Articles

Synthesis and Structure−Activity-Relationships of 1*H*-Imidazo[4,5-*c*]quinolines That Induce Interferon Production

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1*H*-Imidazo-[4,5-*c*]quinolines were prepared while investigating novel nucleoside analogues as potential antiviral agents. While these compounds showed no direct antiviral activity when tested in a number of cell culture systems, some demonstrated potent inhibition of virus lesion development in an intravaginal guinea pig herpes simplex virus-2 assay. We have determined that the in vivo antiviral activity can be attributed to the ability of these molecules to induce the production of cytokines, especially interferon (IFN), in this model. Subsequently, we found that the compounds also induce in vitro production of IFN in human peripheral blood mononuclear cells (hPBMCs). The in vitro results reported herein and the in vivo results reported previously led to the discovery of imiquimod, **26**, which was developed as a topical agent and has been approved for the treatment of genital warts, actinic keratosis, and superficial basal cell carcinoma.

Introduction

Since the discovery of interferon (IFN) in 1957[1] and its potential for the treatment of viral infections and cancer, there has been a search for small-molecule inducers of this cytokine. A number of compounds that induce IFN in mice have been identified, but few are active in human cells.[2] While working on potential antiherpes agents, we discovered a series of 1*H*-imidazo-[4,5-*c*]quinolines that induce IFN, as well as other cytokines, in mice, rats, guinea pigs, monkeys, and humans.[3,4]

At the initiation of this work it was known that (*S*)-2,3-dihydroxypropyladenine ((*S*)-DHPA) (Figure 1) exhibits weak antiviral activity in an in vitro herpes simplex virus-1 (HSV-1) assay with a minimum inhibitory concentration (MIC) of 10−20 μg/mL.[5] Our initial efforts targeted the synthesis of 3-deazaadenine analogues as potential antiviral agents. Our approach was to modify the adenine ring by preparing a 3-deazaadenine with a benzene ring fused across the 2 and 3 positions to give the 1*H*-imidazo[4,5-*c*]quinoline ring system (Figure 1). On the basis of the reported activity of (*S*)-DHPA, we had hoped that compound **1** would give similar results; however, it was found to be inactive. On the other hand, the methyl analogue **2** did exhibit weak in vitro antiviral activity and cytotoxicity at the same concentration (MIC = 5 mg/mL). Compound **2** was further evaluated in an in vivo intravaginal guinea pig HSV-2 infection model and was found to prevent lesion development. Additional analogues were synthesized and many continued to show in vivo anti-HSV-2 activity in the guinea pig model but did not exhibit in vitro activity against HSV-1.[6] These surprising results led to the discovery that the active compounds were potent inducers of IFN and other cytokines, thus explaining the in vivo activity. At this point, we abandoned the search for in vitro antiviral activity and instead focused on preparing compounds that induced IFN production in an in vitro assay using human peripheral blood mononuclear cells (hPBMCs).[7] Herein, we report on the initial synthetic efforts of this novel series of immune

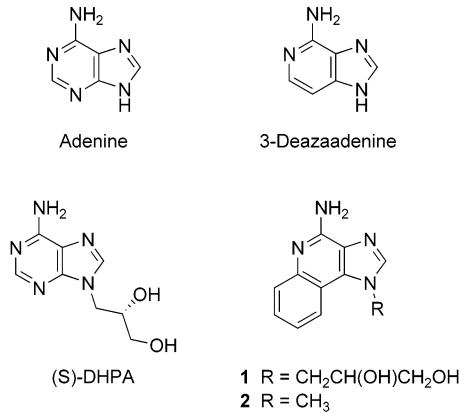

Figure 1.

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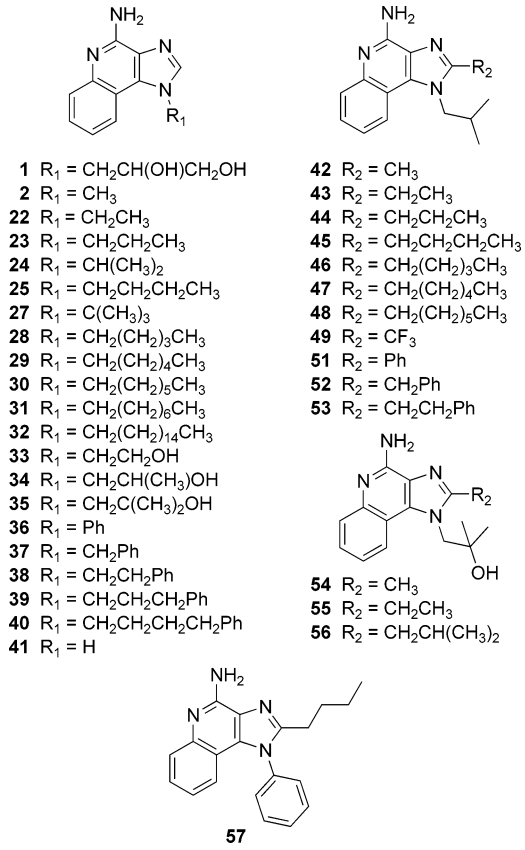


Figure 2.

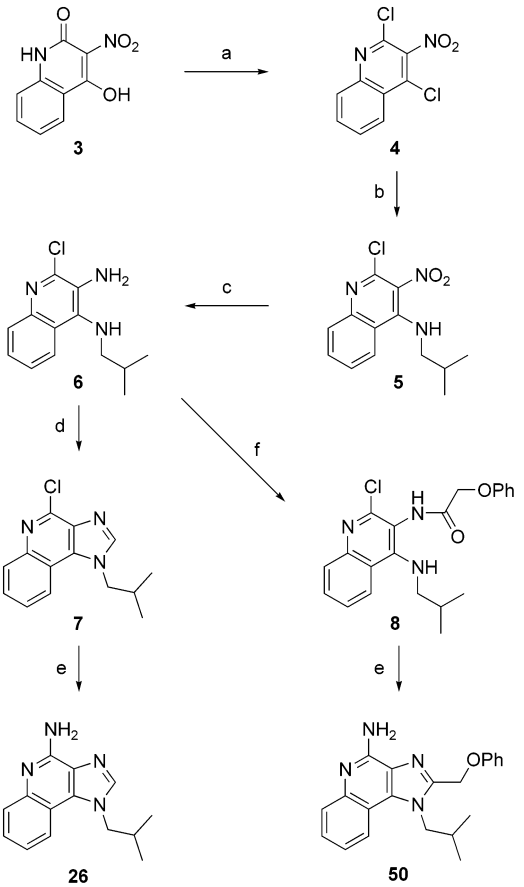
response modifiers and the structure−activity-relationships (SARs) that influence the induction of IFN.

Chemistry

The 1*H*-imidazo[4,5-*c*]quinolin-4-amines were synthesized using two main synthetic routes. Common features in both routes involve the displacement of a 4-chloroquinoline with primary amines and the condensation with acid chlorides or ortho esters to form the imidazole ring. While we show several methods to prepare 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, **26**, similar reaction conditions were utilized to prepare many of the other analogues in our SAR study (Figure 2).

The first route, Scheme 1, began with the chlorination of 4-hydroxy-3-nitro-1*H*-quinolin-2-one, **3**, employing a modification of the method of Gabriel,[8] using phosphorus oxychloride in toluene, with triethylamine as a base, to provide 2,4-dichloro-3-nitroquinoline, **4**. Alternatively, the chlorination can be accomplished using phenylphosphonic dichloride.[9] By careful control of the reaction temperature, the 4-chloro substituent was selectively displaced by a number of primary amines to give the corresponding nitroamines, as demonstrated by the reaction with isobutylamine to give **5**. Catalytic hydrogenation of **5** gave the corresponding diamine **6**. To form the imidazole, diamine **6** was treated with either triethyl orthoformate or diethoxymethyl acetate in refluxing toluene to generate **7**. Amination of the chloro analogue with methanolic ammonia at 150 °C gave 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, **26**. By a change of the primary amine in step b of this route, compounds **1**, **27**, and **33**−**35** (see Figure 2) were also prepared. The 1-H analogue, **41**, was prepared by the

Scheme 1[a]



