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SOTRASTAURIN

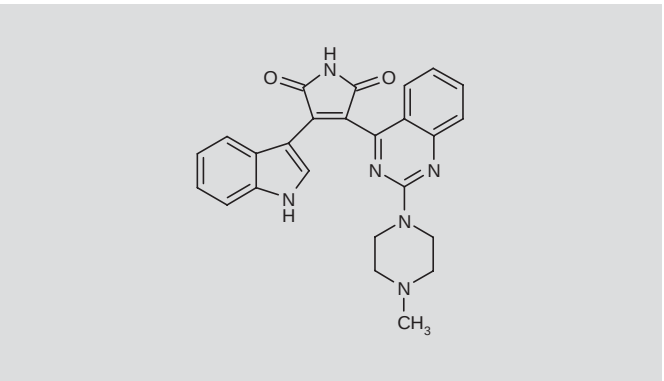
Rec INN; USAN

Protein Kinase C Inhibitor
Treatment of Transplant Rejection
Treatment of Psoriasis
Treatment of Uveitis

AEB-071
NVP-AEB-071

3-(1*H*-Indol-3-yl)-4-[2-(4-methylpiperazin-1-yl)quinazolin-4-yl]-2,5-dihydro-1*H*-pyrrole-2,5-dione

InChI=1S/C25H22N6O2/c1-30-10-12-31(13-11-30)25-27-19-9-5-3-7-16(19)22(28-25)21-20(23(32)29-24(21)33)17-14-26-18-8-4-2-6-15(17)18/h2-9,14,26H,10-13H2,1H3,(H,29,32,33)



$C_{25}H_{22}N_6O_2$
Mol wt: 438.4812
CAS: 425637-18-9
CAS: 908351-31-5 (acetate salt)
EN: 321045

ABSTRACT

Sotrastaurin (AEB-071, NVP-AEB-071) is an orally bioavailable compound that exerts its effects through the selective inhibition of the classic and novel forms of protein kinase C (PKC), thereby inhibiting early T-cell activation and IL-2 production. In preclinical studies, sotrastaurin reduced the rejection of allogeneic solid organ and islet transplants and interacted in a synergistic manner with the immunosuppressive agent ciclosporin. Sotrastaurin is being investigated in a number of clinical trials aimed at exploring its efficacy and safety in T-cell-mediated conditions such as transplant rejection, psoriasis, uveitis and ulcerative colitis. The compound has shown acceptable toxicity profiles in healthy individuals and transplant recipients. Provided sotrastaurin shows continued promise in the ongoing clinical studies, it may be a safe and effective alternative or adjunct to calcineurin inhibitors.

SYNTHESIS**

Chlorination of quinazoline-2,4-dione (I) with $POCl_3$ in the presence of *N,N*-dimethylaniline at reflux affords 2,4-dichloroquinazoline (II). Subsequent condensation of (II) with the sodium salt of ethyl acetoacetate (III) in refluxing toluene/THF followed by deacetylation and amidation in aqueous ammonia leads to 2-(2-chloro-4-quinazolinyl)acetamide (IV). After displacement of the remaining 2-chloride of compound (IV) with *N*-methylpiperazine (V) in NMP at 50 °C, the resulting acetamide (VI) is condensed with methyl 3-indolylglyoxylate (VII) in the presence of *t*-BuOK in THF to give sotrastaurin (1). Scheme 1. The corresponding mesylate and maleate salts are prepared by treatment of sotrastaurin with methanesulfonic acid and maleic acid, respectively, in EtOH at 45 °C (2).

BACKGROUND

Candidate immunosuppressive drugs, although abundant in previous decades, have become increasingly difficult to discover, develop and bring to market. Several recent potential agents did not survive the validation of clinical trials, including fingolimod (FTY-720) (3, 4) and anti-CD154 (5). The prevention of allograft rejection has therefore relied heavily on calcineurin inhibitors (CNIs; tacrolimus, ciclosporin) and mTOR inhibitors (sirolimus, everolimus). These agents, although effective, are associated with a number of toxicities, including nephrotoxicity for CNIs (6) and impaired wound healing and hypercholesterolemia for sirolimus (7). A new agent with an improved side effect profile but at least similar efficacy would therefore have a major impact.

