SYNTHESIS AND EVALUATION OF A RADIOIODINATED COXIB AS A SPECT TRACER FOR CYCLOOXYGENASE-2 EXPRESSION

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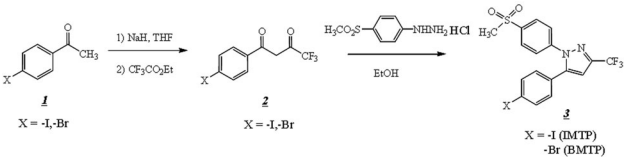
Cyclooxygenase (COX) is a key enzyme in the conversion of arachidonic acid into prostaglandins and thoromboxanes. COX-2, an inducible isoform of the enzyme, has been implicated in a number of pathologic processes, including many human cancers, atherosclerosis, and cerebral and cardiac ischemia. In this regard, non-invasive imaging of COX-2 expression should help understand the pathophysiology of the diseases and contribute to the clinical use of the COX-2 inhibitors. However, only a few attempts have been reported on the radiosynthesis of COX-2 inhibitors as *in vivo* imaging agents. Thus, we intended to develop a radioiodinated coxib as a SPECT tracer for imaging COX-2 expression and designed 5-(4-iodophenyl)-1-[4-(methylsulfonyl)phenyl]-3- (trifluoromethyl)-1H-pyrazole (IMTP) (Figure). In this study, radioiodinated IMTP was synthesized and its potential was assessed.

Methods: IMTP and 5-(4-bromophenyl)-1-[4-(methylsulfonyl)phenyl]- 3-(trifluoromethyl)-1H-pyrazole (BMTP) were synthesized according to the procedure outlined in Figure. Briefly, compound *2* was synthesized by a Claisen condensation of compound *1* and ethyltrifluoroacetate. The product *2* was reacted with 4-methylsulfonylhydrazine hydrochloride to obtain IMTP and BMTP. The radioiodinated IMPT was obtained by a halogen exchange reaction with sodium ^{125}I-iodine, and purified with a reverse-phase high-performance liquid chromatography. COX inhibitory potency of IMTP was assessed using a commercially available kit (Colorimetric COX Inhibitor Screening Assay Kit, Cayman Chemical) according to the manufacturer's instructions. SC-58125, meloxicam, and indomethacin were used as reference compounds.

Results and Discussion: IMPT and BMTP were obtained with the yields of 18% and 25% from the starting material *1*, respectively. The radiosynthesis of ^{125}I-IMTP was achieved with an iodine-bromide exchange reaction. Following separation from the precursor BMTP, ^{125}I-IMTP was obtained with no carrier-being added. The radiochemical yield was 42%, and the radiochemical purity was greater than 95%.



IMTP inhibited COX-2 in a concentration dependent manner, while it showed no inhibitory potency for COX-1 at the concentrations up to 100 μM. The IC_{50} values of IMTP were 5.16 μM for COX-2 and > 100 μM for COX-1. The COX-2 inhibitory potency of IMTP was higher than that of meloxicam (IC_{50} =29.0 μM) and comparable to that of SC-58125 (IC_{50} =1.36 μM), a potent COX-2 selective inhibitor. The IC_{50} ratio (COX-1/COX-2) for IMTP, meloxicam, and SC-58125 were more than 19, 3.5, and 73, indicating a high isoform selectivity of IMTP for COX-2.

Conclusion: A radioiodinated coxib, ^{125}I-IMTP was synthesized. Our results showed a high inhibitory potency and selectivity of IMTP for COX-2, indicating its potential as a SPECT tracer for imaging cyclooxygenase-2 expression.

Keywords: Cyclooxygenase-2 (COX-2), SPECT, Radiopharmaceutical

NO-CARRIER-ADDED RADIOHALOGENATIONS UTILIZING BORONATE ESTERS AND SALTS

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The preparation of no-carrier-added radiopharmaceuticals has become increasingly important in nuclear medicine imaging. For radiohalogenations, organometallic reagents are popular precursors but the separation of excess starting material from the desired product can be somewhat problematic. We have had a continued interest in the use of boronated organics as precursors to radiohalogenated pharmaceuticals. Even though boron-radiohalogen exchange reactions predate similar reactions involving tin, mercury and silicon, preparation of the prerequisite boronated precursors sometimes has proven to be problematic [1]. The situation has improved dramatically with the advent of transition metal catalyzed boronation reactions and other modern boron transformations. It is now possible to convert a wide variety of readily available halogenated reagents to the corrsponding boronate esters that can then be radiohalogenated in especially high yields [2]. In addition, the boronate esters can also be converted into the corresponding trifluoroborate salts which themselves are excellent precursors in radiohalogentation reactions [3].

We wish to present the results of our studies centered on the radioiodination and radiobromination of a wide variety of functionalized boronate esters and salts. The reactions are straightforward and lead to high yields of the desired products. The preparation of no-carrier-added 1-[^{123}I]iodo-2-phenylethyne is representative of the procedure. The potassium trifluoroborate salt of phenylethyne (100 µL of 5.2 x 10^{-2} in 50% aqueous tetrahydrofuran) was placed in a 2 mL Wheaton vial containing no-carrier-added Na^{123}I (37 MBq in 0.1% aqueous NaOH). To this was added peracetic acid (100 µL, 0.3% solution in methanol). The reaction vial was sealed, covered with aluminum foil, and the mixture stirred for 15 min at room temperature. A drop of 10% aqueous sodium thiosulfate was added to decompose the excess iodine and the radiodinated product was isolated by passing it through a silica gel Sep-Pak cartridge using petroleum ether as eluent. The radiochemical purity of the 1-[^{123}I]iodo-2-phenylethyne was determined by radio-TLC (aluminum backed silica gel plate, hexane); $R_f = 0.68$. The decay corrected radiochemical yield was determined to be 92% and radiochemical purity was 98%. The total synthesis time was 20 min. An exciting aspect of the trifluoroborate chemistry is that the starting materials are ionic and are readily separated from the desired products by simple Sep-Pak filtration.

$$R{-}BF_3K \xrightarrow[[O]]{Na^*X} R{-}^*X$$

[where X = ^{123}I, ^{124}I, ^{125}I, and ^{86}Br]

Acknowledgements: Research supported by the U. S. Department of Energy and the Robert H. Cole Foundation.

