4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide, an Orally Active Inhibitor of 5-Lipoxygenase with Improved Pharmacokinetic and Toxicology Characteristics

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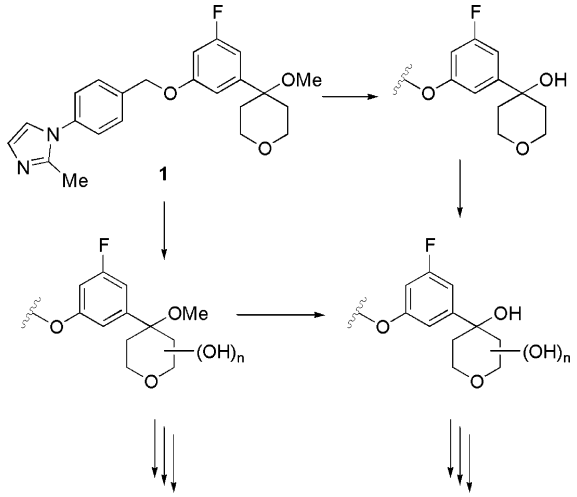
Described herein are structure−activity relationships (SARs) of 4-[5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (**1**, CJ-12,918), an imidazole 5-lipoxygenase (5-LO) inhibitor. When **1** was tested in preclinical studies, cataract formation was observed in rats; however, this compound was metabolized extensively in vivo and showed low systemic exposure. To eliminate this side effect and enhance bioavailability, structural modification was focused on replacing the methoxy group of **1** by modulating lipophilicity (i.e., predicted log *D* at pH 7.4). The SARs led to the discovery of 4-[5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (**10**, CJ-13,454), which was less lipophilic by 1.2 log *D* units and showed in vivo potency (ED_{50} = 4−9 mg/kg) equipotent to **1**. Enhanced metabolic stability resulted in fewer in vivo metabolites, as well as improved bioavailability and a better toxicological profile. Thus, **10** was found to be a more practical lead for an orally active 5-LO inhibitor.

Introduction

In our previous publication on imidazole compounds, structure−activity relationships were explored in order to find a new series of orally active inhibitors of 5-lioxygenase (5-LO), which led to the discovery of **1**.[1] However, the bioavailability of **1** hydrochloride salt (**1**·HCl) in male cynomolgus monkeys (5 mg/kg po vs 3 mg/kg iv) was far from satisfactory. Moreover, unacceptable ocular toxicity, specifically cataract formation, was observed in 1-month preclinical safety evaluation studies when rats were dosed with **1**·HCl.[2] In rats, compound **1** was extensively metabolized, and HPLC/MS/MS analysis of the plasma showed at least 12 metabolites and that of the lenses showed 6 metabolites. The major route of **1** metabolism is speculated to include O-demethylation of the tetrahydropyran (THP) methoxy group, oxidative metabolism of the THP ring, and a combination of both pathways (Scheme 1). Even though the incidence of cataract formation was dose-dependent (25 vs 250 (mg/kg)/day), plasma levels of **1** were equivalent across the doses, which agreed with the fact that **1** was found to be a microsomal cytochrome P-450 inducer as well as a potent autoinducer. Consequently, we postulated that rapid metabolism was responsible for low exposure to the parent drug and that the ocular toxicity was due to metabolites, which encourages us to commence further studies to attempt to block or retard metabolism.

Scheme 1. Speculated Metabolic Path of **1** in Vivo



Results and Discussion

Chemistry. The compounds synthesized for this study (**2**−**12**) are depicted in Table 1 with their in vitro and in vivo 5-LO inhibitory activities. Compounds **2**−**8** were synthesized in a manner similar to that of **1** from the known benzyl alcohol **13** and the requisite phenols **14**−**20**, as illustrated in Scheme 2. Phenols **14** and **15** were obtained from known THP alcohol via direct methods, as depicted in Scheme 3.[3] Under the presence of acid, the THP alcohol was converted with methane thiol to methylthioether **16**, which was selectively oxidized to sulfoxide **17** and sulfone **18** with sodium periodate and *m*-chloroperoxybenzoic acid, respectively. In contrast, THP ester **24** was prepared through THP-ring construction on an α-phenylacetic acid ester, and its acetyl analogue **19** was prepared from **24** by converting the ester group to methyl ketone, as shown in Scheme 4. This common intermediate **24** was also reductively deprotected to give **20**.

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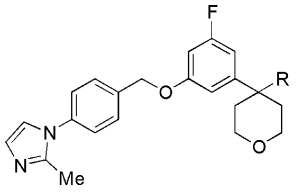
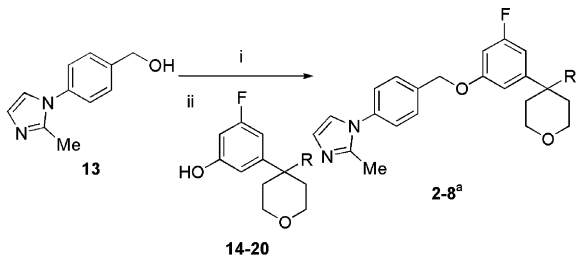
Table 1. Substituent Effect at 4-Position of THP Ring



compd	R	HWB IC_{50} [a] (μM) LTB_4	PAF ED_{50} [a] (mg·kg)	log $D_{7.4}$ [b]
1[c]	OMe	0.060 ± 0.017 (3)	2.0 ± 1.0 (3)	3.59
2[c]	OEt	0.080	5	4.13
3	OH	>1, >1	not tested	3.05
4[c]	SMe	0.072	5	4.45
5[c]	SOMe	>1	not tested	2.40
6[c]	SO_2Me	>1	not tested	2.71
7	COMe	0.13	12	3.62
8	CO_2Et	0.20	16	4.26
9	CO_2H	>1	not tested	0.18
10	$CONH_2$	0.34 ± 0.11 (4)	4, 9	2.39
11	CONHMe	0.28	13	2.63
12	$CONMe_2$	0.81	>20	2.93

[a] IC_{50}'s and ED_{50}'s are shown with ±SD. Results are based on one or two determinations unless otherwise indicated in parentheses. [b] Predicted with *ACD/LogP Suite*, version 5.16. [c] Prepared as the hydrochloride salt.