Sotrastaurin (AEB-071, NVP-AEB-071) is a new, orally bioavailable compound that exerts its effects through the selective inhibition of protein kinase C (PKC). PKC isoforms are involved in the activation of T cells downstream of both signal 1 and signal 2 (8). Sotrastaurin

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**Synthesis prepared by R. Pandian, J. Bolós, R. Castañer.
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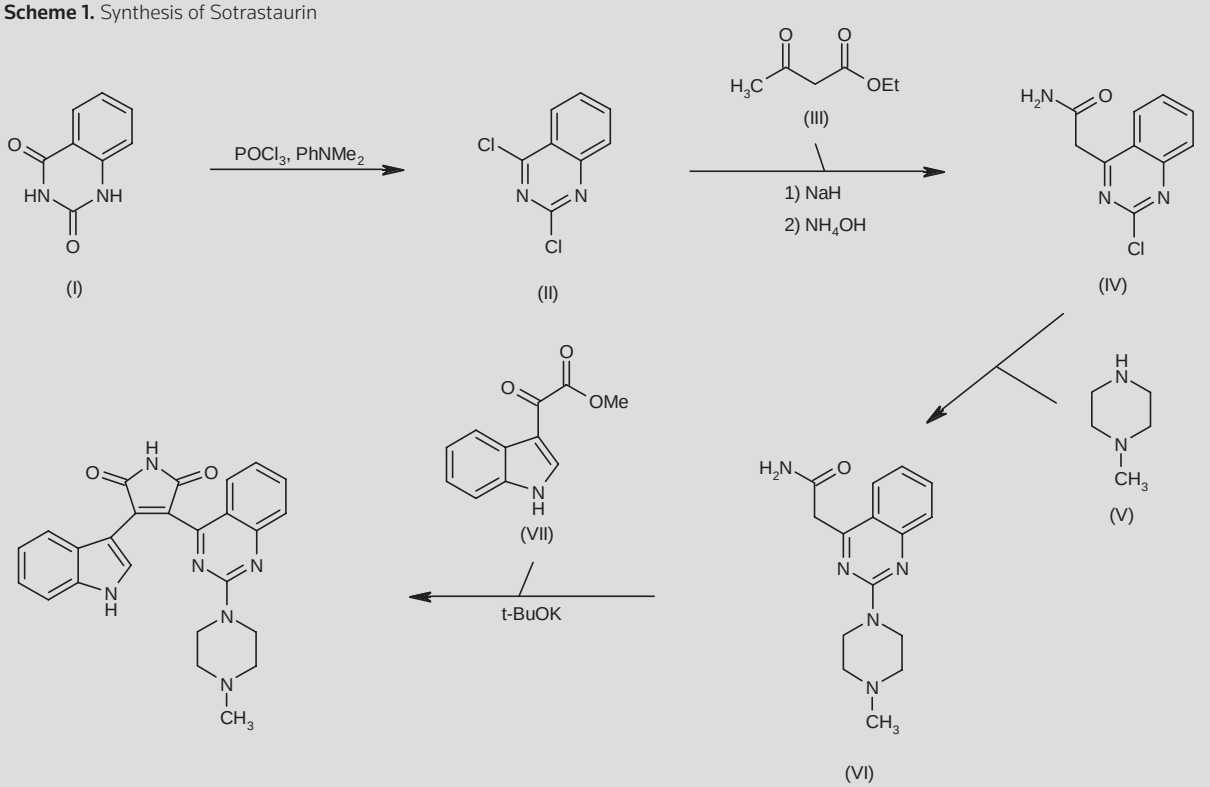
Scheme 1. Synthesis of Sotrastaurin



selectively inhibits the classic (α, β) and novel (δ, ε, η, θ) PKC isoforms, and thus effectively blocks early T-cell activation and subsequent IL-2 production (Fig. 1). Several studies have suggested that the agent may be effective in preventing allograft transplant rejection and may provide a better tolerated alternative to the CNIs. Since pathological T-cell activation is also involved in a number of other disease states, the use of sotrastaurin could potentially be extended to include conditions such as psoriasis and ulcerative colitis.

