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SYNTHESIS AND PRELIMINARY EVALUATION OF L-6-[^{123}I]IODODOPA AS A POTENTIAL SPECT BRAIN IMAGING AGENT

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Abstract

L-6-[^{123}I]Iododopa was synthesized by the exchange of ^{123}I for bromine on L-6-bromodopa in buffer(pH 4) for 35 minutes at 97°C. The synthesis was complete in approximately 1 hour with a radiochemical yield of 50% , a specific activity of 65 Ci/mmol and a radiochemical purity of >95%. A non radioactive standard of L-6-iododopa was synthesized by the iododemercuration of a mercury-dopa derivative using I_2 in chloroform. It was shown that L-6-[^{123}I]iododopa accumulated in the rat striatum with striatum:whole brain ratio of 1.36 at 1 hour and 1.11 at 2 hours.

Key Words: L-6-[^{123}I]iododopa, dopamine metabolism, SPECT, L-dopa.

Introduction

L-6-[^{18}F]Fluorodopa (6-FD) is rapidly becoming one of the most useful imaging agents used in PET to study dopamine metabolism in vivo (1,2,3). The aim of the work described here was to synthesize a ^{123}I labeled analog of 6-FD as a potential agent for studying dopamine metabolism using SPECT.

Recently, Wong and De Jesus (4) synthesized L-6-bromodopa by the direct bromination of L-dopa with molecular bromine. Since the exchange of aryl bromides with iodide is an established method for preparing radioiodine labeled compounds (5,6,7,8,9) the exchange of bromine with iodine on L-6-bromodopa seemed a likely route to L-6-[^{123}I]iododopa (6-ID).

We have also prepared a non radioactive standard of L-6-iododopa by the addition of iodine to a protected mercury-dopa derivative. Upon deprotection of the iodinated compound, with boron tribromide, one obtains L-6-iododopa (structure confirmed by nmr, elemental analysis, mass spectrometry and chiral HPLC) which was used as a chromatographic standard for the identification of 6-ID.

A preliminary investigation of the biodistribution of 6-ID in rats is also reported.

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Experimental

General

L-Dopa was purchased from Sigma. All other chemicals were purchased commercially and were used with no further purification.

Melting points were carried out on a Buchi capillary tube - oil bath apparatus and are uncorrected. Nmr spectroscopy was performed on a 300 or 400 MHz spectrometer. F.A.B. and low resolution mass spectrometry was performed at the B.C. Regional Mass Spectrometry Centre, UBC Chemistry Department, Vancouver, B.C. HPLC analysis was carried out on a Spectrophysics system using a 90 : 10 (0.02 M KOAc / MeOH) eluant adjusted to pH 3.9 (with glacial acetic acid) at a flow rate of 3 mL / min and a Waters RCM C-18 column (8NVC-18) with UV detection at 280 nm or as otherwise indicated in the text. Enantiomeric purity was determined by chiral HPLC as described previously (10) with the modification that pH 3.65 was used.

No carrier added $Na^{123}I$ was obtained from Nordion International and elemental analysis was performed by Canadian Microanalytical Services Ltd., New Westminster, B.C..

Biodistribution Study in Rats

Male Wistar rats (350 g, 5 rats per time point) were injected i.p. with carbidopa (25 mg/Kg) 30 minutes prior to the tail vein injection of 6-ID (3.3 MBq/0.12 mL doses)

Synthesis of L-Methyl-N-carbomethoxy-[β-(3,4-dimethoxyphenyl)]alaninate (4a)

To a stirred suspension of L-dopa **1** (5.92 g, 30 mmol) in methanol (60 mL) at 0° was slowly added thionyl chloride (2.63 mL, 36 mmol). The resulting yellow solution was heated at reflux for 4 h. The reaction mixture was cooled to room temperature and the solvent and excess thionyl chloride were evaporated under reduced pressure. Toluene (3 mL) was added to the residue and then concentrated to dryness. The resulting ester was dried under vacuum overnight and the hygroscopic light yellow solid thus obtained **2** (7.4 g) was suspended in dichloromethane (60 mL). To the stirred and cooled (0°) suspension was added triethylamine (4.18 mL, 30 mmol) dropwise. After 5 min. of stirring, methyl chloroformate (2.32 mL, 30 mmol) was added followed by more triethylamine (4.18 mL, 30 mmol). The mixture was stirred at room temperature under nitrogen for 6 h, taken up into dichloromethane (20 mL), and then washed successively with two 10 mL portions of aqueous HCl (0.5 M) and two 10 mL portions of saturated NaCl solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was dried under vacuum overnight to afford 4.85 g, (18 mmol)