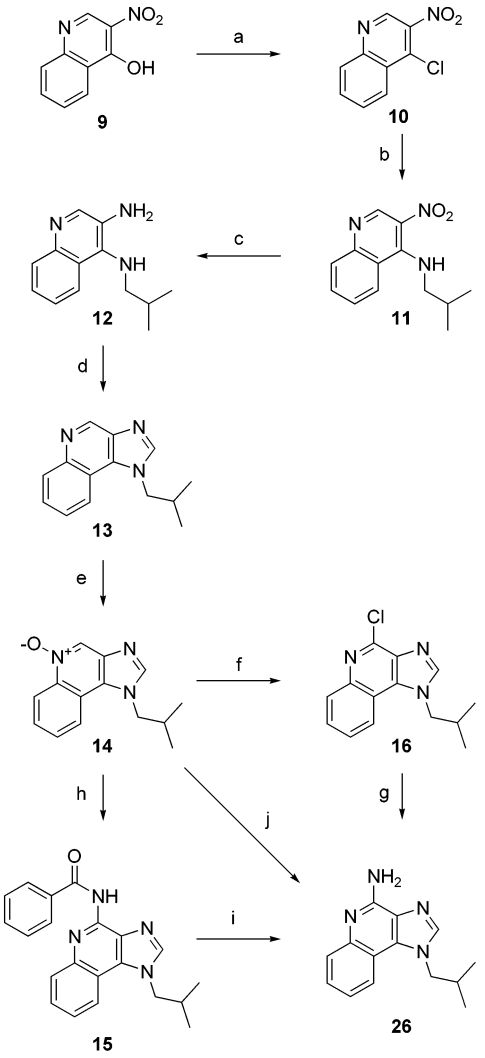
[a] Reagents and conditions: (a) $POCl_3$, toluene, Et_3N, heat or $PhPOCl_2$, heat; (b) isobutylamine, Et_3N, CH_2Cl_2, reflux; (c) 5% Pt/C, H_2, ethyl acetate; (d) $HC(OEt)_3$, toluene, reflux; (e) NH_3/MeOH, 150 °C; (f) $PhOCH_2COCl$, Et_3N, CH_3CN.

acid-induced cleavage of the corresponding 1-*tert*-butyl analogue, **27**, in refluxing 6 N HCl.

Diamine **6** could also be reacted with acid chlorides or ortho esters to give the intermediate amides as illustrated by the condensation with phenoxyactetyl chloride to give **8**. Treatment of **8** with methanolic ammonia at 150 °C resulted in the formation of the imidazole ring as well as the displacement of the 4-chloro substituent to give the corresponding C-2 substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine **50**. By use of the appropriate acid chlorides in step f of this sequence, analogues **45**, **55**, and **56** (see Figure 2) were also prepared to provide examples with substitution at the C-2 position.

A second route to 1*H*-imidazo[4,5-*c*]quinolines (Scheme 2) started with 3-nitro-4-quinolinol, **9**, which was chlorinated using either thionyl chloride and *N*,*N*-dimethylformamide in dichloromethane or phosphorus oxychloride in *N*,*N*-dimethylformamide to give **10**. The 4-chloro substituent was displaced with isobutylamine to give *N*-(2-methylpropyl)-3-nitroquinolin-4-amine (**11**), which was catalytically reduced to provide the diamine **12**. Heating a solution of **12** in diethoxymethyl acetate gave the imidazoquinoline **13**. The *N*-oxide **14** was prepared by oxidation with either peracetic acid or *m*-chloroperbenzoic acid. Reaction of the *N*-oxide with $POCl_3$ in dichloromethane gave the 4-chloro-1*H*-imidazo[4,5-*c*]quinoline analogue **16**, which was converted to **26** by treatment with NH_3 in methanol at 150 °C.

Scheme 2[a]

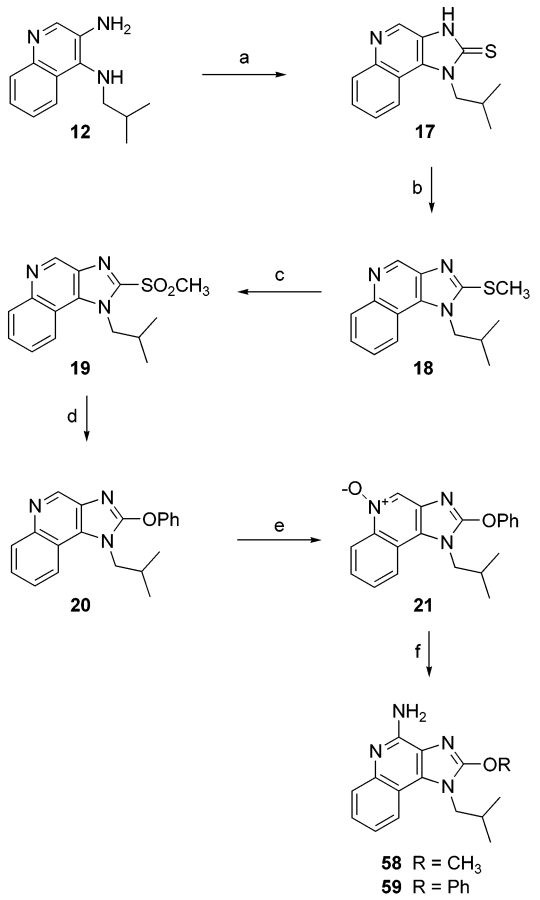


[a] Reagents and conditions: (a) $SOCl_2$, DMF, CH_2Cl_2, reflux or $POCl_3$, DMF, heat; (b) isobutylamine, CH_2Cl_2, reflux; (c) 5% Pt/C, H_2, ethyl acetate; (d) diethoxymethyl acetate, heat or $HC(OEt)_3$, toluene, reflux; (e) CH_3CO_3H, EtOH, heat; (f) $POCl_3$, CH_2Cl_2, reflux; (g) NH_3/MeOH, 150 °C; (h) benzoyl isocyanate, CH_2Cl_2, heat; (i) $NaOCH_3$, CH_3OH; (j) concentrated NH_4OH, CH_2Cl_2, tosyl chloride.

Compounds **2**, **22**, **24**, **25**, **28**−**32**, **36**−**38**, **48**, **51**−**53** (see Figure 2) were also prepared by this route by reacting the appropriate primary amines with **10** in step b and by using the appropriate acid chlorides or ortho esters for the formation of the imidazole ring in step d. In the case of the 2-trifluoromethyl analogue **49**, the imidazole ring was formed by refluxing the diamine in trifluoroacetic acid in step d.

Alternatively, *N*-oxide **14** was treated with benzoyl isocyanate in dichloromethane to provide the corresponding benzoyl derivative **15**. Subsequent saponification with sodium methoxide gave the free 4-amino analogue **26**. In addition, the *N*-oxides could be converted directly to the corresponding 4-amines in a single step using a modification of the Hamana and Hoshino procedure.[10] Compounds **23**, **39**, **40**, **42**−**44**, **46**, **47**, **54**, **57** (see Figure 2) were prepared from their corresponding *N*-oxides by dissolving in dichloromethane and treating sequentially with ammonium hydroxide and tosyl chloride.

Scheme 3[a]



[a] Reagents and conditions: (a) 1,1′-thiocarbonyldiimidazole, DMF, heat; (b) CH_3I, NaOMe, MeOH; (c) $KMnO_4$, acetic acid; (d) potassium phenoxide, DMF; (e) CH_3CO_3H, MeOAc; (f) concentrated NH_4OH, CH_2Cl_2, tosyl chloride.

A method to prepare 1*H*-imidazo[4,5-*c*]quinoline derivatives with heteroatoms directly attached to the C-2 position is described in Scheme 3. The reaction of N^4-(2-methylpropyl)quinoline-3,4-diamine, **12**, with 1,1′-thiocarbonyldiimidazole gave the thione **17**. Treatment of **17** with iodomethane provided the *S*-methylated product **18**. Oxidation to the methyl sulfone, **19**, was achieved with potassium permanganate in acetic acid. The methyl sulfone was readily displaced with nucleophiles, as exhibited by treatment with potassium phenoxide to give intermediate **20**. N-Oxidation of the quinoline nitrogen, followed by reaction with tosyl chloride in ammonium hydroxide/dichloromethane, provided the corresponding 4-amino derivative **59**. Compound **58** was prepared in a similar manner by using sodium methoxide as the nucleophile in step d.

The 4-chloro group of **7** was displaced by a variety of nucleophiles, as shown in Scheme 4, to give the corresponding 4-substituted 1*H*-imidazo[4,5-*c*]quinolines **60**−**62**. The preparation of the 4-hydroxy analogue, **63**, was achieved by acid hydrolysis of the chloro group.

