[*N*-Methyl-^{11}C]-(11β17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one

[*N*-Methyl-^{11}C]Org 34850

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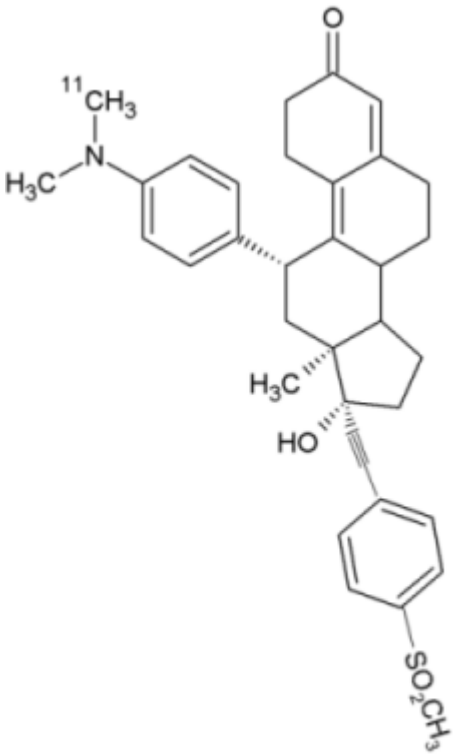
Chemical name:	[*N*-Methyl-^{11}C]-(11β17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one
Abbreviated name:	[*N*-Methyl-^{11}C]Org 34850
Synonym:	
Agent Category:	Compound
Target:	Glucocorticoid receptors
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [*N*-methyl-^{11}C]Org 34850

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Background

[PubMed]

Glucocorticoids are members of the corticosteroid family (the other members of this family are the mineralocorticoid group of compounds, which bind to the mineralocorticoid receptors (MR)) and are often used as anti-inflammatory and immunosuppressive agents for the treatment of diseases such as arthritis, asthma, and cancer, as well as inflammatory bowel disease and autoimmune diseases (1, 2). There is much evidence suggesting that glucocorticoids also have an important role in the development of stress, anxiety, and depression in rodents and humans by disturbing the hypothalamic-pituitary-adrenocortical (HPA) axis functions because these tissues have a high concentration of the glucocorticoid receptors (GR) (3). Normalization of the HPA function in humans is often observed during recovery from a depressive episode, and this has also been observed in preclinical studies with rats regardless of the type of antidepressant drug used to treat depression (4).

It has been suggested that changes in the MR/GR balance could be responsible for regulation of the psychological stress and anxiety that lead to depression. Between the two receptors, the role of GR appears to be more clear because it has been shown that GR levels are increased during periods of anxiety, and GR activity is reduced during times of low anxiety (5). Therefore, investigators in this field believe that imaging of the GR would be an excellent technique to understand the *in vivo* functioning and regulation of the HPA axis. Much effort has been made to develop and evaluate fluoride (^{18}F)-labeled and carbon (^{11}C)-labeled GR binding radiotracers to investigate the activity and function of this receptor with the use of positron emission tomography (PET) under *in vivo* conditions. However, studies with these radiochemicals have had little success in delineating the function of the GR because the tracers are often metabolically unstable, have shown little penetration of the blood–brain barrier, or exhibit high non-specific binding (6). The steroid compound [*N*-methyl-^{11}C]-(11β17α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one ([*N*-methyl-^{11}C]Org 34850) was reported to be a selective GR antagonist in the HPA axis with a high affinity for the receptor under *in vitro* conditions with the use of brain tissue homogenates (7). Because of its high potency against the GR, a ^{11}C-radiolabeled version of Org 34850 was synthesized by Wuest et al. to image GR *in vivo* and to investigate biodistribution of the radiochemical in normal rats (8).

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Synthesis

[PubMed]

The synthesis of [*N*-methyl-^{11}C]Org 34850 was described by Wuest et al. (8). Briefly, [^{11}C]methyl triflate was generated as described by Mock et al. (9) and used to synthesize [*N*-methyl-^{11}C]Org 34850 from the precursor molecule Org 38665 (obtained as a gift from commercial sources). The labeled product, [*N*-methyl-^{11}C]Org 34850, was obtained within 35 min at the end of bombardment and purified on a SPE-cartridge RP-18E. The radiochemical yield of the reaction was 23% with a purity of >98%, as determined with high-performance liquid chromatography. The specific activity of the radiotracer was reported to be 47 ± 12 GBq/μmol (1.27 ± 0.32 Ci/μmol) (n = 15 synthesis reactions) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No references are currently available.

