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Unusual base-catalyzed exchange in the synthesis of deuterated PF-2413873[a]

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The preparation of deuterated PF-2413873 (4-[3-cyclopropyl-1-(methanesulfonylmethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile, 1) is described for use as a bioanalytical standard in clinical trials. Two strategies were investigated. The sulfone-containing substituent was labelled by base-catalyzed exchange, but unacceptable deuterium loss was noted under assay conditions. Alternatively, labelling 4-cyano-3,5-dimethylphenol was achieved by heating with deuterium oxide over platinum oxide. After building up the pyrazole ring we discovered that, during the subsequent alkylation to attach the methylthiomethyl group, the base, potassium *t*-butoxide, caused unwanted scrambling of deuteriums on the aromatic portion and the methylthiomethyl group. Thus, it was necessary to remove all base-labile hydrogens to prevent their exchange. This was accomplished by alkylating the pyrazole with *per*-deuterated chloromethyl methylsulfide, oxidation to the sulfone, and selective removal of its deuteriums by treatment with sodium hydroxide. The unusual sensitivity and selectivity of these base-promoted exchange reactions are discussed. Thus, 4-[3-cyclopropyl-1-(methanesulfonylmethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-[$^2H_6$]2,6-dimethyl-[3,5-^{2}H]benzonitrile (17) was obtained, labelled with eight deuterium atoms and an acceptable D_0/D_8 ratio.

Keywords: progesterone receptor antagonist; pyrazole; sulfone; deuterium exchange; platinum catalysis; base catalysis

Introduction

Deuterated versions of pharmaceutical compounds are needed as analytical internal standards to permit quantification by mass spectroscopy (LC/MS/MS) of the parent (undeuterated) compound in plasma or other biological media, and to measure definitive plasma protein binding.[1,2] Alternatively, or in addition, other stable isotopes such as ^{13}C, ^{15}N or ^{18}O may be used. In connection with a project to discover non-steroidal progesterone receptor antagonists[3] for the treatment of secondary dysmenorrhea,[4,5] we need to prepare a deuterated version of the pyrazole derivative, PF-2413873 (**1**).[6] This compound contains a fully substituted pyrazole ring bearing a tri-substituted phenoxy group, cyclopropyl and methyl groups, and an uncommon methanesulfonylmethyl group[7–10] attached to a ring nitrogen.

To be of use in analysis, the deuterium standard must not generate a peak in the mass spectrum that coincides with the mass of the parent compound (or suitable fragment). For practical purposes, we desire that the most intense peak in the mass spectrum of the deuterated version is at least 1000 times more intense than the species without any deuterium atoms, i.e. $D_0{:}D_X < 0.1\%$. Under normal circumstances, a minimum of three deuterium atoms is sufficient to ensure this, although in this case the compound includes an element with two significant isotopes (^{32}S, ^{34}S). We therefore required a synthesis that would introduce at least four deuterium atoms with high isomeric incorporation.

Results and discussion

The route to unlabelled **1** is shown in Scheme 1. Claisen condensation of acetyl cyclopropane with ethyl acetate gave diketone **2**, which was then chlorinated with N-chlorosuccinimide[11] to give **3**. Without purification, chlorodiketone **3** was then used to alkylate the cyanophenol derivative **4**, affording the product **5** in modest yield. Treatment of **5** with hydrazine in the presence of acetic acid gave pyrazole **6** almost quantitatively. The side chain of **1** was then installed in a two-step process consisting of alkylation of **6** with choromethyl methylsulfide with potassium *t*-butoxide as base. It was important to use an excess of both alkylating agent and base for good yields. The alkylation gave a mixture of pyrazole regioisomers **7** and **8**, from which the desired isomer **8** was obtained by column chromatography. Finally, treatment of **8** with Oxone® gave **1** (6 steps, 10% overall yield).

We considered that the most straightforward way to label **1** would be to employ *per*-deuterated chloromethyl methylsulfide in the alkylation step, as this would be close to the end of the synthesis. Although this reagent has not been reported in the literature, we applied an attractive method consisting of a reaction of dimethylsulfoxide with 'silica chloride',[12,13] which is generated by treating silica gel with excess thionyl chloride at reflux. Thus, reaction of [$^2H_6$]DMSO with silica chloride gave

[a]*This paper is dedicated to Dr Gordon I. Fray, formerly of The School of Chemistry, University of Bristol, UK on the occasion of his 80th birthday, and Stuart Rozze, who retired from Pfizer on September 2008 after 35 years with the company.*

