Discovery and Optimization of a Series of Carbazole Ureas as NPY5 Antagonists for the Treatment of Obesity

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Received December 17, 2001

The hypothesis that antagonists of the neuropeptide Y5 receptor would provide safe and effective appetite suppressants for the treatment of obesity has prompted vigorous research to identify suitable compounds. We discovered a series of acylated aminocarbazole derivatives (e.g., **3a**) that are potent and selective Y5 antagonists, representing interesting starting points but suffering from poor bioavailability and concerns about potential toxicity as a consequence of the embedded aminocarbazole fragment. It proved relatively easy to improve the drug metabolism and pharmacokinetic (DMPK) properties by variation of the side chain (as in **4a**) but difficult to eliminate the aminocarbazole fragment. For compounds in this series to have the potential to be drugs, we believed that both the compound itself and the component aniline must be free of mutagenic activity. Parallel structure−activity relationship studies looking at the effects of ring substitution have proved that it is possible by incorporation of a 4-methyl substituent to produce carbazole ureas with potent Y5 activity, comprised of carbazole anilines that in themselves are devoid of mutagenic activity in the Ames test. Compound **4o** (also known as NPY5RA-972) is highly selective with respect to Y1, Y2, and Y4 receptors (and also to a diverse range of unrelated receptors and enzymes), with an excellent DMPK profile including central nervous system penetration. NPY5RA-972 (**4o**) is a highly potent Y5 antagonist in vivo but does not block neuropeptide Y-induced feeding nor does it reduce feeding in rats, suggesting that the Y5 receptor alone has no significant role in feeding in these models.

Introduction

Obesity represents one of the most significant medical problems facing society today. In the U.S.A., approximately half of the population is now considered at least overweight and both the prevalence and the severity of obesity continue to increase. While the situation in many other countries may be less extreme, the trends are the same, and the worldwide incidence of related diseases such as type II diabetes is escalating rapidly.[1]

Behavioral modification is rarely successful in the long term; therefore, there is a very real need for improved medicines for those most seriously afflicted. At the most basic level, it is necessary to reduce energy intake or increase energy expenditure, and suppression of appetite by promoting satiety is one way to achieve this goal. In recent years, there has been a growing understanding of the biological pathways that control appetite, and a number of specific targets for intervention have been identified.[2] Among the most studied systems, neuropeptide Y (NPY) has been featured highly.[2,3] It is one of the most abundant peptides present in the mammalian brain and has many activities including the most profound ability to acutely stimulate feeding of any peptide discovered thus far. For many years, there has been a debate over which receptor is primarily responsible for this effect, with evidence pointing to a role for both the Y1 and the Y5 subtypes.[3,4] However, a more fundamental question about the importance of the NPY system was prompted by the observations that the NPY peptide and Y1 receptor and Y5 receptor knockout mice are perfectly viable and do not display any profound (body weight-related) phenotype.[5] One view has been that feeding stimulated by NPY only has any real significance in situations of starvation. If hunger is one of the reasons that people fail to adhere to diets, then it is possible that an agent that reduces the sense of "starvation" would prove valuable, and we,[6a−c] along with many others,[6d−u,7] have hoped that a selective Y5 antagonist may provide a useful drug for treating obesity.

Among the published Y5 antagonists are a series of thioether amides reported by Bayer, of which **1** (see Chart 1) is a representative example (see Table 1).[6p] We discovered first that the thioether linkage is not essential for Y5 binding, with the carbon analogue **2** having equivalent activity and second that incorporation of a carbazole anilide, as in **3a** (Chart 2), gave a remarkable increase in potency. This compound represented an interesting starting point but suffered from poor oral bioavailability and real concerns about poten-

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10.1021/jm011125x CCC: $22.00
Published on Web 07/02/2002

Chart 1

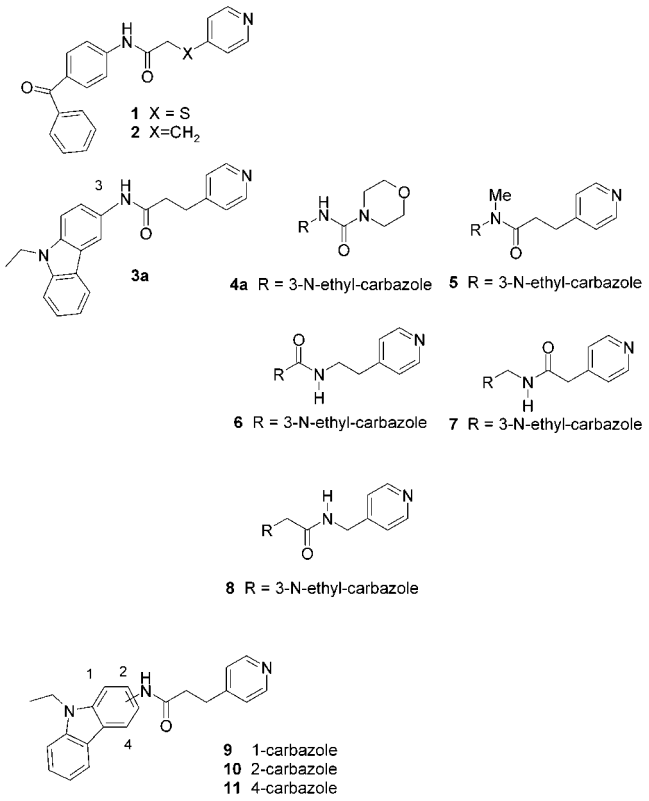


Table 1. Human NPY5 Binding Affinity for Benzophenone and Carbazole Derivatives

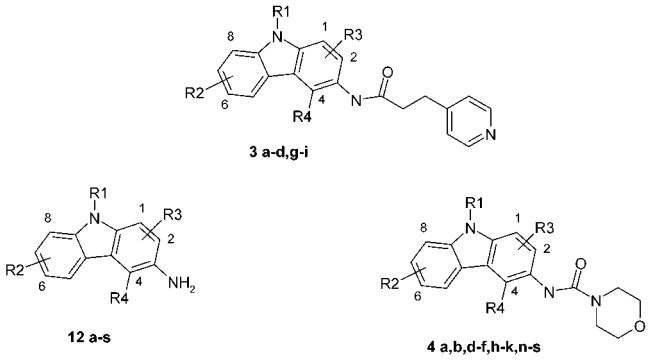
compd[a]	hY5 binding IC_{50}[b] (nM)	compd[a]	hY5 binding IC_{50}[b] (nM)
1	350	**7**	3400
2	300	**8**	2250
3a	2	**9**	440
4a	7	**10**	800
5	2200	**11**[c]	>10 000
6	700		

[a] Samples gave correct CHN analyses within ±0.4 unless otherwise noted. [b] IC_{50} data are the mean of a minimum of two results. CGP-71683[4a] was used as a standard in all assays; IC_{50} = 0.9 nM (95% confidence for any individual result ± 2.6-fold). [c] The sample gave the correct accurate mass, but no ^{13}C NMR spectrum was recorded.

tial toxicity as a consequence of the *N*-ethyl aminocarbazole fragment, which is a known animal carcinogen.[8] In this paper, the work that has been undertaken to address both of these concerns will be described. As a consequence of these studies, we have identified highly potent and selective Y5 antagonists with an improved safety profile and excellent drug metabolism and pharmacokinetic (DMPK) profile including central nervous system (CNS) penetration.

Most of the evidence in support of the Y5 hypothesis has been generated in rodents,[2,3,5a] but recently, there have been reports suggesting that Y5 antagonists have little or no effect in rodent feeding models.[9] The ability to interpret observations of this type is critically dependent on the quality of the compounds used in the studies and a good understanding of their properties. The compounds resulting from the work discussed here have allowed definitive in vivo experiments to be performed, and the outcome of these studies will also be summarized.[10]

Chart 2



for **3,4,12** (R1, R2, R3, R4 = H unless stated otherwise) :

a	R1= Et	**j**	R1= *i*Pr , R2= 6-F
b	R1= Me	**k**	R1= *i*Pr , R2= 8-Me
c	R1= H	**l**	R1= *i*Pr , R3= 2-Me
d	R1= iPr	**m**	R1= *i*Pr , R3= 2-Cl
e	R1= neopentyl	**n**	R1= *i*Pr , R3= 2-F , R4= F
f	R1= THF	**o**	R1= *i*Pr , R4= Me
g	R1= COMe	**p**	R1= *i*Pr , R4= iPr
h	R1= SO2Me	**q**	R1= *i*Pr , R4= OEt
i	R1= SO_2NMe_2	**r**	R1= *i*Pr , R3= 1-Me , R4= Me
		s	R1= *i*Pr , R3= 2-Me , R4= Me

Results and Discussion

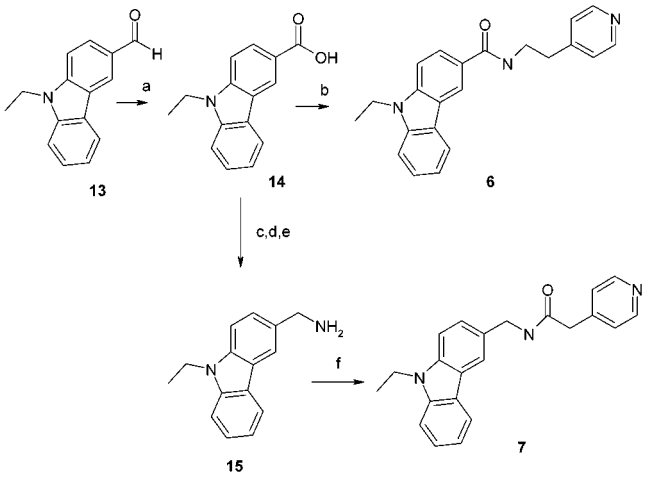
Chemical Synthesis. Compound **1** was prepared as described in the patent literature.[6p] The pyridyl propionate derivatives **2** and **3a**, the ring-substituted analogues **3b**,**c**,**d**,**g**−**i**, and the isomeric carbazole derivatives **9**−**11**) were prepared by condensation of the corresponding aniline with pyridyl propionic acid. The urea derivatives **4a**,**i** were prepared by conversion of 3-amino-*N*-ethylcarbazole to the intermediate *p*-nitrophenyl carbamate followed by reaction with morpholine. The substituted analogues **4d**−**i**,**n**−**s**) were prepared by reaction of the corresponding aminocarbazole with morpholinocarbamoyl chloride. The urea derivatives **4j**,**k** were prepared by rearrangement of the ring-substituted carbazole 3-carboxylic acids to the corresponding isocyanates followed by condensation with morpholine.

The *N*-methyl derivative **5** was synthesized from **3a** by reaction with NaH and methyl iodide. The reversed amide **6** was prepared from *N*-ethyl-carbazole-3-carboxaldehyde (**13**) by oxidation to the acid **14** and condensation with 2-(4-pyridyl)ethylamine, as illustrated in Scheme 1. The acid **14** was also converted to the corresponding primary amide, reduced with $LiAlH_4$ to give the amine **15**, and coupled with pyridyl acetic acid to give **7**.

The synthesis of **8** was achieved by Fischer indole condensation of the commercially available ketone **16** with phenyl hydrazine and N-alkylation to give **17**, followed by ring oxidation to **18** and hydrolysis and amide coupling, as illustrated in Scheme 2.

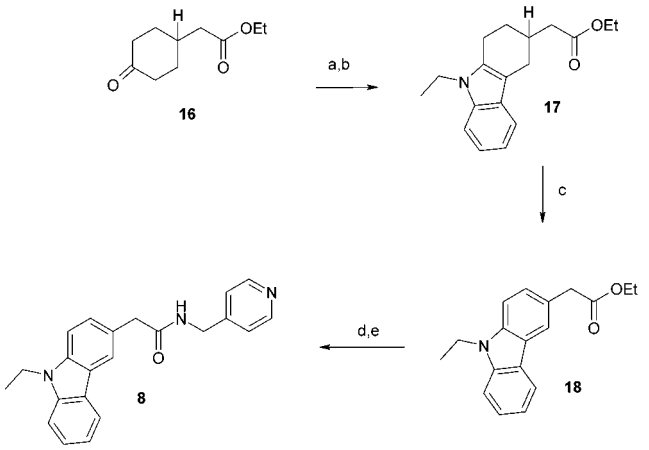
The N-9 (R1)-substituted anilines **12d**−**i** were prepared by derivatization of 3-nitrocarbazole followed by reduction of the nitro group. The 6-substituted and 8-substituted analogues (as in **12j**,**k**) were constructed as illustrated in Scheme 3. The appropriately substituted phenyl hydrazine was condensed with the commercially available ketone **19** to give **20** with unambiguous regiochemistry. Oxidation of the ring and alkylation on nitrogen lead to carbazole ester **21**, which

Scheme 1[a]



[a] Reagents: (a) $KMnO_4$, acetone−water, 87%. (b) EDAC, DMAP, CH_2Cl_2, 30%. (c) EtOCOCl, Et_3N, THF. (d) NH_4OH, 79%. (e) $LiAlH_4$, THF, 17%. (f) 4-Pyridyl acetic acid, $^iPrNEt_2$, HATU, DMF, 31%.

Scheme 2[a]



[a] Reagents: (a) $PhNHNH_2$, HCl, Et_2O, 87%. (b) NaH, EtI, DMF, 97%. (c) 10% Pd/C, 200 °C. (d) NaOH, 37% from **17**. (e) 4-Aminomethyl-pyridine, EDAC, DMAP, 80%.

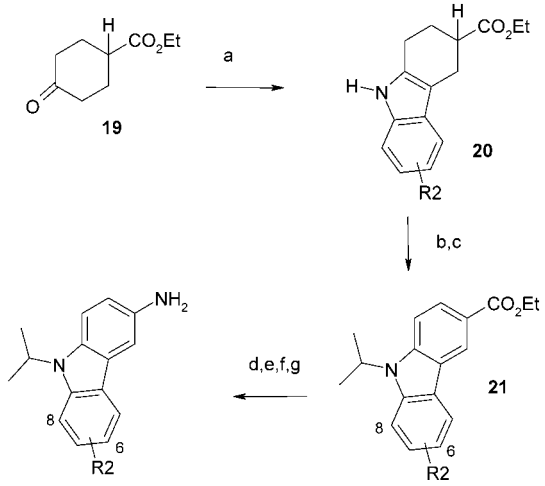
was converted to the desired anilines via hydrolysis to the corresponding acid followed by Curtius rearrangement to the isocyanate, capture as the trimethylsilane (TMS) ethyl carbamate, and hydrolysis with fluoride.[11]

The 2-substituted derivatives (as in **12l**,**m**) were accessed by coupling of the meta-substituted aniline with α-chlorocyclohexanone to give predominantly the 6-substituted indole **22** (equivalent to the 2-carbazole, R3 = Me or Cl, R4 = H), as illustrated in Scheme 4.[12] Nitration on the aromatic ring gave **23** (R3 = Me or Cl, R4 = H), which was converted by a sequence of ring oxidation, alkylation, and nitro reduction to the desired anilines. The dimethyl derivative **12s** (R3 = R4 = Me) was prepared in a similar manner.

The 1,4-substituted derivative **12r** was synthesized from 5-bromo-indole by condensation with hexane-2,5-dione to form 1,4-dimethyl-6-bromocarbazole,[13] followed by alkylation, nitration on the 3-position, and reduction of the nitro and bromine functionality, as illustrated in Scheme 5.

