Discovery and Evaluation of a Series of 3-Acylindole Imidazopyridine Platelet-Activating Factor Antagonists[1]

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Studies conducted with the goal of discovering a second-generation platelet-activating factor (PAF) antagonist have identified a novel class of potent and orally active antagonists which have high aqueous solubility and long duration of action in animal models. The compounds arose from the combination of the lipophilic indole portion of Abbott's first-generation PAF antagonist ABT-299 (**2**) with the methylimidazopyridine heterocycle moiety of British Biotechnology's BB-882 (**1**) and possess the positive attributes of both of these clinical candidates. Structure−activity relationship (SAR) studies indicated that modification of the indole and benzoyl spacer of lead compound **7b** gave analogues that were more potent, longer-lived, and bioavailable and resulted in the identification of 1-(*N*,*N*-dimethylcarbamoyl)-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride (ABT-491, **22m**·HCl) which has been evaluated extensively and is currently in clinical development.

Introduction

Platelet-activating factor (PAF), an endogenous phospholipid inflammatory mediator, is a D-glycerol derivative bearing a phosphorylcholine at C_3, an acetyl group at C_2, and a long-chain alkyl ether moiety at C_1.[2] In rabbit and human neutrophils and platelets, the C_{16}-PAF predominates.[3] Inflammatory cells such as alveolar macrophages, eosinophils, platelets, and neutrophils generate PAF in response to inflammatory and immune stimuli. PAF exerts its influence by acting on specific G-protein-coupled receptors found in a variety of cell types.[4] The specific G-protein(s) involved in PAF signaling is not known and may vary with cell type.

The biological responses associated with such signaling include increased vascular permeability, hemoconcentration, hypotension, ulcerogenesis, bronchoconstriction, triggering of airway hyperresponsiveness, and platelet degranulation.[5] These proinflammatory activities indicate that PAF could be an important mediator in a wide range of pathological conditions that have an inflammatory component. These would include septic shock, asthma, ischemia/reperfusion injury, pancreatitis, inflammatory bowel disease, and rhinitis.[6] In light of the various biological responses and disease states associated with PAF, it would appear that an agent antagonizing its action might have therapeutic value.

In an attempt to prove this point, many research groups have identified PAF antagonists which possess a variety of structural types.[7] While many of these antagonists have failed to show efficacy in clinical trials for asthma and sepsis, the most recent compound to undergo clinical evaluation, BB-882 (**1**),[8] appears to be effective in the treatment of pancreatitis.

Initial Studies

Previous research at Abbott Laboratories identified ABT-299 (**2**), a water-soluble prodrug of A-85783 (**3**), which is a novel, potent, and selective antagonist of PAF (Scheme 1).[9] Following the selection of **2** for clinical development, the search for a followup antagonist was undertaken. It was decided that the followup compound should meet several criteria, including: in vitro and in vivo PAF antagonist activity equal to or better than **3**, sufficient intrinsic solubility so as to avoid the stability issues related to prodrug decomposition, good oral activity which might facilitate its use in numerous disease indications, and a chemical structure which was novel and distinct from **3** so as to avoid any potential structure-related toxicity.

One approach to develop a followup compound entailed examination of the structural elements associated with known PAF antagonists. A common structural arrangement shared by PAF antagonists such as **3**, WEB-2086 (**4**),[10] SR-27417 (**5**),[11] Ro 24-0238 (**6**),[12] and **1** consists of a lipophilic moiety tethered to an sp^2 nitrogen heterocycle by a spacer containing a hydrogen-bond acceptor (Scheme 1).[13] It was presumed that by merging the structural elements of different classes of compounds while retaining the same overall spatial relationship of the lipophile, spacer, and heterocycle, a new series of PAF antagonists could be discovered. One example of this strategy is the combination of the spacer and heterocycle of **1** with the lipophilic portion of **3**. It was hoped that this hybrid compound would retain the high aqueous solubility of **1**, the long duration of action of **3**, and the high PAF antagonism of both compounds. Indeed, the first compound of this series, imidazopyri-

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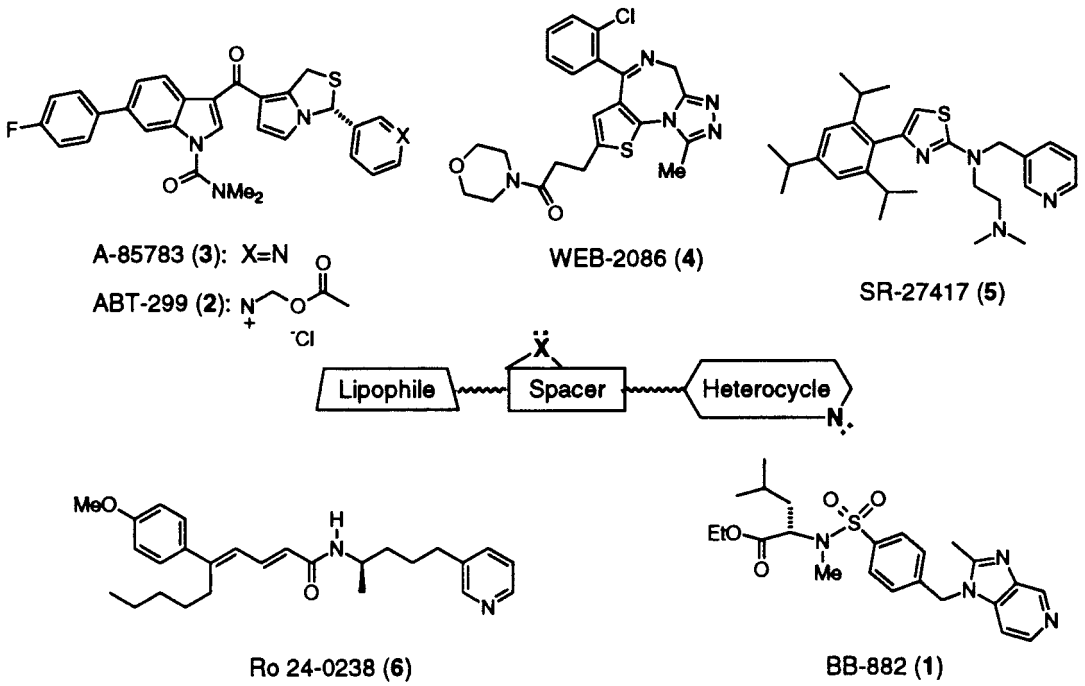
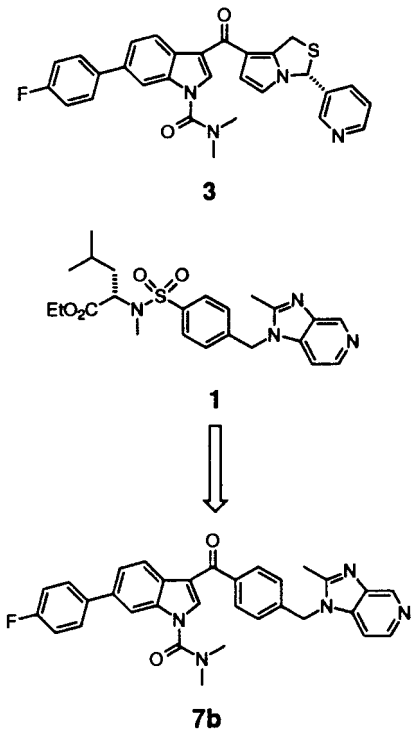
Scheme 1



Scheme 2



dine **7b** (Scheme 2), possessed affinity for the PAF receptor (2.3 nM, receptor binding using rabbit platelet membranes), which compared favorably with both **3** (4 nM) and **1** (0.4 nM), and aqueous solubility (0.1 mg/mL at pH 7) greatly improved over that of **3** (<0.001 mg/mL). However, this initial compound was not as active in vivo (ED_{50} = 0.07 mg/kg, rat skin permeability, iv) as either **3** (0.006 mg/kg) or **1** (0.02 mg/kg). With this lead structure in hand, a program was initiated to investigate additional analogues.

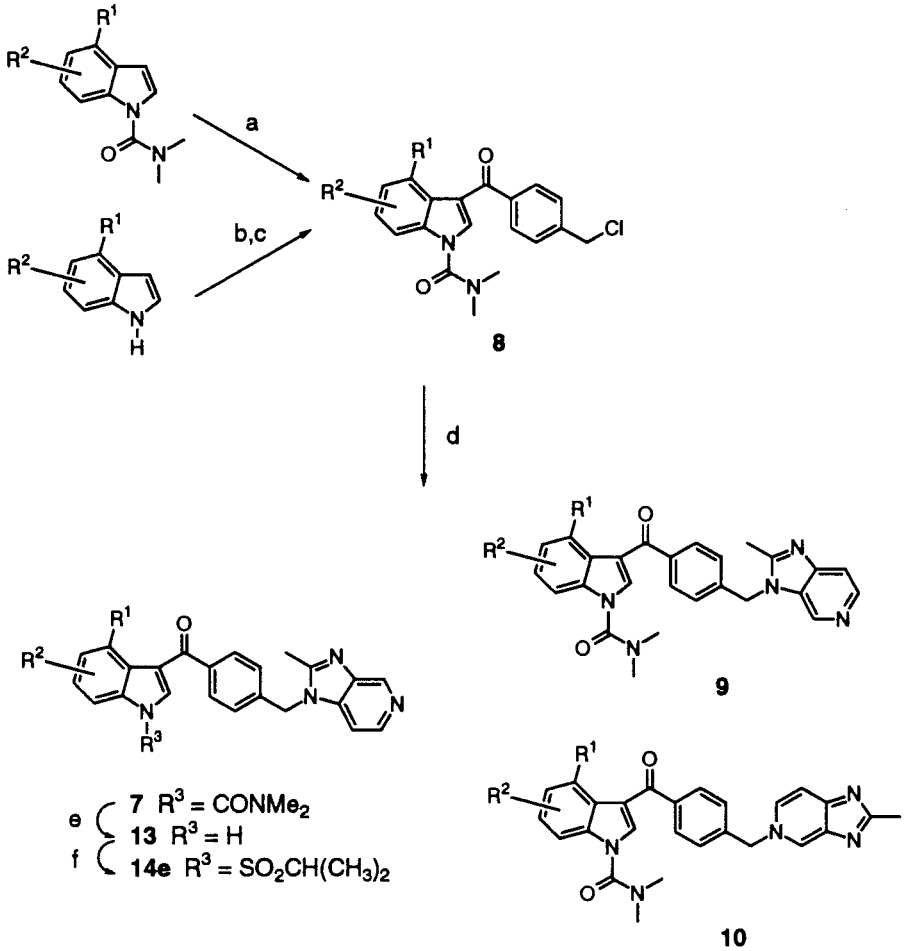
The structure−activity relationships (SAR) associated with this family of compounds were determined by independently modifying the lipophile, spacer, and heterocycle portions of the lead structure and evaluating the effect of these changes on such parameters as PAF receptor binding affinity, in vivo potency, aqueous solubility, duration of action, and bioavailability in multiple species. The synthesis and evaluation of these analogues which led to the discovery of a new PAF antagonist clinical candidate are outlined below.

Chemistry

The synthesis of analogues with an alkyl or aromatic spacer, most commonly methylbenzoyl as in compounds **7a**−**aa** (Table 1), is shown in Scheme 3 and began with the 3-acylation of variously mono- and bis-substituted indoles which were obtained commercially or prepared as described in the Experimental Section. The 3-acylation could be accomplished using two complementary methods, depending on the indole substitution. The first method entailed the treatment of an acid chloride, such as commercially available 4-(chloromethyl)benzoyl chloride, under typical Friedel−Crafts conditions[14] (method A, see the Experimental Section for details) with *N*-carbamoylated indoles to give benzylic chlorides **8** in modest yields. For indoles which were not compatible with these conditions, such as those bearing activating substituents on the phenyl ring, a second procedure was used; this method entailed the in situ formation of the zinc salt of the *N*-unsubstituted indoles[15] and their subsequent addition to the acid chloride (method B, see Experimental Section for details) followed by *N*-carbamoylation to give **8**. In methylene chloride or ethyl ether this reaction gives complete regioselectivity providing only 3-acylated products. Despite the use of Grignard reagent in this procedure it proved to be compatible even with indoles bearing electrophilic substituents such as esters or carbamates.

Typically, the synthesis was completed by the displacement of the benzylic chloride in **8** with the sodium

Scheme 3[a]

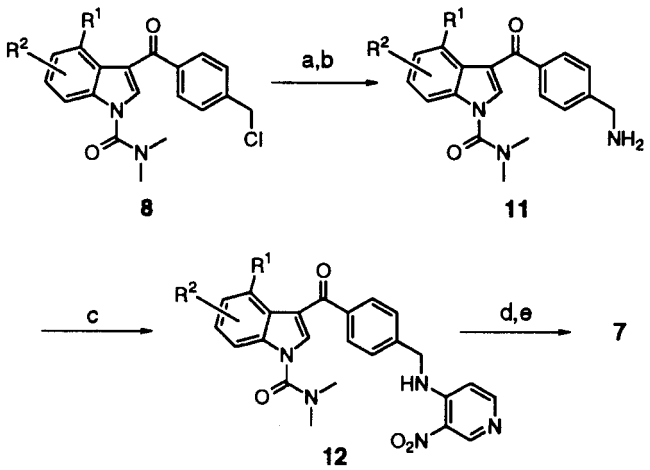


[a] Reagents: (a) 4-(chloromethyl)benzoyl chloride, $AlCl_3$, CH_2Cl_2; (b) EtMgBr, $ZnCl_2$, 4-(chloromethyl)benzoyl chloride, CH_2Cl_2; (c) NaH, $ClCONMe_2$, THF; (d) NaH, 2-methylimidazo[4,5-*c*]pyridine, DMPU/THF; (e) 1 M NaOH, MeOH; (f) KOH, $ClSO_2CH(CH_3)_2$.

salt of the desired heterocycle. In the case of 2-methylimidazopyridine the addition was not regioselective with respect to the heterocycle and gave all three possible regioisomeric heterocycles (e.g., **7**, **9**, and **10** in Scheme 3);[16] chromatography gave the desired isomer **7** in low yield but in large enough quantities for initial testing. An alternate installation of this heterocycle which was used for the preparation of selected compounds is shown in Scheme 4 and involves azide displacement of the benzylic chloride followed by reduction to give amines **11**. This material was then added to 4-chloro-3-nitropyridine to give **12** which after reduction and cyclization gave the 1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl isomer regioselectively in good overall yields. While requiring more steps than the direct displacement route, this synthetic sequence was higher yielding and more amenable to multigram scales.

The linear sequence outlined above was well-suited for the independent modification of the lipophilic, spacer, and heterocyclic portions of **7**. As mentioned above, a number of indoles bearing a wide range of substituents were used. When bromoindoles (**8**, R or R′ = Br) were used, a number of substituents could be added after installation of the heterocycle using transition metal chemistry[17] (conversion of **7x** to **7z** in Scheme 5, for example). In addition, the effect of substitution at nitrogen was explored by the removal of the *N*,*N*-dimethylcarbamoyl substituent under basic conditions

Scheme 4[a]

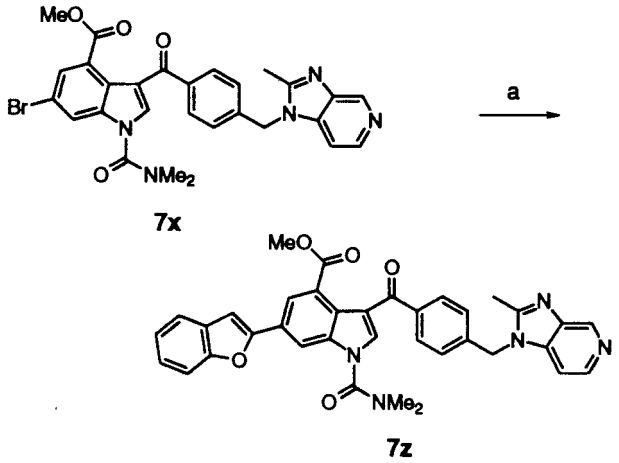


[a] Reagents: (a) NaN_3, DMF; (b) PPh_3, H_2O/THF; (c) 3-nitro-4-chloropyridine·HCl, CH_3CN; (d) H_2, Pd/C, THF; (e) AcOH, Ac_2O.

to give indoles **13** which were then alkylated or acylated at nitrogen to give compounds **14a**−**i** in Table 2.

The indole acylation procedures mentioned above allowed for the installation of a number of spacers including substituted phenyl, heteroaryl, simple alkyl, and cycloalkyl (**15a**−**n** in Table 3). The synthesis of analogues with a sulfone spacer is shown in Scheme 6 and began with the addition of in situ prepared toluene

Scheme 5[a]



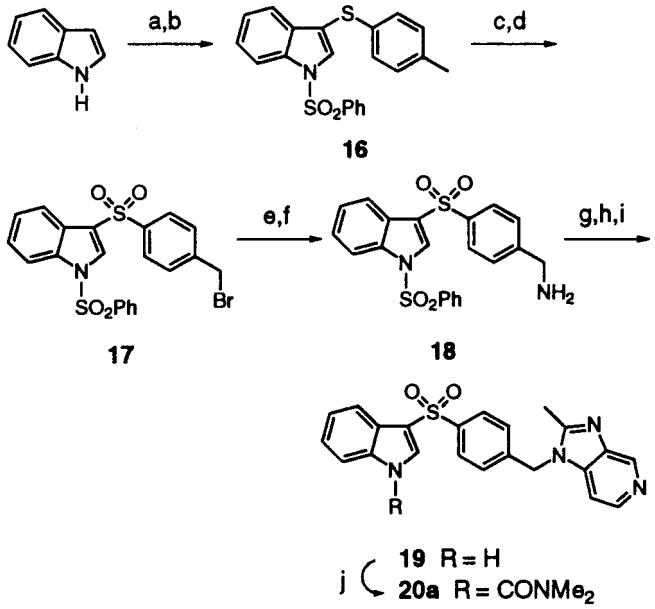
[a] Reagents: (a) tri-*n*-butyl(benzo[*b*]fur-2-yl)stannane, $Pd(PPh_3)_4$, dioxane.

sulfenyl chloride to substituted indoles[18] that was followed by nitrogen protection to give sulfide **16**. After oxidation of the sulfide and benzylic bromination, bromide **17** was regioselectively converted to imidazopyridine **19** which was carbamoylated to afford sulfone **20a**.

