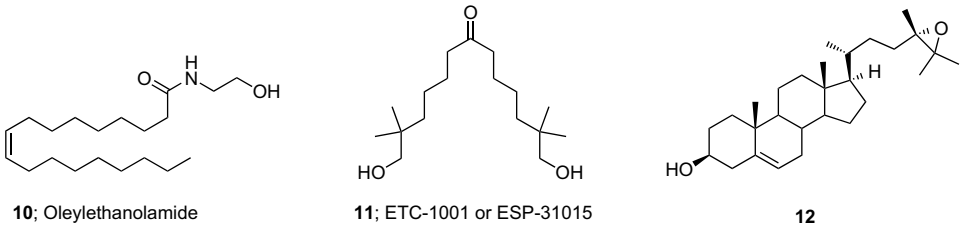
Recently, a novel dioxanecarboxylic acid derivative **9** (NS-220) has been reported as one of the most potent and selective human PPARα agonists (EC_{50}=42 nM).[24] The high potency and selectivity of **9** [EC_{50} (hPPARα)/EC_{50} (hPPARγ)=510 for **9**, compared to 10–180 for other PPARα agonists] were thought to be due to the presence of the unique dioxanecarboxylic acid moiety. An initial synthesis[25] of **9**, associated with a large number of steps and a low yield of product, was found to be unsuitable for large-scale production. Therefore, an alternative and economic process was developed to prepare **9** in high yield under mild reaction conditions (Scheme 10).[26] The key step of this synthesis is a Wittig reaction of the aldehyde **9e** bearing a [1,3]dioxane-2-carboxylate ester with the chloro compound **9i** containing an oxazole moiety to give the olefin **9j** that on subsequent hydrogenation followed by ester hydrolysis affords the target compound **9**. The preparation of **9e** begins with diethyl malonate **9a**, which on reaction with 4-bromo-1-butene provides the 2-but-3-enyl-substituted malonate ester **9b**. Reduction of the ester groups, followed by reaction of the resulting alcohol **9c** with ethyl pyruvate, affords a 75/25 mixture of *cis*/*trans*-5-but-3-enyl-2-methyl[1,3]dioxane-2-carboxylate ester **9d**. Ozonolysis of **9d** and subsequent crystallisations of the resulting **9e** furnished the required pure cis isomer with 99.5% purity. On the other hand, the oxazole intermediate **9i** can be prepared via condensation of tolualdehyde **9f** with 2,3-butadione-monoxime **9g**, followed by treatment of the resulting oxazole-3-oxide **9h** with $POCl_3$.

2.7. Synthesis of oleylethanolamide

The fatty acid ethanolamide, oleylethanolamide (OEA) **10** (Fig. 1), a naturally occurring lipid that lowers body weight and hyperlipidemia in obese rats, has been shown to be a selective and endogenous PPARα agonist at a much lower concentration.[27,28] Experimental results suggest that OEA regulates lipid metabolism and that this effect may contribute to its anti-obesity properties, thereby decreasing the risk of various cardiovascular diseases. The evidence suggests that men or women in the highest obesity category have more than 2- or 4-fold the risk of hypertension, high



Scheme 10. Synthesis of dioxanecarboxylic acid derivative **9** (NS-220).



10; Oleylethanolamide **11**; ETC-1001 or ESP-31015 **12**

Figure 1. Structures of OEA and ETC-1001.

blood cholesterol, or both, compared to men or women of normal weight, respectively. Nevertheless, OEA is prepared[29] from fully refined olive oil. The free fatty acids are first prepared by hydrolysis and the saturated fats are then removed. The resulting fractionated concentrate, containing primarily oleic acid, is free of sterols and other unsaponifiable matter found in olive oil, and is then converted into the corresponding acid chloride. The acid chloride is then reacted with ethanolamide acetate. Finally, the ester is hydrolysed to remove acetic acid under vacuum to provide OEA **10**.

3. Synthesis of long hydrocarbon chain ether diols

It was observed that keto-substituted hydrocarbons with hydroxyl or carboxyl termini can favourably alter lipids in an animal model of metabolic syndrome.[30] While these compounds have less well-defined mechanisms of action, their ability to raise HDL-cholesterol has been demonstrated in animal models. Thus, 1,13-dihydroxy-2,2,12,12-tetramethyltridecan-7-one (ETC-1001 or ESP-31015, Fig. 1) was identified as a novel lipid regulator that can raise HDL-C levels and is presently in a phase 1 clinical trial.[31] Encouraged by this invention, a number of ether derivatives having long-chain hydrocarbons were synthesised and evaluated, when the active compounds were found to be symmetrical with four to five methylene groups separating the central ether functionality and the *gem* dimethyl or methyl/aryl substituents.[32] The most promising compound **11** showed a 34.6% increase in serum HDL cholesterol at the highest dose administered (100 mg/kg) after 2 weeks of treatment (in female obese Zucker fatty rats following daily oral administration) and was found to be safe and well tolerated at all dose levels tested. The symmetrical ether diol **11** was prepared via a Williamson reaction of the THP-protected bromo alcohol **11a** with the sodium salt of alcohol **11b** (Scheme 11) to provide the protected ether intermediate **11c**. The alcohol **11b** was obtained via hydrolysis of **11a** in the presence of K_2CO_3 in DMSO/water at refluxing temperature. Deprotection of **11c** with concentrated HCl in MeOH at reflux furnished the targeted ether diol **11**.

