Discovery of Brivanib Alaninate ((*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate), A Novel Prodrug of Dual Vascular Endothelial Growth Factor Receptor-2 and Fibroblast Growth Factor Receptor-1 Kinase Inhibitor (BMS-540215)

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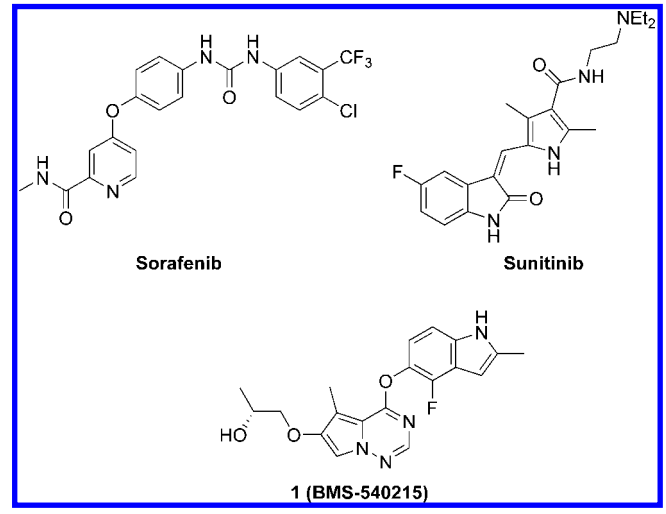
A series of amino acid ester prodrugs of the dual VEGFR-2/FGFR-1 kinase inhibitor **1** (BMS-540215) was prepared in an effort to improve the aqueous solubility and oral bioavailability of the parent compound. These prodrugs were evaluated for their ability to liberate parent drug **1** in in vitro and in vivo systems. The L-alanine prodrug **8** (also known as brivanib alaninate/BMS-582664) was selected as a development candidate and is presently in phase II clinical trials.

Introduction

Vascular endothelial growth factor (VEGF[a]), fibroblast growth factor (FGF), as well as their corresponding tyrosine kinase receptors, VEGFR and FGFR, play a critical role in physiological and pathological angiogenesis, a process of forming new capillaries from existing blood vessels. Angiogenesis is essential for solid tumor growth and metastasis.[1,2] Tumor-induced angiogenesis is mediated by VEGF, FGF, and other cytokines such as platelet-derived growth factor (PDGF). Among them, VEGF is known to be one of the most important angiogenic growth factor in the stimulation of tumor progression.[1,3] Importantly, the specific binding of VEGF ligand to vascular cell surface expressed protein kinase receptor VEGFR-2 triggers effective downstream cell proliferation signaling pathways and leads to tumor vascularization.[4] The interruption of VEGFR-2 signaling by binding of a small molecule inhibitor to the VEGFR-2 kinase domain has been shown to inhibit angiogenesis, tumor progression, and dissemination in a number of preclinical and clinical studies.[5] This approach has been further validated by the recent FDA approval of the antiangiogenic agents, such as bevacizumab (a monoclonal antibody which targets to the VEGF-A ligand) and small molecule inhibitors, sorafenib and sunitinib (Chart 1), for the treatment of solid tumors.[6] Similarly, FGFR-1 is also expressed on endothelial cells and is important in cell survival and proliferation underlying blood vessel development and blood vessel stabilization in tumor angiogenesis.[7] Moreover, the FGFR family of receptors has been associated with a variety of malignant tumors including melanoma,[8] glioma,[9] pancreatic,[10] as well as bladder cancer.[11]

Chart 1. Examples of VEGFR-2 Inhibitors



As part of our continuing effort to identify selective small-molecule kinase inhibitors for antiangiogenic therapies underlying cancer, we discovered a new class of pyrrolo[2,1-*f*]-[1,2,4]triazine-based VEGFR-2 inhibitors. An optimized analog **1** (Chart 1) demonstrated potent inhibition against VEGFR-2 and FGFR-1, excellent kinase selectivity, and potent in vivo efficacy versus H3396 and L2987 human lung carcinoma xenografts implanted in athymic mice.[12] However, oral administration of **1** in rat (at 25 mg/kg) as a micronized suspension produced significantly lower systemic exposure levels of **1** than those obtained from solution formulations. The low aqueous solubility (<1 μg/mL at pH 6.5) of **1** presumably contributed to dissolution rate-limited absorption of the compound, particularly at high doses. Efforts to improve the oral bioavailability and increase drug plasma concentrations of **1** at high doses using different formulation strategies were unsuccessful. To overcome this potential development issue, we decided to investigate a