of a yellow oil **3a** which was mixed with potassium carbonate (6.22 g, 45 mmol) and iodomethane (3.36 mL, 54 mmol) in methyl ethyl ketone (36 mL) and heated at reflux under nitrogen for 6 h. After the reaction mixture had cooled to room temperature, it was filtered to remove the white solid present and the solid washed with ethyl acetate (70 mL). The combined filtrate and washings were evaporated under reduced pressure to dryness, the residue dissolved in ethyl acetate (2-3 mL), passed through a silica Sep Pak cartridge[2]and Millex-SR[3](0.5 μm) filter unit, and eluted with ethyl acetate (25 mL). The solvent was evaporated and the resulting residue was dried further at room temperature under vacuum overnight to afford 4.5 g of a yellow oil. This material was used without purification for the synthesis of **5a**. For structure identification a small amount was purified by column chromatography on silica gel (40-140 mesh) using chloroform-methanol (98:2) as the eluting solvent to give a light yellow solid which was then recrystallized from ethyl acetate-petroleum ether to afford pure **4a** as a white solid (Tables 1 and 2).

L-Methyl-N-carbobenzyloxy-[β-(3,4-dihydroxyphenyl)]alaninate (3b)

To a stirred suspension of **2** (4.95 g, 20 mmol), synthesized as described above, in dichloromethane (40 mL) at 0° was added triethylamine (2.79 mL, 20 mmol) dropwise. After 5 minutes of stirring, benzyl chloroformate (2.86 mL, 20 mmol) was added to the blue-green solution followed by more triethylamine (2.79 mL, 20 mmol). The mixture was stirred at room temperature under nitrogen for 23 h, evaporated under reduced pressure, and the resulting dark grey residue was taken up into ethyl acetate (60 mL). The organic solution was washed successively with two 10 mL portions of aqueous 0.5 M HCl, 10 mL of saturated $NaHCO_3$ solution and two 10 mL portions of saturated NaCl solution. The organic layer was dried and evaporated under reduced pressure to give a yellow oil. This material was purified by column chromatography on 150 g of silica gel (40-140 mesh) using chloroform-methanol (95:5) as the eluting solvent to afford 3.44 g (50%) of **3b** as a pale yellow oil (Table 1).

L-Methyl-N-carbobenzyloxy-[β-(3,4-dimethoxyphenyl)]alaninate (4b)

A stirred mixture of **3b** (3.27 g, 9.48 mmol) , potassium carbonate (3.28 g, 23.7 mmol) and iodomethane (1.77 mL, 28.4 mmol) in methyl ethyl ketone (15 mL) was heated at reflux under nitrogen for 21 h. After the reaction mixture had cooled to room temperature, the white solid was filtered off and was washed with ethyl acetate (50 mL). The combined filtrate and washings were evaporated under reduced pressure to give a yellow oil and white solid. This material was taken up into some chloroform-

[2]Waters Millipore

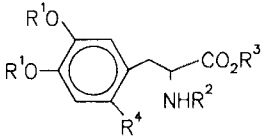
[3]Milli pore Corp.

Table 1. ^{1}H NMR data for compounds (3b–8)

cpd. no.	^{1}H NMR chemical shifts (ppm)[a]							
	$-NHCO_2\underline{CH_3}$	$-NHCO_2\underline{CH_2}\phi$	$-\underline{CH_2}-CH-$	$-O\underline{CH_3}$[b]	$-CH_2-\underline{CH}-$	$-\underline{NH}-$	$Ar-\underline{H}$[c]	$-NHCO_2CH_2Ar\underline{H}$
3b[d]	–	s,5.05	m,2.93	s,3.67	m,4.57	d,5.51	m,6.43–6.70	m,7.25
4a[d]	s,3.75	–	m,3.07	s,3.98 s,3.98 s,3.70	m,4.63	d,5.15	m,6.64–6.84	–
4b[d]	–	s,5.09 s,5.11	m,3.05	s,3.73 s,3.87 s,3.73	m,4.64	d,5.12	m,6.58–6.78	s,7.35
5a[d]	s,3.76	–	d,3.15	s,3.90 s,3.91 s,3.70	m,4.56	d,5.55	s,6.75 s,6.82	–
5b[d]	–	m,5.12	m,3.15	s,3.84 s,3.87 s,3.76	m,4.58	d,5.64	s,6.69 s,6.71	s,7.39
6a[d]	s,3.75	–	dd,3.10 dd,3.25	s,3.83 s,3.87 s,3.65	m,4.65	d,5.27	s,6.70 s,7.22	–
6b[d]	–	m,5.10	dd,3.09 dd,3.22	s,3.76 s,3.83 s,3.75	m,4.67	d,5.31	s,6.70 s,7.20	s,7.35
7[e]	–	–	dd,2.96 dd,3.24	–	dd,3.97	–	s,6.80 s,7.35	–
8[e]	–	–	dd,2.80 dd,3.02	–	dd,4.03	–	s,6.45 s,6.83	–

