^{99m}Tc(CO)$_3$-Labeled Histidine-Arylpiperazines
as Potential Radiotracers for a Neuroreceptor Targeting

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In order to develop radiopharmaceuticals for targeting a serotonin receptor such as 5-HT$_{1A}$, histidine-C$_n$-arylpiperazines (AP) (C = alkyl, n = 2, 3, 4) were prepared in five steps with yields of 25%, 37% and 51%, respectively, and radiolabeled with the [^{99m}Tc(CO)$_3$(H$_2$O)$_3$]$^+$. The ^{99m}Tc(CO)$_3$-Histidine-Cn-APs were prepared with a high yield (>99%) and characterized as a tridentate complex with a neutral charge to pass through the blood-brain barrier (BBB). The rhenium complexes with Re(CO)$_3$ were also synthesised and comparative experiments were achieved to evaluate the nature of the ^{99m}Tc complexes.

Key Words : Neuroreceptor, Arylpiperazine, 5-HT$_{1A}$, Histidine derivative, ^{99m}Tc(CO)$_3$

Introduction

The labeling of biologically active molecules with ^{99m}Tc is the most popular method in the fields of molecular imaging research due to the favorable properties of this isotope; (γ 140 KeV, t$_{1/2}$ = 6.02h). ^{99m}Tc has the accessibility of an oxidation state from +I to +VII. In the past, ^{99m}Tc with the +5 oxidation state was commonly available for a labeled tracer,[1] but recently small sized and neutral charged complex was required for the IAEA Coordinated Research Project on 'the Development of agents for an imaging of the Central nervous system (CNS)'. Therefore, many researches focused on ^{99m}Tc with the +1 oxidation state, [^{99m}Tc(CO)$_3$]$^+$, have been performed to prepare improved neuroreceptor imaging agents.[2] The biological activity of [^{99m}Tc(CO)$_3$]$^+$ complexes with a relation to the CNS requires a high selectivity for the neuroreceptor and moreover it should have specific feature as a neutral charge to pass easily through the blood-brain barrier (BBB), thus an anionic tridentate ligand reacting with *fac*-[^{99m}Tc(CO)$_3$]$^-$ is available to form a neutral compound.[3]