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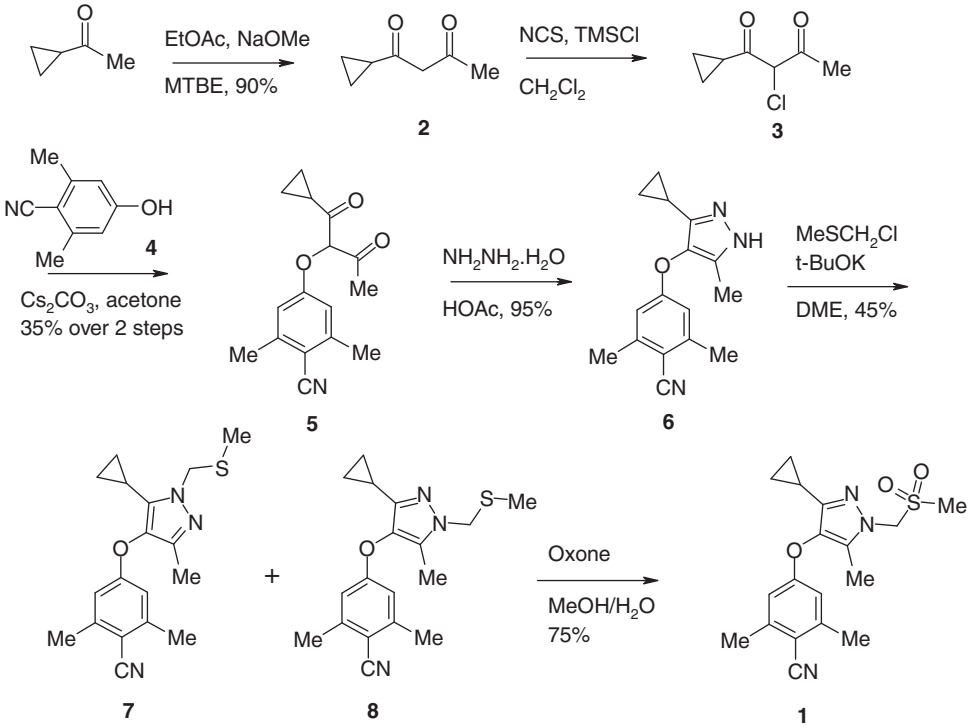
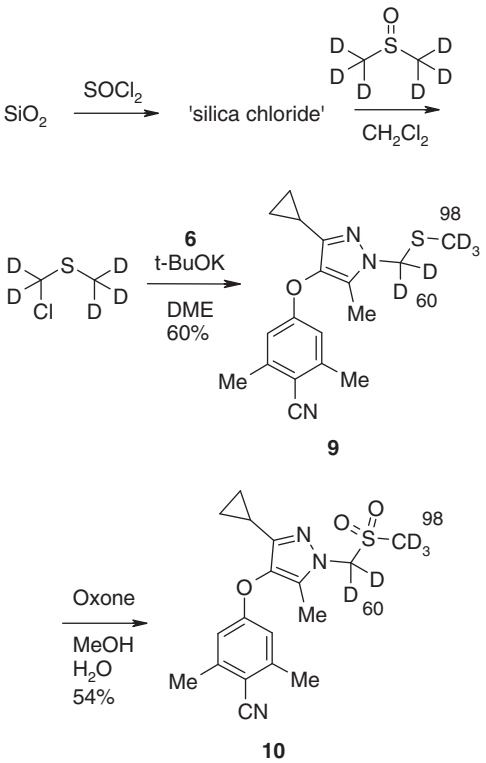
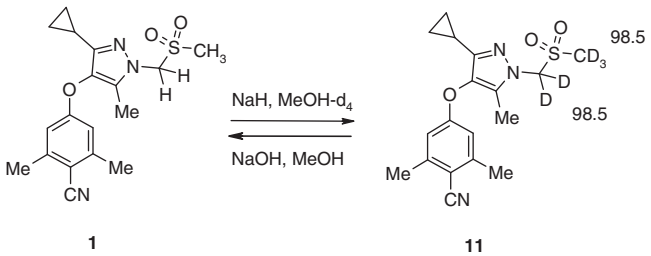


Scheme 1. Original route to PF-2413873 (1).



Scheme 2. First deuterated synthesis. The average percentage deuterium incorporation is indicated by the figures next to structures.



Scheme 3. Base-catalyzed exchange of compound 1.

[$^2H_5$]chloromethyl methylsulfide, which was used directly in the alkylation with **6** (Scheme 2). The resulting mixture of pyrazole isomers was separated. Examination of the NMR data for the desired isomer **9** indicated high deuterium incorporation of the methyl group, but significant loss of deuterium at the adjacent methylene. Oxidation to the sulfone as before gave **10**.

Detailed examination of the ^{1}H NMR spectrum of **10** showed the methylene attached to the pyrazole nitrogen to be a mixture of CH_2 (40%), CHD (20%) and, by implication, CD_2 (40%). Careful comparison of the spectrum with **1** (undeuterated) revealed the presence of two small signals at $\delta = 2.94$ ppm (br) and $\delta = 2.96$ ppm (s), the latter corresponding to the SO_2CH_3 group in the undeuterated spectrum. We assigned these peaks to SO_2CH_2D/SO_2CHD_2 (mixture) and SO_2CH_3, respectively. Accurate integration was not possible, but we estimated these peaks to be approximately 1% of the intensity of the other methyl signals. Measurement of the relative intensities of the D_4 and D_0 peaks in the mass spectrum gave variable ratios between 0.36 and 4% D_0, which was clearly unsatisfactory for use as an internal standard. The variation in the results was a concern and also somewhat at odds with the NMR measure of deuterium loss.

Suspecting that the high D_0 level was caused by exchange of deuterium for hydrogen during isolation or under the mass spectroscopic conditions, we examined the stability of **1** (Scheme 3).

Thus, treatment of undeuterated **1** with acid caused no exchange, whereas 0.9 equivalent of [$^2H_3$]sodium methoxide in [$^2H_4$]methanol overnight gave essentially complete exchange of all hydrogens in the sulfone side chain, but left the rest of the molecule unchanged. Incorporation of deuterium was conveniently monitored by NMR and showed 98.5% average incorporation in the sulfone substituent, but no exchange in the methyl groups of the benzonitrile moiety. Deuterium could also be removed efficiently from the side chain by treatment with excess sodium hydroxide in methanol.

We were somewhat surprised by just how facile and selective the exchange was, since the acidity of sulfones is low (e.g. $CH_3SO_2CH_3$ $pK_a = 31.1$, DMSO solvent)[14] and may be similar to the aryl methyl groups (pK_a of *p*-tolunitrile is 30.8, DMSO solvent,[15] and *o*-tolunitrile has an estimated $pK_a \sim 30$, ether solvent[16]). However, there are many reports of hydrogen–deuterium exchange of sulfones under basic conditions (e.g. NaOD, D_2O, reflux).[17–22]

The D_0:D_5 ratio of **11** was measured by mass spectrometry and again found to vary (<0.1–1%) on a variety of samples. The cause of the variability is not understood; we decided, therefore, to find an alternative, more stable location for the deuterium atoms, avoiding a deuterated sulfone substituent, as this would most likely result in several isotopologues, depending on how samples had been treated.