Compounds with substitution on the benzene ring were also prepared. The following molecules, **64**, **67**, **70**, and **73**, were prepared with a single methyl group attached to the C-6, C-7, C-8, or C-9 position of the ring system (Figure 3). These compounds were synthesized from the appropriately substituted quinolines using the routes shown in Schemes 1 and 2. The C-6, C-7, and

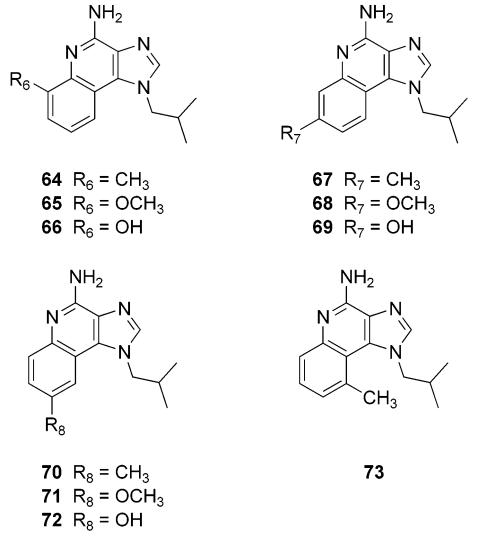
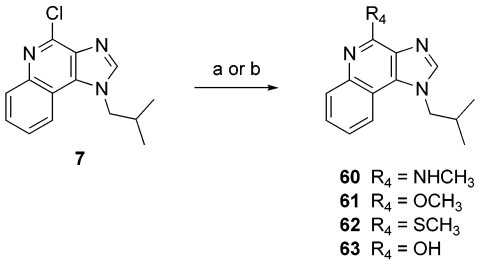


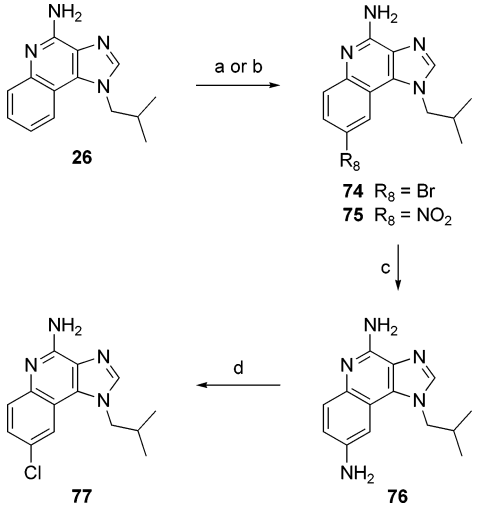
Figure 3.

Scheme 4[a]



[a] Reagents and conditions: for **60**−**62**, (a) nucleophile, solvent, heat; for **63**, (b) 6 N HCl, reflux.

Scheme 5[a]

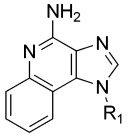


[a] Reagents and conditions: (a) Br_2, HOAc; or (b) HNO_3, H_2SO_4; (c) $SnCl_2$, HCl, EtOH, reflux; (d) $NaNO_2$, HCl, CuCl.

C-8 methoxy analogues, **65**, **68**, and **71**, were prepared in a similar manner. The hydroxyl-substituted derivatives, **66**, **69**, and **72**, were prepared by acid hydrolysis of the corresponding methoxy compounds.

The 1*H*-imidazo[4,5-*c*]quinolin-4-amines can also be modified by direct electrophilic substitution of the tricyclic ring system, as shown in Scheme 5. Bromination or nitration of **26** gave the corresponding 8-bromo (**74**) and 8-nitro (**75**) analogues, respectively.[11] Catalytic reduction of **75** gave the corresponding 8-amino analogue **76**. The 8-chloro derivative, **77**, was prepared from the amine via the Sandmeyer reaction.

Table 1. Effect of R_1 Substitution on IFN Induction



compd	R_1	MEC[a]
1	$CH_2CH(OH)CH_2OH$	5.0
2	CH_3	0.5
22	CH_2CH_3	0.5
23	$CH_2CH_2CH_3$	0.5
24	$CH(CH_3)_2$	0.5
25	$CH_2CH_2CH_2CH_3$	0.5
26	$CH_2CH(CH_3)_2$	0.5
27	$C(CH_3)_3$	NI
28	$CH_2(CH_2)_3CH_3$	0.5
29	$CH_2(CH_2)_4CH_3$	0.5
30	$CH_2(CH_2)_5CH_3$	0.5
31	$CH_2(CH_2)_6CH_3$	NI
32	$CH_2(CH_2)_{14}CH_3$	NI
33	CH_2CH_2OH	0.5
34	$CH_2CH(CH_3)OH$	0.5
35	$CH_2C(CH_3)_2OH$	0.5
36	Ph	NI
37	CH_2Ph	0.1
38	CH_2CH_2Ph	0.5
39	$CH_2CH_2CH_2Ph$	NI
40	$CH_2CH_2CH_2CH_2Ph$	0.1
41	H	0.5

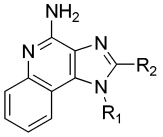
[a] Minimum effective concentration at which IFN induction was observed (μg/mL). NI = no induction of IFN at the highest concentration tested (5.0 μg/mL).

Results and Discussion

The assay used to measure IFN production has been previously described in detail.[7] Human peripheral blood mononuclear cells (hPBMCs) were cultured overnight with each test compound in RPMI medium containing 10% autologous serum at 37 °C. Culture supernatants were collected and analyzed for IFN-α by a virus cytopathic effect assay, using A549 human lung carcinoma cells and encephalomyelitis virus. The compounds were evaluated according to the minimum effective concentration (MEC) at which they induced IFN production. While we observed some variability among hPBMC donors in the amounts of IFN produced, there was generally good consistency in the MEC for a given compound.

The SAR of the 1*H*-imidazo[4,5-*c*]quinoline core with differing substituents at the N-1 position is shown in Table 1. Most compounds with alkyl substituents induce IFN at a similar concentration (0.5 μg/mL), the exceptions being the longer straight-chain analogues **31** and **32** that fail to induce IFN. A single branching substituent at the α position of the carbon backbone is tolerated as seen with N^1-isopropyl, **24**; however, when the substituent is the bulkier *tert*-butyl, **27**, no IFN induction is observed. When the alkyl chain contains hydroxyl substituents, most of the examples (**33**−**35**) also induce IFN production at 0.5 μg/mL, the exception being the dihydroxypropyl analogue **1**, which is weakly active. Direct attachment of a phenyl group at the N-1 position, **36**, gives an analogue that does not induce IFN; however, introduction of a phenyl group at the terminus of an alkyl chain (**37**, **38**, **40**) gives active IFN inducers

Table 2. Effect of R_2 Substitution on IFN Induction



compd	R_1	R_2	MEC[a]
26	$CH_2CH(CH_3)_2$	H	0.5
42	$CH_2CH(CH_3)_2$	CH_3	0.05
43	$CH_2CH(CH_3)_2$	CH_2CH_3	0.05
44	$CH_2CH(CH_3)_2$	$CH_2CH_2CH_3$	0.05
45	$CH_2CH(CH_3)_2$	$CH_2CH_2CH_2CH_3$	0.01
46	$CH_2CH(CH_3)_2$	$CH_2(CH_2)_3CH_3$	0.05
47	$CH_2CH(CH_3)_2$	$CH_2(CH_2)_4CH_3$	0.5
48	$CH_2CH(CH_3)_2$	$CH_2(CH_2)_5CH_3$	1.0
49	$CH_2CH(CH_3)_2$	CF_3	NI
50	$CH_2CH(CH_3)_2$	CH_2OPh	0.1
51	$CH_2CH(CH_3)_2$	Ph	NI
52	$CH_2CH(CH_3)_2$	CH_2Ph	0.05
53	$CH_2CH(CH_3)_2$	CH_2CH_2Ph	1.0
35	$CH_2C(CH_3)_2OH$	H	0.5
54	$CH_2C(CH_3)_2OH$	CH_3	0.05
55	$CH_2C(CH_3)_2OH$	CH_2CH_3	0.05
56	$CH_2C(CH_3)_2OH$	$CH_2CH(CH_3)_2$	0.01
57	Ph	$CH_2CH_2CH_2CH_3$	0.5
58	$CH_2CH(CH_3)_2$	OCH_3	NI
59	$CH_2CH(CH_3)_2$	OPh	NI

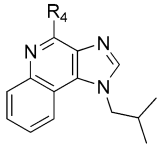
[a] Minimum effective concentration at which IFN induction was observed (μg/mL). NI = no induction of IFN at the highest concentration tested (5.0 μg/mL).

(MEC = 0.1−0.5 μg/mL). The exception to this trend in activity is the 3-phenylpropyl analogue **39**, which is surprisingly inactive in repeated assays. In addition, the unsubstituted derivative **41** is also an active IFN inducer (MEC = 0.5 μg/mL).

To investigate how substitution at other positions of the imidazoquinoline core influences IFN induction, we focused primarily on analogues of compound **26**. While the activity of **26** is similar to many of the compounds shown in Table 1, this molecule was effective in animal models and had progressed as a development candidate. During in vivo studies it was discovered that **26** is metabolized to the 1-(2-hydroxy-2-methylpropyl) derivative **35**,[12] which has similar potency in the hPBMC assay. Therefore, the SAR was further developed using 1-(2-methylpropyl) or 1-(2-hydroxy-2-methylpropyl) as the N-1 substituent.

