P115 NON-SEQUENTIAL CHROMATOGRAPHIC BEHAVIOUR OF AROMATIC ASTATINE COMPOUNDS

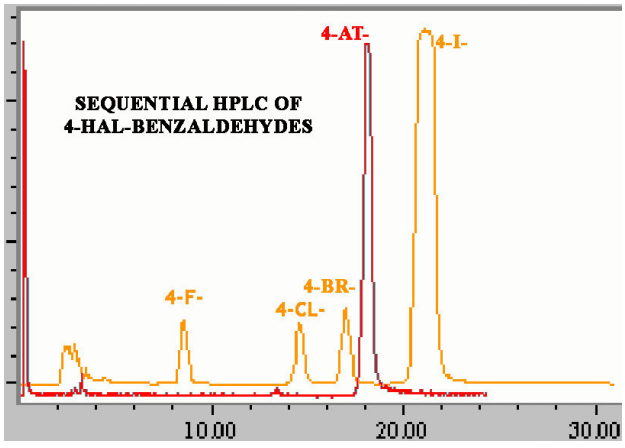
G. J. MEYER*[1], A. HILLER[2], J. STEINBACH[2] and W. H. KNAPP[1]
1. Medical School Hannover, Dpt. Nuclear Medizin, Hannover, Germany; 2. Interdisciplinary Inst. Isotopes, Leipzig, Germany

Objectives: Because of the lack of stable or long-lived astatine isotopes the preparation of astatine compounds requires special analytical approaches to verify their identity.The chemical homology of halogens is used to verify the identity of astatine compounds; i.e. by comparison of the chromatographic- or other partitition-behaviour of the astatinated compound with that of the corresponding I- and Br- derivatives. Using this approach, a continuous sequential behaviour in the halogen series is usually expected. Previously we observed that At-anilines prepared under mild electrophilic conditions, did not fit the expected retention sequence on reversed phase HPLC (F-, Cl-, Br-, I-, At- anilines). The At-anilines eluted before the corresponding I-analogues or even before the corresponding Br-analogues, depending on pH conditions. This led to speculations about the nature of the At-carbon bond in aromatic systems after electrophilic substitution reactions including the possibility of astatoyl derivatives.

Methods: To further analyze the phenomenon of "irregular" elution sequences of astatinated benzene derivatives on reversed phase HPLC, and to further investigate if this might be caused by the formation of oxidized species, we prepared astatinated benzene derivatives by Cu^{+} catalyzed nucleophilic halogen exchange (At for I and At for Br) under strongly reducing conditions at 110°C -140 °C. By this procedure we prepared all isomers of At-benzoic acid, At-benzaldeyde, At-methylbenzoate, 3-At-succinimidylbenzoate, 4-At-nitrobenzene, and 2- and, 4-At-phenylalanines with good yields (65%-95%). For comparison we prepared meta- and para At-benzoic acids, 4-At-phenylalanine, ortho At-methylbenzoate and meta-At-succinimidylbenzoate by destannylation of the corresponding trimethylstannyl compounds. All At-compounds were sequentially analysed on reversed phase HPLC with the corresponding F-, Cl-, Br-, and I-derivatives.

Results: Irregular elution sequences were confirmed for 3- and 4-At-benzoic acids, all At-methylbenzoates, all At-benzaldehydes, meta-At-succinimidylbenzoate, and 4-At-phenylalanine, which all eluted before the corresponding iodine- or even before the corresponding bromine-derivatives. 2-At-benzoic acid, 2-At- phenylalanine and 4-At-nitrobenzene eluted in the expected sequence of F-, Cl-, Br-, I-, At-compounds, although with less separation from the corresponding iodine derivative than would be expected from the F-, Cl-, Br-, and I-compound sequence. Retention times and elution sequences were independent of the preparation pathway, - either electrophilic or nucleophilic substitution.

Conclusions: The observation that either nucleophilic or electrophilic pathways lead to At-benzene derivatives with the same chromatographic behaviour lets us assume that the At-carbon bond is not associated with oxidized forms of astatine. We conclude that the non-sequential elution behaviour of At-benzene derivatives when compared with their F-, Cl-, Br-, and I-homologues stems from the higher polarizability of Astatine. It can be assumed that the 5f electron shell is causing this phenomenon.



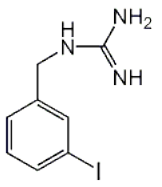
P116 USING H3PO2 IN THE CU+ -NUCLEOPHILIC RADIOIODINATION; AN "EASY-TO-MAKE" REACTION MIXTURE

J. EERSELS*[1], J. MERTENS[2] and J. HERSCHEID[1]

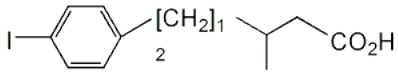
1. VU University Medical Center, Department of Nuclear Medicine & PET Research, Amsterdam, Netherlands; 2. Vrije Universiteit Brussel, Department of Radiochemistry, BEFY, Brussel, Belgium

Objectives: Within a mechanistic study of the Cu^{+}-radioiodination method we reported that the use of hypophosphorous acid (H_3PO_2) as reducing acid [(1)], also allowed to obtain a quantitative labeling yield for ^{123}I-MIBG without the presence of usual reducing agents, like gentisic acid and $SnSO_4$. To prove the versatility of these modified reaction conditions, labeling experiments were performed with other precursors of interest and compared with the labeling results of the "standard reaction conditions" of the Cu^{+}-method [(2)].