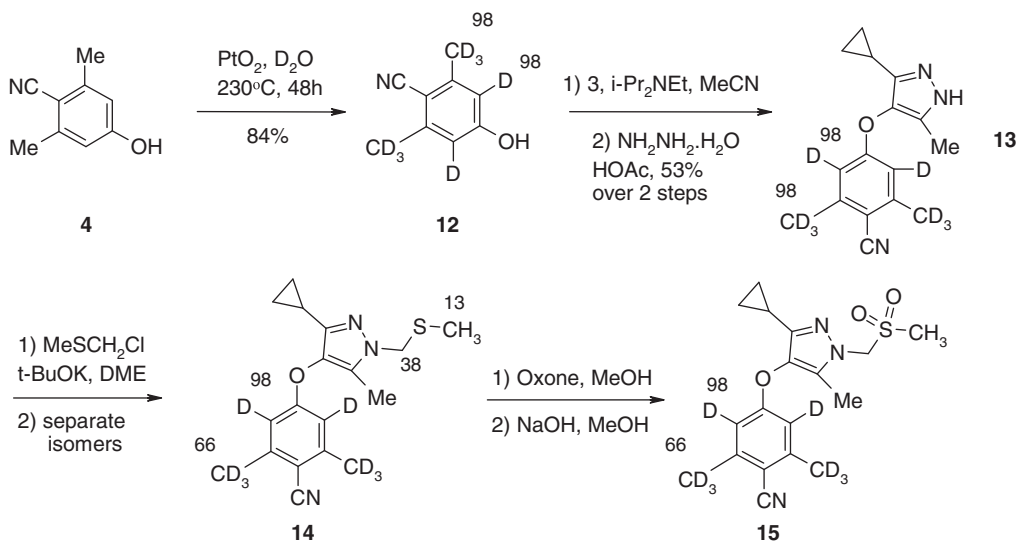
After considering various possibilities including syntheses from [^{13}C, ^{15}N]cyanide and [$^{15}N_2$]hydrazine, we decided to introduce deuterium into the aryl group. Following the pioneering work of Long and Garnett,[23–25] there has been a recent upsurge in interest in noble metal (Pd, Pt, Ru, Rh) catalyzed exchange reactions, with cheap deuterium oxide as the deuterium source, with or without surface activation by a reducing agent such as hydrogen gas or sodium borohydride.[26–29] In particular, we were drawn to examine a method in which the compound to be deuterated is heated in deuterium oxide in the presence of platinum oxide.[30,31] Deuterium exchange of hydrogens of alkyl chains attached to aryl groups can take place as well as aromatic hydrogens, although no examples of methyl-substituted aromatics were included.[32] Application of this method to **4** at around 230°C (the maximum temperature with the apparatus available) afforded **12** with 98% deuterium incorporation at all carbons (Scheme 4).

Compound **12** was then converted into **13** as before; changing the base and solvent for the alkylation by chloroketone **3** improved the yield. Alkylation of **13** with undeuterated chloromethyl methylsulfide, followed by separation of the regioisomers by chromatography gave **14**, whose mass spectrum revealed that extensive exchange of deuterium with hydrogen had taken place. Although deuterium content of the aromatic positions remained unchanged, significant loss of deuterium from the arylmethyl groups had occurred, concurrent with some gain of deuterium in the sulfide side chain. Mass spectrometry showed a range of masses from D_0 to D_{10}, peaking at D_9; however the D_0:D_9 ratio was 1.15%. To be certain that the undeuterated content was unsuitable for this sample, **14** was converted to **15**; NMR confirmed the intended removal of deuterium from the side chain and no change in the deuterium content of the aryl methyl groups. While D_8 was the most abundant ion in the mass spectrum, the intensity of D_0 (0.64%) was too large.

In seeking a possible explanation, the source of the hydrogen atoms and the base causing the exchange need to be identified. The hydrogen could have been provided by the pyrazole NH, or the methylthiomethyl group (post-alkylation, although it is conceivable that exchange occurs prior to alkylation, *via* deprotonation/re-protonation of the chloromethyl group), or adventitious water. The base promoting the exchange could have been excess potassium *t*-butoxide or the pyrazolyl anion prior to reaction with the electrophile.

Performing the alkylation of **13** as before, but introducing the additional precaution of exchanging the NH of the pyrazole for deuterium, afforded **14** with only a slightly modified deuterium content. Thus, the mass spectrum revealed a wide range of masses (from $m/z = 331$ (M+H, D_3) up to $m/z = 338$ (M+H, D_{10})), suggesting that not only was there loss a of deuterium from the aromatic methyl groups but also some deuterium transfer to other parts of the molecule.

Several control experiments were conducted. Compounds **6** and **8** were treated separately with three equivalents each of potassium *t*-butoxide and [$^2H_1$]*t*-butanol (to provide a source of



Scheme 4. Scrambling of deuterium content in the alkylation step. The average percentage deuterium incorporation is indicated by the figures next to structures.

deuterium) in DME and room temperature for a similar time to the alkylation reaction. Partial exchange in the aromatic methyl groups was detected by NMR analysis: 9 and 27% incorporation was noted in **6** and **8**, respectively. Heating **6** with sodium methoxide (0.9 equiv.) in [$^2H_4$]methanol for 20 h at reflux resulted in no exchange of hydrogen. We speculate therefore that excess potassium *t*-butoxide was responsible for the exchange.