The displacement chemistry of intermediate **8** allowed for the synthesis of a variety of heterocycles which included substituted imidazopyridines, benzimidazoles, substituted imidazoles, pyridines, and quinazolinones (**21a**−**g** in Table 4). It was found that use of alternative carboxylic acid/anhydride mixtures in the cyclization of reduced nitroaryl **12** allowed for the efficient modification of the substituent at the imidazopyridine 2-position (methyl in Scheme 3). Additional compounds (**22a**−**q**) made using the above-mentioned sequence are shown in Table 5.

The synthetic sequence used to prepare analogues with spacers bearing amide linkages is shown in Scheme 7. Carboxylation and nitrogen protection of substituted indoles were accomplished in three steps to give acids **23** which were coupled using standard techniques with several amines such as **24**, prepared by the addition of commercially available 4-(aminomethyl)piperidine to 4-ethoxy-3-nitropyridine and subsequent reduction/cyclization, to give amides such as **25**. Finally, the synthesis of the sulfonamide spacer analogues was

Scheme 6[a]



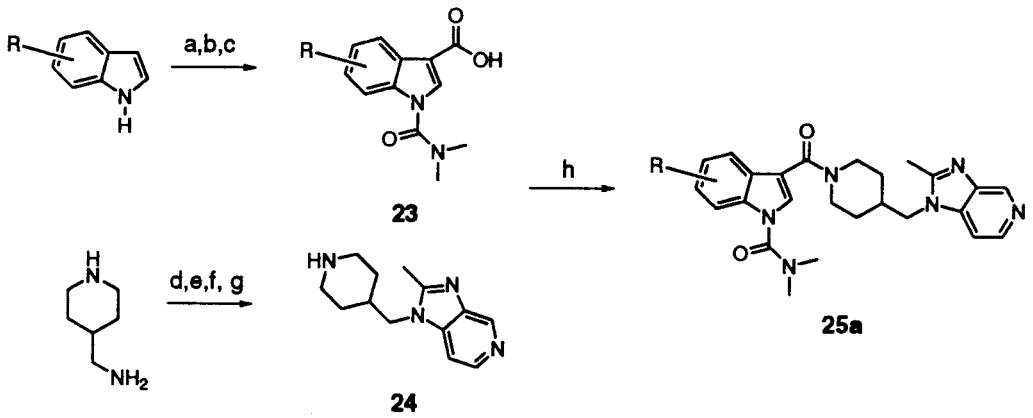
[a] Reagents: (a) *p*-tolyl disulfide, SO_2Cl_2, Et_3N, CH_2Cl_2; (b) KOH, $PhSO_2Cl$, DME; (c) 30% H_2O_2, AcOH; (d) NBS, cat. $(PhCO)_2O_2$, CCl_4; (e) $(Boc)_2NK$, DMF; (f) TFA; (g) 3-nitro-4-chloropyridine, EtOH; (h) H_2, 10% Pd/C, MeOH; (i) Ac_2O, AcOH; (j) KOH, $ClCONMe_2$, THF.

completed using the coupling of sulfonyl chloride **26** in Scheme 8, prepared using the protected 3-bromoindoles, with amines such as **27** to give, after deprotection and carbamoylation, sulfonamides **29a**−**c** (see Table 6).

Results and Discussion

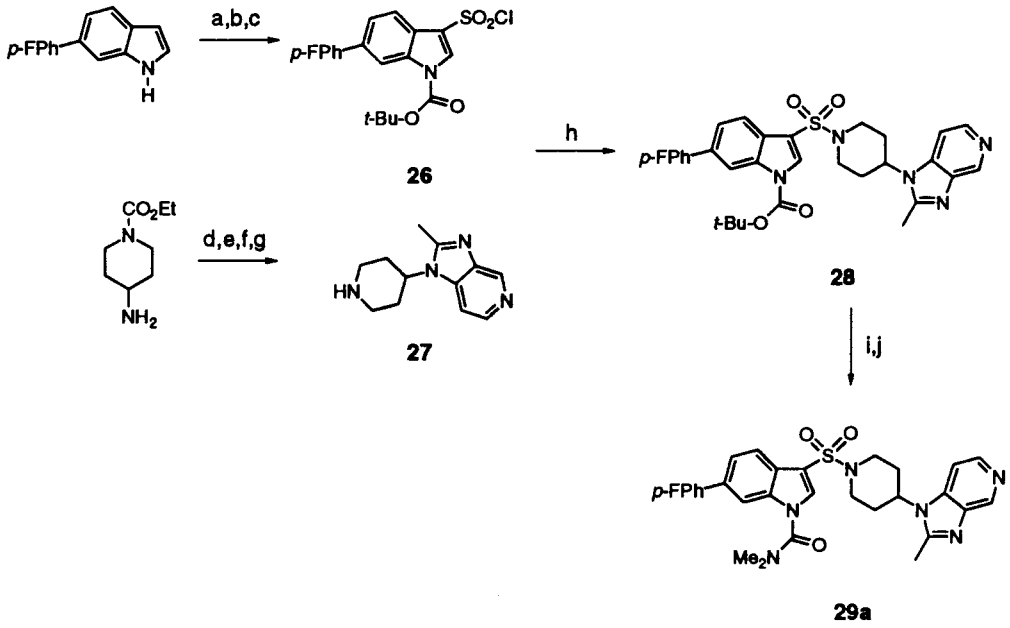
The testing protocol for assessing the pharmacological profiles of the compounds prepared in this study began with the determination of binding potencies using [^{3}H]-C_{18}-PAF and PAF receptors on rabbit platelet membranes (see the Experimental Section for details). Compounds possessing sufficient in vitro potency (generally <500 nM) were then examined in an in vivo model which determined the ability to block the effect of exogenously administered PAF, namely, the PAF-induced rat skin permeability assay. This assay was conducted by measuring the vascular permeability

Scheme 7[a]



[a] Reagents: (a) $SOCl_2$/DMF, CH_2Cl_2; (b) KOH, $ClCONMe_2$, THF; (c) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, THF/*t*-BuOH/H_2O; (d) H_2, 10% Pd/C, EtOH; (f) Ac_2O, AcOH; (g) LiOH, EtOH/H_2O; (h) BOPCl, *i*-Pr_2NEt, THF.

Scheme 8[a]



[a] Reagents: (a) Boc_2O, DMAP, THF; (b) NBS, THF; (c) *t*-BuLi, SO_2, THF, NCS, CH_2Cl_2; (d) 3-nitro-4-ethoxypyridine, CH_3CN; (e) H_2, 10% Pd/C, EtOH; (f) Ac_2O, AcOH; (g) KOH, $EtOH/H_2O$; (h) Et_3N, THF; (i) NaOMe, THF; (j) KOH, $ClCONMe_2$, THF.

caused by the intradermal injection of PAF on the dorsal region of rats and the dose-related inhibition of this effect after a 1-h pretreatment of the antagonist being tested.[19] While it was expected that compounds with high intrinsic potency (low K_i) would possess comparably high activity (low ED_{50}) in the in vivo model, exceptions to this trend can be explained by suggesting a short half-life in the species being tested or an unfavorable pharmacodynamic profile, e.g., rapid metabolism or excretion.

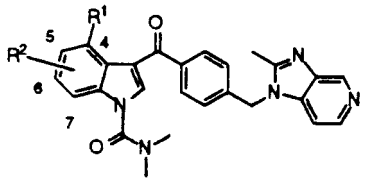
Analogues with good intravenous activity in this assay (<0.05 mg/kg) were also tested orally in this in vivo model. By varying the time of pretreatment of the animals before PAF challenge in this model, the duration of an analogue's antagonist activity could also be determined. Selected compounds were further characterized in models involving exogenously and endogenously induced PAF, for example, the PAF-induced mouse paw edema model and the LPS-induced hypotension rat assay.[20] Finally, various physical properties of compounds possessing the required pharmacological profile were determined such as aqueous solubility and bioavailability.

Indole Substitution. Initial structure−activity studies on this series examined the effect on activity, both in vitro and in vivo, of the substituents on the indole phenyl ring (e.g., 4-fluorophenyl in **7b**). As can be seen for compound **7a** in Table 1, it was found that this substituent was not necessary for good binding potency but was essential for optimal in vivo activity when these compounds were dosed intravenously. After several other 6-substituted analogues failed to give an increase in in vivo potency, compounds with substituents at other positions on the indole were synthesized. Because the aforementioned pharmacophore model indicated that the PAF receptor possesses an important hydrogen-bond donor in the binding site which interacts with the spacer carbonyl, it was anticipated that hydrogen-bond-accepting substituents at the 2- or 4-position might give an additional binding interaction with the receptor and lead to increased potency. To explore this possibility, compound **7c** bearing a 4-methoxycarbonyl moiety was made and tested. While **7c** did not have greater binding potency than lead compound **7b**, this 4-substituent did give a significant boost in in vivo potency (0.003 vs 0.068 mg/kg).

This increase in in vivo potency was seen with a number of other hydrogen-bond-accepting substituents in this position, although there were exceptions. The ethyl (**7f**) and isopropyl (**7g**) ester analogues of **7c** were equally potent, while significantly larger esters such as benzyl (**7d**) had good binding activity but decreased potency in vivo. Ester isosteres were tolerated as exemplified by carbamate **7l** and amide **7m** which were both more potent in vivo than **7b**. As with benzyl ester **7d**, a larger phenyl-containing amide functionality in this position (**7w**) gave a decrease in in vivo activity. In addition, it was found that a methyl ether at the 4-position (**7j**) gave exceptional activity both in vitro and in vivo. Notable exceptions to this activity trend include carboxylic acid **7e**, alcohol **7k**, and nitrile **7n**, all of which were less potent in vitro than the lead compound.

The lack of an increase in binding potency with indole 4-substitution prompted further investigation into the nature of an optimal 4-substituent. These studies indicated that hydrogen-bonding ability was not necessary to give an increase in in vivo potency versus **7b** and that a variety of groups gave greater activity. The first example in this vein was the 4-methyl analogue **7o** which was one of the most potent compounds synthesized. Further examination indicated that the size of this group could be varied somewhat as a 4-fluorophenyl-substituted (**7s**) or 2-furyl-substituted (**7t**) compound was equipotent with an ethyl-substituted (**7v**) or ethynyl-substituted (**7u**) analogue. Somewhat suprisingly, synthetic intermediate **7r** with a 4-bromide substituent had excellent activity in vivo as did chloride-containing antagonist **7q**, while analogue **7p** with the

Table 1. In Vitro and in Vivo Activity of Indole-Modified Imidazopyridines



compd	R^1	R^2	K_i, nM[a]	ED_{50}, mg/kg[b]
7a	H	H	6.8 (6−8)	0.18 (0.18−0.18)
7b	H	6-(4-F)Ph	2.3 (1−4)	0.068 (0.68−0.69)
7c	CO_2Me	H	0.85 (0.1−12)	0.00 (0.003−0.003)
7d	CO_2CH_2Ph	H	0.86 (0.7−1)	0.12 (0.12−0.13)
7e	CO_2H	H	14 (1−230)	>1
7f	CO_2Et	H	5.2 (1−20)	0.006 (0.005−0.007)
7g	CO_2i-Pr	H	4.7 (1−20)	0.006 (0.006−0.007)
7h	H	5-CO_2Me	110 (6−2000)	>1
7i	H	5-(4-F)Ph	190 (77−480)	>1
7j	OMe	H	2.0 (0.1−39)	0.007 (0.006−0.007)
7k	OH	H	6.1 (4−10)	>1
7l	$OCONMe_2$	H	3.6 (3−4)	0.005 (0.003−0.006)
7m	$CONMe_2$	H	11 (7−3800)	0.028 (0.027−0.030)
7n	CN	H	51 (7−350)	0.23 (0.21−0.26)
7o	Me	H	0.82 (0.1−7)	0.004 (0.003−0.005)
7p	F	H	5.1 (3−9)	0.18 (0.16−0.22)
7q	Cl	H	5.4 (2−14)	0.008 (0.006−0.011)
7r	Br	H	11 (7−16)	0.007 (0.005−0.010)
7s	(4-F)Ph	H	2.9 (1−9)	0.004 (0.003−0.004)
7t	2-furyl	H	11 (2.6−44)	0.007 (0.007−0.007)
7u	CCH	H	1.3 (0.5−3)	0.003 (0.003−0.004)
7v	Et	H	0.91 (0.5−2)	0.003 (0.003−0.004)
7w	NHCOPh	H	2.0 (1−4)	0.11 (0.067−0.16)
7x	CO_2Me	6-Br	1.4 (0.5−3)	0.009 (0.006−0.012)
7y	CO_2Me	6-(4-F)Ph	0.15 (0.02−1)	0.002 (0.001−0.003)
7z	CO_2Me	6-(2-benzofuryl)	0.78 (0.4−2)	0.011 (0.009−0.014)
7aa	CO_2Me	6-CCPh	0.95 (0.5−2)	0.004 (0.003−0.006)

[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits.

smaller 4-fluorine substituent was much less active in the animal model. It was found, however, that the position of the substituent on the indole ring was crucial as 5-substituted analogues **7h**,**i** both showed significantly lower activities in vitro and in vivo than their 4-substituted counterparts.

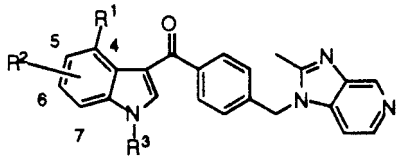
In light of the increase in duration of action of PAF antagonists in the previous Abbott series (**3**) resulting from 6-aryl substitution, a series of imidazopyridine compounds containing 4,6-disubstituted indoles was synthesized. As can be seen in Table 1, analogues possessing a 4-methoxycarbonyl moiety and 6-substituents such as bromide (**7x**), mono- and bicyclic aryls (**7y**,**z**), and phenylacetylene (**7aa**) were very potent in vivo as well as in vitro but gave no increase in duration of action (see below).

It was found that substitution at the 2- and 7-positions of the indole was not synthetically compatible with nitrogen substitution, and as a result these compounds are reported in Table 5 lacking the *N*,*N*-dimethylcarbamoyl group of lead compound **7b**. While 2-substitution or 2,4-disubstitution as in **22a** or **22b** gave poor activity in vivo, analogues with 7-substituents such as **22h**,**i** were quite potent despite lacking the important (vide infra) indole nitrogen substituent.

The importance of indole nitrogen substitution of the lead compounds **7b**,**c** was explored, and the results are shown in Table 2. As in our first generation of indole PAF antagonists (e.g., **3**), it was found that substitution at this position was essential for optimal in vitro and in vivo potency since its removal resulted in a 20−50-fold loss in activity regardless of the indole phenyl substitution (**13a**,**b**). It was found that with the 4-(methoxycarbonyl)indole a wide variety of nitrogen substituents gave compounds with extremely high binding potencies and represented an opportunity to replace the metabolically labile *N*,*N*-dimethylcarbamoyl moiety.[21] Replacement functionalities which gave good binding included other ureas (**14b**,**h**,**i**), alkyl esters (**14g**), and an alkyl amide (**14a**). Other potent replacements which were predicted to provide less probable sites for metabolism included several alkyl groups (**14c**,**f**), an alkylsulfonamide (**14e**), and a sulfonyl urea (**14d**). It was found, however, that few of these replacements gave suitable in vivo activity and none afforded a better pharmacokinetic profile than **7c**.

Spacer Modification. Based on the pharmacophore model for this family of PAF antagonists, it was anticipated that good binding potency would be retained after replacement of the methylbenzoyl spacer of **7b**,**c** with other structural fragments that maintained the required spatial relationship between the heterocycle and lipophilic indole. The fact that alterations to this orientation, such as in **15f** or **15g**, gave significant decreases in binding potency supported this model. However, it was not clear if spacer changes could

Table 2. In Vitro and in Vivo Activity of Indole-Modified Imidazopyridines



compd	R^1	R^2	R^3	K_i, nM[a]	ED_{50}, mg/kg[b]
13a	H	6-(4-F)Ph	H	75 (38−150)	1.3 (1.3−1.4)
13b	CO_2Me	H	H	6.0 (3−12)	0.15 (0.13−0.18)
14a	CO_2Me	H	CH_2CONMe_2	4.4 (0.4−45)	0.012 (0.012−0.013)
14b	CO_2Me	H	CO-pyrrolidine	11 (0.2−670)	0.005 (0.005−0.005)
14c	CO_2Me	H	CH_2CH_2OEt	1.1 (0.2−6)	0.012 (0.012−0.013)
14d	CO_2Me	H	SO_2NMe_2	4.3 (2−10)	0.074 (0.044−0.11)
14e	CO_2Me	H	SO_2*i*-Pr	0.19 (0.2−0.2)	0.120 (0.086−0.16)
14f	CO_2Me	H	*i*-Pr	1.3 (0.6−3)	0.10 (0.065−0.13)
14g	CO_2Me	H	CH_2CO*t*-Bu	0.67 (0.1−5)	0.036 (0.029−0.044)
14h	CO_2Me	H	CONHMe	1.5 (0.9−3)	0.007 (0.003−0.011)
14i	CO_2Me	H	$CONH_2$	1.5 (0.6−4)	0.12 (0.11−0.13)

[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits.

positively affect the overall pharmacological profile of the lead structures or improve the in vitro potencies of these compounds. Initial studies in this vein entailed replacement of the spacer *p*-methylphenyl group of **7b**,**c** with alternate linkers, and the resulting biological data are shown in Table 3. In one of the first changes made, it can be seen that use of a thiophene spacer as in **15a** gave compounds with significant binding potencies but attenuated in vivo activity, while the use of a 2,5-disubstituted thiazole (**15b**) gave unacceptable losses in both. It was also found early in the study that removal of the linker methylene to give **15e** gave a dramatic decrease in binding potency despite the fact that this spacer/heterocycle combination is used in a potent series of previously published antagonists.[22]

Since the spacer phenyl could be a site of metabolism, several changes were made to prevent this potential process. One such modification consisted of altering the electronics of this ring through substitution with an electron-withdrawing (F) or electron-inducing (OMe) moiety; both maneuvers gave compounds possessing high binding potencies (**15c**,**d**) with the fluorinated version being particularly interesting. A second modification consisted of replacing the aromatic ring with an alkyl tether which would have a significantly lower potential of being oxidized in vivo. By looking at several methylene tethers between the heterocycle and indole, as in **15h**−**j**, it was found that a 5-carbon linkage adequately replaced the methylphenyl spacer of **7c**, giving a compound with both excellent binding and in vivo potency. The use of a cyclohexyl tether as in **15l** was tolerated as well. In addition, since oxidative metabolism/*N*-dealkylation at the benzylic methylene of the methylbenzoyl spacer was possible, "reversed" spacer analogue **15m** was prepared, was found to be very potent both in vitro and in vivo, and thus was examined further (see below).

