Drugs of the Future 2001, 26(10): 939-950

CCC: 0377-8282/2001

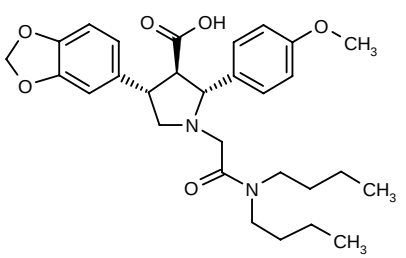
Atrasentan

Prop INN; USAN

Treatment of Prostate Cancer
Endothelin ET_A Antagonist

ABT-627
A-147627

1-(*N*,*N*-Dibutylcarbamoylmethyl)-2(*R*)-(4-methoxyphenyl)-4(*S*)-(3,4-methylenedioxyphenyl)pyrrolidine-3(*R*)-carboxylic acid



$C_{29}H_{38}N_2O_6$ Mol wt: 510.6272

CAS: 173937-91-2
CAS: 195733-43-8 (as monohydrochloride)

EN: 226636

Synthesis

Atrasentan can be obtained by several different ways:

1) Cyclization of 5-(2-nitrovinyl)-1,3-benzodioxole (I) with ethyl 2-(4-methoxybenzoyl)acetate (II) by means of DBU in THF gives the 4-nitrobutyrate (III), which is reduced with H_2 over Ni in ethanol to the corresponding amine, which undergoes immediate cyclization to give the pyrroline carboxylate (IV). Reduction of pyrroline (IV) with $NaCNBH_3$ in THF affords the expected pyrrolidine as a mixture of the (*trans*, *trans*)-(V), (*cis*, *cis*)-(VI) and (*cis*, *trans*)-(VII) isomers. Using chromatography on silica gel, only the (*cis*, *cis*)-isomer (VI) is separated and completely isomerized to the (*trans*, *trans*)-isomer (V) by treatment with NaOEt in refluxing ethanol. Pure (*trans*, *trans*)-isomer (V) or the remaining mixture of (*trans*, *trans*)-(V) and (*cis*, *trans*)-(VII) is *N*-protected with Boc_2O in dichloromethane to provide a mixture of carbamates. Then hydrolysis of the esters is performed with NaOH in ethanol/water at room temperature, and under these conditions only the (*trans*, *trans*)-isomer hydrolyzes, giving the racemic (*trans*, *trans*)-acid (VIII). Unreacted (*cis*, *trans*)-ester (VII) is easily removed by conventional methods. Condensation of the racemic acid (VIII) with the lithium salt of the chiral oxazolidinone (IX) by means of pivaloyl chloride yields the corresponding amide as a diastereomeric mixture of (X) and (XI) that are separated by chromatography. The desired isomer (XI) is deprotected with HCl in dioxane to afford the chiral pyrrolidine (XII), which is condensed with 2-bromo-*N*,*N*-dibutylacetamide (XIII) by means of diisopropylamine in acetonitrile to give the adduct (XIV). Finally, the chiral auxiliary of (XIV) is eliminated by means of LiOOH (LiOH + H_2O_2) in water (1). Scheme 1.

2) Condensation of 1,3-benzodioxole-5-carbaldehyde (XV) with nitromethane by means of ammonium acetate in AcOH gives the nitrostyrene (I), which is condensed with ethyl 2-(4-methoxybenzoyl)acetate (II) – obtained by reaction of acetophenone (XVI), diethyl carbonate and potassium *tert*-amyloxide – by means of NaOEt in THF to yield the 4-nitrobutyrate (III). Reductive cyclization of (III) with H_2 over Ra-Ni in THF affords the (*cis*, *cis*)-pyrrolidine (VI), which is isomerized to the (*trans*, *trans*)-isomer (V) by means of NaOEt in refluxing ethanol. This racemic ester (V) is submitted to optical resolution with (*S*)-(+)-mandelic acid to provide the pure chiral ester (XVII). This compound is condensed with 2-bromo-*N*,*N*-dibutylacetamide (XIII) – obtained by reaction of 2-bromoacetyl bromide (XVIII) with dibutylamine (XIX) in toluene – by means of DIEA in acetonitrile to give the ethyl ester (XX), which is finally hydrolyzed with NaOH in hot ethanol (2, 3). Scheme 2.

3) Reaction of 2-(1,3-dioxol-5-yl)acetic acid (XXI) with pivaloyl chloride and TEA gives the corresponding anhydride (XXII), which is condensed with the chiral oxazolidinone (XXIII) by means of BuLi in THF to yield the amide (XXIV). Condensation of (XXIV) with 2-bromoacetic acid *tert*-butyl ester (XXV) by means of NaHMDS in THF affords the adduct (XXVI). Elimination of the chiral auxiliary of (XXVI) by means of LiOOH in THF/water provides