To explore the effect that C-2 substituents have on IFN induction, we prepared a series of compounds with differing substitution at this position (Table 2). Compared to compound **26**, straight-chain alkyl substituents (C_{1-5}) increase the IFN induction activity by 10- to 50-fold (MEC = 0.01−0.05 μg/mL). Activity begins to decrease when the alkyl substituent is longer (C_{6-7}). While the methyl derivative **42** shows increased activity compared to the parent **26**, the trifluoromethyl substituent at C-2 (**49**) completely eliminates activity. Direct aryl substitution at C-2 (**51**) also abrogates IFN production. However, the phenoxymethyl and benzyl derivatives **50** and **52** show a 5- and 10-fold increase in activity, respectively, when compared to **26**. The phenethyl derivative **53** is 2-fold less active than **26**. The series with the 1-(2-hydroxy-2-methylpropyl) substitution at N-1 showed a similar trend in activity compared to the 1-(2-methylpropyl) series. Compounds **54**−**56** increase the IFN induction activity 10- to 50-fold when compared to **35**. In the case where the N-1 substituent is phenyl, the 2-H-analogue **36** is inactive. However, addition of a 2-butyl group (**57**) gives an active IFN inducer (MEC = 0.5 μg/mL). This clearly illustrates that simple alkyl substitution at the C-2 position is beneficial for IFN activity. On the other hand, having an oxygen atom directly attached to the C-2 position eliminates activity because both the 2-methoxy, **58**, and 2-phenoxy, **59**, derivatives fail to induce IFN.

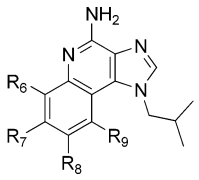
Table 3. Effect of R_4 Substitution on IFN Induction



compd	R_4	MEC[a]
7	Cl	NI
13	H	NI
15	NHC(O)Ph	NI
60	$NHCH_3$	NI
61	OCH_3	NI
62	SCH_3	NI
63	OH	NI
26	NH_2	0.5

[a] Minimum effective concentration at which IFN induction was observed (μg/mL). NI = no induction of IFN at the highest concentration tested (5.0 μg/mL).

Table 4. Effect of R_6, R_7, R_8, and R_9 Substitution on IFN Induction



compd	R_6	R_7	R_8	R_9	MEC[a]
26	H	H	H	H	0.5
64	CH_3	H	H	H	NI
65	OCH_3	H	H	H	NI
66	OH	H	H	H	1.0
67	H	CH_3	H	H	0.5
68	H	OCH_3	H	H	1.0
69	H	OH	H	H	0.5
70	H	H	CH_3	H	NI
71	H	H	OCH_3	H	NI
72	H	H	OH	H	NI
73	H	H	H	CH_3	NI
74	H	H	Br	H	NI
75	H	H	NO_2	H	NI
76	H	H	NH_2	H	NI
77	H	H	Cl	H	NI

[a] Minimum effective concentration at which IFN induction was observed (μg/mL). NI = no induction of IFN at the highest concentration tested (5.0 μg/mL).

The C-4 position of the 1*H*-imidazo[4,5-*c*]quinoline core is unique in that only a primary amino substituent leads to IFN induction (Table 3). Even monomethylation of the primary amino group, **60**, or replacement with a hydroxy group, **63**, completely eliminates the IFN inducing activity. All other C-4 substituents investigated fail to induce IFN production. From these results, it appears that having the unsubstituted 4-amino group is the most important aspect for IFN induction.

Substitution on the benzene ring gives analogues that either retain the IFN induction of the unsubstituted compound or decrease or eliminate the activity (Table 4). Substitution at the C-6 position eliminates activity (**64**, **65**), the exception being the hydroxyl-substituted

analogue **66** that is 2-fold less active than the parent. Substitution at the C-8 position (**70**−**72**, **74**−**77**) and the C-9 position (**73**) also eliminates IFN-inducing activity. However, compounds substituted at the C-7 position have IFN induction (**67**−**69**) comparable to that of the parent **26**.

As previously mentioned, compound **26** was chosen early in the development process as a small molecule with the potential to produce IFN in vivo. While other molecules, especially those with additional substitution at the C-2 position, are more active in the hPBMC assay, compound **26** had the right balance of activity and tolerability for the prevention of lesions caused by HSV-2 infection in the guinea pig model.[6] The observed in vivo antiviral activity is associated with the production of IFN in a cell-mediated immune response. Subsequent studies showed that compound **26** is also a potent inducer of IFN, as well as other cytokines, in a number of species including mice, rats, monkeys, and humans via topical, oral, or parenternal administration.[3b]

Conclusions

1*H*-Imidazo[4,5-*c*]quinolin-4-amines have been prepared and evaluated for the ability to induce IFN-α production in hPBMCs. Investigation of the N-1 substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines lacking substitution at C-2 reveals that most simple alkyl and hydroxyalkyl substituents are tolerated to give active IFN inducers. However, activity is not enhanced compared to the nonsubstituted compound **41**. When longer alkyl chains or bulkier alkyl substituents (i.e., *tert*-butyl) are attached to N-1, activity is eliminated at the concentrations tested. This is also the case when a phenyl group is directly attached to N-1. Straight-chain alkyl substitution at the C-2 position enhances IFN induction for the smaller chains, with butyl being the most active. When the chain length reaches heptyl, activity begins to decrease. Phenoxymethyl and benzyl groups at C-2 also increase activity. The C-2 substiuents that are not tolerated include trifluoromethyl, phenyl, and the methoxy and phenoxy derivatives. The amine at the C-4 position appears to be the most crucial requirement for activity. All other modifications at this position eliminate IFN production. In general, simple substitution on the benzene ring appears to be unfavorable because most of the compounds prepared fail to induce IFN. The exception is substitution at the C-7 position where the compounds retain the activity of the unsubstituted parent molecule.

In summary novel interferon inducers have been discovered. These studies have led to the development of imiquimod, **26**, for clinical use. It has been demonstrated that topical application of imiquimod in humans induces synthesis of IFN and other cytokines in skin at the application site.[3b] Clinical utility has been demonstrated in treating genital warts,[13] basal cell carcinoma,[14] and actinic keratosis.[15] Several related conditions are also reported to respond.[16] We are continuing to explore this novel series of immune response modifiers in an effort to find small molecules that treat diseases involving the immune system.[17]

Experimental Section

Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton resonance (^{1}H NMR) spectra were recorded on a Bruker 300 NMR spectrometer at 300 MHz. Chemical shifts are reported in δ relative to tetramethylsilane. Carbon, hydrogen, and nitrogen analyses were performed by Oneida Research Services, Whitesboro, NY; Robertson Microlit Laboratories, Madison, New Jersey; or 3M Analytical Services and were within ±0.4% of the theoretical values unless otherwise indicated. Solvents employed in developing thin-layer chromatography plates (TLC) are noted in parentheses. The structures of all compounds were consistent with their spectral data. Unless noted otherwise, the reported yields were not optimized.

2-Chloro-*N*-(2-methylpropyl)-3-nitroquinoline (5). Triethylamine (63.5 mL, 0.46 mol) was added in small portions to a well-stirred suspension of 4-hydroxy-3-nitro-1*H*-quinolin-2-one (**3**) (20.8 g, 100 mmol) in toluene (100 mL). Phosphorus oxychloride (15.7 mL, 168 mmol) was added dropwise to the stirred mixture over a 3−5 min period. The temperature of the reaction mixture was maintained below 55 °C during the addition. After the addition was complete, the reaction mixture was heated at 80−90 °C for 4 h, cooled to ambient temperature, diluted with dichloromethane (200 mL), and poured into water with stirring while maintaining the temperature below 60 °C. The resulting mixture was made basic with aqueous sodium hydroxide and stirred at ambient temperature for 2 h. The organic phase was separated from the mixture, washed thoroughly with water, and dried over magnesium sulfate. A solution of triethylamine (15.7 g, 155 mmol) and isobutylamine (8.8 g, 120 mmol) was added to the dried organic phase, and the solution was refluxed for 30 min. The reaction mixture was concentrated in vacuo to dryness. The residue was slurried in water, and the resulting solid was collected by vacuum filtration. The yellow solid was washed thoroughly with water and dried to yield 17.8 g (64%) of product that was pure enough for further use. Recrystallization from propyl acetate gave an analytically pure product as a bright-yellow solid: mp 85−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98−7.88 (m, 2 H), 7.75 (m, 1 H), 7.53 (m, 1 H), 6.19 (br s, 1 H), 3.38−3.30 (m, 2 H), 1.96 (m, 1 H), 1.04 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.69; H, 5.1; N, 14.9.