4. LXR-Ligands

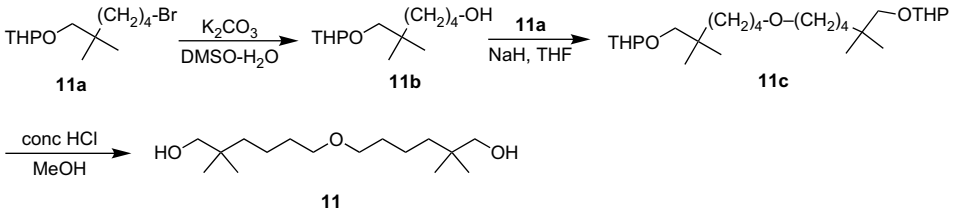
The LXR (liver X receptor) is an orphan nuclear receptor that has α and β forms, i.e., LXRα (NR1H3) and LXRβ (NR1H2). Both forms are involved in controlling cholesterol metabolism by regulating the gene expression of proteins involved in cholesterol efflux from cells. The efflux of free cholesterol from peripheral tissues to nascent HDL particles (a pivotal step in the reverse cholesterol transport or RCT process) is mediated by ABCA1 (the cholesterol transporter adenosine triphosphate binding cassette (ABC) A1) gene. Experimental evidence suggests that upregulation of ABCA1 expression with the help of LXR-ligands could provide a method for promoting reverse cholesterol transport, thereby raising HDL cholesterol levels to prevent cardiovascular diseases.[33] For example, 24(*S*),25-epoxycholesterol **12** (EPC; Fig. 1), a natural ligand for LXRα (i.e., LXRα agonist), has been shown to increase the expression of ABCA1 in the liver.[34,35] Several distinct structural classes of synthetic ligands have also been reported to upregulate ABCA1 expression.

4.1. Synthesis of LXR agonist T0901317

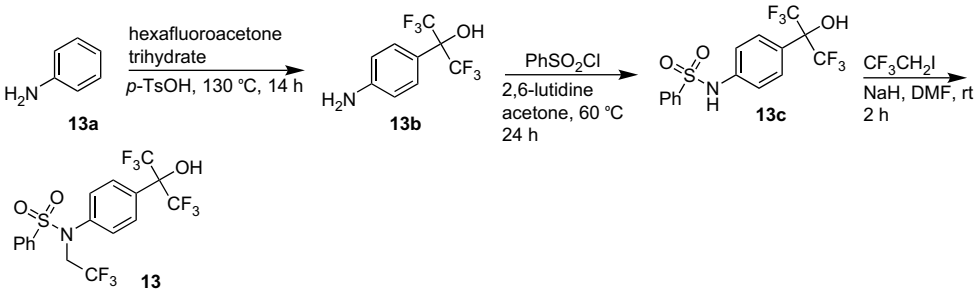
A sulfonamide-based nonsteroidal and synthetic LXR agonist T0901317 (**13**) has been reported to increase ABCA1 expression and raise HDL cholesterol levels in mice.[36,37] This compound contains a 1,1,1,3,3,3-hexafluoro-2-hydroxy-propan-2-yl and a sulfonamido substituent in a 1,4-relationship on the central phenyl ring and, to achieve the desired regiospecificity, the hexafluorocarbinol group was introduced via a Friedel–Crafts type of reaction between an aniline and hexafluoroacetone hydrate in the presence of an acid to provide the required aniline derivative **13b** (Scheme 12).[37] Treatment of **13b** with benzenesulfonyl chloride afforded the sulfonamide intermediate **13c** and the trifluoroethyl group was then introduced via alkylation. In an alternative route, the trifluoroethyl group on aniline **13a** can be introduced prior to the hexafluoro-2-hydroxypropan-2-yl moiety.

4.2. Synthesis of tertiary amine-containing carboxylic acid derivative

A tertiary amine-containing carboxylic acid derivative **14** (GW3965), identified from focused libraries of tertiary amines, was found to be active on LXRα and LXRβ in cell-based reporter gene assays.[38] It increased expression of the reverse cholesterol transporter ABCA1 in the small intestine and peripheral macrophages and increased the plasma concentrations of HDL cholesterol by 30% after oral dosing at 10 mg/kg to C57BL/6 mice. A solid-phase synthesis[38] of this promising lead for the development of anti-atherosclerotic drugs is shown in Scheme 13. The synthesis involves loading of 3-hydroxyphenylacetic acid **14a** on to the solid support to generate **14b**, followed by reaction with 3-bromopropanol under



Scheme 11. Synthesis of tetramethyl-substituted ether diol (**11**).



Scheme 12. Synthesis of T0901317 (**13**).

Mitsunobu conditions to give the resin-bound bromide **14c**. The bromide **14c** was then treated with a solution of diphenylethylamine in DMSO, and the resulting secondary amine **14d** was subjected to reductive amination with 2-chloro-3-trifluoromethylbenzaldehyde to give **14e**. Cleavage from the solid support provided the desired carboxylic acid **14**.

