Efficient Synthesis of 4-(3-Fluoro-5-{[4-(2-methyl-1*H*-imidazol-1-yl)benzyl]-oxy}phenyl)tetrahydro-2*H*-pyran-4-carboxamide, a Novel 5-Lipoxygenase Inhibitor

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Abstract: An efficient synthesis of **1**, a novel orally active 5-lipoxygenase inhibitor, was developed. Key features of the modified synthetic route include facile construction of the benzyl phenyl ether moiety by nucleophilic aromatic substitution and THP ring by cyclization, and base-promoted hydrolysis of the nitrile group to carboxamide. The improved three-step synthesis provides 25 g of **1** for pre-clinical toxicology studies in a total yield of 59%.

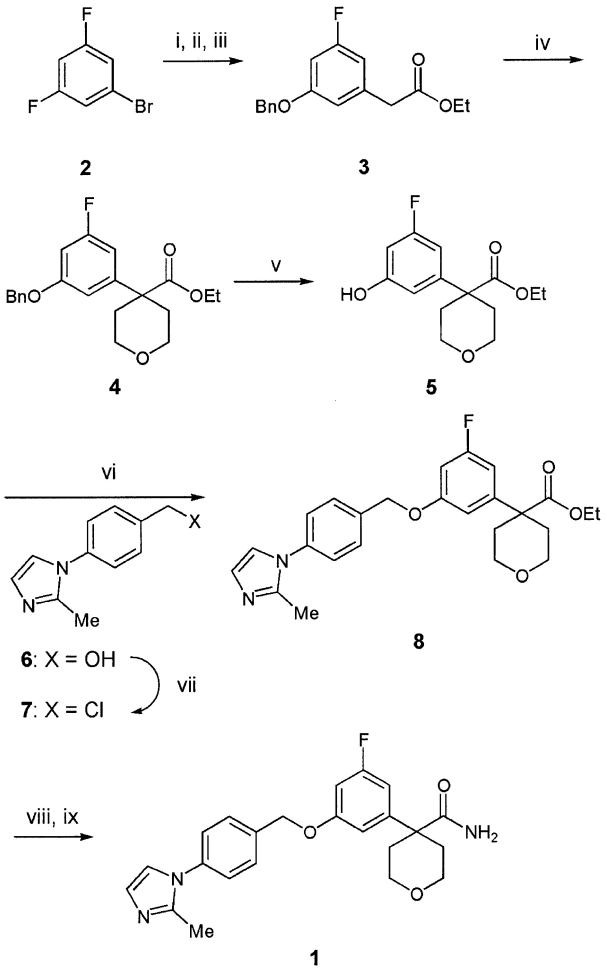
Key words: amides, cyclizations, drugs, nitriles, nucleophilic aromatic substitutions

The leukotrienes (LTs) are potent endogenous mediators with biological activity, and play important roles in a wide range of disease events. 5-Lipoxygenase (5-LO) is the key enzyme in LT biosynthesis and catalyses the initial steps in conversion of arachidonic acid to LTs.[1–3] We have reported on structure–activity relationship (SAR) studies leading to **1**, a novel orally active 5-LO inhibitor as an anti-inflammatory drug.[4,5] The original discovery synthetic route of **1** was lengthy and low yielding (1.3% overall). In this paper, we present an efficient synthetic route amenable to large scale preparation of **1**.

Scheme 1 illustrates the discovery synthesis of **1**. This synthetic route was considered not to be amenable to bulk preparation of **1** due to: (i) the inefficient and low yield synthesis of a-phenyl acetic acid ester **3** from **2** (7.2%), (ii) protection/deprotection steps on route to imidazole benzyl ether **8**, (iii) an inefficient stepwise conversion of the ethyl ester **8** to carboxamide **1**, (iv) required column chromatography purification of most intermediates, and (v) the inherent poor overall yield (1.3%).

Our revised retro-synthesis to **1** is outlined in Scheme 2. We envisaged: (i) a facile one-step synthesis of **1** from precursor **9** (i.e., direct conversion of X to carboxamide); (ii) ether formation by nucleophilic displacement of imidazole benzyl alcohol **6** to the central phenyl ring, and (iii) use of a starting material which would allow facile construction on the THP ring and carboxamide moiety.

