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Short Research Article

New approaches to the synthesis of tritium labelled glitazones†

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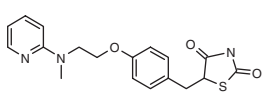
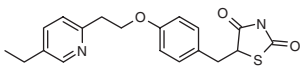
Introduction

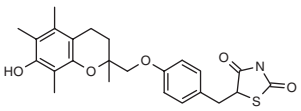
The glitazones are a series of thiazolidinone insulin sensitizers, used for the treatment of Type 2 diabetes. A small representative series of glitazones were selected for radiolabelling to be used in a variety of DMPK and bioscience applications. Tritium was chosen as the isotope of choice for ease and speed of labelling. Our aim was to develop a common labelling approach for all three compounds.



Rosiglitazone (GSK)



Pioglitazone (Takeda)



Troglitazone (Sankyo)

The syntheses of tritium labelled rosiglitazone and pioglitazone have already been described. Thus, [pyridyl-3′,5′-^{3}H]rosiglitazone[1] has been synthesized by tritium–bromine exchange of a dibromo precursor with a specific activity of 58 Ci/mmol and [phenyl-3,5-^{3}H]pioglitazone[2] by tritium–bromine exchange of a dibromo precursor with a specific activity of 31.7 Ci/mmol.

Results and discussion

Tritium–iodine exchange

Mono-iodo derivatives of rosi- and pioglitazone were synthesized using NIS/TFA. Subsequent tritium–iodine exchange using $^3H_2$ gas gave ^{3}H rosiglitazone **1a** with a specific activity of 19.6 Ci/mmol and RCP>97% (RCP = radiochemical purity) and ^{3}H pioglitazone **2** with a specific activity of 26 Ci/mmol and RCP >98% (Figure 1). Unfortunately, attempts to iodinate troglitazone using NIS/TFA or Ag_2SO_4/I_2/EtOH or mercury trifluoroacetate/heptafluorobutyric acid; I_2/DCM all failed. A number of alternative approaches were also unsuccessful including synthesis of a suitable brominated precursor and direct tritium–hydrogen exchange using Crabtree's catalyst.

Tritium reduction of an unsaturated precursor

An unsaturated precursor **3** was synthesized in 3 steps from 2-chloropyridine. This was reduced with $^3H_2$ gas to give ^{3}H rosiglitazone **1b** with a specific activity of 12.7 Ci/mmol and RCP >98%. A similar procedure using a MOM protected unsaturated precursor **4**[3] was used to prepare ^{3}H troglitazone **5** with a specific activity of 15 Ci/mmol after deprotection (Scheme 1). Unfortunately,

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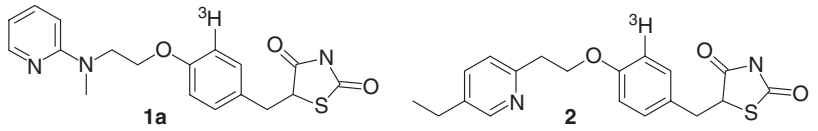
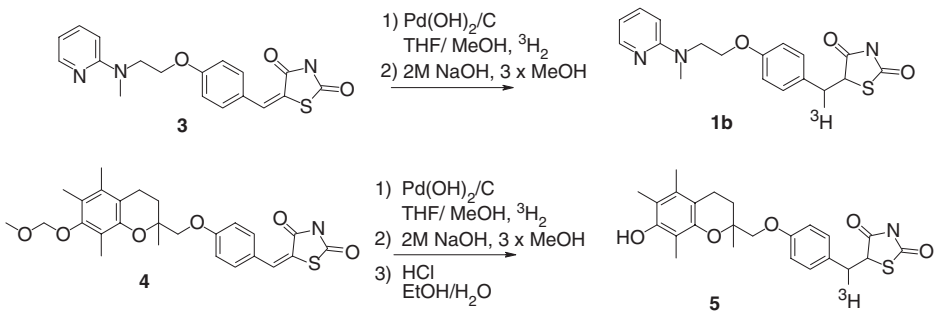


Figure 1 ^{3}H rosiglitazone 1a and ^{3}H pioglitazone 2.



Scheme 1 Synthesis of ^{3}H rosiglitazone 1b and ^{3}H troglitazone 5 using unsaturated precursors.

the product undergoes rapid autoradiolysis with the RCP of freshly purified material dropping from 98 to 92% during processing. The RCP purity of product diluted to 150 mCi/mmol and stored in ethanol at −80°C still dropped 99 to 96% within a week.

Conclusions

[phenyl-^{3}H]rosiglitazone and pioglitazone were synthesized by tritium–iodine exchange of the corresponding mono-iodo derivatives. [benzyl-^{3}H]rosiglitazone was synthesized by tritium reduction of an unsaturated precursor. [benzyl-^{3}H]troglitazone, synthesized by tritium reduction of a MOM-protected unsaturated precursor, undergoes rapid autoradiolysis even at low specific activity.

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