SYNTHESIS OF A CARBON-14 LABELLED VERSION OF BENZOFURAN GR151004B

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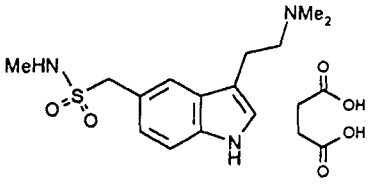
Summary

The $5HT_1$ receptor agonist GR151004B (2b), labelled with carbon-14 at C-3 of the benzofuran ring, was prepared in 19% overall yield in five steps from 5-bromo-2-methoxybenzoic [^{14}C]acid (3b).

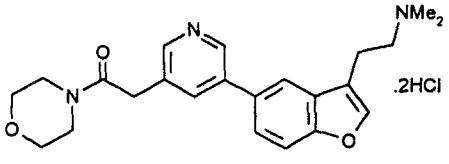
Key words: carbon-14, benzofuran.

Introduction

Sumatriptan (1) is one of a series of indoles that are selective vascular $5HT_1$ receptor agonists and efficacious in the treatment of migraine (1).



(1) GR43175C (Sumatriptan)



(2a) GR151004B

During searches for alternative classes of biologically active compounds, the non-indolic compound GR151004B (2a) was selected for further development (2), and therefore a carbon-14 labelled version was required for metabolism and excretion balance studies. The benzofuran ring of GR151004B (2a) was identified as the optimal position for the radiolabel, based on metabolic and synthetic considerations.

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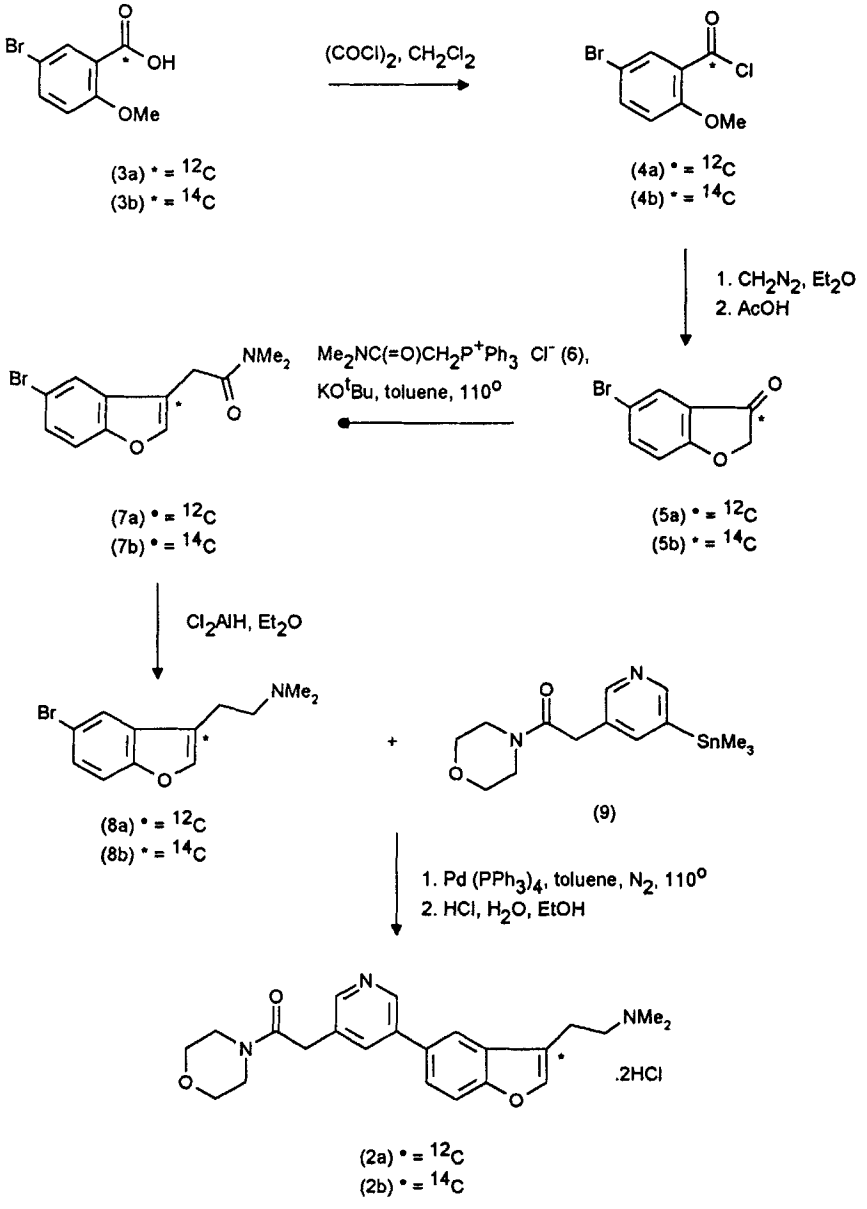
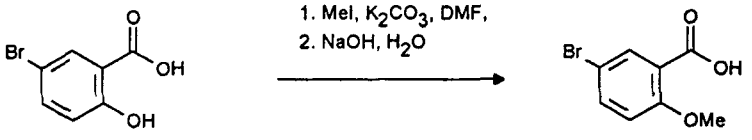
Scheme 1: Synthesis of GR151004



