Microsomal triglyceride transfer protein inhibitors

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Introduction

The microsomal triglyceride transfer protein (MTP) is a heterodimeric lipid transfer protein involved in the assembly and secretion of lipoproteins containing apoB (mostly apoB-100) as the apoprotein [309356]. In particular, MTP adds a lipid load of cholesteryl esters, triglyceride and phospholipid to the nascent apoB-containing very low density lipoprotein (VLDL) [358088]. Accordingly, MTP inhibition in HepG2 liver cells leads to a dose-dependent decrease in apoB secretion. From the available data, it appears that MTP plays a rate-limiting role in VLDL secretion and this holds true both in liver and in intestinal cells. Thus, it is conceivable that, as the secretion and probably the assembly of VLDL depends on the activity of MTP, pharmacological inhibition of the latter would provide a powerful tool in the control of hyperlipidemia. To date, five companies have investigated MTP inhibitors (Table 1): Bristol-Myers Squibb (BMS-201038, BMS-192951, BMS-212122, BMS-197636, BMS-200150), Bayer (Bay-13-9952), Janssen (R-103757), Glaxo Wellcome (GR-328713), and Japan Tobacco (JTT-722).

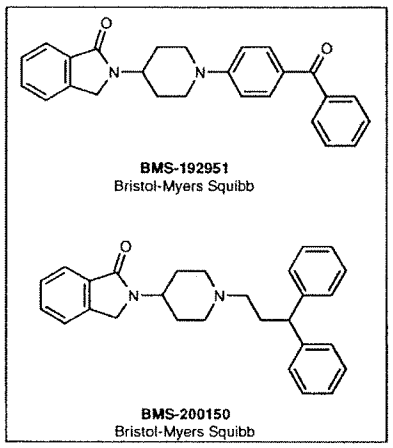
Synthesis and SAR

The compounds developed by Bristol-Myers Squibb are N-piperidinyl isoindolones derivatives, which are synthesized by standard methods as described in the patents [366480,366484].

Pharmacology

BMS-200150, BMS-192951 (both Figure 1) and BMS-197636 - the latter are derivatives of the former - potently inhibit the MTP-mediated transfer of triglycerides *in vitro* and apoB secretion from HepG2 cells [223995]. IC_{50} values are in the low nanomolar and low micromolar ranges, respectively. These compounds act by competitively binding the 97 kDa subunit of the MTP complex. BMS-192951 is a photoactivable molecule that has been utilized in HepG2 cells to prove that MTP is the rate-limiting enzyme in apoB-containing lipoprotein secretion [309356].

Figure 1.



Both BMS-197636 and BMS-192951 have been tested in hamsters [223995], where lowering of cholesterol levels was demonstrated (ED_{50} = 31 mg/kg). R-103757 has been tested in normolipidemic dogs, in which it decreased apoB lipoprotein concentrations (as indicated by decreased plasma cholesterol, phospholipid and triglyceride) with low EC_{50} values of the order of few mg/kg.

BAY-13-9952 potently decreased cholesterol levels in cholesterol-fed rabbits (from 1817 mg/dl to 13.9 and 7.5 mg/dl in rabbits administered 4 and 12 mg/kg, respectively) [348472]. It is noteworthy that these effects were associated with a complete inhibition of aortic fatty streak formation. This compound also dose-dependently blocked the formation of atherosclerotic plaques in apoE knockout mice [348474].

Metabolism

No data on the metabolism of MTP inhibitors are currently available.

Table 1. MTP inhibitors.

Compound	Developing company	Current status
BAY-13-9952	Bayer	Phase II
BMS-192951	Bristol-Myers Squibb	No development reported
BMS-197636	Bristol-Myers Squibb	No development reported
BMS-200150	Bristol-Myers Squibb	No development reported
BMS-201038	Bristol-Myers Squibb	Phase I
BMS-212122	Bristol-Myers Squibb	No development reported
GR-328713	Glaxo Wellcome	Discontinued
JTT-722	Japan Tobacco	Discovery
R-103757	Janssen	Discovery

Toxicity

No data on the toxicity of MTP inhibitors are currently available.

Clinical Development

Phase I

Phase I trials are underway for BMS-201038 [244813,290251,322305,206604], but results have not yet been reported. GR-328713 reached phase I clinical trials, but was subsequently discontinued [366126]; no data have been reported from these trials.

Phase II

The only MTP inhibitor for which a study in human patients has been reported to date is BAY-13-9952. This compound was administered to 61 dyslipidemic patients at doses ranging from 20 to 160 mg/day and caused a dose-dependent decrease in total cholesterol levels ranging from 12 to 54%. A similar decrease was observed for LDL cholesterol [348473].

Side Effects and Contraindications

As with clinical trials, the only MTP inhibitor for which side effects have been reported to date is BAY-13-9952, which was generally well-tolerated but caused nausea and diarrhea at the highest doses [348473].

Current Opinion

MTP is a highly interesting target for the treatment of hypercholesterolemia and hyperlipidemia. Indeed, the key role played by MTP in apoB-lipoprotein assembly and secretion has only recently been recognized [309356]. The interest in this new class of hypolipidemic drugs is further confirmed by the prediction of considerable sales of MTP inhibitors [231092,319225].

To date, five companies have developed MTP inhibitors. *In vitro* activities of these compounds have been described and appear to be very promising, despite the current lack of clinical candidates. For instance, the BMS compounds inhibit MTP at concentrations in the low nanomolar range [223995]. Studies performed in rats, hamsters, rabbits and dogs have also demonstrated the potent antihypercholesterolemic effect of MTP inhibitors. However, MTP inhibitors also induce lowering of the HDL subfraction, contradicting the current guidelines that underline the importance of a high HDL to LDL ratio.

At the time of this review, data on the absorption, metabolism, and kinetics of MTP inhibitors were not available. The only phase II trial described has not reported serious side effects, except for gastrointestinal discomfort, but more extensive clinical studies are required before any potential toxicity of MTP inhibitors can be ruled out.

In conclusion, it appears that MTP inhibitors are very interesting drugs, albeit at an early stage of development, that might be possibly used alone or in conjunction with other lipid-lowering agents.

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