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Short Research Article

Synthesis of isotopically labelled AZD3409 and its metabolites†

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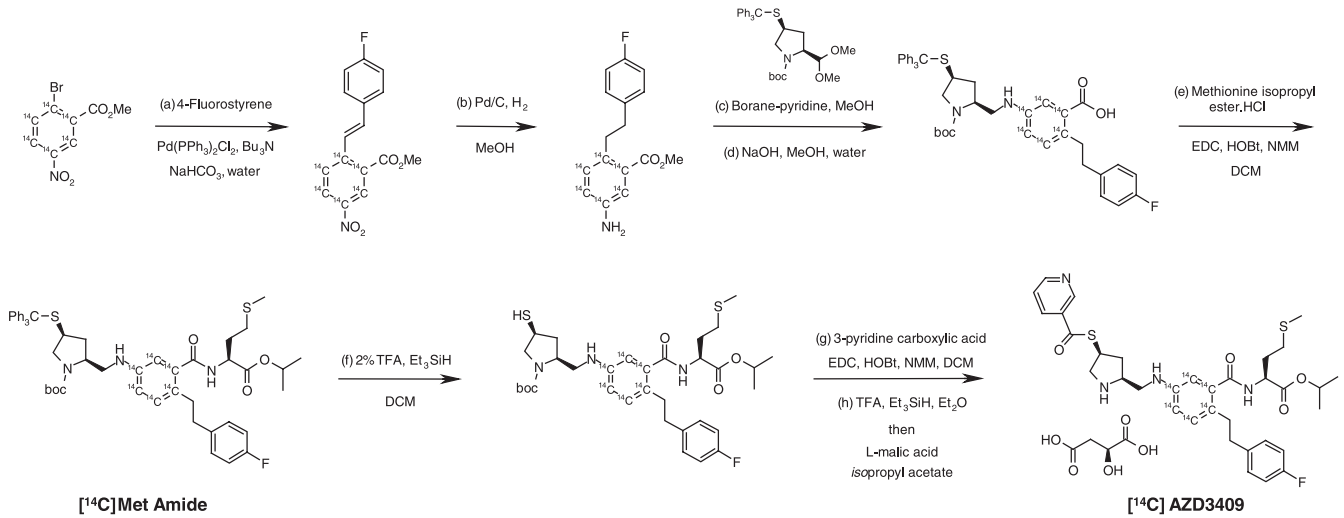
Introduction

AZD3409 is a peptidomimetic farnesyltransferase inhibitor (FTI), intended for the treatment of pancreatic, colon and lung cancers. AZD3409 is a double pro-drug; the parent form being rapidly broken down to thiol-ester (AZ11761313) and thiol-acid (AZ11761441) metabolites. This paper describes the synthesis of labelled forms of AZD3409, AZ11761313 and AZ11761441 that were required to support the development DMPK programme.

Results and discussion

[^{14}C]AZD3409 was prepared as the malate salt from methyl-2-bromo-5-nitro[U-^{14}C]benzoate as shown in Scheme 1. The labelled starting material was coupled to 4-fluorostyrene *via* a Heck reaction. Concomitant reduction of the nitro group and the alkene gave the aniline, which was coupled to the proline acetal *via* reductive amination. Subsequent ester hydrolysis gave the acid, which was coupled with methionine *iso*propyl ester to give the key Met Amide intermediate.



Scheme 1

Selective deprotection of the trityl group gave the thiol, which was coupled with pyridine-3-carboxylic acid to give the thioester. Finally, the *tert*-butoxycarbonyl (BOC) protecting group was removed, and the product was converted to the malate salt to afford [^{14}C]AZD3409, which had a radiochemical purity >98%

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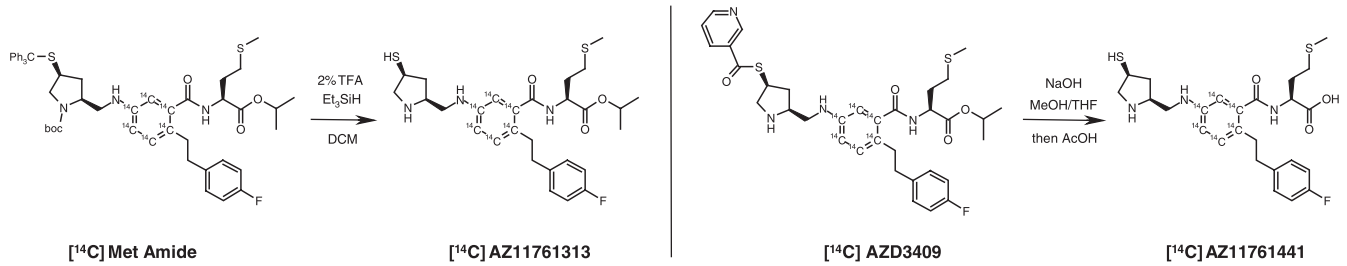
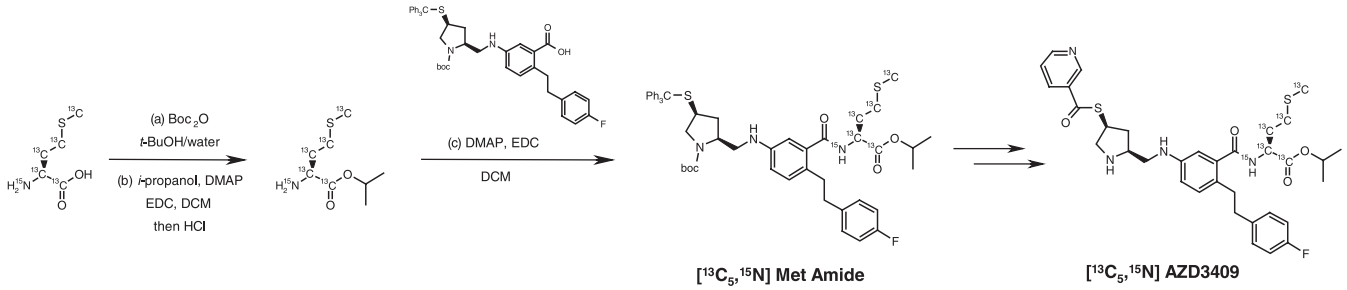


Scheme 2



Scheme 3

and a specific activity of 28 mCi/mmol. The overall radiochemical yield was 9.7%.

The Met Amide intermediate also served as the starting point for the preparation of [^{14}C]AZ11761313, formed by removal of the BOC and trityl protecting groups with dilute acid (Scheme 2). Similarly, [^{14}C]AZ11761441 was prepared from [^{14}C]AZD3409 *via* concomitant hydrolysis of both ester and thioester groups.

Stable labelled AZD3409 was prepared in six stages from [$^{13}C_5$,^{15}N]Methionine to provide internal standards for use in mass spectrometry assays (Scheme 3). [$^{13}C_5$,^{15}N]Methionine was converted to its *iso*propyl ester and coupled to the substituted benzoic acid to afford the key [$^{13}C_5$,^{15}N]Met Amide intermediate. This was converted to [$^{13}C_5$,^{15}N]AZD3409 following the synthetic sequence detailed above.

Stable labelled AZ11761313 and AZ11761441 were prepared from [$^{13}C_5$,^{15}N]Met Amide in a similar fashion to that described above.

Conclusion

The chemical route to AZD3409 has been successfully adapted to provide access to both radiolabelled and stable labelled forms of AZD3409, AZ11761313 and AZ11761441, which were required to support the development Drug Metabolism and Pharmokinetics (DMPK) programme.

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