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[a] Abbreviations: VEGFR-2, vascular endothelial growth factor receptor-2; FGFR-1, fibroblast growth factor receptor-1; PDGF, platelet-derived growth factor; Cbz, benzyloxycarbonyl; AUC, area under curve; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; HATU, 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate; PEG, poly(ethylene glycol); TGI, tumor growth inhibition; CYP450, cytochrome P450 enzyme.

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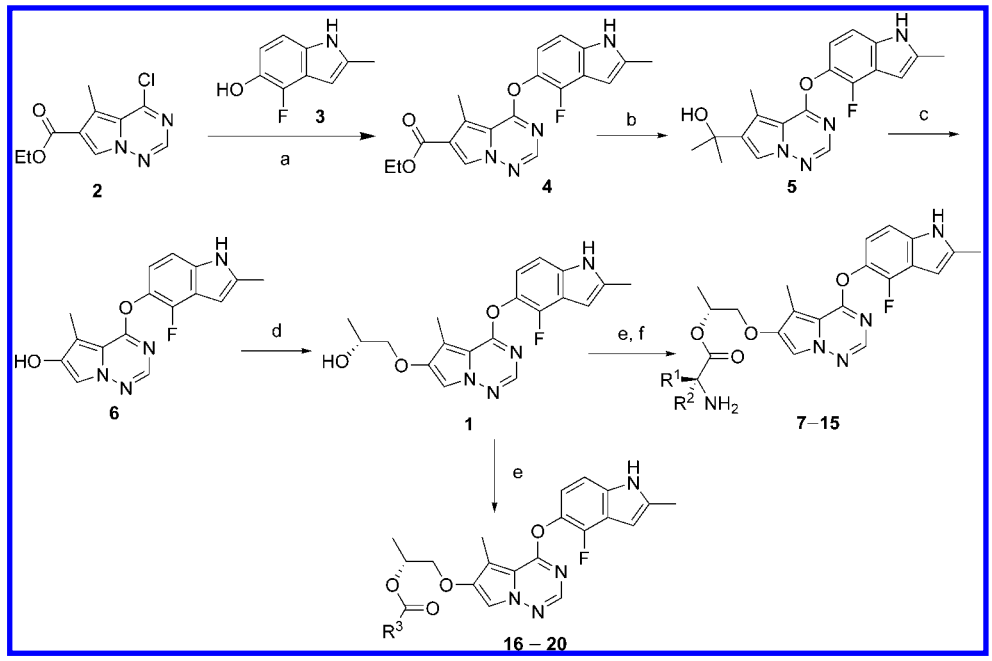
Scheme 1[a]



[a] Reagents and conditions: (a) K_2CO_3, DMF, 16 h; (b) MeMgBr, THF, 0 °C, 2–5 h, 75% yield over two steps; (c) H_2O_2, BF_3/OEt_2, CH_2Cl_2, −15 °C to −25 °C, 1 h, 66%; (d) *R*-(+)- propylene oxide, LiCl, NEt_3 (cat.), EtOH, 3 h, 81%; (e) CbzNHCR^{1}R^{2}COOH (**7**–**15**) or R^{3}CO$_2$H (**16**–**20**), HATU, DIPEA, DMAP (cat.), THF, 5 h, 51–94%; (f) $HCOO^-NH_4^+$, Pd/C, DMF, 69–99%.

prodrug approach. Amino acid ester prodrugs of alcohols have been used successfully in marketed drugs to improve aqueous solubility.[13] Herein, we report our prodrug strategy of incorporating a variety of amino acids onto the secondary alcohol group of **1** through a metabolically labile ester linkage to improve its physicochemical and pharmacokinetic properties.