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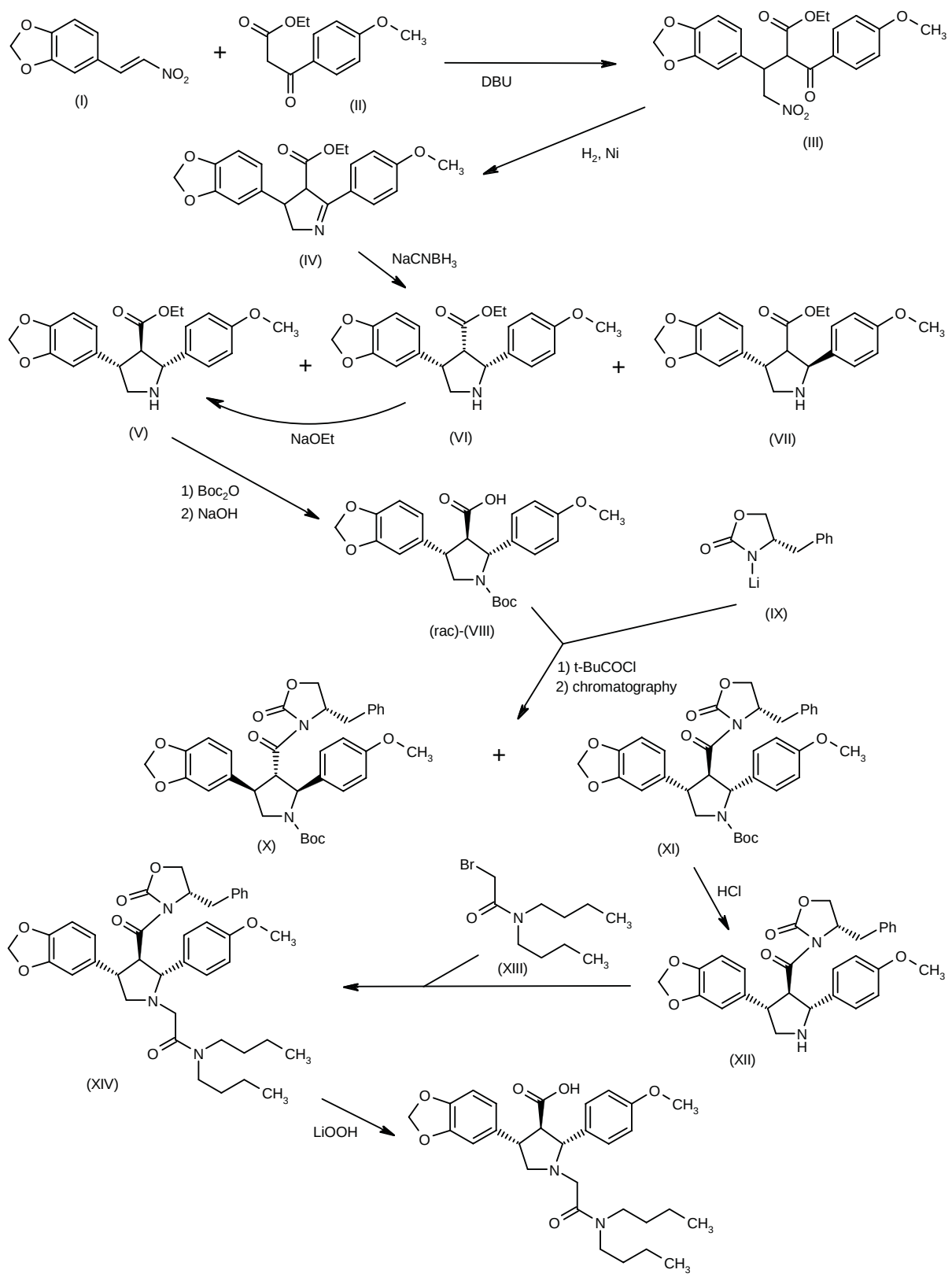
