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Short Research Article

Syntheses of isotopomers of SK&F-S-104864, topotecan HCl†

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Introduction

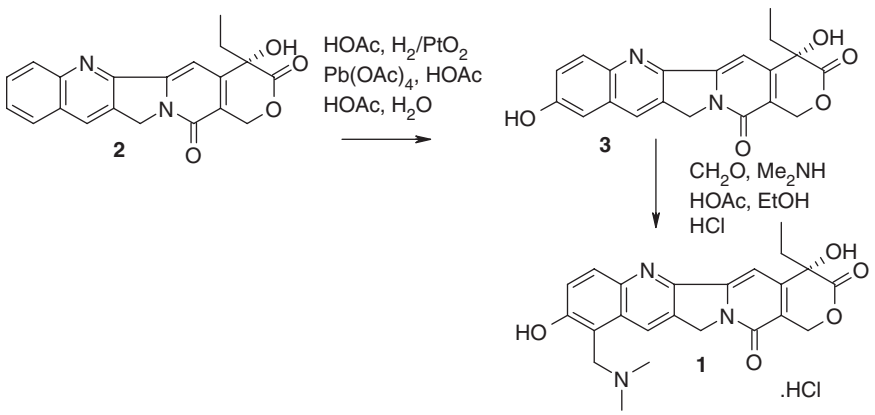
SK&F-S-104864-A **1**, topotecan HCl, is a topo-isomerase-I inhibitor marketed as Hycamtin.

Topotecan[1] is a semi-synthetic derivative of campothecin **2**, an alkaloid first isolated[2] in 1966. Campothecin[1] is converted into the 10-hydroxy derivative **3** by a reduction/oxidation sequence and a subsequent Mannich reaction gives the desired SK&F-S-104864 (Scheme 1).

Results and discussion

Carbon-14 labelled SK&F-S-104864 was required for ADME studies. 10-Hydroxycampothecin **3** is readily available from the synthesis of bulk drug. *N*-demethylation of the dimethylaminomethyl side chain is a known metabolic pathway,[3] however, the exo-methylene carbon remains untouched so we chose to label with carbon-14 as shown in Scheme 2. 10-Hydroxycampothecin was suspended in glacial acetic acid, dimethylamine added followed by [^{14}C]formaldehyde. The mixture was stirred at 75°C until no further reaction was observed (HPLC). The crude SK&F-S-104864 was purified by reverse phase HPLC, the relevant fractions pooled and c. HCl added. The product was isolated by lyophilization giving [^{14}C]SK&F 104864-A in 68% yield from formaldehyde.

[^{3}H]Topotecan was required for mechanistic studies and is prepared in a directly analogous manner using [^{3}H]formaldehyde as the source of radiolabel. The



Scheme 1

crude product is purified by HPLC (C18, acetonitrile/water/TFA) and isolated as the TFA salt by lyophilization. The specific activity was 2.8 Ci/mmol.

Stable isotope labelled topotecan was required as an internal standard in LC/MS/MS assays. 10-Hydroxycampothecin **3** was reacted in glacial acetic acid with aqueous formaldehyde and [$^{2}H_6$] dimethylamine

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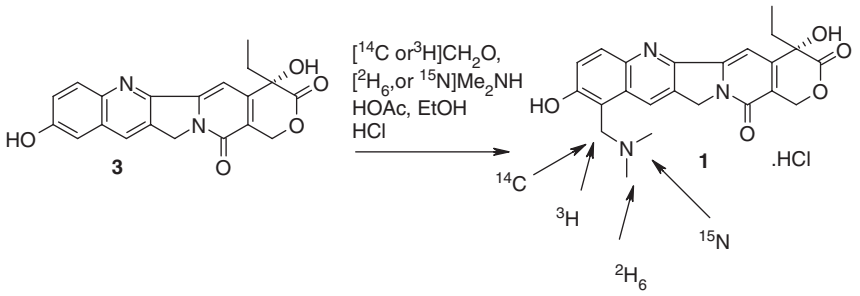

Scheme 2

hydrochloride (3 equivalents) at 55°C until the reaction was complete. The residue was purified by medium pressure chromatography (RP18 silica, methanol/water 1:4 (v/v)). The product was dissolved in DCM/methanol (2:1 (v/v)) and a calculated amount of 10 M HCl in IPA added. The product slowly precipitated. Typical yields from 10-hydroxycampothecin were 50–60%. [^{15}N]SK&F-S-104864 was required for NMR studies in support of pharmaceutical formulation, and was synthesised in a directly analogous manner to [$^{2}H_6$]SK&F-S-104864.

REFERENCES

1. Kingsbury WD, Boehm JC, Jakas DR, Holden KG, Hecht SM, Gallagher GG, Caranfa MJ, McCabe FL, Faucette LF, Johnson RK, Hertzberg RP. *J Med Chem* 1991; **34**: 98.
2. Wall ME, Wani MC, Cook CE, Palmer KH. *J Am Chem Soc* 1976; **88**: 3888.
3. Rosing H, Herben VMM, Van Gortel-Van Zomeren DM, Hop E, Ketenes-Van den Bosch JJ, Ten Bokkel Huinink WW, Beijnen JH. *Cancer Chemother Pharmacol* 1997; **39**: 498.

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