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# The Discovery of Setileuton, a Potent and Selective 5-Lipoxygenase Inhibitor

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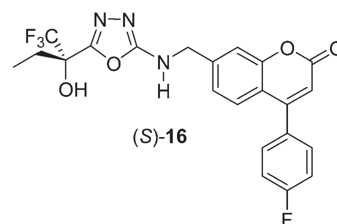
**ABSTRACT** The discovery of novel and selective inhibitors of human 5-lipoxygenase (5-LO) is described. These compounds are potent, orally bioavailable, and active at inhibiting leukotriene biosynthesis in vivo in a dog PK/PD model. A major focus of the optimization process was to reduce affinity for the human ether-a-go-go gene potassium channel while preserving inhibitory potency on 5-LO. These efforts led to the identification of inhibitor (*S*)-**16** (MK-0633, setileuton), a compound selected for clinical development for the treatment of respiratory diseases.

**KEYWORDS** Human 5-lipoxygenase, leukotriene biosynthesis, MK-0633, setileuton, respiratory diseases




Leukotrienes (LTs) are potent lipid inflammatory mediators derived from arachidonic acid metabolism and released from cells involved in the inflammatory process.[1] The synthesis of all LTs requires the action of the enzyme 5-lipoxygenase[2] (5-LO) and its accessory protein, 5-LO-activating protein[3] (FLAP). Inhibition of 5-LO reduces the production of both $LTB_4$ and cysteinyl LTs (CysLTs) $LTC_4$, $LTD_4$, and $LTE_4$. CysLTs increase vascular permeability, contract smooth muscle cells, and are involved in increased mucus production. $LTB_4$ is a potent chemoattractant for neutrophils, macrophages, and other inflammatory cells and induces chemokinesis and adhesion of these cells to the vascular endothelium. Therefore, 5-LO inhibitors have potential therapeutic utility for the treatment of inflammatory disorders.[4] Asthma, an inflammatory disorder of the lower airway, is characterized by variable and reversible bronchoconstriction, airway edema, mucus secretion, and airway remodeling, which leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.[5] The clinical importance of the LTs in asthma has been well-demonstrated both by drugs that inhibit the biosynthesis of these mediators such as zileuton[6] (**1**, Table 1; the only marketed 5-LO inhibitor) and MK-0591[7] (a FLAP inhibitor) and by potent CysLT1 receptor antagonists such as montelukast.[8] Theoretically, 5-LO inhibition could provide added benefit over CysLT1 receptor antagonists by blocking $LTB_4$-mediated inflammation in addition to reducing CysLTs production. LTs are also thought to play an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). COPD is characterized by an inflammatory process in the airways dominated by neutrophils and effector T-cells. $LTB_4$ may be important in contributing to the inflammatory process via both cell types and has been detected in both the sputum and the lungs of patients with COPD. Currently available chronic medications for COPD have limited effectiveness. Thus, COPD could be another indication for inhibitors of 5-LO.[9] Accumulating evidence suggests that 5-LO inhibitors could also be useful for the treatment of atherosclerosis,[10] pain,[11] and cancer.[12] Herein, we describe the design of a novel series of coumarin analogues demonstrating high potency at inhibiting 5-LO, leading to the identification of (*S*)-**16** (MK-0633, setileuton) as a development candidate.

Our effort started with phenylthioether **2** (Table 1), a 5-LO inhibitor identified in a previous research campaign.[13] This compound shows a high potency at inhibiting calcium ionophore-stimulated production of $LTB_4$ in human whole blood (HWB) in vitro, with an $IC_{50}$ of 70 nM. However, its development was hampered by the observation that two major long-lived and active metabolites, the corresponding sulfone and sulfoxide, were circulating in rats and monkeys. This observation triggered the search for structurally distinct 5-LO inhibitors. All compounds prepared were evaluated for their potency to inhibit the oxidation of arachidonic acid by recombinant human 5-LO (H5-LO),[14] and the production of $LTB_4$ in calcium ionophore-stimulated HWB.[15] Each section of the molecule was investigated, but the most interesting modulation of structure−activity relationship (SAR) came from replacement of the central mercaptobenzene moiety of inhibitor **2**. Most structural modifications of this moiety, even subtle ones like replacing the sulfur atom by an oxygen atom (**3**), were deleterious to potency and brought the HWB $IC_{50}$ above 1 $\mu$M. The few analogues that retained submicromolar potency are depicted in Table 1. Among them, thiazole **4** rapidly caught our attention since it retained high potency in the H5-LO assay ($IC_{50}$ = 20 nM) and showed only a 4-fold