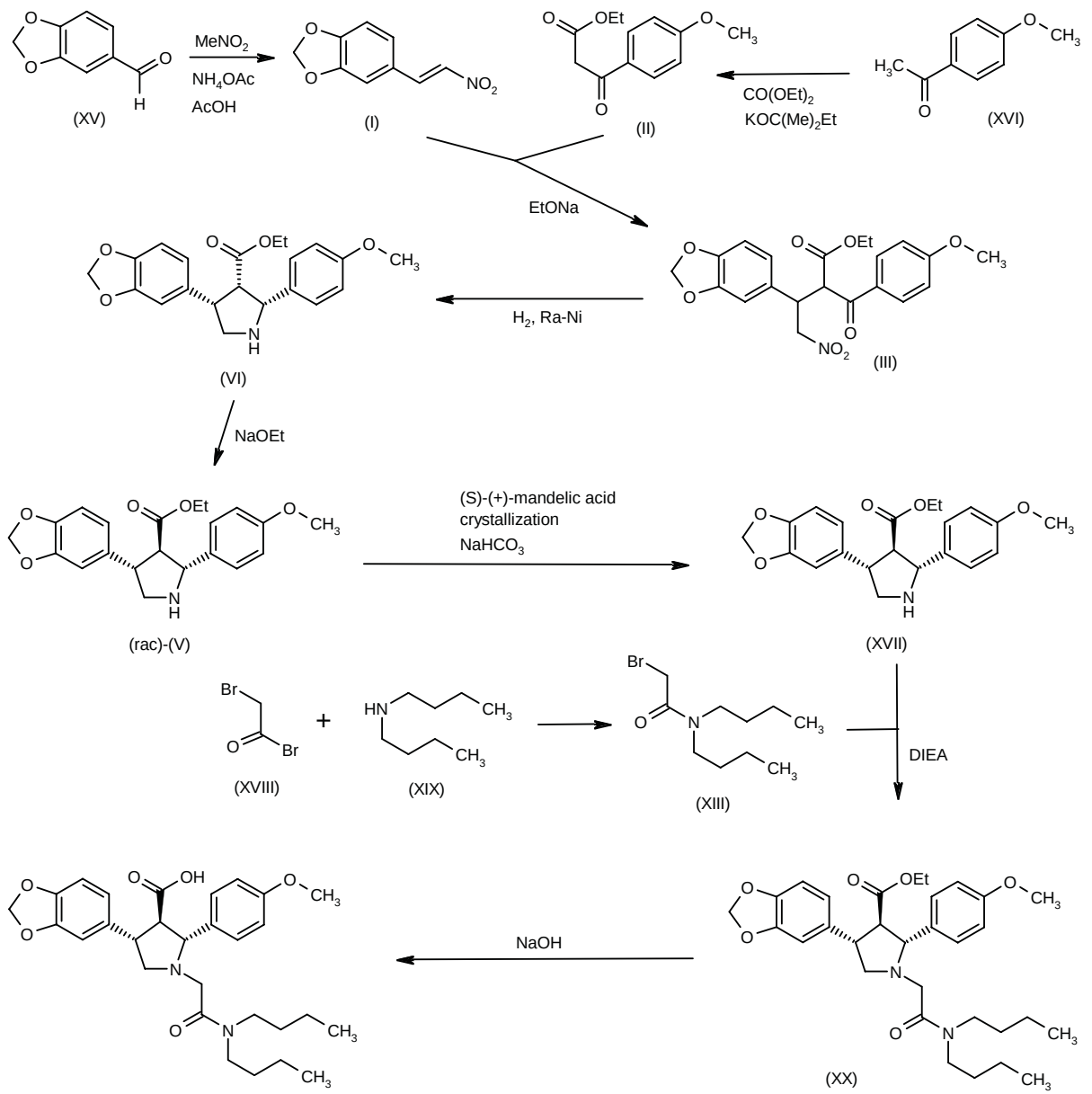
Scheme 1: Synthesis of Atrasentan