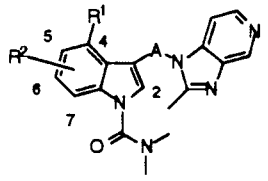
In general, one method of altering the pharmacological profile of a compound is to significantly alter its polarity/ionizability and thus presumably change its absorption, distribution, and/or metabolism. This maneuver was used in this study through the preparation of compounds possessing tertiary amines in the spacer portion. It was found that the use of an alkylamino tether the same length as that in **15i**, namely, **15k**, gave equipotent binding activity with this compound but significantly decreased in vivo activity. A second attempt at this entailed the use of a piperidine/ketone spacer in combination with several indoles to give analogues such as **15n** which was similiar in vitro and in vivo to lead compound **7c** and was also examined further.

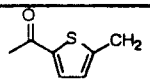
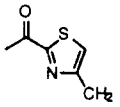
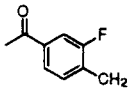
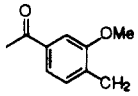
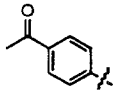
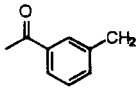
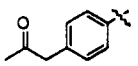
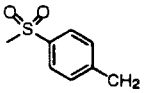
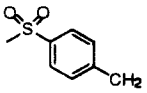
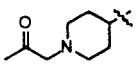
In an attempt to enhance receptor binding through the use of a tetrahedral hydrogen-bond acceptor in the spacer as in **1**, several sulfones and sulfonamides were tested and the results are shown in Tables 3 and 6. It was found that a sulfone replacement of the ketone moiety of **7a**,**c** gave compounds (**20a**,**b**) which possessed attenuated activity in vivo with no improvement in binding potency. The use of a sulfonamide/piperidine linker, as in **29b**, gave high in vitro and in vivo potency in comparison to **7b**, while removal of one methylene (**29a**) or use of an alkylpiperizine group (**29c**) afforded analogues that had significantly lower binding activities. In general, replacement of the ketone or amide carbonyl with a sulfone or sulfonyl group did not lead to increased binding potency.

Finally, it had been shown by another research group[23] that the use of piperidine and piperazine amide spacers afforded potent antagonists of PAF receptor when coupled with a pyridine heterocycle. These spacers were combined with 1*H*-imidazo[4,5-*c*]pyridine and several substituted indoles to give compounds such as **25a**−**c** which, in general, demonstrated attenuated activity in vivo with the exception of analogue **25a**.

Heterocycle Modifications. Based on the SAR work with other PAF antagonists of this family (e.g., **1** and **3**), it was known that the nature of the heterocycle was very important and that even subtle changes could have dramatic effects on binding potency.[24] Furthermore, it was believed that, as in the case of **3**,[25] the pyridine nitrogen would be a likely site of oxidative metabolism. With these factors in mind, the effect of the heterocycle on potency was investigated, and the effort began with examination of the various regioisomers of 2-methylimidazopyridine (Table 4); since these

Table 3. In Vitro and in Vivo Activity of Spacer-Modified Imidazopyridines



Compd	R^1	R^2	A	K_i, nM[a]		ED_{50}, mg/kg[b]	
15a	CO_2Me	H		8.2	(3-22)	0.12	(0.09-0.15)
15b	H	6(4)-PhF		39	(24-65)	0.35	(0.33-0.36)
15c	CO_2Me	H		5	(2-17)	0.006	(0.005-0.007)
15d	CO_2Me	H		10	(3-39)	NT	
15e	H	6(4)-PhF		260	(94-730)	NT	
15f	H	6(4)-PhF		180	(52-640)	NT	
15g	H	6(4)-PhF	$COCH_2$	> 1000		> 1	
15h	CO_2Me	H	$CO(CH_2)_3CH_2$	11	(5-25)	> 1	
15i	CO_2Me	H	$CO(CH_2)_4CH_2$	6.1	(2-500)	0.013	(0.012-0.014)
15j	CO_2Me	H	$CO(CH_2)_5CH_2$	9.4	(5-17)	> 1	
15k	H	6(4)-PhF	$COCH_2N(Me)(CH_2)_2CH_2$	140	(4-5700)	> 1	
15l	CO_2Me	H		2.4	(2-4)	0.020	(0.013-0.028)
15m	CO_2Me	H		0.63	(0.2-2)	0.005	(0.004-0.005)
20a	H	H		12	(4-36)	> 1	
20b	CO_2Me	H		13	(3-59)	0.48	(0.32-0.96)
15n	CO_2Me	H		19	(12-29)	0.006	(0.002-0.009)

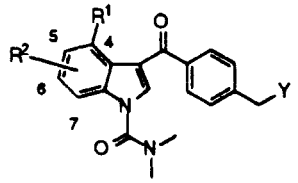
[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits.

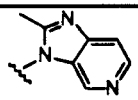
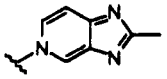
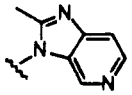
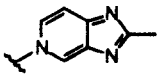
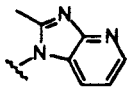
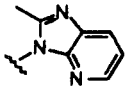
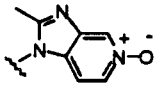
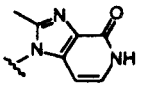
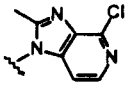
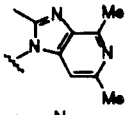
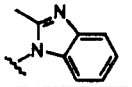
isomers were being made and isolated as byproducts in the alkylation of chloride **8**, this required minimal effort. It can be seen that regardless of indole substitution, the 1*H*-imidazo[4,5-*c*]pyridines **7b**,**c** had superior activity, both in vitro and in vivo, over either the 3*H*-imidazopyridines **9a**,**b** or the 5*H*-imidazopyridines **10a**,**b**. In contrast, it was found that both the 1*H*-imidazo[4,5-*b*]-pyridine (**21a**) and 3*H*-imidazo[4,5-*b*]pyridine (**21b**) analogues had comparable binding potency, with the former possessing excellent in vivo potency as well.

Since in vivo studies in the rat showed that oxidative metabolism of **7c** occurred at the heterocycle to give *N*-oxide **21c**,[21] this compound was independently synthesized and shown to have significantly attenuated activity. Efforts to inhibit this metabolism included the use of oxopyridine (**21d**), 4-chloropyridine (**21e**), and 4,6-dimethylpyridine (**21f**), all of which gave compounds which were poorly active in vivo. In a separate effort, the effect of the 2-substituent on the imidazopyridine was evaluated, and it was found that replacement of the 2-methyl group with other substituents reduced the binding potency significantly.

A second strategy to prevent oxidative metabolism of the imidazopyridine heterocycle was to remove the susceptible nitrogen through use of the benzimidazole heterocycle; this modification was made with the knowl-

Table 4. In Vitro and in Vivo Activity of Imidazopyridines and Derivatives



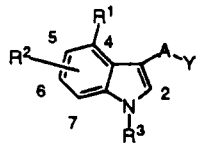
Compd	R^1	R^2	Y	K_i, nM[a]		ED_{50}, mg/kg[b]	
9a	H	6(4)-PhF		610	(550-680)	1.1	(1.1-1.1)
10a	H	6(4)-PhF		> 1000		NT	
9b	CO_2Me	H		16	(0.3-780)	0.24	(0.22-0.25)
10b	CO_2Me	H		> 1000		NT	
21a	CO_2Me	H		2.9	(0.7-13)	0.026	(0.02-0.03)
21b	CO_2Me	H		10	(4-27)	1.2	(1.1-1.4)
21c	CO_2Me	H		23	(9-60)	0.14	(0.13-0.15)
21d	CO_2Me	H		4	(2-8)	0.25	(0.14-0.35)
21e	CO_2Me	H		1.8	(1-3)	NT	
21f	CO_2Me	H		120	(18-840)	> 1	
21g	CO_2Me	H		0.92	(0.1-6)	> 1	

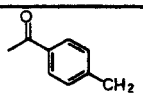
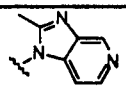
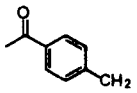
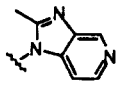
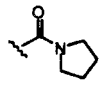
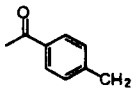
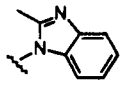
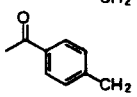
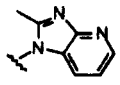
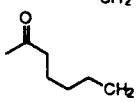
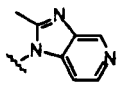
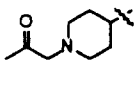
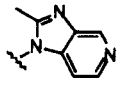
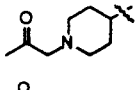
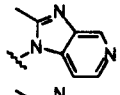
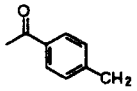
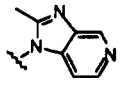
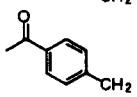
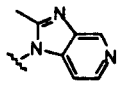
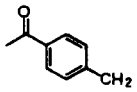
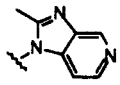
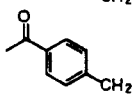
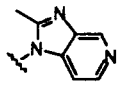
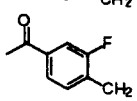
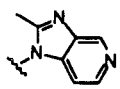
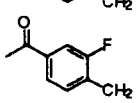
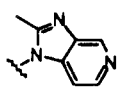
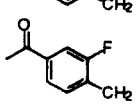
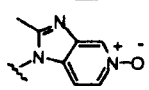
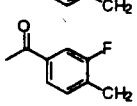
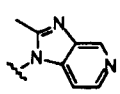
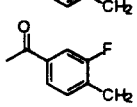
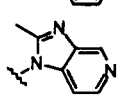
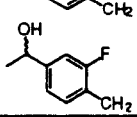
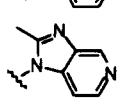
[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits. NT, not tested.

edge that it had been used in other PAF antagonist series with some success.[22,23] It can be seen from the data for compound **21g** in Table 4 that the pyridine nitrogen was not necessary for high in vitro potency as many of the benzimidazoles tested had excellent binding activity. Unfortunately, it was found that the benzimidazoles had marginal activity in vivo which could not be improved through the use of a variety of electron-withdrawing substituents to mimic the pyridine nitrogen of the imidazopyridine. It was also found that replacement of the imidazopyridine moiety with other isosteric groups such as imidazole, pyridine, and quinazolin-4(3*H*)-one gave analogues with poor binding affinities.

Additional Testing and Characterization of ABT-491. As mentioned above, compounds with high binding affinity for the PAF receptor and potent in vivo activity when dosed intravenously in the rat skin permeability model were further evaluated when dosed orally and, when appropriate, for their duration of action in this model (see Table 7). It was found that lead compound **7c** had an oral potency that was less than but comparable to that of **3** (0.223 vs 0.08 mg/kg, respectively) with a duration of action which was shorter (6.2 vs 10.0 h for **3**). It can be seen from the data that, in general, modifications to the indole 4-substituent and compounds possessing 4,6-disubstitution usually exhibited either poor oral activity (e.g., **7f**) or shorter duration of action versus **7c** (e.g., **7q**), while the use of indole nitrogen substituents other than the *N*,*N*-dimethylcarbamoyl group afforded compounds with poor oral activity (**14a**–**c**). The exception to the former observation was the 4-acetylene group which gave an antagonist (**7u**) which

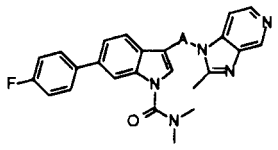
Table 5. In Vitro and in Vivo Activity of Antagonists with Multiple Modifications

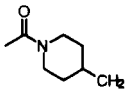
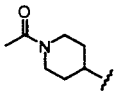
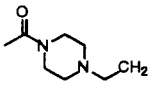
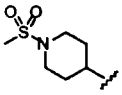
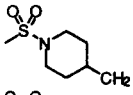
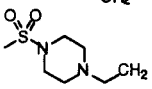


Compd	R^1	R^2	R^3	A	Y	K_i, nM[a]		ED_{50}, mg/kg[a]	
22a	H	2-Me	H			48	(4-640)	> 1	
22b	OMe	2-CO_2Me	H			0.51	(0.2-2)	0.65	(0.51-0.86)
22c	CO_2Me	H				1.7	(0.4-7)	1.0	(0.78-1.6)
22d	Cl	H	$CONMe_2$			0.9	(0.2-4)	0.34	(0.25-0.62)
22e	(4-F)Ph	H	$CONMe_2$			3.2	(1-8)	0.005	(0.004-0.006)
22f	Me	H	$CONMe_2$			2.0	(1-4)	0.005	(0.003-0.007)
22g	Cl	H	CH_2CH_2OEt			15	(2-130)	0.068	(0.055-0.087)
22h	Me	7-Me	H			0.87	(0.2-5)	0.054	(0.027-0.080)
22i	CO_2Me	7-CO_2Me	H			2.9	(2-5)	0.035	(0.024-0.046)
22j	H	7-OCH_2Ph	H			12	(6-23)	0.24	(0.18-0.33)
22k	H	7-(4-F)Ph	H			1.3	(0.7-2)	> 1	
22l	$OCONMe_2$	H	$CONMe_2$			31	(16-59)	0.005	(0.002-0.008)
22m	CCH	H	$CONMe_2$			1.0	(0.5-1)	0.003	(0.002-0.003)
22n	CCH	H	$CONMe_2$			19	(17-20)	> 0.5	
22o	CCH	H	CONHMe			0.63	(0.3-1)	0.006	(0.005-0.007)
22p	CCH	H	H			2.2	(1-4)	0.018	(0.017-0.018)
22q	CCH	H	$CONMe_2$			1.5	(0.8-3)	0.007	(0.006-0.007)

[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits.

Table 6. In Vitro and in Vivo Activity of Amide and Sulfonamide Imidazopyridines



Compd	A	K_i, nM[a]		ED_{50}, mg/kg[b]	
25a		2.5	(2-4)	0.022	(0.018-0.027)
25b		3.4	(1-15)	> 1	
25c		39	(6-260)	> 1	
29a		120	(10-1500)	> 1	
29b		1.2	(0.5-3)	0.019	(0.017-0.022)
29c		53	(24-120)	NT	

[a] Binding assay results are reported along with the 95% confidence limits. [b] Results are presented for the rat skin permeability assay after intravenous dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the 95% confidence limits. NT, not tested.

had better oral activity than **7c** and a duration of action that was similiar.

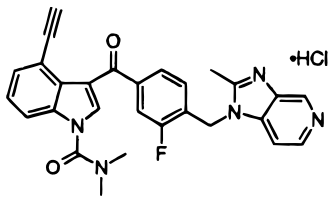
While several spacer modifications gave compounds with high in vivo potency when dosed intravenously, most of these changes led to unacceptable losses in oral activity with the exception of the fluorophenyl spacer in compounds **15c** and **22l** which afforded uniformly longer durations of action (ca. 10 vs 6 h for **7c**). It is not known if this increase in duration of action results from the inhibition of a specific metabolic process or, perhaps, from the subtle adjustment of the distribution or clearance of these compounds.

Several potent compounds resulted from the combination of alternatively substituted indoles, spacers, and heterocycles (**22c**−**g** in Table 5). Gratifyingly, combination of the best indole, spacer, and heterocycle resulted in PAF antagonist **22m** which had, in fact, the best overall activity profile of any compound made in this study. As can be seen in Table 8 this analogue possessed both in vitro and in vivo potency that was as good as or better than that of its progenitors regardless of whether it was dosed orally or intravenously, in the guinea pig or the rat. It was found that in comparative studies, the free base of **22m** and its hydrochloride salt (ABT-491) were indistinguishable under the conditions of the in vitro and in vivo assays and that the salt form was preferred due to enhanced solubility in unbuffered solutions (>20 mg/mL) and a long duration of action when dosed orally. Further testing demonstrated that **22m**·HCl had bioavailabilities of 49% and 56% in the rat and monkey, respectively. A more detailed evaluation of the pharmacology of **22m** and its hydrochloride salt has appeared elsewhere.[26,27]

Table 7. Oral Activity and Duration of Action of Selected Antagonists

compd	ED_{50}, mg/kg[a]	duration, h[b]
7c	0.22 (0.21−0.24)	6
7f	>1	NT
7j	0.22 (0.21−0.24)	4
7l	0.34 (0.3−0.4)	7
7m	1.3 (1.2−1.3)	NT
7o	0.20 (0.20−0.21)	5
7q	0.12 (0.1−0.2)	3
7r	0.13 (0.12−0.14)	NT
7s	0.45 (0.3−0.6)	8
7t	0.79 (0.6−1.0)	NT
7u	0.14 (0.1−0.2)	6
7v	0.078 (0.05−0.1)	4
7x	0.83 (0.44−1.2)	NT
7y	0.64 (0.6−0.7)	8
7aa	0.60 (0.5−0.8)	7
14a	2.4 (2.2−2.7)	NT
14b	1.2 (1.2−1.2)	NT
14c	1.1 (1.1−1.1)	NT
15c	0.36 (0.3−0.4)	9
15i	1.1 (0.97−1.2)	NT
15l	>1	NT
15m	0.17 (0.1−0.2)	6
15n	>1	NT
22e	>1	NT
22f	0.14 (0.09−0.20)	6
22i	0.71 (0.65−0.77)	NT
22l	2.7 (2.3−3.3)	10
22m	0.094 (0.05−0.1)	10
25a	2.2 (1.6−3.1)	6
29a	>1	NT

[a] Results are presented for the rat skin permeability assay after oral dosing (see text). Values represent the dose required to produce 50% inhibition of the response, along with the lower and upper 95% confidence limits. [b] Results are presented in time required for inhibition to fall below 50% in the rat skin permeability assay after dosing of the compound intravenously at a dose expected to produce 70−80% inhibition 1 h after administration. NT, not tested.