Animal Studies

Rodents

[PubMed]

The biodistribution of [*N*-methyl-^{11}C]Org 34850 was studied in male Wistar rats (four animals/time point) injected with the radiochemical through the tail vein (8). The animals were euthanized 5 and 60 min after the administration of [*N*-methyl-^{11}C]Org 34850, and the pituitary gland, the cerebellum, the rest of the brain, and all the other major glands, organs, and tissue were harvested. The accumulated radioactivity was counted, decay-corrected, and expressed as percent injected dose per gram tissue (% ID/g). Blood clearance of the radioactivity was reported to be rapid, decreasing from 0.35 ± 0.05% ID/g at 5 min after the injection to 0.16 ± 0.07% ID/g at 60 min . The pituitary and adrenal glands, which are known to express high levels of GR, showed an accumulation of 0.98 ± 0.48% ID/g and 1.62 ± 0.26% ID/g, respectively, at 5 min after tracer injection; however, at 60 min the pituitary and adrenal levels decreased to 0.23 ± 0.11% ID/g and 0.26 ± 0.10% ID/g, respectively, indicating that the radioactivity was washed out from the glands. The pancreas, liver, and brown adipose tissue showed a similar trend in the accumulation of radioactivity. A low level of radioactivity was reported to be taken up by the brain (0.09 ± 0.01% ID/g at 5 min and 0.05 ± 0.01% ID/g at 60 min), suggesting that there was some unexplained interference in the uptake of this radiochemical in the brain (8). No blocking studies were reported.

PET imaging was performed on a rat 1 h after an injection of [*N*-methyl-^{11}C]Org 34850 through the tail vein (8). The animal was scanned for 60 min, and a review of the two-

dimensional sagittal, transversal, and coronal images of the rat head revealed no uptake of the radiotracer in the brain at 60 min after administration of the radiochemical. No blocking studies were reported.

With results obtained from the biodistribution and PET studies using [*N*-methyl-^{11}C]Org 34850, the investigators concluded that the radiotracer was not suitable for the investigation of GR in the brain (8).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

References

1. Sommer P., Ray D.W. *Novel therapeutic agents targeting the glucocorticoid receptor for inflammation and cancer.* Curr Opin Investig Drugs. 2008;9(10):1070–7. PubMed PMID: 18821468.
2. Angelucci E., Malesci A., Danese S. *Budesonide: teaching an old dog new tricks for inflammatory bowel disease treatment.* Curr Med Chem. 2008;15(24):2527–35. PubMed PMID: 18855676.
3. Pariante C.M., Lightman S.L. *The HPA axis in major depression: classical theories and new developments.* Trends Neurosci. 2008;31(9):464–8. PubMed PMID: 18675469.
4. Reus V.I., Wolkowitz O.M. *Antiglucocorticoid drugs in the treatment of depression.* Expert Opin Investig Drugs. 2001;10(10):1789–96. PubMed PMID: 11772285.
5. Rozeboom A.M., Akil H., Seasholtz A.F. *Mineralocorticoid receptor overexpression in forebrain decreases anxiety-like behavior and alters the stress response in mice.* Proc Natl Acad Sci U S A. 2007;104(11):4688–93. PubMed PMID: 17360585.
6. Steiniger B., Kniess T., Bergmann R., Pietzsch J., Wuest F.R. *Radiolabeled glucocorticoids as molecular probes for imaging brain glucocorticoid receptors by means*

of positron emission tomography (PET). Mini Rev Med Chem. 2008;8(7):728–39. PubMed PMID: 18537728.

7. Bachmann C.G., Linthorst A.C., Holsboer F., Reul J.M. *Effect of chronic administration of selective glucocorticoid receptor antagonists on the rat hypothalamic-pituitary-adrenocortical axis.* Neuropsychopharmacology. 2003;28(6):1056–67. PubMed PMID: 12700716.
8. Wuest F., Kniess T., Henry B., Peeters B.W., Wiegerinck P.H., Pietzsch J., Bergmann R. *Radiosynthesis and radiopharmacological evaluation of [N-methyl-11C]Org 34850 as a glucocorticoid receptor (GR)-binding radiotracer.* Appl Radiat Isot. 2009;67(2):308–12. PubMed PMID: 19071028.
9. Mock B.H., Mulholland G.K., Vavrek M.T. *Convenient gas phase bromination of [11C]methane and production of [11C]methyl triflate.* Nucl Med Biol. 1999;26(4):467–71. PubMed PMID: 10382852.