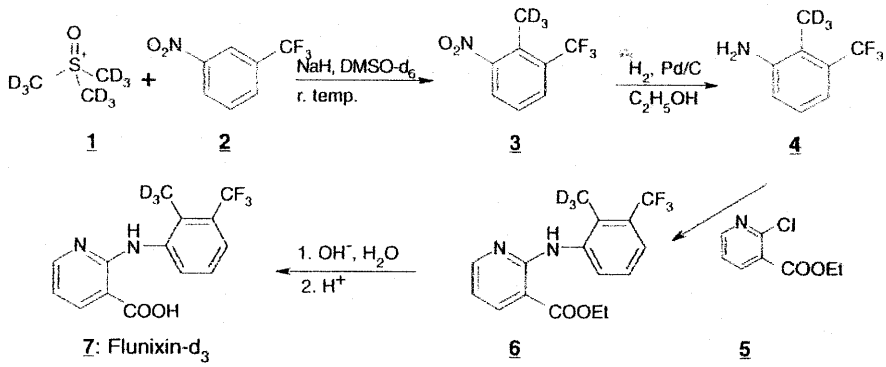


*Fig 2: Synthesis of deuterated flunixin.*

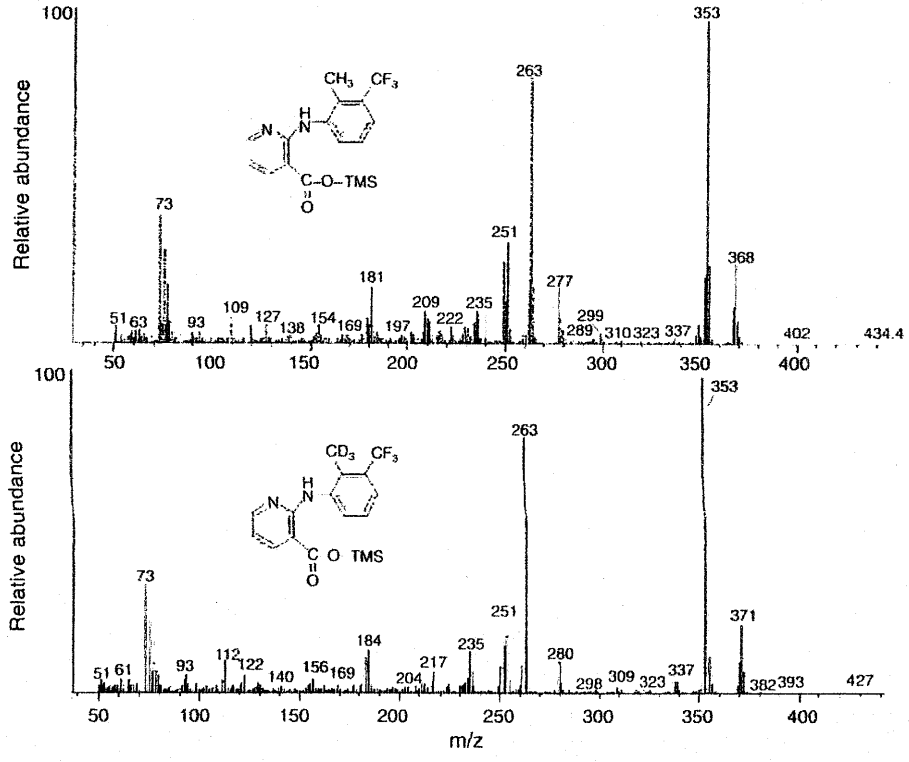


*Fig 3: Mass spectra of silyl derivatives of flunixin-$d_0$ and flunixin-$d_3$ (7).*

methylating agent, trimethyl-$d_9$ sulphoxonium iodide (1). Iodomethane-$d_3$ was reacted with DMSO-$d_6$ according to the procedure described by El-Fayoumy *et al.* (1979), giving with high yield salt 1. This salt (1) was then used to methylate 3-nitro-α,α,α-trifluorotoluene (2) in a vicarious nucleophilic substitution (VNS) reaction in the presence of sodium hydride in DMSO-$d_6$ at room temperature following the procedure described by Lamendola *et al.* 1989), yielding 2-methyl-$d_3$-3-nitro-α,α,α-trifluorotoluene (3). This reaction provided the desired product in moderate yield (50%) in mixture with un-reacted substrate (Lamendola *et al.* 1989). Due to the similar and low polarities of both substrate and product (2 and 3), these compounds are not easily separated by column chromatography and distillation is challenging due to the projected small scale reaction size (under 500 mg). Therefore, the mixture of 2 and 3 was used for the next reduction

