SYNTHESIS OF ANTIARRHYTHMIC [PHENYL-^{14}C]4'-[(4-PIPERIDYL)CARBONYL]-METHANESULFONANILIDES

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SUMMARY

Syntheses of [phenyl-^{14}C]4'-[[1-[2-(6-Methyl-2-pyridyl)ethyl]-4-piperidyl]carbonyl]methanesulfonanilide dihydrochloride dihydrate (**1**) (^{14}C-E-4031) and its pyridylpropyl analogue (**2**), that are selective class III antiarrhythmic agents, are described. A modified Michael reaction of (**6**), a key intermediate amine prepared from [U^{14}C]aniline hydrochloride, with 6-methyl-2-vinylpyridine (**7**) and alkylation of (**6**) with 4-(3-chloropropyl)pyridine (**8**) respectively produced compounds, (**1**) and (**2**), in satisfactory yields.

Key words: Class III antiarrhythmic agent, E-4031, [Phenyl-^{14}C]4'-[[1-[2-(6-Methyl-2-pyridyl)ethyl]-4-piperidyl]carbonyl]-methanesulfonanilide, [Phenyl-^{14}C]4'-[[1-[3-(4-Pyridyl)propyl]-4-piperidyl]carbonyl]methanesulfonanilide.

INTRODUCTION

Selective class III antiarrhythmic agents[1] potential utility for prevention of ventricular tachycardia (VT) and ventricular fibrillation that may be causes of sudden cardiac death.[2,3] In the preceding paper, we described the synthesis and biological evaluation of novel methanesulfonanilides.[4] Of these, 4'-[[1-[2-(6-

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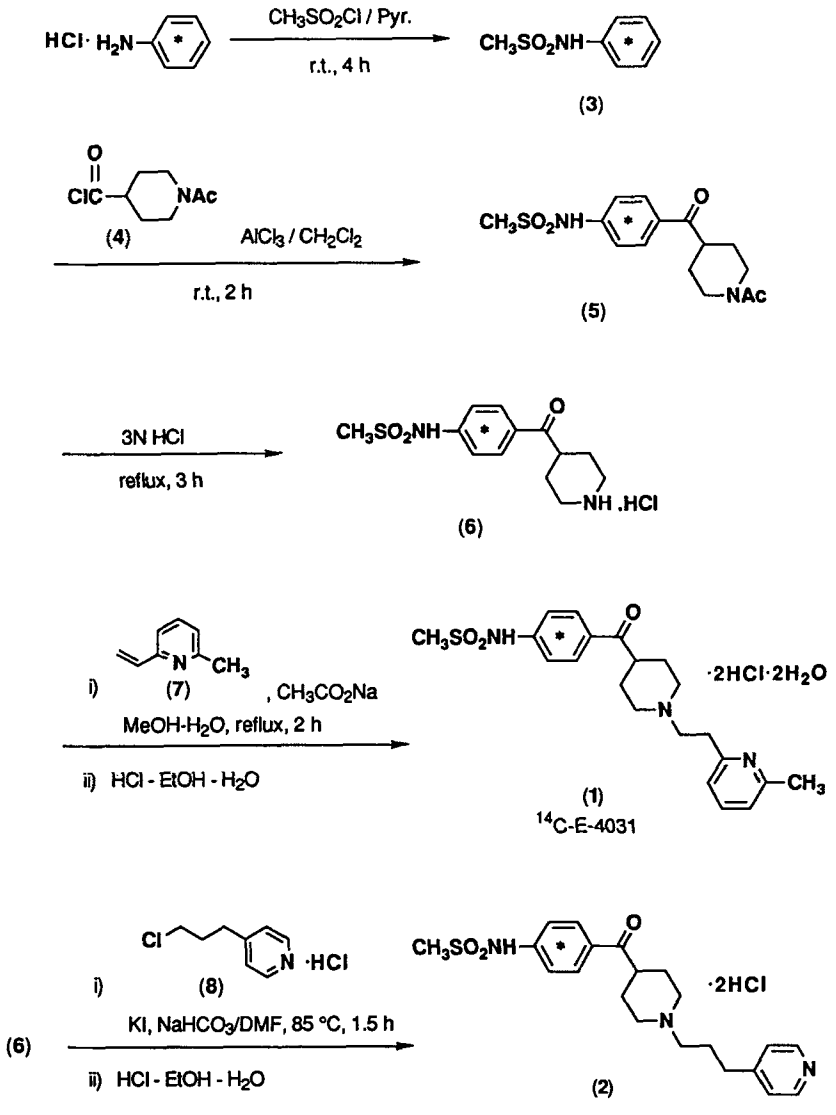
Methyl-2-pyridyl)ethyl]-4-piperidyl]carbonyl]methanesulfonanilide (E-4031) [i.e. unlabelled compound (**1**)] and its pyridylpropyl analogue [unlabelled (**2**)] were the most potent class III antiarrhythmic agents.

This paper describes the synthesis of ^{14}C-E-4031 (**1**) and its pyridylpropyl analogue (**2**) in order to study their pharmacokinetic profiles.

