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Short Research Article

Synthesis of isotopically labelled ZD4054†

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Introduction

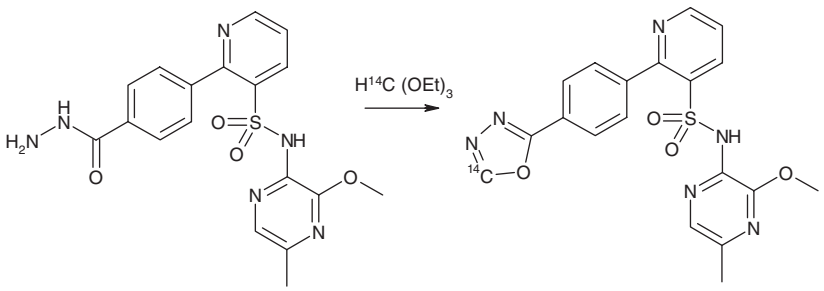
AstraZeneca ZD4054 (3-methoxy-5-methyl-2-({2-[4-(1,3,4-oxadiazol-2-yl)-phenyl]-pyridyl}-sulphonamido)-pyrazine) is a specific endothelin A (ETA) receptor antagonist which is being developed for the treatment of prostate cancer. This paper describes the synthesis of the isotopically labelled forms of ZD4054 that were required to support the development DMPK programme.

[oxadiazol-5-^{14}C]ZD4054 1a

Early exploratory drug metabolism and distribution studies were carried out using [oxadiazol-5-^{14}C] ZD4054 **1a**. This was synthesized in one stage at low specific activity by cyclization of hydrazide **2** using neat triethyl [^{14}C]orthoformate (Scheme 1). The product was obtained in 10% radiochemical yield (based on triethyl [^{14}C]orthoformate) at a specific activity of 15.1 mCi/mmol with a radiochemical purity >98%.

[pyridyl-2,6-^{14}C]ZD4054 1b

Detailed drug metabolism and distribution studies were carried our using [pyridyl-2,6-^{14}C]ZD4054 **1b**. This was synthesized in three stages from 3-amino-2-chloro[2,6-^{14}C]pyridine (Scheme 2). 3-Amino-2-chloro-[2,6-^{14}C]pyridine was converted to 2-chloro[2,6-^{14}C]-pyridine-3-sulphonyl chloride and this was then