ABT-491 (**22m**•HCl)

The metabolic profile of **22m**·HCl in dog and monkey is similar and illustrated in Figure 1 which shows the plasma concentrations of this agent and its metabolites following intravenous administration at a dose of 5 mg/kg in the dog. The most abundant metabolites in the plasma have been identified as the compounds resulting from loss of the *N*,*N*-dimethylcarbamoyl group of the indole (**22p** in Table 5) and reduction of the spacer ketone to an alcohol (**22q**). Metabolites found in lesser amounts were the compound wherein the methyl of the carbamoyl group was cleaved (**22o**) and the expected pyridine *N*-oxide **22n**, although the levels of this metabolite were very low. It is interesting to note that independent synthesis and testing of these compounds revealed that all four were very potent antagonists of PAF, yet it is unclear whether they contribute substantially to the in vivo activity of **22m**·HCl.[28]

Table 8. Comparison of Physical and Biological Data

	2	1	7b	22m
aqueous solubility, mg/mL[a]	>25	>20	0.12	>20
receptor binding, *K*i, nM				
rabbit platelet	3.8[b]	0.40	2.3	1.8
human platelet	0.98	0.38	nd	0.57
PAF-induced vascular permeability, iv ED_{50}, mg/kg				
rat	0.006	0.020	0.068	0.003
guinea pig	0.090	0.027	nd	0.016
oral ED_{50}, mg/kg				
rat	0.08	0.80	0.50	0.09
guinea pig	0.80	10.3	nd	0.29
duration of inhibition in the PAF-induced permeability assay, h[c]	12	2	nd	10
bioavailability				
rat	46	nd	nd	49
monkey	36	nd	nd	56

[a] Determined at pH 3 in lactate buffer. [b] Potency of active form (3). [c] After oral dosing. nd, not determined.

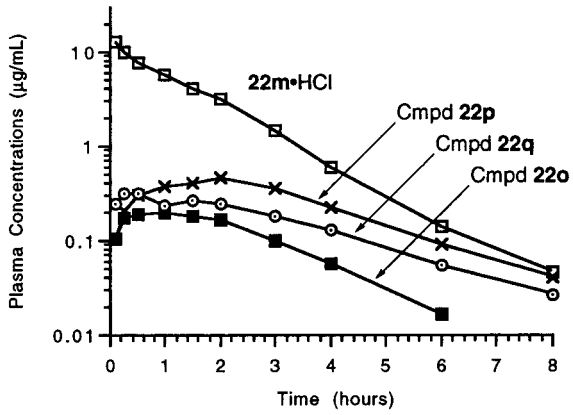


Figure 1. Plasma concentrations of **22m**·HCl and metabolites in the dog following intravenous administration (5 mg/kg).

Conclusions

By combining structural elements common to several PAF antagonists, the 3-{4-[(2-methylimidazopyridyl)-methyl]benzoyl}indoles have been identified as a novel family of potent antagonists of platelet-activating factor. The novel combination of lipophile, spacer, and heterocycle required the reoptimization of each portion to create a compound with the best overall profile. Accordingly, SAR studies revealed that the use of a number of 4-substituted and 4,6-disubstituted indoles gave analogues that were very potent both in vitro and in vivo, while in general, changes to the spacer benzoyl group generally led to losses in in vivo activity with the exception of the fluorinated phenyl version. While several heterocycle changes gave compounds with good binding potency, the 1*H*-2-methylimidazo[4,5-*c*]pyridyl group was far superior in vivo to all others tested. The combination of best indole lipophile, benzoyl spacer, and imidazopyridyl heterocycle afforded antagonist **22m**·HCl (ABT-491), a potent, water-soluble, orally active, and long-acting antagonist of PAF which is currently undergoing clinical evaluation.

Experimental Section

Biological Assays. The [^{3}H]PAF receptor binding method and the PAF-induced rat skin permeability assay were performed as previously described.[19]

Rat, Dog, and Monkey Pharmacokinetic Studies. The pharmacokinetic behavior of selected PAF inhibitors following intravenous and oral administration was evaluated in groups of female *Macaca fascicularis* (long-tailed macaque, 3−4 kg in weight), male Sprague−Dawley derived rat (0.25−0.4 kg; Charles Rivers), and beagle dogs (male/female, 8−12 kg in weight). The dogs and monkeys were selected from the established Drug Analysis colonies which are maintained within the animal facility at Abbott Laboratories. Each dog and monkey was housed within individual stainless steel cages in accordance with the specifications of the Institutional Animal Care and Use Committee (IACUC); paired housing between amicable animals was utilized between study periods. The animals were fasted overnight prior to dosing, but were permitted water ad libitum. Food was returned to each monkey approximately 3 h after drug administration; food was returned to the dogs and rats at the completion of the study. Solutions of the PAF inhibitors were prepared in a 20% ethanol in D5W (dextrose 5% in water) vehicle at a concentration appropriate for a 1.0 mL/kg dose volume in each animal; oral administration in monkey utilized a 2.5 mL/kg dose volume. In a series of parallel studies groups of dogs (n = 3/group) received a single 5 mg/kg oral or intravenous dose. In a similar manner groups of monkeys (n = 3/group) received a single 10 mg/kg intravenous or 25 mg/kg oral dose. The intravenous dose was administered as a slow bolus in the cephalic (dog) or saphenous (monkey) vein; the oral dose was administered by gavage. Groups of rats (n = 4/group) received a 10 mg/kg intravenous or oral dose of selected PAF inhibitors. The intravenous dose was administered as a slow bolus in the jugular vein under light ether anesthetic; the oral dose was administered by gavage. Heparinized blood samples were obtained from the femoral artery or vein of each monkey and from the jugular vein of each dog prior to dosing and throughout the 12 h following drug administration; sequential blood samples were obtained from a tail vein of each rat throughout the 8 h after dosing.

All heparinized blood samples were immediately chilled in an ice bath. Plasma was separated from the red cells by centrifugation (1819*g*, 10 min, 4 °C) and frozen (−2 °C) until analysis. The parent compound and metabolites were removed from plasma at neutral pH using liquid−liquid extraction using a mixture of 10% ethanol in methylene chloride. The extraction mixtures were vortexed for 30 s followed by centrifugation (10 min, 1819*g*, 4 °C). The upper aqueous layer was aspirated to waste. The organic layer was transferred to a conical centrifuge tube and evaporated to dryness with a gentle stream of dry air over low heat (~35 °C). Samples were reconstituted by vortexing with 0.2 mL of mobile phase. Spiked plasma samples were analyzed simultaneously with the samples. **22m** and metabolites were separated from coextracted plasma contaminants on a 5-cm × 4.6-mm, 5-µm Inertsil ODS-2 column (Higgins Analytical, Inc.) with an acetonitrile:methanol:buffer mobile phase (20:5:75, by volume) at a flow rate of 1.0 mL/min with detection of the 100-µL injection at 212 nm. The aqueous buffer portion of the mobile phase contained 0.1% trifluoroacetic acid in 0.01 M tetramethylammonium perchlorate (pH 3.0). The assay method was linear (correlation coefficient > 0.99) over the **22m** concentration range 0−17 or 0−4 (metabolites) mcg/mL with a reproducibility of <6% for the analysis of triplicate standards at seven separate concentrations and an estimated limit of quantitation of 0.02 mcg/mL.

The plasma concentrations of parent drug and metabolites were calculated by least-squares linear regression of the peak area ratio (parent or metabolite/internal standard) of the spiked plasma standards versus concentration. The plasma elimination rate constant was estimated from the log linear regression of the terminal plasma concentrations as a function of time after dosing. The area under the plasma concentration time curve from 0 to t (last measurable plasma concentration time point) after dosing (AUC_{0-t}) was calculated using the linear trapezoidal rule. The residual area extrapolated to infinity, determined as the final measured plasma concentra-

tion (C_t) divided by the terminal elimination rate constant (β), was added to AUC_{0-t} to produce the total area under the curve ($AUC_{0-\infty}$). The bioavailability was calculated as the dose-normalized $AUC_{0-\infty}$ from the oral dose divided by the corresponding value derived from the intravenous dose; bioavailability is expressed as a percent.

General Chemistry Methods. Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz) or a General Electric GN-300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Spectra are reported only for test compounds and selected intermediates. Mass spectra were obtained with a Hewlett-Packard HP5965 spectrometer. The above determinations were performed by the Analytical Department, Abbott Laboratories, and elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ, or Oneida Research Services, Inc., Whitesboro, NY. Analytical results indicated by elemental symbols are within ±0.4% of the theoretical values.

Thin-layer chromatography (TLC) was carried out using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Flash chromatography was carried out using Merck silica gel 60, 200−400 mesh.

Melting points are uncorrected and were determined on a Buchi melting point apparatus. All reactions were performed under anhydrous conditions unless otherwise noted. THF was freshly distilled from sodium benzophenone ketyl. Ethyl ether was purchased as "anhydrous" and used as received. Other solvents were HPLC grade when available, and unless otherwise noted, all chemicals and reagents were obtained commercially and used without purification. All chemical yields are unoptimized and generally represent the result of a single experiment.

3-Acylation of Indoles. Method A: Preparation of 1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7b), 1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{4-[(3*H*-2-methylimidazo[4,5-*c*]pyrid-3-yl)methyl]benzoyl}indole (9a), and 1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{4-[(5*H*-2-methylimidazo-[4,5-*c*]pyrid-5-yl)methyl]benzoyl}indole (10a). To a 0 °C solution of 6-(4-fluorophenyl)indole[17] (2.00 g, 9.48 mmol) in THF (50 mL) was added KOH (2.7 g, 47.4 mmol) in a single portion and the cold bath was removed. After the mixture stirred for 15 min at room temperature, dimethylcarbamoyl chloride (1.3 mL, 14.2 mmol) was added via syringe, and the resulting brown suspension was stirred for 4 h at room temperature. The reaction mixture was poured into a mixture of ethyl acetate and saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indole as a brown solid which was used without further purification.

To a solution of 4-(chloromethyl)benzoyl chloride (804 mg, 4.26 mmol) in CH_2Cl_2 (21 mL) was added $AlCl_3$ (850 mg, 6.39 mmol) in a single portion, and the yellow solution was stirred for 15 min at room temperature. A solution of 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indole (1.00 g, 3.55 mmol) in CH_2Cl_2 was added dropwise, and the dark solution was stirred for 2 h at room temperature. Additional $AlCl_3$ (0.24 g, 1.78 mmol) was added, and the reaction mixture was stirred for 0.5 h. The reaction mixture was poured into a separatory funnel containing ice water and CH_2Cl_2. The layers were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (25%, then 50% ethyl acetate/hexanes) gave 1.33 g of 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)-3-[4-(chloromethyl)benzoyl]indole [**8a**, R^1 = H, R^2 = 6-(4-FPh)] as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.06 (s, 6H), 4.90 (s, 2H), 7.32 (apparent t, 2H, J = 8.7 Hz), 7.6−7.9 (m, 8H), 8.19 (s, 1H), 8.33 (d, 1H, J = 8.4 Hz); MS (DCI/NH_3) *m/e* 435 $(M + H)^+$.

To a solution of 2-methylimidazo[4,5-*c*]pyridine[29] (407 mg, 3.06 mmol) in THF (15 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 5 mL) was added NaH (110 mg, 4.59 mmol) in a single portion, and the resulting solution was stirred for 1 h at room temperature. In a separate flask, NaBr (630 mg, 6.11 mmol) was added to a solution of **8a** (1.33 g, 3.06 mmol) in THF (15 mL) and DMPU (5 mL). The resulting yellow suspension was stirred for 1 h at room temperature, after which the imidazopyridine solution was added dropwise via syringe. The reaction mixture was stirred for 3 h at room temperature and then partitioned between brine and ethyl acetate. The layers were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (2%, then 4% methanol/CH_2Cl_2) provided **7b** (228 mg), **9a** (294 mg), and **10a** (228 mg) as white amorphous solids. Data for **7b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 3.03 (s, 6H), 5.67 (s, 2H), 7.25−7.35 (m, 4H), 7.6−7.7 (m, 2H), 7.7−7.8 (m, 2H), 7.8−7.9 (m, 3H), 8.15 (s, 1H), 8.30 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 5.7 Hz), 8.87 (s, 1H); MS (DCI/NH_3) *m/e* 532 $(M + H)^+$. Anal. ($C_{32}H_{26}FN_5O_2 \cdot 0.8H_2O$) C, H, N. Data for **9a**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.63 (s, 3H), 3.03 (s, 6H), 5.73 (s, 2H), 7.25−7.40 (m, 4H), 7.59 (dd, 1H, J = 5.7, 1.0 Hz), 7.65 (dd, 1H, J = 8.1, 1.5 Hz), 7.7−7.8 (m, 2H), 7.8−7.9 (m, 3H), 8.16 (s, 1H), 8.30 (d, J = 8.1 Hz), 8.31 (d, 1H, J = 5.7 Hz), 8.97 (s, 1H); MS (DCI/NH_3) *m/e* 532 $(M + H)^+$. Anal. ($C_{32}H_{26}FN_5O_2 \cdot 0.9H_2O$) C, H; N: calcd, 12.78; found, 12.27. Data for **10a**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.52 (s, 3H), 3.02 (s, 6H), 5.77 (s, 2H), 7.25−7.35 (m, 2H), 7.57 (apparent d, 2H, J = 8.4 Hz), 7.6−7.7 (m, 2H), 7.7−7.8 (m, 2H), 7.80−7.85 (narrow m, 1H), 7.89 (apparent d, 2H, J = 8.4 Hz), 8.16 (s, 1H), 8.21 (dd, 1H, J = 6.9, 1.8 Hz), 8.31 (d, 1H, 8.4 Hz), 9.00 (d, 1H, J = 1.2 Hz); MS (DCI/NH_3) *m/e* 532 $(M + H)^+$. Anal. Calcd for $C_{32}H_{26}FN_5O_2 \cdot 0.9H_2O$: C, 70.16; H, 5.11; N, 12.78. Found: C, 70.01; H, 5.27; N, 12.75.

3-Acylation of Indoles. Method B: Preparation of 1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7c), 1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(3*H*-2-methylimidazo[4,5-*c*]pyrid-3-yl)methyl]benzoyl}indole (9b), and 1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(5*H*-2-methylimidazo[4,5-*c*]pyrid-5-yl)methyl]benzoyl}indole (10b). To a solution of 4-(methoxycarbonyl)indole (5.14 g, 29.4 mmol) in CH_2Cl_2 (500 mL) was added ethylmagnesium bromide (3.0 M in ether, 9.8 mL, 29.4 mmol) over 5 min. The resulting suspension was stirred for 10 min at room temperature, and $ZnCl_2$ (1.0 M in ether, 88 mL, 88 mmol) was added quickly via syringe. After the mixture stirred for 20 min, during which time the it turned to a light-green suspension, a solution of 4-(chloromethyl)benzoyl chloride (5.83 g, 30.8 mmol) in CH_2Cl_2 (100 mL) was added over 5 min. The reaction mixture was stirred for 20 h at room temperature and then poured into saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography on silica gel (1 L of CH_2Cl_2 then 3% acetone/CH_2Cl_2 then 5% acetone/CH_2Cl_2) gave 7 g of 4-(methoxycarbonyl)-3-[4-(chloromethyl)benzoyl]indole.

To a solution of 3 g (9.15 mmol) of this indole dissolved in 46 mL of THF at 0 °C was added NaH (329 mg, 13.7 mmol) in one portion. After the mixture stirred for 30 min, the cooling bath was removed and dimethylcarbamoyl chloride (1 mL, 10.9 mmol) was added dropwise by syringe. The resulting suspension was stirred at room temperature for 1 h and then poured into a mixture of brine and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the organic layers were dried with $MgSO_4$, filtered, and concentrated. The residue was flash-chromatographed (5% acetone/CH_2Cl_2) to afford 3.15 g of 1-(*N*,*N*-dimethylcarbamoyl)-4-(methoxycarbonyl)-3-[4-(chloromethyl)benzoyl]indole (**8b**, R^1 = CO_2Me, R^2 = H) as a yellow

foam: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.05 (s, 6H), 3.51 (s, 3H), 4.87 (s, 2H), 7.4−7.5 (m, 1H), 7.55−7.65 (m, 3H), 7.85−7.95 (m, 3H), 8.16 (s, 1H); MS (DCI/NH_3) *m/e* 399 $(M + H)^+$.

To a solution of 2-methylimidazo[4,5-*c*]pyridine (234 mg, 1.76 mmol) in THF (7 mL) and DMPU (2 mL) was added NaH (63 mg, 2.64 mmol) in a single portion, and the resulting solution was stirred for 1 h at room temperature. In a separate flask, NaBr (302 mg, 2.93 mmol) was added to a solution of **8b** (585 mg, 1.47 mmol) in THF (7 mL) and DMPU (2 mL). The resulting yellow suspension was stirred for 1 h at room temperature, after which the imidazopyridine solution was added dropwise via syringe. The reaction mixture was stirred for 3 h at room temperature and then partitioned between brine and ethyl acetate. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (3%, then 5% methanol/CH_2Cl_2) provided **7c** (142 mg), **9b** (115 mg), and **10b** (100 mg) as white amorphous solids. Data for **7c**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.57 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.64 (s, 2H), 7.28 (apparent d, 2H, J = 8.4 Hz), 7.4−7.5 (m, 1H), 7.55−7.60 (m, 2H), 7.84 (apparent d, 2H, J = 8.4 Hz), 7.86 (dd, 1H, J = 8.4, 1.2 Hz), 8.10 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.86 (d, 1H, J = 1.0 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{25}N_5O_4 \cdot 0.5H_2O$) C, H, N. Data for **9b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.70 (s, 2H), 7.32 (apparent d, 2H, J = 8.1 Hz), 7.4−7.5 (m, 1H), 7.56 (dd, 1H, J = 2.1, 1.0 Hz), 7.56−7.58 (m, 1H), 7.85 (apparent d, 2H, J = 8.1 Hz), 7.86 (dd, 1H, J = 8.1, 1.2 Hz), 8.11 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.86 (d, 1H, J = 1.0 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{25}N_5O_4 \cdot 1.8H_2O$) C, H, N. Data for **10b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.51 (s, 3H), 3.02 (s, 6H), 3.46 (s, 3H), 5.76 (s, 2H), 7.4−7.65 (m, 3H), 7.54 (d, 2H, J = 8.1 Hz), 7.87 (dd, 1H, J = 9.3, 1.2 Hz), 7.90 (d, 2H, J = 8.1 Hz), 8.13 (s, 1H), 8.18 (dd, 1H, J = 6.9, 1.8 Hz), 8.97 (d, 1H, J = 1.5 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{25}N_5O_4 \cdot 1.6H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7a): prepared by method B using indole; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 3.00 (s, 6H), 5.66 (s, 2H), 7.25−7.45 (m, 4H), 7.6−7.7 (m, 2H), 7.8−7.9 (m, 2H), 8.10 (s, 1H), 8.2−8.3 (m, 1H), 8.31 (d, 1H, J = 5.7 Hz), 8.87 (s, 1H); MS (FAB) *m/e* 438 $(M + 1)^+$. Anal. ($C_{26}H_{23}N_5O_2 \cdot 0.7H_2O$) C, H; N: calcd, 15.56; found, 14.96.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(benzyloxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7d). This was prepared by method B using 4-(benzyloxycarbonyl)indole made as follows. Indole-4-carboxylic acid (1 g, 6.21 mmol) was dissolved in 20 mL of DMF, and to it was added $NaHCO_3$ (1.04 g, 12.4 mmol); this mixture was stirred for 10 min when a solution of benzyl bromide (1.5 mL, 12.4 mmol) in 5 mL of DMF was added dropwise by syringe. The resulting solution was stirred at room temperature for 48 h and then added to ethyl acetate and aqueous saturated $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed (CH_2Cl_2) to give 1.33 g of 4-(benzyloxycarbonyl)indole as a clear oil. Data for **7d**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.6 (s, 3H), 3.01 (s, 6H), 5.01 (s, 2H), 5.67 (s, 2H), 7.0−7.2 (m, 5H), 7.29 (apparent d, 2H, J = 8.1 Hz), 7.4−7.5 (m, 1H), 7.6−7.7 (m, 2H), 7.86 (apparent d, 2H, J = 8.4 Hz), 8.10 (s, 1H), 8.31 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H); MS (DCI/NH_3) *m/e* 572 $(M + H)^+$. Anal. ($C_{34}H_{29}N_5O_4 \cdot 1.1H_2O$) C, H; N: calcd, 11.84; found, 11.26.