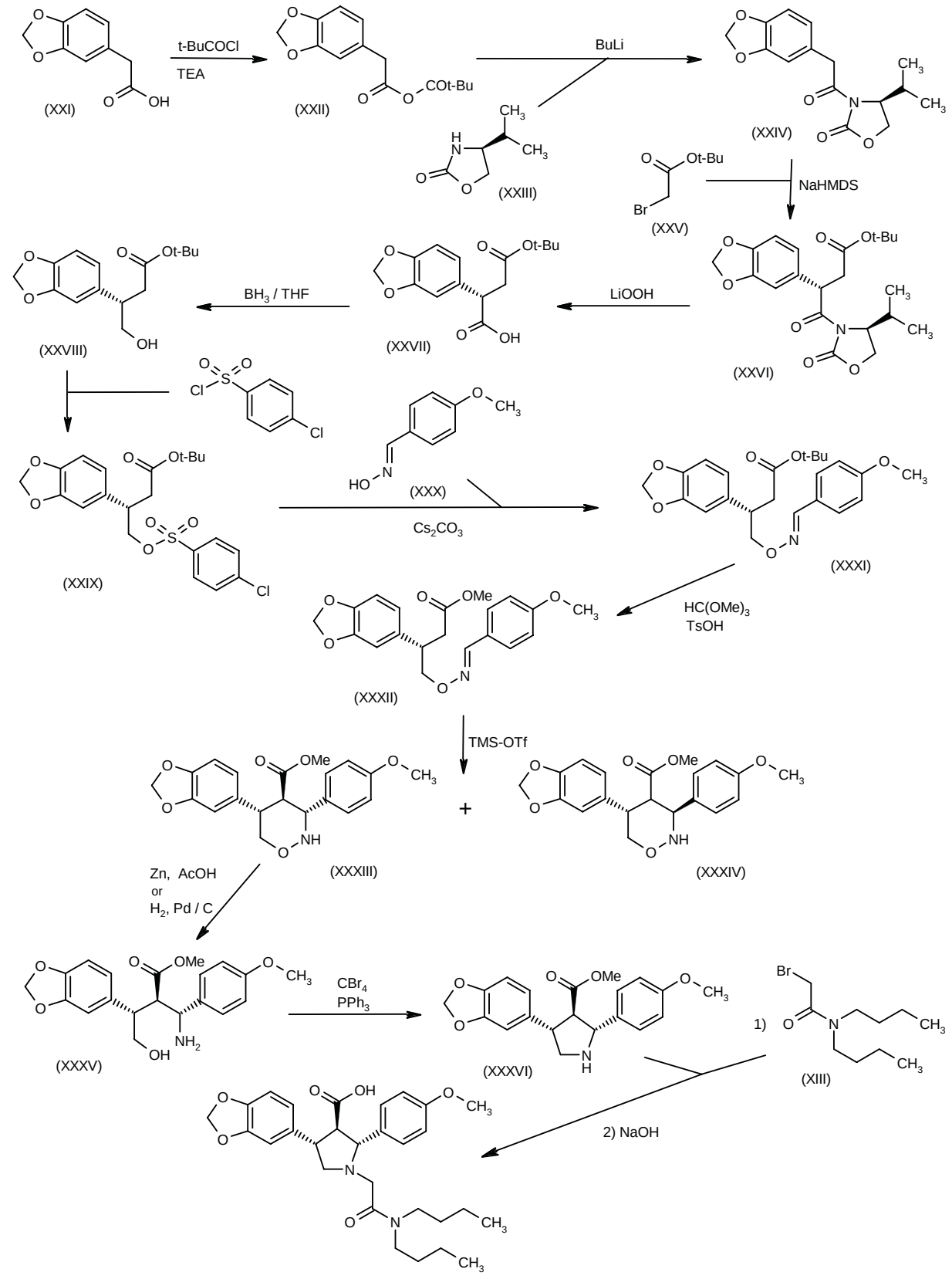


Scheme 2: Synthesis of Atrasentan



the chiral succinic acid hemiester (XXVII) (93% ee), which is selectively reduced with BH_3–THF complex to give the 4-hydroxysuccinate (XXVIII). Reaction of succinate (XXVIII) with 4-chlorophenylsulfonyl chloride, TEA and DMAP in dichloromethane yields the sulfonate (XXIX), which is condensed with 4-methoxybenzaldoxime (XXX) by means of Cs_2CO_3 in hot acetonitrile to afford the oxime ether (XXXI). Transesterification of the *tert*-butyl ester of (XXXI) with trimethyl orthoformate and *p*-toluenesulfonic acid in hot methanol provides the methyl ester (XXXII), which is cyclized by means of trimethylsilyl triflate and tributylamine in dichloroethane to afford a 9:1 diastereomeric mixture of perhydro-1,2-oxazines (XXXIII) and (XXXIV) which is easily separated. The reductive *N-O*-bond cleavage of the major oxazine diastereomer (XXXIII) by means of Zn/AcOH or H_2 over Pd/C gives the trisubstituted 4-aminobutanol (XXXV), which is cyclized by means of CBr_4, PPh_3 and TEA to yield chiral pyrroli-

Scheme 3: Synthesis of Atrasentan



dine (XXXVI) (4). Finally, pyrrolidine (XXXVI) is alkylated with *N,N*-dibutyl-2-bromoacetamide (XIII) followed by ester hydrolysis as before (1, 4). Scheme 3.

Introduction

Endothelins are a family of 3 isopeptides (ET-1, ET-2 and ET-3) composed of 21 amino acids and 2 internal disulfide bonds that have been shown to be potent vasoactive agents. ET-1 has been found in abundance in endothelial and epithelial cells where it acts as an autocrine/paracrine mediator. It has been shown to play a role in modulation of vascular tone, cell proliferation and apoptosis and therefore has been implicated in several cardiovascular disorders and noncardiovascular conditions such as cancer (5-9).

Endothelins exert their action via G-protein-coupled receptors of which 2 types have been cloned (ET_A and ET_B) (9). ET_A is expressed in vascular smooth muscle cells, cardiomyocytes and fibroblasts and exhibits a greater affinity for ET-1 over ET-2 and ET-3. Thus, this receptor is predominantly thought to mediate the vasoconstrictive and proliferative effects of ET-1 (9). ET_B receptors are expressed in medial smooth muscle of human arteries where they also mediate vasoconstriction and are also implicated in clearance mechanisms for excess endothelins and the feedback and regulation of endothelin synthesis and secretion. ET_B has also been shown to be involved in antiproliferative effects in human cells (9-11).

The implication that ET-1 is a pathogenic factor due to its long-lasting vasoconstricting properties and the role it plays as a mitogenic cytokine, has led to the development of numerous mixed nonselective ET receptor antagonists (12-14). However, more selective antagonists may provide better therapeutic benefits. ABT-627 (atrasentan), an orally bioavailable potent endothelin antagonist, is one such selective agent that exhibits higher affinity for the ET_A receptor over the ET_B receptor (approximately 1800-fold) and effectively inhibits the effects of endothelin (1, 15, 16). ABT-627 has displayed promising results suggesting that it may be effective in the treatment of pulmonary hypertension (17), essential hypertension (18, 19), congestive heart failure (20, 21), restenosis (12), cerebral ischemia (23), diabetic neuropathic pain (24), allergic asthma (25) and renal failure (26, 27). It has been suggested that ET_A antagonists, due to their antimitogenic and antiproliferative effects, may be effective agents against advanced cancers. In this regard, ABT-627 has recently been demonstrated to have potent inhibitory effects on tumor growth and angiogenesis and it has been selected for further development as a treatment for advanced cancers, particularly prostate cancer. Another ET_A antagonist under clinical development is YM-598.

