Mapping the Melatonin Receptor. 5. Melatonin Agonists and Antagonists Derived from Tetrahydrocyclopent[*b*]indoles, Tetrahydrocarbazoles and Hexahydrocyclohept[*b*]indoles

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Tetrahydrocyclopent[*b*]indoles, tetrahydrocarbazoles, and hexahydrocyclohept[*b*]indoles have been prepared as melatonin analogues to investigate the nature of the binding site of the melatonin receptor. The affinity of analogues was compared in a radioligand binding assay using chicken brain membranes and agonist and antagonist potency measured in clonal *Xenopus laevis* melanophore cells. Comparison of the *N*-acyl-3-amino-6-methoxytetrahydrocarbazoles (**2**) with *N*-acyl-4-(aminomethyl)-6-methoxy-9-methyltetrahydrocarbazoles (**9**) showed that the latter have much higher binding affinities for the chicken brain receptor. Comparison of *N*-acyl-1-(aminomethyl)-7-methoxy-4-methyltetrahydrocyclopent[*b*]indoles (**10**), 6-methoxytetrahydrocarbazoles (**9**), and *N*-acyl-10-(aminomethyl)-2-methoxy-5-methylhexahydrocyclohept[*b*]indoles (**11**) showed that the tetrahydrocarbazoles had the highest binding affinity with the cyclohept[*b*]indoles and the cyclopent[*b*]indoles having rather lower affinities. All of these observations are in agreement with our postulated model of melatonin orientation at the binding pocket in which the 3-amidoethane side chain is in a conformation close to the 5-methoxyl group, as is shown in the X-ray crystallographic structure of **9m** and in the energy-minimized computed structures. Separation of the enantiomers of members from each of these three systems was accomplished by chiral HPLC. It was found that in all cases the (−)-enantiomer had a higher binding affinity than the (+)-enantiomer. An X-ray crystallographic analysis of the two enantiomers of **9a** showed that the (+)-enantiomer had the (*R*) absolute stereochemistry. Since the sign of the Cotton curves, determined from circular dichroism studies, was the same for all (+)-enantiomers, it is assumed that the absolute stereochemistry at these centers is identical. In the *Xenopus* melanophore assay, the tetrahydrocarbazoles **2** (R = H) were mainly weak antagonists, while those with R = OMe were agonists. The biological behavior of the tetrahydrocarbazoles **9** (R = H) depended on R^1, some being agonists and some antagonists, whereas those with R = OMe were generally agonists. Variation of the R and R^1 groups in compounds of type **9** produced both agonists and antagonists. The tetrahydrocylopentaindoles **10** had similar biological properties to the corresponding analogues of **9**, but the hexahydrocycloheptaindoles **11** showed a much greater propensity to be antagonists. In all cases the (*S*)-enantiomers were found to be more potent agonists than the (*R*)-enantiomers.

Introduction

The pineal hormone melatonin (**1a**), first isolated and characterized by Lerner et al.[1] in 1958 from bovine pineal tissue, has a central role in the regulation of daily and seasonal rhythms in vertebrates. The pineal gland produces and releases melatonin during the hours of darkness under the control of the circadian clock in the suprachiasmatic nuclei of the hypothalamus. As day-length changes through the seasons, the duration of the nightly elevation in circulating melatonin alters, regulating many types of seasonal behavior, including reproduction, coat color, and body weight in photoperiodic mammals.[2] Melatonin has found practical use to induce seasonally breeding animals, such as sheep, to breed out of season.[3] In humans it has been suggested that melatonin might have a variety of clinical uses, for example in jet-lag and shift work disturbances[4] and for circadian rhythm control in the blind. Melatonin also has hypnotic properties in animals and humans, and it has been reported to have an oncostatic action and modulate the immune response.[5−7]

Despite the renewed interest in melatonin in recent years, much remains to be discovered, including its mode of action and the way in which it interacts with its receptor. High-affinity melatonin binding sites have been identified in central and peripheral tissues,[8−11] and molecular cloning experiments have identified three distinct melatonin receptor subtypes.[12−15] A low-affinity

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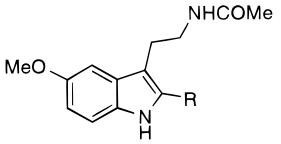
membrane binding site for melatonin has also been reported,[16] and evidence for a nuclear receptor has been presented.[17] Our studies have sought to understand how melatonin interacts with its receptor[18−21] and to use this knowledge to design melatonin agonists and antagonists which may then be useful tools for our further understanding of melatonin action.



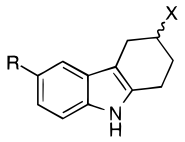
1a R = H
1b R = I

Our earlier studies have shown that acetyl is not the optimum group on the C-3 side chain and that replacement by propanoyl or butanoyl improves binding affinity and agonist potency.[22,23] The finding that 2-iodomelatonin (**1b**) binds to the receptor more strongly than melatonin itself has allowed [2-^{125}I]-**1b** to be used in radioligand binding studies. We[18,20] and others[24] have found that a variety of groups at C-2 increase binding affinity, and we discovered that the 5-methoxyl group is not an essential requirement for agonist activity in *Xenopus* melanophores.[18] The 5-methoxyl group is, however, a major binding site in the attachment of melatonin to its receptor.[18,20,24] We have suggested that the biological response is triggered by inserting the melatonin molecule into the receptor pocket in an orientation controlled by the 5-methoxyl and C-3 amidoethane groups. To determine the conformation of the C-3 amidoethane side chain on binding to the active site of the receptor, we have confined the C-3 amidoethane group in a saturated tetrahydrocarbazole ring and found its optimum position.[19] Other workers, using nonindolic melatonin agonists, have also probed the conformational requirement of this side chain.[25−29] We have now extended the scope of our analysis by changing the size of the annelating ring and the nature of the ring substituents and by resolving the compounds and establishing the absolute stereochemistry of the enantiomers.

Chemistry

3-Amino-1,2,3,4-tetrahydrocarbazole derivatives were prepared via the Fischer indole synthesis using the procedure of Bird and Wee.[30] The appropriate phenylhydrazine was treated with 4-acetoxycyclohexanone, itself prepared from 1,4-cyclohexanediol, and the resulting hydrazones cyclize upon treatment with acetic acid to the tetrahydrocarbazole acetates **2a**. Saponification and treatment with mesyl chloride gave the mesylates **2b** which were then converted to the 3-azides **2c** with sodium azide in ethanol. Reduction with $LiAlH_4$ gave the amine **2d** which was isolated as its hydrochloride and then acylated with the appropriate acid anhydride or chloride to give the amide **2e**.

The [(*N*-acetylamino)methyl]cycloalka[*b*]indoles were prepared by Julia's modification of the Bischler reaction.[31,32] To obtain the desired regioisomer, compounds in which the indole nitrogen had been methylated were prepared. The appropriate *N*-methylaniline was treated



2a (X = OAc)
2b (X = OMs)
2c (X = N_3)
2d (X = NH_2)
2e (X = NHCOR^1)

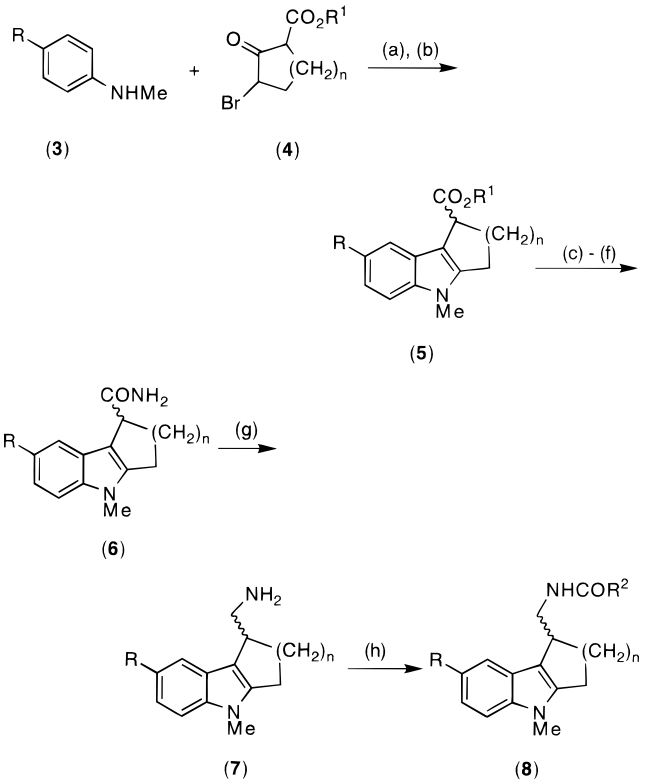
with the appropriate 3-bromo-2-oxocycloalkanecarboxylate as shown in Scheme 1. In the case of the tetrahydrocyclopent[*b*]indoles, both the desired 1-carboxylate and the undesired 3-carboxylate were obtained as Bischler products. The esters were saponified to the acids (**5**, R^1 = H) which are highly crystalline solids suitable for analysis. Formation of the mixed anhydride and ammonolysis gave the amides **6** which were reduced to the amines **7** with $LiAlH_4$ or borane. The amines were then acylated with the appropriate acid anhydride to the amides **8**, which were purified by spinning-plate chromatography.

Pharmacology

The affinity of the annelated indole derivatives at the high-affinity melatonin binding site in chicken brain membranes was determined in a competition radioligand binding assay using [2-^{125}I]melatonin. This radioligand binding assay was conducted as described previously by Sugden and Chong.[22]

The biological activity of the annelated indole derivatives was examined in a specific in vitro model of melatonin action, the pigment aggregation response in *Xenopus laevis* melanophores.[23,33] Addition of melatonin to these cells triggers a rapid redistribution (aggregation) of pigment granules toward the center of the cell. This change in pigment granule distribution in primary cultures of melanophores has been used previously to construct concentration−response curve to define agonist and antagonist potency of melatonin analogues.[23,33] In the present study, a clonal *X. laevis* dermal melanophore cell line,[34] generously provided by Dr. Michael Lerner (Department of Dermatology, University of Texas), was used. Melanophores were grown as described previously in 96-well tissue culture plates,[35] and changes in pigment granule distribution were quantitated by measuring absorbance (630 nm) before and after addition of compounds. Concentration−response curves were determined using a range of concentrations of analogues in 2−4 wells of melanophores. EC_{50} values (concentration of the analogue needed to produce 50% of the maximal pigment aggregation) were determined. Antagonist potency was measured by adding test compounds to melanophores 1 h before challenging with melatonin (10^{-9} M), a concentration which consistently produces a maximal aggregation of pigment. Each concentration of antagonist was tested on 2−4 wells of melanophores. IC_{50} values (concentration of the test compound which blocked melatonin-induced pigment aggregation by 50%) were calculated. All analogues were dissolved in methanol. The maximum concentration of methanol (1%) did not alter specific binding or pigment granule distribution in melanophores.

Scheme 1[a]



[a] Reagents:(a) 50 °C, 3 h; (b) $ZnCl_2$, propan-2-ol, Δ, 16 h; (c) NaOH, H_2O, EtOH, Δ, 6 h; (d) Et_3N, CH_2Cl_2, 0 °C, 4 h; (e) $ClCO_2Me$, CH_2Cl_2, 0 °C, 4 h; (f) NH_3, 20 °C, 16 h; (g) THF, BH_3−THF or $LiAlH_4$, Δ, 4 h (h) R^2COCl or $(R^2CO)_2O$, Et_3N, CH_2Cl_2, 20 °C, 4 h.

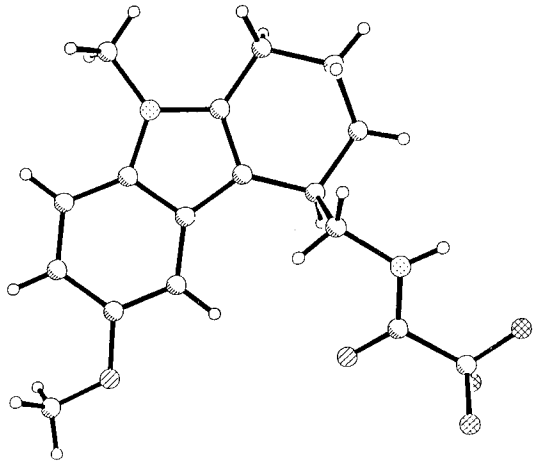


Figure 1. X-ray crystallographic structure of **9m**.

Results and Discussion

The regioselectivity of the Bischler cyclization is controlled by the *N*-methyl substituent on the aniline.[31,32] For the cyclopent[*b*]indole this control is not complete and both regioisomers were obtained, the desired 1-methylcarboxylate in greater amount. An X-ray crystallographic analysis of **9m** showed that it was the desired 4-aminomethyl derivative (Figure 1), and this was correlated with the results from a series of NOE and line sensitive INEPT NMR experiments. The NMR experiments were then carried out with the other derivatives to confirm the assigned structures.

The results of the binding and melanophore assays for the *N*-acyl-3-aminotetrahydrocarbazoles (**2**) are shown in Table 1. The 6-methoxyl derivatives show the expected large improvement in binding affinity compared to the parent compounds, with the propanoyl derivative having the greatest affinity in both cases. The data for the bromomethyl derivatives (**2i**,**o**) may not reflect true affinity constants as these analogues are reactive and may bind irreversibly to the receptor protein. The compound with the highest affinity, **2m**, has about 100-fold lower affinity than melatonin.

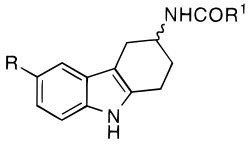
The binding and biological response results for the *N*-acyl-4-(aminomethyl)-9-methyltetrahydrazole derivatives (**9**) are shown in Table 2. Again the 6-methoxy derivatives have a higher binding affinity than the corresponding parent compounds, but both have a much greater binding affinity than the corresponding 3-aminotetrahydrocarbazoles. The butanoyl derivative **9i** shows the greatest binding affinity, slightly greater than melatonin, but the acetyl and propanoyl derivatives are quite similar. The *N*-methyl group on these derivatives probably decreases their binding affinity at the melatonin receptor since *N*-methylmelatonin has a binding affinity (K_i) of 25 ± 4 nM, about 40 times less than that of melatonin itself (0.59 ± 0.06 nM), but the ease of synthesis recommended their initial exploration. If *N*-methylation does decrease affinity, then the NH analogues would have extremely high binding affinities. Replacing the methoxyl group by the trifluoromethoxyl group (**9n**−**p**) leads to a considerable loss of binding affinity, suggesting that the methyl of the methoxyl group is in a neutral hydrophobic pocket into which the polar trifluoromethyl group is less welcome. Replacing the methoxyl group with methyl (**9q**−**s**) leads to a decrease in affinity, but significantly less than with the trifluoromethoxyl group, and replacement by chlorine gives derivatives (**9t**−**v**) of comparable binding affinity to the methoxy derivative.

The effect of decreasing the size of the annelating ring on the binding affinity is shown in Table 3 for the tetrahydrocyclopent[*b*]indole derivatives (**10**). Again the 7-methoxy derivatives have much higher binding affinities than the parent compounds, with the *N*-propanoyl and *N*-butanoyl compounds (**10i**,**j**) showing higher affinity than the *N*-acetyl derivative. The compounds have a lower affinity than the corresponding tetrahydrocarbazole derivatives, **10i**, for example, having a binding affinity 11-fold less than **9h**.

The effect of increasing the size of the annelating ring on the binding affinity is shown in Table 4 for the hexahydrocyclohept[*b*]indole derivatives (**11**). Once again the 10-methoxy derivatives have much higher binding affinities than the corresponding parent compounds, the *N*-propanoyl-10-methoxy derivative (**11i**) showing highest affinity with the *N*-butanoyl derivative (**11c**) having the highest affinity in the parent series. There is a small decrease in binding affinity compared to the tetrahydrocarbazole series, **11i** having a 5-fold lower affinity than **9h**. The tetrahydrocyclopent[*b*]indoles have a reduced affinity compared to the hexahydrocyclohept[*b*]indoles.

These binding affinity data have been obtained from chicken brain which contains Mel_{1a}, Mel_{1b}, and Mel_{1c}

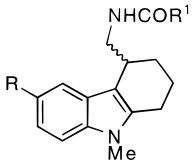
Table 1



				Xenopus melanophores	
compound	R	R^1	receptor binding (K_i, nM)	agonist EC_{50} (nM)	antagonist IC_{50} (μM)
melatonin			0.59 ± 0.06	0.23	NA
luzindole[a]			1606 ± 143	NA	2.1
N-CBCPT[b]			565 ± 46	NA	3.4
2f	H	Me	5350 ± 810	NA	64
2g	H	Et	436 ± 105	3270[c]	NA
2h	H	Pr	1060 ± 160	12600[c]	NA
2i	H	CH_2Br	740 ± 150	NA	39
2j	H	CF_3	4630 ± 1080	NA	43
2k	H	$CHBrC_2H_5$	>10000	NA	32
2l	OMe	Me	219 ± 50	32	NA
2m	OMe	Et	41 ± 6	7	NA
2n	OMe	Pr	560 ± 110	25	NA
2o	OMe	CH_2Br	8.3 ± 1.3	32	11
2p	OMe	CF_3	102 ± 22	32	NA
2q	OMe	c-C_3H_5	143	195	NA

[a] See ref 40. [b] *N*-(Cyclobutylcarbonyl)-2-phenyltryptamine, ref 36. NA = no agonist (or antagonist) effect detected at 100 μM. [c] Partial agonist. Errors given are the standard error of the computer-derived estimates.