PRECLINICAL PHARMACOLOGY

Sotrastaurin has been shown to competitively and reversibly inhibit both classic and novel PKC isoforms with IC_{50} values of approximately 1.5 nM in an in vitro model using human $CD4^+$ T cells (9, 10). This effect was found to be highly selective, sparing other serine/threonine and tyrosine kinases (9). Sotrastaurin can also inhibit the release of IL-2 from both mouse (11) and human (10) T cells with an IC_{50} of 50 nM. More recent reports have shown that the agent inhibits T-cell proliferation induced by a CD3/CD28 antibody and alloantigens and prevents LFA-1-mediated T-cell adhesion at nanomolar concentrations (12).

In contrast to ciclosporin (CsA), it is a very weak inhibitor of nuclear factor of activated T cells (NFAT) with an IC_{50} > 1000 nM (10). From a clinical perspective, this may allow sotrastaurin to avoid some of the side effects associated with NFAT blockade, including an alteration in glucose homeostasis (13). Provided sotrastaurin can produce similar immunosuppressive effects to CsA and other immunosuppressive agents, it may in fact be a much better tolerated option. In addition, sotrastaurin does not have any effect on cytokine- or growth factor-induced cell proliferation, nor does it modulate T-cell apoptosis induced by various stimuli (11). Overall, its mode of action is distinct from that of the CNIs, although it has complementary effects with CsA on T-cell signaling pathways.

Owing to its effects on T-cell activation, sotrastaurin has been explored in the area of cellular and organ transplantation. Using a rat cardiac allograft model, it was shown that sotrastaurin (30 mg/kg p.o. b.i.d.) prolonged graft survival from 7 days to > 28 days. Furthermore, nontherapeutic doses of sotrastaurin (10 mg/kg p.o. b.i.d.) combined with low-dose CsA, everolimus or fingolimod resulted in prolongation of graft survival to 26, > 68 and > 68 days, respectively (14). A further study in nonhuman primates showed renal allograft survival of over 100 days when nontherapeutic doses of sotrastaurin were combined with low-dose CsA (10). These initial preclinical studies demonstrated that the compound can delay allograft rejection either as monotherapy or in conjunction with CNIs in a variety of animal models and transplantation settings.

Our group has expanded these preclinical results to the area of pancreatic islet transplantation (15). Currently, islet transplant recipients

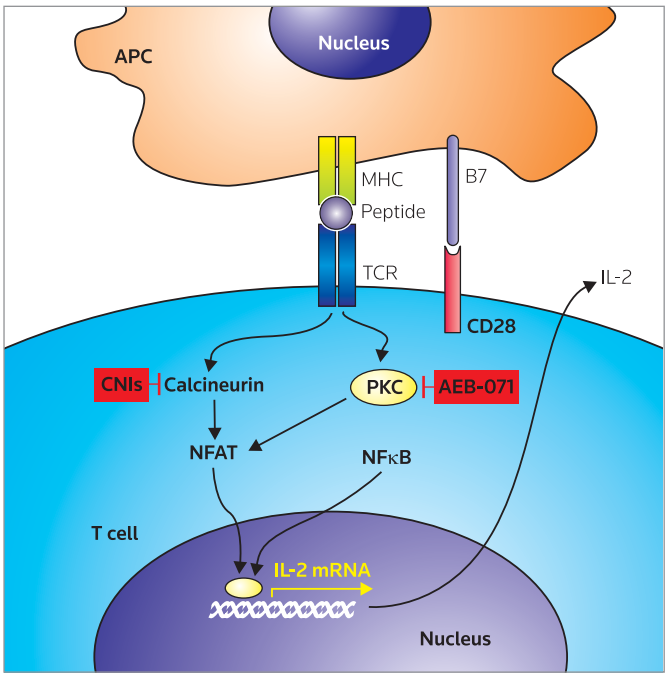


Figure 1. Interaction of calcineurin inhibitors (CNIs) and sotrastaurin (AEB-071) in pathways leading to IL-2 production. APC, antigen-presenting cell; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor of kappa light chain gene enhancer of activated B cells; PKC, protein kinase C; TCR, T-cell receptor.