Scheme 3 shows the improved synthesis of **1**. Commercially available (3,5-difluorophenyl)acetonitrile (**12**) was chosen as starting material since the nitrile group would act as a 'masked' amide and would also allow for THP ring construction, while fluorobenzene is known to be susceptible to displacement by nucleophiles. Firstly, we investigated the THP ring formation from **12** and bis(2-chloroethyl)ether. Reaction conditions for the cyclization investigated included base, solvent,[6–8] additive such as so-



Scheme 1 (i) $PhCH_2OH$, NaH, DMA, 120 °C (37%); (ii) diethyl malonate, NaH, CuBr, dioxane, reflux (34%); (iii) LiCl, H_2O, DMSO, reflux (57%); (iv) $(ClCH_2CH_2)_2O$, NaH, NaI, 15-crown-5, DMF, r.t. (58%); (v) H_2, Pd–C, EtOH, r.t. (quant.); (vi) **7**, K_2CO_3, DMF, 120 °C (61%); (vii) $SOCl_2$, r.t., CH_2Cl_2 (quant.); (viii) LiOH, H_2O, MeOH, THF, reflux (96%); (ix) CH_2Cl_2, $(COCl)_2$, 0 °C/r.t., then NH_3, r.t. (54%).

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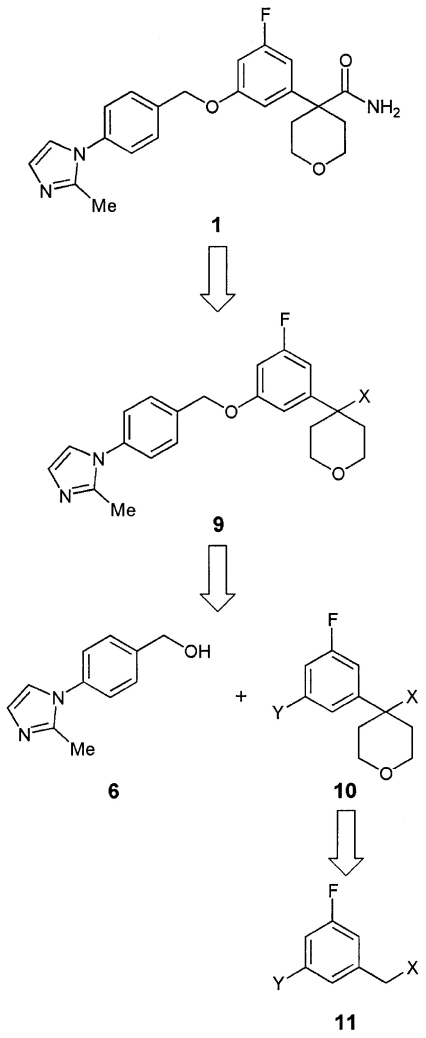
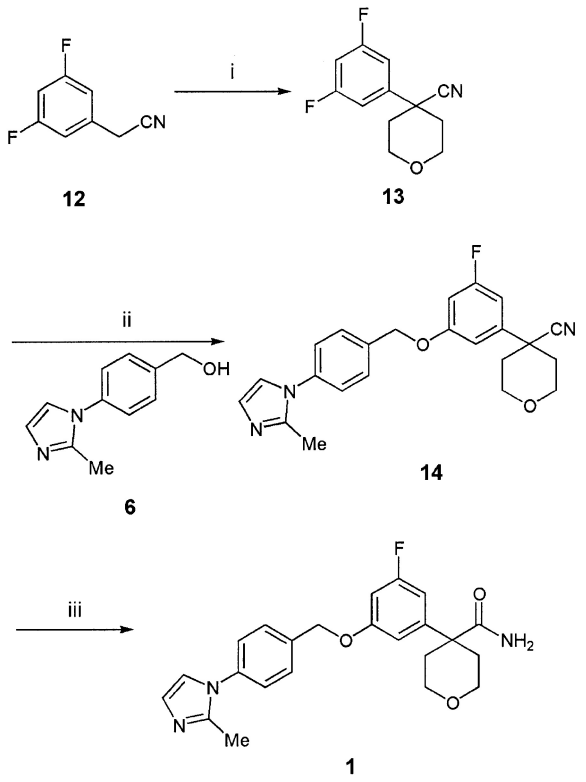