[a]Center of multiplet [b]ArOMe & –COOMe [c]Dopa ring ArH [d]$CDCl_3$ [e]D_2O/DCl

Table 2. Analytical Data for compounds (4a–8)



cpd. no.	R^1	formula	elemental analysis %(calc/found) C	H	N	X**	m.p. (°C)	M.S. (calc/found)
4a	$R^1=R^3=CH_3$, $R^4=H$, $R^2=CO_2CH_3$	$C_{14}H_{19}NO_6$	56.56/56.73	6.44/6.50	4.71/4.77	–	83–84	–
4b	$R^1=R^3=CH_3$, $R^4=H$, $R^2=CO_2CH_2C_6H_5$	$C_{20}H_{23}NO_6$	64.33/64.60	6.21/6.21	3.75/3.81	–	73–74	–
5a	$R^1=R^3=CH_3$, $R^2=CO_2CH_3$, $R^4=Hg(OCOCF_3)$	$C_{16}H_{18}F_3HgNO_8$	31.51/31.48	2.97/2.96	2.30/2.26	–	161.5–162.5	–
5b	$R^1=R^3=CH_3$, $R^2=CO_2CH_2C_6H_5$, $R^4=Hg(OCOCF_3)$	$C_{22}H_{22}F_3HgNO_8$	38.52/38.27	3.23/3.24	2.04/2.01	–	130–131	–
6a	$R^1=R^3=CH_3$, $R^2=CO_2CH_3$, $R^4=I$	$C_{14}H_{18}INO_6$	39.73/39.77	4.29/4.27	3.31/3.28	–	127–128	423/423
6b	$R^1=R^2=CH_3$, $R^2=CO_2CH_2C_6H_5$, $R^4=I$	$C_{20}H_{22}INO_6$	48.11/47.96	4.44/4.41	2.81/2.78	–	140–141	499/499
7	$R^1=R^2=R^3=H$, $R^4=I$	$C_9H_{10}INO_4\cdot H_2O$	31.69/31.92	3.55/3.61	4.11/3.91	37.20/36.35	140(dec)	323/324*
8	$R^1=R^2=R^3=H$, $R^4=Br$	$C_9H_{10}BrNO_4\cdot H_2O$	36.75/36.37	4.11/4.06	4.76/4.70	27.17/27.22	178(dec)$^{\phi}$	277/278*†

**I or Br *(M+1, FAB) $^{\phi}$reference 4 (180°,dec) †276/278 (1:1, $^{79}Br/^{81}Br$)

methanol (98:2) (2-3 mL), passed through a silica Sep Pak cartridge and Millex-SR (0.5 μm) filter unit, and eluted with chloroform-methanol (98:2, 20 mL). The solvent was evaporated under reduced pressure to give 3.23 g of a pale yellow solid. The crude product was recrystallized from ethyl acetate - petroleum ether to afford 2.51 g (71%) of **4b** as a white solid (Tables 1 and 2).

L-Methyl-N-carbomethoxy-[β-(3,4-dimethoxy-6- mercurictrifluoroacetyl-phenyl)] alaninate (5a)

To a stirred solution of crude **4a** (4.5 g, 15.1 mmol) in methanol (15 mL) was added mercuric trifluoroacetate (7.1 g, 16.6 mmol). The resulting solution was stirred at room temperature for 48 h and then evaporated under reduced pressure. The solid was taken up into chloroform (15 mL), passed through two silica Sep Pak cartridges and a Millex-SR (0.5 μm) filter unit and eluted with chloroform (20 mL). The solvent was evaporated under reduced pressure to give a light yellow solid which was dried under vacuum at room temperature. The crude product was recrystallized from ethyl acetate-petroleum ether to afford 4.12 g (45%) of a white solid (Table 1 and 2). When pure **4a** was used, the mercurated derivative **5a** was obtained in 85% yield.