4.3. Synthesis of substituted maleimides

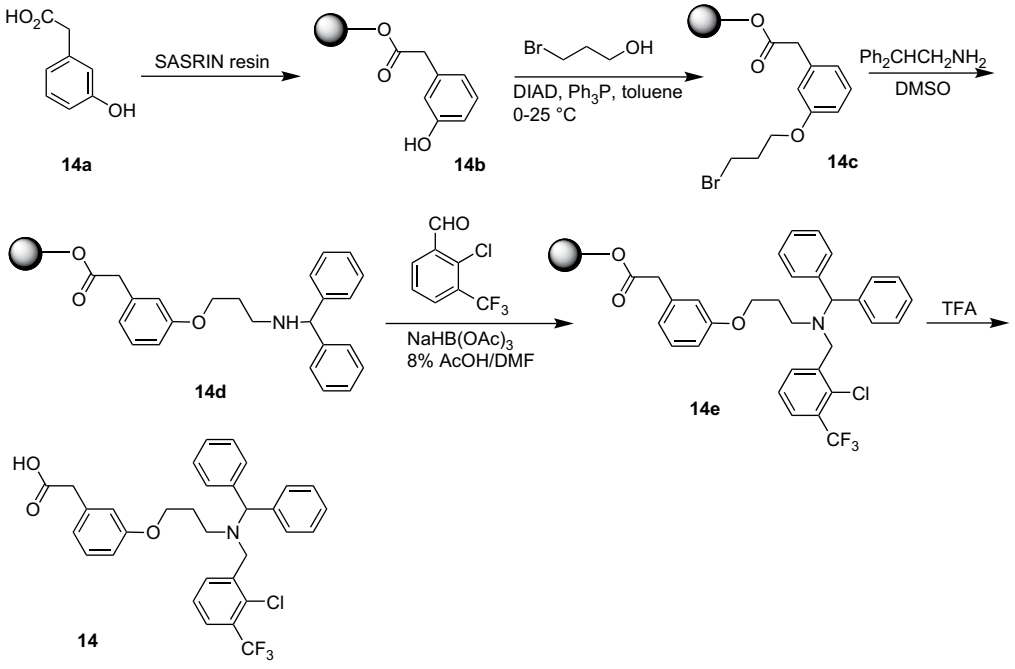
One of the major drawbacks of synthetic LXR agonists is an increase of plasma and hepatic triglycerides, which results from LXR-regulated induction of lipogenic genes including sterol response element binding protein-1c (SREBP-1c) and fatty acid synthase (FAS). In order to develop new LXR agonists that are devoid of lipogenic activity, a number of substituted 3-(phenylamino)-1*H*-pyrrole-2,5-diones (maleimides) were evaluated under a high-throughput screen. This led to the identification of GSK3987 (**15**) as a dual LXRα/β agonist that showed induction of ABCA1.[39] The synthetic route to compound **15** is shown in Scheme 14.[40a,b] Base-induced condensation[40c] of acetamide **15a** with dimethyl oxalate gave the 3-hydroxy-4-arylmaleimide **15b**, which, after treatment with phosphorus oxychloride in *N*,*N*-dimethylaniline or with oxalyl chloride, provided the chloro compound **15c**. Treatment of **15c** with 4-methoxyaniline afforded the desired intermediate **15d**, which, on alkylation with a benzyl halide, can provide the target compound **15**.

5. CETP inhibitors

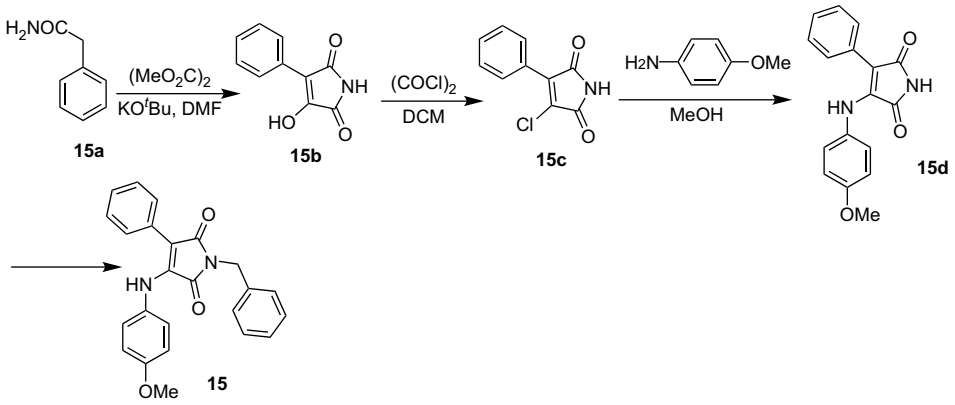
Cholesteryl ester transfer protein (CETP), a hydrophobic glycoprotein with a molecular weight of 74 kDa, is secreted mainly from the liver and circulates in plasma.[41] Bound mainly to HDL, it transfers cholesteryl ester (CE) from HDL to apolipoprotein B (apoB)-containing lipoproteins including very low-density lipoproteins (VLDLs) and LDLs in exchange for triglyceride (TG).[42,43] The outcome is a reduction of cardioprotective HDL levels and an increase of detrimental LDL. CETP thus appears to play a pro-atherogenic role and inhibiting CETP activity should elevate HDL and provide a potential therapeutic benefit for patients with coronary heart diseases. In 1990, CETP was first described as a therapeutic target.