All Chelating agents should show the following proper-ties:[4] 1) high affinity to the organometallic fragment 2) a thermodynamical stability and a kinetical resistant to a ligand exchange 3) no excess of the ligand concentration relative to "hot" technetium and rhenium. A variety of researches on complexes containing [Tc(CO)$_3$]$^-$ and [Re(CO)$_3$]$^-$ has revealed that the histidine complexes show a good stability through *in-vivo* and *in-vitro* studies and they meet all the above requirements.[5] D. R. van staveren *et al.* alluded to the merits of histidine: easily tethering [Tc(CO)$_3$]$^-$ at a low temperature and an enantiomerical purity when it forms the Tc(His-τ(*N*-1)-R)(CO)$_3$ complex.[6] Despite these good pro-perties, it is difficult to introduce a spacer at the τ(*N*-1) position of histidine; nevertheless, it is an interesting fact that a protection of the π(*N*-3) position of histidine induces a selective alkylation under a strong base condition; *e.g. N*-Boc protecting group may cause a steric effect at τ(*N*-3) thus N_α-Boc-histidine undergoes a pure τ(*N*-1) substitution reaction.[7] N_α-trityl-L-histidine also undergoes the τ(*N*-1) reaction (major product) along with the τ(*N*-3) reaction (minor product).[8] These reactions are helpful to develop new chelating agents with a relation to the CNS.
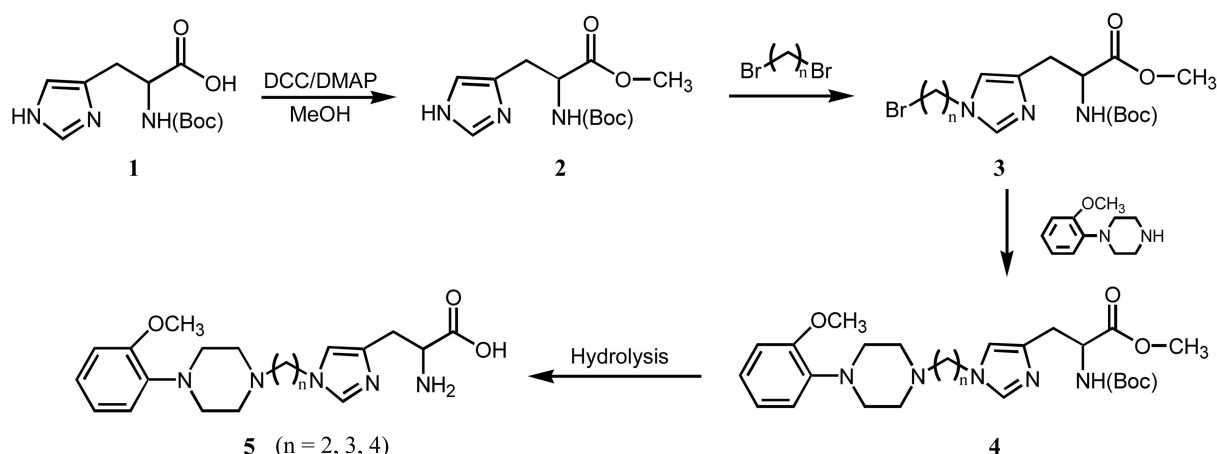
Scheme 1. Reaction pathway of the Histidine-AP derivatives.
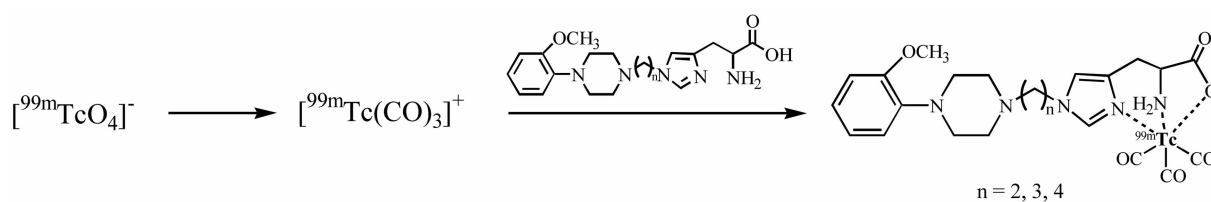
Scheme 2. Labeling of a histidine based arylpiperazine: n – alkyl chain number.

In order to establish the implications in a wide range of neurological disorders, we have concentrated on the neuro-receptors and their tracers with ^{99m}Tc labeled compounds. Especially, serotonin receptors (*e.g.* 5-HT series) have shown an involvement in such as Alzheimer's disease, schizophrenia, and depression.[9] WAY-100135,[10] WAY-100635, BMY 7378 and NAN-190 are well known as potent antagonists of the 5-HT$_{1A}$ receptors.[9,10] These compounds are composed of aryl-piperazine which shows a high affinity to the 5-HT$_{1A}$ receptor.[11] This prototype provides a new opportunity to develop novel radiotracers.

In order to know neurogical disorder such as Alzheimer's disesae and depression, we report herein the synthetic method of novel 5-HT$_{1A}$ antagonist derivatives with attaching histidine chelator, labeling with [^{99m}Tc(CO)$_3$]$^+$ and physical properties.