Scheme 2[a]



13 **2-8**[a] **14-20**

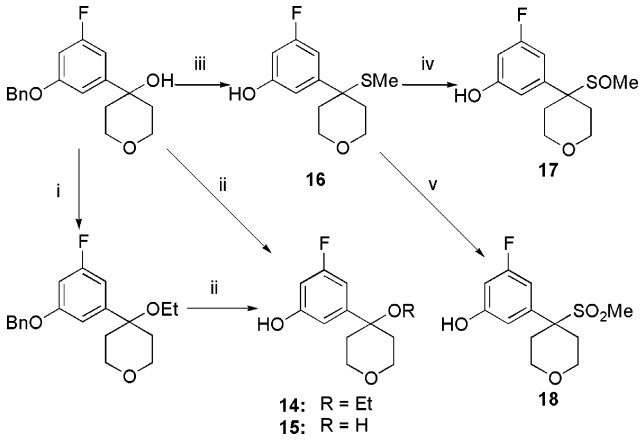
	-R
14	-OEt
15	-OH
16	-SMe
17	-SOMe
18	$-SO_2Me$
19	-COMe
20	$-CO_2Et$

[a] (i) $SOCl_2$; (ii) K_2CO_3, DMF. [b] Generic groups presented as R are defined in Table 1.

Carboxylic acid **9** was obtained by hydrolysis of **8** and was further converted to the amides **10**−**12** by the appropriate amidation, as shown in Scheme 5. Compounds **2** and **4**−**6** were prepared as hydrochloride salts.

Structure−Activity Relationships for 5-LO Inhibitory Activity. The inhibitory activities of the compounds for 5-LO were routinely evaluated in vitro using heparinized human whole blood (HWB).[4] The in vivo potency of the compounds after oral administration to mice was determined by the PAF (platelet activating factor) induced thrombosis assay.[5] Substitution of the methoxy group was sought, since it is one of the metabolic sites of **1**. Replacing methoxy with the more steric ethoxy yielded **2**, which retained the in vivo and in vitro potencies but did not improve the PK (pharmacokinetic) profile. When **2** was orally and intravenously administered to monkeys at 5 and 3 mg/kg, respectively, bioavailability of **2** was found to be less than 1% and more than 10-fold lower than that of **1**. On the basis of this finding and the fact that **1** is metabolized to

Scheme 3[a]



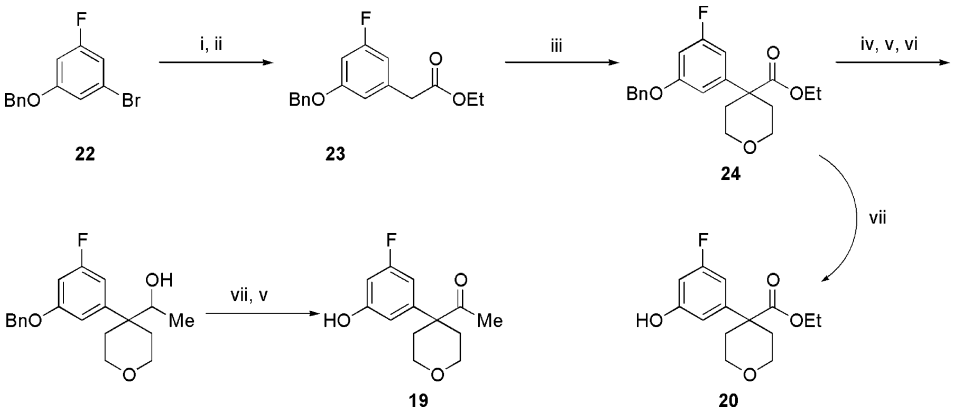
14: R = Et
15: R = H
16 **17** **18**

[a] (i) EtI, NaH, DMF; (ii) H_2, Pd−C; (iii) MeSH, CF_3SO_3H, $BF_3{\cdot}OEt_2$; (iv) $NaIO_4$, MeOH; (v) *m*-chloroperoxybenzoic acid, $CHCl_3$.

numerous metabolites, reducing lipophilicity may be a more profitable way to increase metabolic stability than blocking specific metabolic sites. Lipophilicity is commonly used to predict pharmacokinetics and toxicity for xenobiotics, and lowering log $D_{7.4}$ is reported to reduce metabolic clearance.[6] The log $D_{7.4}$ values for **1**−**12** were predicted, and these are listed in Table 1.[7] The predicted log $D_{7.4}$ value for **1** was 3.59, and that of **2** was higher by 0.54 units. Assuming high lipophilicity accounted for the low exposure of both **1** and **2**, we focused our efforts on synthesizing potent compounds with predicted log $D_{7.4}$ lower than 3.59. Hydroxyl THP **3**, one of major metabolites of **1**, showed no in vitro activity. The methylthio analogue **4** (predicted log $D_{7.4} = 4.45$) was potent in vitro and in vivo but is expected to be metabolized to sulfoxide and sulfone at the thioether linkage. Sulfoxide **5** and sulfone **6** had low predicted log $D_{7.4}$ values (2.40 and 2.71, respectively) but did not show in vitro potency. However, replacing the methoxy oxygen of **1** with acetyl **7** or ethoxycarbonyl **8** did not adversely affect the in vivo potency and only mildly reduced the in vitro potency; therefore, we continued to examine substituents having a carbonyl group connected to the THP ring. While the carboxylic acid analogue **9** was inactive, carboxamide **10** exhibited in vivo potency comparable to that of **1**, although with an approximately 5-fold reduced vitro potency. It would be consistent with our hypothesis if improved metabolic stability resulting in increased systemic exposure were to be caused by the reduced lipophilicity of **10** (predicted log $D_{7.4} = 2.39$). However, monomethylamide **11** suppressed in vivo potency, and dimethylamide **12** reduced in vitro potency as well.

