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# Novel tetrahydrochinoline derived CETP inhibitors

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ABSTRACT

In the course of our efforts to identify orally active cholesteryl ester transfer protein (CETP) inhibitors, we have continued to explore tetrahydrochinoline derivatives. Based on BAY 19-4789 structural modifications led to the discovery of novel cycloalkyl substituted compounds. Thus, example **11b** is a highly potent CETP inhibitor both in vitro and in vivo in transgenic mice with favourable pharmacokinetic properties for clinical development.



Cardiovascular disease is the most common cause for mortality and morbidity in the developed world and it is estimated that mortality from cardiovascular diseases will have increased worldwide by 90% by the year 2020 when compared with the situation in 1990.[1] Despite the fact that a large portion of cardiovascular events cannot be prevented by lowering of low-density lipoprotein cholesterol (LDL-C), guidelines for the prevention of cardiovascular disease still focus on the management of LDL-C.[2,3]

Several epidemiological studies clearly show that a low level of high density lipoprotein cholesterol (HDL-C) is a strong and independent risk factor for the development of CHD and HDL has been proposed to have potential atheroprotective effects.[4]

Inhibition of cholesteryl ester transfer protein (CETP) might be a powerful tool for increasing HDL-C, decreasing LDL-C and very low-density lipoprotein (VLDL-C) thus reducing the development of atherosclerosis.[5]

The recent failure of torcetrapib (**1**) in phase III studies challenged the future perspectives of CETP inhibitors as potential therapeutic agents.[6] Since compound-specific and off-target effects of torcetrapib, such as raising blood pressure and aldosterone were most likely causative for an increase in cardiovascular events and mortality, it has been suggested to continue studying other CETP inhibitors for their potential to reduce cardiovascular risk.[7] Currently the most advanced compounds dalcetrapib, JTT-705, (**3**) and anacetrapib (**2**), which have not been reported to have the off-target effects of torcetrapib, are in phase III clinical trials[8,9] (see Fig. 1).

We have searched for orally active CETP inhibitors suitable for clinical development.[10] Our first compound investigated in humans, BAY 19-4789 (**4**) was discontinued in early clinical development due to unexpected toxicological findings in a 13 week repeat dose toxicology study in dogs.

For a second candidate, BAY 38-1315 (**5**), preclinical development was stopped because of unfavourable pharmacokinetic properties (see Fig. 2).