Alternative Chlorination Procedure Using Phenylphosphonic Dichloride: 2,4-Dichloro-8-methyl-3-nitroquinoline. A mixture of 4-hydroxy-8-methyl-3-nitroquinolin-2-(1*H*)-one[18] (11.0 g, 50 mmol) and phenylphosphonic dichloride (30 mL) was slowly heated to 140 °C with stirring. The temperature of the mixture was maintained between 135 and 140 °C for 3 h, and the mixture was poured into cold water (600 mL) with vigorous stirring. The syrupy mixture gradually solidified upon continued stirring. The solid was collected by vacuum filtration, washed with water, and dried to give 12.2 g (95%) of unpurified product as a tan solid. The solid was recrystallized from heptanes/dichloromethane to give 9.0 g (70%) of pure product as brownish crystals: mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J = 0.4, 8.4 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.68 (t, J = 7.8 Hz, 1 H), 2.79 (s, 3 H). Anal. Calcd for $C_{10}H_6Cl_2N_2O_2$: C, 46.72; H, 2.35; N, 10.90. Found: C, 46.81; H, 2.09; N, 10.61.

2-Chloro-*N*^{4}-(2-methylpropyl)quinoline-3,4-diamine (6). A mixture of **5** (7.5 g, 27 mmol), ethyl acetate (300 mL), magnesium sulfate (5.0 g), and 5% platinum on carbon (200 mg) was hydrogenated in a Parr apparatus at ∼50 psi initial pressure of hydrogen gas. When hydrogen uptake ceased, the solids were filtered from the mixture and the filtrate was concentrated in vacuo to yield 5.8 g of unpurified product. The unpurified solid was reprecipitated from dilute hydrochloric acid by the addition of concentrated ammonium hydroxide to give 4.8 g (71%) of colorless product that was pure enough for further use. Recrystallization of the unpurified solid from ethanol gave analytically pure product as colorless platelets: mp 145−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 1 H), 7.69 (m, 1 H), 7.46−7.35 (m, 2 H), 5.29 (t, J = 6.6 Hz, 1 H), 5.03 (s, 2 H), 3.11 (t, J = 6.7 Hz, 2 H), 1.77 (m, 1 H), 0.91 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{13}H_{16}ClN_3$: C, 62.52; H, 6.46; N, 16.83. Found: C, 62.54; H, 6.44; N, 16.75.

4-Chloro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (7). A mixture of **6** (3.2 g, 12.8 mmol), triethyl orthoformate (2.0 g, 13.2 mmol), and toluene was refluxed for 1.5 h while allowing the ethanol to be distilled from the solution. The volatiles were removed under vacuum to yield an oil that solidified upon cooling to ambient temperature. The solid was crushed in *tert*-butyl methyl ether, collected by vacuum filtration, and dried to yield 3.1 g (94%) of a solid that was judged to be homogeneous by TLC (47:3, dichloromethane/*tert*-butyl methyl ether). The product was recrystallized from 2-propanol to give 2.0 g (61%) of an analytically pure product as a cream-colored solid: mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, J = 1.5, 7.7 Hz, 1 H), 8.09 (dd, J = 1.2, 7.9 Hz, 1 H), 7.93 (s, 1 H), 7.70 (ddd, J = 1.5, 7.0, 8.5 Hz, 1 H), 7.64 (ddd, J = 1.4, 7.1, 8.4 Hz, 1 H), 4.36 (d, J = 7.4 Hz, 2 H), 2.36 (m, 1 H), 1.05 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{14}H_{14}ClN_3$: C, 64.74; H, 5.43; N, 16.18. Found: C, 64.47; H, 5.34; N, 16.16.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (26).[19] A mixture of **7** (3.0 g, 11.6 mmol) and 2 M methanolic ammonia (25 mL, 50 mmol) was placed in a glass tube and heated in a Parr pressure vessel at 150 °C for 7 h. The cooled mixture was reduced in volume in vacuo to remove ammonia and treated with potassium hydroxide (750 mg, 11.6 mmol) dissolved in methanol (10 mL). The mixture was stirred at ambient temperature for 1 h, and the resulting solid was collected by vacuum filtration. The solid was washed consecutively with methanol, water, and methanol and dried to yield 2.5 g (89%) of unpurified product as a colorless solid, which was homogeneous as judged by TLC (47:3, dichlormethane/*tert*-butyl methyl ether). The unpurified product was recrystallized from *N*,*N*-dimethylformamide to give 2.3 g (82%) of an analytically pure product as colorless crystals: mp 292−294 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.18 (s, 1 H), 8.00 (dd, J = 1.0, 8.1 Hz, 1 H), 7.62 (dd, J = 1.1, 8.3 Hz, 1 H), 7.44 (ddd, J = 1.3, 7.0, 8.3 Hz, 1 H), 7.27 (ddd, J = 1.3, 7.1, 8.2 Hz, 1 H), 6.58 (br s, 2 H), 4.40 (d, J = 7.4 Hz, 2 H), 2.18 (heptet, J = 6.7 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31. Found: C, 69.9; H, 6.6; N, 23.4.

1*H*-Imidazo[4,5-*c*]quinolin-4-amine (41).[20] A mixture of **27** (1.5 g, 6.2 mmol) and 6 N HCl (25 mL) was refluxed for 30 min. The mixture was cooled to ambient temperature. The solid that had precipitated was collected by vacuum filtration and slurried in an aqueous saturated sodium carbonate solution. The solid was collected by vacuum filtration, washed with water, and dried. The unpurified solid was recrystallized from ethanol to give 0.6 g (52%) of analytically pure product as a colorless solid: mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.35 (s, 1 H), 8.30 (dd, J = 1.2, 8.4 Hz, 1 H), 8.13 (dd, J = 0.9, 7.8 Hz, 1 H), 7.92 (s, 1 H), 7.73−7.62 (m, 2 H), 7.27 (s, 2 H). Anal. Calcd for $C_{10}H_8N_4$: C, 65.21; H, 4.37; N, 30.42. Found: C, 65.30; H, 4.4; N, 30.3.

1-(2-Methylpropyl)-2-phenoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (50). A solution of **6** (7.5 g, 300 mmol) in acetonitrile (100 mL) was cooled to 5−10 °C. Phenoxyacetyl chloride (5.3 g, 310 mmol) was added dropwise to the vigorously stirred solution. The solution turned yellow and exhibited a slight initial exotherm. The mixture was stirred at ambient temperature for 18 h. The solid that had formed was collected by vacuum filtration, washed with acetonitrile, and dried. The solid was suspended in 7% methanolic ammonia (100 mL), and the mixture was heated in a steel pressure vessel for 8 h at 150−160 °C. The resulting mixture was reduced in volume to remove ammonia and made strongly basic with 25% methanolic sodium methoxide. After the mixture was cooled to ambient temperature, the resulting solid was collected by vacuum filtration, washed successively with methanol and water, and dried to provide 9.3 g (89%) of the unpurified product as a fluffy, white solid that was judged to be homogeneous by TLC (ethyl acetate/methanol). Recrystallization from ethanol/water (90:10) gave an analytically pure sample: mp 195−197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 8.1 Hz, 1 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.44 (t, J = 8.1 Hz, 1 H), 7.36−7.24 (m, 6 H), 6.60 (br s, 2 H), 5.40 (s, 2 H), 4.47 (d, J = 7.8 Hz, 2 H), 2.26 (m, 1 H), 0.93 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.57; H, 6.58; N, 16.24.

3-Nitro-4-quinolinol (9). A mixture of 4-quinolinol (26.2 g, 180 mmol) in propionic acid (250 mL) was heated to 125 °C with stirring. Nitric acid (70%, 25.4 mL, 0.4 mol) was added dropwise to the stirred solution while maintaining the reaction mixture temperature at 125 ± 5 °C. The product began to precipitate before the addition of nitric acid was completed, and the reaction mixture became quite thick. When addition was complete, the mixture was stirred at 125 °C for 15 min and cooled to ambient temperature. The mixture was diluted with ethanol, and the solid was collected by vacuum filtration. The solid was washed successively with ethanol, water, and ethanol. The resulting light-yellow solid was heated in refluxing ethanol and filtered from the hot mixture to give 27.7 g (81%) of analytically pure product as a light-yellow solid: mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.99 (br s, 1 H), 9.19 (s, 1 H), 8.26 (dd, J = 0.9, 8.1 Hz, 1 H), 7.83−7.71 (m, 2 H), 7.52 (ddd, J = 0.9, 7.0, 8.1 Hz, 1 H). Anal. Calcd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.68; H, 3.0; N, 14.6.