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Keywords: Radiohalogenation, Organoborane, No-Carrier-Added

RHODIUM (III) COMPLEXATION WITH TETRADENTATE ACYCLIC N_2S_2 LIGANDS

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For systematic cancer radiotherapy ^{105}Rh is of particular interest due to its nuclear properties [$t_{1/2}$ = 36 h, β^-_1 = 560 keV (70%), β^-_2 = 250 keV (30%), γ_1= 306 keV (5%), γ_2= 319 keV (19%)], with gamma emissions allowing *in vivo* tracking of the radiotherapeutic dose. The 36 h half-life would allow the preparation and delivery of radiopharmaceutical agents for clinical purposes. The availability of high specific activity ^{105}Rh coupled with the kinetic inertness of low-spin d^6 Rh(III) complexes increases its potential utility.

Numerous ligand systems, such as polyazamacrocycles as well as macrocyclic and acyclic tetrathioethers, have been reported to form very stable and kinetically inert complexes with Rh(III). Since N_2S_2 tetradentate chelates are one of the most studied chelating systems for ^{99m}Tc and ^{186}Re, it seemed worthwhile to investigate N_2S_2 tetradentate Rh(III) complexes. In this study, Rh(III) complexes (**L1** and **L2**) derived from two analogous tetradentate acyclic diaminedithioether (DADTE) ligands were synthesized [$RhCl_2(RS(CH_3)_2CCH_2N(CH_2)_mNCH_2C(CH_3)_2)SR)$]X (**L1**: m = 2 **L2**: m = 3; R = —$CH_2C_6H_4OCH_3$; X = Cl^-, PF_6^-) and the effect of the ligand backbone size on the configuration produced (*cis* and *trans*) has been studied. All products were analyzed by ^{1}H-NMR, ^{13}C-NMR and LC-MS.

In the case of **L1**, HPLC spectra showed two complexation products (**L1a** and **L1b**) in approximately a 50:50 ratio, presumably the *cis* and *trans* isomers. An LC-MS spectrum of the product mixture also supported formation of *cis/trans* isomers since the same positive-ion value with the correct isotopic distribution at m/z 649 was observed for each peak. ^{13}C NMR spectra were indicative of two isomers in solution. The complexity of the ^{1}H-NMR spectra made interpretation difficult; however, on the basis of the number of signals for the *p*-methoxybenzyl group of **L1**, it appears as if two products were formed upon complexation.

In the case of **L2**, one predominant product, **L2a**, was observed. **L2a** was fully characterized by ^{13}C NMR, where the signals for the **L2a** complex occur further downfield than for the ligand. The most characteristic peaks of the ^{1}H NMR spectrum for the ligand are the aromatic protons signals around 7 ppm, the methoxy signal at 3.7 ppm and the high-field methyl signal at 1.3 ppm. The formation of the complex is supported by additional phenyl, methyl and the geminal methyl signals from the different environment these groups experience on coordination to Rh(III). LC-MS spectroscopy showed positive-ion peaks with the correct isotopic distribution at m/z 663. Elemental analysis was performed and supported the formation of a 1:1 Metal:Ligand complex. Single crystals were prepared by slow evaporation of an ethanol/acetonitrile solution, and X-ray diffraction analysis confirmed formation of the *trans* isomer. The ORTEP diagram shows the complex to have slightly distorted octahedral geometry with the Rh(III) atom positioned in the center of the N_2S_2 cavity.

Preliminary radiolabeling of the acyclic diaminedithioether ligand **2** was conducted on the microscopic scale with ^{105}Rh(III). Chromatographic results showed a component of identical retention time to **L2a**; however, there were a few additional components that were formed on the radiotracer level. The complexation yield (40%) was determined by radioTLC. This radiolabeling reaction is currently being investigated and optimized. These results indicate the potential utility of using the acyclic diaminedithioether ligand backbone as a stable chelating framework for Rh(III).

Keywords: Rhodium-105, Diaminedithioether, Radiotherapy

RADIOCHEMISTRY AND *IN VIVO* EVALUATION OF THREE NOVEL ^{64}Cu-LABELED CROSS-BRIDGED MACROCYCLIC COMPLEXES

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Due to the decay properties of ^{64}Cu and its applications in both diagnosis and therapy, the use of ^{64}Cu-labeled complexes conjugated to targeting molecules such as proteins and peptides as diagnostic agents has significantly increased over the past two decades. However, ^{64}Cu presents both chemical and biological challenges, since copper, being an essential component of many biological proteins, is very labile and hence very difficult to complex stably for in vivo imaging and therapy. Recently, several novel cross-bridged (CB) macrocyclic ligands, including 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2A) and 4,10-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (CB-DO2A), have been synthesized and biologically evaluated to optimize the ring size and the carboxylate arm length.[1,2] This report describes the radiolabeling and rat biodistribution of 3 new CB ligands: 4,10-bis(carboxyethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (CB-DO2LA or **1**), 4,11-bis(carboxyethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2LA or **2**) and 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.5.2]pentadecane (CB-TR2A or **3**). These ligands differ from other ^{64}Cu CB-ligands by the substitution of acetate with propionate groups on the non-adjacent nitrogens (CB-ligands **1 and 2**) or by a change in the bicyclic framework from [6.6.2] to [6.5.2] (CB-ligand **3**).

