Optimization of Imidazole 5-Lipoxygenase Inhibitors and Selection and Synthesis of a Development Candidate

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Structural modification of imidazole 5-lipoxygenase (5-LO) inhibitors for optimizing inhibitory potency, pharmacokinetic behavior and toxicity (ocular) profile led to 4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]}phenyl-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (6) with no observable ocular toxicity. The orally active and safe imidazole 5-LO inhibitor 6 was selected as a clinical candidate and advanced to clinical studies. An improved synthesis of 6 is also discussed.

Key words lipoxygenase; inhibitor; structure–activity relationship; leukotriene; unsymmetric thioether

The leukotrienes (LTs) are endogenous mediators with potent biological activity. It is known that leukotriene B_4 (LTB_4) is a potent chemotactic agent for leukocytes while peptide leukotrienes (*i.e.*, LTC_4, LTD_4 and LTE_4) are powerful bronchoconstrictor agents. 5-Lipoxygenase (5-LO) is the key enzyme in LT biosynthesis and catalyzes the initial steps in conversion of arachidonic acid to LTs.[1,2] Accordingly, inhibiting the action of 5-LO and antagonizing the action of LTs are expected to be valuable for the treatment of acute and chronic diseases such as asthma, allergic rhinitis and psoriasis. It has been shown that 5-LO inhibitors and LTD_4 antagonists are efficacious in asthmatics.[3—7)]

We have disclosed on imidazole compound **1** as a novel orally active 5-LO inhibitor (Chart 1). Shortcomings of **1** were unsatisfactory pharmacokinetic profile and unwanted side effects (ocular). Preliminary structure–activity relationships (SARs) identified novel imidazole lead-compound **2** with modest oral pharmacology and improved pharmacokinetic profile.[8,9)] Importantly, compared with **1**, ocular toxicity of **2** was significantly reduced. In this paper, we disclose our efforts focused on optimization of **2** leading to the discovery of clinical candidate, a novel 5-LO inhibitor void of ocular toxicity as assessed in preclinical models.

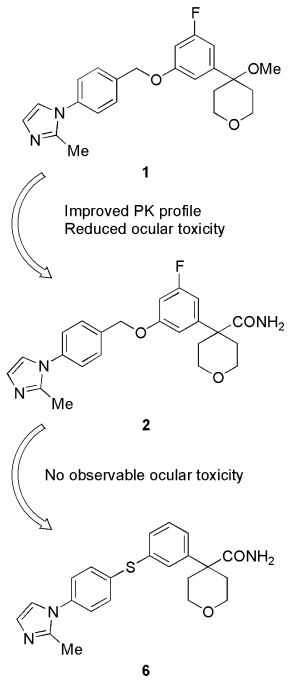

Chart 1. Structures of Representative Imidazole 5-LO Inhibitors and Their Improvement

Chemistry

Imidazole compounds **3**—**8** were synthesized for this study. Compounds **3** and **8** were synthesized as shown in Chart 2. Phenol **10**, which was obtained by demethylation of known 3,4,5,6-tetrahydro-2*H*-pyran (THP) compound **9**,[10)] was treated with benzyl chloride **11** in the presence of K_2CO_3 to give ether **12**.[8)] Selective hydrolysis of nitrile **12** gave amide **3** (approximately 4 equivalents of powdered KOH in *t*-BuOH at 80 °C).[11)] Similarly, nitrile **15**, which was obtained by coupling of **10** with iodide **14** in the presence of cupric oxide, was converted to amide **8**.

Chart 3 illustrates the synthesis of **4**. Aldehyde group was selectively introduced to commercially available 2,5-difluorophenol **16** to give **19**, which was converted to methyl α-phenyl acetate derivative **22** in a stepwise manner. THP ring was constructed by the method reported for the preparation of **2**.[9)] The THP **23** was demethylated to phenol **24**, which was treated with benzyl chloride **11** to give imidazole ester **25**. The ester **25** was converted to amide **4** by standard procedure.[9)]

Synthesis of **5** is depicted in Chart 4. Difluorobenzene **26**[11)] was converted to the monomethylthioether **27**. Oxidation of **27** to the corresponding sulfoxide **28** followed by Pummerer rearrangement yielded thiophenol **29**. Palladium-catalyzed coupling of **29** with iodide **14** gave nitrile **30**, which was selectively hydrolyzed to yield amide **5**.

Chart 5 shows the syntheses of **6** and **7**. Ester **32**, synthesized from ethyl (3-bromophenyl)acetate, was converted to intermediate methyl thioether by lithium–bromine exchange of carboxylic acid **33** with *n*-buthyl lithium followed by treatment with dimethyl disulfide. The intermediate methyl thioether was converted to **35** *via* sulfoxide **34**. Palladium-catalyzed coupling of **35** with iodide **14** gave thioether **36**, which was transformed to amide **6** *via* carboxylic acid **37**.

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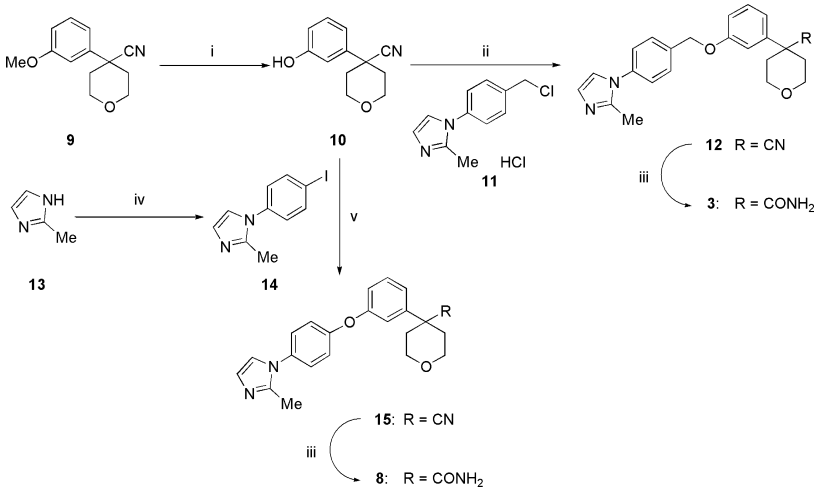
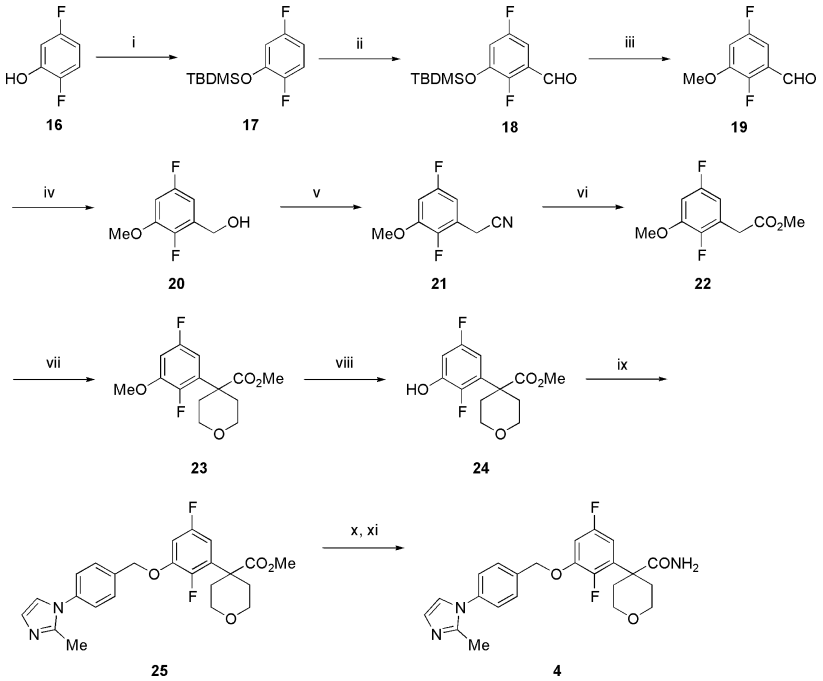


(i) BBr_3, CH_2Cl_2; (ii) K_2CO_3, DMF; (iii) KOH, *t*-BuOH; (iv) NaH, 4-fluoro-1-iodobenzene, DMF; (v) CuO, K_2CO_3, pyridine.

Chart 2. Syntheses of **3** and **8**



(i) NaH, TBDMSCl, DMF; (ii) *sec*-BuLi, THF, then DMF; (iii) KF, MeI, DMF; (vi) $NaBH_4$, EtOH; (v) *p*-toluenesulfonyl chloride, triethylamine, then NaCN, DMSO; (vi) KOH, ethylene glycol, then MeOH, H_2SO_4; (vii) NaH, 15-Crown-5, $(ClCH_2CH_2)_2O$, DMF; (viii) BBr_3, CH_2Cl_2; (ix) **11**, K_2CO_3, DMF; (x) LiOH, THF, MeOH, H_2O; (xi) $(COCl)_2$, CH_2Cl_2, then aqueous NH_3.