***N*-(2-Methylpropyl)-3-nitroquinolin-4-amine (11).** Thionyl chloride (8.1 mL, 110 mmol) was added dropwise to a vigorously stirred suspension of pure and finely divided **9** (19.0 g, 100 mmol), as prepared by the method described above, in dichloromethane (200 mL) and *N*,*N*-dimethylformamide (8.5 mL, 110 mmol). The addition resulted in an exotherm. After the addition of thionyl chloride was completed, the mixture was heated at reflux for 3 h to form intermediate **10**. The mixture was cooled to −15 °C, and a solution of isobutylamine (15.1 mL, 152 mmol) and triethylamine (20.9 mL, 150 mmol) was added to the cold mixture with vigorous stirring. The temperature of the mixture rose to ∼20 °C, and the color changed to yellow. The yellow mixture was refluxed for 15 min, and the volatiles were removed in vacuo. The resulting bright-yellow residue was slurried in water. The solid was collected by vacuum filtration, washed with water, partially dried, and slurried in 75 mL of ethanol. The solid was collected by vacuum filtration, washed with a minimum amount of ethanol, and dried to provide 22.6 g (92%) of product as a bright-yellow solid. Recrystallization from ethyl acetate/hexanes gave an analytically pure sample as a bright-yellow solid: mp 119−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (br s, 1 H), 9.35 (s, 1 H), 8.30 (dd, J = 0.7, 8.5 Hz, 1 H), 7.97 (dd, J = 1.1, 8.3 Hz, 1 H), 7.78 (m, 1 H), 7.49 (m, 1 H), 3.79 (dd, J = 6.5 Hz, 2 H), 2.05 (m, 1 H), 1.10 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.7; H, 6.2; N, 17.1.

Alternative Preparation for *N*-(2-Methylpropyl)-3-nitroquinolin-4-amine (11). Phosphorus oxychloride (9.9 g, 65 mmol) was added in a slow stream to a well-stirred suspension of **9** (10.0 g, 53 mmol) in *N*,*N*-dimethylformamide (75 mL). The internal temperature of the reaction mixture rose to 35 °C during the addition. The reaction mixture was further heated to 50 °C with stirring for 30 min. The resulting solution was cooled to ambient temperature and poured into an ice/water mixture (300 mL). A solid (**10**) was collected by vacuum filtration, washed thoroughly with water, and pressed dry. The moist product was added to a solution of isobutylamine (7.0 mL, 70 mmol) and triethylamine (14.0 mL, 100 mmol) in ethanol (200 mL). The mixture was refluxed for 15 min and then diluted with water to precipitate the unpurified product, which was collected by vacuum filtration and washed with water. The unpurified solid was dissolved in dilute hydrochloric acid (200 mL). A small amount of insoluble material was removed by filtration, and the product was reprecipitated by the addition of concentrated ammonium hydroxide. The solid was collected by vacuum filtration, washed thoroughly with water, and dried to give 11.0 g (85%) of product as a bright-yellow solid. The product was identical to the previously prepared material as judged by melting point and NMR analysis.

***N*⁴-(2-Methylpropyl)quinoline-3,4-diamine (12).** A suspension of **11** (24.5 g, 100 mmol), 5% platinum on carbon (~500 mg), and magnesium sulfate (15 g) in ethyl acetate (350 mL) was hydrogenated on a Parr apparatus with an initial pressure of ~53 psi of hydrogen gas. When uptake of hydrogen ceased, the solids were collected by vacuum filtration and the filtrate was concentrated in vacuo to a volume of ~75 mL. The solution was diluted with an equal volume of hexanes, and a crystalline solid formed. The solid was collected by filtration, washed with 1:1 ethyl acetate/hexanes, and dried to give 11.0 g (51%) of a pale-yellow solid. A second, darker crop of 6.1 g (28%) was obtained by repeating the procedure. Recrystallization of the first crop from *tert*-butyl methyl ether gave analytically pure product as colorless crystals (Note: For general synthetic use, the unpurified diamines were often employed in the subsequent reaction without further purification.) Mp 97−99 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1 H), 8.01 (m, 1 H), 7.73 (m, 1 H), 7.39−7.30 (m, 2 H), 4.97 (s, 2 H), 4.86 (t, J = 6.8 Hz, 1 H), 3.03 (t, J = 6.8 Hz, 2 H), 1.77 (m, 1 H), 0.90 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.67; H, 8.0; N, 19.5.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (13). A mixture of **12** (21.5 g, 100 mmol) and diethoxymethyl acetate (30 mL, 0.18 mol) was heated on a steam bath for 1 h. The solution was diluted with water (30 mL) and acidified with 6 N aqueous HCl. The aqueous mixture was heated on a steam bath for 15 min. The resulting solution was cooled to ambient temperature and made strongly basic with 50% aqueous NaOH to provide an oily liquid that was extracted into dichloromethane. The combined extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The oily material solidified upon cooling to yield 20.3 g (90%) of unpurified product as a tan solid that was judged to be homogeneous by TLC. This material was sufficiently pure for use in the next step. Recrystallization from ether provided an analytically pure sample as a pale-yellow solid: mp 92−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1 H), 8.30 (dd, J = 1.4, 8.4 Hz, 1 H), 8.10 (dd, J = 0.9, 7.9 Hz, 1 H), 7.90 (s, 1 H), 7.76−7.60 (m, 2 H), 4.37 (d, J = 7.4 Hz, 2 H), 2.36 (m, 1 H), 1.05 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.96; H, 6.74; N, 18.71.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline 5*N*-oxide (14). A solution of **13** (9.0 g, 40 mmol) was dissolved in ethanol (100 mL) containing peracetic acid (32% active oxygen, 11.4 g, 48 mmol). The solution was heated at 60 °C (internal temperature) for 2.5 h, and the reaction mixture was concentrated in vacuo. The residue was azeotroped with heptanes (3 × 100 mL) to remove acetic acid. The resulting solid was dissolved in water and made slightly basic with dilute aqueous NaOH to precipitate the *N*-oxide. The solid was collected by vacuum filtration, washed with water, and air-dried to give 9.8 g of unpurified product. The hydrated solid was suspended in 150 mL of toluene, and the resulting mixture was refluxed, while stirring, to remove the water of hydration. When water evolution ceased, the solid was collected by vacuum filtration, washed with toluene, and dried to provide 7.8 g (81%) of product as yellow crystals. Recrystallization from methanol/ether provided an analytically pure sample as yellow crystals: mp 211−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1 H), 8.85 (d, J = 8.4 Hz, 1 H), 8.47 (s, 1 H), 8.37 (d, J = 8.1 Hz, 1 H), 7.98−7.77 (m, 2 H), 4.51 (d, J = 7.4 Hz, 2 H), 2.18 (m, 1 H), 0.94 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.80; H, 6.3; H, 17.4.

4-Chloro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (16). A solution of **14** (3.6 g, 14.9 mmol) was dissolved in dichloromethane (10 mL), and phosphorus oxychloride (2.5 g, 16.3 mmol) was added to the stirred solution in a slow stream. A spontaneous exotherm was observed. The resulting solution was refluxed for 15 min, diluted with 100 mL of dichloromethane, and poured into ice/water (100 mL) containing excess concentrated ammonium hydroxide. The mixture was stirred at ambient temperature for 4 h. The organic phase was separated from the mixture, dried over magnesium sulfate, and concentrated in vacuo to yield 2.9 g (74%) of a tan powder that was pure enough for further reactions. The unpurified product was recrystallized from 2-propanol to yield 1.9 g (49%) of cream-colored crystals: mp 135−137 °C. The product was judged to be homogeneous by TLC and was identical to the product prepared by the previous route (see example **7** above).

***N*-Benzoyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (15).** A solution of **14** (7.3 g, 30 mmol) dissolved in dichloromethane (250 mL) was treated with benzoyl isocyanate (90%, 5.0 g, 30 mmol) at ambient temperature. The reaction mixture became exothermic and was refluxed briefly. The resulting warm solution was refluxed for 15 min and diluted with hexanes until the hot solution became cloudy. Upon standing, a crystalline solid began to form, and further cooling to ambient temperature completed the precipitation of product. The solid was collected by vacuum filtration, washed with hexanes, and dried to give 8.1 g of a colorless crystalline product. A second crop was obtained from the filtrate to give a combined yield of 9.5 g (92%). Recrystallization of the unpurified product from ethanol provided colorless crystals: mp 193−196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (s, 1 H), 8.35 (s, 1 H), 8.35 (m, 1 H), 8.14−8.02 (m, 3 H), 7.76−7.51 (m, 5 H), 4.53 (d, J = 7.4 Hz, 2 H), 2.23 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.29; H, 5.8; N, 16.3.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (26). A solution of **15** (5.0 g, 14.5 mmol) in methanol (50 mL) was treated with 10 drops of 25% sodium methoxide in methanol. The solution was refluxed for 2 h during which time a solid precipitated from the solution. The mixture was cooled to ambient temperature and filtered. The resulting solid was washed successively with water and methanol and dried. The unpurified material (3.3 g, 95%) was judged to be homogeneous by TLC and was identical to the same product prepared by the two previously described methods.

