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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).

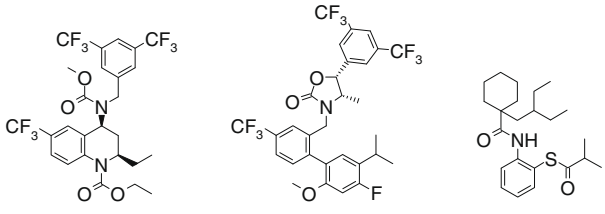

Figure 1. Past and present CETP inhibitors in clinical development.

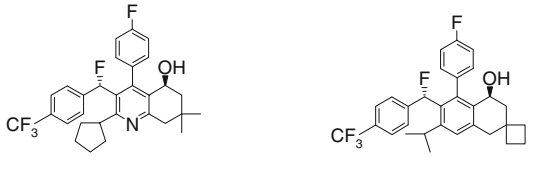

Figure 2. Tetrahydrochinoline and tetrahydronaphtaline derived CETP inhibitors.

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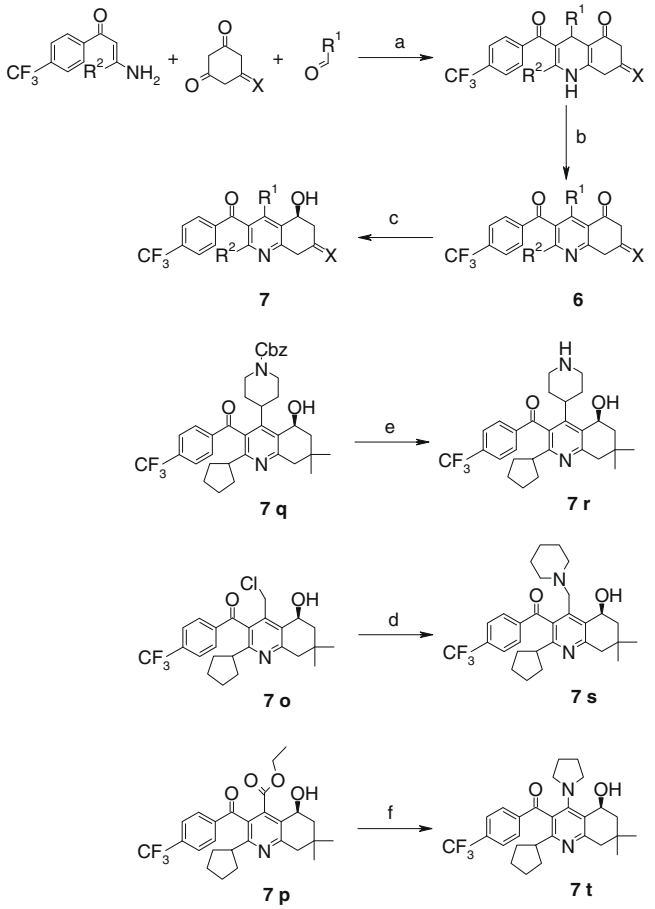
In seeking a backup compound we were interested in replacing the 4-fluorophenyl substituent present both in **4** and **5** without further increasing lipophilicity. Therefore we continued our SAR exploration in the tetrahydrochinoline series only. For the introduction of new 'head' groups we were following 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-