Deprotonation of **13** by potassium *t*-butoxide gives the pyrazolyl anion and *t*-butanol. The proton transfer is anticipated to be complete owing to the difference in basicity between the pyrazolyl anion (pyrazole NH pK_a is 19.8 and 14.2 in DMSO[33] and water,[34] respectively) and *t*-butoxide (*t*-butanol has pK_a 29.4 (DMSO)[35]).

The pyrazolyl anion is resistant to hydrogen–deuterium exchange because its negative charge makes further deprotonation unfavorable; nevertheless, *t*-butoxide is able to achieve it to a small degree, although sodium methoxide is not. However, once **14** starts to form, *t*-butoxide can scramble the hydrogen and deuterium atoms on the methylene next to sulfur and the aromatic methyl group (the anion is stabilized by conjugating to the nitrile), *via* deprotonation and reprotonation from the *t*-butanol.

In the alkylation (Scheme 4), there are six hydrogen atoms (pyrazole NH, CH_2SCH_3) available to exchange with the six aryl methyl group deuteriums, hence the very wide range of isotopologues observed, including D_9 and D_{10} species, where deuterium has been introduced into the side chain. Loss of an average of two deuterium atoms from the aryl methyls was accompanied by 0.76 and 0.4 average deuterium atom incorporation in the sulfide side chain, with the remaining ~0.8 deuterium presumably left as [$^2H_1$]*t*-butanol.

Solvents strongly affect base strength, with much lower basicities measured in protic solvents compared with aprotic solvents such as DMSO (the pK_a of t-butanol in water is 17.6[36]). Neither sodium methoxide in methanol nor sodium hydroxide in water is a strong enough base to deprotonate the aromatic methyl groups or the methylene next to sulfur, unless the sulfur exists as a sulfone. In contrast, potassium *t*-butoxide in dimethoxyethane is a much stronger base and can deprotonate species that methoxide or hydroxide (in methanol or water) cannot. While the pK_a of *t*-butoxide is comparable with both sulfones and tolunitriles and deprotonation would be expected, the acidity of the sulfide should be several pK_a units less acidic[14] and exchange should be more difficult, although it is possible that the delocalizing ability of the pyrazole ring has a stabilizing influence on the anion facilitating exchange.

Our results also clearly demonstrate the large difference in kinetic acidity between hydrogens next to a sulfone and those in a tolunitrile moiety, since methoxide or hydroxide is capable of exchanging the former, but not the latter. We ascribe this to the greater polarization of the relevant C–H bond when the carbon is directly bonded to an electron-deficient sulfur atom.

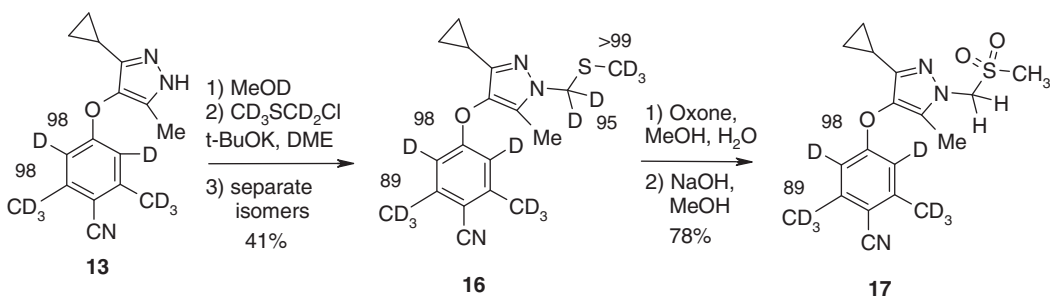
Regardless of the precise mechanism for the exchange, the only way to ensure that it did not take place was to remove all possible sources of exchangeable hydrogen (Scheme 5). Thus, the pyrazole NH of **13** was first exchanged with deuterium by stirring repeatedly with [$^2H_4$]methanol followed by evaporation of the solvent. Next, the alkylation step was performed with potassium *t*-butoxide as before, but with *per*-deuterated chloromethyl methyl sulfide, this time generated from commercial [$^2H_6$]dimethylsulfide, because we had greater confidence in handling the chlorinating agent (NCS vs 'silica chloride') and minimizing the adventitious water each might bring. The final precaution was to quench the reaction mixture with deuterium oxide. When this was carried out, we were pleased to discover that **16** was obtained with only a small loss of deuterium from the methyl groups, which we attribute to adventitious water in the reaction mixture. The percentage of incorporated deuterium at each site was ArD (98%), $ArCD_3$ (89%), NCD_2S (95%), SCD_3 (>99%).

Once we had successfully obtained **16**, all that remained was to remove the deuterium atoms from the side chain, and this was done by oxidation of the sulfone, as before, and treatment with sodium hydroxide in methanol at room temperature to give **17**. No change in the deuterium incorporation of the aromatic group was observed.

Experimental

General

Spectroscopic data were recorded on Finnigan Mat. Navigator (LRMS, either positive (ES^+) or negative (ES^-) electrospray mode), and Varian Unity Inova (^{1}H NMR 400 or 500 MHz, ^{13}C NMR 125 MHz, ^{2}H NMR 77 MHz) instruments and are consistent with the assigned structures. Combustion analyses were performed by Warwick Analytical Service, Coventry, UK. Accurate mass determinations for molecular ions were obtained using a commercially available Apex II Fourier Transform Mass Spectrometer (Bruker Daltonics, Inc. Billerica, MA, USA) equipped with a 4.7 Tesla, passively shielded, superconducting magnet and an electrospray ionization source (ESI), used in positive ion mode (Analytica of Branford, Branford, CT, USA) and calibrated using sodium trifluoroacetate. For accurate measurement of D_0:D_x ratios, a Sciex API 4000 double quadruple mass spectrometer was used under conditions of constant neutral fragment loss (to counteract the presence of high ion background). All reactions