Results And Discussion

Utilisation of 5-bromo-2-methoxybenzoic [^{14}C]acid (3b), in a methodology first exemplified by Jung (3), would afford a label in the benzofuran ring at C-3, a metabolically stable position (Scheme 2). Unlabelled acid (3a) was available

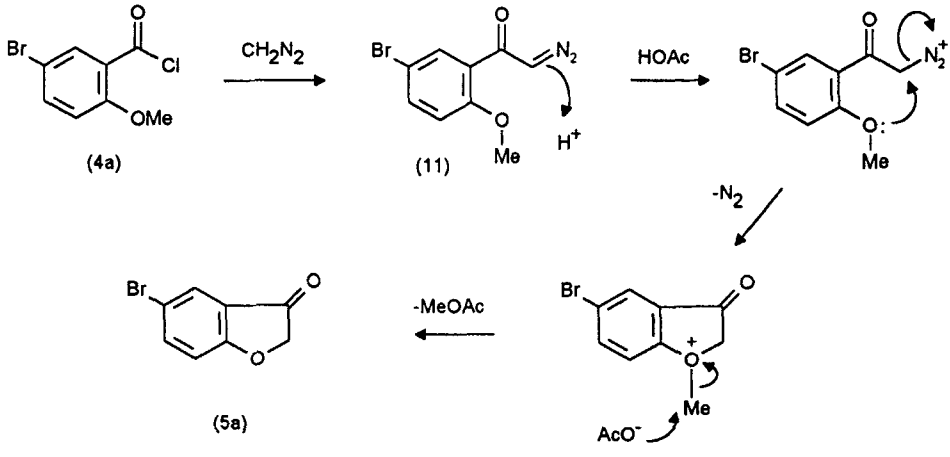
in high yield from 5-bromosalicylic acid (10), by reaction with methyl iodide and potassium carbonate in dimethylformamide (DMF), and subsequent saponification of the intermediate ester.



(10) (3a)

Treatment of the acid (3a) with oxalyl chloride, and reaction of the resulting acid chloride (4a) with a solution of diazomethane in ether, followed by acetic acid to promote cyclisation of the resulting diazoketone (11), gave the furanone (5a) in 76% yield. The proposed mechanism is summarised in Scheme 2.

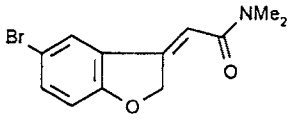
Scheme 2: Mechanism of Synthesis of Benzofuranone (5a)



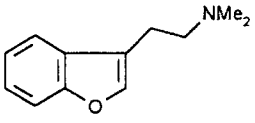
(4a) (11) (5a)

The most successful conditions for the Wittig reaction with ketone (5a) involved generating the ylid [$Me_2NC(=O)CH=PPh_3$] from phosphonium salt (6) and potassium *tert*-butoxide in toluene under reflux. It was beneficial to add the benzofuranone (5a) slowly, in order to avoid both formation of exocyclic olefin (12) and the resulting extended reaction time needed to allow isomerisation into the desired benzofuran (7a). The phosphonium salt (6) was readily prepared from 2-chloro-N,N-dimethylacetamide and triphenylphosphine (4).