Table 2



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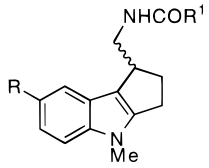
melatonin			0.59 ± 0.06	0.23	NA
luzindole[a]			1606 ± 143	NA	2.1
N-CBCPT[b]			565 ± 46	NA	3.4
9a	H	Me	227 ± 39	599	NA
9a (+)	H	Me	708 ± 59.8	NA	6.4
9a (−)	H	Me	40 ± 3.1	189	NA
9b	H	Et	204 ± 34	862	NA
9c	H	Pr	215 ± 33	966	NA
9d	H	C_4H_9	>10000	NA	17
9e	H	c-C_3H_5	4460 ± 710	NA	15
9f	H	CF_3	>10000	NA	35
9g	OMe	Me	0.97 ± 0.20	0.7	NA
9g (+)	OMe	Me	48.4 ± 8.1	14.8	NA
9g (−)	OMe	Me	0.372	0.30	NA
9h	OMe	Et	1.44 ± 0.18	0.31	NA
9i	OMe	Pr	0.378 ± 0.056	0.44	NA
9j	OMe	C_4H_9	82 ± 11	132	Ant
9k	OMe	c-C_3H_5	30 ± 3.7	119	48
9l	OMe	c-C_4H_7	271 ± 9	139	NA
9m	OMe	CF_3	1.98 ± 0.38	2.1	NA
9n	OCF_3	Me	141.7 ± 39.8	2030[c]	42
9o	OCF_3	Et	40.2 ± 6.3	733[c]	6
9p	OCF_3	c-C_4H_7	1240 ± 240	NA	41
9q	Me	Me	16.1 ± 2.7	108	NA
9r	Me	Et	7.66 ± 1.27	128	NA
9s	Me	c-C_4H_7	555 ± 91.9	1450[c]	NA
9t	Cl	Me	2.12 ± 0.01	5.2	NA
9u	Cl	c-C_3H_5	131.6 ± 39.1	1511[c]	33
9v	Cl	c-C_4H_7	187.2 ± 58.5	NA	14
9w	Et	Et	27.5 ± 4.8	305[c]	62

[a] See ref 40. [b] *N*-(Cyclobutylcarbonyl)-2-phenyltryptamine, ref 36. [c] Partial agonist; NA = no agonist (or antagonist) effect detected at 100 μM; Ant = antagonism detected at 100 μM but no IC_{50} calculated. Errors given are the standard error of the computer-derived estimates.

receptors, and differential binding of the various analogues to these receptor subtypes could have occurred. The analogues may thus show different relative binding affinities to those given in the tables if they were tested on a single melatonin receptor type. We have recently begun to use cloned human mel_{1a} and mel_{1b} receptor

Table 3



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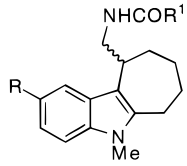
luzindole[a]			1606 ± 143	NA	2.1
N-CBCPT[b]			565 ± 46	NA	3.4
10a	H	Me	516 ± 33	6360[c]	Ant
10b	H	Et	272 ± 33	4045[c]	Ant
10c	H	Pr	239 ± 24	2630[c]	Ant
10d	H	C_4H_9	>10000	NA	46
10e	H	c-C_3H_5	5100 ± 500	NA	59
10f	H	c-C_4H_7	5700 ± 600	NA	50
10g	H	CF_3	>10000	NA	NA
10h	OMe	Me	161 ± 20	423	NA
10i	OMe	Et	16 ± 2.2	408	NA
10i (+)	OMe	Et	243 ± 24.1	789	NA
10i (−)	OMe	Et	1.7 ± 0.14	3.4	NA
10j	OMe	Pr	23 ± 3.6	335[c]	14
10k	OMe	c-C_3H_5	459 ± 46	NA	11

[a] See ref 40. [b] *N*-(Cyclobutylcarbonyl)-2-phenyltryptamine, ref 36. [c] Partial agonist. NA = no agonist (or antagonist) effect detected at 100 μM. Ant = antagonism detected at 100 μM but no IC_{50} calculated. Errors given are the standard error of the computer-derived estimates.

Table 4



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luzindole[a]			1606 ± 143	NA	2.1
N-CBCPT[b]			565 ± 46	NA	3.4
11a	H	Me	424 ± 36	NA	54
11b	H	Et	129 ± 12	NA	Ant
11c	H	Pr	84 ± 9	NA	53
11d	H	C_4H_9	8300 ± 700	NA	42
11e	H	c-C_3H_5	1220 ± 180	NA	56
11f	H	c-C_4H_7	1690 ± 340	NA	44
11g	H	CF_3	>10000	NA	NA
11h	OMe	Me	24 ± 3.5	258[c]	10
11i	OMe	Et	7 ± 0.8	91[c]	Ant
11i (+)	OMe	Et	201.5 ± 20.4	NA	Ant
11i (−)	OMe	Et	6.5 ± 0.7	118[c]	Ant
11j	OMe	Pr	10.3 ± 1.6	140[c]	Ant
11k	OMe	C_4H_9	471 ± 92	NA	39
11l	OMe	c-C_3H_5	44.7 ± 6.9	470[c]	43
11m	OMe	c-C_4H_7	144.8 ± 23.9	NA	18

[a] See ref 40. [b] *N*-(Cyclobutylcarbonyl)-2-phenyltryptamine, ref 36. [c] Partial agonist. NA = no agonist (or antagonist) effect detected at 100 μM. Ant = antagonism detected at 100 μM but no IC_{50} calculated. Errors given are the standard error of the computer-derived estimates.

subtypes stably expressed in NIH 3T3 cells, and it will be interesting to examine the subtype specificity of these analogues.

Energy minimized structures for [(*N*-acetylamino)-methyl]alkanes **9g**, **10h**, and **11h**, together with the energy-minimized structure of *N*-acetyl-3-amino-6-methoxytetrahydrocarbazole (**2l**) are shown in Figure 2. The six- and seven-membered derivatives show a near co-incidence of the aminomethyl side chains with that of the five-membered derivative somewhat displaced, whereas in **2l** the amino methyl group has a remote orientation. This strongly reinforces our view[19] and that of others from modeling on non-indole derivatives[27,28] that the spatial relationship of the methoxy group and the aminoethyl side chain is of major importance in determining the binding affinity of melatonin and its analogues to the melatonin receptor.

Unlike melatonin, the derivatives that we have described are chiral, having one asymmetric center. An investigation of the binding affinity and biological action

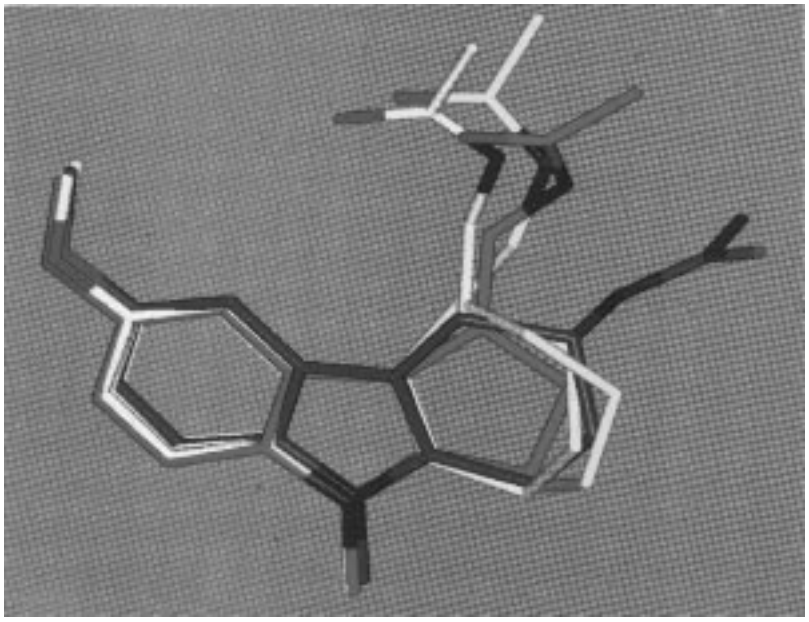

Figure 2. Energy-minimized structures of **2m** (green), **9g** (white), **10h** (red), and **11h** (yellow).

of the separate enantiomers is of interest in order to establish whether the receptor is capable of chiral discrimination and, if it is, to use the absolute stereochemistry of the derivatives to probe its three-dimensional arrangement. We therefore investigated the resolution of a number of the most potent melatonin analogues by chiral HPLC. Recycling was required in most cases, and the purity of the enantiomers was examined by analytical chiral HPLC and by circular dichroism studies. In all of the cases examined the (+)-enantiomer eluted first from the column. (−)-*N*-Acetyl-4-(aminomethyl)-6-methoxy-9-methyltetrahydrocarbazole [(−)-AMMTC, **9g**] has a binding affinity 130-fold greater than that of the (+)-enantiomer [(+)-AMMTC)]. This difference in binding affinity of the enantiomers of **9g** is reflected in a large difference in the agonist potency of the enantiomers in the pigment aggregation assay.[36] This difference in binding affinity is repeated for the parent system despite these compounds having a much lower binding affinity, (−)-*N*-acetyl-9-methyltetrahydrocarbazole (**9a**) having an 18-fold greater binding affinity than the (+)-enantiomer. In both the tetrahydrocyclopent[*b*]indole and hexahydrocyclohept[*b*]indole series, the (−) enantiomer again has the higher binding affinity, 140-fold greater for (−)-*N*-propanoyl-1-(aminomethyl)-7-methoxy-4-methyltetrahydrocyclopent[*b*]indole (**10i**) and 30-fold greater for (−)-*N*-propanoyl-10-(aminomethyl)-2-methoxy-5-methylhexahydrocyclohept[*b*]indole (**11i**). Circular dichroism studies on these enantiomers showed that the (−)-enantiomers all had the same sense of rotation and could therefore be expected to have the same absolute stereochemistry.

An X-ray crystallographic determination was carried out on the two enantiomers (+)-**9a** and (−)-**9a**. The enantiomer (+)-**9a** was found to have the (*R*)-configuration as shown in Figure 3. In the crystal the core of the molecule is virtually planar with C-2, C-3 atoms of the saturated ring forming a half-chair. The methylamine side chain at C-4 is at an angle of 112.7° to the ring plane and is hydrogen bonded through the carbonyl and NH groups to adjacent molecules. The side chain extends away from the core but slightly deviates away from the aromatic ring, probably as a consequence of the hydrogen bonding, but is essentially in the position we suggested earlier.[19,20] Two views of (−)-(*S*)-**9a** are shown in Figure 4. Assuming that the 6-methoxyl group adopts a conformation similar to that calculated, then the conformation of the methoxyl enantiomer (−)-(S)-AMMTC (**9g**) should resemble that shown in Figure 5c.

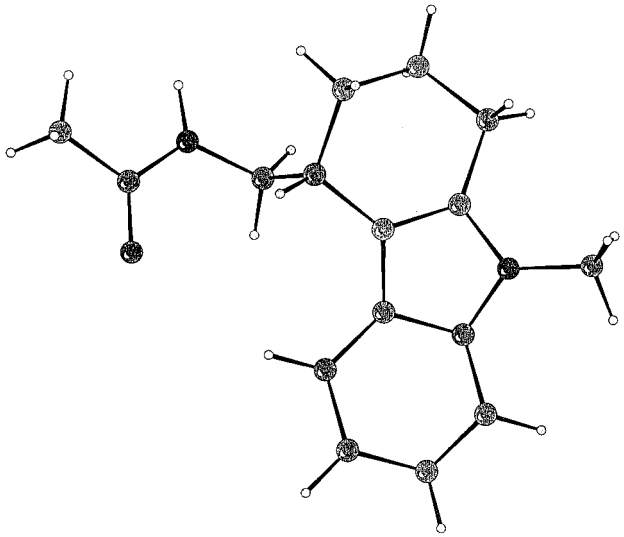

Figure 3. X-ray crystallographic structure of (+)-(*R*)-**9a**.

The biological activity of the four classes of compounds was examined in the *Xenopus* melanophore assay using a clonal cell line. The melanophores are known contain a Mel_{1c} receptor, but both the Mel_{1a} and Mel_{1b} subtypes may also be present. The low pK_b of luzindole (6.60), an antagonist with modest Mel_{1b} selectivity, suggests that the receptor-mediating pigment granule aggregation may be a Mel_{1a} or Mel_{1c} subtype. Some of the compounds are antagonists, but these are much weaker than the agonists (μM cf. nM), a situation which is currently true for all known antagonists. For the type **2** compounds, those with R = H have low binding affinities and the bound molecules evoke little or only

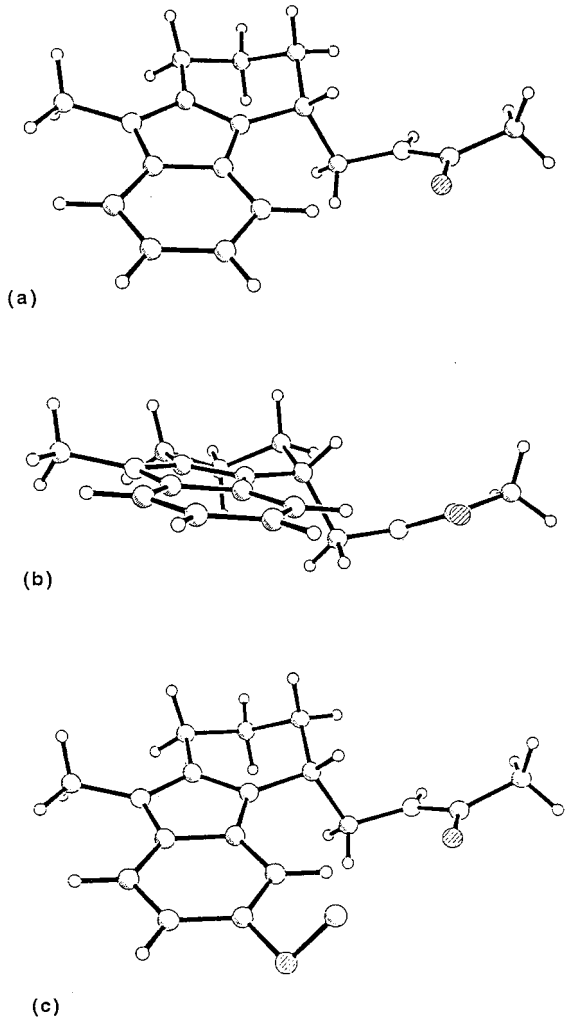

Figure 4. (a, b) Models of (−)-(*S*)-**9a** based on the X-ray crystallographic structure of (+)-(*R*)-**9a**. (c) Model of (−)-(*S*)-**9g** based on the X-ray crystallographic structure of (+)-(*R*)-**9a** and the energy-minimized structure of **9g** illustrated in Figure 2.

a partial agonist effect, although some of them are weak antagonists. The derivatives with R = OMe bind with substantially higher affinity, and the bound molecules evoke a full biological response as agonists at nanomolar concentrations (**2l**−**q**) and no antagonist effect up to 100 μM. Compound **2o**, where the R^1 group CH_2Br is an exception and acts as both an agonist and antagonist which suggests that the highly active α-bromoamide binds indiscriminately via a covalent bond.

For the type **9** compounds, those with R = H again have rather poor binding affinities and show weak biological responses. Analogues with R^1 = Me, Et, Pr are full agonists but have no antagonist action, while analogues with a longer alkyl chain (R^1 = Bu), an alicyclic group (R^1 = c-C_4H_7), or R^1 = CF_3 show no agonist activity but do show weak antagonist activity. In the case of the enantiomers of **9a**, the (*S*)-(−)-enantiomer binds more strongly and is a weak agonist. The more weakly binding (*R*)-(+)-enantiomer has no detectable agonist activity but is an antagonist. Introduction of the OMe group (**9g**−**m**) again both increases the binding affinity and the agonist potency. The (*S*)-(−)-enantiomer **9g** has a much higher affinity (130-fold) and potency (50-fold) than the (*R*)-(+)-**9g**, but both

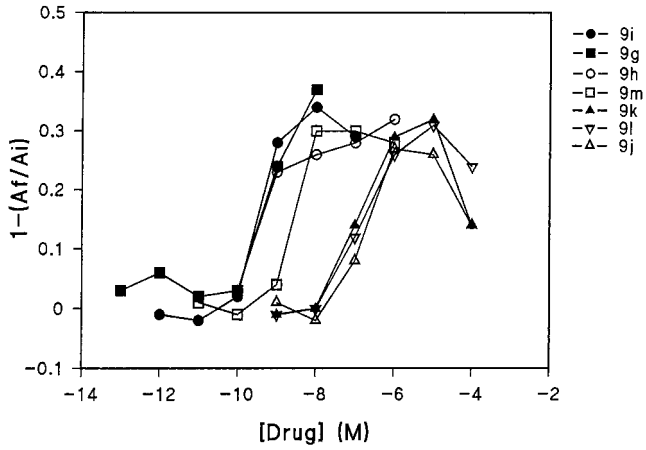

Figure 5. Concentration−response curves for pigment aggregation by melatonin analogues in melanophores. Cells were grown in 96-well plates and growth medium replaced by 0.7 × L-15 culture medium 18 h before testing. Initial absorbance (A_i, 630 nm) of the cells was measured in each well, and cells were then treated with the concentrations of the analogues indicated. The final absorbance (A_f) was measured after 60 min and the fractional change [$1 - (A_f/A_i)$] calculated. This figure shows the effect on agonist potency of changing the R^1 group of the *N*-acyl-4-(aminomethyl)-6-methoxy-9-methyltetrahydrocarbazoles (**9**) shown in Table 2. Each point represents the mean response of duplicate wells of melanophores at each concentration in a single experiment. Results for a single experiment are shown, but similar results were obtained in a second experiment.

enantiomers behave as full agonists on melanophores. Again analogues with R^1 = Me, Et, Pr are full agonists with no antagonist action. The derivatives with longer alkyl **9j** (R^1 = Bu) or alicyclic groups **9k** (R^1 = c-C_3H_5) show agonist and also weak antagonist activity. Interestingly, replacing the 5-OMe with 5-OCF_3 not only reduces binding affinity and agonist potency (**9n** and **9o** are weak partial agonists) but gives compounds with antagonist activity. Substituting Me for OMe does not have a similar effect as these analogues (**9q**−**s**) are agonists and have no antagonist activity up to 100 μM. Although replacing OMe by Cl causes only a modest reduction in binding affinity, it does appear to influence biological activity. Thus **9t**, with R^1 = Me, is an agonist with no antagonist activity (like **9g**), but changing R^1 to an alicycle (**9u**,**v**) gives analogues with very weak partial or no agonist activity but clear, if relatively weak, antagonist activity. The effects of substitution of R^1 and R are shown in Figures 5 and 6.

