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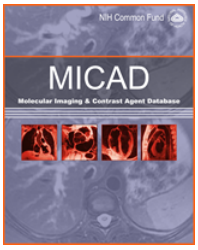

3-[2-[4-(4-[^{18}F]Fluorobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3*H*-quinazolin-4-one

[^{18}F]Altanserin

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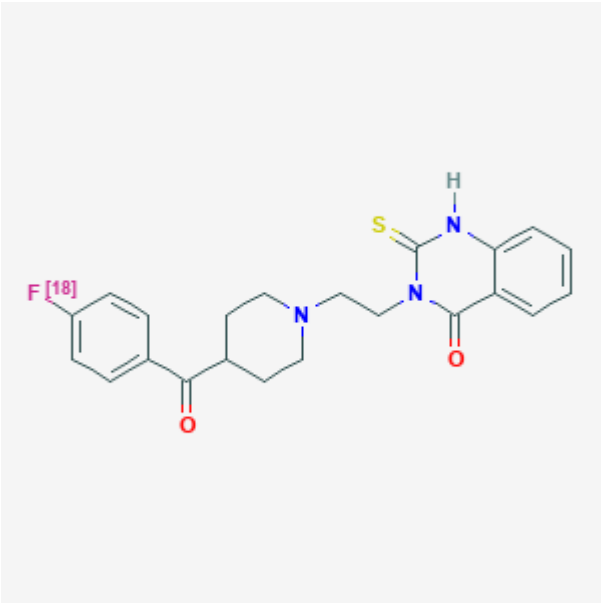
Chemical name:	3-[2-[4-(4-[^{18}F]Fluorobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3*H*-quinazolin-4-one
Abbreviated name:	
Synonym:	[^{18}F]Altanserin
Agent Category:	Compound
Target:	5-HT$_{2A}$ serotonin receptors
Target Category:	Receptor binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[P ubMed]

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiologic roles as a neurotransmitter in the central nervous system (1). It is involved in regulation and modulation of sleep, affective and personality behaviors, and pain. It also is a regulator of smooth muscle function and platelet aggregation. The brain cortical 5-HT system

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has been implicated in several neuropsychiatric disorders, including major depression, anxiety, obsessive-compulsive disorder, and schizophrenia (2, 3). The effects of 5-HT are mediated by as many as seven classes of receptor populations (5-HT_1 to 5-HT_7), many of which include several subtypes (4). There are three receptor subtypes within the G protein-coupled 5-HT_2 receptor family: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}.

5-HT_{2A} receptors are abundantly present in the cerebral cortex, basal forebrain, hippocampus, amygdala, dorsal thalamus, hypothalamus, superior colliculus, substantia nigra, pedunculopontine nucleus, legmental area, and myelencephalon (5). 5-HT_{2A} receptors are involved in mediation of normal and psychotic states, working memory, regulation of GABAergic and cholinergic neuronal cells, sleep, peripheral pain, and cardiovascular functions. 5-HT_{2B} receptors are found mainly in several peripheral tissues, such as the stomach, intestine, and pulmonary smooth muscle, and in the myocardium. In the brain, 5-HT_{2B} receptors are found in discrete nuclei of the cerebellum, lateral septum, dorsal hypothalamus, dorsal raphe, and amygdala. 5-HT_{2C} receptors are found in the choroid plexus, substantia nigra, globus pallidus, and ventromedial thalamus. 5-HT_{2A} receptors are implicated in several psychiatric disorders, such as schizophrenia, depression, and obsessive-compulsive disorder. Thus, there is a need for selective ligands to investigate the pharmacologic role of 5-HT_{2A} receptors.