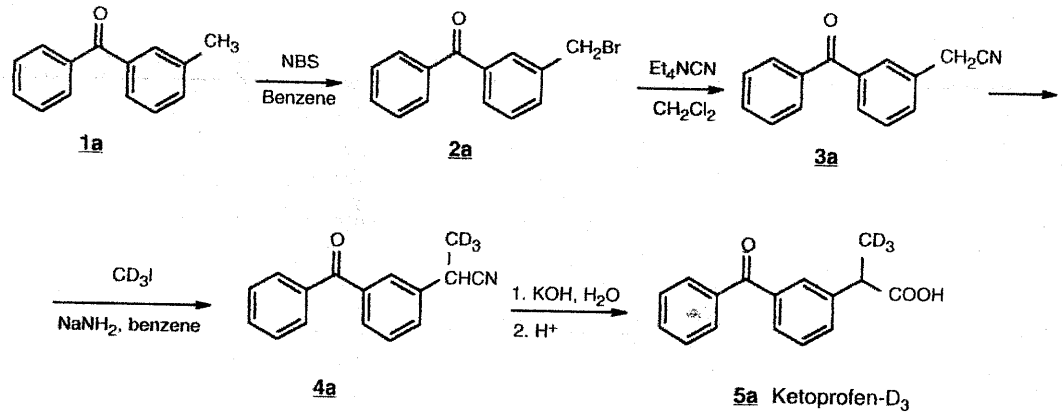


*Fig 4: Synthesis of deuterated ketoprofen.*

step. In this step the nitro group was reduced to amino group by classic hydrogenation using 10% palladium on charcoal as the catalyst in ethyl alcohol. After a 5 h reaction at 60°C, both nitro compounds 2 and 3 were converted to their corresponding aniline derivatives (**4** and 3-triflurometylaniline). This mixture was separated by column chromatography using an eluent system of n-hexane-*tert*-butylmethylether 9:1, to yield methyl-$d_3$-trifluoromethylaniline (**4**) with a 5% admixture of 3-triflurometylaniline. Therefore compound **4** was additionally purified upon crystallisation from n-hexane at -10°C, and next reacted for 12 h with the equimolar amount of ethyl ester of chloronicotinic acid (**5**) (Matrix Scientific Inc.) in ethylene glicol at 160°C, according to the procedure described by Jaouhari and Quinn (1994). The ethyl ester of flunixin-$d_3$ **6** was purified upon column chromatography (n-hexane – ethyl acetate, 3:1) giving a high yield (80%) of the condensation product. Finally, hydrolysis for 4 h at 70°C with potassium hydroxide in methanol/water (4:1) followed by acidification yielded flunixin-$d_3$. Crystallisation from acetone – n-hexane gave 50 mg of fine crystals, mp 216–219°C.

### *Synthesis of ketoprofen-$d_3$*

Synthesis of deuterated ketoprofen (Fig 4) was accomplished using classical methods, first 3-methylbenzophenone (**1a**) was brominated with N-bromosuccinimide in benzene to obtain 3-bromomethylbenzophenone (**2a**), which after reaction with tetraethylaminocyanide in methylene chloride gave the corresponding nitrile (**3a**). After silica gel chromatography (petroleum ether/ethyl acetate 4:1), methylation of this material was achieved with methyl-$d_3$ iodide in the presence of sodium amide in toluene-benzene. The obtained 2-(3-benzoylphenyl)propanenitrile-$d_3$ (**4a**) was purified from the dimethylated product upon column chromatography (petroleum ether/ethyl acetate, 5:1). Next, compound (**4a**) dissolved in small amount of ethyl alcohol was added to an aqueous potassium hydroxide solution (2%) and heated under reflux for 24 h. After diluting with water, washing the aqueous ketoprofen potassium salt solution with ethyl ether, acidification, extraction with ethyl acetate, and evaporation of the solvent, crude ketoprofen-$d_3$ (**5a**), as colorless oil, was obtained. Crystallisation from hexane-ethyl ether gave fine white crystals of **5a**, mp 95–96°C.