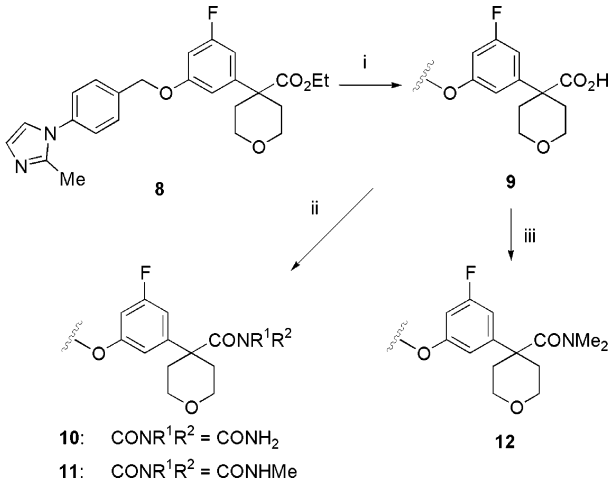
Detailed Characterization of 10. It was proven that the nonsubstituted amide was optimal for in vivo potency, so we decided that it is worthwhile to evaluate **10** further. The oral bioavailability of carboxamide **10** was calculated on the basis of oral and intravenous pharmacokinetic data from studies on several species and was determined to be 88 ± 11% in monkeys (oral, 5 mg/kg; iv, 3 mg/kg), 102 ± 20% in rats (oral, 10 mg/kg; iv, 3 mg/kg), and 108 ± 9% in guinea pig (oral, 10 mg/kg; iv, 3 mg/kg). After oral administration to monkeys (5 mg/kg), the C_{max} of **10** increased by 6.5-fold (1.57 ± 0.32 μg/mL for **10** in contrast to 0.24 ± 0.15 μg/mL as a free base for **1**·HCl; Figure 1). The in vivo potency

Scheme 4[a]



[a] (i) diethyl malonate, NaH, CuBr, dioxane; (ii) LiCl, H_2O, DMSO; (iii) $(ClCH_2CH_2)_2O$, NaH, 15-crown-5, DMF; (iv) $LiAlH_4$, Et_2O; (v) tetra-*n*-propylammonium perruthenate, 3 Å molecular sieves, *N*-methylmorphorin *N*-oxide; (vi) MeMgBr, THF; (vii) H_2, Pd−C, EtOH.

Scheme 5[a]



[a] (i) LiOH, H_2O, MeOH, THF; (ii) $(COCl)_2$, then NH_3 for **10** or NH_2Me for **11**; (iii) $NHMe_2$, NEt_3, diethyl cyanophosphonate.

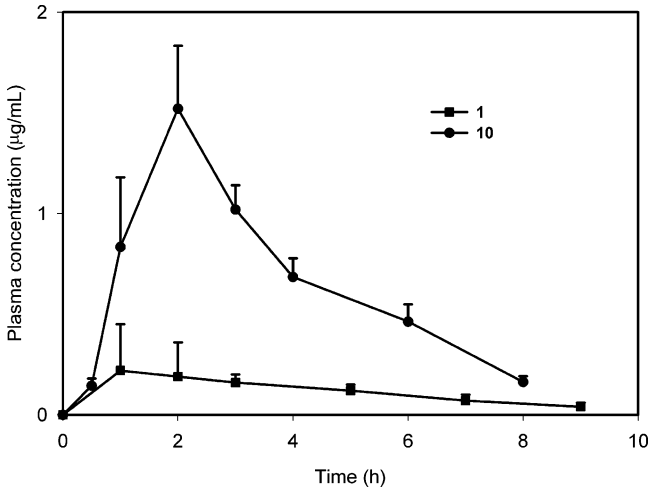


Figure 1. Mean plasma concentration of **1** hydrochloride salt and **10** in three male monkeys following oral administration (5 mg/kg). Each point represents the mean ± SEM ($n = 3$).

of **10** was equivalent to that of **1**·HCl because of its superior PK profile, although **10** had ca. 5-fold lower in vitro potency. Because the low aqueous solubility of the THP 5-LO inhibitors was thought to be responsible for the low systemic exposure and insufficient bioavailability on oral administration, efforts were made to improve aqueous solubility by lowering lipophilicity or incorporating an ionizable functional group into each of these molecules.[8−10] However, it was not consistently shown that improved aqueous solubility resulted in higher oral bioavailability. Furthermore, in discovering **10**, our study showed that, at least for the imidazole series, metabolic stability is a more important consideration for improving oral bioavailability.