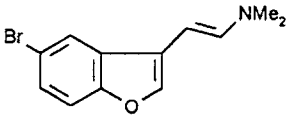
However, attempts to isolate the pure ylid (3,4) invariably afforded material containing triphenylphosphine oxide, and subsequently it was found more effective to generate the ylid *in situ* for reaction with furanone (5a). The triphenylphosphine oxide was then removed by extractive methods after reduction of amide (7a) to amine (8a). A very clean conversion of amide (7a) to amine (8a) was achieved using dichloroalane, prepared *in situ* from $LiAlH_4$ and $AlCl_3$ (5). Other more conventional conditions were less successful. Borane-tetrahydrofuran complex gave a very stable amine-borane complex, which substantially decomposed (>60%) under the acidic conditions required to effect its hydrolysis. Lithium aluminium hydride (3) caused significant (10-25%) debromination of product (8a) to give compound (13), a result which has literature precedent (6,7). The use of alane (7) avoided debromination, but led to the formation of significant, less polar impurities; and diisobutylaluminium hydride (2,8) gave a quantitative yield of a 7:5 mixture of product (8a) and a less polar component, identified by NMR [δ_H (250MHz, $CDCl_3$) 6.72 and 5.03 (each 1H, d, J_{CH}=14Hz, CH=CHN)] as the enamine (14).



(12)



(13)



(14)

The final step in the synthesis, involving a palladium catalysed, Stille coupling of bromide (8a) with pyridylstannane (9), was best performed in toluene under reflux, since a higher reaction temperature using xylene as solvent (2) tended to accelerate catalyst decomposition. Alternative reaction conditions, using dimethylformamide as solvent and silver oxide as halide scavenger (9), resulted in shorter reaction times, but additionally generated small amounts of a dimeric benzofuran derivative (with similar polarity to GR151004 (2a) on TLC), potentially a radiolabelled impurity. The conditions for coupling aryl bromide (8a) to pyridylstannane (9) were optimised by performing a tracer experiment. This revealed that in toluene solution under reflux, the reaction was *ca* 60% complete after 2.5h. However, after 4.5h, in addition to 65% of

the desired product (2a), TLC showed a close running labelled impurity. Thus, for the labelled synthesis, the reaction time was kept to a minimum.

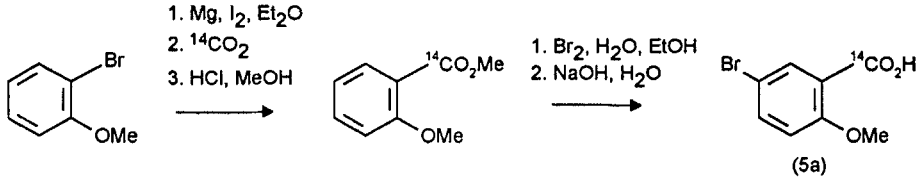
For the radiosynthesis (Scheme 1), 5-bromo-2-methoxybenzoic [^{14}C]acid (3b) (200mCi) was converted into benzofuranone (5b) *via* acid chloride (4b) and ring formation with diazomethane. Benzofuranone (5b) was elaborated into amine (8b), by a Wittig reaction to give amide (7b) and subsequent reduction with dichloroalane. Conversion into [^{14}C]GR151004 free base was then effected by the palladium catalysed cross-coupling reaction of bromoarylamine (8b) and pyridylstannane (9). After chromatographic purification, conversion into the hydrochloride, and crystallisation, [^{14}C]GR151004B (2b) was characterised (37.6mCi; 121μCi/mg, radiochemical purity by TLC and reverse-phase HPLC >99%).

Conclusion

Carbon-14 labelled GR151004B (2b) was prepared in 19% overall radiochemical yield from 5-bromo-2-methoxybenzoic [^{14}C]acid (3b), utilising a method that may have general application in the synthesis of benzofurans, isotopically labelled at C-3.

Experimental

^{1}H NMR spectra were recorded on Bruker AC250 or Varian Unity 400 spectrometers. Microanalyses were performed using a Carlo Erba 1108 elemental analyser. All column chromatography was carried out over silica gel (Sorbsil C60 20/40A from Phase Separations Ltd.). Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} glass plates. Radiochemical purities were determined by TLC using a Berthold Tracemaster 20 automatic TLC linear analyser, or by HPLC using an online Canberra Packard Radiomatic Flo-One βeta detector. 5-Bromo-2-methoxybenzoic [^{14}C]acid was prepared by Amersham International using the route outlined:



(5a)

5-Bromo-2-methoxybenzoic acid (3a)