Chemistry

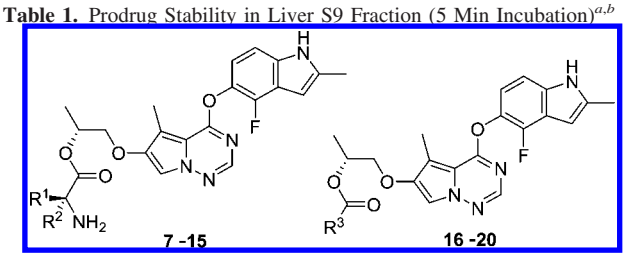
The fluoroindole-substituted pyrrolotriazine ester **4** (Scheme 1) was synthesized in excellent yield by reacting chloroimidate **2**[14] with 4-fluoro-2-methyl-1*H*-indol-5-ol (**3**)[12] in the presence of potassium carbonate in DMF. Treatment of ester **4** with methyl magnesium bromide gave rise to the tertiary alcohol **5**, which underwent BF_3/OEt_2/50% H_2O_2 promoted oxidative rearrangement[15] to afford phenol **6** in good yield. This approach was used as an effective alternative to the Baeyer–Villiger reaction to prepare the key intermediate **6** from the corresponding aldehyde.[12] Base-catalyzed epoxide opening of *R*-(+)-propylene oxide with **6** in ethanol at elevated temperature afforded compound **1** in an enantiomeric excess of >99% ee. The addition of lithium chloride to the reaction mixture enhanced the rate of epoxide ring opening presumably due to chelation of the lithium ion with the epoxide oxygen. The ester prodrugs were generally prepared in excellent yield by coupling alcohol **1** with commercially available Cbz-protected amino acids or the carboxylic acids bearing a tertiary amine in the presence of HATU (2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate), DIPEA, and DMAP in DMF to give esters **7**–**15** and **16**–**20**, respectively. In the case of **7**–**15**, the final products were obtained after deprotection of the Cbz group via a palladium-catalyzed hydrogen transfer reaction with ammonium formate. No racemization of the chiral amino esters occurred during the chemical transformations based on an assessment of their enantiomeric purities in the synthesis of L-alanine ester **8** and its enantiomeric isomer D-alanine ester **9**.

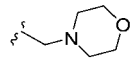
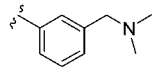
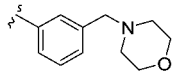
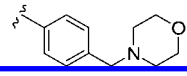
Results and Discussion

In Vitro Assessment of Prodrugs. A number of specific and nonspecific esterases found in the stomach, intestines, liver, and plasma are capable of hydrolyzing amino ester linkages. Our desire was to identify prodrugs of high chemical stability that displayed rapid and quantitative conversion to parent to maximize drug exposure and minimize unproductive metabolism. The prodrugs were initially evaluated to determine their stability in human and mouse liver S9 fractions and in plasma. Generally, the ester prodrugs tested were moderately stable to ester cleavage in mouse plasma, and very stable to ester cleavage in human plasma (data not shown), suggesting metabolic conversion to **1** in the liver would be necessary. No attempts were made to fully evaluate and rank the conversion of prodrugs to **1** in human plasma since all prodrugs appeared to show the remarkably low conversion. Thus, the assay for determining the rate of conversion of prodrugs to parent **1** in liver S9 fraction was considered to be the primary screening method. Table 1 illustrates the influence of the structure of the pro-moiety on the hydrolytic rate. Prodrugs with α-substitution of less hindered groups on amino acids such as **7** (glycinate), **8** (L-alaninate), **9** (D-alaninate), and **13** (L-leucinate) exhibited complete conversion to parent **1** in both human and mouse liver S9 fractions within the 5 min incubation time, with no additional major metabolites detected. Compound **10** (α,α-dimethylglycinate) bearing chemical disubstitution on the α-carbon, also served as an excellent substrate for esterase and was readily hydrolyzed under the assay conditions. The use of more hindered amino acids, such as compounds, **11** (L-valinate), **12** (D-valinate), **14** (L-isoleucinate), and **15** (L-phenylalanine), provided lower rates of conversion to parent drug **1**. *N*,*N*-Dimethylglycinate **16** displayed a low rate of conversion in mouse and moderate rate of conversion in human liver S9 fractions. The 2-morpholinoacetate **17** gave a moderate rate of conversion both in mouse and human liver S9 fraction. Substituted benzoic acid prodrugs **18**–**20**, in general, demonstrated lower hydrolytic conversion rates.