Scheme 5. Successful labelling.

were conducted under a positive pressure of dry nitrogen unless stated otherwise. Anhydrous solvents were purchased from Sigma-Aldrich and used directly. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230–400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualized using uv light or 0.5% aqueous potassium permanganate solution. The following system was used for LCMS: Solvents: A: 0.1% formic acid in water, B: 0.1% formic acid in acetonitrile; Column: C_{18} phase Phenomenex Gemini, 50 × 4.6 mm, 5 μ; Gradient: 95–5% A over 3 min, 1 min hold, 1ml/min, detection by uv: 210–450 nm; temperature 50°C. The identity of deuterated analogues was confirmed by comparison with authentic samples of their unlabelled analogues.[6] Oxone® is a commercially available oxidising agent consisting of a mixture of potassium persulfate, hydrogen sulfate and sulfate. [$^2H_6$]DMSO (99.9 at% deuterium) was purchased from Cambridge Isotope Lab. Inc, Andover, MA, USA, [$^2H_6$]dimethylsulfide was purchased from Sigma-Aldrich. 4-Cyano-3,5-dimethylphenol (cat. no. 1915D, CAS 58537-99-8) was purchased from Apin Chemicals Ltd., Abingdon, Oxon, UK. Silica chloride was prepared as described in the literature.[37] CAUTION: Progesterone antagonists carry the risk phrases R60 (may impair fertility), R61 (may cause harm to the unborn child) and should be handled with care.

[$^2H_5$]Chloromethyl methyl sulfide, method A

[$^2H_6$]DMSO (5.0 ml, 70.7 mmol) was added to a suspension of silica chloride (40 g, 414 mmol active Cl) in dry dichloromethane (150 ml) under nitrogen at 20°C. The mixture was stirred for 1 h, filtered and the solution used directly. GCMS (Cl^+) *m/z* 101, 103 (M^+), 66 (base peak, M^+Cl).

Method B.[38] *N*-chlorosuccinimide (9.60 g, 72 mmol) was dissolved in dichloromethane (200 ml) under nitrogen and cooled to −10°C. A solution of [$^2H_6$]dimethylsulfide (4.90 g, 72 mmol) in dichloromethane (10 ml) was added between −10 and −6°C over 10 min. A white precipitate formed. The cooling bath was removed after 30 min, and the mixture allowed to warm to 20°C overnight. The solvent was distilled off at atmospheric pressure. The residue was stirred in pentane (100 ml), filtered to remove succinimide, and the solvent removed by distillation at atmospheric pressure. The residual oil (3.3 g, 45%) was assumed to be [$^2H_5$]chloromethyl methyl sulfide and was used directly.

^{2}H-Labelled 4-[3-cyclopropyl-1-(methanethiomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile (9)

Potassium *t*-butoxide (2.94 gm, 26.2 mmol) was added to a solution of **6** (3.50 g, 13.1 mmol) in anhydrous DME (40 ml) at 20°C, the mixture was stirred for 30 min. A solution of [$^2H_5$]chloromethyl methyl sulfide (prepared by Method A, 2M in dichloromethane, 26.2 mmol) was added and the mixture was stirred at 20°C for 36 h. Water (50 ml) was added, and the mixture was extracted three times with ethyl acetate. The combined organic solutions were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography, eluting with ethyl acetate: heptane = 10:90, gave **9** (2.30 g, 60%) and its *N*-5 alkylated isomer. δ_H (400 MHz, $CDCl_3$) 6.63 (2H, s, Ar-H), 5.01 (s, 0.8H, NCH_2S), 4.99 (br s, 0.4H, NCD*H*S), 2.47 (6H, s, 2 × $ArCH_3$), 2.16 (not integrated, s, coincident with SCH_3 peak of undeuterated isotopologue), 2.12 (3H, s, 2-CH_3), 1.59 (1H, m, cyclopropyl methine), 0.77 (4H, m, cyclopropyl methylenes).

^{2}H-Labelled 4-[3-cyclopropyl-1-(methanesulfonylmethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile (10)

A solution of compound **9** (1.66 g, 5.02 mmol) in a mixture of methanol (130 ml) and water (30 ml) was treated with Oxone® (6.30 gm) at 20°C for 4 h. The mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by recrystallization from a mixture of ethyl acetate/ether and heptane to afford **10** (977 mg, 54%). δ_H (400 MHz, $CDCl_3$) 6.63 (2H, s, Ar-H), 5.10 (s, 0.8H, NCH_2SO_2), 5.09 (br s, 0.4H, NCD*H*SO_2), 2.96 (s, ~0.02H, SO_2CH_3), 2.94 (br s, ~0.02H, SO_2CDH_2/SO_2CD_2H), 2.48 (6H, s, 2 × $ArCH_3$), 2.17 (3H, s, 2-CH_3), 1.62 (1H, m, cyclopropyl methine), 0.80 (4H, m, cyclopropyl methylenes). *m/z* (MH, relative abundance) 358 (D_0, 0.36%), 359 (5%), 360 (11%), 361 (44%), 362 (100%), 363 (4%).

Base-catalyzed deuteration of 1

Sodium hydride (190 mg, 60% oil dispersion, 4.75 mmol) was added to stirred [$^2H_4$]methanol (50 ml) under nitrogen with ice cooling. Once effervescence had ceased compound **1** (1.90 g, 5.29 mmol) was added in one portion. [$^2H_4$]Methanol (50 ml) was added and the solution was warmed briefly to obtain a solution. The mixture was stirred at 20°C overnight, then warmed to 50°C for 30 min. After being cooled to room temperature, the solution was added to 4M D_2SO_4 in D_2O to produce a precipitate. Most of the methanol was removed under reduced pressure and the residue was treated with water (100 ml) and stirred for 30 min. The solid was collected by filtration and dried under vacuum at 55°C to give **11** (1.90 g, 98%) as a white solid. δ_H (400 MHz, $CDCl_3$) 6.63 (2H, s, Ar-H), 5.09 (s, 0.015H, NCD*H*SO_2), 2.94 (br s, 0.015H, SO_2CD_2H), 2.48 (6H, s, 2 × $ArCH_3$), 2.17 (3H, s, 2-CH_3), 1.62 (1H, m, cyclopropyl methine), 0.80 (4H, m, cyclopropyl methylenes).