Pharmacological Actions

ABT-627 exhibited higher affinity for the human cloned ET_A receptor (K_i = 0.034± 0.001 nM) over the ET_B receptor (K_i = 63.3 ± 19.2 nM) expressed in CHO cell membranes. ABT-627 binding to ET_A was reversible (dissociation $t_{1/2}$ = about 2 h) in contrast to ET-1. Both ABT-627 and ET-1 resulted in partial receptor internalization. However, unlike ET-1, ABT-627 was unable to elicit functional responses (15, 16).

ABT-627 was shown to antagonize ET-1-induced responses. For example, the agent dose-dependently reversed ET-1 (10 nM)-induced contraction of rat aortic rings with almost complete reversal observed at a dose of 1 μM (IC_{50} = 286 nM). Moreover, ABT-627 (0.01 and 0.1 mg/kg/min i.v.) reversed ET-1 (0.01 nmol/kg/min continuous i.v. infusion)-induced pressor responses in anesthetized, ganglionic-blocked rats (16).

The antimitogenic effects of ABT-627 were also demonstrated preclinically. The agent inhibited ET-1 induced mitogenic effects in primary cultures (PMOV1, PMOV2) and cell lines of ovarian carcinoma (OVCA 433, HEY). Moreover, ABT-627 was effective *in vivo* against advanced stage (about 0.5 cm in diameter) HEY ovarian carcinoma xenografts in nude mice. HEY cells produce large amounts of ET-1 and express high-affinity ET_A receptors and treatment with ABT-627 (1 mg/kg/12 h i.p. for 21 days) resulted in a significant reduction in tumor growth (60%) as compared to controls that was similar to the growth inhibition observed with paclitaxel (20 mg/kg i.v.). ABT-627-induced reductions in tumor size were found to be associated with reduced neovascularization and enhanced apoptosis (28). ABT-627 (1 mg/kg/12 h i.p. for 21 days) was also shown to be effective against early and advanced stage cervical carcinoma (CaSki) xenografts where the agent markedly reduced tumor growth (29).

Results from a study using an *in vitro* model of bone metastases involving coculturing of a prostate cancer cell line (MDA PCa 2b) with primary mouse osteoblasts showed that ABT-627 markedly but not completely inhibited the MDA PCa 2b-induced increase in growth and differentiation of primary osteoblasts; the agent had no effect on MDA PCa 2b-induced increases in phosphatase activity and bone matrix deposition by primary osteoblasts. Results suggest that ABT-627 may be effective in combination with other agents to prevent bone metastasis from prostate cancer (30).

Pharmacokinetics

A sensitive reverse phase HPLC method with fluorescence detection was described for the determination of ABT-627 in human plasma. Extraction of plasma using a mixture of hexane: *tert*-butylmethyl ester (1:1, v/v) resulted in recoveries of ABT-627 ranging from 73-78% with no interferences observed with drug-free plasma. The standard curve was linear (0.039-16.61 ng/ml). The

intraassay and interassay coefficients of variation were 1.9-9.3% and 5.2-6.9%, respectively. No reductions in plasma ABT-627 concentrations were observed following 4 freeze-thaw cycles or after storing at –20 °C for more than 30 days (31). Another report has described the efficacy of an HPLC method in reliably determining ABT-627 and evaluating its purity (32).

A pharmacokinetic study in rats administered an i.v. dose of ABT-627 (5 m/kg) reported AUC, volume of distribution of the central compartment, $t_{1/2}$ and total plasma clearance values of 7.96 μg·h/ml, 0.26 l/kg, 3.5 h and 0.7 ml/min, respectively. Following oral administration (10 mg/kg), the AUC, $t_{1/2}$, C_{max} and t_{max} values were 11.2 μg·h/ml, 4.5 h, 3.24 μg/ml and 0.7 h, respectively. An oral bioavailability of 35-70% was obtained (1, 15).

The pharmacokinetics of i.v. and oral ABT-627 (5 mg/kg) were also reported in beagle dogs and cynomolgus monkeys. The half-life and apparent volume of distribution after i.v. dosing in dogs were 1.6 h and 0.13 l/kg, respectively, and 2.5 h and 0.09 l/kg, respectively, in monkeys. The C_{max} and apparent bioavailability following oral dosing were 4.67 μg/ml and 43.2% in dogs, respectively, and 0.32 and 21.7% in monkeys, respectively (15).

Two pharmacokinetic, placebo-controlled crossover studies conducted in a total of 53 healthy male volunteers reported the pharmacokinetics, pharmacodynamic effects and tolerability of single- and multiple (8 days)-dose oral ABT-627 (0.2-40 mg). After single dosing, ABT-627 was rapidly absorbed (with the exception of the 1 mg dose which resulted in a median t_{max} value of 3 h); median t_{max} values of 0.5 and 2 h were obtained for the 20 and 40 mg doses, respectively. The terminal $t_{1/2}$ was approximately 24 h and dose-proportional AUC values were obtained. Treatment was well tolerated following both single and multiple dosing. Transient headache was the most common adverse event (62 *vs.* 4% in placebo following single dosing and 42 *vs.* 60% in placebo following multiple dosing). Administration of a single dose of 20 or 40 mg ABT-627 and multiple dosing with 5 mg or greater resulted in inhibition of ET-1-induced forearm vasoconstriction at 8 h postdosing. Treatment with the agent reduced peripheral resistance significantly more than placebo with only a slight increase in blood pressure noted. In addition, treatment induced a moderate dose-dependent increase in immunoreactive ET levels (50% maximum increase with the 20 mg dose) indicatingdisplacement of ET from its receptor (33).