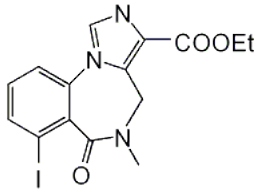
Methods: Precursors were choosen on a well-considered base, i.e. isotopic exchange (*I↔I : MIBG and fatty acid; BMIPP), non-isotopic exchange (*I↔Br : MIBG and iomazenil from brominated precursor), and in mixed-solvent conditions (with EtOH 70%; iomazenil and BMIPP). Reaction parameters (i.e. reaction time, temperature, volume and amount of precursor) were similar under both conditions. Labeling experiments: 2 mg of precursor was dissolved in 1 ml of a 0.9 mM aqueous solution of H_3PO_2, and after addition of Cu^{2+}-solution, heated at appropriate temperatures and times in N_2-atmosphere.



MIBG



BMIPP



IMZ

Results:

Precursor	Standard Conditions	With H_3PO_2
*I/I MIBG 40', 100°C	98-99 %	98-99 %
BMIPP 60', 100°C	93-95	94-96
*I/Br IMZ 40', 100°C	97-98	97-99
MIBG 55', 170°C	97-99	86-90

H_3PO_2 is proven to be an effective reducing agent for the 'in situ' generation of Cu^{+} for the different compounds and in mixed-solvent conditions, like EtOH / water. Labeling experiments performed at a higher temperature (up to 170°C) are not appropriate, as a decrease of the labeling yield was observed. As using a higher concentration of the H_3PO_2-solution (2.2 mM), the labeling yield was restored comparable to the standard conditions. This lower labeling yield was probably due to the decomposition of the reducing agent. Neither cold, nor radioactive side products could be observed by HPLC.

Conclusions: H_3PO_2 can offer an alternative strategy as it gives comparable labeling results as the usual reducing agents used in the Cu^{+}-method.

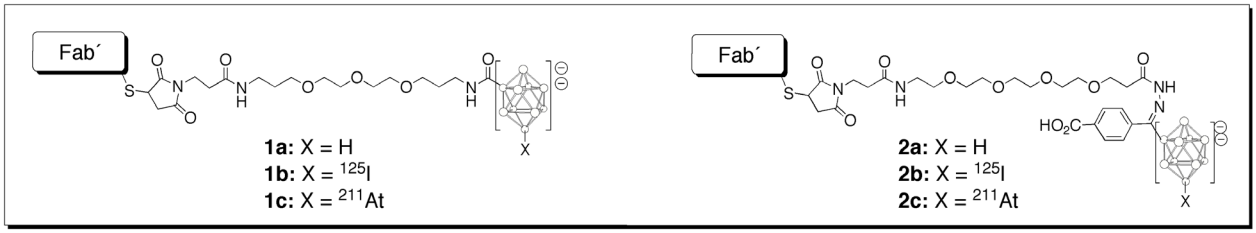
References: (1) Eersels J.L.H., Mertens J., Herscheid J.D.M., Appl Radiat Isot, 2009, submitted. (2) Eersels J.L.H., Travis M.J., Herscheid J.D.M., J Label Compd Radiopharm, 2005; 48: 241-257.

P117 UNEXPECTED DIFFERENCES IN KIDNEY CLEARANCE AND TUMOR ACCUMULATION OF THE SAME CLOSO-DECABORATE(2-)-HYDRAZONE LINKED ANTIBODY FAB FRAGMENT LABELED WITH I-125 AND AT-211

D. WILBUR*, M. CHYAN and D. HAMLIN
Department of Radiation Oncology, University of Washington, Seattle, WA

Objectives: The overall objective of the research effort was to determine if the use of a cleavable hydrazone linker in an anti-PSMA antibody Fab´ fragment conjugated with closo-decaborate(2-) would facilitate clearance of ^{125}I- and ^{211}At-labeled Fab´ from kidney, and (hopefully) have minimal affect on tumor accumulation/retention. To accomplish this objective, a Fab´-closo-decaborate(2-) conjugate containing a hydrazone linker (2a) was radioiodinated and (separately) astatinated, and the in vivo distributions of those compounds were compared with ^{125}I- and ^{211}At-labeled Fab´ conjugated with a closo-decaborate(2-) containing a non-cleavable linker (1a).

