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A new single-photon emission computed tomography (SPECT) imaging agent for serotonin transporters: [^{125}I]Flip-IDAM, (2-((2-((dimethylamino)methyl)-4-iodophenyl)thio)phenyl)methanol

Pinguan Zheng [a], Brian P. Lieberman [a], Karl Ploessl [a], Laetitia Lemoine [a], Sara Miller [a], Hank F. Kung [a,b,*]

[a] Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA
[b] Department of Pharmacology, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

New ligands for in vivo brain imaging of serotonin transporter (SERT) with single photon emission tomography (SPECT) were prepared and evaluated. An efficient synthesis and radiolabeling of a biphenylthiol, FLIP-IDAM, **4**, was accomplished. The affinity of FLIP-IDAM was evaluated by an in vitro inhibitory binding assay using [^{125}I]-IDAM as radioligand in rat brain tissue homogenates (K_i = 0.03 nM). New [^{125}I]Flip-IDAM exhibited excellent binding affinity to SERT binding sites with a high hypothalamus to cerebellum ratio of **4** at 30 min post iv injection. The faster in vivo kinetics for brain uptake and a rapid washout from non-specific regions provide excellent signal to noise ratio. This new agent, when labeled with ^{123}I, may be a useful imaging agent for mapping SERT binding sites in the human brain.

Serotonin transporter (SERT) is located exclusively on the presynaptic terminals on serotonergic neurons in the brain. It plays a crucial role in the regulation of the level of serotonin concentration in the synaptic cleft, as it rapidly transports the neurotransmitter serotonin from the synaptic cleft to the neuron terminal. SERT binding sites are major drug targets for the treatment of depression. By blocking the re-uptake serotonin the SSRIs improve the availability of serotonin in the synaptic cleft. Many selective serotonin re-uptake inhibitors (SSRIs), approved by the FDA, have been prescribed to treat millions of patients with depression. SSRIs also find efficacy in the treatment of anxiety disorders and eating disorders.[1,2] In addition, alterations of SERT could be related to other neuropsychiatric disorders, such as epilepsy, Alzheimer's disease, Parkinson's disease and dementia with Lewy bodies, as well as addictive behaviors, such as cocaine abuse and alcoholism.[3–7] Therefore, a successful molecular imaging agent for SERT will be able to measure the drug occupancy of antidepressants and in turn provide personalized dosage of drugs. A SERT imaging agent will also help elucidate the function of serotonin transmission and alterations in the pathophysiology of various neuropsychiatric conditions.

Molecular imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), provide powerful, noninvasive tools for visualizing biological functions in the diseases. Even though rapid growths of PET in the clinical setting, SPECT is also widely used in clinical applications. Compared with PET, production of SPECT tracers is easier and less costly for those long half-life SPECT radionuclides allowing off-site production of radiotracers and efficient distribution with a national supply network. Therefore, we are interested in the development of SERT-selective SPECT imaging agents labeled with I-123 ($T_{1/2}$, 13 h).

Several structural classes of SERT ligands have been studied in the past two decades, including nitroquipazine,[8] tropanes,[9–11] isoquinoline,[12] as well as diphenyl sulfides.[13–19] Nitroquipazine ligands generally possess high SERT potency (K_i = 0.05–0.3 nM).

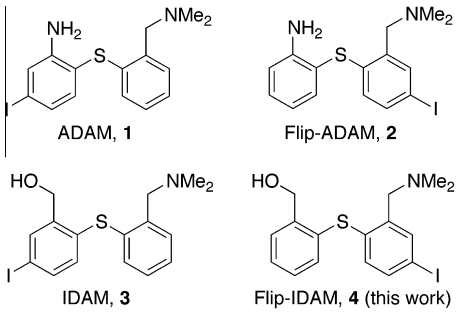

Figure 1. Structure of some SPECT imaging agent for SERT.

* Corresponding author. Tel.: +1 215 662 3096; fax: +1 215 349 5035.
E-mail address: kunghf@sunmac.spect.upenn.edu (H.F. Kung).

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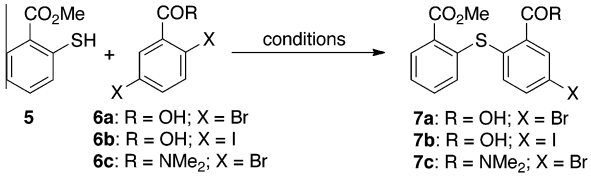
Table 1
Comparison of inhibition constants of selected ligands for serotonin transporter



	Starting material	Conditions	Product	Yield (%)
1	**6a**	NaOMe, DMA, 100 °C, 72 h	**7a**	0
2	**6b**	NaOMe, DMA, 110 °C, 68 h	**7b**	0
3	**6c**	$Pd_2(dba)_3$, dppf, TEA, NMP 60 °C, 2.5 h	**7c**	0
4	**6b**	CuI, glycol, K_2CO_3, *i*-PrOH, 80 °C, 68 h	**7b**	83
5	**6b**	CuI, 1,10-phen, DIPE Tol, 110 °C, 68 h	**7b**	71