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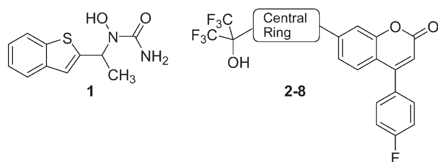
Table 1. SAR at the Central Ring Position

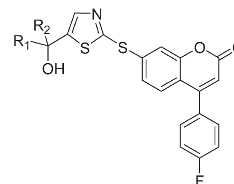



| Compd | Central Ring | $IC_{50}$ (nM)[a] | | $K_i$ (μM)[a] |
|---|---|---|---|---|
| | | H5-LO | HWB | hERG |
| 1 | — | 3700[b] | 2000[b] | - |
| 2 | | 27±16 | 70±24 | 0.42±0.13 |
| 3 | | 1440±560 | 1860±860 | 1.11±0.01 |
| 4 | | 20±16 | 310±160 | 1.2±0.1 |
| 5 | | 115±6 | 610±220 | 1.38±0.03 |
| 6 | | 64±3 | 350±270 | <0.4 |
| 7 | | 145±15 | 430±350 | 1.0±0.1 |
| 8 | | 45±10 | 690±320 | 8.0±0.2 |

[a] Each $IC_{50}$ value corresponds to an average of at least two independent determinations (±SD). [b] Ref 19.

loss of activity in the HWB assay ($IC_{50}$ = 310 nM) as compared to inhibitor **2**. Many analogues of thiazole **4** were prepared, and it became clear that appropriate modification of the substitution pattern at the tertiary alcohol provided a major gain of potency in the HWB assay, as shown in Table 2. Replacing the two trifluoromethyl groups of compound **4** by two methyl groups brought a 2-fold loss of potency in the HWB assay (compound **9**). Conversely, substitution by two ethyl groups was favorable, generating inhibitor **10** with an $IC_{50}$ of 37 nM. Highly potent inhibitors were also obtained by an asymmetric substitution at the tertiary alcohol (compounds **11**−**14**, all racemic). The optimal potency in this series was obtained by keeping one trifluoromethyl and one ethyl group to generate racemic inhibitor **12** (HWB $IC_{50}$ = 50 nM). Both enantiomers of **12** were prepared, and it was observed that (*R*)-**12**, with an $IC_{50}$ of 31 nM in the HWB assay, is more potent than isomer (*S*)-**12**. The stereochemical assignment was established by X-ray crystallography analysis. In contrast to what was observed for inhibitor **2**,[13] thiazole (*R*)-**12** is orally bioavailable in rat, without having to rely on the administration of a hydroxy acid prodrug. Thus, upon dosing male rats with (*R*)-**12** orally at 20 mg/kg in 0.5% methocel, good bioavailability (*F* = 37%) and a maximum concentration

Table 2. SAR at the Tertiary Alcohol Position in the Thiazole Series




| compd | $R_1$ | $R_2$ | $IC_{50}$ (nM)[a] | | $K_i$ (μM)[a] |
|---|---|---|---|---|---|
| | | | H5-LO | HWB | hERG |
| 4 | $CF_3$ | $CF_3$ | 20 ± 16 | 310 ± 160 | 1.2 ± 0.1 |
| 9 | Me | Me | 1230 ± 480 | 520 ± 310 | 2.9 ± 0.1 |
| 10 | Et | Et | 23 ± 6 | 37 ± 20 | 2.1 ± 0.2 |
| 11 | $CF_3$ | Me | 30 ± 4 | 150 ± 40 | 1.5 ± 0.1 |
| 12 | $CF_3$ | Et | 14 ± 4 | 50 ± 18 | 0.9 ± 0.1 |
| 13 | $CF_3$ | *i*-Pr | 12 ± 4 | 88 ± 12 | 1.1 ± 0.1 |
| 14 | $CF_3$ | *t*-Bu | 18 ± 1 | 210 ± 40 | |
| (*S*)-12 | $CF_3$ | Et | 79 ± 15 | 83 ± 33 | 0.9 ± 0.1 |
| (*R*)-12 | Et | $CF_3$ | 7 ± 2 | 31 ± 22 | 1.3 ± 0.2 |

[a] Each $IC_{50}$ value corresponds to an average of at least two independent determinations (±SD).

