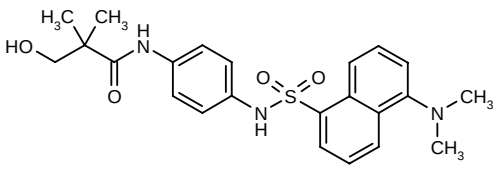
Drugs of the Future 1999, 24(12): 1297-1300

CCC: 0377-8282/99

Bay-38-4766

Anti-Cytomegalovirus Drug

N-[4-[5-(Dimethylamino)-1-naphthylsulfonamido]phenyl]-3-hydroxy-2,2-dimethylpropionamide



$C_{23}H_{27}N_3O_4S$ Mol wt: 441.5493

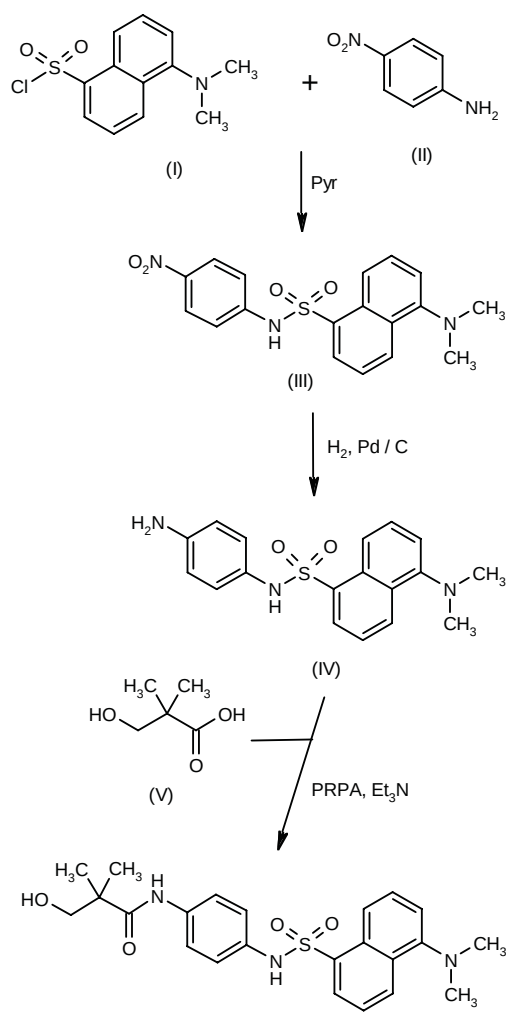
CAS: 233254-24-5

EN: 279333

Synthesis

The reaction of 5-(dimethylamino)naphthalene-1-sulfonyl chloride (I) with 4-nitroaniline (II) in pyridine gives the corresponding sulfonamide (III), which is reduced at the nitro group with hydrogen over Pd/C in ethanol, yielding the expected amine (IV). Finally, this compound is condensed with 3-hydroxy-2,2-dimethylpropionic acid (V) by means of propylphosphonic anhydride (PRPA) and triethylamine in dichloromethane/ethyl acetate (1, 2). Scheme 1.

Scheme 1: Synthesis of Bay-38-4766



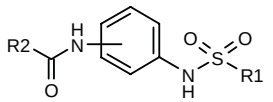
Introduction

Human cytomegalovirus (HCMV), a member of the herpes virus family, is commonly found in the general population and remains latent in individuals with fully intact immune systems, manifested by the presence of IgG antibodies to HCMV. In individuals with impaired immune systems due to conditions such as AIDS or following cancer therapy or organ transplantation, reactivation of HCMV infection can cause HCMV retinitis, a serious and debilitating intraocular infection which results in the gradual destruction of the retina and loss of vision.

The primary goal in the treatment of HCMV is to control the risk of disease extension into the macula or optic nerve, thus decreasing the risk of profound vision loss. Pharmacological treatment does not eradicate HCMV infection.

