Note

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Synthetic approaches to site selective deuterium incorporation in a novel CRTh2 receptor antagonist clinical candidate

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Selection of acidic or basic reaction conditions, combined with appropriate temperatures, allowed for site selective direct incorporation of deuterium at multiple positions in the 7-azaindole-3-acetic acid CRTh2 receptor antagonist clinical candidate NVP-QAV680.

Keywords: selective deuteration; clinical candidate; CRTh2 antagonist; D_2O

Introduction

NVP-QAV680 (Scheme 1, **1**) has been recently disclosed as a novel clinical candidate CRTh2 receptor antagonist for the treatment of allergic diseases.[1] During the development of **1**, the requirement arose for preparation of site selectively deuterated analogues. Deuteration of simple aryl acetic acids has been reported under both basic and acidic conditions.[2–4] Seeking a flexible approach and encouraged by these literature reports, we elected to explore direct deuteration of the parent compound. These efforts uncovered some interesting aspects of selectivity, which are disclosed in the following note.

Results and discussion

We adopted the reported basic thermal conditions[2] and employed K_2CO_3 as base under microwave irradiation (Scheme 1). As expected, based on the acidity of the sulfone moiety, treatment under these conditions gave good conversion to the CD_3SO_2 analogue **2**. Increasing temperature then led to additional exchange at the N-1 CH_2 group to give **3**, although small amounts of exchange α- to the carboxylic acid were evident irrespective of whether three or four equivalents of base were employed. Treatment of **3** under protic basic conditions at lower temperature afforded **4**, albeit with some loss of isotopic purity at N-1 CD_2. Further increase of temperature and base equivalents then exchanged the C-3 CH_2 moiety more efficiently to provide **5**. With prolonged reaction times, C-2 methyl exchange also became evident, although when additional base was added to drive this process further, concurrent partial deuteration on the phenyl sulfone aromatic ring occurred, providing **6**. Application of more forcing conditions was limited by the maximum working pressure of the microwave reactor.

Next, we explored exposure of **1** to acidic deuteration conditions recently described for the arylacetic acid diclofenac[4] (Scheme 2). As expected, C-3 CH_2 exchange occurred, however, deuteration of the C-2 methyl group was a concurrent process, affording **7** in excellent isotopic purity.

Finally, we sought to exploit the reported method for catalytic deuteration of carboxylic esters α- to the carbonyl.[5] In our hands, stoichiometric triazabicyclo[4.4.0]dec-5-ene was required to drive complete exchange of **8** to give **9**. Basic hydrolysis with NaOH in THF/MeOH led to some protic exchange; however, treatment with NaOD in MeOD gave clean conversion to **10**, thus providing a complementary product to those accessible through direct acid or base promoted deuteration of **1** (Scheme 3).

Conclusion

Choice of appropriate acidic or basic reaction conditions allowed for site selective direct incorporation of deuterium into the CRTh2 receptor antagonist NVP-QAV680. In addition, use of the methyl ester as a deuteration precursor allowed access to an additional deuterated analogue not directly accessible from the acid itself. Taken together, these three methods provide flexible methodology for aliphatic deuteration of this clinical candidate molecule. The reaction conditions reported herein are also applicable to analogous CRTh2 antagonists derived from the 7-azaindole-3-acetic acid scaffold.[6]

Experimental section

General considerations

Compounds **1** and **8** were prepared as described previously.[1] Microwave reactions were conducted in a Biotage Initiator instrument. LCMS were recorded using an Agilent 1100 LC system with Waters Xterra MS C18 4.6 × 100 5μM column, eluting for 10 min with gradient of 5–95% MeCN in water (10 mM ammonium bicarbonate or 0.1% trifluoroacetic acid

