Novel Tc(CO)\textsubscript{3} Complexes with WAY-100635 Moiety in the Development of 5-HT\textsubscript{1A} Receptor Imaging Agent,

Kang-Hyuk Choi, Young-Don Hong, Mi-Sun Pyun, Sun-Ju Choi*
Radioisotope R&D LAB, HANARO Application Research, Korea Atomic Energy Research Institute, Daejeon 305-353, Korea.
*E-mail: choisj@kaeri.re.kr

1. Introduction

The significant studies [1] have been made in the past two decades for developing new $^{99m}$Tc-based brain imaging agent, since two brain perfusion agents(ECD(L,L - Ethylecystinate Dimer) and HMPAO (Hexamethyl Propyleneamine Ocime)) were developed. Recently, many efforts are focusing on the development of radiopharmaceuticals specific for brain receptor or brain binding-site, which may lead to improved clinical tools for nuclear medicine. Furthermore, Since 5-HT\textsubscript{1A} receptors are implicated in several neuropsychiatric disorders, their visualization in the human brain has been studied with PET and SPECT. Several approaches for PET imaging agents [2]. However, the short half life of carbon-11 limits these radiopharmaceuticals from being utilized in a local imaging procedure despite their high specific activity for in vivo application. Thus, we have focused on 5-HT\textsubscript{1A} and its antagonist by application of the technetium tricarbonyl technology. we suggest herein a synthesizing method for arylpiperazine derivatives and discussed here the physical properties of their $^{99m}$Tc(CO)\textsubscript{3}\textsuperscript{+} complexes.

2. Methods and Results

All chemicals were purchased from Aldrich and used without any further purification. All the progresses of the reaction were identified with TLC and NMR. Sodium pertechnetate ([$^{99m}$Tc] NaTcO\textsubscript{4}) was obtained from a $^{99m}$Mo-$^{99}$Tc generator. The labeling yield and radiochemical purity were determined by Radio-HPLC as we have previously reported with minor modification on the first flow rate maintained at 1ml/min [3].

2-1 Preparation of histidine based BFCA

For selective alkylation of (N-1) position of histidine, carboxylic group was activated with DCC and protected to form a methylster(2). cpd 2 upon a reaction with dibromoalkane and NaH in DMF at -15 °C, led to form cpd 3 serie [3].

2-2 Histidine based Arylpiperazines

Cpd 3 was reacted with 1-(2-methoxyphenyl)piperazine to give product 4 series. Deprotection of cpd 4 series (C2, C3, C4) was achieved by consecutive reaction with trifluoroacetic acid and 1M NaOH, respectively.

2-3 Cysteine based Arylpiperazines

Arylpiperazine was reacted with 1-bromo-chloroalkane under base condition(K$_2$CO\textsubscript{3}) to give cpd 5. Selective S-alkylation was achieved through activation of cysteine with 2 eq of 0.5 N sodium methoxide solution under a nitrogen bubbling and a reaction with cpd 5 at -10 °C.

2-4 Cysteine based WAY 100635 derivatives

WAY-100635 derivatives were prepared such as below scheme. 2-amino-pyridine was reacted with chloroaetyl chloride to give cpd 7 and cpd 8 was obtained with reaction cpd 7 and arylpiperazines(R=OH, OMe, Cl). Consecutive hydrolysis gave a cpd 9 series with good yield and cpd 10 series were obtained using on-line two reaction.

2-5 Preparation of N.C.A. $^{99m}$Tc(CO)\textsubscript{3} and labeling

A carbonyl reaction kit containing Sodiumbronnocarbonate, sodiunteraborate, sodium titrate and sodiumcarbonate was added to $^{99m}$TcO\textsubscript{4} in saline and heated at 110 °C for 15 min. Prepared
was adjusted to pH 7.4 with PBS buffer. Radiolabeling of derivatives with \(^{99m}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3\) was performed in PBS buffer (pH = 7.4) at 75 °C for 30 min.

2-6 Physical properties

For ideally crossing the blood-brain barrier[4], pharmaceuticals should be less than 650 dalton in the molecular mass, neutral in electrical charge, 0.5~2.5 value in log P. As a result of several experiments, all of the complexes in this presentation meet the majority of these criteria, but cysteine complex (6) showed slightly less lipophilicity comparing to the ideal Log P.

3. Conclusion

1. Histidine is the most efficient chelating system, and it is characterized as a tripodal ligand which easily tethers to \(^{99m}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3\). Our goal was to prepare histidine based BFCA with a functionalized alkyl chain linked to the (N-1) position of a imidazole side chain. The aimed BFCA, \(N_{\alpha}-\text{Boc}-N_{\gamma\gamma\gamma}-\text{(bromoalkyl)}\)-histidine methylste, was achieved through only a 2-step-procedure.

2. A cysteine based chelator has been successfully prepared by direct S-alkylation, which can be conveniently applied to the preparation of other cysteine based complexes. In order to prepare cysteine based WAY 100635 derivatives, we use on-line two reaction with good yield.

3. These results of physical properties demonstrate that the complexes used in this study, which contained different chelators have the stability in an in vitro condition and sufficiently meet most of the criteria required to pass through BBB, suggesting the possibility of these complexes to be used as neuroreceptor imaging agents.

4. References