The five-membered derivatives of type **10** show similar behavior to the corresponding six-membered derivatives of type **9**. The compound with R = H, like **9a**−**f**, have poor binding affinities. Those with shorter acylating chains (R^1 = Me, Et, Pr), however, are now very weak partial agonists rather than full agonists and show some antagonist effect at the highest concentration tested (100 μM). As with the type **9** analogues, compounds with R^1 = Bu or a carbocycle are weak antagonists. Again like the tetrahydrocarbazoles, the compounds with R = OMe have higher binding affinities than those with R = H and show full agonist activity. Again there are exceptions. Thus when R^1 = c-C_3H_5 no agonist activity but rather antagonist activity was detected, and with R^1 = Pr a partial agonist with antagonist activity was found. Compound (*S*)-(−)-**10i**

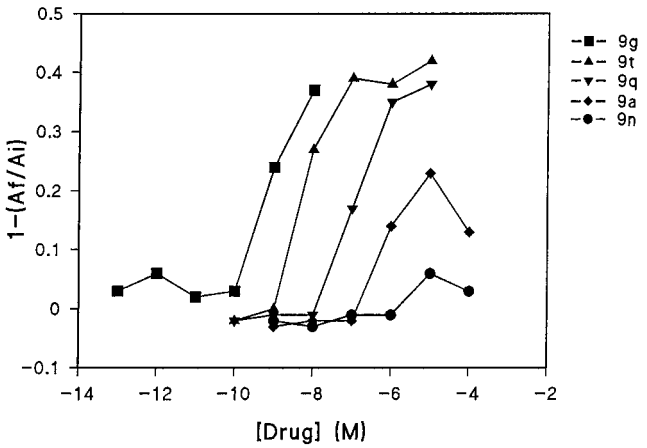

Figure 6. Concentration−response curves for pigment granule aggregation by melatonin analogues in melanophores. Each point represents the mean response of duplicate wells of melanophores at each concentration in a single experiment. See Figure 5 for details. This figure shows the effect on agonist potency of changing the R group of the *N*-acetyl-4-(aminomethyl)-9-methyltetrahdrocarbazoles (**9**) shown in Table 2.

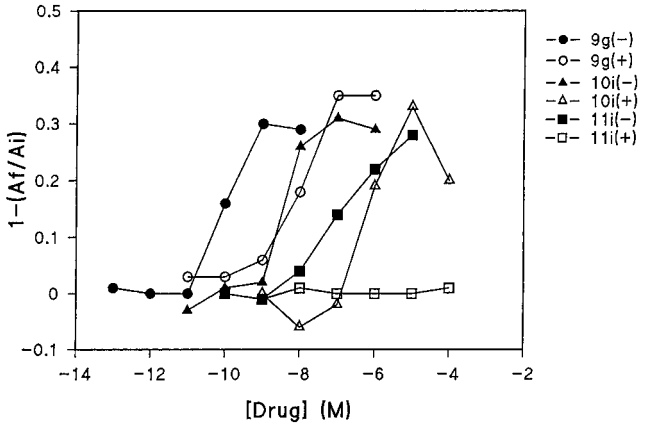

Figure 7. Concentration−response curves for pigment granule aggregation by melatonin analogues in melanophores. Each point represents the mean response of duplicate wells of melanophores at each concentration in a single experiment. See Figure 5 for details. This figure shows the marked differences in potency of the pairs of enantiomers shown in Tables 2−4.

has a higher binding affinity and agonist potency than (*R*)-(+)-**10i** but both enantiomers were full agonists.

The biological response of the seven-membered ring compounds is markedly different from the five- and six-membered ring compounds, although the binding affinities are similar. The R = H compounds are all weak antagonists except for **11g** ($R^1 = CF_3$), which binds extremely weakly and is not active. More strikingly, the compounds with R = OMe are only partial agonists or inactive as agonists, and all show antagonist behavior. Interestingly, however, the enantiomers of **11i** still show a considerable difference in biological potency, as can be seen in Figure 7. The antagonism that is observed with the compounds with R = OMe may arise from competitive binding of these derivatives to the active site without evoking a corresponding biological response.

The binding site for small molecules in G-protein-coupled receptors is thought to involve the residues in the hydrophobic transmembrane domains.[37] The recent cloning of distinct melatonin receptor subtypes from various species has allowed a comparison of the melatonin receptor with that for catecholamines. We have previously suggested[21] that the absence of a conserved serine residue in the fifth transmembrane helix and the occurrence of a conserved histidine residue in all melatonin receptors so far cloned is readily rationalized from a comparison of the molecular structure of melatonin with 5-HT and the catecholamines, with the histidine acting as a proton donor to the C-5 methoxyl group of melatonin. Further differences in the melatonin and catecholamine receptors are also consistent with the low basicity of melatonin (see ref 21). The structure of (−)-(*S*)-AMMTC now allows us to speculate further on the structural requirements of the melatonin receptor pocket. The large difference in activity between (*S*)- and (*R*)-AMMTC (**9g**) suggests that the orientation as well as the distance between the methoxyl and ethanamide side chain is critical. Accommodating the (*R*)-enantiomer in the required manner thus causes destabilizing interactions, probably because the tetrahydrocarbazole core has to tilt so that the ethanamide chain can adopt the correct relative position to the methoxyl group (see Figure 5c). The finding that the (*S*)-enantiomers of the cyclopent[*b*]indole and cyclohept-[*b*]indole derivatives also have higher binding affinities supports this view. The observation that there is still a substantial difference between the enantiomers of the 6-H tetrahydrocarbazole derivative **9a**, however, indicates that the binding site also has a geometrical requirement for the relative orientation of the ethanamine side chain and the tetrahydrocarbazole core, independent of the relative orientation of the ethanamine side chain to the methoxyl group. From the binding affinity data for the racemates, the difference in binding between enantiomers is much greater for the methoxyl derivative, with a 99:1 preference for (*S*)-**9g** compared to (*R*)-**9g**, than for the 6-H derivative, where the preference for (*S*)-**9a** to (*R*)-**9a** is 64:36. The difference for the methoxyl enantiomers of the cyclopent[*b*]indole derivative **10i** is 94:6, and for the cyclohept[*b*]indole **11i** 99.7:0.3. The cyclohept[*b*]indoles, however, although presumably binding at the same site, may either not alter the conformation of the receptor or alter it in a different way to melatonin, the cyclopent-[*b*]indoles, and tetrahydrocarbazoles and thus evoke at best only a partial agonist effect. Figure 8 shows a schematic model for the possible orientation of (*S*)-(−)-AMMTC (**9g**) in the melatonin receptor pocket.

The finding that derivatives lacking a methoxyl group but having an alicyclic acylating group (e.g. *N*-(cyclobutylcarbonyl)-2-phenyltryptamine) can behave as antagonists was observed previously,[20] but interestingly, in the present series of analogues those having a longer chain aliphatic acylating groups (**9d**, **10d**, R^1 = Bu; **11c**, R^1 = Pr) also show antagonist activity. Furthermore, when $R = CF_3$ (**2j**, **9f**), although binding affinity is reduced, antagonist activity is favored. The present series of compounds include melatonin analogues which show antagonist activity while still retaining the methoxyl group that is so important in conferring a high receptor binding affinity. Antagonists of melatonin also containing the 5-methoxy group have recently been reported in the [^{3}H]dopamine response assay of rabbit retina.[38]

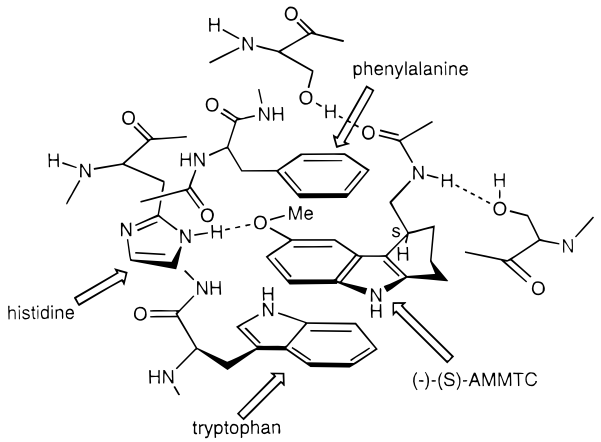

Figure 8. Schematic model of (−)-(*S*)-AMMTC (**9g**) in the melatonin receptor pocket indicating possible molecular interactions with amino acids in the transmembrane loops of the receptor protein. The 6-methoxyl group is shown hydrogen bonded to histidine and the 4-*N*-acetylethanamine side chain hydrogen bonded as a donor and acceptor to serine residues in the receptor protein. The tryptophan and phenylalanine protein residues are depicted as providing π-stacking. Incorporation of the (+)-(*R*)-AMMTC enantiomer in such a pocket would require the tetrahydrocarbazole ring to tilt in order to orientate the side chains into the same relative positions.

Further structure−activity studies should lead to a better understanding of the molecular features required for a compound of high antagonist potency.

Experimental Section

Melting points were determined on a Reichert or Electrothermal melting point apparatus and are uncorrected. EI mass spectra were recorded a VG ZAB-2F or Concept mass spectrometer, CI mass spectra on a VG 12-250 mass spectrometer and FAB mass spectra on a M550 mass spectrometer. Only molecular ions (M^+), base peaks, and the next two peaks due to ions of maximum abundance are given. IR spectra were recorded on a Perkin-Elmer PE−983, Perkin-Elmer 1605 FTIR, or Bruker IF66 spectrophotometer using KBr pellets unless stated otherwise. ^{1}H NMR spectra were recorded in $CDCl_3$ unless stated otherwise on either a Varian VXR-400 or a Bruker AMX-360 spectrometer, and the spectra are reported in δ. ^{13}C NMR spectra were recorded at 100 MHz on a Varian VXR-400 spectrometer or at 90 MHz on a Bruker AMX-360 spectrometer and are reported in δ. Optical rotations were recorded on a Thorn NPL autopolarimeter. Circular dichroism studies were carried out using a JASCO J600 spectrometer by the Physical Sciences Department, Wellcome Foundation Ltd., Beckenham. Microanalyses were carried out by the microanalytical section, Department of Chemistry, University College London. The X-ray crystallographic analysis of (+)- and (−)-**9a** was performed by Oxford University X-ray Services.

Merck Kieselgel 60 F_{254} plates were used for analytical TLC and were visualized with ultraviolet light or developed with *p*-anisaldehyde, iodine, or ninhydrin. Flash column chromatography was performed using Sorbsil c60-A silica (40−60 μm) or Merck silica gel 9385 as the stationary phase. Spinning-plate chromatography (SPC) was carried out using Merck silica gel 60 PF254 with calcium sulfate. Chiral HPLC was carried out using Chiracel OD, OJ, or AD analytical and preparative columns with hexane/ethyl acetate as eluant. Reverse phase HPLC was carried out on Zorbax C8 columns eluting with acetonitrile/water containing 0.2% trifluoroacetic acid.

General Procedures: Bischler Reaction. A mixture of the *N*-methylaniline (2 equiv) and the α-bromo ketone (1 equiv) was stirred under N_2 at 50 °C for 3 h. The resulting dark, viscous material was dissolved in 2-propanol (100 mL per 0.1 mol of aniline) and treated with zinc chloride (3 equiv), which had previously been dried (25 °C, 1 mmHg, 2 d). The mixture was then heated to reflux under N_2 for 16 h and the solvent then removed by evaporation. The product was extracted three times with a mixture of hydrochloric acid and ethyl acetate (100 mL, 2 M; 150 mL). The red organic extract was washed with water (2 × 100 mL) and saturated Na_2CO_3 solution (2 × 100 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the ester of sufficient purity to be used in subsequent reactions.

Saponification of Esters. The crude ester obtained above was dissolved in hot 90% aqueous methanol or ethanol. Sodium hydroxide (10 equiv) was then added and the resulting brown mixture heated to reflux for 6 h. The alcohol was removed by evaporation under reduced pressure and the residue washed twice with CH_2Cl_2. The mixture was then poured into excess ice-cold hydrochloric acid (10%) and the resulting precipitate collected by filtration under reduced pressure, washed with water, and dried (25 °C, 1 mmHg).

Preparation of Primary Amides. The carboxylic acid (1 equiv) was dissolved in CH_2Cl_2 (10 mL g^{-1}), triethylamine (1.1 equiv) was added, and the mixture was cooled to 0 °C. The mixture was stirred, and after 10 min methyl or ethyl chloroformate (1.1 equiv) was added dropwise. If solid precipitated during the addition, more CH_2Cl_2 was added. After 30 min ammonia was bubbled through the mixture for 2 min when a white precipitate formed. Stirring was continued for a further 1 h, and the mixture was then extracted with water (20 mL), HCl (2 M, 2 × 20 mL), and NaOH (2 M, 2 × 20 mL). The organic extract was dried ($MgSO_4$) and the solvent removed by evaporation to give the crude amide which was of sufficient purity to be used in subsequent reactions.

Reduction of Primary Amides: Procedure A. A solution of the amide (1 equiv) in anhydrous THF (10 mL g^{-1}) was added dropwise to a suspension of $LiAlH_4$ (10 equiv) in anhydrous THF (20 mL g^{-1}). After completion of addition the mixture was heated to reflux for 2 h and allowed to cool and the excess $LiAlH_4$ decomposed by the dropwise addition of water (2 mL). The mixture was filtered under reduced pressure and the residue washed with ethyl acetate. The combined filtrate was washed with water (20 mL) and extracted with HCl (2 M, 2 × 20 mL).The aqueous extract was washed with ethyl acetate (20 mL), and NaOH (2 M) was then added to basify the solution. The basic solution was then extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent gave the amine as a colorless oil of a suitable purity for further reactions.

Procedure B. A solution of the amide (1 equiv) in anhydrous THF (10 mL g^{-1}) was added dropwise to a solution of borane−THF (1 M, 2 equiv). After completion of addition the mixture was stirred for 16 h at 25 °C and the excess borane was decomposed by dropwise addition of water (2 mL). The mixture was then worked up as for procedure A.

Preparation of Secondary Amides: Procedure A. The amine (1 equiv) was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (5 mL), the mixture stirred, and the anhydride (1.1 equiv) added. Stirring was continued at room temperature for a further 1 h, the mixture then extracted with ether (20 mL), and the organic extract washed with water (20 mL), HCl (2 M, 2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the product purified by SPC.

Procedure B. The amine (1 equiv) was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (5 mL), the mixture stirred, and a solution of the acid chloride (1.1 equiv) in CH_2Cl_2 (10 mL) added dropwise with stirring. After 30 min the mixture was worked up as for procedure A.

Trifluoroacetamides. The amine (1 equiv) was dissolved in MeOH (20 mL) and ethyl trifluoroacetate (5 equiv). The mixture was stirred at room temperature for 3 h, the solvent removed by evaporation, and the product purified by SPC.

***N*-Acetyl-3-amino-1,2,3,4-tetrahydrocarbazole (2f):** 70%; mp 120−125 °C; ^{1}H NMR δ 1.98−2.12 (m, 2H), 2.12 (s, 3H), 2.56 (dd, 1H, J = 6.2, 15.1 Hz), 2.72−2.78 (m, 2H), 3.01 (dd,

1H, J = 5.1, 15.4 Hz), 4.36 (m, 1H), 5.90 (br d, 1H, J = 5.5 Hz), 7.01−7.10 (m, 2H), 7.24 (d, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 7.7 Hz), 8.31 (br s, 1H); ^{13}C NMR δ 20.3, 23.3, 27.5, 27.9, 45.0, 106.9, 110.5, 117.4, 119.1, 121.1, 127.4, 132.9, 136.1, 169.9; IR 3406, 3300, 1625, 1555, 737 cm^{-1}; EIMS *m*/*z* 228, 169 (100), 143, 58, 43. Anal. ($C_{14}H_{16}N_2O$) C, H, N.

***N*-Propanoyl-3-amino-1,2,3,4-tetrahydrocarbazole (2g):** 78%; mp 190−193 °C; ^{1}H NMR δ 1.13 (t, 3H, J = 7.6 Hz), 1.88−1.93 (m, 1H), 1.93−2.03 (m, 1H), 2.15 (q, 2H, J = 7.6 Hz), 2.51−2.57 (m, 1H), 2.70−2.76 (m, 2H), 3.02 (dd, 1H, J = 5.0, 15.2 Hz), 4.37 (m, 1H), 5.93 (br s, 1H), 7.04 (dd, 1H, J = 7.0, 6.5 Hz), 7.07 (dd, 1H, J = 6.7, 7.1 Hz), 7.25 (d, 1H, J = 7.9 Hz), 7.38 (d, 1H, J = 7.6 Hz), 8.68 (br s, 1H); ^{13}C NMR δ 9.9, 20.4, 27.5, 28.0, 29.6, 45.0, 106.7, 110.6, 117.4, 118.8, 121.0, 127.3, 133.0, 136.1, 173.5; IR 3379, 3279, 1635, 1548, 740 cm^{-1}; EIMS *m*/*z* 242, 169 (100), 143, 58. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

***N*-Butanoyl-3-amino-1,2,3,4-tetrahydrocarbazole (2h):** 82%; mp 227−228 °C; ^{1}H NMR δ 0.96 (t, 3H, J = 7.3 Hz), 1.63−1.67 (m, 2H), 1.90−2.00 (m, 2H), 2.11 (t, 2H, J = 6.7 Hz), 2.54 (dd, 1H, J = 6.2, 15.2 Hz), 2.70−2.75 (m, 2H), 2.96 (dd, 1H, J = 5.0, 14.9 Hz), 4.37 (m, 1H), 5.96 (br s, 1H), 7.00 (dd, 1H, J = 6.8, 7.5 Hz), 7.07 (dd, 1H, J = 6.8, 7.8 Hz), 7.23 (d, 1H, J = 7.2 Hz), 7.35 (d, 1H, J = 7.6 Hz), 8.45 (br s, 1H); ^{13}C NMR δ 13.6, 19.2, 20.3, 27.4, 27.9, 38.5, 45.1, 106.7, 110.5, 117.4, 119.0, 121.0, 127.3, 132.9, 136.1, 173.3; IR 3248, 2924, 1634, 1547 cm^{-1}; EIMS *m*/*z* 257 (100), 169. Anal. ($C_{16}H_{20}N_2O$) C, H, N.