face a decline in metabolic function, probably due to a combination of allograft rejection, recurrence of type 1 diabetes and immunosuppressive toxicity. As a result, new, more effective and less toxic immunomodulating agents have the potential to bring the field into a new era. Sotrastaurin can delay rat islet allograft rejection when used alone (from 7 to 22 days) or in combination with CsA (> 100 days vs. 12 days for CsA alone) (16). These studies also demonstrated that it has no diabetogenic toxic effects, as assessed by glucose tolerance testing and pancreatic insulin content. Furthermore, sotrastaurin placed in culture with human islets for 48 h had no effect on insulin release or islet apoptosis. Finally, human islets transplanted in an immunodeficient mouse model displayed improved engraftment and sustained function when treated with sotrastaurin as compared to sirolimus, a drug commonly used after clinical islet transplantation (17). Sotrastaurin is therefore of particular interest in the setting of islet transplantation, where optimal post-transplant immunosuppression has not been achieved thus far.

Sotrastaurin has been investigated in the setting of other T-cell-mediated diseases, including models of type 1 diabetes. Unfortunately, the effect on diabetes onset in the NOD mouse was only moderate, with a delay of 2 weeks (18).

Overall, it would seem that sotrastaurin has a bright future in the realm of transplantation. It has displayed the ability to prolong graft survival both in solid organ and islet transplantation through the inhibition of PKC, a mechanism totally different from the CNIs. It has also proven potentially synergistic to the CNIs, whereby CNI toxicity could be limited if the two drug classes are combined. Lastly, sotrastaurin has proven to be nontoxic to both native and transplanted pancreatic β-cells.

PHARMACOKINETICS AND METABOLISM

A number of studies have explored the pharmacokinetics and metabolism of sotrastaurin in human subjects. Slade et al. (19) administered doses ranging from 25 to 200 mg p.o. b.i.d. for 14 days to healthy volunteers. They found that the oral clearance was time-independent, with steady state being reached by day 2 (four doses).

An additional study by Skvara et al. (20), who administered oral doses of 10-500 mg to healthy subjects, found a dose-dependent inhibition of T-cell proliferation, which peaked at 1-3 h after dosing. This was associated with a concomitant reduction in IL-2 mRNA expression. The biochemical half-life ($t_{1/2}$) of sotrastaurin in these subjects was 6 h. The maximum plasma concentration (C_{max}) increased in a dose-dependent manner, reaching a high of 4 μM in the 500-mg group (single dose). This study also compared various oral doses to placebo in patients with documented psoriasis. Here, the C_{max} reached a high of 4.5 μM in the group receiving 300 mg b.i.d. Interestingly, the C_{min} in this group was 1.5 μM, higher than the IC_{50} for inhibition of proliferation and IL-2 mRNA expression. Steady-state levels were reached after two doses in psoriasis patients.

Sotrastaurin is known to be highly protein-bound and is metabolized by the liver through the cytochrome P450 system (CYP3A4) (21, 22). This has implications for its use in liver transplantation and in patients with liver failure. Slade et al. (21) showed that in patients with severe liver impairment (Child-Pugh 10-13) there was a 52% decrease in C_{max}, a 19% decrease in the area under the curve (AUC) and a 2-fold increase in the half-life (12.5 h) as compared to healthy subjects. More importantly, unbound (free) sotrastaurin levels were similar between subjects with hepatic impairment and control (normal) subjects. Thus, although there may be lower total levels of sotrastaurin in the case of hepatic impairment, the biologically active (free) exposure is not affected.

Overall, sotrastaurin appears to reach an effective plasma concentration within a few doses. A twice-daily dosing regimen appears adequate. Although it is metabolized by the liver, exposure to its biologically active form is not altered in hepatic failure. This should allow the agent to be further developed in all types of transplantation, including liver transplantation.

