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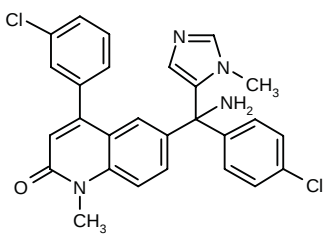
R-115777

Oncolytic
Farnesyl Protein Transferase Inhibitor

6-[1-Amino-1-(4-chlorophenyl)-1-(1-methylimidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methylquinolin-2(1*H*)-one



$C_{27}H_{22}Cl_2N_4O$ Mol wt: 489.4090

CAS: 192185-68-5
CAS: 192185-70-9 (as dihydrochloride)
CAS: 192185-69-6 (as sesquifumarate)

EN: 253457

Synthesis

Cyclization of 3-(3-chlorophenyl)-*N*-phenyl-2-propenamide (I) by means of polyphosphoric acid (PPA) at 100 °C gives 4-(3-chlorophenyl)-1,2,3,4-tetrahydroquinolin-2-one (II), which is condensed with 4-chlorobenzoic acid (III) by means of PPA at 140 °C to yield 6-(4-chlorobenzoyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydroquinolin-2-one (IV). The dehydrogenation of (IV) by means of Br_2 in bromobenzene at 160 °C affords 6-(4-chlorobenzoyl)-4-(3-chlorophenyl)quinolin-2(1*H*)-one (V), which is methylated with iodomethane and NaOH/benzyltrimethylammonium chloride in THF to provide 6-(4-chlorobenzoyl)-4-(3-chlorophenyl)-1-methylquinolin-2(1*H*)-one (VI). Condensation of compound (VI) with 1-methylimidazole (VII) by means of butyllithium in THF gives the triaryl carbinol (VIII), which is finally treated with ammonia in THF to afford R-115777 (1). Scheme 1.

Description

M.p. 220 °C.

Introduction

Several small membrane-bound G-proteins such as Ras, RhoB, RhoE, rhodopsin kinase, lamins A and B, cGMP phosphodiesterase, phosphorylase α and β, Rap 2, CENP-E, CENP-F, tyrosine phosphatase, HDJ-2, transducin and PxF, interact with membrane receptors and are required for signal transduction and cellular transformation. They are produced as cytoplasmic precursors that undergo posttranslational modification to convert them into their mature membrane-bound forms. Protein farnesylation is the first posttranslational process and is a reaction catalyzed by farnesyl protein transferase that enables these cellular proteins to anchor to cell membranes where they can interact with membrane receptors and mediate cell signaling. Protein farnesylation involves the transfer of a farnesyl moiety from farnesyl pyrophosphate to the cysteine residue found in the tetrapeptide sequence CAAX (where C = cysteine, A = an aliphatic amino acid [leucine, isoleucine or valine] and X = methionine, serine, leucine or glutamine) in the carboxyl terminus of these cellular proteins (2-6).

The Ras proteins in particular have become a target for the development of anticancer drugs due to the fact that oncogenic mutations have been identified in ~30% of all known human malignancies (7). *ras* protooncogenes encode 4 highly conserved Ras proteins (H-Ras, N-Ras, K-Ras4A, K-Ras4B) and activating mutations of these protooncogenes can result in constitutive signaling causing stimulation of cell proliferation and inhibition of apoptosis (8, 9). H-*ras* mutations have been found in bladder, kidney and thyroid carcinomas and mutations in N-*ras* have been detected in hepatocellular carcinoma, hematologic malignancies and malignant melanoma. K-*ras* mutations are seen in colorectal, pancreatic and non-small cell lung carcinomas (7).

Due to the crucial role farnesylation plays in Ras maturation, inhibitors of farnesyl protein transferase have emerged as a novel class of antineoplastic agents. Inhibitors of this enzyme ultimately interfere with *ras*-dependent cell transformation and therefore selectively inhibit the growth of *ras*-transformed cells (10-13). The investigational response has been the development of several farnesyl protein transferase inhibitors. Several of these agents are in the advanced stage of preclinical testing or in clinical trials. One of the first farnesyl protein transferase inhibitors discovered was CVFM which