($C_{max}$) of 2.0 μM were observed, with an elimination half-life ($t_{1/2}$) of 4.3 h. The potency of (*R*)-**12** on the ex vivo generation of $LTB_4$ in whole blood stimulated with calcium ionophore A23187 was measured in a dog model.[16] In vitro, thiazole (*R*)-**12** is 3-fold more potent in a dog whole blood assay ($IC_{50}$ = 10 nM) than it is in the HWB assay ($IC_{50}$ = 31 nM). Following oral dosing in dogs at a dose of 4 mg/kg, (*R*)-**12** exhibited > 94% inhibition of $LTB_4$ in dog whole blood ex vivo up to 24 h. This level of inhibition is consistent with the potency of the compound in the dog whole blood assay and the measured plasma concentrations that are greater than 0.18 μM at all time points, up to 24 h. The remarkable profile of this 5-LO inhibitor triggered exploratory ancillary pharmacology studies. One of these studies evaluated the effect of (*R*)-**12** on the cardiovascular system of anesthetized and vagotomized dogs, following the administration of 4 mg/kg/h of the drug by i.v. infusion, for 2 h. Unfortunately, upon examination of the electrocardiograms, a clear $QT_c$ interval prolongation was noted in treated dogs, beginning 45 min after initiation of the infusion. The maximum effect on mean $QT_c$ interval reached +9% (as compared to control) after 90 min of dosing, with an average plasma exposure of 10 μM. Given a targeted trough exposure of 100 nM for efficacy in the clinic, the likely therapeutic margin in humans was estimated to be too low to warrant the clinical development of (*R*)-**12**.

It is known that a variety of drugs that exhibit prolongation of the $QT_c$ interval tend to block the voltage-gated potassium channel encoded by the human ether-a-go-go gene (hERG).[17] The affinity of molecules for this channel can be measured in vitro by using a MK-499 displacement binding assay.[18] 5-LO inhibitor (*R*)-**12** exhibits a relatively high binding affinity in this assay with a $K_i$ of 1.3 μM (Table 2). Because of the correlation between the prolongation of the $QT_c$ interval observed with (*R*)-**12** in vivo in dogs and the potency of

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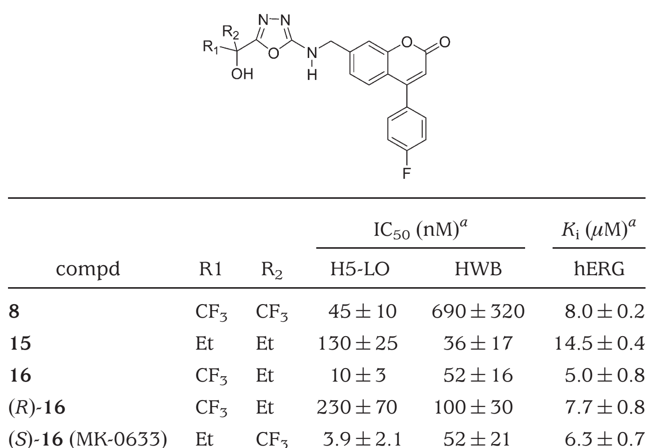
**Table 3.** SAR at the Tertiary Alcohol Position in the Oxadiazole Series

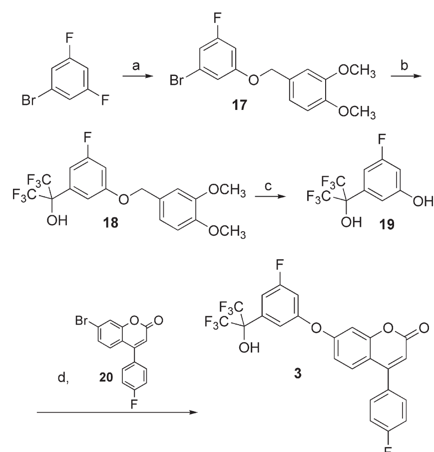


| compd | R1 | $R_2$ | $IC_{50}$ (nM)[a] H5-LO | $IC_{50}$ (nM)[a] HWB | $K_i$ ($\mu$M)[a] hERG |
|---|---|---|---|---|---|
| **8** | $CF_3$ | $CF_3$ | 45 ± 10 | 690 ± 320 | 8.0 ± 0.2 |
| **15** | Et | Et | 130 ± 25 | 36 ± 17 | 14.5 ± 0.4 |
| **16** | $CF_3$ | Et | 10 ± 3 | 52 ± 16 | 5.0 ± 0.8 |
| (*R*)-**16** | $CF_3$ | Et | 230 ± 70 | 100 ± 30 | 7.7 ± 0.8 |
| (*S*)-**16** (MK-0633) | Et | $CF_3$ | 3.9 ± 2.1 | 52 ± 21 | 6.3 ± 0.7 |

[a] Each $IC_{50}$ value corresponds to an average of at least two independent determinations (±SD).