SAFETY

Sotrastaurin has been investigated in healthy subjects, as well as in patients with psoriasis, liver disease and renal transplants. In a study in 48 healthy volunteers given a single dose of sotrastaurin, a total of 12 dose-independent adverse events were observed (20). Self-reported adverse events ranged from mild headache to dizziness. Furthermore, a transient, reversible tachycardia was documented in the group treated with 500 mg b.i.d. lasting from 3 to 12 h after oral dosing (heart rate never exceeded the upper limit of normal).

In a phase I safety trial in patients with psoriasis, an adverse event rate of 45.8% was seen in the sotrastaurin group (vs. 37.5% in the placebo group) (20). These events were mild, with nausea predominating in the higher dose groups. Of note, 2 of 32 patients experi-

Table I. *Clinical trials of sotrastaurin.*

Condition	Purpose of study	Primary outcome	Treatment group	Comparison group	Phase	Status
Healthy volunteers (NCT00416546)	Safety; caucasians vs. Japanese subjects	PK, safety, tolerability	AEB	Placebo	Phase I	Completed
Healthy volunteers (NCT00409929)	Safety and PK of doses > 500 mg	Safety, tolerability, maximum tolerated dose	AEB	Placebo	Phase I	Completed
Renal transplantation (NCT00820911)	Efficacy	Acute rejection, graft loss	AEB + everolimus + basiliximab + CS	Ciclosporin + everolimus + basiliximab + CS	Phase II	Recruiting
Renal transplantation (NCT00504543)	Efficacy and safety	Acute rejection, graft loss	AEB + everolimus + basiliximab + CS	Ciclosporin + everolimus + basiliximab + CS	Phase II	Recruiting
Renal transplantation (NCT00403416 + NCT00555789)	Efficacy and safety	Long-term safety > 12 months (renal)	AEB + Tac with conversion to AEB and MPA at 3 months	Tac + MPA	Phase I/II	Completed
Renal transplantation (NCT00492869)	Efficacy and safety	Acute rejection, graft loss	AEB + basiliximab + MPA + CS	Tac + MPA + basiliximab + CS	Phase II	Completed
Liver transplantation (NCT00545259)	PK	PK, safety, tolerability after single dose	AEB	N/A	Phase I	Completed
Psoriasis (NCT00885196)	Dose-finding using doses of 20-200 mg b.i.d.	Change in plaque severity	AEB	Placebo	Phase II	Recruiting
Ulcerative colitis (NCT00572585)	Efficacy and safety	Rate of remission induction	AEB	Placebo	Phase II	Suspended
Uveitis (NCT00615693)	Safety, tolerability, efficacy	Safety and tolerability	AEB	N/A	Phase II	Recruiting

AEB, sotrastaurin; CS, corticosteroids; MPA, mycophenolic acid; PK, pharmacokinetics; Tac, tacrolimus; N/A, not applicable.

enced elevations in alanine aminotransferase (ALT). In both patients these levels returned to normal with continued treatment. Renal function was reported to be normal throughout the study.

Recently, two trials using sotrastaurin in renal transplant recipients were reported (23, 24). The first compared sotrastaurin (200 mg b.i.d.) plus tacrolimus, with tacrolimus conversion to mycophenolate at 3 months, to tacrolimus plus mycophenolate (23). Safety was comparable between the two groups, with similar rates of drug discontinuation due to adverse events and similar rates of infection. Notably, the sotrastaurin group displayed a lower incidence of neutropenia (3-4%) compared to tacrolimus/mycophenolate (11%). The second study compared sotrastaurin (300 mg b.i.d.) directly to tacrolimus (24). There was a higher incidence of gastrointestinal adverse events (nausea, vomiting or constipation) on sotrastaurin, although the incidence of diarrhea was similar. As in the trial in healthy subjects discussed above (20), heart rate was 2-10 beats/min higher in the sotrastaurin group, with a greater incidence of tachycardia (increase of > 25% from baseline, > 100 beats/min). Patients on sotrastaurin obtained a benefit in renal function as compared to the tacrolimus group (glomerular filtration rate of 70 mL/min vs. 48 mL/min).

Calcineurin inhibitors have long been known for their potent immunosuppressive activity, although they are associated with numerous side effects and toxicities. Sotrastaurin appears to have acceptable tolerability with some benefit on renal function and neutrophil count. Further studies are needed to optimize the dosing of sotrastaurin, but, in terms of toxicity, it appears to be a potentially useful adjunct to the CNIs.