Methods: Two maleimido-decaborate(2-) derivatives were synthesized and conjugated with Fab´-SH to prepare the conjugates 1a and 2a. The Fab´-closo-decaborate(2-) conjugates 1a and 2a were radiolabeled by reaction with chloramine-T and Na[^{125}I]I or Na[^{211}At]At for 1 min at room temperature. Two biodistribution studies were conducted in SCID mice, where [^{125}I]1b & [^{211}At]1c or [^{125}I]2b & [^{211}At]2c were coinjected into 15 mice. Tissue samples were obtained from groups of 5 mice at 1, 4 and 24 h post injection (pi). In the biodistribution study evaluating the Fab´ containing a cleavable linker (i.e. [^{125}I]2b & [^{211}At]2c), the mice had LNCaP human prostate tumor xenografts grown in the hind flank.



Results: Kidney concentrations for the Fab´ containing the non-cleavable linker, [^{125}I]1b or [^{211}At]1c, were similar at 1 h (26.8±1.2 %ID/g vs. 31.6±1.7 %ID/g respt.), 4h (31.0±4.7 %ID/g vs. 37.2±5.1 %ID/g respt.) and 24h (17.9±3.2 %ID/g vs. 23.1±3.7 %ID/g respt.) pi. Kidney concentrations for the Fab´ containing the cleavable hydrazone linker, [^{125}I]2b or [^{211}At]2c, were similar at 1h (51.0±18.3 %ID/g vs. 44.5±15.5%ID/g respt.), but were dramatically different at 4h (13.1±2.0 %ID/g vs. 42.3±16.4 %ID/g respt.) and 24h (4.2±1.6 %ID/g vs. 39.5±15.9 %ID/g respt.). Also, tumor concentrations of [^{125}I]2b or [^{211}At]2c were similar at 1h (11.7±3.6 %ID/g vs. 12.3±3.9 %ID/g respt.), but were quite different at 4h (12.0±1.3 %ID/g vs. 16.0±3.9 %ID/g respt.) and 24h (11.8±5.6 %ID/g vs. 25.6±11.2 %ID/g respt.).

Conclusions: As expected, similar kidney concentrations were obtained for the Fab´-closo-decaborate(2-) containing a non-cleavable linker, [^{125}I]1b or [^{211}At]1c, irrespective of the radionuclide attached. However, when the radioiodinated Fab´-closo-decaborate(2-) conjugate containing a cleavable hydrazone linker [^{125}I]2b was compared with its astatinated counterpart [^{211}At]1c, unexpected differences were seen in kidney and tumor concentrations. Since the neck (thyroid) and stomach concentrations were low it is unlikely that the differences were due to in vivo dehalogenation. More studies need to be conducted to understand the observed in vivo differences.

Research Support: Funding for this research was provided by NIH (CA113431).

P118 EVALUATION OF AN BR-76 LABELED ERB-041 ANALOGUE AS ESTROGEN BETA RECEPTOR SELECTIVE LIGAND: NO-CARRIER-ADDED RADIOLABELING AND IN VIVO BIODISTRIBUTION STUDY

D. ZHOU[1], H. ZHOU[2], C. C. JENKS*[1], T. L. SHARP[1], E. E. PARENT[2], J. LEE[2], J. A. KATZENELLENBOGEN[2] and M. J. WELCH[1]

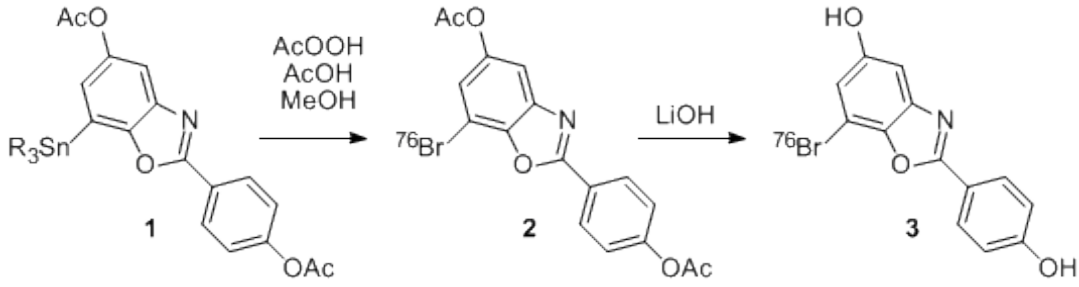
1. Washington University, Mallinckrodt Institute of Radiology, Saint Louis, MO; 2. University of Illinois, Chemistry Dept, Urbana, IL

Objectives: The estrogen receptors, ERa and ERb, are important regulators of estrogen action in target tissues and breast cancer. There is also evidence that the two ER subtypes have distinct patterns of gene regulation. Previous studies have shown that 16a-[^{18}F]fluoroestradiol (FES) is quite selective for ERa. Therefore, the development of an ERb-selective PET imaging agent, that can assess ERb levels, could provide a powerful tool to study ERs at molecular level. Compound 3, a bromine-substituted analogue of ERB-041, binds with even higher affinity for ERb than ERB-041 and maintains excellent selectivity. The objectives of this study are to radiosynthesize [Br-76]3 using very high specific activity [Br-76]bromide and to evaluate it in vivo as an ERb-selective PET agent.