Chart 3. Synthesis of **4**

Oxidation of **6** with hydrogen peroxide gave sulfone **7**.

The improved synthesis of **6** is shown in Chart 6. Several conditions were examined to prepare **39** from **38**. Reactions were carried out in a 1-mmol scale (*i.e.*, 0.24 g of **38**) and the results are summarized in Table 1. The best result was obtained when sodium hydride was used as base in DMSO (run 4: 78%). Phase-transfer catalyst (PTC) also yielded **39** (runs 5 and 6). Especially use of hexadecyltri-*n*-butylphosphonium bromide afforded **39** with 74% yield. However, in a 35-g scale synthesis, several impurities contaminated in the product, and further purification was required.[11] Thus, the condition of run 4 was chosen for a large scale synthesis and the reaction was achieved to provide **39** in a 35-g scale with 75% yield.

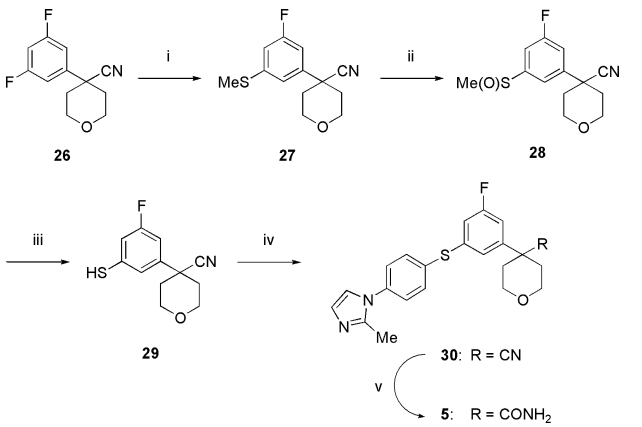
Then, triisopropylsilylthiol was efficiently introduced to **39** under the presence of palladium catalyst to afford **40**. Triisopropylsilylthioether **40** was coupled with iodide **14** to give the desired thioether **41** with 75% yield from **39**. The nitrile of **41** was efficiently hydrolyzed to give **1** selectively, according to the procedure developed for the large scale synthesis of **2**.[11] Thus, 24 g of **6** was obtained with 98% purity by HPLC.

Biological Testing The 5-LO inhibitory activity of the compounds was routinely evaluated *in vitro* using heparinized human whole blood (HWB) quantitating LTB_4.[12] The *in vivo* potency after oral administration of compounds

to mice was determined by PAF (platelet activating factor)-induced thrombosis assay.[13—15)]

Results and Discussion

We have already demonstrated that replacement of the methoxy group of **1** with aminocarbonyl (**2**) is well tolerated, and that metabolic stability was substantially enhanced, resulting in reduced ocular toxicity and improved pharmacokinetic profile. In this paper we disclose SAR leading to development candidate **6**. We have examined both the connection between the left handle and the central phenyl (*viz.*, X in Table 2) and the effect of fluorine atom(s) (*viz.*, Y and Z in Table 2) on the central phenyl ring (Table 2). Removal of the fluorine atom of **2** reduced *in vitro* potency (**3**). Adding a fluorine atom at the 2 position of the central phenyl ring of **2**, exemplified by **4**, slightly reduced *in vitro* and *in vivo* po-



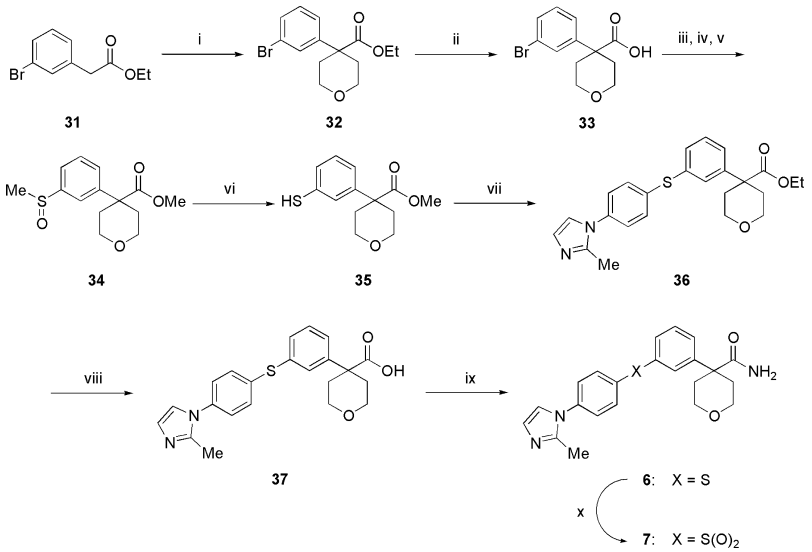
(i) MeSNa, DMF; (ii) $NaIO_4$, MeOH, H_2O; (iii) $(CF_3CO)_2O$, then triethylamine, MeOH; (iv) **14**, $Pd(PPh)_4$, *t*-BuONa, EtOH; (v) KOH, *t*-BuOH.

Chart 4. Synthesis of **5**

Table 1. THP Ring Construction on **39**

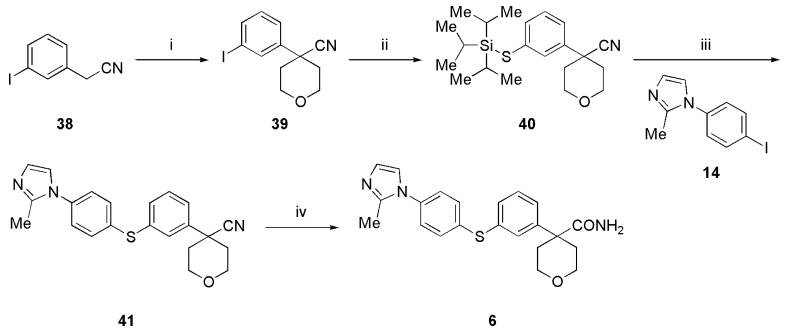
Run	Base	Solvent	Additive	Yield %
1[a)]	*t*-BuOK	DMF	None	20
2[a)]	NaOEt	EtOH	None	<10
3[a)]	$NaNH_2$	DMSO	None	50
4[a)]	NaH	DMSO	None	78
5[b)]	NaOH	Water	$CH_3(CH_2)_{15}P(n\text{-}Bu)_3Br$	74
6[b)]	NaOH	Water	$PhCH_2N(Et)_3Cl$	35

a) The reaction was conducted under a nitrogen atmosphere. *b*) 50% aqueous NaOH.



(i) NaH, 15-Crown-5, $(ClCH_2CH_2)_2O$, DMF; (ii) LiOH, THF, MeOH, H_2O; (iii) *n*-BuLi, MeSSMe, THF; (iv) HCl, MeOH; (v) $NaIO_4$, MeOH, H_2O; (vi) $(CF_3CO)_2O$, then triethylamine, MeOH; (vii) **14**, $Pd(PPh)_4$, *t*-BuONa, EtOH; (viii) LiOH, THF, MeOH, H_2O; (ix) $(COCl)_2$, CH_2Cl_2, then aqueous NH_3; (x) H_2O_2, AcOH.

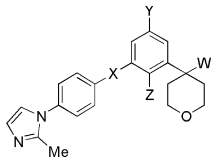
Chart 5. Syntheses of **6** and **7**



(i) NaH, $(ClCH_2CH_2)_2O$, DMSO (75%); (ii) NaH, triisopropylsilylthiol, $Pd(PPh_3)_4$, THF; (iii) *t*-BuOK, $Pd(PPh_3)_4$, EtOH (75% by two steps); (iv) KOH, *t*-BuOH (77%) (44% total yield).

Chaet 6. Improved Symthesis of **6**

Table 2. Effects of Structural Modification of **1**



Compd.	X	Y	Z	W	HWB IC_{50} (μM)[a]	PAF-thrombosis ED_{50} (mg/kg)[a]
1·HCl	CH_2O	F	H	OMe	0.060±0.008 (6)	4.5±1.5 (4)
2	CH_2O	F	H	$CONH_2$	0.34±0.11 (4)	4, 9[b]
3	CH_2O	H	H	$CONH_2$	1.14	5
4	CH_2O	F	F	$CONH_2$	0.47	8
5	S	F	H	$CONH_2$	0.75	3
6	S	H	H	$CONH_2$	0.20, 0.33[b]	3.7±0.3 (3)
6·HCl	S	H	H	$CONH_2$	0.23±0.05 (15)	3.4±0.4 (3)
7	$S(O)_2$	H	H	$CONH_2$	>1	N.D.[c]
8	O	H	H	$CONH_2$	>1	N.D.[c]

a) IC_{50}'s and ED_{50}'s are shown with±S.D. (number of determinations), where three or more determinations were made. *b*) $n=2$. *c*) Not determined.

tency. Replacement with sulfur (X=S) provided **5** with comparable oral *in vivo* potency but marginally reduced *in vitro* inhibitory activity. However, des-fluoro analog **6** essentially had comparable pharmacology with **1**. The effect of fluorine atom was found to be dependent upon the rest part of the linkage and was not clearly understood at the moment. On the other hand, substitution of sulfur with sulfone ($X=S(O)_2$: **7**) or oxygen (X=O: **8**) was not tolerated. Thus, connection between two phenyl rings was found to be critical for potency and sulfur atom was the best as X in the present series of compounds. Accordingly, **6** was selected for further characterization.