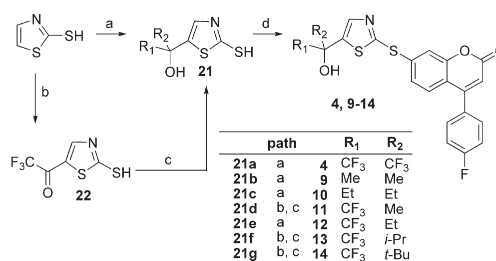
(*R*)-**12** in the hERG binding assay, we have taken the binding affinity for the hERG potassium channel as measured in the MK-499 binding assay as an in vitro indicator for the potential for causing $QT_c$ interval prolongation. Therefore, our efforts focused on identifying those portions of the molecule that could be modified in such a way to decrease the affinity for the hERG channel while maintaining or improving the inhibitory potency against 5-LO. All of the thiazole derivatives described in Table 2 show a similar affinity for the hERG channel ($K_i$ = 0.9−2.9 $\mu$M). On the other hand, modification of the central ring system seems to have a more profound effect on hERG binding affinity, as shown in Table 1. In this regard, oxadiazole derivative **8** is of particular interest with a hERG binding $K_i$ of 8.0 $\mu$M, representing a 6-fold loss of affinity as compared to thiazole (*R*)-**12**. Unfortunately, oxadiazole **8** also shows a considerable loss of potency in the HWB assay ($IC_{50}$ = 690 nM). By applying the lessons learned in the thiazole series to the oxadiazole case, we were hopeful that potency could be restored. The gem-diethyl derivative **15** was prepared and presented a potency equivalent to that shown by inhibitor (*R*)-**12** in the HWB assay ($IC_{50}$ = 36 nM), accompanied by a significantly lower affinity for the hERG channel ($K_i$ = 14.5 $\mu$M, Table 3). The pharmacokinetic profile of this compound was not optimal though. Upon dosing male rats intraveneously with **15**, a short elimination half-life of 1 h was observed. This problem was solved by preparing the asymmetric alcohol **16**, bearing a trifluoromethyl and an ethyl group. Racemic inhibitor **16** presented good potency in the HWB assay with an $IC_{50}$ of 52 nM. Both enantiomers of **16** were prepared, and the stereochemical assignment was again established by X-ray crystallography analysis. Enantiomer (*S*)-**16**, with an $IC_{50}$ of 3.9 nM in the H5-LO assay and an $IC_{50}$ of 52 nM in the HWB assay, is more potent than isomer (*R*)-**16**. This excellent 5-LO inhibitory profile is accompanied by a relatively low affinity for the hERG channel ($K_i$ = 6.3 $\mu$M). Oxadiazole (*S*)-**16** inhibits specifically 5-LO and is not active against 12-LO, 15-LO, and FLAP (>20 $\mu$M). The activity against FLAP was determined by measuring the

**Scheme 1**[a]



[a] Reagents and conditions: (a) NaH, 3,4-dimethoxybenzyl alcohol, DMF, 83%. (b) *n*-BuLi, $CF_3COCF_3$, $Et_2O$/THF, 59%. (c) $HCO_2NH_4$, Pd−C 10%, MeOH, Δ, 80%. (d) 2,2,6,6-Tetramethyl-3,5-heptanedione, CuCl, $Cs_2CO_3$, NMP, 120 °C, 35%.

**Scheme 2**[a]



| | path | | $R_1$ | $R_2$ |
|---|---|---|---|---|
| 21a | a | 4 | $CF_3$ | $CF_3$ |
| 21b | a | 9 | Me | Me |
| 21c | a | 10 | Et | Et |
| 21d | b, c | 11 | $CF_3$ | Me |
| 21e | a | 12 | $CF_3$ | Et |
| 21f | b, c | 13 | $CF_3$ | *i*-Pr |
| 21g | b, c | 14 | $CF_3$ | *t*-Bu |

[a] Reagents and conditions: (a) LDA, $R_1COR_2$, THF, −78 °C. (b) LDA, $CF_3CO_2Et$, THF, −78 to 0 °C, 68%. (c) RM, THF. (d) Compound **20**, $K_2C_3$, NMP, 120 °C.

