AN IMPROVED SYNTHETIC PROCEDURE FOR L-3-IODO- α-METHYL TYROSINE SUITABLE FOR PREPARATION IN KIT FORM

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Summary We describe a modified method for the synthesis of radiolabelled L–3–iodo–α–methyl tyrosine (IMT) based on electrophilic iodination using KI and KIO_3. Purification of the product using reverse phase HPLC gives reproducible radiochemical yields of 85% and chemical purity >99%. The method has been further modified and simplified for the preparation of IMT in kit form.

Keywords: Iodomethyltyrosine, tumour imaging agents, amino acid analogues

INTRODUCTION

There is growing interest in the use of radiolabelled amino acids combined with Positron Emission tomography (PET) for the study of protein synthesis and for tumour imaging. Compounds including ^{11}C–methionine and ^{11}C or ^{18}F labelled tyrosine have been used to delineate tumour extent in a range of cancers (1–5), and may be useful as a rapid and sensitive indicator of response to therapy (6).

Structural analogues radiolabelled with ^{124}I or ^{123}I are being developed for use in PET centres remote from a cyclotron and in conventional Nuclear Medicine departments respectively. The most promising of these analogues appears to be L–3–iodo–α–methyl tyrosine (IMT), a compound originally developed for pancreatic imaging (7). Enhanced uptake of IMT into brain tumours has been demonstrated (8,9,10), and it has been shown that IMT is a probable substrate for the large neutral amino acid (LNAA) membrane transport system (10). IMT is not incorporated into protein however (9), and the principal determinants of IMT uptake into tu-

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mour and normal tissues is largely unknown.

The synthesis of IMT is achieved by electrophilic iodination using chloramine-T or KIO_3 as oxidizing agent. Typical radiochemical yields in the range 50–66% have been reported (11). Both IMT and di-iodomethyl tyrosine (DIMT) are formed during the procedure (12), however their proportional yield and factors influencing their formation have not been reported to date.

The demand for in-house preparation of ^{123}I and ^{124}I labelled IMT for SPECT and PET studies led us to optimise the parameters for IMT synthesis and to consider the possibility of kit formulation. For practical reasons these studies were undertaken using ^{125}I, having a longer half-life of 60 days. Since very small quantities of $Na^{125}I$ ($\approx 10\mu Ci$) were used, KI was added as carrier.

MATERIALS AND METHODS

Methyl tyrosine (MT) was obtained from Sigma (UK), and AR grade KI, KIO_3 and HCl were obtained from BDH Ltd (UK). All reagents were used without further treatment. No carrier added $Na^{125}I$ (100 mCi/ml) was obtained from Amersham International Ltd (UK). Plastic reaction vials containing 1mg predried KIO_3 were prepared and stored at 4°C until required for use. Preliminary labelling studies indicated that MT and KI should be freshly prepared in 0.1M HCl as needed.

A mixture of 100μl 0.1M MT, 10μl 0.1M KI and 20μl $Na^{125}I$ was added to a plastic reaction vial containing the KIO_3. The contents were thoroughly mixed and the reaction vial was placed in a thermostatically heated water bath maintained at 50°C for 5 mins. The radioiodinated products were identified and separated by reverse phase HPLC using a C18 column (HPLC Ltd UK) and on-line uv($\lambda = 254$nm) and radioisotope detectors. Water:ethanol:acetate buffer pH4 (80:10:10) was used as eluent.

RESULTS AND DISCUSSION

Radioabelling could not be achieved using MT concentrations lower than 1mM. Higher concentration of MT resulted in increasing IMT yield accompanied by a decrease in the amount of DIMT produced, the latter remaining nearly constant above a MT concentration of approximately 5mM (Figure 1a). The yields of IMT and DIMT were also found to be influenced by the KI and HCl concentration as shown in Figures 1b and 1c. It is interesting to note that the peak IMT yield was achieved at a KI/KIO_3 ratio of 2 (Figure 1d), substantially lower than the value of 5 expected from stoichiometry considerations.

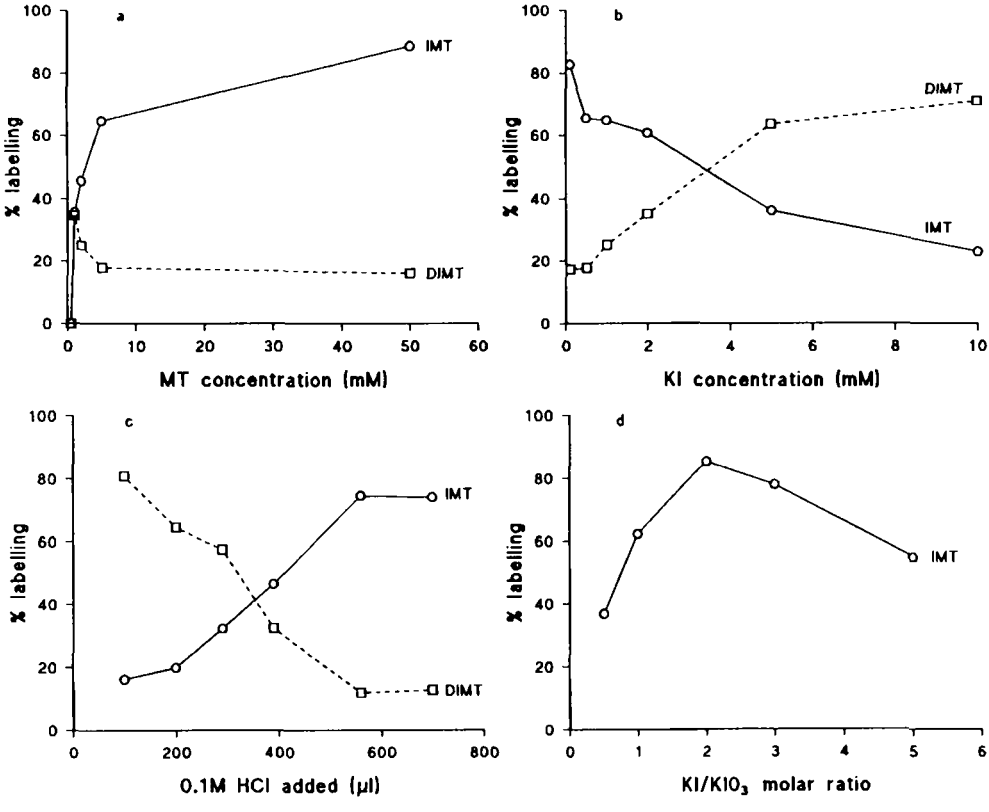

Figure 1 Influence of labelling conditions on IMT yield.

This modified method produces consistently high (85%) radiochemical yields of IMT, a chemical purity >99%, and takes less time than previously reported procedures.

For the kit preparation of IMT, NaI and $NaIO_3$ are substituted for KI and KIO_3. The initial labelling part of the procedure outlined above is followed and the resulting solution is passed through an anion–exchange resin (IC–OH, Alltech Ltd., UK) to remove chloride and unlabelled radioiodide ions. This eliminates the need for HPLC separation of the products and avoids possible contamination of the IMT with potassium ions. The solution is finally passed through a sterile 0.2μm filter ready for use. Employing the optimum labelling conditions described above, similar radiochemical yields of IMT are achievable using this alternative procedure.

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