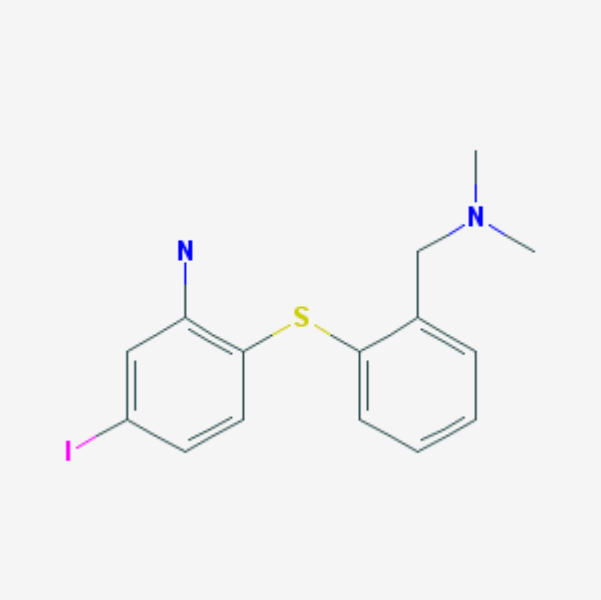
2-((2-((Dimethylamino)methyl)phenyl)thio)-5-[^{123}I]iodophenylamine

Radioiodinated ADAM

The MICAD Research Team

Created: August 6, 2007; Updated: September 6, 2007.

Chemical name:	2-((2-((Dimethylamino)methyl)phenyl)thio)-5-[^{123}I]iodophenylamine
Abbreviated name:	Radioiodinated ADAM
Synonym:	2-[2-(dimethylaminomethyl)phenyl]sulfanyl-5-iodoaniline
Agent Category:	Compound
Target:	Serotonin transporter (SERT)
Target Category:	Binding to SERT
Method of detection:	SPECT, planar scintigraphy
Source of signal:	^{123}I/^{125}I
Activation:	Not required
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



Click on the above structure for additional information in PubChem.

NLM Citation: The MICAD Research Team. 2-((2-((Dimethylamino)methyl)phenyl)thio)-5-[^{123}I]iodophenylamine . 2007 Aug 6 [Updated 2007 Sep 6]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

Serotonin (5-HT) is now known to serve as the gastrointestinal signaling molecule and participate in the development of alcohol dependence (1, 2). It is also involved in a variety of physiological functions such as the post-meal satiety process, as well as the pathogenesis of Alzheimer's and Parkinson's diseases, anxiety, and depression (1-3). Imaging and data obtained by the analysis of resected tissue of epileptic patients and studies in animal models have provided much evidence that endogenous 5-HT, the activity of its receptors, and pharmaceuticals with 5-HT agonist and/or antagonist activities are believed to be involved in the pathogenesis of epilepsy (4). Thus, imaging of the 5-HT system (SERT) is considered important to understand a variety of neurological and psychiatric functions and disorders.

A variety of drugs have been labeled with radioactive iodine (^{123}I), carbon (^{11}C), or fluorine (^{18}F) for imaging of the 5-HT receptor or transporter using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) (5). In general, these compounds are either nonselective or have a low specificity for SERT (6). Subsequently, a new drug, 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine (ADAM), radioiodinated with ^{123}I or ^{125}I, has been evaluated by several investigators for imaging of SERT.