displacement of a radiolabeled FLAP ligand from human polymorphonuclear cell membranes. Oxadiazole (*S*)-**16** presents a good pharmacokinetic profile in many preclinical species (rat, 5 mg/kg iv, 20 mg/kg po, *F* = 66%, and $t_{1/2}$ = 3.3 h; dog, 5 mg/kg iv, 4 mg/kg po, *F* = 64%, and $t_{1/2}$ = 5.3 h; and rhesus monkey, 5 mg/kg iv, 4 mg/kg po, *F* = 54%, and $t_{1/2}$ = 3.6 h). In vitro, 5-LO inhibitor (*S*)-**16** is 2-fold more potent in a dog whole blood assay ($IC_{50}$ = 21 nM) than it is in the HWB assay ($IC_{50}$ = 52 nM). Following oral dosing in dogs at a dose of 2 mg/kg, (*S*)-**16** exhibited >98% inhibition of $LTB_4$ in dog whole blood ex vivo up to 6 h. This level of inhibition is consistent with its potency in dog whole blood and the measured concentration of drug in the plasma that is greater than 0.28 $\mu$M at all time points up to 6 h. Inhibition of $LTB_4$ at 24 h was ∼60%, although the drug concentration in plasma was below the detection limit of 10 nM. Furthermore, and in contrast to what was observed with thiazole (*R*)-**12**, the oxadiazole inhibitor (*S*)-**16** did not show adverse effects on the cardiovascular system of anesthetized and vagotomized dogs. Thus, following the administration of cumulative doses of 1, 3, and 10 mg/kg of the drug by i.v. infusion (each dose infused

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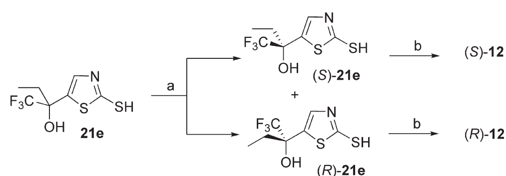
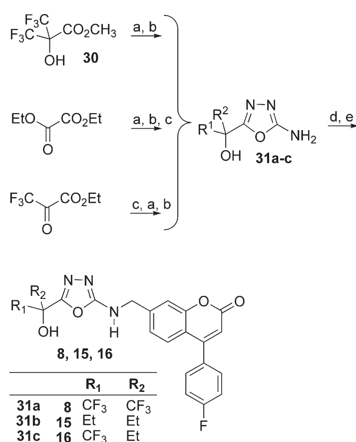
**Scheme 3**[a]




[a] Reagents and conditions: (a) Chiral HPLC, Chiralpak AD column. (b) Compound **20**, $K_2CO_3$, NMP, 120 °C.

**Scheme 4**[a]

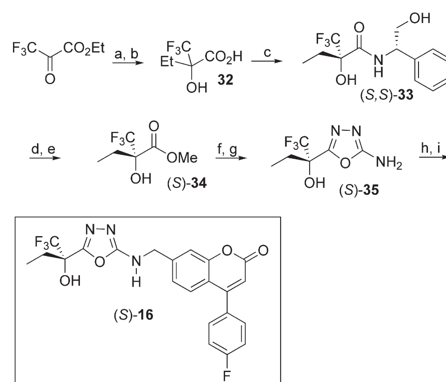



[a] Reagents and conditions: (a) $H_2NNH_2$, Δ; (b) BrCN, $KHCO_3$, $H_2O$; (c) EtMgBr; (d) **25**, toluene, Δ; (e) $NaBH_4$, EtOH.

over 30 min), no treatment-related changes in the PR, QRS, and $QT_c$ intervals were observed, with an average plasma exposure of 9, 14, and 49 $\mu$M at those three doses, respectively.