[$^2H_8$]4-Cyano-3,5-dimethylphenol, (12)

A mixture of 4-cyano-3,5-dimethylphenol (**4**) (5.0 g, 34 mmol) and platinum oxide (1.0 g, 4.4 mmol) in deuterium oxide (200 ml) was placed in a 400 ml stainless steel autoclave and heated with stirring in a sand bath at approximately 230°C for 48 h. The mixture was cooled, and the contents of the vessel stirred with dichloromethane (1.1 L) for 15 min. The mixture was filtered through Arbocel filter aid and the filter cake rinsed with dichloromethane (100 ml). The filtrate phases were separated, and the organic layer washed with water (2 × 500 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was dissolved in 0.7M aqueous sodium hydroxide and washed with ether (100 ml). The aqueous solution was acidified with an excess of 12M hydrochloric acid and extracted with ethyl acetate (100 ml). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give **12** (4.23 g, 84%) as a pale brown solid. δ_H (undeuterated, 500MHz, $CDCl_3$) 6.59 (s, 2H), 5.66 (br s, 1H), 2.47 (s, 6H). δ_H (deuterated, 400 MHz, $CDCl_3$) 6.52 (s, 0.03H), 5.39 (br s, 1H), 2.37 (m, 0.16H). δ_C (undeuterated, 125 MHz, $CDCl_3$) 158.9, 144.7, 117.7, 114.6, 105.2, 20.8. δ_C (deuterated, 125 MHz, $CDCl_3$) 160.6, 143.8, 118.3, 114.6 (t, *J* 24.4 Hz), 103.5, 19.9 (septet, *J* 19.5 Hz). δ_D (deuterated,

77 MHz, $CHCl_3$) 6.63 (s, 2D), 2.44 (s, 6D). *m/z* (ES^-) (MH, relative abundance) 152 (6%), 153 (32%), 154 (100%), 155 (6.4%).

4-[3-Cyclopropyl-5-methyl-1*H*-pyrazol-4-yl]oxy-[$^2H_6$]2,6-dimethyl-[3,5-^{2}H]benzonitrile (13)

A solution of chlorotrimethylsilane (3.60 g, 33 mmol) in anhydrous dichloromethane (5 ml) was added to a solution of 1-cyclopropylbutan-1,3-dione (4.18 g, 33.1 mmol) in anhydrous dichloromethane (25 ml) at 0°C. After being stirred for 30 min at 0–5°C, a solution of *N*-chlorosuccinimide (4.78 g, 30.8 mmol) in anhydrous dichloromethane (110 ml) was added over 1 h, keeping the reaction temperature at 0–2 C. The mixture was stirred for an additional 1.5 h at this temperature and then allowed to warm to 15°C. The solution was washed with 2M aqueous hydrochloric acid (2 × 25 ml), water (2 × 25 ml) and brine (30 ml). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give 2-chloro-1-cyclopropylbutan-1,3-dione **3** (5.1 g, 95%) as an orange oil. Crude **3** was then dissolved in acetonitrile (10 ml) and added over 50 min to a solution of **12** (4.78 g, 30.8 mmol) and ethyldiisopropylamine (4.0 g, 30.9 mmol) in acetonitrile (50 ml) at reflux. The mixture was heated at reflux for 17 h, cooled and the solvent removed under reduced pressure. Isopropanol (35 ml) was added to the residue and the mixture stirred for 1 h at 0–5°C. The resulting solid was collected by filtration, washed with isopropanol (20 ml), and dried under vacuum at 40°C to give 1-(cyclopropyl)-2-(4-cyano-[$^2H_6$]3,5-dimethyl-[2,6-^{2}H]phenoxy)-1,3-butanedione (5.10 g, 55%), as a cream-coloured solid.

The dione (5.10 g, 18.3 mmol) was suspended in a mixture of ethanol (25 ml) and acetic acid (1.05 ml, 18.3 mmol) and hydrazine hydrate (1.06 ml, 18.3 mmol) was added over 10 min, keeping the reaction temperature below 30°C. After 40 min, water (25 ml) was added dropwise over 5 min, followed by more water (50 ml) over 15 min. The resulting suspension was stirred for 1 h, and the solid collected by filtration. The solid was dried *in vacuo* at 55°C overnight to give **13** (4.89 g, 97%). δ_H (400 MHz, $CDCl_3$) 9.53 (br s, 1H, N*H*), 6.64 (0.03H, Ar*H*), 2.44 (m, 0.16H, ArC*H*D_2), 2.08 (s, 3H, 2-Me), 1.66 (m, 1H, cyclopropyl methine), 0.80 (m, 4H, cyclopropyl methylenes). LCMS: R_t = 3.03 min *m/z* (ES^+) M+H (relative abundance) 274 (3.5%), 275 (64%), 276 (D_8, 100%), 277 (70%), 278 (11%).