All ligands were radiolabeled with ^{64}Cu according to established protocols in greater than 95% purity and biodistribution studies were conducted on all three complexes in normal rats. ^{64}Cu-**1** demonstrated slower blood, liver and kidney clearance (%ID/organ at 24 h) than ^{64}Cu-CB-DO2A (blood, 0.66±0.15 vs. 0.14±0.059; liver, 1.31±0.14 vs. 0.39 ±0.03; and kidney, 0.25 ±0.027 vs. 0.051±0.0089). The ^{64}Cu-**2** complex demonstrated slower clearance than ^{64}Cu-CB-TE2A from the blood, liver and kidneys (%ID/organ; 24 h) (blood, 0.22±036 vs. 0.032±0.014; liver, 0.62±0.049 vs. 0.14 ±0.039; and kidney, 0.10±0.013 vs. 0.064±0.012. ^{64}Cu-**3** also demonstrated less optimal clearance from the blood, liver and kidneys compared to ^{64}Cu-CB-TE2A (%ID/organ at 24 h) (0.13±0.025 vs. 0.032 ±0.014); liver, 0.62±0.11 vs. 0.14 ±0.039; and kidney, 0.17±0.046 vs. 0.051±0.0089). These data demonstrate that the optimal chelator for Cu(II) with respect to the most rapid clearance from non-target tissues is CB-TE2A, having a bicyclic [6.6.2] framework, and an acetate functional group on the non-adjacent nitrogens.

Acknowledgements: The authors would like to thank Laura Meyer and Christopher Sherman for technical assistance. This work was supported by NCI grants CA093375 and R24 CA086307 (for ^{64}Cu production).

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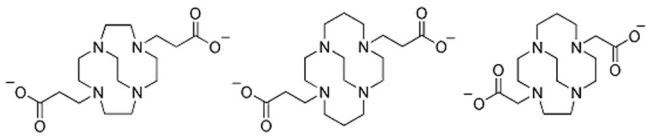

CB-DO2LA (1) CB-TE2LA (2) CB-TR2A (3)

Keywords: Copper-64, Biodistribution, Bifunctional Chelator

A BORON-BASED SYTHESIS OF [^{123}I]IODOSTYRYLBENZOXAZOLE, A POTENTIAL SPECT AGENT FOR IMAGING AMYLOID PLAQUES IN THE BRAIN

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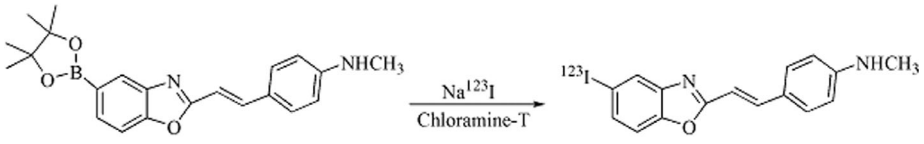
Alzheimer's disease (AD), a progressive memory disorder, affects as many as four million Americans over the age of 65. In AD patients the levels of acetylchloline, a neurochemical responsible for memory and learning, are significantly low (1). The enzyme responsible for the breakdown of acetylcholine is acetylcholinesterase.

[^{123}I]iodostyrylbenzoxazole, **2**, has been proposed as a potent SPECT agent for evaluating amyloid plaques in the brain (2). The reported synthesis involved the radioiodination of a tin precursor. Organotin compounds are potentially problematic since removal of trace amounts of tin side products can be difficult. However, boronic acid and bononate esters are generally considered to be non-toxic. Over the years, we have developed a number of high yield radiohalogenation reactions based on boronic acid intermediates. More recently we have devised more efficient radiohalogenation sequences based on readily prepared boronate esters (3, 4). We have applied the new methods to the synthesis of **2**.

Synthesis of [^{123}I]iodostyrylbenzoxazole **2**: the synthesis of styrylbenzoxazole boronateester **1** was accomplished in eight steps starting from p-anisidine. Compound **1** (100 µL of 5.2 x 10^{-2} *M*



1 **2**

solution in 50% aqueous tetrahydrofuran) was placed in a 2 mL Wheaton vial containing no-carrier-added Na^{123}I (37 MBq in 0.1% aqueous NaOH). To this was added chloramine-T (100 µL of a 1.04 x 10^{-1} *M* solution in 50% aqueous tetrahydrofuran). The reaction vial was sealed, covered with aluminum foil, and the mixture stirred for 30 min at room temperature. A drop of 10% aqueous sodium thiosulfate was added to decompose excess iodine and the radioiodinated product was isolated by passing it through a silica gel Sep-Pak cartridge using petroleum ether: ethyl acetate (35:65) as eluent. The radiochemical purity of [^{123}I]iodostyrylbenzoxazole **2**, was determined by radio-TLC (aluminum backed silica gel plate, petroleum ether: ethyl acetate = 35:65); R_f = 0.48. The TLC retention time was identical to that of authentic sample. The radiochemical purity was 98% and the radiochemical yield was 45%. The total synthesis time was 45 min.

