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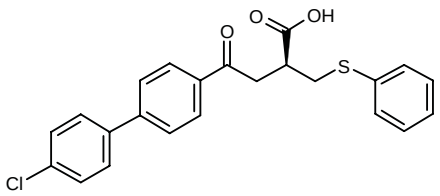
Bay-12-9566

Oncolytic
Antiarthritic
Matrix Metalloproteinase Inhibitor

4-(4'-Chlorobiphenyl-4-yl)-4-oxo-2(*S*)-(phenylsulfanylmethyl)butyric acid



$C_{23}H_{19}ClO_3S$ Mol wt: 410.9191

CAS: 179545-77-8
CAS: 179545-76-7 (as undefined isomer)

EN: 238610

Synthesis

The Friedel-Crafts condensation of 4-chlorobiphenyl (I) with 3-methylenetetrahydrofuran-2,5-dione (II) by means of $AlCl_3$ in tetrachloroethane gives 4-(4'-chlorobiphenyl-4-yl)-2-methylene-4-oxobutyric acid (III), which is treated with thiophenol (IV) and K_2CO_3 in DMF/water, yielding racemic 4-(4'-chlorobiphenyl-4-yl)-4-oxo-2-(phenylsulfanylmethyl)butyric acid (V). Finally, racemic (V) is resolved by means of crystallization with (+)-cinchonine in acetone (1). Scheme 1.

Description

$[\alpha]_D$ +84.8° (c 1.5, acetone); racemic, m.p. 125-6 °C.

Introduction

Matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes that catalyze the hydrolysis of several proteinaceous components of the extracellular matrix (2). There are currently 18 distinct MMPs functionally categorized in three groups according to their substrate target. The three groups include collagenases, stromelysins and gelatinases, which degrade fibrillar collagen, proteoglycans and glycoproteins and denatured and basement membrane collagens, respectively. Collagenase type 1 (interstitial collagenase; MMP-1), stromelysin-1 (MMP-3), matrilysin (MMP-7) and gelatinase-A and -B (MMP-2 and -9) are members of the MMP family. MMPs have been implicated in several clinical conditions including arthritis, tumor growth and metastasis, periodontal disease and multiple sclerosis. Thus, inhibition of MMPs has significant clinical implications (3-6).

MMP inhibitors have been rapidly developed over the past 5 years. Clinical studies have reported the efficacy of marimastat (British Biotech), the most extensively studied MMP inhibitor, as a potential therapy for pancreatic cancer (7, 8). Several MMP inhibitors in addition to marimastat have been reported and are in the early stages of clinical trials for various indications (Table I). Hydroxamic acid-based inhibitors, including Ro-32-3555 (Roche), ilomastat (Sankyo; licensed from Glycomed), D-2163 (Chirosci-ence/Bristol-Myers Squibb) and CGS-27023A (Novartis), are relatively nonspecific and can inhibit other enzymes. However, more selective inhibitors such as AG-3340 (Agouron) and the nonhydroxamic butanoic acid analog Bay-12-9566, have also been described. Bay-12-9566 inhibits MMP-2, which is implicated in the progression and metastasis of several solid tumors, without modifying MMP-1 activity.

Pharmacological Actions

Bay-12-9566 is a potent and selective inhibitor of MMPs *in vitro*, with K_i values of 11, 301, 134 nM and > 5000 nM against recombinant MMP-2, MMP-9, MMP-3 and MMP-1, respectively (Table II). Bay-12-9566 at μM concentrations was found to inhibit HT1080 tumor cell invasion through a layer of reconstituted basement membrane (Matrigel) by 38-66% (9). Moreover,

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Scheme 1: Synthesis of Bay-12-9566