The other major issue for **1**, cataractogenicity, which is speculated to be due to a toxic metabolite(s) in rats, was significantly diminished with **10**. Although the parent drug and its metabolites were found to penetrate into the lens of rats, the incidence of cataract formation with **10** was much lower than that of **1** in the in vivo preclinical safety evaluation study, even though the systemic exposure of **10** was much higher (23- to 38-fold) than that of **1**.[2] It was reported in this study that explanted lens culture was used to assess the cataractogenic potential of **1** and **10**. In the in vitro assay, it was shown that the relative toxicity of **1** and **10** for cataractogenetic potential became more distinct with induced S9 microsomal fractions than without such fractions. Inhibition of metabolism of **1** by coadministration of 1-aminobenzotriazole (a nonspecific cytochrome P-450 suicide inhibitor) in vivo also diminished the incidence and severity of cataract formation. All of this went to support our hypothesis that the cause of cataract formation with **1** was a result of metabolites produced by hepatic or ocular metabolism.

Furthermore, to suppress cataractogenesis resulting from some antipsychotic agents such as phenothiazine derivatives, reducing lipophilicity that induces high permeability to lens is known to be necessary.[11] Therefore, even if **10** were metabolized to compounds whose structures are similar to that of **1**, lipophilicity (and therefore permeability to the lens) is expected to be lower, since the lipophilicity of the parent compound (**10**) is lower than that of **1** by 1.2 log *D* units. In fact, even though the systemic exposure of **10** was substantially higher than that of **1**, the drug levels of **1** and **10** in the lenses were found to be equivalent, showing that **10** has lower permeability that is consistent with the lower lipophilicity. Moreover, **10** is metabolically more stable than **1** and, therefore, transformed to fewer metabolites. Even those metabolites of **10** that did form are less likely to be cataractogenic because of their potential for lower permeability to the lens.[2]

Conclusions

On the basis of our observations of the low exposure/bioavailability of **1** and its apparent cataractogenesis, we hypothesized that metabolic lability was the common factor. Structural modifications of **1** were made by replacing the methoxy group and reducing its lipophilicity while remaining focused on not losing the potency of **1** for 5-LO inhibition. This work led to the identification of carboxamide **10**, which had in vivo potency equivalent to **1** but greatly enhanced oral bioavailability and lowered cataractogenic potential. Thus, **10** was found to be a more practical lead compound than **1**. Further structural modifications of **10** leading to a clinical candidate will be discussed elsewhere.[12] Our work on modulating physiochemical properties, such as lipophilicity, is expected to be useful in directing SAR studies toward discovering more tolerable chemical series.

Experimental Section

Biology. Inhibition has been demonstrated in vitro using heparinized human whole blood (HWB), which determines the inhibitory effect of compounds on the 5-LO metabolism of arachidonic acid. The in vivo potency after oral administration of compounds to IRC mice (male) was determined using a PAF thrombosis assay in a manner similar to that described by J. M. Young et al.[5a] Both assays were reported in our previous publication.[1]

Chemistry. Proton magnetic resonance (^{1}H NMR) spectra were measured on a Joel FX270 spectrophotometer, 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), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet), and br (broad). Melting points were determined on either a Buchi 535 or a Yanagimoto micro-melting-point apparatus and were uncorrected. IR spectra and mass spectra were recorded on a Shimadzu IR-440 spectrometer and a Micromass Quattro II specrtometer, respectively. The results of elemental analyses were within 0.4% of the theoretical values and are reported only with symbols. Chromatography was performed on silica gel (E. Merck, 70−230 mesh).

The following compounds (**2**−**8**) were prepared from benzyl alcohol (**13**) and the appropriate phenols (**14**−**20**) according to the reported procedures similar to those of **1** or **1**·HCl.[1]

4-Ethoxy-4-[5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)-benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (2): mp = 195−197 °C; ^{1}H NMR (DMSO-d_6) δ 7.87 (d, 1 H, J = 2 Hz), 7.77 (d, 1 H, J = 2 Hz), 7.71 (d, 2 H, J = 8 Hz), 7.68 (d, 2 H, J = 8 Hz), 6.92−6.77 (m, 3 H), 5.26 (s, 2 H), 3.7−3.65 (m, 4 H), 3.02 (q, 2 H, J = 7 Hz), 2.56 (s, 3 H), 1.97−1.81 (m, 4 H), 1.05 (t, 3 H, J = 7 Hz); MS (ESI+) *m/e* 411 (M + H)$^+$. Anal. ($C_{24}H_{28}ClFN_2O_3$) C, H, Cl, F, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyl-oxy]phenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (3): mp = 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.57−7.53 (m, 2 H), 7.35−7.31 (m, 2 H), 7.02 (d, 1 H, J = 2 Hz), 7.01 (d, 1 H, J = 2 Hz), 6.96 (m, 1 H), 6.85 (ddd, 1 H, J = 2, 2, 10 Hz), 6.63 (ddd, 1 H, J = 2, 2, 10 Hz), 5.11 (s, 2 H), 3.90−3.83 (m, 4 H), 2.37 (s, 3 H), 2.20−2.08 (m, 2 H), 1.97 (br s, 1 H), 1.70−1.61 (m, 2 H); MS (ESI+) *m/e* 383 (M + H)$^+$. Anal. ($C_{22}H_{23}FN_2O$) C, H, F, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyl-oxy]phenyl]-4-methylthio-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (4): mp = 216−217 °C; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, 1 H, J = 2 Hz), 7.78 (d, 1 H, J = 2 Hz), 7.74 (d, 2 H, J = 8 Hz), 7.66 (d, 2 H, J = 8 Hz), 6.89 (s, 2 H), 6.85 (d, 1 H, J = 2 Hz), 5.26 (s, 2 H), 3.85−3.75 (m, 2 H), 3.62−3.53 (m, 2 H), 2.54 (s, 3 H), 2.14−2.05 (m, 4 H), 1.63 (s, 3 H); MS (ESI+) *m/e* 413 (M + H)$^+$. Anal. ($C_{23}H_{25}FN_2O_2S$) C, H, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyl-oxy]phenyl]-4-methylsulfinyl-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (5): mp = 175−176 °C; IR (KBr) 1055 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.89 (d, 1 H, J = 2 Hz), 7.78 (d, 1 H, J = 2 Hz), 7.74 (d, 2 H, J = 8 Hz), 7.67 (d, 2 H, J = 8 Hz), 7.02 (d, 1H, J = 11 Hz), 6.95−6.87 (m, 2 H), 5.29 (s, 2 H), 3.92 (d, 1 H, J = 12 Hz), 3.80 (d, 1 H, J = 12 Hz), 3.40−3.18 (m, 2 H), 2.55 (s, 3 H), 2.38−2.20 (m, 2 H), 2.19−1.96 (m, 2 H), 1.91 (s, 3 H); MS (ESI+) *m/e* 429 (M + H)$^+$. Anal. ($C_{23}H_{26}ClFN_2O_3S$) C, H, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyl-oxy]phenyl]-4-methylsulfonyl-3,4,5,6-tetrahydro-2*H*-pyran hydrochloride (6): mp = 230−231 °C; IR (KBr) 1330, 1140 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.87 (d, 1 H, J = 2 Hz), 7.78 (d, 1 H, J = 2 Hz), 7.75 (d, 2 H, J = 8 Hz), 7.65 (d, 2 H, J = 8 Hz), 7.11 (s, 1 H), 7.07 (s, 2 H), 5.29 (s, 2 H), 3.89−3.82 (m, 2 H), 3.18−3.02 (m, 2 H), 2.67 (s, 3 H), 2.62−2.48 (m, 2 H), 2.54 (s, 3 H), 2.29−2.14 (m, 2 H); MS (ESI+) *m/e* 445 (M + H)$^+$. Anal. ($C_{23}H_{26}ClFN_2O_4S$) C, H, N.