Pharmacokinetics and Pharmaceutical Properties. Four prodrugs (**7**, **8**, **10**, and **13**) that demonstrated rapid conversion to parent **1** in human and mouse liver S9 fraction were assessed in oral exposure studies in mice (Table 2). All compounds were administered as a 70:30 PEG70/water solution at 50 and 200

Table 1. Prodrug Stability in Liver S9 Fraction (5 Min Incubation)[a,b]



prodrug	R^1	R^2	R^3	Prodrug: % metabolically hydrolyzed mouse	human
7 (gly)	H	H		100	96
8 (L-ala)	Me	H		100	100
9 (D-ala)	H	Me		100	95
10	Me	Me		100	100
11 (L-val)	*i*-Pr	H		28	64
12 (D-val)	H	*i*-Pr		14	75
13 (L-leu)	*i*-Bu	H		100	100
14 (L-ile)	*sec*-Bu	H		26	12
15 (L-phe)	Bz	H		50	56
16				9	84
17				92	84
18				27	73
19				12	42
20				18	21

[a] See Experimental Section for a description of assay conditions. [b] Data are expressed as a mean of at least two determinations (variation < 20%).

Table 2. Oral Exposure of Various Compounds in Mice[a,b,c]

cmpd	dose (mg/kg)	plasma concentration of **1** C_{max} (μM)	AUC (0–4 h; μM·hr)	AUC fold increase[d]
1	50	12 ± 6	45 ± 16	
	200	14 ± 10	52 ± 14	1.2
7	50	21 ± 3	69 ± 26	
	200	126 ± 15	303 ± 63	4.4
8	50	21 ± 5	69 ± 16	
	200	78 ± 20	276 ± 74	4.0
10	50	15 ± 6	46 ± 16	
	200	66 ± 29	213 ± 107	4.6
13	50	31 ± 4	113 ± 26	
	200	152 ± 17	451 ± 37	4.0

[a] Average of three female mice for each dose group. [b] Vehicle: PEG400/water (70:30). [c] For assay condition, see ref 16. [d] AUC (200 mpk)/AUC (50 mpk).

mg/kg doses, and the plasma concentrations of **1** were determined at 0.5, 1, and 4 h time points. Parent drug **1** demonstrated the lowest systemic exposure at 50 mg/kg and no further increase in circulating plasma levels at the high dose of 200 mg/kg. In contrast, prodrugs **7**, **8**, **10**, and **13** produced higher exposure levels of **1**, where the AUC increased proportionally with dose at levels of 50 and 200 mg/kg. These data demonstrated efficient in vivo conversion of these four prodrugs to **1** in mice and suggested our prodrug strategy could serve to overcome the pharmaceutics issues associated with **1**. Among the four prodrugs tested, **10** gave slightly lower levels of exposure of **1** relative to the other three natural amino acid prodrugs (**7**, **8**, and **13**) and was not further pursued.

Table 3. Inhibition of Human CYP Isozymes by Various Prodrugs[a,b,c]

cmpd	IC_{50} for CYP inhibition (μM) 1A2	2C9	2C19	2D6	3A4 (BFC)	3A4 (BzRes)
1	>40	>40	>40	>40	18	>40
7	3.7	0.063	0.16	12	0.16	0.31
8	>40	9.7	2.1	24	0.51	1.6
13	34	2.7	1.8	24	0.095	0.37

[a] Data are expressed as a mean of at least two measurements. [b] Highest test concentration: 40 μM. [c] For assay condition, see ref 16.