***N*-(Bromoacetyl)-3-amino-1,2,3,4-tetrahydrocarbazole (2i):** 78%; mp 205−206 °C; ^{1}H NMR δ 2.06−2.14 (m, 2H), 2.66 (dd, 1H, J = 6.9, 15.2 Hz), 2.80−2.90 (m, 2H), 3.11 (dd, 1H, J = 5.0, 15.4 Hz), 4.04 (s, 2H), 4.42 (m, 1H), 6.68 (br d, J = 7.6 Hz), 7.05−7.15 (m, 2H), 7.28 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 7.6 Hz), 7.89 (br s, 1H); ^{13}C NMR δ 20.5, 27.4, 27.9, 42.6, 45.8, 107.0, 110.5, 117.7, 119.4, 121.4, 127.4, 132.5, 136.1, 165.5; IR 3379, 3272, 1641, 1555, 1448, 744 cm^{-1}; EIMS *m*/*z* 183, 169 (100), 143. Anal. ($C_{14}H_{15}N_2OBr$) C, H, N.

***N*-(Trifluoroacetyl)-3-amino-1,2,3,4-tetrahydrocarbazole (2j):** 88%; mp 205−208 °C; ^{1}H NMR δ 1.77−1.94 (m, 2H), 2.47−2.58 (m, 1H), 2.63−2.71 (m, 2H), 2.80−2.90 (m, 1H), 4.07 (m, 1H), 6.75−6.88 (m, 2H), 7.06 (d, 1H, J = 7.7 Hz), 7.14 (d, 1H, J = 8.0 Hz), 8.31 (br s, 1H), 9.43 (br s, 1H); ^{13}C NMR δ 20.8, 26.3, 27.5, 46.3, 105.9, 110.2, 116.8, 116.9, 118.2, 120.3, 126.7, 132.5, 135.8, 156.1; IR 3386, 3286, 1692, 1551, 744 cm^{-1}; EIMS *m*/*z* 282, 169 (100), 143. Anal. ($C_{14}H_{13}N_2OF_3$) C, H, N.

***N*-(2-Bromobutanoyl)-3-amino-1,2,3,4-tetrahydrocarbazole (2k):** 90%; mp 183−184 °C; ^{1}H NMR δ 1.02 (t, 3H, J = 7.2 Hz), 1.06−1.24 (m, 2H), 1.95−2.19 (m, 2H), 2.60−2.68 (m, 1H), 2.78−2.86 (m, 2H), 3.11 (dd, 1H, J = 3.7, 15.5 Hz), 3.21−3.32 (m, 1H), 4.24 (m, 1H), 6.45 (br d, 1H), 7.06−7.23 (m, 2H), 7.28 (d, 1H, J = 7.9 Hz), 7.42 (d, 1H, J = 7.6 Hz), 7.85 (br s, 1H); ^{13}C NMR δ 11.7, 20.5, 27.4, 27.7, 29.3, 45.9, 53.5, 107.0, 110.6, 117.7, 119.4, 121.6, 127.1, 132.4, 135.9, 167.3; IR 3412, 3271, 1642, 1556, 1448, 744 cm^{-1}; EIMS *m*/*z* 334, 336, 169 (100), 143. Anal. ($C_{16}H_{19}N_2OBr$) C, H, N.

***N*-Acetyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2l):** 93%; mp 91−95 °C; ^{1}H NMR δ 1.83−1.98 (m, 2H), 1.91 (s, 3H), 2.51 (dd, 1H, J = 6.3, 15.0 Hz), 2.68−2.74 (m, 2H), 2.97 (dd, 1H, J = 5.0, 15.2 Hz), 3.78 (s, 3H), 4.36 (m, 1H), 5.96 (br d, 1H), 6.72 (dd, 1H, J = 2.4, 8.7 Hz), 6.82 (d, 1H, J = 2.3 Hz), 7.10 (d, 1H, J = 8.7 Hz), 7.24 (br s, 1H); ^{13}C NMR, δ 20.4, 23.4, 27.6, 27.9, 45.1, 55.8, 99.9, 106.8, 110.8, 111.3, 127.9, 131.2, 133.3, 153.7, 170.0; IR 3300, 3100, 1652, 1625, 1485, 1455, 1431, 1031 cm^{-1}; EIMS *m*/*z* 258, 199 (100), 173, 158. Anal. ($C_{15}H_{18}N_2O_2$) C, H, N.

***N*-Propanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2m):** 59%; ^{1}H NMR δ 1.13 (t, 3H, J = 7.5 Hz), 1.98−2.06 (m, 2H), 2.16 (q, 2H, J = 7.7 Hz), 2.55 (dd, 1H, J = 6.0, 15.2 Hz), 2.75−2.80 (m, 2H), 3.04 (dd, 1H, J = 5.4, 15.4 Hz), 3.82 (s, 3H), 4.42 (m, 1H), 5.62 (br s, 1H), 6.76 (dd, 1H, J = 1.4, 8.7 Hz), 6.87 (d, 1H, J = 1.3 Hz), 7.16 (d, 1H, J = 8.7 Hz), 7.85 (br s, 1H); ^{13}C NMR δ 9.9, 20.5, 27.7, 27.9, 29.9, 44.9, 55.9, 100.0, 107.1, 111.0, 111.2, 127.9, 131.2, 133.7, 153.9, 173.5; IR 3312, 3130, 1651, 1625, 1429, 1034 cm^{-1}; EIMS *m*/*z* 272, 199 (100), 173, 158. Anal. ($C_{16}H_{20}N_2O_2$) Calcd: C, 70.56; H, 7.40; N, 10.29. Found: C, 69.98; H, 7.22; N, 10.08.

***N*-Butanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2n):** 93%; mp 140−144 °C; ^{1}H NMR δ 0.90 (t, 3H, J = 7.4 Hz), 1.57−1.65 (m, 2H), 1.91−2.06 (m, 2H), 2.09 (t, 2H, J = 7.1 Hz), 2.52 (dd, 1H, J = 6.6, 15.4 Hz), 2.69−2.75 (m, 2H), 2.99 (dd, 1H, J = 5.0, 15.4 Hz), 3.79 (s, 3H), 4.37 (m, 1H), 5.85 (br d, 1H, J = 8.2 Hz), 6.73 (dd, 1H, J = 2.5, 8.7 Hz), 6.83 (d, 1H, J = 2.2 Hz), 7.11 (d, 1H, J = 8.7 Hz), 8.26 (br s, 1H); ^{13}C NMR δ 13.6, 19.2, 20.4, 27.6, 27.9, 38.6, 44.9, 55.8, 99.9, 106.8, 110.7, 111.2, 127.8, 131.1, 133.8, 153.7, 172.8; IR 3292, 1641, 1468, 1278 cm^{-1}; EIMS *m*/*z* 286, 199 (100), 173, 158. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

***N*-(Bromoacetyl)-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2o):** 83%; ^{1}H NMR δ 1.95−2.11 (m, 2H), 2.58 (dd, 1H, J = 6.8, 15.4 Hz), 2.68−2.81 (m, 2H), 3.04 (dd, 1H, J = 5.2, 15.2 Hz), 3.78 (s, 3H), 3.81 (s, 2H), 4.35 (m, 1H), 6.53 (br d, 1H, J = 7.3 Hz), 6.74 (dd, 1H, J = 2.4, 8.7 Hz), 6.83 (d, 1H, J = 2.5 Hz), 7.13 (d, 1H, J = 8.7 Hz), 7.20 (br s, 1H); ^{13}C NMR δ 20.6, 27.6, 27.9, 29.4, 46.1, 55.9, 100.1, 106.9, 111.2, 111.3, 127.9, 131.2, 133.5, 154.05, 165.2; IR (film) 3300, 3100, 1651, 1623, 1486, 1031 cm^{-1}; EIMS *m*/*z* 338, 336, 199 (100), 173, 158. Anal. ($C_{15}H_{17}N_2O_2Br$) C, H, N.

***N*-(Trifluoroacetyl)-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2p):** yellow oil; 32%; ^{1}H NMR δ 2.10−2.15 (m, 2H), 2.70 (dd, 1H, J = 6.3, 15.4 Hz), 2.78−2.88 (m, 2H), 3.15 (dd, 1H, J = 5.1, 15.4 Hz), 3.86 (s, 3H), 4.49 (m, 1H), 6.49 (br s, 1H), 6.83 (dd, 1H, J = 2.5, 8.7 Hz), 6.90 (d, 1H, J = 2.3 Hz), 7.20 (d, 1H, J = 8.7 Hz), 7.80 (br s, 1H); ^{13}C NMR δ 20.2, 27.3, 27.4, 46.2, 55.9, 100.0, 106.2, 111.3, 111.4, 117.2, 127.7, 131.1, 133.1, 154.1, 173.8; IR (film) 3300, 3100, 1691, 1620, 1482, 1025 cm^{-1}; EIMS *m*/*z* 312, 199 (100), 173, 158. Anal. ($C_{15}H_{15}N_2O_2F_3$) C, H, N.

***N*-Cyclopropanoyl-3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole (2q):** pale brown oil; 63%; ^{1}H NMR δ 0.70−0.79 (m, 2H), 0.93−1.03 (m, 2H), 1.23 (m, 1H), 1.99−2.07 (m, 2H), 2.58 (dd, 1H, J = 6.0, 15.4 Hz), 2.71−2.81 (m, 2H), 3.04 (dd, 1H, J = 5.1, 15.4 Hz), 3.82 (s, 3H), 4.44 (m, 1H), 5.81 (d, 1H, J = 7.6 Hz), 6.76 (dd, 1H, J = 2.5, 8.7 Hz), 6.87 (d, 1H, J = 2.5 Hz), 7.15 (d, 1H, J = 8.6 Hz), 7.82 (br s, 1H); ^{13}C NMR δ 7.2, 14.9, 20.5, 27.9, 28.1, 45.2, 56.0, 100.1, 107.2, 111.1, 111.2, 128.0, 131.2, 133.8, 154.0, 173.2; IR (film) 3279, 1742, 1692, 1635, 1555, 1478, 1388, 1151 cm^{-1}; EIMS *m*/*z* 284, 199. Anal. ($C_{17}H_{20}N_2O$) C, H, N.

Ethyl 4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxylate (5a, n = 1, R = H, R^1 = Et) and Ethyl 4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-3-carboxylate. The mixture of **5a** and its isomer was obtained as an orange oil (9.10 g, 38 mmol, 75%): ^{1}H NMR δ 1.20−1.40 (m, 3H), 2.28−2.35 (m), 2.71−3.09 (m), 3.67 (s), 3.73 (s), 4.06−4.08 (m), 4.13 (q, J = 7.3 Hz), 4.19 (q, J = 7.2 Hz), 5.04−5.07 (m), 7.05−7.12 (ddd), 7.12−7.20 (ddd), 7.23−7.28 (d), 7.47 (d, J = 7.9 Hz), 7.58 (d, J = 7.5 Hz); IR (film) 2945, 1719, 1483, 1244, 746 cm^{-1}.

Ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[*b*]indole-1-carboxylate (5b, n = 1, R = OMe, R^1 = Et) and ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent-[*b*]indole-3-carboxylate: orange oil; 67%; ^{1}H NMR δ 1.29 (t, J = 7.7 Hz), 2.51−2.54 (m), 2.81−2.86 (m), 3.62 (s), 3.85 (s), 3.93−3.95 (m), 4.04−4.12 (m), 4.19 (q, J = 7.0 Hz), 6.79 (dd, J = 2.3, 8.9 Hz), 6.82 (dd, J = 2.5, 9.0 Hz), 6.93 (d, J = 2.5 Hz), 7.00 (d, J = 2.5 Hz), 7.11 (d, J = 8.8 Hz), 7.14 (d, J = 8.7 Hz); IR (film) 2930, 1721, 1473, 1163, 769 cm^{-1}.

Ethyl 9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (5c, n = 2, R = H, R^1 = Et): yellow oil; 68%. An analytical sample was crystallized from benzene−petroleum spirit (1:10) to give a solid: mp 78−80 °C (lit.[31] mp 86 °C); ^{1}H NMR δ 1.24 (t, 3H, J = 9 Hz), 1.8−2.0 (m, 2H), 2.7−2.8 (m, 4H), 3.6 (s, 3H), 4.12 (m, 2H), 4.45 (m, 1H), 7.10−7.22 (m, 2H), 7.3 (d, 1H, J = 8 Hz),7.52 (d, 1H, J = 8 Hz); IR (film) 2932, 1725, 1468, 1381, 1248, 1174, 1154, 744 cm^{-1}; EIMS *m*/*z* 258 (100), 184, 172.

Ethyl 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (5d, n = 2, R = OMe, R^1 = Et): yellow oil; 71%. An analytical sample was prepared by filtration over a short silica gel column with dichloromethane: mp 69−70 °C;

^{1}H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 1.90−1.97 (m, 2H), 2.18−2.34 (m, 2H), 2.66−2.74 (m, 2H), 3.57 (s, 3H), 3.84 (s, 3H), 4.16−4.21 (m, 1H), 6.81 (dd, 1H, J = 2.5, 8.8 Hz), 7.03 (d, 1H, J = 2.4 Hz),7.14 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 14.4, 20.4, 21.8, 26.4, 29.1, 38.5, 55.9, 60.5, 101.0, 105.7, 109.2, 110.5, 128.3, 132.1, 137.3, 153.7, 175.0; IR 2931, 1718, 1478, 1158, 807; EIMS m/z 288 ($M^+ + 1$, 100), 198, 171. Anal. ($C_{17}H_{21}NO_3$) Calcd: C, 71.65; H, 7.37; N, 4.88. Found: C, 71.03; H, 7.34; N, 4.60.

Ethyl 5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxylate (5e, n = 3, R = H, R^1 = Et): orange solid; 69%.

Ethyl 2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxylate (5f, n = 3, R = OMe, R^1 = Et): orange oil; 63%; IR (film) 2929, 1709, 1474, 1163, 779 cm^{-1}.

4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxylic Acid (5g, n = 1, R = H, R^1 = H) and 4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-3-carboxylic Acid. The crude mixture of ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxylate and ethyl 4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indol-3-carboxylate (9.1 g, 37 mmol) was saponified with sodium hydroxide (15 g, 0.37 mol). A mixture of the two acids (5.1 g, 24 mmol, 64%) was obtained: ^{1}H NMR δ 2.73−2.80 (m, 1H), 2.81−2.90 (m, 2H), 3.00−3.04 (m, 2H), 3.69 (s, 3H), 4.04 (m, 1H), 7.11 (ddd, 1H, J = 1.1, 7.1, 7.9 Hz), 7.17 (ddd, 1H, J = 1.2, 7.0, 8.2 Hz), 7.28 (d, 1H, J = 8.1 Hz), 7.50 (d, 1H, J = 7.5 Hz); ^{13}C NMR δ 23.0, 30.0, 30.8, 42.5, 108.4, 114.0, 117.8, 118.1, 119.2, 122.7, 140.3, 145.8, 175.4; IR 3120, 2937, 1690, 1235, 743 cm^{-1}.

7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxylic Acid (5h, n = 1, R = OMe, R^1 = H) and 7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-3-carboxylic Acid. The crude mixture of ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxylate and ethyl 7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-3-carboxylate (12.4 g, 45 mmol) was saponified with sodium hydroxide (18 g, 0.45 mol): ^{1}H NMR δ 2.40−2.50 (m), 2.81−2.86 (m), 3.64 (s), 3.86 (s), 3.96−3.99 (m), 4.10−4.15 (m), 6.80 (dd, J = 2.3, 9.0 Hz), 6.93 (d, J = 2.4 Hz), 7.07 (d, J = 2.5 Hz), 7.12 (d, J = 8.8 Hz), 7.13 (d, J = 8.8 Hz); IR 3430, 2932, 1692, 1216 cm^{-1}; EIMS m/z 245, 200 (100), 106, 78.

9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (5i, n = 2, R = H, R^1 = H): 80%; mp 174−177 °C (lit.[31] mp 180−181 °C); ^{1}H NMR δ 1.98−2.06 (m, 2H), 2.16−2.21 (m, 1H), 2.27−2.31 (m, 1H), 2.70 (ddd, 1H, J = 6.1, 8.5 Hz), 2.81 (ddd, 1H, J = 16.3, 5.0, 5.0 Hz), 3.64 (s, 3H), 3.97 (dd, 1H, J = 4.9, 5.2 Hz), 7.11 (dd, 1H, J = 7.0, 7.8 Hz), 7.20 (dd, 1H, J = 7.0, 8.1 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.58 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 20.3, 21.7, 26.4, 29.0, 38.2, 105.3, 108.7, 118.5, 119.2, 120.9, 126.4, 136.8, 136.9, 181.1; IR 3100, 2932, 1692, 1221, 740 cm^{-1}; EIMS m/z 229, 184 (100), 156, 90. Anal. ($C_{14}H_{15}NO_2$) Calcd: C, 73.33; H, 6.59; N, 6.11. Found: C, 73.90; H, 6.78; N, 5.83.