4-Acetyl-4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran (7): mp = 122−123 °C; IR (KBr) 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 2 H, J = 8 Hz), 7.34 (d, 2 H, J = 8 Hz), 7.05 (d, 1 H, J = 2 Hz), 7.02 (d, 1 H, J = 2 Hz), 6.72−6.61 (m, 3 H), 5.08 (s, 2 H), 3.84 (ddd, 2 H, J = 4, 4, 12 Hz), 3.58 (ddd, 2 H, J = 3, 10, 12 Hz), 2.38 (s, 3 H), 2.41−2.31 (m, 2 H), 2.20 (ddd, 2 H, J = 4, 10, 14 Hz), 1.95 (s, 3 H); MS (ESI+) *m/e* 409 (M + H)$^+$. Anal. ($C_{24}H_{25}FN_2O_3$) C, H, F, N.

Ethyl 4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (8): mp = 211−213 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2 H, J = 8 Hz), 7.34 (d, 2 H, J = 8 Hz), 7.04 (d, 1 H, J = 2 Hz), 7.01 (d, 1 H, J = 2 Hz), 6.82 (dd, 1 H, J = 2, 2 Hz), 6.75 (ddd, 1 H, J = 2, 2, 10 Hz), 6.62 (ddd, 1 H, J = 2, 2., 10 Hz), 5.09 (s, 2 H), 4.16 (q, 2 H, J = 7 Hz), 3.98−3.88 (m, 2 H), 3.60−3.50 (m, 2 H), 2.51−2.42 (m, 2 H), 2.38 (s, 3 H), 2.01−1.86 (m, 2 H), 1.21 (t, 3 H, J = 7 Hz); MS (ESI+) *m/e* 439 (M + H)$^+$. Anal. ($C_{25}H_{28}ClFN_2O_4$) C, H, Cl, F, N.

4-[5-[4-(2-Methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic Acid (9). A stirred mixture of ethyl 4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**8**, 1.10 g, 25 mmol), an aqueous solution of lithium hydroxide (0.13 g, 30 mmol, 5 mL), methanol (15 mL), and THF (15 mL) was refluxed for 24 h. The reaction mixture was neutralized with 1 N hydrogen chloride. Volatiles were removed by evaporation under reduced pressure. The residue was suspended into a mixture of water (20 mL) and phosphate buffer (5 mL, pH 7) and heated to reflux for 30 min. After the mixteur was cooled to 0 °C, solids were collected by filtration, washed with water and then Et_2O, and dried under vacuum at 80 °C for 14 h to afford the desired compound as white solids (0.98 g, 96%): mp = 222−223 °C; ^{1}H NMR (DMSO-d_6) δ 7.62 (d, 2 H, J = 8 Hz), 7.48 (d, 2 H, J = 8 Hz), 7.30 (d, 1 H, J = 1 Hz), 6.92 (d, 1 H, J = 1 Hz), 6.90−6.76 (m, 3 H), 5.19 (s, 2 H), 3.84−3.75 (m, 2 H), 3.50−3.40 (m, 2 H), 2.36−2.27 (m, 2 H), 2.29 (s, 3 H), 1.88−1.75 (m, 2 H); MS (ESI+) *m/e* 411 (M + H)$^+$. Anal. ($C_{23}H_{23}FN_2O_4$) C, H, N.