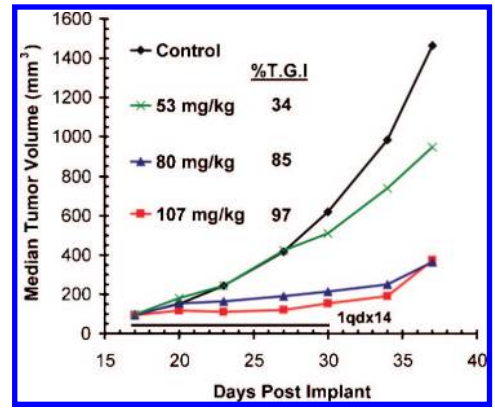


Figure 1. In vivo antitumor activity of **8** vs L2987 xenografts in athymic mice.

When evaluated in a cytochrome P450 panel to assess the potential for drug−drug interactions, compounds **7**, **8**, and **13** were found to be more potent inhibitors of these metabolizing enzymes than parent **1** (Table 3). Although no circulating prodrug was observed for any of these compounds in the mouse oral exposure assay, analogues with modest activity were desirable since it was difficult to rule out the possibility of incomplete conversion of prodrug to parent drug in the clinical setting. Compound **7** was a highly potent inhibitor of the CYP2C9 isoform (IC_{50} = 63 nM), and demonstrated submicromolar potency versus CYP3A4 and CYP2C19. Compound **13** also demonstrated submicromolar activity versus the CYP3A4 isoform. Overall, compound **8** showed the most favorable CYP inhibition profile. The risk of drug−drug interactions was further mitigated by the demonstration that compound **8** was rapidly converted to parent **1** in human intestinal microsomes (18% remaining of **8** after 10 min of incubation).

Prodrug **8** also exhibited high solid state stability (only 0.3% degradation at 50 °C with desiccant over a period of 12 weeks) and acceptable solution state stability up to pH 6.5. The compound was extremely stable at pH 4.2 in buffer solution at 37 °C, with less than 1% of prodrug degrading to parent **1** over a 24 h period. Furthermore, **8** possessed high aqueous solubility (73 mg/mL at pH 5.8). Based on its promising results in the above studies, **8** was selected for in vivo evaluation in tumor xenograft studies.

In Vivo Antitumor Activity of 8. The in vivo antitumor activity of **8** was evaluated in a L2987 nonsmall cell lung tumor xenografts assay in athymic mice (Figure 1).[17] Once daily oral administration of **8** for 14 consecutive days inhibited the growth of the established tumor (80–100 mm^3 size) in a dose-dependent manner. At 80 and 107 mg/kg doses, essentially complete tumor stasis was observed throughout the dosing period, with a percent tumor growth inhibition (%TGI) of 85 and 97%, respectively. No overt toxicity was observed in either cohort of animals,

suggesting good safety margins in mice for this compound. This result supported the concept that prodrug **8** could provide an effective means to improve the pharmaceutical and pharmacokinetic properties of **1** for clinical development.

Conclusions

The synthesis and biological evaluation of a series of amino ester prodrugs of **1** are reported. In vitro assessment of the conversion of various prodrugs to **1** in liver S9 fraction and serum and in vivo evaluation of their oral exposure in mice led to the identification of compounds **7**, **8**, and **13** as potential lead prodrugs. Evaluation of inhibition of human CYP enzymes by these compounds revealed that prodrug **8** possessed favorable CYP profile and least likelihood for drug−drug interactions. Further studies showed that **8** demonstrated excellent pharmaceutical properties and significant antitumor activity against L2987 human lung carcinoma xenografts. Based on these results, **8** was selected for advancement into preclinical toxicity studies to support clinical development of this interesting drug candidate.

Experimental Section

Chemistry. Preparation of 2-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl)propan-2-ol (5). To a solution of freshly prepared chloroimidate **2**[14,18] (167.8 g, 0.7 mol) in DMF (1.1 L) was added K_2CO_3 (267 g, 2.1 mol) and 4-fluoro-2-methyl-1*H*-indol-5-ol **3**[12] (109.5 g, 0.7 mol). The reaction mixture was stirred at rt for 16 h and then cooled to 0 °C. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, 10% aqueous LiCl, and water. The organic extract was concentrated in vacuo, and the residue was coevaporated with toluene to give crude **4**. MS (ESI^+) *m*/*z* 369.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.90 (s, 1H), 7.08 (d, 1H, $J = 8.25$ Hz), 6.98 (dd, 1H), 6.34 (s, 1H), 4.39 (q, 2H, $J = 7.15$ Hz), 2.87 (s, 3H), 2.45 (s, 3H), 1.41 (t, 3H, $J = 7.15$ Hz).