Synthesis

[PubMed]

The synthesis of ADAM has been detailed by Oya et al. (7). A mixture of 2,5-dibromonitrobenzene, 2-thio-*N,N*,-dimethylbenzamide, and potassium carbonate in dimethylformamide was heated at 100°C for 24 h. The mixture was added to cold water, and the precipitates were collected and recrystalized from ethanol. This reaction produced a light yellow solid, 2-(4-bromo-2-nitrophenylthio)-*N,N*-dimethylbenzamide, with a yield of 79%. The light yellow solid was dissolved in tetrahydrofuran (THF), and a mixture of borane (BH_3) in THF was added to it. The mixture was refluxed for 2 h and stirred overnight at room temperature. The solvent was removed under reduced pressure to obtain a residue. Water was added to the residue, and the mixture was refluxed for 30 min with vigorous stirring. The solution was neutralized (pH 7–8) with sodium bicarbonate and extracted three times with a mixture of dichloromethane and methanol. The extractions were combined and dried over sodium sulphate, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography, and a colorless oil, 2-(4-bromo-2-nitrophenylthio)-benzyl)dimethylbenzamide, with a yield of 83%, was obtained.

The nitro group was reduced in a mixture of HCl, methanol, and stannous chloride at 10°C. With this reaction a residue of 5-bromo-2-((2-((diethylamino)methyl)phenyl)thio)phenylamine was obtained with a yield of 78%. This

residue was dissolved in triethylamine, and bis(tributyltin) and tetrakis(triphenylphosphine)palladium were added to it. The mixture was heated to 100°C in a sealed bottle for 48 h, and the solvent was subsequently removed under reduced pressure. A residue of 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(tri-n-butyltin)-phenylamine was obtained as a colorless oil and purified on preparative silica gel plates. The yield of this reaction was 59%.

The colorless oil was dissolved in chloroform, and a solution of iodine in chloroform was added drop-wise until the iodine color persisted. The solution was stirred overnight at room temperature, and a solution of potassium fluoride in methanol was added. A solution of sodium bisulphate was added to the mixture and stirred for 5 min. The organic layer was separated and dried over sodium sulphate, and the solvent was removed under reduced pressure. The final product, ADAM, which is a colorless oil, was purified on preparative silica gel plates. This reaction had a yield of 99%.

To prepare radioiodinated ADAM, ^{123}I/^{125}I-labeled sodium iodide in 1 N HCl was mixed with 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(tri-n-butyltin)-phenylamine in a sealed vial, and hydrogen peroxide was added through a syringe at room temperature. The iodination reaction was terminated after 10 min by the addition of saturated sodium persulphate, and the resulting solution was neutralized with sodium bicarbonate solution. The mixture was extracted with ethyl acetate, and the organic layer (purity, 90%; yield, 94%) was dried over sodium sulphate. The solvent was then removed under a stream of dry nitrogen, and the residue was purified by high-performance liquid chromatography. The radiochemical purity of the product was 99%. The specific activities of the compounds were not reported by the investigators, although the stability of [^{125}I]ADAM was reported to be 3 months under refrigerated conditions. The corresponding [^{123}I]ADAM was reported to be stable for 24 h after labeling. Another group of investigators who prepared [^{123}I/^{125}I]ADAM by a similar method reported the specific activity to be 8.88×10^6 GBq/mmol (240,000 Ci/mmol) for [^{123}I]ADAM and 8.14×10^4 GBq/mmol (2,200 Ci/mmol) for [^{125}I]ADAM (8).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using rat frontal cortical membrane homogenates for saturation binding studies with [^{125}I]ADAM, the radiochemical had a dissociation constant (K_d) of 0.15 ± 0.03 nM and a B_{max} of 194 ± 65 fmol/mg protein (8). In another study, the binding affinity (K_i) of [^{125}I]ADAM toward SERT on cloned LLC-PK1 cell membranes (of pig kidney origin) was 0.013 nM with a >1,000 fold selectivity over the respective norepinephrine (K_i = 699 nM) and dopamine (K_i = 840 nM) transporters.

Animal Studies

Rodents

[PubMed]

Oya et al. observed 60–240 min after administration of [^{125}I]ADAM that the rat brain showed an excellent label uptake (1.4% of the total dose at 2 min) consistently located in the hypothalamus, the organ with the highest concentration of SERT in the body (7). Choi et al. showed that the hypothalamic uptake of [^{125}I]ADAM in rats was blocked by pretreatment with SERT-selective competing drugs such as paroxetine and (+)McN5652 (8).

