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Novel $Tc(CO)_3$ Complexes with WAY-100635 Moiety in the Development of 5-HT_{1A} Receptor Imaging Agent.

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1. Introduction

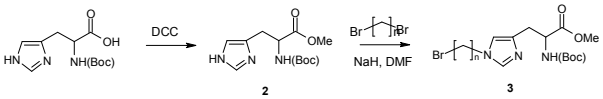
The significant studies [1] have been made in the past two decades for developing new ^{99m}Tc-based brain imaging agent, since two brain perfusion agents(ECD(L,L - Ethylcysteinate Dimer) and HMPAO (Hexamethyl Propyleneamine Ocime)) were developed. Recently, many efforts are focusing on the development of radiopharmaceuticals specific for brain receptor or brain binding-site, which may lead to improved clinical tools for nuclear medicine. Futhermore, Since 5-HT_{1A} receptors are implicated in several neuropsychiatric disorders, their visualization in the human brain has been studied with PET and SPECT. Several approaches with 5-HT_{1A} antagonist ([^{11}C] WAY-100635) have been pursued for PET imaging agents [2]. However, the short half life of carbon-11 limits these radio pharmaceuticals from being utilized in a local imaging procedure despite their high specific activity for *in vivo* application. Thus, we have focused on 5-HT_{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 $^{99m}Tc(CO)_3^+$ 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] $NaTcO_4$) was obtained from a ^{99}Mo-^{99m}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].

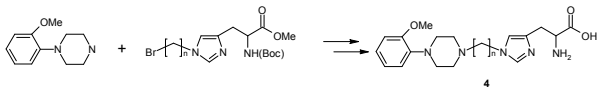
2-1 Preparation of histidine based BFCA

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



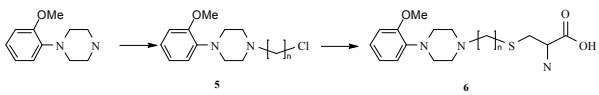
2-2 Histidine based Arylpiperazines

Cpd **3** was reacted with 1-(2-mehoxyphenyl)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.



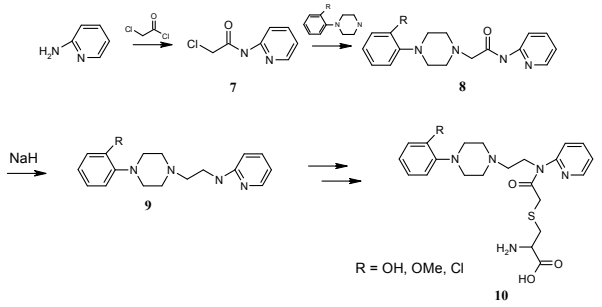
2-3 Cysteine based Arylpiperazines

Arylpiperazine was reacted with 1-bromo-chloroalkane under base condition(K_2CO_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℃.



2-4 Cysteine based WAY 100635 derivatives

WAY-100635 derivatives were prepared such as below scheme. 2-amino-pyridine was reacted with chloroacetyl 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. $^{99m}Tc(CO)_3$ and labeling

A carbonyl reaction kit containing Sodiumbronocarbonate, sodiumteraborate, sodium titrate and sodiumcarbonate was added to $^{99m}TcO_4^-$ in saline and heated at 110 ℃ for 15 min. Prepared

$[^{99m}Tc(H_2O)_3(CO)_3]^+$ was adjusted to pH 7.4 with PBS buffer. Radiolabeling of derivatives with $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was performed in PBS buffer(pH= 7.4) at 75 ℃ 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 $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Our goal was to prepare histidine based BFCA with a functionalized alkyl chain linked to the τ(*N*-1) position of a imidazole side chain. The aimed BFCA, N_α-Boc-$N_{\tau 1}$-(bromoalkyl)-L-histidine methyleste, 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

[1] Ulderico Mazzi et al. Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine(SGEDITORIALI RADOVA), pp. 355~370, **2006**

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