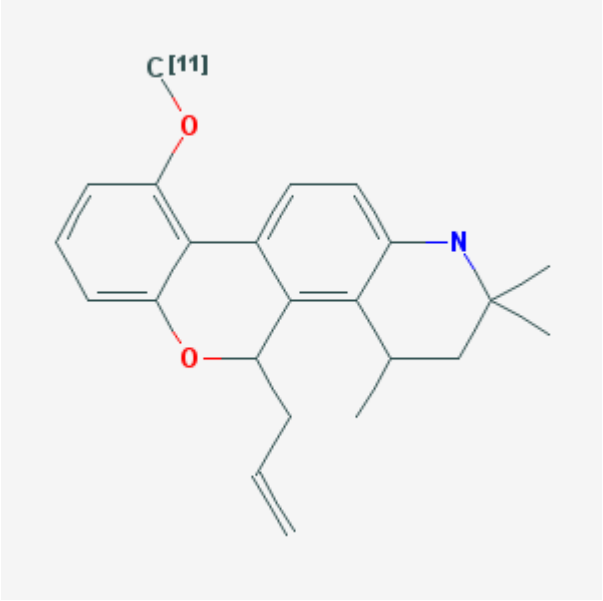
[^{11}C]10-Methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline

[^{11}C]AL-348

Arvind Chopra, PhD[1]

Created: January 13, 2009; Updated: April 6, 2009.

Chemical name:	[^{11}C]10-Methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline
Abbreviated name:	[^{11}C]AL-348
Synonym:	
Agent Category:	Compound
Target:	Glucocorticoid receptor
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

Synthetic oral glucocorticoids (GC) mediate their effects through GC receptors (GR) that are located in cytoplasm of the cell and are known to be widely distributed in all tissues. GCs such as dexamethesone and prednisolone are effective anti-inflammatory agents and are often used to treat inflammation of the muscular, intestinal, dermatological, and respiratory systems (1, 2). GCs are also used for the treatment of neuropsychodepression mediated through the hypothalamic-pituitary-adrenocortical (HPA) axis because GRs are believed to play a major role in the development of anxiety and depression (3). Also, it is well established that these tissues have a very high concentration of GRs; however, because these drugs have many undesirable side effects on the lipid and carbohydrate metabolism, such as development of osteoporosis, water retention, etc., investigators are constantly searching for new GCs (4).

It has also been reported that GR levels in the HPA are increased during episodes of anxiety or depression, and the concentration of this receptor is reduced when the individual returns to normal or low-anxiety behavior (5). To understand the regulation and functioning of the HPA axis, investigators have developed and evaluated steroid GC radiotracers labeled with fluoride (^{18}F) or carbon (^{11}C) to understand the activity and function of the GR system using positron emission tomography (PET) under *in vivo* conditions. However, studies with these radiochemicals have had limited success because the radiotracers were either metabolically unstable, had little penetration of the blood–brain barrier, and/or exhibited high nonspecific binding (6). As an alternative, some non-steroidal GR ligands respectively based on *N*-arylpyrazolo, dibenzenyl aniline, or benzopyrano-quinoline compounds were synthesized to study the GR system (7). Among the benzopyrano-quinoline derivatives, 10-methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline (AL-438) was reported to have a high specificity and affinity for the GR under *in vitro* conditions (8). In another study the anti-inflammatory activity of AL-438 was demonstrated in a rodent model (8). On the basis of these observations, Wuest et al. labeled AL-438 with ^{11}C to yield [^{11}C]AL-438 and used the radiotracer for non-invasive PET imaging of brain GR in rats (9).

Synthesis

[PubMed]

AL-438 was synthesized with a tetracyclic lactone as the starting material as detailed by Wuest et al. (9). The final yield of AL-438 was reported to be 73%. To radiolabel AL-438, ^{11}C-methyl iodide was prepared according to the procedure of Crouzel et al. (10). The sodium salt of AL-438 in 5 N sodium hydroxide and *N*,*N*-dimethylformamide was mixed

NLM Citation: Chopra A. [^{11}C]10-Methoxy-5-(2-propenyl)-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline. 2009 Jan 13 [Updated 2009 Apr 6]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