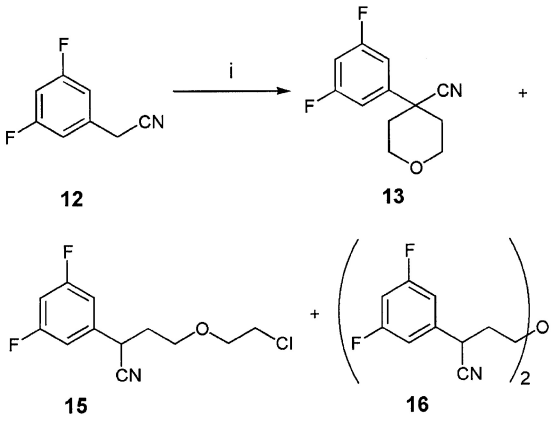
Scheme 2

dium iodide and 15-crown-5,[5,9] and use of a phase-transfer catalyst.[10,11] The results are summarized in Table 1. Phase-transfer catalysis conditions[10] (entry 9) gave alkylated intermediate **15** and dimer **16** in addition to the desired pyran **13** (Scheme 4).[11] Among the reaction conditions tried, the use of sodium hydride in DMSO (entry 8) gave **13** with the highest yield (75%). The reaction was reproducible (5 runs, 1–25 g scale, 69–82%), and the product was obtained in high purity as solids without the need of purification by column chromatography.

Next, the formation of the imidazole benzyl phenyl ether linkage of **1**, by nucleophilic aromatic substitution, was studied. It was found that imidazole benzyl alcohol **6** on treatment with sodium hydride in *N*,*N*-dimethylacetamide (DMA) underwent addition to **13** to give ether **14** in 86% yield.[12] Finally, efficient conversion of nitrile **14** to carboxamide **1**, while avoiding further hydrolysis to the carboxylic acid, was investigated. The results are summarized in Table 2. While use of hydrogen peroxide in DMSO (entry 1) gave **1** in acceptable yield, the large amount of dimethyl sulfone produced as a by-product proved difficult to purge.[13] Running the same reaction in



Scheme 3 (i) $(ClCH_2CH_2)_2O$, NaH, DMSO, r.t. (75%); (ii) NaH, DMA, r.t. (86%); (iii) powdered KOH, *t*-BuOH, 80 °C (92%).

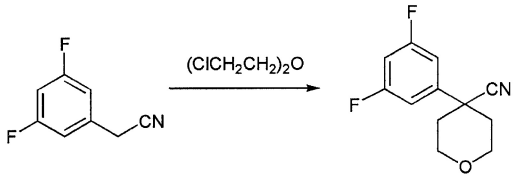


Scheme 4 (i) 50% aq NaOH, $CH_3(CH_2)_{15}P[(CH_3)_2CH_3]_3Br$.

acetone (entry 2) was very slow, requiring a reaction time of at least two days at reflux temperature as assessed by TLC monitoring. The optimal conditions were the use of approximately four equivalents of powdered potassium hydroxide in *t*-BuOH at 80 °C (entry 3) to afford the desired product in 92% yield.[14]

A highly efficient and facile three-step synthesis to target molecule **1** was developed. The total yield was 59%, and all intermediates were crystalline and synthetically amenable to large scale preparations. The improved synthesis enabled rapid progression of pre-clinical toxicology stud-

Table 1 Construction of the THP Ring of **13** from **12**[a]