1-(*N*,*N*-Dimethylcarbamoyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole-4-carboxylic Acid (7e). Benzyl ester **7d** (1.51 g, 2.64 mmol) was dissolved in 35 mL of methanol and 15 mL of CH_2Cl_2 in the presence of 150 mg of 10% Pd/C and treated with H_2 (1 atm) for 4 h. The mixture was filtered through Celite washing with warm 1:1 chloroform/methanol to give after concentration 1.16 g of **7e** as a white amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.55 (s, 3H), 3.02 (s, 6H), 5.62 (s, 2H), 7.25 (d, 2H, J = 8.4 Hz), 7.4−7.5 (m, 1H), 7.55−7.65 (m, 2H), 7.81 (d, 2H, J = 8.4 Hz), 7.8−7.9 (m, 1H), 8.03 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.85 (s, 1H), 12.62 (br s, 1H); MS (DCI/NH_3) *m/e* 482 $(M + H)^+$; HRMS for $C_{27}H_{23}N_5O_4$ theoretical 482.1828, found 482.1808.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(ethoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7f). To a solution in DMF (4 mL) of **7e** (200 mg, 0.42 mmol) were added $NaHCO_3$ (70 mg, 0.83 mmol) and bromoethane (62 μL, 0.83 mmol). The reaction vessel was sealed and heated at 40 °C for 1.5 h. The reaction mixture was cooled to room temperature and partitioned between CH_2Cl_2 and brine. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (5%, then 15% methanol/CH_2Cl_2) to give **7f** (53 mg): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.92 (t, 3H, J = 7.4 Hz), 2.57 (s, 3H), 3.02 (s, 6H), 3.95 (q, 2H, J = 7.0 Hz), 5.65 (s, 2H), 7.30 (d, 2H, J = 7.8 Hz), 7.4−7.5 (m, 1H), 7.5−7.6 (m, 2H), 7.87 (d, 2H, J = 8.1 Hz), 7.8−7.9 (m, 1H), 8.10 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 572 $(M + H)^+$. Anal. ($C_{29}H_{27}N_5O_4 \cdot 0.3Et_2O \cdot 0.5H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-cyano-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole hydrochloride (7n): prepared by method B using 4-cyanoindole;[30] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.70 (s, 3H), 3.01 (s, 6H), 5.88 (s, 2H), 7.39 (d, 2H, J = 8.1 Hz), 7.56 (t, 1H, J = 8.1 Hz), 7.84 (dd, 1H, J = 8.1, 1.2 Hz), 7.94 (d, 2H, J = 8.1 Hz), 8.02 (dd, 1H, J = 8.1, 1.2 Hz), 8.27 (s, 1H), 8.32 (d, 1H, J = 6.3 Hz), 8.68 (d, 1H, J = 6.3 Hz), 9.44 (s, 1H); MS (DCI/NH_3) *m/e* 463 $(M + H)^+$. Anal. ($C_{27}H_{22}N_6O_2 \cdot HCl \cdot 1.4H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-bromo-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7r): prepared by method A using 4-bromoindole;[31] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.56 (s, 3H), 3.01 (s, 6H), 5.63 (s, 2H), 7.27 (d, 2H, J = 8.4 Hz), 7.28 (t, 1H, J = 8.4 Hz), 7.47 (dd, 1H, J = 8.4, 0.3 Hz), 7.57 (dd, 1H, J = 5.7, 0.3 Hz), 7.69 (dd, 1H, J = 8.4, 0.3 Hz), 7.86 (d, 2H, J = 8.4 Hz), 8.03 (s, 1H), 8.38 (d, 1H, J = 5.7 Hz), 8.84 (d, 1H, J = 0.3 Hz); MS (DCI/NH_3) *m/e* 516, 518 $(M + H)^+$. Anal. ($C_{26}H_{22}N_5O_2Br$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7s). To a solution in DMF (6 mL) of **7r** (200 mg, 0.38 mmol) was added tetrakis(triphenylphosphine)palladium(0) (22 mg), and the solution was stirred for 30 min. A solution of 4-fluorophenylboronic acid (80 mg, 0.57 mmol) in DMF (2 mL) was added followed by saturated aqueous $NaHCO_3$ (4 mL). The reaction mixture was stirred at 90 °C for 4 h and at 40 °C for 48 h. Additional tetrakis(triphenylphosphine)palladium(0) (22 mg) was added, and the reaction mixture was stirred at 115 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with H_2O, and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (5% methanol/CH_2Cl_2) gave 4-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole as a white solid (111 mg) which was recarbamoylated using the procedure in method B to give **7s**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 (s, 3H), 3.04 (s, 6H), 5.58 (s, 2H), 6.85 (t, 2H, J = 9 Hz), 7.05−7.13 (m, 5H), 7.43 (t, 1H, J = 9 Hz), 7.50 (d, 2H, J = 9 Hz), 7.60 (d, 1H, J = 6 Hz), 7.68 (d, 1H, J = 9 Hz), 8.01 (s, 1H), 8.30 (br s, 1H), 8.88 (br s, 1H); MS (DCI/NH_3) *m/e* 532 $(M + H)^+$. Anal. ($C_{32}H_{26}N_5O_2F \cdot 0.75H_2O$) C, H, N.

Stille Coupling of Indole Bromides. Preparation of 1-(*N*,*N*-Dimethylcarbamoyl)-4-(fur-2-yl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7t). To a 20-mL pressure bottle were added tri-*n*-butyl(fur-2-yl)-stannane (160 mg, 0.45 mmol), **7r** (153 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 mmol), and dioxane (5 mL). The bottle was flushed thoroughly with N_2, sealed, and heated at 115 °C for 2.5 h. The reaction

mixture was cooled to room temperature, filtered, and concentrated. Chromatography on silica gel twice (5% methanol/CH_2Cl_2) gave **7t** (94 mg): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.53 (s, 3H), 3.03 (s, 6H), 5.57 (s, 2H), 6.17 (dd, 1H, J = 3.9, 3.6 Hz), 6.36 (dd, 1H, J = 3.9, 0.9 Hz), 7.13 (d, 2H, J = 8.7 Hz), 7.26 (dd, 1H, J = 2.4, 0.9 Hz), 7.34 (dd, 1H, J = 8.4, 2.1 Hz), 7.39 (t, 1H, J = 8.4 Hz), 7.57 (dd, 1H, J = 6.3, 1.2 Hz), 7.66 (dd, 1H, J = 8.4, 2.1 Hz), 7.67 (d, 2H, J = 8.7 Hz), 8.01 (s, 1H), 8.31 (d, 1H, J = 6.3 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 504 $(M + H)^+$. Anal. ($C_{30}H_{25}N_5O_3 \cdot 0.2EtOAc \cdot 0.2H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-ethynyl-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7u). To a solution in 2:1 THF/CH_3CN of 1-(*N*,*N*-dimethylcarbamoyl)-4-[(trimethylsilyl)ethynyl]-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (0.39 g, 0.73 mmol), prepared from bromide **7r** and trimethyl[(trimethylsilyl)-ethynyl]stannane[32] using the Stille coupling procedure, was added CsF (0.56 g, 3.66 mmol), and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was filtered, and the filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give **7u** (0.29 g): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.55 (s, 3H), 3.00 (s, 6H), 4.04 (s, 1H), 5.64 (s, 2H), 7.25 (d, 2H, J = 9 Hz), 7.30−7.42 (m, 2H), 7.58 (d, 1H, J = 6 Hz), 7.73 (d, 1H, J = 9 Hz), 7.85 (d, 2H, J = 9 Hz), 8.04 (s, 1H), 8.29 (d, 1H, J = 6 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 462 $(M + H)^+$. Anal. ($C_{28}H_{23}N_5O_2 \cdot 2.0H_2O$) C, H; N: calcd, 13.53; found, 14.07.

1-(*N*,*N*-Dimethylcarbamoyl)-6-bromo-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-benzoyl}indole (7x): prepared by method B using 6-bromo-4-(methoxycarbonyl)indole;[33] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.57 (s, 3H), 3.01 (s, 6H), 3.50 (s, 3H), 5.64 (s, 2H), 7.28 (d, 2H, J = 8.4 Hz), 7.59 (dd, 1H, J = 5.7, 0.6 Hz), 7.67 (d, 1H, J = 2.1 Hz), 7.84 (d, 2H, J = 8.4 Hz), 8.07 (d, 1H, J = 2.1 Hz), 8.17 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 576 $(M + H)^+$, 574. Anal. ($C_{28}H_{24}N_5O_4Br \cdot 0.4EtOAc$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (7y): prepared by method B using 4-(methoxycarbonyl)-6-(4-fluorophenyl)indole, made from 6-bromo-4-(methoxycarbonyl)indole and 4-fluorophenylboronic acid;[17] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.57 (s, 3H), 3.04 (s, 6H), 3.48 (s, 3H), 5.64 (s, 2H), 7.25−7.35 (m, 4H), 7.59 (d, 1H, J = 6.4 Hz), 7.75−7.80 (m, 3H), 7.85 (apparent d, 2H, J = 8.1 Hz), 8.04 (d, 1H, J = 1.7 Hz), 8.14 (s, 1H), 8.30 (d, 1H, J = 5.2 Hz), 8.85 (s, 1H); MS (DCI/NH_3) *m/e* 590 $(M + H)^+$. Anal. ($C_{34}H_{28}N_5O_4F \cdot 1.4H_2O$) C, H; N: calcd, 11.39; found, 10.91.

Saponification of Indole Ureas. Preparation of 4-(Methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]-pyrid-1-yl)methyl]benzoyl}indole (13b). To a 0 °C solution in methanol (4 mL) of **7c** (164 mg, 0.33 mmol) was added aqueous 1 M NaOH (0.9 mL, 0.9 mmol), and the reaction mixture was stirred for 1 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The aqueous phase was acidified with 1 M aqueous HCl and extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give **13b** (140 mg) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.58 (s, 3H), 3.51 (s, 3H), 5.63 (s, 2H), 7.2−7.35 (m, 3H), 7.40 (dd, 1H, J = 7.3, 1.1 Hz), 7.60 (dd, 1H, J = 5.5, 1.1 Hz), 7.69 (dd, 1H, J = 8.1, 1.1 Hz), 7.79 (apparent d, 2H, J = 8.1 Hz), 7.89 (s, 1H), 8.30 (d, 1H, J = 5.6 Hz), 8.86 (s, 1H), 12.17 (br s, 1H); MS (DCI/NH_3) *m/e* 425 $(M + H)^+$. Anal. ($C_{25}H_{20}N_4O_3 \cdot 0.5CH_2Cl_2$) C, N; H: calcd, 4.53; found, 4.11.

6-(4-Fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]-pyrid-1-yl)methyl]benzoyl}indole (13a): prepared from **7b** using the urea saponification procedure; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 (s, 3H), 5.65 (s, 2H), 7.25−7.35 (m, 4H), 7.52 (dd, 1H, J = 8.4, 1.5 Hz), 7.64 (d, 1H, J = 8.7 Hz), 7.7−7.8 (m, 3H), 7.80 (d, 1H, J = 8.1 Hz), 7.97 (s, 1H), 8.28 (d, 1H, J = 8.4 Hz), 8.32 (d, 1H, J = 5.4 Hz), 8.87 (s, 1H), 12.15 (br s, 1H); MS (FAB) *m/e* 461 $(M + 1)^+$. Anal. ($C_{29}H_{21}FN_4O \cdot 1.2H_2O$) C, H, N.

Indole Acylation/Alkylation Procedure. Preparation of 4-(Methoxycarbonyl)-1-(pyrrolidin-1-ylcarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}-indole (14b). To a 0 °C solution of **13b** (150 mg, 0.33 mmol) in DMF (2 mL) and THF (2 mL) was added KOH (91 mg, 1.63 mmol) in a single portion, and the cold bath was removed. After the mixture stirred for 15 min at room temperature, 1-pyrrolidinecarbamoyl chloride (0.08 mL, 0.65 mmol) was added via syringe, and the resulting brown suspension was stirred for 1 h at room temperature. The reaction mixture was poured into a mixture of ethyl acetate and saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a residue which after flash chromatography (5% MeOH/CH_2Cl_2) gave 87 mg of **14b** as a brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7−1.8 (br m, 4H), 2.57 (s, 3H), 3.46 (s, 3H), 3.5−3.6 (br m, 4H), 5.64 (s, 2H), 7.28 (apparent d, 2H, J = 8.4 Hz), 7.4−7.5 (m, 1H), 7.55−7.65 (m, 2H), 7.85 (apparent d, 2H, J = 8.4 Hz), 7.98 (dd, 1H, J = 8.4, 1.2 Hz), 8.19 (s, 1H), 8.30 (d, 1H, J = 5.4 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 522 $(M + H)^+$. Anal. ($C_{30}H_{27}N_5O_4 \cdot 0.7H_2O \cdot 0.7EtOAc$) C, H, N.

1-Carbamoyl-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (14i). Liquid ammonia (10 drops) was condensed into a −78 °C solution in THF (12 mL) of 1-[(4-nitrophenoxy)carbonyl]-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (259 mg), which was prepared from **13b** and 4-nitrophenyl chloroformate using the indole acylation/alkylation procedure. The resulting clear-yellow solution was stirred for 20 min at −78 °C, then saturated aqueous NH_4Cl was added, and the reaction mixture was warmed to room temperature and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 32 mg of **14i** as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.58 (s, 3H), 3.45 (s, 3H), 5.65 (s, 2H), 7.29 (d, 2H, J = 9 Hz), 7.45 (t, 1H, J = 9 Hz), 7.58 (t, 2H, J = 6 Hz), 8.3−7.9 (m, 4H), 8.3 (d, 1H, J = 6 Hz), 8.34 (s, 1H), 8.55 (dd, 1H, J = 3, 9 Hz), 8.86 (s, 1H); MS (FAB) *m/e* 468 $(M + H)^+$; HRMS for $C_{26}H_{22}N_5O_4$ theoretical 468.1672, found, 468.1665.

1-(*N*-Methylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}-indole (14h): prepared from **13b** using the nitrophenyl carbamate intermediate from the preparation of **14i** and substituting methylamine for ammonia; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 (s, 3H), 2.82 (d, 3H, J = 6 Hz), 3.46 (s, 3H), 5.65 (s, 2H), 7.30 (d, 2H, J = 9 Hz), 7.48 (t, 1H, J = 9 Hz), 7.59 (dd, 1H, J = 3, 9 Hz), 7.61 (d, 1H, J = 6 Hz), 7.87 (d, 2H, J = 9 Hz), 8.28 (s, 1H), 8.31 (d, 1H, J = 6 Hz), 8.44 (d, 1H, J = 6 Hz), 8.52 (dd, 1H, J = 3, 9 Hz), 8.90 (br s, 1H); MS (DCI/NH_3) *m/e* 425. Anal. ($C_{27}H_{23}N_5O_4 \cdot 0.6H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]thien-2-oyl}indole Hydrochloride (15a). To a solution of *N*-bromosuccinimide (5.94 g, 33 mmol) in hexanes (16 mL) was added 5-methyl-2-(carboxymethyl)thiophene (5.0 g, 32 mmol) followed by 1 drop of perchloric acid. The reaction mixture was stirred for 22 h at room temperature and then partitioned between ethyl acetate and saturated aqueous $NaHSO_3$ solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give 6.17 g of 5-(bromomethyl)-2-(carboxymethyl)thiophene as a yellow oil.

To a solution of 1*H*-2-methylimidazo[4,5-*c*]pyridine (2.00 g, 15 mmol) in DMSO (150 mL) was added potassium *tert*-butoxide (1.7 g, 17 mmol), and the reaction mixture was stirred until all of the base dissolved (∼15 min). After a further 5 min, 5-(bromomethyl)-2-(carboxymethyl)thiophene (4.0 g, 17 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and then partitioned between ethyl acetate and 1:1 pH 7 buffer/brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatogra-

phy on silica gel (3% then 4% then 5% methanol/CH_2Cl_2) gave 5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-2-(carboxymethyl)thiophene.

To a solution of 5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-2-(carboxymethyl)thiophene (0.360 g, 1.25 mmol) in THF (15 mL) and H_2O (2 mL) was added lithium hydroxide hydrate (0.114 g, 2.70 mmol). The reaction mixture was stirred for 6 h at room temperature, then quenched with 4 N HCl/dioxane (1 mL), and partioned between ethyl acetate and H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 5-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-2-thiophenecarboxylic acid (0.46 g) as an oil.

After conversion of this carboxylic acid to the corresponding acid chloride using NaH and oxalyl chloride, acylation method B with 4-(methoxycarbonyl)indole followed by treatment with 4 M HCl/dioxane and filtration gave **15a** as a light brown powder by filtration: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.84 (s, 1H), 8.36 (d, 1H, J = 6 Hz), 8.30 (s, 1H), 7.97 (dd, 1H, J = 1, 9 Hz), 7.73 (dd, 1H, J = 1, 6 Hz), 7.68 (d, 1H, J = 5 Hz), 7.57 (dd, 1H, J = 1, 7 Hz), 7.46 (m, 1H), 7.22 (d, 1H, J = 5 Hz), 5.84 (s, 2H), 3.54 (s, 3H), 3.04 (s, 6H), 2.68 (s, 3H); MS (DCI/NH_3) *m/e* 502 $(M + H)^+$; IR cm^{-1} (microscope) 3400 (br), 2970, 2950, 2600, 1700, 1640, 1515, 1485. Anal. ($C_{25}H_{23}N_5O_4S\cdot HCl\cdot C_4H_{10}O\cdot 1.5H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]thiazol-2-oyl}indole (15b). This was prepared by acylation method A using 6-(4-fluorophenyl)indole and 4-(chloromethyl)-2-thiazolecarbonyl chloride prepared as follows: A mixture of ethyl thiooxamate (1.0 g, 7.5 mmol) and 1,3-dichloroacetone (1.0 g, 8.3 mmol) in ethanol (25 mL) was heated at reflux for 15 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give an orange oil. 4-(Chloromethyl)-2-(ethoxycarbonyl)thiazole was obtained as a yellow oil by chromatography on silica gel (10% ether/hexanes).