Experimental Section

Materials and instruments. N_α-Boc-L-histidine, 1-(2-methoxyphenyl)piperazine, 1,3-dibropropane and 1,4-di-bromobutane were purchesed from Fluka Chemical Co. 1,2-dibromethane, dicyclohexylcarboimide (DCC), dimethyl-aminopyridien (DMAP) and other solvents were purchesed from Aldrich Chemical Co. All the progresses of the reaction were identified with TLC glass sheets pre-coated with silica-gel 60F$_{254}$, Merck. The NMR spectra were recorded with the Varian Gemini 200 (200 MHz ^{1}H, Dongguk Univ.) and Bruker DMX 600 (600 MHz ^{1}H, Korean Basic Science Institute, Daejeon) spectrometers and the chemical shifts were obtain as a ppm unit ratio versus TMS as an internal standard. Mass spectra were measured with the Hewlett Packard HP 1100 series LC/MSD (Chungnam National Univ.). Sodium pertechnetate ([^{99m}Tc] NaTcO$_4$) was obtained from a ^{99}Mo-^{99m}Tc generator (Sam Young Unitech. Co., LTD.). The labeling yield and radiochemical purity were determined by a Radio-HPLC (system equipped with Waters 2695 pump, UV-Detector (Waters 2487), RI -detector (In/US system) and a Xterra C-18 column (5 μm, 4.6 × 250 mm); condition: gradient elution from TEAP to MeOH; flow rate: 0.9 mL/min). The gradient system is depicted in Figure 1. All the radioactivity was measured by using an ionizing chamber (Atomlab 200, Bio-dex).

N_α-***tert*-Butoxycarbonyl-L-histidine methylester (2).** To a suspension of N_α-*tert*-Butoxycarbonyl-L-histidine (5.00 g, 19.6 mmol) in CH$_3$OH (20 mL) under a N$_2$ condition, a solution of DMAP (2.87 g, 23.52 mmol) in CH$_2$Cl$_2$ was dropwisely added. After 5 min, The reaction mixture was
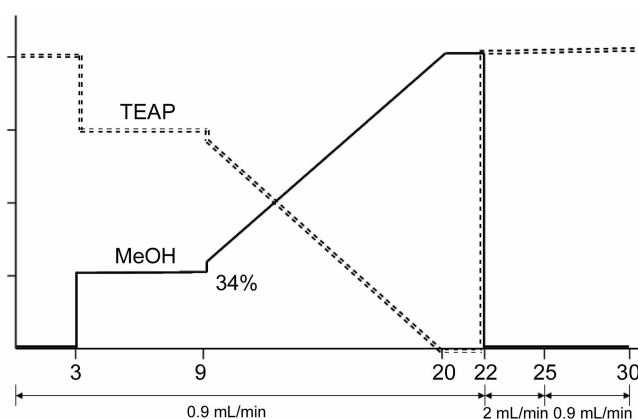
Figure 1. Solvent gradient system with TEAP and MeOH.

cooled down to 0 °C when it turned to a clear solution and followed by a slow addition of a solution of DCC (4.73 g, 23.52 mmol). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was treated with CHCl$_3$ to filter off the precipitate. The remaining solution was evaporated and the crude product was chromatographed by using CH$_2$Cl$_2$-MeOH (15 : 1) on a silica gel column to obtain **2** as a white solid (4.3 g, 80%), mp 120 °C, NMR (CDCl$_3$), δ(ppm) 1.45 (s, 9H), 3.10 (dd, 2H), 3.73 (s, 3H), 4.49 (m, 1H), 5.73 (br d, 1H, NH), 6.80 (br s, 1H), 7.54 (br s, 1H) (LC/MSD M+1): cald. for 270.14 found 270.1.

N_α-**Boc-$N_{\tau l}$-(bromoalkyl)-L-histidine methylester (3).** To a solution of **2** (1 g, 3.71 mmol) in DMF (10 mL) at −15 °C under a N$_2$ condition, NaH (100 mg, 4.17 mmol) was portionwisely added. The mixture was left for 10 min at −15 °C until H$_2$ gas didn't occur. When the mixture turned to a slightly pale suspension, dibroalkane (2 eq) was added. The temperature of the reaction mixture was raised to 0 °C and the mixture was continuously stirred for another 2 hrs. The excess NaH was eliminated by an addition of methanol. The solvent was removed under a reduced pressure and dried *in vacuo* at 40 °C for 2 hrs. The crude product was purified by a column chromatography eluting with CH$_2$Cl$_2$-MeOH (10 : 1) to obtain (**3a, 3b, 3c**) as sticky oil.