2 **1a**

Scheme 1

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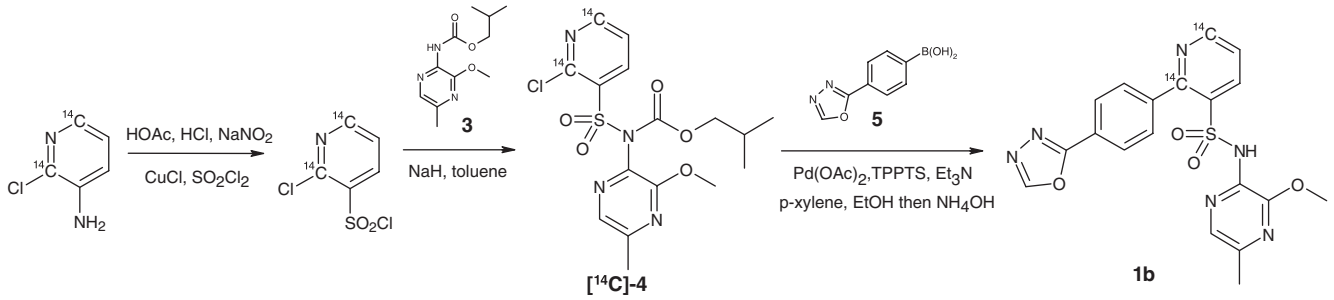
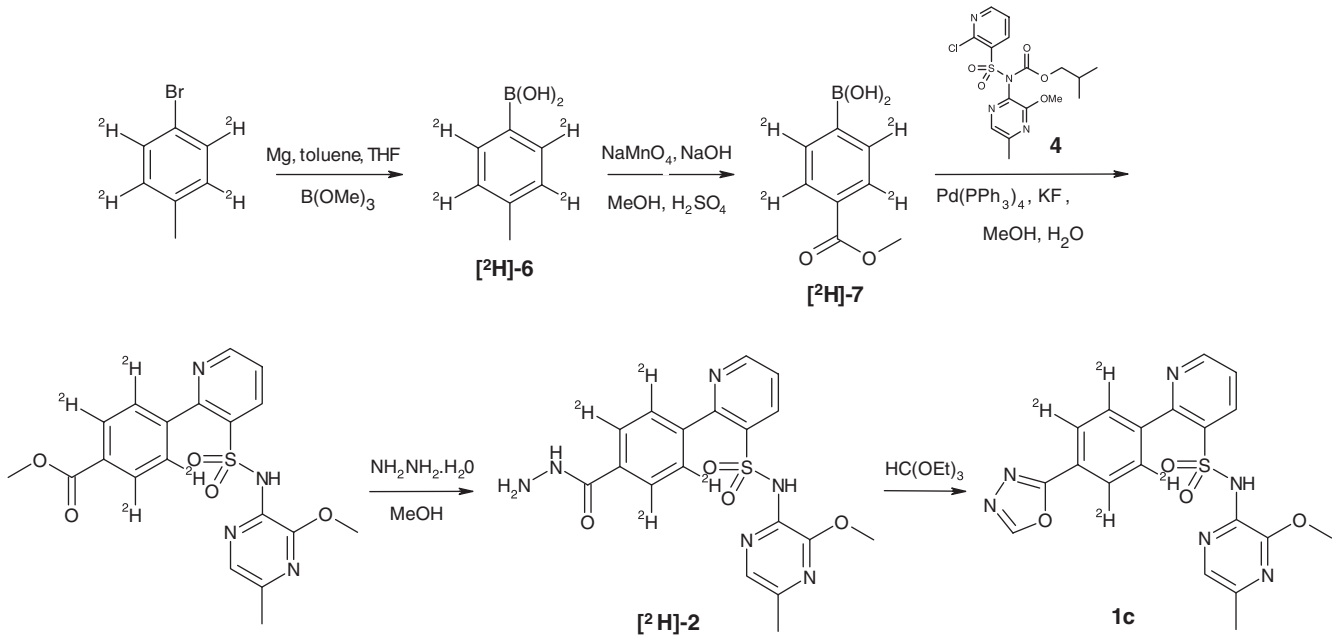


Scheme 2



Scheme 3

reacted with urethane **3** to give the sulphonamide [^{14}C]-**4**. Pd(0) catalysed Suzuki coupling with boronic acid **5** followed by *in situ* hydrolysis of the protected product gave [pyridyl-2,6-^{14}C]ZD4054 **1b**. The product was obtained in 37% overall radiochemical yield at a specific activity of 50.8 mCi/mmol with a radiochemical purity >98%.

[phenyl-2,3,5,6-$^{2}H_4$]ZD4054 1c

[phenyl-2,3,5,6-$^{2}H_4$]ZD4054 **1c** was prepared as an internal standard for use in an LC-MS-MS assay for the quantification of the drug in biological matrices. **1c** was synthesized in six stages from 4-bromo-2,3,5,6-[$^{2}H_4$] toluene (Scheme 3). 4-Bromo-2,3,5,6-[$^{2}H_4$]toluene was converted via a Grignard reaction to the corresponding boronic acid [^{2}H]-**6**. Oxidation of the methyl group and esterfication of the resulting carboxylic acid gave the boronic acid [^{2}H]-**7**. Pd(0) coupling with sulphonamide **4** followed by treatment with hydrazine monohydrate gave hydrazide [^{2}H]-**2**. Cyclization with triethyl orthoformate gave [phenyl-2,3,5,6-$^{2}H_4$]ZD4054 **1c**. The product was obtained in 11% overall yield at an incorporation of >98 at %.

Conclusions

The chemical routes developed to synthesize ZD4054 have been successfully adapted to introduce separate labels into the three directly linked 1,3,4-oxadiazolyl, pyridyl and phenyl rings for different DMPK applications.

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