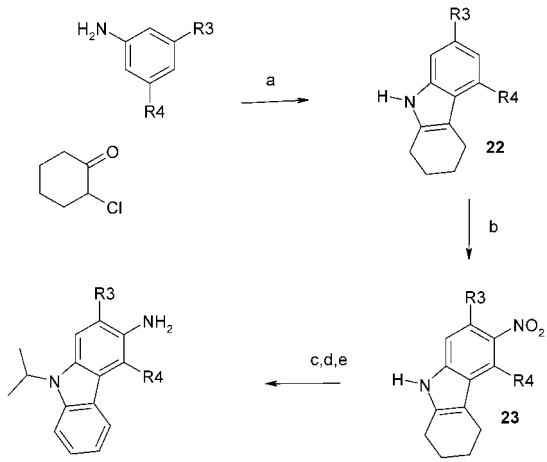
The 2,4 difluoro aniline **12n** was synthesized from 4-bromo-2,6-difluoro-aniline and protected as its diben-

Scheme 3[a]



[a] Reagents: (a) 4-F-$PhNHNH_2$, EtOH, 97% or 2-Me-$PhNHNH_2$, EtOH, 70%. (b) DDQ, xylene, 76% (R2 = 6-F), 68% (R2 = 8-Me). (c) NaH, 2-Br-Pr, 45% (R2 = 6-F) or Cs_2CO_3, 2-Br-Pr, 29% (R2 = 8-Me). (d) LiOH, THF. (e) $(PhO)_2PON_3$, Et_3N, toluene. (f) TMS-ethyl-alcohol. (g) TBAF, THF, 38% (R2 = 6-F, 4 steps), 50% (R2 = 8-Me, 4 steps).

Scheme 4[a]

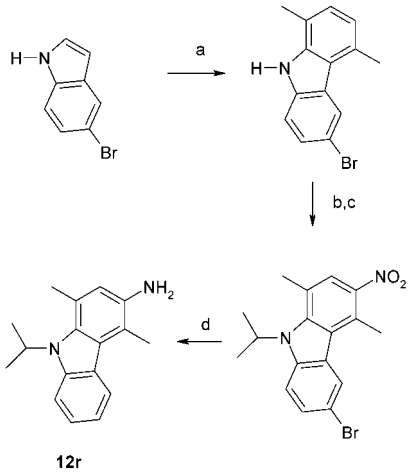


[a] Reagents: (a) HCl, Et_2O, 22% (R3 = Cl, R4 = H). (b) HNO_3, H_2SO_4, 80% (R3 = Cl, R4 = H), 51% (R3 = R4 = Me). (c) NaH, 2-Br-Pr, 58% (R3 = Cl, R4 = H), 74% (R3 = Me R4 = H), 20% (R3 = R4 = Me). (d) DDQ, dioxane, 57% (R3 = Cl, R4 = H), 63% (R3 = Me R4 = H), 69% (R3 = R4 = Me). (e) H_2, Pd, EtOH, 50% (R3 = Cl, R3′ = H), 83% (R3 = Me R4 = H), 92% (R3 = R4 = Me).

zylamine derivative (**24**) as illustrated in Scheme 6. Replacement of the bromo group by benzophenone hydrazine in a Pd-mediated Buchwald reaction[14] gave hydrazone **25**, which under acidic conditions was converted directly to the indole **26**, which was in turn converted by alkylation, oxidation, and hydrogenolysis of the benzyl groups to **12n**.

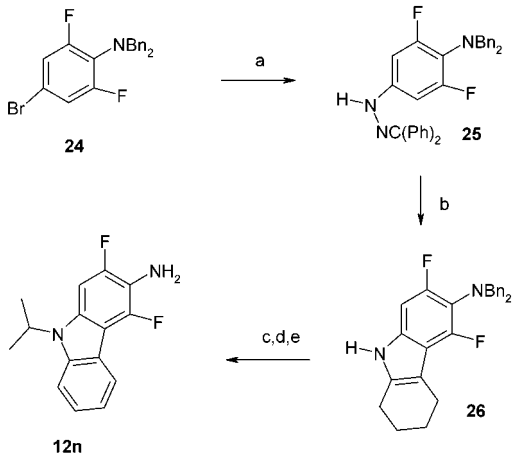
The predominance of 2-substituted carbazoles produced by the Fischer indole route illustrated in Scheme 4 makes access to the 4-substituted carbazoles problematic. It was discovered that reaction of *N*-isopropyl-3-nitrocarbazole with alkyl Grignard (Me, ^iPr),[15] followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the 4-substituted products (**27**, R4 = Me, ^iPr) exclusively and in high yield as shown in Scheme 7. These compounds were converted by reduction of the nitro group to the target aniline (**12o**,**p**). The 4-ethoxy derivative **12q** was prepared in low yield

Scheme 5[a]



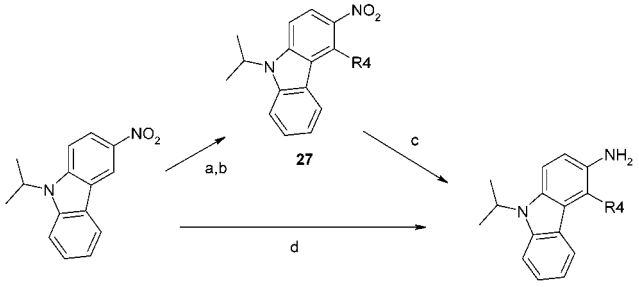
[a] Reagents: (a) Hexane-2,5-dione,[13] 35%. (b) $KN(SiMe_3)_2$, 2-I-Pr, DMF, 27%. (c) HNO_3, acetic acid, 37%. (d) H_2, Pd, EtOAc, 28%.

Scheme 6[a]



[a] Reagents: (a) $(Ph)_2CNNH_2$, $Pd(OAc)_2$, S-BINAP, toluene, 94%. (b) Cyclohexanone, pTSA, 83%. (c) NaH, 2-Br-Pr, 78%. (d) DDQ, dioxane, 63%. (e) $NH4^+HCO_3^-$, MeOH−H_2O, Pd/C, 88%.

Scheme 7[a]



[a] Reagents: (a) R4MgCl. (b) DDQ, 46% (R4 = *i*Pr), 79% (R4 = Me). (c) H_2/Pd, EtOH, 99% (R4 = *i*Pr), 90% (R4 = Me). (d) Zn, EtOH, 11% (R4 = OEt).

by reaction of *N*-isopropyl-3-nitrocarbazole with Zn ethoxide to give the substituted aniline **12q** directly.[16]

Identification of a "Pharmacological Tool" and Attempts to Remove the Aniline Fragment. The binding affinities at the human Y5 receptor were determined in a filter binding assay using [^{125}I] porcine peptide YY (PYY), and the results for the two benzophenone derivatives **1** and **2**, along with the *N*-ethyl carbazole derivatives (**3a**, **4a**, and **5**−**11**) are illustrated in Table 1. The pyridyl propionate derivative (**2**) maintains similar moderate potency to the previously reported sulfur-linked compound **1**.[6p] Incorporation of the 3-substituted carbazole as in **3a** gave a 100-fold increase in affinity for the Y5 receptor. Compound **3a** binds with high affinity to the human and rat receptors (hY5 IC_{50} = 2 nM, rY5 IC_{50} = 7 nM)[17] and has also been shown to be a functional antagonist of NPY activity in cellular calcium flux[6u] (IC_{50} = 2 nM) and reporter gene[10] (IC_{50} = 11 nM) assays, and it demonstrates high selectivity against related receptors (Y1, Y2, Y4 > 10 μM). As such, **3a** represented an interesting starting point for medicinal chemistry but suffered from two major drawbacks, namely, poor pharmacokinetic (PK) properties and concerns about potential toxicity as a consequence of the embedded aminocarbazole fragment.

Improving the DMPK properties of these aminocarbazole derivatives proved relatively straightforward as a wide range of amide and urea side chains were compatible with good Y5 binding (results not shown). Compound **3a** has a short half-life in rats ($T_{1/2}$ = 15 min) and low oral bioavailability (∼1%) primarily as a consequence of poor solubility (∼1 μM) and poor metabolic stability. In contrast, the morpholine urea **4a** has slightly improved solubility (∼3 μM) and greatly enhanced metabolic stability resulting in an improved half-life in rats ($T_{1/2}$ = 3 h) and excellent oral bioavailability (F ∼ 100%). Brain levels of **4a** were 25-fold the unbound drug concentration in plasma (500 and 21 nM, respectively, 90 min after a 2 mg/kg oral dose, see Table 2) indicating that there is little barrier to penetration into the CNS for this compound. Furthermore, cerebrospinal fluid (CSF) concentrations were equivalent to those of free drug in plasma (see Table 2), supporting this conclusion. As such, **4a** was recognized as a valuable pharmacological tool but never considered to be suitable as a potential drug because of genotoxicity concerns.

Initial studies to evaluate the importance of the anilide NH and to eliminate the carbazole aniline fragment focused on alkylation, reversal of the amide linkage, incorporation of an extra methylene group, or replacement of the amide nitrogen. Unfortunately, compounds such as **5**−**8** showed relatively poor Y5 binding activity (hY5 IC_{50} = 700−2200 nM). In analogy with α and β naphthylamine (see, for example, ref 22), it might be hoped that 1- and 4-aminocarbazole might have much reduced genotoxic potential. However, the 1, 2, and 4 isomeric derivatives (**9**−**11**) all had greatly reduced affinity for the Y5 receptor. With the exception of genotoxicity concerns, compounds such as **4a** do have an otherwise interesting profile and this prompted us to consider whether there were other ways of addressing the concerns about the carbazole aniline fragment and, specifically in the work outlined here, whether substitution on the carbazole ring would reduce the toxicity of any potential aniline fragments.

Effects of Ring Substitution on the Mutagenic Activity of Carbazole Anilines and the Y5 Activity of Acylated Derivatives. Carbazoles as a chemical class have been relatively well-studied for carcinogenicity and mutagenicity because they are commonly detected environmental pollutants resulting from coal burning and are a major component of cigarette smoke. Carbazole itself, although hepatocarcinogenic in rats

Table 2. Concentrations of **4a**,**o** in Rat Plasma and the CNS Following Oral Dosing

	dose (mg/kg)	time of analysis (min)	concn (nM)			rat plasma protein binding: fraction free (FF) (%)	estimated free plasma concn [plasma] × FF (nM)
			plasma	whole brain	CSF		
4a	2	90	740	500	17	2.8	21
4o	10.5	60	35 000	nd	153	0.9	315

Table 3. Mutagenicity (Ames Activity) of 9-Ethyl-3-aminocarbazole for *S. typhimurium* TA98 and TA100 in the Presence of Rat Liver S9 Mix

	revertant colonies per plate	
concn (μg/plate)	TA98	TA100
control	35	120
3.3	623	192
10	1416	358
33	1227	466
100	897	483

and mice, is not genotoxic, but a variety of relatively simple substituted carbazoles display in vitro genotoxicity with apparently differing modes of action.[18a−d] In particular, amino-substituted carbazoles have been shown to contribute to the mutagenicity of some tobacco components and behave as reactive frame shift mutagens acting mainly through the formation of esterified (acetylated) hydroxylamines in a similar way to other planar aromatic amines.[19a,b] Alkyl substituents, including 9-methyl and 9-ethyl carbazole, have been shown to be mutagenic in salmonella with the 9-hydroxy metabolites as the probable proximate mutagens.[18c,d]

Although 3-amino-9-ethylcarbazole, an industrial aromatic amine dye intermediate, has been shown to be carcinogenic in the livers of male and female rats and mice,[8] there appear to be no published reports of testing for mutagenicity in vitro. 3-Amino-9-ethyl-carbazole was evaluated in a standard Ames test using five strains of *Salmonella typhimurium*.[20] As expected, the results (illustrated in Table 3) show that it is mutagenic for both TA98 and TA100, in the presence of S9, indicating that its activity resembles that of both 3-aminocarbazole and 9-ethylcarbazole. The very high degree of mutagenicity observed illustrates the sensitivity of this assay for detecting mutagenic compounds of this type.

The primary metabolic product of **4a** (in vitro rat S9) results from N-dealkylation and there is no evidence for formation of 3-amino-9-ethylcarbazole under these conditions. Under accelerated hydrolysis conditions, **4a** is again very stable with an extrapolated half-life of 50 years at pH 7 and 37 °C. However, at extremes of pH, some 3-amino-9-ethylcarbazole is generated, and although plasma stability appears to be very good, the possibility of some enzymic hydrolysis in vivo cannot be discounted. It is considered impossible to establish "no effect" levels for genotoxins; consequently, we realized that regardless of how sensitive the levels of detection it would be impossible to prove that there was "no" carbazole aniline generated in vivo. Therefore, for any potential drugs derived from acylated carbazole anilines, we believed that it would be essential to demonstrate that both the parent compound and the component aniline were Ames negative.

There is precedent for modulating mutagenicity both within the alkyl carbazole series and for amino-substituted carbazoles and a variety of other aromatic anilines. *N*-Isopropyl-carbazole has been shown to be significantly less mutagenic than the corresponding *N*-ethyl and *N*-methyl carbazoles.[18c] The structural factors influencing the mutagenic activity of aromatic amines have been investigated using several chemical series. Shape, lipophilicity, and the reactivity of the ultimate electrophilic (nitrenium) species have all been shown to be important factors. Among the literature reports are several examining the effect of alkyl substitution next to the amino moiety in an attempt to block its metabolic activation.[21] In some series, e.g., benzidine (4,4′-diaminobiphenyl), ortho-methyl substitution reduces mutagenic activity while in others, e.g., aminobiphenyl and amino-naphthalene, it has little effect and in some cases can actually increase it.[22] The loss of mutagenic activity observed in some series by ortho-alkyl substitution may be a structurally specific, rather than a general, phenomenon. In the carbazole series work by André and co-workers,[23] it was shown that addition of a 1,4-dimethyl moiety considerably decreases the Ames activity of 9-methyl-3-aminocarbazole. Encouraged by these limited data suggesting appropriate ring substitution can reduce Ames activity in the carbazole series, we set out to determine in parallel the influence of ring substitution on the Ames activity of substituted carbazole anilines (**12**) and on the Y5 activity of the acylated derivatives (**3** and **4**), recognizing that any substituent would need to be beneficial in both contexts.

The mutagenic activity of the anilines (**12**) was evaluated in the Ames test against strains TA98 and TA100, in both the presence and the absence of a metabolic activation system based on the postmitochondrial supernatant of livers from rats pretreated with Aroclor 1254 (S9).[20] The results for strain TA98 + S9 (the most sensitive conditions) are illustrated in Table 4 and are presented as the maximum increase in mutation frequency observed relative to background across the dose range (6−2000 μg/plate). In parallel, the Y5 binding activity of the pyridyl propionate (**3**) or morpholine urea (**4**) derivatives was evaluated, and again, the results are presented in Table 4.

