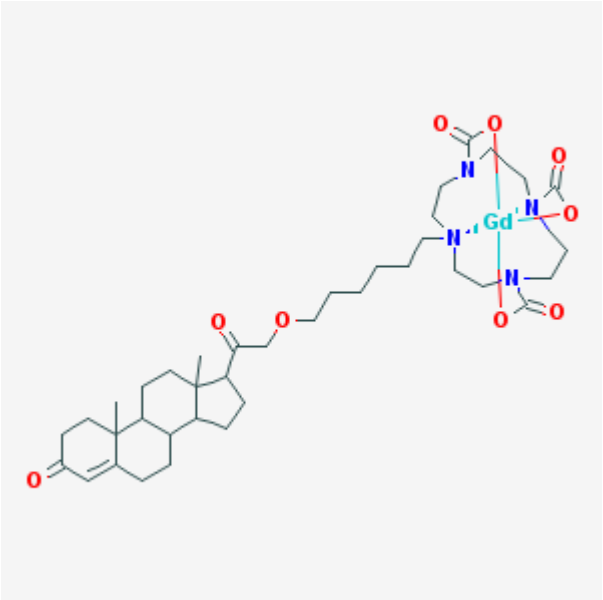
Gadolinium-Hexyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-progesterone

ProGlo

Kam Leung, PhD[1]

Created: May 1, 2012; Updated: August 9, 2012.

Chemical name:	Gadolinium-Hexyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-progesterone
Abbreviated name:	ProGlo, Gd-Hexyl-DO3A-Pro
Synonym:	
Agent category:	Compound
Target:	Progesterone receptor (PR)
Target category:	Receptor
Method of detection:	Magnetic resonance imaging (MRI)
Source of signal:	Gadolinium ($Gd3^{+}$)
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

NLM Citation: Leung K. Gadolinium-Hexyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-progesterone. 2012 May 1 [Updated 2012 Aug 9]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Estrogens and progesterones are endogenous hormones that produce many physiological effects (1). Estrogens act primarily by regulating gene expression. Estrogen receptors (ERs) are found in the cytoplasm and nucleus of cells in the female reproductive tract, breast, pituitary gland, hypothalamus, bone, liver, and other tissues, as well as in various tissues in men. Estrogens are lipophilic in that they enter the cell passively by diffusion through the cellular membrane. They bind to ERs in the cytoplasm and are transported to the nucleus.

Breast cancer is the most common malignancy in women. Approximately 33% of women who have this disease will die of disseminated breast cancer. The growth of breast epithelial cells is dependent on estrogen stimulation to induce progesterone receptor (PR) expression. Two-thirds of breast carcinomas express ERs. It has also been established that the ER status of the tumor is an important prognostic indicator in breast cancer (2). Women with ER-positive and PR-positive breast tumors have a better prognosis than women with ER-negative and PR-negative tumors in terms of responsiveness to anti-estrogen treatment. ER content in breast cancer has been assessed *in vitro* with receptor binding assays, which suffer from inter-assay variability and are also limited by intrinsic receptor heterogeneity of the primary and metastatic tumors. 16α-[^{18}F]Fluoro-17β-estradiol ([^{18}F]FES) has been proven to be a valuable tracer for studies of the ER status of primary and metastatic breast cancer (3). However, [^{18}F]FES is cleared from the blood and metabolized in 20 min with only 20% of [^{18}F]FES intact in a study with 15 breast cancer patients (4). Similarly, a [^{18}F]-labeled progestin is also metabolized rapidly in humans (5). For magnetic resonance imaging (MRI), Sukerkar et al. (6) found that coupling of gadolinium-hexyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (Gd-hexyl-DO3A) to the C21 hydroxyl group of 21-hydroxylprogesterone renders the MRI probe (ProGlo) inaccessible for metabolism but still able to bind specifically to PR(+) breast cancer cells. ProGlo was shown to accumulate in PR-rich uterus and PR(+) tumors *in vivo* in mice.

Related Resource Links:

- Chapters in MICAD (estrogen receptor, progesterone receptor)
- Gene information in NCBI (estrogen receptor, progesterone receptor)
- Articles in OMIM (estrogen receptor, progesterone receptor)

Synthesis

[PubMed]

ProGlo was synthesized with alkylation of the 21-hydroxyl group of 21-hydroxylprogesterone by 1,6-dibromohexane (6). This biphasic alkylation reaction produced bromine-tethered progesterone in 74% yield. A coupling reaction with DO3A

followed by insertion of the Gd^{3+} was performed with incubation with $GdCl_3$ at 60°C with 58% yield. Gd-hexyl-DO3A and Gd-DO3A were also prepared as controls. The log *P* values were 1.40 ± 0.08, –1.21 ± 0.12, and –2.96 ± 0.35 for ProGlo, Gd-hexyl-DO3A, Gd-DO3A, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

T1- and T2-Weighted MRI of ProGlo, Gd-hexyl-DO3A, and Gd-DO3A was performed at 1.4 T at 37°C (6). The r_1 and r_2 relaxivity values for ProGlo were 5.35 ± 0.74 $mM^{-1}s^{-1}$ and 6.14 ± 0.81 $mM^{-1}s^{-1}$, respectively. The r_1 and r_2 relaxivity values for Gd-hexyl-DO3A were 5.55 ± 0.22 $mM^{-1}s^{-1}$ and 6.38 ± 0.38 $mM^{-1}s^{-1}$, respectively. The r_1 and r_2 relaxivity values for Gd-DO3A were 4.05 ± 0.02 $mM^{-1}s^{-1}$ and 4.75 ± 0.35 $mM^{-1}s^{-1}$, respectively. ProGlo and Gd-hexyl-DO3A had similar relaxivities, which were higher than those of Gd-DO3A.