N_α-**Boc-$N_{\tau l}$-(2-bromoethyl)-L-histidine methylester (3a).** The same procedure described above was used with dibromoethane (1.39 g, 7.42 mmol). The desired product gave 0.60 g as 43%. NMR (CDCl$_3$), δ(ppm) 1.45 (s, 9H), 3.07 (dd, 2H), 3.58 (t, 3H), 3.72 (s, 3H), 4.30 (t, 3H), 4.57 (m, 1H), 5.90 (br d, 1H, NH), 6.79 (br s, 1H), 7.46 (br s, 1H) (LC/MSD M+1): cald. for 376.08 found 376.1.

Nα-Boc-*Nτ*-(3-bromopropyl)-L-histidine methylester (3b). The same procedure described above was used with dibromopropane (1.50 g, 7.42 mmol). The desired product gave 0.80 g as 55%. NMR (CDCl₃), δ (ppm) 1.45 (s, 9H), 2.54 (p, 2H), 3.05 (dd, 2H), 3.30 (t, 2H), 3.72 (s, 3H), 4.11 (t, 2H), 4.54 (m, 1H), 5.94 (br d, 1H, NH), 6.72 (br s, 1H), 7.44 (br s, 1H) (LC/MSD M+1): cald. for 390.10 found 390.2.

Nα-Boc-*Nτ*-(4-bromobutyl)-L-histidine methylester (3c). The same procedure described above was used with dibromobutane (1.60 g 7.42 mmol). The desired product gave 1.09 g as 73%. NMR (CDCl₃), δ (ppm) 1.42 (s, 9H), 1.85 (m, 4H, -CH₂-CH₂-CH₂-CH₂-), 3.05 (dd, 2H), 3.38 (t, 2H), 3.68 (s, 3H), 3.91 (t, 2H), 4.55 (m, 1H), 5.96 (br d, 1H, NH), 6.67 (br s, 1H), 7.36 (br s, 1H) (LC/MSD M+1): cald. for 404.11 found 404.1.

Nα-Boc-*Nτ*-((4-(2-methoxyphenyl)piperazin-1-yl)alkyl)-L-histidine methylester (4). To a solution of 3 and 1-(2-methoxyphenyl)piperazine (500 mg, 2.6 mmol) in DMF (10 mmol) at 25 °C under a N₂ condition, K₂CO₃ (539 mg, 3.9 mmol) was added and the mixture was heated at 40 °C for 12 hrs. The solid phase was removed by a filtration and the solvent was removed *in vacuo*. The yellow sticky oil was chromatographed on a silica gel with CH₂Cl₂-MeOH (20 : 1) and the target compound was isolated as a colourless sticky oil.

Nα-Boc-*Nτ*-(2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl)-L-histidine methylester (4a). The same procedure described above was used with 3a (880 mg, 2.34 mmol). The desired product gave a 924 mg as 81%. NMR (CDCl₃), δ (ppm) 1.44 (s, 9H), 2.70 (br s, 4H, piperazine), 2.74 (t, 2H), 3.06 (dd, 2H), 3.09 (br s, 4H, piperazine), 3.71 (s, 3H), 3.87 (s, 3H), 4.01 (t, 2H), 4.57 (m, 1H), 5.96 (br d, 1H, NH), 6.77 (br s, 1H), 6.88 (m, 1H, Aryl), 6.94 (m, 2H, Aryl), 7.01 (m, 1H, Aryl), 7.48 (br s, 1H) (LC/MSD M+1): cald. for 488.28 found 488.3.

Nα-Boc-*Nτ*-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl)-L-histidine methylester (4b). The same procedure described above was used with 3b (913 mg, 2.34 mmol). The desired product gave a 1.09 g as 93%. NMR (CDCl₃), δ (ppm) 1.45 (s, 9H), 1.95 (p, 2H), 2.37 (t, 2H) 2.67 (br s, 4H, piperazine), 3.05 (dd, 2H), 3.13 (br s, 4H, piperazine), 3.30 (t, 2H), 3.70 (s, 3H), 3.86 (s, 3H) 3.98 (t, 2H), 4.52 (m, 1H), 5.94 (br d, 1H, NH), 6.70 (br s, 1H), 6.87 (m, 1H, Aryl) 6.94 (m, 2H, Aryl), 7.01 (m, 1H, Aryl) 7.40 (br s, 1H) (LC/MSD M+1): cald. for 502.30 found 502.3.