The original discovery route of **6** was, however, a ten-step synthesis with 14% total yield. In order to provide large quantity of **6** for further studies including preclinical toxicology studies, synthesis of **6** needed to be improved. Firstly, the original route was not amenable for scaling because of the low yield Pummerer reaction and instability of **35**. Furthermore, carboxylic acid **37** contaminated **6** in a gram-scale preparation. Consequently, an alternative route was required for larger-scale synthesis. We have reported the improved synthesis of **2**, which is structurally similar to **6**, and it was anticipated that some of approaches to the improvement in synthesis of **2** could be adapted to that of **1**, that is, the facile construction of the THP ring and carboxamide moiety.[11] Also as shown in Chart 5, the unsymmetric thioether of **36** was constructed by six-step synthesis from bromide **32** *via* unstable thiol **35** with 31% yield. Therefore, a convenient method of construction the unsymmetric thioether without isolating an unstable thiol was envisaged. On the base of the above consideration, the retro-synthesis of **6** was revised as illustrated in Chart 7, where commercially available 3-iodophenylacetonitrile **38** was chosen as the starting material.

Several methodologies to prepare unsymmetric thiols have been reported[16—18] and the method reported by Miranda and Soderquist was chosen, since it allows to prevent isolation of unstable arylthiol by protecting the thiol function with triisopropylsilyl group.[19,20] This method composed two steps: (i) introduction of triisopropylsilylthiol to one of the aryl iodides under the presence of palladium catalysis to produce the corresponding protected thiol, (ii) reaction of the product

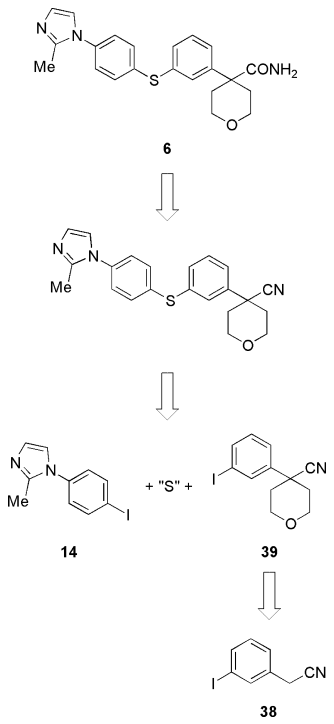


Chart 7. Revised Retro-Synthesis of **1**

with the other aryl iodide under the presence of palladium catalysis to give the desired unsymmetry thioether, without deprotection step. As shown in Chart 6, the thioether construction was improved by reducing synthetic steps from six to two and enhancing yield from 31 to 75%. Nitrile **41** was efficiently hydrolyzed to give **1** selectively, according to the procedure developed for the large scale synthesis of **2**.[11] Thus 24 g of **6** was obtained with 98% purity by HPLC. For preclinical studies, **6** was converted to the hydrochloride salt (**6**·HCl).

It was shown that **6** inhibited LTB_4 synthesis in HWB with an IC_{50} of 0.23±0.05 μM (mean±S.D., $n=15$ (Fig. 1). Also **6** provides dose-dependent protection against PAF induced thrombosis with an ED_{50} of 3.4±0.4 mg/kg *p.o.* (mean±S.D., $n=3$, Fig. 2). Pharmacokinetic profiles of **1**, **2** and **6** in rats are illustrated in Fig. 3. In rats, **6** showed improved exposure

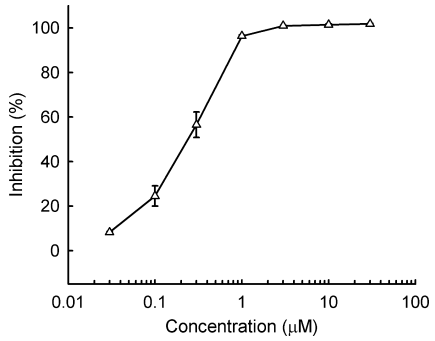


Fig. 1. *In Vitro* Potency of **6**·HCl on Production of 5-LO Metabolites, LTB_4 in Human Whole Blood Stimulated with A23187

Each point represents the mean±S.E.M. (n=15).

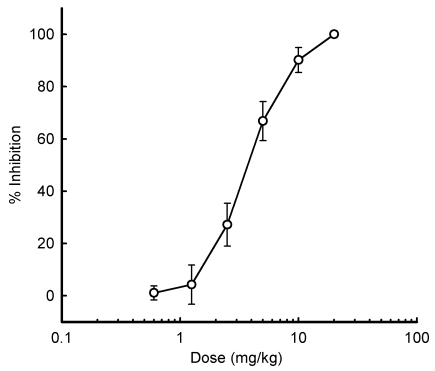


Fig. 2. The Effect of **6**·HCl Inhibition on PAF-Induced Thrombosis in Mice

The compound was perorally administered 45 min prior to PAF challenge. Each point represents the mean±S.E.M. (n=3).

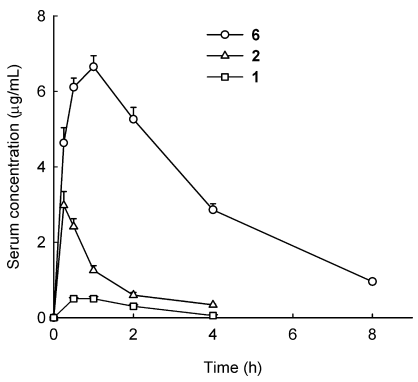


Fig. 3. Mean Plasma Concentration of **6**, **2**, and **1**

Drugs were dosed perorally to three female Sprague-Dawley rats (10 mg/kg). Each point represents the mean±S.E.M.

and extended half-life over **1** and **2**. Furthermore, no overt ocular toxicity was observed with **6**, and consequently **6** was advanced to clinical development.[21—24] As already discussed, the ocular toxicity was speculated due to metabolite(s), and one of the potential explanations was that even though the systemic exposure of **2** in rats was much higher than that of **1**, the incident of cataract formation with **2** was much lower than that of **1**.[9] Therefore, it is likely that the structural modification leading to **6** retarded the metabolism that might produce toxic metabolite(s) and improved the oral exposure (Chart 1).

Conclusion

Structure modification of **2** identified clinical candidate **6**. Furthermore a facile synthesis of **6** was developed, applying the approach developed for **2**. This method has advantages, such as (i) no isolation of unstable thiol, (ii) short synthesis (*i.e.*, four steps), (iii) higher total yield (44%), (iv) no chromatographic purification, (v) 98% purity of the final compound. The new method enabled to provide large quantity of **6**, which was used for preclinical toxicology studies. In rat toxicology studies, no overt ocular toxicity was observed.[21—23] There have been several reports of a role of not only LTD_4 but also LTB_4 in the antigen-induced pulmonary reaction. While $CycLT_1$ receptor antagonists, such as pranlukast, reduce the asthmatic response, protection is incomplete. Furthermore, synergetic effects on inhibitory activity in an asthma model by pranlukast and an LTB_4 antagonist were also reported.[25] The ability of 5-LO inhibitors to inhibit the biosynthesis of both peptido-leukotrienes and LTB_4 may suggest that these drugs could offer distinct advantages over receptor antagonists in the chronic treatment of inflammatory disease states.

Experimental

General Procedures Proton magnetic resonance (^{1}H-NMR) spectra were measured on a Joel FX270 spectrophotometer at 270 MHz and proton chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Melting points were determined on either a Buchi 535 or on a Yanagimoto micro-melting-point-apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. Low-resolution mass spectra were recorded on an Automass spectrometer and a Micromass Quattro II spectrometer for DI-EI and ESI, respectively. High-resolution mass spectra (EI) were recorded on a JOEL JMS-700 spectrometer (MStation) with direct inlet mode, and reported in m/z. Microanalyses (C, H, N, Cl, S) were performed by Analytical R&D, Pfizer Global Research & Development Nagoya Laboratories.