Similar results were obtained in a randomized, placebo-controlled, double-blind study conducted in 72 male volunteers administered single or multiple doses of ABT-627 (1, 5, 10, 15, 20, 25, 30 or 40 mg p.o. on days 1 and 3-9). The 40 mg dose was terminated due to adverse events (*i.e.*, headache). Plasma concentrations of the agent increased rapidly following single- and multiple-administration of all doses except 1 mg and then decreased biexponentially with a half-life of 21 h and a mean total body clearance of 28 l/h. A linear increase in C_{max} trough plasma levels and AUC values was observed with dose following both single and multiple dosing and steady state was achieved after 4 days of dosing. The 1 mg dose group exhibited a lower C_{max} value than what was predicted (34).

A placebo-controlled, double-blind study in 24 healthy male volunteers assessed the pharmacokinetics of single oral doses of ABT-627 (1, 10, 23.25 and 139.5 mg). Results showed that pharmacokinetics were linear for the lower doses (1-23.25 mg), with some dose-dependency seen with the highest dose (139.5 mg). The terminal elimination half-life was similar (20-25 h) for all doses studied. Apparent oral clearance values were 12 l/h for the 139.5 mg dose group and 21-27 l/h for the 1, 20 and 23.25 mg dose groups. The apparent volume of distribution was approximately 6 l/kg and was consistent with extensive tissue distribution. ABT-627 was well tolerated; the most frequently reported adverse events were mild or moderate and included transient headache, rhinitis and nausea (35).

The pharmacokinetics, pharmacodynamics and tolerability of ABT-627 (2.5-95 mg once daily for 28 days) were reported from a phase I trial conducted in 45 patients with refractory adenocarcinoma. Plasma concentrations of the agent increased rapidly and decreased thereafter biexponentially; a $t_{1/2}$ value of about 22 h was obtained. AUC values normalized for dose were linear. A modest and comparable increase in immunoreactive ET plasma concentrations was observed with all doses except 2.5 mg, suggesting maximum displacement of ET from its receptor. Treatment was well tolerated with only mild rhinitis and transient headache observed with ABT-627 treatment (36).

Clinical Studies

The efficacy and safety of ABT-627 (10-75 mg/day and 37.5 mg b.i.d. for 28 days followed by a 7-day rest period) were reported from results of a phase I, dose-escalation study conducted in 29 patients with refractory adenocarcinomas (15 prostate, 8 colon, 2 breast, 2 renal, 1 pancreas, 1 lung). Treatment was well tolerated with minimal toxicities observed. The most common adverse events included transient grade 2 headache (35%), rhinitis (91%), mild anorexia (35%) and fatigue (35%). No severe hematological, cardiovascular, hepatic or renal toxicities were seen. Modest increases in immunoreactive ET plasma concentrations were observed, indicating displacement of ET from its receptor. To date, after 28 days of treatment, reductions in PSA and CEA tumor markers were observed in 10 of 15 (66.7%) evaluable patients. In addition, decreases of more than 2 were observed in the visual analog scale for pain and reductions in narcotic use were observed in 2 of 6 symptomatic men analyzed to date. Following the initial 28-day dosing period, 11 patients continued with stable or improved symptoms (37).

The tolerability of ABT-627 (5-75 mg/day p.o.) was evaluated in a phase I dose-escalation study conducted in 17 women and 11 men with refractory malignancies (8 colorectal, 6 non-small cell lung, 4 sarcoma, 2 cervical,

Box 1: Efficacy and tolerability of atrasentan in hormone-refractory prostate cancer patients (41) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with hormone-refractory prostate cancer (n = 131)
Treatments	Atrasentan, 2.5 mg p.o. o.d.x 12 wks (n = 40) Atrasentan, 10 mg p.o. o.d. x 12 wks (n = 48) Placebo (n = 43)
Withdrawals	81/131 (61.8%) [progression, other reasons]
Results	Stable PSA rate @ 12 wks: A > P Bone metabolism improvement rate @ 12 wks: A > P Pain VAS, % change @ 12 wks: A10* (–40) > P (–15) [*p = 0.004 *vs.* baseline] Rhinitis rate: A > P [p <0.05] Survival rate: A = P
Conclusions	Atrasentan was well tolerated and altered disease activity in hormone-refractory prostate cancer

2 thyroid, 1 pancreas, 1 carcinoid, 1 kidney, 1 adrenal, 1 mesothelioma and 1 unknown primary). Treatment was well tolerated. Preliminary data suggest that women experience slightly higher and longer exposure (*i.e.*, C_{max}, AUC and t_{max}) to the agent as compared to men. Toxicities observed were similar in both men and women; the dose-limiting toxicity has not yet been identified. Adverse events seen in the 17 female patients have been mild to moderate with no drug related grade 3/4 toxicities seen. The most common toxicities included grade 1-2 headache (8 patients), edema (7 patients), fatigue (6 patients) and constipation (5 patients) (38).

