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Synthesis of a new chelating agent derived from phenylenediamine for application in radioimmunotherapy

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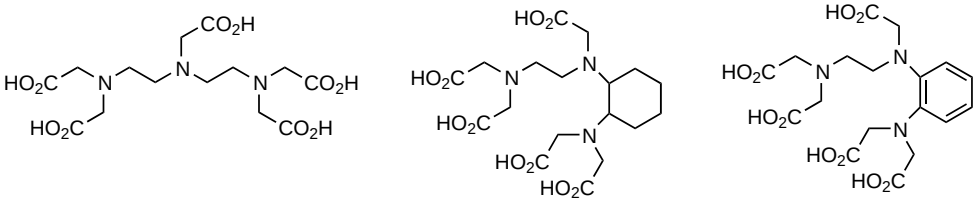
Abstract—We report the synthesis of a new diethylenetriaminepentaacetic acid (DTPA) analogue, Ph-DTPA, possessing an aromatic rigid skeleton. This precursor of a bifunctional chelating agent was synthesized by elaboration of the intermediate *N*-(*o*-aminophenyl)ethylenediamine and obtained in five steps with an overall yield of 42%. Preliminary complexation studies between Ph-DTPA and ^{153}Sm has been carried out.

For many years, complexes combining metals with DTPA and its derivatives have been widely used in magnetic resonance imaging (MRI),[1–5] radiotherapy[6–8] and radiodiagnosis.[9] In particular, the gadolinium–(DTPA) complex is currently used in clinical applications as a contrast agent in MRI.[10,11] Moreover, many complexes combining lanthanides with DTPA analogues have proved stable enough for use in a physiological medium as radiopharmaceuticals.[12,13] Since the introduction of this family of chelating agents, developments have been directed essentially at increasing the stability of the resulting complexes.[14,15] The most promising results have been based on studies to improve the rigidity of the chelating structure. The introduction of a semi-rigid preformed skeleton, which minimizes the freedom of donor atoms, has had a significant effect on the stability of the metal complexes formed.[16] Notably, the teams of R. D. Hancock and then M. W. Brechbiel have shown that DTPA analogues with a semi-rigid structure of cyclohexyl (Cy-DTPA),[17,18] piperidinyl (PIP-DTPA) or azaparyl (AZEP-DTPA)[19] type prove considerably more stable in vivo. On this basis, our recent research has been directed at developing stereoisomer chelating agents based on ethylenediaminetetraacetic acid analogues with a cyclopentanic skeleton.[20] The synthesis of the DTPA analogue phenyleneethylenetriamine pentaacetic acid (Ph-DTPA) reported here provides a chelating agent even more rigid than Cy-DTPA and with an aromatic skeleton (Scheme 1).



Scheme 1.

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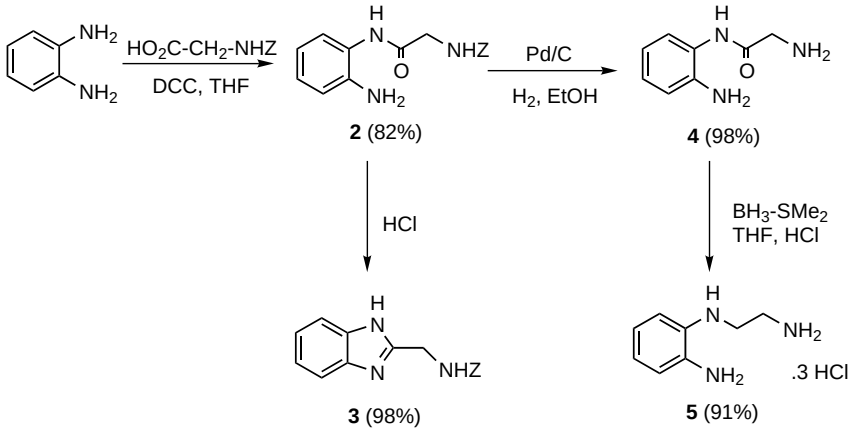
A bifunctional chelating agent is required for the elaboration of bioconjugates suitable for cancer radioimmunotherapy. The functional group commonly used is the *p*-isothiocyanatobenzyl chain, which is generally derived from nitrobenzene that must be introduced during the synthesis of the complexing molecule.[21,22] The octadentate chelating agent Ph-DTPA has a rigid structure, but is also easy to functionalize directly on the aromatic cycle by means of an isothyiocyanate group.