4-{3-[4-(2-Methy-1*H*-limidazol-1-yl)phenyl]thiophenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide Hydrochloride (1·HCl). 4-(2-Methyl-1*H*-imidazol-1-yl)phenyliodide (14) To a stirred solution of 2-methylimidazole (13.6 g, 165 mmol) in DMF (500 ml) was added sodium hydride (60% w/w dispersion in mineral oil, 6.60 g, 165 mmol) in portions over 10 min. The resulting white suspension was stirred at room temperature for 30 min, 4-fluoro-1-iodobenzene (33.3 g, 150 mmol) added and the mixture heated at 100 °C for 16 h. After the bulk of DMF was removed by evaporation, the resulting residue was partitioned between a mixture of ethyl acetate–toluene (2 : 1, 500 ml) and water (250 ml). The organic layer was separated and washed with water (250 ml). Product was extracted with 10% aqueous HCl (2×200 ml) and the combined aqueous extracts neutralized with 30% aqueous KOH solution. The resulting suspension was extracted with a mixture of ethyl acetate–toluene (2 : 1, 3×250 ml) and the combined organic extracts washed with water (2×250 ml), brine (250 ml), dried ($MgSO_4$) and concentrated to dryness. The residue was recrystallized from toluene to afford the titled compound as off-white solids (21.9 g, 51%). mp: 136—138 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.65—7.61 (2H, m), 7.32—7.26 (2H, m), 7.33 (1H, d, J=1.5 Hz), 6.98 (1H, d, J=1.5 Hz), 2.83 (3H, s); *Anal.* Cacl. for $C_{10}H_9N_2I$: C, 42.28, H, 3.19; N, 9.86. Found: C, 42.51; H, 3.19; N, 9.70.

4-Cyano-4-(3-iodophenyl)-3,4,5,6-tetrahydro-2*H*-pyran (39) To a solution of 3-iodophenylacetonitrile (**38**) (36.7 g, 151 mmol) in DMSO (250 ml) cooled to 0 °C was added sodium hydride (60% w/w dispersion in mineral oil, 13.3 g, 332 mmol) portionwise over 10 min. The reaction mixture was stirred for 30 min at room temperature and then bis(2-chloroethyl)ether (23.0 g, 161 mmol) was added slowly and stirring continued for an additional 1 h. The reaction mixture was poured into water (500 ml) and the mixture was extracted with an ethyl acetate–toluene mixture (2 : 1 v/v, 400 ml×3). The combined extracts were washed with 2 N aqueous HCl (300 ml), water (300 ml) and brine (300 ml), dried ($MgSO_4$) and concentrated to 100 ml. The precipitated solids were collected and washed with cold Et_2O (50 ml) to afford 35.5 g (75%) of the titled compound

as off white solids. mp: 106.6—107.3 °C (recrystallized from diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ: 7.83—7.80 (m, 1H), 7.73—7.67 (m, 1H), 7.50—7.44 (m, 1H), 7.16 (dd, 1H, J=8.1, 7.7 Hz), 4.14—4.02 (m, 2H), 3.98—3.81 (m, 2H), 2.20—1.99 (m, 2H); IR (KBr) cm^{-1}: 2240; MS (DI-EI) m/z: 313 (M^+); *Anal.* Calcd for $C_{12}H_{12}NOI$: C, 46.03, H, 3.86, N, 4.47. Found: C, 46.30; H, 3.68; N, 4.13.

4-Cyano-4-{3-[tri-(1-methylethyl)]silylthiophenyl}-3,4,5,6-tetrahydro-2*H*-pyran (40) To a solution of sodium hydride (60% w/w dispersion in mineral oil, 4.66 g, 117 mmol) in THF (180 ml) was added triisopropylsilylthiol (20.14 g, 106 mmol) in portions at 0 °C under an atmosphere of nitrogen. After being stirred for 30 min, the resulting mixture was added in one portion to a solution of 4-cyano-4-(3-iodophenyl)-3,4,5,6-tetrahydro-2*H*-pyran **39** (33.12 g, 106 mmol) and tetrakis(triphenylphosphine)palladium (7.35 g, 6.36 mmol) in toluene (180 ml) at room temperature. The mixture was heated at reflux for 1 h and the resulting mixture was diluted with water (100 ml), and extracted with ethyl acetate (500 ml×2). The combined extracts were washed with brine (150 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The titled compound (45.1 g), contaminated with a small amount of triphenylphosphine, obtained as a brownish oil was used in the next step without further purification. A sample was purified by column chromatography for microanalysis solidified on standing. mp: 52—53 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.62 (t, 1H, J=1.5 Hz), 7.48 (dt, 1H, J=7.0, 1.5 Hz), 7.34 (dt, 1H, J=7.0, 1.5 Hz)), 7.28 (t, 1H, J=7.0 Hz), 4.13—4.02 (m, 2H), 3.96—3.83 (m, 2H), 2.18—1.97 (m, 4H), 1.33—1.16 (m, 1H) , 1.07 (d, 18H, J=6.6 Hz); IR (KBr) cm^{-1}: 2230; *Anal.* Calcd for $C_{21}H_{33}NOSSi$: C, 67.15; H, 8.85; N, 3.73. Found: C, 67.23; H, 8.98; N, 3.52.

4-Cyano-4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (41) To a stirred solution of 4-cyano-4-{3-[tri-(1-methylethyl)]silylthiophenyl}-3,4,5,6-tetrahydro-2*H*-pyran **10** (39.82 g, 106 mmol), tetrakis(triphenylphosphine)palladium (3.67 g, 3.18 mmol) and **14** (29.81 g, 105 mmol) in ethanol (450 ml) was added potassium *tert*-butoxide (14.27 g, 127 mmol) at room temperature under an atmosphere of nitrogen. The mixture was heated to 80 °C overnight, then cooled and solvent removed under reduced pressure. The residual oil was poured into water (100 ml) and extracted with ethyl acetate (700 ml×2). The combined organic extracts were washed with 2 N aqueous HCl (75 ml×2) and discarded. The combined acidic aqueous extracts were neutralized with 3 N aqueous NaOH solution and than extracted with ethyl acetate (700 ml×2). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford 30.04 g (75%) of the titled compound as a brownish oil contaminated with a small quantity of **6**, which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.54—7.57 (m, 1H), 7.48—7.35 (m, 5H), 7.28—7.22 (m, 2H), 7.02 (d, 1H, J=1.5 Hz), 7.00 (d, 1H, J=1.5 Hz), 4.21—4.05 (m, 2H), 3.99—3.80 (m, 2H), 2.40 (s, 3H), 2.19—2.02 (m, 4H); MS (DI-EI) m/z: 375 (M^+). Further characterization was not performed due to the contamination of **6**.

4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)phenylthio]}phenyl-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (6) To a solution of 4-cyano-4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]}phenyl-3,4,5,6-tetrahydro-2*H*-pyran **41** (30.04 g, 80 mmol) in *tert*-butanol (300 ml) was added powdered potassium hydroxide (85%, 15.8 g, 239 mmol) at 50 °C. The mixture was then heated at reflux with stirring for 6 h. The reaction mixture was cooled and volatiles removed under reduced pressure. To the residue was added water (200 ml) and the resulting pale pink precipitates were collected by suction filtration and washed with water (100 ml×2) and then ethyl acetate (100 ml×2) to afford 13.5 g (43%) of the titled compound as a pale pink powder. Further product crystallized out of the filtrate: second crop, 7.5 g (24%) and third crop, 3.0 g (10%). mp: 208—210 °C; ^{1}H-NMR (DMSO-d_6) δ: 7.48—7.33 (m, 8H), 7.30 (br s, 1H), 7.28 (d, 1H, J=1.5 Hz), 7.09 (br s, 1H), 6.91 (d, 1H, J=1.5 Hz), 3.83—3.68 (m, 2H), 3.53—3.40 (m, 2H), 2.48—2.38 (m, 2H), 2.30 (s, 3H), 1.90—1.73 (m, 2H); IR (KBr) cm^{-1}: 1682, 1664; MS (ESI+) m/z: 394 $(M+1)^+$; *Anal.* Calcd for $C_{22}H_{23}N_3O_2S$: C, 67.15; H, 5.89; N, 10.68. Found: C, 67.23; H, 5.96; N, 10.64.

4-{3-[4-(2-Methy-1*H*-limidazol-1-yl)phenyl]thiophenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide Hydrochloride (6·HCl) Free base 4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide **1** (24.15 g, 61 mmol) was suspended into methanol (200 ml) and the suspension was heated to reflux. Thirty milliliters of 10% hydrogen chloride in methanol was then added. The suspension turned into a pale orange solution. The resulting solution was concentrated to dryness to give pale yellow solids. Toluene (200 ml) was added and evaporated under reduced pressure to eliminate remaining hydrogen chloride and methanol. The resulting pale orange solids (35.75 g) were dried to constant weight *in vacuo*. Ethanol (200 ml) was added and the mixture heated to reflux with stirring. To the resulting mixture, which was nearly homogeneous, was added 1.35 g of active charcoal. After stirring at reflux for 5 min, the mixture was filtered while hot. The yellow filtrate was cooled to 0 °C over 30 min with gentle stirring and maintained to 0 °C for a further 30 min. Precipitates were collected by suction filtration, washed with cold ethanol (4 ml×2) and *n*-hexane (10 ml) and dried under vacuum at 80 °C overnight to give 20.45 g of the titled compound as white solids. mp: 218—224 °C (decomposition); ^{1}H-NMR (DMSO-d_6) δ: 7.86 (d, 1H, J=2.2 Hz), 7.76 (d, 1H, J=2.2 Hz), 7.60 (d, 1H, J=8.4 Hz), 7.53—7.50 (m, 1H), 7.48—7.31 (m, 6H), 7.10 (br s, 1H), 3.80—3.69 (m, 2H), 3.52—3.39 (m, 2H), 2.54 (s, 3H), 2.48—2.38 (m, 2H), 1.87—1.75 (m, 2H); IR (KBr) cm^{-1}: 1683, 1669; MS (DI-EI) m/z: 393 (M^+); *Anal.* Calcd for $C_{22}H_{23}N_3O_2S\cdot HCl$: C, 59.71; H, 5.79; N, 9.49, Cl, 8.01; S, 7.25. Found: C, 59.44; H, 5.63; N, 9.29, Cl, 7.82; S, 7.13.