The safety and efficacy of ABT-627 (2.5-95 mg/day p.o.) were also demonstrated in a phase I dose-escalation trial conducted in 26 patients with androgen-resistant prostate cancer. After more than 100 months of treatment, rhinitis was the most common adverse event observed. Other minor toxicities included transient headache and ankle edema. No severe hematological, renal, hepatic or cardiovascular toxicities were observed. Following 1 month of treatment, a reduction in PSA and/or stable disease was observed in 19 patients (73.1%). Stable disease for 11+ and 15+ months was seen in 2 patients (39).

Another open-label, short-term phase I trial conducted in 15 men with metastatic, progressive, hormone-refractory prostate cancer has reported preliminary results on the efficacy and safety of ABT-627 (10, 20, 30, 45, 60 or 75 mg/day p.o. for 28 days followed by a 7-day rest period).Treatment was well tolerated. Two patients withdrew due to disease progression. Only minimal toxicities have been seen of which the most common were grade 2 headache and nasal congestion; no renal, hepatic or hematological toxicities were observed. Following 28 days of treatment, reductions in PSA were seen in 8 of 13 (61.5%) analyzed patients and narcotic use was decreased in some of these individuals. Eight patients with stable disease and/or improved symptoms have continued on after the initial 28-day period (40).

The efficacy and tolerability of ABT-627 (2.5 or 10 mg/day for 12 weeks) were demonstrated in a randomized, double-blind, placebo-controlled phase II trial in 131 men with symptomatic hormone-refractory prostate cancer. Fifty patients completed the 12-week treatment period with disease progression the primary reason for discontinuation. Survival and discontinuation rates were not significantly different among placebo and treatment groups. No serious renal, hepatic or cardiovascular drug-related adverse events were observed. A significantly higher incidence of rhinitis was observed in the drug-treated groups as compared to placebo. The incidence of other adverse events seen, including anorexia, headache, anemia and peripheral edema, was not significantly different between treatment and placebo groups. A significantly higher 40% improvement in VAS pain instrument scores was observed in the 10 mg ABT-627 group as compared to an insignificant 15% improvement on placebo; no changes in analgesic use by patients was noted. However, no significant differences were detected between the 10 mg group and placebo. Improvements in the brief pain inventory (BPI) and quality of life (QOL) subdomains and stabilization in the rate of rise in PSA and improvement in some bone metabolism markers were also observed in the 10 mg ABT-627 group (41) (Box 1).

The tolerability and efficacy of ABT-627 (2.5 or 10 mg once daily) were also shown in a multicenter, randomized, placebo-controlled, double-blind trial in 288 castrated (surgical or chemical) patients with hormone-refractory prostate cancer. Treatment was well tolerated with the most common treatment-related adverse events mild to moderate (10 mg group *vs.* placebo) peripheral edema (35 *vs.* 14%), rhinitis (28 v*s.* 13%) and headache (20 *vs.* 10%). Treatment with ABT-627 resulted in a significant delay in time to clinical progression (184 and 196 days for the 2.5 and 10 mg doses, respectively, *vs.* 129 days in placebo) and PSA progression (155 days in the 10 mg group *vs.* 134 and 71 days in the 2.5 mg group and placebo, respectively). In addition, significant dose-dependent attenuation of bone markers of metastatic progression including acid phosphatase, LDH and alkaline phosphatase were observed with ABT-627 treatment as

Box 2: Effects of atrasentan on quality of life in hormone-refractory prostate cancer patients (43) [Prous Science Integrity database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with hormone-refractory prostate cancer (n = 244)
Treatments	Atrasentan, 2.5 mg p.o. o.d. (n = 95) Atrasentan, 10 mg p.o. o.d. (n = 89) Placebo (n = 104)
Results	Quality-adjusted time to progression: A2.5* ≥ A10* > P [*p <0.05 *vs.* P] Median quality-adjusted time to progression, % change *vs.* P: A2.5 (38) ≥ A10 (28) Delay in clinical and PSA progression: A > P [p <0.05]
Conclusions	Atrasentan may produce a benefit in quality of life in hormone-refractory prostate cancer