L-Methyl-N-carbobenzyloxy-[β-(3,4-dimethoxy-6- mercurictrifluoroacetyl-phenyl)] alaninate (5b)

To a stirred solution of **4b** (902 mg, 2.42 mmol) in methanol (4 mL) was added mercuric trifluoroacetate (1.24 g, 2.90 mmol). The resulting solution was stirred at room temperature for 47 h and then evaporated under reduced pressure. The gummy yellow solid was taken up into chloroform (2-3 mL) passed through a silica Sep Pak cartridge and Millex-SR (0.5 μm) filter unit, and eluted with chloroform (15 mL). The solvent was evaporated under reduced pressure to give 1.87 g of a light yellow solid which was dried under vacuum at room temperature. The crude product was recrystallized from ethyl acetate - petroleum ether to afford 1.15 g (70 %) of **5b** as a white solid (Tables 1 and 2).

L-Methyl-N-carbomethoxy-[β-(3,4-dimethoxy-6-iodophenyl)] alaninate (6a)

To a stirred suspension of **5a** (2.44 g, 4.0 mmol) in chloroform (40 mL) was added solid iodine (1.07 g, 4.2 mmol). The mixture was stirred at room temperature for 4 h, passed through a Millex-SR (0.5 μm) filter unit, and the collected orange solid was washed with chloroform (25 mL). The chloroform layer was washed successively with two 5 mL portions of aqueous (2.5%) sodium thiosulfate and two 5 mL portions of water. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced

pressure to give 1.72 g of a pale yellow solid. The crude product was recrystallized from ethyl acetate to afford 1.51 g (89%) of **6a** as a white solid (Tables 1 and 2).

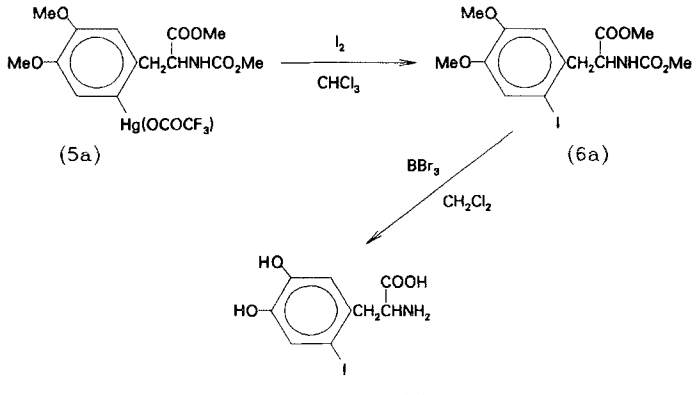
L-Methyl-N-carbobenzyloxy-[β-(3,4-dimethoxy-6-iodophenyl)]alaninate (6b)

To a stirred suspension of **5b** (858 mg, 1.25 mmol) in chloroform (15 mL) was added solid iodine (333 mg, 1.31 mmol). The mixture was stirred at room temperature for 5 h, passed through a Millex-SR (0.5 μm) filter unit and the collected orange-red solid was washed with chloroform (15 mL). The filtrate was diluted with chloroform (10 mL) and then washed successively with two 5 mL portions of aqueous (2.5%) sodium thiosulfate solution and two 5 mL portions of water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow solid. The crude product was recrystallized from ethyl acetate to afford 560 mg (90%) of **6b** as a white solid (Tables 1 and 2).

L-6-Iododopa (7)

To a cold (0°) stirred solution of **6a** (212 mg, 0.53 mmol) in dichloromethane (2 mL) under nitrogen was added boron tribromide (2.5 mL, of 1.0 M boron tribromide, 2.5 mmol) in dichloromethane. The resulting light yellow solution was stirred at room temperature for 4 h, cooled to 0°, quenched with water (10 mL), and then stirred for an additional 10 min. The layers were separated, the organic layer

SYNTHESIS OF L-6-IODODOPA



(5a) (6a)

L-6-Iododopa (7)

was diluted with dichloromethane (10 mL) and then extracted with three 15 mL portions of water. The combined aqueous layers were washed with dichloromethane (5 mL) and then filtered through a small plug of cotton wool. The water was removed by evaporation under reduced pressure and the resulting residue was dissolved in water (4 mL). The brown solution was passed through two C-18 Sep