4-{3-[4-(2-Methy-1*H*-limidazol-1-yl)phenyl]thiophenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (6): Discovery Route. Ethyl 4-(3-Bromophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (32) To a stirred solution of ethyl 3-bromophenylacetate (**31**) (41.3 g, 170 mmol) and 15-crown-5 (3.74 g, 17 mmol) in DMF (1 l) at room temperature was added sodium hydride (14.8 g, 370 mmol, 60% dispersion in mineral oil) in portions. After stirring at room temperature for 40 min, sodium iodide (25.5 g, 170 mmol) and bis(2-chloroethyl)ether (30.4 g, 210 mmol) were added. After 10.5 h the bulk of DMF was removed under reduced pressure. The residue was covered with a mixture of ethyl acetate and toluene (1 : 1, 500 ml) and washed with 0.5 N hydrogen chloride (500 ml). The aqueous layer was extracted with a mixture of ethyl acetate–toluene (1 : 1, 2×500 ml) and the combined extracts were washed with water (250 ml), saturated sodium bicarbonate (250 ml), water (2×250 ml) and brine (250 ml), dried ($MgSO_4$) and concentrated under reduced pressure to give 56.8 g of crude product as an orange liquid. Purification by column chromatography (15% then 20% ethyl acetate in *n*-hexane) gave the titled compound as a yellow liquid (36.5 g, 69%). ^{1}H-NMR ($CDCl_3$) δ: 7.52 (1H, dd, J=1.8, 1.8 Hz), 7.40 (1H, ddd, J=7.7, 1.8, 1.8 Hz), 7.31 (1H, ddd, J=1.8, 1.8, 8.1 Hz), 7.22 (1H, dd, J=8.1, 7.7 Hz), 4.16 (2H, q, J=7.3 Hz), 3.94 (2H, ddd, J=11.7, 4.0, 3.3 Hz), 3.56 (2H, ddd, J=13.6, 11.7, 2.2 Hz), 2.50 (2H, ddd, J=11.4, 3.3, 2.2 Hz), 1.94 (2H, ddd, J=13.6, 11.4, 4.0 Hz), 1.20 (3H, t, J=7.3 Hz).

4-(3-Bromophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic Acid (33) A stirred mixture of ethyl 4-(3-bromophenyl)-3,4,5,6-2*H*-tetrahydro-2*H*-pyran-4-carboxylate (**32**) (36.5 g, 117 mmol), an aqueous solution of lithium hydroxide (6.14 g, 146 mmol, 50 ml), methanol (150 ml) and THF (150 ml) was refluxed for 1 d. The reaction mixture was partitioned between ether (100 ml) and 10% aqueous potasium hydroxide solution (300 ml). The ethereal layer was separated, extracted with 10% aqueous potassium hydroxide solution (2×100 ml) and discarded. The combined aqueous extracts were acidified with concentrated hydrogen chloride and the resulting white precipitate were collected by filtration, washed with water and dried to constant weight under vacuum at 80 °C to give the titled compound as white solids (26.4 g, 79%). ^{1}H-NMR ($CDCl_3$) δ: 7.55 (1H, dd, J=1.8, 1.8 Hz), 7.43 (1H, ddd, J=8.1, 1.8, 1.5 Hz), 7.35 (1H, ddd, J=8.1, 1.8, 1.5 Hz), 7.24 (1H, dd, J=8.1, 8.1 Hz), 3.94 (2H, ddd, J=12.1, 4.0, 3.7 Hz), 3.62 (2H, ddd, J=12.1, 11.7, 1.8 Hz), 2.50 (2H, m), 1.97 (2H, ddd, J=13.9, 11.7, 4.0 Hz) (A peak due to the exchangeable carboxylic acid proton was not observed).

Methyl 4-(3-Methylsulfinylphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (34) To a stirred solution of 4-(3-bromophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid (**33**) (19.1 g, 67 mmol) in THF (650 ml) at −78 °C under a nitrogen atmosphere was added a solution of *n*-butyllithium (1.60 M in *n*-hexane solution, 100 ml, 160 mmol) below −70 °C. After 45 min a solution of dimethyl disulfide (8.84 g, 94 mmol) in THF (50 ml) was added slowly over 30 min and the mixture was stirred at −78 °C for 70 min and then at ambient temperature for 3 h. To the resulting suspension was added 2 N hydrogen chloride (500 ml) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×250 ml) and the combined organic layers washed with water (4×100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated to dryness. The residue (21.5 g) was dissolved in methanol (100 ml) and 10% methanolic hydrogen chloride (100 ml) was added. The mixture was heated to reflux with stirring for 13 h. Another portion of 10% methanolic hydrogen chloride (100 ml) was added and heating was continued for another 7 h. Volatiles were removed by evaporation and the residue was dissolved in ethyl acetate (500 ml), and washed with water (2×250 ml), saturated aqueous sodium bicarbonate (250 ml), water (250 ml) and brine (250 ml). The aqueous layers were combined and extracted with ethyl acetate (2×250 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. This product (17.9 g) was dissolved in methyl alcohol (200 ml) and cooled to 0 °C. A solution of sodium periodate (16.0 g, 75 mmol) in water (200 ml) was added and the resulting

suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (500 ml) and extracted with dichloromethane (200 ml) and 10% methyl alcohol in dichloromethane (3×200 ml). The combined extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated to dryness. Purification by column chromatography (ethyl acetate) gave the titled compound as a colorless liquid (12.2 g, 64%), which solidified on standing. ^{1}H-NMR ($CDCl_3$) δ: 7.71—7.68 (1H, m), 7.55—7.50 (3H, m), 4.02—3.92 (2H, m), 3.69 (3H, s), 3.62—3.50 (2H, m), 2.73 (3H, s), 2.62—2.52 (2H, m), 2.06—1.59 (2H, m).

Methyl 4-(3-Mercaptophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (35) Methyl 4-(3-methylsulfinylphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**34**) (12.2 g, 43 mmol) was dissolved in trifluoroacetic anhydride (50 ml) and heated at reflux for 30 min. Volatiles were removed by evaporation and the residue was dissolved into methyl alcohol (100 ml). Triethylamine (100 ml) was added over 5 min and the mixture concentrated to dryness. The residue was dissolved in ethyl acetate (500 ml), washed with saturated aqueous ammonium chloride (200 ml) and brine (200 ml), dried ($MgSO_4$) and concentrated to dryness to provide crude titled compound as a pale black liquid which was used as such without further purification.

Ethyl 4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (36) A solution of methyl 4-(3-mercaptophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**35**) (1.04 g, 3.5 mmol), 4-(2-methylimidazol-1-yl)phenyliodide (**14**) (0.89 g, 3.5 mmol), sodium *tert*-butoxide (673 mg, 7 mmol) and tetrakis(triphenylphosphine)palladium 162 mg, 0.14 mmol) in dry ethanol (20 ml) was heated to reflux with stirring overnight. Volatiles were removed by evaporation and the residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated to dryness to give 1.09 g of crude product as a brown liquid. Purification by column chromatography (methyl alcohol in dichloromethane, increasing the ratio of methyl alcohol from 0 to 4%) afforded the titled compound (0.90 g, 61%). ^{1}H-NMR ($CDCl_3$) δ: 7.51—6.98 (10H, m), 4.15 (2H, d, J=7.0 Hz), 3.98—3.88 (2H, m), 3.61—3.50 (2H, m), 2.55—2.45 (2H, m), 2.37 (3H, s), 2.01—1.90 (2H, m), 1.18 (3H, t, J=7.0 Hz).