5.1. Synthesis of thioester derivatives

In 1996, it was demonstrated that various cysteine-modifying reagents such as *p*-chloromercuriphenylsulfonic acid, 4,4′-dithiodipyridine or 4,4′-dithiobis(phenyl azide) could inhibit CETP under serum-free conditions.[44] Based on these observations, a series of bis(2-(acylamino)phenyl) disulfides, 2-(acylamino)benzenethiols, *S*-(2-(acylamino)phenyl)alkanethioates and related compounds were investigated to identify the more effective inhibitors. This study led to the identification of *S*-(2-((1-(2-ethylbutyl)cyclohexane)-carbonylamino)phenyl) 2-methylpropanethioate (**16**) (JTT-705 or



Scheme 13. Synthesis of GW3965 (**14**).

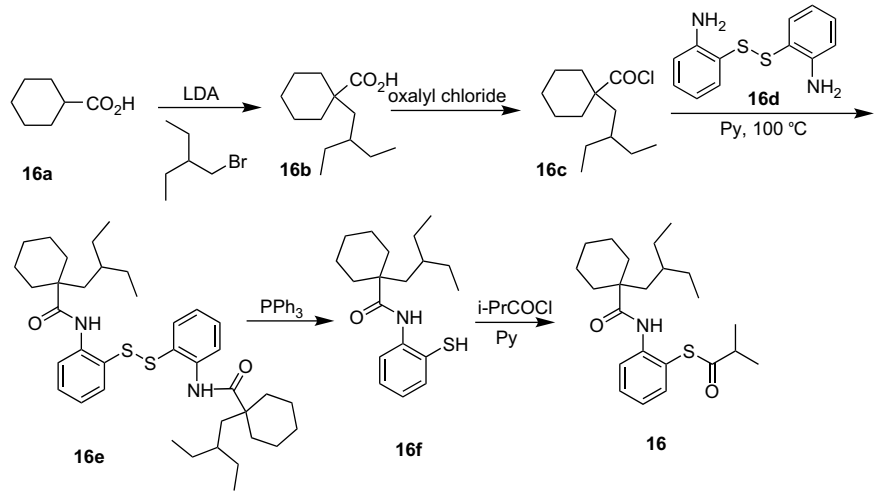


Scheme 14. Synthesis of GSK3987 (**15**).

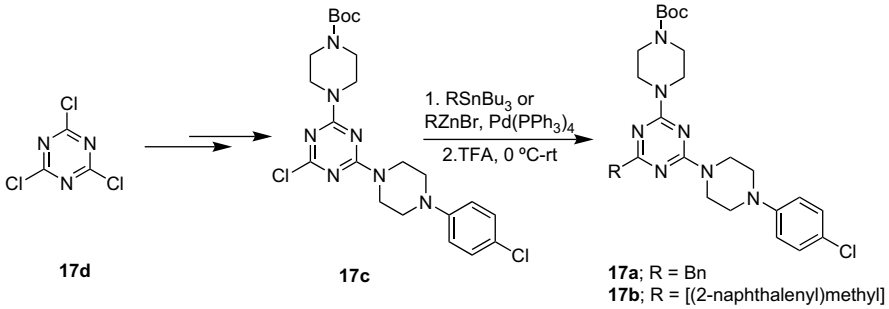
dalcetrapib)[45] that is currently in clinical studies. This compound achieved 50% inhibition of CETP activity in human plasma at a concentration of 9 μM and 95% inhibition of CETP activity in male Japanese white rabbits at an oral dose of 30 mg/kg. It increased the plasma HDL cholesterol level by 27 and 54%, respectively, when given at oral doses of 30 or 100 mg/kg once a day for 3 days to male Japanese white rabbits. The route used for the synthesis of compound **16** is shown in Scheme 15. One of the key starting materials, i.e., 1-alkylcyclohexanecarbonyl chloride **16c**, was prepared by dianion coupling between cyclohexanecarboxylic acid **16a** and 2-ethylbutyl bromide to give **16b**, followed by treatment with oxalyl chloride. N-Acylation of bis(2-aminophenyl) disulfide **16d** with the acid chloride **16c** followed by triphenylphosphine-mediated reduction of the disulfide bond of **16e**, provided the 2-acylaminobenzenethiol (**16f**). The benzenethiol **16f** was then coupled with 2-methylpropanoyl chloride to give the thioester **16**.