Direct Conversion of *N*-Oxide (14) to 1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (26). To a solution of **14** (3.1 g, 12.9 mmol) in dichloromethane (30 mL) was added concentrated ammonium hydroxide (10 mL). *p*-Toluenesulfonyl chloride (2.5 g, 13 mmol), dissolved in dichloromethane (10 mL), was added dropwise to the vigorously stirred solution at ambient temperature over a period of 10 min. A spontaneous exotherm was observed, and a solid precipitated from the solution during addition. When the addition was complete, the mixture was stirred at ambient temperature for 15 min. The solid was collected by vacuum filtration, washed with dichloromethane and water, and pressed partially dry. The moist solid was slurried with methanol, collected by vacuum filtration, and dried to yield a cream-colored solid. The solid was suspended in 50 mL of methanol and refluxed for 5 min, and the solid was collected by vacuum filtration. The resulting colorless solid was recrystallized from *N*,*N*-dimethylformamide (60 mL) to yield 2.2 g (71%) of analytically pure product: mp 292−294 °C. The product was identical to the sample prepared by the previously described method.

2-Methanethio-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]-quinoline (18). To a solution of **12** (12.5 g, 58 mmol) in *N*,*N*-dimethylformamide was added 1,1′-thiocarbonyldiimidazole (90%, 12.7 g, 64 mmol). The resulting mixture was stirred and heated on a steam bath for 30 min. During this time all of the solid dissolved and a new solid began to precipitate from the solution. After the mixture was cooled to ambient temperature, the resulting solid was collected by vacuum filtration, washed with acetone, and dried to provide 13.2 g (88%) of unpurified **17** as a pale-yellow, crystalline solid. Unpurified **17** (18.0 g, 70 mmol), from several sources, was dissolved in a solution of 25% sodium methoxide in methanol (21.6 g, 100 mmol) and methanol (100 mL). To the solution was added methyl iodide (14.2 g, 100 mmol). The resulting solution was maintained at ambient temperature for 18−20 h. The solution was acidified with acetic acid and concentrated in vacuo. The resulting residue was slurried in water to give an oily suspension that was extracted with ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate, filtered,

and concentrated in vacuo to yield 17.7 g of unpurified product as a tan solid. Recrystallization from *tert*-butyl methyl ether gave 10.4 g (55%) of analytically pure product as tan crystals: mp 108−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1 H), 8.25 (dd, J = 1.6, 8.4 Hz, 1 H), 8.09 (dd, J = 1.1, 7.9 Hz, 1 H), 7.63 (m, 2 H), 4.29 (d, J = 7.6 Hz, 2 H), 2.85 (s, 3 H), 2.40 (m, 1 H), 1.04 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 65.83; H, 6.26; N. 15.25.

2-Methanesulfonyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (19). A solution of $KMnO_4$ (1.0 g, 6.3 mmol) in H_2O (35 mL) was added dropwise to a stirred solution of **18** (1.0 g, 3.7 mmol) in glacial acetic acid (15 mL) at ambient temperature. A slight exotherm was observed, and the mixture turned dark-brown. After the mixture was stirred at ambient temperature for 3 h, TLC analysis (10% methanol/ethyl acetate) showed no remaining starting material. To the dark mixture was added solid $NaHSO_3$ until the mixture was decolorized. The mixture was diluted with water, and the product was extracted into dichloromethane. The combined extracts were washed successively with water and saturated aqueous $NaHCO_3$, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 0.9 g (80%) of unpurified product as a colorless solid. Recrystallization from ether gave an analytically pure sample of **19** as a colorless solid: mp 134−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1 H), 8.33 (dd, J = 1.2, 8.4 Hz, 1 H), 8.21 (dd, J = 0.8, 8.1 Hz, 1 H), 7.79 (ddd, J = 1.4, 7.1, 8.3 Hz, 1 H), 7.72 (ddd, J = 1.5, 7.0, 8.3 Hz, 1 H), 4.85 (d, J = 7.7 Hz, 2 H), 3.63 (s, 3 H), 2.51 (m, 1 H), 1.05 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.39; H, 5.65; N, 13.85. Found: C, 59.26; H, 5.57; N, 13.73.

1-(2-Methylpropyl)-2-phenoxy-1*H*-imidazo[4,5-*c*]quinoline (20). A solution of **19** (3.0 g, 9.9 mmol) and potassium phenoxide (1.6 g, 12 mmol) in *N*,*N*-dimethylformamide (50 mL) was refluxed for 1 h. The solution was cooled to ambient temperature and diluted with a large volume of water to precipitate the product. The solid was collected by filtration, washed with water, and dried to yield 2.3 g (73%) of unpurified product that was recrystallized from ether to yield an analytically pure sample as a colorless solid: mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 8.24 (dd, J = 2.2, 7.4 Hz, 1 H), 8.10 (dd, J = 2.2, 7.4 Hz, 1 H), 7.69−7.59 (m, 4 H), 7.51−7.39 (m, 2 H), 7.31 (m, 1 H), 4.41 (d, J = 7.6 Hz, 2 H), 2.46 (m, 1 H), 1.12 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.40; H, 6.04; N, 13.16.

1-(2-Methylpropyl)-2-phenoxy-1*H*-imidazo[4,5-*c*]quinolin-4-amine (59). A solution of **20** (1.2 g, 3.8 mmol) in methyl acetate (15 mL) was refluxed with peracetic acid (32% active oxygen, 1.1 g, 4.5 mmol) for 1 h. Additional peracetic acid (330 mg, 1.4 mmol) was added, and heating was continued for an additional 4 h. The mixture stood at ambient temperature overnight. The resulting solid was collected by vacuum filtration to give 1.2 g (95%) of unpurified **21** as a white powder. The unpurified *N*-oxide (1.2 g, 3.6 mmol) and concentrated NH_4OH (10 mL) were added to dichloromethane (20 mL), and the mixture was stirred vigorously at ambient temperature. *p*-Toluenesulfonyl chloride (0.76 g, 4.0 mmol) dissolved in dichloromethane (10 mL) was added dropwise to the vigorously stirred mixture at ambient temperature. An exotherm was observed, and the mixture turned yellow. The mixture was stirred at ambient temperature for 4 h and diluted with dichloromethane (50 mL). The organic phase was separated, washed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 1.1 g (92%) of the unpurified product that was recrystallized from toluene to give 0.9 g (75%) of product. A second recrystallization from methanol provided analytically pure material as pale-yellow crystals: mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 1.0, 8.2 Hz, 1 H), 7.81 (dd, J = 0.9, 8.4 Hz, 1 H), 7.53−7.21 (m, 7 H), 5.27 (br s, 2 H), 4.31 (d, J = 7.6 Hz, 2 H), 2.40 (m, 1 H), 1.07 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.85. Found: C, 72.45; H, 6.10; N, 16.90.

4-Methoxy-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (61). To a solution of **7** (2.1 g, 8.1 mmol) in methanol (50 mL) was added 25% methanolic sodium methoxide (11.5 g, 53.2 mmol), and the solution was refluxed for 4 h. The solution was then concentrated in vacuo, and the residue was mixed with water. The oily residue solidified rapidly and was collected by vacuum filtration, washed with water, and partially dried. The solid was dissolved in ether, dried over magnesium sulfate, and filtered. The resulting ether solution was diluted with hexanes, and the total volume was reduced under vacuum until crystallization was initiated. After standing at ambient temperature for 15−30 min, the solid was collected by vacuum filtration, washed with hexanes, and dried to give 1.4 g (68%) of product as a light-yellow solid: mp 111−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.97 (m, 2 H), 7.81 (s, 1 H), 7.59 (t, J = 8.4 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 1 H), 4.31 (d, J = 7.4 Hz, 2 H), 4.26 (s, 3 H), 2.35 (m, 1 H), 1.03 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.37; H, 6.89; N, 16.51.

1,5-Dihydro-1-(2-methylpropyl)-4*H*-imidazo[4,5-*c*]quinolin-4-one (63). A solution of **7** (20.0 g, 77.0 mmol) in 6 N HCl (200 mL) was refluxed for 1 h and cooled to ambient temperature. A small amount of dark, gummy material separated and was removed by vacuum filtration. The filtrate was diluted with water (500 mL) and made basic with concentrated aqueous NH_4OH to precipitate the product. The solid was collected by vacuum filtration, washed successively with water, ethanol, and ethyl acetate, and dried to give 16.0 g of unpurified product as an off-white solid. Recrystallization from methanol gave 13.3 g (72%) of analytically pure product: mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1 H), 8.13 (s, 1 H), 7.96 (d, J = 8.1 Hz, 1 H), 7.51−7.43 (m, 2 H), 7.29 (m, 1 H), 4.38 (d, J = 7.5 Hz, 2 H), 2.13 (m, 1 H), 0.91 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.70; H, 6.2; N, 17.4.