4-{3-[4-(2-Methylimidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic Acid (37) To a solution of ethyl 4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**36**) obtained as above in a mixture of tetrahydrofuran (20 ml) and methyl alcohol (20 ml) was added an aqueous solution of lithium hydroxide (0.42 g, 10 mmol) and the mixture heated at reflux with stirring for 11 h. Volatiles were then removed under reduced pressure. The residue was partitioned between ether (100 ml) and water (100 ml) and the ethereal layer was extracted with 1 N aqueous potassium hydroxide (2×50 ml). The combined aqueous layers were neutralized with 1 N aqueous hydrogen chloride and saturated aqueous sodium bicarbonate. Precipitates were collected by filtration, washed with water and dried under vacuum at 80 °C to give the titled compound (488 mg, 35% from methyl 4-(3-methylsulfinylphenyl)-3,4,5,6-2*H*-tetrahydropyran-4-carboxylate. ^{1}H-NMR ($CDCl_3$) δ: 7.49—7.37 (7H, m), 7.34—7.29 (1H, m), 7.30 (1H, d, J=1.1 Hz), 6.91 (1H, d, J=1.1 Hz), 3.90—3.78 (2H, m), 3.49—3.36 (2H, m), 2.38—2.28 (2H, m), 2.28 (3H, s), 1.88—1.76 (2H, m) (A peak due to the exchangeable carboxylic acid proton was not observed).

4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (6) To a stirred suspension of 4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid (**37**) (217 mg, 0.55 mmol) in CH_2Cl_2 (20 ml) at 0 °C was added oxalyl chloride (254 mg, 2.0 mmol). The resulting solution was stirred at 0 °C for 30 min and then at room temperature for 20 min. Volatiles were then removed by evaporation. The residue was added to a stirred aqueous ammonia solution (30 ml) and stirred for 1 h. After cooling to 0 °C, precipitates were collected by filtration, washed with water and dried to constant under vacuum at 80 °C to give the titled compound (207 mg, 96%). mp: 208—210 °C; ^{1}H-NMR (DMSO-d_6) δ: 7.49—7.26 (10H, m), 7.10 (1H, br s), 6.90 (1H, d, J=1.1 Hz), 3.78—3.68 (2H, m), 3.52—3.40 (2H, m), 2.46—2.36 (2H, m), 2.28 (3H, s), 1.86—1.64 (2H, m); IR (KBr) cm^{-1}: 1682, 1664; MS (ESI+) *m/z*: 394 $(M+1)^+$; *Anal.* Calcd for $C_{22}H_{23}N_3O_2S$: C, 67.15; H, 5.89; N, 10.68; Cl, 8.15. Found: C, 66.82; H, 5.83; N, 10.39, Cl, 8.22.

4-{5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (5). 4-Cyano-4-(5-fluoro-3-methylsulfinylphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (28) Methane thiol was bubbled into a stirred suspension of sodium hydride (65% w/w dispersion in mineral oil, 273 mg, 7.4 mmol) in DMF (10 ml) until a clear solution was obtained. 4-Cyano-4-(3,5-difluorophenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**26**)[11] (1.65 g, 7.4 mmol) was added and the resulting mixture was heated at 100 °C for 22 h, cooled and poured into water (100 ml). The mixture was extracted with diethyl ether (100 ml) and extract washed with water (100 ml), brine (100 ml) and dried ($MgSO_4$). Removal of solvent gave 1.87 g of 4-cyano-4-(5-fluoro-3-methylthiophenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**27**) as a tan oil, which was used for the next step without further purification.

To a solution of the product in methyl alcohol (200 ml) stirred at 0 °C a solution of sodium periodate (16.0 g, 75 mmol) in water (200 ml) was added and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (500 ml) and extracted with dichloromethane (200 ml) and methyl alcohol–dichloromethane (1 : 9, 2×200 ml). The combined extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated to dryness. Purification by chromatography using ethyl acetate as an eluent gave the titled compound as a colorless liquid (12.2 g, 64%) , which solidified on standing. ^{1}H-NMR ($CDCl_3$) δ: 7.60—7.54 (1H, m), 7.41—7.30 (2H, m), 4.20—4.15 (2H, m), 3.98—3.81 (2H, m), 2.78 (3H, s), 2.25—2.01 (4H, m).

4-Cyano-4-(5-fluoro-3-mercaptophenyl)-3,4,5,6-tetrahydro-2*H*-pyran (29) 4-Cyano-4-(5-fluoro-3-methylsulfinylphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**28**) (1.24 g, 4.66 mmol) was dissolved in trifluoroacetic anhydride (10 ml) and heated at reflux for 30 min. Volatiles were removed by evaporation, to the residue added 1 : 1 methyl alcohol–triethylamine (100 ml) with stirring, and the mixture concentrated to dryness. The residue was dissolved in methylene chloride (200 ml), washed with saturated aqueous ammonium chloride (100 ml), dried ($MgSO_4$) and concentrated to dryness to provide crude titled compound as a yellow liquid which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.46—6.89 (3H, m), 4.18—4.00 (2H, m), 3.96—3.78 (2H, m), 2.20—1.92 (4H, m) (A peak due to the exchangeable thiol proton was not observed).

4-Cyano-4-{5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (30) A solution of 4-cyano-4-(5-fluoro-3-mercaptophenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**29**) (1.30 g, 5.5 mmol), 4-(2-methylimidazol-1-yl)phenyliodide (**14**) (1.56 g, 5.5 mmol), sodium *tert*-butoxide (1.06 g, 11 mmol) and tetrakis(triphenylphosphine)palladium (578 mg, 0.5 mmol) in dry ethyl alcohol (80 ml) was heated to reflux with stirring for 4.5 h. Volatiles were removed by evaporation and the residue was dissolved into diethyl ether (200 ml), washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated to dryness to give 2.96 g of crude product as a tar oil. Purification by chromatography (1 : 20 methyl alcohol–dichloromethane) afforded the titled compound (1.82 g) as a brown oil, which was contaminated with 4-(2-methylimidazol-1-yl)phenyliodide (**14**). ^{1}H-NMR ($CDCl_3$) δ: 7.75—6.89 (9H, m), 4.15—4.04 (2H, m), 3.96—3.81 (2H, m), 2.40 (3H, s), 2.18—1.98 (4H, m).

4-{5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (5) To a solution of 4-cyano-4-{5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (**30**) (1.71 g, 4.36 mmol) in *tert*-butyl alcohol (20 ml) was added powdered potassium hydroxide (85%, 860 mg, 13 mmol). The resulting mixture was heated at reflux temperature for 4 h, cooled and concentrated *in vacuo*. Water (50 ml) was added and the precipitates were collected by filtration and washed with 50 ml of ethyl acetate. After drying under vacuum, 560 mg (31%) of the titled compound was obtained as a yellow powder. mp: 203—206 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.50 (4H, s), 7.32 (2H, s), 7.21 (1H, s), 7.20—6.98 (3H, m), 6.92 (1H, s), 3.80—3.62 (2H, m), 3.52—3.26 (2H, m), 2.47—2.20 (5H, m), 1.88—1.67 (2H, m); IR (KBr) cm^{-1}: 1683; MS (ESI+) *m/z*: 411 $(M+1)^+$; *Anal.* Calcd for $C_{22}H_{22}FN_3O_2S \cdot H_2O$: C, 61.52; H, 5.63; N, 9.78. Found: C, 61.92; H, 5.27; N, 9.51.

4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)phenoxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (8). 4-Cyano-4-(3-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (10) To a dichloromethane (80 ml) solution of 4-cyano-4-(3-methoxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**9**) (2.32 g, 10.35 mmol)[10] cooled to 0 °C was added boron tribromide (3.15 ml, 33.3 mmol) dropwise over 10 min. The ice-bath was removed and the reaction mixture stirred at ambient temperature for 19 h, and then at reflux for 4 h. The reaction mixture was cooled and poured into water (150 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 ml×3). The combined organic extracts were washed with brine (50 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The crude product was crystallized from isopropyl ether to afford titled compound as off-white solids (1.43 g, 66%). ^{1}H-NMR ($CDCl_3$) δ: 7.29 (1H, t, J=8.1 Hz), 7.04 (1H, dd, J=8.1, 2.2 Hz), 6.98 (1H, dd, J=4.0, 2.2 Hz), 6.83 (1H, dd, J=8.1, 4.0 Hz), 5.14 (1H, br s), 4.09 (2H, ddd, J=11.7, 4.0, 3.3 Hz), 3.90

(2H, ddd, J=12.1, 11.7, 2.2 Hz), 2.14—2.01 (4H, m); *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.80; H, 6.44; N, 6.86.

4-Cyano-4-{3-[4-(2-methyl-1*H*-imidazol-1-yl)phenoxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (15) A mixture of 4-(2-methylimidazol-1-yl)phenyl iodide (**14**) (1.28 g, 4.5 mmol), 4-cyano-4-(3-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**10**) (1.20 g, 5.9 mmol) and K_2CO_3 (4.15 g, 30 mmol) in pyridine (50 ml) was heated at 130 °C, cupric oxide (636 mg, 8.0 mmol) added and the reaction mixture was heated under reflux for 2 d. The reaction mixture was cooled and filtered through a celite pad and the solids were washed with ethyl acetate (100 ml). The filtrate was concentrated under reduced pressure, and the resulting residue was diluted with water (100 ml) and extracted with ethyl acetate (50 ml×3). The combined organic extracts were washed with 1 N aqueous NaOH (100 ml), water (100 ml) and brine (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (E. Merck LiChroprep NH_2, 100 g; eluted with hexane–ethyl acetate (1 : 1)) to afford 620 mg (38%) of the titled compound as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.44 (1H, dd, J=8.1, 7.7 Hz), 7.33—7.21 (4H, m), 7.12—6.98 (5H, m), 4.15—4.04 (2H, m), 3.99—3.82 (2H, m), 2.37 (3H, s), 2.22—2.00 (4H, m).