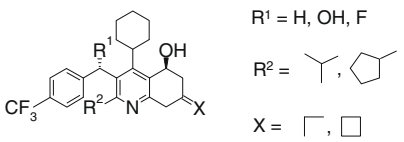
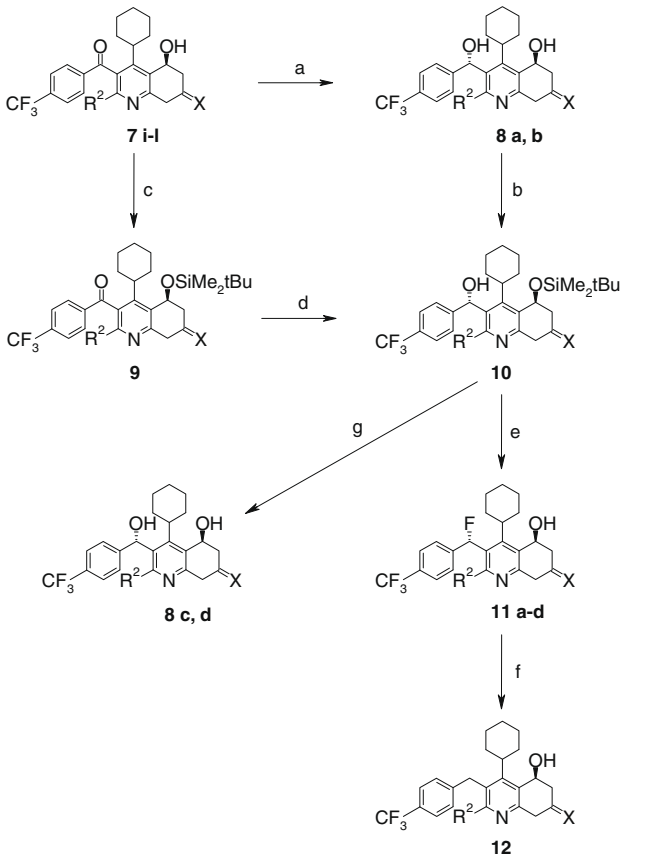


Figure 3. Matrix of 4-cyclohexyl-tetrahydrochinoline CETP inhibitors.



Scheme 2. Synthesis of alcohols **8**–**12**. Reagents and conditions: (a) 5 equiv DIBAL, toluene, −78 °C to rt, 18 h, 70–80%; (b) 7 equiv TBDMSCl, 2.5 equiv DMAP, 6 equiv NEt_3, acetonitrile, rt, 18 h, 79%; (c) 2 equiv TBDMSOTf, 4 equiv 2,6-dimethylpyridine, toluene, −15 to 0 °C, 2 h, 78–99%; (d) 5 equiv DIBAL, toluene, −50 °C to rt, 3 h, 30–40%; (e) (i) 1.5 equiv DAST, CH_2Cl_2, , −78 °C to rt, 2 h, 82–95%; (ii) 2.5 equiv TBAF, THF, 0 °C to rt, 18 h, 65–91%; (f) 7 equiv DIBAL, toluene, −20 to 0 °C, 4 h, 80% and (g) 2.5 equiv TBAF, THF, 0 °C to rt, 18 h, 78–95%.

uene at low temperatures followed by a non selective reduction with DIBAL in toluene to afford **10c–d**. Enantioselective fluorination with diethylaminosulfur trifluoride (DAST) in dichloromethane at low temperatures occurred with complete retention of the configuration. In contrast to the usual S_N2 pathway of DAST-fluorinations the reaction proceeds with retention of configuration at this sterically highly encumbered site. Similar fluorinations following a S_Ni-mechanism have been reported in the literature.[14] Removal of the protecting group proceeded cleanly with TBAF in THF yielding **8c–d** and **11a–d**. Reductive defluorination of **11b** with a high excess of DIBAL in toluene afforded **12** (Scheme 2).

The increase in polarity of the trans-dihydroxy compounds **8** led to a slight loss in activity compared to **7**. On the other hand introduction of the fluorine atom in **11a–d** increased both lipophilicity and CETP inhibitory activity. Activity as well as lipophilicity of the defluorinated compound **12** is in the range of **11a–d** (Table 2).

Table 2
IC_{50} data from CETP fluorescence assay for compounds **8a–d, 11a–d** and **12**

Compds	R^2 =	X =	IC_{50} (nM)	clog *P*[13]
8a	*i*Pr	Dimethyl	80	6.76
8b	*c*Pent	Dimethyl	100	7.39
8c	*i*Pr	Spirocyclobutyl	70	6.59
8d	*c*Pent	Spirocyclobutyl	100	7.23
11a	*i*Pr	Dimethyl	30	8.14
11b	*c*Pent	Dimethyl	25	8.77
11c	*i*Pr	Spirocyclobutyl	17	7.97
11d	*c*Pent	Spirocyclobutyl	22	8.61
12	*c*Pent	Dimethyl	39	9.15

Table 3
IC_{50} data from CETP fluorescence assay in human plasma and from CETP SPA assay for compounds **11a–d** and **12**

Compds	Human plasma assay[12b] IC_{50} (nM)	SPA assay[12c] IC_{50} (nM)
1	20	3
11a	75	23
11b	50	7
11c	70	33
11d	60	62
12	300	n.a.