4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-8-ol (72). A mixture of **71** (3.8 g, 14.1 mmol) and 48% hydrobromic acid (50 mL) was refluxed for approximately 18 h. The cooled solution was diluted with water and neutralized with concentrated ammonium hydroxide. The precipitated product was collected by vacuum filtration, washed with water, and dried. The solid was dissolved in dilute aqueous hydrochloric acid, and the resulting solution was treated with charcoal and filtered through a filter aid pad. The filtrate was treated with saturated aqueous sodium bicarbonate to precipitate a solid that was collected by vacuum filtration. The solid was washed thoroughly with water and dried to yield 3.1 g (85%) of product as a colorless solid: mp 202−205 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.48 (br s, 1 H), 8.03 (s, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 6.96 (s, 1 H), 6.80 (d, J = 8.8 Hz, 1 H), 6.43 (s, 2 H), 4.31 (d, J = 7.4 Hz, 2 H), 2.15 (m, 1 H), 0.91 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{16}N_4O \cdot 1.3H_2O$: C, 60.11; H, 6.70; N, 20.03. Found: C, 59.82; H, 6.72; N, 20.03.

8-Bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (74). Bromine (10.0 g, 62.4 mmol) was added in a slow stream to a suspension of **26** (10.0 g, 41.6 mmol) in acetic acid at ambient temperature, and the mixture was stirred for 18 h. The resulting solid was collected by vacuum filtration, pressed partially dry, and then suspended in a saturated aqueous sodium bisulfite solution. The mixture was made strongly basic with aqueous sodium hydroxide. The resulting colorless solid was collected by vacuum filtration, washed thoroughly with water, and dried. The solid was added to methanol, and the mixture was stirred at ambient temperature for 18−24 h and collected by vacuum filtration. The solid was recrystallized from *N*,*N*-dimethylformamide to give 3.5 g (26%) of analytically pure product: mp 221−223 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1 H), 8.06 (s, 1 H), 7.56 (s, 1 H), 7.55 (s, 1 H), 6.81 (br s, 2 H), 4.41 (d, J = 7.3 Hz, 2 H), 2.07−2.21 (m, 1 H), 0.94 (d, J = 6.7 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}BrN_4$: C, 52.68; H, 4.74; N, 17.55. Found: C, 52.78; H, 4.73; N, 18.08.

1-(2-Methylpropyl)-8-nitro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (75). A solution of **26** (24.0 g, 0.1 mol) in sulfuric acid (150 mL) was prepared by gradual addition of **26** to the sulfuric acid at 35 °C or less. To the solution was added

dropwise 70% nitric acid (10.0 g, 0.11 mol), dissolved in 20 mL of sulfuric acid, with vigorous stirring at 25−30 °C over a period of 15 min. The solution was stirred at ambient temperature for 30 min and poured over ice with stirring. The ice mixture was made basic with a 50% aqueous sodium hydroxide solution while maintaining the temperature at less than 45 °C by the addition of ice. The yellow mixture was stirred at ambient temperature for 1 h, and the solid was collected by vacuum filtration. The yellow solid was washed successively with hot water, methanol, and acetone. The semidry solid was suspended in *N*,*N*-dimethylformamide (400 mL), and the mixture was heated to ∼100 °C and cooled slowly to ambient temperature. The resulting solid was collected by vacuum filtration, washed successively with *N*,*N*-dimethylformamide, methanol, and acetone and dried to yield 22.2 g (78%) of unpurified product as a bright-yellow solid. A 2.5 g sample of the unpurified product was recrystallized from *N*,*N*-dimethylformamide to yield 2.4 g (96% recovery) of analytically pure product as bright-yellow platelets: mp >250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.81 (d, J = 2.5 Hz, 1 H), 8.34 (s, 1 H), 8.22 (dd, J = 2.5, 9.2 Hz, 1 H), 7.68 (d, J = 9.2 Hz, 1 H), 7.45 (br s, 2 H), 4.47 (d, J = 7.2 Hz, 2 H), 2.24 (m, 1 H), 0.99 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.88; H, 5.14; N, 24.73.

1-(2-Methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline-4,8-diamine (76). To a well-stirred mixture of **75** (17.1 g, 0.06 mol) in ethanol (500 mL) was added concentrated hydrochloric acid (100 mL). Stannous chloride (45.1 g, 0.23 mol), dissolved in water (70 mL), was added to the stirred mixture. The mixture was heated at reflux for 1 h, and an additional 7.7 g (0.04 mol) of stannous chloride was added to the hot mixture. Heating was continued for an additional 30 min, and the mixture was concentrated in vacuo to a thick paste. The residue was dissolved in water (500 mL), and a colorless solid precipitated as the solution was made strongly basic with 50% aqueous sodium hydroxide. After the mixture was stirred for 30 min, the solid was collected by vacuum filtration, washed with hot water and methanol, and pressed partially dry. The moist solid was dissolved in dilute hydrochloric acid (1 L), and the product was reprecipitated by the addition of excess aqueous sodium hydroxide. The solid was collected by vacuum filtration, washed successively with hot water, ethanol, and acetone, and dried to yield 13.6 g (89%) of unpurified product as a white powder. This material was pure enough for further use. Recrystallization of 4.0 g of the solid from methanol/dichloromethane gave 2.2 g of analytically pure product as a light-tan solid: mp 277−282 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1 H), 7.36 (d, J = 8.8 Hz, 1 H), 7.12 (d, J = 2.3 Hz, 1 H), 6.84 (dd, J = 2.3, 8.8 Hz, 1 H), 5.99 (s, 2 H), 5.05 (s, 2 H), 4.29 (d, J = 7.4, 2 H), 2.16 (m, 1 H), 0.93 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.59; H, 6.78; N, 27.54.

8-Chloro-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (77). Copper(I) chloride was freshly prepared by the following procedure: sodium chloride (366 mg, 6.25 mmol) was added to a solution of copper(II) sulfate pentahydrate (1.49 g, 6.00 mmol) in water (5 mL). The blue solution was cooled to 0 °C and treated with a solution of sodium bisulfite (624 mg, 6.00 mmol) dissolved in 4 mL of water. After the mixture was stirred for 10 min, the blue color had disappeared and copper(I) chloride had precipitated as a white solid. The aqueous portion was decanted, and the remaining white solid was washed with three small portions of water. The solid was then dissolved in 7.5 mL of concentrated hydrochloric acid, and the solution was set aside at 0 °C. In a separate flask, compound **76** (1.13 g, 4.43 mmol) was dissolved in 42 mL of 2.0 M HCl and cooled to −5 °C. The stirred solution was treated by the dropwise addition of sodium nitrite (336 mg, 4.87 mmol), which was dissolved in 4 mL of water, over a 15 min period. The resulting yellow suspension was then slowly added to the stirred copper(I) chloride solution at 0 °C. Rapid foaming was observed. After addition was complete, the reaction mixture was allowed to warm to ambient temperature and was then heated to reflux for 90 min. The reaction mixture was then cooled to 0 °C and made basic by the addition of concentrated ammonium hydroxide to give a rust-colored solid. The solid was removed by filtration and treated with hot chloroform (100 mL). The hot solution was filtered to remove solids, and the filtrate was concentrated to give 1.05 g of an orange solid. The solid was dissolved in a minimum amount of chloroform and applied to column of silica gel (3 cm × 10 cm). Elution with chloroform followed by 2% ethanol in chloroform gave 0.55 g of the desired product (43%) as a yellow powder. Recrystallization from propyl acetate provided 0.35 g (27%) of analytically pure product as yellow crystals: mp 222−225 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.23 (s, 1 H), 7.93 (d, J = 2.3 Hz, 1 H), 7.61 (d, J = 8.9 Hz, 1 H), 7.45 (dd, J = 2.3, 8.9 Hz, 1 H), 6.75 (s, 2 H), 4.41 (d, J = 7.3 Hz, 2 H), 2.14 (m, 1 H), 0.93 (d, J = 6.6 Hz, 6 H). Anal. Calcd for $C_{14}H_{15}ClN_4$: C, 61.20; H, 5.50; N, 20.39. Found: C, 60.99; H, 5.68; N, 20.48.

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Supporting Information Available: Synthetic routes to and characterization of compounds **1**, **2**, **22**−**25**, **27**−**40**, **42**−**49**, **51**−**58**, **60**, **62**, **64**−**71**, and **73**. This material is available free of charge via the Internet at http://pubs.acs.org.

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