To a solution of 4-(chloromethyl)-2-(ethoxycarbonyl)thiazole (354 mg, 1.73 mmol) in ethanol (10 mL) was added KOH (116 mg, 2.07 mmol). The reaction mixture was stirred for 1 h at room temperature, then concentrated, and azeotroped twice with THF to give potassium 4-(chloromethyl)-2-thiazolecarboxylate. This material was dissolved in 40 mL of CH_2Cl_2 and treated with oxalyl chloride (220 μL, 2.6 mmol) and 1 drop of DMF. After stirring for 1 h the solution was concentrated to give 300 mg of 4-(chloromethyl)-2-thiazolecarbonyl chloride. Data for **15b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.70 (s, 3H), 3.01 (s, 6H), 5.76 (s, 2H), 7.28−7.35 (m, 2H), 7.66 (dd, 1H, J = 9.9, 1.5 Hz), 7.74−7.82 (m, 4H), 8.25 (s, 1H), 8.32−8.37 (m, 2H), 8.75 (s, 1H), 8.85 (s, 1H); MS (DCI/NH_3) *m/e* 539 (M + H). Anal. ($C_{29}H_{23}N_6O_2SF\cdot 1.0H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-benzoyl}indole (15c). This was prepared by acylation method B using 4-(methoxycarbonyl)indole and 3-fluoro-4-(chloromethyl)benzoyl chloride prepared as follows: To a solution of 3-fluoro-4-methylbenzoic acid (5 g, 32.5 mmol) and 1 drop of DMF dissolved in 160 mL of THF at room temperature was added oxalyl chloride (3.1 mL, 35.7 mmol) by syringe. The bubbling solution was stirred at room temperature for 30 min and at reflux for 30 min. The solvent was removed, and the residue was chased with toluene several times to give 6 g of 3-fluoro-4-methylbenzoyl chloride as a yellow liquid.

To a solution of 3-fluoro-4-methylbenzoyl chloride (4.87 g, 28.3 mmol) dissolved in 47 mL of benzene in the presence of catalytic benzoyl peroxide was added sulfuryl chloride (2.73 mL, 34.0 mmol) by syringe. The clear solution was refluxed for 2.5 h and concentrated in vacuo. The residue was distilled to give 3.9 g of 3-fluoro-4-(chloromethyl)benzoyl chloride contaminated with 20% starting material and was used without further purification. Data for **15c**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.86 (s, 1H), 8.31−8.29 (d, 1H, J = 4.4 Hz), 8.19 (s, 1H), 7.88−7.85 (d, 1H, J = 8.5 Hz), 7.71−7.69 (d, 1H, J = 4.4 Hz), 7.66−7.63 (d, 1H, J = 4.4 Hz), 7.59−7.56 (d, 1H, J = 4.4 Hz), 7.49−7.46 (d, 1H, J = 8.1 Hz), 7.16−7.10 (t, 1H, J = 7.8 Hz), 5.69 (s, 2H), 3.51 (s, 3H), 3.34 (s, 6H), 2.62 (s, 3H); MS (DCI/NH_3) *m/e* 514 $(M + H)^+$. Anal. ($C_{28}H_{24}FN_5O_4\cdot 0.5CH_2Cl_2$) C, H, N.

Three-Step Imidazopyridine Installation. Preparation of 1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoyl]indole (15e). To a solution of 3-nitro-4-chloropyridine[34] (4.63 g, 29.2 mmol) in absolute ethanol (100 mL) was added 4-aminobenzonitrile (3.45 g, 29.2 mmol), and the resulting purple-brown solution was stirred for 17 h at room temperature, during which time it became a green-brown suspension. The reaction mixture was poured into cold 10% aqueous NH_4OH and filtered. The solid was suspended in ethanol (75 mL) and heated for 10 min on the steam bath. The suspension was cooled to room temperature and filtered to give 4-[*N*-(3-nitropyrid-4-yl)amino]benzonitrile as a bright-yellow solid. Catalytic hydrogenation (2 atm of H_2, 10% Pd/C) of 4-[*N*-(3-nitropyrid-4-yl)amino]benzonitrile (6.17 g) in 1:1 methanol/CH_2Cl_2 gave 4-[*N*-(3-aminopyrid-4-yl)amino]benzonitrile.

A mixture of 4-[*N*-(3-aminopyrid-4-yl)amino]benzonitrile (5.20 g, 24.7 mmol), acetic anhydride (16 mL, 169 mmol), and acetic acid (16 mL) was warmed to 95 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was azeotroped with benzene to give a brown solid. The brown solid was mixed with 10% aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)-benzonitrile (6.38 g) as a yellow solid which was used without further purification.

HCl gas was bubbled for 10 min into a flask containing 100 mL of methanol and cooled in an ice/acetone bath, during which time the solution temperature rose to 37 °C. The solution temperature was allowed to come down to −5 °C, and a solution of 4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)benzonitrile (5.30 g, 22.6 mmol) in methanol (50 mL) was added dropwise over 15 min. The reaction mixture was warmed slowly to room temperature and stirred for 65 h. The milky white reaction mixture was cooled in an ice/water bath, and H_2O (100 mL) was added dropwise. The resulting clear-yellow suspension was stirred for 3 h at room temperature and again cooled in an ice/water bath. Solid Na_2CO_3 was added until a pH of 8 was achieved, and the white suspension was warmed to room temperature. Water was added until a clear solution was obtained, and the solution was extracted with CH_2Cl_2 (3 × 600 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give methyl 4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)benzoate (5.19 g) as a yellow-white solid.

The methyl ester was converted to the corresponding acid chloride using the procedure from **15b** and added to 6-(4-fluorophenyl)indole using acylation method B to afford **15e** as a solid (mp 307−308 °C): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 3.10 (s, 6H), 7.30−7.40 (c, 2H), 7.61−7.72 (c, 2H), 7.73−7.88 (c, 5H), 8.05−8.16 (c, 2H), 8.30−8.41 (c, 2H), 8.96 (s, 1H), 9.08 (br d, 1H, J = 10.5 Hz); IR (KBr) 1700, 1640, 1600, 1520, 1480, 1440, 1390, 1220, 1180, 1090, 1020, 990, 920 cm^{-1}; MS (DCI/NH_3) *m/e* 518 $(M + H)^+$; HRMS for $C_{31}H_{24}N_5O_2F$ theoretical 518.1992, found 518.1992.

1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]carbonyl}-indole (15g). A solution of 6-(4-fluorophenyl)indole (10.0 g, 47.4 mmol) in dioxane (36 mL) and pyridine (5.8 mL, 71.8 mmol) was heated to 60 °C, and a solution of chloroacetyl chloride (5.7 mL, 71.1 mmol) in dioxane (12.5 mL) was added dropwise over 1 h. The reaction mixture was stirred for 1 h at 60 °C, then cooled to room temperature, and poured into a mixture of H_2O (200 mL) and ether (50 mL). The resulting orange precipitate was filtered and dried. Recrystallization

from ethanol followed by rinsing with cold ether gave 1-chloro-2-[6-(4-fluorophenyl)indol-3-yl]ethanone (2.8 g) as an orange solid.

To a solution 1*H*-2-methylimidazo[4,5-*c*]pyridine (372 mg, 2.80 mmol) in a mixture of THF (13.2 mL) and DMPU (4.4 mL) was added NaH (81 mg, 3.36 mmol), and the resulting yellow suspension was stirred for 50 min at room temperature. In a separate flask, a mixture of 1-chloro-2-[1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indol-3-yl]ethanone (1.00 g, 2.80 mmol), prepared from 1-chloro-2-[6-(4-fluorophenyl)indol-3-yl]-ethanone using the indole *N*-acylation procedure with *N*,*N*-dimethylcarbamoyl chloride, and NaBr (577 mg, 5.60 mmol) in THF (13.2 mL) was cooled to 0 °C. The imidazopyridine/NaH suspension was then added via syringe, and the orange solution was warmed slowly to room temperature and stirred for 17 h. The reaction mixture was partitioned between H_2O (75 mL) and ethyl acetate (75 mL). The layers were separated, the aqueous phase was washed with ethyl acetate, and the combined organic extracts were washed with H_2O. The combined aqueous extracts were extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel (8% methanol/CH_2Cl_2) gave 58 mg of **15g**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.52 (s, 3H), 3.15 (s, 6H), 5.93 (s, 2H), 7.25−7.35 (m, 2H), 7.56 (d, 1H, J = 5.4 Hz), 7.63 (d, 1H, J = 9.3 Hz), 7.7−7.8 (m, 2H), 7.89 (s, 1H), 8.19 (d, 1H, J = 8.4 Hz), 8.28 (d, 1H, J = 5.7 Hz), 8.86 (s, 1H), 8.95 (s, 1H); MS (DCI/NH_3) *m/e* 456 (M + H)$^+$. Anal. ($C_{26}H_{22}FN_5O_2 \cdot 2H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)but-5-yl]carbonyl}-indole (15h): prepared by method A using 4-(methoxycarbony)lindole and 6-bromopentanoyl chloride; ^{1}H NMR (DMSO-d_6) δ 1.59−1.70 (m, 2H), 1.75−1.85 (m, 2H), 2.60 (s, 3H), 2.95 (t, 2H, J = 9 Hz), 3.04 (s, 6H), 3.60 (s, 3H), 4.28 (t, 2H, J = 9 Hz), 7.42 (d, 2H, J = 6 Hz), 7.62 (d,1H, J = 6 Hz), 7.74−7.80 (m, 1H), 8.26 (d, 1H, J = 6 Hz), 8.60 (s, 1H), 8.80 (s, 1H); MS (DCI/NH_3) *m/e* 462(M + H). Anal. ($C_{25}H_{27}N_5O_4 \cdot 1.0H_2O$) C, H; N: calcd, 14.60; found, 14.00.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{[*trans*-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-cyclohex-1-yl]carbonyl}indole Hydrochloride (15l). To a 0 °C solution of *trans*-4-(aminomethyl)-1-cyclohexanecarboxylic acid (6.28 g, 0.04 mol) in 10% aqueous NaOH (16 mL) were added dropwise benzyl chloroformate (8.29 g, 0.049 mol) and 10% aqueous NaOH (20 mL). The cold bath was removed, and the reaction mixture was stirred vigorously for 1 h. The thick white paste was shaken with aqueous 1 M HCl (100 mL), and the white solid was isolated by filtration, washed with H_2O, and dried overnight in vacuo to give *trans*-4-{[*N*-(carbobenzyloxy)amino]methyl}-1-cyclohexanecarboxylic acid. A mixture of *trans*-4-{[*N*-(carbobenzyloxy)amino]methyl}-1-cyclohexanecarboxylic acid (5.02 g, 17.3 mmol) and thionyl chloride was heated at 40 °C for 30 min. The reaction mixture was cooled to room temperature and diluted with pentane (50 mL). *trans*-4-{[*N*-(Carbobenzyloxy)amino]methyl}-1-cyclohexanecarbonyl chloride (4.37 g) was isolated by filtration and drying in vacuo.

To a solution of 4-(methoxycarbonyl)indole (2.33 g, 13.3 mmol) in CH_2Cl_2 (25 mL) was added ethylmagnesium bromide (3 M in ether, 4.4 mL, 13.2 mmol). The reaction mixture was stirred for 5 min, and $ZnCl_2$ (1 M in ether, 40 mL, 40 mmol) was added, and the cloudy, brown suspension was stirred for 15 min. A solution of *trans*-4-{[*N*-(carbobenzyloxy)amino]-methyl}-1-cyclohexanecarbonyl chloride (4.36 g, 14.1 mmol) in CH_2Cl_2 (20 mL) was added, and the reaction mixture was stirred for 3 h. The reaction mixture was poured into a separatory funnel containing saturated aqueous NH_4Cl which left a green-brown gum. The gum was broken up by trituration with aqueous 1 M HCl and CH_2Cl_2/methanol and added to the separatory funnel. The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (1% then 3% methanol/CH_2Cl_2) gave 4-(methoxycarbonyl)-3-[{*trans*-4-[[-(carbobenzyloxy)amino]methyl]cyclohex-1-yl]carbonyl}indole (2.83 g, 48%) as a tan foam.

Catalytic hydrogenation (10% Pd/C, 4 atm of H_2, ethanol, 17 h) of 1-(*N*,*N*-dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{[*trans*-1-[[*N*-carbobenzyloxy)amino]methyl]cyclohex-4-yl]-carbonyl}indole, prepared from 4-(methoxycarbonyl)-3-{[*trans*-4-[[*N*-(carbobenzyloxy)amino]methyl]cyclohex-1-yl]carbonyl}-indole using the *N*-acylation procedure in method A, gave 1-(*N*,*N*-dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{[*trans*-1-(aminomethyl)cyclohex-4-yl]carbonyl}indole. The 2-methylimidazo[4,5-*c*]pyridine heterocycle was installed using the three-step method for compound **15e** and 4-ethoxy-3-nitropyridine.[35] The resulting material was dissolved in THF (10 mL), and 4 N HCl/dioxane (0.15 mL) was added. The resulting precipitate was filtered, washed with ether, and dried to give **15l** (0.212 g): ^{1}H NMR (D_3COD, 300 MHz) δ 9.19 (s, 1H), 8.57 (d, 1H), 8.39 (s, 1H), 8.26 (m, 1H), 7.75 (d, 1H), 7.43 (m, 2H), 4.35 (m, 2H), 3.80 (s, 3H), 3.01 (s, 6H), 2.82 (s, 3H), 2.81 (m, 1H), 2.02 (m, 2H), 1.77 (m, 1H), 1.48 (m, 4H), 1.24 (m, 2H); MS (DCI/NH_3) *m/e* 502 (M + H)$^+$, 244; HRMS for $C_{28}H_{31}N_5O_4$ theoretical 502.2454, found 502.2439.

1-(*N*,*N*-Dimethylcarbamoyl)-3-{[4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]phenyl]sulfonyl}indole (20a). To a −10 °C solution of indole (5.85 g, 50 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (7.0 mL, 50 mmol). In a separate flask a solution of *p*-tolyl disulfide (6.16 g, 25 mmol) in CH_2Cl_2 (50 mL) was cooled to −20 °C, and sulfuryl chloride (2.0 mL, 25 mmol) was added over 10 min. The cold bath was removed, and the reaction mixture was stirred for 1 h and then was added to the indole/triethylamine solution over 15 min. The resulting solution was warmed to room temperature and stirred for 17 h. The reaction mixture was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in toluene and filtered through a plug of silica gel. The filtrate was diluted with an equal volume of hexanes, and the resulting solid was collected to give 4.43 g of the desired material. The mother liquors were concentrated in vacuo, and the residue was purified by chromatography on silica gel (10% ethyl acetate/hexanes). The material from the chromatography was combined with the original solid and recrystallized from toluene/hexanes to give 7.41 g (62% yield) of 3-(4-methylthiopheneyl)indole. To a solution of this indole (7.34 g, 30.7 mmol) in dimethoxyethane (75 mL) were added powdered KOH (85%, 7.01 g, 125 mmol) and benzenesulfonyl chloride (4.25 mL, 33.3 mmol). A white precipitate formed immediately, and the reaction mixture became quite warm. The reaction mixture was stirred for 1 h during which time it cooled to room temperature. Water (50 mL) was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. 1-(Phenylsulfonyl)-3-(4-methylthiopheneyl)indole (**16**) (8.89 g, 76% yield) was obtained by chromatography on silica gel (10% then 20% ethyl acetate/hexanes).

To a solution of **16** (8.89 g, 23.4 mmol) in glacial acetic acid (15 mL) was added 30% H_2O_2 solution (2.45 g, 72 mmol), and the resulting two-phase mixture was heated at reflux for 30 min during which time it became a solid mass. The reaction mixture was cooled to room temperature and diluted with H_2O and ethyl acetate, and the solid was filtered off. The filtrate layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was triturated with ethyl acetate/ether, and the resulting solid was combined with the solid obtained above and recrystallized from ethyl acetate to give 8.15 g of 1-(phenylsulfonyl)-3-[(4-methylphenyl)-sulfonyl]indole. To a suspension of 1-(phenylsulfonyl)-3-[(4-methylphenyl)sulfonyl]indole (7.33 g, 17.8 mmol) and *N*-bromosuccinimide (3.20 g, 17.9 mmol) in CCl_4 (750 mL) was added benzoyl peroxide (100 mg, 0.40 mmol), and the reaction mixture was warmed to reflux, during which time it became homogeneous. The reaction mixture was heated for 3 h at reflux, cooled to room temperature, stirred for 17 h, and concentrated. Pure (1.14 g, mp 194−195.5 °C), and 75% pure

(3.74 g) 1-(phenylsulfonyl)-3-{[(4-bromomethyl)phenyl]sulfonyl}-indole (**17**) was obtained by chromatography on silica gel (20% then 30% then 50% CH_2Cl_2/toluene) followed by recrystallization from toluene/hexanes.

To a suspension in DMF (10 mL) of potassium bis(*tert*-butoxycarbonyl)amide[36] (1.78 g, 6.99 mmol) was added a solution of **17** (2.8 g, 5.7 mmol) in DMF (12 mL). The reaction mixture was heated at 50 °C for 2 h, then cooled to room temperature, and diluted with ethyl acetate (20 mL). The suspension was filtered and the filtrate concentrated in vacuo. The residue was taken up in ethyl acetate, washed with 1 M aqueous $NaHSO_4$, H_2O, 5% aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on silica gel (1:1 toluene/CH_2Cl_2, then CH_2Cl_2, then 5% ethyl acetate/CH_2Cl_2) followed by recrystallization from toluene/hexanes gave 1-(phenylsulfonyl)-3-{[4-[[(di-*tert*-butoxycarbonyl)-amino]methyl]phenyl]sulfonyl}indole (3.10 g, 85% yield). This material and trifluoroacetic acid (5 mL) were stirred for 45 min at room temperature. The reaction mixture was concentrated and the residue partitioned between ethyl acetate (150 mL) and 1 M aqueous Na_2CO_3. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with H_2O and brine and concentrated to give 1-(phenylsulfonyl)-3-{[4-(aminomethyl)phenyl]sulfonyl}-indole (**18**) (2.10 g) which was used without further purification.