with the ^{11}C-methyl iodide in a reaction vessel under a stream of nitrogen at -20°C. The reaction vessel was then sealed and heated for 5 min at 100°C. The labeled product was purified with reverse-phase high-performance liquid chromatography on a C-18 column, and the eluted product was diluted in water. The water-solubalized product was loaded onto a C-18 Sea-Pak Light cartridge, and the cartridge was washed with water. Bound [^{11}C]AL-438 was eluted from the cartridge in 5% ethanol and formulated in 0.9% saline. The radiochemical yield of the labeling process was 30 ± 4% (decay corrected), with a specific activity of 10–15 GBq/μmol (0.27–0.40 Ci/μmol) at the end of synthesis (~35 min). The radiochemical purity of the labeled compound was >95%. Stability of the formulated radiotracer was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The receptor binding characteristics of AL-438 were determined with an indirect receptor binding assay with insect SF21 cells expressing either the GR or the progesterone receptor (PR) as described by Kym et al. (8) The inhibition constant (K_i) of AL-438 was reported to be 2.5 ± 0.5 nM with 94 ± 2% efficiency compared with dexamethasone. Using the same assay, the K_i of AL-438 was determined to be 1,790 ± 480 nM for the PR, suggesting that AL-438 had a high specificity for the GR.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{11}C]AL-438 was studied in corticosterone-treated (for competition studies) and normal male Wistar rats by a bolus injection of the radiotracer (9). The animals (n = 4 per group) were killed 5 and 60 min postinjection (p.i.), and the various tissues, selected parts and the rest of the brain, and the major organs were harvested to determine accumulated radioactivity. The amount of radioactivity in the blood reached its maximum at 5 min p.i. (0.52 ± 0.10% injected dose/gram tissue (% ID/g)) and remained relatively constant thereafter. The adrenal glands, which are rich in GR, showed the highest amount of tracer accumulation at 5 min (7.63 ± 1.38% ID/g), and these levels decreased to 4.40 ± 1.07% ID/g at 60 min. Compared with other tissues such as muscle, testis, and spleen, the accumulation of radioactivity was relatively higher in the liver (2.65 ± 0.38% ID/g), pancreas (2.79 ± 0.55% ID/g), brown fat (5.22 ± 2.50% ID/g), and the pituitary gland (2.49 ± 0.69% ID/g) 5 min p.i. In general, most organs showed little change in radiotracer incorporation between 5 and 60 min. The non–steroid-labeled compound crossed the blood–brain barrier because at 5 min p.i. it was found to be accumulated in the cerebellum (1.39 ± 0.37% ID/g), cortex (1.67 ± 0.32% ID/g), and the hippocampus (1.30 ± 0.34% ID/g). By 60 min the radioactivity had washed out from these parts of the brain and was reported to be between 0.52 ± 0.06 and 0.61 ± 0.09% ID/g.

To investigate the specificity of [^{11}C]AL-438 to bind the GR, the animals were pretreated with corticosterone and injected with the tracer (9). The various tissue and organs were harvested from the rats at the two time points as detailed above. The investigators reported no change in the amount of radioactivity that bound to the adrenal glands, the thymus, the pituitary, the cortex, or cerebellum.

PET imaging was performed on a rat after injection of [^{11}C]AL-438 through the tail vein (9). Various regions of the brain were reported to be clearly visible, which was consistent with the brain biodistribution data with the radiotracer. After a high uptake of the label during the initial period, a steady decline in accumulation of the radioactivity was noted.

On the basis of the incorporated radioactivity in normal and in corticosterone-treated animals, the investigators concluded that, although [^{11}C]AL-438 crossed the blood–brain barrier, it bound non-specifically to brain tissue probably because the compound is lipophilic and therefore the tracer uptake was not GR-mediated.

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. Elmore S.W., Pratt J.K., Coghlan M.J., Mao Y., Green B.E., Anderson D.D., Stashko M.A., Lin C.W., Falls D., Nakane M., Miller L., Tyree C.M., Miner J.N., Lane B. *Differentiation of in vitro transcriptional repression and activation profiles of selective glucocorticoid modulators.* Bioorg Med Chem Lett. 2004;14(7):1721–7. PubMed PMID: 15026058.
2. Rhen T., Cidlowski J.A. *Antiinflammatory action of glucocorticoids--new mechanisms for old drugs.* N Engl J Med. 2005;353(16):1711–23. PubMed PMID: 16236742.

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. Schacke H., Docke W.D., Asadullah K. *Mechanisms involved in the side effects of glucocorticoids.* Pharmacol Ther. 2002;96(1):23–43. PubMed PMID: 12441176.
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. Buijsman R.C., Hermkens P.H., van Rijn R.D., Stock H.T., Teerhuis N.M. *Non-steroidal steroid receptor modulators.* Curr Med Chem. 2005;12(9):1017–75. PubMed PMID: 15892636.
8. Kym P.R., Kort M.E., Coghlan M.J., Moore J.L., Tang R., Ratajczyk J.D., Larson D.P., Elmore S.W., Pratt J.K., Stashko M.A., Falls H.D., Lin C.W., Nakane M., Miller L., Tyree C.M., Miner J.N., Jacobson P.B., Wilcox D.M., Nguyen P., Lane B.C. *Nonsteroidal selective glucocorticoid modulators: the effect of C-10 substitution on receptor selectivity and functional potency of 5-allyl-2,5-dihydro-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinolines.* J Med Chem. 2003;46(6):1016–30. PubMed PMID: 12620078.
9. Wuest F., Kniess T., Bergmann R., Henry B., Pietzsch J. *Synthesis and radiopharmacological characterization of [11C]AL-438 as a nonsteroidal ligand for imaging brain glucocorticoid receptors.* Bioorg Med Chem Lett. 2007;17(14):4035–9. PubMed PMID: 17499506.
10. Crouzel C., Langstrom B., Pike V.W., Coenen H.H. *Recommendations fpr a practical production of [11C]methyl iodide.* Applied Radiation and Isotopes. 1987;38:601–3.