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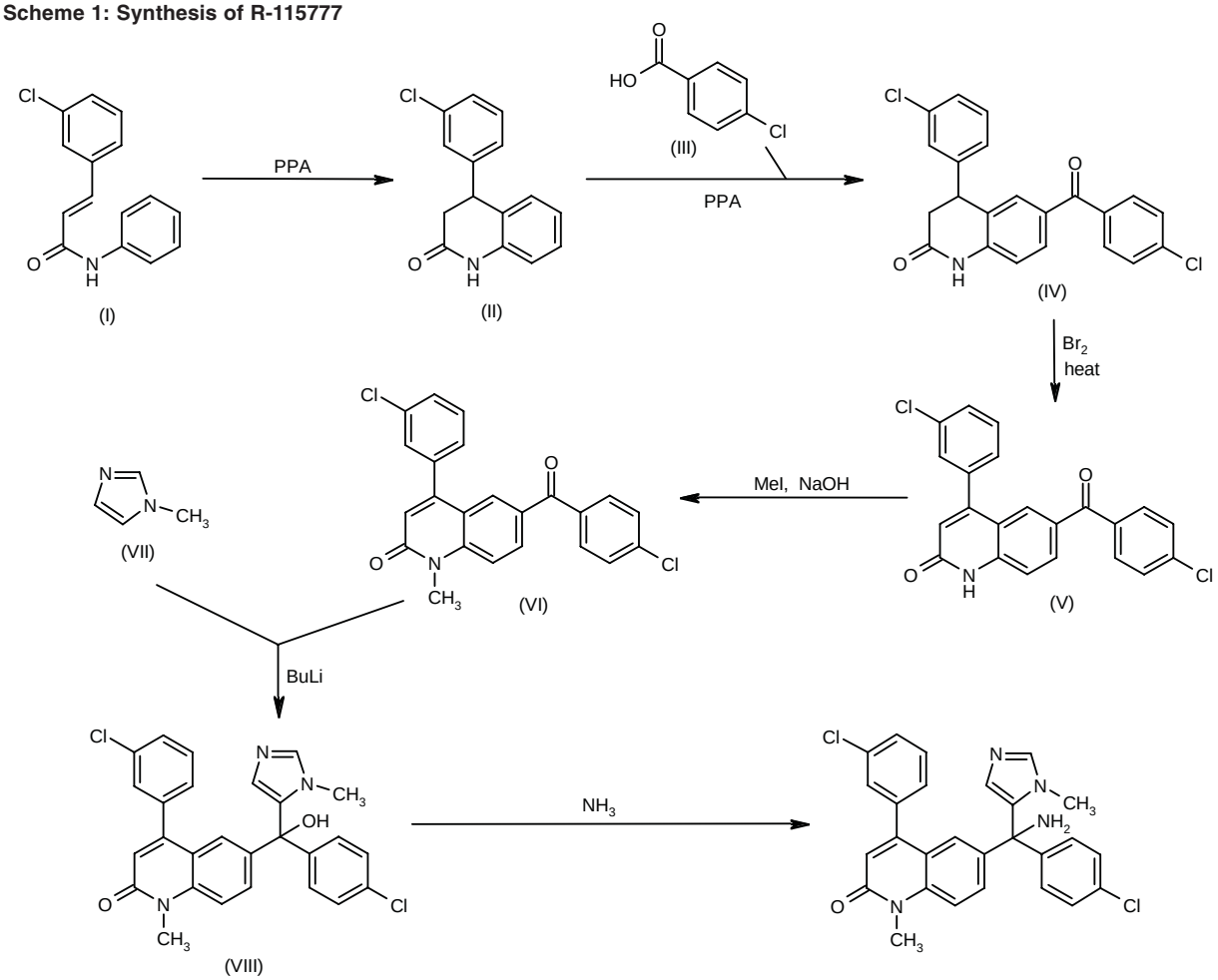
Scheme 1: Synthesis of R-115777



competes with the CAAX motif. CVFM was active at nanomolar concentrations but was found to be incapable of entering intact cells. Therefore, further investigation led to improvements in the compound resulting in agents such as B-956, FTI-276, L-739750 and BZA-5B which all showed good cellular penetration and efficacy against tumor xenografts (14-17). Further high-throughput screening eventually led to the discovery of more effective agents. Those agents currently undergoing clinical trials are shown in Table I. R-115777, in particular, is an orally bioavailable, methyl-quinolone derivative that is a selective nonpeptidomimetic inhibitor of farnesyl protein transferase. R-115777 has exhibited potent *in vivo* and *in vitro* activity and is currently undergoing clinical evaluation.