The 2-methylimidazo[4,5-*c*]pyridine heterocycle was installed on **18** using the three-step method for compound **15e** and 4-ethoxy-3-nitropyridine with loss of the *N*-phenylsulfonyl moiety to give 3-{[4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)-methyl]phenyl]sulfonyl}indole (**19**) (327 mg). Carbamoylation using the procedure in method A gave **20a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.54 (s, 3H), 3.09 (s, 6H), 5.36 (s, 2H), 7.10 (dd, 1H, J = 6.0, 0.9 Hz), 7.12 (d, 2H, J = 8.4 Hz), 7.29 (td, 1H, J = 7.5, 1.5 Hz), 7.58 (dt, 1H, J = 8.4, 2.4 Hz), 7.87 (dt, 1H, J = 7.5, 2.4 Hz), 7.95 (t, 1H, J = 1.8 Hz), 7.96 (s, 1H), 7.99 (t, 1H, J = 1.8 Hz), 8.33 (d, 1H, J = 6.0 Hz), 9.01 (s, 1H); MS (DCI/NH_3) *m/e* 474 $(M + H)^+$. Anal. ($C_{25}H_{23}N_5O_3S \cdot 0.5H_2O$) C, H, N.

3-{[4-(1*H*-2-Methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]acetyl}indole-1,4-dicarboxylic Acid 1-Dimethylamide 4-Methyl Ester (15n). A mixture of ethyl 4-amino-1-piperidinecarboxylate (3.53 g, 20.5 mmol) and 4-ethoxy-3-nitropyridine (3.65 g, 21.7 mmol) in CH_3CN (25 mL) was heated at reflux for 40 h. The reaction mixture was cooled to room temperature and concentrated to give an orange syrup. Catalytic hydrogenation (10% Pd/C, 1 atm of H_2, ethanol) of this material gave 6.22 g of *N*-[1-(ethoxycarbonyl)piperidin-4-yl]-3,4-diaminopyridine which was used without further purification.

A solution of *N*-[1-(ethoxycarbonyl)piperidin-4-yl]-3,4-diaminopyridine (6.22 g) in acetic anhydride (50 mL) was heated at reflux for 70 h. The reaction mixture was cooled to room temperature, and the acetic anhydride was quenched by slow addition of methanol. The reaction mixture was concentrated and the residue partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic phase was concentrated in vacuo. Chromatography on silica gel (1 triethylamine:3 methanol:96 CH_2Cl_2) gave 1*H*-1-[1-(ethoxycarbonyl)piperidin-4-yl]-2-methylimidazo[4,5-*c*]pyridine (3.7 g).

To a solution in 95% ethanol (20 mL) of 1*H*-1-[1-(ethoxycarbonyl)piperidin-4-yl]-2-methylimidazo[4,5-*c*]pyridine (3.7 g, 12.8 mmol) was added a solution of powdered KOH (2.47 g, 44 mmol) in H_2O (8 mL). The reaction mixture was heated at reflux for 72 h. The reaction mixture was cooled to room temperature and diluted with H_2O (50 mL). The solution was continuously extracted into CH_2Cl_2 for 7 h. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 1*H*-1-(piperidin-4-yl)-2-methylimidazo[4,5-*c*]pyridine (**27**; 2.07 g) as a yellow solid.

To a solution of **27** (100 mg, 0.462 mmol) in DMF (1 mL) were added *N*,*N*-diisopropylethylamine (0.16 mL, 0.92 mmol) and a solution of 4-(methoxycarbonyl)-3-(chloroacetyl)indole (127 mg, 0.441 mmol) in THF (2 mL) and DMF (2 mL) over 105 min. The reaction mixture was stirred overnight at room temperature, then diluted with ethyl acetate, and extracted with aqueous 0.1 M NaOH. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give an orange foam (0.18 g). Chromatography on silica gel (50:1 $CHCl_3$/methanol + 0.5% NH_4OH, then 20:1 $CHCl_3$/methanol + 0.5% NH_4OH, then 10:1 $CHCl_3$/methanol + 0.5% NH_4OH) gave 4-carbomethoxy-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]acetyl}-indole (46 mg, 22%) as a light-orange powder. Carbamoylation using the procedure in method A gave **15n**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.84 (d, 2H, J = 12 Hz), 2.24 (q, 2H, J = 12 Hz), 2.41 (t, 2H, J = 11 Hz), 2.61 (s, 3H), 3.07 (d, 2H, J = 12 Hz), 3.12 (s, 6H), 3.69 (s, 2H), 3.80 (s, 3H), 4.33 (m, 1H), 7.45 (t, 1H, J = 7.8 Hz), 7.50 (dd, 1H, J = 0.9, 5.7 Hz), 7.51 (dd, 1H, J = 1.5, 7.4 Hz), 7.82 (dd, 1H, J = 1.3, 7.9 Hz), 8.24 (d, 1H, J = 5.9 Hz), 8.73 (s, 1H), 8.78 (d, 1H, J = 0.7 Hz); IR (microscope) 1111 (m), 1188 (m), 1286 (m), 1358 (m), 1390 (s), 1431 (m), 1606 (w), 1699 (s), 1724 (s), 2948 (w) cm^{-1}; MS (DCI/NH_3) *m/e* 503 $(M + H)^+$. Anal. ($C_{27}H_{30}N_6O_4 \cdot H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo[4,5-*b*]pyrid-1-yl)methyl]benzoyl}-indole (21a) and 1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(3*H*-2-methylimidazo[4,5-*b*]pyrid-3-yl)methyl]benzoyl}indole (21b). These were prepared by method B using 4-(methoxycarbonyl)indole and 2-methylimidazo[4,5-*b*]pyridine. Data for **21a**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.65 (s, 2H), 7.21 (dd, 1H, J = 8.1, 4.8 Hz), 7.29 (apparent d, 2H, J = 8.1 Hz), 7.4−7.5 (m, 1H), 7.57 (dd, 1H, J = 7.5, 1.0 Hz), 7.85 (apparent d, 2H, J = 8.4 Hz), 7.86 (dd, 1H, J = 8.1, 1.2 Hz), 7.95 (dd, 1H, J = 8.1, 1.5 Hz), 8.11 (s, 1H), 8.36 (dd, 1H, J = 4.8, 1.5 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{25}N_5O_4 \cdot 1.0H_2O$) C, H, N. Data for **21b**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.55 (s, 3H), 3.02 (s, 6H), 3.48 (s, 3H), 5.62 (s, 2H), 7.27 (dd, 1H, J = 8.1, 4.8 Hz), 7.34 (apparent d, 2H, J = 8.1 Hz), 7.4−7.5 (m, 1H), 7.56 (dd, 1H, J = 7.2, 1.2 Hz), 7.85 (apparent d, 2H, J = 8.4 Hz), 7.86 (dd, 1H, J = 8.4, 1.2 Hz), 8.00 (dd, 1H, J = 8.1, 1.5 Hz), 8.12 (s, 1H), 8.31 (dd, 1H, J = 5.1, 1.5 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{25}N_5O_4 \cdot 0.8H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(5-oxide 1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (21c). To a 0 °C solution in CH_2Cl_2 (2 mL) of **7c** (25 mg, 0.045 mmol) was added 3-chloroperbenzoic acid (80%, 12.5 mg, 0.045 mmol). The reaction mixture was stirred for 1 h at 0 °C and then was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$/$NaHSO_3$. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Purified **21c** was obtained by HPLC (20−40% CH_3CN/H_2O): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.55 (s, 3H), 3.02 (s, 6H), 3.48 (s, 3H), 5.65 (s, 2H), 7.31 (d, 2H, J = 8.4 Hz), 7.46 (t, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.87 (d, 1H, J = 7.6 Hz), 8.11 (s, 1H), 8.12 (dd, 1H, J =7.6, 2.2 Hz), 8.68 (d, 1H, J = 2.2 Hz); MS (DCI/NH_3) *m/e* 512 $(M + H)^+$; HRMS for $C_{28}H_{25}N_5O_5$ theoretical 512.1934, found 512.1921.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(1*H*,5*H*-2-methyl-4-oxoimidazo[4,5-*c*]pyrid-1-yl)methyl]-benzoyl}indole (21d). A mixture of **21c** (61 mg) and acetic anhydride (1 mL) was heated at 130 °C for 6 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by chromatography on silica gel (5% then 8% methanol/CH_2Cl_2) to give **21d** (42 mg): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.42 (s, 3H), 3.03 (s, 6H), 3.49 (s, 3H), 5.51 (s, 2H), 6.57 (d, 1H, J = 6.7 Hz), 7.13 (t, 1H, J = 6.7 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.46 (t, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.86 (d, 2H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.6 Hz), 8.12 (s, 1H), 11.14 (d, 1H, J = 6.7 Hz); MS (DCI/NH_3) *m/e* 512 $(M + H)^+$, 441, 365, 264, 250, 236, 178. Anal. ($C_{28}H_{25}N_5O_5 \cdot 0.85AcOH \cdot 1.7H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(4-chloro-1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]-benzoyl}indole (21e). A mixture of **21d** (60 mg) and $P(O)Cl_3$ (1 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to room temperature and partitioned between CH_2-

Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (2% methanol/CH_2Cl_2) to give **21e** (34 mg): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.60 (s, 3H), 3.01 (s, 6H), 3.47 (s, 3H), 5.68 (s, 2H), 7.29 (d, 2H, J = 8.4 Hz), 7.45 (t, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 8.6 Hz), 7.68 (d, 1H, J = 6.0 Hz), 7.84 (d, 2H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.6 Hz), 8.11 (s, 1H), 8.12 (d, 1H, J = 6.0 Hz); MS (DCI/NH_3) *m/e* 530 $(M + H)^+$, 364. Anal. ($C_{28}H_{24}ClN_4O_5 \cdot 0.5H_2O \cdot 0.38$ HCl) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-(methoxycarbonyl)-3-{4-[(1*H*-2-methylbenzimidazolyl)methyl]benzoyl}-indole (21g): prepared by method B using 2-methylbenzimidazole;[37] ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.54 (s, 3H), 3.02 (s, 6H), 3.47 (s, 3H), 5.59 (s, 2H), 7.1−7.2 (m, 2H), 7.26 (d, 2H, J = 8.1 Hz), 7.4−7.6 (m, 4H), 7.8−7.9 (m, 3H), 8.10 (s, 1H); MS (DCI/NH_3) *m/e* 495 $(M + H)^+$. HRMS for $C_{29}H_{27}N_4O_4$ theoretical 495.2032, found, 495.2035.

2-Methyl-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)-methyl]benzoyl}indole (22a): prepared by method B using 2-methylindole without carbamoylation; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.35 (s, 3H), 2.57 (s, 3H), 5.64 (s, 2H), 6.99 (dt, 1H, J = 8.1, 1.0 Hz), 7.11 (dt, 1H, J = 8.1, 1.0 Hz), 7.2−7.3 (m, 3H), 7.38 (d, 1H, J = 8.1 Hz), 7.58 (d, 2H, J = 8.1 Hz), 7.55−7.65 (m, 1H), 8.31 (d, 1H, J = 5.4 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 381 $(M + H)^+$. Anal. ($C_{24}H_{20}N_4O \cdot 0.4H_2O$) C, H, N.

4,7-Dimethyl-3-{4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (22h): prepared by method B using 4,7-dimethylindole[38] without carbamoylation; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.45 (s, 3H), 2.52 (s, 3H), 2.59 (s, 3H), 5.63 (s, 2H), 6.85 (d, 1H, J = 7.3 Hz), 6.94 (d, 1H, J = 7.1 Hz), 7.27 (d, 2H, J = 8.3 Hz), 7.59 (d, 1H, J = 5.4 Hz), 7.60 (s, 1H), 7.80 (d, 2H, J = 8.3 Hz), 8.30 (d, 1H, J = 5.6 Hz), 8.86 (s, 1H), 11.85 (s, 1H); MS (DCI/NH_3) *m/e* 395 $(M + H)^+$. IR (microscope) 885 (m), 1222 (m), 1299 (m), 1350 (m), 1391 (m) cm^{-1}. Anal. ($C_{25}H_{22}N_4O \cdot 1.2H_2O$) C, H, N.

4,7-Bis(methoxycarbonyl)-3-{4-[(1*H*-2-methylimidazo-[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (22i). This was prepared by method B without carbamoylation using 4,7-bis-(methoxycarbonyl)indole, made as follows: To a solution of dimethyl nitroterephthlate (10.0 g, 41.8 mmol) in THF (420 mL) at −45 to −40 °C was added vinylmagnesium bromide (1.0 M in THF, 125 mL, 125 mmol) over 10 min, and the reaction mixture was stirred for an additional 40 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted twice with ether. The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated to give 11.9 g of orange oil and yellow granular solid. Chromatography on silica gel (3:1 hexane/ethyl acetate) gave 4,7-bis(methoxycarbonyl)indole (1.90 g) as a bright-yellow waxy solid. Trituration of the mixed fractions with hexanes−ethyl acetate gave an additional 0.66 g of product. Data for **22i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H), 3.72 (s, 3H), 4.02 (s, 3H), 5.41 (s, 2H), 7.14 (d, 2H, J = 8.5 Hz), 7.20 (d, 1H, J = 5.5 Hz), 7.62 (d, 1H, J = 7.7 Hz), 7.70 (d, 1H, J = 2.9 Hz), 7.86 (d, 2H, J = 8.5 Hz), 8.01 (d, 1H, J = 8.1 Hz), 8.40 (d, 1H, J = 4.8 Hz), 9.05 (s, 1H), 10.58 (s, 1H); MS (DCI/NH_3) *m/e* 483 $(M + H)^+$. IR (microscope) 1163 (s), 1198 (m), 1280 (s), 1433 (m), 1520 (m), 1610 (m), 1637 (m), 1721 (s), 2952 (w), 3362 (br) cm^{-1}. Anal. ($C_{27}H_{22}N_4O_5 \cdot 0.35H_2O \cdot 0.65CH_2Cl_2$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-{[(*N*,*N*-dimethylamino)-carbonyl]oxy}-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]-pyrid-1-yl)methyl]benzoyl}indole (22l): prepared by acylation method B using 4-{[(*N*,*N*-dimethylamino)carbonyl]-oxy}indole and 3-fluoro-4-(chloromethyl)benzoyl chloride; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 2.73 (s, 3H), 2.91 (s, 3H), 3.00 (s, 6H), 5.69 (s, 2H), 6.97−7.00 (d, 1H, J = 8.8 Hz), 7.13 (t, 1H), 7.33−7.38 (t, 1H, J = 8.5 Hz), 7.49−7.52 (d, 1H, J = 8.1 Hz), 7.59−7.67 (m, 3H), 8.02 (s, 1H), 8.29−8.31 (d, 1H, J = 8.0 Hz), 8.86 (s, 1H); MS (DCI/NH_3) *m/e* 543 $(M + H)^+$. Anal. ($C_{29}H_{27}N_6O_4F \cdot 0.5H_2O$) C, H; N: calcd, 15.23; found, 13.75.

1-(*N*,*N*-Dimethylcarbamoyl)-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}-indole (22m). To a solution of 3-fluoro-4-(chloromethyl)-benzoyl chloride (9.85 g, 47.6 mmol) dissolved in CH_2Cl_2 at 0 °C was added $AlCl_3$ (12.66 g, 95.2 mmol) in one portion; the cooling bath was removed, and the resulting suspension was stirred at room temperature for 10 min at which time a solution of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromoindole (10.59 g, 39.7 mmol) was added dropwise using a syringe over 15 min. The dark suspension was stirred at room temperature for 2.5 h and then poured into a separatory funnel containing 500 mL of ice chips. The dark solid remaining in the flask was dissolved with alternating amounts of CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the milky organic layer was washed with water and saturated $NaHCO_3$ and then diluted with methanol; this clear solution was dried with $MgSO_4$, filtered, and concentrated. The crude foam was flash-chromatographed (CH_2Cl_2, then 3% acetone/CH_2Cl_2) to give 8.74 g of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromo-3-[3-fluoro-4-(chloromethyl)benzoyl]indole as a yellow foam.

To a solution of this benzylic chloride (15.77 g, 36.1 mmol) dissolved in 180 mL of DMF at room temperature was added NaN_3 (2.81 g, 43.3 mmol) in one portion. The clear-yellow solution, which turned cloudy after 15 min, was stirred for 3 h and then poured into a mixture of water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water, dried with $MgSO_4$, filtered, and concentrated to give 16.0 g of benzylic azide which was used without purification. This material (36.1 mmol) was dissolved in 180 mL of THF and 30 mL of water and cooled to 0 °C, and to it was added PPh_3 (11.3 g, 43.3 mmol) in one portion. The cooling bath was removed, and the solution was stirred at room temperature for 16 h at which time the THF was removed under vacuum. The resulting suspension was diluted with water and CH_2Cl_2, and the separated aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (2% then 4% then 10% MeOH/CH_2Cl_2) to afford 13.59 g of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromo-3-[3-fluoro-4-(aminomethyl)benzoyl]indole.

To a suspension of 3-nitro-4-chloropyridine hydrochloride (8.75 g, 44.9 mmol) in 90 mL of CH_3CN at 0 °C was added a solution of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromo-3-[3-fluoro-4-(aminomethyl)benzoyl]indole (12.59 g, 30.1 mmol) dissolved in 30 mL of CH_3CN by cannula in a stream followed immediately by triethylamine (9 mL, 65.0 mmol) which was added dropwise by syringe. The resulting thick, green suspension was stirred at room temperature for 30 min and at 60 °C for 2 h. The solvent was removed under vacuum, and the residue was dissolved in a mixture of CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried with $MgSO_4$, filtered, and concentrated. Flash chromatography (10% then 15% then 20% acetone/CH_2Cl_2) gave 12.14 g of nitropyridine intermediate.

A solution of this material (15.16 g, 28.1 mmol) dissolved in 1000 mL of THF in the presence of 1.51 g of 5% Pt/C at room temperature was treated with 4 atm of H_2 for 18 h. Filtration and concentration of this mixture gave a residue which was dissolved in 50 mL of acetic acid and 50 mL of acetic anhydride and refluxed for 2 h. Cooling and concentration gave a residue which was dissolved in methanol and concentrated again to dryness. Flash chromatography (2% then 5% then 7% MeOH/CH_2Cl_2) gave contaminated product which was crystallized in ethyl acetate to afford 8.74 g of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromo-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole.