There are 5 approved DNA polymerase inhibitors for the treatment of HCMV retinitis: ganciclovir (Cytovene®/Cymevene®; Roche), foscarnet (Foscavir®; AstraZeneca), cidofovir (Vistide®; Pharmacia & Upjohn) and the ganciclovir ophthalmic implant (Vitrasert®; Chiron and Roche). A new DNA polymerase inhibitor, valganciclovir hydro-

L.A. Sorbera, P.A. Leeson, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.



[I]

chloride (Cymeval®; Roche) is undergoing phase III clinical trials. The antisense phosphorothioate oligodeoxynucleotide, fomivirsen (Vitravene®; Isis and Ciba Vision), was launched in 1998 for the treatment of HCMV retinitis.

New compounds with novel mechanisms of action are being developed for the treatment of HCMV retinitis. Two inhibitors of DNA cleavage, Bay-38-4766 and its active metabolite Bay-43-9695, are being developed by Bayer and are in phase II and I clinical trials, respectively. Glaxo Wellcome's maribavir, an inhibitor of viral DNA synthesis via processing of a DNA replicative intermediate, is in phase II clinical evaluation. According to recently published findings, combination therapy with oral anti-HIV drugs or highly active antiretroviral therapy appears to rejuvenate the immune system of individuals with AIDS and prevent progression of HCMV retinitis (3).

The chemical structures of anti-HCMV drugs launched and under development are shown in Table I.

During the search for anti-HCMV drugs with new mechanisms of action, scientists at Bayer synthesized a series of nonnucleoside compounds of the general formula [I] which were screened for antiviral activity in a cell-based viral replication assay. Structure-activity relationships of these compounds and their characterization in murine CMV-infected SCID mice led to the selection of Bay-38-4766 from 2000 related compounds as a development candidate for the treatment of HCMV disease in immunocompromised patients (2).

Antiviral Activity

Bay-38-4766 is a novel, highly effective nonnucleoside inhibitor of HCMV representing a new chemical class of anti-HCMV drugs which inhibit viral DNA cleavage.

As shown in Table II, the antiviral activity of Bay-38-4766 in cell culture is comparable to or better than that of marketed drugs. Bay-38-4766 has also been reported to be active against ganciclovir-resistant clinical isolates *in vitro* and showed no cross-resistance to marketed drugs, indicating a unique mechanism of action (4). Results from kinetic studies showed that Bay-38-4766 had no effect on the biosynthesis of viral structural proteins or on the formation of subviral particles. However, the agent was found to inhibit a late stage of CMV replication, indicating that viral maturation may be affected. Further analysis revealed that Bay-38-4766 blocked the cleavage of polygenomic concatemeric viral DNA and thereby packaging of unit genome length molecules which results in suppression of propagation and spread of CMV (5).

Pharmacokinetics and Metabolism

Pharmacokinetic analysis of the agent showed 75% and 64% gastrointestinal absorption of [^{14}C]-Bay-38-4766 in rats and dogs, respectively; an absolute bioavailability of 30-50% was obtained. Moderate absolute bioavailability (up to 50%) was observed in mice, rats and dogs after administration of the unlabeled compound. Following oral or i.v. administration, plasma pharmacokinetics were linear in rats while a moderate over-proportional increase in AUC values was observed in dogs. Elimination half-lives ($t_{1/2}$) were rapid (about 1 h) and total plasma clearance was moderate (1/kg·h) in both rats and dogs. High levels of protein binding were found for the agent (fraction unbound = 1% in rats and 2.5% in dogs) and a homogeneous distribution to organs and tissue was observed after both oral and i.v. administration. The major route of excretion was predominantly in bile and feces in rats and dogs. The elimination half-life in NMRI mice was 1.4 h as compared to 0.5 h in SCID mice, although other pharmacokinetics from the two types of mice were similar, including low clearance (0.52 and 0.73 l/kg·h, respectively) and V_{ss} (0.4 l/kg) values (6).

In humans, the maximum plasma C_{max} values (from 0.33 to 4.2 mg/l) were seen at 0.5-5 h following administration of doses of 100-2000 mg; C_{max} values decreased 10-15 h after peak with dominant and terminal half-lives of 3-5 and 12-16 h, respectively. Similar pharmacokinetic parameters were observed for M-1, the major metabolite of Bay-38-4766 (7).