6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid (5j, n = 2, R = OMe, R^1 = H): 93%; mp 177−178 °C; ^{1}H NMR δ 1.91−1.98 (m, 2H), 2.11 (m, 1H), 2.22−2.24 (m, 1H), 2.62 (ddd, 1H, J = 6.6 Hz), 2.75 (ddd, 1H, J = 4.9 Hz), 3.57 (s, 3H), 3.79 (s, 3H), 3.89 (dd, 1H, J = 4.8, 5.3 Hz), 6.80 (dd, 1H, J = 2.5, 8.8 Hz), 7.00 (d, 1H, J = 2.2 Hz), 7.12 (d, 1H, J = 8.9 Hz); ^{13}C NMR δ 20.3, 21.8, 26.4, 29.1, 38.2, 55.9, 100.8, 104.9, 109.4, 110.7, 126.7, 132.1, 137.6, 153.9, 180.7; IR 3413, 2932, 1695, 1218 cm^{-1}; EIMS m/z 259, 214 (100), 120, 80. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxylic acid (5k, n = 3, R = H, R^1 = H): 83%; mp 190−193 °C; ^{1}H NMR δ 1.53−1.65 (m, 1H), 1.79−1.92 (m, 2H), 1.93−2.03 (m, 2H), 2.46−2.49 (m, 1H), 2.82−2.92 (m, 2H), 3.65 (s, 3H), 4.23 (t, 1H, J = 4.2 Hz), 7.13 (t, 1H, J = 7.6 Hz), 7.22 (d, 1H, J = 8.1 Hz), 7.43 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 25.7, 26.8, 26.9, 29.6, 30.5, 40.7, 109.1, 110.6, 117.2, 119.3, 120.8, 127.6, 135.9, 140.3; IR 3410, 2932, 1701, 1216, 735 cm^{-1}; EIMS m/z 243, 198 (100), 170, 107, 84. Anal. ($C_{15}H_{17}NO_2$) Calcd: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.50; H, 6.96; N, 5.21.

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxylic acid (5l, n = 3, R = MeO, R^1 = H): 91%; mp 190−192 °C; ^{1}H NMR δ 1.54−1.68 (m, 1H), 1.77−1.94 (m, 2H), 1.93−2.05 (m, 2H), 2.42−2.48 (m, 1H), 2.83−2.90 (m, 2H), 3.65 (s, 3H), 3.81 (s, 3H), 4.20 (t, 1H, J = 4.1 Hz), 6.85 (dd, 1H, J = 2.3, 8.6 Hz), 6.89 (d, 1H, J = 2.2 Hz), 7.15 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 25.4, 26.7, 26.7, 29.7, 30.8, 40.8, 55.6, 99.7, 105.6, 109.7, 111.0, 127.5, 131.8, 138.9, 154.3, 182.1; IR 3457, 2927, 1616, 1226 cm^{-1}; EIMS m/z 273, 228 (100), 122, 84. Anal. ($C_{16}H_{19}NO_3$) Calcd: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.17; H, 7.07; N, 4.79.

4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxamide (6a, n = 1, R = H): 72%; mp 221−223 °C; ^{1}H NMR δ 2.68−2.73 (m, 1H), 2.84−2.90 (m, 1H), 2.95−3.03 (m, 2H), 3.69 (s, 3H), 3.98 (m, 1H), 5.28 (br s, 1H), 5.80 (br s, 1H), 7.11 (ddd, 1H, J = 1.1, 7.1, 7.7 Hz), 7.17 (ddd, 1H, J = 1.1, 7.0, 8.2 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 7.6 Hz); ^{13}C NMR δ 24.0, 31.0, 34.3, 45.3, 109.8, 114.5, 118.1, 119.9, 120.8, 123.3, 141.7, 148.4, 177.9; IR 3359, 2931, 1693, 742 cm^{-1}; EIMS m/z 214, 170 (100), 142, 63. Anal. ($C_{13}H_{14}N_2O$) Calcd: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.01; H, 6.16; N, 13.32.

7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxamide (6b, n = 1, R = MeO): 44%; mp 205−206 °C; ^{1}H NMR δ 2.61−2.65 (m, 1H), 2.85−2.89 (m, 1H), 2.91−2.98 (m, 2H), 3.63 (s, 3H), 3.83 (s, 3H), 3.88 (d, 1H, J = 7.4 Hz), 5.38 (br s, 1H), 5.72 (br s, 1H), 6.83 (dd, 1H, J = 2.6, 8.8 Hz), 6.92 (d, 1H, J = 2.5 Hz), 7.14 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 23.8, 31.0, 35.7, 45.6, 56.0, 101.5, 110.6, 111.3, 120.0, 124.0, 137.3, 143.3, 154.1, 176.3; IR 3405, 2938, 1651, 1489, 1226 cm^{-1}; EIMS m/z 244, 200 (100), 109, 68. Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (6c, n = 2, R = H): 68%; mp 218−219 °C; ^{1}H NMR δ 1.90−2.02 (m, 3H), 2.33−2.38 (m, 1H), 2.66−2.72 (m, 1H), 2.78 (ddd, 1H, J = 14.6, 4.8, 4.0 Hz), 3.64 (s, 3H), 3.75 (m, 1H), 5.55 (br s, 1H), 5.75 (br s, 1H), 7.09 (dd, 1H, J = 6.9, 8.0 Hz), 7.18 (dd, 1H, J = 7.2, 8.1 Hz), 7.28 (d, J = 8.2 Hz), 7.46 (d, J = 7.9 Hz); ^{13}C NMR δ 20.5, 22.1, 27.4, 29.2, 40.0, 106.6, 108.9, 118.0, 119.5, 121.3, 126.3, 137.0, 137.6, 177.6; IR 3346, 2939, 1692, 740 cm^{-1}; EIMS m/z 228, 184 (100), 156, 93. Anal. ($C_{14}H_{16}N_2O$) C, H, N.

6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (6d, n = 2, R = OMe): 74%; mp 157−158 °C; ^{1}H NMR δ 1.88−1.95 (m, 3H), 2.27−2.31 (m, 1H), 2.62 (ddd, 1H, J = 6.2, 8.1 Hz), 2.72 (ddd, 1H, J = 4.2, 5.0, 16.4 Hz), 3.56 (s, 3H), 3.65 (m, 1H), 3.77 (s, 3H), 5.80 (br s, 1H), 6.30 (br s, 1H), 6.78 (dd, 1H, J = 2.3, 8.7 Hz), 6.88 (d, 1H, J = 2.3 Hz), 7.12 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 20.3, 22.0, 27.3, 29.0, 39.9, 55.7, 100.0, 106.0, 109.3, 110.6, 126.5, 132.1, 137.9, 153.9, 177.7; IR 3393, 2932, 1682, 1481, 1224 cm^{-1}; EIMS m/z 258, 214 (100), 114, 68. Anal. ($C_{15}H_{18}N_2O_2$) Calcd: C, 69.74; H, 7.02; N, 10.84. Found: C, 68.82; H, 6.96; N, 10.83.

5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxamide (6e, n = 3, R = H): 90%; mp 60 °C; ^{1}H NMR δ 1.60−1.66 (m, 1H), 1.73−1.90 (m, 2H), 1.91−2.09 (m, 2H), 2.70−2.75 (m, 1H), 2.83 (ddd, 1H, J = 2.5, 11.5, 16.0 Hz), 3.03 (ddd, 1H, J = 2.0, 6.9, 16.1 Hz), 3.73 (s, 3H), 4.10 (t, 1H, J = 4.2 Hz), 5.70 (br s, 1H), 5.71 (br s, 1H), 7.15 (ddd, 1H, J = 1.0, 6.9, 7.9 Hz), 7.23 (ddd, J = 1.1, 7.0, 8.1 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.50 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 26.1, 26.6, 26.9, 29.7, 30.1, 41.6, 109.2, 110.6, 117.4, 119.7, 121.3, 127.6, 136.2, 139.8, 176.6; IR 3456, 2927, 1677, 734 cm^{-1}; EIMS m/z 242, 198 (100), 170, 107. Anal. ($C_{15}H_{18}N_2O$) Calcd: C, 74.35; H, 7.49; N, 11.56. Found: C, 72.97; H, 7.59; N, 10.97.

2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxamide (6f, n = 3, R = MeO): 63%; mp 185−190 °C; ^{1}H NMR δ 1.54−1.57 (m, 1H), 1.68−1.82 (m, 2H), 1.97−2.00 (m, 2H), 2.66−2.69 (m, 1H), 2.70−2.78 (m, 1H), 3.03 (dd, 1H, J = 1.6, 5.7 Hz), 3.65 (s, 3H), 3.82 (s, 3H), 4.00 (t, 1H, J = 3.6 Hz), 5.47 (br s, 1H), 5.69 (br s, 1H), 6.82 (dd, 1H, J = 2.4, 8.8 Hz), 6.88 (d, 1H, J = 2.1 Hz), 7.13 (d, 1H, J = 8.9 Hz); ^{13}C NMR δ 26.1, 26.6, 26.8, 29.7, 30.1, 41.6, 55.9, 99.3, 109.9, 110.2, 111.2, 127.8, 131.4, 140.3, 154.3, 176.5; IR 3460, 2932,

1671, 1470, 1228, 734 cm^{-1}; EIMS *m/z* 272, 228 (100), 137, 84. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

1-(Aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent-[*b*]indole (7a, *n* = 1, R = H). 4-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (2.40 g, 11 mmol) was reduced with $LiAlH_4$ (3.0 g). A yellow oil (1.70 g, 8.5 mmol, 77%) was obtained which was used directly for subsequent acylations.

1-(Aminomethyl)-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (7b, *n* = 1, R = OMe). 7-Methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole-1-carboxamide (2.0 g, 8.2 mmol) was reduced with $LiAlH_4$ (2.5 g). The product (1.1 g, 4.8 mmol, 58%) was obtained as a yellow oil which was used directly for the subsequent acylation.

4-(Aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (7c, *n* = 2, R = H). 9-Methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (2.0 g, 9 mmol) was reduced with borane (10 mL, 1 M). A yellow oil (1.3 g, 6.2 mmol, 69%) was obtained which was used directly for the subsequent acylation: ^{1}H NMR δ 1.54 (s br, 2H), 1.82−1.90 (m, 3H), 1.97−2.02 (m, 1H), 2.62−2.73 (m, 2H), 2.96 (dd, 1H, J = 7.7, 14.4 Hz), 3.06 (m, 1H), 3.14 (dd, 1H, J = 3.9, 12.3 Hz), 3.60 (s, 3H), 7.06 (dd, 1H, J = 7.3, 7.5 Hz), 7.15 (dd, 1H, J = 7.2, 7.9 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.57 (d, 1H, J = 7.9 Hz); ^{13}C NMR δ 19.9, 22.1, 26.1, 28.9, 35.9, 46.1, 108.6, 110.1, 118.3, 118.7, 120.4, 126.7, 136.6, 136.7; EIMS *m/z* 214, 184 (100), 167.

4-(Aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (7d, *n* = 2, R = OMe). 6-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide (1.0 g, 3.9 mmol) was reduced with borane−THF complex (8 mL, 1 M). The product (0.6 g, 2.5 mmol, 63%) was obtained as a yellow oil which was used directly for the subsequent acylation.

10-(Aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (7e, *n* = 3, R = H). 5-Methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxamide (2.40 g, 10 mmol) was reduced with $LiAlH_4$ (3.0 g). The product (1.30 g, 5.7 mmol, 57%) was obtained as a yellow oil which was used directly for the subsequent acylation.

10-(Aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (7f, *n* = 3, R = OMe). 2-Methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole-10-carboxamide (1.90 g, 7.0 mmol) was reduced with $LiAlH_4$ (2.5 g). The product (1.30 g, 5.0 mmol, 72%) was obtained as a yellow oil which was used directly for the subsequent acylation.

***N*-Acetyl-4-(aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (9a, R = H, R^1 = Me):** 76%; mp 173−173.5 °C; ^{1}H NMR δ 1.75−1.96 (m, 4H), 1.92 (s, 3H), 2.64−2.74 (m, 2H), 3.24 (m, 1H), 3.55−3.67 (m, 2H), 3.60 (s, 3H), 5.59 (br s, 1H), 7.06 (ddd, 1H, J = 1.0, 7.0, 7.9 Hz), 7.15 (ddd, 1H, J = 1.0, 7.0, 8.1 Hz), 7.25 (d, 1H, J = 8.1 Hz), 7.56 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 19.7, 22.0, 23.5, 26.6, 29.0, 32.6, 43.5, 108.7, 109.3, 118.3, 119.0, 120.7, 126.6, 136.8, 137.0, 170.2; IR 3292, 2925, 1645, 1468, 740 cm^{-1}; EIMS *m/z* 256, 197 (100), 184(100), 168, 142. Anal. ($C_{16}H_{20}N_2O$) C, H, N.

***N*-Propanoyl-4-(aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (9b, R = H, R^1 = Et):** 83%; mp 109−111 °C; ^{1}H NMR δ 1.1 (t, 3H, J = 7.5 Hz), 1.78−2.00 (m, 4H), 2.14 (q, 2H, J = 7.7 Hz), 2.65−2.71 (m, 2H), 3.23 (m, 1H), 3.52−3.70 (m, 2H), 3.61 (s, 3H), 5.55 (br s, 1H), 7.06 (ddd, 1H, J = 1.0, 6.9, 8.0 Hz), 7.15 (ddd, 1H, J = 1.1, 7.1, 8.1 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.58 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 9.9, 20.0, 22.1, 26.6, 29.1, 29.8, 32.6, 43.3, 108.7, 109.4, 118.4, 119.0, 120.7, 126.6, 136.8, 136.9, 173.9; IR 3299, 2925, 1635, 1465, 734 cm^{-1}; EIMS *m/z* 270, 197, 184 (100), 168, 142. Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***N*-Butanoyl-4-(aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (9c, R = H, R^1 = Pr):** 91%; mp 113−115 °C; ^{1}H NMR δ 0.92 (t, 3H, J = 7.4 Hz), 1.61−1.68 (m, 2H), 1.78−1.90 (m, 3H), 1.97−2.02 (m, 1H), 2.11 (t, 2H, J = 7.5 Hz), 2.64−2.70 (m, 2H), 3.23 (m, 1H), 3.48−3.55 (m, 1H), 3.60 (s, 3H), 3.68−3.74 (m, 1H), 5.77 (br s, 1H), 7.07 (ddd, 1H, J = 1.0, 6.9, 8.0 Hz), 7.16 (ddd, 1H, J = 1.2, 7.0, 8.1 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.61 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 13.7, 19.0, 19.5, 21.9, 26.4, 28.9, 32.6, 38.7, 43.1, 108.6, 109.3, 118.3, 118.9, 120.5, 126.5, 136.7, 136.9, 173.1; IR 3284, 2929, 1630, 1546, 1456, 738 cm^{-1}; EIMS *m/z* 284, 197 (100), 184 (100), 168, 142. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

***N*-Pentanoyl-4-(aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (9d, R = H, R^1 = Bu):** 91%; mp 146−148 °C; ^{1}H NMR δ 0.89 (t, 3H, J = 7.3 Hz), 1.32 (m, 2H), 1.58 (m, 2H), 1.78−1.85 (m, 2H), 1.85−1.91 (m, 1H), 1.94−2.02 (m, 1H), 2.13 (t, 2H, J = 6.7 Hz), 2.64−2.72 (m, 2H), 3.23 (m, 1H), 3.47−3.54 (m, 1H), 3.59 (s, 3H), 3.62−3.73 (m, 1H), 5.82 (s br, 1H), 7.06 (dd, 1H, J = 7.1, 7.8 Hz), 7.15 (dd, 1H, J = 7.0, 8.0 Hz), 7.25 (d, 1H, J = 8.1 Hz), 7.61 (d, 1H, J = 7.6 Hz); ^{13}C NMR δ 13.7, 19.5, 21.9, 22.3, 26.4, 27.7, 28.9, 32.5, 36.5, 43.1, 108.6, 109.3, 118.3, 118.8, 120.5, 126.5, 136.7, 136.8, 173.3; IR 3279, 2925, 1631, 1548, 740 cm^{-1}; EIMS *m/z* 298, 197 (100), 184 (100), 168, 142. Anal. ($C_{19}H_{26}N_2O$) Calcd: C, 76.47; H, 8.78; N, 9.39. Found: C, 75.70; H, 8.31; N 9.37.

***N*-Cyclopropanoyl-4-(aminomethyl)-9-methyl-1,2,3,4-tetrahydrocarbazole (9e, R = H, R^1 = c-C_3H_5):** 88%; mp 182−182.5 °C; ^{1}H NMR δ 0.98−1.05 (m, 2H), 1.27−1.35 (m, 2H), 1.81−1.87 (m, 4H), 1.87−2.00 (m, 1H), 2.62−2.72 (m, 2H), 3.23−3.26 (m, 1H), 3.46−3.49 (ddd, 1H, J = 5.8, 6 2, 13.6 Hz), 3.60 (s, 3H), 3.71−3.77 (ddd, 1H, J = 5.0, 5.9, 13.5 Hz), 5.20 (br t, 1H, J = 5.8 Hz), 7.09 (ddd, 1H, J = 1.5, 7.5, 7.5 Hz), 7.17 (ddd, 1H, J = 1.0, 7.1, 7.5 Hz), 7.25 (d, J = 7.0 Hz), 7.66 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 6.84, 14.6, 19.3, 21.9, 26.2, 28.8, 32.5, 43.4, 108.5, 109.3, 118.3, 118.8, 120.4, 126.5, 136.7, 136.8, 173.8; IR 3246, 2912, 1631, 1551, 740 cm^{-1}; EIMS *m/z* 282, 197, 184 (100), 168, 142. Anal. ($C_{18}H_{22}N_2O$) C, H, N.