5.2. Synthesis of triazines

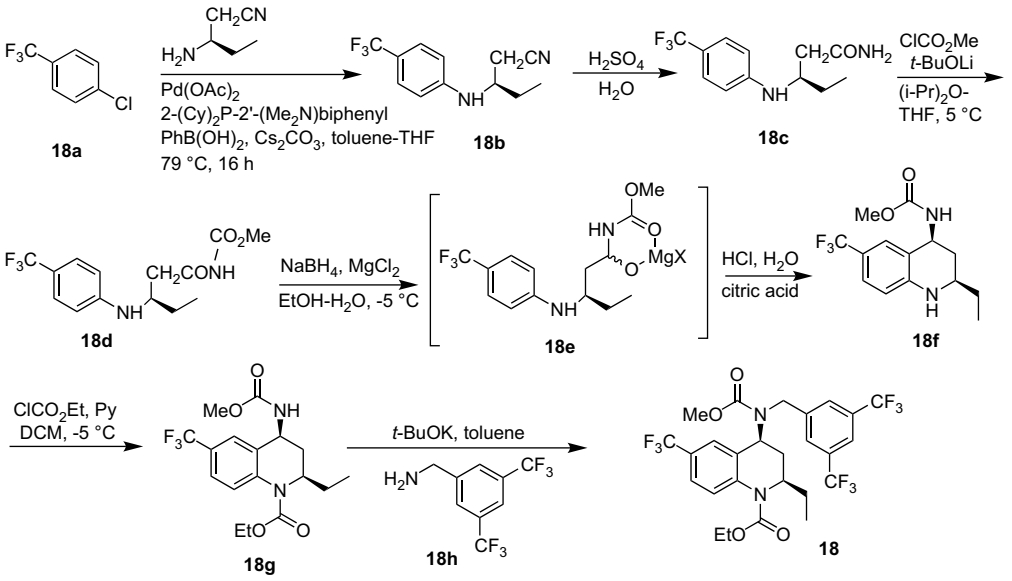
2,4,6-Trisubstituted 1,3,5-triazine derivatives were initially identified as a new class of CETP inhibitors as a result of random screening. Subsequent structure–activity relationship (SAR) studies[46] led to the identification of **17a** [R=Bn (IC_{50}=9 μM)] and **17b** [R=[(2-naphthalenyl)methyl] (IC_{50}=5 μM)] that were found to be the most potent. The synthesis[47,48] of **17a** and **17b**, shown in Scheme 16, involved the use of a key intermediate **17c**. The triazinyl chloride **17c** was prepared from cyanuric chloride **17d** by stepwise



Scheme 15. Synthesis of JTT-705 (**16**).



Scheme 16. Synthesis of 1,3,5-triazines (**17a** and **17b**).



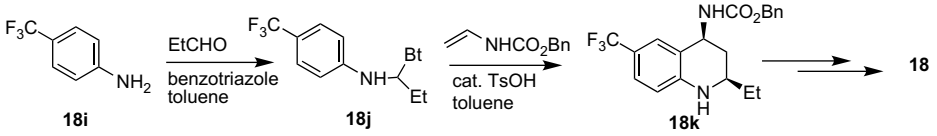
Scheme 17. Synthesis of torcetrapib (**18**).

displacements with the appropriate amines. Palladium-mediated cross-coupling reactions of the appropriate organozinc or organotin reagents to compound **17c** was utilised to introduce carbon nucleophiles, thereby leading to the preparation of **17a** and **17b**.

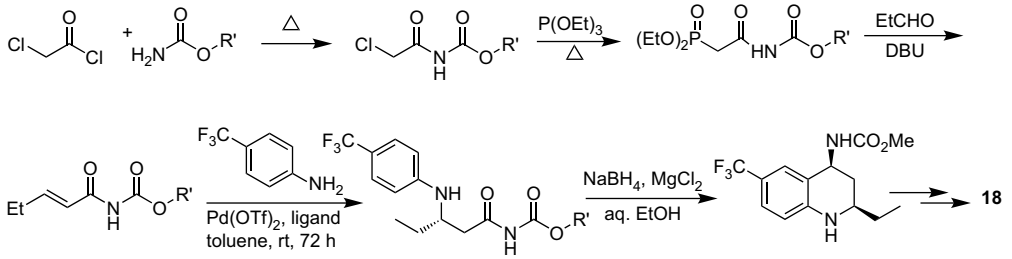
5.3. Synthesis of tetrahydroquinolines

Initially, a series of tetrahydroquinolines was reported as CETP inhibitors with a projected effective dose of 0.1–5 mg/kg/day.[49–51] At a later stage, a representative compound of this class, i.e., a 4-carboxyamino-2-methyl-1,2,3,4-tetrahydroquinoline derivative, torcetrapib (**18**) was developed (in combination with atorvastatin) for the treatment for hypercholesterolemia and atherosclerosis. As an inhibitor of CETP, it could increase the level of HDL-C and lower the LDL-C.[52] Indeed, a phase 3 clinical study in patients treated with torcetrapib showed a 56% increase in HDL and a 27% decrease in LDL. Torcetrapib was the most expensive project in the history of drug development. Hailed at one stage as the most important new development in cardiovascular medicine in years, it was to be the first CETP inhibitor to be developed commercially. Despite a great deal of optimism and anticipation, however, the phase 3 clinical trial was halted in December 2006, due to an increased risk of patient mortality.