The 5-LO inhibitors described in this study were prepared as shown in Schemes 1−5. The synthesis of diaryl ether **3** started by the addition of 3,4-dimethoxybenzyl alcoholate to 1-bromo-3,5-difluorobenzene (Scheme 1) to provide benzyl ether **17**. Bromine−lithium exchange followed by treatment with hexafluoroacetone gave access to tertiary alcohol **18**, which after deprotection afforded phenol **19**. The desired diaryl ether **3** was finally obtained by engaging intermediate **19** with the known aryl bromide **20**[13] under Ullmann ether synthesis conditions. The 2-thiazolyl thioethers **4** and **9−14** were prepared by two different pathways (Scheme 2). Deprotonation of 2-mercaptothiazole with lithium diisopropyl amide (LDA), followed by addition of hexafluoroacetone, acetone, 3-pentanone, or 1,1,1-trifluoro-2-butanone, gave tertiary alcohols **21a**, **b**, **c**, and **e**, respectively. Alternatively, deprotonation of 2-mercaptothiazole with LDA followed by addition of ethyl trifluoroacetate gave ketone **22**. Addition of methylmagnesium bromide, isopropylmagnesium chloride, or *tert*-butyllithium to **22** yielded alcohols **21d**, **f**, and **g**, respectively. The desired thioethers were obtained by heating the appropriate 2-mercaptothiazoles **21** with bromocoumarin **20** in 1-methyl-2-pyrrolidinone (NMP). The two enantiomers of inhibitor **12** were obtained by submitting the racemic mixture of asymmetric alcohol **21e** to a chiral separation on a Chiralpak AD column (Scheme 3). Each

**Scheme 5**[a]




[a] Reagents and conditions: (a) EtMgBr, $Et_2O$, −78 °C, 76%; (b) NaOH, THF/MeOH, 90%; (c) (*S*)-(+)-2-phenylglycinol, HATU, DIPEA, DMF, 41%; (d) $H_2SO_4$, dioxane, 105 °C; (e) $CH_2N_2$, $Et_2O$, 74% (2 steps); (f) $H_2NNH_2$, 120 °C; (g) BrCN, $CHCO_3$, $H_2O$, 71% (2 steps); (h) **25**, toluene, Δ; (i) $NaBH_4$, EtOH 54% (2 steps).

enantiomer was subsequently reacted with bromide **20** to afford inhibitors (*S*)-**12** and (*R*)-**12**. The preparation of analogues **5**, **6**, and **7** is described in the Supporting Information. The preparation of 2-amino-oxadiazole derivatives **8**, **15**, and **16**, described in Scheme 4, involved the synthesis of key intermediates **31a−c**. Reaction of ester **30** [obtained by treatment of 2,2-bis(trifluoromethyl)-2-hydroxyacetic acid with diazomethane], first with hydrazine and then with cyanogen bromide, gave access to oxadiazole **31a**. Alternatively, a similar sequence was applied to diethyloxalate and was followed by the addition of excess ethylmagnesium bromide to produce analogue **31b**. As for asymmetric derivative **31c**, its synthesis involved addition of ethylmagnesium bromide to ethyl trifluoropyruvate and subsequent reaction with hydrazine and with cyanogen bromide. The desired final products were then obtained by reductive amination reactions between the appropriate amines **31** and aldehyde **25** (see Supporting Information). The two enantiomers of inhibitor **16** were first obtained by submitting the racemic mixture to a chiral separation on a Chiralpak AD column. Afterward, larger quantities of the most active enantiomer (*S*)-**16** were produced by following the synthetic route depicted in Scheme 5. Addition of ethylmagnesium bromide to ethyl trifluoropyruvate was followed by hydrolysis of the resulting hydroxy-ester to afford racemic acid **32**. Coupling with (*S*)-2-phenylglycinol afforded a diastereomeric mixture that was purified by flash chromatography on silica gel to deliver diastereomerically pure amide (*S,S*)-**33**. Hydrolysis of the amide bond followed by esterification produced methyl ester (*S*)-**34**. The usual treatment with hydrazine and with cyanogen bromide gave oxadiazole (*S*)-**35**, and reductive amination with aldehyde **25** completed the preparation of multigram quantities of potent 5-LO inhibitor (*S*)-**16**.

In summary, we have discovered a series of novel 5-LO inhibitors that are potent, selective, and orally bioavailable. A major focus of the optimization effort was to preserve the 5-LO inhibitory potency while reducing the affinity for the hERG potassium channel. This work culminated in the identi-

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fication of 4-(4-fluorophenyl)-7-[({5-[(2*S*)-1,1,1-trifluoro-2-hydroxybutan-2-yl]-1,3,4-oxadiazol-2-yl}amino)methyl]-2*H*-chromen-2-one [(*S*)-**16**, MK-0633, setileuton]. On the basis of its overall profile, setileuton was selected for clinical development, and its effect on the treatment of asthma and COPD will be reported in separate papers.

**SUPPORTING INFORMATION AVAILABLE** Experimental synthetic procedures, spectroscopic characterization, and H5-LO assay protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

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