***N*-(Trifluoroacetyl)-4-(methylamino)-9-methyl-1,2,3,4-tetrahydrocarbazole (9f, R = H, R^1 = CF_3):** 63%; mp 134−135 °C; ^{1}H NMR δ 1.86−2.05 (m, 4H), 2.72−2.79 (m, 2H), 3.38 (m, 1H), 3.66 (s, 3H), 3.83−3.89 (m, 2H), 6.94 (s, br, 1H), 7.16 (ddd, J = 1.1, 7.0, 7.3 Hz, 1H), 7.25 (ddd, J = 1.0, 7.0, 7.1 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.65 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 19.1, 21.8, 26.0, 28.9, 31.9, 43.6, 108.2, 108.8, 117.3 (J = 288 Hz), 117.8, 119.1, 120.7, 126.2, 136.8, 137.0, 157.4 (J = 37 Hz); IR 3319, 2932, 1692, 1198, 1157, 740 cm^{-1}; EIMS *m/z* 310, 214, 197, 184 (100), 154, 128. Anal. ($C_{16}H_{17}F_3N_2O$) Calcd: C, 61.93; H, 5.52; N, 9.03. Found: C, 61.08; H, 5.28; N, 8.94.

***N*-Acetyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9g, R = OMe, R^1 = Me):** 73%; mp 162−163 °C; ^{1}H NMR δ 1.74−1.94 (m, 4H), 1.92 (s, 3H), 2.57−2.64 (m, 2H), 3.15 (m, 1H), 3.31−3.44 (m, 1H), 3.52 (s, 3H), 3.54−3.66 (m, 1H), 3.81 (s, 3H), 6.02 (s br, 1H), 6.76 (dd, 1H, J = 2.5, 8.7 Hz), 7.06 (d, 1H, J = 2.5 Hz), 7.09 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 19.3, 21.9, 23.2, 26.2, 28.9, 32.3, 43.0, 55.8, 100.5, 108.9, 109.1, 110.0, 126.7, 131.9, 137.3, 153.6, 170.2; IR 3305, 2929, 1637, 1550, 1216 cm^{-1}; EIMS *m/z* 286, 227 (98), 214 (100), 123, 102. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

***N*-Propanoyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9h, R = OMe, R^1 = Et):** yellow oil; 56%; ^{1}H NMR δ 1.10 (t, 3H, J = 7.6 Hz), 1.75−1.80 (m, 2H), 1.81−1.87 (m, 1H), 1.93−1.97 (m, 1H), 2.15 (q, 2H, J = 7.6 Hz), 2.59−2.65 (m, 2H), 3.16 (m, 1H), 3.45 (ddd, 1H, J = 5.9, 6.2, 13.4 Hz), 3.54 (s, 3H), 3.66 (ddd, 1H, J = 5.2, 5.6, 13.4 Hz), 3.82 (s, 3H), 5.84 (s br, 1H), 6.78 (dd, 1H, J = 2.2, 8.7 Hz), 7.07 (d, 1H, J = 2.3 Hz), 7.11 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 9.8, 19.3, 22.0, 26.3, 28.9, 29.7, 32.4, 42.9, 55.9, 100.8, 109.0, 109.2, 110.1, 126.8, 132.1, 137.3, 153.6, 173.8; IR (film) 3310, 2940, 1645, 1555, 1220 cm^{-1}; EIMS *m/z* 300, 228 (100), 227, 123, 102. Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

***N*-Butanoyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9i, R = OMe, R^1 = Pr):** 83%; mp 128−129 °C; ^{1}H NMR δ 0.91 (t, 3H, J = 7.4 Hz), 1.60−1.68 (m, 2H), 1.76−1.86 (m, 3H), 1.93−1.95 (m, 1H), 2.12 (t, 2H, J = 7.5 Hz), 2.58−2.64 (m, 2H), 3.17 (m, 1H), 3.41 (ddd, 1H, J = 5.4, 6.2, 13.5 Hz), 3.51 (s, 3H), 3.71 (ddd, 1H, J = 4.9, 5.6, 13.5 Hz), 3.82 (s, 3H), 6.12 (t br, 1H, J = 5.6 Hz), 6.78 (dd, 1H, J = 2.3, 8.8 Hz), 7.10 (d, 1H, J = 8.7 Hz), 7.11 (d, 1H, J = 2.5 Hz); ^{13}C NMR δ 13.5, 19.0, 19.2, 21.9, 26.1, 28.8, 32.3, 38.5, 42.8, 55.8, 100.7, 108.9, 109.0, 109.9, 126.7, 132.0, 137.2, 153.5, 173.2; IR 3306, 2932, 1635, 1541, 1221 cm^{-1}; EIMS *m/z* 314, 227 (100), 228 (100), 123, 102. Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

***N*-Pentanoyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9j, R = OMe, R^1 = Bu):** 78%; mp 113−115 °C; ^{1}H NMR δ 0.86 (t, 3H, J = 7.3 Hz), 1.26−1.33 (m, 2H), 1.53−1.60 (m, 2H), 1.75−1.86 (m, 3H), 1.95−1.96 (m, 1H), 2.12 (t, 2H, J = 7.5 Hz), 2.61−2.66 (m, 2H), 3.18 (m, 1H), 3.46 (ddd, 1H, J = 5.9, 6.1, 13.5 Hz), 3.55 (s, 3H), 3.68 (ddd, 1H, J = 5.1, 5.7, 13.5 Hz), 3.83 (s, 3H), 5.73 (t br, 1H), 6.79 (dd, 1H, J = 2.4, 8.7 Hz), 7.07 (d, 1H, J = 2.2 Hz), 7.12 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 13.7, 19.5, 22.1, 22.3, 26.4, 27.8, 29.0, 32.6, 36.6, 42.9, 56.0, 100.8, 108.9, 109.2, 110.2, 126.8, 132.1, 137.5, 153.7, 173.3; IR 3305, 2932, 1635, 1541, 1221 cm^{-1}; EIMS m/z 328, 228 (100), 227, 123, 102. Anal. ($C_{20}H_{28}N_2O_2$) C, H, N.

***N*-Cyclopropanoyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9k, R = OMe, R^1 = c-C_3H_5):** 58%; mp 173−174 °C; ^{1}H NMR δ 0.96−1.03 (m, 2H), 1.24−1.33 (m, 2H), 1.81−1.85 (m, 3H), 1.87−1.92 (m, 1H), 1.96−2.01 (m, 1H), 2.64−2.74 (m, 2H), 3.22 (m, 1H), 3.56−3.69 (m, 2H), 3.60 (s, 3H), 3.86 (s, 3H), 5.98 (t br, 1H, J = 5.3 Hz), 6.83 (dd, 1H, J = 2.4, 8.8 Hz), 7.11 (d, 1H, J = 2.3 Hz), 7.17 (d, 1H, J = 8.9 Hz); ^{13}C NMR δ 7.0, 14.8, 19.4, 22.1, 26.5, 29.1, 32.5, 43.4, 56.0, 100.8, 109.1, 109.3, 110.2, 126.9, 132.1, 137.5, 153.7, 173.6; IR 3265, 2945, 1635, 1558, 1218 cm^{-1}; EIMS m/z 312, 228 (100), 227, 123, 102. Anal. ($C_{19}H_{24}N_2O_2$) C, H, N.

***N*-Cyclobutanoyl-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9l, R = OMe, R^1 = c-C_4H_7):** 82%; mp 160−161 °C; ^{1}H NMR δ 1.75−1.97 (m, 6H), 2.02−2.11 (m, 2H), 2.19−2.36 (m, 2H), 2.61−2.67 (m, 2H), 2.93 (m, 1H), 3.21 (m, 1H), 3.51 (m, 1H), 3.56 (s, 3H), 3.65 (m, 1H), 3.83 (s, 3H), 5.55 (s br, 1H), 6.79 (dd, 1H, J = 2.4, 8.8 Hz), 7.04 (d, 1H, J = 2.5 Hz), 7.13 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 18.1, 19.4, 22.1, 25.2, 26.4, 29.1, 32.5, 40.0, 43.0, 56.0, 100.8, 109.0, 109.3, 110.2, 126.8, 132.1, 137.5, 153.7, 175.1; IR 3301, 1632, 1551, 1228 cm^{-1}; EIMS m/z 326, 228 (100), 227, 123, 102. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***N*-(Trifluoroacetyl)-4-(aminomethyl)-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (9m, R = OMe, R^1 = CF_3):** 63%; mp 163−164 °C; ^{1}H NMR δ 1.77−1.95 (m, 4H), 2.64−2.71 (m, 2H), 3.26 (m, 1H), 3.58 (s, 3H), 3.59 (m, 1H), 3.74 (m, 1H), 3.84 (s, 3H), 6.82 (dd, 1H, J = 2.5, 8.8 Hz), 7.01 (d, 1H, J = 2.5 Hz), 7.16 (d, 1H, J = 8.8 Hz), 7.55 (s br, 1H); ^{13}C NMR δ 19.3, 22.0, 26.4, 29.2, 32.0, 43.7, 56.0, 100.2, 107.8, 109.6, 110.6, 118.2 (J = 280 Hz), 126.5, 132.2, 137.7, 154.0, 175.1 (J = 40 Hz); IR 3305, 2921, 1692, 1553, 1228 cm^{-1}; EIMS m/z 340, 243, 227, 214 (100), 123, 102. Anal. ($C_{17}H_{19}N_2O_2F_3$) C, H, N.

***N*-Acetyl-4-(aminomethyl)-6-(trifluoromethoxy)-9-methyl-1,2,3,4-tetrahydrocarbazole (9n, R = OCF_3, R^1 = Me):** 63%; mp 183−184 °C; ^{1}H NMR δ 1.75−2.04 (m, 4H), 1.93 (s, 3H), 2.58−2.75 (m, 2H), 3.14−3.20 (m, 1H), 3.60 (s, 3H), 3.52−3.60 (m, 2H), 5.55 (br s, 1H), 7.01 (dd, 1H, J = 8.7, 0.9 Hz), 7.19 (d, 1H, J = 8.7 Hz), 7.40 (d, 1H, J = 0.9 Hz); ^{13}C NMR δ 19.7, 22.5, 23.6, 26.8, 29.5, 32.9, 44.0, 109.5, 110.65, 111.2, 114.75, 122.7, 127.3, 135.7, 139.2, 143.2, 170.5; IR 3261, 2955, 1634, 1564, 1435, 1257, 1165 cm^{-1}; EIMS m/z 340, 281, 268 (100), 252, 182. Anal. C, H, N.

***N*-Propanoyl-4-(aminomethyl)-6-(trifluoromethoxy)-9-methyl-1,2,3,4-tetrahydrocarbazole (9o, R = OCF_3, R^1 = Et):** 55%; mp 170−171 °C; ^{1}H NMR δ 1.12 (t, 3H, J = 7.6 Hz), 1.75−2.05 (m, 4H), 2.14 (q, 2H, J = 7.6 Hz), 2.58−2.74 (m, 2H), 3.16−3.24 (m, 1H), 3.60 (s, 3H), 3.50−3.62 (m, 2H), 5.51 (br s, 1H), 7.01 (dd, 1H, J = 7.6, 0.9 Hz), 7.19 (d, 1H, J = 7.6 Hz), 7.40 (m, 1H); ^{13}C NMR δ 10.1, 19.7, 22.6, 26.8, 29.5, 30.2, 43.8, 109.5, 110.7, 111.7, 114.7, 120.5, 122.7, 127.3, 135.7, 139.2, 143.2, 174.2; IR 3439, 2978, 1637, 1256, 1151, 1047, 789 cm^{-1}; EIMS m/z 354, 281, 268 (100), 252, 182. Anal. ($C_{18}H_{21}N_2O_2F_3$) C, H, N.

***N*-Cyclobutanoyl-4-(aminomethyl)-6-(trifluoromethoxy)-9-methyl-1,2,3,4-tetrahydrocarbazole (9p, R = OCF_3, R^1 = C_4H_7):** 21%; mp 152−153 °C; ^{1}H NMR δ 1.75−2.30 (m, 10H), 2.58−2.74 (m, 2H), 2.88−2.98 (m, 1H) 3.14−3.22 (m, 1H), 3.60 (s, 3H), 3.50−3.60 (m, 2H), 5.42 (br s, 1H), 7.05 (dd, 1H, J = 8.7, 1.1 Hz), 7.19 (d, 1H, J = 8.8 Hz), 7.38 (d, 1H, J = 0.9 Hz); ^{13}C NMR δ 18.5, 19.7, 22.6, 25.7, 25.8, 26.8, 29.5, 32.9, 33.0, 40.5, 43.7, 109.4, 110.7, 111.3, 114.7, 127.3, 135.7, 139.2, 143.9, 175.4; IR 3290, 2941, 1637, 1553, 1491, 1257, 1217, 1151 cm^{-1}; EIMS m/z 380, 281, 268 (100), 252, 55. Anal. ($C_{20}H_{23}N_2O_2F_3$) Calcd: C, 63.15; H, 6.05; N, 7.37. Found: C, 62.70; H, 5.98; N, 7.20.

***N*-Acetyl-4-(aminomethyl)-6,9-dimethyl-1,2,3,4-tetrahydrocarbazole (9q, R = Me, R^1 = Me):** 65%; mp 171−172 °C; ^{1}H NMR δ 1.76−2.05 (m, 4H), 1.92 (s, 3H), 2.43 (s, 3H), 2.60−2.70 (m, 2H), 3.16−3.24 (m, 1H), 3.57 (s, 3H), 3.55−3.65 (m, 2H), 5.54 (br s, 1H), 6.97 (dd, 1H, J = 8.3, 1.3 Hz), 7.13 (d, 1H, J = 8.3 Hz), 7.15 (d, 1H, J = 0.6 Hz); ^{13}C NMR δ 20.2, 21.8, 22.5, 23.8, 27.2, 33.0, 44.0, 127.4, 108.8, 109.3, 118.6, 122.6, 125.6, 128.6, 136.0, 137.9, 170.5; IR 3351, 2933, 1651, 1545, 1292, 795 cm^{-1}; EIMS m/z 270 (M^+, 35), 211 (80), 198 (100), 182 (40), 168 (25).

***N*-Propanoyl-4-(aminomethyl)-6,9-dimethyl-1,2,3,4-tetrahydrocarbazole (9r, R = Me, R^1 = Et):** 52%; mp 153−154 °C; ^{1}H NMR δ 1.11 (t, 3H, J = 7.6 Hz), 1.75−2.05 (m, 4H), 2.14 (q, 2H, J = 7.6 Hz), 2.43 (s, 3H) 2.58−2.74 (m, 2H), 3.16−3.24 (m, 1H), 3.57 (s, 3H), 3.55−3.65 (m, 2H), 5.51 (br s, 1H) 6.97 (dd, 1H, J = 8.3, 1.2 Hz), 7.13 (d, 1H, J = 8.3 Hz), 7.35 (m, 1H); ^{13}C NMR δ 10.1, 20.1, 21.8, 22.1, 22.5, 27.2, 29.1, 33.0, 43.9, 108.8, 118.6, 122.6, 125.6, 128.6, 136.0, 136.9, 169.5; IR 3288, 2931, 1659, 1487, 1556, 1238, 789 cm^{-1}; EIMS m/z 284, 211, 198 (100), 182, 168. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

***N*-Cyclobutanoyl-4-(aminomethyl)-6,9-dimethyl-1,2,3,4-tetrahydrocarbazole (9s, R = Me, R^1 = C_4H_7):** 44%; mp 169−170 °C; ^{1}H NMR δ 1.57−2.35 (m, 10H), 2.43 (s, 3H), 2.58−2.74 (m, 2H), 2.85−2.95 (m, 1H), 3.16−3.24 (m, 1H), 3.57 (s, 3H), 3.55−3.65 (m, 2H), 5.45 (br s, 1H), 6.9 (dd, 1H, J = 8.3, 1.4 Hz), 7.13 (d, 1H, J = 8.1 Hz), 7.34 (d, 1H, J = 0.4 Hz); ^{13}C NMR δ 18.6, 20.0, 21.9, 22.5, 25.7, 27.2, 30.5, 31.6, 33.0, 40.6, 43.9, 108.8, 114.5, 118.6, 122.6, 127.0, 128.6, 135.5, 138.0, 170.5; IR 3244, 2937, 1659, 1634, 1560, 1261, 787 cm^{-1}; EIMS m/z 310, 211, 198 (100), 182, 168; $C_{20}H_{27}N_2O$ $(M + 1)^+$ requires 311.2123, found 311.2111.

***N*-Acetyl-4-(aminomethyl)-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole (9t, R = Cl, R^1 = Me):** 55%; mp 163−164 °C; ^{1}H NMR δ 1.75−2.05 (m, 4H), 1.95 (s, 3H) 2.58−2.74 (m, 2H), 3.13−3.20 (m, 1H), 3.60 (s, 3H), 3.50−3.60 (m, 2H), 5.50 (br s, 1H), 7.06−7.18 (m, 2H), 7.51 (d, 1H, J = 1.8 Hz); ^{13}C NMR δ 20.15, 22.5, 23.7, 27.1, 29.3, 31.1, 43.4, 109.1, 109.9, 118.7, 119.5, 121.2, 127.2, 137.2, 137.5, 170.5; IR 3275, 2931, 1739, 1647, 1556, 1473, 1296, 1242, 739 cm^{-1}; EIMS m/z 290, 231, 218 (100), 183, 43. Anal. ($C_{16}H_{19}N_2OCl$) Calcd: C, 71.29; H, 7.74; N, 9.78. Found: C, 70.37; H, 7.87; N, 9.35.