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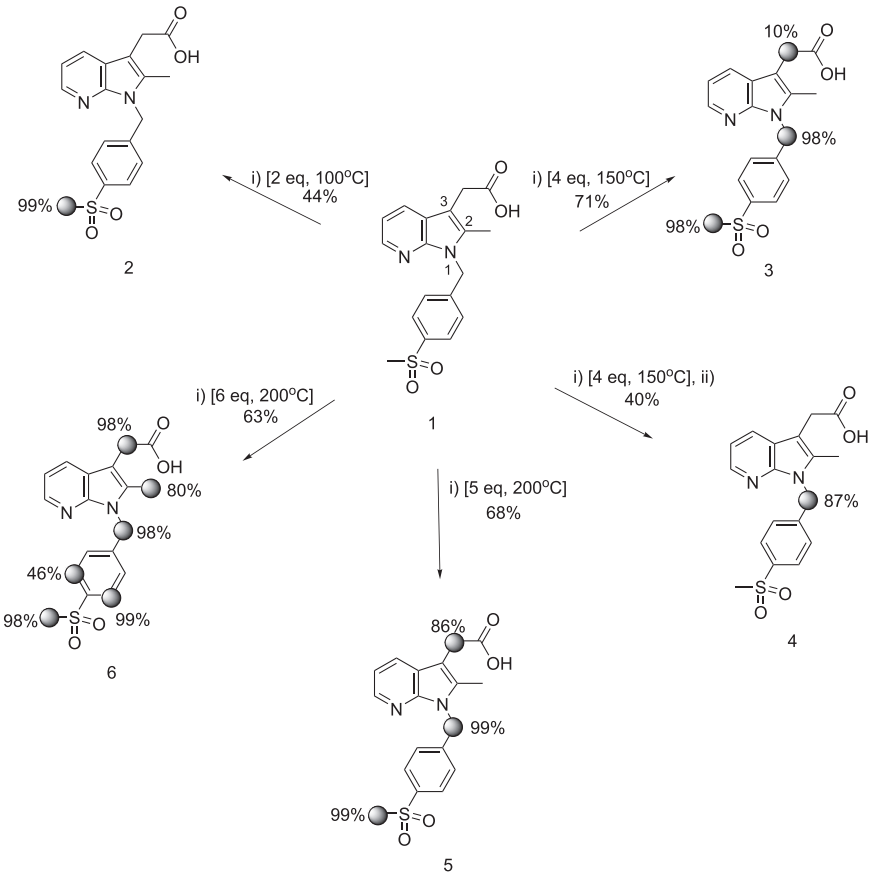
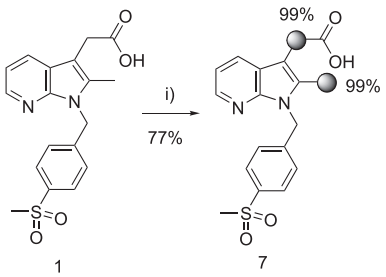


Scheme 1. Base promoted deuteration reactions of **1**. Reagents and conditions: i) K_2CO_3, D_2O, microwave [K_2CO_3 equivalents and temperature]; ii) K_2CO_3 (2 eq), H_2O, 100°C microwave. Isotopic incorporation as determined by ^{1}H NMR denoted in italics.

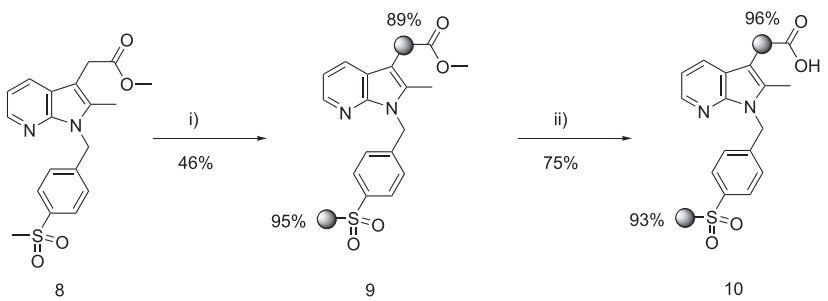
used as buffer). Preparative liquid chromatography was conducted on an ISCO CombiFlash Rf instrument. All final compounds were purified to ≥95% chemical purity as determined by HPLC with UV detection at 254 and 220 nm, together with ELSD. All ^{1}H NMR spectra were obtained on a Bruker AV400 operating at 400 MHz respectively, at 298 K.



Scheme 2. Acid promoted deuteration of **1**. Reagents and conditions: i) DCl-D_2O, 160°C, microwave. Isotopic incorporation as determined by ^{1}H NMR denoted in italics.

2-(2-Methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid ***2***

2-(2-Methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetic acid (30 mg, 0.084 mmol) and K_2CO_3 (23 mg, 0.166 mmol) were dissolved in D_2O (2 mL) in a microwave vial and irradiated at 100°C for 1 h. The reaction mixture was acidified to pH 5 with AcOH, and the resultant precipitate collected by filtration, washed with water and dried in vacuo to afford 2-(2-methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **2** as a white solid (14 mg, 44%). >99% CD_3SO_2- incorporation based on ^{1}H NMR integration. ^{1}H NMR (DMSO-d_6): 2.31 (3H, s), 3.68 (2H, s), 5.63 (2H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.25 (1H, s(br)). $[M+H]^+$ = 362.50.