Nα-Boc-*Nτ*-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-L-histidine methylester (4c). The same procedure described above was used with 3c (944 mg, 2.34 mmol). The desired product gave a 1.13 g as 94%. NMR (CDCl₃), δ (ppm) 1.43 (s, 9H), 1.53 (p, 2H), 1.79 (p, 2H), 2.40 (t, 2H), 2.61 (br s, 4H, piperazine), 3.01 (dd, 2H), 3.06 (br s, 4H, piperazine), 3.69 (s, 3H), 3.85 (s, 3H), 3.92 (t, 2H), 4.55 (m, 1H), 5.94 (br d, 1H, NH), 6.67 (br s 1H), 6.87 (m, 1H, Aryl) 6.94 (m, 2H, Aryl), 7.01 (m, 1H, Aryl), 7.37 (br s, 1H) (LC/MSD M+1): cald. for 517.31 found 517.3.

Nτ-((4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)-L-histidine: Histidine-Cn-AP. To remove the protecting groups, 4 was treated with TFA/CH₂Cl₂ at 25 °C for 2 hrs and the solvent was removed under a reduced pressure. The residue, a crude compound, was dissolved in 1 M NaOH (1 mL). After 12 hrs, the reaction solution was neutralized with 0.1 M HCl solution. The reaction mixture was concentrateed *in vacuo* and this curde 5 was used in the next step (labeling) without any further purification. For an analysis, small portion was purified with a chromatography eluting with BuOH-MeOH-H₂O-25% NH₄OH (1 : 1 : 1 : 0.1) to obtain a yellow sticky oil.

Nτ-(2-(4-(2-Methoxyphenyl)piperazin-1-yl)ethyl)-L-histidine: Histidine-C₂-AP. NMR (CD₃OD), δ (ppm) 2.71(br s, 4H, piperazine), 2.82 (t, 2H), 3.05 (dd, 2H), 3.06 (br s, 4H, piperazine), 3.33 (m, 1H), 3.65 (t, 2H), 3.87 (s, 3H), 6.90 (m, 1H, Aryl), 6.96 (m, 2H, Aryl), 7.01 (m, 1H, Aryl), 7.04 (br s, 1H), 7.65 (br s, 1H) (LC/MSD M+1): cald. for 374.21 found 374.2.

Nτ-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)propyl)-L-histidine: Histidine-C₃-AP. NMR (CD₃OD), δ (ppm) 2.04 (p, 2H), 2.48 (t, 2H), 2.74 (br s, 4H, piperazine), 3.05 (dd, 2H), 3.11 (br s, 4H, piperazine), 3.33 (m, 1H), 3.85 (s, 3H), 4.10 (t, 2H), 6.90 (m, 1H, Aryl), 6.96 (m, 2H, Aryl), 7.01 (m, 1H, Aryl), 7.04 (br s, 1H), 7.65 (br s, 1H) (LC/MSD M+1): cald. for 388.23 found 388.3.

Nτ-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butyl)-L-histidine: Histidine-C₄-AP. NMR (CD₃OD), δ (ppm) 1.58 (p, 2H), 1.85 (p, 2H), 2.72 (t, 2H), 2.79 (br s, 4H, piperazine), 3.05 (dd, 2H), 3.10 (br s, 4H, piperazine), 3.33 (m, 1H), 3.85 (s, 3H), 4.05 (t, 2H), 6.90 (m, 1H, Aryl), 6.96 (m, 2H, Aryl), 7.01 (m, 1H, Aryl), 7.04 (br s, 1H), 7.65 (br s, 1H) (LC/MSD M+1): cald. for 402.24 found 402.2.