4-[5-Fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyl-oxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (10). Under a nitrogen atmosphere at 0 °C, oxalyl chloride (419 mg, 3.3 mmol) was added to a stirred suspension of 4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid (**9**, 616 mg, 1.5 mmol) in dichloromethane (20 mL). The mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. The resulting white suspension was concentrated to dryness, and the residue was added to a stirred aqueous ammonia solution (26%, 20 mL). After the mixture was stirred at room temperature for 70 min, solids were collected by filtration, washed with water, and dried under vacuum at 80 °C overnight to give the desired compound (337 mg, 54%): mp = 207−208 °C; IR (KBr) 1668 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.61 (d, 2 H, J = 8 Hz), 7.48 (d, 2 H, J = 8 Hz), 7.30 (d, 1 H, J = 1 Hz), 7.24 (br s, 1 H), 7.08

(br s, 1 H), 6.92 (d, 1 H, J = 1 Hz), 6.89−6.82 (m, 2 H), 6.80−6.75 (m, 1 H), 5.18 (s, 2 H,), 3.66−3.57 (m, 2 H), 3.51−3.40 (m, 2 H), 2.44−2.35 (m, 2 H), 2.29 (s, 3 H), 1.84−1.72 (m, 2 H); MS (ESI+) *m/e* 410 $(M + H)^+$. Anal. ($C_{23}H_{24}FN_3O_3$) C, H, N.

***N*-Methyl-4-[5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)-benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (11).** The acid chloride obtained from the process described for **10** from 323 mg (0.79 mmol) of 4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid (**9**) was added to a stirred aqueous solution of methylamine (40%, 50 mL). After 30 min, excess methylamine was removed under reduced pressure, and the residue was diluted with water (100 mL) and extracted with dichloromethane (2 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was recrystallized from ethyl acetate to give the desired compound as fine white solids: mp = 159−161 °C; IR (KBr) 1652 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.69 (br s, 1 H), 7.61 (d, 2 H, J = 8 Hz), 7.47 (d, 2 H, J = 8 Hz), 7.29 (d, 1H, J = 1 Hz), 6.91 (d, 1 H, J = 1 Hz), 6.90−6.80 (m, 2 H), 6.79−6.70 (m, 1 H), 5.17 (s, 2 H), 3.75−3.65 (m, 2 H), 3.48−3.36 (m, 2 H), 2.55 (s, 3 H), 2.41−2.31 (m, 2 H), 2.29 (s, 3 H), 1.90−1.77 (m, 2 H); MS (ESI+) *m/e* 424 $(M + H)^+$. Anal. ($C_{24}H_{26}FN_3O_3$) C, H, F, N.

***N*,*N*-Dimethyl-4-[5-fluoro-3-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide (12).** Diethyl cyanophosphonate (44 mg, 0.27 mmol) was added at 0 °C to a stirred suspension of 4-[5-[4-(2-methyl-1*H*-imidazol-1-yl)benzyloxy]-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid (**9**, 100 mg, 0.24 mmol), dimethylamine hydrochloride (98 mg, 1.2 mmol), and triethylamine (253 mg, 2.5 mmol) in THF (50 mL). After 10 min, the reaction was diluted with water (50 mL) and extracted with ethyl acetate (50 mL). The extract was washed with water (50 mL) and then brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the residue was performed by column chromatography (0−5% methanol in dichloromethane) to give 117 mg of crude product as a colorless foam. Recrystallization from a mixture of isopropyl ether−ethyl acetate (1:1) yielded the desired compound (51 mg, 50%): mp = 173−174 °C; IR (KBr) 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (d, 2 H, J = 8 Hz), 7.33 (d, 2 H, J = 8 Hz), 7.04 (d, 1 H, J = 1 Hz), 7.01 (d, 1 H, J = 1 Hz), 6.69−6.58 (m, 3 H), 5.08 (s, 2 H), 3.93−3.85 (m, 2 H), 3.83−3.72 (m, 2 H), 2.67 (br s, 6 H), 2.38 (s, 3 H), 2.28−2.19 (m, 2 H), 2.05−1.92 (m, 2 H); MS (ESI+) *m/e* 438 $(M + H)^+$. Anal. ($C_{25}H_{28}FN_3O_3$) C, H, F, N.

4-(3-Fluoro-5-hydroxyphenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (15). A mixture of 4-[5-(benzyloxy)-3-fluorophenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (5.77 g, 19 mmol) and 10% palladium on activated carbon (0.29 g) in ethanol (50 mL) was stirred under a hydrogen atmosphere for 19 h. The catalyst was removed by filtration, and evaporation of the filtrate gave the desired compound as a colorless liquid (4.19 g, quantitative yield): ^1H NMR ($CDCl_3$) δ 6.74−6.72 (m, 1 H), 6.68 (ddd, 1 H, J = 2, 2, 11 Hz), 6.39 (ddd, 1 H, J = 2, 2, 11 Hz), 5.07 (br s, 1 H), 3.81−3.64 (m, 4 H), 1.95−1.82 (m, 2 H), 1.50−1.42 (m, 2 H).

4-(3-Fluoro-5-hydroxyphenyl)-4-methylsulfinyl-3,4,5,6-tetrahydro-2*H*-pyran (17). $NaIO_4$ (710 mg, 3.3 mmol) was added to a stirred solution of 4-(3-hydroxy-5-fluorophenyl)-4-methylthio-3,4,5,6-tetrahydro-2*H*-pyran[3] (**16**, 749 mg, 3.1 mmol) in methanol−water (1:1, 20 mL) cooled to 0 °C. The ice bath was removed, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (50 mL). The organic extract was washed with water (50 mL) and then brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual solids were purified by column chromatography (ethyl acetate) to afford 752 mg (94%) of the desired compound as white solids: ^1H NMR ($CDCl_3$) δ 8.93 (s, 1 H), 6.77 (s, 1 H), 6.60 (d, 1H, J = 10 Hz), 6.53 (d, 1H, J = 10 Hz), 4.09−3.88 (m, 2 H), 3.66−3.48 (m, 2 H), 2.50−2.29 (m, 2 H), 2.20−2.00 (m, 2 H), 2.06 (s, 3 H).