A wide range of substitution at the N-9 position (R1) appears to be tolerated in terms of the Y5 activity of the derivatives. For the alkyl substituents (**3a**−**d**), there is a clear trend in potency with *i*-propyl (**3d**) being the most potent, with reduction from ethyl (**3a**) to methyl (**3b**) and through to the unsubstituted derivative (**3c**). The potency of the *i*-propyl is also reflected in the ureas (**4a**,**d**) but does not extend to the neopentyl (**4e**) or tetrahydrofuran (THF) (**4f**) side chains. Electron-withdrawing groups on N-9 also seem compatible with good potency (**3g**−**i** and **4h**,**i**). However, in the majority of cases, the component anilines resulting from N-9 substitution (**12f**,**h**,**i**) were at least as mutagenic as *N*-ethylaminocarbazole (**12a**) and in some cases more so. However, although still positive in the Ames test, incorporation of the *i*-propyl group gave a significant

Table 4. Effect of Ring Substitution on the Mutagenic (Ames) Activity of the Carbazole Aniline (**12**) and the Human NPY5 Binding Affinity of the Carbazole Amide (**3**) or Urea (**4**)

substitution				Ames activity in TA 98 + S9 for aniline **12**		Y5 binding activity[a]			
R1	R2	R3	R4	aniline[b]	(max fold increase in mutation frequency)	amide[b]	(nM)	urea[b]	(nM)
Et				**12a**	43	**3a**	2	**4a**	11
Me				**12b**		**3b**	33		
H				**12c**		**3c**[c]	230		
^{i}Pr				**12d**	3	**3d**	1	**4d**	2
neopentyl				**12e**	5			**4e**	78
THF				**12f**	66			**4f**[c]	40
COMe				**12g**		**3g**	3		
SO2Me				**12h**	35	**3h**	1	**4h**	15
SO_2NMe_2				**12i**[d]	39	**3i**	8	**4i**	350
^{i}Pr	6-F			**12j**	15			**4j**	3
^{i}Pr	8-Me			**12k**	6			**4k**	2
^{i}Pr		2-Me		**12l**	3				
^{i}Pr		2-Cl		**12m**	43				
^{i}Pr		2-F	4-F	**12n**[c]	2			**4n**	12
^{i}Pr			4-Me	**12o**	no increase			**4o**	3
^{i}Pr			4-iPr	**12p**	no increase			**4p**	770
^{i}Pr			4-OEt	**12q**[c]	no increase			**4q**	270
^{i}Pr		1-Me	4-Me	**12r**[c]	no increase			**4r**	710
^{i}Pr		2-Me	4-Me	**12s**	no increase			**4s**	390

[a] IC_{50} data are the mean of a minimum of two results. CGP-71683[4a] was used as a standard in all assays; $IC_{50} = 0.9$ nM (95% confidence for any individual result ± 2.6-fold). [b] Except where noted, all samples gave correct CHN analyses within ±0.4 or correct accurate mass in conjunction with ^{13}C NMR. [c] Compounds gave correct accurate masses, but no ^{13}C NMR spectra were recorded. [d] No accurate mass or ^{13}C NMR were recorded for this compound.

reduction in the mutagenicity of the aniline (**12d**) and as already discussed the acylated derivatives (**3d** and **4d**) were also significantly more potent in terms of binding to Y5. Consequently, the *i*-propyl group was selected as the N-9 substituent of choice and we continued to investigate a range of further substituents in conjunction with the N-9 *i*-propyl group.

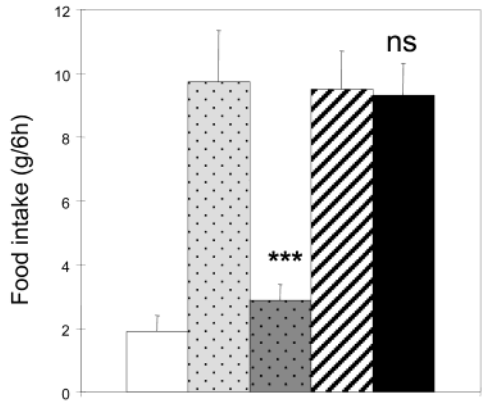
Addition of small groups at C-6 and C-8 was well-tolerated in terms of the Y5 activity of the urea (**4j**,**k**) but showed no benefit in terms of eliminating Ames activity of the anilines (**12j**,**k**). Similarly, a methyl group incorporated at C-2 had little effect on the Ames activity of the aniline (**12l**) but was tolerated in terms of the Y5 activity of related amides (results not shown). The 2-chloro group caused an increase in Ames activity (**12m**). The 2,4-difluoro substitution gave potent Y5 antagonists (as in **4n**) and helped to reduce the Ames activity of the parent aniline (**12n**). However, it was other 4-substituents that had the most dramatic effects, completely eliminating the Ames activity of the parent anilines (**12o**−**s**). In many cases, this was accompanied by a significant reduction in the Y5 binding of the corresponding urea (**4p**−**s**). However, in the case of 4-methyl substitution, excellent Y5 binding affinity was maintained for the urea (**4o**) while at the same time completely eliminating the mutagenic activity of the parent aniline (**12o**).

(It should also be noted that in evaluation of the unsubstituted urea **4d** there was evidence both in vitro[24] and in vivo of cytochrome P450 1a1 (CyP 1a1) induction. These results were consistent with aromatic hydrocarbon (Ah) receptor activation, which is known to cause a multitude of detrimental effects.[25] In contrast, the 4-methyl derivative **4o** showed no CyP1a1 induction in vitro at doses up to 12 μM or in vivo following dosing of 2 × 10 mg/kg for 10 days.)

In Vivo Properties of NPY5RA-972 (4o). Further evaluation of **4o** (also known as NPY5RA-972) showed that it had a very exciting profile (illustrated in Table 5);[10] **4o** was not only bound very potently to the Y5 receptor (rat and human) and was a functional antagonist (human) but also had excellent selectivity with respect to other NPY receptors and to a large and diverse selection of unrelated receptors, enzymes, and transporters. The only other activity observed was a degree of binding to the $5HT_{2b}$ receptor and partial inhibition of adenosine transport, both determined at 10 μM.[26] Compound **4o** has a low level of metabolism in vitro (Rat S9) and displays an excellent PK profile in rats including low clearance, good oral bioavailability, and an iv half-life of 3.7 h. Robust levels of **4o** are seen in the CSF (153 nM at 1 h after 10.5 mg/kg oral dose, see Table 2), and as with **4a**, these correspond fairly closely to estimated free plasma levels, again suggesting that in this case there is little barrier to penetration to the CNS. On the basis of these results, it was anticipated that when dosed at 10 mg/kg orally that free levels of **4o** in the brain would exceed the Y5 binding IC_{50} (rat) by at least 15-fold.

Table 5. Properties of NPY5RA-972 (**4o**)

hY5 binding $IC_{50} = 3$ nM	rY5 binding $IC_{50} = 9$ nM
hY5 functional antagonism	(Ca flux) $IC_{50} = 6$ nM
hY5 functional antagonism	(Bgal reporter assay) $IC_{50} = 37$ nM
selectivity	∼70% inhibition of 5HT2b and adenosine transport at 10 μM Y1, Y2, Y4, plus 80 other receptors > 10 μM
$LogD_{7.4}$	3.5
protein binding (rat)	0.9% free
solubility (24 h, pH 7.4)	9 μM
PK parameters (rat, DMA:PEG:H_2O 1:1:1 solution)	
iv (10 μmol/kg)	$T_{1/2} = 3.7$ h, $V_{ss} = 0.41$ L/kg, CL = 0.08 L/h/kg
po (30 μmol/kg)	$T_{1/2} = 6.4$ h, $C_{max} = 35$ μM, $T_{max} = 1$ h, F = 76%



NPY-5 agonist (nmol, icv)	0	0.6	0.6	-	-
NPY (nmol, icv)	-	-	-	2.0	2.0
4o (mg/kg, po)	0	0	3	0	3

Figure 1. Effect of NPY-5 selective antagonist NPY5RA-972 (**4o**) on food intake induced by NPY and the NPY-5 selective agonist, [cPP$^{1-7}$, NPY$^{19-23}$, Ala^{31}, Aib^{32}, Gln^{34}]hPP. Vehicle or NPY5RA-972 (**4o**, 3 mg/kg) was dosed by oral gavage (po) 1 h before administration of maximal doses of either [cPP$^{1-7}$, NPY$^{19-23}$, Ala^{31}, Aib^{32}, Gln^{34}]hPP (0.6 nmol), or NPY (2.0 nmol) into the third cerebroventricle (icv) of male rats during the light cycle. Control animals received vehicle (HPMC/Tween, po) followed 1 h later by icv vehicle (sterile water) ($n = 5-6$); ***, $P < 0.001$ vs NPY-5 selective agonist; ns, not significant vs NPY (one way analysis of variance, followed by Bonferroni multiple comparisons test).

Injection of the selective Y5 agonist [cPP$^{1-7}$, NPY$^{19-23}$, Ala^{31}, Aib^{32}, Gln^{34}]hPP^{27} directly into the third ventricle of the brain of AP Wistar rats produces a robust and reproducible stimulation of feeding. This effect is completely blocked by **4o** when dosed orally at 3 mg/kg 1 h prior to stimulation, thus proving that this compound is also an extremely potent Y5 antagonist in vivo (Figure 1). However, the same compound (also at 3 mg/kg) is unable to block the feeding induced by icv injection of NPY.[28] Compound **4o** has little or no effect on free feeding or fasting-induced feeding in AP Wistar rats even when dosed at 30 mg/kg po.

Conclusion

A series of carbazole amides and ureas have been identified as highly potent and selective Y5 antagonists with the demonstrated potential for good DMPK properties. Parallel structure−activity studies looking at the effects of ring substitution have proved that it is possible by incorporation of a 4-methyl substituent to produce carbazole ureas with potent Y5 activity, comprised of carbazole anilines that in themselves are devoid of activity in the Ames test. NPY5RA-972 (**4o**) is extremely selective and has an excellent DMPK profile including CNS penetration and consequently is a highly potent Y5 antagonist in vivo. However, NPY5RA-972 (**4o**) does not block NPY-induced feeding nor does it reduce free feeding or fasting-induced feeding in rats, which suggests that the Y5 receptor alone has no significant role in feeding in these models.

Experimental Section

Caution! 3-Amino-*N*-ethyl-carbazole is a known animal carcinogen and several of the carbazole amines discussed in this paper have been shown to be mutagenic in the Ames test. There is also evidence for CyP1A1 induction for some products (**4d**), consistent with Ah receptor activation. Appropriate precautions should be taken in handling the compounds.

Biological Methods. All equipment, which was to come in contact with NPY or PYY, was presiliconized with Sigma-Cote (Sigma Aldrich, catalog no. SL 2).

In Vitro Y5 Membrane Binding Assays. Hi5 insect cells (48 h) infected (baculo virus-infected) with either rat or human NPY-5 receptor were used for preparation of NPY-5 membranes. Human NPY-1, NPY-2, and NPY-4 membranes were prepared from SK-N-MC, KAN-TS, and stable NPY Y4 expressing Chinese hamster ovary (CHO) cells, respectively. Membranes were prepared by sonication (3 × 15 s) in ice-cold hypotonic buffer (12.5 mM Tris, 1.25 mM ethylenediaminetetraacetic acid (EDTA), 2.5% sucrose, pH 7.4) containing complete protease inhibitor tablets (one per 100 mL) (Roche Molecular Biochemicals, East Sussex, U.K.). The lysate was layered onto a 41% sucrose cushion and centrifuged at 100 000*g* for 1 h. The membrane layer was harvested and stored (in 50 mM Tris, 5 mM EDTA, 10% sucrose, pH 7.4) at −80 °C until use.

Binding assays were performed in presiliconized round-bottomed, polypropylene, 96 well plates (Corning Costar, Bucks, U.K.). Compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted (20-fold) in binding buffer (50 mM *N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES), 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.5% bovine serum albumin (BSA), pH 7.4). Each incubate had 0.01 μCi of [125I]PYY (Amersham Pharmacia Biotech, Berks, U.K.) added to 10−80 μL of membranes (sufficient to give a specific binding of 1500 cpm) and 10 μL of compound solution. After 2 h of incubation at room temperature, incubates were filtered onto Canberra Packard GF/C 96 well filter plates (Packard Instruments, Berks, U.K.) pretreated with 0.5% polyethyleneimine using a Brandel harvester. The plates were washed twice with wash buffer (binding buffer + 0.5 M NaCl). The filter plates were dried overnight and counted on a Canberra Packard Top Count (Packard Instruments) after addition of 20 μL of Microscint 40 (Packard Instruments) to each well.

Ames Test.[20] The *S. typhimurium* strains TA98 and TA100 were obtained from Professor B. N. Ames (University of California); the cultures were handled, and the tests performed as described by Maron and Ames (1983). Briefly, plate incorporation assays were done in both the presence and the absence of an exogenous metabolic activation system (S9 mix) comprising the postmitochondrial fraction (S9) from the livers of Aroclor 1254-treated Sprague−Dawley rats, supplemented with cofactors for reduced nicotinamide adenine dinucleotide phosphate (NADPH) generation.

Chemistry Methods. All procedures were carried out at room temperature unless otherwise stated. All commercially available reagents and solvents were used without further purification unless otherwise stated. Organic solvent extracts were dried over anhydrous Na_2SO_4 or $MgSO_4$. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) were recorded on Bruker DPX-300, DPX-400, or Varian Gemini 2000 instruments using $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal reference.

Chemical shifts are in δ (ppm). Mass spectra were recorded on Micromass Platform positive and negative electrospray spectrometers. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 F254, $d = 0.25$ mm) were used. Flash chromatography was performed on silica (Merck Keiselgel: Art.9385) unless otherwise stated.

1-[*N*-(4-Benzoylphenyl)]-2-(mercapto-pyridin-4yl)acetamide (1).[6p] ^{1}H NMR (Me_2SO-d_6): δ 4.1 (s, 2H), 7.32 (d, J = 7 Hz, 2H), 7.52 (t, $J = 7$ Hz, 2H), 7.6−7.8 (m, 7H,), 8.36 (d, J = 7 Hz, 2H), 10.70 (s, 1H). MS (ES^+): 349 (MH^+). Anal. for $C_{20}H_{16}N_2O_2S \cdot 0.5H_2O$.

***N*-(4-Benzoylphenyl)-3-pyridin-4-ylpropanamide (2).** *p*-Aminobenzophenone (404 mg, 2.05 mmol), 3-(4-pyridyl)-propionic acid (309 mg, 2.05 mmol), (dimethylamino)propyl-3-ethylcarbodiimide (EDAC, 422 mg, 2.2 mmol), and (dimethylamino)pyridine (DMAP) (269 mg, 2.2 mmol) were stirred in CH_2Cl_2 (10 mL) at room temperature under an atmosphere of

argon for 2 h and then heated at reflux for a further 4 h. The reaction mixture was cooled, diluted with CH_2Cl_2 (20 mL), and washed with water (20 mL) and partitioned. The organic layer was dried, filtered, and concentrated under vacuum to a yellow oil, which was chromatographed on silica using 20−75% EtOAc/*i*-hexane as eluent. The resulting solid was recrystrallised from MeOH:EtOAc:*i*-hexane to give **2** as a white solid (289 mg, 43%). ^{1}H NMR (Me_2SO-d_6): δ 2.80 (t, J = 7 Hz, 2H), 3.00 (t, J = 7 Hz, 2H), 7.30 (d, J = 7 Hz, 2H), 7.66 (m, 9H), 8.46 (d, J = 7 Hz, 2H), 10.34 (br s, 1H). MS (ES^+): 331 (MH^+). Anal. for $C_{21}H_{18}N_2O_2$.

***N*-(9-Ethyl-9-*H*-carbazol-3yl)-3-pyridin-4-ylpropanamide (3a).** Compound **3a** was prepared in a similar manner as **2** but using 3-amino-9-ethylcarbazole and dimethyl formamide (DMF) as solvent. The resulting solid was recrystallized from EtOAc (100 mL) to give a white solid. Yield, 42%. ^{1}H NMR (Me_2SO-d_6): δ 1.30 (t, J = 7 Hz, 3H) 2.70 (t, J = 7 Hz, 2H), 2.98 (t, J = 7 Hz, 2H), 4.40 (q, J = 7 Hz, 2H), 7.18 (t, J = 7 Hz, 1H), 7.30 (d, J = 7 Hz, 2H), 7.44 (t, J = 7 Hz, 1H), 7.50 (m, 3H), 8.04 (d, J = 7 Hz, 1H), 8.38 (s, 1H), 8.47 (d, J = 7 Hz, 2H), 9.96 (s, 1H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O$.