Methods: No-Carrier-Added radiobromination was carried out via oxidative electrophilic destannylation of an organotin precursor 1, followed by deprotection of the diacetate by 1 M LiOH solution. [Br-76]3 was evaluated at 1, 3, 6, and 24 h post injection in two sets of immature Sprague Dawley (SD) rats, one set of which was injected with estradiol as blocking agent (8 μg/dose). A 3-4 μCi dose of HPLC purified [Br-76]3 was injected in each animal.

Results: Radiobromination of the related tributyltin precursor was first attempted under classical conditions, using various oxidants, either without removing ammonium hydroxide by drying or even with dried [Br-76]bromide. These methods, however, did not afford the desired product 2, leading instead to the formation of unknown byproducts. The failure of radiobromination under these conditions was attributed to the uncontrolled nature of the effective electrophilic brominating agents, the moderate reactivity of the tributyltin precursor, and the high reactivity of minor impurities in solvents and reactants. Radiobromination of 2 was achieved by modification of the leaving group (from Bu_3Sn to Me_3Sn), that increased its reactivity, and the addition of methanol to the reaction mixture that produced a more selective brominating species. [Br-76]2 was then converted to [Br-76]3 in 5 min with 1 M LiOH solution. Finally, reversed phase HPLC purification afforded [Br-76]3 in about 20% yield, with a product specific activity of 900 mCi/μmol (EOS) and radiochemical purity of >99%. In biodistribution studies of [Br-76]3 conducted thus far only in immature SD rats, washout of [Br-76]3 from all tissues was rapid, and no specific uptake of [Br-76]3 in the uterus nor blocking of uptake by an excess of unlabeled estrogen was observed. The lack of specific uptake in the uterus may reflect the very low level of ERb in this organ. Other, more appropriate animal models to monitor ERb-specific target uptake are being developed.

Conclusions: An ERb selective ligand 3 has been synthesized successfully in radiobrominated form. In biodistribution studies in current animal models, no specific uptake of [Br-76]3 was observed in classical estrogen target tissues, leaving ERb still a challenging target.



P119 123I-NIODENE: A NEW SPECT TRACER FOR IMAGING NICOTINIC RECEPTORS

S. PANDEY*, S. PAN, R. KANT, R. COLEMAN, C. CONSTANTINESCU, M. PAN and J. MUKHERJEE
University of California-Irvine, Preclinical Imaging Facility, Department of Psychiatry and Human Behavior, Irvine, CA

Objectives: Nicotinic acetylcholine receptors (nAChR's) are downregulated in disease conditions such as Alzheimer's and substance abuse. Presently, 5-IA-85380 is used in human studies and requires over 6 hrs of scanning time, thus increases patient discomfort. We have designed and synthesized 5-(^{123}I)Iodo-3-[2-{(S)-3-pyrrolinyl}methoxy]pyridine (^{123}I-Niodene), with the aim to have faster binding kinetics compared to 5-IA, which will reduce scanning time (< 2hrs) and hence higher patient acceptance.

Methods: ^{123}I-Niodene was synthesized using 5-Tributyltin-3-[2-{(S)-N-tert-butoxycarbonyl-3-pyrrolinyl}methoxy]pyridine (precursor) by iododestannylation using sodium ^{123}I-iodide, HCl, chloramine-T trihydrate, under no carrier and carrier added (1 mCi sodium ^{123}I-iodide, containing no carrier, or with 1μg, 10μg and 25μg NaI) conditions. The reaction was incubated at room temperature for set time points (0.5hr to 4 hr) after which it was quenched by adding $NaHSO_3$. The labeled 5-(^{123}I)Iodo-3-[2-{(S)-N-tert-butoxycarbonyl-3-pyrrolinyl}methoxy]pyridine (^{123}I-N-Boc-Niodene) was purified by HPLC (Econosil C18; 10x250mm, Gilson HPLC system, flow rate = 2.5mL/min, UV detector = 287nm) under isocratic setting of CH_3CN/H_2O(0.1% Et_3N): 60/40 buffer (t_R =23 min) and deprotected (20%TFA in CH_2Cl_2 at 80ºC for 20 min) to give ^{123}I-Niodene. Rat brain slices (10 μm) and mice brain slices (wild-type and $\alpha_4\beta_2$ knock out) were incubated with ^{123}I-Niodene (0.05μCi/cc) and nonspecific binding measured with 300 μM nicotine. Autoradiograms were analyzed by OptiQuant Image analysis software. Rat brain homogenate assays using ^{3}H-cytisine were carried out to measure the binding affinity (IC_{50}) of niodene, nifene and nicotine to $\alpha_4\beta_2$ receptors.

