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NOTE

SYNTHESIS OF RADIOIODO-[4-(2-IODO-4-FLUORO-BENZOYL)PIPERIDIN-1-YL]-2'-ACETONAPHTHONE.

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SUMMARY

Radioiodo-[4-(2-I-4-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone was synthesised as a potential in vivo tracer of the glutamate release inhibiting system. The labeling was performed by Cu^{1+} assisted non isotopic nucleophilic exchange on [4-(2-bromo-4-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone.
The labeled compound is obtained after HPLC separation and mini-column recovery. The brominated substrate is obtained by KI catalysed coupling of 2-bromo-acetonaphthone to the piperidinyl entity in ethanol at room temperature using triethylamine.

Key Words: Radioiodination, [4-(2-bromo-4-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone, Cu^{1+} assisted exchange.

INTRODUCTION

It was mentioned by Karibe et al. (1) that 2-[4-(p-fluorobenzoyl)piperidin-1-yl]-2'-acetonaphthone (FPA) showes a potent inhibitory effect on glutamate release. We have shown that substituting a radiohalogen in clustered lipophilic compensated position i.e. ortho of the carbonyl and meta of the fluor, results in a limited increase of lipophilicity with preservation of activity (2). For that reason it was decided to synthesize 2-[4-(2-bromo-4-fluorobenzoyl)piperidine-1-yl]-2'-acetonaphtone(Br-FPA) as substrate for radioiodination using Cu^{1+} assisted nucleophilic exchange (3) and try radioiodo-FPA as a potential tracer of the glutamate receptor system.

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MATERIALS and METHODS.

Reagents: 2-Bromo-2'-acetonaphthone (purity 98%) is purchased from Janssen Chemica. 4-(2-bromo-4-fluorobenzoyl)piperidine.HCl was obtained by courtesy of Mallinckrodt Diagnostica BV (Holland). The other reagents used were p.a. grade (Merck) or HPLC grade (Lichrosolve quality Merck).

HPLC Equipment:

Analytical: The equipment consists of a Rheodyne injector (50 µl loop), a Hitachi 655A pump and L-6000 II controller, a 655A variable wavelength UV monitor, a NaI(Tl) detector (Harshow) and appropriate electronics (Canberra), a D2000 Chromato integrator Hitachi and an Ankerschmidt R40 one-channel recorder. Quality control is achieved on a Lichrospher 125x4 mm RP Select B (5µ) Merck column with a methanol/acetonitrile/water//trimethylamine/acetic acid (MeOH/ACN/H_2O//TMA/HOAc): 39/15/46//0.4/0.8 by volume mixture as eluent at a flow rate of 1 ml/min.

Semi-preparative: Rheodyne injector (2 ml loop), a Waters M6000A pump provided of a semi-prep pumphead, a Waters Lambdamax UV-480 monitor, a NaI(Tl) detector (Harshow) connected to Ortec electronics, a HP 3580 and a Intersmat ICR-18 integrator. A MeOH/ACN/H_2O//TMA/HOAc: 39/15/46//0.4/0.6 by volume mixture of pH=4.8 is used as eluent at a flow rate of 6 ml/min. on a Lichrochart 250x10 mm RP select B (10µ) Merck column.

TLC: Performed on Merck Kieselgel 60F_{254} 5x10 plates using chloroform/methanol - 9/1(v/v) as mobile phase. Spots are recovered, extracted and HPLC analysed.

2-[4-(2-Bromo-4-fluorobenzoyl)piperidin-1-yl]-2'acetonaphthone (Br-FPA):

1.5 mmol of 4-(2-bromo-4-fluorobenzoyl)piperidine. HCl is dissolved in 16 ml ethanol containing 1.5 mmol triethylamine by ultrasonication. Then 1.5 mmol of 2-bromo-2'-acetonaphthone, another 1.5 mmol of triethylamine and 4.5 µmol of KI are added and the reaction mixture is stirred at room temperature for 60 minutes. After evaporation to dryness in vacuo at room temperature, the residue is dissolved in dichloromethane and washed with water. The organic layer is dried over sodium sulfate, filtered and evaporated under vacuo. The residue is purified by column chromatography on a Silica 60 column using a mixture of 98% dry chloroform and 2% methanol as eluent. After evaporation of the eluent Br-FPA is stored as its base under dry nitrogen at room temperature.

Physical data :

MS(FAB) (m/c,%RA) : 456(M+2, 6.0) ; 454(M,6.3)

^{1}H NMR (270 MHz,$CDCl_3$) : δ 1.85 - 1.93 (m,4,piper - $N(CCH_2)_2$) ; δ 2.29 - 2.39 (m,2,piper - $N(CH_2C)$, equat.) ; δ 3.06 - 3.10 (m,3,piper - $N(CH_2)$, equat and CHCO) ; δ 3.95 (s,2,$COCH_2N$) ; δ 8.06 - 7.04 (10,H arom).

I-FPA:4-(2-iodo-4-fluorobenzoyl)piperidine is obtained applying the earlier described Cu^{1+} assisted exchange on millimolescale (4). Coupling and purification is achieved as described for Br-FPA.