Cellular accumulation of ProGlo, Gd-hexyl-DO3A, and Gd-DO3A in PR(+) T47D and PR(–) MDA-MB-231 human breast tumor cells were measured at 1, 4, 10, and 24 h of incubation (6). Concentrations of Gd^{3+} were measured with inductively coupled plasma–mass spectrometry (ICP-MS). The accumulation of the lipophilic ProGlo was the highest in both cell types and was two-fold higher than Gd-hexyl-DO3A. Gd-DO3A showed only marginal accumulation because of its hydrophilic nature. The accumulation of ProGlo was higher in the T47D cells than in the MDA-MB-231 cells as ProGlo was retained longer inside the PR(+) cells due to PR binding. NO blocking studies were reported.

Animal Studies

Rodents

[PubMed]

Sukerkar et al. (6) performed *ex vivo* biodistribution studies of ProGlo (n = 5/group), Gd-hexyl-DO3A (n = 3/group), and Gd-DO3A (n = 5/group) in female CD-1 mice at 2, 6, and 24 h after intraperitoneal injection (0.15 mmol Gd/kg). ProGlo (Gd) accumulation measured with ICP-MS in the PR(+) tissues (the uterus (12 μg Gd/g), ovaries (5 μg Gd/g), and mammary glands (4 μg Gd/g)) was significantly higher than that of Gd-hexyl-DO3A and Gd-DO3A at 6 h after injection ($P < 0.05$). The ProGlo accumulation in the liver (>1,000 μg Gd/g) was higher than in the kidney (~10 μg Gd/g). Gd-Hexyl-DO3A exhibited ~25 μg Gd/g in the liver and kidney initially and declined thereafter. There was little accumulation in the PR(+) tissues at the time points studied. Gd-DO3A exhibited a low accumulation in the liver (10 μg Gd/g) but a higher accumulation in the kidney (100 μg Gd/g) at 2–6 h after injection. There was high accumulation in the PR(+) tissues (7–10 μg Gd/g) at 2 h; this accumulation declined to levels below those of ProGlo at 6 h. No apparent acute toxicity was observed at 24 h after injection. NO blocking studies were reported.

In vivo MRI studies in the uteri and ovaries of female CD-1 mice (n = 3/group) were performed at 0, 2, 6, and 24 h after injection (7.05 T) with intraperitoneal injection of ProGlo or Gd-DO3A (6). ProGlo exhibited a significant increase in the contrast/noise ratio (CNR) relative to the CNR before injection through 24 h after injection ($P < 0.05$) in the uteri, whereas the increase in CNR was not significant in the ovaries. No significant increases were observed with Gd-DOA3 in the uteri or ovaries. *Ex vivo* MRI of the uteri or ovaries were also performed. The tissues from mice injected with ProGlo showed increased signal intensity in the PR-rich myometrium and ovarian follicles compared with those injected with Gd-DOA3 and untreated mice.

In vivo MRI studies were performed in nude mice (n = 2–4/group) bearing PR(+) T47D tumor on the right rear flank and PR(–) MDA-MB-231 tumor on left rear flank after intraperitoneal or subcutaneous injection of ProGlo and Gd-DOA3 at 0, 2, 6, and 24 h after injection (7.05 T) (6). ProGlo significantly increased the CNR of PR(+) tumors compared with PR(–) tumors and pre-injection ($P < 0.05$) at 2 h and 6 h, whereas Gd-DOA3 showed no significant difference between the two tumors and pre-injection at 2 h and 6 h. Intraperitoneal and subcutaneous injection of ProGlo exhibited a similar increased tumor accumulation in the PR(+) tumors. However, subcutaneous injection showed less toxicity (death) than intraperitoneal injection.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

R01 EB005866, R21 CA143331, P30 CA060553

References

1. Beato M., Klug J. *Steroid hormone receptors: an update.* Hum Reprod Update. 2000;6(3):225–36. PubMed PMID: 10874567.
2. Vollenweider-Zerargui L., Barrelet L., Wong Y., Lemarchand-Beraud T., Gomez F. *The predictive value of estrogen and progesterone receptors' concentrations on the clinical*

behavior of breast cancer in women. Clinical correlation on 547 patients. Cancer. 1986;57(6):1171–80. PubMed PMID: 3943040.
3. Flanagan F.L., Dehdashti F., Siegel B.A. *PET in breast cancer.* Semin Nucl Med. 1998;28(4):290–302. PubMed PMID: 9800236.
4. Mankoff D.A., Tewson T.J., Eary J.F. *Analysis of blood clearance and labeled metabolites for the estrogen receptor tracer [F-18]-16 alpha-fluoroestradiol (FES).* Nucl Med Biol. 1997;24(4):341–8. PubMed PMID: 9257333.
5. Verhagen A., Studeny M., Luurtsema G., Visser G.M., De Goeij C.C., Sluyser M., Nieweg O.E., Van der Ploeg E., Go K.G., Vaalburg W. *Metabolism of a [18F]fluorine labeled progestin (21-[18F]fluoro-16 alpha-ethyl-19-norprogesterone) in humans: a clue for future investigations.* Nucl Med Biol. 1994;21(7):941–52. PubMed PMID: 9234348.
6. Sukerkar P.A., MacRenaris K.W., Meade T.J., Burdette J.E. *A steroid-conjugated magnetic resonance probe enhances contrast in progesterone receptor expressing organs and tumors in vivo.* Mol Pharm. 2011;8(4):1390–400. PubMed PMID: 21736390.