The synthesis of Ph-DTPA **1** was performed in five steps from the starting product, 1,2-phenylenediamine (Scheme 2). The first step, described previously, which consists in peptidic coupling of carbobenzyloxyglycine and the aromatic amine in the presence of dicyclohexylcarbodiimide, yields compound **2**.[23] The synthesis of compound **4** implies the elimination of the Z group. The usual deprotection method for benzyloxycarbonyl (HBr in acetic acid)[24] could not be used. In fact, substituted aniline **2** proved unstable in acid medium, yielding quantitatively benzimidazole **3**, a product belonging to a pesticide class.[25] The most efficient method for achieving **4**, which provided the best yields (98%) without purification, involved the use of palladium on charcoal as a catalyst under a hydrogen atmosphere. This method proved more suitable than that described by M. R. Bermejo, which uses cyclohexene as hydrogen source, providing yields of no more than 80%.[26,27]

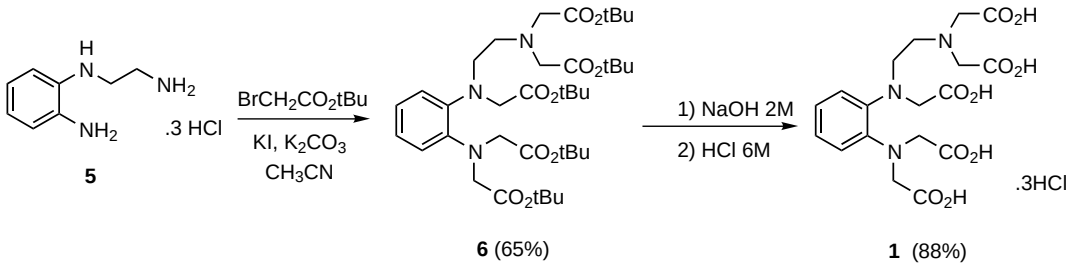
The key intermediate, *N*-(*o*-aminophenyl)ethylenediamine **5**, was obtained with an excellent yield by using the BH_3–Me_2S complex as a reducing agent, followed by treatment with HCl gas.[28,29] The preparation of triamine **5** was previously reported according to a totally different synthesis strategy, which provided an overall yield of no more than 29%.[30] According to the classical alkylation method, penta-*tert*-butyl ester **6** was obtained through the action of excess *tert*-butylbromoacetate in the presence of KI and K_2CO_3 in acetonitrile.[31] Finally, hydrolysis of the ester functions was performed in basic medium, providing Ph-DTPA **1** with a yield of 88% (Scheme 3).

Preliminary complexation studies between Ph-DTPA and ^{153}Sm has been carried out. It shows that the kinetic of complexation of ^{153}Sm to **1** is adapted to radioimmunotherapy.[32] This was evident from the fact that, on incubating for 45 min at 37°C a radioactive solution containing a 1/1 molar ratio of ^{153} Sm/Ph-DTPA, 56% of ^{153}Sm chelating agent complex is formed.[33]

In conclusion, a rigid DTPA analogue was synthesized with a overall yield of 42% after five steps. Studies of the complexing efficiency of this new chelating agent with radioactive metals suitable for radioimmunotherapy (^{90}Y and ^{153}Sm) are in progress.



Scheme 2.



Scheme 3.

Acknowledgements

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33. **Complexation studies with ^{153}Sm**. Stock solution of Ph-DTPA (0.11 mg·mL^{-1}) was prepared in 0.1 M sodium acetate buffer (pH 5.6). To form ^{153}Sm chelating agent complex, 5 μL (3.70 nmol) of ^{153}Sm stock solution (140.5 mCi·mL^{-1}) was added to 1 equiv. of Ph-DTPA. The solution was made up to 500 μL (final pH of the solution was 5.6, with a final ^{153}Sm concentration of 7.5 nmol·mL^{-1}) and incubated at 37°C for 45 min. The complexation was measured on a phosphoimager 445SI after thin-layer chromatography on cellulose plates (Merck 5552/0025) by elution with 0.1 M sodium acetate (pH 5.6)/methanol (2/1).