***N*-Cyclopropanoyl-4-(aminomethyl)-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole (9u, R = Cl, R^1 = C_3H_5):** 21%; mp 173−174 °C; ^{1}H NMR δ 0.64−0.80 (m, 2H), 0.92−1.04 (m, 2H), 1.22−1.30 (m, 1H), 1.70−2.05 (m, 4H), 2.58−2.74 (m, 2H), 3.14−3.22 (m, 1H), 3.58 (s, 3H), 3.52−3.60 (m, 2H), 5.69 (br s, 1H), 7.05−7.15 (m, 2H), 7.54 (d, 1H, J = 1.8 Hz); ^{13}C NMR δ 7.2, 7.4, 15.3, 19.8, 22.5, 26.8, 29.5, 33.0, 44.1, 109.5, 110.1, 118.4, 121.2, 125.3, 128.3, 135.8, 138.7, 172.6; IR 3305, 2931, 1637, 1553, 1473, 1240, 795, 700 cm^{-1}; EIMS m/z 316, 231, 218 (100), 183, 167. Anal. ($C_{18}H_{21}N_2OCl$) Calcd: C, 68.23; H, 6.68; N, 8.84. Found: C, 67.72; H, 6.56; N, 8.71.

***N*-Cyclobutanoyl-4-(aminomethyl)-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole (9v, R = Cl, R^1= C_4H_7):** 36%; mp 185−186 °C; ^{1}H NMR δ 1.75−2.35 (m, 10H), 2.60−2.74 (m, 2H), 2.90−3.00 (m, 1H), 3.14−3.22 (m, 1H), 3.60 (s, 3H), 3.54−3.62 (m, 2H), 5.40 (br s, 1H), 7.07−7.18 (m, 2H), 7.51 (d, 1H, J = 1.8 Hz); IR 3269, 2935, 1635, 1549, 1473, 1256, 791; EIMS m/z 330, 231, 218 (100), 182, 55. Anal. ($C_{19}H_{23}N_2OCl$) Calcd: C, 63.15; H, 6.05; N, 7.37. Found: C, 62.70; H, 5.98; N, 7.20.

***N*-Propanoyl-4-(aminomethyl)-6-ethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (9w, R = Et, R^1 = Et):** 30%; ^{1}H NMR δ 1.10 (3H, t, J = 8 Hz), 1.30 (t, 3H, J = 8 Hz), 1.7−2.05 (m, 4H), 2.13 (q, 2H, J = 8 Hz), 2.58−2.05 (m, 4H), 3.25 (m, 1H), 3.60 (s, 3H), 3.59−3.64 (m, 2H), 5.55 (br s, 1H), 7.0 (d, 1H, J = 8 Hz), 7.20 (d, 1H, J = 8 Hz), 7.38 (bs, 1H); ^{13}C NMR δ 8.0, 14.8, 17.9, 20.3, 25.0, 27.2, 27.3, 28.1, 30.8, 41.8, 106.7, 107.4,

115.2, 119.3, 125.2, 133.3, 133.8, 135.1, 172.0; IR 3308, 2933, 1645, 1551, 1485, 1244, 795 cm^{-1}.

***N*-Acetyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10a, R = H, R^1 = Me):** 91%; mp 148−149 °C; ^{1}H NMR δ 1.97 (s, 3H), 2.21−2.25 (m, 1H), 2.67−2.71 (m, 1H), 2.78−2.85 (m, 1H), 2.88−2.92 (m, 1H), 3.48−3.67 (m, 3H), 3.69 (s, 3H), 5.63 (br s, 1H), 7.11 (ddd, 1H, *J* = 1.1, 7.0, 8.0 Hz), 7.17 (ddd, 1H, *J* = 1.2, 7.0, 8.2 Hz), 7.28 (d, 1H, *J* = 8.1 Hz), 7.45 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR δ 23.5, 24.0, 30.8, 32.6, 38.8, 43.9, 109.6, 117.4, 118.0, 119.3, 120.2, 123.9, 141.4, 147.1, 170.2; IR 3306, 2955, 1638, 1558, 1296, 732 cm^{-1}; EIMS *m*/*z* 242, 183 (100), 170 (100), 154, 128. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

***N*-Propanoyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10b, R = H, R^1 = Et):** 73%; mp 105−107 °C; ^{1}H NMR δ 1.14 (t, 3H, *J* = 7.6 Hz), 2.17 (q, 2H, *J* = 7.5 Hz), 2.22−2.25 (m, 1H), 2.67−2.72 (m, 1H), 2.77−2.87 (m, 1H), 2.89−2.94 (m, 1H), 3.48−3.66 (m, 3H), 3.67 (s, 3H), 5.63 (br s, 1H), 7.10 (ddd, 1H, *J* = 1.0, 7.0, 8.1 Hz), 7.18 (ddd, 1H, *J* = 1.1, 7.1, 8.2 Hz), 7.27 (d, 1H, *J* = 8.2 Hz), 7.44 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR δ 9.6, 23.9, 29.8, 30.8, 32.7, 38.9, 43.8, 109.6, 117.5, 118.0, 119.2, 120.2, 123.9, 141.4, 147.1, 173.9; IR 3309, 2943, 1645, 1544, 734 cm^{-1}; EIMS *m*/*z* 256, 183, 170 (100), 154, 128. Anal. ($C_{16}H_{20}N_2O$) C, H, N.

***N*-Butanoyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10c R = H, R^1 = Pr):** 84%; mp 118−119 °C; ^{1}H NMR δ 0.91 (t, 3H, *J* = 7.3 Hz), 1.63 (m, 2H), 2.10 (t, 2H, *J* = 7.5 Hz), 2.20−2.22 (m, 1H), 2.60−2.70 (m, 1H), 2.75−2.81 (m, 1H), 2.82−2.88 (m, 1H), 3.52−3.57 (m, 3H), 3.66 (s, 3H), 5.55 (br s, 1H), 7.07 (ddd, 1H, *J* =1.1, 7.0, 7.8 Hz), 7.15 (ddd, 1H, *J* = 1.1, 7.1, 8.3 Hz), 7.25 (d, 1H, *J* = 8.1 Hz), 7.43 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR δ 13.8, 19.2, 24.1, 30.9, 32.8, 38.9, 39.1, 43.7, 109.7, 117.6, 118.1, 119.4, 120.3, 124.0, 141.5, 147.2, 173.2; IR 3304, 2958, 1638, 1558, 733 cm^{-1}; EIMS *m*/*z* 270, 183, 170 (100), 154, 128. Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***N*-Pentanoyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[b]indole (10d, R = H, R^1= Bu):** 89%; mp 109−110 °C; ^{1}H NMR δ 0.90 (t, 3H, *J* = 7.4 Hz), 1.30−1.40 (m, 2H), 1.56−1.62 (m, 2H), 2.16 (t, 2H, *J* = 7.5 Hz), 2.20−2.25 (m, 1H), 2.67−2.73 (m, 1H), 2.79−2.86 (m, 1H), 2.88−2.95 (m, 1H), 3.54−3.64 (m, 3H), 3.69 (s, 3H), 5.58 (br s, 1H), 7.09 (ddd, 1H, *J* = 1.2, 7.4, 7.4 Hz), 7.18 (ddd, *J* = 1.2, 7.1, 8.1 Hz), 7.28 (d, 1H, *J* = 8.4 Hz), 7.46 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR δ 13.7, 22.3, 24.0, 27.8, 30.8, 32.6, 36.6, 38.9, 43.6, 109.6, 117.4, 118.0, 119.2, 120.2, 123.8, 141.4, 147.1, 173.3; IR 3305, 2967, 1640, 1541, 736 cm^{-1}; EIMS *m*/*z* 284, 183, 170 (100), 154, 128. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

***N*-Cyclopropanoyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10e, R = H, R^1 = c-C_3H_5):** 60%; mp 160.5−161.5 °C; ^{1}H NMR δ 0.73−0.80 (m, 2H), 0.93−1.05 (m, 2H), 1.31−1.36 (m, 1H), 2.22−2.29 (m, 1H), 2.67−2.75 (m, 1H), 2.80−2.87 (m, 1H), 2.91−2.99 (m, 1H), 3.51−3.60 (m, 3H), 3.70 (s, 3H), 5.90 (s br, 1H), 7.13 (ddd, 1H, *J* = 1.0, 7.6, 8.1 Hz), 7.20 (ddd, 1H, *J* = 1.1, 7.1, 8.1 Hz), 7.29 (d, 1H, *J* = 8.1 Hz), 7.52 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR δ 6.91, 14.1, 23.9, 30.7, 32.6, 39.0, 44.1, 109.5, 117.6, 118.1, 119.2, 120.1, 123.9, 141.4, 147.0, 173.6; IR 3300, 2943, 1638, 1539, 740 cm^{-1}; EIMS *m*/*z* 268, 183, 170 (100), 154, 128. Anal. ($C_{17}H_{20}N_2O$) C, H, N.

***N*-Cyclobutanoyl-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10f, R = H, R^1 = c-C_4H_7):** 76%; mp 100.5−101.5 °C; ^{1}H NMR δ 1.80−1.93 (m, 2H), 2.04−2.12 (m, 1H), 2.15−2.29 (m, 4H), 2.62−2.67 (m, 1H), 2.78−2.85 (m, 1H), 2.86−2.94 (m, 2H), 3.52−3.57 (m, 3H), 3.65 (s, 3H), 5.45 (s br, 1H), 7.06 (ddd, 1H, *J* = 1.1, 7.0, 7.8 Hz), 7.13 (ddd, 1H, *J* = 1.3, 7.1, 8.1 Hz), 7.24 (d, 1H, *J* = 8.1 Hz), 7.39 (d, 1H, *J* = 7.3 Hz); ^{13}C NMR δ 18.2, 24.1, 25.4, 30.9, 32.8, 39.1, 40.1, 43.9, 109.7, 117.7, 118.1, 119.4, 120.3, 124.0, 141.5, 147.2, 175.1; IR 3298, 2931, 1634, 1539, 741 cm^{-1}; EIMS *m*/*z* 282, 183 (100), 170 (100), 154, 128. Anal. ($C_{18}H_{22}N_2O$) C, H, N.

***N*-(Trifluoroacetyl)-1-(aminomethyl)-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10g, R = H, R^1 = CF_3):** 72%; mp 160−161 °C; ^{1}H NMR δ 2.25−2.32 (m, 1H), 2.68−2.77 (m, 1H), 2.78−2.81 (m, 1H), 2.88−2.92 (m, 1H), 2.99 (dd, 1H, *J* = 8.2, 12.9 Hz), 3.27 (dd, 1H, *J* = 3.4, 13.6 Hz), 3.59−3.62 (m, 1H), 3.61 (s, 3H), 6.80 (br s, 1H), 6.99−7.06 (m, 2H), 7.17 (d, 1H, *J* = 8.2 Hz), 7.37 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR δ 23.8, 30.8, 32.5, 37.3, 44.0, 109.7, 114.7, 117.8, 118.0, 119.5, 120.5, 123.4, 141.6, 147.6, 162.2; IR 3306, 2925, 1666, 1527, 1205, 1175, 1146; EIMS *m*/*z* 296, 200, 183, 170 (100), 154, 128. Anal. ($C_{15}H_{15}N_2OF_3$) C, H, N.

***N*-Acetyl-1-(aminomethyl)-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10h, R = OMe, R^1 = Me):** 92%; mp 134−136 °C; ^{1}H NMR δ 1.92 (s, 3H), 2.20−2.25 (m, 1H), 2.65−2.83 (m, 3H), 3.23−3.29 (m, 1H), 3.44−3.46 (m, 1H), 3.66 (s, 3H), 3.62−3.72 (m, 1H), 3.83 (s, 3H), 5.50 (br s, 1H), 6.81 (dd, 1H, *J* = 2.3, 8.9 Hz), 6.90 (d, 1H, *J* = 2.4 Hz), 7.12 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR δ 23.4, 23.5, 31.0, 33.7, 38.2, 42.9, 56.0, 101.3, 110.2, 110.5, 118.6, 124.2, 137.3, 145.9, 154.0, 170.5; IR 3310, 2950, 1643, 1230 cm^{-1}; EIMS *m*/*z* 272, 213, 200 (100), 157, 43. Anal. ($C_{16}H_{20}N_2O_2$) Calcd: C, 70.56; H, 7.40; N, 10.29. Found: C, 69.98; H, 7.21; N, 10.04.

***N*-Propanoyl-1-(aminomethyl)-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10i, R = OMe, R^1 = Et):** 87%; mp 118−120 °C; ^{1}H NMR δ 1.08 (t, 3H, *J* = 7.6 Hz), 2.13 (q, 2H, *J* = 7.6 Hz), 2.20−2.25 (m, 1H), 2.64−2.81 (m, 3H), 3.21−3.27 (m, 1H), 3.44−3.45 (m, 1H), 3.66 (s, 3H), 3.68−3.73 (m, 1H), 3.82 (s, 3H), 5.57 (br s, 1H), 6.80 (dd, 1H, *J* = 2.4, 8.9 Hz), 6.90 (d, 1H, *J* = 2.4 Hz), 7.11 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR δ 9.6, 23.5, 30.5, 30.8, 33.6, 38.3, 43.1, 56.0, 101.2, 110.1, 110.5, 118.6, 124.2, 137.3, 145.9, 154.1, 171.6; IR 3311, 2940, 1644, 1227 cm^{-1}; EIMS *m*/*z* 286, 213, 200 (100), 157, 43. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

***N*-Butanoyl-1-(aminomethyl)-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10j, R = OMe, R^1 = Pr):** 75%; mp 122−123 °C; ^{1}H NMR δ 0.88 (t, 3H, *J* = 7.3 Hz), 1.57−1.64 (m, 2H), 2.08 (t, 2H, *J* = 7.3 Hz), 2.20−2.25 (m, 1H), 2.66−2.82 (m, 3H), 3.26 (ddd, 1H, *J* = 4.6, 6.2, 13.5 Hz), 3.45−3.47 (m, 1H), 3.67 (s, 3H), 3.73 (ddd, 1H, *J* = 3.9, 6.0, 15.2 Hz), 3.83 (s, 3H), 5.41 (s br, 1H), 6.80 (dd, 1H, *J* = 2.5, 8.8 Hz), 6.90 (d, 1H, *J* = 2.5 Hz), 7.12 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR δ 13.8, 19.1, 23.5, 30.5, 33.7, 38.3, 38.7, 42.7, 56.0, 101.2, 110.2, 110.5, 118.6, 124.2, 138.3, 145.9, 154.1, 171.8; IR 3309, 2964, 1646, 1226 cm^{-1}; EIMS *m*/*z* 300, 213, 200 (100), 157, 43. Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

***N*-Cyclopropanoyl-1-(aminomethyl)-7-methoxy-4-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole (10k, R = OMe, R^1 = c-C_3H_5):** 67%; mp 139−140 °C; ^{1}H NMR δ 0.67−0.74 (m, 2H), 0.87−0.99 (m, 2H), 1.21−1.28 (m, 1H), 2.22−2.27 (m, 1H), 2.65−2.87 (m, 3H), 3.23−3.29 (m, 1H), 3.43−3.47 (m, 1H), 3.67 (s, 3H), 3.67−3.75 (m, 1H), 3.83 (s, 3H), 5.72 (s br, 1H), 6.80 (dd, 1H, *J* = 2.3, 9.0 Hz), 6.91 (d, 1H, *J* = 2.4 Hz), 7.13 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR δ 7.2, 14.7, 23.4, 31.0, 33.7, 38.3, 43.1, 56.0, 101.2, 110.2, 110.4, 118.4, 124.2, 137.2, 146.2, 153.9, 174.0; IR 3315, 2924, 1637, 1232 cm^{-1}; EIMS *m*/*z* 298, 226, 215, 159, 43 (100). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

***N*-Acetyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11a, R = H, R^1 = Me):** 82%; mp 151.5−153 °C; ^{1}H NMR δ 1.68−1.72 (m, 1H), 1.88−1.97 (m, 1H), 1.98 (s, 3H), 2.03−2.31 (m, 4H), 2.82 (ddd, 1H, *J* = 3.0, 12.2 Hz, 16.6 Hz), 3.06 (ddd, 1H, *J* = 2.5, 5.6, 15.8 Hz), 3.33 (ddd, 1H, *J* = 4.0, 9.0, 12.8 Hz), 3.60−3.64 (m, 1H), 3.82 (s, 3H), 3.83 (dd, *J* = 6.5, 13.2 Hz), 7.11 (ddd, 1H, *J* = 1.0, 7.4, 7.4 Hz), 7.19 (ddd, 1H, *J* = 1.1, 7.5, 7.7 Hz), 7.35 (d, 1H, *J* = 8.1 Hz), 7.55 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR δ 23.2, 25.6, 25.8, 27.3, 29.4, 30.4, 34.1, 43.0, 108.9, 113.1, 117.2, 119.0, 120.5, 128.1, 135.7, 138.7, 170.0; IR 3246, 2925, 1637, 1548, 731 cm^{-1}; EIMS *m*/*z* 270, 211, 198, 107 (100), 84. Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***N*-Propanoyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11b, R = H, R^1 = Et):** 98%; mp 178−179 °C; ^{1}H NMR δ 1.00 (t, 3H, *J* = 7.5 Hz), 1.51−1.55 (m, 1H), 1.71−1.84 (m, 1H), 2.02 (q, 2H, *J* = 7.7 Hz), 1.87−2.13 (m, 4H), 2.77 (ddd, 1H, *J* = 2.4, 12.1, 15.0 Hz), 3.01 (ddd, 1H, *J* = 2.4, 5.3, 15.3 Hz), 3.30 (ddd, 1H, *J* = 4.0, 9.3, 11.8 Hz), 3.41−3.48 (m, 1H), 3.65 (s, 3H), 3.68 (dd, 1H, *J* = 6.4, 12.9 Hz), 5.48 (br s, 1H), 7.06 (ddd, 1H, *J* = 1.0, 6.9, 7.9 Hz),

7.14 (ddd, J = 1.2, 7.0, 8.0 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 7.6 Hz); ^{13}C NMR δ 9.6, 25.7, 25.8, 27.3, 29.5, 29.7, 30.5, 34.2, 42.9, 108.9, 113.2, 117.3, 119.0, 120.7, 128.1, 135.8, 138.7, 173.6; IR 3245, 2923, 1636, 1552, 735 cm^{-1}; EIMS *m/z* 284, 211, 198, 107 (100), 84. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

***N*-Butanoyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11c, R = H, R^1 = Pr):** 82%; mp 131−132 °C; ^{1}H NMR δ 0.84 (t, 3H, J = 7.5 Hz), 1.51−1.57 (m, 3H), 1.71−2.13 (m, 7H), 2.73−2.81 (m, 1H), 3.00 (ddd, 1H, J = 2.4, 5.8, 15.8 Hz), 3.31 (ddd, 1H, J = 4.2, 9.0, 12.7 Hz), 3.42−3.46 (m, 1H), 3.65 (s, 3H), 3.69 (dd, J = 6.2, 12.6 Hz), 5.49 (br s, 1H), 7.06 (dd, 1H, J = 7.2, 7.6 Hz), 7.13 (ddd, 1H, J = 1.1, 7.6, 9.0 Hz), 7.23 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz); ^{13}C NMR δ 13.6, 18.9, 25.7, 25.8, 27.3, 29.5, 30.4, 34.3, 38.7, 42.8, 108.9, 113.2, 117.3, 119.0, 120.6, 128.1, 135.8, 138.8, 172.9; IR 3244, 2919, 1637, 1559, 732 cm^{-1}; EIMS *m/z* 298, 211, 198, 159, 84 (100). Anal. ($C_{19}H_{26}N_2O$) C, H, N.