***N*-(9-Methyl-9-*H*-carbazol-3yl)-3-pyridin-4-ylpropanamide (3b).** Compound **3b** was prepared in a similar manner as described for **3a** in 58% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.70 (m, 2H), 2.98 (m, 2H), 3.83 (s, 3H), 7.19 (t, J = 7 Hz, 1H), 7.33 (d, J = 6 Hz, 2H), 7.46 (t, J = 7 Hz, 1H), 7.48−7.58 (m, 3H), 8.06 (d, J = 7.5 Hz, 1H), 8.39 (s, 1H), 8.48 (d, J = 6 Hz, 2H), 9.88 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 28.76, 29.89, 36.17, 108.66, 108.90, 111.02, 118.32, 118.84, 119.75, 121.52, 121.74, 123.57, 125.49, 130.98, 137.14, 140.94, 149.25, 150.00, 169.27. MS (ES^+): 330 (MH^+). HRMS for $C_{21}H_{19}N_3O$.

***N*-(9-*H*-Carbazol-3yl)-3-pyridin-4-ylpropanamide (3c).** Compound **3c** was prepared in a similar manner as described for **3a** and purified by chromatography on silica using EtOAc as eluent, to give **3c** in 9% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.65 (t, J = 7 Hz, 2H), 2.95 (t, J = 7 Hz, 2H), 7.11 (t, J = 7 Hz, 1H), 7.28 (d, J = 6 Hz, 2H), 7.35 (m, 2H), 7.45 (m, 2H), 7.99 (d, J = 7 Hz, 1H), 8.32 (s, 1H), 8.46 (d, J = 6 Hz, 2H), 9.89 (s, 1H), 11.05 (s, 1H). MS (ES^+): 316 (MH^+). HRMS for $C_{20}H_{17}N_3O$.

***N*-(9-Isopropyl-9-*H*-carbazol-3yl)-3-pyridin-4-ylpropanamide (3d).** Compound **3d** was prepared in a similar manner as described for **3a** in 67% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.60 (d, J = 7 Hz, 6H), 2.69 (t, J = 8 Hz, 2H), 2.96 (t, J = 8 Hz, 2H), 5.05 (sept, J = 7 Hz, 1H), 7.13 (t, J = 7 Hz, 1H), 7.28 (d, J = 6 Hz, 2H), 7.39 (t, J = 8 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 7.63 (t, J = 9 Hz, 2H), 8.03 (d, J = 8 Hz, 1H), 8.36 (s, 1H), 8.45 (d, J = 6 Hz, 2H), 9.92 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 20.426, 30.014, 36.300, 45.989, 110.326, 110.962, 118.262, 118.674, 119.976, 122.250, 123.763, 125.484, 130.885, 135.481, 139.438, 149.393, 150.221, 169.426. MS (ES^+): 358 (MH^+). HRMS for $C_{23}H_{23}N_3O$.

***N*-(9-Acetyl-9-*H*-carbazol-3yl)-3-pyridin-4-ylpropanamide (3g).** Compound **3g** was prepared in a similar manner as described for **3a** in 14% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.72 (m, 2H), 2.87 (s, 3H), 2.96 (m, 2H), 7.31 (d, J = 6 Hz, 2H), 7.40 (t, J = 8 Hz, 1H), 7.53 (m, 2H), 8.06 (d, J = 8 Hz, 1H), 8.18 (d, J = 8 Hz, 1H), 8.24 (d, J = 8 Hz, 1H), 8.44 (m, 3H), 10.18 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 27.31, 29.86, 36.27, 110.01, 116.27, 116.43, 119.18, 119.81, 123.54, 123.84, 125.47, 125.68, 127.47, 133.99, 135.17, 138.42, 149.21, 150.40, 169.89, 170.11. MS (ES^+): 358 (MH^+). HRMS for $C_{22}H_{19}N_3O_2$.

***N*-[9-(Methylsulfonyl)-9-*H*-carbazol-3yl]-3-pyridin-4-ylpropanamide (3h).** Compound **3h** was prepared in a similar manner as described for **3a** in 28% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.72 (m, 2H), 2.94 (m, 2H), 3.24 (s, 3H), 7.30 (d, J = 6 Hz, 2H), 7.43 (t, J = 8 Hz, 1H), 7.55 (m, 2H), 7.93 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 8.45 (m, 3H), 10.19 (s, 1H). MS (ES^+): 393 (MH^+). Anal. for $C_{21}H_{19}N_3O_3S$.

***N*-{9-[(Dimethylamino)sulfonyl]-9-*H*-carbazol-3yl}-3-pyridin-4-ylpropanamide (3i).** Compound **3i** was prepared in a similar manner as described for **3a** in 47% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.74 (m, 8H), 2.96 (t, J = 8 Hz, 2H), 7.28 (m, 2H), 7.40 (t, J = 8 Hz, 1H), 7.53 (m, 2H), 7.98 (d, J = 9 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H) 8.44 (m, 3H), 10.16 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 29.84, 36.26, 38.19, 110.39, 114.30, 114.45, 119.54, 120.22, 123.34, 123.75, 124.50, 124.63, 127.43, 134.31, 134.97, 138.78, 149.44, 150.04, 169.91. MS (ES^+): 423 (MH^+). HRMS for $C_{22}H_{22}N_4O_3S$.

***N*-(9-Ethyl-9-*H*-carbazol-3-yl)morpholine-4-carboxamide (4a).** A solution of 3-amino-9-ethylcarbazole (25.0 g, 0.12mol) in EtOAc (300 mL) was added dropwise over 30 min to a mixture of *p*-nitrophenyl chloroformate (24.0 g, 0.12mol) and K_2CO_3 (16.6 g, 0.12mol) in EtOAc (200 mL). The mixture was stirred for 18 h and poured into water (500 mL), and the organic layer was separated, was washed with water (500 mL) and brine (250 mL), and dried. The solution was evaporated under vacuum to leave a brown solid. The crude product was stirred in MeOH (500 mL) and then filtered. The filtered solid was washed with Et_2O (2 × 250 mL) and dried in air to give 3-(4-nitrophenoxycarbonylamino)-9-ethylcarbazole as a pale yellow solid (36.0 g, 80%). ^{1}H NMR (Me_2SO-d_6): δ 1.30 (t, J = 8 Hz, 3H), 4.40 (q, J = 8 Hz, 2H), 7.15 (t, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.55 (m, 5H), 8.1 (d, J = 8 Hz, 1H), 8.3 (m, 3H), 10.4 (br s, 1H).

To a solution of 3-(4-nitrophenoxycarbonylamino)-9-ethylcarbazole (250 mg, 0.67 mmol) and DMAP (4 mg, 0.03 mmol) in EtOAc (10 mL) was added morpholine (0.067 mL, 0.73 mmol). The mixture was stirred for 18 h at room temperature and then filtered to give **4a** (145 mg, 67%). ^{1}H NMR (Me_2SO-d_6): δ 1.28 (t, J = 7 Hz, 3H), 3.44 (m, 4H), 3.62 (m, 4H), 4.38 (qu, J = 7 Hz, 2H), 7.14 (t, J = 7 Hz, 1H), 7.4 (t, J = 7 Hz, 1H), 7.47 (s, 2H), 7.53 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 8.50 (s, 1H). MS (ES^+): 324 (MH^+). Anal. for $C_{19}H_{21}N_3O_2$.

***N*-(9-Isopropyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4d).** Under an inert atmosphere, Et_3N (0.43 mL, 3.06 mmol) was added to a solution of 3-amino-9-isopropylcarbazole (**12d**) (624 mg, 2.78 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath. Morpholine carbamoyl chloride (0.36 mL, 3.06 mmol) was added dropwise, and then, the mixture was stirred for 72 h. The mixture was diluted with CH_2Cl_2, washed with aqueous K_2CO_3 solution, dried, filtered, and then concentrated. Chromatography on silica gel (eluent gradient of CH_2Cl_2 to EtOAc) gave **4d** as an off white solid. Yield, 854 mg (91%). ^{1}H NMR (Me_2SO-d_6): δ 1.60 (d, J = 7 Hz, 6H), 3.45 (t, J = 5 Hz, 4H), 3.64 (t, J = 5 Hz, 4H), 5.05 (m, 1H,), 7.13 (dd, J = 8, 8 Hz, 1H), 7.38 (dd, J = 8, 8 Hz 1H), 7.43 (dd, J = 8, 2 Hz 1H), 7.58 (d, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.16 (d, J = 2 Hz, 1H), 8.54 (br s, 1H). MS (ES^+): 338 (MH^+). Anal. for $C_{20}H_{23}N_3O_2$.

***N*-(9-Neopentyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4e).** Compound **4e** was prepared in a similar manner as described for **4d** in 20% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.00 (s, 9H), 3.44 (t, J = 5 Hz, 4H), 3.62 (t, J = 5 Hz, 4H), 4.13 (s, 2H), 7.12 (t, J = 8 Hz, 1H), 7.33−7.46 (m, 2H), 7.50 (d, J = 9 Hz, 1H), 7.57, (d, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 8.13 (d, J = 2 Hz, 1H), 8.49 (s, 1H). MS (ES^+): 366 (MH^+). Anal. for $C_{22}H_{27}N_3O_2$.

***N*-(9-Tetrahydrofuran-3-yl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4f).** Compound **4f** was prepared in a similar manner as described for **4d** in 30% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.20 (m, 1H), 2.40 (m, 1H), 3.45 (m, 4H), 3.65 (m, 4H), 3.75 (m, 1H), 4.00 (m, 1H), 4.15 (dd, 1H), 4.30 (m, 1H), 5.60 (m, 1H), 7.15 (dd, J = 1,7 Hz, 1H), 7.40 (dd, J = 2, 9 Hz, 1H), 7.40 (dd, J = 1, 7 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 7.65 (dd, J = 1, 9 Hz 1H), 8.00 (d, J = 7 Hz, 1H), 8.15 (d, J = 2 Hz, 1H) 8.5 (s, 1H). MS (ES^+): 366 (MH^+). HRMS for $C_{21}H_{23}N_3O_3$.

***N*-(9-Methylsulfonyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4h).** Compound **4h** was prepared in a similar manner as described for **4d** in 55% yield. ^{1}H NMR (Me_2SO-d_6): δ 3.21 (s, 3H), 3.42 (t, J = 5 Hz, 4H), 3.61 (t, J = 5 Hz, 4H), 7.44 (t, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.27 (s, 1H), 8.73 (s, 1H). MS (ES^+): 374 (MH^+). Anal. for $C_{18}H_{19}N_3O_4S$.

***N*-{9-[(Dimethylamino)sulfonyl]-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4i).** Compound **4i** was prepared in a similar manner as described for **4a** in 21% overall yield. ^{1}H NMR (Me_2SO-d_6): δ 1.04 (s, 1H), 1.05 (s, 1H), 3.48 (m, 4H), 3.64 (m, 4H), 7.41 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 8 Hz, 1H,), 7.57 (dd, J = 2, 9 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.29 (d, J = 2 Hz, 1H), 8.73 (s, 1H). ^{13}C NMR (Me_2SO-d_6): δ 38.20, 44.14, 65.97, 111.20, 114.035, 114.30, 120.10, 120.53, 123.17, 124.57, 124.71, 127.20, 133.81, 136.25, 138.76, 155.38. MS (ES^+): 403 (MH^+). HRMS for $C_{19}H_{22}N_4O_4S$.

***N*-(6-Fluoro-9-isopropyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4j) (Scheme 3).** Et_3N (139 μL, 1 mmol) was added to a stirred suspension of 6-fluoro-9-isopropyl-9 H carbazol-3-yl carboxylic acid (see prep of **12j**) (271 mg, 1 mmol) and diphenylphosphoryl azide (275 mg, 1.1 mmol) in dry toluene (15 mL) under argon. The resultant solution was stirred for 1 h and then heated to reflux for 1 h. The heat source was removed, and morpholine (200 μL, 3 mmol) was added, and the resultant solution was stirred overnight at ambient temperature. The mixture was filtered, and the filtrate was diluted with EtOAc (30 mL) and washed with water (10 mL), 1 M HCl (10 mL), 0.2 M NaOH (10 mL), water (10 mL), and saturated brine (10 mL), dried, and evaporated to dryness under reduced pressure. The resultant gum was purified using a Bond Elute column (20 g) eluting with 0.5% MeOH/CH_2Cl_2 to give **4j** (259 mg) as a white solid. ^{1}H NMR (Me_2SO-d_6): δ 1.6 (d, J = 6.8 Hz, 6H), 3.5 (t, J = 4.9 Hz, 4H), 3.65 (t, J = 4.9 Hz, 4H), 5.0 (sept, J = 6.8 Hz, 1H), 7.2 (dt, J = 9.0, 9.0, 2.6 Hz, 1H), 7.4 (dd, J = 2.2, 8.8 Hz, 1H), 7.6 (d, J = 8.8 Hz, 1H), 7.7 (dd, J = 3, 9.1 Hz, 1H), 7.85 (dd, J = 2.8, 9.1 Hz, 1H), 8.2 (d, J = 2.2 Hz, 1H), 8.5 (s, 1H). MS (ES^+): 356 (MH^+). ^{13}C NMR (Me_2SO-d_6): δ 20.88, 44.554, 46.60, 66.43, 105.87 (d, J = 116 Hz), 110.65, 111.59 (d, J = 43 Hz), 113.21 (d, J = 107 Hz), 113.32, 121.66, 122.20, 123.24 (d, J = 46.5 Hz, 132.15, 136.33, 136.66, 156.24, 156.50 (d, J = 1160 Hz). HRMS for $C_{20}H_{22}N_3O_2F$.

***N*-(9-Isopropyl-8-methyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4k).** Compound **4k** was prepared from 8-methyl-9-isopropyl-9*H*-carbazol-3-yl carboxylic acid (see prep of **12k**) in a similar manner as described for **4j** in 31% yield. ^{1}H NMR ($CDCl_3$): δ 1.7 (d, J = 7 Hz, 6H), 2.8 (s, 3H), 3.5 (t, J = 5 Hz, 4H), 3.8 (t, J = 5 Hz, 4H), 5.5 (sept, J = 7 Hz, 1H), 6.4 (s, 1H), 7.0 (m, 1H), 7.2 (d, J = 7.1 Hz, 1H), 7.3 (dd, J = 2.0, 8.9 Hz, 1H), 7.6 (d, J = 8.9 Hz, 1H), 7.8 (d, J = 7.6 Hz, 1H), 8.0 (d, J = 2.0 Hz, 1H). ^{13}C NMR (Me_2SO-d_6): δ 21.30, 21.52, 44.58, 47.52, 66.43, 112.36, 112.60, 118.09, 118.96, 120.27, 120.35, 123.345, 123.93, 129.724, 132.36, 135.284, 139.752, 156.215. HRMS for $C_{21}H_{25}N_3O_2$.

***N*-(2,4-Difluoro-9-isopropyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4n).** Compound **4n** was prepared in a similar manner as described for **4d** in 83% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.67 (d, J = 7 Hz, 6H), 3.54 (t, J = 5 Hz, 4H), 3.76 (t, J = 5 Hz, 4H), 4.87 (sept, J = 7 Hz, 1H,), 5.92 (br s, 1H), 7.06 (dd, J = 10, 1 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.43 (ddd, J = 8, 7, 1 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 8.14 (d, J = 7 Hz, 1H). ^{13}C NMR (Me_2SO-d_6): δ 20.13, 44.20, 46.65, 65.91, 93.55 (d), 106.81, 107.19 (m), 110.80, 119.59, 119.69, 121.65, 125.51, 137.63 (m), 139.02, 153.50 (d), 155.98, 157.34 (d). MS (ES^+): 374 $(MH)^+$. HRMS for $C_{20}H_{21}F_2N_3O_2$.