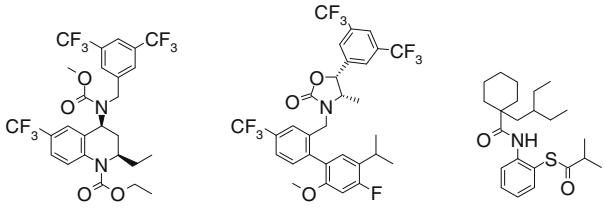


**Figure 1.** Past and present CETP inhibitors in clinical development.

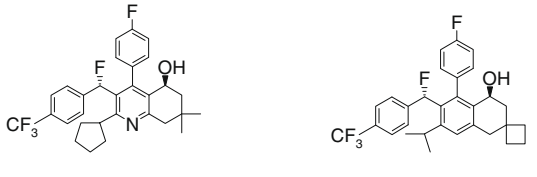


**Figure 2.** Tetrahydrochinoline and tetrahydronaphtaline derived CETP inhibitors.

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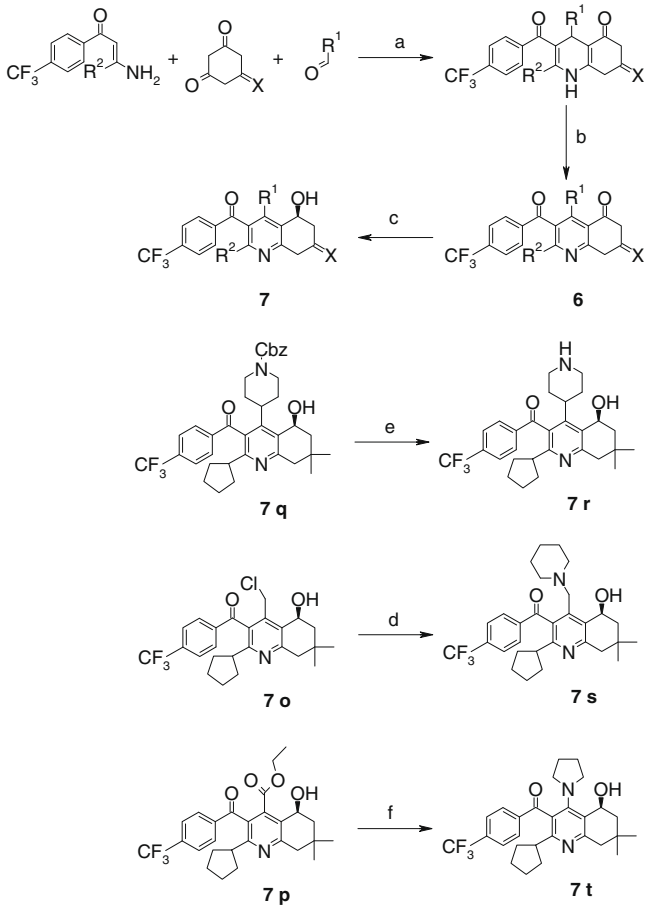
In seeking a backup compound we were interested in replacing the 4-fluorophenyl substituent present both in **4** and **5** without further increasing lipophilicity. Therefore we continued our SAR exploration in the tetrahydrochinoline series only. For the introduction of new 'head' groups we were following a synthetic route using an unsymmetrical Hantzsch-dihydropyrididine synthesis as the key step, followed by an oxidation with DDQ to the pyridines **6** (Scheme 1). Diketone **6** undergoes a completely regioselective CBS-type reduction[11] using (1*R*, 2*S*)-1-aminoindan-2-ol as chiral inductor with high enantioselectivity (>95% ee) to provide the alcohols **7**. Yields for the dihydropyridine formation employing aliphatic aldehydes are generally lower compared to aromatic aldehydes.[10a] However, taking into account the high complexity of the diketones **6** which are being assembled in two steps, a low yielding sequence is acceptable in order for a rapid SAR assessment.

Several SAR trends are apparent comparing the analogues shown in Table 1. CETP inhibition was determined using a CETP fluorescence assay.[12a]

For substituents at $R^1$ a rather steep SAR can be observed with respect to steric bulk and polarity. Branched alkyl substituents are obviously more potent than alkyl chains.




**Scheme 1.** Synthesis of alcohols **7**. Reagents and conditions: (a) 1.2 equiv enamine, 2 equiv TFA, 1 equiv diketone, rt, 10 min, then 1.5 equiv $R^1$ CHO, rt, 18 h, 5–55%; (b) 1.1 equiv DDQ, $CH_2Cl_2$, rt, 1 h, 20–95%; (c) 0.15 equiv (1*R*,2*S*)-1-aminoindan-2-ol, 4 equiv *N*,*N*-diethylaniline–borane (1:1), THF, rt, 15 min, then **6**, 0 °C to rt, 18 h, 58–95%; (d) 4 equiv piperidine, 2 equiv *N*-ethyldiisopropylamin, DMF, 110 °C, 18 h, 80%; (e) Pd/C, $H_2$ 1 bar, THF/MeOH 1:1, 16 h, 68% and (f) (i) 10 equiv 10% NaOH, EtOH, 18 h, 95%; (ii) 2 equiv DPPA, 2 equiv $NEt_3$, 2 equiv $H_2O$, toluene, 90 °C, 18 h, 74% and (iii) 2.5 equiv NaH, THF, 30 min then 1.1 equiv 1,4-dibrombutane, THF, 18 h, 22%.