Results: By using above iododestannylation method, ^{123}I-Niodene was obtained in high radiochemical purity (>95%), but with low radiochemical yield (10%) and specific activity. Even with lower specific activity (10 μg NaI added) ^{123}I-Niodene localized in the thalamus and cortex, which was displaced by nicotine (thalamus to cerebellum ratio = 5 and cortex to cerebellum ratio = 2). Knock-out mice did not have any specific binding compared to the wild-type. In vitro binding affinity (IC_{50}) of Niodene in rat brain homogenate was 1.20nM for$\alpha_4\beta_2$ receptors, comparable to nifene.

Conclusions: ^{123}I-Niodene is a new radiotracer for SPECT imaging of nicotinic ($\alpha_4\beta_2$) receptors. Optimization of labeling chemistry is underway to obtain ^{123}I-Niodene with greater radiochemical yield and high specific activity.

Research Support: NIH R01 AG029479

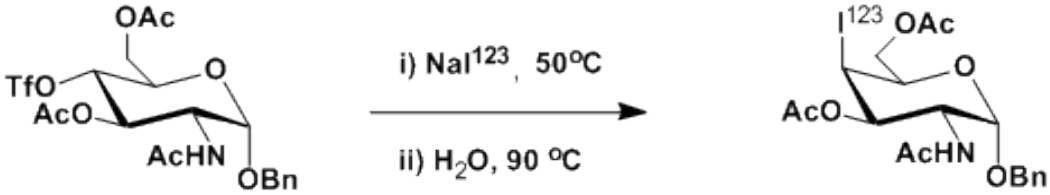
References: Pichika, R. et al, Nuclear Medicine and Biology, 33 (2006) 295-304.

$\alpha_4\beta_2$ Agents	Nicotine (Natural Ligand)	Nifene (PET tracer)	Niodene (SPECT tracer)
Binding Affinity (IC_{50}, nM)	4.60±0.78	1.33±0.37	**1.20±0.02**

P120 SYNTHESIS OF RADIOLABELED (I-123) 2-ACETAMIDO-4-IODO-2-DEOXY--D-HEXOPYRANOSES AS POTENTIAL IMAGING AGENTS FOR THE DETECTION OF ALZHEIMER'S DISEASE

G. W. KABALKA*, S. MAREPALLY and M. YAO
University of Tennessee, Departments of Radiology and Chemistry, Knoxville, TN

Objectives: Alzheimers disease is a protein misfolding disease caused by the accumulation of abnormally folded amyloid β (Aβ) proteins in the brain. Materials that inhibit the binding between heparin sulfate proteoglycan and the amyloid precursor have been found to be effective anti-amyloid agents both in vitro and in vivo. 4-Deoxy-D-glucosamine analogues possess amyloid inhibitory properties in vivo. Accordingly, we designed and synthesized a novel radioiodinated analogue of 4-deoxy-D-glucosamine, Scheme.



Methods: Benzyl-2-acetamido-3,6-di-O-acetyl-2,4-dideoxy-4-O-trifluoromethanesulfonyl-•-D-glucopyranoside) was synthesized from commercially available N-acetyl-glucosamine. The free hydroxyl groups on N-acetyl-glucosamine were acetylated and then the 4-acetyl group was selectively hydrolyzed by using a lipase enzyme. The resultant 4-hydroxy derivative was then treated with trifluoromethanesulfonic anhydride to give the triflate derivativewas then radioiodinated under both no-carrier added conditions and carrier-added conditions to yield the desired product.

Results: 2-Acetamido-3,6-di-O-acetyl-1-benzyl-2,4-dideoxy-4-[123]iodo-α-D-galactopyranose was synthesized in excellent radiochemical yield from the corresponding triflate derivative. The radioiodinations can be carried out in absence of stable iodine.

Conclusions: An iodine-123 labeled analogue of the benzyl derivative of 2-acetamidogalactopryranose was prepared and is currently being evaluated in amyloid bearing mouse models.

Research Support: Financial support from the Robert H. Cole Foundation is gratefully acknowledged.

P121 TRIOLBORATES: WATER-SOLUBLE COMPLEXES OF ORGANOBORONIC ACIDS AS PRECURSORS FOR NO-CARRIER-ADDED RADIO-HALOGENATIONS

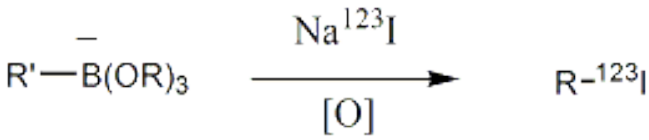
M. AKULA, M. YAO, D. TOWSEND and G. W. KABALKA*
University of Tennessee, Departments of Radiology and Chemistry, Knoxville, TN

Objectives: No-Carrier-added radiohalogenated tracers are of great importance in nuclear medicine imaging. Over the years, we have been investigating the use of organoborane reagents as precursors to radiopharmaceuticals (J. Radiolabelled Compds. Radiopharm. 2007, 50, 446). The object of the current study was to evaluate the feasibility of using ionic triolborates as starting materials in radiohalogenation reactions. The water solubility of the trioborate salts would serve to minimize the time needed to separate the radiolabeled product s from the unreacted starting materials.