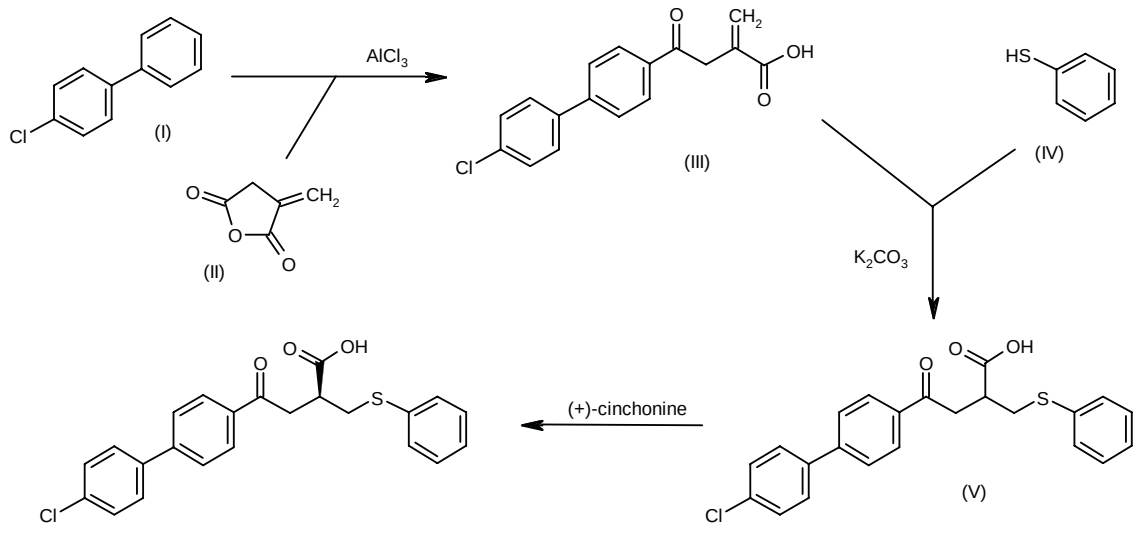


Table I: Matrix metalloproteinase inhibitors in clinical trials (from Prous Science Ensemble database).

Anticancer agents

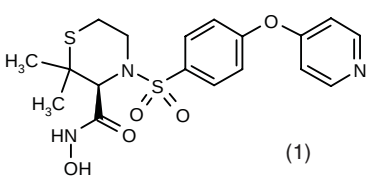
1. AG-3340
   Agouron (phase III)
2. Bay-12-9566[+]
   Bayer (phase III)
3. CGS-27023A
   Novartis (phase I)
4. D-2163[*]
   Chiroscience; Bristol-Myers Squibb (phase I)
5. Marimastat
   British Biotech (phase III)

Antiarthritic agents

6. Ro-32-3555
   Roche (phase I)

Agents for ocular disorders

7. Ilomastat
   Sankyo; licensed from Glycomed (phase II)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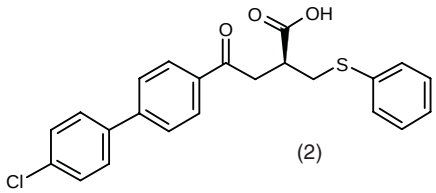
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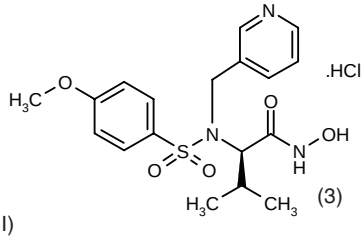
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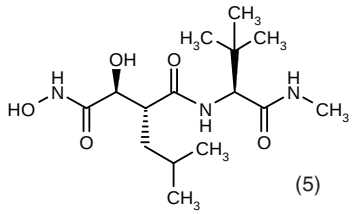
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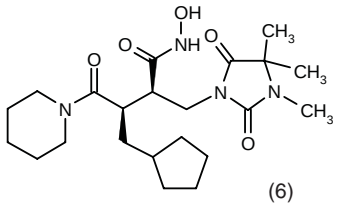
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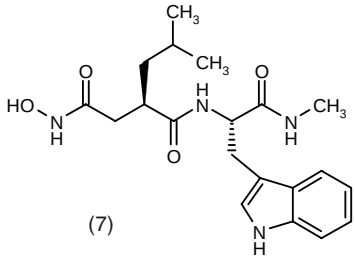
(7)

*Structure not yet detected. [+]Also under development for osteoarthritis.

Bay-12-9566 dose-dependently suppressed the invasion of human umbilical vein endothelial cells (HUVEC) through Matrigel (IC_{50} = 0.91 μM) without affecting HUVEC motility, a process which does not involve matrix degradation (10).

Bay-12-9566 was shown to have antiangiogenic activity *in vivo* using the subcutaneous Matrigel pellet assay, in which angiogenesis is induced by basic fibroblast growth factor (bFGF) mixed with Matrigel and injected s.c. into mice. Mice treated with 50-200 mg/kg p.o.

Table II: Matrix metalloproteinase (MMP) inhibitory activity on MMP subtypes of selected compounds under clinical development (from Prous Science MFLine database).