4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)phenoxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (8) The titled compound was prepared according to the procedure described as the procedure for preparation of 4-{5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (**5**) except that 4-cyano-4-{3-[4-(2-methylimidazol-1-yl)phenoxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (**15**) was used in place of 4-cyano-4-{5-fluoro-3-[4-(2-methylimidazol-1-yl)phenylthio]-phenyl}-3,4,5,6-tetrahydro-2*H*-pyran (**30**). mp: 186—186.5 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.40 (1H, dd, J=8.1, 7.7 Hz), 7.29—7.13 (4H, m), 7.09—6.95 (5H, m), 5.32 (2H, br s), 3.89—3.70 (4H, m), 2.43—2.32 (2H, m), 2.40 (3H, s), 2.16—2.02 (2H, m); IR (KBr) cm^{-1}: 1670; MS (ESI+) m/z: 378 $(M+1)^+$; *Anal.* Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.05; H, 6.21; N, 10.99.

4-{3-[4-(2-Methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (3) The titled compound was prepared according to the procedure reported[8] using 4-(2-methyl-1*H*-imidazol-1-yl)benzyl chloride hydrochloride (**11**) and 4-cyano-4-(3-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**10**) and then the one described as a procedure for 4-{5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)phenylthio]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (**5**). mp: 183—186 °C; ^{1}H-NMR ($CDCl_3$) δ: δ: 7.60—7.54 (2H, m), 7.41—7.32 (3H, m), 7.09—7.00 (4H, m), 6.98—6.91 (1H, m), 5.36—5.22 (2H, br s), 5.12 (2H, s), 3.89—3.76 (4H, m), 2.39 (3H, s), 2.44—2.33 (2H, m) , 2.19—2.02 (2H, m); IR (KBr) cm^{-1}: 1680; MS (ESI+) m/z: 392 $(M+1)^+$; *Anal.* Calcd. for $C_{23}H_{25}N_3O_3\cdot 0.1H_2O$: C, 70.25; H, 6.46; N, 10.68. Found: C, 70.04; H, 6.44; N, 10.67.

4-{2,5-Difluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-caboxamide (4). 1-*O*-*tert*-Butyldimethylsilyloxy-2,5-difluorobenzene (17) To a stirred solution of 2,5-difluorophenol (**16**) (15.1 g, 116 mmol) in DMF (100 ml) was added sodium hydride (65% oil dispersion; 5.13 g, 139 mmol) with ice-cooling. After stirring for 30 min, *tert*-butyldimethylsilyl chloride (17.5 g, 0.116 mmol) was added and the stirring was continued for an additional 1 h. The mixture was poured into water (200 ml) and extracted with ether (300 ml). The extract was washed with brine (200 ml), dried ($NaSO_4$) and solvent removal of by evaporation to give 26.65 g (94%) of the titled compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.05—6.91 (1H, m), 6.70—6.52 (2H, m), 1.00 (9H, s), 0.201 (3H, s), 0.197 (3H, s).

3-*tert*-Butyldimethylsilyloxy-2,5-difluorobenzaldehyde (18) A 1.0 M solution of *sec*-BuLi (21.5 ml, 21.5 mmol) was added dropwise to a stirred solution of 1-*O*-*tert*-butyldimethylsilyloxy-2,5-difluorobenzene (**17**) (5.0 g, 20 mmol) in THF (20 ml) at −78 °C. After 0.5 h, DMF (1.9 ml, 24.6 mmol) was added dropwise while the temperature was kept below −70 °C. After 30 min the mixture was allowed to warm to room temperature over 30 min. To the mixture was added 3 N HCl (30 ml) and the stirring was continued for 30 min. The mixture was extracted with ether (100 ml) and the extract was washed with water (100 ml), brine (100 ml), dried ($NaSO_4$) and evaporated. Column chromatography of the residue eluting with *n*-hexane gave 3.56 g (64%) of the titled compound as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 10.31 (1H, d, J=2.9 Hz), 7.12 (1H, ddd, J=7.7, 4.4, 3.3 Hz), 6.89 (1H, ddd, J=9.2, 7.0, 3.3 Hz), 1.02 (9H, s), 0.245 (3H, s), 0.240 (3H, s).

2,5-Difluoro-3-methoxybenzaldehyde (19) Potassium fluoride (7.79 g, 134 mmol) and iodomethane (4.98 ml, 80 mmol) were added to a stirred solution of 3-*tert*-butyldimethylsilyloxy-2,5-difluorobenzaldehyde (**18**) (19.45 g, 67 mmol) in DMF (100 ml) at room temperature. After 5 h, the mixture was poured into water (100 ml) and extracted with ethyl acetate (200 ml). The extract was washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate/*n*-hexane (1/10) to give 8.58 g (74%) of the titled compound as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 10.35 (1H, d, J=2.9 Hz), 7.08 (1H, ddd, J=7.3, 4.0, 2.9 Hz), 6.94 (1H, ddd, J=9.5, 6.6, 2.9 Hz), 3.94 (3H, s).

2,5-Difluoro-3-methoxybenzyl alcohol (20) Sodium borohydride (2.83 g, 74.7 mmol) was added to a stirred solution of 2,5-difluoro-3-methoxybenzaldehyde (**19**) (8.57 g, 49.8 mmol) in ethanol (100 ml) at room temperature. After 30 min, the mixture was concentrated, the residue was diluted with ether (300 ml) and successively washed with water (200 ml), 10% citric acid (200 ml), water (200 ml), brine (200 ml), and dried ($MgSO_4$). Removal of solvent gave 8.26 g (95%) of the titled compound as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 6.80—6.69 (2H, m), 4.74 (2H, s), 3.86 (3H, s), 2.14 (1H, br s).

2,5-Difluoro-3-methoxyphenylacetonitrile (21) To a stirred solution of 2,5-difluoro-3-methoxybenzyl alcohol (**20**) (8.26 g, 47.4 mmol) in dichloromethane was added *p*-toluenesulfonyl chloride (9.95 g, 52.2 mmol) and triethylamine (7.30 ml, 52.2 mmol) at room temperature. After 3.5 h, the mixture was poured into water (200 ml) and extracted with ether (200 ml). The extract was washed with brine (200 ml), dried ($MgSO_4$) and concentrated consecutively. To the residue was added DMSO (200 ml) and sodium cyanide (3.48 g, 71 mmol). The resulting mixture was stirred for 2 h and then poured into water (200 ml) and extracted with ether (300 ml). The extract was washed with water (100 ml), brine (100 ml) and dried ($MgSO_4$). Removal of solvent gave 5.91 g (63%) of the titled compound as a red oil. ^{1}H-NMR ($CDCl_3$) δ: 6.80—6.65 (2H, m), 3.89 (3H, s), 3.76 (2H, d, J=0.7 Hz).

Methyl 2,5-Difluoro-3-methoxyphenylacetate (22) To a stirred solution of 2,5-difluoro-3-methoxyphenylacetonitrile (**21**) (5.92 g, 30 mmol) in ethylene glycol (150 ml) was added potassium hydroxide (85%; 3.0 g, 45 mmol). The mixture was heated at 120 °C for 1 h and then the mixture was poured into water (100 ml) and washed with ether (100 ml). The aqueous layer was acidified with 6 N HCl (10 ml) and extracted with ether (200 ml). The extract was washed with water (50 ml), brine (50 ml), dried ($MgSO_4$) and evaporated. The residual solid was dissolved in methanol (200 ml) and to the solution was added concentrated sulfuric acid (2 ml). The resulting mixture was heated at reflux for 1 h, cooled and concentrated *in vacuo*. The residue was dissolved in ether (100 ml), washed with water (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), brine (100 ml) and dried ($MgSO_4$). Removal of solvent gave 3.80 g (59%) of the titled compound as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: ($CDCl_3$) 6.70—6.50 (2H, m), 3.87 (3H, s), 3.72 (3H, s), 3.65 (2H, d, J=1.8 Hz).

Methyl 4-(2,5-Difluoro-3-methoxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (23) The titled compound was prepared according to the procedure described for preparation of ethyl 4-(3-bromophenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**32**) except that methyl 2,5-difluoro-3-methoxyphenylacetate (**22**) was used in place of ethyl 3-bromophenylacetate (**31**). ^{1}H-NMR ($CDCl_3$) δ: 6.71—6.59 (2H, m), 3.93—3.73 (4H, m), 3.86 (3H, s), 3.75 (3H, s), 2.45—2.32 (2H, m), 2.14—1.96 (2H, m).