Results from a study examining the *in vivo* biotransformation of oral and intraduodenal [^{14}C]-Bay-38-4766 (3 mg/kg) in rats and dogs reported that the two major pathways of metabolism were demethylation at the dimethylamino group of the dansyl moiety and oxidation of the alcohol group resulting in carboxylic acid derivatives. At 0-7 h, < 5% and about 65% of the dose was recovered in urine and bile, respectively. The major compounds found in plasma of both animals were the unchanged compound and the *N*-monodesmethyl derivative (M-1). In rat urine, the *N*-monodesmethyl carboxylic acid derivative (M-2), the *N*-bisdesmethyl derivative (M-3) and its corresponding carboxylic acid (M-4) were detected with only trace amounts of the unchanged compound observed. In dog urine, M-2, M-3 and the carboxylic derivative (M-5) were the major metabolites detected with only small amounts of the unchanged compound identified. The main metabolites found in bile were M-2, M-3 and M-4 in rat and M-2 and M-5 in dog (8).

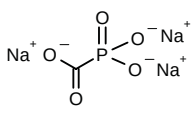
Clinical Studies

A randomized, double-blind, placebo-controlled comparative study in healthy males demonstrated the safety and tolerability of oral single-dose Bay-38-4766 (100, 250, 500, 1000 and 2000 mg). No drug-related adverse events or clinically significant changes in heart rate, blood pressure, ECG or laboratory parameters were reported (7).

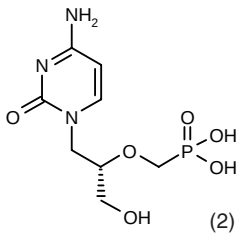
Bay-38-4766 is currently in pilot phase II trials (9).

Table I: Anti-CMV drugs launched and under development (Prous Science Ensemble database).

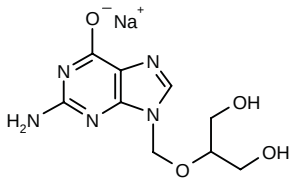
Drug	Manufacturer	Mechanism of action	Route of administration	Status
1. Foscarnet sodium (Foscavir®)	AstraZeneca	CMV DNA polymerase inhibitor	Intravenous	Launched 1989
2. Cidofovir (Vistide®)	Pharmacia & Upjohn	CMV DNA polymerase inhibitor	Intravenous	Launched 1996
3. Ganciclovir sodium (Cymevene®, Cytovene®)	Roche	CMV DNA polymerase inhibitor	Intravenous	Launched 1988
4. Ganciclovir (Cytovene®, Cymevene®)	Roche	CMV DNA polymerase inhibitor	Oral	Launched 1996
5. Ganciclovir sodium (Vitrasert®)	Chiron/Roche	CMV DNA polymerase inhibitor	Ophthalmic implant	Launched 1996
6. Fomivirsen sodium (Vitravene®)	Isis/Ciba Vision	Antisense phosphorothioate oligodeoxynucleotide	Intravitreal injection	Launched 1998
7. Valganciclovir HCl (Cymeval®)	Roche	CMV DNA polymerase inhibitor	Oral	Phase III
8. Maribavir	Glaxo Wellcome	Inhibitor of viral DNA synthesis via processing a DNA replicative intermediate	Oral	Phase II
9. Bay-38-4766	Bayer	Inhibitor of DNA cleavage	Oral	Phase II
10. Bay-43-9695	Bayer	Inhibitor of DNA cleavage	Oral	Phase I
11. ODG-PFA-OMe[1]	Univ. California	DNA polymerase inhibitor	Intravitreal injection	Preclinical
12. RPR-111423	Aventis	Blocker of the initial transcription phase of viral replication at the level of immediate-early proteins	–	Preclinical