[$^2H_9$]4-[3-Cyclopropyl-1-(methanethiomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile ([$^2H_9$]14)

A solution of **13** (5.60 gm, 20.3 mmol) in anhydrous DME (20 ml) was added over 10 min to potassium *t*-butoxide (4.56 gm, 40.7 mmol) in anhydrous DME (20 ml) with cooling using an ice-water bath. The mixture was stirred for 45 min at room temperature. A solution of chloromethyl methyl sulfide (3.93 gm, 40.7 mmol) in anhydrous DME (20 ml) was added over 90 min, and the mixture was stirred at 20°C for 120 min. The reaction mixture was worked up as for **9**. A part of the crude product (1.1 g) was purified by flash chromatography eluting with heptane:EtOAc = 90:10 to give **[$^2H_9$]14** (490 mg). δ_H (400 MHz, $CDCl_3$) 6.65 (s, 0.03H, ArH), 5.01 (s, 1.26H, NCD*H*S), 2.46 (m, 2.0H, ArCD_2*H*), 2.16 (s, 2.6H, SCH_3), 2.13 (s, 3H, 2-CH_3), 1.61 (m, 1H, cyclopropyl methine), 0.79 (m, 4H, cyclopropyl methylenes). LRMS showed a range of masses from D_0 to D_{10}, peaking at D_9, however the D_0:D_9 ratio was 1.15%.

This material was converted to the sulfone **15** by treatment with Oxone®, followed by sodium hydroxide, as described below. δ_H (400 MHz, $CDCl_3$) 6.64 (0.04H, s, Ar-H), 5.10 (s, 2H, NC*H*$_2$$SO_2$), 2.96 (s, 3H, SO_2CH_3), 2.45 (2.0H, m, 2 × ArC*H*D_2), 2.17 (3H, s, 2-CH_3), 1.62 (1H, m, cyclopropyl methine), 0.80 (4H, m, cyclopropyl methylenes). *m/z* (M+H, relative abundance) 360 (0.64%), 361 (0.59%), 362 (5.8%), 363 (23%), 364 (45%), 365 (62%), 366 (68%), 367 (78%), 368 (100%), 369 (24%), 370 (1.1%).

Exchange experiments with compounds 6 and 8

In two separate flasks, compound **6** (47 mg, 0.18 mmol) and compound **8** (57 mg, 0.18 mmol) were treated with a mixture of potassium *t*-butoxide (58 mg, 0.54 mmol) and [$^2H_1$]*t*-butanol (50 µl, 0.54 mmol) in anhydrous DME (0.7 ml) under nitrogen at 20°C for 3.5 h. The mixture was quenched by the addition of 2N hydrochloric acid (1 ml), and worked up as before. The compounds were recovered in ~95% yield.

For compound **6**: NMR (400 MHz, $CDCl_3$) showed hydrogen content unchanged in all positions except the aromatic methyl groups (δ_H 2.44) that integrated for 91% of theory compared with the other signals. LCMS: R_t = 3.00 min, *m/z* (ES^+) M+H (relative abundance) 268 (D_0, 100%), 269 (43%), 270 (15.5%), 271 (5%). For compound **8**: NMR (400 MHz, $CDCl_3$) showed hydrogen content unchanged in all positions except the aromatic methyl groups (δ_H 2.47) that integrated for 73% of theory compared with the other signals. LCMS R_t = 3.47 min, *m/z* (ES^+) M+H (relative abundance) 328 (D_0, 28%), 329 (81%), 330 (100%), 331 (74%), 332 (34%), 333 (12%); M–SCH_3 (relative abundance) 280 (D_0, 31%), 281 (85%), 282 (100%), 283 (71%), 284 (31%), 285 (8%).

4-[3-Cyclopropyl-5-methyl-1^2*H*-pyrazol-4-yl]oxy-[$^2H_6$]2,6-dimethyl-[3,5-^{2}H]benzonitrile (13)

Compound **13** (4.89 g) was dissolved in dichloromethane (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in [$^2H_1$]methanol (33 ml), stirred for 10 min and the solvent removed under reduced pressure. This procedure was repeated twice more. The residue was dried under vacuum at 55°C to give **[$^2H_9$]13**. δ_H (400 MHz, $CDCl_3$) 9.50 (br s, 1H), 6.65 (s, 0.03H), 2.44 (m, 0.28H), 2.08 (s, 3H), 1.66 (m, 1H), 0.80 (m, 4H). δ_C (100 MHz, $CDCl_3$) 161.7 (*C*-O, Ar), 144.5 (C-CD_3), 141.2 (br, *C*-C_3H_5, broad due to exchange), 135.8 (br, *C*-CH_3, broad due to exchange), 133.3 (*C*-CN), 117.6 (*C*-O, pyrazole), 113.9 (t, *J* 22 Hz, *C*-D, Ar), 106.6 (*C*N), 20.5 (pentet, *J* 19 Hz, Ar*C*HD_2), 20.2 (septet, *J* 20 Hz, Ar*C*D_3), 9.70 (*C*H_3), 6.51 (*C*H_2*C*H_2), 6.25 (cyclopropyl *C*H). LCMS: R_t = 3.59 min, *m/z* (ES^+) M+H (relative abundance) 274 (9.5%), 275 (46%), 276 (100%), 277 (33%), 278 (5%). Found: C, 69.61; H, 6.26; N, 15.24; $C_{16}H_8D_9N_3O$ requires C, 69.54; H, 6.20; N, 15.20%.

[$^2H_7$]4-[3-Cyclopropyl-1-(methanethiomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-2,6-dimethylbenzonitrile ([$^2H_7$]14)

A solution of **[$^2H_9$]13** (250 mg, 0.91 mmol) in anhydrous DME (1 ml) was added over 3 min to potassium *t*-butoxide (204 mg, 1.82 mmol) in anhydrous DME (1 ml) with cooling using an ice-water bath. The mixture was stirred for 45 min at room temperature. A solution of chloromethyl methyl sulfide (176 mg, 1.82 mmol) in anhydrous DME (2 ml) was added over 75 min, and the mixture was stirred at 20°C for 20 min. Deuterium oxide (2 ml) was added, and the mixture was extracted with ethyl acetate (8 ml). The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was analyzed by LCMS: the peak

corresponding to **[^{2}H$_7$]14** (R_t = 3.69 min) showed a range of masses D_3–D_{10}; LRMS *m/z* (M–SCD_3, relative abundance) 283 (12%), 284 (47%), 285 (85%), 286 (87%), 287 (100%), 288 (86%), 289 (45%), 290 (14%), 291 (2%); (M+H, relative abundance) 331 (7%), 332 (26%), 333 (51%), 334 (92%), 335 (100%), 336 (74%), 337 (45%), 338 (17%).