Pharmacological Actions

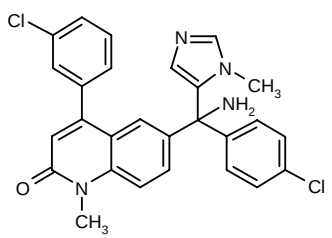
R-115777 inhibited human farnesyl protein transferase isolated from Kirsten virus-transformed human osteosarcoma cell tumors with IC_{50} values of 0.86 and 7.9 nM for lamin B peptide and K-RasB peptide, respectively, The agent was a competitive inhibitor for both the K-ras and lamin B1 substrates (K_i = 0.5 nM) and a noncompetitive inhibitor for the farnesyl pyrophosphate substrate. In contrast, the protein:geranylgeranyl transferase I peptide (PGGT I) was relatively insensitive to the agent (*e.g.*, 40% inhibition seen with 50 μM) (18).

In vitro studies using human peripheral blood lymphocytes revealed an unusual tight binding of R-115777 to farnesyl protein transferase. Inhibition could not be reversed up to 24 h after removal of the agent. The tight binding observed was found to be due to coordination of the imidazole nitrogen with Zn^{2+} from farnesyl protein transferase and extensive hydrophobic interactions (19).

Unlike the first discovered farnesyl protein transferase inhibitors, R-115777 was found to easily penetrate cells. When tested against 53 human tumor cell lines, the agent inhibited growth of approximately 75% of the cancer cell lines, including the following: breast (MCF-7; N-*ras*; IC_{50} = 3.6 nM); human colon (LoVo and HCT116; IC_{50} = 16 and

Table I: Farnesyl protein transferase inhibitors in clinical trials (Prous Science Ensemble database).

Compound	Company	Phase
1. R-115777	Janssen	III
2. BMS-214662	Bristol-Myers Squibb	II
3. L-778123	Merck & Co.	II
4. Sch-66336	Schering Plough	II
5. AZD-3409*	AstraZeneca	I/II
6. CP-609754*	Pfizer/Osi Pharm.	I
7. Arglabin	Inst. Phytochemistry, Kazakstan/NuOncology Lab.	Clinical



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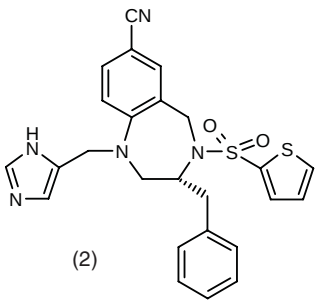

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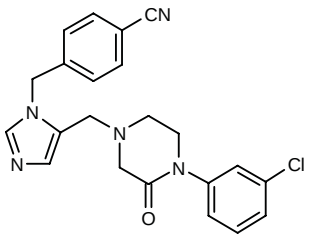

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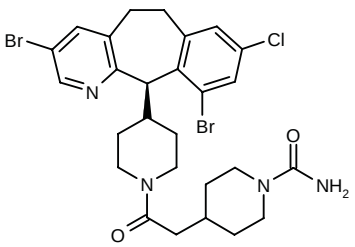

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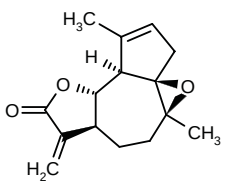

(7)

*Structure not yet detected

22 nM, respectively); pancreatic (CAPAN-2 and SU86.86; IC_{50} = 16 and 9.5 nM, respectively); bladder (RT4 and HT-1197; IC_{50} = 2.7 and 1.7 nM, respectively); melanoma (WM-115, SK-MEL-5; IC_{50} = 3.2 and 6.8 nM, respectively); lung (NCI-H292; IC_{50} = 6.5 nM); and rhabdomyosarcoma (A673 and A204; IC_{50} = 3.9 and 4.8 nM, respectively).Those cell lines bearing H-*ras* or N-*ras* were the most sensitive to R-115777 with IC_{50} values < 10 nM. However, those cell lines bearing K-*ras* mutations required higher concentrations of the agent (IC_{50} = 10-100 nM) and 50% of the lines tested with this mutation were resistant even with concentrations up to 500 nM. However, further analysis revealed that R-115777-induced inhibition of cell growth was independent of *ras* mutational status since cell lines bearing both wild-type or mutated *ras* were sensitive to the agent (18).