Compound	MMP subtype	Parameter	Value (nM)	Refs.
AG-3340	MMP-1	IC_{50}	8.3	30
	MMP-2	IC_{50}	0.05	30
	MMP-3	IC_{50}	0.03	30
	MMP-7	IC_{50}	54.0	30
	MMP-9	IC_{50}	0.26	30
Batimastat	MMP-1	IC_{50}	3.0	31
	MMP-2	IC_{50}	2.0-4.0	30, 31
	MMP-3	IC_{50}	20.0	31
	MMP-7	IC_{50}	6.0	30
	MMP-9	IC_{50}	4.0	30
Bay-12-9566	MMP-1	IC_{50}	>5000	30
	MMP-2	IC_{50}	11.0	30
	MMP-3	IC_{50}	134	30
	MMP-9	IC_{50}	301	30
CGS-27023A	MMP-1	K_i	10.0-33.0	32, 33
	MMP-1	IC_{50}	33.0	34
	MMP-2	IC_{50}	7.0	34
	MMP-2	K_i	20.0	32
	MMP-2	K_i	10.0	33
	MMP-3	IC_{50}	13.0	34
	MMP-3	K_i	10.0-43.0	32, 33
	MMP-9	K_i	8.0	32
Marimastat	MMP-1	IC_{50}	5.0	35
	MMP-2	IC_{50}	6.0	35
	MMP-3	IC_{50}	200-230	30, 35
	MMP-7	IC_{50}	16	35
	MMP-9	IC_{50}	3.0	35
Ro-32-3555	MMP-1	IC_{50}	7.0	36
	MMP-1	K_i	3.0	37
	MMP-2	K_i	154	37
	MMP-8	K_i	4.4	37
	MMP-9	IC_{50}	59.0	36
	MMP-9	K_i	59.1	37
	MMP-10	IC_{50}	527	36
	MMP-10	K_i	527	37
	MMP-13	K_i	3.4	37
Ilomastat	MMP-1	K_i	0.4	38
	MMP-2	K_i	0.5	38
	MMP-3	K_i	27.0	38
	MMP-8	K_i	0.1	38
	MMP-9	K_i	0.2	38

MMP subtypes: interstitial collagenase (MMP-1); gelatinase A (MMP-2); stromelysin-1 (MMP-3); matrilysin (MMP-7); neutrophil collagenase (MMP-8); gelatinase B (MMP-9); stromelysin-2 (MMP-10); collagenase (MMP-13).

Bay-12-9566 beginning on day 1 for 4-7 days exhibited a 40% reduction in hemorrhage surrounding the pellets and a 66% decrease in hemoglobin content. In addition, the number of vessels in the pellet was significantly decreased (9, 10).

The effects of Bay-12-9566 were evaluated *in vivo* using B16 murine melanoma and Lewis lung carcinoma (LLC) metastatic tumor models. Subcutaneous B16 melanoma and LCC tumor growth were inhibited by 50% in mice administered Bay-12-9566 (100 mg/kg p.o.) from days 1-14 and days 3-20 of tumor implantation, respectively. Lung colony formation was inhibited by 58% and the number of colonies > 2 mm^3 in size was reduced by 80% in animals treated with Bay-12-9566 beginning 1 day prior to and continuing through 2 days after i.v. tail injections of B16.F10 tumor cells; when the treatment period was increased to 14 days, colony formation was inhibited by 80% and the number of colonies > 2 mm^3 was further reduced by 87%. Treatment with the agent also reduced the number of metastatic LCC colonies originating from a primary lung tumor which were > 3 mm^3 by 85, 90 and 50% in animals administered 50, 100 or 200 mg/kg p.o. Bay-12-9566, respectively (11, 12).

Bay-12-9566 was also effective in inhibiting spontaneous metastasis in an orthotopic model in which fragments of serially passaged human colon carcinoma tumors (HT116) were implanted s.c. in CD1 nude mice administered the compound (10, 30, 100 or 300 mg/kg/day p.o.) from day 2 after implantation through day 44. The mitotic index was qualitatively reduced in all treated groups as compared to controls. Tumor growth was inhibited by 40% in animals treated with 30 g/kg Bay-12-9566, and a 60% reduction in the incidence of tumor invasion was observed with a dose of 100 mg/kg. Bay-12-9566 was also effective in another orthotopic model in which 2 x 2 mm^3 fragments of HT116 tumors were sutured onto the cecal serosa of SCID mice; mice were administered Bay-12-9566 (25, 50, 100 or 200 mg/kg/day p.o.) from day 5 after surgery until day 28. Treatment with 100 mg/kg inhibited tumor growth by 35% and a dose-dependent reduction in overall incidence of hematogenous, lymphatic and intraperitoneal metastases was observed; a maximum reduction of 50% was observed with 100 mg/kg. Hepatic and pancreatic metastases were also reduced by 60 and 46%, respectively, in animals treated with 100 mg/kg; observed metastases were < 0.5 mm in diameter, as compared to 0.5-3 mm colonies observed in control animals (13, 14).