Box 3: Effects of atrasentan on tumor-induced bone remodeling in hormone-refractory prostate cancer patients (44) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Castrated patients with hormone-refractory prostate cancer (n = 288)
Treatments	Atrasentan, 2.5 mg p.o. o.d. (n = 95) Atrasentan, 10 mg p.o. o.d. (n = 89) Placebo (n = 104)
Results	Total alkaline phosphatase levels, % change: A10 (= baseline) < A2.5 < P* (60) [*p <0.001 *vs.* baseline] Bone alkaline phosphatase levels, % change: A10 (= baseline) < A25 < P* (114) [*p <0.001 *vs.* baseline] Urine N-telopeptide levels: A10 (= baseline) < A2.5 < P* [*p <0.05 *vs.* baseline] Serum C-telopeptide levels: A10 (= baseline) < A2.5 < P* [*p <0.05 *vs.* baseline] Urine deoxypyridinoline levels: A10 (= baseline) < A2.5 < P* [*p <0.05 *vs.* baseline] Changes in clinical bone scan and serum tumor markers: A10 < A2.5 < P
Conclusions	Atrasentan was biologically active in a dose-dependent manner in hormone-refractory prostate cancer by suppressing the increases in biochemical markers of bone resorption and bone deposition

Box 4: Effects of atrasentan on skeletal remodeling activity in hormone-refractory prostate cancer patients (45) [Prous Science Integrity database].

Design	Multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients with hormone-refractory prostate cancer (n = 419)
Treatments	Atrasentan, 2.5 mg p.o. o.d. (n = 135) Atrasentan, 10 mg p.o. o.d. (n = 137) Placebo (n = 147)
Results	Total markers of bone resorption, % change: P* (20-97)(dose-dependent decrease) [*p <0.005 *vs.* baseline] Total alkaline phosphatase levels: P > A2.5 > A10* (= baseline) [*p = 0.001] Bone alkaline phosphatase levels: P > A2.5 > A10* (= baseline) [*p = 0.001] N-telopeptide levels: P > A2.5 > A10* (= baseline) [*p = 0.001] Deoxypyridinoline levels: P > A2.5 > A10* (= baseline) [*p = 0.001]
Conclusions	Atrasentan inhibited the progression of skeletal metastases in hormone-refractory prostate cancer

compared to increases observed on placebo. In addition, ABT-627 maintained a longer favorable health status according to assessment of performance status and QOL as compared to placebo (42-44) (Boxes 2 and 3).

Further analysis of suppression of tumor-induced bone markers of metastatic progression was performed from the results of the above trial pooled with another multicenter, randomized, double-blind, placebo-controlled trial. Data from a total of 419 patients with hormone-refractory prostate cancer administered ABT-627 (2.5 or 10 mg once daily p.o.) or placebo were analyzed. Results indicated that patients receiving the placebo displayed a significant 20-97% increase in total and bone alkaline phosphatase, collagen crosslinked

Box 5: Effects of atrasentan on time to clinical progression in hormone-refractory prostate cancer patients (46) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with hormone-refractory prostate cancer (n = 244)
Treatments	Atrasentan, 2.5 mg p.o. o.d. Atrasentan, 10 mg p.o. o.d. Placebo
Adverse events	A: headache, rhinitis, peripheral edema
Results	Median time to clinical progression (d): A10* (196) ≥ A2.5** (184) > P (129) [**p = 0.035 *vs.* P; *p = 0.021 *vs.* P] Median time to PSA progression (d): A10* (155) ≥ A2.5 (134) ≥ P (71) [*p = 0.002 *vs.* P] Progression-free (Kaplan-Meier estimates) rate (%): A10* (54.0) ≥ A2.5** (53.0) > P (35.0) [*p = 0.018 *vs.* P; **p = 0.022 *vs.* P] Attenuation of the increase in tumor and bone markers, LDH, serum acid phosphatase and alkaline phosphatase: A2.5* ~ A100* > P [*p <0.05 *vs.* P] Quality of life (duration of treatment benefit): A > P
Conclusions	Atrasentan was well tolerated and improved hormone-refractory prostate cancer activity

urine N-telopeptide and urine deoxypyridinoline levels. However, dose-related responses were observed with ABT-627 treatment. Patients receiving 10 mg ABT-627 maintained baseline levels of total and bone alkaline phosphatase while patients receiving 2.5 mg exhibited levels intermediate of placebo and the 10 mg group; N-telopeptide and deoxypyridinoline levels exhibited a similar tendency in treated and placebo groups. The changes in bone markers were found to be associated with progression of bone scans and alterations in serum acid phosphatase and PSA. Results suggest that ABT-627 suppresses skeletal metastases in patients with hormone-refractory prostate cancer (45) (Box 4).

Data from 244 evaluable patients with hormone-refractory prostate cancer treated in a phase II double-blind, randomized study with ABT-627 at doses of 2.5 or 10 mg orally or placebo have been presented. ABT-627 significantly delayed time to clinical progression in these patients from 129 days on placebo to 184 and 196 days, respectively, on 2.5 and 10 mg and time to PSA (prostate-specific antigen) progression from 71 days on placebo to 134 and 155 days, respectively. Moreover, 53 and 54% of patients, respectively, treated with 2.5 and 10 mg ABT-627 were progression-free at 180 days according to Kaplan-Meier estimates, as compared to 35% of those on placebo. ABT-627 also attenuated the increase in tumor and bone markers compared to placebo. Side effects, mainly rhinitis, peripheral edema and headache, were mild to moderate in severity (46) (Box 5).

ABT-627 is currently beginning phase III trials in patients with hormone-refractory prostate cancer (47).

Manufacturer

Abbott Laboratories Inc. (US).

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