There have been several studies to develop specific 5-HT_{2A} radioligands, such as [^{11}C]ketanserin (6), [^{18}F]spiperone (7), [^{11}C]methylspiperone ([^{11}C]NMSP), and [^{18}F]setoperone [PubMed], for positron emission tomography (PET) imaging. However, none has proven specific for 5-HT_{2A} receptors because these compounds also bind to other receptors, such as dopamine receptors and 5-HT_1 receptor subtypes. Altanserin, a fluorobenzoyl derivative related to ketanserin, was reported to be a potent inhibitor of 5-HT_{2A} receptors with >100-fold selectivity over $D_{2/3}$ receptors, 5-HT_{1A}, 5-HT_6, and 5-HT_7 (8, 9). This led to the development of 3-[2-[4-(4-[^{18}F]fluorobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3*H*-quinazolin-4-one ([^{18}F]altanserin) as a useful tool for 5-HT_{2A} receptor PET imaging *in vivo* (10).

Synthesis

[PubMed]

The reported radiosynthesis of [^{18}F]altanserin involved nucleophilic substitution of 3-[2-[4-(4-nitrobenzoyl)-1-piperidyl]ethyl]-2-sulfanyl-3*H*-quinazolin-4-one with K[^{18}F]F/Kryptofix2.2.2 in dimethyl sulfoxide, followed by high-performance liquid chromatography (HPLC) purification (10). The reported overall radiochemical yield of the radiosynthesis was 10% at end of synthesis (EOS), the specific radioactivity was 30-48 GBq/μmol (0.8-1.3 Ci/μmol), and the radiochemical purity was >99%. The time for synthesis and purification was approximately 110 min.

Monclus et al. (11) and Tan et al. (12) reported automatic systems for synthesis of [^{18}F]altanserin using microwave heating and SepPak and HPLC purification. [^{18}F]Altanserin was prepared in 90-114 min with 20% radiochemical yield, a radiochemical purity >99%, and specific radioactivity of 103-115 GBq/μmol (2.8-3.1 Ci/μmol) at EOS.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Altanserin has been reported to have high binding affinities for 5-HT_{2A} receptor sites. Leysen (8) reported K_i values for 5-HT_{2A}, 5-HT_{1A}, D_2, α_1, and H_1 receptors of 0.13, 1400, 62, 4.6, and 7.8 nM, respectively. Tan et al. (9) extended the studies, obtaining K_i values for 5-HT_{2A}, 5-HT_{2c}, 5-HT_6, and 5-HT_7 of 0.3, 6, 1756, and 15 nM, respectively. They also found that the binding of 4-(4-fluorobenzoyl)piperidine (4-FBP) and altanserinol, the major plasma metabolites of altanserin, to these four 5-HT receptor subtypes was negligible. These data support that altanserin is a specific 5-HT_{2A} antagonist.

In vitro studies of [^{18}F]altanserin binding produced K_d values of 0.30, 0.24, and 0.33 nM for rat cerebrum, frontal cortex, and cerebellum, respectively (13). The 5-HT$_{2A}$ B_{max} values were 145, 523, and 8 fmol/mg protein for rat cerebrum, frontal cortex, and cerebellum, respectively. In saturation binding studies using [^{18}F]altanserin, the estimated K_d value was 0.28 ± 0.03 nM (0.35 ± 0.04 nM with 100 nM SB 206553, a selective 5-HT$_{2B/C}$ antagonist) for rat frontal cortex membranes. The B_{max} values were 153 ± 5 and 156 ± 10 fmol/mg protein without and with 100 nM SB 206553, respectively. Similarly, the K_d and B_{max} were almost the same in the presence or absence of prazosin, a selective α_1-receptor antagonist.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in rats showed a moderate accumulation of radioactivity in the whole brain with 0.42%, 0.54%, and 0.21% injected dose (ID)/g, respectively, at 5, 60, and 240 min after injection of [^{18}F]altanserin (10). There was a marked accumulation of the tracer in the frontal cortex within the first 5 min (1.14% ID/g), followed by a slow decrease of radioactivity to 1.00% ID/g at 60 min. The striatum (0.39% ID/g) and thalamus (0.18% ID/g) exhibited slightly lower radioactivity compared with the frontal cortex at 60 min. The maximum frontal cortex-to-cerebellum, striatum-to-cerebellum, and thalamus-to-cerebellum ratios were 10.8, 3.6, and 1.8, respectively, at 120 min. The bulk of accumulation was in the lungs, liver, and kidneys at 5 min. Clearance of radioactivity occurred at 240 min for all tissues except the bone, which showed an increase from 0.18% ID/g at 5 min to 0.31% ID/g at 240 min, most likely because of defluorination. The accumulation of [^{18}F]altanserin in frontal cortex and striatum was blocked by various unlabeled 5-HT$_2$ antagonists (ketanserin, mesulergin, ritanserin, and spiperone) but not by D_2 antagonists (sulpiride and halopemide). The fraction of unchanged [^{18}F]altanserin in blood samples determined by HPLC was 85%, and [^{18}F]altanserin remained 96% intact in the brain at 240 min after injection.