Results from *in vitro* studies using normal light density human bone marrow cells (LDBM), fresh human acute myeloid leukemia (AML) cells and the HL-60 promyelocytic leukemia cell line revealed that the antiproliferative effects of R-115777 may be due, in part, to inhibition of the mitogen-activated protein kinase (MAPK) pathway. Exposure of LDBM to R-115777 (20-1000 nM) resulted in dose-dependent inhibition of the numbers of granulocyte-macrophage colony formation and erythroid burst forming units. In addition, the agent (100 nM or more) inhibited proliferation of fresh AML cells and HL-60 cells after at least 2 days of exposure. HL-60 cells displayed a partial inhibition of MAPK phosphorylation following 2 days of exposure to 10 nM or more R-115777 (20).

When combined with conventional cytotoxic agents, R-115778 was shown to have additive cytotoxic effects *in vitro*. Simple additive antiproliferative effects were observed when R-115777 was combined with paclitaxel or cisplatin against human MCF-7, CAPAN-2, C32 and LoVo cell lines. Combination treatment of human prostate (DU145) carcinoma cells with R-115777 (50 nM) and paclitaxel (1 nM) for 72 h resulted in a cytotoxic response that appeared to be greater than additive. Analysis of the cell cycle revealed an enhanced G2/M block with 38% of the combination-treated cells in the G2/M phase as compared to cells treated with R-115777 (31.1%) or paclitaxel (23.8%) alone. In contrast, combination treatment of MCF-7 cells showed an enhanced G1 block (21, 22).

Additive effects were also observed *in vivo* in a study conducted in mice with LoVo xenografts treated with R-115777 (50 mg/kg p.o. b.i.d. on days 1-32) and cisplatin (5 mg/kg i.p. on days 3, 10 and 17) or paclitaxel

(10 mg/kg x 4 doses over 4 days). Although additive effects were observed, the duration of response was not enhanced with combination treatments. No evidence of synergistic or antagonistic interactions was seen (21).

R-115777 was also found to radiosensitize radioresistant human glioma cell lines (SF763, U87, U251). Treatment with the agent for 48 h prior to irradiation (2 Gy) resulted in a marked reduction in survival after irradiation of 55% for SF763 and U87 and 25% for U251; no effects were seen on the radiosensitive cell line, SF767 (23). Another study using radiosensitive NIH3T3 cells transfected with wild-type RhoB to confer radioresistance showed that treatment with R-115777 reversed the radioprotective phenotype (24).

The resistance mechanisms to R-115777 were examined in an *in vitro* study in which a colon cancer cell line (KM12) was continuously exposed to increasing concentrations of the agent. The result was a subline displaying 12-fold resistance to R-115777. This subline lacked cross-resistance to other anticancer agents such as taxol, etoposide, doxorubicin and cisplatin, to the MEK inhibitor UO-126, to the EGFR tyrosine kinase inhibitor PD-153035, and to the PI_3 kinase inhibitor LY-294002. On the other hand, cross-resistance was observed with the structurally different farnesyl protein inhibitor FTI-227 but not with GGT-1298. The multidrug resistance proteins P-glycoprotein and MRP1 appeared not to be involved in the mechanism of resistance to R-115777 (25, 26).

The *in vivo* efficacy of chronic oral R-115777 (6.25-100 mg/kg b.i.d. for 14-32 days) was demonstrated against several human xenograft nude mice models. The growth of s.c. bladder tumors (T24) was inhibited by 56, 84 and 86% following treatment with 6.25, 12.5 and 25 mg/kg of R-115777, respectively. Higher doses of the agent were needed to inhibit tumor xenografts bearing K-*ras* mutations. For example, doses of 50 and 100 mg/kg for 32 days were required to significantly inhibit LoVo human colon tumors by 68 and 81%, respectively; similar results were obtained with CAPAN-2 pancreatic tumors with 100 mg/kg inhibiting growth by 76%. The agent was also effective against wild-type *ras* tumors such as C32 human melanoma which were inhibited by 48, 76 and 90% with doses of 25, 50 and 100 mg/kg. Interestingly, histological examination of tumors showed differential effects of the agent depending on cell type. Antiangiogenic effects were observed against LoVo colon tumors while antiproliferative effects were detected against CAPAN-2 tumors. In contrast, the agent markedly induced apoptosis against C32 human melanoma tumors (18).

R-115777 treatment (25, 50 and 100 mg/kg p.o. b.i.d. for 10 days) was also effective in mice bearing MCF-7 tumors. On day 24, tumor/control values of 0.61, 0.34 and 0.46 were obtained with the respective doses. In addition, a dose-dependent increase in prelamin A levels was observed in tumors, suggesting that prelamin A may be a marker of R-115777 response (26).