Radioiodination and perification:

A stock solution containing 1 mg tin sulfate, 25 mg gentisic acid, 35 mg citric acid, 30 µl of a 1.3 10^{-2}M copper sulfate solution and 250 µl glacial acetic acid was made up to 2.5 ml with bidistilled water. 1 mg of Br-FPA dissolved in 45 µl of acetic acid, 500µl of stock solution and the radioiodine solution were heated in a septum closed and N_2 flushed V-vial at 100 °C during 30 minutes. A 2 µl sample is taken for HPLC control of the labeling. In one step the reaction mixture is taken up and the V- vial rinsed with HPLC eluent (1.2 ml) by means of a two seringe system. The whole is filtered through a 0.45µ filter which is rinsed with another 0.2 ml of eluent. The filtrate is immediately injected for semi-preparative HPLC. The eluent fraction in which the radioactive peak is recovered is brought to pH 9 and passed through a RP-Bondapack mini column. After rinsing with water, the radioiodo-FPA is recovered in 300µl of ethanol. 2µl are sampled for quality control (HPLC,TLC).

RESULTS and DISCUSSION.

Synthesis of Br - FPA:

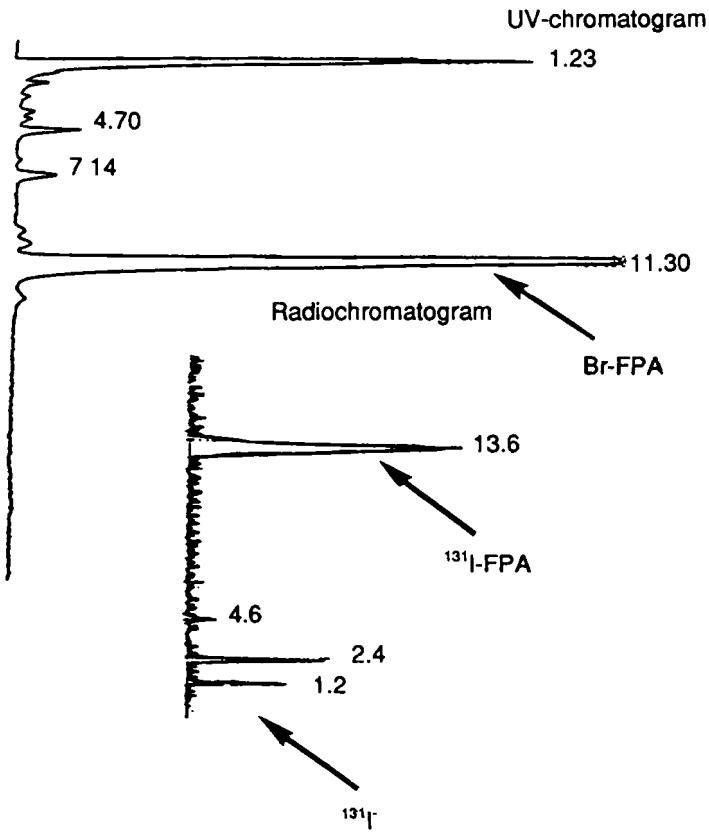
When applying the reaction conditions as described by Karibe et al. (1) the reaction yield does not exceed 40% and a high amount of side products are observed. This is due to both the presence of an excess triethylamine, if the piperidine part is used as its base, and the higher reaction temperature (reflux) promoting secondary reactions at the highly activated bromine in the α position of the arylketone. When performing the reaction in refluxing methyl isobuthyl ketone using potassium carbonate as described for Ketanserin and analogues (5) comparable unsatisfactery results are obtained. When using the present synthesis conditions a yield of at least 97% is obtained within 60 minutes. When using the piperidine as its base in presence of 1.2 mmol of triethanolamine the same yield is obtained within 30 minutes. For high stability 4-(2-Br-4-fluorobenzoyl)piperidine is preferably stored and used as its HCl salt. An equivalent amount of triethylamine is initially added

and the mixture is ultrasonicated until dissolution indicating complete formation of the base.This avoids the kinetically favorable attack of the bromo compound by an excess triethylamine leading to side products. The final product is sensitive to moisture and is stored under dry nitrogen. The HCl salt was found to be stable for at least 9 months. Unfortunately this is not the best substrate for labeling as the Cl-ions interfere in the nucleophilic exchange reaction.

Radioiodination:

The 2-position in the 4-fluorobenzoyl group is deactivated for direct electrophilic radioiodination. For that reason nucleophilic exchange is applied. The labeling method described is a typical application of our Cu^{1+} assisted nucleophilic exchange in mixed solvent conditions: due to its rather high lipophilicity Br-FPA has to be dissolved in concentrated acetic acid or in ethanol prior the addition of the stock solution. A labeling yield of 75 - 80% is obtained with ^{131}I(specific activity 660 Ci/mmol). A typical UV and radio chromatogram is shown in Fig.1. The main

Fig.1: Radioiodination: 2-[4-(p-fluoro-o-bromobenzoyl)piperidin-1-yl]-2'-acetonaphthone: Br-FPA → ^{131}I-FPA.



labeled side product is 4-(2-[^{131}I]iodo-4-fluorobenzoyl)piperidine probably due to the chemical breakdown at the amide function in the labeling conditions applied. Using the more stable ketal of the acetonaphthone ketone for labeling purposes should require an additional deprotection in strong acid conditions which can also lead to degradation. As with FPA (1), the radioiodinated analogue also is unstable in aqueous solution and once diluted with isotonic saline has to be used within the first hour. Radioiodinated piperidine moiety is the major side product.

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