In an autoradiographic study of *in vivo* binding of [^{18}F]altanserin in rat brain, the highest levels were found in the frontal cortex, claustrum, and anterior olfactory nuclei (14). [^{18}F]Altanserin binding to the frontal cortex was reversed (59%) by administration of ketanserin (4 mg/kg) 30 min after tracer injection. Ketanserin (4 mg/kg) and mesulergin (10 mg/kg) pretreatment blocked [^{18}F]altanserin binding by 82% and 85%, respectively. On the other hand, sulpiride and prazosin showed no significant inhibition. The B_{max} values for the frontal cortex were estimated to be 36.7 ± 3.4 and 30.2 ± 4.2 pmol/g tissue by electronic and film optical counting, respectively.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[^{18}F]Altanserin was administered to baboons by bolus (170 MBq, or 4.6 mCi) plus constant infusion (41 MBq/h, or 1.1 mCi/h) (15). PET measurements began after the plasma level was stabilized, by 4-5 h after injection. High accumulation of [^{18}F]altanserin was found in the cortical regions of baboon brains, with nonsignificant levels in the striatum and cerebellum at 8 h. [^{18}F]Altanserin binding to the frontal cortex was reversed (73 ± 13%) by administration of ketanserin (1.5-2.0 mg/kg) 5.5-6.5 h after the tracer injection, whereas there was only a 6 ± 2% decrease in the cerebellum. Injection of 1.5 mg/kg SR46349B (another 5-HT$_{2A}$ antagonist) resulted in a 76%

decrease in the cortical region, but only a 13% decrease in the cerebellum, a tissue thought to have very low density of 5-HT_{2A} receptors.

The brain accumulation of radioactivity was studied by PET imaging in baboons after bolus injection of [^{18}F]altanserin, [^{18}F]altanserinol, or [^{18}F]4-FBP, with accumulations in the frontal cortex of 0.014%, 0.004%, and 0.010% ID/ml, respectively, at 25 min (16). [^{18}F]Altanserin images (35-90 min post injection) displayed radioactivity concentrations that followed a rank order: frontal and temporal cortices > thalamus > basal ganglia > cerebellum. Regionally, specific 5-HT_{2A} receptor binding was not evident in the later [^{18}F]altanserinol or [^{18}F]4-FBP image data. These data were consistent with blood-brain barrier passage and nonspecific localization of [^{18}F]altanserinol, [^{18}F]4-FBP, and/or their secondary radiolabeled metabolites. Therefore, the uniformity of nonspecific binding of these metabolites in all brain regions strengthened the validity of analyses of [^{18}F]altanserin PET data by conventional methods of kinetic rate constants. After bolus injection of [^{18}F]altanserin in baboons, 88 ± 5% and 23 ± 8% of the total plasma radioactivity was intact [^{18}F]altanserin at 2 and 90 min, respectively. [^{18}F]Altanserinol and [^{18}F]4-FBP were 12% and 50% at 90 min. In contrast, no major metabolites of [^{18}F]altanserin were found in rat plasma and brain (10).