Similarly, Bay-12-9566 was effective in the orthotopic model of human breast cancer in athymic mice. MDA-MB-435 cells were injected into mice mammary fat pads and tumors were resected after 8 weeks. Mice were then treated with the vehicle or Bay-12-9566 (100 mg/kg p.o.) daily for 7 weeks. A 51% inhibition in tumor regrowth and a 57% reduction in the number of metastases were observed in treated mice as compared to controls and the average number of pulmonary metastases in treated mice was reduced by 88%. No serious toxic effects were observed and Bay-12-9566 did not suppress proliferation of MDA-MB-435 cells *in vitro* (15).

Bay-12-9566 has also been shown to inhibit the progression of osteoarthritis and rheumatoid arthritis in dog and guinea pig models. Macroscopic tibial lesion surface area was reduced by 62, 60 and 63% in dogs administered 1, 3 and 10 mg/kg/day p.o. Bay-12-9566, respectively. Moreover, cartilage destruction was reduced and the mean length and width of tibial cartilage lesions was

decreased by 54, 52 and 72% in animals treated with the above respective doses. Bay-12-9566 (15 mg/kg/day p.o.) treatment for 2 weeks similarly inhibited cartilage lesion development in the guinea pig (16).

Toxicity

The safety of Bay-12-9566 was evaluated in a preclinical study utilizing the Ames test, an *in vitro* mammalian chromosome aberration test, the HGPRT forward mutation assay and the mouse micronucleus test, with results showing that the compound did not induce mutagenic or clastogenic effects. It was also shown not to interfere with pulmonary, renal or central nervous system function, intestinal motility, ileal and cardiac contractility or hemodynamics. Toxicity studies using rats (up to 400 mg/kg), mice (> 800 mg/kg) and dogs (up to 300 mg/kg) revealed that the primary targets were the erythron, rodent kidney and liver. Rats displayed adaptive hepatocellular hypertrophy, and elevations in transaminases wereobserved only in dogs. Reductions in red blood cell counts, hemoglobin and hematocrit were only observed at the high doses. Tendinitis was not a factor after chronic administration and fertility was unaffected (17).

Pharmacokinetics

The pharmacokinetics of Bay-12-9566 were evaluated in a total of 73 healthy middle aged and elderly subjects administered 10-400 mg/day of the drug for 16-28 days. The agent was well tolerated with a half-life of approximately 90 h. The pharmacokinetics were found to be less than dose-proportional, suggesting that saturation rather than metabolism or excretion occurs at high doses (18). Further studies in which elderly males and females and young males were administered a single dose of Bay-12-9566 (50 mg) showed that the pharmacokinetics of the agent were not influenced by age or gender (19).

Bay-12-9566 was found to have good penetration into synovial fluid. Eight patients with osteoarthritis requiring knee infusions were administered Bay-12-9566 (10 or 25 mg/day) for 15 days and the synovial fluid/plasma concentration ratio ranged from 58-87% and 42-56% with doses of 10 and 25 mg, respectively (19).

The pharmacokinetics of Bay-12-9566 were determined to be similar in both healthy subjects and cancer patients in a study in which 73 healthy subjects and 63 cancer patients were treated with 100-400 mg/day, 400 mg b.i.d or t.i.d. or 800 mg b.i.d. The mean C_{max} and the steady-state AUC(0-24) at a dose of 100 mg/day were 54.1 mg/l and 1101 mg.h/l, respectively, for healthy subjects as compared to 49.9 mg/l and 1061 mg.h/l, respectively, for cancer patients (20).

The pharmacokinetics obtained from a phase I dose-escalation study involving cancer patients were not dose-dependent, further suggesting that there is saturation of absorption of the agent rather than induction of metabolism. When dose splitting was performed in order to improve drug delivery, the respective steady-state $AUC_{(0-24)s}$ at 100 and 400 mg/day, 400 mg b.i.d. or t.i.d. and 800 mg b.i.d. were 1161, 1411, 2300, 3035 and 3135 mg.h/l (21).