A once daily 5-day dosing schedule with R-115777 (50-200 mg/kg p.o.) was also shown to be effective in mice with T24 H-*ras* transformed NIH3T3 tumors. Results showed significant dose-dependent tumor growth suppression with treatment. At day 21 posttreatment when tumor regrowth was evident, additional R-115777 treatment once again resulted in growth arrest, which indicated that tumor growth had not emerged from resistant cells. This dosing schedule was also effective in mice bearing CAPAN-2 tumors (27).

An *in vivo* study in rats demonstrated that R-115777 (50 or 100 mg/kg/day for 28 days) was effective against methylnitrosourea-induced small palpable mammary tumors of which 56% carried the HaRas mutation. More than 50% of the tumors markedly regressed by more than 80% with treatment while none of the tumors without the HaRas mutation responded to treatment. Regressed tumors from treated animals showed both apoptotic and nonapoptotic cell death. Results suggest that the HaRas mutation may be a marker of R-115777 efficacy (28).

Clinical Studies

The pharmacokinetics and toxicity of R-115777 were investigated in several phase I trials. One phase I trial conducted in 12 patients with refractory solid tumors determined the dose-limiting toxicity (DLT) and optimal dose as well as the pharmacokinetics of R-11577 (60-420 mg/m^2 p.o. b.i.d. for 21 days). Peak plasma levels of the agent were achieved 0.8-3 h postdosing and C_{max} (320 to 2266 ng/ml) and $AUC_{0\text{-}12h}$ (1024 to 11276 ng·h/ml) increased linearly on day 1 over the dose range. Plasma elimination was biphasic with the initial $t_{1/2}$ value about 5 h. Steady state was reached within 2-3 days and was maintained throughout the 21 days of treatment. No drug accumulation was observed. DLTs were observed in 3 of 4 patients given doses of 300 mg/m^2 or greater and in 2 of 8 patients receiving a dose of > 300 mg/m^2. DLTs included grade 3-4 neutropenia and thrombocytopenia (seen by day 14 and lasting for about 7 days) in addition to grade 3 fatigue, grade 3 confusion and grade 3 increases in bilirubin. The maximum tolerated dose (MTD) was concluded to be 240 mg/m^2 b.i.d. One patient with parotid cancer and another with hormone-refractory prostate cancer had stable disease and continued on R-115777 for 6+ months (29). The pharmacokinetic parameters of R-115777 in patients with advanced solid tumors compiled from this study and others are shown in Table II.

The DLTs for R-115777 (50-300 mg b.i.d.) were determined in another phase I study in 18 patients with incurable solid tumors (colorectal, pancreas, non-small cell lung, breast, mesothelioma, extra-ovarian celomic and unknown primary cancer). Plasma C_{max} values were achieved 2-4 h postdosing. Very little drug accumulation was observed. The toxicities observed were grade 3 skin hypersensitivity (1 patient at 150 mg), grade 2 leukocytopenia and lymphocytopenia (DLT in 1 patients at 500 mg), grade 4 febrile neutropenia and grade 3 thrombocytopenia (DLT in 1 patient at 500 mg), grade 3 neutropenia

Table II: Mean pharmacokinetic parameters of R-115777 in patients with advanced solid tumors (Prous Science PKline database).

Dose p.o. (mg)	Day	AUC_{0-12} (μg·h/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	R	Ref.
60 b.i.d. x 21 days[f]	1	1.02	0.32	-	0.8-3.0	5.0[a]	-	29
420 b.i.d. x 21 days[f]	1	11.28	2.27	-	0.8-3.0	5.0[a]		
300 b.i.d. x 28 days	1	3.98	0.88	0.01	3.1	-	-	31
	28	3.42	0.89	0.07	2.3	-	0.9	
50-500 b.i.d.[c]	-	-	-	-	2.0-4.0	-	-	37
25 b.i.d. x 5 days[d]	1	0.47	0.15	-	0.8	5.6[a]	-	32
	6	0.51	0.12	0.01	1.1	12.6	1.1	
50 b.i.d. x 5 days[d]	1	1.01	0.27	-	1.4	5.0[a]	-	
	6	1.11	0.29	0.02	1.4	12.8	1.1	
75 b.i.d. x 5 days[d]	1	1.02	0.26	-	1.1	9.1[a]	-	
	6	1.21	0.27	0.03	2.2	11.5	1.3	
125 b.i.d. x 5 days[d]	1	2.48	0.65	-	1.5	4.4[a]	-	
	6	2.54	0.53	0.08	1.9	20.7	1.1	
200 b.i.d. x 5 days[d]	1	2.62	0.71	-	1.3	4.9[a]	-	
	6	2.94	0.78	0.07	1.5	58.3	1.1	
325 b.i.d. x 5 days[d]	1	8.89	2.05	-	1.8	2.7[a]	-	
	6	7.65	1.55	0.15	1.8	18.0	0.9	
500 b.i.d. x 5 days[e]	1	9.30	1.64	-	3.4	3.8[a]	-	
	6	8.70	1.66	0.18	3.7	31.5	1.0	
800 b.i.d. x 5 days[e]	1	7.13	1.48	-	3.0	5.2[a]	-	
	6	6.95	1.59	0.19	2.8	24.6	0.9	
1300 b.i.d. x 5 days[e]	1	11.97	2.52	-	1.8	7.1[a]	-	
	6	5.94	1.12	0.12	1.6	13.0	0.6	