12 **13**

Entry	Base (mol equiv)	Additive (mol equiv)	Temp [°C]	Time [h]	Solvent	Yield [%]
1	NaH (2.2)	None	80	20	DMF	46
2	NaH (4.0)	None	80	20	DMF	51
3	NaH (4.0)	NaI (1.2), 15-Crown-5 (0.1)	r.t.	16	DMF	58
4	NaH (4.0)	NaI (1.2), 15-Crown-5 (0.1)	r.t.	6	DMSO	46
5	$LiNH_2$ (2.2)	None	80	16	DME	<10
6	*t*-BuOK (2.2)	None	40	15	DMA	17
7	$NaNH_2$ (2.2)	None	r.t.	3.5	DMSO	56
8	NaH (2.2)	None	r.t.	1	DMSO	75
9	50% aq. NaOH	$CH_3(CH_2)_{15}P[(CH_3)_2CH_3]_3Br$	r.t.	16		ND[b]

[a] The reaction was conducted under a nitrogen atmosphere.
[b] ND = Not determined. Significant amounts of impurities were also produced.

Table 2 Hydrolysis of Nitrile **14** to Amide **1**

Entry	Conditions	Time	Yield [%]
1	H_2O_2 (30%), K_2CO_3, DMSO, r.t.	5 h	80[a]
2	H_2O_2 (30%), K_2CO_3, acetone, r.t.	2 d	–[b]
3	KOH (powdered), *t*-BuOH, 80 °C	4 h	92

[a] Contaminated with dimethylsulfone.
[b] Very slow.

ies of **1** and it was found that **1** was a safe and practical lead 5-LO inhibitor.[5]

^{1}H NMR spectra were measured on a Jeol FX270 spectrometer and proton chemical shifts are reported as δ values in ppm relative to TMS as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Melting points were determined on either a Büchi 535 or a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu FTIR-8300 Fourier Transform Infrared spectrometer. Mass spectra were recorded on a Waters Integrity spectrometer or a Micromass Quattro II spectrometer. HPLC was performed with a Hewlett-Packard Series 1090 using a Shiseido CAPCELLPAK C_{18} column UG 120 (4.6 × 150 mm, 5 mm) and 0.01 M CH_3COONH_4/CH_3CN mobile phase, detecting at UV 230 nm. The HPLC gradient was programmed as follows: 0–5 min, 25% CH_3CN; 5–20 min, 25–40% CH_3CN; 20–40 min, 40–80% CH_3CN; 40–45 min, 80% CH_3CN.

4-(3,5-Difluorophenyl)tetrahydro-2*H*-pyran-4-carbonitrile (13)
To a solution of (3,5-difluorophenyl)acetonitrile (**12**, 24.2 g, 0.158 mol) in DMSO (240 mL) was added NaH (60% w/w dispersion in mineral oil, 13.3 g, 0.332 mol) portion-wise over 10 min. The reaction mixture was stirred for 40 min at r.t. and then bis(2-chloroethyl)ether (24.9 g, 0.174 mol) was added slowly and stirring continued for an additional hour. The reaction mixture was poured into H_2O (500 mL) and the mixture was extracted with an EtOAc–toluene (2:1, 3 × 400 mL). The combined extracts were washed with 2 N aq. HCl (300 mL), H_2O (300 mL) and brine (300 mL), dried over $MgSO_4$ and concentrated to 100 mL. The precipitated solids were collected and washed with cold Et_2O (50 mL) to afford 26.3 g (75%) of the title compound as an off-white solid.

Mp 127–130 °C.

IR (KBr): 2210 (C≡N) cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.15–7.00 (m, 2 H, aromatic), 6.89–6.78 (m, 1 H, aromatic), 4.20–4.05 (m, 2 H, THP CH_2), 3.98–3.80 (m, 2 H, THP CH_2), 2.20–1.96 (m, 4 H, THP CH_2).

Anal. Calcd for $C_{12}H_{11}F_2NO$: C, 64.57; H, 4.97; N, 6.27. Found: C, 64.54; H, 5.12; N, 6.29.