***N*-Pentanoyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11d, R = H, R^1 = Bu):** 89%; mp 130−132 °C; ^{1}H NMR δ 0.83 (t, 3H, J = 7.3 Hz), 1.19−1.25 (m, 2H), 1.41−1.47 (m, 2H), 1.49−1.54 (m, 1H), 1.71−2.13 (m, 7H), 2.77 (ddd, 1H, J = 2.4, 12.1, 15.0 Hz), 3.00 (ddd, 1H, J = 2.4, 5.8, 16.0 Hz), 3.30 (ddd, 1H, J = 4.3, 9.3, 12.6 Hz), 3.41−3.46 (m, 1H), 3.66 (s, 3H), 3.69 (dd, 1H, J = 6.5, 12.8 Hz), 5.43 (br s, 1H), 7.06 (dd, 1H, J = 7.0, 7.9 Hz), 7.14 (ddd, 1H, J = 1.1, 7.1, 7.9 Hz), 7.23 (d, 1H, J = 8.3 Hz), 7.49 (d, 1H, J = 7.6 Hz); ^{13}C NMR δ 13.7, 22.3, 25.7, 25.8, 27.4, 27.6, 29.5, 30.5, 34.3, 36.5, 42.9, 109.0, 113.2, 117.4, 119.1, 120.6, 128.2, 135.8, 138.8, 173.0; IR 3248, 2924, 1634, 1547 cm^{-1}; EIMS *m/z* 312, 211, 198 (100), 170. Anal. ($C_{20}H_{28}N_2O$) C, H, N.

***N*-Cyclopropanoyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11e, R = H, R^1 = c-C_3H_5):** 75%; mp 130−132 °C; ^{1}H NMR δ 0.58−0.67 (m, 2H), 0.84−0.97 (m, 2H), 1.07−1.12 (m, 1H), 1.52−1.56 (m, 1H), 1.72−2.14 (m, 5H), 2.77 (ddd, 1H, J = 2.6, 6.5, 12.1 Hz), 3.01 (ddd, 1H, J = 2.4, 5.8, 12.0 Hz), 3.31 (ddd, 1H, J = 4.5, 8.7, 15.5 Hz), 3.44−3.48 (m, 1H), 3.66 (s, 3H), 3.67−3.74 (m, 1H), 5.63 (br s, 1H), 7.06 (ddd, 1H, J = 1.0, 7.0, 7.8 Hz), 7.13 (dd, 1H, J = 7.0, 8.0 Hz), 7.23 (d, 1H, J = 8.1 Hz), 7.52 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 6.9, 14.8, 25.7, 25.8, 27.4, 29.5, 30.5, 34.4, 43.3, 108.9, 113.3, 117.5, 119.1, 120.6, 128.2, 135.9, 138.8, 173.5; IR 3248, 2913, 1630, 1556, 739 cm^{-1}; EIMS *m/z* 296, 211, 198 (100), 170, 41. Anal. ($C_{19}H_{24}N_2O$) C, H, N.

***N*-Cyclobutanoyl-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11f, R = H, R^1 = c-C_4H_7):** 68%; mp 177−179 °C; ^{1}H NMR δ 1.51−1.57 (m, 1H), 1.69−2.22 (m, 12H), 2.73−2.81 (m, 2H), 3.01 (ddd, 1H, J = 2.0, 5.5, 10.2 Hz), 3.29 (ddd, 1H, J = 4.0, 8.7, 11.5 Hz), 3.40−3.45 (m, 1H), 3.65 (s, 3H), 3.63−3.71 (m, 1H), 5.35 (br s, 1H), 7.06 (ddd, 1H, J = 1.0, 6.9, 7.8 Hz), 7.13 (ddd, 1H, J = 1.1, 7.1, 8.1 Hz), 7.22 (d, 1H, J = 8.2 Hz), 7.47 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ 17.9, 25.1, 25.2, 25.7, 25.8, 27.3, 29.5, 30.5, 34.3, 39.9, 42.9, 108.9, 113.2, 117.4, 119.0, 120.6, 128.2, 135.8, 138.7, 174.8; IR 3245, 2919, 1634, 1557, 742; EIMS *m/z* 310, 211, 198 (100), 170, 41. Anal. ($C_{20}H_{26}N_2O$) C, H, N.

***N*-(Trifluoroacetyl)-10-(aminomethyl)-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11g, R = H, R^1 = CF_3):** 77%; mp 157−159 °C; ^{1}H NMR δ 1.41−1.50 (m, 1H), 1.75−1.79 (m, 2H), 1.97−2.08 (m, 3H), 2.73 (dd, 1H, J = 2.4, 11.2 Hz), 2.94−3.07 (m, 3H), 3.53−3.55 (m, 1H), 3.65 (s, 3H), 5.67 (br s, 1H), 6.98−7.00 (m, 2H), 7.15 (d, 1H, J = 9.0 Hz), 7.40 (br s, 1H), 7.51 (d, 1H, J = 8.9 Hz); ^{13}C NMR δ 25.5, 25.7, 27.2, 29.6, 29.8, 32.5, 42.7, 109.2, 110.1, 117.3, 117.9, 119.5, 120.8, 127.8, 135.9, 140.0, 161.8; IR 3323, 2930, 1690, 1187, 1159, 740 cm^{-1}; EIMS *m/z* 324, 228, 211, 198 (100), 170, 128. Anal. ($C_{17}H_{19}N_2OF_3$) Calcd: C, 62.95; H, 5.91; N, 8.63. Found: C, 62.49; H, 5.88; N, 8.57.

***N*-Acetyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11h, R = OMe, R^1 = Me):** 69%; mp 132−134 °C; ^{1}H NMR δ 1.49−1.53 (m, 1H), 1.72−2.12 (m, 5H), 1.82 (s, 3H), 2.69−2.77 (m, 1H), 2.95 (ddd, 1H, J = 2.4, 5.7, 12.6 Hz), 3.25 (ddd, 1H, J = 4.0, 9.4, 12.4 Hz), 3.35−3.40 (m, 1H), 3.62 (s, 3H), 3.65−3.72 (m, 1H), 3.83 (s, 3H), 5.45 (br s, 1H), 6.78 (dd, 1H, J = 2.4, 8.8 Hz), 6.95 (d, 1H, J = 2.3 Hz), 7.11 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 23.5, 25.8, 26.1, 27.4, 29.7, 30.6, 34.4, 43.2, 56.0, 99.4, 109.8, 110.7, 112.9, 128.5, 131.2, 139.5, 154.1, 170.1; IR 3332, 2920, 1639, 1531, 1233 cm^{-1}; EIMS *m/z* 300, 241, 228 (100), 137, 122, 43. Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

***N*-Propanoyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11i, R = OMe, R = Et):** 91%; mp 125−127 °C; ^{1}H NMR δ 1.00 (t, 3H, J = 7.7 Hz), 1.49−1.52 (m, 1H), 1.72−2.15 (m, 7H), 2.73−2.77 (m, 1H), 2.94−2.99 (m, 1H), 3.26−3.30 (m, 1H), 3.35−3.40 (m, 1H), 3.62 (s, 3H), 3.64−3.73 (m, 1H), 3.82 (s, 3H), 5.40 (br s, 1H), 6.78 (dd, 1H, J = 2.3, 8.7 Hz), 6.94 (d, 1H, J = 2.0 Hz), 7.11 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 9.7, 25.8, 26.0, 27.4, 29.6, 29.8, 30.6, 34.3, 42.9, 55.9, 99.4, 109.7, 110.6, 112.9, 128.4, 131.1, 139.5, 154.0, 173.6; IR 3338, 2917, 1640, 1524, 1229 cm^{-1}; EIMS *m/z* 314, 241, 228 (100), 137, 122, 43. Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

***N*-Butanoyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11j, R = OMe, R^1 = Pr):** 83%; mp 58−60 °C; ^{1}H NMR δ 0.82 (t, 3H, J = 7.4 Hz), 1.48−1.56 (m, 3H), 1.63−2.11 (m, 5H), 2.00 (t, 2H, J = 6.9 Hz), 2.69−2.77 (m, 1H), 2.93−2.98 (m, 1H), 3.28 (ddd, 1H, J = 4.0, 9.3, 12.1 Hz), 3.34−3.38 (m, 1H), 3.61 (s, 3H), 3.33 (ddd, 1H, J = 6.0, 7.4, 12.7 Hz), 3.82 (s, 3H), 5.47 (br s, 1H), 6.78 (dd, 1H, J = 2.4, 8.8 Hz), 6.95 (d, 1H, J = 2.2 Hz), 7.10 (d, 1H, J = 8.1 Hz); ^{13}C NMR δ 13.7, 19.0, 25.7, 25.9, 27.4, 29.6, 30.5, 34.4, 38.7, 42.8, 56.0, 99.5, 109.7, 110.5, 112.9, 128.3, 131.2, 139.5, 154.0, 172.9; IR 3340, 2923, 1641, 1530, 1234 cm^{-1}; EIMS *m/z* 328, 241, 228 (100), 137, 122, 43 (100). Anal. ($C_{20}H_{28}N_2O_2$) C, H, N.

***N*-Pentanoyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11k, R = OMe, R^1 = C_4H_9):** 76%; mp 78−82 °C; ^{1}H NMR δ 0.81 (t, H, J = 7.3 Hz), 1.17−1.23 (m, 2H), 1.40−1.54 (m, 3H), 1.69−2.11 (m, 5H), 2.00 (t, 2H, J = 7.9 Hz), 2.69−2.77 (m, 1H), 2.94 (ddd, 1H, J = 2.5, 5.6, 13.3 Hz), 3.26−3.35 (m, 1H), 3.37−3.38 (m, 1H), 3.61 (s, 3H), 3.63−3.70 (m, 1H), 3.82 (s, 3H), 5.47 (br s, 1H), 6.78 (dd, 1H, J = 2.5, 9.0 Hz), 6.94 (d, 1H, J = 2.5 Hz), 7.10 (d, 1H, J = 8.9 Hz); ^{13}C NMR δ 13.7, 22.3, 25.7, 25.9, 27.4, 27.6, 29.6, 30.5, 34.3, 36.6, 42.8, 55.9, 99.5, 109.7, 110.5, 112.8, 128.3, 131.2, 139.5, 154.0, 173.1; IR 3337, 2929, 1636, 1230; EIMS *m/z* 342, 241, 228 (100), 137, 122, 43. Anal. ($C_{21}H_{30}N_2O_2$) C, H, N.

***N*-Cyclopropanoyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11l, R = OMe, R^1 = c-C_3H_5):** 92%; mp 160−161 °C; ^{1}H NMR δ 0.58−0.68 (m, 2H), 0.83−0.88 (m, 1H), 0.92−0.98 (m, 1H), 1.11−1.14 (m, 1H), 1.50−1.53 (m, 1H), 1.73−2.14 (m, 5H), 2.71−2.78 (m, 1H), 2.97 (ddd, 1H, J = 3.8, 5.4, 12.1 Hz), 3.28 (ddd, 1H, J = 3.7, 9.1, 12.8 Hz), 3.36−3.41 (m, 1H), 3.62 (s, 3H), 3.33 (m, 1H), 3.83 (s, 3H), 5.71 (br s, 1H), 6.78 (dd, 1H, J = 2.3, 8.8 Hz), 6.98 (d, 1H, J = 2.1 Hz), 7.11 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 6.7, 14.7, 25.7, 26.0, 27.3, 29.6, 30.6, 34.5, 43.2, 55.9, 99.5, 109.7, 110.6, 113.0, 128.4, 131.1, 139.4, 154.0, 173.3; IR 3327, 2924, 1636, 1542, 1236 cm^{-1}; EIMS *m/z* 326, 241, 228 (100), 69, 41. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***N*-Cyclobutanoyl-10-(aminomethyl)-2-methoxy-5-methyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (11m, R = OMe, R^1 = c-C_4H_7):** 69%; mp 119−121 °C; ^{1}H NMR δ 1.48−1.52 (m, 1H), 1.70−2.14 (m, 11H), 2.70−2.80 (m, 2H), 2.97 (ddd, 1H, J = 2.3, 5.7, 13.2 Hz), 3.28 (ddd, 1H, J = 4.0, 9.6, 12.3 Hz), 3.33 (ddd, 1H, J = 5.8, 7.5 Hz, 12.4 Hz), 3.34−3.38 (m, 1H), 3.62 (s, 3H), 3.82 (s, 3H), 5.33 (br s, 1H), 6.78 (dd, 1H, J = 2.4, 8.8 Hz), 6.93 (d, 1H, J = 2.4 Hz), 7.10 (d, 1H, J = 8.7 Hz); ^{13}C NMR δ 18.0, 25.3, 25.9, 26.1, 27.5, 29.7, 30.7, 34.5, 40.1, 42.9, 56.1, 99.6, 109.8, 110.6, 113.0, 128.5, 131.2, 139.6, 154.1, 174.9; IR 3331, 2920, 1638, 1537, 1232 cm^{-1}; EIMS *m/z* 340, 241, 228 (100), 69, 41. Anal. ($C_{20}H_{26}N_2O_2$) Calcd: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.56; H, 8.13; N, 8.23.

Separation of Enantiomers: Tetrahydrocarbazoles. The racemic mixture (0.250 g of **9g**; 1.20 g of **9a**) was dissolved in ethanol (10 mg/mL) and injected in 0.5 mL aliquots onto a

25 cm × 2 cm Chiracel AD preparative HPLC column, eluting with hexane−ethanol (**9g**, 85:15; **9a**, 9:1). Removal of the solvent gave the separate solid enantiomers, each of which was then examined by analytical chiral HPLC for purity.

(+)-(*R*)-9g: 147 mg; $[\alpha]_D$ + 28.5° (*c* = 1.0, EtOH). **(−)-(*S*)-9g:** 117 mg; $[\alpha]_D$ −29.0° (*c* = 1.0, EtOH).

(+)-(*R*)-9a: 410 mg; $[\alpha]_{Hg}$ +15.9° (*c* = 1.0, DCM). **(−)-(*S*)-9a:** 470 mg; $[\alpha]_{Hg}$ −16.5° (*c* = DCM).

Cyclohept[*b*]indole. The racemic mixture (**11h**, 400 mg) was dissolved in ethanol (40 mL) and injected in 0.5 mL aliquots onto a 25 cm × 2 cm Chiracel OD preparative HPLC column, eluting with hexane−ethanol (95:5). Recycling was required, and the (−)-enantiomer appeared to have a slight impurity from the analytical chiral HPLC.

(+)-(*R*)-11h: 142 mg; $[\alpha]_D$ +31.5° (*c* = 1.0, EtOH). **(−)-(*S*)-11h:** 127 mg; $[\alpha]_D$ −30.0° (*c* = 1.0, EtOH).

Cyclopent[*b*]indole. The racemic mixture (**10i**, 43 mg) was dissolved in ethanol (215 mL) and injected in 0.5 mL aliquots onto a 25 cm × 2 cm Chiracel OD preparative HPLC column, eluting with hexane−ethanol (93:7). Recycling was required and only sufficient of the analytically pure material was obtained for biological testing.

(+)-(*R*)-10i: 9.7 mg. **(−)-(*S*)-10i:** 8.3 mg.

Competition Studies. Values for the relative binding affinities of the enantiomers were calculated using the equation $y \cdot f(S) + (1 - y) \cdot f(R) = f(R,S)$, where, *y* is the mole fraction of the *S* enantiomer, $f(S)$ is the binding affinity of the (*S*) enantiomer, $f(R)$ is the binding affinity of the *R* enantiomer, and $f(R,S)$ is the binding affinity of the racemate.

Modeling. All compounds were modeled using Sybyl 6.0 (Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144). Structures were originally generated using CONCORD[39] before minimizing in Sybil using Maximim (Tripos force field, Powell method, minimization to converge when gradient < 0.05 kcal/(mol A), charges: Gasteiger-Marsili).

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Supporting Information Available: Tables of X-ray crystallographic data for structures **9m** and (*R*)-(+)-**9a** and CD spectra for (+)- and (−)-**9g** and (+)- and (−)-**10i** (12 pages); structure factors (10 pages). Ordering information is given on any current masthead page.

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