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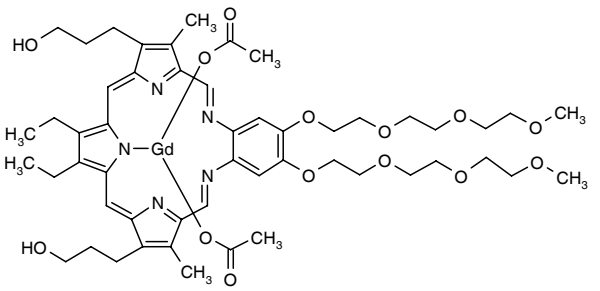
Motexafin Gadolinium

Rec INNM; USAN

Apoptosis Inducer
Radiation Enhancer
Thioredoxin Reductase Inhibitor
Ribonucleotide Reductase Inhibitor

Gd-Tex
GdT2B2
PCI-0120
Gadolinium texaphyrin
Xcytrin®

(PB-7-11-233'2'4)-Bis(acetato-*O*)[9,10-diethyl-20,21-bis[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-4,15-dimethyl-8,11-imino-3,6:16,13-dinitrilo-1,18-benzodiazacycloeicosine-5,14-dipropanolato-*N*1,*N*18,*N*23,*N*24,*N*25]gadolinium



$C_{52}H_{72}GdN_5O_{14}$
Mol wt: 1148.4034

CAS: 246252-06-2

CAS: 156436-89-4 (hydrate)

EN: 216344

Abstract

Motexafin gadolinium (Xcytrin®; Pharmacyclics) is a broad-spectrum anticancer agent in clinical trials as a single agent and in combination with chemotherapy and/or radiotherapy. It is a member of the texaphyrin family of expanded porphyrins designed to coordinate large lanthanide metal ions, of which the paramagnetic gadolinium is particularly useful as a magnetic resonance imaging (MRI) contrast agent. The primary mode of action is through futile redox cycling whereby reactive oxygen species are generated with depletion of intracellular reducing factors. *In vitro* and *in vivo* studies show that motexafin gadolinium inhibits a number of important enzymes for cancer cell survival. Clinical studies have indicated that it is nontoxic at effective concentrations and confers some delay in neurological and neurocognitive progression in lung cancer patients when used as a radiation enhancer.

Synthesis*

Motexafin gadolinium can be synthesized as follows. The condensation of methyl 3-[2-(acetoxymethyl)-5-(benzyloxycarbonyl)-4-methyl-1*H*-pyrrol-3-yl]propionate (I) with 3,4-diethylpyrrole (II) by means of *p*-toluenesulfonic acid in ethanol provides the tripyrrolyl adduct (III). Subsequent reduction of the aliphatic ester groups of (III) with borane-THF complex affords the diol (IV), which undergoes benzyl ester group cleavage by catalytic hydrogenation in the presence of Pd/C and triethylamine, yielding the dicarboxylic acid (V). Decarboxylation of (V) with trifluoroacetic acid, followed by condensation with triethyl orthoformate and aqueous acetal hydrolysis, leads to the dialdehyde (VI). Cyclization of (VI) with the phenylenediamine derivative (VII) in methanolic HCl produces the macrocyclic diimine (VIII) (1-3), which is finally reacted with gadolinium triacetate and triethylamine in methanol with simultaneous air oxidation to furnish the title gadolinium complex (1). Scheme 1.

The phenylenediamine derivative (VII) can be obtained as follows. Triethyleneglycol monomethyl ether (IX) is reacted with *p*-toluenesulfonyl chloride and NaOH in aqueous THF to produce the corresponding tosylate (X), which is then condensed with pyrocatechol (XI) by means of K_2CO_3 in methanol, yielding the aryl ether (XII). After nitration of (XII) with HNO_3 in acetic acid, the resulting dinitro derivative (XIII) is reduced utilizing ethanolic hydrazine in the presence of Pd/C to provide the target diamine intermediate (VII) (1). Scheme 2.