The biodistribution of [^{123}I]ADAM in mice and in individual organs and tissue was studied with whole-body autoradiography (WBAR) (9). The liver was found to have the highest uptake. By WBAR it was demonstrated that the label bound to SERT-rich sites found in the brain stem, lungs, adrenal glands, and the intestinal mucosa. The investigators concluded that radioiodinated ADAM was a suitable agent for the investigation and imaging of SERT in the central and peripheral nervous system, as well as the neuroendocrine tissue. From another study on rats and mice in the same laboratory, it was concluded that [^{123}I]ADAM accumulates in the same SERT-rich areas of the brain in both rats and mice (10). Uptake of the label in SERT-rich areas of the brain was inhibited by treatment with p-chloroamphetamine, a potent neurotoxin that causes the release and depletion of 5-HT in the central nervous system. The investigators concluded that [^{123}I]ADAM was an appropriate radioligand to study SERT function in humans. With a similar study in rats, Chalon et al. also concluded that [^{125}I]ADAM could be used to investigate central 5-HT system dysfunction in humans (11).

In another study, Hwang et al. concluded that SERT availability could be assessed semi-quantitatively in small animals by SPECT with radioiodinated ADAM (12).

Other Non-Primate Mammals

[PubMed]

Ye et al. investigated the biodistribution of [^{123}I]ADAM in the rabbit brain by SPECT. Maximum label was observed to accumulate in the brain stem 90–120 min after injection with a target/background ratio of 1.89 ± 0.02 (13). The investigators concluded that [^{123}I]ADAM was a suitable selective agent to investigate SERTs with SPECT.

Non-Human Primates

[PubMed]

A preliminary SPECT imaging study of [^{123}I]ADAM was conducted in baboons (7). A specific uptake of the label in the midbrain region, with a high concentration of SERT, of the animals was observed 180–240 min after administration of the radiopharmaceutical.

In another study from the same laboratory, the investigators used [^{123}I]ADAM and SPECT imaging to quantify SERT in baboon brains (*Papio anubis*) (14). Acton et al. used dynamic imaging and metabolite-corrected plasma data to determine the distribution volume (*DV*) of different regions of the brain and the distribution volume ratio (*DVR*) of target to cerebellum (CB); the CB was used as the reference tissue because it contains the lowest concentration of SERT compared to other parts of the brain). The mean *DV*s in the midbrain (MB) and CB were 4.86 ± 1.06 mL/mL and 2.25 ± 0.48 mL/mL, respectively. The MB *DVR* was 2.01 ± 0.17. From this study the investigators concluded that dynamic modeling of [^{123}I]ADAM SPECT scans could be used accurately and reproducibly to quantify SERT in non-human primates.

Huang et al. used SPECT with [^{123}I]ADAM in monkeys (*Macaca cyclopis*) to study the imaging of SERT (15). Using CB as the reference tissue, the investigators determined the specific uptake ratios (SURs) of the MB, thalamus (TH), striatum (ST), temporal and frontal cortices, and the whole brain. The SURs were ~3, ~2, and ~1 for the MB, TH, and ST, respectively, and the ratio was <1 for other regions of the brain. The SURs reached equilibrium in the MB, TH, and ST ~210 min after injection.

Human Studies

[PubMed]

SPECT was used in two laboratories to investigate the biodistribution of [^{123}I]ADAM in humans (6, 16). An analysis of the combined data from the two studies revealed that the radiolabel accumulated in the MB with a distribution that was consistent with selective binding to SERT (16). The region/CB ratios for the SPECT scans were 1.95 ± 0.13 for the MB, 1.27 ± 0.10 for the medial temporal regions, and 1.11 ± 0.07 for the ST. The investigators concluded that [^{123}I]ADAM was a safe and suitable radiochemical for SERT imaging in the human brain. In a preliminary study, the binding of [^{123}I]ADAM was investigated in human patients with major depressive disorder and normal healthy controls (17). Results from this study suggested that, compared to the control individuals, there was a decreased binding of the label in the MB region of the major depressive disorder patients that correlated with the severity of the depressive symptoms. The investigators also observed an age-related decrease in binding of the label in the MB SERT of the control subjects.