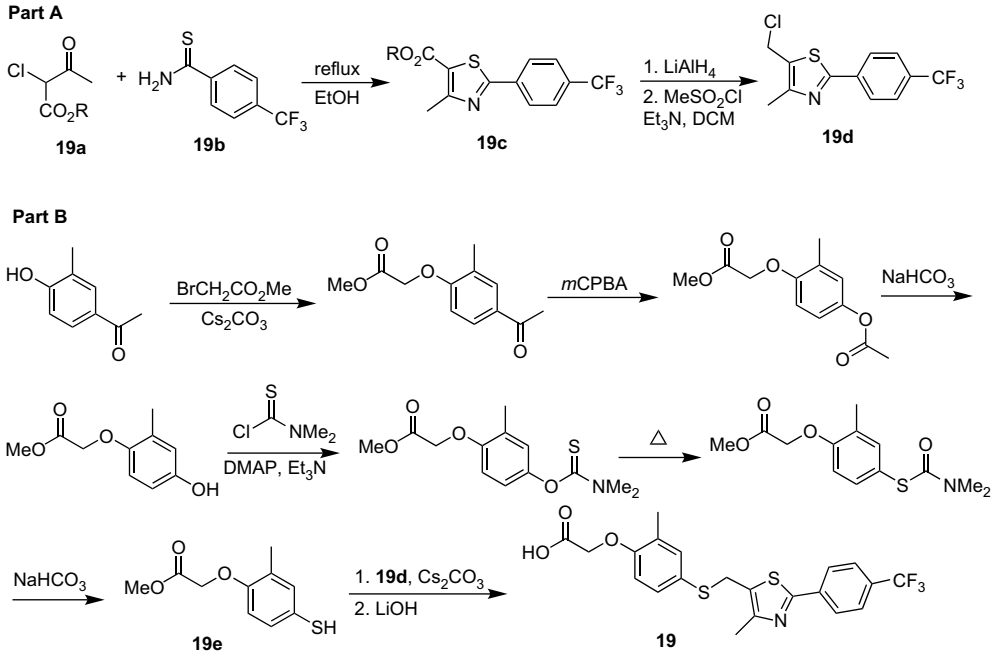
The synthesis of torcetrapib **18** was first disclosed by its inventors in the patent literature[53] and, subsequently, in two journal articles.[54,55] The six-step synthesis (Scheme 17)[55] involves a Pd-catalysed Buchwald N-arylation of the halide **18a** with the enantiopure amine, (*R*)-3-aminopentanenitrile, as the key step. The **18b** obtained was then converted to **18d** via **18c**. Reduction–cyclisation of the imide **18d**, in the presence of a stoichiometric amount of Mg(II), gave an intermediate chelate **18e**, which, on acid-catalysed cyclisation, afforded the tetrahydroisoquinoline **18f** as a single isomer. Compound **18f** was then treated with ethyl chloroformate to give the carbamate **18g** that, on alkylation with **18h**, provided torcetrapib **18**. Alternatively, torcetrapib can be synthesised from 4-trifluoromethylaniline (**18i**), following a seven-step synthesis (Scheme 18), the key reaction being the addition of an *N*-vinylcarbamate to an iminium ion generated from **18j**, followed by an iminium ion cyclisation on to the aryl ring to afford the tetrahydroquinoline ring (**18k**), maintaining the cis relationship of its two substituents.[54] Very recently, another approach towards the synthesis of torcetrapib in seven steps from achiral precursors (without the need for protecting groups), utilising an enantioselective aza-Michael reaction, has been reported (Scheme 19).[56]



Scheme 18. Alternative synthesis of torcetrapib (**18**).



Scheme 19. Recent synthesis of torcetrapib (**18**).



Scheme 20. Synthesis of GW501516 (**19**).

While the discovery of torcetrapib was expected to open up a new category in the field of cardioprevention, the failure of its clinical trial has now raised several questions on the role of LDL-C and HDL-C on atherosclerosis and the future of CETP inhibitors as therapeutic drugs. Moreover, it is still not clear whether the increased risk of mortality observed in patients treated with torcetrapib during the clinical trials was due to an increase in blood pressure or to the some other unknown 'off-target' effect.[57]

6. PPARδ ligands

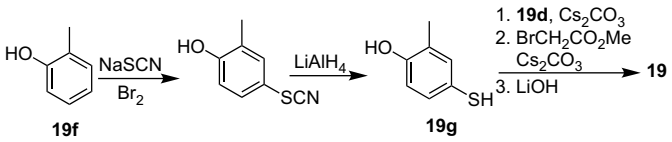
Like the other two PPAR receptors, the PPARδ subtype is also involved in lipid metabolism. Unlike the other two subtypes, however, it is ubiquitously expressed, but the highest expression levels are found in tissues with high lipid metabolism including adipose, skeletal muscle, developing brain, intestine and heart.[58] The PPARδ subtype has both distinct and overlapping functions, particularly with PPARα, as there are many common target genes.[59] The experimental evidence suggests that PPARδ ligands can result in an increase in HDL cholesterol, due to gene induction by PPARδ activation of the ABCA1 transporter, a key gene involved in reverse cholesterol transport (RCT) and HDL-C metabolism. The role of PPARδ in modulating HDL-C levels and RCT was further implicated by an increase in cholesterol efflux in lipid-loaded macrophages and a repression of inflammatory gene expression in macrophages as well as atherosclerotic lesions. A better understanding of its role was, however, obtained during the development of GW501516, a potent and selective PPARδ agonist,[60] presently in a phase 2 clinical trial.