4-(3-Fluoro-5-{[4-(2-methyl-1*H*-imidazol-1-yl)benzyl]oxy}phenyl)tetrahydro-2*H*-pyran4-carbonitrile (14)
To a stirred solution of [4-(2-methyl-1*H*-imidazol-1-yl)phenyl]-methanol (**6**, 20.6 g, 0.109 mmol) in *N*,*N*-dimethylacetamide (DMA) (350 mL) was added NaH (60% w/w dispersion in mineral oil, 4.80 g, 0.120 mmol) at r.t. After stirring for 30 min, 4-(3,5-difluorophenyl)tetrahydro-2*H*-pyran-4-carbonitrile (**13**, 24.4 g, 0.109 mmol) was added and stirring was continued at r.t. After 6 h, the mixture was poured into H_2O (500 mL), and the whole mixture extracted with EtOAc–benzene (2:1, 2 × 700 mL). The combined extracts were washed with H_2O (500 mL) and brine (500 mL) and dried over $MgSO_4$. Removal of the solvent gave a yellow solid which was suspended in Et_2O (ca. 200 mL). Collection of the precipitates by filtration and drying under vacuum afforded 35.6 g (82%) of the title compound as white powder. Concentration of the filtrate followed by filtration and drying afforded additional 1.8 g (4%) of **14**.

Mp 100–105 °C.

IR (KBr): 2210 (C≡N) cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.56 (d, 2 H, *J* = 8.4 Hz, aromatic), 7.35 (d, 2 H, *J* = 8.4 Hz, aromatic), 7.04 (d, 1 H, *J* = 1.5 Hz, imidazole), 7.02 (d, 1 H, *J* = 1.5 Hz, imidazole), 6.97 (br s, 1 H, aromatic), 6.82 (ddd, 1 H, *J* = 9.5, 2.2, 1.8 Hz, aromatic), 6.69 (ddd, 1 H, *J* = 9.5, 2.2, 1.8 Hz, aromatic), 5.13 (s, 2 H, benzylic CH_2), 4.16–4.02 (m, 2 H, THP CH_2), 3.97–3.81 (m, 2 H, THP CH_2), 2.39 (s, 3 H, CH_3), 2.20–1.98 (m, 4 H, THP CH_2).

MS (ESI+): *m/e* = 392 $(M + H)^+$.

Anal. Calcd for $C_{23}H_{22}FN_3O_2 \cdot 0.3\ H_2O$: C, 69.61; H, 5.74; N, 10.59. Found: C, 69.71; H, 5.63; N, 10.29.

4-(3-Fluoro-5-{[4-(2-methyl-1*H*-imidazol-1-yl)benzyl]oxy}phenyl)tetrahydro-2*H*-pyran-4-carboxamide (1)[5]

To the stirred solution of **14** (28.9 g, 72.2 mmol) in *t*-BuOH (300 mL), powdered KOH (85%, 12.4 g, 221 mmol) was added and the mixture was stirred at 80 °C for 4 h, then volatile was removed under reduced pressure. H_2O (200 mL) was added to the residue and the resulting precipitates were collected by suction filtration, washed with water (2 × 100 mL), and dried under vacuum to afford 27.1 g (92%) of the title compound as a white solid with 98.9% purity (HPLC).

Mp 207–208 °C.

IR (KBr): 1668 (C=O) cm^{-1}.

^1H NMR (270 MHz, DMSO-d_6): δ = 7.61 (d, 2 H, *J* = 8 Hz, aromatic), 7.48 (d, 2 H, *J* = 8 Hz, aromatic), 7.30 (d, 1 H, *J* = 1 Hz, imidazole), 7.24 (br s, 1 H, NH_2), 7.08 (br s, 1 H, NH_2), 6.92 (d, 1 H, *J* = 1 Hz, imidazole), 6.89–6.82 (m, 2 H, aromatic), 6.80–6.75 (m, 1 H, aromatic), 5.18 (s, 2 H, benzylic CH_2), 3.66–3.57 (m, 2 H, THP CH_2), 3.51–3.40 (m, 2 H, THP CH_2), 2.44–2.35 (m, 2 H, THP CH_2), 2.29 (s, 3 H, CH_3), 1.84–1.72 (m, 2 H, THP CH_2).

MS (ESI+): *m/e* = 410 $(M + H)^+$.

Anal. Calcd for $C_{23}H_{24}FN_3O_3$: C, 67.47; H, 5.91; N, 10.26. Found: C, 67.45; H, 5.97; N, 10.26.

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