To a mixture of compound **4** and LiCl (140 g) in THF (1.1 L) at 0 °C was added MeMgBr (1 M in toluene, 2.8 mol) at a rate so as to maintain internal temperature below 5 °C. The resulting mixture was stirred at 0 °C for 2 h and 15 °C for 3 h. The mixture was recooled to 5 °C, and additional MeMgBr (0.14 mol) was added. The mixture was stirred at 15 °C for another 1.5 h. The mixture was extracted with EtOAc and 15% aqueous NH_4Cl. The organic extract was concentrated. The residue was dissolved in dichloromethane (DCM) and passed through a short pad of silica gel, eluting with DCM, 5% EtOAc in DCM. The filtrate was concentrated to give a white solid that was recrystallized from EtOAc/heptane afforded **5** (186 g, 75% yield). MS (ESI^+) *m*/*z* 355.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, br, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 7.08 (d, 1H, $J = 8.60$ Hz), 6.97 (dd, 1H), 6.35 (s, 1H), 2.78 (s, 3H), 2.46 (s, 3H), 1.80 (s, OH), 1.70 (s, 6H).

4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol (6). To a solution of BF_3/OEt_2 (120 mL, 0.948 mol) in DCM (200 mL) at 0 °C was added H_2O_2 (50% aqueous solution, 4.6 mL, 0.079 mol). The mixture was stirred at 0 °C for 30 min and then cooled to −20 °C. To this mixture was added a solution of **5** (20 g, 0.0564 mol) in DCM (400 mL) via cannula at a rate so as to keep the reaction temperature between −15 to −25 °C. The resulting mixture was stirred at −15 °C for 40 min. The reaction was quenched with 20% aq Na_2SO_3 (200 mL) and 33% aq ethanolamine (300 mL) and stirred below 0 °C for 2 h. The organic layer was then separated, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with 5% aq citric acid, 10% aq $NaHCO_3$, water, and brine, dried, and then concentrated to give an orange foam. The crude material was dissolved in THF and loaded to a Florisil column, eluting with 30% EtOAc/heptane. The desired fractions were concentrated in vacuo and recrystallized from EtOAc/heptane. The solid was collected and washed with heptane to afford **6** (9.1 g, 52% yield) as an off-white solid. The filtrate was further purified on silica gel using 40% EtOAc/heptane to give additional product **6** (2.5 g, 14% yield). MS (ESI^+) *m*/*z* 313.2 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 9.60 (br s, 1H), 7.85 (s, 1H), 7.51 (s, 1H), 7.13 (d, 1H, $J = 8.7$ Hz), 6.98 (t, 1H, $J = 8.7$ Hz), 6.24 (s, 1H), 2.41 (s, 3H), 2.39 (s, 3H).

(*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-ol (1). A mixture of **6** (7.5 g, 24 mmol), *R*-(+)-propylene oxide (120 mmol), LiCl (3.02 g, 72 mmol), and NEt_3 (300 μL) in EtOH (50 mL) was heated in a sealed tube at 70 °C for 3 h. The solvent was reduced to about 10 mL and the residue was poured into water. The precipitate was collected by filtration and washed with water. The crude solid was dissolved in 5% EtOH/DCM and passed through a short pad of silica gel, eluting with 20% EtOAc/DCM. The filtrate was concentrated, and the solid residue was triturated with 30% EtOH/heptane to afford **1** (7.2 g, 81% yield) as an off-white solid. MS (ESI^+) *m*/*z* 371.2 $(M + H)^+$. ^1H NMR (500 MHz, CD_3OD) δ 7.72 (s, 1H), 7.61 (s, 1H), 7.10 (d, 1H, $J = 8.80$ Hz), 6.90 (t, 1H, $J = 7.15$ Hz), 6.23 (s, 1H), 4.12–4.20 (m, 1H), 3.92 (d, 2H, $J = 6.55$ Hz), 2.48 (s, 3H), 2.43 (s, 3H), 1.29 (d, 3H, $J = 6.6$ Hz). Mp 208–210 °C. Anal. ($C_{19}H_{19}FN_4O_3$): C, H, N, F.