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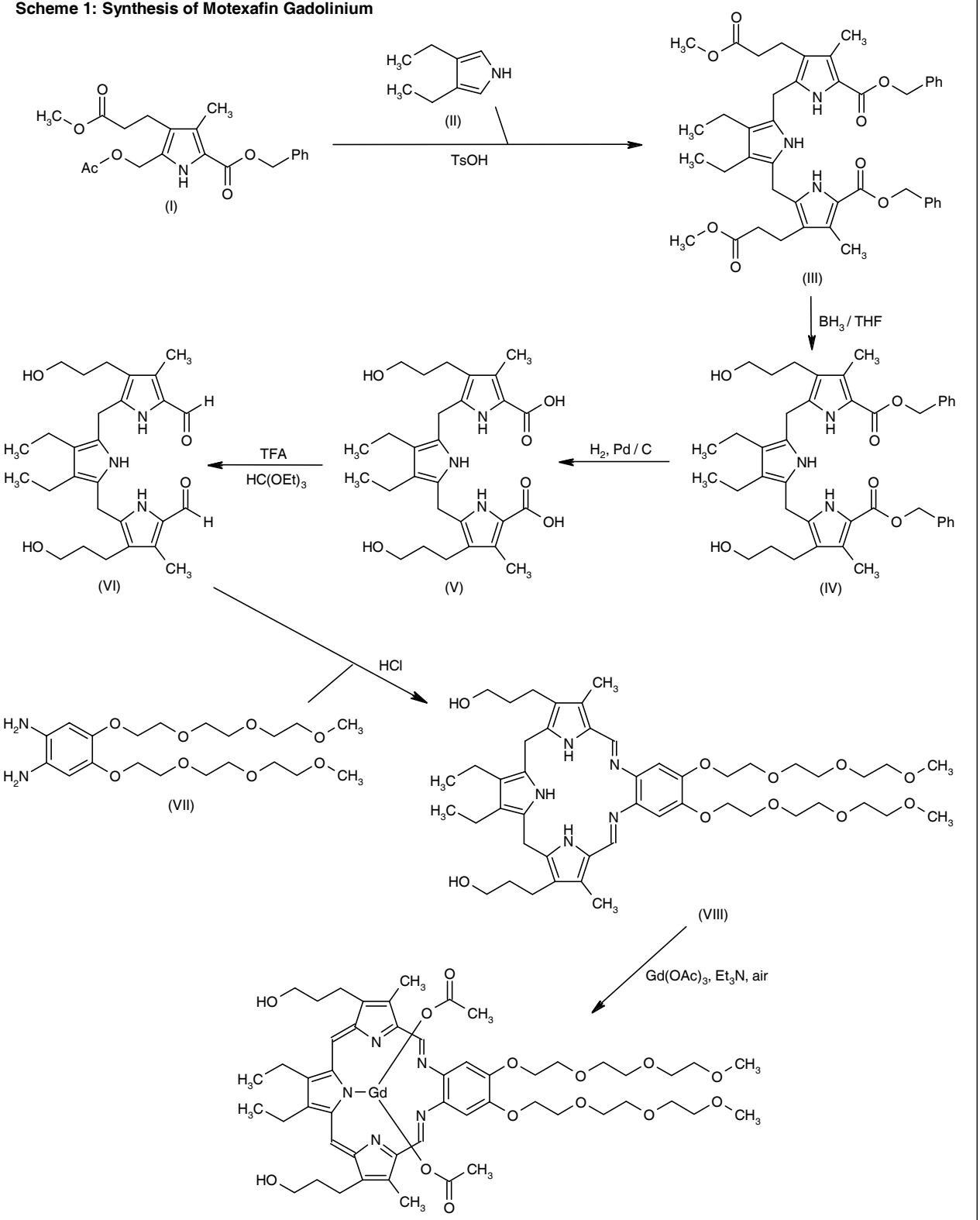
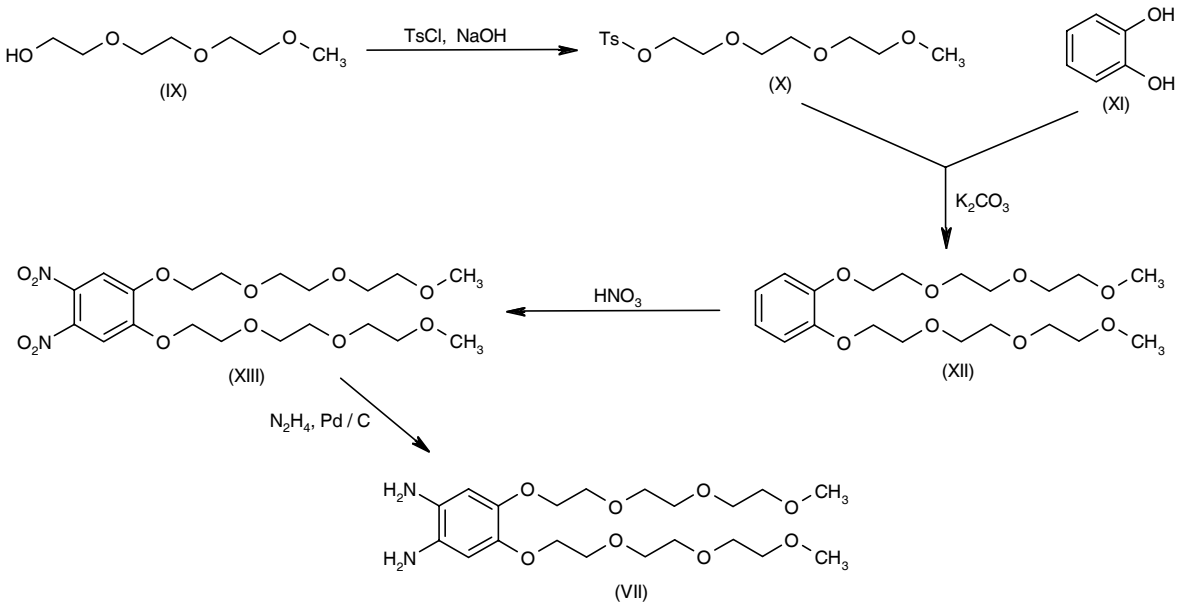
Scheme 1: Synthesis of Motexafin Gadolinium