[a]Initial phase; [b]urinary recovery of unchanged R-115777 < 0.1%; [c]chronic administration; [d]oral solution; [e]pellet capsules; [f]mg/m^2. AUC_{0-12} = area under the plasma concentration-time curve from time zero to 12 h; C_{max} = peak plasma concentration; C_{min} = trough plasma concentration; T_{max} = time to C_{max}; $t_{1/2}$ = half-life; R = accumulation index.

(1 patient at 400 mg), grade 4 neutropenia and fever (DLT in 1 patient at 400 mg). A partial remission with marked clinical improvement for almost 4 months was seen in a patient with platinum refractory non-small cell lung cancer. A patient with metastatic pancreatic cancer had stable disease for 21 weeks and 2 colorectal cancer patients had a 50% reduction in carcinoembryonic antigen levels. *ras* mutations in patient tumors are currently being determined. The recommended dose was 300 mg b.i.d. (30).

A similar phase I, pharmacokinetic trial conducted in 9 patients with advanced solid tumors (colorectal, soft tissue sarcoma, duodenal, gastric, renal and medullary thyroid carcinoma) who had received prior chemotherapy, also reported a recommended dose for R-115777 of 300 mg b.i.d. for 28 days followed by 1-2 weeks of rest. Myelosuppression was concluded to be the DLT. During the trial, patients were administered 200-500 mg p.o. b.i.d. for 28 days, followed by a rest period of 1-2 weeks, for a total of 23 cycles. Only 1 patient out of 6 developed grade 4 neutropenia during the first treatment cycle with 300 mg b.i.d. and other adverse events were infrequent. Nonhematological toxicities observed with treatment were generally mild and not dose-limiting and included fatigue, nausea, vomiting, anorexia and diarrhea. Peak plasma levels of the agent (881 ± 393 ng/ml) were achieved within 1-5 h of dosing and no accumulation was observed over the dosing period. Based on the results from this study and the phase I trial described above (30), this study was prematurely terminated due to the high incidence of grade 3-4 myelosuppression associated with doses of R-115777 higher than 300 mg b.i.d. (31).

Another phase I trial conducted in 27 patients with advanced cancer also determined the MTD, safety and pharmacokinetics of R-11577 (25-850 mg/m^2 solution or 500-1300 mg capsule p.o. b.i.d. for 85 5-day cycles with at least 7 days of rest between cycles). Peak plasma concentrations of the agent were reached at 0.5-4 h postdosing. Elimination was also found to be biphasic, with 5 and 16 h obtained for the two $t_{1/2}$ phases. Steady state was achieved within 2-3 days and only slight drug accumulation was detected. Dose-proportional pharmacokinetics were obtained with doses of 25-325 mg with the oral solution. Urinary excretion of the unchanged compound accounted for less than 0.1% of the oral dose. The DLTs in this study were grade 3 neuropathy seen in 1 patient and grade 2 fatigue observed in 4 of 6 patients treated with 1300 mg b.i.d.; the most common grade 2-3 adverse events were nausea, vomiting, headache, fatigue, anemia and hypotension. Any myelosuppression seen was mild and was infrequent. One patient with metastatic colon cancer and treated with 500 mg b.i.d. had radiographically stable disease for 5 months. The patient had a 46% reduction in carcinoembryonic antigen levels and improvement in cough. The recommended dose for phase II studies was concluded to be 500 mg b.i.d. for 5 consecutive days followed by 9 days of rest (32) (Box 1).

Box 1: Safety and pharmacokinetics of R-115777 in patients with advanced cancer (32) [Prous Science CSline database].