4-(3-Hydroxy-5-fluorophenyl)-4-methylsulfonyl-3,4,5,6-tetrahydro-2*H*-pyran (18). To a stirred solution of 4-(3-hydroxy-5-fluorophenyl)-4-methylthio-3,4,5,6-tetrahydro-2*H*-pyran[3] (**16**, 660 mg, 2.7 mmol) in chloroform (20 mL) was added *m*-chloroperoxybenzoic acid (1.48 g, 6.0 mmol), and the mixture was stirred at room temperature overnight. Calcium hydroxide (3 mmol) was added to the reaction mixture, and the mixture was stirred vigorously. The resulting solids were removed by filtration, and the filtrate was concentrated. The residual solids were purified by column chromatography (hexanes−ethyl acetate (1:2)) to afford 545 mg (81%) of the desired compound as white solids: ^1H NMR ($CDCl_3$) δ 6.86 (dd, 1 H, J = 2, 2 Hz), 6.82 (ddd, 1 H, J = 10, 2, 2 Hz), 6.64 (ddd, 1 H, J = 10, 2, 2 Hz), 5.55 (s, 1 H), 4.08−3.97 (m, 2 H), 3.49−3.36 (m, 2 H), 2.66−2.50 (m, 2 H), 2.53 (s, 3 H), 2.41−2.30 (m, 2 H).

Ethyl 3-Benzyloxy-5-fluorophenylacetate (23). Step 1. Diethyl 5-Benzyloxy-3-fluorophenylmalonate. Under a nitrogen atmosphere at 0 °C, sodium hydride (27.5 g, 688 mmol, 60% dispersion in mineral oil) was added in portions to a stirred solution of diethyl malonate (110.2 g, 688 mmol) in dioxane (1 L). Cuprous bromide (98.7 g, 688 mmol) and a solution of 5-benzyloxy 3-fluorophenylbromide (**22**, 96.7 g, 344 mmol) in dioxane (100 mL) were added after being stirred at 0 °C for 20 min and then at room temperature for 80 min. The resulting suspension was stirred and heated at reflux for 4.5 h. The reaction was quenched by adding 6 N hydrogen chloride (120 mL) at 0 °C, and the mixture was diluted with water (1 L) and extracted with *n*-hexane (3 × 700 mL). The combined extracts were washed with water (2 × 500 mL), saturated sodium bicarbonate (500 mL), water (500 mL), and then brine (500 mL). They were then dried ($MgSO_4$) and finally concentrated under reduced pressure to give 147.5 g of crude product as an amber liquid. Purification was performed by column chromatography (5−20% ethyl acetate in *n*-hexane) to give 60.8 g of a mixture of diethyl malonate and the desired compound (1:1) as a colorless liquid. The compound yield was 34%: ^1H NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 8 Hz), 6.96 (d, 1 H, J = 1 Hz), 6.82 (d, 1 H, J = 1 Hz), 6.79 (d, 2 H, J = 8 Hz), 4.99 (s, 2 H), 2.32 (s, 3 H).

Step 2. Ethyl 3-Benzyloxy-5-fluorophenylacetate (23). A mixture of the product obtained as described above (diethyl 5-benzyloxy-3-fluorophenylmalonate and diethyl malonate (ca. 1:1.2, 1.0 g)), DMSO (10 mL), water (0.1 mL), and LiCl (346 mg) were placed in a round-bottom flask equipped with a magnetic stirrer and fitted with a condenser. The mixture was heated at reflux for 5 h. The mixture was poured into water (50 mL) and extracted with *n*-hexane (2 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and dried (Na_2SO_4). Removing the solvent gave 283 mg (57%) of ethyl 3-benzyloxy-5-fluorophenylacetate as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.50−7.30 (m, 5 H), 6.77−6.50 (m, 3 H), 5.00 (s, 2 H), 4.16 (q, 2H, J = 7 Hz), 3.56 (s, 2H), 1.26 (t, 3H, J = 7 Hz).

Ethyl 4-[5-(Benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (24). Sodium hydride (5.37 g, 134 mmol, 60% dispersion in oil) was added in portions at room temperature to a stirred solution of ethyl [5-(benzyloxy)-3-fluorophenyl]acetate (17.5 g, 61 mmol) and 15-crown-5 (1.32 g, 6 mmol) in DMF (300 mL). After the mixture was stirred at room temperature for 25 min, sodium iodide (1.32 g, 6 mmol) and bis(2-chloroethyl) ether (9.14 g, 61 mmol) were added. After a day, the mixture was diluted with 0.5 N hydrogen chloride (500 mL) and extracted with Et_2O (3 × 500 mL). The combined extracts were washed with water (500 mL), saturated sodium bicarbonate (500 mL), water (500 mL), and brine (500 mL), then dried ($MgSO_4$), and finally concentrated under reduced pressure to give 26.2 g of crude product as a yellow liquid. Column chromatography (ethyl acetate−*n*-hexane (1:4)) gave the desired compound as a colorless liquid (12.7 g, 58%): ^1H NMR ($CDCl_3$) δ 7.45−7.31 (m, 5 H), 6.81−6.78 (m, 1 H), 6.70 (ddd, 1 H, J = 2, 2, 10 Hz), 6.59 (ddd, 1 H, J = 2, 2, 10 Hz), 5.03 (s, 2 H), 4.14 (q, 2 H, J = 7 Hz), 3.92 (ddd, 2 H, J = 3, 4, 12 Hz), 3.54 (ddd, 2 H, J = 2, 11, 12 Hz), 2.50−2.40 (m, 2 H), 1.92 (ddd, 2 H, J = 4, 11, 14 Hz), 1.19, (t, 3 H, J = 7 Hz).