Scheme 2: Synthesis of Intermediate (VII)



Background

Motexafin gadolinium (Xyctrin®) is a symmetrical, highly conjugated, electron-rich expanded porphyrin that binds tightly to gadolinium(III). Five nitrogen atoms coordinate to the Gd^{3+} ion in a planar fashion, while the two more loosely bound acetate ions coordinate axially. The hydroxypropyl and polyethyleneglycol substituents help provide water solubility. Motexafin gadolinium has a Soret-like band at 468 nm and a Q-band at 742 nm. Like natural porphyrins, it accumulates within tumor cells. The paramagnetic properties of the gadolinium ion make it detectable by magnetic resonance imaging (MRI) and confirm the selective localization within tumors (4). The next generation of motexafin gadolinium-based drugs aims to use it as a cancer-localizing carrier for known or promising chemotherapeutic agents, such as methotrexate and cisplatin, that are covalently linked to the texaphyrin moiety (5).

Preclinical Pharmacology

Early studies on motexafin gadolinium confirmed its efficacy as a radiation enhancer (4). The mechanism of its cytotoxicity stems from its ability, unlike naturally occurring porphyrins, to be easily reduced by one electron (6). Reducing agents such as glutathione and other protein thiols, ascorbate and nicotinamide adenine dinucleotide phosphate (NADPH) all reduce motexafin gadolinium to the delocalized radical species (7). The reduced motexafin gadolinium will reduce dioxygen to superoxide, whereby propagation can generate reactive oxygen species. This futile redox cycling alone can trigger apoptosis (8).

A number of other factors may also contribute to the cytotoxicity of motexafin gadolinium in tumor cells. Motaxafin gadolinium disrupts zinc metabolism in human cancer cell lines, leading to an increase in intracellular levels of free zinc and metallothioneins (9). It specifically targets enzymes with redox-active cysteine residues. Of particular importance is the motexafin gadolinium-dependent inhibition of thioredoxin reductase (10), vital for maintaining the redox state of the cell, and ribonucleotide reductase, essential for DNA synthesis. Motexafin gadolinium inhibits heme oxygenase-1, the inducible form of the antiapoptotic enzyme responsible for heme homeostasis (11). As a result of these effects, it can disrupt cellular metabolism, inhibit DNA repair and facilitate apoptosis.

MRI revealed selective motexafin gadolinium uptake in metastases, without uptake in normal brain tissue. There was gradual accumulation of the drug in metastases, as in some instances tumors were only visible after multiple injections (12). *In vitro* studies found motexafin gadolinium to be an effective radiation sensitizer for human colon cancer cell lines (4). *In vivo* studies with transplanted mouse mammary carcinomas showed selective tumor localization of motexafin gadolinium, as observed by MRI, and when administered at 40 μmol/kg i.v. followed by a single or multiple fractions of radiation,

it produced a significant decrease in tumor size (4). Intracellular localization of motaxafin gadolinium within tumor cells was primarily within the lysosomes, endoplasmic reticulum and mitochondria (10).

Pharmacokinetics and Metabolism

The plasma pharmacokinetics of motexafin gadolinium were evaluated in mice following single and multiple doses (14). Motexafin gadolinium was well tolerated at doses of up to 40 mg/kg and was cleared from the plasma with a terminal elimination half-life of 12.9 h. The liver and kidney contained high levels of the drug, which was cleared relatively rapidly as these organs excrete the drug. The concentration of motexafin gadolinium in tumor tissue was estimated to be about 2 μM following a single i.v. dose of 10 μmol/kg (35 mg/kg) (15).

The plasma pharmacokinetics were also evaluated in early phase I and phase III trials. After 24 h of dosing, 63% of plasma motexafin gadolinium remains intact (16), with a terminal elimination half-life of 28 h (17). The concentration of motexafin gadolinium present in tissue is thought to peak at 4-6 h postdosing. Although it appears relatively stable *in vivo*, an *in vitro* study in rat and human liver microsomes and cytosol found that the metabolism of motexafin gadolinium was rapid and primarily catalyzed by NADPH-CYP450 reductase in the microsomes and by DT-diaphorase in the cytosol (18). The metabolite detected was the 4-electron-reduced, metal-free and nonaromatic macrocycle, equivalent to the synthetic precursor (VIII) (see Scheme 1).