Using healthy volunteers, Booij and de Win as well as other investigators reported that the optimal imaging time for [^{123}I]ADAM SPECT was ~5 h after a single injection of the radiochemical (18-20).

To determine the possible involvement of a SERT-related endophenotype for purging or non-purging bulimia nervosa (BN), the binding of [^{123}I]ADAM was investigated in female twins (21). The purging BN women were observed to have a higher binding of the label in the MB compared to the non-purging BN women and the normal controls. The investigators concluded that, because this study was performed in a small group (13 BN patients), the results should be interpreted with caution and the observations should be

verified with a study involving a larger population. In another study, it was shown there was a significant ($P < 0.001$) increase in brainstem SERT availability in individuals suffering from migraines (22). However, the investigators suggested that whether SERT played a direct or an indirect role in the development of this condition remains to be determined.

References

1. Halford J.C., Harrold J.A., Boyland E.J., Lawton C.L., Blundell J.E. Serotonergic drugs : effects on appetite expression and use for the treatment of obesity. Drugs. 2007;**67**(1):27–55. PubMed PMID: 17209663.
2. Schule C. Neuroendocrinological mechanisms of actions of antidepressant drugs. J Neuroendocrinol. 2007;**19**(3):213–26. PubMed PMID: 17280595.
3. Suehiro M., Greenberg J.H., Shiue C.Y., Gonzalez C., Dembowski B., Reivich M. Radiosynthesis and biodistribution of the S-[18F]fluoroethyl analog of McN5652. Nucl Med Biol. 1996;**23**(4):407–12. PubMed PMID: 8832694.
4. Bagdy G., Kecskemeti V., Riba P., Jakus R. Serotonin and epilepsy. J Neurochem. 2007;**100**(4):857–73. PubMed PMID: 17212700.
5. Moresco R.M., Matarrese M., Fazio F. PET and SPET molecular imaging: focus on serotonin system. Curr Top Med Chem. 2006;**6**(18):2027–34. PubMed PMID: 17017972.
6. Kauppinen T.A., Bergstrom K.A., Heikman P., Hiltunen J., Ahonen A.K. Biodistribution and radiation dosimetry of [123I]ADAM in healthy human subjects: preliminary results. Eur J Nucl Med Mol Imaging. 2003;**30**(1):132–6. PubMed PMID: 12483421.
7. Oya S., Choi S.R., Hou C., Mu M., Kung M.P., Acton P.D., Siciliano M., Kung H.F. 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine (ADAM): an improved serotonin transporter ligand. Nucl Med Biol. 2000;**27**(3):249–54. PubMed PMID: 10832081.
8. Choi S.R., Hou C., Oya S., Mu M., Kung M.P., Siciliano M., Acton P.D., Kung H.F. Selective in vitro and in vivo binding of [(125)I]ADAM to serotonin transporters in rat brain. Synapse. 2000;**38**(4):403–12. PubMed PMID: 11044887.
9. Lin K.J., Ye X.X., Yen T.C., Wey S.P., Tzen K.Y., Ting G., Hwang J.J. Biodistribution study of [(123)I] ADAM in mice: correlation with whole body autoradiography. Nucl Med Biol. 2002;**29**(6):643–50. PubMed PMID: 12234588.
10. Lin K.J., Yen T.C., Wey S.P., Hwang J.J., Ye X.X., Tzen K.Y., Fu Y.K., Chen J.C. Characterization of the binding sites for 123I-ADAM and the relationship to the serotonin transporter in rat and mouse brains using quantitative autoradiography. J Nucl Med. 2004;**45**(4):673–81. PubMed PMID: 15073265.
11. Chalon S., Bronquard C., Vercouillie J., Kodas E., Garreau L., Bodard S., Emond P., Besnard J.C., Guilloteau D. ADAM is an effective tool for in vivo study of serotonergic function: validation in rat models. Synapse. 2004;**52**(2):136–42. PubMed PMID: 15034919.