***N*-(9-Isopropyl-4-methyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4o).** Compound **4o** was prepared in a similar manner as described for **4d** in 71% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.71 (d, J = 7 Hz, 6H), 2.77 (s, 3H), 3.49 (t, J = 5 Hz, 4H), 3.73 (t, J = 5 Hz, 4H), 5.00 (m, 1H), 6.20 (br s, 1H), 7.24 (ddd, J = 8, 8, 1 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.46 (ddd, J = 8, 8, 1 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H). MS (ES^+): 352 (MH^+). Anal. for $C_{21}H_{25}N_3O_2$.

***N*-(4,9-Diisopropyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4p).** Compound **4p** was prepared in a similar manner as described for **4d** in 82% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.58 (d, J = 7 Hz, 6H), 1.72 (d, J = 7 Hz, 6H), 3.53 (t, J = 5 Hz, 4H), 3.78 (t, J = 5 Hz, 4H), 4.34 (br m, 1H), 5.03 (m, 1H), 6.18 (br s, 1H), 7.20 (ddd, J = 8, 8, 1 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.43 (ddd, J = 8, 8, 1 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H). MS (ES^+): 380 (MH^+). ^{13}C NMR (Me_2SO-d_6): δ 20.25, 21.02, 29.18, 44.25, 45.71, 66.13, 107.79, 110.27, 118.24, 120.13, 121.93, 122.72, 124.50, 128.05, 129.30, 138.0, 139.35, 140.65, 157.32. HRMS for $C_{23}H_{29}N_3O_2$.

***N*-(4-Ethoxy-9-isopropyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4q).** Compound **4q** was prepared in a similar manner as described for **4d** in 58% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.55 (t, J = 7 Hz, 3H), 1.71 (d, J = 7 Hz, 6H), 3.57 (t, J = 5 Hz, 4H), 3.80 (t, J = 5 Hz, 4H), 4.21 (q, J = 7 Hz, 2H), 4.97 (m, 1H), 7.02 (br s, 1H), 7.22 (ddd, J = 8, 8, 1 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.44 (ddd, J = 8, 8, 1 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H). MS (ES^+): 382 (MH^+). Anal. for $C_{22}H_{27}N_3O_3$.

***N*-(9-Isopropyl-1,4-dimethyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4r).** Compound **4r** was prepared in a similar manner as described for **4d** in 94% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.70 (d, J = 7 Hz, 6H), 2.59 (s, 3H), 2.78 (s, 3H), 3.50 (m, 4H), 3.69 (m, 4H), 5.57 (m, J = 7 Hz, 1H), 7.08 (s, 1H), 7.56 (dd J = 9, 2 Hz, 1H), 7.82 (d, J = 9 Hz, 1H), 8.25 (s, 1H), 8.31 (d, J = 2 Hz, 1H). MS (ES^+): 367 (MH^+). Anal. for $C_{22}H_{27}N_3O_2$.

***N*-(9-Isopropyl-2,4-dimethyl-9*H*-carbazol-3-yl)morpholine-4-carboxamide (4s).** Compound **4s** was prepared in a similar manner as described for **4d** in 80% yield. ^{1}H NMR ($CDCl_3$): δ 1.69 (d J = 7 Hz, 6H), 2.44 (s, 3H), 2.76 (s, 3H), 3.50 (m, 4H), 3.75 (m, 4H), 4.97 (sept, J = 7 Hz, 1H), 5.90 (s, 1H), 7.20 (t, J = 8 Hz, 1H), 7.25 (s, 1H), 7.40 (t, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 8.18 (d, J = 8 Hz, 1H). MS (ES^+): 366 (MH^+). Anal. for $C_{22}H_{27}N_3O_2$.

***N*-(9-Ethyl-9*H*-carbazol-3-yl)-*N*-methyl-3-pyridin-4-yl Propanamide (5).** Sodium hydride (60% dispersion in oil) (65 mg, 1.5 mmol) was added to a solution of **3a** (500 mg, 1.5 mmol) in THF (10 mL) at 0 °C under an argon atmosphere. After it was heated to 50 °C for 2 h, the mixture was allowed to cool to room temperature whereupon MeI (0.1 mL, 1.5 mmol) was added dropwise. After it was heated to 50 °C for 2 h, the mixture was allowed to cool to room temperature. Water (30 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 50 mL). The organics were concentrated and then purified by flash column chromatography to give **5** as a brown solid. Yield, 225 mg (43%). ^{1}H NMR (Me_2SO-d_6): δ 1.30 (t, J = 7 Hz, 3H), 2.35 (t, J = 7 Hz, 2H), 2.78 (t, J = 7 Hz, 2H), 3.25 (s, 3H), 4.42 (q, J = 7 Hz, 2H), 7.05 (d, J = 6 Hz, 2H), 7.19 (t, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.64−7.56 (m, 2H), 7.88 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 8.32 (d, J = 6 Hz, 2H). MS (ES^+): 358 (MH^+). Anal. for $C_{23}H_{23}N_3O$.

9-Ethyl-*N*-(2-pyridin-4-ylethyl)-9*H*-carbazole-3-carboxamide (6) (Scheme 1). To a solution of 9-ethyl-3-formylcarbazole (**13**) (8.3 g, 37.2 mmol) in acetone (25 mL) was added $KMnO_4$ (12.1 g, 76.6 mmol) in water (50 mL), and the mixture was heated at reflux for 18 h, filtered through Celite, and acidified with HCl to give 9-ethyl-3-carboxycarbazole (**14**) as a white solid. Yield, 7.7 g (87%). ^{1}H NMR (Me_2SO-d_6): δ 1.33 (t, J = 7 Hz, 3H), 4.47 (q, J = 7 Hz, 2H), 7.25 (t, J = 7 Hz, 1H), 7.50 (t, J = 7 Hz, 1H), 7.68 (m, 2H), 8.06 (d, J = 7 Hz, 1H), 8.26 (d, J = 7 Hz, 1H), 8.78 (s, 1H), 12.53 (s, 1H). MS (ES^+): 240 (MH^+).

Compound **14** was coupled with 2-(4-pyridyl)ethylamine in a similar manner as described for **2**, and the product was purified by chromatography on silica using 5−10% MeOH/EtOAc as eluent to give **6** as gum, which solidified on standing (30% yield). ^{1}H NMR (Me_2SO-d_6): δ 1.32 (t, J = 7 Hz, 3H) 2.90 (t, J = 7 Hz, 2H), 3.58 (dt, J = 7 Hz, 2H), 4.45 (q, J = 7 Hz, 2H), 7.25 (m, 3H), 7.50 (t, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 2H), 7.95 (d, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 8.45 (d, J = 7 Hz, 2H), 8.55 (t, J = 7 Hz, 1H), 8.65 (s, 1H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O$.

***N*-[(9-Ethyl-9*H*-carbazol-3-yl)methyl]-2-pyridine-4-yl-acetamide (7) (Scheme 1).** To a solution of **14** (7.347 g, 30.7 mmol) and Et_3N (4.32 mL, 31 mmol) in dry THF (100 mL) was

added ethyl chloroformate (2.96 mL, 31 mmol) slowly at 0 °C under an argon atmosphere and allowed to warm to room temperature. Two hours later, NH_4OH (30 mL) was added slowly. After 3 h, the reaction mixture was concentrated, water (100 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL). The organic layer was dried and concentrated to give 9-ethyl-3-carbamoylcarbazole as a yellow solid. Yield, 5.76 g (79%). ^{1}H NMR (Me_2SO-d_6): δ 1.31 (t, J = 7 Hz, 3H), 4.47 (q, J = 7 Hz, 2H), 6.38 (br s, 1H), 7.22 (t, J = 7 Hz, 1H), 7.46 (t, J = 7 Hz, 1H), 7.62 (m, 2H), 8.01 (d, J = 7 Hz, 1H), 8.17 (d, J = 7 Hz, 1H), 8.72 (s, 1H). MS (ES^+): 239 (MH^+).

To a solution of 9-ethyl-3-carbamoylcarbazole (5.5 g, 23.1 mmol) in dry THF (100 mL) was added $LiAlH_4$ (1 M solution in THF; 25 mL, 25 mmol) slowly at 0 °C under an argon atmosphere. After complete addition, the mixture was heated at reflux for 72 h. After it was cooled to 0 °C, water (100 mL) and then 15% w/v NaOH solution (100 mL) were added to the orange mixture before stirring for 1 h. The mixture was filtered under vacuum, and the filtrate was concentrated. Water (100 mL) was added followed by extraction with CH_2Cl_2 (2 × 100 mL). The organic layer was dried and concentrated to give a yellow oil. Chromatography (eluent gradient of CH_2Cl_2 to 5% NH_4OH, 15% MeOH, CH_2Cl_2) gave 9-ethyl-3-aminomethylcarbazole (**15**) as a brown oil, which solidified on standing. Yield, 902 mg (17%). ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7 Hz, 3H), 4.02 (s, 2H), 4.34 (q, J = 7 Hz, 2H), 7.23 (t, J = 7 Hz, 1H), 7.45 (m, 4H), 8.01 (s, 1H), 8.06 (d, J = 7 Hz, 1H). MS (ES^+): 208 ($M^+ - NH_3$).

4-Pyridyl acetic acid (145 mg, 0.836 mmol) was suspended in DMF (2 mL) to which was added diisopropylethylamine (0.265 mL, 1.52 mmol) and *O*-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 323 mg, 0.85 mmol). This was stirred for 10 min, and **15** (170 mg, 0.76 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (3 × 100 mL). The organic layer was dried and concentrated to yield a gum. This was placed under a high vacuum for 12 h, which resulted in a foam. The solid was stirred in 1 N HCl (20 mL) for 3 h and then extracted with EtOAc (3 × 50 mL). The EtOAc was dried and concentrated under vacuum to yield **7** (80 mg, 31%). ^{1}H NMR (Me_2SO-d_6): δ 1.28 (t, J = 7 Hz, 3H), 3.55 (s, 2H), 4.35−4.48 (m, 4H), 7.17 (t, J = 7 Hz, 1H), 7.25−7.38 (m, 3H), 7.42 (t, J = 7 Hz, 1H), 7.5−7.6 (m, 2H), 7.95 (s, 1H), 8.05 (d, J = 7 Hz, 1H), 8.47 (d, 2H), 8.58−8.68 (m, 1H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O$.

2-(9-Ethyl-9*H*-carbazol-3-yl)-*N*-(pyridin-4-ylmethyl)-acetamide (8) (Scheme 2). An amount of 2 M HCl in Et_2O (16.3 mL, 32.6 mmol) was added to a stirred solution of phenylhydrazine (3.52 g, 32.6 mmol) in EtOH (100 mL). The milky suspension was heated to 40 °C, and ethyl(4-oxocyclohexyl)acetate (6 g, 32.6 mmol) was added before heating at reflux for 2 h. The reaction solvent was removed under vacuum, and the residue was partitioned between EtOAc (200 mL) and water (2 × 200 mL). The aqueous layer was extracted with EtOAc (200 mL), and the combined organic layers was dried and concentrated to yield ethyl-1,2,3,4-tetrahydro-1*H*-carbazol-3-yl acetate as a slightly orange solid (7.3 g, 87%). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7 Hz, 3H), 1.65 (m, 2H), 2.43 (m, 4H), 2.78 (m, 2H), 2.92 (m, 1H), 4.15 (q, J = 7 Hz, 2H), 7.10 (m, 2H), 7.26 (d, J = 7 Hz, 1H), 7.43 (d, J = 7 Hz, 1H), 7.71 (br s, 1H). MS (ES^+): 258 (MH^+).

NaH (60% dispersion in mineral oil, 752 mg, 18.8 mmol) was added portion wise to a solution of ethyl-1,2,3,4-tetrahydro-1*H*-carbazol-3-yl acetate (4.40 g, 17.1 mmol) in dry DMF (50 mL) under an inert atmosphere. EtI (1.5 mL, 18.8 mmol) was added dropwise before heating to 65 °C for 1.5 h. The reaction solvent was removed under vacuum, and the residue was partitioned between EtOAc (200 mL) and water (2 × 200 mL). The aqueous layers were further extracted with EtOAc, and the combined organic layer was dried and concentrated to yield **17** as an orange gum (4.74 g, 97%). ^{1}H NMR ($CDCl_3$): δ 1.31 (m, 6H), 1.70 (m, 1H), 2.12 (m, 1H), 2.46 (m, 4H), 2.79 (m, 2H), 2.96 (m, 1H), 4.08 (q, J = 7 Hz, 2H), 4.20 (q, J = 7 Hz, 2H), 7.07 (t, J = 7 Hz, 1H), 7.16 (t, J = 7 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 1H). MS (ES^+): 286 (MH^+).

Compound **17** (4.436 g, 15.56 mmol) was stirred with 10% palladium on carbon (1.24 g) at 200 °C for a total of 6.5 h with argon blown over the reaction mixture. The mixture was allowed to cool and was then diluted with CH_2Cl_2 (200 mL) before the catalyst was filtered off. The catalyst was washed with CH_2Cl_2 (2 × 100 mL), and the combined organics were concentrated to give **18** as a brown oil (4.61 g). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7 Hz, 3H), 1.43 (t, J = 7 Hz, 3H), 3.80 (s, 2H), 4.19 (q, J = 7 Hz, 2H), 4.36 (q, J = 7 Hz, 2H), 7.22 (t, J = 7 Hz, 1H), 7.41 (m, 4H), 8.02 (s, 1H), 8.09 (d, 1H). MS (ES^+): 282 (MH^+).

An amount of 2 M NaOH (40 mL) was added to a solution of **18** (approximately 15.56 mmol) in EtOH (80 mL) and stirred at room temperature for 37 min. The reaction mixture was acidified with 2 M HCl and allowed to stand, and the resulting precipitate was filtered off and washed with water (2 × 50 mL). The product was partitioned between saturated K_2CO_3 solution (2 × 100 mL) and EtOAc (100 mL), and the combined aqueous layer was washed with EtOAc (100 mL) and then acidified with 2 M HCl solution. Extraction with EtOAc (2 × 100 mL) and concentration of the organic layer yielded (9-ethyl-9*H*-carbazol-3-yl)acetic acid as an off-white solid (1.45 g, 37%). ^{1}H NMR (Me_2SO-d_6): δ 1.29 (t, J = 7 Hz, 3H), 3.70 (s, 2H), 4.41 (q, J = 7 Hz, 2H), 7.16 (t, J = 8 Hz, 1H), 7.37 (d, J = 8 Hz 1H), 7.43 (t, J = 7 Hz, 1H), 7.52 (d, J = 8 Hz 1H), 7.56 (d, J = 8 Hz 1H), 8.00 (s, 1H), 8.10 (d, J = 8 Hz, 1H), 12.19 (br s, 1H). MS (ES^+): 254 (MH^+).

(9-Ethyl-9*H*-carbazol-3-yl)acetic acid was coupled with 4-(aminomethyl)pyridine using the conditions equivalent to those described previously for **2** to yield **8** as a white solid (80% yield). ^{1}H NMR (Me_2SO-d_6): δ 1.29 (t, J = 7 Hz, 3H), 3.66 (s, 2H), 4.29 (d, J = 6 Hz, 2H), 4.40 (q, J = 7 Hz, 2H), 7.17 (t, J = 7 Hz, 1H), 7.20 (d, J = 6 Hz, 2H), 7.41(t, J = 7 Hz, 1H), 7.43 (d, J = 7 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 8.01 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 8.44 (d, J = 6 Hz, 2H), 8.57 (t, J = 6 Hz, 1H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O$.