Acknowledgements: This research was supported by the U. S. Department of Energy and the Robert H. Cole Foundation

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Keywords: Arylboronic Ester, Amyloid, Radioiodination

SYNTHESIS AND RADIOIODINATION OF A PNA CONTAINING AN [^{125}I]IODOURACIL MOIETY

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Peptide nucleic acids (PNA) hold potential as agents for delivering radiation to specific gene sequences and mRNA. Previous investigators have shown that ^{111}In-labeled PNA is effective at sequence-specific DNA cleavage [1]. We are interested in PNAs with Auger-electron-emitting radiohalogens directly incorporated into a base such that the radionuclide is held close to the DNA/RNA backbone. As a preliminary investigation, we have prepared a PNA that has an ^{125}I-labeled uracil moiety in the place of a thymine moiety. The base sequence of the PNA was chosen as it has been shown to bind with the insulin-like growth factor type 1 receptor (IGF-1R) [2], which is upregulated in prostate cancer. The initial goal in the study was to produce uracil-containing amino acid derivatives that could be incorporated into a PNA. The sequence of reactions is shown in the figure below. The first step was to prepare the base-reactive amino acid derivative **2**. That synthesis was carried out in four steps as described in the literature [3]. Reaction of **2** with commercially available iodouracil, **1**, was accomplished in 49% yield after purification. Hydrolysis of the ethyl ester **3** in 1N NaOH at room temperature for 4 h gave the free acid **4** in 58% yield, and preparation of the TFP ester **5** was accomplished in 66% yield using tetrafluorophenyl trifluoroacetate (TFP-OTFA) and Et_3N in DMF at rt for 5 min. Unfortunately, low yields (e.g. 30%) of the desired stannyluracil **6** were prepared from **5** using the standard conditions, i.e. $(nBu_3Sn)_2$ / $(Ph_3P)_4Pd$ in anhyd. toluene at reflux. An alternative pathway to **6** began with the preparation of **9** in a two-step synthesis. Reaction of **9** with **1** provided **10** in 44% yield. Conversion of **10** to the stannyluracil derivative **11** was readily accomplished using the standard stannylation conditions. Deprotection of **11** was accomplished in neat TFA at rt for 5 min, and reformation of the N-Boc to form **12** was accomplished with $NaHCO_3$/Boc_2O in acetone/H_2O for 3 h at rt. This was followed by preparation of the TFP ester using TFP-OTFA to give **6**. Once prepared, uracil amino acid derivatives **5 and 6** were reacted with PNA **7** to form PNA **8** (calc. 4181 Da, found 4185 Da; M+4H) and PNA **9** (calc. 4445 Da, found 4484 Da; M+K). Radioiodination of **9** was facile using Na[^{125}I]I and chloramine-T in H_2O/5% HOAc at rt for 5 min, providing a 46% (HPLC) isolated yield of [^{125}I]**8**.

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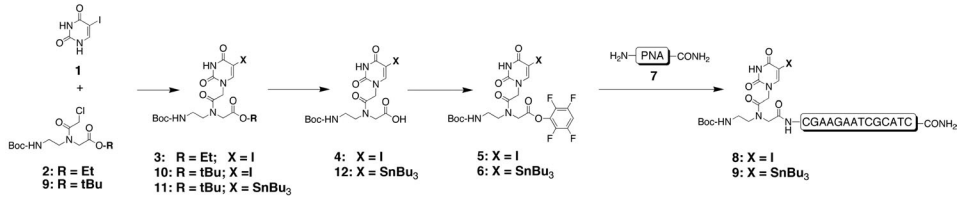

Keywords: Auger-Emitter, Peptide Nucleic Acid, Targeted Radionuclide Therapy

SYNTHESIS OF A N-3 SUBSTITUTED THYMIDINE DERIVATIVE FOR LABELING WITH TRIVALENT RADIONUCLIDES

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Aim

Based on the thymidine analog [^{18}F]3´-deoxy-3´-fluorothymidine (FLT) for imaging proliferation in vivo the development of nucleosides labeled with therapeutic metallic radionuclides for treatment of highly proliferating lymphomas is much promising. However, the attachment of radiometals via chelator without changing the properties of the nucleoside is a challenge. Investigations on nucleosides with carboranylalkyl substituents in N-3 position demonstrated that they are furthermore partial substrats for TK1 [1]. Adapting these results we attached the chelator DO3A (1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane) instead of the carboran cage resulting in compound "D3T" for direct radiometal labeling. The labeled compound may serve for addressing proliferation for use in both, imaging and endo radiotherapy (ERT).

Methods

The synthesis of the labeling precursor D3T is shown in Scheme 1. Analytical data, such as ^{1}H NMR, ^{13}C NMR and MS were in accordance with the described structure. Radiolabeling parameters as reaction pH, reaction time and D3T concentration were compared for n.c.a. ^{68}Ga and ^{111}In.

Results

In precursor synthesis, the overall yield of the three-step synthesis was 64.1 %. Labeling of D3T with $^{68}Ga^{3+}$ shows a very strong dependency of pH-value with an optimal pH range between 3.8 to 4.2. Safe and almost complete $^{68}Ga^{3+}$ complexation occurs at D3T concentrations higher than 10 µM. The incorporation kinetics of n.c.a. $^{68}Ga^{3+}$ followed pseudo-first-order kinetics with observed rate constants $k_{obs} = 1.45 \times 10^{-2}\ s^{-1}$ for ^{68}Ga-D3T and $k_{obs} = 1.3 \times 10^{-2}\ s^{-1}$ for ^{68}Ga-DO3A. Differently, the observed rate constant for ^{111}In-D3T was $k_{obs} = 5 \times 10^{-3}\ s^{-1}$, indicating that Ga ist faster incorporated than In. Also, there are differences in lipophilicity between the two complexes with different metall ions. The HPLC scans on an analytical reversed phase column indicate that ^{68}Ga-D3T is more hydrophilic, with the retention time being 4.7 min shorter than that of ^{111}In-D3T. This finding suggests that gallium and indium chelates do not share the same coordination sphere, even though they are coordinated by the same DO3A conjugate.

Conclusions

Synthesis and labeling properties of the DO3A coupled thymidine derivative D3T were optimized. The synthesis of D3T is reliable and simply enables changes of the tether length between the chelator and the nucleoside scaffold. Changes in lipophilicity with different metal ions correspond to other studies [2]. Further studies will focus on the biological evaluation.