Human Studies

[PubMed]

[^{18}F]Altanserin PET studies of 5-HT_{2A} receptor distribution in human brain have shown a significant major localization of radioactivity in the cortical regions and a minor accumulation in the striatal regions (17-19). Quantitative analysis of [^{18}F]altanserin binding was usually performed using distribution volume (DV) and/or kinetic rate constants (Logan graphic method) from which binding potential (BP; k_3/k_4 or B_{max}/K_d) was derived to measure receptor concentrations. Biver et al. (17) reported on [^{18}F]altanserin PET studies in 12 healthy subjects (27-45 years of age). PET brain scans showed high accumulation of radioactivity in the cortical regions (temporal > frontal > parietal > limbic > occipital) at 90 min after injection of [^{18}F]altanserin (3.7 MBq/kg, or 0.1 mCi/kg). Accumulations in the basal ganglia and cerebellum were very low. The frontal cortex-to-cerebellum ratio was about 2.4. The frontal cortex BP was 2.98 ± 0.917 and 2.97 ± 0.679 by nonlinear regression and Logan graphic analysis, respectively. At 90 min post injection, 45% of [^{18}F]altanserin radioactivity remained intact in plasma. In a later study, Price et al. (20) concluded that the most comprehensive and quantitatively valid analysis for bolus [^{18}F]altanserin PET data was the dual-input method, which specifically accounted for blood-brain barrier-permeable metabolites, although the Logan graphic method was preferred because it provided a good compromise between validity, sensitivity, and reliability of implementation. Sadzot et al. (18) showed that ketanserin (0.1 mg/kg) was able to displace [^{18}F]altanserin binding in all brain regions when administered 57 min after the tracer injection. Smith et al. (19) demonstrated good test-retest reliability of [^{18}F]altanserin Logan DV values in various brain regions.

Meltzer et al. (21) studied the effects of age on the binding of [^{18}F]altanserin to 5-HT_{2A} receptor sites in 9 healthy elderly (ages 61-76 years) and 9 healthy young (ages 18-29 years) subjects by PET imaging. The BPs of the 5-HT_{2A} receptors in the striatum, cingulate, amygdala/hippocampus, occipital cortex, and temporal cortex decreased with age by 49%, 65%, 66%, 47%, and 58%, respectively. In another study with 22 healthy subjects (21-69 years of age), Sheline et al. (22) found an age-dependent decrease of 5-HT_{2A} receptor BP (about 17% per decade) in the hippocampus, cingulate occipital cortex, prefrontal cortex, and occipital cortex. The 5-HT_{2A} receptor loss was progressive from the second decade through the fifth decade (70% loss) and then leveled off. Adams et al. (23) reported, in a study of 52 healthy subjects (ages 21-79 years), that there were significant negative correlations between all cortical regions, except the occipital cortex, in 5-HT_{2A} receptor binding (measured as specific DV, with cerebellum as the reference) and age, with a loss of 6% per decade. The DVs of the caudate, putamen, and thalamus were also unrelated to age. On the other hand, there was a positive

correlation between cerebellar 5-HT_{2A} receptor binding and age. There was no difference in 5-HT_{2A} DV between men and women.

Studies have found significant reductions in 5-HT_{2A} BPs in the orbito-insular cortex (24) and hippocampus (25, 26) of patients with depression but free of any psychotropic medication for at least 10 days. There were some decreases in BP in other cortical regions, but these were not significant. In Alzheimer's disease (27), anorexia nervosa (28, 29), and schizophrenia (30) patients (free of psychotropic medications), there were significant decreases in 5-HT_{2A} receptor binding in various cortical regions. On the other hand, there was a significant increase in 5-HT_{2A} BP in the caudate nuclei in patients with obsessive-compulsive disorder compared with healthy control subjects (31).

[18F]Altanserin PET is useful for objective monitoring of 5-HT_{2A} receptor density in patients with psychological disorders. Internal dosimetry data for [18F]altanserin in humans are not available in the literature.

NIH Support

AG5133, MH52247, MH49936, MH01210, MH55305, MH30929, MH58620, P50 DA84733, MH58444, MH01370, MH54731, K24 MH6542, RR00036, MH49936, MH00295

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