CLINICAL STUDIES

Eleven clinical trials in healthy volunteers and patients undergoing organ transplantation or with psoriasis, ulcerative colitis or uveitis employing sotrastaurin are currently registered under the National Institutes of Health registry (Table I). To date, the only data published in a peer-reviewed journal are from the psoriasis study, which showed a dose-dependent improvement in psoriasis severity during the treatment period (20). The most remarkable clinical improvement was seen in the group treated with 300 mg b.i.d. (the highest dose used), which showed a 69% reduction in psoriasis severity index. The drug was discontinued after 2 weeks and all groups except the 300-mg group returned to baseline severity after this point. Histological changes, more specifically a significant reduction in T cells, were observed in this group.

A recent review published by Vincenti and Kirk shed some light on the preliminary results of several clinical trials (25). The first study used a regimen of sotrastaurin plus tacrolimus with tacrolimus withdrawal at 3 months compared to tacrolimus and mycophenolate in the setting of renal transplantation (23). While efficacy failure was similar at 3 months, the study was terminated prematurely. This

occurred in the absence of tacrolimus (after withdrawal) due to a significant increase in efficacy failure (defined as biopsy-proven acute rejection, graft loss, death or loss to follow-up). In a second study, sotrastaurin was compared directly to tacrolimus (24). This study was also prematurely halted due to an increase in rejection in the sotrastaurin group (26% vs. 5% at 3 months).

In the preliminary renal transplant studies, sotrastaurin was paired with mycophenolate. Our group has shown that this combination is ineffective in preventing rejection of islet transplantation in rats. A more fruitful combination may be sotrastaurin paired with low-dose CsA, a combination we showed to prolong graft rejection by > 100 days. However, it remains to be seen whether the preclinical studies in islet transplantation can be applied in a clinical setting.

The most recent updates presented at the 2009 American Transplant Congress clearly suggest that sotrastaurin must be combined with a CNI (tacrolimus or CsA) in order to maximize protection against acute rejection events (23). Sotrastaurin + mycophenolate mofetil was unable to provide adequate prophylaxis against acute rejection in the absence of CNIs (24). A phase II study of sotrastaurin + everolimus (a rapamycin derivative) is under way in renal transplantation and results are eagerly awaited. It seems most likely that sotrastaurin will need to be combined with half-dose tacrolimus or CsA to find its appropriate niche in the transplantation armamentarium.

DRUG INTERACTIONS

Sotrastaurin has been shown to act synergistically at nontherapeutic doses with CsA, everolimus and fingolimod in various transplantation models (10, 14, 16, 22). The delayed rejection observed in rodent models is not thought to be a result of pharmacokinetic interactions between these drugs (14). However, Slade et al. (22) showed that when sotrastaurin and CsA are combined, there is a dose-dependent increase in the AUC of sotrastaurin. In healthy human subjects, sotrastaurin and CsA work synergistically to provide a significant reduction in markers of T-cell activation and an additive inhibitory effect on lymphocyte proliferation similar to high-dose CsA alone. Additionally, sotrastaurin acts synergistically with mycophenolate to provide an increase in antiproliferative activity (~50% individually vs. 80% in combination) (19).

It is still likely that the significant effects of sotrastaurin combined with CsA are due to synergy through their closely related pathways. This evidence should provide further support for the development of sotrastaurin/low-dose CsA-based immunosuppressive regimens.

CONCLUSION

Organ transplantation continues to be a life-saving procedure performed across the globe. New immunosuppressive agents are constantly being sought in order to provide safer and more effective means of preventing graft rejection. In preclinical studies, sotrastaurin, a PKC inhibitor, has proven to be a viable alternative to the CNIs, a class of drugs that have proven effective yet are associated with numerous side effects. While early clinical trials have proven sotrastaurin to be safe, they have failed to show any activity for the agent as monotherapy. This does not mean that sotrastaurin should be ignored; it may yet find a role in combination with other agents, especially if those agents are given at doses associated with a reduction in their potential side effects.

SOURCE

Novartis AG (CH).

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