4-Acetyl-4-(3-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (19). Step 1. 4-Hydroxymethyl-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran. Lithium aluminum hydride (0.16 g, 4.3 mmol) was added in three portions to a stirred solution of ethyl 4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**24**, 1.54 g, 4.3 mmol) in Et_2O (150 mL). The resulting suspension was stirred at room temperature under a nitrogen atmosphere for 20 min. The excess hydride was hydrolyzed by adding saturated sodium sulfate. The mixture was diluted with 10% aqueous sulfuric acid (100 mL), and the layers were separated. The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), then dried ($MgSO_4$), and finally concentrated to dryness to afford the desired compound as white solids (1.28 g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.44−7.33 (m, 5 H), 6.78−6.58 (m, 3 H), 5.05 (s, 2H), 3.84−3.73 (2m, H), 3.62−3.48 (m, 4 H), 2.13−2.00 (m, 2 H), 1.95−1.82 (m, 2 H), 1.09 (t, 1 H, J = 7 Hz).

Step 2. 4-Formyl-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran. Tetra-*n*-propylammonium perruthenate (70 mg, 0.2 mmol) was added to a stirred mixture of 4-hydroxymethyl-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1.28 g, 4.0 mmol), *N*-methylmorpholine *N*-oxide (0.70 g, 6.0 mmol), and powdered 3 Å molecular sieves (2.0 g) at room temperature under a nitrogen atmosphere. After 20 min, tetra-*n*-propylammonium perruthenate (30 mg, 0.085 mmol) and *N*-methylmorpholine *N*-oxide (0.30 g, 2.6 mmol) were added and the mixture was stirred for an additional 30 min. The mixture was chromatographed (ethyl acetate−*n*-hexane (1:3)) to give the desired compound as a colorless liquid (1.08 g, 86%): ^{1}H NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.44−7.32 (m, 5 H), 6.70−6.58 (m, 3 H), 5.03 (s, 2 H), 3.89 (ddd, 2 H, J = 4, 4, 12 Hz), 3.62−3.51 (m, 2 H), 2.38−2.28 (m, 2 H), 2.09−1.97 (m, 2 H).

Step 3. 4-(1-Hydroxyethyl)-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran. A 0.96 M solution of methylmagnesium bromide (5.3 mL, 5.1 mmol) was added in a dropwise manner to a stirred solution of 4-formyl-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran (1.08 g, 3.4 mmol) in THF (16 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred overnight, diluted with saturated aqueous ammonium chloride (40 mL), and extracted with dichloromethane (2 × 40 mL). The combined organic layers were washed with water (40 mL) and then brine (40 mL), dried ($MgSO_4$), and finally concentrated to dryness. Purification by column chromatography (40−60% ethyl acetate in *n*-hexane) afforded the desired compound as a colorless liquid (0.71 g, 63%): ^{1}H NMR ($CDCl_3$) δ 7.47−7.32 (m, 5 H), 6.73−6.70 (m, 1 H), 6.67−6.60 (m, 2 H), 5.05 (s, 2 H), 3.85−3.75 (m, 2 H), 3.64 (dt, 1 H, J = 7, 7 Hz), 3.47−3.27 (m, 2 H), 2.28−2.20 (m, 1 H), 2.06−2.00 (m, 1 H), 1.93−1.78 (m, 2 H), 1.11 (d, 1 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz).

Step 4. 4-(1-Hydroxyethyl)-4-(3-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran. The desired compound was obtained according to the procedure described for the preparation of 4-(3-fluoro-5-hydroxyphenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (**15**) using 4-(1-hydroxyethyl)-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran: ^{1}H NMR (DMSO-d_6) δ 9.70 (br s, 1 H), 6.60−6.52 (m, 2 H), 6.40 (ddd, 1 H, J = 2, 2, 11 Hz), 4.62 (br d, 1 H, J = 5 Hz), 3.77−3.61 (m, 2 H), 3.54−3.41 (m, 1 H), 3.30−3.12 (m, 2 H), 2.11−2.00 (m, 1 H), 1.95−1.72 (m, 3 H), 0.70 (d, 3 H, J = 6 Hz).

Step 5. 4-Acetyl-4-(3-fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran (19). The desired compound was obtained according to the procedure described for the preparation of 4-formyl-4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran using 4-(1-hydroxyethyl)-4-(3-fluoro-5-benzyloxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran: ^{1}H NMR ($CDCl_3$) δ 6.61 (d, 1 H, J = 2, 2, 10 Hz), 6.55−6.47 (m, 2 H), 5.90 (br s, 1 H), 3.85 (ddd, 2 H, J = 4, 4, 12 Hz), 3.59 (ddd, 2 H, J = 2, 9, 12 Hz), 2.40−2.29 (m, 2 H), 2.19−2.18 (m, 2 H, m), 1.97 (s, 3 H).

Ethyl 4-(3-Fluoro-5-hydroxyphenyl)-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (20). The desired compound was obtained according to the procedure described for the preparation of 4-(3-fluoro-5-hydroxyphenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (**15**) using ethyl 4-[5-(benzyloxy)-3-fluorophenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylate (**24**): ^{1}H NMR ($CDCl_3$) δ 6.72−6.62 (m, 2 H), 6.47 (ddd, 1 H, J = 2, 2, 10 Hz), 5.40 (br s, 1 H), 4.17 (q, 2 H, J = 7 Hz), 3.98−3.89 (m, 2 H), 3.61−3.49 (m, 2 H), 2.50−2.41 (m, 2 H), 2.00−1.86 (m, 2 H), 1.24, (t, 3 H, J = 7 Hz).

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