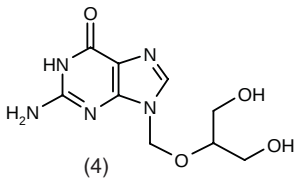
(1)



(2)



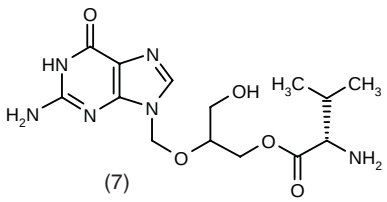
(3) (5)



(4)

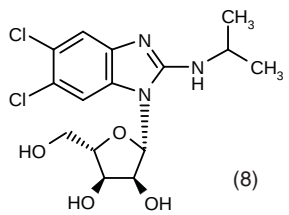
d(*P*-thio)(G-C-G-T-T-T-T-G-C-T-C-T-T-C-T-T-C-T-T-G-C-G)deoxyribonucleic acid eicosa sodium salt

(6)

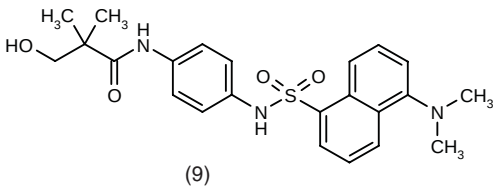


(7)

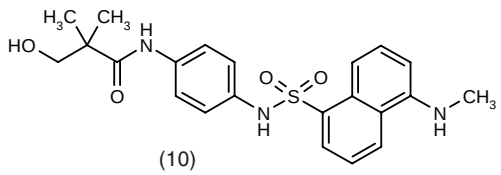
.HCl



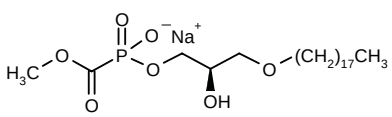
(8)



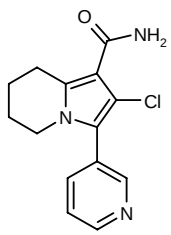
(9)



(10)



(11)



(12)

[1]Long-acting lipid derivative of foscarnet.

Table II: Anti-CMV activity and cytotoxicity of Bay-38-4766 and reference drugs (Prous Science MFLine database).

Drug	IC_{50} (μM) HCMV	MCMV	CC_{50} (μM)	Ref.
Aciclovir	64.2	2.0	719	10-13
Adefovir	117	–	>100	11, 14
Bay-38-4766	1.17	0.049	93	4
Bay-43-9695[a]	0.50	0.033	125	4
Benzimidavir	0.13	28.5	98	4
Cidofovir	0.25	0.25	>250	4, 15
Fomivirsen	0.30	–	300-500	16
Foscavir	80.0	200	>250	4
Ganciclovir	4.60	20.5	>250	4, 12, 15
Lobucavir	4.50	1.30	235	4, 12
Penciclovir	178	–	888	10
QYL-769	2.40	0.37	327	17
RPR-111423	0.005	–	72.4	15
Synadenol	1.30	2.10	>460	17
Synguanol	1.20	0.30	>429	17
TTPR	2.80	–	>22.3	18

[a]One of the most active metabolites of Bay-38-4766. HCMV = human cytomegalovirus; MCMV = murine cytomegalovirus.

Manufacturer

Bayer AG (DE).

References

1. Bender, W., Reefschlaeger, J., Eckenberg, P., Goldmann, S., Haerter, M., Hallenberger, S., Trappe, J., Weber, O. (Bayer AG). *Novel naphthyl-substd. and anilide-substd. sulfonamides.* WO 9937609.

2. Eckenberg, P., Reefschlaeger, J., Bender, W., Goldmann, S., Haerter, M., Hallenberger, S., Trappe, J., Weber, O. *Structure-activity relationships of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F940.

3. Whitcup, S.M., Fortin, E., Lindblad, A.S. et al. *Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis.* JAMA - J Am Med Assoc 1999, 282: 1633-7.

4. Reefschlaeger, J., Bender, W., Eckenberg, P., Goldmann, S., Haerter, M., Hallenberger, S., Paessens, A., Trappe, J., Weber, O. *Antiviral activity and selectivity of BAY 38-4766 - A novel non-nucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F942.