***N*-(9-Ethyl-9-*H*-carbazol-1yl)-3-pyridin-4-ylpropanamide (9).** 1-Amino-*N*-ethyl carbazole was prepared from 1-Nitro-carbazole[29] and condensed with pyridyl propionic acid in a similar manner as described for **3a** to give **9** in 47% overall yield. ^{1}H NMR (Me_2SO-d_6): δ 1.09 (t, J = 7 Hz, 3H) 2.79 (t, J = 7 Hz, 2H), 2.97 (t, J = 7 Hz, 2H), 4.36 (q, J = 7 Hz, 2H), 7.03−7.22 (m, 3H), 7.34 (d, J = 7 Hz, 2H), 7.44 (t, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.50 (d, J = 7 Hz, 2H), 9.90 (s, 1H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O \cdot 0.15C_2H_{10}O$.

***N*-(9-Ethyl-9-*H*-carbazol-2yl)-3-pyridin-4-ylpropanamide (10).** 2-Nitro-carbazole (3.0 g, 14.1 mmol) was added as a solid in portions to a slurry of NaH (60%, 623 mg, 15.5 mmol) in DMF (70 mL) under argon and cooled in an ice bath. Once effervescence had completed, EtI (1.25 mL, 15.5 mmol) was added dropwise and the mixture allowed to warm to room temperature and stirred overnight. The mixture was then partitioned between EtOAc and water, and the organic layer was washed with water and brine and then dried. Filtration and evaporation gave *N*-ethyl-1-nitrocarbazole as a yellow solid (4.21 g) contaminated with DMF. ^{1}H NMR (Me_2SO-d_6): δ 1.48 (t, J = 7 Hz, 3H), 4.42 (d, J = 7 Hz, 2H), 7.30 (t, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 8.13 (s, 2H), 8.16 (d, J = 8 Hz, 1H), 8.34 (s, 1H). MS (ES^+): 241 (MH^+). This material (2.0 g) was dissolved in EtOH (20 mL) and EtOAc (10 mL) and was stirred under an atmosphere of H_2 along with 10% Pd/C (200 mg) as catalyst. After 3 h, the mixture was filtered through Celite, washed with EtOAc, and concentrated. The residue was dissolved in CH_2Cl_2, dried, and filtered. HCl in Et_2O was added to the resulting solution, and the 2-amino-*N*-ethyl-carbazole was precipitated as the HCl salt (1.64 g, 99% over two steps). ^{1}H NMR (Me_2SO-d_6): δ 1.30 (t, J = 7 Hz, 3H), 4.40 (d, J = 7 Hz, 2H), 7.21 (m, 2H), 7.48 (t, J

= 8 Hz, 1H), 7.59 (s, 1H), 7.63(d, J = 8 Hz, 2H), 8.18 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 10.5 (br s, 3H). MS (ES^+): 211 (MH^+).

2-Amino-*N*-ethyl-carbazole was condensed with pyridyl propionic acid in a similar manner as described for **3a** to give **10** in 94% yield. ^{1}H NMR (Me_2SO-d_6): δ 1.40 (t, J = 7 Hz, 3H) 2.71 (t, J = 7 Hz, 2H), 3.08 (t, J = 7 Hz, 2H), 4.31 (q, J = 7 Hz, 2H), 6.87 (dd, J = 1, 8 Hz, 1H) 7.18 (m, 3H), 7.32 (s, 1H), 7.37 (d, J = 7 Hz, 1H), 7.42 (t, J = 7 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 8.0 (d, J = 7 Hz, 1H), 8.05 (s, 1H), 8.48 (d, J = 7 Hz, 2H). MS (ES^+): 344 (MH^+). Anal. for $C_{22}H_{21}N_3O$.

***N*-(9-Ethyl-9-*H*-carbazol-4yl)-3-pyridin-4-ylpropanamide (11).** A mixture of 9-ethyl-1,2,3,4-tetrahydrocarbazol-4-one[30] (2.13 g, 10 mmol), hydroxylamine hydrochloride (1.04 g, 15 mmol), sodium acetate (1.23 g, 15 mmol) in 22 mL of ethanol, and 15 mL of water was heated under reflux for 20 h. After the EtOH was evaporated, the resulting precipitate was filtered, washed with water (3 × 15 mL), and dried to give 2.26 g (99%) of 9-ethyl-1,2,3,4-tetrahydrocarbazol-4-one-oxime as white crystals. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, J = 7 Hz, 3H), 2.1 (quin, J = 6 Hz, 2H), 2.8 (t, J = 6.5 Hz, 2H), 2.9 (t, J = 6.5 Hz, 2H), 4.1(q, J = 7 Hz, 2H), 7.1−7.3 (m, 3H), 7.4 (br s, 1H), 8.0 (m, 1H). MS (ES^+): 229 (MH^+).

A mixture of 9-ethyl-1,2,3,4-tetrahydrocarbazol-4-one-oxime (1.0 g, 4.8 mmol) and 5% Pd/C (600 mg) in diethylene glycol diethyl ether was heated at reflux for 2 h under argon. The mixture was cooled to room temperature, the catalyst was removed by filtration and washed with EtOAc, and the filtrate was treated with 1 N HCl. The resultant precipitate was filtered and washed with EtOAc and then treated with 1 N HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were washed with saturated brine, dried, and evaporated. The residue was purified by chromatography on silica eluting with toluene to give 4-amino-9-ethyl-carbazole (593 mg, 59%). ^{1}H NMR (Me_2SO-d_6): δ 1.3 (t, J = 7 Hz, 3H), 4.5 (q, J = 7 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.4−7.5 (m, 3H), 7.6 (d, J = 8 Hz, 1H), 8.2 (d, J = 8 Hz 1H). MS (ES^+): 211 (MH^+).

4-Amino-9-ethyl-carbazole was condensed with pyridyl propionate in a similar manner as described for **3a** except that HATU was used as a coupling agent to give **11** in 16% yield. ^{1}H NMR ($CDCl_3$): 1.34 (t, J = 7.5 Hz, 3H), 2.89 (t, J = 7 Hz, 2H), 3.08 (t, J = 7 Hz, 2H), 4.41 (q, J = 7.5 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 7.16 (dd, J = 1,7 Hz, 1H), 7.36−7.47 (m, 5H), (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H), 8.52 (d, J = 7.5 Hz, 2H). MS (ES^+): 344 (MH^+). HRMS for $C_{22}H_{21}N_3O$.

9-Isopropyl-9*H*-carbazole-3-amine (12d). Under inert atmosphere at ambient temperature, 3-nitro-9*H*-carbazole (1.03 g, 4.86 mmol)[29] was added portion wise as a solid to a suspension of NaH (60% in oil) (292 mg, 7.29 mmol) in DMF (40 mL) followed by 2-bromo-propane (0.69 mL, 7.29 mmol) and then heated to 60 °C for 18 h. After it was cooled to room temperature, the mixture was diluted with CH_2Cl_2, washed with water, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2) gave 9-isopropyl-3-nitrocarbazole as a yellow solid. Yield, 0.98 g (79%). ^{1}H NMR (Me_2SO-d_6): δ 1.64 (d, J = 7 Hz, 6H), 5.20 (sept, J = 7 Hz, 1H), 7.31 (dd, J = 8, 7 Hz, 1H), 7.54 (ddd, J = 7, 7, 1 Hz, 1H), 7.82 (d, J = 8 Hz, 1H), 7.87 (d, J = 9 Hz, 1H), 8.27 (dd, J = 9, 2 Hz, 1H), 8.40 (d, J = 8 Hz, 1H), 9.15 (d J = 2 Hz, 1H).

9-Isopropyl-3-nitrocarbazole (950 mg, 3.73 mmol) was dissolved in EtOAc (50 mL) and hydrogenated under an atmosphere of H_2 using 10% Pd/C as catalyst (100 mg). After 2 h, the slurry was filtered through Celite, washed with CH_2Cl_2, and concentrated to give **12d** as a pale brown foam. Yield, 834 mg (99%). ^{1}H NMR (Me_2SO-d_6): δ 1.59 (d, J = 7 Hz, 6H), 4.77 (br s, 2H), 4.96 (m, 1H), 6.83 (dd, J = 9, 2 Hz, 1H), 7.07 (dd, J = 8, 7 Hz, 1H), 7.30 (d, J = 2 Hz, 1H), 7.33 (ddd, J = 7, 7, 1 Hz, 1H), 7.40 (d, J = 9 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H). Anal. for $C_{15}H_{16}N_2$:HCl:0.5H_2O.

9-Neopentyl-9*H*-carbazole-3-amine (12e). This procedure was the same as for **12d** using neopentyl iodide and NaH as base, in 20% overall yield. ^{1}H NMR (Me_2SO-d_6): δ 1.00 (s, 9H), 4.03 (s, 2H), 4.68 (s, 2H), 6.78 (dd, J = 2, 8 Hz, 1H), 7.03 (t, J = 8 Hz, 1H), 7.23 (d, J = 2 Hz, 1H), 7.25−7.33, (m, 2H), 7.46 (d, J = 8 Hz, 1H), 7.89 (d, J = 8 Hz, 1H). Anal. for $C_{15}H_{20}N_2$.

9-Tetrahydrofuran-3-yl-9*H*-carbazole-3-amine (12f). This procedure was the same as for **12d** using 3-methanesulfoxy-tetrahydrofuran and cesium carbonate as base, to give 3-nitro-9-(3-tetrahydrofuryl)carbazole in 58% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.20 (m, 1H), 2.55 (m, 1H), 3.75 (m, 1H), 4.00 (m, 1H), 4.25 (m, 1H), 4.35 (m, 1H), 5.80 (m, 1H), 7.30 (dd, J = 1, 7 Hz, 1H), 7.55 (dd, J = 1, 7 Hz, 1H), 7.85 (dd, J = 1, 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 8.30 (dd, J = 2, 9 Hz, 1H), 8.40 (d, J = 7 Hz, 1H), 9.15 (d, J = 2 Hz, 1H).

Hydrogenation gave **12f**. ^{1}H NMR (Me_2SO-d_6): δ 2.20 (m, 1H), 2.40 (m, 1H), 3.75 (m, 1H), 3.95 (m, 1H), 4.15 (m, 1H), 4.25 (m, 1H), 4.70 (s, 2H), 5.50 (m, 1H), 6.80 (dd, J = 2, 9 Hz, 1H), 7.05 (dd, J = 1, 7 Hz, 1H), 7.25 (d, J = 2 Hz, 1H), 7.35 (dd, J = 1, 7 Hz, 1H), 7.40 (d, J = 9 Hz, 1H), 7.60 (dd, J = 1, 9 Hz, 1H), 7.90 (d, J = 7 Hz). MS (ES^+): 253 (MH^+). Anal. for $C_{16}H_{16}N_2O$.

9-Acetyl-9*H*-carbazole-3-amine (12g). This procedure was the same as for **12d** using acetyl chloride and NaH as base, in 68% overall yield. ^{1}H NMR (Me_2SO-d_6): δ 2.80 (s, 3H), 5.14 (br s, 2H), 6.81 (dd, J = 8, 2 Hz, 1H), 7.24 (d, J = 2 Hz, 1H), 7.35 (dd, J = 8, 8 Hz, 1H), 7.44 (dd, J = 8, 8 Hz, 1H), 7.93 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H), 8.2 (d, J = 8 Hz, 1H). MS (ES^+): 225 (MH^+). Anal. for $C_{14}H_{12}NO$.

9-Methylsulfonyl-9*H*-carbazole-3-amine (12h). This procedure was the same as for **12d** using methane sulfonyl chloride and NaH as base, 78% yield. ^{1}H NMR (Me_2SO-d_6): δ 3.07 (s, 3H), 5.16 (s, 2H), 6.80 (dd, J = 2, 9 Hz, 1H), 7.22 (d, J = 2 Hz, 1H), 7.37 (dt, J = 7, 8 Hz, 1H,), 7.47 (dt, J = 7, 8 Hz, 1H), 7.67 (d, J = 9 Hz, 1H), 7.96 (dd, J = 7, 8 Hz, 2H). MS (ES^+): 261 (MH^+). Anal. for $C_{13}H_{12}N_2O_2S$.

9-(Dimethylamino)sulfonyl-9*H*-carbazole-3-amine (12i). This procedure was the same as for **12d** using dimethylamino sulfonyl chloride and NaH as base, 44% yield. ^{1}H NMR (Me_2SO-d_6): δ 2.70 (s, 6H), 5.10 (s, 2H), 6.80 (dd, J = 2, 9 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.45 (t, J = 8 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.95 (d, J = 8 Hz). MS (ES^+): 290 (MH^+).

6-Fluoro-9-isopropyl-9*H*-carbazole-3-amine (12j) (Scheme 3). A stirred mixture of 4-fluorophenylhydrazine hydrochloride (4.4 g, 27 mmol) and ethyl-4-oxocyclohexanecarboxylate (**19**) (4.6 g, 27 mmol) in EtOH (100 mL) was heated under reflux overnight. The solution was cooled in an ice bath, and the resultant white crystals were filtered off and washed with ice cold EtOH to give **20** (R2 = 6-F). Yield, 6.3 g (79%). NMR ($CDCl_3$): δ 1.3 (t, J = 7 Hz, 3H), 1.9−2.1 (m, 1H), 2.3 (m, 1H), 2.7−2.9 (m, 4H), 3.0 (m, 1H), 4.2 (q, J = 7 Hz, 2H), 6.8 (ddd, J = 2, 8.5, 9.5 Hz, 1H), 7.1(dd, J = 2, 9.5 Hz, 1H), 7.2 (dd, J = 4, 8.5 Hz, 1H), 7.7 (s, 1H). MS (ES^+): 262 (MH^+).

Compound **20** (R2 = 6-F) (3.13 g, 12 mmol) in xylene was treated with DDQ (6.45 g, 26 mmol), and the mixture was heated under reflux for 4 h, cooled to ambient temperature, and filtered through Celite, and the filtrate was loaded on to a Bond Elute column (20 g) and eluted with 5% EtOAc/toluene. The eluent was concentrated and then recrystallized from EtOAc/*i*-hexane to give 6-fluoro-3-ethoxycarbonylcarbazole; yield, 2.35 g (76%). NMR ($CDCl_3$): δ 1.5 (t, J = 7 Hz, 3H), 4.4 (q, J = 7 Hz, 2H), 7.2 (ddd, J = 2, 8.5, 9 Hz, 1H), 7.3 (dd, J = 4, 8.5 Hz, 1H), 7.4 (d, J = 8.5, 1H), 7.8 (dd, J = 2, 8.5 Hz, 1H), 8.2 (dd, J = 1.5, 8.5 Hz 1H), 8.3 (s, 1H), 8.8 (d, J = 1.5 Hz, 1H). MS (ES^+): 258 (MH^+).

6-Fluoro-3-ethoxycarbonylcarbazole was alkylated with 2-bromo-propane as described for **12d** to give **21** (R2 = 6-F) in 45% overall yield. NMR ($CDCl_3$): δ 1.4 (t, J = 7 Hz, 3H), 1.7 (d J = 7 Hz, 6H), 4.5 (q, J = 7 Hz, 2H), 5.0 (sept, J = 7 Hz, 1H), 7.2 (ddd, J = 2.5, 8.5, 9 Hz,1H), 7.4 (dd, J = 4, 8.5 Hz, 1H), 7.5 (d, J = 8.5 Hz, 1H), 7.8 (dd, J = 2.5, 8.5 Hz, 1H), 8.2 (dd, J = 1.5, 8.5 Hz, 1H), 8.8 (d, J = 1.5 Hz, 1H). MS (ES^+): 300 (MH^+).