4-[3-Cyclopropyl-1-([^{2}H$_5$]methanethiomethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-[^{2}H$_6$]2,6-dimethyl-[3,5-^{2}H]benzonitrile (16)

A solution of **[^{2}H$_9$]13** (1.77 g, 6.43 mmol) in anhydrous DME (6 ml) was added over 10 min to potassium *t*-butoxide (1.44 g, 12.9 mmol) in anhydrous DME (6 ml) with cooling using an ice-water bath. The mixture was stirred for 45 min at room temperature. A solution of [^{2}H$_5$]chloromethyl methylsulfide (prepared from [^{2}H$_5$]dimethylsulfide, 1.31 g, 12.9 mmol as described above) in anhydrous DME (6 ml) was added over 140 min, and the mixture was stirred at 20°C for 100 min. Deuterium oxide (10 ml) was added, and the mixture was extracted with ethyl acetate (2 × 30 ml). The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography, eluting with ethyl acetate: heptane = 10:90 then 25:75 gave **[^{2}H$_{13}$]16** (900 mg, 41%) and its *N*-5 alkylated isomer (550 mg, 25%). δ_H (400 MHz, $CDCl_3$) 6.65 (s, 0.017H, ArH), 5.01 (br s, 0.1H, NCD*HS*), 2.46 (m, 0.33H, $ArCD_2H$), 2.13 (s, 3H), 1.61 (m, 1H), 0.79 (m, 4H). LRMS *m/z* (M–SCD_3, relative abundance) 287 (7%), 288 (41%), 289 (90%), 290 (100%), 291 (44%), 292 (6%); (M+H, relative abundance) 339 (16%), 340 (61%), 341 (100%), 342 (25%), 343 (7%).

4-[3-Cyclopropyl-1-(methanesulfonylmethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy-[^{2}H$_6$]2,6-dimethyl-[3,5-^{2}H]benzonitrile (17)

A solution of compound **16** (900 mg, 2.64 mmol) in a mixture of methanol (70 ml) and water (16 ml) was treated with Oxone® (3.40 gm) at 20°C for 4 h. The mixture was filtered and the filter cake was washed with methanol (2 × 20 ml). The filtrate was treated with aqueous sodium hydroxide (10 M, 27 ml) at 20°C for 21 h. The mixture was concentrated under reduced pressure. Water (100 ml) was added and the mixture extracted with dichloromethane (2 × 100 ml). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was stirred with isopropanol (8 ml) for 1 h to produce a solid, which was collected by filtration. This gave **17** (700 mg, 78%). δ_H (400 MHz, $CDCl_3$) 6.64 (0.04H, s, Ar-H), 5.10 (s, 2H, NCH_2SO_2), 2.96 (s, 3H, SO_2CH_3), 2.45 (0.07H, m, 2 × $ArCHD_2$), 2.17 (3H, s, 2-CH_3), 1.62 (1H, m, cyclopropyl methine), 0.80 (4H, m, cyclopropyl methylenes). δ_D (77 MHz, $CHCl_3$) 6.69 (s, 2D), 2.46 (s, 6D). δ_C (125 MHz, $CHCl_3$) 161.0 (*C*-O, Ar), 148.5 (*C*-C_3H_5), 144.5 (C-CD_3), 134.6 (*C*-O, pyrazole), 133.1 (*C*-CH_3), 117.3 (*C*N), 113.7 (t, *J* 25 Hz, *C*-D, Ar), 107.1 (*C*-CN), 67.7 (NCH_2SO_2), 40.1 (CH_3SO_2), 20.4 (pentet, *J* 20 Hz, $ArCHD_2$), 20.1 (septet, *J* 19 Hz, $ArCD_3$), 8.8 (CH_3), 7.4 (CH_2CH_2), 6.8 (cyclopropyl *C*H). *m/z* (M+H, relative abundance) 360 (0%), 361 (0.01%), 362 (0.01%), 363 (0.03%), 364 (0.13%), 365 (1.1%), 366 (9.4%), 367 (47%), 368 (100%), 369 (20%), 370 (2%). HRMS *m/z* Found: 368.1884, $C_{18}H_{13}D_8N_3O_3S$ (M+H) requires 368.1892. Found: C, 58.72; H, 5.73; N, 11.38; $C_{18}H_{13}D_8N_3O_3S$ requires C, 58.83; H, 5.76; N, 11.43%.

Conclusions

We have described two strategies for the preparation of deuterated **1**. The simpler method, labelling the sulfone-containing substituent by base-catalyzed exchange, does not give a material that survived the clinical assay conditions without unacceptable loss of deuterium. This result suggests that deuterium labelling of pharmaceutical drug candidates adjacent to a sulfonyl group should be avoided. Labelling of the aromatic portion of **1** was readily achieved by platinum-catalysis. However, the deuterium atoms on the aromatic methyl groups were labile under the conditions of the pyrazole alkylation step. To prevent loss of deuterium, all sources of exchangeable hydrogen were removed. Once satisfactory labelling had been achieved in the preparation of **16**, selective exchange of the side chain deuterium atoms for hydrogen was used to prepare **17**, which possessed an acceptable D_0/D_8 ratio.

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