Design	Open, dose-finding clinical study
Population	Patients with advanced cancer (n = 27)
Treatments*	R-115777, 50 mg b.i.d. p.o. (n = 6) R-115777, 75 mg b.i.d. p.o. (n = 8) R-115777, 125 mg b.i.d. p.o. (n = 7) R-115777, 200 mg b.i.d. p.o. (n = 7) R-115777, 325 mg b.i.d. p.o. (n = 7) R-115777, 500 mg b.i.d. p.o. (n = 9) R-115777, 800 mg b.i.d. p.o. (n = 10) R-115777, 1300 mg b.i.d. p.o. (n = 6)
Withdrawals	2/27 (7.4%) [noncompliance 1/27 (3.7%), adverse event 1/27 (3.7%)]
Adverse Events+	R50: nausea 1/6 (16.7%), anemia 1/6 (16.7%), neutropenia 1/16 (16.7%) R75: nausea 2/8 (25.0%), fatigue 2/8 (25.0%), arthralgia 1/8 (12.5%) R125: headache 2/7 (28.6%) R200: vomiting 2/7 (28.6%), hypertension 1/7 (14.3%), nausea 1/7 (14.3%) R325: anemia 1/7 (14.3%) R500: nausea 2/9 (22.2%), fatigue 2/9 (22.2%), myalgia 1/9 (11.1%) R800: vomiting 3/10 (30.0%), fatigue 2/10 (20.0%), hypokalemia 2/10 (20.0%), hypotension 2/10 (20.0%) R1300: fatigue 4/6 (66.7%), hypokalemia 2/6 (33.3%), nausea 1/6 (16.7%), thrombocytopenia 1/6 (16.7%)]
Results	Progression rate @ 6 wks: 17/25 (68.0%) Stable disease rate @ 6 wks: 8/25 (32.0%) Patients continuing drug after cycle 3: 4/25 (16.0%)
Conclusions	The recommended dose of R-115777 was determined to be 500 mg twice daily for 5 days for the treatment of advanced cancer

*Patients were treated for 5 days times 3 cycles, separated by at least 1 wk. +All were grade 2-3.

Other phase I trials examining the feasibility of R-115777 given in combination with other anticancer agents have reported favorable results. A phase I trial conducted in 22 minimally pretreated patients with advanced solid malignancies showed that R-115777 (100, 200 or 300 mg b.i.d.) could be combined with gemcitabine (1000 mg/m^2 i.v. on days 1, 8 and 15 every 4 weeks) without any risk of pharmacokinetic interactions. In this study, participating patients had received 71 courses. Of the 5 patients given 300 mg b.i.d., 2 experienced dose-limiting hematological toxicity which included grade 4 neutropenia for more than 5 days. Other grade 3 adverse events that were not dose-limiting included neutropenia (5 patients), grade 3 thrombocytopenia (3 patients), grade 3 nausea (1 patient) and fatigue (2 patients). Results also showed that treatment successfully inhibited farnesyl protein transferase since 12 of the 16 evaluable patients treated with 100, 200 and 300 mg R-115777 displayed on day 15 mean increases of 7, 25 and 27%, respectively, in the proportion of unfarnesylated chaperone protein HDJ2 expressed in peripheral blood mononuclear cells; these increases corresponded to steady-state mean trough concentrations of 58, 34 and 65 ng/ml, respectively. The recommended doses for combination treatment in phase II trials were 200 mg b.i.d. R-115777 and 1000 mg/m^2/week gemcitabine (33) (Box 2).

An ongoing phase I trial in 6 previously treated patients with advanced colorectal or pancreatic cancer is evaluating combination treatment including R-115777 (200-500 mg b.i.d. starting on day 4) and 5-FU (400 mg/m^2 i.v. bolus followed by 600 mg/m^2 over 22 h on days 1 and 2) plus leucovorin (200 mg/m^2/2 h). So far, 2 patients have developed DLT of grade 4 hematological toxicity at 500 mg b.i.d. and the main toxicity observed in all patients was myelosuppression. Pharmacokinetic analysis is ongoing (34).

Another ongoing phase I trial is assessing combination treatment with R-115777 (100-300 mg p.o. b.i.d.) plus capecitabine (2000-2500 mg/m^2/day p.o.) for 14 days every 3 weeks. The study includes 12 patients with advanced cancer who have received 29 courses. Hematologic toxicities seen were grade 1/2 neutropenia (in 4 courses) and grade 3 neutropenia (in 1 course) and nonhematologic toxicities included mild to moderate nausea (11 courses), vomiting (4 courses), diarrhea (6 courses), fatigue (13 courses) and grade 1/2 (in 14 courses) and 3 (in course 2) hand-foot syndrome. A patient with melanoma has had stable disease for more than 6 courses and a patient with colon cancer had a minor response. Accrual to 300 mg and pharmacokinetic analysis are ongoing (35) (Box 3).