General Procedure for the synthesis of *N*-Cbz-Protected Compounds 7–15 and 16–20. A mixture of **1** (1 equiv, 0.16 mmol), the appropriate *N*-CbzNHCR^{1}R^{2}COOH or R^{3}COOH (2.5 equiv, 0.4 mmol), HATU (253 mg, 0.4 mmol), DIPEA (103 mg, 0.8 mmol), and DMAP (5 mg) in DMF (1 mL) was stirred overnight. The volatiles were removed in vacuo, and the residue was purified by flash column chromatography or preparative HPLC conditions to afford *N*-Cbz-protected compounds **7**–**15** and **16**–**20**.

General Procedure for the Synthesis of Compounds 7–15. A mixture of the appropriate *N*-Cbz-protected derivatives **7**–**15** (1 equiv, 0.11 mmol), Pd/C (10%, 6 mg), and ammonium formate (200 mg) in DMF (1.5 mL) was stirred at RT for 0.5 to 2 h (the reaction was monitored by HPLC for completion). The mixture was diluted with ethyl acetate and filtered through a pad of celite. The filtrate was washed with water, dried over Na_2SO_4, and passed through a pad of silica gel, eluting with EtOAc. The filtrate was concentrated and if necessary further purified by prep-HPLC conditions. The desired fraction was lyophilized with HCl (1 N in water) to afford the title compounds **7**–**15** as HCl salts.

Pharmacology. Incubation with Liver S9 Fractions. The in vitro metabolism of prodrugs was investigated in incubations with S9 subcellular fractions from mouse (CD-1) and human liver homogenates. Incubation of prodrugs was done in duplicate with S9 fractions from each species. The rate of metabolism was measured under the following conditions: prodrug, 20 μM final concentration (400 μM stock solutions in 4% DMSO/96% water; final incubation solutions contained 0.2% DMSO); 20 μL of S9 per 200 μL incubation, final protein concentration 2 mg/mL; $MgCl_2$, 10 mM; pH 7.4 sodium phosphate buffer, 60 mM. Incubations were performed in 96-well plates at 37 °C under an atmosphere of 5% CO_2. Incubations were initiated by the addition of S9 and were quenched at various times (0, 10, or 30 min) by the addition of an equal volume (0.2 mL) of acetonitrile to each well. Plates were sealed, vortexed, and centrifuged to pellet-precipitated proteins, and the supernatants were transferred to clean plates or HPLC vials. Samples were analyzed using a LC/MS/MS assay.

Stability of Prodrug 8 in Human Intestinal Microsomes. The in vitro metabolism of **8** was investigated in incubations (in duplicate) with human intestinal microsomes. The rate of oxidative metabolism was measured under the following conditions: **8**, 10 μM final concentration for intestinal microsomes (100 μM stock solutions in 2% DMSO/19.5% acetonitrile/80% water; final incubation solutions contained 0.05% DMSO, 1.95% acetonitrile); final protein concentration, 1 mg/mL; NADPH, 0.9 mg/mL; pH 7.4 sodium phosphate buffer, 56 mM. Incubations were performed in 96-well plates at 37 °C under an atmosphere of 5% CO_2. Incubations were initiated by the addition of NADPH and were quenched at various times (0, 10, or 30 min) by the addition of an equal volume (0.2 mL) of acetonitrile to each well. Plates were sealed, vortexed,

and centrifuged to pellet-precipitated proteins, and the supernatants were transferred to clean plates or HPLC vials. Samples were analyzed using a LC/MS/MS assay.

Acknowledgment. The authors thank the Discovery Analytical Sciences Department at BMS for obtaining high resolution MS analyses and enantiomeric excess determinations.

Supporting Information Available: Characterization data for chiral purity determination of **1**, **8**, and **9**, prodrugs **7**–**20**, and a table of reaction yields and HPLC analysis data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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