Safety

Acute toxicity studies were performed in rats and mice administered the drug by i.v. infusion. The LD_{50} was 126 and 108 mg/kg in rats and mice, respectively. Subchronic administration of high doses of motexafin gadolinium in rats produced reversible weight loss and liver toxicity. The effective dose in rats was 6 mg/kg/day (19).

A phase I single-escalating-dose trial was conducted with motexafin gadolinium in patients with incurable cancer receiving radiation therapy (20). The maximum tolerated dose (MTD) delivered by i.v. infusion was 22.3 mg/kg, with dose-limiting and reversible renal toxicity at 29.6 mg/kg. MRI scans showed that motexafin gadolinium selectively accumulated in primary and metastatic tumors. No increase in radiation toxicity to normal tissues was seen. The half-life of a single dose was 7.4 h. Motexafin gadolinium can therefore be safely dosed at the level of 5 mg/kg/day over the course of a 2-week period (21).

In a phase Ib/II multiple-dose trial, patients received 0.3-8.4 mg/kg/day in the phase Ib portion or 5-6.3 mg/kg/day in the phase II portion over the course of 10 days (22). The MTD was 6.3 mg/kg/day based on dose-limiting reversible liver toxicity. The most common side effect upon repeated administration of motexafin gadolinium was reversible discoloration of the skin, urine and sclera related to the dark green color of the complex. In these studies, 16% of the patients experienced grade 3 or 4 toxicity. The most common grade 3 or 4 adverse events were hepatotoxicity, hypertension, brain edema and nausea.

Clinical Studies

Two randomized phase III trials have been completed. The first trial evaluated survival and neurological and neurocognitive function in patients with brain metastases from solid tumors receiving whole-brain radiation therapy (WBRT) with or without motexafin gadolinium (23). The 401 patients consisted of 251 with non-small cell lung cancer (NSCLC), 75 with breast cancer and 75 with other cancers. They were randomly assigned to receive 30 Gy of WBRT in 10 daily fractions with or without 5 mg/kg/day motexafin gadolinium. Overall survival was not statistically significantly different in any group, although patients with lung cancer treated with motexafin gadolinium tended to have improved memory and executive function and improved neurological function.

A recently completed phase III trial involved the treatment of 554 patients with brain metastases from NSCLC with the addition of motexafin gadolinium to WBRT. Investigators found that patients given motexafin gadolinium in addition to WBRT had a median time to neurological progression of 15.4 months compared to 10.0 months for patients who received only WBRT ($p = 0.12$), a difference that was not statistically significant. The study failed to meet the primary endpoint; however, subset analysis of the North American arm (n=348), where patients were introduced to the randomized trial earlier after metastasis diagnosis, showed that motexafin gadolinium prolonged time to neurological progression from 8.8 to 24.2 months ($p = 0.004$) (24). Overall, 805 patients with brain metastases from NSCLC have been treated in randomized clinical trials comparing motexafin gadolinium plus WBRT to WBRT alone. The median time to neurological progression for the motexafin gadolinium-treated patients was 15.4 months *versus* 9.0 months for patients receiving only WBRT ($p = 0.016$) (25).

Ongoing clinical trials with motexafin gadolinium are summarized in Table I (26-31). Pharmacyclics filed an NDA with the FDA in December 2006 seeking approval for the use of motexafin gadolinium in combination with radiation therapy for the treatment of brain metastases from NSCLC. However, following receipt of a refuse to file letter in February citing failure to demonstrate statistically significant differences in the primary endpoint between treatment arms in the pivotal studies, the company filed an NDA over protest in April, to which the FDA has assigned an action date of December 31, 2007. The trials utilized an innovative neurological progression endpoint designed with the FDA to assess clinical benefit (32).

Source

Pharmacyclics, Inc. (US).

Table I: Ongoing clinical trials of motexafin gadolinium.

Phase	Description (Ref.)
I/II	Motexafin gadolinium, temozolomide and radiation therapy for the treatment of newly diagnosed glioblastoma multiforme (25)
II	Combination of motexafin gadolinium and radiation therapy for the treatment of intrinsic pontine glioma of childhood (26)
II	Motexafin gadolinium and pemetrexed (Alimta®) for the second-line treatment of non-small cell lung cancer (NSCLC) (27)
I/II	Motexafin gadolinium, rituximab and yttrium-90 ibritumomab tiuxetan for the treatment of stage II, III or IV relapsed or refractory non-Hodgkin's lymphoma (NHL) (28)
II	Single-agent motexafin gadolinium for the second-line treatment of NSCLC (29)
II	Motexafin gadolinium and docetaxel for the second-line treatment of advanced NSCLC (30)

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