5. Hallenberger, S., Trappe, J., Buerger, I., Bender, W., Eckenberg, P., Goldmann, S., Haerter, M., Reefschlaeger, J., Weber, O. *Mechanism of antiviral action of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F941.

6. Kern, A., Blombach, M. *In vivo metabolism in rat and dog of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F943.

7. Nagelschmitz, J., Möller, J.G., Stass, H.H., Wandel, C., Kuhlmann, J. *Safety, tolerability, and pharmacokinetics of single oral doses of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus (HCMV) replication in healthy male subjects.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F945.

8. Witt-Laido, A., Beckermann, B., Schwarz, T., Steinke, W., Daehler, H., Henninger, K., Buehner, K. *Pharmacokinetics in rat and dog of BAY 38-4766 - A novel nonnucleosidic inhibitor of human cytomegalovirus replication.* 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F944.

9. *Bayer's CMV product advances to phase II.* DailyDrugNews.com (Daily Essentials) December 2, 1999.

10. Iwayama, S., Ono, N., Ohmura, Y. et al. *Antiherpesvirus activities of (1'S,2'R)-9-[[1',2'-bis(hydroxymethyl)cycloprop-1'-yl]methyl]guanine (A-5021) in cell culture.* Antimicrob Agents Chemother 1998, 42: 1666-70.

11. Starrett, J.E. Jr., Tortolani, D.R., Hitchcock, M.J., Martin, J.C., Mansuri, M.M. *Synthesis and in vitro evaluation of a phosphonate prodrug: bis(pivaloyloxymethyl) 9-(2-phosphonylmethoxyethyl)adenine.* Antivir Res 1992, 19: 267-73.

12. Braitman, A., Swerdel, M.R., Olsen, S.J., Tuomari, A.V., Lynch, J.S., Blue, B., Michalik, T., Field, A.K., Bonner, D.P., Clark, J.M. *Evaluation of SQ 34,514: Pharmacokinetics and efficacy in experimental herpesvirus infections in mice.* Antimicrob Agents Chemother 1991, 35: 1464-8.

13. Bhattacharya, B.K., Ojwang, J.O., Rando, R.F., Huffman, J.H., Revankar, G.R. *Synthesis and anti-DNA viral activities in vitro of certain 2,4-disubstituted-7-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)pyrrolo[2,3-d]pyrimidine nucleosides.* J Med Chem 1995, 38: 3957-66.

14. Benzaria, S., Pelicano, H., Johnson, R., Maury, G., Imbach, J.L., Aubertin, A.M., Obert, G., Gosselin, G. *Synthesis, in vitro antiviral evaluation, and stability studies of bis(S-acyl-2-thioethyl) ester derivatives of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as potential PMEA prodrugs with improved oral bioavailability.* J Med Chem 1996, 39: 4958-65.

15. Snoeck, R., Andrei, G., Nemecek, C., De Clercq, E., Roy, C. *In vitro inhibition of HCMV replication by the tetrahydroindolizine RPR111423.* Antivir Res 1999, 41(2): Abst 12.

16. Azad, R.F., Driver, V.B., Tanaka, K., Crooke, R.M., Anderson, K.P. *Antiviral activity of a phosphorothioate oligonucleotide complementary to RNA of the human cytomegalovirus major immediate-early region.* Antimicrob Agents Chemother 1993, 37: 1945-54.

17. Rybak, R.J., Zemlicka, J., Qiu, Y.L., Hartline, C.B., Kern, E.R. *Effective treatment of murine cytomegalovirus infections with methylenecyclopropane analogues of nucleosides.* Antivir Res 1999, 43: 175-88.

18. Tutonda, M.G., Buckheit, R.W. Jr., Agrawal, V.K., Broom, A.D. *Antiviral oligo-and polyribonucleotides containing selected triazolo[2,3-a]purines.* J Med Chem 1998, 41: 4958-64.