The maximum tolerated dose and maximum attainable drug level (MADL) for Bay-12-9566 were determined in a phase I study in which 29 patients with colorectal, ovarian, breast, renal or sarcoma tumors were administered the compound beginning at 100 mg/day p.o., followed by doubling up to 800 mg/day. Patients were subsequently accrued to 7 dose levels (100, 200 or 400 mg/day, 400 or 800 mg b.i.d. or 400 mg t.i.d. or q.i.d.). Bay-12-9566 was well tolerated with saturation of absorption occurring at doses > 400 mg/day. Side effects included mild and reversible increases in transaminases and thrombocytopenia; 2 patients experienced grade 3 increases in transaminases and 2 others displayed grade 1 granulocytopenia. A total daily dose of 1600 mg/day b.i.d. or q.i.d. was determined to be the MADL and the dose comparable to efficacious doses used in preclinical studies (22, 23).

The safety and effect of Bay-12-9566 on surrogate markers were evaluated in a phase I study in 11 patients with solid tumors refractory to standard therapy. Patients were administered oral doses of 400 once daily, 400 b.i.d. or t.i.d. or 800 b.i.d. The only toxicities were grade 1 and included dizziness (1), headache (2), abdominal pain (2), nausea (2) and flu symptoms (1). The median percent changes from baseline in plasma vascular endothelial growth factor (3.78%), urinary pyridinoline crosslink (–12.7%) and deoxypyridinoline crosslink (–5.0%) demonstrated that the compound had no effect on these surrogate markers (24).

A phase I study examined the pharmacokinetics of Bay-12-9566 after prolonged administration to 21 patients with solid malignancies. Patients received 100 mg/day for 4 courses (1 course = 28 days), 400 mg/day for 8 courses, 400 mg b.i.d. for 12 course, 400 mg t.i.d. for 13 courses, 400 mg q.i.d. for 5 courses or 800 mg b.i.d. for 5 courses. Tmax ranged from 4-8 h and increases in C_{ss} were less than dose-proportional. The dosing schedules were determined to be well tolerated with side effects including grade 3 hyperbilirubinemia, grade 2 thrombocytopenia and grade 3 chronic nausea, which required dose reductions in patients receiving the 400 mg t.i.d. and q.i.d. doses (25, 26).

In another phase I trial in which 90 patients with advanced solid tumors were administered Bay-12-9566 at doses of 100-400 mg/day or up to 1600 mg/day in split dosing for 4-5 weeks, low clearances rates of 4-6 ml/min were found with a terminal half-life of 4-5 days. Dose-dependent protein binding was very high and increases in C_{ss} were less than dose-proportional, with 42 and 85 mg/l observed at 100 and 400 mg, respectively (27).

Clinical Studies

Treatment with Bay-12-9566 was found to be well tolerated in a phase I trial in which 90 patients with

Box 1: Tolerability of Bay-12-9566 in patients with advanced solid tumors (27, 28) [from Prous Science CSLine database].

Study Design	Phase I clinical trial
Study Population	Patients with advanced solid tumors (n = 90)
Intervention Groups	Bay-12-9566, 100-400 mg q.d. up to 1600 mg/day p.o. in divided doses x 4/5 weeks. Subsequent patients took medication continuously until disease progression or toxicity
Adverse Events	Mild to moderate thrombocytopenia (2 patients), liver injury test elevations (2 patients), exacerbation of low back pain (1 patient)
Results	Median time to progression was 4 months; 11 patients had stable disease for > 4 months and 3 patients for > 7 months
Conclusions	Treatment with Bay-12-9566 was well tolerated and appears to be a promising compound for the treatment of cancer

advanced solid phase tumors were treated with 100-400 mg/q.d. up to 1600 mg/day in split dosing schedules; treatment continued until disease progression or toxicity. No musculoskeletal events were observed except in 1 patient who experienced exacerbated lower back pain. The median time to progression was 4 months; 11 patients had stable disease for more than 4 months, and 3 had stable disease for more than 7 months. Mild to moderate thrombocytopenia and liver injury were observed in 2 patients (27, 28) (Box 1).

Phase II and III trials with Bay-12-9566 are ongoing in which the agent is being evaluated as a single therapy (800 mg b.i.d. p.o.) or in combination with the cytotoxic compounds doxorubicin (every 3 weeks) or flurouracil (5 day bolus with low doses of leucovorin) (25). In addition, phase III randomized, placebo-controlled studies evaluating Bay-12-9566 as a single agent have been initiated in patients with small cell lung, Stage IIIA and IIIB non-small cell lung, advanced pancreatic and ovarian cancers (29, 30).

Furthermore, based on positive findings in animal models of osteoarthritis, clinical studies are now under way evaluating the compound's ability to slow structural deterioration and disease progression in patients with osteoarthritis (16).

Manufacturer

Bayer AG (DE).

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