Pak cartridges and a Millex-HA (0.45 μm) filter unit and then eluted with water (6 mL). The filtered solution was evaporated under reduced pressure to give a tan colored solid. This solid was dissolved in buffer (pH 5, 4 mL) and then purified by preparative HPLC in several portions (5 X 0.8 mL) on a Whatman Partisil 10, ODS-3 Magnum 9/50 column using water/methanol/acetic acid (80:20:0.1) as the eluant at a flow rate of 4 mL/min (λ280). The combined eluant collected between approximately 12 and 18 min was evaporated under reduced pressure to give a green residue. This residue was dissolved in water (2 mL), passed through a C-18 Sep Pak cartridge and a Millex-HA filter unit, and then eluted with water (8 mL). The filtrate was evaporated to afford 59 mg (37%) of L-6-iododopa **7** as a light grey solid. This solid was dried further at 55° under vacuum to remove residual water and acetic acid (Table 1 and 2). When the reaction was carried out with 250 mg of **6b**, 103 mg (67%) of **7** was obtained.

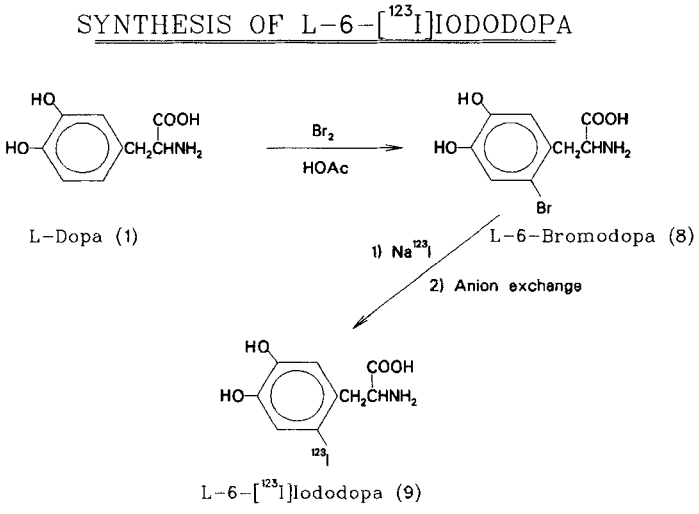
L-6-Bromodopa (8)

To a stirred solution of L-dopa (5.9 g, 29.9 mmol) in glacial acetic acid plus several drops of concentrated HCl (neccessary for dissolution) was added Bromine (4.95 g, 31 mmol) in glacial acetic acid (34 mL) dropwise at room temperature (4). The reaction was monitored by HPLC (Whatman Partisil 10, ODS-3 Magnum 9/50 column, 90:10, 0.02 M KOAc/Methanol), pH adjusted to 3.9 with acetic acid, 4 mL/min, λ280. When the reaction was complete the solvent was evaporated to dryness , dissolved twice in water (10 mL) evaporated to dryness each time. The residue was dissolved in distilled water (90 mL) and the pH adjusted to 3 - 3.5 with saturated sodium carbonate. The L-6-bromodopa crystallized on cooling and was filtered and washed with cold water. Drying under vacuum gave 6.6 g of a white solid (80%) (Tables 1 and 2).

L-6-[^{123}I]Iododopa (9)

To a 100 μL V-vial with a teflon septum and screw cap containing phthalate buffer (20μL, 0.05 M, pH 4) was added L-6-bromodopa (0.1 mg / 20 μL phthalate buffer), ascorbic acid (0.3 mg / 20 μL phthalate buffer) and 30 μL of Na^{123}I solution (25 mCi) and the mixture was heated for 35 min at 97°C. After cooling at room temperature the reaction mixture was loaded on a small column containing AG1-X8 anion exchange resin (2 cm, acetate form, 100 - 200 mesh) and slowly eluted with NH_4OAc (pH 5.8) buffer at a flow rate of 0.25 mL / min. The eluted fraction was evaporated to dryness, the residue dissolved in acetic acid (0.1%, 2 - 3 mL) filtered through a membrane filter and used for the biodistribution study. The radiochemical yield was 50% and the radiochemical purity was >95%. The specific activity (65 Ci/mmol) was determined by quantifying the U.V. peak

area of the remaining L-6-bromodopa and L-6-iododopa after anion exchange column purification and comparing this to previously prepared calibration curves for L-6-bromodopa and L-6-iododopa using the analytical HPLC system described in the General Experimental section. Higher specific activity can be obtained by purifying the product by HPLC to remove the L-6-bromodopa carrier (same HPLC conditions as described for the synthesis of **8**; retention times for L-6-bromodopa: 15.42 min. and for 6-ID: 21.08 min). Using these HPLC conditions or the analytical system (r.t. 3.12 min and 4.42 min respectively) conditions described earlier, the 6-ID always co-eluted with the "authentic" cold standard of L-6-iododopa. No deiodination or radiolysis was observed when the final solution of the



radioactive product was left for 18 h at room temperature and then analyzed by HPLC.