To a solution of 1-(*N*,*N*-dimethylcarbamoyl)-4-bromo-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}-indole (5.93 g, 11.1 mmol) dissolved in 150 mL of toluene under argon were added trimethyl[(trimethysilyl)ethynyl]stannane (3.5 g, 14.1 mmol) and tetrakis(triphenylphosphine)palladium-(0) (642 mg, 0.56 mmol). The resulting suspension was heated

at 120 °C for 3 h (clear solution after 1 h), cooled, and concentrated. This crude material was dissolved in 100 mL of DMF, cooled to 0 °C, and treated with $KF \cdot H_2O$ (2.1 g, 22.2 mmol) which was added in a single portion. The mixture was stirred at 0 °C for 30 min and at room temperature for 1.5 h; the solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed (CH_2Cl_2, then 5% MeOH/CH_2Cl_2) to give 4.27 g of **22m** as a foam. The hydrochloride salt was prepared by treating a solution of the free base in THF with 4 M HCl/dioxane solution followed by filtration. Data for **22m**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.57 (s, 3H), 3.01 (s, 6H), 4.07 (s, 1H), 5.69 (s, 2H), 7.05−7.15 (m, 1H), 7.30−7.45 (m, 2H), 7.55−7.75 (m, 4H), 8.18 (s, 1H), 8.29 (d, 1H, J = 5.7 Hz), 8.85 (s, 1H); MS (DCI/NH_3) *m/e* 480 $(M + H)^+$. Anal. ($C_{28}H_{22}N_5O_2F \cdot 0.2$EtOAc) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-ethynyl-3-{3-fluoro-4-[(5-oxide 1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (22n): prepared in a similar fashion as **21c** using **22m**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69 (s, 3H), 3.04 (s, 1H), 3.10 (s, 6H), 5.43 (s, 2H), 7.01 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 7.6 Hz), 7.37 (t, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.62−7.68 (m, 2H), 7.69 (s, 1H), 7.71 (dd, 1H, J = 10.5, 1.5 Hz), 8.23 (dd, 1H, J = 6.6, 1.0 Hz), 8.79 (d, 1H, J = 1.0 Hz); MS (DCI/NH_3) *m/e* 496 $(M + H)^+$. Anal. ($C_{28}H_{22}N_5O_3F \cdot H_2O \cdot 0.8$EtOAc) C, H, N.

1-(*N*-Methylcarbamoyl)-4-ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (22o): prepared in a similar manner as **14h** from **22p**; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.58 (s, 3H), 2.82 (d, 3H, J = 4.5 Hz), 4.08 (s, 1H), 5.70 (s, 2H), 7.1−7.17 (m, 1H), 7.32−7.42 (m, 2H), 7.58 (d, 1H, J = 5 Hz), 7.65 (d, 1H, J = 8.1 Hz), 7.71 (d, 1H, J = 11.4 Hz), 8.26 (s, 1H), 8.30 (d, 1H, J = 5.7 Hz), 8.35 (dd, 1H, J = 7.8, 1.5 Hz), 8.43 (d, 1H, J = 3.9 Hz), 8.86 (s, 1H); MS (ESI+) *m/e* 466 (M + H). Anal. ($C_{27}H_{20}N_5O_2F \cdot 0.4CH_2Cl_2 \cdot 0.1H_2O$) C, H, N.

4-Ethynyl-3-{3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]benzoyl}indole (22p): prepared in a similar manner as **13b** using the urea saponification method on **22m**; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.58 (s, 3H), 3.98 (s, 1H), 5.68 (s, 2H), 7.08−7.14 (m, 1H), 7.21−7.26 (m, 1H), 7.31 (dd, 1H, J = 8.4, 1.0 Hz), 7.52−7.62 (m, 4H), 7.92 (d, 1H, J = 2.7 Hz), 8.30 (d, 1H, J = 5.4 Hz), 8.86 (s, 1H), 12.19 (s, 1H); MS (ESI+) *m/e* 409 (M + H). Anal. ($C_{25}H_{17}N_4OF \cdot 1.5H_2O$) C, H, N.

1-(*N*,*N*-Dimethylcarbamoyl)-4-ethynyl-3-{1(*RS*)-(hydroxymethyl)-3-fluoro-4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]phenyl}indole (22q). To a solution of **22m** (105 mg, 0.22 mmol) dissolved in 2 mL of ethanol at 0 °C was added $NaBH_4$ (17 mg, 0.44 mmol) in a single portion. The yellow solution was stirred at 0 °C for 2.5 h and then poured into 20 mL of saturated NH_4Cl and 20 mL of CH_2Cl_2. The aqueous phase was made basic with solid $NaHCO_3$ and extracted with CH_2Cl_2; the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The tan foam was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give 86 mg of **22q** as an amorphous solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.54 (s, 3H), 2.97 (s, 6H), 4.34 (s, 1H), 5.51 (s, 2H), 5.85 (d, 1H, J = 4.8 Hz), 6.58 (d, 1H, J = 4.8 Hz), 6.99 (t, 1H, J = 8.1 Hz), 7.2−7.3 (m, 4H), 7.45−7.50 (m, 2H), 7.63 (dd, 1H, J = 8.1, 1.5 Hz), 8.24 (d, 1H, J = 5.7 Hz), 8.81 (s, 1H); MS (DCI/NH_3) *m/e* 482 $(M + H)^+$. Anal. ($C_{28}H_{24}N_5O_2F \cdot 0.5CH_2Cl_2$) C, H, N.

General Coupling Procedure. Preparation of 1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]carbonyl}-indole Hydrochloride (25b). To a suspension in CH_3CN (700 mL) of 1*H*-2-methylimidazo[4,5-*c*]pyridine (5.04 g, 37.9 mmol) was added tris[2-(2-methoxyethoxy)ethyl]amine (1.3 mL, 4.1 mmol) and KOH (10.6 g, 190 mmol). The suspension was stirred at room temperature for 90 min, then 4-nitrobenzyl bromide (8.23 g, 38.1 mmol) was added, and stirring was continued for 2 h. The reaction mixture was partitioned between ethyl acetate and pH 7 buffer. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (5% methanol/CH_2Cl_2) gave 4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-ylmethyl)nitrobenzene (1.07 g) as a tan solid.

A suspension of this material (1.04 g, 3.9 mmol) and $SnCl_2$ (3.25 g, 19.9 mmol) in 8:2 ethyl acetate/methanol (100 mL) was stirred vigorously for 2 h at room temperature. The reaction mixture was poured into 1 M aqueous NaOH and extracted twice with ethyl acetate and once with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.91 g of an orange foam. The foam was dissolved in 30 mL of methanol, and $SnCl_2$ (3.7 g) was added. After stirring for 3 h, the reaction mixture was worked up as above to give 0.79 g of 4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]aniline as an orange oil.

To a solution in THF (25 mL) and *tert*-butyl alcohol (70 mL) of 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indole-3-carboxaldehyde, prepared by Vilsmeier formylation and carbamoylation of 6-(4-fluorophenyl)indole, was added 2-methyl-2-butene (2 M in THF, 8 mL, 16 mmol) followed by a solution of $NaClO_2$ (1.2 g, 13 mmol) and NaH_2PO_4 (2.4 g, 17 mmol) in H_2O (20 mL). After the mixture stirred overnight at room temperature, a solution of $NaClO_2$ (0.25 g) and NaH_2PO_4 (0.50 g) in H_2O (10 mL) was added, and the reaction mixture was stirred for 2 h. The organic solvents were stripped off, and the residue was extracted with ether. The aqueous phase was taken to pH 3 with concentrated HCl, the water was decanted, and the residue was taken up in ethyl acetate. The ethyl acetate solution was dried over $MgSO_4$, filtered, and concentrated to give a dark-brown oil (0.53 g). The oil was dissolved in THF and treated with activated carbon. Filtration and concentration in vacuo gave 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)indole-3-carboxylic acid [**23**; R = 6-(4-F)Ph] (0.426 g) as a red solid.

To a solution in THF (6 mL) of **23** (0.106 g, 0.33 mmol) were added *N*,*N*-diisopropylethylamine (0.1 mL, 0.57 mmol) and bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl; 0.096 g, 0.38 mmol). After 5 min, a solution in THF (3 mL) of **27** (0.100 g, 0.46 mmol; see **15n** experimental for preparation of **27**) was added, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 1-(*N*,*N*-dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]carbonyl}indole (0.146 g) as a tan foam. The hydrochloride salt was prepared by treating a solution in ethyl acetate of the free base with 4 M HCl/dioxane solution followed by filtration: mp 193−195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.02 (s, 1H), 8.38 (d, 1H, J = 6 Hz), 7.80 (s, 1H), 7.78 (d, 1H, J = 6 Hz), 7.60 (m, 3H), 7.52 (m, 1H), 7.39 (m, 1H), 7.16 (m, 2H), 4.52 (m, 1H), 3.20 (m, 2H), 3.16 (s, 6H), 2.71 (s, 3H), 2.46 (m, 2H), 2.03 (m, 2H), 1.50 (m, 2H); IR (microscope) 3400 (br), 3080, 2940, 1690, 1615, 1480, 1440, 1390 cm^{-1}; MS (DCI/NH_3) *m/e* 525 $(M + H)^+$. Anal. ($C_{30}H_{29}FN_6O_2 \cdot HCl \cdot 3H_2O$) C, H; N: calcd, 13.66; found, 12.99.

1-(*N*,*N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[4-[(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)methyl]piperidin-1-yl]carbonyl}indole Hydrochloride (25a). This was prepared by the general coupling procedure using **23** [R = 6-(4-F)Ph; see **25b** experimental for preparation of **23**] and 1*H*-1-(piperidin-4-ylmethyl)-2-methylimidazo[4,5-*c*]pyridine (**24**) made as follows: To a solution in absolute ethanol (40 mL) of 1*H*-1-[(1-acetylpiperidin-4-yl)methyl]-2-methylimidazo[4,5-*c*]pyridine (3.7 g, 13.6 mmol), prepared in a similar manner as **27** using 4-(aminomethyl)piperidine, was added a solution of $LiOH \cdot H_2O$ in H_2O (15 mL). The reaction mixture was heated at reflux for 20 h, then diluted with brine (100 mL), and continuously extracted into CH_2Cl_2 for 20 h. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give **24** (2.51 g) as a yellow foam. Data for **25a**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.79 (s, 1H), 8.29 (d, 1H, J = 6 Hz), 7.88 (s, 1H), 7.80 (d, 1H, J = 1 Hz), 7.73 (m, 3H), 7.66 (dd, 1H, J = 1, 3 Hz), 7.52 (dd, 1H, J = 2, 5 Hz), 7.31 (m, 2H), 4.18 (d, 2H, J = 9 Hz), 3.83 (m, 2H), 3.03 (s, 6H), 2.69 (m, 2H), 2.61 (s, 3H),

2.16 (m, 1H), 1.60 (m, 2H), 1.22 (m, 2H); IR (microscope) 3400, 2930, 1685, 1615, 1515, 1475, 1440, 1385 cm^{-1}; MS (DCI/NH_3) *m/e* 539 $(M + H)^+$, 231. Anal. ($C_{31}H_{31}FN_6O_2 \cdot HCl \cdot 3.25H_2O$) C, H, N.

1-(*N,N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[4-[2-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)ethyl]piperazin-1-yl]carbonyl}indole Hydrochloride (25c). This was prepared by the general coupling method using **23** [R = 6-(4-F)Ph; see **25b** experimental for preparation of **23**] and 1*H*-1-[2-(piperazin-1-yl)ethyl]-2-methylimidazo[4,5-*c*]pyridine which was made as follows: A mixture of 1-(2-aminoethyl)piperazine and 4-ethoxy-3-nitropyridine in CH_3CN was heated at reflux for 40 h. The reaction mixture was cooled to room temperature and concentrated to give 3-nitro-4-{2-(piperazin-1-yl)ethyl]-amino}pyridine which was used without further purification. Catalytic hydrogenation (10% Pd/C, 1 atm of H_2, ethanol) of this material gave 3-amino-4-{[2-(piperazin-1-yl)ethyl]amino}-pyridine which was used without further purification.

A solution of the 3-amino-4-{[2-(piperazin-1-yl)ethyl]amino}-pyridine in acetic anhydride was heated at reflux for 17 h. The reaction mixture was cooled to room temperature, and the acetic anhydride was quenched by slow addition of methanol. The reaction mixture was concentrated and the residue partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic phase was concentrated in vacuo. The crude acetylated intermediate was dissolved in 95% ethanol and treated with aqueous KOH for 70 h at reflux. The solution was evaporated to dryness, and the residual solids were triturated with CH_2Cl_2. The solvent was removed to give 1*H*-1-[2-(piperazin-1-yl)ethyl]-2-methylimidazo[4,5-*c*]pyridine as a brown gum. Data for **25c**: ^1H NMR (DMSO-d_6, 300 MHz) δ 8.79 (s, 1H), 8.29 (d, 1H, J = 6 Hz), 7.89 (s, 1H), 7.81 (br s, 1H), 7.73 (m, 3H), 7.59 (d, 1H, J = 6 Hz), 7.52 (d, 1H, J = 7 Hz), 7.30 (m, 2H), 4.32 (m, 2H), 3.58 (m, 2H), 3.03 (s, 6H), 2.69 (m, 2H), 2.61 (s, 3H), 2.61 (m, 2H), 2.56 (m, 2H), 2.43 (m, 2H); MS (DCI/NH_3) *m/e* 554 $(M + H)^+$.

1-(*N,N*-Dimethylcarbamoyl)-6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]-sulfonyl}indole Hydrochloride (29a). To a solution of 1-(*tert*-butoxycarbonyl)-6-(4-fluorophenyl)indole (2.00 g, 6.42 mmol), prepared from the treatment of 6-(4-fluorophenyl)indole with di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine, in THF (36 mL) was added *N*-bromosuccinimide (1.26 g, 7.08 mmol) in a single portion, and the clear-orange solution was stirred overnight at room temperature. The reaction mixture was diluted with ether and extracted with aqueous $NaHSO_3$ (1−2 M) and saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated to give a viscous, clear-yellow oil (2.58 g), which solidified on standing.

To a −70 °C solution of 1-(*tert*-butoxycarbonyl)-6-(4-fluorophenyl)-3-bromoindole (1.00 g, 2.56 mmol) in THF (6 mL) was added *tert*-butyllithium (1.7 M in pentane, 3.00 mL, 5.10 mmol). The reaction mixture was stirred for 15 min, and then SO_2 gas was bubbled into the solution for 5−10 min. The clear-orange solution was stirred for 2.5 h at −60 to −70 °C and then warmed to 0 °C over 4 h, during which time the excess SO_2 distilled off. Hexane (20 mL) was then added which resulted in formation of a heavy, clear-brown oil. The hexane was decanted and replaced with CH_2Cl_2 (5 mL). The resulting clear-orange solution was cooled in an ice bath, and *N*-chlorosuccinimide (0.53 g, 4.0 mmol) was added. The cold bath was removed, and the thick suspension was stirred for 75 min. The reaction mixture was diluted with CH_2Cl_2 and shaken with aqueous $NaHSO_3$ (1−2 M, 50 mL). The resulting emulsion was broken with brine, and the organic phase was again shaken with aqueous $NaHSO_3$, then extracted with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown foam (1.13 g). Chromatography on silica gel (20:1 then 10:1 hexanes/ethyl acetate) gave 1-(*tert*-butoxycarbonyl)-6-(4-fluorophenyl)indole-3-sulfonyl chloride (**26**) as a pale-yellow oil.

To a solution of **27** (76 mg, 0.35 mmol; see **15n** experimental for preparation of **27**) in THF (2 mL) were added triethylamine (70 μL, 0.50 mmol) and a solution of **26** (137 mg, 0.33 mmol) in THF (1.3 mL), and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was filtered and the filtrate concentrated and azeotroped with CH_2Cl_2 to give an orange foam (220 mg). Chromatography on silica gel (40:1 then 20:1 $CHCl_3$/methanol) gave 1-(*tert*-butoxycarbonyl)-6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]sulfonyl}indole (**28**) (141 mg) as a yellow foam.

Treatment of a solution in THF of **28** (124 mg, 0.21 mmol) with sodium methoxide (25% in methanol, 0.20 mL, 0.88 mmol) gave 6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]sulfonyl}indole (51 mg) which was obtained by recrystallization from ethyl acetate. Carbamoylation of this indole using the procedure from method A and chromatography on silica gel (40:1 then 20:1 $CHCl_3$/methanol) gave 6-(4-fluorophenyl)-3-{[4-(1*H*-2-methylimidazo[4,5-*c*]pyrid-1-yl)piperidin-1-yl]sulfonyl}indole-1-carboxylic acid dimethylamide (**29a**) (69 mg). The hydrochloride salt (52 mg) was prepared by treating a solution in ethyl acetate of the free base with 4 M HCl/dioxane solution followed by filtration: mp 135−145 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.01−2.11 (c, 2H), 2.38 (m, 2H), 2.68 (s, 3H), 2.70 (t, 2H, J = 11 Hz), 3.10 (s, 6H), 4.00 (d, 2H, J = 11 Hz), 4.64 (m, 1H), 7.33 [t, 2H, J(F-H_{ortho},H_{ortho}-H_{meta}) = 8.8 Hz], 7.66 (dd, 1H, J = 1.5, 8.4 Hz), 7.76 [dd, 2H, J(F−H_{meta},H_{ortho}-H_{meta}) = 5.5, 8.8 Hz], 7.90 (d, 1H, J = 1.1 Hz), 7.99 (d, 1H, J = 8.1 Hz), 8.22 (d, 1H, J = 6.6 Hz), 8.35 (s, 1H), 8.50 (d, 1H, J = 6.6 Hz), 9.32 (s, 1H); IR (microscope) 1155 (s), 1336 (m), 1355 (m), 1390 (s), 1477 (s), 1517 (s), 1700 (s), 2597 (br), 3401 (br) cm^{-1}; MS (DCI/NH_3) *m/e* 561 $(M + H)^+$ (free base). Anal. ($C_{29}H_{30}N_6O_3FSCl \cdot 1.75H_2O$) C, H, N.

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Supporting Information Available: Synthetic information and characterization data (NMR and MS) for all compounds in Tables 1−6 which do not appear in the Experimental Section (20 pages). Ordering information is given on any current masthead page.

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