Methods: A variety of aryl and vinyl triolborates was synthesized utilizihng well established literature protocols. No-carrier-added radioiodinations (Na123I/oxidant) of a series of triolborate salts were performed on these triolborates.

Results: The radioiodination reactions proceeded smoothly at room temperature in less then 30 min. to give radioidoinated products in radiochemical yields. In many cases the yields exceeded those previously reported.

Conclusions:



Where: R' = Aryl, Vinyl
R = Alkyl

Research Support: Financial support from the Robert H. Cole Foundation is gratefully acknowledged.

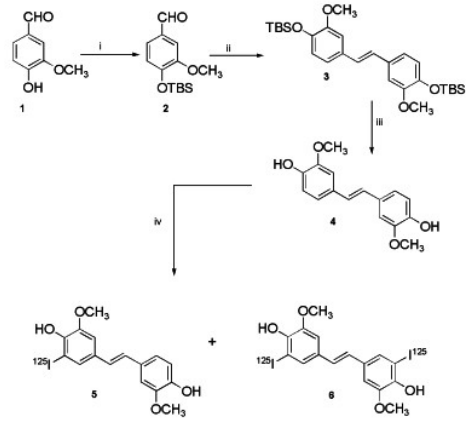
P122 SYNTHESES OF NOVEL 125I-DERIVATIVES OF HYDROXYSTILBENES AND THEIR PRELIMINARY EVALUATION IN BINDING STUDIES WITH MCF-7 CELLS

M. DHYANI*[1], A. G. KORDE[1], U. PANDEY[1], S. CHATTOPADHYAY[2], M. VENKATESH[1] and S. BANERJEE[1]
1. Bhabha Atomic Research Centre, Radiopharmaceuticals Division, Mumbai, India; 2. Bhabha Atomic Research Centre, Bio-Organic Division, Mumbai, India

Objectives: Resveratrol is considered a phytoestrogen due to it's potent estrogenic properties in binding with MCF-7 breast cancer cells, overexpressed in uterine and breast cancer. In the present study, a series of hydroxystilbenes which are resveratrol analogues were synthesized and radiolabeled with 125I. Their efficacy of binding with MCF-7 cell lines were evaluated in preliminary cell binding studies.

Methods: The hydroxystilbenes were synthesized via the McMurry Reaction involving the reductive coupling of aryl aldehydes with Zn and TiCl4, yielding the (E)-stilbenes exclusively as shown in the figure. [IMG] The stilbenes (~0.1 mM) were radioiodinated with 125I (~ 300 mCi) (molar ratios 500:1), at pH 7.5. The reaction was carried out for 60 seconds at room temperature. Iodogen (50 mg, in coated tubes) was used as an oxidizing agent. Radioiodination yield was determined using paper electrophoresis (0.025 M phosphate buffer, pH 7.5, 250 V, 60 minutes). The reaction mixture was then purified using a pre-conditioned C18 cartridge. The purified product was characterized by Jasco PU 1580HPLC system with a C-18 reversed phase HiQ Sil (5μM, 250x4 mm) column. Elution was monitored using both UV signals (270nm) as well as by following the radioactivity profile. Water (A) and acetonitrile (B), both containing 0.1% TFA were used as solvents at flow rate of 1 mL/min with a gradient of 0-4 min 10% B, 4-20 min 10-98% B and 20-30 min 98-100% B. Stability of the product for a period of 24 h at room temperature and 8 days at 4°C was also determined by using HPLC. In vitro cell uptake studies were carried out in MCF-7 cells. In vivo distribution studies were carried out in normal female Swiss mice in order to study its pharmacokinetics pattern and the uterine uptake was determined at 3 h and 24 h p.i.

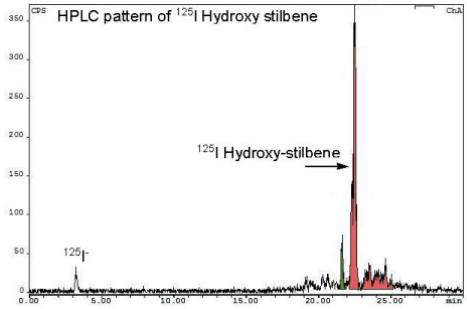
General scheme for the synthesis of Hydroxy-stilbenes and radioiodination



i) TBSCl/ Imidazole/ CH_2Cl_2, ii) $TiCl_4$/ Zn/ THF/Δ, iii) aqueous TFA/ THF, iv) ^{125}INa/ Iodogen.