A mixture of 5-bromosalicylic acid (6.23g, 28.7mmol), potassium carbonate (10g, 72.3mmol), and methyl iodide (5.2ml, 83.6mmol). in dimethylformamide (50ml) was stirred at 22° for 18h. The resulting suspension was added cautiously to 2N hydrochloric acid (200ml), and extracted with ethyl acetate (3x200ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. A solution of the residue in ethanol (60ml) and 5N aqueous sodium hydroxide (50ml) was stirred at 22° for 18h, and then evaporated to remove the ethanol. The residue was treated with 5N hydrochloric acid (100ml), and extracted with ethyl acetate (2x200ml). The combined extracts were dried over (Na_2SO_4), and evaporated to dryness to give the *title compound* (3a) as a colourless solid (6.44g, 97%); δ_H (250MHz, $CDCl_3$) 10.7 (1H, br s, -COOH), 8.29 (1H, m, 6-H), 7.68 (1H, dd, 4-H), 6.77 (1H, d, 3-H), 4.08 (3H, s,-OCH_3); Found: C, 41.4; H, 3.0; Br, 36.2; $C_8H_7BrO_3$ requires C, 41.6; H, 3.05; Br, 34.6%.

5-Bromo-[3-^{14}C]benzofuran-3-one (5b)

A solution of 5-bromo-2-methoxybenzoic [^{14}C]acid (3b) (800mg, 200mCi, δ_H (400MHz, $CDCl_3$) 8.30 (1H, d, 6-H), 7.67 (1H, dd, 4-H), 6.97 (1H, d, 3-H), 4.08 (3H, s, -OCH_3) in dichloromethane (25ml), containing a drop of dimethylformamide, was treated with oxalyl chloride (1ml, 12.4mmol) and stirred at 22°C for 3.25h. The reaction mixture was evaporated to dryness. The residue was dried further under vacuum for 30min to remove final traces of oxalyl chloride and give a yellow solid. An ethereal solution of diazomethane (*ca* 65ml, generated from 5g Diazald) was added directly to this [^{14}C]acid chloride (4b) with ice-bath cooling. The resulting solution was stirred at 0-5° for 30min, and then at 22°C for 2h. Glacial acetic acid (1ml) was added to decompose excess diazomethane, and the mixture was evaporated under reduced pressure to remove the ether. The solution was treated with more glacial acetic acid (10ml) and stirred at 22° for 1.5h. Aqueous sodium carbonate (2N) was added cautiously, to give a mixture at pH10, which was extracted with ethyl acetate (3x40ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness to give an orange solid. Chromatography over silica gel, eluting with dichloromethane-isohexane (6:4), gave the *title compound* (5b) as a

yellow solid (485mg, 123mCi, 61% radiochemical yield); TLC (dichloromethane-isohexane 6:4), radiochemical purity 97%. A sample of unlabelled *title compound (5a)* had been prepared similarly as a pale yellow solid (77%); δ_H (250MHz, $CDCl_3$) 7.79 (1H, d, 4-H), 7.69 (1H, dd, 6-H), 7.06 (1H, d, 7-H), 4.67 (2H, s, 2-H); Found: C, 44.9; H, 2.4; Br, 37.1; $C_8H_5BrO_2$ requires: C, 45.1; H, 2.4; Br, 37.6%.

2-(5-Bromo-[3-^{14}C]benzofuran-3-yl)-N,N-dimethylacetamide (7b)

A stirred mixture of the phosphonium salt (6) (2.13g, 5.54mmol) and potassium *tert*-butoxide (630mg, 5.62mmol) in toluene (25ml) was heated at reflux under nitrogen. A solution of ketone (5b) (485mg, 2.26mmol, 123mCi) in toluene (20ml) was added dropwise over *ca.* 1.25h. Heating under reflux was continued for a further 2h, although TLC showed that the percentage of radioactive product did not change during this period. The cooled toluene solution was washed with 2N hydrochloric acid (50ml), followed by 8% aqueous sodium bicarbonate (50ml). Each aqueous layer was back-extracted with toluene (40ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography over silica gel, eluting with ethyl acetate-isohexane (3:1), to give the *title compound* (7b) (93.2mCi, 76% radiochemical yield), which was stored as a solution in toluene (50ml); TLC (ethyl acetate-isohexane (3:1), radiochemical purity >99%. A sample of unlabelled *title compound (7a)* had been prepared similarly as a yellow oil; δ_H (250MHz, $CDCl_3$) 7.72 (1H, d, 4-H), 7.60 (1H, br t, 2-H), 7.39 (1H, dd, 6-H), 7.34 (1H, d, 7-H), 3.70 (2H, s, CH_2), 3.10 (3H, s, NCH_3), 3.00 (3H, s, NCH_3).