Preparation of ⁹⁹ᵐTc(CO)₃ and a labeling. A carbonyl reaction mixture containing Sodiumbronocarbonate (4.5 mg), sodiumteraborate (2.5 mg), sodium titrate (8.5 mg) and sodiumcarbonate (7.15 mg) was added to [⁹⁹ᵐTcO₄]⁻ in saline (2 mL) and heated at 110 °C for 15 min. Prepared [⁹⁹ᵐTc(H₂O)₃(CO)₃]⁺ was adjusted to pH 7.4 with a PBS buffer and it was cooled down to 0 °C. 100 μL of [⁹⁹ᵐTc(H₂O)₃(CO)₃]⁺ was added to Histidine-Cn-AP (10 mg) in PBS buffer (pH = 7.4, 500 μL) followed by an incubation at 75 °C for 30 min. The ⁹⁹ᵐTc complex was analyzed by a HPLC (Xterra C-18 column with solvent gradient system).

Electrophoresis. Filter paper (2 cm × 35 cm) presoaked in a phosphate buffer was placed in an electrophoresis container with 0.1 M phosphate buffer (pH = 7.4). Each sample ([⁹⁹ᵐTcO₄]⁻, [⁹⁹ᵐTc(H₂O)₃(CO)₃]⁺ and ⁹⁹ᵐTc(CO)₃-Histidine-Cn-APs) was spotted and developed at a constant voltage of 300 V for 120 min. After a drying, each paper chromatogram was analyzed with an ITLC scanner.

Preparation of Re(CO)₃-histidine-C4-arylpiperazine. [NEt₄]₂[ReBr₃(CO)₃] was prepared according to the literature method.[12] To adjust the pH 8-9, 2 drops of tetraethylammonium hydroxide (20 wt.% in water) was added to a solution of [NEt₄]₂[ReBr₃(CO)₃] (63 mg, 0.090 mmol) in methanol (5 mL), and histidine-C4-AP (40 mg, 0.078 mmol) was added continuously. The solution was refluxed for 3 hrs. After a cooling down to room temperature, small portion was
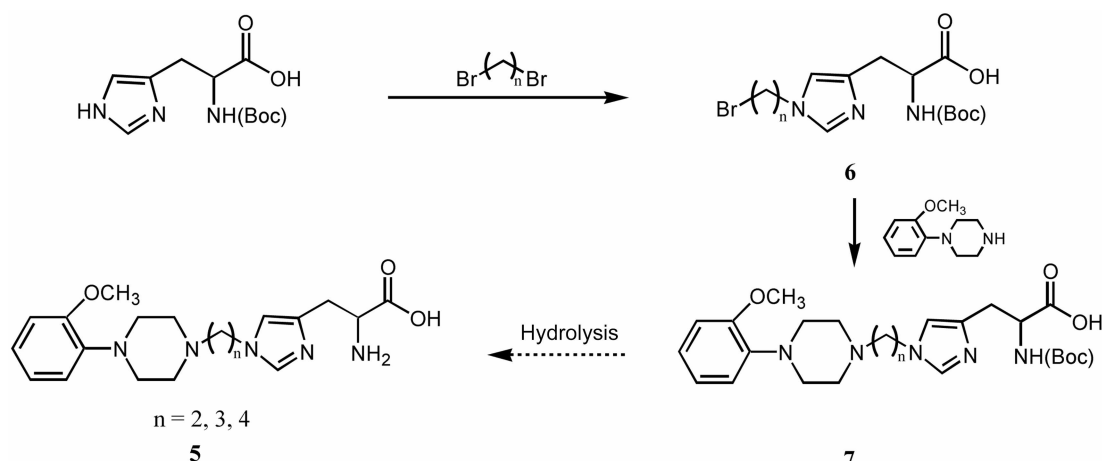
**Scheme 3.** First draft to prepare Histidine-AP derivatives.

diluted to 10-fold with 0.1 M phosphate buffer (pH = 7.4) and identified by a HPLC at 18.15 min.