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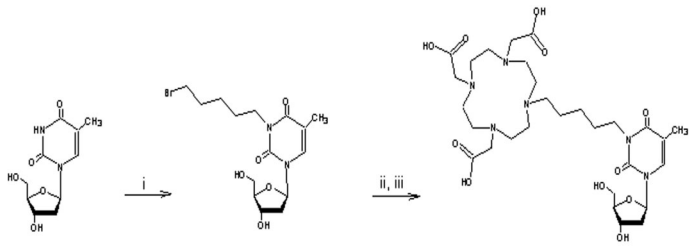
Scheme 1: Synthesis of radioligand D3T. Reagents and conditions: (i) K_2CO_3, $Br(CH_2)_5Br$, DMF, 60°C, (ii) 1,4,7,10-tetraazacyclododecane-1,4,7-tris(acetic acid t-butyl ester), K_2CO_3, MeCN, 60°C, (iii) CF_3COOH, room temperature.

Keywords: Nucleosides,
Endo Radiotherapy,
Radiometal



SYNTHESIS AND BIOLOGICAL EVALUATION OF [^{123}I]QUINONOIDS FOR BRAIN TUMOR IMAGING

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Objective: Some Quinonoids, the long time therapeutic applications of these herbs, have been vindicated through recent studies on the significant pharmacological properties of these compounds. In fact, the bioactive quinonoids, emodin and hypericin have been reported to have antitumor activity. Emodin is constituents in *Aloe vera* leaves and hypericin is naphthodianthrones present in *Hypericum perforatum* L. Recent study showed that emodin and hypericin have the PKC (protein kinase C) inhibitory effect. PKC is well known enzyme system which regulates cellular functions, metabolism and proliferation by phosphorylating proteins in response to transmembrane signals from growth factors including tumor progression. In this investigation, we evaluated I-123 labelled [^{123}I]iodoquinonoids effect on PKC content in C6 glioma cell. **Method**: [^{123}I]iodoquinonoids were prepared by the reaction of precusors with sodium [^{123}I]iodide in the presence of peracetic acid. As for the analysis of those, [^{123}I]iodoquinonoids were separated and purified by HPLC with X-terra RP18 column. The *in vitro* study of [^{123}I]iodoquinonoids were measured on C6 glioma and fibroblast which is used for control at 10 min, 30 min, 60 min and 120 min, respectively. **Results**: The radiochemical yields were about 72% ([^{123}I]iodoemodin), 60% ([^{123}I]iodohypericin) and the radiochemical purity was all over 97%. In case of [^{123}I]iodoemodin, the %ID/g at 120 min for C6 and fibroblast were 9.69, 5.18, respectively and for [^{123}I]iodohypericin, 6.73, 0.65, respectively. **Conclusion:** These results have showed that the cellular uptake of C6 glioma for [^{123}I]iodoemodin is 1.4 fold higher than that of [^{123}I]iodohypericin, however, The ratio of C6 glioma to fibroblast for [^{123}I]iodohypericin is 5 fold higher than that of [^{123}I]iodoemodin. Therefore, [^{123}I]iodohypericin has more possibility as a brain tumor imaging agent than [^{123}I]iodoemodin.

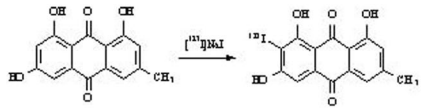

Figure 1. the labelling of [^{123}I]iodoemodin

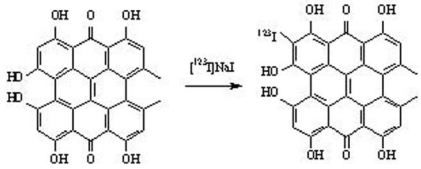

Figure 2. the labelling of [^{123}I]iodohypericin

Keywords: [Iodine-123]Quinonoids, C6 GLIOMA, PKC

ADDITION OF METHIONINE TO RADIOHALOGENATION REACTIONS OF BIOTIN DERIVATIVES DECREASES FORMATION OF BIOTIN SULFOXIDE BY OXIDANTS

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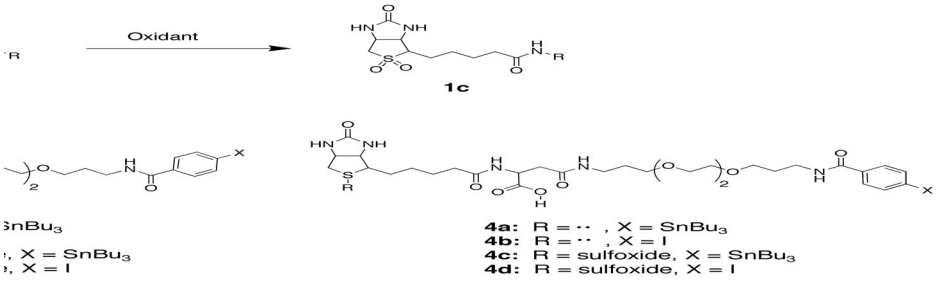
The thioether functionality in biotin derivatives (**1a**) is susceptible to oxidation, producing sulfoxides (**1b**) with mild oxidation and sulfones (**1c**) with more rigorous oxidation. Such oxidation produces biotin derivatives that have poor or no binding with avidin and streptavidin. A side product in radiohalogenation reactions of biotin derivatives, such as **3a** and **4a**, is formation of sulfoxides, e.g. **3d** and **4d**. This reaction can occur very rapidly (<1 min) under the usual radiolabeling conditions. While it can be controlled somewhat by stoichiometry and reagents used, we have not been able to eliminate it. Fortunately the biotin sulfoxide is generally separable from the radiolabeled biotin by reversed-phase HPLC, so we have used this method for purification of the radiohalogenated biotin derivatives. However, under some conditions the reaction product is primarily the sulfoxide derivative. Further, our ultimate goal is to prepare the radiohalogenated biotin derivatives without HPLC purification for simplicity of preparation. So reaction conditions to eliminate the sulfoxide side reaction were sought.