6.1. Synthesis of *para*-alkylthiophenoxyacetic acids

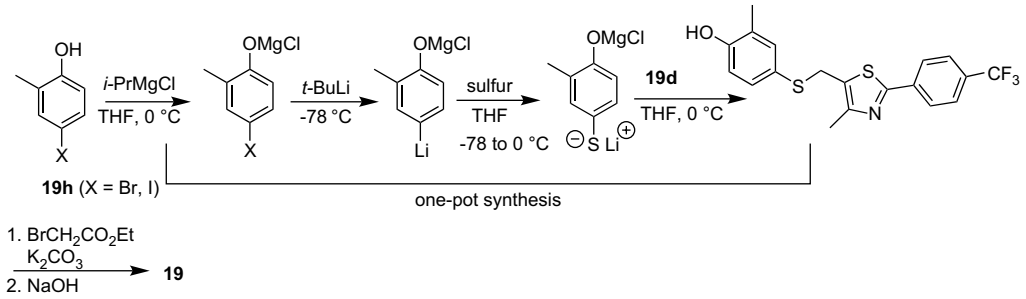
GW501516 (**19**), a *p*-alkylthiophenoxyacetic acid derivative, was discovered with the help of combinatorial chemistry and structure-based drug design.[61] Being the most potent and selective PPARδ agonist (EC_{50} value of 1.1 nM against PPARδ and 1000-fold selectivity over other human subtypes), GW501516 increased circulating HDL-C significantly and reduced TG in early clinical studies with normal male volunteers.[62] The reported initial synthesis of **19** involved the coupling of thiazole chloride (**19d**) with arylthiol (**19e**), prepared from *o*-cresol in more than eight steps with a low overall yield (Part B, Scheme 20).[60] The thiazole ring of **19d** was constructed via a Hantzsch-type condensation of 2-chloroacetoacetate **19a** and thiobenzamide **19b** to give **19c** (Part A, Scheme 20). Later, a more efficient method for the synthesis of **19** was reported that showed an improvement in both the number of synthetic steps and the overall yield (Scheme 21).[63] This process involved a one-pot regiocontrolled dialkylation of mercaptophenol **19g**, generated from *o*-cresol (**19f**) as a key step. This process could, however, suffer from a few limitations, namely dimerisation of **19g** under oxidative conditions, and therefore a new synthesis of **19** involving in situ protection of the phenol group of **19h** with a Grignard reagent and a regiocontrolled one-pot reaction for the formation of a sulfide bond as the key step has been reported (Scheme 22).[64] This synthetic route provided compound **19** with a good overall yield. Very recently, a sequential, position-selective, Pd-catalysed cross-coupling reaction of 2,4-dibromo-5-hydroxymethylthiazole has been reported that provided the required intermediate **19i** (Scheme 23) for the synthesis of **19**.[65] Thus, the trisubstituted thiazole scaffold **19i** was prepared from 2,4-dibromo-5-hydroxymethylthiazole (**19j**) and organometallic reagents.

6.2. Other PPARδ agonists

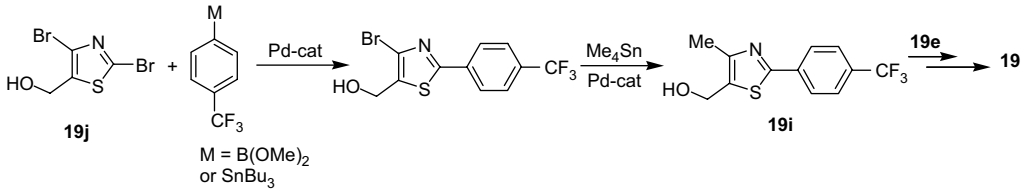
KD3010 (**20**), a potent and selective PPARδ agonist (EC_{50}=1.0 nM, 1000-fold selectivity over PPARα and PPARγ) that belongs to a sulfonyl-substituted bicyclic class of compounds,[66] showed a 21% increase in HDL-C in an obese rhesus model and is presently undergoing phase 1 clinical trials.[67] The reaction of 4-chlorosulfonylindan-2-carboxylic acid with the appropriately



Scheme 21. Shorter synthesis of GW501516 (**19**).



Scheme 22. Alternative synthesis of GW501516 (**19**).

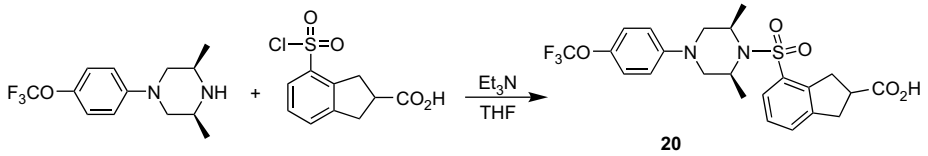


Scheme 23. Pd-mediated synthesis of GW501516 (**19**).

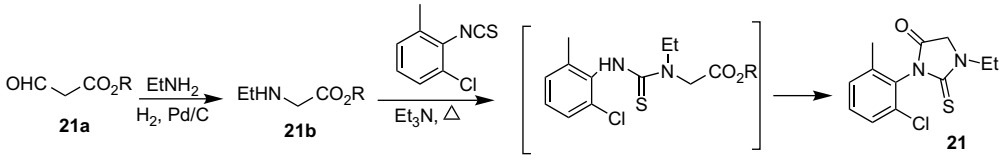
substituted piperizine derivative in the presence of triethylamine is the key step for the synthesis of compound **20** (Scheme 24). Another PPARδ agonist, MBX-8025 (RWJ-800025), is being developed for the potential treatment of type II diabetes and dyslipidemia and is presently in phase 2 clinical trials.[68]