Compound **21** (R2 = 6-F) (1.46 g) was dissolved in THF: MeOH (3:1, 40 mL), 1 M LiOH (19 mL) was added, and the solution was heated at 60 °C for 1 h. After it was cooled, the

organic solvents were removed under vacuum, the resultant aqueous solution was acidified to pH 1 with concentrated HCl, and the resultant precipitate was filtered and dried to give 6-fluoro-9-isopropyl-9*H*-carbazol-3-yl carboxylic acid (1.3 g). NMR ($CDCl_3$): δ 1.6 (d, J = 7 Hz, 6H), 5.1 (sept, J = 7 Hz 1H), 7.3 (dt, J = 2.5, 8.5 Hz, 1H), 7.7 (m, 2H), 8.0 (dd, J = 1.5, 8.5 Hz, 1H), 8.2 (dd, J = 2.5, 9 Hz, 1H), 8.8 (d, J = 1.5 Hz, 1H). MS (ES^+): 272 (MH^+).

Et_3N (139 μL, 1 mmol) was added to a stirred suspension of 6-fluoro-9-isopropyl-9*H*-carbazol-3-yl carboxylic acid (271 mg, 1 mmol) and diphenylphosphoryl azide (216 μL, 1 mmol) in dry toluene (15 mL) under argon. The resultant solution was stirred at ambient temperature for 1 h and then heated to reflux for 1 h. After the solution was allowed to cool to 80 °C, trimethylsilyl ethanol (285 μL, 2 mmol) was added and the heating was continued at 80 °C for 6 h. The mixture was diluted with EtOAc (30 mL) and washed with water (10 mL), 0.5 N NaOH (10 mL), water (10 mL), and saturated brine (10 mL), and then dried, evaporated, and purified by chromatography on silica using a 5 g Bond Elute cartridge and eluting with CH_2Cl_2 to give *N*-carboxytrimethylsilylethyl(6-fluoro-9-isopropyl-9*H*-carbazol-3-yl)-4-amine (295 mg), which was dissolved in 1 M TBAF in THF and heated at 50 °C for 30 min. The solution was allowed to cool, and the solvent was removed at reduced pressure. The residue was dissolved in EtOAc (5 mL), water (5 mL) was added, and the layers were mixed by rapid stirring for 15 min. The organic layer was washed with saturated ammonium chloride and dried, evaporated, and purified by chromatography on silica using a 5 g Bond Elute cartridge and eluting with 1:1 CH_2Cl_2/toluene to give a sticky oil, which was dissolved in EtOAc and treated with a solution of HCl in EtOAc to give 106 mg of off-white solid **12j** as the HCl salt. ^{1}H NMR (Me_2SO-d_6): δ 1.6 (d, J = 7 Hz, 6H), 5.1 (sept, J = 7 Hz, 1H), 7.3 (ddd, J = 3, 9, 9 Hz, 1H), 7.4 (dd, J = 2, 9 Hz, 1H), 7.7 (dd, J = 4, 9 Hz, 1H), 7.8 (d, J = 9 Hz, 1H), 8.05 (dd, J = 3, 9 Hz, 1H), 8.1 (d, J = 2 Hz, 1H). MS (ES^+): 243 (MH^+). Anal. for $C_{15}H_{16}FClN_2$.

9-Isopropyl-8-methyl-9*H*-carbazole-3-amine (12k) (Scheme 3). Compound **12k** was prepared using 2-methylphenylhydrazine in the first step and methods analogous to those described for **12j** in 56% overall yield from the corresponding acid. ^{1}H NMR ($CDCl_3$): δ 1.6 (d, J = 7 Hz, 6H), 2.7 (s, 3H), 5.4 (sept, J = 7 Hz, 1H), 6.8 (dd, J = 2, 8.5 Hz, 1H), 7.0 (t, J = 7.5 Hz, 1H), 7.1 (d, J = 7 Hz, 1H), 7.4 (d, J = 2 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.8 (d, J = 7.5 Hz, 1H). MS (ES^+): 239 (MH^+). Anal. for $C_{16}H_{18}N_2$.

The intermediates were obtained as follows:

8-Methyl-3-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (**20**, R2 = 8-Me) in 70% overall yield. ^{1}H NMR ($CDCl_3$): δ 1.3 (t, J = 7 Hz, 3H), 1.9−2.1 (m, 1H), 2.3 (m, 1H), 2.5 (s, 3H), 2.7−2.9 (m, 4H), 3.0 (m, 1H), 4.2 (q, J = 7 Hz, 2H), 6.9 (d, J = 7 Hz, 1H), 7.0 (t, J = 7 Hz, 1H), 7.3 (d J = 7.5 Hz, 1H), 7.7 (s, 1H).

8-Methyl-3-ethoxycarbonylcarbazole in 68% overall yield. NMR ($CDCl_3$): δ 1.5 (t, J = 7 Hz, 3H), 2.6 (s, 3H), 4.4 (q, J = 7 Hz, 2H), 7.2 (m, 2H), 7.4 (d, J = 8.5 Hz, 1H), 8.0 (d, J = 7.5 Hz, 1H), 8.2 (d, J = 8.5 Hz, 1H), 8.3 (s, 1H), 8.8 (s, 1H). MS (ES^+): 254 (MH^+).

8-Methyl-9-isopropyl-3-ethoxycarbonylcarbazole (**21**, R2 = 8-Me) (using Cs_2CO_3 as base) in 29% overall yield. NMR ($CDCl_3$): δ 1.4 (t, J = 7.1 Hz, 3H), 1.7 (d, J = 7.1 Hz, 6H), 2.8 (s, 3H), 4.4 (q, J = 7 Hz, 2H), 5.6 (sept, J = 7 Hz, 1H), 7.2 (m, 2H), 7.6 (d, J = 9 Hz, 1H), 8.0 (dd, J = 7.5, 1 Hz, 1H), 8.1 (dd, J = 9, 2 Hz, 1H), 8.8 (d, J = 1 Hz, 1H). MS (ES^+): 296 (MH^+).

8-Methyl-9-isopropyl-9*H*-carbazol-3-yl carboxylic acid in 84% overall yield. MS (ES^+): 268 (MH^+).

9-Isopropyl-2-methyl-9*H*-carbazole-3-amine (12l) (Scheme 4). NaH (60% in oil, 454 mg, 11.34 mmol) was added slowly to a solution of **23** (R3 = Me, R4 = H)[12] (1.74 g) in dry DMF at 0 °C under an argon atmosphere. Once effervescence had ceased, 2-bromo-propane (1.06 mL, 11.34 mmol) was added and the reaction mixture was heated at 60 °C for 20 h before cooling. Further NaH (60% in oil, 1.21 g, 30.24 mmol) was added followed by 2-bromo-propane (2.84 mL, 30.24 mmol), and the mixture was heated at 60 °C for 4 h. The reaction mixture was concentrated, diluted with water, and extracted into EtOAc. The organic layers were separated and washed with water and brine and dried. Chromatography (eluent 25% EtOAc/*i*-hexane) yielded 1,2,3,4-tetrahydro-9-isopropyl-7-methyl-6-nitrocarbazole as a yellow solid (1.53 g, 74%). ^{1}H NMR (Me_2SO-d_6): δ 1.50 (d, J = 7 Hz, 6H), 1.77 (m, 2H), 1.87 (m, 2H), 2.64 (m, 5H), 2.75 (m, 2H), 4.68 (m, J = 7 Hz, 1H), 7.52 (s, 1H), 8.13 (s, 1H).

To a stirred solution of 1,2,3,4-tetrahydro-9-isopropyl-7-methyl-6-nitrocarbazole (1.53 g, 5.62 mmol) in 1,4-dioxane at room temperature was added DDQ (2.56 g, 11.24 mmol) portion wise. The reaction mixture was stirred at 100 °C for 20 h before it was concentrated. Chromatography (eluent 10% EtOAc/*i*-hexane) yielded 2-methyl-9-isopropyl-3-nitrocarbazole as a yellow solid (947 mg, 63%). ^{1}H NMR (Me_2SO-d_6): δ 1.63 (d, J = 7 Hz, 6H), 2.76 (s, 3H), 5.17 (sept, J = 7 Hz, 1H), 7.26 (t, J = 7 Hz, 1H), 7.50 (t, J = 7 Hz, 1H), 7.73 (s, 1H), 7.77 (d, J = 7 Hz, 1H), 8.29 (d, J = 7 Hz, 1H), 8.96 (s, 1H).

2-Methyl-9-isopropyl-3-nitrocarbazole (947 mg, 3.5 mmol) was dissolved in EtOAc (20 mL) and hydrogenated under an atmosphere of H_2 using 10% Pd/C as catalyst (180 mg). After 12 h, the slurry was filtered through Celite, washed with EtOAc, and concentrated under vacuum to give **12l** as a brown oil, which solidified on standing (700 mg, 83%). ^{1}H NMR (Me_2SO-d_6): δ 1.57 (d, J = 7 Hz, 6H), 2.26 (s, 3H), 4.45 (br s, 2H), 4.93 (sept, J = 7 Hz, 1H), 7.03 (t, J = 7 Hz, 1H), 7.26 (t, J = 7 Hz, 1H), 7.30 (2 x s, 2H), 7.49 (d, J = 7 Hz, 1H), 7.86 (d, J = 7 Hz, 1H). MS (ES^+): 239 (MH^+). Anal. for $C_{16}H_{18}N_2$.

9-Isopropyl-2-chloro-9*H*-carbazole-3-amine (12m) (Scheme 4). 3-Chloroaniline (18.5 mL, 175.2 mmol) and 2-chlorocyclohexanone (10 mL, 87.6 mmol) were stirred in EtOH at reflux for 3 h. After it was cooled, the reaction mixture was concentrated and the residue was stirred in Et_2O (150 mL). An amount of 2 M HCl in Et_2O (43.8 mL) was added to the mixture and stirred for 2 h before filtering and washing with Et_2O (2 × 50 mL). The filtrate was concentrated, and the residue was purified by chromatography (eluent, CH_2Cl_2). The solid obtained was recrystallized from EtOAc/*i*-hexane to yield **22** (R3 = Cl, R4 = H) as a light brown solid (3.9 g, 22%). ^{1}H NMR (Me_2SO-d_6): δ 1.78 (m, 4H), 2.58 (m, 2H), 2.67 (m, 2H), 6.89 (d, J = 8 Hz, 1H), 7.24 (s, 1H), 7.30 (d, J = 8 Hz, 1H), 10.76 (br s, 1H).

Compound **22** (R3 = Cl, R4 = H) (3.42 g, 16.64 mmol) was stirred in concentrated H_2SO_4 (50 mL) at 0 °C for 30 min. Potassium nitrate (1.68 g, 16.64 mmol) was added slowly before the reaction mixture was stirred at 0 °C for 3 h. The mixture was poured onto ice/water, and the resulting yellow precipitate was filtered and washed with dilute ammonia solution (20%) and then water. The solid was dried at 40 °C under vacuum overnight and then purified by chromatography (eluent, CH_2Cl_2) to give **23** (R3 = Cl, R4 = H) as a yellow solid (3.33 g, 80%). ^{1}H NMR (Me_2SO-d_6): δ 1.78 (m, 4H), 2.60 (m, 2H), 2.70 (m, 2H), 7.46 (s, 1H), 8.11 (s, 1H), 11.44 (br s, 1H).

1,2,3,4-Tetrahydro-7-chloro-9-isopropyl-6-nitrocarbazole was prepared in a similar manner as described for 1,2,3,4-tetrahydro-9-isopropyl-7-methyl-6-nitrocarbazole. A yellow solid was obtained (58%). ^{1}H NMR (Me_2SO-d_6): δ 1.75 (m, 2H), 1.85 (m, 2H), 2.64 (m, 2H), 2.78 (m, 2H), 7.80 (s, 1H), 8.14 (s, 1H). MS (ES^+): 293 (MH^+).

2-Chloro-9-isopropyl-3-nitrocarbazole was prepared in a manner similar to 2-methyl-9-isopropyl-3-nitrocarbazole. A yellow solid was isolated (57%). ^{1}H NMR (Me_2SO-d_6): δ 1.64 (d, J = 7 Hz, 6H), 5.21 (sept, J = 7 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 8.05 (s, 1H), 8.35 (d, J = 8 Hz, 1H), 9.05 (s, 1H).

2-Chloro-9-isopropyl-3-nitrocarbazole (635 mg, 2.2 mmol) was stirred in EtOH/water (35 mL/25 mL) at reflux. Sodium hydrosulfite (2.57 g, 14.76 mmol) was added in one portion, and the reaction mixture was stirred at reflux for 2 h. After it was cooled, the EtOH was removed under vacuum and the remaining aqueous mixture was extracted with EtOAc (2 × 100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried and concentrated. Chromatography (eluent, CH_2Cl_2) yielded **12m** as a brown solid (286 mg,

50%). ^{1}H NMR (Me_2SO-d_6): δ 1.56 (d, J = 7 Hz, 6H), 4.88 (br s, 2H), 4.95 (sept, J = 7 Hz, 1H), 7.08 (t, J = 7 Hz, 1H), 7.34 (t, J = 7 Hz, 1H), 7.50 (s, 1H), 7.56 (d, J = 7 Hz, 1H), 7.57 (s, 1H), 7.93 (d, J = 7 Hz, 1H). MS (ES^+): 259 (MH^+). Anal. for $C_{15}H_{15}ClN_2$.

2,4-Difluoro-9-isopropyl-9*H*-carbazole-3-amine (12n) (Scheme 6). Benzyl bromide (3.72 mL, 31.3 mM) was added to a suspension of 4-bromo-2,6-difluoroaniline (2.17 g, 10.4 mM) and K_2CO_3 (5.77 g, 41.7 mM) in DMF (10 mL) and heated to 100 °C for 18 h. After it was cooled to room temperature, the mixture was diluted with CH_2Cl_2, washed with water, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2:*i*-hexane (1:19)) gives **24** as a colorless, clear oil. Yield, 3.50 g (87%). ^{1}H NMR ($CDCl_3$): δ 7.40−7.15 (10H, m), 7.00−6.85 (2H, m), 4.22 (4H, s). MS (ES^+): 388/390 (1:1) (MH^+).

Benzophenone hydrazone (1.31 g, 6.63 mM), $Pd(OAc)_2$ (15 mg, 0.06 mM), and (*S*)-BINAP (62 mg, 0.1 mM) were suspended in toluene (11 mL) and heated to 100 °C for 3 min under an inert atmosphere. After it was cooled to room temperature, a solution of **24** (2.58 g, 6.63 mM) in toluene (2 mL) was added followed by NaO^{t}Bu (893 mg, 9.29 mM) and the mixture was heated to 100 °C for 3 h. After it was cooled, the mixture was filtered through Celite, and the filter cake was rinsed with Et_2O. Concentration and then chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2) gave **25** as a solid. Yield, 3.13 g (94%). ^{1}H NMR ($CDCl_3$): δ 7.60−7.45 (5H, m), 7.35−7.15 (16H, m), 6.55−6.45 (2H, m), 4.16 (4H, s). MS (ES^+): 504 (MH^+).

Compound **25** (3.05 g, 6.06 mM), cyclohexanone (0.95 mL, 9.09 mM), and *p*-toluenesulfonic acid (3.45 g, 18.19 mM) in EtOH (31 mL) were heated to reflux for 18 h. After it was cooled, the mixture was diluted with CH_2Cl_2, washed with K_2CO_3 solution, dried, and concentrated. Chromatography on silica gel (eluent gradient of Hexane to CH_2Cl_2:*i*-hexane (1:1)) gave **26** as a solid. Yield, 2.03 g (83%). ^{1}H NMR ($CDCl_3$): δ 7.50 (1H, s), 7.45−7.15 (10H, m), 6.63 (1H, d), 4.22 (4H, s), 2.80 (2H, m), 2.59 (2H, m), 1.84 (4H, m). MS (ES^+): 403 (MH^+).