Results and Discussion

Histidine is the most efficient chelating system, and it is characterized as a tripodal ligand which easily tethers to $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Our goal was to prepare histidine based derivatives with a functionalized alkyl chain linked to the $\tau(N\text{-}1)$ position of a imidazole side chain. These derivatives have the worth of a new chelating agent with a specific binding site to biomolecules, which is named as BFCA (Bi-Functional Chelating Agent). The aimed BFCA, N_α-Boc-N_{τ}-(bromoalkyl)-L-histidine methyleste, was achieved through only a 2 step-procedure with a relatively good yield and Histidine-Cn-AP was one of our application results by using this BFCA.

In order to prepare a pure BFCA, we changed the synthetic schemes like below mentions. Histidine-Cn-APs was first designed and prepared with an application of Navneet Kaur's report (Scheme 3).[7] Starting 1 was directly reacted with dibromoalkane to give a bromo alkylated 6. Coupling 6 with 1-(2-methoxyphenyl) piperazine well proceeded as smoothly as we expected, but it is difficult to separate pure 7 because the R_f value of 6, 7 and arylpiperazine is very similar at any solvent conditions. What was more, the tailing in the chromatography made it difficult to obtain a pure 7. In oder to easily separate the compounds and selectively alkylate $\tau(N\text{-}1)$ position of histidine, the carboxylic group was protected to form methylester (Scheme 1).

To prepare 3 with an easy work-up, we attempted to use bromoalkylation with CH_3CN as solvent but couldn't obtain an identical compound. It was because CH_3CN, in spite of a good polar aprotic solvent, might not have an affinity to NaH. At the use of 2 eq of dibromoalkane, the yield of 3 was relatively good with over 45%. Especially, the yield of 3 increased in proportion to the length of the alkyl chain. Bromoalkylation yield (C2, C3, C4) was 43%, 55% and 73%, respectively. Coupling with histidine derivatives and arylpiperazine was achieved under a condition of K_2CO_3 in
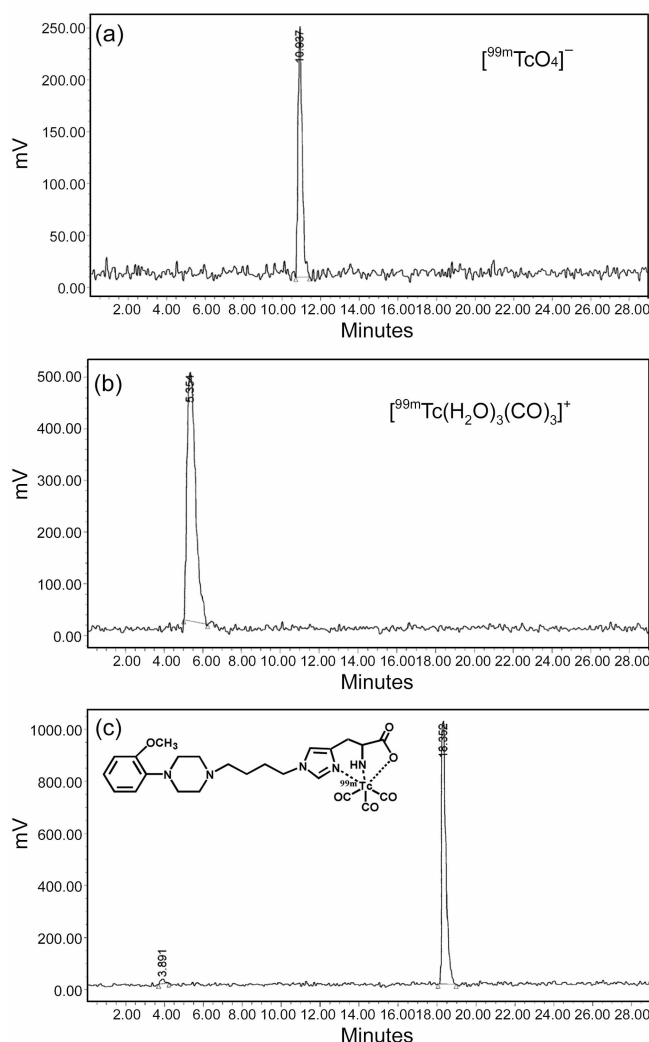
**Figure 2.** Typical analytical chromatograms of $[^{99m}TcO_4]^-$, $[^{99m}Tc(H_2O)_3(CO)_3]$, and $^{99m}Tc(CO)_3$-histidine-C4-AP complex with Xterra C-18 column according to solvent gradient system.