Methyl 4-(2,5-Difluoro-3-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (24) The titled compound was prepared according to the procedure described for preparation of 4-cyano-4-(3-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**10**) except that methyl 4-(2,5-difluoro-3-methoxyphenyl)-3,4,5,6-tetrahydropyran-4-carboxylate (**23**) was used in place of 4-cyano-4-(3-methoxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (**9**). ^{1}H-NMR ($CDCl_3$) δ: 6.80—6.50 (2H, m), 3.96—3.68 (7H, m), 2.49—2.32 (2H, m), 2.16—1.95 (2H, m) (A peak due to the exchangeable phenol proton was not observed).

Methyl 4-{2,5-Difluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)]benzyloxyphenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (25) The titled compound was obtained from methyl 4-(2,5-difluoro-3-hydroxyphenyl)-2*H*-3,4,5,6-tetrahydropyran-4-carboxylate (**24**) and 4-(2-methyl-imidazol-1-yl)benzyl chloride hydrochloride (**11**) as a yellow oil, according to the procedure reported.[8] Yield was 49%. ^{1}H-NMR ($CDCl_3$) δ: 7.57 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 7.05 (1H, d, J=1.5 Hz), 7.01 (1H, d, J=1.5 Hz), 6.90—6.45 (2H, m), 5.13 (2H, s), 3.95—3.62 (7H, m), 2.50—2.30 (5H, m), 2.16—1.94 (2H, m).

4-{2,5-Difluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-caboxamide (4) To a solution of methyl 4-{2,5-difluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)]benzyloxyphenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**25**) in a mixture of tetrahydrofuran (9 ml), methyl alcohol (3 ml) and water (1.5 ml) was added an aqueous 4 N solution of lithium hydroxide (1.5 ml) and the mixture heated at reflux with stirring for 1.5 h. Volatiles were then removed under reduced pressure.

To the residue was added water (100 ml) and extracted with CH_2Cl_2 (2×100 ml). The combined extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated to dryness to give 469 mg of a off-white solid, which was used for the next reaction without further purification.

To a stirred suspension of the product obtained above in CH_2Cl_2 (15 ml) at room temperature was added thionyl chloride (15 ml). The resulting solution was stirred and heated to reflux for 1 h. After cooling to room temperature, volatiles were removed by evaporation. To the residue was added aqueous ammonia solution (20 ml) and stirred for 0.5 h at room temperature. Precipitates were collected by filtration and recrystallized from acetonitrile to give the titled compound (180 mg, 39%). mp: 222—224 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.56 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 7.04 (1H, d, J=1.1 Hz), 7.01 (1H, d, J=1.5 Hz), 6.82—6.69 (2H, m), 5.40 (2H, br s), 5.15 (2H, s), 4.00—3.70 (4H, m), 2.50—2.30 (5H, m), 2.22—2.02 (2H, m); MS (ESI+) m/z: 428 $(M+1)^+$; *Anal.* Calcd for $C_{23}H_{23}F_2N_3O_3$: C, 64.63; H, 5.42; N, 9.83. Found: C, 64.77; H, 5.78; N, 9.64.

4-{3-[4-(2-Methylimidazol-1-yl)phenylsulfonyl]phenyl}-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (7) A mixture of **6** (1.62 g, 4 mmol) and hydrogen peroxide (30% in water, 5 ml) in acetic acid (12 ml) was stirred at room temperature for 12 h, then heated at reflux for 2 h. The reaction mixture was then poured into saturated $NaHCO_3$ (50 ml) and extracted with ethyl acetate (300 ml×2). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure to afford 1.68 g (quant.) of the titled compound as pale yellow solid. Further purification was performed by preparative thin-layer chromatography using CH_2Cl_2–MeOH (10 : 1) as an eluent and recrystallization from EtOH–*n*-hexane. mp: 110—115 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.10—8.01 (3H, m), 7.88 (1H, d, J=7.0 Hz), 7.68 (1H, d, J=7.0 Hz), 7.57 (1H, dd, J=7.0, 7.0 Hz), 7.47 (2H, d, J=8.8 Hz), 7.05 (1H, d, J=1.5 Hz), 7.01 (1H, d, J=1.5 Hz), 5.42 (1H, br s), 3.91—3.70 (4H, m), 2.39 (3H, s), 2.48—2.38 (2H, m), 2.12—1.99 (2H, m); IR (KBr) cm^{-1}: 1300, 1150; HR-MS (EI) m/z: 426.1513 (Calcd for $C_{22}H_{23}N_3O_4S$: 426.1488).

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References

1) Masamune H., Melvin L. S., Jr., "Annual Reports in Medicinal Chemistry," Vol. 24, ed. by Allen R. C., Academic Press, San Diego, 1989, pp. 71—79.
2) Samuelsson B., *Science*, **220**, 568—575 (1983).
3) Turner C. R., Breslow R., Conklyn M. J., Andrese C. J., Patterson D. K., Lopez-Anaya A., Owens B., Lee P., Watson J. W., Showell H. J., *J. Clin. Invest.*, **97**, 381—387 (1996).
4) Jackson W. T., Fleisch J. H., "Progress in Drug Research," Vol. 46, ed. by Jucker E., Birkhauser Verlag, Basel, 1996, pp. 115—168.
5) Henderson W. R., Jr., *J. Allergy Clin. Immunol.*, **79**, 543—553 (1987).
6) Steinhilber D., *Curr. Med. Chem.*, **6**, 71—85 (1999).
7) Vianna E. O., Martin R. J., *Drugs Today*, **34**, 341—351 (1998).
8) Mano T., Stevens R. W., Ando K., Nakao K., Okumura Y., Sakakibara M., Okumura T., Tamura T., Miyamoto K., *Bioorg. Med. Chem.*, **11**, 3879—3887 (2003).
9) Mano T., Okumura Y., Sakakibara M., Okumura T., Tamura T., Miyamoto K., Stevens R. W., *J. Med. Chem.*, **47**, 720—725 (2004).
10) Cuny G. D., Hauske J. R., Heffernan M. L., Holland J. M., Persons P. E., Radeke H., PCT Int. Appl. WO 02083863 A2, October 24, 2002.
11) Mano T., Stevens R. W., Nakao K., Okumura Y., Kawamura K., Ando A., Matsuoka Y., *Synthesis*, **16**, 2625—2628 (2004).
12) Foster S. J., Bruneau P., Walker E. R. H., McMillan R. M., *Br. J. Pharmaco.*, **99**, 113—118 (1990).
13) Young J. M., Maloney P. J., Jubb S. N., Clark J. S., *Prostaglandines*, **30**, 545—551 (1985).
14) Criscuoli M., Subissi A., *Br. J. Pharmaco.*, **90**, 203—209 (1987).
15) Tsunoda H., Abe S., Sakuma Y., Katayama S., Katayama K., *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **39**, 291—294 (1990).
16) Yin J., Pidgeon C., *Tetrahedron Lett.*, **38**, 5953—5954 (1997).
17) Ishiyama T., Mori M., Suzuki A., Miyaura N., *J. Organometallic Chem.*, **525**, 225—231 (1996).
18) Vijaikumar S., Pitchumani K., *J. Mol. Catalysis*, **217**, 225—231 (2004).
19) Miranda E. I., Diaz M. J., Rosado I., Soderquist J. A., *Tetrahedron Lett.*, **35**, 3221—3224 (1994).
20) Rane A. M., Miranda, E. I., Soderquist J. A., *Tetrahedron Lett.*, **35**, 3225—3226 (1994).
21) Aleo M. D., Drupa C. A., Fritz C. A., Walsh C. M., Whitman-Sherman J. L., Fortner J. H., *Toxicol. Sci.* (Suppl.), **60**, 101 (2001).
22) Baltrukonis D. J., Fritz C. A., Render J. A., Tengowski M. W., Costello K., Jakowski A. B., Fortner J. H., Lawton M. P., Nelms L. F., Drupa C. A., Verdugo-Gazdik M. E., Schnellmann R. G., Kajiji S., Aleo M. D., *Toxicol. Sci.* (Suppl.), **60**, 101 (2001).
23) Aleo M. D., Avery M. J., Beierschmitt W. P., Drupa C. A., Fortner J. H., Kaplan A. H., Navetta K. A., Shepard R. M., Walsh C. M., "Annals of the New York Academy of Sciences," Vol. 919 (Toxicology for the Next Millennium), ed. by Isfort R. J., Lederberg J., Academy of Sciences, New York, 2000, pp. 171—187.
24) Fischer L., Steinhilber D., Werz O., *Br. J. Pharmacol.*, **142**, 861—868 (2004).
25) Sakurada T., Abe M., Kodani M., Sakata N., Katsuragi T., *Eur. J. Pharmacol.*, **370**, 153—159 (1999).