The synthetic sequence leading to the ^{14}C-labelled methanesulfonanilides, compound (**1**) and (**2**), is shown in Scheme I. One of the key intermediates, [phenyl-^{14}C]4'-[(4-piperidyl)-carbonyl]methanesulfonanilide (**6**), was prepared from [U^{14}C]aniline hydrochloride by a similar procedure used for the preparation of unlabelled E-4031.[4,5] A modified Michael reaction of (**6**) with 6-methyl-2-vinylpyridine (**7**)[6] and alkylation with 4-(3-chloropropyl)pyridine hydrochloride (**8**)[7] gave target compounds, (**1**) and (**2**), in 81% and 66% yield respectively. The structures of compounds (**1**) and (**2**) were confirmed by comparison with unlabelled authentic specimens of (**1**) and (**2**). ^{14}C-Labelled E-4031 (**1**) and (**2**) had radiochemical purities of 98.1~97.8% and 101.1~99.1%, and specific activities of 112 mCi/mmol and 112 mCi/mmol, respectively.

Scheme I. Synthesis of [Phenyl-^{14}C]4'-[(piperidyl)carbonyl]methanesulfonanilides



EXPERIMENTAL

Solvents were reagents grade. Purity of each products was checked by TLC on silica gel plates (Kieselgel 60 F_{254} and reverse-phase ODS, thickness 0.25mm) . Column chromatography was performed on silica gel (Merck, particle size 0.063-0.200 mm). Measurement of radioactivity was carried out using Aloka LSC-9000 Liquid

Scintillation Spectrometer. Thin-layer radiochromatography was performed by Berthold LB-2842 automatic TLC Linear Analyzer.

[Phenyl-^{14}C]4'-[(4-piperidyl)carbonyl]methanesulfonanilide Hydrochloride (**6**)

A key intermediate (**6**), which was prepared from [U^{14}C]aniline hydrochloride according to the method outlined in Scheme I, was purchased from Amersham International Ltd.: Specific activity; 112 mCi/mmol: Radiochemical purity by TLC; 98% (n-BuOH/ AcOH/H_2O; 12:3:5, R_f = 0.31, silica gel); 96% (MeOH/concentrated HCl; 95:5, R_f = 0.56, silica gel); 98% (MeOH/0.2M NaCl solution/AcOH; 25:25:1, R_f = 0.63, reverse phase ODS): ν_{max}; 3200-2850, 2810, 2710, 2485, 1665, 1600, 1325, 1150, 970 cm^{-1}. Identification of (**6**) was confirmed by comparison of its R_f values on TLC and IR spectrum with those of the unlabelled authentic sample [mp >265°C. Anal. Calcd for $C_{13}H_{18}N_2O_3S \cdot HCl$: C, 48.98; H, 6.01; N, 8.79. Found: C, 48.64; H, 5.77; N, 8.65].

[Phenyl-^{14}C]4'-{[1-[2-(6-methyl-2-pyridyl)ethyl]-4-piperidyl}-carbonyl]methanesulfonanilide Dihydrochloride Dihydrate (**1**)

To a suspension of (**6**) (0.254 g, 0.797 mmol) in MeOH-H_2O (1:1, 3.0 ml) was added 6-methyl-2-vinylpyridine (**7**) (0.220 g) and CH_3COONa (0.150 g). The mixture was refluxed for 2 h and was filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH; 96:4:0.4). The product was converted into its dihydrochloride salt with ethanolic HCl solution and recrystallized from EtOH-MeOH to give anilide (**1**) as white crystals (0.285 g, 81%): Specific activity; 112 mCi/mmol: Radiochemical purity by TLC; 98.1% ($CHCl_3$/MeOH/NH_4OH; 90:9:1, R_f = 0.54, silica gel), 97.8% ($CHCl_3$/MeOH; 9:1, R_f = 0.55, silica gel), 98.1% (AcOEt/EtOH/H_2O; 1:5:1, Rf = 0.52, silica gel), 97.8% (n-BuOH/ AcOH/H_2O; 12:5:3, Rf = 0.72, silica gel). Identification of (**1**) was

confirmed by comparison of its R_f values on TLC and mp with those of the unlabelled authentic sample [mp ~219°C. Anal. Calcd for $C_{21}H_{27}N_3O_3S \cdot 2HCl$: C, 53.16; H, 6.16; N, 8.86. Found: C, 52.94; H, 6.16; N, 8.73].

[Phenyl-^{14}C]4'-{{1-[3-(4-Pyridyl)propyl]-4-piperidyl}carbonyl}-methanesulfonanilide Dihydrochloride (2)

A suspension of (**6**) (0.295 g, 0.926 mmol) and $NaHCO_3$ (0.38 g) in DMF (4 ml) was stirred at 85 °C for 40 min. To the mixture, KI(0.31 g) and 4-(3-chloropropyl)pyridine hydrochloride (**8**) (0.20 g) was added. The mixture was stirred at 85 °C for 1.5 h. After cooling, the reaction mixture was filtered and the filtrate was concentrated. The residual solid was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$; 96:4:0.4). The product was converted into its dihydrochloride salt with ethanolic HCl solution and recrystallized from EtOH-H_2O to give anilide (**2**) as white crystals (0.288 g, total 66%): Specific activity; 112 mCi/mmol: Radiochemical purity; 101.1% ($CHCl_3$/MeOH/ NH_4OH; 90:9:1, R_f = 0.71, silica gel), 99.5% ($CHCl_3$/MeOH; 9:1, R_f = 0.72, silica gel), 99.1% (AcOEt/EtOH/H_2O; 1:5:1, R_f = 0.56, silica gel). Identification of (**2**) was confirmed by comparison of its R_f values on TLC and mp with those of the unlabelled authentic sample [mp ~230°C. Anal. Calcd for $C_{21}H_{27}N_3O_3S \cdot 2HCl$: C, 53.16; H, 6.16; N, 8.86. Found: C, 52.95; H, 6.10; N, 8.73].

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