Additional in vitro tests were performed with compounds **11a–d** and **12** showing the best overall in vitro profile for compound **11b** (Table 3).

The pharmacokinetic profile of **11b** was assessed in mice, rats and dogs revealing good plasma half-lives ($t_{1/2}$ = 5.0, 7.2 and 8.6 h, respectively) and oral bioavailability (F = 44% in rats and 74% in dogs).

In conclusion, we successfully modified the structure of our previous development compounds **4** and **5** by replacing the pF-phenyl moiety with a cyclohexyl group in the 4-position. With its good overall in vitro profile and the favourable pharmacokinetic profile, **11b** improved the lipoprotein profile in human CETP-transgenic mice by increasing HDL-cholesterol and lowering serum triglycerides dose dependently.[15] Consequently, **11b** was selected for advancement as a clinical candidate.

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12. a To assess CETP activity an microemulsion based assay according to Bisgaier et al., (*J. Lipid Res.* **1993**, *34*, 1625–1634) was used with the following modification: (1) Donor liposomes were prepared applying 1 mg Cholesteryl 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-dodecanoate (cholesteryl BODIPY® FL C_{12}, from Molecular Probes), 5.35 mg triolein (Sigma–Aldrich) and 6.67 mg POPC (Sigma–Aldrich), respectively, dissolved in a total volume of 600 μL dioxane and were slowly injected into 63 mL buffer (50 mM Tris/HCl pH 7.3, 150 mM NaCl, 2 mM EDTA) in a water bath sonicator. This suspension is then sonicated with 50 W (Branson Sonifier 450 with a cup-horn resonator) for 30 min under a nitrogen atmosphere at room temperature. (2) Acceptor liposomes were prepared in the same manner as donor liposomes using 86 mg cholesteryl-oleate, 20 mg triolein und 100 mg POPC dissolved in 1.2 mL dioxane and injected into 114 mL buffer. (3) In a total test volume of 100 μL test compounds dissolved in DMSO (2 μL) were incubated at 37 °C for 4 h with 50 μL of a CETP containing sample (1–3 μg CETP, enriched from human plasma) and 48 μL of a liposome emulsion (1 volume donor, 1 volume buffer and 2 volumes acceptor, respectively). The increase of the fluorescence intensity (excitation 485 nm, emission 535 nm) is proportional to the cholesterol ester transfer. The inhibition of the transfer is followed in comparison with a DMSO control.; b To assess CETP activity in the presence of human plasma 6 μL (12% v/v) of donor liposomes and 1 μL (2% v/v) of a solution of the substance to be tested in DMSO are added to 42 μL (86% v/v) of human plasma (Sigma P 9523). The mixture is incubated at 37 °C for 24 h. The change in the fluorescence at 510/520 nm is a measure of the cholesterol ester transfer. The inhibition of the transfer is followed in comparison with a DMSO control.; c To assess CETP activity a scintillation proximity assay the transfer of ^{3}H-cholesterol ester from human HD lipoproteins to biotinylated LD lipoproteins is measured. In the test batch, 10 μL of HDL-^{3}H-cholesterol ester (~50,000 cpm) are incubated at 37 °C for 18 h with 10 μL of biotin-LDL (Amersham) in 50 nM Hepes/0.15 M NaCl/0.1% bovine serum albumin/0.05% NaN_3 pH 7.4 containing 10 μL of CETP (1 mg/ml) and 3 μL of a solution of the substance to be tested (dissolved in 10% DMSO/1% BSA). 200 μL of the SPA-streptavidin bead solution (TRKQ 7005) are then added, incubated further with shaking for 1 h and then measured in a scintillation counter. Corresponding incubations with 10 μL of buffer, 10 μL of CETP serve as controls.
13. For *c*log *P*-calculations the fragment summation method CLOGP (version 4.3 with version 23 of its associated fragment database, as implemented in Sybyl version 8.0, Tripos Inc.) has been used.
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15. Data published in part in WO2006/063828.