A possible solution to the unwanted side reaction is to introduce another thioether containing molecule to the radiohalogenation reaction mixture. Because of its biocompatibility, high aqueous solubility and low lipophilicity, we have focused on the use of L-methionine for this purpose. The excess oxidant used in high specific activity radiohalogenations results in sulfoxide formation. Reactions of **2a, 3b**, and **4b** with chloramine-T (ChT) in H_2O/5% HOAc or N-chlorosuccinimide (NCS) in MeOH/5% HOAc yielded the sulfoxides **2b, 3d** and **4d**. Significantly less sufoxide (10-20%) is produced with NCS in MeOH/HOAc than with ChT in H_2O/HOAc (50-100%) in the 1-5 min reaction times. Importantly, irrespective of the oxidant used, introduction of 10-12 molar equivalents of L-methionine to the amount of oxidant in the reaction mixture resulted in formation of L-methionine sulfoxide with none, or only small quantities (<5%), of the biotin sulfoxides **2b, 3d**, or **4d** being formed. Unfortunately, high specific activity radioiodinations did not occur in the presence of large molar excess of L-methionine. However, addition of 0.5 equivalents L-methionine (relative to the N-halo oxidant) resulted in radioiodinations that had only minor amounts of sulfoxide-containing product. For example, radioiodination of **4a** using ChT/Na[^{125}I]I in H_2O/5% HOAc without addition of L-methionine gave 15% desired [^{125}I]**4b** and 83% of the sufoxide [^{125}I]**4d**. In contrast, [^{125}I]**4b** was formed in 97% yield when 0.5 equivalents L-methionine were added to the reaction mixture.



Keywords: Biotin Sulfoxide, Radiohalogenation, Oxidants

TOWARDS THE VISUALIZATION OF PERIPHERAL BENZODIAZEPINE RECEPTOR BY SPECT

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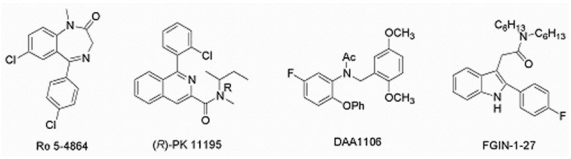
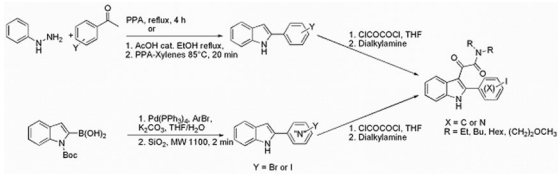
The peripheral benzodiazepine receptor (PBR) is expressed in both peripheral and central nervous system (CNS).[1] The PBR plays critical roles in cell proliferation, porphyrin transport and heme synthesis, immunomodulation, regulation of steroidogenesis and apoptosis.[1-3] Various endogenous molecules including the diazepam-binding inhibitor (DBI), porphyrins and cholesterol have high affinities for PBR. Synthetic ligands can be divided into 4 families: benzodiazepines (Ro 5-4864), isoquinoline carboxamides (PK 11195), *N*-(2-phenoxyphenyl)-*N*-(benzyl)acetamides (DAA1106), and indolylacetamides (FGIN-1-27).[10] With the aim of visualizing PBR in vivo by single photon emission computed tomography (SPECT), we have undertaken the synthesis of new ligands bearing an iodine atom. Those new molecules belong to the indolylglyoxamide family. New iodinated ligands were prepared by either Fischer indole synthesis or Suzuki cross coupling, followed by a bromine-to-iodine exchange and acylation in acceptable to good yields (*Scheme*). *In vitro* binding of new ligands to PBR and central benzodiazepine receptor (CBR) was measured. Despite the presence of the iodine atom, the new molecules exhibited high affinity for PBR (K_i 2-25 nM) and selectivity with respect to CBR (K_i CBR > 10^3). ^{123}I-Radiolabeling of the novel compounds was achieved *via* iododestannylation of the corresponding trimethylstannyl precursors ($Na^{123}I$, peracetic acid in the presence of phosphoric acid) for 15 min at ambient temperature. Radiochemical yields were in the range 85-95%. Radiolabeled compounds were readily purified by reverse-phase HPLC, and their radiochemical purity exceeded 95%.





The authors thank Dr. Anne Schmidt, Pfizer Global Research & Development, for performing the in vitro binding assays.

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Keywords: Peripheral Benzodiazepine receptor, Radio-Labelling, Medical Imaging