[2-(5-Bromo-[3-^{14}C]benzofuran-3-yl) ethyl]dimethylamine (8b)

A solution of aluminium chloride (1.3g, 9.6mmol) in ether (24ml) at 0-5° under nitrogen was treated with lithium aluminium hydride (3.2ml of a 1.0M solution in ether, 3.2mmol) and stirred for 30min. A solution of amide (7b) (91.3mCi, *ca* 1.5mmol) in ether (20ml) was added dropwise. After addition was complete, the ice bath was removed and the reaction mixture allowed to stir at 22°C. After 30min, 5N aqueous sodium hydroxide (50ml) was added cautiously, and the mixture stirred for a further 1.5h. The suspension was partitioned using more ether (150ml), with sodium sulphate being added to help separate an emulsion The aqueous layer was separated and extracted with more ether (3x100ml). The combined ether layers

were extracted with 2N hydrochloric acid (1x75ml, 2x60ml). The combined acidic extracts were basified with 5N aqueous sodium hydroxide, and extracted with ether (1x400ml, 2x20ml). The combined extracts were dried (Na_2SO_4), and evaporated to dryness to give the *title compound* (8b) as a colourless oil, which was stored as a toluene solution (88.2mCi, 97% radiochemical yield); TLC (dichloromethane-methanol-0.88 ammonia (380:19:1), radiochemical purity >97%. A sample of unlabelled *title compound (8a)* had been prepared similarly as a colourless oil; δ_H (250MHz, $CDCl_3$) 7.68 (1H, d, 4-H), 7.48 (1H, br t, 2-H), 7.38 (1H, dd, 6-H), 7.32 (1H, d, 7-H), 2.81 (2H, m, CH_2CH_2N), 2.60 (2H, m, CCH_2N), 2.32 (6H, s, $N(CH_3)_2$).

2-{5-[3-(2-Dimethylaminoethyl)-[3-^{14}C]benzofuran-3-yl]pyridin-3-yl}-1-(morpholin-4-yl)ethanone dihydrochloride (2b)

A solution of the stannane (9) (2) (712mg, 1.93mmol) and the bromide (8b) (86.9mCi, *ca* 1.5mmol) in toluene (30ml) was deoxygenated by passing a stream of nitrogen through it for 45 min. Tetrakistriphenylphosphine palladium (120mg) was added and the reaction mixture was heated under reflux for 3.25h, cooled, and evaporated to dryness. The residue was purified by chromatography over silica gel, eluted with dichloromethane-methanol-0.88 ammonia (180:19:1), to give product containing *ca* 10% of a close running impurity. This material was repurified by chromatography over silica gel, eluted with ethyl acetate-ethanol-0.88 ammonia (80:20:2), to give the free base (2b) as an oil (324mg, 43.0mCi). A solution of this oil in ethanol (20ml) was treated with 2N hydrochloric acid (1.1ml, 2.2mmol), and evaporated to dryness to give a gummy solid. Crystallisation from a hot mixture of ethanol (5ml) and water (0.2ml) gave the *title compound* (2b) as a colourless solid (310mg, 37.6mCi, 43% radiochemical yield); TLC (ethyl acetate-ethanol-0.88 ammonia 70:30:2), radiochemical purity >99%; HPLC: Supelco LC-ABZ column (15x0.46cm) eluted with a gradient (0-20mins, 5-30% B; 20-25mins, 30% B; solvent A = 0.05M aqueous ammonium phosphate at pH 3.0; solvent B = acetonitrile), flow rate = 1ml/min, R_t = 10.5min, chemical impurities 0.96% a/a (UV detection at 238nm), radiochemical purity >99%; specific activity 121μCi/mg, 56.7mCi/mmol; δ_H (400MHz, CD_3OD) 9.18 (1H, br s, 2-H), 8.94 (1H, dd, 4-H), 8.72 (1H, br s, 6-H), 8.33 (1H, d, 4′-H), 7.88 (1H, s, 2′-H), 7.81 (1H, dd, 6′-H), 7.71 (1H, d, 7′-H), 4.21

(2H, s, $C\underline{H}_2C{=}O$), 3.78 (2H, m, $CCH_2C\underline{H}_2N$), 3.70 (4H, m, $OC\underline{H}_2CH_2N$), 3.62 (2H, m, $CC\underline{H}_2CH_2N$), 3.57 (2H, m, $OCH_2C\underline{H}_2N$), 3.29 (2H, m, $OCH_2C\underline{H}_2N$ obscured by CD_3OD), 3.01 (6H, s, $N(C\underline{H}_3)_2$).

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