12. Hwang L.C., Chang C.J., Liu H.H., Kao H.C., Lee S.Y., Jan M.L., Chen C.C. Imaging the availability of serotonin transporter in rat brain with 123I-ADAM and small-animal SPECT. Nucl Med Commun. 2007;**28**(8):615–21. PubMed PMID: 17625383.
13. Ye X.X., Hwang J.J., Hsieh J.F., Chen J.C., Chou Y.T., Tu K.Y., Wey S.P., Ting G. In vivo quantification by SPECT of [123I] ADAM bound to serotonin transporters in the brains of rabbits. Nucl Med Biol. 2004;**31**(8):995–1003. PubMed PMID: 15607481.
14. Acton P.D., Choi S.R., Hou C., Plossl K., Kung H.F. Quantification of serotonin transporters in nonhuman primates using [(123)I]ADAM and SPECT. J Nucl Med. 2001;**42**(10):1556–62. PubMed PMID: 11585873.
15. Huang W.S., Ma K.H., Cheng C.Y., Chen C.Y., Fu Y.K., Chou Y.H., Wey S.P., Liu J.C. Imaging serotonin transporters with 123I-ADAM brain SPECT in healthy non-human primates. Nucl Med Commun. 2004;**25**(5):515–9. PubMed PMID: 15100512.
16. Newberg A.B., Plossl K., Mozley P.D., Stubbs J.B., Wintering N., Udeshi M., Alavi A., Kauppinen T., Kung H.F. Biodistribution and imaging with (123)I-ADAM: a serotonin transporter imaging agent. J Nucl Med. 2004;**45**(5):834–41. PubMed PMID: 15136634.
17. Newberg A.B., Amsterdam J.D., Wintering N., Ploessl K., Swanson R.L., Shults J., Alavi A. 123I-ADAM binding to serotonin transporters in patients with major depression and healthy controls: a preliminary study. J Nucl Med. 2005;**46**(6):973–7. PubMed PMID: 15937308.
18. Booij J., de Win M.M. Brain kinetics of the new selective serotonin transporter tracer [(123)I]ADAM in healthy young adults. Nucl Med Biol. 2006;**33**(2):185–91. PubMed PMID: 16546672.
19. Catafau A.M., Perez V., Penengo M.M., Bullich S., Danus M., Puigdemont D., Pascual J.C., Corripio I., Llop J., Perich J., Alvarez E. SPECT of serotonin transporters using 123I-ADAM: optimal imaging time after bolus injection and long-term test-retest in healthy volunteers. J Nucl Med. 2005;**46**(8):1301–9. PubMed PMID: 16085586.
20. Sacher J., Asenbaum S., Klein N., Geiss-Granadia T., Mossaheb N., Poetzi C., Attarbaschi T., Lanzenberger R., Spindelegger C., Rabas A., Heinze G., Dudczak R., Kasper S., Tauscher J. Binding kinetics of 123I[ADAM] in healthy controls: a selective SERT radioligand. Int J Neuropsychopharmacol. 2007;**10**(2):211–8. PubMed PMID: 16487452.
21. Koskela A.K., Keski-Rahkonen A., Sihvola E., Kauppinen T., Kaprio J., Ahonen A., Rissanen A. Serotonin transporter binding of [123I]ADAM in bulimic women, their healthy twin sisters, and healthy women: a SPET study. BMC Psychiatry. 2007;**7**:19. PubMed PMID: 17511889.
22. Schuh-Hofer S., Richter M., Geworski L., Villringer A., Israel H., Wenzel R., Munz D.L., Arnold G. Increased serotonin transporter availability in the brainstem of migraineurs. J Neurol. 2007;**254**(6):789–96. PubMed PMID: 17351723.