Scheme 3. Base promoted deuteration of **8**. Reagents and conditions: i) Triazabicyclo[4.4.0]dec-5-ene, CDCl3, RT; ii) aq NaOD, THF-MeOD, RT. Isotopic incorporation as determined by ^{1}H NMR denoted in italics.

2-(1-(Dideutero(4-((trideuteromethyl)sulfonyl)phenyl)methyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid ***3***

2-(2-Methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetic acid (30 mg, 0.084 mmol) and K_2CO_3 (46.5 mg, 0.336 mmol) were dissolved in D_2O (2 mL) in a microwave vial and irradiated at 150°C for 1 h (four bar pressure). The reaction mixture was acidified to pH 5 with AcOH, and the resultant precipitate collected by filtration, washed with water and dried in vacuo to afford 2-(1-(dideutero(4-((trideuteromethyl) sulfonyl)phenyl)methyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid **3**, as a white solid (23 mg, 72%). 98% CD_3SO_2-, 98% -NCD_2- and 10% -CD_2CO_2H incorporation based on ^{1}H NMR integration. ^{1}H NMR (DMSO-d_6): 2.31 (3H, s), 3.68 (1.8H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.27 (1H, s(br)). $[M+H]^+$ = 364.50, 366.50.

2-(1-(Dideutero(4-(methylsulfonyl)phenyl)methyl)-2-methyl-1H-pyrrolo [2,3-b]pyridin-3-yl)acetic acid ***4***

2-(2-Methyl-1-(4-(trideuteromethylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **3** (20 mg, 0.055 mmol) and K_2CO_3 (15 mg, 0.109 mmol) were dissolved in water (1.5 mL) in a microwave vial and irradiated at 100°C for 1 h. The reaction mixture was acidified to pH 5 with AcOH, and the resultant precipitate collected by filtration, washed with water and dried in vacuo to afford 2-(1-(dideutero(4-(methylsulfonyl)phenyl)methyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **4** as a white solid (13 mg, 41%); 88% -NCD_2- incorporation based on ^{1}H NMR integration. ^{1}H NMR (DMSO-d_6): 2.31 (3H, s), 3.17 (3H, s), 3.68 (2H, s), 5.63 (0.24H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5). $[M+H]^+$ = 361.30.

2-(1-(Dideutero(4-((trideuteromethyl)sulfonyl)phenyl)methyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid ***5***

2-(2-Methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetic acid **3** (30 mg, 0.084 mmol) and K_2CO_3 (34 mg, 0.246 mmol) were dissolved in D_2O (2 mL) in a microwave vial and irradiated at 150°C for 1 h (six bar pressure). NMR analysis of the reaction mixture indicated the presence of **4**. Further, K_2CO_3 (22 mg, 0.168 mmol) was added and the solution irradiated at 200°C for 1 h (12 bar pressure). The cloudy solution was filtered through a plug of glass wool and acidified to pH 4 with AcOD. The precipitate was collected by filtration, washed with water and dried in vacuo to afford 2-(1-(dideutero(4-((trideuteromethyl)sulfonyl)phenyl) methyl)-2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid **5** as a white solid (21 mg, 68%); 99% CD_3SO_2-, 99% -NCD_2- and 86% -CD_2CO_2H incorporation based on ^{1}H NMR integration. ^{1}H NMR 2.31 (3H, s), 3.68 (0.28H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.28 (1H, s(br)). $[M+H]^+$ = 366.40.

2-(1-(Dideutero(3-deutero-4-((trideuteromethyl)sulfonyl)phenyl)methyl)-2-(trideuteromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid ***6***

2-(2-Methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid (29 mg, 0.081 mmol) and K_2CO_3 (68 mg, 0.492 mmol) were dissolved in D_2O (1 mL) in a microwave vial and irradiated at 200°C for 18 h. The dense slurry was diluted with water (5 mL), filtered through a plug of glass wool and acidified to pH 4 with AcOH. The precipitate was collected by filtration, washed with water and dried in vacuo to afford 2-(1-(dideutero(3,5-dideutero-4-((trideuteromethyl)sulfonyl)phenyl)methyl)-2-(trideuteromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)-2,2-dideuteroacetic acid as a white solid (20 mg, 63%); 98% CD_3SO_2-, 98% -NCD_2-, 98% -CD_2CO_2H, 80% 2-CD_3, 99% Ar-3-D and 46% Ar-3,5-D_2 incorporation based on ^{1}H NMR integration. ^{1}H NMR 2.31 (0.6H, m), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (0.53H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.28 (1H, s(br)). $[M+H]^+$ = 371.40.