7. Other HDL-cholesterol elevators

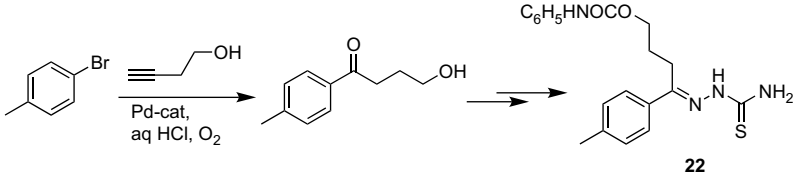
A number of other HDL elevators have been reported, irrespective of the fact that the molecular mechanisms of these agents are either unknown or yet to be established. For example, compound **21** (WAY-135433) that belongs to the *N*-alkyl *N*′-substituted thiohydantoin series caused a dose-dependent elevation in HDL-C, e.g., 26% at 30 mg/kg/day and 54% at 100 mg/kg/day ($p<0.01$) in male hypercholesterolemic hamsters at doses of 3–100 mg/kg/day on oral administration.[69] This compound can be prepared via the reaction of an *N*-substituted amino acid (**21b**), obtained by the reaction of glyoxylic acid (**21a**) with the appropriate amine, with isothiocyanate in the presence of a base such as triethylamine under refluxing conditions (Scheme 25). A thiosemicarbazide derivative **22**, known to be useful for the treatment of atherosclerosis via raising the level of HDL cholesterol, was prepared via the Sonogashira-hydration strategy as a key synthetic step (Scheme 26).[70] A number of other heterocyclic compounds are also under investigation as potential elevators of HDL cholesterol.[71–73]



Scheme 24. Synthesis of KD3010 (**20**).



Scheme 25. Synthesis of thiohydantoin (**21**).



Scheme 26. Synthesis of thiosemicarbazide (**22**).

8. Conclusions

While the increased risk of mortality observed during the clinical trials of torcetrapib has raised several questions on the benefits of raising HDL-C via CEPT inhibition, the importance of the acute raising of HDL levels has recently been demonstrated by the direct infusion of Apo A-I Milano, resulting in significant atheroma regression by IVUS (intravascular ultrasound) evaluation in experimental animals, as well as in coronary patients. A rapid and significant reduction in plaque burden was observed in both cases, confirming the inverse relationship between plasma concentration of HDL-C and incidence of cardiovascular diseases. Moreover, in addition to its ability to act as a cholesterol scavenger, HDL has anti-inflammatory, antithrombogenic and vasoactive effects that are beneficial for the prevention of CHD. Since no evidence suggests that all HDL-based therapies will be ineffective for the prevention of cardiovascular morbidity and mortality, the development of alternative agents and strategies for the potential treatment of atherosclerosis is highly desirable. Currently, the only medication available (other than statins) designed specifically to raise HDL cholesterol levels is niacin, a type of vitamin B. The side effects of niacin therapy, however, include flushing and other skin disturbances. Thus, a sustained-release formulation of niacin was produced that reduced flushing, but was associated with a high incidence of adverse hepatic effects. With the extended-release formulation, there is a reduction in flushing and hepatotoxic events. As evident from the present review, extensive efforts to identify alternatives based on small molecules that are designed to increase HDL-C without troublesome side effects are currently underway. Although several interesting agents and approaches, as listed throughout the text, are being tested, most of the compounds are, however, in the early developmental stage and, except that the improved versions of niacin, there are no late-stage compounds, which could be taken forward in place of CETP inhibitors. Considering all the hard end point trials that will be required to develop a drug which raises HDL-C, it may take another 5–10 years to bring a molecule finally into the clinic.

Acknowledgements

The author thanks Matrix Laboratories Limited for support and encouragement.

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Biographical sketch

Manojit Pal leads the New Drug Discovery Department of Matrix Laboratories Limited in Hyderabad (India). Born in Kolkata (India), Dr. Pal began his university training at the University of Calcutta, followed by I. I. T., Kharagpur (India), where he obtained his M.Sc. degree in Chemistry in 1989. He subsequently moved to the Indian Association for the Cultivation of Science, Kolkata (India), where he worked under the guidance of Professor Nitya G. Kundu with the aid of a research fellowship (1989–1994) awarded by the Council of Scientific and Industrial Research, New Delhi, India. He was awarded his Ph.D. degree by Jadavpur University, Kolkata (India) in 1995. He then moved to Vadodara, Gujarat, where he worked as a Research Officer (1995–1997) in the Department of Microbial Research and Development, Alembic Chemical Works Co. Ltd and as an Executive Organic Synthesis (1997–1998) in the Sun Pharma Advanced Research Center. In 1998, he joined Dr. Reddy's Research Foundation (presently Discovery Research) in Hyderabad as a Senior Scientist and became Senior Director Discovery Chemistry in 2006. In 2007, he joined Matrix Laboratories Ltd, Hyderabad. Dr Pal is a recipient of the CSIR Certificate of Merit 1989 and Bioorganic & Medicinal Chemistry Letters Most Cited Paper 2003–2006 Award and has been listed in the Marquis Who's Who in Medicine and Healthcare, 5th edition (2004–2005) as one of the leading healthcare professionals. His research interests include the development of efficient and practical syntheses of new chemical entities under the new drug discovery program in different therapeutic areas. Dr. Pal has authored/co-authored more than 50 research publications, few review articles and a number of patents.