Results: One derivative of the series of hydroxystilbenes synthesized provided the radioiodinated product in good yield of >90%. Radiochemical purity of Sep-Pak® purified product on HPLC analysis was found to be ~90%. This analogue was taken up for cell binding and in-vivo distribution studies. A comparison of the HPLC retention time of the radioiodinated stilbene with that of the cold iodinated stilbene, which was synthesized independently by McMurry reaction, for the purpose of comparison, were found to be identical. The pure fraction stored in phosphate buffer saline exhibited good stability after 24 h at room temperature, as determined by HPLC. In biodistribution studies, uptake in uterus was found to be 0.85% ID/g at 3h p.i. with uterus/muscle ratio of 2.5. In vivo stability was indicated by negligible uptake in the thyroid. In vitro cell uptake was ~30%.

Conclusions: The stilbene derivative could be synthesized and radiolabeled with 125I in >90% radiochemical yield. Preliminary in vitro binding studies with MCF-7 cells as well as biodistribution studies in female Swiss mice shows favorable features and warrants further investigation.

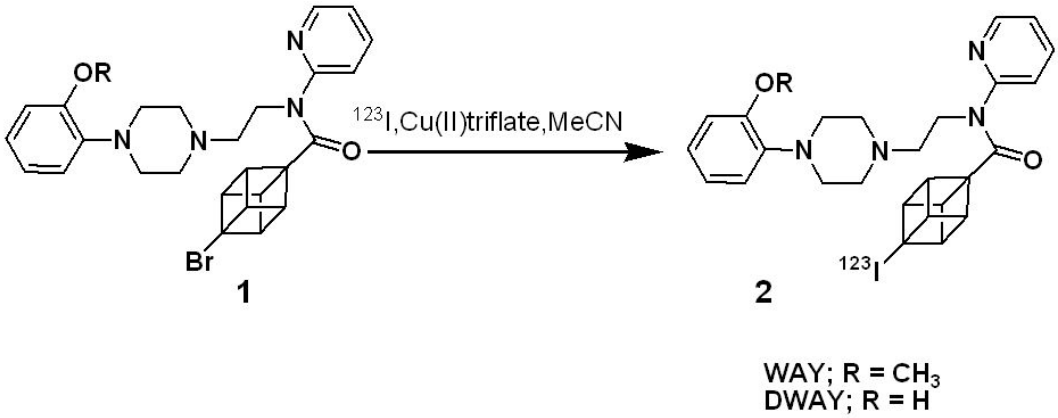


P123 [123I]CUBYL-DWAY AS LIGAND FOR THE 5-HT1A RECEPTOR

R. AL HUSSAINY*[1], J. VERBEEK[1], A. WINDHORST[1], R. KLOL[1], J. BOOIL[2] and J. HERSCHEID[1]
1. Department of Nuclear Medicine & PET Research, VU University Medical Center, Amsterdam, Netherlands; 2. Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, Netherlands

Objectives: As has been reported previously, the in vitro screening of [123I]cubyl-WAY (2, R=CH3) showed a relatively high binding affinity for the HT1A receptor (Kd= 0.7nM). Unfortunately, it was observed that this tracer has a low uptake in rat brain in addition to a slow washout from cerebellum leading to a low hippocampus/cerebellum ratio. A reason for the low brain uptake might be the lipophilicity of [123I]cubyl-WAY. Therefore, the desmethoxy derivative (2, R=H) was synthesized and evaluated in a biodistribution in the rat.

Methods: Labelling: reaction of (1) with water-free radioiodide in dry acetonitrile for 40 minutes at 140 0C using Cu(II)triflate as a catalyst gave (2) in 35% radiochemical yield. Biodistribution:12 male wister rats received an injection of 7 MBq of [123I]cubyl-DWAY (2, R=H) in the tail vein. Four rats were sacrificed at respectively 15 min, 45 min, and 2 h post injection. Several tissues and distinct brain regions were dissected, weighed and counted for radioactivity. The target to non-target ratios were calculated as the % injected dose/gram in the target tissue (hippocampus) divided by the % injected dose/gram in the cerebellum.



Results: In the tissue of interest, [123I]cubyl-DWAY (2, R=H) showed a relatively good brain uptake at 15 minutes which was decreased after 45 minutes and then washed out of the body after 2 h. Interestingly, there was no abnormal uptake in the thyroid, which indicates that there is no deiodination. The target to non-target ratios at 45 minutes are in the same range as for [123I] cubyl-WAY (2, R=CH3) and are shown in the table. [TABLE]

Ratio's	[^{123}I] cubyl-WAY (2, R=CH_3)	[^{123}I] cubyl-DWAY (2, R=H)
Striatum/ Cerebellum	0.91	0.93
OccCortex/ Cerebellum	1.21	1.73
Hippocampus/ Cerebellum	2.21	2.39

Conclusions: [123I]cubyl-DWAY (2, R=H) does not show any better brain uptake compared to [123I]cubyl-WAY (2, R=CH3) nor does it have a better tissue to non-tissue ratio. Moreover, even a higher uptake overall in the body was found for this novel 123I ligand .