Compound **26** (1.97 g, 4.90 mmol) was added to NaH (60% dispersion in oil) (392 mg, 9.80 mmol) in DMF (5 mL) followed by 2-bromo-propane (0.92 mL, 9.80 mmol) and heated to 60 °C for 18 h. After it was cooled, NaH (60% dispersion in oil) (392 mg, 9.80 mmol) was added followed by 2-bromo-propane (0.92 mL, 9.80 mmol) and again heated to 60 °C for 18 h. After this was cooled, the mixture was diluted with CH_2Cl_2, washed with K_2CO_3 solution, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to EtOAc:*i*-hexane (1:9)) gave 9-(prop-2-yl)-7-dibenzylamino-6,8-difluoro-1,2,3,4-tetrahydrocarbazole as a yellow solid. Yield, 1.70 g (78%). ^{1}H NMR ($CDCl_3$): δ 1.49 (d, 6H), 1.74−1.94 (m, 4H), 2.65 (t, 2H), 2.83 (t, 2H), 4.22 (s, 4H), 4.43 (sept, 1H), 6.80 (dd, J = 12 Hz, 1 Hz, 1H), 7.14−7.45 (m, 10H). MS (ES^+): 445 (MH^+).

DDQ (818 mg, 3.60 mmol) was added to 9-(prop-2-yl)-7-dibenzylamino-6,8-difluoro-1,2,3,4-tetrahydrocarbazole (800 mg, 1.80 mmol) in 1,4-dioxan (7.5 mL) and heated to 90 °C for 30 min and then cooled to room temperature. Further DDQ (204 mg, 0.9 mmol) was added and again heated to 90 °C for 30 min. After it was cooled, the mixture was diluted with EtOAc, washed with K_2CO_3 solution, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2:*i*-hexane (2:3)) gave 3-dibenzylamino-2,4-difluoro-9-(prop-2-yl)carbazole as a yellow solid. Yield, 501 mg (63%). ^{1}H NMR ($CDCl_3$): δ 1.63 (d, 6H), 4.30 (s, 4H), 4.79 (sept, 1H), 6.89 (dd, J = 12, 1 Hz, 1H), 7.14−7.50 (m, 13H), 8.13 (d, J = 8 Hz, 1H).

A solution of ammonium formate (284 mg, 4.50 mmol) in water (1 mL) was added to a suspension of 9-(prop-2-yl)-7-dibenzylamino-6,8-difluoro-1,2,3,4-tetrahydrocarbazole (0.50 g, 1.14 mmol) and 10% Pd/C (50% wet with water) (76 mg) in MeOH (4.25 mL) and then refluxed for 1 h. After it was cooled, the mixture was filtered through Celite, diluted with CH_2Cl_2, washed with K_2CO_3 solution, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2) gave **12n** as a pale brown solid. Yield, 261 mg (88%). ^{1}H NMR ($CDCl_3$): δ 1.65 (d, J = 7 Hz, 6H), 4.82 (m, 1H), 7.01 (dd, J = 12, 1 Hz, 1H), 7.19 (ddd, J = 8, 8, 1 Hz, 1H), 7.39 (ddd, J = 8, 8, 1 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H). MS (ES^+): 261 (MH^+). HRMS for $C_{15}H_{14}F_2N_2$.

9-Isopropyl-4-methyl-9*H*-carbazole-3-amine (12o) (Scheme 7). A solution of 9-isopropyl-3-nitrocarbazole (1.13 g, 4.46 mmol) in dry THF (50 mL) was cooled to −15 °C under an argon atmosphere. MeMgCl (3 M solution in THF, 2.23 mL, 6.7 mmol) was added dropwise, and the resultant solution was stirred for a further hour at −15 °C. DDQ (1.71 g, 7.54 mmol) was added keeping the temperature below −10 °C and then allowed to warm to room temperature and left for 48 h (believed to be unnecessary). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (30 mL), and the organic layer was dried. Solvent was removed, and chromatography (eluent, 10−30% CH_2Cl_2/*i*-hexane) yielded **27** (R4 = Me) as a yellow solid (940 mg, 79%). ^{1}H NMR (Me_2SO-d_6): δ 1.64 (d, J = 7 Hz, 6H), 3.01 (s, 3H), 5.20 (sept, J = 7 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz, 1H), 7.74 (d, J = 9 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 8.02 (d, J = 9 Hz, 1H), 8.32 (d, J = 8 Hz, 1H). MS (ES^+): 269 (MH^+).

Compound **27** (R4 = Me) (828 mg, 3.09 mmol) was hydrogenated in a similar manner as described in the preparation of **12d** and chromatographed on silica gel (eluent, 50% EtOAc/*i*-hexane) to give **12o** as a colorless solid (661 mg, 90%). ^{1}H NMR (Me_2SO-d_6): δ 1.55 (d, J = 7 Hz, 6H), 2.56 (s, 3H), 4.50 (br s, 2H), 4.97 (sept, J = 7 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.28 (m, 2H), 7.53 (d, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H). MS (ES^+): 239 (MH^+). Anal. for $C_{16}H_{18}N_2$·HCl.

4,9-Diisopropyl-9*H*-carbazole-3-amine (12p) (Scheme 7). Isopropylmagnesium chloride (2 M solution in THF) (2.23 mL, 4.46 mmol) was added to 9-isopropyl-3-nitrocarbazole (1.13 g, 4.45 mmol) in THF (20 mL) at −15 °C. After 1 h, DDQ (2.22 g, 9.79 mmol) was added and then allowed to warm to ambient temperature for 18 h. The mixture was diluted with CH_2Cl_2, washed with K_2CO_3 solution, dried, and concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2) gave **27** (R4 = ^{i}Pr) as a yellow solid. Yield, 0.56 g (46%). ^{1}H NMR ($CDCl_3$): δ 1.66 (d, 6H), 1.76 (d, 6H), 4.25 (m, 1H), 5.07 (m, 1H), 7.34 (dd, J = 8 Hz, 1H), 7.42 (d, J = 9 Hz, 1H), 7.52 (dd, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.77 (d, J = 9 Hz, 1H), 8.29 (d, J = 8 Hz, 1H). MS (ES^+): 297 (MH^+).

Compound **27** (R4 = ^{i}Pr) (0.55 g, 1.86 mmol) in EtOH (20 mL) was hydrogenated over 10% Pd/C (100 mg) at ambient temperature under atmospheric pressure of hydrogen. The catalyst was filtered off through Celite, and the filtrate was concentrated. Chromatography on silica gel (eluent gradient of *i*-hexane to CH_2Cl_2) gave **12p** as a pale brown foam. Yield, 0.55 g. ^{1}H NMR ($CDCl_3$): δ 1.63 (d, 6H), 1.71 (d, 6H), 4.43 (m, 1H), 4.98 (m, 1H), 6.90 (d, J = 8 Hz, 1H), 7.16 (ddd, J = 8, 8, 1 Hz, 1H), 7.26 (d, J = 8 Hz,1H), 7.41 (ddd, J = 8, 8, 1 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 8.29 (d, J = 8 Hz, 1H). MS (ES^+): 267 (MH^+). Anal. for $C_{18}H_{22}N_2$.

4-Ethoxy-9-isopropyl-9*H*-carbazole-3-amine (12q) (Scheme 7). Compound **12q** was prepared in a similar manner as described in reference 16. Under an inert atmosphere, a hot solution of NaOH (2.27 g, 56.75 mmol) in water (2.27 mL) was added to a refluxing solution of 9-isopropyl-3-nitrocarbazole (0.72 g, 2.83 mmol) in EtOH (68 mL). Zinc powder (1.47 g, 22.49 mmol) was added, and then, the mixture was refluxed for 12 h. After it was cooled, the mixture was filtered through Celite, diluted with CH_2Cl_2, washed with K_2CO_3 solution, dried, and concentrated. Chromatography was performed on silica gel (eluent gradient of toluene to toluene:Et_2O (1:1) to give **12q** as a gum. Yield, 80 mg (11%). ^{1}H NMR ($CDCl_3$): δ 1.58 (t, 3H), 1.68 (d, 6H), 4.21 (q, 2H), 4.90 (m, 1H), 6.95 (d, J = 8 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 7.17 (dt, J = 8, 1 Hz, 1H), 7.0 (dt, J = 8, 1 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H). MS (ES^+): 269 (MH^+). HRMS for $C_{17}H_{20}N_2O$.

9-Isopropyl-1,4-dimethyl-9*H*-carbazole-3-amine (12r) (Scheme 5). 6-Bromo-1,4-dimethylcarbazole[13] (3.5 g, 13 mmol) was added in portions over 10 min to a solution of 18-crown-6 (0.4 g, 1.5 mmol) and potassium bis(trimethylsilyl)amide (2.8

g, 14.3 mmol) in DMF (25 mL). 2-Iodopropane (1.4 mL, 14 mmol) was added in a single portion, and the mixture was heated to 90 °C for 18 h. The solvent was removed under vacuum, and the residue was partitioned between CH_2Cl_2 (50 mL) and 1 N HCl (50 mL). The organic layer was separated, washed with brine (50 mL), dried, and concentrated to leave a red oil. The crude product was purified by flash chromatography eluting with a 5:1 mixture of *i*-hexane:EtOAc to give 6-bromo-1,4-dimethyl-9-*iso*-propylcarbazole as a colorless solid (1.0 g, 27%). ^{1}H NMR ($CDCl_3$): δ 1.56 (d, J = 7 Hz, 6H), 2.65 (s, 3H), 2.68 (s, 3H), 5.44 (sep, J = 7 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.34 (dd, J = 8.7 & 1.9 Hz, 1H), 7.41(d, J = 8.7 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H).

6-Bromo-1,4-dimethyl-9-*iso*-propylcarbazole (1.0 g, 3.2 mmol) was dissolved in glacial acetic acid (20 mL), and the solution was cooled in an ice-bath. Concentrated HNO_3 (d = 1.42, 0.4 mL) was added dropwise over 5 min, and the mixture was stirred in an ice-bath for 1 h. The mixture was poured into water (50 mL), and the resulting precipitate was collected by filtration. The solid was washed with water (2 × 25 mL) and then with MeOH (2 × 25 mL). The product was dried in air to leave 6-bromo-1,4-dimethyl-9-*iso*-propyl-3-nitrocarbazole as a yellow solid (0.405 g, 37%). ^{1}H NMR ($CDCl_3$): δ 1.66 (d, J = 7 Hz, 6H), 2.75 (s, 3H), 2.96 (s, 3H), 5.51 (sep, J = 7 Hz, 1H), 7.49 (dd, J = 9, 2 Hz, 1H), 7.55 (d, J = 9 Hz, 1H), 7.77 (s, 1H), 8.34 (d, J = 2 Hz, 1H).

An amount of 10% Pd/C (0.4 g) was added to a solution of 6-bromo-1,4-dimethyl-9-*iso*-propyl-3-nitrocarbazole (0.49 g, 1.4 mmol) in EtOAc (25 mL). The mixture was stirred under an atmosphere of hydrogen at room temperature for 72 h and then filtered through Celite, and the residue was washed with CH_2Cl_2 (2 × 25 mL). The solvent was evaporated under vacuum, and the residue was purified by preparative high-performance liquid chromatography (HPLC) eluting with 30−95% acetonitrile in water (0.1% TFA) to give **12r** as a colorless solid (95 mg, 28%). ^{1}H NMR (Me_2SO-d_6): δ 1.65 (d, J = 7 Hz, 6H), 2.75 (s, 3H), 2.8 (s, 3H), 5.5 (sept, J = 7 Hz, 1H), 7.22 (m, 1H), 7.25 (s, 1H), 7.45 (m, 1H), 7.83 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 10.15 (br s, 3H). MS (ES^+): 253 (MH^+). HRMS for $C_{17}H_{20}N_2$.

9-Isopropyl-2,4-dimethyl-9*H*-carbazole-3-amine (12s) (Scheme 4). The sequence used to prepare **12s** was similar to that described for **12l**.

Compound **22 (**R3 = R4 = Me**)** was prepared as for **22** (R3 = Cl, R4 = H) but using 3,5-dimethylaniline instead of 3-chloroaniline. The product was isolated as a brown solid (yield 77%). ^{1}H NMR (Me_2SO-d_6): δ 1.75 (m, 4H), 2.27 (s, 3H), 2.49 (s, 3H), 2.63 (m, 2H), 2.86 (m, 2H), 6.43 (s, 1H), 6.80 (s, 1H), 10.30 (br s, 1H).

Compound **23 (**R3 = R4 = Me**)** was prepared in a manner similar to **23 (**R3 = Cl, R4 = H**)**. The product was isolated as an orange solid (yield 51%). ^{1}H NMR (Me_2SO-d_6): δ 1.77 (m, 4H), 2.26 (s, 3H), 2.45 (s, 3H), 2.67 (m, 2H), 2.98 (m, 2H), 7.02 (s, 1H), 10.95 (s, 1H). MS (ES^-): 243 ($M - H^-$).

1,2,3,4-Tetrahydro-5,7-dimethyl-9-isopropyl-6-nitrocarbazole was prepared in a manner similar to 1,2,3,4-tetrahydro-9-isopropyl-7-methyl-6-nitrocarbazole. Product was recrystallized from EtOAc/*i*-hexane to yield a yellow solid (20%). ^{1}H NMR (Me_2SO-d_6): δ 1.48 (d, J = 7 Hz, 6H), 1.77 (m, 4H), 2.30 (s, 3H), 2.45 (s, 3H), 2.73 (m, 2H), 2.90 (m, 2H), 4.65 (sept, J = 7 Hz, 1H), 7.34 (s, 1H). MS (ES^-): 287 (MH^-).

2,4-Dimethyl-9-isopropyl-3-nitrocarbazole was prepared in a manner similar to 2-methyl-9-isopropyl-3-nitrocarbazole. A yellow solid was recrystallized from EtOAc/*i*-hexane (69%). ^{1}H NMR (Me_2SO-d_6): δ 1.63 (d, J = 7 Hz, 6H), 2.45 (s, 3H), 2.73 (s, 3H), 5.17 (sept, J = 7 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.64 (s, 1H), 7.78 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H).

Compound **12s** was prepared in a manner similar to **12l**. The product was isolated as a brown solid (92%). ^{1}H NMR (Me_2SO-d_6): δ 1.56 (d, J = 7 Hz, 6H), 2.30 (s, 3H), 2.59 (s, 3H), 4.28 (br s, 2H), 4.97 (sept, J = 7 Hz, 1H), 7.04 (t, J = 7 Hz, 1H), 7.21 (s, 1H), 7.27 (t, J = 7 Hz, 1H), 7.54 (d, J = 7 Hz, 1H), 8.12 (d, J = 7 Hz, 1H). MS (ES^+): 253 (MH^+). Anal. for $C_{17}H_{20}N_2$.

Acknowledgment. We thank the following people for their invaluable practical and intellectual contributions: Madeleine Vickers and Rob Horton for spectroscopic data and interpretation, George Stratton, Eddie Clayton, Britt-Marie Fihn, Gun-Britt Forsberg, and Brian Law for DMPK support, Paul Clarkson with regard to in vitro biology, and Chris Williams, Steve Bleakley, and John Ashby for valuable discussions relating to genetic toxicology.

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JM011125X