However, the modest target to non-target ratios and the slow pharmacokinetics make this series of tracers unsuitable for PET/SPECT imaging. Hypothalamus an area in the brain which is rich in serotonin transporters, is commonly used as an indicator for SERT specific uptake (target area). Cerebellum (another area in the brain) on the other hand, is devoid of SERT and thus making it a good reference as a background (non-target area). Tropane derivatives, such as βFE*p*ZIENT, displayed good SERT binding affinity (K_i = 0.08 nM) and excellent selectivity over DAT and NET. In vivo distribution studies of βFE*p*ZIENT revealed a ratio of 2.5 for hypothalamus to cerebellum.[9] Isoquinoline scaffold, such as (+)-McN5652, was also under intensive studies in 1990s. However, further biological studies of these ligands were impeded by several limitations, which include low signal to noise ratio and high non-specific binding.[8,12]

Diphenyl sulfide ligands, derived from 403U76, emerged as an interesting SERT ligands.[20] Due to its high binding affinity for SERT and ease of synthesis, a large number of diphenyl sulfide ligands have been synthesized and tested in biological studies (Fig. 1). In 1999, our group reported [^{123}I]IDAM as a SPECT ligand in this series. [^{123}I]IDAM displayed good binding affinity towards SERT (K_i = 0.097 nM) and excellent selectivity (DAT/SERT >100,000; NET/SERT >2400).[13–15,19] Biodistribution study in rat showed favorable pharmacokinetics and good ratio of 2.76 at 60 min for hypothalamus to cerebellum.[21] Further structure–activity studies led to the discovery of [^{123}I]ADAM. [^{123}I]ADAM binds to SERT with high affinity (K_i = 0.013 nM). A peak signal to noise of 4.78 was observed at 120 min post-injection. Since then, [^{123}I]ADAM has become a leading SPECT imaging agent and it is useful for SPECT imaging studies in humans.[22] With an aim to further improve the kinetics of [^{123}I]ADAM, we prepared a novel ligand [^{123}I]Flip-ADAM. A switch of iodo position from ring A to ring B in ADAM led to comparable initial brain uptake and faster brain clearance, albeit a lower target-background ratio than ADAM.[23] Encouraged by the improved biological properties demonstrated by [^{123}I]Flip-ADAM, we herein document a new member of SPECT ligand, [^{123}I]Flip-IDAM. We envision that a similar switching of iodo substitution position in IDAM would maintain the high brain uptake while improving the target-background ratio of IDAM.

Synthesis of the desired Flip-IDAM (**4**) started with an investigation of C–S coupling between aryl thiols and aryl halides (Table 1). Nucleophilic aromatic substitution of aryl halide did not yield any desired product in the presence of sodium methoxide (entries 1 and 2). Attracted by elegant work by Migita et al.[24] and Ortar and co-workers[25] on the palladium-catalyzed C–S coupling, we subjected **5** and **6c** to the catalytic system comprising $Pd_2(dba)_3$ and dppf. However, no desired coupling product was obtained (entry 3). A homo-coupling product (aryl disulfide) was generated exclusively.

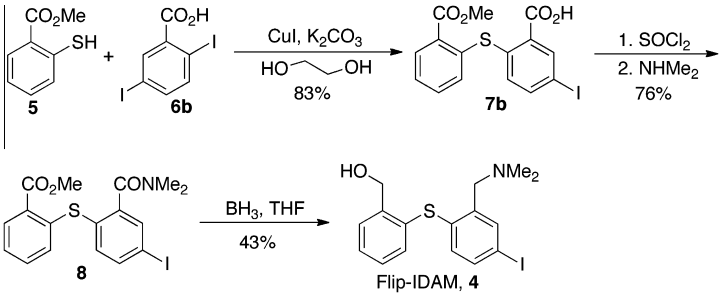
Encouraged by elegant organic synthetic works by Buchwald and co-workers[26] and Sawada et al.,[27] we tested copper catalytic system in our synthesis of **7b**. To our delight, thiol **5** was successfully coupled with aryl iodide **6b** to afford **7b** in good yield (entries 4 and 5). It is noteworthy that Buchwald's catalytic system delivered a higher yield of desired product (entries 4 and 5).

With key intermediate **7b** in hand, **7b** was further converted to amide **8** in 76% yield. Borane reduction of ester and amide afforded final Flip-IDAM **4** in 43% yield (Scheme 1).

Palladium-catalyzed stannylation delivered tin precursor **9** with 75% yield and 98% purity (Scheme 2).

Trace iodide impurity can be removed via HPLC purification. Brief treatment of tin precursor **9** with an ethanolic solution of [^{125}I]NaI, HCl and 3% H_2O_2, yielded [^{125}I]Flip-IDAM in 83% radiochemical yield and >99% radiochemical purity. The radiochemical identity was verified by a co-injection of cold Flip-IDAM, which showed an identical retention time using HPLC analysis (Fig. 2).

The in vitro studies were carried out using literature reported procedures.[28] Membrane homogenates containing serotonin transporter (LLC-SERT) was prepared and used to measure binding



Scheme 1. Synthesis of Flip-IDAM, **4**.