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P124 SYNTHESIS OF 1–(2-DEOXY-BETA-D-RIBOFURANOSYL)-2,4-DIFLUORO-5-[124I]IODOBENZENE (DRF[124I]IB) – A STABLE, NON-POLAR PET TRACER MIMICKING THYMIDINE

A. STAHLSCHMIDT*[1], L. I. WIEBE[2], E. E. KNAUS[2], H. J. MACHULLA[1] and G. REISCHL[1]

1. University Hospital Tuebingen, Radiopharmacy, Tuebingen, Germany; 2. University of Alberta, Pharmacy and Pharmaceutical Sciences, Edmonton, AB, Canada

Objectives: PET imaging of cell proliferation can be performed using natural deoxynucleosides such as [^{11}C]thymidine or chemically altered nucleosides, the latter without the disadvantage of a rapid catabolism, [^{18}F]FLT being a prominent example. Schweitzer et al. [1] developed dRFMB (Fig. 1) with a chemically stable C-C nucleoside bond and with DNA incorporation similar to thymidine. Here, the [^{124}I]iodo-analogue dRFIB was to be synthesized for evaluation in PET studies. A preliminary imaging study in rats using dRF[^{123}I]IB is reported.

Methods: I-124 was produced via the ^{124}Te(p,n)^{124}I (using $^{124}TeO_2$) reaction at the PETtrace™ cyclotron (GE Healthcare) [2]. Iodine was recovered from the target by dry distillation at 720 °C and trapped in NaOH (4 mM; 300 μL). dRFIB was synthesized in 5 steps from 2,4-difluoroiodobenzene acc. to [3]. Radioiodination of dRFIB was performed with [^{124}I]iodide via isotopic exchange [4]. The labeled product was assayed by radio-HPLC. Reaction conditions were optimized for radiochemical yield (RCY) by varying temperature, amounts of precursor, NaOH and reaction time. dRF[^{123}I]IB (labeling as above) was administered to Sprague-Dawley rats via bolus tail vein injection (46.8 μg/kg) for planar imaging in a preliminary study.

Results: I-124 production yields were 3 MBq/μAh. Radiochemical yields (RCY) for labeling of dRFIB were only 2.4 % at 60 °C and increased to ca. 76 % RCY at 100 °C (2 h). Optimization of the amount of precursor (120 °C, 2 h) resulted in a maximum of 66 % RCY with 0.3 μmol (0.11 mg) of dRFIB. Influence of NaOH/[^{124}I]iodide volumes on RCY were determined. No effect was observed up to 20 mg of NaOH per reaction. Above, RCYs decreased rapidly. Three different reaction times and their influence on RCY were investigated. At 140 °C a plateau was reached after ca. 20 min with a RCY of 90 %, at 120 °C 80 % RCY were obtained after 80 min and applying 85 °C RCY max. was ca. 20 % after 20 min. Radiochemical purity of the product was > 95 % and specific activity was 107 MBq/μmol. Imaging of dRF[^{123}I]IB in rats (Fig. 2) depicted rapid soft-tissue clearance and extensive accumulation of radioactivity in bladder/urine and liver/small intestine.

Conclusions: The radiochemical synthesis of dRF[^{124}I]IB via isotopic exchange could be optimized. With the RCYs obtained and the absolute amounts of product available, in vivo evaluations using small animal PET are possible. Tracer dose planar images with dRF[^{123}I]IB were compatible with the reported kinetic model at high doses (5-55 mg/kg), characterized by a rapid distribution phase, extensive urinary excretion and hepatobiliary recycling [5]. References: [1] Schweitzer BA et al., J. Amer. Chem. Soc. 117, 1863-1872 (1995). [2] Reischl G et al., J. Nucl. Med. 45, 471P (2004). [3] Wang ZX et al., Nucleosides, Nucleotides and Nucleic Acids 20, 11-40 (2001). [4] Stahlschmidt A et al., J. Appl. Radiat. Isot. 66, 1221-1228 (2008). [5] Khalili P et al., Biopharm. Drug Dispos. 24, 385-395 (2003).

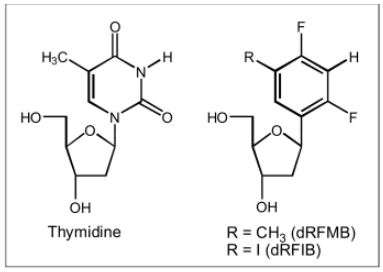

Figure 1: Structures of thymidine and the difluorophenyl mimetics dRFMB and dRFIB.

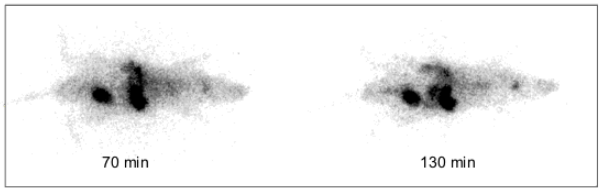

Figure 2: Images of a rat (3.9 MBq of dRF[^{123}I]IB, 20 min/image, isoflurane anaesthesia).