**Table 1**
$IC_{50}$ data from CETP fluorescence assay for compounds **1**, **4**, **5** and **7a–r**

| Compds | $R^1$ = | $R^2$ = | X = | $IC_{50}$ (nM) | clog *P*[13] |
|---|---|---|---|---|---|
| **1** | | | | 18 | 7.55 |
| **4** | | | | 31 | 7.95 |
| **5** | | | | 24 | 8.63 |
| **7a** | Et | *c*Pent | Dimethyl | 4500 | 7.07 |
| **7b** | *n*Pr | *c*Pent | Spirocyclobutyl | 600 | 7.43 |
| **7c** | *n*Pent | *c*Pent | Dimethyl | 2000 | 8.66 |
| **7d** | *i*Pr | *c*Pent | Dimethyl | 600 | 7.30 |
| **7e** | *i*Pr | *c*Pent | Spirocyclobutyl | 300 | 7.47 |
| **7f** | *c*Pr | *c*Pent | Dimethyl | 3000 | 6.98 |
| **7g** | *c*Pent | *c*Pent | Dimethyl | 90 | 8.10 |
| **7h** | *c*Pent | *c*Pent | Spirocyclobutyl | 70 | 7.94 |
| **7i** | *c*Hex | *i*Pr | Dimethyl | 70 | 8.03 |
| **7j** | *c*Hex | *i*Pr | Spirocyclobutyl | 33 | 7.86 |
| **7k** | *c*Hex | *c*Pent | Dimethyl | 60 | 8.66 |
| **7l** | *c*Hex | *c*Pent | Spirocyclobutyl | 55 | 8.50 |
| **7m** |  | *c*Pent | Dimethyl | 2000 | 8.00 |
| **7n** |  | *c*Pent | Dimethyl | 3000 | 6.78 |
| **7o** |  | *c*Pent | Dimethyl | 15,000 | 6.60 |
| **7p** |  | *c*Pent | Dimethyl | >20,000 | 6.08 |
| **7q** |  | *c*Pent | Dimethyl | 500 | 9.36 |
| **7r** |  | *c*Pent | Dimethyl | >20,000 | 6.24 |
| **7s** |  | *c*Pent | Dimethyl | 15,000 | 7.07 |
| **7t** |  | *c*Pent | Dimethyl | 4000 | 6.24 |

Thus, the cyclopentyl and cyclohexyl substituents in compounds (**7g–l**) represent the optimal combination of lipophilicity and steric requirements. Attempts to increase polarity by introducing an amino functionality resulted in a loss of activity. The pyrollidine derivative (**7t**) and the Cbz-protected piperidine (**7q**) still show some activity while the more basic amines (**7r**, **7s**) are inactive.

In accordance to previously observed SAR,[10a] the spirocyclobutyl substituent on the saturated ring of the tetrahydrochinoline adds additional potency compared to the dimethyl substitution pattern. A further increase in CETP inhibition should be achievable by replacing the $sp^2$ keto functionality present in **7i–l** by connecting the pyridine moiety and the 4-$CF_3$-phenyl group via a $sp_3$ carbon (see Fig. 3).

The hydroxy-ketones **7i–l** were reduced with moderate diastereoselectivities (60–70% de) using DIBAL in toluene at low temperatures to give the desired *trans*-dihydroxy derivatives **8a–b** (Scheme 2).

Regioselective protection of the sterically less hindered hydroxyl group was achieved with *t*-butyldimethylsilyl-chloride in refluxing acetonitrile to give **10a–b**. Alternatively, the hydroxy-ketones were first protected using *t*-butyldimethylsilyltriflate in tol-

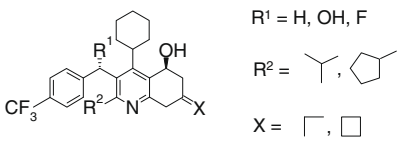



**Figure 3.** Matrix of 4-cyclohexyl-tetrahydrochinoline CETP inhibitors.