Results and Discussion

Preparing 6-ID is difficult if one proceeds by a route similar to that used for the synthesis of 6-FD. It is relatively easy to iodinate a fully protected dopa derivative but we observed that removal of the protecting groups with HI, as is done in the case of the 6-FD preparation, removes the iodine as well. However, the preparation of L-6-iododopa **7** via the two carbamates **6a, 6b**, using boron tribromide, proceeded well with only a small amount of deiodination. The formation of the N-carbomethoxy derivative **3a** is preferred over the N-carbobenzyloxy derivative **3b** because, during the carbamate synthesis, excess methyl cloroformate is much easier to remove than benzyl chloroformate. Unfortunately, the iododemercuration route was not found to be practical for the ^{123}I labeling reaction

because the workup procedure after deprotection requires several purification steps. Therefore, we chose to develop a route that incorporated the iodine in the last step of the synthesis followed by a simple purification.

Recently, Wong and DeJesus synthesized L-6-bromodopa by the direct bromination of L-dopa with molecular bromine (4). Due to the relative ease of the exchange radioiodination of bromine containing compounds we chose this route to prepare 6-ID. Also, since it had been shown that L-6-bromodopa was a substrate for the decarboxylase enzyme and that L-6-bromodopa appears to enter the active transmitter pool (4) we were hopeful that 6-ID would also be a substrate.

The iodide exchange labeling conditions of heating the brominated compound in a phthalate buffer at pH 4 worked well. The ascorbic acid was found to be useful in diminishing oxidation of the catechol moiety. Workup of the reaction by passing the mixture down an anion exchange column removed any iodide along with radioactive oxidation products formed during the heating as well as phthalate from the buffer. After ion exchange the product was obtained in good yield (50%) and in good purity. The exchange reaction works equally well when L-6-iododopa was used as the starting material but since L-6-bromodopa was easier to prepare in large quantities it was more convenient to use the latter. The final product contains any remaining L-6-bromodopa starting material which adds to the carrier level in the final product. Some of the L-6-bromodopa and probably 6-ID is lost due to oxidation during the reaction resulting in a measured specific activity of 65 Ci/mmol which is much higher than that obtained for 6-FD (100 - 500 mCi/mmol). Due to the difference in retention times, under the HPLC conditions described earlier, the L-6-bromodopa can be easily removed from the final product if one desires a higher specific activity.

A preliminary rat biodistribution study was carried out on 6-ID and the results are summarized in Tables 3 and 4. Table 4 shows the percent dose per gram for the major organs at 1 and 2 hour time intervals after injection. This data indicates that the compound is rapidly excreted from the body and that uptake in the brain and other organs is low. However, the uptake in the striatum is similar (within one order of magnitude) to the that obtained with 6-FD in rats and therefore, the low uptake of 6-ID may not preclude it from being a useful agent. The thyroid dose is low after 24 hours and indicates that deiodination is not significant. Table 3 shows that the striatum to whole brain ratios of 1.35 and 1.11 are comparable to those obtained for 6-FD (unpublished data from UBC) and indicates that the target to background ratio may be favourable for imaging. Published data for striatum/cortex ratios of 6-FD in dogs at 1 and 2 hours are 1.65 and 1.5 respectively and the striatum/cerebellum ratios at 1 and 2 hours are 1.03 and 1.19 respectively (11).

Table 3: Rat Striatum/Whole Brain Ratios for ^{123}I-6ID and ^{18}F-6FD*

	1 h	2 h
^{123}I-6ID	1.35	1.11
^{18}F-6FD	1.55	1.44

*Ratio of %dose/gram

Table 4: Biodistribution of L-6-[^{123}I]Iododopa in Rats*

organ	1 h %dose/g	2 h %dose/g
brain	0.020	0.009
striatum	0.027	0.010
heart	0.066	0.055
lung	0.105	0.103
kidney	0.855	0.441
muscle	0.196	0.070
liver	0.215	0.081

*thyroid - 1.5 %dose/g at 24 h

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