DMF and its yield was quantitative.

The labeling to histidine-Cn-AP was performed with a total of 2 steps including the formation of $[^{99m}Tc(H_2O)_3(CO)_3]^+$.
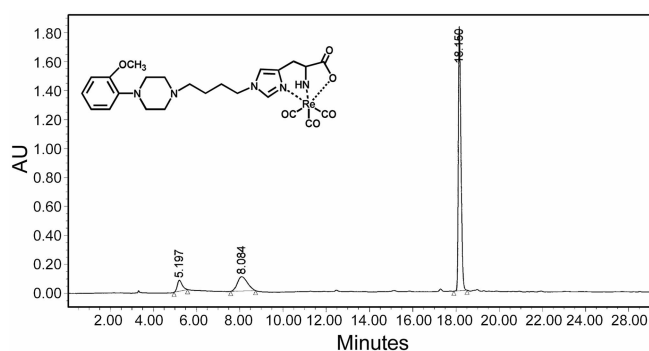
Figure 3. Characteristic chromatogram of Re(CO)₃-histidine-C4-AP for comparative experiment. The peaks of retention time of 8.084 and 18.16 were respectively identified as histidine-C4-AP and Re(CO)₃-histidine-C4-AP.
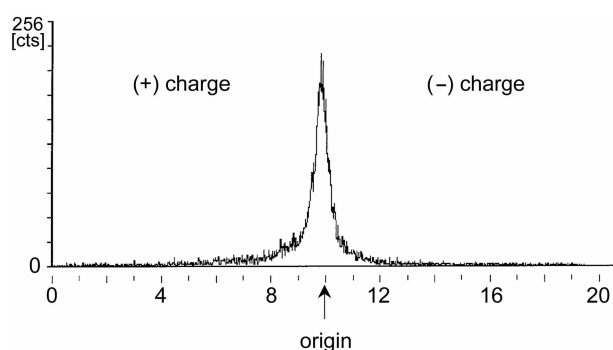
Figure 4. ITLC chromatogram after paper electrophoresis: equipment (ADVANTEC PS-2020 system), electrolyte (0.1 M phosphate buffer, pH = 7.4), potential (300 V), Current (30 mA) and progressing time (120 min).

(Scheme 2) The labeled histidine-Cn-AP was identified with a HPLC gradient system. The HPLC profiles of the [⁹⁹ᵐTcO₄]⁻, [⁹⁹ᵐTc(H₂O)₃(CO)₃]⁺ and ⁹⁹ᵐTc(CO)₃-Histidine-C4-AP complex are shown in Figure 2. The Re-complex as standard compound for a comparative experiment would show a similar result to the ⁹⁹ᵐTc-complex in a HPLC (Fig. 3).

The result of the electrophoresis is given in Figure 4. During the experiment, the temperature rose up to 50 °C. Paper electrophoresis shows that the ⁹⁹ᵐTc-complex is electrically neutral under physiological conditions, and also it is thermodynamically stable during over 2 hrs.

Conclusion

Nₐ-Boc-Nₜ-(bromoalkyl)-L-histidine methylester, histidine based BFCA containing a good leaving group, could be conveniently prepared and it is easily available for introducing a radiochelator to target biomolecules such as a drug,

peptide, antibody, aptamer and so on. In an application of a histidine based BFCA, the Nₜ-((4-(2-methoxyphenyl)-piperazin-1-yl) alkyl)-L-histidine series as a potential radiotracer could be synthesized at a good yield and labeled with [⁹⁹ᵐTc(CO)₃]⁺. The complexes showed high radiochemical yields, a neutral charge and a thermal stability. These results show that the Nₜ-((4-(2-methoxyphenyl)piperazin-1-yl) alkyl)-L-histidine series are promising radiotracers for evaluating the CNS.

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