HYDRALINK IS SUPERIOR TO EDC IN PRESERVATION OF AFFINITY OF AN ANTI-PSMA ANTIBODY IN THE CONJUGATION WITH MORPHOLINOS

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As pretargeting is practiced in this laboratory, it is necessary to prepare an antitumor antibody conjugated with a phosphodiamidate morpholino oligomer (MORF). Because pretargeting of colon cancer xenografts in mice with an antiCEA antibody MN14 conjugated with MORF is providing encouraging results, this laboratory has now included the antiPSMA antibody 3C6 and prostate cancer xenografts. Previously antibody conjugation was achieved using 1-ethyl-3(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC). An alternative involves first converting the amine group on MORF to an aldehyde and the amine on the antibody to an acetone protected hydrazine, followed by the linking of the aldehyde-MORF to the hydrazine-antibody (Hydralink). **OBJECTIVE**: The 3C6 antibody was conjugated by both the EDC and Hydralink methods and the antibody affinity for PSMA using PSMA-positive LNCaP cells evaluated by flow cytometry and binding of radiolabeled antibody-MORF. **METHODS**: Following conjugation and purification, the affinity of 3C6-MORF (EDC) and 3C6-MORF (Hydralink) was evaluated by flow cytometry analysis after incubation with LNCaP prostate cancer cells. Identical incubations were performed with native 3C6 and cyclic DTPA anhydride conjugated 3C6 as positive controls and with cells not exposed to antibody as negative controls. After incubation to equilibrium, the cells were stained with FITC labeled AffiniPure Rabbit Anti-Mouse secondary antibody to detect cell-bound 3C6. Both 3C6-MORF (EDC) and 3C6-MORF (Hydralink) were also radiolabeled with tracer ^{99m}Tc-complementary MORF (cMORF) and used in cell binding studies as a further confirmation of antibody affinity. **RESULTS**: Using the identical conjugation procedures for 3C6 that was used earlier for MN14, the average number of MORF groups attached was 2-3 times higher for both EDC and Hydralink, suggesting that antibody-related factors influence the conjugation. The average number of MORF groups attached per antibody molecule was 1.9 for 3C6-MORF (Hydralink) and 0.78 for 3C6-MORF (EDC). Flow cytometry with FITC-conjugated secondary antibody showed that the affinity to PMSA of the conjugated antibody was almost unchanged for 3C6-MORF(Hydralink) but clearly reduced for 3C6-MORF(EDC) compared to native 3C6. Furthermore, about three fold more radioactivity was bound in the case of 3C6-MORF(Hydralink) compared to 3C6-MORF(EDC) in the cell binding study with 3C6 labeled 99mTc. Therefore, by both methods there were obviously more antibody bound per cell with 3C6-MORF(Hydralink) compared to 3C6-MORF(EDC). Because the affinity of 3C6 conjugated with the cyclic anhydride of DTPA also preserved its affinity, the lower affinity following ECD conjugation may be related to the targeting of carboxylates in the antibody by this method compared to the targeting of amines by both the Hydralink and DTPA methods. **CONCLUSION**: Conjugation of MORF to the amine groups of 3C6 as in the case of 3C6-MORF (Hydralink) preserved its antiPSMA affinity in contrast to the conjugation via EDC to carboxylate groups.

Keywords: Antibody Modification, Flow Cytometry Analysis, Cell Binding Study

SYNTHESIS, RADIOIODINATION AND EVALUATION OF NEW MGMT-INHIBITORS AND THEIR GLUCOSE CONJUGATES

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Aim:

An important type of chemotherapy is the treatment of tumors with alkylating or chloroalkylating drugs causing alkylation of DNA guanine. This results in a blocking of DNA-replication and a decrease in tumor-growth. The enzyme O6-methylguanine-DNA methyltransferase (MGMT) is able to reverse the blocking of the DNA. Since MGMT is also expressed in various tumor types, inhibitors of MGMT like O6-benzylguanine given prior to the actual chemotherapy, are currently investigated (1). To possibly increase the selectivity for tumor cells versus healthy tissues, glucosylated inhibitors have been considered (2). The radioiodination of several MGMT inhibitors with 131I and 123I allows studying tissue and tumor distribution of the new compounds in nude mice ex vivo and in vivo.

Methods:

Both O6-5-iodothenylguanine and O6-3-iodobenzylguanine as well as their N9 conjugated glucose derivatives were synthesized. For the non-radioactive compounds the IC50 values for the inhibition of MGMT were determined (3). Radioiodination with 131I and 123I were conducted with the stannous precursors of all compounds. With the radioactive derivatives the tumor and tissue distribution in nude mice carrying MEX(+) and MEX(-) xenografts was investigated at time points between 30 minutes and 8 h post injection with the 131I-labelled compounds. Non-invasive measurements (123I-labelled analogues) for 2 hours were performed using the I.S.E. YAP-(S)PECT small animal scanner.

Results:

The non-radioactive standard compounds and their corresponding stannous precursors were synthesized successfully. The IC50 values of O6-5-iodothenylguanine and O6-3-iodobenzylguanine were 0.75 μM and 0.1 μM, and those of the glucosylated conjugates 0.8 μM and 0.45 μM, respectively. Whereas all compounds were labeled with iodine-131 in high radiochemical yields of 70 - 98 %, analogue 123I labeling reactions showed lower efficacy. Following product isolation using HPLC, first ex vivo animal studies indicated that the tumor-to-blood radioactivity ratio is best for O6-3-iodobenzylguanine-N9-C8-β-glucose (0.76 at 30 min p.i.).

Conclusions:

The optimized synthetic strategy allows the preparation of different guanine derivatives and their glucose conjugates. Radioiodination via de-stannylation results in high yields of the labeled analogues. Glucosylated derivatives show improved pharmacological properties. The correlation of cell uptake of the radioiodinated compounds with intracellular MGMT-concentration and expression of glucose transporters on the cell membrane, respectively, needs to be investigated in more detail.

Acknowledgement: Co-operation with I.S.E. and A. Del Guerra and co-workers, University of Pisa, is gratefully acknowledged.