2,2-Dideutero-2-(1-(4-(methylsulfonyl)benzyl)-2-(trideuteromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid ***7***

2-(2-Methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl) acetic acid (50 mg, 0.140 mmol) in 35% DCl (0.8 mL) and D_2O (0.1 mL) was irradiated at 160°C (seven bar) in a microwave vial for 7 h. The reaction mixture was dilued with water (5 mL) and carefully adjusted to pH 7 with saturated $NaHCO_3$. The resultant precipitate was washed with water and dried in vacuo to afford 2,2-dideutero-2-(1-(4-(methylsulfonyl)benzyl)-2-(trideuteromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **7** (41 mg, 77%) as a white solid; 99% -CD_2CO_2H, 99% 2-CD_3 incorporation based on ^{1}H NMR integration. ^{1}H NMR 3.17 (3H, s), 5.63 (2H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.23 (1H, s(br)). $[M+H]^+$ = 366.40.

2,2-Dideutero-2-(2-methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid ***10***

Methyl 2-(2-methyl-1-(4-(methylsulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate **8** (100 mg, 0.269 mmol) was added to a solution of triazabicyclo[4.4.0]dec-5-ene (75 mg, 0.537 mmol) in $CDCl_3$ (0.75 mL). The reaction was stirred at room temperature for 2 days then loaded directly on to a 4 g isolute™ silica column and eluted with 20%-100% EtOAc-isohexanes gradient to afford 66 mg clear colourless glass. ^{1}H NMR analysis indicated 79% incorporation of -CD_2CO_2Me and 78% incorporation of CD_3SO_2-. The product was taken into $CDCl_3$ (0.75 mL), triazabicyclo[4.4.0]dec-5-ene (25 mg, 0.179 mmol) added and the reaction stirred at room temperature for 3 days. The reaction mixture was loaded directly on to a 4 g Isolute™ silica column and eluted with 20%-100% EtOAc-isohexanes gradient to afford methyl-2,2-dideutero-2-(2-methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate **9** (47 mg, 46%) as pale yellow glass; 89% -CD_2CO_2Me and 95% CD_3SO_2- incorporation based on ^{1}H NMR integration.. ^{1}H NMR ($CD Cl_3$) 2.34 (3H, s), 3.03 (0.15H, s), 3.71 (3H, s), 3.75 (0.22H, s), 5.62 (2H, s), 7.12 (1H, dd, J = 7.7, 4.8), 7.25 (2H, d, J = 8.0), 7.86 (2H, d, J = 8.0), 7.91 (1H, d, J = 7.8), 8.27 (1H, d, J = 4.7).

Methyl-2,2-dideutero-2-(2-methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate **9** (29 mg, 0.077 mmol) was dissolved in THF (0.4 mL) and MeOD (0.4 mL) at room temperature. 1M NaOD in D_2O (0.1 mL, 0.1 mmol) was added and the reaction stirred overnight. The solvent was evaporated, the residue dissolved in water (2 mL) and acidified to pH5 with AcOD. The resultant white solid was collected by filtration, washed with water and dried in vacuo to afford 2,2-dideutero-2-(2-methyl-1-(4-((trideuteromethyl)sulfonyl)benzyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetic acid **10** (22 mg, 75%); 93% CD_3SO_2- and 96% CD_2CO_2H incorporation based on ^{1}H NMR integration. 2.31 (3H, s), 3.17 (0.21H, s), 3.68 (0.08H, s), 5.63 (2H, s), 7.10 (1H, dd, J = 7.7,4.6), 7.31 (2H, d, J = 8.4), 7.86 (2H, d, J = 8.4), 7.90 (1H, d, J = 7.7), 8.18 (1H, d, J = 4.5), 12.30 (1H, s(br)). $[M+H]^+$ = 364.40.

Conflict of Interest

The author did not report any conflict of interest.

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