## Results and Discussion

Our synthetic pathway (Fig 2) to flunixin-$d_3$ has yielded the desired deuterated product (Fig 3) with an isotopic purity of greater than 98%, and no detection of the $d_0$ analogue, as established by GC/MS of the silyl derivative. Work is in progress to further purify this product.

Ketoprofen-$d_3$ has been produced with satisfactory yield and high chemical and isotopic purity as fine white crystals. Isotopic purity as determined by GC/MS of the silyl derivative is greater than 99% ketoprofen-$d_3$, with 0.72% ketoprofen-$d_0$ calculated from the ratio of the 311/314 m/z spectral peaks (Fig 5).

## Conclusions

Flunixin-$d_3$ has been produced with satisfactory yield and high isotopic purity. Ketoprofen-$d_3$ has been produced with satisfactory yield and high

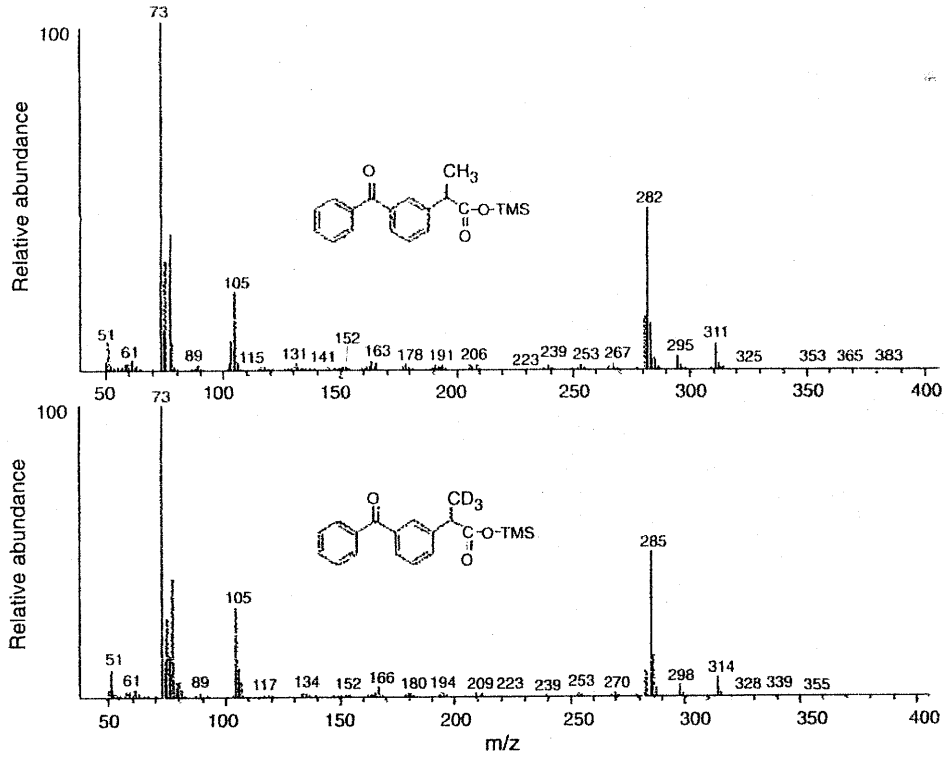


*Fig 5: Mass spectra of silyl derivatives of ketoprofen-$d_0$ and ketoprofen-$d_3$ (5a).*

chemical and isotopic purity. These compounds are of sufficient quality for use as internal standards in the quantitative analysis of their respective non-deuterated analogues.

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