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Keywords: MGMT-Inhibitors, Radioiodination, Biodistribution

RADIOIODINATION OF TALNETANT ANALOGUES FOR SPECT IMAGING STUDIES OF NK-3 RECEPTOR

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The neurokinin B-mediated seven-transmembrane G-protein-coupled NK-3 receptor is expressed predominantly in the central nervous system[1-4], and is known to be involved in a range of disorders such as asthma, emesis, anxiety, depression, epilepsy, schizophrenia and Parkinson's disease[5-6]. With the aim of studying the biodistribution and quantification of this receptor in living brain using SPECT imaging, we recently prepared[7-8] a series of iodinated analogues of Talnetant[9] (SB 223412), a highly potent and selective human NK-3 antagonist. We showed that 3-methoxy-2-phenylquinoline-4-carboxamides **1 and 2**, bearing an iodo substituent at position 7 of the quinoline system, displayed an affinity for the NK-3 receptor similar to that of Talnetant. Here, we report their ^{123}I-labeling starting from the corresponding trimethylstannyl precursors **3** and **4,** respectively. Trimethylstannylquinoline **3** was prepared by the reaction of the iodo compound[7] **1** with hexamethylditin under palladium catalysis[10] in 86% yield. Precursor **4** was obtained starting from 8-fluoroquinoline[7] **5** using a fluorine directed metalation[8] - stannylation sequence (35% yield). Radioiodination was performed *via* iododestannylation under commonly-used conditions (Na^{123}I, peracetic acid in the presence of phosphoric acid). Radiochemical yields in [^{123}I]**1** and [^{123}I]**2** were *ca*. 90 % and 25%, respectively. Full details and biological data will be presented.

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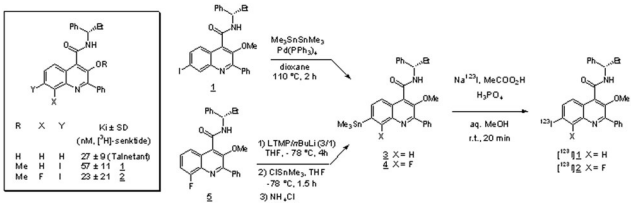

Keywords: Iodine-123, Iodoquinoline, NK-3 Receptor

111-INDIUM LABELED POLYMERIC MICELLES AS NOVEL DRUG DELIVERY SYSTEM FOR MICRO-SPECT/CT IMAGING

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Objectives: Polymeric micelles have potential utility as drug carriers. polymeric micelles for drug delivery offer many advantages, e.g. their high and controllable drug loading and release capacities, their biocompatibility, and the diversity of drugs they can accommodate. Therefore, polymeric micelles are particularly promising carriers of many hydrophobic anticancer agents. Small animal imaging, using SPECT/CT, offers the exciting possibility of studying the time-activity behavior of a radiolabeled drug in vivo. The purpose of the current study was to radiosynthesis and evaluate111In-DOTA-PCL-PEG micelles, a novel drug delivery system for imaging mice using micro-SPECT/CT. **Methods:** DOTA-PCL-PEG micelles were radiolabeled with 111In using different methods. Reaction parameters were investigated in order to optimize the final properties of the labeled micelles, The reaction parameters studied were buffer concentration, pH value, chelation time, temperature, radiolabeling time and separation. Chelation efficiencies of evaluate111In-DOTA-PCL-PEG micelles were determined using radioactive thin layer chromatography (Radio-TLC) using silica precoated strips and chromatography paper as the solid phase and water and different organic solvent as the mobile phase. For purification of the 111In-DOTA-PCL-PEG micelles a Centricon 100K dialysis method was used, the isolated radiochemical yields and radiochemical purity were determined. The stability of the radiolabeled micelles in aqueous solution was tested by incubation of the purified micelles in 0.1M phosphate buffer pH 7 at room temperature for 24 h and degradation of the complex was assessed by Radio-TLC. The desired product was collected for further animal micro-SPECT/CT imaging study.

Results: The radioactive 111In-DOTA-PCL-PEG micelles was prepared by diluting Indium 111 In chloride sterile solution with 0.01 M ammonium acetate buffer pH 6 and 5 mg DOTA-PCL-PEG, and then incubating for 10 minutes at 25°C. The labeling efficiency was 43 %. The free DOTA as the control group also was labeled by 111-Indium, the labeling efficiency was 99%. The 111In-DOTA appeared in mixture during labeling reaction, this result indicated that 111In-DOTA-PCL-PEG partly was decomposed under ammonium acetate buffer as labeling condition. The labeled mixture was separated by Centricon 100K dialysis, The radiochemical yields of 111In-DOTA-PCL-PEG was 36.5 % and radiochemical purity was great than 99%. The stability test shows that no loss in purity was observed during 24 h incubation.**Conclusion:** A novel 111-Indium labeled polymeric micelles as drug delivery system were prepared under moderate condition. The purified DOTA-PCL-PEG could be very efficiently labeled with 111In and a sample dialysis filter was also efficiently used to purify 111In-DOTA-PCL-PEG. The radiochemical yields, radiochemical purity and stability were suitable for further animal studies.

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Keywords: Indium-111, Polymeric Micelles, micro-SPECT

CHELATION PROPERTIES OF PYCLEN BASED MACROCYCLIC LIGANDS

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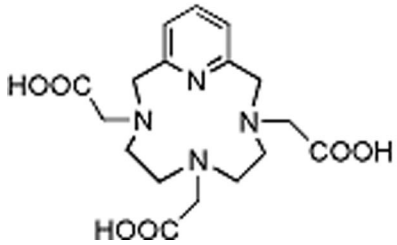
N-acetate and methylenephosphonate derivatives of pyclen have very favorable binding properties for the trivalent lanthanide ions. However, the kinetics of formation and dissociation of their lanthanide complexes have not been studied yet.

In this work, the kinetics of formation of lanthanide complexes with PCTA (pyclen triacetic acid) were measured and found to be about one order of magnitude faster than the analogous LnDOTA complexes. This favorable kinetic behavior makes these ligands attractive candidates for lanthanide-based radiopharmaceuticals where rapid complex formation is very important for those radioisotopes having short half lifes.



PCTA (pyclen triacetic acid)

Keywords: Macrocyclic Chelator, Lanthanide Ions, Formation Kinetics