Results have also been reported from two phase II trials. The first trial involved 39 patients with advanced

Box 2: Inhibition of farnesyl protein transferase with R-115777 and gemcitabine combination treatment in patients with advanced solid malignancies (33) [Prous Science CSline database].

Design	Open, dose-finding clinical study
Population	Patients with minimally pretreated cancer (n = 22)
Treatments	R-115777, 100 mg p.o. b.i.d. + Gemcitabine, 1000 mg/m^2 i.v. on d 1, 8 and 15 q4 wks R-115777, 200 mg p.o. b.i.d. + Gemcitabine, 1000 mg/m^2 i.v. on d 1, 8 and 15 q4 wks R-115777, 300 mg p.o. b.i.d. + Gemcitabine, 1000 mg/m^2 i.v. on d 1, 8 and 15 q4 wks
Results	Unfarnesylated protein increase rate: 12/16 (75%) Median increase (%) in unfarnesylated protein HDJ2 @ d 15: R300 (27) ≥ R200 (25) > R100 (7)
Conclusions	R-115777 at clinically relevant doses in combination with gemcitabine inhibited farnesyl protein transferase

Box 3: Combination treatment with R-115777 and capecitabine in patients with advanced cancer (35) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with advanced solid malignancies (n = 12)
Treatments	Capecitabine, 2000-2500 mg/m^2/d + R-115777, 100-300 mg p.o. b.i.d. x 14 d q3 wks
Adverse Events	Grade 1-2 hand-foot syndrome 14/29 courses (48.3%), fatigue 13/29 courses (44.8%), mild to moderate nausea 11/29 courses (37.9%), diarrhea 6/29 courses (20.7%), neutropenia 4/29 courses (13.8%), vomiting 4/29 courses (13.8%)
Results	Minor response rate: 1/12 (8.3%) Stable disease rate: 1/12 (8.3%)
Conclusions	R-115777 was relatively well tolerated in combination with capecitabine

Box 4: Clinical activity with R-115777 in patients with advanced breast cancer (36) [Prous Science CSline database].

Design	Open clinical study
Population	Patients with advanced breast cancer unresponsive to second-line hormonal therapy and/or 1 chemotherapy regimen (n = 39)
Treatments	R-115777
Adverse Events	Grade 3-4 neutropenia 16/39 (41.0%), grade 2-3 paresthesia 12/39 (30.8%)
Results	Partial response rate: 4/39 (10.3%) Median response duration (mo): 7 Stable disease rate @ 3 mo: 10/39 (25.7%); @ 6 mo: 3/39 (7.7%)
Conclusions	R-115777 showed clinical activity in advanced breast cancer

breast cancer (17 ER+ve, 12 ER-ve, 10 ER unknown, 14 HER2+ve, 10 HER2-ve and 15 unknown) treated with continuous, twice-daily oral R-115777. Patients had previously been treated with second-line hormonal therapy (64%) and/or 1 chemotherapy regimen (46%). Treatment was well tolerated. Myelosuppression was the toxicity most frequently seen and 42% of the patients given 4300 mg b.i.d. developed grade 3/4 neutropenia over a median of 32 days of treatment. After 8 weeks of therapy, 31% of the patients developed grade 2/3 parathesia/numbness. Confirmed partial responses of a mean duration of 7 months (range = 5-9+ months were seen in 4 patients. At 3 months, 10 other patients had stable disease, 3 of whom were stable for > 6 months. The relationship between treatment response and tumor phenotype continues to be under investigation (36) (Box 4).

R-115777 is currently involved in several phase I and II trials including a phase I trial in patients with advanced hematologic malignancies, a phase I/II study in patients with recurrent malignant glioma (glioblastoma multiforme, anaplastic astrocytoma) and a phase II pilot study in patients with superficial bladder cancer. A phase I trial in patients with advanced or metastatic adenocarcinoma is investigating combination treatment with R-115777 and

trastuzumab (Herceptin™). R-115777 is also undergoing phase III clinical trials for the treatment of pancreatic and other cancers (38).

Manufacturer

Janssen Pharmaceutica NV (BE).

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